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SYNTHESIS OF THE C_2-SYMMETRIC 1,3-DICYCLOHEXYL-1,3-PROPANEDIOL AND DIAMINE ENANTIOMERS

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ABSTRACT: The parent C_2-symmetric (R,R)- and (S,S)-1,3-dicyclohexyl-1,3-propanediols and diamines are readily obtained from the corresponding diphenyldiol precursors.

Modern asymmetric synthesis relies heavily on ready access to varied and efficient auxiliaries and ligands which may be utilised in stoichiometric or preferably catalytic quantities to induce product chirality. The recent literature is littered with numerous examples of such applications.[1] Amongst the various compound classes, examples which possess C2-symmetry have achieved a certain prominence.[2] To this end, we have recently reported the syntheses of the optically pure (R,R)- and (S,S)-1,3-diphenyl-1,3-propanediols **1**[3] as well as several dinitrogen derivatives **2-5** (*for clarity, only one enantiomer is depicted*) thereof.[4]

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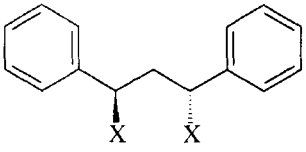
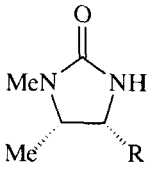


X = OH, (R,R)- **1**
X = NH_2, (R,R)- **2**
X = NHTos, (R,R)- **3**
X = NHBn, (R,R)- **4**
X = NHTFA, (R,R)- **5**

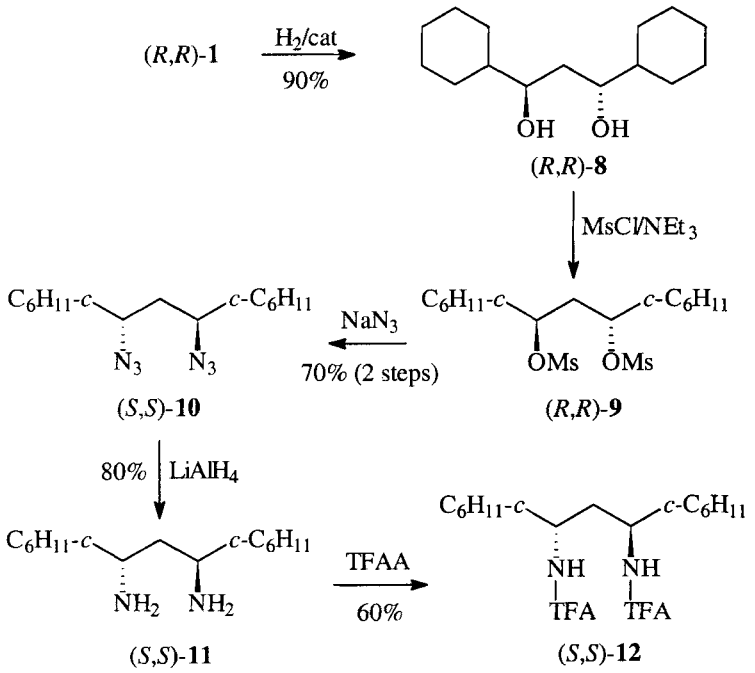


6 R = Ph
7 R = cycloC_6H_{11}

Because of the increased steric demand of the saturated ring, the potential value of cyclohexyl substituents has long been recognised.[5] We have demonstrated the impact of cyclohexyl versus phenyl substituents in studies which exploited the imidazolidin-2-ones **6** and **7**.[6-8] We thus felt that the cyclohexyl analogues **8** of the diols **1** might be useful additions for the subsequent studies of the effectiveness of these C_2-symmetric ligands. These compounds have only been previously reported in racemic form.

Since we had ready access to multigram quantities of both enantiomers of **1**, these compounds were obvious precursors for the desired saturated analogues. The reported method of Blum and co-workers[9] for the hydrogenation of aromatic systems had previously proven efficient in the synthesis of **7**.[6] This protocol, which uses a rhodium chloride / aliquat 336® catalyst system was not envisaged to be accompanied by any attendant racemisation problems.

Following this general procedure both (*R*,*R*)- and (*S*,*S*)-**1** were converted smoothly into the dicyclohexyl analogues **8**[10] in excellent isolated yield (**Scheme**). Analysis of both the ^1H and ^{13}C NMR spectra of the products indicated the absence of any



Scheme : Preparation and interconversion of dicyclohexyl ligands.

corresponding meso diol, whilst chiral shift reagent studies provided proof of their optical integrity.

