Highly Enantioselective Protonation of the 3,4-Dihydro-2-methylnaphthalen-1(2*H*)-one Li-Enolate by TADDOLs

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A series of nine TADDOLs (= $\alpha,\alpha,\alpha',\alpha'$-tetraaryl-1,3-dioxolane-4,5-dimethanols) **1a**–**1i**, have been tested as proton sources for the enantioselective protonation of the Li-enolate of 2-methyl-1-tetralone (= 3,4-dihydro-2-methylnaphthalen-1(2*H*)-one). The enolate was generated directly from the ketone (with $LiN(i\text{-}Pr)_2$ (LDA)/MeLi) or from the enol acetate (with 2 MeLi) or from the silyl enol ether (with MeLi) in CH_2Cl_2 or Et_2O as the solvent (*Scheme*). The Li-enolate (associated with LiBr/LDA, or LiBr alone) was combined with 1.5–3.0 equiv. of the TADDOL at −78° by addition of the latter or by inverse addition. 2-Methyl-1-tetralone of (*S*)-configuration is formed (≤80% yield) with up to 99.5% selectivity if and only if (*R*,*R*)-TADDOLs (**1d**, **e**, **g**) with naphthalen-1-yl groups on the diarylmethanol unit are employed (*Table*). The reactions were carried out on the 0.1- to 1.0-mM scale. The selectivity is subject to non-linear effects (NLE) when an enantiomerically enriched TADDOL **1d** is used (*Fig. 1*). The performance of TADDOLs bearing naphthalen-1-yl groups is discussed in terms of their peculiar structures (*Fig. 2*).

1. Introduction. – Enantioselective deprotonations[2]) and protonations[3]) of suitable carbonyl derivatives by chiral bases or acids are among the most attractive methods of preparing enantiomerically pure compounds[4]). Numerous more or less readily available compounds have been used as chiral acids for enantioselective protonations of enolates, and it has been recognized that the acidity of the proton source should not be too high (*ca.* 3 pK_s units below that of the CH-acid formed in the proton transfer) [9][5]). The TADDOLs (= $\alpha,\alpha,\alpha',\alpha'$-tetraaryl-1,3-dioxolane-4,5-dimethanols) **1**, derived from tartrate, an aldehyde or ketone, and an aromatic *Grignard* reagent [13], have so far not been tested as chiral protonating reagents[6])[7]). Thus, we have used a number of

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[1]) Part of the projected Ph.D. theses of *A. C.* and *D. W.*, University of Valencia and ETH Zürich, respectively.

[2]) For review articles on enantioselective deprotonations, see [1–3].

[3]) For review articles on enantioselective protonations, see [4–7].

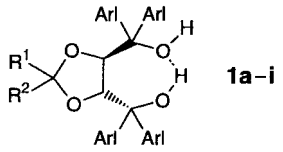
[4]) For recent mechanistic investigations and for catalytic enantioselective protonations, see [8][9].

[5]) This is necessary to avoid kinetic *O*-protonation of the enolate; for a discussion, see [9–11]. Interestingly, the intriguing observations by *Cram*, alluded to as '*conducted tour* for proton transfer' [12], have, so far, not been included in discussions about the mechanism of such enolate protonations!

[6]) For a protonation with kinetic resolution by TADDOL, see [14]. For an enantioselective formation of a TADDOL inclusion compound with a ketone under equilibrating conditions, see [15].

[7]) As indicated in **1**, the two OH groups of TADDOLs form an intramolecular H-bond (evident from numerous X-ray crystal structures [13]), rendering one of them more acidic than the other (see the pronounced tendency for etherification of one of the OH groups, in competition with phenolic OH groups [16]).

C_2- and C_1-symmetrical TADDOLs **1a**–**1i** from our collection to protonate the Li-enolate of 3,4-dihydro-2-methylnaphthalen-1(2*H*)-one (**2**), a favorate substrate for this type of reaction [5][6][17].



1a–i

1	R^1	R^2	ArI
a	Me	Me	Ph
b	H	H	Ph
c	Ph	Ph	Ph
d	Me	Me	Naphthalen-1-yl
e	$-(CH_2)_5-$		Naphthalen-1-yl
f	Ph	Ph	Naphthalen-1-yl
g	*t*-Bu	H	Naphthalen-1-yl
h	Me	Me	Naphthalen-2-yl
i	Me	Me	Phenanthren-9-yl

