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RCM/PCC oxidation strategy for synthesis of functionalized cyclic α,β-unsaturated lactones: synthesis of (+)-triacetoxygoniotriol and its diastereomers

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Abstract—A novel methodology leading to the synthesis of (+)-triacetoxygoniotriol **2** from D-glucose is described. Construction of the core six-membered α,β-unsaturated lactone moiety involved ring closing metathesis (RCM) followed by a PCC oxidation. Later exploiting the pseudo-symmetry of D-glucose three other diastereomers of triacetoxygoniotriol were synthesized using the developed methodology.

1. Introduction

Styryllactones, isolated from the stem bark of *Goniothalamus gigeanteus* (*Annanoceae*) have interesting heterocyclic skeletons.[1] They show significant murine toxicity toward lymphocytic leukemia systems. Goniotriol **1a** is one of the important members of styryllactone family. It showed significant cytotoxicity in the potato disc test and brine shrimp test. Interestingly both enantiomers of goniotriol occur in nature and its stereochemistry varies with the source of extraction.[2] Syntheses of (+)-goniotriol adopting both chiral pool and enantioselective approaches (including our own approach) and its analogues have been reported and their bioactivities were studied.[3,4] Also, synthesis of other styryllactones from goniotriol has been reported. Taking into account the various approaches reported in the literature we embarked on developing a novel unified approach for synthesis of various diastereomers of (+)-goniotriol from D-glucose. In our approach, which is described here we constructed the core α,β-unsaturated lactone moiety by using RCM and PCC oxidation of dialkenyl derivatives. We also showed that the allyl group, which is generally known to be a protection group could be used as a masked acrylic ester moiety during our synthesis. Herein, we wish to report complete details of our approach along with the synthesis of both the enantiomers of goniotriol, thus demonstrating the versatility of our approach (Fig. 1).

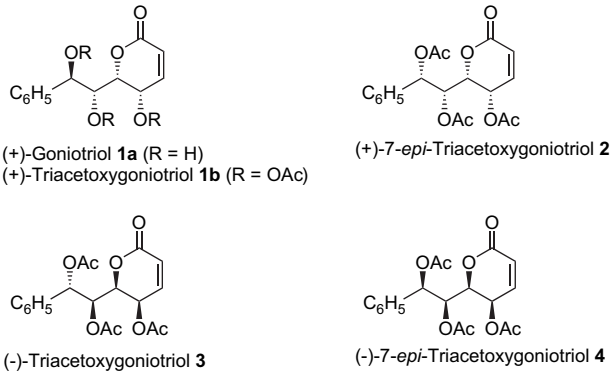

Figure 1.

2. Results and discussion

Retrosynthetic analysis of our approach for the synthesis of goniotriols **1**–**4** is depicted in Scheme 1. The recognition that the core six-membered α,β-unsaturated lactone moiety of the goniotriol could be constructed by ring closing metathesis followed by PCC oxidation guided our planning from the outset. In the synthetic direction (−)-triacetoxygoniotriols **3** and **4** could be synthesized from RCM product of dialkene **5** by a PCC oxidation reaction.[5] Dialkene **5** could originate from the acetonide **6** by incorporation of the required phenyl group. Finally the acetonide **6** can be synthesized from diol **7**, which in turn could be obtained from D-glucose by known steps.[6]

Our synthesis commenced as outlined in Scheme 2. Dialkenyl acetonide **6** was subjected to hydrolysis using acetic

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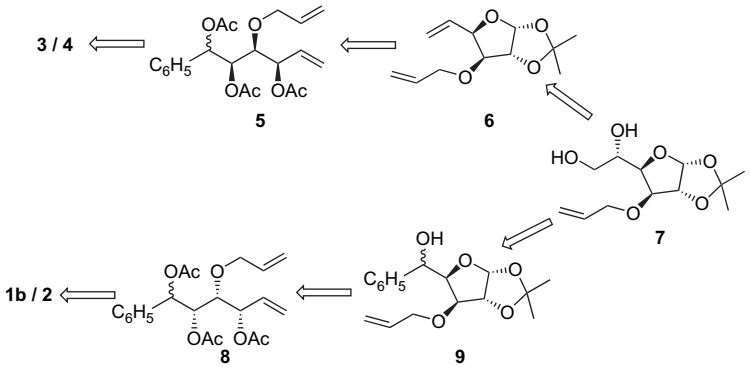
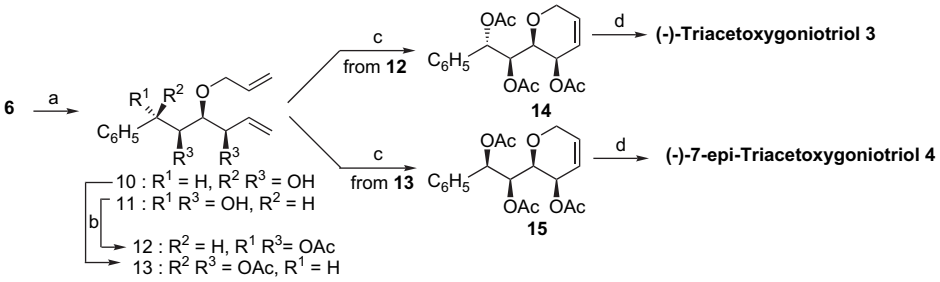


Scheme 1.

