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Diels-Alder Reaction of Furan with Methyl 3-Bromopropiolate: a Route to Methyl 3-Oxo-7-Oxabicyclo[2.2.1]hept-5-en-2-carboxylate

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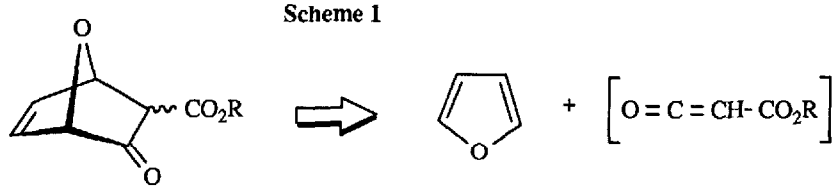
Abstract: The two epimers of methyl 3-oxo-7-oxabicyclo[2.2.1]hept-5-en-2-carboxylate have been prepared from furan and methyl 3-bromopropiolate as a methoxycarbonylketene equivalent. The final step required hydrolysis of acetals by Nafion-H.

7-Oxabicyclo[2.2.1]hept-5-en-2-yl derivatives, in an optically active form, are powerful starting materials as chiral templates ("naked sugars") for the synthesis of numerous natural compounds such as sugars, C-nucleosides, conduritols, etc..[1] On the other hand, as a part of our studies directed toward the synthesis of 6-substituted analogues of shikimic acid *via* the base-promoted opening of bicylic esters,[2] we looked for an access to the previously unknown β-keto esters **1** as potentially useful synthons. Possible routes to such compounds involve a Diels-Alder reaction between furan and a alkoxycarbonylketene equivalent as dienophile (Scheme 1).

Scheme 1



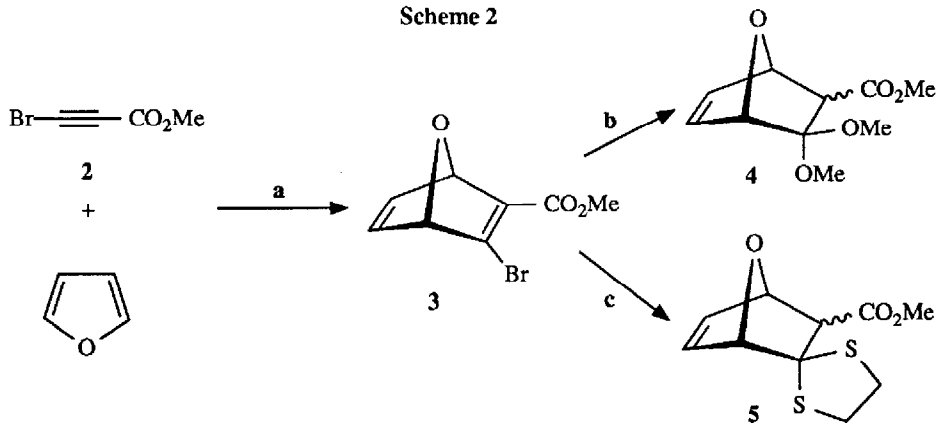
1

A number of such equivalents have been described, including methylthiomaleic anhydride,[3] 1,3-diethoxycarbonylallene,[4] and various 3-substituted propiolates. While preparation of the anhydride proved to be tedious, condensation of the readily available allene with furan, led to the expected adduct as a single *endo* isomer.[5] At this stage, we were faced to the tricky problem of selective ozonolytic cleavage of an exocyclic double bond *vs.* an endocyclic one. As a route to C-nucleosides, Kozikowski and co-workers carried out this cleavage after prior *cis*-dihydroxylation of the more reactive endocyclic double bond then acetonide formation.[4] In our case, as attempted (protective) bromination[6] of this bond led to a complex mixture, we sought another strategy.

Among the envisioned acetylenic equivalents, methyl 3-methoxypropiolate was precluded as too hazardous,[7] whereas preparation of the reactive ethyl 3-phenylsulfonylpropiolate[8] *via* that of its precursor, ethyl 3-phenylthiopropiolate, another ketene equivalent,[7] proved to be delicate in our hands. Finally, we

turned to methyl 3-bromopropiolate (**2**)[9] already used as a methoxycarbonyl ketene equivalent in Diels-Alder reactions with cyclopentadiene and cyclohexadiene.[10] We found that in benzene (80 °C, 24 h) the alkyne **2** also underwent a smooth Diels-Alder reaction with furan, a less reactive diene, affording the fairly stable adduct **3** in 43-60% yield after bulb to bulb distillation (Scheme 2).[11]

Scheme 2



Reagents and conditions: **a**, C_6H_6, 80 °C, 24 h (43-60%); **b**, CH_3ONa, CH_3OH, r.t.-30°C (45-55%); **c**, 1,2-Ethanedithiol, NaH, THF

