Stereoselective Synthesis of 3,5-Alkadienoic Esters from 2,4-Dienoic Isomers

Sadao TSUBOI,* Jun-ichi SAKAMOTO, Akihisa KURODA, Masanori UTAKA, and Akira TAKEDA
Department of Synthetic Chemistry, School of Engineering, Okayama University, Tsushima, Okayama 700
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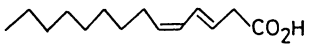
Synopsis. The treatment of (2*E*,4*Z*)-2,4-alkadienoic esters with lithium diisopropylamide (LDA) at −80 °C gave (3*E*,5*E*)-isomers with 81—98% stereoselectivity. In contrast, the treatment of (2*E*,4*E*)-isomers under the same conditions gave (3*E*,5*Z*)-isomers with 72—80% stereoselectivity. The application to the synthesis of megatomoic acid is described. Carbon-13 NMR data regarding these 3,5-dienoates were obtained.

Some natural products containing a 3,5-dienoic acid moiety are reported. For example, an antibiotic mycomycin **1**[1] and an insect pheromone, megatomoic acid **2**,[2] are well-known.

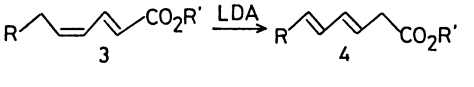
$HC{\equiv}C\text{-}C{\equiv}C\text{-}CH{=}C{=}CH\text{-}CH{=}CHCH{=}CHCH_2CO_2H$
mycomycin **1**



megatomoic acid **2**

Conjugated diene groupings are useful for the synthesis of natural products via a Diels-Alder reaction.[3] To our knowledge, synthetic methods for 3,5-alkadienoic esters are quite limited. The conventional method consists of the combination of a Wittig reaction and a hydrogenation of triple bonds. On the other hand, Chiusoli reported the synthesis of 3,5-alkadienoates via the isomerization of 2,5-alkadienoates.[4] Krebs[5] and Kende et al.[6] reported that deconjugative alkylation of (*E*)- and (*Z*)-2-alkenoates with strong bases, such as lithium diisopropylamide (LDA) or potassium hexamethyldisilazide, gave, respectively, (*Z*)- and (*E*)-3-alkenoate with high stereoselectivities. We recently reported the highly stereo- and regioselective alkylation of alkylidenemalonates.[7] This paper reports a detailed description of the previous communication[8] concerning the deconjugative protonations of (2*E*,4*Z*)- and (2*E*,4*E*)-2,4-alkadienoates with LDA.[9]

In 1982 we reported a convenient synthesis of (2*E*,4*Z*)-alkadienoic esters **3** by the stereoselective rearrangement of β-allenic esters promoted with alumina.[10] As a result of our continuous interest in the chemistry of **3**,[11] we treated **3** with LDA at −80 °C. The reaction gave (3*E*,5*E*)-isomers **4** in good yield. On the other hand, a treatment of (2*E*,4*E*)-2,4-alkadienoates **5** with LDA afforded (3*E*,5*Z*)-isomers **6**. Various alkadienoates **3** and **5** were prepared and treated with LDA in THF/hexamethylphosphoric triamide (HMPA). These results were tabulated in Tables 1 and 2. The transformation of **3** to **4** proceeded with 81—98% stereoselectivity, while that of **5** to **6** proceeded with 72—80%. To improve the stereoselectivity, various lithium amides such as lithium dicyclohexylamide, lithium bis(trimethylsilyl)amide, and lithium diethylamide were used as a base. However, a notable improvement could not be established. The stereoselectivity decreased slightly as the substituent became larger. The geometry of the rearrangement products was determined by ^{1}H NMR spectral data with the aid of a shift reagent Eu(dpm)$_2$ and a proton decoupling technique. For example, both $J_{3,4}$ and $J_{5,6}$ in ethyl (3*E*,5*E*)-3,5-decadienoate (**4c**) were 15 Hz, which shows a trans geometry. The coupling constants of ethyl (3*E*,5*Z*)-3,5-decadienoate were $J_{3,4}$=15.4 Hz and $J_{5,6}$=10.8 Hz. The ^{13}C NMR spectra of compounds prepared in this work were measured and tentatively assigned as shown in Table 3. In general, signals of cis olefinic carbons of **6** appeared at a higher field than those of trans, trans-olefins **4** as a result of a steric effect.[12] These data afford an additional support for the structural assignment of **4** and **6**.



