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Resolution of Racemic Carboxylic Acid Derivatives by Ti-TADDOLate Mediated Esterification Reactions - A General Method for the Preparation of Enantiopure Compounds

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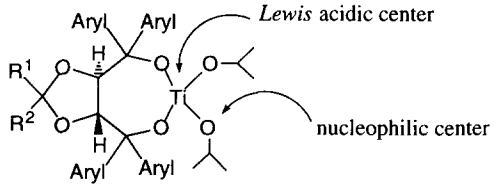
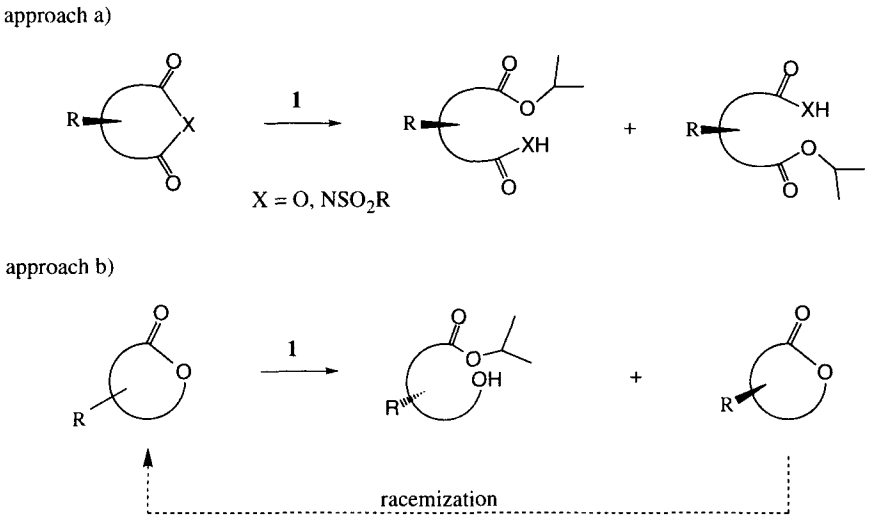
Abstract: The Lewis-acid mediated transfer of an alkoxide ligand from the chiral ligand sphere of Ti-TADDOLates **1** to cyclic carboxylic acid derivatives is described. The kinetic resolution of dioxolanones, azlactones and biaryl lactones by the Ti-TADDOLates affords, after recrystallization, ester products in highly enantioenriched form (er ≥ 97:3). The enantiomer-differentiating ring-opening of a chiral cyclic anhydride by a Ti-TADDOLate leads highly enantioselectively to two constitutional isomers. © 1997 Elsevier Science Ltd.

Introduction

The tartrate derived TADDOLs (α,α,α',α'-**T**etra**a**ryl-1,3-**d**ioxolane-4,5-**d**imethan**ols**) are versatile auxiliaries, which have found numerous applications in catalytic and stoichiometric enantioselective reactions. The easily prepared Ti-TADDOLates **1** have proved to be particularly successful in different *Lewis* acid catalyzed reactions.[6,7] Additions of diethylzinc to aldehydes,[8-10] [2+2] cycloadditions,[11,12] Diels-Alder[13-15] and ene[16] reactions have been performed with high selectivities. Moreover, the combination of a *Lewis*-acidic and a nucleophilic functionality within the same molecule also makes Ti-TADDOLates suitable auxiliaries for an alkoxide transfer from the chiral ligand sphere of **1** to a *Lewis*-acid activated carbonyl group. This alkoxide transfer can be used for the preparation of enantiomerically pure carboxylic esters by two approaches, namely the "desymmetrization" of *meso*-compounds (Scheme 1, Approach a) or the resolution of racemic compounds (Scheme 1, Approach b). Similar strategies are also known and widely used in reactions that are catalyzed by hydrolytic enzymes.[17]



1a $R^1 = R^2 = CH_3$, Aryl = Ph
1b $R^1 = R^2 = CH_3$, Aryl = β-Naph
1c $R^1 = R^2$ = Aryl = Ph
1d R^1 = H, R^2 = Aryl = Ph
1e $R^1 = R^2 = CH_3$, Aryl = α-Naph



Scheme 1. *Two strategies for the preparation of enantiopure carboxylic esters by Ti-TADDOLate* ***1*** *mediated reactions.*

If there is equilibration between the enantiomers under the reaction conditions, this resolution with *in situ* recycling has also been called "dynamic resolution"[18,19] or "asymmetric transformation".[20] We have previously reported the highly enantioselective ring-opening of cyclic *meso*-anhydrides[21] and *meso*-sulfonylimides[22] with Ti-TADDOLates **1** (Scheme 1, Approach a). The attack of the nucleophile occurs predominately at the *Re* carbonyl group, leading to the corresponding isopropyl esters with selectivities up to 99:1.

There is only one report of a kinetic resolution of racemates with a Ti-TADDOLate in the literature.[23] In this paper, we describe kinetic resolutions of dioxolanones, azlactones and biaryl lactones by Ti-TADDOLates **1**. Furthermore, we describe an enantiomer differentiating reaction of a chiral anhydride by a Ti-TADDOLate-mediated ring-opening. After recrystallization all products were obtained in an almost enantiopure form (er ≥ 97:3).

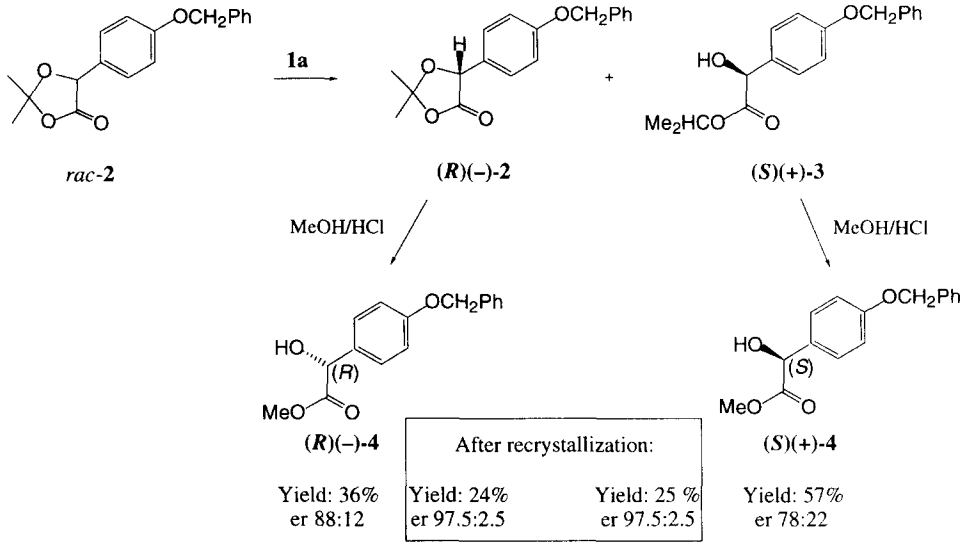
Preparative Results

a) Kinetic Resolution of a 1,3-Dioxolan-4-one

1,3-Dioxolan-4-ones, the acetals of α-hydroxycarboxylic acids, have often been applied in reactions using the principle of the self-regeneration of stereocenters (SRS).[24] Starting with a chiral non-racemic dioxolanone, modified enantiopure α-hydroxycarboxylic acids can thus be prepared without the use of an external chiral auxiliary.[25-27] In these reactions, the dioxolanone ring is readily cleavable, a property which has led us to a new and complementary application of dioxolanones - the kinetic resolution of a racemic dioxolanone using Ti-TADDOLates **1**, leading to an enantiomerically enriched α-hydroxycarboxylic ester.

As a substrate, we chose dioxolanone **2**, which is readily prepared from commercially available racemic 4-hydroxymandelic acid by standard procedures (see Experimental Part). Ring-opening with the Ti-TADDOLate **1a** led to the enantioenriched isopropyl-ester **3**, which was separated by chromatography from the remaining dioxolanone **2**. Subsequently, the isopropyl-ester **3** and the unchanged dioxolanone **2** were both converted to samples of the methyl ester **4**, which were enriched in either enantiomer (Scheme 2).

