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

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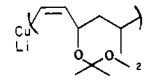
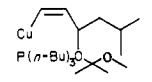
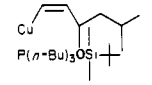
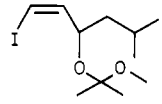
Stereocontrolled synthesis[1] of sterols[2] possessing various kinds of side chains is attracting attention in recent years. Most sterols have the same stereochemistry at C(20*R*) as in cholesta-5,22-dien-3-ol (**1**). We have reported in the preceding paper our solution to elaborate asymmetric centers 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.

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(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.

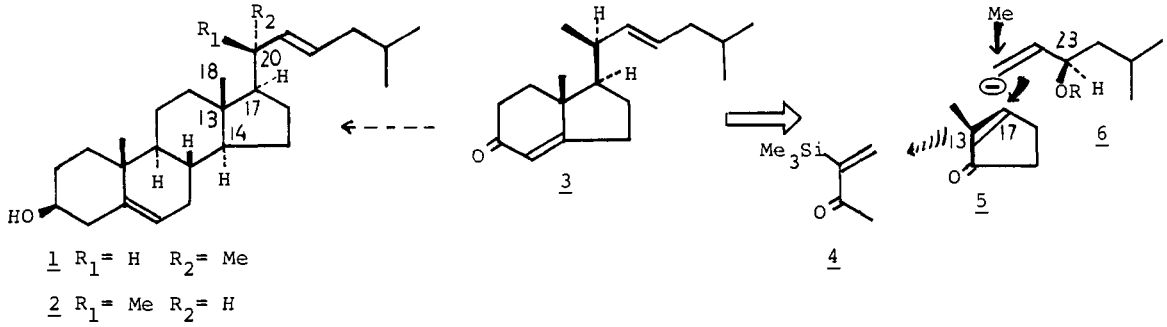
(7) (a) Review: Stork, G. *Pure. Appl. Chem.* **1968**, *17*, 383; **1975**, *43*, 553. (b) Organocopper conjugate addition–α-alkylation: Kretchmer, R. A.; Schafer, W. M. *J. Org. Chem.* **1973**, *38*, 95. Boeckman, R. K., Jr. *Ibid.* **1973**, *38*, 4450. Coates, R. M.; Sandefur, L. O. *Ibid.* **1974**, *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.

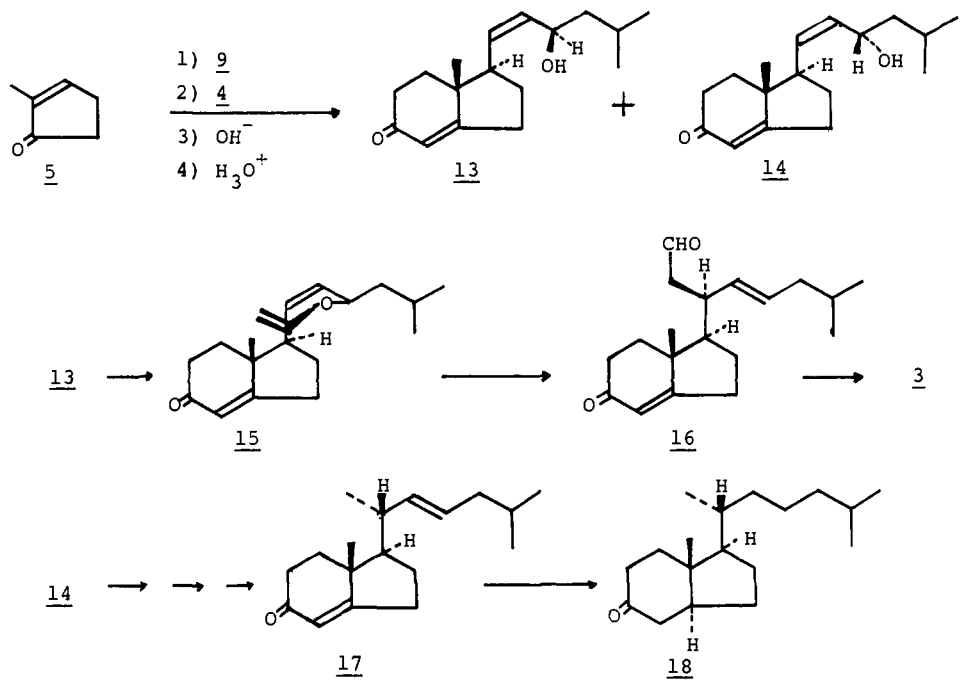
(9) For our new bis- or trisannulation reagents, see: Tsuji, J.; Shimizu, I.; Suzuki, H.; Naito, Y. *J. Am. Chem. Soc.* **1979**, *101*, 5070. Shimizu, I.; Naito, Y.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 487. Tsuji, J.; Kobayashi, Y.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 483 and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

