Tetrahedron Vol. 40, No. 8, pp. 1391 to 1400, 1984
Printed in Great Britain.

0040-4020/84 $3.00 + .00

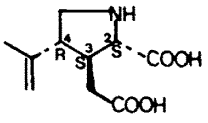
ENANTIOSELECTIVE SYNTHESIS OF (+)-α-ALLOKAINIC ACID BY ASYMMETRIC LEWIS ACID-MEDIATED INTRAMOLECULAR ENE REACTION

W. OPPOLZER,* C. ROBBIANI and K. BÄTTIG
Département de Chimie Organique, Université de Genève, CH-1211 Genève, Switzerland

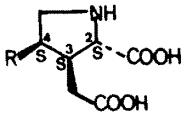
(*Received in USA* 28 *March* 1983)

Abstract—(+)-α-Allokainic acid ((+)-**1**) has been prepared for the ester of *cis*-β-chloroacrylic acid and (−)-8-phenylmenthol by a sequence of four synthetic operations. The crucial step **8d**→**14d** (Scheme 4) is a ~100% diastereo- and 90% enantioselective intramolecular ene reaction proceeding at −35° on treatment of **8d** with Me_2AlCl. Saponification of **14d** regenerated the auxiliary chiral alcohol and yielded (+)-**1** on subsequent decarboxylation. In the analogous cyclization **11d**→**15d** the sense of asymmetric induction (78% d.e.) was opposite as confirmed by the conversion of **15d** to (−)-α-allokainic acid.

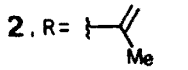
(+)-α-Allokainic acid has been assigned structure **1** on the basis of chemical[1] and X-ray evidence.[2] It co-occurs in the marine algae *Digenea simplex* with its C(4)-epimer (−)-α-kainic acid (**2**).[1,3] Based on an earlier correlation of structures (+)-**1** and (−)-**2**,[4] we recently established the absolute configuration of (+)-**1** by a stereocontrolled synthesis of (−)-**2** from (*S*)-glutamic acid.[5]



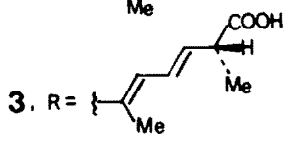
(+)-**1**

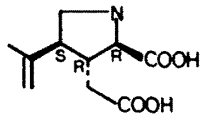


2, R=



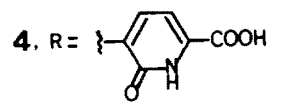
3, R=



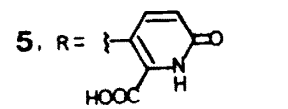


(−)-**1**

4, R=

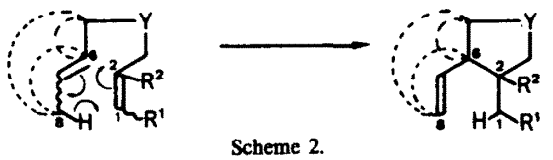


5, R=



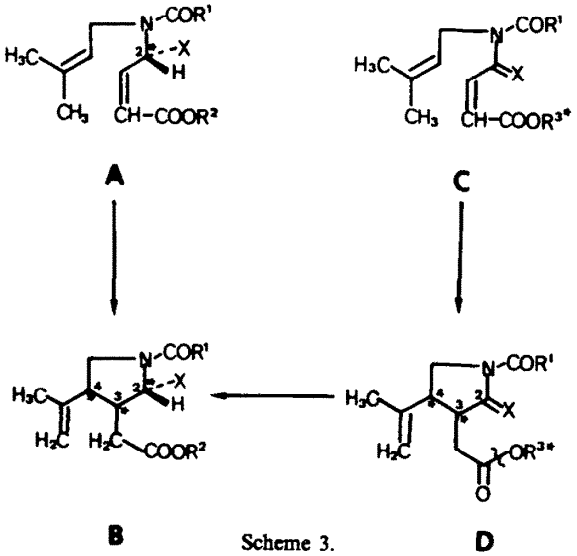
Scheme 1.

(−)-α-Kainic acid (**2**) is a powerful neuroexcitant inducing neurological disorders in mammals,[6] as probably are (−)-domoic acid (**3**) (isolated from algae)[7] and the mushroom constituents acromelic acids A and B (**4**, **5**).[8] Direct, versatile and stereocontrolled syntheses of related kainoids may provide a basis for developing antagonists to be used therapeutically in cases of excessive neuronal excitation.[6]

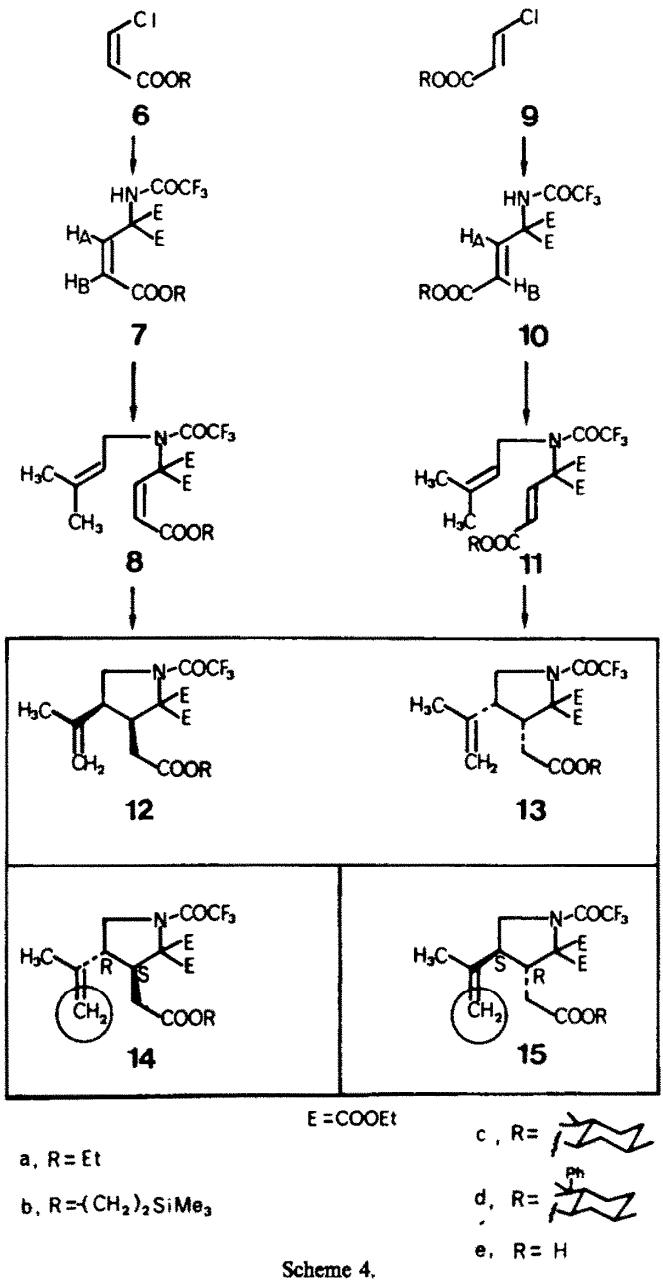


Scheme 2.

This goal converges with our longstanding interest in intramolecular type-I-ene reactions of 1,6-dienes (Scheme 2), a valuable method for the diastereoselective formation of 5-membered rings.[9] Thus, the ene processes outlined in Scheme 3 offer short approaches to both α-kainic and α-allokainic acids. In fact, each of the racemic acids **1**[10] and **2**[11] has been obtained selectively on directing the diastereochemistry of the thermal cyclization by modification of the carboxyl equivalent X and of the enophile geometry. Aiming further at enantioselective syntheses of kainoids, we envisaged achieving asymmetric induction in the crucial ene addition.



Scheme 3.



Scheme 4.

To this end, two basic strategies (Scheme 4) were particularly attractive. The first employs the cyclization **A**→**B**, in which the configurationally pure center C-2 of **A** determines the developing chirality at C-3 and C-4 in **B**; this has been applied successfully to the synthesis of (−)-α-kainic acid (**2**).[5] In the alternative sequence, **C**→**D**→**B**, the chiral ester substituent R^{3*} in **C** first induces centers C-3 and C-4 in **D** which in turn control the configuration at C-2 in **B**. We wish to report here in experimental detail the implementation of the latter concept for the efficient synthesis of (+)-α-allokainic acid, reported previously in a short communication.[12]

Preparation and asymmetric ene-reactions of the dienes **8** *and* **11**

Our chances of success had been considerably increased by our previous finding that diethylaluminium chloride promotes efficient cyclization of the ethyl enoates **8a** and **11a** at −78 to −35°, giving the *trans*-pyrrolidines **14a/15a** with 100% and 89% diastereochemical control, respectively (Scheme 4).[13] The convenient stereospecific routes to **8a** and **11a** were now readily applied to the synthesis of various (*Z*)- or (*E*)- dienoates. Thus, treatment of the menthyl *cis*-β-chloroacrylate **6c** (obtained from (−)-menthol and the acid **6e**[14] by acid catalyzed esterification) with diethyl trifluoroacetamidomalonate[15] in the presence of 1 eq. of potassium t-butoxide furnished the (*Z*)-butenoate **7c** (82%, ^{1}H-NMR: $J_{AB} = 12$ Hz). N-alkylation of **7c** with NaH/1-bromo-3-methyl-2-butene afforded the (*Z*)-menthyl dienoate **8c** (61%). Analogous Michael addition/elimination starting from the *trans*-β-

Table 1. Cyclizations of the (*Z*)- and (*E*)-Menthyl dienoates **8c** and **11c**

Diene	Cyclization conditions	Product ratios	
		12c / 14c 13c / 15c	14c/15c or 15c/14c
8c	70°/80 h	24 : 76	59 : 41
8c	180°/15 min.	24 : 76	56 : 44
8c	$AlEt_2Cl$/-78°	0 :100	50 : 50
11c	70°/48 h	47 : 53	49 : 51
11c	180°/15 min.	50 : 50	50 : 50
11c	$AlEt_2Cl$/-78°	6 : 94	49 : 51

chloroacrylate **9c** yielded the (*E*)-ester **10c** (77%, ^{1}H-NMR: J_{AB} = 16 Hz), which on alkylation gave the (*E*)-diene **11c** (73%).

