Synthesis of (23*R*)- and (23*S*)-23*H*-Isocalysterols. The First Synthesis of a Representative of Marine Sterols with a Cyclopropene Moiety in the Side Chain

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Calysterols are a class of marine sterols[1] of considerable interest because of their unusual structure and supposed biological function as a cell membrane component.[2] Calysterol (**1**) (Figure 1) (first reported in 1975 by the Napoli group[3]) and its isomers differing in the double bond position (23*R*)-23*H*-isocalysterol[4] (**2a**) and (24*S*)-24*H*-isocalysterol[5] (**3**), have been isolated from the Mediterranean sponge *Calyx niceaensis*, where they occur as the principal sterol constituents. The 23-epimer of compound **2a**, (23*S*)-23*H*-isocalysterol (**2b**), together with compounds **1** and **3** and 5,6-dihydro derivatives of compounds **1**, **2b**, and **3**, have been isolated from the Bahamas sponge *Calyx podatypa*.[6] Studies by Djerassi and co-workers on marine sterols have resulted in elucidation of calysterol biosynthesis[7] and have contributed a great deal to the understanding of their chemical and spectral properties.[8] An account of the efforts aimed at the construction of a cyclopropene-containing sterol side chain has been published;[9,10] however, none of the calysterols have so far been synthesized. In this communication, the first preparation of representatives of this group of compounds is described.

The difficulties in the reported attempts to synthesize calysterol ensue from the high reactivity of the cyclopropene system.[11] For this reason we planned to introduce the double bond into a preformed cyclopropane intermediate at the terminal stages of synthesis. On the other hand, the cyclopropene double bond in these compounds is sterically shielded by the isopropyl group and the large steroid fragment. This suggested that steric shielding may be the major obstacle in assembling the properly functionalized, cyclopropane-containing side chain in synthetic intermediates.

We commenced our studies on calysterol synthesis with 23*H*-isocalysterol [23,28-cyclostigmasta-5,24(28)-dien-3β-ol], for which both C_{23} epimers **2a** and **2b** are fully characterized. The tribromocyclopropane derivatives **8** were chosen as the key intermediates (Scheme 1). It has been shown by Baird and others[12] that 1,1,2-trihalocyclopropanes react with alkyllithiums

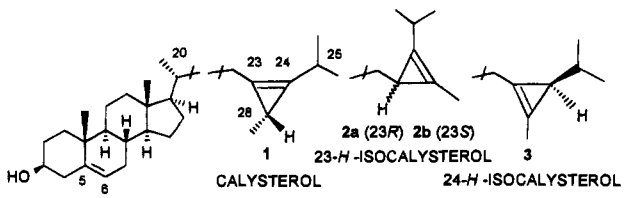
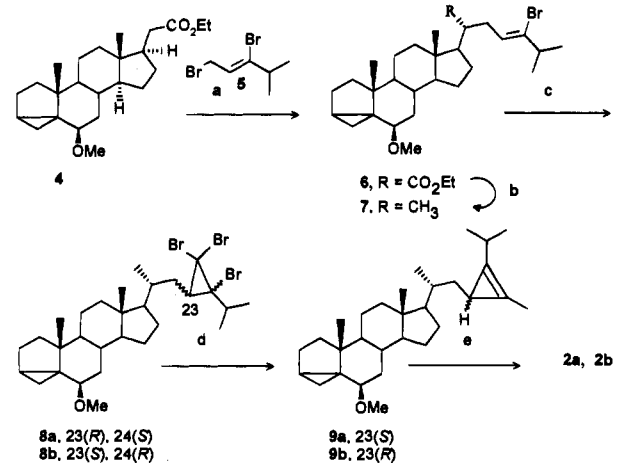


Figure 1.

