Tetrahedron Vol. 43, No. 9, pp. 1969–2004, 1987
Printed in Great Britain.

0040–4020/87 $5.00+.00
Pergamon Journals Ltd.

TETRAHEDRON REPORT NUMBER 216

CAMPHOR DERIVATIVES AS CHIRAL AUXILIARIES IN ASYMMETRIC SYNTHESIS*

WOLFGANG OPPOLZER
Département de Chimie Organique, Université de Genève, CH-1211 Genève, Switzerland

(*Received* 5 *January* 1987)

CONTENTS

* Dedicated to Professor Vladimir Prelog on the occasion of his 80th birthday.

1. INTRODUCTION

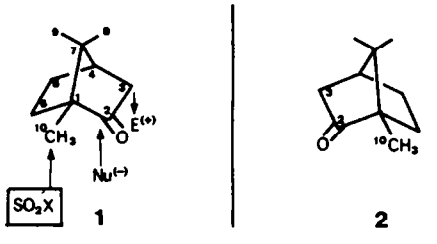
The abundance, crystallinity and manifold transformations of (+)-camphor (**1**) have attracted considerable interest throughout the history of organic chemistry.

By means of various rearrangements and functionalizations at C(3), C(5), C(8), C(9), and C(10), as well as cleavage of the C(1)/C(2) and C(2)/C(3) bonds, camphor has served as a fascinatingly versatile starting material for the syntheses of enantiomerically pure natural products. This chemistry which entails incorporation of the camphor topicity into the target molecules has been reviewed recently.[1]

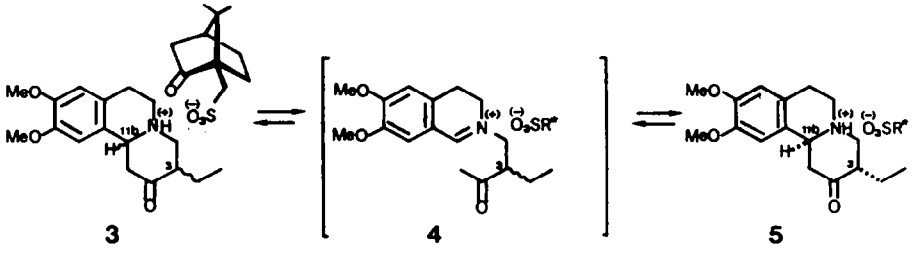
This report, on the other hand, addresses the issue of non-destructive chirality transfer from derivatives of (+)- and (−)-camphor; the chiral information is provided either by covalently bound auxiliary groups or by means of reagents or catalysts.

Selective C-10-sulfonation of camphor, discovered as early as 1898,[2] spawned the classical use of camphor-10-sulfonic acid as a resolving agent for racemic bases via diastereomeric salts.[3] A most spectacular example is the transformation of a racemic diastereoisomer mixture **3** into the single isomer (−)-**5** (85% yield) on heating with (−)-camphor-10-sulfonic acid ($R*SO_3H$) in ethyl acetate[4] (Scheme 2).

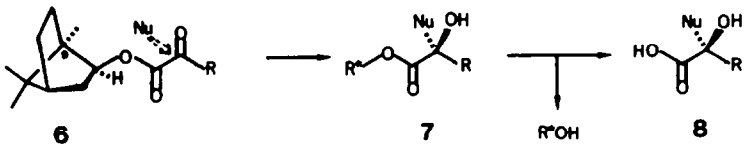
In this case, the chiral acid served simultaneously a threefold purpose: equilibrations at C(11b) (via a reversible Mannich reaction **3** ⇆ **4** ⇆ **5**) and at C(3) (via reversible enol formation) as well as



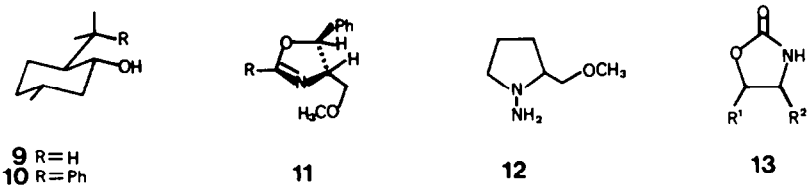
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

the selective precipitation of the least soluble salt of (−)-**5**. Despite its elegance this example remains unique and lacks generality.

Early attempts to effect stereoface-selective addition to substrates carrying a removable ester auxiliary (**6** → **7** → **8**) date back to 1900. Six years later McKenzie found face differentiations on reductions and Grignard reactions (Nu- = RMgX, [H-],) of bornyl (and menthyl) esters **6** → **7**[5] (Scheme 3).

Nevertheless, it was not before 1955 that Prelog rationalized these asymmetric inductions on the basis of preferred conformations and steric repulsions in the transition state[6] (e.g. as depicted in **6**). Although atrolactic esters were obtained in up to 69% d.e. by analogous additions to glyoxalates derived from more complex chiral alcohols only modest inductions could be observed with bornyl esters **6**.[6] This holds also for Reformatsky reactions of bornyl bromoacetates[7] (< 15% d.e.) and aldolizations of bornyl esters[8] (< 36% d.e.) which were reported over the period 1946–1964. The next 15 years witnessed significant progress in asymmetric synthesis, most of it based on derivatives of menthol (**9**, **10**), and oxazolines **11**[9] (Scheme 4). Around 1980 the field of asymmetric induction started to expand at an ever increasing rate with the development of chiral templates (such as **12** and **13**), obtained either from "natural" sources (e.g. amino acids, tartaric acid, sugars, pinene) or of "unnatural" origin (e.g. phosphines, diols, α-alkoxy and α-hydroxy ketones).[9]

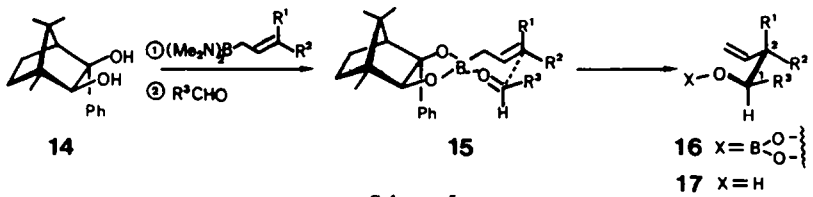
Simultaneously, the advantageous topological bias of the camphor skeleton became apparent owing to the logical and intuitive design of conformationally rigid derivatives where one diastereotopic face of a reactive π-bond is sterically shielded.

2. C(2)/C(3)-FUNCTIONALIZED BORNANE AUXILIARIES

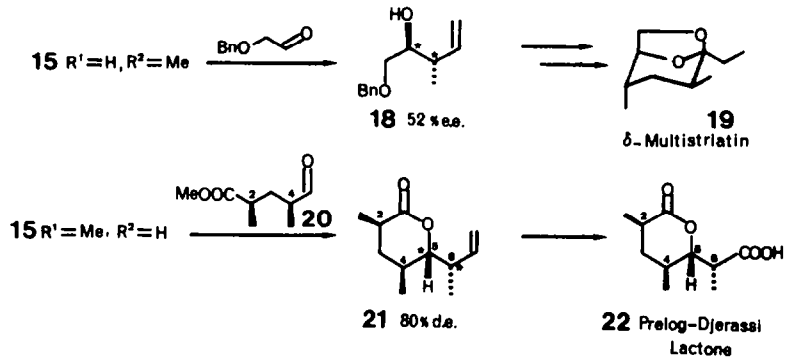
2.1. *Boronates of 3-phenyl-3-hydroxy-isoborneol*

2.1.1. *Additions of allylboronates to aldehydes.* The first example of a 2,3-substituted camphor derived chiral auxiliary was published by Hoffmann in 1978[10] (Scheme 5).

After conversion of **14** to the allylboronates **15** the addition of aldehydes involves an ene-type transfer of boron from carbon to oxygen (**15** → **16**). Thus, the phenyl-substituted bornane unit directed the aldehydes to the less hindered front face of the "ene" double bond inducing the chirality of C(2) in 52–89% d.e. Simultaneously, the relative topicity C(1)/C(2) was controlled (86–95%) by means of the preferred "exo" mode of addition. Regeneration of the auxiliary **14** from the adduct **16** by B/O-cleavage with nitriliotriethanol gave the free homoallylic alcohols **17**. The latter are versatile synthetic intermediates as demonstrated by the syntheses of enantiomerically enriched δ-multistriatin (**19**) and the Prelog–Djerassi lactone[10,11] (**22**), (Scheme 6).



Scheme 5.



Scheme 6.

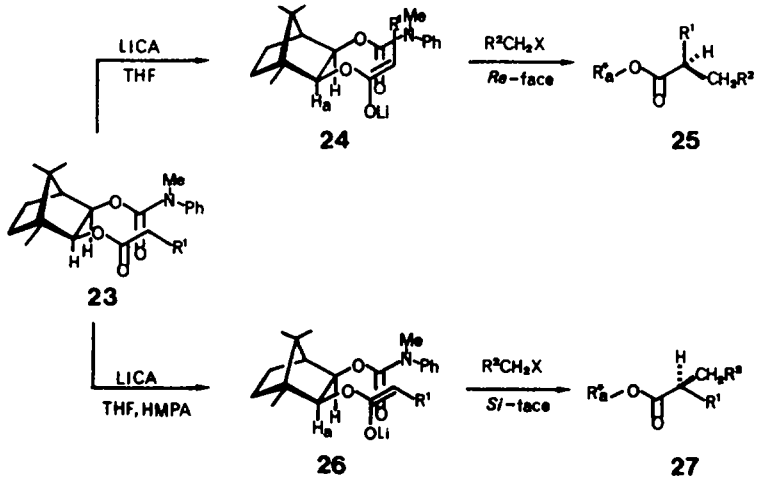
2.2. *Carbamate-shielded isobornyl esters*

2.2.1. *Alkylation of ester-enolates.* Treatment of selectively prepared (*Z*)-enolates **24** (LICA/THF: Method A) or (*E*)-enolates **26** (LICA/THF, HMPA: Method B) with primary alkyl halides at −40° afforded enantiomerically enriched alkylation products **25** or **27**, respectively, which were purified by medium-pressure-chromatography and reduced with $LiAlH_4$ to give enantiomerically pure alcohols[12] (Scheme 7).

The observed stereoface-differentiation was ascribed to a synplanar H_a/C-OLi conformation where the urethane moiety blocks the back face of the enolates **24** and **26** which, consequently, leads to alkylation from the front face.

2.2.2. *Addition of benzene sulfenyl chloride to an acrylate.* More recently, the *N*-phenylcarbamoyl auxiliary was also found to direct the addition of phenylsulfenyl chloride to the less shielded front face of acrylate **28**[13] (Scheme 8).

The formation of chloride **30** (65% from **28**, together with a regioisomeric adduct) in 97% d.e. was attributed to a Walden-inversion of the thiiranium intermediate **29**.

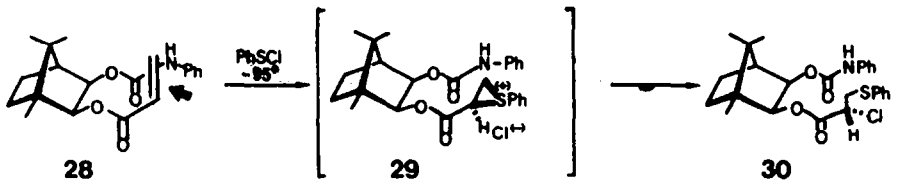


Scheme 7.

Table 1. Asymmetric α-alkylations **23** → **24** → **25** and **23** → **26** → **27**

Entry	R^1	Deprotonation method	R^2CH_2X	Product	Yield (%)[a]	d.e. (%)
a	CH_2Ph	A	MeI	**25**	95	90
b	CH_3	A	$PhCH_2Br$	**25**	96	88
c	CH_3	B	$PhCH_2Br$	**27**	96	40
d	CH_2Ph	A	nC_4H_9I	**25**	93	80
e	CH_2Ph	B	nC_4H_9I	**27**	36(90)	70
f	CH_3	A	iC_4H_9I	**25**	78(90)	86
g	CH_3	B	iC_4H_9I	**27**	60(90)	44

[a] Yield based on recovered ester **23** in parentheses.



Scheme 8.

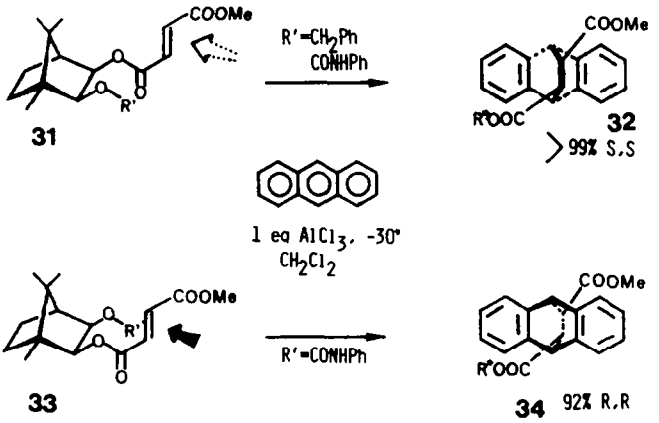
2.2.3. *Diels–Alder additions of fumarates to anthracene.* High π-face discrimination was also observed on $AlCl_3$-promoted cycloaddition of anthracene to fumarates **31** and **33**[14] (Scheme 9).

Shielding of the fumarate π-faces by the benzyloxy- or *N*-phenylcarbamoyl substituents led to the (11*S*, 12*S*)-adduct **32** (from **31**) in up to 99% d.e., or to the (11*R*, 12*R*) isomer **34** (from **33**) in up to 92% d.e.

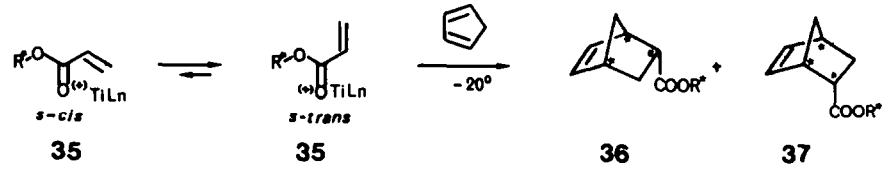
2.3. *Diphenylmethyl- and* 3,3-*dimethylbutyl-shielded acrylates*

2.3.1. *Diels–Alder additions of acrylates to cyclopentadiene.* Independent rational development of various camphor-derived dienophile auxiliaries focused on the synthetically relevant additions of cyclopentadiene to acrylates **35** → **36**+**37**[15] (Scheme 10).

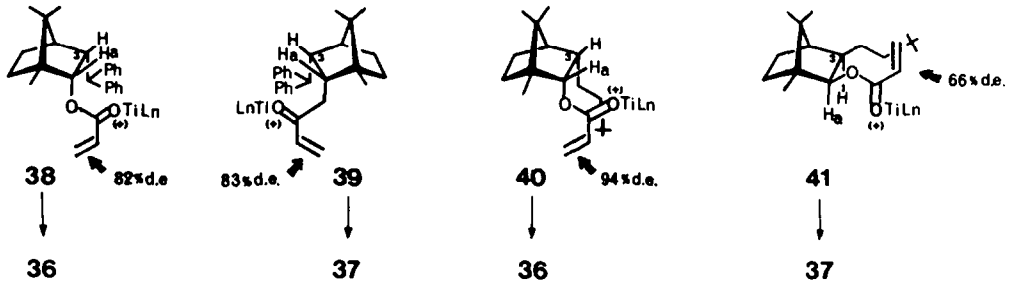
Acrylate-coordination with a Lewis acid seemed to be essential for a stabilization of the acrylate *s-trans*- (relative to its *s-cis*) conformation as well as for increasing reaction rate and *endo*-selectivity of the Diels–Alder process. Scheme 11 displays a series of bornyl and isobornyl acrylates carrying a *cis*-disposed diphenylmethyl- or 3,3-dimethylbutyl-shielding group at C(3).



Scheme 9.



Scheme 10.



Scheme 11.

Scheme 12.

The topological bias provided by the 3-alkylbornyl moiety in **40** is significantly higher than that of its isobornyl counterpart **41** and exceeds that of the diphenylmethyl-shielded acrylates **38** and **39**.

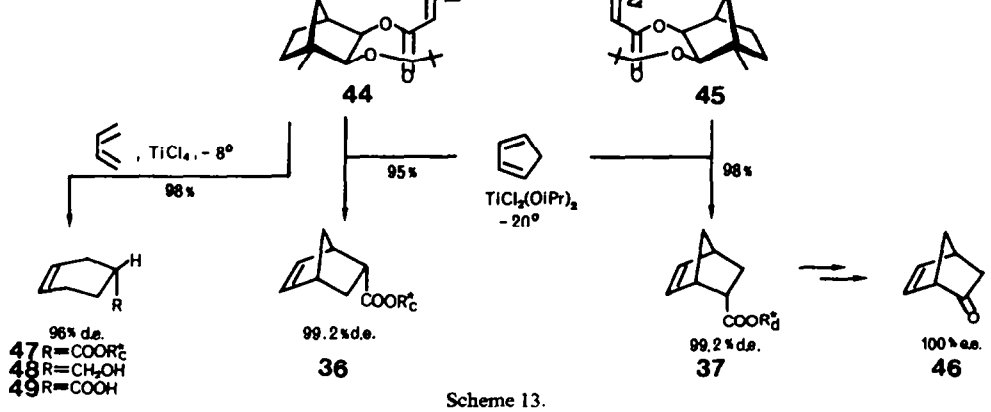
2.4. *Neopentyloxy-shielded isobornyl derivatives*

Originally developed to serve as dienophile auxiliaries in asymmetric Diels–Alder reactions the low-melting but crystalline neopentyl ethers **42** and **43** were prepared in 60% overall yield from (+)- or (−)-camphor, respectively (Scheme 12). The neopentyl ether moiety was supposed to sterically block a reactive π-bond which has been attached to the oxygen at C(3). As described below, unsaturated derivatives of **42** and **43** indeed undergo a variety of reactions with surprisingly high topological control.

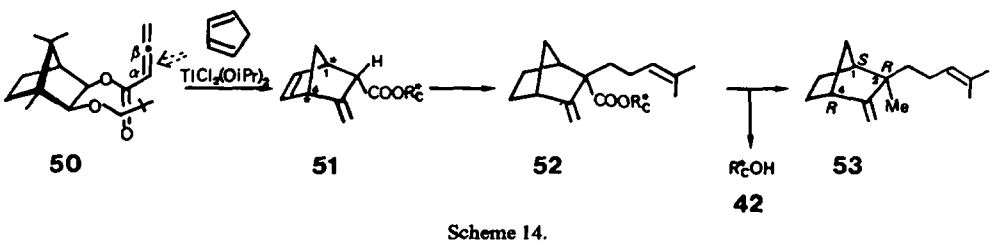
2.4.1. *Diels–Alder additions of cyclopentadiene and of* 1,3*-butadiene to acrylates.* The most dramatic neopentylether-induced face differentiations were found on [4+2]-cycloadditions of 1,3-dienes to enoates derived from the auxiliaries **42** and **43**[16] (Scheme 13).

