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Asymmetric dihydroxylation and regioselective C-3 indole coupling routes to the anticoccidial antibiotic (+)-diolmycin A2

Rodney A. Fernandes, Mandar S. Bodas and Pradeep Kumar*

Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune 411008, India

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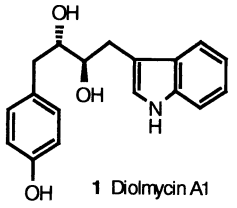
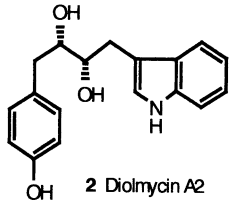
Abstract—A highly enantioselective synthesis of (+)-diolmycin A2 starting from 4-hydroxybenzaldehyde and employing the Sharpless asymmetric dihydroxylation and CH_3NO_2 solvent assisted regioselective C-3 coupling of indole as the key steps is described.

1. Introduction

With a search for new anticoccidial agents, Omura and co-workers isolated diolmycins A1, A2, B1 and B2 (**1**–**4**) from a fermentation broth of *Streptomyces* sp. WK-2955.[1] Diolmycin A1 showed anticoccidial activity at concentrations ranging above 0.02 μg/mL and diolmycin A2 at 0.2 μg/mL. Diolmycins B1 and B2 showed poor anticoccidial activity in comparison.[2] The coupling constants between the vicinal protons of the two chiral carbons of **1** and **2** were 5.4 and 2.2 Hz, respectively, suggesting an *erythro* configuration for **1** and a *threo* configuration for **2**. Omura et al.[2] reported the first total synthesis of the racemate, which further confirmed the presence of an *erythro* vicinal diol moiety in **1**. Subsequently an asymmetric synthesis of diolmycin A1 **1** was also reported by Omura et al.[3] by exploiting the principle of kinetic resolution of an allylic alcohol via the Sharpless asymmetric epoxidation. The use of chiral pool material, such as L-tartaric acid for the preparation of diolmycin A2 has recently been reported by Kotsuki et al.[4] The key step in this report involves ytterbium(III) trifluoromethanesulfonate catalyzed high-pressure ring opening of an intermediate epoxide with indole. As part of our research program aimed at developing enantioselective synthesis of naturally occurring lactones[5a,b] and amino alcohols,[5c–e] the Sharpless asymmetric dihydroxylation[6] (SAD) and subsequent transformation of diols via cyclic sulfites/sulfates were envisaged as powerful tools offering considerable opportunities for synthetic manipulations. Herein we report a new and highly enantiocontrolled total synthesis of (+)-diolmycin A2 **2** employing the SAD and CH_3NO_2 solvent assisted regioselective C-3 coupling of indole as the key steps.



1 Diolmycin A1



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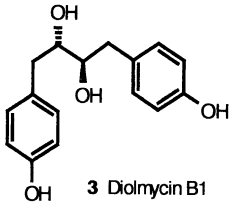
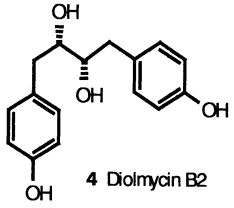


3 Diolmycin B1



4 Diolmycin B2

2. Results and discussion

Scheme 1 summarizes the synthesis of the intermediate epoxide **12**, from the commercially available 4-hydroxybenzaldehyde **5**. The hydroxyl protection of **5** with benzyl bromide in DMF gave **6** in essentially quantitative yield. The subsequent Wittig olefination furnished **7**[7] in 78% yield, which on hydroboration oxidation afforded the alcohol **8** in 88% yield. Compound **8** was subjected to Swern oxidation to furnish the corresponding aldehyde which on treatment with (ethoxycarbonylmethylene) triphenylphosphorane gave the *trans* Wittig product **9**[8] in 72% yield. DIBAL-H reduction of **9** (93% yield) followed by NBS bromination gave the allylic bromide **11** in 83% yield. Compound **11** was treated with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of 1,4-bis(dihydroquinin-9-*O*-yl)-phthalazine [$(DHQ)_2PHAL$] ligand under the SAD reaction conditions[6] to give the diol, which on subsequent treatment with K_2CO_3 in dry

Keywords: asymmetric synthesis; dihydroxylation; epoxide; regioselective alkylation; indole; anticoccidial antibiotic.

