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Asymmetric synthesis of (−)-deoxoprosophylline

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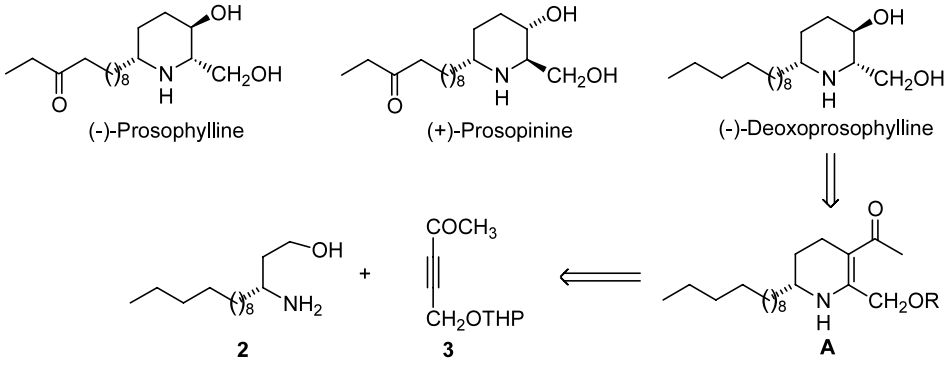
Abstract—Michael addition of γ-amino alcohol **2** to alkynone **3** affords enamine **4**, which is converted into cyclic enamine **6** through its bromide **5**. Diastereoselective hydrogenation of **6** followed by protection and epimerization provides piperidine **8**. Baeyer–Villiger oxidation of **8** and the subsequent deprotection give (−)-deoxoprosophylline. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

A number of alkaloids possessing the 2,6-disubstituted piperidin-3-ol skeleton have been isolated from the leaves of *Prosopis africana*, which have been used in Africa for the treatment of toothache.[1,2] Two representative compounds are (−)-prosophylline and (+)-prosopinine (Scheme 1), which have been found to have noteworthy antibiotic and anaesthetic activities.[1,2] Further studies indicated that their reduction analogues such as (−)-deoxoprosophylline also display similar biological properties.[1,2b] Given these facts it is not surprising that these compounds have been the targets for numerous synthetic efforts and have served as ideal test cases for newly developed synthetic strategies over the past decades.[3–5] Among the synthetic routes reported for (−)-deoxoprosophylline,[5] the strategy often used is to employ either sugars[5g] or amino acids[5b–f] as the chiral pool starting material. Herein we wish to report a short and effective protocol to (−)-deoxoprosophylline.

2. Results and discussion

As outlined in Scheme 1, (−)-deoxoprosophylline is envisioned to be obtainable through the intermediate **A** via a diastereoselective hydrogenation and subsequent conversions. The cyclic enamine **A** may be assembled by Michael addition too and subsequent intramolecular cyclization of alkynone **3** and an enantiopure γ-amino alcohol **2**, which can be prepared from an enantiopure β-amino ester.[6]



Scheme 1.

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The detailed synthesis was illustrated in Scheme 2. After the β-amino ester **1** was obtained using Davies' procedure,[7] LAH reduction was carried out to convert the ester to the corresponding alcohol, which on hydrogenolysis provided the desired γ-amino alcohol **2**. The Michael addition of **2** to the alkynone **3** worked well in DMF at room temperature to give the enamine **4** in 82% yield. It is notable that the reaction in refluxing ethanol[8] gave **4** in lower yield (~40%). Treatment of **4** with triphenylphosphine and carbon tetrabromide assisted by triethylamine produced the bromide **5**, which was refluxed in acetonitrile to afford the cyclic enamine **6**.

