Synthesis of *pyrano*-Agarofurans[‡]

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This paper describes the synthesis of *pyrano*-agarofuran tetraol **8**. The key step of the synthesis lies in the stereoselectivity encountered in the hydrogenation of precursor **13** because of its peculiar *cis*-decalinic conformation.

Introduction

Agarofuran sesquiterpenes are polyesters of various tricyclic polyols, whose general structure (**1**) is formed around the agarofuran backbone **2**, can be related to the eudesmane family with an ether linkage between carbon atoms C-4a and C-11, thus forming a tetrahydrofuran ring, fused to the *trans*-decalinic system A/B (Figure 1).[1] Hydroxy groups can be present on this skeleton on almost every carbon atom, with various stereochemistries. This last feature, and the diversity of the organic acids involved in the esterification of the hydroxy groups, generate a great diversity in this family of sesquiterpenes. In addition, one should also consider an interesting but poorly investigated compound, evuncifer ether **3**,[2] a major constituent of the defensive secretion of the termite *Amitermes evuncifer*. This eudesmane sesquiterpene is very similar to agarofurans apart from the size of the heterocycle, which is in this case a tetrahydropyran involving an ether linkage between carbon atoms C-11 and C-4 in a *cis* configuration of bicycle A/B. In our endeavour to test the antifeedant activity of agarofurans, because we wished to establish structure−activity relationships, we were interested in the design of a versatile synthetic strategy for the synthesis of not only natural *furano*-agarofuran sesquiterpenes but also their *pyrano*-agarofuran analogues related to **3**. The key feature of this strategy would therefore be the control of the configuration of both quaternary stereogenic centers of the decalinic ring junction, C-4a and C-8a.

Most of the reported strategies devoted to the synthesis of the most polyhydroxylated agarofurans are based on the early construction of a decalinic precursor, which is later transformed in order to introduce the remaining carbon and oxygen atoms.[3] Our retrosynthetic analysis of this type of molecule (Scheme 1) was essentially derived from the same principle, and emphasised enone **4** as a valuable precursor.

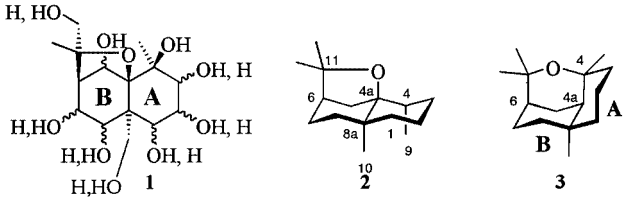

Figure 1. Structures of *furano*-agarofuranes **1**, **2** and *pyrano*-agarofuran **3** (evuncifer ether)

We have mentioned in the preceding papers of the series[4,5] the possible straightforward synthesis of decalinic compound **4** through allylic oxidation of hexahydro naphthalenone **5**, obtained in 10 steps starting from the commercially available 1,4-cyclohexanedione mono-ethylene ketal (4.2% yield over 11 steps). We have subsequently investigated the stereochemical features related to the introduction of a tertiary hydroxy group at the ring junction (C-4a), which we had previously reported[6] as being the key step for controlling the stereochemistry of formation of the heterocycle. Therefore, epoxides **6** and **7** have been synthesised in a stereocontrolled fashion from **4**. The relative configurations at C-4a and C-8a suggest **6** as a *furano*-agarofuran precursor while **7** would allow formation of *pyrano*-agarofurans.

In this paper we report our first results in this field, yielding the total synthesis of *pyrano*-agarofuran tetraol **8**, starting from hydroxy epoxide **7**.

Results and Discussion

The first step of the synthesis is the introduction of the hydroxy isopropyl group at C-6 in order to complete the eudesmane backbone. This introduction has to be achieved

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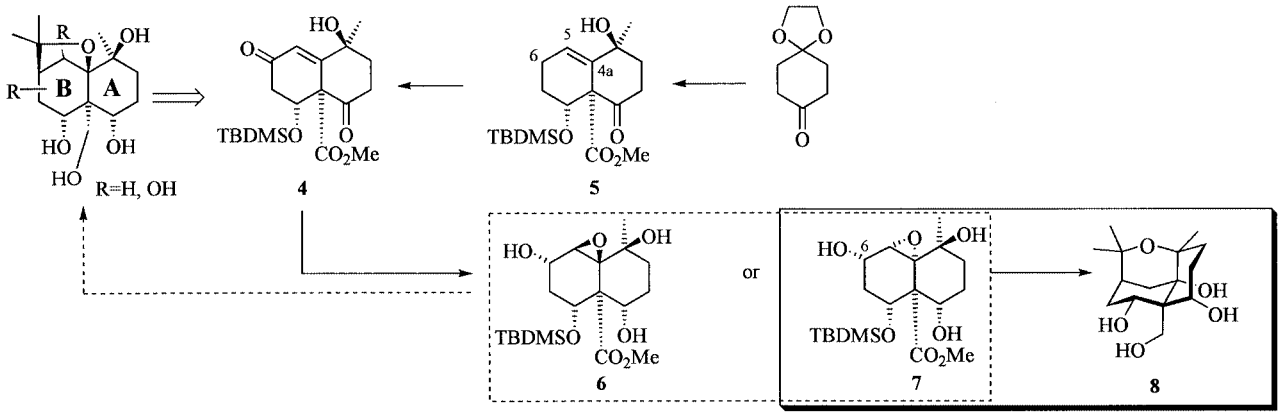


Scheme 1

by substitution of an appropriate leaving group at C-6, so mesylate **9** and triflate **10** were synthesised using standard procedures. Although the hydroxy group at C-6 was in an equatorial position on cycle B and not particularly sterically hindered, its tosylation was completely ineffective. Similarly, substitution of the leaving group at C-6 by a cyanide salt, although allowing the nucleophile to approach the molecule from its less-hindered β-face, required the use of Et_4NCN as the cyanide delivery agent. Moreover, substitution of the mesylate was quite unsuccessful and resulted, when performed in dichloroethane at 60 °C, in the formation, in 60% yield, of the corresponding chloride with inversion of configuration at C-6, formation of which required a preliminary substitution of a chlorine atom of the solvent; in dichloromethane, mesylate **9** was recovered untouched. Nevertheless, in the same conditions, triflate **10** reacted well, affording the desired cyano epoxide **11** in 74% overall yield from **7**. When the reaction was left at room temperature overnight, some formation of the vinylic cyanide **12** was observed, probably owing to remaining traces of the base used in the esterification step. Thereafter, reduction of the nitrile resulted in the formation of the $\Delta^{5,6}$ double bond, and aldehyde **13** was thereby obtained in 67% yield.

