Formal Synthesis of a 2- and 8-Functionalized 1,4,7-Trioxa-10-azaspiro[5.5]undecane

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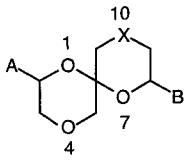
(*E,E*)-(2*R*,6*S*,8*R*)-(+)-*N*-Benzoyl-2,8-dihydroxymethyl-1,4,7-trioxa-10-azaspiro[5.5]undecane was synthesised in seven steps from (*S*)-isopropylideneglycerol as chiral precursor. The final cyclodehydration reaction was carried out on a dihydroxyamidoketone intermediate.

There is permanent interest in the synthesis of spiroacetal structures prompted by the fact that numerous natural products contain this subunit in their skeleton, especially carboxylic polyether antibiotics.[1] In the course of our research directed towards analogues of calcimycin (or A.23187), a well-known calcium ionophore belonging to the polyether antibiotic group, we reported the preparation of new spirobidioxanes bearing functionalized side chains at positions 2 and 8[2,3] which can afford hydrophilic moieties for the design of new calcimycin models. Our study was oriented more specifically towards the *E,E*-isomers, which present helical structures with a C_2 symmetry for identical 2 and 8 substituents.[4,5] These skeletons were all obtained via a cyclodehydration reaction carried out on a ketodiol intermediate.

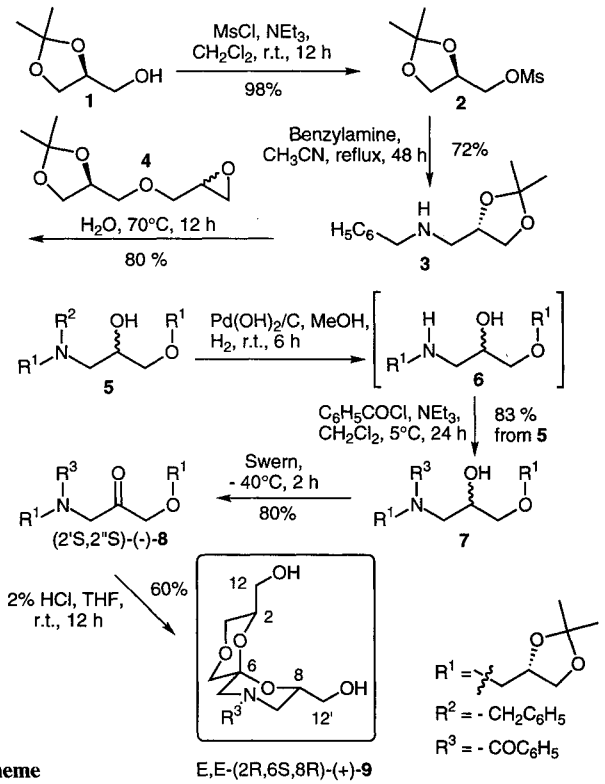
We extended our investigations by introducing a nitrogen atom in place of an oxygen in position 10, which could be further functionalized with an appropriate chain. To our knowledge, no synthesis of such a 2,8-substituted 1,4,7-trioxa-10-azaspiro[5.5]undecane (Figure) has been reported in the literature. However, the unsubstituted compounds 1,4,7-trioxa-10-azaspiro[5.5]undecane and (−)-1,4,7,10-tetraoxaspiro[5.5]undecane have been prepared by Richardson et al.[6,7] by a multistep procedure from D-fructose, and some other related spiranic structures were described containing at least one nitrogen atom, but which was bonded to the anomeric carbon in positions 1 and/or 4.[8]



A = or ≠ B; X = O, $NCOC_6H_5$

Figure

To obtain (2*R*,6*S*,8*R*)-**9** (Scheme), we chose commercially available D-α,β-isopropylideneglycerol (**1**) as starting material. Alcohol **1** was converted into its mesylate **2** in 98% yield. This was refluxed with benzylamine in acetonitrile to give amine **3** (72%). The previously described epoxide **4**[3] reacted with **3** in the presence of water to provide the hydroxyamine **5** (80%). Catalytic hydrogenolysis of **5** in methanol in the presence of palladium hydroxide under neutral conditions[9] gave the hydroxyamine **6**, which was not isolated. The reaction was followed by a selective protection of the amine function with benzoyl chloride[10] in dichloromethane and triethylamine at 5°C.[11] Alcohol **7** was isolated in 83% overall yield from **5**, $[\alpha]_J^{25}$ −19.5 (*c* = 0.064, $CHCl_3$). The Swern oxidation[12] resulted in the chiral ketone **8** (80%) $[\alpha]_J^{25}$ −4 (*c* = 0.082, $CHCl_3$). The deprotection–cyclization of this amidoketone performed in 2% hydrogen chloride in tetrahydrofuran gave the chiral spiroacetal **9** (60%) $[\alpha]_J^{25}$ +36 (*c* = 0.041, $CHCl_3$) with 96% ee.[13]



