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Resolution and Absolute Configuration of the Enantiomeric Spiro[5.5]undecane-3,9-diols

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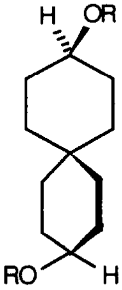
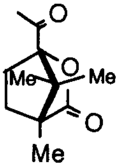
Abstract: The enantiomerically pure spiro[5.5]undecane-3,9-diols (-)-**1** and (+)-**1**, have been prepared via the diastereomerically pure esters (-)-**2** or (+)-**2** made from (±)-**1** and (1*S*,4*R*)- or (1*R*,4*S*)-camphanoyl chloride. The bis(4-methoxybenzoate) (+)-**3** and bis(4-bromobenzoate) (+)-**4** derived from (-)-**1** show chiroptical properties in accordance with Nakanishi's rule for two chromophores having coupled electric dipole transition moments arranged with a right handed (positive) torsion angle. Therefore (+)-**3**, (+)-**4** and (-)-**1** should have the chirality sense given in the conformation formula and described with the (a*S*)-specification symbol.

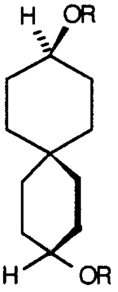
Aschan[1] recognized for the first time that symmetrically substituted spirocyclanes like spiro[5.5]undecane-3,9-diol (**1**) are chiral molecules with C_2 symmetry but lacking a classical asymmetric C-atom. Only one example of this structural type, namely spiro[3.3]heptane-2,6-dicarboxylic acid has been resolved[2] and its absolute configuration determined by an anomalous X-ray diffraction experiment[3] with the barium salt of the (*S*)-(-)-dicarboxylic acid. We have found that the diol **1** can be resolved by recrystallization of the diastereomeric esters with camphanic acid. Both enantiomers of the reagent used to form the esters, (1*S*,4*R*)-(-)-camphanoyl chloride[4] or (1*R*,4*S*)-(+)-camphanoyl chloride[5], are readily available. This fact allows the preparation of the diastereomerically pure esters (-)-**2** and (+)-**2**. Their purity can be checked by inspection of the ^{13}C NMR spectra, showing that the ^{13}C signals of the more soluble diastereomer are disappearing during recrystallisation. Transesterification of the pure biscamphanoates (-)-**2** or (+)-**2** with methanol yields the enantiomerically pure diols (-)-**1** or (+)-**1** and (-)- or (+)-methyl camphanoate[6]. The (±)-**1** diol used in these experiments has been prepared by the method of Dreiding et al.[7]. Naemura et al.[8] recently prepared (-)-**1** of low enantiomeric purity by lipase catalysed acetylation of (±)-**1**.



(-) - **1** R = H

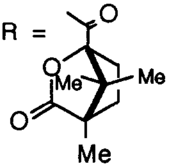
(-) - **2** R =



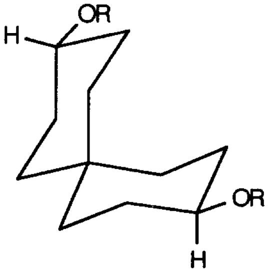


(+) - **1** R = H

(+) - **2** R =



Conformational analysis of the spiro[5.5]undecane-3,9-diol (**1**) allows to draw a more detailed structural formula. For example the molecules of the (*aS*)-enantiomer will exist in solution predominantly in the chair,chair conformation, with the 3- and 9-substituents in equatorial positions. In the ^{1}H NMR spectra, the signal of 3-H and 9-H shows a coupling constant of 8.8 Hz due to diaxial coupling; this observation confirms the conformation derived above. In this conformation, the two C-O bonds define a torsion angle of ca. 70° with positive twist sense. Therefore, the bisbenzoate rule[9-11] can be applied to derive the absolute configuration of the molecule from its chiroptical properties. The bis(4-methoxybenzoate) (+)-**3** of (-)-**1** shows an intense absorption at 255 nm in the UV spectrum. According to Tanaka[12], the corresponding electric dipole transition moment in benzoates is directed along the bond between the benzene ring and the carbon atom of the ester group, which in turn is parallel to the C-O bond of the alcohol part. This implies that the two electric dipole transition moments in (+)-**3** also enclose a torsion angle of 70° with positive twist sense.



