SYNTHESIS OF CHIRAL CYCLOHEXANES FROM LEVOGLUCOSENONE AND ITS APPLICATION TO AN INDOLE ALKALOID RESERPINE[1]

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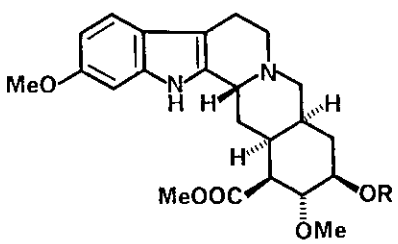
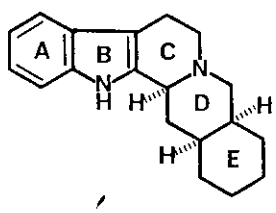
Abstract— The synthetic studies directed toward an indole alkaloid reserpine 1 is described in the form of 40 as optically active manner starting from Diels-Alder cycloaddition to a carbohydrate derivative, levoglucosenone 3.

INTRODUCTION Synthesis of the optically active natural products has recently been of a major interest in the preparation from such practical chiral pool as carbohydrates that can potentially be introduced into the asymmetric frameworks in short steps. As one of our continous studies on the natural product total syntheses starting from carbohydrates[2], we would like to contribute to a new construction of chiral pentacyclic skeletons of indole alkaloids such as reserpine.[3] We have already reported the synthesis of allo-yohimbane 2 along this line.[4] Here is described the principle of above strategy by demonstrating the synthesis of the chiral intermediate for reserpine,[5] in which the key steps are (i) the initial Diels-Alder cycloaddition to afford the E-ring, (ii) further functionalization involving hydroxylation and one-carbon fragment introduction and (iii) cleavage of the notorious 1,6-anhydro pyranoside bridge under eliminative Wolff-Kishner reduction.



Reserpine 1



allo-Yohimbane 2

Diels-Alder Strategy for the Construction of the Chiral Cyclohexanes The chiral dienophile, levoglucosenone 3, was prepared by pyrolysis from cellulose micro-crystalls[6] and the dienes **4a-d** were examined to give the cycloadducts 5 and 6 and a dehydrated derivative 7. The simplest 1,3-butadiene **4a** afforded **5a** with the best result in 98% yield. 1-Acetoxy-1,3-butadiene **4b** (X=OAc) gave the adduct **5b** as the major product with the eliminated product 7 in the ratio of 3:1. Long time heating gave only 7 in quantitative yield (entry 3). Reaction with 1-trimethylsiloxy-1,3-butadiene **4c** yielded a mixture of endo-and exo-adducts, **5c** and **6c** (X=$OSiMe_3$) in a ratio of 2:1 in 91% yield. Introduction of 2-methoxy-5-benzyloxy-1,3-pentadiene **4d** may be suitable for the direct introduction of the carbon-backborn for reserpine, but the products obtained in 38% yield were a mixture of stereoisomers. Shafizadeh et al. have reported the endo-addition in case of the cyclopentadiene as the diene toward levoglucosenone.[7] The strereochemistry of the cyclo-adducts with butadiene has been confirmed to be endo by converting into chiral allo-yohimbane.[4]

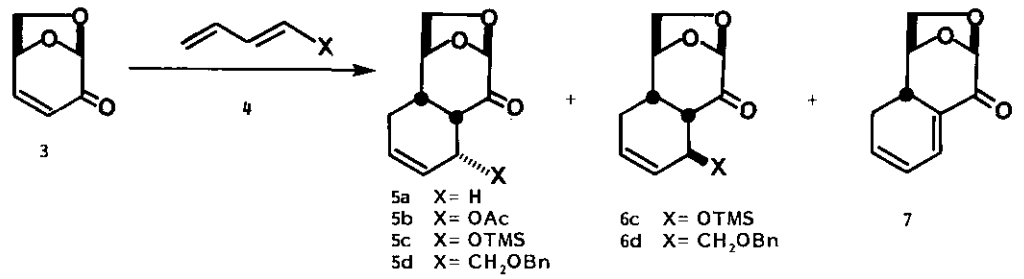


Table 1 Diels-Alder Cyclo Addition to Levoglucosenone

entry	diene 4 X	product ratio 5 : 6 : 7	yield(%)
1	H	1 : 0 : 0	98
2	OAc	3 : 0 : 1	83
3	OAc	0 : 0 : 1	100
4	OTMS	2 : 1 : 0	91
5	CH_2OBn	1 : 1 : 1	38

