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Regio- and Stereoselectivity of Intramolecular Diels–Alder Reactions of Fumarates: An Unusual Rearrangement–Cyclization[1]

Marcel K. Eberle*†

Sandoz Research Institute, Department of Chemistry, East Hanover, New Jersey 07936

Hans-Peter Weber

Chemisch-Physikalische Chemie, Forschungsabteilung, Sandoz AG, 4002 Basel, Switzerland

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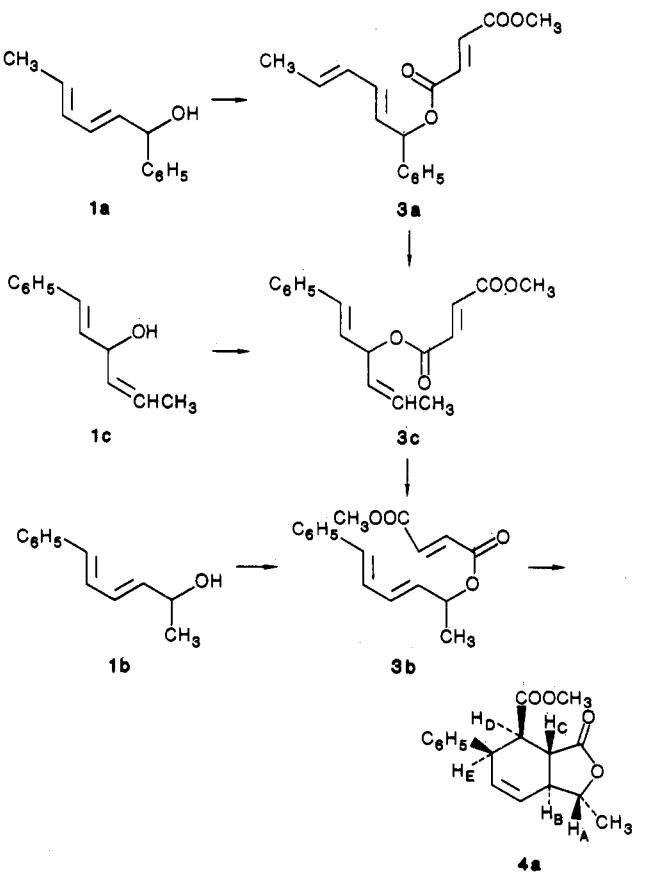
The fumarate esters of the three isomeric phenylhexadienols **1a–c** underwent an intramolecular Diels–Alder reaction to give the single product **4a**. The substituted sorbic alcohol derivatives **1d–f** gave similar products **4b–e**. The assigned stereochemistry of the five centers of asymmetry generated during the cyclization was confirmed by an X-ray analysis of **4e**.

The Diels–Alder[2] reaction represents a powerful tool to prepare compounds with four asymmetric centers in a single step. In the case of the intramolecular Diels–Alder[3] reaction, five asymmetric centers may be generated in a single step. Both of the above statements are well documented[4] for carbocyclic compounds. To our knowledge, no report has been published describing the preparation of hexahydro-3-oxoisobenzofuran-4-carboxylic acids via an intramolecular Diels–Alder addition with concomitant formation of five asymmetric centers.

In order to study the stereochemical course of reactions generating all five possible asymmetric centers in the forementioned system, we started with the addition of some Grignard or lithium reagents[5] to sorbic aldehyde. The allylic alcohols thus generated were esterified with the acid chlorides of fumaric acid monoesters[6] and subjected to conditions favorable for cyclization.

The known[7] dienol **1a** was prepared from sorbic aldehyde via the addition of phenylmagnesium bromide. Reaction of this alcohol with the acid chloride of fumaric acid monomethyl ester in the presence of triethylamine in ether overnight followed by the usual workup gave an oily product. When a sample was distilled in a Kugelrohr apparatus at 180–190 °C under high vacuum, a solid product was obtained, which was assigned structure **4a** (Scheme I) on the basis of the following spectral data. The ^{13}C spectrum of the product was consistent with the presence of a single isomer. A doublet (J = 6 Hz) assigned to the carbon-substituted methyl group appeared at 1.51 ppm. This represents a shift of approximately 0.5 ppm toward lower field than might be expected for a carbocyclic methyl group (see below). The two signals in the region between 4 and 5 ppm were assigned to the methine protons in the vicinity of oxygen and phenyl, respectively. The

Scheme I



† Present address: Preclinical Research, Department of Chemistry, Sandoz Ltd., 4002 Basel, Switzerland.

