JOC Article

Convergency and Divergency as Strategic Elements in Total Synthesis: The Total Synthesis of (−)-Drupacine and the Formal Total Synthesis of (±)-Cephalotaxine, (−)-Cephalotaxine, and (+)-Cephalotaxine

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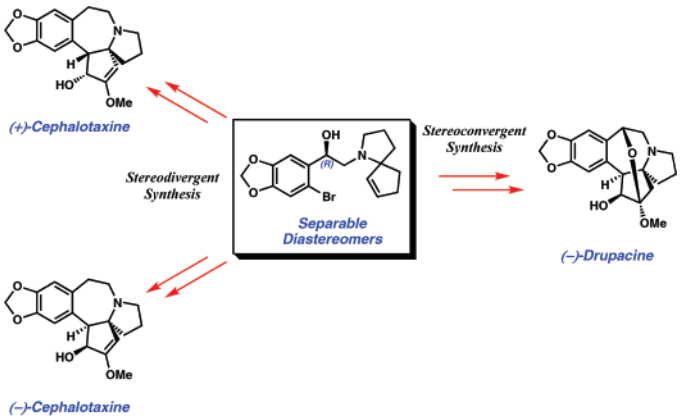

A concise route toward the syntheses of (−)-drupacine and (+)- and (−)-cephalotaxine has been developed. The syntheses rely on Pd(II)-catalyzed aerobic oxidative heterocyclization chemistry, which was employed to rapidly construct an important spirocyclic amine intermediate. A dynamic β-elimination/conjugate addition process was strategically applied to complete the first asymmetric total synthesis of (−)-drupacine.

Introduction

The Cephalotaxus alkaloids are a class of complex cytotoxic natural products first isolated from Asian plum yews *Cephalotaxus drupacea* and *Cephalotaxus fortunei*.[1] Their structures were partially determined through the efforts of McKay et al. and ultimately elucidated by X-ray diffraction analysis.[2] Although the core structures of these alkaloids, namely drupacine (**1**) and cephalotaxine (**3**), are biologically inactive, several members of this family of natural products have shown potent antileukemic activity, especially ester derivatives at C(3) (Figure 1). For example, homoharringtonine (**4**) has an IC_{50} of 0.014 μg/mL against murine lymphoma L1210 and 0.010 μg/mL against human epidermoid carcinoma KB cells. In addition, it has been reported that cancer patients who had become resistant to other forms of chemotherapy responded positively to cephalotaxine esters, indicating possible multiple drug resistance reversing activity.[3] Recently, about a dozen new members of this family have been isolated from *Cephalotaxus harringtonia* var. nana., with several of them (e.g., cephalezomine A (**2**)) demonstrating comparable anticancer activity to homoharringtonine (**4**).[4]

The significant anticancer activities and intriguing chemical structures have made the *Cephalotaxus* alkaloids attractive

(1) For reviews on the *Cephalotaxus* alkaloids, see: (a) Miah, M. A. J.; Hudlicky, T.; Reed, J. W. Cephalotaxus alkaloids. In *The Alkaloids*; Academic Press: New York, 1998; Vol. 51, pp 199−269. (b) Huang, L.; Xue, Z. Cephalotaxus alkaloids. In *The Alkaloids*; Academic Press: New York, 1984; Vol. 23, pp 157−226.

(2) (a) Paudler, W. W.; Kerley, G. I.; McKay, J. *J. Org. Chem.* **1963**, *28*, 2194−2197. (b) Powell, R. G.; Madrigal, R. V.; Smith, C. R., Jr.; Mikolajczak, K. L. *J. Org. Chem.* **1974**, *39*, 676−680. (c) Arora, S. K.; Bates, R. B.; Grady, R. A.; Powell, R. G. *J. Org. Chem.* **1974**, *39*, 1269−1271. (d) Abraham, D. J.; Rosenstein, R. D.; McGandy, E. L. *Tetrahedron Lett.* **1969**, *10*, 4085−4086.

(3) Delfel, N. E. *Phytochemistry* **1980**, *19*, 403−408.

(4) (a) Morita, H.; Arisaka, M.; Yoshida, N.; Kobayashi, J. *Tetrahedron* **2000**, *56*, 2929−2934. (b) Morita, H.; Yoshinaga, M.; Kobayashi, J. *Tetrahedron* **2002**, *58*, 5489−5495.

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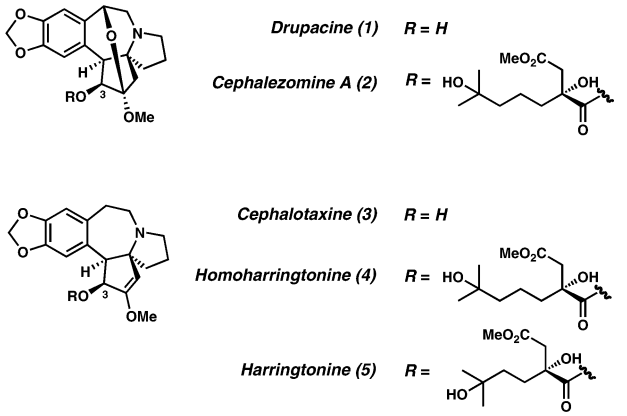


FIGURE 1. Representative examples of *Cephalotaxus* alkaloids.

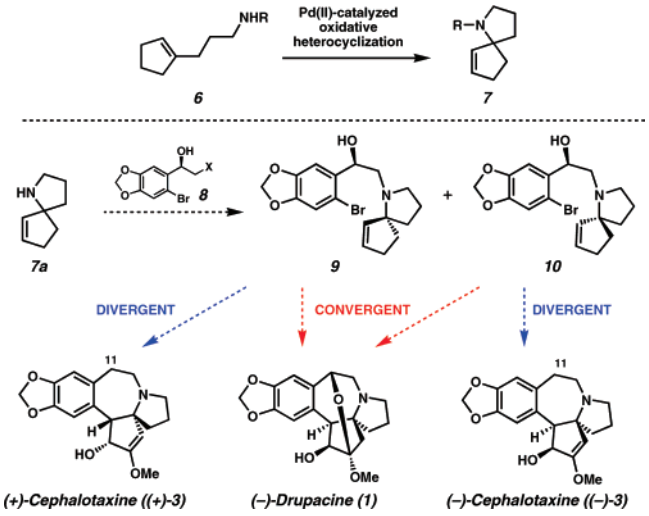
targets for synthetic chemists. Since the report of the first total syntheses of (±)-cephalotaxine by Weinreb[5a] and Semmelhack[5b] in 1972, a number of elegant total syntheses of this family of natural products have been reported in the literature.[5c−q] Although the enantioselective synthesis of (−)-cephalotaxine has been accomplished by several groups, there remains only one total synthesis of (±)-drupacine, disclosed by Fuchs in 1990.[5f] In this report, we present our investigations toward a formal total synthesis of (±)-cephalotaxine, a stereodivergent formal total synthesis of (+)- and (−)-cephalotaxine, and a stereoconvergent asymmetric synthesis of (−)-drupacine.