The next step was the hydrogenation of the double bond, which was not expected to be fully stereoselective. Indeed, our previous studies, on model compounds **A** derived from Wieland−Miescher ketone, reported this hydrogenation to be unselective, affording a mixture of both isomers at C-6. In the case of *trans*-**A**,[6] the mixture was thereafter equilibrated, taking advantage of the possible isomerisation at C-6 in basic conditions and of the driving force given by the heterocycle formation. However, the use of our previously reported experimental conditions for this reduction step (H_2, Pd/C, MeOH) resulted only in the reduction of the aldehyde function and formation of alcohol **14** (Figure 2). Moreover, further treatment of **14** in the same conditions did not yield the reduction of the double bond but formation of alkene **15**. After extensive experimentation, we found that hydrogenation conducted in ethyl acetate in the presence of a small amount of water (2.5%) allowed reduction of the double bond to take place, alcohol **14** being obtained only as a by-product (7%). The major product of the reaction was an inseparable mixture of ketals **17a,b** and hydroxy aldehyde **16**, all three having the same configuration at C-6, resulting from the selective hydrogenation from the α-face of the molecule. Oxidative treatment of this mixture (Jones) was performed to yield δ-lactone **18** (90%). Other oxidative systems were tried but gave lower yields: Fetizon's reagent,[7] which we had previously used in our model study, did not yield any oxidation and PCC in buffered conditions ($AcONa,CH_2Cl_2$) afforded the desired lactone but in only 70% yield.

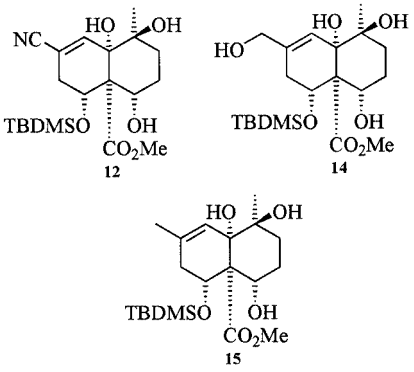
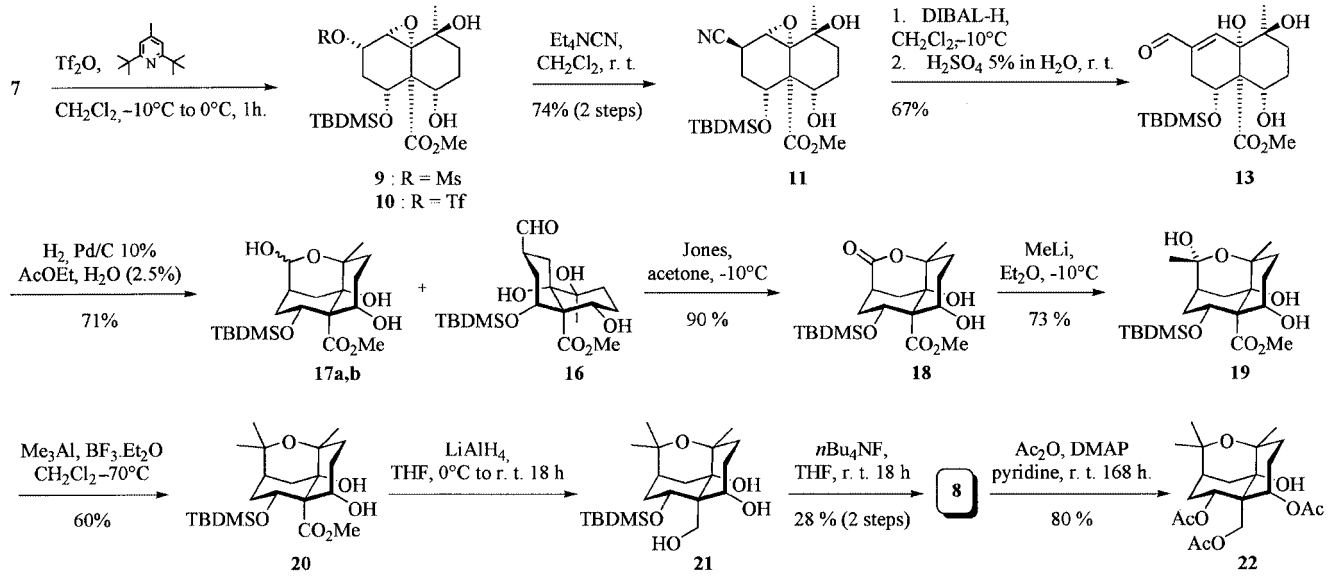


Figure 2. Structures of **12**, **14** and **15**

Completion of the synthesis required the introduction of two methyl groups at C-11. The first one was stereoselectively introduced by the action of methyllithium, affording hemiketal **19.** The configuration at C-11 in **19** was assumed because of the 1,3 diaxial interaction which would have resulted from the attack of the organometallic reagent from the other face of the carbonyl group. Moreover, the stability of the tricyclic structure of **19** did not allow the second methyl group to be introduced in these conditions. Subsequent further alkylation at C-11 had therefore to be achieved in Lewis acid-mediated conditions using trimethyl-



Scheme 2

aluminium as the methyl group delivery reagent.[8] Tetrahydropyran **20** was thereby obtained in 60% yield. Reduction of the ester group in the presence of a large excess of lithium aluminium hydride afforded triol **21**, which was subsequently transformed into the desired *pyrano*-agarofuran tetraol **8** through cleavage of the silyl ether in standard conditions. Peracetylation in standard conditions afforded after 8 days the corresponding triacetate **22**, in which the tertiary hydroxy group remained unesterified. Bioassays have been conducted on the antifeedant activity of **8** and **22** and will be reported elsewhere.