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stereochemistry of compound **4a** was assigned on the basis of decoupling experiments with that compound. The trans assignment was supported by the following coupling constants: $J_{H_A-H_B}$ = 10 Hz, $J_{H_B-H_C}$ = 12.5 Hz, $J_{H_C-H_D}$ = 12.5 Hz, and $J_{H_D-H_E}$ = 7.5 Hz. From these couplings, it may be concluded that all methine protons are present in a trans arrangement to each other with the exception of H_D and H_E, which are cis to each other.

These findings prompted us to prepare the alcohol **1b** by following procedures from the literature.[8] After condensation with the acid chloride **2a** under conditions similar to those described above, distillation under high vacuum gave a product identical in every respect with compound **4a** obtained from the isomeric precursor **1a**.

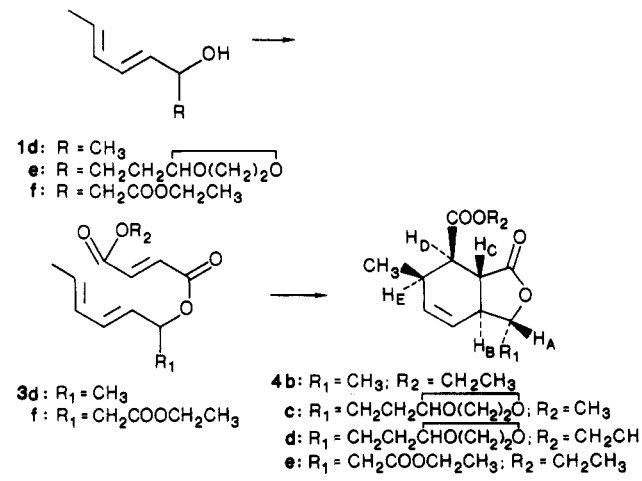
The nonconjugated dienol **1c** was prepared from cinnamaldehyde via the addition of the Grignard reagent prepared from 1-bromo-1-propene[9] (mixture of cis and trans). Chromatography on a silica gel column gave one of the isomers in pure form.

Reaction of **1c** with the acid chloride **2a** gave the same product **4a** that was isolated previously.

Attempts to purify the intermediary noncyclized esters **3a–c** so far have failed. When these esters were kept at room temperature for a few days, a solid began to separate from the crude. These solids were found to be identical with the product **4a**.

From the experiments described above, the possibility of the alcohols **1a** and **1c** rearranging to give **1b** under the reaction conditions cannot a priori be excluded (see ref 7). However, when the alcohol **1a** was acetylated in a mixture of pyridine and acetic anhydride at room temperature, the product isolated after distillation was the acetate of **1b** as indicated by the NMR spectrum of the product. This showed a doublet at 1.33 ppm that was assigned to the methyl group of the alcohol portion. In comparison, the signals for the methyl groups of the alcohols **1a–c** showed the following chemical shifts: **1a**, 1.70 ppm; **1b**, 1.325 ppm; and **1c**, 1.70 ppm. Since these conditions proved to be favorable for a sigmatropic rearrangement of the acetate of **1a** to the acetate of **1b**, one might expect the same to be true for the fumarates **3a** and **3c**. Consecutive (3,3) sigmatropic shifts would lead from **3a** to **3b** via **3c**. This hypothesis was supported by the following experiment: When the alcohol **1a** was dissolved in ether and 0.5 equiv of triethylamine and then stirred in the presence of 1 equiv of triethylammonium hydrochloride overnight, the alcohol **1a** was recovered unchanged.

Scheme II



These observations lead to the conclusion that the acylations of **1a** and **1c** take place without prior rearrangement of the alcohols. Instead the ester **3a** undergoes rearrangement to the ester **3b** via **3c**. All these sigmatropic shifts must then be faster than the intramolecular Diels–Alder addition of **3b** to give **4a**.

In order to support the chemical shift assignments of the compound **4a** described above, we set out to prepare the methyl-substituted lactone **4b** by starting from the known[10] heptadienol **1d** and the acid choloride **2b** in ether and triethylamine as base. The ester **3d** could be distilled under high vacuum at 110–120 °C without any change. The NMR spectrum of this product clearly revealed the presence of six vinylic protons. More dramatic changes occurred when the ester **3d** was distilled under aspirator vacuum. A low-melting solid was obtained that consisted of a single isomer as indicated by its ^{13}C NMR spectrum. The proton NMR spectrum of **4b** gave rise to two doublets at 0.99 and 1.46 ppm, assignable to the carbocyclic and heterocyclic methyl groups, respectively, thus confirming the assignment of the methyl group of **4a**. The coupling constants between the methine protons were found to be very similar to those observed for the respective coupling constants of the methine groups for **4a**, thus pointing to the same stereochemistry for **4b**.