(+) - **3** R = 4-$MeOC_6H_4CO$

(+) - **4** R = 4-BrC_6H_4CO

(*aS*) -(-) - **1** R = H

The dipole-dipole interaction between the two 4-methoxybenzoate chromophores in (+)-**3** creates in the CD spectrum two Cotton effects with opposite sign. The maximum at 261 nm ($\Delta\varepsilon_{max}$ = +19.2) corresponds to the in-phase coupling transition with lower energy; the minimum at 243 nm ($\Delta\varepsilon_{max}$ = -9.7) represents the out-of-phase coupling with higher energy. The magnitude of the Cotton effect is quite great despite the comparatively big distance between the two chromophores. A similar effect has been observed in the CD spectrum of the bis(methoxybenzoate) of the conformationally rigid (-)-adamantane-2,6-diol[5].

In a thorough discussion of the CD spectra of optically active benzoates, Nakanishi et al.[10,11] have shown that the absolute sign of the two Cotton effects can be deduced non-empirically from the sense of spatial arrangement of the two chromophores. If they enclose a torsion angle with positive twist sense as in the conformation formula (+)-**3**, a positive Cotton effect at longer wave length accompanied by a negative effect at shorter wave length is expected. The experiment described above confirms to this prediction, and the chirality sense shown in the conformation formula for (+)-**3** can be deduced. The bis(4-methoxybenzoate) (+)-**3** is derived from the levorotatory spiro[5.5]undecane-3,9-diol [(-)-**1**]. Both compounds will receive the (*aS*)-specification symbol for their absolute configuration according to the specification rules[13] for molecules with a chirality axis. A second derivative of (-)-**1**, the bis(4-bromobenzoate) (+)-**4**, also gives a CD spectrum with a positive cotton effect at longer wave length followed by a negative effect at shorter wave length and confirms the (*aS*)-chirality sense derived for the compounds above.

EXPERIMENTAL SECTION

^{1}H (500.13 MHz) and ^{13}C (125.77 MHz) NMR spectra were recorded on a Bruker AM-500-FT instrument (δ in ppm referenced to residual solvent signal, with chemical shifts referred to TMS; J in Hz, ^{1}H NMR signals were assigned by COSY experiments, ^{13}C signal multiplicities were determined from DEPT spectra). Optical rotations were measured on a Perkin Elmer 241 polarimeter. IR spectra were recorded on a Perkin Elmer 297 instrument. UV spectra were obtained using a Kontron Uvikon 860 instrument. CD spectra were recorded on a Jobin Yvon Mark III Dichrograph. Melting points were determined on a Büchi 510 melting point apparatus. Kieselgel 60 F_{254} glass plates (Merck) were used for TLC, compounds were visualized by conc. H_2SO_4/5min 160°C. All solvents were distilled before use. Ether and THF were filtered through ICN Alox B. Elemental analyses were performed by the Microanalytical Laboratory of Ilse Beetz, D 96317 Kronach.

(-)-Spiro[5.5]undecane-3,9-diyl-bis-(1S,4R)-camphanoate [(-)-**2**)]: A solution of 1.52 g (8.3 mmol) (±)-**1** in 10 ml pyridine was added to 5.24 g (24.2 mmol) (1*S*,4*R*)-(-)-camphanoyl chloride[4] in 30 ml pyridine. The mixture was stirred for 16 h. Subsequently 400 ml 2 N H_2SO_4 were added, and the solution was extracted twice with 200 ml toluene. The extracts were washed with 2 M $KHCO_3$, dried (Na_2SO_4) and the solvent was removed under reduced pressure: 4.45 g (99%) mixture of the diastereomeric esters, m.p. 130-165°C.

Recrystallisation from 99 ml of a mixture of cyclohexane/benzene (2:1) gave 1.30 g (30%) colourless crystals after 24 h, m.p. 170-189°C. These crystals were dissolved in a boiling mixture of 45 ml cyclohexane/benzene (2:1). Crystallisation (24 h at room temperature) afforded 1.01 g (22%) (-)-**2** as colourless needles, $[\alpha]_D = -1.9$ (c = 0.96 in $CHCl_3$). - IR ($CHCl_3$): 1800 cm^{-1} (C=O), 1760 (C=O), 1730 (C=O). - ^{13}C NMR (C_6D_6): 9.80 (q, 2 C), 16.6 (q, 2 C), 16.8 (q, 2 C), 26.5 (t, 2 C), 26.9 (t, 2 C), 28.9 (t, 2 C), 30.9 (t, 2 C), 31.1 (t, 2 C), 31.2 (s, C-6), 34.4 (t, 2 C), 53.8 (s, 2 C), 54.6 (s, 2 C), 73.9 (d, 2 C, C-3, C-9), 90.8 (s, 2 C), 167.1 (s, 2 C, C=O), 177.3 (s, 2 C, C=O); mixture of the diastereomeric esters: additional signals at 26.6 (t, 2 C), 26.8 (t, 2 C), 34.2 (t, 2 C) and 73.8 (d, 2 C, C-3, C-9), which disappear upon recrystallisation.
Anal. Calcd. for : $C_{31}H_{44}O_8$ (544.7) C, 68.36; H, 8.14. Found C, 68.38; H, 8.07.

