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Total Synthesis of (–)-Cotylenol, a Fungal Metabolite Having a Leaf Growth Activity

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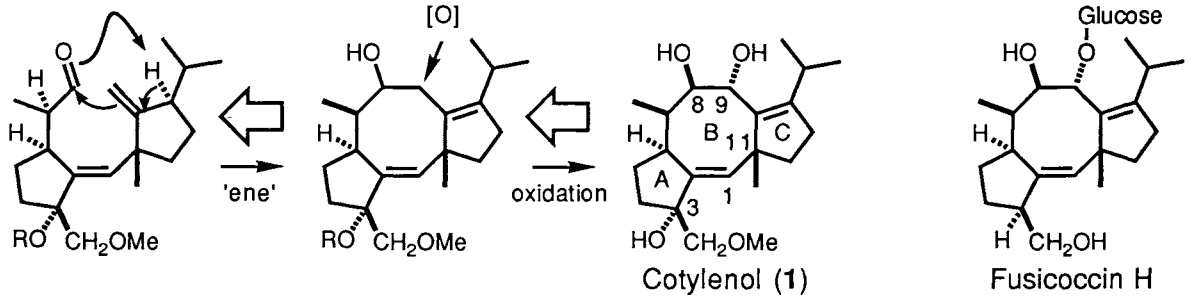
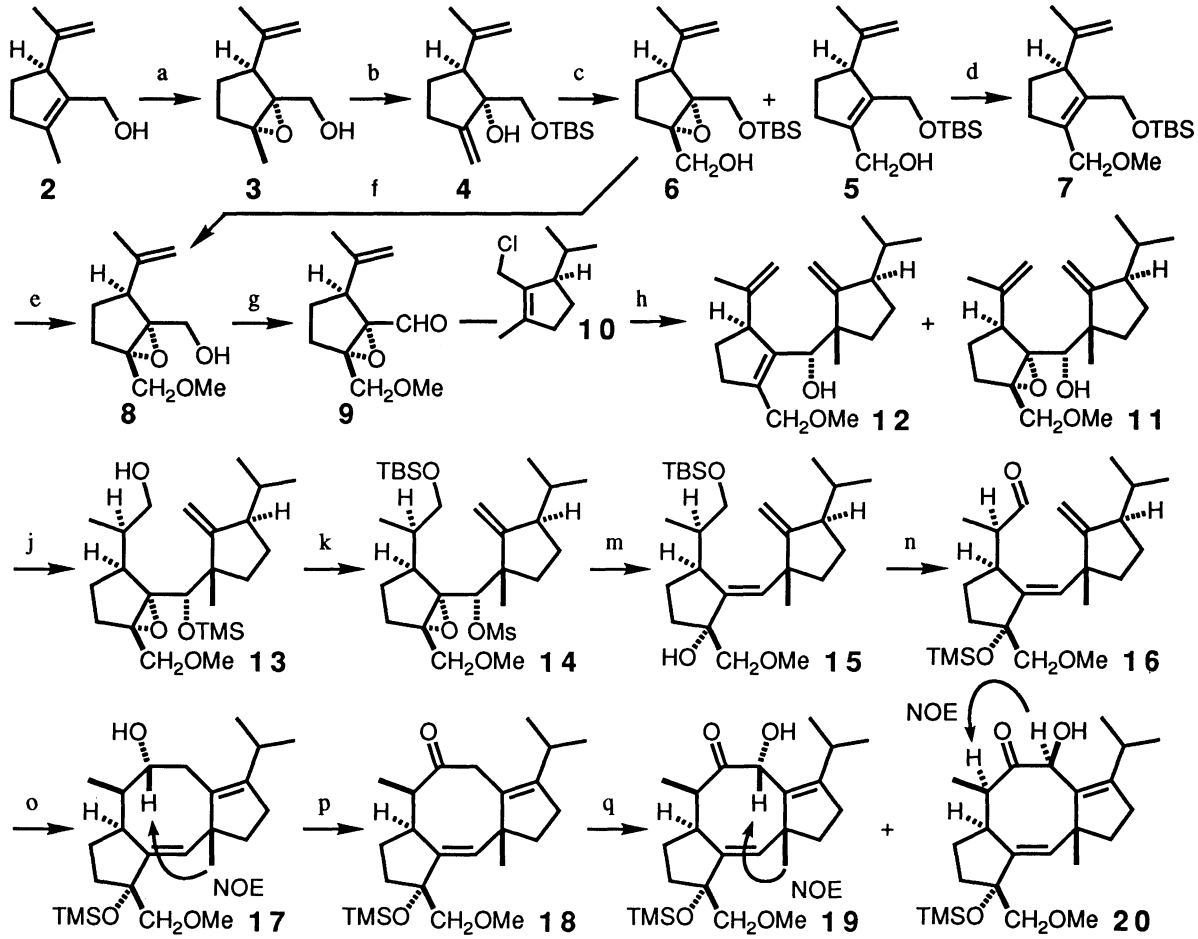
Cotylenol, one of the representative fusicoccane diterpenoids having 5-8-5-membered tricyclic carbon framework, is now synthesized for the first time *via* an eight-membered ring formation by an intramolecular ene reaction followed by an oxidative formation of the 8β,9α-glycol function on the central eight-membered ring.

