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A Second Generation Formal Synthesis of (−)-Cephalotaxine

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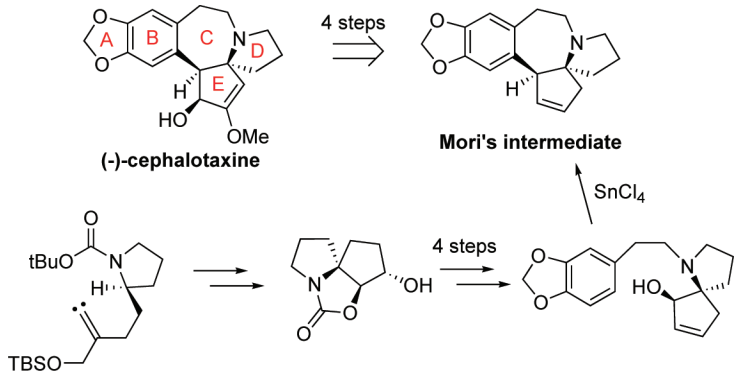

A second generation formal synthesis of the alkaloid (−)-cephalotaxine has been achieved using an alkylidene carbene 1,5-CH insertion reaction to establish a key quaternary stereocenter. The carbene precursor was readily derived from L-proline, and the 1,5-CH insertion reaction was performed under Ohira's conditions using lithiotrimethylsilyldiazomethane (LTDM), which gave the desired spirocyclic product in 74% yield. The hydroxymethyl group was then oxidized and then decarbonylated (93%), and this material was easily transformed into the desired Friedel−Crafts cyclization precursor. Exposure of this material to $SnCl_4$ then gave the desired pentacyclic product, which was identical to that previously prepared by Mori and thus represents a formal total synthesis of (−)-cephalotaxine.

Introduction

The polycyclic alkaloid (−)-cephalotaxine[1] (**1**) is a fascinating target for total chemical synthesis (Figure 1) as its structure contains a number of interesting features, including an embedded 1-azaspiro[4.4]nonane ring system.

While cephalotaxine (**1**) has little known biological activity, it does represent the parent alkaloid core of a larger family of related natural products (e.g., homoharringtonine **2**) that show clinically useful anticancer activity,[2] and as a result, **1** has been the subject of much synthetic interest.[3,4] As part of our ongoing interest in the enantioselective synthesis of **1**,[5a] we have recently reported an enantioselective formal total synthesis,[5b] and this is summarized in Scheme 1.

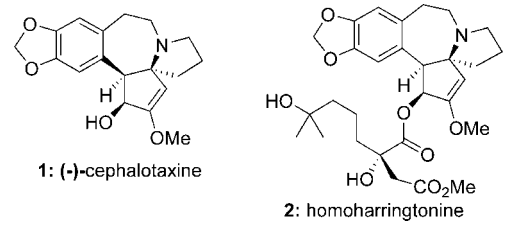

FIGURE 1. Cephalotaxine (**1**) and homoharringtonine (**2**).

All of the steps up to the pentacycle **5** proceeded in acceptable yield (60−80%), but there were some problems associated with the conversion of **5** into "Mori's intermediate" **8**.[4b] Effectively, we needed to remove the methyl group from the cyclopentene ring **5**, and this was done in a six-step sequence (Scheme 1). The first three steps (**5**→**6**) proceeded cleanly,[6] but the subsequent two steps (**6**→**7**) could only be achieved in 31% combined yield. The problems surrounding this low yielding sequence were compounded by the inefficient final decarbonylation reaction (**7**→**8**) which only produced the desired compound **8** in modest yield (20−40%). As a result of these issues, we felt it necessary to explore an alternative synthetic approach (Scheme 2), and we now wish to report the

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(2) (a) Levy, V.; Zohar, S.; Bardin, C.; Vekhoff, A.; Chaoui, D.; Rio, B.; Legrand, O.; Sentenac, S.; Rousselot, P.; Raffoux, E.; Chast, F.; Chevret, S.; Marie, J. P. *Br. J. Cancer* **2006**, *95*, 253. (b) Kantarjian, H. M.; Talpaz, M.; Santini, V.; Murgo, A.; Cheson, B.; O'Brien, S. M. *Cancer* **2001**, *92*, 1591.