(+)-Spiro[5.5]undecane-3,9-diyl-bis-(1R,4S)-camphanoate [(+)-**2**)]: The mother liquors of the described crystallisation were concentrated in vacuo to yield 3.8 g of a mixture of the diastereomeric esters, which was dissolved in 50 ml of 0.1 M NaOMe/MeOH. The solution was gently refluxed for 20 min. The reaction mixture was allowed to attain room temperature and then 5.0 ml 1 N HCl/MeOH were added. Evaporation of the solvent followed by column chromatography (200 g silicagel, AcOEt) gave 3.0 g (1*S*,4*R*)-(-)-methylcamphanoate, $R_f = 0.8$, m.p. 108-109°C (lit.[6] 108-109°C) and 1.26 g (+)-**1** and (±)-**1**, white solid, $R_f = 0.4$. This diol was reacted with (1*R*,4*S*)-(+)-camphanoyl chloride[5] as described above and the diastereomeric esters (3.75 g) were recrystallized twice from cyclohexane/benzene (2:1): 1.52 g (33%) (+)-**2**, white needles, m.p. 195.5-196.5°C, $[\alpha]_D = +2.9$ (c = 1.00 in $CHCl_3$).

(-)-(aS)-Spiro[5.5]undecane-3,9-diol [(-)-**1**]: A solution of 1.03 g (1.89 mmol) (-)-**1** in 20 ml 0.1 M NaOMe/MeOH was gently refluxed for 20 min. The mixture was cooled to room temperature and 4 ml 0.5 M HCl/MeOH were added. Evaporation of the solvent followed by column chromatography (50 g silicagel, AcOEt) gave 335 mg (96%) (-)-**1**, colourless crystals, $R_f = 0.4$ (AcOEt), m.p. 149.2-149.9°C from AcOEt [cp. (±)-**1** lit.[7] m.p. 131-132°C] , $[\alpha]_D = -14.2$ (c = 1.13 in MeOH). - IR ($CHCl_3$): 3600 cm^{-1} (OH), 3450 (OH, br). - ^1H NMR (CD_3OD): 1.08 (m, 2 H, 1-H_a, 7-H_a), 1.17 (m, 2 H, 5-H_a, 11-H_a), 1.33-1.47 (6 H, 2-H_a, 8-H_a, 4-H_a, 10-H_a, 5-H_e, 11-H_e), 1.67 (m, 4 H, 2-H_e, 8-H_e, 4-H_e, 10-H_e), 1.83 (m, 2 H, 1-H_e, 7-H_e), 3.52 (tt, J = 8.8, J = 3.4 Hz, 2 H, 3-H_a, 9-H_a). - ^{13}C NMR (CD_3OD): 31.0 (t, 2 C, C-2, C-8), 31.3 (t, 2 C, C-4, C-10), 31.7 (t, 2 C, C-1, C-7), 32.3 (s, C-6), 39.1 (t, 2 C, C-5, C-11), 71.3 (d, 2 C, C-3, C-9).

(+)-(aR)-Spiro[5.5]undecane-3,9-diol [(+)-**1**]: This compound was prepared as described above from 1.47 g (2.7 mmol) (+)-**2**: 480 mg (95%) (+)-**1**, colourless crystals, R_f = 0.4 (AcOEt), m.p. 148.2-149.3°C from AcOEt [cp. (±)-**1** lit.[7] m.p.131-132°C], $[\alpha]_D$ = +14.3 (c = 1.20 in MeOH).

