(*S,S*)-1,3-Bis[(2-methoxyethoxy)methoxy]-1,3-diphenylacetone – A New Chiral Ketone with C_2 Symmetry

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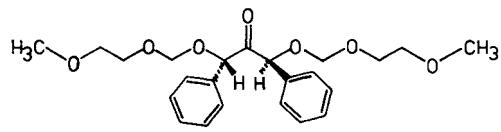
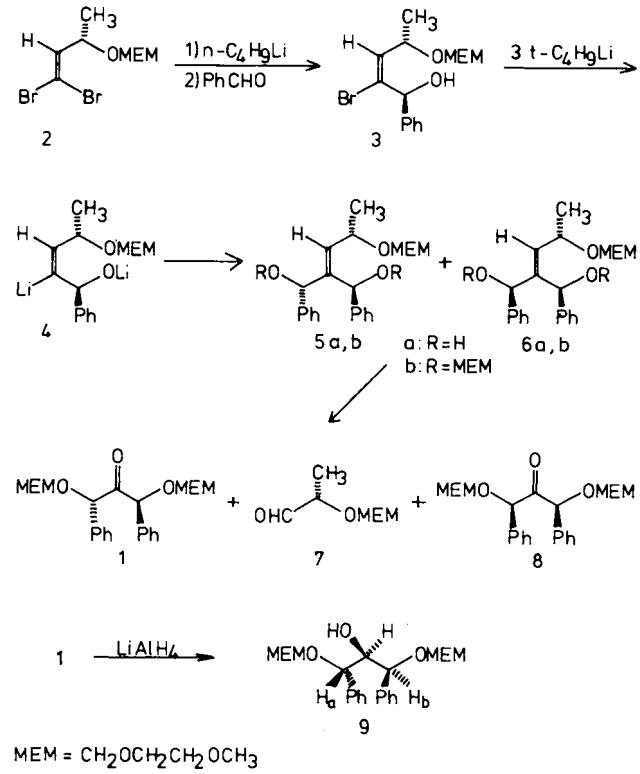
Starting with carbinol 3 [easily accessible from ethyl (*S*)-lactate], the synthesis of enantiomerically pure, C_2-symmetric ketone 8 is achieved; the key step involves the diastereoselective addition of dilithium compound 4 to benzaldehyde.

Enantiomerically pure compounds with C_2 symmetry have proven to be useful auxiliary reagents in asymmetric synthesis. Since Kagan's pioneer work in the field of C_2-symmetric phosphines, designed for catalytic asymmetric hydrogenation[1], organic chemists have also learned to use amines[2] and diols[3] containing a C_2 axis in order to perform highly stereoselective transformations. Furthermore, a large variety of chiral building blocks, which are suited to become incorporated into a target molecule ("chiron approach"[4]), have been prepared from readily available natural products like (*D*)-tartaric acid[5] or (*D*)-mannitol[6]. However, C_2-symmetric ketones are hardly available in enantiomerically pure form[7] and – as a consequence – have neither found wide application as chiral building blocks nor as reagents in asymmetric syntheses. In this note, we report on the synthesis of the new C_2-symmetric ketone (*S,S*)-1,3-bis[(2-methoxyethoxy)methoxy]-1,3-diphenylacetone (**1**).



(S,S)-1

Carbinol **3**, which has been chosen as starting material, is easily prepared with high diastereomeric and enantiomeric excess (> 98% and > 99%, respectively) in a 15–20-g scale from benzaldehyde and dibromoalkene **2**, which in turn is readily available from ethyl (*S*)-lactate[8]. By treatment of carbinol **3** with three[9] equivalents of *tert*-butyllithium, both deprotonation of the hydroxyl group and bromine/lithium exchange are accomplished. When the dianion **4**, generated in this way, is allowed to react with benzaldehyde, a mixture of the diastereomeric allylic alcohols **5a** and **6a** is formed in a 75:25 ratio as shown by ^{1}H-NMR spectroscopy. No attempt has been made to separate the isomers, and the mixture is treated with (2-methoxyethoxy)methyl chloride to give rise to the completely protected triols **5b** and **6b**. The target compound **1** is liberated by ozonolysis of **5b**/**6b** in dichloromethane and subsequent reduction with dimethyl sulfide. The coproduct, lactaldehyde **7**, is evaporated[10], and the residue is subjected to column chromatography. Thus, the minor diastereomer **8** is removed, and finally, the main product **1** is isolated in 40% overall yield (relative to bromoalkene **3**).