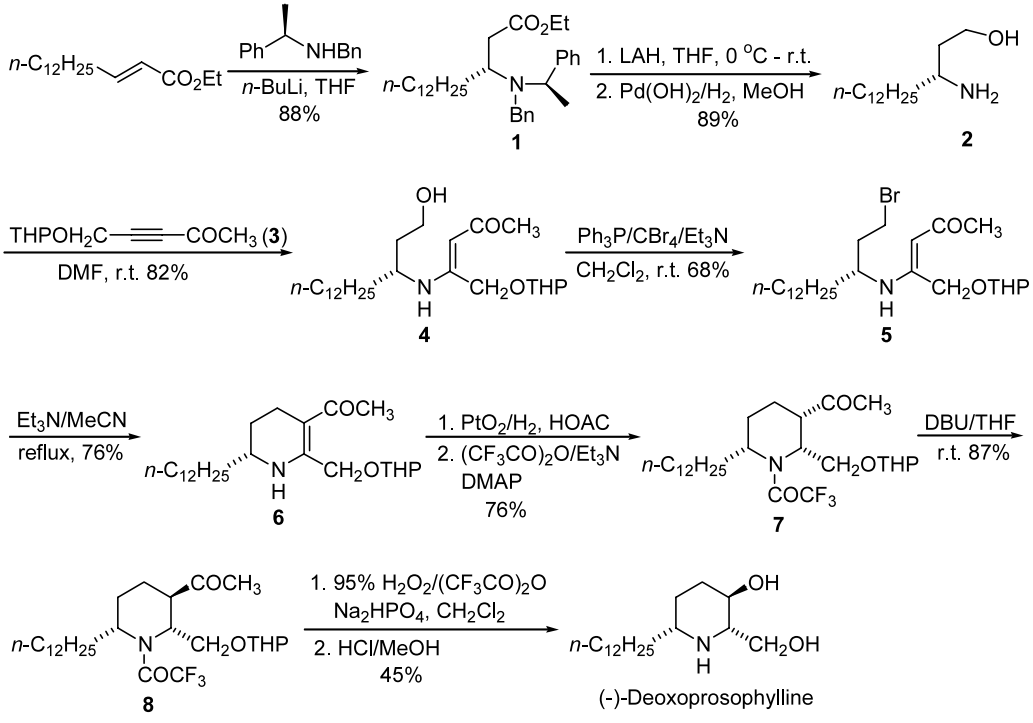
PtO_2-catalyzed hydrogenation of **6** was carried out in acetic acid at 70 atm to afford the corresponding saturated piperidine, which was protected with trifluoroacetic anhydride to provide the amide **7**. The ^1H NMR spectra of **7** indicated that no other isomers were present at this stage. Epimerization of the 3-acetyl group of **7** under the action of DBU produced a mixture of **7** and its thermodynamically more stable isomer **8**. The ratio of **7** and **8** was about 1:10 by ^1H NMR and **8** was isolated pure by column chromatography in 87% yield. Next, we planned to convert this acetyl group to the corresponding acetic ester by a Baeyer–Villiger oxidation.[9] Initially, this reaction was attempted using the oxidizing agents such as *m*-CPBA or peracetic acid. However, no desired product was detected in these cases. After some experimentation, we found that treatment of **8** with trifluoroperacetic acid[10] that was prepared in situ by mixing 95% hydrogen peroxide and trifuoroacetic anhydride afforded the Baeyer–Villiger oxidation product successfully. This oxidation product was hydrolyzed with 6N HCl in methanol to remove all protecting groups and afford (−)-deoxoprosophylline, the analytical data of which were all identical with those reported.[5b]

In summary, we have developed a short and effective protocol to 2,6-disubstituted piperidin-3-ol type alkaloids illustrated by the synthesis of (−)-deoxoprosophylline. It is obvious that this route should allow synthesis of natural (−)-prosophylline and (+)-prosopinine by changing the side chain and the stereochemistry of the hydrogenation step. Further studies are in progress and will be reported in due course.

3. Experimental

3.1. (*R*)-3-Aminopentadecan-1-ol 2

A solution of the β-amino ester **1** (20 g, 42 mmol) in THF was added dropwise into a suspension solution of LAH in THF under 0°C. After the addition, the resultant mixture was allowed to warm to rt. Stirring was continued until the starting material was consumed monitored by TLC. The reaction was quenched by adding water, 15% sodium hydroxide and water in turn. The mixture was stirred until a white solid came out. After the mixture was filtered on silica gel, the filtrate was concentrated to dryness. The residual oil was dissolved in 100 mL of methanol before 10% Pd/C was added. The resultant suspension solution was stirred under hydrogen (50 atm) at 50°C for 20 h. After the Pd/C was filtered off, the filtrate was concentrated to afford 9.0 g (89%) of γ-amino alcohol **2**. $[\alpha]_D^{20} = -5.6$ (*c* 0.75, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, $J = 6.8$ Hz, 3H), 1.24 (m, 18H), 1.28 (m, 2H), 1.71 (m,



Scheme 2.

