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Total Syntheses of (−)-Kopsifoline D and (−)-Deoxoapodine: Divergent Total Synthesis via Late-Stage Key Strategic Bond Formation

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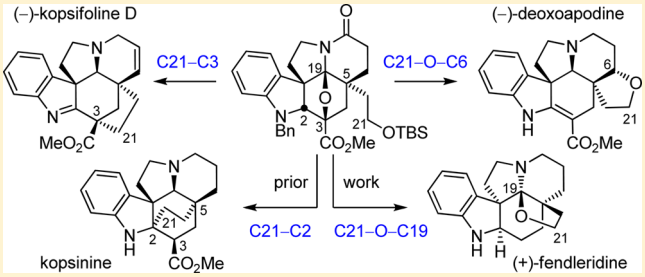
Supporting Information

ABSTRACT: Divergent total syntheses of (−)-kopsifoline D and (−)-deoxoapodine are detailed from a common pentacyclic intermediate **15**, enlisting the late-stage formation of two different key strategic bonds (C21−C3 and C21−O−C6) unique to their hexacyclic ring systems that are complementary to its prior use in the total syntheses of kopsinine (C21−C2 bond formation) and (+)-fendleridine (C21−O−C19 bond formation). The combined efforts represent the total syntheses of members of four classes of natural products from a common intermediate functionalized for late-stage formation of four different key strategic bonds uniquely embedded in each natural product core structure. Key to the first reported total synthesis of a kopsifoline that is detailed herein was the development of a transannular enamide alkylation for late-stage formation of the C21−C3 bond with direct introduction of the reactive indolenine C2 oxidation state from a penultimate C21 functionalized *Aspidosperma*-like pentacyclic intermediate. Central to the assemblage of the underlying *Apidosperma* skeleton is a powerful intramolecular [4 + 2]/[3 + 2] cycloaddition cascade of a 1,3,4-oxadiazole that provided the functionalized pentacyclic ring system **15** in a single step in which the C3 methyl ester found in the natural products served as a key 1,3,4-oxadiazole substituent, activating it for participation in the initiating Diels−Alder reaction and stabilizing the intermediate 1,3-dipole.



INTRODUCTION

The kopsifolines and their unique core hexacyclic ring system were first disclosed in 2003 when Kam and Choo reported the initial members of this new alkaloid class (Figure 1).[1] Kopsifoline A−F (**1**−**6**) were isolated from the leaf extracts of a previously unencountered Malaysian *Kopsia* species later identified as *K. fruticosa* (Ker) A. DC., and their structures were established spectroscopically.[1] Subsequent exploration of *K. singapurensis* led to a second isolation of kopsifoline A (**1**) and characterization of a seventh kopsifoline (singaporentine A, **7**).[2] Related to the *Aspidosperma* alkaloids, their more complex hexacyclic core structure incorporates a previously unprecedented C3−C21 carbon−carbon bond linking the terminal carbon (C21) of the C5 ethyl substituent to C3 bearing a methoxycarbonyl group such that the stereochemically rich central six-membered ring incorporates five or six stereogenic centers, three or four of which are quaternary.

In efforts that served to assign the natural product absolute stereochemistry, we recently disclosed a total synthesis of (+)-fendleridine (**9**, aspidoalbidine), enlisting an intermediate in which the C5 ethyl substituent bears an oxidized terminal C21 methyl group. Closure of this alcohol onto C19 (C21−O−C19 bond formation) via trap of an intermediate iminium ion provided the fendleridine tetrahydrofuran ring and completed the assemblage of its hexacyclic ring system (Figure 2).[3−6] This same intermediate, albeit in the enantiomeric series and by virtue of conversion of the C5 ethyl group primary alcohol to a methyl dithiocarbonate, was enlisted for the total synthesis of kopsinine (**10**),[7,8] featuring a diastereoselective SmI_2-mediated free radical transannular conjugate addition reaction for formation of the bicyclo[2,2,2]octane core central to its hexacyclic ring system with C21−C2 bond formation. This late-stage C21−C2 bond formation not only complemented prior Diels−Alder approaches to its bicyclo[2,2,2]octane core,[9] but it also represented the first synthetic approach that directly provided kopsinine from the underlying pentacyclic *Aspidosperma* alkaloid skeleton (Figure 2).

Herein, we report full details of the use of this same key intermediate in initial exploratory efforts that provided the parent kopsifoline skeleton (named (−)-kopsifoline H, **8**) and the extension of these studies to the first total synthesis of a naturally occurring kopsifoline, (−)-kopsifoline D (**4**).[10] By mimicking what is the likely biosynthesis of the kopsifolines,[1] a late-stage C21−C3 bond formation via a transannular enamide alkylation of an alcohol-derived C21 iodide within the *Aspidosperma* alkaloid skeleton was developed and implemented to complete the assemblage of the kopsifoline skeleton

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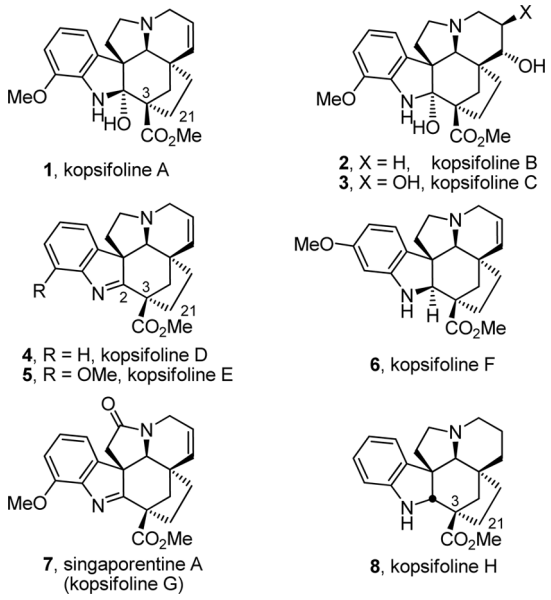


Figure 1. Kopsifolines.

