

A Two-Step Total Synthesis of the Natural Pentacycle Trichodimerol, a Novel Inhibitor of TNF- α Production

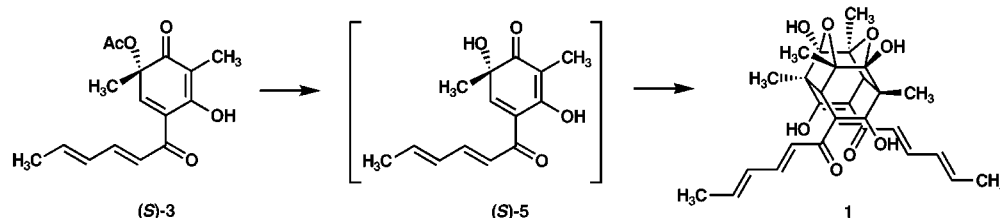
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ABSTRACT



Trichodimerol (1) can be synthesized by a remarkable dimerization of the chiral hydroxy dienone 5.

Trichodimerol (1), a pentacyclic natural product originally isolated from the fungus *Trichoderma longibraciatum*,¹ has been found to inhibit production of the cytokine TNF- α (tumor necrosis factor- α).² The combination of the novel, complex, and compact structure of 1 and its anti-TNF- α activity has made this molecule an intriguing target for chemical synthesis. The clinically demonstrated efficacy of anti-TNF- α monoclonal antibodies against rheumatoid arthritis and Crohn's disease³ have dramatically confirmed basic biological studies that previously had indicated a truly fundamental role of TNF- α (biochemically upstream of interleukin-1, p38 MAP kinase, cyclooxygenase-2, prostaglandins, etc.) in inflammatory disease.⁴ The medical importance of small molecules which can prevent TNF- α -induced inflammation is potentially great and extends to other

disease states having an inflammatory component, e.g., atherosclerosis.⁵ We report herein the first synthesis of trichodimerol (1) in just two steps from a known compound,⁶ sorbicillin (2). Sorbicillin is available in three steps from 2-methylresorcinol by the sequence: (1) *ortho*-formylation,⁷ (2) hydrogenation of formyl to methyl to afford 2,4-dimethylresorcinol,⁸ and (3) Friedel–Crafts acylation of bromomagnesium phenolate by sorbyl chloride.⁹

The synthesis of 1 is outlined in Scheme 1. *C*-Acetoxylation of 2 with 1.2 equiv of 0.04 M lead tetraacetate in 5:1 HOAc–CH₂Cl₂ at 23 °C for 30 min produced a mixture of position isomeric acetoxy dienones 3 (38%) and 4 (35%) which were readily separated by silica gel chromatography

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(5) Therapeutic monoclonal anti-TNF antibodies have recently been approved in the USA for treatment of rheumatoid arthritis and Crohn's disease.

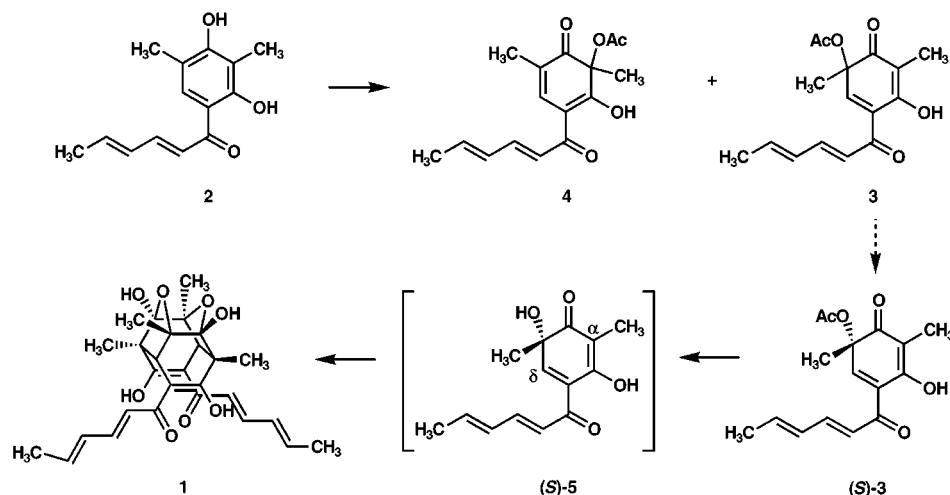
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Scheme 1



from unreacted **2** (17%); the order of chromatographic elution using 4:1 hexanes–EtOAc was **2** then **4** then **3**.¹⁰

