Podocarpane-to-spongian skeleton conversion. Synthesis of (+)-isoagatholactone and (−)-spongia-13(16),14-diene

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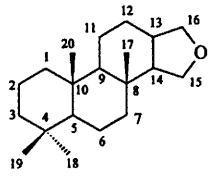
A stereoselective synthesis of the spongian diterpenes (+)-isoagatholactone 5 and (−)-spongia-13(16),14-diene 6 is achieved starting from (+)-podocarp-8(14)-en-13-one 3 (R = H) *via* the common intermediate β-hydroxy ketone 13.

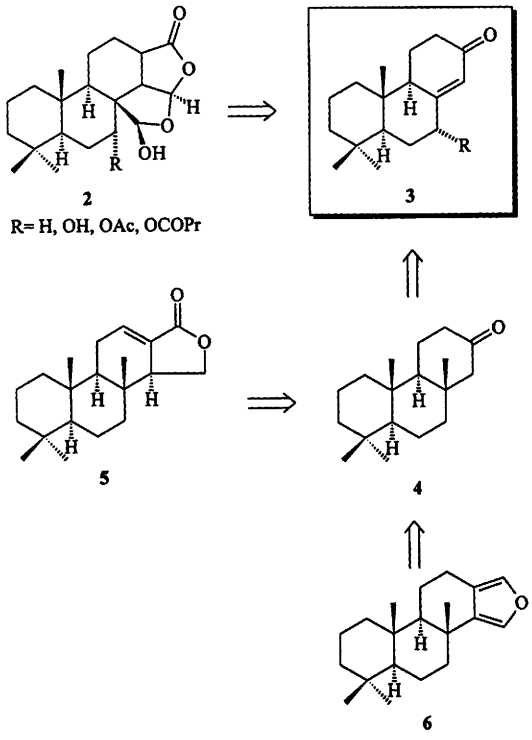
Introduction

A growing number of diterpenes with the spongian **1** carbon skeleton have been isolated from marine sponges and nudibranchs. Despite the wide spectrum of properties shown by



1
spongian skeleton

many of these compounds few synthetic approaches to spongians have been reported.[1] We recently described a general approach to the synthesis of a small group of these diterpenoid compounds, characterized by a common pentacyclic skeleton **2** (Scheme 1).[2] This approach uses as chiral starting material a suitably substituted podocarpenone **3** which is transformed into the pentacyclic spongian framework following an ABC + DE annulation strategy.



2
R= H, OH, OAc, OCOPr

3

4

5

6

Scheme 1

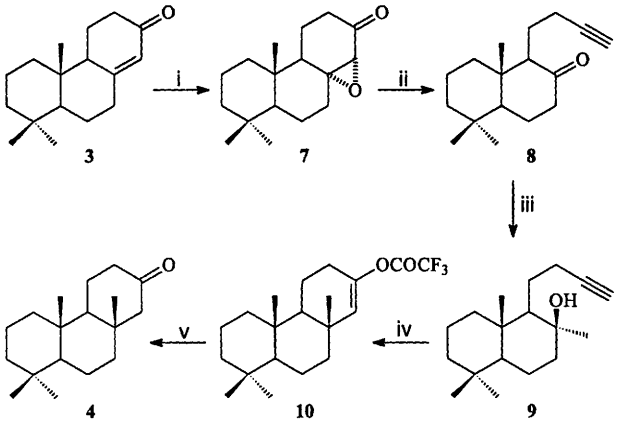
In the present paper we describe the synthesis of spongian diterpenes isoagatholactone and spongia-13(16),14-diene, **5** and **6** respectively, starting from the same podocarpenone **3** (R = H). The synthetic route used for these transformations is based on the conversion of the podocarpane skeleton into the tricyclic system **4**, which is then transformed into target spongian compounds (ABC + D approach). The approach used for the preparation of **5** and **6**, which constitutes a podocarpane-to-spongian skeleton conversion, can be adapted for the preparation of other unfunctionalized C-17 spongianes, since many routes to compounds such as **3** have already been worked out.[3]

Results and discussion

The first stage of the synthesis was the introduction of an angular methyl group at C-8 (podocarpane numbering) of podocarpenone **3** (R = H). Since direct 1,4-addition of organometallic compounds (*e.g.* lithium dimethylcuprate) to podocarpenone **3** takes place from the less hindered α-face leading to a *cis*-fused product,[4] recourse was made to an indirect procedure for introduction of the 8β-methyl group. Utilization of the methodology developed by Ireland[5] provided an excellent means of achieving this transformation. Podocarpenone **3** (Scheme 2) was converted into acetylenic ketone **8** *via* the epoxy ketone **7** and silica gel catalysed Eschenmoser ring-opening reaction.[6] Treatment of **8** with methyllithium afforded the acetylenic alcohol **9** which underwent a stereocontrolled acetylenic-cation cyclization when treated with a mixture of trifluoroacetic acid and trifluoroacetic anhydride, giving the enol trifluoroacetate **10**. Attempts to chromatograph **10** on silica gel resulted in its quantitative conversion to the previously known[7] saturated ketone **4**.† Fortunately, enol trifluoroacetate **10** is obtained in very pure form from the cyclization so it can be used without purification in the next step (*vide infra*). In spite of the number of steps, this route for the introduction of the 8β-methyl group is particularly efficient, allowing the preparation of **10** or **4** in nearly 70% overall yield from **3**.

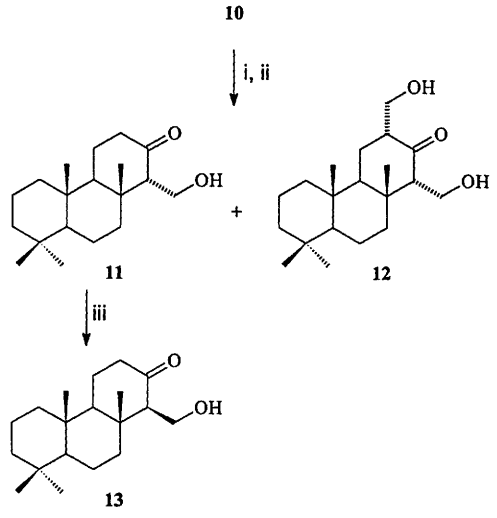
In the next step, incorporation of a hydroxymethyl side chain

† The β-orientation of the methyl group at C-8 (17-H) in both **10** and **4** was derived from nuclear Overhauser effect experiments performed on **10**. In particular, irradiation of the 17-H signal at δ_H 1.03 gave NOE enhancements for 20-H, 14-H, 6β-H and 11β-H. In the same way, irradiation of the 20-H signal at δ_H 0.84 gave NOE enhancements for 17-H, 19-H, 2β-H, 6β-H and 11β-H. These facts can be explained only by assuming a β-disposition of the 8-Me, as indicated in structure **10**.