Cotylenins, diterpenoid glycosides isolated from the culture filtrate of an unidentified species of *Cladosporium*, stimulate the growth of cotyledons in Chinese cabbage seedlings,[1] and are structurally related closely to fusicoccins which were isolated as phytotoxic substances responsible to a wilting disease of peach and almond trees.[2] The cotylenins and fusicoccins commonly possess the *trans*-8β,9α-glycol system on their central eight-membered ring and the stereochemistry of this glycol is reported to be important for their unique biological activities.[3] However, since the derivations of this glycol system from natural sources are limited to give only *cis*-8β,9β-isomers, the biological activities of other stereoisomers are yet not clear. Among them, cotylenol (**1**)[4] is the only characterized sugar-free natural product of these classes of compounds; therefore, synthesizing not only **1** but also its stereoisomers of the glycol system are desirable to clarify the structure-activity relationships and the mechanisms of the biological action. As has been already reported,[5] the carbon framework of **1** can be constructed *via* an eight-membered ring formation by an ene reaction on an appropriately functionalized *B-seco*-fusicoccane derivative. Herein reported is the first total synthesis[6] of **1** utilizing this methodology, which is potentially applicable for all stereoisomeric glycol functions.



At the beginning, the C_{10}-synthone for the A-ring of **1** was derived from (3*S*)-irida-1,8-dien-7-ol (**2**)[7] as follows. Sharpless epoxidation[8] of **2** gave **3**, of which epoxide was opened to give an allylic alcohol **4** after protecting the primary alcohol as a *tert*-butyldimethylsilyl (TBS) ether. The tertiary allylic alcohol of **4** was oxidized by pyridinium chlorochromate (PCC) to give an α,β-unsaturated aldehyde which was subsequently treated with $NaBH_4$ to give an allylic alcohol **5**. The PCC oxidation also produced an epoxy-aldehyde as a minor product which gave **6**, separated from **5** at this stage. The major product **5** was then methylated to **7** and epoxid-

ized again, after deprotection of TBS ether, with Katsuki–Sharpless conditions[9] to afford **8**. The minor product **6** was also employed to form **8** by a methylation and a deprotection procedure. Subsequently, **8** was oxidized to an aldehyde **9**[10] by treating with pyridinium dichromate (PDC).

