78. Nonreductive Enantioselective Ring Opening of *N*-(Methylsulfonyl)dicarboximides with Diisopropoxytitanium α,α,α′,α′-Tetraaryl-1,3-dioxolane-4,5-dimethanolate

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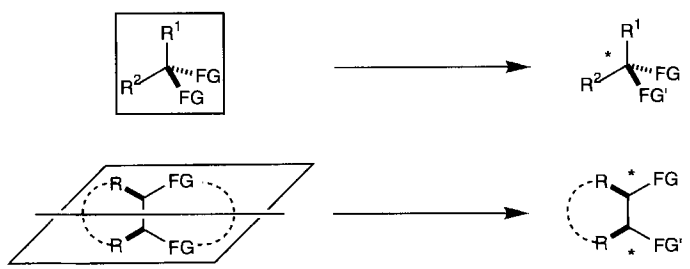
The bicyclic and tricyclic *meso-N*-(methylsulfonyl)dicarboximides **1a–f** are converted enantioselectively to isopropyl [(sulfonamido)carbonyl]-carboxylates **2a–f** by diisopropoxytitanium TADDOLate (75–92% yield; see *Scheme 3*). The enantiomer ratios of the products are between 86:14 and 97:3, and recrystallization from CH_2Cl_2/hexane leads to enantiomerically pure sulfonamido esters **2** (*Scheme 3*). The enantioselectivity shows a linear relationship with the enantiomer excess of the TADDOL employed (*Fig. 3*). Reduction of the ester and carboxamide groups ($LiAlH_4$) and additional reductive cleavage of the sulfonamido group (*Red-Al*) in the products **2** of imide-ring opening gives hydroxy-sulfonamides **3** and amino alcohols **4**, respectively (*Scheme 4*). The absolute configuration of the sulfonamido esters **2** is determined by chemical correlation (with **2a,b**; *Scheme 6*), by the X-ray analysis of the camphanate of **3e** (*Fig. 1*), and by comparative ^{19}F-NMR analysis of the *Mosher* esters of the hydroxy-sulfonamides **3** (*Table 1*). A general proposal for the assignment of the absolute configuration of primary alcohols and amines of *Formula* $HXCH_2CHR^1R^2$, X = O, NH, is suggested (see **11** in *Table 1*). It follows from the assignment of configuration of **2** that the *Re* carbonyl group of the original imide **1** is converted to an isopropyl ester group. This result is compatible with a rule previously put forward for the stereochemical course of reactions involving titanium TADDOLate activated chelating electrophiles (**12** in *Scheme 7*). A tentative mechanistic model is proposed (**13** and **14** in *Scheme 7*).

1. Introduction. – Enantioselective reactions of C_s-symmetrical molecules containing enantiotopic groups on a so-called prochirality center [1] or in compounds of *meso*-configuration[3]) are among the most useful conversions in asymmetric synthesis (*Scheme 1*),

Scheme 1. *Enantioselective Transformations of* C_s*-Symmetrical Molecules.* FG and FG′, functional groups.



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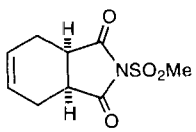
[2]) Nachdiplomstudium at the ETH-Zürich 1994–1995, financed by *Sandoz Pharma AG*, Basel.

[3]) The advantages of using *meso* starting materials have been pointed out in an earlier discussion [2a], and the term '*meso*-trick' introduced therein has subsequently become quite popular; see, *e.g.*, the recent paper [2b].

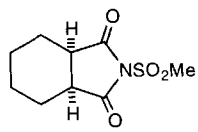
and much methodology can be derived from them. The underlying principle has been called 'asymmetric desymmetrization' [3]. Differentiation between two enantiotopic functional groups in *meso*-compounds leads to the creation of two or more chirality elements, and subsequent manipulation of functional groups provides a straightforward approach to either enantiomer of a desired product in a theoretical yield of 100% [4]. While the ability of enzymes to differentiate between enantiotopic functional groups is well known [5], the utility of nonenzymatic methods to achieve the same goal is less well recognized [6].

The synthesis of enantiomerically pure or enantiomerically enriched compounds from *meso*-dicarboxylic-acid derivatives, using diastereoselective [7] as well as enantioselective steps [8], is one of the most studied methods. However, the analogous reactions of imides [9] have been less well studied and, in every case to date, the transformation has been achieved by enantioselective reduction.

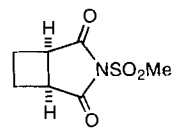
2. Preparative Results. – We now present the first enantioselective ring opening of imides in a nonreducing process, using titanium TADDOLate derivatives as the reagents.



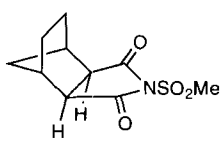
1a



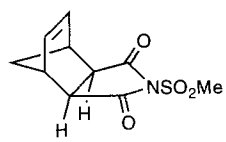
1b



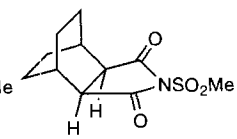
1c



1d



1e



1f

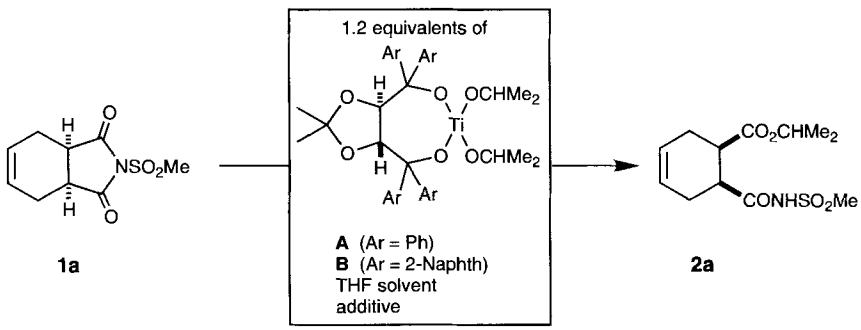
We first used *cis*-*N*-benzylcyclohexane-1,2-dicarboximide and 4-cyclohexene-1,2-dicarboximide and titanium tetraisopropoxide to test the reactivity, where we found that no reaction occurs at room temperature. Since the titanate-mediated alcoholysis [10] of *N*-acylsultams [11] has been reported, we next investigated *N*-sulfonylimide derivatives. Due to difficulties with the preparation of *N*-tosyl- or *N*-triflylimides[4]), we used methylsulfonyl (mesyl) derivatives throughout this work. The mesyl derivatives were prepared by the following procedure: Cyclic anhydrides and NH_4Cl were allowed to react to give the corresponding dicarboximides, and subsequent reaction with a base followed by the

[4]) The procedure described for the preparation of *N*-tosylphthalimide [12] was not applicable to the preparation of the corresponding *N*-tosylimides of the aliphatic derivatives necessary for the present investigation. Also, we were unable to prepare the corresponding *N*-triflylimides. Apparently, the aliphatic *N*-tosyl- and *N*-triflylimides have not been described in the literature!

addition of methanesulfonyl chloride yielded the *N*-mesyldicarboximides **1a,c,e**. The imides **1b,d,f** were obtained by hydrogenation of the corresponding unsaturated *N*-mesyldicarboximide (see *Exper. Part*).

Initially, the reaction of the imides **1** with $[Ti(OCHMe_2)_4]$ was checked, and it was encouraging to find that **1a** was converted to *rac*-**2a** (96%; room temperature, overnight in THF). Subsequently, the diisopropoxytitanium TADDOLate **A** [13] was tested on **1a** at −10° under otherwise identical conditions: in a slow reaction, optically active sulfonamido ester was formed as a mixture of the two enantiomers **2a** and *ent*-**2a** in a ratio of

Scheme 2. *Optimization of Enantioselective Ring Opening of* meso-*Compound* **1a** *with Diisopropoxytitanium TADDOLates*



1a **2a**

Entry	Ar	Temp. [°]	Additive	Time [d]	Yield [%]	Enantiomer ratio (e.r.)
1	Ph	−10	–	7	95	72.5:27.5
2	Ph	−20	–	7	70	79.5:20.5
3	Ph	−30	–	11	45	81.5:18.5
4	Ph	−30	–	21	95	81.5:18.5
5	2-Naphth	−30	–	21	92	86.5:13.5
6	Ph	−30	4 Å molecular sieves	7	94	77.5:22.5
7	2-Naphth	−50	4 Å molecular sieves	21	25	84:16
8	Ph	−30	H_2O[a])	21	45	50:50
9	Ph	−30	MeCN[b])	21	43	79.5:20.5
10[c])	2-Naphth	−30	$[Ti(OCHMe_2)_4]$	21	51	67:33
11[c])	Ph	−30	$[Ti(OCHMe_2)_4]$ 4 Å molecular sieves	21	46	68:32
12[c])	Ph	−30	i-PrOH 4 Å molecular sieves	21	< 1	–

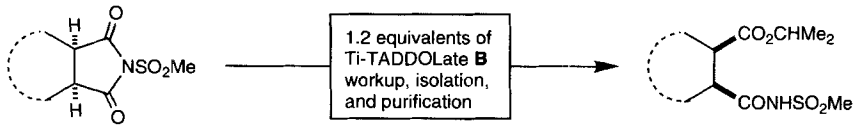
[a]) 1 Equiv. of H_2O was added. [b]) THF/MeCN 1:1 was used. [c]) 20% of TADDOL was used.

72.5:27.5 (for determination of the enantiomer ratio (e.r.) and of the absolute configuration of the major product, see *Sect. 3*). In a subsequent series of experiments (see *Scheme 2*), compound **1a** was chosen as the standard to optimize the conditions for imide 'desymmetrization', and the chiral titanium TADDOLate derivatives **A** and **B** were prepared by mixing equimolar amounts of TADDOL [14–16] and titanium tetraiso-

propoxide in Et_2O with subsequent removal of solvents [8f]. As can be seen from *Scheme 2* (*Entries 1–3*), lowering the temperature led to an increased enantioselectivity but, of course, at the cost of longer reaction times.

We chose to study the influence of other parameters at −30° and left the homogeneous reaction mixtures in a freezer for 3 weeks. The separation of product **2** from the TAD-

Scheme 3. *Ring Opening of* N-*(Methylsulfonyl)dicarboximides* **1a–f** *with the Diisopropoxytitanium TADDOLate* **B** *under Optimized Conditions and Enantiomer Ratios* (e.r.) *of the Products* **2a–f** *before and after Recrystallization from* CH_2Cl_2/*Hexane*. The e.r. were determined by ^{19}F-NMR spectroscopy of the *Mosher* esters obtained from the hydroxysulfonamides (see *Scheme 4* and *Sect. 3*).



1a-f **2a-f**

Starting material	Temp. [°]	Reaction time [d]	Product	Yield [%]	Enantiomer ratio (e.r.)		Number of recryst.	Recovery [%]
					before recryst.	after recryst.		
1a	−30	21	**2a**	92	86.5:13.5	> 99.5:0.5[a])	3	31
1b	−30	14	**2b**	85	92:8	94:6	1	74
1b	−50	28	**2b**	63	92.5:7.5	> 99.5:0.5[a])	3	36
1c	−30	7	**2c**	89	86:14	> 99.5:0.5[a])[b])	3	33
1c	−50	15	**2c**	90	97.5:2.5	–	–	–
1d	−20	21	**2d**	89	87.5:12.5	97.5:2.5	1	72
1d	−30	42	**2d**	85	88.5:11.5	> 99.5:0.5[a])	3	33
1e	−20	21	**2e**	92	90.5:9.5	> 99.5:0.5[a])	3	42
1e	−30	42	**2e**	75	93:7	98.5:1.5	1	71
1f	−20	21	**2f**	83	86.5:13.5	99:1	1	73
1f	−30	42	**2f**	84	87.5:12.5	> 99.5:0.5[a])	3	42

