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Total Synthesis of Desoxoprosophylline: Application of a Lactam-Derived Enol Triflate to Natural Product Synthesis

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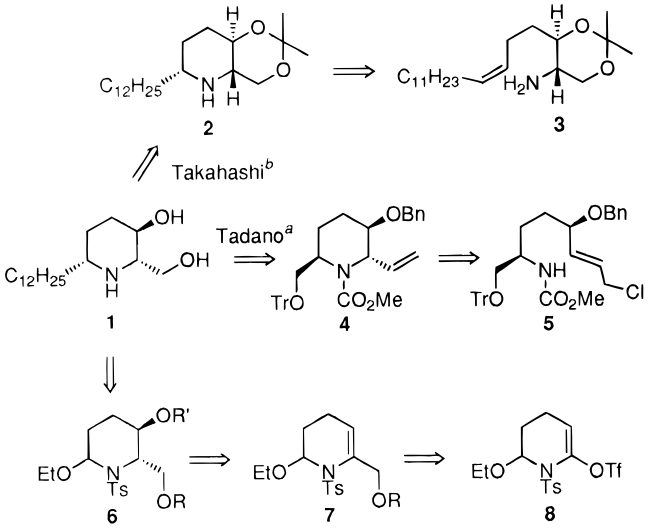
The total synthesis of desoxoprosophylline **1** from a piperidinone-derived enol triflate **8** has been realized and is one of the first applications of such lactam-derived triflates to natural product synthesis. Palladium-catalyzed methoxycarbonylation of **8** followed by 1,2-reduction and protection introduces the required C2 hydroxymethyl group, affording **10**. The C3 hydroxy function is stereoselectively added by a novel *N*-tosylenamide hydroboration (de 88%), and the final C6 dodecyl chain is incorporated with complete stereocontrol, in a single step, *via* an *N*-tosyliminium ion−allylsilane coupling. Deprotection gives the natural product in an efficient 7.5% yield over nine steps.

Introduction

In contrast to the numerous reports describing the formation and functionalization of enol triflates derived from aldehydes, ketones, lactones,[1a] and thiolactones,[1b] there have been relatively few publications concerning extension of this methodology to include lactam-derived variants. Isobe[2a,b] and Comins[2c] have reported the preparation of such lactam-derived triflates; however to the best of our knowledge only a single report of their use in natural product synthesis exists.[2c] We recently disclosed a high-yielding route to *N*-tosyl-α-ethoxypyrrolidinone and -piperidinone derived enol triflates (such as **8**, Scheme 1) and some preliminary studies on the stability and reactivity of these molecules.[3] Triflate **8** is also a precursor to iminium ions, which are now widely regarded as powerful intermediates for organic synthesis.[4] We hoped that molecules such as **8**, which allow access to these two extremely productive areas of synthetic methodology, should be useful in the construction of natural products.

Herein we show that our piperidinone-derived enol triflate **8** is indeed a useful building block for the stereocontrolled synthesis of polysubstituted piperidines, a nucleus present in a wide range of natural products.[5] Desoxoprosophylline **1**, a racemic alkaloid derivative isolated from *Prosopis africana*,[5a] has attracted recent interest as a synthetic target.[6] Scheme 1 summarizes the two previous total syntheses of this molecule, both of which used similar strategies. Tadano utilized an aminopalladation reaction (**5** → **4**) to close the piperidine ring,[6a] an approach which initially gave the incorrect product stereochemistry (later corrected *via* a fortuitous epimerization). Takahashi had earlier reported ring closure *via* a conceptually similar aminomercuration reaction[6b] (**3** → **2**).

Scheme 1



[a] Reference 6a. [b] References 6b,c.

Our retrosynthetic strategy is also shown in Scheme 1. In contrast to the previous routes, we begin with a cyclic starting material, triflate **8**, and hoped that the three reactive moieties present would allow the stereospecific incorporation of the three required piperidine ring substituents. The triflate moiety would allow introduction of the C2 hydroxymethyl group[3] of **7**, hydroboration of the resulting enamide[3] would functionalize C3 affording **6**, and finally *N*-tosyliminium ion generation (from the α-ethoxysulfonamide) would permit introduction of the C6 dodecyl chain.

Results and Discussion

The synthesis of **1** started with triflate **8** which was prepared from the corresponding *N*-tosyl-6-ethoxy-2-

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[5] (a) Khuong-Huu, Q.; Ratle, G.; Monseur, X.; Goutarel, R. *Bull. Soc. Chim. Belg.* **1972**, *81*, 443. (b) Khuong-Huu, Q.; Ratle, G.; Monseur, X.; Goutarel, R. *Bull. Soc. Chim. Belg.* **1972**, *81*, 425. (c) Fodor, G. B.; Colasanti, B. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1985; Vol. 3, p 1. (d) Strunz, G. M.; Findlay, J. A. In *The Alkaloids*; Brossi, A., Ed; Academic Press: San Diego, 1986; Vol. 26, p 89.