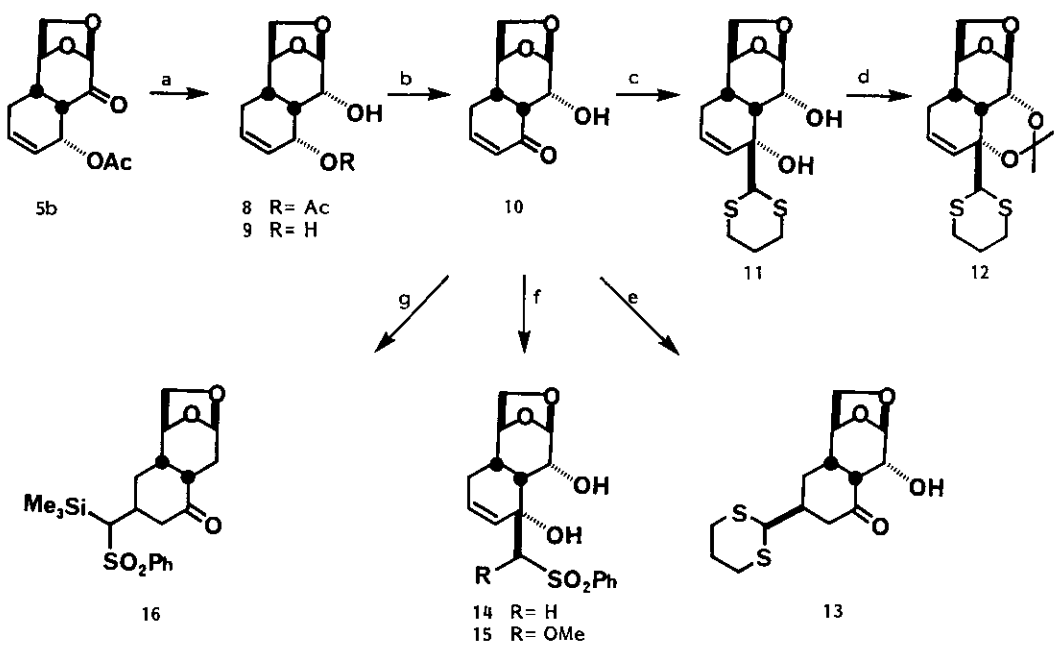
Introduction of a One-carbon Fragment into the Diels-Alder Adduct The Diels-Alder adduct **5b** was not necessarily purified by chromatography at this stage for reserpine synthesis because it was convertible into a crystalline **8** by treatment of the cycloaddition mixture with $NaBH_4$ in MeOH. The oxyacetate **8** was recrystallized to afford colorless plates (mp 122 °C) in 92% yield. Methanolysis of the acetate in **8** with NaOMe/MeOH was followed by neutralization with Amberlite IR-122 to give the diol **9** (mp 132 °C). Its allylic oxidation with MnO_2 afforded the enone **10** (mp 179 °C),

in which the remaining hydroxy group was not protected to prevent from its elimination during the following step.

Introduction of a one-carbon fragment into the enone 10 was rendered with 2-lithio-1,3-dithiane in tetrahydrofuran (THF) at 0°C to afford 11 (mp 178°C) in 93% yield. The diol 11 was convertible into the acetonide 12 indicating the stereochemistry of the hydroxy groups as shown. On the other hand, the same nucleophile was added to the same enone 10 in a mixture of THF and hexamethylphosphoric triamide (HMPA)[8] (3:1) to afford largely the 1,4-adduct which crystallized from the reaction mixture to give 13 (mp 196°C decomp).

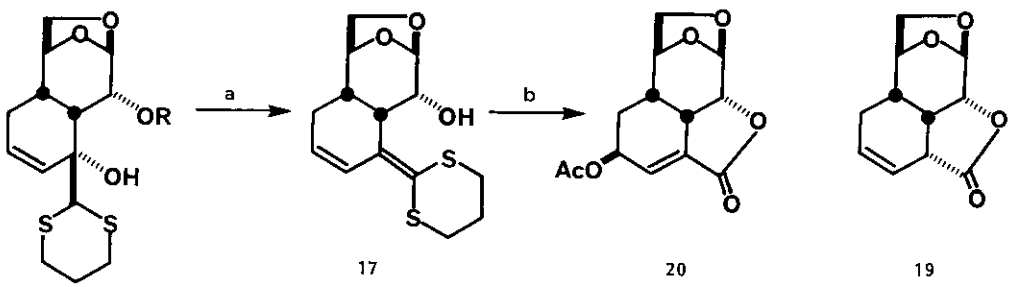
Another one-carbon fragment was introduced in the form of benzensulfonylmethyllithium ($PhSO_2CH_2Li$) into the enone 10 to give 14 and its epimer in the ratio of 10:1 in 96% yield.

The other one-carbon fragment, $PhSO_2(MeO)CHLi$, was introduced into the enone to afford the 1,2-adduct 15 in only 42% yield, which was not used for further synthesis. Addition of $PhS(Me_3Si)CHLi$ to the same enone under the same condition afforded largely the 1,4-adduct 16 in a ratio of 4:1 with the corresponding 1,2-adduct.



Scheme 2 a) $NaBH_4$/MeOH (92%); NaOMe/MeOH (100%). b) MnO_2/CH_2Cl_2 (89%). c) LiCH-$[(SCH_2CH_2)_2CH_2]$/THF (93%). d) $(CH_3)_2C(OMe)_2$/acetone/CSA (99%). e) $LiCH[(SCH_2CH_2)_2CH_2]$/THF-HMPA (80%). f) R= H, $LiClH_2SO_2Ph$/THF (88%); R= OMe, $LiCH(OMe)SO_2Ph$/THF (42%). g) LiCH(TMS)SPh/THF (53%).