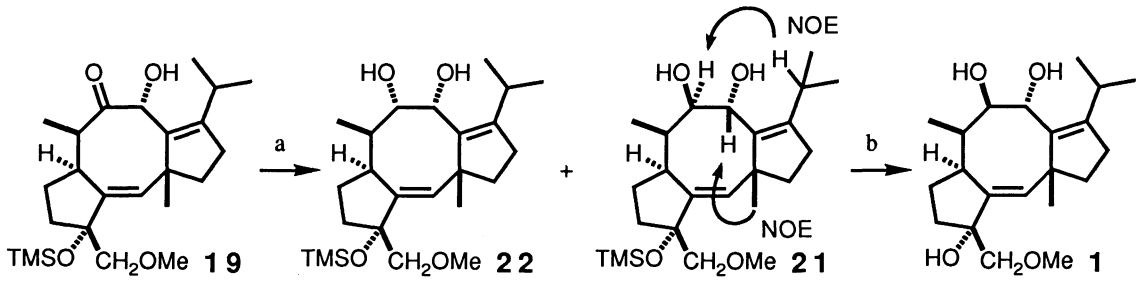


Reagents, conditions, and yields: a) i, ^{t}BuOOH, $VO(acac)_2$, ii, Ac_2O/ pyridine, iii, $LiAlH_4$ (86%); b) i, $(^{i}PrO)_3Al$, ii, TBSCl/ imidazole (91%); c) i, PCC, Celite, ii, $NaBH_4$ (**5**: 40%, **6**: 8%); d) NaH then MeI (88%); e) i, Bu_4NF, ii, (–)-diethyl tartrate, $(^{i}PrO)_4Ti$, ^{t}BuOOH/ M.S.-4A (88%); f) i, NaH then MeI, ii, Bu_4NF (86%); g) PDC (75%); h) $CrCl_3$–$LiAlH_4$/ DMF (**11**: 56%, **12**: 23%); j) i, TMSCl/ pyridine, ii, 9-BBN then H_2O_2–3M NaOH (78%); k) i, Bu_4NF, ii, TBSCl/ imidazole, iii, MsCl/ pyridine (45%); m) Ca ($FeCl_3$)/ liq. NH_3 (72%); n) i, Bu_4NF, ii, TMSCl/ pyridine, iii, pyridinium *p*-toluenesulfonate/ aq. THF, iv, PDC (71%); o) 160 °C (Na_2CO_3)/ xylene (90%); p) PDC (70%); q) LiHMDS then MoOPH (**19**: 44%, **20**: 28%).

Scheme 1.

The aldehyde **9** was then condensed with another C_{10}-synthone of the C-ring, (3*R*)-7-chloroirid-1-ene (**10**)[7] by use of low-valent chromium species[11] in *N*,*N*-dimethylformamide (DMF) to give a desired condensate **11** together with **12**. The minor product **12** must be arisen from a deoxygenated Δ^2-aldehyde, formed prior to the condensation. After protecting the secondary hydroxyl of **11** as a trimethylsilyl (TMS) ether, the site and stereoselective hydroboration[7] on C-8 was performed by 9-borabicyclo[3.3.1]nonane (9-BBN) to afford **13**. A methanesulfonate **14**, derived from **13** in three steps, was reductively converted into **15** in a moderate yield. In this Birch type reduction step, the addition of iron(III) salt[12] was indispensable to minimize an over-reduction product. After protection of C-3 hydroxyl and deprotection of C-8 hydroxyl, the aldehyde **16**, the precursor for the ene-reaction, was obtained by PDC-oxidation.

The thermally-induced ene reaction of **16** occurred in xylene to give a cyclisate **17** in a good yield. The α-orientation of C-8 hydroxyl was clarified by the NOE experiment; an enhancement of 8β-H was observed by irradiation of C-11-Me signal. For the introduction of C-9 hydroxyl, **17** was oxidized to a ketone **18**. Then the enolate, generated with lithium hexamethyldisilazide (LiHMDS), was oxidized by oxodiperoxymolybdenum(pyridine)hexamethylphosphoramide (MoOPH)[13] to give an isomeric mixture of α- and β-hydroxy ketones (**19** and **20**). The configuration of the C-9 hydroxyl of each product was confirmed by NOE experiments shown in scheme 1.



Reagents, conditions, and yields: a) $NaBH(OAc)_3$ (**21**: 70%, **22**: 25%); b) Bu_4NF (100%).

Scheme 2.

As similar to the model studies,[5] reduction of **19** with sodium triacetoxyborohydride mainly gave a desired *trans*-8β,9α-isomer (**21**) together with a *cis*-8α,9α-isomer (**22**), a minor product. The stereochemistry of **21** was confirmed again by NOE experiments as shown in scheme 2. The conversion of **21** to the target, cotylenol (**1**), simply required a deprotection of TMS ether of C-3 hydroxyl; it was accomplished by an ammonium fluoride treatment. Synthetic **1** [colorless prisms, mp. 160 °C[14], $[\alpha]_D^{30}$ −30° (lit.[4] −26°)] was identified with natural **1** in direct comparisons of physical properties.