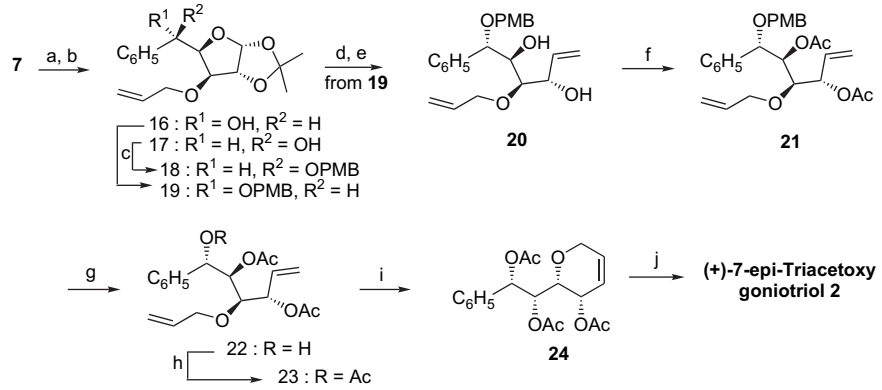


Scheme 2. (a) (i) CH_3CO_2H–H_2O (4:1), reflux, 12 h (86% yield); (ii) PhMgBr, THF, 0 °C to rt, 30 h (74% yield, a:b=3:1); (b) Ac_2O, Et_3N, DMAP, 24 h (88% yield); (c) Grubb's catalyst (5 mol %), DCM, rt, 24 h (90% yield); (d) PCC, Py, DCM, reflux, 8 h (64% yield).

acid in water at 90 °C to furnish an inseparable mixture of anomeric diols in 86% yield. Diols were subjected to a Grignard reaction with phenyl magnesium bromide in dry THF at 0 °C resulting in an inseparable mixture of diastereomeric triols **10** and **11** in 3:1 ratio. The diastereomeric diols on acetylation followed by column chromatography afforded essentially pure triacetates **12** and **13** in 49% combined yield (for two steps). The stereochemistry of the major diastereomer **13** was deduced by the literature analogy and was later unambiguously corroborated by the single crystal X-ray structure of (−)-7-*epi*-triacetoxygoniotriol **4**, which was derived from **13**.[4,7] Treatment of triacetate **12** to ring closing metathesis conditions using Grubb's catalyst [benzylidene-bis(tri-cyclohexylphosphine)-dichlororuthenium (5 mol %)] in dry DCM yielded allyl ether **15** in 90% yield. The allylic methylene moiety in ether **15** was oxidized with 3 equiv of PCC and pyridine in dry DCM furnished the required styryllactone, [7*R*,6*S*,5*S*,4*R*]-7-*epi*-triacetoxy-(−)-goniotriol **4**.[5] *It is appropriate to mention that this is the first example wherein such an oxidation was conducted on densely functionalized intermediate*. The minor isomer **12** was converted into (−)-triacetoxygoniotriol **3** under the same conditions.

In order to synthesize (+)-triacetoxygoniotriols **1b** and **2**, which are enantiomers of **3** and **4**, respectively, we decided to exploit the *pseudo*-symmetry of D-glucose. It was envisioned that the intermediate generated by the addition of phenyl magnesium bromide onto the aldehyde generated by the oxidative cleavage of diol **7** could be converted to triacetoxydialkene **8**, which is enantiomeric to triacetoxydialkene **5**. Intermediate **8** could be converted to triacetoxygoniotriols **1b** and **2** using the conditions described earlier.

Accordingly, the synthesis of (+)-7-*epi*-triacetoxygoniotriol **2** is outlined in Scheme 3. The aldehyde generated by the oxidative cleavage of diol **7** using $NaIO_4$ in MeOH, when allowed to react with phenyl magnesium bromide in dry THF at 0 °C resulted in the formation of the diastereomeric alcohols **16** and **17** in a 8:2 ratio with 77% overall yield. The stereochemistry at the C-5 center in two diastereomers was established by the literature analogy (Fig. 2).[8] The proton on C-3 in the case of alcohol **16** (major diastereomer) having L-*ido* configuration appeared approximately δ 0.4 upfield than that in the alcohol **17** with the D-*gluco* configuration due to the anisotropy of the phenyl moiety. The benzylic alcohol in **16** was then converted to PMB ether **19** using standard reaction conditions. Conversion of the PMB ether **19** to dialkene **20** involved a two-step reaction sequence of acid hydrolysis followed by Wittig reaction. While the Wittig reaction preceded without any complication, albeit moderate yield, the acid hydrolysis was complicated as a result of cleavage of PMB group under the hydrolysis conditions. The most efficient protocol entailed conducting acidic hydrolysis using 4 M HCl in THF at 55 °C and halting the reaction prior to completion (52% yield based on the isolated yield of the anomeric diols after column chromatography; 88% based on the recovered **19**). The recovered diol was resubjected to acidic hydrolysis. Acidic hydrolysis under prolonged reaction conditions or use of strong acids resulted in low yields of the desired product. Peracetylation of diol **20** gave diacetate **21**, which was then exposed to DDQ in moist CH_2Cl_2 to afford alcohol **22** in overall 88% yield. It was then converted into the triacetate **23**, followed by a ring closing metathesis reaction using Grubb's catalyst gave allyl ether **24** in 92% yield. Oxidation of the allyl ether **24** using PCC and pyridine in dry DCM furnished the required lactone in



Scheme 3. (a) $NaIO_4$, MeOH–H_2O (10:1), 0 °C, 4 h (88% yield); (b) PhMgBr, THF, 0 °C to rt, 12 h (74% yield, a:b=8:2); (c) NaH, PMBCl, Bu_4NI (cat), DMF, 0 °C to rt, 18 h (quant); (d) 4 M HCl–THF (1:4), 55 °C, 4 h (88%); (e) $Ph_3P{=}CH_2$, THF, −10 °C to rt, 24 h (55% yield); (f) Ac_2O, Et_3N, DMAP, 0 °C to rt, 24 h (quant); (g) DDQ, moist DCM, rt, 2 h (88%); (h) Ac_2O, Et_3N, DMAP, 0 °C to rt, 24 h (quant); (i) Grubb's catalyst (5%) DCM, rt, 24 h (92% yield); (j) PCC, C_5H_5N, DCM, reflux, 7 h (65% yield).