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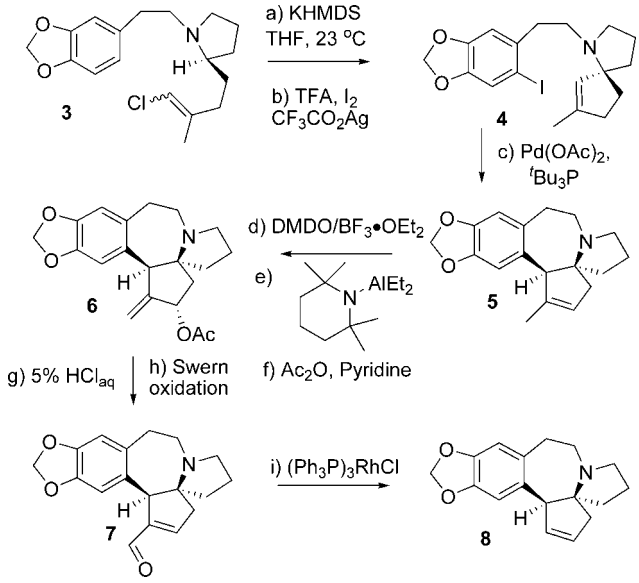
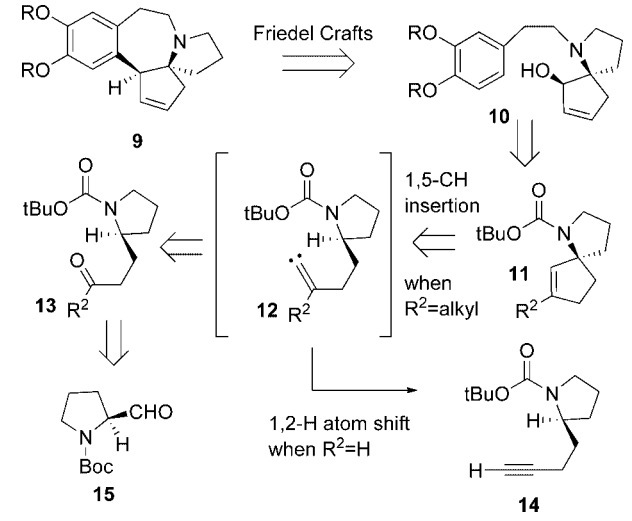
SCHEME 1. Summary of the First Generation Synthesis of 1



SCHEME 2. Revised Retrosynthetic Analysis

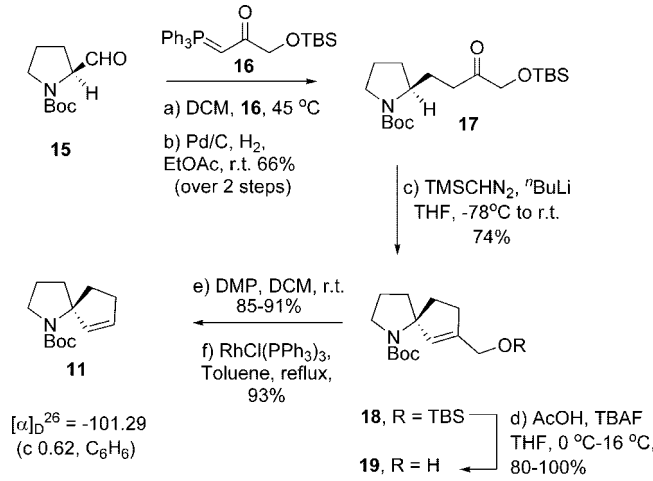


results of this work which have culminated in a second generation formal synthesis of **1**.

