81. Stereospecific, R_2AlCl-Promoted Intramolecular Ene Reaction of a 1,6-Dienoate: Evidence for a Concerted Mechanism

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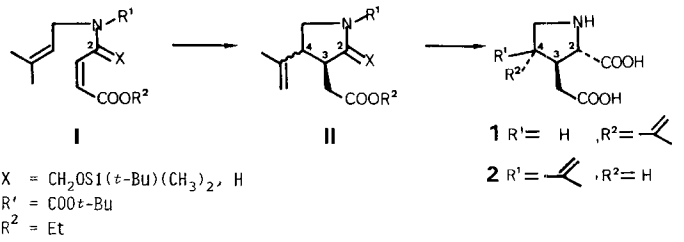
Summary

Treatment of the 83%-*trans*-$^{13}CH_3$-labelled 1,6-dienoate **7** with Et_2AlCl at $-78°$ provided in high yield the ene product **9** containing 83% ^{13}C localized in the olefinic C(8)-methylene group. Accordingly, H-transfer occurs exclusively from the *trans*-methyl group of **7**, consistent with a concerted ene process **7**→**9** thereby ruling out an intermediate cation **8** *(Scheme 4)*.

Introduction. – Recently we have reported direct, efficient, regio-, diastereo- and enantioselective syntheses of the neurophysiologically interesting algae constituents *α*-allokainic acid (**1**) [1][2] and *α*-kainic acid (**2**) [3][4].

Scheme 1

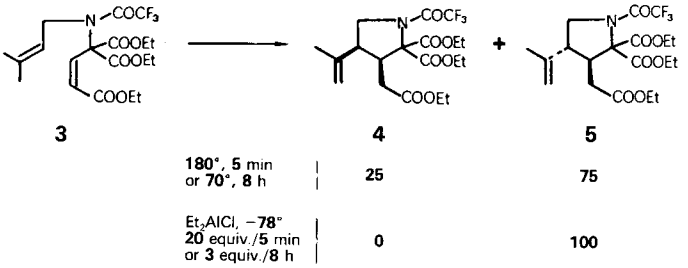


Each of these syntheses features an intramolecular ene reaction[1]) **I**→**II** following one of the two stereochemically different strategies. Thus, either the configurationally pure center C(2) of **I** dictates the chirality at C(3) and C(4) in **II** or, alternatively, the chiral ester substituent R^2 in **I** first induces centers C(3) and C(4) which then in turn control the configuration at C(2) in **1**. A prerequisite for the latter alternative was the ability to control the relative configuration of centers C(3)/C(4) in the process **I**→**II** which was achieved by modifying the masked carboxyl equivalent X and the enophile

[1]) For a review see [5].

geometry in **I**. On thermal cyclization of the bis(ethoxycarbonyl)-substituted (*Z*)-enoate **3**, we [1][6] and others [7] observed an unusual diastereoselectivity in favor of the *trans*-product **5** (ratio **4**/**5** = 1:3 irrespective of the reaction temperature).

Scheme 2



An even more pronounced stereoselectivity was achieved when **3** was cyclized in the presence of Et_2AlCl [6][2]). Thus, treatment of **3** with Et_2AlCl (3 mol-equiv.) in dry CH_2Cl_2 at $-78°$ for 8 h or at $-35°$ for 30 min yielded exclusively the *trans*-product **5** in 86% yield. No trace of the *cis*-isomer **4** was found in the reaction mixture.

Apart from the relevance of this result for the synthesis of racemic and enantiomerically pure (+)-*α*-allokainic acid [1][2], we were interested in the mechanistic origin of this spectacular *Lewis*-acid effect.

Results and Discussion. – *Coordination between* Lewis *Acid and 1,6-Diene.* Given the number of basic functionalities in **3** it was not surprising that the cyclization rate at $-78°$ depended on the excess of Et_2AlCl present (requiring for completion 8 h using 3 mol-equiv. and only 5 min using 20 mol-equiv. of the *Lewis* acid). To study the relevant coordination sites in **3** the ^{1}H-NMR spectra of enoate **6** were monitored in relation to the molarity of Et_2AlCl *(Table)*. On increasing the latter, the signals of the olefinic protons $H-C_\alpha$ and $H-C_\beta$ are shifted down-field; this indicates that the extent of enoate/Et_2AlCl coordination in **3** parallels the rate increase for the reaction **3**→**5**[3]).

