32. α,α,α′,α′-Tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOLs) for Resolutions of Alcohols and as Chiral Solvating Agents in NMR Spectroscopy

Preliminary Communication

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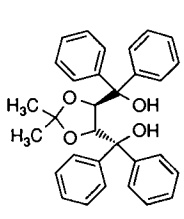
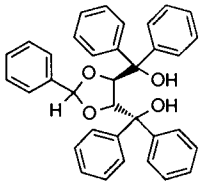
The use of α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanols (= TADDOLs; **1**) as chiral NMR shift reagents (^{1}H, ^{13}C, ^{19}F) is described. In many cases, the ratio of enantiomeric alcohols and amines can be determined under standard conditions of measurement ($CDCl_3$ as solvent, room temperature). The preparation and use of a new type of TADDOL, the tetrakis(dimethylamino) derivative **1d**, is described. Menthol, octan-2-ol, and oct-1-yn-3-ol are partially resolved by crystallization of clathrates with **1c** and **1d**.

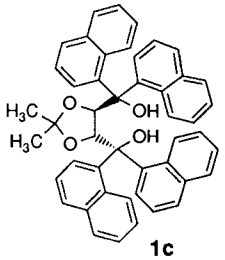
Diols of type **1**, readily available from alkyl tartrates in two steps [1], have been found to be useful chiral auxiliaries for the preparation of enantiomerically pure compounds (EPC) by stoichiometric or catalytic enantioselective reactions [1] [2] as well as by enantiomer separation of ketones by crystallization [3]. A recent report [4] by *Toda et al.* prompts us to describe our experiments aimed at the resolution of alcohols using TADDOLs.



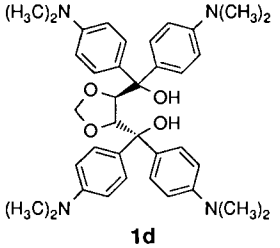
1a



1b



1c



1d

Since it is known from crystal structure analyses of TADDOL clathrates that these chiral diols form H-bonds with O-atoms of C=O groups, and with N-atoms of amines [1c] [3], we thought that, if these interactions were detectable by NMR spectroscopy, then this analytical method might lead the way to efficient enantiomer separation on a preparative scale.

A more or less arbitrarily chosen collection of compounds, which are part of current research projects in our laboratories, was used to prepare $CDCl_3$ solutions containing 2 equiv. of the 'parent' TADDOL **1a** and 1 equiv. of the alcohol of interest. The ^{1}H-, ^{13}C-, and ^{19}F-NMR spectra of these mixtures were measured at ambient temperature. Compounds **2–6** (*Fig. 1*) showed nonequivalence of certain ^{1}H-, ^{13}C-, and ^{19}F-NMR signals (arrows) from enantiomers. The resulting chemical-shift differences $\Delta\delta$ were sufficiently

[1]) Part of the projected Dissertation of *Ch. v. d. B.-H.*, ETH-Zürich.

[2]) Part of the Diplomarbeit of *U. L.*, ETH-Zürich, 1991.

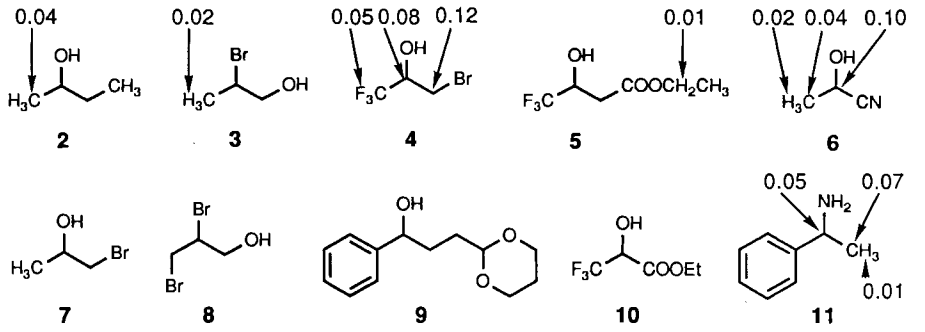


Fig. 1. *^1H-, ^{13}C-, or ^{19}F-NMR spectra of compounds* **2**–**11**, *showing nonequivalence of signals from enantiomers in the presence of* **1a** *as chiral solvating agent* (1:2 ratio; $CDCl_3$, r.t.). Atoms with sufficiently large anisochrony to determine the accurate ratio of the enantiomers are marked with an arrow ($\Delta\delta$'s are given in ppm).

large to determine the ratio of enantiomers accurately. Compounds **7**–**10** also gave enantioselective shift effects, but the degree of anisochrony was smaller so that a reliable determination of enantiomeric excesses was not possible without further optimization of the measuring conditions (ratio of chiral solvating agent to substrate, temperature, solvent, *etc.*). This effect was not only observed with alcohols **2**–**10**, but also with amine **11**, the side-chain C-atoms of which show splitted ^{13}C-NMR signals in the presence of **1a**. Two typical examples are illustrated in *Fig. 2*.

