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## Ficisterol (23-Ethyl-24-methyl-27-norcholesta-5,25-dien-3β-ol). A Biosynthetically Unprecedented Sterol from the Marine Sponge *Petrosia ficiformis*[1]

*Sir:*

Petrosterol (**1**, 26,27-cycloaplysterol), a novel cyclopropane-containing sterol, has recently been identified in a Pacific sponge, *Halichondria* sp.[2] and as the major sterol from *Petrosia ficiformis* collected in the Bay of Naples.[3,4] In view of our interest in the biosynthetic origin of the cyclopropane function in the sterol side chain, we have carefully analyzed the minor and trace components of *P. ficiformis* with the hope of identifying possible related biosynthetic intermediates. We now report the presence of a new $C_{29}$ sterol with an unprecedented side chain, shown to be 23-ethyl-24-methyl-27-norcholesta-5,25-dien-3β-ol (**2**), which we have named ficisterol.

Argentic TLC separation of *P. ficiformis* sterol acetates[3] using 5:2[6] (v/v) hexane–benzene or hexane–toluene gave several bands, the most polar of which contained four major components. Repeated TLC with hexane–toluene (1:1) and reversed-phase HPLC on $C_{18}$ μBondapak[7] gave **2** (0.6% of total sterol fraction), $M^+$ 412.3701 ($C_{29}H_{48}O$), whose GC (OV-17 column) retention time (cholesterol, 1.00) was 1.58, acetate mp 99–100 °C. Since the presence of the usual $\Delta^5$-3β-hydroxy sterol nucleus was demonstrated[8] by the peaks at *m/z* 271, 255, 231, and 213, the sterol must possess one degree of unsaturation in the side chain. The 360-MHz $^1$H NMR spectrum in $C_6D_6$ (δ, parts per million) of the acetate of **2** shows six methyl group signals (see Table I), with one of the signals clearly a triplet, suggesting the presence of a $-CH_2-CH_3$ entity on the side chain. Significantly, doublets due to a terminal isopropyl group are absent. A multiplet at 5.85 is assigned to the vinylic proton at C-25, while other easily recognizable signals are 5.38 (C-6 H) and 4.85 (m) (3α-H acetate). A pair of doublets (2 H) at 5.03 and 5.06 is typical for a terminal methylene group,[9] and double resonance experiments showed that these protons at C-26 are coupled with the C-25 vinylic hydrogen at 5.85.

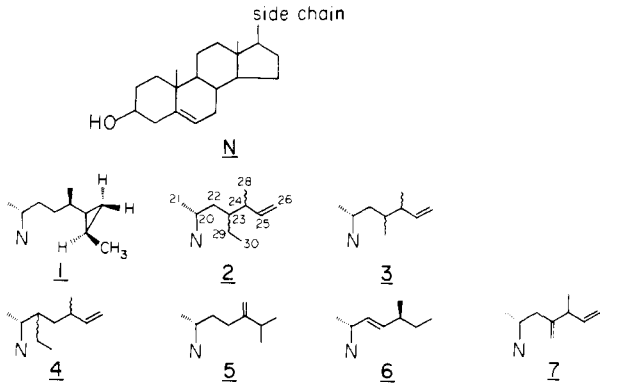
Irradiation of the allylic C-24 proton at 2.27 collapsed the 28-methyl doublet at 0.95 to a singlet, and at the same time simplified the complex vinylic proton region at 5.85. Irradiation of the C-26 geminal protons also simplified the vinylic C-25 hydrogen and the resonance due to the C-24 allylic proton. Irradiation of the vinylic C-25 hydrogen collapses the geminal C-26 protons and simplified the allylic C-24 hydrogen. The presence of part of the side chain as a 3-substituted but-1-ene is thus established, which with the addition of the requisite ethyl group leads to structure **2** or **4**, both of them being unprecedented in terms of a 22- or 23-ethyl substituent.

Triple irradiation experiments performed by simultaneously irradiating the 28-methyl group *and* C-25 vinylic hydrogen clearly produced a *doublet* ($J \sim 5$ Hz) for the allylic hydrogen at C-24, thus demonstrating that position 23 is monosubstituted (i.e., **2**). The lower homologue **3** ($C_{28}H_{46}O$, $M^+$ 398) has also been isolated as a 1:1 acetate mixture with 24-methylenecholesterol (**5**), but the difference in the chemical shift of the C-21 and C-28 methyl protons (Table I) of the acetate suggest differences in stereochemistry.