[6] (a) Takao, K.; Nigawara, Y.; Nishino, E.; Tagaki, I.; Maeda, K.; Tadano, K.; Ogawa, O. *Tetrahedron* **1994**, *50*, 5681. (b) Saitoh, Y.; Moriyama, Y.; Hirota, H.; Takahashi, T.; Khuong-Huu, Q. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 488. (c) Saitoh, Y.; Moriyama, Y.; Takahashi, T.; Khuong-Huu, Q. *Tetrahedron Lett.* **1980**, *21*, 75.

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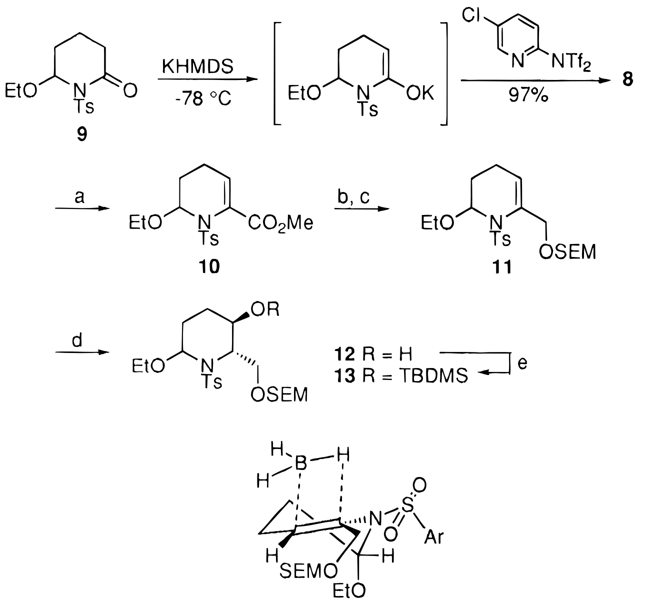
Scheme 2[a]



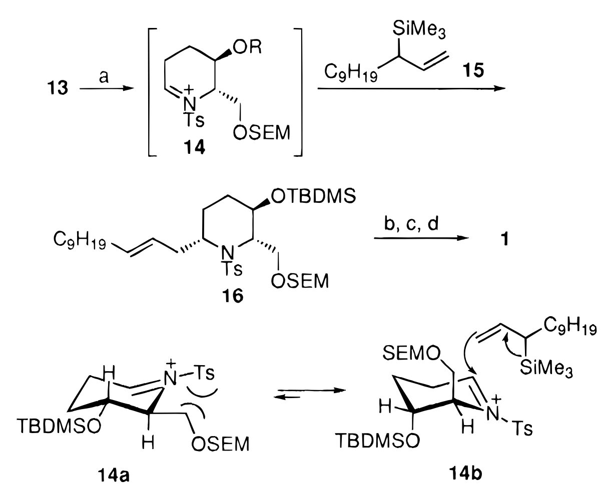
[a] Conditions: (a) Pd(AsPh$_3$)$_4$, CO, MeOH, DMF 61%; (b) DIBALH, THF 70%; (c) SEMCl, iPr$_2$EtN, CH$_2$Cl$_2$ 80%; (d) BH$_3$·THF, −78 → 0 °C then Me$_3$NO, 0 → 65 °C 83%; (e) TBDMSOTf, 2,6-lutidine, CH$_2$Cl$_2$ 92%.

piperidinone (**9**)[3] as shown in Scheme 2. We quickly found that the potassium enolate of **9** reacted more satisfactorily with triflating agents than the corresponding lithium variant. Enolate trapping with triflic anhydride did afford the desired triflate product, albeit in poor yield (ca. 35%). Switching to Comins' *N*-(5-chloro-2-pyridyl)triflimide[7] increased the yield to ca. 60%. Finally we found that Kugelrohr distillation of the commercially obtained Comins' reagent before use (distilled material was stable for >3 months at 0 °C) dramatically increased the yield of **8** to an excellent 97%.

The first challenge was introduction of the C2-hydroxymethyl substituent. Attempts to introduce this substituent in one step *via* reaction of **8** with lithium bis((methoxymethoxy)methyl) cuprate[8] ((MOMOCH$_2$)$_2$CuLi) failed to give the desired coupling product, and so an alternative strategy was sought. Palladium-catalyzed methoxycarbonylation[2c,9] using the previously reported conditions (Pd(OAc)$_2$, PPh$_3$) gave a moderate yield of ester **10**. The reaction was improved both in terms of yield and rate by switching to an *in situ* generated tetrakis(triphenylarsine)palladium(0) catalyst known to accelerate Stille couplings.[10] Selective 1,2-reduction of ester **10** gave an allylic alcohol which was only stable for moderate periods at rt. It was therefore immediately protected as the SEM ((*β*-(trimethylsilyl)ethoxy)methyl) ether **11**. Thus the first of the required piperidine substituents had been efficiently introduced.