Results and Discussion

As the alkylidene carbene 1,5-CH insertion reaction performed well at constructing the key quaternary stereocenter (viz. **3**→**4**),[7] we wanted to retain this in our revised route and we hoped that many of the issues surrounding the removal of the methyl group from **5** could be avoided by changing the order of some of the other key steps. Thus, the pentacycle **9** was disconnected via an intramolecular Friedel−Crafts alkylation in a similar manner to Mori[4b] to reveal the allylic alcohol **10**, with **10** being accessed in only a few steps from the Boc-protected spirocycle **11** (R^2 = H). Further disconnection of **11**, via the alkylidene carbene **12**, revealed the proline-derived ketone **13** to be a suitable precursor.[8] It is well-known that alkylidene carbenes such as **12** undergo rearrangement to the corresponding acetylenes[9] (e.g., **14**) when R^2 = H, so we decided to work with an R^2 group that could act as surrogate for

SCHEME 3. Preparation of Spirocycle 11



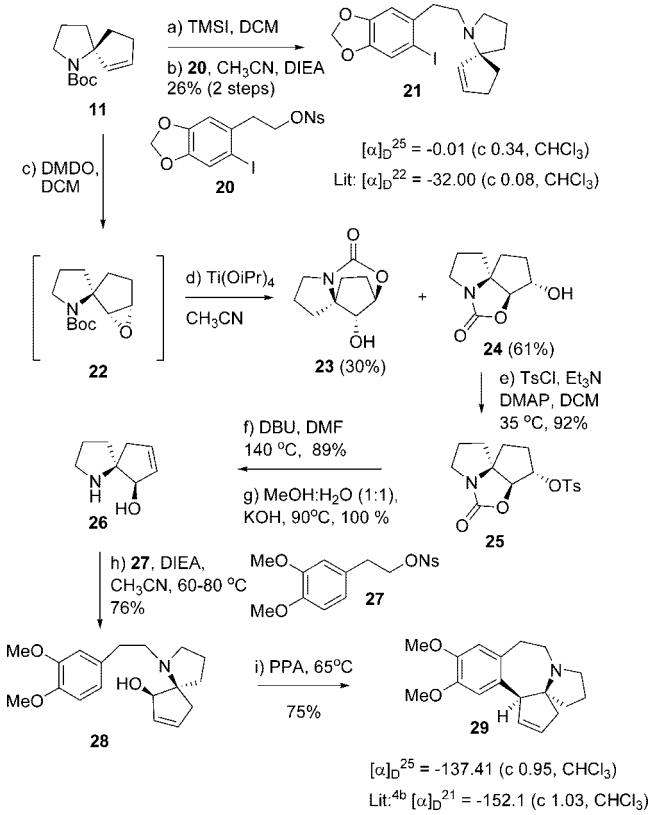
a proton until after the key CH insertion reaction. After considering several options, we decided to prepare the ketone **17** with R^2 as a protected hydroxymethyl group via Wittig reaction of the proline-derived aldehyde **15** and the known ylide **16**[10] (Scheme 3). We felt that the TBS-protected hydroxymethyl moiety would be well suited to the CH insertion step and that rearrangement to the corresponding acetylene would be minimal.[10] Fortunately, this proved to be the case and the desired spirocycle **18** could be isolated in good yield (74%) following exposure of **17** to lithio-TMS-diazomethane.[8] The hydroxymethyl group was then removed in an efficient manner via oxidation to the aldehyde with Dess−Martin periodinane[11](85−91%) and decarbonylation with Wilkinson's catalyst[12] (93%) to afford the desired spirocycle **11** (where R^2 = H).

Pleased by the successful formation of **11**, we next turned our attention to alkylation of the nitrogen with a suitably functionalized electrophile. As a short diversion from our originally planned retrosynthesis (Scheme 2), we briefly explored the possibility of accessing the aryl iodide **21**, which is

