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THE ABSOLUTE CONFIGURATION OF KUROSPONGIN, A NEW FURANOTERPENE FROM A MARINE SPONGE, *SPONGIA* SP.

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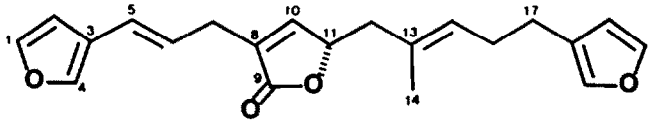
Abstract: Kurospongin (1), a new C_{21} furanoterpene having ichthyotoxic and feeding-deterrent properties has been isolated from a marine sponge, *Spongia* sp. The gross structure was deduced from the spectroscopic data and the absolute configuration by applying the Horeau method to a derivative prepared by the reaction of 1 with ethylmagnesium bromide.

In our search for biologically significant substances from marine organisms inhabiting in Okinawan waters, a sponge of the genus *Spongia* was found to contain a large amount of an oily substance exhibiting ichthyotoxicity and feeding-deterrency. The active compound designated as kurospongin (1)[1] was shown to be a new furanoterpene having a 21-carbon skeleton. In this report we describe the isolation and structure elucidation of 1. Many furanoterpenes of this type have now been reported mainly from the sponge family Spongiidae.[2-4] The biogenetic origin of the 21-carbon skeleton, although suggested as the catabolism of sesterterpenes,[2] still remains to be explored.

A sample of *Spongia* sp. was freeze-dried and extracted with ethyl acetate. The residue on evaporation was chromatographed on silica gel to give kurospongin (1) as an unstable oil. Since the compound amounted to 58% of the crude extract, this single column operation was sufficient to afford a pure sample of 1.

The molecular formula $C_{21}H_{22}O_4$ was determined by high resolution EIMS. The presence of furan rings in the molecule was indicated by IR (3150, 1505, 870 cm^{-1}) and ^1H NMR spectra. The latter revealed signals for four furan α-protons (δ 7.17, 7.31, 7.34, 7.37) and two β-protons (δ 6.24, 6.50), suggesting the existence of two β-monosubstituted furan rings. This was further substantiated by ^{13}C NMR data which showed four doublets (δ 138.4, 139.6, 142.2, 143.0) with $^1J_{CH}$ = 200 Hz and two doublets (δ 107.1, 110.6) with $^1J_{CH}$ = 175 Hz. These C-H coupling constants are typical values observed for the furan α- and β-carbons, respectively.[7]



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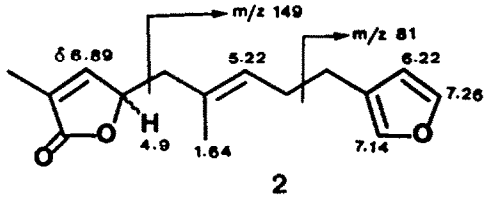

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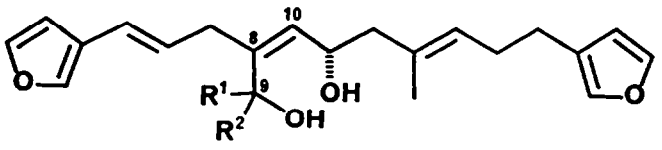
These data suggested that the compound 1 belonged to the class of C_{21} linear furanoterpenes having furan rings at the both ends. The spectral data also revealed the presence of an α,β-unsaturated γ-lactone [1765 cm^{-1}; δ 172.7 (C-9), 148.4 (C-10), 79.8 (C-11); δ 6.96 (H-10), 4.95 (H-11)], a vinyl methyl (δ 1.64), a *trans*-double bond [960 cm^{-1}; δ 6.34 (d, J = 15.8 Hz, H-5), 5.94 (dt, J = 15.8, 7.0 Hz, H-6)], and a tri-substituted double bond [δ 5.25 (t, J = 6.9 Hz, H-15)].



