ASYMMETRIC INTRAMOLECULAR DIELS-ALDER REACTIONS

by

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B.A., Johns Hopkins University
(1981)

SUBMITTED TO THE DEPARTMENT OF

CHEMISTRY IN PARTIAL

FULFILLMENT OF THE

REQUIREMENTS FOR THE

DEGREE OF

DOCTOR OF PHILOSOPHY IN

ORGANIC CHEMISTRY

at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY
DECEMBER 1985

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Submitted to the Department of Chemistry
on December 6, 1985 in partial fulfillment of the
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in Organic Chemistry

ABSTRACT

A review of the stereochemical aspects of Diels-Alder reactions is presented in Chapter 1. Emphasis is placed on the diastereoselectivity obtained in asymmetric bimolecular and intramolecular Diels-Alder reactions.

Stereochemical aspects of intramolecular Diels-Alder reactions of chiral (*E*,*E*,*E*)-trienes 3-5, model precursors of the perhydroindene and decalin ring systems, were investigated (Chapter 2). These trienes were synthesized *via* a coupling of the appropriate diene aldehyde (21, 31, or 34) with chiral β-ketophosphonate (-)-12b using a modification of the Horner-Wadsworth-Emmons reaction. Lewis acid catalyzed cyclizations of trienes 3-5 using zinc chloride or ethylaluminum dichloride were studied. Trienes 3 and 4 gave exclusively the *trans*-fused adducts ((-)-38 and (-)-60 respectively), while 5 gave approximately a 95:5 mixture of *trans*- to *cis*-fused adducts (69:70). The kinetic diastereofacial selectivities of these cyclizations are at least 94%. The absolute configurations of cycloadducts (-)-38 and (-)-60 were assigned by comparison of optical rotations of alcohols 6 and 7, prepared by a three-step degradation of 38 and 60, respectively, with the values reported in the literature. The chiral auxiliary, 1, derived from commercially available (*S*)-mandelic acid, is extremely effective at directing the dienophile to only one face of the diene, thus generating high diastereofacial selectivities in the intramolecular Diels-Alder cyclizations.

Preliminary studies on enol pyruvate 1 as a chiral ketene equivalent in bimolecular Diels-Alder reactions are described in Chapter 3. The thermal Diels-Alder reaction of 1 with cyclopentadiene proceeded in high chemical yield (85%), with excellent facial selectivity giving exclusively one isomer, and with high exo selectivity (93:7 mixture of 17:18). However, 1 suffers from low reactivity. Further studies on the Lewis acid catalyzed reaction of 1 with less reactive dienes are needed to determine whether this reagent is suitable for use in synthesis as a chiral ketene equivalent.

Finally, studies were initiated to probe the effect of the dienophile activating group on the stereoselectivity of the intramolecular Diels-Alder reactions of substituted 1,3,8-nonatrienes (Addendum). Trienes 4-6 were synthesized. Studies of their thermal cyclizations revealed two trends: as the reaction temperature was decreased, selectivity for the *trans*-fused cycloadduct increased, and as the dienophile activating group was varied from $-CON(C_4H_8)$ to $-COCH_3$ to -CHO, the *trans*-selectivity increased. The highest selectivity was obtained with triene 5 at 100°C (92:8 trans:cis). These trends are fully consistent with the nonsynchronous transition state theory.

Thesis Supervisor: Dr. William R. Roush

Title: Associate Professor of Chemistry
Fellow of the Alfred P. Sloan Foundation 1982-1986

To

My Parents

George and Muriel

Acknowledgements

I would like to express my sincere appreciation and thanks to Professor Roush for his patience and guidance over the past four years. His devotion to and concern about the growth and development of his graduate students is to be commended. His high standards of research have been instilled in me and will be used throughout my career.

I would like to thank my high school chemistry teacher, Dr. Dave Goldberg, for sparking my interest in chemistry. His enthusiasm and sense of humor made chemistry seem very appealing. I would also like to thank my professors at Johns Hopkins University for giving me a solid background of chemistry which allowed me to continue my studies in the field.

My thanks to the past and present Roush group members who made my stay at M.I.T. more interesting. Special thanks go to my two bay-mates, Steve P. and Julie, who definitely provided many interesting conversations over the years. I'd also like to express my gratitude to Tim Blizzard who brought to my attention many human interest stories from various newspapers that I otherwise would have missed. I would also like to thank all those members of the group who participated in the early morning coffee breaks over the years.

Most importantly, I would like to express my sincere appreciation to those who helped in the preparation of this thesis, without whose help I never would have finished on time. First, I would like to thank Julie Straub and Lee Hoong who helped draw some of the structures in this thesis. Without their assistance I would surely have had to pull

several all-nighters. Next I would like to thank Sandra Russo-Rodriguez and Michael Michaelides for being the two major proofreaders of my thesis. Between the two of them they caught almost all of the errors. I'd also like to thank Ken Kirschenbaum, Jotham Coe, Ron Halterman, and Julie Straub for proofreading various parts of my thesis.

I am indebted to Professor Roush and the Arthur D. Little Company for financial support in the form of a Research Assistantship and an Industrial Fellowship during my stay at M.I.T..

Abbreviations

COSY	correlation spectroscopy
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
d.e.	diastereomeric excess
DIBAL-H	diisobutylaluminum hydride
4-DMAP	4-dimethoxyaminopyridine
DME	dimethoxyethane
e.e.	enantiomeric excess
equiv.	equivalents
HWE	Horner-Wadsworth-Emmons
LDA	lithium diisopropylamine
mCPBA	meta-chloroperbenzoic acid
MTPA-Cl	α-methoxy-α-(trifluoromethyl)phenylacetyl chloride
NOE	Nuclear Overhauser Effect
ox	oxidation
PCC	pyridinium chlorochromate
Ph or ϕ	phenyl
PTLC	preparative thin layer chromatography
TBDMS	tert-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography

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Chapter 1

Intramolecular Diels-Alder Reactions: A Brief Review

The Diels-Alder reaction, originally discovered in 1928,[1] has enjoyed widespread use in organic synthesis.[2,3,4,5,6,7] This [4+2] cycloaddition reaction is particularly valuable in that it forms two bonds in a cyclohexenyl system with simultaneous creation of up to four new chiral centers. Curiously enough, the intramolecular version of this reaction, in which the diene and dienophile are tethered by a connecting chain, was not investigated for many years. Alder and Schumaker reported the first example of the intramolecular reaction in 1953[8] but it was not until the early 1960's that other examples began to appear in the literature.[9,10,11,12,13] Since the mid 1970's, however, a virtual explosion in interest in this reaction has

1. Diels, O.; Alder, K. Justus Liebigs Ann. Chem. 1928, 98, 460.
2. Sustmann, R.; Sauer, J. Angew. Chem., Int. Ed. Engl. 1980, 19, 779.
3. Martin, J.G.; Hill, R.K. Chem. Rev. 1961, 61, 537.
4. Butz, L.W.; Rytina, A.W. Org. Reactions 1949, 5, 136.
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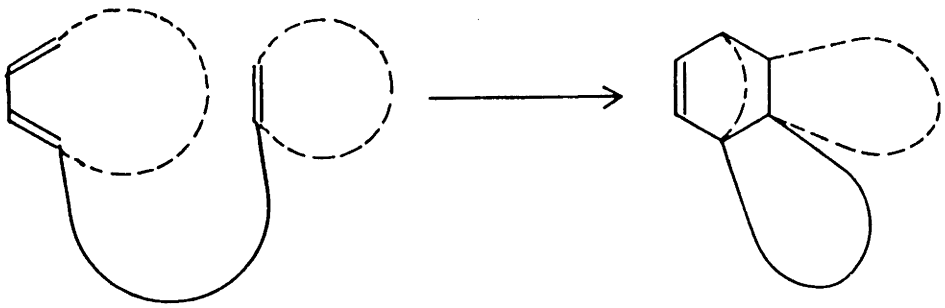
10. (a) Wasserman, H.H.; Douxaux, A.R. Jr. J. Am. Chem. Soc. 1962, 84, 4611. (b) Wasserman, H.H.; Douxaux, A.R. Jr.; Davis, R.E. J. Am. Chem. Soc. 1966, 88, 4517.
11. McBee, E.T.; Stoffer, J.O.; Braendin, H.P. J. Am. Chem. Soc. 1962, 84, 4540.
12. Bilovic, D.; Strojanac, Z.; Hahn, V. Tetrahedron Lett. 1964, 2071.
13. Klemm, L.H.; Lee, D.H.; Gopinath, K.W.; Klopfenstein, C.E. J. Org. Chem. 1966, 31, 2376.

occurred.[14,15,16,17,18,19,20,21] The increased reactivity (due to favorable entropy considerations) and heightened regioselectivity (due to constraints posed by the connecting chain) of the intramolecular case as well as the potential to synthesize stereochemically complex polycyclic systems (Scheme 1) account for the growth of applications of this reaction in the synthesis of natural products. Numerous terpenoids, alkaloids, and steroids have already been synthesized by

Scheme 1

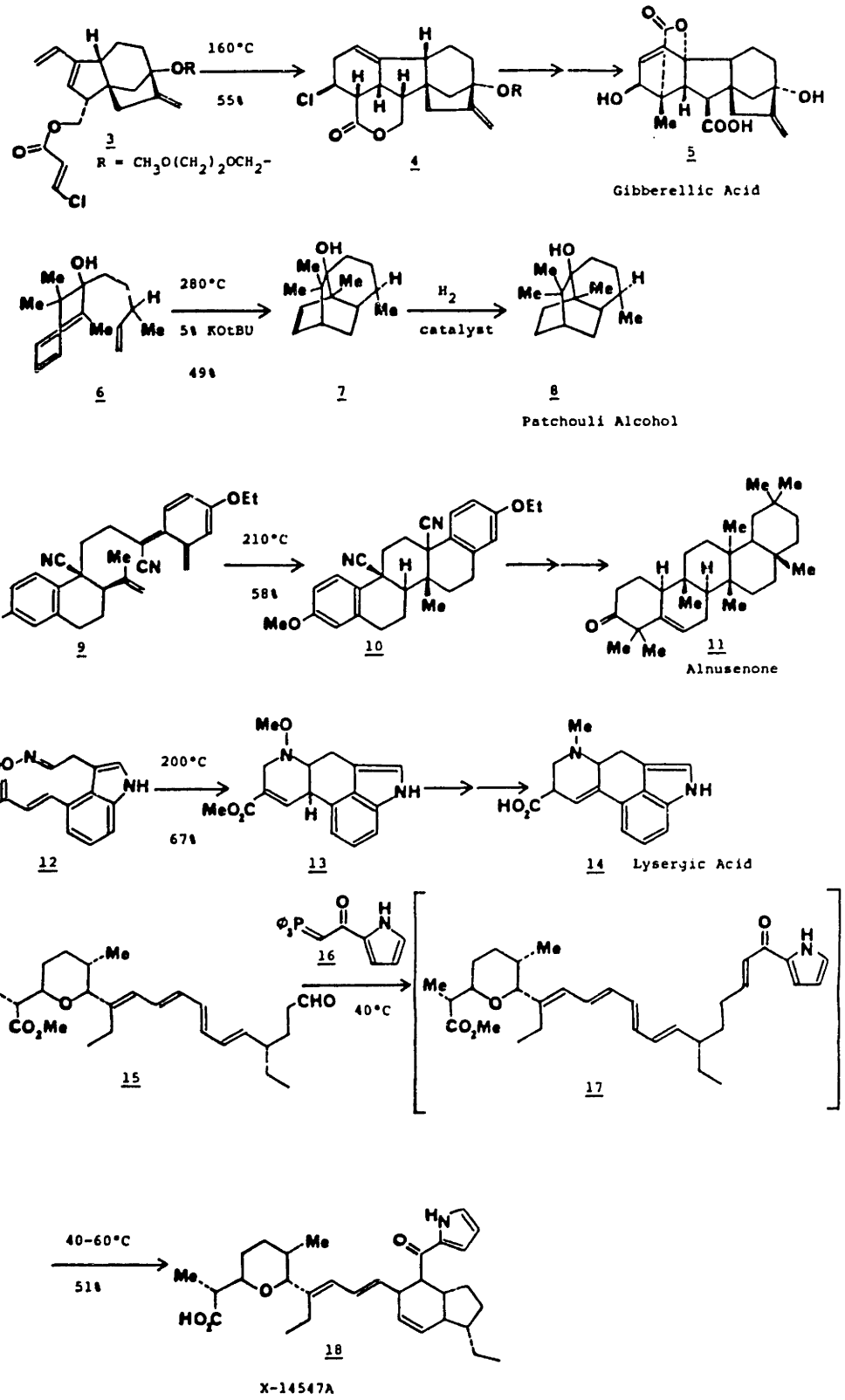


1 2

routes employing intramolecular Diels-Alder reactions. Some

14. Fallis, A.G. Can. J. Chem. 1984, 62, 183.
15. Taber, D.F. "Intramolecular Diels-Alder Reactions and Alder Ene Reactions"; Springer Verlag: New York, 1984.
16. Paquette, L.A. In "Asymmetric Synthesis" Vol. 3; Morrison, J.D. Ed.; Academic Press: New York, 1984; pp 478.
17. Ciganek, E. Organic Reactions 1984, 32, 1.
18. Oppolzer, W. Angew. Chem., Int. Ed. Engl. 1984, 23, 87.
19. Oppolzer, W. Angew. Chem., Int. Ed. Engl. 1977, 16, 10.
20. Brieger, G.; Bennett, J.N. Chem. Rev. 1980, 80, 63.
21. Vollhardt, K.P.C. Chem. Soc. Rev. 1980, 9, 41.

Scheme 2


160°C
55%
R = CH3O(CH2)2OCH2-
3
4
5
Gibberellic Acid
280°C
5% KOtBU
49%
H2
catalyst
6
7
8
Patchouli Alcohol
210°C
58%
9
10
11
Alnusenone
200°C
67%
12
13
14 Lysergic Acid
16
40°C
15
17
40-60°C
51%
18
X-14547A

representative compounds include gibberellic acid (5),[22] patchouli alcohol (8),[23] alnusenone (11),[24] lysergic acid (14),[25] and antibiotic X-14547A (18)[26,27] (Scheme 2).

Much useful information on the intramolecular Diels-Alder reaction has been accumulated through efforts in total synthesis. Except for some specialized cases[8,28] intramolecular Diels-Alder reactions generally are not successful if the diene and dienophile are separated by a bridging chain containing fewer than three atoms.[29] In the vast majority of successful cases the Diels-Alder reaction leads to the fused rather than the bridged product (Scheme 3). The only reported examples of a trans diene forming a bridged product have been cases in which the

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22. (a) Corey, E.J.; Danheiser, R.L.; Chandrasekaran, S.; Keck, G.E.; Gopalan, B.; Larsen, S.D.; Sirel, P.; Gras, J.-L. J. Am. Chem. Soc. 1978, 100, 8034. (b) Corey, E.J.; Brennan, T.M.; Carney, R.L. J. Am. Chem. Soc. 1971, 93, 7316.
23. (a) Naf, F.; Ohloff, G. Helv. Chim. Acta 1974, 57, 1868. (b) Naf, F.; Decorzant, R.; Giersch, W.; Ohloff, G. Helv. Chim. Acta 1981, 64, 1387.
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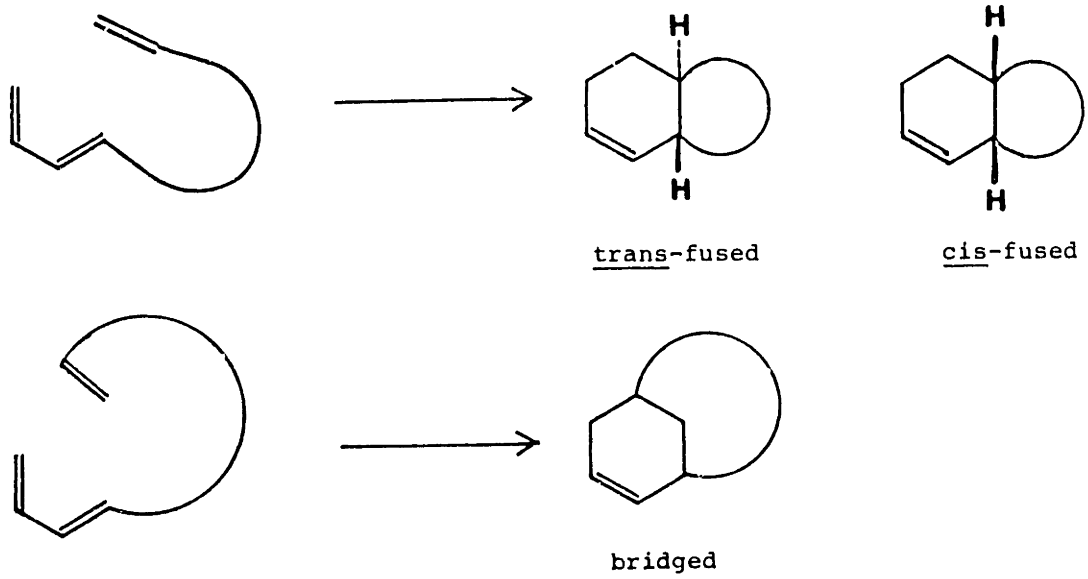
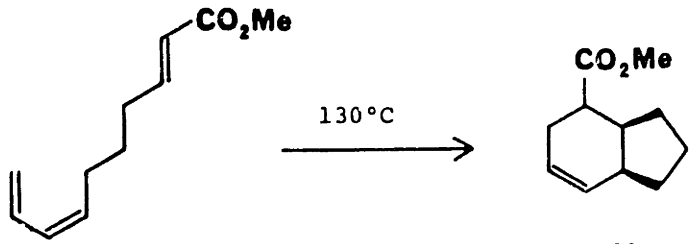
26. Roush, W.R.; Peseckis, S.M.; Walts, A.E. J. Org. Chem. 1984, 49, 3429. (b) Roush, W.R.; Peseckis, S.M. Tetrahedron Lett. 1982, 23, 4879. (c) Roush, W.R.; Myers, A.G. J. Org. Chem. 1981, 46, 1509.
27. Other syntheses: (a) Nicolaou, K.C.; Magolda, R. J. Org. Chem. 1981, 46, 1506. (b) Nicolaou, K.C.; Papahatjis, D.P.; Claremon, D.A.; Dolle, R.E. III J. Am. Chem. Soc. 1981, 103, 6967. 6969. (c) Nicolaou, K.C.; Papahatjis, D.P.; Claremon, D.A.; Magolda, R.L.; Dolle, R.E. III J. Org. Chem. 1985, 50, 1440. (d) Ley, S.V.; Edwards, M.P.; Lister, S.G. Tetrahedron Lett. 1981, 22, 361.
28. Ramamurthy, V.; Liu, R.S.H. J. Org. Chem. 1974, 39, 3435.
29. House, H.O.; Cronin, T. J. Org. Chem. 1965, 30, 1061.

Scheme 3



connecting chains contained ten or more atoms.[30] Even in cases when a (Z)-diene is employed, the fused product is generally obtained.

One complication in the intramolecular Diels-Alder reactions of *trans*-dienes is that transition states leading to *trans*- and *cis*-fused cycloadducts are close in energy and mixtures are often obtained. Fewer possibilities, however, exist in the cyclizations of substrates containing (Z)-dienes since the transition states leading to *trans*-fused cycloadducts are inaccessible for geometric reasons. Consequently, the cyclizations of trienes such as 19 define a potentially useful strategy



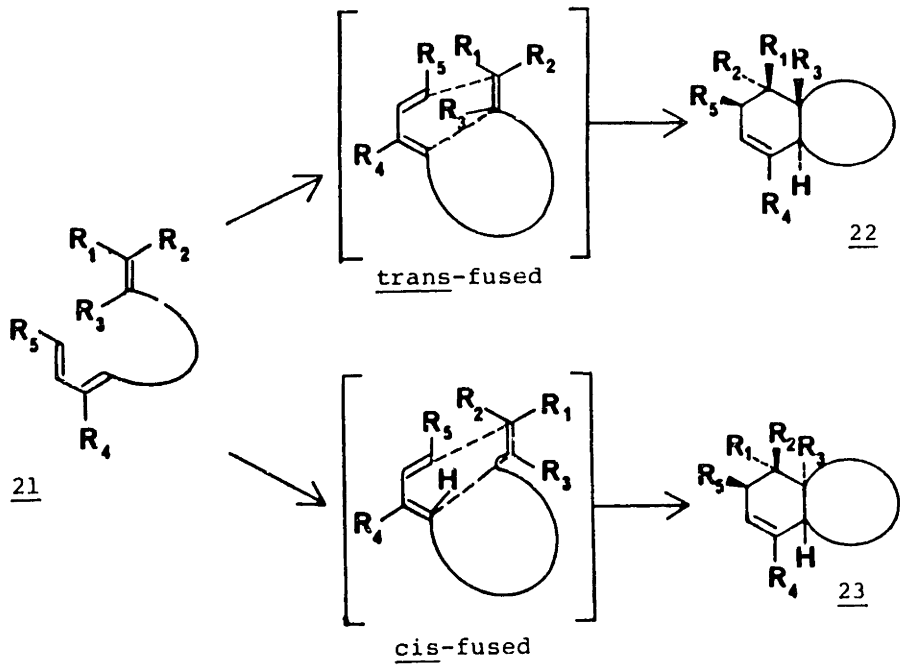
19 20

30. (a) Corey, E.J.; Petrzilka, M. Tetrahedron Lett. 1975, 2537. (b) Thomas, E.J.; Bailey, S.J.; Turner, W.B.; Jarvis, J.A.J. J. Chem. Soc., Chem. Commun. 1978, 11, 474.

for stereoselective synthesis of *cis*-fused cycloadducts.[29,31] It should be noted, however, that not all (Z)-diene systems are well behaved.[32]

Considerable effort has been devoted to elucidation of the factors governing diastereoselectivity in the intramolecular Diels-Alder reactions of (E)-diene systems (Scheme 4). Factors that strongly

Scheme 4



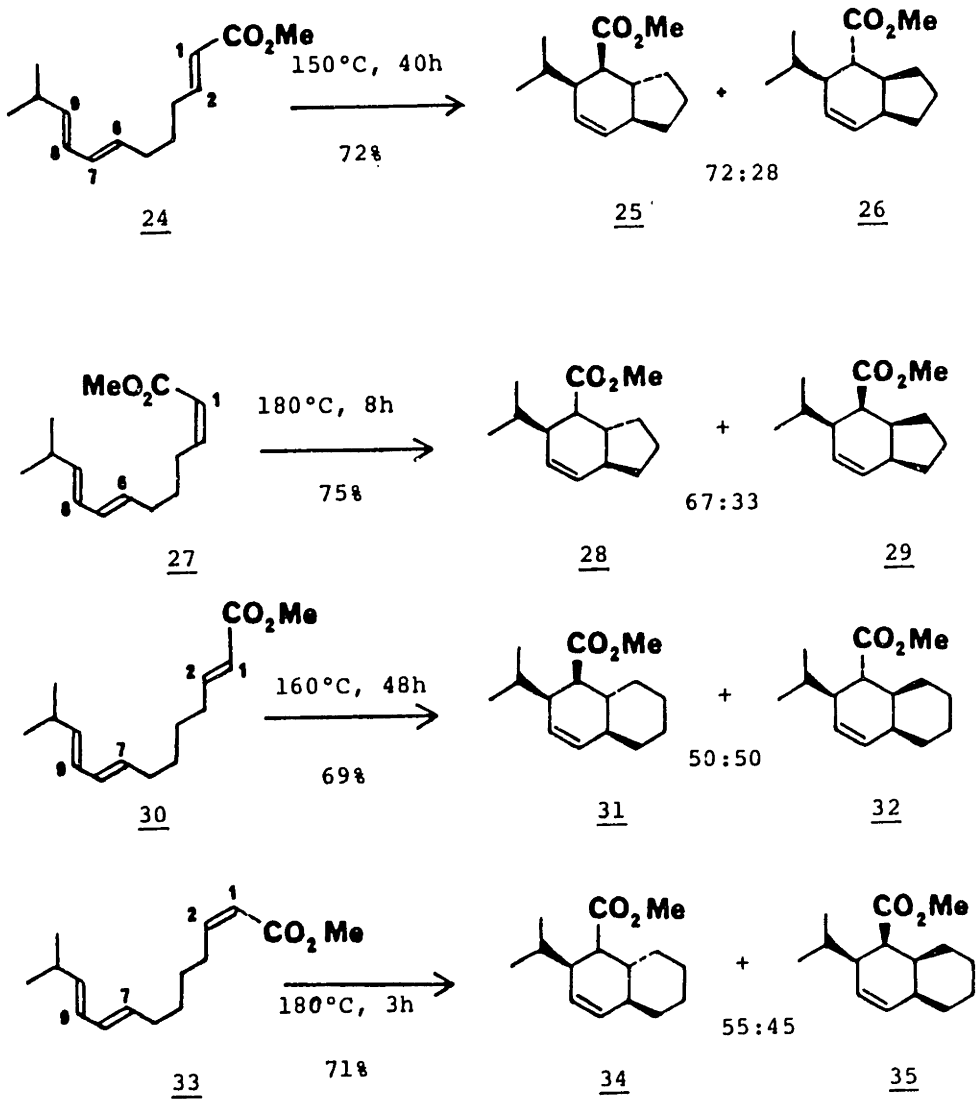
31. (a) Fuchs, P.L.; Pyne, S.G.; Hensel, M J. J. Am. Chem. Soc. 1982, 104, 5719. (b) Boeckman, R.K. Jr.; Alessi, T.R. J. Am. Chem. Soc. 1982, 104, 3216. (c) Ohno, M.; Yoshioka, M.; Nakai, H. J. Am. Chem. Soc. 1984, 106, 1133. (d) Boeckman, R.K. Jr.; Wattanasin, S.; Kathawala, F.G. J. Org. Chem. 1985, 50, 3810.
32. (a) Borch, R.F.; Evans, A.J.; Wade, J.J. J. Am. Chem. Soc. 1977, 99, 1612. (b) Oppolzer, W.; Fehr, C.; Warneke, J. Helv. Chim. Acta 1977, 60, 48. (c) Martin, S.F.; Williamson, S.A.; Gist, R.P.; Smith, K.M. J. Org. Chem. 1983, 48, 5170.

influence the selectivity for *trans*- (22) or *cis*-fused (23) cycloadducts include the number of atoms in the connecting chain and, more importantly, the placement of substituents both on the diene and/or the dienophile. In some cases when R_1 or R_2 are carbonyl derivatives, the ratio of *trans*- to *cis*-fused products can be altered by using Lewis acid catalysts.[33,34,35] The following discussion focuses on these variables as they pertain to the synthesis of perhydroindene and decalin ring systems.

Early stereocnemical studies by Roush and coworkers[33,34,35,36] established that the stereochemical course of the thermal cyclizations of activated 1,6,8-nonatrienes and 1,7,9-decatrienes is not governed by classical secondary orbital interactions. The results summarized in Scheme 5 show that selectivity in these cases is virtually independent of dienophile geometry and that the nonatrienes display a greater preference for cyclization to the *trans*-fused isomers than the homologous decatrienes. These results were interpreted initially in terms of "transition state strain" considerations that appeared to be more significant in the perhydroindene series.[35,36] This

33. Roush, W.R.; Gillis, H.R.; Ko, A.I. J. Am. Chem. Soc. 1982, 104, 2269.
34. Roush, W.R.; Gillis, H.R. J. Org. Chem. 1982, 47, 4825.
35. Roush, W.R.; Gillis, H.R. J. Org. Chem. 1980, 45, 4267.
36. Roush, W.R. J. Org. Chem. 1979, 44, 4008.

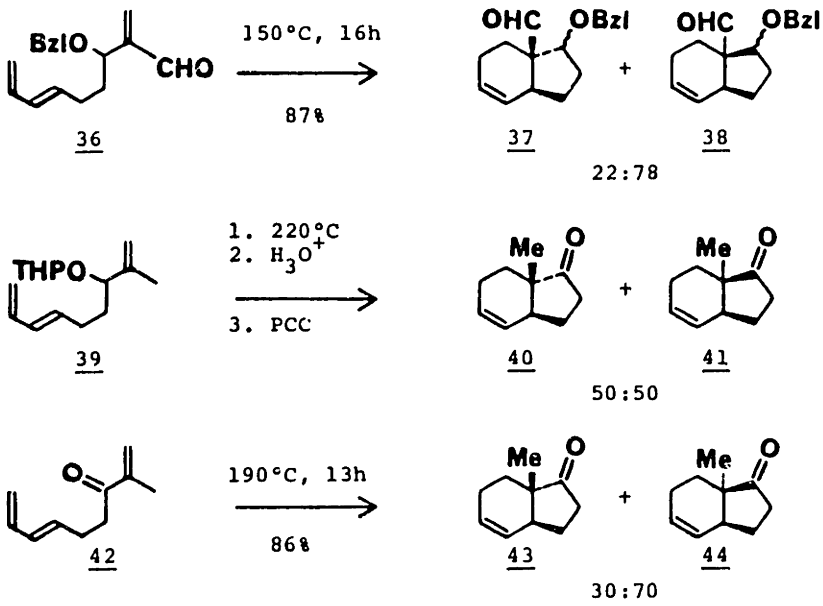
Scheme 5



interpretation was amended when it became apparent that this model failed to account for the cyclizations of nonatrienes lacking terminal dienophile activation (Scheme 6).[37,38a] Four groups suggested almost

37. (a) Jung, M.E.; Halweg, K.M. Tetrahedron Lett. 1981, 22, 3929. (b) Sutherland, J.K.; Bajorek, J.J.S. J. Chem. Soc. Perkin I 1975, 1559.

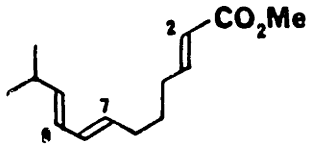
Scheme 6



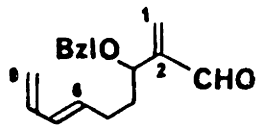
simultaneously that these results could be rationalized in terms of concerted but non-synchronous transition states.[38] Stereochemical results from bimolecular reactions,[39] rate measurements,[2] and theoretical considerations[40] suggest that Diels-Alder reactions involving unsymmetrical components may occur "concertedly" but with bond formation at one of the termini slightly advanced over the other (hence,

38. (a) Roush, W.R.; Peseckis, S.M. J. Am. Chem. Soc. 1981, 103, 6696. (b) Boeckman, R.K. Jr.; Ko, S.S. J. Am. Chem. Soc. 1982, 104, 1033. (c) White, J.D.; Sheldon, B.G. J. Org. Chem. 1981, 46, 2273. (d) Taber, D.F.; Campbell, C.; Gunn, B.P.; Chiu, I.-C. Tetrahedron Lett. 1981, 22, 5141.
39. Konovalov, A.I.; Kamasheva, G.I.; Loskutov, M.P. J. Org. Chem. U.S.S.R. 1973, 9, 2064.
40. Dewar, M.J.S. J. Am. Chem. Soc. 1984, 106, 209.

"unsymmetrical"). Applications of this idea to intramolecular reactions leads to the following predictions. (1) For trienes such as 24 containing terminal dienophile activating groups, the LUMO coefficient at C(3) should be greater than at C(2).[41] Since the HOMO coefficients of the two terminal diene carbons should be comparable,[42]



24



45

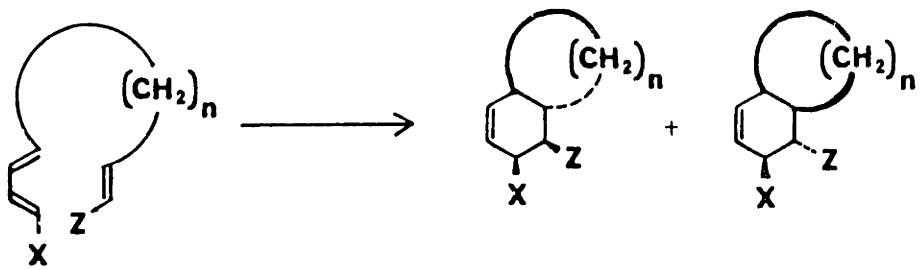
bonding between carbons 3 and 7 should be more advanced early in the reaction than between carbons 2 and 10. Under these circumstances, steric or nonbonded interactions involving atoms or groups attached to the developing five membered ring would be expected to develop at an early stage of the reaction and favor formation of a *trans*-disubstituted cyclopentane system in the transition state. (2) With trienes such as 45, however, the LUMO coefficient at C(1) should be larger than at C(2), and bonding between carbons 1 and 9 then should precede that between carbons 2 and 6. This arrangement is apparently best accomodated by a "skewed" *cis*-fused transition.[38a]

This transition state analysis was recently extended by Houk to

41. Houk, K.N. J. Am. Chem. Soc. 1978, 95, 4092.
42. (a) Fleming, I.; Michael, J.P.; Overman, L.E.; Taylor, G.F. Tetrahedron Lett. 1978, 1313. (b) Fleming, I. "Frontier Orbitals and Organic Chemical Reactions"; Wiley: New York, 1976; p.121.

account for the results summarized in Scheme 7.[43,44,45,46,47] These

Scheme 7



46 47 48

Substituents		Nonatrienes (n=3)		Decatrienes (n=4)	
X	Z	trans:cis	$\Delta\Delta G^{\ddagger}$[a]	trans:cis	$\Delta\Delta G^{\ddagger}$[a]
H	H	25:75[b]	-1.0	47:53[b]	-0.1
CO_2Et	H	43:57[g]	-0.3	50:50[g]	0.0
H	CO_2Et	60:40[c]	0.3	51:49[d]	0.0
*i*Pr	CO_2Et	72:28[c]	0.8	50:50[e]	0.0
Et_2N	CO_2Et	85:15[f]	1.1	55:45[f]	0.1
*i*Pr	$CO_2Et \cdot AlEtCl_2$	>98:2[c]	>2.3	88:12[e]	1.2

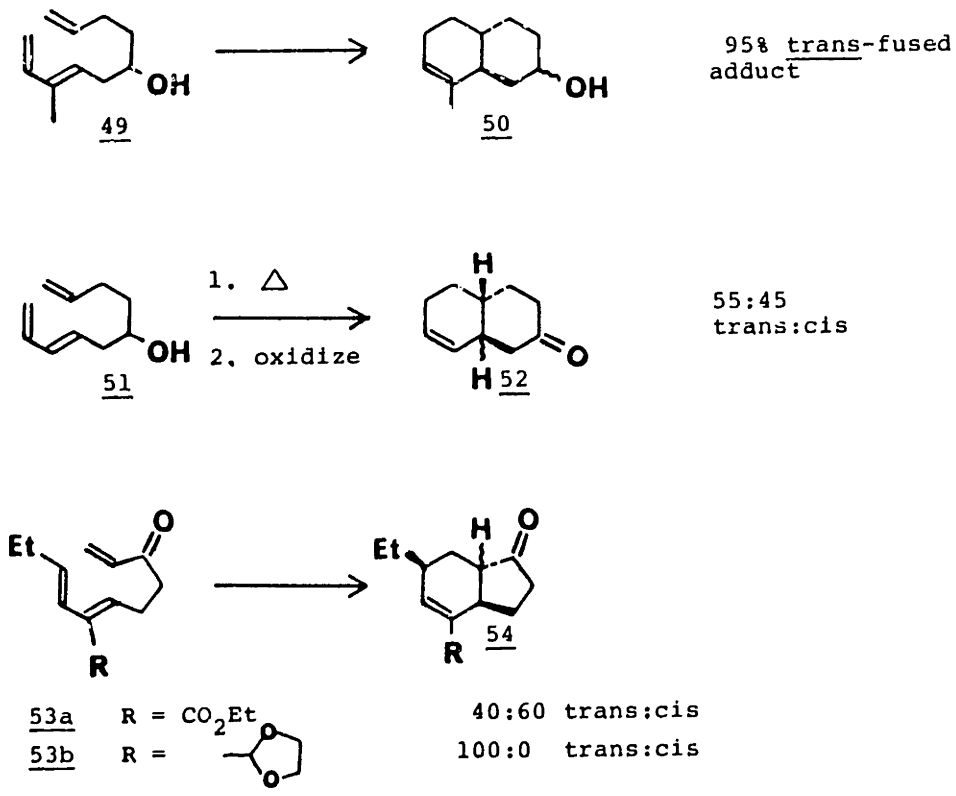
a. $\Delta\Delta G = \Delta G^{\ddagger}$(cis) - $\Delta G^{\ddagger}$(trans) in kcal/mol.
b. Reference 43. c. Reference 33. d. Reference 47.
e. Reference 34. f. Reference 44. g. Reference 45.

43. Houk, K.N.; Lin, Y.-T. Tetrahedron Lett. 1985, 26, 2269.
44. Houk, K.N.; Brown, F.K. Tetrahedron Lett. 1985, 26, 2297.
45. Houk, K.N.; Wu, T.-C. Tetrahedron Lett. 1985, 26, 2293.
46. Houk, K.N.; Lin, Y.-T. Tetrahedron Lett. 1985, 26, 2517.
47. Roush, W.R.; Hall, S.E. J. Am. Chem. Soc. 1981, 103, 5200.

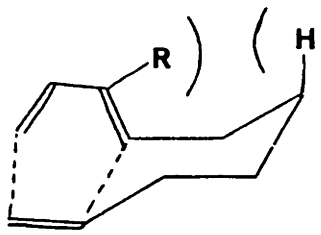
data unambiguously point to the conclusion that the cyclizations of nonatrienes are much more sensitive to substituent effects than those of decatrienes. This phenomenon has been explained in terms of a "twist-asynchronous" model.[44]

Substituents on internal positions of the diene can also have a major influence on the stereochemical course of intramolecular Diels-Alder reactions. Several examples are summarized in Scheme 8.

Scheme 8



Particularly striking is the change in selectivity realized upon varying the substitution pattern at C(8) in 49/51[48] and the corresponding position in 53.[49,50] These results can be rationalized in terms of the steric interactions that substituent R experiences in the *cis*-fused

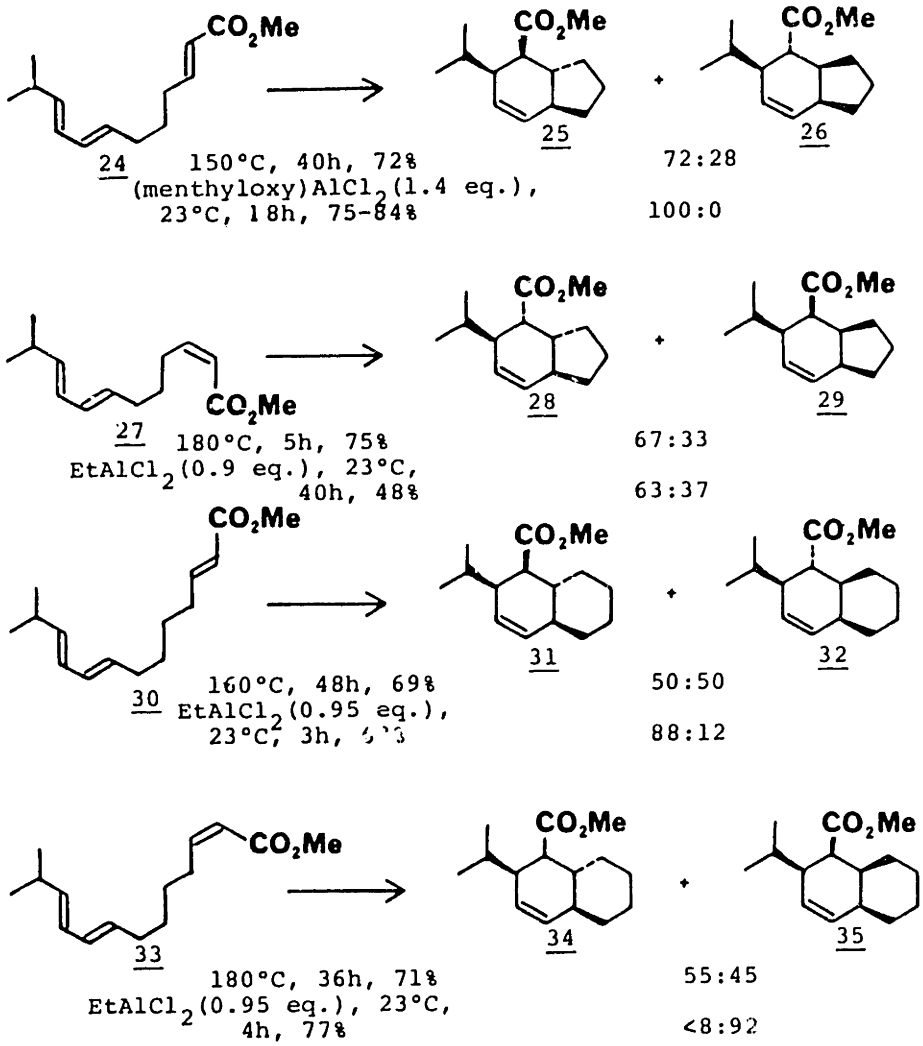


transition state. When R≠H, this mode of cyclization is substantially destabilized relative to the *trans*-fused transition state which does not suffer comparable nonbonded interactions. Use of easily removable substituents ("steric directing groups") such as -Br and -$SiMe_3$ at this position may constitute a synthetically useful strategy for increasing the selectivity for *trans*-fused intramolecular cycloadducts.[51]

Another potentially useful method for increasing the stereoselectivity of intramolecular Diels-Alder reactions involves Lewis acid catalysis. Several results are summarized in Scheme 9.[33,34,52] The thermal cyclization of substituted (E,E,E)-nonatriene 24

48. Wilson, S.R.; Huffman, J.C. J. Org. Chem. 1980, 45, 560.
49. Jung, M.E.; Halweg, K.M. Tetrahedron Lett. 1981, 22, 2735.
50. Ichihara, A.; Kimura, R.; Yamada, S.; Sakamura, S. J. Am. Chem. Soc. 1980, 102, 6353.
51. (a) Roush, W.R.; Kageyama, M. Tetrahedron Lett. 1985, 26, 4327. (b) Boeckman, R.K. Jr.; Barta, T.E. J. Org. Chem. 1985, 50, 3421.
52. Gillis, H.R. Ph.D. Thesis, Massachusetts Institute of Technology, 1982.

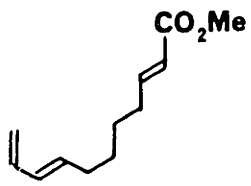
Scheme 9


CO2Me
24
150°C, 40h, 72%
(menthyloxy)AlCl2(1.4 eq.),
23°C, 18h, 75-84%
25
26
72:28
100:0
27
180°C, 5h, 75%
EtAlCl2(0.9 eq.), 23°C,
40h, 48%
28
29
67:33
63:37
30
160°C, 48h, 69%
EtAlCl2(0.95 eq.),
23°C, 3h, 5'3
31
32
50:50
88:12
33
180°C, 36h, 71%
EtAlCl2(0.95 eq.), 23°C,
4h, 77%
34
35
55:45
<8:92

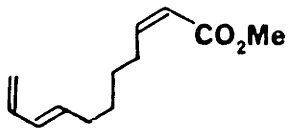
gives a 72:28 mixture of trans:cis fused products but when a Lewis acid catalyst such as (-)-(menthyloxy)aluminum dichloride is used the *trans*-fused isomer 25 is obtained exclusively. In contrast, however, the analogous (E,E,Z)-triene 27 gives a 2:1 mixture of *trans*-fused to *cis*-fused adducts under both thermal and Lewis acid catalyzed conditions. Strikingly different behavior is also exerted by the pair of substituted decatrienes, 30 and 33. Whereas both 30 and 33 give essentially 1:1 mixtures of *cis*- and *trans*-fused cycloadducts under thermal conditions, (E,E,E)-triene 30 gives an 88:12 preference for *trans*-fused 31 when the cyclization is catalyzed by using $EtAlCl_2$ and (Z,E,E)-triene 33 favors *cis*-fused 35 (>92%) under analogous conditions. The differing behavior of (Z,E,E)-trienes 27 and 33 can be explained by Houk's "twist asynchronous" transition state model.

