the pyrene chromophore in the DNA adduct of BePE exists in an environment somewhere between complete intercalation and solvent exposure. Whether this intermediate and heterogeneous environment results from different carcinogen binding sites on an intact nucleic acid structure or is a consequence of variations in local DNA denaturation[20] is a question we will address in future experiments. In any case, it is clear that for these systems, ODMR reveals a substantial amount of detail about carcinogen–DNA interactions not present in conventional phosphorescence results.

Acknowledgment. We thank Dr. Ronald G. Harvey and H. Mee-Lee for their generous gift of BePE. Dr. Victor Ibanez graciously prepared samples used in this work. We also express our gratitude to Professor N. E. Geacintov for very stimulating discussions and making unpublished work available to us. This research was supported by Grant CA 20851, awarded by the National Cancer Institute (DHHS) to N. E. Geacintov and H. C. Brenner.

(20) Grunberger, D.; Weinstein, I. B. In "Chemical Carcinogenesis and DNA"; Grover, P. L., Ed.; CRC Press: Boca Rotan, FL, 1979; pp 59–65.
(21) Charles, S. W.; Fischer, P. H. H.; McDowell, C. A. *Mol. Phys.* **1965**, *9*, 517–524.

Stereoselective Synthesis of Steroid Side Chain: A Route to De-*AB*-cholestan-9-one

Takashi Takahashi, Haruo Yamada, and Jiro Tsuji*

Tokyo Institute of Technology, Meguro Tokyo 152, Japan

Received May 4, 1981

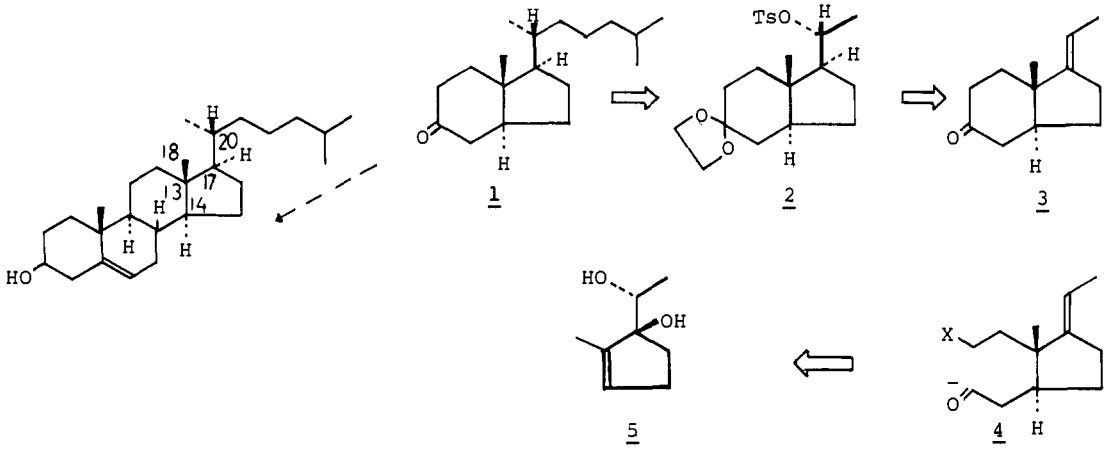
Highly regio- and stereoselective construction of steroid side chains is a current problem[1] in the synthesis of various physiologically active steroids and metabolites of vitamin D. The most crucial problem inherent in the synthesis of steroid side chains is the introduction of asymmetric centers at C(17) and C(20) (steroidal numbering). For this purpose, the Carroll[2] or oxy-Cope[3] rearrangement at the steroidal allylic alcohol moiety and nucleophilic attack at π-allylpalladium intermediates[4] derived from steroidal olefins were previously used as key stereodirecting processes. The conformational rigidity of [2.2.1]heptane derivatives[5] was also quite useful. We describe here the successful construction of the hydrindanone **3** and its stereocontrolled conversion to de-*AB*-cholestan-9-one (**1**).

In our synthetic plan (Scheme I), the key step is the stereospecific displacement (S_N2) of the secondary tosylate **2**, derived from the [17(20)*E*]-olefin of **3**, with the carbanion of **16** to produce the right stereochemistry at C(20). The stereocontrolled construction of **3** involves two Claisen rearrangements of **5**, the first one to introduce the acyl chain at C(14) and the second to introduce the chain at C(13) with the right trans stereochemistry between C(13) methyl (18-methyl) and C(14) hydrogen, as well as the geometry of the [17(20)*E*]-olefin, and subsequent efficient cyclization via acyl carbanion **4**.

