Structures of the [4+2] Bicyclic Adducts from the Diels-Alder Reaction of Methyl Coumalate with Isoprene

Takanao Matsui,* Takeshi Inoue, Mitsuru Nakayama,† and James D. White††
Faculty of Engineering, Miyazaki University, Miyazaki 880
†*Faculty of Science, Hiroshima University, Hiroshima 730*
††*Department of Chemistry, Oregon State University, Corvallis, Oregon 97331, U. S. A.*

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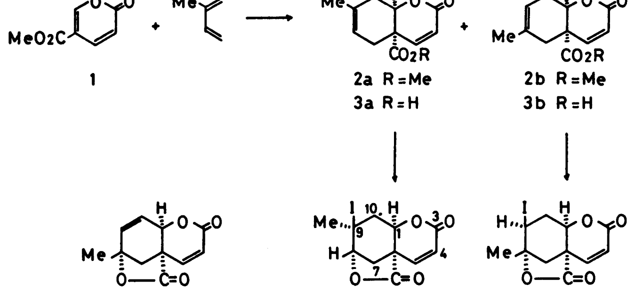
Synopsis. The preparation of 9- and 8-methyl-9-iodo-3-oxo-2-oxabicyclo[4.4.0]dec-4-ene-6,8-carbolactone and 8-methyl-3-oxo-2-oxabicyclo[4.4.0]deca-4,9-diene-6,8-carbolactone from the adducts (**2a** and **2b**) of methyl coumalate with isoprene confirmed the structures of the regioisomers, **2a** and **2b**.

With respect to our studies[1)] on construction of the *cis* A, B ring junction of trichothecane-type sesquiterpenes, the cycloaddition of methyl coumalate (**1**) with isoprene was investigated for the preparation of a potential intermediate for these sesquiterpenoid syntheses.

Although the Diels-Alder reaction of **1** with isoprene was previously reported to produce a mixture of regioisomers (**2a** and **2b**),[2)] no purification of the adducts has been made and the position of methyl substitution seems not to be confirmed. We have found that separation of the adducts by column chromatography on silica gel is unsuccessful, and the ^{1}H NMR spectra of the mixture showed homogeneous signals. Therefore, we tried to carry out the functionalization of **2a** and **2b** in order to confirm their structures.

The cycloaddition of **1** with isoprene at 110—120 °C in an autoclave afforded a mixture of bicyclic adducts (**2a** and **2b**) along with some other products. Hydrolysis of the regioisomeric mixture (the isomeric ratio was appoximately 10 : 1 as indicated by ^{13}C NMR integrals) with aqueous sodium hydroxide solution afforded the corresponding acids (**3a** and **3b**). Without separation and purification, a mixture of **3a** and **3b** was allowed to undergo iodolactonization. Column chromatography of the resultant iodolactones gave **4a** and **4b** in 10 : 1 ratio (63% yield from **2**). Their ^{1}H NMR spectra showed differences, such as the methylene proton signals, and each showed a characteristic pair of one proton quartets at δ 4.11, 4.59 (**4a**), and 4.36, 4.67 (**4b**), due to the methylidyne protons of C-1, C-8, and/or C-9. However, the assignments were ambiguous. The absence of a distinguishing feature between **4a** and **4b** prompted us to examine dehydrohalogenation of **4** as follows. Treatment of **4b** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF gave the desired **5b** in 91% yield. The structure of **5b** was confirmed by elemental analysis and spectral data. On the other hand, **4a** resisted an analogous elimination reaction, suggesting that the proton in an *anti* orientation with respect to the iodine is difficult to abstract by DBU due to the steric shielding by the C-9 methyl group.



This result established that the structure of the major product of the Diels-Alder reaction corresponds to **2a**, which would be expected to provide a synthetic intermediate for the preparation of trichothecanes.

Experimental

All the melting points are uncorrected. IR spectra were recorded in $CHCl_3$ on a Hitachi 260-50 spectrophotometer. ^{1}H NMR spectra and ^{13}C NMR spectra were measured in $CDCl_3$ with a JEOL JNM MH-100 spectrometer (100 MHz) and a JEOL JNM-FX 60 Fourier Transform spectrometer (60 MHz) operating at 15.1 MHz, respectively. Chemical shifts are expressed in terms of δ values (ppm) relative to TMS as an internal standard. Mass spectra were recorded on a JEOL JMS-D 300S mass spectrometer with a direct inlet system operating at 70 eV. Column chromatography was performed with Merck silica gel (0.063 mm).

9- and 8-Methyl-6-methoxycarbonyl-2-oxabicyclo[4.4.0]*deca-4,8-dien-3-one (**2a** and **2b**).* A mixture of 2.0 g (13 mmol) of methyl coumalate and 6 ml (60 mmol) of isoprene in 20 ml of benzene was heated at 110—120 °C for 18 h in an autoclave under N_2. After removal of the solvent and excess of the diene, the residue (3.0 g) was chromatographed on a silica gel with hexane–ethyl acetate (4 : 1) to afford a mixture of **2a** and **2b** as a colorless viscous oil, 0.93 g (32%). IR: 1740, 1720, 1640 cm^{-1}; ^{1}H NMR: 1.68 (3H, s, $-CH=\overset{|}{C}CH_3$), 1.96—2.86 (4H, m, 2 $-CH_2-$), 3.76 (3H, s, $-CO_2CH_3$), 5.00 (1H, dd, J= 3, 5 Hz, C_1–H), 5.44 (1H, m, C_8– and/or C_9–H), 6.05 and 6.93 (each 1H, d, and J=11 Hz, C_4– and C_5–H); ^{13}C NMR: 22.9 (C_9–CH_3), 31.2, 29.1 (weak) and 33.7, 34.7 (weak) (C_7 and/or C_{10}), 45.8 (C_6), 52.9 ($CO_2\underline{C}H_3$), 76.1 and 75.1 (weak) (C_1), 117.8 and 117.4 (weak) (C_8), 120.9 (C_4), 131.2 (C_9), 149.9 (C_5), 163.4 (C_3), 171.8 ($\underline{C}O_2CH_3$); MS: *m/e* 222 (M^+). The other fractions gave the known product, tricyclo[3.2.1.0]octene derivative[2a)] (1.0 g) and unidentified materials (0.4 g).