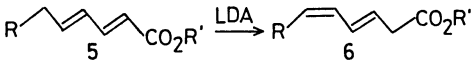
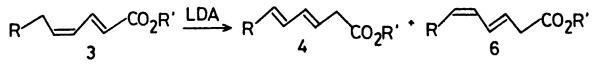


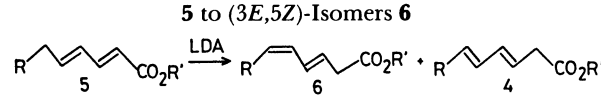
Table 1. Transformation of (2*E*,4*Z*)-2,4-Alkadienoates **3** to (3*E*,5*E*)-Isomers **4**



	3		Yields of products/%[a]			Stereoselectivity
No.	R	R′	**3**	**4**	**6**	**4**/**6**(%)
a	C_2H_5	CH_3	2	77	3	96
b	n-C_3H_7	CH_3	0	56	1	98
c	n-C_4H_9	C_2H_5	0	87	10	90
d	n-C_7H_{15}	C_2H_5	0	68	12	85
e	n-C_8H_{17}	CH_3	23	62	15	81

a) Analyzed by GLC fitted with Golay column (SE-30 silicone gum rubbers, 0.5 mm×45 m) or 10% SE-30 on Chromosorb W column (3 mm×1 m).

Table 2. Transformation of (2*E*,4*E*)-2,4-Alkadienoates **5** to (3*E*,5*Z*)-Isomers **6**



	5		Yields of products/%[a]		Stereoselectivity
No.	R	R′	**6**	**4**	**6**/**4**(%)
a	C_2H_5	CH_3	51	13	80
b	n-C_3H_7	CH_3	66	22	75
c	n-C_4H_9	C_2H_5	72	28	72
e	n-C_8H_{17}	CH_3	75	19	80

a) Analyzed by GLC fitted with Golay column (SE-30 silicone gum rubbers, 0.5 mm×45 m) or 10% SE-30 on Chromosorb W column (3 mm×1 m).

The stereochemical outcome in the present transformation can be explained by the assumption of carbanion intermediates[6] (**3′**, **3″**, **5′**, and **5″**), as shown in Chart 1. The deprotonation of **3** directly yields the minimum energy carbanion stereoisomer **3′**, which gives rise to the observed (3*E*,5*E*)-product. The alternative carbanion **3″** is unfavorable because of a severe 1,3-allylic strain between R and $CH{=}CHCO_2Et$. The deprotonation of **5** gives carbanion intermediates **5′** and **5″**, leading to the (3*E*,5*Z*)-and (3*E*,5*E*)-products, respectively. The formation of the carbanion **5′** leading to (3*E*,5*Z*)-product is favorable, since the cis form for the crotyl anion system is usually more stable than the trans form.[6] A higher stereoselectivity in the transformation of **3** to **4** than that of **5** to **6** is attributable to a larger energy difference between **3′** and **3″** than that between **5′** and **5″**.

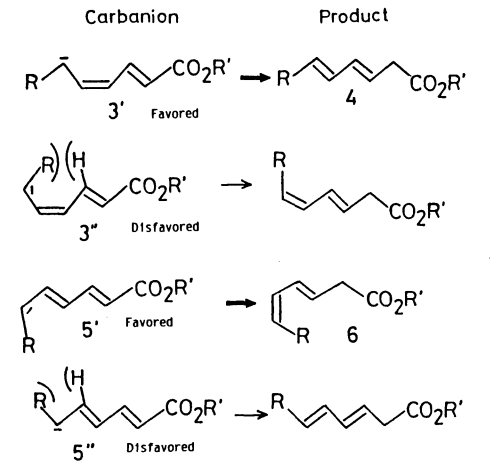
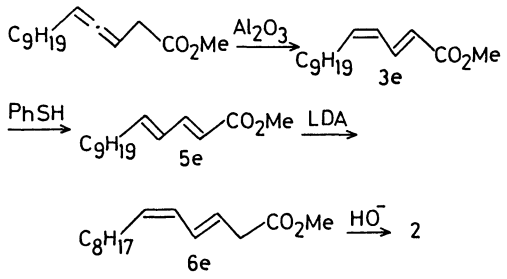


Chart 1.



