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Author manuscript

Angew Chem Int Ed Engl. Author manuscript; available in PMC 2018 October 23.

Published in final edited form as:

Angew Chem Int Ed Engl. 2017 October 23; 56(44): 13857–13860. doi:10.1002/anie.201708088.

Enantioselective Total Synthesis of (−)-Deoxoapodine

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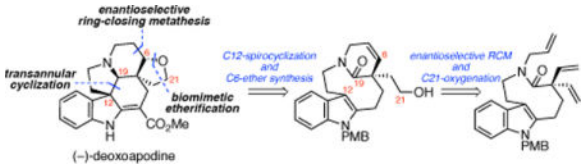
Abstract

The first enantioselective total synthesis of (−)-deoxoapodine is described. Our synthesis of this hexacyclic aspidosperma alkaloid includes an efficient molybdenum-catalyzed enantioselective ring-closing metathesis reaction for desymmetrization of an advanced intermediate that introduces the C5-quaternary stereocenter. After C21-oxygenation, the pentacyclic core was accessed via an electrophilic C19-amide activation and transannular spirocyclization. A biogenetically inspired dehydrative C6-etherification reaction proved highly effective to secure the F-ring and the fourth contiguous stereocenter of (−)-deoxoapodine with complete stereochemical control.

Graphical abstract



Keywords

asymmetric catalysis; alkaloids; metathesis; biomimetic synthesis; total synthesis

The structural diversity and the biological activity of the aspidosperma[1] family of alkaloids has attracted considerable attention from the scientific community over the past decades.[2,3] There are more than 250 natural alkaloids sharing the common pentacyclic aspidosperma core (Figure 1, rings A–E) with several distinct subfamilies possessing C21-oxygenation.[1] (−)-Deoxoapodine (**1**) was first isolated from *Tabernae armeniaca* in 1975,[4a] and later also found in *Hazunta modesta* in 1980.[4b] The hexacyclic C21-oxygenated alkaloid (−)-**1** features a distinct oxolane ring in addition to the archetypal aspidosperma pentacycle, offering a structure with four contiguous stereocenters, including the C5- and C12-quaternary stereocenters. To date, two solutions have been reported for the synthesis of

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deoxoapodine (**1**), with the first providing alkaloid **1** in racemic form[5a] and the second offering enantiomerically enriched alkaloid (−)-**1** by chiral chromatographic separation of an advanced synthetic intermediate.[5b] Herein, we describe the first enantioselective total synthesis of (−)-deoxoapodine (**1**) with excellent absolute and relative stereochemical control. Critical transformations in our concise synthesis of alkaloid (−)-**1** include an efficient molybdenum-catalyzed enantioselective ring-closing metathesis reaction to secure the C5-stereocenter, an anti-Markovnikov C21-oxygenation through a Wacker-Tsuji oxidation,[6e] a highly stereoselective transannular C12-spirocyclization,[6c] an efficient indoline C2-oxidation, and a biogenetically inspired dehydrative C6-etherification reaction.

Recently, one of our laboratories developed a strategy for a highly diastereoselective synthesis of the aspidosperma core via electrophilic lactam activation and transannular cyclization.[6] As an outgrowth of these studies, we sought the development of a catalytic enantioselective method to access (−)-deoxoapodine (**1**) from the versatile lactam **11** (Scheme 1). In addition, we aimed to introduce the oxolane F-ring of alkaloid (−)-**1** via a biogenetically inspired intramolecular C6-etherification strategy. Our retrosynthetic analysis of (−)-deoxoapodine (**1**) is illustrated in Scheme 1. We envisioned hexacycle **7**, possessing both the aspidosperma core and the F-ring of deoxoapodine (**1**), to serve as an advanced intermediate en route to alkaloid (−)-**1**. We posited that the oxolane ring of hexacycle **7** might be secured through interception of the C6-carbon of the transient iminium ion **8** by its C21-hydroxyl group. Given the natural existence of related *N*-oxide aspidosperma alkaloids,[7] we were inspired to consider a net dehydrative strategy to introduce the F-ring of (−)-deoxoapodine (**1**). We planned to access the pentacyclic *N*-oxide **9** through electrophilic activation of 5-lactam **10** to give the aspidosperma core[6] followed by N9-oxide formation. While we had previously prepared a derivative of δ-lactam **10** (R = *p*-methoxybenzyl) in enantiomerically enriched form via an enzymatic kinetic resolution,[6e] we sought to develop an efficient catalytic enantioselective synthesis of this type of lactam, enabling access to either enantiomer of this intermediate, for the preparation of other C21-oxygenated aspidosperma alkaloids. Specifically, we aspired to convert the readily available triene **11** to the desired enantiomer of lactam **10** by sequential catalytic enantioselective ring-closing metathesis (RCM) desymmetrization of triene **11** followed by C21-oxygenation of the resulting diene.