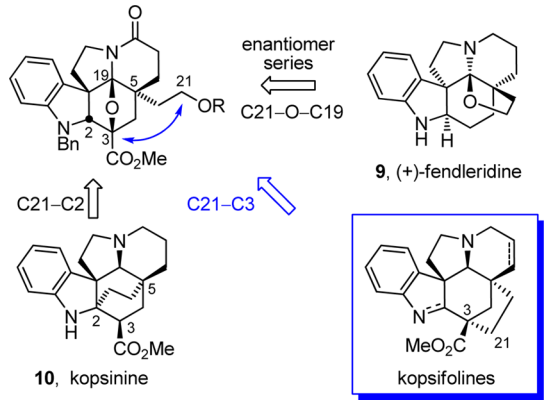
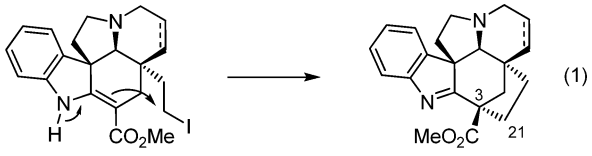


Figure 2. Key strategic bond disconnections for approaching the natural products from a common precursor.

(eq 1) in a route that directly provides the natural product in its final indolenine oxidation state. The studies further established



the kopsifoline absolute configuration as enantiomeric to the *Aspidosperma* alkaloids including fendleridine, but analogous to that found within kopsinine.

An additional attribute of the approach is that the same key intermediate was also used herein to access natural (−)-deoxoapodine (**11**),[11] originally isolated from *Tabernae armeniaca*, by virtue of C21−O−C6 bond formation. These efforts represent only the second total synthesis of the natural product[5] and the first to provide **11** in optically active form, confirming the anticipated absolute configuration assignment.[11c] Thus, a common *Aspidosperma*-like pentacyclic intermediate, bearing a terminally functionalized C5 ethyl substituent (primary alcohol), was used in the divergent total synthesis[12] of a suite of alkaloids, entailing linkage of the C21 primary alcohol oxygen to C19 (fendleridine)[3] and C6 (deoxoapodine) or through linkage of C21 itself to C2 (kopsinine)[7] and C3 (kopsifoline D) using the C21 functionality to conduct complementary nucleophilic or electrophilic C−C bond-forming reactions (Figure 3). The

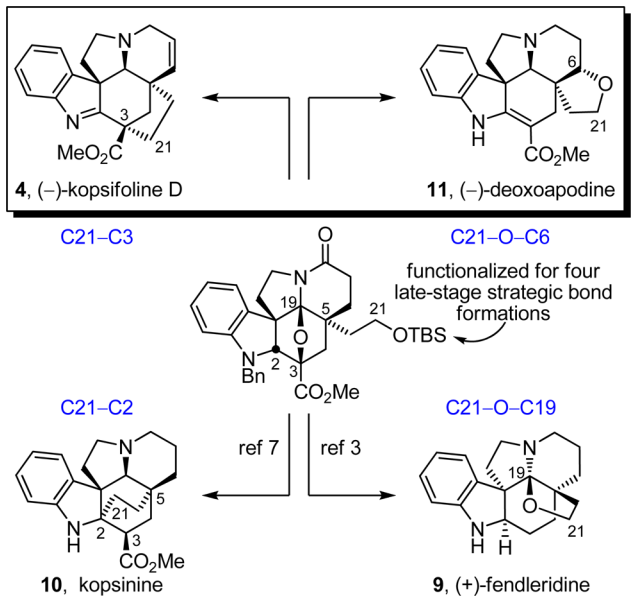


Figure 3. Divergent total syntheses of a series of naturally occurring alkaloids containing deep-seated structural differences from a common cascade cycloaddition product.

combined efforts represent the total syntheses of members of four different classes of natural products from a common intermediate deliberately functionalized for late-stage formation of four different key strategic bonds[13] embedded in each unique core structure.

RESULTS AND DISCUSSION

The basis of the approach and key to the assemblage of the underlying *Aspidosperma* skeleton is a powerful intramolecular [4 + 2]/[3 + 2] cycloaddition cascade of a 1,3,4-oxadiazole that provides the fully functionalized pentacyclic ring system in a single step (Scheme 1).[14] Assembled in two steps from *N*-benzyltryptamine and subsequent N-acylation of the amino-1,3,4-oxadiazole **12** with 4-(2-*tert*-butyldimethylsilyloxy)pent-4-enoic acid (**13**), thermal cyclization of **14** (230 °C, *o*-dichlorobenzene (*o*-DCB)) provided the key pentacyclic skeleton **15** (71%) as a single diastereomer. As disclosed in our initial work,[3] the initiating intramolecular [4 + 2] cycloaddition[15] is followed by a retro Diels−Alder loss of N_2 to provide an intermediate 1,3-dipole[14] stabilized by the two substituents on the carbonyl ylide. In turn, the stabilized 1,3-dipole undergoes a subsequent diastereoselective [3 + 2] cycloaddition[16] with the tethered indole exclusively through an endo transition state and with an intrinsic regioselectivity that is reinforced by the linking tether to provide the cascade cycloadduct **15**. Inherent in the approach, the C3 methyl ester found in the kopsifolines, deoxoapodine, and kopsinine serves as a key 1,3,4-oxadiazole substituent, activating it for participation in the initiating Diels−Alder reaction and stabilizing the intermediate 1,3-dipole. As detailed in our preceding studies albeit with improvements in the originally disclosed conversions,[7] diastereoselective reductive cleavage of