MEM = $CH_2OCH_2CH_2OCH_3$

The decision, whether (*S,S*) configuration of **1** or the *meso* form of **8** has to be assigned to the main isomer, could be made on the basis of optical rotation and reduction of the keto group to the alcohol. Since (*S,S*) diastereomer **1** is the only chiral one out of **1** and **8**, the optical rotation $[\alpha]_D^{25}$ of the pure main product (+212.4) clearly indicates that the configuration of **1** has to be assigned. When ketone **1** is heated to 150°C for 90 min, not only epimerization to a 1:1 mixture of **1** and **8** is observed, but also complete racemization of **1**, as indicated by an optical rotation of approximately zero. A further proof for structure **1** comes from the reduction with lithium aluminum hydride, delivering carbinol **9** as single compound. Its ^{1}H-NMR spectrum unambiguously shows two doublets of the diastereotopic benzylic protons H_a and H_b. On the other hand, the reduction of the *meso* compound **8** turns out to afford mainly one product, too. In this case, however, the enantiotopic benzylic protons are indeed found to show a single doublet. Thus, the structure of the C_2-symmetric ketone (*S,S*)-**1** can be assigned to the main product. Since (*R*)-lactic acid is now also commercially available, a possibility for the synthesis of (*R,R*)-**1** is also opened. It might be interesting to study the capability of the ketone **1** to serve as a host compound for cations.

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Experimental

General: IR spectra: Perkin-Elmer 710 B spectrophotometer. – NMR spectra: Varian VXR 300; all spectra were recorded with $CDCl_3$ as solvent and tetramethylsilane as internal standard. – Mass spectra: Varian MAT CH-5. – Specific rotations were determined with a Perkin-Elmer 141 polarimeter. – TLC: Polygram-Sil-G/UV_{254}-Fertigfolien (Macherey-Nagel). – Preparative thin-layer chromatography: Kieselgel-Fertigplatten Sil G-60, UV_{254} (Merck). – Column chromatography: Kieselgel 60, mesh size 0.2–0.5 (Merck). – Ozonolyses: Ozone generator 502 (Fischer). – The solvents THF and diethyl ether are distilled first from sodium and then under nitrogen from $LiAlH_4$; they can be taken from receiving flasks, which are closed by septums, with syringes or cannulas. General remarks concerning the handling of organolithium reagents are given in ref.[11]. Reactions which are performed at low temperature, are monitored by introducing a thermocouple, connected with a resistance thermometer (Ebro), through a septum into the reaction mixture.