Retrosynthetic Analysis of (−)-Drupacine, (−)-Cephalotaxine, and (+)-Cephalotaxine

Arguably the most synthetically challenging structural feature of the *Cephalotaxus* alkaloids is the spirocyclic amine moiety. Recently, we have reported the use of palladium(II)-catalyzed aerobic oxidations to access a variety of heterocyclic compounds.[6] We reasoned that this chemistry could be utilized to access this challenging fragment in an efficient fashion. Unfortunately, efforts to extend the oxidation chemistry to enantioselective variants have met with limited success to date. In the design of our synthetic approach, however, this drawback was not restrictive, but empowering.

We anticipated that the generation of racemic spirocyclic amine **7** via our palladium-catalyzed heterocyclization could be

SCHEME 1



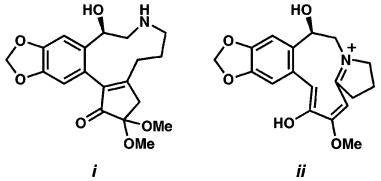
used as a starting point for a divergent approach toward the syntheses of both (+)- and (−)-cephalotaxine and for a convergent approach toward the synthesis of (−)-drupacine (Scheme 1). Specifically, alkylation of amine **7a** with enantiopure benzylic alcohol **8** would produce diastereomers **9** and **10**. First, we envisioned using the diastereomeric mixture in a divergent fashion; upon separation of **9** and **10**, each compound could be used as a precursor toward the synthesis of each enantiomer of cephalotaxine (i.e., **9** → (+)-**3**, and **10** → (−)-**3**). Crucial to the success of this approach would be the deoxygenation of the benzylic alcohol moiety at C(11), which was initally used to define the diastereomers in the key alkylation. Second, we hoped to apply diastereomers **9** and **10** in a convergent manner toward the enantioselective synthesis of (−)-drupacine; each compound would undergo an identical synthetic sequence to access the natural product. The success of this strategy would hinge on a thermodynamic equilibration process, redefining the configuration of the tertiary amine stereocenter via a unique β-elimination/conjugate addition process (vide infra).

Thus, our retrosynthetic analysis for a stereodivergent synthesis of (−)-drupacine and (+)-and (−)-cephalotaxine is shown in Scheme 2. We envisioned that (−)-drupacine could arise from amino alcohols **15** and **16** through a sequence of oxidations and functional group manipulations. We were intrigued by the notion that we could take advantage of the known susceptibility of cephalotaxine-based diketones to undergo a β-elimination/conjugate addition process. Therefore, we hypothesized that ketal **11** could be derived from a mixture of diastereomers **12** and **14**, which would equilibrate via proposed intermediate **13**.[7] The α-methoxy enone moiety in diastereomer **14** is positioned in close proximity to the benzylic alcohol at C(11), thus allowing the formation of the bridging acetal under acidic conditions.

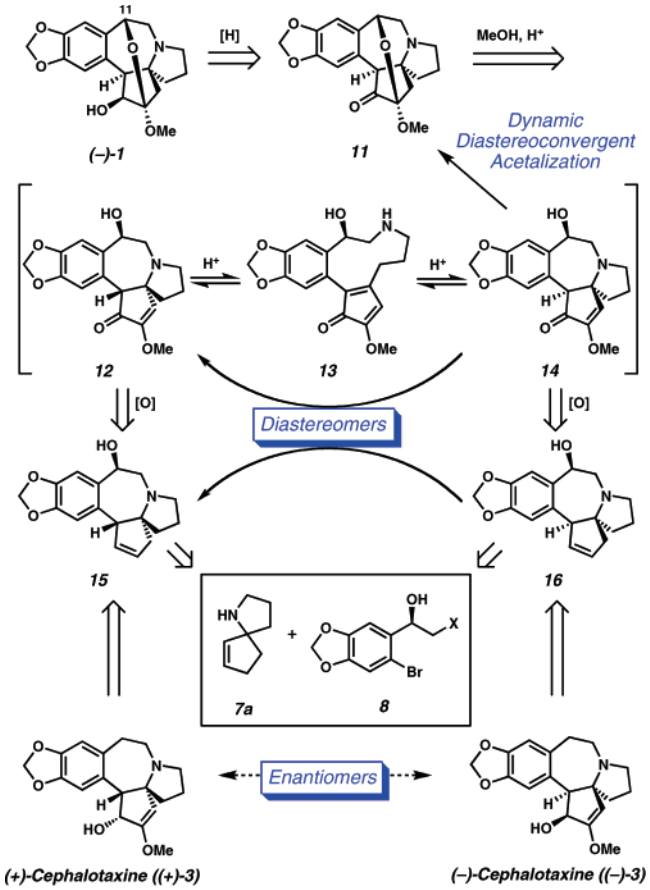
(5) (a) Auerbach, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1972**, *94*, 7172−7173. (b) Semmelhack, M. F.; Chong, B. P.; Jones, L. D. *J. Am. Chem. Soc.* **1972**, *94*, 8629−8630. (c) Yasuda, S.; Yamada, T.; Hanaoka, M. *Tetrahedron Lett.* **1986**, *27*, 2023−2026. (d) Kuehne, M. E.; Bornmann, W. G.; Parsons, W. H.; Spitzer, T. D.; Blount, J. F.; Zubieta, J. *J. Org. Chem.* **1988**, *53*, 3439−3450. (e) Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem. Soc.* **1988**, *110*, 2341−2342. (f) Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem. Soc.* **1990**, *112*, 9601−9613. (g) Ikeda, M.; Okano, M.; Kosaka, K.; Kido, M.; Ishibashi, H. *Chem. Pharm. Bull.* **1993**, *41*, 276−281. (h) Isono, N.; Mori, M. *J. Org. Chem.* **1995**, *60*, 115−119. (i) Lin, X.; Kavash, R. W.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 7335−7347. (j) Tietze, L. F.; Schirok, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1124−1125. (k) Nagasaka, T.; Sato, H.; Saeki, S. I. *Tetrahedron: Asymmetry* **1997**, *8*, 191−194. (l) Tietze, L. F.; Schirok, H. *J. Am. Chem. Soc.* **1999**, *121*, 10264−10269. (m) Suga, S.; Watanabe, M.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 14824−14825. (n) Koseki, Y.; Sato, H.; Watanabe, Y.; Nagasaka, T. *Org. Lett.* **2002**, *4*, 885−888. (o) Li, W.-D. Z.; Wang, Y.-Q. *Org. Lett.* **2003**, *5*, 2931−2934. (p) Eckelbarger, J. D.; Wilmot, J. T.; Gin, D. Y. *J. Am. Chem. Soc.* **2006**, *128*, 10370−10371. (q) Li, W.-D. Z.; Wang, X.-W. *Org. Lett.* **2007**, *9*, 1211−1214.