Our next target molecule was the lactone **4c**. To this end, the dienol **1e** was prepared from sorbic aldehyde and the Grignard reagent of 3-bromopropionaldehyde acetal.[11] Esterification with the acid chloride **2a** under the usual conditions gave **4c** as a solid after distillation (Scheme II). A single isomer was obtained as indicated by its ^{13}C NMR spectrum. In the NMR spectrum of **4c**, the carbocyclic methyl group gave rise to a doublet at 0.96 ppm. All methine protons appeared as distinct signals. The splitting patterns of all the methine protons were reminiscent of those observed in the compounds described above. Selective decoupling experiments provided unequivocally the following coupling constants: $J_{H_A-H_B}$ = 10.25 Hz and $J_{H_B-H_C}$ = 13.7 Hz, indicative of the trans arrangement of the respective protons.

The ethyl ester **4d** was prepared in analogy to its methyl ester **4c** and was obtained as a liquid. Since one might expect possible isomers of **4d** to have a similar boiling point, which would render a separation by Kugelrohr

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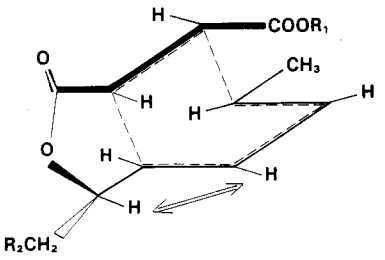

Figure 1.

distillation difficult, it was gratifying to learn from its ^{13}C spectrum that **4d** consisted of a single isomer of approximately 90% purity.

The last example to be described in this series is the diester **4e**. This was obtained from the known[5] hydroxy ester **1f** and the acid chloride **2b**. The intermediary triene **3e** was isolated, purified, and characterized with the aid of its NMR spectrum. Distillation under high vacuum provided the conditions for cyclization to the lactone **4e**, which was obtained as a single isomer (^{13}C NMR spectrum). In the NMR spectrum of **4e**, the carbocyclic methyl group was detected as a doublet at 0.98 ppm. Only two of the signals attributable to the methine protons H_A and H_B were separated enough from the other signals.

Decoupling experiments provided the coupling constants $J_{H_A-H_B}$ = 9.8 Hz and $J_{H_B-H_C}$ = 11–12 Hz, again indicating a trans arrangement of the corresponding protons.

In order to corroborate the stereochemistry of these compounds, an X-ray analysis was carried out on the lactone **4e**. The colorless prismatic crystals had the following characteristics: elemental composition $C_{16}H_{22}O_6$; molecular weight 310.326; belong to the monoclinic space group $P2_1/c$ and have a = 8.284 (6), b = 23.621 (5), and c = 8.141 (1) Å; β = 92.62° (5); and V = 1591.3 Å^3 with Z = 4 molecules per cell and a calculated density (d_{calcd}) of 1.30 g/cm^3.

Intensity data were measured on an Enraf-Nonius CAD4F diffractometer with Cu Kα radiation (λ = 1.542 Å, graphite monochromator) in the range $\sin\theta/\lambda \leq 0.609$ Å^{-1}. Of a total of 3005 independently measured reflections, 2505 reflections showed significant intensity [$I > 3\sigma(I)$]. Data reduction and absolute scaling[12] yielded an overall temperature factor $\bar{B}$ = 4.8 Å^2 and the E averages $\langle|E|\rangle$ = 0.787, $\langle|E^2 - 1|\rangle$ = 0.998, $\langle|E^2|\rangle$ = 1.001.

The structure was solved with the SHELX suite of programs and refined by block-diagonal least-squares calculations to R = 0.069. The parameters refined included anisotropic temperature factors for C and O atoms, isotropic B's for hydrogen, a scale factor, and an isotropic extinction coefficient.[13]

The mean esd of C and O atomic positions are 0.005 Å and for hydrogen 0.05 Å.

A perspective view of the molecule **4e** showing the relative configuration and the atomic numbering scheme is given in Figure 2. A list of fractional coordinates is given in Table I. Bond lengths are all close to expected values with the exception of two terminal ethyl groups that appear shortened (1.45 Å), probably due to their large anisotropic vibrations.

From these observations it may be concluded that the transition state for the Diels–Alder reaction for fumarates of dienols is similar to the one described for the analogous carbon triene leading to indene systems;[4g,h] see Figure 1.