The absolute configuration of (*R*)- and (*S*)-**4** has not yet been determined, however, considering the optical rotations of a series of known mandelic acid derivatives,[28-30] we assign (*S*)-configuration to that enantiomer of **2** which is reacting more rapidly and which leads to the dextrorotatory esters **3** and **4** (see Scheme 2).



Scheme 2. *Kinetic resolution of dioxolanone* rac-*2*.

Investigation of the reaction kinetics (Figure 1) showed that an effective kinetic resolution can be achieved, with the typical feature that high enantiopurities may be achieved in the unchanged enantiomer of the starting material.[31]

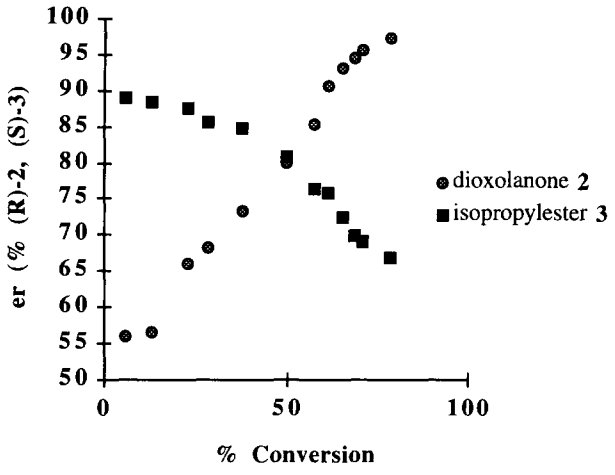


Figure 1. *Enantiomer purities of recovered starting material* **2** *and of product* **3** *as a function of conversion of dioxolanone* **2** *in the reaction with* ***1a***.

As the reaction proceeded, the enantiopurity of the remaining dioxolanone **2** increased, whereas that of the product **3**, decreased, with a conversion of between 58 and 62% being most appropriate for the preparation of both enantiomers.

A conversion of 60% (determined by ^{1}H NMR) was achieved after five days (the flask with the homogeneous reaction mixture was sealed and stored for this period of time at ambient temperature). Chromatographic separation of enantioenriched (*R*)-**2** and (*S*)-**3**, subsequent hydrolysis of the dioxolanone and conversion of both products to the corresponding methyl esters **4** gave an overall yield of 36% for (*R*)-**4** (er 88:12) and of 57% for (*S*)-**4** (er 78:22). Two recrystallizations increased the enantiomer ratios to 97.5:2.5 in both cases, yielding 24% of (*R*)-**4** and 25% of (*S*)-**4**.

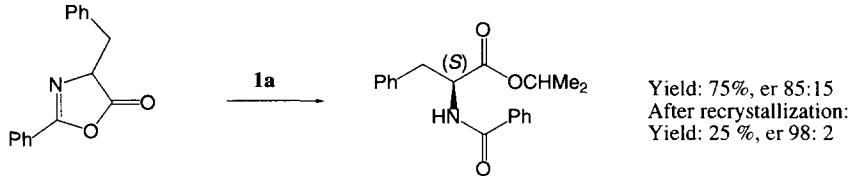
While the optimization of the process was carried out on small scale, we have achieved similar yields and selectivities on a larger scale, starting with 10 g of *rac*-**2**.

b) Enantioselective Ring-Opening of an Azlactone

Oxazol-5-(4*H*)-ones, also known as azlactones, are readily prepared from *N*-protected amino acids by dehydration.[32-35] They are configurationally labile due to the aromatic character of the enol, which is formed as an intermediate during racemization, and they have been found to play an important role in the racemization of amino acids - in peptide synthesis, the formation of azlactones is a frequent, yet undesirable side reaction.[36,37] On the other hand, enantioenriched α-amino acids can be prepared *via* kinetic resolution of azlactones with *in situ* racemization of the substrate. Several examples of enantioselective ring-opening reactions have been reported, which use cyclodextrins,[38,39] hydrolytic enzymes[40-43] or diastereoselective ring-opening with chiral

auxiliaries.[44-49] In this report, we present an application of this principle to an azlactone, which is ring-opened by Ti-TADDOLates, leading to an enantiomerically enriched *N*-protected phenylalanine ester.

It is a prerequisite for this kind of resolution that the relative rate of equilibration is large compared to the rate of ring-opening. This is the case for azlactones derived from *N*-benzoylated aromatic amino acids.[36,37,50,51] We therefore chose azlactone **5** derived from *N*-benzoyl phenylalanine as a substrate for our investigations (Scheme 3). Phenylalanine was *N*-benzoylated with benzoyl chloride under *Schotten-Baumann* conditions. Subsequent dehydration using acetic anhydride led to formation of the azlactone in good yield. Reaction of **5** with 1.2 equivalents of the Ti-TADDOLate **1a** afforded *N*-benzoyl phenylalanine isopropyl ester **6**.



rac-**5** **6**

Scheme 3. *Kinetic resolution with* in situ *recycling of azlactone* rac-*5*.

The reaction was optimized with respect to the solvent, reaction temperature and the substituents on the TADDOLate, as shown in Table 1.

Table 1. *Variation of Solvent, Ti-TADDOLate* ***1*** *and Temperature for the Conversion of Azlactone* ***5*** *to Enantioenriched Bz-Phe-OCHMe$_2$ (**6**).*

Entry	Solvent	Ti-TADDOLate	Temperature [°C]	Time for complete conversion [d]	Enantiomer ratio of **6** er
1	toluene [a]	**1a**	-28	6	75:25
2	dioxane	**1a**	12 -> rt	< 2	55:45
3	^{i}PrOH [a]	**1a**	-28	6	74:26
4	$^{i}Pr_2O$ [a]	**1a**	-28	6	76:24
5	diglyme	**1a**	-28	6	74:26
6	CH_2Cl_2	**1a**	0	5	52:48
7	CH_3CN	**1a**	rt	<1	60:40
8	THF	**1a**	-28	6	85:15
9	THF	**1a**	-22	4	75:25
10	THF	**1a**	0	3.5	67:23
11	THF	**1b**	0	n.d.[b]	58:42
12	THF	**1d**	-30	5	80:20
13	THF	**1e**	-28	>20	53:47

[a] Addition of THF (2-30%) was necessary to dissolve the substrate; [b] Not determined.

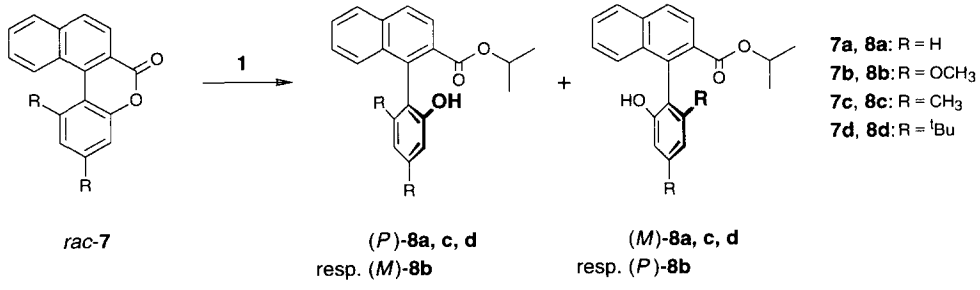
The best substrate solubility and highest selectivity was obtained in THF (Entries 1-8). Reducing the temperature from room temperature to -30°C increased the selectivity, but was, however, accompanied by a decrease in the reaction rate (Entries 8-10). TADDOLates **1b** and **1d** (Entries 11 and 12) resulted in a selectivity and reaction rate slightly inferior to the ones observed with TADDOLate **1a** (Entry 8). Reaction with the α-naphthyl-substituted TADDOLate **1e** showed strongly reduced reactivity and selectivity (Entry 13), a feature which is already known from other reactions with **1e**.[52]

The best result was achieved in THF at -28°C with TADDOLate **1a** (Table 1, Entry 8 and Scheme 3, above), leading to (*S*)-**6** with a selectivity of 85:15, as confirmed by comparison of its optical rotation with that of an authentic sample synthesized from (*S*)-phenylalanine. Six days were required for complete conversion with the yield being 75%. One recrystallization increased the enantiomer ratio of **6** from 85:15 to 98:2 with 25% yield.

