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TETRAHEDRON: *ASYMMETRY*

Synthesis and resolution of 2,2-dimethyl-1,3-diphenyl-1,3-propanediol, a new C_2-symmetric and conformationally rigid acyclic diol†

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Abstract—Diastereomerically pure (+)- and (−)-2,2-dimethyl-1,3-diphenyl-1,3-propanediols were synthesized starting from diethyl malonate and resolved through diesters of (−)-camphanic acid and also *N*-carbethoxy-L-proline. The absolute configuration of the (−)-enantiomer was established by X-ray crystallography.

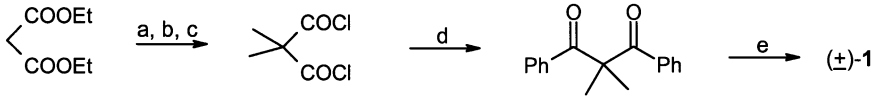
1. Introduction

C_2-Symmetric chiral diols are known to be useful chiral auxiliaries and ligands in asymmetric synthesis.[1] Amongst these, hydrobenzoin (a 1,2-diol),[2] BINOL (a 1,4-diol)[3] and TADDOL (a 1,4-diol)[4] have been applied with particular success. Although a few C_2-symmetric chiral 1,3-diols are known in the literature,[5] none have proved to be very good sources of chirality. It is important that the diol is conformationally rigid for it to be an effective chiral auxiliary/ligand. The present report describes our efforts to develop one such chiral molecule, (+)-/(−)-2,2-dimethyl-1,3-diphenyl-1,3-propanediol **1**.

2. Results and discussion

Chiral 1,3-diols can be obtained via the following three methods: (a) diastereoselective reduction of chiral β-hydroxy ketones; (b) enantioselective reduction of β-diketones and (c) diastereoselective reduction of β-diketones followed by resolution of the resulting diol. For the synthesis of the title diol **1**, the first two methodologies failed: we were unable to bring about an enantioselective Mukaiyama aldol condensation between benzaldehyde and the silyl enol ether of isobutyrophenone.[6] Also, attempts at reduction using either BH_3 in the presence of an oxazaborolidine catalyst[7] or Ipc_2BCl[8] failed to reduce the starting dione, dimethyl dibenzoyl methane **2**. We therefore resorted to the third option, reduction followed by resolution. The required dione **2** could be easily obtained in four known steps as shown in Scheme 1.[9,10]

Prior to our work, Maier et al. had described the reduction of the diketone **2** with LAH in moderate diastereoselectivity.[10] In order to enhance the selectivity, we examined various reducing agents including $LiBH_4$, $Zn(BH_4)_2$ and a few modified reagents derived



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Scheme 1. *Reagents and conditions*: (a) Me_2SO_4, NaOEt; (b) KOH/MeOH, reflux; (c) $SOCl_2$, reflux; (d) C_6H_6, $AlCl_3$; (e) $LiAl(O^tBu)_2H_2$, THF, 0°C.

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† Dedicated to Professor H. C. Brown on his 90th birthday.

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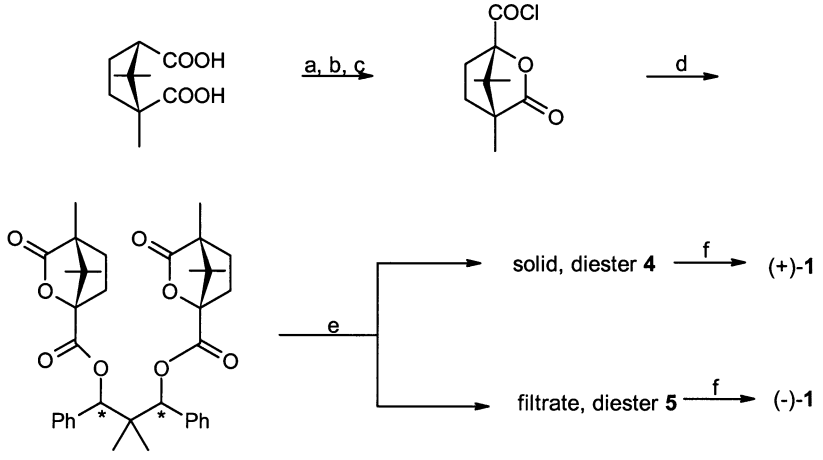
from LAH. It was found that lithium di-*tert*-butoxyaluminium hydride reduces **2** with very high diastereoselectivity, providing (±)-**1** in almost quantitative yield. No *meso*-diol was detected by ^{1}H NMR.