(6) (a) Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2892−2895. (b) Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778−17788.

(7) A similar intermediate to **13** was proposed by Mori; see ref 5h. The dimethyl acetal derivative of **13** (i.e., **i**) is also a possible intermediate, as is retro-Mannich-type intermediate **ii**.



SCHEME 2

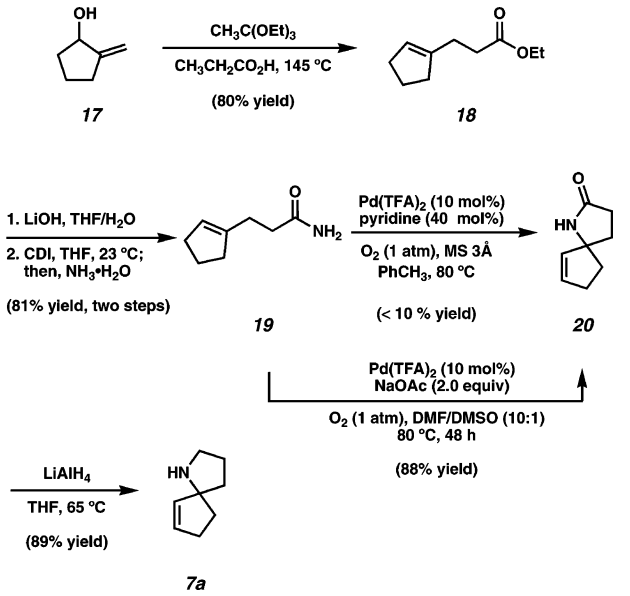


The same acetal cannot form in diastereomer **12** because the alcohol is anti to the enone ring, and consequently it undergoes the β-elimination/conjugate addition process. We expected that this dynamic isomerization equilibrium would eventually funnel the mixture to ketal **11**. Therefore, once the stereocenter at C(11) is defined, we could access enantiomerically pure (−)-**1** from a diastereomeric mixture of **15** and **16**. (+)- and (−)-cephalotaxine, meanwhile, could be derived from the same diastereomeric precursors via deoxygenation at C(11) followed by chemistry developed by Mori. **15** and **16** could be obtained from spirocyclic amine **7a** and enantiopure alcohol **8** via a C−N bond formation and subsequent intramolecular Heck reaction. The key spiroamine derivative (**7a**) would be constructed via our palladium(II)-catalyzed heterocyclization chemistry. Importantly, the implementation of this strategy obviates an enantioselective synthesis of the spiroamine functionality.

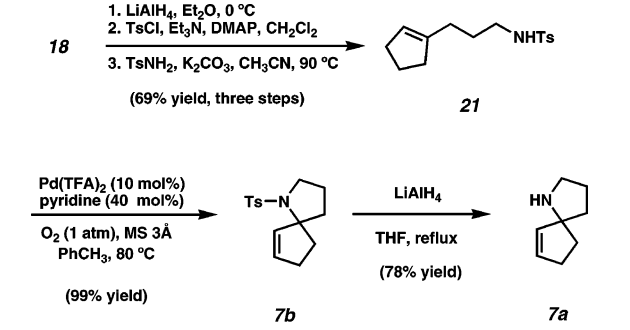
Results and Discussion

Synthesis of Spirocyclic Amine 7a. Our synthesis of spirocyclic amine **7a** began from known allylic alcohol **17**,[8] which was treated with triethyl orthoacetate under Johnson orthoester−Claisen conditions to afford ethyl ester **18** (Scheme 3). Ester **18** was smoothly transformed into primary amide **19** via saponification (LiOH/THF/H_2O) followed by amide formation mediated by the Staab reagent (1,1′-carbonyldiimidazole).[9] Despite extensive experimentation, the oxidative heterocyclization of **19** under our standard catalytic conditions (Pd(II)/O_2/pyridine/toluene) did not proceed efficiently (i.e., <10% yield). However, optimization of the solvent and the catalyst system revealed that a mixture of DMF and DMSO as solvent and Pd(TFA)$_2$ as catalyst are optimal conditions, affording spiroamide **20** in 88% yield.[10] The resulting amide was reduced by $LiAlH_4$ to provide desired spirocyclic pyrrolidine **7a**.

SCHEME 3



SCHEME 4



As the primary amide **19** proved to be an unsuitable substrate for our Pd(II)-catalyzed heterocyclization reaction in aprotic solvents such as toluene, we turned our attention to sulfonamide-based nucleophiles, which are generally more reactive substrates in this oxidative cyclization chemistry.[11] Thus, ester **18** (Scheme 4) was reduced by $LiAlH_4$ to an alcohol, which was subsequently converted in two steps to sulfonamide **21**, setting the stage for the key palladium(II)-catalyzed heterocyclization reaction. Gratifyingly, the oxidative cyclization of **21** proceeded efficiently to provide spirocyclic tosylamide **7b**. This reaction could be easily performed on gram-scale (e.g., 1.1 g, 99% yield), allowing access to this key intermediate in sufficient laboratory quantities. Reductive cleavage of the tosyl group with $LiAlH_4$[12] furnished the desired spirocyclic amine (**7a**).

(8) Dreiding, A. S.; Hartman, J. A. *J. Am. Chem. Soc.* **1953**, *75*, 939−943.

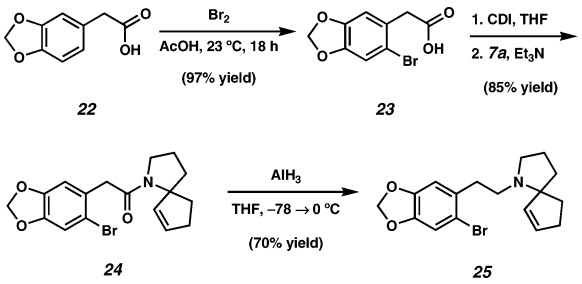
(9) Staab, H. A.; Wendel, K. *Org. Synth.* **1968**, *48*, 44−46.