Before pursuing the cyclization of **8c** and **11c**, a method of readily assessing the expected induction was required. To this end we explored the possibility of NMR-analysis of the pure diastereoisomer pair **14c/15c** (1:1), independently accessible from the racemic monoacid **14e/15e**. The latter in turn was prepared by $AlEt_2Cl$-promoted cyclization of the trimethylsilylethyl ester **8b** (obtained *via* the route **6b**→**7b**→**8b**), followed by selective fluoride-induced ester cleavage.[16] Esterification of racemic **14e/15e** with (−)-menthol (DCC, DMAP) afforded the desired 1:1-mixture **14c/15c**, which after the addition of $Eu(FOD)_3$ showed two well-separated CF_3-signals in a 1:1 ratio in the ^{19}F-NMR spectrum.

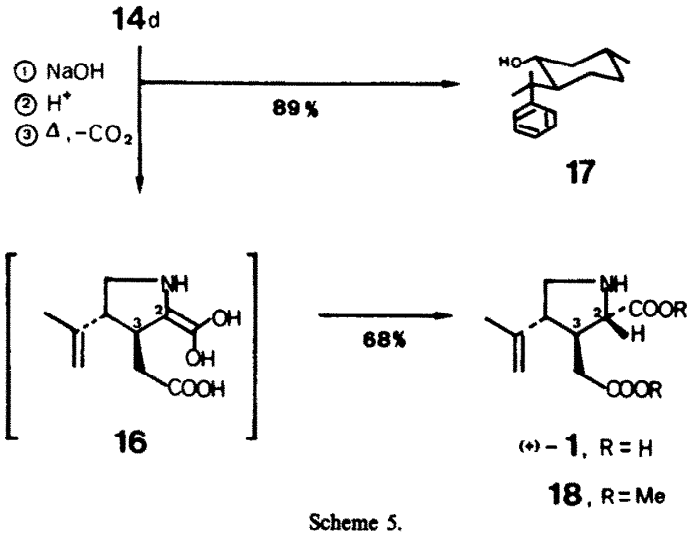
With this easy analytical method in hand, we proceeded to thermal and Et_2AlCl-promoted cyclizations of the (−)-menthyl dienoates **8c** and **11c**. Disappointingly, little if any (≤18% d.e.) chiral induction at the newly formed centers was realized, as indicated in Table 1. The 1:3-ratio of *cis* (**12c/13c**) to *trans* (**14c/15c**) products follows from their chromatographic separation and from the ^{1}H-NMR-signals of the olefinic protons by assigning two singlets at $\delta = 4.75$ and 5.17 ppm to the *cis*-products and a narrow signal at $\delta = 4.85$–5.1 ppm to the *trans*-products.[5,17] Moreover, the isolated *cis*-pair **12c/13c** shows in the ^{19}F-NMR spectrum two signals (≃1:1) different from those displayed by the *trans*-pair **14c/15c**.

Then, in view of the known asymmetric Diels–Alder additions of 8-phenylmenthyl acrylates,[18] we envisaged the ene-type-I cyclization of the dienes **8d** and **11d**. Esters **6d** and **9d** were efficiently obtained by treatment of the *cis*- and *trans*-β-chloroacryloylchlorides with (−)-phenylmenthol[18] and AgCN.[19] Subsequent conjugate addition/elimination followed by alkylation furnished the (*Z*)-diene **8d** in 55% overall yield from **6d** and the (*E*)-diene **8d** in 62% overall yield from **9d**. Thermal cyclizations of the 1,6-dienes **8d** and **11d** proceeded again with moderate diastereochemical control and without enantioselectivity, as evident from Table 2. The product ratios were easily determined by integration of the ^{1}H-NMR (360 MHz)—singlets of the olefinic protons; those corresponding to **12d/13d** appear at δ 4.66, 4.68, 5.00 and 5.09 ppm and exhibit 20% of the intensity of the singlets at 4.83, 4.90, 4.98 and 5.013 ppm, which correspond to **14d/15d**. The assignment of the **14d/15d**-signals was confirmed by ^{1}H-NMR-measurement of a pure 1:1-mixture of **14d/15d**, prepared by esterification of the racemic monoacid **14e/15e** with (−)-8-phenylmenthol. (Additional characteristic signals of **14d** and **15d** are listed in the Experimental.)

On the other hand, we were pleased to find that treatment of the (*Z*)-phenylmenthylester **8d** with 3 eq. of dimethylaluminium chloride[20] in dry CH_2Cl_2 at

Table 2. Cyclizations of the (*Z*)- and (*E*)-Phenylmenthyl dienoates **8d** and **11d**

Diene	Cyclization conditions	Product ratios	
		12d / 14d 13d / 15d	14d/15d
8d	70°/80 h	20 : 80	50 : 50
8d	180°/15 min	20 : 80	50 : 50
8d	$AlMe_2Cl$/-35°	0 :100	95 : 5
11d	180°/15 min	50 : 50	50 : 50
11d	$AlMe_2Cl$/-35°	<5 :>95	11 : 89



Scheme 5.

−35° for 18 hr furnished the isomers **14d** and **15d** (60% yield) in a ratio of 95:5. As expected, the *opposite* sense of induction prevailed on Me_2AlCl-mediated cyclization of the (*E*)-phenylmenthylester **11d** which gave the *trans*-isomers **14d** and **15d** (81% yield) in a ratio of 11:89.

Conversion of the cyclization products **14d** *and* **15d** *to* (+)-α-*allokainic acid and to* (−)-α-*allokainic acid*

So far the analytical results (Table 2) permitted us to determine only the extent of asymmetric induction but not its absolute sense. This was, however, readily proven by conversion of the 95:5-mixture **14d/15d** (obtained from **8d**) to (+)-α-allokainic acid, carried out in the following manner (Scheme 5). Alkaline saponification furnished on extraction unchanged (−)-8-phenylmenthol (89%). Successive decarboxylation of the malonic acid *in situ* at $p_H = 6$ to 3 and precipitation of the copper salt of (+)-**1** with aq. H_2S provided the enantiomerically pure (+)-α-allokainic acid (68% yield from 95% pure **14d**), identified by comparison with (+)-**1** of natural origin (m.p., chiroptic properties, IR, ^{1}H-NMR and MS). Moreover, the synthetic and natural amino-acids were shown to be identical and enantiomerically pure by comparing the ^{1}H-NMR spectra of the dimethylester **18** derived from natural and synthetic (+)-**1**, using a chiral shift reagent ($Eu(TFC)_3$). In close analogy, the 11:89-mixture **14d/15d** (obtained from **11d**) was converted to (−)-α-allokainic acid (62% overall yield) which exhibits ^{1}H-NMR (360 MHz) and mass spectra identical to those of (+)-**1**; its absolute configuration and enantiomeric purity were determined by ^{1}H-NMR-comparison of its dimethylester with **18** and the corresponding racemic ester in the presence of $Eu(TFC)_3$.

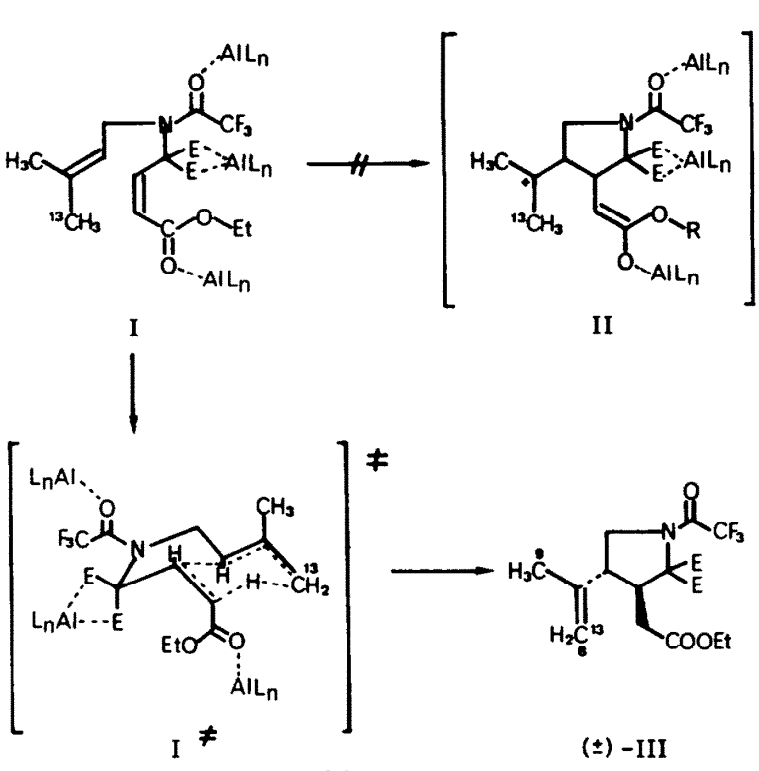
The observed induction of center C-2 in the final decarboxylation step merits further comment. Presumably this control derives from internal C-protonation of intermediate **16** by the acetic acid chain; its extent was checked by successive treatment of the soluble Cu-salts with H_2S and ion exchange resin which yielded a 1:2.5-mixture of **1** and a stereoisomer, tentatively assigned as the C-2 epimer (β-allokainic acid).[21] This indicates the induction at C-2 to be significant but not quantitative.