Although three of the four examples listed in Scheme 9 demonstrate substantial improvement in reaction rate and stereoselectivity over the thermal cyclizations, use of Lewis acid catalysis in intramolecular Diels-Alder reactions is somewhat restricted in scope. The major disadvantages to using Lewis acid catalysts are that they tend to promote polymerization of some dienes[45,52], and some functional groups are incompatible with the catalysts[33,38a,52]. When the triene has a potential leaving group, like an alkoxy substituent allylic to the diene, then Lewis acids catalyze competitive pentadienyl carbonium ion

Scheme 10



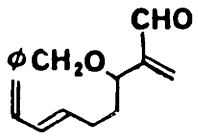
55



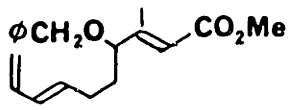
56

Work Done in Our Laboratory By:

S. Hall

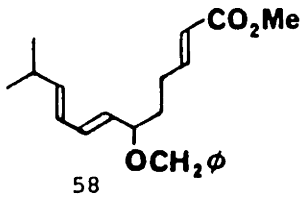


45

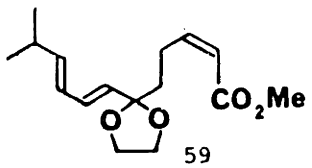


57

S. Peseckis



58

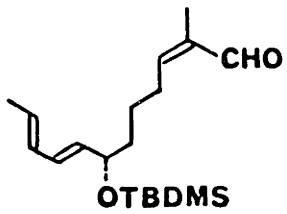


59

W. Roush
H. Gillis

formation which leads to decomposition of the triene. The substrates listed in Scheme 10 polymerize or decompose in the presence of Lewis acids and have not been successfully cyclized under these conditions. A recent report by Marshall, however, indicates that Lewis acid catalysis can be used with trienes such as 60 that incorporates a more reactive aldehydic unit in the dienophile.[53]

53. Marshall, J.A.; Audia, J.E.; Grote, J. J. Org. Chem. 1984, 49, 5277.



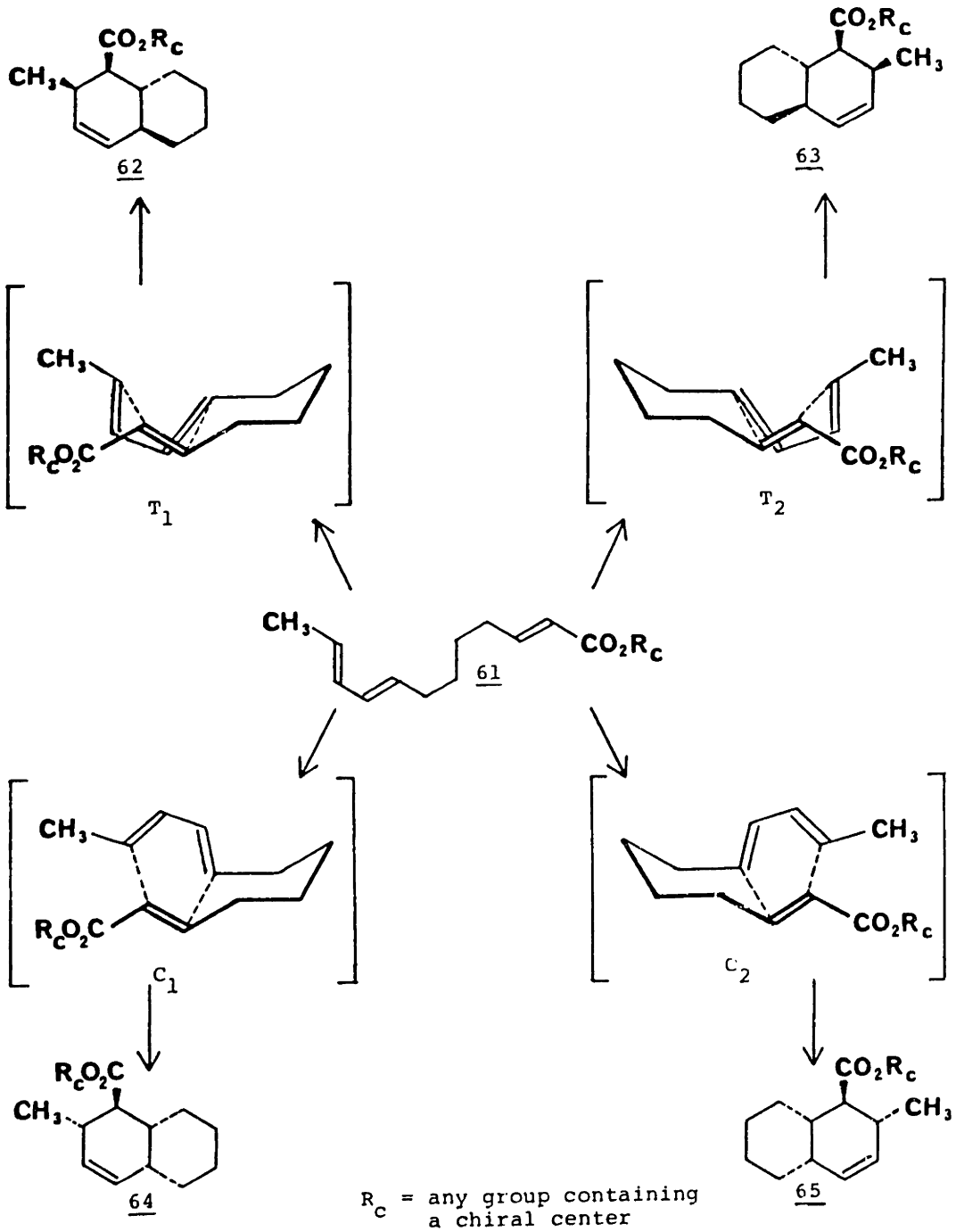
60

Asymmetric Diels-Alder Reactions

The intramolecular Diels-Alder reaction is particularly useful when applied to the synthesis of the perhydroindene and decalin ring systems that occur with high regularity in natural product structures. The preceding discussion has focused exclusively on the factors that influence trans vs. cis ring fusion diastereoselection. One problem that still remains to be solved, however, concerns the development of methodology for performing intramolecular Diels-Alder reactions enantioselectively.

Four transition states are potentially accessible in the cyclization of a triene containing an (E)-diene and a short connecting chain. These four possibilities are depicted for an (E,E,E)-undeca-2,8,10-triene in Scheme 11. When R_c=Me, the two faces of the dienophile

Scheme 11


CO2Rc
CH3
62
63
T1
T2
61
C1
C2
64
65
Rc = any group containing a chiral center

are enantiotopic and consequently transition state pairs T_1-T_2 and C_1-C_2 are enantiomeric; hence two racemic cycloadducts will be produced in such reactions. When, however, a chiral center is located within the triene substrate (e.g., Rc in 61), transition states T_1-T_2 and C_1-C_2 are no longer enantiomeric, but rather are diastereomeric and four products can be produced. The placement of Rc at the acyl function is purely arbitrary: the four possible reaction transition states are always mutually diastereomeric whenever a chiral center is (a) present within the dienophilic activating group (either as a chiral auxiliary or chiral Lewis acid), (b) located on the chain linking the the diene and dienophile, or (c) contained within one of the substituents attached to the diene.

Relatively little work has been published on the use of chiral auxiliaries for accomplishing intramolecular Diels-Alder reactions enantioselectively. A considerable body of literature, however, has accumulated in the area of asymmetric bimolecular Diels-Alder reactions.[18] We begin, therefore, by briefly reviewing those systems (chiral dienophiles, chiral dienes, and chiral Lewis acids) that have been successfully applied in the bimolecular reaction.

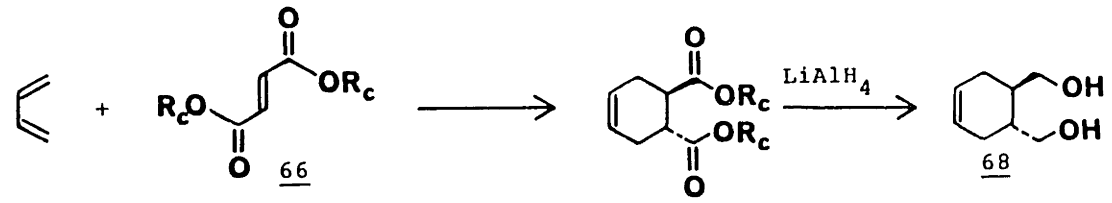
A. Chiral Dienophiles

One of the earliest examples of the use of a chiral dienophile in a Diels-Alder reaction was reported by Walborsky in 1963.[54] He observed that low diastereoselection occurred in the thermal reaction of 1,3-

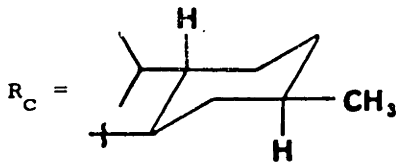
54. Walborsky, H.M.; Barash, L.; Davis, T.C. Tetrahedron 1963, 19, 2333.

butadiene with bis((-)-menthyl)fumarate, but found that addition of a Lewis acid catalyst greatly improved the diastereomeric excess[55] (Scheme 12). This high diastereodifferentiation is due presumably to the

Scheme 12



Conditions	Yield	%d.e. of 67
180°C	30%	3%
65°C	72%	1%
25°C, $TiCl_4$	80%	78%

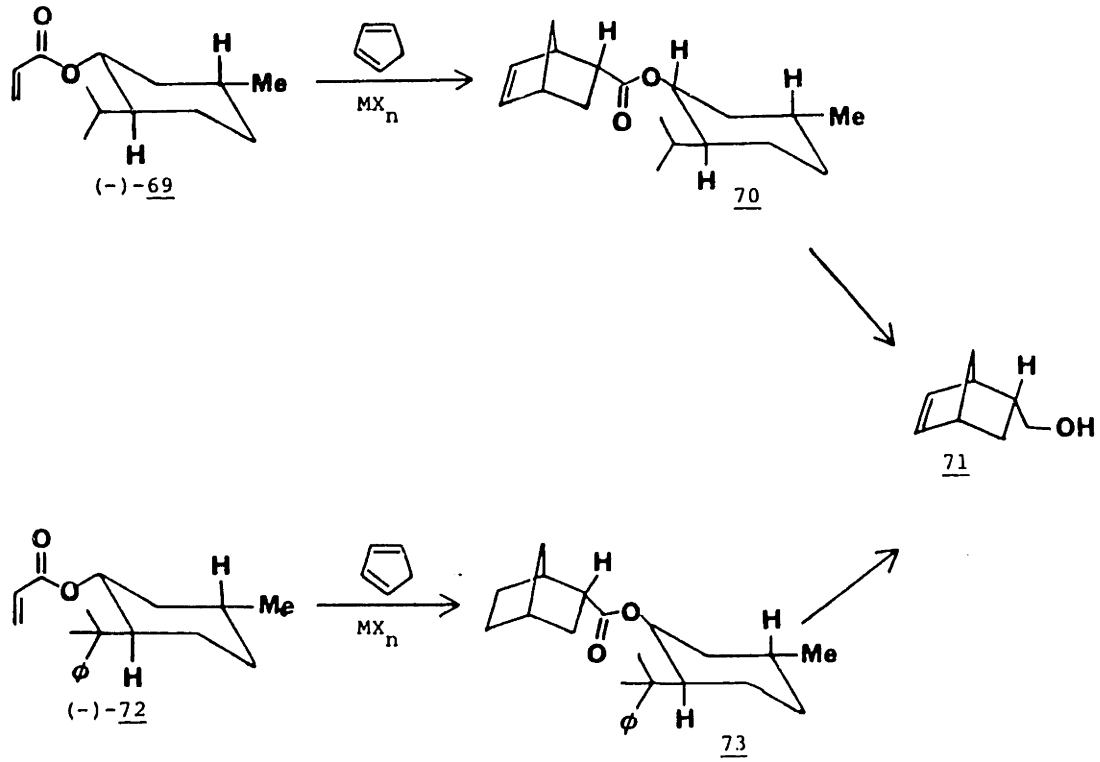


cooperative effects of two chiral groups, (-)-menthyl esters, in the dienophile. In contrast, when only one menthyl auxiliary is employed, as in the cyclization of (-)-menthyl acrylate and cyclopentadiene, the

55. For a reaction that generates a mixture of diastereomers A and B, the diastereomeric excess (d.e.) is defined as the difference between the percentage of the two isomers in the mixture; that is, d.e. = %A - %B. This definition is exactly analogous to the definition of enantiomeric excess (e.e.).

level of diastereoselection is considerably lower (Scheme 13, entries 1-2).[56]

Scheme 13



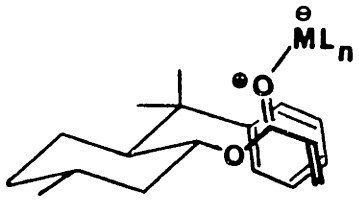
Entry	Acrylate	MX_n	Temp (°C)	Yield	endo/exo	%e.e.[a]
1	(-)-69	$SnCl_4$(1.0eq)	0°C	--	--	51
2	(-)-69	$TiCl_4$(1.5eq)	-20°C	65%	92:8	62
3	(-)-72	$SnCl_4$(1.5eq)	0°C	95%	84:16	89
4	(-)-72	$TiCl_4$(1.5eq)	-20°C	83%	89:11	90

a The enantiomeric excess of 71.

56. Oppolzer, W.; Kurth, M.; Reichlin, D.; Moffat, F. Tetrahedron Lett. 1981, 22, 2545.

The first highly enantioselective and synthetically useful Diels-Alder chiral auxiliary was introduced in 1975 by Corey and Ensley.[57] As indicated in entries 3 and 4 of Scheme 13, acrylate esters of (-)-phenylmenthol, prepared by a three step procedure from (-)-pulegone, react with cyclopentadiene in the presence of either $SnCl_4$ or $TiCl_4$ to give endo cycloadduct 73 with *ca.* 90% d.e..

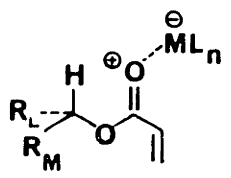
The high facial bias exerted by the (-)-8-phenylmenthyl group can be rationalized in terms of steric and aryl-acrylate π-stacking effects as



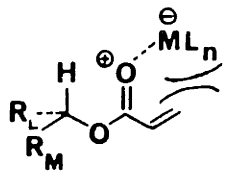
74

indicated in structure 74.[58] The Lewis acid presumably binds to the ester carbonyl in the position anti to the ethereal C-O bond, an arrangement observed in x-ray structure determination of crystalline Lewis acid-ester complexes. The enoate adopts the s-trans conformation, as in 75, and not the s-cis conformation (76) in order to avoid the

57. Corey, E.J.; Ensley, H.E. J. Am. Chem. Soc. 1975, 97, 6908.
58. (a) Oppolzer, W.; Kurth, M.; Reichlin, D.; Chapuis, C.; Mohnhaupt, M.; Moffat, F. Helv. Chim. Acta 1981, 64, 2802. (b) Stork, G.; Atwai, K.S. Tetrahedron Lett. 1983, 24, 3819.



75



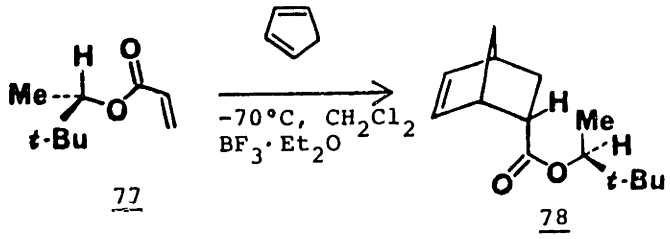
76

unfavorable steric interaction between the Lewis acid and the C=C unit in 76.[18] Then, assuming that aryl-acrylate π-stacking occurs as indicated in 74, which serves to lock the chiral auxiliary into the conformation indicated in 75, the diene will approach the dienophile from the side shielded by R_m. All of the data summarized in Scheme 13 are consistent with this analysis.

A comparably enantioselective chiral auxiliary was developed in 1966 by Sauer.[59] As shown in Scheme 14, acrylate ester (77) of (+)-3,3-dimethyl-2-butanol reacts with cyclopentadiene to give endo cycloadduct 78 with up to 88% d.e. (Scheme 14).[59,60] The stereochemical

59. Sauer, J.; Kredel, J. Tetrahedron Lett. 1966, 6359.
60. LeDrian, C.; Greene, A. J. Am. Chem. Soc. 1982, 104, 5473.

Scheme 14



77 78

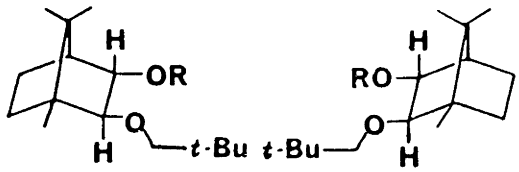
Entry	Yield	endo/exo	d.e.%[a]	Ref.
1	44%	> 95:5	88	59
2	75%	97:3	80-85	60

a Diastereomeric excess of endo product 78.

outcome of these reactions are fully consistent with predictions based on conformation 75 (R_m = Me, R_L = *t*Bu) being the reactive conformation. This auxiliary system has received only limited attention by synthetic chemists due to the fact that a resolution must be performed in order to obtain 3,3-dimethyl-2-butanol in enantiomerically pure form.

Increased levels of enatioselectivity have been achieved by using 79a and 80a as chiral auxiliaries. These compounds are readily prepared from either (+)- or (-)-camphor in roughly 60% overall yield.[61]

61. (a) Oppolzer, W.; Chapuis, C.; Dao, G.M.; Reichlin, D.; Godel, T. Tetrahedron Lett. 1982, 23, 4781. (b) Oppolzer, W.; Nozaki, H. In "Current Trends in Organic Synthesis"; Pergamon Press: London 1983; pp 131-149.

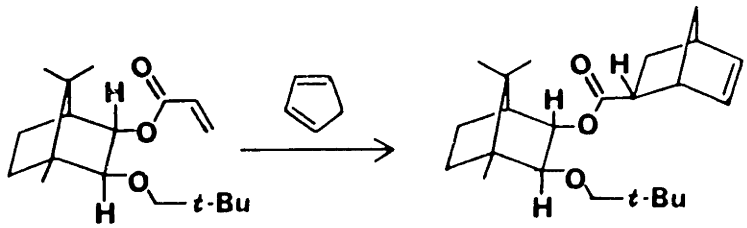


79a R = H 80a R = H

79b R = COCH=CH$_2$ 80b R = COCH=CH$_2$

Their derived acrylates 79b and 80b, when treated with cyclopentadiene and $TiCl_2(OiPr)_2$, give Diels-Alder adducts in 96-98% chemical yield with

Scheme 15

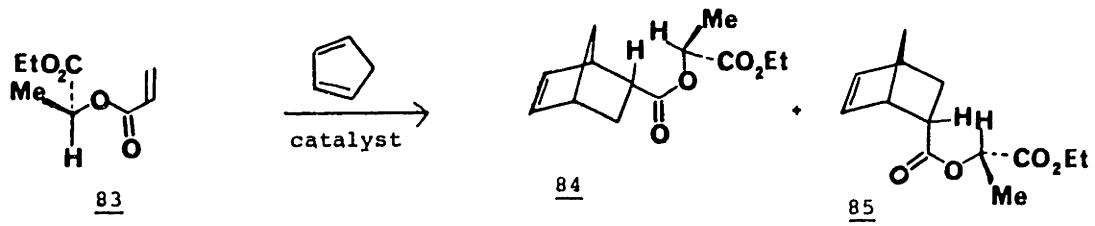


81 82

over 99% d.e. (Scheme 15).[61] These auxiliaries, like the (-)-8-phenylmenthyl system, have the attractive feature that they can be removed and recycled by reduction of the Diels-Alder adduct with lithium aluminum hydride.

Curiously enough there are cases reported in the literature where changing the Lewis acid catalyst actually reverses the facial selectivity of the Diels-Alder reaction. When the acrylate ester of ethyl lactate, 83, was treated with cyclopentadiene in the presence of titanium tetrachloride, diastereomer 84 was obtained in 86% d.e. (Scheme 16). However when the reaction was performed in the presence of boron trifluoride etherate the opposite diastereomer, 85, was formed preferentially (32% d.e.).[62a] These results become clear in light of

Scheme 16

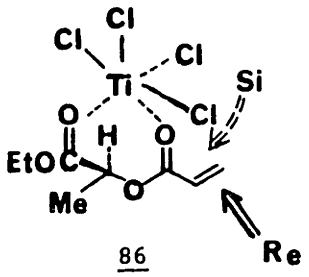


83 84 85

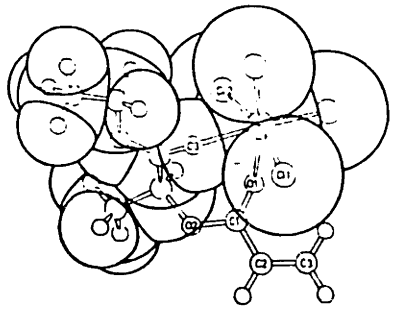
Catalyst	
$TiCl_4$	93:7
$BF_3 \cdot Et_2O$	34:66

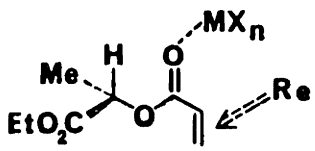
the crystal structure analysis of the Lewis acid-chiral dienophile complex, 86.[62b] In this structure, the enoate group adopts an s-cis

62. (a) Poll, T.; Helmchen, G.; Bauer, B. Tetrahedron Lett. 1984, 25, 2191. (b) Helmchen, G.; Poll, T.; Metter, J.O. Angew. Chem., Int. Ed. Engl. 1985, 24, 112. (c) Helmchen, G.; Poll, T.; Sobczak, A.; Hartmann, H. Tetrahedron Lett. 1985, 26, 3095.

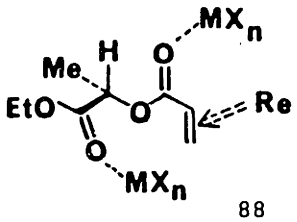


86





87



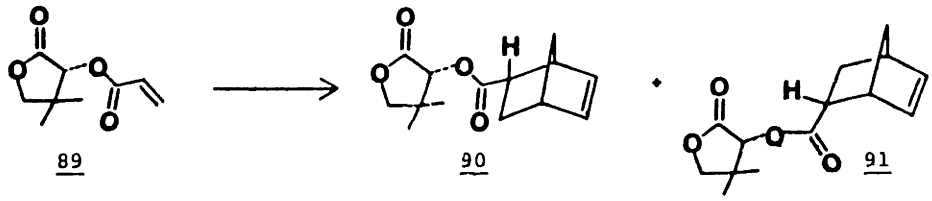
88

conformation, and not the more common s-trans arrangement, with titanium tetrachloride chelated between the two ester carbonyl groups. Assuming that 86 is also the reactive conformation when in solution, approach of the diene from the *Re* face is blocked by one of the chlorine atoms on titanium which accounts for the predominance of 84 when $TiCl_4$ is used. However with boron trifluoride etherate as the catalyst, the reactive species are believed to be 87 and 88 which lead predominantly to 85.

Under certain reaction conditions it appears that 87 and 88 may also be involved in the $TiCl_4$ catalyzed reaction of 83 and

cyclopentadiene. Helmchen found, for example, that as the number of equivalents of $TiCl_4$ was increased above 1.0, the diastereoselectivity decreased steeply.[62c] He also observed that as the temperature was increased from -80°C to 0°C, the diastereoselectivity decreased. This indicates that reactive species besides 86, possibly 87 and 88, compete more favorably in the presence of excess $TiCl_4$ and at higher temperatures. Chiral dienophile 89 affords 90 with high diastereoselection and, in contrast to 83, is insensitive to variations in reaction temperature as shown in Scheme 17.[62c]

Scheme 17



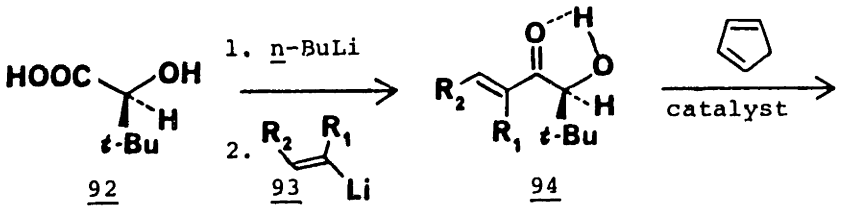
89 90 91

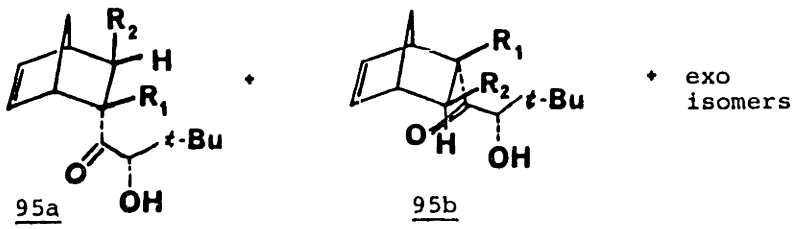
Temperature	
-80°C	97:3
-10°C, 1h	97:3
0°C	97:3

All of the previously discussed chiral dienophiles have been unsaturated ester derivatives of chiral alcohols. A structurally novel

chiral dienophile was recently developed by Masamune.[63,64] This system incorporates an α-hydroxy ketone (94) as the key stereodifferentiating element and is prepared as outlined in Scheme 18. The Diels-Alder reactions of 94 occur even at -20°C without Lewis acid catalysis to give

Scheme 18



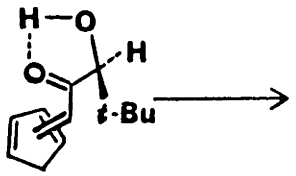


Entry	R^1	R^2	Catalyst	T(°C)	t(h)	Yield[a]	95a:95b	endo/exo
1	H	H	--	-20	24	90	100:1	89/11
2	H	H	$ZnCl_2$	-43	< 1	95	>100:1	94/6
3	H	Me	--	23	72	84	75:1	83/17
4	H	Me	$ZnCl_2$	-20	16	90	>100:1	94/6
5	Me	H	$ZnCl_2$	0	24	100	12:1	--

a Combined yield of endo and exo adducts.

63. Masamune, S.; Choy, W.; Reed, L.A. III J. Org. Chem. 1983, 48, 1137.
64. Masamune, S.; Reed. L.A. III; Davis, J.T.; Choy, W. J. Org. Chem. 1983, 48, 4441.

endo cycloadduct 95 in 99% d.e.. This high level of facial selectivity is a result of the strong intramolecular hydrogen bonding that effectively locks the dienophile in a rigid conformation. The enone undoubtedly adopts an s-cis conformation, and the bulky *tert*-butyl group then directs the diene to the opposite (less hindered) face of the

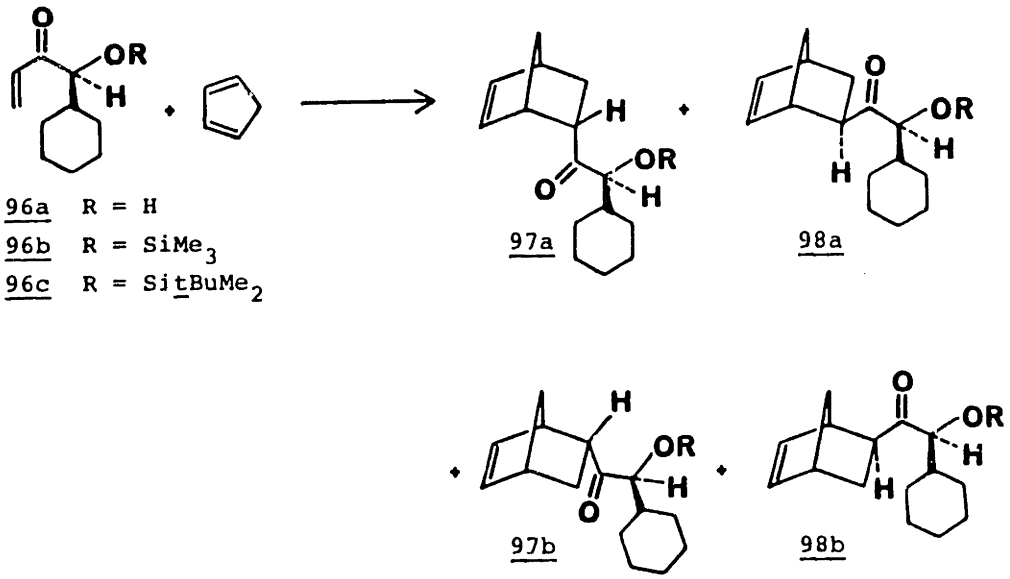


95a

enone. By comparing entries 1 and 2 or entries 3 and 4 in Scheme 18, it is clear that the addition of zinc chloride increases not only the selectivity but also the reaction rate.

Masamune has also investigated the asymmetric Diels-Alder reaction of cyclopentadiene and chiral dienophile 96 as outlined in Scheme 19.[63] Examination of the results summarized in the table reveals some interesting features. First, the silylated dienophiles, 96b and 96c, are less reactive than α-hydroxyketone, 96a, and are also less endo selective. Second, the diastereofacial selectivities (97a:97b and 98a:98b) are insignificant when the silylated dienophiles are used. In contrast, the dienophile 96a, gives reasonable endo/exo ratios (6/1 to 9/1) and very high diastereoselectivities (86-93% d.e.) for the endo

Scheme 19



96a R = H
96b R = $SiMe_3$
96c R = $SitBuMe_2$

97a 98a

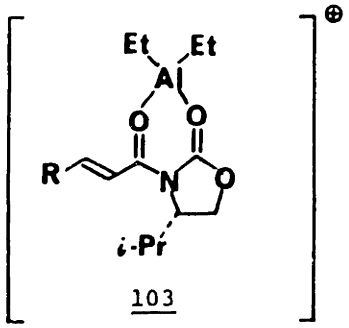
97b 98b

Dienophile	Conditions (°C, h)	(97a+97b)/(98a+98b)	97a:97b	98a:98b
96a	23°C, 2 h	8/1	13:1	1:8
96a	-20°C, 18 h	9/1	20:1	1:6
96a	-55°C, 170 h[a]	6/1	28:1	1:7
96b	23°C, 12 h	3/1	40:60	1:1
96b	-20°C, 210 h[b]	3/1	36:64	1:1
96c	23°C, 18 h	3/1	60:40	40:60
96c	-20°C, 190 h	78/22	60:40	36:64

a 80% conversion.
b 94% conversion.

adduct. Although dienophile 96a is less selective than the bulkier system 94 (Scheme 18), it is likely that the selectivity of 96a can be improved by using Lewis acid catalysis.

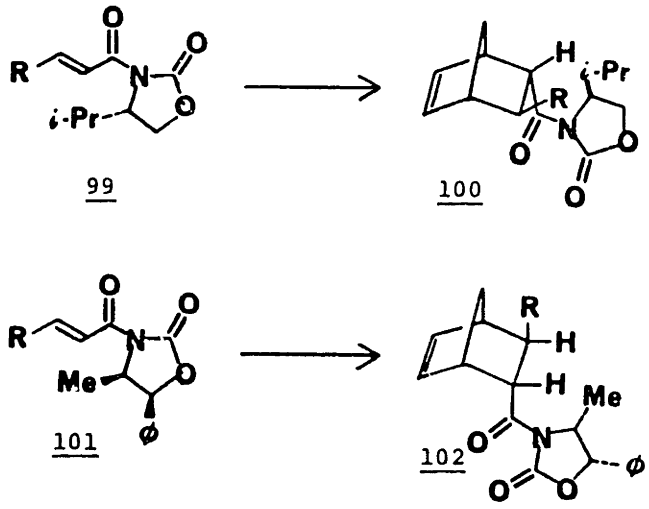
Several chiral oxazolidine auxiliaries developed by Evans also exhibit exceptionally high diastereoselection in Diels-Alder reactions (Scheme 20).[65] The reactions of N-acyloxazolidones 99 and 101 with cyclopentadiene in the presence of 1.4 equivalents of diethylaluminum chloride give 80% yields of endo cycloadducts 100 and 102 with 86-96% diastercofacial differentiation. The cycloadducts can be recrystallized to give pure product (>98% d.e.) in good yield. The sense of asymmetric induction can be rationalized in terms of the rigid Lewis acid complex 103, with reaction occurring on the face away from the bulky substituents on the chiral oxazolidine system.



103

65. (a) Evans, D.A.; Chapman, K.T.; Bisaha, J. J. Am. Chem. Soc. 1984, 106, 4261. (b) Evans, D.A.; Chapman, K.T.; Bisaha, J. Tetrahedron Lett. 1984, 25, 4071.

Scheme 20

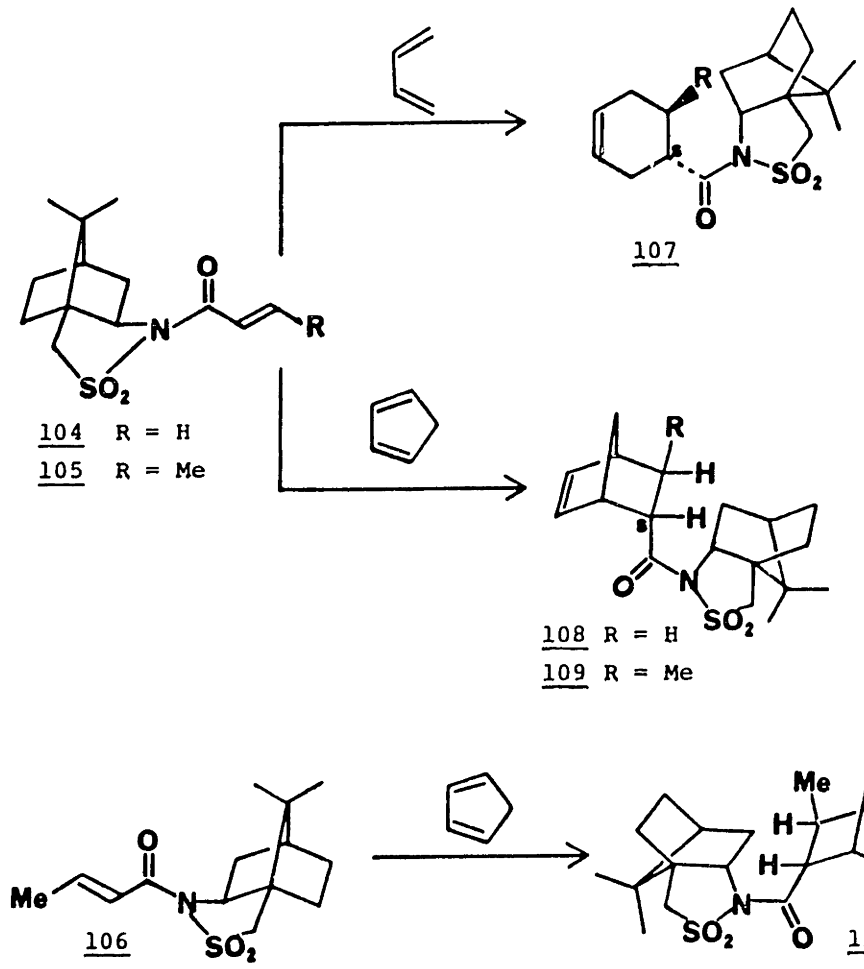


Dienophile	R	Yield %	endo/exo	d.e.[a]	d.e.[b]
99	H	81	> 100:1	86	> 98
99	Me	82	48:1	90	> 98
101	H	82	100:1	90	> 98
101	Me	88	60:1	96	> 98

a Diastereomeric excess of endo cycloadduct purified by chromatography.
b Diastereomeric excess of endo cycloadduct after recrystallization.

N-acryloylsultams, 104-106, have proven to be extremely diastereoselective in Diels-Alder reactions with cyclopentadiene and

Scheme 21

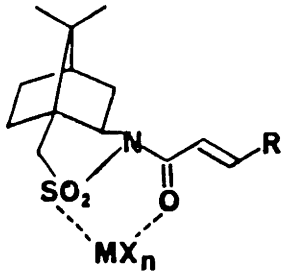


Dienophile	Product	Conditions[a]	Yield %[b]	endo/exo	d.e.[c]	d.e.[d]
104	107	A	81	--	97	99
104	108	B	84	99.5:0.5	95	99
105	109	C	83	99:1	93	99
105	109	A	--	96:4	98	--
106	110	A	--	98:2	94	--

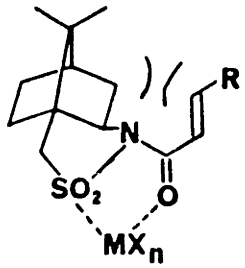
a Reaction conditions. Method A: $EtAlCl_2$ (1.5 equiv.), CH_2Cl_2, -78°C, 18 h; Method B: $EtAlCl_2$ (1.5 equiv.), EtCl, -130°C, 6 h; Method C: $TiCl_4$ (0.5 equiv.), CH_2Cl_2, -78°C, 1 h.
b Yield of recrystallized adducts relative to dienophile.
c Diastereomeric excess of crude product.
d Diastereomeric excess of recrystallized adducts, 100% endo.

1,3-butadiene (Scheme 21).[66] These dienophiles can be synthesized from (+)- or (-)-camphor-10-sulfonyl chloride in four steps (65% overall yield). N-acryloylsultams 104 and 105, upon treatment with 1,3-butadiene or cyclopentadiene in the presence of ethylaluminum dichloride or titanium tetrachloride afford adducts 107-109 in 93-98% d.e.. The opposite facial selectivity was obtained by using the enantiomeric N-acryloylsultam 106, prepared from (-)-camphor.

66. Oppolzer, W.; Chapuis, C.; Bernardinelli, G. Helv. Chim. Acta 1984, 67, 1397.



111

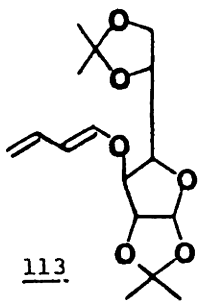


112

The results of these reactions have been rationalized in terms of structure 111 in which the Lewis acid is complexed by the SO_2 and C=O functionalities. It is assumed that the acrylic unit adopts an s-cis conformation, as in 111, to avoid the steric interactions indicated in 112. If so, approach of the diene to the top face of 111 is blocked by the methyl group on the bridge, and the Diels-Alder reaction then occurs preferentially from the endo face.

B. Chiral Dienes

Considerably less research has been devoted to the synthesis of dienes that incorporate chiral auxiliaries. 1,3-Dienol ethers derived



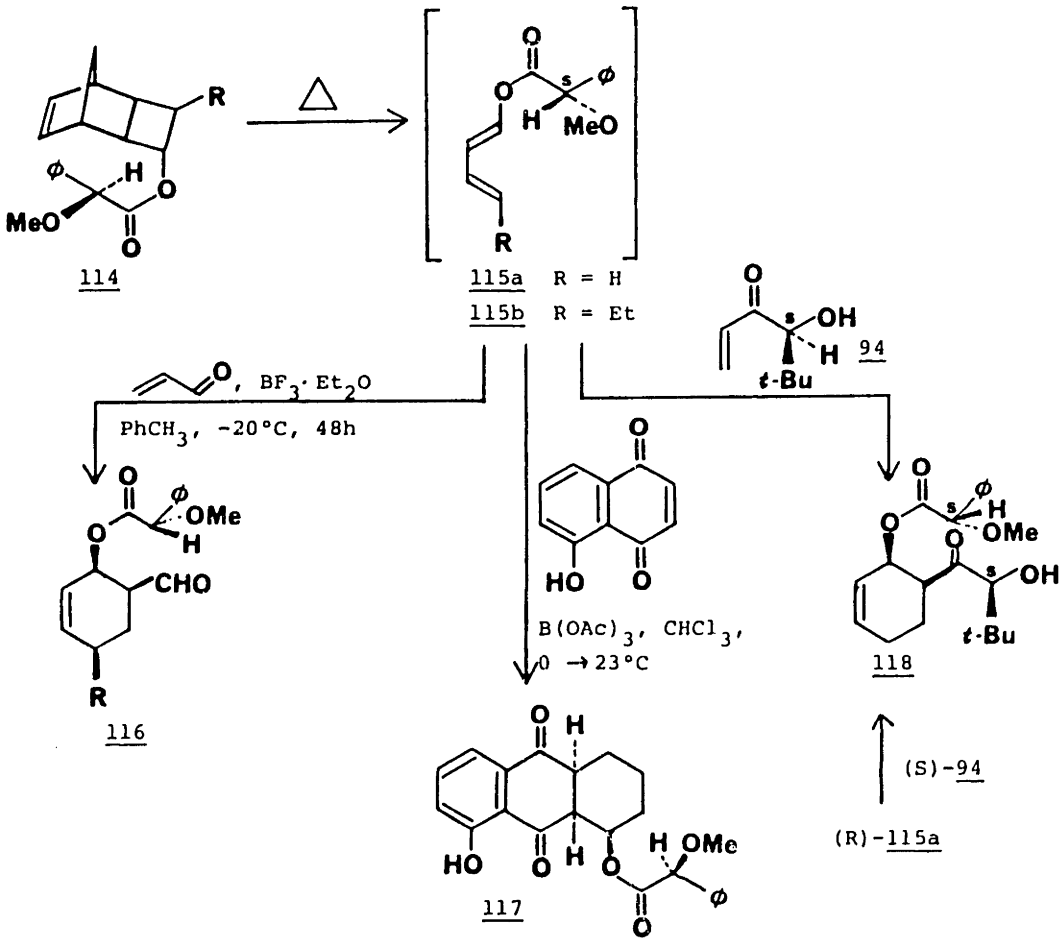
113

from sugars, such as 113, have been investigated but have proven to give poor endo/exo ratios (2:1).[67] Diene 115 which incorporates (*S*)-O-methylmandelic acid as the chiral auxiliary has been studied with several dienophiles (Scheme 22).[68] Moderate facial selectivity (60-64% d.e) was realized in the reaction of 115a,b with acrolein catalyzed by boron trifluoride etherate (Scheme 22, entry 1). However, almost total asymmetric induction was obtained when 115a was treated with juglone and $B(OAc)_3$ (Scheme 22, entry 2). It has been proposed that the asymmetry in this system arises from π-stacking of the mandelate phenyl group and the diene, which thus directs the dienophile to the opposite face of the diene.

It is interesting to note that the directing ability of this mandelate substituent is substantially less than that of the Masamune chiral auxiliary. This is clearly shown by analysis of the reactions of

67. David, S.; Eustache, J.; Lubineau, A. J. Chem. Soc., Perkin Trans. I 1979, 1795.
68. Trost, B.M.; O'Krongly, D.; Belletire, J. J. Am. Chem. Soc. 1980, 102, 7595.

Scheme 22



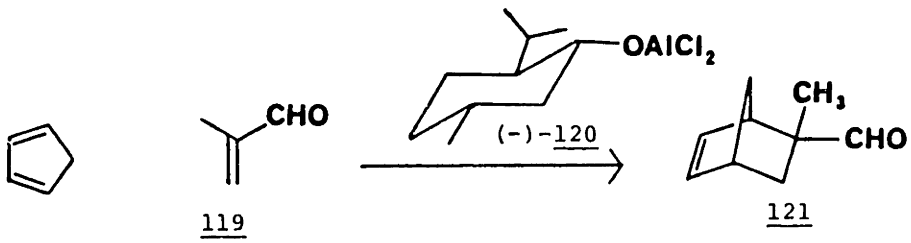
Entry	dienophile	diene	product	yield	% d.e.
1	acrolein	(*S*)-115	116	98	60-64
2	juglone	(*S*)-115	117	98	> 97
3	(*S*)-94	(*S*)-115a	118	70	99
4	(*S*)-94	(*R*)-115a	118	73	94

both enantiomers of 115 with 94. Thus in the "matched" case (reaction of (*S*)-115a and (*S*)-94), 118 was obtained in 99% d.e., whereas the "mismatched" combination ((*R*)-115a and (*S*)-94) gives 118 in 94% d.e.[64]. This an interesting illustration of the principle of "double asymmetric synthesis".[69]

C. Chiral Catalysts

A third option for effecting high diastereo- or enantiofacial selection in Diels-Alder reactions is to employ a chiral catalyst. Research in this area has so far revealed only two examples where asymmetric induction was even moderate. The best case (Scheme 23)

Scheme 23



119 121

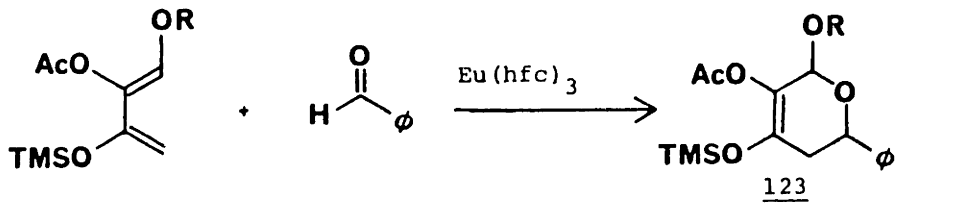
involves the reaction of cyclopentadiene and methacrolein catalyzed by (-)-menthyloxyaluminum dichloride which gives 121 in 60% e.e..[70]

69. Masamune, S.; Choy, W.; Petersen, J.S.; Sita, L.R. Angew. Chem., Int. Ed. Engl. 1985, 24, 1.
70. Hashimoto, S.; Komeshima, N.; Koga, K. J. Chem. Soc., Chem. Commun. 1979, 437.