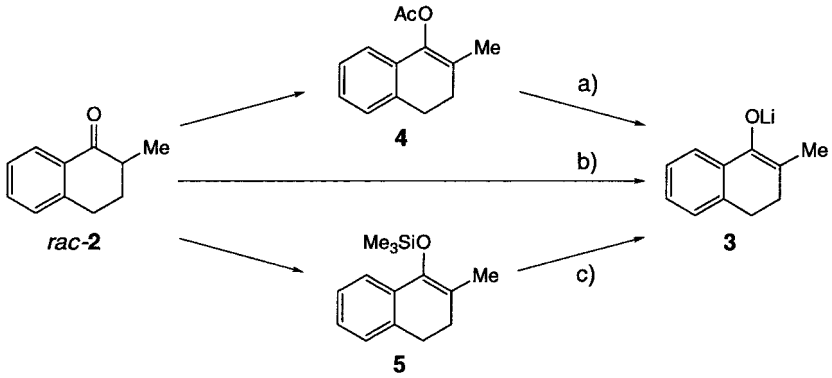
2. Results and Discussion. – The Li-enolate **3** of the tetralone was generated by three different methods (*Scheme*): *a*) the reaction of the enol acetate **4** with MeLi [18], *b*) the deprotonation of the ketone *rac*-**2** by LDA, with subsequent deprotonation of the $(i\text{-Pr})_2NH$ by MeLi [19], and *c*) the desilylation of the silyl enol ether **5** by MeLi [20]. Since it is known that enolate protonations occur with higher selectivity in the presence of Li halides [5][6][17], we carried out all reactions with the commercial Et_2O solution of MeLi · LiBr and used the poorer donating solvents Et_2O and CH_2Cl_2, rather than the better coordinating THF [8][9].

The solutions of the Li-enolate **3** were combined with the TADDOLs **1** by adding a solution of the diol in CH_2Cl_2 (or in Et_2O) at $-75°$. Slow addition was achieved by allowing the TADDOL solution to run down the inner wall of the flask at such a rate that the reaction mixture did not warm to above $-73°$ (internal *Pt-100* thermometer). A more elaborate procedure involved addition of the Li-enolate solution from a dropping funnel with cooling jacket to a TADDOL solution kept at $-75°$ (inverse addition) [28]. The reactions were carried out on 0.1-, 0.5-, and 1.0-mM scale. After allowing the reaction mixture to warm to $-35°$, saturated aqueous NH_4Cl was added, and the usual workup with Et_2O and chromatography on silica gel furnished the ketone

[8] In the absence of LiBr and in THF as the solvent, we have observed lower enantioselectivities, following all three routes *a*, *b*, and *c* in *Scheme 1*.

[9] For articles in which the complexity of generations and reactions of Li-enolates are discussed, see [21–27]. Considering this complexity, it is remarkable that Li-enolates are so well-behaved as synthetic intermediates. *E. M. Arnett* of Duke University once called Li-enolates 'benign' [... to the synthetic organic chemist] (22nd Reaction Mechanisms Conference, Pittsburgh, 1988).

Scheme. *Generation of Li-Enolate* **3** *under Different Conditions*



	Conditions [a])	Li-Enolate
a)	2.2 MeLi · LiBr in CH_2Cl_2/Et_2O	**3** · 2.2 LiBr · *t*-BuOLi
b)	1.1 LiN(i-Pr)$_2$ · LiBr, then 1.1 MeLi · LiBr in Et_2O	**3** · 2.2 LiBr · 1.1 LiN(i-Pr)$_2$
c)	1.2 MeLi · LiBr in CH_2Cl_2/Et_2O	**3** · 1.2 LiBr

[a]) The commercial MeLi · LiBr complex was employed as a 1.5M solution in Et_2O for all experiments.

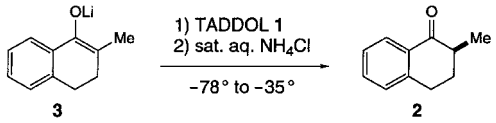
2 in yields between 60 and 80% [10]). The enantiomer purity of **2** was determined by measuring its optical activity (enantiomerically pure **2** has $[\alpha]_D^{r.t.} = 51.2$ ($c = 2.5$, dioxane [30]) and/or by HPLC analysis on a *Chiralcel OD-H* column. Results are collected in the *Table*. The following comments seem to be appropriate: *i*) Best results with up to 99.5 : 0.5 enantiomer ratios were obtained with the TADDOLs **1d**, **1e**, and **1g**, carrying naphthalen-1-yl groups. *ii*) With these TADDOLs, all three procedures of generating the Li-enolate **3** (with its different additives, see *a*, *b*, and *c* in the *Scheme*) gave enantioselectivities above 95 : 5, with the (−)-(*S*)-form of the ketone **2** prevailing [11]), when the (*R*,*R*)-TADDOLs are employed (rel. topicity *unlike* or *ul* [31]). *iii*) Inverse combinations of the reactants and other quenching conditions (phosphate buffer or CF_3CH_2OH/phosphate buffer instead of aq. NH_4Cl) had only small effects on the enantioselectivities, in most cases. *iv*) At temperatures higher than −75°, the selectivity decreased (conditions *a*, TADDOL **1g** at −75° and −50° gave enantiomer ratios (er) of 97.5 : 2.5 and 65 : 35, resp.). *v*) The number of equivalents of TADDOL necessary under optimized conditions are 1.5 for the silyl enol ether route (*c*), 3.0 for the enol acetate route (*a*) and ≥2.5 for the LDA route (*b*). *vi*) While there were clear CH_2Cl_2 solutions at all times when the reactions were carried out under conditions *a* and *c* (*Scheme*), precipitations

[10]) Since the SiO_2 column on which we put the crude product mixture (TADDOL **1** and non-racemic methyltetralone) is a 'chiral' column, the ratio (*R*)-**2**/(*S*)-**2** could possibly differ in different fractions [29]. We have, therefore, made sure that all ketone is eluted from the column, and we have performed the er analysis with the entire ketone sample recovered. The ketone **2** is eluted from the column with pentane/Et_2O 20 : 1; **2** has a characteristic smell of low threshold, and can thus also be detected by this property. We encountered no problems with racemization of **2** during isolation or er analysis. After the ketone has been removed from the column, the TADDOL is washed out with Et_2O.