* Corresponding author. Tel.: +91-20-5893300; fax: +91-20-5893614; e-mail: tripathi@dalton.ncl.res.in

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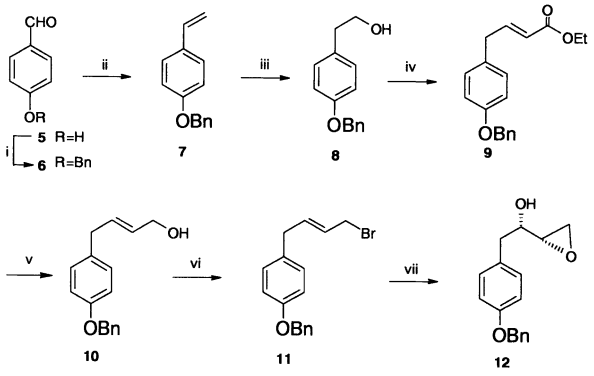
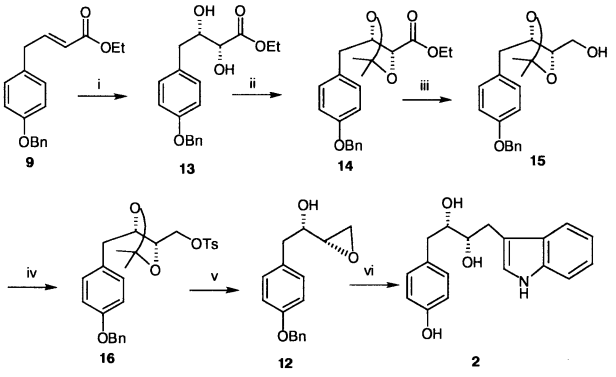


Scheme 1. (i) BnBr, K_2CO_3, DMF, TBAI (cat), rt, 24 h, (99%); (ii) $Ph_3P{=}CH_2$, THF, rt, 24 h, (78%); (iii) (a) BH_3·DMS, THF, rt, 4 h, (b) NaOH in EtOH/H_2O (2:1), then 30% aq. H_2O_2, 0°C, 3 h (88%); (iv) (a) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, Et_3N, −60°C, 1 h, (b) $Ph_3P{=}CHCO_2Et$, THF, rt, 24 h (72%); (v) DIBAL-H, Et_2O, 0°C, 1 h—rt, 30 min (93%); (iv) NBS, Ph_3P, CH_2Cl_2, −30°C, 4 h (83%); (vii) (a) $K_3Fe(CN)_6$, K_2CO_3, $(DHQ)_2PHAL$, OsO_4 (cat), $NaHCO_3$, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), 0°C, 18 h, (b) MeOH, K_2CO_3, rt, 10 h (73%).

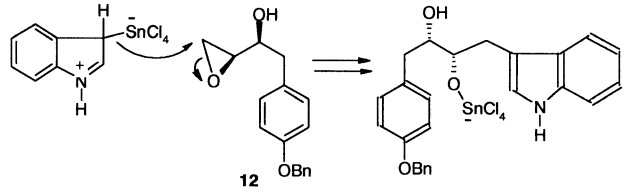
methanol afforded the epoxide **12**[9] $[\alpha]_D^{20}=+11.07$ (c=1, $CHCl_3$) [lit. +11.2 (c=0.98, $CHCl_3$)[4]] in 73% yield.

Alternatively the epoxide **12** could be obtained from **9** following the reaction steps as shown in Scheme 2. The dihydroxylation of olefin **9** using the SAD procedure gave the diol **13** $[\alpha]_D^{20}=-29.8$ (c=1, $CHCl_3$) in 91% yield. The dihydroxyl protection of **13** was carried out with 2,2-dimethoxypropane in presence of catalytic amount of *p*-TSA to give the acetonide **14** in quantitative yield. Ester group reduction of **14** with lithium aluminium hydride gave the alcohol **15**[9] $[\alpha]_D^{20}=-11.00$ (c=1.2, $CHCl_3$) in 97% yield. The primary hydroxyl group was then converted into the tosylate **16** in 90% yield. Deprotection of the acetonide was effected with 3N HCl in MeOH followed by subsequent treatment with K_2CO_3 in dry MeOH to furnish the epoxide **12**[9] $[\alpha]_D^{20}=+11.12$ (c=1, $CHCl_3$) in 85% yield.