Scheme 2 *Reagents and conditions:* i, H_2O_2, NaOH, MeOH, 0 °C (86%); ii, *p*-$TsNHNH_2$, silica gel, CH_2Cl_2, −30 to 30 °C, (82%); iii, MeLi, THF, −78 °C (90%); iv, CF_3CO_2H, $(CF_3CO)_2O$, −25 °C (100%); v, silica gel

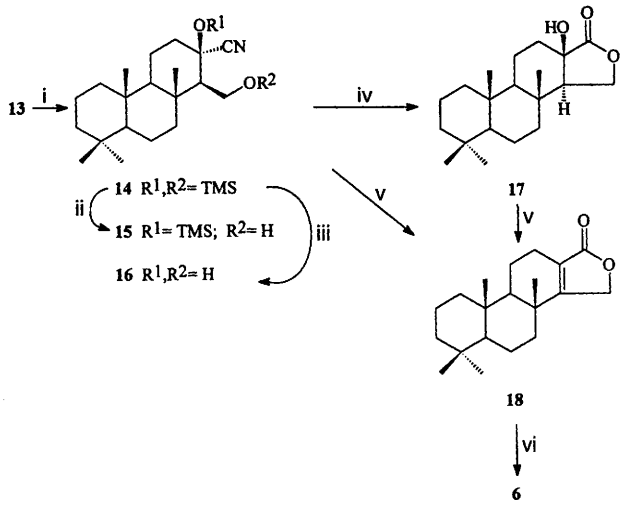
at C-14 of **4** was effected by treatment of the enolate generated from the reaction of **10** with two equivalents of methyllithium with formaldehyde (Scheme 3). After rapid work-up and careful



Scheme 3 *Reagents and conditions:* i, MeLi, THF, −78 °C; ii, HCHO (75% of **11** and 9% of **12**); iii, NaOMe, MeOH, −20 °C (85%)

column chromatography of the crude product, the hydroxy ketone **11** was obtained in 75% yield together with dihydroxymethylated ketone **12** in 9% yield. The axial position of the C-14 hydroxymethylene group in **11**, and also in **12**, was inferred from its spectroscopic data and in particular from the ^{13}C NMR signal due to C-9 which is shifted upfield appreciably in this compound with respect to ketone **4**, due to the shielding effect (γ-effect) exerted by the CH_2OH group on C-9. Isomerization of **11** to the most stable 14β-isomer was smoothly effected in 90% yield by treatment of **11** with methanolic sodium methoxide at −20 °C for four days. The conditions of this reaction were somewhat critical to ensure a good yield of the hydroxy ketone **13**; the use of higher temperatures led to substantial amounts of the enone produced by elimination of the β-hydroxy group of **11**.

With **13** in hand, we were ready to introduce at C-13 the carbon atom necessary for future elaboration of the D-ring. A variety of methods based on the use of phosphorus and sulfur ylides were explored for the one-carbon homologation at the C-13 carbonyl group of **13**, or its tetrahydropyranyl ether derivative, with poor results. In the end, it was found that treatment of **13** with trimethylsilyl cyanide [8] in the presence of ZnI_2 afforded a quantitative yield of trimethylsiloxy cyanide **14** (Scheme 4). Addition of wet diethyl ether to the reaction mixture



Scheme 4 *Reagents and conditions:* i, Me_3SiCN, ZnI_2, CH_2Cl_2, 0 °C (97%); ii, wet diethyl ether (99% from **13**); iii, HCl, THF–H_2O (95%); iv, HCl, THF, 60 °C (91%); v, HCl, AcOH, 120 °C (95% from **17**, 84% from **14**); vi, DIBAL-H, THF, −20 °C; then aqueous H_2SO_4, 0 °C (86%)

produced the hydrolysis of the primary trimethylsiloxy moiety, affording the nitrile **15** in nearly quantitative yield. The 13β-trimethylsiloxy stereochemistry of both **14** and **15** was established unambiguously by NMR spectroscopy. Of special significance was the NOE effect observed between the 8β-Me (irradiated) and the methyls of the trimethylsiloxy group of **15**.

Completion of the D ring of target spongian compounds required elimination of the trimethylsiloxy moiety at C-13 and hydrolysis of the cyanide group. Toward this end, the silyl ether was cleaved under mild acid conditions and the resulting dihydroxy cyanide **16** hydrolysed by treatment with hydrochloric acid in THF at 50–60 °C for 24 h. Not surprisingly, the initially formed alcohol-acid could not be isolated since spontaneous internal lactone formation took place, furnishing the tetracyclic compound **17** in 92% yield for the whole process. In practice, the two last steps were unnecessary since treatment of **14** with hydrochloric acid in AcOH at 60 °C for 24 h afforded directly the hydroxy lactone **17** in 90% yield after purification by chromatography.

All attempts to transform the α-hydroxy lactone **17** into the target lactone **5** were unsuccessful. Instead of **5**, the α,β-unsaturated lactone **18** was formed in all the dehydration procedures investigated.‡ The best results were obtained by treatment of **17** with hydrochloric acid in AcOH at 120 °C in a sealed tube for 2 h. For synthetic purposes, conversion of trimethylsiloxy cyanide **14** into lactone **18** could be realized in a single operation in 84% yield by treatment of **14** with hydrochloric acid in AcOH under the above stated conditions. The regioselective formation of the C-13–C-14 double bond in the dehydration reaction of **17** is probably a consequence of the thermodynamic control followed by the dehydration process. *Ab initio* calculations (performed at the 3-21G level using the GAUSSIAN 92 package) [9] indicate that **18** is significantly more stable (4.4 kcal mol^{-1})§ than its C-12–C-13 regioisomer **5**.

