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TOTAL SYNTHESIS OF (S)-(-) AND (R)-(+)-FRONTALIN AND OF (-)-MALYNGOLIDE FROM THE BRANCHED-CHAIN SUGAR "α"-D-ISOSACCHARINO-LACTONE AS CHIRAL TEMPLATE

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Abstract - *Highly enantiomerically pure (S)-(-) 2 and (R)-(+)-frontalin 3 and (-)-malyngolide 4 were synthesized from the common chiral building block, (2R)-1,2-O-isopropylidene-2-hydroxymethyl-pent-4-ene-1,2-diol 9 readily prepared in five steps and 35% overall yield from α-D-isosaccharino-1,4-lactone 1.*

INTRODUCTION

Monosaccharides and their readily available derivatives have been widely used over the last ten years[1,2] as versatile precursors in the synthesis of optically active compounds. When this approach is used to generate a chiral building block with only one asymmetric center, it is necessary to employ a cheap and readily available starting material in order to be competitive with other enantioselective syntheses. Saccharinic acids are a good illustration of this requirement since they are obtained in one step by the well known rearrangement involving prolonged treatment of hexoses with aqueous alkali[3]. In this way, α-D-isosaccharinic acid, isolated as its crystalline lactone, 1, was prepared in good yield from lactose[4]. Curiously enough, the potential of this compound in synthesis has seldom been exploited[5-7] as we discovered during our work on the synthesis of anthracyclinones such as daunomycinone[8,9] or γ-rhodomycinone[9] analogs. Two new applications of this versatile synthon for the preparation of the title compounds[10] 2,3 and 4 are now reported.

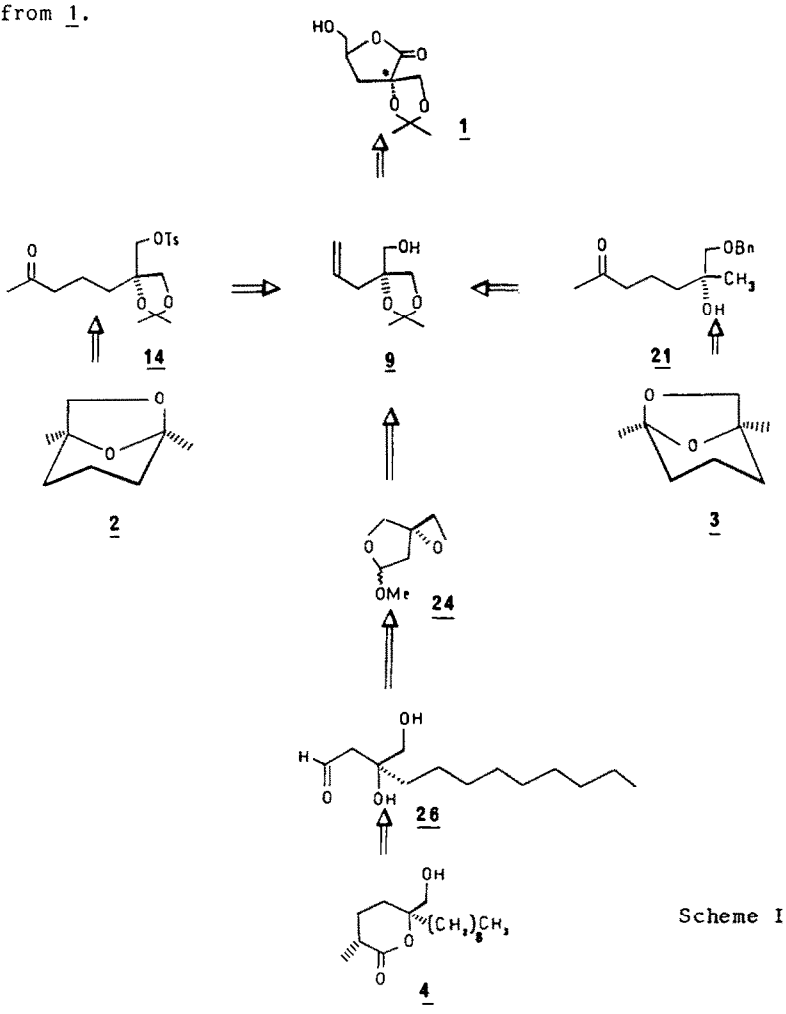
RESULTS AND DISCUSSION

1. Total synthesis of natural and unnatural frontalin

(S)-(-)-frontalin 2 is known to be the aggregation pheromone of the southern pine beetle Dendroctonus frontalis[11]. The biologically active form of this 1,5-dimethyl-6,8-dioxabicyclo[3.2.1.]octane pheromone is the (1S,5R) enantiomer[12] Previous reports on the synthesis giving optically pure frontalin have relied on the incorporation of chiral building blocks[13] asymmetric syntheses (e.g. self reproduction of chirality[14] Sharpless asymmetric epoxidation of allylic alcohol[15], baker's yeast mediated transformations,[16] use of chiral auxiliary)[17] and optical resolution.[18]
Although frontalin contains two asymmetric centers, only the (1S) center needs to be considered since the correct configuration at C-5 is dictated by this carbon center during the formation of the bicyclic structure. The substitution pattern at C-1 is rarely observed in the usually available chiral building blocks. However

α-D-isosaccharino-1,4-lactone 1 does possess the desired functionality and for this reason it was chosen as starting material for the preparation of both enantiomers of frontalin (which is of interest for the evaluation of the behavioural and physiological aspects of this pheromone).

The retrosynthetic analysis as shown on scheme I indicates that the dioxabicyclo-[3.2.1.]octane compounds 2 and 3 can be viewed as being formed by internal ketalization of the hydroxyketone derivatives 14 and 21 themselves obtained from 9 easily prepared from 1.

