181. C_2-Symmetric Bicyclic Diols as Chiral Ligands in the Titanate-Catalyzed Enantioselective Addition of Alkylzinc Reagents to Aldehydes

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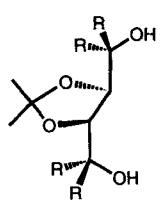
Enantiomerically pure C_2-symmetric 1,4-diols embodying bicyclic C-frameworks were synthesized by means of asymmetric *carbo-Diels-Alder* reactions as key steps (*Scheme 1*). They were investigated as chiral ligands in the enantioselective addition of $ZnEt_2$ to aromatic aldehydes. In the presence of 20–40 mol-% of the titanates formed from these diols and $[Ti(i\text{-}PrO)_4]$ at −78°, the respective 1-arylpropanols were obtained with enantiomer ratios up to 93:7 (*Scheme 2, Table*).

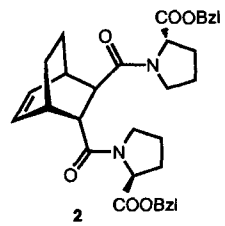
Introduction. – The development of catalytic enantioselective transformations has been the subject of numerous research efforts in recent years, and a variety of efficient asymmetric catalysts for different organic reactions has been introduced [1]. In the course of these studies, it has become evident that the attachment of C_2-symmetric difunctional ligands to metal atoms often results in particularly effective stereoselecting and catalytically active species (for reviews covering the consequences associated with the introduction of the C_2 symmetry into chiral auxiliary groups, see [2]). Representative examples in which this principle was realized are the highly enantioselective transformations catalyzed by $\alpha,\alpha,\alpha',\alpha'$-*t*etra*a*ryl-1,3-*d*ioxolane-4,5-*d*imetha*n*o*l*(TADDOL)-derived titanates (see **1**) developed by *Seebach* and coworkers [3] and *Narasaka* and coworkers [4]. The TADDOL ligands are built up from (*R,R*)- or (*S,S*)-tartaric acid, *i.e.*, from the chiral pool. Primarily, they introduce the element of C_2 symmetry in the respective titanates by means of the 1,3-dioxolane structure which, however, is relatively far from the Ti-atom acting as the accelerating *Lewis* acid in the reactions investigated. However, this symmetry element is further relayed into the close vicinity of the metal center by means of the four aryl substituents present which preferably adopt quasi-equatorial or quasi-axial positions on either side of the Ti-center [2]. Thereby a C_2-type arrangement of the substituents around the Ti-atom is created which directs the steric course of the catalyzed transformations. The principle to employ stereodirecting auxiliaries embodying a substructure which introduces C_2 symmetry and to combine it with a second substructure, which relays the symmetry element to a catalytically active metal center, has also successfully been realized in the development of other ligands, *e.g.* the stilbenediamine derivatives introduced by *Corey* and coworkers [5].

In the course of studies directed at the use of amino-acid esters as chiral auxiliary groups for the asymmetric steering of the *carbo-Diels-Alder* reaction [6], we prepared the

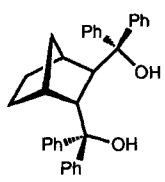
bicyclo[2.2.2]octene derivative **2**. This compound and several related bicyclic *Diels-Alder* adducts were readily prepared in both enantiomeric forms making use of various conveniently available chiral auxiliary groups [6] [7]. In addition, from these cycloadducts, chiral ligands which fulfill the criteria mentioned above should be available in a straightforward way by only a few synthetic operations. Since, in earlier investigations, we had already demonstrated that the bicyclo[2.2.1]octane-derived diol **3** which is not C_2-symmetric may be employed as an efficient mediator of chirality in titanate-catalyzed transformations [8], the use of the related C_2-symmetric diols **4**–**7** as ligands in enantioselective catalysis was investigated.



