appendix, which appears in the microfilm edition, for selected data), **14** ($[\alpha]^{24}_D$ 7.6° (*c* 1.0, CH_2Cl_2)), and **3** in optically pure form. The latter was compared spectrally as well as by melting point (113–114 °C, lit.[5] 114 °C), mixture melting point (113–114 °C), and rotation ($[\alpha]^{24}_D$ 36.2° (*c* 0.395, CH_3OH) (authentic, $[\alpha]^{24}_D$ 36.5° (*c* 1.0, CH_3OH)) with an authentic sample.

Acknowledgment. We thank the National Institutes of Health, General Medical Sciences, for their generous support of our programs. We especially thank Professor B. Lythgoe for a generous sample of diol **3** and Sandoz, Ltd., for very generous supplies of starting materials.

Supplementary Material Available: Key spectral data for compounds **4**, **6**, **8**, and **10–14** (2 pages). Ordering information is given on any current masthead page.

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(8) All new compounds have been characterized by spectroscopic means and elemental composition, either by high resolution mass spectroscopy and/or elemental analysis. For some key spectral data, see the appendix which appears in the microfilm version.
(9) A small amount of reaction at O of $PhSO_2^-$ to give the sulfinate ester was observed. It could be hydrolyzed back to the alcohol and thus recycled.
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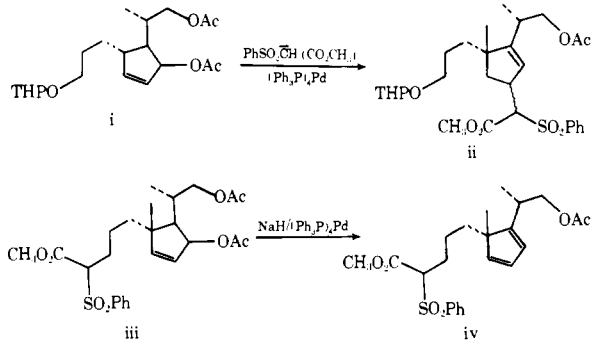
(13) Attempts to use palladium-catalyzed reactions led to an alkylation product in the intermolecular reaction (i → ii) involving a profound rearrangement of the allylic system. An intramolecular alkylation only led to cyclopentadiene formation (iii → iv). The structure of the products must be considered tentative.



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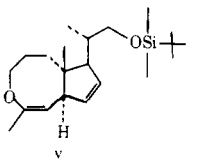
(18) The major byproduct was v, the result of O alkylation which was hydrolyzed back to keto alcohol. The observation of such a reaction (O alkylation with formation of an eight-membered ring) in competition with the desired cyclization to a six-membered ring is unprecedented to our knowledge.



v

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(22) On leave from Sandoz, Ltd., Basel, Switzerland.

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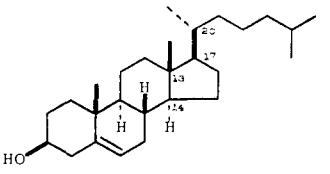
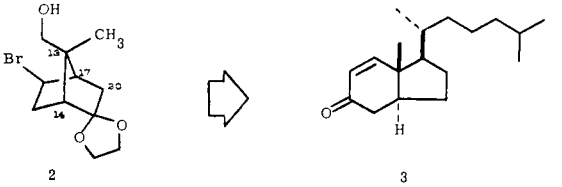
Bicyclo[2.2.1]heptanes in Organic Synthesis. Stereocontrolled Approach to Sterol Side-Chain Construction: Synthesis of De-*AB*-cholest-11-en-9-one

Sir:

The vast majority of sterols, including insect and crustacean moulting hormones, and the active metabolites of vitamin D possess the *R* configuration at C(20) (cf. cholesterol (**1**)). The



problems associated with generating and controlling chirality in acyclic systems have primarily been responsible for the limited success recorded to date for elaborating the stereochemistry at C(17) and at C(20) of sterol side chains.[1,2] A potential solution to this problem is embodied in the bicyclo[2.2.1]heptane derivative **2** whose conformational rigidity allows for elaboration of not only the chirality at C(20), but also that encountered at C(13), C(14), and C(17). We detail below the conversion of (−)-**2** into (+)-de-*AB*-cholest-11-en-9-one (**3**), a known precursor to tachysterol[3] and precalciferol[3].