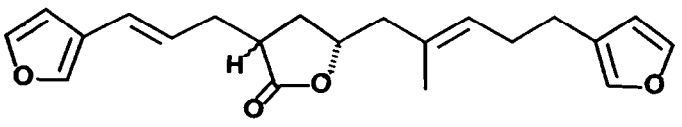
3a,b $R^1 = R^2 = H$, 8,10-dihydro

5 $R^1 = R^2 = H$

6 $R^1 = R^2 = CH_3$

8 $R^1 = R^2 = CH_2CH_3$

9 $R^1 = CH_2CH_3$, $R^2 = H$



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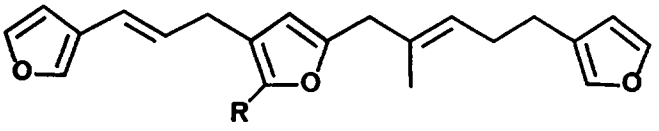
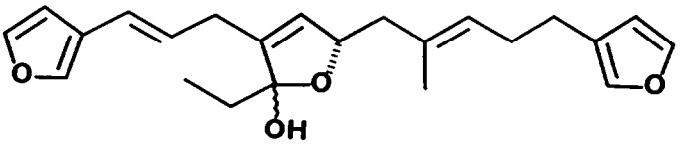
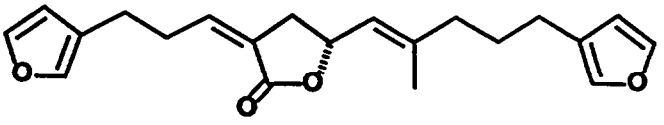


7 $R = CH_3$

10 $R = CH_2CH_3$



11



12

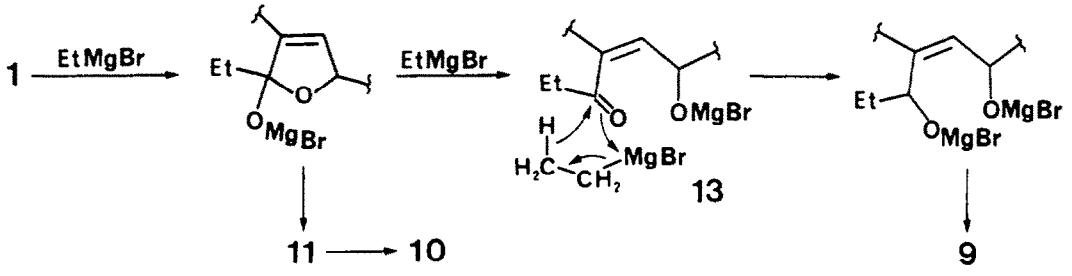
The olefinic signal at δ 5.25 which appeared as a broad triplet was sharpened by irradiation of the methyl singlet at δ 1.64 (H-14) and shown to be coupled to a methylene resonance at δ 2.24 (dt, J = 6.9, 7.2 Hz, H-16). The latter in turn is coupled to a methylene triplet at δ 2.44 (J = 7.2 Hz, H-17). These results along with EIMS [m/z 257 and 81 (C-16/C-17 fission), 189 and 149 (C-11/C-12 fission)] suggested a partial structure which was comparable with that of sesquiterpene freelingnite (2).[8] The configuration of the tri-substituted double bond was assigned as *E* by ^{13}C NMR chemical shift (δ 16.3) of the vinyl methyl carbon.

The structure for the left-half of the molecule was secured by double resonance experiments. Thus, irradiation of the signal at δ 5.94 (H-6) collapsed both the doublet at δ 6.34 (H-5) and a broad doublet at δ 3.10 (2 H, J = 7 Hz, H-7) to singlets. The signal [δ 6.95 (J = 1.5 Hz, H-10)] appeared as a quartet was transformed into a doublet by irradiation of the resonance at δ 3.10 and into a triplet by irradiation of the signal at δ 4.95 (ddd, J = 6.8, 6.8, 1.5 Hz, H-11). The signal at δ 3.10 was assigned to a doubly allylic methylene having a long range coupling with a lactonic β-proton (δ 6.96). The methine proton at δ 4.95 was shown to be adjacent to non-equivalent methylene protons at δ 2.26 and 2.38 (both dd, J = 13.9, 6.8 Hz, H-12) by irradiation. These results led to formulate the gross structure of kurospongin (1) as shown.

