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Preparation of TADDOL Derivatives for New Applications

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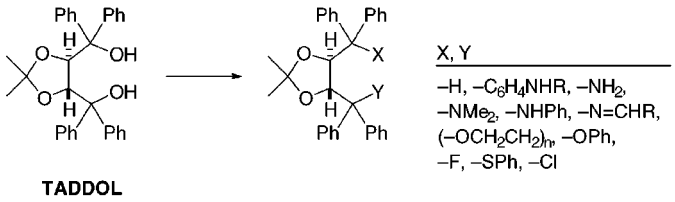
ABSTRACT



Substitution of one or both TADDOL OH groups by other functional groups X, Y is key to new applications of this cheap chiral auxiliary. The Appel reaction and treatment with $SOCl_2$ provide the mono- and dichlorides, respectively. The chlorides are, in turn, replaced by various nucleophiles, and further modifications give a large variety of derivatives, including mono- and ditritylated dioxolanes. The new compounds—available in either enantiomeric form—are ready to be used in enantioselective synthesis and as dopants in liquid crystals.

TADDOLs and their derivatives **A** have found many applications, ranging from chiral ligands on metals to chiral NMR shift reagents, to hosts in inclusion compounds for enantiomer separation,[6] to dopants for generating cholesteric liquid crystal phases.[7] This multitude of usages is due to the fact that TADDOLs are subject to simple, highly combinatorial structural variations: not only is there a large number of aryl halides for the introduction of different aryl groups through Grignard reactions,[6,8] an even larger number of aldehydes and ketones for forming the dioxolane ring,[6,8] and a variety of chiral diesters for switching to other ring systems,[9] but there is also the possibility of modifying or replacing the original OH group(s) on the diarylmethanol unit(s) by other functionalities Y and Z[10−16] (see Figure 1).

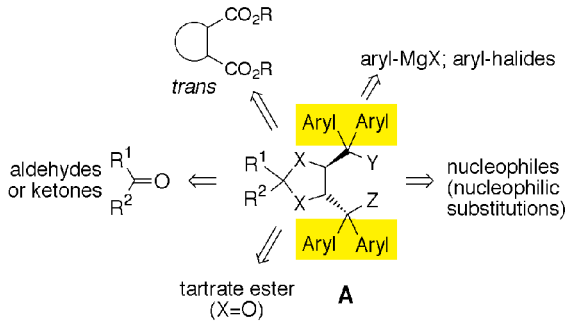


Figure 1. Combinatorial variation of the TADDOL structure **A** by employing five readily available types of precursors.

It is the purpose of this paper to disclose the preparation and some structures of new compounds **8**−**18** derived from the parent TADDOL **1** by the last mentioned variation,

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(5) Laboratorium für Kristallographie, Sonneggstrasse 5, ETH Zürich, CH-8092 Zürich, Switzerland.
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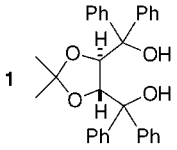
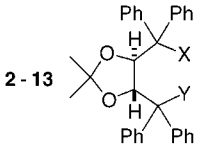
through intermediates **2**−**7** (see Tables 1 and 2 and Figures 2 and 3). There is no doubt in our minds that these readily available products, being mono-, di-, tri-, and tetradentate ligands for metals, will be used for syntheses of enantiopure compounds (EPC) by us and by others.

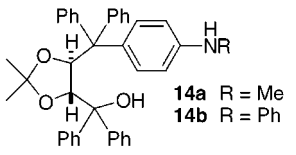
Table 1. Derivatives **2**−**13** of the Parent TADDOL **1**



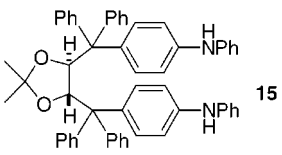


TADDOL derivative	X	Y	ref
2	Cl	OH	10, 13, this paper
3	Cl	Cl	10,13
4	NH_2	OH	10,13
5	NH_2	NH_2	10,13,16, this paper
6	NMe_2	OH	10,13
7	NMe_2	Cl	10, this paper
8	NMe_2	H	this paper
9	NMe_2	PhS	this paper
10	NHPh	OH	this paper
11	4-*t*BuPhO	OH	this paper
12	F	OH	this paper
13	F	F	this paper