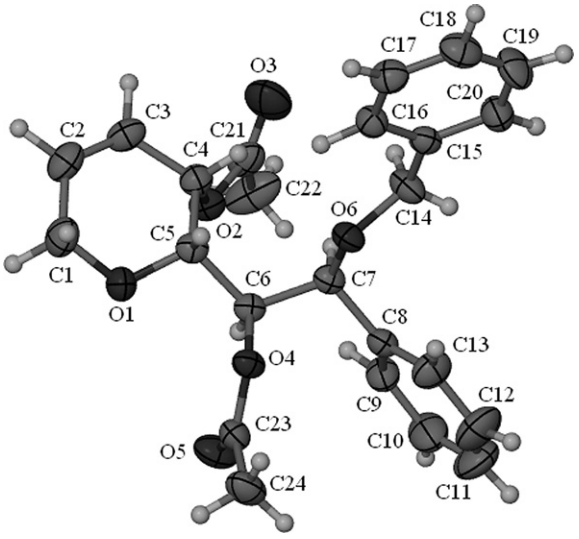


Figure 2.

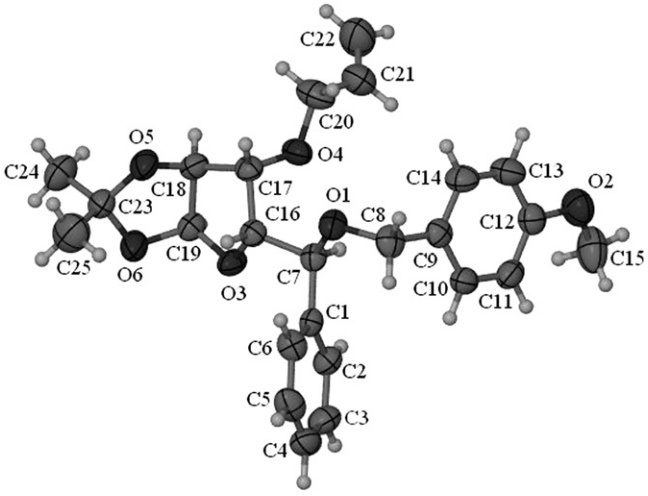


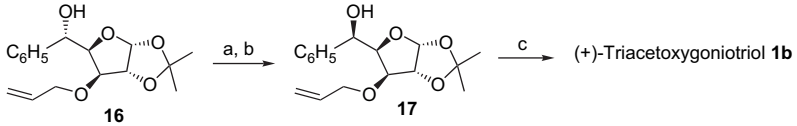
Figure 3.

65% yield. The (+)-7-*epi*-triacetoxygoniotriol thus obtained showed same optical rotation but with opposite sign as that of (−)-7-*epi*-triacetoxygoniotriol **4** ($[\alpha]_D^{22}$ +134.1 (*c* 0.2, MeOH)).[4] The absolute stereochemistry of (−)-7-*epi*-triacetoxygoniotriol **4** was further confirmed from single crystal X-ray of the 8-*O*-benzyl derivative of the compound **24**.[8]

The reversal of the stereochemistry at the C-6 center of **16** was accomplished by first oxidizing the benzylic alcohol in acetonide **16** followed by reduction with $NaBH_4$ at 0 °C.[9] Single crystal X-ray structure of the PMB ether of **17** unambiguously ascertained the stereochemistry at the benzylic position (Fig. 3).[10] Alcohol **17** was later converted to (+)-triacetoxygoniotriol **1b** using the same reaction sequence as described in Scheme 4.

3. Conclusion

Synthesis of natural products containing six-membered α,β-unsaturated lactones as a core feature using RCM reactions has been reported.[11] These approaches involve intramolecular RCM reactions of appropriately substituted acrylyl alkenylic esters. However, in some cases acrylyl esters are known to be reluctant to undergo a ring closing metathesis reaction due to the formation of stable seven-membered metal chelates formed between the ester carbonyls and the intermediate metal carbene species.[12] In the present case we have used allyl ether as a masked acrylic ester moiety to overcome such difficulties. Since allyl ethers withstand many harsher reaction conditions the developed



Scheme 4. (a) PDC, DCM, rt, 4 h (80% yield); (b) $NaBH_4$, 0 °C, 4 h (90% yield, 9:1 (**17**:**16**)); (c) Scheme 2c–j.

methodology offers an attractive alternative to acrylyl ester derived synthesis of cyclic lactones. Also D-glucose offers possibility of manipulating the stereochemistry around a given carbon atom at a time. Hence it is possible to synthesize all stereoisomers of goniotriol from D-glucose using the developed methodology.

4. Experimental

4.1. General

Optical rotations were measured with a JASCO DIP-370 digital polarimeter using a sodium lamp (λ=589 nm) at 24 °C. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using Me_4Si as an internal standard on a Varian spectrometer. Thin-layer chromatography was performed on E. Merck glass plates silica gel sheets (Silica Gel F_{254}) and visualized under UV light and/or stained with ceric ammonium molybdate–aqueous H_2SO_4 solution. Column chromatography was carried out on silica gel (E. Merck 230–400 mesh). All solvents were distilled before use.