Thus the allyl alcohol **5** was our initial synthetic target and easily prepared from 2-methylcyclopentenone (**6**) in the following way (Scheme II). Addition of the enone **6** (50 mmol), at −78 °C under nitrogen, to a solution of (α-ethoxyvinyl)lithium,[6] prepared from ethyl vinyl ether (90 mmol) and *tert*-butyllithium (75 mmol) in dry THF at 0 °C, and the hydrolysis of the resulting vinyl ether with aqueous acid (0.1 N HCl/THF, 10 min at 0 °C) gave the ketone **7** in 70% overall yield.[7] The highly stereoselective reduction of the ketone **7** with sodium borohydride in THF/H_2O at 0 °C gave the diol **5**[7] (R_f = 0.27, 4:1 ether–*n*-hexane) in 80% yield, and its isomer (R_f = 0.20) was formed in 8% yield. They were easily separated by chromatography on silica gel (elution with 25% ether in *n*-hexane). The selective acetylation of the secondary alcohol in the diol **5** with acetyl chloride in pyridine at room temperature gave the acetate **8** in 71% yield. The Johnson Claisen rearrangement [$CH_3C(OEt)_3$, propionic acid, at 120 °C for 3 h] of the allyl alcohol **8** gave the ester **9a** in 57% yield. The hydrolysis of the acetate **9a** in methanolic K_2CO_3 at 0 °C for 3 h gave the ester **9b** in 70% yield: NMR (CCl_4) δ 1.23 (3 H, d, J = 6 Hz, CH_3), 1.63 (3 H, br s, C=CCH_3), 3.67 (3 H, s, $OCOCH_3$), 4.67 (2 H, q, J = 6 Hz, C*H*(OH)CH_3); IR (neat) 3400 and 1735 cm^{-1}.

Then we attempted to establish the right stereochemistry between C(13) and C(14) by the second Claisen rearrangement of the vinyl ether of the allyl alcohol **9b** based on the consideration of two possible Claisen chair-like transition states **10a** and **10b** (Scheme III). In **10b** clearly there are greater steric interactions than in **10a**. Consequently, the Claisen rearrangement should proceed via the transition state **10a** which gives the trans stereochemistry at C(13) methyl and C(14) hydrogen as well as the

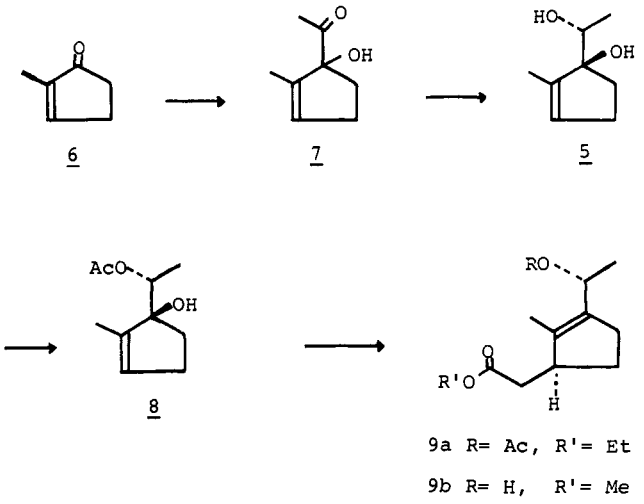
Scheme I



(1) Bolton, I. J.; Harrison, R. G.; Lythoge, B. *J. Chem. Soc. C* **1971**, 2950. For a review: Piatak, D. M.; Wicha, J. *Chem. Rev.* **1978**, *78*, 199.
(2) Tanabe, M.; Hayashi, K. *J. Am. Chem. Soc.* **1980**, *102*, 862.
(3) Koreeda, M.; Tanaka, Y.; Schwartz, A. *J. Org. Chem.* **1980**, *45*, 1172.
(4) (a) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1978**, *100*, 3435. (b) Temple, J. S.; Schwartz, J. *Ibid.* **1980**, *102*, 7381.
(5) (a) Trost, B. M.; Bernstein, P. R.; Funfschilling, P. C. *J. Am. Chem. Soc.* **1979**, *101*, 4378. (b) Grieco, P. A.; Takigawa, T.; Moore, D. R. *Ibid.* **1979**, *101*, 4380.
(6) Baldwin, J. E.; Höfle, G. A.; Lever, O. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7125.
(7) This compound was soluble in water; continuous extraction with CH_2Cl_2 was required for isolation.

