

Studies on the Total Synthesis of the Saponaceolides. 1. Enantioselective Synthesis of the Spiroketal Subunit

Giovanni Vidari,* Gianluigi Lanfranchi, Natalina Pazzi, and Stefano Serra

Dipartimento di Chimica Organica, Università di Pavia, Via Taramelli 10, Pavia, Italy

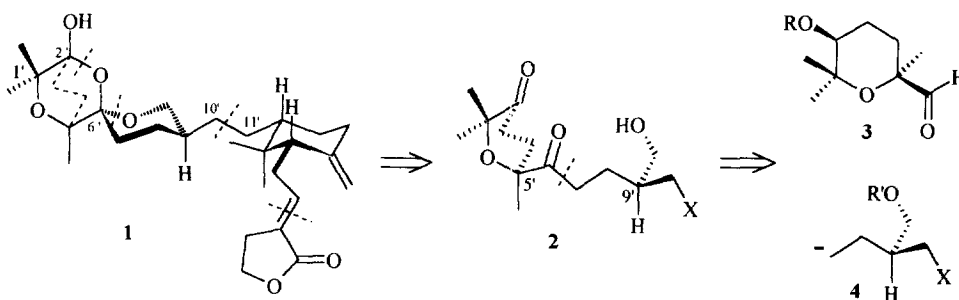
Received 11 December 1998; accepted 17 February 1999

Abstract

An asymmetric synthesis of the tricyclic spiroketal subunit of the saponaceolides is described in which the absolute stereochemistry at C-2' and C-6' is established through a conformationally and stereoelectronically controlled cyclization of a dihydroxyketone pyran intermediate. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Spiro compounds; Terpenoids; Fungi; Natural products

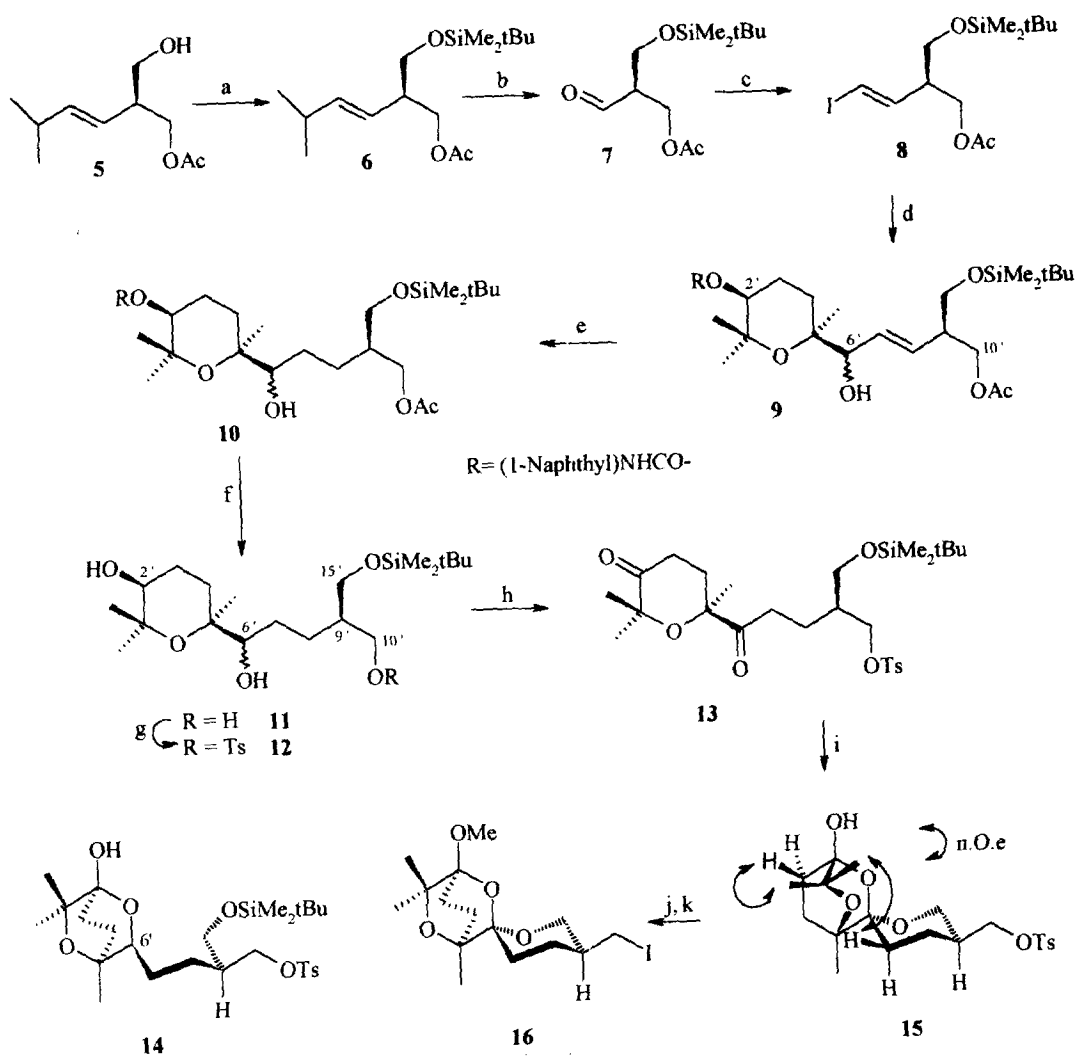
Saponaceolides are biologically active spiroketal containing natural products of novel biosynthetic origin, isolated from the fruiting bodies of a few *Tricholoma* species (Basidiomycetes) [1-4]. Notably saponaceolide B (1) exhibits a potent *in vitro* cytotoxicity [2] and antitumor activity in the NCI test against 60 human cancer cell lines [5]. Structural features of these fungal metabolites include the unique oxygenated tricyclic spiroketal subunit and the 1,2,3-trisubstituted methylenecyclohexane moiety, each presenting a non-trivial synthetic problem. No total synthesis of saponaceolides has appeared so far, though a few related synthetic studies have been published [5-7]. In our convergent and enantioselective approach to saponaceolide B (1), we envisioned installation of C2' and C6' stereochemistry and construction of the major fragment representing the C1'-C10' left half through a steric and



