

Notiz / Note

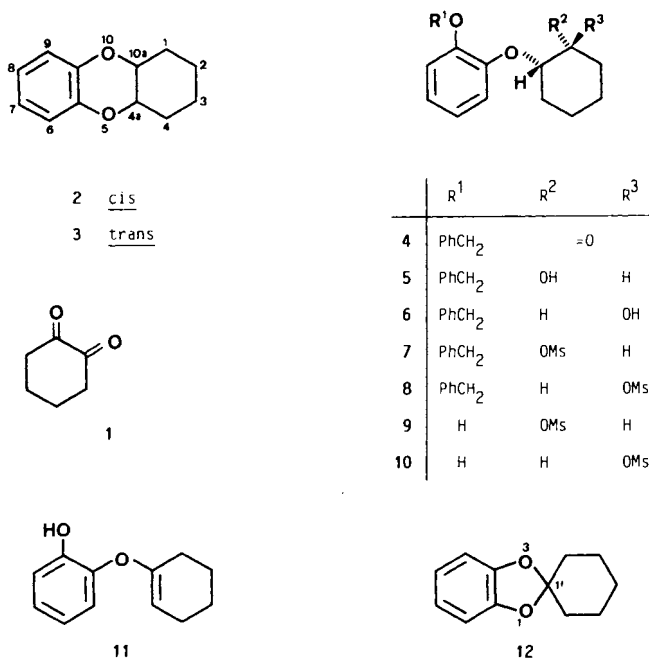
A Novel Highly Stereoselective Synthesis of Tetrahydrodibenzo-1,4-dioxanes

Sándor Antus^{*a}, Eszter Baitz-Gács^b, Günter Snatzke^{*c}, and Tamás S. Tóth^aResearch Group for Alkaloid Chemistry, Hungarian Academy of Sciences^a, H-1521 Budapest, POB 91 (Hungary)Central Research Institute for Chemistry, Hungarian Academy of Sciences^b, H-1525 Budapest, POB 14 (Hungary)Lehrstuhl für Strukturchemie, Ruhruniversität Bochum^c, D-4630 Bochum 1, POB 102148 (F. R. Germany)

Received January 5, 1989

Key Words: Dichotomy in S_N2 reactions / 1,4-Benzodioxanes, potential biological activity of**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 antihypertensive¹⁾, sedative²⁾, and hepatoprotective³⁾ activity. For the synthesis of the ring system a number of methods has been described in the literature⁴⁻¹⁰⁾. 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 experiments¹¹⁾, and therefore we describe here our stereoselective synthesis of 2 and 3, starting from 2-bromo-1-cyclohexanone¹²⁾.



tone 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 12¹⁴⁾ 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.

The Budapest authors thank the *Ministry of Culture and Education*, Project Number 5-631, and G. S. the *Fonds der Chemie* for valuable financial support. For the elemental analysis we thank Mrs. I. Balogh-Batta.

Experimental

Melting points were determined on a Kofler hotstage and are not corrected. — The 100-MHz ¹H- and the ¹³C-NMR spectra were recorded on a Varian XL 100 spectrometer with TMS as internal standard in CDCl₃, the 400-MHz ¹H- and 101-MHz ¹³C-NMR spectra (marked by an asterisk *) with a Varian XLAA 400 spectrometer in C₆D₆. — Mass spectra were obtained on a Jeol 0156-2 instrument (10 kV, 75 eV). — For workup, the solutions were dried with MgSO₄ and evaporated in vacuo.

2-(2-Benzyloxyphenoxy)-1-cyclohexanone (4): A mixture of 2-benzyloxyphenol¹³⁾ (25.8 g, 130 mmol), 2-bromocyclohexanone¹²⁾ (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-

Alkylation of 2-benzyloxyphenol¹³⁾ with 2-bromo-1-cyclohexanone in the presence of potassium carbonate gave the 2-aryloxyke-

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-H₂), 4.64 (m, 1H, *J* = 8.5 and 4.5 Hz, 2-H), 5.09 (s, 2H, benzylic CH₂), 6.80–7.50 (m, 9H, arylc H).