0002-7863/81/1503-5259$01.25/0

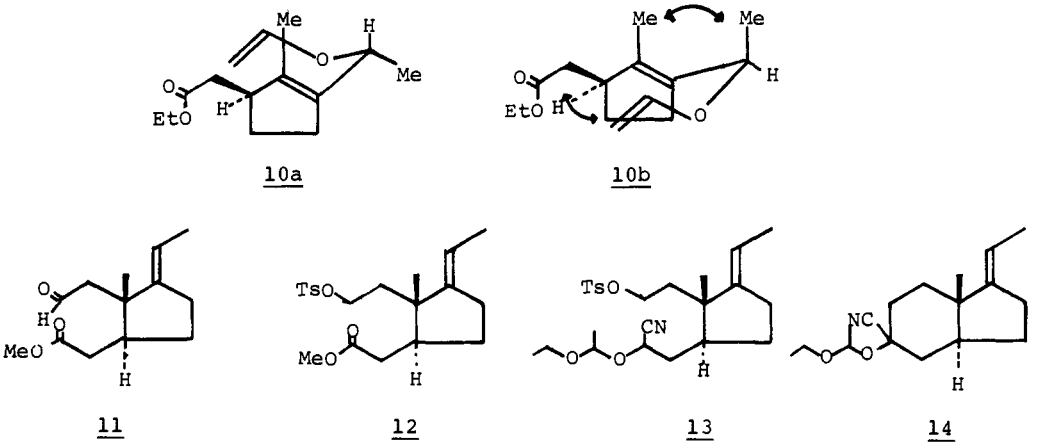
Scheme II



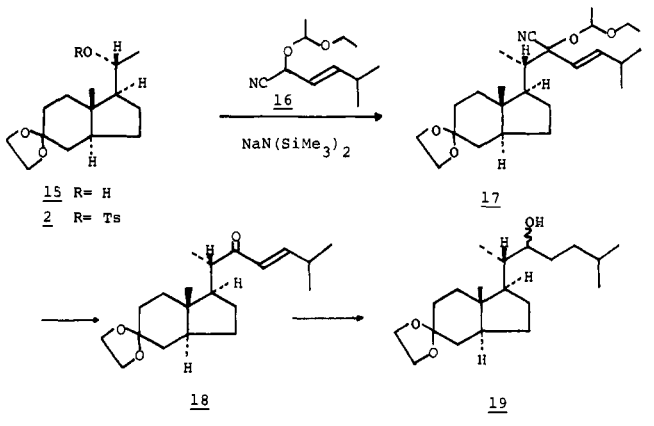
(81%), ethyl vinyl ether/*p*-TsOH]. The cyclization of protected cyanohydrin **13** was carried out[8] in 90% yield by refluxing for 1 h in dry THF with 3 equiv of sodium bis(trimethylsilyl)amide. Removal of the ethoxyethyl group from the cyclized product **14** with aqueous acid (3 N HCl), followed by base treatment (4% aqueous NaOH in ether, 10 min, 0 °C) afforded the hydrindanone **3** in 90% overall yield as a single product:[9,10] NMR (CCl_4) δ 0.95 (3 H, s, CH_3), 4.9–5.3 (1 H, m, olefinic); IR (neat) 1710 cm^{-1}.

Then the stereoselective conversion of the hydrindanone **3** into de-*AB*-cholestan-9-one (**1**) was carried out. The protection ($HOCH_2CH_2OH$/*p*-TsOH) of the ketone **3** and the stereoselective hydroboration[11] of the olefin [diborane in THF at 0 °C, then H_2O_2/NaOH (90%)] were carried out, and the resulting alcohol **15** was converted to the tosylate **2** in two steps[12] [*p*-toluenesulfinyl chloride in pyridine/Et_2O (98%), *m*-chloroperbenzoic acid/CH_2Cl_2 (76%)]. The side chain was stereospecifically (SN_2) introduced to the tosylate **2** by the following reaction. A mixture of the tosylate **2** (0.1 mmol) and 1.8 equiv of the protected cyanohydrin[13] **16** in dry benzene was added to a solution of 3 equiv of sodium bis(trimethylsilyl)amide in dry benzene at 80 °C to give **17** in