The method presented here allows the transformation of a racemic *N*-protected amino acid to an almost enantiomerically pure ester in one step followed by one recrystallization. Investigations of substituent effects of the azlactone and the extension of this methodology to the synthesis of various other amino acid derivatives will be reported separately.

c) Enantioselective Ring Opening of Biaryl Lactones

A new approach has recently been developed for the construction of axially chiral biaryls.[53-55] Biaryl lactones, such as **7**, which are readily prepared by intramolecular aryl coupling,[56] are used as precursors. These lactones contain a biaryl axis of chirality, but they are configurationally labile, as the lactone bridge facilitates rotation for **7a-c** about the biaryl bond at room temperature. This offers the possibility for an enantioselective or diastereoselective cleavage of the lactone bridge leading to configurationally stable chiral products. Whereas enantioselective ring-opening reactions with chiral hydride-transfer reagents were very successful,[57,58] *O*-nucleophiles have so far been used only in diastereoselective processes - using chiral alkoxides for modell lactones **7**[54,55,59] or achiral *O*-nucleophiles for substrates diposing of additional stereo centers, *e.g.* in the course of efficient syntheses of naphthylisoquinoline alkaloids.[60,61] We therefore decided to test the Ti-TADDOLates **1** as reagents for the atropo-enantioselective ring-opening of biaryl lactones **7**.



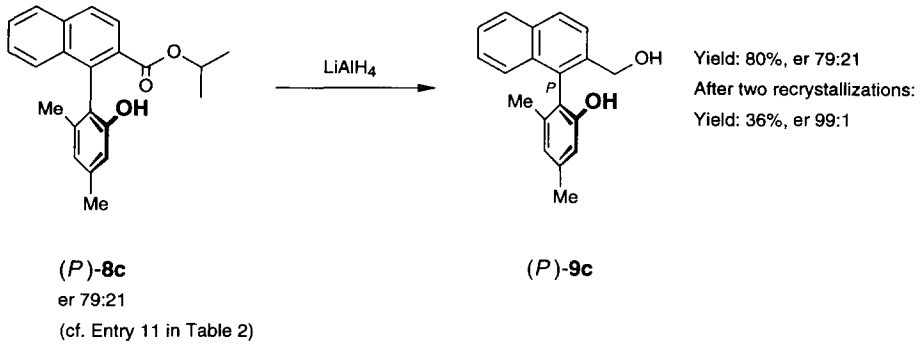
Scheme 4. *Enantioselective ring-opening of biaryl lactones 7 by Ti-TADDOLates 1.*

Table 2. *Variation of the Reaction Conditions and of the Ti-TADDOLate* ***1*** *for the Enantioselective Ring-Opening of the Biaryl Lactones* ***7****.*

Entry [a]	Lactone	Ti-TADDOLate	Temperature [°C]	Time [d]	Conversion [%]	Yield [%]	Enantiomer ratio er
1	**7a**	**1d**	- 25/rt	12	-	-	-
2	**7b**	**1d**	- 25/rt	4 + 8	35	-	54:46
3	**7c**	**1d**	- 25/- 15	10 + 8	10	-	75:25
4	**7d**	**1d**	- 25/rt	12	-	-	-
5[b]	**7c**	**1a**	- 8	1	> 95	-	56:44
6[c]	**7c**	**1a**	- 10	0.67	> 95	-	59:41
7	**7c**	**1a**	- 25/- 15	10/3	19	-	73:27
8	**7c**	**1b**	- 25/- 15	4/8	16	-	83:17
9	**7c**	**1c**	- 25/- 15	10/8	30	-	78:22
10	**7c**	**1a**	- 25/- 15/rt	10/3/4	76	-	62:38
11	**7c**	**1b**[d]	- 15	21	> 98	93 (52)[e]	79:21 (95:5)[e]
12	**7c**	**1b**[f]	- 15	28	85	70	79:21

[a] If not otherwise noted, all reactions were carried out in THF with 0.25 mmol of **7** and 1.25 equivalents of **1**. [b] The reaction was carried out in CH_2Cl_2. [c] The reaction was performed in toluene. [d] 1.00 mmol of **7c** and 3 equivalents of **1b** were used. [e] Mother liquor after recrystallization from Et_2O/pentane. [f] 1.00 mmol of **7c** and 1.8 equivalents of **1b** were used.

Initally, we investigated the conversion of the biaryl lactones **7**, with Ti-TADDOLate **1d** (Table 2, Entry 1-4). While **7a** and **7d** did not undergo ring-opening at room temperature, **7b** and **7c** were transformed to the corresponding isopropyl esters **8** at low temperature. Although the conversion of both substrates was low, the enantiomer ratio observed with the methyl-substituted biaryl lactone **7c** was encouraging and therefore **7c** was used as the test compound in all further experiments. Changing the solvent from THF to dichloromethane or toluene led to high conversions, but only low enantiomer ratios (Entry 5 and 6). We next investigated the variation of the Ti-TADDOLate **1** (Entry 1, 7-9). The best result was obtained with the β-naphthyl-substituted Ti-TADDOLate **1b** (83:17). Raising the temperature led to a rapid decrease in selectivity (Entry 10). Longer reaction times at low temperature and a higher amount of Ti-TADDOLate **1b** finally gave **8c** in good chemical yield with moderate enantioselectivity (Entry 11 and 12). A single recrystallization step led to nearly racemic, crystalline **8c** (er 58:42) and a highly enriched mother liquor with an enantiomer ratio of 95:5. In principle, the wrong enantiomer of **8** or racemic material of **8** is not lost, but can be recycled by re-cyclization to give back the configuratively unstable lactone **7**, which can be submitted to renewed cyclization. This has been demonstrated in other cases.[62]



Scheme 5. *Determination of the absolute configuration of* ***8c*** *by conversion to the known diol* ***9c*** *and enantiomer enrichment by recrystallization.*

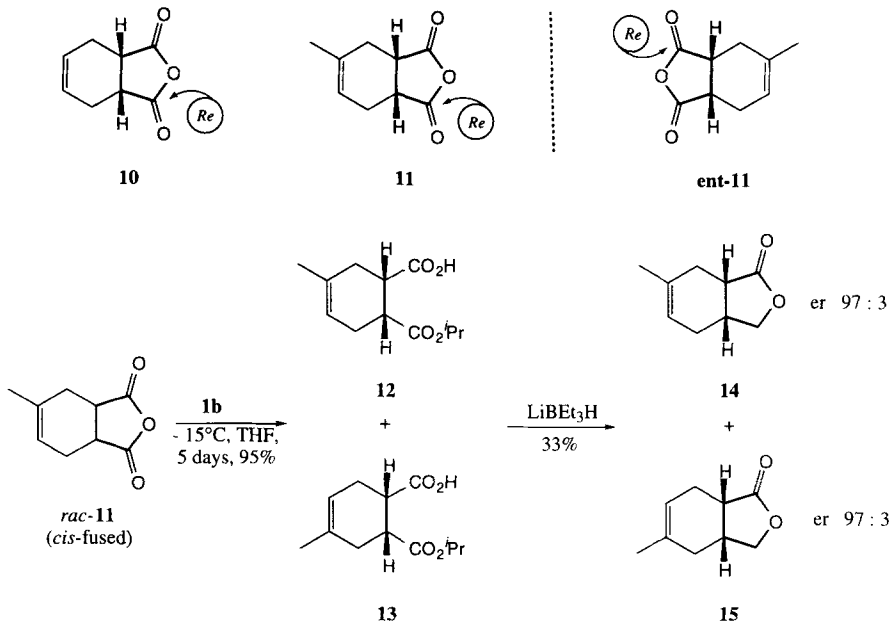
The absolute configuration of **8c** was determined by reduction to the known[57] diol **9c**. HPLC analysis showed no loss in enantiomer purity during this reaction. After two recrystallization steps, solid **9c** was obtained in almost enantiopure form.[57,58]

