Synthetic Modification of Cotylenol. Synthesis of 3α-Cotylenyl Methyl Dithiocarbonates with Four Diastereomeric Glycol Moieties and Their Plant Growth Regulating Activity

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To confirm the role of an electronegative substituent on the C-3 position of the cotylenol framework in exhibiting the biological activity, four diastereomers at the 8,9-glycol moieties of 3α-sulfur analogs, 3α-cotylenyl methyl dithiocarbonates, were synthesized. The 8β,9α-dihydroxy compound, which had the same stereochemistry regarding the glycol moiety with natural products, revealed similar biological activity in stimulating the germination of lettuce seeds.

Cotylenins, diterpenoid glycosides, were isolated as leaf growth substances from an unidentified species of *Cladosporium* in 1970's by T. Sassa et al.[1] In 1968, two independent groups isolated fusicoccins from *Fusicoccum amygdali* as phytotoxic substances responsible for a wilting disease of peach and almond trees.[2] In spite of the inconsistency of their isolation processes, the structures of their aglycones, fusicoccane diterpenoids having 5-8-5-membered tricyclic skeleton, are closely related to each other, and their fundamental biological activities are regarded to be identical in principle,[3] so the mechanism of the biological action has been intensively studied.

Their activities, i.e., a stimulation of the seed germination, the cell enlargement, and the stomatal opening, have been clarified as the results of the promotion of H^+ extrusion associated with the uptake of K^+ in H^+/K^+ exchange system of higher plants.[4] Thus, since these metabolites mimic auxin, gibberellic acid, and cytokinin, and antagonize abscisic acid, they have been widely utilized as a powerful and general tool in plant physiology.[5]

The structure-activity relationships of these compounds and their analogs were also studied.[6,7] However, since derivations from natural products are limited to achieve the fewest modifications,[7,8] wider functional modifications via synthetic routes are desirable for further investigations. The 3α-hydroxyl of cotylenol **1**, a common aglycone of cotylenins having similar activities with its glycosides, is reported to be important for the biological activities (Fig. 1). At the same time, instability of **1** in an acidic medium is due to the feasible elimination of this tertiary allylic hydroxyl.[9] Therefore, the modification of this tertiary alcohol is interesting as regards both activities and stabilities. Herein reported are the synthesis and the biological activity of 3α-cotylenyl methyl dithiocarbonate **3**, which could be an equivalent to 3α-thiocotylenol **2** in a living system, together its three stereoisomers regarding the glycol system (**4**—**6**) (Fig. 2).

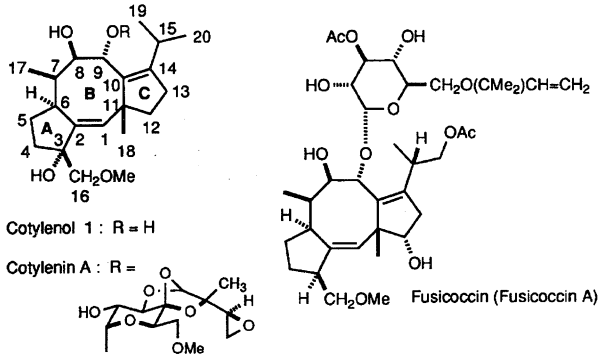


Fig. 1. Absolute stereostructure of cotylenol **1** and the representatives of cotylenins and fusicoccins.

We have recently accomplished the total synthesis of cotylenol **1**,[10] starting from the condensate **7** of two optically active iridoid synthones, **8** and **9** (Scheme 1).[11] The first step of the synthesis, the chromium(II) chloride mediated reductive condensation,[12] afforded an allylic alcohol **10** as a minor product. The formation of **10** involves reductive elimination of the epoxy group.

During our synthetic studies of **1**, we have accumulated some knowledge of allyl rearrangement for the particular type of allylic alcohols. And we thought that **10** could be used for synthesis of various 3α-substituted analogs of **1**. Therefore, **10** should be prepared directly from the allylic aldehyde, (3*S*)-6-methoxyirida-1,8-dien-

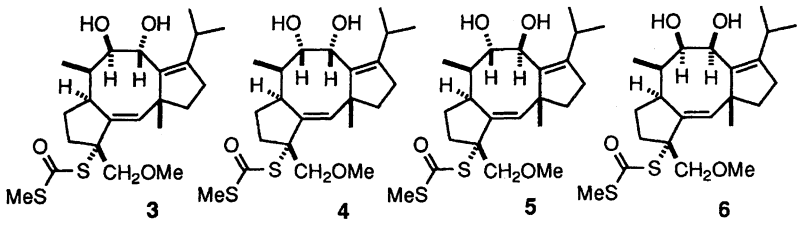
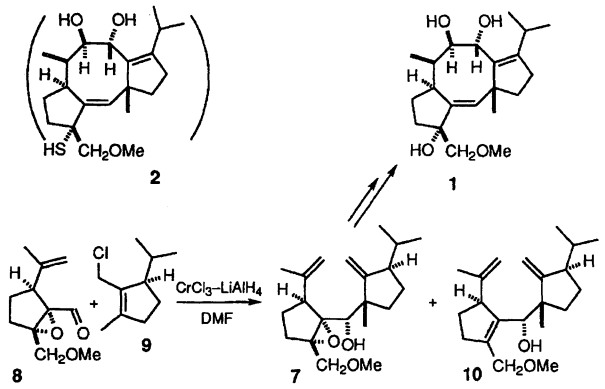


Fig. 2. Stereoisomeric 3α-cotylenyl dithiocarbonates.



Scheme 1.

7-al (**11**) and **9**. Herein described is the convenient synthesis of **3** and its stereoisomers (**4**, **5**, and **6**) in the glycol system, with a slightly modified procedure from the previous model studies,[13] in which the tricyclic fusicoccane skeleton was constructed via an intramolecular ene reaction of an appropriately functionalized *B-seco*-fusicoccane derivative.