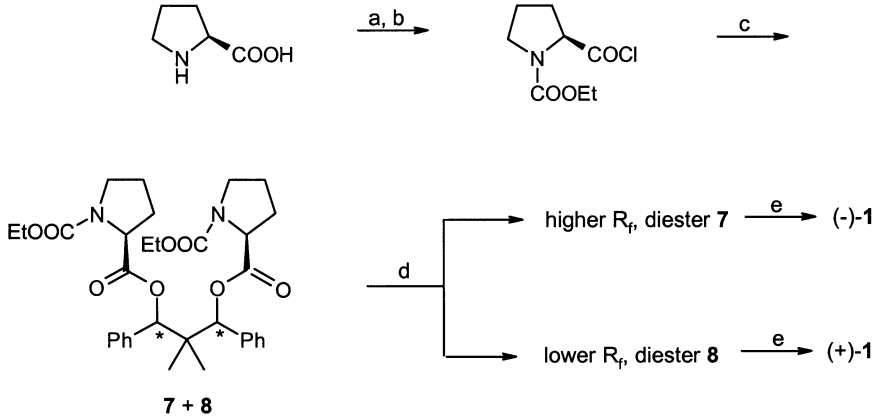
We then examined various procedures known for the resolution of the diols. These included the separation of diastereomeric ester derivatives of (−)-menthylacetic acid,[11] (+)-hydratropic acid,[12] (−)-5-oxo-2-tetrahydrofurancarboxylic acid,[13] ketals of (+)-camphor[14] and resolution with boric acid/L-proline.[15] However all of these methods failed to resolve (±)-**1**. We were eventually successful with the esters of (−)-camphanic acid.[16] It was found that the diesters **4** and **5** could be easily separated by crystallization from toluene. The diastereomeric purity could be monitored by TLC and estimated by ^{1}H NMR (benzylic protons). The solid diester **4** was obtained in >99% de, whereas the diester **5** obtained from the mother liquor was of 66% de. These were saponified with methanolic KOH to obtain (+)-**1** (>99% ee) and (−)-**1** (66% ee), respectively (Scheme 2). The enantiomeric purity was further confirmed by chiral HPLC analysis on a Chiralcel-OD® column.

Since (−)-camphanic acid is an expensive resolving reagent, we examined the possibility of using *N*-carbethoxy-L-proline, a cheap alternative. To the best of our knowledge, this acid has never been used as a resolving agent for alcohols or amines. It was obtained in almost quantitative yield by reacting sodium L-prolinate with ethyl chloroformate in aqueous THF. The acid was converted to the corresponding acid chloride **6** by treatment with $SOCl_2$ at room temperature for 12 h. Esterification of (±)-**1** with 2.5 equiv. of **6** gave the diastereomeric diesters **7** and **8** which could not be separated by crystallization, but were separable by flash chromatography on silica gel. Subsequent saponification of the diesters provided (−)-**1** (40% yield, >99% ee) from the less polar diester **7** and (+)-**1** (33% yield, >99% ee) from more polar diester **8** as depicted in Scheme 3.

Both the resolution procedures described above were optimized at 20 mmol of the diol. We recommend the first method (crystallization) for procuring multigram quantities of diastereomerically pure (+)-diol. On the other hand, when both enantiomers are required in relatively small amounts, the second procedure (separation by chromatography) can be adopted. Finally the



Scheme 2. *Reagents and conditions*: (a) PCl_5; (b) 0.1N H_2SO_4, reflux; (c) $SOCl_2$, reflux; (d) (±)-**1**, C_5H_5N, CH_2Cl_2, 0°C; (e) crystallization; (f) KOH/MeOH, reflux.