Stereochemical Working Hypothesis. The question arose whether the Et_2AlCl-promoted cyclization **3**→**5** is in fact a concerted ene reaction or rather proceeds *via* a cationic intermediate resulting from electrophilic attack of the coordinated enoate at

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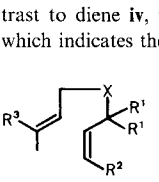
[2]) For $RAlCl_2$- and R_2AlCl-catalyzed bimolecular ene reactions see [8]; for a review see [9].

[3]) The significance of enoate coordination and 'ene' substitution on the rate of the Et_2AlCl-induced cyclization **3**→**5** is also illustrated by the following observations [10]. All 1,5-dienes **i** to **v** underwent thermal ene reactions to give 5-membered ring systems. However, *only* the enoates **iv** and **v** cyclized at room temperature in the presence of an excess of Et_2AlCl in dry CH_2Cl_2 (50 to 100 h). The relative rates of the thermal reactions (**iv**: 170°, 20 h/ **v**: 220°, 16 h/ **3**: 70°, 80 h) reflect those of the Et_2AlCl-induced cyclizations; under all reaction conditions **3** cyclized most rapidly, probably owing to entropic reasons. Furthermore, in contrast to diene **iv**, no Et_2AlCl-promoted cyclization of diene **iii** was observed under identical conditions which indicates the importance of CH_3-substitution in the 'ene' unit.



i $R^1 = R^2 = H$, $R^3 = Me$, $X = N-COCF_3$
ii $R^1 = COOEt$, $R^2 = H$, $R^3 = Me$, $X = CH_2$
iii $R^1 = H$, $R^2 = COOEt$, $R^3 = H$, $X = CH_2$
iv $R^1 = H$, $R^2 = COOEt$, $R^3 = Me$, $X = CH_2$
v $R^1 = R^2 = COOEt$, $R^3 = Me$, $X = CH_2$

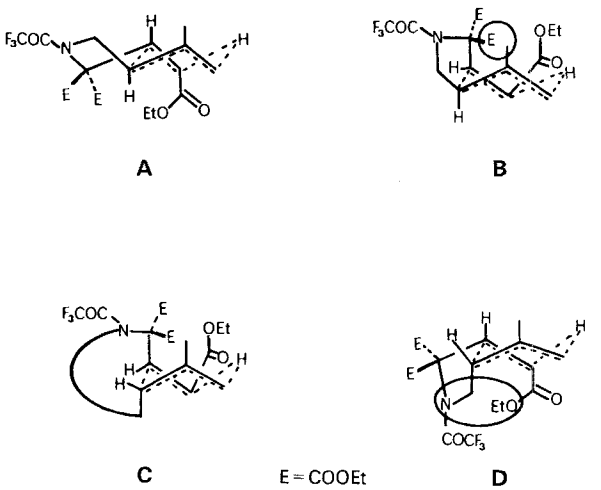
Table. *^{1}H-NMR Signal Shifts* (in ppm, $CDCl_3$) *of* (Z)-$H_3C-N(COCF_3)-C(COOEt)_2-_\beta CH=_\alpha CH-COOEt$ (**6**) *in Relation to* Et_2AlCl-*Molarity*

Mol-equiv. Et_2AlCl	$CH_3-C^a)$	$CH_3-N^a)$	$CH_2-O^a)$	$H-C_\alpha$	$H-C_\beta$
–	1.24	3.33	4.17	6.12	6.51
2	1.28	3.33	4.24	6.20	6.55
3	1.29	3.33	4.28	6.28	6.61
6	1.32	3.33	4.36	6.44	6.69

[a]) Center of the signal group.

the isolated olefinic bond[4]). This mechanistic problem may be particularly relevant in terms of the observed stereoselection which is kinetically controlled in both the thermal and *Lewis*-acid-induced cyclizations of **3**[5]). Assuming the operation of a concerted ene process, we thus attempted to rationalize the observed stereochemistry by examination of the transition states *(Scheme 3)*. This analysis accounts for H-transfer from both

Scheme 3



the allylic *trans*-methyl (**A** and **B**) and *cis*-methyl group (**C** and **D**). Transition states **B** and **C** are readily excluded: **B** on the basis of steric repulsion (malonate/olefinic methyl) and **C** due to angle strain[6]). Orientation **A** seems to be favored over **D** which suffers from 1,3-diaxial perturbation; this steric repulsion should increase on coordi-

