Highly Efficient Synthesis of 13-Dehydroprostaglandins by 1,4-Addition Reaction of Alkynyl ω-Side-Chain Unit onto Cyclopentenone Framework

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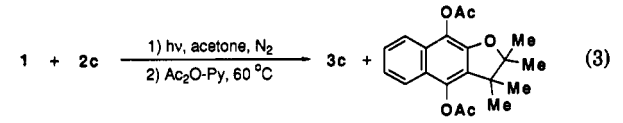
conditions.[7] The trans disposition of the acetoxyl and methyl groups attached to C-2 and C-3 of photoproduct **5** was assigned by its ^{1}H NMR spectrum ($J_{2\text{-H-3-H}}$ = 1.98 Hz). Treatment of naphthofurandione **5** with potassium *tert*-butoxide in THF at 0 °C resulted in the elimination of acetic acid, giving maturinone (**6**) in 52% yield.

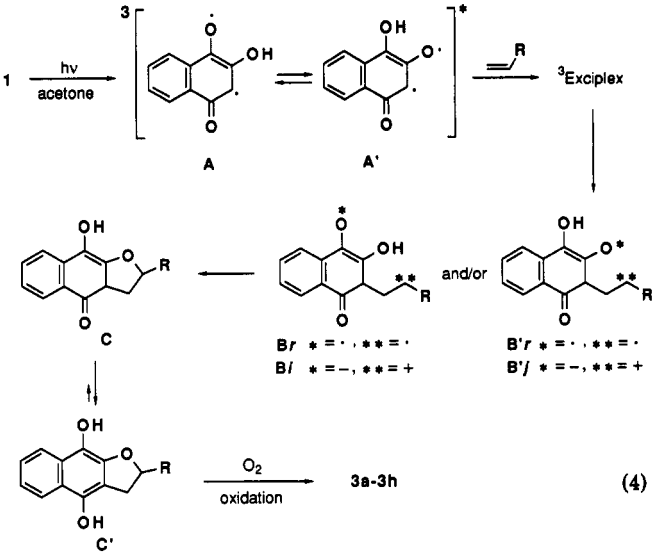
The initial products in the present photoaddition are furanohydroquinones; 4,9-diacetoxy-2,3-dihydro-2,2,4,4-tetramethylnaphtho[2,3-*b*]furan (**7**)[9] can be isolated in 36% yield together with 2,2,4,4-tetramethylnaphtho[2,3-*b*]furan (**3c**) (18%) when the crude products from the photoaddition between hydroxynaphthoquinone **1** (1 mmol) and 2,3-dimethyl-2-butene (10 mmol) in acetone (40 mL) are treated with acetic anhydride (1 mL) and pyridine (1 mL) under nitrogen for 2 h at 60 °C (eq 3).



(3)

7

The probable gross reaction pathway of the addition leading to the hydroquinones is outlined in eq 4. A comparison of the electronic absorption spectrum of 2-hydroxy-1,4-naphthoquinone (**1**) with that of 2-methoxy-1,4-naphthoquinone[10] indicates that no orthoquinone form of 2-hydroxynaphthoquinone exists in solution. The initial events in this photochemical addition can be explained within the framework of an accepted model of $[2 + 2]_\pi$ photochemical additions.[11] Irradiation of **1** in acetone or benzene generates tautomeric exited triplets (A) and (A′), which react with an alkene through a triplet exciplex to give biradical (B_r) and/or (B_r'). In view of the strong electron-accepting character of naphthoquinone,[12] it seems likely that the exciplex or these biradical intermediates have appreciable polar character or are ionic intermediates (B_i) and (B_i') generated by electron transfer. The regioselectivity found in the present addition is a clear in-



(4)

dication of the involvement of a more stabilized polar biradical or ionic intermediate, such as B_i and B_i', in the formation of dihydronaphtho[2,3-*b*]furan-4,9-diones. Intramolecular cyclization of the intermediate gives hydroquinones (C) and (C′). In contrast to the photoaddition[13] of 1,4-naphthoquinone with alkenes, no trace of $[2 + 2]_\pi$ cycloadducts were observed in the present photoadditions. 2,3-Dihydronaphthofuran-4,9-dione is then formed by air oxidation of the hydroquinone during the workup and isolation procedures.

