Highly Enantioselective Ring Opening of Cyclic *Meso*-Anhydrides to Isopropyl Hemiesters with Ti−TADDOLates: An Alternative to Hydrolytic Enzymes?

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The Lewis acid mediated transfer of an alkoxide ligand from the chiral ligand sphere of Ti−TADDOLate (**1**) to cyclic *meso* anhydrides to afford the corresponding hemiesters is described. By using this method a variety of structurally different anhydrides can be converted to isopropyl hemiesters with high enantioselectivities (enantiomer ratios up to 99:1). We have also investigated Lewis acidic titanium complexes, which differ from **1** in the chiral ligand or the alkoxide ligand that is transferred. Finally, a catalytic version, which allows the substoichiometric use of Ti−TADDOLate in the presence of stoichiometric amounts of Al(O*i*-Pr)$_3$, is presented.

Hydrolytic enzymes, such as esterases and peptidases, are exceptionally effective for the enantioselective hydrolysis of carboxylic acid derivatives,[1] and the amount of literature published in this area is still growing rapidly. So far, practical, nonenzymatic versions of these reactions are rare and often restricted to only a few examples.[2−8] We have therefore initiated a program directed toward enantioselective ester formation using as chiral titanium Lewis acids the Ti−TADDOLates **1**. These readily accessible chiral titanates[9] have been successfully used as catalysts in enantioselective addition reactions of carbon-centered nucleophiles to aldehydes,[10−14] in [2 + 2] cycloadditions,[15,16] and in Diels−Alder reactions.[17−20] Moreover, the presence of a Lewis acidic and a nucleophilic moiety within the same molecule offers the possibility of an alkoxide transfer from the chiral ligand sphere of **1** to the Lewis acid activated substrate.[21] For the preparation of enantiomerically pure carboxylic acid derivatives by such an alkoxide transfer, two different approaches can be envisaged: on one hand, "desymmetrization" of a *meso* compound can be achieved by differentiating enantiotopic carbonyl groups; on the other hand, kinetic resolution of racemic compounds can be carried out. These very same strategies are also used in reactions that are catalyzed by hydrolytic enzymes. To make sure that the Ti−TADDOLate mediated alcoholysis is irreversible, we investigated more reactive substrates than those usually used in enantioselective enzymatic reactions. For example, diesters were replaced by cyclic *meso*-anhydrides,[22] monoesters by dioxolanones,[23] and hydantoins by azlactones[23] (Scheme 1).

We have previously published a preliminary report on the use of this methodology in the Ti−TADDOLate mediated ring opening of cyclic *meso*-anhydrides[22] and a full paper has appeared describing the ring opening of *meso*-sulfonylimides[24] to the corresponding sulfonylamido isopropyl esters, with selectivities up to 99:1. Recently, we also described the Ti−TADDOLate mediated kinetic resolution of racemic dioxolanones, azlactones, and biaryl lactones giving highly enantioenriched products.[23]

In this paper the Ti−TADDOLate mediated enantioselective ring opening of cyclic C_s-symmetric anhydrides is reported in full detail.[22] Additionally, we describe a procedure for carrying out this process, using substoichiometric amounts of Ti−TADDOLates in the presence of stoichiometric amounts of Al(O*i*-Pr)$_3$.

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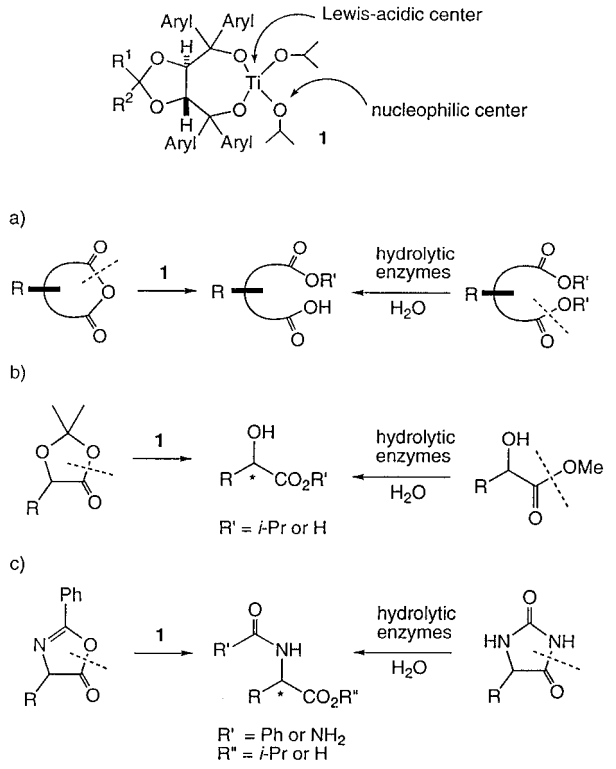
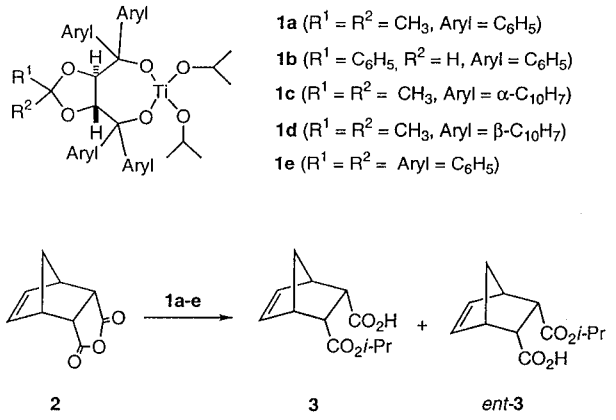
Scheme 1



Scheme 2



Results and Discussion

Ring-Opening Reaction with the Norbornene-Derived Anhydride 2. $Ti(O\textit{i}\text{-}Pr)_4$ is known to catalyze transesterification and deacylation processes very cleanly under mild conditions.[25] Similarly, the Ti−TADDOLate mediated ring opening reaction of cyclic anhydrides afforded the corresponding hemiesters without formation of any side products (Scheme 2).

To optimize the reaction conditions, the commercially available *endo*-Diels−Alder adduct **2** of maleic anhydride and cyclopentadiene was studied as a model compound. Isolation of the ring-opened product **3** is quite simple: the hemiester is separated from the TADDOL−ligand by extraction into an alkaline aqueous solution. The chiral ligand was recovered in quantitative yield from the organic phase. The influence of solvent on the selectivity was investigated first: in diethyl ether, methylene chloride, toluene, or pentane, only low enantioselectivities were obtained (Table 1, entries 1−4); a dramatic increase in selectivity was, however, obtained in THF (entry 5), the solvent which was therefore used in all further experiments. The effect of temperature was then studied by using Ti−TADDOLate **1b**: reducing the temperature from room temperature or 0 °C to −30 °C resulted in a considerable increase in the enantioselectivity (85:15 to 96:4), but was, of course, accompanied by a decrease in the reaction rate (entries 6, 8). A somewhat higher temperature (−12 °C instead of −30 °C) led to shorter reaction times, but also resulted in a significant decrease in the enantioselectivity (entries 7 and 8). The following experiments were therefore carried out at −30 °C. Finally, the reaction was optimized with respect to the substituents on the TADDOLate, as shown in Scheme 2; by using the *β*-naphthyl- or hexaphenyl-substituted titanium TADDOLates **1d** and **1e** the hemiester **3** was obtained, after several days, in almost enantiopure form (er 99:1) and in high yield (entries 11, 12). With the original titanium TADDOLate **1a** and the C_1-symmetrical Ti−TADDOLate **1b**, only slightly lower selectivities were observed (entries 8 and 9, er 96:4 and 97:3). The reaction with the α-naphthyl-substituted Ti−TADDOLate **1c**, however, occurred much more slowly, and with poorer selectivity (entry 10), a feature which has already been observed in other reactions mediated by **1c**.[23,26] All further reactions were carried out under the optimized conditions by using the *β*-naphthyl- or hexaphenyl-substituted Ti−TADDOLates **1d** and **1e** at low temperature in THF.