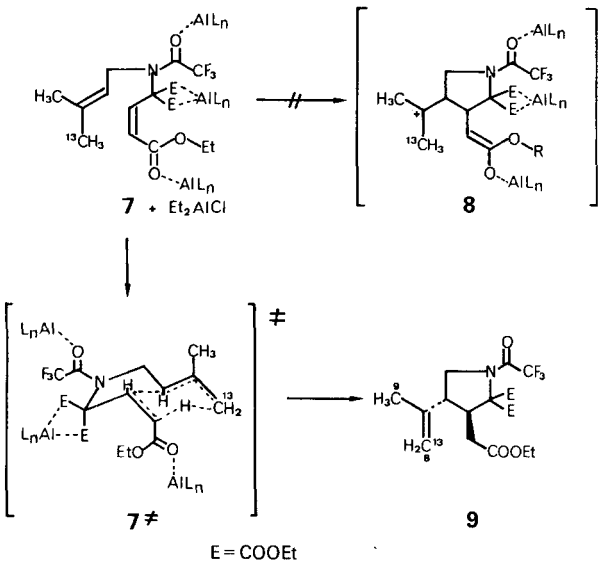
[4]) So far, the dichotomy between concerted and cationic mechanisms of intermolecular *Lewis*-acid-mediated ene reactions has been studied only by means of H/D-isotope effects and product distributions [9].

[5]) A 1:1 mixture of **4** and **5** remained virtually unchanged either on heating at 180° for 10 min or on treatment with Et_2AlCl (30 mol-equiv.) in CH_2Cl_2 at 25° for 10 min.

[6]) This angle strain argument is in accord with the stereochemistry of numerous other intramolecular ene reactions [5] [11] [12].

nation of the ester and amide units with the *Lewis* acid. Consequently, *trans*-product **5** is formed exclusively in the presence of Et_2AlCl *via* **A**. We may thus predict that in a concerted Et_2AlCl-promoted ene process **3**→**5**, H-atom is transferred selectively from the *trans*-positioned allylic CH_3-group[7]). Its specific labelling with ^{13}C[8]) should lead to **9** with all ^{13}C localized in the olefinic methylene C(8)-atom *(Scheme 4)*. Alternatively, if C,C-bond closure and H-transfer are non-concerted such as in the formation of carbocation **8** the ^{13}C-label would be scrambled between C(8) and C(9) in the cyclization product.

Scheme 4



Synthesis and Et_2AlCl-Promoted Cyclization of ^{13}C-Labelled Diene **7**. The essential problem thus boiled down to a stereospecific preparation of the *trans*-^{13}C-methyl-labelled bromide **14**. To establish selectively the desired alkene geometry, alkyne carbometallation[9]) appeared to be the method of choice. Esterification [16] of 2-butynoic acid (**10**) with (+)-borneol/DCC/DMAP furnished, after chromatography and sublimation, the crystalline butynoate **11** in 98% yield. Stereospecific *syn*-addition [17] of ^{13}C-dimethylcopperlithium (prepared *in situ* from 99% isotopically pure [^{13}C]MeI) to butynoate **11** in THF at $-78°$ afforded after chromatography olefin **12** in 99% yield. The

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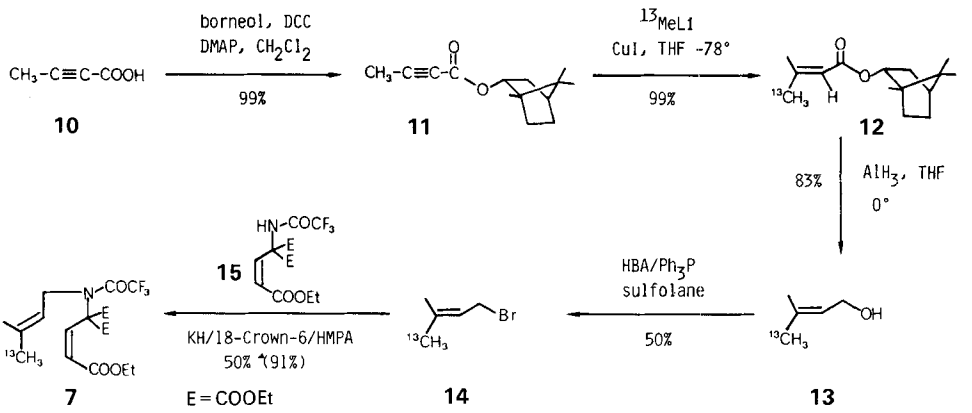
[7]) As a working model we postulate a chair-like transition state for the ene reaction. The above-mentioned prediction that the H-atom should be transferred exclusively from the allylic *trans*-methyl group of **3** holds also for the traditional model [13] which assumes that the migrating H-atom lies on the axis which joins the termini of the ene and enophile units.

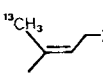
[8]) To avoid the interference with kinetic H/D isotope effects [9] and for reasons of NMR-analytical convenience [14] we preferred ^{13}C- over ^{2}H-labelling.

[9]) For a review see [15].

