A NOVEL, ONE-STEP ANNULATION PROCESS FOR THE SYNTHESIS OF RING-FUSED 2-CYCLOPENTENONES

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Summary: The reaction of the dilithio derivative of dimethyl *cis*-4-cyclohexen-1,2-dicarboxylate with 3-substituted propiolic acid phenyl esters proceeds via an unusual mechanistic path to generate fused bicyclic 2-cyclopentenones in a single step.

The first total synthesis of a member of the gingkolide family, (\pm) -bilobalide (1),¹ has recently been realized using as a key intermediate bicyclic keto ester 2, which contains all of the carbon atoms required for the construction of 1.² The synthesis of 2 can be accomplished in a single step starting from dimethyl *cis*-4-cyclohexen-1,2-dicarboxylate by a highly useful new synthetic process which is detailed herein. These results substantially extend the annulation methodology described in a previous report.³

Dimethyl *cis*-4-cyclohexen-1,2-dicarboxylate was converted to the dilithio derivative **3** (2.2 equiv of LDA, 3 equiv of HMPA in THF at -78°C for 0.5 h and 0°C for 0.25 h)³⁻⁵ and treated at -45°C with 1 equiv of phenyl 3*t*-butylpropiolate.⁶ After 30 min at -45°C and 2 h at 0°C the reaction mixture was quenched by addition of acetic acid and the product was isolated by extraction (after removal of THF *in vacuo* and addition of water) and sg column chromatography. Pure bicyclic keto ester **2** was obtained in 70% yield and was identical with material prepared from keto ester **5**³ by the sequence: (1) α -phenylselenation; (2) oxidation with H₂O₂ and elimination; (3) addition of di-*t*-butylcopperlithium; (4) α -phenylselenation; and (5) oxidation with H₂O₂ and elimination.²



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The reaction of dilithio derivative **3** with phenyl phenylpropiolate proceeded in a similar manner under the conditions described for **2** to give bicyclic enone **6** in 59% yield. Similarly, reaction of dianion **3** with phenyl 3-n-amylpropiolate afforded bicyclic enone **7** in 48% yield.

We have not investigated the reaction of phenyl propiolate esters such as 4 with other vicinal diester dianions, or other types of vicinal dianions. However, it is not unlikely that annulation reactions paralleling those described herein will occur. Esters other than phenyl esters of propiolic acids also have not yet been investigated, although this variable could be significant.

A plausible mechanism for this annulation process is shown on a following page. Conjugate addition of the dilithio reagent to the propiolic ester with loss of phenoxide would lead to ketene 8. Ketene intermediates have been proposed previously for the reaction of 3 with aryl acrylates to form annulated products such as $5.^3$ Ketene 8, which may possibly be in equilibrium with the bicyclo[4.1.0]heptane 9, is not well structured geometrically for ring closure since the distance between the electrophilic ketene carbonyl group and the nucleophilic enolate α -carbon atom is great. It is possible that the cyclization of 8 (or 9) to 11 takes place after electron transfer to a species such as 10. Proton transfer from diisopropylamine to 11 would then give the observed product 2.

Evidence for the intermediacy of **11** in the cyclization was obtained by the study of the reaction of dilithio derivative **3** with propiolic ester **12**. The product of this reaction, obtained in 47% yield, was the tricyclic keto ester **13** as expected on the basis of the intermediate occurrence of a 2-lithio-2-cyclopentenone such as **11**.

The following procedures are presented to provide experimental detail.

Phenyl 3-t-Butylpropiolate (4). To a flame-dried round-bottomed flask were added 0.82 g (10 mmol) of tbutylacetylene and 10 ml of dry THF. After cooling to -78°C, a solution of *n*-butyllithium in hexane (1.4 M solution, 7.1 ml, 10 mmol) was added slowly by syringe. After completion of addition, the reaction mixture was stirred at -78°C for 3.0 h and phenyl chloroformate (1.32 ml, 10.5 mmol) was added. The resulting solution was stirred at -78°C for 30 min and was allowed to warm to 0°C gradually over 3.0 h. Water was introduced and organic phase was separated. The aqueous phase was extracted once with 25 ml of ether and the combined organic extracts were washed with saturated brine, dried (MgSO₄) and evaporated. The phenyl ester 4 was isolated by sg chromatography using 3-10% ether in hexane as eluent; yields ranged between 80-90%.

Keto Diester 2. A solution of *n*-butyllithium (1.57 ml 2.2 mmol) was added by syringe to a solution of 0.31 g (2.2 mmol) of diisopropylamine in 3 ml of dry THF under argon at 0°C. After 20 min at 0°C, the resulting LDA solution was cooled to -78°C and a solution of HMPA (0.50 ml, 2.8 mmol) in 0.5 ml of dry THF was added via cannula followed by a solution of dimethyl 4-cyclohexene-1,2-dicarboxylate (198 mg, 1.0 mmol) in 1.0 ml of



dry THF. The resulting solution was stirred at -78° C for 40 min at which time the cooling bath was removed. The reaction mixture was allowed to warm to 23° C (*ca.* 15 min) and stirred at 23° C for a further 30 min. The deep-red dianion solution was then cooled to -45° C and a solution of phenyl 3-*t*-butylpropiolate (4) (202 mg, 1.0 mmol) in 2.0 ml of dry THF was added via cannula. After stirring at -45° C for 30 min, the reaction mixture was warmed to 0° C and stirred at 0° C for 2.0 h. The reaction was quenched by addition of acetic acid. Dilution with 5% aqueous hydrochloric acid, extraction with ether (3 x 10 ml), washing with saturated brine, drying (MgSO₄) and evaporation furnished crude product which was purified by sg chromatography using 5% EtOAc in hexane as eluent to give 216 mg (70%) of **2**, as a solid mp 64-58°C.^{7,8}

REFERENCES AND NOTES

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- 2. E. J. Corey and W-g. Su, J. Am. Chem. Soc., submitted July, 1987.
- 3. E. J. Corey, W-g. Su, and I. N. Houpis, Tetrahedron Letters, 27, 5951 (1986).
- 4. K. G. Billyard, P. J. Garratt, and R. Zahler, Synthesis, 389 (1980) and refs. therein.
- 5. Abbreviations used herein: LDA, lithium diisopropylamid; HMPA, hexamethylphosphoric triamide; THF, tetrahydrofuran; sg, silica gel. All reactions involving air-sensitive reactants or products were conducted under an atmosphere of dry nitrogen or argon.
- Synthesized from t-butylacetylene by sequential treatment in ether solution with n-butyllithium and phenyl chloroformate at -20°C. See, M. J. Tashner, T. Rosen and C. H. Heathcock, Org. Synth., 64, 108 (1985).
- Found for 2: ¹H NMR (500 MHz, CDCl₃): δ 6.25 (1H, s), 5.86 (2H, m), 3.66 (6H, s), 2.92 (1H, dd, J=2.0 15.2Hz), 2.71 (2H, m), 2.48 (1H, dd, J=2.4, 14.8Hz), 1.20 (9H, s); IR (neat): 3020-2880, 1745, 1710 cm⁻¹; HRMS: calcd. 306.14671, found 306.14669.
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