Ring Expansion – Formation of Optically Active 3-Hydroxypiperidines from Pyrrolidinemethanol Derivatives

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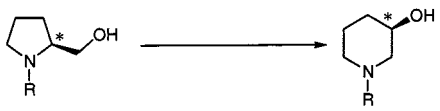
Treatment of pyrrolidinemethanol derivatives **(–)-1**, **(–)-6**, **(–)-7**, **8**, **(–)-9**, **(+)-10**, **(–)-11**, and **(–)-21** with trifluoroacetic anhydride and then with Et_3N afforded, after hydrolysis of the trifluoroacetyl group with NaOH, the optically active 3-hydroxypiperidines **(–)-14**, **(+)-15**, **(–)-16**, **17**, **(+)-18**, **(–)-19**, **(–)-20**, and **(+)-22**, respectively. The yields are good and the enantiomeric excess excellent (up to 95 %).

Introduction

The 3-hydroxypiperidine skeleton is present in a great number of natural products such as Bao Gong Teng A[1], pseudoconhydrine[2], cassine[3], and deoxocassine[4]. Different methods allow the access to this skeleton, such as intramolecular substitution of a halide[5] or a mesylate[6] by an amine, nucleophilic attack of an epoxide[7] or attack of an hydroxy ester[8] by an amine, and attack of a π-allyl palladium complex by an oxazolidinone[9] as well as an intramolecular Michael reaction[10] and radical cyclizations[11]. Allyl metals[12], vinylsilanes[13], and enolates[14] have been also used to build up 3-hydroxylated piperidines. Thermal reactions such as ene[15] or Diels–Alder[16] reactions can produce 3-hydroxypiperidines. Reduction of 3-hydroxypyridines[17] or 3-piperidinones[18], or alternatively oxidation of unsaturated piperidine[19] may engender 3-hydroxypiperidines. A mixture of 3-hydroxypiperidine and pyrrolidine-2-methanol was obtained when aziridinium ions were treated with NaOH[20].

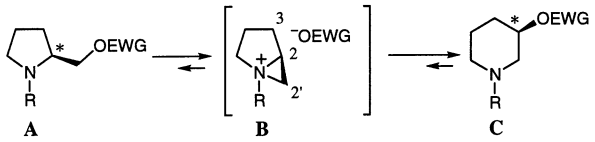
Herein, we give a full account of the rearrangement of *N*-alkylpyrrolidine-2-methanol derivatives which generates 3-hydroxypiperidines with good yield and high enantiomeric purity[21] (Scheme 1).



Scheme 1

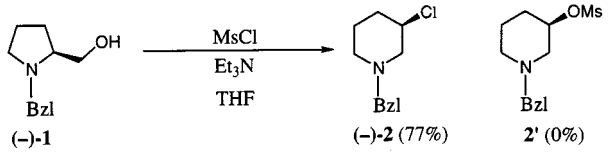
Results and Discussion

Pyrrolidine-2-methyl derivatives **A**, with a good nucleofugal group (OEWG), were expected to form reactive aziridinium intermediates of type **B**, which should undergo ring opening by nucleophilic attack at C-2 of intermediate **B** to produce piperidines of type **C** (Scheme 2). In principle, the reverse reaction **C** → **B** → **A** is also possible. Because of ring strain difference between **A** and **C**[22], the latter should be obtained under conditions of thermodynamic control.



Scheme 2

With the aim of obtaining nonracemic chiral 3-mesylpiperidines, *N*-benzylprolinol **(–)-1** was treated with methanesulfonyl chloride in the presence of triethylamine in THF. Under these conditions, 3-chloropiperidine **(–)-2** was obtained in 77% yield[21e]. No trace of mesylate **2′** was detected in the crude reaction mixture (Scheme 3). 3-Chloropiperidine **(–)-2** was the only product formed even in the presence of AgCN, which was expected to quench the chloride anion, or in the presence of acetic acid (AcOH) which can compete as nucleophile with the mesylate anion. This suggests that tight ion pairs (aziridinium chloride) are involved in the reaction **(–)-1** + MsCl → **(–)-2** + MsOH. In order to introduce an oxygenated function at C-3 of the piperidine ring, prolinol **(–)-1** was treated with acetic acid under Mitsunobu conditions [DEAD (diethyl azodicarboxylate), PPh_3].[23] Under these conditions, the acetylated prolinol **(–)-3** and 3-acetyl piperidine **4**[24] were formed in a 74:26 ratio. We have to point out that the acetylated prolinol **(–)-3** was the only product isolated (62%) when prolinol **(–)-1** was treated with pure acetic anhydride (Scheme 4).



Scheme 3

In contrast with this reaction course, treatment of **(–)-1**, with trifluoroacetic anhydride (TFAA), and with triethyl-

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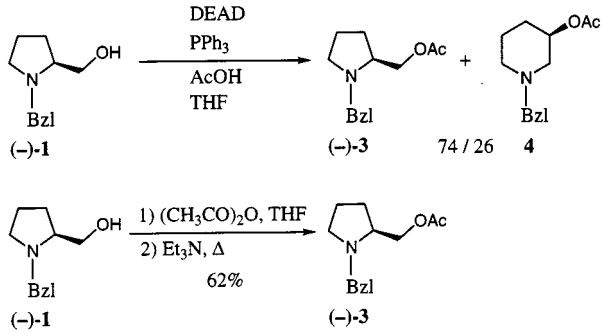
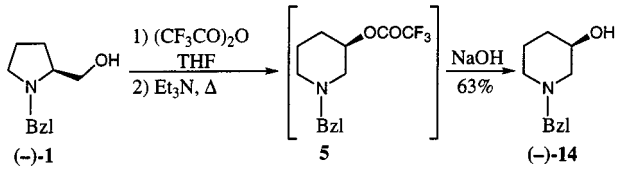


Scheme 4

amine in THF, led to 3-hydroxypiperidine **(−)-14**[24][25] (63%) after saponification (NaOH, H_2O) of the intermediate ester **5**. The enantiomeric excess of **(−)-14** was 95%[26] (Scheme 5). The ring expansion **(−)-1** → **(−)-14** did not work in solvents such as toluene or hexane. In CH_2Cl_2, the only product formed was the 3-chloropiperidine **(−)-2**. The formation of compounds **(−)-2**, **4**, **(−)-14** is consistent with the mechanism of Scheme 2.



