Total synthesis of desoxoprosophylline: application of a lactam-derived enol triflate to natural product synthesis
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Published in:
Journal of Organic Chemistry

Citation for published version (APA):
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-tosylamide hydroboration (de 88%), and the final C6 dodecyl chain is incorporated with complete stereocontrol, in a single step, via an N-tosylmimium 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, and thiolactones, there have been relatively few publications concerning extension of this methodology to include lactam-derived variants. Isobe and Comins 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. We recently disclosed a high-yielding route to N-tosyl-α-ethoxypropyrolidinone 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 stereocontrolled 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 to close the piperidine ring, 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.

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 of 7, hydroboration of the resulting enamide would functionalize C3 affording 6, and finally N-tosylmimium 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-
piperidinone (9) 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 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 (MOMCH<sub>2</sub>LiCuI) failed to give the desired coupling product, and so an alternative strategy was sought. Palladium-catalyzed methoxy-carbonylation<sup>26</sup> using the previously reported conditions (Pd(OAc)<sub>2</sub>, PPh<sub>3</sub>) 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.<sup>10</sup> 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 (l-(trimethylsilyl)ethoxymethyl) ether 11. Thus the first of the required piperidinyl 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-tosylamidine moiety. Only a few reports have appeared concerning the hydroboration of cyclic enecarbamates<sup>12ab</sup> and enamides.<sup>11c</sup> All contained disubstituted double bonds, and in all but one case<sup>11c</sup> 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<sup>12</sup> 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,<sup>11c</sup> resulting from the transition state shown in Scheme 2. A<sup>11,3</sup> 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 <sup>1</sup>H NMR spectra prevented 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, <sup>11d</sup> and so the final challenge remaining was the stereospecific introduction of the C6-dodecyl substituent.

We intended to generate the N-tosyliminium ion<sup>14</sup> 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,<sup>15</sup> hydroboration of 3-chloro-1-(trimethylsilyl)-1-propyne with dinonylborane followed by reac...
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 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 attack\(^1\) by the silane derivated enol triflate as useful synthetic intermediates.

In conclusion, the synthesis of desoxoprosophylline has been achieved in nine steps and 7.5% overall yield from a one-pot process. Coupling of 3594 J. Org. Chem., Vol. 62, No. 11, 1997

**Experimental Section**

**General.** Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Dichloromethane, triethylamine, disopropylethylamine, 2,6-lutidine, and DMF were distilled from CaH\(_2\) prior to use and stored under nitrogen. THF was distilled from Na/benzophene. 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 nitrogen atmosphere unless otherwise indicated. During workup, where drying of the organic solutions is indicated, Na\(_2\)SO\(_4\) was used with subsequent filtration in all cases. IR spectra were recorded as CHCl\(_3\) solutions. NMR spectra were measured in CDC\(_3\) and are reported in units of ppm. J values are in hertz. Carbon resonances are reported as q (CH\(_3\)), t (CH\(_2\)) 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-toluenesulfonyl-2-((trifluoromethanesulfonyl)oxy)-1,4,5,6-tetrahydropyridine \((\text{11})\). To a solution of 8 (0.324 g, 0.755 mmol), Pd(dba)\(_2\) (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), 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); \(^{13}\)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\(^+\) (58); HRMS calc'd for C\(_{20}\)H\(_{27}\)NO\(_2\)F\(_2\)S: 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 \((\text{10})\). A solution of triflate 8 (0.324 g, 0.755 mmol), Pd(\text{dba})\(_2\) (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 nitrogen for 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); \(^{13}\)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\(^+\) (58); HRMS calc'd for C\(_{20}\)H\(_{27}\)NO\(_2\)F\(_2\)S: C, 41.95; H, 4.23; N, 3.26. Found: C, 42.42; H, 4.60; N, 3.42.

6-Ethoxy-1-p-toluenesulfonyl-2-((trimethylsilyl)ethoxy)methyl)-1,4,5,6-tetrahydropyridine \((\text{11})\). To a solution of ester 10 (0.630 g, 1.858 mmol) in THF (12 mL) at 0 °C was added DBU (0.29 mL of a 1 M solution in THF, 9.29 mmol, 5 equiv), and the solution was warmed to 10 °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 (1:1 ethyl acetate/light petroleum ether, on SiO\(_2\)) afforded triol 11 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, d, J = 9.7, 7.1), 3.20 (1 H, d, 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); \(^{13}\)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 calc'd for C\(_{20}\)H\(_{27}\)NO\(_2\)F\(_2\)S: C, 41.95; H, 4.23; N, 3.26. Found: C, 42.42; H, 4.60; N, 3.42.
**Total Synthesis of Desoxoprosophylline**

In vacuo placed in a refrigerator at 0 °C for 16 h. Trimethylamine was added (4.0 mmol) dropwise. After 5 min of stirring, the flask was sealed and stirred vigorously for 16 h. Saturated aqueous sodium bicarbonate solution (1 mL), and the reaction mixture was warmed to 78 °C while the ammonia was evaporated under reduced pressure (freezer) over 2.5 h. Saturated sodium bicarbonate solution (3 mL) was added, and the reaction mixture was warmed to 78 °C while the ammonia was evaporated under reduced pressure. The organic layer was then extracted with dichloromethane (3 × 5 mL). The combined organics were dried, and the solvent was removed in vacuo. Column chromatography (300 × 7.8 cm, silica gel 60, eluent: CHCl3/MeOH 3:1) afforded compound **16** as a colorless oil (0.080 g, 0.115 mmol) and 10% Pd/C (0.020 g) in MeOH (5 mL) was added to afford compound **16** as a colorless oil (0.080 g, 0.115 mmol) and 10% Pd/C (0.020 g) in MeOH (5 mL).

**N-p-toluenesulfonylprosophylline.** Alkene **16** (0.080 g, 0.115 mmol) was oxidized with PCC (0.240 g, 1.2 equiv) in CH2Cl2 (3 mL) to afford compound **16** as a colorless oil (0.080 g, 0.115 mmol). The combined organics were dried, and the solvent was removed in vacuo. Column chromatography (1:6 ~ 3:1 ethyl acetate/light petroleum ether, on SiO2 afforded alkene **16** as a colorless oil (0.080 g, 0.115 mmol) and 10% Pd/C (0.020 g) in MeOH (5 mL) was added to afford compound **16** as a colorless oil (0.080 g, 0.115 mmol) and 10% Pd/C (0.020 g) in MeOH (5 mL).
°C from ethyl acetate [lit mp 83 °C,6° 83–83.5 °C6b]; \( ^1 \)H NMR (400 MHz) \( \delta \) 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, d, \( J = 12.3, 4.1 \)), 2.03 (3 H, v br s), 1.74 (1 H, d, \( J = 13.2, 3.1 \)), 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) \( \delta \) 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).

**Acknowledgment.** The European Union (TMR fellowship) and the Royal Society (Science Exchange fellowship) are acknowledged for generous financial support.

**Supporting Information Available:** \( ^1 \)H NMR spectra of compounds 8, 10, 11, 12, 13, 16, and N-p-toluenesulfonyl-desoxoprosopine and \( ^1 \)H and \( ^{13} \)C NMR spectra of desoxoprosopine (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.

J O962347j