In comparision to the expensive direct reduction of **7c**[57,58] with *Corey*'s oxazaborolidine[63] and to the diastereoselective ring-opening of **7c** with menthol, separation of the atropoisomers and subsequently reduction,[54,55] the enantioselective sequence, ring-opening of **7c** with Ti-TADDOLate **1b**, reduction and crystallization, is an excellent alternative route for large scale processes to the enantiopure diol **9c**.

d) Enantiomer Differentiating Reaction of a Chiral Anhydride

In a previous publication, we have reported the highly enantioselective ring-opening of cyclic *meso* anhydrides by Ti-TADDOLates **1**.[21] Starting from the bicyclic *meso*-anhydride **10**, the isopropoxy group is transferred preferentially (10:1) to the *Re*-carbonyl group. This result led us to use Ti-TADDOLates **1** also in a ring-opening reaction of a racemic anhydride **11**, i. e. the *Diels-Alder* adduct from isoprene and maleic anhydride.

A 1:1 mixture of the two constitutional isomers **12** and **13** was obtained as the result of the Ti-TADDOLate **1b** mediated ring-opening of *rac*-**11**. The enantiomer ratios in these isomers were determined by reduction and cyclization of the half-esters **12** and **13** to the corresponding lactones **14** and **15**, which were separated on a chiral GC-column. In both cases, the same enantiomer ratio of 97:3 was determined. Assuming that the additional methyl group in **11**, compared with the *meso*-anhydride **10**, has only a minor influence on the outcome of the reaction, the two enantiomers of **11** should both be attacked preferentially at the *Re* carbonyl group and this leads, indeed, to the two constitutional isomers **12** and **13**, both in highly enantioenriched form.



Scheme 6. *Enantiomer-Differentiating Reaction of Anhydride* ***11*** *with Ti-TADDOLate* ***1b****.*

The absolute configurations of the products **12** and **13**, and thus also of **14** and **15**, are assigned solely by analogy with the known[22] stereochemical course of the ring-opening by **1a** of the *meso* anhydride **10**. According to the definition of *Izumi* and *Tai*, the reaction of *rac*-**11** is classified as an enantiomer differentiating reaction,[64] which leads to different constitutional isomers. Such reactions are rare in organic synthesis[65] and the most prominent examples are asymmetric *Baeyer-Villiger* oxidations of racemic ketones catalyzed by enzymes[66] or organometallic complexes.[67]

EXPERIMENTAL

General Remarks

1. Abbreviations: CC (column chromatography), FC (flash chromatography), HV (high vacuum, 0.01-0.1 Torr), R_t (retention time in min), tlc (thin layer chromatography).

2. Reagents and Equipment: All reactions were carried out under an Ar or N_2 atmosphere in oven- or flame-dried glassware. Solvents used for reactions and crystallizations were purchased from *Fluka* (puriss.). Dry THF and Et_2O was freshly distilled from K or Na under Ar atmosphere. Solvents used for extraction and flash chromatography were distilled as follows: AcOEt, acetone and CH_2Cl_2 from P_2O_5, Et_2O from KOH/$FeSO_4$, petroleum ether (50/70), pentane, hexane and toluene from Sikkon. Solvents used for HPLC were purchased from *Riedel-de Haën* (Chromosolv).

Tlc separations were run on *Merck* silica gel 60-F_{254} analytical plates; FC was performed on *Fluka* silica gel 60 (0.040-0.063 mm), pressure 0.2-0.4 bar, CC on *Merck* silica gel (0.063-0.200 mm). Melting points were determined on a *Büchi-510* or a *Kofler hot-stage* apparatus and are uncorrected. Optical rotations were measured with a *Perkin-Elmer 241* polarimeter at room temperature (10 cm, 1 ml cell). HPLC: *Knauer* HPLC system (pump type *64*, integration system Eurochrom 2000, UV-detector (variable wavelength monitor)); a) column WHELK-01, 4.6 x 250 mm, 5 µm (*Regis*), $\lambda = 254$ nm, flow 2 ml/min b) column DNBPG, 4.6 x 250 mm, 5 µm (*Baker*), $\lambda = 254$ nm, flow 1 ml/min resp. $\lambda = 280$ nm, flow 1.2 ml/min. Capillary gas chromatography (GC): *Carlo-Erba HRGC 5160* MEGA SERIES; FS Lipodex (γ-cyclodextrin (50 m x 0.25 mm ID)), injector temperature 225°C, detector temperature 225°C (FID), flow 3 ml/min, carrier gas 1.2 bar H_2, temperature program: 15 min 100°C, 1°/min until 200°C. NMR spectra were recorded in $CDCl_3$ with TMS ($\delta = 0$) as internal standard on *Varian-Gemini 200* or a *Bruker AC 200* (200 MHz (^{1}H), 50 MHz (^{13}C)), a *Bruker AC 250* (250 MHz (^{1}H), 63 MHz (^{13}C)) or *Varian-Gemini 300* (300 MHz (^{1}H), 75 MHz (^{13}C)). Chemical shifts are given in ppm. IR spectra: *Perkin-Elmer 782* or *Perkin-Elmer 1420* infrared spectrophotometer. Mass Spectra: MS *VG-Tribrid* spectrometer (EI), *Finnigan MAT 8200* mass spectrometer (EI) and *Hitachi Perkin-Elmer RMU-6M* spectrometer (FAB), fragment ions in *m/z* with relative intensities (%) in parentheses. Elemental analyses were performed by the Microanalytical Services of the Laboratorium für Organische Chemie ETH or of the University of Würzburg on a *Carlo-Erba M 1106* apparatus.

a) Kinetic Resolution of a Dioxolanone

rac-5-(4-Benzyloxyphenyl)-2,2-dimethyl-1,3-dioxolan-4-one (2)

rac-4-Hydroxy mandelic acid monohydrate (15.0 g, 26.9 mmol) was converted to its acetonide (*rac*-2,2-dimethyl-5-(4-hydroxyphenyl)-1,3-dioxolan-4-one)) in analogy to standard procedures[26] with acetone (150 ml) and boron trifluoride etherate (15.2 ml, 40.3 mmol) with 67% yield and was directly used for the next step. Benzyl bromide (6.02 ml, 5.92 mmol) was slowly added to a cooled solution (0°C) of the acetonide (11.2 g, 5.38 mmol) and K_2CO_3 (12.7 g, 10.8 mmol) in DMF (90 ml). After stirring at room temperature overnight, the mixture was poured into a mixture of water (100 ml), ethyl acetate (150 ml) and hexane (80 ml) under continous stirring. The organic layer was separated, washed twice with sat. NaCl soln., dried over $MgSO_4$ and evaporated *in vacuo*. FC (pentane:ethyl acetate 9:1 - 5:1) and recrystallization from ethyl acetate (30

ml) and pentane (300 ml) yielded 8.73 g (64%) of **2**, mp. 105°C. Further 4.04 g (29%) of the product could be recovered from the mother liquor in two crystallizations from ethyl acetate (10 ml) and pentane (100 ml).
^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.45-7.30 (*m*, 7H), 7.01 (*d*, 2H, J = 8.9 Hz), 5.34 (*s*, 1H), 5.08 (*s*, 2H), 1.72 (*s*, 3H), 1.67 (*s*, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.78, 159.40, 136.74, 128.58, 128.14, 128.01, 127.44, 126.77, 115.09, 110.65, 75.67, 69.92, 27.07, 25.83. MS (EI): *m/z* = 298 (3) [M^+], 254 (7), 196 (5), 163 (4), 91 (100). IR ($CHCl_3$): $\tilde{\nu}$ = 3007m, 2942w, 2871w, 1789s, 1612s, 1587w, 1513s, 1455m, 1388m, 1381m, 1248s, 1122m, 1012m, 898m, 827m. Anal. calcd. for $C_{18}H_{18}O_4$ (298.34): C 72.47, H 6.08; found: C 72.36, H 6.02.