C₁₉H₂₀O₃ (296.4) Calcd. C 77.00 H 6.80
Found C 69.92 H 6.82

cis-**(5)** and *trans*-2-(2-Benzoyloxyphenoxy)-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-H₂), 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 CH₂), and 6.90–7.50 (m, 9H, arylc H). — MS: M⁺ calcd. for C₁₉H₂₂O₃ 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-H₂), 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 CH₂), 6.80–7.50 (m, 9H, arylc H). — MS: M⁺ calcd. for C₁₉H₂₂O₃ 198.1568, found 198.1570.

cis-2-(2-Benzoyloxyphenoxy)-1-mesyloxy-cyclohexane (**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-H₂), 2.84 (s, 3H, mesyloxy-CH₃), 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 CH₂), 6.90–7.50 (m, 9H, arylc H).

C₂₀H₂₄O₅S (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-Benzoyloxyphenoxy)-1-mesyloxy-cyclohexane (**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-H₂), 2.88 (s, 3H, mesyloxy-CH₃), 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 CH₂), 6.90–7.50 (m, 9H, arylc H). — MS: M⁺ calcd. for C₂₀H₂₄O₅S 376.1543, found 376.15437.

cis-2-(2-Hydroxyphenoxy)-1-mesyloxy-cyclohexane (**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 H₂ 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-H₂), 3.02 (s, 3H, mesyloxy-CH₃), 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, arylc H).

C₁₃H₁₈O₃S (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-mesyloxy-cyclohexane (**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-H₂), 3.06 (s, 3H, mesyloxy-CH₃), 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, arylc H). — MS: M⁺ calcd. for C₁₃H₁₈O₃S 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). — ¹³C 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).

C₁₂H₁₄O₂ (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). — ¹³C 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).

C₁₂H₁₄O₂ (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'-H₂), 6.68 (s, 4H, arylc H).

CAS Registry Numbers

2: 75459-45-9 / **3**: 75768-17-1 / **4**: 119657-49-7 / **5**: 119657-50-0 / **6**: 119657-51-1 / **7**: 119657-52-2 / **8**: 119657-53-3 / **9**: 119657-54-4 / **10**: 119657-55-5 / **12**: 182-55-8 / *o*-PhCH₂OC₆H₄OH: 6272-38-4 / 2-bromocyclohexanone: 822-85-5

¹ R. D. Clark, J. M. Caroon, A. F. Kluge, D. R. Repke, A. P. Roszkowski, A. M. Strosberg, S. Baker, S. M. Bitter, M. D. Okoda, *J. Med. Chem.* **26** (1983) 567.

² W. L. Nelson, J. E. Wennerstrom, C. D. Dyer, M. J. Engel, *J. Med. Chem.* **26** (1983) 881.

³ H. Wagner in *Plant Constituents with Antihepatotoxic Activity in Natural Products as Medicinal Agent*, (J. L. Beal, E. Reinhard, Eds.), p. 217, Hippokrates, Stuttgart 1980.

⁴ E. C. Elderfield, *Heterocycl. Compd.* **6** (1957) 71.

⁵ A. Goosen, C. W. McClelland, *J. Chem. Soc. Chem. Commun.* **1975**, 655.

⁶ W. L. Nelson, J. E. Wennerstrom, *J. Chem. Soc. Chem. Commun.* **1976**, 921.

⁷ R. D. Clark, L. J. Kurz, *Heterocycles* **23** (1985) 2005.