[11]) There is only one exception: the TADDOL **1b** with four Ph groups, lacking substituents at the 2 position of the dioxolane ring (a formaldehyde acetal) gave mainly the (*R*)-enantiomer (er 61 : 39; see *Table*).

were observed when TADDOLs **1d** and **1e** (in Et_2O) were added to the enolate solution generated under conditions *b*. *vii*) The simplest way of converting a small sample of *rac*-**2** to ketone of an er value of 98:2 is the LDA route (*b*)[12]), because it does not require preparation of an enol derivative from which the Li-enolate is generated.

Table. *Protonations of Li-Enolate* **3** *by TADDOLs* **1**. The three conditions *a*, *b*, and *c* for generation of **3** are given in the *Scheme*. The addition mode *add.* refers to addition of TADDOL to the enolate solution, *inv.* refers to inverse addition, *i.e.*, of the Li-enolate to the TADDOL solution. The enantioselectivity is given as % es (major enantiomer of (*S*)-configuration except in one case[a]). For determination of the enantiomer ratios (er) see *Exper. Part*. Yields of the rather volatile ketone **2** range from 60 to 80% in 0.1- to 1-mM batches.



3 **2**

Enolate-generation method (*cf. Scheme*)	TADDOL			Enantioselectivity		
	1	No. of equiv.	Addition mode	es [%]	determined by	
a	**a**	3.0	*inv.*	74	$[\alpha]_D$	–
c	**a**	1.5	*add.*	75/75	$[\alpha]_D$	HPLC
a	**d**	3.0	*inv.*	>99	$[\alpha]_D$	–
b	**d**	4.0	*add.*	98	–	HPLC
c	**d**	1.5	*add.*	97/97	$[\alpha]_D$	HPLC
c	**d**	1.5	*inv.*	97/97	$[\alpha]_D$	HPLC
a	**g**	3.0	*inv.*	97	$[\alpha]_D$	–
c	**g**	1.5	*add.*	94/94	$[\alpha]_D$	HPLC
a	**b**	3.0	*inv.*	61[a])	$[\alpha]_D$	–
a	**c**	3.0	*inv.*	74	$[\alpha]_D$	–
b	**e**	2.5	*add.*	97/98	$[\alpha]_D$	HPLC
c	**f**	1.5	*add.*	84/81	$[\alpha]_D$	HPLC
a	**h**	3.0	*inv.*	62	$[\alpha]_D$	–
b	**i**	3.0	*add.*	81/83	$[\alpha]_D$	HPLC

[a]) *ent*-**2**, the (+)-(*R*)-form was formed in this case!

Although we are dealing with the seemingly simplest of all chemical reactions, a proton transfer, the mechanism of the enantioselective protonation of the Li-enolate **3** by TADDOLs, is most complex when we consider that the reaction mixture not only contains a variety of species (Li-enolate, LiBr, $LiN(i\text{-}Pr)_2$, and various aggregates and complexes between them)[9]), but that the composition of the reaction mixture changes when new species are generated[13]) during addition of the TADDOL (with formation of Li-TADDOLate). Thus, it is not surprising that there is a nonlinear relation between the enantiomer excesses of the TADDOL used and of the non-racemic ketone **2** formed, as demonstrated for the protonation of the enolate **3** by the TADDOL **1d** (*Fig. 1*). Since a nonlinear effect (NLE) indicates involvement of more than one chiral

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[12]) We hesitate to call this process a *deracemization* (a frequently used term), since what actually happens in the decisive step is an enantioselective protonation of an achiral Li-enolate. A *Web of Science* search (*ISI*® *Institute of Scientific Information*. The *Web of Science*℠ Version 4.1 (ISI2), Citation Databases) performed on July 12, 2000, provided 43 publications with the term 'deracemization' in their titles!

[13]) For a discussion of RLi reactions with changing enantioselectivities upon increasing conversion, see the review article [32] and the discussions in [21].