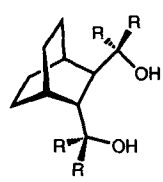
1 R = Aryl
TADDOL's



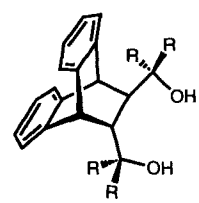
2



3



4 R = H
5 R = Ph



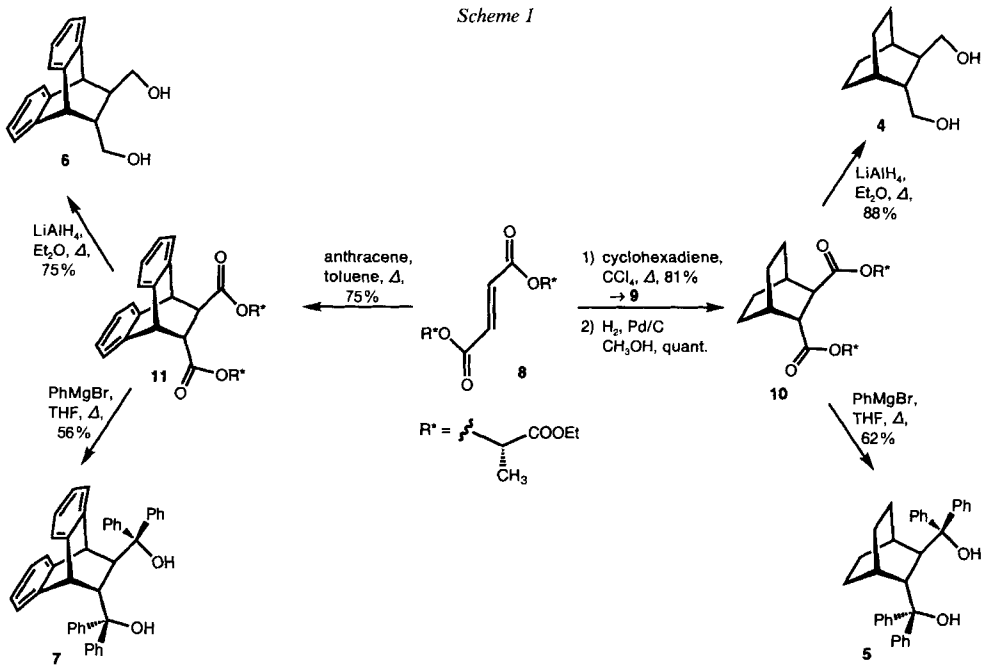
6 R = H
7 R = Ph

To be able to compare the efficiency of diols **4**–**7** with the performance of **3** and the TADDOL's **1**, the use of **4** and **5** as ligands in the enantioselective titanate-catalyzed addition of alkylzinc reagents to aromatic aldehydes developed by *Seebach* and coworkers [3] was studied as a representative transformation.

Synthesis of the Chiral Ligands. – The chiral diols **4**–**7** were built up by means of asymmetric *carbo-Diels-Alder* reactions as the key step. To avoid unnecessary manipulations (*e.g.* the intermediary conversion of an *N*-prolylamide to an ester), instead of the (*S*)-benzylprolinate-derived diamide of fumaric acid [6] [8] according to *Helmchen* and coworkers [7] [9], the corresponding (*S*)-ethyllactate-derived diester **8** was employed as chiral dienophile. Thus, **8** was treated with cyclohexa-1,3-diene and anthracene to yield the bicyclic *Diels-Alder* adducts **9** (= 5,6-didehydro-**10**) and **11**, respectively, which were obtained in enantiomerically pure form after recrystallization [9] (*Scheme 1*). Adduct **9** was then hydrogenated to **10** and the latter reduced with $LiAlH_4$ to diol **4** or reacted with PhMgBr to give the desired TADDOL analogue **5** in good yield. Similarly, **11** was converted to the diols **6** and **7** (*Scheme 1*).

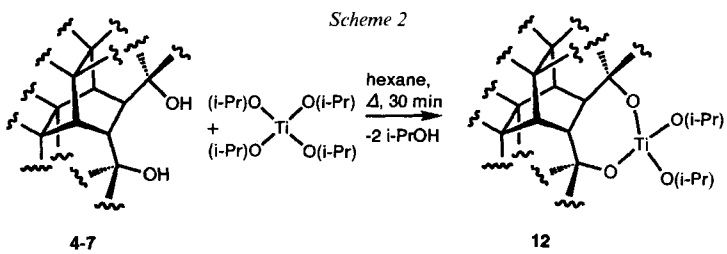
By means of these operationally simple reactions, the enantiomerically pure C_2-symmetric bicyclic diols **4**–**7** were readily available in multigram amounts.