**Table I.** $^1$H Chemical Shifts of the Acetates of Ficisterol (**2**) and 23,24-Dimethyl-27-norcholesta-5,25-dien-3β-ol (**3**) (360 MHz, $C_6D_6$)

| carbon | 2 | 3 |
|---|---|---|
| 18-$CH_3$ | 0.686 (s) | 0.684 (s) |
| 19-$CH_3$ | 0.918 (s) | 0.925 (s) |
| 21-$CH_3$ | 0.984 (d, $J$ = 6.5)[a] | 1.017 (d, $J$ = 6.9) |
| 30-$CH_3$ | 0.887 (t, $J$ = 7.3) | |
| 29-$CH_3$ | | 0.867 (d, $J$ = 6.7) |
| 28-$CH_3$ | 0.955 (d, $J$ = 6.9) | 0.972 (d, $J$ = 6.4) |
| C-25 H | 5.85 (m) | 5.78 (m) |
| C-26 (2 H) | 5.03, 5.06 (d) | 5.03, 5.06 (d) |
| C-6 H | 5.35 (m) | 5.38 (m) |
| C-3 ($COCH_3$) | 1.75 (s) | 1.75 (s) |
| 3-α-H of acetate | 4.85 (m) | 4.86 (m) |

[a] Coupling constants $J$ are in hertz.




Ficisterol (**2**) is biosynthetically intriguing since it lacks the normal terminal isopropyl functionality and therefore resembles occelasterol (**6**), isolated from a marine annelid.[10] Even more unusual is the presence of the C-23 ethyl substituent; although several marine sterols (e.g., gorgosterol,[11] 23,24-dimethylcholesta-5,22-dien-3β-ol,[12] and dinosterol[13]) have been shown to be methylated at C-23 and C-24, ficisterol (**2**) is the first example of C-23 ethylation in a naturally occurring sterol. This suggests that methylation of a hitherto undetected 23-methylene sterol (e.g., **7**) is a new mode of sterol-side-chain bioalkylation and we are actively engaged in searching in marine organisms for further examples.

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## Helixanes. The First Primary Helical Molecules: Polyoxapolyspiroalkanones

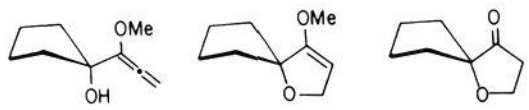
*Sir.*

The suggestion in the early fifties that the secondary structure of polypeptides has an $\alpha$-helix conformation[1] led the way for extensive studies of helical topology, especially in biopolymers.[2] In particular the far-reaching double-stranded helical conformation for DNA[3] and the helical nature of many polymers[2,4] highlight the fact that helical molecules have a preeminent place in macromolecular chemistry. Molecules that have helical topology but do not fall into the above classes are helicene,[5] skewed paracyclophane,[6] and helical triphenylmethane systems.[7]

All of the above helical molecules owe their helical topology to their secondary and tertiary structure.[8] To date that is no molecule that is helical because of the primary bonding structure.

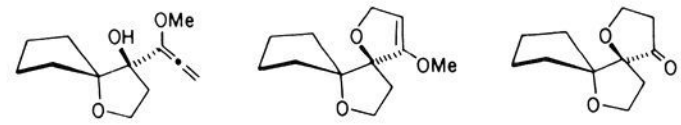
Here we report a rational synthesis of the *first primary helical molecules,* based upon the shape (bond angles and bond lengths) of the *tetrahydrofuran ring system.*

The adduct **1** between cyclopentanone (a starting block) and $\alpha$-lithio-$\alpha$-methoxyallene, on treatment with potassium *tert*-butoxide (0.2 equiv) in *tert*-butyl alcohol containing 18-crown-6 (0.05 equiv) heated at reflux for 15 h gave **2.**[9] Acid hydrolysis (6 N $H_2SO_4$) of **2** gave **3.** The choice of conditions for the release of the dihydrofuranone carbonyl group is crucial in this step and in the subsequent hydrolysis procedures of the enol ethers described, since 1 N $H_2SO_4$ or two-phase systems (oxalic acid–dichloromethane) gave **3** contaminated with decomposition products, whereas increasing the strength of the acid to 6 N $H_2SO_4$ eliminated degradation and produced only a clean high-yield conversion of **2** into **3** (82% overall yield on a 8.0-g scale).