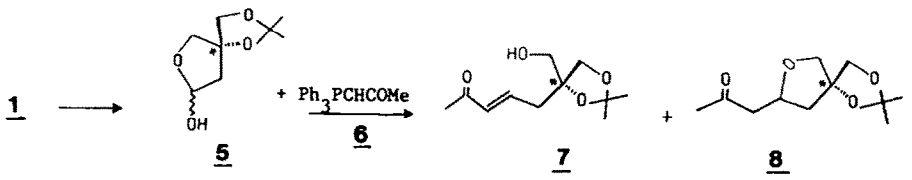


Scheme I

1a. Synthesis of natural frontalin

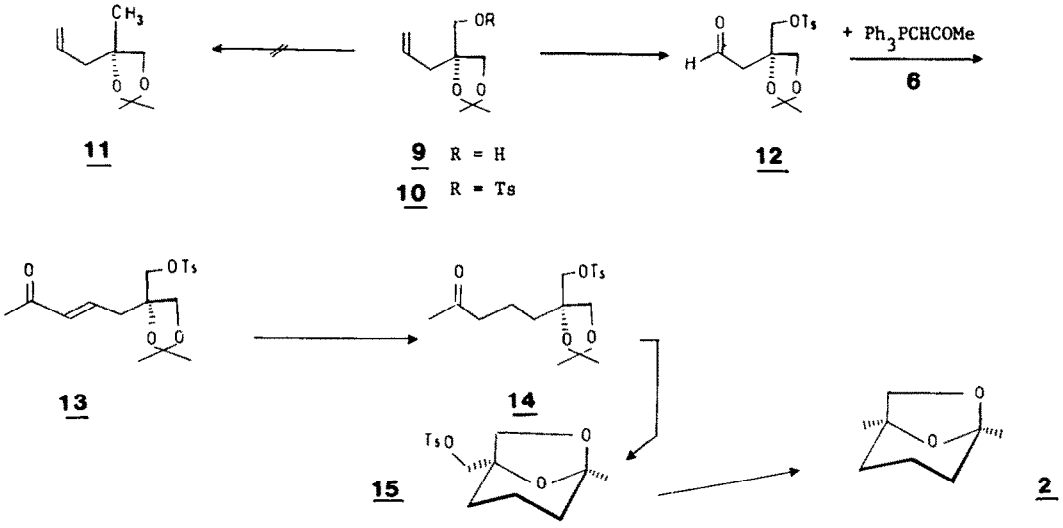
Firstly, condensation of aldehyde 5, prepared[8a] from isosaccharino-lactone 1, with the stabilized 1-(triphenyl-phosphoranylidene)-2-propanone 6[19] was attempted. The expected albeit unstable product 7 was obtained (scheme II) as a minor component of the reaction mixture along with 8 resulting from an intramolecular Michael reaction. All attempts to prevent this intramolecular reaction met with little success. Similar difficulties have been already reported by Fraser-Reid *et al.*[13] for a closely related system.

Since protection of the primary alcohol of 5 could not be satisfactory achieved in the presence of the highly reactive aldehyde function, we turned our attention towards the γ,δ-unsaturated alcohol derivative 9 in order to obtain a clean Wittig reaction. Compound 9 was synthesized from 1 in four steps in 30-35% overall yield[9] and, as depicted in scheme III, was transformed into the corresponding tosyl compound 10 in 75% yield. Reduction of the tosyl group giving 11 with a methyl as present at C-1



Scheme II

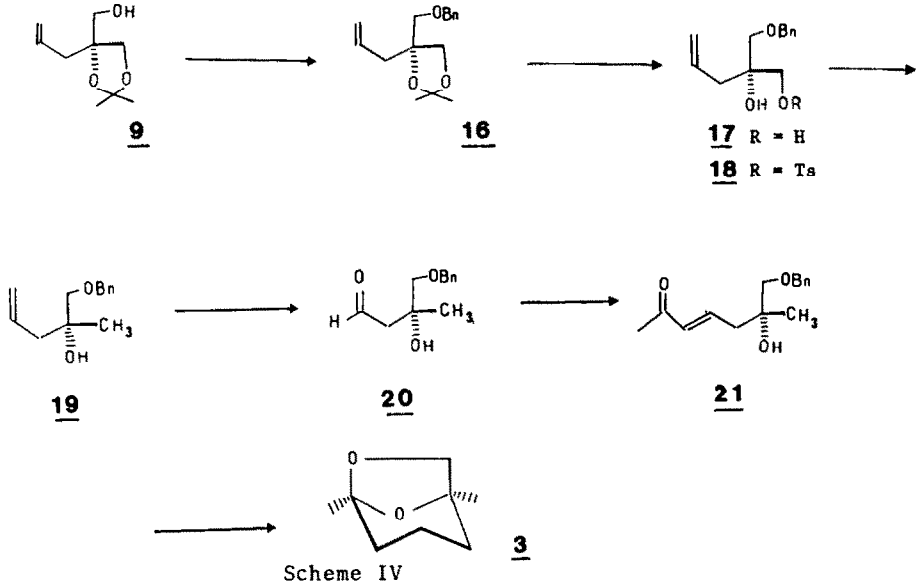
in the final compound, natural frontalin 2, was unsuccessful. Indeed when 10 was reacted with LAH, it was recovered unchanged whereas several by-products were formed when the reduction was attempted in the presence of $LiEt_3BH$. In consequence, we decided to keep the tosyl group until the last step and to carry out the reduction at the dioxabicyclo derivative stage. Oxidation of the terminal double bond of 10 was carried out by ozonolysis in dichloromethane at -78°C followed by reductive work-up in the presence of triphenylphosphine. The aldehyde 12 obtained in 85% yield was then condensed with 1-(triphenylphosphoranylidene)-2-propanone, 6, affording stereospecifically the trans unsaturated ketone 13 in 60% yield. When the hydrogenation of 13 was realized in the presence of 10% Pd/C, a mixture of the acyclic derivative 14 and of the dioxabicyclo analog 15 was obtained in a 2:1 ratio. In contrast, exclusive formation of 14 was observed when triethylamine was added to remove any traces of acid present in the catalyst[20]. Compound 14 was easily converted into the dioxabicyclo precursor of frontalin 15 in 95% yield by treatment with Amberlyst-15 ion exchange resin. Finally, reduction of 15 into (S)-(-)-frontalin 2 was readily accomplished in 95% yield with $LiEt_3BH$ as reducing agent.