Reaction of 2 with Ti-TADDOLate 1a (large scale)
$Ti(OiPr)_4$ (19.3 ml, 65.4 mmol) was added to a solution of the tetraphenyl TADDOL (31.3 g, 67.1 mmol) in Et_2O (350 ml) at room temperature under an argon atmosphere. The resulting clear solution of the TADDOLate **1a** was stirred for 3 h. The solvent was removed under HV and the residual oil dried for an additional hour.
A solution of **2** (10 g, 33.5 mmol) in THF (150 ml) was added to a solution of the TADDOLate in THF (300 ml) at room temperature under stirring. The mixture was stirred at room temperature for 3 d, then poured under stirring into a mixture of sat. $NaHCO_3$ soln. (300 ml), water (300 ml) and ethyl acetate (500 ml). The resulting precipitate was filtered off and the filtrate washed twice with sat. NaCl soln., dried over $MgSO_4$ and concentrated *in vacuo*. FC (pentane:ethyl acetate 8:1) gave two fractions: one containing enantioenriched unreacted **2** ((*R*):(*S*) = 86:14, Whelk-01, hexane:^{i}PrOH = 90:10, R_t: 13.7 (*R*), 24.8 (*S*)) together with recovered TADDOL (total 34.5 g), the other one containing enantioenriched **3** (5.77 g, 57%, (*S*):(*R*) = 77:23, Whelk-01, hexane:^{i}PrOH = 90:10, R_t: 14.6 (*S*), 17.5 (*R*)); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.50-7.25 (*m*, 7H), 6.97 (*d*, 2H, J = 8.7 Hz), 5.15-5.00 (*m*, 4H), 3.41 (*d*, 1H, J = 5.9 Hz), 1.28 (*d*, 3H, J = 6.2 Hz), 1.12 (*d*, 3H, J = 6.2 Hz).

(*R*)-(4-Benzyloxy-phenyl)-hydroxy-acetic acid methyl ester ((*R*)-4)
To the residual mixture of (*R*)-**2** and TADDOL in THF (250 ml) and methanol (200 ml) 1N NaOH (250 ml) was added at room temperature. After stirring at room temperature for 5 h, the mixture was evaporated *in vacuo*. The residue was adjusted to pH 9-10 with 1N NaOH. Ethyl acetate (300 ml) was added to the solution under stirring. The organic layer was separated, washed twice with sat. NaCl soln., dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was recrystallized from ethyl acetate (15 ml) and pentane (150 ml) to yield 25.0 g (80%) of TADDOL. From the mother liquors, another 4.5 g (14%) of TADDOL could be obtained (total recovery 94%).
The aqueous layer was adjusted to pH 2-3 with 1N HCl and extracted twice with ethyl acetate (200 ml). The combined organic layers were washed twice with sat. NaCl soln., dried over $MgSO_4$ and concentrated *in vacuo* to give (4-benzyloxy-phenyl)-hydroxy-acetic acid (3.69g, 36%) which was used without further purification. A solution of this acid (3.69 g, 14.3 mmol) in THF (10 ml) was added under ice-cooling to a solution of methanol (40 ml) and acetyl chloride (2.03 ml, 29.0 mmol). This mixture was stirred at room temperature overnight, concentrated *in vacuo* and the residue dissolved in a mixture of ethyl acetate (100 ml) and sat. $NaHCO_3$ soln. (50 ml). The organic layer was washed twice with sat NaCl soln., dried over $MgSO_4$ and evaporated. FC (pentane:ethyl acetate 5:1) yielded 3.07 g **4** (34% relative to dioxolanone **2**) as colourless crystals ((*R*):(*S*) = 84:16, Whelk-01, hexane:^{i}PrOH = 90:10, flow 2 ml/min, R_t: 13.7 (*R*), 16.8 (*S*)). The crystals were dissolved in a mixture of pentane (50 ml) and ethyl acetate (40 ml) and this solution was allowed

to stand at room temperature for 2 d. The precipitate (0.97 g, 11%, (*R*):(*S*) = 57:43) was filtered off, the filtrate afforded after evaporation 2.1 g (23%) (*R*)-**4** ((*R*):(*S*) = 95:5). A second recrystallization from pentane (70 ml) and ethyl acetate (30 ml) gave 0.19 g (2%) (*R*)-**4**, ((*R*):(*S*) = 60:40). The mother liquors yielded after evaporation 1.73 g (19%) of (*R*)-**4**, mp. 77°C, ((*R*):(*S*) = 95:5), $[\alpha]_D^{RT}$ = −109.5 (c = 1.0, $CHCl_3$).
^1H NMR (200 MHz, $CDCl_3$): δ = 7.45-7.25 (*m*, 7H), 6.98 (*d*, 2H, J = 8.8 Hz), 5.14 (*d*, 1H, J = 5.5 Hz), 5.07 (*s*, 2H), 3.77 (*s*, 3H), 3.36 (*d*, 1H, J = 5.5 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): 174.24, 158.97, 136.8, 130.75, 128.56, 127.89, 127.41, 114.94, 69.98, 52.87. MS (EI): *m/z* = 272 (9) [M^+], 213 (94), 91 (100). IR ($CHCl_3$): $\tilde{\nu}$ = 3414m, 1719m, 1607w, 1510w, 1463s, 1377s, 1242m, 1172m, 1071m, 1018m. Anal. calcd. for $C_{18}H_{18}O_4$ (298.34): C 72.47, H 6.08; found: C 72.36, H 6.02.

(*S*)-(4-Benzyloxy-phenyl)-hydroxy-acetic acid methyl ester ((*S*)-4)

A solution of **3** (5.76 g, 19.5 mmol) in THF (10 ml) was added to a solution of methanol (60 ml) and acetyl chloride (2.73 ml, 39 mmol) under ice-cooling. The mixture was stirred at room temperature overnight and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (200 ml), washed with sat. $NaHCO_3$ soln. and sat NaCl soln., dried over $MgSO_4$ and evaporated *in vacuo*. FC (pentane:ethyl acetate 5:1) afforded 4.84 g (93%) of **4** ((*S*):(*R*) = 78:22)).
Recrystallization from ethyl acetate (60 ml) and pentane (80 ml) gave 2.22 g (24%) of colourless crystals with an enantiomer ratio of 55:45. The mother liquor was evaporated and the residue (2.59 g, 28%, (*S*):(*R*) 93:7) recrystallized from ethyl acetate (40 ml) and pentane (120 ml). The resulting crystals (0.2 g, 9%, (*S*):(*R*) = 54:46) were filtered off, the filtrate evaporated *in vacuo* and dried under HV to afford 2.44 g (27%) of (*S*)-**4**, mp. 79°C, (*S*):(*R*) = 97:3, $[\alpha]_D^{RT}$ = 111.7 (c = 0.9, $CHCl_3$).

b) Enantioselective Ring-Opening of an Azlactone

(*S*)-2-Benzoylamino-3-phenyl-propionic acid isopropyl ester (6)

