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Diene-transmissive Diels-Alder Reaction Using 2-Ethoxy-3-methylene-1,4-pentadiene and 2-(2-Bromo-1-ethoxyethyl)-1,3-butadiene

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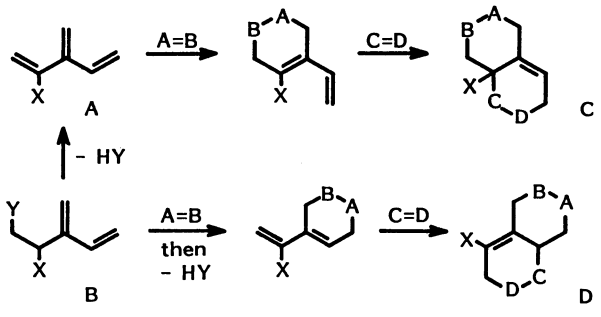
A new cross-conjugated triene, 2-ethoxy-3-methylene-1,4-pentadiene, and a triene equivalent, 2-(2-bromo-1-ethoxyethyl)-1,3-butadiene, have been synthesized and their diene-transmissive Diels-Alder cycloadditions are investigated. The initial Diels-Alder reaction selectively occurs not across the diene part substituted with the alkoxyl moiety but the monosubstituted diene. Some cross types of diene-transmissive Diels-Alder reaction are demonstrated using the triene equivalent and two different dienophiles.

Recently, polyconjugated molecules of cross type called dendralene have received increasing attention in synthetic and theoretical field of chemistry.[1] Of special interest in organic synthesis is cross-conjugated triene because its reiterative Diels-Alder cycloadditions offer a useful process leading to substituted hydrocarbons of fused [6.6] ring systems.[2] We have reported a simple synthesis of bis(silyloxy) cross-conjugated trienes as functionalized dendralenes[3] and their multiple Diels-Alder reaction process termed diene-transmissive Diels-Alder reaction.[3,4] Stepwise sequence of this reaction using cross-conjugated triene equivalents is useful as a process for the cross type of reiterative Diels-Alder cycloaddition.[5]

The diene-transmissive Diels-Alder reaction starts with the first Diels-Alder cycloaddition across one of the two diene units of cross-conjugated triene and the second reaction is followed across the diene part which has been constructed in the first cycloaddition step. An attractive extension of this process is cross type of reaction in which two different dienophiles are used separatedly in each step.

We have planned to synthesize 2-ethoxy-3-methylene-1,4-pentadiene **1** from its precursor 2-(2-bromo-1-ethoxyethyl)-1,3-butadiene **2** with an aim of establishing a finely controlled diene-transmissive Diels-Alder reaction system of cross type.



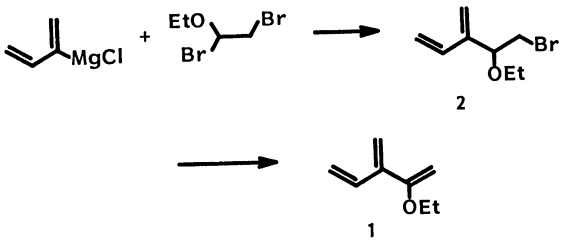
Scheme 1.

Scheme 1 shows a possible reaction mode of a cross-conjugated triene **A** with a diene-activating group X and its precursor **B**. As the diene-activating group X not only activates the diene as its carrier but also directs the regiochemistry of cycloaddition, it would be possible that the initial Diels-Alder reaction occurs across the diene part substituted with X under a regioselective control. The second cycloaddition with another dienophile, which is presumed also regioselective, gives a cross bis-cycloadduct **C**. On the other hand, the stepwise sequence of double cycloaddition of the precursor **B** using the same combination of dienophiles will lead to another bis-cycloadduct **D** which corresponds to an isomer of **C**.

Results and Discussion

The cross-conjugated triene **1** was synthesized in two steps starting from (1-methylene-2-propenyl)-magnesium chloride which is readily available from chloroprene. The cross-coupling reaction of (1-methylene-2-propenyl)magnesium chloride with 1-ethoxy-1,2-dibromoethane at 0 °C gave, after chromatography over silica gel and then distillation under vacuum, pure 2-(2-bromo-1-ethoxyethyl)-1,3-butadiene **2** in only 14% yield (Scheme 2). Although **2** was obtained in a better yield (40%, purity 68% (GLC)) in the same reaction using a catalyst Li_2CuCl_4[6] under milder conditions (−40 to −50 °C), the separation of **2** from one of the side products ended in failure.[7]

The dehydrobromination of **2** is a trouble-making



Scheme 2.

process. In order to avoid the polymerization of **1** as a labile product, **1** was separated from the reaction mixture by a vacuum distillation as soon as it was formed by the reaction of **2** with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) at 100—110 °C. Consequently, the cross-conjugated triene **1** isolated in 82% yield was contaminated with the unreacted **2** (18% (GLC)). As repeated distillation was found helpless, the triene of this purity (82%) was used for the following reactions.

A smooth cycloaddition took place between the triene **1** and *N*-methylmaleimide **3** under mild conditions (at room temperature for 24 h) to give 66% yield of a bis-cycloadduct **4** as the only isolated product, indicating that the initial Diels-Alder reaction was highly chemoselective. To our surprise, however, **4** was assigned as the bis-cycloadduct derived from the mono-cycloadduct **E** as shown in Scheme 3. Consequently the initial Diels-Alder reaction has favored the mono-substituted diene part which we assumed less reactive (See Scheme 1). As the stereostructure of **4** could not be determined only on the basis of the spectral data, the electronically and sterically most favorable approach in the second cycloaddition stage was taken into account.[8]

A similar reaction of **1** with dimethyl acetylenedicarboxylate **5** also produced the unexpected bis-cycloadduct **6** in 63% yield, which was readily dehydrogenated into tetramethyl 4-ethoxynaphthalene-1,2,6,7-tetracarboxylate **7** (81%) by the action of chloranil.

These unexpected diene reactivity is explained from a conformational point of view as shown in Fig. 1. There are two diene parts involved in the triene **1**, the monosubstituted "a" diene and the disubstituted "b" diene. The diene "b" can hardly occupy a planar s-cis conformation because of the steric hindrance between the two adjacent substituents (OEt and vinyl), while no such serious hindrance exists in the monosubstituted diene "a". Accordingly the initial Diels-Alder cycloaddition has occurred selectively across the diene "a".

