Radical Addition Reactions to Allylstannanes Having Substituents at C-1. Highly Efficient Synthesis of Enantiomerically Pure α-Alkylcyclopentenones, the Key Component for Synthesis of Prostaglandins by the Two-Component Coupling Process

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Summary: A highly efficient and practical method for the synthesis of enantiomerically pure 4-alkoxy-2-alkyl-2-cyclopenten-1-ones **1**, the key component for the preparation of prostaglandins via the two-component coupling process, has been developed. The method involves the preparation of 4-alkoxy-2-methylene-3-(tributylstannyl)-cyclopentan-1-one **6** from readily available 4-alkoxy-2-[(diethylamino)methyl]-2-cyclopenten-1-one **5** and its reaction with alkyl radicals.

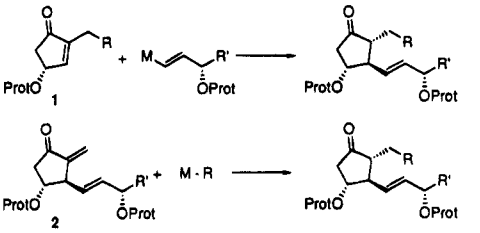
Prostaglandins (PGs), which play an important role in human physiology, have attracted substantial interest in their pharmacology and therapeutic potential.[1] Development of a general and efficient chemical synthesis of PGs has been the subject of much research over a period of about 25 years because organic synthesis is the only means to supply sufficient quantities and to create more effective compounds.[2]

Three general and efficient synthetic methods have emerged: the Corey synthesis,[3] the three-component process,[4] and the two-component process. The two-component process consists of two independent but complementary routes: introduction of the ω side-chain to an *endo*-enone bearing an α side-chain **1**[5] and introduction of the α side-chain to an *exo*-enone bearing an ω side-chain **2**[6] (Scheme 1, Prot: protective group).

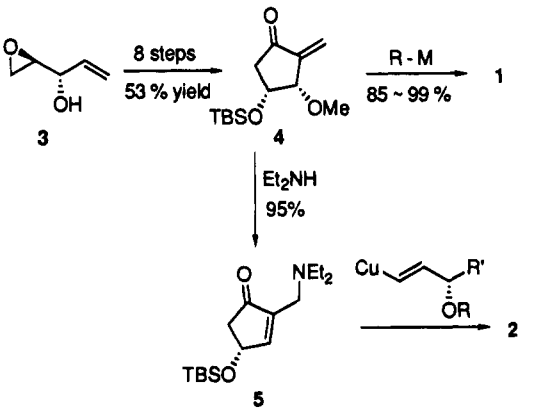
Recently, this two-component approach has become truly practical because of the development of highly efficient syntheses of requisite key intermediates **1** and **2** in our laboratory[7] and by others.[8] Our approach to **1** and **2**, which starts from readily available optically pure epoxy alcohol **3**, via the common intermediate **4**, is summarized in Scheme 2.

We now report another highly efficient synthesis of enones **1**, including those that have been difficult to access. The synthesis involves (i) preparation of the allylstannane **6** from amino enone **5** (readily made from **4** as shown in Scheme 2) and (ii) the reaction of **6** with alkyl radicals[9] (Scheme 3).

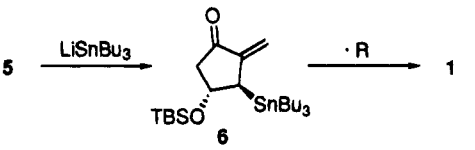
Scheme 1



Scheme 2



Scheme 3



Homolytic allyl transfer reactions using allylstannanes are now well documented and have been used for syntheses of complex molecules, including PG derivatives.[10,11] The use of allylstannanes substituted at C-1, however, has been severely restricted because of a competing 1,3-rearrangement of the stannyl group under

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(1) For a recent review, see: Collins, P. W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533.