Scheme E,E-(2R,6S,8R)-(+)-**9**

Because of the presence of the amide group, all the NMR spectra for **7**, **8** and **9** were poorly resolved at room temperature, due to the amide conformers. For **8** and **9** ^1H and ^{13}C NMR spectra were recorded at 370 K in DMSO-d_6 solutions. Under these experimental conditions spectra were conveniently simplified. The results are given in the experimental section; the chemical shifts obtained agree with those given by Richardson et al[7] for the spiroacetal subunit.

In conclusion, we have shown that the synthesis of the chiral 1,4,7-trioxa-10-azaspiroacetal system via a cyclodehydration reaction of a dihydroxyketone is possible using an amido group to protect the amine function. We

are presently working on the total synthesis of calcimycin analogues incorporating this new spirosystem; polyether macrocyclic structures are also under investigation.

Optical rotations were measured on a Perkin-Elmer 141 polarimeter for the mercury J line ($\lambda = 578$ nm) at 25°C (c in g/mL). IR spectra were determined on a Perkin-Elmer 881 spectrometer. NMR spectra were recorded at 300 MHz for ^1H and 75.47 MHz for ^{13}C on a Bruker MSL 300 spectrometer and at 400 MHz for ^1H and 100 MHz for ^{13}C on a Bruker AC 400 spectrometer. $CHCl_3$ ($\delta = 7.27$), $CDCl_3$ ($\delta = 77.1$) and DMSO ($\delta = 2.54$), DMSO-d_6 ($\delta = 49.5$) was used as the respective internal standard expressed in ppm. Mass spectra were obtained from a ZAB-SEQ (FAB^+) spectrometer. Column chromatography was performed on Merck Kieselgel 60. All solvents were distilled before use. Anhydr. Et_3N and benzylamine were obtained after distillation over KOH and anhydr. MeCN over P_2O_5. Satisfactory microanalyses obtained for all new compounds: C ± 0.27, H ± 0.14, N ± 0.12.

(2*R*)-2,3-*O*-Isopropylideneglycerol-1-mesylate (2):
To a solution of alcohol **1** (0.139 mol, 17.1 mL) and Et_3N (25 mL) in CH_2Cl_2 (325 mL), was added dropwise $MeSO_2Cl$ (0.182 mol, 14.2 mL) with stirring at 5°C. Stirring was continued for 12 h at 20°C. The organic phase was washed with 5% $NaHCO_3$, dried ($MgSO_4$) and concentrated. The crude product was chromatographed on silica gel using EtOAc/cyclohexane (30:70) to give the mesylate **2** as a colourless oil; yield: 28.62 g (98%); $[\alpha]_J^{25} - 3$ ($c = 0.028$, $CHCl_3$).

^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 25.0-26.5$ [$(\underline{C}H_3)_2C$], 37.4 (CH_3SO_3), 65.6 (C3), 69.3 (C1), 73.1 (C2), 110.1 [$(CH_3)_2\underline{C}$].

(2*S*)-1-*N*-Benzylamino-2,3-*O*-isopropylideneglycerol (3):
A solution of mesylate (2*R*)-**2** (7.88 g, 37.5 mmol) and benzylamine (16.2 g, 150 mmol) in MeCN (100 mL) was refluxed for 48 h. Evaporation of the solvent was followed by treatment with 10% $NaHCO_3$. The product was extracted with EtOAc, the organic phase dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography on silica gel (cyclohexane/EtOAc, 20:80) gave **3** as a colourless oil; yield: 6.01 g (72.5%); $[\alpha]_J^{25} = +5.5$ ($c = 0.054$, $CHCl_3$).

^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 25.5-26.9$ [$(\underline{C}H_3)_2C$], 51.8 ($\underline{C}H_2C_6H_5$ or C1), 54.0 (C1 or $\underline{C}H_2C_6H_5$), 67.6 (C3), 75.5 (C2), 109.1 [$(CH_3)_2\underline{C}$], 127.0 to 128.4 (CH_{arom}), 140.2 (C_{arom}).