Nevertheless, we had to obtain confirmation of the stereoselectivity of the hydrogenation step and to find an explanation for this unexpected selectivity. In fact, the hypothesis of the inverse stereochemical course for this reduction step implies that a γ-lactonic compound, involving the oxygen atom at C-4a and exhibiting a five-membered heterocycle, would have been formed after oxidation. In this compound, the conformations of ring A and ring B would necessarily have been the same as in **16** (with the opposite configuration for the substituent at C-6), in order to allow the axial position on ring B of the hydroxy group at C-4a. The silyloxy group would thereby be in an axial position. In fact, the observed coupling pattern of H-8 (δ = 3.98 ppm, dd, J = 11, 6.5 Hz) in the obtained product clearly demonstrated the equatorial position of the silyloxy group on ring B. Moreover, in order to confirm the presence of a δ-lactone in compound **18**, definite proof was afforded by the infrared spectrum, which exhibited a strong absorption at 1740 cm^{-1}, as expected for such a six-membered lactonic ring. The discrepancies between these results and those previously obtained with model compounds **A** have probably to be explained by the difference of conformation of *cis*-**A** and nitrile **12**. This conformation of *cis*-**A** was derived from its NMR spectroscopic data[6] and is depicted in Figure 3 with rings A and B also exhibiting a chair and half-chair conformation respectively, but with the α-silyloxy group at C-1 being axial. Indeed, **12**, probably in order to minimise the interactions between the methyl ester group and the silyloxy group and to favour hydrogen bonding between the carbonyl of the methyl ester and the hydroxy group at C-1, has adopted a more folded conformation, as described in the next paragraph, in which the steric hindrances of the two faces of the molecule are quite different, allowing the α approach to be favoured (Figure 3).

Indeed, an important feature of the reaction sequence **11** → **18** lies in the successive changes of conformation of the decalinic system, which have to occur to allow the six-membered heterocycle to be formed. First of all, during the $\Delta^{5,6}$ formation through opening of the oxirane ring, ring B flipped from a boat-like conformation[9] (established through its NMR spectroscopic data, which show the equatorial position of both the hydroxy group at C-1 and the silyloxy group at C-8, see Figure 3) to a half-chair conformation, with only slight changes in the conformation of the other six-membered ring (ring A). Indeed, in compounds **12**–**15**, exhibiting a $\Delta^{5,6}$ double bond, the NMR spectroscopic data clearly showed ring A to be in a chair-like conformation where both hydroxy groups at C-1 and C-4 are equatorial (in fact, the same conformation as that observed in **11**) and ring B in the half-chair conformation where the silyloxy group is in an axial position. In this conformation, proton H-1, easily differentiated in the NMR spectrum from H-8 because of its coupling constant with the OH proton, was shifted at low field ($\Delta\delta > 1.2$ ppm) owing to the anisotropic effect of the double bond of ring B (the chemical shift of H-1 in **11**, **12** and **15** is δ = 3.57, 4.79 and 4.83 ppm respectively; moreover, in these compounds

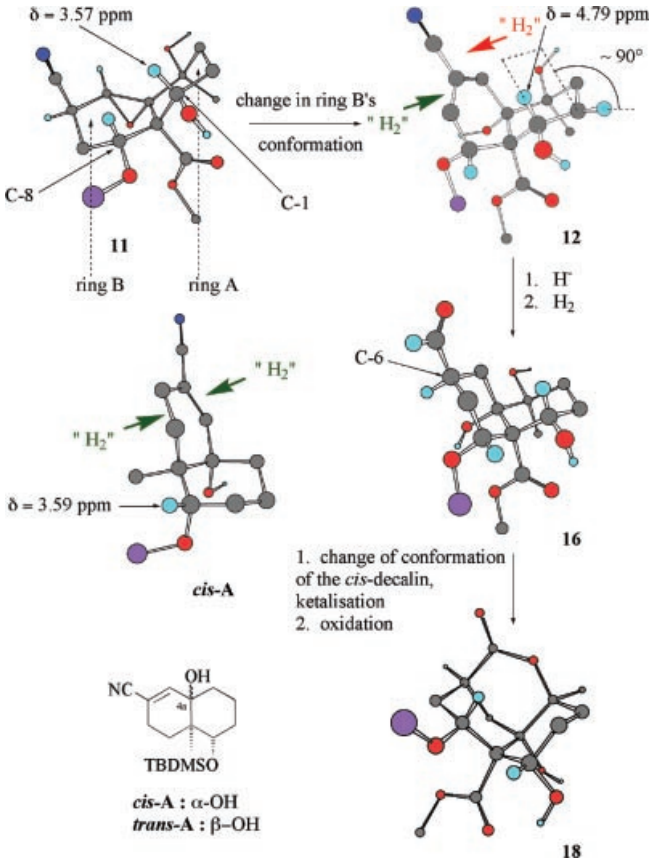


Figure 3. Conformational changes of the *cis*-decalinic system

(**12**−**15**), H-1 appeared as a triplet due to a distortion in the chair conformation of ring A, the dihedral angle H-1/C-1/C-2/H-2_{eq} becoming nearly 90°.

