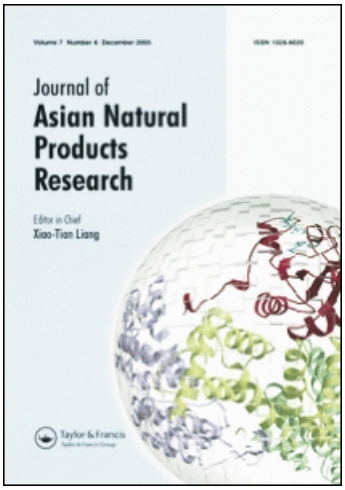

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TOTAL SYNTHESIS OF (−)-INCRUSTOPORIN

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(−)-Incrustoporin (**1**) has been synthesized using aldol condensation of ethyl p-tolyl-acetate (**2**) and (2*R*)-benzoyloxy-butanal (**3**), followed by acid-catalyzed deprotection of the benzoyl group, lactone ring-closure, and elimination of the β-OH in a one-pot manner. The aldehyde **3** was prepared from the commercially available D-mannitol by a two-directional strategy.

Keywords: Antibiotic; Incrustoporin; Aldol condensation; Two-directional strategy

INTRODUCTION

(−)-Incrustoporin (**1**) was isolated from the culture of the Basidyomycete *Incrustoporia carneola* (strain 9170) by Zalf *et al.* in 1995 [1]. It is a weak but quite selective antifungal lactone, which shows hightest activity against *Absidia glauca*, *Botrytis cinerea*, *Mucor miehei* and *Rhodotorula glutinis* [2]. The first and the only synthesis of this compound was reported by K. Mori [3], using alkylation of the lithium enolate with chiral epoxide prepared from D-mannitol [4] or (R)-(−)-α-amino-n-butyric acid by several steps [5] in 53% yield, followed by alkaline hydrolysis, acidification, and the introduction of the double bond. Their synthesis also confirmed that the natural incrustoporin had the *R* configuration. Herewith we would like to report a short and efficient synthesis of **1** based on a strategy similar to what we used in synthesizing the lactone segment of Annonaceous acetogenin [6].

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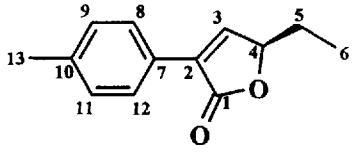
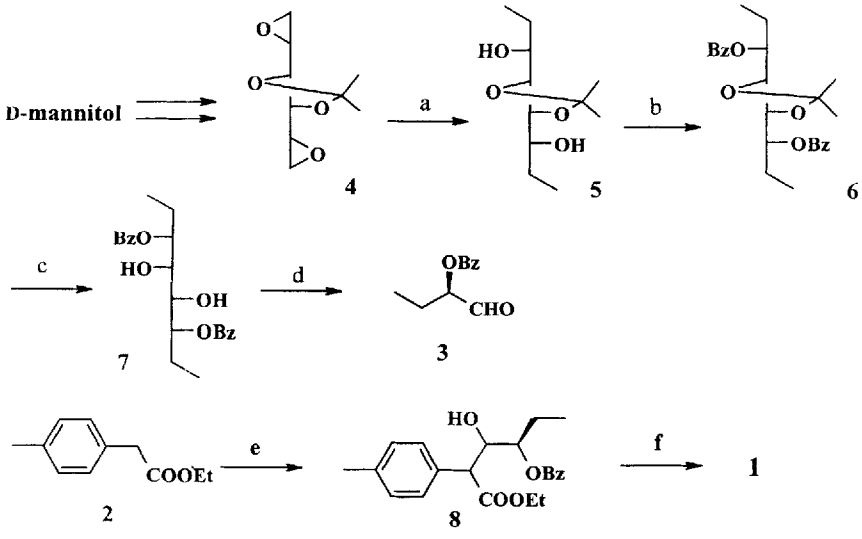
RESULTS AND DISCUSSION

As shown in Scheme 1, the synthesis of the aldehyde **3** starts from the known diepoxide **4** [7] employing a two-directional strategy. The Cu(I)-catalyzed Grignard reaction of **4** with methyl iodide afforded diol **5** in good yield. Protection of the hydroxyl group with benzoyl chloride yielded compound **6**. Then hydrolysis of the acetonide afforded diol **7**. The oxidation of diol **7** gave two equivalents of **3** in high yield. The aldol condensation of **2** with **3** was performed with LDA as the base to give the alcohol **8** in 77% yield. Finally, the transformation of **8** to **1** via hydrolysis of the benzoyl group, followed by lactone closure and elimination of the β-OH in one step was achieved in 60% yield by using conc. HCl/MeOH under refluxing. All physical data of the synthetic (−)-incrustoporin were in good agreement with those reported by Zalf [1] and Mori [3].