Additional mechanistic and synthetic aspects of the present *formal* [2 + 3] photoaddition are presently under investigation and will be reported in a forthcoming full paper.

Supplementary Material Available: Experimental details for the synthesis of **3a–g** and maturinone (**6**) and for isolation of diacetoxyfuranohydroquinone **7** from the photoaddition between hydroxynaphthoquinone **1** and 2,3-dimethyl-2-butene (4 pages). Ordering information is given on any current masthead page.

(10) Singh, I.; Ogata, R. T.; Moore, R. E.; Chang, C. W. J.; Scheuer, P. J. *Tetrahedron* **1968**, *24*, 6053.
(11) For reviews, see: (a) Baldwin, S. W. In *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York, 1981; Vol. 5, pp 123–225. (b) Weedon, A. C. In *Synthetic Organic Photochemistry*; Horspool, W. M., Ed.; Plenum: New York, 1980; pp 91–143.
(12) E.g.: Rao, P. S. *Nature* **1973**, *243*, 344. Rao, P. S.; Hayon, E. *J. Am. Chem. Soc.* **1974**, *96*, 1287.
(13) (a) Otsuki, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2596. (b) Maruyama, K.; Narita, N. *Ibid.* **1980**, *53*, 757. (c) Ochiai, M.; Arimoto, M.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1981**, 460. (d) Liu, H. J.; Chan, W. H. *Can. J. Chem.* **1980**, *58*, 2196. (e) Maruyama, K.; Otsuki, T.; Tai, S. *J. Org. Chem.* **1985**, *50*, 52.

Highly Efficient Synthesis of 13-Dehydroprostaglandins by 1,4-Addition Reaction of Alkynyl ω Side-Chain Unit onto Cyclopentenone Framework

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Received March 19, 1991

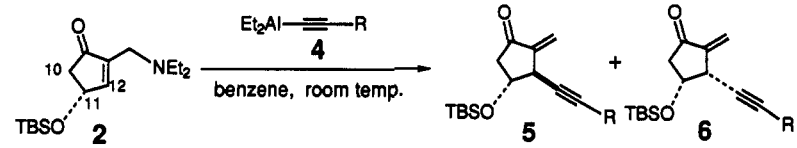
Summary: Optically active 2-((diethylamino)methyl)-4-siloxy-2-cyclopentenone (**2**) reacts with a diethyl(3-(*tert*-butyldimethylsiloxy)-1-alkynyl)aluminum compound via 1,4-addition pathway to afford the enone **5**, useful intermediate for synthesis of PGs via two-component coupling process, in excellent yield, thus making it easy to synthesize 13-dehydro-PGs.

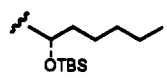
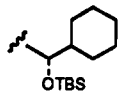
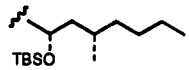
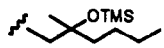
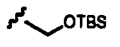
The synthesis of analogues of prostaglandins (PGs) has attracted much interest for use in biological and clinical investigations.[1] A number of analogues in which the double bond at C-13 (PG numbering) has been replaced by triple bond have been prepared and some of which have deserved particular attention as promising therapeutic agents.[2]

(1) Bindra, J. S.; Bindra, R. *Prostaglandin Synthesis*; Academic: New York, 1977. Mitra, A. *Synthesis of Prostaglandins*; Wiley-Interscience: New York, 1977. *New Synthetic Routes to Prostaglandins and Thromboxanes*; Roberts, S. M., Scheinmann, F., Eds.; Academic: New York, 1982. Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847.

0022-3263/91/1956-3205$02.50/0

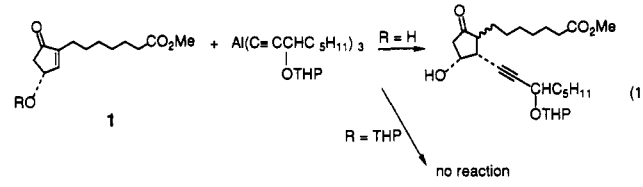
Table I. Yields, Characteristic NMR Data, and $[\alpha]_D$ Values of 5 and 6