A conformational change of the whole decalinic system then took place after the hydrogenation step. Indeed, the NMR spectroscopic data of aldehyde **16** show that the conformation of ring A is always the same as in the previous compounds while ring B has adopted the chair conformation in which the silyloxy group is axial. In this conformation both the carbonyl group at C-6 and the hydroxy group at C-4 are in equatorial positions, and no heterocycle formation can occur. The energetic demand of the conformational change of the *cis*-decalin thus explains the obtaining of a mixture of ketals **17a,b** and aldehyde **16**. These changes of the decalin conformation are depicted in Figure 3 (for the sake of clarity the TBDMS groups have been hidden except for the Si atoms).

Conclusion

This first synthesis of a polyhydroxylated *pyrano*-agarofuran demonstrates the versatility of our synthetic strategy, which will be now applied to the synthesis of *furano*-agarofuran, using isomeric epoxide **6** as the starting material.

Experimental Section

General Remarks: See preceding paper.[5]

Mesylate 9: Mesyl chloride (0.032 mL, 0.41 mmol) was added dropwise to a solution of alcohol **7** (114 mg, 0.28 mmol), Et_3N (0.120 mL, 0.86 mmol) in CH_2Cl_2(1.6 mL) under argon at 0 °C. The mixture was warmed slowly to room temperature, diluted with Et_2O (5 mL), and poured into a mixture of H_2O and ice (5 mL). The aqueous phase was extracted with Et_2O (2 × 5 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by chromatography (EtOAc/cyclohexane, 70:30) to give **9** (100 mg, 0.20 mmol, 74%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.06 (dd, *J* = 11.5, 4.5 Hz, 1 H), 4.03 (dd, *J* = 12, 5 Hz, 1 H), 3.94 (d, *J* = 12 Hz, 1 H, OH), 3.83 (s, 1 H), 3.74 (s, 3 H), 3.38−3.24 (m, 1 H), 3.09 (s, 3 H), 2.36 (q, *J* = 12 Hz, 1 H), 2.15 (br. s, 1 H, OH), 2.04−1.87 (m, 3 H), 1.77 (td, *J* = 15.5, 2 Hz, 1 H), 1.60−1.48 (m, 1 H), 1.18 (s, 3 H), 0.80 (s, 9 H) 0.06 (s, 3 H), 0.04 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0 (s), 78.9 (d), 75.1 (d), 74.4 (d), 70.5 (s), 67.1 (s), 55.6 (d), 54.9 (s), 51.8 (q), 39.1 (q), 34.1 (t), 33.2 (t), 29.2 (t), 25.7 (3 C, q), 24.2 (q), 17.9 (s), −4.5 (q), −4.8 (q). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3513, 2951, 2930, 2897, 2856, 1711, 1356, 1255, 1111, 924, 832, 778.

Triflate 10: 2,6-Di-*tert*-butyl-4-methylpyridine (200 mg, 0.97 mmol) and, dropwise, Tf_2O (0.110 mL, 0.65 mmol) were added to a solution of triol **7** (98.2 mg, 0.24 mmol) in dry CH_2Cl_2 (2.6 mL) at −10 °C. The reaction mixture was stirred for 1 h with the formation of a green-gray precipitate and warmed to 0 °C and diluted with Et_2O (20 mL). The solution was washed with HCl (10 mL of a 0.2 N solution), saturated sodium bicarbonate solution (10 mL), and brine, and dried ($MgSO_4$). Solvents were evaporated under reduced pressure and the residue of **10** (138 mg) was used in the next step without further purification. ^{1}H NMR: δ = 5.28 (dd, *J* = 11, 4.5 Hz, 1 H), 4.07 (dd, *J* = 12, 5 Hz, 1 H), 3.98 (d, *J* = 12 Hz, 1 H, OH), 3.88 (s, 1 H), 3.79 (s, 3 H), 3.38−3.29 (m, 1 H), 2.56 (q, *J* = 12 Hz, 1 H), 2.12−1.98 (m, 4 H), 1.90−1.80 (m, 1 H), 1.24 (s, 3 H), 0.86 (s, 9 H), 0.12 (s, 3 H), 0.10 (s, 3 H). ^{13}C NMR: δ = (*C*F_3 signal not observed) 167.5 (s), 84.0 (d), 79.1 (d), 74.3 (d), 70.6 (s), 67.7 (s), 55.0 (d), 54.8 (s), 51.9 (q), 34.1 (t), 33.1 (t), 29.2 (t), 25.7 (q), 24.3 (q), 17.9 (s), −4.6 (q), −4.8 (q).

Nitrile 11: $Et_4N^+CN^-$ (325 mg, 2.05 mmol) was added rapidly to a solution of the crude triflate **10** (138 mg) in CH_2Cl_2 (10 mL) . The reaction mixture was stirred for 15 min at room temperature and was evaporated under reduced pressure. The residue was diluted with Et_2O (20 mL), filtered, and concentrated under reduced pressure. The crude product (97 mg) was purified by chromatography (EtOAc/cyclohexane, 20:80 to 50:50) to give **11** (74 mg, 0.18 mmol, 74%, 2 steps) as a white solid. M.p. 114 °C (EtOAc/cyclohexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.30 (dd, *J* = 11, 5 Hz, 1 H), 4.01 (d, *J* = 12 Hz, 1 H, OH), 3.79 (d, *J* = 4 Hz, 1 H), 3.72 (s, 3 H), 3.57 (td, *J* = 12, 4.5 Hz, 1 H), 3.37 (dd, *J* = 7, 4 Hz, 1 H), 2.18 (ddd, *J* = 13, 11, 5 Hz, 1 H), 2.05−1.50 (m, 5 H), 1.17 (s, 3 H), 0.81 (s, 9 H), 0.08 (s, 3 H), 0.05 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2 (s), 118.4 (s), 78.4 (d), 71.7 (d), 70.5 (s), 65.1 (s), 55.3 (s), 52.9 (d), 51.7 (q), 34.3 (t), 29.3 (t), 28.3 (t), 25.7 (q), 24.1 (q), 17.9 (s), −4.7 (q), −4.8 (q). GC analysis (MDN5S, 0.32 mm id. × 30 m, 80−300 °C, 10 °C/min), retention

time 20.80 min. CI NH_3 MS: *m/z* (%) = 429 ($[M + NH_4]^+$, 20), 412 (MH^+, 100), 394 (15), 118 (60). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3502, 2951, 2929, 2898, 2856, 2242, 1711, 1253, 1107, 835.