Given the ready availability of lactam **12** (Scheme 2), prepared in seven steps from crotonyl chloride,[6e] we focused on its RCM to afford lactam **13** in enantiomerically enriched form. We chose to explore the utility of molybdenum-monoaryloxide pyrrolide (Mo-MAP) complexes for the anticipated catalytic desymmetrization reaction. This was largely based on one of our laboratories' previous discovery that members of this class of complexes can promote a related desymmetrization reaction en route to (−)-quebrachamine[8,9] efficiently and with exceptional enantioselectivity. However, a key difference between this precedent and the present study is the presence of the C19-amide carbonyl in lactam **12**, which can coordinate with the Lewis acidic transition metal to significantly reduce activity.[10] While dichloro complex **Mo-1** was highly effective (98:2 e.r.) in the synthesis of quebrachamine,[8,9] the use of this complex for the RCM of lactam **12** offered only moderate enantioselectivity (82:18 e.r., Scheme 2).[11] Interestingly, the major product was

heterochiral with respect to the major product in the quebrachamine case,[8] highlighting the impact of the C19-amide on the absolute stereochemical outcome of the RCM reaction. Nevertheless, as the size of the halide substituent on the complex increased, so did the level of enantioselection (Scheme 2), with diiodo complex **Mo-3** (5.0 mol%) efficiently delivering diene (−)-**13** with 93:7 e.r. (>98% conversion, 22 °C, 3 h). Notably, lactam (−)-**13** correlates well with a key intermediate in our synthesis of haplocidine and related aspidosperma alkaloids,[6e] thus enabling an enantioselective approach to these alkaloids as well. Since our planned synthesis of (−)-deoxoapodine (**1**) required the opposite enantiomer of the RCM product, the use of *ent*-**Mo-3** (5 mol%) under the optimal conditions allowed conversion of lactam **12** to the desired diene (+)-**13** in 92% yield (94:6 e.r., Scheme 2).[11]

We next focused on the synthesis of pentacycle (+)-**16** from lactam (+)-**13** (Scheme 3). The necessary C21-oxygentation was introduced through Wacker-Tsuji oxidation[12] of lactam (+)-**13** and subsequent reduction of the resulting C21-aldehyde to furnish the corresponding primary alcohol (79% yield).[6e] The resulting alcohol was converted to the corresponding *p*-nitrobenzoate ester (+)-**14** (95% yield) to set the stage for pentacycle formation. Electrophilic C19-amide activation of lactam (+)-**14** with trifluoromethanesulfonic anhydride, followed by spontaneous stereoselective spirocyclization, and in situ C2-reduction with tri-*n*-butyltin hydride led to the iminium ion **15**, which was subjected to reduction with sodium trimethoxyborohydride to afford the desired pentacycle (+)-**16** in 75% yield as a single diastereomer.[11]

In the early stages of our studies, we secured the oxolane F-ring of deoxoapodine (**1**) employing an oxymercuration step to introduce the C6-ether (Scheme 4). Removal of the *p*-nitrobenzoyl group of pentacyclic ester (±)-**16**, prepared as described previously with a second-generation Ru catalyst for the RCM of triene **12**,[6e] provided the pentacyclic alcohol (±)-**17**. Exposure of alcohol (±)-**17** to mercury(II) trifluoroacetate at 23 °C in tetrahydrofuran[5a] led to oxymercuration which was followed by reductive demercuration using sodium borohydride and sodium hydroxide to give the desired hexacyclic product in 20–40% yield. We found that this transformation was complicated due to the nucleophilic N9-amine,[13] likely a contributing factor to similar observations regarding a recalcitrant C6-etherification in a prior synthesis of deoxoapodine.[14] Through in situ ^{1}H NMR analysis, we realized that higher temperature was required to complete the oxymercuration. Additionally, we developed conditions for more efficient reductive demercuration. Under optimal conditions, exposure of alcohol (±)-**17** to mercury(II) trifluoroacetate at 55 °C for 2 h resulted in complete oxymercuration, which upon treatment with sodium borohydride in presence of triethylborane[15] at −78 °C followed by warming produced hexacycle (±)-**18** in 82% yield. Despite these improved conditions for the introduction of the C6-ether, we continued to evaluate alternative strategies to securing the F-ring of deoxoapodine (**1**).

