

Stereoselective Total Synthesis of Goniiothalesdiol A *via* Chiron Approach

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The stereocontrolled synthesis of goniiothalesdiol A, a dihydroxylated tetrahydropyran compound, has been accomplished using D-ribose as chiral precursor. The key steps involved are aryl *Grignard* reaction, stereoselective alkoxy-directed keto reduction, and intramolecular oxy-*Michael* addition.

Introduction. – Goniiothalesdiol A (**1**) and goniiothalesacetate, a new class of styryl lactones [1], were isolated from the stems of a southern Taiwan tree *Goniiothalamus amuyon*. The styryl lactones and acetogenins are two major types of bioactive compounds isolated from the *Goniiothalamus* (Annonaceae) species. The structure and relative configuration of **1** were determined on the basis of NMR spectroscopy, and the absolute configuration was predicted by biosynthesis [2] (*Fig.*).

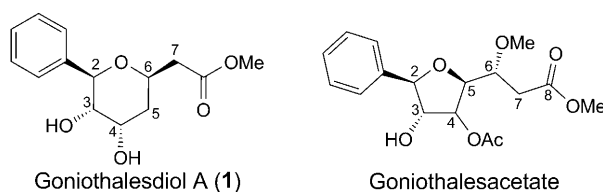
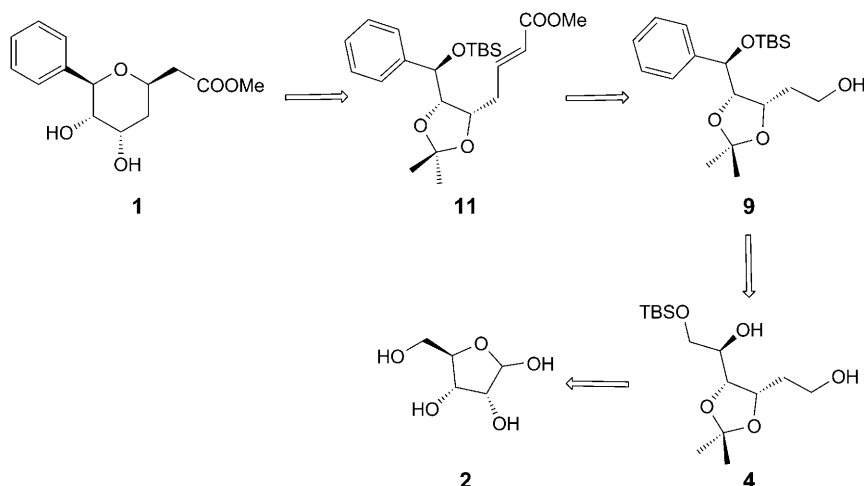


Figure. Chemical structures of goniiothalesdiol A and goniiothalesacetate

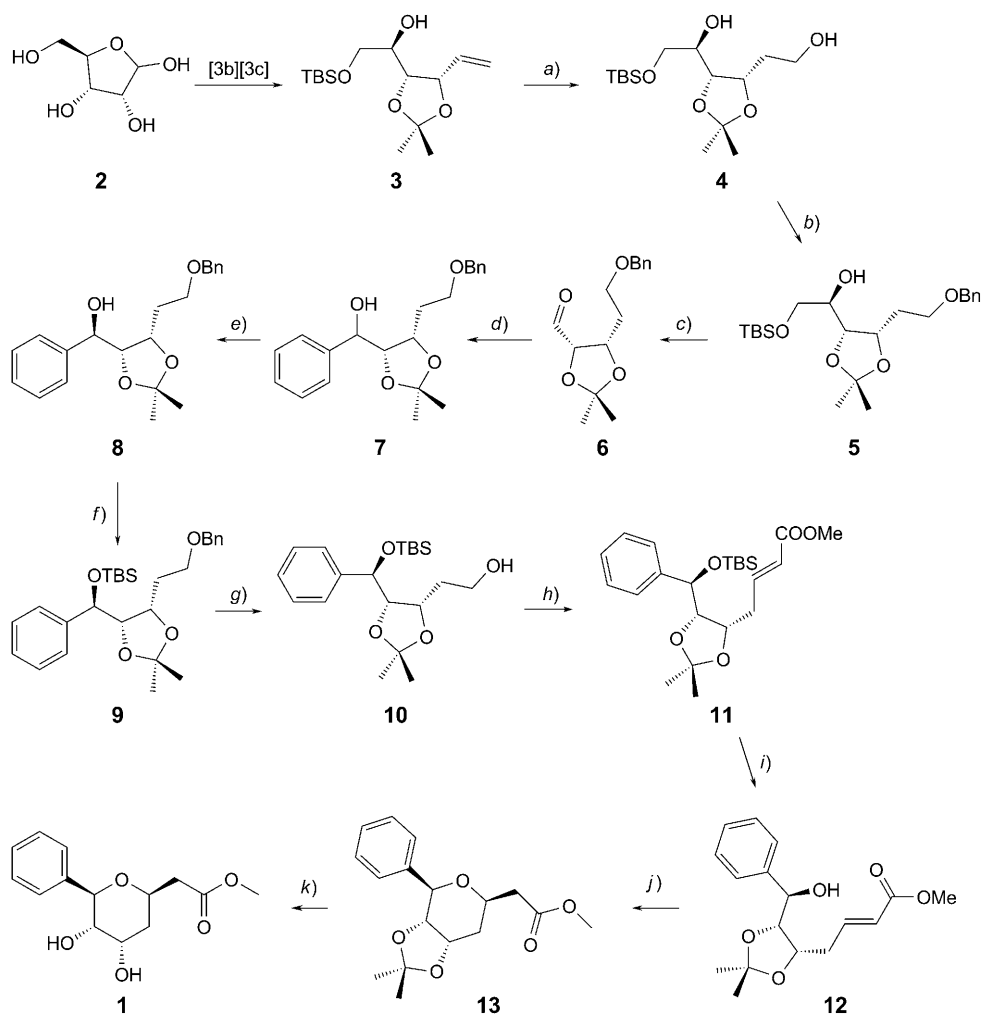
Recently, we have reported the first stereoselective total synthesis of goniiothalesdiol A [3] employing the *Sharpless* kinetic resolution to construct the stereogenic center C(2) and the C(3)/C(4) *syn*-diol arrangement. In the present study, we wish to report the stereocontrolled total synthesis of natural goniiothalesdiol A utilizing inexpensive and readily available D-ribose (**2**) *via* the chiron approach. The retrosynthetic analysis is presented in *Scheme 1*. Our synthetic approach began with enantiomerically pure D-ribose (**2**) which was converted into the pyran moiety through a series of stereocontrolled chemical transformations, which include *Grignard* addition and C₁ *Wittig* reaction for extending a C-chain by incorporating the C=C bond in the final precursor, which in turn permits the intramolecular oxy-*Michael* reaction.