Thus, $TiCl_2(OiPr)_2$-mediated cycloaddition of cyclopentadiene to acrylates **44** and **45** provided adducts **36** or **37**, respectively, in 94–98% chemical yield with 93–96% *endo*-selectivity and in over 99% diastereofacial excess. The auxiliary could be efficiently regenerated as illustrated by the conversion of adduct **37** to enantiomerically pure norbornenone[17] **46** which has served as a key intermediate for the synthesis of (+)-brefeldin A.[18] Analogous Diels–Alder reaction of acrylate **44** with 1,3-butadiene in the presence of $TiCl_4$ (−8°, 115 h) gave the cyclohexene **47** in 98% yield.[17] Reduction/oxidation **47** → **48** → **49** ($LiAlH_4$, Jones' reagent, 84% overall yield) furnished (3*R*)-cyclohexenyl derivatives **48** and **49** in 96% e.e., which are potential precursors for syntheses of (−)-sarkomycin[19] and shikimic acid.[20]

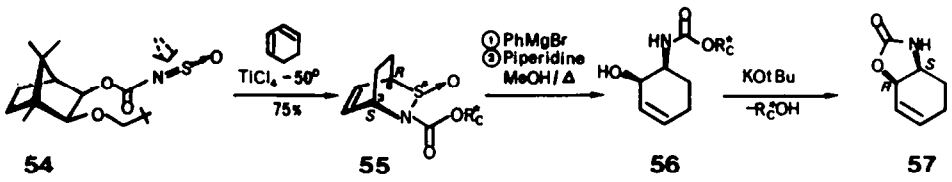
2.4.2. *Enantioselective synthesis of* (−)-*β-santalene by Diels–Alder addition of cyclopentadiene to an allenic ester.* A synthesis of the enantiomerically pure sandalwood constituent (−)-β-santalene (**53**) relied on the $TiCl_2(OiPr)_2$-promoted cycloaddition of the allenic ester **50** to cyclopentadiene (−20°, 6 h) which gave adduct **51** in 98% yield with 98% *endo*-selectivity and in 99% d.e.[17,21] (Scheme 14).



Scheme 13.



Scheme 14.



Scheme 15.

Subsequent routine transformation of **51** into **53** involved notably a crystallization of intermediate **52**. Ester **52** was thus obtained in *ca* 100% d.e. (82% yield from crude **51**).

2.4.3. *Diels–Alder addition of* 1,3-*cyclohexadiene to an* N-*sulfinyl carbamate.* Neopentylether-shielded *N*-sulfinylcarbamate **54**, readily prepared from **42**, also undergoes smooth $TiCl_4$-promoted [4+2]-addition to 1,3-cyclohexadiene to give a single cycloadduct **55** in 75% yield[22] (Scheme 15).

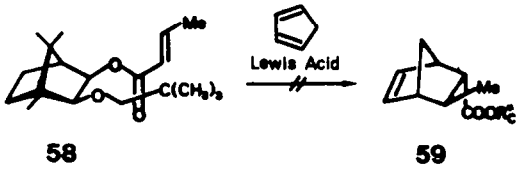
The Lewis acid clearly plays an important role in this asymmetric induction, probably by chelation of the dienophile. Although the topicity of cycloadduct **55** at sulfur was not determined its (3*S*, 6*R*)-configuration was established by S/N-cleavage and allylsulfoxide/sulfenate-[2,3]-rearrangement **55** → **56**. Subsequently, base-induced cyclization regenerated the auxiliary **42** to give carbamate **57** (> 32% yield from **55**).

2.4.4. *Scope and limitations of Diels–Alder reactions of enoate dienophiles: attempted addition of cyclopentadiene to a crotonate.* It thus follows that 1,3-dienes undergo efficient [4+2]-cycloadditions (with good to outstanding π-face stereodifferentiation) to inherently *reactive* dienophiles such as fumarates, acrylates, allenic esters and *N*-sulfinyl carbamates where one face is sterically encumbered. However, this shielding generally entails a decrease of the dienophilicity, as exemplified by the sluggish addition of cyclopentadiene to crotonate **58** which leads preferentially to polymerization[17] (Scheme 16).

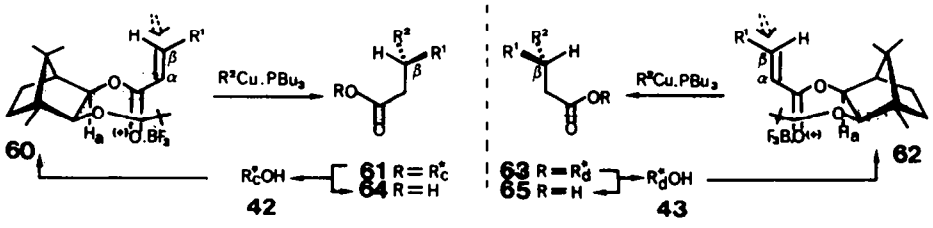
Nevertheless, this limitation was surmounted by the development of "activating" dienophile auxiliaries as described in 3.3.1.

2.4.5. *Conjugate additions of organocopper reagents to enoates.* Similar topological considerations apply to the BF_3-mediated conjugate addition of organocopper reagents to (*E*)-enoates[23–25] (Scheme 17).

The starting (*E*)-enoates **60** and **62** were easily prepared by heating the corresponding C*β*-*Re*- or C*β*-*Si*-directing alcohols **42** or **43** with the appropriate acid chloride and AgCN in benzene. Addition of an excess of an equimolar mixture of RLi, CuI, Bu_3P and $BF_3 \cdot OEt_2$ led to efficient (81–94%) *β*-substitution. The predicted and observed (92–99%) π-face discrimination of the additions **60** → **61** and **62** → **63** was attributed to transition states which feature *syn*-periplanar C=O/C—H_a- and *s-trans* C=O/C*α*, C*β* bonds resulting in selective shielding of the Lewis acid-coordinated enoate by the neopentylether group. Subsequent saponification furnished the free carboxylic acids **64** or **65** which were easily separated from the recovered auxiliaries.



Scheme 16.



Scheme 17.

Table 2. Conjugate additions/saponifications **60** → **61** → **64** and **62** → **63** → **65**

Series	Enoate	R^1	R^2	Adduct (yield %)	Carboxylic acid	e.e. (%)	Config.	Ref.
a	**60**	nC_4H_9	CH_3	82	**64**	94	R	23
b	**60**	C_2H_5	CH_3	85	**64**	92	R	23
c	**60**	CH_3	$Me_2C{=}CH{-}(CH_2)_2{-}$	81	**64**	98	S	23
d	**62**	$Me_2C{=}CH{-}(CH_2)_2{-}$	CH_3	90	**65**	92	S	23
e	**62**	nC_8H_{17}	CH_3	90	**65**	98	S	25b
f	**62**	$nC_{18}H_{37}$	CH_3	94	**65**	97	S	25b
g	**60**	CH_3	$CH_2{=}CH{-}$	85	**64**	94	R	24
h	**62**	CH_3	$CH_2{=}CH{-}$	85	**65**	94	S	24
i	**60**	CH_3	$CH_2{=}CMe{-}$	86	**64**	99	R	24
j	**60**	$H_2C{=}CH{-}(CH_2)_2{-}$	$CH_2{=}CMe{-}$	89	**64**	98	R	24

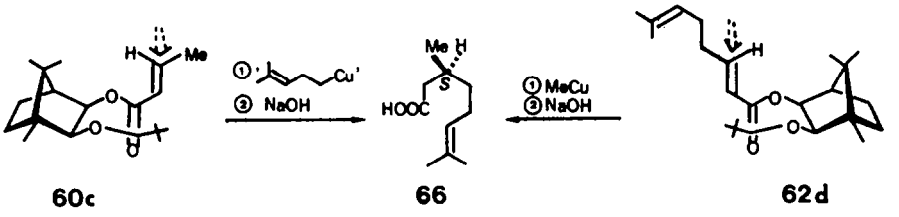
The absolute configuration of **64** or **65** could be readily directed in each possible sense by alternating either the order of group introduction or the antipodal nature of the auxiliary. Accordingly, (*S*)-citronellic acid (**66**) was obtained (in 98% e.e.) via addition of 4-methyl-3-pentenylcopper to crotonate **60c** as well as in 92% e.e. via addition of methylcopper to 7-methyl-2,6-octadienoate **62d**[23] (Scheme 18).

Bu_3P-stabilized 1-alkenylcopper reagents add smoothly to enoates **60** and **62** and thus provide access to β-substituted γ,δ-unsaturated carbonyl derivatives. Thus, starting from the corresponding 2-propenyl adduct **61j** an efficient synthesis of the California-Red-Scale-pheromone **70** was accomplished[24] (Scheme 19).

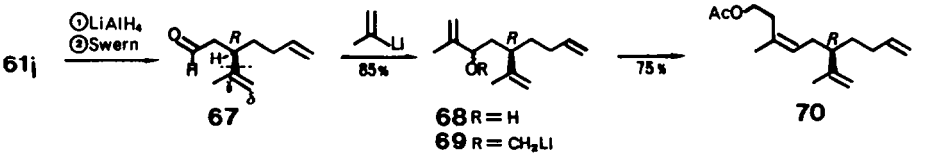
Furthermore, both the olefinic acids **64g** and **65h** have served as chiral intermediates for the syntheses of lasalocid-A,[26] monensin[27] and eldanolide[28] since the chiral center C(3) may induce the topicity of various functionalizations at C(1), C(4) and C(5). This versatility is also exemplified by the conversion of **61h** to enantiomerically pure α-skytanthine (**73**)[29] (Scheme 20).

For assembling several stereocenters in acylic molecules it is advantageous that the topological bias of the auxiliary overrides that of pre-existing centers. Thus, starting from (*R*)-citronellic acid (**74**) the vitamin E sidechain **78** is obtained in 48% overall yield in six steps featuring a 98% C*β*-*Re*-selective addition of methylcopper to enoate **77**[25a] (Scheme 21).

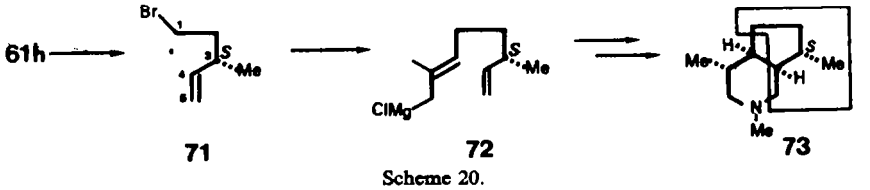
Similarly, aliphatic chains with 1,3-disposed methyl groups are readily accessible via combinations of Horner–Wittig and 1,4-addition reactions. Thus, enantiomerically pure mycolipenic acid **83** was synthesized in 9% overall yield from nonadecanal[25b] (Scheme 22).



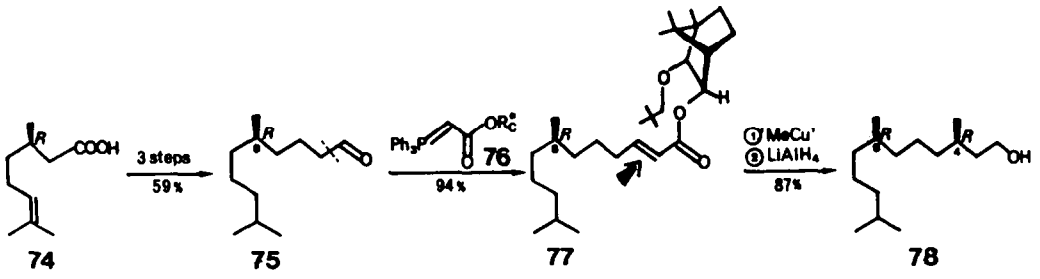
Scheme 18.



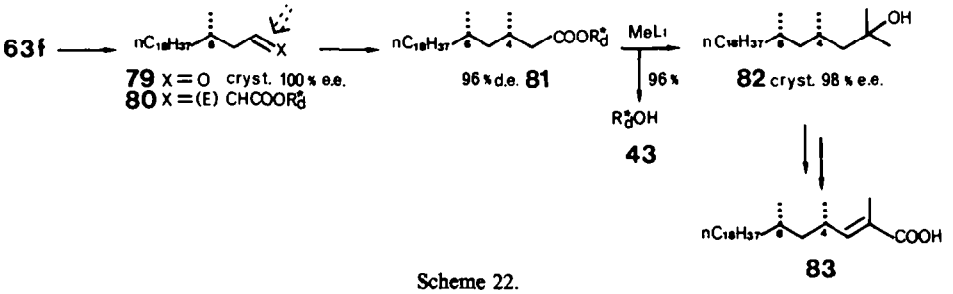
Scheme 19.



Scheme 20.



Scheme 21.



Scheme 22.

The key steps were olefinations by means of a chiral phosphonate (antipode of **76**) $n$$C_{18}H_{37}$-CHO → **62f** and **79** → **80**, each one followed by a C*β-Si*-face selective MeCu-addition **62f** → **63f** (97% d.e.) and **80** → **81** (96% d.e.), respectively.

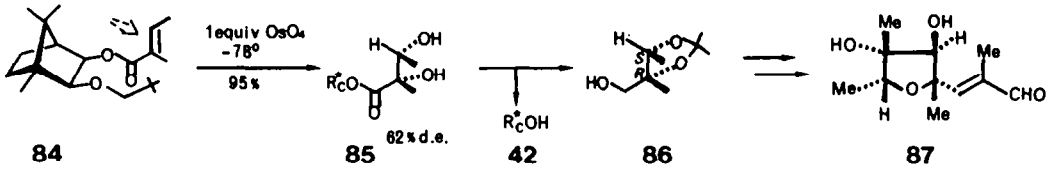
2.4.6. *Osmylation of a tiglate ester.* The topological influence provided by the auxiliary **42** was also applied to the bis-hydroxylation of tiglate **84** (1 equiv. of OsO_4, THF-pyridine, −78°)[30] (Scheme 23).

The expected glycol **85** was obtained in 95% yield although in only 62% diastereomeric excess. In comparison, osmylation of the tiglate derived from (−)-phenylmenthol (**10**) furnished glycol **85**, (R* = phenylmenthyl) in slightly higher (66% d.e.) which could be increased to *ca* 100% d.e. by crystallization. Subsequent acetalization and reduction ($LiAlH_4$) gave **86** which was converted to (+)-citroviral (**87**).

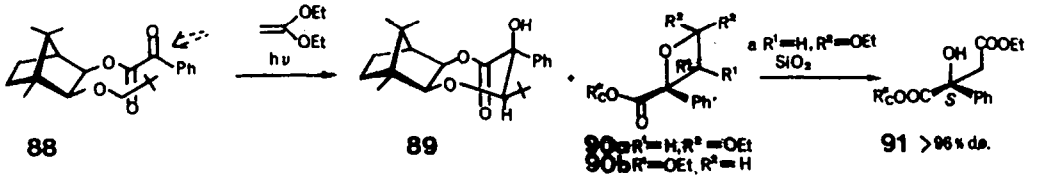
2.4.7. *Paterno–Büchi photoaddition of* 1,1-*diethoxyethylene to a glyoxalate.* The same face-shielding concept holds also for non-concerted photo-[2+2]-additions. For instance, irradiating phenylglyoxalate **88** in the presence of 1,1-diethoxyethylene furnished the regioisomeric Paterno–Büchi adducts **90a** (37% yield) and **90b** (16% yield) both in > 96% d.e.[31] (Scheme 24).

This result is consistent with the depicted reactive conformation **88** with the two carbonyl groups in an *s-trans* disposition. The proximity of the blocking chain and reacting keto group manifests itself by the competing photocyclization **88** → **89** (22% yield).

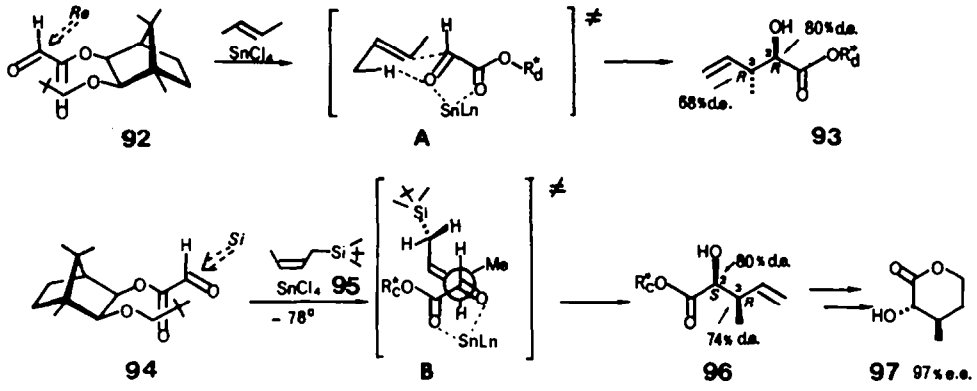
2.4.8. *Ene- and crotylsilane additions to glyoxalates.* In the presence of Lewis acids, however, the two carbonyl groups of glyoxalates are supposed to be *s-cis* because of chelation. Accordingly,



Scheme 23.



Scheme 24.



Scheme 25.

$SnCl_4$-mediated ene-type addition of *trans*-2-butene to glyoxalate **92** took place predominantly to the C(2)-*Re*-face of the enophilic carbonyl group.[32] The formation of the major (83%) (2*R*, 3*R*)-*anti*-product **93** is also consistent with a "closed" transition state **A** which governs the relative configuration C(2)/C(3) (Scheme 25).

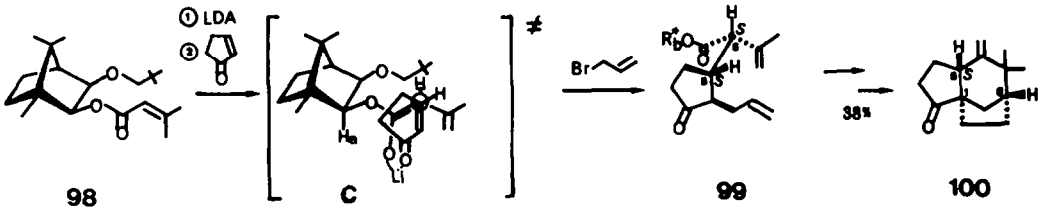
In contrast, the opposite relative C(2)/C(3)-topicity was observed on $SnCl_4$-mediated Sakurai reaction of (*Z*)-crotylsilane **95** to the glyoxalate **94** which appears to proceed via an "open" transition state **B**. These conditions furnished a stereoisomer mixture (76% yield) containing the *syn*-homoallylic alcohol **96** as the major (86%) isomer. Crude **96** was then converted into crystalline verrucarinolactone **97** (2 steps, 40% overall yield, 97% e.e. on both stereocenters). Good inductions were also reported for analogous reactions of the glyoxalate derived from phenylmenthol (**10**);[33] however, the *Si*-face directing phenylmenthol analogue of **94** is almost inaccessible.