stereoelectronically controlled acid catalyzed spirocyclization of hydroxydiketone **2**. The latter contains the C5' and C9' stereocenters of the target molecule and, in principle, could be obtained by coupling aldehyde **3** (R = (1-naphthyl)NHCO) [8], ee 98% , mp 148-149°C, $[\alpha]_{\text{D}}^{20} +39.1$ ($c=1$, CHCl₃) [9], with a nucleophilic asymmetric bis(hydroxymethyl)propyl synthon **4**. In the accompanying Letter [10], we report the synthesis of the entire saponaceolide structure *via* synthesis of the right part and its coupling with the left fragment.

Synthesis of **2** (Scheme 1) started with the conversion of Guanti's monoester **5** [11], ee 97%, $[\alpha]_{\text{D}}^{20} -25.8$ ($c=2$, CHCl₃) [Lit. -25.3 ($c=2$, CHCl₃)] [11], into bis(hydroxymethyl)acetaldehyde **7** which was immediately submitted to Takai's conditions [12] to afford a good yield [13] of iodoalkene **8** (*E/Z* ratio 20:1), $[\alpha]_{\text{D}}^{20} +12.1$ ($c=1$, CHCl₃), with no evidence of racemization of the stereocenter. Iodide **8** was then subjected to the Nozaki-Hiyama-Kishi protocol [14] to furnish a nucleophilic organometallic species suitable for coupling with the sterically demanding aldehyde **3**. The desired alcohol **9** was thus obtained as a 9:1 mixture of C6' diastereomers (configuration not assigned; saponaceolide numbering) in modest yield, even using an excess of **8**. After recovery of starting materials **3** and **8** and three recycles, the isolated yield of alcohol **9** was improved to 65%. Conversion of **9** into diketone **13** was then pursued *via* triol **11**. Hydrogenation of the double bond of **9** at atmospheric pressure proved unexpectedly difficult; uptake of hydrogen was extremely low, using either homogeneous or heterogeneous catalysts. On the other hand, when hydrogenation was carried out under moderate pressure, destructive fission of the allylic hydroxy group readily took place. Finally, it was found that exposure of **9** to *in situ* generated nickel boride [15] smoothly afforded the saturated alcohol **10**, as a mixture of stereoisomers, $[\alpha]_{\text{D}}^{20} +19.0$ ($c = 2$, CH₂Cl₂), with no appreciable cleavage of the allylic OH. Strongly basic conditions, necessary for removing both the ester and carbamate groups of **10**, were considered harmful to the integrity of C9' stereochemistry; reduction of **10** with LiEt₃BH in THF was thus explored, since protection of the ensuing OH group at C-10' as a boron derivative was expected to prevent migration of adjacent silyl group. Indeed, hydride reduction of **10** proceeded with complete retention of configuration at C9', as shown by the reconversion of triol **11**, $[\alpha]_{\text{D}}^{20} +25.6$ ($c = 1.2$, CH₂Cl₂), to the original compound **10**, on treatment with Ac₂O followed