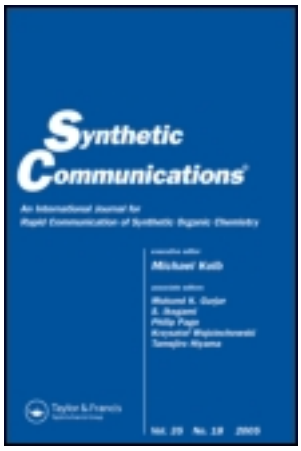

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A Total Synthesis of the Antibiotic DB-2073

Adrián Covarrubias-Zúñiga [a] , José G. Avila-Zárraga [b] & David Arias Salas [a]

[a] Instituto de Química, Universidad Nacional Autónoma de México, Ciudad Universitaria, Coyoacán, México

[b] Facultad de Química, Universidad Nacional Autónoma de México, Ciudad Universitaria, Coyoacán, México

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A Total Synthesis of the Antibiotic DB-2073

Adrián Covarrubias-Zúñiga,[1,*] José G. Avila-Zárraga,[2] and David Arias Salas[1]

[1]Instituto de Química, and [2]Facultad de Química,
Universidad Nacional Autónoma de México,
Ciudad Universitaria, Coyoacán, México

ABSTRACT

A convergent aromatic annulation strategy based on the Michael addition of the dimethyl-1,3-acetonedicarboxylate **1** anion to 2-hexynal **2**, followed by a regiocontrolled Dieckmann-type cyclization, has been applied to a total synthesis of the antibiotic, DB-2073 **I.** This tandem annulation reaction generates the fully substituted aromatic intermediate **3**, which was transformed by a five-step sequence to **I**.

*Correspondence: Adrián Covarrubias-Zúñiga, Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, Coyoacán 04510, México; E-mail: adriancz@servidor.unam.mx.

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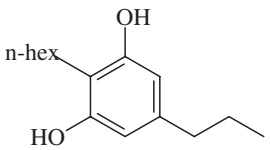
In recent years we have developed a total and a formal synthesis of mycophenolic acid [Covarrubias-Zúñiga, A.; González-Lucas, A. Tetrahedron Lett. **1998**, *39*, 2881; Covarrubias-Zúñiga, A.; Díaz-Domínguez, J.; Olguín-Uribe, J.S. Synthetic Communications **2001**, *31*, 1373.] using as key step tandem reactions based on Michael addition and intramolecular Dieckmann-cyclization; In this article we utilize this synthetic approach for the total synthesis of the resorcinol DB-2073 **I**. This tetrasubstituted resorcinol was isolated and purified from *pseudomonas B-9004*, showing antibacterial and antifungal activities [Kanda, N.; Ishizaki, N.I.; Oshima, M.; Handa, A.; Kitahara, T.J. Antibiotics **1975**, *28*, 935.]. The molecular formula of DB-2073 was established by spectroscopic methods [Kitahara, T.; Kanda, N. J. Antibiotics **1975**, *28*, 943.], as 2-hexyl-5-propyl-resorcinol **I**.

DB-2073 was first synthetized by Danheiser[5] using an elegant regiocontrolled annulation approach to highly substituted resorcinols based on a thermal-photochemical step combination of alkynyl ethers and vinyl ketenes derived from cyclobutenones. A second synthesis has been developed by Kotnis starting from 5-propyl-1,3-cyclohexanedione with iodine in refluxing methanol.[6]