With quantities of **11** in hand, we were now in a position to attempt the novel hydroboration of the trisubstituted *N*-tosylenamide moiety. Only a few reports have appeared concerning the hydroboration of cyclic enecarbamates[11a,b] and enamides.[11c] All contained disubstituted double bonds, and in all but one case[11c] the diastereoselection was poor. Hindered boranes such as 9-BBN-H failed to react with **11**, even after protracted reaction times or elevated temperatures. We eventually found that reaction of **11** with excess borane−THF at low temperature (−10 °C) resulted in slow but clean hydroboration; however, upon warming to rt, the resulting organoborane was unstable, giving a plethora of unidentified products. Fortunately, at 0 °C the reaction proceeded both smoothly and at a reasonable rate. Oxidative workup with alkaline hydrogen peroxide gave complex product mixtures. Pleasingly, oxidation with trimethylamine *N*-oxide[12] afforded the desired alcohol **12** in a high-yielding, stereocontrolled process (15:1 mixture, de 88%). Thus we had efficiently introduced the second of the ring substituents required for the natural product. A 3,6-*trans* product was expected as the major isomer,[11c] resulting from the transition state shown in Scheme 2. A$^{(1,3)}$ strain from the *N*-tosyl group imposes an axial orientation on the C6-ethoxy group, and hydroboration from the least hindered face affords the 3,6-*trans* product. Unfortunately, this relative stereochemistry could not be proven (noncrystallinity prevented X-ray analysis, and overlapping proton resonances in the ^{1}H NMR spectra inhibited NOE studies). As a new C6-substituent was to be introduced shortly, the uncertain stereochemistry of the ethoxy group was viewed of minor importance and not pursued further. Protection of the secondary alcohol under standard conditions gave TBDMS ether **13**,[13] and so the final challenge remaining was the stereospecific introduction of the C6-dodecyl substituent.

Scheme 3[a]



[a] Conditions: (a) **15**, BF$_3$·Et$_2$O, −78 → −30 °C 55%; (b) Pd/C, H$_2$, MeOH; (c) HCl (0.4 M in MeOH) 75% (two steps); (d) Na/NH$_3$ 75%.

We intended to generate the *N*-tosyliminium ion[14] **14** from **13** and introduce the 12-carbon chain in one step *via* allylsilane **15** (Scheme 3). The synthesis of **15** was surprisingly straightforward. Using the conditions described by Arase,[15] hydroboration of 3-chloro-1-(trimethylsilyl)-1-propyne with dinonylborane followed by reac-

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[12] Kabalka, G. W.; Hedgecock, H. C., Jr. *J. Org. Chem.* **1975**, *40*, 1776.

[13] The Lewis acidity of the TBDMSOTf occasionally caused partial elimination of EtOH from **13**, affording an *N*-tosylenamide byproduct (ca. 5−15%). However, this was of little consequence as both **13** and the byproduct reacted with silane **15** in the next step.

[14] Åhman, J.; Somfai, P. *Tetrahedron* **1992**, *48*, 9537 and references therein.

tion with MeLi gave, after quenching, **15** in 56% yield from a one-pot process. Coupling of **13** and **15** proceeded in reasonable yield, mediated by boron trifluoride etherate, affording **16** as a single diastereomer (no traces of diastereomeric impurities were detected in either the ^{1}H- or ^{13}C-NMR spectra of the crude reaction product). Although the relative stereochemistry at the newly formed stereocenter was not known until the last step of the synthesis (NOE studies proved fruitless), we predicted **16** to have the correct natural product stereochemistry from analysis of the possible transition states. Due to a strong A$^{(1,2)}$ strain between the C2-hydroxymethyl substituent and the *N*-tosyl group of the iminium ion, transition state **14a** was expected to be less stable than **14b**, which contains the axial C2-hydroxymethyl.[16] Stereoelectronically preferred axial attack[17] by the silane nucleophile on **14b** would account for the 2,6-*cis*-substituted piperidine isolated. Interestingly, but for less obvious reasons, the C3-hydroxyl group is also known to direct such incoming nucleophiles, but in a *trans* manner,[16b] further reinforcing the observed stereoselectivity.

Hydrogenation of olefin **16**, followed by deprotection of the hydroxy and amino groups, afforded desoxoprosophylline **1** in excellent yield. Mp and NMR data were identical with those previously reported.[5a,6a,b]

In conclusion, the synthesis of desoxoprosophylline has been achieved in nine steps and 7.5% overall yield from *N*-tosyl-6-ethoxy-2-piperidinone. Our route to **1** has lead to the development of novel methodology including a highly diastereoselective trisubstituted enamide hydroboration and a completely stereoselective "internal" allylsilane–*N*-tosyliminium ion coupling. The work presented should go some way toward establishing lactam-derived enol triflates as useful synthetic intermediates.

