A Short Chiral Synthesis of 2- and 8-Differently Functionalized 1,4,7,10-Tetraoxaspiro[5.5]Undecane

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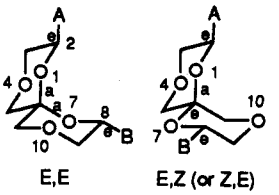
Many biologically active natural products contain a spiroacetal moiety in their skeleton. This has prompted considerable interest in the synthesis of enantiomerically pure spiroacetals, functionalized or not, mainly in the dioxaspiro domain.[1] In the course of our research directed toward analogues of calcimycin (or A.23187), a well-known calcium ionophore, we recently reported the preparation of new spirobidioxanes bearing functionalized side chains at the 2,8 positions. A cyclodehydrative reaction was carried out on keto diol precursors[2,3] obtained from racemic or optically active triglycerols. This synthetic route gave stable spiroacetals with two identical sidechains (A = B, Chart 1). The structures of the stereoisomers were determined and proved to be identical to those postulated in the dioxa series;[4,5] and they were governed by stereoelectronic effects under thermodynamically controlled cyclization.[5] The configurations of the carbons bearing the two alcohols, which reacted intramolecularly with the ketone function in the keto diol, determined the stereochemistry of the resulting spirobicycles, giving only an *E,E* structure from identical configurations and an *E,Z* structure (+ *Z,E* for A ≠ B) from opposite configurations, as represented in Chart 1. Subsequent cyclization of enantiomerically pure *R,R* or *S,S* keto diols gave a chiral *E,E* skeleton with known configurations for carbons 2,8 and consequently for the C-6 spiroacetal center,[3,4] using described rules for its determination.[6]

To differentiate functions in the 2 and 8 positions, we previously used a lipase as a selective cleaving reagent.[2] This approach necessitated a multistep procedure especially if an amine function was required in the place of terminal hydroxyl groups. In this work, we investigated a novel synthetic route for a 1,4,7,10-tetraoxygenated spiroacetal, giving a (+)-*E,E* structure bearing two different side chains in few steps (Scheme 1). The chiral precursors 1 and 8 were commercially available. The nitrogen atom was introduced in the first step, and the use of (*S*)-glycidol[7] (1) gave the protected amino alcohol (2*R*,4*RS*)-5 in 82% yield *via* (*tert*-butylamino)propane-1,2-diol (3), following an efficient synthesis[8] which could be conveniently modified for further developments. To prepare product 9 directly, addition of alcohol 5 to the epoxide, (2*RS*,2′*S*)-1,2-epoxy-3-(2′,3′-*O*-isopropylideneglycerol)propane,[3] was tried, but this reaction failed. However, epoxide 7 was prepared in 85% yield and reacted readily in DMF with the alkoxide of (*S*)-isopropylideneglycerol (8) to afford the desired alcohol 9 (90% yield). We applied Ley's oxidation method[9] to obtain the ketone (2′*R*,2″*S*,4′*RS*)-10 in 68% yield. Removal of the oxazolidine and acetonide functions followed by a cyclodehydrative cyclization was carried out in dilute aqueous H_2SO_4. After neutralization and purification on alumina, the aminospiroacetal (*E,E*)-(2*R*,6*S*,8*R*)-(+)-11 was isolated in 42% yield.

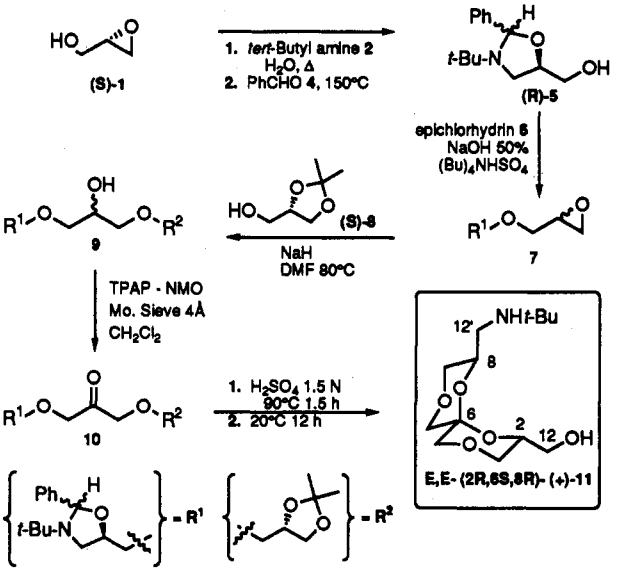
The presence of diastereoisomers for products 3, 5, 7, 9, and 10 gave complex, only partially assigned ^1H spectra. For product 11, ^1H–^1H COSY and ^1H–^{13}C heteronuclear correlation enabled us to assign proton and carbon resonances. Analysis of ^1H–^1H coupling constants and chemical shifts confirmed the *E,E* stereochemistry of the skeleton with equatorial side chains at the 2,8 positions and axial C6–O bonds, as already discussed for closely related structures in previous work.[2,3] Enantiomeric purity of 11 was determined by NMR using the chiral reagent $Eu(hfc)_3$, and no satisfactorily resolved ^1H spectra were obtained for the racemic compound,[10] but by using quantitative ^{13}C NMR it was possible to estimate the ee to be 98% on the resonance at 43.4 ppm corresponding to carbon 12′.