(2) (a) Bindra, J. S.; Bindra, R. *Prostaglandin Synthesis*; Academic Press: New York, 1977; p 7. (b) Bindra, J. S. *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1981; Vol. 4, p 353. (c) Roberts, S. M.; Scheinmann, F. *New Synthetic Routes to Prostaglandins and Thromboxanes*; Academic Press: New York, 1982. See also ref 1.

(3) (a) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675. (b) Corey, E. J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 455.

(4) (a) Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847. (b) Noyori, R.; Suzuki, M. *Science* **1993**, *259*, 44. (c) Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc.* **1988**, *110*, 4726.

(5) (a) Sih, C. J.; Price, P.; Sood, R.; Salomon, R. G.; Peruzzotti, G.; Casey, M. *J. Am. Chem. Soc.* **1972**, *94*, 3643. (b) Kluge, A. F.; Untch, K. G.; Fried, J. H. *Ibid.* **1972**, *94*, 9256.

(6) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 4745.

(7) (a) Okamoto, S.; Kobayashi, Y.; Kato, H.; Hori, K.; Takahashi, T.; Tsuji, J.; Sato, F. *J. Org. Chem.* **1988**, *53*, 5590. (b) Tsujiyama, H.; Ono, N.; Yoshino, T.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1990**, *31*, 4481. (c) Yoshino, T.; Okamoto, S.; Sato, F. *J. Org. Chem.* **1991**, *56*, 3205.

(8) (a) Babiak, K. A.; Ng, J. S.; Dygos, J. H.; Weyker, C. L.; Wang, Y.-F.; Wong, C.-H. *J. Org. Chem.* **1990**, *55*, 3377. (b) Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014.

(9) The synthesis of prostaglandins via radical additions to **2** has been carried out: Ono, N.; Yoshida, Y.; Tani, K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1993**, *34*, 6427.

(10) For recent reviews: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon Press: Oxford, 1986. (b) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (c) Curran, D. P. *Synthesis* **1988**, 417 and 489.

(11) Synthesis of PG derivatives, see: Toru, T.; Yamada, Y.; Ueno, T.; Maekawa, E.; Ueno, Y. *J. Am. Chem. Soc.* **1988**, *110*, 4815.

(12) (a) Keck, G. E.; Yates, J. B. *J. Organomet. Chem.* **1983**, *248*, C21. (b) Baldwin, J. E.; Adlington, R. M.; Birch, D. J.; Crawford, J. A.; Sweeney, J. B. *J. Chem. Soc., Chem. Commun.* **1986**, 1339. (c) Easton, C. J.; Scharfbillig, I. M. *J. Org. Chem.* **1990**, *55*, 384. (d) Watanabe, Y.; Yoneda, T.; Okumura, T.; Ueno, Y.; Toru, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3030.

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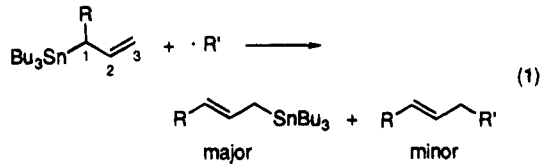
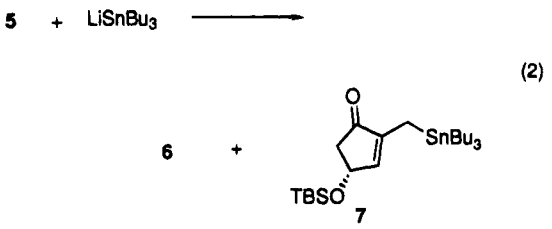
homolytic reaction conditions (eq 1).[12] However, we ex-



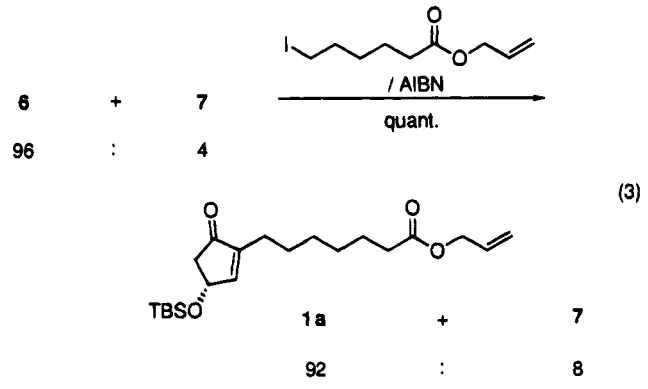
pected that C-1-substituted allylstannanes having an electron-withdrawing substituent at the olefinic position, such as **6**, might react with nucleophilic radicals more readily[10] to afford allyl transfer products in synthetically useful yields; this expectation prompted us to plan the synthetic route shown in Scheme 3.