Attempts to extend this result to other dienes, dienophiles, and use of related chiral catalysts in inter- or intramolecular reactions have been considerably less effective.[18,33]

A second interesting case involving the use of chiral Lewis acid catalysts has been reported by Danishefsky. When the chiral europium catalyst $Eu(hfc)_3$ was used in the hetero Diels-Alder reaction between siloxydiene 122a and benzaldehyde, the cycloadduct 123a was obtained in 42% e.e.. However when $Eu(hfc)_3$ was used in the cycloaddition of chiral diene 122b and benzaldehyde, cycloadduct 123b was produced with 86% e.e.

Scheme 24



122a R = tBu
122b R = (3R)-menthyl

123

42% e.e.
86% e.e.

(Scheme 24).[71] This result suggests that an additive (synergistic) effect may be operative here.

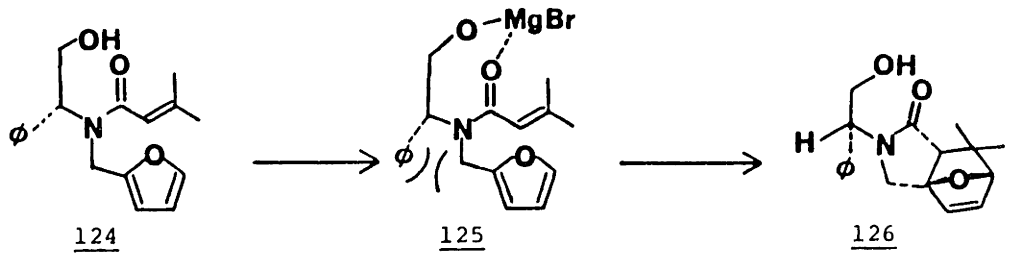
71. Danishefsky, S.; Bednarski, M. J. Am. Chem. Soc. 1983, 105, 3716, 6968.

Asymmetric Intramolecular Diels-Alder Reactions

Up to this point the discussion has focused on the use of chiral auxiliaries in bimolecular Diels-Alder reactions. The use of removable chiral auxiliaries in intramolecular Diels-Alder reactions, however, is still in an early stage of development. Nevertheless, several studies have appeared in which removable auxiliaries have been attached either to the dienophilic double bond or placed within the chain linking diene and dienophile.

The first example illustrating the use of a removable chiral auxiliary in intramolecular Diels-Alder reactions was reported by Mukaiyama and is outlined in Scheme 25.[72] When the cyclization was

Scheme 25



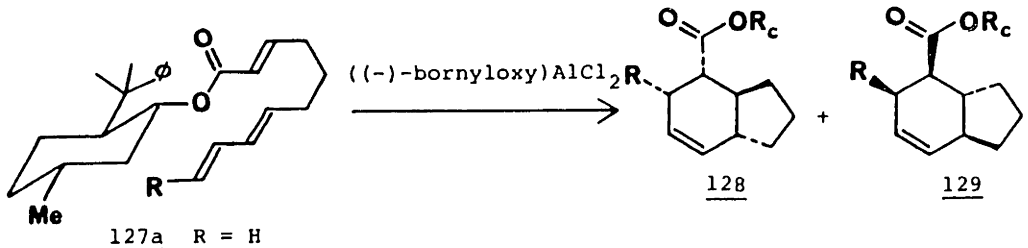
124 125 126

72. (a) Takebayashi, T.; Iwasawa, N.; Mukaiyama, T. Bull. Chem. Soc. Jpn. 1983, 56, 1107. (b) Mukaiyama, T.; Iwasawa, N. Chem. Lett. 1981, 29.

performed on the nonchelated triene 124, the reaction was slow and showed no facial selectivity. However when 124 is first converted to the corresponding magnesium alkoxide, 125, in which the metal ion is presumably chelated by the amide carbonyl, the rate of cyclization is accelerated and facial selectivity is improved (76% d.e.).

Shortly after the Mukaiyama study was published, Roush and coworkers reported several examples of intramolecular Diels-Alder reactions incorporating chiral dienophilic units.[33] This study focused on trienes 127a and 127b which are derivatives of 8-phenylmenthol. Best

Scheme 26



127a R = H
127b R = iPr

128 129

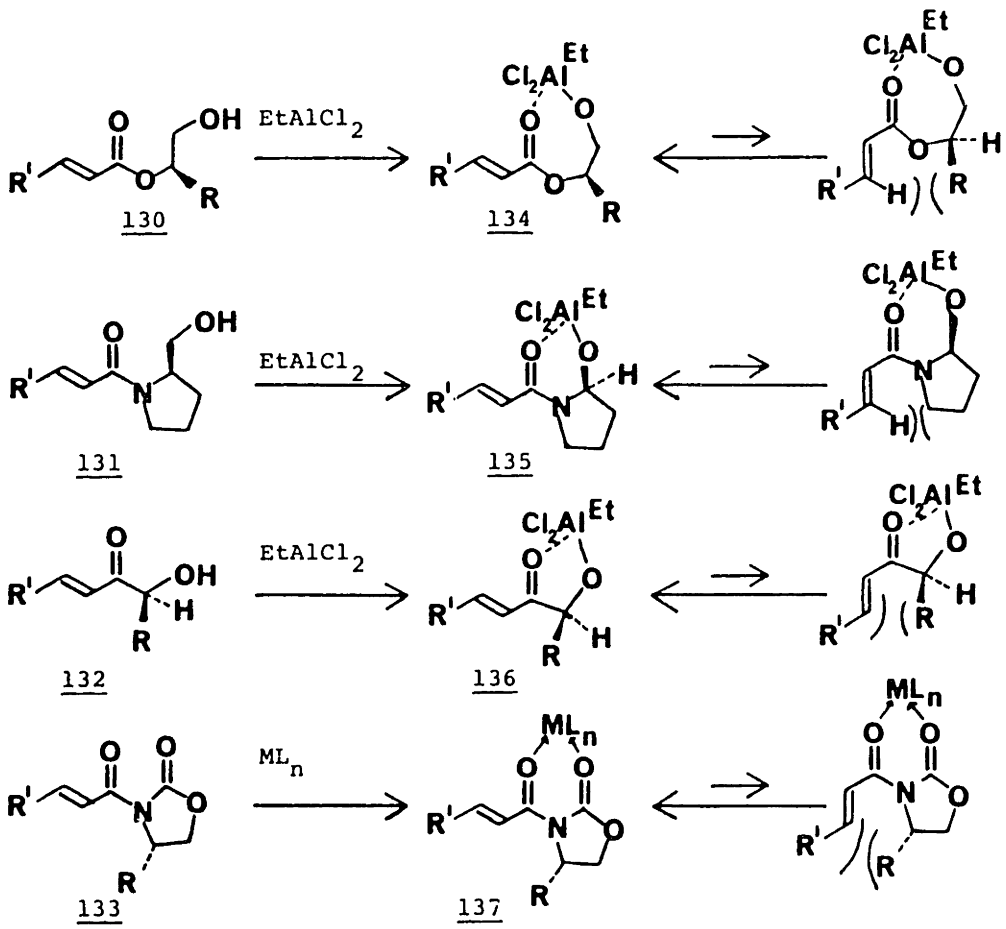
Triene	Conditions (°C, h)	Yield (%)	128:129
127a	8°C, 33 h	72	86:14
127a	23°C, 36 h	77-82	82:18
127b	23°C, 92 h	61	67:33
127b	23°C, 92 h*	75	68:32

* (-)-(menthyloxy)$AlCl_2$ was used as the catalyst.

results in terms of yield and diastereoselectivity were realized when [(-)-bornyloxy]aluminum dichloride was used as the catalyst, giving cycloadducts in 34-72% d.e. (Scheme 26).

These results are clearly less impressive than those obtained using this auxiliary system in bimolecular Diels-Alder reactions (refer to Scheme 13). This difference in behavior was attributed to the higher temperatures required for the intramolecular reactions, which undoubtedly increases the probability that cyclization can occur from reactive conformations other than 74. This prompted Roush to initiate studies on the design of new chiral auxiliary systems that would be more rigid, and hence would have fewer degrees of freedom available during the Diels-Alder reaction. Systems selected for study included 130-133 (for a discussion, see the Ph.D. thesis of H.R. Gillis cited in reference 52); dienophiles 132 and 133, of course, are the systems ultimately developed by Masamune and Evans, respectively. Each was expected to react with a Lewis acid to generate an internally coordinated complex (134-137) which "locks" the dienophile into one

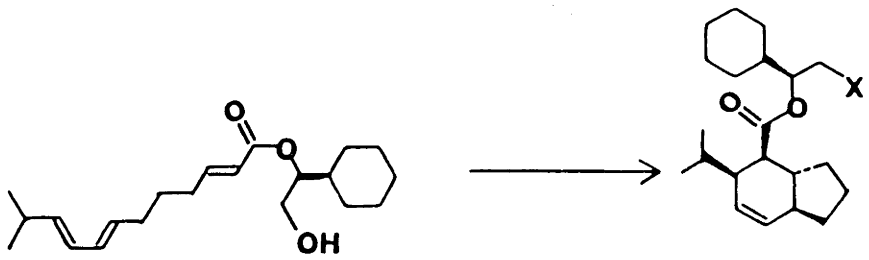
Scheme 27



conformation. It was also expected that each dienophile would adopt the s-cis conformation so as to avoid the indicated non-bonded interactions in the s-trans arrangements.

Initial studies performed with trienes 130 and 131 are summarized

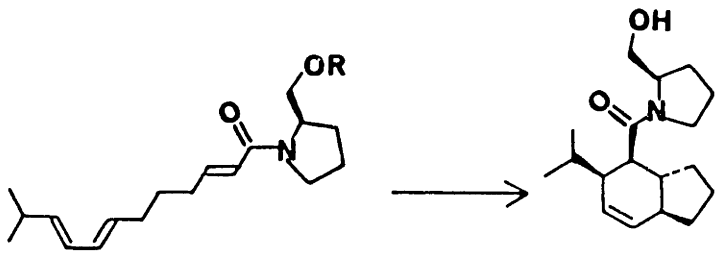
Scheme 28



130 138

	X = OH	X = Cl
$MeNbCl_4$, 15 h, 23°C	22% (67:33)*	17%
$EtAlCl_2$, 1 h, 23°C	32% (60:40)*	--
$MeTiCl_3$, 64 h, 23°C	--	25% (73:27)*

* Diastereomeric ratios are noted in parentheses next to product yields.



131a R = Me_3Si
131b R = TBDMS

139

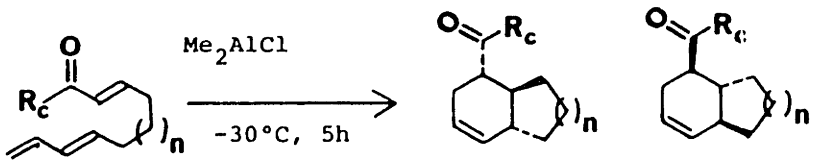
Triene	Conditions	Yield
131a	$TiCl_4$ (0.95 eq), 23°C, CH_2Cl_2, 20 h	5% (5:1)[a]
131b	$TiCl_4$ (1.0 eq), 23°C, CH_2Cl_2, 72 h	10% (5:1)[a]

a A 5:1 mixture of *trans*-fused diastereomers was obtained (66% d.e.).

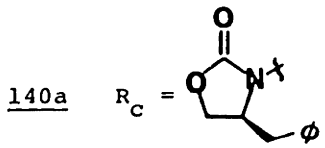
in Scheme 28.[52,73] The results reveal that in these intramolecular cases the yields are fairly low and the diastereoselectivities are moderate.

Very recently, Evans has found that good diastereofacial selectivity can be achieved by using chiral oxazolidines as depicted in

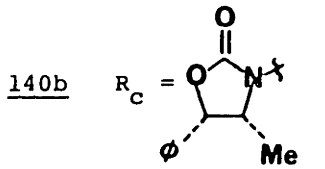
Scheme 29



141 142



140a



140b

Triene	n	Yield[a]	141:142[b]
140a	1	73	95:5
140a	2[c]	88	97:3
140b	1	70	15:85
140b	2[c]	70	6:94

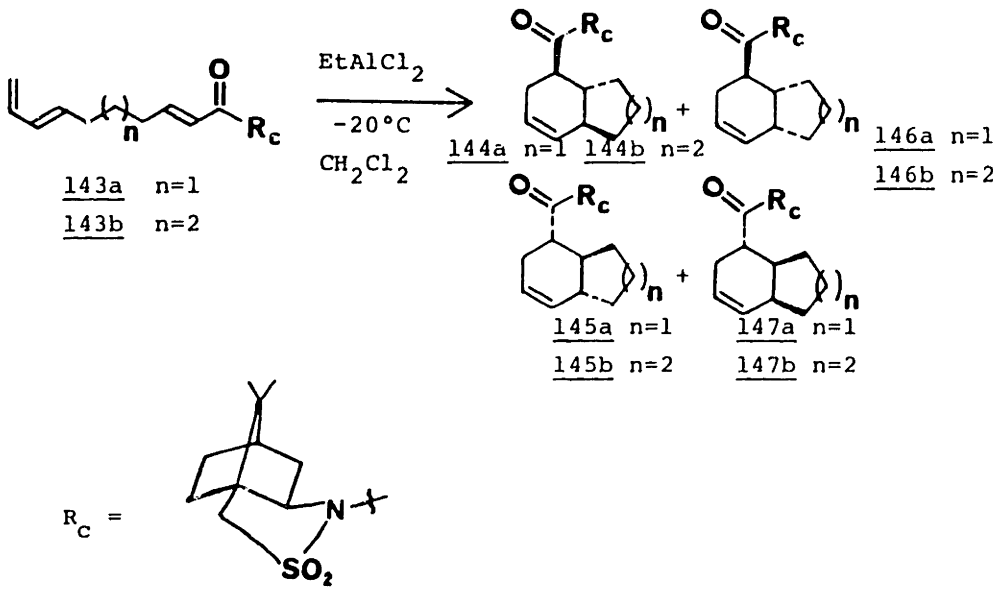
a Yield of > 99% diastereomerically pure major cycloadduct.
b Ratio of products prior to purification of the major isomer.
c The endo to exo ratio was 30:1.

73. Roush, W.R.; Gillis, H.R.; Essenfeld, A. J. Org. Chem. 1984, 49, 4674.

Scheme 29.[65b] After chromatography, the pure (>99% d.e.) major cycloadduct in each case was obtained in 70-88% yield.

Finally, Oppolzer has also recently reported a study of asymmetric intramolecular Diels-Alder reactions employing his chiral auxiliary

Scheme 30



Triene	Ratio[a] of 144:145:(146+147)	Yield of cryst. 144[b]
143a	> 97.4 : 2.5 : < 0.1	75%
143b	94.0 : 2.6 : 3.4	53%

a Ratio from crude adducts by GC analysis.
b Crystallized 144 was > 99% d.e..

(Scheme 30).[74] Triene 143a, when treated with 1.6 equivalents of ethylaluminum dichloride, afforded a mixture of 144a-147a in 82% yield. The endo:exo ratio was >200:1 (144a + 145a : 146a + 147a) and the diastereomeric excess of the endo adducts was 95%. Triene 143b, when treated with 1.8 equivalents of ethylaluminum dichloride, gave in a slower reaction adducts 144b-147b in 81% yield. The endo:exo ratio in this series was somewhat lower (28:1) and the diastereomeric excess of the endo adducts was 94.6%.

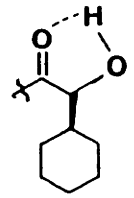
Since little work had been done in the area of chiral auxiliaries in intramolecular Diels-Alder reactions prior to 1983, we chose to investigate the efficiency of the Masamune auxiliary with several representative trienes. This work, which was begun in August 1983, is described in Chapter 2. At the time that we initiated this research, Evan's results on the irtramolecular Diels-Alder reaction of triene 140 and Oppolzer's work with triene 143 had not been published.

74. Oppolzer, W.; Dupuis, D. Tetrahedron Lett. 1985, 26, 5437.

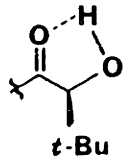
Chapter 2

Introduction

This chapter describes our study of asymmetric intramolecular Diels-Alder reactions employing α-hydroxyketone 1 as the chiral



1



2

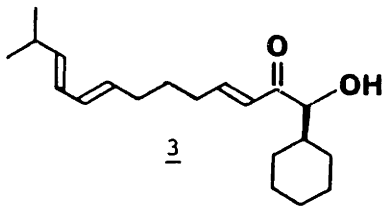
auxiliary. This system, and not the bulkier *t*-butyl substituted auxiliary 2, was selected on the basis of the following considerations. First, the optimum auxiliary system must be easily synthesized and attached to the substrate. Second, the cycloaddition reaction should proceed in high chemical yield and with high facial stereodifferentiation. Third, the major cycloadduct (if complete stereoselection is not realized) should be easily purified to almost 100% d.e.. Fourth, the chiral auxiliary should be readily available in both enantiomeric forms, preferably without recourse to chemical resolution. Lastly, if the auxiliary or a synthetic precursor is not commercially available in optically pure form, one should be able to remove it nondestructively from the adduct without loss of optical purity. Although Masamune has shown that 2 is a more effective auxiliary than 1 in bimolecular Diels-Alder reactions,[1] we opted to use

1. Masamune, S.; Choy, W.; Reed, L.A. III J. Org. Chem. 1983, 48, 1137.

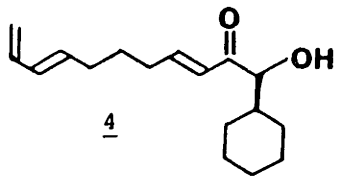
1 since both enantiomers of mandelic acid (precursor to 1) are commercially available whereas optically active precursors to 2 are not.

Synthesis of Trienes 3-5

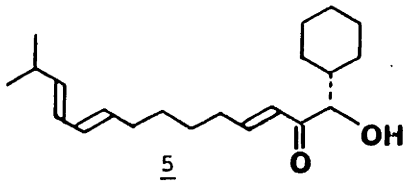
This study focused on trienes 3-5 as model precursors of the perhydroindene and decalin ring systems. These systems are cogeners of triene esters that have previously been studied in these laboratories.[2]



3



4



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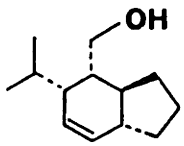
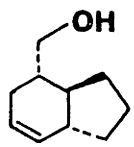


(+)-6

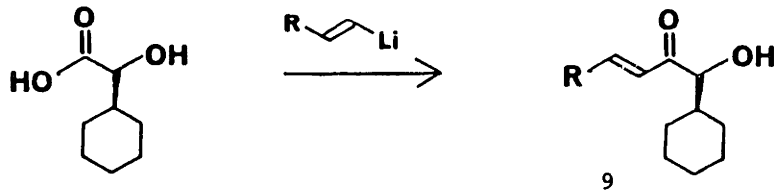


(+)-7

2. (a) Roush, W.R.; Gillis, H.R.; Ko, A.I. J. Am. Chem. Soc. 1982, 104, 2269. (b) Roush, W.R.; Gillis, H.R. J. Org. Chem. 1982, 47, 4825.

It was desirable to study 3 and 4, in particular, because the absolute configurations of (+)-6 and (+)-7 had already been determined.[2a] These compounds would serve as reference points for assessing the diastereoselectivity (and hence enantioselectivity) of the cyclizations of 3 and 4.

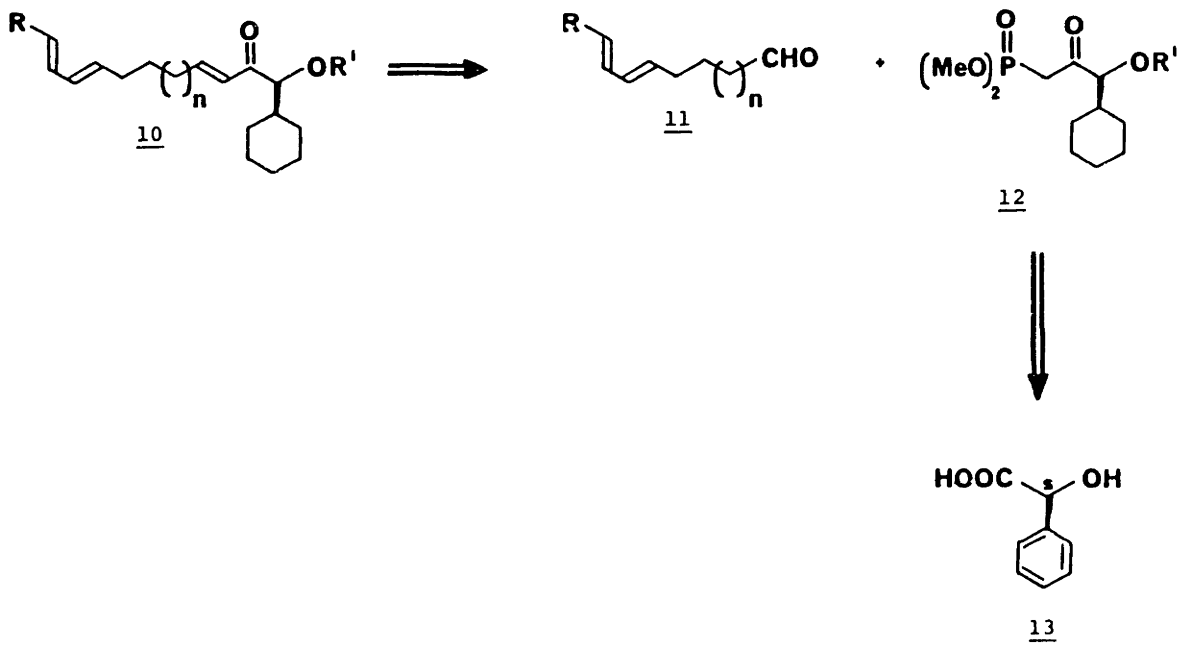
The first problem addressed in this research was the development of an efficient method for synthesis of 3-5. Masamune and coworkers had previously prepared dienophiles incorporating unit 9 by treatment of



8 9

hexahydromandelic acid with 3.5 equivalents of the appropriate vinyllithium reagent. We regarded this method unsuitable for use with valuable trienic systems and therefore focused instead on the more convergent sequence summarized in Scheme 1. According to this plan, the chiral auxiliary, deriving ultimately from commercially available (S)-mandelic acid, would be coupled to diene aldehydes 11 by using a Horner-Wadsworth-Emmons reaction.

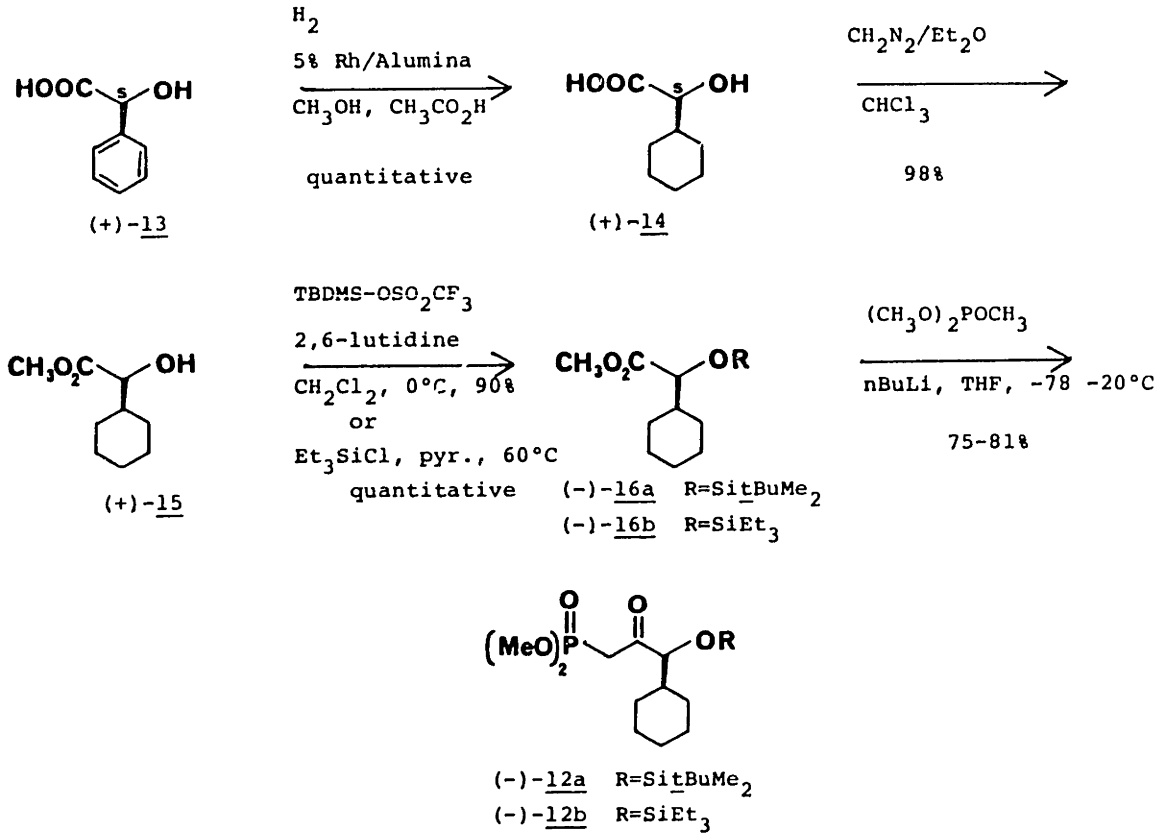
Scheme 1



β-Ketophosphonate reagents 12a and 12b were synthesized as outlined in Scheme 2. Hydrogenation of (S)-mandelic acid over 5% Rh on alumina at 45 psi in methanol with a trace of acetic acid afforded hexahydromandelic acid, 14, in quantitative yield.[3] Treatment of 14

3. (a) Masamune, S.; Aldrichimica Acta 1982, 15, 62. (b) Masamune, S.; Choy, W.; Kerdesky, F.A.J.; Imperiali, B. J. Am. Chem. Soc. 1981, 103, 1566. (c) Hirano, T. Makromol. Chem. 1976, 3227.

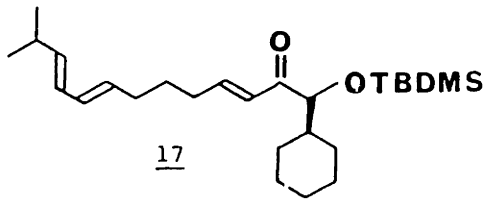
Scheme 2



with ethereal diazomethane[4] then gave α-hydroxyester (+)-15 ($[\alpha]_D$ +28°, c = 1.45, $CHCl_3$) in 98% yield. At this point a suitable protecting group for the alcohol had to be found. We initially selected the *t*-butyldimethylsilyl ether protecting group which was introduced by using

4. Fales, H.M.; Jaouni, T.M.; Babashak, J.F. Analytical Chemistry 1973, 45, 2302.

t-butyldimethylsilyl triflate and 2,6-lutidine in 90% yield.[5] TBDMS ether (-)-16a ($[\alpha]_D$ -33°, c = 0.78, $CHCl_3$) was then treated with the lithium anion of dimethyl methylphosphonate which provided the desired β-ketophosphonate (-)-12a ($[\alpha]_D$ -15.5°, c = 0.56, $CHCl_3$) in 75-81% yield.[6] As it was subsequently discovered that the TBDMS group could not be removed from 17 without substantial destruction of the desired triene system, phosphonate (-)-16b containing the more acid labile



17

triethylsilyl protecting group was also prepared (see Scheme 2). Thus, sequential treatment of (+)-15 with triethylsilyl chloride in pyridine and then with $LiCH_2PO(OMe)_2$ gave (-)-12b ($[\alpha]_D$ -11.9°, c = 2.13, $CHCl_3$) in 75-81% overall yield.

An important question to answer at this stage was whether any racemization had occurred during the synthesis of (-)-12b. A chiral NMR shift study using Eu(tfc)$_3$, (tris[3-(trifluoromethylhydroxymethylene)-d-camphorato] europium (III)), was performed on racemic and optically active (-)-12b indicating that the optical purity of (-)-12b was at least 98% e.e. (only one enantiomer was detected). Table 1 summarizes

5. Treatment of (+)-15 with *t*-butyldimethylsilyl chloride and imidazole in DMF was ineffective.
6. Dauben, W.G.; Beasley, G.H.; Broadhurst, M.D.; Muller, B.; Peppard, D.J.; Pesnelle, P.; Suter, C. J. Am. Chem. Soc. 1975, 97, 4973.

the proton resonances that were used for this analysis; maximum separation of the two enantiomers occurred when one equivalent of the chiral shift reagent was used.

Table 1

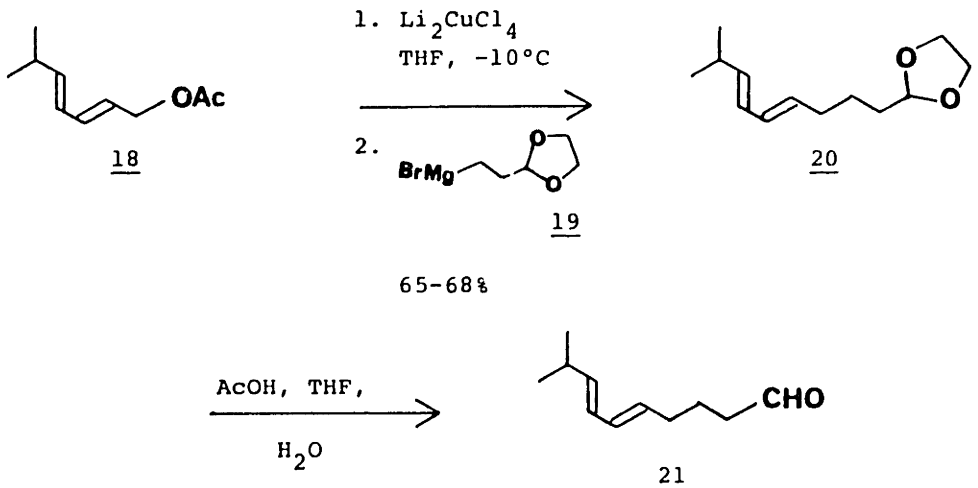
Diagnostic Resonances of 12b in the presence of 1.0 eq. of $Eu(tfc)_3$

^1H Assignment	Multiplicity	Racemic 12b	(-)-12b
$-OCH_3$	s	1.57, 1.68	1.57
$-CH_2P$	br d[a]	6.32, 6.45, 6.55, 6.75	6.45, 6.55

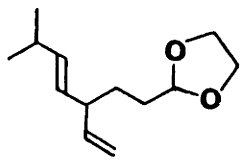
a These methylene protons each appeared as a broad doublet with J = 11 Hz.

With Horner-Emmons reagent (-)-12b in hand, we turned to the olefination reaction that would complete the synthesis of trienes 3-5. Aldehyde 21, used in the synthesis of 3, was synthesized from diene

Scheme 3



acetate 18[2a] as outlined in Scheme 3.[2a] A THF solution of Grignard reagent 19[7] was added slowly to a mixture of 18 and 0.04 equivalents of Li_2CuCl_4 in THF at -10°C. The mixture was stirred at 0°C for 7 h and then at room temperature overnight. After standard workup and column chromatography, acetal 20 was obtained in 65-68% yield. About 10% of



22

the regioisomeric coupling product 22 was also formed and was separated from 20 by chromatography. Aldehyde 21 was produced from 20 in 90-96% yield by hydrolysis with THF-H_2O-HOAc (2:2:1) at reflux.

Initial attempts to attach the chiral auxiliary to 21 were performed using the TBDMS-protected phophonate (-)-12a. We assumed that this transformation would be effected under normal Horner-Wadsworth-Emmons conditions,[8] i.e. by using a strong base like NaH in an aprotic solvent such as dimethoxyethane. Much to our surprise, however, numerous attempts to use these and related protocols proved fruitless

7. Buchi, G.; Wuest, H. J. Org. Chem. 1969, 34, 1122.
8. (a) Wadsworth, W.S.; Emmons, W.D. J. Am. Chem. Soc. 1961, 83, 1733. (b) Horner, L.; Hoffmann, H.; Wippel, H.G.; Klahre, G. Chem. Ber. 1959, 92, 2499. (c) Horner, L.; Hoffmann, H.; Wippel, H.G. Chem. Ber. 1958, 91, 61. (d) Wadsworth, W.S. Organic Reactions 1977, 25, 77.

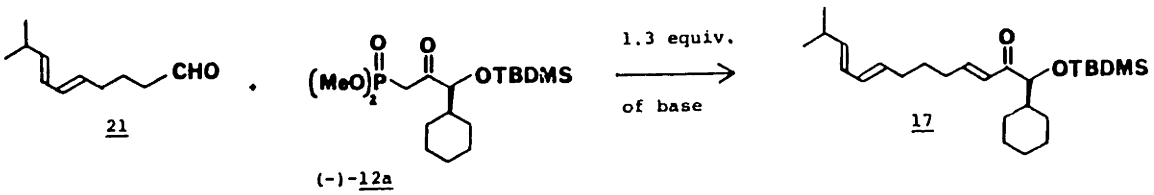


Table 2

Base Used	Conditions	Yield %
NaH	DME, 0-23°C, 23 h	0
NaH	DME, 0-reflux, 3 h	0
LDA	THF, -78-23°C, 24 h	0
*t*BuOK	DME, 0-23°C, 20 h	34
*t*BuOK	DME, 0-70°C, 20 h	37

(see Table 2). The only base that proved even marginally effective was potassium *t*-butoxide which gave 17 in 34-37% yield after chromatography. Similar results were obtained when tetradecanal, $CH_3(CH_2)_{12}CHO$, was used

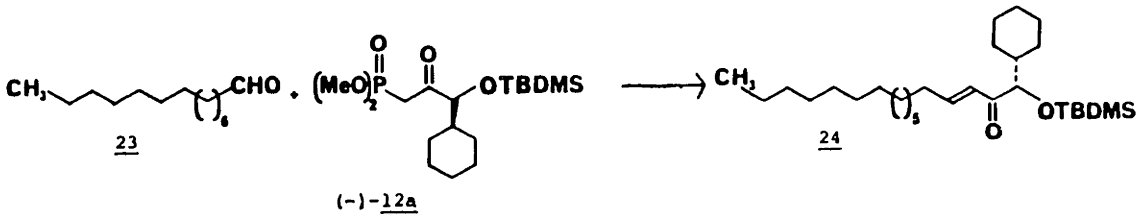


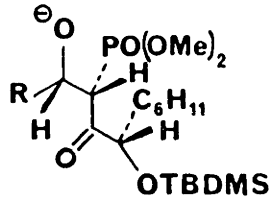
Table 3

Base Used	Conditions	Yield %
NaH	DME, 0-23°C, 23 h	0
NaH	DME, 0-reflux, 3 h	0
LDA	HMPT (3 eq.), THF, -78-23°C, 19 h	0
*t*BuOK	DME, 0-23°C, 7 h	38
*t*BuOK	DME, 0-70°C, 6 h	37

as the substrate (Table 3). Aldehydes 21 and 23 were completely consumed in all cases, presumably *via* self-condensation reactions leading to intractable material. Phosphonate (-)-12a, however, was recovered in nearly quantitative yield and, interestingly, without measurable racemization ($[\alpha]_D$ -16.1°, c = 0.94, $CHCl_3$).

We concluded from these results that the bulkiness of the (-)-12a and the base-sensitivity of aldehydes 21 and 23 had played some part in the failure of these reactions. Evidently, the rate of self

condensation of the aldehydes is faster than the rate of formation and/or decomposition of the necessary HWE intermediate 25.



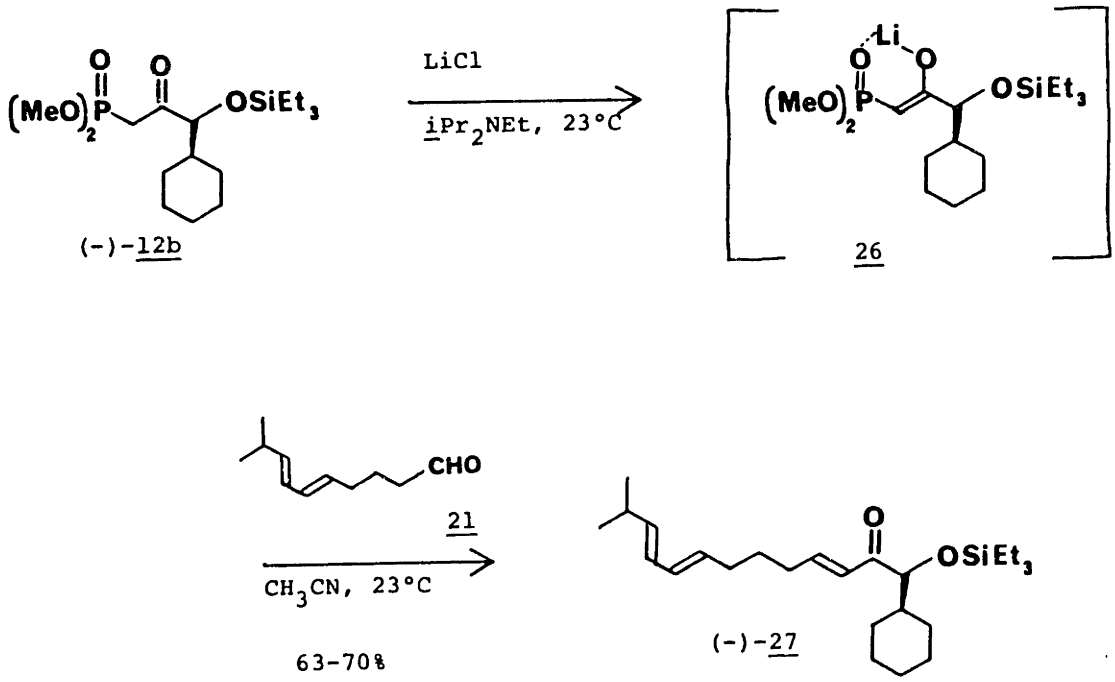
25

In spite of the inefficiency of the HWE coupling reaction, attempts were made to deprotect 17 in order to prepare samples of 3 for initiating studies of the intramoleculr Diels-Alder reaction. Unfortunately, treatment of 17 either with aqueous HF in acetonitrile or nBu$_4$NF in THF at room temperature destroyed the sensitive triene system. These results prompted us to prepare the triethylsilyl-protected (-)-12b (refer to Scheme 2) for use in subsequent chemistry.

While these studies were in progress we learned that the Masamune group was developing modifications of the Horner-Wadsworth-Emmons reaction for use with base-sensitive aldehydes.[9] The preferred method involves use of LiCl and a tertiary amine (iPr$_2$NEt or DBU) as a base in acetonitrile as solvent, and is illustrated in Scheme 4 for the reaction

9. Blanchette, M.A.; Choy, W.; Davis, J.T.; Essenfeld, A.; Masamune, S.; Roush, W.R.; Sakai, T. Tetrahedron Lett. 1984, 25, 2183.

Scheme 4

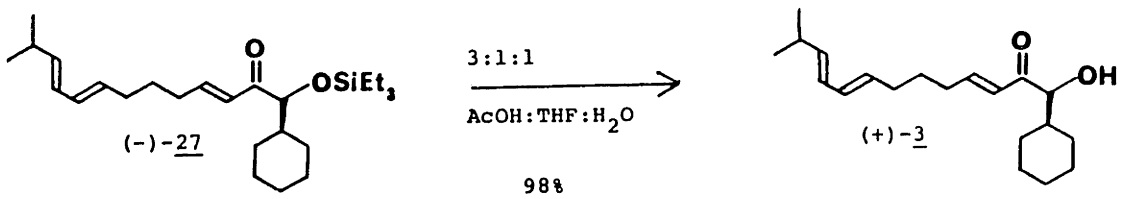


of (-)-12b and aldehyde 21. The rationale behind this modification is that the acidity of β-ketophosphonate reagents can be increased by chelation with Li^+ such that a tertiary amine (iPr_2NEt or DBU) will be sufficiently basic to form the phosphonate anion intermediate (e.g., 26). These reaction conditions, however, are not sufficiently basic to promote enolization or aldolization of the aldehyde, thus minimizing the amount of aldehyde that undergoes side reactions. Application of these

conditions to the coupling of (-)-12b and 21 gave triene 27 ($[\alpha]_D$ -48.0°, c = 1.15, $CHCl_3$) in 63-70% yield after chromatography (Scheme 4).

Deprotection of (-)-27 was smoothly accomplished by treatment with HOAc-THF-H_2O (3:1:1) at room temperature. These mild conditions afforded the desired triene 3 ($[\alpha]_D$ +65.5°, c = 1.15, $CHCl_3$) in 98%

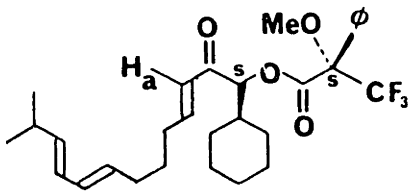
Scheme 5



yield. The optical purity of (+)-3 was shown to be at least 97% e.e. by using the Mosher ester method.[10] Samples of racemic and optically active (+)-3 were esterified by using (S)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, pyridine and catalytic 4-DMAP. The olefinic protons (H_a) α to the carbonyl group in the diastereomeric Mosher ester derivatives 28 and 29 were easily resolved at 250 MHz and

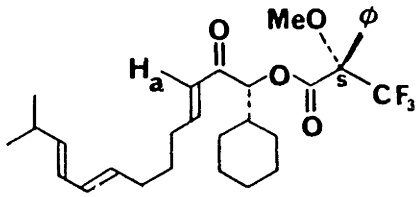
10. Mosher, H.S.; Dale, J.A.; Dull, D.L. J. Org. Chem. 1969, 34, 2543.

Scheme 6



28

(H_a) = 6.25 (d, J = 15.9 Hz)



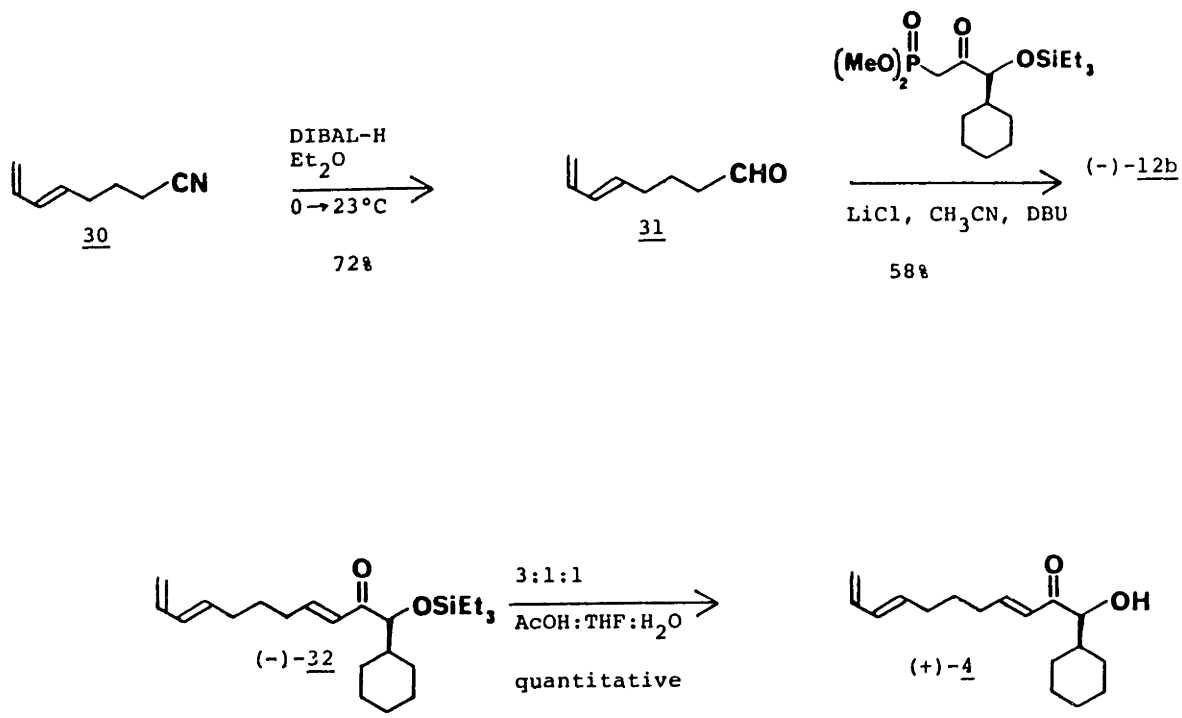
29

(H_a) = 6.18 (d, J = 15,8 Hz)

were used for this analysis (Scheme 6). This result clearly showed that racemization did not occur during the previously described HWE reaction.