With the enantiomerically pure epoxide **12** in hand, we then proceeded for the total synthesis of diolmycin A2 **2**



Scheme 2. (i) $K_3Fe(CN)_6$, K_2CO_3, $(DHQ)_2PHAL$, OsO_4 (cat), $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), 0°C, 24 h (91%); (ii) 2,2-DMP, *p*-TSA (cat), $(CH_3)_2CO$, rt, overnight (99%); (iii) $LiAlH_4$, Et_2O, 0°C to rt, overnight (97%); (iv) *p*-TSCl, Pyridine, CH_2Cl_2, rt, 12 h (90%); (v) (a) 3N HCl, MeOH, rt, 12 h, (b) K_2CO_3, MeOH, rt, 10 h (85%); (vi) (a) Indole, $SnCl_4$, CH_2Cl_2/CH_3NO_2 (4:3), 0°C—rt, 12 h, (b) 10% Pd–C, EtOH, H_2, rt, 18 h, (53%).



Scheme 3. Alkylation of the complex indole–$SnCl_4$.

employing the regioselective C-3 coupling reaction with indole as the key step. Although, the 3-position is the most reactive site for electrophilic attack, low yields are usually encountered due to the competitive formation of 1-alkylated and/or 1,3-dialkylated products often associated with self polymerization of indole as a side product.[10] However, a recent report about an improved synthesis of 3-acylindoles by Ottoni et al.[11] prompted us to explore the Lewis acid catalyzed regioselective C-3 coupling of indole with epoxide **12** for diolmycin synthesis. It has been observed that in C-3 acylation of indole using Lewis acid, the addition of CH_3NO_2 as co-solvent greatly increases the solubility of the solid indole–Lewis acid complex in the reaction media, shortening the reaction time and raising the yields significantly.[11] Indeed following the above procedure, the treatment of epoxide **12** with indole in a mixture of CH_2Cl_2 and CH_3NO_2 (4:3) in the presence of $SnCl_4$ as the Lewis acid gave the C-3 coupled product in good yield. A probable mechanism of this reaction is depicted in Scheme 3. Presumably the Lewis acid $SnCl_4$ complexes at 3-position of indole, being the most reactive site for electrophilic attack. The intermediate thus formed would then collapse in a nucleophilic attack toward the epoxide eventually leading to the C-3 coupled indole. The subsequent deprotection of benzyl group with 10% Pd–C in EtOH under H_2 atmosphere furnished diolmycin A2 **2** $[\alpha]_D^{20}=+46.32$ (c=0.2, MeOH) [lit. +49.2 (c=0.24, MeOH)[4]] in 53% yield.

3. Conclusion

In conclusion a highly enantioselective synthesis of (+)-diolmycin A2 **2** from readily accessible starting material by a simple and operationally feasible procedure was achieved. The versatility of the route employed lies in the fact that all the diolmycins A1, A2, B1, B2 can be synthesized by employing either α or β-dihydroxylation and using either *cis* or *trans* olefin for step (vii) and (i) in Schemes 1 and 2, respectively.

4. Experimental

4.1. General information

Solvents were purified and dried by standard procedures before use; petroleum ether of boiling range 60–80°C was used. Melting points are uncorrected. Optical rotations were measured using sodium D line on a JASCO P-1020 microprocessor based polarimeter. Infrared spectra were recorded on ATI MATTSON RS-1 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on Bruker AC-200 spectrometer. Mass spectra were obtained with a TSQ 70,

Finningen MAT mass spectrometer. Elemental analyses were carried on a Carlo Erba CHNS–O analyzer.

4.1.1. 4-Benzyloxybenzaldehyde (6). To a stirred suspension of K_2CO_3 (34 g, 246 mmol) in dry DMF (200 mL) at room temperature was added 4-hydroxybenzaldehyde **5** (20 g, 163.93 mmol) and TBAI (cat). The mixture was stirred for 30 min and then benzylbromide (28.5 g, 166.6 mmol) was added. The reaction mixture was stirred at room temperature for 24 h and then quenched with water and extracted with EtOAc (3×100 mL). The combined organic extracts were washed with water (2×100 mL), brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (85:15) as eluent gave **6** (34.41 g, 99%) as a white solid; mp 78–79°C; IR ($CHCl_3$): ν_{max} 2728, 1690, 1601, 1578, 832, 758 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.16 (s, 2H), 7.1 (d, J=8 Hz, 2H), 7.3 (m, 5H), 7.85 (d, J=8 Hz, 2H), 9.9 (s, 1H); MS (EI), *m/e* (%): 212 [M^+] (4.3), 91 (100), 65 (9.5); Anal. Calcd for $C_{14}H_{12}O_2$ (212.3): C, 79.23; H, 5.69. Found: C, 79.18; H, 5.74.

