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TOWARDS THE SYNTHESIS OF 9,11-SECOSPONGIANES[†]

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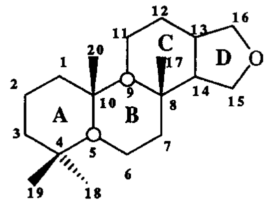
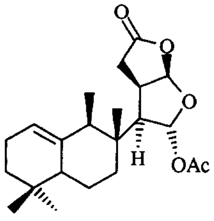
Abstract: A convenient synthesis of 9,11-secospongianes is reported, starting from methyl isoanticopalate **4**. This compound has been obtained readily from labdanolic acid and sclareol, two abundant, bicyclic natural products.

The spongianes are a group of tetracyclic diterpenes widely found in sponges and nudibranchs.[1] Structurally they are considered as derivatives of a hypothetical spongiane skeleton.



Spongiane skeleton

Several groups of spongianes have been established according to structural variations of the basic skeleton. One of the groups most widespread in natural sources is the 9,11-secospongianes. The key structural feature in these compounds is the absence of the C9-C11 linkage. Compounds of this class are macfarlandins C, D and E (**1**, **2** and **3**). Several 9,11-secospongianes exhibit interesting biological activities.[2]



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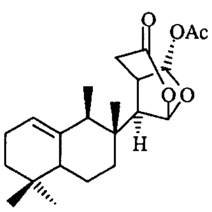

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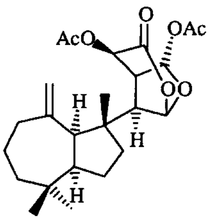

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† *This paper is dedicated to the memory of Prof. J. de Pascual Teresa*

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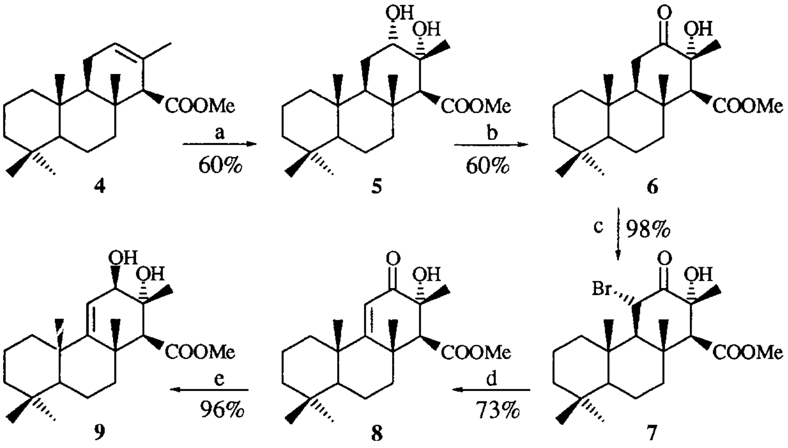
Spongianes of different types have been synthesized. However, to the best of our knowledge, the preparation of 9,11-secoderivatives has not yet been accomplished. The aim of this work was to set up a method that allowed the introduction of a $\Delta^{9\text{-}11}$ double bond and its subsequent cleavage. This is a first step in the conversion of bicyclic diterpenes to secospongianes.

The starting material for this work was methyl isoanticopalate **4**. This compound can be synthesized in a straightforward way from labdanolic acid[3] and sclareol,[4] two abundant, bicyclic natural products.

The reaction sequence leading to the cleavage of the $\Delta^{9\text{-}11}$ double bond was developed in the isoanticopalanes, tricyclic analogs of the spongianes. It was assumed, *a priori*, that it would be easier to work with the tricyclic derivatives rather than the tetracyclic ones. The transformation of **4** into **9** is shown in scheme 1.