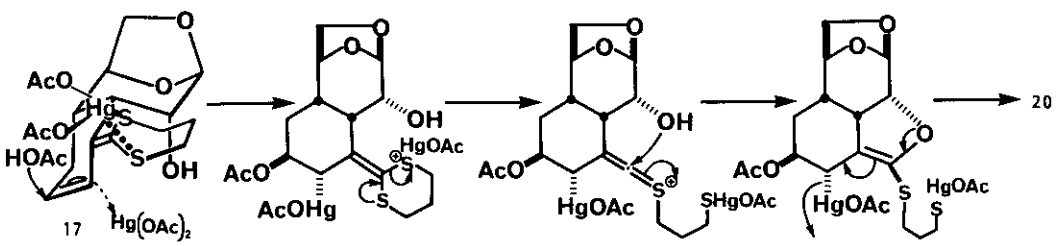
Functionalization and Stereochemistry of E-ring for Reserpine Treatment of the diol 11 with ethyl chlorocarbonate and diazabicycloundecene (DBU) in benzene at 80°C for 2 h gave the dithioketene acetal 17 [102.3, 125.2, 127.4 and 131.9 ppm] in quantitative yield. When this reaction was carried out at room temperature, 11 was first converted into the carbonate 18 [ir 3430, 1738, 1720 cm^{-1}] which was then heated to cyclize into a cyclic carbonate with loss of water. Attempted lactonization to 19 occurred under no condition. Instead, this oil 17 was converted into the lactone 20 [mp 135°C, ir 1772, 1740 cm^{-1}] by treatment with mercury(II) acetate at 60°C for 4 h in 85% yield. The conformation of the cyclohexene ring in 20 was a twist boat judging from the coupling constants [$J_{9,10}$= 9.0, 5.0Hz]. This was supported by comparing with the released conformation which showed the corresponding numbers of the methyl ester 21 [J= 5.0, 1.0Hz] to conclude the acetoxy group in 20 and 21 to be beta, equatorial. The stereochemistry at C-9 was further established by the sequence shown in Scheme 5, which leads to the inversion of configuration at this center by sodium borohydride reduction. Each diastereoisomer due to the asymmetric center on THP, 22 and 26, was respectively separated but none of them was identical to each other. In 25, the coupling constant between H-9 and H-10-alpha was 10 Hz which indicated that the hydroxy group elaborated by the reduction should be equatorial.



11 R= H
18 R= COOEt

17 20 19

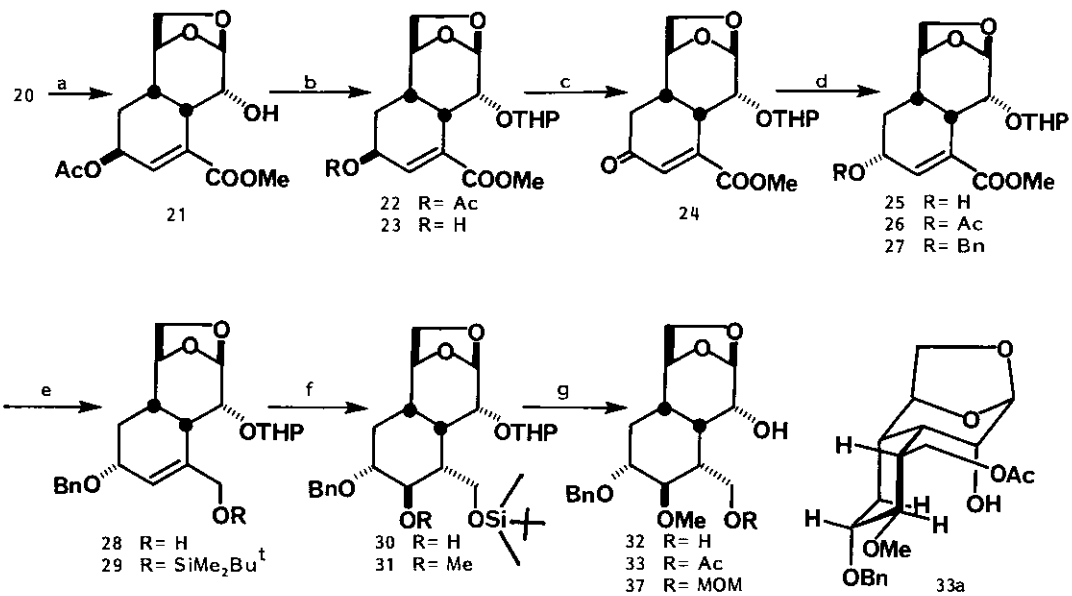
Scheme 3 a) EtOCOCl/DBU/PhH/80°C (quant.). b) $Hg(OAc)_2$/AcOH/60°C (85%).



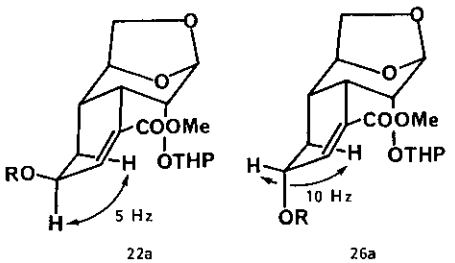
Scheme 4

A possible mechanism of the formation of the gamma-lactone 20 is illustrated in Scheme 4. Initial step may be the coordination of Hg^{++} with one of the sulfur atoms to block the beta-face of the diene. Another mercury approaches to the endo-olefin from the opposite alpha-face so that the acetoxy group should attack from the beta-face in diaxial manner. Mercurium group can be eliminated by accepting the electron donated from the hemithioketene acetal group to form the olefin of 20.

The hydroxy group of 25 was protected as benzyl ether 27, and its ester carbonyl was reduced with lithium aluminum hydride into 28, which was protected as 29. Hydroboration was designed on 29 so that the reagent should attack the olefin from beta-face, and in fact diborane afforded the alcohol 30 in 96% yield, which was methylated to 31. Acidic treatment with CSA produced the diol 32 in 71% overall yield in 5 steps. Pmr analysis of its mono-acetate 33 at 500 MHz showed that the protons H-7, H-8, H-9 and H-10 couple in 10.8, 10.8 and 8.4 Hz to each other to conclude the all axial protons. Thus, the stereochemistry of the E-ring for reserpine was established.