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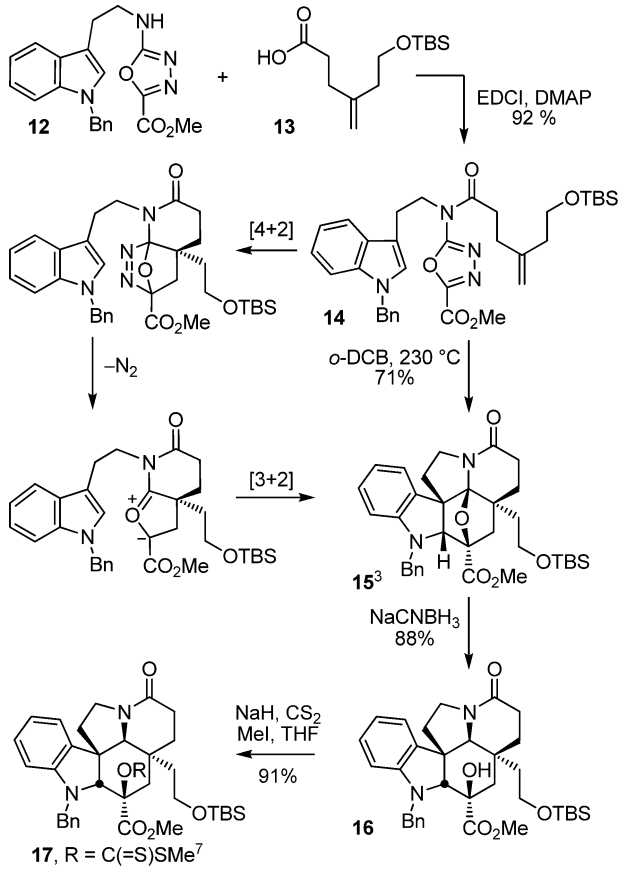
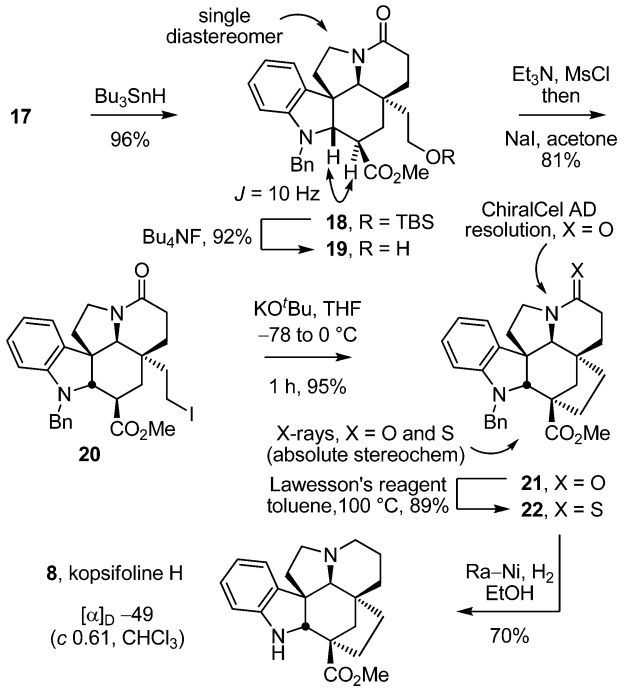
Scheme 1



Scheme 2. Synthesis of Kopsifoline H



the oxido bridge in **15** ($NaCNBH_3$, 88%) with exclusive convex face hydride reduction of an intermediate iminium ion flanked by two quaternary centers and subsequent methyl dithiocarbonate formation (NaH, CS_2; MeI; 91%) provided **17**[7] in superb conversions.

