Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 3449–3455

TETRAHEDRON: *ASYMMETRY*

Chemoenzymatic synthesis of azacycloalkan-3-ols

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Received 27 July 1999; accepted 11 August 1999

Abstract

Optically active ω-bromocyanohydrins are easily synthesized through an enantioselective (*R*)-oxynitrilase-catalyzed reaction from their corresponding ω-bromoaldehydes. These cyanohydrins are starting materials for the preparation of medium size nitrogen heterocycles. The reduction of (*R*)-(+)-5-bromo-2-hydroxypentanenitrile affords, in one-pot, piperidin-3-ol. Azepan-3-ol and azocan-3-ol are readily obtained from their corresponding cyanohydrins in high enantiomeric excesses. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

The synthesis of optically active cyanohydrins by chemical or enzymatic procedures has received a considerable amount of attention over recent years.[1] (*R*)-Oxynitrilase from almonds has been used to catalyze the enantioselective addition of hydrogen cyanide to aromatic and aliphatic aldehydes[2] or aliphatic ketones,[3] giving the corresponding (*R*)-cyanohydrins. One of the most successful procedures for the preparation of (*R*)-cyanohydrins has been the use of powdered defatted almond meal as a rich source of (*R*)-oxynitrilase.[4]

In a previous report,[5] we have prepared, in high yield and enantiomeric excess, (*R*)-(+)-5-bromo-2-hydroxypentanenitrile **3a** and (*R*)-(+)-6-bromo-2-hydroxyhexanenitrile **3b** through an enzymatic trans-cyanation process catalyzed by (*R*)-oxynitrilase. We have also shown that cyanohydrin **3b** is a suitable starting material for the preparation of (*S*)-pipecolic acid and 2-substituted piperidine alkaloids.[6]

In this paper, we propose an approach to the synthesis of some optically active azacycloalkan-3-ols, structures which are constituents of several bioactive compounds. In particular, piperidin-3-ol is an attractive target because of its widespread occurrence in natural products. Medicinally important examples containing 3-piperidinol fragments include cholinotoxic agents,[7] antihypertensives and calcium antagonists,[8] 2,3-oxydosqualene cyclase inhibitors,[9] 5-HT4 agonists,[10] nootropics[11] or antiarrhythmic

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0957-4166/99/$ - see front matter
PII: S0957-4166(99)00351-1

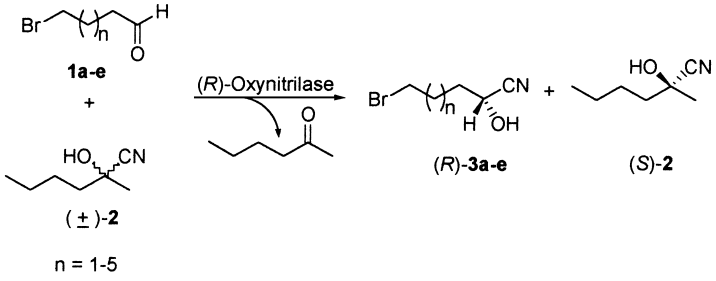
agents.[12] In view of these applications, as expected, several routes for the preparation of these compounds have been described. The total syntheses of (*S*)-(−)-piperidin-3-ol have been reported from D-manitol,[13] (*S*)-malic acid,[14] or L-(+)-glutamic acid;[14] nevertheless, no experimental details or yields are contained in the first report and poor or moderated yields (10 and 37%, respectively) are reported in the second one. In a more recent report, Cossy et al.[15] have prepared (*R*)-(−)-*N*-alkylpiperidin-3-ols from 2-hydroxymethyl-*N*-alkylpyrrolidines by a ring expansion. The resolution of racemic piperidin-3-ol through fractional recrystallization[16] or by enzymatic hydrolysis of several ester derivatives[17] has also been described.

On the other hand, monocyclic medium ring nitrogen heterocycles are an important class of compounds, especially in view of their pharmacological properties.[18] However, synthetic methods for the preparation of these compounds are, in general, very specific in each class.

In this article we describe a simple and stereoselective method for the preparation of these hydroxyazacycles.