2 3

The synthetic plan centered around the key bicyclic lactone **4** in which the carbonyl unit of the lactone serves to introduce the remaining carbon atoms of the side chain (cf. **4** → **5**). The oxygen function at C(16) (steroid numbering) provides a handle for establishing the stereochemistry at C(14) via a C–O → C–C chirality transfer (cf. **5** → **6**).

Alcohol **7**, $[\alpha]^{25}_D$ −115° (*c* 1.01, $CHCl_3$), obtained in near-quantitative yield by dehydrohalogenation (DBU, DMF, 170–180 °C, 1 h) of (−)-bromo alcohol **2**,[3] was subjected to (a) benzylation (NaH, $C_6H_5CH_2Br$, Bu_4NI, benzene–Me_2SO (20:1)) and (b) hydrolysis (10% HCl, THF) giving rise (~86% overall yield) to the bicyclo[2.2.1]heptenone **8**: $[\alpha]^{25}_D$ −479°

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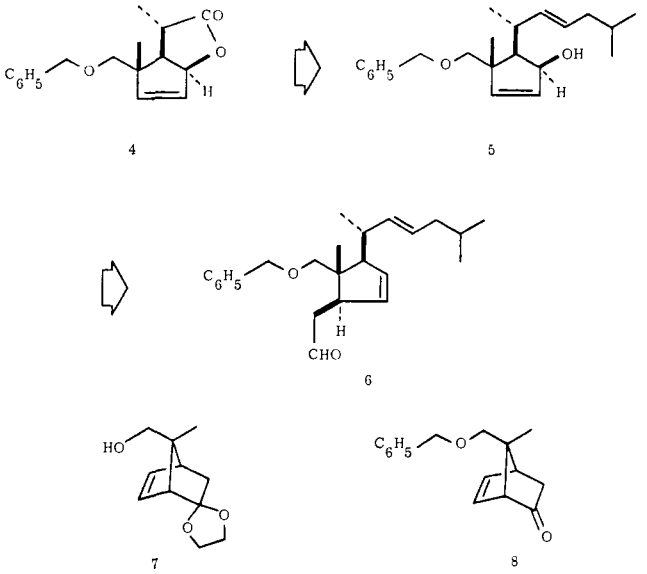
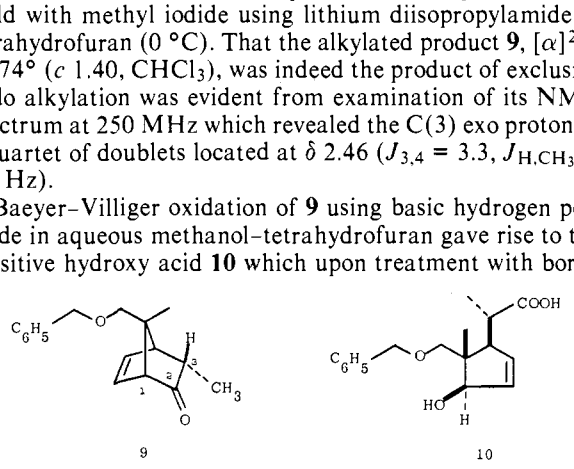


4 5 6 7 8

(c 1.35, $CHCl_3$), IR (CCl_4) 1749 cm^{-1}. Exclusive endo alkylation of ketone **8** was accomplished, as anticipated, in 90% yield with methyl iodide using lithium diisopropylamide in tetrahydrofuran (0 °C). That the alkylated product **9**, $[\alpha]^{25}_D$ −474° (c 1.40, $CHCl_3$), was indeed the product of exclusive endo alkylation was evident from examination of its NMR spectrum at 250 MHz which revealed the C(3) exo proton as a quartet of doublets located at δ 2.46 ($J_{3,4}$ = 3.3, J_{H,CH_3} = 7.0 Hz).

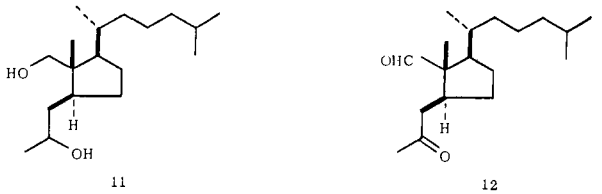
Baeyer-Villiger oxidation of **9** using basic hydrogen peroxide in aqueous methanol-tetrahydrofuran gave rise to the sensitive hydroxy acid **10** which upon treatment with boron