To determine the absolute configuration Horeau's partial resolution method[9] was attempted on several diols prepared from 1. First, 1 was treated with sodium borohydride to give a pair of epimeric diols 3a and 3b and 8,10-dihydrokurospongin (4). Application of the Horeau method to each of the epimers was unsuccessful, as the rotation of resulting 2-phenylbutanoic acid was marginal in each case. Diol 5 prepared by reduction of 1 with lithium aluminum hydride was too unstable to apply the Horeau method. Our next strategy was to prepare a diol in which the generated

hydroxyl group at C-9 is unreactive to the acylating reagent. Such diol should be easily prepared by reacting the lactone 1 with a Grignard reagent. Treatment of 1 with methylmagnesium iodide gave diol 6 and furan 7 in 56.8 and 40.9% yield, respectively. The structures of these derivatives were established by spectroscopic data. The Horeau procedure was applied to the diol 6. A recovered sample of 2-phenylbutanoic acid was levorotatory ($[\alpha]_D$ -1.1°), suggesting (*S*) configuration at C-11. However, the optical yield was only 4.6%, and it was felt to be too low to make the conclusion from this result. To increase the optical yield it appeared to be necessary to introduce bulkier groups than methyl at C-9. Thus, the Grignard reaction was carried out using ethylmagnesium bromide. Four products, 8-11 were isolated in 99% total yield. The structures of these compounds, except for 11, were secured by spectroscopic analysis. Compound 11 readily decomposed to give the furan 10, and its structure was tentatively assigned on this ground. The formation of the diol 9 can be rationalized as the result of the reduction[10] of the intermediate ketone 13 by the Grignard reagent (see Scheme 1).

Scheme 1



The diol 8 was treated with 2-phenylbutanoic anhydride and pyridine. Resulting samples of 2-phenylbutanoic acid showed levorotation with significantly improved optical yields (21 and 13% in two runs), confirming the (*S*) configuration of kurospongin (1). This indicates the same stereostructure with that of nitenin (12) which has been reported from *Spongia nitens*.[11]

Kurospongin (1) was ichthyotoxic, killing goldfish at the concentration of 5 μg/ml within 4 h. In feeding experiments using the omnivorous fish *Tilapia mosambica*, 1 impregnated in feed completely deterred its consumption at the concentration level of 0.3%

EXPERIMENTAL

Infrared spectra were measured on a Hitachi 260-10 infrared spectrophotometer and optical rotations on an Atago AA-5 digital polarimeter. Ultraviolet spectra were taken on a Jasco UVIDEC 610 Spectrometer and mass spectra on a JEOL JMN-D300 instrument. ^{1}H NMR spectra were recorded mostly at 60 MHz on a JEOL JNM-PMX60 and one at 300 MHz on a Nicolet NT-300 instrument, and ^{13}C NMR spectra were recorded at 22.5 MHz on a JEOL FX-90Q spectrometer.

Extraction and Isolation

A sample of *Spongia* sp. was collected at the intertidal zone of Yonaha Bay, Miyako Island in April, 1983 and kept frozen during transportation. The sample was freeze-dried (dry weight 473 g) and extracted by soaking in ethyl acetate (2 l.) for 2 days. After decantation the sponge was extracted again with fresh solvent in the same manner. The combined extracts were concentrated to give 11.3 g of an oil. The oil was separated on silica gel using hexane with increasing amounts of acetone. Fractions giving the same single spot on TLC were combined to afford 6.56 g (58% of

the extract) of kurospongin (1) as a slightly yellow, unstable oil: $[\alpha]_D$ -16.8° (c 1.24, $CHCl_3$); UV λ_{max} (MeOH) 213 nm (ε 19000); IR (CCl_4) 3150, 2925, 1765, 1655, 1505, 1335, 1165, 1065, 1030, 960, and 870 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.64 (3 H, s), 2.24 (2 H, dt, J = 6.9, 7.2 Hz), 2.26 (1 H, dd, J = 13.9, 6.8 Hz), 2.38 (1 H, dd, J = 13.9, 6.8 Hz), 2.44 (2 H, t, J = 7.2 Hz), 3.10 (2 H, br d, J = 7.0 Hz), 4.95 (1 H, ddd, J = 6.8, 6.8, 1.5 Hz), 5.25 (1 H, t, J = 6.9 Hz), 5.94 (1 H, dt, J = 15.8, 7.0 Hz), 6.24 (1 H, br s), 6.34 (1 H, d, J = 15.8 Hz), 6.50 (1 H, br s), 6.95 (1 H, dt, J = 1.5, 1.5 Hz), 7.17 (1 H, br s), 7.31 (1 H, br s), 7.34 (1 H, br s), and 7.37 (1 H, br s); ^{13}C NMR ($CDCl_3$) δ 16.3 (q), 24.2 (t), 28.0 (t), 28.2 (t), 42.9 (t), 79.8 (d), 107.1 (d), 110.6 (d), 122.0 (d), 123.5 (s), 123.9 (d), 124.2 (s), 128.0 (d), 129.6 (s), 132.3 (s), 138.4 (d), 139.6 (d), 142.2 (d), 143.0 (d), 148.4 (d), and 172.7 (s); EIMS m/z 338 (M^+, 23), 257 (4), 244 (3), 189 (10), 149 (12), 131 (10), 94 (12), and 81 (100 rel%); high resolution EIMS m/z 338.1522 (calcd for $C_{21}H_{22}O_4$ 338.1517).

