ORGANIC LETTERS

1999
Vol. 1, No. 9
1503−1504

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

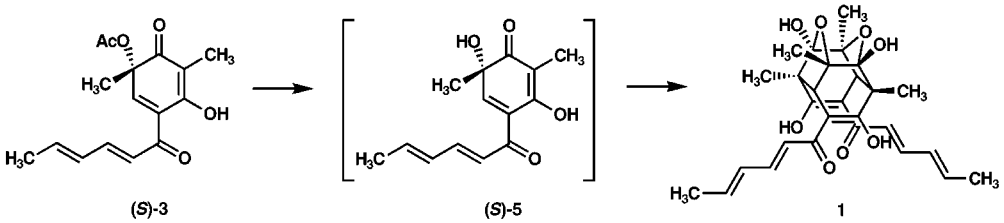
David Barnes-Seeman and E. J. Corey*

Department of Chemistry and Chemical Biology Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138

corey@chemistry.harvard.edu

Received September 20, 1999

ABSTRACT



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

Trichodimerol (**1**), a pentacylic 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 disease[3] 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−CH_2Cl_2 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

(1) Andrade, R.; Ayer, W. A.; Mebe, P. P. *Can. J. Chem.* **1992**, *70*, 2526.

(2) Gao, Q.; Leet, J. E.; Thomas, S. T.; Matson, J. A.; Bancroft, D. P. *J. Nat. Prod.* **1995**, *58*, 1817.

(3) (a) O'Dell, J. R. *New Eng. J. Med.* **1999**, *340*, 310. (b) Weinblatt, M. E.; Kremer, J. M.; Bankhurst, A. D.; Bulpitt, K. J.; Fleischmann, R. M.; Fox, R. I.; Jackson, C. G.; Lange, M.; Burge, D. J. *New Eng. J. Med.* **1999**, *340*, 253. (c) Williams, R. O.; Mason, L. J.; Feldmann, M.; Maini, R. N. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 2762. (d) Elliott, M. J.; Maini, R. N.; Feldmann, M.; Long-Fox, A.; Charles, P.; Katsikis, P.; Brennan, F. M.; Walker, J.; Bijl, H.; Ghrayeb, J.; Woody, J. N. *Arthritis Rheum.* **1993**, *36*, 1681.

(4) (a) Brennan, F. M.; Maini, R. N.; Feldmann, M. *Brit. J. Rheumatol.* **1992**, *31*, 293. (b) Palladino, M. A., Jr.; Finkle, B. S. *Trends Pharmacol.* **1986**, 388.

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

(6) Trifonov, L. S.; Bieri, J. H.; Prewo, R.; Dreiding, A. S.; Hoesch, L.; Rast, D. M. *Tetrahedron* **1983**, *39*, 4243.

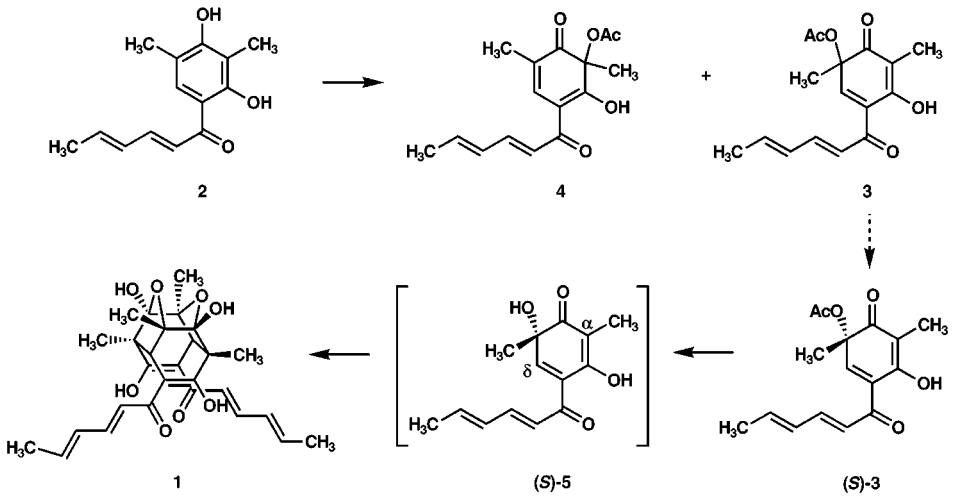
(7) (a) Maruyama, K.; Nagai, N.; Naruta Y. *J. Org. Chem.* **1986**, *51*, 5083. (b) Baker, W.; Bondy, H. F.; McOmie, J. F. W.; Tunnicliff, H. R. *J. Chem. Soc.* **1949**, 2834.

(8) Sassa, T.; Aoki, H.; Munakata, K. *Tetrahedron Lett.* **1968**, *54*, 5703.

(9) Bigi, F.; Casiraghi, G.; Casnati, G.; Marchesi, S.; Sartori, G.; Vignali, C. *Tetrahedron* **1984**, *40*, 4081.

10.1021/ol991070h CCC: $18.00
Published on Web 09/30/1999

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 $^{1}H-^{13}C$ couplings. Racemic **3** was resolved chromatographically on a Daicel (Chiral Technologies) AD column using 5:15:80 CH_3OH−*i*-PrOH−hexanes containing 0.1% CF_3CO_2H; the order of elution was first (*S*)-**3**, $[\alpha]^{23}_D$ −606 (*c* = 0.9 in CH_3OH), and then (*R*)-**3**, $[\alpha]^{23}_D$ +615 (*c* = 1.0 in CH_3OH). 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 ($NaH_2PO_4 \cdot H_2O$ 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, $[\alpha]^{23}_D$ −351 (*c* = 0.08 in CH_3OH).[12] The identities of synthetic **1** and natural trichodimerol[13] were confirmed by comparison of the ^{1}H and ^{13}C 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 Cα of (*S*)-**5** to Cδ 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** → **3**.

Acknowledgment. This research was assisted by graduate fellowships to D.B.-S. from the National Science Foundation and the Eli Lilly Co. and a research grant from the National Science Foundation. We are grateful to Dr. He Xia for expert assistance with HPLC separations.

OL991070H

(10) A solution of sorbicillin (**2**) (0.5021 g, 2.16 mmol) in acetic acid (50 mL) and CH_2Cl_2 (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 CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 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); ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{16}H_{18}O_5$ $[M]^+$, *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); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{16}H_{18}O_5$ $[M]^+$, *m*/*z* calcd 290.1154, found 290.1157.

(11) (a) Müller, L. *J. Am. Chem. Soc.* **1979**, *101*, 4481. (b) Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093.

(12) Reported: $[\alpha]_D$ −376 (*c* = 0.3 in CH_3OH).[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.