Discussion of the asymmetric ene-reactions **8d**→**14d** *and* **11d**→**15d**

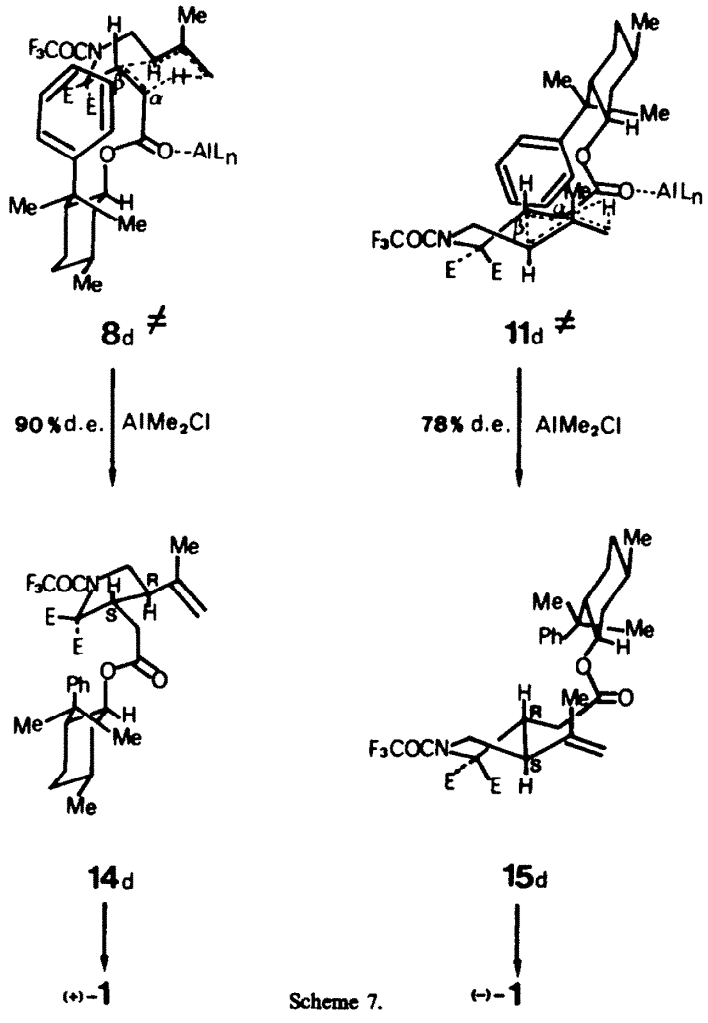
First the question arose if the Me_2AlCl-promoted cyclization **8d**→**14d** is in fact a concerted ene-reaction or rather proceeds via a cationic intermediate. We believe that mechanistic studies of the related cyclization **8a**→**14a/15a** (Scheme 6) may be relevant in this context. For geometrical reasons, hydrogen should be transferred exclusively from the *trans*-positioned allylic methyl in a concerted reaction.[13] Indeed, Et_2AlCl-induced cyclization of 1,6-dienoate I carrying a ^{13}C-labelled *trans*-Me furnished (±)-III which contains all of the ^{13}C in the methylene group.[22] In contrast, the intermediacy of cation II would have caused scrambling of ^{13}C at positions 8 and 9 in the cyclization product. We thus propose the operation of a transition state I where coordination of AlR_2Cl with the conjugated ester carbonyl is mainly responsible for the acceleration of the ene process by lowering the enophile LUMO energy.[23]

Assuming a concerted mechanism, then, the remarkable asymmetric induction (90% d.e.) during the cyclization **8d**→**14d** may be rationalized by a transition state geometry **8d*** (Scheme 7);[24] in this arrangement the enoate CO group is antiplanar with the $C_\alpha = C_\beta$- and synplanar with the alkoxy-C,H-bond[25] and the phenyl ring shields the C_β-*si* face of the enophile. In support of such a conformation, the phenylmenthylester **8d** shows, even in the absence of Me_2AlCl, the ^{1}H-NMR signal of H-C_α shifted up-field by 1.01 and 1.04 ppm compared to the ethyl- and menthyl enoates **8a** and **8c**. Accordingly, the ene addition is directed preferentially to the C_β-*re* face. Similar stereochemical analysis of the Lewis-acid-induced cyclization of the (*E*)-phenylmenthylester **11d** (transition state **11d***) predicted shielding of the C_β-*re* face and consequently, predominant ene attack from the C_β-*si* face as confirmed experimentally.

In summary, the cyclizations **8d**→**14d** and **11d**→**15d** are the first examples of ene reactions which proceed with high asymmetric induction and



Scheme 6.



Scheme 7.

permit regeneration of the chirality directing group. The possibilities to manipulate the absolute sense of induction by variation of the enoate geometry as well as of the chiral auxiliary group[26] may stimulate further applications in synthesis.[27]

EXPERIMENTAL

General. All reactions were carried out under argon with magnetic stirring. Solvents were dried by distillation from drying agents, as follows: diethylether (Et_2O, KH), tetrahydrofurane (THF, K-metal), hexamethylphosphoramide (HMPA, CaH_2), t-BuOH (Na-metal), CH_2Cl_2 (CH_2Cl_2, P_2O_5). "Work-up" denotes washing of the organic phase with sat. NaCl aq, drying with solid $MgSo_4$, and removal of solvent by distillation *in vacuo* using a rotatory evaporator. Column chromatography was carried out on SiO_2 (Merck, Kieselgel 60, 0.063–0.2). For medium pressure chromatography, SiO_2 (Woelm ICN, 0.032–0.063 mm) and a FMI RP-pump were used. M.ps were determined on a Kofler hot stage and are uncorrected; temps are expressed in degrees Celsius. UV spectra: λ_{max} in nm ($\log \epsilon$). IR absorptions are reported as $\tilde{\nu}_{max}$ in cm^{-1}. ^{1}H-NMR spectra were recorded in $CDCl_3$ soln at 100 MHz, unless otherwise specified, with an internal standard of TMS δ (ppm) = 0; abbreviations used are: *s* = singlet, d = doublet, *t* = triplet, *qa* = quadruplet, *m* = multiplet, *J* = spin–spin coupling constant (Hz). Mass spectral data (MS) are given as *m/z* (rel%). Optical rotations, [α], were measured at 25°, unless otherwise specified, using a Perkin–Elmer 241 automatic polarimeter (concentration C, solvent).

Preparation of the (Z)- *and* (E)-*chloroacrylates* **6** *and* **9** 2-*Trimethylsilylethyl* (Z)-3-*chloroacrylate* (**6b**).

A soln of N,N-dicyclohexyl carbodiimide (5.32 g, 26 mmol) in CH_2Cl_2 (3 ml) was added dropwise to a stirred mixture of (*Z*)-3-chloroacrylic acid[14] (2.50 g, 23.5 mmol), 2-trimethylsilylethanol (3.49 g, 29.6 mmol) and 4-dimethylaminopyridine (200 mg, 1.64 mmol) in CH_2Cl_2 (30 ml) at 0°. Stirring of the mixture at r.t. for 3 hr, filtration, evaporation and distillation of the residue at 101°/25 torr furnished ester **6b** (oil, 4.34 g, 89%. IR: 3065, 2960, 1725, 1620, 1352, 1285, 1231, 1170, 1065, 948, 867, 845. ^{1}H-NMR: 0.0 (*s*, 9H); 0.9–1.3 (2H); 4.15–4.4 (2H); 6.16 (*d*, *J* = 3, 1H); 6.67 (*d*, *J* = 8, 1H). MS: 207 (0.3, $C_8H_{15}{}^{37}ClO_2Si^+$), 205 (1, $C_8H_{15}{}^{35}ClO_2Si^+$), 171(37), 163(67), 93(61), 75(98), 73(100).

(−)-*Menthyl* (Z)-3-*chloroacrylate* (**6c**). A soln of (*Z*)-3-chloroacrylic acid (3 g, 28.2 mmol), (−)-menthol (7.65 g, 49,2 mmol) and *p*-toluenesulfonic acid (450 mg) in benzene (50 ml) was heated under reflux for 4 days using a Dean–Stark water separator. Evaporation of the solvent, shaking of the residue with ether sat $NaHCO_3$ aq, work-up, chromatography (ether–hexane 2:1) and crystallization (pentane) furnished ester **6c** (6.75 g, 97%), m.p. 62.5–63.5°. IR (CCl_4): 2980, 2870, 1732, 1628, 1465, 1220, 1170, 988. ^{1}H-NMR: 0,7–2.2 (18H); 4.8 (*d* × *t*, *J* = 4.5 and 11, 1H); 6.19 (*d*, *J* = 8, 1*H*); 6.70 (*d*, *J* = 8, 1H). MS: $C_{13}H_{21}ClO_2{}^+$ not visible, 138(100), 123(31), 109(9), 95(80), 89(57), 81(57). $[\alpha]_D = -96.8°$, $[\alpha]_{578} = -101.4°$, $[\alpha]_{546} = -114.6°$, $[\alpha]_{436} = -194.3°$, $[\alpha]_{365} = -303.8°$ (*c* = 2.5, $CHCl_3$).