Reduction of 1 with Sodium Borohydride

To a solution of 1 (305 mg) in methanol (2 ml) was added a suspension of sodium borohydride (560 mg) in methanol (4 ml), and the mixture was stirred at 50 °C for 3 h. After cooling water was added, and the mixture was concentrated and extracted with ethyl acetate. The product mixture was separated on a Lobar Si-60 column by eluting with hexane-ethyl acetate (1:1) to give 43.3 mg(14%) of lactone 4, 33 mg (11%) of diol 3a (less polar epimer), and 84 mg (27%) of diol 3b (more polar epimer). 4: IR (CCl_4) 2925, 1780, 1290, 1160, 1075, 1030, 960, and 870 cm^{-1}; ^1H NMR (CCl_4) δ 1.62 (3 H, s), 2.0-2.6 (11 H, m), 4.33 (1 H, m), 5.11 (1 H, m), 5.73 (1 H, dt, J = 16, 6 Hz), 6.07 (1 H, br s), 6.15 (1 H, d, J = 16 Hz), 6.34 (1 H, br s), 7.02 (1 H, br s), and 7.18 (3 H, br s); EIMS m/z 340 (M^+, 11), 259 (5), 119 (28), 107 (87), and 81 (100 rel%). 3a: $[\alpha]_D$ -7.4° (c 0.34, $CHCl_3$); IR (CCl_4) 3420, 2925, 1435, 1160, 1065, 1020, 960, and 870 cm^{-1}; ^1H NMR (CCl_4) δ 1.3-1.6 (3 H, m), 1.58 (3 H, s), 2.0-2.4 (8 H, m), 3.50 (3 H, m), 3.72 (2 H, br s), 5.13 (1 H, m), 5.75 (1 H, dt, J = 16, 7 Hz), 6.12 (1 H, d, J = 16 Hz), 6.12 (1 H, br s), 6.35 (1 H, br s), 7.07 (1 H, br s), and 7.22 (3 H, br s); EIMS m/z 344 (M^+, 0.1), 326 (0.2), 263 (0.7), 150 (22), 135 (25), 107 (27), and 81 (100 rel%). 3b: $[\alpha]_D$ +4.5° (c 0.59, $CHCl_3$); IR (CCl_4) 3330, 2925, 1440, 1165, 1070, 1025, 965, and 870 cm^{-1}; ^1H NMR (CCl_4) δ 1.3-1.7 (3 H, m), 1.59 (3 H, s), 2.0-2.3 (8 H, m), 3.53 (3 H, m), 4.27 (2 H, br s, OH), 5.17 (1 H, m), 5.79 (1 H, dt, J = 16, 6 Hz), 6.14 (1 H, d, J = 16 Hz), 6.16 (1 H, br s), 6.40 (1 H, br s), 7.10 (1 H, br s), and 7.23 (3 H, br s); EIMS m/z 344 (M^+, 0.1), 326 (0.3), 245 (0.6), 150 (20), 135 (25), 107 (25), and 81 (100 re%).

Reduction of 1 with Lithium Aluminum Hydride

To a suspension of $LiAlH_4$ (60 mg) in ether (2 ml) was added dropwise a solution of 1 (101.4 mg) in ether (3 ml), and the mixture was stirred for 2 h. After addition of water the organic layer was separated to give an oily residue which was chromatographed on silica gel with hexane-acetone (10:3) furnishing 61.7 mg (60%) of diol 5 as an unstable oil: IR (CCl_4) 3400, 2925, 1500, 1440, 1385, 1165, 1070, 1025, 965, and 870 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63 (3 H, s), 2.05-2.44 (6 H, m), 2.60 (2 H, br s, OH), 2.95 (2 H, d, J = 6 Hz), 4.00 (1 H, d, J = 12 Hz), 4.22 (1 H, d, J = 12 Hz), 4.50 (1 H, q, J = 7 Hz), 5.30 (2 H, m), 5.88 (1 H, dt, J = 16, 6 Hz), 6.23 (1 H, m), 6.26 (1 H, d, J = 16 Hz), 6.46 (1 H, m), 7.18 (1 H, m), and 7.33 (3 H, br s).