(10) For leading references on the Pd(II)/DMSO oxidative system for heterocyclizations, see: (a) Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298−5300. (b) Rönn, M.; Bäckvall, J.-E.; Andersson, P. G. *Tetrahedron Lett.* **1995**, *36*, 7749−7752. (c) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584−3585.

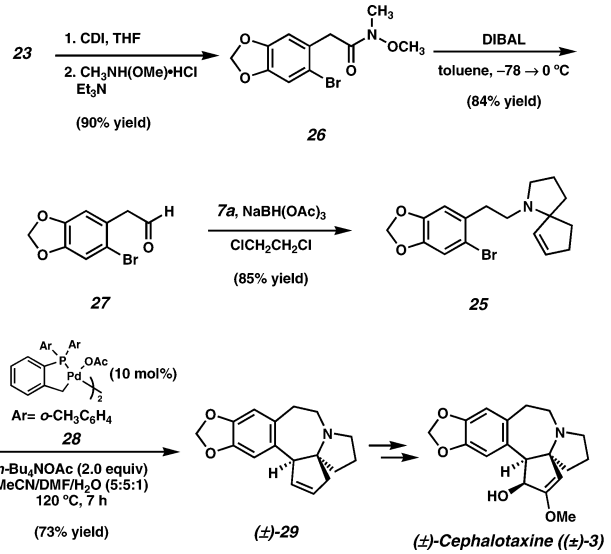
(11) For an example, see: Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 164−166.

(12) Brosius, A. D.; Overman, L. E.; Schwink, L. *J. Am. Chem. Soc.* **1999**, *121*, 700−709.

SCHEME 5



SCHEME 6



A Formal Total Synthesis of (±)-Cephalotaxine

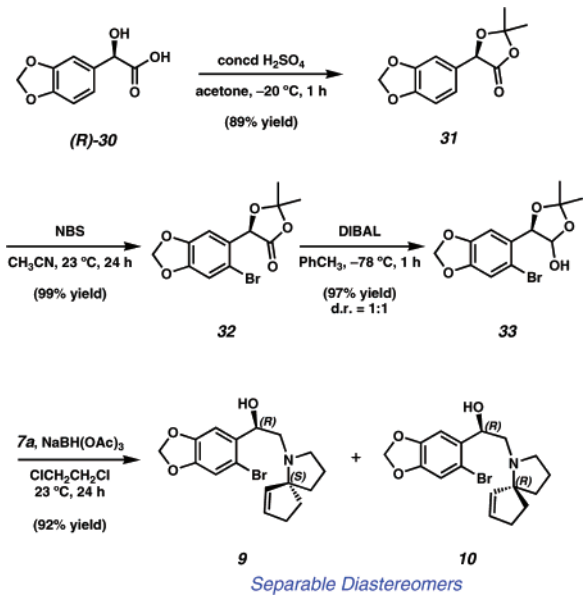
With a facile route to spirocyclic amine **7a** in hand, we set out to pursue a formal total synthesis of (±)-cephalotaxine ((±)-**3**) to demonstrate the utility of this new methodology. Our approach targeted **29** (Scheme 6), a known intermediate en route to cephalotaxine (**3**) in Mori's synthesis.[5h]

Our synthesis commenced with regioselective bromination of homopiperonylic acid (**22**) to yield carboxylic acid **23** (Scheme 5). Amide bond formation between spirocyclic amine **7a** and acid **23** afforded **24** in good yield. Reduction of amide **24** with a variety of reducing agents was complicated by the formation of an inseparable des-bromo side product. Eventually, alane (AlH_3) was found to be capable of generating the desired tertiary amine (**25**) in 70% yield without concomitant dehalogenation.

While we were investigating conditions for the amide reduction, an alternative synthetic route was also pursued. To this end, carboxylic acid **23** was converted to Weinreb amide **26**, which was reduced by DIBAL to give aldehyde **27**. Carbon-nitrogen bond formation was achieved via a reductive amination[13] joining the aldehyde and spirocyclic pyrrolidine fragments. The resulting tertiary amine (**25**), obtained by either method described, was subjected to the stereoselective Heck conditions developed by Tietze[5j,l] to afford the target intermediate (**29**), thus completing the formal total synthesis of (±)-cephalotaxine ((±)-**3**, 11 total steps to **29**, 8 longest linear).

(13) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849−3862.

SCHEME 7



Synthesis of (−)-Drupacine and Formal Total Synthesis of (−)- and (+)-Cephalotaxine

After the completion of our concise formal synthesis of (±)-cephalotaxine ((±)-**3**), we turned our attention to our initial synthetic routes toward (+)- and (−)-cephalotaxine and (−)-drupacine. Enantiomerically enriched 3,4-methylenedioxymandelic acid[14] ((*R*)-**30**, 97.5% ee) was protected as a 1,3-dioxolan-4-one under acidic conditions in acetone (Scheme 7). Although bromination of **31** in several common solvents (e.g., Et_2O, $CHCl_3$, and acetic acid) was problematic, acetonitrile proved optimal for this transformation and afforded aryl bromide **32** quantitatively. The resulting dioxolanone (**32**) was reduced with DIBAL at −78 °C to give hemiacetal **33** as a 1:1 mixture of diastereomers. The diastereomeric mixture was reacted with spirocyclic amine **7a** under reductive amination conditions to furnish diastereomers **9** and **10** in an approximately 1:1 ratio, which could be readily separated by silica gel column chromatography.