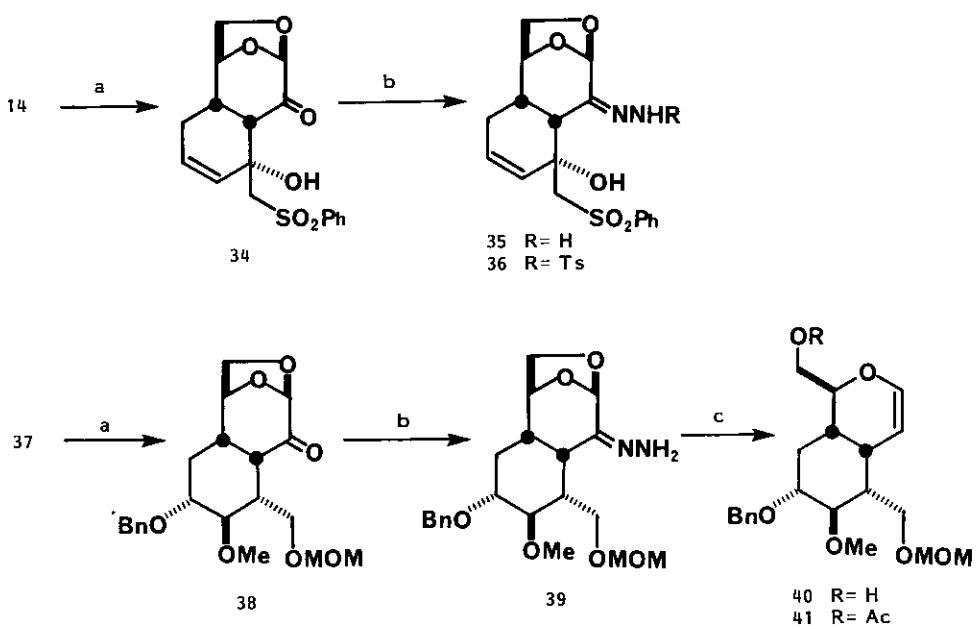


Scheme 5 a) Et_3N/MeOH (82%). b) DHP/CH_2Cl_2/PPTS (86%); NaOMe/MeOH (89%). c) PDC/CH_2Cl_2 (96%). d) $NaBH_4$/MeOH (86%); Ac_2O/Py; BnBr/NaH/DMF/KI (60%). e) $LiAlH_4$/THF; TMDBSCl/imidazol/THF. f) BH_3/THF; H_2O_2/NaOH; MeI/LiN(TMS)/DMF (71% overall yield in 5 steps). g) Ac_2O/Py/CH_2Cl_2; $MeOCH_2Cl$/$(i\text{-}Pr)_2EtN$/THF (95%).



Cleavage of the 1,6-Anhydrobridge Carbonyls of C-2 position would be utilized according to our eliminative Wolff-Kishner strategy established in the allo-yohimbane synthesis.[4] So the major isomer **14** (mp 150°C) was converted into the hydrazones **35** and **36** via the ketone **34** (mp 175°C, decomp), but a base treatment of the hydrazones **35** and **36** decomposed into a mixture of enones with concomitant C-C bond cleavage indicating no production of the corresponding vinyl-ether.

Oxidation of the diol **32** with Jones reagent ended up with the formation of five-membered lactone and hemiketal. The primary hydroxy group in **32** was protected as MOM-ether **37** (mp 98°C, 95% yield) and then converted into the ketone **38** in 73% yield. It was first converted into the hydrazone **39** and then treated with dimsyl anion [$NaCH_2S(O)CH_3$] at room temperature to produce **40** in 67% overall yield. It was characterized as its acetate **41** (mp 92°C). The final steps for coupling with tryptamine residue have already been established in the allo-yohimbane synthesis, which would applicable to the reserpine intermediate **40**.



Scheme 6 a) Jones/acetone (73%). b) $NH_2NH_2/Et_3N/70°C$. c) $NaCH_2S(O)CH_3$/DMSO (67% overall yield in 2 steps)

The Diels-Alder cycloaddition strategy to levoglucosenone **3** was demonstrated to be practically useful for production of chiral cyclohexanes.

EXPERIMENTAL

Diels-Alder cycloaddition with levoglucosenone 3: A mixture of levoglucosenone [crude partly purified mass of the pyrolysis[5] (15.0 g)] and 1,3-butadiene (35 ml) was heated in a sealed glass cylinder for 10 h at 140°C. After cooling, the reaction mixture was dissolved in CH_2Cl_2 [200 ml] and the solution was passed through a glass column containing SiO_2 and brine. The product was eluted with ether, and the eluate was evaporated to dryness affording solid, which was crystallized and re-crystallized from a mixture of CH_2Cl_2 and hexane. 5a (mp 66.0°C colorless rods) amounted in 20.9 g (98% yield); ^{13}C nmr 20.4, 24.1, 38.1, 40.5, 67.2, 77.2, 101.5, 123.8, 124.4, 201.7 ppm; ir 1740, 1660 cm^{-1}; $[\alpha]_D$ -55.2° (c= 1.00, $CHCl_3$).

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.66; H, 6.75.

Levoglucosenone [10.0 g] was heated with 1-acetoxy-1,3-butadiene [52.5 g as a mixture of E/Z= 2:1] at 80°C for 7 h, and the reaction mixture was evaporated to give residue of crude 5b [17.3 g]. Part of this residue [1.38 g] was dissolved in MeOH[46 ml] and stirred with $NaBH_4$ [330 mg] for 6 min at 0°C. The product 8 was taken with CH_2Cl_2 and crystallized from a mixture of CH_2Cl_2 and hexane to give crystals 8 (mp 122.0°C, ^{13}C nmr 20.9, 26.0, 31.1, 34.7, 66.6, 67.7, 69.5, 75.8, 102.5, 125.7, 130.3, 170.1 ppm; ir 3600, 1755, 1735 cm^{-1}; $[\alpha]_D$ +14.3° (c= 1.00, $CHCl_3$).

Anal. Calcd. for $C_{12}H_{16}O_5$: C, 60.00; H, 6.71. Found: C, 59.92; H, 6.67.

