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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-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. Triflate 8 is also a precursor to iminium ions, which are now widely regarded as powerful intermediates for organic synthesis. 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 stereoselective synthesis of polysubstituted piperidines, a nucleus present in a wide range of natural products. Desoxoprosophylline 1, a racemic alkaloid derivative isolated from Prosopis africana, has attracted recent interest as a synthetic target. Scheme 1 summarizes the two previous total syntheses of this molecule, both of which used similar strategies. Tadano utilized an aminopalladation reaction (4) 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 of 7, hydroboration of the resulting enamide would functionalize C3 and finally N-tosyliminium ion generation from the α-ethoxysulfonylamide) 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-

piperidinone (9) as shown in Scheme 2. We quickly found that the potassium enolate of 9 reacted more satisfactorily with trifling 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 increased the yield to 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 failed (MOMCH2CuLi) to give the desired coupling product, and so an alternative strategy was sought. Palladium-catalyzed methoxy-carbonylation using the previously reported conditions (Pd(OAc)2, PPh3) 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 coupling (11c) giving the desired coupling product, and so an alternative strategy was sought. Palladium-catalyzed methoxy-carbonylation using the previously reported conditions (Pd(OAc)2, PPh3) 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. 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)ethoxymethyl) ether 11. Thus the first of the required piperidinone 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 and enamides. All contained disubstituted double bonds, and in all but one case 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 afforded the desired alcohol 12 in a high-yielding, stereoccontrolled 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, resulting from the transition state shown in Scheme 2. A 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 1H NMR spectra precluded 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, and so the final challenge remaining was the stereospecific introduction of the C6-dodecyl substituent.

We intended to generate the N-tosyliminium ion 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, hydroboration of 3-chloro-1-(trimethylsilylethyl)1-propyne with dimethylborane followed by reaction 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 afforded the desired alcohol 12 in a high-yielding, stereoccontrolled 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, resulting from the transition state shown in Scheme 2. A 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 1H NMR spectra precluded 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, and so the final challenge remaining was the stereospecific introduction of the C6-dodecyl substituent.

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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 1H- or 13C-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 attack17 by the silane substituent and the 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, toluene, and THF were distilled from CaH2 prior to use. Dichloromethane, triethylamine, diisopropylethylamine, and stored under nitrogen. THF was distilled from Na/2,6-lutidine, and DMF were distilled from CaH2 prior to use from commercial suppliers and used without further purification.

From a one-pot process. Coupling of 14b with MeLi gave, after quenching, 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 SiO2 afforded trflate 8 as white crystals (1.660 g, 96%): mp 67–70 °C from light petroleum ether; IR 3413, 1677 cm−1; 1H NMR (400 MHz) δ 7.67 (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 = 13.6, 6.6, 1.4), 1.16 (1 H, m), 1.16 (3 H, t, J = 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, 1.3), 1.16 (3 H, m, J = 11.0, 7.1), 1.09 (1 H, m, J = 11.0, 7.1), 1.06 (3 H, m, J = 11.0, 7.1), 0.98 (3 H, m, J = 11.0, 7.1), 0.97 (3 H, m, J = 11.0, 7.1); 13C NMR (100 MHz) δ 118.7 (s) = 321.1, 110.7 (d), 86.4 (d), 64.7 (t), 25.4 (t), 21.8 (s), 18.4 (t), 11.6 (s); MS 429 M+ [(58); HRMS calc for C15H18NO6F3S2; 429.0528, found 429.0512. Anal. Calcld for C15H18NO6F3S2: C, 41.95; H, 4.23; N, 3.26. Found: C, 42.42; H, 4.60; N, 3.42.

6-Ethoxy-1-(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 (0.929 mL of a 1 M solution in THF, 9.29 mmol, 5 equiv), and the solution was warmed to 50 °C. 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 1-1 ethyl acetate/light petroleum ether, on SiO2 afforded ester 11 as a colorless oil which occasionally partially crystallized to a waxy white solid (0.155 g, 61%): IR 1727, 1645 cm−1; 1H 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, ddd, J = 19.8, 11.6, 7.6, 3.6), 2.03 (1 H, ddd, 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, ddd, J = 13.8, 10.5, 7.4, 3.0), 1.01 (3 H, t, J = 7.1); 13C 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 calcld for C16H22N2O5S2: 339.1140, found 339.1138.


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(25,3R,3R*,3S*)-6-Ethoxy-3-hydroxy-1-p-toluenesulfonyl-2-((1-(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-trimethylsilylamine complex (1.1 mL; 2.5 equiv), dropwise. After 5 min of stirring, the flask was sealed 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 water (12×10 mL), brine (2×10 mL), and dried (Na2SO4). The solvent was removed in vacuo. Column chromatography (1:3–1:2 ethyl acetate/petroleum ether, on SiO2) afforded alkene 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 (frozeer) 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 organic layers were dried, and the solvent was removed in vacuo. Column chromatography (0.1 → 1:10 ethyl acetate/petroleum ether, on SiO2) afforded alkene 16 as a colorless oil (0.080 g, 55%): IR 2955, 2928, 1602 cm−1; 1H 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), 2.60 (1 H, m), 1.94 (2 H, m), 1.76 (2 H, m), 1.72 (2 H, m), 1.48 (12 H, m), 0.88 (3 H, t, J = 7.2), 0.72 (3 H, m). HRMS calcd for C24H40NO₃S 422.2729, found 422.2694.

N-p-Toluenesulfonyl-desoxoprosophylline. Alkene 16 (0.080 g, 0.115 mmol) in CH2Cl2 (250 μL) and toluene (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 1H NMR to confirm complete alkene reduction (disappearance of resonances at δ 5.42 and 5.25 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 washed with 1:2 ethyl acetate/petroleum ether (5 mL) and 1:2 ethyl acetate/petroleum ether (3 mL). The combined organics were dried, and the solvent was removed in vacuo. Column chromatography (1:6 → 3:1 ethyl acetate/petroleum ether, on SiO2) afforded the title dial as a colorless oil (0.039 g, 75%): IR 3503, 2927 cm−1; 1H 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, d, J = 11.0, 7.1), 3.64 (1 H, dd, J = 10.9, 8.3), 2.73 (1 H, m), 2.70 (1 H, m), 1.80 (2 H, m), 1.48 (12 H, m), 0.87 (3 H, t, J = 7.2), 0.74 (3 H, m), 0.68 (3 H, m). HRMS calcd for C24H40NO₃S 422.2729, found 422.2694.

Desoxoprosophylline (1). Small pieces of sodium metal were periodically added to a solution of N-p-toluenesulfonyl-desoxoprosophylline (0.100 g, 0.230 mmol) in THF (75 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 reextracted with dichloromethane (4 × 10 mL). The 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,1a 83–83.5 °C2b]; 1H 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); 13C 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: 1H NMR spectra of compounds 8, 10, 11, 12, 13, 16, and N-p-toluenesulfonyl/desoxoprosophylline and 1H and 13C 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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