Although the above results precluded the utilisation of the

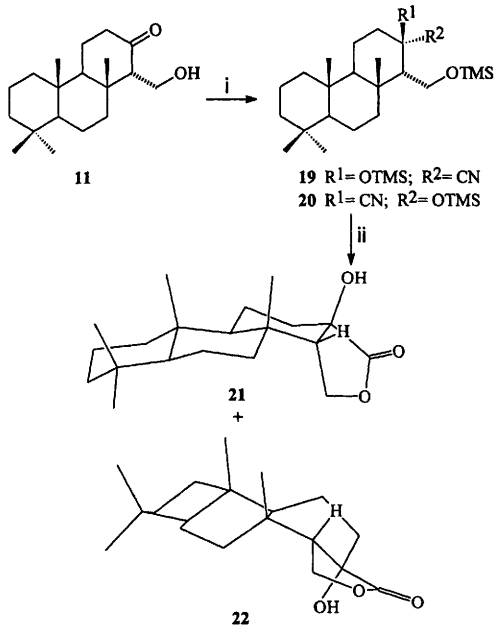
‡ The exclusive formation of the C-13–C-14 double bond in the dehydration reaction of **17** took place not only under acid-catalysed reaction conditions but also in basic medium (*e.g.* $SOCl_2$, pyridine). Attempts to form the C-12–C-13 double bond by pyrolysis (150 °C at 20 mmHg during 2.5 h) of the corresponding acetate (prepared by reaction of **17** with acetic anhydride and a catalytic quantity of 4-pyrrolidinopyridine at 80 °C for 18 h) also resulted in the exclusive formation of **18**. An E1 mechanism should be admitted for the last reaction since control experiments demonstrated that isoagatholactone **5** (C-12–C-13 double bond) was not converted into **18** (C-13–C-14 double bond) under the reaction conditions used in the pyrolysis.

§ 1 cal = 4.2 J.

easily obtained hydroxy lactone **17** for the preparation of isoagatholactone **5**, they offered an easy chemical access for the construction of the furan ring system of **6** and related furanospongianes. Thus, treatment of the α,β-unsaturated lactone **18** with DIBAL-H in THF cleanly provided the intermediate lactol, which then underwent dehydration–aromatization upon quenching with 10% aqueous H_2SO_4 to yield furanospongiane **6** in 86% for the whole process. The spectral data of **6**, including its optical rotation, were identical with those reported for the natural substance.[10] The synthesis of **6** requires nine steps from podocarpenone **3** (R = H) and provides the furanospongiane in 34% overall yield.

After completion of the synthesis of furanospongiane **6** and since it seemed to be no obvious reason for not using directly the 14α-hydroxymethylene ketone **11** in the above sequence, thus avoiding the epimerization step (**11**→**13**), we investigated the application of the sequence of reactions used for the elaboration of the furan ring system of **6** from **13** to the 14α-epimer **11**.

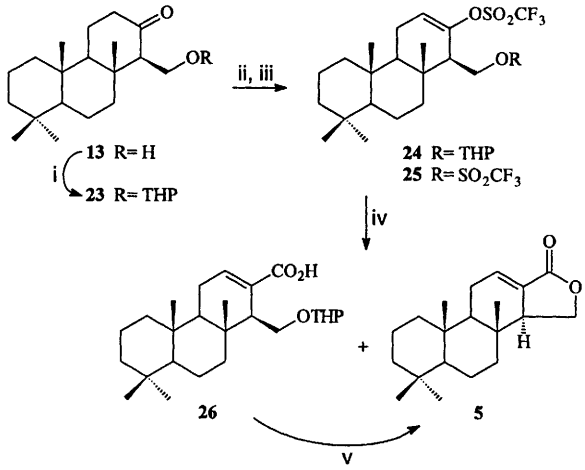
In the event, treatment of **11** with trimethylsilyl cyanide and ZnI_2 resulted in the formation of two epimeric trimethylsiloxy cyanides **19** and **20** (Scheme 5) in a ratio of 65:35 (^{1}H NMR



Scheme 5 *Reagents and conditions:* i, Me_3SiCN, ZnI_2, CH_2Cl_2, 0 °C (96%); ii, HCl, THF, room temp. (48% of **21** and 18% of **22**)

analysis), that could not be separated by chromatography on silica gel. Hydrolysis of the mixture of unpurified **19** and **20** with concentrated HCl in THF at room temperature for four days afforded the correspondent hydroxy lactones **21** and **22**,¶ which were separated by chromatography on silica gel (70% combined yield for the two steps). The stereochemistry of both diastereoisomers‖ was established as shown in **21** and **22** on the basis of their spectroscopic data; of particular significance was the enhancement observed at the hydroxy proton signal of **21** upon irradiation of the 8β-Me at δ_H 1.19, in a NOE experiment. The 13α-OH stereoisomer **22** cleanly afforded the α,β-unsaturated lactone **18** under the same reaction conditions used above for **17**. The 13β-OH epimer was stable to these conditions and although it could be dehydrated to **18** at higher temperatures (250 °C, 4 h) the yield obtained for this conversion was very low (20%).

The nonutility of hydroxy lactone **17** for obtaining isoagatholactone **5** prompted us to the exploration of an alternative approach for achieving its synthesis from the intermediate β-hydroxy ketone **13**. In the end, the synthesis of target isoagatholactone **5** from **13** was achieved in the following way. Firstly, the hydroxy group was protected as the tetrahydropyranyl ether by reaction of **13** with 3,4-dihydro-2*H*-pyran in CH_2Cl_2 in the presence of pyridinium toluene-*p*-sulfonate (PPTS) (Scheme 6). Treatment of the kinetically



Scheme 6 *Reagents and conditions:* i, 3,4-Dihydro-2*H*-pyran, PPTS, CH_2Cl_2 (95%); ii, NaHMDS, THF, −78 °C; iii, *N*-(5-chloro-2-pyridyl)trifluoromethanesulfonimide, THF, −78 °C (80%); iv, $Pd(OAc)_2$, Ph_3P, Et_3N, DMF, MeOH, CO, 60 °C (70%); v, MeOH, PPTS, 60 °C (100%)

generated sodium enolate of **23** with *N*-(5-chloro-2-pyridyl)trifluoromethanesulfonimide[11] in THF afforded the enol triflate **24** in 80% yield.** In turn, **24** underwent a palladium catalysed carbonylation[12] to afford a 1:9 mixture of acid **26** and isoagatholactone **5**, which were readily separated by chromatography on silica gel. In practice, however, separation of the mixture was unnecessary since treatment of the unpurified product obtained from this carbonylation with PPTS in MeOH effected complete conversion of acid **26** into **5**. This two-step sequence cleanly provided the desired isoagatholactone **5** in 70% global yield, which was identical in all spectral characteristics to the natural product.[13] The synthesis of **5** requires nine steps from the starting podocarpenone **3** (R = H) and provides this spongian diterpene in 25% overall yield.

Experimental

General conditions are as described previously.[2b] (+)-Podocarpenone **3** was obtained from abietic acid or commercial colophony following the procedure previously described by us.[14] Complete assignments of NMR data were made on the basis of a combination of homonuclear COSY, DEPT, inverse-detected heteronuclear multiple quantum coherence (HMQC) and NOE experiments. *J* Values are given in Hz. In all compounds, NMR assignments are given with respect to the numbering scheme shown in structure **1**.