Our findings regarding the challenging C6-etherification step (vide supra) served as the impetus for examination of a potentially biogenetically relevant strategy for formation of the F-ring. Specifically, given the existence of related N9-amine oxide alkaloids[7] we hypothesized that upon electrophilic activation a net dehydration may lead to the desired C6-ether bond formation. We conjectured that the use of pentacyclic *N*-oxide **9** (Scheme 1) under Polonovski–Potier reaction[16] conditions could provide a new strategy to access the

characteristic F-ring. Treatment of pentacycle (+)-**16** with *p*-nitroperbenzoic acid and potassium carbonate afforded the desired pentacyclic *N*-oxide (+)-**19** in 94% yield (Scheme 5).[17] Exposure of *N*-oxide (+)-**19** to trifluoroacetic anhydride led to rapid formation of the unsaturated iminium ion **20** as confirmed by in situ ^{1}H NMR analysis.[18] Unveiling of the C21 -alcohol through mild in situ methanolysis resulted in the spontaneous cyclization to provide hexacyclic enamine **22**.[19] Reduction of enamine **22** with sodium triacetoxyborohydride in the presence of acetic acid afforded the desired hexacycle (−)-**18** in 74% yield from *N*-oxide (+)-**19**. This strategy offers a new and efficient strategy for accessing the F-ring of (−)-deoxoapodine (**1**) from an advanced pentacyclic *N*-oxide.

Treatment of hexacycle (−)-**18** with thiophenol in trifluoroacetic acid at 55 °C followed by methanolysis, provided hexacycle (−)-**7** in 82% yield (Scheme 6). Exposure of indoline (−)-**7** to *N*-*tert*-butylbenzenesulfinimidoyl chloride[20] in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene efficiently provided the corresponding C2-imine in 85% yield, offering a new and efficient method for C2-oxidation of the aspidosperma core.[3k,21] This new oxidation of the indoline substructure of aspidosperma avoids an undesired (methylthio)methylation side-product[22, 23] that is commonly formed using Swern conditions. The resulting imine was deprotonated by treatment with *n*-butyllithium, and the corresponding metaloenamine was captured with methyl cyanoformate[24, 3h, 3k] to provide (−)-deoxoapodine (**1**) in 61% yield. All spectroscopic data as well as the optical rotation data [observed $[\alpha]_D^{25} = -512$ (*c* = 0.18, $CHCl_3$); lit. $[\alpha]_D^{25} = -432$ (*c* = 0.76, $CHCl_3$)[4a] and $[\alpha]_D^{25} = -522$ (*c* = 0.17, $CHCl_3$)[5b]] for our synthetic (−)-deoxoapodine (**1**) were consistent with the previously reported values.[4, 5]

In summary, we have developed a concise total synthesis of (−)-deoxoapodine (**1**) with excellent absolute and relative stereochemical control for the four contiguous stereogenic centers, including the C5- and C12-quaternary carbons. Our synthesis is the first enantioselective synthesis of any C21-oxygenated hexacyclic aspidosperma alkaloid. An efficient molybdenum-catalyzed enantioselective ring-closing metathesis reaction was utilized to access an enantiomerically enriched versatile lactam. After the anti-Markovnikov C21-oxygenation, the pentacyclic core was accessed by a highly stereoselective transannular spirocyclization. Our synthesis of (−)-deoxoapodine (**1**) was completed via our biogenetically inspired dehydrative C6-etherification reaction to forge the F-ring, followed by an efficient late-stage C2-oxidation of the aspidosperma core to enable methoxy carbonylation of the C-ring.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

M.M., T.K., and K.L.W. acknowledge financial support by NIH-NIGMS (GM074825). A.H.H. and T.J.M. acknowledge financial support by NIH-NIGMS (GM59426). M.M. acknowledges additional support from Amgen. K.L.W. acknowledges a National Science Foundation graduate fellowship and an Amgen Graduate Research Fellowship. M.M. and K.L.W. thank Dr. Marius Mewald for helpful discussions.

