PAPERS

New and Efficient Lewis Acid Catalysts in Intramolecular Ene Reactions

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The thermal or Lewis acid catalyzed intramolecular ene reaction of the Knoevenagel adduct **3** from citronellal and dimethyl malonate affords the two diastereoisomeric dimethyl (5-methyl-2-*trans*-isopropenylcyclohexyl)malonates **4a** and **4b**. Anhydrous iron(III) chloride on basic alumina proved to be the best catalyst giving, at −78 °C, the two diastereoisomers **4a** and **4b** in a ratio of 98.8:1.2 in 92% yield.

The intramolecular ene reaction[1] is a valuable method for the formation of substituted cyclopentane[2] and cyclohexane[3] derivatives.

In the course of our investigations aiming at the synthesis of enantiomerically pure sesquiterpenoid natural products[4] we studied the cyclization of the chiral 1,7-diene **3** and related compounds.[5] Methyl (5*R*)-2-methoxycarbonyl-5,9-dimethyl-2,8-decadienoate (**3**) can be obtained by Knoevenagel condensation of citronellal[6] (**1**) with dimethyl malonate (**2**) in 82% yield. The kinetically controlled intramolecular ene reaction of **3** in boiling *o*-dichlorobenzene afforded the 1,2-*trans*-substituted products **4a** and **4b** in a 89.7:10.3 ratio[7] and in 75% yield. In order to improve the induced diastereoselectivity (i-de) in favour of **4a**[3,5] the reaction was examined in different solvents like mesitylene, *m*-xylene, toluene, benzene, and dichloromethane with and without the addition of Lewis acids.[8]

As expected, the selectivity is increased by lowering the temperature (see Table 1.), but this is limited by a marked decrease in reactivity already at 164 °C (mesitylene). However, the reaction rate of ene reactions can be dramatically enhanced by the addition of Lewis acids such as zinc(II) halides,[9] iron(III) chloride,[10] and alkylaluminium halides.[8,11]

No reaction was obtained with soft Lewis acids such as copper(I) salts. On the other hand, the use of Brönsted acids such as formic acid or sulfuric-acetic acid mixtures afforded only lactone **5** or mixtures of lactones **5** and **6**. The formation of **5** can be conceived as a Brönsted acid initiated cyclization of **4a** via the carbenium ion **7**.

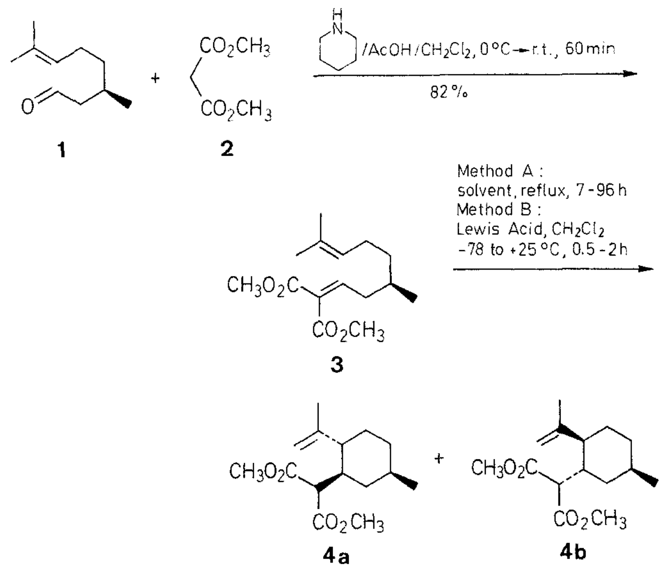
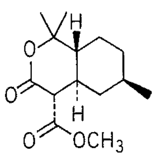


Table 1. Thermal Cyclization of 1,7-Diene **3** in Different Solvents in the Absence Lewis Acids (Method A)

Solvent	Reaction Temperature (°C)	Reaction Time (h)	Yield (%)	Ratio **4a** : **4b**	i-de[3] (%)
o-dichlorobenzene	179.5	7	75	89.7 : 10.3[a]	79.4
				88.0 : 12.0[b]	76.0
mesitylene	164.5	15	69	90.8 : 9.2[a]	81.6
m-xylene	138.5	48	58	91.6 : 8.4[a]	83.2
toluene	111.0	[c]	24	92.1 : 7.8[a]	84.3
benzene	80.0	[c]	–	–	–

[a] GLC analysis of crude product.
[b] ^{13}C-NMR analysis of crude product.
[c] The reaction was interrupted after 96 h.