Unsaturated Nitrile 12: Prepared from the crude nitrile **11** by keeping for 18 h at room temperature before chromatography on silica gel (EtOAc/cyclohexane, 20:80 to 50:50). M.p. 152 °C (Et_2O). ^1H NMR: δ = 6.48 (br. s, 1 H), 4.79 (t, *J* = 7 Hz, 1 H), 4.68 (s, 1 H, OH), 4.58−4.54 (br. s, 1 H), 4.21 (d, *J* = 7 Hz, 1 H, OH), 3.75 (s, 3 H), 2.61 (ddd, *J* = 18, 7, 2 Hz, 1 H), 2.27−1.98 (m, 4 H), 1.87−1.78 (m, 1 H), 1.30 (s, 3 H), 0.86 (s, 9 H), 0.06 (s, 6 H). ^{13}C NMR: δ = 173.9 (s), 145.0 (d), 118.1 (s), 113.5 (s), 78.4 (s), 75.1 (s), 69.0 (d), 66.1 (d), 59.3 (s), 52.4 (q), 36.3 (d), 28.7 (t), 26.5 (q), 25.6 (q), 23.3 (t), 25.7 (q), 17.9 (s), −3.8 (q), −4.9 (q). GC analysis (MDM5S, 0.32 mm id. × 30 m, 180−300 °C, 10 °C/min), retention time 9.10 min. EI MS: *m/z* (%) = 393 (10) [$M^+ - H_2O$], 354 ($M^+ - t$Bu, 1), 336 ($M^+ - H_2O - t$Bu, 5), 322 (5), 304 (10), 75 (100). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3470, 2929, 2856, 2221, 1711, 1253, 1084.

Aldehyde 13: Diisobutylaluminium hydride (3.2 mL, 3.2 mmol, 1 M solution in CH_2Cl_2) was added dropwise under argon to a solution of nitrile **11** (100 mg, 0.24 mmol) in CH_2Cl_2 (10 mL) at −10 °C. The reaction mixture was stirred for 2 h 30 min and was quenched with aqueous sulfuric acid (2.5 mL of a 5% solution). The mixture was stirred for 15 min at room temperature and the aqueous phase was separated and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (35 mL) and brine (35 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by chromatography (EtOAc/cyclohexane, 50:50) to give **13** (67 mg, 0.16 mmol, 67%) as a white solid. M.p. 163 °C (CH_2Cl_2). ^1H NMR: δ = 9.50 (s, 1 H), 670−6.60 (br. s, 1 H), 4.84 (t, *J* = 6.5 Hz, 1 H), 4.80 (s, 1 H), 4.59 (s, 1 H), 4.13 (d, *J* = 6.5 Hz, 1 H), 3.69 (s, 3 H), 2.69 (dd, *J* = *J* = 18, 6.5 Hz, 1 H), 2.35−1.15 (m, 5 H), 1.35 (s, 3 H), 0.86 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H). ^{13}C NMR: δ = 192.6 (s), 174.4 (s), 149.7 (d), 141.9 (s), 78.8 (s), 75.1 (s), 69.2 (d), 67.0 (d), 60.5 (s), 52.2 (q), 31.3 (t), 28.8 (t), 26.7 (t), 25.7 (q), 23.5 (q), 17.9 (s), −3.7 (q), −4.9 (q). CI MS: *m/z* (%) = 432 ($[M + NH_4]^+$, 50), 415 (MH^+, 100), 397 ($MH^+ - H_2O$, 75). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3452, 2929, 2855, 1699, 1684, 1652, 1245.

Ketal 17a,b and Hydroxy Aldehyde 16: Pd/C 10% (20 mg) was added to a solution of aldehyde **13** (67 mg, 0.16 mmol) in EtOAc/H_2O (10 mL/0.25 mL) and the resultant mixture stirred for 3 h under H_2. The reaction mixture was filtered through Celite and concentrated under reduced pressure. The crude product was purified by chromatography (EtOAc/cyclohexane, 50:50 to 90:10) to give **16−17a,b** (47.9 mg, 0.11 mmol, 71%) and **14** (4.9 mg 0.01 mmol, 7%) as white solids. **16−17a,b:** inseparable mixture. White solid. ^1H NMR: δ = 9.55 (br. s, 1 H, 11%), 5.22 (br. s, 1 H, 62%), 5.05 (br. s, 1 H, 27%), major isomer: 4.80 (br. s, 1 H), 4.60−4.20 (m, 3 H), 4.80 (s, 1 H), 3.80 (s, 3 H), 2.60 (dd, *J* = 14.5, 5 Hz, 1 H), 2.30−1.40 (m, 8 H), 1.31 (s, 3 H), 0.83 (s, 9 H), 0.05 (s, 3 H), 0.03 (s, 3 H). ^{13}C NMR: δ = 203.4 (d), 174.7 (s), 174.6 (s), 174.5 (s), 97.1 (d), 92.5 (d), 78.9 (s), 73.1 (s), 72.6 (s), 70.5 (d), 70.3 (d), 69.7 (d), 69.1 (d), 68.9 (d), 68.5 (d), 61.1 (s), 61.0 (s), 60.5 (s), 51.8 (q), 45.4 (d), 36.4 (d), 36.2 (d), 34.8 (t), 31.7 (t), 30.3 (t), 30.2 (t), 29.7 (t), 29.5 (t), 29.2 (t), 29.1 (t), 27.0 (q), 26.9 (t), 25.7 (q), 25.6 (q), 24.5 (t), 23.5 (t), 23.2 (t), 20.4 (q), 17.9 (s), 17.8 (s), −3.7 (q), −4.8 (q), −4.9 (q), −5.0 (q). GC analysis (MDN5S, 0.32 mm id. × 30 m, 180−300 °C, 10 °C/min), 11.00 min (11%), 11.20 min (89%). CI NH_3 MS (11.00 min): *m/z* (%) = 434 ($[M + NH_4]^+$, 0.5), 416 ($[M + NH_4]^+ - H_2O$, 0.5), 399 ($MH^+ - H_2O$, 10), 380 (10), 361 (5), 249 (100), 166 (95); (11.20 min): 417 (MH^+, 20), 399 ($MH^+ - H_2O$, 15), 359 (100). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3427, 2952, 2930, 2856, 1719, 1701, 1472, 1239, 1067.