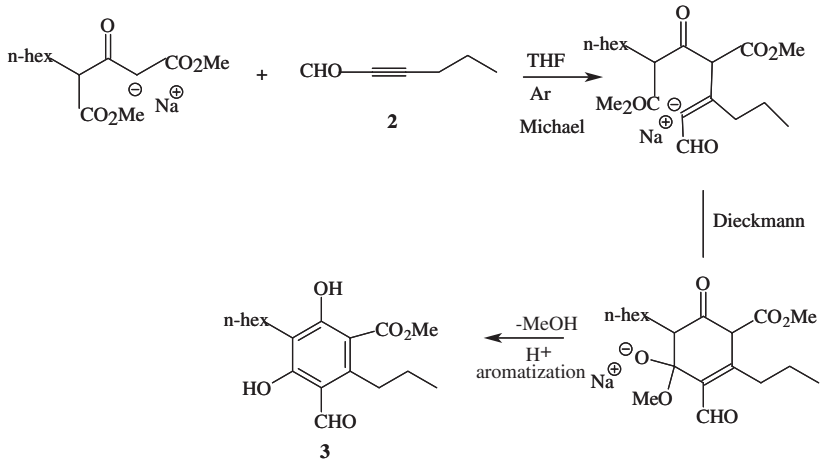


I

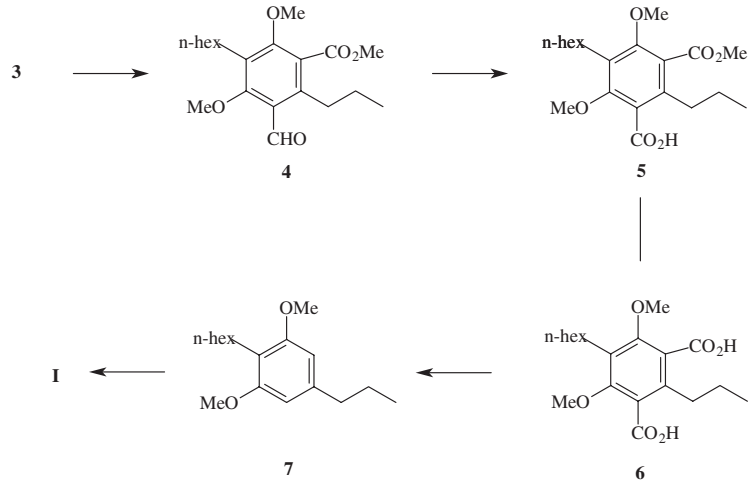
RESULTS AND DISCUSSION

Our approach involves the Michael addition of the 2-hexyl-1,3-dimethyl-acetone-dicarboxylate **1** anion to 2-hexynal (**2**) and intramolecular Dieckmann-cyclization followed by spontaneous aromatization (Sch. 1) to produce the hexasubstituted resorcinol (**3**) in 25% yield.

Compound **1** was prepared in three steps: formation of the enol methyl ether of 1,3-dimethyl acetone dicarboxylate, alkylation with



Scheme 1.



Scheme 2.

1-iodohexane in dry DMF and hydrolysis with a mixture of HCO_2H-hexane.[7] Aldeyde **2** was prepared according to the method reported by Brandsma.[8] With compound **3** at hand, the completion of this synthesis was accomplished by employing the five-step sequence shown in Sch. 2. Methylation of resorcinol **3** with NaH and MeI in dry DMF gave

compound **4** in 90% yield and the subsequent oxidation of the formyl group with Jones reagent[9] in acetone gave acid **5** in 82% yield presumably for steric reasons it was necessary to modify the standard conditions of Jones oxidation from 0°C or room temperature to 40°C. **5** was hydrolyzed under vigorous conditions with KOH in an ethylene glycol–water mixture (6:4) to give compound **6** in 90% yield. The diacid **6** was decarboxylated with CuO/quinoline[10] at 125°C over argon atmosphere in 54% yield. Finally the demethylation was accomplished employing trimethylsilyl iodide[11] in acetonitrile under reflux, furnished DB-2073 as colorless crystals, m.p. 86–88°C (Lit.[2] m.p. 86–88°C) with properties identical to the natural compound.

In conclusion, the synthesis reported herein highlights the utility of our aromatic regiocontrolled annulation method as an efficient method in the synthesis of polysubstitued aromatic compounds. This convergent route, delivers resorcinol **I** in five steps from **3** (8% overall yield). The application of this methodology to other natural product synthesis is in progress and will be reported in due course.

EXPERIMENTAL SECTION

Melting points are uncorrected. Thin-layer chromatography was performed on silica gel 60 F_{254} and visualized by UV irradation. ^{1}H NMR spectra were recorded either at 200 or 300 MHz; while ^{13}C NMR spectra were run at 75 MHz in $CDCl_3$ solution. Mass spectra were measured at 70 eV (EI). Elemental analyses were performed by Galbrait Laboratories, Inc.; column chromatography purifications were carried out using gel (70–230 mesh).