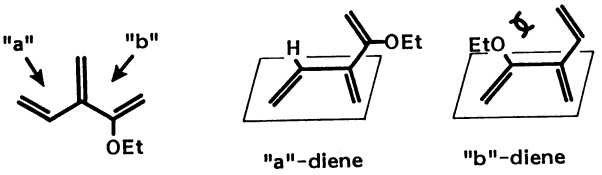


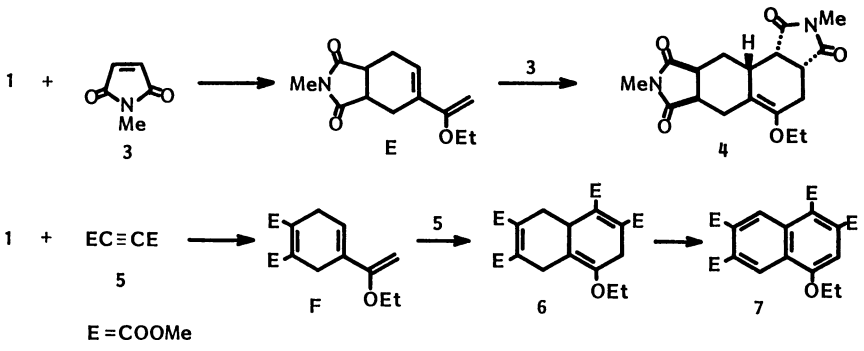
Fig. 1. s-cis Conformation for each diene part contained in the cross-conjugated triene **1**.

The use of two different dienophiles at each step of the above reaction, a cross type of cycloaddition, looks quite hard. Even though it is possible, a cross cycloadduct from this process can be obtained more easily by the stepwise sequence of double cycloaddition using the triene equivalent **2**. With this reason and because of the thermal instability of **1**, the stepwise cycloadditions of **2** were investigated.

The Diels-Alder cycloadditions of diene **2** with a variety of dienophiles **3**, **5**, **8**—**10** proceeded smoothly giving almost quantitative yields of cycloadducts **11**—**15** (Scheme 4). The results and reaction conditions are listed in Table 1. In the reactions with **3**, **8**, and **9**, each two diastereoisomeric cycloadducts were formed, but their ratios being slightly different (**11**, **12**: 1/2 and **14**: 1/1). The ratio of two regioisomeric cycloadducts of **15** was found to be 68/32 (para/meta) based on the GLC analysis, and about the same to that observed in the reaction of isoprene with **10** at 120 °C (para/meta=7/3).[9]

The diene functionality was revealed by dehydrobromination of the cycloadducts obtained above. Although **11** as an example resisted the dehydrobromination either when heated in benzene with triethylamine or refluxed in toluene with pyridine, successful dehydrobromination occurred by use of DBU. Thus, **12**, **14**, and **15** were converted into the corresponding dienes **16**, **18**, and **20**, respectively (Scheme 5 and Table 1). As these dienes are subject to the ready hydrolysis leading to enones, some of them were lost during the purification by column chromatography over silica gel.

The enones **17**, **19**, and **21** correspond to the Diels-Alder adducts of 2-acetyl-1,3-butadiene which can not be isolated because of its too easy dimerization.[10]

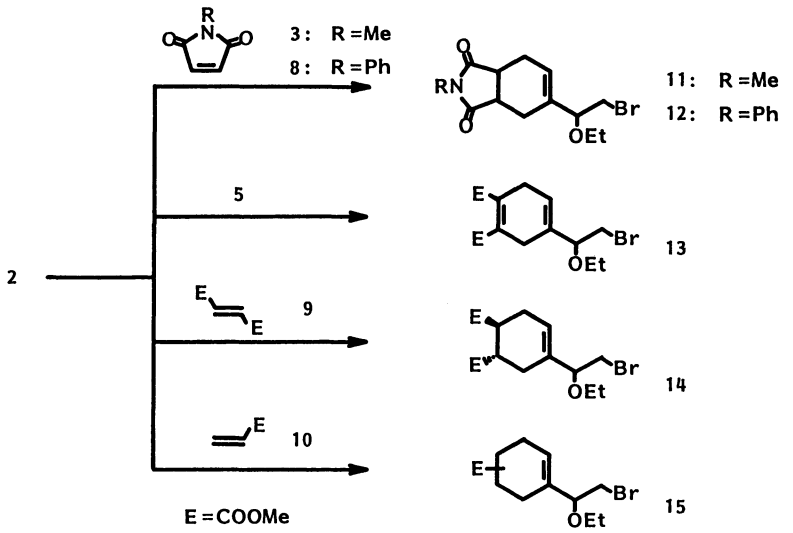


Scheme 3.

Accordingly, the diene **2** is a useful synthetic equivalent of 2-acetyl-1,3-butadiene.[11] An attempt of the second Diels-Alder reaction of the above dienes will be described later.

Dehydrobromination of the acetylene cycloadduct **13** with DBU gave no expected diene **F**, but instead the 4-(1-ethoxyethyl)- **22** and 4-vinylphthalate **23** in 95% of combined yield. The ready formation of **22**, presumably through a hydrogen migration of **F**, may have been driven by the aromatization on the six-membered ring. An attempt to trap the diene **F** with methyl propiolate **26** ended in failure, the same result being obtained.

The second Diels-Alder reactions were carried out using acetylenic dienophiles **5** and **26** (Scheme 6 and Table 1). The reaction of **16** with **5** gave a stereoselective cross bis-cycloadduct **24** along with its dehydrogenated derivative **25** in 78% of combined

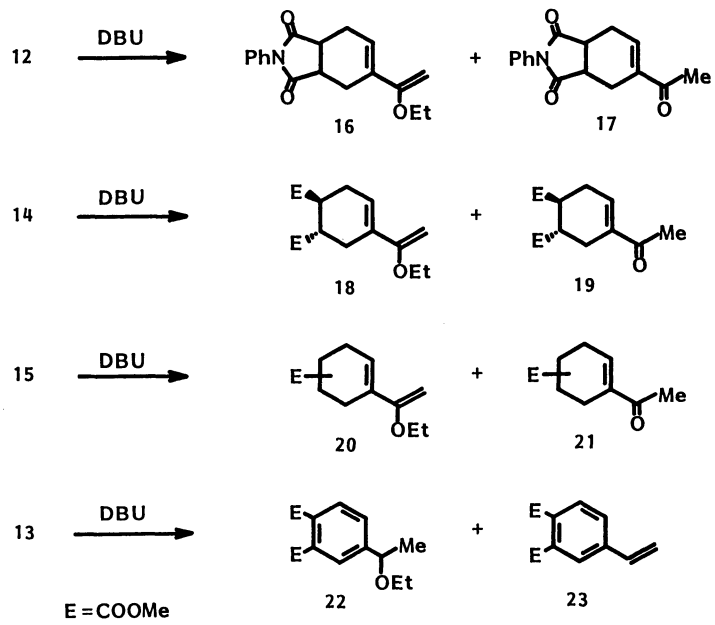


Scheme 4.