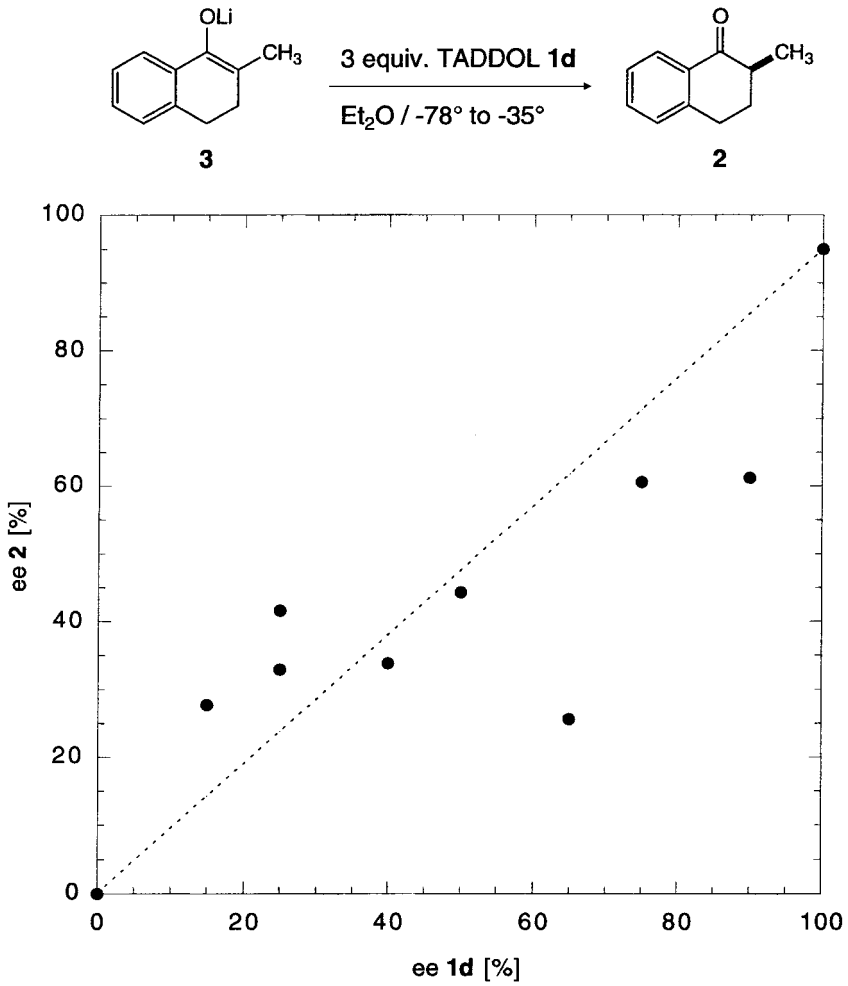

Fig. 1. *Nonlinear effect (NLE) in the enantioselective protonation of the Li-enolate* **3** (generated under conditions *b*) *by addition of 3 equiv. of TADDOL* **1d**. As mentioned in the accompanying text, under the conditions used for these experiments, the reaction mixture is not homogeneous. Therefore, the reproducibility is not very good. We, therefore, hesitate to draw a curve into this graph. It must, however, also be pointed out that the value obtained with enantiomerically pure TADDOL has been reproduced many times and is $95 \pm 1\%$ ee. For scholarly discussions of NLE and interpretations, see [33]. For a detailed procedure, see the *Exper. Part.*

reactant molecule in the stereoselectivity-determining step of a reaction, it is also not surprising that polymer- [34] and silica-gel-bound [35] TADDOLs gave very poor selectivities[14]) in the protonation of enolate **3**.

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[14]) The polystyrene-bound $(Ph)_4$- and (naphthalen-1-yl)$_4$-TADDOL [36] were used to protonate **3** under conditions *c* (*Scheme 1*) with inverse addition; the ketone **2** was thus formed in an (*R*)/(*S*) ratio of 70:30 and 30:70, respectively (reversal of preferred steric course of reaction!) (*D. Weibel*, *H. Sellner*, *A. Heckel*, hitherto unpublished results, ETH-Zürich 1999).

The striking difference in enantioselectivities observed, when going from TADDOLs with Ph or naphthalen-2-yl groups (miserable selectivities) to those with naphthalen-1-yl groups on the diarylmethanol moiety (excellent selectivities) calls for comment. It is not for the first time that we observe an unusual behavior of TADDOLs carrying naphthalen-1-yl groups [13]: in the $(Me_2CHO)_2Ti$-TADDOLate-catalyzed addition of dialkylzinc reagents to aldehydes, there is a breakdown of enantioselectivity when going from naphthalen-2-yl (> 99% es) to naphthalen-1-yl groups (64% es) [37]. Also in the Cl_2Ti-TADDOLate-catalyzed *Diels-Alder* addition of crotonoyl-oxazolidinone to cyclopentadiene, there is a reversal of the stereochemical course when switching from naphthalen-2-yl (94% es of laevorotatory product) to naphthalen-1-yl (86% es of dextrorotatory product) [38]. TADDOLs with naphthalen-1-yl (and phenanthren-9-yl) groups differ from those with simple Ph and naphthalen-2-yl groups also by exhibiting broad signals in the NMR spectra at room temperature that sharpen upon heating in (D_6)DMSO or upon cooling in CD_2Cl_2 [39][40]; thus, there are rotamers with slow rotation (on the NMR time scale) around the C-aryl bonds (lying on chirality axes)[15]). Calculations at various levels of theory have produced [42] a single lowest-energy conformation for the TADDOL **1e**, which is essentially identical to the crystal structure of **1e** [38][39]. A comparison of the crystal structures of the prototypal TADDOL with four Ph groups with that carrying four naphthalen-1-yl groups reveals that there is more steric hindrance near the H-bonded OH groups (C–O–H···O(H)–C) in the latter (*Fig. 2*). This is probably decisive for creating the chiral environment in the proton-transfer step[15]).