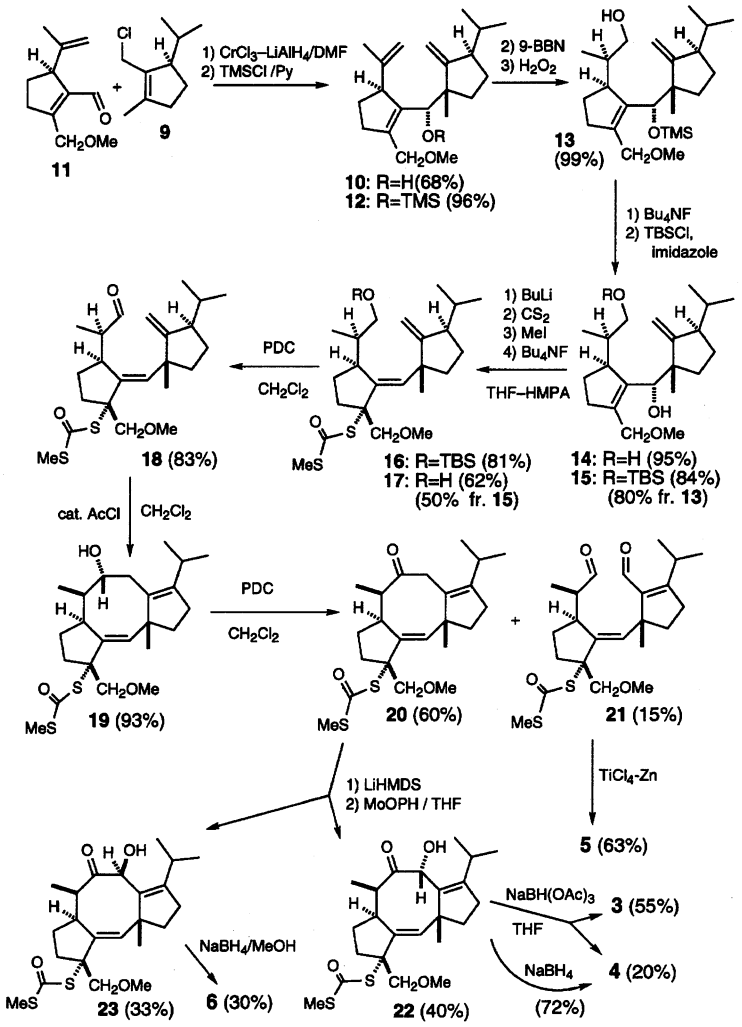
Results and Discussion

Thus, after protection of secondary hydroxyl group of **10** as a trimethylsilyl (TMS) ether (**12**), the isopropenyl substituent on A-ring was hydroborated by use of 9-borabicyclo[3.3.1]nonane (9-BBN) to give **13** stereoselectively.[11] The TMS ether of **13** was once deprotected to a glycol (**14**), of which the primary alcohol function was protected again with a bulky *t*-butyldimethylsilyl (TBS) group to afford **15** (Scheme 2). Treatment of **15** with butyllithium, carbon disulfide, and methyl iodide in a mixture of tetrahydrofuran (THF) and hexamethylphosphoric triamide (HMPA) afforded a dithiocarbonate (**16**), which was purified after the deprotection of TBS ether to give **17**, via a [3,3]sigmatropic rearrangement of an initially formed lithium *O*-(C-1)-allyl dithiocarbonate to lithium *S*-(C-3)-allyl dithiocarbonate. Using this rearrangement, a thiol function was conveniently introduced stereoselectively at C-3 position with the correct stereochemistry in a protected form. At the same time, C-1–C-2 double bond, one of the structural features of fusicoccane diterpenoids, was also introduced with a proper geometry, which was confirmed by a nuclear Overhauser effect (NOE); an enhancement (19.6%) of an olefinic proton (C-1-H) signal was observed by irradiation with one of the methylene proton signals on the carbon bearing methoxyl group (C-16). The primary alcohol of **17** was oxidized with pyridinium dichromate (PDC) to afford an aldehyde **18**, a precursor of the intramolecular ene reaction. The acid-catalyzed ene reaction of **18** occurred smoothly at ambient temperature to give the desired 5-8-5-membered tricyclic compound **19**. The α-orientation of C-8 hydroxyl was confirmed by an NOE between C-11-Me and C-8-H (10.8%).

Subsequently, the C-8 hydroxyl of **19** was converted into a ketone **20** and a dialdehyde **21** by PDC oxidation. Then an enolate of **20**, generated by lithium hexamethyldisilazanide (LiHMDS) was oxidized with oxodi(peroxo)molybdenum(VI)(pyridine)-HMPA complex[14] (MoOPH) to afford an epimeric mixture of α- and β-hydroxy ketones, **22** and **23**. The major product **22** was the desired α-hydroxy derivative, according to an NOE experiment. Reduction of **22** with sodium triacetoxyhydroborate[15] gave mainly an 8β,9α-glycol **3** (colorless prisms, mp. 124°C, $[\alpha]_D^{24}$ −110°), the target compound of this study, together with an 8α,9α-dihydroxy isomer **4** as a minor product; reduction of the related keto alcohol with sodium borohydride is known to give the *cis*-glycol **4** as the sole product in 72% yield.[10]

The remaining two isomers were easily prepared as follows: The reductive cyclization of the dialdehyde **21** gave 8α,9β-isomer (**5**), and the reduction of **23** with sodium borohydride afforded 8β,9β-isomer (**6**).

The stereochemistry of the glycol system of these compounds, **3** to **6**, was confirmed on the basis of NOE experiments. In the ^{1}H NMR spectrum of **3**, there are distinct NOE's between C-11-Me and C-9β-H (9.9%) and between C-8α-H and C-15-H (8.4%), which is conformationally located at the α-face of the eight-membered ring. The diaxial nature of the C-8β-H and C-9α-H clarified that the structure was as depicted. On the other hand, **5** showed the NOE's between C-11-Me and C-8β-H (12.6%) and between C-15-H and C-9α-H (17.4%) to deduce the diepi-structure. In addition, **4** showed NOE's C-11-Me and both C-8β-H (5.6%) and C-9β-H (9.6%) to rule out other possibilities. Although it was difficult to perform the spectroscopic analyses for the configuration of **6**, there is no ambiguity about the structure, since the structures of other three isomers have been deduced. Its ^{1}H NMR spectrum revealed a strongly low-field shifted singlet methyl signal at δ=1.43, which suggests the presence of a 9β-hy-



Scheme 2.

droxyl group.[16] The precursor (**23**) leading to **6** again provided some NOE evidence; the large magnitude of the NOE between C-15-H and C-9α-H (20.0%), which additionally showed an NOE with C-7α-H (5.9%). The observed NOE's are shown in Fig. 3.

