Radical Additions to 7-Oxabicyclo[2.2.1]hept-5-en-2-one. Facile Preparation of All-*Cis*-Corey Lactone

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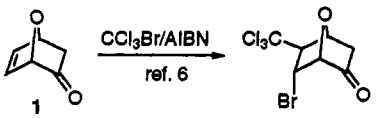
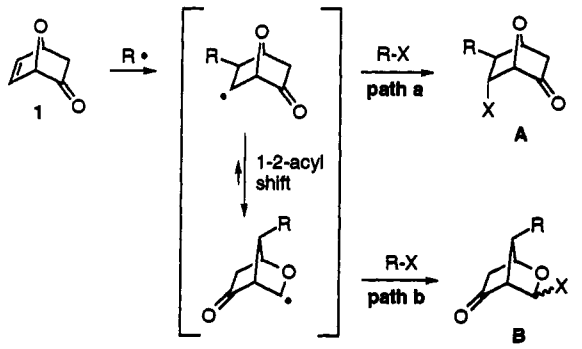
Summary: Regioselective addition of a malonyl radical to 7-oxabicyclo[2.2.1]hept-5-en-2-one followed by rearrangement of the radical adduct was used as a key step for the synthesis of all-*cis*-Corey lactone, a potent intermediate for the preparation of prostaglandins and 12-*epi*-prostaglandins.

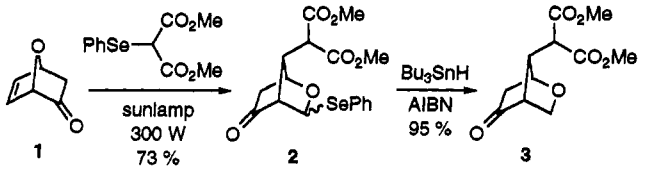
The use of 7-oxabicyclo[2.2.1]hept-5-en-2-one (1), readily available in both enantiomeric forms,[1] has recently attracted much attention for the preparation of sugar derivatives, natural products, C-branched carbohydrates, and other products of biological interest.[2] Introduction of carbon residues to this system has been largely limited to the C(3) position by aldol type reactions.[3,4] We have recently examined the possibility of using intra-[5] and intermolecular[6] radical additions for this purpose. For instance, we have demonstrated that addition of electrophilic radicals, such as the trichloromethyl radical, to 1





takes place preferentially at C(5) with complete *exo*-selectivity and was followed by a rapid bromine atom transfer (path a) to form the product of direct addition (**A**). We report here our study on the use of other radical precursors RX which transfer the X group more slowly in order to favor a possible rearrangement of the radical (path b).

Recent work of Byers has demonstrated that the phenylselenenyl group may be efficiently transferred from dimethyl phenylselenenylmalonate via a radical mechanism.[7] This reagent was ideal for our goal for three reasons: (1) The electrophilic nature of the malonyl radical should ensure a high regioselectivity.[6] (2) The phenylselenenyl group transfer is reported to be slow. (3) The final product (type **B**), which is a Se,O-acetal, is expected to be stable. Indeed, irradiation (300 W sun lamp) over a period of 12 h of a solution of (±)-1[8] and dimethyl phenylselenenylmalonate in benzene gave mainly the rearranged product **2** (73% yield after chromatography and recrystallization, *endo*/*exo* 3:1). The rearrangement occurs presumably via a cyclopropyloxy radical.[9] Small amounts (17%) of isomeric compounds coming principally from the addition of the malonyl radical at the C(5) position were also formed but were easily separated by chromatography.[10] Reduction of **2** with tributyltin hydride gave **3** whose structure was elucidated from ^{1}H-NMR spectra.



The synthetic utility of the reaction was demonstrated by conversion of **2** to the aldehyde **5** and alcohol **6** (all-*cis*-Corey lactone), which are attractive precursors of prostaglandins[11] and 12-*epi*-prostaglandins.[12] Treatment of **2** with $NaBH_4$ in methanol afforded exclusively the *endo* alcohol (92%) which was then saponified (NaOH/MeOH) and decarboxylated (DMSO, 140 °C, 85%).

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(7) (a) Byers, J. H.; Lane, G. C. *Tetrahedron Lett.* **1990**, 5697–5700. (b) Byers, J. H.; Gleason, T. G.; Knight, K. S. *J. Chem. Soc., Chem. Commun.* **1991**, 354–356. (c) Byers, J. H.; Harper, B. C. *Tetrahedron Lett.* **1992**, *33*, 6953–6954. (d) Byers, J. H.; Lane, G. C. *J. Org. Chem.* **1993**, *58*, 3355–3360.

