First Stereoselective Synthesis of the Cytotoxic Polyketide (4*R*)-1-(3,5-Dihydroxyphenyl)-4-hydroxypentan-2-one

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The first stereoselective synthesis of the cytotoxic polyketide (4*R*)-1-(3,5-dihydroxyphenyl)-4-hydroxypentan-2-one (**1**) was achieved from readily available propylene oxide and 3,5-dimethoxybenzyl alcohol. The synthesis involves *Jacobsen*'s hydrolytic kinetic resolution (HKR) and *Grignard* reaction as key steps.

Introduction. – 5-Substituted resorcinols (benzene-1,3-diols) are interesting biologically active, polyketide-derived compounds occurring in many different living organisms such as lower and higher plants, algae, mosses, fungi, bacteria, and animals [1]. The 5-alkylresorcinols exhibit a broad range of biological and pharmacological properties, including antimicrobial, antiparasitic, antifungal, antitrypanosomal, antileishmanial activities, and cytotoxic activity by cleavage of DNA in the presence of Cu^{II} and O_2 [2]. In addition, 5-substituted resorcinols also serve as handy building blocks in the synthesis of cannabis derivatives [3]. (4*R*)-1-(3,5-Dihydroxyphenyl)-4-hydroxypentan-2-one (**1**; *Fig.*) was isolated in 2011 by *Lin* and co-workers from the soil-derived fungus *Exophiala pisciphila* [4]. It exhibited moderate cytotoxic activity against A-549, HeLa, PANC-28, and BEL-7402 cell lines. The absolute configuration of compound **1** was confirmed by modified *Mosher*'s method. Considering the structure as well as its biological profile, and in continuation of our interest in the syntheses of biologically active natural products [5], we report a simple and facile route for the synthesis of compound **1** using *Jacobsen*'s hydrolytic kinetic resolution (HKR) and *Grignard* reaction as key steps. The retrosynthesis of the planar structure **1** is depicted in *Scheme 1*, starting from (3,5-dimethoxybenzyl)magnesium bromide (**9**) and propylene oxide (=2-methyloxirane; **2**).

The target molecule **1** can be easily envisaged from the oxidation of compound **6** (*cf. Scheme 2*). Compound **6** is prepared *via Grignard* reaction of an aldehyde derived from

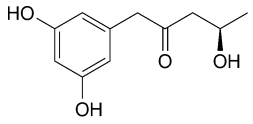

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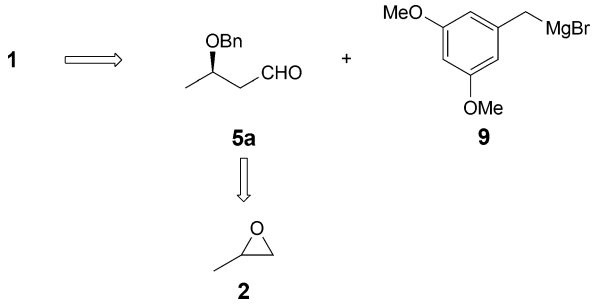
Figure. *Structure of (4*R*)-1-(3,5-Dihydroxyphenyl)-4-hydroxypentan-2-one* (**1**)

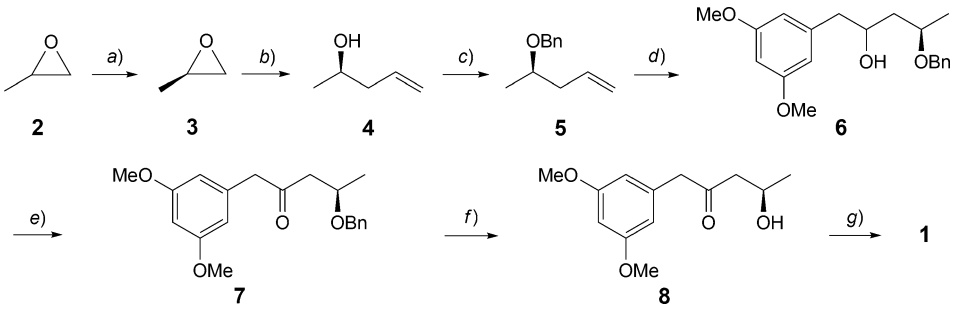
Scheme 1. *Retrosynthetic Analysis of* **1**



the corresponding alkene **5**. The latter was prepared from (*R*)-propylene oxide (**3**) by regioselective epoxide opening, followed by the protection of OH group.