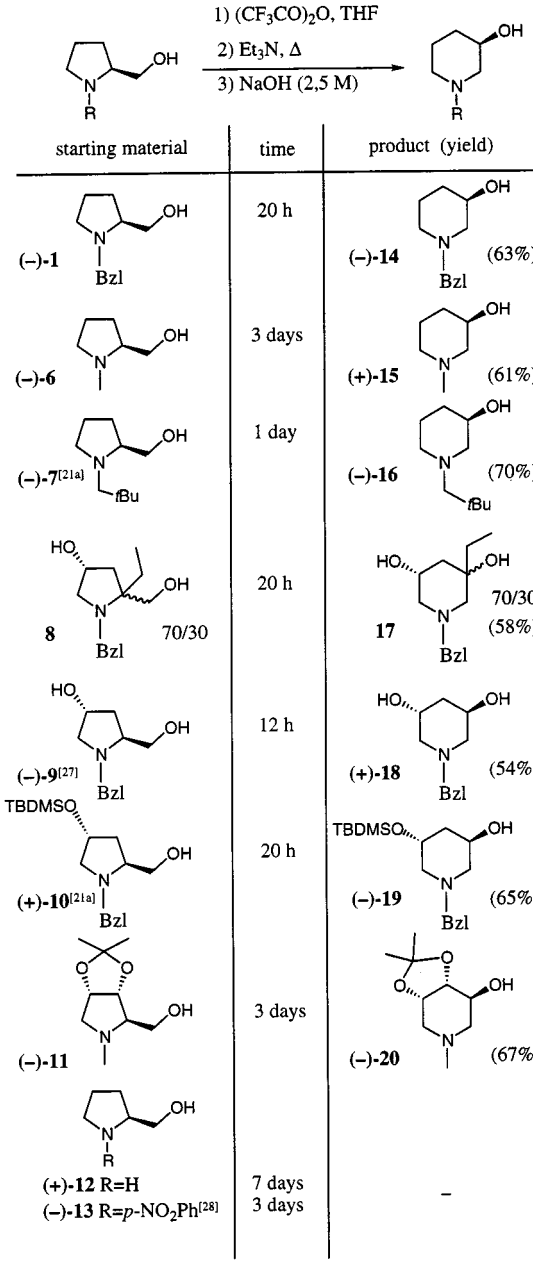
Scheme 5

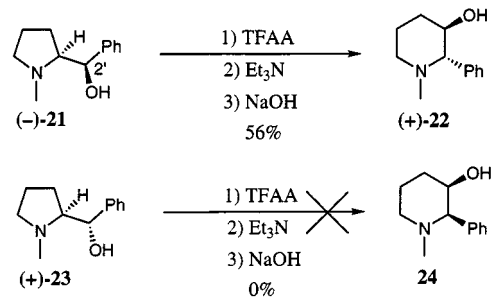
As seen from Table 1, the ring expansion of *N*-alkylated prolinol appears to be general and highly stereoselective except for prolinol **(+)-12** or for the *N*-(4-nitrophenyl) derivative **(−)-13**. In these two cases, the products of ring expansion were not detected. The nucleophilicity of the amino moiety of the prolinol derivative has to be high enough for the rearrangement to occur. We have to point out that acid- or base-sensitive hydroxy protecting groups [compounds **(+)-10**, **(−)-11**] were tolerated under our conditions. The (4*R*)-hydroxyprolinol derivative **(−)-9** was isomerized smoothly into a single diastereomeric diol **(+)-18** with a yield of 54%. The $[\alpha]_D^{20}$ value (+151) of this compound proves the (3*R*,5*R*) configuration of **(+)-18** and strongly supports the mechanism of Scheme 2 (inversion of configuration during the nucleophilic attack at C-2 of aziridinium intermediates **B**) (Table 1).

Pyrrolidine-2-methanol derivatives with secondary and tertiary alcohols were submitted to our rearrangement conditions. Pyrrolidine-2-methanol **(−)-21**[29] was transformed to substituted piperidinol **(+)-22** in 56% yield and with an enantiomeric excess of 95%. In contrast, diastereoisomer **(+)-23**[29] was not reactive under the same conditions[21e,21g] (Scheme 6).

The nonreactivity of **(+)-23** can be attributed to a gauche effect (steric interactions) between the phenyl and the C-2−C-3 bond in the aziridinium ion intermediate **23A**. On the contrary, pyrrolidinemethanol **(−)-21** was transformed