Triene 4 was prepared as outlined in Scheme 7. Diene nitrile 30 was synthesized by known procedures.[2a] Reduction of 30 by using 1.5 equivalents of diisobutylaluminum hydride afforded aldehyde 31 in 72% yield. This compound was Kugelrohr distilled and used immediately in the Horner-Wadsworth-Emmons reaction. Triene 32 ($[\alpha]_D$ -50.2°, c = 0.75, $CHCl_3$) was obtained in 58% yield from 31, and the triethylsilyl group was then removed under mildly acidic conditions which provided triene 4 ($[\alpha]_D$ +94.1°, c = 0.14, $CHCl_3$) in quantitative yield.

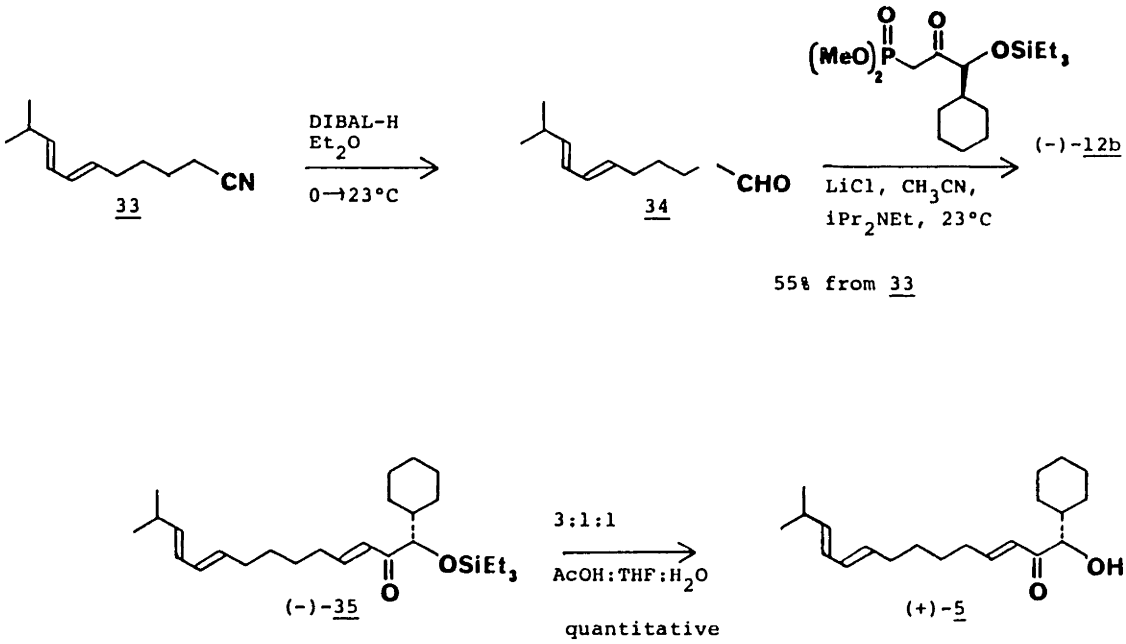
Scheme 7



The third triene (5) was synthesized by using an analogous sequence as outlined in Scheme 8. Diene nitrile 33 was prepared by known procedures[11] by reduction of aldehyde 21 with sodium borohydride in ethanol, followed by mesylation (CH_3SO_2Cl, Et_3N, CH_2Cl_2) and subsequent displacement with potassium cyanide in 80% ethanol at reflux. Reduction of 33 with diisobutylaluminum hydride afforded diene aldehyde 34. The modified Horner-Wadsworth-Emmons procedure was once again employed, giving triene 35 ($[\alpha]_D$ -42.0°, c = 0.95, $CHCl_3$) in 55% yield from diene

11. Gillis, H.R. Ph.D. Thesis, Massachusetts Institute of Technology, 1982.

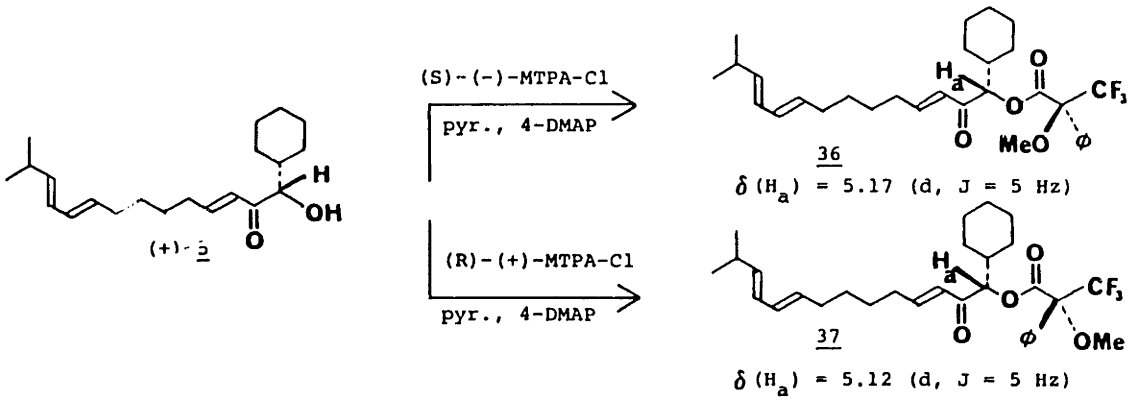
Scheme 8



nitrile 33. The somewhat lower yield of the modified HWE reaction in this series may be a consequence of the greater instability of aldehyde 34 than 21 or 31. Compound 34 could not be stored at -20°C for more than a day or so without substantial decomposition. Hydrolysis of (-)-35 using the conditions previously described gave triene 5 ($[\alpha]_D$ +66.3°, c = 1.17, $CHCl_3$) in excellent yield.

The optical purity of (+)-5 was established by the Mosher ester technique. Since racemic 5 was unavailable, optically active samples of (+)-5 were esterified by using both (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride and (S)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (Scheme 9). The NMR signals for

Scheme 9

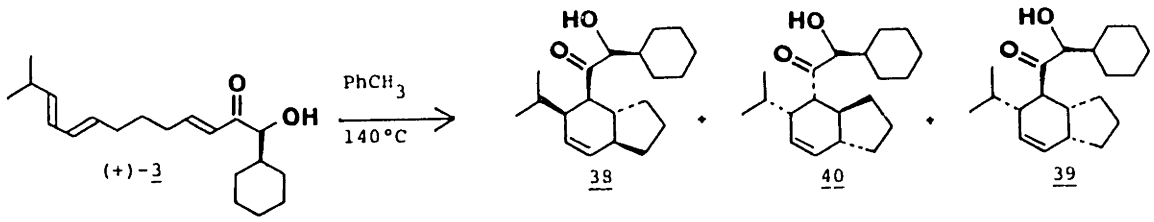


the methine proton (H_a) adjacent to the ketone in the diastereomeric MTPA esters 36 and 37 appeared at well resolved chemical shifts at 250 MHz (Scheme 9). Since only one diastereomer could be detected in the NMR spectra of 36 and 37, triene (+)-5 must be at least 98% e.e..

Cyclization of 3

This investigation focused almost exclusively on Lewis acid catalyzed reactions since in preliminary experiments we observed that the thermal cyclization of 3 (sealed tube, toluene, 140°C, 22 h) afforded a mixture of (at least) three cycloadducts (Scheme 10). These

Scheme 10



compounds were produced in a ratio of approximately 3:1:1 (NMR analysis; proton resonances appearing at δ 4.2, 3.8, and 4.0 were assigned to -$C\underline{H}(OH)C_6H_{11}$ of 38, 40 and 39, respectively). The endo (38 + 40) to exo (39) ratio was shown to be 83:17 by using the analytical method subsequently described.

The results obtained in the cyclizations of 3 under several sets of experimental conditions are summarized in Table 4. The Lewis acid catalyzed reactions generally required one day at room temperature to go to completion. Analysis of the crude reaction mixtures was complicated by the presence of unconsumed 3 and its decomposition products. Consequently, product mixtures were isolated chromatographically, with care taken to collect a wider than normal cut of fractions to insure that 39 and 40, if produced, would not be separated (39 and 40 are slower moving than 38, but all three cycloadducts are more mobile

Table 4

Intramolecular Diels-Alder Reactions of 3

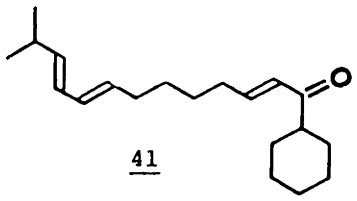
Lewis Acid[a]	Conditions	Yield[b]	Product Ratios[c]		
			38	40	39
--	140°C, toluene	71%	3	1	1
$ZnCl_2$	0→23°C, CH_2Cl_2	63-70%	only[d]	-	-
$EtAlCl_2$	-78→23°C, CH_2Cl_2	58-65%	only[d]	-	-
Et_2AlCl	-78→23°C, CH_2Cl_2	42%	only[d]	-	-
$BF_3 \cdot Et_2O$	-78→23°C, CH_2Cl_2	47-55%	7	1	-

a 0.95 Equivalent of catalyst used in each experiment.
b Combined yield of cycloadducts isolated by chromatography.
c Determined by proton NMR analysis.
d Cycloadduct 38 was the only product detected by NMR.

chromatographically than 3). The cycloadduct obtained from the $ZnCl_2$, $EtAlCl_2$ and Et_2AlCl catalyzed cyclizations appeared to be diastereomerically pure by 250 MHz proton NMR analysis; the signal to noise level, however, was such that 2-3% of other diastereomers could have gone undetected. Only in the $BF_3 \cdot Et_2O$ catalyzed reaction was any diastereomer detected. In this case a 7:1 mixture of 38 and 40 was obtained.

Two other Lewis acids (Me_3Al and $Ti(OiPr)_4$) were tried, but failed to promote cyclization of 3. Use of trimethylaluminum resulted in

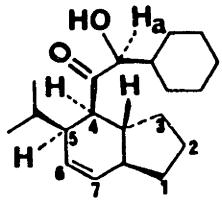
decomposition of the triene whereas titanium isopropoxide produced



41

41 in 15% yield. This compound presumably results from a Meerwein-Ponndorf-Verley reduction of 3 (using $Ti(OiPr)_4$ as reductant), followed by a pinacol rearrangement (with H^- as the migrating group) and subsequent double bond migration.

Compound 38 was assigned the *trans*-fused hexahydroindene skeleton on the basis of the multiplicity of the NMR resonance for H_4 which



(-)-38

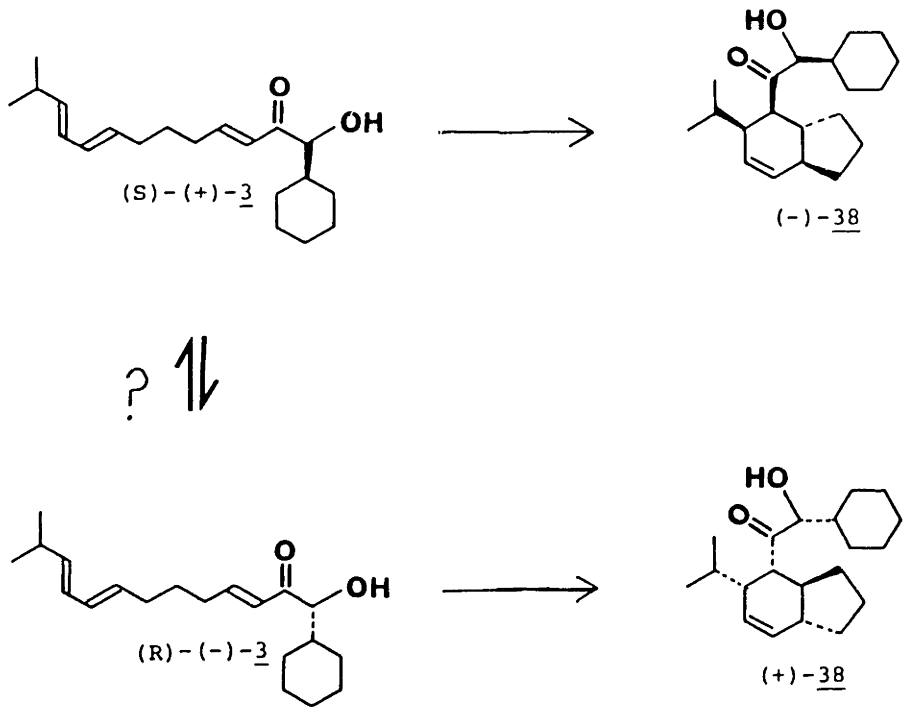
appeared as a doublet of doublets with $J_{4,5}$ = 7.7 Hz and $J_{3a,4}$ = 10.6 Hz, and the appearance of a C=C stretching band at 1635 cm^{-1} in the infrared spectrum. These data are characteristic of *trans*-fused hexahydroindene cycloadducts deriving from all-trans triene precursors.[2a,12] The absolute configuration of the perhydroindene

12. (a) Roush, W.R.; Gillis, H.R. J. Org. Chem. 1980, 45, 4283. (b) Roush, W.R.; Peseckis, S.M. J. Am. Chem. Soc. 1981, 103, 6696.

nucleus (as shown) was established by the degradation method subsequently described.

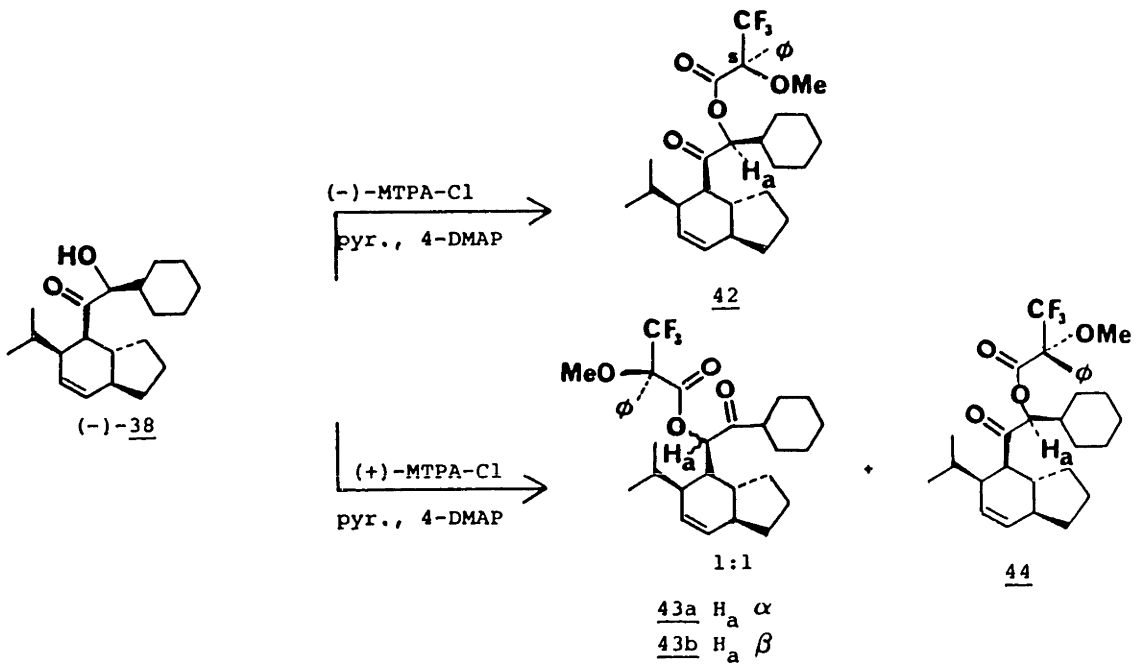
The results summarized in Table 4 showed that the $ZnCl_2$, $EtAlCl_2$, and Et_2AlCl catalyzed cyclizations of 3 are highly diastereoselective. It remained to be determined, however, whether these reactions were also highly enantioselective. If (S)-(+)-3 epimerized to (R)-(-)-3 prior to cyclization, the optical purity of 38 would be affected (Scheme 11).

Scheme 11



This point was addressed by performing an optical purity determination on 38. Because the racemic compound was not available, the cycloadduct produced in the $ZnCl_2$ catalyzed cyclization was derivatized by using both (S)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride and (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (Scheme 12). The

Scheme 12



reaction of (-)-38 with (-)-MTPA-Cl gave one predominant (>97%) ester 42. When (-)-38 was esterified by using (+)-MTPA-Cl, however, three products were obtained. The two major products, produced in roughly a

1:1 ratio, were assumed to be 43a and 43b resulting from carbonyl transposition of (-)-38 prior to acylation. The third, minor, product was assigned structure 44 by virtue of the similarity of the chemical shift of H_a to that in MPTA ester 42 (see Table 5). Although this

Table 5

Chemical Shifts of H_a of MTPA Esters 42-44

MTPA Ester	Multiplicity	δ
42	d	5.37
43a*	d	5.02
43b*	d	4.72
44	d	5.39

* The structures 43a and 43b were arbitrarily assigned.

analysis is very complex, it can be used to establish the optical purity of 38. If any of (+)-38 were produced in the intramolecular Diels-Alder reaction (Scheme 11), then signals at δ 5.39, 5.02, and 4.72 corresponding to the enantiomers of 44, 43a, and 43b, respectively, should have appeared in the proton NMR spectrum of the esters prepared from 38 and (-)-MTPA-Cl. They did not. Similarly, a resonance at δ 5.37 corresponding to the enantiomer of 42 was not observed in the NMR spectrum of the Mosher ester derivatives prepared from 38 and (+)-MTPA-

Cl. On the basis of these data we concluded that (-)-38 was >98% optically pure and that triene 3 did not epimerize (racemize) during the Diels-Alder reaction.[13]

Careful analysis of the NMR spectrum of 42 prepared from 38 and (-)-MTPA-Cl, however, revealed that a minor (*ca.* 3%) MTPA ester was present (δ 5.16 for H_a). This immediately suggested that 38 was not diastereomerically pure as originally presumed. Recrystallization of 38 prepared *via* the $ZnCl_2$ catalyzed cyclization gave pure cycloadduct (mp 137-138°C) in 72-79% yield along with 21-28% of crystalline 38 recovered in the mother liquors. Our hope was that the minor product would be concentrated in the mother liquors. Indeed, whereas the 250 MHz NMR spectrum of recrystallized 38 again indicated that this material was diastereomerically pure, the NMR spectrum of the mother liquors revealed that this sample was 93-97% pure with 3-7% of minor isomer 45 present. The characteristic doublet of doublet pattern for H_a of 45 was clearly evident (δ 4.85). The recrystallized and mother liquor samples of 38 were derivatized by using (S)-(-)-MTPA-Cl and the results are summarized in Table 6. These analyses confirmed our observation that the minor cycloadduct 45 had been concentrated in the mother liquor fraction. They also provided additional insight into the optical purity

13. In support of our conclusion that epimerization of 3 does not occur during the Diels-Alder reaction, a sample of 3 was subjected to the usual reaction conditions ($ZnCl_2$, CH_2Cl_2, 0→23°C) and the reaction was worked up after a 4 h reaction period. Triene 3 was recovered chromatographically (63% yield; 38 was obtained in 20% yield) and was shown not to have epimerized by comparison of optical rotation measurements before and after the reaction ($[\alpha]_D^{25}$ +66° (c = 0.95, $CHCl_3$)).

Scheme 13

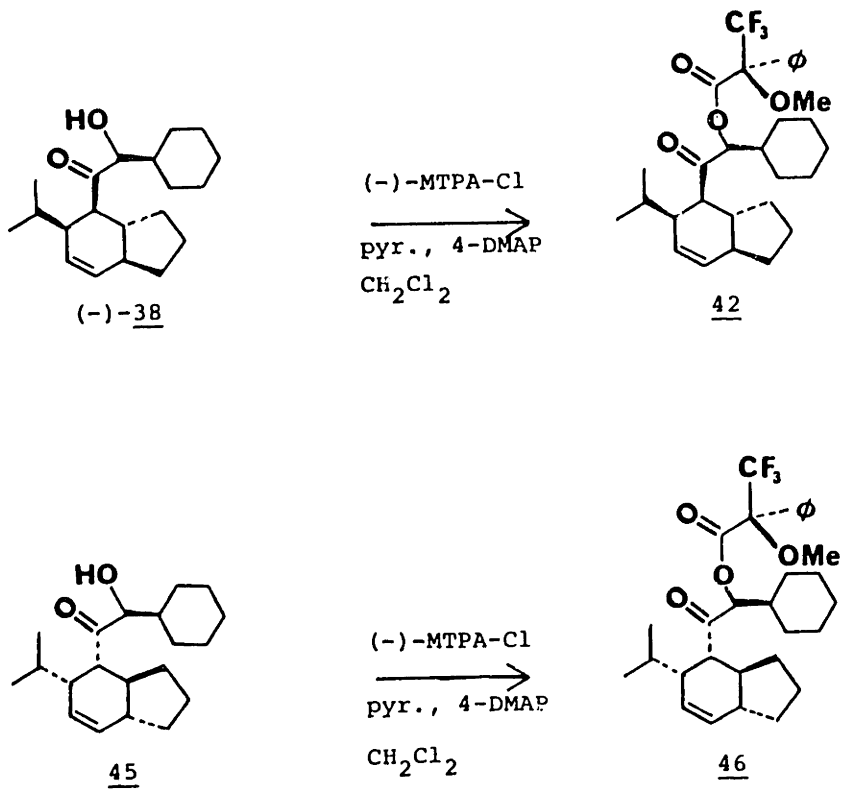


Table 6

Mosher Ester Analyses of Pure 38 and Mixtures of 38 and 45

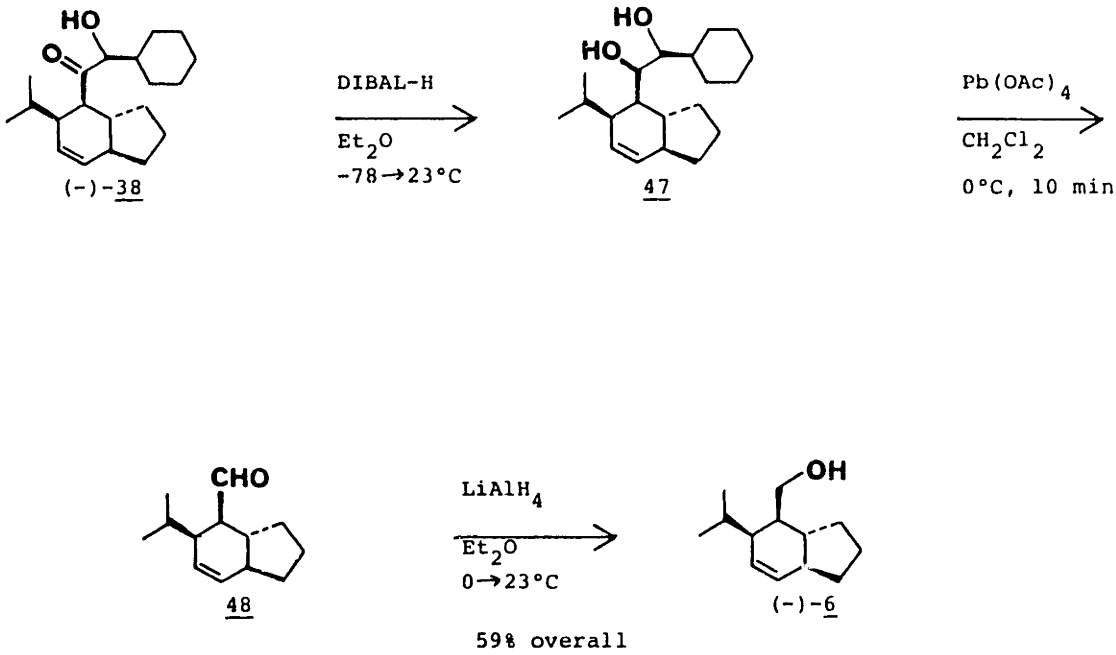
Source of Sample[a]	Mosher Acid	δ of H_a in 42, 46	%d.e.
chromatography	(S)-(-)-MTPA-Cl	5.37, 5.16	>94
recrystallization	(S)-(-)-MTPA-Cl	5.37	100
mother liquors	(S)-(-)-MTPA-Cl	5.37, 5.16	86

a Mixture of cycloadducts isolated from the $ZnCl_2$ catalyzed cyclization of 3. See text for specific details.

of 38 since resonances for 43a, 43b, and 44 (refer to Scheme 12, Table 5) were not observed in the NMR spectrum of the MTPA esters prepared from the impure mother liquors.

The absolute configuration of (-)-38 was established by the degradation sequence summarized in Scheme 14. Treatment of 38 with

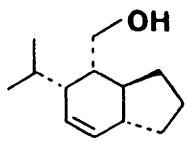
Scheme 14



diisobutylaluminum hydride in ether gave a single epimer of diol 47[14]

14. When lithium aluminum hydride was used, a 1:1 mixture of epimers was produced.

which when exposed to lead tetraacetate in methylene chloride (0°C, 10 min) was smoothly converted to aldehyde 48. Finally reduction of 48 with lithium aluminum hydride afforded (-)-6 in 59% overall yield from (-)-38. The optical rotation of (-)-6 ($[\alpha]_D^{25}$ -171° (c = 0.86, EtOH)) was roughly equal in magnitude but opposite in sign to that of (+)-6 ($[\alpha]_D^{25}$ -170° (c = 0.53, EtOH)) whose absolute configuration had previously been established by Gillis in these laboratories.[2a]

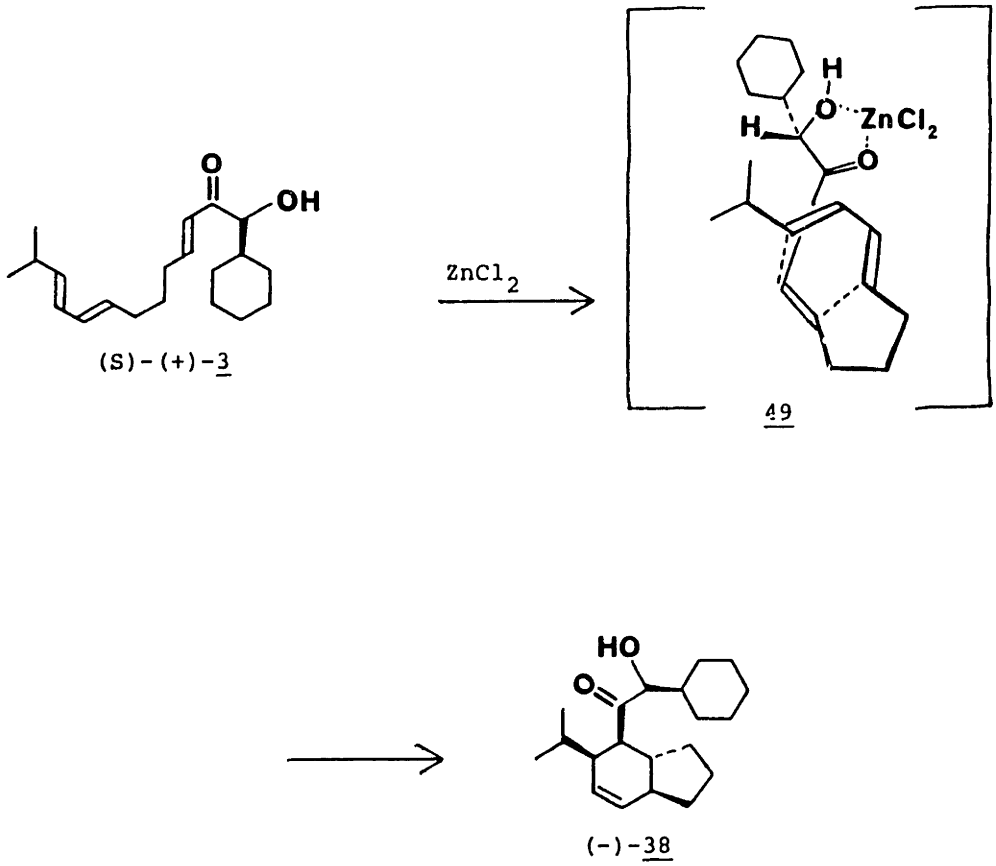


(+)-6

Therefore, the absolute configurations of (-)-6 and consequently also (-)-38 are as depicted in Scheme 14.

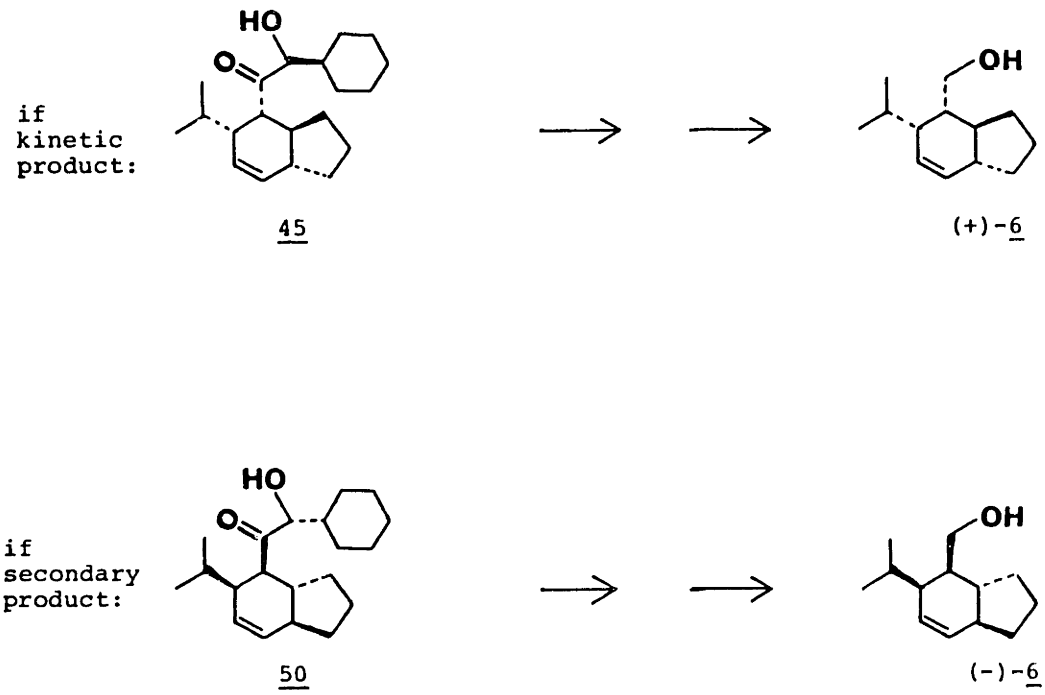
On the basis of these results, we believe that the intramolecular Diels-Alder reaction of 3 proceeds *via* transition state 49 as outlined in Scheme 15. This transition state is completely analogous to that proposed by Masamune for bimolecular Diels-Alder reactions.[1]

Scheme 15



The degradation sequence summarized in Scheme 14 was used to establish the absolute configuration of the minor diastereomer produced in the intramolecular Diels-Alder reaction (45 or 50). If 45 is actually a kinetic product of this reaction, then the degradation will produce (+)-6. If, on the other hand, 50 is a secondary product, produced by epimerization of 38 after the Diels-Alder reaction, then (-)-6 would be produced.

Scheme 16



This issue was resolved by degrading the mother liquor fraction, consisting of a *ca.* 93:7 mixture of (-)-38 and 45 by proton NMR analysis, from the previously described recrystallization. An optical purity analysis was then performed on the resulting sample of 6 (see Scheme 17 and Table 7). The diastereomeric purity of the Mosher ester derivatives was either determined by careful integration of the $-CH_2OCO-$ resonances at 400 MHz or, more conveniently, by ^{19}F analysis at 300 MHz (see Experimental).

Scheme 17

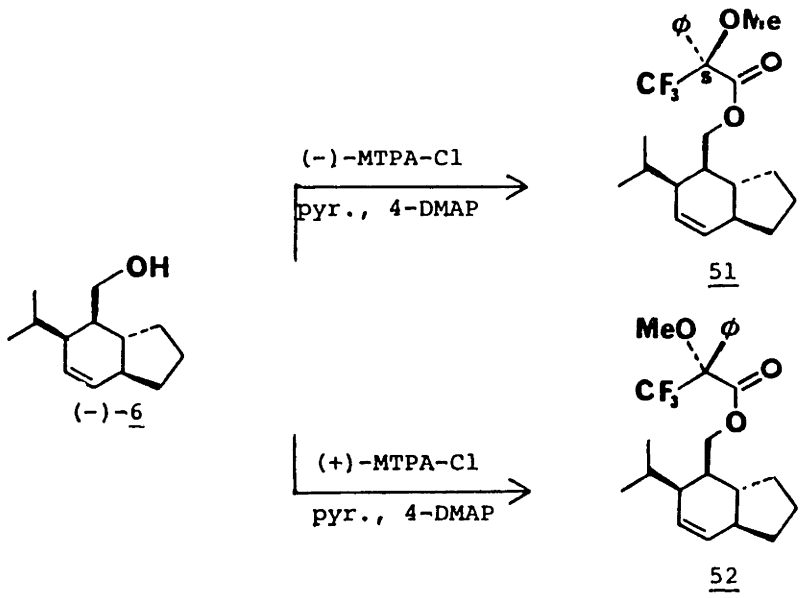


Table 7

Optical Purity Determination of 6

	Ratio of 51/52	
Source of Sample	(-)-MTPA-Cl	(+)-MTPA-Cl
Recrystallized 38	96:4	< 1:99
Mother liquors from recrystallization of 38, containing *ca.* 7% of 45	88:12	9:91

This analysis showed that 6 prepared from the mixture of 38 and 45 was not optically pure, establishing therefore that the absolute configuration of 45 is as depicted in Scheme 13. We were surprised to

find, however, that the optical purity of 6 was substantially lower when (-)-MTPA-Cl was used than expected based on the data summarized in Table 6. On the other hand, when (+)-MTPA-Cl was used in this analysis the optical purities of 6 prepared both from the recrystallized and mother liquor samples of 38 were fully consistent with the expected values.

This discrepancy led us to question the optical purity of the (-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid purchased from Aldrich. We, therefore, decided to develop an analytical method to check the optical purity of these key reagents. We selected diacetone-D-glucose for this feeling that it was reasonable to assume that this compound could be obtained in optically pure form. A sample of (-)-53 was recrystallized from ether to constant melting point (mp 114.5°C) and constant optical rotation ($[\alpha]_D^{25}$ -19.0° (c = 0.54, H_2O); literature[15] $[\alpha]_D^{25}$ -18.5° (c = 5, H_2O)). The Mosher ester derivatives 54 and 55 were then prepared (Scheme 18). These compounds are easily distinguished by using the NMR data summarized in Table 8. The MTPA ester prepared from (-)-53 and (-)-MTPA-Cl proved to be a 97:3 mixture of 54 and 55 (94% d.e.) while 55 appeared to be >98% d.e. by this analysis. Therefore, we concluded that the batch of (-)-MTPA-Cl used in these analyses was only 94% optically pure while the (+)-MTPA-Cl was virtually optically pure. It should be noted since the two enantiomers of MTPA-OH are separated by a chemical resolution,[10] it is likely that

15. Fischer, E.; Rund, C. Chem. Ber. 1916, 49, 85.

Scheme 18

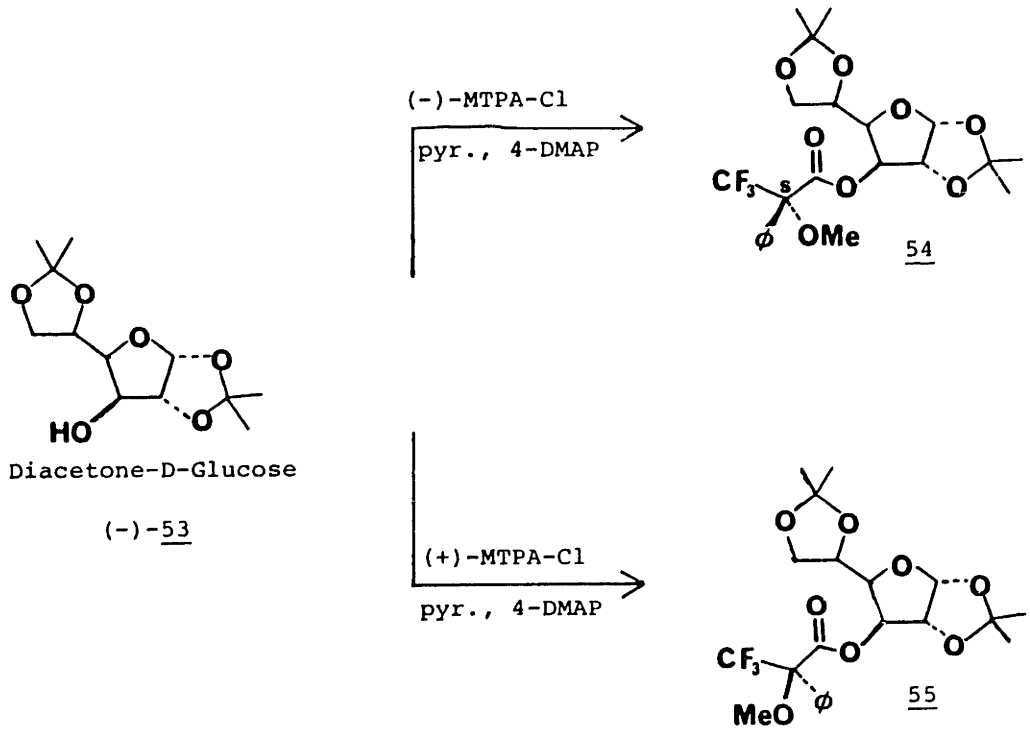


Table 8

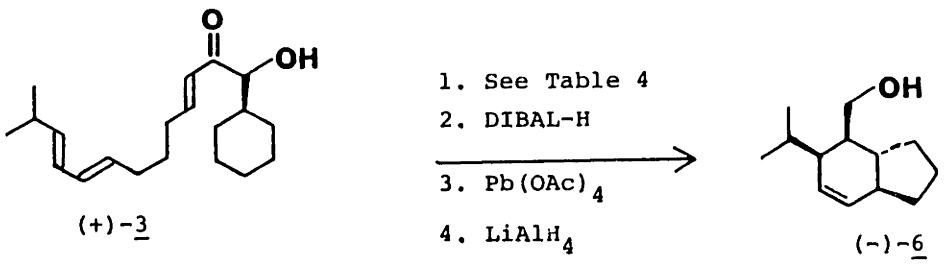
Chemical Shift Data for 54 and 55

Ester 54		Ester 55	
^{1}H NMR	^{19}F NMR	^{1}H NMR	^{19}F NMR
δ 5.87	δ 10.00	δ 5.73	δ 10.45
5.51		5.48	
4.51		4.43	

the optical purity of these reagents will vary from batch to batch. It is also obvious in retrospect that the optical purity of each new batch should be determined before use.

The degradation summarized in Scheme 14 served one final, but critical role in defining the stereoselectivity of the Diels-Alder reaction of 3. We were concerned whether exo cycloadduct 39, if produced in the reactions summarized in Table 4, may have been inadvertently separated during the chromatographic clean up of 38. Consequently, each reaction was repeated and the crude reaction mixtures

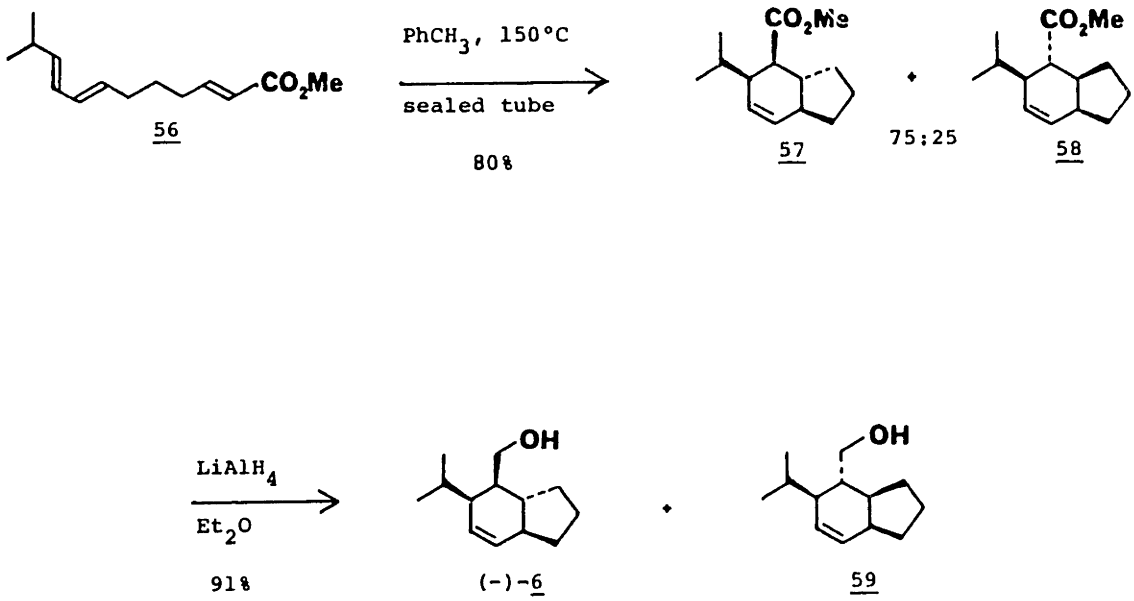
Scheme 19



(+)-3 (-)-6

were carried through the degradation sequence to 6 without any purifications along the way. Control experiments established that authentic mixtures of 6 and 59, prepared as outlined in Scheme 20 and which are not separable by TLC, are easily analyzed by proton NMR (see Table 9). By using this technique it was possible to establish that

Scheme 20



less than 2% (the limit of detection) of exo cycloadduct 39 was produced in the Lewis acid catalyzed reactions. The endo:exo ratio in the thermal reaction, however, was 83:17.

Table 9

Diagnostic ^{1}H Resonances for 6 and 59

Proton Assignment	6	59
isopropyl -CH_3	0.99(d, J = 6.9 Hz)	--[a]
	0.81(d, J = 6.8 Hz)	0.73(d, J = 6.6 Hz)
olefin	5.95(br d, J = 10.1 Hz)	5.75(br d, J = 10.1 Hz)
	5.62(br d, J = 10.1 Hz)	--[a]

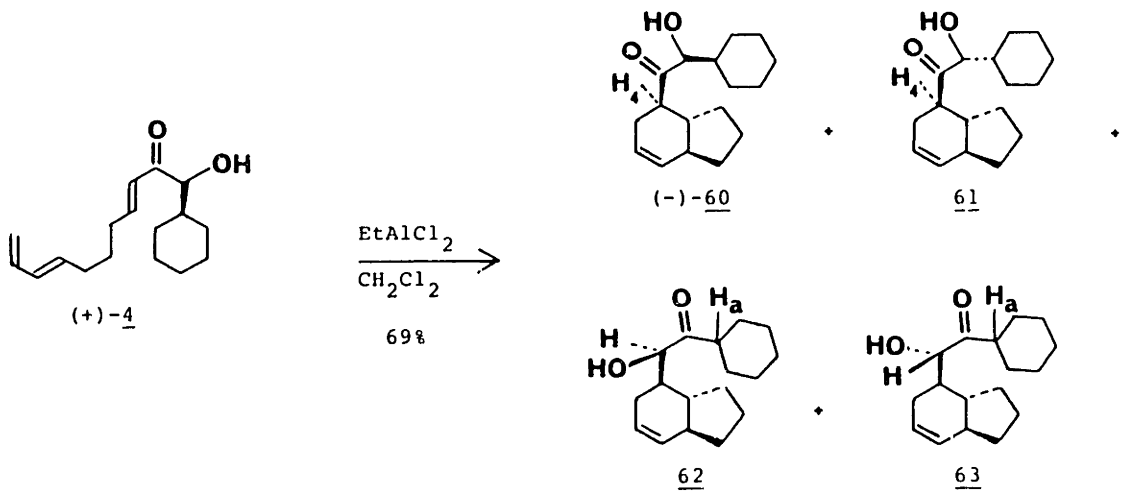
a This resonance appeared under the corresponding signal for 6.

