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Cycloaddition of Ketene Acetals with 4-Bromo-6-spiroepoxycyclohexa-2,4-dienone†

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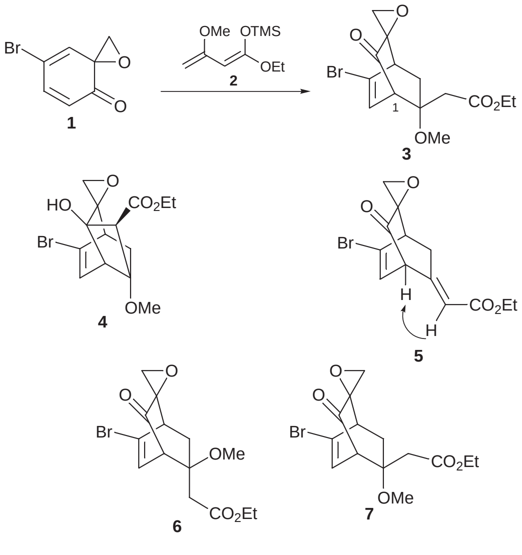
4-Bromo-6-spiroepoxycyclohexa-2,4-dienone reacts as a diene in an inverse electron-demand reaction with 1-ethoxy-3-methoxy-1-trimethylsilyloxybuta-1,3-diene but as a dienophile with 1-ethoxy-3-methylene-4-(ethoxy trimethylsilyloxymethylene)-1-cyclohexene.

Cyclohexadienones such as pyrones, pyridones,[1] quinols and quinol acetates,[2] orthobenzoquinones[3] and spiroepoxycyclohexadienones have been largely used as dienes in inter- and intra-molecular Diels–Alder cycloadditions. The latter, which are easily obtained by periodate oxidation of salicyl alcohols,[4] have been shown to react with neutral (dienes, styrenes, *etc.*)[5] and electron-rich (enol ethers, enamides, *etc.*)[6] dienophiles to give *endo*- or *exo-syn* adducts. With simple dienes (cyclopentadiene, fulvenes, *etc.*), adducts resulting from inverse-electron demand or normal Diels–Alder cycloaddition have been isolated.[5] In this respect, we became interested in a study of the reactivity of 4-bromo-6-spiroepoxycyclohexa-2,4-dienone **1** (dimerization of **1** is only observed at a significant rate above 60 °C)[6] with electron-rich unsaturated ketene acetals such as **2**[7] and **10**.[8] To our knowledge, only one example of cycloaddition of a ketene acetal related to **2** with a protected orthobenzoquinone has been reported by Coleman,[9] giving a highly functionalized naphthalene derivative.



Scheme 1

Cycloaddition of **2** (1.5 equiv.) with **1** proceeded rapidly at 0 °C in THF (2 h) to afford different adducts depending on acid, neutral or basic work-up (Scheme 1, Table 1). In each case, as expected, the main adduct resulted from regio- and stereo-specific *syn* addition but following work-up the methoxy derivative **3** (50%), the strained aldol **4** (31%, as a single diastereoisomer) or the unsaturated ester **5** (48%) were isolated together with minor adducts **6** and **7**.[10] The proposed structures of adducts **3**–**7** are consistent with their MS, ^{1}H and ^{13}C NMR data. Thus, characteristic signals are those of the methylene protons of the CH_2CO_2R group which appear as doublets in *exo* position (δ 2.47 and 2.78 for **3**; δ 2.29 and 2.83 for **7**) and as a singlet in *endo* position (δ 2.67 for **6**). Similarly, the epoxide methylene protons experience significantly different chemical shifts for *syn* adducts (δ 3.08 and 3.20 for **3**; δ 3.02 and 3.25 for **6**) compared to the *anti* adduct (δ 2.88 and 3.14 for **7**). The proposed structure of cyclobutanol **4** is in agreement with the lack of a keto group and the presence of both a tertiary carbinol (IR: 3601 and 3580 cm^{-1}; ^{13}C NMR: δ 64.7 or 68.9) and a methyne proton ($CHCO_2Et$, δ 3.27). Furthermore, upon treatment with K_2CO_3 retroaldolisation of **4** quantitatively gave **3**, thereby confirming the *endo* configuration of the methoxy group for the latter. The relative configuration of the ethoxycarbonyl group for **4** could not be determined by NOE experiments and is proposed to be *syn* to the bridgehead hydrogen (C-1) for steric reasons. For **5**, the *E* configuration of the double bond was secured by the observation of a 10% NOE effect between H-1 and the vinylic proton.