Tetraol 14: M.p. 185 °C (*n*-hexane/EtOAc). ^1H NMR: δ = 5.64 (br. s, 1 H), 4.90 (t, *J* = 7.5 Hz, 1 H), 4.62 (s, 1 H), 4.62−4.56 (br. s, 1 H), 4.09−4.04 (br. s, 2 H), 3.72 (s, 3 H), 2.38 (dd, *J* = 18, 6.5 Hz, 1 H), 2.20−1.45 (m, 5 H), 1.27 (s, 3 H), 0.87 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H). ^{13}C NMR: δ = 175.1 (s), 140.3 (s), 124.2 (d), 78.5 (s), 74.4 (s), 69.5 (d), 67.1 (d), 66.0 (t), 60.6 (s), 52.0 (q), 35.2 (t), 28.0 (t), 26.4 (q), 25.7 (q), 23.7 (t), 17.9 (s), −3.7 (q), −4.8 (q). GC analysis (MDN5S, 0.32 mm id. × 30 m, 180−300 °C, 10 °C/min), 7.90 min. CI NH_3 MS: *m/z* (%) = 434 ($[M + NH_4]^+$, 0.1), 417 (MH^+, 1), 399 ($MH^+ - H_2O$, 20), 381 ($MH^+ - 2 H_2O$, 2), 249 (100), 166 (80). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3426, 2928, 2856, 1701, 1667, 1462, 1256, 1095.

Triol 15: Pd/C 10% (50 mg) was added to a solution of alkene **14** (50 mg, 0.12 mmol) in MeOH (8 mL) and the resultant mixture stirred for 3 h under H_2. The reaction mixture was filtered through Celite and concentrated under reduced pressure. The crude product was purified by chromatography (EtOAc/cyclohexane, 50:50) to give **15** (45 mg, 0.11 mmol, 91%) as a white solid. M.p. 131−132 °C (*n*-hexane). ^1H NMR: δ = 5.38 (br. s, 1 H), 4.83 (t, *J* = 7.5 Hz, 1 H), 4.58 (s, 2 H), 4.18 (d, *J* = 7.5 Hz, 1 H), 3.72 (s, 3 H), 2.25 (dd, *J* = 18, 7 Hz, 1 H), 2.12−2.02 (m, 2 H), 1.92 (dd, *J* = 18, 9 Hz, 1 H), 1.78 (s, 3 H), 1.58−1.42 (m, 2 H), 1.25 (s, 3 H), 0.88 (s, 9 H), 0.06 (s, 3 H), 0.02 (s, 3 H). ^{13}C NMR: δ = 175.2 (s), 137.8 (s), 123.3 (d), 78.7 (s), 74.2 (s), 69.6 (d), 67.1 (d), 60.1 (s), 52.0 (q), 39.7 (t), 27.7 (t), 26.6 (q), 25.7 (q), 23.7 (t), 23.3 (q), 17.9 (s), −3.7 (q), −4.8 (q). GC analysis (MDN5S, 0.32 mm id. × 30 m, 180−300 °C, 10 °C/min), 9.00 min. CI NH_3 MS: *m/z* (%) = 418 ($[M + NH_4]^+$, 50), 401 (MH^+, 90), 383 ($MH^+ - H_2O$, 100), 381 ($MH^+ - 2 H_2O$, 2), 249 (100), 166 (80). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3465, 2951, 2929, 2856, 1701, 1257, 1094.

Lactone 18: Jones' reagent[10] (330 μL) was added to a solution of **16−17** (190 mg, 0.45 mmol) in acetone (25 mL) at −10 °C. The reaction mixture was stirred for 2 h at −10 °C and diluted with Et_2O (50 mL) and H_2O (10 mL). The aqueous phase was extracted with Et_2O (3 × 25 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and the solvents evaporated under reduced pressure. The residue was purified by chromatography (EtOAc/cyclohexane, 40:60) to give **18** (172 mg, 0.41 mmol, 90%) as a white solid. M.p. 82−83 °C (EtOAc/cyclohexane). ^1H NMR: δ = 4.71 (t, *J* = 2.5 Hz, 1 H), 4.67 (s, 1 H), 4.53 (br. s, 1 H), 3.98 (dd, *J* = 11, 6.5 Hz, 1 H), 3.84 (s, 3 H), 2.93 (m, 1 H), 2.67 (dd, *J* = 13.5, 2 Hz, 1 H), 2.37−1.67 (m, 7 H), 1.47 (s, 3 H), 0.82 (s, 9 H), 0.01 (s, 6 H). ^{13}C NMR: δ = 173.9 (s), 173.5 (s), 86.7 (s), 71.6 (s), 69.6 (d), 68.4 (d), 61.1 (s), 52.3 (q), 37.9 (d), 35.6 (t), 28.5 (t), 28.3 (t), 25.6 (q), 25.4 (q), 23.1 (t), 17.8 (s), −3.7 (q), −5.1 (q). GC analysis (MDN5S, 0.32 mm id. × 30 m, 180−300 °C, 10 °C/min), 11.10 min. EI MS: *m/z* (%) = 357 ($M^+ - t$Bu, 100), 339 ($M^+ - t$Bu − H_2O, 10), 325 (5), 307 (5), 73 (80). CI NH_3 MS: *m/z* (%) = 432 ($[M + NH_4]^+$, 10), 415 (MH^+, 40), 357 (100). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3438, 2951, 2932, 2856, 1736, 1710, 1445, 1237, 1221, 1099, 1079.