Kopsifoline H. As our studies began, we first focused on the synthesis of **8**, the parent kopsifoline skeleton. Although **8** has not yet been isolated as a naturally occurring substance, lacking a $\Delta^{6,7}$-double bond and containing a saturated indoline, it possesses the parent hexacyclic skeleton and represents the tetrahydro derivative of kopsifoline D. Barton–McCombie deoxygenation[17] of methyl dithiocarbonate **17** (Bu_3SnH, cat. AIBN, toluene, reflux, 1 h, 96%) cleanly provided **18** as a single diastereomer arising from exclusive convex face hydrogen atom reduction of the intermediate stabilized radical and inversion of the C3 stereochemistry (Scheme 2). Silyl ether cleavage of **18** (Bu_4NF, tetrahydrofuran (THF), −78 to 25 °C, 1 h, 92%) provided the primary alcohol **19** that in turn was converted to the iodide **20** (Et_3N, CH_3SO_2Cl, THF, −78 °C, 1 h then NaI, acetone, −78 to 50 °C, 12 h, 81%), setting the stage for studies on its cyclization to the kopsifoline skeleton. After exploration of several alternatives, treatment of **20** with KO^{t}Bu in THF (3 equiv, −78 to 0 °C, 1 h) proved to be highly effective and afforded **21** (95%), whose structure and stereochemistry were confirmed with a single-crystal X-ray structure determination.[18a] Initial, albeit limited, attempts to promote the cyclization of the intermediate mesylate (0%) or corresponding tosylate (32–36%) were not as productive. Chromatographic separation of the enantiomers of **21** (α = 1.2, 10% *i*-PrOH/hexane) was carried out on a semipreparative Daicel ChiralCel AD column, providing (+)-**21** and *ent*-(−)-**21**. Treatment of each enantiomer of **21** with Lawesson's reagent[19] (1.1 equiv, toluene, 100 °C, 0.5 h) furnished the thiolactam **22** (89%). The absolute configuration of (+)-**22** was unambiguously established by an X-ray structure determination conducted on this intermediate containing a heavy atom (S).[18b] Concomitant reduction of the thioamide and removal of the *N*-benzyl group was accomplished by the treatment of (+)-**22** with Raney-nickel (Ra–Ni, H_2, EtOH, 80 °C, 0.5 h) to furnish (−)-**8** (70%), which we have come to refer to as kopsifoline H, designating its hydrogenated (H) state.

Biomimetic C21–C3 Bond Formation: 6,7-Dihydrokopsifoline D. The additional key question addressed in initial studies was whether a late-stage C21–C3 bond formation via a transannular enamide alkylation of an alcohol-derived C21 electrophile was feasible for formation of the kopsifoline core, permitting the direct introduction of the correct C2 indolenine oxidation state of the natural products (see eq 1). These efforts began with **25**, originally prepared in prior studies[7] and bearing a readily removable indoline *N*-carboxybenzyl (Cbz) group. In efforts that impact the regioselectivity of the Chugaev elimination,[20] conversion of **16** to the corresponding Cbz carbamate **23**, followed by an improved methyl dithiocarbonate formation (NaH, CS_2 then MeI, THF, 0 to 25 °C, 3 h, 93%) provided **24** (Scheme 3). The intermediate xanthate **24** underwent clean thermal elimination under mild reaction conditions (toluene, 100 °C bath, 48 h or 150 °C bath, 36 h), providing good yields (60%) of **25**. Here, the indoline Cbz carbamate (vs *N*-benzyl) activates C2–H for xanthate syn elimination, favoring formation of the more substituted and stable olefin.[7]

Silyl ether cleavage in **25** (3 equiv Bu_4NF, THF, 25 °C, 1 h, 98%) and conversion of the primary alcohol **26** to the primary iodide **27** (Et_3N, CH_3SO_2Cl, THF then NaI, acetone, 50 °C, 12 h, 80%) followed by reduction of the amide **27** to the tertiary amine **28** (5 equiv BH_3·THF, THF, 0 °C, 1.5 h, 79%) set the stage for examination of the transannular cyclization. After optimization of the conditions, we were delighted to find that

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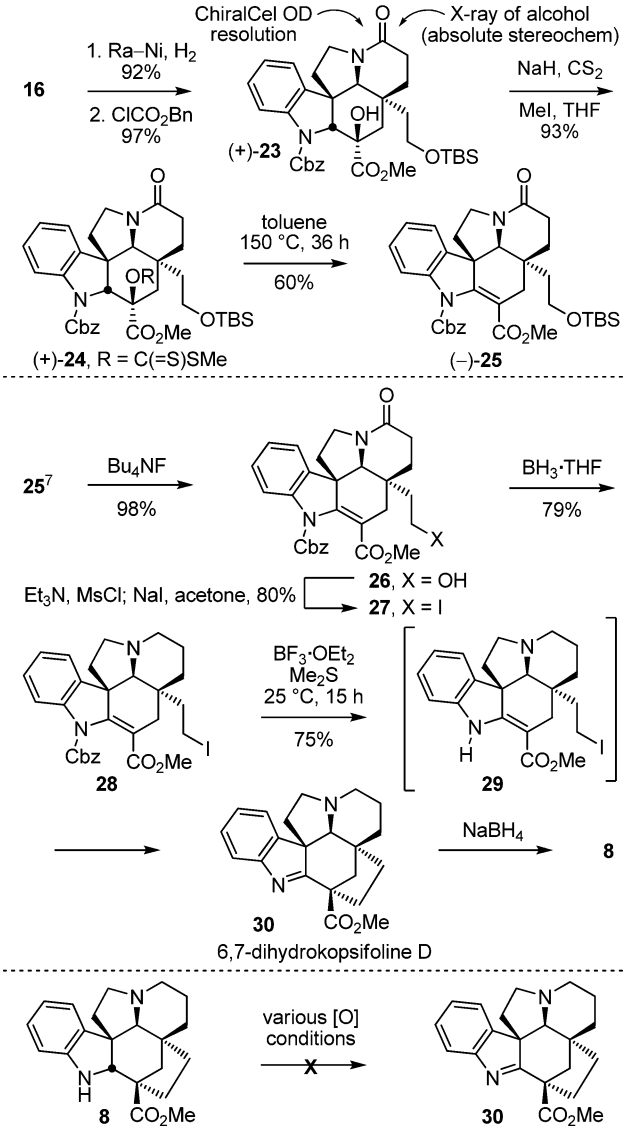
Scheme 3. Synthesis of 6,7-Dihydrokopsifoline D