Conversion of podocarp-8(14)-en-13-one 3 (R = H) into 15,16,17-trinorlabd-13-yn-8-one 8[15]

To a solution of podocarpenone **3** (1.7 g, 6.91 mmol) in MeOH (70 cm^3) were added 10% NaOH (4 cm^3) and 30% H_2O_2 (4 cm^3)

¶ The figures used in Scheme 5 for **21** and **22** correspond to the most stable conformations of both molecules, as obtained by MM calculations.

‖ It is interesting to note that in compound **22** the lactone ring forces the C ring to adopt a boatlike conformation in which the 13β-OH is, as in compound **21**, axially oriented.

** Although the β-hydroxy ketone **13** could also be triflated using two equiv. of base and an excess of triflating reagent, the resultant compound **25** was very unstable and underwent very easy loss of trifluoromethanesulfonic acid.

at 0 °C. After stirring for 12 h at 0 °C, the mixture was diluted with H_2O and extracted with diethyl ether. Usual work-up afforded chromatographically-pure epoxide **7**, which could be either used in the next step without further purification or chromatographed on silica gel, using hexane–EtOAc (9:1) as eluent, to give crystalline **7** (1.54 g, 86%), mp 106–106.5 °C (from pentane) (lit.,[16] 102–103 °C).

To a stirred suspension of silica gel 60 (0.015–0.040 mm, previously activated at 300 °C overnight) (1 g) in CH_2Cl_2 (10 cm^3) at −30 °C, epoxide **7** (1 g, 3.81 mmol) in CH_2Cl_2 (15 cm^3) and toluene-*p*-sulfonohydrazide (0.71 g, 3.81 mmol) in CH_2Cl_2 (15 cm^3) were added. The reaction mixture was warmed to 15 °C over a period of 16 h and then stirred at 30 °C for 3 h. Removal of the solvent afforded a residue which was purified by chromatography using hexane–EtOAc (9:1) as eluent to give the *acetylene* **8** (0.77 g, 82%) as a low melting point solid, mp 38–39 °C (from pentane) (lit.,[15] an oil); $[\alpha]_D^{20}$ −26 (*c* 0.7 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3300, 1715, 1450 and 1200; δ_H(300 MHz; $CDCl_3$) 2.42 (1 H, ddd, *J* 13.5, 5.8 and 2.3, 7β-H), 2.38–2.26 (4 H, m, 7α-H, 9α-H and 12-H), 1.92 (1 H, t, *J* 2.9, 14-H), 0.94 (3 H, s, 18-H), 0.82 (3 H, 19-H) and 0.69 (3 H, s, 20-H); δ_C see Table 1; *m*/*z* (EI) 246 (M^+, 3%), 231 (4), 218 (1), 179 (46), 137 (27), 109 (37), 95 (25) and 83 (100).

15,16-Dinorlabd-13-yn-8β-ol 9

A solution of ketone **8** (600 mg, 2.44 mmol) in THF (7.5 cm^3) was cooled to −78 °C and a 1.6 M solution of MeLi in Et_2O (*ca.* 4.11 cm^3, *ca.* 6.58 mmol) was slowly added. The reaction mixture was stirred at the same temperature for 2 h and then quenched by the dropwise addition of MeOH (5 cm^3). The reaction mixture was poured into water and extracted with diethyl ether. Usual work-up afforded a residue which was purified by chromatography using hexane–ethyl acetate (9:1) as eluent, to afford the *alcohol* **9** (575 mg, 90%) as a solid, mp 84.5–85.5 °C (from hexane) [Found: M^+ (EI), 262.2293. $C_{18}H_{30}O$ requires *M*, 262.2296]; $[\alpha]_D^{26}$ +27.1 (*c* 5.2, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3560, 3300, 2110, 910 and 780; δ_H(300 MHz, $CDCl_3$) 2.21 (2 H, m, 12-H), 1.96 (1 H, dd, *J* 2.7 and 2.7, 14-H), 1.13 (3 H, s, 17-H), 0.93 (3 H, s, 20-H), 0.84 (3 H, s, 18-H) and 0.80 (3 H, s, 19-H); δ_C see Table 1; *m*/*z* 263 (M^+ + 1, 4%), 262 (M^+, 18), 247 (11), 229 (20), 177 (39) and 109 (100).

Conversion of the acetylenic alcohol 9 into the enol trifluoroacetate 10 and the ketone 4

To 313 mg (1.19 mmol) of the acetylenic alcohol **9** cooled to −40 °C under an argon atmosphere was added a mixture of trifluoroacetic anhydride (3 cm^3) in trifluoroacetic acid (6 cm^3). The mixture was stirred at −25 °C during 1 h and the solvent removed at reduced pressure to give crude enol trifluoroacetate **10** (427 mg, 100%), whose ^1H NMR was shown to have a purity higher than 95%. Since attempts to purify **10** by chromatography on silica gel resulted in its complete conversion to the *ketone* **4**, it was used directly in the next experiment without further purification.

8β-Methylpodocarp-13-en-13-yl trifluoroacetate 10. ν_{max}(KBr)/cm^{-1} 1795, 1225, 1140 and 895; δ_H(300 MHz, $CDCl_3$) 5.26 (1 H, dd, *J* 2.0 and 0.8, 14-H), 2.27 (1 H, dddd, *J* 16.5, 10.5, 6.5 and 2, 12α-H), 2.17 (1 H, dddd, *J* 16.5, 7.0, 1.5 and 0.8, 12β-H), 1.80 (1 H, dddd, *J* 12.5, 6.5, 2.0 and 1.5, 11α-H), 1.03 (3 H, s, 17-H), 0.85 (3 H, s, 18-H), 0.84 (3 H, s, 20-H) and 0.81 (3 H, s, 19-H); δ_C see Table 1.

8β-Methylpodocarpan-13-one 4. Mp 155–156 °C (from hexane) (lit.,[7] a gummy solid) [Found: M^+ (EI), 262.2300. $C_{18}H_{30}O$ requires *M*, 262.2297]; $[\alpha]_D^{22}$ +53 (*c* 4.8, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1725; δ_H(400 MHz, $CDCl_3$) 2.35 (1 H, dddd, *J* 14.1, 4.9, 2.4 and 2.4, 12β-H), 2.21 (1 H, ddd, *J* 14.1, 13.0 and 7.0, 12α-H), 2.12 (1 H, d, *J* 13.3, 14α-H), 1.93 (1 H, dd, *J* 13.3 and 2.4, 14β-H), 0.86 (3 H, s, 19-H), 0.85 (3 H, s, 18-H), 0.82 (3 H, s, 20-H) and 0.80 (3 H, s, 17-H); *m*/*z* 263 (M^+ + 1, 19%), 262 (M^+, 90), 247 (53) and 111 (100).