Besides the linear (**17**) and cyclic (crown ether[17] **18**, see Figures 3 and 4) triethylene glycol derivatives and the oxazolines[18] **19** (Figure 3), all other new compounds arise from mono- and disubstitutions of the TADDOL OH group(s). The key intermediates in these transformations are the previously described C_1-symmetrical chloro (**2**) and amino alcohols (**4**, **6**) and the C_2-symmetrical dichloride (**3**) and diamine (**5**). We have now greatly improved the transformation of **1** to the monochloride **2** by using the Appel reaction[19] which does not proceed to the dichloride at all,[20] and we found a way around the intermediacy of a diazide[13] by going directly from the dichloride **3** to the diamine **5** in NH_4Cl-buffered ammonia (heating the neat components in an autoclave),[21] see Tables 1 and 2. Thus, the mono- and diamines **4**−**6** are now readily accessible in three simple steps from commercial tartrate acetonide. One additional step, the



14a R = Me
14b R = Ph



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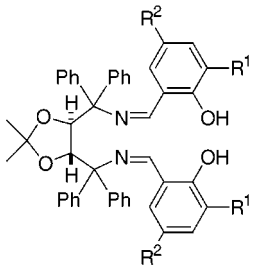

16a $R^1 = R^2 = H$
16b $R^1 = R^2 = t\text{Bu}$
16c $R^1 = t\text{Bu}$, $R^2 = \text{Me}$

Figure 2.

Table 2. Melting Points and Specific Rotations of the TADDOL Derivatives (for more details and full characterization, see Supporting Information)

TADDOL derivative	yield[a] (from) [%]	mp [°C]	$[\alpha]_D^{rt}$ (*c* in $CHCl_3$)	
2[b]	72 (**1**)	135−137	−18.1	(0.4)
3	(**1**)	171−172	−11.1	(1.0)
4	(**2**)	210−211	−58.1	(0.2)
5[c]	63[d] (**3**)	198−200	−45.2	(1.0)
6	(**2**)	181−183	−23.0	(1.2)
7[e]	(**6**)	130−131	−36.4	(1.2)
8[f]	47 (**7**)	68−70	−83.5	(0.7)
9[g]	23 (**7**)	97−98	−99.9	(0.9)
10[h]	80 (**2**)	192−193	−73.6	(1.2)
11[i]	47 (**2**)	154−155	−50.5	(0.7)
12[k]	59[l] (**1**)	138−140	+61.1	(1.2)
13[m]	84 (**1**)	139−140	+108.3	(1.2)
14a[n]	54 (**2**)	223−225	+7.1	(1.1)
14b[n]	83 (**2**)	200−202	−2.1	(1.0)
15[n]	72 (**3**)	168−169	−65.4	(1.0)
16a[p]	54[q] (**5**)	209−210	+41.5	(0.6)
16b[p]	67[q] (**5**)	182−183	+45.5	(1.0)
16c[p]	37[q] (**5**)	245−246	+37.9	(0.6)
17[r]	30[s] (**1**)	232−235	−10.0	(1.0)
18[t]	58 (**1**)	155−157	+41.0	(1.1)
19a[u]	39	182−185	+18.3	(1.0)
19b[u]	48	186−187	−10.6	(1.2)

[a] After purification. [b] **1** and 2 equiv of $P(Ph)_3$, 3 equiv of CCl_4, 2 equiv of pyridine in CH_2Cl_2, rt, 3 d (see footnote 20). [c] **3** and NH_3 (neat), 30 equiv of NH_4Cl, autoclave, 85 °C, 2 d (see footnote 21). [d] In addition, 20% product of cyclization, see compound **7** in ref 10. [e] Fully characterized, including X-ray structure. [f] **7** and 7 equiv of Ph_2PH, THF reflux, 2 d. [g] **7** and PhSH (neat), 60 °C, 1 d. [h] **2** and $PhNH_2$ in CH_2Cl_2, rt, 5 d. [i] **2** and 5 equiv of 4-*t*Bu-C_6H_4OH in CH_2Cl_2, 2 equiv of NEt_3, reflux, 12 h. [k] **1** and 1 equiv of diethylaminosulfur trifluoride (DAST) in CH_2Cl_2, −78 → 0 °C, X-ray structure, see Figure 4. [l] **13** as side product (12%). [m] **1** and 2.5 equiv of DAST, CH_2Cl_2, −78 → 0 °C. [n] **2** or **3** and 10 equiv of of amine in CH_2Cl_2, rt, 3−5 d. [p] **5** and 2 equiv of aldehyde in toluene, reflux, *p*-toluenesulfonic acid (PTSA), 3−7 d. [q] In addition, the monocondensation product is isolated. [r] **1** and triethylenglycol ditosylate in THF, 2 equiv of KO*t*Bu, reflux, 9 h. [s] In addition, 21% of a side product. [t] **1** and triethylenglycol ditosylate in THF, 4 equiv of NaH, reflux, 16 h, X-ray structure, see Figure 4. [u] Half-ester of (*R*,*R*)-tartaric acid acetonide and 3 equiv of PhMgBr, then condensation with (*R*)- or (*S*)-2-amino-2-phenylethanol.