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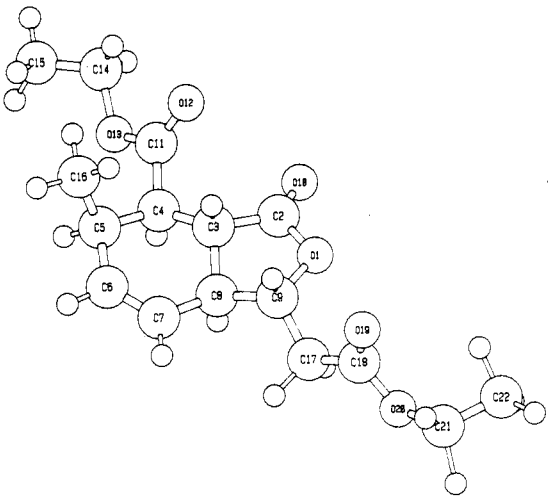

Figure 2. Perspective view of molecular conformation of **4e**.

Table I. Atomic Coordinates of 4e[a]

	atom	x/a	y/b	z/c
1	O1	0.1964 (3)	0.58753 (8)	0.0939 (2)
2	C2	0.2114 (4)	0.5357 (1)	0.0215 (3)
3	C3	0.2663 (3)	0.4945 (1)	0.1536 (3)
4	C4	0.2381 (3)	0.4315 (1)	0.1388 (3)
5	C5	0.3137 (4)	0.4028 (1)	0.2980 (4)
6	C6	0.2885 (5)	0.4378 (2)	0.4515 (4)
7	C7	0.2343 (4)	0.4905 (1)	0.4561 (3)
8	C8	0.1830 (4)	0.5201 (1)	0.2991 (3)
	C9	0.2224 (4)	0.5820 (1)	0.2726 (3)
10	O10	0.1780 (3)	0.5297 (1)	−0.1223 (2)
11	C11	0.3125 (4)	0.4057 (1)	−0.0103 (4)
12	O12	0.4104 (3)	0.4280 (1)	−0.0928 (3)
13	O13	0.2597 (3)	0.35308 (9)	−0.0341 (3)
14	C14	0.3359 (6)	0.3201 (2)	−0.1611 (5)
15	C15	0.3438 (7)	0.2610 (2)	−0.1132 (6)
16	C16	0.4931 (5)	0.3898 (2)	0.2881 (5)
17	C17	0.1150 (5)	0.6240 (1)	0.3544 (4)
18	C18	0.1827 (5)	0.6835 (1)	0.3603 (4)
19	O19	0.3226 (4)	0.6947 (1)	0.3569 (4)
20	O20	0.0658 (4)	0.7216 (1)	0.3827 (4)
21	C21	0.1119 (7)	0.7800 (2)	0.4227 (6)
22	C22	0.1087 (8)	0.8149 (2)	0.2772 (6)
23	H3	0.378 (5)	0.502 (2)	0.169 (4)
24	H4	0.117 (4)	0.421 (1)	0.132 (4)
25	H5	0.255 (4)	0.365 (1)	0.320 (4)
26	H6	0.313 (4)	0.417 (2)	0.558 (4)
27	H7	0.222 (5)	0.512 (2)	0.558 (5)
28	H8	0.061 (4)	0.512 (2)	0.291 (4)
29	H9	0.348 (4)	0.591 (1)	0.309 (4)
30	H14A	0.254 (9)	0.323 (3)	−0.264 (9)
31	H14B	0.43 (1)	0.335 (3)	−0.175 (9)
32	H15A	0.397 (6)	0.240 (2)	−0.203 (5)
33	H15B	0.43 (1)	0.265 (4)	−0.01 (1)
34	H15C	0.25 (1)	0.243 (4)	−0.05 (1)
35	H16A	0.518 (8)	0.365 (3)	0.183 (7)
36	H16B	0.560 (5)	0.424 (2)	0.279 (5)
37	H16C	0.541 (5)	0.368 (2)	0.396 (5)
38	H17A	0.003 (5)	0.621 (2)	0.285 (5)
39	H17B	0.100 (6)	0.611 (2)	0.487 (6)
40	H21A	0.003 (7)	0.803 (3)	0.508 (7)
41	H21B	0.224 (4)	0.781 (2)	0.492 (4)
42	H22A	0.139 (4)	0.859 (2)	0.314 (4)
43	H22B	0.212 (9)	0.788 (3)	0.22 (1)
44	H22C	0.005 (6)	0.808 (3)	0.207 (6)

[a] Positional esd in parentheses.

Experimental Section

Proton magnetic resonance spectra were obtained on a JEOL FX 200 spectrometer and are recorded in hertz or δ values (parts per million) relative to TMS (tetramethylsilane) as internal standard. Infrared spectra were recorded on an Analect Instrument FX-6200 FTIR. Thin-layer chromatography (TLC) was carried out on glass plates coated with silica gel HF-254, E. Merck

AG. Mass spectra were measured on a LKB 9000 (low resolution) or on a VG 7070E (high resolution) mass spectrometer.