Scheme 1. Retrosynthetic Analysis of Goniiothalesdiol A



Results and Discussion. – Our synthesis started with compound **3**, which was prepared from D-ribose (**2**) according to reported procedures [4][5]. The olefin derivative **3** was converted to the corresponding primary alcohol **4** by hydroboration with a dicyclohexyl borane – dimethyl sulfide (DMS) complex in dry THF, followed by oxidation with H_2O_2 to give product **4** in 81% yield [6] (Scheme 2). The chemoselective protection of **4** with benzyl bromide (BnBr) in the presence of NaH afforded benzyl ether **5** in 97% yield. Deprotection of the (*t*-Bu) Me_2Si (TBS) ether **5** using Bu_4NF (TBAF) gave the diol in 95% yield [4]. Oxidative cleavage of the diol with silica gel-supported NaIO_4 furnished the aldehyde **6** in 95% [7]. Addition of PhMgBr to the aldehyde in Et_2O gave the secondary alcohol **7** in 63% yield as inseparable mixture of diastereoisomers [8]. To obtain the required diastereoisomer as the major product, **7** was oxidized with IBX (= 1-hydroxy-1 λ^3 ,2-benziodoxol-3(1*H*)-one 1-oxide) in DMSO/ CH_2Cl_2 1 : 3 to give a keto product, which was subsequently subjected to stereoselective alkoxy-directed keto reduction with $\text{Zn}(\text{BH}_4)_2$ in THF at -20° to afford compound **8** as the major isomer in 57% yield in two steps [9]. The chiral precursor **8** was protected as TBS ether **9** in 95% yield using (*t*-Bu) Me_2SiCl (TBSCl) and 1*H*-imidazole. Oxidative cleavage of **9** with DDQ gave the primary alcohol **10** in 95% yield. The Swern oxidation of **10** gave the corresponding aldehyde in quantitative yield, which was further subjected to Horner–Wadsworth–Emmons olefination with methyl (diethoxyphosphoryl)acetate ($(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{COOMe}$) to furnish the α,β -unsaturated ester **11** in 93% yield [10]. Deprotection of the TBS ether with TBAF in dry THF at room temperature afforded the hydroxy ester **12** in 95% yield. Compound **12** was treated with TsOH in benzene at room temperature to form the pyran skeleton in **13** by means of intramolecular oxy-*Michael* addition of OH at C(2) onto the (*E*)-configured C(6)=C(7) bond. Eventual deprotection of acetonide using TsOH in MeOH at room temperature afforded the target molecule goniiothalesdiol A (**1**) in 78% yield (Scheme 2) [11].

Scheme 2



a) BH_3 –DMS (dimethyl sulfide), cyclohexene, then H_2O_2 , 0° to r.t., 12 h; 81%. b) NaH, BnBr, Bu_4NI (TBAI), dry THF, reflux, 3 h; 97%. c) 1. Bu_4NF (TBAF), dry THF; 95%; 2. NaIO_4 –silica gel, CH_2Cl_2 , 30 min, 95%. d) PhMgBr , THF, -78° to r.t., overnight; 63% (inseparable mixture of diastereoisomers). e) 1. 1-Hydroxy-1 λ^3 ,2-benzodioxol-3(1*H*)-one 1-oxide (IBX), CH_2Cl_2 /DMSO 3:1, 180–200°, 12 h; 67%; 2. $\text{Zn}(\text{BH}_4)_2$, THF, -20° , 12 h; 85% (de 90%). f) $(t\text{-Bu})\text{Me}_2\text{SiCl}$ (TBSCl), 1*H*-imidazole, CH_2Cl_2 , 0 – 25° , 4 h; 95%. g) 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), CH_2Cl_2 , 25° , 2 h; 95%. h) 1. Oxalyl chloride, dry DMSO, dry CH_2Cl_2 , -78° , Et_3N ; quant.; 2. $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{COOMe}$, $t\text{-BuOK}$, THF, -78 to 0° ; 93% ((*E*)/(*Z*) 8:1). i) TBAF, dry THF, 25° , 2 h; 95%. j) TsOH, benzene, 4 h. k) TsOH, MeOH, 25° , 2 h; 78% (for 2 steps).