(1S,1'S,2E,4S)-1-Hydroxy-2-(1'-hydroxy-1'-phenylmethyl)-4-[(2''-methoxyethoxy)methoxy]-1-phenyl-2-pentene (**5a**) *and (1R,1'S,2E,4S)-1-Hydroxy-2-(1'-hydroxy-1'-phenylmethyl)-4-[(2''-methoxyethoxy)methoxy]-1-phenyl-2-pentene* (**6a**): A solution of 0.69 g (2.0 mmol) of **3** in 25 ml of THF is stirred under nitrogen in a 100-ml two-necked flask, which has been equipped with a magnetic stirrer, closed with a septum, and connected with a combined vacuum-nitrogen line. At −105°C, 3.53 ml (6.0 mmol) of a 1.7 M solution of *tert*-butyllithium in pentane is slowly injected from a syringe through the septum into the vigorously stirred mixture. Thereby a slight yellow colour appears, and a white precipitate of lithium bromide forms gradually. The mixture is allowed to warm up to −40°C, stirred at this temperature for 10 min, and then, cooled to −110°C. After the addition of 0.32 g (3.0 mmol) of benzaldehyde, the solution is warmed up to −70°C, treated with 10 ml of a satd. ammonium chloride solution, and finally allowed to reach room temp. The mixture is extracted three times with a total amount of 60 ml of diethyl ether. When the combined organic layers have been dried with $MgSO_4$, the solvent is removed in a rotary evaporator. The remaining volatile impurities are collected in a −130°C cold trap at 0.004 Torr to give 0.68 g (92%) of **5a/6a** as yellowish oily residue, which is used in the following step without further purification. The ratio of diastereomers **5a**:**6a** is shown to be 75:25 by ^1H NMR: **5a**: δ = 1.02 (d, *J* = 6.3 Hz, 3H, 5-H), 3.35 (s, 3H, OCH_3), 3.48–3.80 (m, 6H, OCH_2CH_2O), 4.57 (dq, J_d = 9.6 Hz, J_q = 6.3 Hz, 1H, 4-H), 4.66 (d, *J* = 7 Hz, 1H, OC*H*HO), 4.70 (d, *J* = 7 Hz, 1H, OCH*H*O), 5.20 (s, 1H, C_6H_5CH), 5.45 (s, 1H, C_6H_5CH), 5.36 (d, *J* = 9.6 Hz, 1H, 3-H), 7.17–7.33 (m, 10H, Aryl H); **6a**: δ = 0.93 (d, *J* = 6.3 Hz, 3H), 3.34 (s, 3H), 3.48–3.80 (m, 6H), 4.46 (dq, J_d = 9.6 Hz, J_q = 6.3 Hz, 1H), 4.69 (d, *J* = 7 Hz, 1H), 4.72 (d, *J* = 7 Hz, 1H), 5.22 (s, 1H), 5.39 (s, 1H), 5.65 (d, *J* = 9.6 Hz, 1H), 7.17–7.33 (m, 10H). – IR (neat): $\tilde{\nu}$ = 3430 cm^{-1}, 3080, 3050, 3000, 2950, 2900, 1600, 1490, 1450, 1370, 1220, 1180, 1100, 1030, 840, 750, 730, 690. – MS (70 eV): *m/z* (%) = 267 (5) [M^+ − $OCH_2OCH_2CH_2OCH_3$], 249 (16), 248 (61), 107 (18), 105 (100), 91 (14), 89 (10), 77 (20), 59 (41).