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Dichloromethane, triethylamine, diisopropylethylamine, 2,6-lutidine, and DMF were distilled from CaH_2 prior to use and stored under nitrogen. THF was distilled from Na/benzophenone. *N*-(5-Chloro-2-pyridyl)triflimide was Kugelrohr distilled before use and could be stored at 0 °C for 3 months. All reaction mixtures were stirred under a nitrogen atmosphere unless otherwise indicated. During workup, where drying of the organic solutions is indicated, Na_2SO_4 was used with subsequent filtration in all cases. IR spectra were recorded as $CHCl_3$ solutions. NMR spectra were measured in $CDCl_3$ and are reported in units of ppm. J values are in hertz. Carbon resonances are reported as q (CH_3), t (CH_2), d (CH), or s (C) as determined by APT (attached proton test) or DEPT experiments. Mass spectra were determined using the electron-impact method unless otherwise indicated, with data reported as m/z (relative intensity).

6-Ethoxy-1-*p*-toluenesulfonyl-2-((trifluoromethanesulfonyl)oxy)-1,4,5,6-tetrahydropyridine (8). To a stirred solution of *N*-tosyl-6-ethoxy-2-piperidinone[3] (1.200 g, 4.04 mmol) in THF (24 mL) at −78 °C was added KHMDS (10.1 mL of a 0.5 M solution in toluene, 5.05 mmol, 1.25 equiv), and the pale yellow solution was stirred for 45 min. A solution of *N*-(5-chloro-2-pyridyl)triflimide (1.983 g, 5.05 mmol, 1.25 equiv) in THF (3 mL) was added rapidly in one portion. After 45 min of stirring, the reaction mixture was warmed to ca. 0 °C. Saturated ammonium chloride solution (15 mL) followed by dichloromethane (20 mL) and water (15 mL) were added, and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 25 mL), the combined organic solutions were dried, and the solvent was removed *in vacuo*. Column chromatography (1:5 → 1:1 dichloromethane/light petroleum ether, on SiO_2) afforded triflate **8** as white crystals (1.660 g, 96%): mp 67–70 °C from light petroleum ether; IR 3413, 1677 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.76 (2 H, d, $J = 8.3$), 7.36 (2 H, d, $J = 8.2$), 5.41 (1 H, t, $J = 4.6$), 5.40 (1 H, t, $J = 2.6$), 3.81 (1 H, dq, $J = 9.3, 7.1$), 3.51 (1 H, dq, $J = 9.3, 7.0$), 2.46 (3 H, s), 2.32 (1 H, dddd, $J = 18.9, 12.1, 7.3, 3.6$), 2.02 (1 H, ddd, $J = 18.6, 6.4, 4.3$), 1.81 (1 H, ddd, $J = 13.6, 6.6, 1.4$), 1.16 (1 H, m), 1.16 (3 H, t, $J = 7.0$); ^{13}C NMR (50 MHz) δ 145.1 (s), 137.2 (s), 135.1 (s), 130.2 (2d), 128.0 (2d), 118.7 (s; q $J = 321.1$), 108.7 (d), 86.4 (d), 64.2 (t), 25.4 (t), 21.8 (q), 18.4 (t), 11.6 (q); MS 429 M$^+$ (58); HRMS calcd for $C_{15}H_{18}NO_6F_3S_2$ 429.0528, found 429.0512. Anal. Calcd for $C_{15}H_{18}NO_6F_3S_2$: C, 41.95; H, 4.23; N, 3.26. Found: C, 42.42; H, 4.60; N, 3.42.

2-Carbomethoxy-6-ethoxy-1-*p*-toluenesulfonyl-1,4,5,6-tetrahydropyridine (10). A solution of triflate **8** (0.324 g, 0.755 mmol), Pd_2dba_3 (0.017 g, 0.018 mmol, 0.03 equiv), and triphenylarsine (0.046 g, 0.151 mmol, 0.20 equiv) in DMF (3.5 mL) was flushed with carbon monoxide for 10 min. Triethylamine (0.42 mL, 3.02 mmol, 4 equiv) and methanol (1.22 mL, 30.21 mmol, 40 equiv) were added, and the solution was attached to a balloon of carbon monoxide and stirred for 12 h. After the solution was flushed with nitrogen, ethyl acetate (10 mL) and water (6 mL) were added and the organic phase was separated. The aqueous phase was extracted with ethyl acetate (2 × 10 mL), the combined organics were washed with brine (2 × 10 mL) and dried, and the solvent was removed *in vacuo*. Column chromatography (1:5 ethyl acetate/light petroleum ether, on SiO_2) afforded ester **10** as a colorless oil which occasionally partially crystallized to a waxy white solid (0.155 g, 61%): IR 1727, 1645 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.83 (2 H, d, $J = 8.3$), 7.30 (2 H, d, $J = 8.2$), 6.33 (1 H, t, $J = 3.6$), 4.99 (1 H, t, $J = 2.7$), 3.83 (3 H, s), 3.59 (1 H, dq, $J = 9.7, 7.1$), 3.20 (1 H, dq, $J = 9.7, 7.0$), 2.42 (3 H, s), 2.23 (1 H, dddd, $J = 19.8, 11.6, 7.6, 3.6$), 2.03 (1 H, dddd, $J = 19.8, 7.3, 4.1, 0.8$), 1.77 (1 H, ddt, $J = 13.8, 7.6, 1.2$), 1.35 (1 H, dddd, $J = 13.8, 10.5, 7.4, 3.0$), 1.01 (3 H, t, $J = 7.1$); ^{13}C NMR (100 MHz) δ 166.3 (s), 144.4 (s), 135.5 (s), 129.8 (2d), 128.2 (2d), 127.7 (s), 127.4 (d), 82.0 (d), 63.3 (t), 52.4 (q), 25.2 (t), 21.8 (q), 19.0 (t), 14.7 (q); MS 339 M$^+$ (96); HRMS calcd for $C_{16}H_{21}NO_5S$ 339.1140, found 339.1138.