4.1.2. 4-Benzyloxystyrene (7). To a mixture of triphenylmethylphosphonium iodide (24 g, 59.35 mmol) and sodium amide (3.48 g, 89.23 mmol) was added dry THF (150 mL) and stirred for 12 h at room temperature. The yellow supernatant liquid was added through a syringe to the solution of **6** (10 g, 47.11 mmol) in dry THF (20 mL). The reaction mixture was stirred for 24 h at room temperature and then quenched with 2% aq. HCl and extracted with EtOAc (3×100 mL). The combined organic extracts were washed with water (2×100 mL), brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (95:5) as eluent gave **7** (7.72 g, 78%) as a white solid; mp 71–72°C (lit. 68–69°C[12]); IR ($CHCl_3$): ν_{max} 1606, 1510, 836, 759 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.09 (s, 2H), 5.59 (s, 1H), 5.68 (s, 1H), 6.7 (m, 1H), 6.95 (d, J=8 Hz, 2H), 7.35–7.44 (m, 7H); ^{13}C NMR ($CDCl_3$): δ 69.94, 111.6, 114.9, 127.36, 127.84, 128.46, 130.7, 136.18, 136.95, 158.57; MS (EI), *m/e* (%): 210 [M^+] (38), 91 (100), 65 (3.6); Anal. Calcd for $C_{15}H_{14}O$ (210.26): C, 85.67; H, 6.71. Found: C, 85.49; H, 6.86.

4.1.3. 2-(4′-Benzyloxyphenyl) ethanol (8). To a solution of **7** (10 g, 47.56 mmol) in dry THF (100 mL) at 0°C under argon atmosphere was added BH_3.DMS (24 mL, 48 mmol, 2 M solution in THF) and the reaction mixture was allowed to warm to room temperature and stirred for 4 h. The reaction flask was cooled to 0°C and then a solution of NaOH (24 g, 96 mmol) in EtOH/H_2O (2:1, 60 mL), followed by H_2O_2 (16.4 mL, 144 mmol, 30% w/v solution in water) were added dropwise over 30 min. It was then allowed to stir at room temperature for 3 h. The product was taken up in EtOAc and the aqueous layer extracted with EtOAc (3×25 mL). The combined organic layers were washed with brine, water, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) as eluent gave **8** (9.55 g, 88%) as a white solid; mp 85–86°C; IR ($CHCl_3$): ν_{max} 3402, 1611, 1511, 824, 757 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.72 (br s, 1H), 2.82 (t, J=6 Hz, 2H), 3.83 (t, J=6 Hz, 2H), 5.07 (s, 2H), 6.95 (d, J=8 Hz, 2H), 7.2 (d, J=8 Hz, 2H), 7.3–7.4 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 38.12, 63.45, 69.95, 114.91, 127.26, 127.70, 128.36, 129.79, 130.86, 137.07, 157.36; MS (EI), *m/e* (%): 228 [M^+] (29), 210 (1.2), 107 (6.6), 91 (100), 65 (5.4); Anal. Calcd for $C_{15}H_{16}O_2$ (228.28): C, 78.91; H, 7.06. Found: C, 79.12; H, 6.95.

4.1.4. Ethyl-4-(4′-benzyloxyphenyl)but-2-enoate (9). To a solution of oxalyl chloride (5.48 g, 46 mmol) in dry CH_2Cl_2 (50 mL) at −78°C was added dropwise DMSO (6.53 mL, 91.98 mmol) in CH_2Cl_2 (5 mL) over 15 min. The reaction mixture was stirred for 30 min and a solution of **8** (7 g, 30.66 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 15 min. The reaction mixture was stirred for 30 min at −78°C and 30 min at −60°C and then Et_3N (15 mL) in CH_2Cl_2 (10 mL) was added dropwise and stirred for 1 h. The reaction mixture was poured into 10% aq. HCl (100 mL) and the organic layer separated. The aqueous layer was extracted with EtOAc (3×50 mL) and the combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated to give the crude aldehyde. This was used for the next step without further purification.