by 1-naphthyl isocyanate. Mono *p*-toluenesulphonate **12**, $[\alpha]_{\text{D}}^{20} +13.1$ ($c = 2.3$, CH₂Cl₂), was prepared under standard conditions, while in the subsequent conversion of the diol to the corresponding diketone **13**, several oxidants failed to give the desired compound. Actually, treatment of **12** with PDC or Dess-Martin periodinane, or Swern reagents led to a preferential oxidation of the 2'-OH group and rapid acetalisation of the resulting ketone to afford bicyclic compound **14** in which the 6'-OH was masked and thus protected from further oxidation. Eventually, oxidation of **12** with TPAP (tetrapropylammonium perruthenate) [16] readily produced diketone **13**, $[\alpha]_{\text{D}}^{20} +12.4$ ($c = 1.6$, CH₂Cl₂) in excellent yield. On exposure to 3M HCl

in THF, compound **13** underwent silyl group removal, followed by smooth spirocyclization to the trioxa-tricyclic subunit **15**, $[\alpha]_D^{20} +21.4$ ($c = 1.2$, CH_2Cl_2), as the only detectable stereoisomer (HPLC and ^{13}C NMR).



Scheme 1 : a) $^t\text{BuMe}_2\text{SiCl}$, imidazole, DMF, 20°C , 2.5h, 96%; b) O_3 , $\text{MeOH}-\text{CH}_2\text{Cl}_2$ (1.7:1), -78°C , then Me_2S , cat. pyridine, 90%; c) CHI_3 (2 eq.), CrCl_2 (6 eq.), THF, 0°C , 3h, 75%; d) CrCl_2 (10 eq.), cat. NiCl_2 , DMSO, 20°C , add **3** ($\text{R} = (1\text{-Naphthyl})\text{NHCO}-$), 20°C , 40% (65% over 3 recycles); e) NaBH_4 (10 eq.), $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (2 eq.), MeOH, $0^\circ \rightarrow 20^\circ\text{C}$, 12h, 90%; f) LiEt_3BH (6 eq.), THF, 60°C , 4h, 90%; g) *p*-TsCl (1.2 eq.), CH_2Cl_2 , pyridine (2 eq.), 60% (85% based on recovered **11**); h) cat. TPAP, 4-methylmorpholine N-oxide (6 eq.), 4\AA MS, MeCN, 4h, 91%; i) THF- 3M aq. HCl (15:1), 20°C , 3h, 90%; j) cat. *p*-TsOH, MeOH, 40°C , 2h, 96%; k) NaI (10 eq.), Me_2CO , reflux, 4h, 80%.

The configuration of **15** [17] was established as depicted in the formula by n.O.e experiments and the full agreement of the NMR signals with those assigned to the corresponding subunit of natural saponaceolides [1-4]. Conversion of **15** to iodide **16** occurred smoothly in two simple steps.

In summary, we have achieved the synthesis of a major moiety of the saponaceolides with complete stereocontrol and in an enantioselective fashion. This sequence provides an efficient route to the left portion of the saponaceolide structure in a form (**16**) appropriately functionalized for coupling with a building block representing the right part [10] and thus for assembling the entire skeleton of the natural products.

Acknowledgements

We are indebted to Dr Mariella Mella for NMR measurements. Financial support for this work was provided by the Italian CNR and MURST (ex 40%), and the EU Commission (Contract No ERBF AIRCT961781).