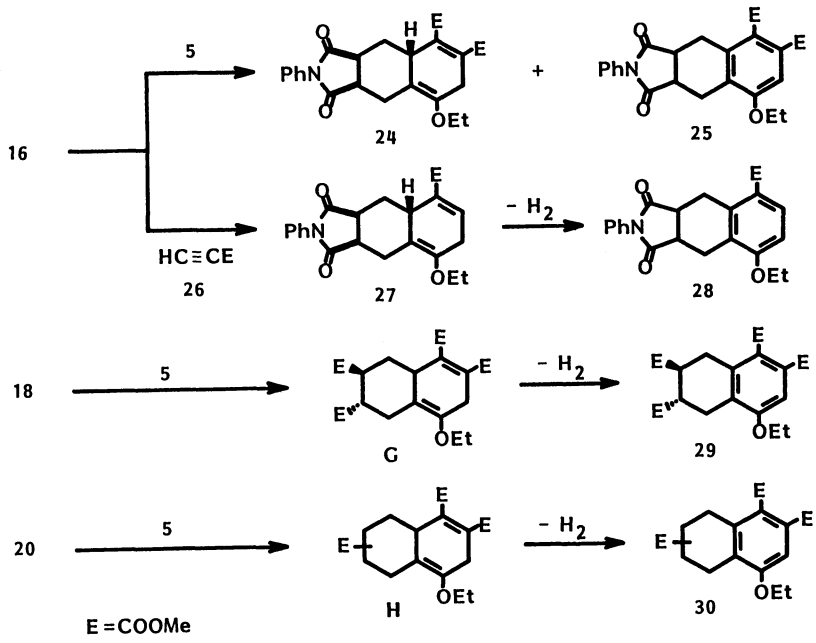
TABLE 1. STEPWISE SEQUENCE OF DIENE-TRANSMISSIVE DIELS-ALDER REACTIONS OF A CROSS-CONJUGATED TRIENE EQUIVALENT **2**

First cycloaddition		Reaction conditions			Product (yield/%)[a]
Diene	Dienophile	Solvent	Temperature	Time/h	
2	**3**	benzene	reflux	6	**11** (96)
2	**8**	benzene	reflux	6	**12** (98)
2	**5**	benzene	reflux	20	**13** (97)
2	**9**	benzene	reflux	24	**14** (96)
2	**10**	benzene	reflux	40	**15** (80)[b]
Diene formation		Reaction conditions			Product (yield/%)[a]
Bromide	DBU/Bromide	Solvent	Temperature	Time/h	
12	1.3	toluene	reflux	8	**16** (76), **17** (4)
14	1.5	toluene	reflux	20	**18** (59), **29** (20)
15	1.5	toluene	reflux	20	**20** (40), **21** (41)[c]
13	1.9	benzene	reflux	3	**22** (67), **23** (27)
Second cycloaddition		Reaction conditions			Product (yield/%)[a]
Diene	Dienophile	Solvent	Temp./°C	Time/h	
16	**5**	toluene	reflux	20	**24** (62), **25** (17)
16	**26**	toluene	110[d]	68	**27** (49)
18	**5**	toluene	reflux	6+15[e]	**29** (66)
20	**5**	toluene	reflux	6+15[e]	**30** (67)[c]

a) All isolated yields. b) Mixture of regioisomers (para : meta=68 : 32 (GLC)). c) Mixture of regioisomers (para : meta=2 : 1 (^{1}H-NMR)). d) Performed in a sealed tube. e) The latter is the reaction time after chloranil is added.



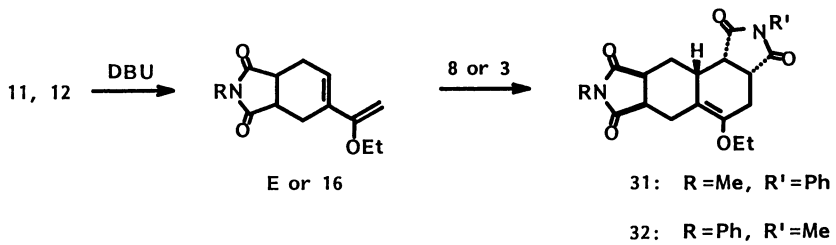
Scheme 5.



Scheme 6.

yield. As anticipated, an unsymmetrical acetylene **26** cycloadded to **16** under high regioselection, the stereo- and regioselective cross bis-cycloadduct **27** being isolated as the single product. The structures of **24** and **27** were hardly determined only on the basis of the spectral data, therefore based on the steric consideration in the approaches. These cycloadducts **24** and **27** were easily dehydrogenated with chloranil into the aromatic derivatives **25** and **28**, respectively, in high yields. A one-pot procedure for the second cycloaddition and dehydrogenation could be performed between **18** and **5** (similarly **20** and **5**) under the conditions shown in Table 1. This procedure gave the tetrahydronaphthalene derivatives **29** and **30** in good yields.

The both procedures of the diene formation by dehydrobromination and the second cycloaddition could be achieved in the same flask. First, the maleimide cycloadduct **11** or **12** was allowed to react with DBU under reflux in toluene and the excess or unreacted DBU was completely consumed by the action with methyl iodide (Scheme 7). Then, the diene **E** or **16** formed in solution was subjected to the second cycloaddition with **8** or **3**. Thus, a



Scheme 7.

stereoselective cross bis-cycloadduct **31** (56%) or **32** (65%) was isolated through a column chromatography of the crude mixture.

