Trapping of Cyclopentadienone as a 4π Component in Diels–Alder Reactions with Ethyl Acrylate: a Simple Synthesis of (±)-Sarkomycin

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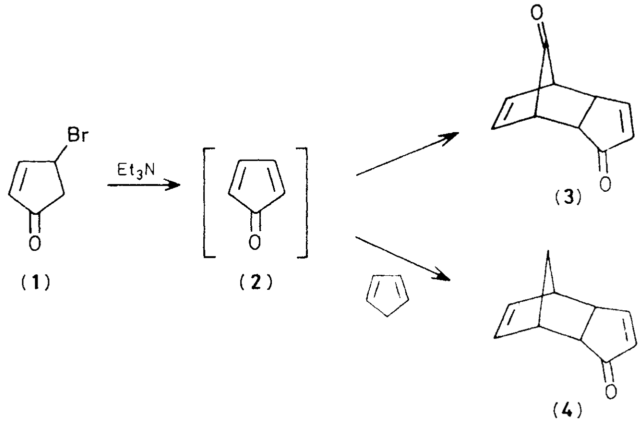
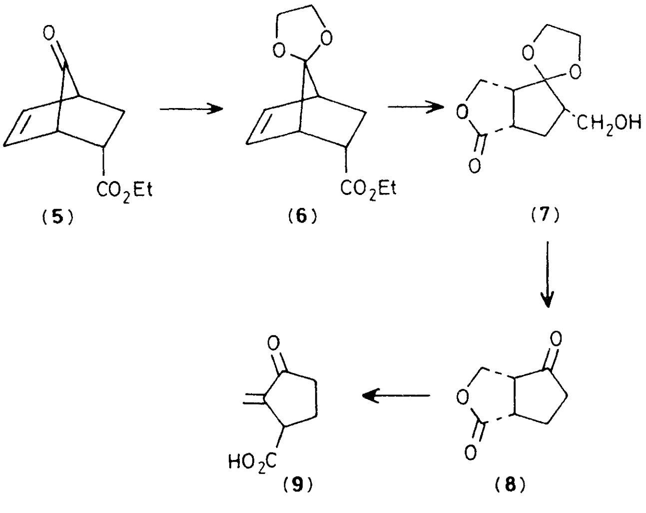
The ability of cyclopentadienone to act as the diene counterpart in Diels–Alder reactions was demonstrated through the isolation of the cycloadduct with ethyl acrylate, which was utilized as the starting point for an expeditious synthesis of (±)-sarkomycin.

The existence of free cyclopentadienone (**2**) has been the subject of debate for many years.[1] Its intermediacy has been invoked to account for the very fast dimerization to give (**3**) and to explain the reaction with cyclopentadiene to produce (**4**)[2] (Scheme 1). However, attempts to force it to act as the 4π component in Diels–Alder reactions using a wide variety of dienophiles were unsuccessful and cast some doubt on its intermediacy.[3]

We now report for the first time the isolation in preparative yield (20%, unoptimized) of the Diels–Alder adduct (**5**) between (**2**), functioning as a diene, and ethyl acrylate, and its utilization as starting material for a straightforward synthesis of sarkomycin (**9**) (Scheme 2). The key for success in the hitherto unsuccessful trapping of (**2**) as a mixed adduct with dienophiles[†] probably lies in its slow generation by simple heating of (**1**) (0.03 mol) in the presence of a ten-fold excess of ethyl acrylate in dimethoxyethane (60 ml) in the absence of base for 3 days. In this way the mixed *endo*-adduct (**5**)[‡] can be isolated from the accompanying dimer (**3**) by simple flash-chromatography.



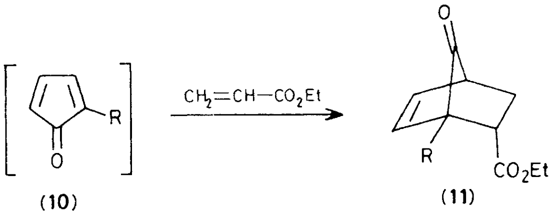
Scheme 1



Scheme 2

Acetalization of (**5**) with 2-methyl-2-ethyl-1,3-dioxolane at room temperature in the presence of toluene-*p*-sulphonic acid proceeded smoothly to give (**6**) in essentially quantitative yield. Ozonolysis of (**6**) (MeOH, −78 °C) followed by reductive quenching with sodium borohydride afforded a 70% yield of crystalline (**7**),[§] the oxidation of which with Jones reagent proceeded with concomitant deacetalization and decarboxylation giving rise to the known cyclosarkomycin (**8**) (38% overall yield). This known precursor was converted into sarkomycin following a published procedure.[5]

We hope that these results will allow the as yet unexplored[6] cyclopentadienone-based strategies for the construction of five-membered rings to be used in syntheses of natural cyclopentanoids. 2-Substituted cyclopentadienones such as (**10a**) or (**10b**), generated in a similar way, gave higher yields (40—50%) of the isolated cycloadducts (**11a**) and (**11b**) with



Scheme 3. **a**; R = Me
b; R = $CH_2CO_2Bu^n$.

[†] The transient (**2**) can be trapped, albeit in less satisfactory yield, by other electron-deficient dienophiles: *e.g.* methyl crotonate (12.5%) and methyl fumarate (7%) but not by electron-rich species (vinyl ethers for instance). These results run counter to calculations of frontier orbital energies, which predict that cyclopentadienones, in the light of the very low energies of their LUMOs, should be more readily trapped by electron-rich species than by electron-deficient compounds.[4]

[‡] Selected spectral data: (**5**), i.r. (neat): 1790 and 1735 cm^{-1}; ^1H n.m.r. (80 MHz; $CDCl_3$): δ 1.27 (t, 3H, *J* 7 Hz), 1.75 (dd, 1H, *J* 5 and 12 Hz), 2.22 (ddd, 1H, *J* 3, 12 and 10Hz), 2.87—3.4 (m, 3H), 4.2 (q, 2H, *J* 7 Hz), 6.4 (dd, 1 H, *J* 7 and 2 Hz), and 6.72 (dd, 1 H, *J* 7 and 3 Hz).

[§] Selected data: (**7**), m.p. 96—97 °C: i.r. (Nujol): 3450 and 1765 cm^{-1}; ^1H n.m.r. (80 MHz; $CDCl_3$): δ 1.82—2.6 (m, 4H), 3.1 (m, 1H), 3.67 (s, 1H), 3.75 (m, 2H), 4.1 (m, 4H), and 4.4 (m, 2H).

ethyl acrylate in view of their much lower tendency to dimerize than (**2**) (Scheme 3).

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