6-Ethoxy-1-*p*-toluenesulfonyl-2-(((β-(trimethylsilyl)ethoxy)methoxy)methyl)-1,4,5,6-tetrahydropyridine (11). To a solution of ester **10** (0.630 g, 1.858 mmol) in THF (12 mL) at 0 °C was added DIBALH (9.29 mL of a 1 M solution in THF, 9.29 mmol, 5 equiv), and the solution was warmed to rt. After 5 h, the reaction was carefully quenched with saturated aqueous Rochelle's salt. Water (25 mL) was added, and the solution was extracted with ethyl acetate (4 × 35 mL). The combined extracts were dried, and the solvent was removed *in vacuo*. Column chromatography (1:4 → 1:3 ethyl acetate/light petroleum ether, on SiO_2) afforded an allylic alcohol product (0.407 g, 70%) as a colorless oil. This compound was of low thermal stability and so was immediately protected as its SEM ether before full characterization: ^{1}H NMR (400 MHz) δ 7.67 (2 H, d, $J = 8.3$), 7.31 (2 H, d, $J = 8.1$), 5.41 (1 H, t, $J = 3.5$), 5.35 (1 H, t, $J = 5.3$), 4.54 (1 H, dd, $J = 13.2, 7.0$), 4.13 (1 H, dd, $J = 13.2, 8.3$), 3.83 (1 H, dq, $J = 9.8, 7.2$), 3.62 (1 H, dq, $J = 9.8, 7.0$), 3.16 (1 H, dd, $J = 8.2, 7.0$), 2.43 (3 H, s), 2.17 (1 H, m), 1.73 (2 H, m), 1.20 (3 H, t, $J = 7.0$), 0.96 (1 H, m).

To a solution of this alcohol (0.353 g, 1.135 mmol) in dichloromethane (5 mL) were added diisopropylethylamine (0.58 mL, 3.41 mmol, 3 equiv) and SEMCl (0.54 mL, 3.07 mmol, 2.7 equiv). After 12 h, the volatiles were removed *in vacuo*. Column chromatography (1:6 → 1:4 ethyl acetate/light petroleum ether, on SiO_2) afforded SEM ether **11** as a colorless oil which slowly crystallized upon standing (0.399 g, 80%): mp 67–69 °C from ethyl acetate/light petroleum ether; IR 3023,

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(16) For similar results with *N*-acyliminium ions, see: (a) Ludwig, C.; Wistrand, L.-G. *Acta Chem. Scand.* **1994**, *48*, 367 and references therein. (b) Shono, T.; Matsumura, Y.; Onomura, O.; Sato, M. *J. Org. Chem.* **1988**, *53*, 4118.

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1683 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.67 (2 H, d, J = 8.0), 7.29 (2 H, d, J = 8.2), 5.38 (1 H, d, J = 3.7), 5.26 (1 H, t, J = 2.4), 4.72 (1 H, d, J = 6.7), 4.67 (1 H, d, J = 6.7), 4.59 (1 H, d, J = 13.1), 4.31 (1 H, d, J = 13.1), 3.75 (1 H, dq, J = 9.6, 7.0), 3.69 (1 H, q, J = 8.9), 3.62 (1 H, q, J = 8.8), 3.51 (1 H, dq, J = 9.6, 6.9), 2.42 (3 H, s), 2.16 (1 H, dt, J = 18.1, 9.6), 1.71 (2 H, m), 1.14 (3 H, t, J = 7.0), 1.05 (1 H, m), 0.956 (2 H, t, J = 8.6), 0.03 (9 H, s); ^{13}C NMR (100 MHz) δ 143.8 (s), 136.3 (s), 130.7 (s), 129.8 (2d), 127.4 (2d), 118.7 (d), 93.3 (t), 83.6 (d), 68.5 (t), 65.4 (t), 63.1 (t), 25.5 (t), 21.7 (q), 18.5 (t), 18.3 (t), 14.9 (q), −1.2 (3q); MS 368 (M − TMS)$^+$ (11), 296 (M − OCH$_2$O(CH$_2$)$_2$TMS)$^+$ (16). Anal. Calcd for $C_{21}H_{35}NO_5SSi$: C, 57.12; H, 7.99; N, 3.17. Found: C, 56.70; H, 8.09; N, 3.04.