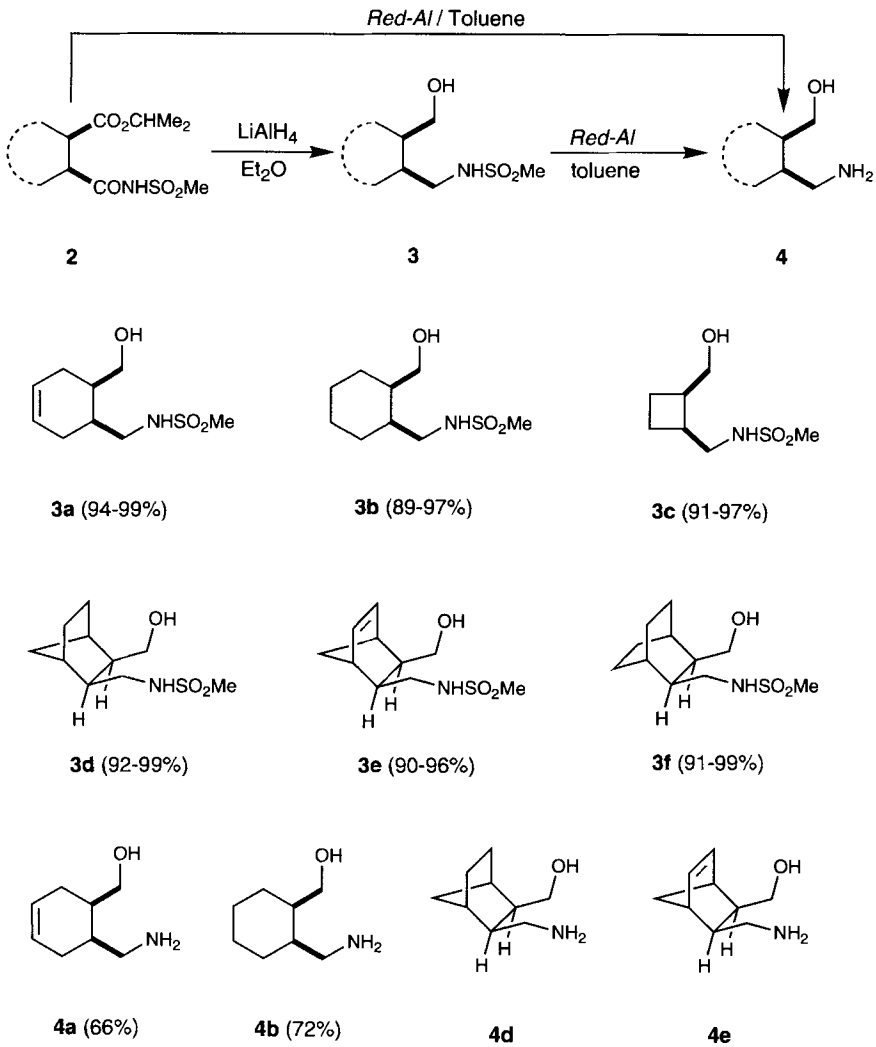
[a]) Only one enantiomer detected.
[b]) Recrystallized from $CHCl_3$/hexane.

DOL auxiliary was easily achieved by aqueous workup: an aqueous NH_4Cl solution was added, the aqueous phase extracted with CH_2Cl_2, and **2** removed from the organic phase into 1N NaOH from which it was liberated by acidification with HCl. The crude products **2** thus isolated crystallized and were purified without chromatography. The following observations are noteworthy: *i*) the (2-naphthyl)-substituted TADDOL **B** gave slightly better selectivities than **A** (*cf. Entries 4* and *5* in *Scheme 2*), *ii*) addition of molecular sieves[5]) increased the rate of reaction by a factor of *ca.* 3, but decreases the selectivity somewhat (*Entries 4* and *6*); *iii*) after 45% conversion, the product had the same e.r. as after complete conversion (*cf. Entries 3* and *4*); *iv*) addition of MeCN as a cosolvent led to a decrease in rate but to hardly any change in selectivity (*cf. Entries 4* and *9*); *v*) in the

[5]) In the case of the transesterifying kinetic resolution with *S*-(pyridin-2-yl) 2-phenylbutanthioate, molecular sieves caused a drastic improvement of enantioselectivity and allowed the reaction to be carried out catalytically [17].

presence of 0.5 equiv. of H_2O, the selectivity was still 75:25 (yield 54%), whereas when 1 equiv. of H_2O was added, the reaction (yield 45%) was no longer enantioselective (*Entry 8*)[6]); *vi*) attempts to carry out the reaction under catalytic conditions (using

Scheme 4. *Reduction of the Methanesulfonamido Esters* **2** *to the Hydroxy-sulfonamides* **3** *and Reductive Sulfonamide Cleavage to Amino Alcohols* **4**. *Mosher* esters of the hydroxy compounds **3** were used for e.r. determination and for configurational correlation (see *Sect. 3*). The amino alcohols **4** were characterized as (hydroxymethyl)-3,5-dinitrobenzamides **4a′**, **b′**, **d′**, **e′**. *Red-Al* = $NaAlH_2[O(CH_2)_2OMe]_2$.



[6]) In the case of titanium BINOLates, addition of H_2O led to a complex which was more effective in the enantioselective catalysis of ene [18] and *Mukaiyama* aldol reactions [19].

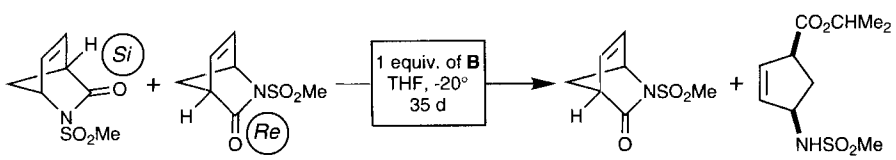
i-PrOH or $[Ti(OCHMe_2)_4]$ as source for the Me_2CHO group in **2a** and only 20% of titanium TADDOLate) led to poorer results (*Entries 10–12*)[7]); *vii*) a mixture of 1.2 equiv. of achiral titanate and 0.2 equiv. of titanium TADDOLate **A** gave rise to a 2:1 preference for the formation of one enantiomer (*vs.* 5:1 with 1.2 equiv. of **A**), evidencing the higher reactivity of the Ti-center bearing the bulky chelating alkoxide ligand, a phenomenon which we have previously observed with many other reactions[8]).

Under the optimized conditions established for **1a**, the *N*-mesyldicarboximides **1b–f** were opened to the sulfonamido esters **2b–f**. The results[9]) are collected in *Scheme 3*. The yields were generally in the 80–90% range, all products were solid and, except for **2a**, laevorotatory, the enantiomer excesses varying from 70 to 95%. Enantiomerically pure products could easily be obtained by recrystallization. For assignment of the absolute configuration, see *Sect. 3*.

The carboxylate and carboxamide groups of the sulfonamido esters **2** were reduced with $LiAlH_4$ to give the hydroxy-sulfonamides **3** in excellent yields (*Scheme 4*; a yield range is given since we performed this reduction many times for the e.r. determination (*vide infra*)).

While the methanesulfonamido group of **3** resisted all cleavage attempts including treatment with 48% aqueous HBr solution/phenol and Li/naphthalene, it was smoothly converted to an amino group with the hydride complex *Red-Al* [23] yielding the amino alcohols **4** (*Scheme 4*). These amino alcohols could also be obtained in one step from the sulfonamido esters **2** by reaction with *Red-Al*, the yields being comparable to those of the two-step process.

Scheme 5. *Cleavage of an* N-*Mesyllactam with TADDOLate* **B**



5 *ent*-**5** *ent*-**5** **6**

$[\alpha]_D = +2.05$ $[\alpha]_D = -28.27$

e.r. 52 : 48 e.r. 63 : 37

In one case, we also applied the reaction conditions optimized for sulfonylimide opening to a kinetic resolution of an *N*-mesyllactam (*Scheme 5*). The reaction of lactam *rac*-**5** was stopped at *ca.* 15% conversion, the starting material and the sulfonamido ester

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[7]) With $[TiCl(OCHMe_2)(TADDOLate)]$, the reaction was slower than with **A** and the selectivity dropped to 73:27.

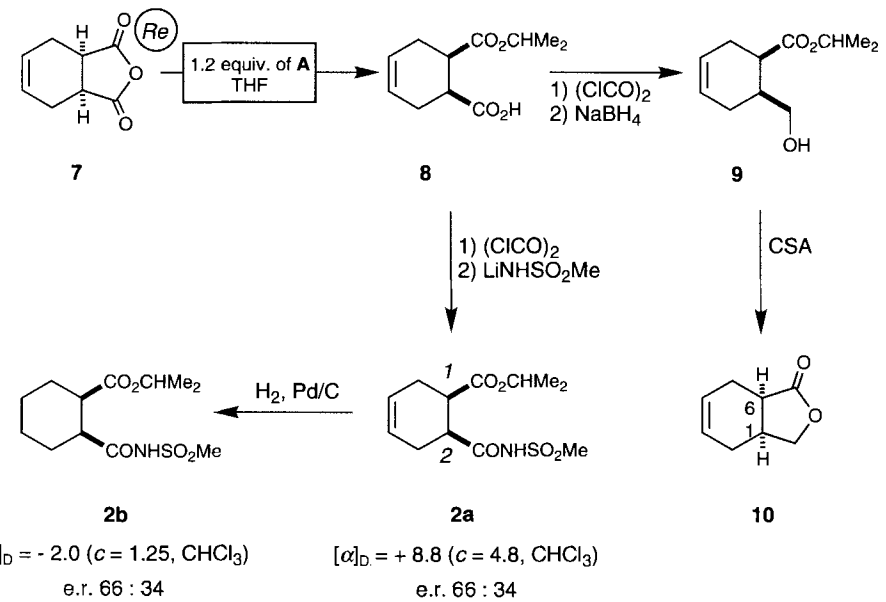
[8]) Nucleophilic addition of R_2Zn and of $[TiR(OCHMe_2)_3]$ to aldehydes [15] [20] [21], *Diels-Alder* additions of 2-crotonyl-oxazolidinone to cyclopentadiene [16] [22], and opening of cyclic anhydrides to half-esters [8f].

[9]) Much to our surprise, we were not able to cleave the *N*-(methylsulfonyl)-bicyclo[2.2.2]oct-5-ene-2,3-dicarboximide (**1f'**), the unsaturated analog of **1f** (with a double bond in the '*syn*' bridge). It was stable to the standard conditions, even when the mixture was heated at the reflux temperature of the solvent!

6 were separated, and both were found to be optically active. The ring-opened product **6** was chemically correlated with the corresponding lactam [24] (see *Exper. Part*), which proved that the enantiomer having the carbonyl group in the *Si* half-space was cleaved more rapidly.

3. Configurational Assignments. – The sulfonamido ester **2a**, which had been used in all the optimization experiments, was chemically correlated with the known half-ester **8** of cyclohex-4-ene-1,2-dicarboxylic acid and with the known lactone **10** as shown in *Scheme 6*. To this end, anhydride **7** was opened enantioselectively with diisopropoxytitanium TADDOLate **A** to the half-ester **8** in 85% yield [8f]. Reaction of the latter with oxalyl chloride and subsequent reduction with $NaBH_4$ [25] led to the hydroxy ester **9** in

Scheme 6. *Configurational Assignments by Chemical Correlation.* CSA = camphorsulfonic acid.



90% yield (e.r. 91:9, determined by ^{19}F-NMR spectroscopy of the corresponding *Mosher* esters, *vide infra*). The lactonization in refluxing toluene, catalyzed by camphorsulfonic acid (CSA), gave lactone **10** in 92% yield and with $[\alpha]_D^{r.t.} = +46.7$ ($CHCl_3$); for the (1*S*,6*R*)-isomer of 96% ee, $[\alpha]_D^{r.t.} = +45.1$ was reported [9d]. These reactions establish the absolute configuration of half-ester **8** and alcohol **9**. Therefore, it only remained to synthesize compound **2a** from **8**. The reaction of **8** with oxalyl chloride, as above, followed by addition of lithium methanesulfonamide gave the sulfonamido ester **2a** in 92% yield and with the same sense of rotation as the product obtained from the direct reaction of imide **1a** with diisopropoxytitanium TADDOLate, but with an ee of only 32%. The partial racemization which occurred is probably due to a reversible cyclization of the intermediate lithium derivative of compound **2a** to give the achiral dicarboximide **1a** and lithium isopropoxide. There is no indication of a *cis*/*trans*-isomerization *en route*

from anhydride **7** to the sulfonamido esters **2a** and **2b**. In any case, a comparison of the optical activity and of the ^{19}F-NMR spectra of the *Mosher* esters from **2a**, which were prepared by two routes, proves that the absolute configuration of **2a** must be (1*R*,2*S*) (see *Schemes 2*, *3*, and *6*).

Thus, the *Re*-carbonyl group of both anhydride **7** and imide **1a** are attacked by the isopropoxy nucleophile in the ring-opening processes. Hydrogenation of **2a** to the saturated analog **2b** also confirms the configurational assignment of this compound (*Scheme 6*).