1H), 1.87 (m, 1H), 2.00 (m, 1H), 3.46 (m, 1H), 4.06 (m, 2H), 7.82 (m, 2H); ESI-MS m/z 244.3 (M^++H^+); HRMS calcd for $C_{15}H_{34}NO$ (M^++H^+) 244.2562; found: 244.2634.

3.2. (*R*)-4-[1-(2-Hydroxyethyl)-tridecylamino]-5-(tetrahydropyran-2-yloxy)-pent-3-en-2-one 4

To a stirring solution of **2** (2.8 g, 12 mmol) in 100 mL of DMF was added alkynone **3** (3.2 g, 23 mmol) at rt. The resultant solution was stirred at the same temperature until the starting material was consumed as monitored by TLC. The mixture was concentrated in vacuo and the residue was chromatographed eluting with 1/5 ethyl acetate/petroleum ether to afford 4.0 g (82%) of **4**. $[\alpha]_D^{20}=+8.7$ (c 0.36, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, $J=6.9$ Hz, 3H), 1.26 (m, 21H), 1.40–1.78 (m, 10H), 2.00 (s, 3H), 2.50–2.90 (m, 5H), 4.11 (m, 2H), 4.66 (d, $J=7.8$ Hz, 1H), 5.12 (d, $J=7.8$ Hz, 1H), 10.18 (m, 1H); EIMS m/z: 425 (M^+), 342, 341, 426, 343, 427, 310, 309; HRMS calcd for $C_{25}H_{47}NO_4$ (M^+) 425.3505; found 425.3491.

3.3. (*R*)-4-[1-(2-Bromoethyl)-tridecylamino]-5-(tetrahydropyran-2-yloxy)-pent-3-en-2-one 5

To a stirring solution of the enamine **4** (4.0 g, 9.4 mmol) in dichloromethane was added CBr_4 (4.3 g, 13 mmol) at 0°C. After all CBr_4 had dissolved, Ph_3P (3.7 g, 14 mmol) in dichloromethane was added dropwise. The resultant mixture was warmed to rt and the stirring was continued until **4** disappeared monitored by TLC. To this solution 1.3 mL of triethylamine was added and the resultant solution was stirred for another hour. After the solvent was removed in vacuum, the residue was chromatographed eluting with 1/5 ethyl acetate/*n*-hexane to afford 3.1 g (68%) of **5** as a yellow oil. $[\alpha]_D^{20}=+10$ (c 0.06, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, $J=6.9$ Hz, 3H), 1.26 (m, 21H), 1.40–1.78 (m, 10H), 2.01 (s, 3H), 2.50–2.90 (m, 5H), 3.28 (m, 2H), 4.66 (d, $J=7.8$ Hz, 1H), 5.12 (d, $J=7.8$ Hz, 1H), 10.18 (m, 1H); ESI-MS m/z 488.4 (M^+); ESI-HRMS calcd for $C_{25}H_{46}NO_3NaBr$ 510.2559 (M^++Na^+); found 510.2553.

3.4. (*R*)-1-[6-Dodecyl-2-(tetrahydropyran-2-yloxymethyl)-1,4,5,6-tetrahedropyridin-3-yl]ethanone 6

To a solution of compound **5** (3.0 g, 6.16 mmol) in 200 mL of anhydrous acetonitrile was added triethylamine (677 mg, 6.8 mmol). The mixture was heated at 80–85°C until the starting material disappeared monitored by TLC. The solvent was evaporated in vacuo and the residue was separated by column chromatography eluting with 1/4 ethyl acetate/*n*-hexane to afford 1.9 g (76%) of the cyclic enamine **6**. $[\alpha]_D^{20}=+57.6$ (c 0.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, $J=6.3$ Hz, 3H), 1.24 (m, 22H), 1.52 (m, 10H), 2.09 (s, 3H), 2.45 (m, 2H), 3.22 (m, 1H), 3.52 (m, 1H), 3.87 (m, 1H), 4.63 (s, 1H), 4.91 (m, 2H), 6.15 (s, 1H); EI-MS m/z 407 (M^+), 323, 324, 136, 281, 306, 305, 85; HRMS calcd for $C_{25}H_{45}NO_3$ (M^+) 407.3399; found 407.3382.