Scheme 1



[a] Reagents and conditions: (a) LDA/THF, −78 °C, and then **5**, −78 °C to room temperature, 80% yield; (b) DIBAL/hexane−CH_2Cl_2, −23 °C, then TsCl−Py/CH_2Cl_2 and then Et_3BHLi/THF, 0 °C, 80% yield; (c) $CHBr_3$−50% NaOH−CETRIMID, 50% yield (separation of the diastereomers on SiO_2); (d) MeLi/ether, −78 °C to room temperature and then MeI, −78 °C to room temperature, 60% yield; (e) TsOH/aqueous dioxane.

to generate the corresponding 1-lithiocyclopropene derivatives, which can be alkylated with alkyl halides.

Ester **4**[13] (Scheme 1) was alkylated[14] with (*Z*)-1,3-dibromo-4-methylpent-2-ene[15] (**5**) to afford the (20*R*) derivative **6** in 80% yield. Three-step reduction of the carbethoxy group in **6** with the reagents indicated in Scheme 1 gave **7** in 80% overall yield. The latter was subjected to reaction with dibromocarbene, generated by the method of Mąkosza and Fedoryński,[16] to provide **8** in 50% yield. Application of sonication to this reaction allowed the reaction time to be shortened significantly (from 18 to 2 h); the yield could not be improved, however. HPLC analysis of **8** indicated that two diastereomers were formed in a ratio of ca. 1:1.[17] The mixture was separated by chromatography on a silica gel column to give pure diastereomers.

Isomer **8a**[18] (TLC, $R_f = 0.43$, hexane−CH_2Cl_2, 2:1, developed three times) was treated with an excess of methyllithium in ether

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(17) HPLC was performed using Merck LiChrospher 100 RP-18, 5 μm, 250 × 4 mm column; mobile phase 1% H_2O in methanol, 0.6 mL/min flow rate.
(18) The configuration was assigned from the configuration of the respective final products, **2a** or **2b**. It is assumed that during the transformation the chiral center at C_{23} was not affected, and that no double-bond isomerization occurred during the reaction of **7** with dibromocarbene.

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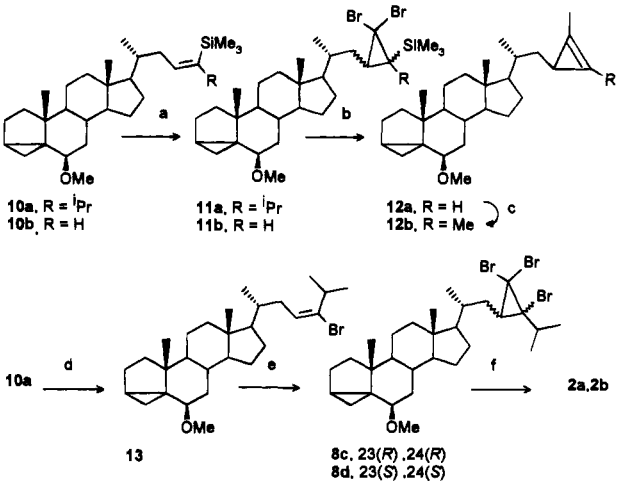
and then with methyl iodide. After chromatographic purification of the product, **9a** was obtained in 60% yield. The final stage of the synthesis consisted of removal of the protective group. Compound **9a** was hydrolyzed in aqueous dioxane containing some TsOH, at 80 °C for 30 min.[19] The 500-MHz ^{1}H NMR spectrum of the product, isolated by chromatography,[20] showed signals at δ 2.014 (three-proton doublet, $J = 1.54$ Hz) for the methyl group adjacent to the cyclopropene ring (C_{29} H), at δ 1.119 and 1.094 (two three-proton doublets, $J = 6.83$ and 6.90 Hz, respectively) for the C_{26} and C_{27} methyl groups, at δ 1.011 (three-proton doublet, $J = 6.48$ Hz) for the C_{21} methyl group, and at δ 1.012 and 0.687 (two three-proton singlets) for the angular methyl groups, C_{19} and C_{18}, respectively. The observed signals correspond to those reported for **2a** isolated from *C. podatypa*.[6,21] The low-resolution and high-resolution mass spectra of this product were consistent with structure **2a**.