In conclusion, we describe the preparation of the optically pure amino spiroacetal 11 by a short protocol

Chart 1



Scheme 1



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(10) Compound (±)-(*E,E*) 11 was prepared according to the procedure described in this paper and separated from the *Z,E* and *E,Z* isomers obtained.

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giving an overall yield three times greater than our previous approach, in five steps instead of eight. We are presently investigating the synthesis with amines bearing chemically labile substituents in order to incorporate this structure into macrocyclic systems or calcimycin analogues.

Experimental Section

General information concerning instrumentation and materials was described previously.[3] DMF was distilled from BaO and kept under argon. Benzaldehyde was freshly distilled before use. NMR spectra were recorded at 300 or 400 MHz for ^1H and 75.47 or 100 MHz for ^{13}C on a Bruker MSL 300 or Bruker AC 400 spectrometer with $CDCl_3$ as solvent. All signals were expressed in ppm, and the signal of $CHCl_3$ for ^1H was set to 7.27 and for ^{13}C was set to 77.1.

(2*R*)-(+)-3-(*tert*-Butylamino)propane-1,2-diol (3). To a solution of *tert*-butylamine (2) (189 mL, 1.8 mol) and water (18 mL) was added (2*S*)-glycidol (1) (13.33 g, 0.18 mol). The resulting mixture was refluxed overnight. The excess water and amine were removed under vacuum, and a pale yellow oil was obtained. This oil was scratched to induce crystallization. The crude product (28.18 g) was pure enough to be used in the next step. Purification of 3 could be performed by recrystallization in hexane: white powder; mp 76–78 °C (hexane); $[\alpha]^{25}_J$ +29° (*c* 0.021, HCl 1 N); ^{13}C NMR (75 MHz) δ 70.3 (C2), 66.0 (C1), 50.5 (C quat. *t*-Bu), 45.5 (C3), 28.8 (C *t*-Bu).

(2*R*,4*RS*)-3-*N*,2-*O*-Benzylidene-*N*-*tert*-butylglycerol (5). A mixture of crude product 3 (8.0 g, 0.054 mol) and benzaldehyde (4) (10 mL) was heated to 150 °C. The azeotrope was removed by distillation, and 4 was added to keep constant volume. When distillation of the azeotrope stopped, the mixture was cooled to 30 °C. The excess benzaldehyde was removed under vacuum. The residue was chromatographed on silica gel with cyclohexane/ethyl acetate (60/40), and 5 was obtained in 82% (9.84 g) yield from (*S*)-1: yellow liquid; $[\alpha]^{25}_J$ 0° (*c* 0.024, $CHCl_3$); ^1H NMR (300 MHz) δ 7.59 (2H, m), 7.34 (3H, m), 5.61 and 5.56 (1H, s), 4.11 (1H, m), 3.78 and 3.62 (1H, dd), 3.62 and 3.49 (1H, dd), 3.29 and 3.16 (1H, dd), 2.95 (1H, dd), 2.38 (1H, s), 1.12 and 1.07 (9H, s); ^{13}C NMR (75 MHz) δ 143.5–143.0, 127.2–128.8, 92.7–91.8, 77.5–76.1, 64.8 –62.8, 53.3–53.5, 48.1–48.3, 28.0–27.3.