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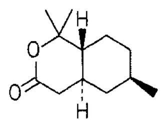

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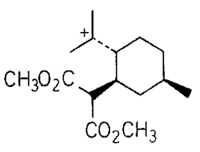

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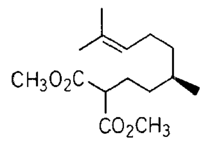

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With anhydrous zinc(II) bromide (e.g., 1.1 equiv) in dichloromethane, the transformation 3 → **4a** + **4b** occurred already at room temperature within 15–30 min with an i-de of 93.2%[3,5] (**4a**:**4b** = 96.6:3.4). Further investigations proved that the reaction could also be run in benzene, toluene, chloroform, tetrachloromethane, 1,2-dichloroethane, and even in pentane and *tert*-butyl methyl ether (however, in the latter two solvents with considerably longer reaction times). No reaction took place when solvents were used that have to be regarded as Lewis bases, such as methanol or acetonitrile. Results similar to those obtained with zinc(II) bromide could be obtained by using anhydrous zinc(II) chloride and zinc(II) iodide (Table 2). With zinc(II) halides, all reactions had to be carried out at 25 °C to achieve reasonable reaction rates.

To further improve the ratio **4a**:**4b** we examined the reaction **3** → **4** in the presence of trimethylaluminium and alkylaluminium halides at – 78 °C. The use of 1.1 equivalent of trimethylaluminium in dichloromethane repeatedly led to complex, unseparable mixtures containing 20% of **4a** + **4b** (GLC). The use of diethylaluminium chloride yielded 88% of **4a** + **4b** in a ratio of 97.9:2.1. In some runs, an additional compound was formed, which could not be separated; from GLC-MS spectra it can be assumed that this compound is the ester **8**, which could be produced by hydride transfer to **3**.[11]

The reaction of **3** with 1 equivalent of dimethylaluminium chloride produced **4a** + **4b** in 68% yield (GLC) in a 97.8:2.2 ratio. In addition, 20% (GLC) of a by-product of unknown structure was formed.

Use of the strong Lewis acids aluminium trichloride, titanium(IV) chloride, and tin(IV) chloride at 25 °C and at – 35 °C resulted in the formation of complex mixtures.

Finally, we found that anhydrous iron(III) chloride, which induces the cyclization **3** → **4a** + **4b** at room temperature already in a concentration of 0.01 equivalents, was superior to all previously used catalysts. Further, the cyclization using iron(III) chloride can be run at low temperature (Table 2). In this way, products **4a** and **4b** were formed in 94% yield in a ratio of 98.8:1.2 (i-de = 97.6%) using 0.1 equivalents of catalyst at – 78 °C. However, compound **5** was in some cases obtained as a side product in this transformation. To avoid this undesirable side reaction, which can be attributed to the presence of traces of water or Brönsted acid, the cyclization was performed using silica gel- or alumina-supported iron(III) chloride.[12] The supported catalysts are easily accessible by stirring anhydrous iron(III) chloride and chromatography-grade adsorbents in anhydrous dichloromethane under argon and then removing the solvent. The best results were obtained with iron(III) chloride on

Table 2. Lewis Acid Catalyzed Reaction **3** → **4a** + **4b**

Catalyst	Equivalents	Solvent	Reaction Temp. (°C)	Reaction Time (h)	Yield[a] of **4a** + **4b** (%)	Ratio[b] of **4a** : **4b**	i-de[3] (%)
$ZnBr_2$	1.1	CH_2Cl_2	25	0.5	86	96.6 : 3.4	93.2
$ZnBr_2$	1.1	$CHCl_3$	25	0.75	84	–	–
$ZnBr_2$	1.1	CCl_4	25	2	80	–	–
$ZnBr_2$	1.1	1,2-dichloroethane	25	0.75	83	–	–
$ZnBr_2$	1.1	C_6H_6	25	0.75	82	96.9 : 3.1	93.8
$ZnBr_2$	1.1	toluene	25	1.5	79	–	–
$ZnBr_2$	1.1	pentane	25	16		–	–
$ZnBr_2$	1.1	*t*-BuOMe	25	12			
$ZnBr_2$	1.1	CH_3CN	25	[c]	–	–	–
$ZnBr_2$	1.1	MeOH	25	[c]	–	–	–
$ZnCl_2$	1.1	C_6H_6	25	0.3	80	96.0 : 4.0	92.0
ZnI_2	1.1	C_6H_6	25	1.5	83	96.4 : 3.6	92.8
$FeCl_3$	0.1	CH_2Cl_2	25	0.08	–	–	–
$FeCl_3$	0.01	CH_2Cl_2	25	0.25	84	96.0 : 4.0	92.0
$FeCl_3$	0.1	CH_2Cl_2	–30	2.0	94	97.5 : 2.5	95.0
$FeCl_3$	0.1	CH_2Cl_2	–40	2.0	94	97.8 : 2.2	95.6
$FeCl_3$	0.1	CH_2Cl_2	–78	[d]	94	98.8 : 1.2	97.6
$FeCl_3/Al_2O_3$[e]	0.1	CH_2Cl_2	–78	[d]	92	98.8 : 1.2	97.6
$Al(CH_3)_3$[h]	1.1	CH_2Cl_2	–78	[d]	20	–	–
$Al(CH_3)_2Cl$[h]	1.1	CH_2Cl_2	–78	[d]	68[f]	97.8 : 2.2	95.6
$Al(C_2H_5)_2Cl$[h]	1.1	CH_2Cl_2	–78	[g]	88	97.9 : 2.1	95.8