Conversion of trifluoroacetate 10 to 14α-hydroxymethyl-8β-methylpodocarpan-13-one 11

To a stirred solution of 1.6 M MeLi (1.5 cm^3, 2.4 mmol) in THF (3 cm^3) cooled at −78 °C, was added a solution of the enol trifluoroacetate **10** (427 mg, 1.2 mmol) in THF (3 cm^3). After stirring at the same temperature for 45 min, a saturated solution of formaldehyde in THF[17] cooled at −78 °C was quickly added. After this, the reaction mixture was poured into a cooled (0 °C) saturated aqueous NH_4Cl solution, and the product was isolated by diethyl ether extraction. Usual work-up afforded a residue which was purified by column chromatography, using hexane–AcOEt (1:1) as eluent, to give in order of elution the hydroxy ketone **11**[18] (261 mg, 75%) as an amorphous solid [Found: M^+ (EI), 292.2405. $C_{19}H_{32}O_2$ requires *M*, 292.2402]; $[\alpha]_D^{23}$ +11.5 (*c* 4.0, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3000–3600, 1710, 1390 and 1030; δ_H(300 MHz, $CDCl_3$) 3.99 (1 H, dd, *J* 10.0 and 6.2, 14α-CH_2OH), 3.90 (1 H, dd, *J* 10.0 and 8.0, 14α-CH_2′OH), 2.37 (2 H, m, 12-H), 2.08 (1 H, dd, *J* 8.0 and 6.2, 14-H), 0.92 (3 H, s, 17-H), 0.86 (3 H, s, 18-H), 0.83 (3 H, s, 20-H) and 0.80 (3 H, s, 19-H); δ_C see Table 1; *m*/*z* 293 (M^+ + 1, 3%), 292 (M^+, 13), 274 (28), 236 (15), 262 (72), 247 (75) and 111 (100); followed by the *dihydroxy ketone* **12** (35 mg, 9%) as a white solid, mp 140–141 °C (from hexane–Et_2O) [Found: M^+ + 1 (FAB), 323.2588. $C_{20}H_{34}O_3$ requires *M* + 1, 323.2586]; $[\alpha]_D^{24}$ +45.8 (*c* 1.8, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3000–3600, 1695, 1380 and 1025; δ_H(400 MHz, $CDCl_3$) 4.00 (1 H, dd, *J* 11.2 and 10.1, 12-CH_2OH), 3.89 (1 H, dd, *J* 11.3 and 9.8, 14α-CH_2OH), 3.85 (1 H, dd, *J* 11.2 and 6.5, 12-CH_2′OH), 3.62 (1 H, dd, *J* 11.3 and 6.5, 14α-CH_2′OH), 2.74 (1 H, m, 12-H), 2.27 (1 H, ddd, *J* 9.8, 6.5 and 1.0, 14-H), 1.86 (1 H, ddd, *J* 13.8, 13.8 and 8.4, 11β-H), 1.02 (3 H, s, 17-H), 0.84 (3 H, s, 20-H), 0.83 (3 H, s, 18-H) and 0.78 (3 H, s, 19-H); δ_C see Table 1; *m*/*z* 289 (24%), 287 (11), 284 (11) and 283 (100).

Conversion of the hydroxy ketone 11 into its C-14 epimer 13

A solution of the hydroxy ketone **11** (219 mg, 0.75 mmol) in anhydrous MeOH (5 cm^3) was treated with a 3 M solution of sodium methoxide in MeOH (15 cm^3) at −40 °C. After being stirred at −20 °C for four days the mixture was poured into an ice-cooled saturated aq. solution of KH_2PO_4 and extracted with diethyl ether. The diethyl ether solution was washed with water and brine, dried and concentrated. The residue was chromatographed over silica gel using hexane–ethyl acetate (6:4) as eluent to give 14β-*hydroxymethyl*-8β-*methyl*-*podocarpan*-13-*one* **13** (186 mg, 85%) as a white solid, mp 139–140 °C (from hexane) [Found: M^+ (EI), 292.2408. $C_{19}H_{32}O_2$ requires *M*, 292.2402]; $[\alpha]_D^{26}$ +26.6 (*c* 5.3, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3000–3700, 1710, 1380 and 1035; δ_H(300 MHz, $CDCl_3$) 3.96 (1 H, ddd, *J* 11.2 and 9.3 and 3.9, 14α-CH_2OH), 3.58 (1 H, ddd, *J* 11.2, 10.5 and 3.4, 14α-CH_2′OH), 2.38 (4 H, m, 12-H + 14-H + OH), 2.0 (1 H, dddd, *J* 12.8, 7.9, 2.6 and 2.6, 11α-H), 0.89 (3 H, s, 18-H), 0.87 (3 H, s, 20-H) and 0.82 (6 H, s, 19-H + 17-H); δ_C see Table 1; *m*/*z* 293 (M^+ + 1, 8%), 292 (M^+, 28), 277 (7), 274 (32), 259 (21), 247 (14) and 191 (100).

Conversion of the hydroxy ketone 13 into the trimethylsiloxy cyanides 14 and 15

To a stirred mixture of hydroxy ketone **13** (165 mg, 0.56 mmol) and zinc iodide (111.5 mg, 0.35 mmol) in dry CH_2Cl_2 (7.5 cm^3) was added trimethylsilyl cyanide (745 cm^3, 5.58 mmol) at 0 °C. The stirring was continued for 1 h at the same temperature. The reaction mixture was diluted with diethyl ether. The diethyl ether solution was washed with water and brine, dried and evaporated to afford nearly pure (^1H NMR analysis) 8β-methyl-13β-trimethylsilyloxy-14α- trimethylsilyloxymethyl-podocarpan-13α-yl cyanide **14** (255 mg, 97%) as a solid, mp 147.5–148 °C (from methanol) [Found: M^+ (EI), 463.328 92. $C_{26}H_{49}O_2NSi_2$ requires *M*, 463.3302]; $[\alpha]_D^{23}$ −22 (*c* 3.3, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1455, 1390, 1255, 1100, 875 and 845; δ_H(300 MHz, $CDCl_3$) 3.78 (1 H, dd, *J* 10.8 and 6.4, 14α-

Table 1 ^{13}C Chemical shifts (δ_C in ppm from $SiMe_4$) of compounds **4–6**, **9–18** and **21–24**[a]