(3) Racemic total syntheses: (a) Auerbach, J.; Weinreb, S. M *J. Am. Chem. Soc.* **1972**, *94*, 7172. (b) Semmelhack, M. F.; Chong, B. P.; Jones, L. D. *J. Am. Chem. Soc.* **1972**, *94*, 8629. (c) Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* **1975**, *97*, 2507. (d) Weinreb, S. M.; Auerbach, J. *J. Am. Chem. Soc.* **1975**, *97*, 2503. (e) Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem. Soc.* **1988**, *110*, 2341. (f) Kuehne, M. E.; Bornmann, W. G.; Parsons, W. H.; Spitzer, T. D.; Blount, J. F.; Zubieta, J. *J. Org. Chem.* **1988**, *53*, 3439. (g) Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem. Soc.* **1990**, *112*, 9601. (h) Ishibashi, H.; Okano, M.; Tamaki, H.; Maruyama, K.; Yakura, T.; Ikeda, M. *J. Chem. Soc., Chem. Commun.* **1990**, 1436. (i) Ikeda, M.; Okano, M.; Kosaka, K.; Kido, M.; Ishibashi, H. *Chem. Pharm. Bull.* **1993**, *41*, 276. (j) Lin, X.; Kavash, R. W.; Mariano, P. S. *J. Am. Chem. Soc.* **1994**, *116*, 9791. (k) Lin, X.; Kavash, R. W.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 7335. (l) Tietze, L. F.; Schirok, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1124. (m) Koseki, Y.; Sato, H.; Watanabe, Y.; Nagasaka, T. *Org. Lett.* **2002**, *4*, 885. (n) Suga, S.; Watanabe, M.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 14824. (o) Li, W.-D. Z.; Wang, Y.-Q. *Org. Lett.* **2003**, *5*, 2931. (p) Li, W.-D. Z.; Ma, B.-C. *J. Org. Chem.* **2005**, *70*, 3277. (q) Ma, B.-C.; Wang, Y.-Q.; Li, W.-D. Z. *J. Org. Chem.* **2005**, *70*, 4528. (r) Li, W.-D. Z.; Wang, X.-W. *Org. Lett.* **2007**, *9*, 1211.

(4) Enantioselective total syntheses: (a) Zhong, S.; Liu, W.; Ling, Y.; Li, R. *Zhongguo Yaowu Huaxue Zazhi* **1994**, *4*, 84. (b) Isono, N.; Mori, M. *J. Org. Chem.* **1995**, *60*, 115. (c) Nagasaka, T.; Sato, H.; Saeki, S.-I. *Tetrahedron: Asymmetry* **1997**, *8*, 191. (d) Ikeda, M.; El Bialy, S. A. A.; Hirose, K.-I.; Kotake, M.; Sato, T.; Bayomi, S. M. M.; Shehata, I. A.; Abdelal, A. M.; Gad, L. M.; Yakura, T. *Chem. Pharm. Bull.* **1999**, *47*, 983. (e) Tietze, L. F.; Schirok, H. *J. Am. Chem. Soc.* **1999**, *121*, 10264. (f) El Bialy, S. A. A.; Ismail, M. A.; Gad, L. M.; Abdelal, A. M. M. *Med. Chem. Res.* **2002**, *11*, 293. (g) Planas, L.; Perard-Viret, J.; Royer, J. *J. Org. Chem.* **2004**, *69*, 3087. (h) Eckelbarger, J. D.; Wilmot, J. T.; Gin, D. Y. *J. Am. Chem. Soc.* **2006**, *128*, 10370. (i) Zhao, Z.; Mariano, P. S. *Tetrahedron* **2006**, *62*, 7266. (j) Liu, Q.; Ferreira, E. M.; Stoltz, B. M. *J. Org. Chem.* **2007**, *72*, 7352.