Experimental

General and Materials. Melting points were measured on a Yanagimoto micro melting point apparatus and uncorrected. IR spectra were recorded on a JASCO A-702 and JEOL JIR-100 FT-IR spectrometers. ^{1}H-NMR spectra were taken at either 90 MHz (Hitachi R-40) or 100 MHz (JEOL FX-100), and ^{13}C-NMR at 25.05 MHz (JEOL FX-100). ^{1}H- and ^{13}C-NMR chemical shifts are recorded in δ values (ppm) relative to internal Me_4Si. Mass spectra were measured with a JEOL JMS-01SG-2 spectrometer at 75 eV of ionization energy. Elementary analyses were performed on a Hitachi 026 CHN micro analyzer. Analytical gas-liquid chromatography (GLC) was accomplished on a Yanaco G-2800 gas chromatograph equipped with a flame ionization detector (column: SE-30, 3.5×300 mm). Wakogel C300 and Florisil (100—200 mesh) were used for preparative column chromatography. Thin-layer chromatography (TLC) was accomplished on 0.2 mm precoated plates of silica gel 60 F-254 (Merck) and of aluminum oxide 60 F-254 type-E (Merck). Visualization was with ultraviolet light (254 and 365 nm) and iodine. Micro vacuum distillation was carried out with a Sibata GTO-250R Kugelrohr distilling apparatus. Solvents were evaporated with a Tokyo Rikakikai rotary evaporator type V.

Tetrahydrofuran (THF), benzene, and toluene were distilled over sodium wire immediately prior to their use. 1-Ethoxy-1,2-dibromoethane was prepared by the bromination of ethyl vinyl ether.[12] Methyl propiolate **26** was obtained by the esterification of commercial propiolic acid in the presence of *p*-toluenesulfonic acid.[13] Li_2CuCl_4 was prepared by mixing LiCl and $CuCl_2$ in 2:1 ratio.

2-(2-Bromo-1-ethoxyethyl)-1,3-butadiene **2** *and 2-Ethoxy-3-methylene-1,4-pentadiene* **1**. To a 0.1 M solution of (1-methylene-2-propenyl)magnesium chloride (20 ml, 20 mmol) was added dropwise a solution of 1-ethoxy-1,2-dibromoethane (2.7 ml, 20 mmol) in dry THF (20 ml) at 0 °C. The mixture was stirred at 0 °C for 6 h under nitrogen and then treated with water. Products were extracted in ether, the ether washed with 5% sodium hydrogencarbonate solution and with brine, dried over $MgSO_4$, and finally evaporated *in vacuo*. The residue was chromatographed over silica gel. An elution with hexane–benzene (2:1) gave 1.66 g (40%, purity 52% by GLC) of **2** which was purified by a vacuum distillation on Kugelrohr to afford pure **2** (0.58 g, 14%).

This compound **2** was also available by the following procedure: To a mixture of 1-ethoxy-1,2-dibromoethane (1.4 ml, 10 mmol) and Li_2CuCl_4 (220 mg, 1 mmol) in dry THF (10 ml) was added slowly a 0.1 M solution of (1-methylene-2-propenyl)magnesium chloride in THF (12 ml, 12 mmol) at −40 to −50 °C. The mixture was stirred at the same temperature for 4 h and treated with water. The same work up described above and a vacuum distillation gave 0.81 g of **2** (40%, purity 68% by GLC).

2: Colorless liquid; bp 80 °C (267 Pa) (bulb-to-bulb); IR (neat) 1580, 1120, and 1100 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ=1.20 (3H, t, $C\underline{H}_3CH_2$), 3.22—3.66 (4H, m, CH_2Br and $C\underline{H}_2Me$), 4.21 (1H, dd, J=4.3 and 7.8 Hz, $C\underline{H}OEt$), 5.10 (1H, d, J_{4-3}=11.0 Hz, one of 4-H), 5.26, 5.28 (each 1H, s, 1-H), 5.35 (1H, d, J_{4-3}=18.0 Hz, the other of 4-H), 6.32 (1H, dd, J_{3-4}=11.0 and 18.0 Hz, 3-H); ^{13}C-NMR ($CDCl_3$) δ=15.21 (q, Me), 35.21 (t), 64.82 (t), 79.79 (d, $\underline{C}HOEt$), 114.66, 117.24 (each t, 1- and 4-C), 135.56 (d, 3-C), and 143.66 (s, 2-C); MS *m/z* 206 and 204 (M^+).

Found: *m/z* 204.0125. Calcd for $C_8H_{13}OBr$: M, 204.0150.

A mixture of **2** (266 mg, 1.3 mmol) and DBU (395 mg, 2.6 mmol) was heated in a micro distilling flask at 100—110 °C under a reduced pressure (2666 Pa) while being distilled. The distillate collected in 30 min was purified by distillation on Kugelrohr to give **1** (132 mg, 82%, purity 82% by GLC).

1: Colorless liquid; GC/FT-IR (gas) 1585 and 980 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ=1.33, 3.78 (5H, $OC\underline{H}_2C\underline{H}_3$), 4.14, 4.26 (each 1H, d, J_{gem}=2.0 Hz, 1-H), 5.14 (1H, dd, J_{5-4}=10.5 and J_{gem}=2.0 Hz, one of 5-H), 5.22, 5.43 (each 1H, d, J_{gem}=2.0 Hz, 3-CH_2=), 5.43 (1H, dd, J_{5-4}=17.5 and J_{gem}=2.0 Hz, the other of 5-H), and 6.40 (1H, dd, J_{4-5}=17.5 and 10.5 Hz, 4-H); ^{13}C-NMR ($CDCl_3$) δ=14.47 (q, Me), 62.96 (t), 84.74 (t, 1-C), 114.47, 116.42 (each t, 5-C and 3-CH_2=), 135.56 (d, 4-C), 143.31 (s, 3-C), and 159.35 (s, 2-C); GC–MS *m/z* 124 (M^+).

Found: *m/z* 124.0872. Calcd for $C_8H_{12}O$: M, 124.0888.

Reaction of **1** *with* **3** *Leading to* **4**. A mixture of **1** (108 mg, purity 84%, 0.73 mmol) and **3** (193 mg, 1.74 mmol) in dry benzene (3 ml) was stirred at room temperature for 2 h. The residue which was obtained by evaporation of the solvent was chromatographed over silica gel using hexane–ethyl acetate (1:3) as an eluent to give 167 mg (66%) of **4**: Colorless solid; mp 113—116 °C; IR (KBr) 1770 and 1700 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ=1.12 (3H, t, $CH_2C\underline{H}_3$), 1.84—3.32 (11H, m, 3×CH_2 and 5×CH), 2.88, 2.92 (each 3H, s, NMe), and 3.63 (2H, q, $C\underline{H}_2Me$); ^{13}C-NMR ($CDCl_3$) δ=15.01 (q, Me), 21.00, 23.54 (each t), 24.85 (d),

† 1 M=1 mol dm^{-3}.

25.68 (t), 32.75, 39.03, 40.15, 43.22 (each d), 64.76 (t), 113.25, 147.80 (each s), 177.47, 179.03, 179.77, and 180.11 (each s, CON); MS *m/z* 346 (M^+).