All other ring-opening products **2** are assigned (*R*)-configuration at the ester and (*S*)-configuration at the amide positions by analogy, on the basis of the following three facts: *i*) All but **2a** are laevorotatory, *ii*) the X-ray crystal structure of the camphanate of the hydroxy-sulfonamide **3e** establishes its (2*S*,3*R*)-configuration (see *Fig. 1*), and *iii*) all

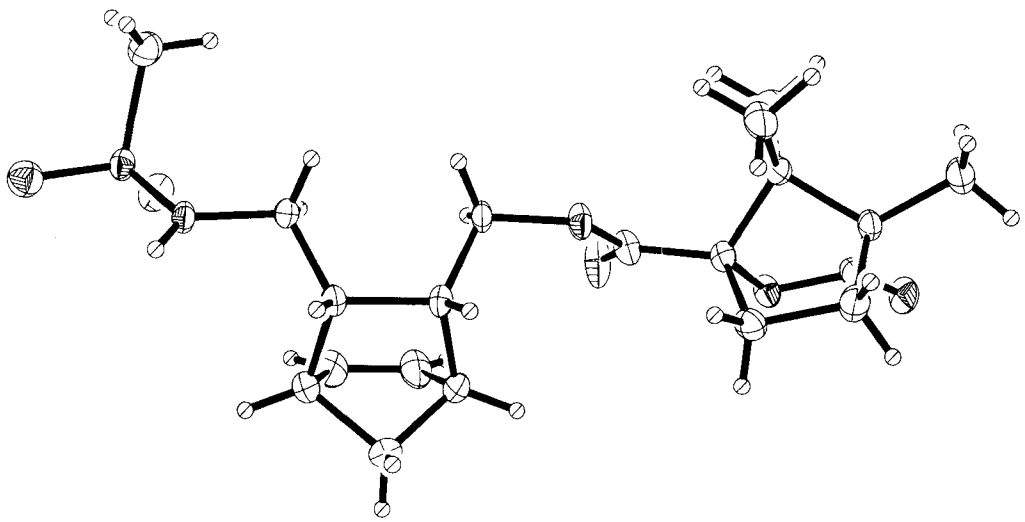


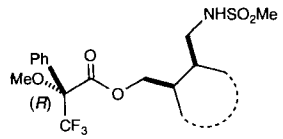
Fig. 1. *ORTEP Plot of the crystal structure of the camphanate of* **3e**. For the preparation of this ester (from (1*S*,4*R*)-camphanoyl chloride), its characterization, and the crystal data, see *Exper. Part* (*Sect. 8*). The coordinates have been deposited in the *Cambridge Crystallographic Data Base*.

Mosher esters (= methoxy(phenyl)(trifluoromethyl)acetates = MPTA) [26] of the hydroxy-sulfonamides **3** obtained from the major enantiomer of the sulfonamido esters have the ^{19}F-NMR signal at higher field with (*R*)-MPTA and at lower field with (*S*)-MPTA (see *Table*).

We felt that this observation may be applicable to other primary alcohols and primary amines with a chirality center in the β-position, with the same correlation between the CF_3-shift of their *Mosher* derivatives and the relative configuration being found[10]). Thus, a number of such esters and amides were prepared from precursors of known absolute

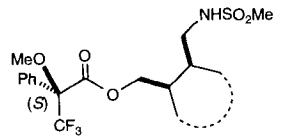
[10]) Analogous NMR assignments of absolute configurations of secondary alcohols and of primary amines with a chirality center in α-position through their *Mosher* esters or amides have turned out to be very reliable [27] [28].

Table. *Correlation of the Relative Configuration of* Mosher *Amides and Esters Derived from Primary Alcohols and Primary Amines of the General Formula* $HX-CH_2-CHR^{lg}R^{sm}$ *with the* ^{1}*F-NMR Chemical Shift of the* CF_3 *Group*



3-[(*R*)-MPTA][a])

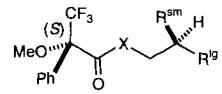
higher field



3-[(*S*)-MPTA][a])

lower field

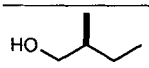
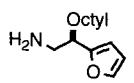
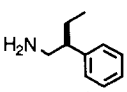
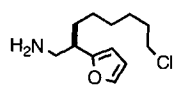
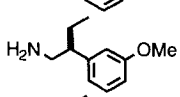
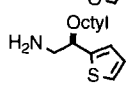
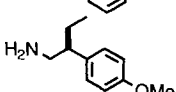
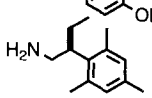
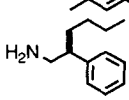
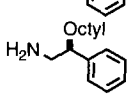
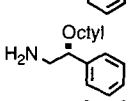
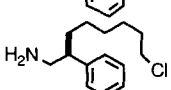
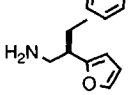
^{19}F-NMR signal



11, X = O or NH[a])

(*S*, *S*) if priority is $XCH_2 > R^{lg} > R^{sm}$

Higher-field ^{19}F-NMR-signal as compared to epimer

Compound[b])	Config.	δ(F) of MPTA[c])		Compound[b])	Config.	δ(F) of MPTA[c])	
		(*S*)	(*R*)			(*S*)	(*R*)
	*S*	−72.12	−72.10		*R*	−69.47	−69.41
	*S*	−69.55	−69.50		*R*	−69.46	−69.39
	*S*	−69.54	−69.48		*R*	−69.42	−69.35
	*S*	−69.49	−69.46	**3a**	*R*	−71.97	−72.02
	*S*	−69.50	−69.38	**3b**	*R*	−71.58	−71.87
	*S*	−69.54	−69.48	**3c**	*R*	−71.51	−71.84
	*S*	−69.55	−69.50	**3d**	*R*	−71.76	−71.98
	*R*	−69.50	−69.55	**3e**	*R*	−71.76	−72.00
	*S*	−69.44	−69.40	**3f**	*R*	−71.81	−71.98
	*R*	−69.70	−69.40	**9**	*S*	−72.10	−72.07

[a]) The conformation of the 3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl (MPTA) group as presented in the *Formula* **3**-[MPTA] and **11** was chosen by comparison with an X-ray structure of a *Mosher* ester [30] in the *Cambridge Crystallographic Data Base* (code: WEVCOP).

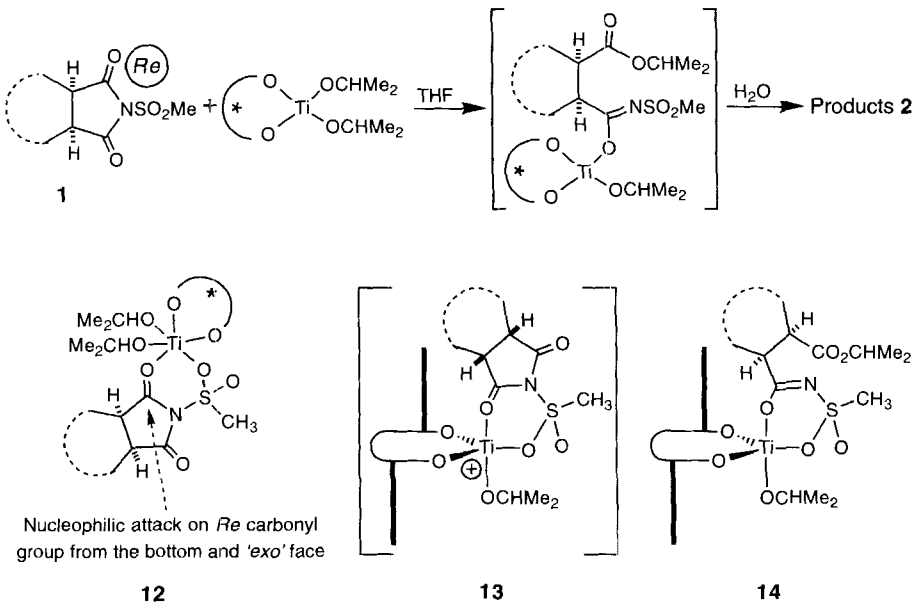
[b]) The hydroxy-sulfonamides **3a**–**f** are described in the *Exper. Part*, 2-methylbutanol is commercially available, and the 2-arylalkylamines have been described and configurationally assigned in a recent paper [29]. For the preparation of the MPTA derivatives, see *Exper. Part*.

[c]) Chemical shifts δ in ppm relative to the internal standard CCl_3F.

configuration at the chirality center in β-position, and the ^{19}F-NMR spectra of both diastereoisomers were measured. The results (*Table*) show that we can be quite confident in applying the correlation shown by *Formula* **11** in the *Table* for configurational assignments.

4. Mechanistic Considerations. – So far, full mechanistic investigations of the enantioselective ring opening of anhydrides or *N*-(methylsulfonyl)dicarboximides by titanium TADDOLates have not been completed. However, it is possible to put forward some models for describing the course of the reaction leading to the observed products **2**.

Scheme 7. *Reaction Leading to* N-*(Methylsulfonyl)dicarboximide Ring Opening and Corresponding Mnemonic Picture and Mechanistic Model*



In all cases, the *Re*-carbonyl group of the *meso*-starting materials reacts with an isopropoxy nucleophile, with formation of a titanio-sulfonamido ester (see equation in *Scheme 7* and **2a'** in *Fig. 2*). As can be seen from *Fig. 3*, there is a linear correlation between the enantiomer excesses of the TADDOL employed and of the product **2a** formed. This suggests, but does not rigorously prove, that only one TADDOL moiety is involved in the rate-determining step of the ring opening[11]). If we apply the mnemonic rule derived

[11]) A linear relationship such as shown in *Fig. 3* is usually taken as evidence for the involvement of only one chiral ligand in the poduct-forming step. In cases in which two chiral ligands are cooperating, a linear relationship may, *e.g.*, result if their homochiral combinations are product-forming and the heterochiral ones are not formed at all. For a detailed discussion of all the possibilities, see [31] [32].

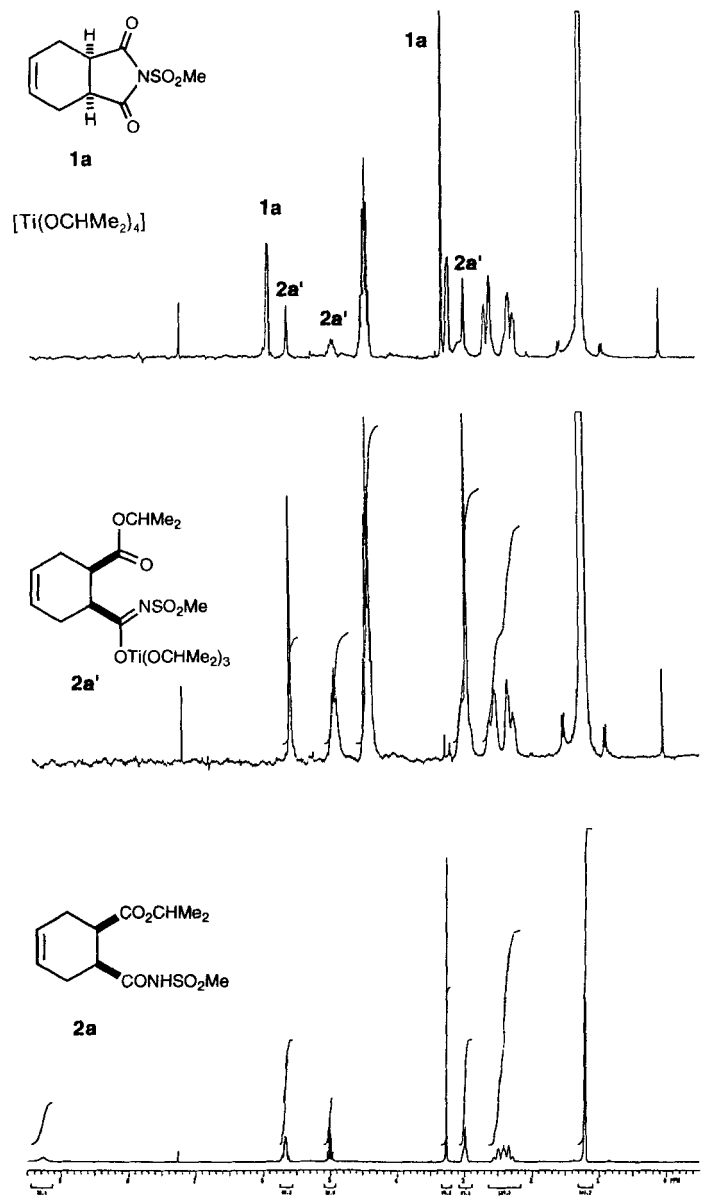


Fig. 2. *^{1}H-NMR Spectra of the starting materials [Ti(OCHMe$_2$)$_4$] and* **1a**, *of the initial product, a* N-*(methylsulfonyl)*-O-*titaniocarboxamide* **2a'**, *and of the amino ester* **2a** *isolated after aqueous workup.* Only one enantiomer of **2a** and **2a'** is shown. A derivative similar to **2a'**, bearing a TADDOLate and an isopropoxy group on the Ti-atom, must be formed in the enantioselective reaction, see equation in *Scheme 7*.

