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Simple Synthesis of *trans*-3,4-Bis(methoxycarbonylmethyl)cyclopentanone

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A simple procedure is described for the synthesis of *trans*-3,4-bis(methoxycarbonylmethyl)-cyclopentanone (**4**), starting with dimethyl muconate or dimethyl 3,4-dibromoadipate and dimethyl sodiomalonate.

Keywords——3,4-disubstituted cyclopentanone; Michael reaction; dimethyl muconate; dimethyl 3,4-dibromoadipate; Dieckmann condensation

Farmer and Mehta,[1] and Blood *et al.*[2] have independently reported that the reaction of diethyl muconate with diethyl sodiomalonate yielded the mono-addition product, and the formation of the five-membered ring ketone was not observed under the reaction conditions employed. Farmer[3a] has also reported that the reaction of diethyl 3,4-dibromoadipate with diethyl sodiomalonate resulted in the formation of diethyl muconate, instead of the direct substitution reaction.

During our synthetic studies[4] on biologically active compounds containing a five-membered ring, such as prostaglandins, we have found a simple synthetic method for *trans*-3,4-bis(methoxycarbonylmethyl)cyclopentanone (**4**) starting with dimethyl muconate or dimethyl 3,4-dibromoadipate (**1**) and dimethyl sodiomalonate.

A mixture of the dibromide **1** (1 eq),[3b] dimethyl malonate (3 eq), and MeONa (3 eq) in tetrahydrofuran (THF) was vigorously stirred at room temperature for 20 h, and usual work-up afforded an inseparable oily mixture (**2**, **3**). Demethoxycarbonylation of the mixture was accomplished by heating under reflux in 20% HCl for 1.5 h, and the mixture was treated with diazomethane to afford the dimethyl ester (**4**) and the diketone (**5**)[5] in 29% and 2% yields, respectively (Chart 1).

The structure of **4** was determined by direct comparison with a standard sample, which was synthesized by a conventional method involving the elongation of the C_1-unit from the ester (**6**),[6] as shown in Chart 2.

The structures of the intermediates (**2** and **3**) were deduced on the basis of the isolation of two demethoxycarbonylation products (**4** and **5**). The reaction of dimethyl muconate with dimethyl sodiomalonate gave a result similar to that obtained with the bromide **1**. Therefore, reaction of **1** with dimethyl sodiomalonate is considered to proceed *via* dimethyl muconate, which is easily formed under basic conditions. The finding that the *trans*-diester **4** was obtained as the main product suggests that the Michael reaction proceeded in a stereocontrolled manner to afford the *trans*-adduct, followed by Dieckmann condensation. The formation of **5** is considered to arise from the *cis*-adduct.

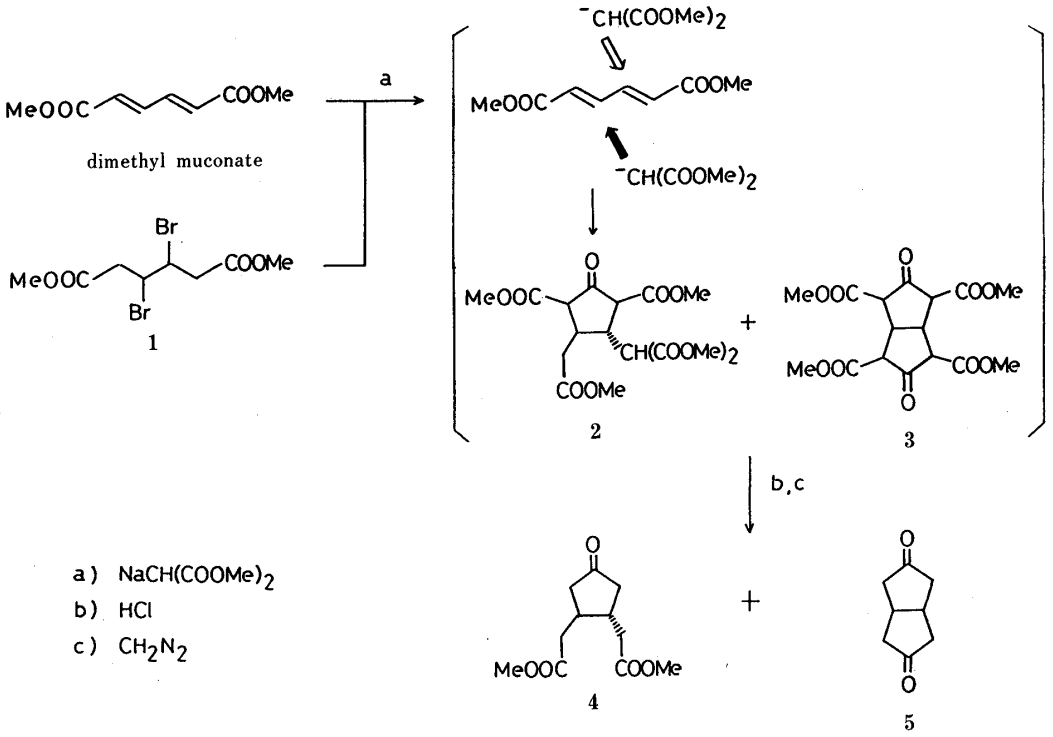
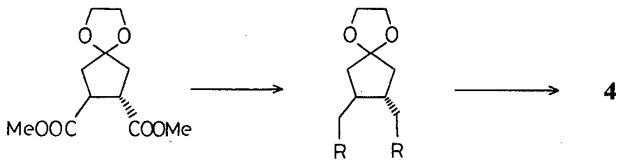