Scheme III



Scheme IV

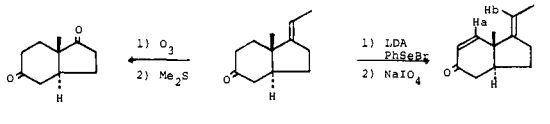


70% yield (Scheme IV). Hydrolysis of the 1-ethoxyethyl group (pyridinium *p*-toluenesulfonate[14] in MeOH, 40 °C for 1 h) and a base treatment (2% NaOH/THF, 0 °C) gave the enone **18**[15] in 70% overall yield: NMR (CCl_4) δ 0.72 (3 H, s, CH_3), 6.0 (1 H, d, J = 15 Hz, olefinic), 6.71 (1 H, dd, J = 15, 7 Hz, olefinic); IR (neat) 1690, 1660, 1620 cm^{-1}. The enone **18** was reduced to

[17(20)*E*]-olefin. We confirmed that this expectation was the correct one in the following way. The allyl alcohol **9b** was converted to the vinyl ether **10** [10 equiv of CH_2=CHOEt, Hg(OAc)$_2$] in 74% yield (recovered alcohol **8**, 6%), which was heated for 1 h at 160 °C in collidine under nitrogen to give the aldehyde **11**: NMR (CCl_4) δ 0.91 (3 H, s, CH_3), 1.55 (3 H, br d, J = 7 Hz, C=CCH_3), 4.9–5.4 (1 H, m, olefinic); IR (neat) 1735 and 1720 cm^{-1}. The reduction of the aldehyde **11** with $NaBH_4$ and the tosylation (1.5 equiv of *p*-TsCl in pyridine) of the resulting alcohol gave the ester **12** in 70% overall yield from **10**. The ester **12** was converted to the protected cyanohydrin **13** in four steps [3 equiv of *i*-Bu_2AlH in THF at −78 °C (97%), Collins oxidation in CH_2Cl_2 (83%), excess $NaHSO_3$ and NaCN in H_2O at 0 °C

(8) Stork, G.; Depezay, J. C.; D'Angelo, J. *Tetrahedron Lett.* **1975**, 389. Stork, G.; Takahashi, T. *J. Am. Chem. Soc.* **1977**, *99*, 1275.

(9) The [17(20)*E*]-olefin configuration and trans stereochemistry between C(13) methyl and C(14) hydrogen were confirmed in the following way. The diketone i derived from **3** was identical in all respects (NMR, IR) with an authentic sample:[10] NMR (CCl_4) δ 1.04 (3 H, s, CH_3); IR (neat) 1705 and 1735 cm^{-1}. The ketone **3** was converted to the enone ii: NMR (CCl_4) δ 1.00 (3 H, s, CH_3), 1.67 (3 H, br d, J = 7 Hz, C=CCH_3), 5.91 (1 H, d, J = 10 Hz, olefinic), 7.40 (1 H, d, J = 10 Hz, olefinic); the Nuclear Overhauser Effect (NOE) indicated that irradiation of H_a increased the intensity of H_b (41%). We are grateful to Professor S. Ito (Tohoku University) for helpful suggestions for determining the *E* configuration of the olefin.



(10) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1973**, *38*, 3239.
(11) Krubiner, A. M.; Oliveto, E. P. *J. Org. Chem.* **1966**, *31*, 24.
(12) Coates, R. M.; Chen, J. P. *Tetrahedron Lett.* **1969**, 2705.
(13) Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* **1971**, *93*, 5286.
(14) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.
(15) Further stereoselective introduction of alkyl groups at C_{24} by using this enone moiety and its application to synthesis of sterols possessing unusual side chains is in progress.

the alcohol **19** [Li/NH_3/THF (70%)] which was converted to the ketone **1** in three steps (*p*-TsCl/pyridine, $LiAlH_4$/THF, 3 N HCl/THF, overall yield 89%). The relative stereochemistry among C(13), C(14), C(17), and C(20) was identical in all respects (NMR, IR, TLC, HPLC)[16] with that of an authentic sample.[17]

Acknowledgment. We thank Y. Nakamura of this institute and JEOL Co. for measurement of the NMR spectra.