1-Phenyl-2,4-hexadien-1-ol (1a).[7] A solution of 0.22 g (0.001 25 mol) of dienol **1a** and 0.06 g (0.0006 mol) of triethylamine in 5 mL of ether was stirred at room temperature overnight in the presence of 0.175 g (0.001 25 mol) of triethylamine hydrochloride. The starting material was recovered unchanged according to GLC analysis.

1-Phenyl-1,4-hexadien-3-ol (1c). The Grignard reagent was prepared from 3.6 g (0.15 mol) of magnesium and 18.3 g (0.15 mol) of commercial 1-bromo-1-propene (mixture of cis and trans) in 100 mL of THF. The solution was cooled to −70 °C. A solution of 13.2 g (0.1 mol) of *trans*-cinnamaldehyde was added. The cooling bath was removed, and when the internal solution reached 0 °C, the reaction mixture was quenched with water, extracted with CH_2Cl_2, and dried over $MgSO_4$. The product was distilled in a Kugelrohr apparatus: bp 90–100 °C (0.1 mmHg); yield 9.1 g (52%); NMR ($CDCl_3$) δ 1.78 (d, 3, J = 5 Hz, CH_3), 2.5 (1, exchangeable with D_2O, OH), 5.2 (t, 1, J = 7.5 Hz, C*H*OH), 5.5–5.9 (m, 2, $CH_3CH{=}CH$), 6.2–6.36 (dd, 1, J_1 = 15 Hz, J_2 = 5 Hz, $C_6H_5CH{=}CH$), 6.65 (d, 1, J = 15 Hz, C_6H_5CH), 7.2–7.5 (m, 5, C_6H_5).

α-(1,3-Pentadienyl)-1,3-dioxolane-2-propan-3-ol (1e). To 4.8 g (0.2 mol) of Mg and 100 mL of dry tetrahydrofuran was added 38.2 g (0.2 mol) of commercial 3-bromopropionaldehyde ethylene acetal in 100 mL of THF at such a rate that the temperature during the reaction did not exceed 35 °C.[11] Following the addition, the mixture was kept at room temperature for 3 h. The Grignard reagent was cooled to −60 °C, and a solution of 19.2 g (0.2 mol) of freshly distilled sorbic aldehyde in THF (100 mL) was added. The low temperature was maintained for 30 min. Then, 100 mL of a saturated solution of ammonium chloride was added followed by the addition of 500 mL of ether. The organic phase was separated, dried over $MgSO_4$, and evaporated to give 39 g of crude product. This was distilled under high vacuum: bp 120–135 °C (0.3 mm); yield 25.2 g (64%); ^{1}H NMR ($CDCl_3$) δ 1.4–2.0 (m, 7, CH_3 + 2 CH_2), 2.6 (br, 1, exchangeable in D_2O, OH), 3.8–4.2 (m, 5, CHO + OCH_2CH_2O), 4.8–5.1 (m, 1, OCHO), 5.3–6.4 (m, 4, 4 vinyl H).

Monoethyl Fumarate of 3,5-Heptadien-2-ol (3d). An ice-cold mixture of 4.48 g (0.04 mol) of 3,5-heptadien-2-ol[10] and 8.1 g (0.08 mol) of triethylamine in 100 mL of ether was treated with 7.0 g (0.043 mol) of fumaric acid chloride monoethyl ester.[6] The mixture was kept at room temperature for 3 h. After the addition of water, the product was extracted with ether and gave, after drying over $MgSO_4$, evaporation of the solvent, and distillation in a Kugelrohr apparatus, 7.3 g (77%) of the ester **3d**: bp 110–120 (0.5 mmHg); NMR ($CDCl_3$) δ 1.2–1.5 (m, 6, 2 CH_3), 1.75 (d, 3, CH_3), 3.0–3.4 (m, 1, OCH), 4.26 (q, 2, OCH_2), 5.2–6.7 (m, 4, vinyl), 6.85 (s, 2, vinyl).

Monoethyl Fumarate of 3-Hydroxy-4,6-octadienoic Acid Ethyl Ester (3f). A mixture of 3.7 g (0.02 mol) of **1f**[6] in 100 mL of ether and 5.0 g (0.05 mol) of triethylamine was treated with 3.9 g (0.02 mol) of the acid chloride[6] in 50 mL of ether. The mixture was stirred at room temperature overnight. Water and more ether were added. The organic phase was separated and dried over Na_2SO_4 to give 6.9 g of an oil: NMR ($CDCl_3$) δ 1.20 (t, J = 6 Hz, 3, CH_3), 1.30 (t, J = 6 Hz, 3, CH_3), 1.73 (d, 2, J = 6 Hz, CH_3), 2.68 (d, 2, J = 6 Hz, $CHCH_2$), 3.9–4.5 (m, 4, 2 OCH_2), 5.2–5.7 (m, 5, 4 vinyl + OCH), 6.8 (s, 2, vinyl).

