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(10) Fellow of the Alfred P. Sloan Foundation.

Alan P. Kozikowski,* [10] Anthony Ames

Department of Chemistry, University of Pittsburgh
Pittsburgh, Pennsylvania 15260

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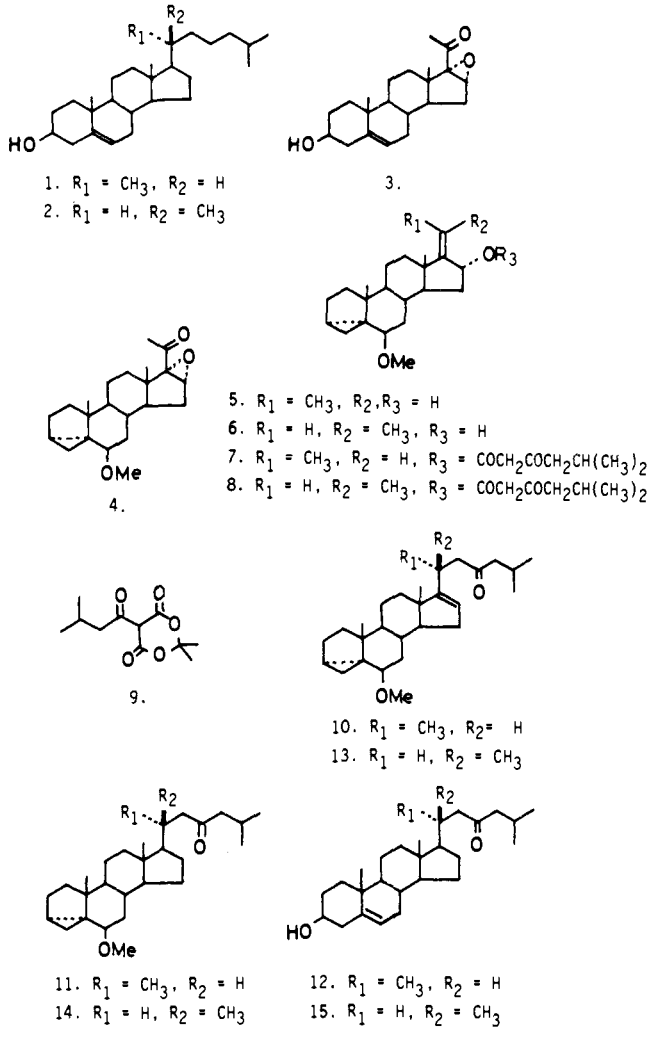
Stereocontrolled Synthesis of Sterol Side Chains†

Sir:

The recent discovery from marine and animal sources of many new sterols[1] with novel side-chain structures has focused attention on developing stereocontrolled methods to introduce these side chains onto tetracyclic steroidal starting materials. An important problem that arises from this approach is the stereospecific control of the C-20 stereochemistry. Many previous attempts[2] to control this center have relied upon catalytic hydrogenation of $\Delta^{17(20)}$ or $\Delta^{20(22)}$ olefins which have invariably led to an epimeric mixture of 20*R* and 20*S* isomers.[3,4]

To exemplify our approach we report on a highly stereocontrolled synthesis of either cholesterol (**1**) or 20-isocholesterol (**2**) from the readily available 16α,17α-epoxy-20-ketopregnane derivative (**3**) that relies on a Claisen rearrangement for stereocontrol of the C-20 center. Protection of **3** as the 3α,5α cyclo ether derivative (**4**) followed by Wharton reaction[5] with hydrazine in *N,N*-dimethylethanolamine yielded a crystalline allylic alcohol (**5**, 63%) [mp 108–110 °C; $[\alpha]_D$ +19°; NMR 0.91 (s, 3 H, C-18 Me), 1.03 (s, 3 H, C-19 Me), 1.73 ppm (d, J = 7 Hz, 3 H, C-21 Me)] and an oil isomer (**6**, 27%) [$[\alpha]_D$ +33°; NMR 0.77 (s, 3 H, C-18 Me), 1.03 (s, 3 H, C-19 Me), 1.79 ppm (d, J = 7 Hz, 3 H, C-21 Me)] which were separated by crystallization.[6] Assignment of the 17(20) *E* olefin stereochemistry to the crystalline isomer (**5**) and the 17(20) *Z* configuration to the minor isomer (**6**) was achieved by correlation of the C-18 methyl shifts in the ^{1}H NMR in accord with Benn's earlier observations.[7]