(2*RS*,2′*R*,4′*RS*)-3-(3′-*N*,2′-*O*-benzylidene-*N*-*tert*-butyl-1′-glyceroxy)-1,2-epoxypropane (7). A mixture of 50% aqueous NaOH (13.3 mL), epichlorhydrin (6) (8.4 mL), and $(Bu)_4NHSO_4$ (0.282 g) was vigorously stirred at room temperature. Alcohol 5 (4.57 g, 19.4 mmol) was added slowly while the temperature was maintained below 25 °C. The resultant mixture was stirred at room temperature for 3.5 h and poured into wet ice (50 mL). The solution was extracted with ethyl acetate (3 × 40 mL). The combined extracts were washed with brine and dried over $MgSO_4$. After evaporation to dryness, the residue was chromatographed on silica gel with cyclohexane/ethyl acetate (60/40) to give the epoxide compound 7 (4.82 g) in 85% yield: yellow liquid; $[\alpha]^{25}_J$ 0° (*c* 0.029, $CHCl_3$); IR 1210, 1240, 1260, 1110 cm^{-1}; ^1H NMR (400 MHz) δ 7.68 and 7.71 (2H, d), 7.44 (3H, m), 5.70 and 5.81 (1H, s), 4.29 (1H, m, H2), 3.71–3.94 (2H, m), 3.48–3.63 (2H, m), 3.30 and 3.48 (1H, m), 3.27 (1H, m), 2.94 (2H, m), 2.73 (1H, dd), 1.20 and 1.26 (9H, s); ^{13}C NMR (100 MHz) δ 143.5–143.6, 127.1–128.0, 92.6–91.8, 76.1–76.2, 74.6–74.7, 72.0–72.1–72.2-72.3, 53.3–53.7, 50.7–50.8, 49.2–49.5, 44.3–44.3, 27.4–28.2; MS (FAB$^+$) *m*/*e* 292.2 (M + H); exact mass calcd for $C_{17}H_{26}NO_3$ (M + H) 292.1913, found 292.1914. Anal. Calcd for $C_{17}H_{25}NO_3$ (291): C, 70.10; H, 8.59; N, 4.81. Found: C, 69.82; H, 8.52; N, 4.66.

(2*RS*,2′*R*,2″*S*,4′*RS*)-(+)-1-(3′-*N*,2′-*O*-benzylidene-*N*-*tert*-butyl-1′-glyceroxy)-3-(2″,3″-*O*-isopropylidene-1″-glyceroxy)propan-2-ol (9). D-α,β-Isopropylideneglycerol (2.178 g, 16.5 mmol) ($[\alpha]^{20}_D$ +11.5° (*c* 5, CH_3OH) (8) was added to a suspension of NaH (1 g) in anhydrous DMF (25 mL). The mixture was stirred and heated to 50 °C under argon until evolution of hydrogen ceased. Epoxide 7 (4.82 g, 16.5 mmol) was then added. The resulting mixture was heated to 80 °C for 36 h, and the reaction was followed by TLC. Water and ice were added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over $MgSO_4$. After evaporation to dryness, the residue was chromatographed on silica gel with cyclohexane/ethyl acetate (40/60) to give the alcohol 9 (6.29 g) in 90% yield: yellow liquid; $[\alpha]^{25}_J$ +14° (*c* 0.021, $CHCl_3$); IR 3480br, 1230–1260, 1050–1150 cm^{-1}; ^1H NMR (400 MHz) δ 7.53 and 7.55 (2H, d), 7.25–7.30 (3H, m), 5.54 and 5.68 (1H, s), 4.25 (1H, m), 4.12 (1H, m), 4.03 (1H, pt), 3.89 and 3.94 (1H, m), 3.70 (1H, m), 3.61 (1H, d), 3.35–3.57 (8H, m), 3.16 and 3.34 (1H, dd), 2.80 (1H, m), 1.34–1.41 (6H, s), 1.04 and 1.11 (9H, s); ^{13}C NMR (100 MHz) δ 143.3–143.4, 127.0–127.9, 109.4, 92.5–91.6, 76.0, 74.6, 73.9, 72.1–72.2–72.4–72.5–72.7–72.8, 69.2–69.3–69.4, 66.5–66.6, 53.2–53.6, 49.0–49.1-49.3, 27.2–28.1, 25.3–26.7; MS (FAB$^+$) *m*/*e* 424.2 (M + H); exact mass calcd for $C_{23}H_{38}NO_6$ (M + H) 424.2699, found 424.2664. Anal. Calcd for $C_{23}H_{37}NO_6$ (423): C, 65.25; H, 8.74; N, 3.30. Found: C, 64.96; H, 8.80; N, 2.99.