9 10

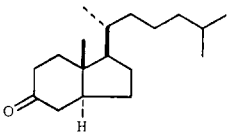
trifluoride etherate in methylene chloride at 0 °C rearranged (85% overall) solely to intermediate **4**, $[\alpha]^{25}_D$ +153° (c 1.50, $CHCl_3$), with the expected transfer of chirality from C(14) → C(16) (steroid numbering). Reduction (i-Bu_2AlH, toluene, −78 °C) of lactone **4**, followed by condensation with isopentylidenetriphenylphosphorane (generated with sodium *tert*-amylate in benzene), provided in 50% overall yield dienol **5** as a mixture of double-bond isomers about the C(22)–C(23) olefinic linkage. The required transfer of chirality from C(16) → C(14) was achieved classically by a two-step process. Allylic alcohol **5** was converted (ethyl vinyl ether, $Hg(OAc)_2$, reflux) into its corresponding vinyl ether (82% yield) which upon heating in decalin at 200 °C (5 h) under nitrogen generated aldehyde **6** in 90% yield.[7]

Addition of methyllithium to aldehyde **6**, followed by simultaneous catalytic hydrogenation (H_2, 10% Pd/C, EtOH) of the two olefins and hydrogenolysis of the benzyl ether, gave diol **11** in 90% overall yield as a mixture of diastereomers.



11 12

Oxidation (Jones reagent, −10 °C, 5 min) of diol **11** afforded a 74% yield of keto aldehyde **12** (IR (CCl_4) 2690, 1720 cm^{-1}; NMR (CCl_4) δ 2.01 (s, 3 H, CH_3CO), 9.24 (s, 1 H, -CHO)) which cyclized (10% KOH, CH_3OH) in 74% yield to the known enone **3**:[8] $[\alpha]^{25}_D$ +40.8° (c 3.45, $CHCl_3$); IR (CCl_4) 1678, 1601 cm^{-1}; NMR (CCl_4) δ 6.45 (AB q, 2 H, J = 10, $\Delta\nu_{AB}$ = 93.5 Hz). Enone **3** was analyzed as its 2,4-dinitrophenylhydrazone: mp 174–175 °C, $[\alpha]^{25}_D$ +21.8° ($CHCl_3$) (lit.[8] mp 176–177 °C, $[\alpha]^{25}_D$ +21.9° ($CHCl_3$)). Reduction (H_2, 5% Pd/C, EtOH) of de-*AB*-cholest-11-en-9-one (**3**) gave in near-quantitative yield the known de-*AB*-cholestan-9-one (**13**) which was characterized as its semicarbazone: mp



13

190–193 °C, mmp 190–193 °C, $[\alpha]^{25}_D$ +52.0° ($CHCl_3$) (lit.[8] mp 193–195 °C, $[\alpha]^{25}_D$ +52° ($CHCl_3$)).[9]

Acknowledgments. This investigation was supported by a Public Health Service Research Grant (CA 13689-07) from the National Cancer Institute, the National Institutes of Health NMR Facility for Biomedical Studies (RR-00292), and, in part, by G. D. Searle and Co. We thank Mr. George Majetich and Mr. Robert Bittner for recording the 250-MHz NMR spectra.

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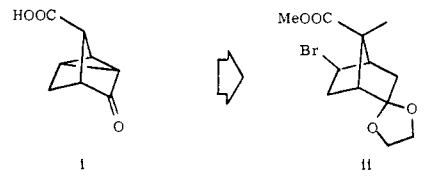
(3) Bromo alcohol **2**, $[\alpha]^{25}_D$ −26° (c 1.80, $CHCl_3$), was prepared (90%) by reduction ($LiAlH_4$, THF, 60 °C) of bromo ketal ester ii[4] (mp 87–88 °C, $[\alpha]^{25}_D$



i ii

−22.6° (c 1.00, $CHCl_3$)) whose synthesis from cyclopropyl keto acid i[5] (mp 137–138 °C, $[\alpha]^{25}_D$ +74° (c 1.00, CH_3OH)[6]) has previously been described.[4]
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(6) Our $[\alpha]^{25}_D$ for optically pure i in methanol (c 1.00) was +75.2°; however, this value rapidly drops to +60°. Use of dioxane (c 1.00) gave $[\alpha]^{25}_D$ +81.8° consistently.
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(9) We are indebted to Professor Basil Lythgoe for providing us with an infrared spectrum of **13** and for a generous sample of the semicarbazone of de-*AB*-cholestan-9-one (**13**).

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α,β Dehydrogenation of Carboxamides

Sir:

Dehydrogenation of the readily available saturated fatty acids to the synthetically more useful α,β-unsaturated deriv-

0002-7863/79/1501-4381$01.00/0