Results and Discussion. – As outlined in *Scheme 2*, the synthesis of **1** started with commercially available racemic propylene oxide (**2**), which was subjected to *Jacobsen*'s hydrolytic kinetic resolution (HKR), using (*R*,*R*)-(salen)Co^{III} · OAc catalyst to afford (*R*)-propylene oxide (**3**) [6]. Compound **3** was reacted with vinylmagnesium bromide to furnish homoallyl alcohol **4** in 85% yield [7]. The secondary OH group in **4** was protected as its Bn ether **5** in 81% yield by treatment with BnBr and NaH in dry THF. The terminal C=C bond of compound **5** was then subjected to OsO_4-catalyzed dihydroxylation and $NaIO_4$-mediated cleavage to furnish the corresponding aldehyde **5a**, which was subjected to *Grignard* reaction with (3,5-dimethoxybenzyl)magnesium bromide [8] to afford the diastereoisomer mixture **6** in 85% yield. The secondary OH group in **6** was oxidized with 2-iodoxybenzoic acid (IBX) in dry DMSO/CH_2Cl_2 to give the corresponding ketone **7** in 90% yield. The Bn group in **7** was removed by treatment

Scheme 2



a) (*R*,*R*)-(salen)Co^{III} · OAc (salen = 2,2′-ethylenebis(nitrilomethylidene)diphenol = ethylenebis(salicylimine)) (0.5 mol-%), dist. H_2O (0.55 equiv), 0° – r.t., 16 h; 48%. *b*) Vinylmagnesium bromide (1.0M soln. in THF), THF, CuI, –20°, 1 h; 85%. *c*) NaH, BnBr, THF, 0° to r.t., 6 h; 81%. *d*) 1) OsO_4, 4-Methylmorpholine *N*-oxide (NMO), acetone/H_2O 8 : 2, r.t., 2 h. 2) $NaIO_4$, THF/H_2O 2 : 1, 0° to r.t., 1 h; 80%. 3) *(3,5-Dimethoxybenzyl)magnesium bromide* (**9**) [8], dry Et_2O, –78°, 1 h; 85%. *e*) 2-Iodoxybenzoic acid, DMSO, dry CH_2Cl_2, 4 h; 90%. *f*) $TiCl_4$, CH_2Cl_2, 0°, 2 h; 80%. *g*) AlI_3, Bu_4NI, benzene, 10°; 75%.

with $TiCl_4$ in CH_2Cl_2 to give **8** in 80% yield. Finally, demethylation of compound **8** by using AlI_3 and Bu_4NI [9] afforded the desired natural product (4*R*)-1-(3,5-dihydroxyphenyl)-4-hydroxypentan-2-one (**1**) in 75% yield. The physical and spectroscopic properties of **1** are in complete agreement with those reported in [4].

In conclusion, the first stereoselective synthesis of the natural polyketide **1** has been reported, starting from the commercially available propylene oxide (**2**), by applying *Jacobsen*'s hydrolytic kinetic resolution (HKR) and *Grignard* reactions as the key steps.

The authors *K. R. P.* and *S. P. R.* are thankful to *CSIR-IICT*, director IICT, and head of division of natural products chemistry.

Experimental Part

General. All the reagents and solvents were of reagent grade and used without further purification unless otherwise stated. Technical-grade AcOEt and hexanes used for column chromatography (CC) were distilled before use. THF, when used as solvent for the reactions, was freshly distilled from Na/benzophenone ketyl. All the reactions were performed under N_2 in flame- or oven-dried glassware with magnetic stirring. Column chromatography (CC): silica gel (SiO_2, 60–120 mesh) packed in glass columns. Optical rotations: *Anton Paar MLP 200* modular circular digital polarimeter by using a 2-ml cell with a path length of 1 dm. FT-IR Spectra: *Perkin–Elmer 683* infrared spectrophotometer; neat or as thin films in KBr optics; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker Avance 300* instrument at 300 and 75 MHz, resp.; in $CDCl_3$ and CD_3OD, at r.t.; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: *Agilent Technologies LC-MSD trap SL* spectrometer; in *m*/*z*.