$C_{22}H_{28}O_5$ (372.5) Calcd. C 70.94 H 7.58
Found C 70.97 H 7.62

(1S,1'S,2E,4S)-1,4-Bis[(2''-methoxyethoxy)methoxy]-2-[1'-(2''-methoxyethoxy)methoxy-1'-phenylmethyl]-1-phenyl-2-pentene (**5b**) *and (1R,1'S,2E,4S)-1,4-Bis[(2''-methoxyethoxy)methoxy]-2-[1'-(2''-methoxyethoxy)methoxy-1'-phenylmethyl]-1-phenyl-2-pentene* (**6b**): A solution of 0.744 g (2.0 mmol) of **5a/6a** (75:25 mixture) in 10 ml of dichloromethane is magnetically stirred at 0°C under nitrogen in a 50-ml two-necked flask, equipped with a dropping funnel and a reflux condenser. After the dropwise addition of 1.030 g (8.0 mmol) of ethyldiisopropylamine, the mixture is stirred at 25°C for 30 min. At the same temperature, 1.000 g (8 mmol) of (2-methoxyethoxy)methyl chloride is added dropwise. Stirring is continued for 10 min at room temp., 1 h under reflux, and another 10 h at 25°C. The mixture is treated with 10 ml of water, stirred for 30 min at room temp. and poured into 50 ml of dichloromethane. The organic layer is separated, and the aqueous layer is extracted twice with a total amount of 40 ml of dichloromethane. The combined organic solutions are washed twice with 10 ml of water, once with 5% hydrochlorid acid, and twice with water and are dried with $MgSO_4$. Evaporation of the solvent delivers the crude mixture **5b/6b** in 100% yield (1.090 g). – ^1H NMR: **5b**: δ = 1.23 (d, *J* = 6.4 Hz, 3H, 5-H), 3.25–3.75 (m, 21H, OCH_3 and OCH_2CH_2O), 4.35–4.86 (m, 6H, OCH_2O), 4.87–4.99 (m, 1H, 4-H), 5.07 (s, 1H, C_6H_5CH), 5.56 (s, 1H, C_6H_5CH), 5.79 (d, *J* = 9 Hz, 1H, 3-H), 6.95–7.53 (m, 10H, Aryl H); ^1H NMR of **6b** differs from that of **5b** in δ = 1.27 (d, *J* = 6.4 Hz, 3H), 4.99 (s, 1H), 5.60 (s, 1H), 6.02 (d, *J* = 9 Hz, 1H). – IR (neat): $\tilde{\nu}$ = 3070 cm^{-1}, 3050, 2950, 2900, 1600, 1490, 1450, 1360, 1220, 1200, 1100, 1020, 840, 750, 690. – MS (70 eV): *m/z* (%) = 353 (3) [M^+ − $CH(C_6H_5)OCH_2OCH_2CH_2OCH_3$], 248 (40), 233 (4), 205 (6), 105 (35), 91 (7), 90 (10), 89 (100), 77 (3), 59 (97), 45 (48).

$C_{30}H_{44}O_9$ (584.7) Calcd. C 65.67 H 8.08
Found C 64.79 H 8.20

(S,S)-1,3-Bis[(2-methoxyethoxy)methoxy-1,3-diphenyl-2-propanone (**1**): A stream of ozone is passed through a dichloromethane solution of 0.55 g (1.0 mmol) of the crude mixture of **5b/6b** at 0°C until the blue colour persists in the reaction mixture. After addition of 0.30 g (5.0 mmol) of dimethyl sulfide, the mixture is allowed to reach room temp. within 3 h, washed three times with 10 ml of water and dried with $MgSO_4$. The solution is concentrated in a rotary evaporator to deliver 0.58 g of a yellow oil. This is first heated to 50°C at 0.005 Torr in order to evaporate (*S*)-2-[(2-methoxyethoxy)methoxy]propanal. Purification of the residue by column chromatography on silica gel with hexane/ethyl acetate (1:1) affords:

8 [0.059 g (14%)]: R_f 0.43. – ^1H NMR: δ = 3.30 (s, 6H, OCH_3), 3.30–3.53 (m, 8H, OCH_2CH_2O), 4.49 (d, *J* = 7 Hz, 2H, OC*H*HO), 4.56 (d, *J* = 7 Hz, 2H, OCH*H*O), 5.43 (s, 2H, 1-H and 3-H), 7.27–7.35 (m, 10H, Aryl H) (the material is still contaminated with about 20% of isomer **1**).

1 [0.178 g (43%)]: R_f 0.29. – $[\alpha]_D^{25}$ = +212.4 (*c* = 0.58 in 95% aqueous ethanol). – ^1H NMR: δ = 3.29 (s, 6H, OCH_3), 3.29–3.51 (m, 8H, OCH_2CH_2O), 4.59 (d, *J* = 7 Hz, OC*H*HO), 4.63 (d, *J* = 7 Hz, 2H, OCH*H*O), 5.33 (s, 2H, 1-H and 3-H), 7.27–7.33 (m, 10H, Aryl H). – IR (neat): $\tilde{\nu}$ = 3060 cm^{-1}, 3040, 2940, 2900, 1720, 1480, 1440, 1190, 1100, 1020, 840, 730, 690. – MS (70 eV): *m/z* (%) = 208 (3) [M^+ − 2 $OCH_2OCH_2CH_2OCH_3$], 195 (14), 105 (5), 91 (3), 90 (9), 89 (100), 77 (4), 59 (74), 45 (10).