Table 1. Formation of 3-hydroxypiperidines from pyrrolidinemethanol derivatives

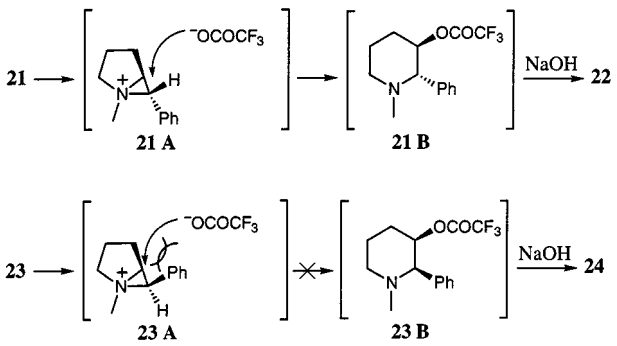




Scheme 6

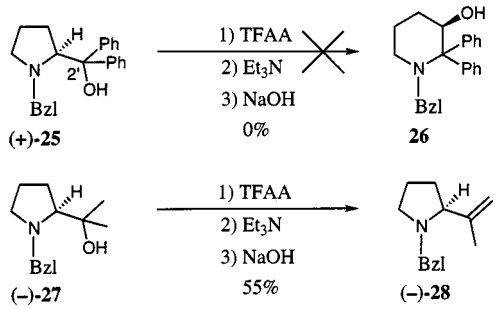
to piperidinol **(+)-22**, as no serious steric repulsions are developed during the formation of the aziridinium intermedi-

ate **21A**, the phenyl group and the C-2−C-3 bond being antiperiplanar (Scheme 7). This interpretation implies that the amino moiety participates (anchimeric effect) in the heterolysis of the trifluoroacetate intermediate generated by esterification of the benzyl alcohol **(−)-21**[30].



Scheme 7

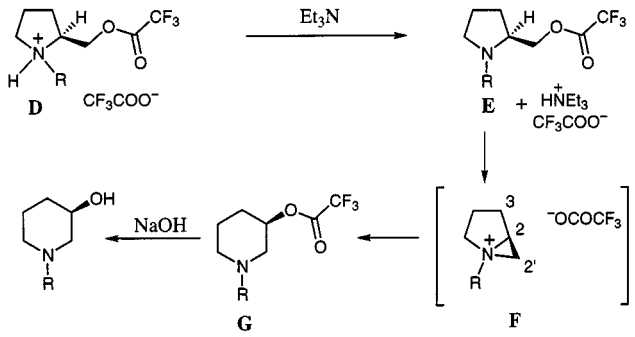
Treatment of pyrrolidinemethanol derivatives **(+)-25**[31] with a tertiary alcohol at C-2′ did not lead to the ring expanded product, under our conditions, whereas **(−)-27**[31] underwent water elimination to produce alkene **(−)-28**[31] (55% yield) (Scheme 8). These results are consistent with the fact that **(+)-25** and **(−)-27** can generate ion-pairs without the participation of the amino moiety, giving stable tertiary carbenium ion intermediates[30].



Scheme 8

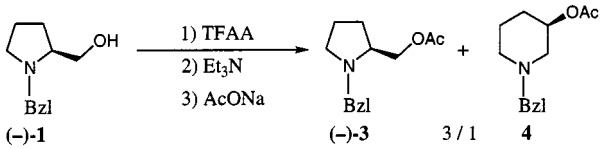
The first step for the formation of 3-hydroxypiperidines from pyrrolidinemethanol derivatives implies the esterification of the hydroxy group of the pyrrolidine-2-methanol by trifluoroacetic anhydride and the formation of the corresponding quaternary ammonium salt **D**. In the absence of triethylamine, no rearrangement is observed. With triethylamine, amino esters **E** are formed and undergo a S_Ni process to give the tight ion-pairs **F** that react to generate the stable esters **G**. Finally, saponification of the esters **G** by NaOH (2.5 M) affords the observed 3-hydroxypiperidines[21a,21d] (Scheme 9).

This hypothesis is consistent with our observation that the treatment of **(−)-1** with TFAA, then with Et_3N, then



Scheme 9

with sodium acetate furnished only the ratio of products **(−)-3** and **4** (3:1) (Scheme 10).



Scheme 10

Conclusion

Consecutive treatment of pyrrolidine-2-methanol compounds with trifluoroacetic anhydride and then with triethylamine results in a rearrangement that produces the ring-expanded 3-hydroxypiperidines as the trifluoroacetyl esters. Following hydrolysis of the trifluoroacetyl group with NaOH, the corresponding 3-hydroxypiperidines are isolated in good yields and with excellent enantiomeric excesses (up to 95%).

Experimental Section

General: Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. − THF was distilled from Na/benzophenone ketyl immediately prior to use. − CH_2Cl_2 and Et_3N were distilled from calcium hydride under argon. − Moisture-sensitive reactions were conducted in oven-dried glassware under an argon atmosphere. − Analytical thin-layer chromatography was performed on Merck precoated silica gel (60 F_{254}) plates and flash column chromatography was accomplished on Merck Kieselgel 60 (230−400 mesh). − Melting points are uncorrected. − IR: Perkin−Elmer 298. − Optical rotations: Perkin−Elmer 241MC polarimeter. − Elemental analyses: Service Régional de Microanalyse de l′Université P. et M. Curie. − HRMS: Centre de Spectrochimie Organique de l′Université P. et M. Curie. − NMR: Bruker AC 300 spectrometer (300 MHz and 75 MHz for ^1H and ^{13}C, respectively). Spectra were recorded in $CDCl_3$ as solvent, and chemical shifts (δ) were expressed in ppm

relative to residual $CHCl_3$ at δ = 7.27 for ^1H and to $CDCl_3$ at δ = 77.1 for ^{13}C. − MS: Mass spectra were obtained by GC/MS with electron impact ionization on a 5971 Hewlett Packard instrument at 70 eV; only selected ions are reported.