In summary, the cyclization of (+)-3 in the presence of $ZnCl_2$ proceeded with exceptional selectivity for *trans*-fused cycloadduct (-)-38. Less than 3% of *trans*-fused diastereomer 45, and none of the *cis*-fused exo adduct 39, was detected, indicating that the reaction proceeded with approximately 94% diastereofacial selectivity. Lastly, there was no epimerization of 3 under the reaction conditions, and cycloadduct (-)-38 was obtained in enantiomerically and diastereomerically pure form by recrystallization of the product mixture. Although the $EtAlCl_2$ and Et_2AlCl catalyzed reactions were not examined in as much detail, these experiments also provided (-)-38 with excellent selectivity. With these encouraging results in hand, we proceeded to initiate studies on the cyclizations of 4 and 5.

Intramolecular Diels-Alder Reactions of 4 and 5

Because zinc chloride and ethylaluminum dichloride were the most effective catalysts identified in our studies of 3, these were the only reagents used for catalyzing the Diels-Alder reaction of 4 and 5. Much to our surprise, treatment of 4 with 0.95 equivalent of $EtAlCl_2$ in methylene chloride using the protocol described previously gave a mixture of (at least) four products (see Scheme 21). Analysis of the

Scheme 21



NMR spectrum of the crude reaction mixture indicated that these were produced in an approximate ratio of 1:1:1:1. Careful chromatography of this mixture effected partial separation and gave several fractions enriched in one or more of these products. Structures were tentatively assigned as shown based on the characteristic multiplicities of H_4 in 60-61 (δ 2.8-2.9, dt, J = 6.0, 10.6 Hz) and H_a in 62-63 (δ 2.5-2.7, br tt, J = 10, 3 Hz). Mixtures are most easily analyzed by integrating the -C<u>H</u>(OH)- and -O<u>H</u> resonances listed in Table 10.

Table 10

Characteristic ^{1}H NMR Resonances of 60-63[a]

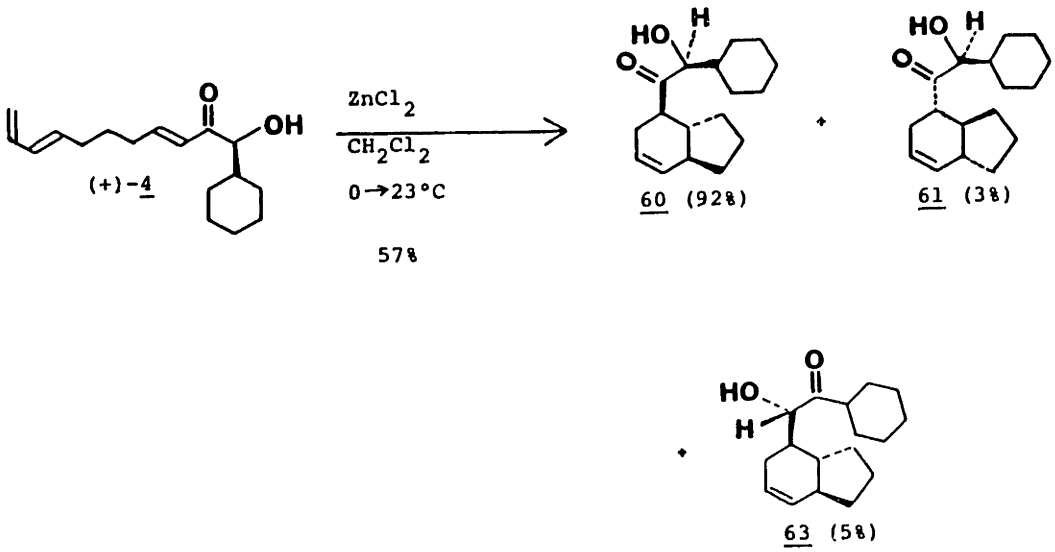
	-CH(OH)-	-OH
60	4.10(dd, J = 6, 2 Hz)	3.33(d, J = 6 Hz)
61	4.03(dd, J = 5, 2 Hz)	3.42(d, J = 5 Hz)
62[b]	4.44(br d, J = 5 Hz)	3.49(d, J = 5 Hz)
63[b]	4.13(br d, J = 5 Hz)	3.55(d, J = 5 Hz)

a NMR measurements were performed at 250 MHz.
b Assignments for 62 and 63 are arbitrary and may be reversed.

The presence of 62 and 63 in the reaction mixture suggests that carbonyl transposition occurred after the cyclization. Although 61 could arise *via* epimerization of 60, it also could be produced as a kinetic product of the Diels-Alder reaction. However, since enolization clearly must occur for 62 and 63 to be formed, we assume that the epimerization pathway accounts for a significant amount of 61. For this reason the absolute configuration is assumed to be as shown. Owing to the complexity of this reaction mixture, this experiment was not examined any further.

The reaction of 4 catalyzed by zinc chloride was much cleaner (Scheme 22) and gave a product mixture consisting of 92% of 60, 3% of 61, and 5% of 63 (NMR analysis). If any of 62 was produced, it escaped

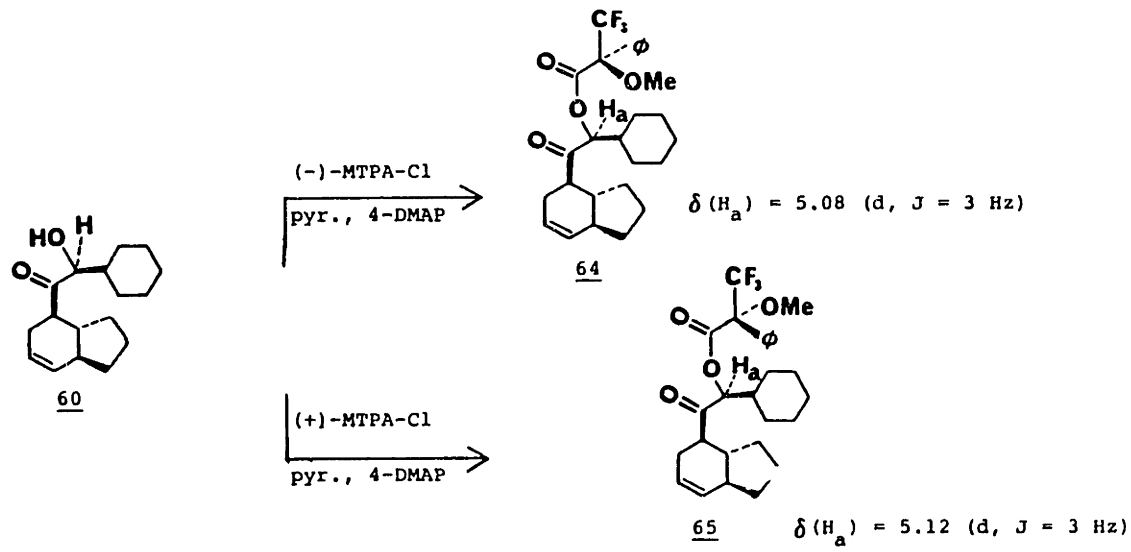
Scheme 22



detection. Since 63 is clearly a post-cyclization isomerization product of 60, the kinetic diastereoselection of this reaction is at least 94% (as noted previously, the origin of 61 is ambiguous).

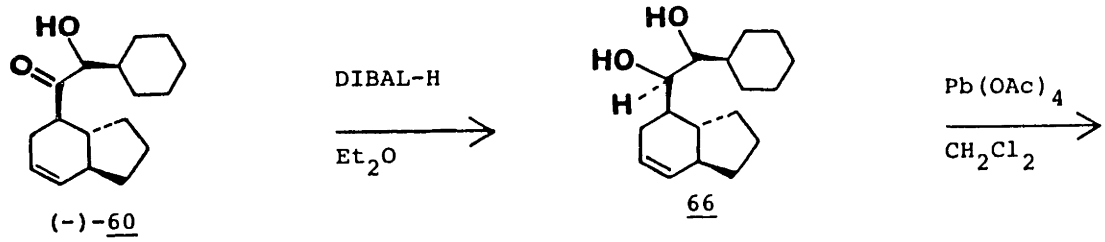
Recrystallization of this mixture of 60, 61, and 63 gave diastereomerically pure 60 (mp 71-72°C) which also proved to be enantiomerically pure (within the limits of detection) by Mosher ester analysis (see Scheme 23).

Scheme 23

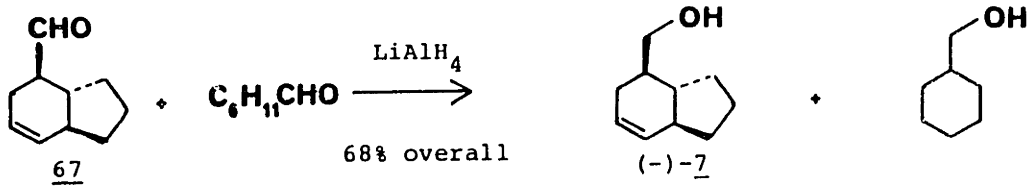


The absolute stereochemistry of (-)-60 was rigorously established by degradation to (-)-7 as summarized in Scheme 24. Unfortunately, however, 7 was very difficult to separate from cyclohexylmethanol, and pure samples of 7 were not obtained. Nevertheless, the optical rotation of mixtures of 7 and cyclohexylmethanol were negative in sign. Since the absolute configuration of (+)-7 is known,[2a] the absolute stereochemistries of (-)-7 and (-)-60 must be as shown in Scheme 24. We conclude, therefore, that (-)-60 is produced *via* transition state 68.

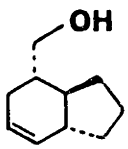
Scheme 24



(-)-60 66

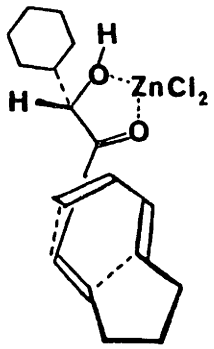


67 (-)-7



(+)-7 ($[\alpha]_D^{25}$ +45°)

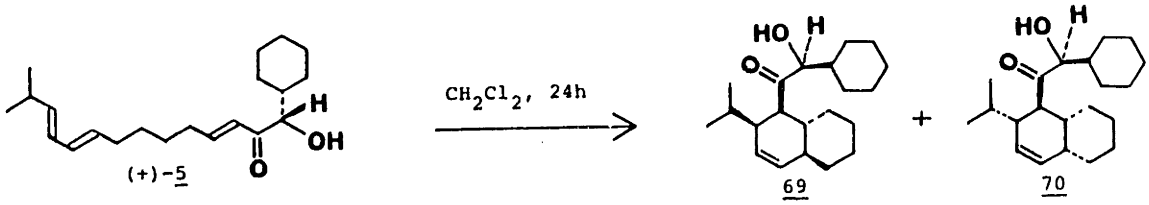
Results obtained in the Lewis acid catalyzed Diels-Alder reactions of 5 are summarized in Table 11. These reactions yielded a mixture of cycloadducts 69 and 70 in a combined yield of 82-87%. The ratio of



68

these isomers was easily determined by integration of the methine α-hydroxyketone proton which appears at δ 5.08 for 69 and δ 5.00 for 70. The major product, 69, was purified from the mixture either by chromatography or recrystallization. The *trans*-fused decalin skeleton was assigned initially on the basis of the characteristic chemical shift and multiplicity of H_5 (δ 2.97 (dd, $J_{5,6}$ = 7.1 Hz, $J_{5,4a}$ = 11.1 Hz)).[2b,16]

Scheme 25



16. Roush, W.R.; Hall, S.E. J. Am. Chem. Soc. 1981, 103, 5200.

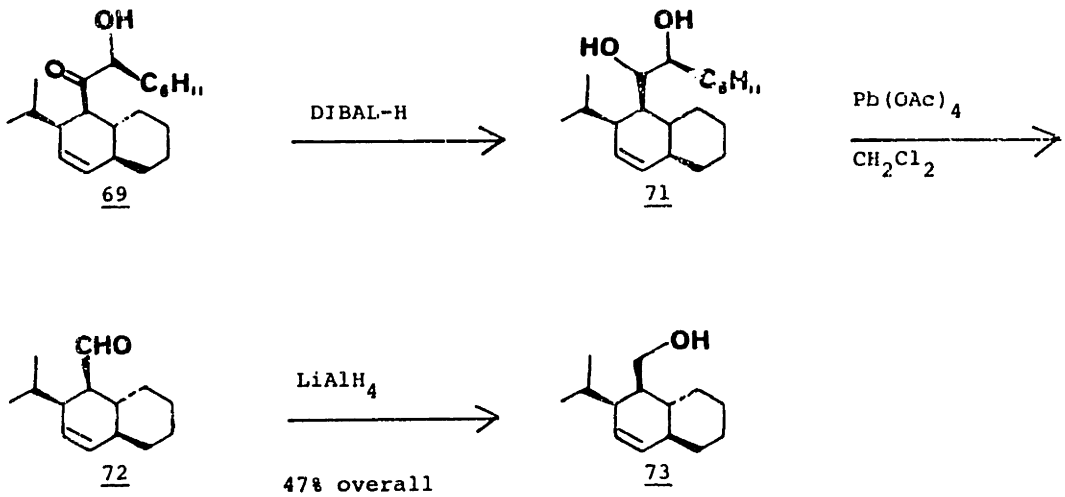
Table 11

Lewis Acid	Temperature	Products[a] 69:70	Yield[b]
$EtAlCl_2$(0.95 eq.)	-78→23°C	93:7	82%
$ZnCl_2$(0.95 eq.)	0→23°C	96:4	87%

a Determined by NMR analysis of the crude reaction mixtures.
b Combined yield of 69 and 70 isolated by chromatography.

This assignment was confirmed by degradation of 69 to the known alcohol[17] 73 as outlined in Scheme 26.

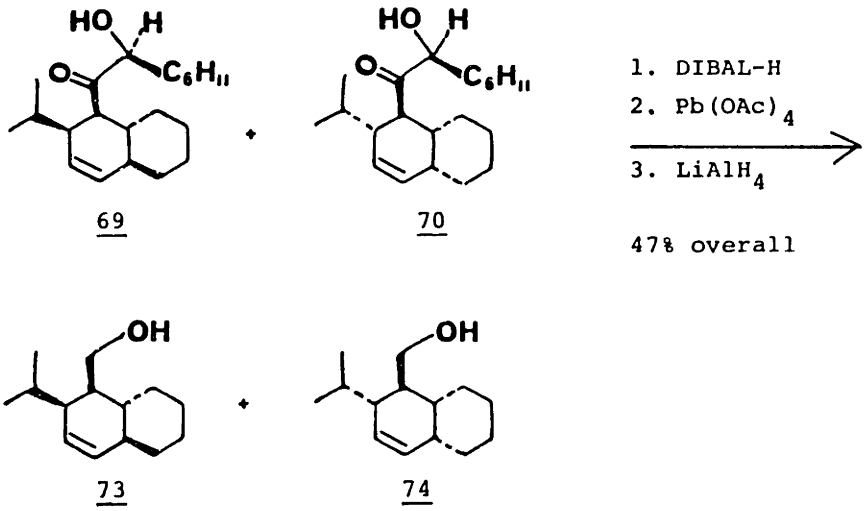
Scheme 26



17. Roush, W.R.; Gillis, H.R.; Essenfeld, A. J. Org. Chem. 1984, 49, 4674.

The minor product 70 of this Diels-Alder reaction is not the hydroxyl epimer of 69, but rather is a *cis*-fused cycloadduct resulting from an exo cyclization. This point was established by converting mixtures of 69 and 70 to the corresponding mixture of alcohols 73 and 74. These compounds are easily analyzed by integrating the isopropyl methyl resonances as previously described.[17]

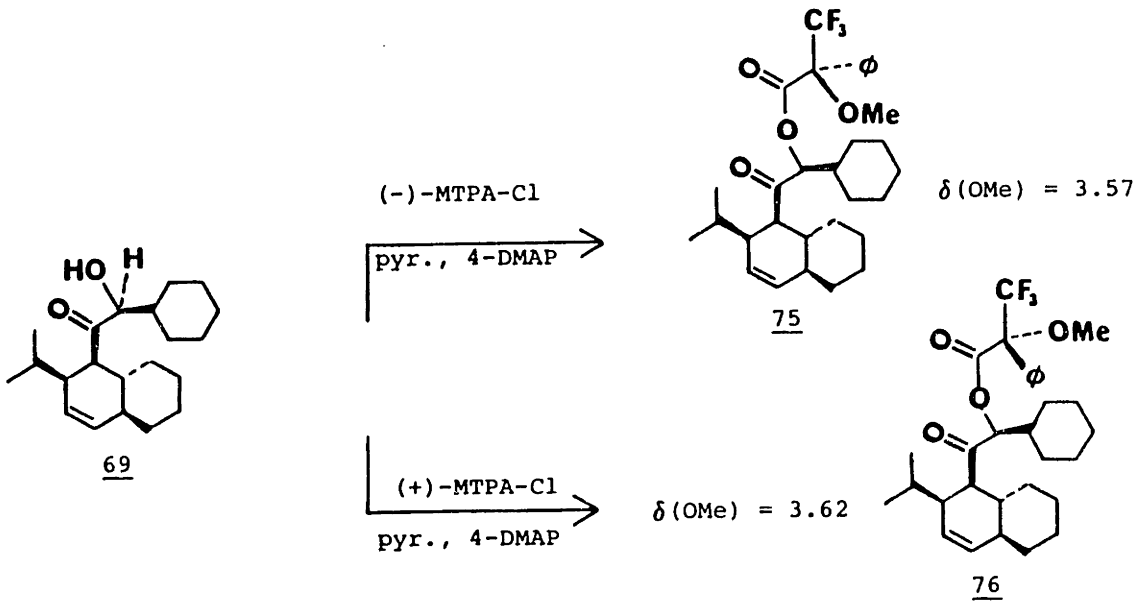
Scheme 27



69 70 73 74

The optical purity of recrystallized samples of 69 was shown to be >96% e.e. by the Mosher ester method. The methoxyl resonances of the

Scheme 28

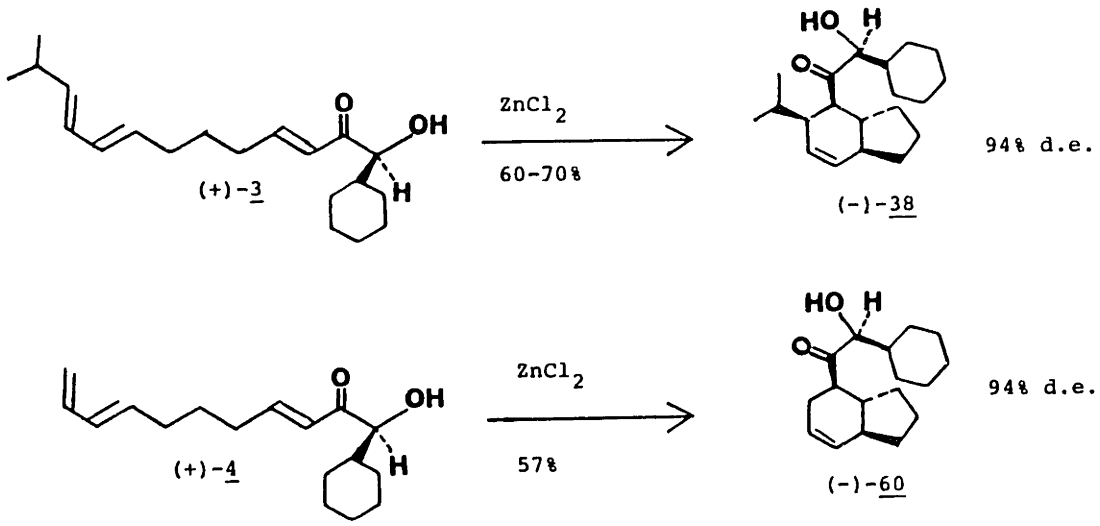


diastereomeric MTPA esters are easily distinguished and were used for this analysis. The absolute configuration of 69 is assumed to be as shown by analogy to the other cases described herein.

Summary

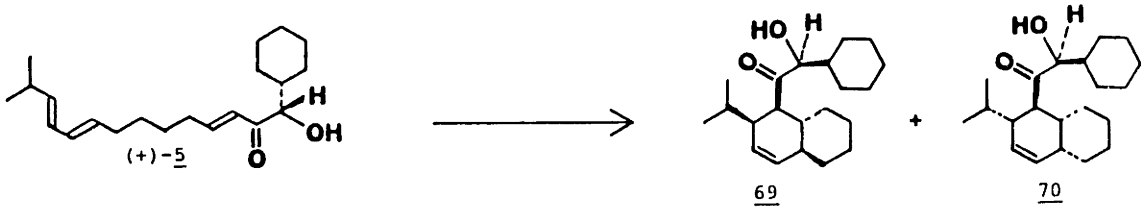
We have shown that the zinc chloride catalyzed intramolecular Diels-Alder reactions of 3 and 4 give *trans*-fused cycloadducts exclusively. The kinetic diastereofacial selectivities of each reaction

Scheme 29

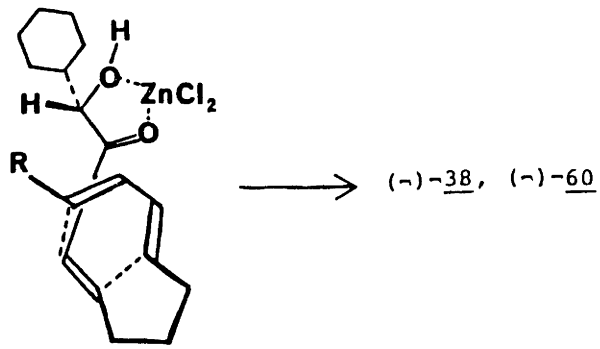


are at least 94% (Scheme 29). Diastereo- and enantiomerically pure samples of cycloadducts (-)-38 and (-)-60 were easily isolated from the reaction mixtures by recrystallization. On the other hand, the zinc chloride catalyzed cyclization of triene 5 gave a 96:4 mixture of *trans*- and *cis*-fused cycloadducts (Scheme 30). The *trans*-fused cycloadduct was purified by recrystallization from hexane and its optical purity was determined to be at least 96%. The absolute configuration of cycloadducts (-)-38 and (-)-60 were assigned by comparison of optical rotation of alcohols 6 and 7, prepared by a simple three-step procedure

Scheme 30



from 38 and 60, respectively, with the values reported in the literature. The high diastereoselection of these Diels-Alder reactions, therefore, can be rationalized by transition state 77. The absolute configuration of 69 was not established rigorously. It is reasonable to assume, however, that the cyclization of 5 proceeds *via* a transition state analogous to 77.

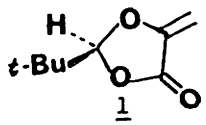


77

The synthetic utility of this chiral auxiliary for intramolecular Diels-Alder reactions must be assessed in terms of the design criteria stated at the beginning of this chapter. These cyclizations proceed in good chemical yields (60-80%) and with high diastereofacial differentiation. The major cycloadduct can be purified to essentially 100% e.e. by recrystallization and optically pure precursors to the chiral auxiliary are commercially available in both enantiomeric forms. Finally, the auxiliary is readily cleaved from the cycloadduct in three steps (47-68% overall yield).

Chapter 3

This chapter describes preliminary studies on the use of enol pyruvate 1 as a chiral ketene equivalent[1] in bimolecular Diels-Alder reactions. This investigation was prompted by a previous study in these

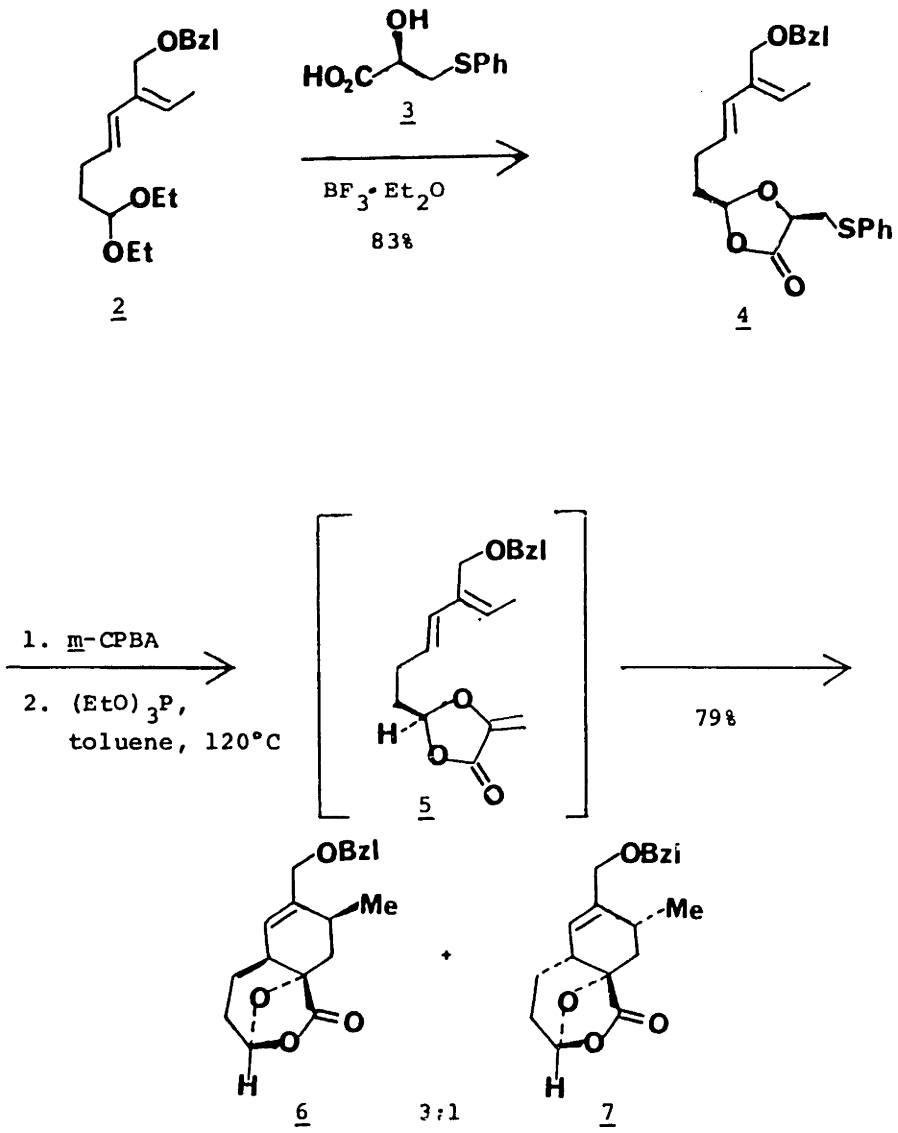


1

laboratories by Dr. Kageyama who observed that the intramolecular Diels-Alder reaction of chiral triene 5 occurred with exceptional diastereofacial selectivity (Scheme 1).[2] Although two cycloadducts differing in the sense of facial approach of the diene to the dienophile were obtained, diastereofacial selectivity relative to the dienophile was perfect: no other diastereomeric cycloadducts were detected in the crude reaction mixture. A second, important observation was that the condensation of acetal 2 with α-hydroxy acid 3 occurred with near perfect asymmetric induction to give 4 as a single diastereomer in 83-89% isolated yield. This suggested to us that it should be possible to

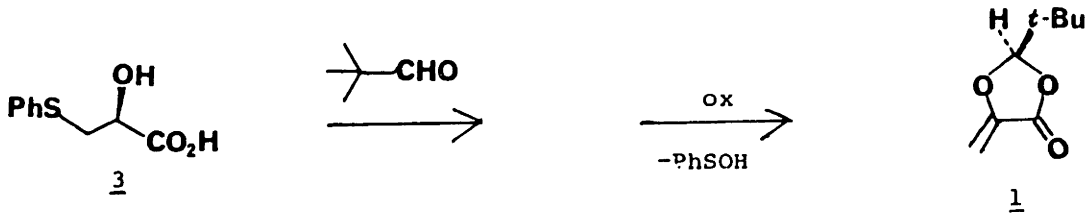
1. Ranganathan, S.; Ranganathan, D.; Mehrotra, A.K. Synthesis 1977, 5, 289.
2. Dr. Masanori Kageyama, unpublished results.

Scheme 1


OBzl
OEt
OEt
2
OH
HO2C
SPh
3
BF3·Et2O
83%
OBzl
O
O
SPh
O
4
1. m-CPBA
2. (EtO)3P,
toluene, 120°C
OBzl
H
O
O
O
5
79%
OBzl
Me
O
O
H
6
3:1
OBzl
Me
O
O
H
7

synthesize homochiral 1 by an analogous sequence involving condensation

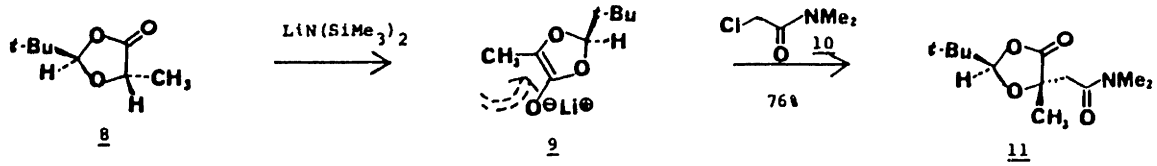
Scheme 2



of pivalaldehyde with homochiral 3 (Scheme 2). Then, if the reactions of 1 with various dienes proved to be highly stereoselective, this dienophile could become a valuable chiral ketene equivalent in organic synthesis.

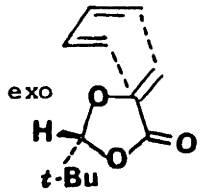
Applications of chiral 2-alkyl-1,3-dioxolan-4-ones in asymmetric synthesis have been reported.[3] These studies have focused on alkylation reactions such as that shown in Scheme 3. In these cases, reaction

Scheme 3

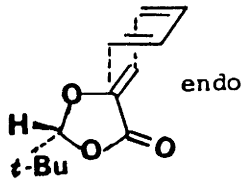


3. Seebach, D.; Naef, R.; Calderari, G. Tetrahedron 1984, 40, 1313.

occurs preferentially on the face shielded only by the hydrogen atom. The diastereoselectivities for all the cases reported were greater than 95%. Given this precedent, we believed that Diels-Alder reactions of 1 should also show excellent facial selectivity. Since, however, mixtures



12



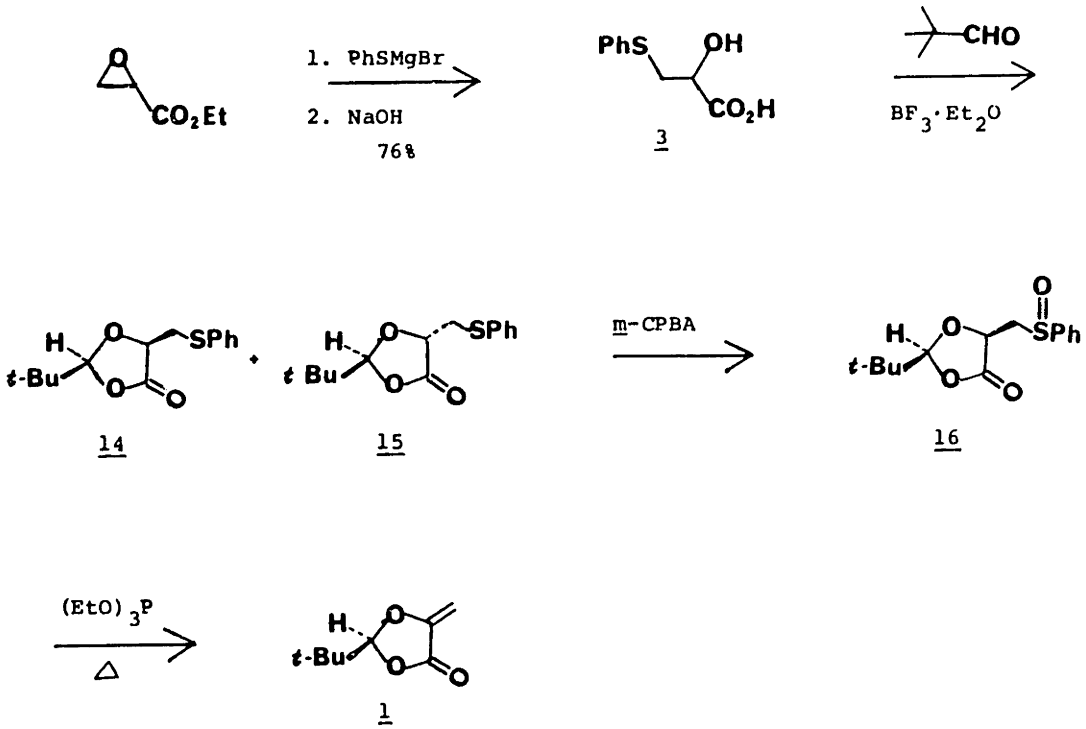
13

of endo and exo products are often obtained in the Diels-Alder reactions with α-heterosubstituted acrylates,[1,4] it was important to study the reactions of 1 with several representative dienes.

Racemic 1 was synthesized as outlined in Scheme 4. Treatment of ethyl glycidate[5] with PhSMgBr in THF followed by alkaline ester hydrolysis afforded 3 in 76% overall yield.[6] The synthesis of 1,3-dioxolan-4-ones by condensation of aldehydes (or acetals) with α-hydroxy

4. Creary, X.; Inocencio, P.A.; Underiner, T.L.; Kostromin, R. J. Org. Chem. 1985, 50, 1932.
5. Farines, M.; Soulier, J. Bull. Soc. Chim. Fr. 1970, 332.
6. This procedure was performed by Dr. Masanori Kageyama in our laboratories.

Scheme 4



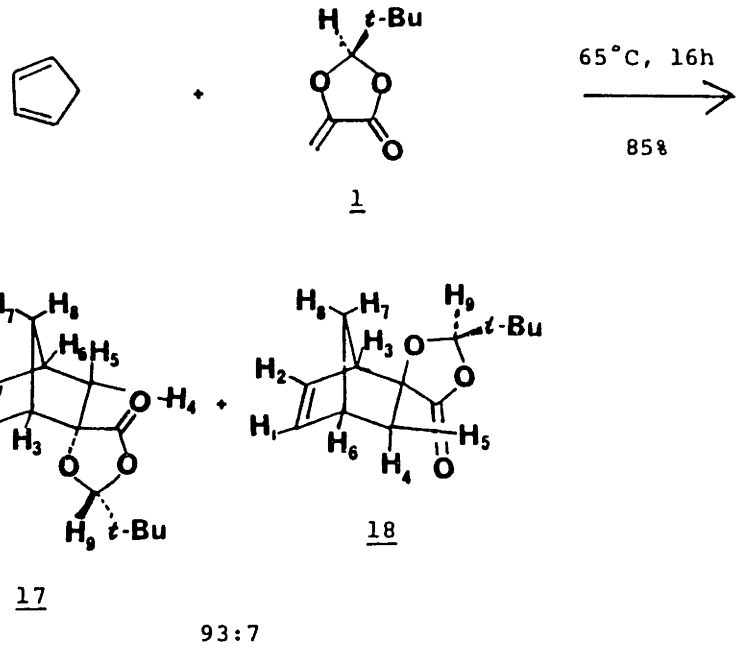
acids is a well established synthetic method.[3,5,7] We chose to condense pivalaldehyde with α-hydroxy acid 3 at 0°C in the presence of boron trifluoride etherate.[5] This procedure gave a 93:7 mixture of 1,3-dioxolan-4-ones 14 and 15 in 87% yield. An identical mixture was obtained when the diethyl acetal of pivalaldehyde was used. The major product, 14, assigned cis stereochemistry by literature analogy, was

7. Asabe, Y.; Takitani, S.; Tsuzuki, Y. Bull. Chem. Soc. Jpn. 1975, 48, 966.

easily separated from the mixture by recrystallization from ether/pentane. The sulfide 14 was then oxidized to the sulfoxide 16 in 93% yield by using *m*-CPBA at -78°C. The sulfoxide elimination step proceeded smoothly by analogy to Dr. Kageyama's example (Scheme 1), but isolation of 1 was problematic due to its volatility and acid sensitivity. The cleanest samples of 1 were obtained by heating a solution of sulfoxide 16 in dry benzene at reflux in the presence of two equivalents of triethyl phosphite (as a thiophile). The crude product was then purified by chromatography to give 1 in 32% yield. This compound was either used immediately or stored at -20°C to prevent decomposition.

With chiral dienophile 1 in hand, we proceeded to explore its Diels-Alder reaction with cylopentadiene as summarized in Scheme 5. This reaction was performed in dry benzene at 0.2 M with respect to the dienophile and with six equivalents of cyclopentadiene in a sealed Carius tube at 65°C. When the reaction was performed at 45°C, no cycloadduct was detected by gas chromatography after 6 h. The progress of the reaction was monitored by gas chromatography. After 6 h, additional cyclopentadiene was added because the rate of dimerization of cyclopentadiene at this temperature is competitive with its rate of reaction with 1 and considerable dicyclopentadiene was detected by gas chromatography. Analysis of the reaction product by ^{1}H NMR revealed that two cycloadducts, 17 and 18, were produced in a ratio of 93:7,

Scheme 5



respectively. The NMR analysis was easily performed at 250 MHz by integrating the characteristic resonances summarized in Table 1.

Table 1

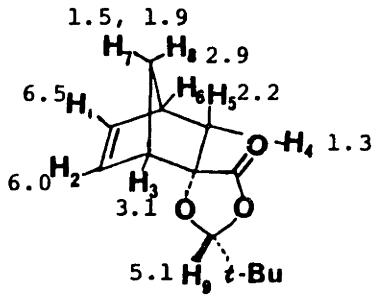
Characteristic ^{1}H NMR Data of Cycloadducts 17 and 18

Proton Assignments	17	18
H_1	6.43	6.39
H_2	6.06	5.96
H_9	5.13	5.18

Analysis of the product mixture by capillary gas chromatography (SE-54 column, 50 meters long) also gave a product ratio of 93:7. Purification of the reaction mixture by chromatography gave a 93:7 mixture of 17 and 18 (inseparable) in 85% yield.

The stereochemistry of the acetal center of the major cycloadduct 17 was determined as follows. A two dimensional COSY spectrum was obtained in order to establish the proton assignments summarized in

Scheme 6



17

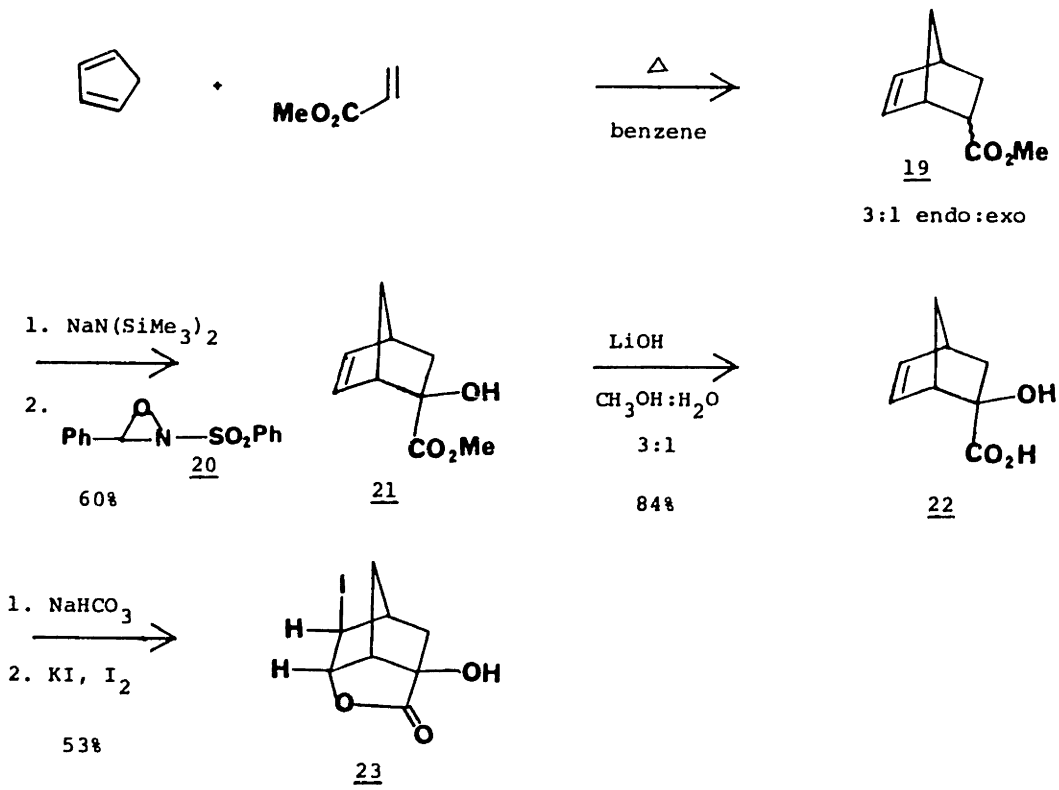
Coupling Constants

$J_{1,2}$ = 5.6 Hz
$J_{1,6}$ = 3.0 Hz
$J_{2,3}$ = 3.0 Hz
$J_{5,6}$ = 3.5 Hz
$J_{7,8}$ = 9.1 Hz
$J_{4,5}$ = 12.5 Hz
$J_{4,6}$ = 3.9 Hz

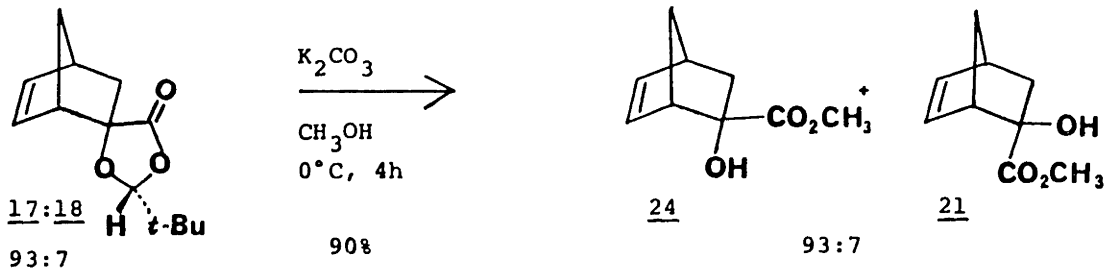
Scheme 6. A difference NOE experiment was then performed by irradiating the acetal proton (H_9). Enhancement (approximately 12%) of H_3, but not H_4 or H_5, was observed, thereby establishing that the acetal stereochemistry is as shown in Scheme 6.

To establish that 17 was, in fact, an exo cycloadduct, as shown in Schemes 5 and 6, an independent structure proof was performed as summarized in Schemes 7 and 8. An authentic sample of endo carboxylic

Scheme 7



Scheme 8



acid 22 was synthesized as shown in Scheme 7 starting from the known 3:1 endo:exo mixture of 19.[8] Hydroxylation of the sodium enolate of 19 was effected by using 2-(phenylsulfonyl)-3-phenyloxaziridine (20) as the oxidant.[9,10] Alkaline hydrolysis of 21 then provided 22 in 84% yield, the stereochemistry of which was established by conversion to iodolactone 23. Methanolysis of the 93:7 mixture of Diels-Alder adducts 17 and 18 gave a 93:7 mixture of 24 and 21 in 90% yield (Scheme 8), thus establishing that 24 is in fact an exo cycloadduct.

8. Nakagawa, K.; Ishii, Y.; Ogawa, M. Chem. Lett. 1976, 5, 511.
9. (a) Davis, F.A.; Vishwakarma, L.C.; Billmers, J.M.; Finn, J. J. Org. Chem. 1984, 49, 3241. (b) Davis, F.A.; Lamendola, J. Jr.; Nadir, U.; Kluger, E.W.; Sedergran, T.C.; Panunto, T.W.; Billmers, R.; Jenkins, R. Jr.; Turchi, I.J.; Watson, W.H.; Chen, J.S.; Kimura, M. J. Am. Chem. Soc. 1980, 102, 2000. (c) Davis, F.A.; Stringer, O.D. J. Org. Chem. 1982, 47, 1774.
10. Evans, D.A.; Morrissey, M.M.; Dorow, R.L. J. Am. Chem. Soc. 1985, 107, 4346.