$Ti(O^iPr)_4$ (0.350 ml, 1.19 mmol) was added to a solution of the tetraphenyl TADDOL (0.579 g, 1.24 mmol) in Et_2O (10 ml) at room temperature under an argon atmosphere. The resulting clear solution was stirred for 4 h, the solvent removed under HV and the resulting Ti-TADDOLate **1a** dried for 1 h. A cooled solution (ca. -30°C) of azlactone **5** (prepared according to literature procedures[68]) was added to a precooled solution (-30°C) of **1a** (1.19 mmol) in THF (10 ml). The resulting homogeneous solution was stirred at this temperature for 15 min. The reaction mixture was then allowed to stand at -28°C (freezer) for 6 d. The reaction was monitored by ^1H NMR and tlc. After completion of the reaction, 5 ml of sat. NH_4Cl soln. were added and the resulting colloidal precipitate was filtered off. The precipitate was resuspended in ethyl acetate and Et_2O (10 ml each), stirred for 5 min and filtered off again. The filtrates were extracted three times with CH_2Cl_2 (20 ml). The combined organic layers were washed with water and sat. NaCl soln., dried over Na_2SO_4 and evaporated in *vacuo*. FC (toluene:ethyl acetate 95:5) yielded 0.234 g (75%) of **6** as a colourless oil which gave colourless crystals on standing, mp. 117°C. ((*S*):(*R*) = 85:15, DNBPG, hexane:^{i}PrOH = 95:5, λ = 254 nm, flow 1.0 ml/min; R_t: 12.0 (*S*), 14.2 (*R*)) as well as 0.463 g (80%) of the recovered TADDOL. Recrystallization from diisopropyl ether gave 0.077 g (25%) of enantioenriched product **6** ((*S*):(*R*) = 98:2), $[\alpha]_D^{RT}$ = 41.1 (*c* =1, $CHCl_3$) (of a sample with er 72:28, compared to an authentic homochiral sample prepared from (*S*)-phenylalanine: $[\alpha]_D^{RT}$ = 91.4 (*c* =1, $CHCl_3$)).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.76-7.71 (*m*, 2H), 7.53-7.15 (*m*, 8H), 6.71-6.67 (*br d*, 1H), 5.11-4.99 (*m*, 2H), 3.27-3.23 (*m*, 2H), 1.26 (*s*, 3H), 1.24 (*s*, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.27, 166.92, 136.02, 134.12, 131.78, 129.56, 128.66, 128.54, 127.35, 127.24, 69.51, 53.51, 37.82, 21.64, 21.57. MS (FAB): *m/z* = 934 (1) [M_3H^+], 623 (26) [M_2H^+], 312 (100) [MH^+], 224 (16), 136 (15), 105 (47), 73 (21). IR ($CHCl_3$): $\tilde{\nu}$ = 3432m, 2985m, 1729s, 1660s, 1603m, 1581m, 1517s, 1486s, 1375s, 1105s. Anal. calcd. for $C_{19}H_{21}NO_3$ (311.38): C 73.29, H 6.80, N 4.50; found: C 73.03, H 6.90, N 4.43.

c) Enantioselective Ring-Opening of Biaryl Lactones

General Procedure for the Ring-Opening of 7 (for experimental details see Table 2)

$Ti(O^iPr)_4$ (1.25 equivalents) was added to a solution of the respective original TADDOL (1.00 equivalents) in Et_2O (20 ml/mmol **1**) at room temperature under an argon atmosphere. The resulting clear solution of the Ti-TADDOLate **1** was stirred for 3 h. The solvent was removed under HV and the residual oil dried for an additional hour.

A solution of the respective biaryl lactone **7** in THF (8 ml/mmol **7**) was added to a precooled solution (-50°C) of **1** in THF (20 ml/mmol **7**). The ring-opening reaction was allowed to proceed under the conditions as outlined in Table 2.

HPLC determination of enantiomer ratio and conversion: Sat. NH_4Cl soln. (2 ml) was added to 0.5 ml of the reaction mixture. The resulting solution was extracted with Et_2O (2 ml) and the solvent evaporated to dryness. The crude product mixture, containing **7** and **8**, was analyzed by HPLC. (Conditions: DNBPG, hexane:^{i}PrOH = 97:3, λ = 280 nm, flow 1.2 ml/min; **7b/8b**: R_t: 25.8 (**7b**), 38.6 (**8b**, (*M*)), 49.7 (**8b**, (*P*)); **7c/8c**: R_t: 10.1 (**7c**), 13.9 (**8c**, (*P*)), 15.9 (**8c**, (*M*))[69]; the ratio of **7**:**8** was calculated from the UV absorption integrals of the HPLC signals after correlating some samples with the ratio of **7**:**8** determined by ^{1}H NMR.).

1-(2-Hydroxy-4,6-dimethoxyphenyl)naphthyl-2-carboxylic acid isopropyl ester (*rac*-8b)

78.4 mg (3.37 mmol) of NaH were added to isopropanol (9 ml) at room temperature under an argon atmosphere. After stirring for 15 min, 200 mg (0.653 mmol) of **7b** were added and stirring continued for 3 h. The solvent was evaporated, the residue suspended in water (10 ml), neutralized with 2N HCl, extracted three times with Et_2O (10 ml each), dried over $MgSO_4$ and evaporated *in vacuo*. CC (petroleum ether:Et_2O 3:1) afforded **8b** as a yellow oil. Crystallization from pentane/Et_2O gave 184 mg (77%) of *rac*-**8b** as a colourless solid, mp. 166°C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.00-7.87 (*m*, 3H), 7.64-7.38 (*m*, 3H), 6.29 (*d*, 1H, J = 2.3 Hz), 6.22 (*d*, 1H, J = 2.3 Hz), 5.06 (*sept*, 1H, J = 6.3 Hz), 4.65 (*s*, 1H), 3.86 (*s*, 3H), 3.56 (*s*, 3H), 1.12 (*d*, 3H, J = 6.1 Hz), 1.09 (*d*, 3H, J = 6.1 Hz). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 167.80, 161.44, 158.66, 154.72, 135.04, 132.99, 131.67, 131.08, 128.70, 128.14, 127.68, 127.12, 126.77, 125.89, 107.00, 93.17, 91.67, 68.50, 55.71, 55.42, 21.47, 21.38. MS (EI): *m/z* = 366 (23) [M^+], 306 (100), 291 (8), 263 (8), 235 (6). IR (KBr): $\tilde{\nu}$= 3310br s, 3040w, 2960m, 2920w, 2830w, 1655s, 1600s, 1585s, 1460s, 1370s, 1340s, 1280s, 1155s, 1135s, 1100s, 815s, 770s. Anal. calcd. for $C_{22}H_{22}O_5$ (366.41): C 72.12, H 6.05; found C 71.84, H 5.87.

(*P*)-1-(2-Hydroxy-4,6-dimethylphenyl)naphthyl-2-carboxylic acid isopropyl ester ((*P*)-8c) (Table 2, Entry 11): The reaction mixture, prepared according to the general procedure, was treated with sat. NH_4Cl soln. (50 ml), extracted three times with Et_2O (50 ml each), dried over $MgSO_4$ and evaporated *in vacuo*. CC (petroleum ether:acetone 10:1) afforded 310 mg (93%) of **8c** ((*P*):(*M*) = 79:21)) as a yellow oil. Crystallization from pentane/Et_2O gave 126 mg (38%) of *rac*-**8c** as a white solid ((*P*):(*M*) = 58:42), mp. 135°C (racemic sample), and from the mother liquor 173 mg (52%) of (*P*)-**8c** as a yellow oil ((*P*):(*M*) = 95:5). Crystallization of the mother liquor from pentane/Et_2O yielded (*P*)-**8c** (48.9 mg, 15%) as colourless needles, mp. 120°C, (*P*):(*M*) = 95:5, $[\alpha]_D^{RT}$ = 16.9 (c = 1.2, $CHCl_3$).
^1H NMR (200 MHz, $CDCl_3$): δ = 7.99-7.87 (*m*, 3H), 7.63-7.35 (*m*, 3H), 6.73 (*s*, 1H), 6.72 (*s*, 1H), 5.03 (*sept*, 1H, J = 6.3 Hz), 4.44 (*s*, 1H), 2.38 (*s*, 3H), 1.78 (*s*, 3H), 1.07 (*d*, 3H, J = 6.1 Hz), 1.01 (*d*, 3H, J = 6.1 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.67, 153.12, 138.77, 137.65, 134.98, 134.08, 132.44, 130.92, 128.65, 128.16, 127.83, 127.31, 126.56, 125.74, 122.86, 122.16, 113.55, 68.64, 21.28, 21.13, 19.70. MS (EI): *m/z* = 334 (17) [M^+], 274 (100), 259 (13), 231 (12), 202 (15), 101 (10). IR (KBr): $\tilde{\nu}$ = 3350br. s, 3040w, 2950m, 2900m, 2840w, 1700s, 1600s, 1565s, 1450s, 1440s, 1365s, 1285s, 1255s, 1135s, 1090s, 830s, 815s, 765s. Anal. calcd. for $C_{22}H_{22}O_3$ (334.42): C 79.02, H 6.63; found C 78.86, H 6.67.