Table 1. Optimization of the Reaction Conditions for the Ti−TADDOLate Mediated Ring Opening of the Cyclic Anhydride 2 to the Hemiester 3[a]

entry	**1**	solvent	temp (°C)	time (d)	yield (%)	er
1	**1a**	Et_2O	0 → rt	0.66	91	44:56
2	**1a**	CH_2Cl_2	0 → rt	0.66	89	40:60
3	**1a**	toluene	0 → rt	0.66	30	50:50
4	**1a**	pentane	0 → rt	0.66	62	60:40
5	**1a**	THF	0 → rt	0.66	70	86:14
6	**1b**	THF	0 → rt	0.66	71	85:15
7	**1b**	THF	−12	0.5	40	93:7
8[b]	**1b**	THF	−30	5	88	96:4
9[b]	**1a**	THF	−30	5	91	97:3
10	**1c**	THF	−20	3	25	69:31
11[b]	**1d**	THF	−30	7	88	99:1
12[b]	**1e**	THF	−30	6	87	99:1

[a] 1.05 equiv of the Ti−TADDOLate were used under standard conditions. The enantiomer ratios were determined by GC-analysis of the methylisopropyl ester obtained by reaction of **3** with diazomethane or $(CH_3)_3OBF_4$. [b] 1.20 equiv of Ti-TADDOLate were used.

Investigation of Other Cyclic Anhydrides. With this result in hand (Table 1, entries 11 and 12), we next evaluated the scope of the reaction. For this purpose, we investigated the opening of tricyclic (**4**−**8**), bicyclic (**9**−**13**), and monocyclic (**14**−**16**) anhydrides.

Due to their strained structures, the tricyclic anhydrides **4**−**8** reacted at the same temperature (−30 °C) as the model compound **2**: even if they contained additional heteroatoms (see **7** and **8**), the anhydride substrates were ring opened by the Ti−TADDOLates **1d** or **1e** in good

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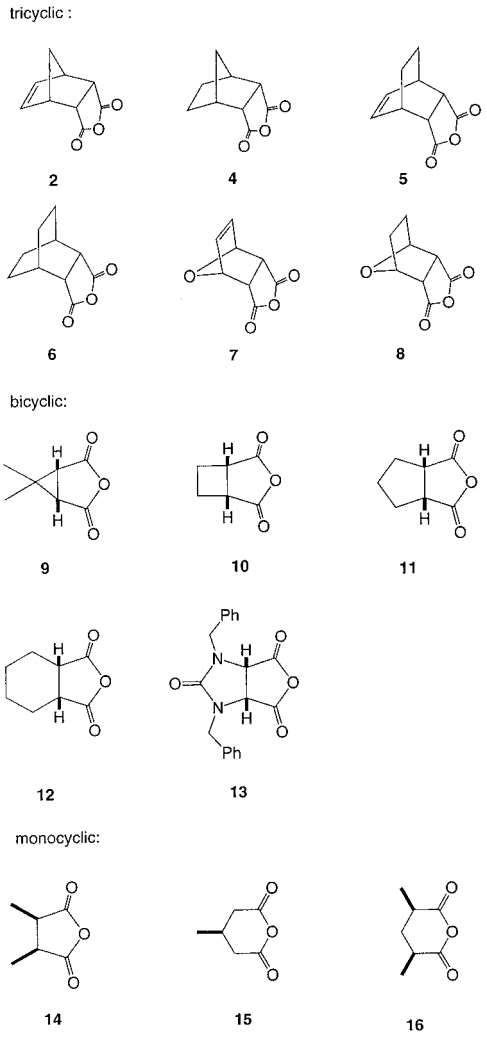

yields and with enantioselectivities up to 99:1 (Table 2, entries 2−6). The bicyclic anhydrides **9**−**13** are less reactive than the tricyclic compounds, and the reactions were carried out at temperatures ranging from −15 to −20 °C. The anhydrides with a carbocyclic backbone (three- to six-membered rings, **9**−**12**) were transformed to the corresponding hemiesters in a highly enantioselective fashion (er from 94:6 to 98:2). Only the opening of anhydride **13**, which contains a carbamate group, proceeded with low selectivity (entry 11, er 63:37). Of the three monocyclic anhydrides investigated, only **14** was ring opened with high enantioselectivity (entry 12, er 98:2), while with the glutaric acid derivatives **15** and **16**, poor selectivities were observed (entries 13 and 14).

In our investigation of different anhydrides, we tried to identify the structural features which were a prerequisite for the occurrence of highly enantioselective ring opening. As a working hypothesis, we can now propose the following two rules:

(i) An additional heteroatom within the anhydride can, but not necessarily will, lead to a decrease in selectivity (Table 2, entries 5, 6, and 11).

(ii) The nucleophilic attack must occur from one side of the plane containing the three oxygen atoms of the anhydride group, while the other side must be sterically shielded by substituents.

The last rule is fulfilled for all tricyclic and bicyclic anhydrides as well as for the monocyclic anhydride **14**, but not for the glutaric acid derivatives **15** and **16** (containing the substituents more or less *in* the plane of the anhydride CO−O−CO moiety!).

Table 2. Reaction Conditions, Yields, and Enantioselectivities of the Isopropyl Hemiesters Obtained from the Anhydrides 2 and 4−16 with Ti−TADDOLates[a]

entry	anhydride	time (d)	temp (°C)	yield (%)	er
1	**2**	7	−30	88	99:1
2	**4**	6	−30	91	99:1
3[b]	**5**	5	−30	91	99:1
4	**6**	5	−30	92	97:3
5	**7**	6	−30	63	99:1[c]
6	**8**	6	−30	82	98:2[c]
7	**9**	5	−15	59	98:2
8	**10**	5	−15	76	97:3
9	**11**	5	−15	74	94:6[c]
10	**12**	5	−15	87	>95:5
11	**13**	9	−20	80	63:37[c]
12	**14**	5	−18	73	98:2
13	**15**	5	−15	64	75:25
14	**16**	9/4	−20/0	99	50:50[c]

[a] Standard conditions: 1.20 equiv of Ti−TADDOLate **1d** were used. The enantiomer ratios were determined by GC-analysis of the methylisopropyl ester obtained from the hemiesters and diazomethane or $(CH_3)_3OBF_4$. [b] The Ti−TADDOLate **1e** was used. [c] The enantiomer ratios were determined by GC or HPLC analysis of the corresponding lactones, which were obtained from the hemiesters by reduction with $LiBEt_3H$ and lactonization (see Experimental Section).

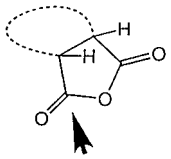

Figure 1.

The Absolute Configuration of the Products. The absolute configurations of the hemiesters **3**, **18**, **20**, and **22** were determined by selective reduction of the ester group (with $LiBEt_3H$) and lactonization (in one case (**19**), the C−C double bond was also hydrogenated) to give the known lactones **17**,[27,28] **21**,[29] and **23** (Scheme 3).[30] The senses of optical rotation for these lactones were then compared with those reported in the literature. The hemiester **24** was converted ($SOCl_2$, (*S*)-phenylethylamine) to the crystalline amide **25**. The relative configuration of **25**, and thus the absolute configuration of **24**, was determined by X-ray analysis.

In all cases, the stereochemical outcome of the reaction is uniform: by using the projection shown in Figure 1, the isopropoxy ligand is transferred to the marked carbonyl group. For the anhydrides containing a carbocyclic backbone, this is the *Re*-carbonyl group; due to reversal of the CIP-priorities it is the *Si*-carbonyl group of the furan-derived anhydrides **7** and **8**.

