Tetrahedron: *Asymmetry* 23 (2012) 659–661

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

A simple and efficient synthesis of goniothalesdiol A

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ARTICLE INFO

Article history:
Received 26 March 2012
Accepted 3 May 2012
Available online 8 June 2012

ABSTRACT

A concise, simple, and efficient stereoselective total synthesis of goniothalesdiol A starting from commercially available 2-deoxy-D-ribose is described herein using a stereocontrolled Grignard reaction, olefin cross-metathesis, and oxy-Michael addition reactions as the key steps.

1. Introduction

In recent years, the synthesis of substituted tetrahydropyrans has gained significant interest due to their potent biological properties. Tetrahydropyrans containing substituents at the 2- and 6-positions on the ring are observed in a large number of biologically important natural products. A few examples which come under this class include phorboxazole,[1a] ratjadone,[1b] lasnolide,[1c] leucascandrolide,[1d] scytoohycins,[1e] soranicin-A,[1f] swinholides,[1g] laulimalide,[1h] and zamponolide.[1i] The two major types of bioactive compounds styryl lactones[2] and acetogenins[3] can be isolated from *Goniothalamus* species belonging to the annonaceae family. Recently goniothalesdiol A **1** and goniothalesacetate **2** (Fig. 1) were isolated from the stems of a southern Taiwan tree *Goniothalamus amuyon*. Goniothalesdiol A has been shown to possess a 2,3,4,6-tetrasubstituted pyran ring. The structure and relative configuration of **1** were determined on the basis of NMR spectroscopy and the absolute configuration was predicted by biosynthesis.[4] Previously five syntheses have been reported, one based on a Sharpless kinetic resolution; the second synthesis based on a cross metathesis using Grubb's second generation catalyst; a third involves a chiron approach; the fourth is based on a Prins cyclization and last one is using tandem aminoxylation–allylation reaction.[5] Among those, She et al. achieved the asymmetric total synthesis of goniothalesdiol A in six steps with an overall yield of 30%.[5] We have achieved a concise, simple, and efficient total synthesis of goniothalesdiol A in six steps and with 31% overall yield.

According to our retro-synthetic analysis, the construction of the tetrahydropyran ring of goniothalesdiol A would arise from the key intermediate hydroxyl ester **3** by intramolecular oxy-Michael addition which can be manipulated further by acetonide deprotection to give the target compound goniothalesdiol A. Ester **3** can in turn be obtained by olefin cross-metathesis of **4** with methyl acrylate. Olefinic alcohol **4** was synthesized from commercially available 2-deoxy-D-ribose involving a chiral pool approach using selective acetonide protection, one carbon homologation by a Wittig reaction and stereocontrolled Grignard reaction with phenyl magnesium bromide (Scheme 1).

2. Results and discussion

Initially, the synthesis began with the isopropylidine formation at the secondary hydroxyl groups at C3 and C4 of 2-deoxy-D-ribose **6** with 2,2-dimethoxy propane in the presence of a catalytic amount of PTSA to give compound **5**.[6] One carbon homologation using a Wittig protocol on lactol **5** with methyltriphenylphosphonium iodide in the presence of KHMDS yielded olefenic alcohol **7**.[7] The primary alcohol in the resultant product **7** was oxidized to the aldehyde by a Swern oxidation and the crude aldehyde was used directly for the Grignard reaction with phenyl magnesium bromide in dry ether at −78 °C. The required anti-alcohol **4** was obtained as the major diastereomer in 63% yield after column chromatography.[8] The olefenic cross-metathesis reaction of **4** with methyl acrylate employing Grubbs' 2nd generation catalyst gave the desired conjugated ester **3** as the exclusive product in 97% yield.[9] The key intermediate **3** has the required carbon chain with the appropriate stereochemistry. One pot cyclization and deprotection of **3** using *p*-TSA in benzene produced the tetrahydropyran moiety and the acetonide group was subsequently removed by the addition of a protic solvent (methanol) to give the desired target molecule goniothalesdiol A **1** in 86% (Scheme 2).[10] The authenticity of synthetic goniothalesdiol A was confirmed by comparison of all of the spectroscopic data and the specific rotation with that of the natural product.[4,5]

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http://dx.doi.org/10.1016/j.tetasy.2012.05.002