A preliminary study on the biological activity of **3**

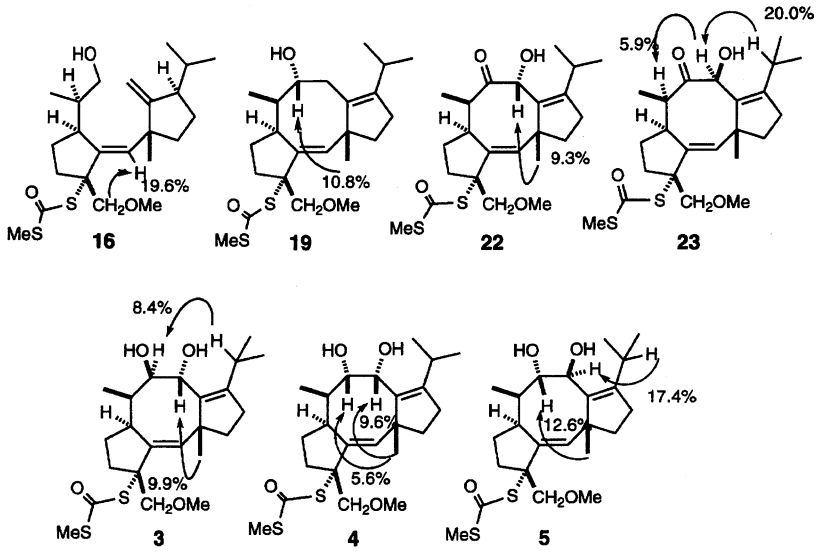


Fig. 3. The stereochemistries of key compounds, **3**, **4**, **5**, **16**, **19**, **22**, and **23**, deduced from NOE measurements.

and **5** was also carried out by a method described before;[7] the results of the germination test of lettuce seeds in the presence of 5 ppm of (±)-abscisic acid are shown in Fig. 4, from which, as expected, **3** is positive, although the activity is somewhat retarded when compared with that of natural **1**. Consequently, the replacement of the hydroxyl group with the thioester group still retained the activity. In earlier stage, the germination was overwhelming with **1** itself, but in later stage, the thio analog **3** exceeded in great deal. Thus, this induction period to develop the activity might indicate the generation of the active principle prior to the biological action; it should mean that there was hydrolysis of the thioester group to a thiol derivative **2** or a carboxythio derivative **24** (Chart 1).

Biological activity of **3** evaluated via the identical method for that of cotylenol **1** was promising one. On the other hand, **5** was inactive up to after 15 d. This suggests that *diepi*-glycol (**25**) of **1** might also be inactive; previously, derivation of **25** from the natural products has not been achieved.

Detailed evaluation of the biological activities of **3** and several other synthetically modified cotylenols will be performed by an expert, and results will be reported independently.

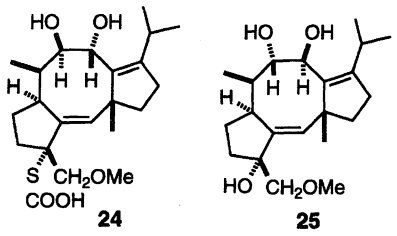


Chart 1.

Experimental

The elemental analyses were carried out by Mrs. Y. Hatazoe of the Institute of Advanced Material Study, Kyushu University. The melting points were measured with a Yanagimoto Micro Melting Point Apparatus and are uncorrected. The NMR spectra were measured by means of JEOL FX 100 Model and GSX 270H Model spectrometers in $CDCl_3$; the chemical shifts are expressed in δ units. The mass spectra were measured with a JEOL 01SG-2 spectrometer; among the data, only the molecular ion peak, or the nearest peak as the alternative, and the base peak were recorded for each sample. The IR spectra were taken as KBr disks for crystalline compounds or as liquid films inserted between NaCl plates for oily compounds, using a JASCO IR-A102 spectrometer. The stationary phase for column chromatography was Wakogel C-300 and the eluent was a mixture of hexane and EtOAc.

Condensation of 11 and 9. Characterization of the Condensate as a TMS Ether 12. To an anhydrous THF solution (100 cm^3) of $CrCl_3$ (8 g, 50.5 mmol) was added LAH (970 mg, 25.5 mmol) under an N_2 atmosphere for 30 min. After the solvent was removed in vacuo, the residue was diluted with anhydrous DMF (200 cm^3); to this a DMF solution (20 cm^3) of **9** (3.7 g, 21.4 mmol) was added and the mixture was stirred for another 2 h. The mixture was then treated at room temperature with a DMF solution (5 cm^3) of **11** (2.5 g, 13.9 mmol) and stirring was continued for 12 h. The mixture was diluted with water, extracted with ether, and washed with aq NaCl. The organic extract was chromatographed on a silica-gel column to give **10** [colorless needles, 3.0 g, 68%, mp 74 °C, $[\alpha]_D^{29}$ +200° (*c* 0.88, $CHCl_3$). Found: C, 78.85; H, 10.72%. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76%. MS *m/z* 183 ($[M-135]^+$; 3.0) and 181 (100); ^{1}H NMR δ=0.76 (3H, d, J=7.0 Hz), 0.98 (3H, d, J=7.0 Hz), 1.7 (3H, s), 1.24—1.44 (2H, m), 1.55—1.69 (2H, m), 1.70—1.82 (1H, m), 1.66 (3H, s), 1.88—2.04 (2H, m), 2.28—2.40 (2H, m), 2.49 (1H, br m), 2.93 (1H, d, J=3.5 Hz) 3.31 (1H, d, J=3.5 Hz), 3.36 (3H, s), 3.97 (1H, d, J=2.0 Hz),

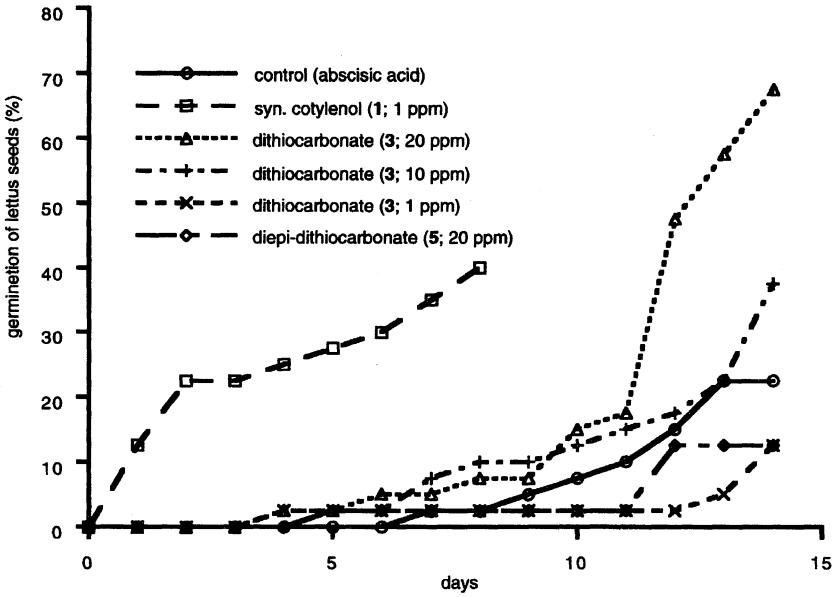


Fig. 4. Germination of lettuce seeds in the presence of abscisic acid.