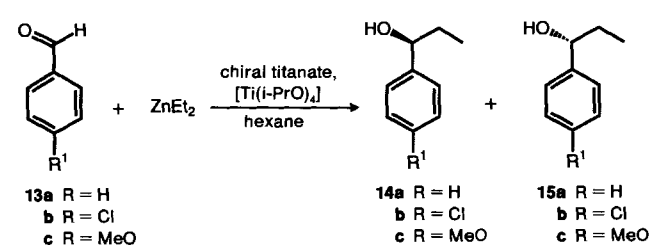
Scheme 1



Enantioselective Addition of $ZnEt_2$ to Aldehydes Catalyzed by Titanates Derived from 4–7. – To prepare catalytically active titanates **12**, the diols **4–7** were heated with [Ti(i-PrO)$_4$] according to the procedure devised by *Seebach* and coworkers [3] (*Scheme 2*). After evaporation of the solvent, the residues which were expected to consist of the corresponding titanates **12** were used without further characterization as catalysts for the

Scheme 2





enantioselective addition of $ZnEt_2$ to representative aromatic aldehydes **13**. To this end, the aldehydes were treated with 2 equiv. of $ZnEt_2$ in hexane in the presence of one of the chiral titanates **12** and in the presence of additional [Ti(i-PrO)$_4$]. In all enantioselective transformations, the (*S*)-enantiomer **14** was formed in excess. The results of the investigations are summarized in the *Table*.

Table. *Results of the Enantioselective Addition of $ZnEt_2$ to the Aldehydes* **13** *Catalyzed by the Titanates* **12** *Derived from the Chiral Bicyclic Diols* **4**–**7** (*Scheme 2*)

Entry	Diol	R	Equiv. of aldehyde	Equiv. of titanate **12**	Equiv. of [Ti(i-PrO)$_4$]	*T* [°C]	Reaction time [h]	Conversion[a]) [%]	Enantiomer ratio **14**/**15**[b])
1	**5**	H	1	0.2	1.2	– 30	12	93	82:18
2	**5**	H	1	0.2	1.2	– 78	120	quant. (83[c]))	91:9
3	**5**	H	1	0.4	1.2	– 78	120	quant. (89[c]))	93:7
4	**5**	H	1	0.2	0.6	– 30	14	quant.	81:19
5	**5**	H	1	0.2	0.2	– 30	72	93	72:28
6	**5**	H	1	0.2	0	– 30	72	80	55:45
7	**5**	Cl	1	0.2	1.2	– 78	120	95 (84[c]))	90:10
8	**5**	Cl	1	0.4	1.2	– 78	120	quant. (81[c]))	90:10
9	**5**	MeO	1	0.2	1.2	– 78	120	83 (68[c]))	91:9
10	**5**	MeO	1	0.4	1.2	– 78	120	quant. (81[c]))	93:7
11	**7**	H	1	0.2	1.2	– 30	20	quant.	70:30
12	**7**	H	1	0.4	1.2	– 30	20	quant.	72:28
13	**4**	H	1	0.2	1.2	– 30	24	quant.	50:50
14	**6**	H	1	0.2	1.2	– 30	24	quant.	50:50

[a]) Determined by capillary gas chromatography.
[b]) Determined by capillary gas chromatography employing a column carrying a chiral stationary phase (see *Exper. Part* for details).
[c]) Isolated yield.

The most effective of the ligands **4**–**7** clearly is diol **5**. In the presence of the titanate derived from this bicyclic compound, the differently substituted secondary alcohols **14** and **15** are obtained in enantiomer ratios up to 93:7 (*Table, Entries 1–10*). If **7** is employed as chiral ligand, the stereoselectivity is markedly lower (compare *Entries 1* and *2* with *Entries 11* and *12*), and in the presence of the titanates derived from **4** and **6**, the addition of the alkylzinc reagent to the aldehydes is accelerated, but without any stereodiscrimination (*Entries 13* and *14*). Thus, by analogy to the TADDOL's (*vide supra*), the presence of two sterically demanding substituents is crucial to obtain a high level of stereoselection. The enantioselectivity in the reaction steered by the C_2-symmetric ligand **5** increases with decreasing reaction temperature. Thus, in the presence of 20 mol-% of the catalyst at −78°, the enantiomer ratio for the formation of **14a** is 91:9, whereas at −30°, the respective value is only 82:18 (*Entries 1* and *2*). If, however, 0.4 equiv. of the titanate are employed at −78°, an enantiomer ratio of 93:7 is reached (*Entry 3*). The stereoselectivity is particularly influenced by the amount of [Ti(i-PrO)$_4$] added. If the molar ratio of this additive is reduced from 1.2 to 0.2 equiv., the enantiomer ratio drops markedly, and if no additional achiral titanate is present, an almost racemic product mixture is obtained (*cf. Entries 1* and *4–6*). Finally, a higher stereodiscrimination can be achieved by raising the concentration of the chiral catalyst. Thus, if instead of 0.2 equiv. of the titanate derived