To a solution of (ethoxycarbonylmethylene)triphenyl phosphorane (10.5 g, 30.14 mmol) in dry THF (30 mL) was added a solution of the above aldehyde in dry THF (10 mL). The reaction mixture was stirred at room temperature for 24 h. It was then concentrated and purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to give **9** (6.54 g, 72%) as a pale yellow oil; IR (neat): ν_{max} 1713, 1651, 1609, 1509, 910, 733 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.30 (t, J=8 Hz, 3H), 3.50 (d, J=6 Hz, 2H), 4.23 (q, J=8 Hz, 2H), 5.07 (s, 2H), 5.85 (dt, J=16, 2 Hz, 1H), 6.98 (d, J=8 Hz, 2H), 7.14 (m, 3H), 7.4 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 14.07, 37.41, 59.98, 70.02, 115.12, 122.10, 127.25, 127.73, 128.39, 129.64, 130.00, 137.10, 147.35, 157.65, 159.52, 166.25; MS (EI), *m/e* (%): 296 [M^+] (13.7), 251 (1.8), 127 (10.7), 91 (100), 65 (2.9); Anal. Calcd for $C_{19}H_{20}O_3$ (296.35): C, 77.00; H, 6.80. Found: C, 77.02; H, 6.72.

4.1.5. 4-(4′-Benzyloxyphenyl)-but-2-ene-1-ol (10). To a stirred solution of **9** (1.5 g, 5.06 mmol) in dry ether (75 mL) at 0°C was added DIBAL-H (12.7 mL, 12.7 mmol, 1 M solution in toluene) dropwise over 15 min. The reaction mixture was stirred for 1 h at 0°C and 30 min at room temperature. It was cooled again to 0°C and quenched with 2N HCl. The resulting gel was dissolved by adding 6N HCl. The organic layer was separated and aqueous layer extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave **10** (1.2 g, 93%) as a colorless liquid; IR (neat): ν_{max} 3339, 1611, 1600, 1510, 811, 755 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.15 (br s, 1H), 3.35 (d, J=6 Hz, 2H), 4.15 (m, 2H), 5.06 (s, 2H), 5.62–5.93 (m, 2H), 6.95 (d, J=8 Hz, 2H), 7.31 (d, J=8 Hz, 2H), 7.4–7.48 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 37.52, 62.96, 69.98, 114.90, 127.17, 127.62, 128.28, 128.31, 130.08, 131.29, 132.36, 137.14, 157.17; MS (EI), *m/e* (%): 254 [M^+] (7.4), 228 (1.9), 91 (100), 77 (6.0), 65 (20.7); Anal. Calcd for $C_{17}H_{18}O_2$ (254.3): C, 80.29; H, 7.13. Found: C, 80.52; H, 7.01.

4.1.6. 4-(4′-Benzyloxyphenyl)-1-bromo-but-2-ene (11). To a solution of **10** (1 g, 3.93 mmol) in dry CH_2Cl_2 (15 mL) cooled at −30°C was added Ph_3P (1.237 g, 4.72 mmol) followed by NBS (0.84 g, 4.72 mmol). After 4 h of stirring, the reaction mixture was diluted with water (10 mL). The organic layer was separated and aqueous layer extracted with CH_2Cl_2 (2×15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (24:1) gave **11** (1.03 g, 83%) as a pale yellow liquid; IR (neat): ν_{max} 1608, 1508, 1454, 825, 736, 695 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.39 (d, J=7 Hz, 2H), 4.00 (d, J=8 Hz, 2H), 5.07 (s, 2H), 5.8–5.97 (m, 2H), 6.95 (d, J=8 Hz, 2H), 7.14 (d, J=8 Hz, 2H), 7.38–7.48 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 37.46, 53.45, 70.03, 115.05, 127.37, 127.77, 128.47, 129.24, 129.5, 131.63, 134.10, 135.01, 137.26, 157.47; MS (EI), *m/e* (%): 318 [M^++1] (6.0), 317 [M^+] (5.0), 292 (1.5), 236 (5.0), 196 (1.6), 91 (100), 77 (5.0), 65 (24.4), 57 (8.8); Anal. Calcd for $C_{17}H_{17}BrO$ (317.3): C, 64.35; H, 5.40. Found: C, 64.50; H, 5.72.