With these parent diols **8** in hand, the general utility of diamines as ligands in asymmetric transformations[11] prompted us to prepare the as yet unreported primary dicyclohexyl diamines (*R,R*)- and (*S,S*)-**11**. For this, a route *via* substitution of the mesylate **9** and reduction of the azide product **10** reproducibly afforded the desired diamines **11** in very good overall yields. They were unfortunately isolated as slightly impure oils that were not amenable to final purification by chromatography. Distillation and attempted isolation as salts were

also unsuccessful as means of obtaining these compounds in analytically pure form. As a consequence, the diamines **11** were derivatised and characterised as their bistrifluoroacetates **12**. The spectral data of these enantiomerically pure compounds (*R,R*)- and (*S,S*)-**12** was entirely consistent with the proposed structures.

EXPERIMENTAL:

The diol enantiomers **1** were prepared as previously described.[3] Other reagents were obtained commercially and used without further purification. Melting points are reported uncorrected. All N.M.R. spectra were recorded on a Bruker ADVANCE DPX 300 spectrometer at 25°C in $CDCl_3$, unless otherwise indicated. HRMS were measured on a VG Autospec Mass Spectrometer and optical rotations were recorded at 20°C using a Optical Activity PolAAr 2001 polarimeter. Column chromatography refers to slurries of Merck silica gel 60 (70-230 mesh) with preadsorption on Merck silica gel 60 (35-70 mesh, and thin layer chromatography refers to aluminium plates coated with Merck Kieselgel 60 F_{254}.

(-)-(S,S)-1,3-Dicyclohexyl-1,3-propanediol (8).

A thick walled glass container was charged with (*S,S*)-**1** (200 mg, 0.88 mmol), dichloroethane (8 ml), water (4 ml), rhodium chloride (22.98 mg, 0.088 mmol, 10 mol%) and Aliquat 336® (170 mg, 353 mmol, 40 mol%). A pressure of 50 psi of hydrogen was applied and the reaction mixture shaken vigorously for 22h. Water (15 ml) and dichloromethane (15 ml) were added and the organic layer separated.

The aqueous phase was extracted with further dichloromethane (3x15 ml), the organics combined, washed with water (15 ml) and brine (15 ml), dried with $MgSO_4$ and the solvents removed *in vacuo*. The crude product was introduced onto a silica gel column and eluted with 20% ethyl acetate-light petroleum to yield the product (*S,S*)-**8** (191 mg, 0.808 mmol, 91.5%), which was recrystallised from dichloromethane as fine white needles, mp. 138-139.5°C; lit.[10] (rac.) 148-150°C; $[\alpha]_D$ -40.9° (c 0.2, CH_3OH); ^1H NMR δ 0.91-1.49 (m, 12H), 1.60-1.95 (m, 12H), 2.23 (d, *J* 4 Hz, 2H) and 3.65 (dt, *J* 11 and 6 Hz, 2H); ^{13}C NMR δ 25.6, 25.7, 26.0, 28.1, 28.5, 35.8, 43.1, 73.1.

(+)-(R,R)-1,3-Dicyclohexyl-1,3-propanediol (8).

Using (*R,R*)-**1** (200 mg, 0.88 mmol) and the above method (*R,R*)-**8** was obtained in 90.5% yield and recrystallised from dichloromethane as fine white needles mp. 138-139 °C; $[\alpha]_D$ 40.5° (c 0.2, CH_3OH). Spectral data were identical to those of the (*S,S*)-compound.

(S,S)-1,3-Dicyclohexyl-1,3-propanediazide (10).

The (*R,R*)-dicyclohexyl diol **8** (309 mg, 1.30 mmol) and triethylamine (330 mg, 3.26 mmol) were stirred in THF (5 ml) at 0°C and methanesulfonyl chloride (0.24 ml, 3.10 mmol) added dropwise *via* syringe. The temperature of the reaction mixture containing the dimesylate **9** was allowed to rise to room temperature and stirred overnight. Precipitated triethylamine hydrochloride was filtered off and the filtrate washed with further portions of THF (3x2 ml). The THF was removed *in*

vacuo, and DMF (1.5 ml) and sodium azide (337 mg, 5.19 mmol) added. The reaction mixture was stirred at 60-80°C overnight and the DMF removed *in vacuo*. Ether (25 ml) and water (25 ml) added, the water layer was washed with a further portion of ether (25 ml), the organic fractions combined, washed with brine (20 ml), dried ($MgSO_4$) and the solvents removed *in vacuo*. The crude material was purified by column chromatography to afford the slightly impure product as a pale yellow oil (262 mg, 0.903 mmol, 69.4%); IR ν_{max} 2928, 2854 and 2101 (N_3); ^{1}H NMR δ 1.00-1.84 (m, 24H) and 3.32 (dt, *J* 8 and 6 Hz, 2H); ^{13}C NMR δ 25.5, 25.6, 25.7, 28.4, 29.1, 32.9, 42.6, 65.2; HRMS Calcd. for $C_{15}H_{26}N_6$ M^++1, 291.2297; Found 291.2748.