SCHEME 4. Completion of Synthesis of Tetracycle 29

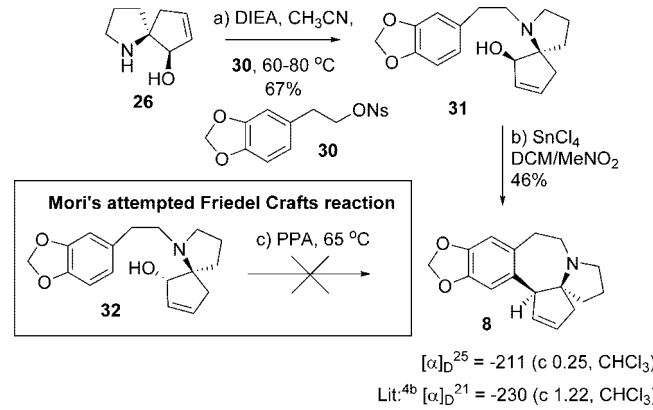


a known precursor to **8**,[13] from the protected spirocycle **11** (Scheme 4). We quickly found that racemization occurs at the quaternary stereocenter upon deprotection of **11** under a variety of acidic conditions.[14] Furthermore, only low yields of the racemic alkylated product **21** could be obtained, and despite much effort, we were not able to find acceptable conditions for this transformation. We therefore returned to our original synthetic approach to **8**.

Epoxidation of **11** with DMDO gave the epoxide **22** as a single diastereoisomer, with delivery of the oxygen occurring on the alkene face opposite to the bulky Boc group. Purification of this material by column chromatography (SiO_2) gave the desired epoxide **22** (48%), along with smaller amounts of two new compounds that were not present in the crude reaction mixture. These were later identified as the isomeric carbamates **23** (4%) and **24** (9%), which are obviously products of acid-mediated intramolecular epoxide opening. Rather than being problematic, we decided to exploit this intramolecular epoxide opening by immediately treating the DMDO epoxidation product **22** with a Lewis acid ($Ti(O^iPr)_4$, MeCN) to provide **23** (30%) and **24** (61%) in much improved yields. The stereochemistry of **24** was confirmed by X-ray crystallography (see Supporting Information).

Although both materials are potentially useful for the synthesis of cephalotaxine, we decided to advance the most abundant isomer **24** through the remaining steps. Thus, **24** was converted into its tosylate **25**, and this material was then treated with DBU to induce elimination to provide the corresponding cyclopentene **35** (structure

SCHEME 5. Shorter End-Game for the Formal Synthesis of (−)-Cephalotaxine



shown in Supporting Information). Hydrolysis of the carbamate (KOH, MeOH/H_2O) then gave the amino alcohol **26** in excellent yield. Alkylation of **26** with the known nosylate **27** produced the desired Friedel−Crafts cyclization precursor **28**, which is the diastereoisomer of a compound previously used by Mori.[4b] Upon treatment with neat polyphosphoric acid (PPA, 65 °C), **28** cyclized to give the desired tetrahydroazepine **29**, whose spectroscopic and analytical data were identical to those previously reported by Mori.[4b]

Although we were pleased to have completed a formal synthesis of (−)-cephalotaxine (**1**) by accessing the known intermediate **29**, we felt that the synthesis could be improved further if we were able to access **8** directly via Friedel−Crafts cyclization of allylic alcohol **31** (Scheme 5). Mori prepared **8** from the dimethoxy aromatic derivative **29** in a two-step process on the way to his total synthesis of **1**,[4b] so if this reaction was possible (viz. **31** → **8**, Scheme 5), then our formal synthesis would be shortened by two steps.

The reason for not trying this transformation (**31** → **8**) earlier was based on the fact that Mori reported that **32**, the diastereomer of **31**, did not undergo the desired Friedel−Crafts cyclization and instead had to resort to using the dimethoxy aromatic derivative (i.e., the diastereoisomer of **28**). We were slightly puzzled by this observation as Kuehne[3f] had previously shown that Friedel−Crafts cyclization of a very closely related amide derivative of **32** was possible.[15]Furthermore, we successfully performed an electrophilic

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(6) For regioselective rearrangement of epoxides to allylic alcohols, see: Yasuda, A.; Tanaka, S.; Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 6513.

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(8) Ohira, S.; Okai, K.; Moritani, T. *J. Chem. Soc., Chem. Commun.* **1992**, 721.

(9) For a comprehensive review, please see: Knorr, R. *Chem. Rev.* **2004**, *104*, 3795.

(10) Bradley, D. M.; Mapitse, R.; Thomson, N. M.; Hayes, C. J. *J. Org. Chem.* **2002**, *67*, 7613.

(11) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(12) Ohno, K.; Tsuji, J. *J. Am. Chem. Soc.* **1968**, *90*, 99.