2.4.9. *Conjugate addition of an ester dienolate to 2-cyclopentenone.* Enolate-face shielding by the neopentylether group seems to be only moderately efficient. Nevertheless, an interesting example is the "one-pot" transformation of senecioate **98** into cyclopentanone **99** which controls the formation of three stereocenters[34] (Scheme 26).

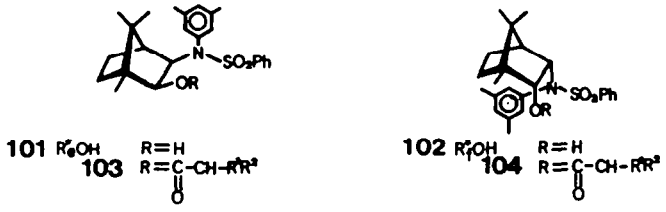
The observed double π-face selection at C(6) (61% d.e.) *and* at C(5) (49% d.e.) of **99** could be rationalized by postulating the intermediacy of an (*E*)-dienolate with *syn*-planar C–H_a/C–OLi bonds. Attack of the less shielded dienolate *Si*-face to the enone *Si*-face (transition state **C**) should be favored over enone *Re*-face attack which entails steric repulsion between the cyclopentenone methylenes and the dienolate methyl groups. The major (5*S*, 6*S*) isomer **99**, conveniently isolated by simple chromatography and crystallization (37% from cyclopentenone) was then transformed (38% overall) into the odoriferous norsesquiterpene (−)-khusimone **100** (*ca* 100% e.e.).

2.5. cis-3-N-*Arylsulfonamido-bornyl and isobornyl esters*

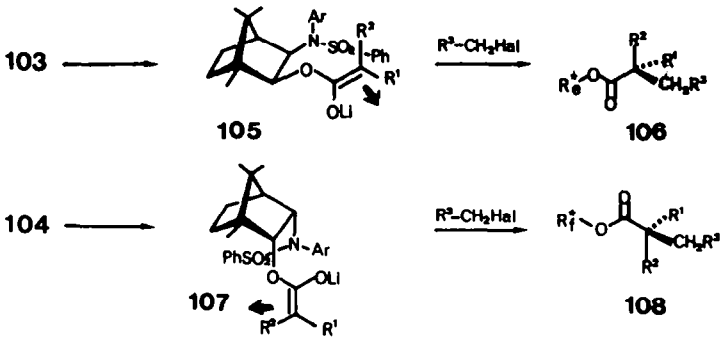
Saturated esters **103** and **104** derived from auxiliary alcohols **101** and **102**, respectively, exhibit interesting π-face differentiations upon electrophilic α-substitutions.



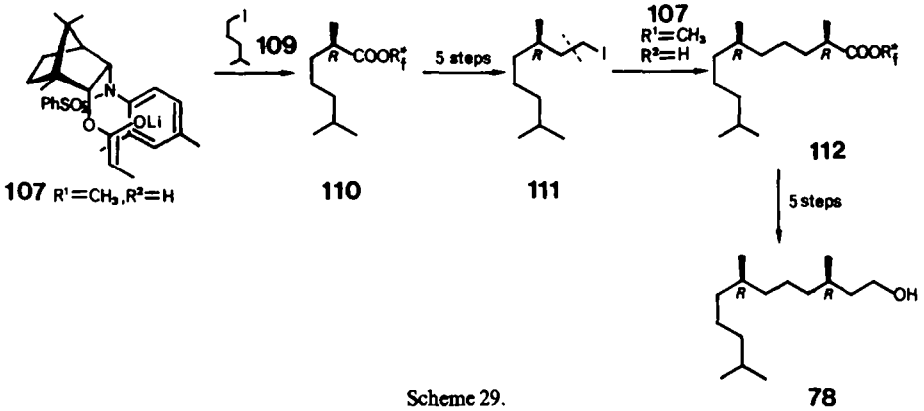
Scheme 26.



Scheme 27.



Scheme 28.



Scheme 29.

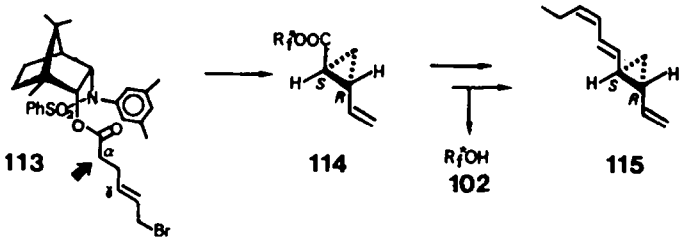
2.5.1. *Ester enolate alkylations.* The results of asymmetric alkylations of Cα-monosubstituted lithium enolates **105** → **106** and **107** → **108** are summarized in Scheme 28 and Table 3.[12,35,36]

Entries a–h describe the deprotonation of propionates to give either (*E*)-enolates (LICA, THF, Method A) or (*Z*)-enolates (LICA, THF, HMPA, Method B) which on alkylation with primary iodides and benzyl bromide furnished the expected products **106** or **108**, respectively. Notably, the less accessible bornyl propionate **104** provided a significantly higher induction (90–96% d.e., entries d, h) than its isobornyl counterpart **103** (52–88% d.e., entries b, f) under the conditions of Method B. On the other hand, Cα-alkylation of *O*-benzyl glycolates **103** and **104** (entries i–p) took place only via the (*E*)-enolates independent of using Method A or B; the resulting α-benzyloxy esters **106** and **108** (87.5–94.5% d.e.) afforded partially protected 1,2-diols on reductive cleavage ($LiAlH_4$).

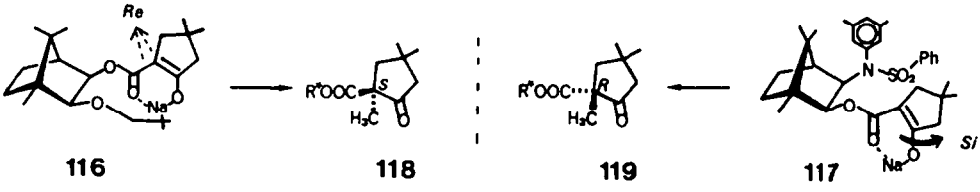
Applications of this methodology include a 12-step synthesis of the vitamin E sidechain **78** featuring two asymmetric alkylations of the *E*-enolate **107**, (R^1=CH_3, R^2=H) + **109** → **110** (98% d.e.) and **111** → **112** (97% d.e., Scheme 29).[37]

Table 3. Asymmetric α-alkylations **103** → **105** → **106** and **104** → **107** → **108**

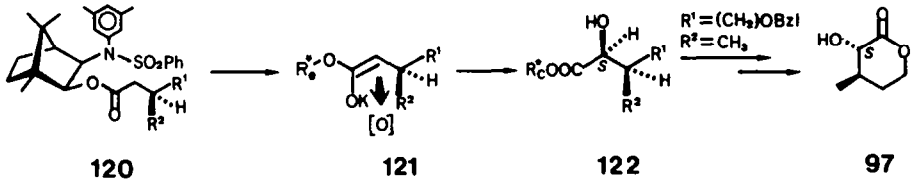
Entry	Starting ester	Deprotonation method	R^1	R^2	$R^3CH_2Hal.$	Product	Yield (%)	d.e. (%)	Ref.
a	**103**	A	CH_3	H	$nC_{14}H_{29}I$	**106**	84	97	12
b	**103**	B	H	CH_3	$nC_{14}H_{29}I$	**106**	75	88	12
c	**104**	A	CH_3	H	$nC_{14}H_{29}I$	**108**	74(91)	95	35
d	**104**	B	H	CH_3	$nC_{14}H_{29}I$	**108**	77(93)	96	35
e	**103**	A	CH_3	H	$PhCH_2Br$	**106**	87(90)	96	35
f	**103**	B	H	CH_3	$PhCH_2Br$	**106**	70(98)	52	35
g	**104**	A	CH_3	H	$PhCH_2Br$	**108**	89(97)	94	35
h	**104**	B	H	CH_3	$PhCH_2Br$	**108**	94(98)	90	35
i	**103**	A	OBn	H	C_2H_5I	**106**	80(94)	87.5	36
j	**103**	B	OBn	H	C_2H_5I	**106**	86	92.5	36
k	**104**	A	OBn	H	CH_3I	**108**	—	88	36
l	**104**	B	OBn	H	CH_3I	**108**	97	91	36
m	**104**	A	OBn	H	C_2H_5I	**108**	75(88)	88	36
n	**104**	B	OBn	H	C_2H_5I	**108**	86(87)	94.5	36
o	**104**	A	OBn	H	$nC_{10}H_{21}I$	**108**	82(95)	91	36
p	**104**	B	OBn	H	$nC_{10}H_{21}I$	**108**	82(98)	93	36



Scheme 30.



Scheme 31.



Scheme 32.

Analogous syntheses of 15,19,23-trimethylheptatriacontane and mycolipenic acid (**83**) have been announced.[37]

A synthesis of dictyopterene B (**115**) relies on a highly face selective S_{cN}, reaction of allyl bromide **113**[38] (Scheme 30).

Treatment of **113** with KO*t*Bu (3.6 equiv.)/H_2O (1.8 equiv.) at $-80°$ furnished a 2:96.5:0.5:1 mixture of stereoisomeric cyclopropanes from which the main isomer **114** was obtained in 99% d.e. upon crystallization. Thus the Cγ stereocenter as well as the Cα one were formed with an excellent π-face differentiation. The same reaction sequence furnished the antipode of **115** starting from auxiliary **101**.

To generate selectively a quaternary center the sodium enolates **116** (NaH, DMF/toluene 3:2) and **117** (THF/HMPA 3:2) were alkylated with MeI ($-5° \rightarrow +20°$, Scheme 31).[39]

Under these reaction conditions the asymmetric bias of both auxiliaries was opposite to each other but comparatively modest (**116** → **118**: 58% d.e.), (**117** → **119**; 62% d.e.). Chelate formation seems to be important to restrict rotations of **116** or **117** but methylation of the corresponding lithium enolates was not reported. On the other hand, lithiation of the enamine prepared from (*S*)-valin *t*-butyl ester and the related β-keto methylester followed by alkylation with MeI created the quaternary center at Cα with 86% d.e.

2.5.2. *Cα-hydroxylations.* Successive treatment of chiral esters **120** with $KN(SiMe_3)_2$ (2 equiv.)/*s*BuOK (8 equiv.) and the $MoO_5 \cdot Py \cdot HMPT$ complex (MoOPh, 1.5 molequiv.) yielded α-hydroxy esters **122** in 90–98% d.e.[40] (Scheme 32).

This excellent face discrimination depends critically on the nature and stoichiometry of bases and is consistent with a Cα-*Si*-face oxidation of enolates **121**. Saponification (KOH, aq. MeOH) of esters **122** gave free α-hydroxy acids without notable racemization except during the conversion of **122c** into verrucarinolactone **97** (obtained as a 91:9 diastereoisomer mixture).

Table 4. Asymmetric hydroxylations **120** → **122**

Entry	R^1	R^2	Yield (%)	d.e. (%)
a	Ph	H	73	98
b	H	H	74	98
c	$(CH_2)_2OBzl$	CH_3	48	98
d	CH_2COOR*	H	47	90

Table 5. Asymmetric aldolizations **123** → **125** and **124** → **126**

Entry	Starting ester	R^1	R^2	Yield[a] 125+126	Major product	d.e. (%)
a	**123**	H	C_2H_5	67(83)	**125**	86
b	**123**	H	nC_7H_{15}	59(68)	**125**	86
c	**123**	H	iC_3H_7	51(89)	**125**	94
d	**124**	H	iC_3H_7	62(80)	**126**	90
e	**124**	H	Ph	69(83)	**126**	88

[a] Yields in parentheses account for recovered ester.

2.5.3. *Aldolizations.* Whereas the lithium enolates of acetates **123** and **124** added to aldehydes with only low asymmetric induction Mukaiyama type ($TiCl_4$-promoted) aldolization of the corresponding *O*-silylketene acetals provided aldols **125** or **126** in 86–90% d.e.[41] (Scheme 33).

Analogous deprotonation (LICA/THF, −80°) of the propionate homologue of **123**, followed by *O*-silylation and addition of isobutyraldehyde/$TiCl_4$ furnished mainly the *anti*-aldol **127** together with three minor stereoisomers in the ratio of 92 : 5 : 1.5 : 1.5. Comparison of this latter result with that of entry d reveals that Mukaiyama aldolizations of acetates and propionates proceed with an opposite induction at the hydroxylated center Cβ. This was explained (*cf.* 3.2.6.) by postulating "closed" transition states **D** and **E** which differ with respect to their conformation around the X*O–Cα bond.

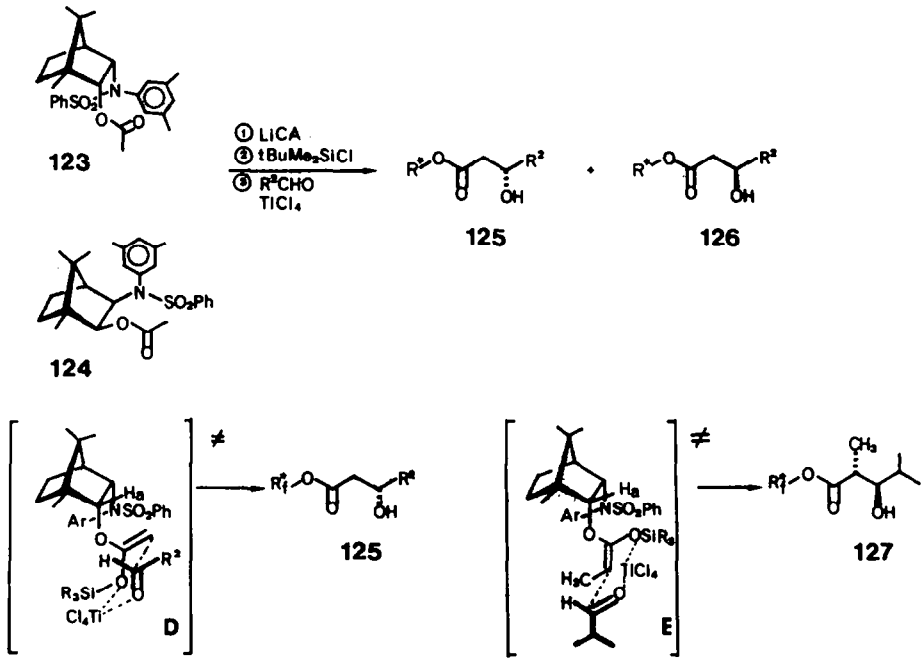
2.5.4. *Conjugate additions to enoates.* In close analogy to previously reported $RCu \cdot BF_3$/enoate additions (e.g. **60** → **61** and **62** → **63**) organocopper reagents and BF_3 (5 equiv. each, THF or Et_2O, −80° → −20°) were added to enoates **128** and **130** to give β-branched esters **129** or **131**, respectively, in 76–97% yield and in 96 to > 98% d.e.[42] (Scheme 34).

Interestingly, 1,4-addition of the sterically encumbered "Cl_3CMgCl reagent" (*i*PrMgCl/CCl_4) to crotonate **128**, R^1=Me afforded **129**, R^1=Me, R^2=CCl_3 in 97.6% d.e. which was raised to > 99% d.e. (90% yield) by crystallization.[43]

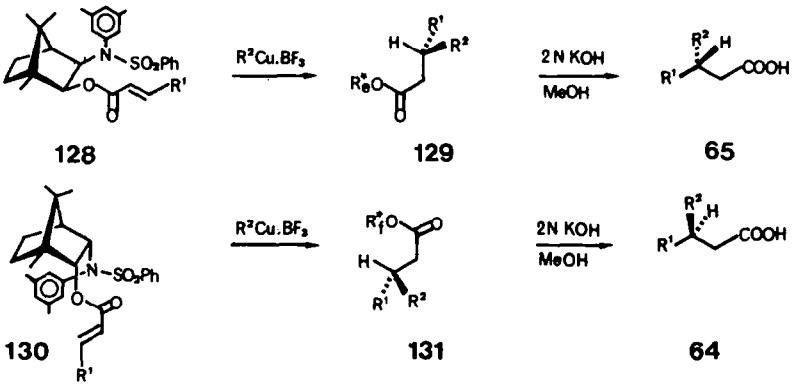
2.6. *Various* C(2)/C(3)*-disubstituted bornane derivatives*

2.6.1. *Carbenoid cyclizations.* 2-Diazo-3-ketoesters **133** (prepared from alcohol **132**) which carry hydrogens in position 6 afforded cyclopentanone **135** (55–62% yield) when treated with Rh_2OAc_4 (CH_2Cl_2, r.t., Scheme 35).[44]

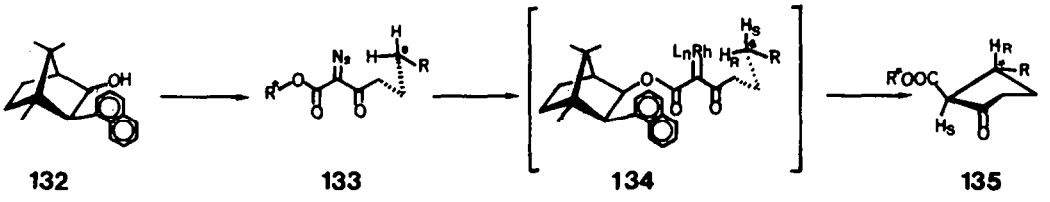
The observed stereodifferentiation (66–86% d.e.) is consistent with a preferred conformation



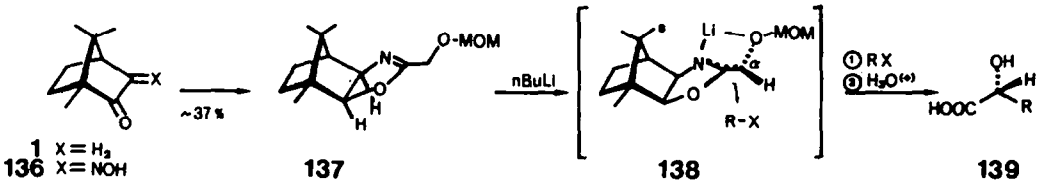
Scheme 33.



Scheme 34.



Scheme 35.



Scheme 36.

134 where the hydrocarbon chain is folded towards the back face of the planar dicarbonylcarbenoid unit, followed by a selective transfer of H_S.

2.6.2. *Alkylations of bornane-2,3-oxazolines.* Comparing the face-differentiations observed on alkylations of oxazolines **11**, R=OMe[45] (12–42% d.e.) and **137** (> 77% d.e.) highlights again the asymmetric bias of the bornane skeleton[46] (Scheme 36).