(R,R)-1,3-Dicyclohexyl-1,3-propanediazide (10).

Using the (*S,S*)-diol (330 mg, 1.39 mmol) and the above method the (*R,R*)-diazide was obtained in 66.4% yield as a slightly impure pale yellow oil. Spectral data was identical to those of the (*S,S*)-enantiomer.

(R,R)-1,3-Dicyclohexyl-1,3-propanediamine (11).

The (*R,R*)-diazide (167 mg, 0.58 mmol) was dissolved in THF (10 ml) and stirred at room temperature while $LiAlH_4$ (43.7 mg, 1.15 mmol) was added portionwise. The reaction mixture was refluxed for 3h, cooled and moist ether (30 ml) added. The reaction mixture was stirred for a further 5 minutes before the addition of $MgSO_4$. Filtration and removal of the solvents *in vacuo* revealed the product **11** as a slightly impure clear oil (120 mg, 0.51 mmol, 87.6%); ^{1}H NMR δ 0.77-2.08 (m,

26H) and 4.09 (broad s, 4H); ^{13}C NMR δ 26.4, 26.5, 26.7, 29.3, 29.5, 33.9, 42.9, 54.2.

(S,S)-1,3-Dicyclohexyl-1,3-propanediamine (11).

Using the (*S,S*)-diazide (154 mg, 0.53 mmol) and the above method the (*S,S*)-diamine was obtained in 80.6% yield as a slightly impure clear oil. Spectral data was identical to those of the (*R,R*)-isomer.

(-)-(R,R)-N,N'-Bis(trifluoroacetyl)-1,3-dicyclohexyl-1,3-propanediamine (12).

The (*R,R*)-diamine (120 mg, 0.50 mmol) and pyridine (96 mg, 1.21 mmol) were stirred in THF (20 ml) at room temperature, TFAA (0.173 ml, 1.21 mmol) was added dropwise *via* syringe and the reaction mixture stirred overnight. Ether (30 ml) and HCl (1M, 20 ml) were added, the organic layer separated, washed with saturated sodium bicarbonate solution (15 ml), water (15 ml) and brine (15 ml), dried ($MgSO_4$) and the solvents removed *in vacuo*. The oily residue was purified by column chromatography using 10-20% ethyl acetate-light petroleum as the gradient eluent to yield the product **12** (173 mg, 0.40 mmol, 79.8%) which was recrystallised from chloroform-light petroleum as fine white needles mp. 196.5-197.5°C. $[\alpha]_D$ -9.4° (c 0.1, MeOH); IR ν_{max} 3324, 2932, 2858, 1692, 1189; ^{1}H NMR δ 0.76-1.19 (m, 9H), 1.26-1.74 (m, 11H), 1.76-1.97 (m, 4H), 3.68-3.82 (m, 2H) and 7.96 (d, *J* 8 Hz, 2H); ^{13}C NMR δ 26.7, 26.9, 29.4, 30.3, 32.5, 43.4, 52.3, 121.9 (q, *J* 287.3 Hz, CF_3), 162.2 (q, *J* 36.3 Hz, CO); HRMS Calcd. for $C_{19}H_{28}N_2O_2F_6$ 430.2055; Found 430.2035. Anal. Calcd. for $C_{19}H_{28}N_2O_2F_6$ C, 53.0; H, 6.6; N, 6.5; Found: C, 53.0; H, 6.6; N, 6.4.

(+)-(S,S)-N,N'-Bis(trifluoroacetyl)-1,3-dicyclohexyl-1,3-propanediamine (12).

Using the (*S,S*)-diamine (65 mg, 0.27 mmol) and the above method the (*S,S*)-bistrifluoroacetate was obtained in 60.4% yield as fine white needles mp. 195-195.5 °C. $[\alpha]_D$ 9.3° (c 0.25, MeOH). Spectral data was identical to those of the (*R,R*)-compound.

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