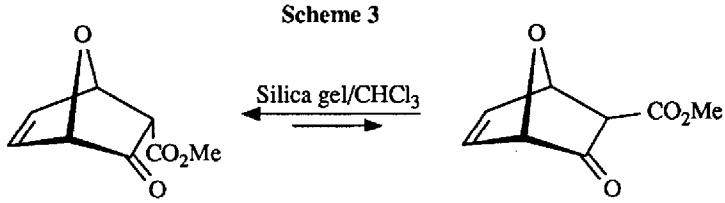
The diene **3** reacted exothermically with sodium methoxide in methanol to give a *ca.* 90:10 *endo/exo* mixture of the epimeric acetals **4**.[12] These two isomers were readily separated by column chromatography on silica gel (45-55% overall yield) and unambiguously identified on the basis of their ^{1}H NMR spectra. Particularly, in such systems, it has been well established that $J_{H1,H2}$= 0 or ~ 4 Hz whether H-2 is in an *endo* or an *exo* position.[13]

In contrast with their carbocyclic analogues, these acetals were found to be dramatically reluctant to hydrolysis into ketones. Mild reagents such as oxalic or sulfuric acid on wet silica gel,[14] lithium tetrafluoroborate in wet acetonitrile,[15] and 1 N aqueous hydrochloric acid in tetrahydrofuran[16] (2 days, r. t.) left the adduct *endo*-**4** unchanged. On the other hand, dilute aqueous sulfuric acid in THF led to uncomplete hydrolysis with concomitant partial epimerization of the expected keto ester as indicated by ^{1}H NMR analysis. Amberlyst-15 in wet acetone,[17] although leading to clean hydrolysis without epimerization, required an exceedingly long reaction time since only a 7% conversion was reached within the first 6 days (92% conversion needed weeks despite renewal of the resin). Finally, the perfluorosulfonic acid resin Nafion®-501, H^+ form (Nafion-H), was found to be the best catalyst.[18] In the absence of additional water, the acetal functions of the epimers *endo*- and *exo*-**4** were decomposed sluggishly into ketones, affording the corresponding β-keto esters *endo*- and *exo*-**1a** (Scheme 1, **1**: R= Me) within 3-4 days without noticeable epimerization (68-83% yield after bulb to bulb distillation. Contamination by diacetone alcohol *i.e.* 4-hydroxy-4-methyl- pentan-2-one, resulting from the acid catalyzed acetone self-condensation, appeared after 3 days).[19] Attempts of shortening the reaction time by the use of aqueous acetone failed since no hydrolysis was observed within 5 days, even with a fivefold excess of Nafion-H with respect to Olah's conditions.[18]

As their carbocyclic analogues, the two keto esters **1a** appeared to exist exclusively in the keto form, as indicated by IR, ^{1}H and ^{13}C NMR. In contrast to these analogues, no epimerization was observed during distillation at 70-90 °C whereas this reaction accompanied all attempts of purification by silica gel

chromatography on plates or columns; starting from one epimer or the other led invariably to a mixture of the both. This observation was confirmed by an equilibration experiment. When the epimer *endo*-**1a** was stirred for 20 h with silica gel in chloroform, a 75:25 *endo*-**1a**/*exo*-**1a** mixture was obtained (Scheme 3). Thermal equilibration of the carbocyclic analogues of **1a** led to an opposite ratio of 40:60.[10]

Scheme 3



Endo-**1a** *Exo*-**1a**

As our initial attempts of acetal hydrolysis failed, we examined also the dithioacetal moiety, another masked ketone form. When the diene **3** was added to a slurry of sodium dithiolate in THF prepared from 1,2-ethanedithiol (1 equiv) and sodium hydride (1.3 equiv), a 63:37 mixture of the epimeric dithiolanes *endo*- and *exo*-**5** was obtained. The two compounds were separated by silica gel column chromatography (34% overall yield) and submitted to removal of the dithioacetal protecting group. Some mild reagents were examined either on *endo*- or *exo*-**5**. *N*-Chlorosuccinimide (NCS) in presence of silver nitrate[20] led to a few untractable mixture whereas mercury (II) chloride/calcium carbonate in acetonitrile/water[21] or "claycop"[22] (prepared from copper (II) nitrate trihydrate and K 10 montmorillonite) left the starting compound unchanged. This inertness still contrasts with the "normal" reactivity of the (*exo*) carbocyclic analogue when treated with NCS/silver nitrate.[10] Although *S,S*-acetals are currently more resistant to hydrolysis than *O,O*-acetals, especially when cyclic,[23] the unusual lack of reactivity of **5** can be attributed to the retarding inductive effect of the 7-oxa bridge on the formation of cationic intermediates at C-3. This effect may also account for the reluctance of the acetal **4** to hydrolysis. An opposite effect *i.e.* rate enhancing, has been observed by Vogel *et al.* in one-carbon ring expansions of 7-oxabicyclo[2.2.1]heptan-2-one derivatives with diazomethane.[24]

References and Notes

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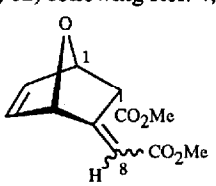
5. Condensation was conducted with the dimethyl ester (Bryson, T. A.; Dolak, T. M. *Organic Syntheses* *57*, 62) following Ref. 4, in benzene at 40 °C for 24 h.