Scheme III

2a. Synthesis of unnatural frontalin 3.

Transformation of the other hydroxymethyl group in 9 into a methyl group would lead, according to the above sequence steps to the 1R,5S compound enantiomer of frontalin. Thus, as depicted in scheme IV, 9 was temporarily protected as a benzyl ether, using the Czernecki procedure[21] to afford 16 in 80% yield. After hydrolysis of the acetal ring to the diol 17 (80%) followed by tosylation of the primary alcohol, compound 18 was obtained in 90% yield. Reduction of the tosyl group was easily achieved using LAH in THF at reflux which led to the suitable methyl derivative 19 in 90% yield. Ozonolysis of the terminal double bond of 19 at low temperature followed by a reductive work-up with triphenylphosphine provided the aldehyde 20 in 65% yield. The same sequence of reactions used for the synthesis of frontalin 2 was again employed to conver 20 to (1R,5S) unatural frontalin 3 in 70% overall yield: i) Wittig reaction with 1-(triphenylphosphoranylidene)-2-propanone ; ii) hydrogenation with Pd-on-charcoal 10% Interestingly, cleavage of the benzyl ether, hydrogenation of the double bond and ring closure simultaneously occurred during the last reaction.



Scheme IV

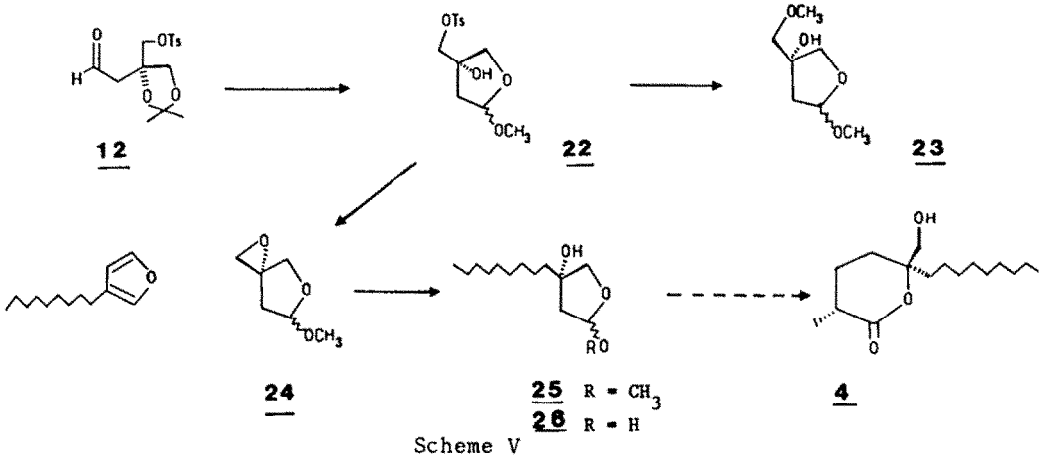
In summary, the synthesis of both enantiomers of frontalin has been achieved in few steps and 13% and 8% respective overall yield for 2 and 3 from isosaccharinolactone 1.

2. Total synthesis of (-)-Malyngolide.

(-)-Malyngolide 4 is an antibiotic active against Mycobacterium smegmatis and Streptococcus pyogenes which has been isolated from the lipid extract of the blue-green marine alga Lyngbya majuscula Gomont[22]. Malyngolide has been the target of a large number of syntheses including six asymmetric total synthesis of natural antibiotic[17b,23] two syntheses of its antipode[24], twelve syntheses of the racemic form[25] and a synthesis of dihydro and isomalyngolide analogs[26]. The retrosynthetic pathway (Scheme I) shows that aldehyde 26 is a good target since it could be obtained by ring opening of the epoxide 24 followed by hydrolysis. Epoxide 24 was itself readily prepared from the tosyl intermediate 12 used in the synthesis of frontalin (vide supra).

Thus synthesis of malyngolide was achieved as depicted in scheme V. Treatment of 12

with Amberlyst-15 ion-exchange resin in methanol afforded the 2-deoxy apioside derivative 22 in 90% yield. When formation of the oxirane system was attempted by treatment of 22 with potassium methoxide at room temperature , 23 was obtained instead of epoxide 24. Since the epoxide ring appeared to be unstable in the presence of base even when the temperature of the reaction was decreased to 0°C, a methanolic solution of 22 was stirred in the presence of IRA-410 (OH^-) resin. Under these conditions, epoxide 24 was quantitatively and specifically obtained.



Scheme V

The reaction of epoxide 24 with octyl magnesium bromide in the presence of a catalytic amount of cuprous iodide at -40°C in THF afforded the alkyl derivative 25 as a mixture of diastereoisomers. While hydrolysis of 25 in the presence of dilute HCl afforded a mixture of the hemiacetal 26 with the corresponding furane derivative 27, the former was exclusively obtained in the presence of diluted AcOH.

