Supporting Information

Chemoenzymatic Synthesis of (+)-Aspicilin from Chlorobenzene

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General Information. Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Varian Gemini 300 or Varian Mercury 300 spectrometer operating at 300 MHz for hydrogen and 75.4 MHz for carbon nuclei. Chemical shifts were recorded as δ values in parts per million (ppm). Spectra were acquired in deuterochloroform ($CDCl_3$) at 20 ºC unless otherwise stated. For ^{1}H NMR spectra recorded in $CDCl_3$, the peak due to residual $CHCl_3$ (δ 7.26) was used as the internal reference. ^{1}H NMR data are reported as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral and (where possible) assignment]. Multiplicities are defined as: s = singlet; d = doublet; t = triplet; q = quartet; quintet; septet; m = multiplet or combinations of the above. The central peak (δ 77.0) of the $CDCl_3$ triplet was used as the reference for proton-decoupled ^{13}C NMR spectra. For ^{13}C NMR spectra, the data are reported as: chemical shift (δ) (protonicity), where protonicity is defined as: C = quaternary; CH = methine; CH_2 = methylene; CH_3 = methyl; C/CH_2 = quaternary or methylene; CH/CH_3 = methine or methyl. The assignment of signals observed in various NMR spectra was often assisted by conducting attached proton test (APT), homonuclear (^{1}H/^{1}H) correlation spectroscopy (COSY), nuclear Overhauser effect (nOe), and/or heteronuclear (^{1}H/^{13}C) correlation spectroscopy (HETCOR) experiments.

Infrared spectra (ν_{max}) were recorded on either a Perkin-Elmer 1800 Fourier Transform Infrared Spectrophotometer or a Perkin-Elmer Spectrum One instrument. Samples were analysed as KBr discs (for solids) or as thin films on KBr plates (for liquids/oils).

Low and high resolution mass spectra were recorded on a VG Fisons AutoSpec three sector (E / B / E) double focussing mass spectrometer, using (unless otherwise specified) positive-ion electron impact techniques at the voltages indicated. Mass spectral data are listed as: mass-to-charge ratio (*m/z*) [assignment (where possible), intensity relative to the base peak (%)].

Optical rotations were measured with a Perkin-Elmer 241 polarimeter at the sodium D-line (589 nm) using the spectroscopic grade solvents specified at 20 ºC and the concentrations (*c*) (g/100 mL) indicated. The measurements were carried out in a cell with a path length of 1 dm. Specific rotations $\{[\alpha]_D^{20}\}$ were calculated using the equation $[\alpha]_D = (100.\alpha) / (c.l)$ and are given in $10^{-1}.deg.cm^2.g^{-1}$.

Melting points were recorded on a Reichert hot-stage apparatus and are uncorrected.

Elemental analyses were performed by the Australian National University Microanalytical Services Unit based in the Research School of Chemistry, The Australian National University, Canberra, Australia.

Analytical thin layer chromatography (TLC) was conducted on aluminium-backed 0.2 mm thick silica gel 60 F_{254} plates (Merck) and the chromatograms were visualised under a 254 nm UV lamp and/or by treatment with an anisaldehyde/sulfuric acid/ethanol (3 mL : 4.5 mL : 200 mL) dip or, occasionally, with a phosphomolybdic acid/ceric sulfate/sulfuric acid/water (37.5 g : 7.5 g : 37.5 mL : 720 mL) dip, followed by heating. The retention factor (R_f) quoted is rounded to the nearest 0.1. Flash chromatography was conducted according to the method of Still and co-workers [W. C. Still *et. al. J. Org. Chem.*, 1978, **43**, 2923] using silica gel 60 (mesh size 0.040-0.063 mm) as the stationary phase and the analytical reagent (AR) grade solvents indicated.

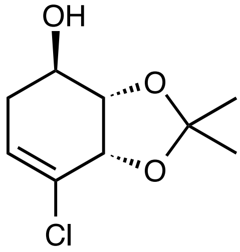
Many starting materials and reagents were available from the Aldrich Chemical Company or EGA-Chemie and were either used as supplied or simply distilled. Drying agents and other inorganic salts were purchased from AJAX or BDH Chemicals. Reactions employing air- and/or moisture-sensitive reagents and intermediates were carried out under an atmosphere of dry, oxygen-free nitrogen in flame-dried apparatus.

Room temperature is assumed to be 18 ºC.

Tetrahydrofuran (THF) and diethyl ether were dried with sodium and distilled, as required, from sodium benzophenone ketyl. Methanol was distilled from magnesium methoxide. Dichloromethane was distilled from calcium hydride. Dimethylformamide (DMF) and hexane were refluxed over calcium hydride for 16 h then distilled and stored over 3 Å molecular sieves.

Organic solutions obtained from work-up of reaction mixtures were dried with magnesium sulfate ($MgSO_4$). Petrol refers to petroleum spirits boiling in the range 40-60 °C unless otherwise specified. Organic solutions were concentrated under reduced pressure on a rotary evaporator with the water bath generally not exceeding 30 °C.