4.09 (1H, d, J=12.0 Hz), 4.39 (1H, d, J=12.0 Hz), 4.69 (1H, m), 4.73 (1H, m), 4.86 (1H, d, J=2.2 Hz), and 5.00 (1H, d, J=2.5 Hz); ^{13}C NMR δ=16.2, 19.6, 22.0, 23.3, 23.5, 28.0, 28.9, 34.3, 35.0, 50.6, 52.1, 58.3, 58.6, 70.5, 75.3, 105.8, 110.9, 138.6, 141.1, 147.8, and 160.8; IR ν 3450, 2960, 2820, 1640, 1460, 1370, 1090, 940, and 890 cm^{-1}].

Then, an anhydrous pyridine solution (30 cm^3) of the above crude mixture (2.6 g, 8.2 mmol) was treated with TMSCl (1.6 cm^3, 12.2 mmol) for 8 h. The mixture was then diluted with aq $NaHCO_3$, extracted with ether, and washed with aq $KHSO_4$. The organic extract was chromatographed on a silica-gel column to give **12** [a colorless oil, 3.1 g, 96%. $[\alpha]_D^{25}$ +163° (c 1.36, $CHCl_3$). Found: C, 73.67; H, 10.88%. Calcd for $C_{24}H_{42}O_2Si$: C, 73.78; H, 10.84%. MS m/z 256 ([M−134]$^+$; 4.2) and 254 (100); ^{1}H NMR δ=0.09 (9H, s), 0.79 (3H, d, J=7.0 Hz), 0.99 (3H, d, J=6.6 Hz), 1.05 (3H, s), 1.25—1.38 (2H, m), 1.67 (3H, br s), 1.55—2.01 (5H, m), 2.23 (1H, m), 2.38—2.50 (2H, m), 3.34 (1H, m), 3.36 (3H, s), 4.15 (1H, br s), 4.34 (2H, br s), 4.69 (1H, m), 4.73 (1H, m), 4.84 (1H, d, J=2.5 Hz), and 4.93 (1H, d, J=2.9 Hz); ^{13}C NMR δ=0.5 (3C), 16.7, 19.5, 22.2, 23.6, 26.2, 28.3, 28.5, 33.2, 34.0, 51.6, 52.0, 57.7, 58.6, 70.7, 77.6, 105.9, 111.2, 139.5, 140.2, 148.2, and 160.2; IR ν 2900, 2850, 1680, 1490, 1400, 1280, 1130, 1100, 910, and 860 cm^{-1}].

Hydroboration of 12 to 13. To an anhydrous THF solution (100 cm^3) of **12** (1.26 g, 3.22 mmol) was added 9-BBN (2.3 g, 9.7 mmol) under an N_2 atmosphere for 3 h. The mixture was then treated with aq 3 M NaOH (46 cm^3, 1M=1 mol dm^{-3}) and 35%-H_2O_2 (33 cm^3) at 40 °C for 40 min. After being cooled to room temperature, the mixture was extracted with ether, washed with aq NaCl and water, and evaporated in vacuo to leave a colorless oily residue. Silica-gel column chromatography of the residue afforded **13** [a colorless oil, 1.3 g, 99%. $[\alpha]_D^{24}$ +66.7° (c 1.10, $CHCl_3$). Found: C, 70.66; H, 10.84%. Calcd for $C_{24}H_{44}O_3Si$: C, 70.53; H, 10.85%. MS m/z 344 ([M−64]$^+$; 1.0) and 181 (100); ^{1}H NMR δ=0.13 (9H, s), 0.77 (3H, d, J=7.0 Hz), 0.95 (3H, d, J=7.0 Hz), 0.97 (3H, d, J=7.0 Hz), 1.04 (3H, s), 1.22—1.38 (3H, m), 1.50—1.80 (5H, m), 1.83—2.06 (2H, m), 2.18 (1H, m), 2.22—2.43 (2H, m), 2.26 (1H, br d, J=8.8 Hz), 3.32 (3H, s), 3.33 (1H, m), 3.64 (1H, dd, J=10.0, 4.0 Hz), 4.26 (1H, br d, J=11.7 Hz), 4.31 (3H, s), 4.34 (1H, br d, J=11.7 Hz), 4.79 (1H, d, J=2.2 Hz), and 4.91 (1H, d, J=2.9 Hz); ^{13}C NMR δ=0.4 (3C), 16.7, 17.1, 22.1, 23.3, 23.6, 26.7, 28.4, 32.7, 33.8, 37.4, 51.8, 52.1, 53.6, 58.5, 64.4, 70.7, 77.7, 105.3, 139.0, 140.5, and 160.6; IR ν 3450, 2950, 2850, 1630, 1450, 1360, 1240, 1050, 870, and 830 cm^{-1}].