Ketal 19: Methyllithium (1.2 mL, 1.68 mmol, 1.4 M solution in Et_2O) was added dropwise to a solution of lactone **18** (45 mg, 0.098 mmol) in anhydrous Et_2O (4.2 mL) at −20 °C. The reaction mixture was stirred for 4 h, warmed to −10 °C, and methyllithium

(1.2 mL, 1.68 mmol, 1.4 M solution in Et_2O) was added. The reaction mixture was stirred overnight at 0 °C and water (5 mL) was added. The organic phase was separated and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and the solvents evaporated under reduced pressure. The crude product (41 mg) was purified by chromatography (EtOAc/cyclohexane, 40:60) to give **19** (33.5 mg, 0.077 mmol, 73%) as a colourless oil. ^{1}H NMR: δ = 4.75 (s, 1 H), 4.47 (s, 1 H), 4.34 (s, 1 H), 4.18 (m, 1 H), 3.80 (s, 3 H), 2.45−1.20 (m, 9 H), 1.46 (s, 3 H), 1.38 (s, 3 H), 0.83 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H). ^{13}C NMR: δ = 174.6 (s), 95.5 (s), 78.7 (s), 73.0 (s), 70.2 (d), 68.0 (d), 61.1 (s), 51.9 (q), 39.3 (d), 33.1 (t), 30.5 (t), 28.9 (q), 26.4 (t), 25.7 (q), 25.5 (q), 23.3 (t), 17.8 (s), −3.6 (q), −4.8 (q). GC analysis (MDN5S, 0.32 mm id. × 30 m, 180−300 °C, 10 °C/min), retention time 11.20 min. EI MS: *m*/*z* (%) = 373 ($M^+ - t$Bu, 10), 355 ($M^+ - t$Bu − H_2O, 20), 337 ($M^{+\cdot} - t$Bu − 2 H_2O, 4), 155 (20), 75 (100). IR (neat, cm^{-1}): ṽ = 3447, 2952, 2928, 2856, 1704, 1373, 1240, 1087.

Pyran 20: Me_3Al (0.175 mL, 0.35 mmol, 2 M solution in hexane) and $BF_3{\cdot}Et_2O$ (0.036 mL, 0.28 mmol) were added successively to a solution of ketal **19** (33.5 mg, 0.077 mmol) in CH_2Cl_2 (1 mL) at −70 °C under argon. The reaction mixture was stirred for 2 h at −70 °C and saturated sodium bicarbonate solution (2 mL) was added. The resultant mixture was warmed to room temperature and the aqueous phase extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with HCl (5 mL of 2 N solution) and brine (5 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product (41 mg) was purified by chromatography (EtOAc/cyclohexane, 20:80 to 30:70) to give **20** (19.7 mg, 0.046 mmol, 60%) as a white solid. M.p. 86−88 °C (*n*-hexane). ^{1}H NMR: δ = 4.69 (m, 1 H), 4.47 (br. s, 1 H), 4.32 (dd, *J* = 11, 6 Hz, 1 H), 4.23 (s, 1 H), 3.80 (s, 3 H), 2.49 (dd, *J* = 13, 3 Hz, 1 H), 2.20−1.20 (m, 8 H), 1.36 (s, 3 H), 1.35 (s, 3 H), 1.19 (s, 3 H), 0.84 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H). ^{13}C NMR: δ = 174.7 (s), 77.8 (s), 74.3 (s), 73.2 (s), 70.4 (d), 68.4 (d), 61.3 (s), 51.8 (q), 39.4 (d), 33.1 (t), 31.1 (t), 29.8 (t), 29.0 (q), 28.9 (q), 27.2 (t), 25.7 (q), 23.3 (t), 17.9 (s), −3.6 (q), −4.8 (q). GC analysis (MDN5S, 0.32 mm id. × 30 m, 220−300 °C, 10 °C/min), retention time 6.95 min. EI MS: *m*/*z* (%) = 371 ($M^{+\cdot} - t$Bu, 20), 353 ($M^+ - t$Bu − H_2O, 5), 321 (5), 75 (90), 73 (100). IR (neat, cm^{-1}): ṽ = 3490, 2950, 2930, 2898, 2857, 1730, 1705, 1372, 1239, 1091.