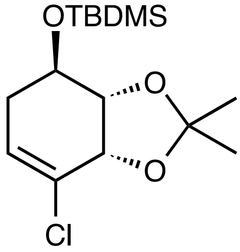
Compound 6



DIBAL-H (93.8 mL of a 1 M solution in hexane, 93.8 mmol) was added, dropwise, to a magnetically stirred solution of epoxide **5** (9.50 g, 46.9 mmol) in diethyl ether (500 mL) maintained at -40 °C under a nitrogen atmosphere. The resulting solution was allowed to warm to -20 °C over 1 h, then treated with tartaric acid (300 mL of a 1 M aqueous solution). The mixture thus obtained was partitioned between diethyl ether (300 mL) and brine (200 mL). The separated aqueous layer was extracted with diethyl ether (3 x 200 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a clear, colourless oil. Subjection of this material to flash chromatography (silica, 30% v/v ethyl acetate/petrol elution) provided, after concentration of the appropriate fractions (R_f 0.3), the *title compound* ***6*** (8.30 g, 87%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 5.92 (dd, *J* 5.2 and 3.5 Hz, 1H), 4.59 (d, *J* 6.0 Hz, 1H), 4.11 (t, *J ca.* 6.0 Hz, 1H), 3.91 (m, 1H), 2.50 (br dt, *J ca.* 17.3 and 5.2 Hz, 1H), 2.25 (br s, 1H), 2.15 (dddd, *J* 17.3, 8.5, 3.5 and 1.5 Hz, 1H), 1.50 (s, 3H), 1.42 (s, 3H).
^{13}C NMR (75 MHz) δ 129.0 (C), 125.5 (CH), 110.0 (C), 78.8 (CH), 75.7 (CH), 67.7 (CH), 30.6 (CH_2), 28.0 (CH_3), 26.0 (CH_3).
IR (KBr) ν_{max} 3428, 1653, 1381, 1219, 1074 cm^{-1}.
Mass Spectrum (70 eV) *m/z* 207 and 205 [$(M+H)^+$, <1 and <1%], 206 and 204 ($M^{+\cdot}$, <1 and <1), 191 and 189 [$(M-H_3C\cdot)^+$, 49 and 95], 131 and 129 {[$M-(CH_3)_2CO-HO\cdot)^+$, 51 and 100}.
HRMS Found: $(M-H_3C\cdot)^+$, 189.0319. $C_9H_{13}{}^{35}ClO_3$ requires $(M-H_3C\cdot)^+$, 189.0318.
Specific Rotation $[\alpha]_D$ -55 (*c* 1.5, $CHCl_3$).

Compound 7



tert-Butyldimethylsilyl chloride (TBDMS-Cl) (16.1 g, 106.6 mmol) was added to a magnetically stirred solution of compound **6** (10.9 g, 53.3 mmol) and imidazole (9.1 g, 133.3 mmol) in anhydrous DMF (100 mL) maintained at 18 °C under an atmosphere of nitrogen. After 8 h the reaction mixture was poured in water (800 mL) then extracted with diethyl ether (3 x 800 mL). The combined organic phases were washed with HCl (1 x 500 mL of a 1% v/v aqueous solution), water (2 x 500 mL) and brine (1 x 800 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale-yellow oil (*ca*. 24 g). Subjection of this material to flash chromatography (silica, 3% v/v ethyl acetate/petrol elution) provided, after concentration of the appropriate fractions (R_f 0.3), the *title compound* ***7*** (15.5 g, 91%) as microcrystalline masses, m.p. 36-39 °C.

^{1}H NMR (300 MHz) δ 5.82 (t, *J ca*. 5.0 Hz, 1H), 4.53 (d, *J* 5.7 Hz, 1H), 4.14 (t, *J* 5.7 Hz, 1H), 4.02 (m, 1H), 2.43 (dtd, *J* 17.3, 5.0 and 2 Hz, 1H), 2.11 (dt, *J* 17.3 and 5.0 Hz, 1H), 1.45 (s, 3H), 1.41 (s, 3H), 0.87 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (75 MHz) δ 129.8 (C), 124.2 (CH), 109.8 (C), 78.2 (CH), 75.6 (CH), 67.7 (CH), 31.3 (CH_2), 27.9 (CH_3), 26.3 (CH_3), 25.6 (3 x CH_3), 17.9 (C), -4.8 (CH_3), -4.9 (CH_3).

IR (KBr) ν_{max} 1654, 1472, 1381, 1251, 1095 cm^{-1}.

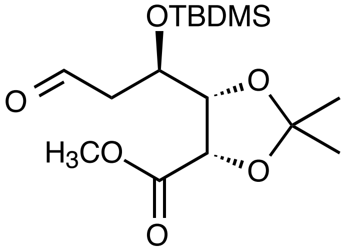
Mass Spectrum (70 eV) *m/z* 305 and 303 $[(M-H_3C\cdot)^+$, 3 and 8%], 205 and 203 $[(M-C_6H_{15}Si\cdot)^+$, 59 and 100].

HRMS Found: $(M-H_3C\cdot)^+$, 303.1172. $C_{15}H_{27}{}^{35}ClO_3Si$ requires $(M-H_3C\cdot)^+$, 303.1183.

Elemental Analysis Found: C, 56.20; H, 8.27; Cl, 11.21. $C_{15}H_{27}ClO_3Si$ requires C, 56.49; H, 8.53; Cl, 11.12%.

Specific Rotation $[\alpha]_D$ -30 (*c* 1.4, $CHCl_3$).