Now that we identified 17 as an exo Diels-Alder adduct and assigned the relative configuration at the acetal carbon, we turned to exploring the reactivity of 1 with other dienes. Attempts were made to accomplish Diels-Alder reactions with cyclohexadiene and isoprene. These reactions were performed in benzene (0.2 M) at temperatures up to 150°C for 43 h (sealed tubes). Reaction products, however, could not be detected by gas chromatography analysis; only starting materials were present. Preliminary attempts to use Lewis acid catalysis also proved fruitless. No products were detected in experiments using zinc chloride or ethylaluminum dichloride at -78°C to 23°C for up to 89 hours; the dienophile, however, was recovered. In spite of these negative results, further work should be performed to see if a suitable set of reaction conditions can be developed.

The dienophilic reactivity of 1 appears to be on the low side. Of the three systems studied, reaction was seen only with cyclopentadiene. Cyclopentadiene, which dimerizes with a half-life of 25 h at 25°C,[11] is a much more reactive diene than cyclohexadiene, which dimerizes only under much more strenuous conditions (200°C, 24 h).[12] It appears, therefore, that this difference in reactivity is sufficient to preclude rapid reaction of cyclohexadiene or isoprene with 1. The reactivity of

11. Rammash, B.Kh.; Gladstone, C.M.; Wong, J.L. J. Org. Chem. 1981, 46, 3036.
12. Valentine, D.; Turro, N.J. Jr.; Hammond, G.S. J. Am. Chem. Soc. 1964, 86, 5202.

1 with cyclopentadiene is also on the borderline of acceptability since cyclopentadiene dimerizes at a rate competitive with its reaction with 1.

In conclusion, dienophile 1 undergoes a thermal Diels-Alder reaction with excess cyclopentadiene in high yield (85%), with excellent facial selectivity (only one isomer is formed), and with high exo selectivity (93:7 exo:endo). Preliminary results indicate, however, that 1 suffers from low reactivity. Further studies on the Lewis acid catalyzed reaction of 1 with less reactive dienes are needed to determine whether this reagent is suitable for use in synthesis as a chiral ketene equivalent.

Chapter 4

Proton (^{1}H) NMR spectra were measured at 250 and 270 MHz on Bruker 250 and 270 instruments and at 400 MHz on a Varian XL-400 instrument. Chemical shifts are reported in δ units using the 7.24 ppm resonance of residual chloroform as internal reference. ^{19}F NMR spectra were measured at 376 MHz on the Varian XL-400 instrument. Infrared spectra were measured on Perkin-Elmer Model 283B or 237B Infrared Spectrophotometers and were calibrated with the 1601 cm^{-1} absorption of polystyrene. IR spectra are reported in wave numbers (cm^{-1}). Optical rotations were measured on a Rudolph Autopol III Automatic Polarimeter using a 1 cm^3 quartz cell (10 cm path length). Low and high resolution mass spectra were measured at 70 eV on a Finnegan MAT 8200 instrument. Melting points were recorded on a Fisher-Johns hot stage melting point apparatus or a Thomas Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Robertson Laboratory, Inc. of Florham Park, New Jersey.

Capillary GC analyses were performed on a Hewlett-Packard Model 5890 Gas Chromatograph equipped with a Hewlett-Packard Model 3392A Integrator. These analyses were performed on Alltech SE-54 (0.2 mm x 50 m) fused silica columns using helium as carrier gas (1 mL/min flow rate and 100:1 split ratio). Packed column GC analyses were performed on a Perkin-Elmer Sigma 3 Model Gas Chromatograph using a 10% SE-30 on Chrom G column (0.25 in x 10 ft) with nitrogen as carrier gas.

All reactions were conducted in oven dried (125°C) or flame dried glassware under atmospheres of dry argon. All solvents were purified before use. Ether, THF, benzene and toluene were distilled from sodium

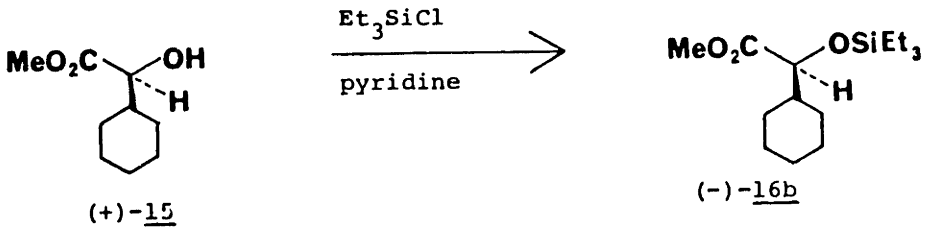
benzophenone ketyl. Methylene chloride, acetonitrile and pyridine were distilled from CaH_2.

Analytical thin layer chromatography (TLC) was performed by using 2.5 cm x 10 cm plates coated with 0.25-mm thickness of silica gel containing PF 254 indicator (Analtech). Preparative thin layer chromatography (PTLC) was performed by using 20 cm x 20 cm plates coated with 0.25- or 0.5-mm thicknesses of silica gel containing PF 254 indicator (Analtech). Compounds were visualized either by short-wave UV light, staining with iodine vapor or charring with ethanolic H_2SO_4. Compounds were eluted from the adsorbents with ether or ethyl acetate. Flash column chromatography was performed by using Kieselgel 60 (230-400 mesh) or Kieselgel 60 (70-230 mesh) as described by Still[1]. All chromatography solvents were distilled prior to use.

1. Still, W.C.; Kahn, M.; Mitra, A. J. Org. Chem. 1978, 43, 2923.

Experimental Procedures

Part A: Experimentals For Chapter 2

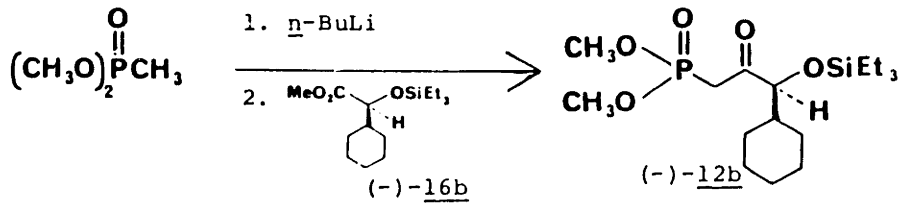


(+)-15 (-)-16b

Methyl (S)-[(Triethylsilyl)oxy]hexahydromandelate (16b)

A solution of 5.82 g (33.8 mmol) of methyl hexahydromandelate in 75 mL of pyridine was treated with 11.4 mL (10.2 g, 67.6 mmol) of chlorotriethylsilane. A white precipitate formed within minutes. The mixture was gently heated in a 60°C oil bath for 20 h. The reaction mixture was then diluted with methylene chloride and washed repeatedly with aqueous 1N HCl. The organic extracts were passed through a cotton plug and concentrated *in vacuo*. The residue was diluted with heptane and again concentrated to remove residual pyridine, yielding 13.0 g of crude product. This compound was purified by flash column chromatography using 9:1 hexane-ether as eluant (R_f 0.75) to yield 9.67g (99% yield) of pure 16b.

Data for 16b: $[\alpha]_D^{25}$ -28.5° (c = 1.25, $CHCl_3$); NMR (250 MHz, $CDCl_3$) δ 3.93 (d, J = 5.5 Hz, 1H), 3.69 (s, 3H), 1.76-1.45 (m, 6H), 1.30-1.00 (m, 5H), 0.92 (t, J = 7.8 Hz, 9H), 0.58 (q, J = 7.8 Hz, 6H); IR (neat) 2920, 2865, 1760, 1740, 1450 cm^{-1}; mass spectrum, m/e 257 (M-29); high resolution mass spectrum, calcd for $C_{13}H_{25}O_3Si$ 257.1573, found 257.1573 $\pm$ 0.0005.

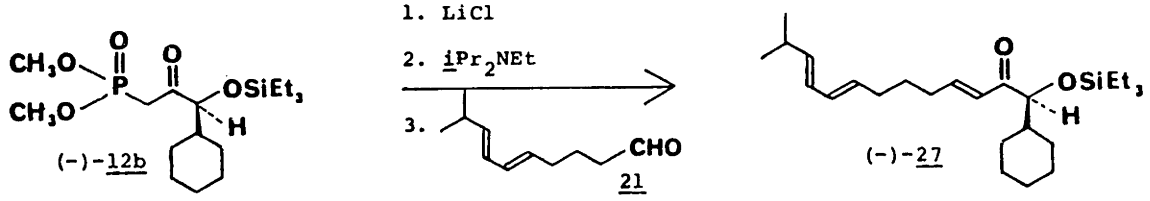


(S)-3-Cyclohexyl-1-(dimethoxyphosphinyl)-3-[(triethylsilyl)oxy]-2-propanone (12b)

To a -78°C solution of 9.18 g (8.0 mL, 74.0 mmol) of dimethyl methylphosphonate in 60 mL of dry tetrahydrofuran was added a 2.1 M solution of *n*-BuLi in hexane (32.5 mL, 68.3 mmol) at a rate such that a temperature below -70°C was maintained. A solution of 8.15 g (28.4 mmol) of ester (-)-16b in 60 mL of dry tetrahydrofuran was then added dropwise. The solution was stirred at -70°C for one hour and then was warmed to -20°C and stirred for an additional 1.5 h. Saturated aqueous NH_4Cl solution was added, and the mixture was allowed to warm to room temperature. At this point it was diluted with ether and washed quickly with aqueous 1N HCl. The aqueous layer was back extracted twice with ether. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give 8.89 g of crude 12b. This material was purified by flash column chromatography using 2:1 ether-hexane as eluant (R_f 0.15 (1:1 ether-hexane)) to give 8.07 g (75%) of (-)-12b as a colorless liquid.

Data for (-)-12b: $[\alpha]_D^{20}$ -11.9° (c = 2.13, $CHCl_3$); NMR (250 MHz, $CDCl_3$) δ 3.80 (d, partially obscured by -OMe, 1H), 3.78 (d, J = 2.7 Hz,

3H), 3.74 (d, J = 2.9 Hz, 3H), 3.18 (ABX, J_{AB} = 15.9 Hz, J_{AX} = 19.5 Hz, J_{BX} = 21.5 Hz, 2H), 1.65 (m, 6H), 1.10 (m, 5H), 0.92 (t, J = 7.8 Hz, 9H), 0.57 (q, J = 7.8 Hz, 6H); IR (neat) 2920, 1720, 1445, 1255, 1020 cm^{-1}; mass spectrum, m/e 378 (parent ion); high resolution mass spectrum, calcd for $C_{15}H_{30}O_5PSi$ 349.1600, found 349.1599 $\pm$ 0.0005.



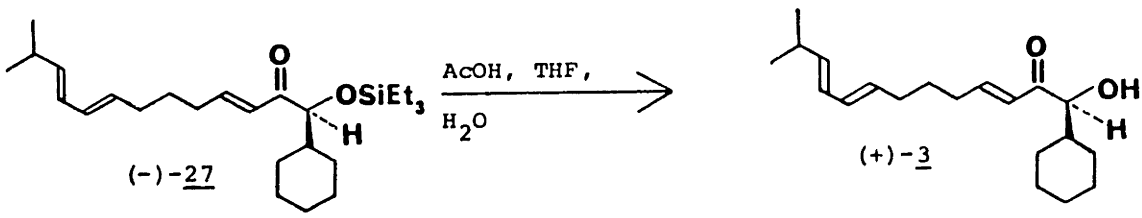
(S)-1-Cyclohexyl-12-methyl-1-[(triethylsilyl)oxy]trideca-3(E),8(E),10(E)-trien-2-one ((-)-27)

To a solution of 70.1 mg (1.67 mmol) of anhydrous LiCl in 6 mL of dry acetonitrile was added 631 mg (1.67 mmol) of phosphonate (-)-12b in 6 mL of dry acetonitrile. The mixture was stirred for 15 minutes and then 264 μL (196 mg, 1.52 mmol) of diisopropylethylamine was added, followed, 30 min later, by a solution of 252 mg (1.52 mmol) of aldehyde 21[2] in 3 mL of dry acetonitrile. After being stirred at room temperature for 24 h the mixture was diluted with ether. The precipitate was filtered and washed with ether. The combined filtrate was evaporated *in vacuo* yielding 948 mg of crude product which was purified by flash column chromatography using 6:1 hexane-ether as eluant (R_f 0.67 (6:1 hexane-ether)) to give 445 mg (70%) of triene (-)-27 as a pale yellow oil.

Data for (-)-27: $[\alpha]_D^{20}$ -48.0° (c = 1.15, $CHCl_3$); NMR (250 MHZ, $CDCl_3$) δ 6.94 (dt, J = 15.7, 6.9 Hz, 1H), 6.51 (d, J = 15.7 Hz, 1H), 5.94 (m, 2H), 5.54 (m, 2H), 3.77 (d, J = 6.2 Hz, 1H), 2.22 (m, 3H), 2.07

2. Roush, W.R.; Gillis, H.R.; Ko, A.I. J. Am. Chem. Soc. 1982, 104, 2269.

(q, J = 7.1 Hz, 2H), 1.80-1.05 (m, 13H), 0.97 (d, J = 6.7 Hz, 6H), 0.91 (t, J = 7.9 Hz, 9H), 0.55 (q, J = 7.9 Hz, 6H); IR (neat) 2940, 1690, 1620, 1450, 1240, 1100, 1005, 985 cm^{-1}; mass spectrum, m/e 418 (parent ion); high resolution mass spectrum, calcd for $C_{26}H_{46}O_2Si$ 418.3267, found 418.3269 $\pm$ 0.0006.

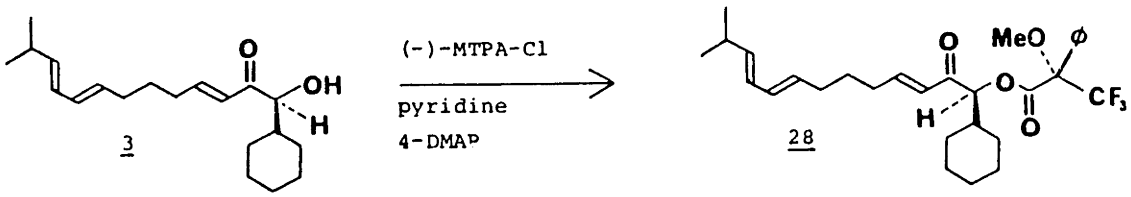


(-)-27 (+)-3

(S)-1-Cyclohexyl-1-hydroxy-12-methyltrideca-3(E),8(E),10(E)-trien-2-one ((+)-3)

The silylated triene (-)-27 (2.66 g, 6.37 mmol) was dissolved in 39 mL of a 3:1:1 mixture of acetic acid, tetrahydrofuran and water. This solution was stirred at room temperature for 6 h. The solvent was then evaporated *in vacuo* and the residue was concentrated repeatedly from heptane to azeotrope residual acetic acid and water. This afforded 1.89 g (98%) of chromatographically homogeneous (+)-3 which was somewhat unstable towards chromatography.

Data for (+)-3: R_f 0.42 (6:1 hexane-ether); $[\alpha]_D^{20}$ +65.5° (c = 1.15, $CHCl_3$); NMR (250 MHz, $CDCl_3$) δ 7.00 (dt, J = 15.6, 6.9 Hz, 1H), 6.23 (d, J = 15.6 Hz, 1H), 5.97 (m, 2H), 5.54 (m, 2H), 4.17 (dd, J = 5.4, 2.4 Hz, 1H), 3.46 (d, J = 5.4 Hz, 1H), 2.25 (m, 3H), 2.08 (q, J = 7.2 Hz, 2H), 1.85-1.10 (m, 13H), 0.98 (d, J = 6.7 Hz, 6H); IR (neat) 3470, 2930, 2860, 1685, 1625, 1450, 985 cm^{-1}; mass spectrum, m/e 304 (parent ion); high resolution mass spectrum, calcd for $C_{20}H_{32}O_2$ 304.2402, found 304.2402 $\pm$ 0.0004.

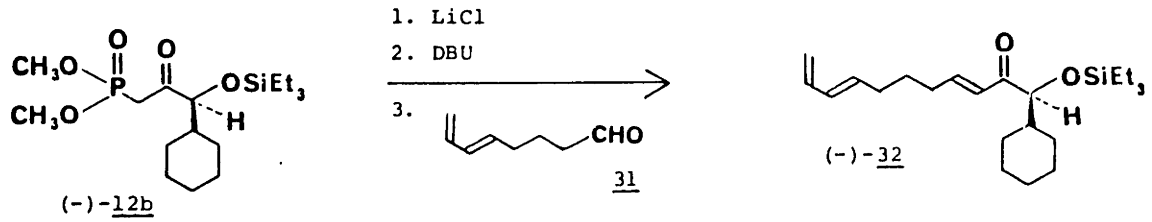


3 28

Optical Purity Determination of (+)-3

Alcohol (+)-3 and its racemate were esterified with (-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, pyridine and a catalytic amount of 4-DMAP in methylene chloride.[3] The enantiomeric excess of (+)-3 was determined to be >97% by integration of the olefinic proton adjacent to the ketone in the diastereomeric esters [$\delta_{(S,S)}$ = 6.25 (d, J = 15.9 Hz), $\delta_{(R,S)}$ = 6.18 (d, J = 15.8 Hz)] in the 250 MHz NMR spectrum.

3. Mosher, H.S.; Dale, J.A.; Dull, D.L. J. Org. Chem. 1969, 34, 2543.

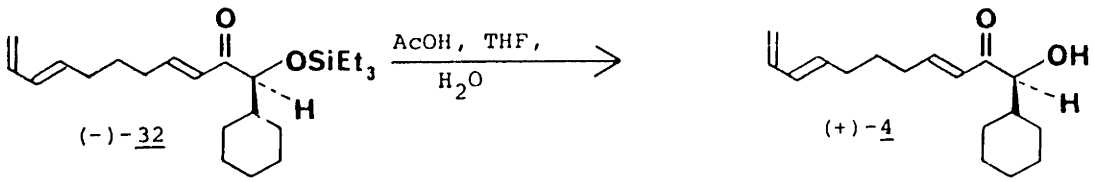


(S)-1-Cyclohexyl-1-[(triethylsilyl)oxy]-undeca-3(E),8(E),10-trien-2-one ((-)-32)

A mixture of lithium chloride (12 mg, 0.28 mmol) and phosphonate (-)-12b (104 mg, 0.28 mmol) in 1 mL of dry acetonitrile was stirred for 15 minutes at room temperature. 1,5-Diazabicyclo[5.4.0]undec-5-ene (38 mg, 0.038 mL, 0.250 mmol) was then added dropwise via syringe. Thirty minutes later a solution of freshly distilled aldehyde 31[2] (31 mg, 0.250 mmol) in 1 mL of dry acetonitrile was added dropwise. The mixture was stirred for 21 h and then was worked up as described for the preparation of triene (-)-27. Purification of the crude product (175 mg) by flash column chromatography using 6:1 hexane-ether as an eluant then gave 55 mg (58%) of pure triene (-)-32 as a colorless oil.

Data for (-)-32: R_f 0.74 (6:1 hexane-ether); $[\alpha]_D^{20}$ -50.2° (c = 0.75, $CHCl_3$); NMR (250 MHz, $CDCl_3$) δ 6.94 (dt, J = 15.6, 7.0 Hz, 1H), 6.52 (d, J = 15.6 Hz, 1H), 6.29 (dt, J = 16.9, 10.3 Hz, 1H), 6.03 (dd, J = 15.1, 10.3 Hz, 1H), 5.65 (m, 1H), 5.08 (d, J = 16.8 Hz, 1H), 4.95 (d, J = 9.9 Hz, 1H), 3.77 (d, J = 6.3 Hz, 1H), 2.21 (br q, J = 6.9 Hz, 2H), 2.09 (br q, J = 7.2 Hz, 2H), 1.75-0.99 (m, 13H), 0.91 (t, J = 7.8 Hz, 9H), 0.55 (q, J = 7.8 Hz, 6H); IR (neat) 2960, 2910, 2890, 1685, 1620,

1450, 1080 cm^{-1}; mass spectrum, m/e 376 (parent ion); high resolution mass spectrum, calcd for $C_{23}H_{40}O_2Si$ 376.280, found 376.281 $\pm$ 0.001.

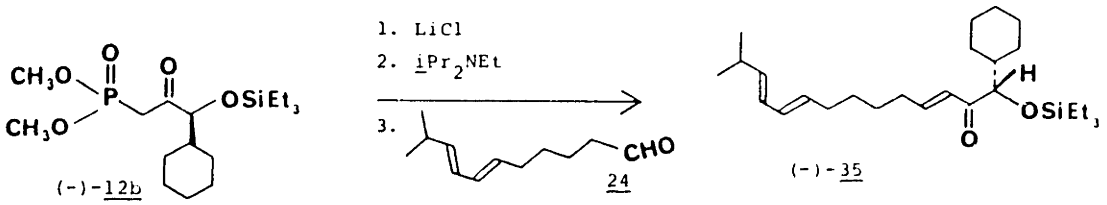


(-)-32 (+)-4

(S)-1-Cyclohexyl-1-hydroxyundeca-3(E),8(E),10-trien-2-one ((+)-4)

A solution of silylated triene (-)-32 (79 mg, 0.21 mmol) in 8 mL of a 3:1:1 acetic acid : tetrahydrofuran : water mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated *in vacuo* and the residue was repeatedly concentrated from heptane to remove the residual acetic acid and water (azeotrope). Triene alcohol (-)-32 was obtained in quantitative yield (55 mg) as a colorless oil. This triene was used immediately due to its instability.

Data for (-)-32: R_f 0.30 (6:1 hexane-ether); $[\alpha]_D^{20}$ +94.1° (c = 0.135, $CHCl_3$); NMR (250 MHz, $CDCl_3$) δ 7.01 (dt, J = 15.6, 6.9 Hz, 1H), 6.29 (dt [superimposed on δ 6.23], J = 16.9, 10.3 Hz, 1H), 6.23 (d [superimposed on δ 6.29], J = 15.6 Hz, 1H), 6.04 (dd, J = 15.0, 10.3 Hz, 1H), 5.64 (m, 1H), 5.09 (d, J = 16.9 Hz, 1H), 4.97 (d, J = 10.4 Hz, 1H), 4.18 (d, J = 2.5 Hz, 1H), 2.25 (br q, J = 6.9 Hz, 2H), 2.11 (br q, J = 7.2 Hz, 2H), 1.81-1.06 (m, 13H); IR (CH_2Cl_2) 3465, 2935, 2860, 1685, 1660, 1620, 1450 cm^{-1}; mass spectrum, m/e 262 (parent ion).



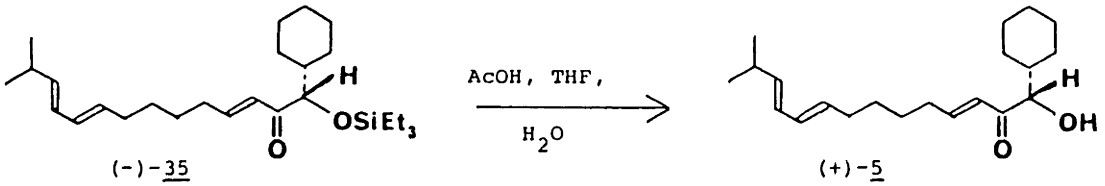
(S)-1-Cyclohexyl-13-methyl-1-[(triethylsilyl)oxy]-tetradeca-3(E),9(E),11(E)-trien-2-one ((-)35)

A solution of 764 mg (2.02 mmol) of phosphonate (-)-12b in 10 mL of dry acetonitrile was added to lithium chloride (85 mg, 2.02 mmol) in 10 mL of dry acetonitrile and the resulting mixture was stirred for 15 minutes. Diisopropylethylamine (237 mg, 0.32 mL, 1.84 mmol) was added followed, 30 min later, by a solution of 331 mg (1.84 mmol) of aldehyde 24[4] in 4 mL of dry acetonitrile. The reaction mixture was stirred for 24 h at room temperature and then was diluted with ether. The solution was filtered and the precipitate was washed with ether. The combined filtrates were concentrated *in vacuo* yielding 1.51 g of crude product. The pure triene (434 mg, 55% yield) was isolated by flash column chromatography (6:1 hexane-ether, R_f 0.83).

Data for (-)-35: $[\alpha]_D^{20}$ -42.0° (c = 0.95, $CHCl_3$); NMR (250 MHz, $CDCl_3$) δ 6.94 (dt, J = 15.6, 6.9 Hz, 1H), 6.51 (d, J = 15.6 Hz, 1H), 5.95 (m, 2H), 5.53 (m, 2H), 3.78 (d, J = 6.2 Hz, 1H), 2.26 (m, 3H), 2.05 (br q, J = 6.9 Hz, 2H), 1.76-1.00 (m, 15H), 0.97 (d, J = 6.8 Hz, 6H), 0.91 (t, J = 7.8 Hz, 9H), 0.55 (q, J = 7.8 Hz, 6H); IR (neat) 2950,

4. Roush, W.R.; Gillis, H.R. J. Org. Chem. 1982, 47, 4825.

1675, 1620, 1430 cm^{-1}; mass spectrum, m/e 432 (parent ion); high resolution mass spectrum, calcd for $C_{27}H_{48}O_2Si$ 432.3423, found 432.3425 $\pm$ 0.0004.

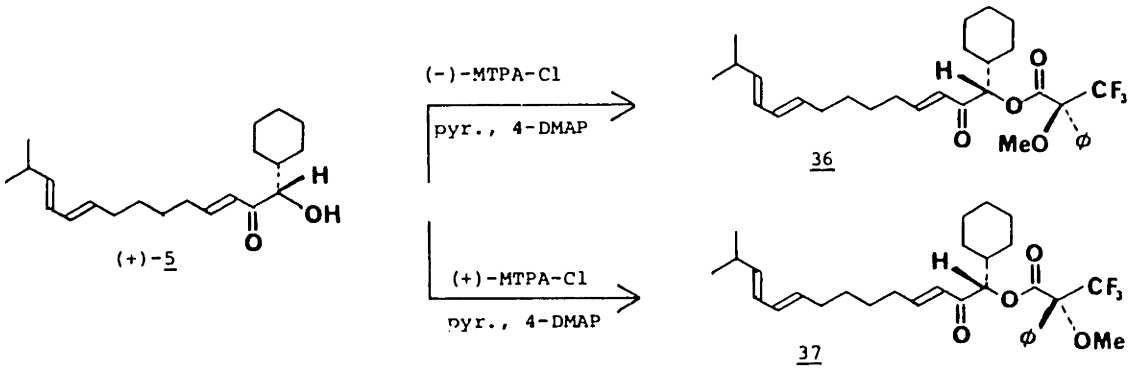


(-)-35 (+)-5

1-Cyclohexyl-1-hydroxy-13-methyltetradeca-3(E),9(E),11(E)-trien-2-one ((+)-5)

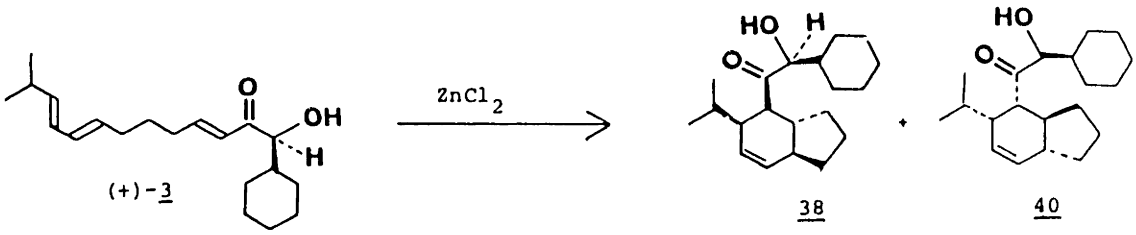
A solution of 680 mg (1.57 mmol) of silylated triene (-)-35 in 70 mL of a 3:1:1 acetic acid : tetrahydrofuran : water mixture was stirred at room temperature for 4.5 h. The mixture was concentrated *in vacuo* and then was repeatedly evaporated from heptane to remove residual acetic acid and water. This work up produced 493 mg (99%) of triene alcohol (+)-5. This compound is not stable at room temperature and was stored under argon at -20°C.

Data for (+)-5: R_f 0.35 (6:1 hexane-ether); $[\alpha]_D^{20}$ +66.3° (c = 1.17, $CHCl_3$); NMR (250 MHz, $CDCl_3$) δ 6.98 (dt, J = 15.5, 7.0 Hz, 1H), 6.21 (d, J = 15.5 Hz, 1H), 5.93 (m, 2H). 5.51 (m, 2H), 4.15 (dd, J = 5.5, 2.5 Hz, 1H), 3.47 (d, J = 5.5 Hz, 1H), 2.24 (m, 3H), 2.03 (br q, J = 7.0 Hz, 2H), 1.78-1.04 (m, 15H), 0.95 (d, J = 6.7 Hz, 6H); IR (neat) 3500, 2950, 2870, 1695, 1635, 1460 cm^{-1}; mass spectrum, m/e 318 (parent ion); high resolution mass spectrum, calcd for $C_{21}H_{34}O_2$ 318.2559, found 318.2561 $\pm$ 0.0006.



Optical Purity Determination of Triene (+)-5

Alcohol (+)-5 was esterified using both (-)- and (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. The methine proton adjacent to the ester group [-CH(OMTPA)-] had different chemical shifts in the two diastereomeric esters (δ(36) 5.17 (d, J = 5 Hz) and δ(37) 5.12 (d, J = 5 Hz)). By integration of the 250 MHz NMR spectra, the optical purity of alcohol (+)-5 was determined to be 98% e.e..



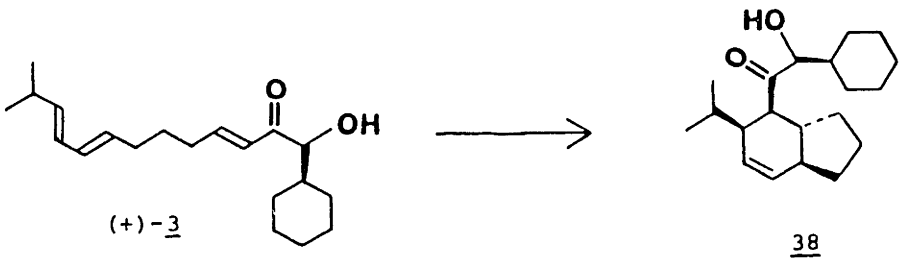
ZnCl$_2$ Catalyzed Intramolecular Diels-Alder Reaction of (+)-3

A solution of 50 mg (0.165 mmol) of triene alcohol (+)-3 in 3 mL of dry methylene chloride was cooled to 0°C. Freshly fused, anhydrous zinc chloride (21 mg, 0.156 mmol) was added as a solid. The reaction mixture was stirred and allowed to slowly warm to room temperature over 1 h. After being stirred at room temperature for 24 h the reaction mixture was diluted with ether and saturated aqueous $NaHCO_3$ solution (1 mL) . This mixture was stirred for 1 h, then solid Na_2SO_4 was added and stirring was continued for another hour. The reaction mixture was filtered, solids were washed with ether, and the filtrate was evaporated *in vacuo*. The crude mixture, which contained cycloadduct, a trace of starting material and some triene derived material, was applied to a 0.5-mm silica gel preparative plate and developed using 6:1 hexane-ether. A wide band, essentially everything above the UV band at R_f 0.42 (residual triene (+)-3), was isolated, giving 35 mg (70%) of cycloadduct 38, as a white solid. This material was recrystallized from hexane to give diastereomerically pure 38 in 72-79% yield (up to 55% yield from (+)-3).

Data for 38: R_f 0.58 (6:1 hexane-ether); mp 137-138°C; $[\alpha]_D^{20}$ -75.5° (c = 0.41, $CHCl_3$); NMR (250 MHz, $CDCl_3$) δ 5.99 (d, J = 10.0 Hz, 1H), 5.55 (br d, J = 10.0 Hz, 1H), 4.14 (dd, J = 6.2, 2.0 Hz, 1H), 3.42 (d, J = 6.2 Hz, 1H), 3.00 (dd, J = 10.6, 7.7 Hz, 1H), 2.63 (m, 1H), 2.00-1.10 (m, 20H), 0.92 (d, J = 6.9 Hz, 3H), 0.76 (d, J = 6.7 Hz, 3H); IR (CH_2Cl_2) 3680, 3480, 2925, 2855, 1700, 1635 cm^{-1}; mass spectrum, m/e 304 (parent ion); high resolution mass spectrum, calcd for $C_{20}H_{32}O_2$ 304.2402, found 304.2403 $\pm$ 0.0006.

The mother liquors from the recrystallization (21-28% of total product) were predominantly 38 (93-97% pure), but also contained 3-7% of diastereomer 40. This compound had previously been isolated from the boron trifluoride etherate catalyzed cyclization of (+)-3 and also had been observed in the thermal cyclization of (+)-3.

Partial data for 40: R_f 0.49 (6:1 hexane-ether); NMR (250 MHz, $CDCl_3$) δ 3.85 (dd, J = 6, 3 Hz, 1H), 3.25 (d, J = 5 Hz, 1H), 3.05 (m, 1H), 0.90 (d, J = 7 Hz, 3H), 0.88 (d, J = 7 Hz, 3H).



(+)-3 → 38

General Procedure for $EtAlCl_2$, Et_2AlCl, and $BF_3 \cdot Et_2O$ Catalyzed Cyclizations of (+)-3

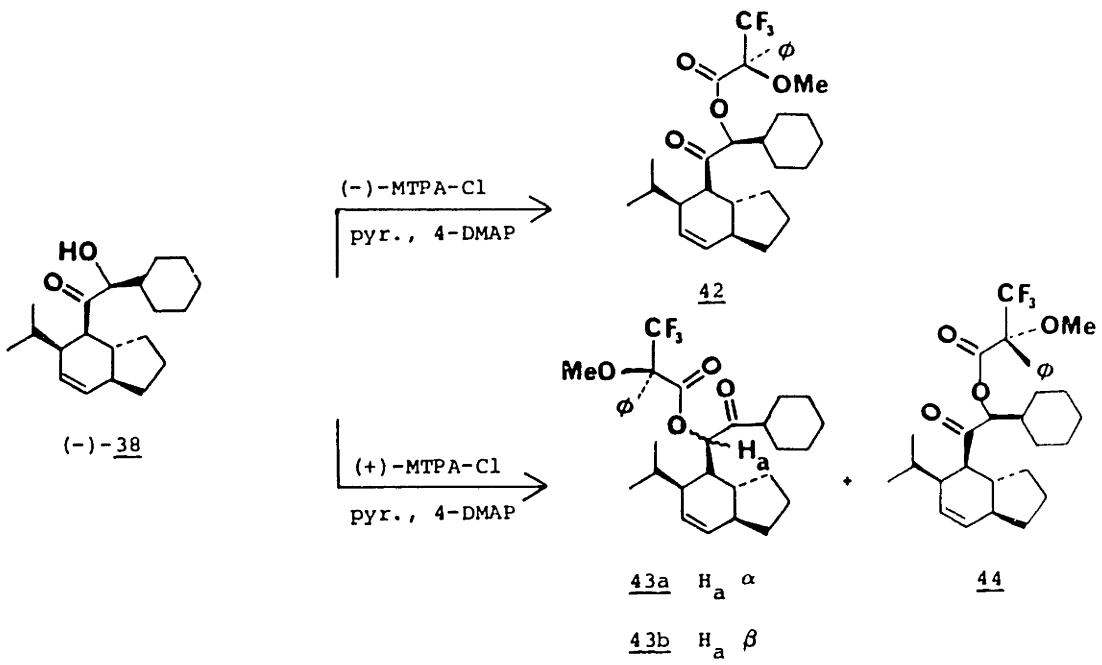
A solution of 50 mg (0.165 mmol) of (+)-3 in 3 mL of dry methylene chloride was cooled to -78°C. The appropriate Lewis acid (0.95 equivalent)[5] was added dropwise and the reaction mixture was gradually warmed to room temperature. After being stirred for 24 h, the reaction was diluted with ether and worked up by using the procedure described for the zinc chloride catalyzed reaction. The crude product was applied to a 0.5-mm silica gel preparative plate and developed using 6:1 hexane-ether (R_f 0.58). Reaction products were then isolated by taking a very wide band to insure that minor cycloadducts were not separated accidently. Results are summarized in Table 4, Chapter 2.

$EtAlCl_2$: Solution in hexane (0.11 mL, 0.16 mmol, 1.44 M); 65% yield.

Et_2AlCl: Solution in hexane (0.15 mL, 0.15 mmol, 1.0 M); 42% yield.

$BF_3 \cdot Et_2O$: 1:1 complex (0.02 mL, 0.16 mmol, 22 mg); 46% yield.

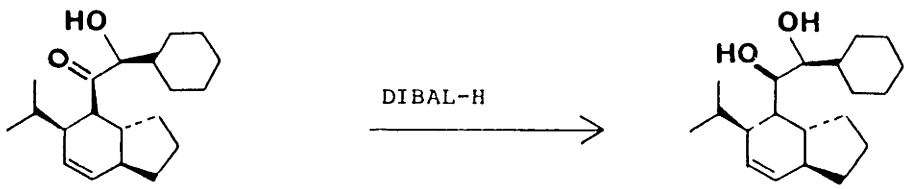
5. (a) $EtAlCl_2$ was used as a 1.44 M solution in hexane; (b) Et_2AlCl was used as a 1.0 M solution in hexane; (c) $BF_3 \cdot Et_2O$ was distilled before use and was added neat.



Optical Purity Determination of Cycloadduct (-)-38

Cycloadduct (-)-38 was derivatized with both (+)- and (-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. The reaction of (-)-38 with (-)-MTPA-Cl gave a single ester derivative that displayed the -CH(OMTPA)- resonance at δ 5.37 (d, J = 2.5 Hz). In contrast, the reaction of (-)-38 with (+)-MTPA-Cl gave three Mosher este derivatives with -CH(OMTPA)- resonances appearing at δ 5.02 (d, J = 3 Hz), 4.72 (d, J = 3 Hz), and 5.39 (d, J = 2.5 Hz). The resonances at δ 5.02 and 4.72 were equal in intensity and were greater individually than the signal at δ 5.39. By integrating these resonances, it could be established that recrystallized (-)-38 and also that appearing in the mother liquors was enantiomerically pure. The NMR spectra of the Mosher esters prepared using (-)-MTPA-Cl and either chromatographed or mother liquor samples of

(-)-38 also contained a resonance at δ 5.16 (d, J = 2.5 Hz) that was assigned to the -CH(OMTPA)- resonance of diastereomer 40. This signal was not seen when recrystallized (-)-38 was derivatized.

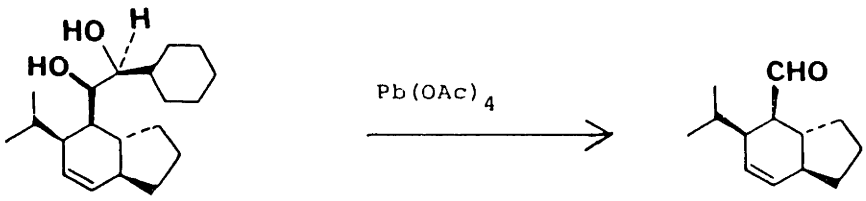


(-)-38 47

Diol 47

To a -78°C solution of 63 mg of recrystallized α-hydroxyketone (-)-38 (0.21 mmol) in 4 mL of dry ether was added 0.64 mL of a 0.97 M solution of diisobutylaluminum hydride in hexane (0.62 mmol). The reaction mixture was allowed to warm to room temperature and was stirred for 5 h before again being cooled to -78°C. The reaction was then quenched cautiously by the addition of methanol (1 mL) and aqueous 1N HCl (4 mL). The solution was extracted twice with ether, washed with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to give 47 (65 mg) in quantitative yield.

Data for 47: R_f 0.65 (1:1 hexane-ether); NMR (250 MHz, $CDCl_3$) δ 6.00 (br d, J = 9.5 Hz, 1H), 5.76 (br d, J = 9.5 Hz, 1H), 3.73 (m, 1H), 3.32 (br t, J = 6.6 Hz, 1H), 2.26 (br t, J = 6.5 Hz, 1H), 2.01-1.02 (m, 21H), 0.97 (d, J = 6.5 Hz, 3H), 0.94 (d, J = 6.3 Hz, 3H); IR (CH_2Cl_2) 3630, 2930, 2850, 1420, 1265, 990 cm^{-1}; mass spectrum, m/e 306 (parent ion); high resolution mass spectrum, calcd for $C_{20}H_{34}O_2$ 306.2559, found 306.2559 $\pm$ 0.0005.

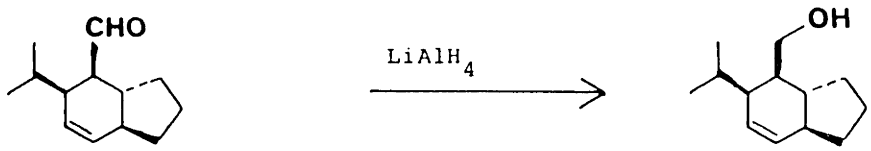


47 48

5β-(2-Propyl)-2,3,3aβ,4,5,7aα-hexahydroindene-4β-carboxaldehyde (48)

To a 0°C solution of 109 mg(0.25 mmol) of lead tetraacetate in 3 mL of dry methylene chloride was added dropwise a solution of crude diol 47 (65 mg, 0.21 mmol) in 1 mL of dry methylene chloride. The reaction was stirred for 10 minutes at 0°C and then was diluted with ether. Saturated aqueous $NaHCO_3$ solution (0.5 mL) was added and the reaction was warmed to room temperature and stirred for 1 h. The reaction mixture was then filtered, solids were washed with ether, and the filtrate was concentrated *in vacuo*. The residue (53 mg) was a pale yellow oil consisting of a 2:1 mixture of aldehyde 48 (R_f 0.60 (6:1 hexane-ether)) and cyclohexanecarboxaldehyde (R_f 0.56 (6:1 hexane-ether)). This mixture was used directly in the next step without purification.

Data for 48: NMR (250 MHz, $CDCl_3$) δ 9.83 (d, J = 3.0 Hz, 1H), 6.00 (d, J = 10.0 Hz, 1H), 5.60 (dt, J = 10.0, 2.8 Hz, 1H), 2.73 (m, 1H), 2.58 (ddd, J = 11.0, 7.8, 3.0 Hz, 1H), 2.03-1.03 (m, 9H), 0.98 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H); IR (CH_2Cl_2) 2960, 1685 cm^{-1}.



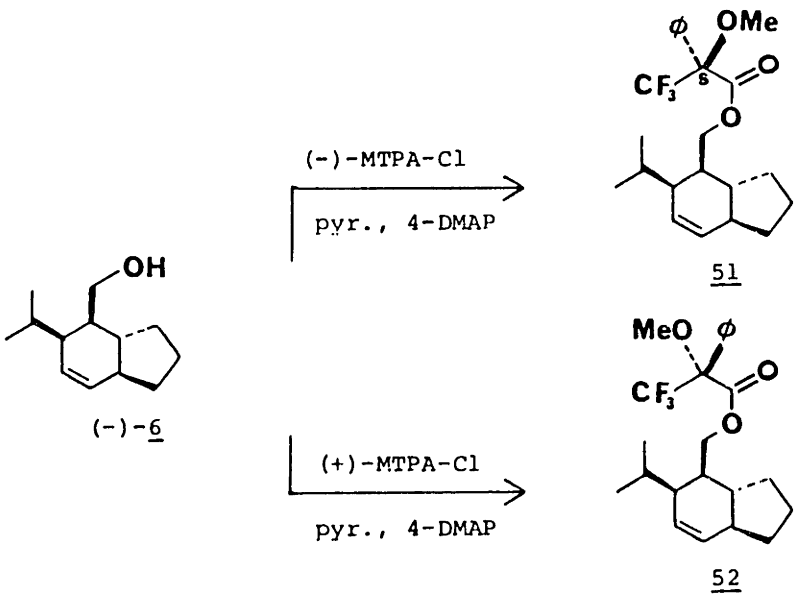
48 (-)-6

(-)-4β-(Hydroxymethyl)-5β-(2-propyl)-2,3,3aβ,4,5,7aα-hexahydroindene ((-)-6)

To a 0°C solution of lithium aluminum hydride (10 mg, 0.25 mmol) in 2 mL of dry ether was added dropwise a solution of aldehyde 48 (53 mg of a 2:1 mixture of aldehyde 48 and cyclohexanecarboxaldehyde) in 1 mL of dry ether. The reaction mixture was allowed to warm to room temperature and was stirred for 3.5 h. The reaction was cooled to 0°C, quenched with methanol, and diluted with aqueous 1N HCl. The mixture was extracted three times with ether, dried over Na_2SO_4 and filtered. Concentration of the ether extracts *in vacuo* produced 53 mg of a 2:1 mixture of alcohol (-)-6 and cyclohexylmethanol. Pure (-)-6 was isolated by chromatography on a 0.5-mm silica gel preparative plate developed in 1:1 hexane-ether. The band at R_f 0.57 yielded 23.5 mg of pure (-)-6 (59% overall yield).