Chart 1



7a: R=OH
7b: R=OMs
7c: R=CN

Chart 2

Experimental

Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were measured with a JASCO A-202 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured on a JEOL JNM-PS-100 spectrometer with Me_4Si as an internal standard. Mass spectra (MS) were taken on a JEOL JMS-D 300 spectrometer. For column chromatography, silica gel (Merck, Kieselgel 60, 70—230 mesh) was used. Thin layer chromatography (TLC) was performed on Silica gel 60 F_{254} plates (Merck). All organic solvent extracts were washed with brine and dried over anhydrous sodium sulfate.

***trans*-3,4-Bis(methoxycarbonylmethyl)cyclopentanone (4)**——a) From Dimethyl 3,4-dibromoadipate (**1**): Dimethyl malonate (30.05 g, 228 mmol) was added dropwise to MeONa solution [freshly prepared from sodium metal (4.75 g, 207 mmol) and MeOH (65 ml)] with vigorous stirring at 0 °C over 20 min. The mixture was stirred for 20 min, then MeOH (40 ml) was removed *in vacuo* to afford dimethyl sodiomalonate, which was suspended in anhydrous THF (80 ml). Dimethyl 3,4-dibromoadipate **1** (22.85 g, 69 mmol) was added portionwise with vigorous stirring to the above suspension. The whole was vigorously stirred for 20 h at room temperature, then diluted with 5% HCl (300 ml), and extracted with AcOEt (200 ml × 2). The combined extracts were washed, and dried. Removal of the solvent *in vacuo* afforded an oily residue (38.13 g), which was roughly chromatographed on silica gel (150 g). The fraction eluted with 30—45% AcOEt in hexane (v/v) was collected, and the solvent was removed *in vacuo* to afford an inseparable mixture (17.32 g) of **2** and **3** as a colorless oil.

The mixture (2.033 g) of **2** and **3** was heated under reflux in 20% HCl (100 ml) for 1.5 h, then diluted with brine (200 ml) and extracted with AcOEt (100 ml × 4). The combined extracts were dried, and the solvent was removed *in vacuo* to afford an oily residue (1.315 g), which was treated with CH_2N_2 in the usual manner. The crude oil (1.255 g)

was subjected to column chromatography on silica gel (20 g), and the fraction eluted with 20—35% AcOEt in hexane (v/v) afforded the *trans*-diester **4** (0.526 g, 29% from **1**) as a colorless oil. The fraction eluted with 35—50% AcOEt in hexane (v/v) afforded the diketone **5** (0.025 g, 2% from **1**) as a colorless needles,[5] mp 85 °C, recrystallized from AcOEt–hexane. **4**: IR(neat): 1730, 1440, 1160 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.80—2.90 (10H, m), 3.64 (6H, s, $CH_3 \times 2$). MS *m/z*: 228 (M^+), 197, 168, 154. High-resolution MS *m/z*: Calcd for $C_{11}H_{16}O_5$(M^+) 228.09975. Found: 228.09867.

b) From Dimethyl Muconate: A solution of dimethyl muconate (5.03 g, 29.6 mmol), dimethyl sodiomalonate (4.56 g, 29.6 mmol) and dimethyl malonate (7.81 g, 59.2 mmol) in a mixture of MeOH (5 ml) and anhydrous THF (50 ml) was vigorously stirred at room temperature for 38 h. The reaction mixture was diluted with ice-water (150 ml) containing 7% HCl (40 ml) and extracted with AcOEt (100 ml × 2). The combined extracts were washed, and dried. Removal of the solvent *in vacuo* afforded an oily residue (15.15 g), which was roughly chromatographed on silica gel (100 g). The fraction eluted with 60—90% AcOEt in hexane (v/v) afforded a mixture (4.57 g) of **2** and **3**. In a manner similar to that described in a), demethoxycarbonylation of the mixture (**2** and **3**, 4.57 g) and subsequent esterification yielded the *trans*-diester **4** (1.96 g, 29% from dimethyl muconate) and the diketone **5**[5] (0.14 g, 3%).