Since 26 has previously been converted to (-)-malyngolide by HO et al.[23d], our route to this intermediate by a conceptually different approach constitutes a new formal synthesis of this antibiotic.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer, calibrated against polystyrene film and are expressed in cm^{-1}. ^1H NMR spectra were obtained on a Bruker HX 270 in $CDCl_3$. Chemical shifts are relative to TMS (δ = 0.0) and coupling constants are in Hertz. Mass spectra (DCI,DEI) were recorded on a Nermag R 1010C. Silica gel for column chromatography was Merck silica gel 60 n°9385. Microanalyses were performed by the "Laboratoire de Microanalyses du CNRS" de Gif-sur-Yvette.

(6R)-6,7-dihydroxy-6,7-O-isopropylidene-6-hydroxymethyl-hept-3-ene-2-one (7) and (2R,S)-(4R)-2-(propanone)-4-hydroxy-4-hydroxymethyl-4;4'-O-isopropylidene-tetrahydrofurane (8). To a stirred solution of aldehyde 5 (100 mg, 0.57 mmol) in acetonitrile (30 ml) was added 6 (500 mg, 1.6 mmol). After the reaction mixture was refluxed for 2h, the solvent was removed under reduced pressure. A flash chromatography using hexane-ethylacetate (2:1) as eluent afforded 7 (15 mg, 12%) and then 8 (100 mg, 80%).

Compound 7 : ν_{max} (film) : 3450, 1630 and 1370 cm^{-1}; ^1H NMR: δ 6.80 (m, 1H, J = 16, H-4), 6.17 (dd, 1H, J = 8, J'= 16, H-3), 3.90 (d, 1H) and 3.70 (d, 1H) (AB syst., J= 8, CH_2-7), 3.55 (m, 2H, CH_2-6'), 2.56 (d, 2H, J= 8, CH_2-5), 2,26 (s, 3H, CH_3-1), 1.55 (s, 6H, 2Me).
Compound 8 : ν_{max} (film) : 1710 and 1380 cm^{-1}; ^1H NMR: δ 4.33 (m, 1-H, H-2), 3.95 (d, 2H, CH_2-5), 3.91.

(2S)-1,2-O-isopropylidene-2-p-toluenesulfonyloxymethyl-pent-4-ene-1,2-diol (10).
To a solution of alcohol 9 (0.51 g, 3 mmol) in anhydrous pyridine (5 ml) was added p-toluenesulfonyl chloride (1.15 g, 6 mmol). The mixture was stirred at room temperature overnight and then poured into ice water before extraction with ether. The organic layer was washed with 10% aqueous H_2SO_4, water and then saturated aqueous $NaHCO_3$. Evaporation of the ether solution under reduced pressure afforded a syrup (0.85 g). Column chromatography using hexane-acetone (6:1) as eluent gave 10 (0.72 g, 75%) as a syrup, $|\alpha|_D^{20}$ -5° (c 3, $CHCl_3$); ν_{max} (film): 1640, 1600 and 1375 cm^{-1}; ^1H NMR: δ 7.70 (d, 2H) and 7.3 (d, 2H) (J= 9, 4H arom.), 5.65 (m, 1H, H-4), 5.10 (d, 1H, J= 8, H-5a), 5.02 (d, 1H, J= 16, H-5b), 3.85 (d, 1H) and 3.83 (d, 1H) (J= 8, CH_2-1), 3.84 (d, 1H) and 3.72 (d, 1H) (J= 10, CH_2-2'), 2.42 (s, 3H, Me), 2.33 (d, 2H, CH_2-2), 1.32 (s, 3H) and 1.29 (s, 3H) (2 Me); MS (DCI/NH_3): m/z 344 ($M+NH_4^+$, 100) , 325 ($M+H^+$). Anal. Calcd for $C_{16}H_{25}O_5S$: C, 58.88; H, 6.80. Found: C, 59.02; H, 6.89.

(3S)-3,4-O-isopropylidene-3,4-dihydroxy-3-p-toluenesulfonyloxymethyl-butanal (12)
To a solution of 10 (10 g, 30 mmol) in methanol (250 ml) cooled at -78°C was bubbled a flow of O_3/O_2. After 3h, the ozonide was destroyed by addition of 16 g of triphenylphosphine in dichloromethane (250 ml) and stirring for 48 h. Evaporation of the mixture under reduced pressure afforded a crude material which was purified by flash chromatography using hexane-acetone (4:1) as eluent. Compound 12 (8.75 g, 85%) was obtained as a crystalline compound; m.p. 76-78 (hexane); $|\alpha|_D^{20}$ +11° (c 1.5 in $CHCl_3$); ν_{max} ($CHCl_3$): 2740, 1720, 1600 and 1360 cm^{-1}; ^1H NMR: δ 9.60 (d, 1H, CHO) , 7.70 (d, 2H) and 7.26 (d, 2H) (J= 10, 4H arom.), 4.02 (m, 2H, CH_2-4), 3.96 (d, 2H) and 3.78 (d, 2H) (J= 10, CH_2-4'), 2.81 (dd, 2H) and 2.64 (dd, 2H) (J= 20, J' = 2, CH_2-2), 2.42 (s, 3H, Me), 1.32 (s, 6H, 2 Me); Anal. Calcd for $C_{15}H_{20}O_6S$: C, 54.88; H, 6.14. Found: C, 55.01; H, 6.10.

(6S)-6,7-O-isopropylidene-6,7-dihydroxy-6-p-toluenesulfonyloxymethyl-hept-3-ene-(E)-2-one (13)
To a stirred solution of aldehyde 12 (3.28 g, 10 mmol) in acetonitrile (100 ml), was added 6 (5 g, 16 mmol). The reaction mixture was refluxed for 2h and concentrated under reduced pressure to give a syrup. Flash chromatography using hexane-ethylacetate (2:1) as eluent gave 13 (5 g, 68%); $|\alpha|_D^{20}$ -8° (C 1 in $CHCl_3$); ν_{max} ($CHCl_3$): 1670 1630, 1600 and 1360 cm^{-1}; ^1H NMR: δ 7.70d, 2H) and 7.30 (d, 2H) (J= 10, 4H arom.), 6.64 (m, 1H, J= 16, J'= 3.5, J"= 3.5, H-4), 5.98 (d, 1H, J= 16, H-3), 3.92 (d, 1H) and 3.87 (d, 1H) (J= 5, CH_2-6'), 3.78 (d, 1H) and 3.72 (d, 1H) (J= 4.5, CH_2-7), 2.46 m, 2H, CH_2-5), 2.20 (s, 3H, Me), 1.33 (s, 3H, Me) and 1.31 (s, 3H, Me); Anal. Calcd for $C_{18}H_{24}O_6S$: C, 58.69; H, 6.57. Found: C, 58.75; H, 6.38.