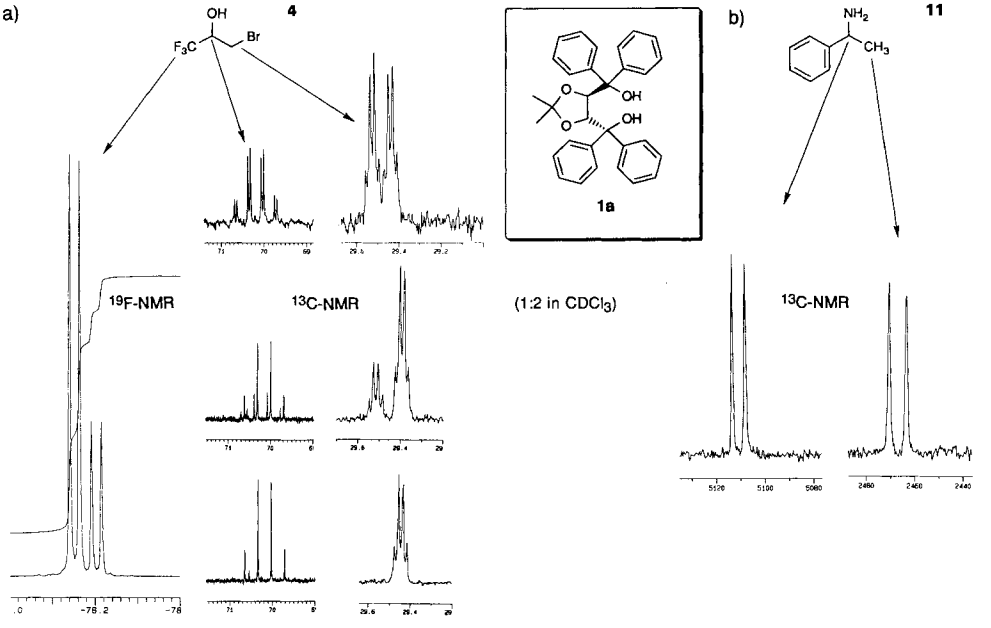
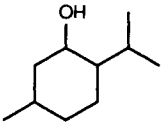


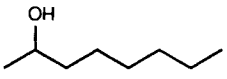
Fig. 2. a) *Sections of the ^{13}C- and the ^{19}F-NMR spectra* (100 and 282 MHz, resp.; $CDCl_3$, r.t.) *of bromohydrine* **4** *in the presence of diol* **1a** (the 1:2 ratio of **4**/**1a** was chosen for the NMR measurements, because **4** and **1a** crystallize together in this ratio). Enantiomerically pure (bottom), enantiomerically enriched (middle), and racemic sample (top) of **4**. b) *Aliphatic region of the ^{13}C-NMR spectrum* (100 MHz; $CDCl_3$, r.t.) *of 1-phenylethylamine* (**11**) *measured in the presence of* **1a** (ratio 1:2).

To our surprise[3]), we found that when the pentaphenyl derivative[4]) **1b** was used as a chiral additive, the anisochrony was either absent or *very* small as compared with **1a**. The results with the TADDOL **1a** are promising, and further investigations are in progress. We are especially interested in the use of a combination of this diol with an achiral lanthanide shift reagent. Recently, a thorough, up-to-date review of chiral solvating agents (CSA) appeared in the literature [5].

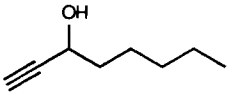
The preparative work, *i.e.* experiments involving resolution by crystallization, was carried out mainly with the α-naphthyl and the 4-(dimethylamino)phenyl derivative **1c** [1c] and **1d**, respectively. The α-naphthyl substituents in **1c** make its OH groups sterically highly hindered, and we thought, its complexation highly specific. The combination of four dimethylamino groups and a formaldehyde-derived dioxolane ring in **1d** was chosen to allow for ready separations and recovery of this TADDOL from nonbasic partners by non-destructive (!) acidic aqueous extraction. A single crystallization of **1c** from *rac*-menthol (*rac*-**12**) and of **1d** from the alcohols *rac*-**13** and *rac*-**14** gave clathrates containing the



rac-**12**



rac-**13**



rac-**14**

alcohols and the TADDOLs in a 1:1 (**1c**/**12**, **1d**/**13**) or 1:2 (**1d**/**14**) ratio; recovery of the secondary alcohols and measurement of their optical rotation showed that an enantiomer enrichment had occurred (50% optical purity for (−)-**12**, 33% optical purity for (−)-**13**, and 60% optical purity for (−)-**14**). The tetramine **1d** was removed from the alcohols by extraction into 1N aq. HCl, and recovered in high yield.