(2′*S*,2*RS*,2″*S*)-*N*-Benzyl-1-*N*-(2′,3′-*O*-isopropylideneglycerol)amino-3-(2″,3″-*O*-isopropylideneglycerol)propan-2-ol (5):
A mixture of (2*S*)-**3** (5.53 g, 25 mmol), (2*RS*,2′*S*)-1,2-epoxy-3-(2′,3′-*O*-isopropylideneglycerol)propane **(4)**[3] (4.17 g, 25 mmol) and H_2O (3.8 mL) was vigorously stirred at 70°C for 12 h. The water was then eliminated under vacuum. The crude product was chromatographed on a column of silica gel (cyclohexane/EtOAc, 60:40) to give the alcohol **5** (yellow oil); yield: 8.22 g (80%); $[\alpha]_J^{25} = +13$ ($c = 0.054$, $CHCl_3$).

IR (neat): $\nu = 3470\ cm^{-1}$.

^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.34-1.37-1.39-1.42$ [12H, 4s, $2\times(C\underline{H}_3)_2C$], 2.64 (2H, m, H1 or H1′), 2.70 (2H, m, H1 or H1′), 3.45–3.57 (4H, m, H1″-H3), 3.51 (2H, d, $C\underline{H}_2C_6H_5$), 3.60–3.90 (4H, m, H2, H3′B, H3″B, OH), 4,01 (2H, m, H3′A-H3″A), 4.23 (2H, m, H2′-H2″), 7.30 (5H, m, C_6H_5).

^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 25.6-26.8$ [$2\times(\underline{C}H_3)_2C$], 57.4–57.5–57.6 (C1, C1′), 59.9–60.0 ($\underline{C}H_2C_6H_5$), 66.7 (C3″), 67.6 (C2), 67.9–68.2 (C3′), 72.6 (C1″), 74.0 (C3), 74.1 (C2′ or C2″), 74.7 (C2′ or C2″), 109.3–109.4 [$2\times(CH_3)_2\underline{C}$], 127.4–128.4–129.0 ($CH_{arom}$), 138.6 ($C_{arom}$).

MS (EI): m/z (%) = 409.2 (M^+, 0.1), 308.1 (38.6), 234.1 (23.8), 134.1 (21), 91 (100), 43.1 (18.5).

(2′*S*,2*RS*,2″*S*)-*N*-Benzoyl-1-*N*-(2′,3′-*O*-isopropylideneglycerol)amino-3-(2″,3″-*O*-isopropylideneglycerol)-propan-2-ol (7):
Debenzylation: To a solution of alcohol **5** (3.00 g, 7.3 mmol) in anhydr. MeOH was added a powdered Pearlman catalyst (20% $Pd(OH)_2$ on carbon) (367 mg). Hydrogenolysis was performed in a Parr's apparatus at 60 psi for 6 h at r.t. The mixture was filtered through a pad of Celite, and the Pd/C was rinsed several times with MeOH. The solvent was evaporated under vacuum to give a crude product pure enough for the next step.

Selective Protection of the Amine Function: To the crude product **6** (7.3 mmol), were added CH_2Cl_2 (30 mL) and Et_3N (0.808 g, 8 mmol). The mixture was cooled to 5°C, and benzoyl chloride (0.93 mL, 8 mmol) was added dropwise. The resulting solution was stirred at 5°C for 24 h. The solvent was evaporated and the crude product was chromatographed on silica gel (EtOAc/cyclohexane, 70:30, 80:20 and EtOAc). Alcohol **7** was isolated as a colourless liquid; yield: 2.58 g (83% from **5**); $[\alpha]_J^{25} = -19.5$ ($c = 0.064$, $CHCl_3$).

IR (neat): $\nu = 3440$, $1630\ cm^{-1}$.

^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.21-1.42$ [12H, br, $2\times(C\underline{H}_3)_2C$], 3.18–3.70 (10H, unresolved), 3.87–4.50 (6H, unresolved), 7.34 ($5H_{arom}$, m).

^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 25.2-26.5$ [$2\times(\underline{C}H_3)_2C$], 49.3–50.2–53.9 (C1–C1′), 66.4 (C3″), 67.1–67.2 (C3′), 67.9–69.0–69.8 (C2), 72.3 (C1″), 73.1–73.5 (C3), 74.0–74.9 (C2′), 74.5 (C2″), 109.2–109.3 [$2\times(CH_3)_2\underline{C}$], 126.9–127.4–128.2–129.4 (CH_{arom}), 136.0 (C_{arom}), 175.6 (C=O).