Use of Different Titanium Lewis Acids. In the many different applications of Ti−TADDOLates as chiral Lewis acids, the diisopropoxy derivatives **1** have been

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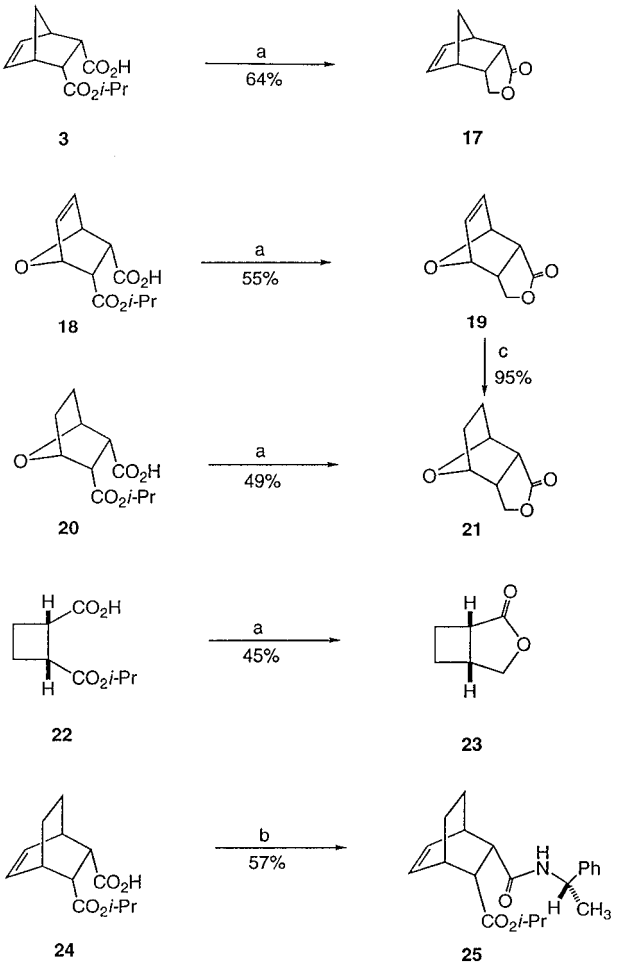
Scheme 3[a]



[a] Reagents and conditions: (a) (1) $LiBEt_3H$; (2) H^+, H_2O; (b) (1) $SOCl_2$, (2) (*S*)-phenylethylamine, (c) Pd/C, H_2.

employed most frequently.[31] With some titanium Lewis acids (e.g. **30**), replacement of the isopropoxy ligand by a *tert*-butoxy ligand results in a dramatic increase in selectivity for certain Lewis acid-catalyzed reactions.[32] In the case of the enantioselective ring opening of cyclic anhydrides, investigation of different alkoxide ligands was of particular interest for the possible preparation of other synthetically useful esters. For this reason, we studied the Ti−TADDOLates **28** and **29** in this reaction (eq 1).

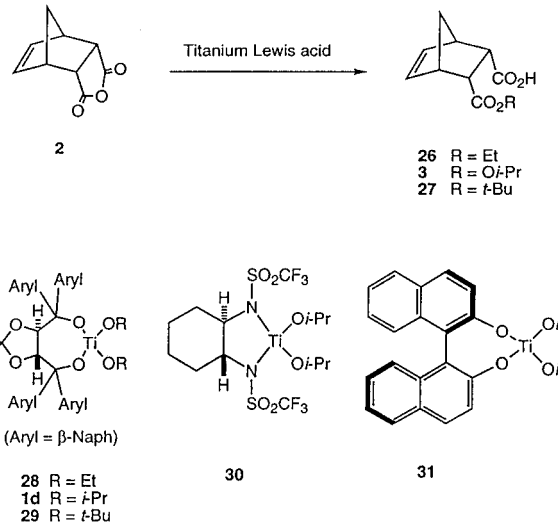
With diethoxy Ti−TADDOLate (**28**), a fast ring opening of anhydride **2** to the hemiester **26** was observed. However, the enantioselectivity was considerably lower than that obtained with **1d** (Table 3, entries 1 and 2). The transfer of the *tert*-butoxy ligand from **29** was—even at room temperature—very slow, and the hemiester **27** was isolated in low yield and with low enantioselectivity (entry 3).

Besides the Ti−TADDOLates, the Ti−CYDISate[33] **30** and the Ti−BINOLate **31** are among the most successful chiral Lewis acids used in catalytic asymmetric synthesis.

Table 3. Investigation of Different Chiral Ti−Lewis Acids for the Anhydride Ring Opening of 2[a]

entry	Ti−Lewis acid	time (d)	temp (°C)	yield (%)	er
1[b]	**28**	7	−30	91	85:15
2	**1d**	7	−30	88	99:1
3[b]	**29**	10	25	5	59:41
4	**30**	6	−22	95	45:55
5	**31**	6	−22	20	7:93

[a] Standard conditions: 1.20 equiv of Ti−Lewis acid were used. [b] The enantiomer ratios were determined by GC-analysis of the lactone **17**, which was obtained from **26** or **27** by reduction with $LiBEt_3H$ and lactonization.



For a comparison, we investigated these complexes in the ring opening of anhydride **2**. The Ti−CYDISate mediated reaction led to good conversion, but the hemiester **3** was obtained in almost racemic form (entry 4). Ti−BINOLate, on the other hand, reacted much slower than Ti−TADDOLate. Even after 6 days the reaction was still incomplete, and the hemiester **3** was isolated in low yield, but with good enantioselectivity (entry 5, er 93:7). Interestingly, an opposite sense of asymmetric induction was observed when going from (*R*,*R*)-Ti−TADDOLate to (*M*)-BINOLate, giving **3** and *ent*-**3**, respectively. This is another demonstration of the fact that the topicities of reactions mediated by (*R*,*R*)-TADDOLates and (*P*)-BINOLates are often the same. This observation has been previously rationalized and discussed in detail by us.[17]

Substoichiometric Use of 1. Since a dramatic effect of ligand acceleration[34] has been observed in the Ti−TADDOLate catalyzed addition of dialkylzinc or alkyl titanium compounds to aldehydes,[10,12,13,35] we wondered if such an effect would also be present in the ring opening of anhydrides mediated by **1**. We therefore carried out a ring opening of **2** using a substoichiometric amount of Ti−TADDOLate **1d** in the presence of a stoichiometric amount of $Ti(O\textit{i}\text{-}Pr)_4$ (Scheme 4). We hoped that, as in the alkyl addition, the $Ti(O\textit{i}\text{-}Pr)_4$ would regenerate the catalyst, but not compete with it in a nonstereoselective ring opening reaction. Indeed, we found that the Ti−TADDOLate mediated reaction was slightly faster (2−3

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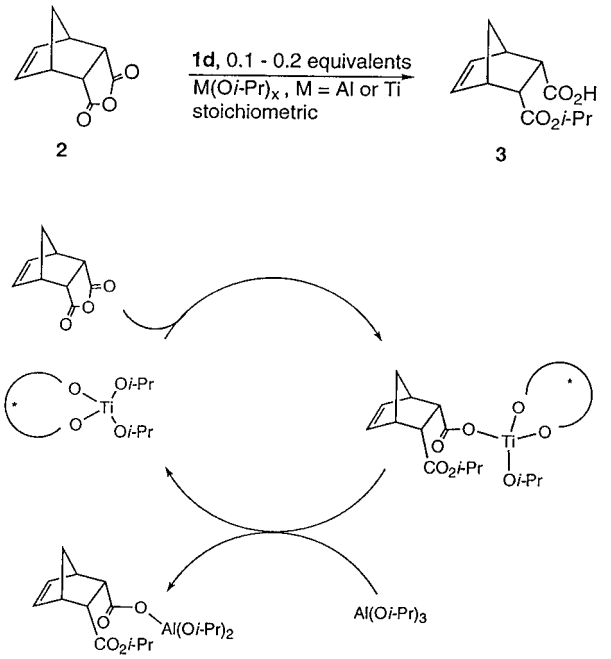
Table 4. Substoichiometric Use of Ti−TADDOLate 1d for the Ring Opening 2 → 3

entry	anhydride	**1d** (mol %)	Al(O*i*-Pr)$_3$ (mol %)	time (d)	temp (°C)	yield (%)	er
1	**2**	15	80[a]	20	−30	80	67:33
2	**2**	20	80	24	−34	74	98:2
3	**2**	10	90	12	−20	88	94:6
4	**7**	20	80	24	−34	83	76:24
5	**10**	20	80	24	−15	78	89:11
6	**14**	20	80	24	−15	84	86:14

[a] Ti(O*i*-Pr)$_4$ was used instead of Al(O*i*-Pr)$_3$.