	4	**5**	**6**	**9**	**10**	**11**	**12**[b]	**13**	**14**[c]	**15**[d]	**16**	**17**	**18**	**21**	**22**	**23**[f,g]	**24**[f,h]
C-1	40.05	39.72	39.97	39.26	39.58	40.24	40.10	40.17	39.98	39.92	39.99	40.09	39.68	40.10	40.05	40.15	39.81
C-2	18.53	18.24	18.54	18.28	18.50	18.47	18.45	18.49	18.55	18.50	18.46	18.50	18.39	18.50	18.42	18.53	18.50
C-3	42.02	41.66	42.13	41.96	42.15	41.87	41.78	41.86	41.92	41.87	41.92	42.03	41.97	41.99	42.20	41.89	41.70
C-4	33.30	33.15	33.37	33.26	33.38	33.25	33.21	33.23	33.25	33.26	33.28	33.18	33.36	33.40	33.39	33.24	33.09
C-5	56.69	56.65	56.76	55.77	56.87	56.80	56.77	56.33	56.29	56.33	56.41	57.17	56.77	57.12	57.16	56.36	55.99
C-6	18.58	18.24	18.05	18.13	18.54	18.22	18.39	18.59	17.94	17.85	17.95	17.57	18.20	17.69	19.28*	18.71	18.35
C-7	43.14	40.71	41.16	42.26	40.59	37.67	37.10	40.56	41.18	40.98	41.29	41.07	37.64	38.49	37.48	40.57	40.75
C-8	42.00	34.44	34.35	72.96	35.75	40.59	40.58	41.65	38.23	38.43	38.77	37.05	37.03	34.88	35.30	42.47	37.51
C-9	56.91	54.39	56.29	58.19	54.88	50.67	50.68	58.24	59.66	59.62	59.82	60.62	55.76	52.94	50.87	58.68	53.72
C-10	38.94	37.23	37.63	38.78	37.24	37.72	37.78	37.98	37.45	37.41	37.46	37.51	37.60	37.37	37.69	37.96	37.19
C-11	22.00	24.14	18.80	24.38	17.67	22.01	22.80	22.13	16.02	15.91	16.00	16.72	17.01	15.79	15.79*	22.84	21.39
C-12	41.49	136.40	20.71	21.37	27.48	38.67	56.70	41.75	41.55	40.64	39.27	33.31	21.59	34.07	31.87	42.11	118.46
C-13	211.79	126.88	119.87	84.76	145.71	214.62	217.20	214.86	70.38	71.26	72.16	72.87	170.91	72.90	74.15	210.89	150.16
C-14	59.88	51.14	137.77	68.30	128.62	67.02	64.87	65.57	60.21	61.26	55.69	58.07	123.30	54.59	54.10	64.18	53.48
C-15		67.20	134.97			60.77	64.07	57.57	58.98	60.38	61.00	67.78	68.19	66.61	67.48	62.72	63.39
C-16		170.17	136.67						122.80	122.95	122.89	176.93	—[e]	180.16	176.39		
C-17	20.47	14.08	26.28	30.72	22.69	23.07	24.24	16.71	17.25	17.45	18.50	17.94	22.02	23.00	24.35	16.44	15.37
C-18	33.44	33.34	33.37	33.42	33.30	33.35	33.27	33.36	33.21	33.19	33.18	33.38	33.26	33.26	33.12	33.39	33.36
C-19	21.53	21.56	21.43	21.66	21.32	21.55	21.48	21.49	21.35	21.32	21.28	21.31	21.29	21.41	20.98	21.48	21.60
C-20	15.86	15.26	16.33	15.11	16.25	16.35	16.07	16.20	16.42	16.34	16.23	16.20	16.48	16.83	16.90	16.13	15.88

[a] At 75.4 MHz in $CDCl_3$. The signals with the same superscript (*) may be interchanged within the same column. [b] δ_C of 12α-CH_2OH at 59.99. [c] δ_C of 13- and 15-$Si(CH_3)_3$ groups at 1.18 and −0.54, respectively. [d] δ_C of 13-$Si(CH_3)_3$ at 1.11. [e] Not observed. [f] Mixture of diastereomers. Only the signals of the main diastereomer are given. [g] Carbon atoms of the THP moiety at δ_C 100.16 (CH), 30.69 (CH_2), 19.89 (CH_2), 25.45 (CH_2) and 61.75 (CH_2). [h] Carbon atoms of the THP moiety at δ_C 98.55 (CH), 30.22 (CH_2), 18.88 (CH_2), 25.49 (CH_2) and 61.83 (CH_2); δ_C of CF_3 at 120.74.

CH_2OH), 3.72 (1 H, dd, *J* 10.8 and 3.9, 14α-$CH_2'OH$), 2.24 (1 H, ddd, *J* 13.9, 3.2 and 3.2, 12β-H), 0.83 (3 H, s, 17-H), 0.82 (3 H, s, 18-H), 0.79 (3 H, s, 20-H), 0.77 (3 H, s, 19-H), 0.22 and 0.12 (18 H, two s, 2 × $SiMe_3$); δ_C see Table 1; *m/z* 449 (35%), 448 (100), 422 (11), 421 (37) and 374 (18).

Addition of wet diethyl ether (5 cm^3) to the above reaction mixture and stirring for 30 min at room temperature, afforded quantitatively 14α-hydroxymethyl-8β-methyl-13β-trimethylsilyloxypodocarpan-13α-yl cyanide **15** (220 mg, 99%); δ_H(400 MHz, $CDCl_3$) 3.96 (1 H, dd, *J* 10.9 and 4.4, 14α-CH_2OH), 3.90 (1 H, dd, *J* 10.9 and 3.5, 14α-$CH_2'OH$), 2.28 (1 H, ddd, *J* 13.9, 3.3 and 3.3, 12β-H), 1.93 (1 H, ddd, *J* 12.5, 3.1 and 3.1, 7β-H), 1.86 (1 H, ddd, *J* 13.9, 13.9 and 5.0, 12α-H), 0.92 (3 H, s, 17-H), 0.85 (3 H, s, 18-H), 0.82 (3 H, s, 20-H), 0.80 (3 H, s, 19-H) and 0.26 (9 H, s, $SiMe_3$); δ_C see Table 1.

Conversion of trimethylsiloxy cyanide 14 into cyanohydrin 16

A solution of trimethylsiloxy cyanide **14** (192 mg, 0.414 mmol) and 3 M HCl (1.1 cm^3) in THF (1.9 cm^3) was stirred at room temperature for 2 h. Usual work-up afforded nearly pure 13β-hydroxy-14β-hydroxymethyl-8β-methylpodocarpan-13α-yl cyanide **16** (126 mg, 95%), which could be used without further purification for the next step; δ_H(400 MHz, $CDCl_3$) 4.35 (1 H, dd, *J* 11.1 and 4.1, 14α-CH_2OH), 4.29 (1 H, dd, *J* 11.1 and 1.7, 14α-$CH_2'OH$), 2.28 (1 H, ddd, *J* 10.6, 2.1 and 2.1, 12β-H), 1.93 (1 H, ddd, *J* 10.7, 2.0 and 2.0, 7β-H), 1.23 (3 H, s, 17-H), 0.84 (3 H, s, 20-H), 0.83 (3 H, s, 18-H) and 0.79 (3 H, s, 19-H); δ_C see Table 1.