(16) NMR ($CDCl_3$, 200 MHz) δ 0.87 (3 H, d, J = 6.6 Hz, $C(CH_3)$), 0.873 (3 H, d, J = 6.6 Hz, $C(CH_3)_2$), 0.921 (3 H, s, CH_3), 0.938 (3 H, d, J = 6.3 Hz, CH_3); IR (neat) 1715 cm^{-1}; R_f = 0.59 (1:1 ether–n-hexane); HPLC retention time, 6.7–7.3 min (SI-60-5 μm, 4 o.d. × 250 mm, 5 mL/min, 1.5% AcOEt in *n*-hexane).

(17) We are indebted to Professor P. A. Grieco for providing an authentic sample of **1**.[5b]

A Simple Synthesis of De-*AB*-cholesta-8(14),22-dien-9-one by Highly Stereoselective Double Michael Addition Involving Alkenylcopper–Phosphine Complex, Vinyl Ketone, and 2-Methyl-2-cyclopentenone Followed by Claisen Rearrangement and Rhodium-Promoted Decarbonylation

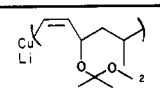
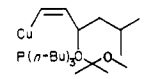
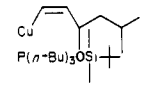
Takashi Takahashi, Yoichiro Naito, and Jiro Tsuji*

Tokyo Institute of Technology, Meguro Tokyo 152, Japan

Received May 4, 1981

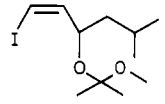
Stereocontrolled synthesis[1] of sterols[2] possessing various kinds of side chains is attracting attention in recent years. Most sterols have the same stereochemistry at C(20*R*) as in cholesta-5,22-dien-3-ol (**1**). We have reported in the preceding paper our solution to elaborate asymmetric centers at C(20) and C(17), including stereoselective construction of the CD ring.[3] On the other hand, in 1977 Djerassi and co-workers[4] isolated from a sea pen, Ptilosarcus gurneyi, four sterols which have the unexpected C(20*S*) stereochemistry. At the same time two groups[5] proposed the existence of 20-isocholesta-5,22-dien-3β-ol (20*S*) (**2**) in sterols of marine sources. Koreeda also pointed[6] out the 20-isocholesterol (20*S*) shows significant in vitro inhibitory activity for the conversion of cholesterol to pregnenolone. These findings on sterols with 20*S* structure prompted us to find out the stereocontrolled synthesis of the asymmetric center at C(20*S*) (or 20β-H). We describe here the stereoselective synthesis of (±)-de-*AB*-20-isocholesta-8(14),22-dien-9-one (**3**) as a precursor of **2**. As outlined in Scheme I, the key steps in our synthesis are a highly stereoselective Michael addition of a functionalized organocopper reagent **6**, in which the C(23) allyl alcohol moiety serves to control the stereochemistry at C(17), to 2-methyl-2-cyclopentenone (**5**) and subsequent conjugate addition[7] of the resulting enolate to α-silyl vinyl ketone **4**[7c,d] which introduces the right cis stereochemistry between C(13)-methyl and the side chain at C(17). After formation of the C ring by intramolecular aldol condensation, the allyl alcohol is utilized again to introduce the C-(20)-methyl stereoselectively by combination of Claisen rearrangement and decarbonylation promoted by a rhodium complex.[8] These overall transformations provide the required stereochemistry at C(13), C(17), and C(20) in **3**. This methodology, if successful, can offer a solution to the chiral synthesis of 20-*epi*-sterols starting from the optically active allyl alcohol **6** with *R* configuration and suitable bis- or trisannulation reagents[9] corresponding to **4**.

Table I

conditions[a]	reagent	relative yields of 11 and 12: 11	12	total yield of 11 and 12, %
a	 **8**	6	1	67
b	 **9**	9	1	70
c	 **10**	4.5	1	54

[a] (a) **7** (6.6 mmol), *n*-BuLi (6.18 mmol), CuI/$P(n\text{-Bu})_3$ (3.1 mmol), **5** (1.0 mmol). (b) **10** (1.2 mmol), *n*-BuLi (1.3 mmol), CuI (1.2 mmol), $P(n\text{-Bu})_3$ (3.2 mmol), **5** (1.0 mmol). (c) **10** (1.2 mmol), *n*-BuLi (1.3 mmol), CuI (1.2 mmol), $P(n\text{-Bu})_3$ (3.2 mmol), **5** (1.0 mmol).