(*P*)-1-(2-Hydroxy-4,6-dimethylphenyl)naphthalene-2-methanol ((*P*)-9c) (Table 2, Entry 12 and subsequent reduction): The reaction mixture, prepared according to the general procedure, was treated with sat. NH_4Cl soln. (50 ml), extracted three times with Et_2O (50 ml each), dried over $MgSO_4$ and evaporated *in vacuo*. CC (petroleum ether:acetone 10:1) afforded 69.2 mg (25%) of recovered lactone **7c** and 235 mg (70%) of **8c** ((*P*):(*M*) = 79:21)) as a yellow oil, which was dissolved in THF (10 ml) under an argon atmosphere and displaced at room temperature with 79.7 mg (2.10 mmol) $LiAlH_4$. After 10 min, water (10 ml) and 2N HCl (10 ml) were added, the resulting solution extracted three times with Et_2O (10 ml each), dried over $MgSO_4$ and evaporated *in vacuo*. CC (petroleum ether:Et_2O 1:1) afforded 157 mg (56%) of **9c** ((*P*):(*M*) = 79:21)) as a yellow oil. Crystallization from pentane/Et_2O gave 90.4 mg (33%) of (*P*)-**9c** as a white solid ((*P*):(*M*) = 97:3). Recrystallization resulted in (*P*)-**9c** (70.4 mg, 25%) as a white solid ((*P*):(*M*) = 99:1).
^1H NMR (200 MHz, $CDCl_3$): δ = 7.92 (m_c, 2H), 7.70 (*d*, 1H, J = 8.5 Hz), 7.55-7.32 (*m*, 3H), 6.79 (*s*, 1H), 6.73 (*s*, 1H), 4.78 (*s*, 1H), 4.52 (m_c, 2H), 2.38 (*s*, 3H), 1.80 (*s*, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 153.07, 139.16, 138.03, 137.36, 133.45, 132.52, 131.16, 128.94, 128.19, 126.77, 126.46, 126.18, 125.44, 123.37, 121.01, 114.04, 63.70, 21.28, 19.73. MS (EI): *m/z* = 278 (16) [M^+], 260 (100), 259 (80), 245 (23), 217 (8). IR (KBr): $\tilde{\nu}$ = 3380br s, 3040w, 2910w, 1605s, 1570s, 1440m, 1315s, 1060s, 1045s, 840m, 830m, 805s, 780m, 755m, 740m. Anal. calcd. for $C_{19}H_{18}O_2$ (278.35): C 81.99, H 6.52; found C 81.98, H 6.73. Mp. and $[\alpha]_D^{RT}$ are fully identical with material obtained previously.[57]

d) Enantiomer Differentiating Reaction of a Chiral Anhydride

4-Methyl-cyclohex-4-ene-1,2-dicarboxylic acid-1-isopropylester (12) and
4-Methyl-cyclohex-4-ene-1,2-dicarboxylic acid-2-isopropylester (13)
$Ti(O^iPr)_4$ (0.565 ml, 1.92 mmol) was added dropwise to a solution of β-naphthyl-TADDOL (1.332 g, 2 mmol) in Et_2O (15 ml) under argon and the mixture was stirred for 3 h at room temperature to give **1b**. The

solvent was removed *in vacuo* . The residue was dried for 30 min in HV and was dissolved in THF (12 ml). The solution was cooled to -78°C. A precooled solution (-78°C) of the anhydride **11** (0.266 g, 1.6 mmol) in THF (5 ml) was added. The mixture was sealed and stored for 6 d in a freezer (-15°C). Subsequently, the reaction mixture was poured into 1N NaOH (30 ml), Et_2O (50 ml) was added, and the aqueous phase was separated. The organic phase was further extracted with 1N NaOH (30 ml), and the combined aqueous phases were washed with Et_2O. Acidification with 1N HCl to pH 1-2, followed by extraction with Et_2O (150 ml), drying with $MgSO_4$, and evaporation of the solvent yielded 0.331 g of **12** and **13** (92%) as a colourless oil. $[\alpha]_D^{RT}$ = 0.6 (c = 0.9, ethyl acetate). ^1H NMR (200 MHz, $CDCl_3$): δ = 5.35 (*s*, 2H); 5.04-4.95 (*m*, 2H); 3.01-2.98 (*m*, 4H); 2.65-2.09 (*br*, 8H); 1.66 (*s*, 6H); 1.19 (*d*, J = 6.2 Hz, 12H).^{13}C NMR (50 MHz, $CDCl_3$): δ = 180.11, 179.67, 179.73, 172.65, 172.59, 132.62, 132.43, 132.21, 119.16, 119.00, 118.81, 68.08, 40.14, 39.79, 39.45, 39.10, 30.37, 29.99, 29.89, 25.99, 25.67, 25.45, 23.32, 23.26, 21.48. MS (EI): *m/z* = 226 (6) [M^+], 167 (30), 138 (100), 93 (93). IR ($CHCl_3$): $\tilde{\nu}$ = 3010m, 1709s, 1437w, 1374w, 1177w, 927w, 600w. Anal. calcd. for $C_{12}H_{18}O_4$ (226.3): C 63.70, H 8.02; found: C 63.79, H 7.88.

6-Methyl-3a,4,7,7a-tetrahydro-3H-isobenzofuran-1-one (14) and
5-Methyl-3a,4,7,7a-tetrahydro-3H-isobenzofuran-1-one (15)

$LiBEt_3H$ (2.1 mmol, 2.1 ml of a 1M solution in toluene) was added dropwise to a solution of hemiesters **12** and **13** (0.0786 g, 0.35 mmol) in THF (5 ml) under argon and the mixture was stirred for 3 h at room temperature. Subsequently it was carefully hydrolyzed with water (10 ml). The reaction mixture was stirred for 6 h in 1N HCl. Extraction with ethyl acetate (100 ml) and evaporation *in vacuo* yielded 17.8 mg **14** and **15** (33%); er = 97:3 (determined by GC-analysis on a FS Lipodex column, R_t: 67.4, 68.3, 72.2, 74.7). ^1H NMR (200 MHz, $CDCl_3$): δ = 5.45 (*s*, 2H); 4.38-4.29 (*m*, 2H); 4.06-3.69 (*m*, 2H); 2.82-1.91 (*br*, 12H); 1.69 (*s*, 6H).

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REFERENCES AND NOTES

Dedicated to Professor Wolfgang Beck on the occasion of his 65th birthday.