4.1.7. (2*S*,3*S*)-4-(4′-Benzyloxyphenyl)-1,2-epoxy-3-hydroxybutane (12). To a mixture of $K_3Fe(CN)_6$ (1.55 g, 4.727 mmol), K_2CO_3 (0.653 g, 4.727 mmol), $(DHQ)_2PHAL$ (12.27 mg, 15.75 μmol, 1 mol%) and $NaHCO_3$ (0.4 g, 4.727 mmol) in *t*-BuOH/H_2O (1:1, 20 mL) at 0°C was added osmium tetroxide (79 μL, 0.1 M solution in toluene, 0.5 mol%), followed by methanesulfonamide (0.150 g, 1.575 mmol). After stirring for 2 min at 0°C, the allylic bromide **11** (0.5 g, 1.575 mmol) was added in one portion. The reaction mixture was stirred at 0°C for 18 h and then quenched with solid sodium sulfite (1 g). The stirring was continued for additional 15 min and then the solution was extracted with EtOAc (3×20 mL). The combined organic phases were washed with 10% KOH and brine, dried (Na_2SO_4) and concentrated. To the residue was added dry MeOH (10 mL) and K_2CO_3 (0.262 g, 1.9 mmol) and the mixture stirred at room temperature for 10 h. Water (20 mL) and EtOAc (20 mL) were added. The organic layer was separated and aqueous layer extracted with EtOAc (2×20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (4:1) as eluent gave **12** (0.310 g, 73%) as a white solid; mp 67–69°C; $[\alpha]_D^{20}$=+11.07 (c=1, $CHCl_3$) (lit. +11.2 (c=0.98, $CHCl_3$)[4]); IR ($CHCl_3$): ν_{max} 3443, 1611, 1511, 1177, 1025, 759, 697, 668 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.09 (s, 1H), 2.62–2.65 (dd, J=2, 4 Hz, 1H), 2.77 (t, J=4 Hz, 1H), 2.86–2.89 (dd, J=4, 2 Hz, 2H), 3.04 (m, 1H), 3.66 (m, 1H), 5.06 (s, 2H), 6.96 (d, J=8 Hz, 2H), 7.18 (d, J=8 Hz, 2H), 7.37–7.48 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 40.02, 44.87, 54.61, 70.09, 72.41, 115.04, 127.32, 127.80, 128.42, 129.60, 130.26, 137.14, 157.68; MS (EI), *m/e* (%): 270 [M^+] (10.8), 197 (10.2), 107 (3.4), 91 (100), 77 (5.4), 65 (21.6); Anal. Calcd for $C_{17}H_{18}O_3$ (270.3): C, 75.53; H, 6.71. Found: C, 75.63; H, 6.98.

4.1.8. Ethyl-(2*R*,3*S*)-4-(4′-benzyloxyphenyl)-2,3-dihydroxybutanoate (13). To a mixture of $K_3Fe(CN)_6$ (9.93 g, 30.4 mmol), K_2CO_3 (4.2 g, 30.4 mmol) and $(DHQ)_2PHAL$ (78.9 mg, 101 μmol, 1 mol%) in *t*-BuOH/H_2O (1:1, 120 mL) at 0°C was added osmium tetroxide (411 μL, 0.1 M solution in toluene, 0.4 mol%), followed by methanesulfonamide (0.964 g, 10.12 mmol). After stirring for 5 min at 0°C, the olefin **9** (3 g, 10.13 mmol) was added in one portion. The reaction mixture was stirred at 0°C for 24 h and then quenched with solid Na_2SO_3 (5 g). The stirring was continued for an additional 45 min and then the solution was extracted with EtOAc (5×30 mL). The combined organic layers were washed with 10% KOH, brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:3) as eluent gave **13** (3.05 g, 91%) as a white solid; mp 104–106°C; $[\alpha]_D^{20}$=−29.8 (c=1, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3488, 1732, 1611, 1514, 757 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.30 (t, J=7 Hz, 3H), 2.70 (br s, 2H), 2.90 (d, J=8 Hz, 2H), 4.12 (m, 2H), 4.3 (q, J=7 Hz, 2H), 5.06 (s, 2H), 6.95 (d, J=8 Hz, 2H), 7.22 (d, J=8 Hz, 2H), 7.4 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 13.9, 38.9, 61.6, 69.8, 71.9, 73.5, 114.86, 127.17, 127.65, 128.28, 129.89, 130.23, 136.99, 157.43, 159.41, 173.38; MS (EI), *m/e* (%): 330 [M^+] (14), 312 (9), 239 (25.6), 197 (14), 107 (16.6), 91 (100), 65 (2.5); Anal. Calcd for $C_{19}H_{22}O_5$ (330.36): C, 69.07; H, 6.71. Found: C, 68.85; H, 6.82.