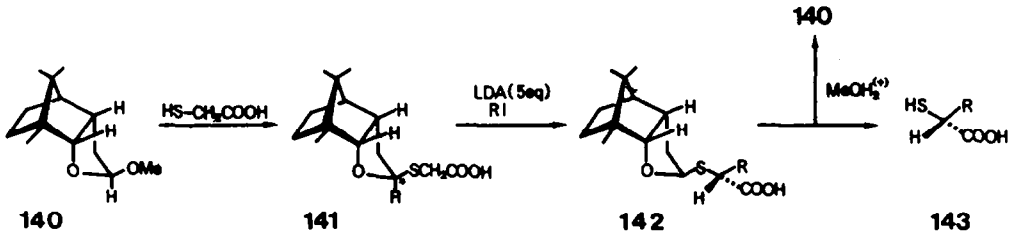
Thus, successive treatment of **137** with *n*BuLi (Et_2O, −78°) and benzyl bromide or alkyl iodides (Et_2O/THF, 1 : 4, −78°) followed by acidic hydrolysis gave α-hydroxycarboxylic acids **139** in 77–92% e.e. The chiral induction may be rationalized on assuming that the (*E*) "enolate" **138** is selectively formed and conformationally locked because of CαO/N-chelation which causes the C(8)-methyl group to shield its top face. Whereas alkylations of **138** usually proceeded efficiently the final hydrolyses (4 N aq. H_2SO_4, reflux, 24 h) gave acids **139** in low yields and appears to destroy the auxiliary.

2.6.3. *Alkylation of mercaptoacetic acid.* The asymmetric information provided by the acetal **140** governed moderately the α-alkylation of bis-lithiated acids **141** to give **142** in 54–60% d.e.[47] (Scheme 37).

Chromatography of **142** followed by methanolysis afforded pure (*R*)-mercapto acids **143**, R = Me or Et.

Table 6. Asymmetric alkylations **137** → **138** → **139**

Entry	Alkylating agent	Yield (%) **137** → **139**	e.e. (%) **139**
a	$PhCH_2Br$	70	92
b	Me_2CH–CH_2–I	72	88
c	Me_2CH–I	26	87
d	*n*Pr–I	57	86
e	Et–I	42	77



Scheme 37.

3. C(2)/C(10)-FUNCTIONALIZED BORNANE AUXILIARIES

3.1. 10-*Mercapto-isobornyl derivatives*

3.1.1. *Synthesis of* O-*methyl-atrolactic acid.* The use of a covalently bound, chiral auxiliary prepared from camphor-10-sulfonic acid was first exemplified in 1979[48] (Scheme 38).

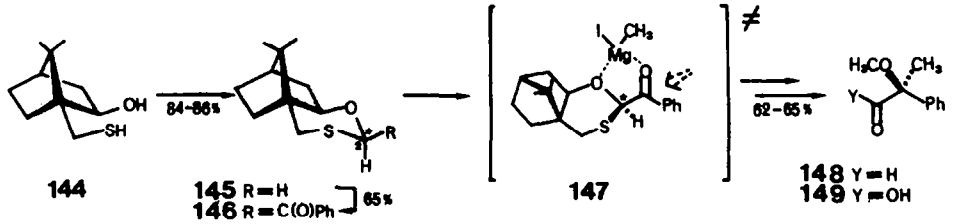
Treating the conformationally locked 1,3-oxathiane **145** successively with *s*-BuLi (THF, −78°) and benzaldehyde gave a mixture of alcohols which was converted by Swern-oxidation and NEt_3-promoted equilibration to the equatorially substituted, crystalline ketone **146**. Addition of **146** (in Et_2O/THF 2:1) to methylmagnesium iodide (Et_2O, 0° to +25°) furnished an alcohol (92–100% yield) which on O-alkylation (NaH, MeI) and removal of the auxiliary (MeI, $CaCO_3$, aq. MeCN, reflux) afforded aldehyde **148** (62–65% yield). Oxidation of **148** with Jones' reagent provided (*S*)-acid **149** in 97±2% enantiomeric purity. The topicity of the crucial Grignard reaction of ketone **146** is consistent with an intermediate C=O/O-chelate **147** which undergoes nucleophilic attack from the side of the hydrogen (opposite to the larger sulfur atom). Similar to the above-mentioned case (**140** → **141** → **142**) this example involves two sequential asymmetric inductions where the bornane chirality is first transferred to the oxathiane-C(2) center (**145** → **146**) and from there to the exocyclic center (**146** → **148**).

3.1.2. *Diels–Alder addition of cyclopentadiene to vinylsulfoxides.* The above strategy of inducing first a chiral center which in turn directs the topicity of the key reaction was applied much more recently to the Diels–Alder process[49] (Scheme 39).

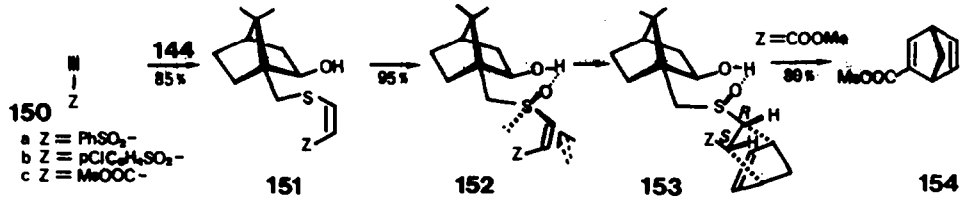
Michael addition of 10-mercaptoisoborneol (**144**) to acetylenes **150** furnished (*Z*)-vinylsulfides **151** which underwent a hydroxy-group-directed oxidation (MCPBA, CH_2Cl_2, O°) to give the (sulfur-*R*)-vinylsulfoxides **152** (80–92% d.e.). Diels–Alder addition of cyclopentadiene (1.3 equiv., CH_2Cl_2, +5°) to the purified, bisactivated dienophiles **152** proceeded smoothly in a virtually quantitative *endo*-fashion from the face opposite to the H-bonded sulfoxide–oxygen. Adduct **153c**, thus obtained in >98% d.e. (>90% yield) was subjected to a DBU-induced elimination affording enantiomerically pure norbornadiene **154**.

3.2. 10-*Sulfonamido-isobornyl derivatives*

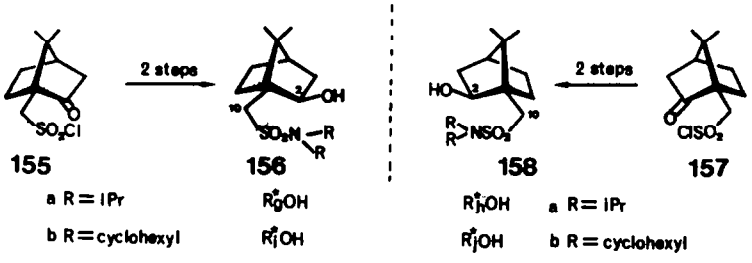
The availability of both enantiomers of camphor-10-sulfonic acid as inexpensive bulk chemicals has prompted a most rewarding development of practical chiral auxiliaries. Thus, crystalline sul-



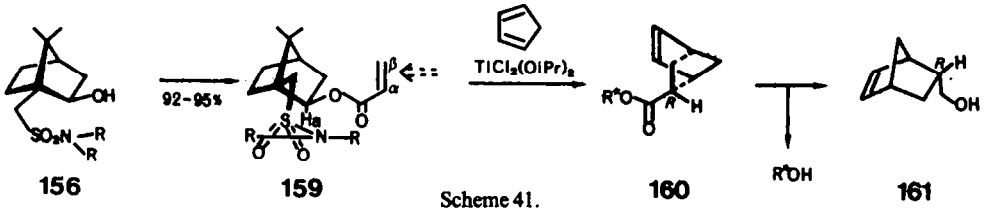
Scheme 38.



Scheme 39.



Scheme 40.



Scheme 41.

fonamides **156** and **158** are conveniently prepared from sulfonyl chlorides **155** and **157** by successive amidation and carbonyl reduction[50] (Scheme 40).

Commercially available auxiliaries **156** and **158** confer good to excellent π-face topological differentiations to reactions of their enoyl as well as enolate derivatives. Chiral products were obtained in >90% diastereomeric excess many of which could be purified to almost 100% by recrystallization. **156** and **158** were easily attached to the substrates by acylation and non-destructively removed from the products (e.g. by hydrolysis, transesterification and reduction) to give synthetically useful building blocks in high enantiomeric purity. This holds for a rapidly expanding variety of reaction types as illustrated below.

3.2.1. *Diels–Alder additions of cyclopentadiene to enoates.* Sulfonamides **156** and **158** were initially designed to serve as dienophile auxiliaries. Acylation of **156** (acrylic acid, α-chloro-*N*-methylpyridinium iodide, NPr_3, toluene, reflux) provided crystalline acrylates **159** (92–95% yield). Dienophiles **159** underwent *endo*-selective (96–97%) $TiCl_2(OiPr)_2$-promoted additions to cyclopentadiene at −20° to give adducts **160** (97–98% yield) in 88–93% d.e.[50,51] (Scheme 41).

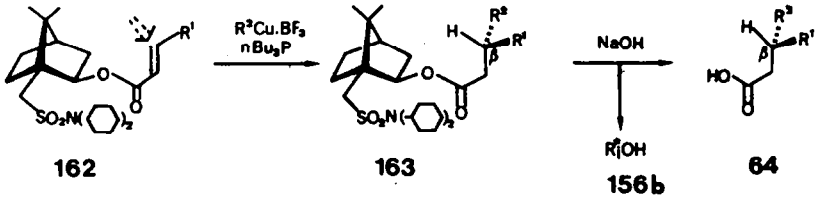
Adduct **160a** could be purified (→ 99% d.e.) by crystallization. Reductive cleavage of adducts **160** ($LiAlH_4$) regenerated auxiliaries **156** which were easily separated from alcohol **161** by direct crystallization.

The observed topological differentiations in the additions **159** → **160** are in agreement with the results of an X-ray diffraction study.[50] In the crystal the non-complexed acrylate **159b** adopts a strictly *s-trans* arrangement of the Cα,Cβ- and C=O bonds; the latter lies *ca* 30° out of the $C-H_a$ plane. As a result of sulfonamide conjugation the lone pair on nitrogen bisects the O–S–O angle. Accordingly, the surface of one cyclohexane ring R is projected firmly on top of the olefinic Cα-*Re*-face.

Although the scope of **156** (and **158**) as dienophile auxiliaries is similarly limited as that of other hindered secondary alcohols (*cf.* the sluggish reaction **58** → **59**) more useful applications to other reaction types emerged as a result of this study.

3.2.2. *Conjugate additions of organocopper reagents to enoates.* Similar to alcohols **42** and **43** the more practical auxiliaries **156b** and **158b** provided excellent π-face differentiations on conjugate addition of RCu to their *trans*-enoates **162**[52] (Scheme 42).

Treatment of **162** (prepared in >95% yield by acylation of **156b**) with $RLi/CuI \cdot PBu_3/BF_3 \cdot OEt_2$



Scheme 42.

Table 7. Preparation of β-substituted carboxylic acids **64** via conjugate addition **162** → **163**

Entry	Series	R^1	R^2	Yield (%) of **163**	e.e. (%) of **64**	Configuration of **64**
1	a	nC_4H_9	CH_3	93	97	R
2	k	CH_3	nC_4H_9	89	97	S
3	l	nC_3H_7	CH_3	89	94	R
4	m	CH_3	nC_3H_7	98	95	S
5	g	CH_3	CH_2=CH—	80	98	R
6	i	CH_3	CH_2=CMe	84	94	R

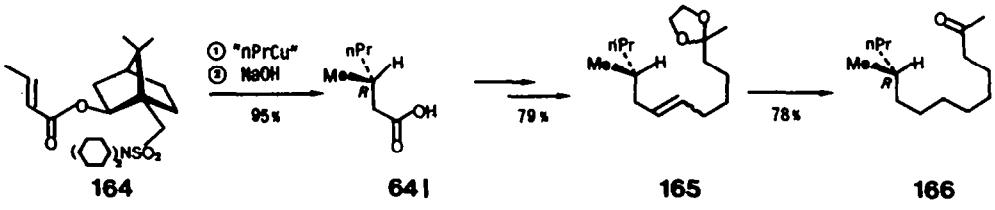
in Et_2O/THF (15:1, −78° → −40°) furnished 1,4-adducts **163** (80–98% yield). Saponification of **163** gave the β-substituted carboxylic acids **64** with virtually complete recovery of the crystalline auxiliary.

The induced chirality of **163** agrees with a reactive *s-trans*-conformation of **162** (stabilized by C=O·BF_3 coordination). Both, (2*S*) or (2*R*) acids **64/65** were obtained in 94–98% e.e. either by interchanging R^1 and R^2 (*cf.* Table 7, series a/k, l/m) or, by alternating the antipodal inductor groups (**156b/158b**).

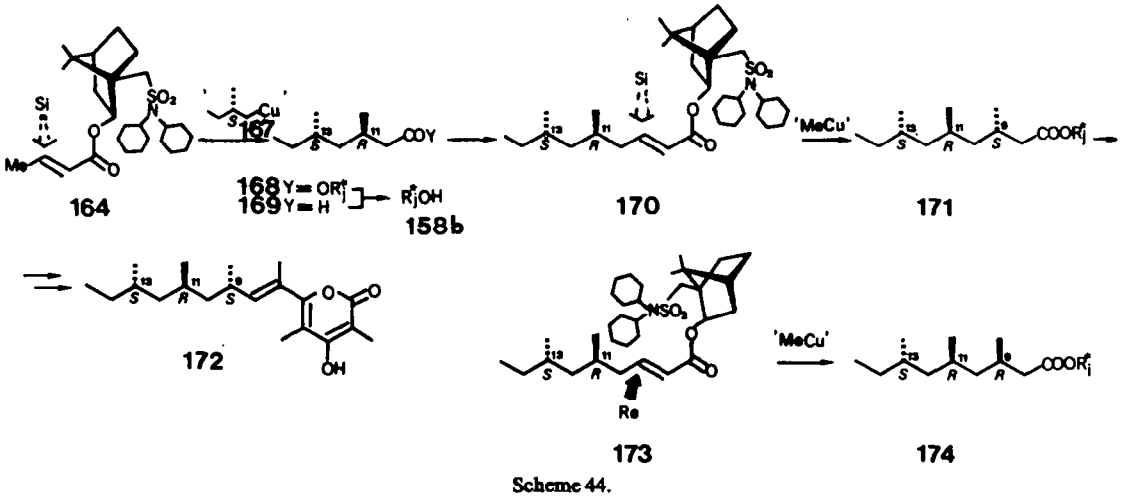
Acid **64l**, obtained in 97% e.e. from **164** (or in 94% e.e. from **162**, R^1 = *n*-Pr), served as a key intermediate for a synthesis of enantiomerically pure Southern Corn Rootworm pheromone **166**[52] (Scheme 43).

The applicability of this method for stereorational syntheses of various, topologically different deoxypolypropionates is illustrated by the synthesis of enantiomerically pure structure **172** which had been assigned to the pulmonate metabolite norpectinatone (Scheme 44).[53]

Two highly Cβ-selective RCu additions **164** → **168** (98% d.e.) and **170** → **171** (94% d.e.), combined with the Wittig–Horner reaction **169** → **170** generated the (9*S*, 11*R*, 13*S*)-configuration of **172**. On the other hand, MeCu addition to **173** proceeded with an equally high (92.4% d.e.) Cβ-*Re*-face preference affording the (9*R*, 11*R*, 13*S*)-chain **174**. It follows that during the formation of center C(9) the auxiliary-derived π-facial bias overrides that of the the preexisting centers C(11) and C(13). It is also worth noting that on carrying out the syntheses of **171** and **174** all intermediate enoates as well as their adducts were routinely purified by crystallization.

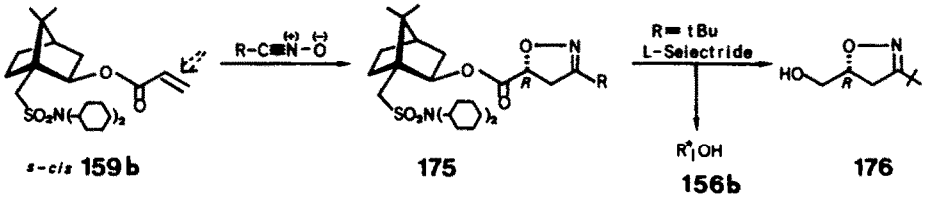


Scheme 43.

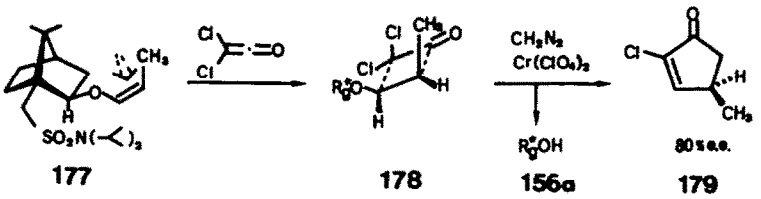


Scheme 44.

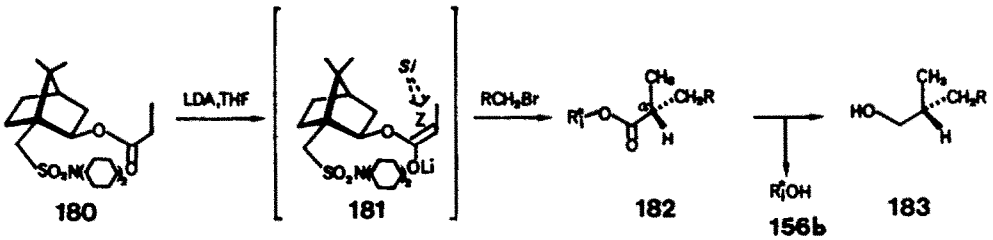
3.2.3. *Dipolar cycloadditions of nitriloxides to an acrylate.* Nitriloxides added smoothly to acrylate **159b** in the absence of a Lewis acid (0°, toluene) to give oxazolines **175**[54] (Scheme 45).



Scheme 45.



Scheme 46.



Scheme 47.

The observed face differentiations were modest (R = *t*Bu: 54% d.e.; R = Ph: 56% d.e.) but, interestingly, compatible with a preferred dipolar addition to the *s-cis*-conformer of **159b**. The major product **175**, R = *t*Bu could be purified by chromatography and cleaved by reduction affording enantiomerically pure **176**.

3.2.4. *Cycloaddition of dichloroketene to an enolether.* Significant asymmetric induction has been found in the cycloaddition reactions of dichloroketene with various chiral enol ethers. Among those the 10-sulfonamide-shielded isobornyl ether **177** turned out to be the most suitable one in terms of accessibility and chiral efficiency[55] (Scheme 46).

Treatment of **177** with CCl_3COCl/Zn–Cu (Et_2O, +20°) yielded **178** which on ring enlargement [CH_2N_2, $Cr(ClO_4)_2$] afforded the intact auxiliary **156a** and the α-chlorocyclopentenone **179** (*ca* 60% yield from **177**) in 80% enantiomeric purity.