Preparation of 13β-hydroxyspongian-16-one 17 from cyanohydrin 16

To a solution of cyanohydrin **16** (36 mg, 0.113 mmol) in THF (1 cm^3) was added conc. HCl (0.5 cm^3) at room temperature. The mixture was stirred at 50–60 °C for 24 h, poured into water and extracted with ethyl acetate. The residue obtained after usual work-up was purified by chromatography on silica gel using hexane–ethyl acetate (3:2) as eluent to give 13β-*hydroxyspongian*-16-*one* **17** (33 mg, 91%) as a solid, mp 212–213 °C (from hexane–diethyl ether) [Found: M^+ (EI), 320.2353. $C_{20}H_{32}O_3$ requires *M*, 320.2351]; $[\alpha]_D^{24}$ +36.8 (*c* 0.9, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3460, 3430, 1770, 1760, 1250, 1180, 1100, 990, 980 and 970; δ_H(400 MHz, $CDCl_3$) 4.40 (1 H, dd, *J* 11.3 and 7.7, 15-H), 4.19 (1 H, dd, *J* 7.7 and 7.0, 15-H'), 1.99 (1 H, ddd, *J* 13.9, 3.1 and 3.1, 12β-H), 1.12 (3 H, s, 17-H), 0.87 (3 H, s, 20-H), 0.83 (3 H, s, 18-H) and 0.80 (3 H, s, 19-H); δ_C see Table 1; *m/z* 320 (M^+, 5%), 305 (8), 276 (8), 193 (12), 192 (24) and 191 (100).

Preparation of spongi-13-en-16-one 18

Hydroxylactone **17** (75 mg, 0.23 mmol) was treated with a 1:1 mixture of conc. HCl and AcOH (1.5 cm^3) at 120 °C in a sealed tube for 2 h. The mixture was poured into water and extracted with hexane. The combined organic layers were washed with 5% $NaHCO_3$ solution followed by work-up as usual. Purification of the residue left after evaporation of the solvent by column chromatography, using hexane–ethyl acetate (4:1) as eluent, furnished the α,β-*unsaturated lactone* **18** (67.5 mg, 95%) as a white solid, mp 215.5–216.5 °C (from diethyl ether–CH_2Cl_2) [Found: M^+ (EI), 302.2245. $C_{20}H_{30}O_2$ requires *M*, 302.2246]; $[\alpha]_D^{23}$ −53.2 (*c* 3.5, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1770, 1750, 1680, 1010 and 740; δ_H(300 MHz, $CDCl_3$) 4.74 (1 H, ddd, *J* 16.9, 2.7 and 2.7, 15-H), 4.64 (1 H, ddd, *J* 16.9, 3.7 and 1.7, 15-H'), 2.39 (1 H, m, 12β-H), 2.10 (1 H, m, 12α-H), 1.88 (1 H, m, 11α-H), 1.17 (3 H, s, 17-H), 0.91 (3 H, s, 20-H), 0.87 (3 H, s, 18-H) and 0.84 (3 H, s, 19-H); δ_C see Table 1; *m/z* 303 (M^+ + 1, 6%), 302 (M^+, 21), 288 (9), 287 (41), 258 (21) and 257 (100).

Preparation of spongia-13(16),14-diene 6

Diisobutylaluminium hydride (0.1 cm^3 of a 1 M solution in cyclohexane, 0.1 mmol) was added at −20 °C to a stirred solution of the lactone **18** (20 mg, 0.066 mmol) in THF (0.35 cm^3). After stirring for 2.5 h at the same temperature the mixture was treated with 10% aqueous sulfuric acid (0.12 cm^3) and the stirring was continued at 0 °C for 5 h. The mixture was diluted with hexane and worked up as usual to give an oily residue which was chromatographed on silica gel, using hexane–ethyl acetate (98:2) as eluent, to afford compound **6** (16.4 mg, 86%) as a solid, mp 111.5–112.9 °C (from methanol) (lit.,[10] 115–116 °C) [Found: M^+ (EI), 286.2295. $C_{20}H_{30}O$ requires *M*, 286.2297]; $[\alpha]_D^{26}$ −30.1 (*c* 2.7, $CHCl_3$) (lit.,[10] −32.7); ν_{max}(KBr)/cm^{-1} 1460, 1390, 1380, 1370, 1040, 895 and 770; δ_H(300 MHz, $CDCl_3$) 7.06 (1 H, d, *J* 1.6, 15-H), 7.02 (1 H, ddd, *J* 1.6, 1.6 and 1.2, 16-H), 2.74 (1 H, dddd, *J* 16.2, 6.2, 1.7 and 1.2, 12β-H), 2.42 (1 H, dddd, *J* 16.2, 12.0, 7.1 and 1.6, 12α-H), 2.07 (1 H, m, 7β-H), 1.20 (3 H, d, *J* 0.7, 17-H), 0.88 (3 H, s, 20-H), 0.85 (3 H, s, 18-H) and 0.82 (3 H, s, 19-H); δ_C see Table 1; *m/z* 287 (M^+ + 1, 13%), 286 (M^+, 63), 272 (20) and 271 (100).

Preparation of 13β-hydroxy-14β-spongian-16-one 21 and 13α-hydroxy-14β-spongian-16-one 22

Following the same procedure used to prepare **14** from **13**, the hydroxy ketone **11** (33.4 mg) was converted into a mixture of epimeric trimethylsiloxy cyanide **19** and **20** (50.8 mg, 96%), which was treated with a 2:1 mixture of THF and conc. HCl (0.6 cm^3) at room temperature for four days. Water was added, and the mixture was extracted with diethyl ether. Work-up as usual gave a crude mixture of epimeric α-hydroxy lactones **21** and **22**. The two isomers were separated by chromatography with hexane–ethyl acetate (9:1) as eluent.

Compound 21. (16.7 mg, 48%; Second isomer eluted): mp 185–187 °C (from hexane–ether) [Found: M^+ (EI), 320.2352. $C_{20}H_{32}O_3$ requires *M*, 320.2351]; $[\alpha]_D^{26}$ +91.4 (*c* 1.4, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3440, 1770, 1385, 1220, 1150 and 1005; δ_H(400 MHz, $CDCl_3$) 4.26 (1 H, dd, *J* 8.8 and 8.8, 15-H), 4.13 (1 H, dd, *J* 11.6 and 8.8, 15-H'), 2.22 (1 H, ddd, *J* 11.6, 8.8 and 2.0, 14-H), 1.81 (1 H, m, 12β-H), 1.71 (1 H, m, 1β-H), 1.19 (3 H, s, 17-H), 0.86 (3 H, s, 20-H), 0.83 (3 H, s, 18-H), 0.80 (3 H, s, 19-H) and 0.74 (1 H, dd, *J* 12.1 and 2.4, 5α-H); δ_C see Table 1; *m/z* 321 (M^+ + 1, 17%), 320 (M^+, 90), 306 (18), 305 (100) and 191 (84).