[a] Yield of isolated product.

[b] GLC analysis of crude product.

[c] The reaction was interrupted after 24 h.

[d] The reaction mixture was stirred at – 78 °C for 2 h and then warmed to r.t. over a period of 2 h.

[e] Basic alumina.

[f] The yield was determined by GLC.

[g] The reaction mixture was stirred at – 78 °C for 1 h and then warmed to r.t. over a period of 1 h.

[h] The Lewis acid was added dropwise to the solution of 3.

basic alumina. The ene reaction of **3** using 0.1 equivalents of iron(III) chloride on basic alumina afforded **4a** + **4b** in 92% yield in a ratio of 98.8:1.2.

The structure of the chromatographically separable **4a** was deduced from ^1H- and ^{13}C-NMR-spectra. Thus, for **4a** with a *trans*-diequatorial arrangement of the isopropenyl and the dimethyl malonate substituents, the coupling constant for the cyclohexyl 1'-H-2'-H coupling is $J = 11.5$ Hz. The equatorial arrangement of the methyl group at C-5' of the cyclohexane ring can be deduced from its chemical shift at $\delta = 22.54$[13] in the ^{13}C-NMR-spectrum, the 1,3-*cis*-diequatorial arrangement of the methyl group and the dimethyl malonate group follows from the coupling pattern of 6'-H_{ax} which shows three couplings of $J = 11.5$ Hz. The 1,4-*trans*-diequatorial arrangement of the methyl and isopropenyl groups is proven by comparison with the ^{13}C-NMR data for *trans*-8-*p*-menthene; both compounds show similar signals for the methyl group and the ring carbons C-3', C-4', C-5', and C-6'.[13] In addition, the structure of **4a** was confirmed by acid-catalyzed cyclization to **5** using trifluoroacetic acid.

The ^{13}C-NMR-spectrum of (not separated) **4b** shows the signal for axial arrangement of the methyl group at $\delta = 17.89$. The *trans*-diequatorial arrangement of the isopropenyl and the dimethyl malonate groups can be deduced from the similarity of their shifts in **4a** and **4b**. The 1,4-*cis*-arrangement of the methyl and isopropenyl groups follows from comparison of the ^{13}C-NMR data with those of *cis*-8-*p*-menthene and *cis*-4-methyl-1-vinylcyclohexane. These compounds show similar signals for the methyl group as well as for the ring carbons C-3', C-4', and C-5'.[13]

Methyl (5*R*)-2-Methoxycarbonyl-5,9-dimethyl-2,8-decadienoate (3):

To a stirred solution of (*R*)-citronellal (**1**; 15.4 g, 0.10 mol) and dimethyl malonate (**2**; 14.5 g, 0.11 mol) in anhydrous CH_2Cl_2 (50 mL) at 0 °C are added AcOH (0.60 g, 10.0 mmol) and piperidine (0.85 g, 10.0 mmol). The mixture is warmed to room temperature and stirred for 45 min, then additional AcOH (0.60 g, 10.0 mmol) and piperidine (0.85 g, 10.0 mmol) are added, and stirring is continued for 15 min. The mixture is evaporated in vacuo, diluted with Et_2O (100 mL), and washed with H_2O (2 × 25 mL), and the aqueous washes are re-extracted with Et_2O (2 × 25 mL). The combined organic phases are washed with saturated $NaHCO_3$ solution (25 mL), H_2O (25 mL), and brine (25 mL), and dried (Na_2SO_4). Solvent and excess dimethyl malonate are removed under reduced pressure. The remaining light yellow oily product **3** is pure enough for use in further reactions; yield: 25.4 g (95%). Flash chromatography of 2.54 g of this crude product on silica gel (petroleum ether/acetone, 98:2) affords analytically pure **3**; yield: 2.20 g (82%); R_f 0.51 (Et_2O/hexane 1:1); $[\alpha]_D^{20}$ – 8.2° ($c = 1.0$, CH_3CN).

