The first example of a tweezer-like structure in diterpene derivatives of the kaurane series

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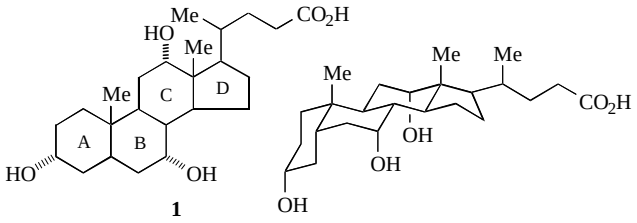
The first compound with a tweezer-like structure in diterpene derivatives of the kaurane series was obtained in the reaction of the acid chloride of isosteviol with diethylene glycol.

The literature provides a great number of examples on the molecular receptors for binding organic and natural compounds, and considerable attention has been directed towards these studies in steroid chemistry.[1] Cholic acid was used as the starting point for obtaining so-called tweezer-like molecules where two tetracyclic steroid moieties are linked together through a conformationally flexible chain and placed above each other to form a cavity capable of binding different guest molecules.[1] These compounds show association with glucopyranosides[2] and are known for their DNA binding affinity.[3]



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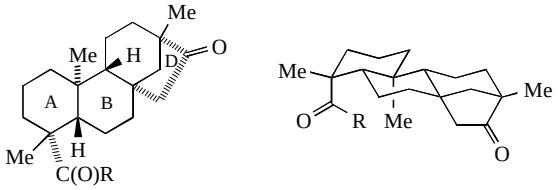
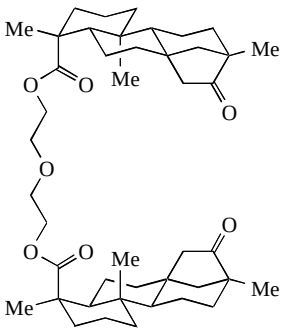


2a R = OH
2b R = Cl



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Analogous tweezer-like molecules can also be obtained using diterpene derivatives of the kaurane series **2**. Like cholic acid, they have a rigid tetracyclic framework but differ by the position of ring D and the way in which rings A and B are condensed (*cis* for steroid **1** and *trans* for compounds **2**). We suppose that such bis-isosteviol compounds will also exhibit binding affininity, which can differ from properties of steroid-based receptors. Note that starting material isosteviol **2a** forms molecular complexes with medium-sized molecules.[4]

The key rigid tetracyclic fragment of the tweezer-like diterpene derivatives, namely, (4α,8β,13β)-13-methyl-16-oxo-17-norkauran-18-oic acid (isosteviol, **2a**), was obtained earlier by the acid hydrolysis of glycoside stevioside extracted from the plant *Stevia rebaudiana Bertoni*.[5] A convenient starting reagent for binding two diterpenes into a tweezer-like structure is acid chloride **2b**, which was synthesised by the reaction of isosteviol **2a** with an excess of thionyl chloride.†[6] In fact, product **3** obtained by the reaction of compound **2b** with diethylene glycol in the 2:1 ratio in the presence of triethylamine‡ appears to have a tweezer-like structure according to single crystal X-ray diffraction (Figure 1).§

The unit cell of bis-isosteviol derivative **3** contains one symmetrically independent molecule of **3**. The oxyethylene chain binding the two isosteviol fragments has mainly *syn*-clinal conformation, which is in agreement with published data[10] on the structure of 1,2-dioxy-substituted ethanes. The torsion angles (°) are as follows: O(1B)–C(21B)–C(22B)–O(1) 71.7(9), C(21B)–C(22B)–O(1)–C(22A) –156.4(7), C(22B)–O(1)–C(22A)–C(21A) –173.2(12), O(1)–C(22A)–C(21)–O(1A) –48.5(15). The distances between the ether oxygen atom O1 and the carbonyl oxygen atoms O(2A) and O(2B) of two isosteviol fragments are 4.43 Å and 4.51 Å, respectively. Tetracyclic fragments of compound **3** are located above each other in the crystal, forming a cavity. The cavity size can be characterised by the distances between the carbonyl atoms O(16A) and O(16B) (5.54 Å), the carbon atoms of methyl groups C(20A) and C(20B) (4.97 Å) and the atoms C(6A) and C(6B) of cyclohexane rings B (7.09 Å).