Scheme 3. *Reagents and conditions*: (a) ClCOOEt, Na_2CO_3, H_2O/THF; (b) $SOCl_2$; (c) (±)-**1**, C_5H_5N, CH_2Cl_2, 0°C; (d) chromatography; (e) KOH/MeOH, reflux.

absolute configuration of the diol was determined by X-ray crystallography using the anomalous dispersion method. It was found that (−)-**1** has (*R*,*R*)-configuration. The ORTEP diagram reveals that there are two molecules in the asymmetric unit (Fig. 1).

3. Conclusion

We have thus established synthesis resolution and absolute configuration of a new chiral C_2-symmetric acyclic 1,3-diols. It is likely that the procedure can be extended to several variations in the structure depending upon the starting material. We are currently examining these diols as chiral auxiliaries as well as ligands for certain enantioselective reactions.

4. Experimental

4.1. General

Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Dichloromethane was distilled from calcium hydride and stored over molecular sieves. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 200. Optical rotations were measured on Bellingham+Stanley ADP220 digital polarimeter. HPLC analysis was performed on DIACEL Chiralcel-OD® column. The diketone **2** was synthesized starting from diethylmalonate as described in the literature.[9,10] (−)-Camphanic acid was prepared from (+)-camphoric acid following the literature procedure.[17]

4.2. Reduction of 2 to (±)-1

To a stirred suspension of LAH (3.42 g, 90 mmol) in anhydrous THF (30 mL), *t*-butyl alcohol (17.2 mL, 180 mmol) was added dropwise. The resulting solution was cooled to 0°C and treated dropwise with a solution of the diketone **2** (7.56 g, 30 mmol) dissolved in THF (30 mL). After the addition, stirring at 0°C was continued for 2 h. The reaction was quenched by the addition of MeOH (5 mL) followed by water (5 mL). The resulting mixture was filtered and the solid was repeatedly washed with EtOAc. Combined organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was crystallized from aqueous MeOH to obtain pure (±)-**1** (6.9 g, 90% yield); >99% de by ^{1}H NMR; mp 110–112°C; IR (cm^{-1}) 3288; ^{1}H NMR δ 0.81 (s, 6H), 1.85 (br. s, 2H), 4.62 (s, 2H), 7.25–7.35 (m, 10H); ^{13}C NMR δ 21.3, 41.1, 80.8, 127.2, 127.5, 127.8, 141.4. Anal. calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86; found: C, 79.75; H, 7.96%.

4.3. Preparation of (−)-camphanoyl chloride 3

The literature procedure was slightly modified as follows. A mixture of (−)-camphanic acid (9.9 g, 50 mmol) and thionyl chloride (30 mL) was heated under reflux for 3 h. Excess thionyl chloride was distilled off and the remaining traces were removed under vaccum to obtain an almost quantitative yield of **3**, mp 72–73°C (lit.[17] 69–71°C). It was dissolved in CH_2Cl_2 to obtain a 1 M stock solution.

4.4. Preparation and resolution of diesters 4 and 5

To the above described solution of **3** (50 mL, 50 mmol), a solution of (±)-**1** (5.12 g, 20 mmol) in anhydrous pyridine (12.9 mL, 160 mmol) was added dropwise at 0°C. The progress of the reaction was monitored by TLC. After 2 h the reaction mixture was diluted with CH_2Cl_2 and washed successively with 1N HCl, water and saturated aqueous $NaHCO_3$. The organic solution was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain a mixture of the diesters **4** and **5** (12 g, 98% crude yield). The above