1. Part of the projected Ph. D. Theses of G. J. and K. G., ETH Zürich.
2. On the leave from *Fujisawa Pharmaceutical Co.*, LTD., 1995-1996.
3. Part of the Diplomarbeit (Master's Thesis) of R. F., ETH Zürich, 1996.
4. On the leave from *Chiroscience LTD.*,1995.
5. Part of the projected Ph. D. Thesis of M. B., Universität Würzburg.
6. Minireview covering the literature up to 1994: Dahinden, R.; Beck, A. K.; Seebach, D. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.-in-Chief; Wiley: Chichester, GB, 1995; p 2167.
7. Narasaka, K. *Synthesis* **1991**, 1.
8. Seebach, D.; Behrendt, L.; Felix, D. *Angew. Chem.* **1991**, *103*, 991; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1008.
9. Schmidt, B.; Seebach, D. *Angew. Chem.* **1991**, *103*, 1383; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1321.
10. Seebach, D.; Beck, A. K.; Schmidt, B.; Wang, Y. M. *Tetrahedron* **1994**, *50*, 4363.
11. Hayashi, Y.; Narasaka, K. *Chem. Lett.* **1990**, 1295.
12. Engler, T. A.; Letavic, M. A.; Reddy, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 5068.
13. Seebach, D.; Beck, A. K.; Imwinkelried, R.; Roggo, S.; Wonnacott, A. *Helv. Chim. Acta* **1987**, *70*, 954.
14. Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340.
15. Seebach, D.; Dahinden, R.; Marti, R. E.; Beck, A. K.; Plattner, D. A.; Kühnle, F. N. M. *J. Org. Chem.* **1995**, *60*, 1788.
16. Narasaka, K.; Hayashi, Y.; Shimada, S. *Chem. Lett.* **1988**, 1609.
17. Wong, C. H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Elsevier Science Ltd: Oxford, 1994; Vol. 12, p 41.
18. Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36.
19. Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475.
20. Eliel, E. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962.
21. Seebach, D.; Jaeschke, G.; Wang, Y. M. *Angew. Chem.* **1995**, *107*, 2605; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2395.
22. Ramon, D. J.; Guillena, G.; Seebach, D. *Helv. Chim. Acta* **1996**, *79*, 875.
23. Narasaka, K.; Kanai, F.; Okudo, M.; Miyoshi, N. *Chem. Lett.* **1989**, 1187.
24. Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem.* **1996**, *108*, 2880; *Angew. Chem. Int. Ed. Engl.* **1996**, *108*, 2708.
25. Seebach, D.; Naef, R. *Helv. Chim. Acta* **1981**, *64*, 2704.

26. Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313.
27. Calderari, G.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1592.
28. Pratesi, P.; Manna, A. L.; Campiglio, A.; Ghislandi, V. *J. Chem. Soc.* **1958**, 2069.
29. Hoover, J. R. E.; Dunn, G. L.; Jakas, D. R.; Lam, L. L.; Taggart, J. J.; Guarini, J. R.; Phillips, L. *J. Med. Chem.* **1974**, *17*, 34.
30. Brussee, J.; Loos, W. T.; Kruse, C. G.; v. d. Gen, A. *Tetrahedron* **1990**, *46*, 979.
31. Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.
32. Plöchl, J. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2815.
33. Erlenmeyer, E. *Justus Liebigs Ann. Chem.* **1893**, *275*, 1.
34. Rao, Y. S.; Filler, R. In *Oxazoles*; Turchi, I. J., Ed.; Wiley: New York, 1986; Vol. 45; p 361.
35. Maryanoff, B. E. In *Oxazoles*; Turchi, I. J., Ed.; Wiley: New York, 1986; Vol. 45; p 988.
36. Kemp, D. S. In *The Peptides*; Gross, E. and Meienhofer, J., Eds.; Academic Press: New York, 1979; p 315.
37. Benoiton, N. L. In *The Peptides*; Gross, E. and Meienhofer, J., Eds.; Academic Press: New York, 1983; p 218.
38. Daffe, V.; Fastrez, J. *J. Am. Chem. Soc.* **1980**, *102*, 3601.
39. Daffe, V.; Fastrez, J. *J. Chem. Soc. Perkin Trans. II* **1983**, 789.
40. Bevinakatti, H. S.; Banerji, A. A.; Newadkar, R. V.; Mokashi, A. A. *Tetrahedron: Asymmetry* **1992**, *3*, 1505.
41. Gu, R.-L.; Lee, I.-S.; Sih, C. J. *Tetrahedron Lett.* **1992**, *33*, 1953.
42. Crich, J. Z.; Brieva, R.; Marquart, P.; Gu, R.-L.; Flemming, S.; Sih, C. J. *J. Org. Chem.* **1993**, *58*, 3252.
43. Turner, N. J.; Winterman, J. R. *Tetrahedron Lett.* **1995**, *36*, 1113.
44. Steglich, W.; Weygand, F.; Barocio de la Lama, X. *Tetrahedron Suppl.* **1966**, *8*, 9.
45. Steglich, W.; Frauendorfer, E.; Weygand, F. *Chem. Ber.* **1971**, *104*, 687.
46. Tomida, I.; Senda, S.; Kuwabara, T.; Katayama, K. *Agr. Biol. Chem.* **1976**, *40*, 2033.
47. Miyazawa, T.; Otomatsu, T.; Higashi, K.; Yamada, T.; Kuwata, S. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4161.
48. Obrecht, D.; Spiegler, C.; Schönholzer, P.; Müller, K. *Helv. Chim. Acta* **1992**, *75*, 1666.
49. Obrecht, D.; Bohdal, U.; Broger, C.; Bur, D.; Lehmann, C.; Ruffieux, R.; Schönholzer, P.; Spiegler, C.; Müller, K. *Helv. Chim. Acta* **1995**, *78*, 563.
50. Siemion, I. Z.; Baran, G. *Bull. Acad. Pol. Sci.* **1975**, *23*, 317.
51. Slebioda, M.; St-Amand, M. A.; Chen, F. M. F.; Benoiton, N. L. *Can. J. Chem.* **1988**, *66*, 2540.
52. Seebach, D.; Plattner, D. A.; Beck, A. K.; Wang, Y. M.; Hunziker, D.; Petter, W. *Helv. Chim. Acta* **1992**, *75*, 2171.
53. Bringmann, G.; Walter, R.; Weirich, R. In *Methods of Organic Chemistry Houben Weyl. 4th ed.*; Helmchen, G.; Hoffmann, R.W.; Mulzer, J.; Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E21a, p. 567.
54. Bringmann, G.; Göbel, L.; Schupp, O. *GIT Fachz. Lab.* **1993**, *37*, 189.
55. Bringmann, G.; Schupp, O. *S. Afr. J. Chem.* **1994**, *47*, 83.

56. Bringmann, G.; Hartung, T.; Göbel, L; Schupp, O.; Ewers, C. L. J.; Schöner, B.; Zagst, R.; Peters, K.; von Schnering, H. G.; Burschka, C. *Liebigs Ann. Chem.* **1992**, 225.
57. Bringmann, G.; Hartung, T. *Angew. Chem.* **1992**, *104*, 782; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 761.
58. Bringmann, G.; Hartung, T. *Tetrahedron* **1993**, *49*, 7891.
59. Bringmann, G.; Ewers, C. L. J.; Göbel, L.; Hartung, T.; Schöner, B.; Schupp, O.; Walter, R. In *Selective Reactions of Metal-Activated Molecules*; Werner, H.; Griesbeck, A. G.; Adam, W.; Bringmann, B.; Kiefer, W., Eds.; Vieweg: Braunschweig, 1992; p. 183.
60. Bringmann, G.; Reuscher, H. *Angew. Chem.* **1989**, *101*, 1725; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1672.
61. Bringmann, G.; Pokorny, F. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1995; p. 127.
62. Bringmann, G.; Reuscher, H. *Tetrahedron Lett.* **1989**, *30*, 5249.
63. Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem.Soc.* **1987**, *109*, 7925.
64. Izumi, Y.; Tai, A. *Stereo-Differentiating Reactions*; Kodansha Ltd.: Tokyo, 1977, p 113.
65. Kagan, H. B. *Croatica Chem. Acta* **1996**, *69*, 669.
66. Petit, F.; Furstoss, R. *Tetrahedron: Asymmetry* **1993**, *4*, 1341.
67. Bolm, C.; Schlinghoff, G.; Weickhardt, K. *Angew. Chem.* **1994**, *106*, 1944; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1848.
68. Sofia, M. J.; Chakravarty, P. K.; Katzenellenbogen, J. A. *J. Org. Chem.* **1983**, *48*, 3318.
69. The faster eluting enantiomers of **8b** and **8c** are stereochemically identical, but have different *Cahn-Ingold-Prelog* descriptors for formal reasons. The configuration of **8b** was assigned by chromatographic comparision with the corresponding products from the enantioselective reduction of the lactones[57,58] using *Corey*'s oxazaborolidine.[63]

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