Hydrolysis of TMS Group of 13 to a Diol (14). An anhydrous THF solution (50 cm^3) of **13** (1.1 g, 2.69 mmol) was treated with Bu_4NF (3.2 cm^3, 3.2 mmol) under an N_2 atmosphere and this mixture was stirred for 4 h. It was then treated with aq $NaHCO_3$ and extracted with ether. Silica-gel column chromatography of the organic extract gave **14** [a colorless oil, 860 mg, 95%. $[\alpha]_D^{25}$ +81.0° (c 0.94, $CHCl_3$). Found: C, 74.88; H, 10.66%. Calcd for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78%. MS m/z 319 ([M−17]$^+$; 2.3) and 95 (100); ^{1}H NMR δ=0.77 (3H, d, J=7.0 Hz), 0.91 (3H, d, J=7.0 Hz), 0.98 (3H, d, J=7.0 Hz), 1.10 (3H, s), 1.28—1.45 (2H, m), 1.51—1.86 (4H, m), 1.94 (1H, sept. d, J=7.0, 4.0 Hz), 2.14 (1H, dqd, J=13.2, 6.6, 3.5 Hz), 2.24—2.54 (4H, m), 2.70 (1H, br d, J=8.8 Hz), 3.31 (2H, m), 3.35 (3H, s), 3.59 (1H, dd, J=11.0, 7.0 Hz), 4.02 (1H, br d, J=11.7 Hz), 4.25 (1H, br d, J=2.6 Hz), 4.39 (1H, br d, J=11.7 Hz), 4.85 (1H, d, J=2.2 Hz), and 5.02 (1H, d, J=2.9 Hz); ^{13}C NMR δ=16.5, 16.9, 22.1 22.5, 23.4, 23.9, 28.8, 34.1, 35.3, 37.9, 50.9, 51.8, 54.6, 58.4, 65.0, 70.7, 75.2, 105.6, 137.5, 142.4, and 160.9; IR ν 3400, 2950, 2850, 1640, 1450, 1360, 1080, 1020, and 890 cm^{-1}].

Selective Protection of Primary Alcohol of 14. An anhydrous DMF solution (50 cm^3) of **14** (797 mg, 2.36 mmol) was treated with TBSCl (546 mg, 2.36 mmol) and imidazole (4.84 mg, 7.1 mmol) for 4 h. The mixture was then treated with aq $NaHCO_3$ and extracted with ether. Silica-gel column chromatography of the extract afforded **15** [colorless needles, mp 57 °C, 895 mg, 84%. $[\alpha]_D^{29}$ +58.0° (c 0.90, $CHCl_3$). Found: C, 72.12; H, 11.09%. Calcd for $C_{27}H_{50}O_3Si$: C, 71.94; H, 11.18%. MS m/z 314 ([M−136]$^+$; 20.4) and 95 (100); ^{1}H NMR δ=0.03 (6H, s), 0.77 (3H, d, J=6.6 Hz), 0.89 (9H, s), 0.95 (3H, d, J=6.6 Hz), 0.98 (3H, d, J=7.0 Hz), 1.10 (3H, s), 1.24—1.43 (2H, m), 1.51—1.82 (4H, m), 1.88—2.03 (2H, m), 2.20—2.46 (3H, m), 2.66 (1H, br m), 2.99 (1H, d, J=3.7 Hz), 3.34 (3H, s), 3.34 (1H, dd, J=10.0, 8.0 Hz), 3.59 (1H, dd, J=10.0, 4.4 Hz), 4.05 (1H, br d, J=11.7 Hz), 4.34 (1H, br d, J=11.7 Hz), 4.19 (1H, br d, J=2.6 Hz), 4.85 (1H, d, J=2.2 Hz), and 5.02 (1H, d, J=3.0 Hz); ^{13}C NMR δ=−5.4, −5.3, 16.52, 16.54, 18.4, 22.1, 23.4, 23.7, 23.9, 26.0 (3C), 28.9, 34.1, 35.2, 37.8, 50.9, 52.1, 53.9, 58.2, 64.8, 70.7, 75.4, 105.6, 137.4, 142.0, and 161.0; IR ν 3450, 2950, 2850, 1640, 1460, 1360, 1250, 1080, and 830 cm^{-1}].

Treatment of 15 with CS_2 and MeI. Formation of 17. To a mixed solution of THF–HMPA (10:1, 8 cm^3) and thus obtained **15** (46 mg, 0.1 mmol) was added a hexane solution of BuLi (0.1 cm^3, 0.23 mmol) at −78 °C under an N_2 atmosphere. After 30 min of stirring, the mixture was further treated with CS_2 (0.03 cm^3, 0.45 mmol) and gradually the temperature was raised to 15 °C, where MeI (0.023 cm^3, 0.38 mmol) was added. The mixture was stirred for another 12 h to complete the reaction. The mixture was then treated with aq NH_4Cl and extracted with ether. Silica-gel column chromatography of the extract afforded **16** [a colorless oil, 45 mg, 81%. MS m/z 541 ([M+1]$^+$; 2.9) and 270 (100); ^{1}H NMR δ=0.035 (3H, s), 0.039 (3H, s), 0.79 (3H, d, J=6.6 Hz), 0.90 (9H, s), 0.95 (3H, d, J=7.0 Hz), 1.00 (3H, d, J=7.0 Hz), 1.19 (3H, s), 1.36—1.56 (2H, m), 1.58—2.12 (7H, m), 2.27 (1H, m), 2.35 (3H, s), 2.48 (1H, m), 2.97 (1H, br t, J=6.6 Hz), 3.35 (1H, dd, J=10.0, 7.3 Hz), 3.36 (3H, s), 3.65 (1H, dd, J=9.5, 3.6 Hz), 3.79 (1H, d, J=10.0 Hz), 3.91 (1H, d, J=9.5 Hz), 4.84 (1H, d, J=2.2 Hz), 4.92 (1H, d, J=2.9 Hz), and 5.58 (1H, d, J=1.8 Hz); ^{13}C NMR δ=−5.5, −5.4, 12.7, 16.2, 16.3, 18.3, 22.0, 22.9, 25.0, 25.9 (3C), 26.2, 28.7, 32.4, 39.6, 39.8, 42.4, 49.1, 49.3, 59.2, 65.2, 67.4, 76.0, 105.5, 137.3, 142.5, 162.1, and 190.5].

Subsequently, a THF solution (10 cm^3) of **16** (57.5 mg, 0.11 mmol) treated with Bu_4NF (0.16 cm^3, 0.16 mmol in THF) and this was stirred for 3 h. The mixture was then diluted with aq $NaHCO_3$, extracted with ether, and washed with aq NaCl. Silica-gel column chromatography of the organic extract afforded **17** [a colorless oil, 28 mg, 62%. $[\alpha]_D^{25}$ −53.0° (c 1.05, $CHCl_3$). Found: C, 64.83; H, 9.08%. Calcd for $C_{23}H_{38}O_3S_2$: C, 64.74; H, 8.98%. MS m/z 320 ([M−106]$^+$; 17.3) and 182 (100). ^{1}H NMR δ=0.78 (3H, d, J=7.0 Hz), 0.84 (3H, d, J=7.0 Hz), 0.99 (3H, d, J=6.6 Hz), 1.23 (3H, s), 2.35 (3H, s), 2.30—2.52 (2H, m), 2.94 (1H, m),

3.28 (1H, dd, J=12.0, 3.5 Hz), 3.36 (3H, s), 3.63 (1H, dd, J=12.0, 8.0 Hz), 3.83 (1H, d, J=9.5 Hz), 4.10 (1H, d, J=9.5 Hz), 4.84 (1H, d, J=2.6 Hz), 4.93 (1H, d, J=2.9 Hz), and 5.49 (1H, d, J=2.2 Hz); ^{13}C NMR δ=12.7, 16.3, 17.5, 22.0, 22.9, 24.2, 24.4, 28.7, 32.6, 40.2, 41.0, 42.6, 48.9, 49.0, 59.1, 65.1, 67.6, 74.3, 105.4, 137.8, 141.6, 161.8, and 190.5; IR ν 3500, 3000, 2900, 1720, 1650, 1460, 1110, and 860 cm^{-1}].