(+)-Spiro[5.5]undecane-3,9-diyl-bis-(4-methoxybenzoate) [(+)-**3**]: This compound was prepared from 90 mg (0.49 mmol) (-)-**1** and 418 mg (2.44 mmol) 4-methoxybenzoyl chloride in pyridine: 142 mg (64%) (+)-**3**, colourless crystals, R_f = 0.40 (cyclohexane/AcOEt, 4:1), m.p. 107.5-104.0°C, $[\alpha]_D$ = +68.9 (c = 1.42 in MeCN). - IR (CCl_4): 1710 cm^{-1} (C=O). ^1H NMR (C_6D_6): 0.88-1.60 (4 H, 1-H_a, 5-H_a, 7-H_a, 11-H_a), 1.26 (m, 2 H, 5-H_e, 11-H_e), 1.44-1.62 (6 H, 1-H_e, 2-H_a, 4-H_a, 7-H_e, 8-H_a, 10-H_a), 1.62-1.74 (4 H, 2-H_e, 4-H_e, 8-H_e, 10-H_e), 3.15 (s, 6 H, OCH_3), 5.09 (tt, J = 8.2, J = 4 Hz, 2 H, 3-H_a,9-H_a), 6.70 (d, J = 8.9 Hz, 4 H, arom.H), 8.25 (d, J = 8.9 Hz, 4 H, arom.H). - UV (MeCN): λ_{max} (lg ε) = 255 nm (4.568). - CD(MeCN): $\Delta\varepsilon_{max}$ = +19.2 (261 nm), -9.7 (243 nm). -
Anal. Calcd. for : $C_{27}H_{32}O_6$ (450.0) C, 71.66; H, 7.13. Found C, 71.67; H, 6.98.

(+)-Spiro[5.5]undecane-3,9-diyl-bis-(4-bromobenzoate) [(+)-**4**]: This compound was prepared from 89 mg (0.48 mmol) (-)-**1** and 582 mg (2.66 mmol) 4-bromobenzoyl chloride in pyridine: 247 mg (94 %) (+)-**4**, colourless crystals, R_f = 0.46 (benzene), m.p. 165.7-166.1°C from MeCN, $[\alpha]_D$ = +50 (c = 0.1 in MeCN), $[\alpha]_D$ = +49.7 (c = 0.67 in dioxane). - IR (CCl_4): 1710 cm^{-1} (C=O). ^1H NMR (C_6D_6): 0.80-1.00 (4 H, 1-H_a, 5-H_a, 7-H_a, 11-H_a), 1.18 (m, 2 H, 5-H_e, 11-H_e), 1.36-1.52 (6 H, 1-H_e, 2-H_a, 4-H_a, 7-H_e, 8-H_a, 10-H_a), 1.54-1.67 (4 H, 2-H_e, 4-H_e, 8-H_e, 10-H_e), 5.00 (tt, J = 8, J = 4 Hz, 2 H, 3-H_a,9-H_a), 7.20 (d, J = 8.6 Hz, 4 H, arom.H), 7.85 (d, J = 8.9 Hz, 4 H, arom.H). - UV (MeCN): λ_{max} (lg ε) = 243 nm (4.050). - CD(MeCN): $\Delta\varepsilon_{max}$ = +22.9 (249 nm), -6.8 (232 nm). -
Anal. Calcd. for : $C_{25}H_{26}Br_2O_4$ (550.3) C, 54.57; H, 4.76. Found C, 54.45; H, 4.69.

References

1. O. Aschan, *Ber. Dtsch. Chem. Ges.* **1902**, *35*, 3389-3399.
2. H.J. Backer, H.B.J. Schurink, *Rec. Trav. Chim. Pays-Bas* **1931**, *50*, 921-927.
3. L.A. Hulshof, H. Wynberg, B. van Dijk, J.L. de Boer, *J. Am. Chem. Soc.* **1976**, *98*, 2733-2740.
4. D. Kappes, H. Gerlach, R. Boeckman, G.G.N. Maw, *Org. Synth.* **1993**, *71*, 48-55.
5. H. Gerlach, *Helv. Chim. Acta* **1985**, *68*, 1815-1821.

6. V. Sunjic, F. Kajfez, M. Oklobzija, M. Stromar, *Croat. Chem. Acta* **1973**, *45*, 569-578.

7. G. Farges, A. Dreiding, *Helv. Chim. Acta* **1966**, *49*, 552-561.

8. K. Naemura, A. Furutani, *J. Chem. Soc., Perkin Trans. 1*, **1991**, 2891-2892.

9. G. Snatzke, *Angew. Chem.* **1979**, *99*, 389-393.

10. N. Harada, S.L. Chen, K. Nakanishi, *J. Am. Chem. Soc.* **1975**, *97*, 5345-5352.

11. N. Harada, K. Nakanishi, *Acc. Chem. Res.* **1972**, *5*, 257-263.

12. J. Tanaka, *Bull. Chem. Soc. Jpn.* **1963**, *36*, 833-847.

13. R.S. Cahn, C.K. Ingold, V. Prelog, *Angew. Chem.* **1966**, *78*, 413-447.

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