4.1.9. Ethyl-(2*R*,3*S*)-4-(4′-benzyloxyphenyl)-2,3-*O*-isopropylidenedioxybutanoate (14). To a solution of **13** (2.5 g, 7.56 mmol) and *p*-TSA (cat) in dry acetone (75 mL) was added 2,2-dimethoxypropane (1.2 g, 1.4 mL, 11.35 mmol) and stirred overnight. A pinch of $NaHCO_3$ was added and stirred for 10 min. The reaction mixture was filtered through a short pad of neutral alumina and concentrated. Column chromatography of the crude product using petroleum ether/EtOAc as eluent (9:1) gave **14** (2.77 g, 99%) as a colorless oil; $[\alpha]_D^{20}$=−17.74 (c=1, $CHCl_3$); IR (neat): ν_{max} 1752, 1611, 1512, 1382, 1297, 1024, 757 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.27 (t, J=7 Hz, 3H), 1.44 (s, 3H), 1.48 (s, 3H), 2.98–3.10 (m, 2H), 4.15–4.22 (m, 3H), 4.38 (m, 1H), 5.06 (s, 2H), 6.95 (d, J=8 Hz, 2H), 7.30 (d, J=8 Hz, 2H), 7.47 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 13.7, 25.47, 26.8, 38.0, 60.6, 69.65, 77.5, 79.35, 110.49, 114.5, 126.95, 127.39, 128.06, 128.9, 130.26, 136.95, 137.03, 157.43, 170; MS (EI), *m/e* (%): 370 [M^+] (9), 312 (6.4), 239 (12.8), 173 (23), 155 (15.4), 91 (100), 65 (3.8); Anal. Calcd for $C_{22}H_{26}O_5$ (370.42): C, 71.33; H, 7.07. Found: C, 71.52; H, 6.97.

4.1.10. (2*S*,3*S*)-4-(4′-Benzyloxyphenyl)-2,3-*O*-isopropylidenedioxy-butan-1-ol (15). To a stirred suspension of $LiAlH_4$ (307 mg, 8.1 mmol) in dry ether (100 mL) at 0°C was added **14** (2 g, 5.4 mmol) in ether (10 mL) dropwise. The reaction mixture was warmed to room temperature and stirred overnight. Excess $LiAlH_4$ was destroyed by slow addition of 5% aq. NaOH followed by addition of EtOAc (100 mL). The white cake was filtered and washed with EtOAc (3×50 mL) and MeOH (2×20 mL). The filtrate was dried (K_2CO_3) and concentrated. Column chromatography of the crude product using petroleum ether/EtOAc (4:1) gave **15** (1.72 g, 97%) as a white solid; mp 58–59°C; $[\alpha]_D^{20}$=−11.00 (c=1.2, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3468, 1610, 1510, 1216, 1038, 763 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.43 (s, 6H), 2.8 (m, 1H), 2.99 (m, 1H), 3.15 (br s, 1H), 3.35 (m, 1H), 3.5 (m, 1H), 3.83 (m, 1H), 4.12 (m, 1H), 5.05 (s, 2H), 6.95 (d, J=8 Hz, 2H), 7.18 (d, J=8 Hz, 2H), 7.4 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 26.72, 26.94, 38.15, 61.86, 69.69, 77.34, 80.90, 108.35, 114.64, 126.99, 127.43,

128.09, 129.31, 129.37, 136.92, 157.32; MS (EI), *m/e* (%): 328 [M^+] (6.6), 313 [M^+-15] (2.4), 198 (4.2), 131 (55.4), 91 (100), 65 (3.0), 58 (10.2); Anal. Calcd for $C_{20}H_{24}O_4$ (328.4): C, 73.14; H, 7.36. Found: C, 73.18; H, 7.45.