E-Methyl-4-carbomethoxy-3-methoxy-2-butenoate[12]

A mixture of 50 g of 1,3-dimethyl acetonedicarboxylate (0.28 mol, 42 mL, 97%), 400 mL of dry methanol, 18.8 g (0.177 mol) of trimethyl orthoformiate and 0.1 g of *p*-TsOH were refluxed 40 h. The mixture was poured over 0.5 of Na_2CO_3 in 300 mL of water and extracted with ethyl acetate (3×100 mL). The combined organic phase was dried over anhyd. Na_2SO_4 and concentrated. The residue was purified by column chromatography (750 g of silica gel) and methyl-4-carbomethoxy-3-methoxy-2-butenoate **III** (49.8 g, 95% yield) was eluted using 5% ethyl acetate in hexane. IR (neat) 1142, 1119, 1633, 1712, 1745, and 2953 cm^{-1}. ^{1}H NMR

δ ppm 3.68 (s, 3H), 3.69 (s, 3H), 3.71 (s, 3H), 3.84 (s, 2H), 5.20 (s, 1H). ^{13}C NMR δ ppm 38.10, 50.98, 52.06, 55.90, 92.95, 167.66, 168.05. 169.45. MS (EI) m/z (relative intensity) 188 (M^+, 24), 157 (100), 156 (46), 125 (55). Anal. calcd. for $C_8H_{12}O_5$: C, 51.06%; H, 6.38. Found: C, 51.10; H, 6.36.

E-Methyl-4-carbomethoxy-4-hexyl-3-methoxy-2-butenoate[12]

To 2.34 g of NaH (58 mmol, 60%) in dry DMF (130 mL) was dropped 13.3 g (49 mmol of methyl-4-carbomethoxy-2-butenoate, 17.7 g (73.5 mmol) of 1-iodohexane was added and the mixture was stirred 36 h at 40°C. The mixture was poured in 650 mL of water and extracted with ethyl acetate 4×50 mL. The organic phase was washed with H_2O 2×25 mL, dried over Na_2SO_4, and concentrated. The residue was subjected to column chromatography (eluant ethyl acetate: hexane 4: 96, 300 g of silica gel) affording methyl-4-carbomethoxy-4-hexyl-3-methoxy-2-butenoate (9.58 g, 76% yield). IR (neat) 1146, 1197, 1631, 1715, 1744, 2859 cm^{-1}. ^{1}H NMR δ ppm 0.88 (t, 3H, $J = 6.9$ Hz), 1.15–1.35 (m, 8H), 1.65–2.05 (m, 2H), 3.65 (s, 3H), 3.67 (s, 3H), 3.69 (s, 3H), 4.93 (dd, 1H, $J = 6.38$ Hz and $J = 6.26$ Hz). ^{13}C NMR δ ppm 14.01, 22.54, 29.01, 31.57, 31.58, 46.03, 50.97, 52.02, 55.83, 90.92, 92.44, 167.64, 171.73, 171.98; MS (EI) m/z (relative intensity) 272 (M^+, 13), 169 (100), 156 (98), 128 (68), 241 (48). Anal. calcd. for $C_{14}H_{24}O_5$: C, 61.69; H, 8.81. Found: C, 61.71; H, 8.79.

2-Hexyl-1,3-dimethyl Acetonedicarboxylate (1)

Methyl-4-carbomethoxy-4-hexyl-3-methoxy-2-butenoate (15 g, 55.14 mmol), HCO_2H (50 mL, $\approx$1.15 mol) and hexane (50 mL) were stirred to 35°C for 36 h. The mixture reaction was poured in 200 mL of water and extracted with ether (3×120 mL). The organic layer was separated, washed with water (3×50 mL) and Na_2CO_3 (5 g) in 50 mL of water, dried Na_2SO_4 filtered, and concentrated. The residue was purified by column chromatography (eluant ethyl acetate: hexane, 5:95, 300 g of silica gel) affording **1** (12.1 g, 85% Yield). IR (neat) 1660, 1747, 2859 cm^{-1}. ^{1}H NMR δ ppm 0.87 (t, 3H, $J = 6.9$ Hz), 1.10–1.18 (m, 8H), 1.63–1.91 (m, 2H), 3.57–3.66 (m, 3H), 3.73 (s, 6H). ^{13}C NMR δ ppm 13.88, 22.40, 27.14, 28.04, 28.86, 31.37, 47.76, 52.29, 58.76, 90.43, 167.07, 169.75, 197.53. MS (EI) m/z (relative intensity) 272 (M^+, 13), 169 (100),