from **5** 0.4 equiv. are present, the enantiomer ratio increases significantly (compare *Entries 2* and *3* as well as *Entries 9* and *10*).

From these findings, it may be concluded that the mechanism and the enantioselectivity of the addition of $ZnEt_2$ to the aldehydes **13** catalyzed by the chiral titanates **12** are determined by the same factors being operative in the presence of the TADDOL's **1**. Thus, the product alcohols **14**/**15** initially are bound to the chiral catalyst giving rise to catalytically active *Lewis* acids which obviously are less effective, and the role of excess $[Ti(i\text{-}PrO)_4]$ is to reconstitute the original catalyst by binding the product alkoxides [3]. The efficiency and the direction of the stereoselection can be explained by assuming that catalytically active Ti-complexes are formed in which the C_2 symmetry introduced by the bicyclic structure is relayed into the close vicinity of the metal center by means of the four phenyl substituents (*vide supra*). However, obviously the fulfillment of these two prerequisites alone is not sufficient to reach high levels of enantioselection, a fine tuning of the ligand structure appears to be particularly important. On the one hand, both **5** and **7** meet the criteria mentioned above, but **5** exerts a significantly higher enantioselecting influence. On the other hand, diol **5** clearly is less efficient than the TADDOL's **1**. For a detailed discussion of the influence of the ligand structure on the efficiency of the enantioselection, the reader is referred to the accompanying paper by *Seebach* and coworkers [10].

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Experimental Part

General. THF was distilled over K and benzophenone. Hexane was distilled over $LiAlH_4$. All aldehydes and $[Ti(i\text{-}PrO)_4]$ (*Merck*) were distilled and stored under Ar. Et_2Zn was used as 1M soln. in hexane (*Merck*). TLC: precoated silica gel *60 F_{254}* plates (*Merck*); visualization by UV_{254} light, development using phosphomolybdic acid soln. (phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot 4\,H_2O$ (10 g), H_2SO_4 (60 ml)), H_2O (940 ml). Flash chromatography (FC): SiO_2 (0.04–0.06 mm, *Baker*). Distillation: *Büchi GKR-51*. M.p.: open glass capillaries, *Büchi 510* (*Tottoli* apparatus); uncorrected. $[\alpha]_D$: at r.t. (*ca.* 20°); *Perkin-Elmer-241* polarimeter. Capillary gas chromatography (GC): *HP-5890-II*, gas chromatograph (*Hewlett-Packard*); column: *FS-Cyclodex β-I/P*, 50 m × 0.32 mm i.d. (*CS-Chromatographie-Service*). NMR Spectra: *Bruker AM 400* (400 (^1H) or 100 MHz (^{13}C)) and *Bruker AC 250* (250 MHz); δ in ppm downfield of $SiMe_4$ (= 0 ppm), J in Hz.

