Notiz / Note

A Novel Highly Stereoselective Synthesis of Tetrahydrodibenzo-1,4-dioxanes

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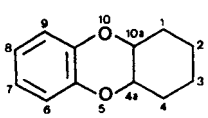
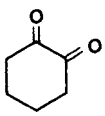
The *cis*- and *trans*-tetrahydrodibenzo-1,4-dioxanes 2 and 3 were synthesized from 2-bromocyclohexanone in five steps.

1,4-Benzodioxanes are a class of heterocyclic compounds with antihypertensive[1], sedative[2], and hepatoprotective[3] activity. For the synthesis of the ring system a number of methods has been described in the literatur[4-10]. Amongst them a simple one-step reaction of 1,2-cyclohexanedione (**1**) with vicinal diols was reported by Mincione et al.[10]. Although the reaction of **1** with *cis*- or *trans*-1,2-cyclohexanediol, promoted by dichlorobis(benzonitrile)palladium(II), was reported to furnish the tetrahydrodibenzo-1,4-dioxanes **2** and **3** in 65% and 50% yield, resp., we have been unable to reproduce these experiments[11], and therefore we describe here our stereoselective synthesis of **2** and **3**, starting from 2-bromo-1-cyclohexanone[12].



2 cis

3 trans



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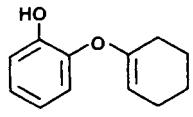

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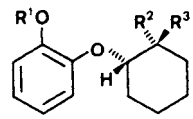
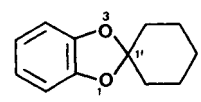


	R^1	R^2	R^3
4	$PhCH_2$	=O	
5	$PhCH_2$	OH	H
6	$PhCH_2$	H	OH
7	$PhCH_2$	OMs	H
8	$PhCH_2$	H	OMs
9	H	OMs	H
10	H	H	OMs



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Alkylation of 2-benzyloxyphenol[13] with 2-bromo-1-cyclohexanone in the presence of potassium carbonate gave the 2-aryloxyketone **4** in 62% yield. Treatment of this with sodium borohydride in ethanol at room temperature yielded a ca. 1:2 mixture of the *cis*/*trans*-diastereomeric alcohols **5** and **6**, which could easily be separated by chromatography. The configuration of the secondary hydroxy group relative to the aryloxy group in both alcohols was determined by ^1H NMR and in the case of **6** also by independent synthesis starting from cyclohexene oxide. Subsequent steps were the formation of the 1-mesylate (**5/6** → **7/8**), removal of the benzyl ether group (**7/8** → **9/10**), and finally ring closure by means of sodium methoxide (**9/10** → **3/2**).

In the synthetic steps, a single inversion (**9** → **3** and **10** → **2**) occurred in each sequence, the yields in these steps were, however, very different. The *cis* compound **2** was obtained in 81% yield, while the *trans* isomer **3** could only be isolated by chromatography on silica gel as a byproduct in 4% yield. According to the ^1H-NMR spectrum of the crude product mixture in this latter reaction the major component was the enol ether **11** (δ = 4.95, m, 2-H) which could not be isolated since it converted into **12**[14] during attempted isolation.

The different reactivities of these two stereoisomers **9** and **10** can be explained by their different conformations. In **9** the mesyl group and the neighbouring hydrogen atom can assume antiperiplanar positions, which favours elimination instead of S_N2-type ring closure to give **3**.

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Experimental

Melting points were determined on a Kofler hotstage and are not corrected. – The 100-MHz ^1H- and the ^{13}C-NMR spectra were recorded on a Varian XL 100 spectrometer with TMS as internal standard in $CDCl_3$, the 400-MHz ^1H- and 101-MHz ^{13}C-NMR spectra (marked by an asterisk *) with a Varian XLAA 400 spectrometer in C_6D_6. – Mass spectra were obtained on a Jeol 0156-2 instrument (10 kV, 75 eV). – For workup, the solutions were dried with $MgSO_4$ and evaporated in vacuo.

2-(2-Benzyloxyphenoxy)-1-cyclohexanone (**4**): A mixture of 2-benzyloxyphenol[13] (25.8 g, 130 mmol), 2-bromocyclohexanone[12] (46.1 g, 260 mmol), and anhydrous potassium carbonate (40 g) was refluxed with stirring in dry acetone (250 ml) for 20 h. The potas-

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sium carbonate was removed by filtration and the solution evaporated. The residue was dissolved in 250 ml of dichloromethane, washed with water, with 10% HCl, and again with water until neutral. The organic layer gave 48 g of an oil, which could be crystallized from benzene to give colourless needles (23.8 g, 62%), m. p. 51–53°C. – IR (KBr): $\tilde{\nu}$ = 1720 cm^{-1} (C=O). – ^1H NMR: δ = 1.50–2.70 (m, 8H, 3,4,5,6-H_2), 4.64 (m, 1H, J = 8.5 and 4.5 Hz, 2-H), 5.09 (s, 2H, benzylic CH_2), 6.80–7.50 (m, 9H, arylic H).