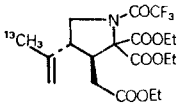
Scheme 5



^{13}C-NMR spectrum of **12** shows a single peak at $\delta = 27.2$ ppm, assigned to be labelled *trans*-methyl group. Its corresponding proton signal appears in the ^{1}H-NMR spectrum as a doublet centered at $\delta = 1.90$ ppm (^{13}C, H-coupling constant $^1J_{(C,H)} = 126$ Hz). The *cis*-methyl signal at $\delta = 2.17$ ppm is split into a doublet with $^3J_{(C,H)} = 4.5$ Hz. Not a trace of a signal is visible at $\delta = 1.90$ ppm (unlabelled *trans*-CH_3) consistent with virtually 100% stereospecific incorporation of the ^{13}C-label. Reduction of the bornyl ester **12** with (prepared *in situ*) AlH_3 in THF at 0° provided the labelled methyl-butenol **13** in 83% yield after bulb-to-bulb distillation (25°/2 Torr). Inspection of the ^{13}C-NMR spectrum of **13** reveals a major peak at $\delta = 25.5$ (*trans*-$^{13}CH_3$) and a minor peak at $\delta = 16.8$ ppm[10]) (integral ratio 20:1). The ^{1}H-NMR spectrum shows the *trans*-methyl signals as two doublets centered at $\delta = 1.72$ ppm ($^1J_{(C,H)} = 124$ Hz, 2.54 H) and ($^3J_{(C,H)} = 4$ Hz, 0.46 H) and the complementary *cis*-methyl doublets centered at $\delta = 1.68$ ppm ($^1J_{(C,H)} = 124$ Hz, 0.48 H) and ($^3J_{(C,H)} = 4$ Hz, 2.52 H). Accordingly, the ^{1}H-NMR integrals indicate some scrambling of the ^{13}C-label on reduction of **12** resulting in a 5:1 mixture of **13**/**16**[10]). Conversion of the allylic alcohol **13**/**16** to the bromide **14**/**17** was successfully accomplished[11]) using hexabromoacetone/Ph_3P in sulfolane, analogous to



16 X = OH
17 X = Br
18 X = (*Z*)-N($COCF_3$)-C($COOEt)_2$-CH=CH-COOEt



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[10]) Since the ^{13}C-signals of the *trans*- and *cis*-methyl groups in unlabelled 3-methyl-2-butenol appear at $\delta = 25.3$ and $\delta = 17.4$ ppm (integral ratio 1:1), the minor peak at $\delta = 16.8$ ppm could not be clearly assigned.

[11]) The desired *N*-alkylation **15**→**7** could not be achieved using the corresponding tosylate or chloride.

the preparation of volatile chlorides by means of hexachloroacetone/Ph_3P [18]. The *trans*- and *cis*-methyl groups of **14/17** exhibit two ^{13}C-NMR peaks at δ = 25.7, 17.4 ppm (integral ratio 7:1) and four ^{1}H-NMR doublets at δ = 1.78, 1.74 ppm, respectively. Integration of both ^{1}H-NMR signal pairs ($^1J_{(C,H)}$ = 125 Hz *vs.* $^3J_{(C,H)}$ = 4 Hz) centered at δ = 1.78 and 1.74 ppm showed the same stereoisomer ratio **14/17** = 5.2:1.

N-Alkylation of amide **15** with the thus obtained bromide **14/17** proceeded most reliably after deprotonation of **15** with KH/18-crown-6 in HMPA to afford the crystalline diene **7/18** in 52% yield. ^{13}C-NMR analysis of **7/18** shows two peaks at δ = 25.5 and 18.0 ppm (integral ratio 8:1). Integration of the ^{1}H-NMR methyl signals centered at δ = 1.70 and 1.53 ppm reveals a 5.1:1 ratio for **7/18**.

Having thus prepared the ^{13}C-labelled 1,6-diene **7** the stage was set for the crucial cyclization. Treatment of the above **7/18** mixture with Et_2AlCl (3 mol-equiv.) at $-78°$ in CH_2Cl_2 for 8 h provided the *trans*-substituted pyrrolidine **9/19** in 86% yield. The olefinic methylene (C(8)) and the allylic methyl (C(9)) groups of the cyclization product **9/19** show two ^{13}C-NMR peaks at δ = 116.6, 18.0 ppm (integral ratio 6:1) and two pairs of ^{1}H-NMR signals centered at δ = 4.93, 1.70 ppm, respectively. The ^{1}H-NMR integrals of both signal pairs and $^{13}CH_2(^1J_{(C,H)} = 154$ Hz)/$^{12}CH_2(^3J_{(C,H)} = 6$ Hz)/$^{12}CH_3(^3J_{(C,H)} = 6$ Hz)/$^{13}CH_3(^1J_{(C,H)} = 126$ Hz) exhibit the same ratio of 5:1 for **9/19**.