(6S)-6,7-isopropylidene-6,7-dihydroxy-6-p-toluenesulfonyloxymethyl-hepta-2-one (14).
A methanolic solution of the ketone 13 (3.7 g, 10 mmol in 100 ml) was stirred overnight under H_2 atmosphere in the presence of 10% Pd/C (500 mg) and triethylamine (10 ml). Filtration through a short path of celite with subsequent evaporation the filtrate under reduced pressure gave 14 (3.6 g, 97%) as a crystalline compound:

m.p. 61°C; $|\alpha|_D^{20}$ +1.5° (c 0.9 in $CHCl_3$); λ_{max} ($CHCl_3$): 1710, 1600 and 1360 cm^{-1}; ^{1}H-NMR: δ 7.70 (d, 2H) and 7.22 (d, 2H)(J= 10, 4H arom.), 3.81 (d, 2H) and 3.63 (d, 1H)(H= 10, CH_2-7), 3.80 (s, 2H, CH_2-6'), 2.44 (s, 3H, Me), 2.37 (m, 2H), CH_2-3), 2.09 (s, 3H, COMe), 1.54 (m, 4H, CH_2-4 and CH_2-5), 1.28 (s, 3H) and 1.31 (s, 3H) (2Me); MS (DCI/NH_3): 388 ($M+NH_4^+$), 330 ($M+NH_4^+$-MeCO, 100%), 313. Anal. Calcd for $C_{18}H_{26}O_6S$: C, 58.37; H, 7.08. Found: C, 58.43; H, 7.15.

(1S,5R)-5-methyl-1-p-toluenesulfonyloxymethyl-6,8-dioxabicyclo|3,2,1|octane (15).

From 13: an ethanolic solution of 13 (224 mg, 0.6 mmol) was treated as described above (cf. preparation of 14) but without triethylamine. This gave after flash chromatography using hexane-EtOAc (3:1), 120 mg of 14 and 65 mg of 15.

From 14: to a solution of 14 (2.55 g, 7 mmol) in chloroform (50 ml) were added 5 g of Amberlyst-15 resin. The reaction mixture was stirred at room temperature for 0.5 h and filtered over a short path of celite. The filtrate was evaporated under reduced pressure to give 15 (2.03 g, 95%) as a crystalline compound. A sample was recrystallized from hexane: m.p. 110°C; $|\alpha|_D^{20}$ -20°; ν_{max} ($CHCl_3$): 1600 and 1630 cm^{-1}; ^{1}H NMR: δ 7.70 (d, 2H) and 7.32 (d, 2H)(J= 10, H arom.), 4.03 (s, 2H, CH_2-1), 3.85 (d, 1H) and 3.52 (d, 1H)(J= 7, CH_2-7), 2.42 (s, 3H, Me), 1.75-1.60 (m, 4H, CH_2-2 and CH_2-3), 1.38 (s, 3H, Me); MS (DCI/NH_3): m/z 330 ($M+NH_4^+$, 100%), 313 ($M+H^+$); Anal. Calcd for $C_{15}H_{20}O_5S$: C, 57.68; H, 6.46. Found; C, 57.60, H, 6.50.

(1S,5R)-(-)-1,5-dimethyl-6,8-dioxabicyclo|3,2,1|octane or (S)-(-)-frontalin (2).

To a stirred solution of tosylate 15 (2 g, 6.5 mmol) in THF (40 ml) at 0°C, were added 200 ml of a 1M solution of $LiEt_3BH$ in THF. After stirring under reflux for 3 h, the reaction mixture was poured into ice-water (150 ml). Extraction was carried out with ether after acidification with 1M aqueous HCl (50 ml). The organic solution was washed with saturated aqueous solution of $NaHCO_3$, with water, dried (Na_2SO_4) and evaporated under reduced pressure at low temperature. Natural frontalin 2 was obtained as a liquid (880 mg, 95%): b.p. 92°C/110 mmHg and $|\alpha|_D^{20}$ -52° (c 1 in ether); litt.[18] b.p. 91°C / 100 mm Hg and $|\alpha|_D^{20}$ -52° (c 1.63, in ether).

(2R)-2-benzyloxymethyl-1,2-O-isopropylidene-pent-4-ene-1,2-diol (16)

To a cold (0-5°C) solution of alcohol 9 (6 g, 35 mmol) in THF (200 ml), was slowly added NaH (1.6 g, 53 mmol, 80% in oil) and then tetrabutylammonium iodide (8.98 g, 52 mmol). After stirring for 0.5 h, benzyl bromide (9g, 52 mmol) was added and the mixture was stirred, overnight at room temperature. Excess of benzyl bromide was hydrolyzed by careful addition of water (200 ml) before extraction with ether. Usual work-up afforded a residue which was purified by chromatography over silica gel using hexane and then hexane-acetone (2:1) as eluent. This gave 16 (7g, 80%) as a syrup; $|\alpha|_D^{20}$ -50° (c 4 in ether); ν_{max} (film): 1640, 1380 and 1370 cm^{-1}; ^{1}H NMR: δ 7.26 (m, 5H arom.), 5.76 (m, 1H, H-4), 5.06 (d, J= 12, CH_2-5), 4.51 (s, 2H, CH_2-Ph), 3.92 (d, 1H) and 3.74 (d, 1H)(J= 9, CH_2-2'), 3.37 (s, 2H, CH_2-1), 2.42 (d, 2H, J= 7, CH_2-3), 1.38 (s, 3H, Me) and 1.39 (s, 3H, Me); MS (EI): m/z 262 (M^+, traces), 247 (M^+-15,10), 221 (38), 204 (M^+-acetone, traces), 141 (M^+, $C_6H_5CH_2OCH_2^+$,60), 91 (100). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 72.98; H, 8.53).