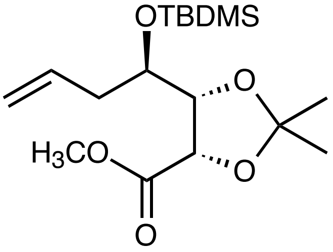
Compound 8



A magnetically stirred solution of compound **7** (5.0 g, 15.7 mmol) in MeOH (250 mL) was cooled to -78 °C and treated with a stream of ozone (*ca.* 40% ozone in oxygen). When the blue colour of ozone persisted and TLC analysis indicated that no starting material remained (*ca.* 1 h) the reaction mixture was purged with nitrogen (20 mins) then warmed to 0 °C (over 30 mins). $NaBH_4$ (1.2 g, 31.4 mmol) was then added, in potions over 5 mins, whilst maintaining the temperature of the reaction mixture at 0 °C. After 30 mins at 0 °C the reaction mixture was treated with NH_4Cl (40 mL of a saturated aqueous solution) and diluted with water (150 mL). The resulting mixture was extracted with diethyl ether (3 x 300 mL) and the combined organic phases were washed with water (2 x 500 mL) and brine (1 x 800 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a light-yellow oil. This somewhat unstable material was immediately subjected to the next step in the reaction sequence.

^{1}H NMR (300 MHz) δ 9.78 (d, *J* 2.5 Hz, 1H), 4.53 (d, *J* 6.2 Hz, 1H), 4.24 (m, 2H), 3.74 (s, 3H), 2.74 (dd, *J* 16.4 and 2 Hz, 1H), 2.59 (dm, *J* 16.4 Hz, 1H), 1.60 (s, 3H), 1.37 (s, 3H), 0.84 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H).
^{13}C NMR (75 MHz) δ 200.0 (C), 170.0 (C), 110.8 (C), 80.6 (CH), 75.2 (CH), 67.2 (CH), 52.0 (CH_3), 48.0 (CH_2), 26.6 (CH_3), 25.8 (3 x CH_3), 25.2 (CH_3), 18.1 (C), -4.2 (CH_3), -4.8 (CH_3).
IR (KBr) ν_{max} 1759, 1730, 1254, 1106 cm^{-1}.
Mass Spectrum (70 eV) *m/z* 331 [$(M-H_3C\cdot)^+$, 24%], 289 {[$M-(CH_3)_3C\cdot]^+$, 29}, 231 [$(M-C_6H_{15}Si\cdot)^+$, 34], 213 (100).
HRMS Found: [$M-(CH_3)_3C\cdot]^+$, 289.1106. $C_{16}H_{30}O_6Si$ requires [$M-(CH_3)_3C\cdot]^+$, 289.1107.

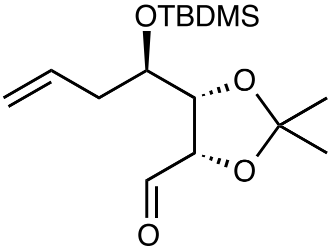
Compound 9



A magnetically stirred solution of methyltriphenylphosphonium bromide (13.4 g, 37.4 mmol) in anhydrous THF (350 mL) maintained at 0 °C under a nitrogen atmosphere was treated with potassium *bis*(trimethylsilyl)amide (62.4 mL of a 0.5 M solution in toluene, 31.2 mmol). The resulting yellow solution was allowed to warm to 18 °C over 1 h then re-cooled to 0 °C. A solution of aldehyde **8** (5.40 g, 15.6 mmol) in THF (50 mL) was then added, *via* cannula, to the reaction mixture. After 2 h at 18 °C the reaction mixture was treated sequentially with NH_4Cl (100 mL of a saturated aqueous solution) and water (350 mL). The resulting mixture was extracted with diethyl ether (3 x 300 mL) and the combined organic phases were washed with HCl (1 x 300 mL of a 5% v/v aqueous solution), water (2 x 500 mL) and brine (1 x 600 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a light-yellow oil. Subjection of this material to flash chromatography (silica, 2% v/v ethyl acetate/petrol elution) provided, after concentration of the appropriate fractions (R_f 0.4), the *title compound* ***9*** (3.82 g, 71% from compound **7**) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 5.88 (m, 1H), 5.12-5.05 (complex m, 2H), 4.50 (d, *J* 6.2 Hz, 1H), 4.15 (dd, *J* 8.4 and 6.2 Hz, 1H), 3.74 (s, 3H), 3.66 (m, 1H), 2.37 (m, 1H), 2.20 (m, 1H), 1.59 (s, 3H), 1.35 (s, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H).
^{13}C NMR (75 MHz) δ 170.7 (C), 134.5 (CH), 117.3 (CH_2), 110.6 (C), 81.0 (CH), 75.5 (CH), 71.4 (CH), 51.8 (CH_3), 38.8 (CH_2), 26.5 (CH_3), 25.9 (3 x CH_3), 25.6 (CH_3), 18.4 (C), -4.2 (CH_3), -4.7 (CH_3).
IR (KBr) ν_{max} 1760, 1737, 1642, 1250, 1101 cm^{-1}.
Mass Spectrum (70 eV) *m/z* 329 [$(M-H_3C\cdot)^+$, 7%], 287 {[$M-(CH_3)_3C\cdot]^+$, 26}, 229 [$(M-C_6H_{15}Si\cdot)^+$, 29], 185 [$(M-C_7H_{11}O_4\cdot)^+$, 47], 159 ($C_7H_{11}O_4^{+\cdot}$, 100).
HRMS Found: $(M-H_3C\cdot)^+$, 329.1777. $C_{17}H_{32}O_5Si$ requires $(M-H_3C\cdot)^+$, 329.1784.
Elemental Analysis Found: C, 59.05; H, 9.11. $C_{17}H_{32}O_5Si$ requires C, 59.27; H, 9.36%.
Specific Rotation $[\alpha]_D$ +23 (*c* 1.7, $CHCl_3$).