In conclusion, we have described a concise synthesis of goniiothalesdiol A (**1**) from D-ribose (**2**) in a highly stereoselective manner. Goniiothalesdiol A has been synthesized in nine steps using an oxy-*Michael* reaction for the construction of the

cis-tetrahydropyran-2,6-diyl moiety. The two key reactions, *i.e.*, a *Grignard* addition to aldehyde **6**, followed by a stereoselective alkoxy-directed keto reduction, are involved in the formation of the precursor **8** as the major product, which is a key intermediate for the total synthesis of goniothalesdiol A (**1**).

Experimental Part

General. Solvents were dried over standard drying agents and freshly distilled prior to use. The reagents were purchased from *Aldrich* and *Acros*, and were used without further purification unless otherwise stated. All moisture-sensitive reactions were carried out under N₂. Org. solns. were dried over anh. Na₂SO₄ and concentrated *in vacuo* below 40°. Column chromatography (CC): silica gel (SiO₂; *Acme's* 60–120 mesh). Optical rotations: *Horiba* high sensitive polarimeter *SEPA-300* at 25°. IR Spectra: *Perkin-Elmer IR-683* spectrophotometer with NaCl optics. ¹H- (200 and 300 MHz) and ¹³C-NMR (50 and 75 MHz) spectra: *Varian Gemini FT-200* and *Bruker Avance 300* instruments with TMS as internal standard in CDCl₃; *J* values in Hz. MS: *Agilent Technologies 1100 Series* (*Agilent Chemstation Software*).

6-O-[(*tert*-Butyl)(dimethyl)silyl]-1,2-dideoxy-3,4-O-(1-methylethylidene)-D-ribo-hex-1-enitol (**3**). To a stirred suspension of D-ribose (**2**; 8 g, 53.29 mmol) in acetone (100 ml) was added dropwise conc. H₂SO₄ (0.24 ml) at r.t., and the mixture was stirred at r.t. for 3 h. The mixture was neutralized with solid NaHCO₃ (5 g), filtered, and evaporated under reduced pressure to give a colorless syrup. The resulting syrup was purified by CC (SiO₂; hexane/AcOEt 1:2) to give acetonide-protected ribose (9.42 g, 93%) as a colourless syrup.

To a stirred soln. of acetonide-protected ribose (7.0 g, 36.8 mmol) in dry CH₂Cl₂ (50 ml) were added 1*H*-imidazole (6.26 g, 88.0 mmol) and TBSCl (6.44 g, 42.8 mmol) at r.t., and the mixture was stirred for 3 h at r.t. The reaction was quenched with ice-cold H₂O, and the mixture was diluted with AcOEt. The org. layer was extracted with AcOEt, and the org. layers were washed with brine, dried (Na₂SO₄), and evaporated under reduced pressure. The resulting syrup was purified by CC (SiO₂; hexane/AcOEt 7:3) to give TBS protected ribose acetonide (10.0 g, 89%) as a colorless oil (9:1 anomeric mixture).

To a mixture of methyl(triphenyl)phosphonium iodide (52 g, 130 mmol) and *t*BuOK (7.4 g, 64 mmol) was added dry THF (240 ml), and the mixture was stirred at r.t. under N₂ for 4 h. Then, the stirring was stopped, and the solid was allowed to settle down. The clear supernatant orange-yellow liquid was transferred into the soln. of TBS-protected ribose acetonide (10 g, 32 mmol) in dry THF (40 ml) at –78°. The mixture was then slowly allowed to attain r.t. After 3 h, the reaction was quenched with crushed ice, and the mixture was diluted with AcOEt. The org. layer was separated and dried (Na₂SO₄), filtered, and evaporated under reduced pressure. The resulting syrup was purified by CC (SiO₂; hexane/AcOEt 3:2) to give **3** (9.2 g, 82%). Pale-yellow syrup. $[\alpha]_D^{25} = -3.5$ (*c* = 1.0, CHCl₃). IR (neat): 3557, 2931, 2858, 1746, 1641, 1466, 1376, 1254, 1217, 1117, 1060, 838, 779, 671. ¹H-NMR (300 MHz, CDCl₃): 5.99 (*ddd*, *J* = 6.0, 10.5, 17.0, 1 H); 5.38 (*td*, *J* = 1.5, 17.0, 1 H); 5.23 (*td*, *J* = 1.5, 10.5, 1 H); 4.64 (*t*, *J* = 6.0, 1 H); 3.98 (*dd*, *J* = 6.7, 9.8, 1 H); 3.77 (*dd*, *J* = 3.0, 9.8, 1 H); 3.71–3.52 (*m*, 2 H); 2.34 (*d*, *J* = 6.0, 1 H); 1.44 (*s*, 3 H); 1.33 (*s*, 3 H); 0.91 (*s*, 9 H); 0.08 (*s*, 6 H). ¹³C-NMR (75 MHz, CDCl₃): 134.2; 117.5; 108.7; 78.81; 77.4; 69.4; 64.4; 27.8; 25.4; 18.3. HR-ESI-MS: 325.1812 (*[M + Na]*⁺, C₁₅H₃₀NaO₄Si⁺; calc. 325.1811).