Scheme 1.

The present system was applied for the synthesis of megatomoic acid **2**, the sex attractant of the black carpet beetle.[2] The reaction sequence is shown in Scheme 1. The starting material, (2*E*,4*E*)-2,4-tetradecadienoate (**3e**), was prepared in 70% yield by a highly stereoselective rearrangement of methyl 3,4-tetradecadienoate, promoted with alumina, as reported previously.[7] The conversion of **3e** to methyl (2*E*,4*E*)-2,4-tetradecadienoate (**5e**) was established in 81% yield by a thermal treatment catalyzed by thiophenol and 2,2′-azobis(isobutyronitrile)(AIBN).[13] The treatment of **5e** with LDA gave a mixture of methyl (3*E*,5*Z*)-3,5-tetradecadienoate (**6e**) and the (3*E*,5*E*)-isomer **4e** (75:19). Spectral data were consistent with those reported previously.[11a] It has been reported that the hydrolysis of **6e** purified with GLPC gave megatomoic acid.[11a]

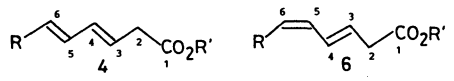
The present method will be useful for the stereoselective synthesis of polyenoic compounds, such as insect pheromones and leukotrienes.

Experimental

The boiling points are uncorrected. Elemental analyses were carried out by Mr. Eiichiro Amano of our laboratory. Analytical determinations by GLC were performed on a Hitachi Model 163 gas chromatograph fitted with 10% Silicone SE-30 on Chromosorb W column (3 mm×1 m) or Golay column (SE-30 silicone gum rubbers, 0.5 mm×45 m). IR spectra were taken on a JASCO Model A-102 spectrometer. ^1H NMR spectra (60 MHz) were recorded with a JEOL JNM-PMX60SI apparatus. ^{13}C NMR spectra (25 MHz) were obtained with a JEOL JNM-FX100 apparatus, using $CDCl_3$ as a solvent. Column chromatography was accomplished with 100—200 mesh Wakogel C-200. High-performance liquid chromatography (HPLC) was obtained with Yanagimoto liquid chromatograph L-2000 fitted with Yanapak SA-I (6 mm×250 mm). Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under an atmosphere of nitrogen. Hexamethylphosphoric triamide (HMPA) was distilled from CaH_2 under reduced pressure. All experiments of the isomerization were carried out under an atmosphere of argon.

(2*E*,4*Z*)-2,4-Alkadienoates **3** was prepared according to the procedure reported previously.[10] (2*E*,4*E*)-2,4-Alkadienoates **5** was obtained from **3** by the procedure of the literature[13] and purified by preparative TLC (SiO_2, hexane/ethyl acetate=15/1) developed twice. The sample was purified by preparative TLC (SiO_2, hexane/ethyl acetate=15/1) developed twice. Some representative preparation of **4** and **6** are described below.

Table 3. ^{13}C NMR Data of (3*E*,5*E*)-3,5-Alkadienoates **4** and (3*E*,5*Z*)-3,5-Alkadienoates **6**



Compd	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	C_{11}	C_{12}	C_{13}	C_{14}
4a	171.9	38.0	122.4	134.2	128.4	136.4	25.6	13.5						
4b	172.1	37.9	122.3	134.7	129.7	134.2	34.7	22.4	13.7					
4c	171.8	38.2	122.5	134.8	129.6	134.1	29.1	31.4	22.3	14.0				
4e	172.1	37.8	122.2	134.4	129.4	134.1	28.3	29.5*	29.3*	28.5*	28.5*	31.9	22.7	14.1
6a	171.9	38.2	124.6	134.0	127.2	129.3	21.2	14.3						
6b	172.1	38.1	124.5	132.1	127.9	129.3	29.8	22.8	13.7					
6c	171.8	38.2	123.9	132.4	126.9	128.0	28.3	31.7	22.3	14.0				
6e	172.0	38.1	124.5	132.4	127.7	129.5	27.8	29.3*	29.3*	29.6*	29.6*	31.9	22.7	14.1

* May be exchangeable.