4[a] R		products: isolated yield,[b] % 5	6	^{1}H NMR coupling constants $J_{11,12}$[c] (Hz) 5	6	^{13}C NMR chemical shifts of C-11 and C-12[d] (ppm) 5: C-11/C-12	6: C-11/C-12	$[\alpha]^{25}_D$ (c, $CHCl_3$),[e] deg, of 5
4a		82	14	6.8[f]	4.0	73.3/43.6	69.5/42.1	−54.6 (c 1.03)
4b		90	4	6.8	4.2	73.3/43.6	69.6/42.3	−50.0 (c 1.20)
4c		83	8	6.8	4.8	73.3/43.5	69.6/42.3	−51.2 (c 1.38)
4d		50	19	7.0[g]	4.0	73.5/43.8	69.8/42.4	–[e]
4e		54	45	6.8	4.0	73.2/43.5	69.6/42.1	−30.3 (c 1.12)
4f		59	39	7.2[g]	3.8[g]	73.7/43.8	69.9/42.5	−45.1 (c 1.50)

[a] Prepared from the corresponding alkyne by sequential treatment with n-BuLi (1.66 M, hexane) and 1.2 equiv of Et_2AlCl (1.0 M, hexane) in benzene. The enantiomerically pure alkynes used for preparation of **4a**, **4b**, and **4c** were synthesized according to the procedure reported by us (ref 15). [b] The enone **2** was treated with 1.3 equiv of **4**, and the yield is based on **2**. R_f values (analytical TLC (E. Merck, silica gel 60 F_{254} plates), hexane/Et_2O = 6/1) are as follows: **5a**/**6a** = 0.60/0.38, **5b**/**6b** = 0.60/0.34, **5c**/**6c** = 0.60/0.38, **5d**/**6d** = 0.58/0.40, **5e**/**6e** = 0.50/0.26, **5f**/**6f** = 0.53/0.37. [c] Unless otherwise indicated, on decoupling of C-10 protons, the signal of C-11 proton was observed as a doublet with the coupling constant given. Full data of ^{1}H NMR of **5** and **6** are available as supplementary material. [d] Full data of ^{13}C NMR of **5** and **6** are available as supplementary material. [e] $[\alpha]_D$ values of **5d** and **6** were not determined. [f] On decoupling of C-15 proton, the signal of C-12 proton was observed as a doublet with the coupling constant given. [g] The signal of C-12 proton was observed as a doublet-triplet: **5d** ($J_{12,15}$ = 2.4 Hz), **5f** ($J_{12,15}$ = 2.2 Hz), **6f** ($J_{12,15}$ = 2.2 Hz).

A conjugate addition of organometallic derivatives to cyclopentenones which is classified into two- and three-component coupling process provides an attractive, convergent approach to PGs. This method has been widely applied to the synthesis of naturally occurring PGs and pharmaceutically important PG analogues.[1,3] The synthesis of 13-dehydro-PGs by introduction of alkynyl moiety into cyclopentenones, however, remains unsolved. For example, 2-(6-carbomethoxyhexyl)-4-hydroxy-2-cyclopentenone (1) reacted with tris(3-(tetrahydropyranyloxy)-1-octynyl)aluminum to give 1,4-addition product; however, the addition occurred at the same face of C-11 hydroxyl group giving only undesired 12α-isomer (eq 1). While protection of the hydroxyl group of 1 by a tetrahydropyranyl group prevented reaction with the aluminum reagent.[4]



Recently we have directed our efforts to make the two-component coupling synthesis of PGs as an industrially viable process by developing efficient, practical methods to prepare the required key intermediates such as cyclopentenones[5] and ω side-chain units.[6] Thus, we have succeeded in synthesizing 2-((diethylamino)-methyl)-4-siloxy-2-cyclopentenone (**2**)[7] in 50% overall yield starting from readily available (2R,3S)-1,2-epoxypent-4-en-3-ol and have shown that **2** thus prepared reacts with organocopper compounds derived from an ω side chain to