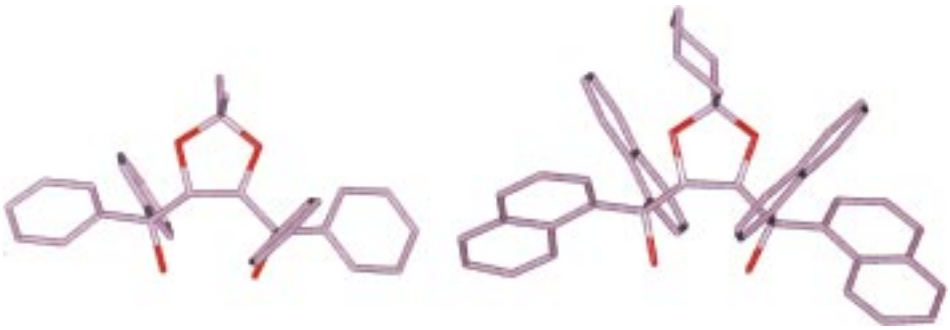

Fig. 2. *X-Ray crystal structures of the TADDOLs* **1a** (left) *and* **1d** (right). The *pseudo-axial* naphthalen-1-yl groups in **1d** have the 'second' benzene ring pointing backwards, towards the dioxolane ring and the ketal C-atom, while the *pseudo-equatorial* naphthalen-1-yl groups are turned such that the 'second' benzene ring is located in the front. The X-ray structures have been published [38][39]; see *Cambridge* file codes KOGJAR and YONVEC. For a different presentation of the structures of **1d**, see [38], and for a general discussion of numerous TADDOL structures, see the review article [13].

3. Conclusion. – Thus, we have shown for the first time that TADDOLs can be used for a highly enantioselective protonation of a Li-enolate. As always, the great structural

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15) It is normally considered important for successful enantioselective protonations of Li-enolates by alcohols that the OH group is directly attached to a chirality center. Protonations with alcohols in which the OH group is not bonded to a stereogenic center have, so far, always led to modest selectivities [10][41].

variability of TADDOLs was useful in finding the best derivative for the purpose, and, of course, samples of either enantiomer of the ketone **2** are equally readily prepared, since both TADDOL enantiomers are available (from the tartaric acids). Experiments with other Li-enolates are in progress[1]).

We thank *A. Heckel* and *H. Sellner* for performing some experiments with heterogeneous TADDOL derivatives, and *R. Dahinden* and *C. Müller* for preparing the TADDOLs **1i** and **1f**, respectively. The presentation of **1a** and **1d** in *Fig. 2* was generated with the program *Insight II* Version 98.0; we thank *A. Heckel* for his help to produce the figure. Continuing support by *Novartis Pharma AG* and *Novartis Agro AG* is gratefully acknowledged. *A. C.* thanks *Generalitat Valenciana* for a grant.

Experimental Part

1. *General.* All reactions were carried out under Ar atmosphere with glassware dried overnight at 140°. Et_2O (*p. a.*, Baker) was stored over activated molecular sieves (4 Å). CH_2Cl_2 (*p. a.*, Baker) was either stored over activated molecular sieves (4 Å) or was freshly distilled from CaH_2. THF was freshly distilled from Na. Solvents for flash chromatography and workup were distilled over P_2O_5 (*Merck*). TADDOLs **1a**, **1b**, **1d**, **1e**, **1g** [39], **1c** [43], and **1h** [44], were prepared according to literature procedures. MeLi · LiBr (1.5M solution in Et_2O; *Fluka*) and *2-methyl-1-tetralone (3,4-dihydro-2-methylnaphthalen-1(2*H*)-one*; **2**; *Aldrich*; b.p. 127–131°/12 Torr; [45]: 85–100°/0.1 Torr) were used as purchased. All indicated temp. were monitored with an internal thermometer (*Ebro-TTX-690* digital thermometer). TLC: *Merck* silica gel *60* F_{254} plates; detection by UV or a soln. of $Ce(SO_4)_2$/phosphomolybdic acid (25 g of phosphomolybdic acid, 10 g of $Ce(SO_4)_2 \cdot 2\,H_2O$, 60 ml of conc. H_2SO_4 in 940 ml of H_2O); followed by heating. Flash chromatography (FC): *Fluka* silica gel *60* (0.040–0.063 mm), pressure 0.3 bar. Anal. HPLC: *Waters* system (*515 HPLC* pump, *484* tunable absorbance detector, detection at $\lambda = 254$ nm), automated gradient controller; *Chiralcel OD-H* column (*Daicel Chemical Industries, Ltd.*); t_R in min (only for the major enantiomer). M.p.: *Büchi-510* apparatus; uncorrected. Optical rotations: *Perkin-Elmer 241* polarimeter (10 cm, 1-ml cell) at r.t. IR Spectra: *Perkin-Elmer-1620-FT-IR* spectrometer, in cm^{-1}. NMR Spectra: *Bruker AMX 500* (^1H: 500 MHz, ^{13}C: 125 MHz) *Varian-Gemini 300* (^1H: 300 MHz, ^{13}C: 75 MHz) or *Gemini 200* (^1H: 200 MHz); chemical shifts (δ) in ppm downfield from TMS ($\delta = 0.0$); *J* values in Hz; unless stated otherwise, $CDCl_3$ solns. MS: *Finnigan-MAT-TSQ 7000* (ESI); *VG ZAB-2 SEQ* (FAB; 3-nitrobenzylalcohol matrix) spectrometer; in *m/z* (% of basis peak). Elemental analyses were performed by the Microanalytical Laboratory of the Laboratorium für Organische Chemie, ETH Zürich.