Found: *m/z* 346.1562. Calcd for $C_{18}H_{22}O_5N_2$: M, 346.1527.

Reaction of 1 with 5 Leading to 6 and Its Dehydrogenation into 7. A solution of **1** (103 mg, purity 82%, 0.68 mmol) and **5** (236 mg, 1.7 mmol) in dry benzene (2 ml) was refluxed for 6 h. The solvent was removed off *in vacuo* and the residue was chromatographed over silica gel. An elution with hexane–ethyl acetate (1:1) gave 176 mg (63%) of **6**: Colorless viscous liquid; IR (neat) 1725 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ=1.26 (3H, t, $CH_2C\underline{H}_3$) 2.00—2.40 (1H, m), 2.60—3.98 (8H, m), 3.73, 3.86, and 3.90 (12H, s, COOMe); ^{13}C-NMR ($CDCl_3$) δ=15.40 (q, Me), 26.80, 27.24, 32.89 (each t), 36.60 (d), 52.29, 52.39 (each q, each 2×C, COO<u>Me</u>), 63.89 (t), 109.16, 129.28, 133.23, 134.98, 137.03, 142.58 (each s), 166.71, 167.77 (each s, <u>C</u>OOMe), and 168.07 (s, 2×C, <u>C</u>OOMe); MS *m/z* 408 (M^+).

Found: *m/z* 408.1373. Calcd for $C_{20}H_{24}O_9$: M, 408.1419.

A mixture of **6** (276 mg, 0.68 mmol) and chloranil (665 mg, 2.7 mmol) in toluene (6 ml) was refluxed for 72 h. Evaporation of the solvent and the chromatography over silica gel (hexane–ethyl acetate 1:1) gave 222 mg (81%) of **7**: Colorless prisms from hexane–ethyl acetate; mp 157—158 °C; IR (KBr) 1720 cm^{-1} (CO) ^{1}H-NMR ($CDCl_3$) δ=1.56, 4.26 ($OC\underline{H}_2C\underline{H}_3$), 3.92 (9H, s, COOMe), 4.01 (3H, s, COOMe), 7.28 (1H, s, 3-H), 8.14 (1H, s, 5-H), and 8.64 (1H, s, 8-H); ^{13}C-NMR ($CDCl_3$) δ=14.53 (q, Me), 52.95 (q, 4×C, COO<u>Me</u>), 64.89 (t), 105.83, 124.89 (each d), 126.60, 127.19 (each s), 127.83 (d), 129.66, 129.89, 131.01, 156.25 (each s), 166.37, 168.72 (each s, <u>C</u>OOMe), and 167.83 (s, 2×C, <u>C</u>OOMe); MS *m/z* 404 (M^+).

Found: C, 59.25; H, 4.97%. Calcd for $C_{20}H_{20}O_9$: C, 59.41; H, 4.99%.

Cycloadditions of 2 to Dienophiles 3, 5, and 8—10. General procedure is as follows: A mixture of **2** and dienophiles (1.2—2 equivalents) in dry benzene (2—3 ml per 1 mmol of **2**) was refluxed for the time shown in Table 1. The solvent was evaporated *in vacuo* and the residue was chromatographed over silica gel. The yields of cycloadducts are given in Table 1.

11: The reaction between **2** (308 mg, purity 85%, 1.28 mmol) and **3** (167 mg, 1.50 mmol) was followed by the chromatography with hexane–ethyl acetate (1:1) to give 389 mg (96%) of **11** in 2:1 ratio of diastereomers whose separation failed: Colorless viscous liquid; IR (neat) 1775 and 1710 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ=1.12 (3H, t, $CH_2C\underline{H}_3$), 1.90—3.48 (10H, m), 2.88 (3H, s, NMe), 3.78 (1H, t, J=6.0 Hz, C<u>H</u>OEt), and 5.86 (1H, m, 6-H); ^{13}C-NMR ($CDCl_3$) the major: δ=14.91 (q, Me), 22.54, 23.66 (each t), 24.89 (q, NMe), 32.11 (t), 38.92, 39.22 (each d), 64.23 (t), 81.96 (d, <u>C</u>HOEt), 126.46 (d, 6-C), 136.68 (s, 5-C), and 179.42 (s, 2×C, CON); the minor: δ=14.68 (q, Me), 23.48 (t), 24.66 (q, NMe), 32.76 (t), 81.08 (d, <u>C</u>HOEt), 125.81 (d, 6-C), and 179.12 (s, CON); MS *m/z* 222 (M^+-CH_2Br).

Found: C, 49.36; H, 5.73; N, 4.43%. Calcd for $C_{13}H_{18}O_3NBr$: C, 49.38; H, 5.74; N, 4.43%.

12: The reaction between **2** (512 mg, purity 74%, 1.85 mmol) and **8** (539 mg, 3.11 mmol) and the followed chromatography using hexane–ethyl acetate (2:1) gave 685 mg (98%) of **12** as a mixture of two diastereomers in a ratio of 2:1, which could not be separated: Colorless viscous liquid; IR (neat) 1780 and 1720 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ=1.07, 1.17 (3H, each t, $CH_2C\underline{H}_3$), 2.00—2.96 (4H, m), 3.08—3.52 (6H, m), 3.85 (1H, t, J=6.5 Hz, C<u>H</u>OEt), 5.98 (1H, m, 6-H), and 7.08—7.60 (5H, m, Ph); ^{13}C-NMR ($CDCl_3$) the major: δ=15.15 (q, Me), 23.20, 24.02, 33.04 (each t), 39.03, 39.42 (each d), 64.71 (t), 82.21 (d, <u>C</u>HOEt), 125.97 (d, 6-C), 126.16, 128.35, 128.89 (each d), 131.96 (s), 137.32 (s, 5-C), 178.60, and 178.74 (each s, CON); the minor: δ=14.86 (q, Me), 22.95, 23.88 (each t), 81.62 (d, <u>C</u>HOEt), 137.17 (s, 5-C), and 178.35 (s, CON); MS *m/z* 379 and 377 (M^+).

Found: C, 57.06; H, 5.27; N, 3.89%. Calcd for $C_{18}H_{20}O_3NBr$: C, 57.16; H, 5.33; N, 3.70%.