(+)-8-*Phenylmenthyl* (Z)-3-*chloroacrylate* **6d**. AgCN (83 mg, 0.6 mmol) was added to a soln of (*Z*)-3-chloroacryloyl chloride[14] (80 mg, 0.64 mmol) and (−)-8-phenylmenthol[18] (100 mg, 0.43 mmol) in benzene (2 ml). The mixture was refluxed for 5 hr, then filtered through Celite. Evaporation of the filtrate and chromatography of the residue (toluene) provided ester **6d** (oil, 123 mg, 89%). IR (CCl_4): 2978, 1728, 1622, 1221, 1170, 1130, 990. ^{1}H-NMR: 0.87 (*d*, *J* = 6.5, 3H); 0.9–2.2 (8H); 1.22 (*s*, 3H); 1.31 (*s*, 3H); 4.9 (*d* × *t*, *J* = 4.5 and 11, 1H); 5.41 (*d*, *J* = 8, 1H); 6.46 (*d*, *J* = 8, 1H); 7.0–7.4 (5H). MS: 322 (0.3, $C_{19}H_{25}{}^{37}ClO_2{}^+$), 320 (1, $C_{19}H_{25}{}^{35}ClO_2{}^+$), 215(9), 200(2), 144(4), 130(5), 120(10), 119(100), 118(22), 91(34), 89(33). $[\alpha]_D = +5.3°$, $[\alpha]_{578} = +6.6°$, $[\alpha]_{546} = +10.6°$, $[\alpha]_{436} = +51.4°$, $[\alpha]_{365} = +165.0°$ (*c* = 1.0, $CHCl_3$).

(−)-*Menthyl* (E)-3-*chloroacrylate* (**9c**). Following the procedure described for the preparation of ester **6c** acid-catalyzed esterification of (*E*)-3-chloroacrylic acid[14] (3 g, 28.2 mmol) with (−)-menthol (7.69 g, 49.2 mmol) afforded ester **9c** (oil, 6.31 g, 91%), IR (CCl_4): 2980, 2875, 1722, 1613, 1301, 1265, 1162, 945, 868. ^{1}H-NMR: 0.78 (*d*, *J* = 6.5, 3H); 0.9-2.2 (9H); 0.91 (br. *d*, *J* = 7, 6H); 4.78 (*d* × *t*, *J* = 4.5 and 10.5, 1H); 6.26 (*d*, *J* = 14, 1H); 7.36 (*d*, *J* = 14, 1H). MS: $C_{13}H_{21}ClO_2{}^+$ not visible, 138(100), 123(40), 95(98), 89(76), 81(78). $[\alpha]_D = -75.0°$, $[\alpha]_{578} = -78.3°$, $[\alpha]_{546} = -88.8°$, $[\alpha]_{436} = -148.5°$, $[\alpha]_{365} = -224.5°$ (*c* = 10, EtOH).

(−)-8-*Phenylmenthyl*-(E)-3-*chloroacrylate* (**9d**). AgCN (800 mg, 6 mmol) was added to a soln of (*E*)-3-chloroacryloyl chloride (1.08 g, 8.6 mmol) and (−)-8-phenylmenthol (1.0 g, 4.3 mmol) in benzene (25 ml). Refluxing of the mixture for 5 hr, filtration through Celite, evaporation of the filtrate and chromatography (toluene) furnished ester **9d** (oil, 1.086 g, 79%). IR (CCl_4): 2982, 1720, 1615, 1270, 1165, 942. ^{1}H-NMR (360 MHz): 0.90 (*d*, *J* = 6.5, 3H); 0.95 (*m*, 1H); 1.2 (*m*, 1H); 1.21 (*s*, 3H); 1.30 (*s*, 3H); 1.45–1.6 (2H); 1.72 (*m*, 1H); 1.8–1.95 (2H); 2.13 (*m*, 1H); 4.85 (*d* × *t*, *J* = 4.5 and 11, 1H); 5.65 (*d*, *J* = 15, 1H); 6.49 (*d*, *J* = 15, 1H); 7.1–7.35 (5H). MS: $C_{19}H_{25}ClO_2{}^+$ not visible, 215(2), 214(5), 199(2), 149(2), 119(100), 91(16). $[\alpha]_D = -10.8°$, $[\alpha]_{578} = -12.0°$, $[\alpha]_{546} = -12.3°$, $[\alpha]_{436} = -7.1$, $[\alpha]_{365} = +25.0°$ (*c* = 2.2, $CHCl_3$).

General procedure for the substitution of 3-*chloroacrylates with diethyltrifluoroacetamidomalonate* (**6**→**7**) and (**9**→**10**)

0.33 N t-BuOK in t-BuOH was added dropwise to a 2 N soln of diethyl trifluoroacetamidomalonate[15] (1 equiv) in t-BuOH at r.t. After 10 min, addition of the corresponding 9-chloroacrylate **6** or **9**, (1.0–1.1 equiv), subsequent stirring of the mixture at r.t. for 16 hr, acidification with AcOH, evaporation, shaking of the residue with ether–H_2O and work-up gave the corresponding diethoxycarbonyl-4-trifluoroacetamido-2-butenoate (**7** or **10**).

2-*Trimethylsilylethyl* (Z)-4,4-*diethoxycarbonyl*-4-*trifluoroacetamido*-2-*butenoate* **7b**. Following the general procedure, conversion of **6b** (2.19 g, 10.6 mmol) to **7b**, subsequent chromatography (toluene/EtOAc 19:1) and bulb-to-bulb distillation at 150° (bath)/30 Torr gave unchanged chloroacrylate **6b** (1.17 g) and pure **7b** (oil, 2.17 g, 47% or 99% based on recovered **6b**), IR (CH_2Cl_2): 3400, 3060, 2990, 1758, 1735, 1525, 1285, 1220, 1175, 1045, 865. ^{1}H-NMR: 0.02 (*s*, 9H); 0.85–1.1 (2H); 1.25 (*t*, *J* = 7, 6H); 4.1–4.5 (6H); 6.04 (*d*, *J* = 12, 1H); 7.24 (*d*, *J* = 12, 1H); 8.26 (br. *s*, 1H). MS: $C_{17}H_{26}F_3NO_7Si^+$ not visible, 426(12), 398(31), 368(24), 324(15), 322(14), 251(16), 205(20), 171(34), 73(100).

(−) - *Menthyl*(Z) - 4,4 - *diethoxycarbonyl* - 4 - *trifluoroacetamido* - 2 - *butenoate* (**7c**). Following the general procedure conversion of **6c** (2.99 g, 12.2 mmol) to **7c** and subsequent chromatography (ether/hexane 1:4) afforded unchanged **6c** (680 mg) and pure **7c** (3.66 g, oil, 63% or 82% based on recovered 6c), UV (hexane), 209.5 (4.05). IR (CH_2Cl_2): 3400, 2960, 2870, 1760, 1740, 1215, 1175. ^{1}H-NMR: 0.72 (*d*, *J* = 7, 3H), 0.8–2.1 (8H); 0.90 (*d*, *J* = 7, 3H); 0.93 (*d*, *J* = 7, 3H); 1.26 (t, *J* = 7, 6H); 4.1–4.5 (4H); 4.74 (*d* × *t*, *J* = 4.5 and 10.5, 1H); 6.04 (*d*, *J* = 12, 1H); 7.27 (*d*, *J* = 12, 1H); 8.3 (br. *s*, 1H). MS: 478 (4, $C_{22}H_{31}F_3NO_7{}^+$), 405(6), 342(17), 269(15), 251(15), 223(30), 205(19), 139(53), 138(100). $[\alpha]_D = -41.9°$, $[\alpha]_{578} = -45.3°$, $[\alpha]_{546} = -49.7°$, $[\alpha]_{436} = -84.9°$, $[\alpha]_{365} = -135.3°$ (*c* = 2.75, $CHCl_3$).

(+) - *Phenylmenthyl* (Z) - 4,4 - *diethoxycarbonyl* - 4 - *trifluoroacetamido* - 2 - *butenoate* **7d**. Following the general procedure, conversion of **6d** (3.52 g, 11 mmol) to **7d** and subsequent chromatography (toluene, then toluene, EtOAc 19:1) provided unchanged **6d** (1.48 g) and pure **7d** (oil, 3.89 g, 64% or 92% based on recovered **6d**), IR (CCl_4): 3400, 2960, 1762, 1735, 1710, 1405, 1212, 1175, 820, 200. ^{1}H-NMR: 0.88 (*d*, *J* = 7, 3H); 0.9–2.2 (20H); 4.1–4.5 (4H);

4.84 (*d* × *t*, *J* = 4.5 and 10.5, 1H); 5.20 (*d*, *J* = 12, 1H); 7.08 (*d*, *J* = 12, 1H); 7.1–7.4 (5H); 8.3 (br. *s*, 1H). MS: 555 (4, $C_{28}H_{36}F_3NO_7^+$), 437(10), 342(19), 324(26), 296(5), 214(24), 119(100), 118(35), 105(13), 91(15). $[\alpha]_D = +15.2°$, $[\alpha]_{578} = +16.4°$, $[\alpha]_{546} = +20.2°$, $[\alpha]_{436} = +52.4°$, $[\alpha]_{365} = +130.4°$ (*c* = 1.5 $CHCl_3$).

(−) - *Menthyl* (E) - 4,4 - *diethoxycarbonyl* - 4 - *trifluoroacetamido* - 2 - *butenoate* (**10c**). Following the general procedure conversion of **9c** (2.0 g, 8.20 mmol) to **10c** and subsequent chromatography (hexane–ether 4:1) furnished unchanged **9c** (840 mg) and after crystallization (pentane–ether) pure **10c** (1.75 g, 45% or 77% based on recovered **9c**) m.p. 49–50°. UV (hexane): 202 (4.11). IR (CH_2Cl_2): 3395, 2960, 2870, 1750, 1725, 1520, 1370, 1270, 1240, 1175, 1095, 1010. ^{1}H-NMR: 0.78 (*d*, *J* = 7, 3H); 0.8–2.2 (8H); 0.90 (*d*, *J* = 7, 3H); 0.93 (*d*, *J* = 6, 3H); 1.31 (*t*, *J* = 7, 6H); 4.1–4.6 (4H); 4.79 (*d* × *t*, *J* = 4.5 and 10.5, 1H); 5.90 (*d*, *J* = 16, 1H), 7.44 (*d*, *J* = 16, 1H); 7.80 (br *s*, 1H). MS: 478 (3, $C_{22}H_{31}F_3NO_7^+$), 406(14), 366(14), 342(16), 269(16), 223(34), 205(23), 139(18), 138(100). $[\alpha]_D = -41.5°$, $[\alpha]_{578} = -42.4°$, $[\alpha]_{546} = -47.7°$, $[\alpha]_{436} = -80.3°$, $[\alpha]_{365} = -123.3°$ (*c* = 1.0, $CHCl_3$).