Hydrolysis of the acetate 8 A solution of 8 [19.6 g in MeOH 400 ml] was stirred with MeONa [2.16N, 10 ml] for 1 h at room temperature. Neutralization with Amberlite IR-122 was followed by filtration and crystallization from a mixture of CH_2Cl_2 and hexane to give 9 (mp 132.0°C, ^{13}C nmr 26.0, 33.0, 34.9, 66.5, 67.7, 75.9, 102.7, 127.8, 130.5 ppm; ir 3450, 1660 cm^{-1}; $[\alpha]_D$ +4.2° (c= 1.01, $CHCl_3$);

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.40; H, 7.08.

Oxidation of the allyl alcohol 9 The diol 9 [12.3 g] was dissolved in CH_2Cl_2 [400 ml] and the solution was stirred with MnO_2 [54.0 g] at room temperature for 18 h. The mixture was filtered through a Celite cake, and the filtrate was concentrated to give crystals, which were re-crystallized from a mixture of CH_2Cl_2 and hexane to produce the enone 10 [mp 179.0°C, 11.0 g in 89% yield]: ^1H nmr 2.21(1H, q, J= 6.0), 2.42(2H, br; 1H D_2O exchangeable, 1H, dt, J= 18.5, 6.0), 2.79(1H, dd, J= 6.5, 4.5), 2.96(1H, ddt, J= 18.5, 11.8, 2.5), 3.88(2H, ABq), 3.96(1H, br), 4.41(1H, br), 5.43(1H, s), 6.14(1H, dd, J= 10.2, 2.0), 7.11(1H, ddd, J= 10.2, 8.2, 2.0); ^{13}C nmr (in $CDCl_3$:CD_3OD 1:1) 27.7, 37.0, 42.9, 67.1, 68.7, 75.3, 102.4, 129.9, 152.3, 200.3 ppm; ir 3400, 1665 cm^{-1}; $[\alpha]_D$ +223.8° (c= 1.00, $CHCl_3$).

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.22; H, 6.17. Found: C, 61.07; H, 6.12.

1,2-Addition of lithio m-dithiane to the enone 10 n-BuLi [1.55M in hex. 49 ml] was added to a solution of 1,3-dithiane [9.48 g in THF 100 ml] at 0°C and stirred for 30 min. The enone 10 [5.00 g in THF 50 ml] was added to this anionic solution at 0°C. After half an hour, to the reaction mixture was added sat. NH_4Cl and the product was extracted with EtOAc. The crude product was purified with silica gel chromatography (ether:hexane 1:1) and the eluate was crystallized and re-crystallized from a mixture of CH_2Cl_2 and hexane to give 11 in 93% yield as colorless rods (mp 178°C): ^1H nmr 3.14(1H, s), 3.84(1H, br), 3.84(1H, dd, J= 7.2, 5.0), 3.97(1H, d, J= 7.2), 4.20(1H, s), 4.34(1H, d, J= 5.0), 5.44(1H, d, J= 2.5), 5.76(1H, d, J= 10), 6.04(1H, ddd, J= 10.0, 4.8, 2.5): ^{13}C nmr (in $CDCl_3$:CD_3OD 1:1) 25.5, 29.6, 30.2, 34.6, 35.3, 59.6, 66.0, 67.9, 73.0, 75.3, 101.9, 129.5, 129.7 ppm: ir 3440 cm^{-1}: $[\alpha]_D$ + 75.3° (c= 1.00, $CHCl_3$).

Anal. Calcd. for $C_{14}H_{20}O_4S_2$: C, 53.14; H, 6.37. Found: C, 53.21; H, 6.40.

1,4-Addition of lithio m-dithiane to the enone 10 To a solution of lithiated m-dithiane [3.67 g in THF (100 ml) generated with n-BuLi (17.2 ml)] was added HMPA (60 ml) and the enone 10 [2.0 g (10.2 mmol)] at -78°C and the mixture was stirred at this temperature for 1.75 h and then at ambient temperatures by removing the cooling bath. The product was worked-up with CH_2Cl_2 and crystallized from a mixture of CH_2Cl_2 and hexane to produce the 1st crystals (1.845 g in 67% yield) of 13 [mp 196°C decomp.]: ^1H nmr 3.85(2H, m), 3.95(1H, d, J= 8), 4.42(1H, m), 5.40(1H, d, J= 2.5): ir 1700 cm^{-1}.

Anal. Calcd. for $C_{14}H_{20}O_4S_2$: C, 53.14; H, 6.37. Found: C, 53.12; H, 6.46.

Preparation of the acetonide 12 The adduct 11 [27 mg] was dissolved in acetone [0.5 ml] and mixed with 2,2-dimethoxypropane [0.3 ml] in the presence of a few miligram of CSA (camphor sulfonic acid) at room temperature for 50 min. The reaction mixture was poured into sat. $NaHCO_3$ and extracted with ether. The product was purified on tlc (ether:hexane 2:1) to produce the acetonide 12 (30 mg quantitative yield). ^1H Nmr 1.36(3H, s), 1.48(3H, s), 1.7-2.3(4H, m), 2.6-3.0(6H, m), 3.62(1H, dd, J= 5.0, 2.0), 3.76-4.04(2H, ABX, centered at 3.90, J_{AX}= 5.0), 4.32(1H, s), 4.38(1H, d, J= 5.0), 5.45(1H, d, J= 2.0), 5.57-6.26(2H, ABX, centered at 5.92, J= 6, 3, 2).