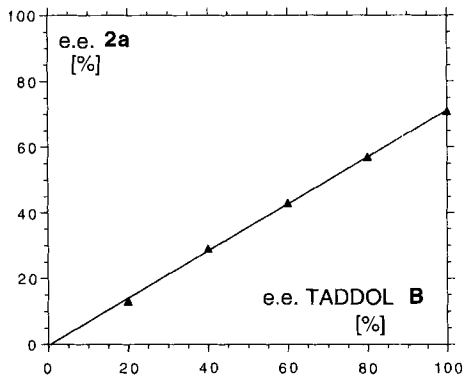


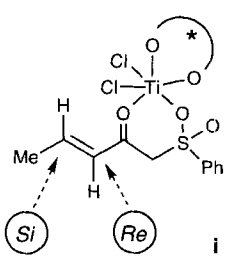
Fig. 3. *Correlation of enantiomer excesses of the TADDOL* **B** *and of the product* **2a** *in the ring opening of imide* **1a**. The reaction was carried out at −20° for 10 d and gave yields greater than 90% in all five cases.

for reactions of bidentate electrophiles activated by titanium (*R*,*R*)-TADDOLates, the course of the reaction can be pictured as shown in **12** (*cf.* Chart 4 in [16])[12])[13]).

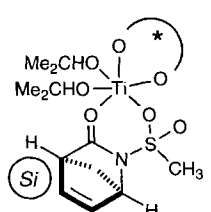
How does this strictly formalistic rule translate into a mechanistic model? For this, we need to make some assumptions: *i*) the *N*-sulfonylimide acts as a bidentate ligand on a neutral hexacoordinate or on a positively charged pentacoordinate Ti-center, *ii*) the product-forming complex undergoes nucleophilic attack on the carbonyl group which is attached to the Ti-atom[14]), *iii*) nucleophile approach from the '*exo*' face of the bi- and tricyclic substrates **1** is preferred over '*endo*' attack[15]).

The conclusion is, therefore, that the active complex (shown with a pentacoordinate, positively charged Ti-center) might be as pictured in **13** and the product complex as pictured in **14** (*Scheme 7*).

We gratefully acknowledge the polishing of our English by Dr. *Jennifer L. Matthews*. We wish to thank the *Ministerio de Educación y Ciencia*, Spain, for a post-doctoral grant to one of us (*D.J.R.*) and *Sandoz Pharma AG*



i



ii

[12]) Since we compiled the examples in our previous paper [16], several new cases have been published to which the rule may be applied. One of these are *Diels-Alder* additions involving α,β-unsaturated α′-sulfonyl ketones [33] [34] (see **i**).

[13]) Note that the faster-reacting enantiomer of the *N*-mesyllactam **5** is the one which has its *exo* face at the back when drawn according to the mnemonic rule: see **ii** in *Footnote 12* and compare with **12** in *Scheme 7*.

[14]) We consider the alternative posibility assuming attack on the non-complexed carbonyl group to be less likely. In this case, the complexation with Ti would create a leaving group rather than a highly electrophilic carbonyl C-atom. The conclusions drawn here would, of course, therefore, be reversed!

[15]) We have no way of telling whether the Me_2CHO group is transferred from Ti to the CO group by an *intra*molecular shift in the reactive complex or by *inter*molecular attack. Sophisticated kinetic investigations will be necessary to find out!

(fellowship to *G.G.*). We also thank Dr. *David Chaplin* of the *Chiroscience Company*, Cambridge, GB, for providing us with a sample of the starting lactam and *Paul Seiler* of the X-ray service group, Laboratorium für Organische Chemie, ETH-Zürich, for X-ray analysis of the camphanoat of **3e**. The considerable help of *Albert K. Beck* and *Georg Jaeschke* during the preparation of this manuscript is gratefully acknowledged.

Experimental Part

1. *General.* All solvents were either *puriss p.a.* quality or distilled over appropriate drying agents. TLC: *Merck-TLC-F_{254}* precoated glass plates; detection by UV_{254} light, staining with phosphomolybdic acid (25 g of phosphomolybdic acid, 10 g of $Ce(SO_4)_2 \cdot 4\,H_2O$, 60 ml of conc. H_2SO_4, and 940 ml of H_2O), with Cl_2 ($KMnO_4$/aq. HCl soln.), or with ninhydrin (5.25 g of *N,N,N′,N′*-tetramethyl-4,4′-diaminodiphenylmethane (= 4,4′-methylenebis[*N,N*-dimethylbenzenamine]), 34 mg of ninhydrin, 10.2 g of NaI, 25 ml of AcOH and 375 ml of H_2O). Flash chromatography (FC): silica gel *60* (*Merck*) 40–63 μm. Enantiomer ratios (e.r.) were determined by GC, anal. HPLC, and *Mosher* derivatives. GC: *Carlo-Erba-Fractovap-5160-HRGC*, injector temp. 220°, detector temp. 250°, H_2 carrier gas using a *FS-Lipodex E* (50 m × 0.25 mm, *γ-CD* column). HPLC: *Kontron* HPLC system (UV detector *Uvikon LCD-75*, programmer *200*, integrator *Shimadzu C-R 1B Chromatopak*) using a *Daicel* column (*Chiralcel OD*, 250 × 4.6 mm, 10 μm), hexane/i-PrOH (%); flux in ml/min; t_R in min. *Mosher* derivatives: One crystal of 4-(dimethylamino)pyridine and a small drop of *Mosher* acyl chloride derivative was added to 2–10 mg of the appropriate amine or alcohol, which had been dissolved in $CDCl_3$ in a NMR tube, and the ^{19}F-NMR spectrum was recorded. Melting points: *Büchi 510*; not corrected. Specific rotation: *Perkin-Elmer-241* polarimeter. IR Spectra: *Perkin-Elmer-297* spectrometer; in KBr, $CHCl_3$ soln., or film. ^1H-, ^{13}C-, and ^{19}F-NMR Spectra: *Varian Gemini 300* (300, 75, and 282 MHz, resp.); chemical shifts δ in ppm rel. to internal $SiMe_4$ or CCl_3F, coupling constants *J* in Hz. MS: *VG-Tribrid* spectrometer; in *m/z* (rel. intensities (%)). Elemental analysis: Microanalytical Laboratory of the ETH-Zürich.

2.1. *Preparation of Imides.* According to [35], AcONa (19 mmol) was added to a suspension of anhydride (5 mmol) and NH_4Cl (15 mmol) in AcOH (100 ml) at r.t., and the mixture was refluxed for 3 d. The resulting suspension was allowed to cool to r.t., H_2O (150 ml) was added, and the mixture was extracted with CH_2Cl_2 (3 × 100 ml). The combined org. layers were dried (Na_2SO_4) and evaporated. Chromatography of the residue yielded the expected imides.

cis-*Cyclobutane-1,2-dicarboximide*: Yield 72%. R_f 0.60 (Et_2O). M.p. 133–134° ([36]: 137.5–138°). IR (KBr): 3446*s*, 3189*m*, 3070*m*, 1706*w*, 1172*m*. ^1H-NMR ($CDCl_3$): 2.20–2.35, 2.60–2.75, 3.20–3.40 (3*m*, 2 CH_2CH); 8.80 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 180.45; 39.85; 22.9. EI-MS: 125 (53, M^+), 82 (51), 55 (15), 54 (100), 53 (14).

*Bicyclo[2.2.1]hept-5-ene-2-*endo,*3-*endo-*dicarboximide*: Yield 87%. R_f 0.36 (hexane/AcOEt 1:1). M.p. 170–172° (CH_2Cl_2/hexane). IR (KBr): 3164*m*, 3063*m*, 1767*w*, 1700*w*, 1187*m*. ^1H-NMR ((D_6)DMSO): 1.40–1.60 (*m*, CH_2); 3.10–3.45 (*m*, H–C(1), H–C(2), H–C(3), H–C(4)); 6.10–6.15 (*m*, CH=CH); 10.85 (*s*, NH). ^{13}C-NMR ((D_6)DMSO): 179.1; 134.8; 134.6; 52.15; 47.0; 44.4. EI-MS: 163 (8, M^+), 98 (19), 91 (15), 66 (100).

*Bicyclo[2.2.2]oct-5-ene-2-*endo,*3-*endo-*dicarboximide*: Yield 77%. R_f 0.85 (Et_2O). M.p. 198–199° (CH_2Cl_2/pentane). IR (KBr): 3230*w*, 3068*s*, 1759*m*, 1707*w*, 1184*m*. ^1H-NMR ($CDCl_3$): 1.30–1.70 (*m*, 2 CH_2); 2.80–2.90, 3.00–3.15 (2*m*, H–C(1), H–C(2), H–C(3), H–C(4)); 6.10–6.30 (*m*, CH=CH); 8.75 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 179.7; 132.4; 45.5; 41.4; 23.4. EI-MS: 177 (25, M^+), 149 (20), 99 (43), 80 (71), 79 (29), 78 (100), 77 (12), 51 (10).

2.2. N-*Mesylimides* **1a,c**. According to [37], Et_3N (40 mmol) was added to a soln. of imide (20 mmol) in dry MeCN (60 ml) at 0° under Ar. After 10 min, $MeSO_2Cl$ (40 mmol) in MeCN (20 ml) was added within 30 min. The resulting mixture was stirred for 2 h. The precipitate was filtered off and the filtrate evaporated. Et_2O (40 ml) was added to the residue and the org. layer washed with cold HCl soln. (2 × 20 ml), dried (Na_2SO_4), and evaporated. The resulting residue was purified by FC.

cis-N-*(Methylsulfonyl)cyclohex-4-ene-1,2-dicarboximide* (**1a**): Yield 82%. R_f 0.48 (Et_2O). M.p. 116–117° (CH_2Cl_2/hexane). IR (KBr): 3004*s*, 1806*m*, 1736*w*, 1371*w*, 1253*w*, 1175*m*. ^1H-NMR ($CDCl_3$): 2.20–2.35, 2.60–2.70 (2*m*, 2 CH_2); 3.20–3.25 (*m*, 2 CHCO); 3.32 (*s*, Me); 5.90–5.95 (*m*, CH=CH). ^{13}C-NMR ($CDCl_3$): 175.35; 127.5; 42.2; 39.55; 23.25. EI-MS: 229 (10, M^+), 150 (25), 122 (33), 84 (15), 81 (56), 79 (100), 78 (17), 77 (16).

cis-N-*(Methylsulfonyl)cyclobutane-1,2-dicarboximide* (**1c**): Yield 78%. R_f 0.15 (Et_2O). M.p. 109–110° (CH_2Cl_2/hexane). IR (KBr): 1723*w*, 1359*m*, 1174*m*. ^1H-NMR ($CDCl_3$): 2.30–2.40, 2.70–2.80 (2*m*, 2 CH_2); 3.30–3.40 (*m*, CHCO); 3.42 (*s*, Me). ^{13}C-NMR ($CDCl_3$): 174.8; 42.2; 38.5; 23.1. EI-MS: 203 (4, M^+), 82 (18), 54 (100).

2.3. N-*Mesylimides* **1e,f′** *and* rac-N-*Mesyllactam* **5**/ent-**5**. BuLi (7.30 mmol) was added to a soln. of the imide or lactam (7.25 mmol) in THF (75 ml) at −78° under Ar. After 15 min, $MeSO_2Cl$ (14 mmol) was added and the resulting mixture stirred overnight as the temp. rose to r.t. The mixture was quenched with H_2O (30 ml) and

extracted with CH_2Cl_2 (2 × 30 ml), the combined org. layer dried (Na_2SO_4) and evaporated, and the resulting residue recrystallized from CH_2Cl_2/Et_2O/pentane.

N-*(Methylsulfonyl)bicyclo[2.2.1]hept-5-ene-2-*endo,*3-*endo-*dicarboximide* (**1e**): Yield 72%. R_f 0.26 (Et_2O). M.p. 167–169° (CH_2Cl_2/pentane). IR (KBr): 3006*s*, 1798*s*, 1731*w*, 1370*w*, 1246*m*, 1178*w*. ^{1}H-NMR ($CDCl_3$): 1.50–1.60, 1.70–1.85 (2*m*, CH_2); 3.25 (*s*, Me); 3.35–3.50, 3.50–3.60 (2*m*, H–C(1), H–C(2), H–C(3), H–C(4)); 6.25–6.30 (*m*, CH=CH). ^{13}C-NMR ($CDCl_3$): 173.0; 135.0; 52.0; 46.1; 42.2. EI-MS: 241 (1, M^+), 176 (100), 66 (64).