- ⁸⁾ A. M. Haruta, J. Y. Satoh, *Chem. Letters* **1980**, 473.
⁹⁾ A. Delago, G. Leclerc, C. Labato, B. Mauleon, *Tetrahedron Lett.* **29** (1988)3671.
¹⁰⁾ E. Mincione, A. Sirma, D. Covini, *J. Org. Chem.* **46** (1981) 1010.
¹¹⁾ Using the conditions given in ref.¹⁰⁾ we obtained **2** and **3** only as byproducts in 6% and 12% yield, resp. The main products were in both cases the bisacetals of 1,2-cyclohexanedione with *cis*- and *trans*-1,2-cyclohexanediol. Details will be published elsewhere.
¹²⁾ A. Kötzt, C. Gotz, *Liebigs Ann. Chem.* **358** (1907) 195.
¹³⁾ O. Schmidt, W. Blank, *Chem. Ber.* **89** (1956) 283.
¹⁴⁾ A. J. Birch, *J. Chem. Soc.* **1947**, 102.

[3/89]

Dieses Heft wurde am 9. Mai 1989 ausgegeben.

© VCH Verlagsgesellschaft mbH, D-6940 Weinheim, 1989 — Printed in the Federal Republic of Germany.

Verantwortlich für den Inhalt: Prof. Dr. Heinrich Nöth, München (Teil A), Prof. Dr. Henning Hopf, Braunschweig (Teil B). Redaktion: Dr. Robert Temme, Weinheim.

VCH Verlagsgesellschaft mbH (Geschäftsführer: Hans Dirk Köhler), Pappelallee 3, Postfach 101161, D-6940 Weinheim.

Anzeigenleitung: R. J. Roth, Weinheim.

Die Wiedergabe von Gebrauchsnamen, Handelsnamen, Warenbezeichnungen und dgl. in dieser Zeitschrift berechtigt nicht zu der Annahme, daß solche Namen ohne weiteres von jedermann benutzt werden dürfen. Vielmehr handelt es sich häufig um gesetzlich geschützte eingetragene Warenzeichen, auch wenn sie nicht als solche gekennzeichnet sind.

Alle Rechte, insbesondere die der Übersetzung in andere Sprachen, vorbehalten. Kein Teil dieser Zeitschrift darf ohne schriftliche Genehmigung des Verlages in irgendeiner Form — durch Photokopie, Mikrofilm oder irgendein anderes Verfahren — reproduziert oder in eine von Maschinen, insbesondere von Datenverarbeitungsmaschinen verwendbare Sprache übertragen oder übersetzt werden. — All rights reserved (including those of translation into other languages). No part of this issue may be reproduced in any form — by photoprint, microfilm, or any other means — nor transmitted or translated into a machine language without the permission in writing of the publishers. — Von einzelnen Beiträgen oder Teilen von ihnen dürfen nur einzelne Vervielfältigungsstücke für den persönlichen oder sonstigen eigenen Gebrauch hergestellt werden. Die Weitergabe von Vervielfältigungen, gleichgültig zu welchem Zweck sie hergestellt werden, ist eine Urheberrechtsverletzung. — Der Inhalt dieses Heftes wurde sorgfältig erarbeitet. Dennoch übernehmen Autoren, Herausgeber, Redaktion und Verlag für die Richtigkeit von Angaben, Hinweisen und Ratschlägen sowie für eventuelle Druckfehler keine Haftung. — This journal was carefully produced in all its parts. Nevertheless, authors, editors and publisher do not warrant the information contained therein to be free of errors. Readers are advised to keep in mind that statements, data, illustrations, procedural details or other items may inadvertently be inaccurate.

Valid for users in the USA: The appearance of the code at the bottom of the first page of an article in this journal (serial) indicates the copyright owner's consent that copies of the article may be made for personal or internal use, or for the personal or internal use of specific clients. This consent is given on the condition, however, that the copier pay the stated percopy fee through the Copyright Clearance Center, Inc., for copying beyond that permitted by Sections 107 or 108 of the U.S. Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective work, or for resale. For copying from back volumes of this journal see »Permissions to Photo-Copy: Publisher's Fee List« of the CCC.

In der Zeitschrift werden keine Rezensionen veröffentlicht; zur Besprechung eingehende Bücher werden nicht zurückgesandt.
 Herstellung: Krebs-Gehlen Druckerei, Hemsbach/Bergstraße.