Preparation of the dithio-ketene acetal 17 The adduct 11 [1.00 g] was dissolved in benzene [23 ml] and the solution was stirred with ethyl chlorocarbonate [1 ml] and DBU [5 ml] at 80°C for 2 h. The reaction mixture, after cooling, was diluted with ether and it was washed with 1N HCl, water, aq. $NaHCO_3$ and sat. NaCl. The ethereal solution was passed through a glass column containing Na_2SO_4 and SiO_2 and the eluate was evaporated to give 17 [940 mg]: ^{13}C nmr 24.6, 27.3, 29.4, 34.4, 35.4, 66.9, 69.0, 76.0, 102.3, 125.2, 127.4, 131.9 ppm; ir 3500 cm^{-1}; $[\alpha]_D$ + 342.7° (c= 0.07, $CHCl_3$).

Unsaturated lactone 20 from the dithioketeneacetal 17 A solution of 17 [486 mg in 1% H_2O in AcOH (16.5 ml)] was stirred with $Hg(OAc)_2$ [4.95 g] at 60°C for 4 h. The reaction mixture was evaporated to dryness and the residue was suspended in CH_2Cl_2 and filtered. The filtrate was concentrated and crystallized by addition of hexane to the residual solution. The product 20 was obtained in 85% yield (370 mg): mp 135°C: ^1H nmr 1.98(1H, ddd, J= 13.5, 9.0, 4.5), 2.08(3H, s), 2.20(1H, dt, J=13.5, 5.0), 2.38(1H, br), 3.15(1H, br), 3.70(2H, ABq), 4.34(1H, d, J= 4.0), 4.42(1H, d, J= 8.5), 5.36(1H, s), 5.60(1H, br), 6.74(1H, t, J= 4.0): ^{13}C nmr 20.8, 31.7, 31.9, 34.8, 67.0, 71.1, 74.5, 100.6, 131.7, 133.1, 168.0, 170.1 ppm: ir 1772, 1740 cm^{-1}: $[\alpha]_D$ -149.0° (c= 1.03, $CHCl_3$).

Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58.65; H, 5.30. Found: C 58.73; H, 5.35.

Opening of the lactone to 21 The unsaturated lactone 20 [235 mg] was dissolved in MeOH [7.5 ml] and stirred with Et_3N [0.2 ml] at room temperature for 1 h. The product was concentrated to dryness and the residue was separated with SiO_2 tlc to afford 21 in 82% yield: mp 167°C: ^1H nmr 1.71(1H, d, J= 11, D_2O exchangeable), 1.88(2H, br), 2.04(3H, s), 2.34(1H, td, J= 15.2, 4.5), 3.04(1H, t, J= 4.7), 3.76(3H, s), 3.90(1H, dd, J= 7.2, 5.0), 3.94(1H, br), 3.97(1H, d, J= 7.2), 4.40(1H, d, J= 5.0), 5.43(1H, d, J= 2.0), 5.51(1H, td, J= 5.0, 1.0), 7.14(1H, d, J= 5.0): ^{13}C nmr 21.0, 29.3, 31.9, 32.6, 51.9, 66.0, 67.4, 67.5, 76.1, 101.7, 133.8, 136.5, 166.1, 169.8 ppm: ir 3500, 1735, 1720, 1650 cm^{-1}: $[\alpha]_D$ -188° (c= 1.00, $CHCl_3$).

Anal. Calcd. for $C_{14}H_{18}O_7$: C, 56.37; H, 6.08. Found: C, 56.34; H, 6.07.

Protection of the hydroxy group in 21 to 22 The methyl ester 21 [187 mg] was dissolved in CH_2Cl_2 [9 ml] and mixed with dihydropyran [0.5 ml] in the presence of PPTS [30 mg] at room temperature for 2.5 h. The product, after usual work-up, was separated into two isomers respective to the diastereoisomer caused by the protective group THP.

The polar 22 ^1H nmr 2.04(3H, s), 2.54(1H, td, J= 15.0, 5.0), 3.16(1H, t, J= 4.5), 3.34(1H, br), 3.52(1H, br), 3.74(3H, s), 3.83-3.99(2H, ABX, centered at 3.93; J_{AX}=5.2, J_{BX}= 0.7), 3.92(1H, br), 4.38(1H, d, J= 5.2), 4.61(1H, brs), 5.42(1H, d, J= 2.2), 5.52(1H, brt, J= 4.5), 7.09(1H, d, J= 5).

The less polar 22 ^1H nmr 2.04(3H, s), 2.56(1H, td, J= 15.0, 5.0), 3.11(1H, t, J= 5.0), 3.46(1H, br), 3.76(3H, s), 3.78(1H, br), 3.82(1H, br), 3.83-3.98(2H, ABX, centered at 3.94, J_{AX}= 5.0, J_{BX}= 0.5), 4.30(1H, br s), 4.38(1H, d, J= 5.0), 5.49(1H, t, J= 5.0), 5.57(1H, d, J= 2.2), 7.06(1H, d, J= 5.0).

Inversion of the configuration of the hydroxy group in 23 to 25 A solution of 22 [206 mg in MeOH (6.5 ml)] was stirred with MeONa [2.16N in MeOH, 0.2 ml] at room termperature for a quarter hour to the alcohol 23 (89% yield). The hydroxy group in 23 [236 mg] was oxidized in CH_2Cl_2 [8 ml] with PDC [1.5 g] at room temperature for 7 h. The reaction mixture was diluted with ether [40 ml]

and then passed through a glass column containing silica gel. Evaporation of the eluate afforded the enone **24** in 96% yield. The ketone **24** [96.3 mg in MeOH (4 ml)] was reduced with $NaBH_4$ until the starting carbonyl disappeared. The regular work-up afforded **25** (83 mg) in 86% yield. Acetylation of **25** with Ac_2O in pyridine gave the corresponding acetate **26**: ^1H nmr 2.04(1H, br), 2.10(3H, s), 2.37(1H, m), 3.03(1H, brt, J= 4.5), 3.46(1H, br), 3.75(3H, s), 3.81(1H, t, J= 2.2), 3.81-3.93(2H, ABX, centered at 3.87, J_{AX}= 5.0, J_{BX}= 1.0), 3.90(1H, br), 4.33(2H, br), 5.50(1H, ddd, J= 10.0, 7.0, 2.0), 5.60(1H, d, J= 2.2), 6.90(1H, br).