The tribromocyclopropane **8b** ($R_f = 0.47$) was treated in an analogous way to give 23*H*-isocalysterol **2b** *via* intermediate **9b** (with similar yields). The diagnostic difference between ^{1}H NMR spectra of **2b** and its epimer **2a** was apparent in the signals due to C_{29}, C_{26}, and C_{27} methyl groups. Thus, in the spectrum of **2b** these signals occurred at δ 1.994 (three-proton doublet, $J = 1.54$ Hz, C_{29} H) and at δ 1.117 and 1.102 (doublets, $J =$ 6.94 and 7.01 Hz, respectively) (C_{26} and C_{27}). The ^{1}H NMR and mass spectra of **2b** were in agreement with those reported for the product isolated from *C. niceaensis*.[4,6]

An unseparated mixture of **8a** and **8b**, obtained from the reaction of **7** with dibromocarbene, was also transformed into a mixture of calysterols **2a** and **2b** using the reactions described above. Separation of these calysterols proved to be much more difficult than separation of intermediates **8**. In fact, **2a** and **2b** could be separated only by HPLC (retention time[17] 30.35 and 32.35 min, respectively).

In a parallel series of experiments we attempted to explore methodology employing organosilicon chemistry. It is well documented that the cyclopropene double bond can be generated under mild conditions from β-halo silanes.[22] First we examined the possibility of preparing **11a** (Scheme 2), which was expected to yield a product with the calysterol side chain, on treatment with fluoride anion. Vinylsilane **10a** was prepared by alkylation of **4** with (*Z*)-1-bromo-4-methyl-3-(trimethylsilyl)pent-2-ene,[23] followed by reduction of the ester group. Compound **10a** resisted reaction with dibromo- or dichlorocarbene generated under phase-transfer conditions or from the Seyferth reagent. Our efforts to obtain **11a** failed, apparently due to steric shielding of the double bond in **10a**. On the other hand, **10b**[24] was transformed into the dibromocyclopropane derivative **11b** in good yield (Scheme 2). One of the bromine atoms in **11b** was replaced by a methyl group using the method of Hiyama et al.,[25] and the resulting derivative was treated with tetrabutylammonium fluoride (TBAF) to afford cyclopropene **12a**. Methylation of **12a** with butyllithium and methyl iodide[26] smoothly gave compound **12b**. However, all attempts to attach the isopropyl group to cyclopropanes **11b** and **12a** were unsuccessful.

Scheme 2



[a] Reagents and conditions: (a) (**10b**) $CHBr_3$–50% NaOH–TEBA–Cl, 73% yield (**11b**); (b) (**11b**) BuLi–MeI/THF–HMPA, −78 °C, and then Bu_4NF/THF, 88% overall yield; (c) MeLi–TMEDA–MeI/THF, room temperature, 69% yield; (d) Br_2/CCl_4 and then Bu_4NF, 80% yield; (e) $CHBr_3$–50% NaOH–TEBA–Cl, 50% yield; (f) MeLi–MeI/ether, room temperature (40% yield), and then TsOH/aqueous dioxane.

Bromination of **10a**, followed by desilylation with TBAF, gave exclusively **13** with the *E* configuration of the double bond (it is noteworthy that this result is in conflict with the stereochemical prediction[27] regarding sterically unshielded vinylsilanes). Bromide **13** was subjected to cyclopropanation under conditions similar to those used for its *Z* counterpart **7**. The resulting diastereomeric tribromocyclopropanes **8c** and **8d**, which could be separated only by HPLC,[17] were transformed into calysterols **2a** and **2b**, following the procedure developed for **8a** and **8b**.

In conclusion, we have described a seven-step synthesis of representative calysterols **2a** and **2b** from readily available steroid intermediate **4**. Some new methods for generation of the cyclopropene moiety were developed in the course of the synthesis.

Supplementary Material Available: Selected spectral and analytical data for compounds **2a**, **2b**, **6**, **7**, **8a**, **8b**, **10a**, **10b**, **11b**, **12a**, **12b**, and **13** (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(20) Calysterol **2a** was accompanied by minor side products. Their separation and structure elucidation are in progress.

(21) We are indebted to Professor Donato Sica for providing information on chemical properties and stability of calysterols.

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