(-)-Incrustoporin 1



SCHEME 1 *Reagents and conditions*: a = CH_3MgI, CuI, THF-Et_2O, −50°C, 92%; b = PhCOCl, Py, CH_2Cl_2, 95%; c = CF_3COOH : H_2O (9 : 1), 0°C, 69%; d = $NaIO_4$, THF, H_2O, 93%; e = i-Pr_2NH, n-BuLi, HMPA, then aldehyde **3**, −78°C, 77%; f = conc. HCl : MeOH (1 : 10), reflux, 60%.

EXPERIMENTAL SECTION

General Experimental Procedures

Melting points were uncorrected. Optical rotations were measured on a Perkin-Elmer 241 MC Autopol polarimeter. IR Spectra were obtained on an IR-440 or Perkin-Elmer 983 Spectrophotometer. ^{1}H NMR Spectra were taken on a Varian EM-390 or AMX-300 Spectrometer. Mass Spectra were obtained on an HP 5989A spectrometer. Flash column chromatography was performed on silica gel H (10–40 μ).

(3*R*,4*R*,5R,6*R*)-4,5-*O*-Isopropylidene-3,4,5,6-octanetetraol (5)

A dry three-necked round-bottomed flask equipped with a reflux condenser and a pressure-equalizing dropping funnel was charged with magnesium turnings (1.509 g, 62.09 mmol) and dry ether (5 mL) under N_2 atmosphere. The dropping funnel was filled with a solution of MeI (3.9 mL, 62.60 mmol) in dry ether (15 mL) and a portion was added to initiate the reaction. After the reaction had commenced, the remainder of the MeI solution was added slowly at a rate to maintain the reaction under reflux. Finally, the mixture was stirred and refluxed for 1 h until all the magnesium was consumed. A dry 100-mL three-necked flask was filled with anhydrous CuI (600 mg, 3.15 mmol) and THF (20 mL), then the mixture was cooled to −50°C. The prepared methyl magnesium iodide was dropped in and stirred for 30 min, the diepoxide **4** (1.86 g, 10.0 mmol) in THF (20 mL) was added dropwise. The mixture was stirred at −50°C for 1 h, then at −30°C for 1 h. sat. NH_4Cl was added to quench the reaction. The mixture was allowed to warm to rt, before being extracted with ether for several times. The combined organic phases were washed with brine, dried over Na_2SO_4 and chromatographed on silica gel to give **5** (2.00 g, 92%). mp 46–47°C; $[\alpha]_D$ 11.7 (c 1.1, $CHCl_3$); IR(KBr) ν_{max} 3294 (OH), 2970 and 2879 (CH), 1371, 1218, 1171, 1077 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 4.05 (s, -OH), 3.7 (4H, m), 1.8–1.4 (10H, m), 1.05 (6H, t, $J = 7$ Hz) ppm; EI MS m/z $[MH]^+$ 219 (19), 203 (18), 201 (4), 162 (9), 161 (100), 159 (17).

(3*R*,4*R*,5*R*,6*R*)-3, 6-*O*-Dibenzoyl-4,5-*O*- isopropylidene-3,4,-5,6-octanetetraol (6)

To an ice-cooled solution of **5** (1.231 g, 5.64 mmol) in CH_2Cl_2 (13 mL) was added pyridine (0.92 mL, 11.37 mmol) and benzoyl chloride (2.0 mL, 17.23 mmol). The mixture was stirred at rt for 20 h. Then it was quenched by

sat. NH_4Cl and extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over Na_2SO_4 and chromatographed to yield **6** (2.295 g, 95%). $[\alpha]_D^{12}$ 26.4 (c 0.4, $CHCl_3$); IR (film) ν_{max} 2990 and 2950 (CH), 1730 (C=O), 1450, 1270, 1070, 720 cm^{-1}; ^1H NMR (CCl_4, 90 MHz) δ 7.8 (4H, d, $J = 8$ Hz), 7.3 (6H, m), 5.1 (2H, m), 4.05 (2H, m), 2.1 (4H, m), 1.3 (6H, m), 0.9 (6H, t, $J = 7$ Hz) ppm, EIMS m/z $[MH]^+$ 427 (trace), $[M\text{-}CH_3]^+$ 411 (8), 410 (11), 368 (2), 263 (9), 205 (59), 141 (20), 105 (100). Anal. C 70.31%, H 7.26%; calcd. for $C_{25}H_{30}O_6$, C 70.40%, H 7.09%.

