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USEFUL NEW ANNULATION REACTIONS OF VICINAL DICARBOXYLIC ESTERS

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Summary: A new annulation process has been developed for the efficient synthesis of the bicyclic keto esters **1** and **6**, desired intermediates for the total synthesis of bilobalide (**2**). A number of other annulations are described which allow the generation from **3** of a variety of functionalized products (**7**-**11**).

The bicyclic keto ester **1** is a potential intermediate for the synthesis of bilobalide (**2**)[1] which contains all the carbon atoms of **2** except for the *t*-butyl group. This report describes a simple and effective method for the synthesis of **1** and illustrates more generally an annulation methodology which leads to a variety of useful functional group patterns in the annulated unit.

The readily available *cis*-4-cyclohexen-1,2-dicarboxylic acid dimethyl ester was transformed into the known dianion **3**[2] (2.2 equiv. LDA, 3 equiv. HMPA in THF at –78°C for 0.5 hr. and 0°C for 0.25 hr.)[3] which was treated at –78°C with 2,6-dichlorophenyl acrylate. After 3 hr. at –78°C the mixture was quenched with acetic acid and the product was isolated by extractive workup and column chromatography on silica gel to give the desired ketone **1** in 67% yield. The formation of **1** is considered to proceed by Michael addition-phenoxide elimination to form an intermediate ketene **4** which cyclizes to give the enolate **5**. Support for this pathway as opposed to a Claisen-Dieckmann ring closure comes from the observation that phenyl acrylate affords **1** in considerably lower yield (*ca.* 40%). The enolate **5** can be trapped and isolated as the trimethylsilyl (TMS) enol ether by reaction with TMS chloride or converted via the α-phenylseleno ether to the α,β-enone **6**.[4,5]

The successful conversion of **3** to **1** prompted the study of a number of other tranformations of **3** to bicyclic products in which the newly appended ring was functionalized differently. Reaction of **3** with methyl 2-bromomethylacrylate[6] (rapid addition, 1.5 equiv., –78°C, 15 min.) gave the bicyclic α-methylene ketone **7**[5] in 83% yield; none of the double Michael product was detected. This process provides an unusually direct entry into the biologically interesting α-methylene cyclopentanone system.

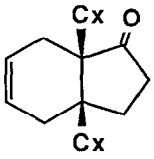
The synthesis of the bicyclic sulfone **8** was best accomplished from the mono anion of 4-cyclohexen-1,2-dicarboxylic acid dimethyl ester (1.1 equiv. LDA in THF at –78°C for 20 min.) by reaction with 1.5 equiv. of phenyl 1-bromomethylvinyl sulfone[7] (–78°C, 15 min.) to form the monoalkylation product (75% isolated yield) followed by cyclization in THF solution at 23°C with 0.08 equiv. of potassium *t*-butoxide as catalyst for 3 hr. The sulfone **8** was obtained in 80% yield as a 4:1 mixture of diastereomers differing in orientation of the sulfonyl group. Treatment of the diastereomeric mixture **8** with 2 equiv. of LDA in THF at –78°C for 30 min. followed by oxidation of the resulting anion with MoO_5.pyridine.HMPA[8] (–78°C, 30 min.) yielded bicyclic keto ester **9** (79%).[5]

The dianion **3** was directly transformed into the bicyclic diene **10**[5] by reaction with 2-chloromethylallyl chloride in THF solution (0 to 20°C over 15 min.) in 71% yield. The reaction of **3** in THF-HMPA at –78°C with *t*-butyl (Z)-2-tosyloxy-vinyl ketone[9] for 4 hr. afforded the double Michael product **11** (82% yield)[5] rather than the alternative Michael-aldol adduct **12**. The conversion of **3** to **11** is an unusual example of cyclopropanation by the Michael pathway.

The annulations of the Diels-Alder adduct of butadiene and dimethyl maleate described herein lead to a variety of versatile synthetic intermediates (**1**, **6**-**11**) in good yield. Sequential use of these new annulations with the Diels-Alder process is potentially a very powerful tactical combination of considerable scope and utility. Since similar reactions with other vicinal dianionoid systems should be possible, the implications of the present results are broad. The use of **1** as a key intermediate in the total synthesis of **2** is currently under study. The following procedures are illustrative.[10]

Bicyclo[4.3.0]non-7-en-2-one (**1**). A solution of 2.2 mmole of lithium diisopropylamide in 10 ml. of dry THF (prepared from 0.31 ml. (2.2 mmole) of freshly distilled diisopropylamine and 1.38 ml. of a 1.6 N solution of *n*-BuLi in hexane at 0°) was cooled to –78° and treated with 0.5 ml. of HMPA. A solution of 198 mg. (1.0 mmole) of dimethyl *cis*-4-cyclohexen-1,2-dicarboxylate in 2.0 ml. of dry THF was added dropwise by cannula over 2 min. and the resulting solution was stirred at –78° for 40 min. to generate the orange-yellow monoanion. A red solution of dianion **3** was formed upon warming to 0° and stirring at 0° for 15 min. This solution was cooled to –78° and a solution of 2,6-dichlorophenyl acrylate (217 mg. 1.0 mmole) in 2.0 ml. of THF was added by cannula. The reaction mixture was stirred at –78° for 3.0 hours and quenched by addition of 5 mmoles of acetic acid in 5 ml. of diethyl ether. After warming to 23°, the mixture was poured into 10 ml. of 1 N hydrochloric acid solution. The organic phase was separated and the aqueous layer was extracted with three 20-ml. portions of ether. The combined organic extracts were washed sequentially with 10 ml. of 1 N sodium hydroxide solution, 10 ml. of water and 10 ml. of brine. Drying over magnesium sulfate, concentration in vacuo and flash chromatograph on silica gel (30g. using 8:1 hexane-ethyl acetate as eluent) provided 169 mg. (67%) of ketone **1** as an oil which solidified in a freezer at –20°. Found for **1**; PMR (270 MHz, $CDCl_3$): δ(ppm) 2.00 (m, 1H), 2.13 (dm, J=17Hz, 1H), 2.30-2.70 (m, 6H), 3.71 (s, 3H), 3.72 (s, 3H), 5.65 (s, 2H); IR (neat): 2960, 1755, 1730 (cm^{-1}); MS (FAB): calcd: 252; found: m/e 253 ($M + H^+$).