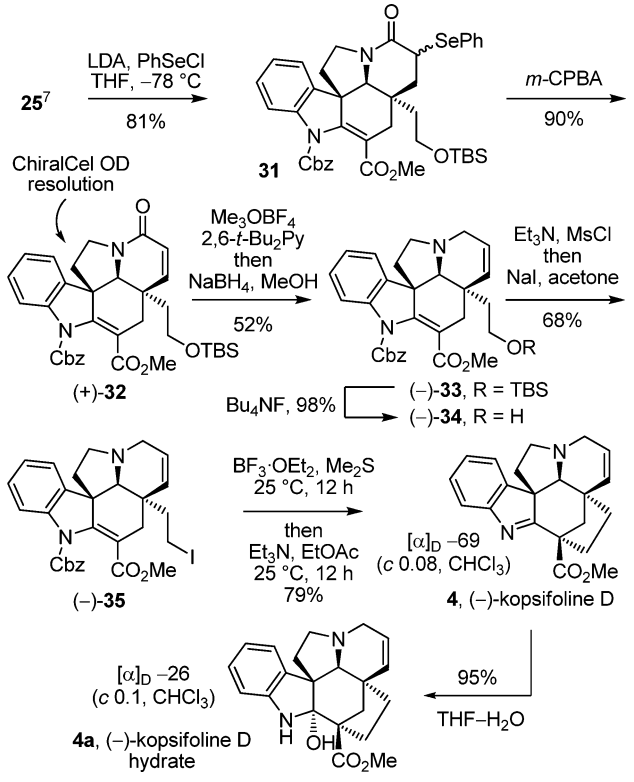


the treatment of **28** with $BF_3{\cdot}OEt_2$ and dimethyl sulfide (Me_2S) in CH_2Cl_2 (25 °C, 15 h)[21] proceeded smoothly not only to promote Cbz deprotection but also to afford **30** directly in 75% yield as a single diastereomer, providing 6,7-dihydrokopsifoline D. Shorter reaction times led to detection and isolation of the intermediate Cbz deprotection product **29** that itself undergoes slow cyclization to the indolenine **30** simply upon standing at room temperature. Notably, the corresponding carbinol amine derived from water addition to C2 of **30** could also be isolated if the chromatographic purification (SiO_2) of **30** was carried out without the presence of Et_3N (ethyl acetate (EtOAc) vs 2% Et_3N in EtOAc). Reduction of **30** ($NaBH_4$, EtOH, 0 to 25 °C) provided **8**, confirming the structure of **30** and providing an alternative synthesis of kopsifoline H.

Finally, limited efforts to convert **8** to **30** by oxidation (MnO_2, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, $Me_2{}^+S{-}Cl$, $KMnO_4$) to the C2 imine have not yet proved productive (Scheme 3), suggesting that direct indolenine introduction from intermediates such as **28** may constitute a more effective approach.

Total Synthesis of (−)-Kopsifoline D. Adoption of the approach for the total synthesis of kopsifoline D required installation of the $\Delta^{6,7}$-double bond. Toward this end, *α*-phenylselenation of **25** was achieved by treatment of the lactam enolate (lithium diisopropylamide, −78 °C) with phenylselenyl chloride (PhSeCl, 1 equiv) to provide **31** (81%, Scheme 4).

Scheme 4. Total Synthesis of (−)-Kopsifoline D



The mixture of isomeric phenylselenides (8:1, *β*:*α*) was treated with *m*-chloroperoxybenzoic acid (*m*-CPBA, 1.5 equiv) in CH_2Cl_2 at −78 °C to yield the corresponding selenoxides, and their subsequent in situ syn elimination proceeded smoothly (−78 to 25 °C) to afford **32** (90%). The enantiomers of **32** were easily separated (*α* = 1.48, 20% *i*-PrOH/hexane) on a semipreparative Chiralcel OD column, affording natural (+)-**32** and *ent*-(−)-**32**. Clean 1,2-reductive removal of the lactam carbonyl was best accomplished by *O*-methylation of (+)-**32** and subsequent reduction of the resulting methoxyiminium ion (3 equiv Me_3OBF_4, 2,6-*t*-Bu_2Py, CH_2Cl_2, 25 °C; $NaBH_4$, MeOH, 25 °C, 52%)[22] to afford natural (−)-**33**. Nearly as effective, direct lactam reduction of (+)-**32** by treatment with diisobutylaluminum hydride (Dibal-H, 5 equiv, THF, −20 °C, 20 min) also afforded (−)-**33** (48%) in a single step. Alternatively, treatment of (+)-**32** with Lawesson's reagent[19] (1.1 equiv, toluene, 100 °C, 0.5 h, 65%), subsequent *S*-methylation of the intermediate thioamide (3 equiv Me_3OBF_4, 2,6-*t*-Bu_2Py, CH_2Cl_2, 25 °C) and reduction of the resulting *S*-methyliminium ion (10 equiv $NaBH_4$, MeOH, 0 °C, 45 min) also provided **33** (40% overall), albeit in lower overall conversions. Silyl ether cleavage (Bu_4NF, THF, 25 °C, 1 h, 98%) followed by conversion of the primary alcohol (−)-**34** to the primary iodide (−)-**35** (Et_3N, CH_3SO_2Cl, THF, −78 °C then NaI, acetone, 90 °C bath temperature, 12 h, 68%) set the stage for the key transannular cyclization. Cbz deprotection and subsequent intramolecular ring closure of **35** ($BF_3{\cdot}OEt_2$, Me_2S, CH_2Cl_2, 25 °C, 12 h followed by treatment with Et_3N, EtOAc, 25 °C, 12 h) provided (−)-kopsifoline D (**4**) in superb