Preparation of the diol **32** The alcohol **25** [80 mg dissolved in DMF (2 ml)] was introduced into the suspension of NaH [60 mg in DMF (2 ml)]. This solution was stirred with benzyl bromide [0.1 ml] with ca. 100 mg of KI at room temperature for 1 h. The reaction mixture was damped into an ice with NH_4Cl and the product was extracted with ether, purified with silica gel (ether:hexane 3:1) to afford **27** in 60% yield (61 mg).

The benzyl ether **27** [499 mg in THF (20 ml)] was stirred with $LiAlH_4$ [200 mg] at room temperature for 10 min. To the reaction mixture was added EtOAc, after 5 min the organic layer was washed with sat. potassium sodium tartrate and sat. NaCl, dried over Na_2SO_4 and silica gel column. The product **28** was used for the following reaction without purification. The product was dissolved in THF [20 ml] and stirred with t-butyldimethylchlorosilane [300 mg, imidazole 1.09 g] at room temperature for 20 min. The silyl ether **29** was taken into ether [60 ml] and the crude product **29** was used without purification for the next step.

To a solution of **29** in THF [20 ml] was added diborane [1M THF, 6 ml] at 0°C and stirred for 40 min. The reaction mixture was further stirred for 4h at room temperature by mixing with 1N NaOH [6 ml] and hydrogen peroxide [30%, 6 ml]. A solution of sodium sulfite was added to this reaction mixture, while KI starch test paper became negative. The alcohol **30** was taken by ethereal work-up and used without purification for the next step. **30** was dissolved in a mixture of THF [5 ml] and DMF [5 ml] and stirred with MeI [1 ml] and lithium bis-trimethylsilylamide [1.2M hexane solution 2 ml] at room temperature for 30 min. The product **31** was dissolved in MeOH [30 ml] and stirred with CSA [100 mg] at 50°C for 50 min. The reaction mixture was concentrated to 15 ml in vacuo, neutralized with $NaHCO_3$ and then extracted with EtOAc. The product was purified with silica gel tlc (EtOAc:ether 1:1) to afford **32** (290 mg) in 71% overall yield for 5 steps: crystallized mp 139.0°C: ^1H nmr 1.52(1H, m), 1.72(1H, m), 1.94-2.20(2H, m), 2.78(1H, s, D_2O exchangeable), 3.06(1H, d, J= 8.0, D_2O exchangeable), 3.41(1H, m), 3.73(3H, s), 3.6-4.0(6H, m), 5.30(1H, brs), 4.59-4.72(2H, ABq, centered at 4.66), 6.36(1H, d, J= 2.2), 7.34(5H, m): ir 3450 cm^{-1}: $[\alpha]_D$ -21.9° (c= 0.96, $CHCl_3$).

Anal. Calcd. for $C_{14}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 65.14; H, 7.71.

Mono-acetate 33 The diol 32 [157 mg] was dissolved with CH_2Cl_2 [2.5 ml], stirred with pyridine [2.2 ml] and acetic anhydride [1.1 ml] at room temperature for 16 h. The reaction mixture was evaporated to dryness and crystallized from a mixture of CH_2Cl_2 and hexane to produce 33 (150 mg) in 85% yield: colorless needles, mp 125°C: ^{1}H nmr (500 MHz) 1.56(td, J= 12.0, 4.8, H_4), 1.84(d, J= 7.8, D_2O exchangeable), 1.98-2.06(3H, m, H_7, 2xH_{10}), 2.06(3H, s), 2.19(q, J= 4.8, H_3), 3.40(ddd, J= 10.8, 8.4, 5.4, H_9), 3.58(3H, s), 3.64(dd, J= 10.8, 8.4, H_8), 3.64(1H, br), 3.82-3.88(ABX, centered at 3.85, J_{AX}= 4.8, 2xH_6), 4.32(t, J= 10.8, H_{11}), 4.33(brd, J= 4.8, H_5), 4.44(dd, J= 10.8, 3.6, H_{11}), 4.65-4.70(ABq, centered at 4.68), 5.34(d, J= 2.2, H_1), 7.2-7.4(5H): ir 3450, 1730 cm^{-1}.
Anal. Calcd. for $C_{21}H_{28}O_7$: C, 64.27; H, 7.19. Found: C, 64.23; H, 7.14.

Protection of the primary hydroxy group in 32 A mixture of the diol 32 [398 mg], ethyl-diisopropylamine [2 ml], methyl chloromethyl ether [0.2 ml] and KI [1.0 g] in THF [12 ml] was stirred at room temperature for 20 h, and then this mixture was further stirred with additional chloromethyl methyl ether [0.2 ml] for additional 3 h at 50°C. The crude material (480 mg) was purified with a silica gel column (ether) to give the alcohol 37 (425 mg in 95% yield): white needles, mp 98.0°C: ^{1}H nmr 1.3-2.4(5H, br), 3.02(1H, d, OH),3.38(3H, s), 3.38(1H, m), 3.58(3H, s), 3.63-3.84(5H, m), 3.92(1H, dd, J= 9.6, 6.3), 4.32(1H, br), 4.58-4.72(4H, m), 5.40(1H, d, J= 2.2), 7.23-7.39(5H): ir 3400 cm^{-1}: $[\alpha]_D$ -39.5° (c= 1.04, $CHCl_3$).
Anal. Calcd. for $C_{21}H_{30}O_7$: C, 63.94; H, 7.67. Found: C, 64.04; H, 7.64.