(−)-(3*R*)-1-Benzyl-3-chloropiperidine (**2**): To a solution of pyrrolidine **1** (0.7 g, 3.66 mmol) in THF (30 mL) at 0°C was added MsCl (0.31 mL, 4.03 mmol), followed by Et_3N (1.9 mL, 14.6 mmol). After 12 h reflux, the reaction mixture was poured into an aqueous 2.5 M NaOH solution (7 mL). After extraction with CH_2Cl_2 (2× 20 mL), the organic phase was dried with $MgSO_4$ and filtered. The solvent was removed in vacuo to afford an oil, which was purified by flash column chromatography on silica gel (EtOAc/cyclohexane, 50:50) to give 0.59 g (77%) of oily **2**. − $[\alpha]_D^{20}$ = −2 (*c* = 7.2, MeOH). − IR (neat): $\tilde{\nu}$ = 1490, 1465, 1450, 1435, 1365, 1345, 1150 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.45−1.69 (m, 2 H), 1.72−1.84 (m, 1 H), 2.01−2.27 (m, 3 H), 2.64−2.75 (m, 1 H), 2.96−3.09 (m, 1 H), 3.53 (s, 2 H), 3.92−4.04 (m, 1 H), 7.20−7.38 (m, 5 H). − ^{13}C NMR ($CDCl_3$): δ = 24.8, 34.8, 52.7, 56.0, 61.2, 62.6, 127.0, 128.2, 128.9, 137.9. − MS (70 eV); *m*/*z* (%): 211 (9) [M^+], 210 (11), 209 (26) [M^+], 208 (25), 134 (14), 132 (39), 120 (15), 118 (53), 92 (19), 91 (100), 65 (12). − $C_{12}H_{16}NCl$ calcd 209.7181; found 209,7189 (MS).

(−)-(2*S*)-(1-Benzylpyrrolidin-2-yl)methyl Acetate (3): To a stirred solution of pyrrolidine **1** (0.1 g, 0.52 mmol) in THF (5 mL) at −78°C, Ac_2O (0.054 mL, 0.57 mmol) was added dropwise. After 2 h, Et_3N (0.26 mL, 2 mmol) was added dropwise. The reaction mixture was stirred for a further 1 h at −78°C and then heated at reflux for 20 h. After hydrolysis with water (5 mL), the reaction mixture was extracted with CH_2Cl_2 (2× 10 mL). The combined organic layers were dried with $MgSO_4$ and filtered. The solvent was removed in vacuo to afford an oil, which was purified by flash column chromatography on silica gel (EtOAc/cyclohexane, 30:70) to give 75 mg (62%) of pure **3** as an oil. − $[\alpha]_D^{20}$ = −46 (*c* = 1.0, MeOH). − IR (neat): $\tilde{\nu}$ = 1735, 1450, 1365, 1230, 1030 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.59−1.84 (m, 2 H), 1.84−2.04 (m, 2 H), 2.07 (s, 3 H), 2.23−2.35 (m, 1 H), 2.79−2.90 (m, 1 H), 2.91−3.01 (m, 1 H), 3.46 (d, *J* = 12.8 Hz, 1 H), 4.05 (dd, *J* = 11 and 5,1 Hz, 1 H), 4.08 (d, *J* = 12.8 Hz, 1 H), 4.13 (dd, *J* = 11 and 5.1 Hz, 1 H), 7.21−7.37 (m, 5 H). − ^{13}C NMR ($CDCl_3$): δ = 21.4, 23.3, 28.8, 54.8, 59.8, 62.3, 67.4, 127.4, 128.6, 129.3, 170.9. − MS (70 eV); *m*/*z* (%): 233 (1) [M^+], 161 (12), 160 (100), 92 (8), 91 (99), 65 (7). − $C_{14}H_{19}NO_2$ (233.31): calcd. C 72.07, H 8.21, N 6.00; found C 72.14, H 8.21, N 6.02.

(2*SR*,4*R*)-1-Benzyl-2-ethyl-4-hydroxy-2-hydroxymethylpyrrolidine (8): To a stirred solution of diisopropylamine (0.6 mL, 4.27 mmol) in THF (6 mL) at −40°C, was added dropwise a 2.5 M solution of *n*-butyllithium in hexane (1.69 mL, 4.22 mmol). After 10 min at −40°C, the reaction mixture was cooled to −78°C and a solution of (*2S,4R*)-1-benzoyl-4-hydroxypyrrolidine-2-carboxylic acid methyl ester[32] (0.5 g, 2.01 mmol) in THF (6 mL) was added dropwise. After 30 min at −78°C, EtI (0.2 mL, 2.5 mmol) was added. After 2 h at −30°C, the reaction was quenched with water (5 mL). After extraction with CH_2Cl_2 (3× 10 mL), the combined organic layers were dried with $MgSO_4$ and filtered. The solvent was removed in vacuo to afford an oil, which was purified by flash column chromatography on silica gel (EtOAc/cyclohexane, 50:50) to give 290 mg (52%) of an inseparable mixture of (2*SR*,4*R*)-1-benzoyl-2-ethyl-4-hydroxypyrrolidine-2-carboxylic acid methyl ester (ratio 70:30 according to ^1H NMR) as a yellow oil. − IR (neat): $\tilde{\nu}$ = 3420, 1740, 1630, 1410, 1200, 1170 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 0,84 (t, *J* = 7.4 Hz, 2.1 H), 0.88 (t, *J* = 7.4 Hz, 0.9 H), 1.78−2.09 (m, 2 H), 2.20 (dd, *J* = 14.7 and *J* = 5.2 Hz, 0.7 H), 2.31−2.49 (m, 1.3 H), 3.20 (dd, *J* = 10.3 and 8.1 Hz, 0.3 H), 3.48−3,57 (m, 1.7 H), 3.62 (s, 0.9 H), 3.74 (s, 2.1 H), 4.13−4.37 (m, 1.3 H), 4,56 (d, *J* = 10.7 Hz, 0.7 H), 7.20−7.50 (m, 5 H). − $C_{15}H_{19}NO_4$ (277.32): calcd. C 64.97, H 6.91, N 5.05; found C 65.03, H 6.95, N 4.98.