Compound 3

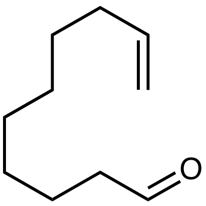


DIBAL-H (3.2 mL of a 1 M solution in hexane, 3.2 mmol) was added, dropwise, to a magnetically stirred solution of ester **9** (1.0 g, 2.9 mmol) in hexane (29 mL) maintained at –78 °C under a nitrogen atmosphere. The reaction mixture was kept at –78 °C for a further 45 min, then treated with tartaric acid (10 mL of a 1 M aqueous solution) and allowed to warm to 18 °C. The resulting mixture was extracted with diethyl ether (3 x 80 mL) and the combined organic phases were washed with brine (1 x 100 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a light-yellow oil. Subjection of this material to flash chromatography (silica, 10% v/v ethyl acetate/petrol elution) provided, after concentration of the appropriate fractions (R_f 0.3), the *title compound* ***3*** (760 mg, 83%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 9.70 (d, *J* 2.3 Hz, 1H), 5.81 (m, 1H), 5.15-5.02 (complex m, 2H), 4.30 (m, 2H), 3.82 (app q, *J ca.* 6 Hz, 1H), 2.42 (m, 1H), 2.23 (m, 1H), 1.58 (s, 3H), 1.39 (s, 3H), 0.88 (s, 9H), 0.06 (s, 6H).
^{13}C NMR (75 MHz) δ 200.9 (C), 133.9 (CH), 117.8 (CH_2), 110.4 (C), 81.2 (CH), 80.6 (CH), 70.2 (CH), 38.0 (CH_2), 27.0 (CH_3), 25.9 (3 x CH_3), 25.1 (CH_3), 18.2 (C), -4.1 (CH_3), -4.3 (CH_3).
IR (KBr) ν_{max} 1734, 1641, 1372, 1252, 1221, 1094 cm^{-1}.
Mass Spectrum Satisfactory mass spectral data could not be obtained on this compound.
Specific Rotation $[\alpha]_D$ +17 (*c* 2.8, $CHCl_3$).

Preparation of Compound 10 *via* the Route Outlined in Footnote 12.

9-Decenal (Compound b)



Dimethyl sulfoxide (23.6 mL, 0.3 mol) was added, dropwise, to a magnetically stirred solution of oxalyl chloride (13.4 mL, 0.15 mol) in dry dichloromethane (400 mL) maintained at -78 °C under a nitrogen atmosphere. After 30 mins, a solution of 9-decen-1-ol (**a**) (20 g, 0.13 mol, ex Aldrich) in dry dichloromethane (200 mL) was added, dropwise and *via* cannula, to the reaction mixture. After a further 4 h triethylamine (46.4 mL, 0.33 mol) was added, dropwise, and the resulting homogenous solution was stirred at -78 °C for 30 min and for a further 10 mins after warming to -10 °C. The reaction mixture was then diluted with dichloromethane (500 mL) and $NaHCO_3$ (500 mL of a saturated aqueous solution). The separated organic phase was washed with water (2 x 500 mL) and brine (2 x 500 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give 9-decenal (**b**)* (16.6 g, 84%) as a clear, colourless oil. This material was used, without purification, in the next step of the reaction sequence.

^{1}H NMR (300 MHz) δ 9.75 (t, *J* 1.8 Hz, 1H), 5.80 (m, 1H), 5.02-4.90 (complex m, 2H), 2.41 (td, *J* 7.3 and 1.8 Hz, 2H), 2.14-2.00 (complex m, 2H), 1.65-1.57 (complex m, 2H), 1.42-1.31 (complex m, 8H).
^{13}C NMR (75 MHz) δ 202.0 (C), 138.6 (CH), 113.9 (CH_2), 43.5 (CH_2), 33.4 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 28.6 (CH_2), 28.5 (CH_2), 21.7 (CH_2).
IR (KBr) ν_{max} 2927, 1726, 1640, 1463, 909 cm^{-1}.
Mass Spectrum (70 eV) *m/z* 154 ($M^{+\cdot}$, 3%), 110 [$(C_8H_{14})^{+\cdot}$, 62], 83 (64), 69 (90), 55 (100).
HRMS Found: $M^{+\cdot}$, 154.1357. Calculated for $C_{10}H_{18}O$ $M^{+\cdot}$, 154.1357.