N-*(Methylsulfonyl)bicyclo[2.2.2]oct-5-ene-2-*endo,*3-*endo-*dicarboximide* (**1f'**): Yield 81%. R_f 0.42 (Et_2O). M.p. 189–190° (CH_2Cl_2/Et_2O/hexane). IR (KBr): 3056*s*, 3025*s*, 1784*m*, 1738*w*, 1369*w*, 1241*w*, 1174*w*. ^{1}H-NMR ($CDCl_3$): 1.35–1.65 (*m*, 2 CH_2); 2.95–3.05, 3.20–3.25 (2*m*, H–C(1), H–C(2), H–C(3), H–C(4)); 3.26 (*s*, Me); 6.25–6.30 (*m*, CH=CH). ^{13}C-NMR ($CDCl_3$): 174.1; 132.7; 44.5; 42.1; 32.0; 23.3. EI-MS: 255 (< 1, M^+), 80 (100), 79 (19), 78 (70), 70 (12).

rac-N-*(Methylsulfonyl)-2-azabicyclo[2.2.1]hept-5-en-3-one* (**5**/*ent*-**5**): Yield 77%. R_f 0.68 (Et_2O). HPLC (*Chiracel OD*; hexane/i-Pr-OH (5%) 1 ml/min): t_R 53.40, 61.5. M.p. 94.5–95.3° (CH_2Cl_2/pentane). IR (KBr): 3098*s*, 3006*s*, 1744*w*, 1348*w*, 1166*m*. ^{1}H-NMR ($CDCl_3$): 2.20–2.30, 2.35–2.55 (2*m*, CH_2); 3.08 (*s*, Me); 3.45–3.55 (*m*, CHCO); 5.00–5.10 (*m*, CHN); 6.70–6.80, 6.95–7.05 (2*m*, CH=CH). ^{13}C-NMR ($CDCl_3$): 176.8; 140.0; 137.75; 64.9; 55.6; 54.5; 40.0. EI-MS: 187 (< 1, M^+), 66 (100).

2.4. N-*Mesylimides* **1b**,**d**,**f**. Pd/C (10%, 1.3 g) was added to a soln. of the corresponding *N*-mesylimide (12.5 mmol) in AcOEt (150 ml). The resulting mixture was stirred overnight under H_2. The Pd/C was filtered off and the filtrate evaporated: pure hydrogenated *N*-mesylimide.

cis-N-*(Methylsulfonyl)cyclohexane-1,2-dicarboximide* (**1b**): Yield 81%. R_f 0.43 (Et_2O). M.p. 160–161° (CH_2Cl_2/Et_2O/hexane). B.p. 157–163°/0.4 Torr. IR (KBr): 1785*w*, 1743*w*, 1723*w*, 1364*w*, 1251*w*, 1175*w*. ^{1}H-NMR ($CDCl_3$): 1.40–1.55, 1.70–2.00 (2*m*, 4 CH_2); 2.90–3.05 (*m*, 2 CHCO); 3.37 (*s*, Me). ^{13}C-NMR ($CDCl_3$): 174.3; 42.25; 40.9; 23.75; 21.85. EI-MS: 231 (5, M^+), 82 (100), 81 (10), 67 (49), 54 (24).

N-*(Methylsulfonyl)bicyclo[2.2.1]heptane-2-*endo,*3-*endo-*dicarboximide* (**1d**): Yield 70%. R_f 0.26 (Et_2O). M.p. 142–143° (CH_2Cl_2/pentane). IR (KBr): 1800*s*, 1733*w*, 1364*w*, 1241*w*, 1174*w*. ^{1}H-NMR ($CDCl_3$): 1.40–1.50, 1.60–1.70 (2*m*, 3 CH_2); 2.85–2.90, 3.15–3.20 (*m*, H–C(1), H–C(2), H–C(3), H–C(4)); 3.37 (*s*, Me). ^{13}C-NMR ($CDCl_3$): 173.6; 48.8; 42.5; 41.85; 40.4; 24.7. EI-MS: 243 (1, M^+), 177 (57), 94 (14), 67 (18), 66 (100).

N-*(Methylsulfonyl)bicyclo[2.2.2]octane-2-*endo,*3-*endo-*dicarboximide* (**1f**): Yield 79%. R_f 0.50 (Et_2O). M.p. 148–149° (CH_2Cl_2/pentane). IR (KBr): 1728*w*, 1369*w*, 1246*w*, 1179*w*. ^{1}H-NMR ($CDCl_3$): 1.50–1.80 (*m*, 4 CH_2); 2.20–2.25, 2.90–3.00 (2*m*, 4 CH); 3.39 (*m*, Me). ^{13}C-NMR ($CDCl_3$): 175.2; 44.0; 42.3; 26.4; 24.5; 21.3. EI-MS: 257 (4, M^+), 108 (100), 107 (21), 80 (41), 79 (12).

3. *Reaction of* N-*Mesylimides with [Ti(OCHMe$_2$)$_4$]*. [Ti(OCHMe$_2$)$_4$] (2.7 mmol) was added to a soln. of the appropriate imide (2.2 mmol) in THF (20 ml) at r.t. under Ar, and the soln. was stirred overnight. A sat. NH_4Cl soln. (75 ml) was added, and the mixture was extracted with CH_2Cl_2 (3 × 30 ml). The combined org. layers were dried (Na_2SO_4) and evaporated: ester **2**.

4. *Reaction of* N-*Mesylimides with Chiral Titanium Derivatives.* [Ti(OCHMe$_2$)$_4$] (1.10 mmol) was added to a soln. of TADDOL (1.15 mmol) in Et_2O (20 ml) at r.t. under Ar. After 3 h, the solvent was removed and the residue dried for 1 additional h under high vacuum. THF (10 ml) was added and the resulting soln. cooled to the required temp. After 10 min, *N*-mesylimide (1.0 mmol) was added as a soln. in THF (10 ml). The resulting mixture was kept at this temp. for several days. Sat. NH_4Cl soln. (20 ml) was added and the pH adjusted to 1–2 with 1N HCl. The mixture was extracted with CH_2Cl_2 (3 × 20 ml) and the org. layer washed with 1N NaOH (2 × 30 ml), dried (Na_2SO_4), and evaporated to give back the TADDOL. The basic aq. layer was acidified with 1N HCl to pH 1–2 and extracted with CH_2Cl_2 (3 × 20 ml) and the combined org. layer dried (Na_2SO_4) and evaporated: sulfonamido esters **2**. The e.r. of **2** were determined by conversion to the hydroxysulfonamides **3** and NMR analysis of the derived *Mosher* esters (see *Scheme 3*). The following anal. and spectroscopic data refer to racemic (*rac*) and enantiomerically pure (e.p.) **2**, as obtained after recrystallization(s) from CH_2Cl_2/hexane (see *Scheme 3*). The racemic samples were prepared by reaction of the *N*-sulfonyldicarboximides **1** with [Ti(OCHMe$_2$)$_4$] in THF at r.t.

Isopropyl cis-*6-[(Methylsulfonyl)aminocarbonyl]cyclohex-3-ene-1-carboxylate* (**2a**): R_f 0.75 (Et_2O). M.p. 104–106° (*rac*), 119.4–120.0° (e.p.). $[\alpha]_D^{r.t.} = +18.00$ ($c = 0.5$, $CHCl_3$). E.r. > 99.5:0.5. IR (KBr): 3273*m*, 3026*s*, 1724*w*, 1325*w*, 1171*w*, 1127*w*. ^{1}H-NMR ($CDCl_3$): 1.20, 1.22 (2*d*, $J = 6.3$, 2 Me); 2.20–2.60 (*m*, 2 CH_2); 2.93–3.04 (*m*, 2 CHCO); 3.26 (*s*, Me); 5.67 (*sept.*, $J = 6.3$, CHO); 5.60–5.74 (*m*, CH=CH); 9.30 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 173.2; 172.5; 125.4; 124.1; 68.8; 41.1; 40.85; 40.2; 26.0; 25.45; 21.55. EI-MS: 289 (< 1, M^+), 230 (16), 152 (27), 124 (67), 122 (20), 96 (12), 80 (30), 79 (100), 78 (21), 77 (13), 43 (17), 41 (11). Anal. calc. for $C_{12}H_{19}NO_5S$: C 49.81, H 6.62, N 4.84; found: C 49.57, H 6.55, N 4.77.

Isopropyl cis-*6-[(Methylsulfonyl)aminocarbonyl]cyclohexane-1-carboxylate* (**2b**): R_f 0.50 (Et_2O). M.p. 96–97° (*rac*), 118.2–119.4° (e.p.). $[\alpha]_D^{r.t.} = -8.80$ ($c = 0.60$, $CHCl_3$). E.r. > 99.5:0.5. IR (KBr): 3207*m*, 1731*w*, 1339*w*, 1175*w*, 1119*w*. ^{1}H-NMR ($CDCl_3$): 1.22, 1.23 (2*d*, $J = 6.3$, 2 Me); 1.30–1.55, 1.55–1.80, 1.80–2.00, 2.05–2.20 (4*m*, $(CH_2)_4CH$); 2.65–2.75, 2.80–2.90 (2*m*, 2 CHCO); 3.28 (*s*, Me); 5.00 (*sept.*, $J = 6.3$, CHO); 8.90 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 173.45; 173.3; 68.4; 43.85; 43.1; 41.1; 26.3; 25.95; 23.5; 23.1; 21.6. EI-MS: 291 (< 1, M^+), 231 (41), 203 (15), 196 (17), 170 (19), 155 (23), 154 (52), 129 (18), 128 (77), 126 (60), 124 (18), 110 (19), 109 (33), 108 (33), 99 (12), 96 (19), 83 (13), 81 (91), 80 (100), 79 (16), 78 (37), 73 (10), 68 (16), 67 (63), 55 (18), 54 (29), 53 (12), 45 (20), 43 (43), 41 (35). Anal. calc. for $C_{12}H_{21}NO_5S$: C 49.47, H 7.26, N 4.81; found: C 49.27, H 7.20, N 4.72.

Isopropyl cis-*2-[(Methylsulfonyl)aminocarbonyl]cyclobutane-1-carboxylate* (**2c**): R_f 0.24 (Et_2O). M.p. 120–121° (*rac*), 138.8–140.2° (e.p.). $[\alpha]_D^{r.t.} = -20.20$ ($c = 0.5$, $CHCl_3$). E.r. > 99.5:0.5. IR (KBr): 3207*m*, 1736*w*, 1326*w*, 1168*w*, 1128*w*. ^{1}H-NMR ($CDCl_3$): 1.24 (*d*, $J = 6.3$, 2 Me); 2.10–2.45 (*m*, 2 CH_2); 3.30 (*s*, Me); 3.35–3.45 (*m*, 2 CHCO); 5.00 (*sept.*, $J = 6.3$, CHO); 8.92 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 172.75; 172.0; 68.75; 41.1; 41.75; 22.25; 21.65; 21.4. EI-MS: 204 (3, $[M - 59]^+$), 169 (100), 127 (14), 55 (24), 54 (21), 53 (11), 43 (20). Anal. calc. for $C_{10}H_{17}O_5S$: C 45.61, H 6.51; found: C 45.43, H 6.34.

*Isopropyl 3-*endo-*[(Methylsulfonyl)aminocarbonyl]bicyclo[2.2.1]heptane-2-*endo-*carboxylate* (**2d**): R_f 0.75 (Et_2O). M.p. 148.4–148.8° (*rac*), 168.6–169.0° (e.p.). $[\alpha]_D^{r.t.} = -15.57$ ($c = 1.9$, $CHCl_3$). E.r. > 99.5:0.5. IR (KBr): 3219*w*, 1701*w*, 1446*w*, 1343*w*, 1227*w*, 1143*w*. ^{1}H-NMR ($CDCl_3$): 1.14, 1.15 (2*d*, $J = 6.2$, 2 Me); 1.30–1.50, 1.55–1.75 (2*m*, 3 CH_2); 2.45–2.60, 2.80–3.00 (2*m*, H–C(1), H–C(2), H–C(3), H–C(4)); 3.22 (*s*, Me); 4.92 (*sept.*, $J = 6.2$, CHO); 9.30 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 172.1; 171.5; 67.7; 47.4; 47.0; 41.0; 40.6; 39.85; 39.4; 23.9; 23.3; 21.7; 21.5. EI-MS: 303 (< 1, M^+), 177 (25), 96 (10), 94 (25), 79 (16), 67 (29), 66 (100), 45 (38), 43 (11), 41 (13). Anal. calc. for $C_{13}H_{21}NO_5S$: C 51.47, H 6.98, N 4.62; found: C 51.27, H 7.12, N 4.59.