*{[(2*R*)-Pent-4-en-2-yloxy]methyl}benzene* (**5**). To a stirred soln. of **4** [7] (0.5 g, 5.813 mmol) in dry THF (40 ml) was added NaH (0.28 g, 11.62 mmol; 60% (*w*/*w*) in paraffin oil) at 0°. After 30 min, BnBr (0.7 ml, 5.906 mmol) was added at 0° and the mixture was stirred for 8 h. After completion, the reaction was quenched with sat. aq. NH_4Cl soln. (10 ml) at 0°, and the mixture was extracted with AcOEt (2 × 20 ml). The combined org. extracts were washed with brine (10 ml), dried (Na_2SO_4), and evaporated under reduced pressure. The crude product was purified by CC (hexanes/AcOEt 97:3) to afford **5** (0.82 g, 81%). Colorless liquid. $[\alpha]_D^{25} = +45.60$ ($c = 0.5$, $CHCl_3$). IR (neat): 3018, 1712, 1549, 1514, 1216, 771, 667. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.34–7.18 (*m*, 5 H); 5.86–5.76 (*m*, 1 H); 5.09–5.00 (*m*, 2 H); 4.57–4.43 (*m*, 2 H); 3.59–3.50 (*m*, 1 H); 2.39–2.31 (*m*, 1 H); 2.25–2.17 (*m*, 1 H); 1.18 (*d*, $J = 7.0$, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 134.9; 128.2; 127.7; 127.5; 127.4; 116.9; 74.4; 70.3; 40.9; 19.5. ESI-MS: 177 ($[M+H]^+$).

*(4*R*)-4-(Benzyloxy)-1-(3,5-dimethoxyphenyl)pentan-2-ol* (**6**). A soln. of OsO_4 in H_2O (4% soln., 0.9 ml, 0.141 mmol) was added to a cooled (0°) soln. of **5** (0.5 g, 2.840 mmol) in THF/H_2O 1:1 (30 ml). $NaIO_4$ (3.0 g, 14.20 mmol) was added after 15 min, and the suspension was stirred at r.t. for 4 h. The mixture was then treated with a 10% aq. soln. of $Na_2S_2O_3$ (30 ml) and extracted with Et_2O. The org. phase was washed with 10% aq. soln. of $Na_2S_2O_3$ (30 ml) and brine (30 ml), and dried ($MgSO_4$). The org. extract were concentrated *in vacuo* to give crude **5a** (0.404 g, 80%), which was directly used for the next step.

To a stirred suspension of Mg (0.16 g, 6.808 mmol) in anh. Et_2O (10 ml) at r.t. in a condenser (cool-water circulation) was added 1-(bromomethyl)-3,5-dimethoxybenzene [8] (0.542 g, 4.537 mmol) in anh. Et_2O (10 ml), and the mixture was stirred for 0.5 h. Then, the mixture was cooled to 0°, and the crude aldehyde **5a** (0.4 g, 2.247 mmol) in anh. Et_2O (5 ml) was added. The mixture was warmed to r.t. and stirred at r.t. for 1 h. Then, the reaction was quenched with sat. aq. NH_4Cl soln. (15 ml), and the mixture was extracted with AcOEt (3 × 10 ml). The combined org. extracts were washed with brine (10 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give a crude product, which was purified by CC (AcOEt/hexane 2:8) to afford a mixture of diastereoisomers **6** (0.63 g, 85%). Clear liquid. $[\alpha]_D^{34} = -91.4$ ($c = 0.7$, $CHCl_3$). IR (neat): 3466, 2930, 1599, 1461, 1152, 1063, 832, 669. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.40–7.22 (*m*, 5 H); 6.37 (*d*, $J = 1.7$, 2 H); 6.33 (*t*, $J = 1.7$, 1 H); 4.69–4.58 (*m*, 1 H); 4.50–4.37 (*m*, 1 H); 4.22–4.09

(*m*, 1 H); 3.96–3.84 (*m*, 1 H); 3.77 (*s*, 6 H); 2.82–2.55 (*m*, 2 H); 1.74–1.62 (*m*, 2 H); 1.24 (*d*, $J = 6.2$, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 160.8, 160.7; 141.0, 140.9; 138.4, 138.0; 128.4, 128.3; 127.8, 127.7; 127.6; 107.4, 107.3; 98.3, 98.2; 72.5, 72.4; 70.6, 70.3; 69.2; 55.2; 44.4, 44.3; 42.9, 42.5; 19.6, 19.3. ESI-MS: 353 ($[M + Na]^+$).