(2S)-2-benzyloxymethyl-pent-4-ene-1,2-diol (17).

To a solution of 16 (14 g, 53 mmol) in methanol (250 ml) was added 15 ml of 0.05N aqueous HCl. The mixture was stirred overnight at room temperature, neutralized with IR 45 (OH^-) Amberlyst and filtered. After evaporation of the solvent under reduced

pressure, chromatography of the residue using hexane-acetone (3:1) as eluent led to 17 (9.4g, 80%) as a syrup; $|\alpha|_D^{20}$ +5° (c 1 in $CHCl_3$); ν_{max}(film): 3400 and 1060 cm^{-1}; ^1H NMR: δ 7.30 (m, 5H, arom.), 5.60 (m, 1H, H-4), 5.10 (d, 1H, J= 14, H-5a), 5.00 (d, 1H, J= 6, H-5b), 4.50 (s, 2H, CH_2Ph), 3.60 (d, 1H) and 3.20 (d, 1H)(J=5.5, CH_2-2'), 3.46 (d, 1H) and 3.41 (d, 1H) (J= 4, CH_2-1), 2.44 (s, 2H, OH), 2.30 (d, 2H, J= 3.5, CH_2-3); MS (DCI/NH_3): m/z 240 ($M+NH_4^+$, 100), 223 ($M+H^+$). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.33; H, 8.20.

(2R)-2-benzyloxymethyl-1-p-toluenesulfonyloxy-pent-4-ene-2-ol (18).

To a solution of 17 (11.1g, 50 mmol) in anhydrous pyridine (45 ml) was added TsCl (11.5g, 60 mmol) and the mixture was stirred overnight at room temperature. After the addition of 45 ml of water, extraction with ether and usual work-up afforded after evaporation of the solvent under reduced pressure, 18 (17g, 90%) as a syrup; $|\alpha|_D^{20}$ -5° (c 1 in $CHCl_3$); ν_{max} (film); 3520 and 1640 cm^{-1}; ^1H NMR: δ 7.90-7.00 (m, 9H, arom.),5.72 (m, 1H, H-4), 5.03 (d, 1H, J= 6, H-5a) and 5.00 (d, 1H, J= 17, H-5b), 4.42 (s, 2H, CH_2Ph), 3.96 (d, 1H) and 3.87 (d, 1H)(J= 8, CH_2-2'), 3.39 (d, 1H) and 3.30 (d, 1H) (J= 7, CH_2-1), 2.38 (s, 3H, Me), 2.24 (d, 2H, J= 7, CH_2-3). Anal. Calcd for $C_{20}H_{24}O_5S$: C, 63.82; H, 6.43. Found: C, 63.90; H, 6.50.

(2R)-2-benzyloxymethyl-pent-4-ene-2-ol (19)

To a cooled solution of the tosyl derivative 18 (15g, 40 mmol) in THF (150 ml), was slowly added lithium aluminum hydride 2.5g, 60 mmol). The mixture was refluxed for 15h and after cooling, excess of LAH was destroyed in usual manner by successive addition of water (2.5 ml), 0.25% aqueous NaOH (2.5 ml) and finally, water (7.5 ml). The suspension was filtered through celite and the filtrate evaporated under reduced pressure. The remaining oil was coevaporated with toluene to give 19 (7.6 g, 90%) as a pale yellow syrup; $|\alpha|_D^{20}$-2° (c 0.5 in $CHCl_3$); ν_{max} (film) 3420 and 1640 cm^{-1}; ^1H NMR δ 7.32 (s, 5H, arom.), 5.76 (m, 1H, H-4), 5.04 (d, 1H, J= 14, H-5a), 5.02 (d, 1H, J= 12, H-5b), 4.51 (s, 2H, CH_2Ph), 2.18 (d, 1H) and 2.09 (d, 1H)(J= 10, CH_2-1), 2.27 (m, 2H, CH_2-3), 1.21 (s, 3H, Me); MS (DCI/NH_3): m/z 224 ($M+NH_4^+$, 100), 206 (M^+), 189 ($M+H^+$-18), 91. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.53; H, 8.85.

(3R)-3-benzyloxymethyl-3-hydroxy-butanal (20)

A stream of ozone was bubbled for 15 min. through a cold solution (-78°C) of 19 (1 g, 4 mmol) in dichloromethane (20 ml). Dimethylsulfide was then added and the mixture was stirred at room temperature for 3 h. Evaporation under reduced pressure followed by a flash chromatography using dichloromethane-methanol (99:1) as eluent afforded 20 (670 mg, 65%) as an oil; $|\alpha|_D^{20}$ +10° (c 1 in $CHCl_3$); λ_{max} (film): 3440, 2740 and 1715 cm^{-1}; ^1H NMR δ 9.75 (t, 1H, H-1), 7.26 (m, 5H, arom.), 4.51 (s, 2H, CH_2-Ph), 3.37 (s, 2H, CH_2-4), 2.82 (broad s, 1H, OH), 2.68 (dd, 1H, J= 18, J'= 2, H-2a), 2.48 (dd, 1H, J= 18, J'= 2, H-2b), 1.27 (s, 3H, Me); MS (DCI/NH_3): m/z 226 ($M+NH_4^+$, 100), 208 (M^+). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.50; H, 7.80.