Bis[(S)-2-ethoxy-1-methyl-2-oxoethyl] (2R,3R)-Bicyclo[2.2.2]octane-2,3-dicarboxylate (**10**). To a soln. of diester **9** [9] (8 g, 20 mmol) in MeOH (100 ml), 10% Pd/C (15 mg) was added and the mixture stirred vigorously at r.t. under H_2. After 12 h, the mixture was filtered through *Celite* and MeOH was evaporated: 7.9 g (quant.) of **10**. White crystals. M.p. 46°. $[\alpha]_D^{r.t.} = -15.2$ ($c = 0.5$, CH_2Cl_2). ^1H-NMR (250 MHz, $CDCl_3$): 5.04 (*q*, $J = 7$, 2 MeCHOOC); 4.15 (*q*, $J = 7$, 2 $MeCH_2O$); 3.14 (*s*, H–C(2), H–C(3)); 2.20 (*s*, H–C(1), H–C(4)); 1.65–1.49 (*m*, H–C(5), H–C(6), H–C(7), H–C(8)); 1.45 (*d*, $J = 7$, 2 *Me*CHOOC); 1.23 (*t*, $J = 7$, 2 *Me*CH_2O). ^{13}C-NMR (100 MHz, $CDCl_3$): 174.34 (*C*O–C(2), *C*O–C(3)); 170.80 (*C*OOEt); 68.72 (2 MeCHOOC); 61.24 (2 MeCH_2O); 43.51 (C(2), C(3)); 27.50 (C(1), C(4)); 25.39 (C(6), C(8)); 21.16 (C(5), C(7)); 16.89 (*Me*CHOOC); 14.06 (*Me*CH_2O). Anal. calc. for $C_{20}H_{30}O_8$ (398.45): C 60.29, H 7.59; found: C 60.15, H 7.47.

(2R,3R)-Bicyclo[2.2.2]octane-2,3-dimethanol (**4**). To a suspension of $LiAlH_4$ (1.14 g, 30 mmol) in Et_2O (50 ml), a soln. of **10** (3.98 g, 10 mmol) in Et_2O (50 ml) was added dropwise with stirring. The mixture was heated to reflux for an additional h, then cooled to 5° before H_2O (25 ml) was added dropwise with stirring keeping the temp. below 10°. After acidifying with 1N HCl, the aq. layer was extracted with Et_2O (3 × 20 ml) and the combined org. phase washed with sat. NaCl soln. (50 ml), dried ($MgSO_4$), and evaporated: 1.50 g (88%) of **4**. White needles. M.p. 107°. $[\alpha]_D^{r.t.} = +101$ ($c = 0.5$, CH_2Cl_2). ^1H-NMR (250 MHz, $CDCl_3$): 3.64–3.51 (*m*, CH_2O, H–C(2), H–C(3)); 1.58–1.38 (*m*, H–C(1), H–C(4), H–C(5), H–C(6), H–C(7), H–C(8)). ^{13}C-NMR (100 MHz, $CDCl_3$): 66.86 (2 CH_2OH); 45.18 (C(2), C(3)); 27.11 (C(6), C(8)); 26.77 (C(1), C(4)); 21.19 (C(5), C(7)). Anal. calc. for $C_{10}H_{18}O_2$ (170.25): C 70.55, H 10.66; found: C 70.66, H 10.71.

(11R,12R)-9,10-Dihydro-9,10-ethanoanthracene-11,12-dimethanol (**6**). As described for **4**, **10** (5 g, 10 mmol) was reduced by $LiAlH_4$ (1.14 g, 30 mmol): 2 g (75%) of **2a**. White powder. M.p. 125°. $[\alpha]_D^{r.t.} = +55.8$ ($c = 0.5$, CH_2Cl_2). ^{1}H-NMR (250 MHz, $CDCl_3$): 7.27–7.05 (*m*, 8 arom. H); 4.18 (*s*, H–C(9), H–C(10)); 3.45 (*dd*, $J = 10$, $J = 6$, 2 H, 2 CH_2O); 2.99 (*dd*, $J = 10$, $J = 9$, 2 H, 2 CH_2O); 2.72 (*s*, 2 OH); 1.69–1.64 (*m*, H–C(11), H–C(12)). ^{13}C-NMR (100 MHz, $CDCl_3$): 143.58, 140.62, 126.07, 125.73, 125.03, 123.25 (arom. C); 66.02 (2 CH_2OH); 46.29 (C(9), C(10)); 46.19 (C(11), C(12)). Anal. calc. for $C_{18}H_{18}O_2$ (266.34): C 81.17, H 6.81; found: C 81.16, H 6.87.