4.1.1. 2,4,5-Tri-*O*-acetyl-3-*O*-allyl-5,6-dideoxy-1-*O*-phenyl-hex-1-enitol 12/13. Dialkene **6** (0.5 g, 2.2 mmol) was dissolved in aqueous AcOH (10 ml, 1:4) and refluxed for 12 h. Removal of the solvents in vacuo yielded a yellow oil, which was then dissolved in DCM (10 ml) and washed with satd aqueous $NaHCO_3$ solution (5 ml). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The resultant crude diol was dissolved in dry THF (10 ml) and was added drop wise (15 min) to a solution of phenyl magnesium bromide (2 g, 11.0 mmol) in THF (15 ml) at 0 °C. After stirring for 2 h at 0 °C and then for 30 h at rt, cold 1 M HCl (5 ml) was added and extracted with EtOAc (10 ml). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (1:1, hexane–EtOAc) afforded triols **10/11** (0.36 g, 1.36 mmol, 74%) as a 3:1 mixture of diastereomers. The triols **10** and **11** (0.36 g, 1.36 mmol) were dissolved in Et_3N (2 ml) at 0 °C and DMAP (20 mg) was added. Acetic anhydride (0.83 g, 8.1 mmol) was added and the resultant mixture was stirred for 24 h at rt. Et_3N was evaporated and flash column chromatography of the resultant crude mixture afforded triacetoxydialkenes **12** and **13** (0.46 g, 1.20 mmol, 88% yield) in 3:1 ratio, respectively, as a pale viscous oil. HRMS (FAB) *m/z* 391.1741 (MH^+, $C_{21}H_{27}O_7$, requires 391.1757).

Compound **13**: 0.35 g, $[\alpha]_D^{22}$ +8.5 (*c* 2, $CHCl_3$); ν_{max} (liquid film) 3120, 1743, 1643, 1604, 1434, 1335, 1130 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38–7.30 (m, 5H, Ph), 5.95–5.81 (m, 2H, C*H*=CH_2), 5.86 (d, *J*=8.0 Hz, 1H, PhC*H*(OAc)), 5.40–5.35 (m, 2H, C*H*(OAc) and AcOC*H*CH=CH_2), 5.30–5.19 (m, 4H, CH=CH_2), 4.25 (dd, *J*=4.5, 13.0 Hz, 1H, OCH_2CH=CH_2), 4.10 (dd, *J*=5.5, 13.0 Hz, 1H, OCH_2CH=CH_2), 3.69 (dd, *J*=3.0, 7.5 Hz, 1H, C*H*Oallyl), 2.09 (s, 3H, OA*c*), 2.02 (s, 3H, OA*c*), 1.81 (s, 3H, OA*c*). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.0, 169.5, 169.4, 136.6, 134.5, 132.4, 128.8, 128.4, 127.9, 118.5, 118.2, 77.7, 74.3, 73.9, 73.4, 72.3, 21.4, 21.3, 20.8.

^{1}H NMR of compound **23** was similar to that of compound **13** ($[\alpha]_D^{22}$ −8.4 (*c* 2, $CHCl_3$)).

Compound **12**: 0.10 g, $[\alpha]_D^{22}$ −18.5 (*c* 2, $CHCl_3$); ν_{max} (liquid film) 3110, 1740, 1638, 1610, 1444, 1342 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36–7.28 (m, 5H, Ph), 6.03 (d, *J*=8.0 Hz, 1H, PhC*H*(OAc)), 5.94–5.81 (m, 2H, C*H*=CH_2), 5.46 (q, *J*=3.5 Hz, 1H, CH=CH_2), 5.42–5.40 (m, 1H, CH=CH_2), 5.30 (d, *J*=2.0 Hz, 1H, CH=CH_2), 5.27 (d, *J*=2.0 Hz, 1H, CH=CH_2), 5.24 (dd, *J*=2.0, 7.0 Hz, 1H, OC*H*CH=CH_2), 5.19 (dd, *J*=2.0, 10.5 Hz, 1H, C*H*OAc), 4.15 (dd, *J*=5.0, 10.0 Hz, 1H, OCH_2CH=CH_2), 3.89 (dd, *J*=4.0, 10.0 Hz, 1H, OCH_2CH=CH_2), 3.51 (dd, *J*=3.0, 7.0 Hz, 1H, C*H*Oallyl), 2.06 (s, 3H, OA*c*), 2.05 (s, 3H, OA*c*), 2.03 (s, 3H, OA*c*). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.1, 169.6, 169.4, 136.6, 134.4, 132.4, 128.5, 128.4, 128.0, 118.5, 118.3, 77.8, 74.5, 73.6, 73.4, 72.5, 21.6, 21.3, 20.6.

^{1}H NMR of (8*R*) diastereomer of compound **23** was similar to that of compound **12** ($[\alpha]_D^{22}$ +18.4 (*c* 2, $CHCl_3$)).

4.1.2. 1,2,4-Tri-*O*-acetyl-3,7-anhydro-5,6-dideoxy-1-*O*-phenylhept-5-enitol 14/15. To a degassed solution of dialkene **12/13/23** (0.10 g, 0.25 mmol) in anhydrous DCM (3 ml) was added Grubb's catalyst (10 mg, 0.012 mmol) and stirred for 24 h at rt. The reaction mixture was diluted with DCM (2 ml) and air was bubbled through the solution to deactivate the catalyst. The reaction mixture was filtered through Celite and concentrated in vacuo. Flash column chromatography (10% EtOAc in hexane) afforded pyran **14/15/24** (82 mg, 0.23 mmol, 90% yield) as a colorless semi solid. HRMS (FAB) *m/z* 362.3737 (MH^+, $C_{19}H_{22}O_7$, requires 362.3729).

Compound **15**: $[\alpha]_D^{22}$ −152.1 (*c* 0.2, MeOH); ν_{max} (liquid film) 3080, 1742, 1646, 1430, 1335 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38–7.31 (m, 5H), 6.04–5.98 (m, 3H), 5.52 (t, *J*=5.4 Hz, 1H), 5.00–4.95 (m, 1H), 4.30 (d, *J*=19.8 Hz, 1H), 4.08 (d, *J*=19.8 Hz, 1H), 3.55 (dd, *J*=2.5, 5.5 Hz, 1H), 2.09 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.3, 169.6, 136.5, 131.8, 128.6, 126.9, 122.2, 74.2, 73.5, 73.1, 66.1, 65.5, 21.0, 20.9, 20.8.