Scheme 4



times) than the Ti(O*i*-Pr)$_4$ mediated one (Table 4, entry 1). Better results were obtained by replacing Ti(O*i*-Pr)$_4$ with Al(O*i*-Pr)$_3$. By using 20 mol % of the Ti−TADDOLate and 80 mol % Al(O*i*-Pr)$_3$, the hemiester **3** was obtained in good yield with an enantioselectivity of 98:2 (entry 2). Assuming that the Ti−TADDOLate and the Al(O*i*-Pr)$_3$ mediated reactions do not interfere with each other, the difference in the reaction rates was estimated to be in the range of 100! A proposed catalytic cycle is shown in Scheme 4. Reduction of the amount of Ti−TADDOLate and a higher reaction temperature led to a slight decrease in selectivity (entry 3).

We next examined the ring opening of anhydrides **7**, **10**, and **14** using the catalytic reaction conditions described above. The ring opening of anhydride **7** proceeded with low enantioselectivity (er 76:24, Table 4, entry 4), while hemiester **18** had been obtained with high enantioselectivity with stoichiometric amounts of Ti−TADDOLate (Table 2, entry 5). Possibly, the additional heteroatom in **7** was responsible for the lower enantioselectivity (for example through coordination with Al(O*i*-Pr)$_3$). The bicyclic and monocyclic anhydrides **10** and **14** were ring opened with moderate to good (er 89:11 and 86:14, respectively), although lower selectivities, as compared with the corresponding stoichiometric reactions (Table 2, entries 8 and 12).

Summary

The Ti−TADDOLate (**1**) mediated ring opening of cyclic anhydrides is applicable to a variety of structurally different cyclic anhydrides and leads to the corresponding hemiesters of high enantiopurity (er up to 99:1). Similarly, Ti−BINOLate was found to mediate the ring opening reaction of the model compound **2** with good enantioselectivity (er 93:7), albeit at a much slower reaction rate when compared with the TADDOLate **1**. The higher reaction rate of the Ti−TADDOLate mediated reaction compared with that induced by other Lewis acidic complexes was used for developing a catalytic variant of the reaction. By using substoichiometric amounts of Ti−TADDOLate **1** and stoichiometric amounts of Al(O*i*-Pr)$_3$, we obtained an enantioselectivity of up to 98:2. We hope that this strategy offers a general route for esterification reactions mediated by catalytic quantities of **1**.

Experimental Section

General. Abbreviations used: GP (general procedure), HV (high vacuum, 0.01−0.001 Torr). Ti(O*i*-Pr)$_4$ was distilled under Ar. Et$_2$O was distilled over Na, THF over K, pentane over P_2O_5, and ethyl acetate over sikkon. The TADDOLs **1a**−**e** (4*R*,5*R*) were prepared following reported procedures.[9,20,36] The anhydrides **2**, **5**, **7**, **10**, **12**, and **15** were commercially available. **4**, **6**, and **8** were obtained from **2**, **5**, and **7** by hydrogenation of the double bond (H_2/Pd, ethyl acetate). The anhydrides **9**,[37] **11**,[38] and **16**[39] were prepared according to literature procedures. **13** and **14** were obtained from the corresponding diacids (commercially available) by refluxing in acetic anhydride. The enantiomer ratios of the hemiesters resulting from the anhydride ring opening were determined as follows: (a) the isopropyl esters were transformed with diazomethane[40] or $(CH_3)_3OBF_4$[41] to the methylisopropyl esters, which were analyzed by GC, or (b) the hemiesters were reduced with $LiBEt_3H$ and cyclized to the corresponding lactones (see GP2), which were analyzed by GC or HPLC. The reaction temperatures given correspond to bath temperatures. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} plates. The compounds were visualized by $UV_{254\ nm}$ light or iodine or by spraying with phosphomolybdic acid solution [phoshomolybdic acid (25 g), $Ce(SO_4)_2 \cdot 4H_2O$ (10 g), H_2SO_4 (60 mL), H_2O (940 mL)]. Flash chromatography (FC) was carried out using kieselgel 60 (0.040−0.063 mm). Melting points were measured in open glass capillaries with a Tottoli apparatus and are uncorrected. Optical rotations $[\alpha]_D$ were determined at rt (ca. 20 °C) using puriss. solvents. Capillary gas chromatograms (CGC) were obtained using the following columns: (a) FS-Lipodex E: 2,6-*O*-Pentyl-3-*O*-butyryl-γ-CD (50 m × 0.25 mm ID); (b) FS-Hydrodex β-PM (50 m × 0.25 mm ID); (c) FS-Hydrodex β-3P (50 m × 0.25 mm ID). Injector temperature 230 °C, detector temperature 250 °C.

HPLC with two pumps, computer-controlled with the program Eurochrom Version 1.57, using a Chiralcel OD column 4,6 × 250 mm, 10 μm, λ = 254 nm, flow 1.5 mL/min. For the detection a variable wavelength monitor was used. IR spectra of $CHCl_3$ solution were measured. ^{1}H and ^{13}C NMR spectra were measured on 200/300 or 50/75 MHz spectrometers, respectively. Elemental analyses were performed by the Microanalytical Service Laboratory of the Laboratorium für Organische Chemie (ETH).

General Procedure for the Ti−TADDOLate Mediated Ring Opening of Cyclic *Meso* Anhydrides (GP1). Ti(O*i*-Pr)$_4$ (0.707 mL, 2.40 mmol) was added dropwise to a solution of 1.67 g of β-naphthyl-TADDOL (2.50 mmol) in Et$_2$O

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(6−10 mL/mmol TADDOL) under argon, and the mixture was stirred for 3 h at rt to produce the Ti-TADDOLate **1**. The solvent was removed under HV, and the residue was dried for 30 min. The residue was then dissolved in THF (10 mL), and the solution was cooled to − 30 °C. A cold solution (ca. − 30 °C) of the anhydride (2.0 mmol) in THF (2.5−5 mL/mmol anhydride, for **13** 30 mL/mmol) was added. The homogeneous solution was sealed and stored for several days in a freezer or alternatively was kept in a cooling bath under stirring (as outlined in Tables 1−3). Subsequently, the reaction mixture was poured into 0.5 N NaOH (80 mL), Et_2O (ca. 100 mL) was added, and the aqueous phase was separated. The organic phase was extracted with further 0.5 N NaOH (80 mL), and the combined aqueous phases were washed with Et_2O (ca. 100 mL). Acidification with 1 N HCl to pH 1−2, followed by extraction with Et_2O or ethyl acetate (2 × 100 mL), drying with $MgSO_4$, and evaporation of the solvent yielded the corresponding hemiesters. If necessary the hemiesters were purified by FC (Et_2O).

All reactions were carried out on a 1−3 mmol scale. The following analytical and spectroscopic data refer to racemic (rac) and enantioenriched (en) hemiesters. The racemic samples were obtained by reaction of the anhydrides with $Ti(Oi\text{-}Pr)_4$ in THF at rt.

