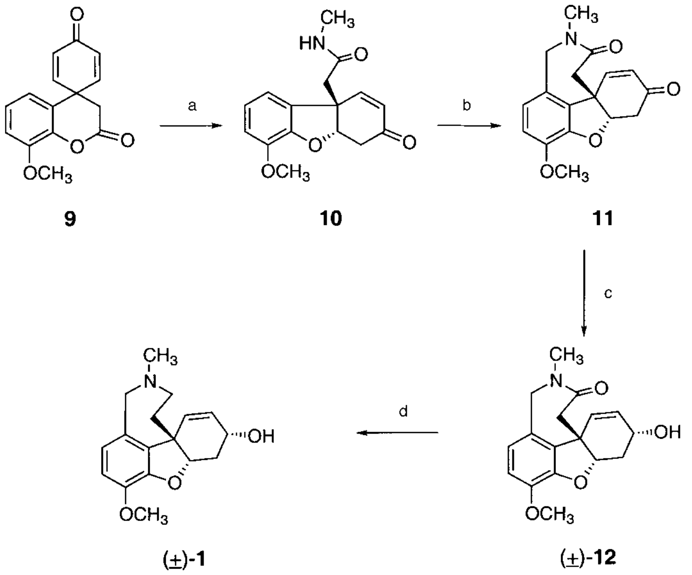
with an excess of $(PhSeO)_2O$ or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone were unsuccessful.[10] Moreover, it was not possible to introduce a halogen atom α to the ketone group or to prepare the corresponding enol ether in order to obtain the required dienone **9**. We found that the transformation of **8** to **9** can be accomplished by nonclassical oxidation. The dienone **9** was obtained in 50 % yield by using $(PhSeO)_2O$ in the presence of 4 Å molecular sieves. A 1/1 mixture of alumina and silica could also be used instead of the molecular sieves. These oxidative systems have not been previously described.

The reaction of **9** with 40 % aqueous methylamine at room temperature resulted in the spontaneous Michael addition of the resulting phenol to cyclohexadienone to afford amide **10** in quantitative yield. Compound **10** was cyclized by the action of paraformaldehyde and trifluoroacetic acid to give **11** in 63 % yield. Enone **11** was reduced with L-Selectride to give alcohol **12** in 93 % yield. Finally, reduction of **12** with $LiAlH_4$ in DME afforded (±)-galanthamine (**1**) in 80 % yield (Scheme 2).



Scheme 2. a) 40 % $MeNH_2$, THF, 20 °C, 20 min, 100 %; b) $(CH_2O)_n$, TFA, $Cl(CH_2)_2Cl$, 60 °C, 20 h, 63 %; c) L-Selectride, THF, −78 °C, 1 h, 93 %; d) $LiAlH_4$, DME, 50 °C, 12 h, 80 %. DME = 1,2-dimethoxyethane, TFA = trifluoroacetic acid.

Thus, (±)-galanthamine was synthesized in eight steps with an overall yield of 12 %. This is the shortest and most efficient nonbiomimetic total synthesis of (±)-galanthamine to date. An intramolecular Heck reaction followed by a nonclassical dehydrogenation reaction provided the key intermediate spirocyclohexadienone **9**. Syntheses of compounds related to galanthamine and narwedine (**3**) are in progress.

Received: July 3, 2001 [Z17414]

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Trimerization of a Steroid Ketone To Form a Chiral Molecular Cleft[**]

Robert A. Pascal, Jr.,[*] Mary S. Mathai, Xianfeng Shen, and Douglas M. Ho

The acid-catalyzed trimerization of cyclic ketones to give hexasubstituted benzenes has long been known, and various acid catalysts have been employed for this transformation.[1] Unlike the trimerization of alkynes, this triple aldol condensation is inherently directional, and, if an enantiomerically pure starting ketone is used, then only a single, enantiomerically pure, C_3-symmetric product will be obtained. We now show that the trimerization of steroid ketones with *cis* A/B ring fusions yields a new class of chiral molecular bowls.