The structures of **3** and **4** were established by HMQC^{11a} and HMBC^{11b} NMR analysis of one-, two-, and three-bond ¹H–¹³C couplings. Racemic **3** was resolved chromatographically on a Daicel (Chiral Technologies) AD column using 5:15:80 CH₃OH–*i*-PrOH–hexanes containing 0.1% CF₃–CO₂H; the order of elution was first (*S*)-**3**, [α]_D²³ –606 (*c* = 0.9 in CH₃OH), and then (*R*)-**3**, [α]_D²³ +615 (*c* = 1.0 in CH₃OH). Cleavage of the acetoxy dienone (*S*)-**3** to the corresponding hydroxy dienone (*S*)-**5** was effected by treatment with 10 equiv of sodium methoxide in methanol (0.015 M) at 23 °C for 6 h. Careful neutralization of the reaction

mixture (NaH₂PO₄·H₂O and then methanolic HCl), filtration, and removal of methanol in vacuo afforded a mixture of products derived from hydroxy dienone **5**. Silica gel chromatography of the mixture using 3:1 hexanes–EtOAc gave pure trichodimerol (**1**) in 10% yield, [α]_D²³ –351 (*c* = 0.08 in CH₃OH).¹² The identities of synthetic **1** and natural trichodimerol¹³ were confirmed by comparison of the ¹H and ¹³C NMR, UV, IR, and mass spectra and TLC mobilities on silica gel with three different solvent systems.

The remarkable spontaneous assembly of the complicated pentacyclic system of **1** from the hydroxy dienone **5** can be explained mechanistically by the following stepwise sequence of events: (1) intermolecular Michael addition of the nucleophilic C α of (*S*)-**5** to C δ of a second molecule of (*S*)-**5**, (2) a second (intramolecular) Michael addition forming a head-to-tail [4 + 4] cycloaddition dimer of **5**, and (3) a sequence of two hemiketal-forming ring closures by intramolecular addition of hydroxyl to keto carbonyl. The yield reported above for this interesting dimerization has not been optimized and may be subject to considerable improvement. Research is underway on this point and also to develop an enantioselective version of the reaction **2** \rightarrow **3**.

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(10) A solution of sorbicillin (**2**) (0.5021 g, 2.16 mmol) in acetic acid (50 mL) and CH₂Cl₂ (10 mL) at 23 °C was treated with lead tetraacetate (1.1606 g, 2.62 mmol). The resulting solution was stirred for 30 min. After addition of water the product was isolated by extraction with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and concentrated to a residue which was chromatographed (1:4 to 1:2 EtOAc–hexanes gradient elution, 500 mL of silica gel) to give **3** (0.2390 g, 38%) as a yellow crystalline solid **4** (0.2202 g, 35%) as a yellow oil and **2** as a solid (85.5 mg, 17%). Found for **3**: mp 110–111 °C; FTIR (film) 2935, 1738, 1651, 1556, 1372, 1244, 1072, 1019 cm^{–1}; UV (MeOH) ν_{\max} nm (log ϵ) 286 (3.99), 218 (3.97); ¹H NMR (500 MHz, CDCl₃) δ 11.89 (s, 1H), 7.45 (dd, 1H, *J* = 14.8, 10.8 Hz), 7.25 (s, 1H), 6.66 (d, 1H, *J* = 14.8 Hz), 6.37 (m, 1H), 6.30 (m, 1H), 2.13 (s, 3H), 1.91 (d, 3H, *J* = 5.8 Hz), 1.84 (s, 3H), 1.48 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 194.9, 193.2, 169.9, 162.5, 151.8, 148.3, 144.8, 130.0, 125.4, 120.1, 111.6, 78.1, 24.0, 20.4, 19.1, 7.1; HRMS (EI) for C₁₆H₁₈O₅ [M]⁺, *m/z* calcd 290.1154, found 290.1155. Found for **4**: FTIR (film) 2931, 1739, 1679, 1607, 1537, 1377, 1248, 1080, 1029, 996, 950, 936, 881 cm^{–1}; UV (MeOH) ν_{\max} nm (log ϵ) 404 (3.98), 298 (4.01), 262 (3.86), 210 (3.98); ¹H NMR (400 MHz, CDCl₃) δ 15.06 (s, 1H), 7.41 (dd, 1H, *J* = 14.7, 10.3 Hz), 7.36 (s, 1H), 6.45 (d, 1H, *J* = 14.7 Hz), 6.33–6.26 (m, 2H), 2.18 (s, 3H), 1.97 (s, 3H), 1.92 (d, 3H, *J* = 5.9 Hz), 1.53 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 200.4, 194.5, 173.6, 169.9, 144.1, 141.7, 136.2, 130.8, 124.7, 117.2, 105.5, 82.9, 23.4, 20.1, 19.0, 16.0; HRMS (EI) for C₁₆H₁₈O₅ [M]⁺, *m/z* calcd 290.1154, found 290.1157.

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(12) Reported: [α]_D²³ –376 (*c* = 0.3 in CH₃OH).¹ The absolute configuration of **1** had been assigned using the exciton chirality method.¹

(13) We are grateful to Prof. W. A. Ayer of the University of Alberta for generously providing a sample of natural trichodimerol.