3.2.5. *Cα-alkylations of an ester enolate.* Kinetically controlled deprotonation of propionate **180** (LDA, THF, −78°) followed by addition of a primary bromide to the lithium enolate **181** gave the α-substituted esters **182** in 84–89% yields and with 78–89% diastereoface differentiation[52] (Scheme 47).

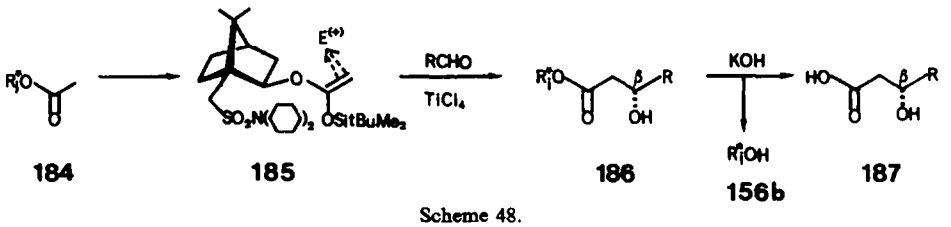
The diastereomeric purity of **182a** was raised to 98% d.e. by crystallization. Reductive cleavage of esters **182** gave the unchanged auxiliary **156b** and the (*R*)-alcohols **183** in 78–98% e.e.

3.2.6. *Aldolization reactions.* The potential of auxiliaries **156** and **158** for Cα,C-bond formations is also exemplified by the $TiCl_4$-mediated Mukaiyama-type aldolizations.[56]

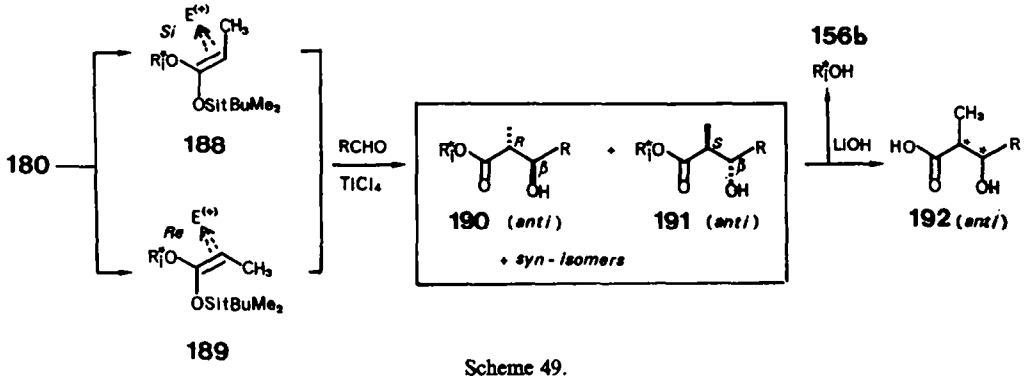
Table 8. Asymmetric alkylation/reduction **180** → **182** → **183**

Entry	RCH_2Br	Solvent	Yield (%)[a] of **182**	e.e. (%)[a] of **183**
a	$PhCH_2Br$	THF	84(61)	89(98)
b	$CH_2{=}CH{-}CH_2Br$	THF	94	88
c	$CH_3{-}CH_2{-}CH_2Br$	THF/HMPA	92	78

[a] Values in parentheses refer to recrystallized **182**.



Scheme 48.



Scheme 49.

O-Silylation of lithiated acetate **184** followed by treatment of the crude *O*-silylketene acetal **185** with aldehydes and $TiCl_4$ at $-78°$ gave aldols **186** in 94–99% d.e. after crystallization (Scheme 48, Table 9).

"Kinetic" deprotonation/*O*-silylation of propionate **180** followed by $TiCl_4$-mediated reaction of the resulting (*E*)-ketene acetal **188** with aldehydes gave preferentially *anti*-aldols **190** readily purified to 99% d.e. by flash chromatography and crystallization (Scheme 49, Table 10, entries 7–9).

Thermodynamically controlled lithiation/silylation **180** → **189** and subsequent treatment of the (*Z*)-ketene acetal **189** with $BF_3 \cdot Et_2O$ and isobutyraldehyde provided aldol **191b** with excellent *anti*-selection. Non-destructive removal of the auxiliary with KOH (**186** → **187**) or with LiOH (**190** → **192** and **191** → **192**) yielded enantiomerically pure β-hydroxycarboxylic acids without α-epimerization.

Table 9. Asymmetric acetate-aldolization/saponification **184** → **186** → **187**

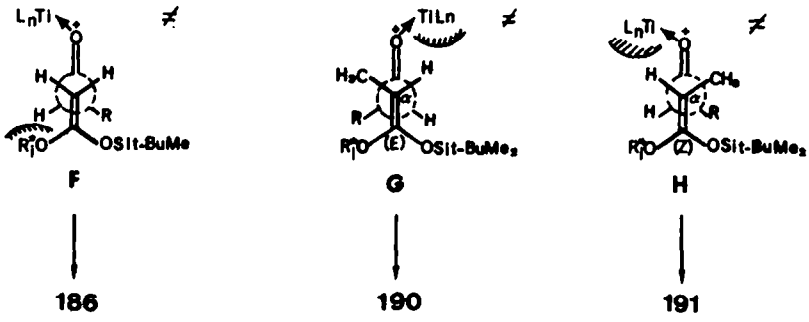
Entry	Series	R	Method[a]	Yield (%)[b] crude **186**	d.e. (%) crude **186**	Yield (%)[b] cryst. **186**	d.e. (%) cryst. **186**	Yield (%) **186** → **187**	e.e. (%) **187**
1	a	C_6H_5	A	56(62)	84	45(50)	99	65	99
2	b	*i*-C_3H_7	A	47(55)	98	45(53)	99	59	98
3	c	*n*-C_3H_7	A	48(57)	84	42(49)	96	60	98
4	d	*n*-C_8H_{17}	A	51(63)	84	36(44)	94	66	92
5	a	C_6H_5	B	30(42)	84	—	—	—	—
6	b	*i*-C_3H_7	B	44(52)	90	—	—	—	—

[a] A: (1) **184** + LICA, THF $-78°$; (2) TBSCl, HMPA (2 equiv.) $-78° \rightarrow 0°$; (3) add to RCHO, $TiCl_4$, CH_2Cl_2 $-78°$. B: Analogous to A, but using LDA as a base and $BF_3 \cdot OEt_2$ as a Lewis acid.
[b] Yields based on recovered **184** in parentheses.

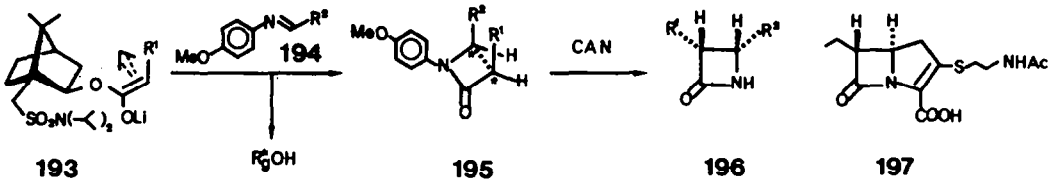
Table 10. Asymmetric propionate aldolization/saponification **188** → **190** and **189** → **191**

Entry	Series	R	Method[a]	Yield (%)[b] **190** + **191** + *syn* isomer(s)	Ratio **190**/**191**/*syn*	Major[b] product Yield (%) (cryst.)	Yield (%) **192**	Config. **192**	e.e. (%) **192**
7	a	C_6H_5	A	44(71)	77:4:19	30(53)	83	(2*R*, 3*S*)	99
8	b	*i*-C_3H_7	A	60(84)	91:7:2	—	—	—	—
9	c	*n*-C_3H_7	A	50(90)	87:7:6	42(75)	83	(2*R*, 3*R*)	99
10	b	*i*-C_3H_7	B	58(85)	71:2:27	—	—	—	—
11	b	*i*-C_3H_7	C	57(81)	6:88:6	49(70)	80	(2*S*, 3*S*)	99

[a] A and B analogous to Table 9; C: **180** + LDA, THF/HMPA 3:1, $-78°$, 1 h; (2) TBSTf, $-78° \rightarrow 0°$ (3) add $BF_3 \cdot Et_2O$ + RCHO, $-78°$, 0.5 h.
[b] Yields in parentheses are based on recovered **180**.



Scheme 50.



Scheme 51.

Accordingly, Mukaiyama aldolizations of acetate- (**185** → **186**) and propionate-derived (*Z*)-ketene acetals (**189** → **191**) show an induction at Cβ which is opposite to that obtained from (*E*)-ketene acetals (**188** → **190**). The observed stereoselectivities were rationalized on the plausible assumptions that the aldehyde (O-coordinated *cis* to its H-atom) approaches preferably the less shielded face of the silyl ketene acetal conformations depicted in formulas **185**, **188** and **189** via the "open" transition states **F**–**H** (Scheme 50).

Accordingly, "acetate aldolizations" **185** → **186** prefer transition state **F** thereby avoiding the gauche interaction R/OR*. In the "propionate" series it is the more powerful repulsion between the Cα–CH_3 and the coordinated Lewis acid which favors the transition states **G** and **H**. In agreement with this model "acetate aldolizations" (**185** → **186**) display similar inductions with $BF_3 \cdot OEt_2$ or $TiCl_4$ whereas the nature of the Lewis acid is critical with the propionate-derived (*E*)-ketene acetals (**188** → **190**, entries 8, 10).

3.2.7. *Preparations of β-lactams via ester–imine condensations.* In favorable contrast to ester enolates derived from menthol, condensation of 10-sulfonamide-shielded enolates **193** with aldimines **194** gave β-lactams **195** (accompanied by 2.5–9% of their *trans*-isomers) in high enantiomeric purity together with the regenerated auxiliary **156a**[57] (Scheme 51).

Oxidative (ceric ammonium nitrate) N/aryl-cleavage provided free *cis*-β-lactams **195** in 56–92% e.e. The relevance of this method is highlighted by the conversion of product **196**, R^1 = Et, R^2 = CH=CH—Ph (91% e.e.) to the carbapenem antibiotic (+)-PS-5 (**197**).

3.2.8. *α-Acetoxylations of esters.* Cα-oxygen bonds were formed with high π-face differentiation on successive treatment of the *O*-silylated esters **199** with $Pb(OAc)_4$ and $NEt_3 \cdot HF$ to give recrystallized α-acetoxyester **200** or **201** in 95–100% d.e.[58] (Scheme 52).

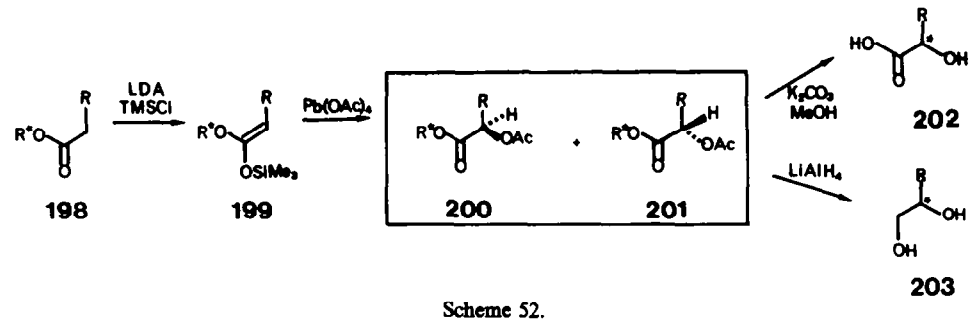
Starting from conjugated enoates **162** addition of R^2Cu, crystallization of 1,4-adduct **163** followed by acetoxylation yielded α,β-bifunctionalized esters **204** with > 95% configurational control at both Cα and Cβ (Scheme 53).

Interestingly, the stereofacial influence of the auxiliary on the generation of Cα overrides that

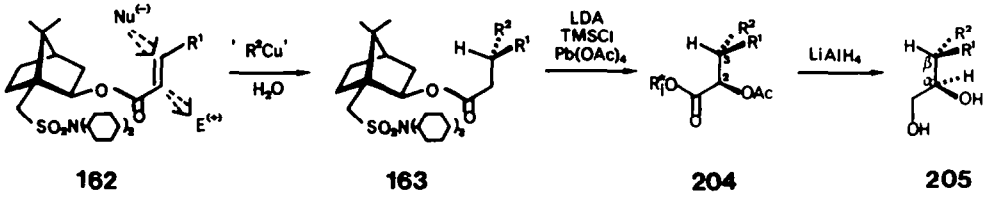
Table 11. Asymmetric α-acetoxylations of straight chain esters **198** → **200** + **201**

Entry	Auxiliary R*OH	R	Ratio **200**/**201**[a]	Major product yield (%)[b]	d.e. (%)[b]	Config. C(α)[b]
a	**156a**	CH_3	94:6	60	100	(*R*)
b	**156b**	nC_4H_9	95:5	55	95	(*R*)
c	**158b**	nC_8H_{17}	2:98	67	99	(*S*)

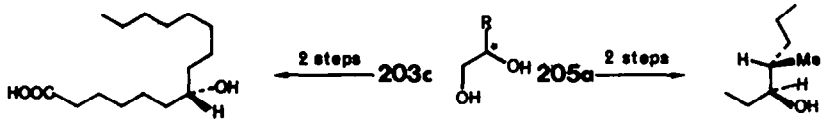
[a] Crude reaction mixture.
[b] Recrystallized product.



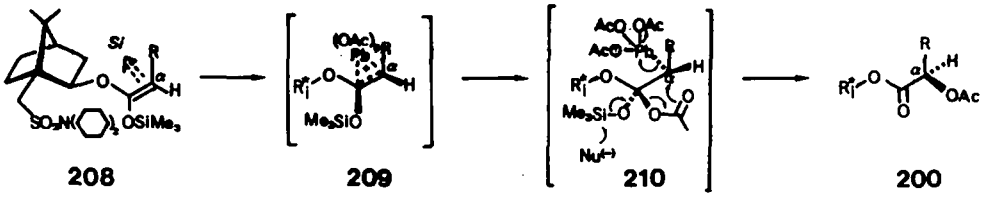
Scheme 52.



Scheme 53.



Scheme 54.



Scheme 55.

of the adjacent center Cβ in the acetoxylation **163** → **204** which opens selective routes to each of the four possible stereoisomers of **205** (by interchanging R^1 with R^2 as well as by alternating the auxiliaries **156** and **158**). The resulting α-acetoxy esters furnished readily the intact auxiliary and either α-hydroxycarboxylic acids **202** or terminal glycols **203**, **205** in virtually 100% enantiomeric purity.

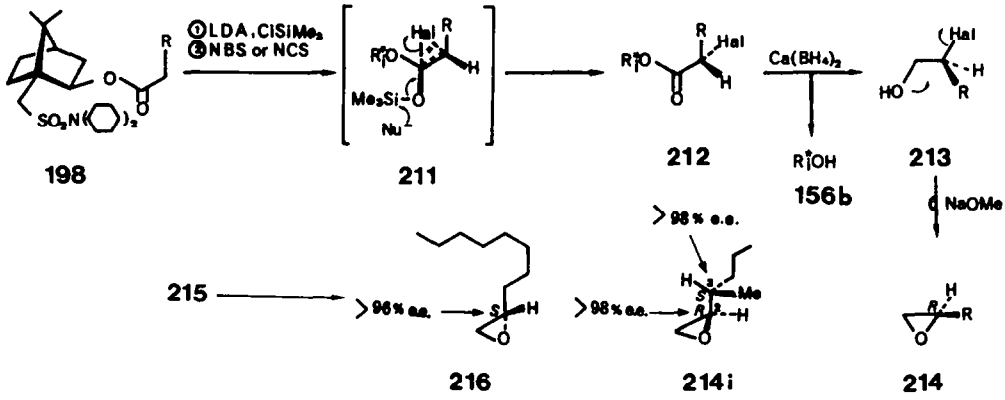
Glycols **203c** and **205a** are key intermediates for the syntheses of the spore germination inhibitor **206**[59] and of the Elm Bark Beetle pheromone **207**,[60] respectively (Scheme 54).

Mechanistically, the observed topicity is consistent (Scheme 55) with (1) an attack of the electrophilic metal from the less hindered Cα-*Si*-face **208** → **209**, (2) opening of the transient plumbonium ion by acetate **209** → **210**, and (3) inversion on internal acetate/lead substitution **210** → **200**.

Table 12. Consecutive asymmetric 1,4-additions and α-acetoxylations: **162** → **163** → **204**

Entry	R^1	R^2	d.e. (%)[a] **204**-Cα	Yield (%)[b,c] **204**	d.e. (%)[b] **204**-Cβ	d.e. (%)[b] **204**-Cα	Configuration **204**
a	CH_3	nC_3H_7	92	66(83)	99	99	(2*R*, 3*S*)
b	nC_3H_7	Ch_3	94	57(76)	>99	>99	(2*R*, 3*R*)

[a] Crude product.
[b] After crystallization from hexane.
[c] Based on **162** (accounting for recovered **162** in parentheses).



Scheme 56.

3.2.9. *α-Halogenations of esters: preparations of enantiomerically pure halohydrins, epoxides and α-amino acids.* Analogous formation of bromonium or chloronium ions **211** may govern the topicity of the α-halogenations **198** → **212**[61] (Scheme 56).

Kinetically controlled deprotonation/*O*-silylation of **198** (LDA, TMSCl, THF, −78°) followed by the addition of *N*-bromo- or *N*-chloro succinimide at −78° afforded α-bromo- or chloro esters **212**. Their initial diastereomeric purity (76–96% d.e.), determined by direct ^{1}H-NMR and HPLC analyses was routinely increased to almost 100% by crystallization. The controlled generation of two centers of asymmetry using the same auxiliary is exemplified by entry 11 where Cβ has been first created by addition of *n*PrCu to the (*E*)-crotonate **162**, R^1 = Me prior to α-bromination.

Reduction of **212** with $Ca(BH_4)_2$ in THF regenerated the auxiliary and afforded conveniently the chiral halohydrins **213** (70–95% yield) which on NaOMe-promoted cyclization gave enantiomerically pure terminal epoxides **214** in 54–86% yield.

The utility of such epoxides in organic chemistry is well established and *inter alia* demonstrated by the direct conversion of **214i** and **216** (prepared from the antipode of **212h**≡**215**) to the natural products **207** and **206**, respectively.