(2*S*,3*R*)-*cis-endo*-3-(2-Isopropoxycarbonyl)bicyclo[2.2.1]-hept-5-ene-2-carboxylic acid (3) (hemiester from **2**): R_f = 0.20 (Et_2O); mp 85−87 °C (rac), 89−90 °C (en); $[\alpha]^{rt}_D = +7.5$ (c = 2.5, $CHCl_3$); er = 99:1 [GC-analysis of the methylisopropyl ester: β-3P-CD, 1.0 bar, 135 °C (isotherm), t_1 = 65.6 (major enantiomer), t_2 = 68.6]; IR ($CDCl_3$) 3190, 2985, 2941, 1730, 1456, 1374, 1339, 1174, 1108, 1005, 908, 862, 641 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (t, J = 6.6, $2CH_3$); 1.29 (d, J = 8.5, 1H); 1.43 (d, J = 8.5, 1H); 3.12 (br. s, 2H); 3.15−3.31 (m, 2H); 4.88 (sept, J = 6.6, C*H*$(CH_3)_2$); 6.21 (ddd, J = 2.9, 5.3, 15.6, CH=CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 21.7, 46.1, 46.2, 46.4, 48.0, 48.6, 67.8, 134.3, 135.2, 171.7, 178.8; EI-MS m/z 225 (M + 1, 18), 207 (6), 182 (6), 165 (83), 159 (45), 137 (37), 119 (25), 117 (100), 99 (41), 91 (25), 66 (63). Anal. Calcd for $C_{12}H_{16}O_4$ (224.26): C, 64.27; H, 7.19. Found: C, 64.05; H, 7.01.

(1*R*,2*S*)-*exo*-3,6-Epoxy-2-(2-isopropoxycarbonyl)hex-4-ene-1-carboxylic acid (18) (hemiester from **7**): R_f = 0.15 (Et_2O); mp 107−108 °C (rac), 94−95 °C (en); $[\alpha]^{rt}_D = +22.1$ (c = 1.75, ethyl acetate); er = 99:1 [GC-analysis of **21**: γ-CD, 1.0 bar, 100 °C (50 min), heating rate 3.0 °C/min, up to 180 °C, t_1 = 99.1 (major enantiomer), t_2 = 105.5]; IR($CDCl_3$) 3284, 2986, 2940, 1734, 1466, 1375, 1308, 1107, 999, 971 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, J = 6.2, CH_3); 1.22 (d, J = 6.2, CH_3); 2.77 (d, J = 9.0, 1H); 2.83 (d, J = 9.0, 1H); 5.04 (sept, J = 6.2, C*H*$(CH_3)_2$); 5.22 (s, 1H); 5.29 (s, 1H); 6.39−6.50 (m, CH=CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 21.7, 46.7, 47.3, 68.9, 80.3, 80.6, 136.2, 136.9, 170.6, 177.4; EI-MS m/z 227 (M + 1, 1), 183 (62), 181 (4), 166 (2), 159 (62), 139 (30), 121 (17), 117 (68), 100 (20), 99 (100), 68 (77). Anal. Calcd for $C_{11}H_{14}O_5$ (226.23): C, 58.40; H, 6.24. Found: C, 58.15; H, 6.20.

(1*R*,2*S*)-*exo*-3,6-Epoxy-2-(2-isopropoxycarbonyl)hexane-1-carboxylic acid (20) (hemiester from **8**): R_f = 0.15 (Et_2O); mp 132−133 °C (rac), 110−111 °C (en); $[\alpha]^{rt}_D = +9.3$ (c = 1.80, ethyl acetate); er = 98:2 [GC-analysis of **21**: γ-CD, 1.0 bar, 100 °C (55 min), heating rate 3.0 °C/min, up to 180 °C, t_1 = 104.6 (major enantiomer), t_2 = 110.2]; IR($CDCl_3$) 3263, 1733, 1466, 1375, 1296, 1108, 1001, 939, 910, 863 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.20 (d, J = 6.2, CH_3); 1.22 (d, J = 6.2, CH_3); 1.46−1.60 (m, 2H); 1.78−1.90 (m, 2H); 2.95 (d, J = 9.6, 1H); 3.03 (d, J = 9.6, 1H); 4.83−4.96 (m, 2H); 4.99 (sept, J = 6.2, C*H*$(CH_3)_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.3, 21.6, 28.9, 52.1, 52.3, 68.7, 78.3, 78.6, 170.3, 176.9; EI-MS m/z 229 (M + 1, 15), 211 (9), 200 (6), 187 (9), 169 (100), 158 (16), 142 (33), 141 (59), 124 (46), 123 (75), 118 (18), 100 (28), 99 (23). Anal. Calcd for $C_{11}H_{16}O_5$ (228.24): C, 57.89; H, 7.07. Found: C, 57.71; H, 7.07.

(1*S*,2*R*)-*cis*-2-(2-Isopropoxycarbonyl)cyclobutane-1-carboxylic acid (22) (hemiester from **10**): R_f = 0.20 (Et_2O); Colorless oil; $[\alpha]^{rt}_D = 14.0$ (c = 0.47, ethyl acetate); er = 97:3 [GC-analysis of the methylisopropyl ester: β-CD, 1.0 bar, 80 °C (30 min), heating rate 0.4 °C/min, up to 120 °C (30 min), t_1 = 117.7 (major enantiomer), t_2 = 118.64]; IR($CDCl_3$) 3191, 2986, 2952, 1723, 1466, 1375, 1108, 1006, 913 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (d, J = 6.2, CH_3); 1.23 (d, J = 6.2, CH_3); 2.10−2.50 (m, 4H); 3.30−3.55 (m, 2H); 5.03 (sept, J = 6.2, C*H*$(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 21.7, 22.0, 40.4, 40.7, 68.1, 172.6, 179.4; EI-MS m/z 187 (M + 1, 6), 169 (6), 145 (11), 144 (3), 140 (2), 128 (8), 127 (100), 99 (15), 43 (5). Anal. Calcd for $C_9H_{14}O_4$ (186.21): C, 58.05; H, 7.58. Found: C, 57.98; H, 7.45.

(2*S*,3*R*)-*cis-endo*-3-(2-Isopropoxycarbonyl)bicyclo[2.2.2]-oct-5-ene-2-carboxylic acid (24) (hemiester from **5**): R_f = 0.20 (Et_2O); mp 100−102 °C (rac), 84−85 °C (en); $[\alpha]^{rt}_D = 15.4$ (c = 0.75, ethyl acetate); er = 99:1 [GC-analysis of the methylisopropyl ester: β-3P-CD, 1.0 bar, 155 °C (isotherm), t_1 = 64.1 (major enantiomer), t_2 = 66.1]; IR($CDCl_3$) 3518, 3046, 2985, 2946, 2871, 1728, 1467, 1415, 1374, 1313, 1282, 1170, 1169, 1108, 908, 869 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, J = 6.4, $2CH_3$); 1.22−1.60 (m, 4H); 2.83−3.06 (m, 4H); 4.89 (sept, J = 6.4, C*H*$(CH_3)_2$); 6.20−6.40 (m, CH=CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 21.7, 24.4, 24.6, 32.3, 32.5, 47.4, 47.7, 67.9, 131.8, 132.6, 172.1, 179.2; EI-MS m/z 239 (M + 1, 10), 238 (8), 196 (25), 179 (97), 178 (25), 160 (35), 151 (24), 133 (15), 118 (86), 106 (29), 105 (22), 100 (40), 91 (17), 80 (100), 79 (55), 78 (70), 77 (21). Anal. Calcd for $C_{13}H_{18}O_4$ (238.28): C, 65.53; H 7.61. Found: C, 65.77; H, 7.49.

***cis-endo*-3-(2-Isopropoxycarbonyl)bicyclo[2.2.1]heptane-2-carboxylic acid** (hemiester from **4**): R_f = 0.20 (Et_2O); mp 70−72 °C (rac), colorless oil (en); $[\alpha]^{rt}_D = +8.7$ (c = 1.50, ethyl acetate); er = 99:1 [GC-analysis of the methylisopropyl ester: β-3P-CD, 1.0 bar, 135 °C (isotherm), t_1 = 62.9 (major enantiomer), t_2 = 63.7]; IR($CDCl_3$) 2994, 2953, 2872, 1728, 1467, 1451, 1369, 1292, 1174, 1108, 908, 641 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (d, J = 6.2, CH_3); 1.14 (d, J = 6.2, CH_3); 1.37 (br. s, 4H); 1.67−1.83 (m, 2H); 2.49 (br. s, 2H); 2.81−2.99 (m, 2H); 4.91 (sept, J = 6.2, C*H*$(CH_3)_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4, 21.6, 23.7, 39.7, 40.1, 40.2, 46.6, 46.8, 67.5, 171.6, 179.0; EI-MS m/z 227 (M + 1, 18), 209 (4), 168 (10), 167 (100), 166 (30), 160 (58), 159 (7), 148 (15), 139 (14), 138 (23), 118 (40), 117 (20), 111 (3), 100 (19), 99 (12), 93 (9), 91 (7), 67 (10), 66 (11). Anal. Calcd for $C_{12}H_{18}O_4$ (226.27): C, 63.70; H 8.02. Found: C, 63.43; H, 8.23.