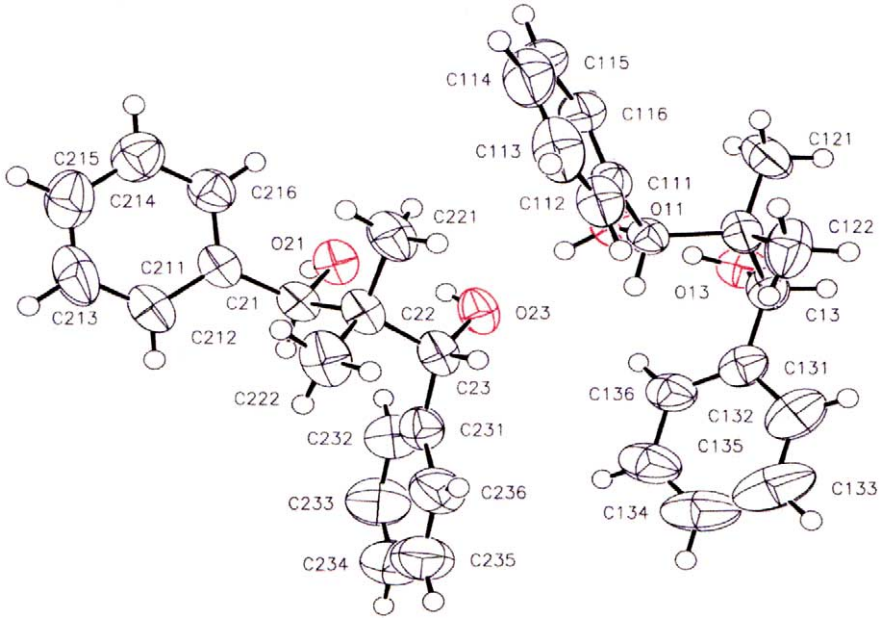


Figure 1. ORTEP diagram of (*R*,*R*)-(−)-**1**.

crude mixture was dissolved in the minimum volume of hot toluene and cooled gradually to 0°C over a period of 24 h. The crystals were separated from the mother liquor and recrystallized from toluene to obtain pure **4** (5.2 g, 43% overall yield); ^{1}H NMR revealed >99% de of the product: mp 234–235°C; $[\alpha]_D$ +1.6 (*c* 1, $CHCl_3$); IR (cm^{-1}) 1794, 1747; ^{1}H NMR δ 0.86 (s, 6H), 0.88 (s, 6H), 1.03 (s, 6H), 1.12 (s, 6H), 1.49–2.61 (m, 8H), 6.05 (s, 2H), 7.30–7.40 (m, 10H); ^{13}C NMR δ 9.5, 16.4, 18.1, 28.8, 30.9, 42.0, 54.2, 54.8, 78.6, 90.9, 127.6, 128.2, 136.5, 166.5, 178.3. Anal. calcd for $C_{37}H_{44}O_8$: C, 72.06; H, 7.19; found: C, 71.93; H, 7.54%.

4.5. Preparation of *N*-carbethoxy-L-proline

A solution of L-proline (6.9 g, 60 mmol) in water (60 mL) at 0°C, was treated with sodium carbonate (7.63 g, 72 mmol) and the resulting solution was stirred for 30 min. To this mixture, a solution of ethyl chloroformate (6.9 mL, 72 mmol) in THF (15 mL) was added dropwise at 0°C. After the addition, stirring was continued for 2 h. The reaction mixture was brought to ambient temperature and washed with $CHCl_3$ (30 mL). The aqueous portion was acidified to pH 3 and extracted with $CHCl_3$. The extract was dried over anhydrous Na_2SO_4 and concentrated to obtain *N*-carbethoxy-L-proline as a viscous liquid which solidifies upon trituration with cold petroleum ether; 11 g (quantitative yield); mp 65°C; $[\alpha]_D$ −98.2 (*c* 1, $CHCl_3$); IR (cm^{-1}): 1740, 1664, 1651; ^{1}H NMR δ 1.08–1.50 (m, 3H), 1.75–2.44 (m, 4H), 3.29–3.83 (m, 2H), 3.96–4.58 (m, 3H), 10.53 (br. s, 1H); ^{13}C NMR δ 14.2, 23.1, 23.9, 29.4, 30.5, 46.2, 46.4, 58.4, 58.7, 61.3, 61.4, 154.7, 155.5, 176.0, 176.5. Anal. calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48; found: C, 51.38; H, 7.17; N, 7.29%.

4.6. Preparation of the acid chloride 6

N-Carbethoxy-L-proline (9.35 g, 50 mmol), thionyl chloride (10 mL) and benzene (10 mL) were stirred at room temperature for 12 h (reaction monitored by the rate of HCl and SO_2 evolution). Benzene and excess thionyl chloride were removed under reduced pressure using a rotavapor. The light yellow residue was almost pure **6** in quantitative yield. It was dissolved in CH_2Cl_2 to obtain a 1 M solution, which can be kept for several days with gradual decomposition.