*Isopropyl 3-*endo-*[(Methylsulfonyl)aminocarbonyl]bicyclo[2.2.1]hept-5-ene-2-*endo-*carboxylate* (**2e**): R_f 0.72 (Et_2O). M.p. 136.6–137.0° (*rac*), 160.2–160.4° (e.p.). $[\alpha]_D^{r.t.} = -11.51$ ($c = 0.9$, $CHCl_3$). E.r. > 99.5:0.5. IR (KBr): 3231*w*, 3032*s*, 1710*w*, 1445*w*, 1338*w*, 1207*w*, 1133*w*. ^{1}H-NMR ($CDCl_3$): 1.20, 1.21 (2*d*, $J = 6.3$, 2 Me); 1.30–1.50 (*m*, CH_2); 3.10–3.25, 3.30–3.40 (2*m*, H–C(1), H–C(2), H–C(3), H–C(4)); 3.27 (*s*, Me); 4.92 (*sept.*, $J = 6.3$, CHO); 6.15–6.25, 6.35–6.40 (2*m*, CH=CH); 8.91 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 171.7; 171.4; 135.4; 134.6; 68.3; 49.55; 49.3; 48.5; 46.9; 46.6; 40.8; 21.75; 21.65. EI-MS: 301 (< 1, M^+), 176 (14), 91 (15), 66 (100), 45 (16). Anal. calc. for $C_{13}H_{19}NO_5S$: C 51.81, H 6.35, N 4.65; found: C 51.96, H 6.47, N 4.54.

*Isopropyl 3-*endo-*[(Methylsulfonyl)aminocarbonyl]bicyclo[2.2.2]octane-2-*endo-*carboxylate* (**2f**): R_f 0.72 (Et_2O). M.p. 184.4–184.6° (*rac*), 188.6–188.8° (e.p.). $[\alpha]_D^{r.t.} = -2.67$ ($c = 1.8$, $CHCl_3$). E.r. > 99.5:0.5. IR (KBr): 3194*m*, 1703*w*, 1456*w*, 1342*w*, 1222*m*, 1132*w*. ^{1}H-NMR ($CDCl_3$): 1.23 (*d*, $J = 6.2$, 2 Me); 1.40–1.90, 2.00–2.15 (2*m*, 5 CH_2); 2.80–2.85 (*m*, 2 CHCO); 3.31 (*s*, Me); 4.99 (*sept.*, $J = 6.2$, CHO); 8.54 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 172.9; 172.4; 68.2; 45.9; 43.9; 41.2; 27.1; 26.2; 25.65; 25.45; 21.8; 21.7; 21.15; 21.1. EI-MS: 317 (< 1, M^+), 178 (20), 177 (19), 81 (14), 80 (100), 79 (23), 45 (31). Anal. calc. for $C_{14}H_{23}NO_5S$: C 52.98, H 7.30, N 4.41; found: C 52.71, H 7.06, N 4.31.

5.1. *Reduction of Sulfonamido Esters* **2** *with* $LiAlH_4$. A soln. of **2** (1.0 mmol) in Et_2O or THF (5 ml) was added to a suspension of $LiAlH_4$ (8.0 mmol) in Et_2O (10 ml) under Ar at 0°. After 30 min, the mixture was poured into a sat. NH_4Cl soln. (75 ml), and the pH was adjusted to 1–2 with 1N HCl. The mixture was extracted with CH_2Cl_2 (3 × 30 ml), the combined org. layer dried (Na_2SO_4) and evaporated, and the residue chromatographed to yield the expected mesylamino alcohol **3**. If not otherwise stated, the $[\alpha]_D$ values given for **3** refer to those samples which were prepared from recrystallized, enantiomerically pure amido esters **2** (see also *Scheme 3*). The e.r. of **3** were determined by NMR analysis of the corresponding *Mosher* esters.

N-{[cis-*6-(Hydroxymethyl)cyclohex-3-en-1-yl]methyl*}*methanesulfonamide* (**3a**): R_f 0.22 (Et_2O). B.p. 185–190°/0.5 Torr (*rac*). $[\alpha]_D^{r.t.} = +7.60$ ($c = 0.5$, $CHCl_3$). E.r. > 99.5:0.5. IR (film): 3517*w*, 3284*w*, 3022*m*, 1309*w*, 1148*w*. ^{1}H-NMR ($CDCl_3$): 1.80–2.25 (*m*, 2 C=CCH_2CH); 2.71 (*s*, OH); 2.94 (*s*, Me); 3.00–3.25 (*m*, CH_2N); 3.50–3.70 (*m*, CH_2O); 5.48 (*t*, $J = 6.3$, NH); 5.55–5.70 (*m*, CH=CH). ^{13}C-NMR ($CDCl_3$): 125.55; 124.95; 63.0; 44.05; 39.8; 36.6; 34.85; 27.3; 26.55. ^{19}F-NMR ($CDCl_3$, *Mosher* ester): −71.97; −72.02. EI-MS: 219 (< 1, M^+), 124 (33), 122 (25), 108 (72), 106 (27), 105 (10), 95 (16), 94 (59), 93 (100), 92 (30), 91 (51), 82 (17), 81 (15), 80 (25), 79 (78), 78 (33), 77 (38), 69 (11), 68 (12), 67 (15), 44 (22), 42 (12). Anal. calc. for $C_9H_{17}NO_3S$: C 49.29, H 7.81, N 6.39; found: C 49.03, H 7.53, N 6.83.

N-{[cis-*2-(Hydroxymethyl)cyclohex-1-yl]methyl*}*methanesulfonamide* (**3b**): R_f 0.27 (Et_2O). B.p. 210–215°/0.4 Torr (*rac*). $[\alpha]_D^{r.t.} = -3.10$ ($c = 1.00$, $CHCl_3$). E.r. 92:8. IR (film): 3512*w*, 3280*w*, 1450*m*, 1311*w*, 1152*w*. ^{1}H-NMR ($CDCl_3$): 1.30–1.60 (*m*, 2 CH_2CH_2); 1.80–2.05 (*m*, 2 CH); 2.25 (*s*, OH); 2.94 (*s*, Me); 3.00–3.20 (*m*, CH_2N); 3.50–3.80 (*m*, CH_2O); 5.34 (*t*, $J = 6.2$, NH). ^{13}C-NMR ($CDCl_3$): 63.9; 44.65; 39.9; 39.0; 37.8; 27.3; 27.2; 23.8; 23.35. ^{19}F-NMR ($CDCl_3$, *Mosher* ester): −71.58; −71.87. EI-MS: 203 (3, $[M - 18]^+$), 167 (26), 150 (12), 149 (100), 142 (24), 129 (11), 125 (18), 124 (42), 113 (15), 112 (23), 108 (29), 104 (18), 96 (40), 95 (64), 93 (11), 83 (22), 82

(13), 81 (49), 79 (23), 76 (12), 71 (43), 70 (50), 69 (26), 68 (25), 67 (62), 57 (79), 56 (27), 55 (75), 54 (25), 53 (16), 44 (13), 43 (58), 42 (74), 41 (83).

N-{*[cis-2-(Hydroxymethyl)cyclobut-1-yl]methyl*}*methanesulfonamide* (**3c**): R_f 0.31 (Et_2O). B.p. 230–235°/0.4 Torr (*rac*). $[\alpha]_D^{r.t.} = -17.60$ ($c = 0.05$, $CHCl_3$). E.r. > 99.5:0.5. IR (film): 3499*w*, 3282*w*, 1314*w*, 1150*w*. ^{1}H-NMR ($CDCl_3$): 1.40–1.70, 1.90–2.15 (2*m*, CH_2CH_2); 2.50 (*s*, OH); 2.60–2.85 (*m*, 2 CH); 2.94 (*s*, Me); 3.09–3.32 (*m*, CH_2N); 3.62–3.86 (*m*, CH_2O); 5.73 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 62.6; 44.1; 39.8; 37.6; 36.2; 22.1; 20.05. ^{19}F-NMR ($CDCl_3$, *Mosher* ester): −71.51; −71.84. EI-MS: 175 (2, $[M - 18]^+$), 134 (27), 114 (40), 108 (49), 97 (13), 96 (60), 84 (13), 81 (17), 80 (23), 78 (43), 70 (18), 69 (22), 68 (52), 67 (66), 65 (11), 58 (19), 57 (88), 56 (92), 55 (26), 54 (19), 53 (15), 43 (24), 42 (27), 41 (82), 30 (100). Anal. calc. for $C_{13}H_{19}NO_3S$: C 51.81, H 6.35, N 4.65; found: C 51.96, H 6.47, N 4.54.

N-{*[3-endo-(Hydroxymethyl)bicyclo[2.2.1]hept-2-endo-yl]methyl*}*methanesulfonamide* (**3d**): R_f 0.30 (Et_2O). B.p. 245–250°/0.4 Torr (*rac*). $[\alpha]_D^{r.t.} = -0.49$ ($c = 3.25$, $CHCl_3$). E.r. 97.5:2.5. IR (film): 3504*w*, 3283*w*, 1314*w*, 1151*w*. ^{1}H-NMR ($CDCl_3$): 1.20–1.50 (*m*, $(CH_2)_2CHCH_2$); 2.00–2.30 (*m*, 4 CH); 2.92 (*s*, OH); 2.93 (*s*, Me); 3.00–3.15, 3.15–3.25 (2*m*, CH_2N); 3.55–3.80 (*m*, CH_2O); 6.90–6.95 (*m*, NH). ^{13}C-NMR ($CDCl_3$): 61.4; 42.65; 41.9; 41.2; 40.9; 40.5; 39.6; 39.45; 22.5; 22.2. ^{19}F-NMR ($CDCl_3$, *Mosher* ester): −71.76; −72.00. EI-MS: 233 (< 1, M^+), 154 (71), 137 (28), 136 (36), 120 (16), 109 (19), 108 (72), 107 (41), 97 (26), 96 (15), 94 (18), 93 (29), 92 (14), 91 (28), 81 (39), 80 (52), 79 (100), 78 (14), 77 (16), 70 (13), 69 (12), 68 (16), 67 (54), 66 (66), 65 (10), 57 (27), 56 (14), 55 (14), 53 (10), 41 (29).

N-{*[3-endo-(Hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-endo-yl]methyl*}*methanesulfonamide* (**3e**): R_f 0.24 (Et_2O). M.p. 107–108° (CH_2Cl_2/Et_2O/hexane; *rac*). $[\alpha]_D^{r.t.} = -20.97$ ($c = 3.0$, $CHCl_3$). E.r. 98.5:1.5. IR (KBr): 3507*w*, 3159*w*, 3005*s*, 1297*w*, 1149*w*. ^{1}H-NMR ($CDCl_3$): 1.30–1.55 (*m*, CH_2CH); 2.19 (*s*, OH); 2.40–2.60, 2.75–2.95, 3.00–3.15 (3*m*, 4 CH, Me, CH_2O); 3.20–3.45, 3.55–3.75 (2*m*, CH_2O); 5.85–6.00 (*m*, NH); 6.05–6.15 (*m*, CH=CH). ^{13}C-NMR ($CDCl_3$): 135.35; 134.8; 63.2; 49.6; 47.2; 46.4; 44.8; 43.8; 42.85; 39.75. ^{19}F-NMR ($CDCl_3$, *Mosher* ester): −71.76; −71.95. EI-MS: 232 (< 1, M^+), 147 (36), 145 (15), 67 (12), 66 (13), 66 (100). Anal. calc. for $C_{10}H_{17}NO_3S$: C 51.92, H 7.41, N 6.06; found: C 52.18, H 7.36, N 6.00.

N-{*[3-endo-(Hydroxymethyl)bicyclo[2.2.2]oct-2-endo-yl]methyl*}*methanesulfonamide* (**3f**): R_f 0.28 (Et_2O). M.p. 70–71° (CH_2Cl_2/pentane; *rac*). $[\alpha]_D^{r.t.} = -4.19$ ($c = 2.6$, $CHCl_3$). E.r. 99:1. IR (film): 3466*w*, 3177*w*, 1301*w*, 1145*w*. ^{1}H-NMR ($CDCl_3$): 1.25–1.55, 2.00–2.20 (2*m*, 2 $(CH_2)_2CHCH$); 2.40 (*s*, OH); 2.95 (*s*, Me); 3.00–3.20, 3.35–3.50 (2*m*, CH_2N); 3.60–3.75, 3.80–4.00 (2*m*, CH_2O); 6.00–6.25 (*m*, NH). ^{13}C-NMR ($CDCl_3$): 64.0; 44.2; 40.8; 39.8; 39.0; 28.85; 27.9; 26.45; 26.4; 20.9; 20.6. ^{19}F-NMR ($CDCl_3$, *Mosher* ester): −71.81; −71.98. EI-MS: 248 (< 1, $[M + 1]^+$), 168 (82), 151 (42), 149 (25), 139 (14), 123 (13), 122 (89), 121 (71), 110 (11), 109 (39), 108 (54), 107 (20), 105 (13), 96 (13), 95 (24), 94 (51), 93 (88), 92 (10), 91 (31), 81 (41), 80 (100), 79 (99), 78 (13), 77 (21), 68 (12), 67 (47), 57 (11), 55 (17), 41 (14).