***cis-endo*-3-(2-Isopropoxycarbonyl)bicyclo[2.2.2]octane-2-carboxylic acid** (hemiester from **6**): R_f = 0.20 (Et_2O); mp 108−109 °C (rac); 91−92 °C (en); $[\alpha]^{rt}_D = +7.7$ (c = 2.52, ethyl acetate); er = 97:3 [GC-analysis of the methylisopropyl ester: β-3P-CD, 1.0 bar, 155 °C (isotherm), t_1 = 76.0 (major enantiomer), t_2 = 77.3]; IR($CDCl_3$) 3513, 3237, 2985, 2943, 2870, 1730, 1457, 1374, 1292, 1106, 1005, 912, 867, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (d, J = 6.2, CH_3); 1.18 (d, J = 6.2, CH_3); 1.29−1.47 (m, 2H); 1.48−1.68 (m, 4H); 1.73−1.90 (m, 2H); 2.01 (s, 2H); 2.78−2.95 (m, 2H); 4.96 (sept, J = 6.2, C*H*$(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 21.5, 21.7, 25.6, 25.7, 26.5, 43.9, 44.0, 67.7, 172.8, 180.2; EI-MS m/z 241 (M + 1, 4), 222 (26), 194 (5), 181 (83), 180 (100), 162 (35), 160 (38), 152 (29), 135 (22), 118 (20), 117 (20), 108 (40), 107 (20), 80 (49), 79 (27). Anal. Calcd for $C_{13}H_{20}O_4$ (240.30): C, 64.98; H, 8.39. Found: C, 64.72; H, 8.45.

***cis*-3,3-Dimethyl-2-(2-isopropoxycarbonyl)cyclopropane-1-carboxylic acid** (hemiester from **9**): R_f = 0.20 (Et_2O); mp 62−63 °C (rac), 76−77 °C (en); $[\alpha]^{rt}_D = +3.3$ (c = 0.64, ethyl acetate); er = 98:2 [GC-analysis of the methylisopropyl ester: β-CD, 1.0 bar, 110 °C (isotherm), t_1 = 49.5 (major enantiomer), t_2 = 51.5]; IR($CDCl_3$) 3517, 2984, 2666, 1730, 1654, 1434, 1377, 1102, 906 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.31 (d, J = 6.2, $CH(CH_3)_2$); 1.35 (s, CH_3); 1.39 (s, CH_3); 1.92 (d, J = 8.2, CH); 2.06 (d, J = 8.2, CH); 5.11 (sept, J = 6.2, C*H*$(CH_3)_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.2, 21.6, 21.7, 27.5, 28.2, 33.2, 33.4, 69.4, 171.2, 173.1; EI-MS m/z 201 (M + 1, 51), 159 (14), 158 (11), 143 (21), 141 (75), 114 (20), 113 (100), 95 (22), 67 (12). Anal. Calcd for $C_{10}H_{16}O_4$ (200.23): C, 59.98; H, 8.05. Found: C, 60.24; H, 7.78.

***cis*-2-(2-Isopropoxycarbonyl)cyclopentane-1-carboxylic acid** (hemiester from **11**): R_f = 0.20 (Et_2O); colorless oil; $[\alpha]^{rt}_D = +5.6$ (c = 0.40, ethyl acetate); er = 94:6 [GC-analysis

of the corresponding lactone[30] (prepared according to GP2): γ-CD, 1.0 bar, 80 °C (0 min), heating rate 1.0 °C/min, up to 180 °C (30 min), t_1 = 64.1 (major enantiomer), t_2 = 66.3]; IR($CDCl_3$) 3156, 2976, 2256, 1719, 1372, 1106, 908, 642 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.20 (d, J = 6.2, CH_3); 1.21 (d, J = 6.2, CH_3); 1.55−1.78 (m, 1H); 1.78−2.14 (m, 5H); 2.85−3.17 (m, 2H); 4.99 (sept, J = 6.2, C*H*(CH_3)$_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.5, 21.6, 23.7, 28.7, 28.8, 46.7, 47.0, 67.9, 173.3, 180.2; EI-MS *m*/*z* 201 (M + 1, 1), 182 (2), 159 (4), 142 (8), 141 (100), 140 (21), 114 (16), 112 (15), 95 (10). Anal. Calcd for $C_{10}H_{16}O_4$ (200.23): C, 59.98; H, 8.05. Found: C, 59.70; H, 8.15.

***cis*-2-(2-Isopropoxycarbonyl)cyclohexane-1-carboxylic acid** (hemiester from **12**): R_f = 0.20 (Et_2O); colorless oil; $[\alpha]^{rt}_D$ = +2.50 (c = 0.25, ethyl acetate); er > 95:5 [GC-analysis of the methylisopropyl ester: γ-CD, 1.0 bar, 80 °C (30 min), heating rate 0.3 °C/min, up to 120 °C (30 min), t_1 = 127.2, t_2 = 127.8 (major enantiomer)]; IR($CDCl_3$) 3162, 2939, 2860, 1719, 1453, 1375, 1305, 1178, 1109, 962, 911, 600 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.23 (d, J = 6.2, $2CH_3$); 1.30−1.66 (m, 4H); 1.67−1.89 (m, 2H); 1.90−2.17 (m, 2H); 2.77−2.90 (m, 2H); 5.04 (sept, J = 6.2, C*H*(CH_3)$_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.5, 23.4, 23.8, 25.8, 26.3, 42.4, 42.5, 67.8, 173.0, 180.4; EI-MS *m*/*z* 215 (M + 1, 12), 197 (7), 196 (6), 173 (5), 172 (4), 168 (10), 156 (9), 155 (100), 154 (32), 128 (19), 127 (13), 126 (43), 109 (24), 108 (15), 81 (38). Anal. Calcd for $C_{11}H_{18}O_4$ (214.26): C, 61.66; H, 8.47. Found: C, 61.55; H, 8.66.

1,3-Dibenzyl-2-imidazolidinone-*cis*-5-(2-isopropoxycarbonyl)-4-carboxylic acid (hemiester from **13**): R_f = 0.30 (Et_2O); colorless oil; er = 63:37 [HPLC-analysis of the corresponding lactone[42] (prepared according to GP2): Chirasphere, Hexan/i-PrOH (90/10), 1.5 mL/min: t_1 = 26.0 (major enantiomer), t_2 = 37.4]; IR($CDCl_3$) 3674, 3011, 1740, 1713, 1449, 1420, 1360, 1105, 1040, 908, 612 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.18 (d, J = 6.2, CH_3); 1.19 (d, J = 6.2, CH_3); 3.95−4.15 (m, 4H); 4.90−5.06 (m, 3H), 7.19−7.33 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.3, 21.5, 46.6, 46.7, 56.7, 57.2, 70.1, 127.9, 128.6, 128.7, 135.6, 135.7, 159.8, 167.5, 171.1; EI-MS *m*/*z* 397 (M + 1, 5), 396 (16), 353 (2), 352 (5), 351 (9), 350 (10), 337 (6), 336 (25), 310 (21), 309 (100), 308 (9), 305 (6), 266 (9), 265 (50), 264 (39), 263 (8), 173 (7), 132 (4), 92 (4), 91 (60). Anal. Calcd for $C_{22}H_{24}N_2O_5$ (396.44): C, 66.65; H, 6.10; N, 7.07. Found: C, 66.55; H, 6.22; N, 6.99.