(2R,3R)-α,α,α′,α′-Tetraphenylbicyclo[2.2.2]octane-2,3-dimethanol (**5**). Under Ar, **10** (10 g, 25 mmol) in THF (50 ml) was added dropwise to PhMgBr (300 mmol; prepared from Mg (7.29 g) and PhBr (47.1 g) in THF (150 ml)) at −10°. The mixture was refluxed for 1 d, cooled to 0°, quenched by addition of sat. NH_4Cl soln. (100 ml) and stirred for 30 min. The aq. layer was extracted with Et_2O (3 × 50 ml), the combined org. layer washed with sat. NaCl soln. (50 ml), dried ($MgSO_4$), and evaporated, and the residue purified by FC (hexane/AcOEt 15:1 (*v*/*v*)) and recrystallized from Et_2O/hexane: 7.37 g (62%) of **5**. Colorless amorphous solid. M.p. 226–228°. $[\alpha]_D^{r.t.} = -150.4$ ($c = 0.5$, CH_2Cl_2). ^{1}H-NMR (250 MHz, $CDCl_3$): 7.50–7.21 (*m*, 20 arom. H); 4.22 (*s*, 2 OH); 3.46 (*s*, H–C(2), H–C(3)); 1.70 (*s*, H–C(1), H–C(4)); 1.37–1.20 (*m*, H–C(5), H–C(6), H–C(7), H–C(8)); 0.75–0.66 (*m*, H–C(6), H–C(8)); 0.19–0.07 (*m*, H–C(5), H–C(7)). ^{13}C-NMR (100 MHz, $CDCl_3$): 149.45, 146.39, 128.38, 128.14, 127.22, 127.04, 126.89 (arom. C); 79.89 (2 Ph_2COH); 45.73 (C(2), C(3)); 29.59 (C(6), C(8)); 29.12 (C(1), C(4)); 20.75 (C(5), C(7)). Anal. calc. for $C_{34}H_{34}O_2$ (474.64): C 86.04, H 7.22; found: C 85.91, H 7.18.

(11R,12R)-9,10-Dihydro-α,α,α′,α′-tetraphenyl-9,10-ethanoanthracene-11,12-dimethanol (**7**). As described for **5**, **11** (12.36 g, 25 mmol) afforded **7** (8 g, 56%). Yellowish amorphous solid. M.p. 125°. $[\alpha]_D^{r.t.} = -14.6$ ($c = 0.5$, CH_2Cl_2). ^{1}H-NMR (250 MHz, $CDCl_3$): 7.37–6.47 (*m*, 28 arom. H); 4.36 (*s*, H–C(9), H–C(10)); 3.96 (*s*, H–C(11), H–C(12)); 1.32 (*s*, 2 OH). ^{13}C-NMR (100 MHz, $CDCl_3$): 147.91, 146.20, 144.56, 141.59, 128.08, 127.87, 126.54, 126.46, 126.44, 126.21, 125.61, 125.06, 124.02 (arom. C); 80.50 (2 Ph_2COH); 48.59 (C(11), C(12)); 48.21 (C(9), C(10)). Anal. calc. for $C_{42}H_{34}O_2$ (570.73): C 88.39, H 6.00; found: C 88.51, H 6.19.

General Procedure for the Addition of $ZnEt_2$ to Aldehydes: Under N_2 (reflux condenser and septum), a soln. of the respective diol **4**–**7** (0.2 or 0.4 mmol, 0.2 or 0.4 equiv.) and $[Ti(i\text{-}PrO)_4]$ (58 or 116 µl, 0.2 or 0.4 mmol; 0.2 or 0.4 equiv.) in hexane (5 ml) was refluxed for 30 min and then evaporated. The yellowish residue was dissolved again with hexane (15 ml) and $[Ti(i\text{-}PrO)_4]$ (353 µl, 1.2 mmol, 1.2 equiv.), and 1M $ZnEt_2$ in hexane (2 ml, 2 equiv.) was injected at r.t. After 15 min, the soln. was cooled to −78° and aldehyde **13** (1 mmol) dissolved in hexane (5 ml) was added slowly. After 120 h (GC monitoring), the mixture was quenched by addition of sat. aq. NH_4Cl soln. (10 ml) and stirred for 30 min with additional Et_2O (50 ml). After filtration through *Celite*, the mixture was extracted with sat. aq. $NaHSO_3$ soln. (20 ml) and finally with sat. aq. NaCl soln. (25 ml). The org. layer was dried ($MgSO_4$) and evaporated and the residue bulb-to-bulb distilled: **14**/**15**. The ratio of the enantiomers was measured by GC and the absolute configuration of the predominantly formed enantiomer determined by means of the $[\alpha]_D$ of **14**/**15**.

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