To a suspension of $LiAlH_4$ (0.13 g, 3.42 mmol) in THF (3 mL) at 0°C, a solution of (2*SR*,4*R*)-1-benzoyl-2-ethyl-4-hydroxypyrrolidine-2-carboxylic acid methyl ester (0.29 g, 1.05 mmol) in THF (1 mL) was added dropwise. After 15 min at 0°C, the reaction mixture was heated at reflux for 3 h and cooled to 0°C. Water (0.02 mL), an aqueous 3.75 M NaOH solution (0.2 mL) and water (0.6 mL) were successively added. The reaction mixture was filtered over Celite, and the residue was washed with THF (15 mL). The organic solvent was removed in vacuo to afford an oil, which was purified by flash column chromatography on silica gel (EtOAc/cyclohexane, 50:50) to give 145 mg (59%) of an inseparable mixture of isomers **8** (ratio 70:30 according to ^1H NMR) as a colourless oil. − IR (neat): $\tilde{\nu}$ = 3340, 1450, 1365, 1150, 1040 cm^{-1}. − ^1H NMR ($CDCl_3$) (major isomer): δ = 0.91 (t, *J* = 7.4 Hz, 3 H), 1.43−1.57 (m, 2 H), 1.87 (ddd, *J* = 14.3, 1.5, and 1.5 Hz, 1 H), 2.20 (dd, *J* = 14.3 and *J* = 6.3 Hz, 1 H), 2.77 (dd, *J* = 10.3 and 4.4 Hz, 1 H), 2.87 (ddd, *J* = 9.9, 1.5, and 1.5 Hz, 1 H), 3.24 (broad s, 2 H), 3.32−3.47 (m, 2 H), 3.48 (d, *J* = 13.2 Hz, 1 H), 3.87 (d, *J* = 13.2 Hz, 1 H), 4.16−4.19 (m, 1 H), 7.20−7.35 (m, 5 H). − ^{13}C NMR ($CDCl_3$) (major isomer): δ = 8.6, 25.4, 42.6, 51.0, 60.3, 64.2, 66.1, 68.9, 126.8, 128.1, 128.3, 139.7. − ^1H NMR ($CDCl_3$) (minor isomer): δ = 0.94 (t, *J* = 7.4 Hz, 3 H), 1.39−1.61(m, 1 H), 1.71−1.79 (m, 2 H), 2.15−2.22 (m, 1 H), 2.52 (dd, *J* = 9.2 and 6.2 Hz, 1 H), 3.12 (dd, *J* = 9.2 and 6.6 Hz, 1 H), 3.24 (broad s, 2 H), 3.32−3.48 (m, 3 H), 3.77 (d, *J* = 12.9 Hz, 1 H), 4.18−4.29 (m, 1 H), 7.20−7.35 (m, 5 H). − ^{13}C NMR ($CDCl_3$) (minor isomer): δ = 8.5, 24.7, 41.0, 51.2, 58.8, 63.5, 66.5, 68.8, 126.9, 128.2, 128.4, 139.4. − MS (70 eV); *m*/*z* (%): 205 (7), 204 (45), 92 (8), 91 (100), 65 (7). − $C_{13}H_{18}NO$ [$M^+ - CH_2OH$] calcd 204.2913; found 204,2918 (MS).

(−)-(3a*R*,4*R*,6a*S*)-4-Hydroxymethyl-2,2,5-trimethyltetrahydro-4*H*-1,3-dioxolo[4,5-*c*]pyrrole (11): To a suspension of $LiAlH_4$ (0.11 g, 2.89 mmol) in THF (2 mL) at 0°C, a solution of (2*R*,3*R*,4*S*)-*N*-(*tert*-butoxycarbonyl)-3,4-isopropylidenedioxy-2-hydroxymethylpyrrolidine[33] (0.19 g, 0.7 mmol) in THF (1 mL) was added dropwise. After stirring at 0°C for 20 min, the reaction mixture was heated at reflux for 4 h and then cooled to 0°C. Water (0.01 mL), an aqueous 3.75 M NaOH solution (0.1 mL), and water (0.3 mL) were successively added, and the obtained precipitate was collected on a Celite pad and washed with THF (15 mL). The organic solvent was removed in vacuo to afford an oil, which was purified by flash column chromatography on silica gel (EtOAc/cyclohexane, 50:50) to give 130 mg (99%) of **11** as a colourless oil. − $[\alpha]_D^{20}$ = −41 (*c* = 2.3, MeOH). − IR (neat): $\tilde{\nu}$ = 3400, 1465, 1450, 1380, 1370, 1250, 1205, 1155, 1065 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.31 (s, 3 H), 1.50 (s, 3 H), 2.35 (s, 3 H), 2.46−2.55 (m, 2 H), 2.67 (broad s, 1 H), 3.30−3.40 (m, 1 H), 3.62 (dd, *J* = 11.4 and *J* = 2.7 Hz, 1 H), 3.70 (dd, *J* = 11.4 and *J* = 3.7 Hz, 1 H), 4.52−4.63 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 25.2, 27.4, 40.1, 59.4, 62.1, 71.7, 77.8, 82.3, 113.2. − MS (70 eV); *m*/*z* (%): 187 (0.7) [M^+], 172 (5), 156 (100), 98 (18), 82 (32), 70 (18), 55 (11). − $C_9H_{17}NO_3$ (187.24): calcd. C 57.73, H 9.15, N 7.48; found C 57.71, H 9.10, N 7.47.