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17. The absence of base significantly diminished the yield, and required excess oxidant for complete N-oxide formation.
18. We observed resonances consistent with iminium ion 20 by in situ ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) analysis: ō 8.76 (br-s, 1H, C_8H), 6.93 (d, J = 9.6 Hz, 1H, C_6H), 6.46 (d, J = 9.5 Hz, 1H, C_7H). Assignments were made using additional gCOSY data.
19. We observed resonances consistent with enamine 22 by ^{1}H NMR (400 MHz, CDCl3, 25 °C) analysis of a crude sample: δ 6.35 (d, J = 7.5 Hz, 1H, C_8H), 4.56 (dd, J = 7.5, 5.3 Hz, 1H, C_7H), 3.50 (d, J = 5.3 Hz, 1 H, C_6H). Assignments were made using additional gCOSY data.
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23. The undesired (methylthio)methylation side-product can be substantial. For example, the oxidation of 4a-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole under the conditions described here cleanly provides the desired indolenine in 79% yield, whereas using the Swern conditions the desired product was obtained in 37% yield along with 15% yield of 4a-methyl-8-[(methylthio)methyl]-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole.
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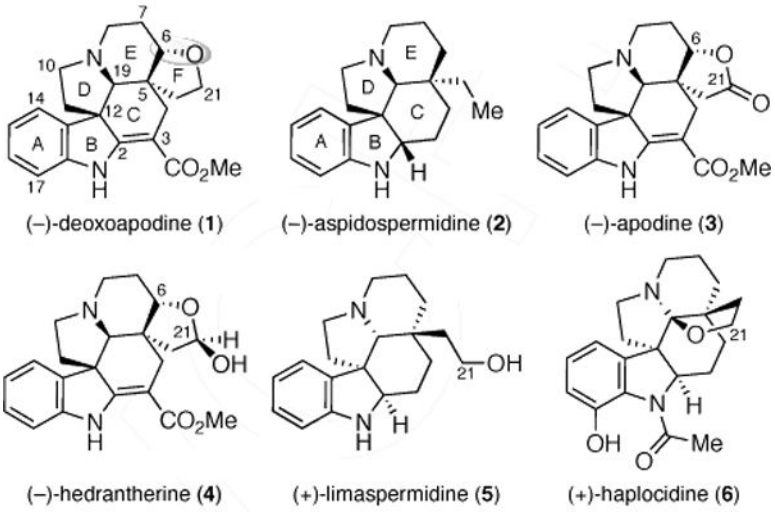
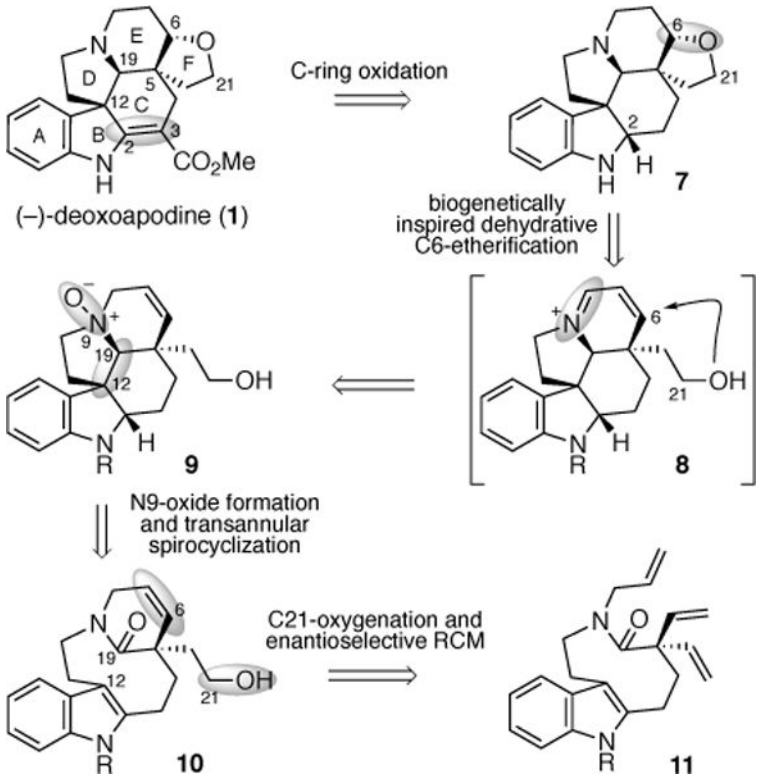
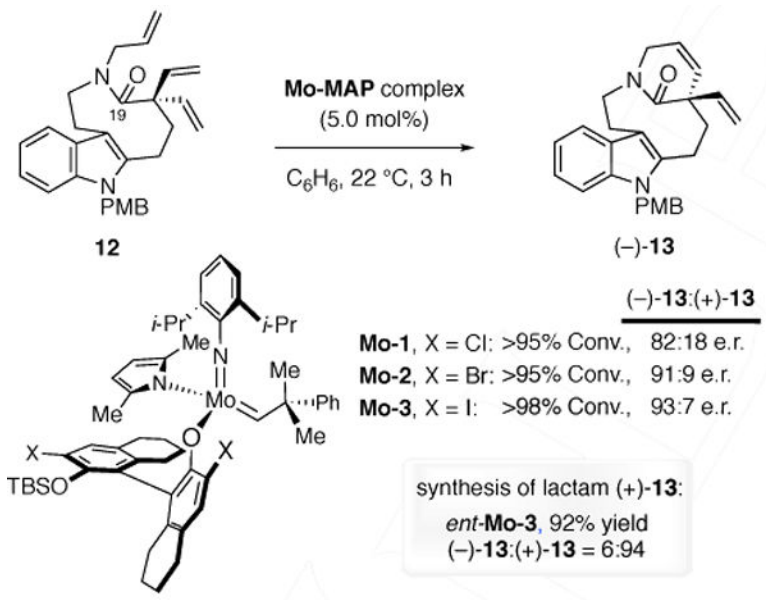