6-O-[(*tert*-Butyl)(dimethyl)silyl]-2-deoxy-3,4-O-(1-methylethylidene)-D-ribo-hexitol (**4**). To the stirred soln. of cyclohexene (12.03 ml, 11.9 mmol) in dry THF (15 ml) was added BH₃·DMS (5.65 ml, 59.6 mmol) dropwise at 0°, and stirring was continued for 1 h at 0°. At the same temp., a soln. of **3** in dry THF (100 ml) was added to the mixture, and, after 1 h, the mixture was allowed to warm to r.t. and stirred for further 12 h. The mixture was cooled to 0°, then H₂O₂ (20 ml, 30%) and NaOH (20%, 63 ml) were added, and the mixture was stirred for 4 h. Then, the mixture was extracted with AcOEt (2 × 500 ml). The org. extracts were washed with H₂O and brine, and dried (Na₂SO₄). Evaporation of the solvent, followed by purification of the crude product by CC (SiO₂; hexane/AcOEt 95:5), afforded **4** (7.2 g, 81%). Pale liquid. $[\alpha]_D^{25} = -18.1$ (*c* = 1.0, CHCl₃). IR (neat): 3447, 2932, 2853, 1641, 1473, 1376, 1254, 1110, 1055, 835. ¹H-NMR (300 MHz, CDCl₃): 4.92–4.87 (*m*, 1 H); 4.40–4.29 (*m*, 2 H); 3.92–3.77 (*m*, 4 H); 2.28 (*br. s*, 1 H); 1.83–1.60 (*m*, 2 H); 1.45 (*s*, 3 H); 1.35 (*s*, 3 H); 0.90 (*s*, 9 H); 0.05 (*s*, 3 H); 0.04 (*s*,

3 H). ^{13}C -NMR (50 MHz, CDCl_3): 108.4; 75.7; 74.5; 72.1; 62.2; 60.5; 31.7; 27.7; 25.7; 25.5; 21.2; 18.5. HR-ESI-MS: 343.4888 ($[M + \text{Na}]^+$, $\text{C}_{15}\text{H}_{32}\text{NaO}_5\text{Si}^+$; calc. 343.1917).

1-O-Benzyl-6-O-[(tert-butyl)(dimethyl)silyl]-2-deoxy-3,4-O-(1-methylethylidene)-D-ribo-hexitol (**5**). To a mixture of NaH (0.55 g, 60 wt.-% in mineral oil, 13.7 mmol) in dry THF (80 ml) was added a soln. of **4** (4 g, 12.5 mmol) in dry THF (20 ml) at 0°. After 20 min, BnBr (1.65 ml, 13.7 mmol) was added, and the stirring was continued for 2 h at r.t. The reaction was quenched by the addition of a sat. soln. of NH_4Cl (20 ml), and the mixture was extracted with AcOEt. The org. extracts were washed with H_2O and brine, and dried (Na_2SO_4). Evaporation of the solvent, followed by purification of the crude product by CC (SiO_2 ; hexane/AcOEt 95:5) afforded **5** (4.97 g, 92%). Pale-yellow liquid. $[\alpha]_{\text{D}}^{25} = -10$ ($c = 0.5$, CHCl_3). IR (neat): 3547, 2932, 2853, 1746, 1641, 1464, 1376, 1254, 1210, 1110, 1060, 838, 756. ^1H -NMR (300 MHz, CDCl_3): 7.39–7.17 (*m*, 5 H); 4.83 (*d*, $J = 11.3$, 1 H); 4.42 (*d*, $J = 11.3$, 1 H); 4.31–4.23 (*m*, 1 H); 4.06 (*dd*, $J = 5.7$, 9.0, 1 H); 3.99 (*dd*, $J = 1.9$, 11.3, 1 H); 3.77–3.63 (*m*, 2 H); 3.49 (*ddd*, $J = 2.1$, 5.1, 9.0, 1 H); 2.0 (*br. s*, 1 H); 1.79–1.64 (*m*, 2 H); 1.36 (*s*, 3 H); 1.24 (*s*, 2 H); 0.84 (*s*, 9 H); 0.01 (*s*, 6 H). ^{13}C -NMR (50 MHz, CDCl_3): 138.5; 128.3; 127.6; 108.0; 76.9; 72.7; 67.5; 64.5; 29.9; 28.2; 25.8; 25.7; 18.3; –5.5; –5.4. HR-ESI-MS: 433.6126 ($[M + \text{Na}]^+$, $\text{C}_{22}\text{H}_{38}\text{NaO}_5\text{Si}^+$; calc. 433.2386).