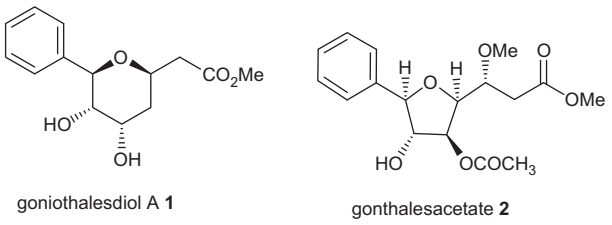
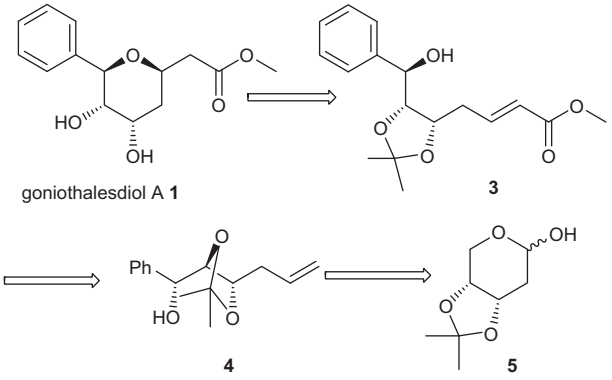


Figure 1.



Scheme 1.

3. Conclusion

In conclusion, we have achieved a simple, versatile, and efficient stereoselective total synthesis of goniothalesdiol A in six steps with 31% overall yield starting from the 2-deoxy-D-ribose. The key reactions involved are the stereocontrolled Grignard reaction, olefin cross-metathesis, and acid-catalyzed oxy-Michael addition.

4. Experimental

4.1. General

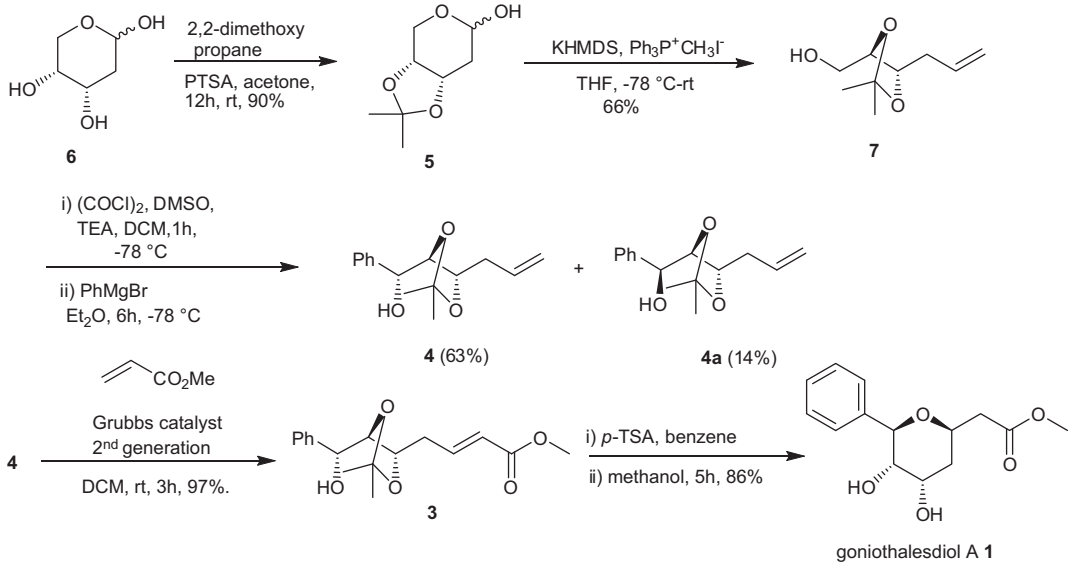
The reactions were carried out under N_2 in anhydrous solvents such as CH_2Cl_2, THF, and EtOAc. THF used was freshly distilled over benzophenone prior to use. All reactions were monitored by TLC (silica-coated plates and visualized under UV light). Yields refer to isolated yields. Air-sensitive reagents were transferred by a syringe or a double-ended needle. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on Brucker Avance 300 spectrometers. Chemical shifts are reported relative to TMS as an internal standard. Column chromatography was performed on silica gel (60–120 mesh) supplied by Acme Chemical Co., India. TLC was performed on Merck 60 F-254 silica gel plates. IR (FT-IR) spectra were recorded either on KBr pellets or neat as thin film. Optical rotations were recorded on JASCO DIP-360 digital polarimeter.