(6R)-6-benzyloxymethyl-6-hydroxy-hept-3-ene-(E)-2-one (21).

Treatment of 20 (416 mg, 2 mmol) as described for the preparation of 13 afforded after flash chromatography using hexane-acetone (4:1) as eluent, 21 (425 mg, 86%); $|\alpha|_D^{20}$ +12° (c 1.8 in $CHCl_3$); ν_{max} (film): 3420, 1665 and 1625 cm^{-1}; ^1H NMR: δ 7.33 (m, 5H, arom.), 6.88 (m, 1H, J= 16, J'= 8, J"= 7. H-4), 6.10 (d, 1H, J= 16, H-3), 4.57 (s, 2H, CH_2Ph), 3.33 (s, 2H, CH_2-7), 2.49 (dd, 1H, J= 14, J'= 7, H-5a), 2.36 (dd, 1H, J= 14, J'= 8, H-5b), 2.20 (s, 3H, Me) and 1.20 (s, 3H, Me). MS

(DCI/NH_3): m/z 266 ($M+NH_4^+$, 100), 231 ($M+H^+-H_2O$). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.48; H, 8.27.

(1R,5S)-(+)-1,5-dimethyl-6,8-dioxabicyclo[3,2,1]octane or (+)-frontalin 3

A methanolic solution of 21 (400 mg in 50 ml) was stirred overnight under H_2 in the presence of 10% Pd/C (50 mg). The mixture was filtered, diluted with water and extracted with dichloromethane. Evaporation of the organic layer under reduced pressure gave 3 (184 mg, 80%) as a liquid: $[\alpha]_D^{20}$ +52° (c 1, ether) or +29° (c 0.95 methanol); λ_{max} (film) and ^1H NMR were in agreement with the literature[13,14,18].

Methyl 2-deoxy-3'-O-p-toluenesulfony-apioside (22).

To a stirred solution of 12 (8g, 24 mmol) in MeOH (250 ml) was added Amberlyst A15 (4 g). After 72h, the suspension was filtered and evaporation of the filtrate afforded 22 (6.84g, 93%). A flash chromatography using hexane-acetone (3:1) as eluent gave both anomers as pure compounds.

Anomer 22a (less polar): $[\alpha]_D^{20}$ +3° (c 0.8 in $CHCl_3$); ν_{max} ($CHCl_3$): 3680, 3580, 3530 cm^{-1}; ^1H NMR: δ 7.85 (d, 2H) and 7.32 (d, 2H)(J= 10, H arom.), 5.00 (d, 1H, J= 6, H-1), 4.00 (s, 2H, CH_2-3'), 3.85 (s, 2H, CH_2-4), 3.34 (s, 3H, OMe), 2.42 (s, 3H, Me), 2.06 (dd, 1H, J= 13, J'= 6, H-2a), 1.96 (d, 1H, J= 13, H-2b). Anal. Calcd for $C_{13}H_{18}O_6S$: C, 51.65; H, 6.00. Found: C, 51.80; H, 6.02.

Anomer 22b (more polar): $[\alpha]_D^{20}$ -38° (c 1.2 in $CHCl_3$); ^1H NMR: δ 7.77 (d, 2H) and 7.30 (d, 2H)(J= 10, H arom.), 5.08 (dd, 1H, J= 6, J'= 2, H-1), 4.10 (s, 2H, CH_2-3'), 3.76 (s, 2H, CH_2-4), 3.26 (s, 3H, OMe), 2.46 (s, 3H, Me), 2.16-1.89 (m, 2H, CH_2-2); MS (EI): m/z 301 (M^+-1,traces), 271 (M^+-31, 6 %), 252 ($^5_5$ %). Anal. Found; C, 51.57; H, 5.93.

Methyl 2-deoxy-3'-O-methyl-apioside (23).

To a cold (0°C) solution of crude tosylate 22 (mixture of anomers, 0.9 g, 3 mmol) in 50 ml of methanol, was added 1M aqueous solution of MeOK (5 ml). The mixture was stirred overnight at room temperature and neutralized by filtration through Amberlite IR (50 H^+) resin. Evaporation of the solvent under reduced pressure gave 23 (0.37 g, 90%). A flash chromatography using hexane-acetone (4:1) as eluent afforded successively the anomers a and b.

Anomer 23a (less polar): ^1H NMR: δ 5.00 (d, 1H, J= 6, H-1), 3.91 (d, 1H) and 3.85 (d, 1H)(J= 11, CH_2-4), 3.43 (s, 3H, OMe), 3.41 (s, 3H, OMe), 2.07 (dd, 1H, J= 14, J'= 6, H-2a), 1.96 (d, 1H, J= 14, H-2e); Anal. Calcd for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 52.03; H, 8.80.

Anomer 23b (more polar); ^1H NMR: δ 5.15 (dd, J= 6, J'= 2, H-1), 3.85 (d, 1H) and 3.83 (d, 1H)(J= 9, CH_2-3'), 3.52 (d, 1H) and 3.45 (d, 1H)(J= 8, CH_2-4), 3.41 (s, OMe), 3.32 (s, 3H, OMe), 2.20 (dd, 1H, J= 15, J'= 6, H-2a), 1.91 (dd, 1H, J= 7, J'= 2.5, H-2b); MS (DCI/NH_3): m/z 180 ($M+NH_4^+$), 148 ($M+ NH_4^+$ - 32,100). Anal. Found: C, 51.75; H, 8.65.

Methyl 3,3'-anhydro-2-deoxy-apioside (24).