2. *Preparation of TADDOLs. (4*R,5R*)-2,2-Diphenyl-α,α,α′,α′-tetra(naphthalen-1-yl)-1,3-dioxolane-4,5-dimethanol* (**1f**). Following the procedure described in [39], dimethyl (4*R*,5*R*)-2,2-diphenyl-1,3-dioxolane-4,5-dicarboxylate (6.85 g, 20 mmol) [43] in THF (65 ml) was added dropwise to a soln. of (naphthalen-1-yl)magnesium bromide (88 mmol, prepared from 18.22 g of 1-bromonaphthalene and 2.20 g of Mg) in THF (65 ml). After workup, the crude product (17.54 g) was purified by FC (270 g of SiO_2; CH_2Cl_2) and dried *in vacuo* at 80° for 6 h (removal of naphthalene). The isolated product was then dissolved in refluxing CH_2Cl_2 and precipitated with hexane (*ca.* 60 ml). The precipitate (4.83 g) was filtered off and dried *in vacuo* at 80°. Repeating the precipitation with the residue from the mother liquor gave a second crop (1.33 g). Total yield: 6.16 g (39%) of **1f**. White powder. M.p. 305–309°. R_f (toluene) 0.6. $[\alpha]_D^{r.t.} = +293$ ($c = 1$, $CHCl_3$). IR ($CHCl_3$): 3608*w*, 3557*s*, 3088*w*, 3055*m*, 3008*m*, 2970*w*, 1950*w*, 1885*w*, 1820*w*, 1700*w*, 1598*m*, 1510*m*, 1489*w*, 1450*m*, 1396*m*, 1348*m*, 1160*m*, 1110*s*, 1049*s*, 1026*s*, 990*w*, 930*m*, 897*m*, 640*m*, 610*m*. ^1H-NMR (500 MHz, (D_6)DMSO, 160°; at r.t. only broad signals were obtained): 8.02–8.22 (*m*, 2 H); 8.00–8.02 (*m*, 2 H); 7.85–7.87 (*m*, 4 H); 7.57–7.66 (*m*, 8 H); 7.34–7.37 (*m*, 2 H); 7.29 (*m*, 2 H); 7.15–7.18 (*m*, 2 H); 7.05–7.08 (*m*, 2 H); 6.85–6.95 (*m*, 12 H); 6.72–6.75 (*m*, 2 H); 5.91 (*s*, 2 H). ^{13}C-NMR (125 MHz, (D_6)DMSO, 160°; at r.t. only broad signals were obtained): 142.38, 140.16, 138.90, 133.53, 133.49, 131.44, 131.34, 130.49, 128.34, 127.75, 127.49, 127.27, 126.78; 126.60, 126.49, 126.38, 126.26, 125.44, 124.41, 123.95, 123.78, 123.61, 123.57, 123.40, 123.19, 122.97 (arom. C); 109.90 (C(2)); 83.05 (C(4), C(5)); 80.05 (C–OH). ESI-MS (pos.): 808 (100, $[M + NH_4]^+$), 813 (38, $[M + Na]^+$), 829 (80, $[M + K]^+$). ESI-MS (neg.): 789 (100, $[M - H]^-$). Anal. calc. for $C_{57}H_{42}O_4$ (790.96): C 86.56, H 5.35, O 8.09; found: C 86.42, H 5.55.

*(4*R,5R*)-2,2-Dimethyl-α,α,α′,α′-tetra(phenanthren-9-yl)-1,3-dioxolane-4,5-dimethanol* (**1i**) [40]. Following the procedure described in [39], dimethyl (4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (37 g, 170 mmol) in THF (250 ml) was added dropwise to (phenanthren-9-yl)magnesium bromide (840 mmol, prepared from 215 g of 9-bromophenanthrene and 21 g of Mg) in THF (660 ml). After workup, the isolated