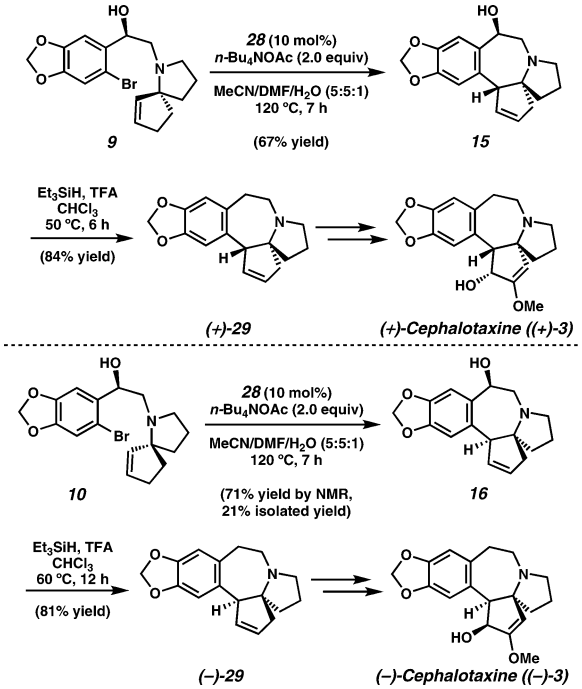
Upon the facile separation of diastereomers **9** and **10**, we first utilized each diastereomer in a divergent fashion toward the formal total synthesis of (+)- and (−)-cephalotaxine. As mentioned above, we anticipated that **9** and **10** could be transformed into (+)- and (−)-**29**, respectively, which can subsequently be transformed to (+)- and (−)-cephalotaxine via a four-step sequence described by Mori.[5h] To that end, diastereomer **9** was exposed to the identical Heck reaction conditions described above to produce **15** as a single diastereomer and enantiomer (Scheme 8). The benzylic hydroxyl group in **15** was removed via an ionic deoxygenation procedure (Et_3SiH, CF_3COOH)[15] to give (+)-**29** ($[\alpha]_D^{27.3}$ +191° (*c* = 0.15, $CHCl_3$), lit.[5l] $[\alpha]_D$ −200° (*c* = 1.0, $CHCl_3$) for (−)-**29**), which completed the formal total synthesis of (+)-cephalotaxine ((+)-**3**). The other diastereomer (**10**) can be converted to (−)-cephalotaxine ((−)-**3**) using the identical synthetic route.

Having completed the stereodivergent formal synthesis of (+)- and (−)-**3**, we then turned our attention to a stereocon-

(14) Neilson, D. G.; Zakir, U.; Scrimgeour, C. M. *J. Chem. Soc. C* **1971**, 898−904.

(15) Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633−651.

SCHEME 8



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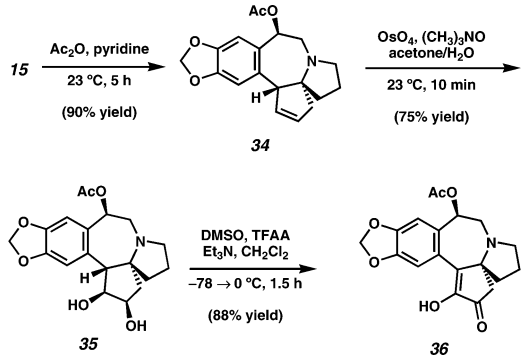

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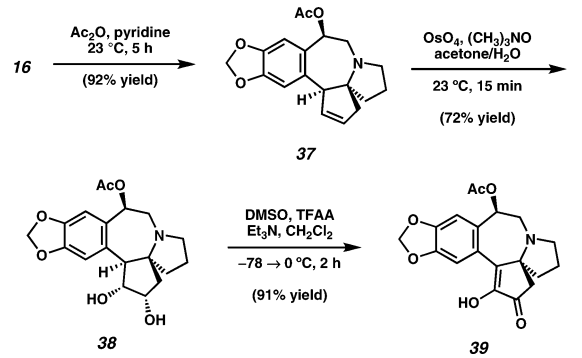
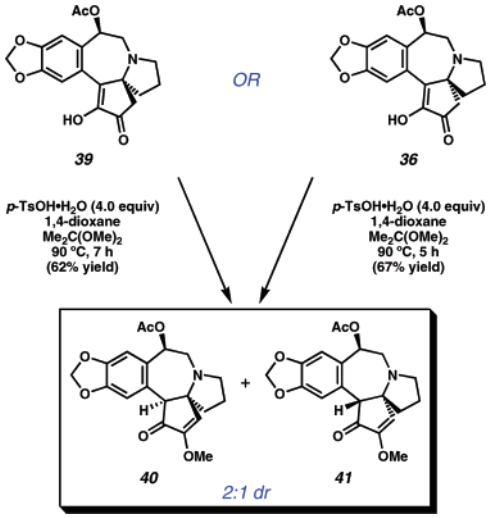


vergent synthesis of (−)-drupacine from diastereomers **9** and **10**. Therefore, the benzylic alcohol in **15** was masked as an acetate to provide **34**, which was converted to α-hydroxy enone **36** via a two-step sequence (Scheme 9). The same transformations were carried out to produce the other diastereomer (i.e., **39**) from **16** (Scheme 10).

With syn α-hydroxy enone **39** in hand, exposure to conditions that are known to promote racemization in the cephalotaxine series[5h] through a conjugate addition process, formed two

SCHEME 11



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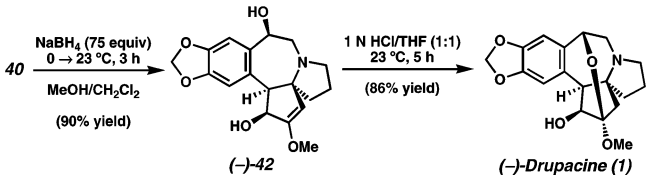
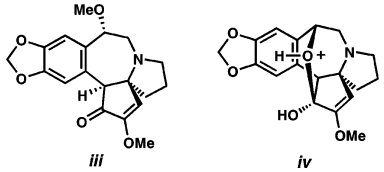


diastereomers (**40** and **41**), with the desired syn isomer (**40**) as the major product (Scheme 11). This observation indicated that an equilibrium through an open ring intermediate leads to a diastereomeric interconversion, and syn isomer **40** is thermodynamically more stable than anti isomer **41**. To our delight, when the anti α-hydroxy enone diastereomer (**36**) was subjected to the same conditions for 5 h, nearly identical results were observed.[16] Therefore, we succeeded in the conversion of both diastereomers **36** and **39** to the desired syn isomer of α-methoxy enone (**40**) by employing this diastereoconvergent isomerization process.

To complete the synthesis of (−)-drupacine (**1**), α-methoxy enone **40** was reduced with $NaBH_4$, with concomitant cleavage of the acetate ester, to produce enantiopure 11-hydroxycephalotaxine ((−)-**42**), another *Cephalotaxus* alkaloid (Scheme 12).[2b] Under acidic conditions, the benzylic hydroxyl group in ((−)-**42**) engaged in an acetal linkage with the enol ether, forming (−)-drupacine (**1**) in 86% yield. The spectroscopic data for the synthetic material was identical to published data for the natural product in every respect, representing the first asymmetric total synthesis of (−)-drupacine.