4.7. Preparation of the diesters 7 and 8

To the above described solution of **6** (50 mL, 50 mmol), a solution of (±)-**1** (5.12 g, 20 mmol) in anhydrous pyridine (12.9 mL, 160 mmol) was added dropwise at 0°C. The progress of the reaction was monitored by TLC. After 2 h the reaction mixture was diluted with CH_2Cl_2 and washed successively with 1N HCl, water and saturated aqueous $NaHCO_3$. The organic solution was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain a mixture of the diesters **7** and **8** as a viscous liquid (11.4 g, 96% crude yield).

Since the two diesters were easily separable on TLC, they were purified by flash chromatography on silica gel (300–400 mesh) using petroleum ether–ethyl acetate (4:1) as the eluent. The diester **7** (R_f = 0.37) eluted first; 4.78 g (42% overall yield); mp 62°C; $[\alpha]_D$ −84.3 (*c* 1, $CHCl_3$); IR (cm^{-1}): 1742, 1707, 1693; ^{1}H NMR δ 0.67–1.1 (m, 9H), 1.21–1.49 (m, 2H), 1.71–2.41 (m, 9H), 3.43–4.62 (m, 10H), 5.66–5.93 (m, 2H), 7.17–7.44 (m, 10H); ^{13}C NMR δ 14.2, 14.9, 18.4, 23.7, 24.2, 29.1, 29.3, 30.4, 41.9, 46.3, 46.8, 59.5, 61.4, 78.2, 127.8, 128.2, 137.0, 137.3, 154.7, 155.1, 171.4. Anal. calcd for $C_{33}H_{42}N_2O_8$: C, 66.65; H, 7.12; N, 4.71; found: C, 66.56; H, 7.55; N, 4.56%.

The diester **8** (R_f = 0.28) eluted next; 4.1 g (36% overall yield); mp 68°C; $[\alpha]_D$ +15.1 (*c* 1, $CHCl_3$); IR (cm^{-1}): 1749, 1715, 1699; ^{1}H NMR δ 0.73–0.99 (m, 9H), 1.18–1.36 (m, 2H), 1.82–2.41 (m, 9H), 3.37–4.64 (m, 10H), 5.76–5.96 (m, 2H), 7.22–7.47 (m, 10H); ^{13}C NMR δ 14.3, 14.7, 18.3, 23.5, 24.3, 41.9, 46.3, 46.7, 59.0, 59.3, 61.2, 78.3, 127.7, 128.2, 137.4, 154.6, 155.0, 171.5. Anal. calcd for $C_{33}H_{42}N_2O_8$: C, 66.65; H, 7.12; N, 4.71; found: C, 66.21; H, 7.01; N, 4.68%.

4.8. Preparation of (+)-1

The diester **4** or **8** (4 g) was heated under reflux with 1N KOH in methanol (20 mL) for 1 h. Excess solvent was removed on a rotavapor, water (20 mL) was added and the reaction mixture was extracted with ether. The extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue of the diol (+)-**1** was crystallized from hexane–THF (10:1); mp 125–126°C; $[\alpha]_D$ +8.0 (*c* 1, $CHCl_3$). The spectral data of the product was identical to that of the racemate. The enantiomeric excess was found to be >99% by HPLC analysis on Chiralcel-OD® column using hexane–isopropyl alcohol as the solvent.

4.9. Preparation of (−)-1

Saponification of the diester **5** or **7** as described above provided (−)-**1** which was also crystallized from hexane–THF (10:1) to obtain white needles; mp 125–126°C; $[\alpha]_D$ −8.0 (*c* 1, $CHCl_3$). Absolute configuration of the enantiomer was found to be (*R*,*R*) by X-ray crystallography.

4.10. Crystallographic analysis of (−)-1

Colourless, needle-like crystals were grown from hexane–THF (10:1), $C_{17}H_{20}O_2$, M = 256.35, a = 11.8587 (6), b = 10.0497 (3), c = 12.3563 (11) Å, v = 1472.4 (3) Å, T = 299 K, Z = 4, D_{calcd} = 1.16 g/cm^3. Final goodness of fit = 1.045, R = 0.031, wR = 0.088. Absolute structure determination was completed using the Flack parameter.[18]

Crystallographic data (excluding structure factors) for (*R*,*R*)-(−)-**1** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 179858. Copies of the data can be obtained, free of charge, on application to CCDC,

12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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