Tetrahedron Letters, Vol. 34, No. 16, pp. 2685-2688, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Diastereoselective Synthesis of the Saponaceolide Tricyclic Spiroketal Substructure

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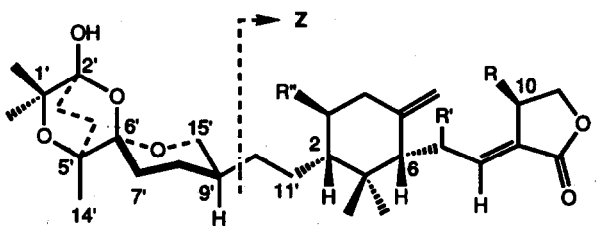
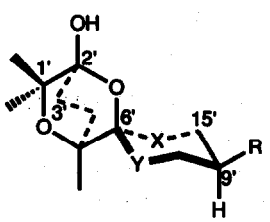
Abstract: Starting from geraniol we prepared the tricyclic spiroketal substructure **5a** of saponaceolide molecules. *Cis-* and *trans-* tetrahydropyran linalool oxides **18a** and **18b** were also synthesized during these studies.

The saponaceolides A - D (**1** - **4**) form a small group of triterpenoids recently isolated by us from the mushroom *Tricholoma saponaceum*.[1,2] Our synthetic efforts in this field were stimulated by the unprecedented nature of the base structure of compounds **1** - **4**, their *in vitro* anticancer activity on a human colon adenocarcinoma cell line and their intriguing biosynthetic origin. In this paper we describe the synthesis of the trioxa-tricyclic spiroketal substructure **5a** which was not found so far in other natural products.[3]

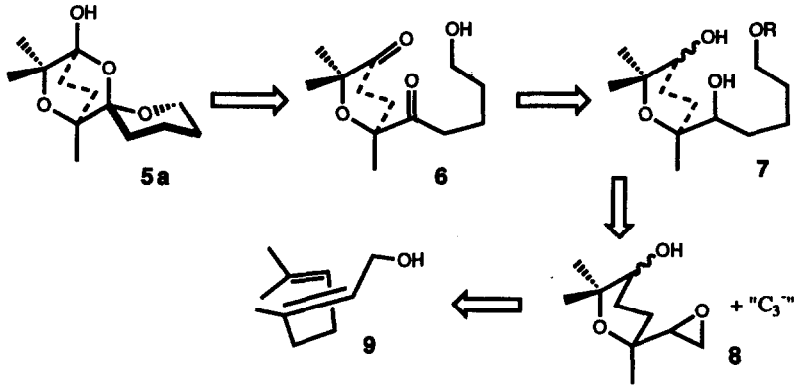




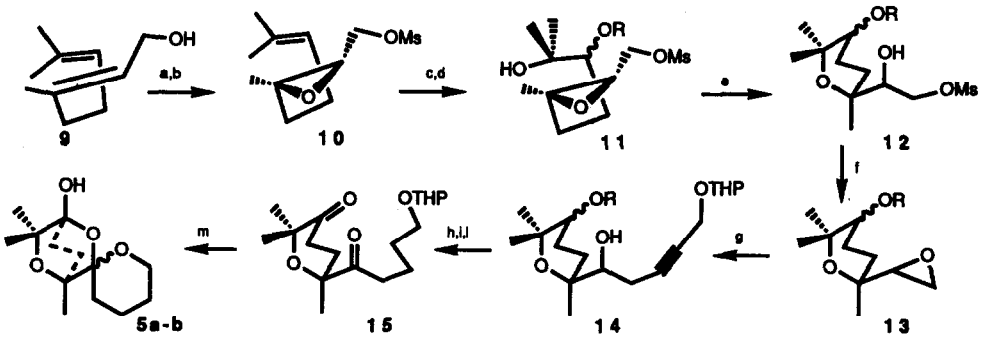
R=OH	R'=R"=H	saponaceolide A (**1**)	**5a**	R=H,	X=O,	Y=CH_2
R=R'=R"=H		saponaceolide B (**2**)	**5b**	R=H,	X=CH_2,	Y=O
R=R'=OH	R'=H	saponaceolide C (**3**)	**5c**	R=Z,	X=O,	Y=CH_2
R=R"=OH	R'=H	saponaceolide D (**4**)				