The reaction of **5** with $LiSnBu_3$ in THF at −78 °C provided **6** and regioisomer **7** in ratios ranging from 15:1 to 30:1 in 70−80% total yield (eq 2).[7a,c,13] Since compounds



6 and **7** are difficult to separate by column chromatography on silica gel, the mixture was used for the subsequent radical reaction.

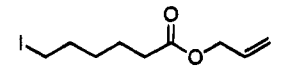
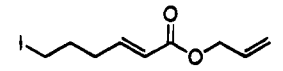
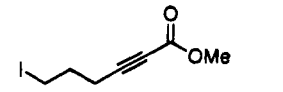
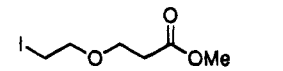
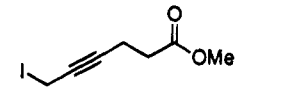
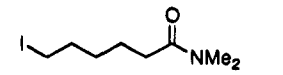
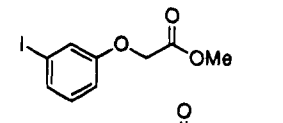
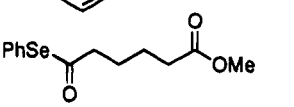
The reaction of a 96:4 mixture of **6** and **7** with allyl 6-iodohexanoate in the presence of a catalytic amount of AIBN in benzene at 80 °C for 3 h provided a 92:8 mixture of **1a**[14] (addition reaction) and **7** in essentially quantitative yield (^1H NMR analysis) (eq 3). That **7** did not react



at all under these conditions strongly indicated that the alkyl transfer reaction took place preferentially over the 1,3-rearrangement reaction. With this encouraging result in hand, we carried out the synthesis of various enones **1**. The results are summarized in Table 1.

As shown in Table 1, a wide variety of alkyl halides provided the corresponding addition−elimination products in excellent yields when allowed to react with **6**.

Table 1. α-Alkylcyclopentenones (1) from 6 and Radical Precursors via Homolytic Allyl Transfer Reactions[a]

Entry	Radical precursor	1 Isolated yield
1		a[b] 82%
2		b[c] 82%
3		c[d] 86%
4		d 74%
5		e 87%
6		f 86%
7		g[e] 10%[f]
8		h[g] 19%[h]

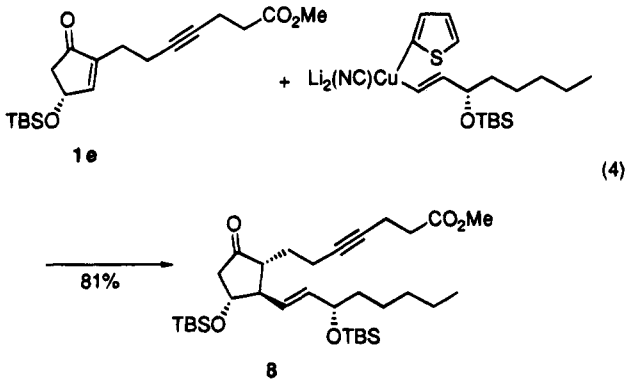
[a] Reagents and conditions: **6** (0.2 mmol), radical precursor (0.4 mmol), azoisobisbutyronitrile (AIBN, 5%); benzene (2 ml); reflux; 3 h. [b] Key component for synthesis of PGs having natural α side-chain.[14] [c] Key component for synthesis of Δ^2-*trans*-PGs such as limaprost.[15] [d] See ref. 7b. [e] May be useful for synthesis of the inter-*m*-phenylene-PG derivatives.[16] [f] Stannanes **6** and **7** were obtained in 60% and 14% yields, respectively. [g] Key component for synthesis of 6-keto-PGs such as ornoprostil.[17] [h] Stannane **7** was recovered in 70% yield.