(−)-(3*R*)-1-Benzylpiperidin-3-ol (**14**): Trifluoroacetic anhydride (0.66 mL, 4.69 mmol) was added dropwise to a solution of pyrrolidine **1** (0.81 g, 4.26 mmol) in THF (45 mL), cooled to −78°C. After 3 h at −78°C, triethylamine (2.2 mL, 17.05 mmol) was added

dropwise. The reaction mixture was stirred for 15 min at −78°C and then heated at reflux for 20 h. After addition of an aqueous 2.5 M NaOH solution (15 mL), the mixture was stirred for 3 h at room temp., then extracted with CH_2Cl_2 (2× 20 mL), dried with $MgSO_4$, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/cyclohexane, 50:50) to give 510 mg (63%) of **14** as an oil. − $[\alpha]_D^{20} = -10$ (c = 7.74, EtOH) {ref.[23] $[\alpha]_D^{20} = -13.3$ (c = 0.22, MeOH)}. − IR (neat): $\tilde{\nu}$ = 3360, 1600, 1450 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.43−1.69 (m, 3 H), 1.71−1.90 (m, 1 H), 2.14−2.61 (m, 5 H), 3.51 (s, 2 H), 3.74−3.89 (m, 1 H), 7.12−7.43 (m, 5 H). − ^{13}C NMR ($CDCl_3$): δ = 21.6, 31.6, 53.3, 60.1, 62.9, 66.1, 127.0, 128.1, 129.0, 137.8. − MS (70 eV); *m/z* (%): 191 (34) [M^+], 190 (17), 146 (10), 134 (24), 114 (21), 100 (45), 91 (100), 71 (10), 65 (11). − $C_{12}H_{17}NO$ (191.27): calcd. C 75.35, H 8.96, N 7.32; found C 75.05, H 8.91, N 7.16.

(+)-(3*R*)-1-Methylpiperidin-3-ol (**15**): Trifluoroacetic anhydride (0.26 mL, 1.85 mmol) was added dropwise to a solution of pyrrolidine **6** (0.2 mL, 1.68 mmol) in THF (15 mL), cooled to −78°C. After 1 h at −78°C, triethylamine (0.87 mL, 6.74 mmol) was added dropwise. The reaction mixture was stirred for 1 h at −78°C and then heated at reflux for 72 h. After addition of an aqueous 3.75 M NaOH solution (5 mL), the mixture was stirred for 1 h at room temp., then extracted with CH_2Cl_2 (3× 10 mL), dried with $MgSO_4$, and evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/cyclohexane, 90:10) to give 120 mg (61%) of **15** as a yellow oil. − $[\alpha]_D^{20} = +5$ (c = 2.01, EtOH) {ref.[34] $[\alpha]_D^{20} = +5.4$ (c = 2.1, EtOH)}. − IR (neat): $\tilde{\nu}$ = 3350, 1465, 1445, 1370, 1250, 1165, 1135, 1070, 1020 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.39−1.73 (m, 3 H), 1.75−1.90 (m, 1 H), 2.23−2.65 (m, 4 H), 2.27 (s, 3 H), 3.49 (broad s, 1 H), 3.77−3.87 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 21.6, 31.3, 46.1, 55.3, 62.3, 66.1. − MS (70 eV); *m/z* (%): 115 (25) [M^+], 114 (13), 71 (16), 58 (75), 44 (55), 43 (100), 42 (87), 41 (24), 39 (20). − $C_6H_{13}NO$ (115.17): calcd. C 62.57, H 11.38, N 12.16; found C 62.61, H 11.36, N 12.16.

(−)-(3*R*)-1-(2,2-Dimethylpropyl)piperidin-3-ol (**16**): Trifluoroacetic anhydride (0.25 mL, 1.75 mmol) was added dropwise to a solution of pyrrolidine **7** (0.2 g, 1.17 mmol) in THF (11 mL), cooled to 0°C. After 3 h, triethylamine (0.45 mL, 3.51 mmol) was added dropwise. The reaction mixture was stirred for 15 min at 0°C and then stirred for 24 h at room temp. After addition of an aqueous 2.5 M NaOH solution (5 mL), the reaction mixture was stirred for 3 h at room temp., then extracted with CH_2Cl_2 (2× 6 mL), dried with $MgSO_4$, and evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/cyclohexane, 50:50) to give 140 mg (72%) of **16** as a solid, m.p. 42°C. − $[\alpha]_D^{20} = -3$ (c = 1.53, EtOH). − IR ($CHCl_3$): $\tilde{\nu}$ = 3300, 1460, 1355, 970 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 0.87 (s, 9 H), 1.43−1.56 (m, 3 H), 1.76−1.83 (m, 1 H), 2.05 (s, 2 H), 2.28−2.35 (m, 1 H), 2.51−2.63 (m, 4 H), 3.72−3.80 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 21.8, 27.7, 30.9, 32.9, 56.5, 63.2, 66.5, 69.9. − MS (70 eV); *m/z* (%): 171 (1) [M^+], 156 (6), 114 (100). − $C_{10}H_{21}NO$ (171.28): calcd. C 70.12, H 12.36, N 8.18; found C 70.11, H 12.42, N 8.36.