As pointed out in many reviews on the Claisen rearrangement[8] reaction, a highly ordered six-membered transition state in the concerted cyclic process accounts for the high stereoselectivity observed. From examination of the respective

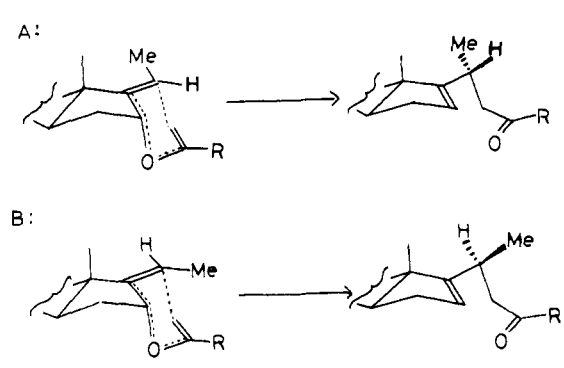


Claisen rearrangement transition states A and B for the two allylic alcohols (**5** and **6**) (Scheme I), it was reasoned that the *E* isomer **5** would give the natural (20*R*) configuration at C-20 and the *Z* isomer **6** would yield the unnatural C-20 isomer. This strategy was successfully realized with the Carroll variant[9] of the Claisen rearrangement on the respective allylic β-ketoacetates **7** and **8**.

The key allylic β-ketoacetates were prepared by taking advantage of Yonemitsu's[10] recent findings that 5-acyl Meldrum's acid, 2,2-dimethyl-1,3-dioxane-4,6-dione derivatives, react with allylic alcohols (1 h in refluxing xylene) to afford β-ketoacetates. The 5-isovaleryl Meldrum's acid (**9**) in turn was prepared by pyridine-catalyzed acylation of Meldrum's acid with isovaleryl chloride.

Carroll reaction of the ester **7** in boiling xylene yielded after 2.5 h in 90% yield a single rearranged material,[11] characterized

Scheme I



Dedicated to Professor Tetsuo Nozoe on the occasion of his 77th birthday.

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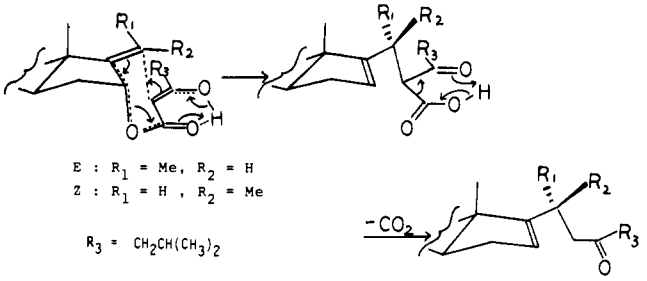
Scheme II



as an oil (**10**): $[\alpha]_D$ +38°; NMR 0.82 (s, 3 H, C-18 Me), 0.88 (d, J = 7 Hz, 6 H, C-26,27 Me), 1.04 (s, 3 H, C-19 Me), 2.79 (t, J = 2.5 Hz, 1 H, C-6α H), 3.33 (s, 3 H, C-6β OMe), 5.31 (br s, 1 H, C-16 H); IR 1710 cm^{-1}. Catalytic hydrogenation of the 16-ene **10** with platinum black in ethyl acetate from the α side[12] fixes the C-17α H stereochemistry and yielded the crystalline dihydro compound **11** (96%): mp 72 °C; $[\alpha]_D$ +38°; NMR 0.75 (s, 3 H, C-18 Me), 0.90 (d, J = 7 Hz, 6 H, C-26,27 Me), 1.01 (s, 3 H, C-19 Me), 2.76 (t, J = 2.5 Hz, 1 H, C-6α H), 3.28 (s, 3 H, C-6β OMe); IR 1710 cm^{-1}. Hydrolysis of the cyclo protecting group with dilute sulfuric acid yielded the known 23-ketocholesterol[13] **12** (84%): mp 145-146 °C; $[\alpha]_D$ −43°; NMR 0.72 (s, 3 H, C-18 Me), 0.92 (d, J = 6 Hz, 6 H, C-26,27 Me), 1.02 (s, 3 H, C-19 Me), 3.50 (br m, C-3α H), 5.39 (br s, 1 H, C-6 H); IR 3350, 1710 cm^{-1}. Wolff-Kishner reduction of **12** gave cholesterol (**1**) in 97% yield, that was identical in all respects (^1H NMR, ^{13}C NMR MS, IR, and GLC retention time) with an authentic sample.