solid orange foam (195 g) was dissolved in Et_2O (250 ml) and treated with EtOH (900 ml), leading to a white precipitate. After 3 h standing at r.t., the bright-yellow solid was isolated by filtration and dried *in vacuo*. To remove the EtOH from the inclusion compound, the powder was dissolved twice in toluene (2 × 600 ml), and the solvent was subsequently removed on the rotatory evaporator to yield a solid orange foam (156 g). The crude product was purified by FC (350 g of SiO_2; CH_2Cl_2), then divided into three portions, which were purified one after another on the same column by FC (1 kg of SiO_2; toluene). In case the product remains slightly yellow after purification, it can be dissolved in acetone, whereby a white precipitate forms immediately. Drying of the isolated product *in vacuo* at 110° for 24 h afforded **1i** (29.5 g, 20%). White powder. M.p. 246–248°. R_f (toluene) 0.35. $[\alpha]_D^{r.t.} = +128.8$ ($c = 1.485$, $CHCl_3$). IR ($CHCl_3$): 3578*m*, 3353 (br.), 3064*m*, 3008*s*, 1596*w*, 1494*s*, 1449*s*, 1433*m*, 1381*s*, 1063 (br.), 952*m*, 896*s*, 880*s*. ^{1}H-NMR (300 MHz, CD_2Cl_2, −65°; at r.t. only broad signals were obtained): 9.11 (*s*); 8.99 (*s*); 8.86 (*s*); 8.78–8.45 (*m*); 8.33–8.26 (*m*); 8.11–6.95 (*m*); 6.87–6.76 (*m*); 6.67 (*t*, $J =$ 7.8); 6.60 (*s*); 6.33 (*d*, $J = 5.9$); 6.23–6.18 (*m*); 6.02–5.97 (*m*); 5.89–5.84 (*m*); 4.09 (*s*); 3.73 (*s*); 1.82 (*s*); 1.58 (*s*); 0.46 (*s*); 0.19 (*s*); 0.10 (*s*). ^{13}C-NMR (75 MHz, CD_2Cl_2, −65°; at r.t. only broad signals were obtained): 140.40; 140.16; 139.11; 138.26; 138.19; 137.49; 134.58; 131.94; 131.65; 131.54; 131.48; 131.37; 131.32; 131.26; 131.17; 130.96; 130.82; 130.70; 130.44; 130.28; 130.14; 129.91; 129.79; 129.61; 129.48; 129.33; 129.19; 128.97; 128.82; 128.67; 128.37; 128.11; 127.82; 127.75; 127.60; 127.33; 127.08; 126.72; 126.56; 126.43; 126.28; 126.19; 125.98; 125.80; 125.44; 125.38; 125.31; 125.05; 124.99; 124.75; 124.61; 124.16; 123.89; 123.85; 123.63; 123.47; 123.38; 123.15; 122.89; 122.60; 121.79; 121.55; 113.81; 112.42; 82.47; 82.04; 81.61; 81.00, 79.73; 78.75; 30.01; 29.12; 27.65; 27.58; 27.53. FAB-MS: 866 (2, M^+), 831 (7), 468 (18), 467 (49), 466 (20), 465 (21), 438 (10), 437 (26), 409 (25), 408 (55), 407 (22), 395 (14), 385 (10), 384 (41), 383 (100), 380 (13), 379 (33), 368 (15), 367 (40), 365 (10), 205 (36), 177 (18), 154 (14), 137 (10), 136 (12). Anal. calc. for $C_{63}H_{46}O_4$ (867.05): C 87.27, H 5.35; found: C 87.31, H 5.45.

3. *Preparation of 2-Methyl-3,4-dihydronaphthalen-1-yl Acetate* (**4**). Compound *rac*-**2** (1.2 g, 7.5 mmol) and Ac_2O (7 ml, 75 mmol) were dissolved in CCl_4 (5 ml) at 0°. Some drops of conc. $HClO_4$ were added, and the stirred mixture was allowed to warm to r.t. After 1.5 h, the mixture was diluted with precooled sat. aq. $NaHCO_3$ soln. and extracted three times with Et_2O. The combined org. phases were washed with H_2O, dried ($MgSO_4$), and the solvents were removed *in vacuo*. The residue was purified by FC (60 g of SiO_2; hexane/AcOEt 25 :1) to afford **4** (1.0 g, 73%). Colorless crystals. ^{1}H-NMR Data are in accordance with those in [46].

4. *Preparation of 1,2-Dihydro-3-methyl-4-(trimethylsilyloxy)naphthalene* (**5**). To a soln. of LiN(i-Pr)$_2$ (LDA; prepared from (i-Pr)$_2$NH (0.85 ml, 6 mmol) and BuLi (1.5M in hexane, 4.0 ml, 6 mmol)) in THF (25 ml) at −78° was added *rac*-**2** (0.61 ml, 4 mmol). The mixture was stirred for 30 min and then Me_3SiCl (3.16 ml, 25 mmol) was added. After warming to 0°, the mixture was quenched with Et_3N (4 ml) and $NaHCO_3$ (10 ml), and extracted twice with pentane. The combined org. phases were washed with sat. aq. solns. of NH_4Cl and $NaHCO_3$, dried ($MgSO_4$), and the solvents were removed *in vacuo*. The residue was purified by FC (25 g of SiO_2; pentane/Et_2O 25 :1) to afford **5** (1.14 g, 98%). Colorless oil. ^{1}H-NMR Data were in accordance with those in [47].