(16) When diastereomeric α-hydroxy enones **36** and **39** were independently subjected to the dynamic isomerization conditions for prolonged reaction times (3 days), a single major product (>60% yield) was isolated and characterized as **iii**, which is optically active ($[\alpha]_D^{25.6} = -41.9$ (c = 0.21, $CHCl_3$)). When **40** was subjected to basic conditions (NaOMe/MeOH), compound **iii** ($[\alpha]_D^{27.3} = -44.2$ (c = 0.22, $CHCl_3$)) was produced as the sole product. One possible intermediate (**iv**) for these transformations is proposed.



Conclusions

In summary, we have developed a concise route toward the syntheses of (−)-drupacine (**1**) and (+)- and (−)-cephalotaxine (**3**). Our synthesis features a rapid and efficient construction of the spirocyclic amine (**7a**) employing Pd(II)-catalyzed oxidative heterocyclization chemistry, followed by a series of transformations that include a reductive amination and an intramolecular Heck reaction to establish the frameworks of the target molecules. A dynamic isomerization process was strategically applied to funnel two diastereomers (**36** and **39**) into a single enantiomer of (−)-drupacine (**1**) to complete the first asymmetric total synthesis of this alkaloid. This work is highly illustrative of the synthetic utility of the aerobic palladium(II)-catalyzed heterocyclization chemistry we have developed thus far. It also highlights how stereoconvergency and stereodivergency can be employed as strategic elements that can enable the facile synthesis of a family of naturally occurring compounds. Investigations into an enantioselective version of the oxidative heterocyclization and the applications of convergence and divergence to other synthetic problems are currently underway.

Experimental Section

Spirolactam 20. DMF (20 mL) and DMSO (2 mL) were added to a 250 mL two-necked, round-bottomed flask charged with a magnetic stir bar. Under an atmosphere of O_2, $Pd(TFA)_2$ (333 mg, 1.0 mmol), NaOAc (1.64 g, 20 mmol), and amide **19** (1.39 g, 10.0 mmol) were added successively. The resulting mixture was heated at 80 °C for 48 h with vigorous stirring. After the reaction mixture was cooled to room temperature, it was passed through a short pad of silica gel to remove insoluble solid. The filtrate was concentrated in vacuo to give a red oil, which was purified by flash chromatography (100% EtOAc) to give the spirolactam **20** (1.22 g, 87.8% yield): R_f 0.30 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.06 (br s, 1H), 5.81−5.78 (m, 1H), 5.59−5.56 (m, 1H), 2.46−2.23 (m, 4H), 2.07−1.85 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 135.2, 133.2, 71.4, 37.9 33.9, 30.9; IR (film) 3191, 1690, 1366, 753 cm^{-1}; HRMS-EI (*m*/*z*) $[M]^+$ calcd for $C_8H_{11}NO$ 137.0841, found 137.0835.

Cyclic Sulfonamide 7b. Toluene (20 mL) was added to a 250 mL two-necked, round-bottomed flask charged with a magnetic stir bar. Under an atmosphere of O_2, 3 Å molecular sieves (1.0 g), $Pd(TFA)_2$ (133 mg, 0.4 mmol), pyridine (128 mg, 131 μL, 1.6 mmol), and sulfonamide **21** (1.12 g, 4.0 mmol) were added successively. The resulting mixture was heated at 80 °C for 42 h with vigorous stirring. After the reaction mixture was cooled to room temperature, the mixture was passed through a short pad of silica gel to remove the insoluble solid. The filtrate was concentrated in vacuo to give a brown oil, which was purified by flash chromatography (4:1 hexanes/EtOAc) to give the cyclic sulfonamide **7b** (1.10 g, 99% yield): R_f 0.25 (4:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 8.1 Hz, 2H), 5.76 (dt, J_1 = 5.7 Hz, J_2 = 2.1 Hz, 1H), 5.33 (dt, J_1 = 5.4 Hz, J_2 = 2.1 Hz, 1H), 3.56−3.49 (m, 1H), 3.30−3.22 (m, 1H), 2.58−2.48 (m, 1H), 2.47−2.30 (m, 1H), 2.33 (s, 3H), 2.77−2.12 (m, 2H), 1.87−1.67 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 138.7, 133.6, 132.9, 129.5, 127.5, 78.7, 49.5, 41.4, 37.3, 31.2, 23.4, 21.7; IR (film) 2927, 1598, 1494, 1446, 1335, 1153, 1092, 1060 cm^{-1}; HRMS-EI (*m*/*z*) $[M]^+$ calcd for $C_{15}H_{19}NO_2S$ 277.1136, found 277.1149.

Alcohols 9 and 10. To a solution of hemiacetal **33** (1.0 g, 3.17 mmol) in 1,2-dichloroethane (10 mL) was added a solution of spiroamine **7a** (410 mg, 3.33 mmol) in 1,2-dichloroethane (5 mL). The resulting solution was treated with $NaBH(OAc)_3$ (1.0 g, 4.76 mmol) and stirred at room temperature for 24 h. The reaction was poured into saturated $NaHCO_3$ (50 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (4 × 50 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (1:1 hexanes/EtOAc → EtOAc) to give **9** (525 mg, 45.4% yield) and **10** (538 mg, 46.5% yield) as yellow oils.

9: R_f 0.25 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (s, 1H), 6.92 (s, 1H), 5.94 (dd, J_1 = 5.4 Hz, J_2 = 1.5 Hz, 2H), 5.85 (dt, J_1 = 5.7 Hz, J_2 = 2.1 Hz, 1H), 5.40 (dt, J_1 = 5.7 Hz, J_2 = 2.1 Hz, 1H), 4.90 (dd, J_1 = 10.2 Hz, J_2 = 3.0 Hz, 1H), 4.22 (br, 1H), 3.32−3.25 (m, 1H), 2.57−2.49 (m, 2H), 2.38−2.16 (m, 3H), 1.91−1.71 (m, 5H), 1.55−1.46 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 147.6, 135.9, 135.3, 133.6, 112.5, 112.0, 107.7, 101.9, 78.0, 69.1, 55.3, 50.4, 38.1, 32.0, 28.1, 21.6; IR (film) 3401, 2938, 1502, 1475, 1236, 1038 cm^{-1}; HRMS-FAB (*m*/*z*) $[M + H]^+$ calcd for $C_{17}H_{20}BrNO_3$ 366.0705, found 366.0689; $[\alpha]_D^{25.8}$ −17.5 (*c* 2.0, CH_2Cl_2).