(8) Racemic 1 was prepared according to ref. 1b.

(9) Formation of cyclopropyloxy radicals has been invoked in acyl migration leading to ring expansion by one carbon atom: (a) Beckwith, A. L. J.; O'Shea, D. M.; Gerba, S.; Westwood, S. W. *J. Chem. Soc., Chem. Commun.* **1987**, 666–667. (b) Dowd, P.; Choi, S.-C. *J. Am. Chem. Soc.* **1987**, *109*, 3493–3494. (c) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1990**, *55*, 5442–5444. For related rearrangements in polycyclic systems, see: (d) Zhang, W.; Dowd, P. *Tetrahedron* **1993**, *49*, 1965–1978.

(10) Tetra(methoxycarbonyl)ethylene was formed as side product but was easily removed during the flash chromatography. Byers has also reported the formation of this side product: ref 7d.

(11) Epimerization at C(12) (PG numbering) is necessary to lead to prostaglandins. Spontaneous epimerization has been reported during the Wittig–Horner reaction used for the introduction of the ω-chain: (a) De Clercq, P.; Coen, R.; Van Hoof, E.; Vandewalle, M. *Tetrahedron* **1976**, *32*, 2747–2752. (b) Chen, L.-Y.; Ghosez, L. *Tetrahedron: Asymmetry* **1991**, *2*, 1181–1184. For catalyzed epimerization at the aldehyde and enone stages see: (c) Corey, E. J.; Shimoji, K.; Shih, C. *J. Am. Chem. Soc.* **1984**, *106*, 6425–6427. (d) Libit, L. U.S. Patent 4,005,109, 1977.

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Protection of the *endo*-alcohol by deprotonation with LiHMDS and treatment with *p*-phenylbenzoyl chloride (*p*-PBzCl) afforded **4** (85% yield). Acetal hydrolysis (H_2O_2, acetone–water) and lactonization (pyridinium *p*-toluenesulfonate/$CHCl_3$) were carried out under extremely mild conditions, and the aldehyde **5** was isolated in good yield (90%) along with less than 5% of β-eliminated product **7**. Reduction with $NaBH_4$/MeOH gave the all-*cis*-Corey lactone **6** (91%) which showed physical and spectral data clearly distinct from pure (±)-Corey lactone (**8**). Filtration of **5** through silica gel gave the α,β-unsaturated aldehyde **7** (95%) identical in every respect with an authentic sample prepared from (±)-Corey lactone.[13]

In summary, aldehyde **5** was prepared in five steps and 44% yield from 7-oxabicyclo[2.2.1]hept-5-en-2-one (**1**). The reaction sequence is not only short but also characterized by easy and complete stereocontrol. Conversion of **5** to prostaglandins and 12-*epi*-prostaglandins is currently being investigated in our laboratory.

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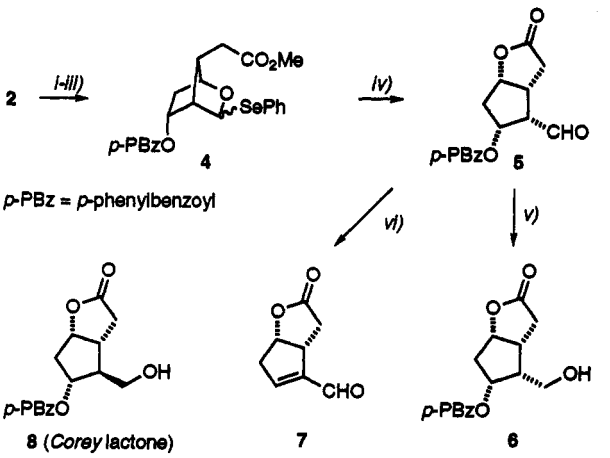
Scheme I[a]



[a]Key: (i) $NaBH_4$ (92%); (ii) NaOH/MeOH, DMSO 140 °C, (85%); (iii) LiHMDS, *p*-PBzCl (85%); (iv) H_2O_2, acetone–water, PPTS (90%); (v) $NaBH_4$ (91%); (vi) chromatography on silica gel (95%).

Supplementary Material Available: Experimental procedures and spectral data for compounds **2-6** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.