Thus, the first total synthesis of **1** has been completed. Although this synthetic pathway involves several non-stereospecific steps, the by-products obtained are considered to be useful for the synthesis of isomers of **1**; e.g., 9β-hydroxy ketone **20** is a promising precursor for the 8β,9β- and 8α,9β-isomers. Since, as mentioned above, those isomeric glycols are of interest in regards of the structure-activity relationships, results on the syntheses and biological activities will be reported in due course.

Sincere thanks are due to Professor Takeshi Sassa, Yamagata University, for generous gift of natural cotylenol and an authoritative identification of both samples with respects of NMR spectral comparisons.

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6) For the total syntheses of other terpenoids having 5-8-5-membered tricyclic skeleton, see, N. Kato, X. Wu, H. Nishikawa, K. Nakanishi, and H. Takeshita, *J. Chem. Soc., Perkin Trans. 1*, **1994**, 1047; M. Row-

ley, M. Tsukamoto, and Y. Kishi, *J. Am. Chem. Soc.*, **111**, 2735 (1989); R. K. Boeckman, Jr., A. Arvanitis, and M. E. Voss, *ibid.*, **111**, 2737 (1989); L. A. Paquette, T.-Z. Wang, N. H. Vo, *ibid.*, **115**, 1676 (1993); T. F. Jamison, S. Shambayati, W. E. Crowe, and S. L. Schreiber, *ibid.*, **116**, 5505 (1994), and references cited therein.

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10) The ^{1}H and ^{13}C NMR data (270 and 67.5 MHz, respectively, in $CDCl_3$ otherwise stated) of key compounds are compiled.

9: δ(H)=1.49(1H, dddd, *J*=12.5, 5.5, 2.5, 0.5 Hz), 1.77(1H, m), 1.82(3H, br s), 2.00–2.15(2H, m), 3.01 (1H, d, *J*=8 Hz), 3.38(3H, s), 3.73(1H, d, *J*=11 Hz), 3.77(1H, d, *J*=11 Hz), 4.75(1H, br s), 4.86(1H, m), and 9.61(1H, s). δ(C)=21.8, 26.5, 28.1, 46.2, 59.5, 70.3, 72.0, 75.0, 112.2, 144.7, and 196.2.

11: δ(H)=0.77(3H, d, *J*=6.5 Hz), 0.99(3H, d, *J*= 7 Hz), 1.15(3H, s), 1.25–1.49(3H, m), 1.58–1.72(2H, m), 1.72(3H, br s), 1.85–2.11(4H, m), 2.53(1H, m), 2.68(1H, d, *J*=5 Hz; OH), 2.77(1H, br d, *J*=8 Hz), 3.42(3H, s), 3.88(1H, d, *J*=11 Hz), 3.92(1H, d, *J*=11 Hz), 4.07(1H, d, *J*=5 Hz), 4.73(1H, br s), 4.79(1H, m), 4.86(1H, d, *J*= 2.5 Hz), and 4.98(1H, d, *J*=3 Hz). δ(C)=16.3, 21.6, 22.1, 22.9, 24.1, 25.6, 28.3, 28.6, 33.7, 50.4, 51.6, 52.3, 59.2, 71.1, 72.1, 72.4, 74.3, 105.7, 112.0, 146.7, and 161.3.