Conversion of 17 into Tricyclic Compound (19) via PDC-Oxidation and Acid-Catalyzed Ene Reaction. A CH_2Cl_2 solution (8 cm^3) of **17** (23 mg, 0.054 mmol) was oxidized with PDC (31 mg, 0.081 mmol) in the presence of Molecular Sieves 4A (40 mg) for 12 h. The mixture was diluted with ether (5 cm^3) and briefly passed through a Florisil column. Silica-gel column chromatography of the organic fractions afforded **18** [a colorless oil, 19 mg, 83%. $[\alpha]_D^{25}$ −82.5° (c 0.40, $CHCl_3$). Found: C, 65.30; H, 8.63%. Calcd for $C_{23}H_{36}O_3S_2$: C, 65.05; H, 8.55%. MS m/z 317 ([M−107]$^+$; 25.6) and 137 (100); ^{1}H NMR δ=0.78 (3H, d, J=6.5 Hz), 0.99 (3H, d, J=7.0 Hz), 1.00 (3H, d, J=7.0 Hz), 1.22 (3H, s), 1.38—1.54 (2H, m), 1.57—1.78 (3H, m), 1.88—2.08 (3H, m), 2.30 (1H, m), 2.34 (3H, s), 2.47 (1H, m), 2.73 (1H, qd, J=7.0, 6.0 Hz), 3.18 (1H, br t, J=5.5 Hz), 3.30 (3H, s), 3.76 (1H, d, J=9.5 Hz), 3.96 (1H, d, J=9.5 Hz), 4.87 (1H, d, J=2.5 Hz), 4.94 (1H, d, J=3.0 Hz), 5.64 (1H, d, J=1.5 Hz), and 9.77 (1H, d, J=1.5 Hz); ^{13}C NMR δ=12.4, 12.7, 16.2, 22.0, 22.8, 25.4, 25.9, 28.8, 31.9, 39.9, 42.2, 49.1(2C), 51.7, 59.2, 66.7, 75.7, 105.9, 138.0, 141.3, 161.2, 190.2, and 206.4; IR ν 2950, 2850, 1720, 1640, 1440, 1100, and 860 cm^{-1}].

Then, a CH_2Cl_2 solution (10 cm^3) of the above-obtained **18** (40 mg, 0.094 mmol) was treated with a catalytic amount of AcCl for 3 h. The mixture was washed with aq $NaHCO_3$ and extracted with ether (5 cm^3). Silica-gel column chromatography of the organic fractions afforded **19** [colorless needles, mp 144°C, 37 mg, 93%. $[\alpha]_D^{24}$ −42.0° (c 0.38, $CHCl_3$). Found: C, 65.15; H, 8.55%. Calcd for $C_{23}H_{36}O_3S_2$: C, 65.02; H, 8.54%. MS m/z 317 ([M−107]$^+$;10.5) and 194 (100); ^{1}H NMR δ=0.94 (3H, d, J=6.5 Hz), 0.96 (3H, d, J=6.5 Hz), 0.97 (3H, d, J=6.5 Hz), 1.21 (3H, s), 1.20—1.80 (4H, m), 1.95—2.90 (6H, m), 2.33 (3H, s), 2.62 (1H, dd, J=14.7, 11.0 Hz), 2.79 (1H, sept., J=7.0 Hz), 3.36 (3H, s), 3.51 (1H, br t, J=7.0 Hz), 3.61 (1H, td, J=5.0, 3.7 Hz), 3.84 (1H, d, J=9.9 Hz), 3.90 (1H, d, J=9.9 Hz), and 5.62 (1H, d, J=2.2 Hz); ^{13}C NMR δ=12.7, 13.5, 22.0, 21.3, 26.6, 27.2, 27.4, 29.2, 33.8, 34.9, 37.6, 41.3, 47.0, 53.8, 59.5, 67.5, 72.5, 76.0, 134.0, 137.6, 138.8, 142.7, and 190.5; IR ν 3350, 2900, 1710, 1640, 1450, 1100, and 840 cm^{-1}].