Conclusion. – The localization of ^{13}C-label in the precursors **14** and **7**, as well as in the ene product **9** has been measured by reliable integration of the relevant ^{1}H-NMR signals ($\approx$ 5% precision). The corresponding ^{13}C-NMR spectra confirm these findings in a qualitative sense. Accordingly, the 5:1 stereoisomer ratio of *trans*/*cis*-^{13}C-labelled olefinic precursors **14/17** and **7/18** corresponds well to the 5:1 ratio of ^{13}C-labelled C(8)-methylene/C(9)-methyl groups in the pyrrolidine products **9/19**. Thus, *only* the *trans*-methyl group in diene **7** is transformed to the olefinic methylene group in **9** during the cyclization. This result strongly supports a concerted mechanism for the ene process **7**→**9** where (for geometrical reasons) hydrogen is transferred exclusively from the *trans*-positioned allylic methyl group of **7**. Within experimental error the intermediacy of cation **8** can be excluded. We thus propose a transition state **7**$^{\neq}$ where coordination of R_2AlCl with the conjugated ester carbonyl is mainly responsible for the acceleration of the ene reaction by lowering the enophile LUMO energy [9].

The mechanistic understanding achieved by this study may help to stimulate further rational applications of diastereoselective and π-facial-selective ene reactions in synthesis[12]).

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[12]) For recent examples of π-face-selective *Lewis*-acid-promoted ene reactions see [6] [19] [20].

Experimental Part

General. All reactions were carried out under Ar-atmosphere 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), dichloromethane (CH_2Cl_2, P_2O_5). 'Workup' denotes washing of the org. phase with sat. aq. NaCl, drying over solid Na_2SO_4 and removal of solvent by distillation *in vacuo* using a rotatory evaporator. Column chromatography was carried out on SiO_2 (*Merck*, Kieselgel *60*) using hexane/Et_2O (ratio in parentheses). Melting points (m.p.) were determined on a *Kofler* hot stage and are uncorrected. IR spectra in CCl_4, unless otherwise specified, $\tilde{\nu}_{max}$ in cm^{-1}. NMR spectra in $CDCl_3$, ^{1}H-NMR spectra at 360 MHz, unless otherwise specified, ^{13}C-NMR spectra at 90.561 MHz, standard TMS (ppm) = 0.

*Ethyl (Z)-4,4-bis(ethoxycarbonyl)-4-(*N*-methyltrifluoroacetamido)-2-butenoate* (**6**). KH (washed with pentane, 28 mg, 0.7 mmol) was added to a solution of *ethyl (Z)-4,4-bis(ethoxycarbonyl)-4-(trifluoroacetamido)-2-butenoate* (**15**) (185 mg, 0.5 mmol), 18-crown-6 (291 mg, 1.1 mmol) in HMPA (1.5 ml) at 0°. After 15 min at 0° CH_3I (44 μl, 0.7 mmol) was added to the mixture which then was stirred at r.t. for 24 h and finally poured into 10% aq. citric acid. Workup and chromatography (5:1) furnished **6** (oil, 184 mg, 96%). IR (film): 1757, 1733, 1703, 1650, 1192, 1054, 1022. ^{1}H-NMR (100 MHz): 1.1–1.4 (9H); 3.33 (*m*, 3H); 3.9–4.4 (6H); 6.12 (*d*, J = 12, 1H); 6.51 (*d*, J = 12, 1H). MS: 383 (49, $C_{15}H_{20}F_3NO_7^+$), 338 (44), 311 (14), 310 (100), 282 (24), 265 (43).

1,7,7-Trimethylbicyclo[2.2.1]hept-2-yl 2-butynoate (**11**). A solution of dicyclohexylcarbodiimide (4.9 g, 23.8 mmol) in CH_2Cl_2 (20 ml) was added dropwise to a mixture of 2-butynoic acid (**10**, 2.0 g, 23.8 mmol), (–)-borneol (4.0 g, 25.97 mmol) and dimethylaminopyridine (30 mg, 0.25 mmol) in CH_2Cl_2 (20 ml) at 0°. Subsequent stirring of the mixture at 0° for 24 h, dilution with CH_2Cl_2, filtration through *Celite*, evaporation of the filtrate and chromatography (9:1) of the residue gave the crystalline ester **11** (5.12 g, 97.7%) which was sublimed (150° (bath)/0.2 Torr), m.p. 59°. IR ($CHCl_3$): 2242, 1697. ^{1}H-NMR (100 MHz): 0.87 (*s*, 3H); 0.89 (*s*, 3H); 0.91 (*s*, 3H); 0.9–2.1 (6H); 2.0 (*s*, 3H); 2.35 (*m*, 1H); 4.97 (*m*, 1H). MS: 220 (34, $C_{14}H_{20}O_2^+$), 136 (100), 121 (46), 111 (31), 110 (46), 109 (31), 95 (89).