The *endo* isomer (49% yield after silica gel column chromatography) was characterized by ^{1}H NMR: ($CDCl_3$, 200 MHz) δ (ppm)/TMS 3.67 (s, 6 H, Me), 3.97 (dd, 1 H, $J_{2,1}$ 4.4 and $J_{2,8}$ 2.2 Hz, H-2), 5.23 (~ quint, 1 H, J ~ 0.8 Hz, H-4), 5.28 (br dm, 1 H, $J_{1,2}$ 4.4 Hz, H-1), 6.04 (dt, 1 H, $J_{8,2}$ 2.2 and J 0.6 Hz, H-8), 6.38 (dd, 1 H, J 5.7 and 1.6 Hz, H-5 or H-6), 6.53 (dd, 1 H, J 5.7 and 1.8 Hz, H-6 or H-5). The stereochemistry at C-8 is uncertain.

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11. All new compounds reported here gave satisfactory spectroscopic and analytical data. Compound **3**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.79 (s, 3 H, Me), 5.33 (t, 1 H, *J* 1.7 Hz, H-1 or H-4), 5.70 (t, 1 H, *J* 1.6 Hz, H-4 or H-1), 7.19 (dd, 1 H, *J* 5.3 and 1.8 Hz, H-5 or H-6), 7.24 (dd, 1 H, *J* 5.3 and 1.7 Hz, H-6 or H-5).
12. In a typical experiment, the diene **3** in MeOH was added dropwise to 1 M sodium methoxide in MeOH. During the addition, the temperature was not allowed to exceed 30 °C by external cooling. After the addition, stirring was continued overnight and the products extracted with diethyl ether after acidification with dilute aqueous hydrochloric acid. A 46:54 *endo/exo* ratio of the epimers **4** was also incidentally obtained in these conditions.
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19. In a typical experiment, the acetal *endo*-**4** (650 mg, 3.03 mmol) was stirred in freshly distilled acetone (13 ml) with Nafion-501, H^+ form (346 mg) for 3-4 days (monitoring by ^{1}H-NMR: progress of hydrolysis was ≥ 96% within 3 days with diacetone alcohol appearing beyond 3 days. After 4 days, *ca.* 2% of acetal were still present). After filtration, the solvent was removed by rotary evaporation at 20-30 °C under water-pump pressure, leaving an oil which was bulb to bulb distilled at 70 °C (oil bath) under *ca.* 0.05 mmHg to give the ketone *endo*-**1a** as a colourless oil (420 mg, 83%). An analytical sample was obtained by an aqueous washing/extraction (diethyl ether) treatment. After drying ($MgSO_4$) of the organic extracts, filtration, evaporation and distillation as above gave the *ketone endo*-**1a**. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.41 (d, 1 H, $J_{2,1}$ 4.0 Hz, H-2), 3.72 (s, 3 H, Me), 4.77 (dd, 1 H, $J_{4,5}$ 2.0 and *J* 0.8 Hz, H-4), 5.37 (br d~quint, 1 H, $J_{1,2}$ 4.0 and *J* ~0.8 Hz, H-1), 6.44 (br dd, 1 H, $J_{5,6}$ 5.7 and *J* 2.0 Hz, H-5), 6.99 (dd, 1 H, $J_{6,5}$ 5.7 and *J* ~1.6 Hz, H-6). Epimer *exo*-**1a**: 2.93 (s, 1 H, H-2), 3.78 (s, 3 H, Me), 4.70 (~dt, 1 H, *J* ~1.9 and 0.9 Hz, H-4), 5.59 (br t, 1 H, *J* ~0.9 Hz, H-1), 6.58 (br dd, 1 H, $J_{5,6}$ 5.8 and *J* 1.9 Hz, H-5), 6.76 (dd, 1 H, $J_{6,5}$ 5.8 and *J* 1.7 Hz, H-6). For the both epimers, H-5 and H-6 signals were tentatively assigned. A NOESY experiment on the *endo*-**1a** epimer was not fully satisfactory, while homonuclear irradiation of H-1 (both epimers) gave a single doublet for the most deshielded vinylic proton signal. IR (CCl_4) ν (cm^{-1}): *endo*-**1a**, 1728, 1768; *exo*-**1a**, 1732, 1770.
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