Methyl (3*E*,5*E*)-3,5-Octadienoate (4a). To a solution of diisopropylamine (0.289 ml, 2.10 mmol) in THF (4.5 ml) was added dropwise 1.18 ml of 1.65 M BuLi (1M=1 mol dm^{-3}) at 0 °C. After 30 min, HMPA (0.4 ml) was added and the mixture was cooled to −80 °C. A solution of **3a** (236 mg, 0.992 mmol) in THF (1.5 ml) was added dropwise; then, the mixture was stirred for 1 h and poured into ice water. After the mixture was acidified with dil. HCl, the organic materials were extracted with ether. The combined extracts were washed with water, dried over $MgSO_4$, and concentrated. The residual oil was chromatographed on SiO_2 to give 189 mg of an oil, of which GLC analysis (golay column, 130 °C) showed two peaks at R_t 3.2 and 3.4 min in a ratio of 4:96. Each component was separated by preparative GLC. The major fraction was identified as **4a**.[13] The minor fraction gave **6a**:[14] IR (neat) 1640 and 1600 cm^{-1}; ^1H NMR (CCl_4) δ=0.95 (t, 3H, CH_3), 2.16 (m, 2H, $C\underline{H}_2CH_3$), 3.05 (d, 2H, J=7 Hz, CH_2CO), 3.59 (s, 3H, CO_2CH_3), 5.05—6.48 (m, 4H, $(CH{=}CH)_2$).

Ethyl (3*E*,5*E*)-3,5-Decadienoate (4c). To a solution of 0.046 ml (0.38 mmol) of dicyclohexylamine in 2 ml of dry THF was added at −15 °C 0.208 ml (0.38 mmol) of 1.65 M butyllithium in hexane. After 20 min, 0.1 ml of HMPA was added and then a solution of 65 mg (0.33 mmol) of **3c** in 2.5 ml of THF was added dropwise at −80 °C. The mixture was stirred for 1 h at −80 °C and then poured into ice water. The organic materials were extracted with ether, washed with water, dried over $MgSO_4$, and the solvent was evaporated. Analysis of the residual oil (67 mg) with GLC [column, SE-30 (3 mm×1 m), 120 °C; carrier gas, N_2 (0.5 kg cm^{-2})] gave two peaks. The structure was determined by comparison of the retention time with that of the authentic sample. The peaks, compounds, retention times, and integrated percentages were as follow: 1, **6c**, 3.9, 10%; 2, **4c**,[15] 4.1, 87%.

Methyl (3*E*,5*Z*)-3,5-Tetradecadienoate (6e). A solution of **5e** (98 mg, 0.41 mmol) in THF (0.1 ml) was treated with LDA prepared from diisopropylamine (0.069 ml, 0.5 mmol), 1.65 M butyllithium (0.273 ml, 0.5 mmol), and HMPA (0.15 ml) at −72 °C for 1 h, as shown in the preparation of **4c**. The mixture was worked up as usual and a crude product was obtained as an oil (93 mg) which was analyzed by GLC [column: SE-30 (3 mm×1 m), 170 °C; carrier gas, N_2 (0.5 kg cm^{-2})]. The peaks, retention times, and integrated peak areas are as follows: 1, 3.7 min, 80%; 2, 4.4 min, 20%. Component 1 was identified as **6e** (75% yield) by comparison of spectral data and the retention times with those of an authentic sample.[11a] Component 2 was identified as **4e** (19% yield) by a comparison of the spectral data and the retention time with those of a sample prepared from **3e**.

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