Compound 22. (6.2 mg, 18%; First isomer eluted): ν_{max}(KBr)/cm^{-1} 3460, 3420, 1760, 1750, 970 and 760; δ_H(400 MHz, $CDCl_3$) 4.40 (1 H, dd, *J* 11.3 and 7.9, 15-H), 4.25 (1 H, dd, *J* 7.9 and 7.2, 15-H'), 1.08 (3 H, s, 17-H), 0.84, 0.82 and 0.80 (3 H, each, each s, 18-H, 19-H and 20-H); δ_C see Table 1.

Conversion of the β-hydroxy ketone 13 into its tetrahydropyranyl ether 23

To a solution of the hydroxy ketone **13** (100 mg, 0.34 mmol) and pyridinium toluene-*p*-sulfonate (PPTS; 17.2 mg, 0.068 mmol) in CH_2Cl_2 (4 cm^3) was added 3,4-dihydro-2*H*-pyran (1.55 cm^3) at −78 °C. The reaction mixture was allowed to warm to 0 °C and then stirred at this temperature for 24 h. The reaction was treated with 5% aqueous $NaHCO_3$ solution, poured into water, extracted with hexane and worked up as usual. Purification by chromatography on silica gel, using hexane–ethyl acetate (4:1) as eluent, afforded the tetrahydropyranyl ether **23** (122.4 mg, 95%) as a diastereoisomeric mixture; ν_{max}(KBr)/cm^{-1} 1710, 1380, 1115, 1020 and 970; δ_H(300 MHz, $CDCl_3$) 4.56 (1 H, m, OCHO), 4.16, 3.95, 3.76, 3.49 and 3.27 (total 4 H, each m), 0.85, 0.81, 0.78, 0.71 and 0.70 (total 12 H, each s); δ_C see Table 1.

Preparation of spongi-12-en-16-one (isoagatholactone) 5

To a solution of the ketone **23** (68 mg, 0.181 mmol) in THF (0.9 cm^3) was added dropwise a 1 M solution of sodium bis(trimethylsilyl)amide (NaHMDS) in THF (0.2 cm^3, 0.2 mmol) at −78 °C. After being stirred at the same temperature for 3 h, a solution of *N*-(5-chloro-2-pyridyl)trifluoromethanesulfonimide (85.5 mg, 0.218 mmol) in THF (0.9 cm^3) was added. The mixture was stirred at −78 °C for 2.5 h, diluted with hexane, washed successively with water, 10% NaOH and brine, dried and concentrated. The residue was

chromatographed on silica gel, using hexane–ethyl acetate (95:5) as eluent, to give vinyl trifluorosulfonate **24** (73.5 mg, 80%) as a mixture of diastereoisomeric tetrahydropyranyl ethers; ν_{max}(film)/cm^{-1} 1420, 1210, 1150, 1030, 880 and 735; δ_H(300 MHz, $CDCl_3$) 5.74 (1 H, m, 12-H), 4.58 (1 H, m, OCHO), 3.82, 3.50, 3.28 (total 4 H, each m), 0.866, 0.87, 0.84, 0.79 and 0.77 (total 12 H, each s); δ_C see Table 1.

A mixture of the above obtained vinyl trifluorosulfonate **24** (30 mg, 0.06 mmol), palladium acetate (3.4 mg, 0.015 mmol), triphenylphosphine (7.8 mg, 0.03 mmol), triethylamine (0.017 cm^3, 0.118 mmol), MeOH (0.3 cm^3) and DMF (0.3 cm^3) was purged with carbon monoxide for 5 min. The resulting black mixture was stirred under a CO balloon at 60 °C for 6.5 h, diluted with wet diethyl ether and worked up as usual. The residue left after evaporation of the solvent was dissolved in MeOH (2 cm^3) and treated with a catalytic amount of PPTS. After being stirred at 60 °C for 2 h, the reaction mixture was poured into water and extracted with diethyl ether. Usual work-up followed by column chromatography of the residue on silica gel, using hexane–ethyl acetate (8:2) as eluent, afforded isoagatholactone **5** (12.6 mg, 70%) as a solid, mp 154–154.5 °C (from hexane–diethyl ether) (lit.,[13] 153–155 °C) [Found: M$^+$ (EI), 302.2246. $C_{20}H_{30}O_2$ requires *M*, 302.2246]; $[\alpha]_D^{26}$ +7.5 (*c* 1.6, $CHCl_3$) (lit.,[13] +6.3); ν_{max}(KBr)/cm^{-1} 1765, 1690, 1490, 1220, 1200, 1000, 990 and 735; δ_H(300 MHz, $CDCl_3$) 6.85 (1 H, ddd, *J* 3.4, 3.4 and 3.4, 12-H), 4.36 (1 H, dd, *J* 9.1 and 9.1, 15-H), 4.02 (1 H, dd, *J* 9.1 and 9.1, 15-H′), 2.78 (1 H, m, 14-H), 2.32 (1 H, dddd, *J* 20.3, 5.6, 3.4 and 3.4, 11α-H), 2.08 (1 H, dddd, *J* 20.3, 11.5, 4.9 and 3.4, 11β-H), 0.90 (3 H, s, 20-H), 0.85 (3 H, s, 18-H), 0.81 (3 H, s, 19-H) and 0.75 (3 H, s, 17-H); δ_C see Table 1; *m*/*z* 302 (M$^+$, 6%), 287 (7.5), 193 (13) and 192 (100).

When the chromatographic purification was effected prior to the MeOH–PPTS treatment, isoagatholactone **5** was obtained in 60–65% yield, and a more polar product, identified as the intermediate acid **26**, in 5–10% yield was also obtained. The later product, obtained as a mixture of diastereoisomeric tetrahydropyranyl ethers, was an amorphous solid: δ_H(400 MHz, $CDCl_3$) 6.90 (1 H, m, 12-H), 4.50 and 4.40 (total 1 H, each br s, OCHO), 4.15, 3.90, 3.85, 3.45 and 3.35 (total 4 H, each m, 15-H + OCHOCH_2), 0.92, 0.89, 0.85, 0.81 and 0.80 (total 12 H, each s, 17-H, 18-H, 19-H and 20-H).

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