Noteworthy is the fact that the presence of an additional double or triple bond in the halide does not present any problems arising from competing cyclization reactions[18] and/or dimerization reactions (entries 2 and 3). Although the yields were not high, an aryl iodide and a phenyl selenoester[19] afforded the arylated (entry 7) and acylated (entry 8) products, respectively.

The introduction of the α side-chain onto the cyclopentenone framework in the two-component prostaglandin synthesis has previously been carried out with organometallic derivatives (see Schemes 1 and 2). Radical reactions have a few synthetic advantages over ionic reactions: (i) radical reactions proceed under mild and neutral conditions, (ii) they do not need dry and vigorously degassed solvents or reagents, and moreover, (iii) radicals are compatible with various functional groups that usually cannot coexist with organometallic derivatives. The present finding, therefore, opens up easy access not only to natural PGs and PG analogs presently

(13) Still, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 4836.
(14) Prostaglandin allyl ester can be readily converted into free carboxylic acid by a chemical method (HCOOH−Et_3N or morpholine/Pd cat.). (a) Ono, N.; Tsuboi, M.; Okamoto, S.; Tanami, T.; Sato, F. *Chem. Lett.* **1992**, 2095. (b) Okamoto, S.; Ono, N.; Tani, K.; Yoshida, Y.; Sato, F. *J. Chem. Soc., Chem. Commun.* **1994**, 279.
(15) Hashimoto, H.; Sakai, A.; Iwasaka, T.; Onoyama, H.; Yoshioka, H.; Murata, H.; Shiota, T. *Jpn. Circl. J.* **1981**, *45*, 975; *Drugs Future* **1982**, *7*, 116. See also ref 1.
(16) Morton, D. R.; Thompson, J. L. *J. Org. Chem.* **1978**, *43*, 2102.
(17) *Drugs Future* **1987**, *12*, 1023; *Res. Discl.* **1985**, *256*, 400; *Chem. Abstr.* **1986**, *104*, 224747C. See also ref 1.
(18) The radical cyclization reaction of ω-iodo alkynyl esters has been reported: Lowinger, T. B.; Weiler, L. *J. Org. Chem.* **1992**, *57*, 6099.
(19) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1992**, *57*, 1429.

in clinical trials (see the footnotes *c*,[15] *e*,[16] and *g*[17] of Table 1) but also to new PG analogs that have been difficult to synthesize so far. Indeed, the bis-silyl ether of 4,4,5,5-tetradehydro-PGE_1 methyl ester (**8**)[9] was readily synthesized by 1,4-addition of the ω side-chain unit onto novel compound **1e** as shown in eq 4.[20]



(4)

In summary, a highly efficient synthesis of **1**, the intermediate for synthesis of PGs by the two-component coupling process, has been accomplished by means of radical addition reactions to allylstannane **6**. Since we have previously developed an efficient synthesis of PGs via radical addition of the α side-chain to **2**,[9] the required steps for introduction of the α side-chain in both routes of the two-component prostaglandin synthesis shown in Scheme 1 can now be carried out via a radical rather than an ionic pathway.

The radical reaction of C-1-substituted allylstannanes having an electron-withdrawing substituent at the olefinic position, the key methodology in the present synthesis, was proved to be synthetically useful. Further studies to determine the full scope of the reaction are under way in our laboratory.

Supplementary Material Available: Experimental procedures for synthesis of **6** and **8**, a typical procedure for the preparation of **1a–h**, and spectroscopic data for **6**, **8**, **1a–h** and the halides and phenyl selenoester employed (6 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.

(20) The prostaglandin derivative **8** was previously synthesized by the radical addition reaction of the α-side-chain onto enone **2** (R = n-C_5H_{11}) in a rather low yield of 33%. See ref 9.