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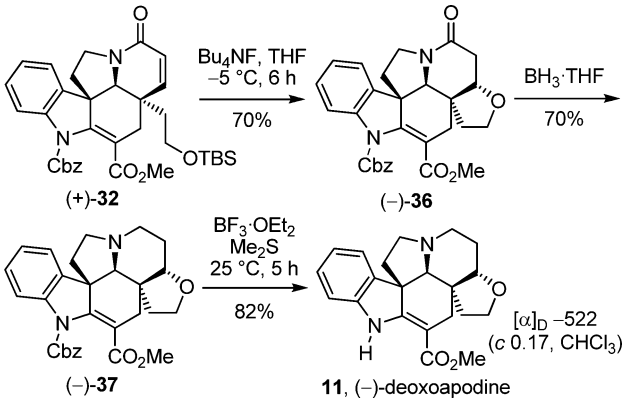
conversion (79%) and identical in all respects compared to those of the authentic material[1] except for its distinctly different optical rotation ($[\alpha]_D$ −69 (*c* 0.08, $CHCl_3$) vs reported $[\alpha]_D$ −27 (*c* 0.09, $CHCl_3$)[1b]). Use of the intermediate mesylate (0%) and corresponding tosylate (22%) was less effective than the primary iodide **35**, and its intramolecular ring closure to provide **4** was slower than that providing **30**, requiring a longer reaction time and deliberate base treatment (Et_3N) for completion. Initial concerns over the discrepancy in the optical rotations between our synthetic **4** versus that reported for natural **4** led us to explore several origins of the distinctions and entailed repeated preparations of synthetic material. In the course of these efforts, the water addition product to kopsifoline D (kopsifoline D hydrate, **4a**) was also isolated and characterized (Scheme 4). Unexpectedly, the optical rotation of this synthetic hydrate, which could be deliberately prepared by simply stirring a solution of **4** in THF−H_2O (95%, 25 °C, 3 h), perfectly matched that reported for kopsifoline D ($[\alpha]_D$ −26 (*c* 0.08, $CHCl_3$) vs reported $[\alpha]_D$ −27 (*c* 0.09, $CHCl_3$)[1b]). This suggests that, while the spectroscopic characterization of natural kopsifoline D was effectively conducted with **4**, the optical rotation itself was measured on a sample that had undergone hydration. The ease of kopsifoline D hydration also suggests that this corresponding hydrate is a natural product as well and that it likely will be isolated and characterized in the years ahead. The unambiguous assignment of the absolute configuration of **4** was accomplished with a single-crystal X-ray structure determination conducted on the natural enantiomer of the primary alcohol derived from **23**,[18c] which was correlated with (+)-**32** (see Supporting Information [SI]).

Total Synthesis of (−)-Deoxoapodine. With the natural enantiomer (+)-**32** in hand, our efforts turned to the divergent total synthesis of (−)-deoxoapodine (Scheme 5). Complementary to the approach to kopsifoline D, silyl ether deprotection prior to lactam carbonyl removal was anticipated to permit the requisite C21−O−C6 strategic bond formation by conjugate addition of the primary alcohol. Silyl ether deprotection upon treatment of (+)-**32** with Bu_4NF (3 equiv) in THF at −5 °C (6 h) under basic conditions smoothly provided only the primary alcohol conjugate addition product (−)-**36** (70%) as a single diastereomer without the detection or isolation of the intermediate alcohol. Higher reaction temperatures (0−25 °C) led to generation of an additional minor diastereomer of the conjugate addition product, whereas lower reaction temperatures (−40 °C) resulted in little deprotection and cyclization. In contrast, silyl ether deprotection under acidic conditions conducted by treatment of (+)-**32** with HF·pyridine (3 equiv, THF, 0 °C, 2 h) afforded only the deprotected primary alcohol (84−95%) with little or no cyclization even under prolonged reaction times (10 h). Reductive removal of the lactam carbonyl of (−)-**36** upon treatment with BH_3·THF (THF, 0 °C, 1.5 h) provided (−)-**37** (70%) and subsequent cleavage of the Cbz group (BF_3·OEt_2, Me_2S, 25 °C, 5 h, 82%)[21] afforded natural (−)-deoxoapodine (**11**, $[\alpha]_D$ −522 (*c* 0.17, $CHCl_3$) vs $[\alpha]_D$ −432 (*c* 0.76, $CHCl_3$)[11a] and $[\alpha]_D$ −593 ($CHCl_3$)[11b]), which proved identical in all respects to those of the natural product. By virtue of the crystallographic assignment of the absolute configuration of intermediates in route to **11** ((+)-**23**[18c] and (+)-**32**), the correlation serves to unambiguously confirm the anticipated absolute configuration for the natural product.[11c]