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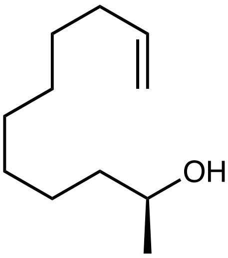
* S. Sakaguchi, Y. Yamamoto, T. Sugimoto, H. Yamamoto and Y. Ishii, *J. Org. Chem.*, 1999, **64**, 5954

(*S*)-10-Undecen-2-ol (Compound c)



Titanium (IV) isoproproxide (1.16 mL, 3.89 mmol) was added, dropwise, to a magnetically stirred suspension of (1*R*-*trans*)-*N*,*N*-(cyclohexane-1,2-diyl)*bis*(trifluoromethanesulfonamide)† (98 mg, 0.26 mmol) in dry toluene (5 mL) maintained at 18 °C under a nitrogen atmosphere. After the addition was complete, the reaction mixture was heated to 40 °C for 20 min, then cooled to -78 °C and treated with dimethylzinc (7.13 mL of a 2 M solution in toluene, 14.27 mmol). The resulting orange solution was treated, dropwise and *via* cannula, with a solution of aldehyde **b** (1.0 g, 6.5 mmol) in toluene (1 mL). The resulting mixture was maintained at -25 °C for 4 h and then treated with HCl (30 mL of a 10% v/v aqueous solution) and extracted with diethyl ether (3 x 100 mL). The combined organic phases were washed with brine (1 x 200 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a light-yellow oil. Subjection of this material to flash chromatography (silica, 7% v/v ethyl acetate/petrol elution) provided, after concentration of the appropriate fractions (R_f 0.2), the title compound **c**[4j] (920 mg, 83%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 5.80 (m, 1H), 5.02-4.91 (complex m, 2H), 3.78 (br s, 1H), 2.03 (app q, *J ca.* 7 Hz, 2H), 1.42-1.29 (complex m, 12H), 1.18 (d, *J* 6.2 Hz, 3H) (signal due to the OH proton not observed).
^{13}C NMR (75 MHz) δ 138.9 (CH), 114.0 (CH_2), 67.7 (CH), 39.2 (CH_2), 33.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 25.6 (CH_2), 23.2 (CH_3).
IR (KBr) ν_{max} 3351, 1640, 1464, 1373, 1121 cm^{-1}.
Mass Spectrum (70 eV) *m/z* 170 ($M^{+\cdot}$, 3%), 152 [$(M-H_2O)^{+\cdot}$, 16], 124 (26), 110 (54), 82 (86), 55 (100).
HRMS Found: $M^{+\cdot}$, 170.1671. Calculated for $C_{11}H_{22}O$ $M^{+\cdot}$, 170.1671.
Specific Rotation $[\alpha]_D$ +6.0 (*c* 1.0, $CHCl_3$), {lit.[13] $[\alpha]_D$ +6.8 (*c* 1.03, $CHCl_3$)}.

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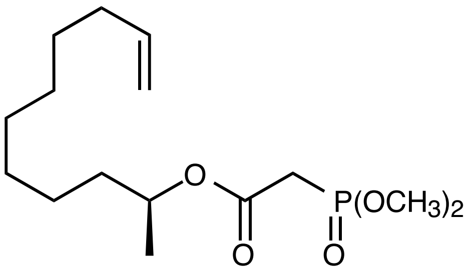
† Prepared by the method of M. Yoshioka, T. Kawakita and M. Ohno, *Tetrahedron Lett.*, 1989, **30**, 1657.

Compound 10



A solution of trimethyl phosphonoacetate (2 mL, 12.4 mmol), 4-(*N*,*N*-dimethylamino)pyridine (151 mg, 1.24 mmol) and alcohol **c** (700 mg, 4.12 mmol) in toluene (12 mL) was heated at reflux (111 °C) under an atmosphere of nitrogen. After 14 h the reaction mixture was cooled and the solvents removed under reduced pressure. The pale-yellow oil obtained in this manner was subjected to flash chromatography (silica, 40% v/v ethyl acetate/petrol elution) and concentration of the appropriate fractions (R_f 0.2) then provided the title compound **10**[4j] (1.15 g, 87%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 5.80 (m, 1H), 5.03-4.88 (complex m, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 2.95 (d, $J_{\text{H-P}}$ 21.7 Hz, 2H), 2.02 (q, *J ca.* 7 Hz, 2H), 1.64-1.47 (complex m, 2H), 1.36-1.25 (complex m, 10H), 1.23 (d, *J* 6.2 Hz, 3H).

^{13}C NMR (75 MHz) δ 165.1 (d, $J_{\text{C-P}}$ 5.8 Hz, PCH_2**C**=O), 138.9 (CH), 114.0 (CH_2), 72.6 (CH), 52.9 (d, $J_{\text{C-P}}$ 3 Hz, P-O**C**H_3), 52.8 (d, $J_{\text{C-P}}$ 3 Hz, P-O**C**H_3) 35.6 (CH_2), 34.4 (CH_2), 33.6 (CH_2), 32.6 (CH_2), 29.2 (CH_2), 28.9 (CH_2), 28.7 (CH_2), 25.1 (CH_2), 19.6 (CH_3).

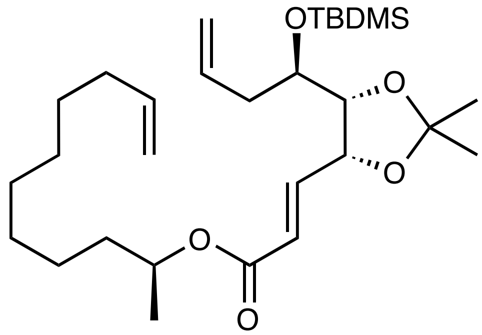
IR (KBr) ν_{max} 2927, 1731, 1640, 1462, 1275, 1115, 1035 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 321 [(M+H)$^+$, 6%], 169 (100), 151 (98).