2. Results and discussion

Since ω-bromocyanohydrins are suitable starting materials for the preparation of heterocycles, we decided to extend our method of preparation of these compounds, via an (*R*)-oxynitrilase-catalyzed transcyanation,[5] to longer chain ω-bromocyanohydrins **3c**–**e** (*n*=3–5). Firstly, we have prepared the corresponding bromoaldehydes **1c**–**e** by reduction of the commercially available esters or acids with DIBA-H and, secondly, we have carried out the transcyanation process of **1c**–**e** under the optimal conditions found for **1a**,**b**, that is, using (±)-2-methyl-2-hydroxyhexanenitrile **2** as the hydrogen cyanide donor (Scheme 1). Thus, cyanohydrins (*R*)-**3c**–**e** were obtained in moderate yields and high enantiomeric excess (see Experimental).

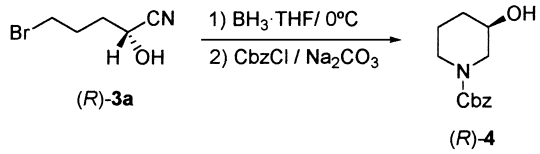


Scheme 1.

The enantiomeric excesses of (*R*)-**3c**–**e** were determined by derivatization with Mosher's acid chloride followed by ^{19}F NMR analysis. The (*R*)-configuration of the cyanohydrins was assigned on the basis of the specificity of the enzyme and by analogy with the results obtained for (*R*)-**3a** and (*R*)-**3b**.

*2.1. Synthesis of (*R*)-1-(benzyloxycarbonyl)piperidin-3-ol*

The optically active (*R*)-(+)-5-bromo-2-hydroxypentanenitrile **3a** could be transformed by reduction into the corresponding 1,2-aminoalcohol. Due to the presence of the leaving group at C-5 position, the resulting amine function could undergo a nucleophilic substitution to yield piperidin-3-ol; thus treatment of the cyanohydrin **3a** with $BH_3 \cdot THF$ gives, after protection of the resulting amine with benzylchloroformate, (*R*)-1-(benzyloxycarbonyl)piperidin-3-ol **4** in good yield (Scheme 2).

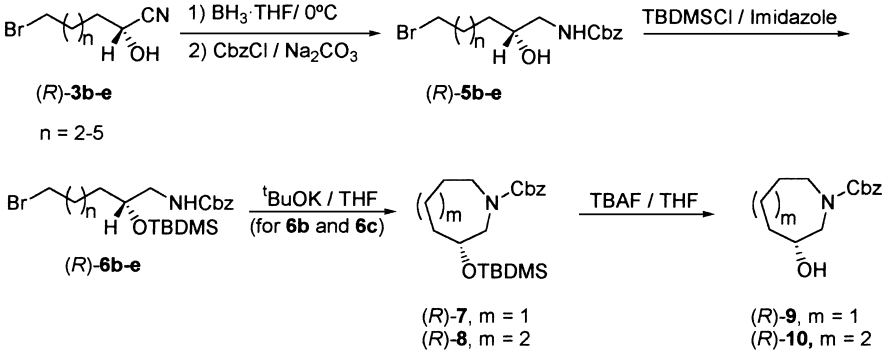


Scheme 2.

To ensure that no racemization has occurred during the process, the enantiomeric excess of (*R*)-**4** was determined by derivatization with Mosher's acid chloride followed by ^{19}F NMR analysis. The enantiomeric excess for (*R*)-**4** was 96%, the same as its precursor (*R*)-**3a**.[5]

*2.2. Synthesis of (*R*)-1-(benzyloxycarbonyl)azepan-3-ol and (*R*)-1-(benzyloxycarbonyl)azocan-3-ol*