(2) (a) Gandolfi, C.; Pellegata, R.; Dradi, E.; Forgione, A.; Pella, E. *Farmaco Ed. Sci.* **1976**, *31*, 763. (b) Gandolfi, C.; Dorio, G.; Gaio, P. *Ibid.* **1972**, *27*, 1125. (c) Franceschini, J.; Mizzotti, B.; Ceserani, R.; Mandelli, V.; Usardi, M. M. *Pharmacol. Res. Commun.* **1977**, *9*, 899. (d) Impicciatore, M.; Usardi, M. M.; Bertaccini, G. *Ibid.* **1976**, *8*, 187. (e) Jarabak, J.; Brathwaite, S. *Arch. Biochem. Biophys.* **1976**, *177*, 245. (f) O-Yang, C.; Fried, J. *Tetrahedron Lett.* **1983**, *24*, 2533. (g) Fried, J.; Barton, J. *Proc. Natl. Acad Sci. U.S.A.* **1977**, *74*, 2199. (h) Garmelo, A.; Ryszard, J. G. *Pharmacol. Res. Commun.* **1978**, *10*(10), 885. (i) Fried, J.; Mitra, D. K.; Nagarajan, M.; Mehrotra, M. M. *J. Med. Chem.* **1980**, *23*, 234. (j) Skuballa, W.; Vorbrüggen, H. *Adv. PG TX LT Res.* **1983**, *11*, 299. (k) Skuballa, W.; Vorbrüggen, H. *Ibid.* **1985**, *15*, 271. (l) Skuballa, W.; Schillinger, E.; Stürzebecher, C.-St.; Vorbrüggen, H. *J. Med. Chem.* **1986**, *29*, 313.

(3) Recent synthesis via conjugate addition approach, see: Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 4718. Johnson, C. R.; Penning, T. D. *Ibid.* **1988**, *110*, 4726. Danishefsky, S. J.; Cabal, M. P.; Chow, K. *Ibid.* **1989**, *111*, 3456. Morita, Y.; Suzuki, M.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 1785. Lipshutz, B. H.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 7440. Babiak, K. A.; Behling, J. R.; Dygos, J. H.; McLaughlin, K. T.; Ng, J. S.; Kalish, V. J.; Kramer, S. W.; Shone, R. L. *Ibid.* **1990**, *112*, 7441 and see also ref 5.

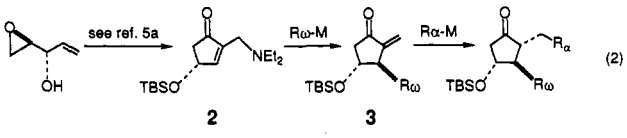
(4) Pappo, R.; Collins, P. W. *Tetrahedron Lett.* **1972**, 2627. Collins, P. W.; Dajani, E. Z.; Bruhn, M. S.; Brown, C. H.; Palmer, J. R.; Pappo, R. *Ibid.* **1975**, 4217.

(5) (a) Okamoto, S.; Kobayashi, Y.; Kato, H.; Hori, K.; Takahashi, T.; Tsuji, J.; Sato, F. *J. Org. Chem.* **1988**, *53*, 5590. (b) Okamoto, S.; Kobayashi, Y.; Sato, F. *Tetrahedron Lett.* **1989**, *30*, 4379. (c) Tsujiyama, H.; Ono, N.; Yoshino, T.; Okamoto, S.; Sato, F. *Ibid* **1990**, *31*, 4481.

(6) Okamoto, S.; Shimazaki, T.; Kobayashi, Y.; Sato, F. *Tetrahedron Lett.* **1987**, *28*, 2033. Kitano, Y.; Matsumoto, T.; Okamoto, S.; Shimazaki, T.; Kobayashi, Y.; Sato, F. *Chem. Lett.* **1987**, 1523. Kitano, Y.; Matsumoto, T.; Wakasa, T.; Okamoto, S.; Shimazaki, T.; Kobayashi, Y.; Sato, F.; Miyaji, K.; Arai, K. *Tetrahedron Lett.* **1987**, *28*, 6351.