Figure 1.
Structure of (−)-deoxoapodine (**1**) and related alkaloids.

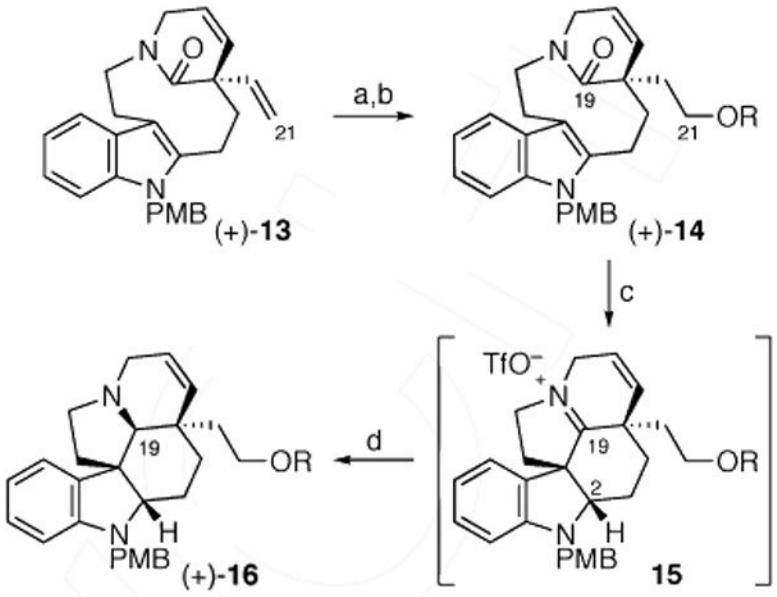


Scheme 1.
Retrosynthetic Analysis of (−)-Deoxoapodine (**1**)



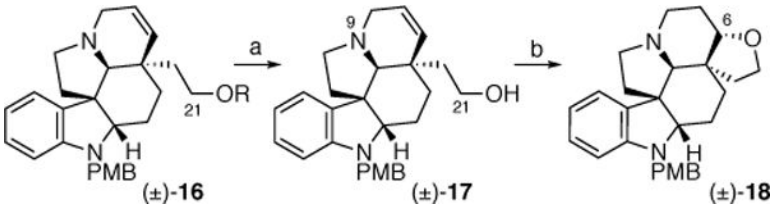
Scheme 2.