1-O-Benzyl-2-deoxy-3,4-O-(1-methylethylidene)-5-C-phenyl-D-erythro-pentitol (**7**). To a well-stirred soln. of **5** (4.5 g, 10.9 mmol) in anhyd. THF (50 ml) was added 1M Bu_4NF (13.2 ml, 13.2 mmol) at 0°. Then, the reaction was quenched with ice flakes, and the mixture was concentrated under reduced pressure. The mixture was extracted with AcOEt (3 $\times$ 50 ml). The combined org. layers were washed with H_2O and brine, and dried (Na_2SO_4). After removing the volatiles under reduced pressure, the crude product was purified by CC (SiO_2 ; hexane/AcOEt 85:15) to afford the pure vicinal diol (3.06 g, 95%). Colorless liquid. $[\alpha]_{\text{D}}^{25} = +4.8$ ($c = 0.15$, CHCl_3). IR (neat): 3650, 3554, 2952, 1744, 1464, 1377, 1254, 1210, 1060, 840, 757. ^1H -NMR (300 MHz, CDCl_3): 7.41–7.26 (*m*, 5 H); 4.67 (*d*, $J = 11.7$, 1 H); 4.48 (*d*, $J = 10.7$, 1 H); 4.41–4.35 (*m*, 1 H); 4.21 (*dd*, $J = 5.8$, 8.8, 1 H); 3.93 (*dd*, $J = 3.9$, 11.7, 1 H); 3.84 (*dd*, $J = 1.9$, 11.7, 1 H); 3.82–3.71 (*m*, 2 H); 3.57–3.52 (*m*, 1 H); 2.05 (*br. d*, $J = 14.6$, 1 H); 1.84–1.76 (*m*, 2 H); 1.44 (*s*, 3 H); 1.35 (*s*, 2 H). ^{13}C -NMR (50 MHz, CDCl_3): 138.6; 128.5; 128.4; 127.7; 108.1; 76.8; 72.7; 71.1; 67.4; 64.3; 29.8; 28.0; 25.8; 25.7. HR-ESI-MS: 297.5447 ($[M + \text{H}]^+$, $\text{C}_{16}\text{H}_{24}\text{O}_5$; calc. 297.5449).

NaIO_4 (25.7 g, 120.0 mmol) was dissolved in 50 ml of hot H_2O (70°) in a 250-ml round-bottomed flask. To the hot soln. was added SiO_2 (230–400 mesh, 100 g) with vigorous swirling and shaking. The resulting SiO_2 coated with NaIO_4 was in a powder form and was free-flowing. The reagent can be kept in a bottle for 1 month with negligible loss of activity. To a vigorously stirred suspension of SiO_2 -supported NaIO_4 reagent (23.6 g) in CH_2Cl_2 (75 ml) in a 25-ml round-bottomed flask was added a soln. of the vicinal diol (3.5 g, 11.8 mmol) in CH_2Cl_2 (75 ml). The reaction was monitored by TLC until disappearance of the starting material (generally 10–30 min). The mixture was filtered through a sintered glass funnel, and the filter cake was thoroughly washed with CHCl_3 (45–150 ml). Removal of solvents from the filtrate afforded the aldehyde **6**, which was directly used for the next reaction.

A suspension of PhMgBr was generated *in situ* with Mg turnings (0.95 g, 39 mmol) and PhBr (2.78 ml, 26 mmol) in dry THF at r.t. under N_2 . Then, a soln. of **6** (3.5 g, 13 mmol) in THF (15 ml) was added slowly at –78° under inert atmosphere. After 2 h, the mixture was warmed to r.t. and left overnight until completion of the reaction, and then the reaction was quenched by addition of sat. aq. NH_4Cl (25 ml), and the mixture extracted with AcOEt (3 $\times$ 100 ml). The combined org. layers were washed with H_2O and brine, and dried (Na_2SO_4). Removal of solvent, followed by CC (SiO_2 ; hexane/AcOEt 95:5) gave **7** (3.0 g, 63%). Colorless oil. IR (neat): 3434, 2924, 2855, 1718, 1603, 1492, 1455, 1377, 1205, 1074, 889, 755. ^1H -NMR (300, CDCl_3): 7.42–7.22 (*m*, 10 H); 4.58–4.53 (*m*, 1 H); 4.53 (*s*, 2 H); 3.93–3.7 (*m*, 1 H); 3.68–3.55 (*m*, 2 H); 3.30–3.20 (*m*, 1 H); 2.85 (*d*, $J = 9.0$, 1 H); 2.20–1.92 (*m*, 1 H); 1.90–1.76 (*m*, 1 H); 1.56 (*s*, 3 H); 1.39 (*s*, 3 H). ^{13}C -NMR (75 MHz, CDCl_3): 139.3; 137.5; 128.3; 127.7; 127.4; 127.1; 98.8; 73.0; 72.5; 66.6; 34.1; 29.6. HR-ESI-MS: 365.1731 ($[M + \text{Na}]^+$, $\text{C}_{21}\text{H}_{26}\text{NaO}_4$; calc. 365.1728).

(5R)-1-O-Benzyl-2-deoxy-3,4-O-(1-methylethylidene)-5-C-phenyl-D-erythro-pentitol (**8**). To a stirred soln. of IBX (4.6 g, 16.4 mmol) in DMSO (2.33 ml, 32.8 mmol) was added **7** (3.0 g, 8.21 mmol) in anhyd. CH_2Cl_2 (50 ml) dropwise at r.t. The mixture was kept under reflux at 180–200° for 12 h; then it was cooled to r.t., extracted with Et_2O (3 $\times$ 100 ml), and filtered through a *Celite* pad. The filtrate was washed with sat. NaHCO_3 and brine. The org. layer was dried (Na_2SO_4). The evaporation of solvent, followed by

purification of the crude product by flash-CC (SiO₂; hexane/AcOEt 6 : 4) yielded the pure ketone (2 g, 67%), which was directly used for the next reaction.