(3*RS*,5*R*)-1-Benzyl-3-ethyl-5-hydroxypiperidin-3-ols (**17**): Trifluoroacetic anhydride (0.09 mL, 0.60 mmol) was added dropwise to a solution of the mixture of pyrrolidines **8** (0.2 g, 1.17 mmol) in CH_2Cl_2 (5 mL), cooled to 0°C. After 3 h, Et_3N (0.28 mL, 2.18 mmol) was added dropwise. The reaction mixture was stirred for 15 min at 0°C and then for 20 h at room temp. After addition of an aqueous 2.5 M NaOH solution (8 mL), the mixture was stirred for 3 h at room temp., then extracted with CH_2Cl_2 (2× 7 mL), dried with $MgSO_4$, and evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/cyclohexane, 70:30) to give 74 mg (58%) of an inseparable mixture of isomers **17** (ratio 70:30 according to ^1H NMR) as an oil. − IR (neat): $\tilde{\nu}$ = 3320, 1730, 1450 cm^{-1}. − ^1H NMR ($CDCl_3$) (major isomer): δ = 0.89 (t, J = 7.4 Hz, 3 H), 1.35−1.55 (m, 3 H), 1.91 (ddd, J = 14.3, 5.0 and 2.2 Hz, 1 H), 2.01 (d, J = 11.43 Hz, 1 H) 2.15 (dd, J = 11.8 and 2.2 Hz, 1 H), 2.73 (ddd, J = 11.4, 2.0 and 2.0 Hz, 1 H), 2.92−3.02 (m, 1 H), 3.15 (broad s, 2 H), 3.59 (d, J = 13.8 Hz, 1 H), 3.64 (d, J = 13.8 Hz, 1 H), 3.95−4.03 (m, 1 H), 7.14−7.30 (m, 5 H). − ^{13}C NMR ($CDCl_3$) (major isomer): δ = 6.8, 33.1, 39.3, 59.3, 62.3, 63.0, 66.4, 71.2, 127.0, 128.2, 128.8, 137.7. − ^1H NMR ($CDCl_3$) (minor isomer): δ = 0.90 (t, J = 7.4 Hz, 3 H), 1.38−1.62 (m, 3 H), 1.67−1.83 (m, 1 H), 1.86−1.93 (m, 1 H), 2.16−2.26 (m, 1 H), 2.72−2.80 (m, 1 H), 2.65−2.90 (m, 1 H), 3.15 (broad s, 2 H), 3.77 (d, J = 12.9 Hz, 1 H), 3.87 (d, J = 13.2 Hz, 1 H), 4.15−4.22 (m, 1 H), 7.14−7.30 (m, 5 H). − ^{13}C NMR ($CDCl_3$) (minor isomer): δ = 8.6, 41.0, 42.6, 58.8, 62.4, 63.8, 68.9, 71.0, 126.8, 128.3, 128.4, 139.4. − MS (70 eV); *m/z* (%): 235 (5) [M^+], 144 (9), 134 (61), 120 (10), 91 (100), 65(7). − $C_{14}H_{21}NO_2$ calcd 235.3254; found 235.3254 (MS)

(+)-(3*R*,5*R*)-1-Benzylpiperidine-3,5-diol (18): Trifluoroacetic anhydride (0.28 mL, 1.97 mmol) was added dropwise to a solution of pyrrolidine **9** (0.21 g, 1.79 mmol) in THF (20 mL), cooled to −78°C. After 3 h at −78°C, Et_3N (0.92 mL, 6.60 mmol) was added dropwise. The reaction mixture was stirred for 15 min at −78°C and then heated at reflux for 12 h. After addition of an aqueous 2.5 M NaOH solution (2.3 mL), the mixture was stirred for 3 h at room temp. and then extracted with CH_2Cl_2 (2× 10 mL), dried with $MgSO_4$, and evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/cyclohexane, 95:5) to give 200 mg (54%) of **18** as an oil. − $[\alpha]_D^{20} = +151$ (c = 0.5, EtOH). − IR (neat): $\tilde{\nu}$ = 3400, 1465, 1455, 1210 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.71−1.86 (m, 2 H), 2.06 (broad s, 2 H), 2.31−2.43 (m, 2 H), 2.56−2.69 (m, 2 H), 3.57 (d, J = 13.0 Hz, 1.H) 3.62 (d, J = 13.0 Hz, 1 H), 3.97−4.09 (m, 2 H), 7.23−7.40 (m, 5 H). − ^{13}C NMR ($CDCl_3$): δ = 40.1, 59.5, 62.1, 65.0, 127.3, 128.3, 128.9, 137.4. − MS (70 eV); *m/z* (%): 207 (11) [M^+], 134 (13), 130 (11), 120 (15), 116 (30), 91 (100). − $C_{12}H_{17}NO_2$ (207.27): calcd. C 69.54, H 8.27, N 6.76; found C 69.66, H 8.19, N 6.73.

(−)-(3*R*,5*R*)-1-Benzyl-5-[(*tert*-butyldimethylsilyl)oxy]piperidin-3-ol (19): Trifluoroacetic anhydride (0.44 mL, 3.10 mmol) was added dropwise to a solution of pyrrolidine **10** (0.904 g, 2.82 mmol) in THF (30 mL), cooled to −78°C. After 3 h, Et_3N (1.45 mL, 10.4 mmol) was added dropwise. The reaction mixture was stirred for 15 min at −78°C and then heated at reflux for 20 h. After addition of an aqueous 2.5 M NaOH solution (10 mL), the mixture was stirred for 3 h at room temp. and then extracted with CH_2Cl_2 (2× 15 mL), dried with $MgSO_4$, and evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/cyclohexane, 50:50) to give 590 mg (65%) of **19** as an oil. − $[\alpha]_D^{20} = -34$ (c = 0.5, EtOH). − IR (neat): $\tilde{\nu}$ = 3360, 1600, 1490, 1465, 1460, 1450, 1385, 1355, 1255, 1150, 1100, 1035 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = −0.03 (s, 3 H), 0.00 (s, 3 H), 0.82 (s, 9 H), 1.32 (ddd, J = 13.2, 10.6, and 2.9 Hz, 1 H), 1.87−2.10 (m, 3 H), 2.16 (dd, J = 11.5 and 1.5 Hz, 1 H), 2.71−2.93 (m, 3 H), 3.51 (d, J = 13.2 Hz, 1 H), 3.63 (d, J = 13.2 Hz, 1 H), 3.86−3.95 (m, 1 H), 3.98 (dddd, J = 14.7, 9.7, 4.7 and 4.7 Hz, 1 H), 7.15−7.30 (m, 5 H). − ^{13}C NMR ($CDCl_3$): δ = −4.9, −4.8, 17.9, 25.7, 40.6, 58.2, 60.7, 62.0, 64.9, 65.7, 127.3, 128.2, 129.0, 137.2. − MS (70 eV); *m/z* (%): 321 (3) [M^+], 264 (24), 134 (17), 101 (9), 92 (9), 91 (100), 75 (11), 73 (12). − $C_{18}H_{31}NO_2Si$ calcd 321.5339; found 321.5342 (MS).