The complex hemiacetal-spiroketal **5a** may theoretically be formed by acid catalyzed spirocyclization of the fully functionalized monocyclic precursor **6** (Scheme 1). Extending to our particular case this general strategy for spiroketal construction[4] , we were well aware of two drawbacks usually not present in assembling simpler bicyclic spiro structures: the greater strain of the tricyclic system **5a** with respect to **6** and the impossibility of taking full advantage of the so-called anomeric effect[4,5] in establishing the desired configuration of the C-6' spiro center (saponaceolide numbering). In fact, given the boat conformation of the 1,4-dioxane ring in **5a-b**, neither configuration at C-6' can have the preferred bis-axial C-O orientation.[6] However, the merit of this approach is to be highly stereoconvergent (**6** contains only one stereocenter) and we expect that in the synthesis of the natural compound (**5c**), steric biases of the C-9' substituent should

dictate the desired stereochemistry at the spiro carbon. Following our retrosynthetic analysis (Scheme 1) we expected that alkylation of the epoxide **8** by an appropriate C_3 nucleophile would secure the required precursor of the key intermediate, the hydroxyketone **6**. As compound **8** is formally a monoterpene, it can in principle be obtained by a careful functionalization of the readily available geraniol (**9**), which then provides ten of the 13 carbons of the target molecule.



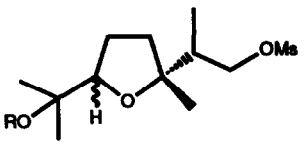
Scheme 1 - Retrosynthetic analysis of saponaceolide spiroketal substructure **5a**



Scheme 2 - Reagents and conditions: a) $VO(acac)_2$, ^tBuOOH, C_6H_6, 87%; b) MsCl, Et_3N, CH_2Cl_2, 90%; c) OsO_4, NMO, Py-^tBuOH-H_2O-THF, 93%; d) 1-Naphthyl isocyanate, Py-CH_2Cl_2, 92%; e) cat. CSA, CH_2Cl_2, - 20°C to 22°C, 40 h, 62%; f) K_2CO_3, MeOH, 86%; g) $HC{\equiv}CCH_2OTHP$, THF, ^nBuLi, -40°C then $BF_3.Et_2O$, -70°C to -40°C, 17 h, 30%; h) H_2, 5% Pd-C, EtOH, 91%; i) MeONa, MeOH, reflux, 90', 98%; l) TPAP, NMO,4 A molecular sieves, MeCN, 90', 73%; m) THF, 1N HCl, 22°C, 3h, 85%.

Diastereoselective Sharpless epoxidation[7] of geraniol gave the corresponding epoxy alcohol,[7] which was easily converted into the methanesulphonate **10** (78% over two steps).[8] For the dihydroxylation of compound **10**, the easy isomerization of diol **11** (R=H) to tetrahydrofurans **17** (R=H) by 5-*exo*-tet cyclization, required modification of the original Van Rheenen osmilation procedure.[9] Solvent composition was carefully adjusted until compound **11** (R=H) was obtained in excellent yield (93%) using the quaternary mixture Py-THF-^tBuOH-H_2O (0.2:11:3.4:1.2). The secondary alcohol of **11** (R=H) was then protected as 1-naphthyl carbammate (92%) since more traditional protective groups (THP, TBDMS, MEM, SEM, PhCO) proved unsatisfactory either for the low yields or the poor discrimination between the 2° and 3° OH groups. **11**-Acetate (R=Ac) was indeed obtained in quantitative yield, however acid conditions employed for the

subsequent catalytic cyclization (*vide infra*) readily promoted a 1,2 shift of the acyl residue, giving rise to a mixture of tetrahydrofuran (**16**, R=Ac) and tetrahydropyran (**17**) compounds. As anticipated, the more sterically demanding 2,2-dimethylpropanoyl group was not prone to migration. In this case protection of the secondary alcohol was extremely sluggish.