Reaction of 1 with Methylmagnesium Iodide

To a suspension of the Grignard reagent prepared from methyl iodide (364 mg) and

magnesium turnings (71 mg) in ether (10 ml) was added dropwise a solution of 1 (200 mg) in ether (5 ml) under nitrogen atmosphere. The mixture was stirred at room temperature for an additional 1 h, and an excess of the reagent was destroyed by adding several drops of acetone. After addition of 0.1 N hydrochloric acid solution (20 ml), the mixture was extracted with ether. The organic layer was separated on silica gel (hexane-ethyl acetate) to furnish 122.6 mg (56.8%) of 6 and 81.3 mg (40.9%) of 7. Compound 6: colorless oil, $[\alpha]_D$ +6.9° (c 0.72, $CHCl_3$); IR (CCl_4) 3450, 2930, 1165, 1030, 965, and 870 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (6 H, s), 1.59 (3 H, s), 2.05-2.35 (6 H, m), 2.79 (2 H, d, J = 6 Hz), 3.72 (2 H, br s, OH), 4.79 (1 H, q, J = 7 Hz), 5.16 (1 H, d, J = 7 Hz), 5.21 (1 H, m), 5.79 (1 H, dt, J = 15, 6 Hz), 6.16 (1 H, d, J = 15 Hz), 6.19 (1 H, br s), 6.44 (1 H, br s), 7.14 (1 H, br s), and 7.29 (3 H, br s); EIMS m/z 352 (M - H_2O, 0.2), 334 (6), 253 (2), 185 (25), 107 (100), and 81 (73 rel%). High resolution EIMS m/z 352.2023 (calcd for $C_{23}H_{28}O_3$ 352.2036). Compound 7: colorless oil, $[\alpha]_D$ 0° (c 3.74, $CHCl_3$); IR (CCl_4) 2930, 1505, 1435, 1390, 1195, 1165, 1075, 1025, 960, and 870 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (3 H, s), 2.19 (3 H, s), 2.30-2.64 (4 H, m), 3.15 (2 H, d, J = 6 Hz), 3.20 (2 H, s), 5.25 (1 H, br t, J = 6 Hz), 5.79 (1 H, s), 5.94 (1 H, dt, J = 16, 6 Hz), 6.24 (1 H, d, J = 16 Hz), 6.26 (1 H, br s), 6.47 (1 H, br s), 7.17 (1 H, br s), and 7.27 (3 H, m); EIMS m/z 336 (M^+, 100), 201 (11), 187 (21), 159 (27), 107 (32), and 81 (44 rel %). High resolution EIMS m/z 336.1733 (calcd for $C_{22}H_{24}O_3$ 336.1726).