Scheme 5. Total Synthesis of (−)-Deoxoapodine



CONCLUSIONS

Divergent total syntheses of (−)-kopsifoline D and (−)-deoxoapodine that unambiguously established their absolute stereochemistry are detailed from a common pentacyclic intermediate **15** with the late-stage formation of two different key strategic bonds unique to their hexacyclic ring systems, complementing its prior use in the total syntheses of kopsinine and (+)-fendleridine. The combined efforts represent the total syntheses of members of four different classes of natural products from a common intermediate functionalized for late-stage formation of four different key strategic bonds uniquely embedded in each natural product core structure. The basis of the approach and central to the assemblage of the underlying skeleton is a powerful intramolecular [4 + 2]/[3 + 2] cycloaddition cascade of a 1,3,4-oxadiazole.[14,23−32] This reaction provided the C21 functionalized pentacyclic ring system **15** in a single step in which the C3 methyl ester found in the natural products served as a key 1,3,4-oxadiazole substituent, activating it for participation in the initiating Diels−Alder reaction and stabilizing the intermediate 1,3-dipole.

ASSOCIATED CONTENT

Supporting Information

Full experimental details and copies of $^1H/^{13}C$ NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Kam, T.; Choo, Y. *Tetrahedron Lett.* **2003**, *44*, 1317. (b) Kam, T.; Choo, Y. *Helv. Chim. Acta* **2004**, *87*, 991. (c) Kam, T.; Choo, Y. *Phytochemistry* **2004**, *65*, 2119.