The seven-, eight-, nine- and ten-membered rings cannot be synthesized in a one-pot procedure by the reduction of the nitrile function. Under the same conditions as for the synthesis of (*R*)-**4**, treatment of the cyanohydrins (*R*)-**3b**–**e** (*n*=2–5, respectively) with $BH_3 \cdot THF$ and subsequent reaction with benzylchloroformate yielded the open chain bromoaminoalcohols (*R*)-**5b**–**e** (Scheme 3). Nevertheless, the ring closure took place easily on treatment of the protected bromoaminoalcohols (*R*)-**6b,c** with ^{t}BuOK. Attempts to cyclize them under milder basic conditions (pyridine or NaOH/Bu_4NCl) were unsuccessful. The hydroxyl protecting group can be quantitatively removed by treatment with tetrabutylammonium fluoride (TBAF) to obtain the heterocycles (*R*)-**9** and (*R*)-**10** in good yields. Attempts at cyclization of the bromoaminoalcohols (*R*)-**6d**,**e** failed under all the tested conditions. Besides the previously mentioned basic media, we attempted the nine- and ten-membered ring closures using silver perchlorate, but unsuccessfully.



Scheme 3.

To ensure that no racemization has occurred during the processes, the enantiomeric excesses of (*R*)-**9** and (*R*)-**10** were determined by ^1H NMR analysis of their acetyl derivatives in the presence of the chiral shift reagent Eu(hfc)$_3$. The enantiomeric excesses for (*R*)-**9** and (*R*)-**10** were 91% and 90%, the same as their precursors (*R*)-**3b**[5] and (*R*)-**3c**, respectively.

In conclusion, the reduction of the nitrile function in the (*R*)-ω-bromocyanohydrins permits (*R*)-ω-bromo-1,2-aminoalcohols to be obtained which, depending on their chain length, are suitable starting materials for the preparation of optically active piperidin-3-ol, azepan-3-ol and azocan-3-ol. To the best of our knowledge, the asymmetric syntheses of the two last heterocycles have not been described before.

3. Experimental

Melting points were taken using a Gallenkamp apparatus and were uncorrected. Optical rotations were measured using a Perkin–Elmer 241 polarimeter and specific rotations are quoted in units of 10^{-1} deg cm^2 g^{-1}. ^1H and ^{13}C NMR were obtained with TMS (tetramethylsilane) as internal standard, using a Bruker AC-300 (^1H 300 MHz and ^{13}C 75.5 MHz) spectrometer. Mass spectra were recorded on a Hewlett–Packard 5987A and Finnigan MAT/95 spectrometers. Microanalyses were performed on a Perkin–Elmer 240B elemental analyzer. All reagents were purchased from Aldrich Chemie. Solvents were distilled over an adequate desiccant and stored under nitrogen. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh).

*3.1. (*R*)-Oxynitrilase catalyzed transcyanation of ω-bromoaldehydes. General procedure*

The defatted ground almond meal (2 g) was incubated with 5 ml of 0.02 M citrate buffer (pH 5.5) in a 250 ml reaction vessel. After 15 min, 50 ml of diisopropyl ether, distilled substrate ω-bromoaldehyde (8.4 mmol) and the (±)-2-hydroxy-2-methylhexanenitrile (1.6 g, 12.6 mmol) were added to the suspension. The mixture was shaken at 30°C and 250 rpm in a rotatory shaker. After 24 h, the reaction mixture was filtered and washed with CH_2Cl_2. The combined filtrates were concentrated in vacuo, and the residue was purified by flash chromatography on silica gel with hexane:H_2CCl_2:AcOEt (7.5:2.5:1), to give the (*R*)-cyanohydrin **3**.

*3.1.1. (*R*)-(+)-7-Bromo-2-hydroxyheptanenitrile (*R*)-**3c***

Colourless oil; yield 65%; $[\alpha]_D^{25}$ +7.8 (*c*=1.1, $CHCl_3$), ee 90%; ^1H NMR ($CDCl_3$) δ 1.48–1.61 (m, 4H), 1.80–1.98 (m, 4H), 3.27 (br s, 1H), 3.35 (t, 2H), 4.50 (t, 1H); ^{13}C NMR ($CDCl_3$) δ 23.6, 27.3, 32.2, 33.5, 34.7, 61.0, 119.9; MS (EI) m/z 207 [M^+(^{81}Br), 8], 205 [M^+(^{79}Br), 8], 189 (13), 187 (13), 81 (92), 69 (45), 55 (100).