(+) - *Phenylmenthyl* (E) - 4,4 - *diethoxycarbonyl* - 4 - *trifluoroacetamido* - 2 - *butenoate* (**10d**). Following the general procedure conversion of **9d** (336 mg, 1.1 mmol) to **10d**, and subsequent chromatography (toluene–EtOAc 39:1 then 19:1) provided unchanged **9d** (147 mg) and after crystallization (pentane) pure **10d**) (250 mg, 41% or 76% based on recovered **9d**), m.p. 113–115°. IR (KBr): 3480, 2970, 2920, 1760, 1720, 1650, 1540, 1375, 1300, 1262, 1230, 1170, 1093, 1005, 975, 898, 855, 770, 730, 705, 640, 605. ^{1}H-NMR (360 MHz): 0.89 (*d*, *J* = 7, 3H); 0.9–1.6 (16H); 1.67 (*m*, 1H); 1.76 (*m*, 1H); 1.90 (*m*, 1H); 2.06 (*m*, 1H); 4.2–4.46 (4H), 4.92 (*d* × *t*, *J* = 4.5 and 10.5, 1H); 5.14 (*d*, *J* = 15.5, 1H); 7.05–7.35 (6H); 7.68 (*s*, 1H). MS: 555 (3, $C_{28}H_{36}F_3NO^+$), 436(9), 342(4), 324(7), 296(3), 214(56), 119(100), 118(67), 105(10), 91(10). $[\alpha]_D = +0.5°$, $[\alpha]_{578} = +1.2°$, $[\alpha]_{546} = +3.2°$ $[\alpha]_{365} = +69.6°$ (*c* = 1.25, $CHCl_3$).

General procedure for the N-alkylation of 4,4 - *diethoxycarbonyl* - 4 - *trifluoroacetamido* - 2 - *butenoates with* 1 - *bromo* - 3 - *methyl* - 2 - *butene* (**7→8**) *and* (**10→11**). NaH (2.0 equiv. 50% dispersion in mineral oil) was added portionwise at 0° to a solution of the corresponding amide **7** or **10** and 1-bromo-3-methyl-2-butene (2.0 equiv.) in HMPA (1 ml/mmol of **7** or **10**). After 20 hr at r.t. the mixture was poured into 10% aq. citric acid, extracted with ether and subjected to work-up yielding the corresponding diene **8** or **11**.

2 - *Trimethylsilylethyl* (Z) - 4,4 - *diethoxycarbonyl* - 4 - [N-(3 - *methyl* - 2 - *butenyl*)*trifluoroacetamido*] - 2 - *butenoate* (**8b**). Following the general procedure, alkylation of **7b** (1.0 g, 2.26 mmol) and subsequent medium-pressure chromatography (ether–hexane 1:4) afforded unchanged **7b** (250 mg) and the pure diene **8b** (654 mg, 57 or 76% based on recovered **7b**), IR (CH_2Cl_2): 2990, 1760, 1705, 1460, 1290, 1210, 1150, 1060, 865, 785. ^{1}H-NMR: 0.03 (*s*, 9H); 0.8–1.05 (2H); 1.26 (*t*, *J* = 7, 6H); 1.52 (br *s*, 3H); 1.70 (*d*, *J* = 2, 3H); 4.0–4.5 (8H); 5.25 (*m*, 1H), 6.10 (*d*, *J* = 12, 1H); 6.34 (*d*, *J* = 12, 1H). MS: $C_{22}H_{34}F_3NO_7Si^+$ not visible, 398(1), 323(2), 256(2), 229(8), 184(30), 180(100), 156(29), 138(9).

(−) - *Menthyl* (Z) - 4,4 - *diethoxycarbonyl* - 4 - [N - (3 - *methyl* - 2 - *butenyl*)*trifluoroacetamido*] - 2 - *butenoate* (**8c**). Following the general procedure alkylation of **7c** (200 mg, 0.42 mmol) and subsequent chromatography furnished unchanged **7c** (24 mg) and the pure diene **8c** (oil, 120 mg, 52% or 61% based on recovered **7c**), IR (CCl_4): 2960, 2885, 1750, 1715, 1292, 1208, 1150, 1100, 820. ^{1}H-NMR: 0.76 (*d*, *J* = 7, 3H); 0.8–2.2 (9H); 0.90 (*d*, *J* = 7, 3H); 0.92 (*d*, *J* = 6, 3H); 1.26 (*t*, *J* = 7, 6H); 1.50 (br *s*, 3H); 1.70 (*m*, 3H); 4.05–5.5 (6H); 4.72 (*d* × *t*, *J* = 4.5 and 10.5, 1H); 5.28 (*m*, 1H); 6.13 (*d*, *J* = 12.5, 1H); 6.37 (*d*, *J* = 12.5, 1H). MS: 547 (0.8, $C_{27}H_{40}F_3NO_7^+$), 408(47), 367(11), 335(20), 289(20), 240(22), 229(100), 183(44), 179(60), 137(20). $[\alpha]_D = -35.3°$, $[\alpha]_{578} = -37.0°$, $[\alpha]_{546} = -41.8°$, $[\alpha]_{436} = -72.5$, $[\alpha]_{365} = -114.9$ (*c* = 1.25, $CHCl_3$).

(+) - 8 - *Phenylmenthyl* (Z) - 4,4 - *diethoxycarbonyl* - 4-[N - (3 - *methyl* - 2 - *butenyl*)*trifluoroacetamido*] - 2 - *butenoate* (**8d**). Following the general procedure, alkylation of **7d** (3.6 g, 6.5 mmol) and subsequent chromatography (toluene, then toluene–EtOAc 39:1) yielded unchanged **7d** (2.13 g) and the diene **8d** (oil, 965 mg, 24% or 60% based on recovered **7d**), IR(CCl_4): 2987, 2965, 2885, 1750, 1715, 1456, 1207, 1145. ^{1}H-NMR (360 MHz): 0.89 (*d*, *J* = 7, 3H); 0.9–1.2 (2H); 1.2–1.4 (12H); 1.48 (*m*, 1H); 1.55–1.8 (3H); 1.56 (*s*, 3H); 1.73 (*s*, 3H); 1.94 (*m*, 1H); 2.06 (*m*, 1H); 4.1–4.45 (6H); 4.80 (*d* × *t*, *J* = 4.5 and 10.5, 1H); 5.26 (*m*, 1H); 5.31 (*d*, *J* = 12, 1H); 6.18 (*d*, *J* = 12, 1H); 7.1–7.35 (5H). MS: 623 (12, $C_{33}H_{44}F_3NO_7^+$), 505(12), 409(100), 364(12), 336(27), 318(21), 290(25), 241(29), 230(43), 214(65), 180(42). $[\alpha]_D = +9.1°$, $[\alpha]_{578} = +10.4°$, $[\alpha]_{546} = +13.0°$, $[\alpha]_{436} = +32.8°$, $[\alpha]_{365} = +77.9°$ (*c* = 1.4, $CHCl_3$).

(−) - *Menthyl* (E) - 4,4 - *diethoxycarbonyl* - 4 - [N - (3 - *methyl* - 2 - *butenyl*)*trifluoroacetamido*] - 2 - *butenoate* (**11c**). Following the general procedure alkylation of **10c** (900 mg, 1.88 mmol) and subsequent chromatography (hexane–ether 4:1) furnished the pure diene **11c** (oil, 745 mg, 73%), IR (CCl_4): 2960, 2885, 1750, 1714, 1460, 1210, 1148, 1047. ^{1}H-NMR: 0.78 (*d*, *J* = 7, 3H); 0.8–2.2 (9H); 0.90 (*d*, *J* = 7, 3H); 0.93 (*d*, *J* = 6, 3H); 1.30 (*t*, *J* = 7, 6H); 1.58 (br *s*, 3H); 1.74 (*m*, 3H); 4.1–4.5 (6H); 4.80 (*d* × *t*, *J* = 4.5 and 10.5, 1H); 5.20 (*m*, 1H); 6.26 (*d*, *J* = 16, 1H), 7.13 (*d*, *J* = 16, 1H). MS: 548 (6, $C_{27}H_{40}F_3NO_7^+$), 409(100), 391(21), 363(33), 336(57), 318(27), 317(30), 290(79), 230(60), 139(39), 138(36). $[\alpha]_D = -36.5°$, $[\alpha]_{578} = -37.7°$, $[\alpha]_{546} = -42.6°$, $[\alpha]_{436} = -71.9°$, $[\alpha]_{365} = -108.9°$ (*c* = 2.3, $CHCl_3$).