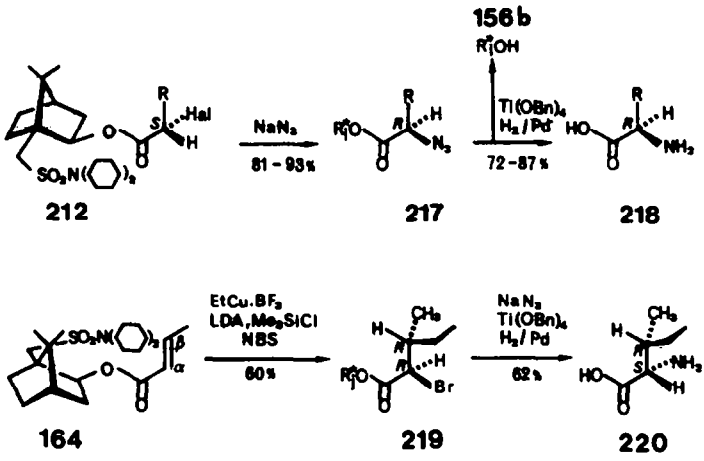
Table 13. Asymmetric α-halogenations **198** → **212**

Entry	Series	R	Hal	Yield (%) **212** cryst.	d.e. (%) **212** cryst.	Ref.
1	a	CH_3	Cl	77	98	61
2	b	C_2H_5	Cl	75	>99	62
3	c	nC_3H_7	Cl	75	97	62
4	d	nC_4H_9	Cl	72	>96	62
5	d	nC_4H_9	Br	77	96	62
6	e	$(CH_3)_2CHCH_2$	Cl	72	>96	62
7	e	$(CH_3)_2CHCH_2$	Br	66	>96	61
8	f	nC_6H_{13}	Cl	82	>94	62
9	g	C_6H_5	Cl	54	>96	61
10	h	nC_8H_{17}	Cl	62	>99	61
11	i	(*S*)-nC_3H_7CHMe	Br	59	>96	61

Table 14. Preparation of enantiomerically pure halohydrins and expoxides from α-haloesters **212** → **213** → **214**

Entry	Series	R	Hal.	Yield (%) of **213**	Yield (%) of **214**	e.e. (%) of **214**	Config. of **214**
1	a	CH_3	C	40	—[a]		
2	d	nC_4H_9	Br	73	—[a]	96	R
3	d	nC_4H_9	Cl	85	54	>98	R
4	e	Me_2CHCH_2	Br	95	86	>96	R
5	g	C_6H_5	Cl	70	67	>90	R
6	i	(*S*)-nC_3H_7CHMe	Br	72	72	98	(2*R*, 3*S*)

[a] Yield not determined.



Scheme 57.

Table 15. Preparation of enantiomerically pure α-amino acids **218** from α-halogenated esters

Entry	R	X	Yield (%)[a] 217	d.e. (%)[a] 217	Yield (%)[b] 218	e.e. (%)[b] 218
a	C_2H_5	Cl	87	—	72	94
b	n-C_3H_7	Cl	93	97	87	94
c	n-C_4H_9	Br	88	96	72	94
d	$(CH_3)CHCH_2$	Cl	81	98	80	96
e	n-C_6H_{13}	Cl	89[c]	100[c]	78	98

[a] Crystallized.
[b] Crude.
[c] After flash chromatography.

α-Halogenated esters **212** provide also a new entry to enantiomerically pure α-amino acids[62] (Scheme 57).

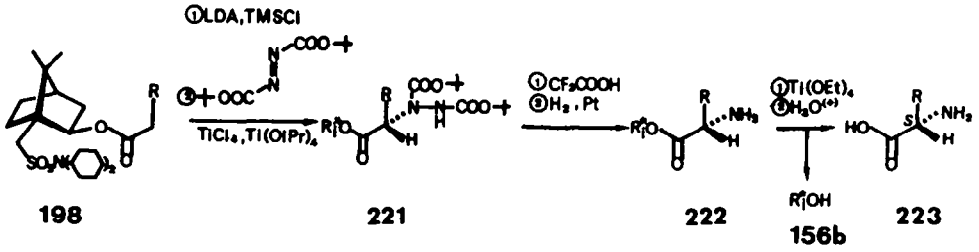
Treatment of chlorides or bromides **212** with NaN_3 in DMF furnished efficiently azides **217** (93–100% yield). HPLC-analyses of crude **217** revealed initial diastereomeric purities of 91–97% which were raised to 96–100% d.e. by crystallization or, in the case of oily **217e**, by flash chromatography. $Ti(OCH_2Ph)_4$-mediated transesterification of **217** regenerated auxiliary **156b**. The resulting benzyl esters underwent concomitant hydrogenolyses of the benzyloxy and the azide groups to afford (*R*)-α-amino acids **218** (72–80% overall yield from **212**) in 94–98% enantiomeric excess.

As expected, (*S*)-amino acids were obtained by the same efficient reaction sequence but employing the antipodal auxiliary **158b**. For example, combination of conjugate addition with Cα-bromination, azide exchange, transesterification and hydrogenolysis **164** → **219** → **220** provided L-*allo*-isoleucine (**220**) [(2*S*): 99.3% e.e.; (3*R*): 97.8% e.e.] an essential precursor for the preparation of the psychotropic ergot peptide, epicriptine.

These results exemplify the first practical, enantioselective approach to α-amino acids via formation of the Cα,N bond.

3.2.10. *α-Aminations of esters: preparations of α-amino acids.* Direct asymmetric closure of the Cα,N bond was accomplished on treating esters **198b** with LDA/Me_3SiCl and then with di-*t*-butylazo dicarboxylate (DTBAD/$TiCl_4$–$Ti(O\mathit{i}Pr)_4$, −78°)[63] (Scheme 58).

The resulting *N,N*-diacylhydrazo esters **221** (81–95% yield) were routinely purified by flash chromatography (→ > 99% d.e.). Cleavage of the *t*-butoxycarbonyl groups (CF_3COOH) and *N,N*-hydrogenolysis (H_2, Pt-cat., EtOH) smoothly afforded crystalline aminoesters **222**. (Entry h shows that hydrogenation of the phenyl ring occurs under these conditions.) $Ti(OEt)_4$-mediated transesterification of **221** yielded intact auxiliary **156b** (> 95%) together with amino acid ethyl esters which on heating with 6 N aq. HCl provided amino acid hydrochlorides **223**. HCl in 94.7–99.6% e.e. This methodology, particularly its application to the preparation of β-branched α-amino acids (*cf.* entry d) compares favorably with independently reported aminations of lithium or *O*-silyl "enolates" derived from oxazolidines **12**[64a] or from *N*-methylephedrine.[64b]



Scheme 58.

Table 16. Enantioselective preparation of α-amino acids **223** from esters **198** and DTBAD

Entry	R	Yield **221**[a] chromat.	d.e. (%) **221**[b] chromat.	Yield (%) **222** cryst.	Yield (%) **223** HCl	e.e. (%) **223**
a	CH_3	81	>99 (93.7)	80	83	94.7
b	C_2H_5	84	>99 (96)	77	91	99.6
c	n-C_3H_7	72(88)	>99 (96.4)	81	86	99.1
d	i-C_3H_7	73(95)	99 (95)	71	90	99.1
e	i-C_4H_9	71(87)	>99 (93)	70	86	97.4
f	n-C_4H_9	85	>99 (92.5)	80	95	97.4
g	n-C_6H_{13}	69(93)	>99 (91)	55	89	97.0
h	$PhCH_2$	76(82)	>99 (96.3)	64[c]	88[c]	98.5[c]
i	1-adamantyl-CH_2	65(81)	>99 (64)	78	65	97.2

[a] Yield based on recovered starting ester **198** in parentheses.
[b] d.e. of crude adducts **221** in parentheses.
[c] R = CH_2-cyclohexyl.

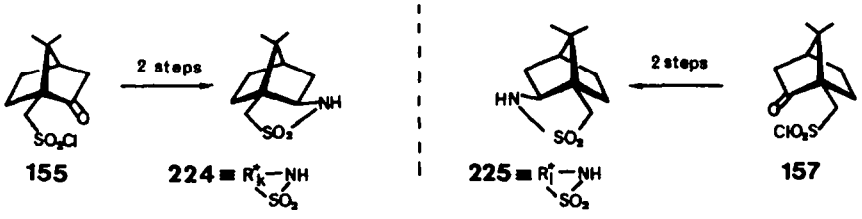
3.3. *Bornane-10,2-sultam derivatives*

Equally accessible by two simple steps from the inexpensive (+)- and (−)-camphor-10-sulfonyl chlorides, the antipodal sultams **224** and **225** are today among the most fascinating chiral auxiliaries[65] (Scheme 59).

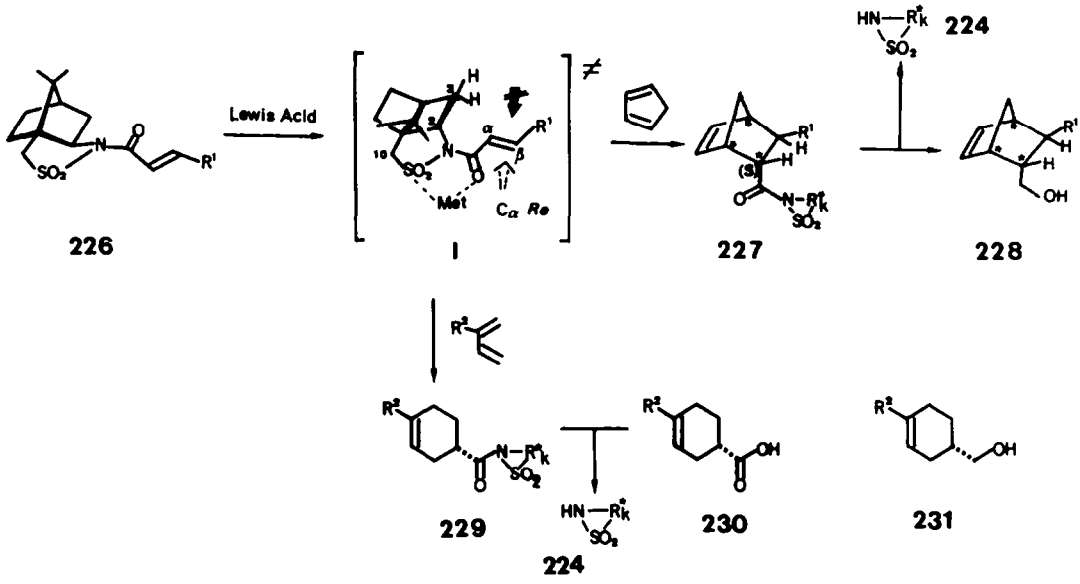
They are readily *N*-acylated by successive treatment with sodium hydride and acyl chlorides. Almost all of their *N*-acyl derivatives are stable and can be (1) readily purified by crystallization, (2) directly analyzed by ^{1}H-NMR and/or GC to determine their stereochemical purity, and (3) cleaved (e.g. with $LiAlH_4$, LiOH, etc.) under mild conditions without loss of the induced chirality and with virtually complete recovery of the auxiliary.

3.3.1. *Diels–Alder reactions.* Sultams **224** and **225** were initially conceived as dienophile auxiliaries with the goal to enhance electronically the dienophilicity of their *N*-enoyl derivatives (in agreement with MINDO/3 calculations) and thereby to extend the scope of asymmetric Diels–Alder reactions.[15b] Indeed, in the presence of $EtAlCl_2$ or $TiCl_4$ cyclopentadiene added readily to the acryloyl sultam **226**, R^1 = H even at −130° and (in favorable contrast to crotonate **58**) to the less reactive crotonyl sultam **226**, R^1 = Me at −78°[65] (Scheme 60).

Adducts **227** formed with excellent *endo*- and face selectivities were obtained virtually pure in 83% yield after crystallization. Also $EtAlCl_2$-promoted [4+2]-cycloadditions of butadiene (entry c) and isoprene (entry d) proceeded readily at −78° and −90° to give recrystallized adducts **229**, R^2 = H and **229**, R^2 = Me, respectively, in good yields and in *ca* 100% purity. Reduction of cycloadducts **227** and **229** with $LiAlH_4$ refurnished the sultam **224** (89–95% after crystallization) and gave the pure alcohols **228** and **231** on simple bulb-to-bulb distillation. Alternatively, saponification of adduct **229**, R^2 = H with LiOH afforded acid **230**, R^2 = H (a potential precursor for



Scheme 59.



Scheme 60.

Table 17. Intermolecular Diels–Alder reactions of enoyl sultams **226** → **227** and **226** → **229**

Entry	R^1	Diene	Lewis[a] acid	Reaction temp. (°)	Adduct	Yield (%)[b]	d.e. (%)[b]
1	H	cyclopentadiene	$EtAlCl_2$	−130	**227**	83	99
2	Me	cyclopentadiene	$TiCl_4$	−78	**227**	83	>99
3	H	1,3-butadiene	$EtAlCl_2$	−78	**229**, R^2 = H	85	99
4	H	isoprene	$EtAlCl_2$	−94	**229**, R^2 = Me	68	>99

[a] $EtAlCl_2$ (1.5 molequiv.); $TiCl_4$ (0.5 molequiv.).
[b] After crystallization.

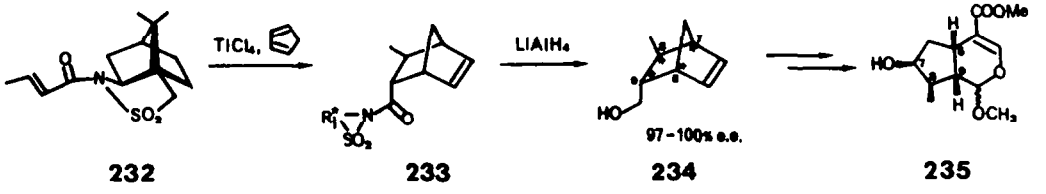
a synthesis of (−)-shikimic acid[20]) *without* epimerization. The observed reactivity and topological control of the $EtAlCl_2$- or $TiCl_4$-promoted Diels–Alder reactions are consistent with a chelation of the SO_2 and C=O groups by the metal which directs the diene to the less hindered C*α*-*Re*-face of the rigid conformation **I**. On the other hand, X-ray diffraction studies of the non-coordinated (*E*)-crotonyl sultam also displayed *s-cis*-related C=O/C*α*,C*β* bonds but an *anti* C=O/SO_2 disposition as depicted by formula **226**.

Using auxiliary **225** the sense of asymmetric induction was reversed (**232** → **233**). The recrystallized cyclopentadiene adduct **233** was then transformed into enantiomerically pure (−)-1-*O*-methyl loganin aglucone **235**[66] (Scheme 61).

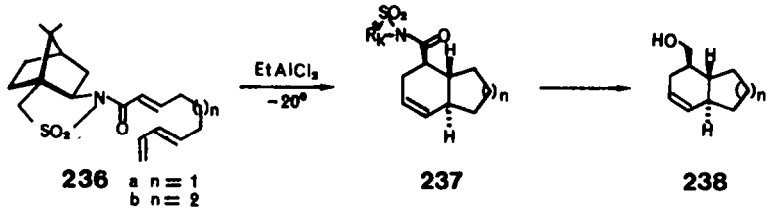
This synthesis highlights the potential of asymmetric Diels–Alder reactions which in one step **232** → **233** created three centers C(5), C(8) and C(9) with the desired and one center C(7) with the opposite configuration (requiring C,O-inversion).

Extension of this concept to intramolecular Diels–Alder reactions proved to be equally successful and predictable[67] (Scheme 62).

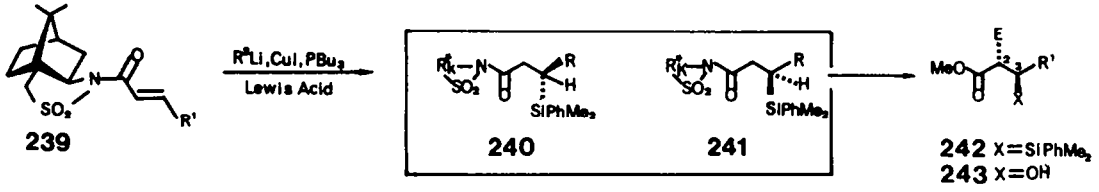
Crystalline trienoyl sultams **236a** and **236b** cyclized on treatment with $EtAlCl_2$ (1.6 molequiv., −20°, 4h) with exceptional *endo*-selectivity to give after crystallization the product **237a** (75% yield)



Scheme 61.



Scheme 62.



Scheme 63.

or **237b** (53% yield), each one in >99% d.e. Subsequent reductive cleavage ($LiAlH_4$) afforded enantiomerically pure bicyclic alcohols **238**.

It follows that the *same* dienophile auxiliary provides a strong and predictable bias to *inter-* and *intra*-molecular Diels–Alder additions in terms of rate acceleration, as well as *endo-* and π-face-stereodifferentiations, thus surmounting inherent problems usually encountered with enoate dienophiles (*cf.* Scheme 15). Enoates of sultams **224** and **225** compare favorably even with excellent dienophiles derived from oxazolidines **13**[68] (requiring variations of R^1 and R^2 relative to the substrates) or hydroxyketones[69] (which implies destructive removal of the auxiliary).

3.3.2. *β-Silylcarboxyl derivatives by 1,4-additions of organocopper reagents.* A new approach to these versatile building blocks is the $EtAlCl_2$-mediated *Cβ-Re*-face selective 1,4-addition of phosphine-stabilized alkenyl- and alkyl-copper reagents R^2Cu to *N*-(β-silylenoyl) sultams **239** ($R^1 = SiPhMe_2$) → **241** (86–96% d.e., entries 2–10, Table 18, Scheme 63).[70]

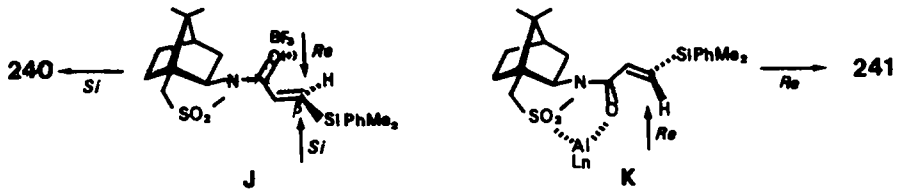
Entries 10 and 11 exemplify a permutation of R^1 and R^2: conjugate addition of $PhMe_2SiCu$ (entry 11) to **239**, R^1 = Ph gave after crystallization the epimer **240**, R = Ph in 97% d.e. Methanolysis (MeOMgCl/MeOH) of **240** and **241** afforded esters **242** which were transformed into enantiomerically pure aldols **243** exploiting the topological bias of the C(3)-silyl substituent on Cα-methylation (→ **242**, *E* = Me) as well as its convertibility into an OH group with retention of configuration. Further synthetic possibilities are offered by the γ,δ-alkenyl-β-silyl-carboxyl products **240** and **241**.