$C_{23}H_{30}O_7$ (418.5) Calcd. C 66.01 H 7.23
Found C 65.95 H 7.13

(S,S)-1,3-Bis[(2-methoxyethoxy)methoxy]-1,3-diphenyl-2-propanol (**9**): A solution of 0.087 g (0.20 mmol) of **1** in 10 ml of diethyl

ether is added drop by drop to a mixture of 0.010 g (0.26 mmol) of $LiAlH_4$ in 10 ml of diethyl ether, which is vigorously stirred in an ice bath. After 5 h stirring at room temp., 10 ml of water is added to the mixture, and the precipitate is dissolved by the addition of a few drops of 2 N sulfuric acid. The organic layer is separated, and the aquous layer is washed three times with 10 ml of diethyl ether. The combined organic solutions are dried with $MgSO_4$, the solvent is removed in a rotary evaporator, and the residue is purified by preparative thin-layer chromatography on silica gel with ethyl acetate to afford 0.055 g (65%) of **9**. – $[\alpha]_D^{25} = +107.5$ ($c = 1.43$ in 95% aqueous ethanol). – ^1H NMR: $\delta = 2.80$ (d, $J = 4.5$ Hz, 1H, OH), 3.28 and 3.29 (2 s, 3H each, OCH_3), 3.30–3.80 (m, 8H, OCH_2CH_2O), 4.13 (m, 1H, H-2), 4.45 (d, $J = 5.6$ Hz, 1H) and 4.52 (d, $J = 5.8$ Hz, 1H) (1-H and 3-H), 4.55, 4.61, 4.67, 4.70 (4 d, $J = 6.7$ Hz, 1H each, OCH_2O), 7.27–7.33 (m, 10H, Aryl H). – IR (neat): $\tilde{\nu} = 3450\ cm^{-1}$, 3060, 3040, 2930, 2890, 1480, 1440, 1190, 1160, 1100, 1020, 900, 830, 720, 690. – MS (70 eV): *m/z* (%) = 195 (14) [$CH_3OCH_2CH_2OCH_2OCHC_6H_5^+$], 105 (57), 91 (22), 90 (9), 89 (100), 77 (43), 59 (87).

$C_{23}H_{32}O_7$ (420.5) Calcd. C 65.70 H 7.67
Found C 65.81 H 7.60

CAS Registry Numbers

1: 119945-33-4 / **3**: 114091-69-9 / **5a**: 119909-44-3 / **5b**: 119909-45-4 / **6a**: 119945-31-2 / **6b**: 119945-32-3 / **7**: 86163-01-1 / **8**: 119909-46-5 / **9**: 119909-47-6

[1] H. B. Kagan, *Pure Appl. Chem.* **43** (1975) 401.