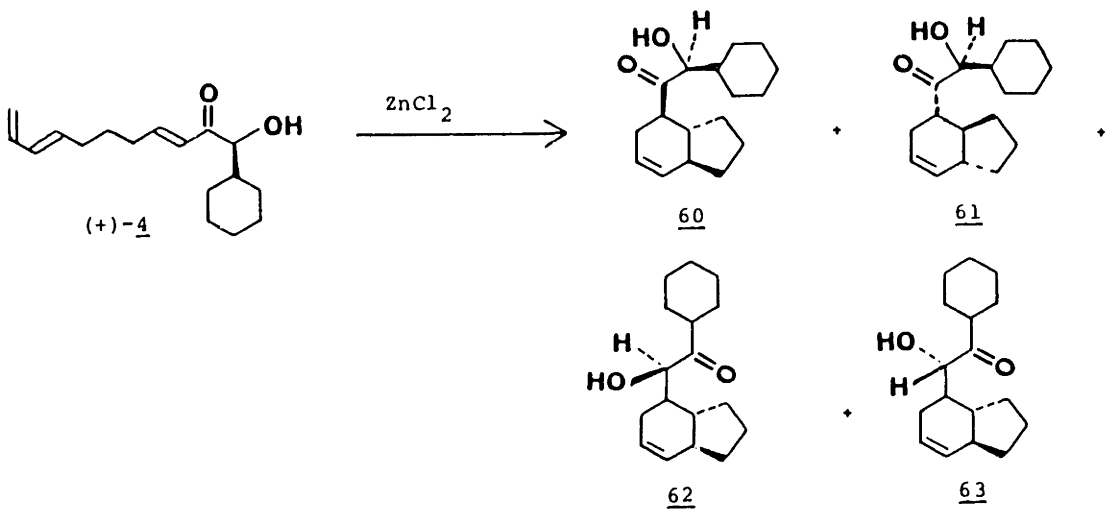
Data for (-)-6: $[\alpha]_D^{20}$ -170° (c = 0.86, EtOH), [literature[2] $[\alpha]_D^{25}$ -170° (c = 0.53, EtOH)]; NMR (250 MHz, $CDCl_3$) δ 5.95 (br d, J = 10.1 Hz, 1H), 5.62 (br d, J = 10.1 Hz, 1H), 3.72 (m, 2H), 2.42 (m, 1H), 2.08-1.04 (m, 10H), 1.00 (d, J = 6.9 Hz, 3H), 0.81 (d, J = 6.8 Hz, 3H); IR (CH_2Cl_2) 3610, 2955, 2865, 1460, 1380, 1365, 1000, 770 cm^{-1}; mass

spectrum, m/e 194 (parent ion), m/e 195 (M+1); high resolution mass spectrum, calcd for $C_{13}H_{22}O$ 194.1671, found 194.1670 $\pm$ 0.0004.



Optical Purity Determination of Alcohol (-)-6

Optically active (-)-6 was derivatized by using both (-)- and (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. The enantiomeric excess was determined to be >98% by inspection of the ^{19}F NMR spectrum (376 MHz, δ(51) 10.35, δ(52) 10.45) and by integration of the ^{1}H NMR in the region of the -CH_2OMTPA methylene resonance (δ(51) 4.39 (m, 2H), δ(52) 4.30 (t, J = 10 Hz) and 4.48 (dd, J = 10, 4 Hz)).



(+)-4 60 61 62 63

Zinc Chloride Catalyzed Cyclization of (+)-4

To a 0°C solution of triene (+)-4 (100 mg, 0.38 mmol) in 6 mL of dry methylene chloride was added freshly fused zinc chloride (49 mg, 0.36 mmol). After being stirred at room temperature for 24 h the reaction was worked up following the procedure described for cycloadduct (-)-38. Purification of the crude product (95 mg) by chromatography on two 0.5-mm silica gel preparative plates (6:1 hexane-ether, a wide band between R_f 0.35-0.70) produced 57 mg (57%) of a mixture consisting of 92% of 60, 3% of 61 and 5% of 63. Recrystallization of this mixture from hexane gave diastereomerically pure 60 (37 mg) and mother liquors (19 mg) consisting of a mixture enriched in 61 and 63..

Data for 60: mp 71-72°C; R_f 0.43 (6:1 hexane-ether); $[\alpha]_D^{20}$ -40.6° (c = 0.33, EtOH); NMR (250 MHz, $CDCl_3$) δ 5.85 (br d, J = 9.8 Hz, 1H), 5.54 (m, 1H), 4.11 (dd, J = 5.7, 2.1 Hz, 1H), 3.33 (d, J = 5.7 Hz, 1H),

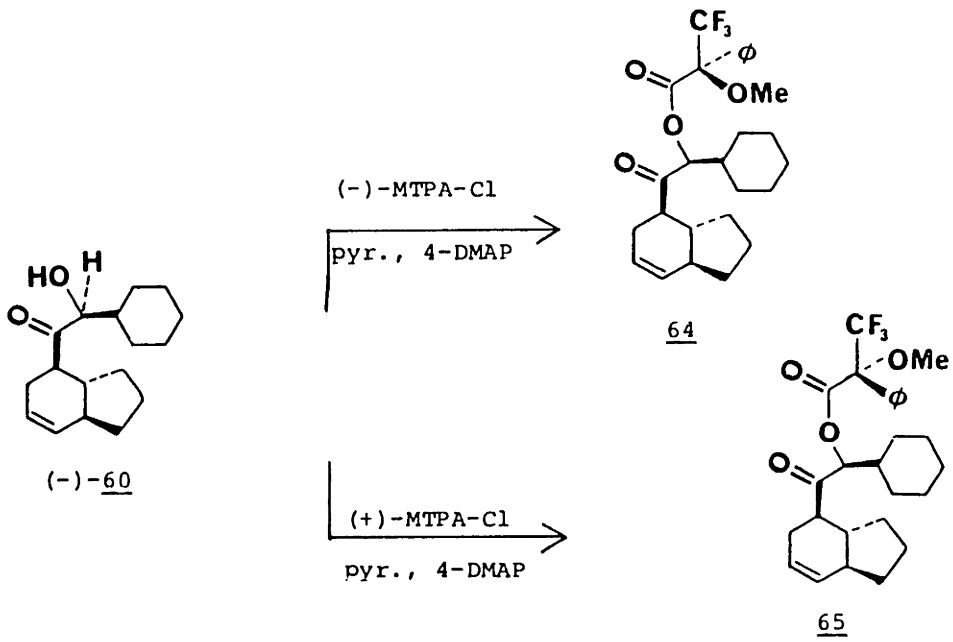
2.87 (m, 1H), 2.36 (m, 1H), 2.02-1.13 (m, 20H); IR (CH_2Cl_2) 3510, 2950, 1685 cm^{-1}; mass spectrum, m/e 262 (parent ion); high resolution mass spectrum, calcd for $C_{17}H_{26}O_2$ 262.1933, found 262.1933 $\pm$ 0.0005.

The minor products 61 and 63 were identified by comparison with the NMR data for these products obtained from the cyclization of triene (+)-4 using ethylaluminum dichloride. This reaction also produced substantial quantities of diastereomer 62. The ratio of 60:61:63:62 in this reaction was roughly 1:1:1:1. The stereochemical assignments for 63 and 62 are arbitrary and can be reversed.

Partial data for 61: NMR (250 MHz, $CDCl_3$) δ 5.78 (br d, J = 10.9 Hz, 1H), 4.03 (dd, J = 5.3, 2.2 Hz, 1H), 3.43 (d, J = 5.3 Hz, 1H), 2.84 (dt, J = 6.0, 10.5 Hz, 1H),

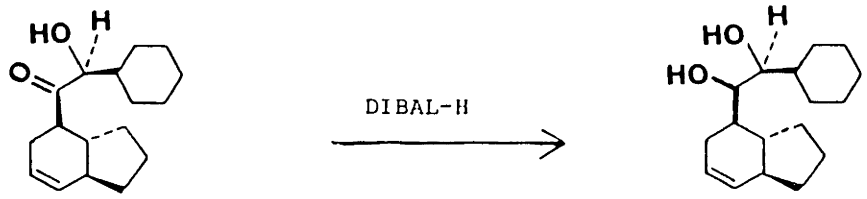
Partial data for 62: NMR (250 MHZ, $CDCl_3$) δ 5.83 (br d, J = 11.7 Hz, 1H), 5.59 (m, 1H), 5.49 (m, 1H), 4.44 (dd, J = 4.9, 1.3 Hz, 1H), 3.49 (d, J = 4.9 Hz, 1H),

Partial data for 63: NMR (250 MHz, $CDCl_3$) δ 5.77 (br d, J = 9.5 Hz, 1H), 5.60 (m, 1H), 4.13 (dd, J = 4.8, 1.2 Hz, 1H), 3.55 (d, J = 4.8 Hz, 1H), 2.62 (m, 1H), 2.42-1.10 (m, 21H).



Optical Purity Determination of Cycloadduct (-)-60

Cycloadduct (-)-60 was derivatized by using both (+)- and (-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. The -CH(OMTPA)- resonance appears at different chemical shifts for the diastereomeric esters (δ 5.08 for 64 and 5.12 for 65). The optical purity of cycloadduct (-)-60 was determined to be at least 95% (the limit of detection) by integration of these signals in the 400 MHz NMR spectra.

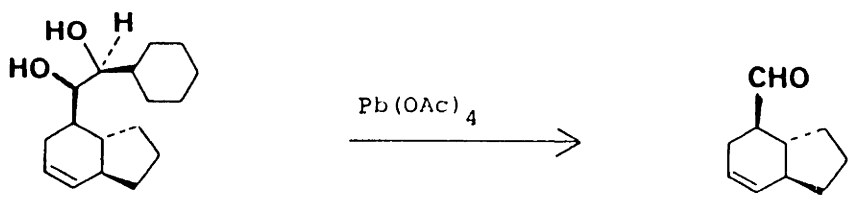


(-)-60 66

Diol 66

To a -78°C solution of 37 mg (0.14 mmol) of cycloadduct (-)-60 in 1.5 mL of dry ether was added dropwise a 0.97 M solution of diisobutylaluminum hydride (0.44 mL, 0.424 mmol) in hexane. The reaction was allowed to slowly warm to room temperature. After 1.5 h the reaction was worked up following the procedure described for diol (-)-47 to yield 41 mg of crude 66. The crude material was taken on to the next step without purification.

Data for 66: R_f 0.13 (6:1 hexane-ether); NMR (250 MHz, $CDCl_3$) δ 5.79 (br d, J = 9.7 Hz, 1H), 5.57 (br d, J = 9.7 Hz, 1H), 3.77 (br d, J = 6.8 Hz, 1H), 3.46 (m, 1H), 2.15-1.04 (m, 22H); IR (CH_2Cl_2) 3630, 2930, 2860, 1680, 1440, 1060(br), 920 cm^{-1}; mass spectrum m/e 264 (parent ion); high resolution mass spectrum, calcd for $C_{17}H_{28}O_2$ 264.2089, found

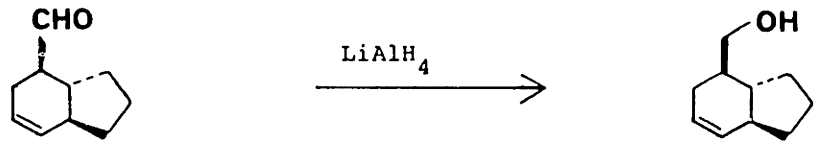


66 67

2,3,3aβ,4,5,7aα-Hexahydroindene-4β-carboxaldehyde (67)

Lead tetraacetate (75 mg, 0.17 mmol) in 2 mL of dry methylene chloride was cooled to 0°C. Crude diol 66 (37 mg, 0.141 mmol) in 1.5 mL of dry methylene chloride was added dropwise and the reaction mixture was stirred for 10 minutes at 0°C. The reaction was worked up according to the procedure described for aldehyde 48 to yield 54 mg of crude product consisting of a 55:45 mixture of aldehyde 67 and cyclohexanecarboxaldehyde. This material was used in the next transformation without further purification.

Data for 67: R_f 0.59 (6:1 hexane-ether); NMR (250 MHz, $CDCl_3$) δ 9.65 (d, J = 2.9 Hz, 1H), 5.84 (dd, J = 9.8, 1.6 Hz, 1H), 5.60 (ddd, J = 9.8, 6.5, 3.3 Hz, 1H), 2.46 (m, 1H), 2.26 (m, 2H), 1.97-1.16 (m, 8H); IR (CH_2Cl_2) 2920, 2850, 2715, 1720, 1450, 1265, 1075, 900 cm^{-1}.

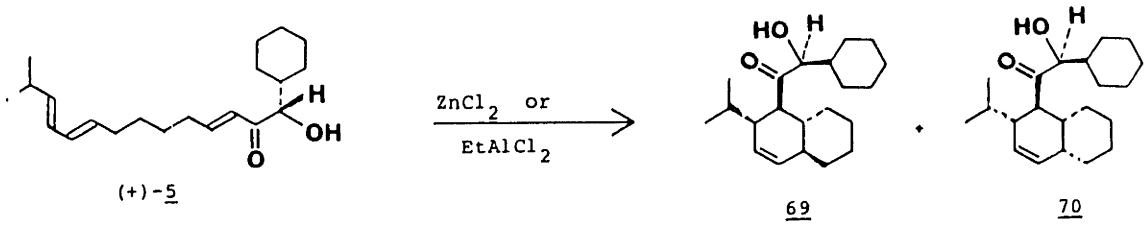


67 (-)-7

4β-(Hydroxymethyl)-2,3,3aβ,4,5,7aα-hexahydroindene ((-)-7)

To a 0°C solution of lithium aluminum hydride (6.4 mg, 0.17 mmol) in 1.2 mL of dry ether was added a solution of aldehyde 67 (34 mg of a 55:45 mixture with cyclohexanecarboxaldehyde, 0.141 mmol) in 1 mL of dry ether. The reaction was allowed to warm to room temperature and was stirred for 3 h. The reaction mixture was then worked up following the procedure described for the preparation of alcohol (-)-6 to give 32 mg of crude product. This material was purified by chromatography (0.5-mm silica gel preparative plate, 1:1 hexane-ether) to afford 21 mg of a mixture that was 70% by weight alcohol (-)-7 (R_f 0.47, 1:1 hexane-ether) and 30% by weight cyclohexylmethanol. These two compounds were not easily separated by TLC. The overall yield of alcohol (-)-7 from cycloadduct (-)-60 was 68%.

Data for (-)-7: $[\alpha]_D^{25}$ -34.1° (c = 0.293, EtOH; sample contained cyclohexylmethanol); lit[2] $[\alpha]_D^{25}$ -45.0° (c = 0.23, EtOH); NMR (250 MHz, $CDCl_3$) δ 5.80 (br d, J = 9.6 Hz, 1H), 5.59 (m, 1H), 3.59 (ABX, J_{AB} = 10.6 Hz, J_{AX} = 6.4 Hz, J_{BX} = 4.6 Hz, 2H), 2.28 (m, 1H), 1.91-1.08 (m, 10H).



(+)-5 69 70

Cyclization of Triene (+)-5

Method A: Zinc Chloride Procedure

A solution of 100 mg of triene alcohol (+)-5 (0.32 mmol) in 5 mL of dry methylene chloride was cooled to 0°C. Solid freshly fused zinc chloride (41 mg, 0.30 mmol) was added and the reaction mixture was slowly allowed to warm to room temperature. After being stirred for 24 h, the reaction was worked up using the procedure described for the cyclization of (+)-3. The crude product (92 mg) was purified by chromatography on two 0.5-mm silica gel preparative plates using 6:1 hexane-ether as eluant, giving 72 mg (72%) of a 96:4 endo:exo mixture as a white solid. The ratio of endo to exo adducts was determined by integration of the methine hydrogen adjacent to the hydroxy group in the proton NMR spectra (δ(69) 5.08, δ(70) 5.00). The endo adduct could be purified by recrystallization from hexane.

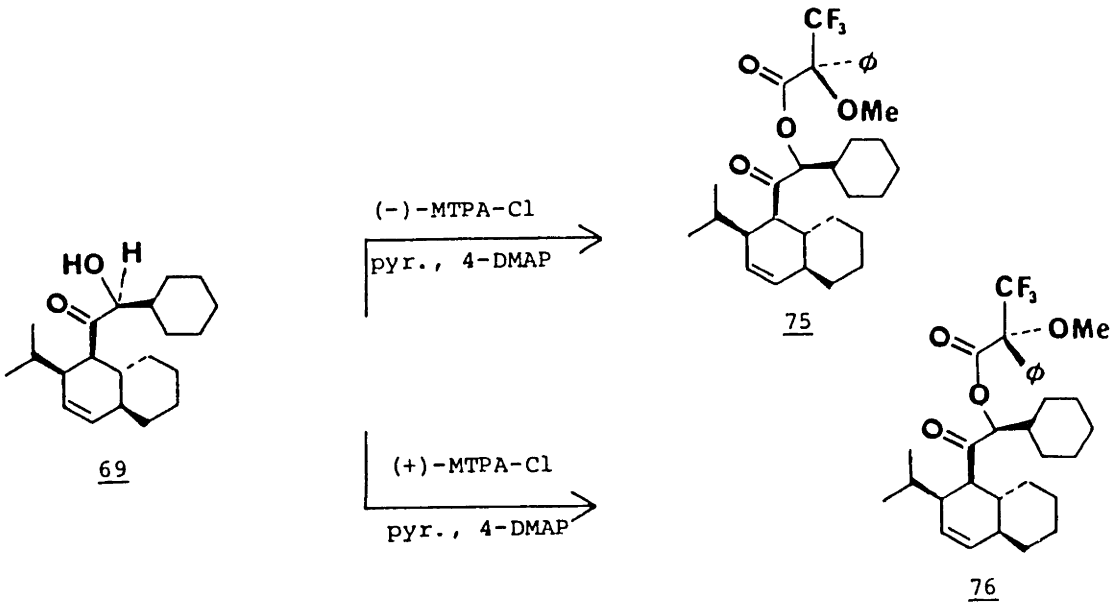
Data for 69: R_f 0.58 (6:1 hexane-ether); mp 150-151°C; $[\alpha]_D^{20}$ -50.6° (c = 0.372, $CHCl_3$); NMR (250 MHz, $CDCl_3$) δ 5.58 (s, 2H), 4.09 (dd, J = 6.2, 2.0 Hz, 1H), 3.43 (d, J = 6.2 Hz, 1H), 2.97 (dd, J = 11.1, 7.1 Hz, 1H), 2.44 (m, 1H), 1.89-1.05 (m, 22H), 0.89 (d, J = 6.8 Hz, 3H),

0.76 (d, J = 6.7 Hz, 3H); IR (CH_2Cl_2) 3480, 2930, 2855, 1700, 1450, 1365 cm^{-1}; mass spectrum, m/e 318 (parent ion); high resolution mass spectrum, calcd for $C_{21}H_{34}O_2$ 318.2559, found 318.2556 ± 0.0008. Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 78.95; H, 11.08.

Partial data for 70 (exo): NMR (250 MHz, $CDCl_3$) δ 4.02 (d, J = 7 Hz, 1H), 3.20 (d, J = 7 Hz, 1H), 0.92 (d, J = 7 Hz, 3H), 0.82 (d, J = 7 Hz, 3H).

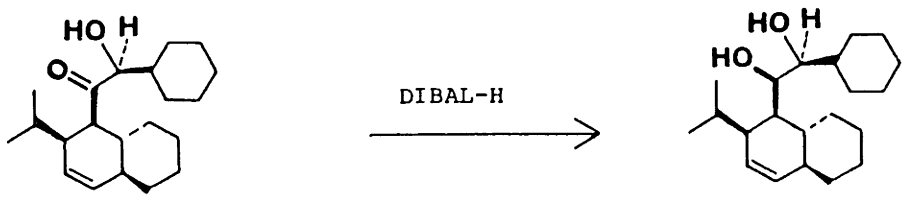
Method B: Ethylaluminum Dichloride Procedure

To a -78°C solution of triene alcohol (+)-5 (100 mg, 0.32 mmol) in 5 mL of dry methylene chloride was added dropwise 0.21 mL (0.30 mmol) of a 1.44 M solution of ethylaluminum dichloride in hexane. The mixture was allowed to warm to room temperature and was stirred for 24 h before being diluted with ether and saturated aqueous $NaHCO_3$ solution. The mixture was stirred for 1 h and then solid sodium sulfate was added. One hour later the solution was filtered, the solids were rinsed with ether and the combined filtrate was concentrated *in vacuo* to yield 97 mg of a solid crude product. Purification of the cycloadduct was carried out by chromatography on two 0.5-mm silica gel preparative plates using 6:1 hexane-ether as eluant. The band located between R_f 0.40 and 0.70 was isolated to give 82 mg (82% yield) of a 93:7 mixture of endo and exo cycloadducts.



Optical Purity Determination of Cycloadduct 69

Cycloadduct 69 was derivatized by using both (+)- and (-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. The methoxy resonances for the two diastereomers are well resolved at 400 MHz (δ(76) 3.62, δ(75) 3.57). The pure endo cycloadduct was determined to be 96% e.e. by this technique.

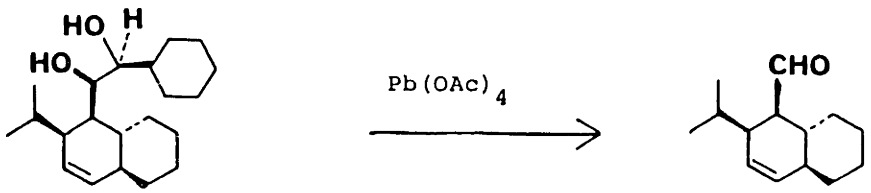


69 71

Diol 71

To a -78°C solution of 82 mg (0.26 mmol) of cycloadduct 69 (96:4 endo/exo) in 5 mL of dry ether was added dropwise 0.8 mL of an 0.97 M solution of diisobutylaluminum hydride in hexane. After being warmed to room temperature and stirred for 6 h, the reaction was worked-up following the procedure for the synthesis of diol 47. This produced 73 mg of crude diol 71.

Data for 71: $[\alpha]_D^{20}$ -8.7° (c = 0.75, $CHCl_3$); NMR (250 MHz, $CDCl_3$) δ 5.55 (m, 2H), 3.89 (dd, J = 9.0, 2.4 Hz, 1H), 3.60 (br d, J = 9.0 Hz, 1H), 2.42-1.08 (m, 24H), 0.93 (d, J = 7.1 Hz, 3H), 0.87 (d, J = 6.7 Hz, 3H); IR (neat) 3420(br), 2940, 2875, 1425, 1360, 1340 cm^{-1}; mass spectrum, m/e 320 (parent ion); high resolution mass spectrum, calcd for $C_{21}H_{36}O_2$ 320.2715, found 320.271 $\pm$ 0.001.

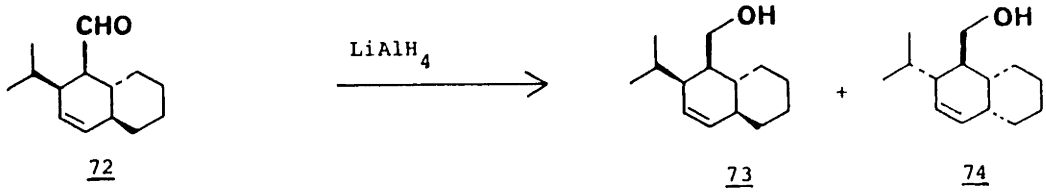


71 72

6β-(2-Propyl)-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5β-carboxaldehyde (72)

Lead tetraacetate (121 mg, 0.27 mmol) in 4 mL of dry methylene chloride was cooled to 0°C. A solution of crude diol 71 (73 mg, 0.23 mmol) in 1 mL of dry methylene chloride was added dropwise. The reaction mixture was stirred at 0°C for 10 min and then was worked up following the procedure described for the preparation of aldehyde 48. The product so obtained (69 mg) was a 4:3 mixture of adehyde 72 and cyclohexanecarboxaldehyde and was carried on to the next step without further purification.

Partial data for 72: R_f 0.67 (6:1 hexane-ether); NMR (250 MHz, $CDCl_3$) δ 9.76 (d, J = 4.3 Hz, 1H), 5.60 (s, 2H), 2.42 (m, 2H), 1.89-1.07 (m, 11H), 0.95 (d, J = 6.9 Hz, 3H), 0.91 (d, J = 6.7 Hz, 3H); IR (neat) 2945, 2870, 1720, 1440 cm^{-1}.



72 73 74

5β-Hydroxymethyl-6β-(2-propyl)-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene (73)

To a solution of lithium aluminum hydride (11 mg, 0.27 mmol) in 2 mL of dry ether at 0°C was added a solution of crude aldehyde 72 (47 mg, 0.23 mmol) in 1 mL of dry ether. The reaction was stirred at 23°C for 4 h, and then was worked up according to the procedure described for the preparation of alcohol (-)-6. The crude product (42 mg) was purified by chromatography on a 0.5-mm silica gel preparative plate (developed with 1:1 hexane-ether) to give 25 mg (47% overall yield from cycloadduct 69) of alcohol 73 as a 92:8 endo:exo mixture.

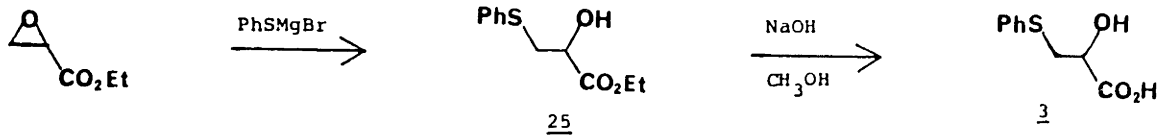
Data for 73[6]: R_f 0.57 (1:1 hexane-ether); NMR (250 MHz, $CDCl_3$) δ 5.60 (m, 2H), 3.84 (dd, J = 10.7, 5.3 Hz, 1H), 3.64 (dd, J = 10.7, 8.9 Hz, 1H), 2.25 (m, 1H), 2.00 (m, 1H), 1.85-1.10 (m, 11H), 0.97 (d, J = 6.9 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H).

Partial data for 74[6] (exo): NMR (250 MHz, $CDCl_3$) δ 4.32 (dd, J = 7, 2 Hz, 1H), 4.16 (d, J = 4 Hz, 1H), 0.77 (d, J = 7 Hz, 3H).

6. Roush, W.R.; Gillis, H.R.; Essenfeld, A. J. Org. Chem. 1984, 49, 4674.

Experimental Procedures

Part B: Experimentals For Chapter 3



25 3

2-Hydroxy-3-phenylthiopropanoic acid (3)[7]

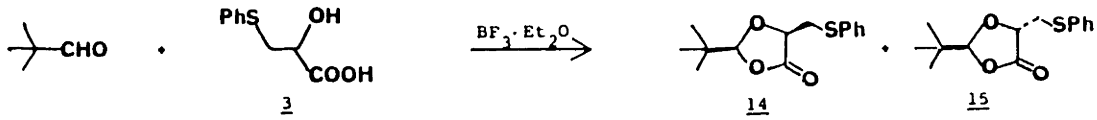
To a 0°C solution of 41 mL (2.9 M in ether, 120 mmol) of ethylmagnesium bromide in 160 mL of dry THF was added a solution of 12.3 mL (120 mmol) of thiophenol in 15 mL of dry THF over 10 min. Fifteen minutes later, a solution of 9.28 g (80 mmol) of ethyl glycidate[8] in 10 mL of dry THF was added dropwise. The reaction mixture was stirred at room temperature for 3 h, and then was diluted with 600 mL of water, acidified to pH 3 by using 10% HCl, and was extracted with ether. The organic extracts were washed with aqueous 10% NaOH, water, and brine to give 17.5 g of crude ester 25 as a pale yellow oil. (R_f 0.44, 1:1 hexane-ether).

To a solution of 17.5 g (78 mmol) of crude ester 25 in 160 mL of methanol was added 77 mL (230 mmol) of 3 M aqueous sodium hydroxide. The reaction mixture was stirred for 2 h at room temperature, and then most of the methanol was evaporated *in vacuo* at 50°C. The residue was diluted with 100 mL of water and the mixture was extracted with ether. The aqueous layer was acidified with 10% HCl and then extracted with

7. This experiment was performed by Dr. Masanori Kageyama.
8. Rastetter, W.H.; Richard, T.J.; Lewis, M.D. J. Org. Chem. 1978, 43, 3163.

ether (2x). The organic extracts were washed with water, brine, dried over $MgSO_4$ and concentrated *in vacuo* to give crude 3 as a crystalline solid. Recrystallization of this material from benzene-ether afforded 9.43 g of acid 3. Recrystallization of the mother liquors gave an additional 2.67 g of 3, and a total yield of 12.1 g (76%).

Data for 3: mp 87-88°C; NMR (250 MHz, $CDCl_3$) δ 7.33 (m, 5H), 4.40 (dd, J = 6.5, 4.1 Hz, 1H), 3.45 (dd, J = 14.2, 3.9 Hz, 1H), 3.26 (dd, J = 14.1, 6.5 Hz, 1H); IR (neat) 3460(br), 1720(s), 1585(w), 1090(s) cm^{-1}; mass spectrum, m/e 198 (parent ion). Anal. Calcd for $C_9H_{10}O_3S$: C, 54.43; H, 5.09. Found: C, 54.70; H, 5.13.



3 14 15

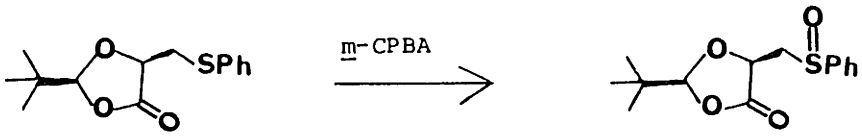
2-(2'-Methylpropyl)-5-[(thiophenyl)methyl]-1,3-dioxolan-4-one (14)

To a solution of 1.20 g (6.0 mmol) of 2-hydroxy-3-thiophenylpropanoic acid in 25 mL of dry ether was added 0.72 mL (570 mg, 6.64 mmol) of neat pivalaldehyde. The mixture was cooled to 0°C and 2.23 mL (2.57 g, 18.12 mmol) of boron trifluoride etherate was added dropwise. The reaction was stirred at 0°C for 4 hours and then was quenched carefully with saturated aqueous $NaHCO_3$ solution. The product was extracted with ether (3 x 50 mL). The ether extracts were washed with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, filtered and concentrated. This procedure afforded 1.41g (87%) of 1,3-dioxolan-4-ones 14 and 15 in a 93:7 mixture, respectively. The ratio could be enriched to a 97:3 cis:trans mixture by one recrystallization and to virtually pure cis by two successive recrystallizations from ether/pentane at 0°C.

Data for 14: R_f 0.75 (2:1 ether:hexane); mp 55.0-55.5°C; NMR (250 MHz, $CDCl_3$) δ 7.43-7.17 (m, 5H), 5.13 (s, 1H), 4.47 (dd, J = 7.1, 3.5 Hz, 1H), 3.48 (A of ABX, J_{AB} = 14.5 Hz, J_{AX} = 3.5 Hz, 1H), 3.18 (B of ABX, J_{AB} = 14.5 Hz, J_{BX} = 7.1 Hz, 1H), 0.92 (s, 9H); IR (CH_2Cl_2) 3080(w), 2980, 2925, 2895, 1795(s), 1570(w), 1480, 1430, 1400, 1360, 1340, 1285, 1220(br), 1115, 1055, 980, 930 cm^{-1}; mass spectrum, m/e 266

(parent ion); high resolution mass spectrum, calcd for $C_{14}H_{18}O_3S$ 266.0983, found 266.0979 ± 0.0005. Anal. Calcd for $C_{14}H_{18}O_3S$: C, 63.13; H, 6.81; S, 12.04. Found: C, 63.13; H, 6.84; S, 12.08.

Partial data for 15: NMR (250 MHz, $CDCl_3$) δ 7.43-7.17 (m, 5H), 5.28 (s, 1H), 4.62 (dd, J = 5.1, 4.0 Hz, 1H), 3.44 (A of ABX, J_{AB} = 14.5 Hz, J_{AX} = 4.0 Hz, 1H), 3.22 (B of ABX, J_{AB} = 14.5 Hz, J_{BX} = 5.3 Hz, 1H), 0.89 (s, 9H).



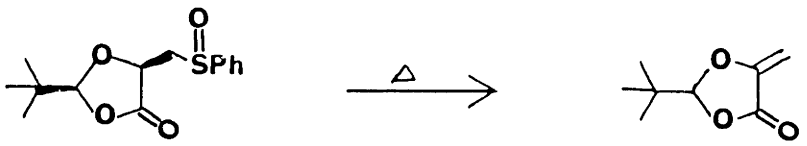
14 16

2-(2'-Methylpropyl)-5-[(phenylsulfinyl)methyl]-1,3-dioxolan-4-one (16)

To a -78°C solution of 1.58 g (5.95 mmol) of sulfide 14 in 20 mL of dry methylene chloride was added dropwise a solution of 1.18 g (6.54 mmol) of mCPBA in 20 mL of dry methylene chloride. After being stirred at -78°C for 2 h, the reaction was quenched with saturated aqueous $NaHSO_3$. The crude mixture was extracted three times with ether. The extracts were washed with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and concentrated to afford 2.22 g of crude product. The sulfoxide was purified by flash column chromatography employing 2:1 ether:hexane as an eluant yielding 1.56 g (93%) of pure sulfoxide 16 as a mixture of diastereomers.

Data for 16: R_f 0.31 (2:1 ether:hexane); m.p. 70.5-71.5°C; NMR (250 MHz, $CDCl_3$) δ 7.68-7.47 (m, 5H), 5.23 (d, J = 0.8 Hz, 0.5H), 5.04 (s, 0.5H), 4.79 (dd, J = 8.3, 1.1 Hz, 0.5H), 4.72 (dd, J = 8.4, 2.9 Hz, 0.5H), 3.45 (A of ABX, J_{AB} = 14.0 Hz, J_{AX} = 3.1 Hz, 0.5H), 3.27 (A of ABX, J_{AB} = 13.7 Hz, J_{AX} = 2.3 Hz, 0.5H), 3.03 (B of ABX, J_{AB} = 14.0 Hz, J_{BX} = 8.6 Hz, 0.5H), 2.93 (B of ABX, J_{AB} = 13.7 Hz, J_{BX} = 10.3 Hz, 0.5H), 0.98 (s, 9/2H), 0.76 (s, 9/2H); IR (CH_2Cl_2) 3105(w), 2995, 2945, 2910, 1795(s), 1575(w), 1480, 1445, 1410, 1365, 1305, 1215(s), 1165,

1110, 1080, 1040, 960 cm^{-1}; mass spectrum, m/e 282 (parent ion); high resolution mass spectrum, calcd for $C_{14}H_{18}O_4S$ 282.0926, found 282.0925 ± 0.0004. Anal. Calcd for $C_{14}H_{18}O_4S$: C, 59.55; H, 6.43; S, 11.35. Found: C, 59.64; H, 6.66; S, 11.21.

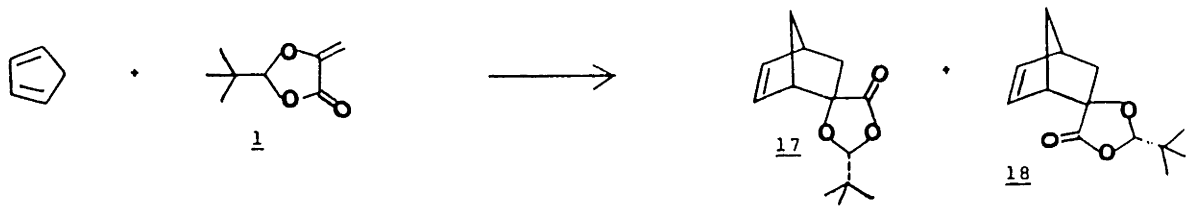


16 1

2-(2'-Methylpropyl)-5-methylene-1,3-dioxolan-4-one (1)

To a solution of 1.50 g (5.32 mmol) of sulfoxide 16 in 6 mL of dry benzene was added 1.82 mL (1.77g, 10.6 mmol) of triethyl phosphite. The solution was degassed for 10 minutes using a stream of argon. The Carius tube was sealed and the reaction mixture was heated to reflux in an oil bath at 105°C. After 38 hours, the reaction mixture was cooled to room temperature and benzene was removed *in vacuo*. The crude material was purified by column chromatography using flash silica gel and eluting the material with pentane to afford 265 mg (32%) of 1 as a volatile yellow liquid. (R_f 0.43, 24:1 pentane:ether).

Data for 1: NMR (250 MHz, $CDCl_3$) δ 5.41 (s, 1H), 5.11 (d, J = 2.6 Hz, 1H), 4.83 (d, J = 2.6 Hz, 1H), 0.95 (s, 9H); IR (CH_2Cl_2) 2965, 2900, 1790, 1265, 1035 cm^{-1}; mass spectrum, m/e 156 (parent ion).



1 17 18

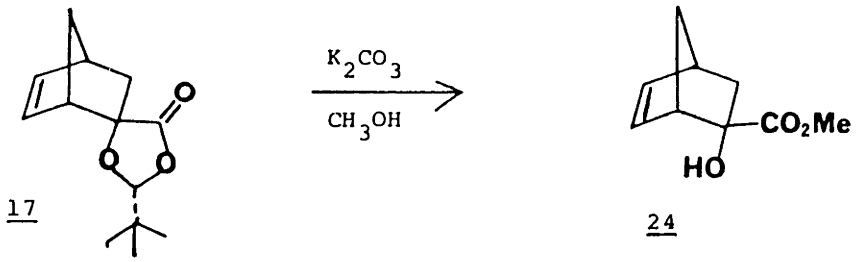
Reaction of 1 with Cyclopentadiene

A solution of 100 mg (0.641 mmol) of freshly prepared dienophile 1 in 3 mL of dry benzene was added to a Carius tube and degassed using a stream of argon. Cyclopentadiene (0.32 mL, 254 mg, 3.85 mmol) was added *via* syringe and the tube was sealed. The Carius tube was placed in a 65°C oil bath. After 5 h at 65°C, the reaction mixture still contained approximately 15% of the dienophile as determined by gas chromatography (10' 10% SE-30, 100-175°C, 10°C/min, hold at 175°C for 25 min, t(1) = 10 min, t(17) = 26.7 min.). Additional cyclopentadiene (0.11 mL, 0.641 mmol) was added and heating was continued for 16 hours. The cooled solution was concentrated *in vacuo* to give 382 mg of crude product. The cycloadduct was purified by chromatography (two 0.5-mm preparative plates, 24:1 pentane:ether, 1 development) to afford 120 mg (85%) of a 93:7 exo:endo mixture determined by integration of the olefinic region of the proton NMR spectrum (δ(17) = 6.06, δ(18) = 5.97) and confirmed by capillary gas chromatography (SE-54, 50 m, 100-175°C, 10°C/min, t(17) = 10.50, t(18) = 10.88).

Data for 17: R_f 0.32 (24:1 pentane:ether); mp 44.5-45.0°C; NMR (250 MHz, $CDCl_3$) δ 6.43 (dd, J = 5.6, 3.0 Hz, 1H, H1), 6.06 (dd, J =

5.6, 3.0 Hz, 1H, H2), 5.12 (s, 1H, H9), 3.14 (br s, 1H, H3), 2.96 (br s, 1H, H6), 2.28 (dd, J = 12.5, 3.5 Hz, 1H, H5), 1.93 (br d, J = 9.1 Hz, 1H, H8), 1.48 (dt, J = 2.0, 9.1 Hz, 1H, H7), 1.31 (dd, J = 12.5, 3.9 Hz, 1H, H4), 0.90 (s, 9H, H10); IR (CH_2Cl_2) 2990, 2900, 1780, 1720(w), 1490, 1410, 1365(w), 1345, 1235, 1210, 1165, 1130, 1105, 1065, 965 cm^{-1}; mass spectrum, m/e 222 (parent ion); high resolution mass spectrum, calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1256 ± 0.0003.

Partial data for 18 (endo): NMR (250 MHz, $CDCl_3$) δ 6.39 (dd, J = 5.5, 3 Hz, 1H), 5.96 (dd, J = 5.5, 3 Hz, 1H), 5.18 (s), 3.18 (br s).



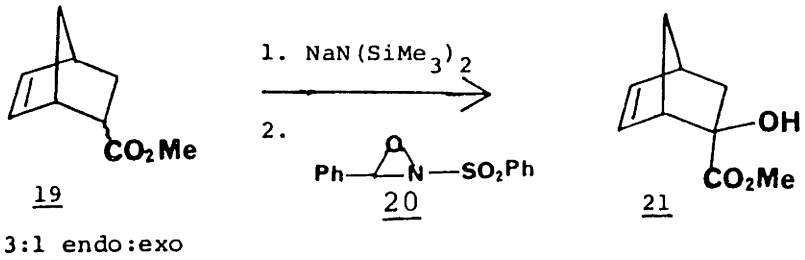
17 24

Methyl 2(Endo)-Hydroxybicyclo[2.2.1]-hept-5-en-2(exo)-carboxylate (24)

To a 0°C solution of a 93:7 mixture of cycloadducts 17 and 18 (41 mg, 0.19 mmol) in 1.5 mL of methanol was added solid anhydrous K_2CO_3 (51 mg, 0.37 mmol). The reaction mixture was stirred at 0°C for 4 h and then was diluted with water and ether. After being neutralized with aqueous 1N HCl solution, the mixture was extracted three times with ether. The ether extracts were washed with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, filtered and concentrated to afford 28 mg (90%) of ester 24 which was a 93:7 mixture of exo and endo carbomethoxy isomers. The major product is different from an authentic sample of endo adduct prepared by an independent route.

Data for 24: NMR (250 MHz, $CDCl_3$) δ 6.44 (dd, J = 3.0, 5.6 Hz, 1H, H1), 6.17 (dd, J = 3.1, 5.6 Hz, 1H, H2), 3.81 (s, 3H, -OMe), 2.95 (m, 3H, H3, H6, H10), 2.39 (dd, J = 12.3, 3.6 Hz, 1H, H5), 1.88 (br d, J = 8.9 Hz, 1H, H8), 1.49 (m, 1H, H4), 1.20 (dd, J = 3.6, 12.4 Hz, 1H, H7); IR (CH_2Cl_2) 3600, 3545, 2975, 1715(s), 1435, 1415, 1330, 1250(br), 1160, 1120, 1045, 955(w), 875 cm^{-1}; mass spectrum, m/e 168 (parent ion); high resolution mass spectrum, calcd for $C_9H_{12}O_3$ 168.0786, found 168.0785 $\pm$ 0.0005.

Partial data for 21: NMR (250 MHz, $CDCl_3$) δ 6.26 (dd, J = 6, 3 Hz, 1H), 5.88 (dd, J = 6, 3 Hz, 1H), 3.69 (s, 3H), 2.77 (s, 1H), 1.95 (m, 2H), 1.69 (dd, J = 12, 4 Hz, 1H), 1.60 (m, 1H).



19

3:1 endo:exo

20

21

Methyl 2(Exo)-Hydroxybicyclo[2.2.1]hept-5-en-2(endo)-carboxylate (21)

To a -78°C solution of sodium hexamethyldisilazane in tetrahydrofuran (1.58 mL, 1.0 M, 1.58 mmol) was added dropwise a solution of 19[9] (200 mg, 1.32 mmol) in 1 mL of dry tetrahydrofuran. The reaction was stirred at -78°C for 30 minutes. To the yellow solution was added dropwise 515 mg (1.97 mmol) of 2-(phenylsulfonyl)-3-phenyloxaziridine in 2 mL of dry tetrahydrofuran.[10] The reaction mixture was stirred for 40 min and then was quenched with 732 mg (2.63 mmol) of camphorsulfonic acid. The product was extracted with ether and aqueous $NaHCO_3$ solution. The organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude material was purified by column chromatography using flash silica gel and eluting with 9:1 hexane:ether for the first fifty fractions (10 mL) and then eluting with 3:1 hexane:ether to afford 74 mg (60% based on recovered starting material) of alcohol 21 (from fractions 81-110) as a yellow oil. Ester 19 (87 mg, 44%) was also recovered (fractions 10-20).