These results show that the intermediate adduct **8** is hydrolyzed under neutral conditions to give **3** which undergoes a water-catalyzed aldol condensation owing to a strong proximity effect. However, if base is added, the cyclobutanol is unstable and gives back **3**. On the other hand, under acidic conditions, the stabilized allylic oxonium ion **9** is produced (Scheme 2) and affords **5** (**3** does not give **5** upon exposure to 0.5 M H_2SO_4). The observed *E* configuration of **5** may thus result from deprotonation of conformer **9a** which should be more stable than **9b**.

Then, cycloaddition of ketene acetal **10** with **1** was carried out and a single sensitive tricyclic adduct **11** was isolated in 46% yield (Scheme 3). The proposed structure of **11** is consistent with ^{1}H and ^{13}C NMR spectra and the relative configurations of the three stereogenic centers are proposed on the basis of an anticipated *syn-endo* addition.

In conclusion, cycloaddition of **1** with unsaturated ketene acetal **2** afforded, under very mild conditions (0 °C), highly functionalized adducts (depending on work-up conditions) resulting from inverse electron demand Diels–Alder. Such a process was not observed for the conformationally locked

Table 1 Isolated yields of adducts from condensation of **2** and **1**

Work-up procedure	**3**	**4**	**5**	**6**	**7**
K_2CO_3, 2 h, 0 °C	50	0	0	6	4
Water, 20 °C, 14 h	3	31	0	5	0
0.5 M, H_2SO_4, 20 °C, 3 h	9	0	48	7	0

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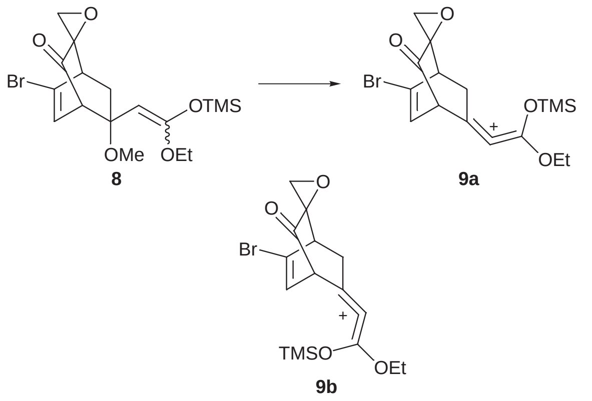
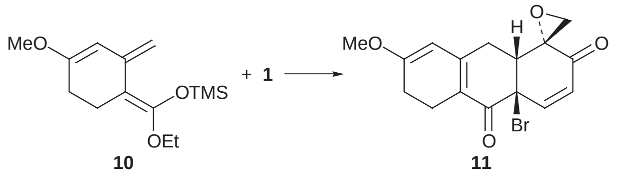


Scheme 2



Scheme 3

10 which led to tricyclic adduct **11**. This may be a useful strategy for the regioselective synthesis of linear polycyclic compounds.

Experimental

Melting points were measured on a Tottoli Büchi 510 apparatus and are uncorrected. NMR spectra were determined on a Brüker WP 200 SY, by using $CDCl_3$ as solvent with TMS as internal standard. Assignment of all ^1H NMR and ^{13}C NMR spectra were achieved using DEPT and 2D (HETCOR) methods. IR spectra were recorded on a Nicolet Magna 750 FT.IR, using CCl_4 as solvent. High resolution MS were performed by the 'Service Central de Microanalyse' (CNRS, Lyon).