(−) - 8 - *Phenylmenthyl* (E) - 4,4 - *diethoxycarbonyl* - 4-[N - (3 - *methyl* - 2 - *butenyl*)*trifluoroacetamido*] - 2 - *butenoate* (**11d**). Following the general procedure alkylation of **10d** (850 mg, 1.53 mmol) and subsequent chromatography (hexane/ether 4:1) afforded the pure diene **11d** (oil, 788 mg, 82%), IR (CCl_4): 2989, 2964, 1766, 1749, 1714, 1446, 1300, 1214, 1150, 1052, 909. ^{1}H-NMR (360 MHz): 0.89 (*d*, *J* = 7, 3H); 1.0 (*m*, 1H); 1.12 (*m*, 1H); 1.2–1.4 (12H); 1.4–1.85 (10H); 1.90 (*m*, 1H); 2.05 (*m*, 1H); 4.06–4.35 (6H); 4.88 (*d* × *t*, *J* = 4.5 and 10.5, 1H); 5.18 (*m*, 1H); 5.64 (*d*, *J* = 16, 1H); 6.98 (*d*, *J* = 16, 1H); 7.1–7.35 (5H). MS: 623 (10, $C_{33}H_{44}F_3NO_7^+$), 503(10), 410(76), 409(26), 336(17), 318(12), 290(16), 214(38), 119(100). $[\alpha]_D = -2.2°$, $[\alpha]_{578} = -2.5°$, $[\alpha]_{546} = -2.3°$, $[\alpha]_{436} = -4.2°$, $[\alpha]_{365} = +28.6°$.

Preparation and esterification of the racemic acid **14e/15e** *and NMR-analysis of the diastereoisomer pairs* **14c/15c** *and* **14d/15d**

2 - *Trimethylsilyl* (±) - trans - (2,2 - *diethoxycarbonyl* - 4 - *isopropenyl* - 1 - *trifluoroacetylpyrrolidin* - 3 - *yl*)*acetate* (**14b/15b**). A soln of diethylaluminium chloride (3 ml, 23.5 mmol) in CH_2Cl_2 (18 ml) was added over 30 min to a soln of **8b** (400 mg, 0.78 mmol) in CH_2Cl_2 (5 ml) at −78°. Keeping the mixture at −78° for 1 hr, addition of water at −78°, shaking with water–CH_2Cl_2 and work-up provided the cyclized ester **14b/15b** (oil, 361 mg, 90%). IR (CCl_4): 2990, 1745, 1718, 1449, 1245, 1150, 1070. ^{1}H-NMR: 0.01 (*s*, 9H); 0.8–1.1 (2H); 1.15–1.5 (6H); 1.76 (s, 3H); 2.2–3.3 (4H); 3.67 (*t*, *J* = 10.5, 1H); 3.9–4.5 (7H); 4.9–5.1 (2H). MS: $C_{22}H_{34}F_3NO_7Si^+$ not visible, 480(30), 465(28), 407(22), 361(39), 333(35), 283(78), 281(52), 279(43), 154(100).

(±) - trans - (2,2 - *Diethoxycarbonyl* - 4 - *isopropenyl* - 1 - *trifluoroacetylpyrrolidin* - 3 - *yl*)*acetic acid* (**14e/15e**). Tetrabutyl-ammonium fluoride (315 mg, 1 mmol) was added to a soln of **14b/15b** (300 mg, 0.59 mmol) in THF (6 ml). Stirring the mixture at r.t. for 16 hr, evaporation, shaking of the residue with CH_2Cl_2/5% aq. citric acid and work-up furnished the racemic acid **14e/15e** (oil, 240 mg, ~100%), IR (CCl_4): 2990, 1720, 1445, 1260, 1150, 1065. ^{1}H-NMR: 1.30 (*t*, *J* = 7, 3H); 1.33 (*t*, *J* = 7, 3H); 1.77 (*s*, 3H); 2.3–3.5 (5H); 3.68 (*t*, *J* = 10.5, 1H); 3.9–4.5 (4H); 5.04 (br *s*, 2H);

8.23 (br *s*, 1H). MS: 409 (19, $C_{17}H_{22}F_3NO_7^+$), 334(34), 289(25), 288(100), 261(28).

Menthyl trans - (2,2 - *diethoxycarbonyl* - 4 - *isopropenyl*- 1 - *trifluoroacetylpyrrolidin* - 3 - *yl*) *acetates*; 1:1-*mixture* **14c/15c**. Dicyclohexylcarbodiimide (90 mg, 0.44 mmol) was added portionwise to a mixture of the racemic acid **14e/15e** (150 mg, 0.36 mmol), (−)-menthol (117 mg, 0.75 mmol), 4-dimethylaminopyridine (25 mg, 0.2 mmol) and CH_2Cl_2 (6 ml) at r.t. Stirring the mixture at r.t. for 16 hr, filtration, evaporation of the filtrate and chromatography (toluene–EtOAc 19:1) of the residue furnished the 1:1-mixture of **14c/15c** (solid, 169 mg, 85%), melting between 97–106°, IR (KBr): 2960, 1762, 1740, 1707, 1460, 1395, 1300, 1270, 1248, 1225, 1181, 1150, 1095, 1010, 905. ^{1}H-NMR: 0.73 (*d*, $J = 7$, 1.5H); 0.80 (*d*, $J = 7$, 1.5H); 0.8–2.5 (22H); 1.75 (*s*, 3H); 2.6–3.3 (3H); 3.69 (*t*, $J = 10.5$, 1H); 4.02 (*m*, 1H), 4.2–4.5 (4H); 4.70 (br *d* × *t*, $J = 4.5$ and 10.5, 1H), 4.85–5.1 (2H)). ^{19}F-NMR (94.1 MHz) shows 2 signals, intensity ratio 1:1 in the presence of Eu(FOD)$_3$. MS: 547 (2, $C_{27}H_{40}F_3NO_7^+$), 409(35), 336(69), 318(28), 290(98), 231(40), 138(100).

8 - *Phenylmenthyl* trans - (2,2 - *diethoxycarbonyl* - 4 - *isopropenyl* - 1 - *trifluoroacetylpyrrolidin* - 3 - *yl*) *acetates*; 1:1-*mixture* **14d/15d**. Following the procedure described for the esterification **14e/15e**→**14c/15c**, acid **14e/15e** (50 mg, 0.12 mmol) was esterified with (−)-8-phenylmenthol to give a 1:1-mixture of **14d/15d** (oil, 48 mg, 63%), IR (CCl_4): 2980, 1740, 1450, 1392, 1245, 1150, 910. ^{1}H-NMR (360 MHz): 0.8–1.9 (19.5H); 0.87 (*d*, $J = 7$, 1.5H); 0.90 (*d*, $J = 7$, 1.5H); 1.69 (*s*, 1.5H); 1.79 (*s*, 1.5H); 1.9–2.1 (2H); 2.34 (*d* × *d*, $J = 4.5$ and 16, 0.5H); 2.68 (*m*, 0.5H); 2.80 (*m*, 0.5H); 2.9–3.1 (1H); 3.61 (*t*, $J = 11$, 0.5H); 3.65 (*t*, $J = 11$, 0.5H); 3.96 (br *t*, $J = 9$, 0.5H); 3.99 (br *t*, $J = 9$, 0.5H); 4.15–4.4 (4H); 4.7–4.83 (1H); 4.83 (*s*, 0.5H); 4.90 (*s*, 0.5H); 4.98 (*s*, 0.5H); 5.03 (*s*, 0.5H); 7.0–7.4 (5H). MS: 623 (13, $C_{33}H_{44}F_3NO_7^+$), 502(31), 411(35), 337(8), 290(8), 214(16), 119(100).

Cyclizations of the (Z) *and* (E)-*menthyl esters* **8c** *and* **11c**

Thermal cyclization of **8c**. (a) A soln of the (*Z*)-diene **8c** (320 mg, 0.59 mmol) in toluene (35 ml) was heated at 70° for 80 hr. Evaporation of the solvent furnished a crude mixture **12c/13c/14c/15c** (325 mg ≃ 100%). ^{1}H-NMR: 0.6–2.2 (27H), 2.2–3.3 (4H); 3.5–4.2 (2H); 4.2–4.5 (4H), 4.5–5.1 (3H). ^{19}F-NMR (94.1 MHz): 89 ppm (*s*, 3F, ref. C_6D_6, $\delta = 0$); addition of Eu(FOD)$_3$→2 singlets corresponding to the *cis*-pyrrolidines **12c/13c** (intensity ratio 46:54) and at lower field 2 singlets corresponding to the *trans*-pyrrolidines **14c/15c** (intensity ratio 41:59, identical chemical shift as signals of **14c/15c**, obtained by esterification of acid **14e/15e**). The observed signal ratio of *cis*-(**12c/13c**) to *trans*-(**14c/15c**) products is 24:76 (see Table 1), as confirmed below. Medium-pressure-chromatography (hexane–ether 3:1) of the crude ester mixture gave the *trans*-pyrrolidines **14c/15c** (126 mg, solid, m.p. 92–97°) showing ^{1}H-NMR and ^{19}F-NMR (in the presence of Eu(FOD)$_3$) spectra almost identical to those of **14c/15c** obtained from the acid **14e/15e**. Further elution gave a mixture of **12c/13c/14c/15c** (116 mg) followed by the *cis*-pyrrolidines **12c/13c** (oil, 21 mg): ^{1}H-NMR: 0.74 (*d*, $J = 7$, 1.5H); 0.75 (*d*, $J = 7$, 1.5H); 0.8–3.1 (19H); 0.91 (*d*, $J = 7$, 6H); 1.76 (*s*, 3H); 3.3–4.5 (6H); 4.62 (*m*, 1H); 4.75 (*s*, 1H); 5.07 (*s*, 1H). ^{19}F-NMR in the presence of Eu(FOD)$_3$ shows two singlets (ratio 1:1) at the same position as the ^{19}F-NMR-signals of the crude cyclization-mixture, which have been assigned to **12c/13c**.

(b) Neat **8c** (45 mg) was heated at 180° for 15 min. ^{19}F-NMR-analysis in the presence of Eu(FOD)$_3$ showed 4 singlets identical to that described above (Table 1).