(2*S,3*R**)-6-Ethoxy-3-hydroxy-1-*p*-toluenesulfonyl-2-(((*β*-(trimethylsilyl)ethoxy)methoxy)methyl)piperidine (12).** To a solution of SEM ether **11** (0.150 g, 0.340 mmol) in THF (16 mL) at −78 °C was added a borane−THF complex (1.1 mL of a 1 M solution in THF, 1.1 mmol, 3.4 equiv) dropwise. After 5 min of stirring, the flask was sealed and placed in a refrigerator at 0 °C for 16 h. Trimethylamine *N*-oxide (0.450 g, 4.049 mmol) was added to the vigorously stirred hydroboration mixture at 0 °C, a reflux condenser was quickly attached, and the reaction mixture was transferred to a preheated oil bath at 65 °C (maintain vigorous stirring while heating). After 2 h the reaction mixture was cooled to rt and ethyl acetate (30 mL) added. The organic solution was washed with brine (2 × 15 mL) and dried and the solvent removed *in vacuo*. Column chromatography (1:3 → 1:2 ethyl acetate/light petroleum ether, on SiO$_2$) afforded alcohol **12** as a colorless oil (0.108 g, 83%): 16:1 mixture of inseparable diastereomers by ^{1}H NMR (integration of proton resonances at 5.27 and 5.18 ppm, respectively); IR 3588, 2954 cm^{-1}; ^{1}H NMR (400 MHz) δ (major only) 7.75 (2 H, d, J = 8.3), 7.29 (2 H, d, J = 8.0), 5.27 (1 H, t, J = 3.1), 4.63 (1 H, d, J = 6.7), 4.60 (1 H, d, J = 6.7), 3.98 (1 H, br s), 3.80 (2 H, m), 3.69 (1 H, dq, J = 9.7, 7.2), 3.63−3.56 (3 H, m), 3.49 (1 H, dq, J = 9.7, 7.1), 2.41 (3 H, s), 2.02 (1 H, tt, J = 13.8, 2.9), 1.84 (1 H, tt, J = 13.6, 4.0), 1.67 (1 H, m), 1.49 (1 H, m), 1.24 (1 H, br s), 1.18 (3 H, t, J = 7.0), 0.94 (1 H, q, J = 7.2), 0.92 (1 H, q, J = 7.2), 0.03 (9 H, s); ^{13}C NMR (100 MHz) δ 143.6 (s), 137.7 (s), 129.8 (2d), 127.4 (2d), 95.2 (t), 81.8 (d), 68.6 (t), 65.5 (t), 64.2 (d), 63.0 (t), 58.7 (d), 24.3 (t), 21.8 (q), 20.7 (t), 18.3 (t), 15.0 (q), −1.2 (3q); MS (FAB) 482 MNa$^+$ (40); HRMS calcd for $C_{21}H_{37}NO_6SSiNa$ 482.2008, found 482.2054.

(2*S,3*R**)-3-((*tert*-Butyldimethylsilyl)oxy)-6-ethoxy-1-*p*-toluenesulfonyl-2-(((*β*-(trimethylsilyl)ethoxy)methoxy)methyl)piperidine (13).** To a solution of alcohol **12** (0.108 g, 0.235 mmol) in dichloromethane (2 mL) at 0 °C were added 2,6-lutidine (164 μL, 1.41 mmol, 6 equiv) and TBDMSOTf (108 μL, 0.471 mmol, 2 equiv), and the solution was warmed to rt over 12 h. Saturated aqueous sodium bicarbonate (1 mL), water (5 mL), and dichloromethane (5 mL) were then added. The organic phase was separated, and the aqueous phase was extracted with dichloromethane (2 × 5 mL). The combined organics were dried, and the solvent was removed *in vacuo*. Column chromatography (1:10 → 1:8 ethyl acetate/light petroleum ether, on SiO$_2$) afforded TBDMS ether **13** as a colorless oil (0.124 g, 92%) (contaminated with small amounts of an uncharacterized enamide byproduct): IR 2955, 2930 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.73 (2 H, d, J = 8.0), 7.72 (2 H, d, J = 8.0), 5.15 (1 H, t, J = 2.6), 4.66 (1 H, d, J = 6.6), 4.63 (1 H, d, J = 6.6), 4.03 (1 H, s), 3.73 (4 H, m), 3.60 (1 H, t, J = 8.6), 3.60 (1 H, t, J = 8.1), 3.48 (1 H, dq, J = 9.6, 7.0), 2.38 (3 H, s), 2.05 (1 H, tt, J = 13.8, 3.0), 1.90 (1 H, tt, J = 13.2, 3.2), 1.61 (1 H, m), 1.39 (1 H, m), 1.16 (3 H, t, J = 6.8), 0.95 (2 H, m), 0.72 (9 H, s), 0.03 (9 H, s), −0.09 (3 H, s), −0.13 (3 H, s); ^{13}C NMR (100 MHz) δ 143.0 (s), 138.4 (s), 129.6 (2d), 127.5 (2d), 94.9 (t), 81.9 (d), 68.6 (t), 65.4 (t), 64.8 (d), 62.9 (t), 59.2 (d), 26.1 (3q), 24.4 (t), 21.6 (q), 21.5 (t), 18.4 (s), 18.3 (t), 15.1 (q), −1.2 (3q), −4.8 (q), −4.9 (q).