*(4*R*)-4-(Benzyloxy)-1-(3,5-dimethoxyphenyl)pentan-2-one* (**7**). To stirred soln. of IBX (0.173 g, 0.618 mmol) in dry DMSO (0.5 ml) and dry CH_2Cl_2 (2 ml) was added a soln. of **6** (0.102 g, 0.309 mmol) in dry CH_2Cl_2 (2 ml) at r.t., and the mixture was stirred for 3 h at r.t. After completion of the reaction, the mixture was filtered, diluted with H_2O (5 ml), and extracted into CH_2Cl_2 (2 × 10 ml). The combined org. layer was washed with brine (5 ml), dried (Na_2SO_4), and evaporated to give crude **7**, which was purified by CC (hexanes/AcOEt 9:1) to afford pure **7** (0.090 g, 90%). Colorless liquid. $[\alpha]_D^{34} = -98.3$ ($c = 0.9$, $CHCl_3$). IR (neat): 2931, 1713, 1600, 1461, 1152, 1062, 743, 697. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.32–7.17 (*m*, 5 H); 6.31–6.23 (*m*, 3 H); 4.55–4.35 (*m*, 2 H); 4.06–3.93 (*m*, 1 H); 3.72 (*s*, 6 H); 3.57 (*s*, 2 H); 2.76 (*dd*, $J = 15.8$, 7.3, 1 H); 2.41 (*dd*, $J = 15.8$, 5.2, 1 H); 1.18 (*d*, $J = 6.2$, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 205.9; 161.0; 138.5; 136.0; 128.3; 127.6; 127.5; 107.4; 99.2; 71.7; 70.9; 55.5; 55.1; 48.7; 19.9. ESI-MS: 329 ($[M + H]^+$).

*(4*R*)-1-(3,5-Dimethoxyphenyl)-4-hydroxypentan-2-one* (**8**). To a stirred soln. of **7** (0.070 g, 0.213 mmol) in dry CH_2Cl_2 (5 ml) was added a soln. of $TiCl_4$ (0.47 ml, 0.426 mmol) in anh. CH_2Cl_2 (5 ml) under N_2 at 0°, and the mixture was stirred at this temp. for 2 h. On completion (TLC), the mixture was diluted with H_2O (10 ml) and extracted with CH_2Cl_2 (2 × 10 ml). The combined org. extracts were washed with aq. $NaHCO_3$ soln. and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude residue was purified by CC (hexanes/AcOEt 7:3) to afford **8** (0.040 g, 80%). Viscous liquid. $[\alpha]_D^{25} = +2.00$ ($c = 0.1$, MeOH). IR (neat): 2921, 2851, 1716, 1598, 1461, 1218, 772, 670. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.36 (*t*, $J = 2.0$, 1 H); 6.32 (*d*, $J = 2.0$, 2 H); 4.21–4.13 (*m*, 1 H); 3.77 (*s*, 6 H); 3.60 (*s*, 2 H); 2.64–2.49 (*m*, 2 H); 1.14 (*d*, $J = 6.0$, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 208.9; 161.0; 135.6; 107.4; 99.1; 63.8; 55.2; 50.9; 49.5; 22.3. ESI-MS: 239 ($[M + H]^+$).

*(4*R*)-1-(3,5-Dihydroxyphenyl)-4-hydroxypentan-2-one* (**1**) [4]. I_2 (216 mg, 1.701 mmol) was added to a mixture of Al powder (31 mg, 1.148 mmol) in anh. benzene (3 ml). The mixture was heated at reflux for 0.5 h and cooled to 0°, then Bu_4NI (2 mg) and **8** (15 mg, 0.063 mmol) in benzene (2 ml) were added. The mixture was stirred for 15 min at 0°, then the reaction was quenched with 2N HCl (5 ml) at 0°, and the mixture extracted with AcOEt (3 × 10 ml). The org. phase was washed with sat. aq. $NaHCO_3$ soln. (3 ml) and brine (5 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by CC (hexanes/AcOEt 3:7) to afford **1** (9.9 mg, 75%). Colorless solid. $[\alpha]_D^{25} = +13.2$ ($c = 0.22$, MeOH). IR (KBr): 3496, 3262, 2924, 1517, 1154, 996, 770. ^{1}H-NMR (300 MHz, CD_3OD): 6.16 (*t*, $J = 2.0$, 1 H); 6.80 (*d*, $J = 2.0$, 2 H); 4.19–4.14 (*m*, 1 H); 3.56 (*s*, 2 H); 2.65–2.51 (*m*, 2 H); 1.27 (*d*, $J = 6.1$, 3 H). ^{13}C-NMR (75 MHz, CD_3OD): 209.8; 159.8; 137.6; 109.1; 102.3; 65.0; 51.6; 51.4; 23.4. HR-ESI-MS: 211.0974 ($[M + H]^+$, $C_{11}H_{15}O_4^+$; calc. 211.0965).

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Received Mai 3, 2014