10: R_f 0.20 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (s, 1H), 6.92 (s, 1H), 5.94 (dd, J_1 = 5.1 Hz, J_2 = 1.5 Hz, 2H), 5.76 (dt, J_1 = 5.7 Hz, J_2 = 2.1 Hz, 1H), 5.65 (dt, J_1 = 5.7 Hz, J_2 = 2.1 Hz, 1H), 4.87 (dd, J_1 = 10.2 Hz, J_2 = 3.3 Hz, 1H), 4.05 (br, 1H), 3.21−3.15 (m, 1H), 2.67−2.60 (m, 2H), 2.33−2.18 (m, 3H), 1.91−1.81 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 147.6, 135.5, 133.6, 132.5, 112.6, 112.0, 107.6, 101.9, 77.7, 69.3, 56.1, 51.8, 38.6, 34.0, 31.2, 22.2; IR (film) 3401, 2942, 1502, 1475, 1235, 1039 cm^{-1}; HRMS-FAB (*m*/*z*) $[M + H]^+$ calcd for $C_{17}H_{20}BrNO_3$ 366.0705, found 366.0688; $[\alpha]_D^{25.8}$ −36.4 (*c* 2.0, CH_2Cl_2).

***anti*-Amino Alcohol 15.** The amino alcohol **9** (200 mg, 0.55 mmol) was dissolved in a mixture of solvents ($DMF/CH_3CN/H_2O$ = 5 mL:5 mL:1 mL). The solution was degassed with argon for 15 min and then treated with *trans*-di-μ-acetatobis[2-(di-*o*-tolylphosphino)benzyl]dipalladium(II) (52 mg, 0.055 mmol) and tetra-*n*-butylammonium acetate (332 mg, 1.1 mmol). The resulting solution was heated at 120 °C for 7 h. The reaction was cooled to room temperature and filtered through a short pad of Celite. The filtrate was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (50 mL) and extracted with saturated $NaHCO_3$ (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash chromatography (1:4 hexanes/EtOAc → EtOAc) to give alcohol **15** (107 mg, 67% yield) as a foamy solid: R_f 0.15 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (s, 1H), 6.63 (s, 1H), 5.89 (dd, J_1 = 9.0 Hz, J_2 = 1.5 Hz, 2H), 5.81−5.79 (m, 1H), 5.52−5.50 (m, 1H), 5.20 (dd, J_1 = 9.9 Hz, J_2 = 6.9 Hz, 1H), 3.87 (t, J = 2.4 Hz, 1H), 3.04−2.97 (m, 1H), 2.83−2.73 (m, 2H), 2.58 (t, J = 10.8 Hz, 1H), 2.45−2.35 (m, 2H), 2.04−1.89 (m, 3H), 1.77−1.68 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 146.2, 136.0, 132.1, 129.5, 128.8, 110.9, 104.5, 101.1, 68.3, 66.6, 62.0, 56.7, 53.4, 43.0, 34.9, 20.2; IR (film) 3256, 2961, 1501, 1482, 1261, 1242, 1040 cm^{-1}; HRMS-EI (*m*/*z*) $[M]^+$ calcd for $C_{17}H_{19}NO_3$ 285.1365, found 285.1370; $[\alpha]_D^{27.0}$ +57.6 (*c* 1.6, $CHCl_3$).

***syn*-Amino Alcohol 16.** The amino alcohol **10** (200 mg, 0.55 mmol) was dissolved in a mixture of solvents ($DMF/CH_3CN/H_2O$ = 5 mL:5 mL:1 mL). The solution was degassed with argon for 15 min and then treated with *trans*-di-μ-acetatobis[2-(di-*o*-tolylphosphino)benzyl]dipalladium(II) (52 mg, 0.055 mmol) and tetra-*n*-butylammonium acetate (332 mg, 1.1 mmol). The resulting solution was heated at 120 °C for 7 h. The reaction was cooled to room temperature and filtered through a short pad of Celite. The filtrate was concentrated in vacuo. The residue was dissolved in Et_2O (50 mL) and extracted with saturated $NaHCO_3$ (50 mL). The aqueous phase was extracted with Et_2O (3 × 50 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash chromatography (5% → 10% $MeOH/CH_2Cl_2$) to yield *syn*-amino alcohol **16** (33 mg, 21% yield) as a clear oil. (*Note: The low isolation yield of **16** is due to its poor solubility in most organic solvents. When crude **16** was taken to the next step, typically 60−70% yield was obtained for two steps. Since pure **16** can be acylated in 92% yield, the yield of*

this Heck reaction approximately 71%.) **16**: R_f 0.07 (EtOAc), 0.1 (1:9 MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (s, 1H), 6.72 (s, 1H), 6.00−5.97 (m, 1H), 5.94 (s, 2H), 5.90−5.88 (m, 1H), 4.75 (dd, J_1 = 8.7 Hz, J_2 = 4.8 Hz, 1H), 3.85 (m, 1H), 3.37 (dd, J_1 = 14.1 Hz, J_2 = 8.7 Hz, 1H), 2.96−2.91 (m, 1H), 2.72−2.66 (m, 3H), 2.16 (dq, J_1 = 18.5 Hz, J_2 = 1.8 Hz, 1H), 1.98 (dt, J_1 = 8.1 Hz, J_2 = 3.3 Hz, 2H), 1.89−1.71 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.3, 147.0, 136.1, 134.1, 132.0, 131.3, 111.4, 110.8, 101.4, 74.0, 71.0, 59.4, 55.6, 52.9, 40.0, 37.6, 20.3; IR (film): 3376, 2871, 1496, 1474, 1261, 1038 cm^{-1}; HRMS-EI (*m*/*z*) [M]$^+$ calcd for $C_{17}H_{19}NO_3$ 285.1365; found 285.1360; $[\alpha]_D^{23.9}$ −72.8 (*c* 0.3, $CHCl_3$).

α-Methoxy Enones 40 and 41. Diketone (**39** or **36**) (20 mg, 0.056 mmol) was dissolved in a mixture of 1,4-dioxane (5 mL) and 2,2-dimethoxypropane (5 mL). The solution was treated with *p*-toluenesulfonic acid monohydrate (42.6 mg, 0.224 mmol, 4.0 equiv) and heated at 90 °C for 5 or 7 h. After the reaction mixture was cooled to room temperature, the solvent was removed in vacuo. The residue was partitioned between saturated $NaHCO_3$ (15 mL) and CH_2Cl_2 (20 mL). The aqueous phase was extracted with CH_2Cl_2 (4 × 20 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (19:1 CH_2Cl_2/MeOH) to yield enone **40** (8.3 mg, 42% yield) and **41** (4.0 mg, 20% yield).