(2) Awang, K.; Ahmad, K.; Thomas, N. F.; Hirasawa, Y.; Takeya, K.; Mukhtar, M. R.; Mohamad, K.; Morita, H. *Heterocycles* **2008**, *75*, 3051.
(3) Campbell, E. L.; Zuhl, A. M.; Lui, C. M.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 3009.
(4) (a) Ban, Y.; Ohnuma, T.; Seki, K.; Oishi, T. *Tetrahedron Lett.* **1975**, *10*, 727. (b) Honma, Y.; Ohnuma, T.; Ban, Y. *Heterocycles* **1976**, *5*, 47. (c) Yoshida, K.; Sakuma, Y.; Ban, Y. *Heterocycles* **1987**, *25*, 47. (d) Tan, S. H.; Banwell, M. G.; Willis, A. C.; Reekie, T. A. *Org. Lett.* **2012**, *14*, 5621.
(5) Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 2598.
(6) Isolation: (a) Burnell, R. H.; Medina, J. D.; Ayer, W. A. *Can. J. Chem.* **1996**, *44*, 28. (b) Burnell, R. H.; Medina, J. D.; Ayer, W. A. *Chem. Ind.* **1964**, *1*, 33. (c) Walser, A.; Djerassi, C. *Helv. Chim. Acta* **1965**, *48*, 391. (d) Brown, K. S., Jr.; Budzikiewicz, H.; Djerassi, C. *Tetrahedron Lett.* **1963**, *25*, 1731.
(7) Xie, J.; Wolfe, A. L.; Boger, D. L. *Org. Lett.* **2013**, *15*, 868.
(8) Isolation: (a) Crow, W. D.; Michael, M. *Aust. J. Chem.* **1955**, *8*, 129. (b) Crow, W. D.; Michael, M. *Aust. J. Chem.* **1962**, *15*, 130. (c) Kump, W. G.; Schmid, H. *Helv. Chim. Acta* **1961**, *44*, 1503. (d) Kump, W. G.; Count, D. J. L.; Battersby, A. R.; Schmid, H. *Helv. Chim. Acta* **1962**, *45*, 854. (e) Kump, W. G.; Patel, M. B.; Rowson, J. M.; Schmid, H. *Helv. Chim. Acta* **1964**, *47*, 1497.
(9) (a) Kuehne, M. E.; Seaton, P. J. *J. Org. Chem.* **1985**, *50*, 4790. (b) Ogawa, M.; Kitagawa, Y.; Natsume, M. *Tetrahedron Lett.* **1987**, *28*, 3985. (c) Wenkert, E.; Pestchanker, M. J. *J. Org. Chem.* **1988**, *53*, 4875. (d) Magnus, P.; Brown, P. *J. Chem. Soc., Chem. Commun.* **1985**, 184. (e) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183. (f) Harada, S.; Sakai, T.; Takasu, K.; Yamada, K.; Yamamoto, Y.; Tomioka, K. *Chem.—Asian J.* **2012**, *7*, 2196.
(10) Synthetic studies on the kopsifolines: (a) Hong, X.; France, S.; Mejia-Oneto, J. M.; Padwa, A. *Org. Lett.* **2006**, *8*, 5141. (b) Hong, X.; France, S.; Padwa, A. *Tetrahedron* **2007**, *63*, 5962. (c) Corkey, B. K.; Heller, S. T.; Wang, Y.; Toste, F. D. *Tetrahedron* **2013**, *69*, 5640.
(11) Isolation: (a) Inglesias, R.; Diatta, L. *Rev. CENIC, Cienc. Fis.* **1975**, *6*, 135. (b) Bui, A. M.; Das, B. C.; Potier, P. *Phytochem.* **1980**, *19*, 1473. (c) Although the structure of deoxoapodine, as well as apodine, have been depicted with the correct absolute configuration in the literature, we were unable to find work that unambiguously established the absolute configuration.
(12) (a) Boger, D. L.; Brotherton, C. E. *J. Org. Chem.* **1984**, *49*, 4050. (b) Mullican, M. D.; Boger, D. L. *J. Org. Chem.* **1984**, *49*, 4033. (c) Mullican, M. D.; Boger, D. L. *J. Org. Chem.* **1984**, *49*, 4045.
(13) Corey, E. J.; Howe, W. J.; Orf, H. W.; Pensak, D. A.; Petersson, G. *J. Am. Chem. Soc.* **1975**, *97*, 6116.
(14) (a) Wilkie, G. D.; Elliott, G. I.; Blagg, B. S. J.; Wolkenberg, S. E.; Soenen, D. R.; Miller, M. M.; Pollack, S.; Boger, D. L. *J. Am. Chem. Soc.* **2002**, *124*, 11292. (b) Elliott, G. I.; Fuchs, J. R.; Blagg, B. S. J.; Ishikawa, H.; Tao, H.; Yuan, Z. Q.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 10589.
(15) Reviews: (a) Margetic, D.; Troselj, P.; Johnston, M. R. *Mini-Rev. Org. Chem.* **2011**, *8*, 49. (b) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869. (c) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781.
(16) Padwa, A.; Price, A. T. *J. Org. Chem.* **1998**, *63*, 556.
(17) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, *16*, 1574.
(18) (a) The structure and stereochemistry of **21** were confirmed with a single crystal X-ray structure determination conducted on white monoclinic crystals of **21** obtained from Et_2O (CCDC 977766). (b) The structure, stereochemistry, and absolute configuration of (+)-**22** (natural enantiomer) were established with a single crystal X-ray structure determination conducted on a colorless parallelpiped crystal obtained from acetone (CCDC 978175). (c) The enantiomers of **23** were separated by chiral phase HPLC (Chiracel OD, 2 cm × 20 cm, 20% *i*-PrOH/hexane, 7 mL/min, α = 1.8) and the structure, stereochemistry, and absolute configuration of the natural enantiomer ((+)-**23**) were established with a single-crystal X-ray structure determination conducted on crystals of the corresponding primary alcohol obtained from MeOH (CCDC 977767).
(19) Yde, B.; Yousif, N. M.; Pedersen, U.; Thomsen, I.; Lawesson, S. O. *Tetrahedron* **1984**, *40*, 2047.
(20) DePuy, C. H.; King, R. W. *Chem. Rev.* **1960**, *60*, 431.
(21) Sanchez, I. H.; Lopez, F.; Soria, J. J.; Larraza, M. I.; Flores, H. J. *J. Am. Chem. Soc.* **1983**, *105*, 7640.
(22) Blowers, J. W.; Saxton, J. E.; Swanson, A. G. *Tetrahedron* **1986**, *42*, 6071.
(23) Wolkenberg, S. E.; Boger, D. L. *J. Org. Chem.* **2002**, *67*, 7361.
(24) Yuan, Z. Q.; Ishikawa, H.; Boger, D. L. *Org. Lett.* **2005**, *7*, 741.
(25) Lajiness, J. P.; Jiang, W.; Boger, D. L. *Org. Lett.* **2012**, *14*, 2078.
(26) (a) Choi, Y.; Ishikawa, H.; Velcicky, J.; Elliott, G. I.; Miller, M. M.; Boger, D. L. *Org. Lett.* **2005**, *7*, 4539. (b) Elliott, G. I.; Velcicky, J.; Ishikawa, H.; Li, Y.; Boger, D. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 620. (c) Ishikawa, H.; Elliott, G. I.; Velcicky, J.; Choi, Y.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 10596. (d) Ishikawa, H.; Boger, D. L. *Heterocycles* **2007**, *72*, 95. (e) Kato, D.; Sasaki, Y.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 3685. (f) Sasaki, Y.; Kato, D.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 13533.
(27) (a) Ishikawa, H.; Colby, D. A.; Boger, D. L. *J. Am. Chem. Soc.* **2008**, *130*, 420. (b) Gotoh, H.; Sears, J. E.; Eschenmoser, A.; Boger, D. L. *J. Am. Chem. Soc.* **2012**, *134*, 13240.
(28) Ishikawa, H.; Colby, D. A.; Seto, S.; Va, P.; Tam, A.; Kakei, H.; Rayl, T. J.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2009**, *131*, 4904.
(29) Va, P.; Campbell, E. L.; Robertson, W. M.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 8489.
(30) Schleicher, K. D.; Sasaki, Y.; Tam, A.; Kato, D.; Duncan, K. K.; Boger, D. L. *J. Med. Chem.* **2013**, *56*, 483.
(31) Campbell, E. L.; Skepper, C. K.; Sankar, K.; Duncan, K. K.; Boger, D. L. *Org. Lett.* **2013**, *15*, 5306.
(32) (a) Tam, A.; Gotoh, H.; Robertson, W. M.; Boger, D. L. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6408. (b) Gotoh, H.; Duncan, K. K.; Robertson, W. M.; Boger, D. L. *ACS Med. Chem. Lett.* **2011**, *2*, 948. (c) Leggans, E. K.; Barker, T. J.; Duncan, K. K.; Boger, D. L. *Org. Lett.* **2012**, *14*, 1428. (d) Leggans, E. K.; Duncan, K. K.; Barker, T. J.; Schleicher, K. D.; Boger, D. L. *J. Med. Chem.* **2013**, *56*, 628. (e) Barker, T. J.; Duncan, K. K.; Otrubova, K.; Boger, D. L. *ACS Med. Chem. Lett.* **2013**, *4*, 985.