3-(Trimethylsilyl)-1-dodecene (15). The title compound was prepared from nonene and 3-chloro-1-(trimethylsilyl)-1-propyne by an identical route to that reported by Arase for the preparation of the 3-(trimethylsilyl)-1-heptene homologue.[15] The reaction afforded silane **15** as a colorless oil (56%) after column chromatography (pentane, on SiO$_2$): ^{1}H NMR (250 MHz) δ 5.61 (1 H, dt, J = 16.9, 9.4), 4.87 (1 H, d, J = 10.1), 4.81 (1 H, d, J = 17.1), 1.57−1.27 (17 H, m), 0.89 (3 H, t, J = 5.8), −0.02 (9 H, s); ^{13}C NMR (100 MHz) δ 140.5 (d), 111.6 (t), 34.9 (d), 31.9 (t), 29.7 (t), 29.6 (t), 29.5 (t), 29.4 (t), 29.3 (t), 28.4 (t), 22.7 (t), 14.1 (q), −3.3 (3q).

(2*S,3*R**,6*S**)-3-((*tert*-Butyldimethylsilyl)oxy)-6-(2(*E*)-dodecenyl)-1-*p*-toluenesulfonyl-2-(((*β*-(trimethylsilyl)ethoxy)methoxy)methyl)piperidine (16).** To a solution of α-ethoxy sulfonamide **13** (0.120 g, 0.209 mmol) and allylsilane **15** (0.251 g, 1.047 mmol, 5 equiv) in dichloromethane (3 mL) at −78 °C was added boron trifluoride etherate (77 μL, 0.63 mmol, 3 equiv) dropwise, and the solution was stirred at this temperature for 30 min before being warmed to −30 °C (freezer) over 2.5 h. Saturated sodium bicarbonate solution (3 mL) was added, and the reaction mixture was warmed to rt. The organic layer was separated and the aqueous layer extracted with dichloromethane (2 × 5 mL). The combined organics were dried, and the solvent was removed *in vacuo*. Column chromatography (0:1 → 1:10 ethyl acetate/light petroleum ether, on SiO$_2$) afforded alkene **16** as a colorless oil (0.080 g, 55%): IR 2955, 2928, 1602 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.85 (2 H, d, J = 8.3), 7.23 (2 H, d, J = 8.1), 5.42 (1 H, dt, J = 15.4, 6.5), 5.26 (1 H, dt, J = 15.3, 8.1), 4.71 (1 H, d, J = 6.6), 4.68 (1 H, d, J = 6.6), 4.09 (1 H, dd, J = 10.0, 4.5), 4.05 (1 H, t, J = 1.2), 3.63 (4 H, m), 3.55 (1 H, m), 2.40 (3 H, s), 2.40−2.24 (2 H, m), 1.98 (2 H, m), 1.76 (2 H, m), 1.27 (16 H, m), 0.97 (2 H, m), 0.88 (3 H, t, J = 6.2), 0.86 (9 H, s), 0.05 (9 H, s), 0.03 (3 H, s), 0.02 (3 H, s); ^{13}C NMR (100 MHz) δ 142.5 (s), 138.4 (s), 133.8 (d), 129.3 (2d), 127.4 (2d), 126.5 (d), 94.8 (t), 69.5 (t), 65.4 (t), 65.2 (d), 59.2 (d), 52.3 (d), 38.5 (t), 32.5 (t), 31.9 (t), 29.6 (t), 29.5 (t), 29.4 (t), 29.3 (t), 29.1 (t), 25.9 (3q), 22.7 (t), 22.0 (t), 21.5 (q), 18.4 (t), 18.2 (s), 18.1 (t), 14.1 (q), −1.4 (3q), −4.8 (q), −5.0 (q); MS 638 (M − *t*-Bu)$^+$ (12); HRMS calcd for $C_{33}H_{69}NO_5SSi_2$ 638.3731, found 638.3766.