15: δ(H)=0.03(6H, s), 0.78(3H, d, *J*=7 Hz), 0.89(9H, s), 0.92(3H, d, *J*=7 Hz), 0.98(3H, d, *J*=6.5 Hz), 1.19(3H, s), 1.36–2.05(10H, m), 2.26(1H, br s; OH), 2.47(1H, m), 3.04(1H, br m), 3.30(2H, s), 3.36 (1H, dd, *J*=9.5, 7 Hz), 3.40(3H, s), 3.54(1H, dd, *J*=9.5, 3.5 Hz), 4.80(1H, d, *J*=2 Hz), 4.90(1H, d, *J*=3 Hz), and 5.64(1H, d, *J* =2 Hz). δ(C)=–5.42, –5.37, 16.3, 16.4, 18.4, 22.0, 23.2, 25.96(3C), 26.02, 28.8, 35.5, 38.2, 39.2, 42.5, 48.7, 49.7, 59.4, 65.8, 79.7, 81.5, 105.2, 135.5, 145.6, and 162.9.

17: δ(H)=0.07(9H, s), 0.86(3H, d, *J*=7 Hz), 0.96(3H, d, *J*=7 Hz), 0.98(3H, d, *J*=6.5 Hz), 1.18(3H, s), 1.40(1H, m), 1.60–2.22(9H, m), 2.31(1H, dq, *J*=14.5, 3 Hz), 2.61(1H, dd, *J*=14.5, 9.5 Hz), 2.85(1H, sept, *J*=7 Hz), 3.21(1H, d, *J*=10.5 Hz), 3.31(1H, d, *J*=10.5 Hz), 3.35(1H, m), 3.37(3H, s), 3.64(1H, br m), and 5.48(1H, d, *J* =2 Hz). δ(C)=2.3(3C), 13.7, 20.4, 21.2, 27.27, 27.30, 27.5, 29.0, 32.5, 35.7, 36.5, 40.8, 45.7, 53.3, 59.3, 73.2, 78.8, 85.3, 133.6, 135.0, 141.5, and 143.8.

19: δ(H)=0.10(9H, s), 0.81(3H, d, *J*=6.5 Hz), 1.00(3H, d, *J*=6.5 Hz), 1.08(3H, d, *J*=7.5 Hz), 1.31(3H, s), 1.49(1H, m), 1.76–2.24(8H, m), 2.67(1H, qd, *J*=7.5, 1.5 Hz), 2.75(1H, sept, *J*=6.5 Hz), 3.07(1H, dd, *J*=10, 1 Hz), 3.23(1H, tm, *J*=9 Hz), 3.31(1H, d, *J*=10 Hz), 3.36(3H, s), 3.80(1H, br d, *J*=4.5 Hz; OH), 4.82(1H, d, *J*=4.5 Hz), and 5.63(1H, d, *J*=2.5 Hz). δ(C)=2.3(3C), 13.5, 19.6, 21.1, 26.3, 27.1, 27.6, 30.3, 34.2, 39.1, 40.9, 50.1, 52.5, 59.2, 69.4, 77.5, 85.1, 133.3, 135.5, 139.8, 150.8, and 212.0.

1: δ(H)=0.81(3H, d, *J*=7.5 Hz), 0.96(3H, d, *J*=7 Hz), 1.04(3H, d, *J*=7 Hz), 1.22(3H, s), 1.25–1.46(2H, m), 1.69(1H, ddd, *J*=12, 10, 8.5 Hz), 1.78 (1H, br s; OH), 1.85(1H, ddd, *J*=12, 6, 3 Hz),1.90–2.22 (5H, m), 2.53(1H, br s; OH), 2.94(1H, td, *J*=8.5, 2.5 Hz), 2.96(1H, br s; OH), 3.09(1H, dd, *J*=9.5, 1 Hz), 3.27(1H, sept, *J*=7 Hz), 3.36(1H, d, *J*=9.5 Hz), 3.41(3H, s), 3.94(1H, dd, *J*=10, 4.5 Hz), 4.07 (1H, d, *J*=10 Hz), and 5.52(1H, d, *J*=2.5 Hz). δ(C, 125 MHz)=8.4, 20.3, 21.5, 26.5, 27.1, 28.1, 31.6, 35.3, 40.2, 41.7, 42.5, 51.8, 59.3, 67.9, 77.4, 77.5, 82.0, 134.3, 136.9, 139.7, and 150.4.

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14) Although the melting point of **1** was originally reported[4] to be 157 °C, both synthetic and natural **1** melt at this temperature in our measurement (Yanagimoto Micro Melting Point Apparatus, uncorrected).

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