(7) The compound **2** is now commercially available from Nissan Chemical Industries, Ltd. (Japan).

afford **3** in excellent yields, which in turn reacts with an α side chain as reported by Stork and his co-workers to afford PGs (eq 2).[5]



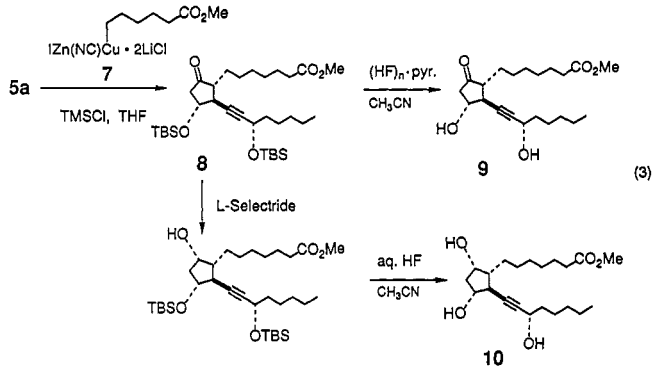
(2)

2 **3**

We expected that the amino group present in **2** would activate an alkynylaluminum compound by coordination, thus making it possible to introduce an alkynyl moiety into **2** at the opposite face of the C-11 hydroxyl group via a 1,4-addition pathway. Herein reported is the successful realization of this idea which undoubtedly simplifies the synthesis of 13-dehydro-PGs.[8]

When **2** was reacted with diethyl(3-(*tert*-butyldimethylsiloxy)-1-octynyl)aluminum (**4a**) in benzene at room temperature, 1,4-addition did occur to afford, after hydrolysis, a mixture of two diastereoisomers.[9,10] These were readily separated by column chromatography (SiO_2) to give **5a** having the desired 12β configuration and **6a** (12α isomer) in 82% and 14% yields, respectively. The assignment of the configuration of the two isomers follows from the ^1H NMR coupling constant between the two protons at C-11 and C-12 (PG numbering, J = 4.0 Hz for cis and J = 6.8 Hz for trans) and ^{13}C NMR chemical shifts of C-11 and C-12, since the resonances for these carbons in **6** (cis configuration) are always upfield of those in **5** (trans configuration).[11] Table I shows the yields, characteristic ^1H and ^{13}C NMR data, and $[\alpha]_D$ values of the products obtained by the reaction of **2** with various diethylalkynylaluminum compounds **4a-f**. As can be seen from the table, in every case, the 12β-isomer **5** was major; however, somewhat diminished diastereoselectivities were observed with the decrease of the steric bulk of alkynyl moiety.

With the compounnd **5a** in hand, we then carried out the synthesis of the methyl ester of 13-dehydro-PGE_1 and -PGF_1 by 1,4-addition of α side-chain unit onto it (eq 3).



(3)

Thus the reaction of **5a** with organocopper reagent **7**, prepared from the corresponding organozinc reagent and CuCN·2LiCl, in the presence of Me_3SiCl provided, after hydrolysis, disilyl ether of 13-dehydro-PGE_1 methyl ester (**8**) ($[\alpha]^{25}_D$ -47.3° (*c* 1.96, $CHCl_3$)) in 78% yield.[5c] Protodesilylation of **8** with $(HF)_n$-pyridine in acetonitrile afforded 13-dehydro-PGE_1 methyl ester (**9**) ($[\alpha]^{24}_D$ -43.8° (*c* 0.484, $CHCl_3$), mp 46.0-46.5 °C (lit.[12] mp 46 °C)) in 85% yield. While the reduction of **8** with L-Selectride (Aldrich) followed by protodesilylation (aqueous HF, CH_3CN) gave 13-dehydro-PGF_1 methyl ester (**10**) ($[\alpha]^{22}_D$ +21.7° (*c* 0.60, $CHCl_3$) in 58% overall yield from **8**, mp 68.0-68.5 °C (lit.[12] mp 68 °C)). The spectroscopic data (^1H NMR, IR, and MS) of **9** and **10** are in good agreement with the literature.[12]

Since PG analogues having 17-methyl-15-hydroxy[13] and 15-dehydroxy-16-methyl-16-hydroxy[14] moiety as an ω side chain have been accepted as promising therapeutic agents, the synthesis of 13-dehydro version of these PGs using the enones **5c** and **5d** is in progress in our laboratory.

Supplementary Material Available: Experimental procedure for preparation of **5** and **6** and spectroscopic data (IR and ^1H and ^{13}C NMR) of **5a-f**, **6a-f**, **8-10**, and the disilyl ether of **10** (6 pages). Ordering information is given on any current masthead page.