*3.1.2. (*R*)-(+)-8-Bromo-2-hydroxyoctanenitrile (*R*)-**3d***

Colourless oil; yield 41%; $[\alpha]_D^{25}$ +8.8 (*c*=1.2, $CHCl_3$), ee 92%; ^1H NMR ($CDCl_3$) δ 1.35–1.61 (m, 6H), 1.80–1.97 (m, 4H), 3.29 (br s, 1H), 3.42 (t, 2H), 4.47 (t, 1H); ^{13}C NMR ($CDCl_3$) δ 24.3, 27.8, 28.0, 32.4, 33.7, 34.9, 61.1, 119.9; MS (EI) m/z 221 [M^+(^{81}Br)<1], 219 [M^+(^{79}Br)<1], 176 (45), 174 (45), 150 (65), 148 (65), 69 (100).

*3.1.3. (*R*)-(+)-9-Bromo-2-hydroxynonanenitrile (*R*)-**3e***

Colourless oil; yield 40%; $[\alpha]_D^{25}$ +7.7 (*c*=1.1, $CHCl_3$), ee 97%; ^1H NMR ($CDCl_3$) δ 1.31–1.60 (m, 8H), 1.80–1.97 (m, 4H), 3.04 (br s, 1H), 3.42 (t, 2H), 4.50 (t, 1H); ^{13}C NMR ($CDCl_3$) δ 24.7, 28.2, 28.8 29.0, 32.9, 34.3, 35.3, 61.5, 120.4. MS (EI) m/z 235 [M^+(^{81}Br)<1], 233 [M^+(^{79}Br)<1], 164 (44), 162 (44), 109 (56), 83 (71), 55 (100).

*3.2. (*R*)-(−)-1-Benzyloxycarbonylpiperidin-3-ol (*R*)-**4***

To a vigorously stirred solution of the bromocyanohydrin (*R*)-**3a** (1.4 g, 7.8 mmol) in 200 ml of dry THF at 0°C, were added dropwise 47 ml of a 1 M solution of BH_3·THF. The resulting mixture was allowed to warm to rt and stirred for 6 h. Then 47 ml of 6 N HCl were added and the organic solvent was removed under reduced pressure. The resulting solution was cooled to 0°C and adjusted to basic pH by addition of NaOH pellets. The aqueous phase was extracted with CH_2Cl_2 (3×50 ml) and the solvent

of the combined organic fractions was almost completely removed under reduced pressure. Without any further purification 10 ml of distilled H_2O and Na_2CO_3 (82.8 mg, 7.8 mmol) were added to the resulting mixture, cooled to 0°C and benzylchloroformate (1.1 ml, 7.8 mmol) was added dropwise and stirred for 6 h. Then, the mixture was extracted with CH_2Cl_2 (3×50 ml) and the combined organic fractions were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel with hexane:AcOEt (7:3), to give the piperidin-3-ol (*R*)-**4** as a colourless oil in 40% yield. $[\alpha]_D^{25}$ −11.9 (*c*=1.0, $CHCl_3$), ee 96%; ^{1}H NMR ($CDCl_3$) δ 1.54 (m, 1H), 1.92 (m, 3H), 3.16 (m, 1H), 3.51 (m, 1H), 3.79 (m, 2H), 4.00 (m, 1H), 5.11 (s, 2H), 5.12 (br s, 1H), 7.35, (s, 5H); ^{13}C NMR ($CDCl_3$) δ 25.7, 28.3, 44.7, 66.5, 67.9, 77.7, 127.9, 128.3, 136.4, 157.6; MS (EI) m/z 235 (M^+, 23), 191, (26), 144 (40), 91 (74), 71 (100); HRMS calcd for $C_{13}H_{17}NO_3$ 235.1207, found 235.1208.