Eliminative Wolff-Kishner reduction to 40 The alcohol 37 [83.6 mg in acetone (9 ml)] was stirred with Jones reagent [2.63M 0.1 ml] at 0°C for 10 min. To this reaction mixture was added a few drops of i-PrOH and then ice. The ketone 38 was isolated in 73% (60.9 mg) yield.
The ketone 38 [14 mg in EtOH (0.5 ml)] was heated with hydrazine hydrate [10 micro litter] and Et_3N [5 micro litter] at 50°C for 3 h and then additional 1.5 h at 70°C. The hydrazone was dissolved in DMSO [0.5 ml] and then treated with sodium salt of DMSO prepared separately at room temperature for 13 min. The reaction mixture was poured into ice cold NH_4Cl and then extracted with EtOAc for 3 times and the combined extracts were washed with sat. NaCl and then dried to give 39 (9 mg) in 67% yield: ^{1}H nmr 1.4-2.2(5H, br), 2.60(1H, br), 3.34(3H, s), 3.51(3H, s), 2.9-4.0(7H, m), 4.62(5H, m), 6.19(1H, dd, J= 6.5, 2.5), 7.1-7.4(5H).
The alcohol 39 [9 mg] was dissolved in pyridine [0.4 ml] and acetic anhydride [0.2 ml] and heated at 60°C for 15 min. The reaction mixture was evaporated to dryness and worked up to give 40 (10 mg): mp 92.0°C: ir 1740 cm^{-1}: $[\alpha]_D$ +117.5° (c= 1.08, $CHCl_3$): ^{1}H nmr, 2.08(3H, s), 2.62(1H, br), 3.36(3H, s), 3.51(3H, s), 4.62(5H, m), 6.17(1H, dd, J= 6.5, 2.5).
Anal. Calcd. for $C_{23}H_{32}O_7$: C, 65.70; H, 7.67. Found: C, 65.54; H, 7.65.

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REFERENCES AND NOTES

1. Dedicated to our mentor and friend Gilbert Stork on his 65th birthday.

2. a) M. Isobe, M. Kitamura, and T. Goto, Tetrahedron Lett., 20, 3465 (1979). b) M. Isobe, M. Kitamura, and T. Goto, ibid., 239 (1981); idem , J. Am. Chem. Soc., 104, 4997 (1982). c) M. Kitamura, M. Isobe, Y. Ichikawa, and T. Goto, J. Am. Chem. Soc., 106, 3252 (1984). d) idem , J. Org. Chem., 49, 3517 (1984). e) M. Isobe, Y. Funabashi, Y. Ichikawa, and T. Goto, Tetrahedron Lett., 25, 2021 (1984). f) M. Isobe, Y. Ichikawa, H. Masaki, and T. Goto, Tetrahedron Lett., 25, 3607 (1984). g) Y. Ichikawa, M. Isobe, and T. Goto, Tetrahedron Lett., 25, 5049 (1984). h) M. Isobe, Y. Ichikawa, and T. Goto, Tetrahedron Lett., 42, 5199 (1985). i) M. Isobe, Y. Ichikawa, Dong-lu Bai, and T. Goto, Tetrahedron Lett., 42, 5203 (1985). j) M. Isobe, Y. Ichikawa, Y. Funabashi, S. Mio, and T. Goto, Tetrahedron, 42, 2863 (1986). k) M. Isobe, Y. Ichikawa, and T. Goto, Tetrahedron Lett., 27, 963 (1986).

3. a) R.B. Woodward, F.E. Bader, H. Bickel, A.J. Frey, and R.W. Kierstead, Tetrahedron, 2, 1 (1958). b) B.A. Pearlman, J. Am. Chem. Soc., 101, 6404 (1979). c) P.A. Wender, J.M. Schaus, and A.W. White, ibid., 102, 6159 (1980). d) M.E. Jung and L.A. Light, ibid., 106, 7614 (1984). e) S.F. Martin, S. Grzejszczak, H. Rueger, and S.A. Williamson, ibid., 107, 4072 (1985).

4. M. Isobe, N. Fukami, and T. Goto, Chemistry Lett., 71 (1985).

5. M. Isobe, N. Fukami, and T. Goto, 1st IUPAC Symposium on Medicinal Natural Product, Shanghai, China (Nov. 1985).

6. Commercially available as food-additive Avicell from Asahi Kasei Co. Ltd.,

7. a) Preparation of levoglucosenone; F. Shafizadeh, and P.P.S. Chin, Carbohydrate Research ,58, 79 (1977). b) Cycloaddition of levoglucosenone; D. D. Ward, and F. Shafizadeh, ibid., 95, 155 (1981); M.G. Essig, T.T. Stevenson, F. Shafizadeh, R.E. Stenkamp, and L.H. Jensen, J. Org. Chem., 49, 3652 (1984).

8. a) D. Seebach, and R. Burstinghaus, Angew. Chem., 37 (1975). b) A.-R.B. Manes and R.A. J. Smith, J. Chem. Soc. Chem. Comm., 216 (1975). c) K. Ogura, M. Yamashita, and G. Tsuchihashi, Tetrahedron Lett., 1303 (1978). d) R.J. Cregge, J.L. Herrmann, J.E. Richman, R.F. Romanet, and R. H. Schlessinger, ibid., 2595, 3276 (1973). e) C.A. Brown, and A. Yamaichi, J. Chem. Soc. Chem. Comm., 100 (1979).

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