Interestingly, *Cβ-Si*-face-predominant (→ **240**, 46% d.e.) addition of vinylcopper was observed in the presence of $BF_3 \cdot OEt_2$ (entry 1) to give the almost pure Cβ-epimer **240** after crystallization. This striking difference in sense and extent of induction was attributed to a BF_3-mono-coordinated transition state **J** with *anti*-disposed SO_2/C=O groups (entry 1) and, alternatively, to the Al-chelated

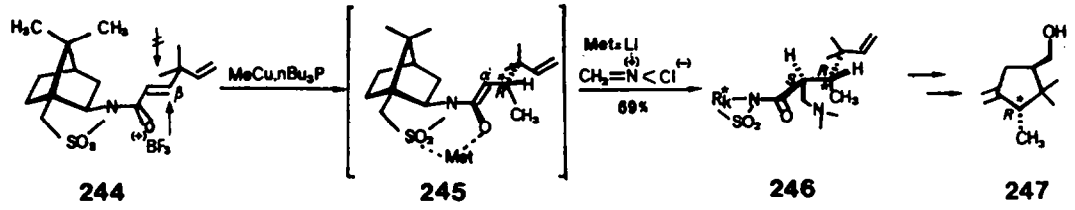
Table 18. Asymmetric conjugate additions **239** + R^2Cu → **240** + **241**

Entry[a]	R^1	R^2	Lewis acid	Ratio (%) of crude **240/241**	Ratio (%) of crystallized **240/241**	Yield (%) of crystallized **240+241**
1	$SiPhMe_2$	Vinyl	BF_3-OEt_2	73:27	97:3	60
2	$SiPhMe_2$	Vinyl	$EtAlCl_2$	5:95	2:98	57
3	$SiPhMe_2$	(*Z*)-Prop-1-enyl	$EtAlCl_2$	2:98	1:99	65
4	$SiPhMe_2$	(*E*)-Prop-1-enyl	$EtAlCl_2$	2:98	2:98	67
5	$SiPhMe_2$	Me	$EtAlCl_2$	7:93	3.3:96.7	61
6	$SiPhMe_2$	Et	$EtAlCl_2$	7:93	4:96	62
7	$SiPhMe_2$	Pr	$EtAlCl_2$	6:94	2:98	57
8	$SiPhMe_2$	*i*-Pr	$EtAlCl_2$	7:93	3:97	64
9	$SiPhMe_2$	Bu	$EtAlCl_2$	4.3:95.7	1.6:98.4	61
10	$SiPhMe_2$	Ph	$EtAlCl_2$	2.6:97.4	0:100	86
11	Ph	$SiPhMe_2$	$EtAlCl_2$	90.4:10.6	98.5:1.5	43

[a] Entries 1–10: R = R^2; entry 11: R = R^1. Entries 1–4: Et_2O/THF 8:1; entries 5–11: Et_2O.



Scheme 64.



Scheme 65.

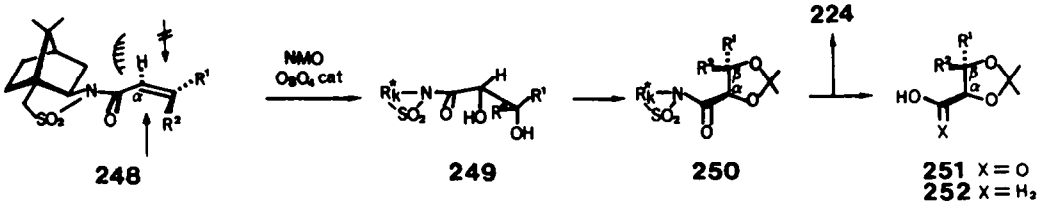
transition state **K** (entries 2–10) favoring bottom-side attack analogous to the Diels–Alder reactions of enoyl sultams (Scheme 64).

3.3.3. *Enantioselective synthesis of β-necrodol.* A total synthesis of β-necrodol (**247**), isolated from the defensive secretion of a carrion beetle, relies on a conjugate addition of methylcopper to $BF_3 \cdot OEt_2$-coordinated dienoyl sultam **244** which creates the Cβ-(*R*)-configuration in 98% d.e.[71] (Scheme 65).

The transient enolate **245** was then trapped by consecutive additions of BuLi and *N,N*-dimethylmethylidene ammonium chloride to give the crystalline (2*S*, 3*R*)-Mannich product **246** (69% yield from **244**).

The observed topicity of the transformation **244** → **246** seems to proceed via a BF_3-monocoordinated sultam **244** in a SO_2/C=O-*syn*-conformation (in contrast to the less crowded transition state J) thereby avoiding a steric repulsion between the SO_2 groups and the substituents of the quaternary γ-C-atom. Addition of methylcopper to the less shielded Cβ-*Re*-(bottom)-face of **244**, transmetalation (Cu → Li) of the transient (*Z*)-enolate **245** which undergoes a Cα-*Re*-(bottom)-face attack to the imminium electrophile giving **246**. Structure **246** was confirmed by an X-ray-diffraction analysis which, accounting for the successful conversion **246** → **247**, proved unequivocally the absolute configuration of the natural product **247**.

3.3.4. OsO_4-*Catalyzed bis-hydroxylations.* Oxidations of β-substituted α,β-enoyl sultams **248** with

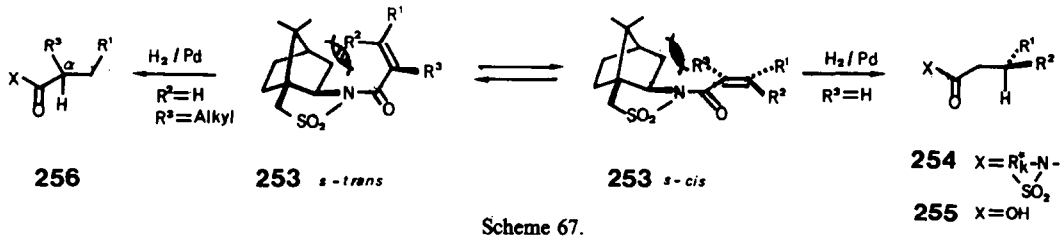


Scheme 66.

Table 19. O_sO_4 catalysed bis-hydroxylations of enoyl sultams **248** → **249** → **250**

Entry	R^1	R^2	Yield (%) of **250** from **248**	d.e. (%)[a] of **250**
a	CH_3	H	74	>99
b	H	CH_3	66	>99
c	nC_3H_7	H	79	>99
d	C_2H_5	CH_3	63	>99
e	CH_3	C_2H_5	67	>99

[a] After flash chromatography (entries a, c–e) or crystallization (entry b).



Scheme 67.

N-methylmorpholine-*N*-oxide-monohydrate (2 molequiv.) in the presence of OsO_4 (0.3 molequiv., DMF/*t*-BuOH 1 : 1, −20°, 5 h) provided glycols **249** which were converted into their more stable acetals **250** (Table 19, Scheme 66).[72]

The diastereomeric excess of **250** (initially 80–90% d.e.) was directly analyzed by GC and raised to > 99% d.e. by flash chromatography or crystallization. Depending on the *E*/*Z*-geometry of the enoyl sultam **248** the formation of secondary or quaternary centers at Cβ could be directed in either sense (*cf.* entries a/b, d/e). Hydrolytic (aq. LiOH) or reductive ($LiAlH_4$) cleavage regenerated the sultam **224** (82–100%) and gave enantiomerically pure carboxylic acids **251** (92–94% yield) or alcohols **252** (75–82% yield).

The observed reaction topicity agrees with a reactive conformation featuring a *syn*-orientation of C=O and SO_2 groups, *s-cis*-related C=O/Cα,Cβ bonds and an approach of the reagent from the less hindered Cα-*Re*-(bottom) face. In support of this postulate α-substituted enoyl sultams were bishydroxylated much slower and with low (*ca* 20% d.e.) π-facial differentiation due to the steric repulsion between the Cα-substituent and the bornane skeleton. (Reflecting its fundamentally different conformation α-substituted chiral enoate **84** was bishydroxylated in up to 67% topological excess by means of stoichiometric amounts of OsO_4, *cf.* 2.4.6.)

3.3.5. *Catalytic hydrogenations.* Unprecedented high (91–98%) topological control was also achieved on strikingly simple hydrogenations (100 psi H_2, 4 mol.% Pd/C, EtOH, r.t.) of β,β-disubstituted enoyl sultams **253**[73] (Scheme 67, entries a–h).

Saponification of the resulting β-substituted imides **254** (**254a** and **254g** obtained in > 99% d.e. by crystallization) afforded free carboxylic acids **255** in 92–100% yield. Comparison of entries g and h illustrates the expected correlation of induction with olefin geometry.

The topicity of the reaction **253** → **254** may be rationalized on assuming a coordination of the metal surface with the *syn*-disposed SO_2 and C=O groups as well as with the *s-cis*-disposed olefinic bond from the sterically less hindered Cα-*Re*-face followed by H-transfer to the same face. When the α-substituent R^3 = alkyl such a conformation would suffer from repulsion between R^3 and the bornane. It was therefore not unexpected, that analogous hydrogenations of α-substituted enoyl sultams **253** gave α-substituted carboxyl derivatives **256** with low and/or opposite face differentiation (entries i–k).

3.3.6. *Conjugate hydride-additions/enolate trapping.* In surprising contrast, however, conjugated enoyl sultams **253** underwent efficient 1,4-hydride additions from the Cα-*Si*-face as depicted in Scheme 68 (*cf.* series a, b, c. Tables 21 and 22).[74]

Table 20. Hydrogenation of enoyl sultams **253** → **254** and **253** → **256**

Entry series	R^1	R^2	R^3	Yield[a]	Product	d.e. (%)[b] Config.	
a	C_2H_5	CH_3	H	99(88)	**254**	>99(>99)	Cβ *R*
b	nC_3H_7	CH_3	H	95	**254**	96(98)	Cβ *R*
c	nC_4H_9	CH_3	H	95	**254**	90(94)	Cβ *R*
d	iC_3H_7	CH_3	H	97	**254**	91(93)	Cβ *R*
e	nC_6H_{13}	CH_3	H	99	**254**	92(96)	Cβ *R*
f	nC_8H_{17}	CH_3	H	93	**254**	92(93)	Cβ *R*
g	$(CH_2)_2CH{=}C(CH_3)_2$	CH_3	H	96(69)	**254**	90(95)	Cβ *R*
h	CH_3	$(CH_2)_2CH{=}C(CH_3)_2$	H	96	**254**	91(95)	Cβ *S*
i	C_2H_5	H	CH_3	99	**256**	21	Cα *S*
j	H	H	nC_3H_7	99	**256**	30	Cα *S*
k	H	H	iC_3H_7	98	**256**	80	Cα *S*

[a] Yields in parentheses refer to recrystallized product of > 99% d.e.
[b] d.e. of crude product (in parentheses accounting for the *E*/*Z* ratio of enoyl sultams **253**).

Table 21. Conjugate hydride-additions to β-substituted enoyl sultams/enolate trapping **253** → **257** → **258**

Entry	Series	R^1	R^2	E	Electrophile	Yield (%)[a] of **258**	d.e. (%)[a] Cβ Config.	d.e. (%)[a] Cα Config.
1	a	C_2H_5	CH_3	H	aq. NH_4Cl	72	94 *S*	—
2	b	nC_3H_7	CH_3	H	aq. NH_4Cl	75	92 *S*	—
3	c	nC_4H_9	CH_3	H	aq. NH_4Cl	90	90 *S*	—
4	l	CH_3	nC_4H_9	H	aq. NH_4Cl	97	90 *R*	—
5	m	CH_3	$CH(OMe)_2$	H	aq. NH_4Cl	41	90 *R*	—
6	n	CH_3	H	CH_3	CH_3I(HMPA)	85	—	⩾98 *R*
7	o	nC_4H_9	CH_3	CH_3	CH_3I(HMPA)	82(64)	90(98) *S*	88 (>99) *R*
8	p	CH_3	nC_4H_9	CH_3	CH_3I(HMPA)	76(55)	92(96) *R*	74 (>99) *R*

[a] Values in parentheses after crystallization.

Table 22. Conjugate hydride-additions to α-substituted enoyl sultams/enolate protonation **260** → **261** → **262**

Entry	Series	R^1	R^3	Yield (%) of **262**	d.e. (%) Cα	Configuration Cα
9	q	H	nC_3H_7	85	86	*R*
10	r	C_2H_5	CH_3	85	82	*S*
11	s	CH_3	CH_3	95	80	*S*

Treatment of β,β-disubstituted enoyl sultams **253** with lithium tri-*s*-butylborohydride in toluene at −85° to −40° followed by quenching with aq. NH_4Cl afforded β-substituted imides **258** in 72–94% yield and in 90–94% d.e. (products **258a–c** are epimers of **254a–c**). Entries 3, 4 illustrate the relation between *E*/*Z*-geometry of enoyl sultam **253** and the induced configuration of **258**. Entry 6 shows the efficient generation of an asymmetric center at Cα: trapping of the intermediate enolate **257n** with MeI afforded **258n** (85% yield, > 98% d.e.).

Employing this tandem 1,4-addition/α-alkylation two centers of asymmetry (at Cβ and Cα) were conveniently induced in one synthetic operation (entries 7, 8). Thus, sequential treatment with L-*selectride* and MeI (HMPA) followed by flash chromatography and crystallization provided diastereo- and enantiomerically pure (2*R*, 3*S*)-product **258o** from the (*E*)-enoyl sultam **253o** or its *anti*- (2*R*, 3*R*)-epimer **258p** from the (*Z*)-enoyl sultam **253p**. Products **258** were saponified without α-epimerization by means of LiOH in aq. THF at r.t. to give free carboxylic acids **259**.

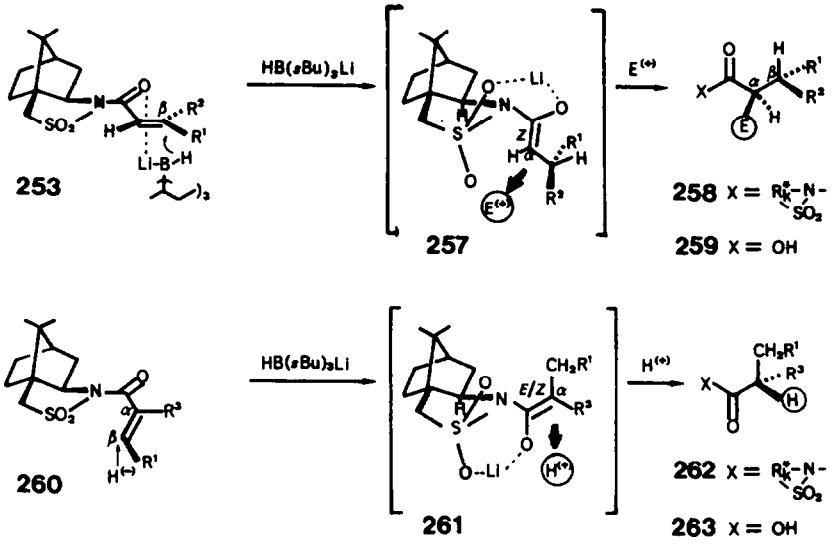
To rationalize the observed inductions at Cβ it is assumed that the *α-unsubstituted* enoyl sultams **253** react in a conformation where the carbonyl is *anti* to the SO_2 group and *s-cis* to the Cα,Cβ bond; the face-differentiation is then dictated by hydride attack from the less hindered bottom face to generate enolates **257**. The described *Cα-stereodifferentiations* are consistent with the postulate that (1) the enoyl-*s-cis*-conformation translates into the (*Z*)-configuration of the enolate **257** and (2) the enolates **257** are reorganized to the depicted Li-chelated conformers which are approached by the electrophile E^+ from the Cα-*Re* face.

As observed previously (*cf.* 3.3.4 and 3.3.5), the topological situation changes on subjecting *α-substituted* enoyl sultams **260** to the tandem hydride addition/protonation (entries 9–11).

α-Substituted products **262** were formed with good stereofacial control as a result of the depicted C=O/Cα,Cβ-*s-trans*- and -C=O/SO_2-*anti* conformation which avoids a steric repulsion between R^3 and the SO_2 group. Hydride addition to **260** provides, consequently, enolates **261** with well-defined (*E*, *Z*)-configurations (X-ray analysis of *O*-acetylated **261r**). Stabilization of enolates **261** by lithium chelation with the lower sulfur-bonded oxygen minimizes steric interactions and directs its protonation to the front face. This novel control of (tetrasubstituted) enolate geometries is highlighted by entry 9: **260q** → (*Z*)-**261q** → (2*R*)-**262q** and by entry 10: **260r** → (*E*)-**261r** → (2*S*)-**262r**.

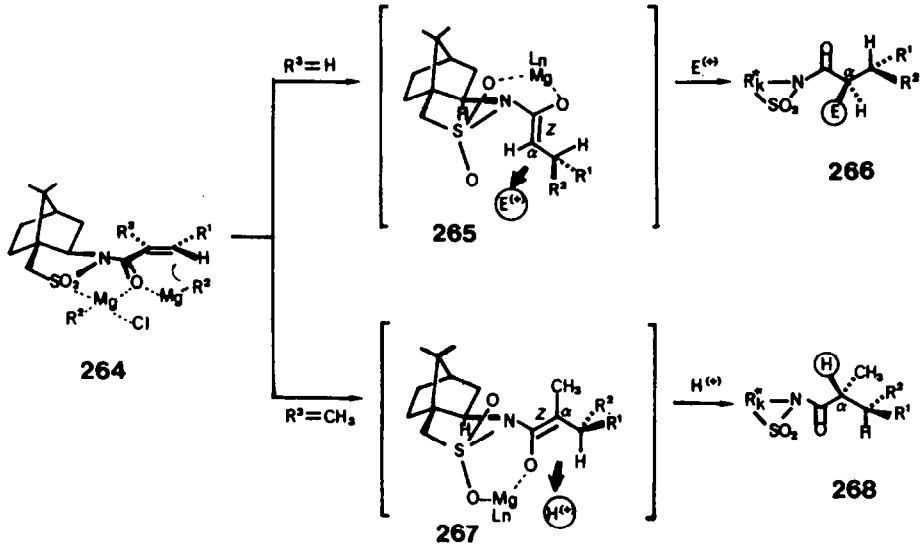
3.3.7. *Conjugate additions of Grignard reagents/enolate trapping.* Most conveniently, simple alkylmagnesium chlorides added smoothly in a 1,4-fashion to *β-trans*-substituted enoyl sultams **264**, R^3 = H to give (on subsequent protonation) imides **266**, E = H in 77–90% d.e.[75] (Scheme 69).

Trapping of the transient enolates **265** with methyl iodide/HMPA furnished after crystallization virtually pure (2*R*, 3*R*)-imides **266** (Table 23).



Scheme 68.

This stereochemistry agrees with the postulate that chelation by the magnesium assures the SO_2/C=O synplanarity of **264** and that the operation of a 6-membered cyclic mechanism for 1,4-additions of Grignard reagents requires the C=O/Cα,Cβ-*s*-*cis*-conformation. Addition of R^2 at the Cβ-bottom face gives the (*Z*)-magnesium enolate **265** which undergoes electrophilic attack from the front side.



Scheme 69.