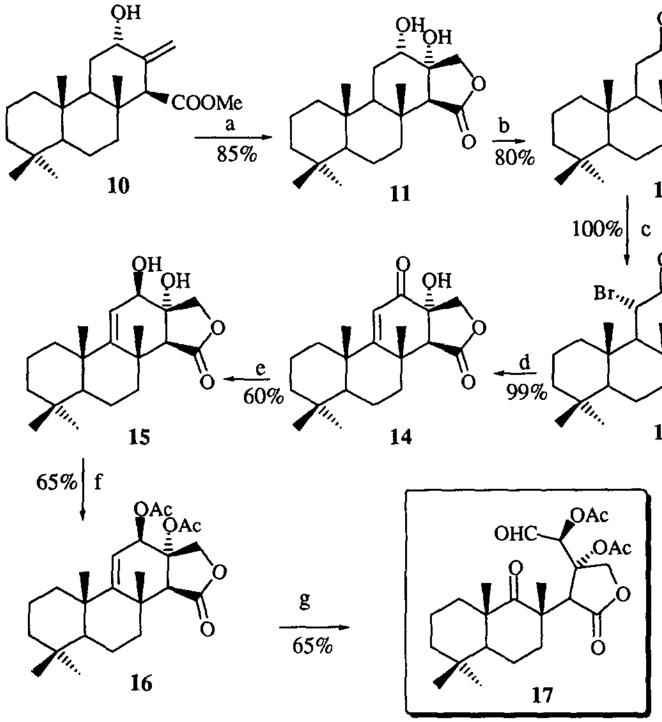


a) OsO_4; b) Swern; c) PTAP; d) LiBr, Li_2CO_3; e) $NaBH_4$. Scheme 1

However, all attempts to cleave the double bond in **8** proved unsuccessful. The ozonolysis of its reduction derivative, **9**, failed as well. Molecular mechanics studies on **8** and **9** tell us that both compounds have poor accessibility to both sides of the double bond.[8] The β side is hindered by the two axial methyls and lack of access to the α side is due to the particular conformation of the molecule, the double bond being in the concave part of the molecule.

Compound **10** was synthesized from **4** by Ruveda's method:[6] treatment of **4** with *m*-CPBA followed by cleavage of the epoxide with $Al(iPrO)_3$ gave the hydroxyderivative **10**. The route set up earlier for the isoanticopalanes was used to introduce the double bond in **12** as follows: osmylation of the terminal double bond gave the hydroxylactone **11**, which was oxidized to the ketone **12** with TPAP.[7] Compound **13** was obtained by α-bromination of **12** on the α-face with PTAP[8] (phenyltrimethylammonium perbromide) and was then submitted to elimination with $Li_2CO_3/LiBr$[9] to give the α,β-unsaturated ketone **14**. Reduction of this last compound with $LiAlH_4$ and acetylation of the resulting diol **15** gave the desired **16**.

Ozonolysis of **16** affords the secospongiane **17**.[10] Thus, for spongianes, unlike for isoanticopalanes, it is possible to perform the cleavage of the double bond.



a) OsO_4; b) TPAP; c) PTAP; d) LiBr, Li_2CO_3; e) LAH; f)Ac_2O, Py; g) O_3. Scheme 2

In view of the difference in reactivity between the lactone **16** and the ester, **9**, models were constructed of each of these compounds and conformational studies were performed.[11] The lactone has one conformer in the C ring and the lactone-like conformer of the ester will be sparsely populated at r.t. because there are other conformers with significantly lower calculated heats of formation. The energy of the HOMO is slightly lower for the lactone than for low-lying conformations of the ester suggesting that the differences in reactivity may stem from the orbital coefficients rather than from the orbital energy. The conformational preferences of these two compounds affect the coefficients of the HOMO at the reacting centres in a way which may well account for the lower reactivity of the double bond of the more flexible ester with respect to the lactone.

The sequence that allows the homochiral synthesis of secospongianes using bicyclic diterpenes as starting material has been set up in this paper. Further work remains in order to apply this methodology to the synthesis of natural spongianes.

References and notes:

1. Faulkner, D. J. *Nat. Prod. Rep.*, **1994**, *11*, 355-394; b) Faulkner, D. J. *Nat. Prod. Rep.*, **1997**, *14*, 259-302.
2. Molinski, T. F.; Faulner, D. J. Cung-Heng, H.; Duyne, V.; Clardy, J. *J. Org. Chem.*, **1986**, *51*, 4564-4567. b) Bobzin, S.; Faulkner, D.J., *J. Nat. Prod.*, **1991**, *54*, 225-232; c) Hambley, T. W.; Poiner, A.; Taylor, W.C.

Tetrahedron Lett., **1986**, *27*, 3281-3282.