(13) Yoshida has prepared racemic **21** (see ref 3n) and has shown that it will undergo Heck cyclization under Tietze's conditions (see ref 4e). Mariano has recently reported an enantioselective synthesis of **21** (see ref 4i) but does not report the use of this material in the Heck cyclization.

aromatic iodination on a similar methylenedioxo-substituted aromatic ring to afford the iodide **20**,[3n] so, in principle, we felt that the aromatic ring present in **31** should be nucleophilic enough to react with the putative allylic cation electrophile that is produced during the Friedel−Crafts reaction.

We therefore prepared **31** by alkylation of **26** with the known nosylate **30**, and we exposed this material to Kuehne's conditions ($SnCl_4$, DCM/$MeNO_2$).[3f] We avoided using polyphosphoric acid as we felt that the dioxolane ring present in **31** could decompose under these harshly acidic conditions. Pleasingly, we were able to isolate the desired pentacycle **8** as the major new product from the reaction, and its spectroscopic data were identical to those previously reported.[4b] Since it has been shown that **8** can be converted into (−)-cephalotaxine (**1**), we have successfully completed a second generation formal synthesis of the natural product **1**.

Experimental Section

(*R*)-*N*-Boc-7-[(*tert*-butyldimethylsilyloxy)methyl]-1-azaspiro[4.4]non-6-ene 18. *n*-Butyl lithium (11.1 mL, 2.28 M solution in hexanes, 25.4 mmol) was added dropwise to a cold (−78 °C) stirring solution of trimethylsilyldiazomethane (14.6 mL, 2 M solution in hexanes, 29.2 mmol) in THF (39 mL), and the resulting mixture was stirred for 1 h and 40 min at −78 °C. The ketone **17** (7.1 g, 19.1 mmol) in THF (25 mL) was added dropwise, and the resulting mixture was stirred for a further 80 min. The reaction mixture was warmed to 0 °C and stirred for 20 min. The reaction was quenched with NH_4Cl (24 mL of a saturated solution diluted with water (20 mL)), extracted with ether (100 and 50 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo to give the crude product. Purification by column chromatography (petrol/Et_2O; 10/1−5/1) afforded the product **18** (5.16 g, 74%) as a colorless oil: $[\alpha]^{28}_D$ −49.56 (*c* 1.36, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 2954, 2929, 2857, 1731, 1668, 1457; δ_H (500 MHz, C_6D_6, 343 K) 5.35 (1H, s); 4.12 (1H, d, J = 13.5 Hz), 4.08 (1H, d, J = 13.5 Hz), 3.38 (1H, br s), 3.27 (1H, app q, J = 8 Hz), 2.52−2.30 (2H, m), 2.16 (1H, app quint, J = 8 Hz), 1.70 (1H, m), 1.59 (2H, m,), 1.49−1.62 (2H, m), 1.41 (9H, s), 0.93 (9H, s), 0.04 (6H, s); δ_C (125 MHz, 298 K) (2.9:1 mixture of rotamers; signals from major rotamer marked with *) 154.6* (C), 153.1 (C), 143.5 (C), 142.8* (C), 129.8* (CH), 129.2 (CH), 78.6* (C), 78.3 (C), 74.0* (C), 62.5 (CH_2), 62.2* (CH_2), 47.7 (CH_2), 47.5* (CH_2), 40.9* (CH_2), 39.5 (CH_2), 36.3* (CH_2), 35.2 (CH_2), 30.9* (CH_2), 28.5 (3 × CH_3), 28.4* (3 × CH_3), 25.9 (3 × CH_3), 22.8 (CH_2), 22.5* (CH_2), 18.3* (C), −5.4* (2 × CH_3); *m*/*z* (ES^+) 390.2430 (M + Na, $C_{20}H_{37}NNaO_3Si$ requires 390.2435); Anal. Calcd for $C_{20}H_{37}NO_3$: C, 65.3; H, 10.2; N, 3.8. Found: C, 64.9; H, 10.1; N, 3.9.