9- and 8-Methyl-9-iodo-3-oxo-2-oxabicyclo[*4.4.0*]*dec-4-ene-6,8-carbolactone (**4a** and **4b**).* A mixture of 2.3 g (10.3 mmol) of **2** in 300 ml of 5% aqueous sodium hydroxide solution was stirred for 12 h at room temperature. The solution was acidified with 5% hydrochloric acid under ice-cooling and the mixture was extracted with $CHCl_3$. The extract was washed with brine and dried over Na_2SO_4. Removal of the solvent gave 2.0 g of crude acids (**3a** and **3b**). Without further purification, a mixture of the acids in 77 ml of 0.5 M aqueous sodium hydrogencarbonate solution was added to a solution of 6.35 g (25.0 mmol) of iodine and 12.8 g (76.6 mmol) of potassium iodide in 38 ml of water. The mixture was allowed to stand in a dark room for 48 h with occasional shaking. The reaction mixture was extracted with CH_2Cl_2. The extract was washed with 5% aqueous sodium thiosulfate and brine, and dried over Na_2SO_4. The solvent was evaporated *in vacuo* to give 2.7 g of pale yellow solid, which was repeatedly chromatographed on a silica gel using CH_2Cl_2 as the eluent to afford 2.0 g of **4a** and 0.2 g of **4b**. **4a**: Mp 184.5—187.5 °C (recrystallized from CH_2Cl_2); IR: 1760, 1740 cm^{-1}; ^1H NMR: 1.66 (3H, s, C_9–CH_3), 2.40—2.70 (4H, m, 2 –CH_2–), 4.11 (1H, t, J=9 Hz, C_8–H), 4.59 (1H, dd, J=7, 10 Hz, C_1–H), 6.13 and 7.26 (each 1H, d, and J=11 Hz, C_4– and C_5–H); ^{13}C NMR: 22.5 (C_9–CH_3), 26.4 (C_9), 33.9 and 35.5 (C_7 and/or C_{10}), 43.4 (C_6), 74.5 (C_1), 84.3 (C_8), 122.3 (C_4), 143.6 (C_5), 161.9 (C_3), 169.6 (–CO_2– of C_6); MS: *m/e* 334 (M^+); Found: C, 39.60; H, 3.26%. Calcd for $C_{11}H_{10}O_4I$: C, 39.66; H, 3.03%. **4b**: Mp (decomp) 184—186 °C (recrystallized from CH_2Cl_2); IR: 1785, 1740 cm^{-1}; ^1H NMR: 1.79 (3H, s, C_8–CH_3), 2.0—3.2 (4H, m, 2 –CH_2–), 4.36 (1H, dd, J=2, 4 Hz, C_9–H), 4.67 (1H, dd, J=2, 3 Hz, C_1–H), 6.21 and 7.26 (each 1H, d, and J=11 Hz, C_4– and C_5–H); ^{13}C NMR: 20.7 (C_8–CH_3), 25.5 (C_9), 36.1 and 37.9 (C_7 and/or C_{10}), 49.4 (C_6), 73.6 (C_1), 86.7 (C_8), 123.5 (C_4), 144.4 (C_5), 161.0 (C_3), 169.2 (–CO_2– of C_6); MS: *m/e* 334 (M^+); Found: C, 39.64; H, 3.29%. Calcd for $C_{11}H_{10}O_4I$: C, 39.66; H, 3.03%.

*Dehydrohalogenation of **4a** and **4b**.* To a solution of 100 mg (0.3 mmol) of **4b** in 10 ml of dry THF was added 0.13 ml (0.9 mmol) of DBU with stirring at 10 °C under N_2. After being stirred for 1 h at room temperature and for 30 min at 40—45 °C, the mixture was acidified with aqueous 5% hydrochloric acid under ice-cooling and taken up in benzene. The extract was washed with brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed (benzene–ethyl acetate, 92 : 8) to give 56 mg (91%) of **5b** as a colorless solid. Mp 140—141 °C (recrystallized from benzene–hexane); IR: 1780, 1755, 1740, 1605 (weak) cm^{-1}; ^1H NMR: 1.67 (3H, s, C_8–CH_3), 2.28 and 2.52 (each 1H, d, and J=13 Hz, –CH_2–), 4.98 (1H, d, J=4 Hz, C_1–H), 6.03 (1H, dd, J=4, 10 Hz, C_{10}–H), 6.27, 6.39, and 7.02 (each 1H, d, and J=10 Hz, C_4–, C_9–, and C_5–H); ^{13}C NMR ($(CD_3)_2CO$): 22.9 (C_8–CH_3), 42.1 (C_7), 49.3 (C_6), 72.9 (C_1), 82.0 (C_8), 123.3 (C_4), 128.0 (C_{10}), 139.6 (C_9), 146.0 (C_5), 162.5 (C_3), 175.7 (–CO_2– of C_6); MS: *m/e* 206 (M^+); Found: C, 63.98; H, 4.92%. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89%; whereas an analogous reaction of **4a** with DBU led to recovery of the starting material, and to decomposition of **4a** under vigorous conditions.

References

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