Table 23. Organomagnesium 1,4-additions to β-substituted enoyl sultams/enolate trapping **264** → **265** → **266**

Entry	R^1	R^2	E	Electrophile	Yield (%) **266**	d.e. (%) Cβ Config.	d.e. (%) Cα Config.
a	CH_3	C_2H_5	H	aq. NH_4Cl	85	90 *R*	—
b	CH_3	nC_3H_7	H	aq. NH_4Cl	90	84 *R*	—
c	CH_3	nC_4H_9	H	aq. NH_4Cl	82	84 *R*	—
d	CH_3	iC_3H_7	H	aq. NH_4Cl	91	77 *R*	—
e	CH_3	nC_6H_{13}	H	aq. NH_4Cl	73	84 *R*	—
f	CH_3	nC_8H_{17}	H	aq. NH_4Cl	81	82 *R*	—
g	C_2H_5	nC_4H_9	H	aq. NH_4Cl	89	82 *R*	—
h	CH_3	nC_4H_9	CH_3	CH_3I/HMPA	82	82 *R*	98 *R*
i	C_2H_5	nC_4H_9	CH_3	CH_3I/HMPA	57	84 *R*	97 *R*

Table 24. Organomagnesium 1,4-addition to α-substituted enoyl sultams/enolate protonation **264** → **267** → **268**

Entry	R^1	R^2	Yield (%)[a] **268**	d.e. (%)[a] Cβ Config.	d.e. (%)[a] Cα Config.
a	H	CH_3	45	—	>99 *R*
b	H	C_2H_5	92(70)	—	90(98) *R*
c	H	nC_3H_7	80(70)	—	96(>99) *R*
d	H	nC_4H_9	81(62)	—	84(98) *R*
e	H	iC_3H_7	93(84)	—	90(98) *R*
f	CH_3	C_2H_5	90(81)	>99(>99) *R*	99(>99) *R*
g	CH_3	nC_4H_9	73(66)	98(>99) *R*	98(>99) *R*
h	C_2H_5	nC_4H_9	83(78)	97(>99) *R*	95(>99) *R*

[a] Values in parentheses after crystallization.

The *overall* topological scenario changed again on successive treatment of α-methyl-substituted enoyl sultams **264**, R^3 = Me with alkylmagnesium chlorides and aq. NH_4Cl. Under these reaction conditions methacryloyl sultam **264**, R^1 = H, R^3 = Me yielded (*R*)-2-methyl imides **268** in 94 to >99% d.e. (entries a–e, Table 24). (*E*)-α,β-disubstituted enoyl sultams **264** (R^1 = alkyl, R^3 = Me) gave (after crystallization) (2*R*, 3*R*)-products **268** in >99% d.e. at both induced centers (entries f–h).

It follows that the topicity of transformations **264** (R^3 = H) → **266** and **264** (R^3 = Me) → **268** are identical at Cβ but opposite at Cα. This can be explained as follows: (1) a cyclic transition state C=O · · Mg-R^2 · · Cβ which enforces the C=O/Cα,Cβ-*s-cis* conformation of **264** (regardless of R^3) in the conjugate addition step; (2) a different conformation of the resulting (*Z*)-enolate **267** minimizing repulsions between the Cα-Me group and the auxiliary unit, as well as protonation of **267** from the front face.

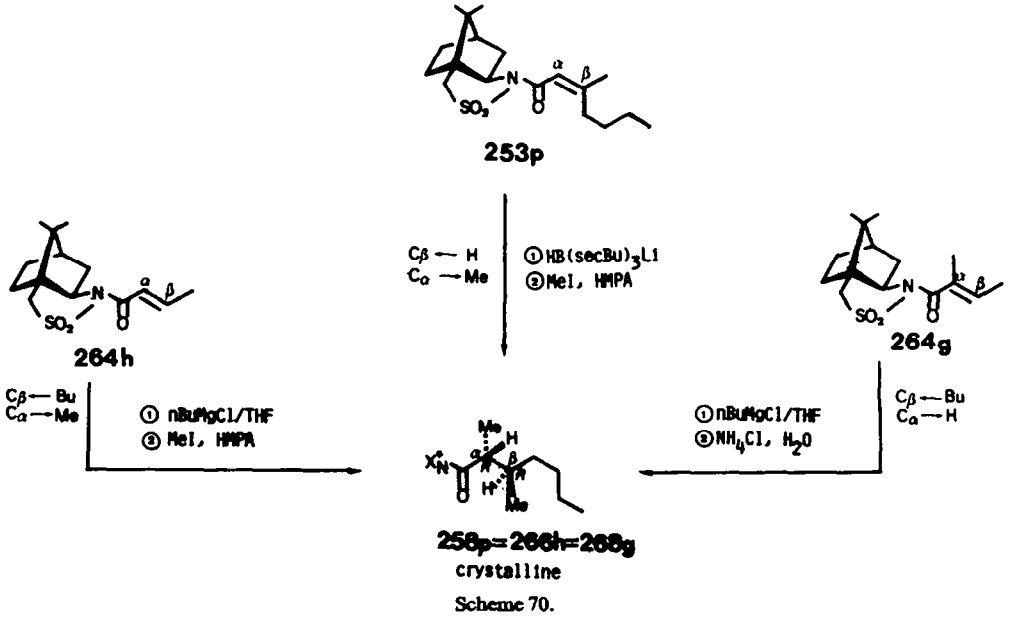
To illustrate the versatility of the sultam-directed 1,4-addition/enolate trapping concept three different options to prepare the same pure (2*R*, 3*R*)-imide **258p** = **266h** = **268g** are displayed in Scheme 70.

4. VARIOUS C(2)-FUNCTIONALIZED BORNANE AUXILIARIES

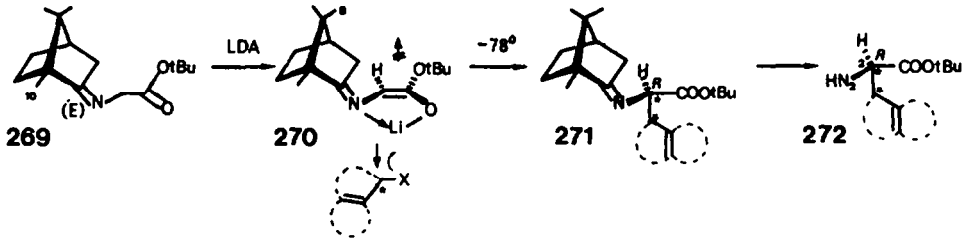
4.1. *Alkylation of a glycinate imine*

The direct use of camphor (**1**) as a chiral auxiliary is exemplified by the alkylation of the lithiated *t*-butyl glycinate imine **270** by benzylic or allylic halides[76] (Scheme 71).

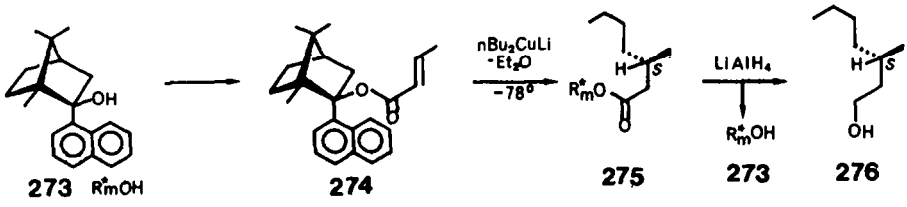
(*E*)-imine **269** was prepared selectively by condensation of *t*-butyl glycinate with camphorthione



Scheme 70.



Scheme 71.



Scheme 72.

owing to the steric influence of the C(10)-methyl group. Treatment of **269** with lithium diisopropylamide gave an enolate to which the chelated structure **270** was assigned. Attack of the allylic (benzylic) halide from the Cα-*Re*-(bottom) face [opposite to the C(8)-methyl group] generated (2*R*)-imines **271** in 69 to > 98% d.e. However, aliphatic or ester-conjugated alkylating agents reacted slower and with only 0–60% stereofacial differentiation. It is obvious that a stereoelectronic interaction of the allylic (benzylic) π-system with the enolate is essential. In support of this postulate alkylation of **270** with 2 molequiv. of racemic 1-phenethyl bromide (entry d) or 3-bromocyclohexene (entry e) proceeded with a clean kinetic resolution of the halide to form (2*R*)-esters **271** containing a second, diastereomerically pure center at C(3). The free aminoester **272d** was obtained by transamination of **271d** with hydroxylamine acetate.

4.2. *Conjugate addition of an organocopper reagent to an enoate*

An intriguingly simple, but isolated example of an asymmetric 1,4-addition utilizes the auxiliary **273**, readily available from camphor and 1-naphthylmagnesium bromide[77] (Scheme 72).

Treatment of crotonate **274** with Li*n*-Bu_2Cu (−78°, Et_2O, 10–30 min) afforded ester **275** in 74% yield and with 95% d.e. Reductive cleavage of **275** regenerated **273** and furnished (*S*)-**276**. The unique role of the naphthalene substituent (vs CH_3 or Ph substituents) in increasing the rate and face selectivity of the addition **274** → **275** remains to be clarified.

5. REAGENTS AND CATALYSTS

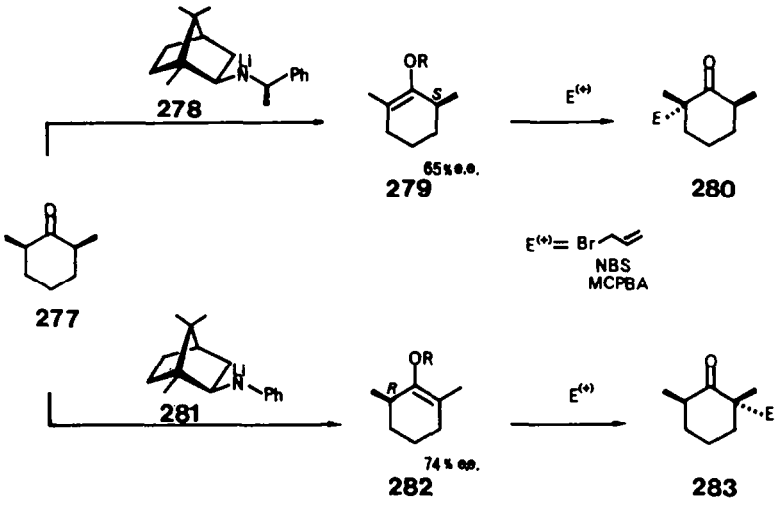
5.1. *General*

In 1946–1951 asymmetric carbonyl reductions with isobornyl or isobornyloxy magnesium chlorides have afforded chiral alcohols in up to 72% or 36% e.e., respectively.[78] Even more impressive advances in the development and application of chiral reagents and catalysts have been accomplished during the last years.[79] However their application is still relatively restricted to specific substrates and reactions. Despite the fundamental practical importance progress is presently slowed down by the difficulties in rationalizing the observed enantioselectivities.

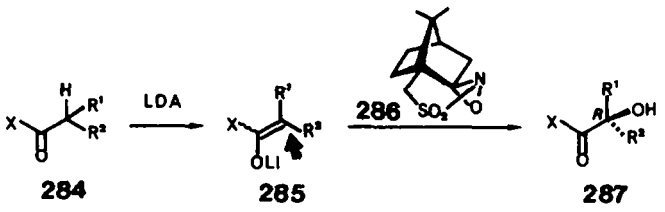
Recent examples of camphor-derived reagents and catalysts are presented as follows.

Table 25. Asymmetric alkylation of a glycinate imine **269** → **271**

Entry	R	X	Yield (%) of **271**	d.e. (%) C(2) of **271**
a	$PhCH_2$	Br	89	>98
b	allyl	Br	85	76
c	methallyl	Cl	79	76
d	1-phenethyl	Br	60	80
e	3-cyclohexenyl	Br	67	89



Scheme 73.



Scheme 74.

Table 26. Asymmetric α-hydroxylations of esters and amides **284** → **287**

Entry	R^1	R^2	X	Cosolvent	Temp. (°)	Yield (%) of **287**	e.e. (%) of **287**
a	Ph	H	OtBu	—	−90	84	71
b	$PhCH_2$	H	OMe	HMPA	−90	63	85.5
c	Ph	Me	$N(CH_2)_4$	—	−78	60	77

5.2. *Reagents*

5.2.1. *Deprotonation of* cis-2,6-*dimethylcyclohexanone.* Enantioselective deprotonation of the prochiral ketone **277** by means of the chiral camphor-derived lithium amides **278** or **281** in THF led to the chiral lithium enolates **279**, R = Li (65% e.e.) and **282**, R = Li (74% e.e.), respectively[80] (Scheme 73).

Successive enolate trapping with allyl bromide furnished ketones **280** or **283** (E = $CH_2CH{=}CH_2$ in *ca* 65% overall yield). Alternatively, successive treatment of the chiral enolates with $ClSiMe_3$ and NBS or MCPBA afforded chiral ketones **280**, **283**, E = Br or OH.

5.2.2. *α-Hydroxylation of enolates.* Prochiral lithium enolates **285**, derived from esters or *N*-pyrrolidine amides **284** have been recently oxidized with the camphorsulfonyl oxaziridine **286**[81] (Scheme 74).

The reagent, prepared in three steps from camphor-10-sulfonyl chloride, gave α-hydroxycarbonyl products **287** in up to 85.5% enantiomeric excess.

5.3. *Catalysts*

5.3.1. *Metal complexes of* 3-(*perfluoro-acyl*) *camphor.* Coordination compounds of 3-trifluoroacetyl or 3-heptafluoropropionyl camphor with europium, praseodymium and ytterbium have been introduced 15 years ago as chiral shift reagents for the NMR analyses of enantiomer mixtures.[82] Only a few years later complexes, particularly nickel(II)-bis[3-heptafluoropropionyl camphorate] were shown to be of use as enantiospecific stationary phases for the separation of oxygen- and nitrogen-containing enantiomers by complexation gas chromatography.[82]

More recently it was found that $Eu(hfc)_3$ (**289**, 0.5–5 mol.%) catalyzes hetero-Diels–Alder reactions of silyloxydienes to arylaldehydes[83] (Scheme 75).

Table 27. Europium-complex-catalysed Diels–Alder reactions of dienes **288** with benzaldehyde to give adducts **290**

Entry	Series	R	EuL_3	C(2)	e.e. (%) C(2)
1	a	*t*-Bu	**289**	*R*	42
2	b	(3*R*)-menthyl	**289**	*R*	86
3	c	(3*S*)-menthyl	**289**	*R*	18
4	d	(3*R*)-menthyl	$Eu(fod)_3$	*S*	10

Table 28. Cobalt-catalysed asymmetric cyclopropanations

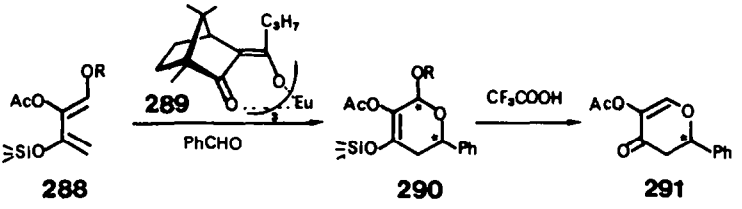
Entry	R	Yield (%) **299**+**300**	e.e. (%) **299**	e.e. (%) **300**
a	H	92	67	75
b	Ph	95	70	—[a]
c	COOMe	92	71	37

[a] **299b** = **300b**.

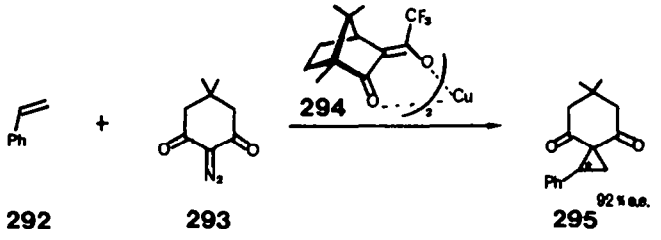
Dienes **288** reacted smoothly with benzaldehyde at room temperature in a highly *endo*-selective manner to give exclusively *cis*-substituted dihydropyrans **290** which on acid-promoted elimination furnished dihydropyrones **291** in good overall yield. Thus (*R*)-**291** was obtained from the prochiral diene **288a** in only moderate e.e. (42%) but in 86% e.e. from the chiral menthyloxy-substituted diene **288b**. Interestingly, the interactivity of diene auxiliary group and catalyst is optimal (entry 2) when the individual π-facial influences (*cf.* entries 1, 4) are of opposite sense.

The copper complex of 3-trifluoroacetyl camphor (**294**) can also serve as a catalyst for asymmetric cyclopropanations, e.g. for the transformation **292**+**293** → **295** proceeding at +80° with 92% face-discrimination[84] (Scheme 76).

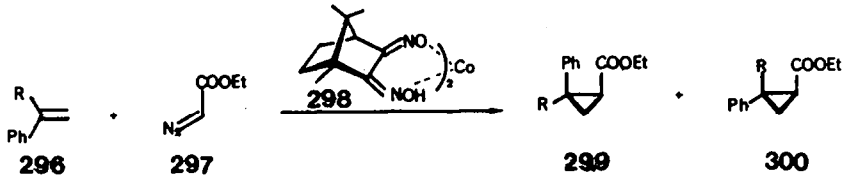
5.3.2. *Cobalt-catalyzed cyclopropanation.* Analogous carbenoid-type reactions between conjugated terminal olefins such as **296** and diazoester **297** proceed readily at 0° in the presence of 3 mol.% of bis[(−)-camphorquinone-α-dioximato] cobalt (**298**) to give mixtures of *cis* and *trans* substituted cyclopropane carboxylates **299** and **300** in good overall yield with up to 75% induction[85] (Scheme 77).



Scheme 75.



Scheme 76.



Scheme 77.

6. CONCLUSION

Chiral templates containing the bornane skeleton have contributed essentially to the current, breathtaking progress in asymmetric synthesis. Covalently bound but recoverable camphor-derived auxiliaries deserve particular attention. They confer a host of valuable properties to the substrate facilitating handling, analysis and purification (crystallinity) of intermediates and products. Their topological bias usually overrides that of pre-existing centers simplifying stereorational planning in synthesis.

Thus, a large number of reactions yield chiral building blocks in greater than 90% enantiomeric excess. Numerous applications to the syntheses of natural products testify to the practical utility of this class of auxiliaries. Increasing commercial availability of key reagents may foster their broad exploitation.

The future will certainly provide more insight into the transition state topologies, nevertheless, the depicted hypothetical rationalizations have proved to be of predictive value.

In summary, the evidence presented leaves no doubt that camphor derivatives are a valuable asset for the organic chemist interested in reliable and versatile preparations of enantiomerically pure compounds.

Acknowledgements—It is a privilege to acknowledge the crucial contributions of my coworkers whose names appear in the references. Our own work mentioned in this article was supported financially by the Swiss National Science Foundation, Sandoz AG, Basel and Givaudan SA, Vernier. We thank Professors D. P. Curran and K. N. Houk for kindly providing an unpublished manuscript.

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