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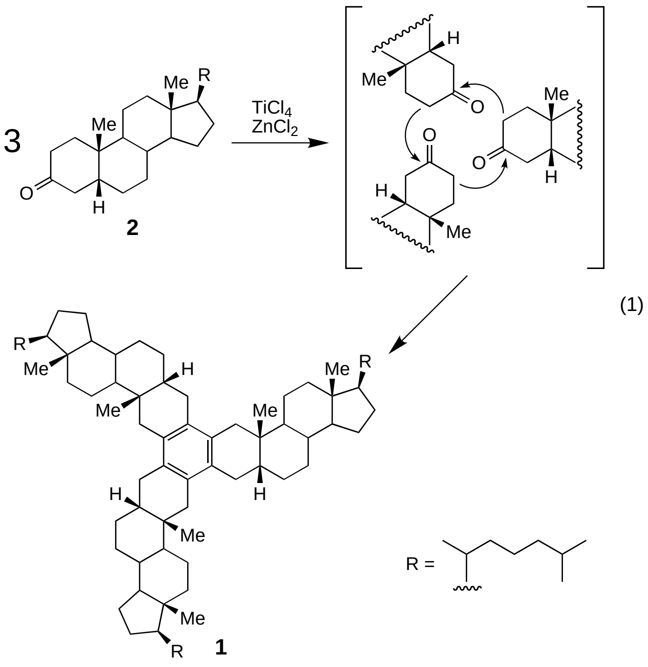
[**] This work was supported by a National Science Foundation Grant (CHE-0077990).

Molecular mechanics calculations (MMFF[2, 3]) indicate that trimers of *trans* A/B steroids are relatively flat molecules, but trimers derived from *cis* A/B steroids, such as **1**, should contain deep, chiral clefts. The one-step synthesis of a new class of chiral bowls was a very attractive prospect, but all attempts to trimerize steroid ketones by using H_2SO_4, HCl/HOAc, $SiCl_4$, and polyphosphoric acid as catalysts were unsuccessful. However, when coprostanone (**2**, 5β-cholestan-3-one) was heated with $TiCl_4$ and $ZnCl_2$ in hexanes, the trimer **1** was obtained in 31% yield [Eq. (1)]. This material was easily purified, and its C_3 symmetry was unambiguously established by its 27-line ^{13}C NMR spectrum. Similar reactions of 5α-cholestan-3-one and 5β-androstan-3-one gave the corresponding steroid trimers in 66% and 29% yields, respectively (data not shown).[4]



(1)

Trimer **1** is a remarkable hydrocarbon. Crystals of **1** suitable for X-ray analysis[5] were obtained from $CHCl_3$/EtOH, and the molecular structure of one of the two crystallographically independent molecules is shown in Figure 1. As expected, the B, C, and D rings of the tri-steroid core of **1** define a C_3-symmetric cavity above its aromatic base. This cavity is further extended by the steroid side chains, and it has an overall depth of around 14 Å. The strongly slanting walls of the C_3-symmetric cleft make it impossible to assign a single value to its width, but, for example, the C1–C64 distance is 5.8 Å (see Figure 1, right). When van der Waals radii are taken into account, the cavity appears to be large enough to accommodate a small alkane guest, although no guest molecule was observed in the crystal.

The experimental structure of compound **1** is significantly more compact than predicted by gas-phase calculations as can be seen from Figure 2. The tight packing of compound **1** in the crystal may explain the difference between the calculated and observed structures. The molecules form columnar dimers through interacting side chains, and these dimers stack side by side to form the layered structure illustrated in Figure 3. If nothing else, these results suggest that the relatively rigid cavity in **1** may be able to flex enough to accommodate guest molecules of varying sizes.

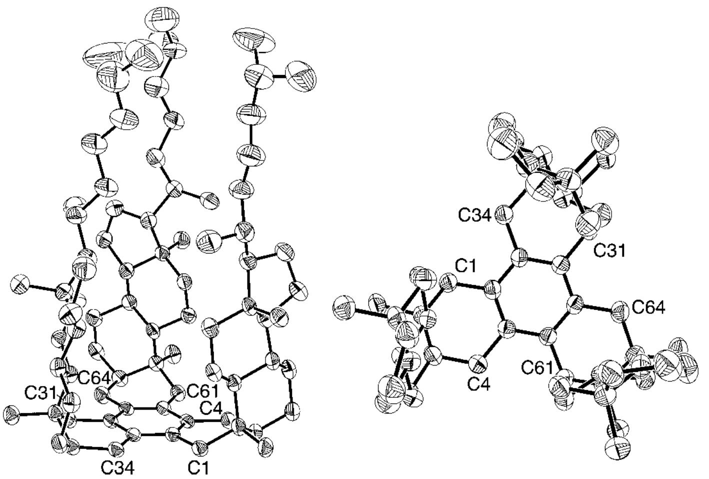


Figure 1. Two views of the molecular structure of one of the two crystallographically independent molecules of compound **1**. Thermal ellipsoids are drawn at the 40% probability level, hydrogen atoms have been omitted for clarity, and in the right structure the steroid side chains have been omitted.