*3.3. (*R*)-(−)-Benzyl* N-*(6-bromo-2-hydroxyhexyl)carbamate (*R*)-**5b***

The title compound was prepared as described for (*R*)-**4**. White solid; yield 75%; mp 50–52°C; $[\alpha]_D^{25}$ −8.5 (*c*=1.0, $CHCl_3$), ee 91%; ^{1}H NMR ($CDCl_3$) δ 1.45 (m, 4H), 1.83 (m, 2H), 2.51 (br s, 1H), 3.07 (m, 1H), 3.34 (m, 1H), 3.42 (t, 2H), 3.73 (s, 1H), 5.09 (s, 2H), 5.34 (br s, 1H), 7.37 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 24.0, 32.4, 33.4, 33.5, 46.8, 66.8, 70.9, 128.0, 128.1, 128.4, 136.8, 157.1; MS (EI) m/z 331 [M^+(^{81}Br)<1], 329 [M^+(^{79}Br)<1], 165 (34), 108 (32), 104 (95), 91 (100); HRMS calcd for $C_{14}H_{20}BrNO_3$ 329.0625, found 329.0626. Anal. calcd for $C_{14}H_{20}BrNO_3$: C, 50.92; H, 6.10; N, 4.24, found: C, 51.10; H, 6.17; N, 4.18.

*3.4. (*R*)-(−)-Benzyl* N-*(7-bromo-2-hydroxyheptyl)carbamate (*R*)-**5c***

The title compound was prepared as described for (*R*)-**4**. White solid; yield 78%; mp 55–58°C; $[\alpha]_D^{25}$ −4.6 (*c*=1.0, $CHCl_3$), ee 90%; ^{1}H NMR ($CDCl_3$) δ 1.43 (m, 6H), 1.82 (m, 2H), 2.64 (br s, 1H), 3.11 (m, 1H), 3.33 (m, 1H), 3.41 (t, 2H), 3.69 (s, 1H), 5.10 (s, 2H), 5.32 (br s, 1H), 7.36 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 24.52, 27.91, 32.5, 33.7, 34.28, 46.8, 66.8, 70.9, 128.0, 128.4, 136.2, 157.0; FABS m/z 346 [$(M+1)^+$(^{81}Br), 15], 344 [$(M+1)^+$(^{79}Br), 15], 91 (100). Anal. calcd for $C_{15}H_{22}BrNO_3$: C, 52.48; H, 6.17; N, 4.08; found: C, 52.55; H, 6.48; N, 4.02.

*3.5. (*R*)-(−)-Benzyl* N-*(8-bromo-2-hydroxyoctyl)carbamate (*R*)-**5d***

The title compound was prepared as described for (*R*)-**4**. White solid; yield 77%; mp 57–59°C; $[\alpha]_D^{25}$ −8.8 (*c*=0.9, $CHCl_3$), ee 92%; ^{1}H NMR ($CDCl_3$) δ 1.43 (m, 8H), 1.86 (m, 2H), 2.49 (br s, 1H), 3.06 (m, 1H), 3.34 (m, 1H), 3.41 (t, 2H), 3.69 (s, 1H), 5.10 (s, 2H), 5.32 (br s, 1H), 7.35 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 25.1, 27.8, 28.5, 32.5, 33.8, 34.3, 46.8, 66.7, 71.0, 127.9, 127.9, 128.3, 136.1, 156.9; MS (EI) m/z 359 [M^+(^{81}Br)<1], 357 [M^+(^{79}Br)<1], 165 (31), 108 (29), 91 (100). Anal. calcd for $C_{15}H_{22}BrNO_3$: C, 53.79; H, 6.49; N, 3.92; found: C, 53.59; H, 6.88; N, 3.90.

*3.6. (*R*)-(−)-Benzyl N-(9-bromo-2-hydroxynonyl)carbamate (*R*)-**5e***

The title compound was prepared as described for (*R*)-**4**. White solid; yield 30%; mp 70–72°C; $[\alpha]_D^{25}$ −5.6 (*c*=1.0, $CHCl_3$), ee 97%; ^{1}H NMR ($CDCl_3$) δ 1.28–1.59 (m, 10H), 1.90 (m, 2H), 2.29 (br s, 1H), 3.10 (m, 1H), 3.34 (m, 1H), 3.43 (t, 2H), 3.71 (s, 1H), 5.12 (s, 2H), 5.23 (br s, 1H), 7.35 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 25.3, 28.0, 28.5, 25.3, 32.6, 33.9, 34.6, 46.9, 66.8, 71.2, 128.0, 128.1, 128.5, 136.3,

157.0; MS (EI) m/z 373 [M^+(^{81}Br), 3], 371 [M^+(^{79}Br), 3], 330 (9), 328 (10), 266 (5), 264 (6), 238 (5), 236 (5), 194 (34), 104 (70), 91 (100).