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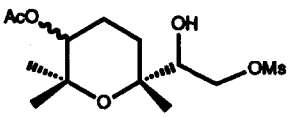

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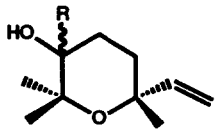
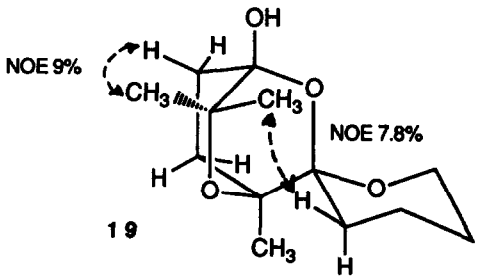


18a R = βH
18b R = αH

CSA catalyzed epoxy ring opening of carbammate **11** afforded the desired tetrahydropyran **12** (62%) which resulted enriched in the *cis* stereoisomer.[10] To confirm the structure each stereoisomer was separately converted [a) MsCl, Et_3N; b) Zn/NaI, DMF, reflux][11] into the corresponding *cis* and *trans* tatrahydropyran linalool oxides **18a-b**.[12,13]

Conversion of the entire diastereomeric mixture **12** to epoxide **13** paved the way to the crucial C_3 elongation step by alkylation with an appropriate nucleophile (Scheme 1). The reagent prepared from THP-$OCH_2C{\equiv}CLi$ and $BF_3.Et_2O$ [14] afforded the desired neopentyl alcohol **14** with complete regio- and chemoselectivity, albeit in only 30% yield. $LiClO_4$ catalyzed alkynylation[15] of **13** gave poorer results. Similarly higher order mixed alkenylcuprates,[16] prepared via hydrostannation[17] or hydrozirconation[18] of protected propynol failed to react with epoxide **13**. Catalytic hydrogenation of the triple bond of **14**, followed by secondary OH deprotection and TPAP oxidation[19] of the resulting diol produced diketone **15** in 65% overall yield. Upon exposure to 1N HCl at room temperature for 15 h, compound **15** underwent THP removal, followed by smooth spirocyclization. IR, EIMS and CIMS spectra of the product (85 % yield) fully supported the targeted trioxa-tricyclic model structure, while NMR spectra revealed a mixture (5:1 ratio) of the two spiroketals **5a-b**. The stereochemical assignments at the spiroketal junction of the separated major diastereomer was determined by NOE measurements, two of the most informative of which are illustrated in the structure of **19**.[20]



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Furthermore, the ^1H- and ^{13}CNMR signals[21] of the major spiroketal **5a** are in perfect agreement with those assigned to the corresponding subunit of saponaceolides A - D (**1** - **4**).[1,22]

In conclusion, synthesis of the saponaceolide trioxa-tricyclic moiety was completed in 11 steps from geraniol following a biomimetic approach. Further studies on the total synthesis of these compounds are in progress.

Aknowledgements - MURST funds 40% provided financial support of this project. We thank Prof. Kim Albizati for helpful discussions and Dr Mariella Mella for recording the NMR spectra.

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2) Previous drawings[1] of compounds **1-4** might not clearly show that O-6'a and the bridge C-3'-C-4' are *cis* with respect to the plane C-1', C-6', O-2'a and that H-9' is axial and *trans* to O-2'a. In addition the absolute configuration of saponaceolide A was incorrectly reported[1b] as 2R, 6R, 10R, 2'S, 5'S, 6'S, 9'R. This should be corrected as 2R, 6S, 10R, 2'S, 5'S, 6'S, 9'S.