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

Scheme I



Scheme II



reagents **8**–**10** were prepared by applying Syntex's[10] (in the case of **8**) or Noyori's procedure[11] (in the cases of **9** and **10**) under the conditions shown in Table I. Each reaction gave a remarkably high degree of stereoselectivity and a reasonable yield (67–54%), although the structure of the side chain and the cyclopentenone moiety, the protecting group of the alcohol (in case of **10**), and vinylcopper reagent (in cases of **9** and **10**) are quite different from those used in prostaglandin synthesis.[12] It is worth emphasizing that the advantage of using the reagent **9** over the corresponding reagent **8** is clear in the synthesis of the optically active form, since half of the valuable optically active side chain has to be wasted when using the reagent **8**.

On the basis of the above results, we attempted to construct the CD ring by the double Michael addition using reagent **9** and **4** and subsequent aldol condensation in the following way under reaction conditions b shown in Table I. The vinyl iodide **7** was metalated in dry hexane with *n*-BuLi at −70 °C for 30 min under argon. A copper–phosphine complex was prepared separately from CuI and P(*n*-Bu)$_3$ in dry ether at room temperature. The solution of the above complex in ether was added over 30 min at −70 °C to a solution of lithiated **7**. The reaction mixture was stirred for an additional 2 h at −50 °C and cooled to −70 °C. A solution of the enone **5** in ether was added over 30 min at −70 °C (Scheme II). The resulting enolate was allowed to warm to −20 °C over 30 min. Then a solution of 3-(trimethylsilyl)-3-buten-2-one (**4**) in ether was added at −20 °C over 30 min. The reaction mixture was stirred for 2 h and quenched with aqueous NH_4Cl solution. Base (NaOMe, refluxing in MeOH for 3 h) treatment promoted aldol condensation of the resulting diketone, and subsequent acid treatment (1 N HCl, 0 °C for 5 min) removed the methoxyisopropyl protecting group to give the enone **13**[13] in 56% overall yield. The C(23)-epimer **14**[13] was formed in only 6% yield. The cis

(10) Kluge, A. F.; Untch, K. G.; Fried, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 2956. Lüthy, C.; Konstantin, P.; Untch, K. G. *Ibid.* **1978**, *100*, 6211.
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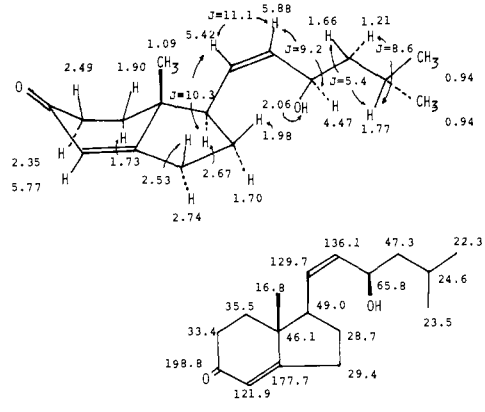
(13) We were unable to detect any cis isomers [C(13)-Me and C(17)-H] of **13** and **14** even after careful examination (TLC, NMR, HPLC). ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) data of the enone **13** are depicted in the following diagram



IR (neat) 3400 and 1670 cm^{-1}; R_f = 0.33 (1:2 hexane–AcOEt); HPLC retention time, 8.7–10.0 min (SI −60 - 5 μm, 4 o.d. × 250 mm, 5 mL/min,

stereochemistry between the C(13) methyl and vinyl chain at C(17) in both **13** and **14** was confirmed on the basis of ^{1}H NOE.[14]