*3.7. (*R*)-(−)-Benzyl N-[6-bromo-2-(*tert*-butyldimethylsilyloxy)hexyl]carbamate (*R*)-**6b***

A solution of compound (*R*)-**5b** (300 mg, 0.87 mmol), *tert*-butyldimethylsilyl chloride (263 mg, 1.7 mmol), imidazole (178 mg, 2.6 mmol) and a catalytic quantity of 4-(dimethylamino)pyridine (DMAP) in dry CH_2Cl_2 (8 ml) under N_2 atmosphere was stirred for 24 h at rt. Then, 15 ml of a saturated solution of NH_4Cl were added and the resulting mixture was extracted with CH_2Cl_2 (3×10 ml). The combined organic fractions were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (hexane:AcOEt 9:1) to afford the compound (*R*)-**6b** as a colourless oil in a 90% yield; $[\alpha]_D^{25}$ −1.7 (*c*=1.0, $CHCl_3$), ee 91%; ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 6H), 0.88 (s, 9H), 1.45 (m, 4H), 1.84 (m, 2H), 3.19 (m, 2H), 3.39 (t, 2H), 3.76 (s, 1H), 4.98 (br s, 1H), 5.10 (s, 2H), 7.36 (s, 5H); ^{13}C NMR ($CDCl_3$) δ −4.7, −3.6, 17.9, 23.8, 25.7, 32.6, 33.5, 33.8, 46.2, 66.6, 70.8, 128.1, 128.4, 136.4, 156.4; MS (EI) m/z 445 [M^+(^{81}Br), 20], 443 [M^+(^{79}Br), 20], 388 (63), 386 (65), 344 (65), 342 (65), 283 (74), 281 (74), 131 (30), 115 (33), 91 (100).

*3.8. (*R*)-(−)-Benzyl* N-*[7-bromo-2-(*tert*-butyldimethylsilyloxy)heptyl]carbamate (*R*)-**6c***

The title compound was prepared as described for (*R*)-**6b**. Colourless oil; yield 90%; $[\alpha]_D^{25}$ −2.1 (*c*=0.9, $CHCl_3$), ee 90%; ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.88 (s, 9H), 1.42 (m, 6H), 1.86 (m, 2H), 3.20 (m, 2H), 3.39 (t, 2H), 3.76 (s, 1H), 4.99 (br s, 1H), 5.12 (s, 2H), 7.37 (s, 5H); ^{13}C NMR ($CDCl_3$) δ −4.0, 17.9, 24.3, 25.7, 28.5, 32.5, 33.7, 34.6, 46.2, 66.6, 70.9, 128.0, 128.4, 136.4, 156.4; MS (EI) m/z 459 [M^+(^{81}Br), 4], 457 [M^+(^{79}Br), 4], 402 (45), 400 (45), 295 (58), 293 (58), 91 (100).

*3.9. (*R*)-(−)-1-(Benzyloxycarbonyl)-3-(*tert*-butyldimethylsilyloxy)azepane (*R*)-**7***