A solution of tosylate 22 (1 g, 3.3 mmol) in chloroform (50 ml) was stirred at room temperature for 48 h in the presence of Amberlyst IRA 410 resin (5 g). Filtration and evaporation of the filtrate afforded 24 (420 mg, 98%) as a syrup. The two diastereoisomers were separated by flash chromatography using hexane-acetone (4:1) as eluent and isolated in a 3:2 ratio.

Anomer 24a (less polar): $|\alpha|_D^{20}$-174° (c 1 in $CHCl_3$); ^1H NMR: δ 5.17 (d, 1H, J= 6, H-1), 4.07 (d, 1H) and 3.70 (d, 1H)(J= 12, CH_2-4), 3.37 (s, 3H, OMe), 3.10 (d, 1H) and 2.90 (d, 1H)(J= 5, CH_2-3'), 2.27 (dd, 1H, J= 14, J'= 6, H-2a), 2.16 (d, J= 14, H-2b). Anal. Calcd for $C_6H_{10}O_3$: C, 55.38; H, 7.74. Found; C, 55.40; H, 7.80.

Anomer 24b: $|\alpha|_D^{20}$ +158° (c 1 in $CHCl_3$); ^1H NMR: δ 5.08 (d, 1H, J= 6, H-1), 3.98 (d, 1H) and 3.83 (d, 1H) (J= 14, CH_2-4), 3.41 (s, 3H, Ome), 2.95 (d, 1H) and 2.10 (d, 1H) (J= 5, CH_2-3'), 2.42 (dd, 1H, J= 14, J'= 6, H-2a), 1.87 (d, 1H, J= 14, H-2b). Anal. Found: C, 55.25; H, 7.65.

Methyl 2,4-dideoxy-3-C-nonyl-D-glycero-tetrofuranoside (25)

To a solution of octylmagnesium bromide (prepared from octyl bromide (0.99 g, 5.14 mmol) and magnesium (0.13 g, 5.15 mmol) in THF (20 ml) at -40°C was added CuI (0.1 g, 0.51 mmol). After stirring at -40° for 2 h, a solution of epoxide 24 (0.53 g, 4 mmol) in 5 ml of THF was added whereas the temperature was allowed to reach room temperature. 15 min later, a saturated solution of NH_4Cl (150 ml) was added and the reaction mixture was extracted with ether. This led after evaporation of the solvent under reduced pressure to a residue which was chromatographed using hexane-acetone (3:1) as eluent. The two anomers were separated in an overall yield of 40% (0.39 g).

Anomer 25a: $|\alpha|_D^{20}$ +79° (c 1 in $CHCl_3$); ^1H NMR: δ 5.00 (dd, 1H, J= 6, J'= 4, H-1), 3.92 (d, 1H) and 3.74 (d, 1H) (J= 8, CH_2-4), 3.25 (s, 3H, OMe),2.0(dd, 1H, J= 14, J'= 6, H-2a), 1.87 (dd, 1H, J= 14, J'= 6, H-2b), 1.56 (m, 2H), 1.21 (m,14H) and 0.94 (t, 3H) (octyl). Anal. Calcd for $C_{14}H_{28}O_3$: C, 68.81; H, 11.55. Found: C, 68.95; H, 11.52.

Anomer 25b: $|\alpha|_D^{20}$ -89° (c 0.9 in $CHCl_3$); ^1H NMR: δ 5.13 (dd, 1H, J= 2, J'= 6, H-1), 3.70 (d, 1H) and 3.64 (d, 1H)(J = 10, CH_2-4), 3.32 (s, 3H, OMe), 2.20 (dd, J= 14, J'= 6, H-2a), 1.87 (dd, J= 14, J'= 2, H- b), 1.63 (m, 2H), 1.25 (m,14H) and 0.88 (t, 3H) (octyl); MS (DCI.NH_3): m/z 262 ($M+NH_4^+$), 230 ($M+NH_4^+$-32, 100); Anal. Calcd for $C_{14}H_{28}O_3$. Found: C, 68.80; H, 11.51.

2,4-dideoxy-3-C-nonyl-D-glycero-tetrofuranose (26).

Method A: To a solution of methyl glycoside 25 (62 mg, 0.25 mmol) in acetone (10 ml) was added 0.25 ml of 1N HCl. The mixture was refluxed for 15 min and after cooling, neutralized with saturated solution of $NaHCO_3$. Extraction with dichloromethane followed by flash chromatography using hexane as eluent gave 17 mg (30%) of 26 along with the corresponding aromatic derivative 27 (19 mg, 40%); ^1H NMR: 7.19 (s, 1H, H-1), 7.06 (s, 1H, H-3), 6.20 (s, 1H, H-2), 2.40 (m, 2H), 1.55 (m, 2H), 1.29 (m, 14H), 0.88 (t, 3H) (octyl); MS (DCI/NH_3): m/z 195 ($M+H^+$), 130 (and 74).

Method B: The solution of 25 (100 mg, 0.4 mmol) in 25% aqueous AcOH was refluxed for 3-4 h. Neutralization with solution of $NaHCO_3$ followed by extraction with dichloromethane yielded 26 (64 mg, 70%) as a mixture of anomers in a 5:1 ratio: $|\alpha|_D^{20}$ +23° (c 0.6, $CHCl_3$); ^1H NMR: δ 5.70 (dd, J= 5, J'= 6, H-1a), 5.51 (d, J= 5, H-1b), 4.05 and 3.92 (2d), 3.74 and 3.68 (2d) (H-4a)and H-4b), 2.3-1.85 (m, 2H, CH_2-2), 1.62 (m, 2H), 1.25 (m,14H) and 0.88 (t, 3H) (octyl); MS (DCI/NH_3): m/z 248 ($M+NH_4^+$), 230 ($M+NH_4^+$ -18), 204 (100); Anal. Calcd for $C_{13}H_{26}O_3$: C, 67.79; H, 11.38. Found: C, 67.90; H, 11.22.

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