^{1}H NMR of compound **24** was similar to that of compound **15** ($[\alpha]_D^{22}$ +152.1 (*c* 0.2, MeOH)).

Compound **14**: $[\alpha]_D^{22}$ +90.2 (*c* 0.2, MeOH); ν_{max} (KBr) 3100, 1740, 1644, 1440, 1320 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38–7.29 (m, 5H), 6.04–5.96 (m, 2H), 5.83 (d, *J*=5.5 Hz, 1H), 5.52 (d, *J*=6.0 Hz, 1H), 5.01–4.97 (m, 1H), 4.33 (d, *J*=18.0 Hz, 1H), 4.10 (d, *J*=18.0 Hz, 1H), 3.57 (dd, *J*=4.0, 8.0 Hz, 1H), 2.09 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 169.8, 136.5, 131.6, 128.9, 126.7, 122.0, 74.1, 73.5, 73.2, 66.2, 65.3, 21.1, 20.9, 20.7.

^{1}H NMR of (8*R*) diastereomer of compound **24** was similar to that of compound **15** ($[\alpha]_D^{22}$ −90.0 (*c* 0.2, MeOH)).

4.1.3. General procedure for the oxidation of cyclic allyl ethers to lactones. To a solution of pyran **14/15/24** (80 mg,

0.20 mmol) in anhydrous DCM were added PCC (142 mg, 0.6 mmol) and pyridine (0.1 ml) and refluxed for 7 h. The solvent was evaporated and ethyl ether (5 ml) was added and filtered through Celite. The solvent was evaporated and flash column chromatography (5–20% EtOAc in hexane, gradient elution) afforded triacetoxygoniotriol **3/4/2** (54.5 mg, 65% yield) as a white solid. HRMS (FAB) *m/z* 376.1158 (MH^+, $C_{19}H_{20}O_8$, requires 376.1164).

7-*epi*-7,6,4-Triacetoxy-(−)-goniotriol **4**: $[\alpha]_D^{22}$ −135.0 (*c* 0.2, MeOH); ν_{max} (KBr) 3100, 1742, 1640, 1448, 1336 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34 (m, 5H), 6.93 (dd, *J*=5.4, 9.5 Hz, 1H), 6.16 (d, *J*=9.5 Hz, 1H), 6.05 (d, *J*=6.2 Hz, 1H), 5.62 (dd, *J*=5.1, 6.2 Hz, 1H), 5.24 (dd, *J*=3.2, 5.1 Hz, 1H), 4.43 (dd, *J*=3.2, 5.1 Hz, 1H), 2.1 (s, 6H), 2.08 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.1, 169.4, 169.2, 140.3, 129.3, 129.2, 127.2, 124.7, 100.1, 75.7, 74.0, 71.8, 62.9, 21.1, 21.0.

^1H NMR of 7-*epi*-7,6,4-triacetoxy-(+)-goniotriol **2** was similar to that of compound **4** ($[\alpha]_D^{22}$ +135.0 (*c* 0.2, MeOH)).

7,6,4-Triacetoxy-(−)-goniotriol **3**: $[\alpha]_D^{22}$ −121 (*c* 0.8, MeOH); ν_{max} (KBr) 3124, 1742, 1644, 1440, 1327 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.42–7.33 (m, 5H), 6.93 (dd, *J*=6.0, 10.2 Hz, 1H), 6.16 (d, *J*=9.8 Hz, 1H), 5.96 (d, *J*=5.2 Hz, 1H), 5.76 (dd, *J*=4.8, 7.1 Hz, 1H), 5.30 (dd, *J*=3.2, 6.0 Hz, 1H), 4.53 (dd, *J*=3.2, 6.8 Hz, 1H), 2.10 (s, 3H), 2.08 (s, 3H), 2.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 169.4, 169.1, 140.4, 129.4, 129.0, 127.3, 124.5, 100.3, 76.1, 74.2, 71.6, 62.7, 21.3, 21.1.

^1H NMR of 7,6,4-triacetoxy-(+)-goniotriol **1b** was similar to that of compound **3** ($[\alpha]_D^{22}$ +121 (*c* 0.8, MeOH)).

4.1.4. 1,2-*O*-(1-Methylethyledene)-3-*O*-allyl-5-*C*-phenyl-α-D-*xylo*-furanose 16/17. To vigorously stirred slurry of silica gel (10 g, Acme 60–120 mesh) in DCM (100 ml) a solution of $NaIO_4$ (5.83 g, 22.27 mmol in 15 ml water) was added and continued stirring at rt for 10 min after which a solution of diol **7** (4 g, 18.18 mmol) in methanol (20 ml) was added. The reaction mixture was further stirred for 4 h and solids were filtered. Solvents were evaporated to give the aldehyde as a colorless oil, which was dried in vacuo over P_2O_5 (88% yield). The resultant crude aldehyde was dissolved in anhydrous THF (60 ml) and the solution was added drop wise (30 min) to a solution of phenyl magnesium bromide (6.8 g, 37.8 mmol) in anhydrous THF (150 ml) at 0 °C. After stirring for 4 h at 0 °C and then 12 h at rt, cold 1 M HCl (25 ml) was added and extracted with EtOAc (30 ml). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (1:1, hexane–EtOAc) afforded diastereomeric alcohols **16/17** (3.9 g, 12.8 mmol, 74% yield) as 8:2 (**16**:**17**) mixtures of diastereomers as a yellow oil separable by column chromatography. HRMS (FAB) *m/z* 329.1350 (MNa^+, $C_{17}H_{22}O_5Na$, requires 329.1365).