(*R*)-*N*-Boc-1-azaspiro[4.4]non-6-ene 11. To a stirring solution of **33** (260 mg, 1.03 mmol) in toluene (5.20 mL) at room temperature was added $Rh(PPh_3)_3Cl$ (953 mg, 1.03 mmol), and the mixture was heated at reflux for 14 h. The reaction mixture was cooled to room temperature and diluted with EtOAc (23 mL). Then, 2 N NaOH (40 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (50 mL × 2). The combined organic layers were washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo to give a brown oil, which was purified by column chromatography (ether/pentane, 1/5−1/4) to give **11** as a yellow oil (213 mg, 93%): $[\alpha]^{26}_D$ −101.3 (*c* 0.62, C_6H_6); ν_{max}/cm^{-1} (C_6H_6) 2928, 2870, 1698, 1685, 1408; δ_H (270 MHz, C_6D_6, 343 K) 5.61 (1H, br s), 5.47 (1H, br s), 3.45 (1H, br s), 3.37−3.26 (1H, m), 2.52 (1H, m), 2.36 (1H, m), 2.15 (1H, m), 1.63 (1H, m), 1.57 (2H, m), 1.46 (9H, s), 1.43−1.35 (2H, m); δ_C (125 MHz, 298 K) (1.0:0.8 mixture of rotamers) 154.2 (C), 153.1 (C), 137.3 (CH), 135.1 (CH), 130.9 (CH), 129.0 (CH), 78.4 (C), 78.1 (C), 74.7 (C), 74.3 (C), 48.1 (CH_2), 4.9 (CH_2), 40.9 (CH_2), 40.1 (CH_2), 36.1 (CH_2), 35.2 (CH_2), 32.0 (CH_2), 31.5 (CH_2), 28.7 (3 × CH_3), 28.6 (3 × CH_3), 23.2 (CH_2), 22.6 (CH_2); *m*/*z* (ES^+) 246.1457 (M + Na, $C_{13}H_{21}NNaO_2$ requires 246.1465).

(3a*S*,13b*S*)-3,5,6,8,9,13b-Hexahydro-l1,12-dimethoxy-4*H*-cyclopenta[*a*]pyrrolo[2,1-*b*]-[3]benzazepine 29. A mixture of **28** (32 mg, 0.105 mmol) and polyphosphoric acid (0.85 g) was stirred at 65 °C for 43 h. The reaction mixture was diluted with DCM (1.5 mL) quenched with saturated $NaHCO_3$ (15 mL), and the solution was made basic (pH = 14) by 15% NaOH (10 mL) solution. The mixture was extracted with DCM (10 mL × 2), $CHCl_3$ (10 mL), and finally with $CHCl_3$/IPA (2/1, 15 mL × 2), and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo to give **29** as a light yellow solid (22 mg, 73%). The crude material was judged >90% pure by ^1H and ^{13}C NMR, and purification on neutral alumina with eluents (EtOAc/hexane, 1:3−3:1 and 1% Et_3N in EtOAc) gave purified **29** (11 mg, 36%) for analytical purposes: $[\alpha]^{25}_D$ −137.4 (*c* 0.95, $CHCl_3$), Lit. $[\alpha]^{21}_D$ −152.1 (*c* 1.03, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 2930, 2808, 1747, 1693, 1608, 1488; δ_H (400 MHz, $CDCl_3$, 298 K) 6.68 (1H, s), 6.62 (1H, s), 5.79 (1H, app dq, J = 6, 2.2 Hz), 5.54 (1H, app dq, J = 6, 2.4 Hz), 3.89 (1H, m), 3.86 (3H, s), 3.84 (3H, s), 3.20 (1H, ddd, J = 14, 12.4, 7.6 Hz), 3.08 (1H, app td, J = 9.2, 4.8 Hz), 2.94 (1H, app td, J = 12, 6.8 Hz), 2.76 (1H, app dq, J = 17.6, 2.4 Hz), 2.56 (1H, dd, J = 11.2, 7.6 Hz), 2.45−2.59 (2H, m), 2.04−1.90 (3H, m), 1.83−1.61 (2H, m); δ_C (100 MHz, $CDCl_3$, 298 K) 147.7 (C), 147.2 (C), 132.6 (CH), 131.2 (C), 130.9 (C), 128.7 (CH), 144.2 (CH), 113.1 (CH), 68.2 (C), 62.4 (CH), 56.2 (CH_3), 56.8 (CH_3), 53.8 (CH_2), 49.2 (CH_2), 43.5 (CH_2), 34.8 (CH_2), 30.6 (CH_2), 20.0 (CH_2); *m*/*z* (ES^+) 286.1794 (M + H, $C_{18}H_{24}NO_2$ requires 286.1802). These data are identical to those previously reported.[4b]