† A mixture of isosteviol **2a** (0.5 g, 1.57 mmol) and freshly distilled thionyl chloride (0.5 ml, 2.5 mmol) was refluxed for 1 h. The unreacted excess of thionyl chloride was removed at a reduced pressure. The residue was recrystallised from hexane to give **2b**; mp 143–145 °C (yield 0.36 g, 68%). IR spectrum (mineral oil, ν/cm^{-1}): 1740 (C=O, ketone), 1800 (ClC=O). Found (%): Cl, 9.93. Calc. for $C_{20}H_{29}ClO_2$ (%): Cl, 10.52.

‡ A solution of diethylene glycol (0.045 ml, 0.47 mmol) and triethylamine (0.13 ml, 0.93 mmol) was added to a solution of acid chloride **2b** (0.32 g, 0.9 mmol) in carbon tetrachloride (5 ml). The reaction mixture was refluxed for 37 h. Then, it was washed with water and dried over $CaCl_2$. The compound was isolated by column chromatography (silica gel, CCl_4) and then recrystallised from hexane to give **3**; mp 153–155 °C (yield 0.24 g, 71%). IR spectrum (mineral oil, ν/cm^{-1}): 1130, 1180, 1720 (ester); 1740 (ketone). Found (%): C, 74.27; H, 9.83. Calc. for $C_{44}H_{66}O_7$ (%): C, 74.75; H, 9.41.

§ Single-crystal X-ray data collection for compound **3** was performed on an Enraf-Nonius CAD4 four-circle diffractometer (graphite monochromator, CuKα radiation, $\omega/2\theta$ scan method, $\theta \leq 74.3°$) using a colourless prismatic crystal (crystal dimensions 0.45×0.35×0.30 mm). Twenty five centered reflections gave a refined orthorhombic unit cell of the dimensions a = 12.137(4), b = 18.24(1), c = 18.462(8) Å, V = 4086(4) Å^3, Z = 4, d_{calc} = 1.149 g cm^{-3}. A total of 4388 reflections were measured, of which 2631 were unique with $I > 3\sigma(I)$. The structure was solved in the space group $P2_12_12_1$ by direct methods using the SIR program[7] and by difference Fourier syntheses. All non-hydrogen atoms were refined anisotropically, while hydrogen atoms were refined isotropically. The final R values were R = 0.064, R_ω = 0.086 for 2349 unique reflections with $F^2 \geq 3\sigma$. All calculations were carried out on a DEC Alpha Station 200 computer with the MolEN system.[8] The selected bond distances and torsion angles were obtained using the PLATON program.[9] Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2000. Any request to the CCDC should quote the full literature citation and the reference number 1135/68.

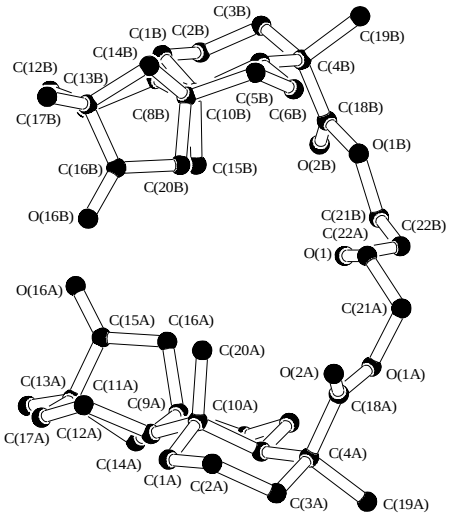

Figure 1 The crystal structure of bis-diterpene **3**. Hydrogen atoms are omitted for clarity.

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