(5*S*)-Isomer **16**: $[\alpha]_D^{22}$ −5.0 (*c* 1, MeOH); ν_{max} (liquid film) 3480–3060 (br), 1610, 1434, 1335, 1130 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.49–7.34 (m, 5H, Ph), 6.03 (d, *J*=6.5 Hz, 1H, OC*H*O), 5.92–5.78 (m, 1H, C*H*=CH_2), 5.35–5.20 (m, 2H, CH=CH_2), 5.06 (dd, *J*=3.0, 13.0 Hz, 1H, PhC*H*(OH), 4.57 (d, *J*=6.0 Hz, 1H, C*H*OCMe_2), 4.33 (dd, *J*=6.0, 13.0 Hz, 1H, PhCH(OH)C*H*), 4.04 (dd, *J*=5.5, 12.5 Hz, 1H, O$CH_2$$CHCH_2$), 3.77 (dd, *J*=5.5, 12.5 Hz, 1H, O$CH_2$$CHCH_2$), 3.50 (d, *J*=5.0 Hz, 1H, C*H*Oallyl), 2.89 (d, *J*=2.5 Hz, 1H, O*H*), 1.51 (s, 3H, C(CH_3)$_2$), 1.33 (s, 3H, C(CH_3)$_2$). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.0, 133.8, 128.6, 128.4, 127.5, 118.0, 112.1, 105.5, 84.9, 82.4, 82.2, 72.8, 71.1, 27.0, 26.5.

(5*R*)-Isomer **17**: $[\alpha]_D^{22}$ −34.9 (*c* 1, MeOH); ν_{max} (liquid film) 3450–3050 (br), 1620, 1424, 1340, 1140 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.42–7.35 (m, 4H, Ph), 7.31–7.26 (m, 1H, Ph), 6.02 (d, *J*=5.5 Hz, 1H, OC*H*O), 5.95–5.86 (m, 1H, C*H*=CH_2), 5.32 (d, *J*=17.0 Hz, 1H, CH=CH_2), 5.25 (d, *J*=10.5 Hz, 1H, CH=CH_2), 5.11 (t, *J*=6.5 Hz, 1H, PhC*H*(OH)), 4.55 (d, *J*=2.5 Hz, 1H, C*H*OCMe_2), 4.33 (t, *J*=2.5 Hz, 1H, PhCH(OH)C*H*), 4.16–4.12 (m, 1H, OCH_2CH=CH_2), 3.96–3.92 (m, 1H, OCH_2CH=CH_2), 3.88–3.86 (m, 1H, C*H*Oallyl), 3.51 (d, *J*=7.0 Hz, 1H, O*H*), 1.47 (s, 3H, C(CH_3)$_2$), 1.31 (s, 3H, C(CH_3)$_2$). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.5, 133.4, 128.6, 127.8, 126.2, 118.7, 105.4, 83.1, 82.5, 81.9, 72.4, 71.3, 26.9, 26.4.

4.1.5. 1,2-*O*-(1-Methylethyledene)-5-*O*-(4-methoxybenzyl)-3-*O*-allyl-5-*C*-phenyl-5-*O*-α-D-*xylo*-furanoses 18 and 19. To pentane-washed NaH (0.16 g, 6.5 mmol) in anhydrous DMF (5 ml) was added alcohol **16/17** (1 g, 3.2 mmol) at 0 °C and stirred for 15 min. 4-Methoxybenzylchloride (0.77 g, 4.9 mmol) and tetrabutylammonium iodide (20 mg) were added and the resultant reaction mixture was stirred for 18 h at rt. HCl (1 M, 10 ml) was added slowly and extracted twice with DCM (10 ml). The organic layers were collected dried and concentrated in vacuo. Flash column chromatography (10% EtOAc in hexane) afforded acetonide **18/19** (1.40 g, 3.13 mmol, 98% yield) as a colorless oil. HRMS (FAB) *m/z* 449.1938 (MNa^+, $C_{25}H_{30}O_6Na$, requires 449.1940).

(5*S*)-Isomer **18**: $[\alpha]_D^{22}$ +18.2 (*c* 1, $CHCl_3$); ν_{max} (liquid film) 3110, 1634, 1595, 1410, 1340, 1044 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.42–7.35 (m, 5H, Ph), 7.23 (d, *J*=9.0 Hz, 2H, *Ph* of PMB), 6.83 (d, *J*=8.0 Hz, 2H, *Ph* of PMB), 6.02 (d, *J*=4.0 Hz, 1H, OC*H*O), 5.76–5.68 (m, 1H, C*H*=CH_2), 5.22 (d, *J*=17.5 Hz, 1H, CH=CH_2), 5.14 (d, *J*=10.5 Hz, 1H, CH=CH_2), 4.68 (d, *J*=9.0 Hz, 1H, PhC*H*(OPMB)), 4.48–4.45 (m, 2H, C*H*OCMe_2, PhCH(OPMB)C*H*), 4.49 (d, *J*=11.5 Hz, 1H, OCH_2PhOMe), 4.32 (d, *J*=11.5 Hz, 1H, OCH_2PhOMe), 3.82 (dd, *J*=5.0, 12.0 Hz, 1H, O$CH_2$$CHCH_2$), 3.77 (s, 3H, O*Me*), 3.48 (dd, *J*=6.0, 12.5 Hz, 1H, O$CH_2$$CHCH_2$), 3.20 (d, *J*=3.5 Hz, 1H, C*H*Oallyl), 1.50 (s, 3H, CMe_2), 1.29 (s, 3H, CMe_2). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.1, 138.7, 133.9, 130.7, 129.5, 128.4, 117.6, 113.7, 111.7, 105.7, 84.1, 82.2, 81.6, 79.9, 70.9, 70.2, 55.4, 27.0, 26.4.