$C_{19}H_{20}O_3$ (296.4) Calcd. C 77.00 H 6.80
Found C 69.92 H 6.82

cis- (**5**) *and trans-2-(2-Benzyloxyphenoxy)-1-cyclohexanol* (**6**): To a stirred solution of **4** (536 mg, 1.8 mmol) in 25 ml of dry ethanol, sodium borohydride (268 mg, 7.1 mmol) was added at room temp. After 12 h a few drops of acetic acid were added to decompose the excess of the reagent. After dilution with water the product was extracted with dichloromethane. The organic layer was washed with sodium hydrogen carbonate solution and with water. Usual workup gave 450 mg of a colourless oil, which was further separated on a silica gel column (benzene/ethyl methyl ketone, 20:1).

5: 149 mg (27%), colourless oil, R_f = 0.43. – ^1H NMR: δ = 1.20–2.20 (m, 8H, 3,4,5,6-H_2), 3.85 (m, 1H, J = 6.0, 3.0 and 3.0 Hz, 1-H), 4.19 (m, 1H, J = 8.5, 3.0 and 3.0 Hz, 2-H), 5.10 (s, 2H, benzylic CH_2), and 6.90–7.50 (m, 9H, arylic H). – MS: $M^{+\cdot}$ calcd. for $C_{19}H_{22}O_3$ 198.1568, found 198.1566.

6: 272 mg (50%) of colourless needles from *n*-hexane, m. p. 58 to 60°C, R_f = 0.39. – ^1H NMR: δ = 1.20–2.30 (m, 8H, 3,4,5,6-H_2), 3.64 (m, 1H, J = 11.0, 9.0, and 5.0 Hz, 1-H), 3.80 (m, 1H, J = 11.0, 9.0, and 4.0 Hz, 2-H), 5.10 (s, 2H, benzylic CH_2), 6.80–7.50 (m, 9H, arylic H). – MS: $M^{+\cdot}$ calcd. for $C_{19}H_{22}O_3$ 198.1568, found 198.1570.

cis-2-(2-Benzyloxyphenoxy)-1-mesyloxycyclohexane (**7**): To a solution of **5** (307 mg, 1 mmol) in 3 ml of dry pyridine, methanesulfonyl chloride (0.1 ml, 1.2 mmol) was added, and the mixture was allowed to stand overnight. The product was extracted with dichloromethane, washed with water until neutral and worked up: 372 mg (96%) of a white crystalline product with m. p. 85–87°C (from methanol). – ^1H NMR: δ = 1.20–2.30 (m, 8H, 3,4,5,6-H_2), 2.84 (s, 3H, mesyloxy-CH_3), 4.31 (m, 1H, J = 9.0, 3.5, and 2.5 Hz, 2-H), 5.04 (m, 1H, J = 6.0, 3.5, and 2.5 Hz, 1-H), 5.05 (s, 2H, benzylic CH_2), 6.90–7.50 (m, 9H, arylic H).

$C_{20}H_{24}O_5S$ (376.5) Calcd. C 63.80 H 6.42 S 8.51
Found C 63.77 H 6.40 S 8.62

trans-2-(2-Benzyloxyphenoxy)-1-mesyloxycyclohexane (**8**): In a similar procedure as described for **7**, 227 mg (0.76 mmol) of **6** in 3 ml of dry pyridine was treated with 0.07 ml (0.91 mmol) of methanesulfonyl chloride. The product (263 mg, 92%) was a viscous oil. – ^1H NMR: δ = 1.20–2.40 (m, 8H, 3,4,5,6-H_2), 2.88 (s, 3H, mesyloxy-CH_3), 4.29 (m, 1H, J = 9.5, 9.0, and 4.5 Hz, 2-H), 4.68 (m, 1H, J = 9.5, 8.5, and 4.0 Hz, 1-H), 5.06 (s, 2H, benzylic CH_2), 6.90–7.50 (m, 9H, arylic H). – MS: $M^{+\cdot}$ calcd. for $C_{20}H_{24}O_5S$ 376.1543, found 376.15437.

cis-2-(2-Hydroxyphenoxy)-1-mesyloxycyclohexane (**9**): A solution of **7** (388 mg, 1.03 mmol) in a mixture of 10 ml of methanol and 5 ml of tetrahydrofuran was hydrogenated at room temp. in the presence of 10% Pd-C until 1 equivalent of H_2 had been absorbed. Filtration and usual workup gave colourless plates: 252 mg (76%), m. p. 82–84°C. – ^1H NMR: δ = 1.30–2.30 (m, 8H, 3,4,5,6-H_2), 3.02 (s, 3H, mesyloxy-CH_3), 4.34 (m, 1H, J = 2.5, 6.5, and 6.5 Hz, 2-H), 5.10 (m, 1H, J = 2.5, 2.5, and 6.5 Hz, 1-H), 6.32 (bs, 1H, OH), 6.80–7.00 (m, 4H, arylic H).