(8) Previous synthesis of 13-dehydro-PGs: via epoxide ring opening by alkynyl anion; Fried, J.; Sih, J. C. *Tetrahedron Lett.* **1973**, 3899. Fried, J.; Lin, C. H. *J. Med. Chem.* **1973**, *16*, 429. Fried, J.; Lee, M.-S.; Gaede, B.; Sih, J. C.; Yoshikawa, Y.; McCracken, J. A. *Adv. Prostaglandin Thromboxane Res.* **1976**, *1*, 183. Ohno, K.; Nishiyama, H.; Nagase, H.; Matsumoto, K.; Ishikawa, M. *Tetrahedron Lett.* **1990**, *31*, 4489. See also ref 2g and 2j. Via dehydrohalogenation of 14-halo-PG intermediate; Smith, H. W.; Mich, K. U.S. Patent 4,029,681 (1977). Takahashi, A.; Shibasaki, M. *J. Org. Chem.* **1988**, *53*, 1227. See also ref 2b and 21.

(9) The nucleophilic S_N2' addition of organometallic reagents to allylamine derivatives has been reported: Doomes, E.; Clarke, U.; Neitzel, J. J. *J. Org. Chem.* **1987**, *52*, 1540. Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1985**, *107*, 6137. Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1987**, *109*, 4755.

(10) ^1H and ^{13}C NMR studies of the reaction mixture (before hydrolysis) demonstrated the formation of the aluminum enolate.

(11) For 2-alkynylcyclopent-3-en-1-ol: Briggs, A. J.; Walker, K. A. M. *J. Org. Chem.* **1990**, *55*, 2962. For 2-methylcyclopentanol: Christl, M.; Reich, H. J.; Roberts, J. D. *J. Am. Chem. Soc.* **1971**, *93*, 3463. For prostaglandins: Cooper, G. F.; Fried, J. *Proc. Natl. Acad. Sci. U.S.A.* **1973**, *70*, 1579. Mizsak, S. A.; Slomp, G. *Prostaglandins* **1975**, *10*, 807. Arroniz, C. E.; Gallina, J.; Martinez, E.; Muchowski, J. M.; Velarde, E.; Rooks, W. H. *Ibid.* **1978**, *16*, 47.

(12) Smith, H. W.; Mich, K. U.S. Patent 4,058,564 (1977).

(13) (a) Tsuboi, T.; Fujitani, B.; Maeda, J.; Yoshida, K.; Shimizu, M.; Kawasaki, A.; Okegawa, T.; Tsuboshima, M. *Thrombosis Res.* **1980**, *20*, 573. (b) Tsuboi, T.; Hatano, N.; Nakatsuji, K.; Fujitani, B.; Yoshida, K.; Shimizu, M.; Kawasaki, A.; Sakata, M.; Tsuboshima, M. *Adv. Prostaglandin Thromboxane Res.* **1980**, *6*, 347. (c) *Pharmaproject*, Vol. 7, Prostaglandin (H4B); Sochynsky, R., Hardcastle, J., Eds.; V&O Publications Ltd.: Surrey, 1986.

(14) Larsen, K. R.; Jensen, N. F.; Davis, E. K.; Jensen, J. C.; Moody, F. G. *Prostaglandins* **1981**, *21* (*Suppl*), 119. Collins, P. W.; Dajani, E. Z.; Pappo, R.; Gasiecki, A. F.; Bianchi, R. G.; Woods, E. M. *J. Med. Chem.* **1983**, *26*, 786. Kaymakcalan, H.; Wilson, D. E.; Khader, M.; Ramsamooj, E.; Adams, A. *Clin. Res.* **1981**, *29*, 758A. Wilson, D. E.; Levendglu, H.; Adams, A.; Ramsamooj, E. *Prostaglandins* **1984**, *28*, 5. Collins, P. W. *J. Med. Chem.* **1986**, *29*, 437. See also ref 13c.

(15) Ito, T.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1989**, *30*, 7083.

A Novel Method for the Synthesis of Spiroketal Systems. Synthesis of the Pheromones of the Common Wasp and the Olive Fruit Fly

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Received March 8, 1991

Summary: Total syntheses of the pheromones of the common wasp and the olive fruit fly were accomplished by a strategy in which the key transformation involved the cleavage of tetrahydrofuran with (*tert*-butyldimethylsilyl)manganese pentacarbonyl followed by sequential insertion of ethyl acrylate.

0022-3263/91/1956-3207$02.50/0