PDC-Oxidation of 19 to 20 and 21. A CH_2Cl_2 solution (8 cm^3) of **19** (16.5 mg, 0.039 mmol) was oxidized with PDC (29 mg, 0.076 mmol) in the presence of Molecular Sieves 4A (35 mg) for 12 h. The mixture was diluted with ether (5 cm^3) and stirred for a further 30 min. Silica-gel column chromatography of the organic fractions afforded **20** [a colorless oil, 10 mg, 60%. $[\alpha]_D^{14}$ +40.2° (c 0.92, $CHCl_3$). Found: C, 65.38; H, 8.21%. Calcd for $C_{23}H_{34}O_3S_2$: C, 65.36; H, 8.11%. MS m/z 316 ([M−106]$^+$; 76.7) and 284 (100); ^{1}H NMR δ=0.98 (3H, d, J=7.0 Hz), 0.99 (3H, d, J=6.6 Hz), 1.03 (3H, d, J=6.6 Hz), 1.12 (3H, s), 1.61—1.82 (3H, m), 2.02—2.29 (4H, m), 2.33 (3H, s), 2.77 (1H, sept., J=7.0 Hz), 2.86 (1H, m), 2.93 (1H, dt, J=14.3, 3.0 Hz), 3.35 (3H, s), 3.45 (1H, d, J=14.3 Hz), 3.70 (1H, d, J=10.3 Hz), 3.72 (1H, d, J=10.3 Hz), 3.85 (1H, m), and 5.64 (1H, d, J=2.2 Hz); ^{13}C NMR δ=11.5, 12.8, 20.1, 21.1, 26.9, 27.4, 27.5, 28.8, 34.2, 40.0, 40.9, 41.6, 51.2, 53.9, 59.5, 67.0, 76.2, 131.9, 137.1, 140.3, 144.6, 190.0, and 211.4. IR ν 2950, 1710, 1650, 1470, 1100, and 850 cm^{-1}] and **21** [a colorless oil, 2.5 mg, 15%. $[\alpha]_D^{15}$ +2160° (c 0.43, $CHCl_3$). Found: C, 63.28; H, 7.81%. Calcd for $C_{23}H_{34}O_4S_2$: C, 62.98; H, 7.81%. ^{1}H NMR δ=1.02 (3H, d, J=7.0 Hz), 1.12 (3H, d, J=7.0 Hz), 1.13 (3H, d, J=6.6 Hz), 1.39 (3H, s), 1.50—2.20 (7H, m), 2.33 (3H, s), 2.57 (1H, dd, J=8.8, 6.0 Hz), 2.71 (1H, m), 3.27 (1H, m), 3.32 (3H, s), 3.45 (1H, sept., J=7.0 Hz), 3.70 (1H, d, J=9.5 Hz), 3.93 (1H, d, J=9.5 Hz), 5.81 (1H, d, J=2.2 Hz), 9.71 (1H, d, J=1.0 Hz), and 9.94 (1H, s); ^{13}C NMR δ=12.8, 12.9, 21.3, 21.4, 25.6, 26.2, 26.8, 30.3, 32.1, 36.2, 42.8, 50.5, 50.7, 59.2, 66.6, 75.9, 136.4, 140.8, 143.6, 169.8, 187.0, 190.4, and 206.1].

Oxidation of 20 to 22 and 23. To an anhydrous THF solution (10 cm^3) of BuLi (1.5 cm^3, 2.5 mmol) in hexane was added $(Me_3Si)_2NH$ (0.62 cm^3, 3.0 mmol) at −78 °C and stirring was continued for 40 min. The mixture was transferred dropwise into an anhydrous THF solution (5 cm^3) of **20** (15 mg, 0.035 mmol) at −78 °C and this was stirred for 1 h. After the temperature was raised to −40 °C, the mixture was treated with MoOPH(107 mg, 0.25 mmol) for 1 h. The mixture was washed with aq Na_2SO_3 and extracted with ether. Silica-gel column chromatography of the organic extract afforded **22** [a colorless oil, 6 mg, 40%. Found: m/z 439.1989 ([M+1]$^+$) and 438.1895 (M$^+$). Calcd for $C_{23}H_{34}O_4S_2$: (M+H), 439.1977, M, 438.1899. MS m/z 439 ([M+1]$^+$; 21.0), 421 (10.2), 331 (42.6), 313 (34.5), 304 (10.7), and 299 (100); ^{1}H NMR δ=0.84 (3H, d, J=7.0 Hz), 0.98 (3H, d, J=6.6 Hz), 1.16 (3H, d, J=7.3 Hz), 1.28 (3H, s), 1.73 (1H, dt, J=12.4, 8.0 Hz), 1.85 (1H, ddd, J=12.4, 7.3, 5.5 Hz), 2.10—2.40 (6H, m), 2.34 (3H, s), 2.75 (1H, sept., J=7.0 Hz), 2.76 (1H, m) 3.33 (1H, m), 3.37 (3H, s), 3.83 (1H, d, J=4.8 Hz), 3.85 (2H, s), 4.70 (1H, d, J=4.8 Hz), and 5.88 (1H, d, J=2.2 Hz); ^{13}C NMR δ=12.8, 15.3, 19.6, 20.9, 25.9, 27.0, 27.9, 33.3, 33.7, 39.8, 40.1, 52.1, 53.2, 59.4, 67.7, 70.0, 76.0, 133.4, 138.9, 139.5, 150.4, 190.1, and 211.5] and **23** [colorless prisms, mp 116°C, 5 mg, 33%. $[\alpha]_D^{16}$ +130° (c 0.30, $CHCl_3$). Found: m/z 439.1963 ([M+1]$^+$), 438.1900 (M$^+$). Calcd for $C_{23}H_{34}O_4S_2$: (M+H), 439.1977, M, 438.1899. MS m/z 439 ([M+1]$^+$; 5.6), 421 (10.3), 369 (18.3), 367 (12.8), 331 (10.9), 329 (11.8), and 313 (100); ^{1}H NMR δ=1.07 (3H, d, J=7.0 Hz), 1.08 (3H, d, J=6.6 Hz), 1.09 (3H, d, J=7.3 Hz), 1.13 (3H, s), 1.62—1.84 (3H, m), 2.02—2.35 (5H, m) 2.34 (3H, s), 2.71 (1H, qd, J=6.6, 6.0 Hz), 3.02 (1H, sept., J=7.0 Hz), 3.34 (3H, s), 3.75 (1H, d, J=9.9 Hz), 3.85 (1H, d, J=9.9 Hz), 3.91 (1H, d, J=4.4 Hz), 3.99 (1H, m), 5.15 (1H, d, J=4.7 Hz), and 5.53 (1H, d, J=2.2 Hz); ^{13}C NMR δ=10.0, 12.8, 20.4, 21.7, 27.27, 27.30, 27.5, 28.7, 34.0, 38.5, 42.2, 50.4, 53.6, 59.5, 67.3, 72.5, 75.8, 134.4, 137.0, 139.7, 151.5, 190.0, and 212.3].