[^{13}C]Methyllithium. [^{13}C]CH_3I (99%, ^{13}C, 2.2 ml, 35 mmol) was added to a suspension of Li-powder (30% suspension in mineral oil, 2.26 g, 96.9 mmol, washed with pentane) in Et_2O at such a rate (*ca.* 1 h) that the mixture is kept at gentle reflux. Stirring of the mixture at 25° for 24 h, filtration, washing of the solid with Et_2O (10 ml) and combination of the filtrates gave a solution of [^{13}C]CH_3Li which was analyzed by *Gilman*'s titration [21] (40 ml, 0.67N, 26.8 mmol, 77%).

1,7,7-Trimethylbicyclo[2.2.1]hept-2-yl (E)-3-methyl[4-^{13}C]-2-butenoate (**12**). 0.67N [^{13}C]CH_3Li (Et_2O, 35 ml, 22.4 mmol) was added dropwise to a suspension of CuI (2.45 g, 12.89 mmol) in dry THF (48 ml) at 0°. After stirring the mixture at 0° for 15 min a solution of **11** (2.45 g, 14 mmol) in THF (12 ml) was added dropwise over 1 h at – 78°. Stirring of the mixture at – 78° for 3 h, followed by addition of MeOH (2.5 ml) and sat. aq. NH_4Cl (25 ml) at – 78°, workup and chromatography (19:1) furnished the labelled ester **12** (oil, 2.6 g, 99%). ^{1}H-NMR: 0.85 (*s*, 3H); 0.88 (*s*, 3H); 0.91 (*s*, 3H); 0.98 (*m*, 1H); 1.18–1.38 (2H); 1.6–1.83 (2H); 1.90 (*d*, J = 126, 3H); 1.96 (*m*, 1H); 2.17 (*d*, J = 4.5, 3H); 2.38 (*m*, 1H); 4.91 (*m*, 1H); 5.72 (br. *d*, J = 8.5, 1H). ^{13}C-NMR: 27.3.

1,7,7-Trimethylbicyclo[2.2.1]hept-2-yl 3-methyl-2-butenoate. Butynoate **11** (400 mg, 1.82 mmol) was treated with dimethylcopperlithium as described above to give the unlabelled ester (oil, 382 mg, 89%), IR (film): 1716, 1650, 1229, 1146, 851. ^{1}H-NMR: 0.85 (*s*, 3H); 0.88 (*s*, 3H); 0.91 (*s*, 3H); 0.98 (*m*, 1H); 1.18–1.4 (2H); 1.62–1.85 (2H); 1.90 (*s*, 3H); 1.96 (*m*, 1H); 2.17 (*s*, 3H); 2.38 (*m*, 1H); 4.91 (*m*, 1H); 5.72 (*s*, 1H). ^{13}C-NMR: 167.0 (*s*); 155.5 (*s*); 116.7 (*d*); 78.9 (*d*); 48.7 (*s*); 47.7 (*s*); 45 (*d*); 36.9 (*q*); 28.0 (*t*); 27.2 (*t* + *q*); 20.1 (*t*); 19.7 (*q*); 18.8 (*q*); 13.5 (*q*). MS: 236 (13, $C_{15}H_{24}O_2^+$), 153 (4), 137 (8), 136 (26), 110 (23), 83 (100).

(E)-3-Methyl[4-^{13}C]-2-butenol (**13**). Solid $LiAlH_4$ (57 mg, 15 mmol) was added in one portion to a solution of anh. $AlCl_3$ (665 mg, 5 mmol) in THF (50 ml) at 0°. After stirring the mixture at 0° for 30 min a solution of **12** (2.71 g, 11.43 mmol) in THF (15 ml) was added dropwise at 0°. Stirring of the mixture at 0° for 2 h, slow addition of sat. aq. Na_2SO_4, filtration, concentration of the filtrate by evaporation of the solvent at 1 atm through a *Vigreux* column followed by distillation of the residue (25°/2 Torr) gave **13** (oil, 820 mg, 83%). ^{1}H-NMR: 1.68 (*d*, J = 124, 0.48H); 1.68 (*d*, J = 4, 2.52H); 1.72 (*d*, J = 4, 0.46H); 1.72 (*d*, J = 124, 2.54H); 4.1 (*d*, J = 7, 2H); 5.38 (*m*, 1H). ^{13}C-NMR: 25.5, 16.8 (integral ratio 20:1).