***N*-*p*-Toluenesulfonyldesoxoprosophylline.** Alkene **16** (0.080 g, 0.115 mmol) and 10% Pd/C (0.020 g) in MeOH (5 mL) were stirred under a balloon of hydrogen for 15 h. The solution was filtered through Celite and solvent removed *in vacuo* to yield a pale yellow oil (0.080 g). This was analyzed by ^{1}H NMR to confirm complete alkene reduction (disappearance of resonances at δ 5.42 and 5.26 ppm) and then dissolved in HCl (0.4 M in MeOH, 5 mL) and stirred at 40 °C for 15 h. Saturated sodium bicarbonate solution (4 mL) and dichloromethane (5 mL) were then added. The organic phase was separated, and the aqueous phase was extracted with dichloromethane (2 × 8 mL). The combined organics were dried, and the solvent was removed *in vacuo*. Column chromatography (1:6 → 3:1 ethyl acetate/light petroleum ether, on SiO$_2$) afforded the title diol as a colorless oil (0.039 g, 75%): IR 3503, 2927 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.81 (2 H, d, J = 8.3), 7.27 (2 H, d, J = 8.2), 4.00 (1 H, t, J = 8.8), 3.93 (1 H, br s), 3.81 (1 H, br s), 3.70 (1 H, dd, J = 11.0, 7.1), 3.64 (1 H, dd, J = 10.9, 8.3), 2.73 (1 H, br s), 2.40 (3 H, s), 2.00 (1 H, br s), 1.75 (2 H, m), 1.60 (1 H, m), 1.44 (2 H, m), 1.25 (21 H, m), 0.877 (3 H, t, J = 6.6); ^{13}C NMR (100 MHz) δ 143.2 (s), 137.7 (s), 129.6 (2d), 127.3 (2d), 64.3 (d), 64.2 (t), 61.4 (d), 52.5 (d), 35.5 (t), 31.9 (t), 29.7 (t), 29.6 (3t), 29.5 (t), 29.4 (t), 29.3 (t), 27.2 (t), 22.7 (t), 22.0 (t), 21.5 (q), 20.2 (t), 14.1 (q); MS 422 (M − CH$_2$OH)$^+$ (10); HRMS calcd for $C_{24}H_{40}NO_3S$ 422.2729, found 422.2694.

Desoxoprosophylline (1). Small pieces of sodium metal were periodically added to a solution of *N*-*p*-toluenesulfonyldesoxoprosophylline (0.027 g, 0.060 mmol) in THF (0.5 mL) and liquid ammonia (10 mL) at −78 °C, such that a blue color persisted for 5 h. Solid ammonium chloride was then added to discharge the blue color, and the solution was warmed to room temperature while the ammonia was evaporated under a stream of nitrogen. The residue was taken up in HCl (2 M, 5 mL) and extracted with dichloromethane (3 × 8 mL). The acidic aqueous phase was neutralized by the addition of saturated aqueous sodium bicarbonate (ca. 8 mL, pH ca. 10), and the now basic aqueous phase was extracted with dichloromethane (4 × 10 mL). These latter organics were combined and dried, and the solvent was removed *in vacuo* to afford pale yellow crystals. NMR analysis showed them to be virtually pure desoxoprosophylline. A single recrystallization afforded the natural product in pure form (0.013 g, 75%): mp 83−83.5

°C from ethyl acetate [lit mp 83 °C,[5a] 83−83.5 °C[6b]]; ^{1}H NMR (400 MHz) δ 3.84 (1 H, dd, J = 10.7, 5.0), 3.70 (1 H, dd, J = 10.8, 5.4), 3.46 (1 H, ddd, J = 10.9, 9.1, 4.6), 2.57 (1 H, dt, J = 9.0, 5.2), 2.52 (1 H, m), 2.04 (1 H, dq, J = 12.3, 4.1), 2.03 (3 H, v br s), 1.74 (1 H, dq, J = 13.2, 3.1), 1.44−1.25 (23 H, m), 1.12 (1 H, tdd, J = 13.4, 11.1, 3.7), 0.88 (3 H, t, J = 6.6); ^{13}C NMR (100 MHz) δ 70.92 (d), 64.96 (t), 63.18 (d), 55.93 (d), 36.64 (t), 34.01 (t), 31.91 (t), 31.23 (t), 29.79 (t), 29.66 (t), 29.65 (t), 29.64 (t), 29.59 (t), 29.57 (t), 29.34 (t), 26.19 (t), 22.68 (t), 14.11 (q).

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Supporting Information Available: ^{1}H NMR spectra of compounds **8**, **10**, **11**, **12**, **13**, **16**, and *N*-*p*-toluenesulfonyldesoxoprosophylline and ^{1}H and ^{13}C NMR spectra of desoxoprosophylline (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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