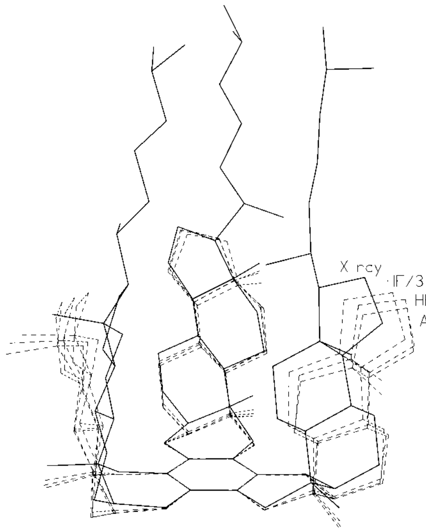


Figure 2. Superposition of the X-ray structure of **1** and the structures of its tri-steroid core calculated by three different computational methods (AM1[9] and low-level ab initio methods[10]).

It has been argued[11, 12] that the ideal enantioselective host molecule should contain a chiral cavity, strongly complementary to only one enantiomer of the chiral guest, and it should possess a single, clearly defined, minimum energy conformation. Practical applications require that the host should be preparable from readily available starting materials by way of a short, simple synthesis. Compound **1** is the first example of a new class of molecules that may meet these criteria. The C_3-symmetric ground state conformation of its tri-steroid nucleus (ignoring the flexible side chains) is more than 5 $kcal\,mol^{-1}$ below the next most stable conformation (MMFF), thus the

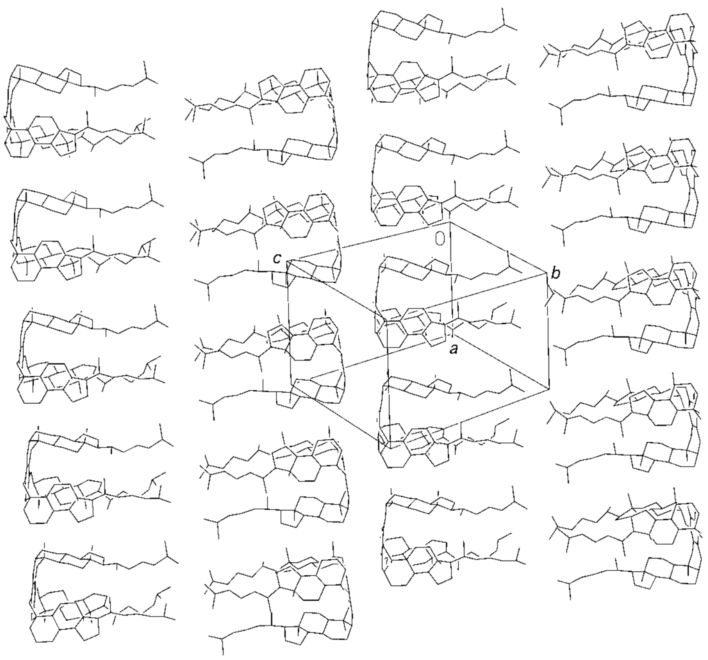


Figure 3. Crystal packing diagram showing one layer of molecules of **1**.

tri-steroid may be considered to be "conformationally homogeneous".[12] Furthermore, the facile synthesis of **1** suggests that similar compounds could be prepared from a variety of naturally occuring ketones, and such trimers may prove to be good frameworks for the construction of new chiral auxilliaries or enantioselective hosts.