(3a*S*,14b*S*)-3,5,6,8,9,14b-Hexahydro-4*H*-cyclopenta[*S*]-[1,3]dioxolo[4,5-*h*]pyrrolo[2,l-*b*]-[3]benzazepine 8. To the solution of **31** (20 mg, 0.067 mmol) in DCM/$MeNO_2$ (1:1, 2 mL) was added $SnCl_4$ (80 μL, 0.68 mmol) dropwise at −78 °C, and the mixture was then warmed to 50 °C and stirred at this temperature for 14 h. The reaction mixture was cooled to room temperature and diluted with EtOAc (5 mL). Then, 1 N HCl (1 mL) was added, and the pH was adjusted to 14 by addition of 2 N NaOH. The layers were separated, and the aqueous solution was extracted with EtOAc (10 mL), DCM (10 mL × 2), and finally with $CHCl_3$/MeOH (9:1, 10 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to give a brown oil, which was purified by column chromatography [1% Et_3N in EtOAc/pentane (1:1)] to yield **8** (9.2 mg, 46%) as a light yellow oil: $[\alpha]^{24}_D$ −210.5 (*c* 0.25, $CHCl_3$), Lit. $[\alpha]^{22}_D$ −230.8 (*c* 1.22, $CHCl_3$); δ_H (400 MHz, $CDCl_3$, 298 K) 6.65 (1H, s), 6.59 (1H, s), 5.89 (1H, d, J = 1.6 Hz), 5.88 (1H, d, J = 1.6 Hz), 5.79 (1H, app dq, J = 5.9, 2.4 Hz), 5.52 (1H, app dq, J = 5.9, 2.2 Hz), 3.86 (1H, m), 3.19 (1H, ddd, J = 13.9, 12.5, 7.4 Hz), 3.06 (1H, app td, J = 9.0, 4.4 Hz), 2.90 (1H, app td, J = 11.7, 6.8 Hz), 2.74 (1H, app dq, J = 18, 2.4 Hz), 2.54 (1H, dd, J = 11.2, 7.5 Hz), 2.40 (1H, app td, J = 10, 6.1 Hz), 2.33 (1H, dd, J = 14.4, 6.4 Hz), 2.02−1.90 (3H, m), 1.83−1.64 (2H, m); δ_C (100 MHz, $CDCl_3$, 298 K) 146.4 (C), 146.0 (C), 132.5 (CH), 131.9(C), 128.8 (CH), 110.9 (CH), 109.9 (CH), 100.9 (CH_2), 68.1 (C), 62.5 (CH), 53.7 (CH_2), 49.1 (CH_2), 43.4 (CH_2), 34.8 (CH_2), 30.7 (CH_2), 20.0 (CH_2); *m*/*z* (ES^+) 270.1489 (M + H, $C_{17}H_{20}NO_2$ requires 270.1498), 271 (19, M + 2H). These data are identical to those previously reported.[4b]

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Supporting Information Available: Experimental procedure for preparation of **17**, **19**, **21**, **22**, **24**, **25**, **26**, **28**, **31**, **34**, and **35**, X-ray structure of **24**, and copies of the ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) We have recently observed epimerization of a similar spirocycle under acidic conditions: Asari, A.; Angelov, P.; Auty, J. M.; Hayes, C. J *Tetrahedron Lett.* **2007**, *48*, 2631.

(15) Royer has independently confirmed the success of the Kuehne Friedel−Crafts reaction. See ref 4g.