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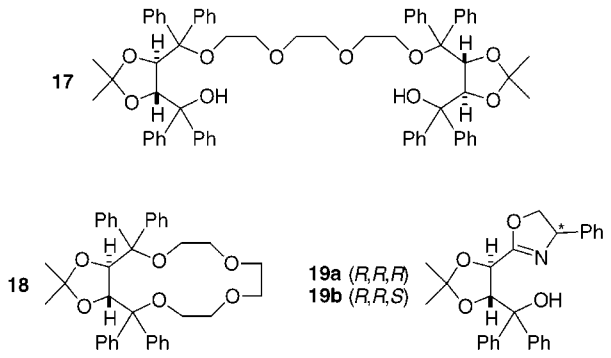

Figure 3.

condensation with salicylic aldehydes, converts the diamine to the tetradentate bis-imines **16**.

While substitutions of chloride with aniline (→**10**), a phenol (→**11**), and thiophenol (→**9**) occurred as expected,

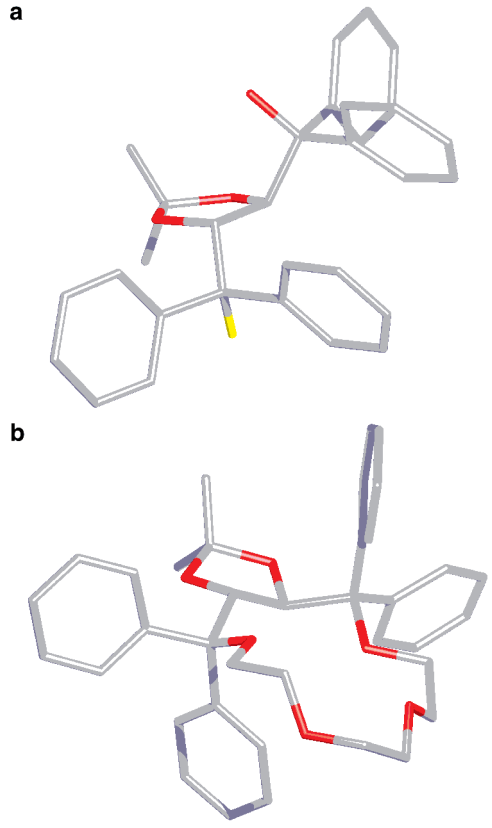

Figure 4. X-ray crystal structures[22] of the fluoro alcohol **12** (a) and of the crown ether **18** (for details see Supporting Information and CCDC 118716 and 118717). As expected,[23] there is no OH···F hydrogen-bond-forming conformation of **12** present in the crystal. Rather, **12** has the rare conformation with the heteroatom (F) above the dioxolane ring, just like the dichloride and the diazide (ref 13). It is intriguing that this compound, like the difluoro derivative **13**, has the opposite sense of rotation (Table 2), as compared to all other simple TADDOL derivatives.

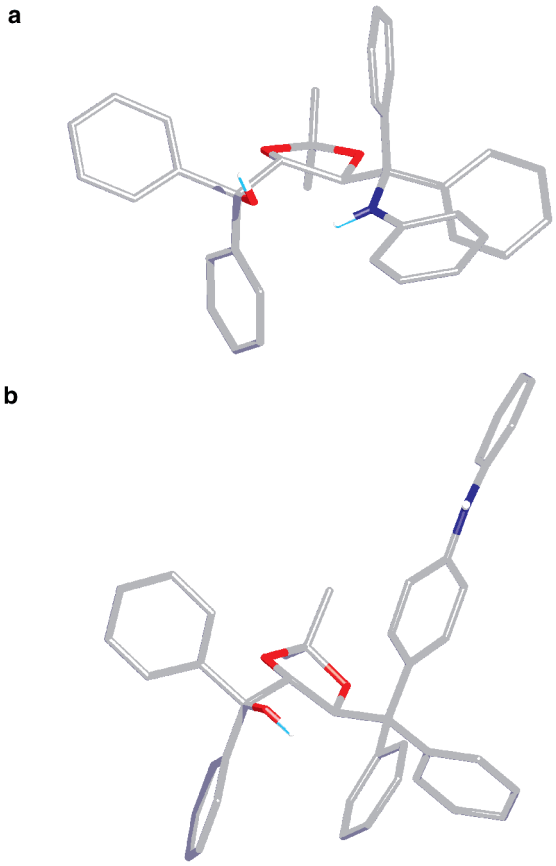

Figure 5. X-ray crystal structures[22] of the amino alcohols **10** (a) and **14b** (b) (for details see Supporting Information and CCDC 118718 and 118719).

we were surprised to isolate trityl derivatives **14** and **15** with *N*-methylaniline and diphenylamine by simply mixing the components in CH_2Cl_2 at room temperature;[24−27] see the structures of **10** and **14b** in Figure 5.

