Tetrahedron Letters,Vol.27,No.25,pp 2885-2888,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

A NOVEL LITHIUM IODIDE-PROMOTED VINYLCYCLOPROPANE-CYCLOPENTENE REARRANGEMENT: EFFICIENT SYNTHESIS OF BICYCLO[3.3.0]OCT-6-EN-2-ONE, VERSATILE BUILDING BLOCK FOR POLYCYCLOPENTANOID NATURAL PRODUCTS[¶]

Shun-ichi Hashimoto, Tomohiro Shinoda, and Shiro Ikegami*
Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-01, Japan

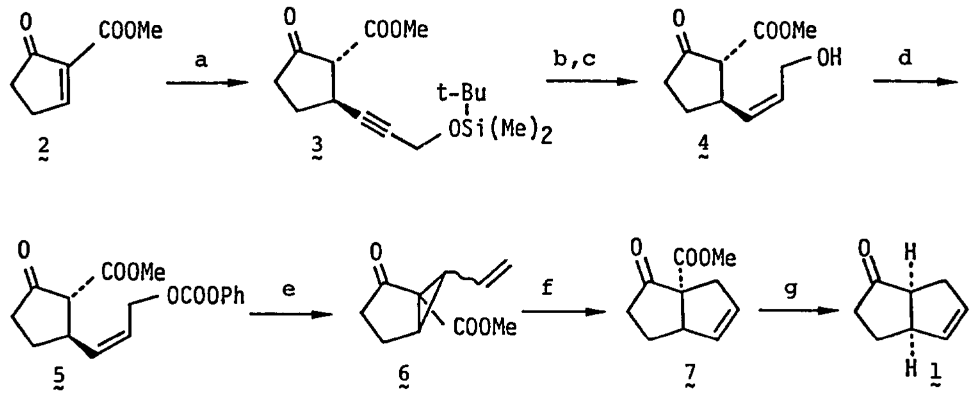
Summary: *Bicyclo[3.3.0]oct-6-en-2-one, a versatile building block for polycyclopentanoid natural products, has been efficiently synthesized from 2-methoxycarbonyl-2-cyclopentenone by employing palladium-catalyzed cyclopropanation and lithium iodide-promoted vinylcyclopropane rearrangement.*

The presence of the bicyclo[3.3.0]octane ring system shared by a wide range of structurally and biologically active polycyclopentanoid natural products has stimulated considerable interests in expedient methods for the synthesis of its functionalized derivatives.[1,2] In connection with synthetic studies in this area, we required a large quantity of bicyclo-[3.3.0]oct-6-en-2-one (1) as a potentially versatile building block. Although several synthetic routes to 1 have been reported,[3,4] their utilities seem to be quite limited because of a troublesome separation of the regioisomers,[3] the requirement of the strictly defined high temperature in thermolysis step,[4] and so on.[4c] Here we wish to report a facile synthesis of 1 starting with the readily available 2-methoxycarbonyl-2-cyclopentenone (2)[5] *via* a stepwise [3+2] annulation process, in which a key feature is the combination of a palladium-catalyzed cyclopropanation and a novel lithium iodide-promoted vinylcyclopropane-cyclopentene rearrangement.

Our initial synthetic approach was the direct cyclization of 2-methoxycarbonylcyclopentanone with a *Z*-allyl unit at the C_3 position (Scheme I). Toward this end, incorporation of a *Z*-allyl unit into 2 was effected as follows.[6] Conjugate addition of 3-(*tert*-butyldimethylsiloxy)propynyldiethylalane (1.5 equiv) to 2 proceeded smoothly in toluene at -78~-40°C to produce the 1,4-adduct (3)[7] [C_2-H, δ3.25, d, $J_{2,3}$=10 Hz] with a C_2-C_3 *trans* relationship[8] in 85% yield. Partial catalytic hydrogenation of 3 with Lindlar catalyst in the presence of quinoline, followed by desilylation with hydrogen fluoride-pyridine in acetonitrile, afforded the *Z*-allyl alcohol (4)[7] [C_2-H, δ2.97, d, $J_{2,3}$=12 Hz; olefinic protons, δ5.43 and 5.79, J=10 Hz] in 95% yield.