3.5. 1-[(2*R*,3*S*,6*R*)-3-Acetyl-6-dodecyl-2-(tetrahydropyran-2-yloxymethyl)-piperdin-1-yl]-2,2,2-trifluoroethanone 7

A mixture of **6** (1.9 g, 4.7 mmol) and 150 mg of PtO_2 in 60 mL of acetic acid was hydrogenated under 1 atm and rt until no more hydrogen was taken up. The catalyst was filtered off and the filtrate was evaporated under vacuum. The residue oil was dissolved in dichloromethane before triethylamine (3.7 g, 37 mmol) and 0.2 g of DMAP were added. To this stirring solution was added trifluoroacetic anhydride (3.9 g, 18.5 mmol) with cooling by ice-water. The resultant mixture was stirred at rt for 2 h, and then concentrated in vacuo. The residue was separated by column chromatography eluting with 1/2 ethyl acetate/*n*-hexane to afford 1.8 g (76%) of **7**. $[\alpha]_D^{20}=+33$ (c 0.8, EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, $J=6.9$ Hz, 3H), 1.28 (m, 22H), 1.63–1.80 (m, 4H), 1.90 (m, 4H), 2.25 (s, 3H), 2.28 (d, $J=4.8$ Hz, 2H), 2.66 (m, 1H), 3.46–3.75 (m, 3H), 3.93 (q, $J=6.0$ Hz, 1H,), 4.4–4.8 (m, 2H), 5.36 (m, 1H); ESI-MS m/z 528.4 (M^++Na^+); ESI-HRMS calcd for $C_{27}H_{46}F_3NO_4Na$ (M^++Na^+) 528.3277; found 528.3272.

3.6. 1-[(2*R*,3*R*,6*R*)-3-Acetyl-6-dodecyl-2-(tetrahydropyran-2-lyoxymethyl)-piperdin-1-yl]-2,2,2-trifluoroethanone 8

A solution of **7** (1.6 g, 3.2 mmol) and DBU (1.6 mmol) in 20 mL of THF was stirred for 16 h at rt. The mixture was partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography eluting with 1/2 ethyl acetate/*n*-hexane to afford 1.4 g (87%) of **8**. $[\alpha]_D^{20}=-7.5$ (c 1.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, $J=6.6$ Hz, 3H), 1.25 (m, 22H), 1.57–1.78 (m, 10H), 2.20 (s, 3H), 2.84 (m, 1H), 3.56 (m, 2H), 3.63 (t, $J=4.6$ Hz, 1H), 3.77–3.89 (m, 2H), 4.66 (m, 1H), 5.21 (m, 1H); ESIMS m/z 528.4 (M^++Na^+); ESI-HRMS calcd for $C_{27}H_{46}NO_4F_3Na$ (M^++Na^+) 528.3277; found 528.3271.

3.7. Synthesis of (−)-deoxoprosophylline

Trifluoroacetic anhydride (750 mg, 3.56 mmol) was added dropwise to a solution of 95% H_2O_2 (110 mg, 3.97 mmol) in cold dichloromethane. After the addition this solution was added dropwise to a mixture of **8** (1.0 g, 1.98 mmol) and Na_2HPO_4 (281 mg, 1.98 mmol) in dichloromethane. The resultant mixture was heated at reflux for 30 min before the cooled solution was filtrated. After the filtrate had been washed with saturated $Na_2S_2O_3$, the organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed sequentially with water and brine. The solution was dried over Na_2SO_4, and concentrated. The residue was dissolved in methanolic HCl and then the solution was heated at 65°C for 24 h. The solvent was removed and the residue

was dissolved in MeOH. After 30% NaOH was added, the mixture was extracted with chloroform. The combined organic layers were dried over Na_2SO_4, and concentrated. The column chromatography of the residue afforded 199 mg (45%) of deoxoprosophylline. $[\alpha]_D^{20} = -13.6$ (c 0.3, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, $J = 6.6$ Hz, 3H), 1.25–1.40 (m, 22H), 1.57–1.86 (m, 2H), 1.96–2.06 (m, 2H), 2.45–2.56 (m, 5H), 3.49 (m, 1H), 3.75 (dd, $J = 10.2$, 5.5 Hz, 1H), 3.89 (dd, $J = 10.2$, 4.7 Hz, 1H); ESI-MS m/z 300.3 ($M^+ + H^+$); HRMS calcd for $C_{18}H_{38}NO_2$ ($M^+ + H^+$) 300.2903, found 300.2879.

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