4.1.1. (2*R*,3*S*)-Hex-5-ene-1,2,3-triol 2,3-acetonide 7

To a stirred suspension of methyltriphenylphosphonium iodide (13.9 g, 34.5 mmol) in 50 mL of THF was added KHMDS (0.5 M in toluene, 57.5 mL, 28.7 mmol) at −78 °C. The solution was warmed up to 0 °C and stirred for 30 min before being cooled down to −78 °C. Compound **5** (2 g, 11.5 mmol) in 10 mL of THF was added and the solution was stirred at rt overnight (10 h) before being quenched with a saturated aqueous NH_4Cl solution and extracted with EtOAC (120 mL × 3). The organic layers were combined and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified on a silica gel column using petroleum ether/EtOAc (4/1) as the eluant to afford **7** as a colorless oil (1.30 g, 66%). $R_f = 0.2$ (SiO_2, 3:7 EtOAc in hexane). $[\alpha]_D^{29} = +54.8$ (*c* 1.2, $CHCl_3$); IR (neat) ν_{max}: 3434, 2986, 2934, 2879, 1642, 1371, 1381, 1218 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.90–5.78 (m, 1H), 5.19–5.09 (m, 2H), 4.29–4.23 (m, 1H), 4.18 (q, *J* = 7.3 Hz, 1H), 3.65 (d, *J* = 5.7 Hz, 2H), 2.46–2.36 (m, 1H), 2.33–2.24 (m, 1H), 1.49 (s, 3H), 1.38 (s, 3H); ^{13}CNMR (100 MHz, $CDCl_3$); δ 134.2, 117.4, 108.2, 77.2, 76.2, 61.6, 33.6, 28.1, 25.4.

4.1.2. (*R*)-[(4*R*,5*S*)-5-Allyl-2,2-dimethyl-1,3-dioxolan-4-yl](phenyl)methanol 4

A solution of DMSO (1.65 mL, 23.2 mmol) in CH_2Cl_2 (10 mL) was added to a solution of $(COCl)_2$ (1.0 mL, 22.9 mmol) in CH_2Cl_2 (10 mL) at −78 °C. After stirring for 15 min, a solution of **7** (1.0 g, 5.8 mmol) in CH_2Cl_2 (20 mL) was added to the reaction mixture and stirring was continued at the same temperature for an additional hour. Next, Et_3N (4.8 mL, 34.8 mmol) was added to the reaction mixture, which was then gradually warmed to rt and diluted with CH_2Cl_2 (20 mL). The organic layer was washed with water (1 × 30 mL), brine (1 × 20 mL), dried over anhydrous Na_2SO_4, and



Scheme 2.

concentrated under reduced pressure. The crude aldehyde was used directly for the next reaction.

To a pre-cooled (−78 °C) stirred solution of the PhMgBr [prepared from PhBr (1.2 mL, 11.6 mmol) and Mg (348 mg, 14.5 mmol) in anhydrous ether (20 mL) at room temperature], the above prepared aldehyde was added dropwise in anhydrous ether (10 mL), and the resulting mixture was stirred at the same temperature for 6 h. The reaction was quenched with an aqueous saturated ammonium chloride solution (10 mL), and the reaction mixture was diluted with Et_2O (15 mL). The organic layer was washed with NH_4Cl (aq) (30 mL), and dried over anhydrous Na_2SO_4 which upon evaporation of the solvent, yielded a mixture of diastereomers, which were carefully separated by column chromatography 230–400 silica gel (ethylacetate/hexane 1:9) to afford **4a** (0.20 g, 14%), followed by pure major diastereomer **4** (0.90 g, 63%) as a colorless oil. R_f = 0.4 (20% EtOAc/hexane).

4.1.2.1. Analytical data for compound 4. $[\alpha]_D^{29} = -2.1$ (*c* 0.3, $CHCl_3$); IR (KBr): 3448, 2933, 2984, 1641, 1454, 1380, 1219, 1058; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.43–7.28 (m, 5H), 5.80–5.69 (m, 1H), 5.11–5.04 (m, 2H), 4.70 (d, *J* = 57 Hz, 1H), 4.35 (t, *J* = 5.7 Hz, 1H), 4.21–4.15 (m, 1H), 2.85 (br s, 1H), 2.54–2.44 (m, 1H), 2.29–2.20 (m, 1H), 1.58 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 134.5, 128.6, 128.1, 127.3, 117.2, 108.4, 80.7, 76.7, 72.1, 34.3, 27.7, 25.2.