(5*R*)-Isomer **19**: $[\alpha]_D^{22}$ −45.0 (*c* 1, MeOH); ν_{max} (liquid film) 3120, 1640, 1602, 1420, 1344, 1045 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.46–7.31 (m, 5H, Ph), 7.18 (d, *J*=14.5 Hz, 2H, *Ph* of PMB), 6.84 (d, *J*=15.0 Hz, 2H, *Ph* of PMB), 5.80–5.86 (m, 1H, C*H*=CH_2), 5.84 (d, *J*=6.5 Hz, 1H, OC*H*O), 5.34–5.20 (m, 2H, CH=CH_2), 4.65 (d, *J*=15.0 Hz, 1H, PhC*H*(OPMB)), 4.55 (d, *J*=6.5 Hz, 1H, C*H*OCMe_2), 4.31 (d, *J*=18.5 Hz, 1H,

OCH_2Ph(OMe$_2$)), 4.27 (d, J=5.0 Hz, 1H, PhCH(OPMB)CH), 4.20 (d, J=17.5 Hz, 1H, OCH_2-Ph(OMe)), 4.16 (d, J=9.0 Hz, 1H, OCH_2CHCH$_2$), 4.10 (d, J=4.0 Hz, 1H, CHOallyl), 4.06 (dd, J=9.0, 21.0 Hz, 1H, OCH_2CHCH$_2$), 3.79 (s, 3H, OMe), 1.39 (s, 3H, CMe_2), 1.26 (s, 3H, CMe_2). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.4, 139.8, 134.6, 130.6, 129.7, 128.6, 128.2, 128.1, 117.6, 114.0, 111.7, 105.3, 83.1, 82.5, 81.8, 78.2, 71.8, 70.3, 55.5, 27.0, 26.5.

4.1.6. 3-*O*-Allyl-5,6-dideoxy-1-*O*-(4-methoxybenzyl)-1-*O*-phenyl-hex-5-enitol (6*S*)-20 and (6*R*)-20. To acetonide **18/19** (0.3 g, 0.7 mmol) dissolved in THF (3 ml) was added 4 M HCl (2 ml) and the resultant mixture was heated to 55 °C for 4 h. The reaction mixture was cooled, neutralized with satd aqueous $NaHCO_3$ solution (5 ml) and extracted twice with EtOAc (5 ml). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (10–30% gradient elution) afforded diol (0.13 g, 52%) as anomeric mixture and acetonide **18/19** (0.10 g, 44%) was recovered. The diol (0.1 g, 0.2 mmol) was dissolved in anhydrous THF (0.5 ml) and added drop wise to methylenetriphenylphosphine ylide (prepared from methyltriphenylphosphonium bromide (0.46 g, 1.3 mmol) and *n*-BuLi (0.79 ml of 1.6 M in hexane, 1.2 mmol) at −5 °C) at −10 °C. The reaction mixture was stirred at −10 °C for 2 h and then at rt for 24 h, then quenched with cold satd aqueous NH_4Cl (2 ml), and extracted twice with EtOAc (5 ml). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (10–20% EtOAc in hexane, gradient elution) afforded pure dialkene (6*S*)-**20**/(6*R*)-**20** (54.6 mg, 1.4 mmol, 55% yield) as a colorless liquid. HRMS (FAB) *m*/*z* 407.1826 (MNa^+, $C_{23}H_{28}O_5Na$, requires 407.1835).

Compound (6*S*)-**20**: $[\alpha]_D^{22}$ −88.0 (*c* 1, $CHCl_3$); ν_{max} (liquid film) 3450–3100 (br), 1638, 1610, 1450, 1342, 1145 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42–7.36 (m, 5H), 7.23 (d, J=14.0 Hz, 2H), 6.90 (d, J=12.0 Hz, 2H), 5.90–5.83 (m, 2H), 5.40–5.18 (m, 4H), 4.43–4.37 (m, 2H), 4.32 (t, J=10.5 Hz, 1H), 4.20 (d, J=19.0 Hz, 1H), 4.19 (d, J=19.0 Hz, 1H), 4.07 (dd, J=9.0, 20.5 Hz, 1H), 3.83 (s, 3H), 3.82–3.76 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.6, 139.3, 137.4, 134.9, 130.0, 128.8, 128.5, 128.1, 117.4, 117.3, 114.0, 81.4, 80.3, 75.2, 74.6, 74.5, 70.2, 55.5.

Compound (6*R*)-**20**: $[\alpha]_D^{22}$ +47.0 (*c* 2, $CHCl_3$); ν_{max} (liquid film) 3500–3100 (br), 1640, 1610, 1440, 1135, 1095 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42–7.35 (m, 5H), 7.20 (d, J=8.5 Hz, 2H), 6.87 (d, J=8.0 Hz, 2H), 5.93–5.85 (m, 1H), 5.83–5.76 (m, 1H), 5.33–5.21 (m, 2H), 5.15 (d, J=10.0 Hz, 1H), 4.57 (d, J=7.5 Hz, 1H), 4.41 (d, J=11.5 Hz, 1H), 4.31 (m, 1H), 4.23 (d, J=11.0 Hz, 1H), 4.23–4.17 (m, 2H), 3.95–3.91 (m, 2H), 3.81 (s, 3H), 3.05–3.02 (m, 1H), 2.99 (br s, 1H), 2.67 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.6, 138.4, 138.0, 135.0, 130.0, 128.9, 128.7, 128.2, 117.0, 116.7, 114.1, 81.7, 80.8, 76.1, 73.8, 70.6, 55.5.