Reduction of 22 to 3 and 4. To an anhydrous THF solution (3 cm^3) of **22** (5.5 mg, 0.013 mmol) was added $NaBH(OAc)_3$ (9 mg, 0.04 mmol) gradually and this mixture was stirred for 12 h. This was then washed with aq $NaHCO_3$ and extracted with ether. Silica-gel column chromatography of the organic extract afforded **3** [colorless needles, mp 121—122°C, 3 mg, 55%. Found: m/z 441.2140 ([M+1]$^+$), 440.2050 (M$^+$). Calcd for $C_{23}H_{36}O_4S_2$: (M+H), 441.2133, M, 440.2055. $[\alpha]_D^{24}$ −100° (c 0.1, $CHCl_3$). MS m/z 441 ([M+1]$^+$; 18.4), 333 (23.8), 331 (27.5), 315 (62.4),

313 (11.1), 301 (61.1), 299 (20.9), and 283 (100); ^{1}H NMR δ=0.84 (3H, d, J=7.0 Hz), 1.02 (3H, d, J=7.0 Hz), 1.03 (3H, d, J=7.0 Hz), 1.20 (3H, s), 1.42—1.82 (5H, m), 1.96—2.28 (5H, m), 2.33 (3H, s), 2.88 (1H, br s, OH), 2.99 (1H, m), 3.27 (1H, sept., J=7.0 Hz), 3.36 (3H, s), 3.57 (1H, d, J=10.0 Hz), 3.72 (1H, d, J=10.0 Hz), 3.93 (1H, dd, J=10.0, 4.0 Hz), 4.02 (1H, d, J=10.0 Hz), and 5.66 (1H, d, J=2.2 Hz); ^{13}C NMR δ=9.7, 12.8, 20.3, 21.5, 26.4, 27.0, 28.1, 33.9, 34.8, 40.8, 42.4, 43.0, 52.3, 59.4, 68.0, 68.1, 76.0, 77.3, 136.7(2C), 138.3, 150.5, and 189.6] and **4** [a colorless oil, 1 mg, 20%. Found: m/z 441.2133 ([M+1]$^+$), 440.2066 (M$^+$). Calcd for $C_{23}H_{36}O_4S_2$: (M+H), 441.2133, M, 440.2055 (M). MS m/z 441 ([M+1]$^+$; 15.4), 423 (9.6), 391 (15.5), 331 (25.4), 301 (46.2), 315 (93.8), and 283 (100); ^{1}H NHR δ=0.92 (3H, d, J=7.0 Hz), 1.00 (3H, d, J=6.6 Hz), 1.01 (3H, d, J=7.0 Hz), 1.17 (3H, s), 1.66—1.74 (2H, m), 1.87—2.32 (9H, m), 2.33 (3H, s), 3.36 (3H, s), 3.44 (1H, m), 3.58 (1H, sept., J=7.0 Hz), 3.66 (1H, td, J=6.2, 2.0 Hz), 3.82 (1H, d, J=9.9 Hz), 3.86 (1H, d, J=9.9 Hz), 4.44 (1H, br s), and 5.64 (1H, d, J=2.2 Hz); ^{13}C NMR δ=12.7, 14.2, 20.6, 21.8, 26.7, 27.5, 27.7, 31.8, 33.9, 36.4, 41.6, 42.3, 53.3, 59.4, 67.7, 72.5, 75.8, 77.5, 134.8, 137.0, 139.1, 148.0, and 190.3].

Reduction of 22 with NaBH$_4$ to 4. An MeOH solution (5 cm^3) of **22** (5 mg, 0.01 mmol) was treated with $NaBH_4$ (2 mg, 0.05 mmol) for 1 h at 0 °C. The mixture was diluted with aq $NaHCO_3$, extracted with ether, and washed with water. Silica-gel column chromatography of the organic extract afforded **4** (a colorless oil, 3.5 mg, 72%), which was identical with the sample obtained from the preceding experiment.

Ti(II)-Mediated Coupling of 21 to 5. To an anhydrous THF solution (8 cm^3) of $TiCl_4$ (0.08 cm^3, 0.72 mmol) was added Zn powder (120 mg, 1.8 mmol) at 0 °C; this mixture was stirred for 30 min. After pyridine (0.08 cm^3, 0.9 mmol) was added to the mixture, an anhydrous THF solution (1 cm^3) of **21** (8 mg, 0.18 mmol) was introduced dropwise in a 1-h period. The mixture was then treated with aq K_2CO_3 and extracted with ether. Silica-gel column chromatography of the residue afforded **5** [colorless needles, mp 139 °C, 5 mg, 63%. Found: C, 62.36; H, 8.16%. Calcd for $C_{23}H_{36}O_4S_2$: C, 62.67; H, 8.23%. ^{1}H NMR δ=0.98 (3H, d, J=7.0 Hz), 1.01 (3H, d, J=6.6 Hz), 1.08 (3H, d, J=6.6 Hz), 1.35 (3H, s), 1.56—1.84 (4H, m), 1.88 (1H, br s, OH), 1.92—2.32 (5H, m), 2.33 (3H, s), 2.72 (1H, br s, OH), 2.93 (1H, sept., J=7.0 Hz), 3.33 (1H, m), 3.37 (3H, s), 3.57 (1H, br t, J=10.0 Hz), 3.85 (1H, d, J=10.0 Hz), 3.92 (1H, d, J=10.0 Hz), 4.44 (1H, br d, J=10.0 Hz), and 5.60 (1H, d, J=2.2 Hz); ^{13}C NMR δ=12.7, 12.9, 20.1, 22.1, 27.0, 27.5, 28.6, 28.7, 33.9, 37.7, 42.1, 43.4, 53.5, 59.5, 67.6, 71.5, 74.8, 75.9, 136.5, 137.2, 139.2, 150.8, and 190.4].

Reduction of 23 to 6. An MeOH solution (5 cm^3) of **23** (5 mg, 0.01 mmol) was treated with $NaBH_4$ (3 mg, 0.08 mmol). The mixture was diluted with aq $NaHCO_3$, extracted with ether, and washed with water. Silica-gel column chromatography of the organic extract afforded **6** [a colorless oil, 3.0 mg, 30% (in a 50% purity. ^{1}H NMR J=0.96 (3H, d, J=7.0 Hz), 1.07 (6H, d, J=6.5 Hz), 1.43 (3H, s), 1.55—2.32 (10H, m), 2.36 (3H, s), 2.65 (1H, m), 2.91 (1H, sept., J=7.0 Hz), 3.38 (3H, s), 3.45 (1H, m), 3.81 (1H, d, J=9.0 Hz), 3.94 (1H, m), 4.13 (1H, d, J=9.0 Hz), 4.63 (1H, m), and 5.57 (1H, d, J=2.2 Hz)] which constitutes an inseparable mixture with an identified product. Attempted isolation of compounds has been unsuccessful.

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16) It has been noticed that the singlet methyl signal of C-11 can be a good measure of the stereochemistry of substituents on C-9; e.g., 8β,9β-dihydroxy-1α-(trimethylsiloxy)-fusicocca-2,10(14)-diene showed at δ=1.20, whereas 8β,9α-isomer showed at 1.04 in $CDCl_3$, respectively. Regularity of chemical shifts for the methyl group as well as other groups will be reported elsewhere.