5. *Generation of Li-Enolate* **3**. *By Route* a *from* **4** (*cf. Scheme 1*). To a soln. of **4** (0.202 g, 1 mmol) in Et_2O (9 ml) at 0° was added MeLi · LiBr (1.467 ml, 2.2 mmol). The mixture was stirred for 30 min and then cooled to −78°.

By Route b *from* rac-**2** (*cf. Scheme 1*). To a soln. of (i-Pr)$_2$NH (0.078 ml, 0.55 mmol) in Et_2O (2 ml) at −78° was added MeLi · LiBr (0.367 ml, 0.55 mmol). The soln. was allowed to warm to 0° and immediately recooled to −78°. Then, a soln. of *rac*-**2** (0.080 ml, 0.5 mmol) in Et_2O (1 ml) was added, and the mixture was stirred for 15 min, followed by MeLi · LiBr (0.367 ml, 0.55 mmol). The mixture was stirred for another 15 min.

By Route c *from* **5** (*cf. Scheme 1*). MeLi · LiBr (0.733 ml, 1.1 mmol) was added to neat **5** (0.232 g, 1 mmol) at 0°, and the mixture was stirred for 2 h. Then, Et_2O (9 ml) was added, and the soln. was cooled to −78°.

6. *General Procedure for Enantioselective Protonation*. Via *Enol Acetate* **4**. To a soln. of TADDOL **1g** (2.082 g, 3 mmol) in CH_2Cl_2 (35 ml) at −78° was added dropwise a soln. of Li-enolate **3** (1.0 mmol) in Et_2O (9 ml), prepared by route *a*, *via* a dropping funnel with a cooling jacket at −78°. The mixture was stirred for 1.5 h, then allowed to warm to −35°[16]), quenched with sat. aq. NH_4Cl soln. (20 ml), and extracted twice with CH_2Cl_2. The combined org. phases were washed with sat. aq. solns. of NH_4Cl, $NaHCO_3$, then H_2O and brine, dried ($MgSO_4$), and the solvents were removed *in vacuo*. The residue was purified by FC (23 g of SiO_2; hexane/

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[16]) This can be simply achieved by removing the pieces of dry ice from the cooling bath *Dewar* cylinder and waiting until the desired temp. of the reaction mixture is reached.

AcOEt 25:1) to afford **2** (0.152 g, 75%). Colorless oil. $[\alpha]_D^{r.t.} = -47.5$ ($c = 2.5$, 1,4-dioxane) ([30]: $[\alpha]_D^{r.t.} = -52.1$). ^{1}H-NMR Data were in accordance with those in [46].

Via rac-**2**. To a soln. of Li-enolate **3** (0.5 mmol) in Et_2O (2 ml) at $-78°$, prepared by route *b*, was added a soln. of TADDOL **1d** (1.334 g, 2.0 mmol) in Et_2O (4 ml) by running it slowly down the inner wall of the flask (*ca.* 15 min). The internal temp. should not exceed $-73°$. The mixture is stirred for 2 h before it was allowed to warm slowly to $-35°$[16]). The mixture is quenched with sat. aq. NH_4Cl soln. (20 ml) and extracted twice with Et_2O. The combined org. phases were washed with sat. aq. solns. of NH_4Cl, $NaHCO_3$, then H_2O and brine, dried ($MgSO_4$), and the solvent was removed *in vacuo*. The residue was purified by FC (75 g of SiO_2; pentane/Et_2O 20:1) to afford **2** (0.060 g, 75%). Colorless oil. HPLC (hexane/i-PrOH 400:1; flow rate 0.4 ml/min): t_R 20.9 min. $[\alpha]_D^{r.t.} = -50.2$ ($c = 3.0$, 1,4-dioxane) ([30]: $[\alpha]_D^{r.t.} = -52.1$). ^{1}H-NMR Data were in accordance with those in [46].

Via *Silyl Enol Ether* **5**. To a soln. of Li-enolate **3** (1 mmol) in CH_2Cl_2 (15 ml), prepared by route *c* was added a soln. of TADDOL **1d** (1.000 g, 1.5 mmol) in CH_2Cl_2 (10 ml) by running it slowly down the inner wall of the flask. The internal temp. should not exceed $-73°$. The mixture was stirred for 30 min at $-78°$, then warmed to $-35°$[16]), quenched with sat. aq. NH_4Cl soln. (20 ml), and extracted twice with CH_2Cl_2. The combined org. phases were washed with sat. aq. solns. of NH_4Cl, $NaHCO_3$, then H_2O and brine, dried ($MgSO_4$), and the solvents were removed *in vacuo*. The residue was purified by FC (75 g of SiO_2; pentane/Et_2O 20:1 or hexane/AcOEt 15:1) to afford **2** (0.110 g, 79%). Colorless oil. HPLC (hexane/i-PrOH 400:1, flow rate 0.4 ml/min): t_R 16.8 min. $[\alpha]_D^{r.t.} = -48.3$ ($c = 3.0$, 1,4-dioxane) ([30]: $[\alpha]_D^{r.t.} = -52.1$). ^{1}H-NMR Data were in accordance with those in [46].

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