The stereoselective introduction of the methyl group at C(20) from the allyl alcohol **13** was carried out in the following way. The vinyl ether of **13** was prepared [$Hg(OAc)_2$, CH_2=$CHOEt$ at reflux; recovered alcohol **13**, 37%], and the Claisen rearrangement of the resulting vinyl ether **15** gave the single product **16**[15] in quantitative yield. Decarbonylation of the aldehyde **16** with $Rh(PPh_3)_3Cl$ in refluxing benzene for 90 min gave the enone **3**[16] in 64% yield. The same treatment of the C(23)-epimer **14**, as above, gave also the single product **17**.[16] For an examination of the relative stereochemistry among C(13), C(17), and C(20), the enone **17** derived from **14** was converted to the ketone **18** which was identical in all respects (NMR, IR, HPLC)[3] with an authentic sample of **18**.[17] These results revealed that the initial 1,4 addition of **9** to **5** led predominantly to the relative stereochemistry between C(17) and C(23) as shown in **13**, and the high degree of stereoselectivity of Claisen rearrangement on **13** and **14** provided the asymmetric center at 20β-H and 20α-H, respectively.

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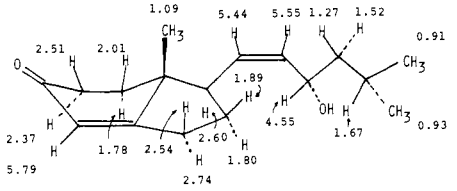
3% isopropyl alcohol in hexane). ^{1}H NMR (400 MHz) data of the enone **14** are shown in the following diagram.



IR (neat) 3400 and 1660 cm^{-1}; R_f = 0.36 (1:2 hexane-AcOEt); HPLC retention time, 10.5-12.4 min (3% isopropyl alcohol in hexane). We thank Iwao Miura (Otsuka Pharmaceutical Co.) for his help in the interpretation of the NMR spectra.

(14) The irradiation of the C(13)-methyl caused a significant increase (17% in **13**, 25% in **14**) of the absorption due to the olefinic protons.

(15) The careful examination of the reaction mixture by TLC and HPLC indicated that Claisen rearrangement of **15** proceeded via one transition state. Aldehyde **16**: NMR (CCl_4, 90 MHz) δ 0.87 (3 H, d, J = 6 Hz, $C(CH_3)_2$), 0.89 (3 H, d, J = 6 Hz, $C(CH_3)_2$), 1.12 (3 H, s, CH_3), 5.0-5.75 (2 H, m, olefinic), 5.62 (1 H, s, enone), 9.72 (1 H, t, J = 2 Hz, CHO); IR (neat) 1720 and 1665 cm^{-1}.

(16) C(20)α-methyl resonances are 0.08 ppm higher field in NMR spectrum than C(20)β-methyl. Enone **3**: NMR ($CDCl_3$, 100 MHz) δ 0.91 (6 H, d, J = 6.35 Hz, $-C(CH_3)_2$), 1.02 (3 H, d, J = 7.3 Hz, CH_3), 1.00 (3 H, s, CH_3), 5.23 (1 H, dd, J = 16.2 and 8.7 Hz, CC*H*=CH—), 5.29-5.59 (1 H, m, CCH=C*H*—), 5.74 (1 H, s, enone); IR (neat) 1670 and 975 cm^{-1}; HPLC retention time, 10.0-10.8 min (Si-60-5μm, 4 o.d. × 250 mm, 5 mL/min, 3.7% AcOEt in hexane. Enone **17**: NMR ($CDCl_3$, 100 MHz) δ 0.91 (6 H, d, J = 6.3 Hz, $-C(CH_3)_2$), 1.10 (3 H, d, J = 7.8 Hz, CH_3), 1.13 (3 H, s, CH_3), 5.26 (1 H, dd, J = 15.2 and 7.0 Hz, CC*H*=CH—), 5.29-5.62 (1 H, m, CCH=C*H*—), 5.76 (1 H, s, enone); IR (neat) 1675 and 975 cm^{-1}; HPLC retention time 11.0-12.1 min (3.7% AcOEt in hexane).