HRMS Found: $M^{+\cdot}$, 320.1746. Calculated for $C_{15}H_{29}O_5P$ $M^{+\cdot}$, 320.1753.

Specific Rotation $[\alpha]_D$ +3.1 (*c* 1.0, $CHCl_3$).

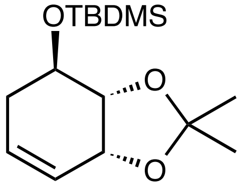
Compound 11



A solution of phosphonate **10** (408 mg, 3.4 mmol) in THF (25 mL) was added, dropwise and *via* cannula, to a magnetically stirred suspension of NaH (82 mg, *ca*. 60% dispersion in mineral oil, 3.4 mmol) in THF (10 mL) maintained at 0 °C under an atmosphere of nitrogen. After 30 min, a solution of aldehyde **3** (714 mg, 2.3 mmol) in THF (15 mL) was added, again dropwise and *via* cannula. The resulting mixture was maintained at 0 °C for 1 h, then treated with NH_4Cl (40 mL of a saturated aqueous solution) and diluted with water (50 mL). The resulting mixture was extracted with diethyl ether (3 x 100 mL) and the combined organic phases were washed with brine (1 x 200 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a light-yellow oil. Subjection of this material to flash chromatography (silica, 5% v/v ethyl acetate/petrol elution) provided, after concentration of the appropriate fractions (R_f 0.4), the *title compound **11*** (1.05 g, 91%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 6.90 (dd, *J* 15.6 and 7 Hz, 1H), 6.01 (dd, *J* 15.6 and 1 Hz, 1H), 5.91 5.73 (complex m, 2H), 5.06-4.90 (complex m, 5H), 4.58 (t, *J ca*. 7 Hz, 1H), 4.12 (dd, *J* 8 and 6 Hz, 1H), 3.72 (m, 1H), 2.26 (m, 1H), 2.12 (m, 1H), 2.04 (app q, *J ca*. 7 Hz, 2H), 1.51 (s, 3H), 1.36 (s, 3H), 1.30 (m, 12H), 1.24 (d, *J* 6.3 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H).
^{13}C NMR (75 MHz) δ 165.5 (C), 143.1 (CH), 139.1 (CH), 134.6 (CH), 124.1 (CH), 117.3 (CH_2), 114.1 (CH_2), 109.0 (C), 81.0 (CH), 76.3 (CH), 71.3 (CH), 71.2 (CH), 38.2 (CH_2), 36.0 (CH_2), 33.8 (CH_2), 29.3(9) (CH_2), 29.3(6) (CH_2), 29.0 (CH_2), 28.9 (CH_2), 27.8 (CH_3), 25.9 (3 x CH_3), 25.4 (CH_2), 25.3 (CH_3), 20.0 (CH_3), 18.3 (C), -4.2 (CH_3), -4.6 (CH_3).
IR (KBr) ν_{max} 2929, 1720, 1658, 1641, 1370, 1251 cm^{-1}.
Mass Spectrum (70 eV) *m/z* 493 [$(M-H_3C\cdot)^+$, 7%], 451 {[$M-(CH_3)_3C\cdot)^+$, 5}, 393 [$(M-C_6H_{15}Si\cdot)^+$, 26], 185 (91), 170 (100).
HRMS Found: $(M-H_3C\cdot)^+$, 493.3347. $C_{29}H_{52}O_5Si$ requires $(M-H_3C\cdot)^+$, 439.3349.
Specific Rotation $[\alpha]_D$ +34 (*c* 0.5, $CHCl_3$).

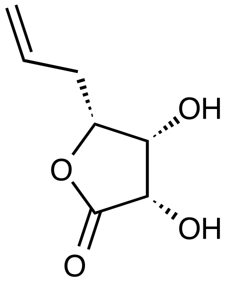
Compound 13



A solution of Grubbs' catalyst [$(PCy_3)_2Cl_2Ru{=}CHPh$] (6 mg, 0.008 mmol, ex Strem Chemicals, Inc.) in dichloromethane (8 mL) was added, dropwise and *via* syringe pump (addition rate: 2 mL/h), to a magnetically stirred solution of compound **11** (40 mg, 0.08 mmol) in dichloromethane (70 mL) maintained at 18 °C under an atmosphere of nitrogen. After the addition was complete, TLC analysis indicated that no starting material remained so the reaction mixture was concentrated under reduced pressure to afford a dark oil. Subjection of this material to flash chromatography (silica, 5% v/v ethyl acetate/petrol elution) provided, after concentration of the appropriate fractions (R_f 0.3), the *title compound **13*** (17 mg, 81%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 5.80 (m, 2H), 4.60 (m, 1H), 3.97 (dd, *J ca.* 6 and 5 Hz, 1H), 3.81 (m, 1H), 2.28 (m, 1H), 2.00 (dd, *J* 17 and 8 Hz, 1H), 1.47 (s, 3H), 1.38 (s, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H).
^{13}C NMR (75 MHz) δ 128.5 (CH), 124.5 (CH), 108.6 (C), 78.7 (CH), 72.8 (CH), 69.6 (CH), 31.9 (CH_2), 28.2 (CH_3), 26.0 (CH_3), 25.8 (3 x CH_3), 18.1 (C), -4.5 (CH_3), -4.8 (CH_3).
IR (KBr) ν_{max} 2929, 1656, 1379, 1248, 1118, 1098 cm^{-1}.
Mass Spectrum (70 eV) *m/z* 269 [$(M-H_3C\cdot)^+$, 2%], 227 {[$M-(CH_3)_3C\cdot]^+$, 1}, 169 (100).
HRMS Found: $(M-H_3C\cdot)^+$, 269.1565. $C_{15}H_{28}O_3Si$ requires $(M-H_3C\cdot)^+$, 269.1573.
Specific Rotation $[\alpha]_D$ -72 (*c* 1.3, $CHCl_3$).