References

- [1] De Bernardi M, Garlaschelli L, Gatti G, Vidari G, Vita Finzi P. *Tetrahedron* 1988;44:235-240.
- [2] De Bernardi M, Garlaschelli L, Toma L, Vidari G, Vita Finzi P. *Tetrahedron* 1991;47:7109-7116.
- [3] Geraci C, Piattelli M, Tringali C. *Magn. Reson. Chem.* 1991;29:603-606.
- [4] Pang Z, Berquist KE, Sterner O. *Acta Chem. Scand.* 1994;48:453-454.
- [5] Vidari G, Lanfranchi G, Sartori P, Serra S. *Tetrahedron: Asymmetry* 1995;6:2977-2990.
- [6] Vidari G, Franzini M, Garlaschelli L, Maronati A. *Tetrahedron Lett.* 1993;34:2685-2688.
- [7] De Haan RA, Heeg MJ, Albizzati KF. *J. Org. Chem.* 1993;58:291-293.
- [8] Vidari G, Giori A, Dapiaggi A, Lanfranchi G. *Tetrahedron Lett.* 1993;34:6925-6928.
- [9] Spectral data for **3**: ^1H NMR (CDCl_3 , 300 MHz): δ 1.10 (s, 3H), 1.13 (s, 3H), 1.32 (s, 3H), 1.5-1.7 (m, 2H), 1.9-2.0 (m, 1H), 2.35-2.45 (m, 1H), 4.75 (dd, $J=11.0$ and 4.5 Hz, 1H), 6.82 (bs, 1H, NH), 7.42-7.90 (m, 7H), 9.6 (s, 1H). ^{13}C NMR (CDCl_3 , 75 MHz): δ 21.2 (Me), 22.4 (CH_2), 23.9 (Me), 28.7 (Me), 29.1 (CH_2), 75.0 (C-O), 76.1 (CH-O), 78.2 (C-O), 120.4 (CH), 120.6 (CH), 125.5 (CH), 125.7 (CH), 126.1 (CH), 126.3 (CH), 128.7 (CH), 132.3 (C), 134.1 (C), 141.0 (C), 154.9 (C=O), 204.3 (CH)
- [10] Vidari G, Pazzi N, Lanfranchi G, Serra S. *Tetrahedron Lett.* 1999;40: 3067-3070.
- [11] Guanti G, Banfi L, Narisano E. *J. Org. Chem.* 1992;57:1540-1554.
- [12] Takai K, Nitta K, Utimoto K. *J. Am. Chem. Soc.* 1986;108:7408-7410.
- [13] Yields refer to homogeneous compounds fully characterized by analytical and spectroscopic data.
- [14] Kishi Y. *Pure Appl. Chem.* 1992;64:343-350 and references cited therein.
- [15] Grieco PA, Inanaga J, Lin N-H, Yanami T. *J. Am. Chem. Soc.* 1982;104:5781-5784.
- [16] Ley SV, Norman J, Griffith WP, Marsden SP. *Synthesis* 1994:639-666.
- [17] Spectral data for **15**: ^1H NMR (CDCl_3 , 300 MHz): δ 1.08 (s, 3H), 1.20 (s, 3H), 1.28 (s, 3H), 1.4-2.2 (m, 10H), 2.47 (s, 3H), 3.65 (dd, $J=10.5$ and 4.5 Hz, 1H), 3.72 (bd, $J=10.5$ Hz, 1H), 3.76 (dd, $J=10.0$ and 8.0 Hz, 1H), 3.85 (dd, $J=10.0$ and 5.5 Hz, 1H), 7.35 (d, $J=9$ Hz, 2H), 7.75 (d, $J=9$ Hz, 2H). ^{13}C NMR (CDCl_3 , 75 MHz): δ 20.5 (CH_2), 20.7 (Me), 21.6 (Me), 22.3 (Me), 25.8 (Me), 27.8 (CH_2), 28.4 (CH_2), 28.4 (CH_2), 35.1 (CH), 62.4 (CH_2O), 71.4 (CH_2O), 72.6 (C-O), 77.5 (C-O), 96.8 (C-O), 100.8 (C-O), 127.8 (2 CH), 129.8 (2 CH), 132.7 (C), 144.8 (C).