156 (98), 128 (68), 241 (48). Anal. calcd. for $C_{14}H_{24}O_5$: C, 60.46; H, 8.52. Found: C, 60.49; H, 8.50.

Methyl-3-formyl-5-hexyl-4,6-dihydroxy-2-propylbenzoate (3)

(4 g, 15.5 mmol) of **1** were added dropwise to a suspension of NaH (60%, 0.87 g, 21.7 mmol) in dry THF (40 mL) with magnetic stirring. To the resulting solution with argon atmosphere 2-hexynal 1.94 g (20 mmol) were added and, after 0.5 h, the mixture was poured into diluted HCl (15 mL). The organic layer was separated and the aqueous phase washed with brine (25 mL), dried over anhyd. Na_2SO_4 and concentrated. The residue was subjected to column chromatography, the resorcinol **3** (1.25 g, 25%) being eluted with 5% ethyl acetate in hexane (120 g of silica gel): IR (neat) 1632, 1660, 1727, 2857, 2958, 3360 cm^{-1}. ^1H NMR δ ppm 0.60–2.00 (m, 16H), 2.62 (t, $J = 7.9$, 2H), 3.11–3.16 (m, 2H), 3.98 (s, 3H), 10.19 (s, 1H), 12.09 (s, 1H), and 13.10 (s, 1H). ^{13}C NMR δ ppm 14.1, 14.45, 22.15, 26.81, 28.33, 29.49, 29.73, 31.01, 31.82, 52.69, 106.09, 112.62, 116.00, 151.21, 166.02, 166.37, 171.73, 194.23. MS m/z (relative intensity) 322 (M^+, 44), 219 (100), 290 (18), 251 (18). Anal. calcd. for $C_{18}H_{26}O_5$: C, 67.08; H, 8.07. Found: C, 67.22; H, 8.10.

Methyl-3-formyl-5-hexyl-4,6-dimethoxy-2-propylbenzoate (4)

3 (0.6 g, 1.86 mmol) was dissolved in dry DMF (12 mL) and NaH (89 mg, 2.23 mmol, 60%) was added portionwise with stirring. MeI (0.3 mL, 4.80 mmol) was added and stirring continued for 1.5 h. NaH (89 mg, 2.23 mmol, 60%) and MeI (0.3 mL, 4.80 mmol) were added and stirring continued for 3 h the reaction mixture was poured into water (50 mL) and extracted with ether (3×20 mL). The organic layer was separated, washed with water (10 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (eluant ethyl acetate:hexane, 0.3:9.7, 18 g of silica gel) affording **4** (587 mg, 90%). IR (neat) 1632, 1661, 2857 cm^{-1}. ^1H NMR δ ppm 0.82–1.05 (m, 2H), 1.20–1.70 (m, 10H), 2.54–2.65 (m, 2H), 2.72–2.82 (m, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 3.93 (s, 3H), 10.40 (s, 1H). ^{13}C NMR δ ppm 14.04, 14.53, 22.56, 24.12, 24.92, 29.78, 30.00, 31.54, 32.77, 52.36, 62.42, 64.32, 123.93, 126.97, 128.54, 142.44, 160.43, 165.29, 168.37, 191.22. MS m/z (relative intensity) 350 (M^+, 40), 318 (17), 279 (16), 247 (100). Anal. calcd. for $C_{20}H_{30}O_5$: C, 68.48; H, 8.56. Found: C, 68.72; H, 8.53.