3. Urones, J.G., Sexmero, J. Lithgow, A.; Basabe, P.; Estrella, A.; Gómez, A.; Marcos, I.S.; Díez, D.; Carballares, S.; Broughton, H.B.; *Nat. Prod. Letters*, **1995**, *6*, 285-290.
4. Urones, J.G.; Marcos, I. S.; Basabe, P.; Gómez, A.; Estrella, A; *Nat. Prod. Letters*, **1994**, *5*, 217-220
5. **9**. IR: vmax (film) cm^{-1}: 3500 (wide), 1730, 1640, 1460, 1440, 1390, 1370. ^1H NMR: (200 MHz, $CDCl_3$) δ (ppm): 5.24 (1H, s, H-11); 4.26 (1H, s broad, H-12); 3.70 (3H, s, COOMe); 2.62 (1H, s, H-14); 1.49 (3H, s, Me-16); 1.19 (3H, s, Me-17); 1.03 (3H, s, Me-20); 0.85 (6H, s, Me-18 and Me-19). ^{13}C NMR: (50.3 MHz, $CDCl_3$): 172.7 (C15); 154.4 (C9); 119.3 (C11); 77.0 (C12); 73.4 (C13); 63.2 (C14); 55.0 (C5); 51.0 (COOMe); 43.7 (C7); 42.1 (C3); 40.6 (C10); 41.0 (C8); 39.8 (C1); 34.0(C4); 33.2 (C18); 22.4 (19); 22.4 (C16); 21.6 (C17); 19.1 (C2);18.6 (C6); and 18.4 (C20).
6. Mischne, M.P.; González Sierra, M.; Rúveda, E. *J. Org. Chem.*, **1984**, *49*, 2035-2037.
7. Ley, S. V. *Aldrichima Acta*, **1990**, *23*, 13.
8. Gensler, W. J. and Solomon, P. H. *J. Org. Chem.*, **1973**, *38*, 1726-1731.
9. Paquette, l and Wang, X. . *J. Org. Chem.*, **1994**, *59*, 2052-2057.
10. **17**. $[\alpha]_{\lambda=578\ nm}$= +49.06° ($CHCl_3$, c=1.1 g/100 ml). IR: ν_{max} (film) cm^{-1}: 1770, 1740, 1700, 1470, 1380, 1250, 1220, 1040. ^1H NMR: (200 MHz, $CDCl_3$) δ (ppm): 9.39 (1H, s, H-11); 5.62 (1H, s, H-12); 4.92 (1H, d, J=10.0 Hz, H-16); 4.28 (1H, s, H-14); 4.22 (1H, d, J=10.0 Hz, H-16); 2.21 (3H, s, MeCOO); 2.16 (3H, s, MeCOO); 1.27 (3H, s, Me-17); 1.20 (3H, s, Me-20); 0.88 (3H, s, Me-18); 0.76 (3H, s, Me-19).^{13}C NMR: (50.3 MHz, $CDCl_3$): 217.9 (C9); 194.2 (C11); 171.5 (C15); 170.3 (OOCMe); 169.3 (OOCMe); 83.8 (C13); 75.9 (C12); 73.2 (C16); 56.8 (C14); 49.6 (C5); 47.9(C8); 41.1 (C3); 38.0 (C10); 35.2 (C1); 34.1(C7); 33.7 (C4); 32.9 (C18); 24.2 (C17); 21.3 (C20); 24.2 (C17); 20.8 (OOCMe); 20.5 (OOCMe); 19.7 (C2) and 18.5 (C6).
11. Conformational searching of relatively rigid structures by the stochastic "randomsearch" method in Sybyl has been shown[12] to be an effective means of generating candidate conformations even with limited search (1000) and minimisation (100) cycles. Therefore, each of the structures was submitted to 5000 cycles of the randomsearch process, the termination criterion being set to finding every conformation at least 12 times. In neither case was this criterion met, and therefore the full 5000 cycles were used. An energy cutoff of 40 kcal/mol above the energy of the minimised initial structure was used for each randomsearch run, and up to 2000 iterations of minimisation using Gasteiger-Huckel charges and the Sybyl forcefield were permitted. Other parameters were set to default values. Those conformations estimated by the Sybyl forcefield to lie within 10 kcal/mol of the lowest energy conformation found in the search were then further minimised using MOPAC[13] with the PM3 hamiltonian and eigenvector following geometry optimisation subject to precise convergence criteria. While the lactone **16** only had one conformer in the C ring based on heavy-atom least-squares superposition of the ring and immediate substituent atoms, the ester **9** showed three clusters of low-energy conformations; (groups **I**, **II** and **III**). The group **I** conformers corresponded closely with those found for the lactone, but the lowest energy conformer, was from group **III** (calculated heat of formation -202.60 kcal/mol). The lowest energy conformer in group **II**, had a similar energy (calculated heat of formation -201.21 kcal/mol) while the lowest energy conformation in group **I** was more than 4.5 kcal/mol more strained than the best group **III** conformer found. This lactone-like conformer of the ester will therefore probably be sparsely populated at room temperature. Ozone is an electrophilic reagent and therefore it is probable that the HOMO will play an important part in the reactivity of the double bond, and this can be quantified by the energy and electrophilic frontier values (square of the orbital coefficient) for this orbital. In this case the energy of the HOMO is slightly lower for the lactone (-10.31 eV) (higher ionization potential) than for the ester (-9.98 eV), suggesting that differences in reactivity may stem from the orbital coefficients rather than from the orbital energy. In the ester **9** case the squares of the HOMO coefficients on carbons 9 and 11 of the lowest-energy conformer are 0.333 and 0.381 respectively, whilst in the lactone **16** case they are notably higher at 0.348 and 0.441. Smaller squared coefficients are also seen for the other low-energy conformer of the ester, with values at C9 and C11 of 0.344 and 0.405 respectively, and only in the (much higher-energy) conformer which most closely corresponded to the lactone ring-C conformer are the coefficients comparable, at 0.354 and 0.433 respectively. Hence, the conformational preferences of these two compounds may affect the coefficients of the HOMO at the reacting centres in such a way as to reduce the reactivity of the double bond of the more flexible ester with respect to the lactone.
12. Treasurywala, A.M.; Jaeger, E.P. and Peterson, M.L.; *J. Comp. Chem.*; **1996**, *17*, 1171.
13. Stewart, J.J.P., MOPAC version 6.00, QCPE Program 455.