40: R_f 0.45 (1:1 CH_2Cl_2/Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (s, 1H), 6.76 (s, 1H), 6.21 (s, 1H), 5.94 (d, J = 9.6 Hz, 2H), 5.74 (d, J = 8.1 Hz, 1H), 3.81 (s, 3H), 3.56 (s, 1H), 3.34−3.27 (m, 1H), 3.08−3.01 (m, 1H), 2.81−2.73 (m, 2H), 2.18−2.08 (m, 1H), 2.03−1.95 (m, 1H), 1.93−1.82 (m, 2H), 1.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.3, 170.4, 159.2, 148.3, 147.2, 129.0, 127.9, 122.0, 114.5, 112.3, 101.7, 75.2, 66.3, 60.5, 57.4, 52.8, 52.4, 39.7, 20.9, 20.3; IR (film) 2961, 1726, 1629, 1506, 1489, 1371, 1231 cm^{-1}; HRMS-FAB (*m*/*z*) [M + H]$^+$ calcd for $C_{20}H_{21}NO_6$ 372.1447, found 372.1451; $[\alpha]_D^{25.0}$ −63.6 (*c* 0.3, CH_2Cl_2).

41: R_f 0.55 (1:1 CH_2Cl_2/Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.71 (s, 1H), 6.38 (s, 1H), 5.95 (dd, J_1 = 3.9 Hz, J_2 = 1.5 Hz, 2H), 5.55 (dd, J_1 = 9.9 Hz, J_2 = 6.9 Hz, 1H), 3.83 (s, 3H), 3.56 (s, 1H), 3.05 (m, 1H), 2.96 (dd, J_1 = 11.1 Hz, J_2 = 7.2 Hz, 1H), 2.72 (q, J = 7.8 Hz, 1H), 2.63 (t, J = 10.2 Hz, 1H), 2.12 (s, 3H), 2.04−1.99 (m, 2H), 1.83−1.79 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.9, 169.6, 159.0, 147.8, 147.0, 130.2, 126.0, 124.0, 112.9, 105.2, 101.5, 69.4, 65.5, 60.9, 57.8, 53.0, 52.7, 39.1, 21.2, 20.7; IR (film) 2931, 1724, 1624, 1504, 1485, 1370, 1233 cm^{-1}; HRMS-FAB (*m*/*z*) [M + H − H_2]$^+$ calcd for $C_{20}H_{21}NO_6$ 370.1291, found 370.1299; $[\alpha]_D^{25.0}$ +13.2 (*c* 0.2, $CHCl_3$).

11-Hydroxycephalotaxine (42). Enone **40** (7.0 mg, 18.8 μmol) was dissolved in a mixture of MeOH (2.0 mL) and CH_2Cl_2 (0.4 mL) at 0 °C and treated with $NaBH_4$ (18 mg, 0.47 mmol, 25 equiv). The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The second portion of $NaBH_4$ (18 mg, 0.47 mmol, 25 equiv) was added, and the mixture was stirred for an additional 1 h. The third portion of $NaBH_4$ (18 mg, 0.47 mmol, 25 equiv) was added, and the reaction was stirred for an additional 1 h. The solvent was removed in vacuo. The residue was partitioned between saturated NaCl (10 mL) and CH_2Cl_2 (10 mL). The aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (9:1 CH_2Cl_2/MeOH) to yield diol **42** (5.5 mg, 90% yield) as a white powder: R_f 0.15 (9:1 CH_2Cl_2/MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (s, 1H), 6.63 (s, 1H), 5.93 (q, J = 7.5 Hz, 2H), 4.82 (t, J = 7.2 Hz, 1H), 4.68 (s, 1H), 4.50 (d, J = 8.4 Hz, 1H), 3.73 (s, 3H), 3.52 (d, J = 8.1 Hz, 1H), 3.40−3.32 (m, 1H), 3.16−3.09 (m, 1H), 2.92−2.87 (m, 2H), 1.98−1.86 (m, 2H), 1.77−1.68 (m, 2H) (note: 2 protons of the hydroxyl groups were not observed); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 147.5, 147.4, 135.9, 127.0, 113.3, 113.1, 101.5, 100.2, 74.8, 74.6, 73.7, 58.2, 57.5, 51.4, 50.9, 40.0, 21.9; IR (film): 3369, 2922, 1651, 1504, 1489, 1227 cm^{-1}; HRMS-EI (*m*/*z*) [M]$^+$ calcd for $C_{18}H_{21}NO_5$ 331.1420, found 331.1417; $[\alpha]_D^{24.4}$ −72.6 (*c* 0.13, $CHCl_3$).

(−)-Drupacine (1). Diol **42** (2.6 mg, 7.85 μmol) was dissolved in a mixture of THF (1.0 mL) and 1 N HCl (1.0 mL) at room temperature. The reaction mixture was stirred at room temperature for 5 h and then was poured into saturated $NaHCO_3$ (10 mL). The mixture was extracted with CH_2Cl_2 (5 × 10 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by preparative TLC (9:1 CH_2Cl_2/MeOH) to yield (−)-drupacine (**1**) (2.2 mg, 86% yield) as a white film: R_f 0.60 (9:1 CH_2Cl_2/MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.67 (s, 1H), 6.65 (s, 1H), 5.95 (q, J = 1.5 Hz, 2H), 4.88 (d, J = 3.9 Hz, 1H), 4.05 (d, J = 9.9 Hz, 1H), 3.49 (d, J = 9.3 Hz, 1H), 3.48 (s, 3H), 3.24−3.19 (m, 1H), 3.07 (m, 1H), 3.03 (d, J = 13.2 Hz, 1H), 2.66 (d, J = 14.4 Hz, 1H), 2.46 (q, J = 9.0 Hz, 1H), 2.26−2.20 (m, 1H), 2.09−2.00 (m, 1H), 1.88−1.76 (m, 2H), 1.52 (d, J = 14.1 Hz, 1H) 1.36 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.1, 146.7, 131.2, 130.2, 112.2, 108.8, 107.9, 101.5, 78.5, 73.8, 65.5, 59.9, 56.9, 54.2, 52.4, 43.6, 35.9, 22.5; IR (film) 3369, 2929, 1503, 1488, 1372, 1060 cm^{-1}; HRMS-EI (*m*/*z*) [M]$^+$ calcd for $C_{18}H_{21}NO_5$ 331.1420, found 331.1433; $[\alpha]_D^{24.7}$ −64.0 (*c* 0.1, $CHCl_3$).

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Supporting Information Available: Experimental details, characterization data, and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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