[2] J. K. Whitesell, S. W. Felman, *J. Org. Chem.* **42** (1977) 1663; J. K. Whitesell, S. W. Felman, *J. Org. Chem.* **45** (1980) 755; K. E. Harding, S. R. Burks, *J. Org. Chem.* **46** (1981) 3920; K. E. Harding, T. H. Marman, *J. Org. Chem.* **49** (1984) 2838; R. H. Schlessinger, E. J. Iwanowicz, J. P. Springer, *J. Org. Chem.* **51** (1986) 3070; R. Schlessinger, J. R. Tata, J. P. Springer, *J. Org. Chem.* **52** (1987) 708; R. H. Schlessinger, E. J. Iwanowicz, *Tetrahedron Lett.* **28** (1987) 2083; Y. Kawanami, Y. Ito, T. Kitagawa, Y. Taniguchi, T. Katsuki, M. Yamaguchi, *Tetrahedron Lett.* **25** (1984) 857; T. Katsuki, M. Yamaguchi, *Tetrahedron Lett.* **26** (1985) 5807; S. Ikegama, T. Hayama, T. Katsuki, M. Yamaguchi, *Tetrahedron Lett.* **27** (1986) 3403; H. Hogeveen, L. Zwart, *Tetrahedron Lett.* **23** (1982) 105; M. B. Eleveld, H. Hogeveen, *Tetrahedron Lett.* **27** (1986) 631, 635; J. A. Marshall, J. Lebreton, *J. Am. Chem. Soc.* **110** (1988) 2925; R. E. Gawley, S. R. Chemburkar, A. L. Smith, T. V. Anklekar, *J. Org. Chem.* **53** (1988) 5381; J. K. Whitesell, M. A. Minton, K.-M. Chen, *J. Org. Chem.* **53** (1988) 5383.

[3] J. Casanova, Jr., E. J. Corey, *Chem. Ind.* **1961**, 1664; J. M. McNamara, Y. Kishi, *J. Am. Chem. Soc.* **104** (1982) 7371; P. A. Bartlett, W. S. Johnson, J. D. Elliott, *J. Am. Chem. Soc.* **105** (1983) 2088; V. M. F. Choi, J. D. Elliott, W. S. Johnson, *Tetrahedron Lett.* **25** (1984) 591; W. S. Johnson, P. H. Crackett, J. D. Elliott, J. J. Jagodzinski, S. D. Lindell, S. Natarajan, *Tetrahedron Lett.* **25** (1984) 3951; W. S. Johnson, M. F. Chan, *J. Org. Chem.* **50** (1985) 2598; S. D. Lindell, J. D. Elliott, W. S. Johnson, *Tetrahedron Lett.* **25** (1984) 3947; W. S. Johnson, C. Edington, J. D. Elliott, I. R. Silverman, *J. Am. Chem. Soc.* **106** (1984) 7588.

[4] S. Hanessian, *Total Synthesis of Natural Products: The 'Chiron' Approach*, Pergamon Press, Oxford 1983.

[5] D. Seebach in *Modern Synthetic Methods 1980* (R. Scheffold, Ed.), p. 91–171, Salle und Sauerländer, Frankfurt, Aarau 1980.

[6] J. Jurczak, S. Pikul, T. Bauer, *Tetrahedron* **42** (1986) 447; J. Mulzer, *Nachr. Chem. Tech. Lab.* **32** (1984) 146.

[7] C_2-symmetric α,α′-diphenyl- and -dialkylacetone derivatives with alkylthio, azido, or acetoxy substituents in α,α′ position have been synthesized, however, only as racemic compounds: B. Föhlisch, W. Gottstein, *Liebigs Ann. Chem.* **1979**, 1768; B. M. Trost, P. J. Whitman, *J. Am. Chem. Soc.* **96** (1974) 7421.

[8] H. Mahler, M. Braun, *Tetrahedron Lett.* **43** (1987) 5145.

[9] The third equivalent of *tert*-butyllithium is added in order to destroy *tert*-butyl bromide, which arises from Br/Li exchange; see: E. J. Corey, D. J. Beames, *J. Am. Chem. Soc.* **94** (1972) 7210; H. Neumann, D. Seebach, *Tetrahedron Lett.* **1976**, 4839; D. Seebach, H. Neumann, *Chem. Ber.* **107** (1974) 847.

[10] The recovered lactaldehyde **7** may be used in order to prepare **2**; see ref.[8].

[11] U. Mahler, R. M. Devant, M. Braun, *Chem. Ber.* **121** (1988) 2035; R. Devant, M. Braun, *Chem. Ber.* **121** (1988) 397.

[52/89]