A soln. of ketone (2.0 g, 7.25 mmol), obtained from the oxidation of alcohol **7** (2 g, 7.25 mmol) in THF (20 ml) under N₂, was cooled to –20°, and Zn(BH₄)₂ (2.8 ml of a 2 M soln. in THF, 5.45 mmol) was added slowly during 10 min. After stirring for 12 h at the same temp., the reaction was quenched by addition of sat. aq. NH₄Cl. The resulting mixture was extracted with AcOEt. The combined org. layers were washed with brine, dried (Na₂SO₄), and evaporated *in vacuo*. The residue was subjected to CC (SiO₂; hexane/AcOEt 9 : 1) to give **8** (1.68 g, 85%). Colorless oil. $[\alpha]_D^{25} = -51.4$ (*c* = 0.7, CHCl₃). IR (neat): 3434, 2924, 2855, 1718, 1603, 1492, 1455, 1377, 1205, 1074, 889, 755. ¹H-NMR (300 MHz, CDCl₃): 7.42–7.23 (*m*, 10 H); 4.56 (*d*, *J* = 3.0, 1 H); 4.53 (*s*, 2 H); 3.92–3.80 (*m*, 1 H); 3.69–3.56 (*m*, 2 H); 3.30–3.20 (*t*, *J* = 9.1, 1 H); 2.93 (*d*, *J* = 2.3, 1 H); 2.0–1.90 (*m*, 1 H); 1.90–1.77 (*m*, 1 H); 1.60 (*s*, 3 H); 1.40 (*s*, 3 H). ¹³C-NMR (75 MHz, CDCl₃): 139.3; 137.5; 128.3; 127.7; 127.4; 127.1; 98.8; 73.0; 72.5; 66.6; 34.1; 29.6. HR-ESI-MS: 365.1729 ($[M + Na]^+$, C₂₁H₂₆NaO₄⁺; calc. 365.1728).

(5R)-1-O-Benzyl-5-O-[(*tert*-butyl)(dimethyl)silyl]-2-deoxy-3,4-O-(1-methylethylidene)-5-C-phenyl-D-erythro-pentitol (**9**). To a stirred soln. of **8** (1.50 g, 4.37 mmol) and 1H-imidazole (0.357 g, 5.25 mmol) in anhyd. CH₂Cl₂ (800 ml) was added TBSCl (0.65 g, 4.8 mmol) dropwise at 0°, and stirring was continued for 4 h at r.t. The reaction was quenched with ice flakes, and the mixture was extracted with CH₂Cl₂ (3 × 500 ml). The combined org. layers were washed with H₂O and brine, and dried (Na₂SO₄). Removal of solvent, followed by CC (SiO₂; hexane/AcOEt 95 : 5), furnished **9** (1.89 g, 95%). Colorless liquid. $[\alpha]_D^{31} = -4.1$ (*c* = 1, CHCl₃). IR (neat): 3031, 2925, 2854, 1719, 1603, 1452, 1377, 1205, 1075, 899, 755. ¹H-NMR (300 MHz, CDCl₃): 7.26–7.19 (*m*, 10 H); 4.53 (*s*, *J* = 8.7, 1 H); 4.47 (*s*, 2 H); 4.28 (*qd*, *J* = 2.3, 5.5, 1 H); 4.32–4.24 (*m*, 1 H); 4.11 (*dd*, *J* = 5.5, 8.5, 1 H); 3.66–3.52 (*m*, 2 H); 2.12–2.02 (*m*, 1 H); 1.86–1.74 (*m*, 1 H); 1.28 (*s*, 3 H); 1.15 (*s*, 3 H); 0.78 (*s*, 9 H); –0.5 (*s*, 3 H). ¹³C-NMR (75 MHz, CDCl₃): 141.6; 140.5; 128.4; 127.7; 126.7; 108.5; 85.4; 77.4; 74.0; 72.5; 69.0; 34.3; 29.7; 27.2; 26.3; 18.5; –4.4. HR-ESI-MS: 479.2592 ($[M + Na]^+$, C₂₇H₄₀NaO₄⁺; calc. 479.2596).

(5R)-5-O-[(*tert*-Butyl)(dimethyl)silyl]-2-deoxy-3,4-O-(1-methylethylidene)-5-C-phenyl-D-erythro-pentitol (**10**). To a stirred soln. of **9** (1.75 g, 3.85 mmol) in 9 : 1 CH₂Cl₂ (18 ml) and H₂O (2 ml) was added DDO (6.75 g, 15.35 mmol) at 0°. The mixture was stirred at r.t. for 4 h. The reaction was quenched with NaHCO₃, and the aq. layer was extracted with AcOEt (3 × 100 ml). The combined org. layer was washed with brine and dried (Na₂SO₄). Removal of solvent followed by CC (SiO₂; hexane/AcOEt 85 : 15) afforded **10** (1.33 g, 95% yield). Colorless liquid. $[\alpha]_D^{31} = +28$ (*c* = 0.25, CHCl₃). IR (neat): 3448, 2925, 2854, 1604, 1455, 1375, 1072, 895, 763. ¹H-NMR (300 MHz, CDCl₃): 7.38–7.25 (*m*, 5 H); 4.48 (*d*, *J* = 8.56, 1 H); 3.95 (*td*, *J* = 2.4, 8.6, 1 H); 3.83–3.71 (*m*, 2 H); 3.38 (*t*, *J* = 8.6, 1 H); 2.35 (*br. d*, 1 H); 2.11–1.94 (*m*, 1 H); 1.76–1.56 (*m*, 1 H); 1.62 (*s*, 3 H); 1.46 (*s*, 3 H); 0.75 (*s*, 9 H); 0.13 (*s*, 3 H); –0.97 (*s*, 3 H). ¹³C-NMR (75 MHz, CDCl₃): 137.8; 128.3; 127.5; 126.7; 109.2; 85.4; 78.4; 61.2; 34.3; 27.6; 27.4; 26.2; 18.5; –4.5. HR-ESI-MS: 389.2125 ($[M + Na]^+$, C₂₀H₃₄NaO₄Si⁺; calc. 389.2124).