General Procedure for Cycloaddition.—A solution of dienone **1** (400 mg, 2 mmol) and diene **2** (1.5 equiv) in THF (4 mL) was allowed to react at 0 °C for 2 h. Work-up with a solution of K_2CO_3 (2 h, 0 °C), extraction with CH_2Cl_2 and flash chromatography (hexane–EtOAc, 95:5 to 50:50) gave **3** (50%), **6** (6%) and **7** (oil, 4%). After work-up with water (14 h, r.t.) and extraction as usual, flash chromatography using hexane–EtOAc as eluent (95:5) gave 4 (white solid, 31%) together with **3** (3%) and **6** (5%). Work-up with 0.5 M H_2SO_4 (3 h, r.t.) followed by extraction as usual and flash chromatography using hexane–EtOAc (95:5 to 50:50) gave **5** (white solid, 48%) together with adducts **3** (oil, 9%) and **6** (oil, 7%).

3: ν_{max}/cm^{-1} 1748, 1618; δ_H 1.26 (t, $J = 7.3$ Hz, 3 H, CH_3), 2.09 (dd, $J = 14.6$ and 3.6 Hz, 1 H, H-8), 2.47 and 2.78 (ABq, $J = 14$ Hz, 2 H, CH_2CO_2), 2.57 (dd, $J = 14.6$ and 2.4 Hz, 1 H, H-8), 2.71 (app. q, $J = 2.4$ Hz, 1 H, H-4), 3.08 and 3.20 (ABq, $J = 6.8$ Hz, 2 H, CH_2), 3.23 (s, 3 H, OCH_3), 3.73 (d, $J = 7.3$ Hz, 1 H, H-1), 4.17 (q, $J = 7.3$ Hz, 2 H, OCH_2), 6.30 (dd, $J = 7.3$ and 2.3 Hz, 1 H, H-6); (C 14.0 (CH_3), 36.7 (C-8), 41.6 (CH_2CO_2), 48.2 (C-4), 50.5 (OCH_3), 52.4 (C-9), 57 (C-3), 59.1 (C-1), 60.6 (OCH_2), 79.3 (C-7), 124 (C-5), 125.4 (C-6), 168.8 (COO), 202 (C-2); HRMS EI; *m/z* (M^+) calc. 344.02591, found 344.02593.

4: mp 136-137 °C; ν_{max}/cm^{-1} 3601, 3580, 1747, 1618; δ_H 1.28 (t, $J = 7.3$ Hz, 3 H, CH_3), 1.43 (d, $J = 13.1$, 1 H, H-8), 2.33 (m, 1 H, H-4), 2.66 and 3.0 (2 d, $J = 4.4$ Hz, 2 H, CH_2 epoxide), 2.94 (d, $J = 5.9$ Hz, 1 H, H-1), 3.24 (d, $J = 13.1$ Hz, 1 H, H-8), 3.27 (s, 4 H, $CHCO_2$, OCH_3), 4.20 (m, 2 H, OCH_2), 6.17 (dd, $J = 5.9$ and 2 Hz, 1 H, H-6); δ_H 14.1 (CH_3), 27.9 (C-8), 47.7 (C-9), 49.0 (C-4), 52.4 (OCH_3), 53.6 (C-1), 57.2 (CH), 60.6 (CO_2CH_2), 64.7 and 68.9 (C-3 and C-2), 76.3 (C-7), 124.6 (C-6), 125.7 (C-5), 169.4 (CO); MS CI (NH_3) *m/z* 362 and 364 $(M + NH_4)^+$.

5: mp 97–98 °C; ν_{max}/cm^{-1} 1750, 1719, 1654, 1605; δ_H 1.28 (t, $J = 7.3$ Hz, 3 H, CH_3), 2.90 (q, $J = 2.4$ Hz, 1 H, H-4), 3.17 (m, 4 H, H-8 and H-9), 3.95 (d, $J = 6.6$ Hz, 1 H, H-1), 4.18 (q, $J = 7.3$ Hz, OCH_2), 5.93 (t, $J = 2.2$ Hz, 1 H, HC =), 6.45 (dd, $J = 6.6$ and 2.4 Hz, 1 H, H-6); δ_C 14.2 (CH_3), 31.3 (C-8), 48.8 (C-4), 52.4 (C-9), 56.8 (C-3), 60.2 (OCH_2), 62.2 (C-1), 117.8 (HC =), 124.8 (C-5), 125.8 (C-6), 151 (C-7), 165.4 (CO), 198 (C-2); HRMS EI *m/z* (M^+) calc. 311.9997, found 311.9997.