5.2. *Reductive Cleavage of Mesyl Group.* According to [23], sodium bis(2-methoxyethoxy)aluminium hydride (*Red-Al*; 109.3 mmol) was added to a soln. of mesylamino alcohol **3** (13.7 mmol) in toluene (300 ml) under Ar. The resulting soln. was refluxed for 2 d. After cooling to r.t., 10 ml of 1N NaOH were added, and this was followed by the addition of anh. Na_2SO_4. After filtration, the filtrate was evaporated and the residue distilled: amino alcohol **4**.

cis-*6-(Aminomethyl)cyclohex-3-enemethanol* (**4a**): B.p. 145–150°/0.5 Torr. IR (film): 3296*w*, 3021*m*, 2897*w*, 1043*m*. ^{1}H-NMR ($CDCl_3$): 1.80–2.25 (*m*, 2 C=CCH_2CH); 2.63, 2.77 (2*dd*, $J = 3.5$, 12.4, 8.3, 12.4, CH_2N); 2.95–3.75 (*m*, CH_2OH, NH_2); 5.50–5.70 (*m*, CH=CH). ^{13}C-NMR ($CDCl_3$): 126.3; 124.7; 63.7; 42.3; 38.75; 38.6; 29.4; 26.0. EI-MS: 141 (9, M^+), 124 (22), 123 (21), 120 (12), 119 (16), 111 (16), 110 (14), 106 (19), 105 (11), 104 (10), 95 (14), 94 (32), 93 (61), 92 (28), 91 (75), 83 (12), 82 (21), 80 (38), 79 (100), 78 (43), 77 (60), 70 (13), 69 (22), 68 (44), 67 (20), 66 (13), 64 (18), 58 (18), 57 (29), 56 (19), 55 (17), 53 (17), 50 (15), 44 (42), 43 (47), 42 (13), 41 (32).

cis-*2-(Aminomethyl)cyclohexanemethanol* (**4b**): B.p. 145–150°/0.5 Torr. IR (film): 3374*m*, 1029*m*. ^{1}H-NMR ($CDCl_3$): 1.10–1.85 (*m*, 2 CH_2CH_2CH); 1.90 (*s*, OH); 2.60 (br. *s*, NH_2); 3.50–3.60, 3.65–3.80 (2*m*, CH_2N, CH_2O). ^{13}C-NMR ($CDCl_3$): 64.25; 39.85; 27.20; 24.05. EI-MS: 126 (< 1, $[M - 17]^+$), 111 (11), 97 (18), 96 (100), 95 (72), 93 (16), 83 (15), 82 (29), 81 (60), 79 (15), 69 (17), 68 (22), 67 (58), 57 (12), 55 (24), 54 (12), 41 (13).

5.3. *Esterification of Amino Alcohols* **4**. At 0°, 3,5-dinitrobenzoyl chloride (3.1 mmol) was added to a soln. of amino alcohol **4** (1 mmol) and Et_3N (5 mmol) in CH_2Cl_2 (10 ml). After 3 h, the mixture was quenched with 1N HCl (10 ml) and extracted with CH_2Cl_2 (2 × 30 ml). The combined org. layer was washed with cold 1N NaOH (10 ml), dried (Na_2SO_4) and evaporated and the resulting residue chromatographed: amido esters (rather labile ester group). Only the bis(3,5-dinitrobenzoyl) derivative of **4a** was isolated and purified. In all other cases, the dinitrobenzoate group was saponified, and the resulting (hydroxymethyl)-dinitrobenzamide characterized (see **4a′**, **b′**, **d′**, **e′** in *Sect. 5.4*).

{cis-{*[6-(3,5-Dinitrobenzoyl)amino]methyl*}*cyclohex-3-en-1-yl*}*methyl 3,5-Dinitrobenzoate* (*Bis(3,5-dinitrobenzoyl) Derivative of* **4a**): Yield 73%. R_f 0.41 (pentane/AcOEt 7:3). M.p. 157–159° (AcOEt/pentane; *rac*).

$[\alpha]_D^{r.t.} = -5.20$ ($c = 0.15$, $CHCl_3$). IR (film): 3419*m*, 3101*m*, 3069*m*, 1728*m*, 1666*m*, 1542*w*, 1344*m*. ^{1}H-NMR (CD_3COCD_3): 2.10–2.75 (*m*, 2 CH_2CH); 3.30–3.60, 3.65–3.90 (2*m*, CH_2N); 4.35–4.80 (*m*, CH_2O); 5.74 (*s*, CH=CH); 8.62 (br. *s*, NH); 9.10–9.25 (*m*, arom. H). ^{13}C-NMR ((D$_6$)DMSO): 162.8; 162.3; 148.6; 148.3; 137.1; 132.9; 129.1; 127.6; 125.7; 125.3; 122.7; 120.9; 67.0; 40.4; 33.8; 33.7; 27.5; 26.2. EI-MS: 529 (< 1, M^+), 195 (33), 149 (28), 106 (38), 105 (15), 103 (13), 93 (27), 92 (16), 91 (44), 79 (22), 78 (25), 77 (26), 76 (11), 75 (100), 74 (34), 63 (18), 58 (11), 53 (12), 50 (13), 44 (41), 43 (92).

5.4. *Hydrolysis of Dinitrobenzoate Derivatives.* The dinitrobenzoate group (see *5.3*) was cleaved to give the (hydroxymethyl)-dinitrobenzamides **4′**: NaOH (5.1 mmol) was added to a mixture of dinitrobenzoyl derivatives (1 mmol; see *5.3*) in THF (10 ml) and H_2O (5 ml). The mixture was stirred overnight at r.t. and extracted with CH_2Cl_2 (2 × 10 ml). The combined org. layer was dried (Na_2SO_4) and evaporated and the resulting residue chromatographed: **4′**.

N-{[cis-*6-(Hydroxymethyl)cyclohex-3-en-1-yl]methyl*}*-3,5-dinitrobenzamide* (**4a′**): Yield 59% (from **4a**). R_f 0.53 (pentane/AcOEt 1:1). M.p. 125–127° (CH_2Cl_2/pentane; *rac*). $[\alpha]_D^{r.t.} = +14.67$ ($c = 0.3$, $CHCl_3$). E.r. 71.5:28.5. HPLC (*Chiracel OD*, hexane/i-PrOH (5%), 1 ml/min): t_R 121.4, 140.3 (major). IR (film): 3340*m*, 3206*m*, 3105*m*, 3034*s*, 1649*w*, 1536*w*, 1340*w*. ^{1}H-NMR ($CDCl_3$): 1.80–2.35 (*m*, 2 CH_2CH); 3.30–3.45, 3.55–3.90 (2*m*, CH_2N, CH_2O, OH); 5.55–5.65 (*m*, CH=CH); 8.48 (*t*, $J = 5.6$, NH); 9.00–9.10 (*m*, arom. H). ^{13}C-NMR ($CDCl_3$): 163.1; 148.5; 137.9; 127.4; 125.6; 125.0; 120.8; 63.7; 41.1; 37.2; 34.2; 28.1; 26.3. EI-MS: 335 (11, M^+), 225 (23), 224 (36), 208 (14), 194 (63), 149 (35), 124 (10), 107 (11), 106 (100), 105 (10), 102 (13), 94 (20), 93 (89), 92 (21), 91 (56), 81 (10), 80 (13), 79 (31), 78 (30), 77 (34), 75 (44), 67 (11). Anal. calc. for $C_{15}H_{17}N_3O_6$: C 53.73, H 5.11, N 12.53; found: C 53.61, H 5.32, N 12.42.

N-{[cis-*2′-(Hydroxymethyl)cyclohex-1-yl]methyl*}*-3,5-dinitrobenzamide* (**4b′**): Yield 49% (from **4b**). R_f 0.49 (pentane/AcOEt 1:1). M.p. 119–121° (CH_2Cl_2/pentane; *rac*). $[\alpha]_D^{r.t.} = +6.00$ ($c = 0.5$, $CHCl_3$). E.r. 95:5. HPLC (*Chiracel OD*, hexane/i-PrOH (5%), 1 ml/min): t_R 143.6 (major), 158.5. IR (film): 3311*m*, 3103*m*, 1649*w*, 1542*w*, 1344*w*. ^{1}H-NMR ($CDCl_3$): 1.35–1.60 (*m*, 2 CH_2CH_2); 1.95–2.05, 2.15–2.20 (2*m*, CHCH); 3.10 (*s*, OH); 3.45–3.60, 3.70–3.80 (2*m*, CH_2N, CH_2O); 8.20 (*s*, NH); 9.00–9.10 (*m*, arom. H). ^{13}C-NMR ($CDCl_3$): 162.5; 148.5; 138.1; 127.2; 120.7; 64.2; 41.4; 40.0; 36.0; 28.7; 26.4; 24.2; 23.1. EI-MS: 337 (9, M^+), 225 (28), 224 (20), 212 (16), 195 (45), 149 (33), 142 (13), 125 (22), 108 (78), 103 (15), 96 (39), 95 (100), 93 (23), 82 (11), 81 (28), 80 (10), 79 (22), 75 (60), 69 (14), 68 (12), 67 (50), 55 (29), 54 (12), 41 (24). Anal. calc. for $C_{15}H_{19}N_3O_6$: C 53.41, H 5.68, N 12.46; found: C 53.19, H 5.66, N 12.37.

N-{[*3*-endo-*(Hydroxymethyl)bicyclo[2.2.1]hept-2*-endo-*yl]methyl*}*-3,5-dinitrobenzamide* (**4d′**): Yield 43% (from **4d**). R_f 0.52 (pentane/AcOEt 1:1). M.p. 163–165° (CH_2Cl_2/pentane; *rac*). $[\alpha]_D^{r.t.} = -25.17$ ($c = 0.6$, $CHCl_3$). E.r. 95:5. HPLC (*Chiracel OD*, hexane/i-PrOH (5%), 1 ml/min): t_R 82.1 (major), 102.6. IR (film): 3310*m*, 3100*m*, 1647*w*, 1540*w*, 1340*w*. ^{1}H-NMR ($CDCl_3$): 1.20–1.65, 1.95–2.40 (2*m*, CH_2CH_2, $CH_2(CH)_4$, OH); 3.25–3.34, 3.90–4.20 (2*m*, CH_2N, CH_2O); 8.50–8.55 (*m*, NH); 9.00–9.15 (*m*, arom H). ^{13}C-NMR ($CDCl_3$): 161.8; 148.7; 138.6; 127.2; 120.6; 62.6; 43.4; 41.9; 41.3; 41.2; 40.0; 39.0; 31.0; 22.8; 22.6. EI-MS: 349 (9, M^+), 212 (14), 195 (75), 149 (41), 138 (100), 137 (12), 121 (12), 120 (100), 110 (16), 109 (25), 108 (22), 107 (63), 105 (15), 103 (14), 95 (14), 94 (23), 93 (15), 92 (26), 91 (31), 81 (26), 80 (22), 79 (74), 78 (10), 77 (13), 75 (49), 67 (28), 66 (29), 57 (13), 41 (18).

N-{[*3*-endo-*(Hydroxymethyl)bicyclo[2.2.1]hept-5-en-2*-endo-*yl]methyl*}*-3,5-dinitrobenzamide* (**4e′**): Yield 41% (from **4e**). R_f 0.34 (pentane/AcOEt 1:1). M.p. 164–166° (CH_2Cl_2/pentane; *rac*). $[\alpha]_D^{r.t.} = -2.00$ ($c = 0.4$, $CHCl_3$). E.r. 86:14. HPLC (*Chiracel OD*, hexane/i-PrOH (5%), 1 ml/min): t_R 99.5 (major), 121.5. IR (film): 3364*m*, 3097*s*, 1630*m*, 1543*w*, 1344*w*. H-NMR (CD_3COCD_3): 1.30–1.45 (*m*, CH_2CH); 2.45–2.60, 2.90–2.95 (2*m*, 2 CHCH); 3.20–3.30, 3.40–3.60 (2*m*, CH_2N, CH_2O); 4.12 (*t*, $J = 4.7$, OH); 6.15–6.20, 6.20–6.30 (2*m*, CH=CH); 8.70–8.75 (*m*, NH); 9.05 (*s*, arom. H). ^{13}C-NMR (CD_3COCD_3): 162.5; 149.4; 139.1; 135.9; 135.8; 127.9; 121.2; 62.7; 49.5; 47.1; 46.8; 45.5; 42.7; 40.9. EI-MS: 347 (< 1, M^+), 264 (11), 195 (13), 149 (11), 75 (14), 66 (100).