$C_{15}H_{24}O_4$	calc.	C 67.14	H 9.01
(268.4)	found	67.19	9.03

MS (70 eV): $m/z = 268$ (M^+, 1%); 237 ($M^+ - OCH_3$, 2); 236 ($M^+ - CH_3OH$, 3), 209 ($M^+ - C_2H_3O_2$, 2), 208 ($M^+ - C_2H_4O_2$, 5), 204 (16), 136 ($C_{10}H_{16}^+$, 47), 126 (15), 121 (24), 109 (C_8H_{13}, 23), 93 (20), 82 (16), 69 (C_5H_9, 57), 67 ($C_5H_7^+$, 19); 59 ($C_2H_3O_2^+$, 17), 55 ($C_4H_7^+$, 29), 41 ($C_3H_5^+$, 100).

IR (film): $\nu = 1730$ (C=O); 1645 (C=C); 1260, 1235, 1060 cm^{-1} (C–O).

UV (CH_3CN): λ_{max} (lg ε) = 210 (sh) nm (4.13).

^1H-NMR (C_6D_6): $\delta = 0.78$ (d, 3H, $J = 6.5$ Hz, 5-CH_3); 0.94–1.46 (m, 3H, 5-H, 6-H_2); 1.53 (br s, 3H, 10-H_3); 1.66 (br s, 3H, 9-CH_3); 1.76–2.38 (m, 4H, 4-H_2, 7-H_2); 3.39 (s, 3H, OCH_3); 3.51 (s, 3H, OCH_3); 5.1 (tm, 1H, $J = 7$ Hz, 8-H); 7.06 (t, 1H, $J = 8$ Hz, 3-H).

^{13}C-NMR (C_6D_6): $\delta = 17.66$ (C-10); 19.59 (5-CH_3); 25.81 (9-CH_3); 25.81 (C-7); 32.68 (C-5); 36.99, 37.03 (C-4, C-6); 51.69, 51.81 (OCH_3); 124.89 (C-8); 129.80 (C-2); 131.25 (C-9); 148.48 (C-3); 164.20 (2-$\underline{C}O_2CH_3$); 165.76 (C-1).

Dimethyl (1'*R*,2'*R*,5'*R*)-2-(2'-Isopropenyl-5'-methylcyclohexyl)propanedioate (4a); Typical Procedures:

Method A, Thermal Cyclization: A solution of methyl (5*R*)-2-methoxycarbonyl-5,9-dimethyl-2,8-decadienoate (**3**; 2.68 g, 10.0 mmol) in *o*-dichlorobenzene (10 mL) is heated to refluxing for 7 h under argon. The solvent is then removed under reduced pressure and the residue is chromatographed on silica gel (petroleum ether/Et_2O 4:1 as eluent); yield: 2.02 g (75%) of a 89.7:10.3 mixture of **4a** and **4b** (GLC retention times: **4a** 16.88 min, **4b** 17.11 min).

Method B, Lewis Acid Catalyzed Cyclization: The Lewis acid (Table 2), e.g. anhydrous $ZnBr_2$ 2.48 g, 11.0 mmol), is placed in a flame-dried and argon-flushed reaction flask. Anhydrous solvent, e.g. CH_2Cl_2 (25 mL), is added, followed by the dropwise addition with stirring, of methyl (5*R*)-2-methoxycarbonyl-5,9-dimethyl-2,8-decadienoate (**3**; 2.68 g, 10.0 mmol). Stirring is continued for 30 min and the mixture then evaporated under reduced pressure. The residue is diluted with Et_2O (40 mL) and H_2O (10 mL). The organic layer is separated and washed with H_2O (2 × 10 mL) and the combined aqueous layers are extracted with Et_2O (2 × 20 mL). The organic phases are combined and washed with saturated $NaHCO_3$ solution (10 mL) and brine (10 mL), and dried (Na_2SO_4). The solvent is removed under reduced pressure and the residue is chromatographed on silica gel (petroleum ether/Et_2O 4:1 as eluent); yield: 2.20 g (86%) of a 96.6:3.4 mixture (GLC) of **4a** and **4b**. Repeated chromatography gives pure **4a** (99.5% **4a**, GLC); bp 128–129 °C/0.5 mbar; R_f: 0.56 (Et_2O/hexane 1:1); $[\alpha]_D^{20}$ – 31.5° ($c = 1.0$, CH_3CN).