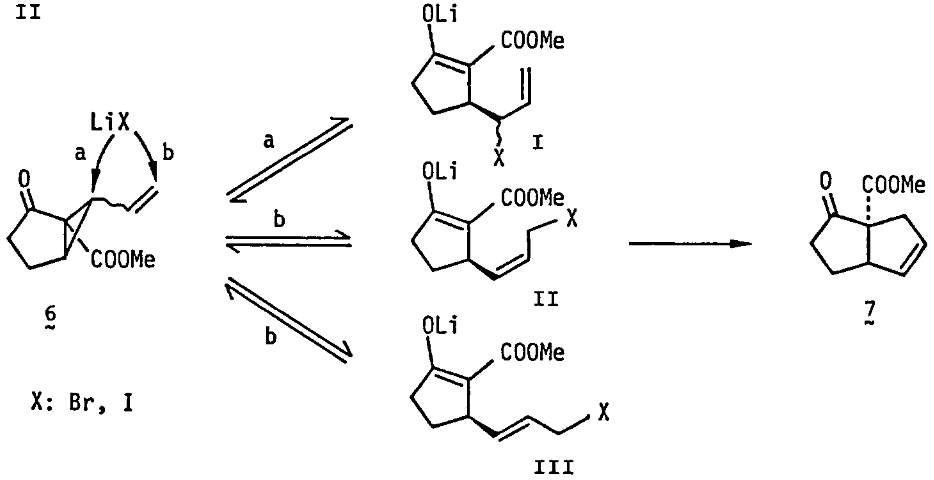
The stage was now set for an examination of the key cyclopentene annulation. Since intramolecular cyclization of the corresponding allyl halide was anticipated to lead to the formation of the three-membered ring on stereoelectronic grounds, cyclization of the *Z*-allyl carbonate (5)[7] *via* a zwitterionic intermediate consisting of π-allylpalladium and stabilized anion moieties was attempted.[9] Treatment of 5 with 3 mol% $Pd(PPh_3)_4$ in the presence of 3 mol% PPh_3 in THF at 10°C for 3 h led to an 82% yield of the vinylcyclopropane (6)[7] as a 3:1 mixture of *exo*- and *endo*-isomers.[10] The structural and stereochemical proof was established by the fact that hydrogenation of the isomers (6) yielded 2-methoxycarbonyl-

Scheme I



(a) $Et_2Al\text{-}C{\equiv}CCH_2OSi(^tBu)Me_2$ (1.5 eq), toluene, -78 to -40°C, 1 h; pH 2.2 buffer soln. (b) 1 atm H_2, Lindlar catalyst, quinoline (7%), benzene, 5°C, 2 h. (c) HF-pyridine, CH_3CN, 20°C, 1 h. (d) PhOCOCl (1.5 eq), pyridine (2 eq), benzene, 20°C, 15 min. (e) $Pd(PPh_3)_4$ (3%), PPh_3 (3%), THF, sealed tube, 10°C, 3 h. (f) LiI or LiBr (2 eq), DMF, 110°C, 3 h. (g) 135°C, 4.5 h.

Scheme II



3-propylcyclopentanone as a sole product,[7] and furthermore by comparison with ^1H and ^{13}C NMR spectra of the pure exo-isomer prepared by the reported method.[11] Under harsh conditions (50°C, 2 h), (E)-2-methoxycarbonyl-3-(1-propenyl)-2-cyclopentenone[7] [olefinic protons, δ 6.65 and 7.30, J=16 Hz] was obtained in 87% yield, no trace of the cyclopentene-annulated product (7) being detected.