Experimental Section

Preparation of **1**: Ketone **2** (468 mg, 1.21 mmol) was dissolved in hexanes (15 mL) in a screw-capped tube. Anhydrous $ZnCl_2$ (165 mg, 1.21 mmol) and $TiCl_4$ (1.21 mL of a 1M solution in CH_2Cl_2) were added to give a light yellow mixture. The tube was placed in an oil bath, heated to 120 °C, and left overnight. After cooling, water was added, and the resulting mixture was extracted twice with CH_2Cl_2. The combined organic layers were washed four times with water, dried over Na_2SO_4, and concentrated to leave a light yellow solid (400 mg). Fractionation of this material by silica gel column chromatography (45:1 hexanes:EtOAc) gave trimer **1** as a white crystalline solid (140 mg, 0.127 mmol, 31 % yield). Melting behavior: 175 °C, begins to darken and shrink; 270 °C, fully melted with decomposition. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.66$ (s, 9H), 0.849 (d, $J = 7$ Hz, 9H), 0.852 (d, $J = 7$ Hz, 9H), 0.87 (d, $J = 6$ Hz, 9H), 1.12 (s, 9H), 0.9–2.1 (methylene envelope, ca. 80H), 2.49 (dd, $J = 16$ Hz, 7 Hz, 3H), 2.82 (m, 6H); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 12.2$, 19.0, 21.9, 22.8, 23.0, 23.3, 24.5, 25.1, 26.3, 26.5, 28.2, 28.3, 28.7, 28.9, 34.5, 35.4, 36.6, 38.2, 39.6, 39.8, 40.4, 41.2, 43.0, 56.8, 57.2, 130.4, 131.0 (27 of 27 expected resonances); FAB MS: m/z (%): 1105 (M^+ [$^{12}C_{80}{}^{13}C_1$], 100); $[\alpha]_D^{25} = +45$ ($c = 1$ in $CHCl_3$);[13, 14] UV (cyclohexane): λ_{max} (ε) = 300 (300, sh), 284 (460, sh), 276 (490), 254 (490, sh), 230 (2100, sh), 216 nm (2800); CD (cyclohexane): $[\theta]_{300} = +520$, $[\theta]_{286} = +630$, $[\theta]_{275} = +540$; CD (heptane): $[\theta]_{299} = +500$, $[\theta]_{286} = +620$, $[\theta]_{275} = +500$.

Received: July 30, 2001 [Z17637]

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[1] Typical examples of such trimerizations include the following (with the catalyst in parentheses): a) C. Mannich, *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 153–158 (H_2SO_4); b) R. Seka, W. Kellermann, *Ber. Dtsch. Chem. Ges.* **1942**, *75*, 1730–1738 ($ZnCl_2$/HOAc); c) S. S. Elmorsy, A. Pelter, K. Smith, *Tetrahedron Lett.* **1991**, *32*, 4175–4176 ($SiCl_4$/EtOH); d) A. N. Pyrko, *Zh. Org. Khim.* **1992**, *28*, 215–216 ($TiCl_4$); e) R. B. M. Ansems, L. T. Scott, *J. Am. Chem. Soc.* **2000**, *122*, 2719–2724 ($TiCl_4$).

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[5] X-ray crystal structure determination for **1**: Formula $C_{81}H_{132}$, $M = 1105.87$, crystal size $0.33 \times 0.23 \times 0.15$ mm, triclinic, $P1$, $a = 11.6885(2)$, $b = 13.2846(3)$, $c = 24.5806(6)$ Å, $\alpha = 87.117(1)$, $\beta = 84.528(1)$, $\gamma = 68.063(1)°$, $V = 3523.9(1)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.042$ Mg m^{-3}, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), $2\theta_{max} = 45.1°$, $T = 200(2)$ K, Nonius Kappa CCD diffractometer. A total of 44081 reflections were indexed, integrated, and corrected for Lorentz and polarization effects by using DENZO-SMN and SCALEPACK.[6] Data reduction gave 18424 unique reflections ($R_{int} = 0.053$), of which 13497 had $I > 2\sigma(I)$. The structure was solved by the direct methods program CRUNCH,[7] and it was refined by full-matrix least-squares on F^2 using SHELXTL.[8] All carbon atoms were refined with anisotropic displacement coefficients, and hydrogens were included with a riding model and isotropic displacement coefficients [$U(H) = 1.2U(C)$ or $1.5U(C_{methyl})$]. Moderate disorder in two of the steroid side chains warranted the inclusion of a disorder model and some restraints. $R(F) = 0.059$, $wR(F^2) = 0.131$, and $S = 1.07$ for the 13497 reflections with $I > 2\sigma(I)$, and $R(F) = 0.091$, $wR(F^2) = 0.148$, and $S = 1.02$ for all unique reflections, 1522 parameters, and 55 restraints. The residual electron density ranged from -0.16 to 0.35 e A^{-3}. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-163715. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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