6: ν_{max}/cm−1 1754, 1741, 1608; δ_H 1.29 (t, $J = 7.3$Hz, 3H, CH_3), 2.17 (dd, $J = 13.9$ and 2.9 Hz, 1 H, H-8), 2.33 (dd, $J = 13.9$ and 3 Hz, 1 H, H-8), 2.64 (s, 2 H, CH_2CO_2), 2.70 (m, 1 H, H-4), 3.02 and 3.25 (ABq, $J = 5.9$ Hz, 2 H, CH_2 epoxide), 3.30 (s, 3 H, OCH_3), 3.74 (d, $J = 7.3$ Hz, 1 H, H-1), 4.16 (q, $J = 7.3$ Hz, OCH_2), 6.30 (dd, $J = 7.3$ and 2.3 Hz, 1 H, H-6); δ_C 14.1 (CH_3), 35.1 (C-8), 41.5 (CH_2CO_2), 49.2 (C-4), 50.4 (OCH_3), 52.1 (C-9), 55.9 (C-3), 58.9 (C-1), 60.9 (OCH_2), 80.9 (C-7), 125.9 (C-6), 126.7 (C-5), 169.1 (CO), 199.8 (C-2); HRMS EI *m/z* (M^+) calc. 344.02591, found 344.02593.

7: δ_H 1.26 (t, $J = 7.3$ Hz, 3 H, CH_3), 2.11 (dd, $J = 14.6$ and 3.4 Hz, 1 H, H-8), 2.29 (d, $J = 14.3$ Hz, 1 H, CH_2CO_2), 2.54 (dd, $J = 14.6$ and 2.8 Hz, 1 H, H-8), 2.71 (m, 1 H, H-4), 2.83 (d, $J = 14.3$ Hz, 1 H, CH_2CO_2), 2.88 and 3.14 (ABq, $J = 6.6$ Hz, 2 H, CH_2 epoxide), 3.25 (s, 3 H, OCH_3), 3.73 (d, $J = 7.3$ Hz, 1 H, H-1), 4.17 (q, $J = 7.3$ Hz, OCH_2), 6.32 (dd, $J = 7.3$ and 2.3 Hz, 1 H, H-6); δ_C 14.1 (CH_3), 38.2 (C-8), 42.0 (CH_2CO_2), 48.4 (C-4), 50.7 (OCH_3), 52.3 (C-9), 57.7 (C-3), 59.7 (C-1), 60.9 (OCH_2), 78.4 (C-7), 124 (C-6), 125.4 (C-5), 169 (CO), 202 (C-2).

11: to a solution of **1** (692 mg, 3.44 mmol) in THF (7 mL) at −20 °C, was added a solution of **10** (923 mg, 3.44 mmol) in THF (1 mL). The reaction was then slowly warmed to room temperature and stirring was continued until completion of the reaction (*ca.* 2 h). Evaporation of THF and crystallisation from diethyl ether (0 °C, overnight) gave **11**. This material slowly decomposes on standing and in solution. Mp 138 °C (decomp.); ν_{max}/cm^{-1} 1690, 1646, 1638, 1600, 1549; δ_H 2.37 (broad t, $J = 8.9$ and 8.4 Hz, 2 H), 2.68 (m, 4 H), 2.87 (td, $J = 8.3$ and 1.8 Hz, 1 H, H-9a), 3.16 and 3.20 (ABq, $J = 6.2$ Hz, 2 H, CH_2O), 5.04 (s, 1 H, H-8), 6.25 (d, $J = 9.7$ Hz, 1 H, H-3), 6.89 (dd, $J = 9.7$ and 1.8 Hz, 1 H, H-4); δ_C 21.0, 27.3 and 31.0 (C-5, C-6 and C-9), 49.2 (C-9a), 55.8 (OCH_3), 56.8 (C-11), 59.6 and 64.5 (C-4a and C-1), 96.0 (C-8), 121.0 (C-10a), 129.2 (C-3), 145.0 (C-4), 154.0 and 170.1 (C-7, C-8a), 185.7 (CO), 191.0 (CO); MS EI *m/z* (M^+) 350 and 352.

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