Triol 21: A solution of $LiAlH_4$ (0.5 mL, 0.5 mmol, 1 M solution in THF) was added dropwise to a solution of ester **20** (7.4 mg, 0.017 mmol) in Et_2O (1 mL) under argon at room temperature. The reaction mixture was stirred for 18 h, warmed to 0 °C, quenched with water (0.019 mL), NaOH (0.019 mL of a 15% solution), and water (0.057 mL), and further stirred for 1 h. The resultant mixture was filtered, the solid residue was washed with diethyl ether, and solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel (EtOAc/cyclohexane, 50:50) to give **21** (6.8 mg, 100%) as a white solid. ^{1}H NMR ($CDCl_3$): δ = 4.58 (dd, *J* = 11.5, 6 Hz, 1 H), 4.44 (m, 1 H), 4.33 (s, 1 H, OH), 4.30 (s, 2 H), 3.23 (t, *J* = 7 Hz, 1 H, OH), 3.06 (d, *J* = 4 Hz, 1 H, OH), 2.15−1.92 (m, 4 H), 1.80−1.50 (m, 5 H), 1.43 (s, 3 H), 1.33 (s, 3 H), 1.21 (s, 3 H), 0.90 (s, 9 H), 0.13 (s, 3 H), 0.10 (s, 3 H). ^{1}H NMR (C_6D_6): δ = 4.66−4.59 (m, 2 H), 4.55−4.51 (m, 2 H), 4.38 (dd, *J* = 12, 3 Hz, 1 H), 3.24 (dd, *J* = 11.5, 3 Hz, 1 H, OH), 3.17 (d, *J* = 5 Hz, 1 H, OH), 2.25−2.00 (m, 3 H), 1.82−1.20 (m, 6 H), 1.43 (s, 3 H), 1.12 (s, 3 H), 1.07 (s, 3 H), 0.87 (s, 9 H), 0.01 (s, 3 H), −0.04 (s, 3 H). ^{13}C NMR (C_6D_6): δ = 77.5 (s), 73.9 (s), 72.9 (s), 72.4 (d), 69.5 (d), 62.0 (t), 48.9 (s), 39.5 (d), 34.0 (t), 31.5 (t), 30.0 (t), 29.1 (q), 28.9 (q), 26.4 (t), 26.0 (q), 23.7 (q), 18.0 (s), −3.8 (q), −4.6 (q). CI NH_3 MS: *m*/*z* (%) = 418 ([M + NH_4]$^+$, 30), 401 (MH^+, 100), 383 ($MH^+ - H_2O$, 5), 371 (7), 299 (40), 282 (70). IR (neat, cm^{-1}): ṽ = 3416, 2955, 2923, 2853, 1463, 1377, 1250, 1053, 1030, 998, 858, 778.

Tetraol 8: A solution of nBu$_4$NF (0.2 mL, 0.2 mmol, 1 M solution in THF) was added to a solution of silyl ether **21** (6.8 mg, 0.013 mmol) in THF (0.2 mL) under argon at room temperature. The reaction mixture was stirred for 18 h, solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (EtOAc/cyclohexane, 50:50) to give **8** (1.1 mg, 28%, 2 steps from ester **20**) as a white solid. ^{1}H NMR ($CDCl_3$): δ = 4.60 (dd, *J* = 7.5, 5.5 Hz, 1 H), 4.58 (br. s, 1 H), 4.38 (br. d, *J* = 12 Hz, 1 H), 4.30 (d, *J* = 12 Hz, 1 H), 4.14 (s, 1 H, OH), 3.07 (br. s, 1 H, OH), 3.04 (br. s, 1 H, OH), 2.20−2.12 (m, 2 H), 2.00 (td, *J* = 13.5, 4.5 Hz, 1 H), 1.82−1.52 (m, 5 H), 1.40 (dd *J* = 13.5 Hz, 3 Hz, 1 H), 1.34 (s, 6 H), 1.21 (s, 3 H). ^{1}H NMR (CD_3OD): δ = 4.60 (dd, *J* = 12, 3 Hz, 1 H), 4.49 (br. s, 1 H), 4.30 (d, *J* = 12 Hz, 1 H), 4.24 (d, *J* = 12 Hz, 1 H), 2.20−1.94 (m, 4 H), 1.88−1.76 (m, 2 H), 1.62−1.40 (m, 3 H), 1.31 (s, 3 H), 1.28 (s, 3 H), 1.18 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ = 1 s under solvent signal, 74.2 (s), 72.5 (s), 70.5 (d), 68.9 (d), 61.3 (t), 48.4 (s), 39.4 (d), 33.9 (t), 30.9 (t), 30.0 (t), 29.0 (q), 28.6 (q), 26.0 (t), 23.0 (q). ^{13}C NMR (CD_3OD): δ = 78.6 (s), 75.7 (s), 74.2 (s), 70.5 (d), 68.7 (d), 61.8 (t), 54.7 (s), 40.5 (d), 34.3 (t), 31.2 (t), 30.2 (t), 29.2 (q), 28.8 (q), 26.4 (t), 25.0 (q). CI NH_3 MS: *m*/*z* (%) = 304 ([M + NH_4]$^+$, 100), 287 (MH^+, 80), 269 ($MH^+ - H_2O$, 60), 256 (50), 239 (55). IR (neat, cm^{-1}): ṽ = 3276, 2925, 2854, 1453, 1359, 1341, 1241, 1111, 1049, 1028.

Triacetate 22: Ac_2O (0.1 mL) and one crystal of DMAP were added to a solution of tetraol **8** (1.1 mg, 0.0038 mmol) in pyridine (0.2 mL) under argon at room temperature. The reaction mixture was stirred for 7 days and benzene (3 × 5 mL) was added. The resulting solution was taken almost to dryness in a rotavapor. The residue was purified by chromatography on silica gel (EtOAc/cyclohexane, 50:50) to give **22** (1.25 mg, 80%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ = 5.78 (dd, *J* = 11.5, 5.5 Hz, 1 H), 5.23 (br. s, 1 H), 4.81 (d, *J* = 12 Hz, 1 H), 4.57 (d, *J* = 12 Hz, 1 H), 3.08 (br. s, 1 H, OH), 2.22−2.12 (m, 2 H), 2.09 (s, 3 H), 2.02 (s, 9 H), 1.85−1.50 (m, 5 H), 1.37 (s, 3 H), 1.36 (s, 3 H), 1.31 (s, 3 H). CI NH_3 MS: *m*/*z* (%) = 430 ([M + NH_4]$^+$, 100), 353 (50), 338 (30).

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