1,3,3a,4,5,7a-Hexahydro-1-methyl-3-oxo-5-phenylisobenzofuran-4-carboxylic Acid Methyl Ester (4a). A. From 1-Phenyl-2,4-hexadien-1-ol (1a). A mixture of 8.7 g (0.05 mol) of the dienol **1a**,[7] 7.5 g (0.075 mol) of triethylamine, and 7.5 g (0.05 mol) of the acid chloride **2a**[6] in 100 mL of ether was stirred at room temperature overnight. The mixture was poured on ice and extracted with ether and dried over $MgSO_4$ to give 14.8 g (100%) of crude ester **4a**. A 4.0-g (0.014-mol) sample was distilled under reduced pressure, bp 180–200 °C (0.3 mmHg), to give a viscous liquid, which started to crystallize and was treated with ether to give 1.8 g (45%) of product: mp 154–159 °C; a sample was recrystallized from CH_2Cl_2/hexane and had mp 165–167 °C; mass spectrum, m/e 286 [M^+]; ^{1}H NMR ($CDCl_3$) δ 1.51 (d, 3, J = 6 Hz, CCH_3), 2.43 (t, 1, J = 12.5 Hz, C_{7a}-H), 2.88 (t, 1, J = 12.5 Hz, C_{3a}-H), 3.1–3.3 (m, 1, C_4-H), 3.28 (s, 3, OCH_3), 3.95–4.1 (br, 1, C_5-H), 4.3–4.5 (m, 1, C_1-H), 5.75–5.9 (m, 1, vinyl H), 6.0–6.1 (d, 1, J = 10 Hz, vinyl H), 7.0–7.4 (m, 5, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 18.2 (q, $CHCH_3$), 41.2 (d, C_{3a}), 44.2 (d, C_5), 45.4 (d, C_4), 47.4 (d, C_{7a}), 51.2 (q, OCH_3), 79.0 (d, C_1), 123.4 (d, C_7), 127.5 (d, C_{11}), 128.2 (d, C_9), 129.1 (d, C_{10}), 132.1 (d, C_6), 139.1 (s, C_8), 170.2 (s, C_3), 173.5 (s, CO_2CH_3); IR (CH_2Cl_2) 1789 (lactone), 1741 (ester) cm^{-1}. Anal. Calcd for $C_{17}H_{18}O_4$ (286.33): C, 71.3; H, 6.3. Found: C, 71.5; H, 6.4.

B. From 1-Phenyl-1,3-hexadien-5-ol (1b). A mixture of 3.48 g (0.02 mol) of the dienol **1b**[8] and 3.03 g (0.03 mol) of triethylamine in 100 mL of ether was treated with 3.0 g (0.02 mol) of the acid chloride **2a**.[6] The mixture was stirred at room temperature overnight. The crude ester was isolated as described above, yield 5.3 g (93%). A sample was distilled in a Kugelrohr apparatus, bp 160–180 °C (0.2 mm) to give the product **4a**, which crystallized after the addition of ether: yield 0.352 g (35%); mp 164–166 °C; ^{1}H NMR and IR spectra were identical with those described above.

C. From 1-Phenyl-1,4-hexadien-3-ol (1c). A mixture of 3.48 g (0.02 mol) of the dienol **1c**, 3.03 g (0.03 mol) of triethylamine, and 3.00 g (0.02 mol) of the acid chloride **2a**[6] in 100 mL of ether was kept at room temperature overnight. More ether was added, and the mixture was washed twice with water. The organic phase was dried over $MgSO_4$. The solvent was evaporated to give 5.6 g (98%) of crude ester. A sample of 1.0 g was distilled in a Kugelrohr apparatus, bp 190–195 °C (0.2 mmHg). The product **4a** crystallized after addition of ether, mp 160–162 °C to give 0.430 g (43% over two steps) of a solid; ^{1}H NMR and IR spectra were identical with those described above.