13: The reaction of **2** (557 mg, purity 68%, 1.85 mmol) with **5** (493 mg, 3.47 mmol) was followed by the chromatography using hexane–ethyl acetate (4:1) to afford **13** (619 mg, 97%): Colorless viscous liquid; IR (neat) 1725 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ=1.20 (3H, t, $CH_2C\underline{H}_3$), 2.80—3.60 (8H, m), 3.76 (6H, s, COOMe), 3.91 (1H, t, J=6.5 Hz, C<u>H</u>OEt), and 5.76 (1H, m, 5-H); ^{13}C-NMR ($CDCl_3$) δ=15.15 (q, Me), 25.78, 28.26, 32.84 (each t), 52.24 (q, 2×C, COO<u>Me</u>), 64.66 (t), 82.55 (d, <u>C</u>HOEt), 122.17 (d, 5-C), 131.28, 131.86, 132.55 (each s), 167.92, and 168.12 (each s, <u>C</u>OOMe); MS *m/z* 315 (M^+-OMe).

Found: C, 48.19; H, 5.42%. Calcd for $C_{14}H_{19}O_5Br$: C, 48.43; H, 5.52%.

14: The reaction between **2** (327 mg, purity 74%, 1.18 mmol) and **9** (286 mg, 1.98 mmol) were followed by the chromatography with hexane–ethyl acetate (4:1) to give **14** (395 mg, 96%) as a 1:1 mixture of diastereomers: Colorless liquid; IR (neat) 1740 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ=1.20 (3H, t, $CH_2C\underline{H}_3$), 1.90—2.50, 2.70—3.00 (6H, m), 3.69 (6H, s, COOMe), 3.84 (1H, t, J=6.5 Hz, C<u>H</u>OEt), and 5.74 (1H, m, 2-H); ^{13}C-NMR ($CDCl_3$) δ=15.21 (q, Me), 25.42, 25.77, 27.30, 27.65, 32.94, 33.41 (each t), 40.92, 41.21 (each d), 51.96 (q, 2×C, COO<u>Me</u>), 64.46, 64.58 (each t), 82.84 (d, <u>C</u>HOEt), 124.52, 124.99 (each d, 2-C), 133.39, 133.63 (each s, 1-C), 174.72, and 174.84 (each s, <u>C</u>OOMe); MS *m/z* 319 and 317 (M^+-OMe).

Found: C, 48.01; H, 6.07%. Calcd for $C_{14}H_{21}O_5Br$: C, 48.25; H, 6.06%.

15: The reaction of **2** (284 mg, 1.4 mmol) with **10** (0.25 ml, 2.8 mmol) and the followed chromatography with hexane–ethyl acetate (9:1) gave 322 mg (80%) of **15** as a mixture of two regioisomers in a ratio of 68:32 (GLC) whose separation was unsuccessful: Colorless liquid; IR (neat) 1735 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ=1.19, 1.20 (3H, each t, $CH_2C\underline{H}_3$), 1.48—2.76 (7H, m), 3.20—3.60 (4H, m), 3.67 (3H, s, COOMe), 3.82 (1H, t, J=6.5 Hz, C<u>H</u>OEt), and 5.73 (1H, m, 2-H); ^{13}C-NMR ($CDCl_3$) including four sets of signals: δ=14.91 (q, Me), 21.78, 22.25, 23.66, 24.07, 24.60, 24.78, 25.36, 27.01, 27.12, 33.17, 33.64 (each t), 38.51, 38.63, 38.98 (each d), 51.31 (q, COO<u>Me</u>), 63.88, 64.05 (each t), 83.02 (d, <u>C</u>HOEt), 124.58, 125.23, 126.05, 126.35 (each d), 133.16, 133.45, 134.50, 134.68 (each s), 175.19, and 175.36 (each s, <u>C</u>OOMe); MS *m/z* 261 and 259 (M^+-OMe).

Found: C, 49.27; H, 6.56%. Calcd for $C_{12}H_{19}O_3Br$: C, 49.50; H, 6.58%.

Dehydrobromination of 12 Leading to 16 and 17. A solution of **12** (413 mg, 1.09 mmol) and DBU (216 mg, 1.42 mmol) in dry toluene (5 ml) was refluxed for 8 h. The

mixture was chromatographed over Florisil with hexane–ethyl acetate (2:1) giving 248 mg (76%) of **16**. Further elution with hexane–ethyl acetate (1:2) afforded **17** (11 mg, 4%).

16: Colorless solid; mp 66—69 °C; IR (KBr) 1780 and 1710 cm^{-1} (CO); ^{1}H-NMR (C_6D_6) δ=1.13, 3.42 (OCH_2CH_3), 1.66—2.08 (2H, m), 2.40—2.80 (3H, m), 2.92 (1H, dd, J_{gem}=15.0 and J_{vic}=2.5 Hz), 3.97, 4.37 (each 1H, d, J_{gem}=2.5 Hz, $=CH_2$), 6.38 (1H, m, 6-H), and 6.90—7.36 (5H, m, Ph); MS *m/z* 297 (M^+).

Found: C, 72.66; H, 6.49; N, 4.88%. Calcd for $C_{18}H_{19}O_3N$: C, 72.71; H, 6.44; N, 4.71%.

17: Colorless leaflets from dichloromethane–hexane; mp 114—115 °C; IR (KBr) 1770, 1700, and 1665 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ=2.30 (3H, s, MeCO), 2.32—3.40 (6H, m), 7.02 (1H, ddd, *J*=2.0, 4.0, and 6.5 Hz, 6-H), and 7.10—7.74 (5H, m, Ph); MS *m/z* 269 (M^+).

Found: C, 71.26; H, 5.66; N, 5.38%. Calcd for $C_{16}H_{15}O_3N$: C, 71.36; H, 5.61; N, 5.20%.

*Dehydrobromination of **14** Leading to **18** and **19**.* A mixture of **14** (253 mg, 0.72 mmol) and DBU (165 mg, 1.08 mmol) in dry toluene (3 ml) was refluxed for 20 h and the solvent was removed *in vacuo*. The residue was chromatographed over Florisil with hexane–ethyl acetate (9:1) to give 115 mg (59%) of **18** as unstable material. Further elution with hexane–ethyl acetate (1:1) afforded 34 mg (20%) of **19**.

18: Colorless liquid; ^{1}H-NMR (C_6D_6) δ=1.13, 3.52 (OCH_2CH_3), 2.10—3.02 (6H, m), 3.38, 3.40 (each 3H, s, COOMe), 3.92, 4.10 (each 1H, d, J_{gem}=2.5 Hz, $=CH_2$), and 6.07 (1H, m, 2-H); ^{13}C-NMR (C_6D_6) δ= 14.57 (q, Me), 28.17, 28.36 (each t), 41.32, 41.96 (each d), 51.51 (q, 2×C, COOMe), 62.81 (t), 122.41 (d, 2-C), 130.84 (s, 1-C), 159.59 (s), and 174.70 (s, 2×C, COOMe).