Thus, a cyclopentene annulation involving a vinylcyclopropane rearrangement was undertaken. The existing procedures involving thermolytic and rhodium-promoted rearrangement proved to be inappropriate for 6,[4,12,13] and therefore the expeditious method was sought.

After several unsuccessful attempts, we were quite surprised to find that this goal could be readily achieved by heating a mixture of **6** and lithium iodide in DMF. Namely, heating a solution of **6** in DMF containing anhydrous lithium iodide (2 equiv) at 110°C for 3 h and then at 135°C for 4.5 h produced the desired compound (**1**)[14] in 70% yield (83% GLC yield) *via* the rearrangement and subsequent demethoxycarbonylation. Under the same conditions, 6-*exo*-vinylbicyclo[3.1.0]hexan-2-one[4c] resulted in the complete recovery of the starting cyclopropane, suggesting that the presence of a methoxycarbonyl group is essential for the rearrangement. Lithium bromide caused the rearrangement well,[15] but other salts such as LiCl, NaI, or NaBr gave a complex mixture.

The novel lithium iodide-promoted vinylcyclopropane-cyclopentene rearrangement might be explained by the mechanism as shown in Scheme II. Two options exist for a homoconjugate addition to **6** (path a and b).[16] The addition *via* 1,5-mode gives I, which recyclizes exclusively to **6**, because 5-*endo*-trigonal process is disfavored (path a).[17] On the other hand, the addition *via* 1,7-mode produces II and III (path b). III can smoothly recyclize to **6** *via* the favored 3-*exo*-trigonal process,[17] while II can undergo not only a facile cyclopropanation, but also a seemingly infeasible cyclopentene annulation with an interception of p orbitals overlapping in an allyl system. Accordingly, the efficiency of the rearrangement is highly dependent on the factor that only the cyclopentene annulation is irreversible, while the competitive cyclopropanation steps are reversible. Finally, that the cyclopentene annulation process is feasible has been indicated by the reaction of the *Z*-allyl bromide[7] prepared from **4** with lithium hydride (2 equiv) in DMF at -20°C for 3 h to give **7**[18] and **6**[19] in 51% and 28% yields, respectively. Combining the results obtained with NaH (**7**, 21%; **6**,[19] 48%) and KH (**7**, 4%; **6**,[19] 46%), it could be assumed that the lithium cation plays some role probably through chelation in this cyclopentene annulation.

The synthesis of bicyclo[3.3.0]oct-6-en-2-one (**1**) developed here has advantages in allowing operational simplicity and practical value as well as high overall yield (43% from **2**). Furthermore, the route would be, at least in principle, amenable to a chiral synthesis *via* asymmetric conjugate addition.[20]

Exploitation of **1** for the synthesis of biologically active bi- and tricyclopentanoids as well as the scope and potential of the rearrangement is under investigation.

Acknowledgement: We are grateful to Mr. Y. Shimada for his skillful technical assistance and also thank Misses K. Takahashi, M. Nakamura, and J.Takeda for spectral measurements. The partial financial support to this research by Japan Research Foundation for Optically Active Compounds and by Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture is gratefully acknowledged.

References and Notes

¶ This paper is dedicated to Prof. Shun-ichi Yamada on the occasion of his 70th birthday.

1. Reviews: (a) L.A.Paquette, ed., *Tetrahedron*, **37**, 4359~4559 (1981); (b) B.M.Trost, *Chem. Soc. Rev.*, **11**, 141 (1982); (c) M.Demuth and K.Schaffner, *Angew. Chem. Int. Ed. Engl.*, **21**, 820 (1982); (d) L.A.Paquette, *Top. Curr. Chem.*, **79**, 41 (1979); **119**, 1 (1984); (e) M.Ramaiah, *Synthesis*, 529 (1984).