(17) We are indebted to Professor P. A. Grieco for providing an authentic sample of **18**.[1d]

A Novel Methoxy-Directed Ketal Hydrolysis and Its Application to a Convergent, Regiospecific Synthesis of (±)-Daunomycinone

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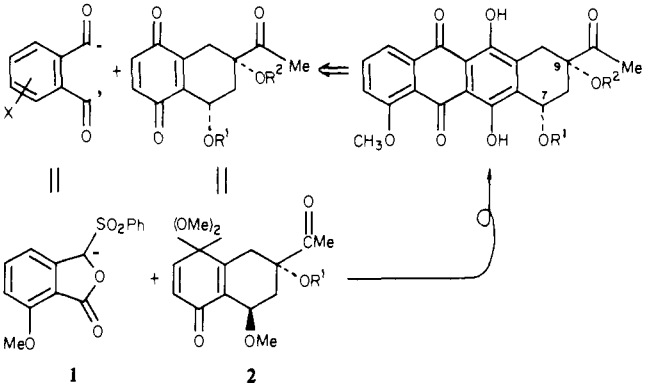
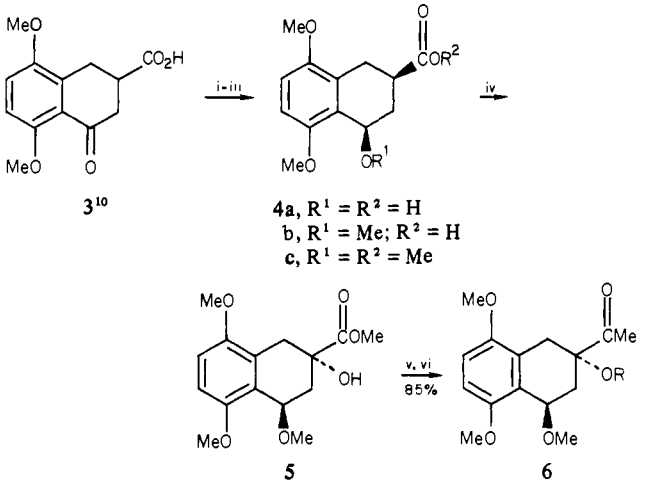
Quinone monoketals, readily available via anodic oxidation of 1,4-dimethoxy aromatic systems followed by monohydrolysis, are of demonstrated utility in organic synthesis.[1] However, the hydrolyses of quinone bisketals to the respective monoketals usually show only poor to moderate regioselectivity unless a suitable substituent (i.e., Br, OMe, SMe) is unsymmetrically substituted on the molecule.[1,2] Recent studies have established the utility of quinone monoketals in the regiospecific synthesis of anthrones[3] and anthraquinones.[4] Thus, a combination of any one of the available 1,4-dipole equivalents[3-5] with an appropriate quinone monoketal (i.e., **2**) would effect a one-step synthesis of an anthracyclinone fully functionalized in the A ring (Scheme I). The latter consideration is especially important since, in spite of a number of excellent syntheses of 7,9-dideoxy- and 7-deoxyanthracyclinones,[6] procedures for introduction of the 7,9-dioxygen[7] or 7-oxygen[8] substituents are less than adequate, especially for

Scheme I. 1,4-Dipole-Quinone Strategy for Anthracyclinone Synthesis



1 **2**

Scheme II.[a] Synthesis of A,B-Ring Fragment



3[10]

4a, $R^1 = R^2 = H$
b, R^1 = Me; $R^2 = H$
c, $R^1 = R^2$ = Me

5 **6**

[a] (i) $NaBH_4$, EtOH; (ii) NaH, MeI; (iii) CH_2N_2; (iv) LiCA, MoOPH; (v) Me_3SiCl, HMDS, Py; (vi) $LiCH_2SOMe$, KF, Al(Hg)

† Conoco Oil Fellow, 1980-1981.
‡ The Ohio State University Presidential Fellow, 1980-1981.

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(7) Smith, T. H.; Fujiwara, A. N.; Lee, W. W.; Wu, H. Y.; Henry, D. W. *J. Org. Chem.* **1977**, *42*, 3653-3660. Kende, A. S.; Tsay, Y. G.; Mills, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 1967-1968.

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