$C_{13}H_{18}O_5S$ (286.3) Calcd. C 54.53 H 6.34 S 11.19
Found C 54.32 H 6.30 S 11.24

trans-2-(2-Hydroxyphenoxy)-1-mesyloxycyclohexane (**10**): Compound **8** (263 mg, 0.7 mmol) was hydrogenated as described for **9** and gave **10** (177 mg, 89%), colourless oil. – ^1H NMR: δ = 1.25–2.30 (m, 8H, 3,4,5,6-H_2), 3.06 (s, 3H, mesyloxy-CH_3), 4.31 (m, 1H, J = 9.0, 9.5, and 4.0 Hz, 2-H), 4.71 (m, 1H, J = 8.0, 9.0, and 4.3 Hz, 1-H), 6.10 (br. s, 1H, OH), 6.75–7.10 (m, 4H, arylic H). – MS: $M^{+\cdot}$ calcd. for $C_{13}H_{18}O_5S$ 286.0874, found 286.0879.

cis-1,2,3,4,4a,10a-Hexahydrodibenzo[b,e][1,4]dioxin (**2**): A mixture of **10** (197 mg, 0.69 mmol) in 10 ml methanol and 0.69 ml 1 N sodium methoxide was refluxed for 2 h. After evaporation of the solvent dichloromethane (25 ml) and 10% HCl (2 ml) were added. The organic layer gave after usual workup a pure product, which was chromatographed on TLC (*n*-hexane) to afford **2** (106 mg, 81%) of m. p. 52–54°C (from methanol, ref.[10] 43–44°C). – IR (KBr): $\tilde{\nu}$ = 2942, 2914, 2870 (C–H), 1584, 1480, 1414 (C=C), 1242, and 1042 cm^{-1} (C–O). – ^1H NMR*: δ = 0.94 (m, 2H, 2-H_{ax}, 3-H_{ax}), 1.26 (m, 2H, 1-H_{ax}, 4-H_{ax}), 1.41 (m, 2H, 2-H_{eq}, 3-H_{eq}), 1.74 (m, 2H, 1-H_{eq}, 4-H_{eq}), 3.83 (m, 2H, ΣJ = 14.5 Hz, 4a-H and 10a-H), 6.75 (m, 2H, 6-H, 9-H), 7.04 (m, 2H, 7-H, 8-H). – ^{13}C NMR*: δ = 21.51 (C-2, C-3), 27.99 (C-1, C-4), 72.09 (C-4a, C-10a), 117.60 (C-6, C-9), 121.57 (C-7, C-8), 143.02 (C-6a, C-9a).

$C_{12}H_{14}O_2$ (190.2) Calcd. C 75.76 H 7.42
Found C 75.71 H 7.44

trans-1,2,3,4,4a,10a-Hexahydrodibenzo[b,e][1,4]dioxin (**3**) *and Spiro[1,3-benzodioxole-2,1'-cyclohexane]* (**12**): **9** (2.25 g, 7.68 mmol) was refluxed in 40 ml of methanol with 8 ml of 1 N sodium methoxide for 2 h. The same workup procedure as described for **2** gave an oil (1.08 g), which was chromatographed on a silica gel column with *n*-hexane/acetone (100:1) to yield 60 mg (4%) of **3**, m. p. 115–117°C (from *n*-hexane, ref.[10] non-crystalline compound) and 540 mg (36%) of **12**, m. p. 51–52°C (ref.[14] 47°C).

3: IR (KBr): $\tilde{\nu}$ = 2950, 2870 (C–H), 1570, 1477, 1442, 1428 (C=C), 1242, and 1028 cm^{-1} (C–O). – ^1H NMR*: δ = 0.80 (m, 2H, 2-H_{ax}, 3-H_{ax}), 1.16 (m, 2H, 1-H_{ax}, 4-H_{ax}), 1.25 (m, 2H, 2-H_{eq}, 3-H_{eq}), 1.92 (m, 2H, 1-H_{eq}, 4-H_{eq}), 3.38 (m, 2H, ΣJ = 26.5 Hz, 4a-H_{ax}, 10a-H_{ax}), 6.76 (m, 2H, 6-H, 9-H), 7.05 (m, 2H, 7-H, 8-H). – ^{13}C NMR*: δ = 23.76 (C-2, C-3), 30.30 (C-1, C-4), 76.55 (C-4a, C-10a), 117.52 (C-6, C-9), 121.67 (C-7, C-8), 144.66 (C-6a, C-9a).

$C_{12}H_{14}O_2$ (190.2) Calcd. C 75.76 H 7.42
Found C 75.47 H 7.40

12: ^1H NMR: δ = 1.40–2.02 (m, 10H, 2',3',4',5',6'-H_2), 6.68 (s, 4H, arylic H).

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