20-Isocholesterol (**2**) was synthesized in a similar way from the isomeric Z-allylic acetoacetate (**8**). Carroll reaction of the Z-olefinic ester **8** (oil) [$[\alpha]_D$ −30°; NMR 0.80 (s, 3 H, C-18 Me), 0.89 (d, J = 7 Hz, 6 H, ester dimethyl), 1.03 (s, 3 H, C-19 Me), 1.59 (d, J = 8 Hz, 3 H, C-21 Me), 5.48 (d, q, J = 2 and 8 Hz, 1 H, C-20 H), 5.83 (br s, 1 H, C-16 βH)] in refluxing xylenes for 4 h yielded the rearranged product **13** (62% yield, oil) [$[\alpha]_D$ +32°; NMR 0.87 (s, 3 H, C-18 Me), 0.92 (d, J = 6 Hz, 6 H, C-26,27 Me), 1.07 (s, 3 H, C-19 Me), 1.07 (d, J = 6 Hz, 3 H, C-21 Me), 5.41 (br s, 1 H, C-16 H); IR 3040, 1710 cm^{-1}] with 33% recovery of **8**[14] (see Scheme II). After catalytic hydrogenation of **13**, the dihydro compound **14** (an oil) [$[\alpha]_D$ +38°; NMR 0.73 (s, 3 H, C-18 Me), 0.90 (d, J = 6 Hz, 6 H, C-26,27 Me), 1.02 (s, 3 H, C-19 Me); IR 3030, 1710 cm^{-1}] was converted into 23-keto-20-isocholesterol (**15**, 82%) [mp 143-145 °C; $[\alpha]_D$ −45°; NMR 0.71 (s, 3 H, C-18 Me), 0.75 (d, J = 7 Hz, 3H, C-21 Me), 0.91 (d, J = 6 Hz, 6 H, C-26,27 Me), 1.00 (s, 3 H, C-19 Me), 3.50 (br m, 1 H, C-3 H), 5.39 (m, 1 H, C-6 H); IR 3250, 1710, 1080 cm^{-1}] from **14** by treatment with dilute sulfuric acid. Wolff-Kishner reduction of **15** gave 20-isocholesterol (**2**) in quantitative yield [mp 149-151 °C; $[\alpha]_D$ −55° (lit.[15] mp 152-154 °C; $[\alpha]_D$ −42 °); NMR 0.69 (s, 3 H, C-18 Me), 0.82 (d, J = 6 Hz, 3 H, C-21 Me), 0.88 (d, J = 6 Hz, 6 H, C-26,27 Me), 1.02 (s, 3 H, C-19 Me), 3.49 (br m, 1 H, C-3 H), 5.35 (m, 1 H, C-6H)], which showed a depression of the melting point on admixture with authentic cholesterol. The retention time of **2** on GLC is shorter than that of cholesterol (**1**). Thus, these results provide a useful method for stereocontrolled introduction of the desired C-20 stereochemistry in steroid side-chain synthesis via Claisen rearrangement and related reactions.

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Masato Tanabe*
Bio-Organic Chemistry Laboratory
SRI International, Menlo Park, California 94025

Koji Hayashi
Faculty of Pharmaceutical Sciences
Hokkaido University, Kita-12, Nishi-6, Kita-ku
Sapporo, 060 Japan
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An Efficient and Versatile Generation of *o*-Xylylenes by Fluoride Anion Induced 1,4 Elimination of *o*-(α-Trimethylsilylalkyl)benzyltrimethylammonium Halides

Sir:

Cycloaddition of olefins to *o*-xylylenes provides a convenient synthetic method for the preparation of tetrahydronaphthalene derivatives. The *o*-xylylene moiety is generated in situ by the metal induced[1] or thermal[2] 1,4 elimination reactions of the corresponding *o*-xylylene derivatives such as *o*-xylylene dihalides and *o*-methylbenzyltrimethylammonium hydroxides. Intramolecular cycloaddition of *o*-xylylenes generated by electrocyclic ring opening of substituted benzocyclobutenes was reported recently,[3] which constitutes a new approach to the synthesis of polycyclic ring systems including natural products.

Herein we report an efficient and versatile method for the generation of *o*-xylylene intermediates (**2**) by fluoride anion induced 1,4 elimination[4] of *o*-(α-trimethylsilylalkyl)benzyltrimethylammonium halides (**1**). A simple and mild gen-

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