4.1.7. 2,4-*O*-Acetyl-3-*O*-allyl-5,6-dideoxy-1-*O*-(4-methoxybenzyl)-1-*O*-phenyl-hex-5-enitol 21 and its (6*R*) diastereomer. To a mixture of diol **20** (50 mg, 0.13 mmol) and DMAP (7 mg) in Et_3N (0.5 ml) at 0 °C was added acetic anhydride (53 mg, 0.52 mmol). The resultant mixture was stirred for 24 h at rt. Et_3N was evaporated and flash column chromatography of the resultant crude mixture gave diacetate (60 mg, 0.12 mmol, 98% yield) as a pale yellow oil. HRMS (FAB) *m*/*z* 491.2052 (MNa^+, $C_{27}H_{32}O_7Na$, requires 491.2045).

(6*S*)-Isomer **21**: $[\alpha]_D^{22}$ −15.5 (*c* 2, $CHCl_3$); ν_{max} (liquid film) 3180, 1742, 1610, 1550, 1320 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39–7.28 (m, 5H), 7.20 (d, J=8.0 Hz, 2H), 6.87 (d, J=8.0 Hz, 2H), 5.93–5.87 (m, 1H), 5.85–5.78 (m, 1H), 5.35 (t, J=6.5 Hz, 1H), 5.24 (d, J=17.0 Hz, 1H), 5.20 (d, J=17.0 Hz, 1H), 5.18–5.16 (m, 3H), 4.57 (d, J=9.5 Hz, 1H), 4.37 (d, J=11.5 Hz, 1H), 4.24–4.18 (m, 2H), 4.05 (dd, J=4.5, 12.0 Hz, 1H), 3.98 (d, J=8.5 Hz, 1H), 3.80 (s, 3H), 2.07 (s, 3H), 1.70 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.0, 169.1, 159.1, 138.0, 135.0, 132.6, 130.0, 129.9, 128.6, 128.4, 118.4, 117.3, 114.0, 78.8, 74.7, 74.5, 73.9, 70.3, 55.5, 21.4, 20.8.

(6*R*)-Isomer **21**: $[\alpha]_D^{22}$ +32.5 (*c* 2, $CHCl_3$); ν_{max} (liquid film) 3210, 1740, 1605, 1520, 1142 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39–7.30 (m, 5H), 7.19 (d, J=9.0 Hz, 2H), 6.87 (d, J=8.5 Hz, 2H), 5.95–5.80 (m, 2H), 5.35–5.30 (m, 2H), 5.24–5.19 (m, 2H), 5.14 (dd, J=4.0, 8.5 Hz, 1H), 4.60 (d, J=5.0 Hz, 1H), 4.43 (d, J=11.5 Hz, 1H), 4.16 (d, J=12 Hz, 2H), 4.12 (dd, J=6.0, 12.5 Hz, 1H), 3.93 (dd, J=6.0, 12.5 Hz, 1H), 3.82 (s, 3H), 3.47 (t, J=5.0 Hz, 1H), 2.08 (s, 3H), 2.00 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 170.0, 159.4, 138.0, 134.7, 133.0, 130.4, 130.2, 129.5, 128.8, 128.6, 128.0, 118.1, 117.1, 114.0, 79.5, 79.0, 74.9, 74.0, 73.9, 70.4, 55.5, 21.3, 21.2.

4.1.8. General procedure for PMB cleavage: synthesis of 2-4-di-*O*-acetyl-3-*O*-allyl-5,6-dideoxy-1-*O*-phenyl-hex-5-enitol 22 and its (6*R*)-diastereomer. To a stirred solution of diacetate **21** (55 mg, 0.11 mmol) in wet DCM (0.2 ml) was added DDQ (35.0 mg, 0.15 mmol) and stirred for 2 h at rt. DCM (2 ml) and satd aqueous $NaHCO_3$ (1 ml) were added to the reaction mixture and extracted. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography afforded alcohol (6*S*)-isomer **22**/(6*R*)-isomer **22** (34 mg, 0.096 mmol, 88% yield) as a colorless oil. HRMS (FAB) *m*/*z* 371.1486 (MNa^+, $C_{19}H_{24}O_6Na$, requires 371.1471).

(6*S*)-Isomer **22**: $[\alpha]_D^{22}$ −32.0 (*c* 2, $CHCl_3$); ν_{max} (liquid film) 3550–3100 (br), 1740, 1605, 1450, 1140 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41–7.30 (m, 5H), 6.03–5.93 (m, 1H), 5.82–5.73 (m, 1H), 5.42–5.29 (m, 2H), 5.27–5.22 (m, 2H), 5.17–5.12 (m, 1H), 4.97–4.95 (m, 1H), 4.32–4.28 (m, 1H), 4.19–4.11 (m, 1H), 3.81 (dd, J=2.5, 7.0 Hz, 1H), 2.10 (d, J=4.5 Hz, 1H), 2.06 (s, 3H), 1.92 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.9, 169.7, 140.5, 134.4, 132.5, 128.6, 128.3, 126.7, 118.7, 118.2, 78.5, 74.3, 74.1, 73.3, 21.3, 21.1.

(6*R*)-Isomer **22**: $[\alpha]_D^{22}$ +28.0 (*c* 2, $CHCl_3$); ν_{max} (liquid film) 3500–3100 (br), 1738, 1610, 1450, 1245 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37–7.29 (m, 5H), 5.91–5.86 (m, 2H), 5.51–5.48 (m, 1H), 5.32–5.28 (m, 2H), 5.20 (dd, J=2.0, 11.0 Hz, 1H), 4.97 (d, J=5.5 Hz, 1H), 4.22–4.18 (m, 1H), 4.15–4.10 (m, 2H), 4.02–3.98 (m, 1H), 3.58 (d,

J=4.5 Hz, 1H), 2.06 (s, 3H), 1.99 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.4, 170.5, 140.4, 134.4, 132.5, 128.8, 126.7, 119.6, 118.3, 117.7, 117.5, 79.1, 75.3, 73.8, 60.6, 21.3, 21.1.

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