Methyl (2E)-4-[(4S,5S)-5-[(*R*)-[(*tert*-Butyl)(dimethyl)silyl]oxy](phenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl]but-2-enoate (**11**). To a stirred soln. of oxalyl chloride (0.3 ml, 3.56 mmol) in dry CH₂Cl₂ (15 ml) was added DMSO (0.33 ml, 4.64 mmol) in dry CH₂Cl₂ (10 ml) dropwise at –78°. The mixture was stirred for 15 min at the same temp. To this mixture was added dropwise a soln. of **10** (1.0 g, 2.73 mmol) in dry CH₂Cl₂ (10 ml), and stirring was continued for another 1 h at –78°. Then, Et₃N (2.28 ml, 16.4 mmol) was added to the mixture, and the mixture was warmed to r.t. After addition of H₂O (50 ml), the layers were separated, and the aq. layer was extracted with CH₂Cl₂ (3 × 50 ml). The combined org. layers were washed with H₂O and brine, dried (Na₂SO₄), and concentrated *in vacuo*. The resulting residue (quant. yield) was used directly for the next step.

(EtO)₂P(O)CH₂COOMe (0.8 g, 8.3 mmol) was added to a suspension of ^tBuOK (0.47 g, 4 mmol) in THF (10 ml) at 0° under N₂. After stirring at r.t. for 30 min, the soln. was cooled to –78°, and a soln. of aldehyde (0.8 g, 2 mmol) in THF (5 ml), obtained from **10**, was added. After 30 min, the mixture was allowed to warm to 0° and stirred for another 30 min. Then, the reaction was quenched with sat. aq. NH₄Cl (8 ml) and extracted with AcOEt (3 × 30 ml), washed with brine, and dried (Na₂SO₄). Filtration and evaporation of the solvent *in vacuo* furnished the crude **11** (0.79 g, 93%), which was subjected to CC (SiO₂; hexane/AcOEt 9 : 1). $[\alpha]_D^{25} = -53$ (*c* = 0.3, CHCl₃). IR (neat): 2925, 2854, 1727, 1657, 1463, 1437, 1381, 1261, 1165, 1095, 864, 836, 778. ¹H-NMR (300 MHz, CDCl₃): 7.37–7.20 (*m*, 5 H); 7.00–6.87 (*m*,

1 H); 5.83 (*d*, *J* = 15.8, 1 H); 4.43 (*d*, *J* = 9.0, 1 H); 3.80–3.65 (*m*, 1 H); 3.70 (*s*, 3 H); 3.31 (*t*, *J* = 9.0, 1 H); 2.70–2.60 (*m*, 1 H); 2.28–2.15 (*m*, 1 H); 1.54 (*s*, 3 H); 1.34 (*s*, 3 H); 0.73 (*s*, 9 H); 0.14 (*s*, 3 H); 0.04 (*s*, 3 H). ¹³C-NMR (75 MHz, CDCl₃): 145.7; 128.7; 128.3; 122.7; 78.1; 73.8; 73.1; 34.8; 29.4; 25.8; 19.4; –4.1; –5.7. HR-ESI-MS: 443.2228 ([*M* + Na]⁺, C₂₃H₃₆NaO₅Si⁺; calc 443.2229).

Methyl (2E)-4-[(4S,5R)-5-[(R)-Hydroxy(phenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl]but-2-enoate (12). To a well-stirred soln. of **11** (0.7 g, 1.58 mmol) in anh. THF (15 ml) was added 1M Bu₄NF (1.9 ml, 1.9 mmol) at 0°. Then, the reaction was quenched with ice flakes, and the mixture was concentrated under reduced pressure. The mixture was extracted with AcOEt (3 × 50 ml). The combined org. layers were washed with H₂O and brine, and dried (Na₂SO₄). After removing the volatiles under reduced pressure, the crude product was purified by CC (SiO₂; hexane/AcOEt 85:15) to afford **12** (0.49 g, 95%). Colorless liquid. [*α*]_D²⁵ = +8.4 (*c* = 0.4, CHCl₃). IR (neat): 3434, 2924, 1728, 1657, 1464, 1437, 1380, 1260, 1166, 1096, 865, 836, 778. ¹H-NMR (300 MHz, CDCl₃): 7.36–7.20 (*m*, 5 H); 6.98–6.88 (*m*, 1 H); 5.83 (*d*, *J* = 15.8, 1 H); 4.20 (*d*, *J* = 4.5, 1 H); 4.15–4.08 (*m*, 1 H); 3.90–3.86 (*m*, 1 H); 3.70 (*s*, 3 H); 2.70–2.62 (*m*, 1 H); 2.28–2.16 (*m*, 1 H); 1.54 (*s*, 3 H); 1.36 (*s*, 3 H). ¹³C-NMR (75 MHz, CDCl₃): 168.0; 145.8; 141.1; 128.3; 122.9; 78.1; 73.8; 73.1; 52.0; 34.8; 29.4. HR-ESI-MS: 329.1359 ([*M* + Na]⁺, C₁₇H₂₂NaO₅Si⁺; calc 329.1360).