4.1.2.2. Analytical data for compound 4a. $[\alpha]_D^{29} = -8.5$ (*c* 0.3, $CHCl_3$); IR (KBr): 3411, 2925, 2854, 1641, 1600, 1494, 1452, 916, 700; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.56–7.01 (m, 5H), 6.04–5.86 (m, 1H), 5.09 (ddd *J* = 15.9, 11.0, 1.3 Hz, 2H), 4.56 (d, *J* = 9.3 Hz, 1H), 3.91–3.83 (m, 1H), 3.27 (t, *J* = 9.3, Hz, 1H), 2.60–2.50 (m, 1H), 2.36–2.25 (m, 1H), 1.59 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7, 134.5, 128.4, 127.5, 126.5, 117.0, 108.4, 76.2, 72.8, 72.2, 36.8, 29.5, 19.4.

4.1.3. (*E*)-Methyl 4-{(4*S*,5*R*)-5-[(*R*)-hydroxy(phenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}but-2-enoate 3

Compound **4** (0.3 g, 1.2 mmol) and methyl acrylate (0.728 g, 8.5 mmol) were added via syringe to a stirring solution of Grubbs 2nd generation catalyst (50 mg, 0.05 mmol, 5.0 mol %) in dichloromethane (1.5 mL). The flask was capped with a rubber septum, flushed with dry nitrogen, and stirred under nitrogen for 3 h at rt. The reaction mixture was then reduced in volume to 0.5 mL and purified directly by silica gel column chromatography (6% EtOAc/hexane) to provide **3** (0.356 g, 97% yield) as a brown oil. R_f = 0.40 (50% EtOAc in hexane). $[\alpha]_D^{28} = -87.2$ (*c* 0.15, $CHCl_3$); IR (KBr): 3451, 2935, 2987, 1722, 1658, 1437, 1219, 1059; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.41–7.30 (m, 5H), 6.92–6.83 (m, 1H), 5.84 (dt, *J* = 15.9, 1.3 Hz, 1H), 4.67 (dd, *J* = 4.4, 1.3 Hz, 1H), 4.41 (t, *J* = 6.2 Hz, 1H), 4.23–4.17 (m, 1H), 3.71 (, 3H), 2.79 (d, 1H), 2.67–2.57 (m, 1H), 2.38–2.29 (m, 1H), 1.57 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 144.9, 140.1, 128.7, 128.4, 127.3, 123.1, 108.7, 80.6, 75.7, 75.2, 51.5, 33.0, 27.7, 25.2; (ESI-MS): *m/z* 307 ($M+H^+$). HRMS: calcd for $C_{17}H_{22}NaO_5$: 329.1364 (M+Na), found: 329.1372.

4.1.4. Goniothalesdiol A 1

To compound **3** (69 mg, 0.2 mmol) in benzene (2 ml) was added TsOH (3.9 mg, 0.02 mmol). The reaction mixture was stirred at rt for 3 h and the solvent was removed under reduced pressure, the obtained crude residue was dissolved in 2 ml MeOH, and TsOH (3.9 mg, 0.02 mmol) was added and stirred overnight at rt. The solvent was removed under reduced pressure. The crude residue was subjected to column chromatography on silica gel (hexane/AcOEt 6:4) to afford goniothalesdiol A (51 mg, 86%) as white solid. Mp 91 °C (lit.[5a] mp 92 °C); $[\alpha]_D^{28} = -25.5$ (*c* 1.2, $CHCl_3$); Lit.[5a] $[\alpha]_D^{25} = -27.2$ (*c* 0.3, $CHCl_3$); IR (neat): 3425, 2924, 2856, 1732, 1441, 1168. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.42–7.29 (m, 5H), 4.54 (d, *J* = 9.52 Hz, 1H), 4.43–4.33 (m, 1H), 4.23–4.17 (m, 1H), 3.65 (s, 3H), 3.49 (d, *J* = 9.5 Hz, 1H), 2.60 (dd, *J* = 15.4, 7.3 Hz, 1H), 2.44 (dd, *J* = 14.6, 5.7 Hz, 1H), 2.12–2.04 (m, 1H), 1.81 (br s, 1H), 1.78–1.69 (m, 1H) 1.53 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 139.2, 128.4, 128.2, 127.3, 77.7, 72.6, 68.4, 67.0, 51.6, 40.3, 37.1. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{19}O_5$: 267.1232: found: 267.1224.

Acknowledgments

We are thankful to Dr. Reddy's Laboratories Ltd for support and Maithili Life Sciences Pvt. Ltd for financial assistance.

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