We did not succeed, as yet, in replacing TADDOL OH by R_2P groups, inspite of many attempts;[28] the reaction leading to the product **8** of reduction[29−30] was one such attempt, and the fluoro alcohol **12**, as well as the difluoride **13**, was involved in another one.[31−32]

(17) For use of analogous BINOL derivatives in enantioselective reactions, see: Kyba, E. P.; Gokel, G. W.; de Jong, F.; Koga, K.; Sousa, L. R.; Siegel, M. G.; Kaplan, L.; Sogah, G. D. Y.; Cram, D. J. *J. Org. Chem.* **1977**, *42*, 4173.

(18) For the corresponding bis-oxazolines, see: (a) Imai, Y.; Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron: Asymmetry* **1996**, *7*, 2453. (b) Bedekar, A. V.; Koroleva, E. B.; Andersson, P. G. *J. Org. Chem.* **1997**, *62*, 2518.

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(20) Preparation of **2**: triphenylphosphine (4.5 g, 17.0 mmol) and **1** (4.0 g, 8.6 mmol) were dissolved in anhydrous dichloromethane (15 mL) under an argon atmosphere. Pyridine (1.4 mL, 17.0 mmol) and carbon tetrachloride (1.7 mL, 17.0 mmol) were added, and the reaction mixture was stirred for 3 d at room temperature. After concentration to a volume of 5 mL, the solution was flash chromatographed (silica gel (250 g), pentane/ether 4:1, R_f 0.58) and the obtained product recrystallized (pentane/ether 6:1 (20 mL)) to yield **2** (3.0 g, 72%). For analytical data, see Table 2 and Supporting Information.

All new compounds have been fully characterized, and the data not presented in Table 2 are included in the Supporting Information. Besides the four crystal structures of **10**, **12**, **14b**, and **18**, shown in Figures 4 and 5, that of the chloro amine **7** has also been determined.

Work on the use of the TADDOL derivatives described herein in enantioselective synthesis (and for material studies, cf. **15**) is underway. Thus, **19b** (0.02 equiv) catalyzes the addition of Et_2Zn to PhCHO (−20 °C, toluene) with formation of 1-phenylpropanol, (*R*)/(*S*) = 92:8.

Acknowledgment. We thank Dr. P. B. Rheiner for determination of the X-ray structure of **18** and L. Audergon, H.-U. Bichsel, Ch. Müller, and Ch. Fischer for carrying out preliminary experiments. Financial support from the Swiss National Science Foundation (CHiral2) and from Novartis Pharma AG (Basel) is gratefully acknowledged.

Supporting Information Available: Experimental details and full characterization of all new compounds, including the crystal data of five single crystals used for the X-ray structure determinations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Preparation of **5**: **3** (5.0 g, 10.0 mmol), NH_4Cl (30 equiv, 16.0 g, 300 mmol), and a magnetic stirring bar were placed in an autoclave (250 mL) under an argon atmosphere. The autoclave was cooled to −78 °C, and ammonia (44 g) was condensed in. The reaction was stirred for 30 min at room temperature and then heated to 85 °C (25 bar) and stirred for 2 d. The autoclave was cooled to room temperature, and the unreacted NH_3 was vented. The crude product was dissolved in dichloromethane/water and neutralized (1 N HCl). The organic phase was washed, dried ($MgSO_4$), and evaporated. The crude product was flash-chromatographed (silica gel (100 g), ether, R_f 0.10) to yield **5** (2.9 g, 63%). For analytical data, see Table 2 and Supporting Information.

(22) The figures have been generated by K. Gademann using MolMol (Koradi, R.; Billeter, M.; Wüthrich, K. *J. Mol. Graphics* **1996**, *14*, 51).

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(24) The mild conditions (in the absence of Lewis acid) for this electrophilic aromatic substitution to occur, even twice (→**15**), are remarkable. For analogous reactions, see refs 25−27.

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(28) For an enumeration of the routes tested so far, see the discussion in ref 15.

(29) Cf. Bezombes, J.-P.; Carré, F.; Chuit, C.; Corriu, R. J. P.; Mehdi, A.; Reyé, C. *J. Organomet. Chem.* **1997**, *535*, 81.

(30) Cf. Lambert, J. B.; So, J.-H. *J. Org. Chem.* **1991**, *56*, 5960.

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