Enantioselective Desymmetrization of Lactam **12** by Catalytic RCM: Reactions were performed under N_2 in a glove-box (C_6H_6, 0.1 M). Conversions were determined by analysis of ^1H NMR spectra of the unpurified product mixtures. Enantiomeric ratios were determined by HPLC analysis of the pure product samples.



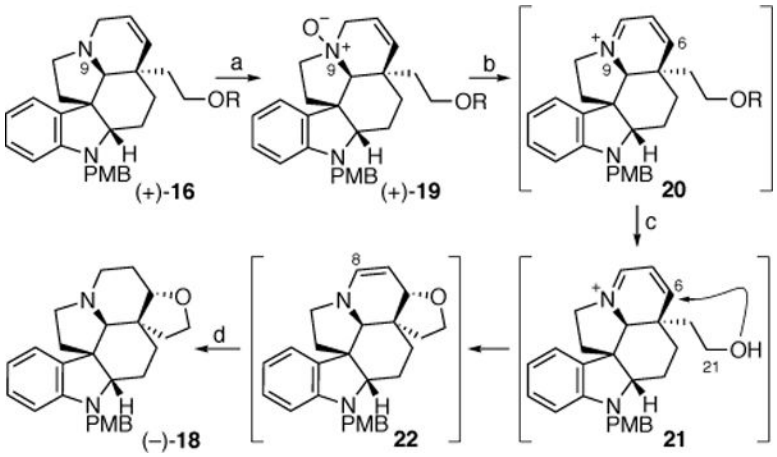
Scheme 3.

Efficient Synthesis of Pentacycle (+)-**16**: a) $Pd(OAc)_2$, *p*-benzoquinone, $HClO_4$, MeCN, H_2O, PhMe; $NaBH_4$, 79%; b) *p*-nitrobenzoyl chloride, DMAP, CH_2Cl_2, 95%; c) *n*-Bu_3SnH, Tf_2O, MeCN, −40 °C; d) $NaBH(OMe)_3$, THF, 75% from (+)-**14**. R = *p*-nitrobenzoyl.



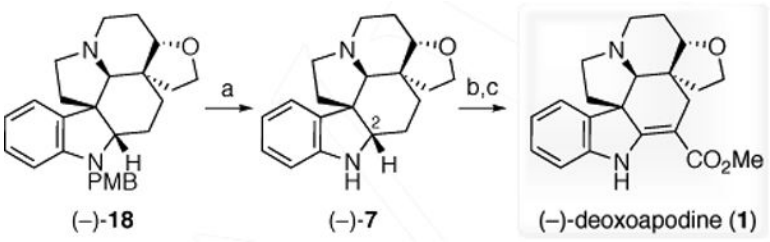
Scheme 4.

Initial C6-Etherification Strategy: a) K_2CO_3, MeOH, 93%; b) $Hg(OCOCF_3)_2$, THF, 23 → 55 °C; BEt_3, $NaBH_4$, −78 → 23 °C, 82%. R = *p*-nitrobenzoyl.



Scheme 5.

Biogenetically Inspired C6-Etherification Strategy: a) *p*-nitroperbenzoic acid, K_2CO_3, CH_2Cl_2, 0 °C, 94%; b) TFAA, CH_2Cl_2, 0 → 23 °C; c) 1,8-diazabicyclo[5.4.0]undec-7-ene, MeOH; d) $NaBH(OAc)_3$, AcOH, 0 → 23 °C, 74% from (+)-**19**. R = *p*-nitrobenzoyl.



Scheme 6.

Total Synthesis of (−)-Deoxoapodine (**1**): a) PhSH, TFA, 55 °C; K_2CO_3, MeOH, 82%; b) *N*-*tert*-butylbenzenesulfinimidoyl chloride, 1,8-diazabicyclo[5.4.0]undec-7-ene, CH_2Cl_2, −78 °C, 85%; c) *n*-BuLi, methyl cyanoformate, THF, −78 → 23 °C, 61%.