$AlEt_2Cl$-*Promoted cyclization of* **8c**. 7 ml (13.5 mmol) of a soln of diethylaluminium chloride (3.5 ml) in CH_2Cl_2 (12 ml) was added over 25 min to a soln of **8c** (292 mg, 0.53 mmol) in CH_2Cl_2 (5 ml) at −78°. After 1 hr at −78°, addition of water at −78°, shaking with water–CH_2Cl_2, work-up and rapid chromatography afforded pure *trans*-pyrrolidines **14c/15c** (240 mg, 85%, m.p. 98–100°) showing identical IR (KBr), ^{1}H-NMR, ^{19}F-NMR(Eu(FOD)$_3$), and mass spectra as a sample of **14c/15c** obtained from the acid **14e/15e**. No signals of the *cis*-products **12c/13c** are visible in the NMR-spectra.

Cyclizations of the **11c**. (a) **11c** (50 mg) was heated in toluene (6 ml) at 70° for 48 hr. Evaporation of solvent gave a mixture **12c/13c/14c/15c** (50 mg). The *cis*- and *trans*-diastereoisomer pairs **12c/13c** and **14c/15c** were separated by chromatography and characterized by ^{19}F-NMR (Eu(FOD)$_3$). (b) Neat **11c** (50 mg) was heated at 180° for 15 min to give the crude cyclization mixture (50 mg). (c) **11c** (30 mg (0.055 ml) was treated with $AlEt_2Cl$ (1.65 mmol) at −78° as described above to give the cyclized products (26.5 mg, 88%). The crude reaction mixtures obtained by cyclization of **11c** were analyzed as described above (Table 1).

Cyclizations of the (Z) *and* (E)-8-*Phenylmenthyl esters* **8d** and **11d**

Thermal cyclization of **8d**. A soln of **8d** (30 mg, 0.05 mmol) in toluene (3 ml) was heated at 70° for 80 hr and then evaporated to give a crude mixture **12d/13d/14d/15d** showing an ^{1}H NMR spectrum identical to that of the mixture obtained on heating neat **8d** at 180° for 15 min. The product ratios (Table 1) were determined by integration of the ^{1}H-NMR (360 MHz) signals of the olefinic protons; those corresponding to **12d/13d** appear at $\delta = 4.66$ (*s*, 1H), 4.68 (*s*, 1H), 5.00 (*s*, 1H) and 5.09 (*s*, 1H) ppm and show 20% of the intensity of the signals at 4.83 (1H), 4.90 (1H), 4.98 (1H), 5.03 (1H) ppm which correspond to **14d/15d**.

$AlMe_2Cl$-*Promoted cyclization of* **8d**. 2N dimethylaluminium chloride in hexane (Alfa, 1.2 ml, 2.4 mmol) was added dropwise to a soln of the (*Z*) diene **8d** (500 mg, 0.8 mmol) in CH_2Cl_2 (10 ml) at −78°. The mixture was kept at −35° for 18 hr, then quenched at −78° with sat Na_2SO_4 aq, diluted with CH_2Cl_2 and subjected to work-up giving a crude product showing no *cis*-pyrrolidines **12d/13d** to be present (^{1}H-NMR). Chromatography (toluene/EtOAc 100:1) gave a 95:5-mixture of the *trans*-pyrrolidines **14d/15d** (oil, 301 mg, 60%). IR (CCl_4): 2970, 2935, 1740, 1712, 1500, 1394, 1250, 1150, 1095, 1070, 1032, 910, 705. ^{1}H-NMR (360 MHz): 0.8–1.9 (19H); 0.87 (*d*, $J = 7$, 3H); 1.07 (*m*, 1H); 1.69 (*s*, 3H); 1.98 (br *t*, $J = 11.5$, 1H); 2.34 (*d* × *d*, $J = 4.5$ and 16, 1H); 2.80 (*m*, 1H); 2.97 (*m*, 1H); 3.61 (*t*, $J = 11$, 1H); 3.96 (br *t*, $J = 9$, 1H); 4.27 (*qa*, $J = 7$, 2H); 4.35 (*qa*, $J = 7$, 2H); 4.78 (*m*, 1H); 4.83 (*s*, 1H); 4.90 (*s*, 1H); 7.1 ≃ 7.4 (5H); the singlets corresponding to the olefinic protons of **15d** are visible at $\delta = 4.98$ (0.05H) and 5.03 (0.05H). MS: $C_{33}H_{44}F_3NO_7^+$ not visible, 504(3), 410(38), 364(5), 336(15), 318(18), 290(30), 262(8), 119(100); field desorption: 623 ($C_{33}H_{44}F_3NO_7^+$).

Thermal cyclization of **11d**. Neat diene **11d** (20 mg) was heated at 180° for 15 min. ^{1}H-NMR (360 MHz) of the crude mixture (20 mg) shows eight singlets of equal intensity at $\delta = 4.66$, 4.68, 4.83, 4.90, 4.98, 5.00, 5.03 and 5.09 ppm indicating a 1:1:1:1-ratio of **12d/13d/14d/15d**.

$AlMe_2Cl$-*Promoted cyclization of* **11d**. 2N $AlMe_2Cl$ in hexane (2.25 ml, 4.48 mmol) was added dropwise to a soln of the (*E*)-diene **11d** (700 mg, 1.12 mmol) in CH_2Cl_2 (20 ml) at −35°. The mixture was kept at −35° for 20 min, then quenched with sat Na_2SO_4 aq, diluted with CH_2Cl_2 and subjected to work-up and chromatography (toluene–EtOAc 50:1) yielding unchanged **11d** (61 mg) and a 11:89-mixture of **14d/15d** (oil, 514 mg, 71% or 81% based on recovered **11d**). ^{1}H-NMR (360 MHz): 0.8–2.1 (19H); 0.90 (*d*, $J = 7$, 3H); 1.79 (*s*, 3H); 1.9–2.1 (3H); 2.68 (*m*, 1H); 3.01 (*m*, 1H); 3.66 (*t*, $J = 11$, 1H); 3.99 (br *t*, $J = 9$, 1H); 4.15–4.4 (4H); 4.78 (*m*, 1H); 4.89 (*s*, 1H); 5.03 (*s*, 1H); 7.05–7.4 (5H); the singlets corresponding to the olefinic protons of **14d** appear at $\delta = 4.83$ (0.11H) and 4.90 (0.11H) ppm; further low-intensive signals of **14d** are visible at $\delta = 2.34$ (*d* × *d*, $J = 4.5$ and 12) and 2.80 (*m*) ppm.

Preparation of (+)- *and* (−)-α-*allokainic acid* (**1**)

(+)-α-*Allokainic acid* ((+)-**1**). The 95:5-mixture **14d/15d**

(299 mg, 0.48 mmol), obtained by Me_2AlCl-mediated cyclization of **8d**, was heated in 1N NaOH in EtOH–water 1:1 (8 ml) in a tightly stoppered alkali resistant flask at 100° for 20 hr. The soln was carefully evaporated *in vacuo* and then, after addition of water (5 ml), extracted with ether (3×). The ether extracts were washed with water (5 ml), sat NaCl aq, dried (Na_2SO_4) and evaporated to give (−)-8-phenylmenthol (99 mg, 89%). The aqueous phase was acidified with HCl aq to $p_H = 5$, the precipitated silicic acid filtered and washed with water. The combined aq. soln was then stirred in an open flask, immersed into a hot (110°) oil-bath for 15 min, then acidified to $p_H = 4.5$ and heated for further 15 min. The soln ($p_H = 5$) was acidified to $p_H = 4.0$, heated for 10 min and after acidification to $p_H = 3.0$, heated for another 20 min. The soln was brought to $p_H = 4.5$ (NaOH) and after addition of $Cu(OAc)_2$ (240 mg) heated (bath, 110°) for 30 min, then set aside for 1 hr. The precipitated Cu–salt was washed successively with 2.5% aq HOAc (2 ml), hot water (3 × 2 ml), then stirred under H_2S for 3 hr.

Filtration of the mixture through Celite, washing of the ppt with water and evaporation of the combined aq solns gave pure (+)-allokainic acid ((+)-**1**) as a solid residue (69 mg, 68%), m.p. (dec) 238–242° (crystallization from H_2O). IR (KBr): 3440, 3135, 2940, 1725, 1635, 1578, 1452, 1400, 1322, 1265, 1240, 1218, 1187, 1160, 1089, 1045, 1012, 918, 900, 870, 840, 660, 632, 595, 560, 530, 520, 502. ^{1}H-NMR (D_2O, 360 MHz): 1.68 (*s*, 3H); 2.53–2.94 (4H); 3.28 (*t*, $J = 11$ Hz, 1H); 3.50 (*d* × *d*, $J = 7.5$ and 11, 1H); 3.90 (*d*, $J = 9$, 1H); 4.95 (*s*, 2H). MS: 213 (7, $C_{10}H_{15}NO_4^+$), 195(12), 168(100), 153(19), 136(12), 122(12), 108(15), 88(33), 80(26), 69(24). $[\alpha]_D^{23} = +7.0°$, $[\alpha]_{578}^{23} = +7.4°$, $[\alpha]_{546}^{23} = +8.7°$, $[\alpha]_{465}^{23} = +19.4°$, $[\alpha]_{365}^{23} = +40.0°$ ($c = 0.7$, H_2O).

Recrystallized natural (+)-α-allokainic acid, m.p. 238–242° (dec), $[\alpha]_D^{23} = +7.4°$, $[\alpha]_{578}^{23} = +8.1°$, $[\alpha]_{546}^{23} = +9.6°$, $[\alpha]_{465}^{23} = +20.5°$, $[\alpha]_{365}^{23} = +42.0°$ ($c = 0.7$, H_2O) showed IR, ^{1}H-NMR and mass spectra identical to those of synthetic (+)-**1**. Synthetic and natural (+)-**1** were, furthermore, shown to be identical and enantiomerically pure by ^{1}H-NMR comparison of their dimethylester **18** using a chiral shift reagent as described below.