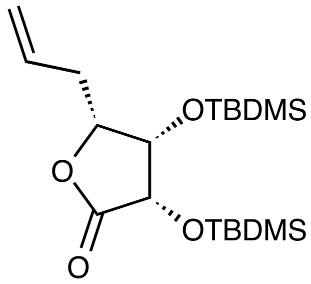
Compound 14



A solution of compound **9** (374 mg, 1.1 mmol) in HCl (5 mL of a 2 M solution in MeOH) was stirred at 0 °C under an atmosphere of nitrogen. After 3 h the reaction mixture was concentrated under reduced pressure to afford a white solid. Subjection of this material to flash chromatography (silica, 60% v/v ethyl acetate/petrol elution) provided, after concentration of the appropriate fractions (R_f 0.2), the *title compound* ***14*** (155 mg, 91%) as a white solid which could be used directly in the next step of the reaction sequence. Recrystallisation (3:1/ethyl acetate:petrol) of a sample of this material afforded an analytically pure sample of compound **14** as fine white needles, m.p. 111-113 °C.

^{1}H NMR (300 MHz) δ 5.84 (m, 1H), 5.24 (m, 2H), 4.51-4.37 (complex m, 3H), 3.16 (m, 1H), 2.67 (m, 3H).
^{13}C NMR (75 MHz, CD_3OD) δ 178.6 (C), 134.5 (CH), 118.8 (CH_2), 81.7 (CH), 72.6 (CH), 71.7 (CH), 34.3 (CH_2).
IR (KBr) ν_{max} 3451, 3301, 1753, 1642, 1431, 1208, 1157 cm^{-1}.
Mass Spectrum (70 eV) *m/z* 159 [$(M+H)^+$, <1%], 140 [$(M-H_2O)^{+\cdot}$, 1], 83 (100).
HRMS Found: $(M-H_2O)^{+\cdot}$, 140.0471. $C_7H_{10}O_4$ requires $(M-H_2O)^{+\cdot}$, 140.0473.
Elemental Analysis Found: C, 53.07; H, 6.41. $C_7H_{10}O_4$ requires C, 53.16; H, 6.37%.
Specific Rotation $[\alpha]_D$ +42 (*c* 0.9, MeOH).

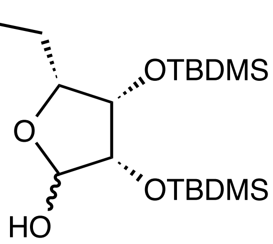
Compound 15



tert-Butyldimethylsilyl chloride (393 mg, 2.61 mmol) was added to a magnetically stirred solution of compound **14** (165 mg, 1.04 mmol) and imidazole (212 mg, 3.12 mmol) in anhydrous DMF (2 mL) maintained at 18 °C under an atmosphere of nitrogen. After 12 h the reaction mixture was poured in water (5 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with HCl (1 x 50 mL of a 1% v/v aqueous solution), water (1 x 50 mL) and brine (1 x 50 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale-yellow oil. Subjection of this material to flash chromatography (silica, 5% v/v ethyl acetate/petrol elution) afforded, after concentration of the appropriate fractions (R_f 0.3), the *title compound* ***15*** (382 mg, 95%) as a microcrystalline solid, m.p. 67-69 °C.

^{1}H NMR (300 MHz) δ 5.86 (m, 1H), 5.16 (m, 2H), 4.38 (d, *J* 3.8 Hz, 1H), 4.31-4.24 (complex m, 2H), 2.60 (m, 1H), 2.38 (m, 1H), 0.95 (s, 9H), 0.90 (s, 9H), 0.21 (s, 3H), 0.17 (s, 3H), 0.13 (s, 3H), 0.10 (s, 3H).
^{13}C NMR (75 MHz) δ 174.2 (C), 132.9 (CH), 117.9 (CH_2), 79.8 (CH), 73.4 (CH), 72.9 (CH), 33.4 (CH_2), 25.9 (3 x CH_3), 25.7 (3 x CH_3), 18.6 (C), 18.3 (C), -4.1 (CH_3), -4.6 (CH_3), -4.8 (CH_3), -5.0 (CH_3).
IR (KBr) ν_{max} 2930, 1792, 1643, 1472, 1254, 1162 cm^{-1}.
Mass Spectrum (70 eV) *m/z* 371 [$(M-H_3C\cdot)^+$, 3%], 329 {[$M-(CH_3)_3C\cdot]^+$, 57}, 73 (100).
HRMS Found: $(M-H_3C\cdot)^+$, 371.2074. $C_{19}H_{38}O_4Si_2$ requires $(M-H_3C\cdot)^+$, 371.2074.
Elemental Analysis Found: C, 59.05; H, 9.60. $C_{19}H_{38}O_4Si_2$ requires C, 59.02; H, 9.90%.
Specific Rotation $[\alpha]_D$ +3 (*c* 1.3, $CHCl_3$).