Reaction of 1 with Ethylmagnesium Bromide

To a suspension of ethylmagnesium bromide prepared from ethyl bromide (807 mg) and magnesium turnings (180 mg) in ether (25 ml) was added a solution of 1 (500 mg) in ether (5 ml). The mixture was allowed to react and worked up in the same manner as above except that 1 instead of 0.1 N hydrochloric acid was used for the hydrolysis of the reaction mixture. Separation of the product mixture by HPLC (μ-Porasil, hexane-ethyl acetate 3:1) gave 271 mg (46%) of 8, 51 mg (9%) of 9, 167 mg (32%) of 10, and 67 mg (12%) of 11. Compound 8: colorless oil, $[\alpha]_D$ -4.4° (c 0.57, $CHCl_3$); IR (CCl_4) 3470, 2980, 2940, 1500, 1460, 1385, 1165, 1075, 1025, 965, and 870 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (6 H, t, J = 7 Hz), 1.61 (3 H, s), 1.34-1.81 (4 H, m), 2.17-2.41 (6 H, m), 2.70 (2 H, d, J = 6 Hz), 3.17 (2 H, br s, OH), 4.77 (1 H, q, J = 7 Hz), 5.22 (1 H, m), 5.41 (1 H, d, J = 7 Hz), 5.79 (1 H, dt, J = 16, 6 Hz), 6.16 (1 H, d, J = 16 Hz), 6.22 (1 H, m), 6.46 (1 H, m), 7.15 (1 H, br s), and 7.32 (3 H, br s); EIMS m/z 398 (M^+, 0.1), 380 (0.2), 351 (1), 249 (11), 231 (14), 135 (21), and 107 (100 rel%). High resolution EIMS m/z 380.2356 (calcd for $C_{25}H_{32}O_3$ 380.2351). Compound 9: colorless oil, $[\alpha]_D$ -6.8° (c 0.37, $CHCl_3$); IR (CCl_4) 3420, 2930, 1500, 1440, 1385, 1165, 1070, 1025, 965, and 870 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (3 H, t, J = 7 Hz), 1.64 (3 H, s), 2.02-2.61 (8 H, m), 2.86 (2 H, d, J = 6 Hz), 4.35 (1 H, t, J = 7 Hz), 4.56 (1 H, q, J = 7 Hz), 5.22 (1 H, m), 5.30 (1 H, d, J = 7 Hz), 5.87 (1 H, dt, J = 15, 6 Hz), 6.21 (1 H, m), 6.23 (1 H, d, J = 15 Hz), 6.45 (1 H, m), 7.16 (1 H, m), and 7.29 (3 H, m); EIMS m/z 352 (M - H_2O, 1), 350 (2), 221 (14), 203 (12), 150 (11), 107 (100), and 81 (45 rel%). High resolution EIMS m/z 352.2033 (calcd for $C_{23}H_{28}O_3$ 352.2035). Compound 10: Colorless oil, $[\alpha]_D$ 0° (c 0.63, $CHCl_3$); IR (CCl_4) 2940, 1505, 1455, 1385, 1165, 1070, 1025, 960, and 875 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (3 H, t, J = 7 Hz), 1.60 (3 H, s), 1.92-2.86 (6 H, m), 3.17 (2 H, d, J = 6 Hz), 3.20 (2 H, s), 5.25 (1 H, m), 5.78 (1 H, s), 5.94 (1 H, dt, J = 16, 6 Hz), 6.25 (1 H, d, J = 16 Hz), 6.25 (1 H. br s), 6.47 (1 H, m), 7.17 (1 H, br s), and 7.30 (3 H, br s); EIMS m/z 350 (M^+, 100), 231 (19), 201 (19), 173 (22), 107 (59), and 81 (66 rel%). High resolution EIMS m/z 350.1902 (calcd for $C_{23}H_{26}O_3$ 350.1882). Compound 11: Colorless oil, $[\alpha]_D$ +40° (c 0.25, $CHCl_3$); IR (CCl_4) 3630, 2940, 1500, 1465, 1385, 1165, 1070, 1025, 965, and 875 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65 (3 H, s), 4.30 (1 H, m), 5.19 (1 H, m), 5.90 (1 H, dt, J = 15, 6 Hz), 6.23 (1 H, br s),

6.24 (1 H, d, J = 15 Hz), 6.45 (1 H, br s), 7.17 (1 H, m), and 7.30 (3 H, m).

Application of the Horeau Method to Diols 6 and 8

Diol 6 (100 mg) was treated with 2.5 molar equivalent (209 mg) of 2-phenylbutanoic anhydride in pyridine (1 ml) at room temperature overnight. After addition of saturated sodium bicarbonate solution, the mixture was extracted with ethyl acetate. The organic layer gave 113 mg of the monoester, 2-phenylbutanoate of 6: $[\alpha]_D$ +12.2° (c 0.54, $CHCl_3$), high resolution EIMS m/z 498.2769 [calcd for $C_{33}H_{38}O_4$ (M - H_2O) 498.2769]. The aqueous layer was acidified (2 N HCl) and extracted with ethyl acetate to give 137 mg of 2-phenylbutanoic acid which exhibited $[\alpha]_D$ -1.1° (c 2.23, benzene) and optical yield 4.6%. Two samples (100 mg each) of 8 were similarly treated with 2.5 and 3 equivalents of the anhydride, giving the ester of 8 in 86 and 78% yield, respectively, $[\alpha]_D$ +22° (c 3.06, $CHCl_3$); high resolution EIMS m/z 526.3079 [calcd for $C_{35}H_{42}O_4$ (M - H_2O) 526.3080]. The recovered samples (125 and 161 mg, respectively) of 2-phenylbutanoic acid showed $[\alpha]_D$ -3.0° (c 1.66, benzene) and -4.0° (c 1.26, benzene) which correspond to the optical yield of 13 and 21%, respectively.

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