$C_{15}H_{24}O_4$	calc.	C 67.14	H 9.01
(268.4)	found	67.22	9.07

MS (70 eV): $m/z = 268$ (M^+, 4%), 250 ($M^+ - H_2O$, 1), 237 ($M^+ - OCH_3$, 3), 236 ($M^+ - CH_3OH$, 3), 209 ($M^+ - C_2H_3O_2$, 3), 208 ($M^+ - C_2H_4O_2$, 7), 145 (17), 137 ($C_{10}H_{17}^+$, 19), 136 ($C_{10}H_{16}^+$, McLafferty, 100), 133 (29), 132 ($C_5H_8O_4^+$, 16), 121 (C_9H_{13}, 35), 107 ($C_8H_{11}^+$, 41), 94 ($C_7H_{10}^+$, RDA, 14), 93 ($C_7H_9^+$, 34), 81 (18), 79 ($C_6H_7^+$, 21), 67 (16), 59 ($C_2H_3O_2^+$, 10), 55 (16).

IR (film): $\nu = 3065$ (C=CH_2); 1750, 1735 (C=O); 1645 (C=C); 1155, 1035, 1020 (C–O); 895 cm^{-1} (C=CH_2).

^1H-NMR ($CDCl_3$): $\delta = 0.91$ (d, 3H, $J = 6.5$ Hz, 5'-CH_3); 0.95 (dq, 1H, $J = 3.5$, 12 Hz, 4'-H_{ax}); 1.11 (q, 1H, $J = 11.5$ Hz, 6'-H_{ax}); 1.24–1.57 (m, 2H, 3'-H_{ax}, 5'-H_{ax}); 1.65 (mc, 3H, 2''-CH_3); 1.57–1.94 (m, 3H, 3'-H_{eq}, 4'-H_{eq}, 6'-H_{eq}); 2.05 (dt, 1H, $J = 3.0$, 11.5 Hz, 2'-H); 2.13 (tt, 1H, $J = 3.5$, 11.5 Hz, 1'-H); 3.56 (d, 1H, $J = 3.5$ Hz, 2-H); 3.73 (s, 6H, 2OCH_3); 4.74 (mc, 1H, 1''-H); 4.79 (m, 1H, 1''-H).

^{13}C-NMR ($CDCl_3$) of **4a/4b**: $\delta = 18.96/19.36$ (C-3''); 22.54/17.89 (5'-CH_3); 32.35/26.27 (C-3'); 32.73/27.32 (C-5'); 34.68/31.09 (C-4'); 36.59/33.47 (C-6'); 39.88/34.33 (C-1'); 48.68 (C-2'); 51.80, 52.22 (OCH_3); 53.22/53.14 (C-2); 112.43/112.22 (C-1''); 147.52 (C-2''); 169.03, 170.11/169.95 (C-1, C-3).

Iron(III) Chloride on Silica Gel or on Alumina:

Iron(III) chloride (10.0 g, 61.6 mmol) is added to anhydrous CH_2Cl_2 (160 mL) under argon. The mixture is vigorously stirred and chromatography-grade adsorbent (50 g of silica gel or basic alumina) is added in small portions under argon. Stirring is continued for 1 h to achieve homogeneous adsorption and the solvent then removed under reduced pressure. The procedure yields adsorbent-supported $FeCl_3$, which can be stored under argon for several months without remarkable loss of catalytic activity.

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(6) Here, the configuration referring to (*R*)-(+)-citronellal is given.

(7) In fact, while we had originally[5] reported a ratio **4a**:**4b** of 86:14 for the reaction in boiling *o*-dichlorobenzene, a more recent investigation showed that the minor diastereoisomer **4b** represented only 10.3% of the product.
The ratio of **4a**:**4b** in the present study was determined by GLC analysis using capillary colums: (1) 0.13 μm Cp Sil 5; 0.32 mm × 25 m; fused silica; temperature 100 °C → 250 °C, 3 and 5 °C/min; detector FID; (2) 0.25 μm chemical bound SE 30; 0.32 mm × 50 m; fused silica; temperature 100 °C → 250 °C, 5 °C/min; detector FID; and in some cases by additional analysis of the ^{13}C-NMR-spectra of the crude product mixtures.

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