6. *Reaction of* rac-N-*Mesyllactam* **5**/ent-**5** *with Chiral Titanium Derivatives.* [Ti(OCHMe$_2$)$_4$] (1.20 mmol) was added to a soln. of TADDOL (1.20 mmol) in Et_2O (20 ml) at r.t. under Ar. After 3 h, the mixture was evaporated and the residue dried for 1 additional h. THF (10 ml) was added and the resulting soln. cooled to −20°. After 10 min, *rac*-**5** (2.4 mmol) in THF (10 ml) was added. The resulting mixture was kept at −20° for 35 days. Sat. NH_4Cl (20 ml) was added, the mixture extracted with CH_2Cl_2 (3 × 20 ml), the org. layer dried (Na_2SO_4) and evaporated, and the resulting residue chromatographed: *ent*-**5** and *isopropyl 4-[(Methylsulfonyl)amino]cyclopent-2-ene-1-carboxylate* (**6**). **6**: R_f 0.81 (Et_2O). M.p. 61–63° (CH_2Cl_2/pentane, *rac*). B.p. 215–220°/0.4 Torr (*rac*). $[\alpha]_D^{r.t.} = -28.27$ ($c = 1.0$, $CHCl_3$). E.r. 63:37. GC (γ-CD; 0.9 KPa, 155° (for 5 min), rate 0.1°/min, 190° (for 10 min)): t_R 140.84 (**6**), 144.71 (*ent*-**6**). IR (film): 3620*m*, 3550*m*, 3281*w*, 3023*s*, 1718*w*, 1437*m*, 1323*w*, 1199*m*, 1151*m*. ^{1}H-NMR ($CDCl_3$): 1.19, 1.20 (2*d*, $J = 6.3$, 2 Me); 1.98, 2.42 (2*dt*, $J = 3.45$, 13.9, 8.3, 13.9, CH_2); 2.95 (*s*, Me); 3.35–3.45 (*m*, CHCO); 4.45–4.55 (*m*, CHN); 4.94 (*sept.*, $J = 6.3$, CHO); 5.12 (*d*, $J = 9.7$, NH); 5.85–5.92 (*m*, CH=CH). ^{13}C-NMR ($CDCl_3$): 173.65; 133.9; 132.4; 68.7; 58.65; 49.45; 41.6; 34.65; 21.5. EI-MS: 204 (1,

$[M - 43]^+$), 168 (27), 160 (27), 126 (27), 108 (13), 96 (11), 82 (25), 81 (22), 80 (85), 67 (10), 66 (100), 53 (16), 43 (76), 41 (14). Anal. calc. for $C_{10}H_{17}NO_4S$: C 48.57, H 6.93, N 5.66; found: C 48.60, H 6.90, N 5.61.

7.1. *Absolute Configuration of Sulfonamido Ester* **2a** *and* **2b**. $[Ti(OCHMe_2)_4]$ (11.50 mmol) was added to a soln. of TADDOL (12.0 mmol) in Et_2O (50 ml) at r.t. under Ar. After 3 h, the solvent was evaporated and the residue dried for 1 additional h. THF (80 ml) was added and the resulting soln. cooled to −20°. After 10 min, the anhydride 7 (10.0 mmol) in THF (20 ml) was added. The resulting mixture was kept at −20° for 10 days. Sat. NH_4Cl soln. (80 ml) was added and the pH adjusted to 1–2 with 1N HCl. The mixture was extracted with CH_2Cl_2 (3 × 50 ml) and the org. layer washed with 1N NaOH (2 × 50 ml), dried (Na_2SO_4), and evaporated: TADDOL. The basic aq. layer was acidified with 1N HCl to pH 1–2, the mixture extracted with CH_2Cl_2 (3 × 50 ml), and the org. layer dried (Na_2SO_4) and evaporated: *(1S,6R)-6-(isopropoxycarbonyl)cyclohex-3-ene-1-carboxylic acid* (**8**). B.p. 155–160°/0.5 Torr (*rac*). $[\alpha]_D^{r.t.} = +5.46$ ($c = 1.85$, $CHCl_3$). IR (film): 2986*w*, 1738*w*, 1189*w*. ^{1}H-NMR ($CDCl_3$): 1.20 (*d*, $J = 6.2$, 2 Me); 2.25–2.65, 3.00–3.10 (2*m*, 2 CH_2CHCO); 5.02 (*sept.*, $J = 6.2$, CHO); 5.60–5.75 (*m*, CH=CH); 11.0 (br. *s*, OH). ^{13}C-NMR ($CDCl_3$): 179.7; 172.5; 125.25; 124.9; 68.2; 39.7; 25.85; 21.6. EI-MS 212 (< 1, M^+), 153 (14), 152 (17), 124 (56), 80 (13), 79 (100), 77 (13), 43 (12).

According to [25], oxalyl chloride (7.0 mmol) was added to a soln. of **8** (5 mmol) in CH_2Cl_2 at 0°. The resulting mixture was stirred at r.t. for 3 h. The solvent was removed under high vacuum to yield the acyl chloride derivative. IR ($CHCl_3$): 3020*s*, 1800*w*, 1760*w*, 1205*m*, 1110*m*. The resulting residue was dissolved in 10 ml of dry THF and divided into two portions.

First portion: BuLi (2.5 mmol) was added to a soln. of methanesulfonamide (2.5 mmol) in THF (20 ml) at −78° under Ar. The resulting milky suspension was warmed to r.t., and after 20 min at r.t., the mixture was cooled to −78° and the acyl chloride derivative added (2.5 mmol in 5 ml of THF, see above). The temp. was allowed to reach to r.t. overnight. Sat. NH_4Cl soln. (10 ml) was added and the pH adjusted to 1–2 with 1N HCl. The mixture was extracted with CH_2Cl_2 (3 × 20 ml) and the org. layer washed with H_2O (2 × 10 ml), dried (Na_2SO_4), and evaporated: **2a**. Pd/C (10%; 25 mg) was added to a soln. of **2a** (0.9 mmol) in AcOEt (20 ml). The resulting mixture was stirred overnight under H_2. Pd/C was filtered off and the filtrate evaporated: pure **2b**.

Second portion: According to [25], the acyl chloride derivative (2.5 mmol in 5 ml of THF, see above) was added to $NaBH_4$ (5.0 mmol) in EtOH (15 ml) at −40° under Ar. The mixture was stirred at −40° for 3 h. Then 4N H_2SO_4 (5 ml) was added, the mixture extracted with CH_2Cl_2 (3 × 50 ml), the combined org. layer washed with H_2O (2 × 10 ml), dried (Na_2SO_4), and evaporated, and the residue chromatographed: *isopropyl (1R,6S)-6-hydroxymethyl)cyclohex-3-ene-1-carboxylate* (**9**): R_f 0.60 (hexane/AcOEt 1:2). E.r. 91:9 (^{19}F-NMR). ^{1}H-NMR ($CDCl_3$): 1.20, 1.22 (2*d*, $J = 6.3$, 2 Me); 1.80–2.80 (*m*, 2 CH_2CHCO, OH); 3.40–3.70 (*m*, CH_2O); 4.97 (*sept.*, $J = 6.3$, CHO); 5.50–5.65 (*m*, CH=CH). ^{19}F-NMR ($CDCl_3$, *Mosher* ester): −72.07; −72.10.

According to [25], camphorsulfonic acid (0.02 mmol) was added to a soln. of **9** (1.4 mmol) in toluene (100 ml) at r.t. The resulting soln. was refluxed with azeotropic removal of i-PrOH for 5 h (*Dean-Stark* apparatus). The solvent was removed and the residue filtered through silica gel (25 g) using AcOEt (200 ml). After evaporation, the residue was distilled: *(1S,6R)-8-oxabicyclo[4.3.0]non-3-ene-7-one* (**10**) [9d]. R_f 0.74 (hexane/AcOEt 1:1). B.p. 130–135°/0.5 Torr. $[\alpha]_D^{r.t.} = +46.7$ ($c = 1.0$, $CHCl_3$). IR (film): 3034*m*, 1770*w*, 1208*w*, 1144*w*, 1022*w*. ^{1}H-NMR ($CDCl_3$): 1.70–1.95, 2.10–2.85 (2*m*, 2 CH_2CHCO); 3.96, 4.26 (2*dd*, $J = 2.0$, 8.8, 5.1, 8.8, CH_2O); 5.55–5.75 (*m*, CH=CH). ^{13}C-NMR ($CDCl_3$): 178.9; 124.85; 124.7; 72.6; 37.0; 31.7; 24.45; 21.8. EI-MS: 138 (51, M^+), 197 (55), 93 (100), 92 (16), 91 (34), 80 (20), 79 (85), 78 (16), 77 (63), 66 (17), 53 (11), 51 (11).

7.2. *Absolute Configuration of* N-*Mesyllactam* ent-**5** *and Mesylamino Ester* **6**. Compound *ent*-**5** was prepared from (1*S*,4*R*)-2-azabicyclo[2.2.1]hept-5-en-3-one according to the procedure of *2.3*: *(1S,4R)-N-(methylsulfonyl)-2-azabicyclo[2.2.1]hept-5-en-3-one* (*ent*-**5**). M.p. 88.4–88.6° (CH_2Cl_2/pentane). $[\alpha]_D^{r.t.} = +204.7$ ($c = 1.52$, $CHCl_3$). E.r. > 99.5:0.5.

Compound *ent*-**5** (1.4 mmol) was ring-opened with $[Ti(OCHMe_2)_4]$ (1.6 mmol) at r.t. over 3 days to give *ent*-**6** (see above): M.p. 86.8–87.4° (CH_2Cl_2/pentane). $[\alpha]_D^{r.t.} = +114.96$ ($c = 1.25$, $CHCl_3$). E.r. > 99.5:0.5.

8. *Crystal-Structure Analysis of the Camphanate of* **3e**. *Synthesis*: A soln. of camphanoyl chloride (0.18 mmol) in CH_2Cl_2 (2 ml) was added at r.t. to the soln. of **3e** (0.15 mmol) and Et_3N (0.23 mmol) in CH_2Cl_2 (5 ml). The mixture was stirred overnight and then hydrolyzed with H_2O (20 ml) and extracted with CH_2Cl_2 (2 × 20 ml). The org. layer was dried (Na_2SO_4) and evaporated and the residue chromatographed: 84% of the camphanate of **3e**. R_f 0.53 (Et_2O). ^{1}H-NMR ($CDCl_3$): 6.21, 6.15 (2*m*, CH=CH); 4.79 (*t*, $J = 3.1$, NH); 4.17, 3.85 (*dd*, $J = 3.8$, 5.3, CH_2O); 2.97 (*s*, SO_2Me); 2.78–3.06 (*m*, CH_2N, CH); 2.35–2.62, 1.86–2.11, 1.62–1.80, 1.50–1.60, 1.32–1.40 (5*m*, 3 CH_2, 3 CH); 1.11 (*s*, Me); 1.06 (*s*, Me); 0.98 (*s*, Me).

Structure: Recrystallization of the camphanate of **3e** from CH_2Cl_2 gave a suitable crystal for X-ray analysis. Determination of the parameters and collection of the reflection intensities were performed on an *Enraf-Nonius-*

CAD4 four-circle diffractometer (graphite monochromatized CuK_α radiation, $\lambda = 1.5418$ Å) at 295 K. Orthorhombic, space group $P2_12_12_1$, $a = 9.263$ (1) Å, $b = 10.222$ (1) Å, $c = 21.786$ (1) Å, $V = 2062.8$ (4) Å^3, $Z = 4$, $\rho_{calc.} = 1.32$ gcm^{-3}, $\mu = 1.70$ mm^{-1}, $F(000) = 880$. Number of reflections measured 1512 (scan type ω/θ, $0 < 2\theta < 110°$); 1512 unique reflections, of which 1453 with $I > 2\sigma(I)$ were used for the determination (direct method, SHELXS 86 [38]). The non-H-atoms were refined anisotropically (SHELXS PLUS). The H-atoms were located from differential *Fourier* syntheses and refined isotropically. Neither extinction nor absorption corrections were applied. The refinement converged at $R = 0.039$ ($wR2 = 0.047$, number of variables 279).

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