To a stirred solution of compound (*R*)-**6b** (163 mg, 0.37 mmol) in 25 ml of dry THF under N_2 atmosphere at rt was added, in small portions, ^{t}BuOK (7.2 mg, 0.64 mmol). The resulting mixture was stirred for 15 h. Then, 15 ml of a saturated solution of NH_4Cl were added and the resulting mixture was extracted with AcOEt (3×20 ml). The combined organic fractions were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (hexane:AcOEt 9.5:0.5) to afford the compound (*R*)-**7** as a colourless oil in a 50% yield; $[\alpha]_D^{25}$ −13.7 (*c*=1.0 $CHCl_3$), ee 91%; ^{1}H NMR ($CDCl_3$) δ −0.01 (d, 3H), 0.11 (d, 3H), 0.90 (d, 9H), 1.78 (m, 6H), 2.88 (q, 1H), 3.05 (m,1H), 3.82 (m, 2H), 3.95 (m, 1H), 5.15 (s, 2H), 7.36 (s, 5H); ^{13}C NMR ($CDCl_3$) δ −5.0, 17.9, 20.5, 25.6, 27.2, 36.9, 47.4, 53.6, 66.9, 70.6, 127.5, 128.0, 128.3, 136.8, 155.9; MS (EI) m/z 363 (M^+<1), 306 (76), 262 (45), 91 (100) ($M+2^+$<1); HRMS calcd for $C_{20}H_{33}NSiO_3$ 363.2222, found 363.2229.

*3.10. (*R*)-(−)-1-(Benzyloxycarbonyl)-3-(*tert*-butyldimethylsilyloxy)azocane (*R*)-**8***

The title compound was prepared as described for (*R*)-**7**. Colourless oil; yield 30%; $[\alpha]_D^{25}$ −15.6 (*c*=1.0, $CHCl_3$), ee 90%; ^{1}H NMR ($CDCl_3$) δ −0.05 (d, 3H), 0.13 (d, 3H), 0.91 (d, 9H), 1.71 (m, 8H), 2.7 (q, 1H), 2.9 (m, 1H), 3.68 (m, 1H), 3.88 (m, 1H), 4.05 (m, 1H), 5.17 (s, 2H), 7.36 (s, 5H); ^{13}C NMR ($CDCl_3$) δ −5.0, 18.0, 21.1, 25.7, 26.4, 27.2, 34.2, 49.3, 52.7, 67.1, 69.6, 127.5, 128.2, 128.4, 136.6, 155.9; MS (EI) m/z 377 (M^+, 5) 362 (17), 320 (13), 91 (100).

3.11. (R)-(−)-1-(Benzyloxycarbonyl)azepan-3-ol (R)-9

To a stirred solution of compound (*R*)-**8** (400 mg, 1.1 mmol) in 25 ml of dry THF under N_2 atmosphere at rt was added dropwise a solution of 1 M tetrabutylammonium fluoride (1.33 ml). The resulting mixture was stirred for 5 h. After removal of the solvent under reduced pressure, the crude residue was purified by flash chromatography on silica gel (hexane:AcOEt 3:2) to yield the compound (*S*)-**9** as a colourless oil in a quantitative yield; $[\alpha]_D^{25}$ −13.5 (*c*=1.0, $CHCl_3$), ee 91%; ^{1}H NMR ($CDCl_3$) δ 1.3–1.8 (m, 6H), 3.25 (m, 2H), 3.42 (m, 1H), 3.65 (m, 2H), 3.97 (br s, 1H), 5.15 (s, 2H), 7.36 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 20.8, 28.4, 35.6, 48.1, 53.4, 67.2, 70.5, 127.6, 127.8, 127.9, 128.4, 136.5, 157.6; MS (EI) m/z 249 (M^+, 1.5), 114 (18), 91 (100).

3.12. (R)-(−)-1-(Benzyloxycarbonyl)azocan-3-ol (R)-10

The title compound was prepared as described for (*R*)-**9**. Colourless oil; quantitative yield; $[\alpha]_D^{25}$ −2.6 (*c*=1.1, $CHCl_3$), ee 90%; ^{1}H NMR ($CDCl_3$) δ 1.25–1.82 (m, 8H), 3.03 (m, 1H), 3.30 (m, 1H), 3.81 (m, 3H), 4.29 (br s, 1H), 5.18 (s, 2H), 7.36 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 22.4, 26.6, 26.8, 32.7, 49.3, 53.5, 67.5, 70.9, 127.7, 128.0, 128.4, 136.4, 158.2; MS (EI) m/z 263 (M^+, 1.5), 128 (61), 91 (100).

Acknowledgements

Financial support of this work by CICYT (Project BIO-98-0770) is gratefully acknowledged.

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