***cis*-2,3-Dimethyl-4-(2-isopropoxycarbonyl)butyric acid** (hemiester from **14**): R_f = 0.20 (Et_2O); colorless oil; $[\alpha]^{rt}_D$ = −1.8 (c = 1.05, ethyl acetate); er = 98:2 [GC-analysis of the methylisopropyl ester: γ-CD, 1.0 bar, 65 °C (50 min), heating rate 0.4 °C/min, up to 85 °C (20 min), t_1 = 71.2, t_2 = 72.6 (major enantiomer)]; IR($CDCl_3$) 3105, 2984, 2941, 1713, 1466, 1376, 1272, 1178, 1107, 1080, 937, 899, 867, 635 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.18−1.28 (m, $4CH_3$); 2.68−2.87 (m, 2C*H*CH_3); 5.05 (sept, J = 6.3, C*H*(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 14.8, 21.7, 42.3, 68.1, 174.0, 180.7; EI-MS *m*/*z* 189 (M + 1, 12), 171 (5), 169 (1), 160 (2), 147 (8), 146 (2), 142 (2), 130 (7), 129 (100), 128 (6), 116 (12), 102 (8), 101 (17), 100 (5), 87 (10). Anal. Calcd for $C_9H_{16}O_4$ (188.22): C, 57.43; H, 8.57. Found: C, 57.30; H, 8.32.

3-Methyl-5-(2-isopropoxycarbonyl)glutaric acid (hemiester from **15**): R_f = 0.20 (Et_2O); colorless oil; $[\alpha]^{rt}_D$ = −0.9 (c = 0.90, ethyl acetate); er = 3:1 [GC-analysis of the methylisopropyl ester: β-CD, 1.0 bar, 85 °C (90 min), heating rate 0.2 °C/min, up to 105 °C (60 min), t_1 = 140.3, t_2 = 141.3]; IR($CDCl_3$) 2984, 1720, 1456, 1375, 1289, 1146, 1107, 1040, 978, 908 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.05 (d, J = 6.3, CH_3); 1.23 (d, J = 6.2, $2CH_3$); 2.12−2.52 (m, 5H); 5.02 (sept, J = 6.2, C*H*(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) 19.7, 21.8, 27.3, 40.5, 41.1, 67.7, 171.8, 178.2; EI-MS *m*/*z* 189 (M + 1, 12), 188 (1), 172 (1), 171 (9), 170 (2), 169 (1), 160 (1), 147 (4), 146 (4), 142 (2), 130 (7), 129 (100), 128 (19), 118 (3), 102 (5), 101 (17), 100 (14), 87 (4). Anal. Calcd for $C_9H_{16}O_4$ (188.22): C, 57.43; H, 8.57. Found: C, 57.69; H, 8.74.

***cis*-2,4-Dimethyl-5-(2-isopropoxycarbonyl)glutaric acid** (hemiester from **16**): R_f = 0.20 (Et_2O); colorless oil; er = 1:1 [GC-analysis of the corresponding lactone[43] (prepared according to GP2): γ-CD, 130 °C (isotherm), t_1 = 20.9, t_2 = 21.9]; IR($CDCl_3$): 3690, 3011, 2984, 1721, 1454, 1376, 1272, 1178, 1107, 1080, 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.14−1.26 (m, $4CH_3$); 1.49 (quin, J = 7.0, C*H*CH_3); 2.12 (quin, J = 7.8, C*H*CH_3); 2.38−2.61 (m, 2H); 5.01 (sept, J = 6.2, C*H*(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8, 17.1, 21.6, 36.7, 37.0, 37.4, 67.6, 175.7, 182.5; EI-MS *m*/*z* 203 (M + 1, 8), 185 (8), 184 (1), 161 (2), 160 (2), 156 (4), 144 (8), 143 (100), 142 (30), 132 (5), 116 (6), 115 (41), 114 (25). Anal. Calcd for $C_{10}H_{18}O_4$ (202.25): C, 59.39; H, 8.97. Found: C, 59.44; H, 8.71.

General Procedure for Reduction of the Hemiesters to the Corresponding Lactones (GP2). The hemiester was dissolved in THF and at 0 °C 3−7 equiv of a 1 M $LiBEt_3H$ solution in THF was added and the mixture was stirred for 3−16 h at room temperature. H_2O (5 mL) and 1 M HCl (10 mL) were added, and the mixture was stirred for 1−3 h. The aqueous phase was extracted twice with Et_2O or ethyl acetate (50 mL), the combined organic phases were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by FC.

(+)-(2*S*,3*R*)-*cis*-*endo*-3-(Hydroxymethyl)bicyclo[2.2.1]-hept-5-ene-2-carboxylic Acid Lactone (17). According to GP2, 100 mg (0.45 mmol) of **3** was dissolved in THF (3 mL), and $LiBEt_3H$ (1.55 mL, 1 M) was added. After FC (Et_2O/pentane 1/1), 43 mg (0.29 mmol, 64%) of **17** was isolated. R_f = 0.25 (Et_2O/pentane 1/1); $[\alpha]^{rt}_D$ +147.1 (c = 0.466, $CHCl_3$), lit. +143.2 (c = 5.2, $CHCl_3$);[44] ^1H NMR (200 MHz, $CDCl_3$) δ 1.48 (d, J = 8.6, 1H); 1.67 (d, J = 8.6, 1H); 3.03−3.19 (m, 2H); 3.21−3.39 (m, 2H); 3.82 (dd, J = 3.4, 9.6, 1H); 4.31 (dd, J = 8.2, 9.6, 1H); 6.25−6.38 (m, 2H).

For further spectroscopic and analytical data see the literature.[44]

(+)-(1*R*,2*S*)-*exo*-3,6-Epoxy-2-(hydroxymethyl)hex-4-ene-1-carboxylic Acid Lactone (19). According to GP2, 70 mg (0.31 mmol) of **18** was dissolved in THF (7 mL), and $LiBEt_3H$ (1.01 mL, 1 M) was added. A fter FC (Et_2O/pentane 1/2), 26 mg (0.17 mmol, 55%) of **19** was isolated. R_f = 0.1 (Et_2O/pentane 1/2); ^1H NMR (200 MHz, $CDCl_3$): 1.65−1.90 (m, 2H); 4.19 (dd, J = 3.5, 9.6, 1H); 4.50 (dd, J = 8.6, 9.6, 1H); 4.97 (d, J = 4.8, 1H); 5.27 (d, J = 4.8, 1H); 6.38−6.52 (m, CH=CH).

For further spectroscopic and analytical data see the literature.[29]

(+)-(1*R*,2*S*)-*exo*-3,6-Epoxy-2-(hydroxymethyl)hexane-1-carboxylic Acid Lactone (21). (**a**) According to GP2, 90 mg (0.39 mmol) of **20** was dissolved in THF (7 mL), and $LiBEt_3H$ (1.55 mL, 1 M) was added. After FC (Et_2O/pentane 1/2), 30 mg (0.19 mmol, 49%) of **21** was isolated. R_f = 0.10 (Et_2O/pentane 1/2); $[\alpha]^{rt}_D$ = +105 (c = 0.53, $CHCl_3$), lit. $[\alpha]^{rt}_D$ = +110 (c = 1.0, $CHCl_3$);[29] ^1H NMR (200 MHz, $CDCl_3$) δ 1.48−1.62 (m, 2H); 1.70−1.90 (m, 2H); 2.68−2.84 (m, 2H); 4.11 (dd, J = 5.4, 9.3, 1H); 4.43 (t, J = 8.5, 1H); 4.54 (d, J = 5.0, 1H); 4.87 (d, J = 4.8, 1H).

For further spectroscopic and analytical data see the literature.[29]

(**b**) A 26 mg (0.17 mmol) amount of **19** was dissolved in ethyl acetate (5 mL), 20 mg of Pd/C (10%) was added, and the mixture was stirred under an atmosphere of hydrogen for 12 h. The reaction mixture was filtered through a short silica gel column (5 cm), and the column was washed with ethyl acetate (30 mL). The solvent was removed under reduced pressure to yield 24 mg (0.16 mmol, 91%) of **21**.

For further spectroscopic and analytical data see above.