1,5-Dimethyl-1,3,3a,4,5,7a-hexahydro-3-oxoisobenzofuran-4-carboxylic Acid Ethyl Ester (4b). When 1.8 g (0.0075 mol) of the ester **3a** was distilled in a Kugelrohr apparatus under water aspirator vacuum, the product was isolated as a solid after the addition of ether/hexane: mp 76–78 °C; MS, m/e calcd for $C_{13}H_{18}O_4$ 238.1205, found 238.1178 [M^+]; ^{1}H NMR ($CDCl_3$) δ 0.99 (d, 3, J = 7 Hz, C_5-CH_3), 1.30 (t, 3, J = 7 Hz, CH_2CH_3), 1.46 (d, 3, J = 5 Hz, C_1-CH_3), 2.34 (t, 1, J = 12.5 Hz, C_{7a}-H), 2.69 (t, 1, J = 12.5 Hz, C_{3a}-H), 2.75–2.95 (br, 1, C_5-H), 2.9–3.0 (m, 1, C_4-H), 4.2 (m, 1, C_1-H), 4.25 (q, 2, J = 7 Hz, OCH_2), 5.65–5.8 (m, 2, vinyl H); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_2CH_3), 17.6 (C_5-CH_3), 18.3 (C_1-CH_3), 32.7 (C_5), 41.7 (C_{3a}), 43.4 (C_4), 47.9 (C_{7a}), 60.6 (OCH_2), 78.9 (C_1), 121.6 (C_7), 135.7 (C_6), 171.1 (C=O), 173.9 (C=O).

1-(2-Dioxolanylethyl)-1,3,3a,4,5,7a-hexahydro-5-methyl-3-oxoisobenzofuran-4-carboxylic Acid Methyl Ester (4c). A mixture of 10.0 g (0.05 mol) of the ketal **1e** and 10.0 g (0.1 mol) of triethylamine in 100 mL of ether was treated with 8.0 g (0.054 mol) of acid chloride **2a** in 100 mL of ether. After 3 h, the ether layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was distilled in a Kugelrohr apparatus, bp 180–200 °C (0.3 mm). The distillate was treated with ether to give the solid product **4c**: mp 104–106 °C, after one recrystallization from CH_2Cl_2/hexane, the mp was 106–108 °C; yield 20% (over two steps); mass spectrum, m/e 310 [M^+]; ^{1}H NMR ($CDCl_3$) δ 0.96 (d, 3, J = 7 Hz, CCH_3), 1.7–1.9 (m, 2, CH_2), 1.9–2.1 (m, 2, CH_2), 2.41 (m, 1, C_{7a}-H), 2.69 (t, 1, J = 12 Hz, C_{3a}-H), 2.7–2.9 (br, 1, C_5-H), 2.9–3.1 (m, 1, C_4-H), 3.77 (s, 3, OCH_3), 3.9–4.1 (m, 4, OCH_2-CH_2O), 4.17 (m, 1, C_1-H), 4.92 (m, 1, OCHO), 5.6–5.9 (m, 2, HC=CH); ^{13}C NMR ($CDCl_3$) δ 17.6 (q, CCH_3), 27.4 (t, CH_2CH_2CHOO), 29.6 (t, CH_2CHOO), 32.7 (d, C_5), 41.7 (d, C_{3a}), 43.4 (d, C_4), 46.3 (d, C_{7a}), 51.7 (q, OCH_3), 65.0 (t, OCH_2CH_2O), 82.4 (d, C_1), 103.7 (d, OCHO), 122.0 (d, C_7), 135.7 (d, C_6), 171.6 (C=O), 173.8 (C=O); IR (CH_2Cl_2) 1730 (ester), 1780 (lactone) cm^{-1}. Anal. Calcd for $C_{16}H_{22}O_6$ (310.4): C, 61.9; H, 7.1. Found: C, 62.0; H, 7.3.

1-(2-Dioxolanylethyl)-1,3,3a,4,5,7a-hexahydro-5-methyl-3-oxoisobenzofuran-4-carboxylic Acid Ethyl Ester (4d). A mixture of 7.1 g (0.036 mol) of ketal **1e** and 7.0 g (0.07 mol) of triethylamine in 100 mL of ether was treated with a solution of 7.0 g (0.043 mol) of acid chloride **2b** in 100 mL of ether. The mixture was stirred at room temperature overnight, washed with water, and dried over Na_2SO_4. The solvent was evaporated, and the residue of 11.8 g was distilled in a Kugelrohr apparatus. The fraction with the boiling point 160–180 °C (0.2 mm) was collected, yield 6.1 g (53% over two steps): mass spectrum, m/e 324 [M^+]; ^{1}H NMR ($CDCl_3$) δ 0.96 (d, 3, J = 7 Hz, CH_3), 1.27 (t, 3, J = 7 Hz, CH_2CH_3), 1.5–2.1 (m, 4, 2 CH_2), 2.1–3.3 (m, 4, 4 CH), 3.8–4.5 (m, 7, 3 OCH_2 + OCH), 4.93 (t, 1, J = 3 Hz, OCHO), 5.6–5.9 (m, 2, HC=CH); ^{13}C NMR ($CDCl_3$) δ 14.2 (q, CH_2CH_3), 17.5 (q,

C_5-CH_3), 27.4 (t, CH_2CH_2CHOO), 29.6 (t, CH_2CHOO), 32.7 (d, C_5), 41.6 (d, C_{3a}), 43.5 (d, C_4), 46.3 (d, C_{7a}), 60.6 (t, OCH_2CH_3), 64.9 (t, OCH_2CH_2O), 82.3 (d, C_1), 103.6 (d, OCHO), 122.0 (d, C_7), 135.7 (d, C_6), 171.1 (s, C=O), 173.8 (s, C=O); IR (film) 1730 (ester), 1780 (lactone) cm^{-1}.