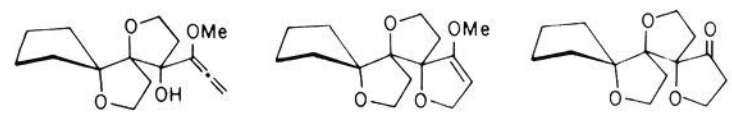

1 2 3

Since we started with a carbonyl compound, cyclopentanone, and spiroannulated a dihydrofuranone onto it, and since we have ended up with a new carbonyl compound, namely 1-oxaspiro[4.4]nonan-4-one (**3**), the product in principle is capable of being subjected to another spiroannulation sequence. The carbonyl group of **3** is relatively hindered, but it reacts cleanly with $\alpha$-lithio-$\alpha$-methoxyallene to give the adduct **4,** after aqueous ammonium chloride workup, in 95–98% yield.[10] The adduct **4** on treatment with KOBu$^t$ (0.1 equiv)/HOBu$^t$/18-crown-6 (0.05 equiv) heated at reflux for 15 h gave **5,** which on acid hydrolysis (6 N $H_2SO_4$) gave **6** (70%).[11]




4 5 6

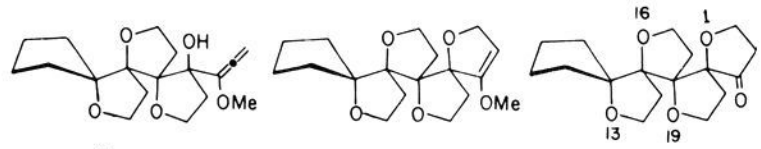
At this point we have reached a crucial stage. The first and only stereochemical issue arises. The carbonyl group in **6** has two diastereotopic faces available for the addition of a nucleophilic species. Dreiding models and space-filling models indicate that one face of **6** is severely hindered by the two five-membered rings already present. In particular the cyclopentane ring sits under one face of the carbonyl group in **6.** In the event, **6** adds $\alpha$-lithio-$\alpha$-methoxyallene to give a single crystalline adduct **7,** mp 133–137 °C in ≥90% yield.[12] Treatment of this adduct with KOBu$^t$ (0.2 equiv)/HOBu$^t$ 18-crown-6 (0.05 equiv) heated at reflux led to **8,** which on acid hydrolysis (6 N $H_2SO_4$) gave the beautifully crystalline cyclopentyl[3]helixane **9,** mp 88.5–90 °C (67% overall from **7**).




7 8 9

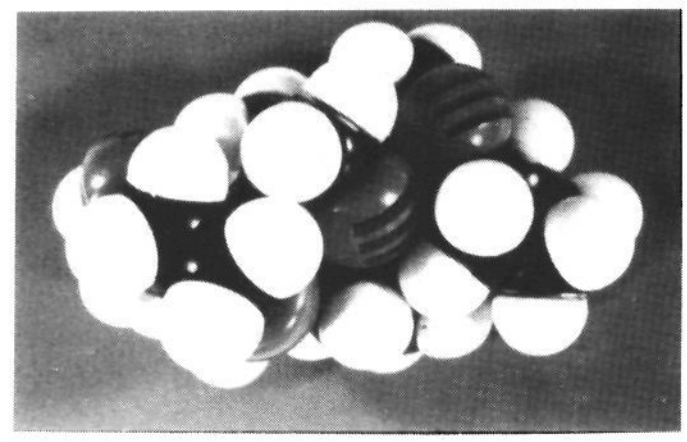
We hoped that, as we extended the spiro rings, the allenyl adducts would undergo ring closure under increasingly mild conditions. This optimistic view is based upon the idea that the steric compression of the alkoxide of **10** would favor cyclization since covalent association of a metal counterion (Li or K in the cases described) is sterically hindered, and furthermore **10** may act as its own crown ether ionophore and effectively remove the counterion (Li or K) from covalent association with the alkoxide.

Treatment of **9** with $\alpha$-lithio-$\alpha$-methoxyallene gave **10,** mp 92–99 °C (45%),[13] which cyclized to **11** at *room temperature* (28 °C) when treated with KOBu$^t$ (0.2 equiv)/HOBu$^t$/18-crown-6 (0.05 equiv) to give cyclopentyl[4]helixane **12,** mp 123–124 °C (67%), after acid (6 N $H_2SO_4$) hydrolysis. Models




10 11 12

(CPK) (see photograph) show that cyclopentyl[4]helixane **12** is a helix-shaped molecule. The oxygen atoms and methylene groups spiral around the central core of the molecule. To establish the structure of **12** unequivocally and confirm speculations concerning stereochemistry, a single-crystal X-ray analysis was conducted. The results are as follows.



Cyclopentyl[4]helixane crystallized in the triclinic space group $P\bar{1}$ with four molecules per unit cell. Accurate lattice parameters are $a$ = 13.881 (4), $b$ = 8.853 (2), $c$ = 13.668 (3) Å; $\alpha$ = 104.83 (2), $\beta$ = 76.60 (2), $\gamma$ = 78.71°. The structure was solved by direct methods and has currently been refined

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