3-Methyl-2-butenol. 1,7,7-Trimethylbicyclo[2.2.1]hept-2-yl 3-methyl-2-butenoate (1.18 g, 5 mmol) was reduced with AlH_3 as described above to give unlabelled 3-methyl-2-butenol (oil, 300 mg, 70%). ^{1}H-NMR (100 MHz): 1.70 (*s*, 3H); 1.76 (*s*, 3H); 4.14 (*d*, J = 7, 2H); 5.44 (*m*, 1H). ^{13}C-NMR: 135.0 (*s*); 123.7 (*d*); 58.6 (*t*); 25.3 (*q*); 17.4 (*q*).

(E)-1-Bromo-3-methyl[4-^{13}C]-2-butene (**14**). Hexabromoacetone [22] (3.69 g, 6.93 mmol) was added portionwise over 20 min to a stirred mixture of **12** (0.8 g, 9.2 mmol), Ph_3P (3.26 g, 12.4 mmol) in sulfolane (10 ml) at 0°. Then the mixture was allowed to warm to r.t. and to give after distillation at 25°/2 Torr the bromide **14** (oil, 680 mg, 49%). ^{1}H-NMR: 1.74 (*d*, *J* = 125, 0.49 H); 1.74 (*d*, *J* = 4, 2.51 H); 1.78 (*d*, *J* = 4, 0.48 H); 1.78 (*d*, *J* = 125, 2.52 H); 4.02 (*d*, *J* = 8.4, 2H); 5.53 (*m*, 1H). ^{13}C-NMR: 25.7, 17.4 (integral ratio 7:1).

1-Bromo-3-methyl-2-butene. 3-Methyl-2-butenol (280 mg, 3.26 mmol) was treated with hexabromoacetone/Ph_3P as described above to give unlabelled 1-bromo-3-methyl-2-butene (oil, 195 mg, 40%). IR: 1664, 860, 693. ^{1}H-NMR (100 MHz): 1.73 (*s*, 3H); 1.78 (*s*, 3H); 3.88 (*d*, *J* = 8.4, 2H); 5.47 (*m*, 1H). ^{13}C-NMR: 140 (*s*); 120.9 (*d*); 29.6 (*t*); 25.7 (*q*); 17.5 (*q*).

Ethyl (Z)-4,4-bis(ethoxycarbonyl)-4-[N-((E)-3-methyl[4-^{13}C]-2-butenyl)trifluoroacetamido]-2-butenoate (**7**). KH (washed with pentane, 100 mg, 2.5 mmol) was added portionwise at 0° to a solution of **15** [23] (720 mg, 1.95 mmol) and 18-crown-6 (1.14 g, 4.32 mmol) in HMPA (5 ml). After 15 min at 0°, **14** (550 mg, 3.67 mmol) was added dropwise to the mixture, which then was stirred at r.t. for 24 h and finally poured into 10% aq. citric acid. Workup and chromatography (7:3) furnished unchanged amide **15** (325 mg) followed by the more polar diene **7** (428 mg, 50% or 91% based on recovered **15**) which was recrystallized (Et_2O/pentane, – 23°), m.p. 48–49°. ^{1}H-NMR[13]): 1.2–1.4 (9H); 1.53 (*d*, *J* = 124, 0.49 H); 1.53 (*d*, *J* = 2, 2.51 H); 1.70 (*m*, *J* ≦ 4, 0.50 H); 1.70 (*d*, *J* = 124, 2.5 H); 4.1–4.4 (8H); 5.25 (*m*, 1H); 6.13 (*d*, *J* = 12, 1H); 6.31 (*d*, *J* = 12, 1H). ^{13}C-NMR: 25.5, 18.0 (integral ratio 8:1).