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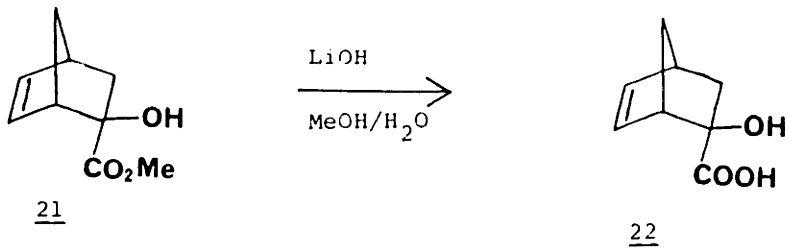
9. Nakagawa, K.; Ishii, Y.; Ogawa, M. Chem. Lett. 1976, 5, 511.
10. Evans, D.A.; Morrissey, M.M.; Dorow, R.L. J. Am. Chem. Soc. 1985, 107, 4346.

Data for 21: R_f 0.10, 6:1 hexane-ether; NMR (250 MHz, $CDCl_3$) δ 6.26 (dd, J = 5.7, 2.9 Hz, 1H, H1), 5.88 (dd, J = 5.7, 3.1 Hz, 1H, H2), 3.69 (s, 3H, $-CO_2Me$), 2.91 (br s, 2H, -OH, H3), 2.77 (s, 1H, H6), 1.95 (m, 2H, H4, H8), 1.69 (dd, J = 12.4, 3.6 Hz, 1H, H5), 1.60 (m, 1H, H7); IR (CH_2Cl_2) 3580(br), 3055(w), 2980, 2950, 1790(w), 1725, 1435, 1330, 1235, 1200, 1150, 1105, 1090, 1080, 1035 cm^{-1}; mass spectrum, m/e 168 (parent ion); high resolution mass spectrum, calcd for $C_9H_{12}O_3$ 168.0786, found 168.0785 $\pm$ 0.0002.

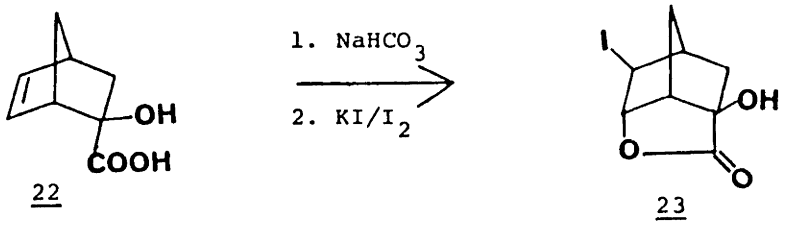


21 22

2(Exo)-Hydroxybicyclo[2.2.1]-hept-5-en-2(Endo)carboxylic acid (22)

Lithium hydroxide (11 mg, 0.45 mmol) was added to a 0°C solution of ester 21 (15 mg, 0.089 mmol) in 0.9 mL of 3:1 methanol:water. The reaction was allowed to warm to room temperature. After 14 hours, the mixture was acidified with 1N HCl solution and extracted with ethyl acetate (3x). The combined extracts were dried over Na_2SO_4, filtered and concentrated to afford 11.5 mg (84%) of acid 22 as a yellow solid.

Data for 22: NMR (250 MHz, $CDCl_3$) δ 6.29 (dd, J = 5.5, 3.2 Hz, 1H), 5.97 (dd, J = 5.5, 3.1 Hz, 1H), 2.94 (br s, 1H), 2.82 (br s, 1H), 1.96 (m, 2H), 1.74 (dd, J = 12.5, 3.4 Hz, 1H); IR (CH_2Cl_2) 3625(br), 3300-2800(br), 1705, 1075 cm^{-1}; mass spectrum, m/e 154 (parent ion); high resolution mass spectrum, calcd for $C_8H_{10}O_3$ 154.0630, found



22 23

Iodolactone 23

Solid $NaHCO_3$ (19 mg, 0.22 mmol) was added to a solution of acid 22 (11 mg, 0.075) in 0.5 mL of water. The mixture was stirred until gas evolution ceased, at which point a solution of 37 mg (0.22 mmol) of KI and 19 mg (0.075 mmol) of I_2 in 1 mL of water was added dropwise. The resulting solution was stirred at room temperature for 1.5 h. The mixture was extracted six times with ether and the extracts were washed (2x) with 20% aqueous $Na_2S_2O_3$ solution. The ether extracts were dried over Na_2SO_4, filtered and concentrated to afford 11 mg (53%) of iodolactone 23.

Data for 23: R_f 0.71 (ether); mp 116-117°C; NMR (250 MHz, $CDCl_3$) δ 5.09 (d, J = 4.7 Hz, 1H), 3.83 (d, J = 2.5 Hz. 1H), 3.03 (br d, J = 5.4 Hz, 1H), 2.81 (s, 1H), 2.73 (br s, 1H), 2.40 (dd, J = 11.6, 2.1 Hz, 1H), 2.16 (m, 2H), 1.86 (dd, J = 13.8, 4.2 Hz, 1H); IR (CH_2Cl_2) 3555(br), 2980, 2890, 1785, 1150, 1130, 1105, 990 cm^{-1}; mass spectrum, m/e 280 (parent ion); high resolution mass spectrum, calcd for $C_8H_9IO_3$ 279.9596, found

Addendum

It has been suggested that Diels-Alder reactions involving unsymmetrical components may proceed *via* concerted but nonsynchronous transition states.[1] Several groups have suggested that the stereochemical course of intramolecular Diels-Alder reactions can be rationalized in this manner,[2] and Houk has recently introduced a "twist-asynchronous" model to account for the results summarized in Table 1.[3,4]

The nonsynchronous transition state model suggests that the selectivity for the trans-fused product should increase as the size of the coefficients at C(2) and/or C(n+2) are increased. This tendency is readily apparent in the nonatriene cyclizations and can be brought about either by manipulating the substituents on the terminal diene carbon atom (entries 3-5) or by using a Lewis acid catalyst (entries 4,6). Although the decatrienes are less sensitive to variations in the diene substituent, Lewis acid catalysis is somewhat effective in increasing the trans selectivity (entries 4,6).

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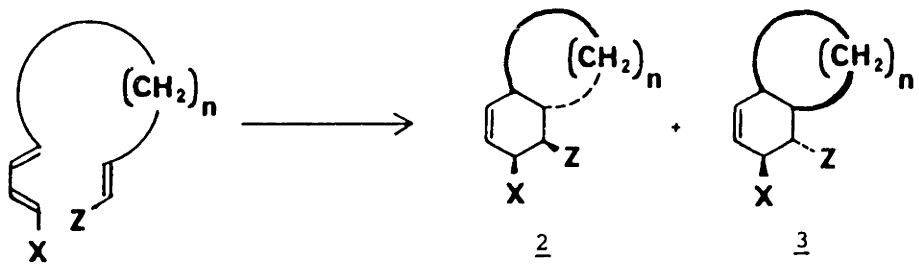
1. (a) Dewar, M.J.S. J. Am. Chem. Soc. 1984, 106, 209. (b) Konovalov, A.I.; Kamasheva, G.I.; Loskutov, M.P. J. Org. Chem. U.S.S.R. 1973, 9, 2064. (c) Sustmann, R.; Sauer, J. Angew. Chem., Int. Ed. Engl. 1980, 19, 779.
2. (a) Roush, W.R.; Peseckis, S.M. J. Am. Chem. Soc. 1981, 103, 6696. (b) Boeckman, R.K. Jr.; Ko, S.S. J. Am. Chem. Soc. 1982, 104, 1033. (c) White, J.D.; Sheldon, B.G. J. Org. Chem. 1981, 46, 2273. (d) Taber, D.F.; Campbell, C.; Gunn, B.P.; Chiu, I.-C. Tetrahedron Lett. 1981, 22, 5141.
3. (a) Houk, K.N.; Lin, Y.-T. Tetrahedron Lett. 1985, 26, 2269. (b) Houk, K.N.; Brown, F.K. Tetrahedron Lett. 1985, 26, 2297. (c) Houk, K.N.; Wu, T.-C. Tetrahedron Lett. 1985, 26, 2293. (d) Houk, K.N.; Lin, Y.-T. Tetrahedron Lett. 1985, 26, 2517.
4. (a) Roush, W.R.; Gillis, H.R.; Ko, A.I. J. Am. Chem. Soc. 1982, 104, 2269. (b) Roush, W.R.; Gillis, H.R. J. Org. Chem. 1982, 47, 4825. (c) Roush, W.R.; Hall, S.E. J. Am. Chem. Soc. 1981, 103, 5200.



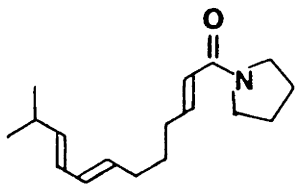
1 2 3

Table 1

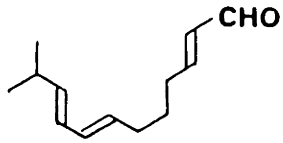
Entry	Substituents		Nonatrienes (n=3)		Decatrienes (n=4)	
	X	Z	trans:cis[h]	ΔΔG‡[a]	trans:cis[h]	ΔΔG‡[a]
1	H	H	25:75[b]	-1.0	47:53[b]	-0.1
2	CO_2Et	H	43:57[g]	-0.3	50:50[g]	0.0
3	H	CO_2Et	60:40[c]	0.3	51:49[d]	0.0
4	*i*Pr	CO_2Et	72:28[c]	0.8	50:50[e]	0.0
5	Et_2N	CO_2Et	85:15[f]	1.1	55:45[f]	0.1
6	*i*Pr	$CO_2Et \cdot AlEtCl_2$	98:2[c]	2.3	88:12[e]	1.2

a. $\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}(cis) - \Delta G^{\ddagger}(trans)$ in kcal/mol
b. Reference 3a. c. Reference 4a. d. Reference 4c.
e. Reference 4b. f. Reference 3b. g. Reference 3c.
h. The ratio of *trans*-fused to *cis*-fused adducts.

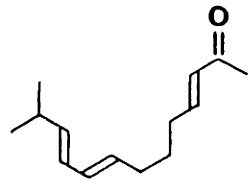
In order to further probe the effect of the dienophile activating group on the stereoselectivity of the intramolecular Diels-Alder reactions of substituted 1,6,8-nonatrienes, we decided to synthesize and study the cyclizations of trienes 4-6. Since the reactivity and



4



5



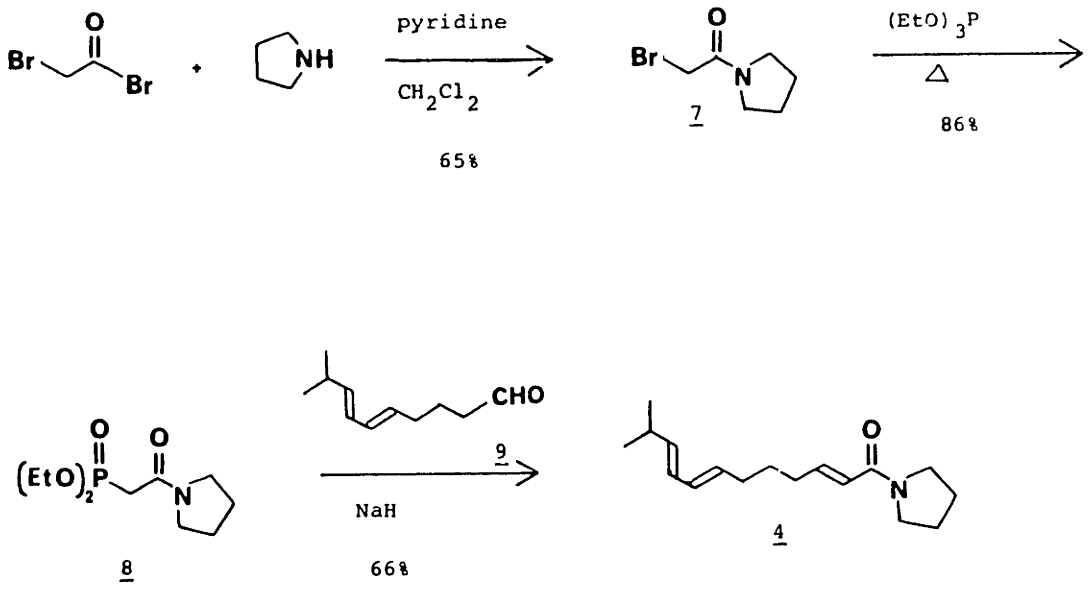
6

effectiveness of dienophile activating groups as endo directors in bimolecular Diels-Alder reactions varies as $-CO_2Me \cdot AlEt_2Cl$ > -CHO > $-COCH_3$ > $-CO_2Me$ > $-CONR_2$,[1c,5] which undoubtedly correlates with the size of the LUMO coefficient at C(3) of the dienophilic double bond, we expected to see a corresponding change in stereoselectivity in the intramolecular reactions.

Trienes 4-6 were constructed from diene aldehyde 9[4a] as summarized in Schemes 1-3. Bromoacetyl bromide was treated with pyrrolidine and pyridine in methylene chloride to give amide 7 in 65% yield (Scheme 1). An Arbuzov reaction involving triethyl phosphite and 7 afforded phosphonate 8 (86% yield), which was treated with NaH followed by aldehyde 9 to yield triene 4 in 66% yield after chromatography. Approximately 6% of the (E,E,Z)-triene isomer was also formed; however it could be separated from the desired product by chromatography.

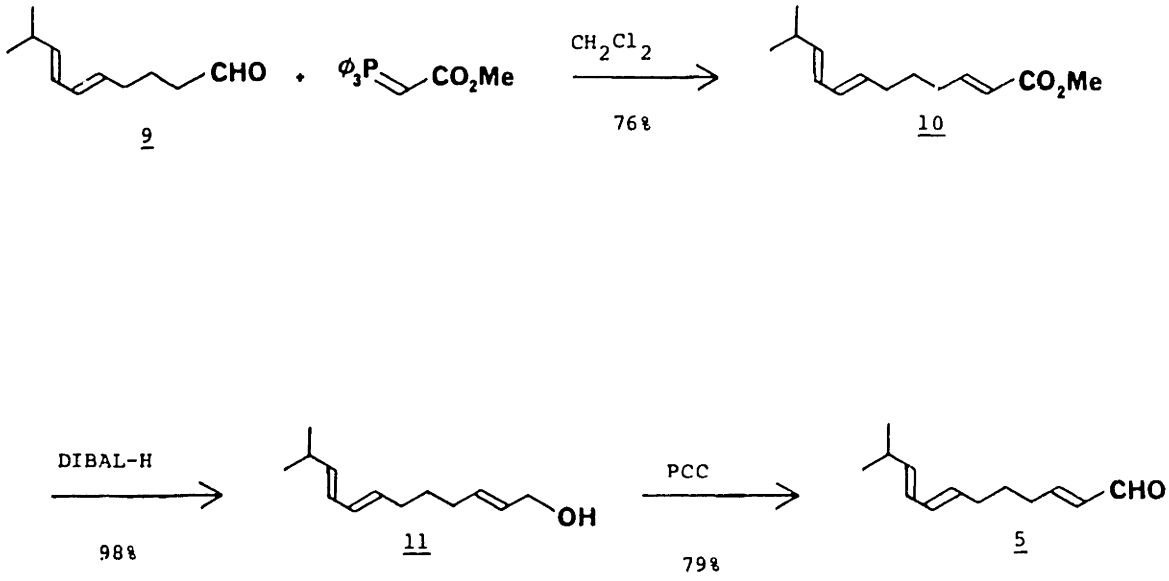
5. (a) Vedejs, E.; Gadwood, R.C. J. Org. Chem. 1978, 43, 377. (b) Sauer, J.; Wiest, H.; Mielert, A. Chem. Ber. 1964, 97, 3183.

Scheme 1



The synthesis of triene 5, as outlined in Scheme 2, began with the Wittig reaction of aldehyde 9 and ((carbomethoxy)methylene)triphenylphosphorane to afford triene 10.[4a] The carbomethoxyl group of 10 was reduced with diisobutylaluminum hydride to give allylic alcohol 11 (98% yield). Oxidation of 11 with PCC afforded triene aldehyde 5 in 79% yield.

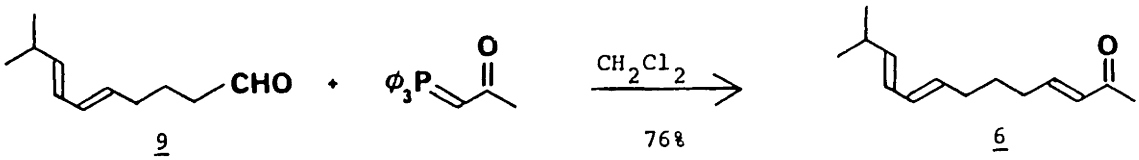
Scheme 2



9 10 11 5

Triene 6 was synthesized by treatment of 9 with 1-triphenylphosphoranylidene-2-propanone in 76% yield (Scheme 3).

Scheme 3



9 6

The results of cyclizations of 4-6 are summarized in Table 2.

Scheme 4

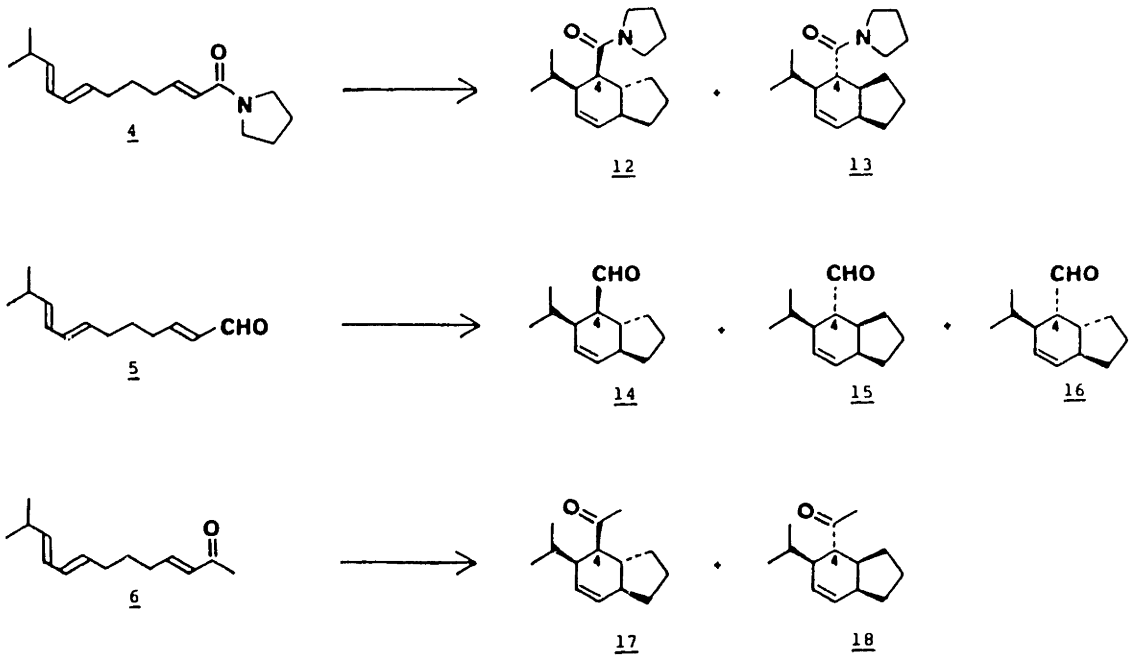


Table 2

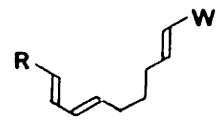
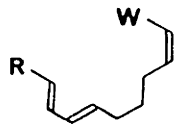
Triene	Temp. (°C)	Yield[a]	trans:cis[b]
4	150	59 (97)	51:49[c]
4	200	60 (74)	43:57[d]
5	100	45	(87:5)[e]:8[f]
5	150	48 (68)	(76:13)[e]:11[f]
6	100	--	89:11[f]
6	120	55	86:14[f]
6	150	81	85:15[f]

a The isolated yield of all the cycloadducts. The number in parentheses is the yield based on recovered triene.
b The ratio of trans-fused to cis-fused cycloadducts.
c Ratio determined by product isolation.
d Ratio determined by NMR analysis of the crude reaction mixture.
e The ratio of 14 to 16. f Ratio determined by capillary gas chromatography analysis of the crude mixture of cycloadducts.

All reactions were performed in sealed Carius tubes with toluene as the solvent. Crude product mixtures were analyzed by ^{1}H NMR and/or capillary GC analysis. Cycloadducts 12 and 13 were easily separated by silica gel chromatography and structures were assigned by NMR. In particular, the multiplicities of H(4) for 12 (2.70, dd, J = 10.1, 7.0 Hz) and 13 (2.27, dd, J = 10.7, 10.5 Hz) are characteristic of these structures.[4a] The mixtures of cycloadducts produced from 5 and 6 could not be separated chromatographically. However, it was readily apparent from the NMR spectra of the mixtures that the major products possessed trans ring fusion as shown: for 14, H(4) appears as a doublet of doublets of doublets with J = 11.0, 7.9, and 3.0 Hz, whereas for 15 H(4) appears as a doublet of doublets with J = 10.5 and 7.6 Hz. The third product (16) detected in the cyclization of 5 was shown to be the epimer of 14 by base catalyzed equilibration experiments. We believe that this compound is produced from 14 by epimerization under the conditions of intramolecular Diels-Alder reactions.

Two trends are apparent in the data summarized in Table 2. First, as we had hoped, at the same reaction temperature (150°C), triene aldehyde 5 (89:11) is more selective than methyl ketone 6 (85:15) or triene amide 4 (51:49). Second, for each activating group, trans selectivities increased as the reaction temperature was decreased.

Table 3

Entry	Triene						Ref
	R	W	Temp	trans:cis[a]	Temp	trans:cis[a]	
1	H	H	190°	25:75	--	-- --	b
2	*i*Pr	$CON(C_4H_8)$	150°	51:49	--	-- --	c
3	H	CO_2Me	150°	60:40	150°	65:35	d
4	*i*Pr	CO_2Me	150°	72:28	150°	67:33	d
5	*i*Pr	$COCH_3$	120°	86:14	--	-- --	c
6	Me	NO_2	80°	89:11	23°	53:47	e
7	*i*Pr	CHO	100°	92:8	--	-- --	c
8	H	$CO_2Me{\cdot}AlEtCl_2$	23°	>99:1	23°	52:48	d
9	*i*Pr	$CO_2Me{\cdot}AlEtCl_2$	23°	>99:1	23°	63:37	d

a. Ratio of trans:cis fused cycloadducts. b. Reference 3a.
c. Reference 6a. d. Reference 4a. e. Reference 6b.

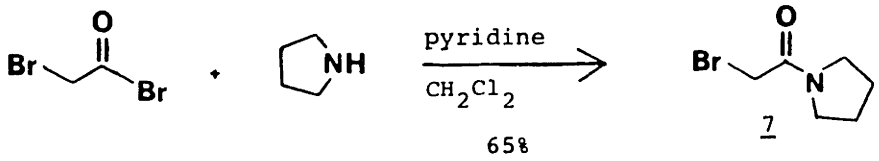
Table 3 summarizes the results obtained with trienes 4-6 and other terminally activated 2,7,9-nonatrienes.[6] These data show that as long

6. (a) Essenfeld, A. Ph.D. Thesis, Massachusetts Institute of Technology, 1985. (b) Kurth, M.J.; O'Brien, M.J.; Hope, H.; Yanuck, M. J. Org. Chem. 1985, 50, 2626.

as the dienophile geometry is trans, selectivity for the trans-fused cycloadduct can be increased by rational modification of the activating substituent W. A correlation also exists between triene reactivity and stereoselectivity. Because the trans-fused cycloadduct in these cases corresponds to the one predicted by the Alder endo rule, it is tempting to speculate that the better activating groups (e.g., -CHO, $-NO_2$, $-CO_2Me \cdot AlEtCl_2$) increase stereoselectivity by increasing endo-stabilizing secondary orbital interactions. However, since a similar correlation does not exist with the (Z)-substituted dienophiles (compare entries 3,4,6,8 and 9), it is likely that secondary orbital interactions are not the sole control element in these reactions.

We believe that the data summarized in Table 3 are consistent with the nonsynchronous transition state hypothesis previously outlined. Whereas use of increasingly powerful activating groups should increase the preference for cyclization to a trans-fused isomer in both the (E)- and (Z)-dienophile series, secondary orbital interactions reinforce this transition state preference only with (E)-dienophiles. The endo cycloadduct from a (Z)-dienophile containing substrate must possess a cis-ring fusion; the data summarized in Table 3 suggest that secondary orbital control is insufficient to overwhelm the "twist-asynchronous" mode of bond formation, or *vice versa*, in these cases.

Experimental Procedures

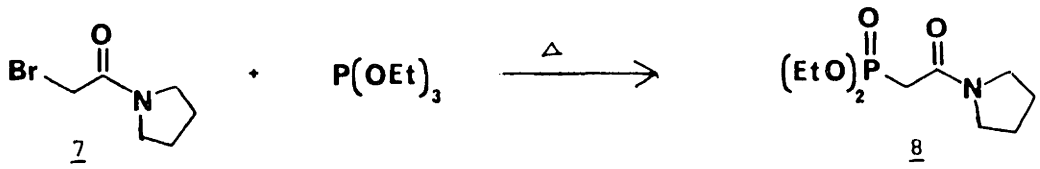


7

2-Bromoacetylpyrrolidine (7)

To a solution of 0.46 mL (392 mg, 5.52 mmol) of freshly distilled pyrrolidine in 35 mL of dry methylene chloride was added pyridine (0.54 mL, 523 mg, 6.62 mmol) neat. The mixture was cooled to 0°C and bromoacetyl bromide (0.56 mL, 1.28 g, 6.35 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 1.5 h, and then was diluted with 20 mL of 1 N HCl and extracted with ether (3x). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield 690 mg (65%) of pure 7 as a yellow oil.

Data for 7: R_f 0.15 (1:1 hexane-ether); NMR (60 MHz, $CDCl_3$) δ 3.80 (s, 2H), 3.60 (m, 4H), 2.05 (m, 4H).



7 8

Diethyl Pyrrolidinylacetamidophosphonate (8)

To a solution of 690 mg (3.59 mmol) of amide 7 in 5 mL of dry toluene was added freshly distilled triethyl phosphite (0.68 mL, 656 mg, 3.95 mmol). The resulting solution was heated to reflux for 2 h, and then was concentrated *in vacuo*. The residue was placed under high vacuum to remove residual triethyl phosphite, giving 744 mg (86%) of pure phosphonate 8.

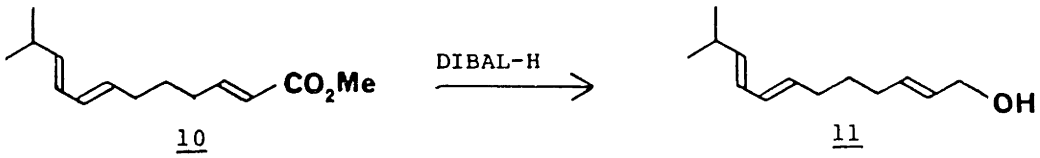
Data for 8: NMR (250 MHz, $CDCl_3$) δ 4.08 (m, 4H, $-OCH_2$), 3.51 (t, J = 6.6 Hz, 2H, $-NCH_2$), 3.40 (dt, J = 1.6, 6.6 Hz, 2H, $-NCH_2$), 2.90 (d, J = 22.0 Hz, 2H, $-CH_2P(O)$), 1.82 (m, 4H, $-CH_2CH_2$), 1.25 (t, J = 7.0 Hz, 6H, $-OCCH_3$); IR (neat) 2975, 2875, 1640(s), 1435(s), 1395, 1255(s), 1165, 1040(s), 965(s) cm^{-1}.

Pyrrolidinyl (E,E,E)-11-Methyldodeca-2,7,9-trienecarboxamide (4)

To a 0°C solution of 391 mg (1.57 mmol) of phosphonate 8 in 4 mL of dry DME was added sodium hydride (89 mg of a 50% oil dispersion, 1.86 mmol). When gas evolution ceased, the solution was warmed to room temperature and then a solution of 237 mg (1.43 mmol) of aldehyde 9 in 2 mL of dry DME was added. After being stirred for 5 min., the reaction mixture was diluted with 7 mL of saturated aqueous $NaHCO_3$. The mixture was extracted with ether (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford 404 mg of crude product. The triene was purified by column chromatography (25 mm column, 10 mL fractions, 3:1 ether-hexane). Concentration of fractions 50-90 afforded 246 mg (66%) of (E,E,E)-triene 4. From fractions 32-47, 23 mg (6%) of the (E,E,Z)-triene isomer was obtained.

Data for 4: NMR (250 MHz, $CDCl_3$) δ 6.88 (dt, J = 15.1, 7.0 Hz, 1H), 6.07 (br d, J = 15.1 Hz, 1H), 5.94 (m, 2H), 5.53 (m, 2H), 3.49 (m, 4H), 2.29 (m, 1H), 2.19 (q, J = 6.9 Hz, 2H), 2.07 (q, J = 7.3 Hz, 2H), 1.90 (m, 4H), 1.58 (m, 2H), 0.97 (d, J = 6.7 Hz, 6H); IR (CH_2Cl_2) 2985, 2960, 2900, 1660, 1615, 1430, 1340(w), 1040(w), 990 cm^{-1}; mass spectrum, m/e

261 (parent ion); high resolution mass spectrum, calcd for $C_{17}H_{27}NO$ 261.2092, found 261.2093 $\pm$ 0.0003.

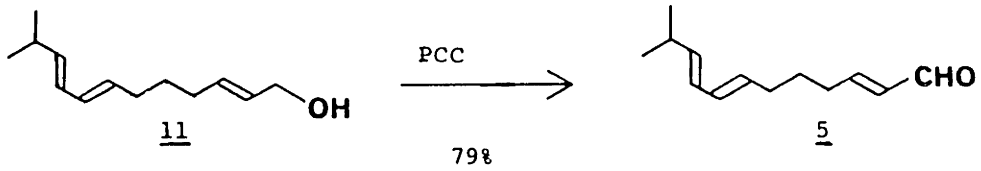


10 11

(E,E,E)-11-Methyldodeca-2,7,9-trien-1-ol (11)

To a -78°C solution of 680 mg (3.06 mmol) of triene ester 10[4a] in 20 mL of dry ether was added dropwise 9.2 mL of a solution of diisobutylaluminum hydride in hexane (9.19 mmol). The reaction was allowed to warm to room temperature. After 1 h, the reaction was cooled to -78°C and was quenched with methanol, followed by 1 N HCl. The product was extracted with ether (3x), the organic extracts were washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford 661 mg of crude product, most of which was used in the next step without purification. A 50 mg sample of the crude product was purified by chromatography on a 0.5-mm preparative silica gel plate (1:1 hexane-ether, 1 development, R_f 0.50), giving 44 mg (98% yield) of pure alcohol 11.

Data for 11: NMR (250 MHz, $CDCl_3$) δ 5.96 (m, 2H), 5.58 (m, 4H), 4.07 (d, J = 3.9 Hz, 2H), 2.29 (m, 1H), 2.05 (m, 4H), 1.48 (m, 2H), 0.97 (d, J = 6.7 Hz, 6H); IR (CH_2Cl_2) 3330(br), 3010, 2950, 2920, 2860, 1675(w), 1460, 1440, 1385, 1365, 1080, 975, 960 cm^{-1}; mass spectrum, m/e 194 (parent ion); high resolution mass spectrum, calcd for $C_{13}H_{22}O$ 194.1671, found 194.1671 $\pm$ 0.0003.

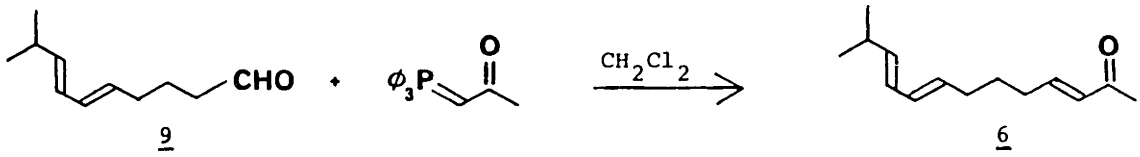


11 79% 5

(E,E,E)-11-Methyldodeca-2,7,9-trienal (5)

To a solution of 333 mg (1.55 mmol) of PCC in 5 mL of dry methylene chloride was added 34 mg (0.41 mmol) of sodium acetate. This mixture was stirred at room temperature for a few minutes. Then a solution of 200 mg (1.03 mmol) of crude alcohol 11 in 5 mL of dry methylene chloride was added dropwise. After 45 min., the reaction was diluted with ether and was filtered through a pad of Florisil in a sintered glass funnel. The solids were washed repeatedly with ether and the filtrate was then concentrated *in vacuo* to afford 156 mg (79%) of aldehyde 5.

Data for 5: NMR (250 MHz, $CDCl_3$) δ 9.48 (d, J = 8.0 Hz, 1H), 6.82 (m, 1H), 6.02 (m, 3H), 5.54 (m, 2H), 2.31 (m, 3H), 2.10 (q, J = 7.2 Hz, 2H), 1.58 (m, 2H), 0.98 (d, J = 6.7 Hz, 6H); IR (CH_2Cl_2) 3020, 2960, 2930, 2870, 2725(w), 1685, 1640(w), 1460(w), 1120, 985 cm^{-1}; mass spectrum, m/e 192 (parent ion); high resolution mass spectrum, calcd for $C_{13}H_{20}O$ 192.1514, found 192.1514 $\pm$ 0.0003.

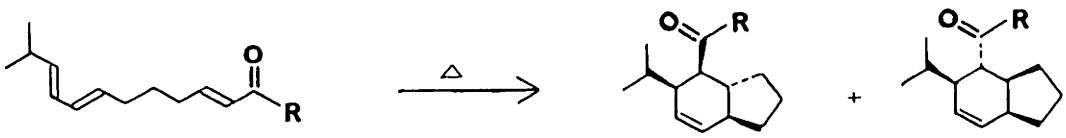


9 6

(E,E,E)-12-Methyltrideca-3,8,10-trien-2-one (6)

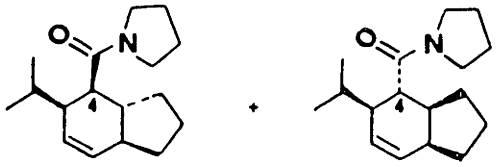
To a solution of 646 mg (2.03 mmol) of 1-triphenylphosphoranylidene-2-propanone in 4 mL of dry methylene chloride was added a solution of 281 mg (1.69 mmol) of aldehyde 9 in 4 mL of dry methylene chloride. The reaction mixture was stirred at room temperature for 73 h, at which time it was concentrated *in vacuo* and the solid residue was triturated with hexane (7x). The hexane extracts were evaporated *in vacuo* to afford 420 mg of crude product. Triene 6 was purified by chromatography (two 1.5-mm silica gel preparative plates, 19:1 hexane-ether, two developments, R_f 0.32) to give 228 mg (65%; 76% based on recovered starting material) of 6. Isolation of the band at R_f 0.49 afforded 40 mg (14%) of recovered 9.

Data for 6: NMR (250 MHz, $CDCl_3$) δ 6.77 (dt, J = 16.0, 6.9 Hz, 1H), 6.05 (d partially superimposed on δ 5.97, J = 16.0 Hz, 1H), 5.97 (m, 2H), 5.54 (m, 2H), 2.25 (m, 6H), 2.08 (br q, J = 7.3 Hz, 2H), 1.56 (m, 2H), 0.98 (d, J = 6.7 Hz, 6H); IR (CH_2Cl_2) 3020(w), 2965, 2870, 1670, 1625, 1365, 995, 910 cm^{-1}; mass spectrum, m/e 206 (parent ion); high resolution mass spectrum, calcd for $C_{14}H_{22}O$ 206.1671, found



General Procedure for Cyclization of Trienes 4, 5, and 6

A solution of triene in dry toluene (0.2-0.3 M) was placed in a Carius tube and was degassed using a stream of argon. The solution was then heated in an oil bath at the temperature specified in Table 2 for 28-90 h. The reaction mixture was then concentrated *in vacuo* and the crude mixture was analyzed by NMR or capillary gas chromatography. The cycloadducts were then purified by chromatography (PTLC). Only in the case of triene amide 4 were the endo and exo adducts separable by TLC; mixtures of 14/15 and 17/18 were isolated, respectively, from the cyclizations of trienal 5 and methyl ketone 6. Analysis of these mixtures by capillary gas chromatography revealed that no isomer enrichment occurred during the purification step.



12 13

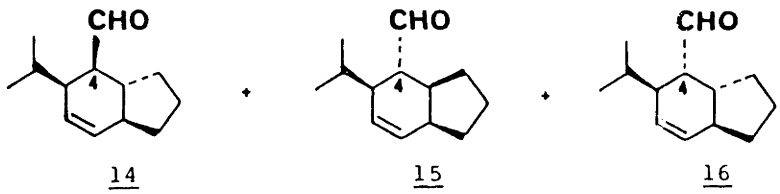
Pyrrolidinyl 5β-(2-Propyl)-2,3,3aβ,4,5,7aα-hexahydroindene 4β-carboxamide (12) and Pyrrolidinyl 5β-(2-Propyl)-2,3,3aα,4,5,7aα-hexahydroindene-4α-carboxamide (13)

Crude mixtures of 12 and 13 were analyzed by integrating the olefin region (δ(12) 5.96, δ(13) 5.82) in the 250 MHz proton NMR spectrum. Mixtures were separated by chromatography (0.5-mm silica gel preparative plate, 2:1 ether-hexane, 1 development, R_f(12) 0.48, R_f(13) 0.33).

Data for 12: mp 116-117°C; NMR (250 MHz, $CDCl_3$) δ 5.96 (br d, J = 10.0 Hz, 1H), 5.55 (br d, J = 10.0 Hz, 1H), 3.45 (m, 4H), 2.70 (dd, J = 10.1, 8.0 Hz, 1H), 2.50 (br s, 1H), 2.02-1.59 (m, 12H), 1.18 (m, 1H), 0.93 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 6.7 Hz, 3H); IR (CH_2Cl_2) 3025(w), 2955, 2870, 1630, 1435 cm^{-1}; mass spectrum, m/e 261 (parent ion); high resolution mass spectrum, calcd for $C_{17}H_{27}NO$ 261.2093, found 261.2092 ± 0.0004.

Data for 13: mp 61-62°C; NMR (250 MHz, $CDCl_3$) δ 5.82 (dt, J = 10.1, 3.3 Hz, 1H), 5.54 (br d, J = 10.1 Hz, 1H), 3.48 (m, 4H), 2.42 (m, 3H), 2.27 (dd, J = 10.7, 10.5 Hz, 1H), 1.95-1.55 (m, 10H), 1.29 (m, 1H), 0.95 (d, J = 6.8 Hz, 3H), 0.74 (d, J = 6.8 Hz, 3H); IR (CH_2Cl_2) 3065(w), 2990, 2915, 1625, 1435 cm^{-1}; mass spectrum, m/e 261 (parent ion); high

resolution mass spectrum, calcd for $C_{17}H_{27}NO$ 261.2093, found 261.2093 $\pm$ 0.0005.



14 15 16

5β-(2-Propyl)-2,3,3aβ,4,5,7aα-hexahydroindene-4β-carboxaldehyde (14) and 5β-(2-Propyl)-2,3,3aα,4,5,7aα-hexahydroindene-4α-carboxaldehyde (15)

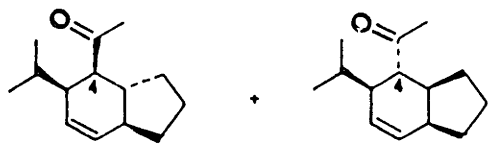
Capillary GC analysis revealed that the crude reaction mixtures contained three cycloadducts: endo 14, exo 15 and epimerized endo 16 (50 m, SE-54 column, 70-150°C, 10°C/min, hold at 150°C for 20 min, t(14) = 16.6, t(15) = 15.9, t(16) = 15.6). The reaction at 100°C gave a 87:5:8 mixture of 14:16:15, whereas at 150°C the ratio was 76:13:11. Such mixtures were purified by chromatography (0.5-mm silica gel preparative plate, 6:1 hexane-ether, 1 development, R_f 0.56).

To verify that the minor product was indeed the epimer of the major cycloadduct 14, we subjected an 76:13:11 mixture of 14:16:15 to K_2CO_3/methanol (2 equivalents) at room temperature for 26 h. The reaction mixture was neutralized with 1N HCl and extracted with ether. The combined extracts were washed with saturated aqueous $NaHCO_3$, and concentrated *in vacuo*. The crude product was analyzed by capillary gas chromatography (same conditions as above) and was found to consist of a 11.5:77.5:11 mixture of 14:16:15 where the epimeric adduct now predominated. In addition, the total endo adduct (endo + epimerized endo) to exo ratio was unchanged.

Data for 14 (obtained on a 87:5:8 mixture of 14:16:15): NMR (250 MHz, $CDCl_3$) δ 9.82 (d, J = 3.0 Hz, 1H), 5.99 (br d, J = 10.0 Hz, 1H), 5.60 (dt, J = 10.0, 3.2 Hz, 1H), 2.73 (m, 1H), 2.58 (ddd, J = 11.0, 7.9, 3.0 Hz, 1H), 1.99 (m, 1H), 1.90-1.42 (m, 6H), 1.13 (m, 2H), 0.98 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.7 Hz, 3H); IR (neat) 3025, 2960, 2870, 1725, 1470, 1390, 1370, 900 cm^{-1}; mass spectrum, m/e 192 (parent ion); high resolution mass spectrum, calcd for $C_{13}H_{20}O$ 192.1514, found

Partial data for 15(obtained on a 87:5:8 mixture of 14:16:15): NMR (250 MHz, $CDCl_3$) δ 9.47 (d, J = 5.0 Hz, 1H), 0.75 (d, J = 6.8 Hz, 3H).

Partial data for 16 (obtained on a 11.5:77.5:11 mixture): NMR (250 MHz, $CDCl_3$) δ 9.80 (d, J = 4.0 Hz, 1H), 5.95 (br d, J = 8.8 Hz, 1H), 5.60 (br d, J = 8.8 Hz, 1H).



17 18

4β-Acetyl-5β-(2-Propyl)-2,3,3aβ,4,5,7aα-hexahydroindene (17) and 4α-Acetyl-5β-(2-Propyl)-2,3,3aα,4,5,7aα-hexahydroindene (18)

Mixtures of 17 and 18 were analyzed by capillary gas chromatography (50 m, SE-54 column, 70-150°C, 10°C/min, hold at 150°C for 25 min, t(17) = 17.88, t(18) = 18.31). The adducts were purified by chromatography (0.5-mm silica gel preparative plate, 6:1 hexane-ether, R_f 0.48). Capillary GC analysis and integration of the olefin region in the NMR spectrum (δ(17) 5.98, δ(18) 5.84) confirmed the endo:exo ratio.

Data for 17 (obtained on an 85:15 mixture): mp 41.5-42.5°C; NMR (250 MHz, $CDCl_3$) δ 5.98 (br d, J = 10.0 Hz, 1H), 5.58 (dt, J = 10.0, 3.0 Hz, 1H), 2.78 (dd partially superimposed on δ 2.71, J = 10.5, 7.6 Hz, 1H), 2.71 (m, 1H), 2.41 (s, 3H), 1.98 (m, 1H), 1.80-1.52 (m, 7H), 1.17 (m, 1H), 0.96 (d, J = 6.8 Hz, 3H), 0.77 (d, J = 6.3 Hz, 3H); IR (CH_2Cl_2) 3040, 2975(s), 2885, 1710(s), 1475, 1390, 1370, 1360, 1150 cm^{-1}; mass spectrum, m/e 206 (parent ion); high resolution mass spectrum, calcd for $C_{14}H_{22}O$ 206.1671, found

Partial data for 18: NMR (250 MHz, $CDCl_3$) δ 5.84 (br d), 0.75 (d).