(3*R*,4*R*,5*R*,6*R*)-3,6-*O*-Dibenzoyl-3,4,5,6-octanetetraol (7)

A solution of **6** (280 mg, 0.657 mmol) in 90% trifluroacetic acid (5.0 mL) was stirred at 0°C for 3 h. The mixture was diluted with H_2O (18 mL), then extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried and chromatographed to give **7** (175 mg, 69%). $[\alpha]_D^{26}$ −5.6 (c 0.8, $CHCl_3$); IR (film) ν_{max} 3500 (OH), 2990 and 2950 (CH), 1730 (C=O), 1450, 1270, 1110, 1070, 710 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 8.05 (4H, d, $J = 8$ Hz), 7.5 (6H, m), 5.1 (2H, m), 3.65 (2H, d, $J = 8$ Hz), 3.1 (s, OH), 2.0 (4H, m), 0.95 (6H, t, $J = 7$ Hz) ppm; EI MS m/z $[MH]^+$ 387 (10), $[MH\text{-}H_2O]^+$ 369 (31), $[MH\text{-}2H_2O]^+$ 351 (1), 265 (15), 247 (9), 223 (6), 105 (100).

(2*R*)-Benzoyloxy-butanal (3)

To a solution of **7** (128 mg, 0.33 mmol) in THF (1 mL) and H_2O (1 mL) was added $NaIO_4$ (144 mg, 0.67 mmol). The mixture was stirred at rt for 3 h, then, filtered. The filter cake was washed with ether. The filtrate was seperated into two phases and the organic phase was washed with brine. Drying and concentrating gave **3** (118 mg, 93%). IR (film) ν_{max} 2990 and 2950 (CH), 1730 (C=O), 1720 (C=O), 1450, 1270, 1110, 1070, 710 cm^{-1}; ^1H NMR (CCl_4, 90 MHz) δ 9.5 (s, 1H), 8.0 (2H, d, $J = 7$ Hz), 7.4 (3H, m), 5.1 (1H, m), 1.8 (2H, m), 1.0 (3H, t, $J = 7$ Hz) ppm.

Aldol Product (8)

To a solution of i-Pr_2NH (1.2 mL, 8.56 mmol) in anhydrous THF (40 mL) was added BuLi (2.5 N, 3.4 mL, 8.5 mmol) at −78°C under N_2 atmosphere. After being stirred for 20 min, anhydrous HMPA (6 mL) was added and stirred for additional 30 min. Then, a solution of **2** (1.29 g, 7.24 mmol) in THF (10 mL) was added and the stirring was continued for another 20 min. A solution of **3** (1.36 g, 7.08 mmol) in THF (10 mL) was added dropwise

and the mixture was stirred for 3.5 h. One N HCl was added to quench the reaction and the mixture was stirred for 15 min at −78°C, then allowed to warm to rt. The organic phase was separated and the aqueous phase was extracted with ether (10 mL × 3). The combined organic phases were washed with brine and dried. The solvent was removed and the residue was purified by chromatography on silica gel to give **8** as a clear oil (mixture of diastereomers, 2.006 g, 77%). IR (film) ν_{max} 3472 (OH), 2971 and 2878 (CH), 1716 (C=O), 1510, 1458, 1371, 1274, 1179, 1115, 1073, 716 cm^{-1}; EI MS m/z $[M]^+$ 370 (2), [M-H_2O] 352 (49), 325 (4), 306 (5), 249 (23), 231 (7), 193 (11), 178 (23), 105 (100).

Incrustoporin (1)

To a solution of **8** (238 mg, 0.64 mmol) in MeOH (5 mL) was added conc. HCl (0.5 mL). The mixture was stirred at rt for 30 min, then refluxed for 3 h, cooled to rt and extracted with ether. The combined organic phases were washed with brine and purified on silica gel column to give **1** (78 mg, 60%) as white needles, mp 38–39°C (Lit. colorless oil [1] or 43°C [3]); $[\alpha]_D$ -6.6 (c 0.56, $CHCl_3$) (Lit. $[\alpha]_D$ −4 (c 0.3, $CDCl_3$) [1] or −6.8 (c 0.3, $CHCl_3$) [3]; IR (film) ν_{max} 3087, 3035, 2974, 2937, 2883, 1743, 1630, 1615, 1514, 1458, 1340, 1126, 1030, 968, 824, 524 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.75 (2H, d, J = 8.2 Hz), 7.49 (1H, d, J = 1.7 Hz), 7.19 (2H, d, J = 8.0 Hz), 4.95 (1H, m), 2.35 (s, 3H), 1.78 (m, 2H), 1.03 (3H, t, J = 7.4 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) 171.98 (C-1), 146.96 (C-3), 139.33 (C-10), 131.51 (C-2), 129.34 (C-9 and C-11), 126.94 (C-7, C-8 and C-12), 81.51 (C-4), 26.75 (C-5), 21.37 (C-13), 9.20 (C-6); EI MS m/z $[MH]^+$ 203 (10), $[M]^+$ 202 (54), [M-Et] 173 (6), 159 (2), 145 (36), 117 (100), 115 (26). Anal. C 77.55%, H 7.12%, calcd. for $C_{13}H_{14}O_2$, C 77.21%, H 6.98%.

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