3-Carbomethoxy-5-hexyl-4,6-dimethoxy-2-propyl Benzoic Acid (5)

4 (0.4 g, 1.14 mmol) was dissolved in acetone (6 mL) and 2 mL of Jones Reagent[9] was added with stirring. The reaction mixture was heated (40–50°C) for 5 h, and then poured into water (30), extracted with ether (4×15 mL). The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (eluant ethyl acetate:hexane, 15:85) affording **5** (343 mg, 82%). IR: 1160, 1575, 1704, 1734, 2872, 3210 cm^{-1}. ^1H NMR δ ppm 0.84–1.02 (m, 6H), 1.20–1.80 (m, 10H), 2.54–2.68 (m, 4H), 3.81 (s, 3H), 3.86 (s, 3H), 3.93 (s, 3H), 3.50–4.00 (bs, 1H). ^{13}C NMR δ ppm 14.05, 14.47, 22.57, 24.57, 24.76, 29.85, 29.90, 31.53, 33.45, 52.36, 62.56, 62.86, 123.82, 125.72, 128.33, 137.67, 157.76, 168.36, 171.26. MS *m/z* (relative intensity) 366 (M^+, 100), 335 (54), 295 (78). Anal. calcd. for $C_{20}H_{30}O_6$: C, 65.57; H, 8.19. Found: C, 65.92; H, 8.09.

4,6-Dimethoxy-5-hexyl-2-propyl-1,3-benzenodioic Acid (6)

5 (80 mg, 0.218 mmol) was dissolved in ethylene glycol (1.6 mL), KOH (120 mg) in water (1.1 mL) was added and Ar was bubbled. The reaction mixture was heated to 115–120°C for 2 h, cooled at room temperature, and poured into water (10 mL), extracted with ether (2×10 mL). The aqueous layer was separated and acidified to pH 4 with aqueous HCl (10%), extracted with ether (4×10 mL), the organic layer were separated, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (eluant ethyl acetate: hexane, 20:80) affording **6** (69 mg, 90%). IR: 1574, 1704, 2930, 3403 cm^{-1}. ^1H NMR 0.70–1.00 (m, 6H), 1.15–1.70 (m, 10H), 2.45–2.70 (m, 4H), 3.66 (s, 3H), 3.77 (s, 3H), 4.70-5.15 (bs, 2H). ^{13}C NMR δ ppm 13.98, 14.34, 22.48, 24.49, 24.77, 29.77, 29.84, 31.44, 33.44, 62.69, 125.13, 128.23, 136.97, 157.35, 170.93. MS *m/z* (relative intensity) 352 (M^+, 99), 221 (100), 337 (60), 263 (40). Anal. calcd. for $C_{20}H_{30}O_6$: C, 68.18; H, 8.52. Found: C, 68.22; H, 8.50.

2-Hexyl-5-propyl-1,3-dimethoxybencene (7)

6 (60 mg, 0.17 mmol), dry quinoline (1 mL) and CuO (22 mg), were heated under argon atmosphere to 215°C for 15 min. The reaction mixture was cooled at room temperature and poured into aqueous HCl

(5 mL, 10%) extracted with ether (3×10 mL), the organic layer was separated, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (eluant ethyl acetate:hexane, 1: 99) affording **7** (25 mg, 55.6%). IR: 1575, 2872, 2957 cm^{-1}. ^1H NMR δ ppm 0.80–1.10 (m, 6H), 1.20–1.80 (m, 10H), 2.50–2.70 (m, 4H), 3.79 (s, 6H), 6.36 (s, 2H). MS *m*/*z* (relative intensity) 264 (M^+, 41), 193 (100), 133 (12). Anal. calcd. for $C_{17}H_{28}O_2$: C, 77.27; H, 10.60. Found: C, 77.55; H, 10.24.

2-Hexyl-5-propyl-1,3-bencenediol (I)

7 (50 mg, 0.189 mmol) was dissolved in dry acetonitrile (3 mL) and NaI (142 mg, 0.945 mmol) and Me_3SiCl (103 mg, 0.947 mmol) were added with stirring. The reaction mixture was refluxed under Ar atmosphere for 48 h. the reaction mixture was poured into H_2O (10 mL) and extracted wih ether (3×10 mL). Drying, filtration, and concentration of the organic layer gave an oily residue that was purified by column chromatography using ethyl acetate:hexane (1:99) as eluant **I** (40 mg) was obtained in 89% yield.

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