2. For other more recent works, see: (a) M.Koreeda and S.G.Mislankar, J. Am. Chem. Soc., **105**, 7203 (1983); (b) D.L.Boger and C.E.Brotherton, ibid., **106**, 805 (1984); (c) J.P.Marino and E.Laborde, ibid., **107**, 734 (1985); (d) P.Magnus, C.Exon, and P.A.-Robertson, Tetrahedron, **41**, 5861 (1985); (e) I.Shimizu, Y.Ohashi, and J.Tsuji, Tetrahedron Lett., **26**, 3825 (1985).
3. (a) L.A.Paquette, O.Cox, M.Oku, and R.P.Henzel, J. Am. Chem. Soc., **96**, 4892 (1974); (b) Y.Sugihara, T.Sugimura, and I.Murata, ibid., **103**, 6738 (1981); (c) M.Nee and J.D.Roberts, J. Org. Chem., **46**, 67 (1981); (d) J.K.Whitesell, M.A.Minton, and W.G.Flanagan, Tetrahedron, **37**, 4451 (1981).
4. (a) R.D.Miller, J. Chem. Soc., Chem. Commun., 277 (1976); (b) E.J.Corey and R.H. Wollenberg, J. Org. Chem., **40**, 2265 (1975); (c) T.Hudlicky, F.J.Koszyk, T.M.Kutchan, and J.P.Sheth, ibid., **45**, 5020 (1980).
5. A modification of the procedure of Reich et al. was employed. H.J.Reich, J.M.Renga, and I.L.Reich, J. Am. Chem. Soc., **97**, 5434 (1975).
6. Conjugate addition with the mixed cuprate reagent generated from (E)-1-tributylstannyl-1-propenyl-3-tetrahydropyranyl ether[4b] (THF, -78~-35°C, 1 h) produced the 1,4-adduct only in 45% yield. Thus the experiment with the corresponding Z-appendage was not attempted.
7. Satisfactory infrared, pmr, and mass spectroscopic data were obtained for this substance.
8. B.M.Trost and L.N.Jungheim, J. Am. Chem. Soc., **102**, 7910 (1980).
9. For palladium-catalyzed neutral inter- and intramolecular allylation using allylic carbonates, see: (a) T.Takahashi, Y.Jinbo, K.Kitamura, and J.Tsuji, Tetrahedron Lett., **25**, 5921 (1984); (b) J.Tsuji, I.Shimizu, I.Minami, Y.Ohashi, T.Sugiura, and K.Takahashi, J. Org. Chem., **50**, 1523 (1985).
10. The corresponding E-isomer gave the similar result (70%, exo/endo=3/1), implying that the syn-anti isomerization of π-allylpalladium complex via π-σ-π mechanism is more rapid than the nucleophilic attack.[9a]
11. E.Piers and E.H.Ruediger, J. Org. Chem., **45**, 1725 (1980).
12. T.Hudlicky, T.M.Kutchan, and S.M.Naqvi, "Organic Reactions", Vol.33, pp.247-335, John Wiley & Sons, New York (1985).
13. It has been reported that dienylcyclopropanes rearrange to vinylcyclopentenes in the presence of a Pd(0) catalyst, whereas vinylcyclopropanes do not isomerize under similar conditions. Y.Morizawa, K.Oshima, and H.Nozaki, Tetrahedron Lett., **23**, 2871 (1982).
14. The spectroscopic properties were identical with those of the authentic sample.[4c]
15. Considering the subsequent demethoxycarbonylation step, lithium iodide has proven to be superior to lithium bromide.
16. For a review on ring opening of activated cyclopropanes with nitrogen, sulfur, and carbon centered nucleophiles, see: S.Danishefsky, Acc. Chem. Res., **12**, 66 (1979).
17. J.E.Baldwin, J. Chem. Soc., Chem. Commun., 734 (1976).
18. S.Danishefsky, M.Y.Tsai, and J.Dynak, J. Chem. Soc., Chem. Commun., 7 (1975).
19. Only the exo-isomer was formed.
20. K.Tomioka and K.Koga, "Asymmetric Synthesis", ed. by J.D.Morrison, Vol. 2, pp.201-224, Academic Press, New York (1983).

(Received in Japan 24 March 1986)