At first, conjugate additions of *cis*-divinylcuprate **8** and *cis*-vinylcopper–phosphine complexes **9** and **10** to the enone **5** were carried out in order to examine the stereoselectivity of the reaction. The synthesis of the *cis*-vinyl iodide **7** was carried out in 46%



7

overall yield from the corresponding acetylenic carbinol by the method of Kluge, Untch, and Fried.[10] The *cis*-vinylcopper

(1) For a review, see: (a) Piatak, D. M.; Wicha, J. *Chem. Rev.* **1978**, *78*, 199. (b) For recent work on π-allylpalladium intermediates, see: Trost, B. M.; Matsumura, Y. *J. Org. Chem.* **1977**, *42*, 2036. Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1978**, *100*, 3435. Temple, J. S.; Schwartz, J. *Ibid.* **1980**, *102*, 7381. (c) For Carroll, oxy-Cope, or ene reactions, see: Koreeda, M.; Tanaka, Y.; Schwartz, A. *J. Org. Chem.* **1980**, *45*, 1172. Tanabe, M.; Hayashi, K. *J. Am. Chem. Soc.* **1980**, *102*, 862. Dauben, W. G.; Brookhart, T. *Ibid.* **1981**, *103*, 237. (d) For [2.2.1]Heptane derivatives, see: Trost, B. M.; Bernstein, P. R.; Funfschilling, P. C. *Ibid.* **1979**, *101*, 4378. Grieco, P. A.; Takigawa, T.; Moore, D. R. *Ibid.* **1979**, *101*, 4380. (e) Schow, S. R.; McMorris, T. C. *J. Org. Chem.* **1979**, *44*, 3760. Trost, B. M.; Taber, D. F.; Alper, J. B. *Tetrahedron Lett.* **1976**, 3857.

(2) (a) Minale, L.; Sodano, G. "Marine Natural Products Chemistry"; Faulkner, D. J., Fenical, W. H., Eds.; Plenum Press: New York, 1977; p 87. (b) Nes, W. R.; McKean, M. L. "Biochemistry of Steroids and Other Isoprenoids"; University Park Press: Baltimore, MD, 1977.

(3) Takahashi, T.; Yamada, H.; Tsuji, J., *J. Am. Chem. Soc.*, preceding paper in this series.

(4) Vanderah, D. J.; Djerassi, C. *J. Org. Chem.* **1978**, *43*, 1442.

(5) Idler, D. R.; Khalil, M. W.; Gilbert, J. D.; Brooks, C. J. W. *Steroids* **1976**, *27*, 155. Tsuda, K.; Sakai, K.; Ikegawa, N. *Chem. Pharm. Bull.* **1961**, *9*, 835.

(6) Koreeda, M.; Koizumi, N. *Tetrahedron Lett.* **1978**, 1641. Teicher, B. A.; Koizumi, N.; Koreeda, M.; Shikita, M.; Talalay, P. *Eur. J. Biochem.* **1978**, *91*, 11.

(7) (a) Review: Stork, G. *Pure. Appl. Chem.* **1968**, *17*, 383; **1975**, *43*, 553. (b) Organocopper conjugate addition–α-alkylation: Kretchmer, R. A.; Schafer, W. M. *J. Org. Chem.* **1973**, *38*, 95. Boeckman, R. K., Jr. *Ibid.* **1973**, *38*, 4450. Coates, R. M.; Sandefur, L. O. *Ibid.* **1974**, *39*, 275. Posner, G. H.; Sterling, J. J.; Whitten, C. E.; Lentz, C. M.; Brunell, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 107. (c) Double conjugate addition: Boeckman, R. K., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 6867; **1974**, *96*, 6179. (d) α-Silyl vinyl ketones: Stork, G.; Singh, J. *J. Am. Chem. Soc.* **1974**, *96*, 6181. Stork, G.; Ganem, B. *Ibid.* **1973**, *95*, 6152.

(8) Ohno, K.; Tsuji, J. *J. Am. Chem. Soc.* **1968**, *90*, 99. Tsuji, J.; Ohno, K. *Synthesis* **1969**, 157.

(9) For our new bis- or trisannulation reagents, see: Tsuji, J.; Shimizu, I.; Suzuki, H.; Naito, Y. *J. Am. Chem. Soc.* **1979**, *101*, 5070. Shimizu, I.; Naito, Y.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 487. Tsuji, J.; Kobayashi, Y.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 483 and references therein.

0002-7863/81/1503-5261$01.25/0