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Experimental Part

General. The (*R,R*)-dimethyl *O,O*-alkylidenetartrate acetals were prepared as described in [1c]. Solvents (*Fluka, puriss.*) were used without further purification. M.p.: *Büchi 510*; uncorrected. Optical rotation: *Perkin-Elmer-241* polarimeter, in 1-dm cells. IR: *Perkin-Elmer 983* or *Perkin-Elmer 297*. NMR: Unless otherwise indicated, at r.t. using a *Bruker AMX 400, Varian XL-300, Bruker WM 300*, or a *Varian Gemini 200* spectrometer. Chemical shifts (δ) in ppm rel. to internal TMS, coupling constants *J* in Hz. MS: *VG Tribrid*. Microanalyses were performed by Mikroanalytisches Laboratorium der ETH-Zürich.

The NMR shift-experiments were performed on 100–150 mg of a 1:2 molar mixture alcohol or amine/**1**, dissolved in 1 ml of $CDCl_3$, at r.t. No difference was observed between the spectra obtained from a freshly prepared soln. and a soln. which was several days old.

(4R,5R)-α,α,α′,α′-Pentaphenyl-1,3-dioxolane-4,5-dimethanol (**1b**): Following the procedure described in [1c], 109 g (409 mmol) of (*R,R*)-dimethyl *O,O*-benzylidenetartrate in 1.09 l of THF were added to 1943 mmol of PhMgBr (prepared from 48.5 g of Mg and 305 g of bromobenzene) in 1.05 l of THF. The resulting crude product (285 g) was dissolved in 500 ml of boiling toluene, and to the stirred soln. were added 500 ml of hexane. After cooling to r.t. overnight, the soln. was cooled to 4° for 2 h and then filtered. Drying *in vacuo* yielded 164 g (78%) of colourless crystalline **1b**. M.p. 196.4–198.2°. $[\alpha]_D^{r.t.} = +10.4$ ($c = 1.0$, $CHCl_3$)[4]). IR ($CHCl_3$): 3560*w*, 3400 (br.),

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[3]) In applications of the pentaphenyl-substituted diolate from **1b** as a chiral ligand of titanates, higher enantioselectivities are often observed than with the tetraphenyl-substituted diolate from **1a**!

[4]) The m.p. and optical rotation of **1b** given in [1b] turned out not to be correct (see *Exper. Part*).

3060*m*, 3000*m*, 2900*w*, 1950*w*, 1890*w*, 1810*w*, 1600*w*, 1490*m*, 1450*m*, 1400*m*, 1090*m*, 1030*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.09 (*s*, OH); 3.28 (*s*, OH); 5.13 (*d*, *J* = 5.0, H–C(4)); 5.16 (*s*, H–C(2)); 5.32 (*d*, *J* = 5.0, H–C(5)); 7.09–7.58 (*m*, 25 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 146.2; 144.4; 144.2; 143.0; 137.1; 129.4; 128.2; 127.9; 127.8; 127.5; 127.4; 127.3; 127.1; 126.9; 126.8; 105.0; 81.6; 80.9; 78.7; 78.6. Anal. calc. for $C_{35}H_{30}O_4$ (514.62): C 81.69, H 5.88; found: C 81.75, H 5.75.