3-Methylenebicyclo[4.3.0]non-7-en-2-one (**7**). A solution of 2.2 mmole of lithium diisopropylamide in 17 ml. of dry THF[3,5] was prepared from 0.42 ml. (*ca.* 3 mmole) of diisopropylamine and 0.94 ml. of 2.35 N solution of *n*-BuLi in hexane, cooled to –78° and treated with 0.5 ml. of HMPA. A solution of 198 mg. (1 mmole) of dimethyl *cis*-4-cyclohexene-1,2-dicarboxylate in 1 ml. of THF was added dropwise over 1 min. and the solution was stirred for 30 min. at –78° by which time the orange color characteristic of the monoanion has developed. Formation of the deep red dianion[4] occurs upon warming to 0° and maintaining the solution at that temperature for 15 min. The solution of **3** was cooled to –78°, and treated with a cold (–78°) solution of 269 mg. (1.5 mmole) of methyl 2-bromomethylacrylate[6] (added rapidly via a dry-ice cooled stainless steel cannula). The reaction mixture immediately became colorless. After stirring for an additional 15 min. at –78° the reaction was quenched by addition of 10 mmoles of propionic acid in 3 ml. of THF, brought to 20° and concentrated *in vacuo*. The product was isolated by partitioning between chloroform and water, washing of the chloroform layer, concentration and chromatography on silica gel (ether-hexane, 2:1) to afford 206 mg. (83%) of enone **7** as a colorless oil. Found for **7**; PMR (270 MHz, $CDCl_3$): δ(ppm) 2.04 (dt, J=3Hz, 19Hz, 1H), 2.52-2.70 (m, 4H), 3.16 (dt, J=3Hz, 17Hz, 1H), 3.67 (s, 3H), 3.68 (s, 3H), 5.49 (s, 1H), 5.62 (m, 2H), 6.20 (t, J=2Hz, 1H); IR (neat): 3030, 2950, 1740, 1730, 1640 (cm^{-1}); MS (EI): calcd: 264; found: 264 (M^+); UV (λmax): 228 nm (MeOH).



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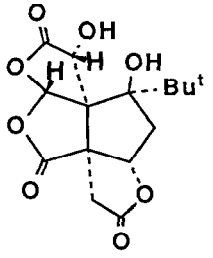

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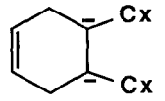

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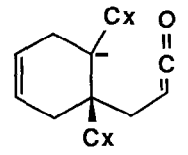

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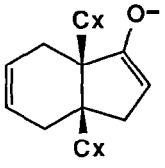

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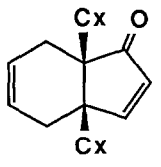

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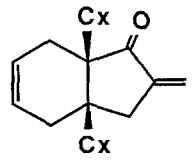

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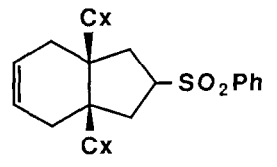

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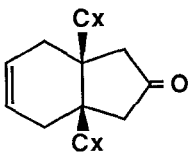

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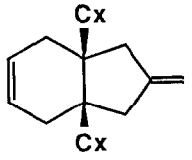

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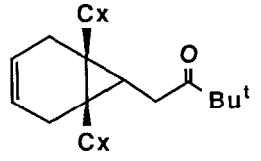

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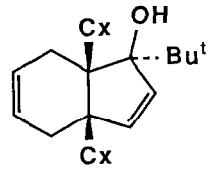

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Cx=COOCH$_3$

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2. Bilyard, K. G.; Garratt, P.J.; Zahler, R., *Synthesis,* **1980**, 389 and refs. therein.

3. Abbreviations used herein: LDA, lithium diisopropylamide; HMPA, hexamethylphosphoric triamide; THF, tetrahydrofuran. All organometallic reactions were conducted with dry solvents.

4. The dianion **3** has previously[2] been converted to annulated products by double S_N2 reaction with 1,3- or 1,4-dihalides. Reaction of **3** with ethyl 4-bromobutyrate to form *cis*-dimethyl 1,2,3,5-tetrahydro-1-oxo-4a(4H), 8a(8H)-napthalene dicarboxylate has also been reported: Bilyard, K.G.; Garratt, P. J., *Tetrahedron Letters,* **1981**, *22*, 1755.

5. Since chromotographic and 270 MHz PMR spectral analysis indicates the formation of a single stereoisomer in the annulation the ring fusion is doubtless *cis*. All organometallic reactions were conducted under an inert atmosphere.

6. Villieras, J.; Rambaud, M., *Synthesis,* **1982**, 924.

7. Knochel, P.; Normant, J. F., *Tetrahedron Letters,* **1985**, *26*, 425.

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9. This ketone was synthesized from pinacolone by α-formylation (ethyl formate-NaH) and subsequent reaction with tosyl chloride. The *Z*-stereochemistry is assigned from an observed coupling constant for the olefinic protons of 7.25 Hz.

10. This research was supported by grants from the National Institutes of Health and the National Science Foundation.

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