1,3,3a,4,5,7a-Hexahydro-5-methyl-3-oxo-4-(ethoxycarbonyl)isobenzofuran-1-acetic Acid Ethyl Ester (4e). The crude product **3b** (6.9 g) was distilled in a Kugelrohr apparatus. The fraction boiling at 160–180 °C (0.2 mm) was treated with ether/hexane to give 1.9 g (31% over two steps) of the crystalline product **4e**: mp 108–110 °C; mass spectrum, *m/e* calcd for $C_{14}H_{17}O_5$ 265.107, found 265.115 [M^+ – OEt]; ^1H NMR ($CDCl_3$) δ 0.98 (d, 3, J = 7 Hz, $CHCH_3$), 1.23 (t, 3, J = 7.5 Hz, CH_3CH_3), 1.30 (t, 3, J = 7.5 Hz, CH_2CH_3), 2.5 (t, 1, J = 12.5 Hz, C_{7a}-H), 2.7–3.0 (m, 5, CH_2CO_2 + 3 CH), 4.15–4.3 (2 q, 4, 2 OCH_2), 4.5–4.65 (m, 1, C_1-H), 5.5–5.8 (m, 2, HC=CH); ^{13}C NMR ($CDCl_3$) δ 14.2 (q, 2 CH_2CH_3), 17.5 (q, $CHCH_3$), 32.7 (d, C_5), 38.3 (t, CH_2COOEt), 41.4 (d, C_{3a}), 43.5 (d, C_4), 46.2 (d, C_{7a}), 60.7 (t, OCH_2), 61.2 (t, OCH_2), 78.2 (d, C_1), 121.6 (d, C_7), 135.9 (d, C_6), 169.4 (C=O), 170.9 (C=O), 173.2 (C=O); IR (CH_2Cl_2) 1792 (lactone), 1736 (ester) cm^{-1}. Anal. Calcd for $C_{16}H_{22}O_6$ (310.4): C, 61.9; H, 7.1. Found: C, 61.8, H, 7.2.

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Synthesis of β-Arylvinyl Ethers by the Palladium-Catalyzed Reaction of Aroyl Chlorides with Vinyl Ethers

Carl-Magnus Andersson and Anders Hallberg*

Division of Organic Chemistry 1, Chemical Center, University of Lund, P.O. Box 124, S-221 00 Lund, Sweden

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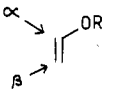
Reaction of aroyl chlorides with butyl vinyl ether in the presence of a palladium catalyst and an amine base affords β-arylvinyl ethers in 40–60% yield. Both with regard to regioselectivity and reaction rate, aroyl chlorides were superior to aryl bromides or iodides as starting materials. Thus, benzoyl chloride favored substitution at the terminal (β) carbon atom of the vinyl ether by a factor of about three, as compared to iodobenzene. Furthermore, the substituents in the aroyl chloride were found to have a profound influence on regioselectivity, with electron-withdrawing groups giving the best results. For example, a threefold improvement in β-selectivity was observed in going from benzoyl chloride to 4-nitrobenzoyl chloride.

Introduction

Interest in enol ethers, earlier regarded simply as derivatives of aldehydes and ketones, as synthetic intermediates has increased as a result of the development of new areas of application.[1] Although arylacetaldehyde enol ethers are valuable substrates in synthetic chemistry,[2] they have not been easily available, and recently a series of new approaches has been reported for the preparation of this class of compounds.[3]

The Heck arylation of olefins[4] has become an important, general method for the preparation of arylalkenes and would in principle be expected to provide a convenient entry to β-arylvinyl ethers. However, palladium-catalyzed arylations of electron-rich olefins, such as enol ethers, furnish mixtures of regioisomers and low yields have been reported.[5,6] Recent work in our laboratories has shown that the regiochemical outcome of these arylations is in fact to a great extent governed by the conditions and reactants employed and that a fair degree of regiochemical control can be achieved.



From this basic study[7] we anticipated that catalytic reactions involving arylpalladium chloride intermediates[8] would favor the desired β-arylation of alkyl vinyl ethers.

A valuable extension of the Heck reaction developed by Blaser and Spencer, introducing benzoyl chlorides as arylating agents,[9] gives indirect access to these interme-

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