(+)-(1*S*,2*R*)-*cis*-2-(Hydroxymethyl)cyclobutane-1-carboxylic Acid Lactone (23). According to GP2, 94 mg (0.50 mmol) of **22** was dissolved in THF (3 mL), and $LiBEt_3H$ (3 mL, 1 M) was added. After FC (Et_2O/pentane 1/1), 25 mg (0.22 mmol, 44%) of **23** was obtained. R_f = 0.25 (Et_2O/pentane 1/1); $[\alpha]^{rt}_D$ = +108.4 (c = 0.98, $CHCl_3$), lit. $[\alpha]^{rt}_D$ = +118.7 (c = 10, $CHCl_3$);[30] ^1H NMR (200 MHz, $CDCl_3$) δ 2.00−2.22 (m, 2H);

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(43) Brown, K.; Burton, M.; Robins, D. J.; Sim, G. A. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1261−1265.

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2.30−2.60 (m, 2H); 3.05−3.25 (m, 2H); 4.22 (d, J = 6.4, 1H); 4.34 (dd, J = 4.1, 6.4, 1H).

For further spectroscopic and analytical data see the literature.[30]

(2*R*,3*S*)-*cis*-*endo*-3-(1-(*S*)-Phenylethylcarbamoyl)bicyclo-[2.2.2]oct-5-ene-2-carboxylic Acid Isopropyl Ester (25). A 44 mg (0.18 mmol) amount of **24** was dissolved in THF (2 mL), and SO_2Cl_2 (0.016 mL, 0.22 mmol) was added at 0 °C. The mixture was stirred for 15 min, Et_3N (0.090 mL, 0.65 mmol) and (*R*)-α-phenylethylamine (0.027 mL, 0.21 mmol) were added, and the mixture was stirred for a further 2 h at 0 °C. The reaction mixture was quenched with saturated $NaHCO_3$ solution (10 mL), and the aqueous phase was extracted twice with Et_2O (50 mL). After recrystallization from Et_2O, 39 mg (0.11 mmol, 57%) **25** was obtained as colorless crystals. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.12 (d, J = 6.3, CH_3); 1.19 (d, J = 6.3, CH_3); 1.10−1.80 (m, 4H); 1.39 (d, J = 6.9, CH_3); 2.70−3.10 (m, 4H); 4.78−5.05 (m, 2H); 5.82 (br. d, J = 7.0, 1H); 6.23 (t, J = 7.5, 1H); 6.57 (t, J = 7.8, 1H); 7.16−7.40 (m, 5 H).

***cis*-*endo*-3-(Ethoxycarbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (26).** According to GP1, 833 mg (1.25 mmol) of β-naphthyl-TADDOL was treated with $Ti(OEt)_4$ (0.251 mL, 1.21 mmol) to afford **28**, and then 164 mg (1.00 mmol) of **2** was added. After 7 days at −30 °C, 191 mg (0.91 mmol, 91%) of **26** was obtained. er = 85:15 [GC-analysis of **17** (prepared according to GP2): γ-CD, 152 °C (isotherm), t_1 = 35.1 (major enantiomer), t_2 = 37.9]; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.17 (t, J = 7.2, CH_3); 1.30 (d, J = 8.4, 1H); 1.45 (d, J = 8.6, 1H); 3.15 (br. s, 2H); 3.16−3.37 (m, 2H); 3.90−4.15 (m, 2H); 6.23 (ddd, J = 2.9, 5.4, 19.4, CH=CH).

***cis*-*endo*-3-(*tert*-Butoxycarbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (27).** According to GP1, 833 mg (1.25 mmol) of β-naphthyl-TADDOL was treated with $Ti(Ot\text{-}Bu)_4$ (0.460 mL, 1.20 mmol) to afford **29**, and then 164 mg (1 mmol) of **2** was added. After 10 days at rt, 12 mg (0.05 mmol, 5%) of **27** was obtained after FC (Et_2O/pentane 2/1). R_f = 0.25 (Et_2O/pentane 1/1); er = 59:41 [GC analysis of **17** (prepared according to GP2): γ-CD, 152 °C (isotherm), t_1 = 35.1 (major enantiomer), t_2 = 37.9]; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.30−1.52 (m, 2H); 1.42 (s, $C(CH_3)_3$); 3.17−3.23 (m, 2H); 3.24−3.30 (m, 2H); 6.22−6.36 (m, CH=CH).

(1*R*,2*R*)-Ti−CYDISate Mediated Reaction: *cis*-*endo*-3-(2-isopropoxycarbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (3). According to GP1, 946 mg (2.50 mmol) of CYDIS[33] was treated with $Ti(Oi\text{-}Pr)_4$ (0.72 mL, 2.44 mmol) to give the Ti−CYDISate. The Ti−CYDISate was dissolved in THF (10 mL) and cooled to −68 °C, and a solution of 328 mg (2.00 mmol) of anhydride **2** in THF (5 mL) was added dropwise. After 6 days at −22 °C (freezer), the solution was quenched with phosphate buffer (40 mL) and the aqueous phase was extracted with Et_2O (1 × 100 mL, 3 × 50 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by FC to yield 426 mg **3** (1.90 mmol, 95%). Er: 45:55 [GC-analysis of the methylisopropyl ester (see above)].

(*M*)-Ti−BINOLate Mediated Reaction: *cis*-*endo*-3-(2-isopropoxycarbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (3). According to GP1, 716 mg (2.50 mmol) of BINOL was treated with $Ti(Oi\text{-}Pr)_4$ (0.72 mL, 2.44 mmol) to give the Ti−BINOLate. The Ti−BINOLate was dissolved in THF (10 mL) and cooled to −68 °C, and a solution of 328 mg (2.00 mmol) of anhydride **2** in THF (5 mL) was added dropwise. After 6 days at −22 °C (freezer), the solution was quenched with phosphate buffer (40 mL) and the aqueous phase was extracted with Et_2O (1 × 100 mL, 3 × 50 mL). The combined organic extracts were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by FC to yield 90 mg (0.40 mmol, 20%) of **3**. Er: 7:93 [GC-analysis of the methylisopropyl ester (see above)].

General Procedure for the Ring Opening of Anhydride 2 by Using Substoichiometric Amounts of 1 (GP3). $Ti(Oi\text{-}Pr)_4$ (0.295 mL, 1.0 mmol) was added dropwise to a solution of β-naphthyl-TADDOL (667 mg, 1.0 mmol) in Et_2O (10 mL) under argon, and the mixture was stirred for 3 h at rt to produce the Ti−TADDOLate **1d**. The solvent was removed under vacuum and the residue was dried for 30 min. The residue was then dissolved in THF (5 mL), and the solution was cooled to − 30 °C. A cold solution (ca. −30 °C) of the anhydride (5.0 mmol) in THF (1 mL/mmol anhydride, or 3.6 mL/mmol anhydride for **7**) and 4.00 mmol $Al(Oi\text{-}Pr)_3$ or $Ti(Oi\text{-}Pr)_4$ were added. The homogeneous solution was sealed and stored for several days in a freezer as outlined in Table 4. Subsequently, the reaction mixture was poured into 0.5 N NaOH (150 mL), ca. 200 mL of Et_2O was added, and the aqueous phase was separated. The organic phase was extracted with further 0.5 N NaOH (80 mL), and the combined aqueous phases were washed with Et_2O (ca. 100 mL). Acidification with 1 N HCl to pH 1−2, followed by extraction with Et_2O or ethyl acetate (2 × 100 mL), drying with $MgSO_4$, and evaporation of the solvent yielded the corresponding hemiesters. If conversion was incomplete the hemiesters were purified by FC (Et_2O).

The reaction for entry 5 (Table 4) was carried out according to GP3 with the following change: 10 mol % of Ti−TADDOLate **1d** (0.75 mmol) was used, the Ti-TADDOLate was dissolved in 10 mL of THF and the anhydride **2** in 5 mL, and except for the first day, the reaction mixture was stirred. In the reaction for entry 1 (Table 4) 15 mol % of Ti−TADDOLate **1d** (0.75 mmol) was used.

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