3) Part of this work was presented at the 18th IUPAC Symposium on the Chemistry of Natural Products, Strasbourg (France), 8.30 - 9.4.1992, Abstracts Book p. 372.

4) a) Perron, F.; Albizati, K. F. *Chem Rev.* **1989**, *89*, 1617. b) Vaillancourt, V.; Pratt, N. E.; Perron, F.; Albizati, K. F. "The Total Synthesis of Spiroketal-Containing Natural Products." In "*The Total Synthesis of Natural Products.*"; ApSimon, J. Ed.; Vol 8, Wiley: New York, 1992; pp. 533-691.

5) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry;* Pergamon Press: Oxford, 1983.

6) Dreiding models suggest that steric and stereoelectronic effects should slightly favour **5a** over **5b**.

7) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.

8) Yields refer to homogeneous compounds, which were fully characterized by analytical and spectroscopic data.

9) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *23*, 1973.

10) Diastereomerically homogeneous starting material (~15%) was recovered from the reaction mixture.

11) Rama Rao, A. V.; Mysorekar, S. V.; Gurjar, M. K.; Yadow, J, S. *Tetrahedron Lett.* **1987**, *28* 2183.

12) **18a**: m.p. 65-66°C; **18b**: sticky oil - The IR, ^{1}HNMR and MS spectra of each compound match those reported for the natural sample (Felix, D.; Melero, A.; Seibl, J.; Kovats, E. *Helv. Chim. Acta* **1963**, *46*, 1513).

13) Compounds **18a-b** were recently obtained by a chemoenzymatic approach (Furstoss, R. et al. *Synthesis* **1991**, 681).

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18) Lipshutz, B. H.; Kato, K. *Tetrahedron Lett.* **1991**, *32*, 5647.

19) TPAP = Tetrapropylammonium perruthenate (Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13).

20) For comparison we performed the same NOE experiments by irradiation of the corresponding signals of saponaceolide B (**2**).[1b, 22] NOEDS spectra were identical with those of synthetic spiroketal **5a**.

21) ^{1}HNMR (300 MHz, $CDCl_3$) of **5a**: δ 1.09 (s, 3H, H_3-14'), 1.21 and 1.29 (2s, 2x3H, H_3-12' and H_3-13'), 1.4-1.7 (m, 6H, H_2-8', H_2-9', H-4'a, H-7'a), 1.86 (m, 1H, H-4'b), 1.95 (bd, 1H, J = 12.7 Hz, H-7'b), 2.0 (ddd, 1H, J = 13.0, 11.0, 1.8 Hz, H-3'a), 2.17 (ddd, 1H, J = 13.0, 11.0, 1.8 Hz, H-3'-b), 3.62 (ddt, 1H, J = 11.2, 4.5, 2.0 Hz, H_{eq}-15'), 4.10 (m, 1H, J_{gem} = 11.2 Hz, H_{ax}-15'); ^{13}CNMR (75.5 MHz, $CDCl_3$): δ 17.8 (CH_2, C-9'), 20.9 (CH_3, C-14'), 22.4 (CH_3, C-13'), 25.4 (CH_2, C-8'), 25.9 (CH_3, C-12'), 27.9 (CH_2, C-3'), 28.5 (CH_2, C-4'), 29.3 (CH_2, C-7'), 61.1 (CH_2, C-15'), 72.9 (C, C-5'), 77.2 (C, C-1'), 96.6 (C, C-2'), 101.3 (C, C-6').

22) Geraci, C,; Piattelli, M.; Tringali, C. *Magn. Res. Chem.* **1991**, *29*, 603.

Note added in proof: Prof. Kim Albizati has recently synthesized O-methyl **5a** via 2-furyl ketone oxidation rearrangement (De Haan, R. A.; Heeg, M. J.; Albizati, K. F. *J. Org. Chem.* **1993**, *58*, 291).

(Received in UK 22 September 1992)