19: Colorless liquid; IR (neat) 1740 and 1670 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ=2.29 (3H, s, MeCO), 2.10—3.00 (6H, m), 3.67, 3.68 (each 3H, s, COOMe), and 6.84 (1H, m, 2-H); MS *m/z* 240 (M^+) and 43.

Found: C, 59.97; H, 6.76%. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71%.

*Dehydrobromination of **15** Leading to **20** and **21**.* A solution of **15** (228 mg, 0.78 mmol) and DBU (179 mg, 1.18 mmol) in dry toluene (3 ml) was refluxed for 20 h. The residue obtained by the evaporation of solvent was chromatographed over Florisil with hexane–ethyl acetate (9:1) gave 66 mg (40%) of unstable diene **20**. Further elution with hexane–ethyl acetate (2:1) afforded **21** (59 mg, 40%).

20: Colorless liquid as a mixture of two regioisomers (2:1); ^{1}H-NMR (C_6D_6) δ=1.10, 3.50 (OCH_2CH_3), 1.40—2.60 (7H, m), 3.30, 3.34 (3H, each s, COOMe), 3.94 (1H, d, J_{gem}=2.0 Hz, $=CH_2$), 4.17, 4.23 (1H, each d, J_{gem}=2.0 Hz, $=CH_2$), and 6.43 (1H, m, 2-H).

21: Colorless liquid as a 2:1 mixture of regioisomers; IR (neat) 1735 and 1685 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ=1.50—2.68 (7H, m), 2.28 (3H, s, MeCO), 3.68, and 3.69 (3H, each s, COOMe); MS *m/z* 182 (M^+).

Found: *m/z* 182.0994. Calcd for $C_{10}H_{14}O_3$: M, 182.0942.

*Dehydrobromination of **13** Leading to **22** and **23**.* A mixture of **13** (236 mg, 0.68 mmol) and DBU (193 mg, 1.27 mmol) in dry toluene (4 ml) was refluxed for 3 h and the solvent was evaporated *in vacuo*. The residue was chromatographed over silica gel using hexane–ethyl acetate (3:1) to give **23** (41 mg, 27%) and then **22** (122 mg, 67%).

22: Colorless viscous liquid; IR (neat) 1725 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ=1.19, 3.36 (OCH_2CH_3), 1.42 (3H, d, *J*=6.5 Hz, Me), 3.87, 3.89 (each 3H, s, COOMe), 4.46 (1H, q, *J*=6.5 Hz, CH(Me)OEt), 7.48 (1H, dd, *J*=1.5 and 8.0 Hz, 5-H), 7.63 (1H, d, *J*=1.5 Hz, 3-H), and 7.72 (1H, d, *J*=8.0 Hz, 6-H); ^{13}C-NMR ($CDCl_3$) δ=15.03, 23.66 (each q, Me), 52.19 (q, 2×C, COOMe), 63.99 (t), 76.62 (d, CH(Me)OEt), 126.11, 128.16, 128.98 (each d), 130.22, 132.22 (each s), 148.01 (s, 4-C), 167.32, and 167.79 (each s, COOMe); MS *m/z* 266 (M^+) and 251 (M^+—Me, base peak).

Found: C, 63.08; H, 6.69%. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81%.

23: Colorless liquid; IR (neat) 1725 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ=3.88, 3.89 (each 3H, s, COOMe), 5.39 (1H, dd, J_{gem}=0.5 and J_{vic}=11.0 Hz, one of $=CH_2$), 5.84 (1H, dd, J_{gem}=0.5 and J_{vic}=17.5 Hz, the other of $=CH_2$), 6.71 (1H, dd, *J*=11.0 and 17.5 Hz, CH=), 7.49 (1H, dd, *J*=2.0 and 8.0 Hz, 5-H), 7.66 (1H, d, *J*=2.0 Hz, 3-H), and 7.70 (1H, d, *J*=8.0 Hz, 6-H); MS *m/z* 220 (M^+) and 189 (M^+—OMe, base peak).

*Cycloaddition of **16** to **5** Leading to **24** and **25**.* A mixture of **16** (248 mg, 0.83 mmol) and **5** (237 mg, 1.67 mmol) in toluene (4 ml) was refluxed for 20 h and the solvent was evaporated *in vacuo*. The residue was chromatographed over silica gel with hexane–ethyl acetate (1:1) gave 227 mg (62%) of **24** and then 63 mg (17%) of **25**. A mixture of **24** (68 mg, 0.15 mmol) and chloranil (42 mg, 0.17 mmol) in toluene (3 ml) was refluxed for 36 h. Column chromatography of the crude mixture over silica gel (hexane–ethyl acetate (1:1)) afforded 53 mg (78%) of **25**.

24: Colorless solid; mp 85—87 °C; IR (KBr) 1775 and 1720 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ=1.25 (3H, t, CH_2CH_3), 1.40—2.10 (2H, m), 2.50—3.92 (9H, m), 3.73, 3.79 (each 3H, s, COOMe), and 7.10—7.56 (5H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ=15.30 (q, Me), 25.78, 27.34, 29.04 (each t), 37.33, 40.20, 40.30 (each d), 52.34 (q, 2×C, COOMe), 64.03 (t), 110.81 (s), 126.16 (d, 2×C), 128.35 (d), 129.04 (d, 2×C), 129.13, 131.86, 137.86, 143.12 (each s), 166.60, 167.77 (each s, COOMe), 177.04, and 177.91 (each s, CON); MS *m/z* 439 (M^+).

Found: C, 65.47; H, 5.80; N, 3.56%. Calcd for $C_{24}H_{25}O_7N$: C, 65.59; H, 5.73; N, 3.19%.

25: Colorless prisms from ethanol; mp 159—160 °C; IR (KBr) 1775 and 1720 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ=1.42, 4.05 (OCH_2CH_3), 2.60—3.80 (6H, m), 3.84, 3.90 (each 3H, s, COOMe), 6.90—7.08, and 7.14—7.48 (each 3H, m, Ph and Ar); MS *m/z* 437 (M^+).

Found: C, 65.71; H, 5.37; N, 3.23%. Calcd for $C_{24}H_{23}O_7N$: C, 65.90; H, 5.30; N, 3.20%.