The filtrate containing the soluble Cu-salts was stirred under H_2S for 3 hr to give after filtration and evaporation a residue which was adsorbed onto strongly acidic ion exchange resin (Merck I, 10 ml). Washing with water (100 ml), elution of the amino diacids with 1N NH_4OH (250 ml) and evaporation of the eluate provided a residue (23 mg) which show two singlets at $\delta = 0.82$ and 0.85 ppm (CH_3, ratio 1:2.5) and two doublets ($J = 9$) at $\delta = 4.02$ and 4.37 ppm (H-C(2), ratio 1:2.5) indicating the presence of **1** and a stereoisomer, tentatively assigned as its C(2)-epimer (β-allokainic acid).

(−)-α-Allokainic acid ((−)-**1**). The 11:89-mixture **14d/15d** (100 mg, 0.16 mmol, obtained by Me_2AlCl-mediated cyclization of **11d**) was successively hydrolyzed, decarboxylated and purified as described above to give pure (−)-α-allokainic acid (solid, 21 mg, 62%); its absolute configuration and enantiomeric purity were determined by ^{1}H-NMR-comparison of its dimethylester with the ester **18** and the corresponding racemic ester in the presence of $Eu(TFC)_3$. The ^{1}H-NMR (D_2O, 360 MHz) and mass spectra of (−)-**1** are identical to those of (+)-**1**.

α-Allokainic acid dimethylester (**18**). Freshly distilled $SOCl_2$ (0.1 ml) was added dropwise to MeOH (0.6 ml) at −15°. The resulting soln was added rapidly to a stirred suspension of **1** (9 mg, 0.04 mmol) in MeOH (0.2 ml) at −15°. Stirring of the mixture at −15° for 15 min, then at r.t. for 2 hr, evaporation, shaking of the residue with 1N Na_2CO_3/ether and work-up afforded **18** (oil, 7 mg, 69%). IR (CCl_4): 2956, 1750, 1440, 1320, 1215, 1130, 900. ^{1}H-NMR: 1.74 (br *s*, 3H); 2.17 (br *s*, 1H); 2.4–2.7 (4H); 2.8–3.3 (2H); 3.6 (*m*, 1H); 3.68 (*s*, 3H); 3.77 (*s*, 3H); 4.84 (br *s*, 2H). MS: 241 (14, $C_{12}H_{19}NO_4^+$), 209(11), 182(95), 150(14), 122(100), 101(59), 80(92).

The dimethylesters derived from (+)-**1**, (−)-**1** and (±)-**1** show identical spectra as described above. Their chirality was determined as follows. The racemic ester **18** showed in the ^{1}H-NMR (360 MHz) after addition of $Eu(TFC)_3$ each one of the signals corresponding to the protons of one O-Me group and of the allylic Me group split into two equally intense signals. Addition of the diester **18** derived from both, natural or, either synthetic (+)-α-allokainic acid increased the low field signal of all three signal pairs. Under identical conditions, the diester **18** derived from natural, as well as from synthetic (+)-**1** showed only one signal corresponding to the olefinic protons. The O–Me and the allylic Me groups, which after addition of racemic **18** overlapped with the low field signals of the three signal pairs displayed by racemic **18**. Proceeding in an analogous fashion, the corresponding signals of the diester **18** derived from (−)-**1** overlapped with the high field signals of the three characteristic signals pairs of racemic **18**.

Acknowledgements—Financial support of this work by the Swiss National Science Foundation, Sandoz Ltd, Basel and Givaudan SA, Vernier, is gratefully acknowledged. We are indebted to Professors H. Morimoto and T. Takemoto for kindly providing samples of natural (+)-allokainic acid and for ^{1}H-NMR spectra of its stereoisomers. We also thank Mr. J. P. Saulnier, Mr. A. Pinto and Mrs. D. Clément for NMR and MS measurements.

REFERENCES

[1]H. Morimoto, *J. Pharm. Soc. Jpn.* **75**, 766 (1975); S. Murakami, K. Daigo, N. Takagi, T. Takemoto and Z. Tei, *Ibid.* **75**, 1252 (1955); H. Morimoto and R. Nakamori, *Ibid.* **76**, 26 (1956).

[2]H. Watase, *Bull. Chem. Soc. Jpn.* **31**, 932 (1958).

[3]S. Murakami, T. Takemoto and Z. Shimizu, *J. Pharm. Soc. Jpn.* **73**, 1026 (1953); H. Morimoto, *Ibid.* **75**, 937 (1955).

[4]R. Nakamori, *Proc. Jpn. Acad.* **32**, 35 (1956); *J. Pharm. Soc. Jpn.* **76**, 279 (1956).

[5]W. Oppolzer and K. Thirring, *J. Am. Chem. Soc.* **104**, 4978 (1982).

[6]*Kainic Acid as a Tool in Neurobiology* (Edited by E. G. McGeer, J. W. Olney and P. L. McGeer). Raven Press, New York (1978); *Glutamate: Transmitter in the Central Nervous System* (Edited by P. J. Roberts, J. Storm-Mathesen and G. A. R. Johnston). Wiley, Chichester (1981); O. Goldberg, A. Luini and V. I. Teichberg, *J. Med. Chem.* **26**, 39 (1983).

[7]T. Takemoto, K. Daigo, Y. Kondo and K. Kondo, *J. Pharm. Soc. Jpn.* **86**, 874 (1966); Y. Ohfune and M. Tomita, *J. Am. Chem. Soc.* **104**, 3511 (1982).

[8]K. Konno, H. Shirahama and T. Matsumoto, *Tetrahedron Letters* **24**, 939 (1983).

[9]Review: W. Oppolzer and V. Snieckus, *Angew. Chem.* **90**, 506 (1978); *Ibid.* Int. Ed. Engl. **17**, 476 (1978); see also: W. Oppolzer and K. Bättig, *Helv. Chim. Acta* **64**, 2489 (1981).

[10]W. Oppolzer and H. Andres, *Tetrahedron Letters* 3397 (1978).

[11]W. Oppolzer and H. Andres, *Helv. Chim. Acta* **62**, 2282 (1979).

[12]W. Oppolzer, C. Robbiani and K. Bättig, *Helv. Chim. Acta* **63**, 2015 (1980).

[13]W. Oppolzer and C. Robbiani, *Helv. Chim. Acta* **63**, 2010 (1980).

[14]A. N. Kurtz, W. E. Billups, R. B. Greenlee, H. F. Hamil and W. T. Pace, *J. Org. Chem.* **30**, 3141 (1965).

[15]Y. Kishida and A. Terada, *Chem. Pharm. Bull.* **17**, 2417 (1969).

[16]H. Gerlach, *Helv. Chim. Acta* **60**, 3039 (1977).

[17]K. Kondo, Y. Kondo, T. Takemoto and T. Ikenoue, *Bull. Chem. Soc. Jpn.* **35**, 1899 (1962); P. D. Kennewell, S. S. Matharu, J. B. Taylor and P. G. Sammes, *J. Chem. Soc.* Perkin Trans. 1, 2542 (1980).

[18]E. J. Corey and H. E. Ensley, *J. Am. Chem. Soc.* **97**, 6908 (1975).
[19]S. Takimoto, J. Inanaga, T. Katsuki and M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **49**, 2335 (1976).
[20]Treatment of **8d** with $AlEt_2Cl$ in CH_2Cl_2 at $-78°$, at $-35°$ and at $+20°$ gave in each case a 9:1-mixture **14d/15d**.
[21]In the ^{1}H-NMR spectrum (D_2O) of this mixture the H–C(2)-doublets of **1** and its isomer appear at $\delta = 4.02$ and 4.37 ppm, respectively, as compared to those of α- and β-kainic acids, which appear at $\delta = 4.15$ and 4.42 ppm, respectively.
[22]W. Oppolzer and S. Mirza, unpublished work.
[23]For a review on Lewis-acid catalyzed ene reactions see: B. B. Snider, *Acc. Chem. Res.* **13**, 426 (1980).
[24]For simplicity only the coordination of the Lewis acid with the enoate moiety is depicted in **8d** and **11d**.
[25]Such a conformation was shown to be the preferred one in crystalline acrylates derived from secondary alcohols: J. D. Dunitz and P. Strickler, *Structural Chemistry and Molecular Biology* (Edited by A. Rich and N. Davidson), p. 595. W. H. Freeman, San Francisco; W. B. Schweizer and J. D. Dunitz, *Helv. Chim. Acta* **65**, 1547 (1982).
[26]For highly asymmetric C,C-bond formations using enoates derived from various chiral alcohols see: W. Oppolzer, M. Kurth, D. Reichlin, C. Chapuis, M. Mohnhaupt and F. Moffatt, *Helv. Chim. Acta* **64**, 2802 (1981); W. Oppolzer and H. J. Löher, *Ibid.* **64**, 2808 (1981); W. Oppolzer, C. Chapuis, G. M. Dao, D. Reichlin and T. Godel, *Tetrahedron Letters* **23**, 4781 (1982).
[27]Bimolecular Lewis-acid-promoted ene-type additions of phenylmenthyl glyoxalate proceed with high asymmetric induction: J. K. Whitesell, A. Battacharya, D. A. Aguilar and K. Henke, *J. Chem. Soc.* Chem. Commun. 989 (1982); analogous reactions of menthyl glyoxalate afford adducts in much lower diastereomeric excess: O. Achmatowicz, Jr. and B. Szechner, *J. Org. Chem.* **37**, 964 (1972).