***trans*-3,4-Bis(hydroxymethyl)cyclopentanone Ethylene Acetal (7a)**——The ester **6** (7.80 g, 32.0 mmol) in ether (40 ml) was added dropwise with stirring to a suspension of $LiAlH_4$ (3.03 g, 79.9 mmol) in ether (40 ml) at 0—5 °C. After 5 h, the reaction mixture was decomposed with 4% aq.NaOH (12 ml), and the resulting precipitate was filtered off and washed with $CHCl_3$. The combined organic fractions were concentrated *in vacuo* to afford an oily residue, which was purified by column chromatography on silica gel (60 g). The fraction eluted with 60—90% AcOEt in benzene (v/v) afforded **7a** (6.84 g, 88%) as a colorless oil. IR(neat): 3400, 1430, 1140, 1006 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.15—3.75 (4H, m, $CH_2O \times 2$), 3.80 (4H, s, OCH_2CH_2O).

***trans*-3,4-Bis(mesyloxymethyl)cyclopentanone Ethylene Acetal (7b)**——MsCl (4.88 g, 42.6 mmol) was added dropwise to a stirred solution of **7a** (2.73 g, 14.5 mmol) in pyridine (15 ml) at −10—0 °C. After being stirred for 3 h at 0 °C, the reaction mixture was diluted with brine, and extracted with AcOEt (100 ml × 3). The AcOEt extract was washed, and dried. The solvent was removed *in vacuo* to leave an oily residue, which was subjected to column chromatography on silica gel (50 g). The fraction eluted with 40—60% AcOEt in hexane (v/v) afforded **7b** (3.43 g, 69%) as colorless needles, mp 77 °C, recrystallized from AcOEt and hexane. IR(Nujol): 1275, 1185, 875 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.01 (6H, s, $CH_3SO_2 \times 2$), 3.90 (4H, s, OCH_2CH_2O), 4.25 (4H, d, J=6.0 Hz, $CH_2O \times 2$). *Anal.* Calcd for $C_{11}H_{20}O_8S_2$: C, 38.37; H, 5.81. Found: C, 38.39; H, 5.92.

***trans*-3,4-Bis(cyanomethyl)cyclopentanone Ethylene Acetal (7c)**——NaCN (1.73 g, 35.3 mmol) was added portionwise to a stirred solution of **7b** (3.32 g, 9.65 mmol) in dimethyl sulfoxide (DMSO) (20 ml) at room temperature. The mixture was heated for 2 h at 100—120 °C, diluted with brine, and then extracted with AcOEt (100 ml × 3). The AcOEt extract was washed, dried, and then concentrated *in vacuo* to give an oily residue, which was purified by column chromatography on silica gel (30 g). The fraction eluted with 35—50% AcOEt in hexane (v/v) afforded **7c** (1.82 g, 92%) as a colorless oil. IR(neat): 2240, 1330, 1135, 1110 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.90 (4H, s, OCH_2CH_2O).

4 from 7c——The nitrile **7c** (1.70 g, 8.25 mmol) in MeOH (5 ml) was added dropwise with stirring to MeOH (30 ml) satd. with HCl gas at 0—5 °C. After 2 h, the reaction mixture was diluted with H_2O (100 ml), stirred for 0.5 h at 30 °C, and then extracted with AcOEt (100 ml × 3). The AcOEt extract was washed, and dried. Removal of the solvent *in vacuo* afforded an oily residue, which was purified by column chromatography on silica gel (30 g). The fraction eluted with 35—50% AcOEt in hexane (v/v) afforded **4** (1.38 g, 61%) as a colorless oil.

References and Notes

1) E. H. Farmer and T. N. Mehta, *J. Chem. Soc.*, **1931**, 1762. The reaction was carried out by heating under reflux in ether for 5 h.
2) C. T. Blood, N. J. Cartwright, and R. P. Linstead, *J. Chem. Soc.*, **1952**, 2268. The reaction was carried out by stirring in EtOH at room temperature for a week.
3) *a*) E. H. Farmer, *J. Chem. Soc.*, **1923**, 3332; *b*) *Idem, ibid.*, **1923**, 2531.
4) *a*) S. Amemiya, K. Kojima, and K. Sakai, *Chem. Pharm. Bull.*, **32**, 805, 913 (1984); *b*) K. Kojima, S. Amemiya, H. Suemune, and K. Sakai, *ibid.*, **33**, 2750 (1985).
5) The diketone (**5**) was identical with a commercial sample.
6) K. Sakai, J. Ide, and O. Oda, *Tetrahedron Lett.*, **1975**, 3021.