*Cycloaddition of **16** to **26** Leading to **27** and Dehydrogenation of **27** into **28**.* A solution of **16** (180 mg, 0.61 mmol) and **26** (255 mg, 3.03mmol) in dry toluene (6 ml) was heated in a sealed glass tube at 110 °C for 68 h. The solvent was evaporated *in vacuo* and the residue was chromatographed over silica gel using hexane–ethyl acetate (1:1) to give 113 mg (49%) of **27**. This product **27** (43 mg, 0.11 mmol) and chloranil (42 mg, 0.17 mmol) were refluxed in toluene (2 ml) for 48 h and the crude mixture was chromatographed, after evaporation of the solvent, over silica gel with hexane–ethyl acetate (1:1) to afford 33 mg (77%) of **28**.

27: Colorless prisms from ether; mp 140—141 °C; IR (KBr) 1775 and 1710 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ=1.24

(3H, t, $CH_2C\underline{H}_3$), 1.20—1.60 (1H, m), 1.70—2.04 (1H, m), 2.72—3.90 (9H, m), 3.72 (3H, s, COOMe), 6.87 (1H, t, J=3.0 Hz, =CH), and 7.16—7.56 (5H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ=15.15 (q, Me), 26.42, 27.01, 30.41 (each t), 35.05, 40.28, 40.57 (each d), 51.49 (q, COO$\underline{Me}$), 63.58 (t), 112.72 (s), 125.99 (d, 2×C), 128.05 (d), 128.75 (d, 2×C), 130.63, 131.86 (each s), 135.21 (d), 142.72 (s), 166.09 (s, $\underline{C}$OOMe), 177.07, and 178.07 (each s, CON); MS m/z 381 (M^+).

Found: C, 69.28; H, 6.08; N, 3.67%. Calcd for $C_{22}H_{23}O_5N$: C, 69.12; H, 6.04; N, 3.62%.

28: Colorless prisms from ethanol; mp 200—202 °C; IR (KBr) 1775 and 1705 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ=1.42, 4.05 ($OC\underline{H}_2C\underline{H}_3$), 2.60—3.74 (6H, m), 3.84 (3H, s, COOMe), 6.74 (1H, d, J=9.0 Hz, 6-H), 6.84—7.00 (2H, m), 7.24—7.50 (3H, m), and 7.80 (1H, d, J=9.0 Hz, 7-H); MS m/z 379 (M^+).

Found: C, 69.44; H, 5.67; N, 3.66%. Calcd for $C_{22}H_{21}O_5N$: C, 69.65; H, 5.58; N, 3.69%.

*Cycloaddition of **18** to **5** and Subsequent Dehydrogenation Leading to **29**.* A solution of **18** (97 mg, 0.36 mmol) and **5** (77 mg, 0.54 mmol) in dry toluene (2 ml) was refluxed for 6 h. Chloranil (133 mg, 0.54 mmol) was added and the resulting mixture was further refluxed for 15 h. Column chromatography of the crude product over silica gel with hexane-ethyl acetate (2:1) gave 97 mg (66%) of **29**: Colorless needles from ethanol; mp 128—129 °C; IR (KBr) 1725 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ=1.43, 4.08 ($OC\underline{H}_2C\underline{H}_3$), 2.40—3.40 (6H, m), 3.70, 3.72, 3.84, 3.87 (each 3H, s, COOMe), and 7.22 (1H, s, 3-H); MS m/z 408 (M^+).

Found: C, 59.03; H, 6.00%. Calcd for $C_{20}H_{24}O_9$: C, 58.82; H, 5.92%.

*Cycloaddition of **20** to **5** and Subsequent Dehydrogenation Leading to **30**.* A mixture of **20** (43 mg, 0.2 mmol) and **5** (44 mg, 0.31 mmol) in toluene (1.5 ml) was first refluxed for 6 h and further 15 h after chloranil (75 mg, 0.31 mmol) was added. The crude product was chromatographed over silica gel with hexane-ethyl acetate (3:1) to give **30** (48 mg, 67%) as a 2:1 mixture of regioisomers: Colorless solid; mp 117—123 °C; IR (KBr) 1725 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ=1.43, 4.07 ($OC\underline{H}_2C\underline{H}_3$), 1.60—3.20 (7H, m), 3.69, 3.72, 3.84, 3.88, 3.89 (9H, each s, COOMe for the major and minor regioisomers), and 7.21 (1H, s, 3-H); MS m/z 350 (M^+).

Found: C, 61.77; H, 6.41. Calcd for $C_{18}H_{22}O_7$: C, 61.71; H, 6.33%.

*Cycloaddition of **11** to **8** Leading to **31**.* A mixture of **11** (167 mg, 0.53 mmol) and DBU (88 mg, 0.58 mmol) in dry toluene (4 ml) was refluxed for 6 h and then cooled to room temperature. After iodomethane (a few drops) and **8** (205 mg, 1.18 mmol) were added, the mixture was stirred at room temperature for 12 h. The crude product was chromatographed over silica gel with hexane-ethyl acetate (1:1) to afford **11** (34 mg, 20% recovered) and then **31** (121 mg, 56%): Colorless solid; mp 188—191 °C; IR (KBr) 1770 and 1700 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ=1.16, 3.66 ($OC\underline{H}_2C\underline{H}_3$), 1.90—3.40 (11H, m), 2.93 (3H, s, NMe), and 7.00—7.56 (5H, m, Ph); MS m/z 408 (M^+).

Found: C, 67.46; H, 5.96; N, 6.86%. Calcd for $C_{23}H_{24}O_5N_2$: C, 67.63; H, 5.92; N, 6.86%.

*Cycloaddition of **12** to **3** Leading to **32**.* A mixture of **12** (160 mg, 0.42 mmol) and DBU (71 mg, 0.47 mmol) in toluene (4 ml) was refluxed for 6 h and cooled to room temperature. After iodomethane (a few drops) and **3** (94 mg, 0.85 mmol) were added, the mixture was stirred at room temperature for 24 h. The crude product was chromatographed over silica gel. An elution with hexane-ethyl acetate (2:1) gave **12** (18 mg, 11% recovered) and with hexane-ethyl acetate (1:2) **32** (112 mg, 65%): Colorless needles from ethanol; mp 105—107 °C; IR (KBr) 1770 and 1700 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ=1.16, 3.64 ($OC\underline{H}_2C\underline{H}_3$), 2.00—3.40 (11H, m), 2.91 (3H, s. NMe), and 7.04—7.56 (5H, m, Ph); MS m/z 408 (M^+).

Found: m/z 408.1696. Calcd for $C_{23}H_{24}O_5N_2$: M, 408.1684.

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