(−)-(3a*R*,7*R*,7a*S*)-2,2,5-Trimethylhexahydro-4*H*-1,3-dioxolo[4,5-*c*]-pyridin-7-ol (**20**): Trifluoroacetic anhydride (0.08 mL, 0.58 mmol) was added dropwise to a solution of pyrrolidine **11** (98 mg, 0.52 mmol) in THF (5 mL) cooled to −78°C. After 1 h, Et_3N (0.27 mL, 1.94 mmol) was added dropwise. The reaction mixture was stirred for 1 h at −78°C and then heated at reflux for 72 h. After addition of an aqueous 3.75 M NaOH solution (2 mL), the mixture was stirred for 1 h at room temp. and then extracted with CH_2Cl_2 (3× 5 mL), dried with $MgSO_4$, and evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel ($CHCl_3$/MeOH, 92:8) to give 65 mg (67%) of **20** as a yellow oil. − $[\alpha]_D^{20}$ = −21 (*c* = 0.35, MeOH). − IR (neat): $\tilde{\nu}$ = 3400, 1465, 1455, 1385, 1275, 1210 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.36 (s, 3 H), 1.52 (s, 3 H), 2.29−2.41 (m, 1 H), 2.32 (s, 3 H), 2.52−2.71 (m, 3 H), 3.38 (broad s, 1 H), 3.92−4.01 (m, 2 H), 4.31 (dd, 1 H, *J* = 10.8 and 5.3 Hz). − ^{13}C NMR ($CDCl_3$): δ = 26.1, 28.1, 45.7, 56.7, 57.5, 68.0, 72.1, 76.6, 109.2. − MS (70 eV); *m/z* (%): 187 (11) [M^+], 172 (5), 129 (6), 112 (16), 82 (15), 58 (25), 57 (100), 55 (9). − $C_9H_{17}NO_3$ calcd 187.2382; found 187,2379 (MS).

(+)-1-Methyl-2-phenylpiperidin-3-ol (**22**): Trifluoroacetic anhydride (0.04 mL, 0.28 mmol) was added dropwise to a solution of pyrrolidine **21** (35 mg, 0.18 mmol) in THF (6 mL) cooled to −78°C. After 1 h, Et_3N (0.81 mL, 0.58 mmol) was added dropwise. The reaction mixture was stirred for an additionnal 1 h at −78°C and then heated at reflux for 48 h. After addition of an aqueous 3.75 M NaOH solution (4 mL), the mixture was stirred for 1 h at room temp. and then extracted with CH_2Cl_2 (3× 4 mL), dried with $MgSO_4$, and evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc) to give 19 mg (56%) of **22** as a yellow oil. − $[\alpha]_D^{20}$ = +45 (*c* = 0.12, EtOH). − IR (neat): $\tilde{\nu}$ = 3380, 1450, 1260, 1120, 1060, 1010 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.33−1.49 (m, 1 H), 1.74−1.85 (m, 4 H), 2.00 (s, 3 H), 2.08−2.21 (m, 2 H), 2.64 (d, *J* = 8.8 Hz, 1 H,), 2.92−3.03 (m, 1 H), 3.65 (ddd, *J* = 11.0, 8.8, and 4.4 Hz, 1 H), 7.27−7.43 (m, 5 H). − ^{13}C NMR ($CDCl_3$): δ = 23.4, 32.1, 44.0, 56.6, 73.0, 77.6, 128.0, 128.4, 128.8, 140.1. − MS (70 eV); *m/z* (%): 191 (22) [M^+], 190 (15), 146 (40), 134 (40), 132 (24), 118 (100), 117 (11), 114 (13), 91 (51), 77 (14), 65 (11), 51 (12). − $C_{12}H_{17}NO$ calcd 191.1310; found 191,1311 (MS).

(−)-1-Benzyl-2-(1-methylethenyl)pyrrolidine (**28**): Trifluoroacetic anhydride (0.15 mL, 1.06 mmol) was added dropwise to a solution of pyrrolidine **27** (0.22 g, 1 mmol) in THF (9 mL) cooled to −78°C. After 1 h, Et_3N (0.51 mL, 3.65 mmol) was added dropwise. The reaction mixture was stirred for an additional 1 h at −78°C and then heated at reflux for 7 days. After addition of an aqueous 3.75 M NaOH solution (5 mL), the mixture was stirred for 1 h at room temp. and then extracted with CH_2Cl_2 (3× 7 mL), dried with $MgSO_4$, and evaporated to dryness in vacuo. The residue was purified by flash column chromatography on alumina (EtOAc/cylohexane, 50:50) to give 110 mg (55%) of **28** as a colourless oil. − $[\alpha]_D^{20}$ = −43 (*c* = 1, $CHCl_3$). − ^1H NMR ($CDCl_3$): δ = 1.64−1.98 (m, 4 H), 1.82 (s, 3 H), 2.01−2.14 (m, 1 H), 2.85−3.05 (m, 2 H), 3.00 (d, *J* = 13.2 Hz, 1 H), 3.97 (d, *J* = 13.2 Hz, 1 H), 4.87−4.93 (m, 1 H), 5.04−5.06 (m, 1 H), 7.15−7.45 (m, 5 H). − ^{13}C NMR ($CDCl_3$): δ = 17.3, 22.2, 29.8, 53.3, 57.9, 71.0, 112.1, 126.5, 128.0, 128.6, 139.9, 146.4. − MS (70 eV); *m/z* (%): 201 (11) [M^+], 161 (20), 160 (93), 91 (100), 65 (15). − $C_{14}H_{19}N$ calcd 201.3108; found 201,3099 (MS).

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