(2′*R*,2″*S*,4′*RS*)-(+)-1-(3′-*N*,2′-*O*-benzylidene-*N*-*tert*-butyl-1′-glyceroxy)-3-(2″,3″-*O*-isopropylidene-1″-glyceroxy)propanone (10). To a suspension of 4-Å molecular sieves (powder) in anhydrous CH_2Cl_2 (60 mL) were added *N*-methylmorpholine oxide (NMO) (1.9 g) and alcohol 9 (3.90 g, 9.2 mmol), and the mixture was stirred vigorously at room temperature for 1.5 h. Tetrapropylammonium perruthenate (TPAP) (160 mg) was added, and the resulting mixture was stirred at room temperature for 3 h. The molecular sieve powder was filtered and washed several times with CH_2Cl_2. The combined filtrates were then concentrated. The residue was subjected to column chromatography on silica gel with cyclohexane/ethyl acetate (60/40) to give the ketone 10 in 68% (2.67 g) yield: yellow oil; $[\alpha]^{25}_J$ +11° (*c* 0.023, $CHCl_3$); IR 1740, 1220–1260, 1050–1150 cm^{-1}; ^1H NMR (400 MHz) δ 7.52 and 7.55 (2H, d), 7.24–7.31 (3H, m), 5.54 and 5.67 (1H, s), 4.28 and 4.30 (4H, s), 4.14 –4.25 (2H, m), 4.03 and 4.05 (1H, dd), 3.73 and 3.75 (1H, m), 3.67 (1H, dd), 3.61 (1H, dd), 3.54 (1H, pd), 3.41 and 3.52 (1H, pd), 3.18 and 3.37 (1H, dd), 2.79 and 2.84 (1H, dd and pt), 1.33–1.40 (6H, s), 1.05 and 1.11 (9H, s); ^{13}C NMR (100 MHz) δ 205.7, 143.3–143.4, 127.0–127.9, 109.4, 92.6–91.7, 76.0, 74.9–75.0–75.1–75.2, 74.5–74.6, 74.1, 72.2–72.7, 66.4, 53.2–53.6, 48.8–49.0, 27.2–28.1, 25.3–26.7; MS (FAB$^+$) *m*/*e* 422.3 (M + H); exact mass calcd for $C_{23}H_{36}NO_6$ (M + H) 422.2543, found 422.2527. Anal. Calcd for $C_{23}H_{35}NO_6$ (421): C, 65.56; H, 8.31; N, 3.32. Found: C, 65.41; H, 8.07; N, 3.09.

(*E*,*E*)-(2*R*,6*S*,8*R*)-(+)-2-(Hydroxymethyl)-8-[(*N*-*tert*-butylamino)methyl]-1,4,7,10-tetraoxaspiro[5.5]undecane (11). A solution of ketone 10 (1.903 g, 4.5 mmol) in 20 mL of 1.5 N H_2SO_4 was stirred and heated at 90 °C for 1.5 h. The mixture was then stirred at room temperature overnight. The aqueous phase was made basic with K_2CO_3 to pH 8–9 and saturated with NaCl. The resulting mixture was extracted with $CHCl_3$ (3 × 20 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude spiroacetal 11 was chromatographed on neutral alumina with first $CHCl_3$ and then $CHCl_3$/MeOH (98/2) and obtained in 42% (520 mg) yield: pale yellow wax; $[\alpha]^{25}_J$ +8° (*c* 0.031, $CHCl_3$), ee ≥ 98% (by NMR); IR 3400br, 3280, 1120, 1070–1080 cm^{-1}; ^1H NMR (300 MHz) δ 4.18 (1H, m, *J* = 11.0, 7.5, 4.7, and 2.5 Hz), 4.12 (1H, m, *J* = 11.0, 5.5, 4.5, and 2.6 Hz), 3.86 (1H, dd, *J* = 11.0 and 2.5 Hz), 3.84 (1H, dd, *J* = 11.0 and 2.6 Hz), 3.65 (1H, AB system, *J* = 11.9 and 4.5 Hz), 3.62 (1H, d, *J* = 11.5 Hz), 3.60 (1H, d, J = 11.5 Hz), 3.58 (1H, AB system, *J* = 11.9 and 5.5 Hz), 3.43 (1H, pt, *J* = 11.0 and 11.0 Hz), 3.34 (1H, pt, *J* = 11.0 and 11.0 Hz), 3.24 (2H, d, *J* = 11.5 Hz), 2.63 (1H, AB system, *J* = 11.3 and 7.5 Hz), 2.55 (1H, AB system, *J* = 11.3 and 4.7 Hz), 1.11 (9H, s); ^{13}C NMR (75 MHz) δ 91.7, 69.1, 68.8, 68.7, 67.9, 67.5, 62.1, 50.7, 43.4, 28.7; MS (FAB$^+$) *m*/*e* 276.5 (M + H); exact mass calcd for $C_{13}H_{26}NO_5$ (M + H) 276.1811, found 276.1801. Anal. Calcd for $C_{13}H_{25}NO_5$ (275): C, 56.72; H, 9.09; N, 5.09. Found: C, 56.48; H, 9.17; N, 5.07.

Supplementary Material Available: Additional NMR spectral data of compounds 5, 7, 9, 10, and 11 and ^1H–^1H, ^1H–^{13}C, and chiral shift reagent NMR spectra of 11 (13 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.