4.1.11. (2*S*,3*S*)-4-(4′-Benzyloxyphenyl)-2,3-*O*-isopropylidenedioxy-1-*p*-toluenesulfonyloxybutane (16). To a solution of **15** (0.5 g, 1.52 mmol) in dry CH_2Cl_2 (10 mL) was added pyridine (1 mL) followed by *p*-TsCl (435 mg, 2.28 mmol) and stirred at room temperature for 12 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with water (2×20 mL), brine, dried (Na_2SO_4) and concentrated. Column chromatography of the crude product using petroleum ether/EtOAc (9:1) gave **16** (0.66 g, 90%) as a white solid; mp 83–84°C (lit. 83.5–84);[4] $[\alpha]_D^{20}=-19.62$ (c=1, $CHCl_3$) [lit. −19.7 (c=1.07, $CHCl_3$)[4]]; IR ($CHCl_3$): ν_{max} 1611, 1512, 1370, 1241, 1217, 1177, 1020, 982, 830, 815, 757, 668 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.33 (s, 3H), 1.37 (s, 3H), 2.44 (s, 3H), 2.7–3.01 (m, 2H), 3.8–4.06 (m, 4H), 5.07 (s, 2H), 6.9 (d, J=8 Hz, 2H), 7.10 (d, J=8 Hz, 2H), 7.3–7.45 (m, 7H), 7.75 (d, J=8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 20.91, 26.31, 26.8, 37.82, 68.88, 69.57, 77.40, 77.62, 108.91, 114.6, 126.88, 127.36, 128.02, 128.72, 129.38, 129.93, 132.76, 136.88, 144.34, 157.35; MS (EI), *m/e* (%): 482 [M^+] (12.7), 467 [M^+-15] (4.0), 285 (8.7), 227 (27.0), 91 (100), 65 (12.7); Anal. Calcd for $C_{27}H_{30}O_6S$ (482.51): C, 67.21; H, 6.27. Found: C, 67.52; H, 6.05.

4.2. Epoxide 12 from tosylate 16

To a solution of tosylate **16** (0.5 g, 1.03 mmol) in MeOH (15 mL) was added 3N HCl (4 mL) and stirred at room temperature for 12 h. A pinch of $NaHCO_3$ was added and stirred for 10 min. The reaction mixture was filtered through a pad of neutral alumina and concentrated. The residue was dissolved in dry MeOH and K_2CO_3 (0.151 g, 1.1 mmol) was added and stirred for 10 h at room temperature. Water (20 mL) and EtOAc (20 mL) were added and the organic layer was separated and aqueous layer extracted with EtOAc (2×20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (4:1) as eluent gave **12** (0.238 g, 85%) as a white solid; mp 67–69°C; $[\alpha]_D^{20}=+11.12$ (c=1, $CHCl_3$).

4.3. Diolmycin A2 (2)

To a stirring solution of indole (21 mg, 179 μmol) in dry CH_2Cl_2 (4 mL) under argon atmosphere at 0°C was added $SnCl_4$ (25 μL, 207 μmol). The icebath was removed and the reaction mixture was stirred for 45 min at room temperature. The epoxide **12** (40 mg, 148 μmol) was added in small portions to the suspension, followed by CH_3NO_2 (3 mL). The mixture was stirred for 10 h at room temperature and then quenched with cold water (10 mL) and EtOAc (20 mL). The mixture was filtered and the organic layer was separated. The aqueous layer was extracted with EtOAc (2×15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to a syrupy liquid. This was dissolved in dry EtOH (10 mL) and 10% Pd–C (25 mg) was added carefully. The reaction mixture was stirred under an atmosphere of H_2 filled in a balloon for 18 h at room temperature. The mixture was filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using $CHCl_3$/MeOH (5:1) as eluent to give diolmycin A2 **2** (21 mg, 53%) as a thick syrupy liquid; $[\alpha]_D^{20}=+46.32$ (c=0.2, MeOH) [lit. +49.2 (c=0.24, MeOH)[4]]. Spectroscopic data are in full agreement with those reported.[4]

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