α,α,α′,α′-Tetra[4-(dimethylamino)phenyl]-1,3-dioxolane-4,5-dimethanol (**1d**): Following the procedure described in [1c], 9.51 g (50 mmol) of (*R,R*)-dimethyl *O,O*-methylidenetartrate in 110 ml of THF were added to 220 mmol of [4-(dimethylamino)phenyl]magnesium bromide (prepared from 5.77 g of Mg and 44.07 g of 4-bromo-*N,N*-dimethylaniline) in 75 ml of THF. The resulting brownish oil (31.48 g) was stirred with 100 ml of Et_2O for 20 h at r.t. to afford 17.97 g of brownish crystals. This product was purified by chromatography (420 g of silica gel, CH_2Cl_2, then Et_2O/pentane 10:1). Evaporation of the Et_2O/pentane fraction yielded 17.16 g of **1d**, which was recrystallized from 450 ml of pentane/toluene 1:2 to give 14.34 g (47%) of **1d** as pale green crystals, containing 1 equiv. of toluene. M.p. 134.8–137.6°. $[\alpha]_D^{r.t.} = -61.0$ (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): 3560*w*, 3000*m*, 2880*w*, 2800*w*, 1610*s*, 1560*w*, 1520*s*, 1480*w*, 1440*w*, 1350*s*, 1160*s*, 1100*m*, 1060*w*, 950*m*, 820*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.35 (*s*, $CH_3C_6H_5$); 2.54 (*s*, OH); 2.90 (*d*, *J* = 13.8, CH_3); 4.63 (*s*, H–C(4), H–C(5)); 4.95 (*s*, CH_2); 6.57, 6.67 (2*d*, *J* = 9.0, H–C(3′), H–C(5′)); 7.18–7.24 (*m*, $CH_3C_6H_5$); 7.23, 7.35 (2*d*, *J* = 9.0, H–C(2′), H–C(6′)). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.5 (toluene); 40.5; 40.6; 78.1; 81.1; 96.7; 111.8; 111.9; 125.3 (toluene); 127.9; 128.2 (toluene); 128.5; 129.0 (toluene); 132.3 (toluene); 133.7 (toluene); 149.4; 149.5. MS (*D*esorption *E*lectronic *I*onisation): 574 (*51*), 516 (7), 398 (7), 324 (8), 293 (29), 269 (98), 253 (82), 237 (19), 224 (8), 165 (6), 148 (97), 134 (28), 120 (15), 77 (10), 44 (26), 28 (36), 18 (100). Anal. calc. for $C_{37}H_{46}N_4O_4 \cdot C_7H_8$ (702.95): C 75.18, H 7.74, N 7.97; found: C 74.90, H 7.78, N 8.20.

To obtain solvent free **1d**, 1.00 g of **1d**·$CH_3C_6H_5$ was dissolved in 10 ml of CH_2Cl_2, extracted with 4 × 10 ml 1N HCl. The aq. layer was diluted with 80 ml of H_2O followed by the addition of 30 ml of 3N NaOH. The precipitate was isolated and dried at r.t. *in vacuo* to yield 0.85 g of **1d** as solvent-free product (^{1}H-NMR).

Resolution Experiments. rac-*Menthol* (*rac*-**12**): To 2 g of **1c** [1c] suspended in 20 ml of boiling pentane was added *rac*-**12** in portions, until a clear soln. was formed (*ca.* 5 g). The soln. was then stored for 2 weeks in a freezer (−18°), and the crystals formed were isolated and dried under oil-pump vacuum: 1.55 g of colourless crystals as a 1:1 clathrate according to ^{1}H-NMR. Flash chromatography [6] (15 × 2 cm, SiO_2, CH_2Cl_2, 0.2 bar) to separate **1c** from (−)-**12**, and bulb-to-bulb distillation gave 300 mg of (−)-**12** in 52% optical purity. $[\alpha]_D^{r.t.} = -25$ (*c* = 2.2, EtOH; [7]: (1*R*,2*S*,5*R*)-menthol, $[\alpha]_D^{r.t.} = -48$ (*c* = 2.5, EtOH)).

rac-*Octan-2-ol* (*rac*-**13**): To 1 g of **1d**·$CH_3C_6H_5$ were added 30 ml of *rac*-**13** at 120°, until a clear soln. resulted. After cooling to r.t., the precipitate was isolated, washed with pentane (3 × 10 ml), and dried at oil-pump vacuum: 1 g of the colourless 1:1 clathrate (^{1}H-NMR). A CH_2Cl_2 soln. of the clathrate was extracted with 1N HCl, dried ($MgSO_4$), and the solvent evaporated. Bulb-to-bulb distillation of the residue gave 120 mg of (−)-**13** in 33% optical purity. $[\alpha]_{546}^{r.t.} = -3.3$ (*c* = 1.1, $CHCl_3$; [7]: (*R*)-octan-2-ol, $[\alpha]_{546}^{r.t.} = -9.9$ (*c* = 1.0, $CHCl_3$)).

rac-*Oct-1-yn-3-ol* (*rac*-**14**): As described above, to 1 g of **1d**·$CH_3C_6H_5$ was added 5 ml of *rac*-**14** at 120°. From the resulting clathrate (TADDOL/alcohol 1:2; ^{1}H-NMR) were isolated 280 mg of (−)-**14** in 60% optical purity. $[\alpha]_D^{r.t.} = -4.0$ (*c* = 2.4, $CHCl_3$; [8]: (*R*)-oct-1-yn-3-ol, $[\alpha]_D^{r.t.} = -6.7$ (*c* = 1.0, $CHCl_3$)).

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