Ethyl (Z)-4,4-bis(ethoxycarbonyl)-4-[N-(3-methyl-2-butenyl)trifluoroacetamido]-2-butenoate. Treatment of **15** (152 mg, 0.41 mmol) with KH, 18-crown-6 and unlabelled 1-bromo-3-methyl-2-butene as described above furnished unchanged **15** (61 mg) and unlabelled ethyl (*Z*)-4,4-bis(ethoxycarbonyl)-4-[*N*-(3-methyl-2-butenyl)trifluoroacetamido]-2-butenoate (93 mg, 52% or 86% based on recovered **15**), m.p. 48–49° (Et_2O/pentane, – 10°). IR: 1747, 1710, 1292, 1260, 1210, 1145, 1100, 1030. ^{1}H-NMR: 1.2–1.4 (9H); 1.51 (*s*, 3H); 1.70 (*d*, *J* = 1, 3H); 4.1–4.4 (8H); 5.24 (*m*, 1H); 6.13 (*d*, *J* = 12, 1H); 6.31 (*d*, *J* = 12, 1H). ^{13}C-NMR: 165.1 (*s*); 165.0 (*s*); 136.5 (*d*); 133.9 (*s*); 126.0 (*d*); 121.4 (*d*); 72.9 (*s*); 62.8 (*t*); 62.4 (*s*); 60.8 (*t*); 45.5 (*t*); 45.3 (*t*); 25.4 (*q*); 17.9 (*q*); 14.0(*q*); 13.6 (*q*). MS: 437 (5, $C_{19}H_{26}F_3NO_7^+$), 392 (5), 324 (29), 258 (57), 251 (20), 212 (95), 184 (32), 180 (100), 156 (22).

Ethyl trans-[2,2-bis(ethoxycarbonyl)-4-(1-methyl[2-^{13}C]vinyl)-1-(trifluoroacetyl)pyrrolidin-3-yl]acetate (**9**). Et_2AlCl (2.08N in hexane, 0.33 ml, 0.69 mmol) was added dropwise to a solution of diene **7** (100 mg, 0.23 mmol) in CH_2Cl_2 (1 ml) at – 78°. The mixture was stirred at – 78° for 8 h, then quenched at – 78° with sat. aq. Na_2SO_4, diluted with CH_2Cl_2 and dried with anh. Na_2SO_4. Evaporation and chromatography (3:1) afforded **9** (oil, 86 mg, 86%). ^{1}H-NMR: 1.16–1.4 (9H); 1.70 (*d*, *J* = 6, 2.5 H); 1.70 (*d*, *J* = 126, 0.5 H); 2.31 (*dd*, *J* = 16.6 and 7, 1H); 2.62 (*dd*, *J* = 16.6 and 7, 1H); 2.85 (*m*, 1H); 3.0 (*m*, 1H); 3.62 (*t*, *J* = 11, 1H); 4.0 (*t*, *J* = 9, 1H); 4.08 (*q*, *J* = 7.3, 2H); 4.2–4.3 (4H); 4.93 (*t*, *J* = 6, 0.34 H); 4.93 (br. *d*, *J* = 154, 1.66 H). ^{13}C-NMR: 116.6, 18.0 (integral ratio 6:1).

Ethyl trans-*[2,2-bis(ethoxycarbonyl)-4-isopropenyl-1-(trifluoroacetyl)pyrrolidin-3-yl]acetate.* Treatment of unlabelled ethyl (*Z*)-4,4-bis(ethoxycarbonyl)-4-[*N*-(3-methyl-2-butenyl)trifluoroacetamido]-2-butenoate (100 mg, 0.23 mmol) with Et_2AlCl at – 78° as described above furnished the unlabelled ethyl *trans*-[2,2-bis(ethoxycarbonyl)-4-isopropenyl-1-trifluoroacetylpyrrolidin-3-yl]acetate (oil, 89 mg, 89%). IR: 1744, 1713, 1445, 1244, 1150, 1095, 1069, 1040, 912. ^{1}H-NMR: 1.16–1.4 (9H); 1.72 (*s*, 3H); 2.33 (*dd*, *J* = 16.6 and 7, 1H); 2.63 (*dd*, *J* = 16.6 and 7, 1H); 2.85 (*m*, 1H); 3.07 (*m*, 1H); 3.63 (*t*, *J* = 11, 1H); 4.02 (*t*, *J* = 9, 1H); 4.09 (*q*, *J* = 7.3, 2H); 4.2–4.3 (4H); 4.95 (br. *s*, 2H). ^{13}C-NMR: 170.6 (*s*); 166.2 (*s*); 165.2 (*s*); 139.2 (*s*); 116.6 (*t*); 114.4 (*s*); 74.5 (*s*); 62.4 (*t*); 60.7 (*t*); 51.0 (*d*); 50.3 (*t*); 45.5 (*d*); 33.7 (*t*); 18.0 (*q*); 14.0 (*q*); 13.9 (*q*); 13.8 (*q*). MS: 437 (21, $C_{19}H_{26}F_3NO_7^+$), 392 (7), 364 (37), 318 (100), 290 (74), 272 (21), 262 (15), 259 (18), 216 (12).

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[13]) The integrals of overlapping satellite bands were assigned as being equal to those of the corresponding isolated satellite bands.

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