MS (EI): m/z (%) = 424.2 ($M + H^+$, 0.1), 408 (5.3), 105 (100), 77 (27), 43 (37.2).

(2′*S*,2*RS*,2″-*S*)-*N*-Benzoyl-1-*N*-(2′,3′-*O*-isopropylideneglycerol)amino-3-(2″,3″-*O*-isopropylideneglycerol)-propan-2-one (8):
A solution of **7** (6.40 g, 15.1 mmol) and anhydr. DMSO (1.67 mL) in anhydr. CH_2Cl_2 (60 mL) was cooled to −78°C. Oxalyl chloride (1.86 mL) in anhydr. CH_2Cl_2 (30 mL) was carefully added. The resulting mixture was stirred (< −40°C) for 1 h. Et_3N (8.5 mL) was added and stirring continued for 1 h at −40°C. The mixture was left to stand at r.t. The organic phase was washed with 10% $NaHCO_3$ (60 mL), dried and concentrated. The crude ketone was chromatographed on a column of silica gel (EtOAc/cyclohexane, 80:20 then EtOAc) to give (2′*S*,2″*S*)-**8** as a yellow oil; yield: 5.12 g (80%); $[\alpha]_J^{25} = -4$ ($c = 0.082$, $CHCl_3$).

IR (neat): $\nu = 1740$, $1640\ cm^{-1}$.

^1H NMR (400 MHz, DMSO-d_6, 370 K): $\delta = 1.34-1.37$ [12H, 2s, $2(C\underline{H}_3)_2C$], 3.45 (2H, m), 3.55 (2H, m), 3.65 (2H, m), 4.02 (2H, s, H1), 4.19 (2H, s, H3), 4.26 (2H, m), 4.43 (2H, m, H2′, H2″).

^{13}C NMR (100 MHz, DMSO-d_6, 370 K): $\delta = 24.7-25.9$ [$2\times(\underline{C}H_3)_2C$], 50.4–53.9 (C1′, C1), 65.4 (C3″), 66.1 (C3′), 71.6 (C1″), 73.6 (C2′ or C2″), 73.7 (C2″ or C2′), 74.2 (C3), 107.9–108.0 [$2\times(CH_3)_2\underline{C}$], 125.9–127.6–128.6 ($CH_{arom}$), 135.6 ($C_{arom}$), 170.8 (C=O), 202.8 (C2).

MS (EI): m/z (%) = 422 ($M + H^+$, 0.1), 276 (27.8), 105 (100), 77 (19.5), 43 (16.6).

(*E*,*E*)-(2*R*,6*S*,8*R*)-(+)-*N*-Benzoyl-2,8-dihydroxymethyl-1,4,7-trioxa-10-azaspiro[5.5]undecane (9):
To a solution of 2% HCl (0.4 mL) in THF (20 mL) was added ketone (2′*S*,2″*S*)-**8** (1.436 g, 3.4 mmol) and the mixture was stirred at r.t. for 12 h. 10 N NaOH (0.40 mL) was added to slightly basify the reaction mixture which was filtered and concentrated. The residue was chromatographed on a column of silica gel (EtOAc/MeOH, 95:5) to give the spiroacetal (2*R*,6*S*,8*R*)-**9** as a yellow viscous liquid; yield: 0.657 g (60%); $[\alpha]_J^{25} = +36$ ($c = 0.041$, $CHCl_3$).

IR (neat): $\nu = 3430$, $1620\ cm^{-1}$.

^1H NMR (400 MHz, DMSO-d_6, 370 K): $\delta = 2.89$ (1H, pseudo t, $J = 13$ Hz), 3.0 (1H, d, $J = 13$ Hz), 3.26 (1H, d, $J = 12$ Hz), 3.29 (1H, pseudo t, $J = 11$ Hz), 3.42–3.64 (4H, m), 3.59 (1H, d, $J = 12$ Hz), 3.76 (1H, m), 3.83 (1H, pseudo q, $J = 3$, 11 Hz), 3.96 (2H, m), 4.21 (1H, m), 7.47 (5H, m).

^{13}C NMR (100 MHz, DMSO-d_6, 370 K): $\delta = 44.9$ (C9), 48.3 (C11), 60.8–61.6 (C12, C12′), 66.8 (C3), 68.2 (C2-C8), 68.6 (C5), 91.5 (C6), 126.4–127.5–128.6 (CH_{arom}), 135.5 (C_{arom}), 169.5 (C=O).

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