Goniothalesdiol A (= Methyl (7R)-3,7-Anhydro-2,4-dideoxy-7-phenyl-D-ribo-heptonate; 1). To a stirred soln. of **12** (0.3 g, 0.51 mmol) in benzene (4 ml) was added TsOH (0.03g, 0.1 mmol). The mixture was stirred at r.t. for 3 h, and the solvent was removed under reduced pressure. The crude residue **13** was dissolved in 2 ml MeOH, and TsOH was added; the resulting mixture was stirred overnight at r.t. The solvent was removed under reduced pressure. The crude residue was subjected to CC (SiO₂; hexane/AcOEt 6:4) to afford **1** (0.15 g, 78%). White solid. M.p. 92°. [*α*]_D²⁵ = –27 (*c* = 0.3, CHCl₃). IR (neat): 3405, 2918, 2848, 2373, 1730, 1435, 1200, 1170, 1068. ¹H-NMR (300 MHz, CDCl₃): 7.40–7.28 (*m*, 5 H); 4.54 (*d*, *J* = 9.8, 1 H); 4.45–4.35 (*m*, 1 H); 4.24–4.19 (*m*, 1 H); 3.68 (*s*, 3 H); 3.49 (*dd*, *J* = 9.8, 3.0, 1 H); 2.61 (*dd*, *J* = 15.1, 7.5, 1 H); 2.45 (*dd*, *J* = 15.1, 6.0, 1 H); 2.11 (*ddd*, *J* = 13.5, 3.0, 2.2, 3 H); 1.76 (*ddd*, *J* = 12.0, 3.0, 2.2, 1 H); 1.40 (*s*, 1 H). ¹³C-NMR (75 MHz, CDCl₃): 171.3; 139.2; 128.4; 128.2; 127.3; 77.7; 72.6; 68.4; 67.0; 51.6; 40.3; 37.1. HR-ESI-MS: 267.1228 ([*M* + H]⁺, C₁₄H₁₉O₅⁺; calc. 267.1232).

REFERENCES

- [1] A. A. E. El-Zayat, N. R. Ferringi, T. G. McCloud, A. T. McKenzie, S. R. Byrn, J. M. Cassady, C.-J. Chang, J. L. McLaughlin, *Tetrahedron Lett.* **1987**, 26, 955; T. W. Sam, S.-Y. Chew, S. Matsjeh, E. K. Gan, D. Razak, A. L. Mohamed, *Tetrahedron Lett.* **1987**, 28, 2541; X.-P. Fang, J. E. Anderson, C.-J. Chang, P. E. Fanwick, J. L. McLaughlin, *J. Chem. Soc., Perkin Trans. 1* **1990**, 1655; X.-P. Fang, J. E. Anderson, C.-J. Chang, P. E. Fanwick, J. L. McLaughlin, *Tetrahedron* **1991**, 47, 9751; X.-P. Fang, J. E. Anderson, X.-X. Qiu, J. F. Kozlowski, C.-J. Chang, J. L. McLaughlin, *Tetrahedron* **1993**, 49, 1563.
- [2] Y.-H. Lan, F.-R. Chang, Y.-L. Yang, Y.-C. Wu, *Chem. Pharm. Bull.* **2006**, 54, 1040.
- [3] J. S. Yadav, N. Rami Reddy, V. Harikrishna, B. V. Subba Reddy, *Tetrahedron Lett.* **2009**, 50, 1318.
- [4] D. Naveen Kumar, B. Venkateshwara Rao, G. S. Ramanjaneyulu, *Tetrahedron: Asymmetry* **2005**, 16, 1611.
- [5] Y. H. Jin, P. Liu, J. Wang, R. Baker, J. Huggins, C. K. Chu, *J. Org. Chem.* **2003**, 68, 9012.
- [6] M. Lombardo, S. Morganti, C. Trombini, *J. Org. Chem.* **2000**, 65, 8767.
- [7] Y.-L. Zhong, T. K. M. Shing, *J. Org. Chem.* **1997**, 12, 2622.
- [8] V. Popsavin, G. Benedeković, B. Srećo, M. Popsavin, J. Francuz, V. Kojić, G. Bogdanović, *Org. Lett.* **2007**, 9, 4235.
- [9] S. Ghosh, C. Nageshwer Rao, S. Dutta, *Synlett* **2007**, 1464; T. Takahashi, M. Miyazawa, J. Tsuji, *Tetrahedron Lett.* **1985**, 26, 5139.
- [10] S. Nakamura, F. Kikuchi, S. Hashimoto, *Tetrahedron. Asymmetry* **2008**, 19, 1059.
- [11] I. Paterson, E. A. Anderson, S. M. Dalby, J. Genovino, J. H. Lim, C. Moessner, *Chem. Comm.* **2007**, 1852; J. S. Yadav, N. Rami Reddy, V. Harikrishna, B. V. Subba Reddy, *Tetrahedron Lett.* **2009**, 50, 1318.

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