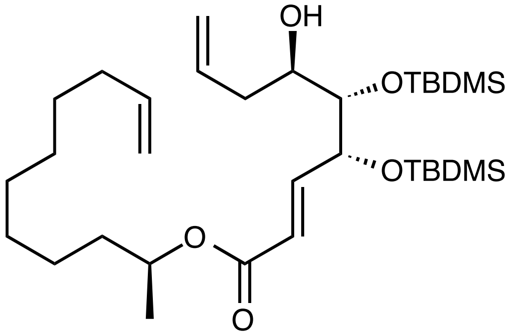
Compound 16



DIBAL-H (4.9 mL of a 1 M solution in hexane, 4.93 mmol) was added, dropwise, to a magnetically stirred solution of lactone **15** (1.27 g, 3.28 mmol) in hexane (76 mL) maintained at -78 °C under a nitrogen atmosphere. The reaction mixture was kept at -78 °C for a further 5 min then treated with tartaric acid (50 mL of a 1 M aqueous solution) and allowed to warm to 18 °C. The resulting mixture was extracted with diethyl ether (3 x 100 mL) and the combined organic phases were washed with brine (1 x 100 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the *lactol **16*** (*ca.* 1.2 g) which was used, without purification, in the next step of the reaction sequence.

^{1}H NMR (300 MHz) δ 5.88 (m, 1H), 5.13 (m, 2H), 5.00 (br s, 1H), 4.07 (m, 1H), 4.02 (m, 1H), 3.90 (m, 1H), 2.50 (m, 1H), 2.33 (m, 1H), 1.77 (br s, 1H), 0.94 (s, 9H), 0.93 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H), 0.13 (s, 3H), 0.11 (s, 3H).

Compound 17



A solution of phosphonate **10** (540 mg, 4.5 mmol) in THF (45 mL) was added, dropwise and *via* cannula, to a magnetically stirred suspension of NaH (108 mg, *ca*. 60% dispersion in mineral oil, 4.5 mmol) in THF (10 mL) maintained at 0 °C under an atmosphere of nitrogen. After 30 min, a solution of lactol **16** (1.00 g, 3.00 mmol) in THF (30 mL) was added, dropwise and *via* cannula. The reaction mixture was maintained at 0 °C for 30 min then treated sequentially with NH_4Cl (50 mL of a saturated aqueous solution) and water (50 mL). The resulting mixture was extracted with diethyl ether (3 x 100 mL) and the combined organic phases were washed with brine (1 x 200 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a light-yellow oil. Subjection of this material to flash chromatography (silica, 5% v/v ethyl acetate/petrol elution) provided, after concentration of the appropriate fractions (R*f* 0.3), the *title compound 17* (1.40 g, 80% from compound **15**) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 6.89 (dd, *J* 15.7 and 6.2 Hz, 1H), 5.98 (dd, *J* 15.7 and 1.5 Hz, 1H), 5.92-5.74 (complex m, 2H), 5.14-4.90 (complex m, 5H), 4.33 (dt, *J* 6.0 and 1.5 Hz, 1H), 3.73 (m, 1H), 3.54 (dd, *J* 5.9 and 2.4 Hz, 1H), 2.57 (br s, 1H), 2.25 (m, 2H), 2.04 (m, 2H), 1.63-1.46 (complex m, 3H), 1.36-1.25 (complex m, 9H), 1.23 (d, *J* 6.3 Hz, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (75 MHz) δ 165.9 (C), 147.7 (CH), 139.1 (CH), 135.1 (CH), 123.1 (CH), 117.1 (CH_2), 114.1 (CH_2), 76.9 (CH), 74.2 (CH), 71.1 (CH), 70.9 (CH), 38.9 (CH_2), 35.9 (CH_2), 33.8 (CH_2), 29.4 (2 x CH_3, coincident), 29.0 (CH_2), 28.9 (CH_2), 26.0 (3 x CH_3), 25.9 (3 x CH_3), 25.3 (CH_2), 20.0 (CH_3), 18.2 (C), 18.1 (C), -3.7 (CH_3), -4.1 (CH_3), -4.2 (CH_3), -4.5 (CH_3).

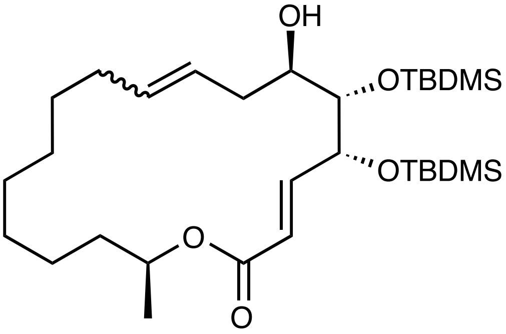
IR (KBr) ν_{max} 3535, 2929, 1719, 1659, 1641, 1256, 1100 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 582 ($M^{+\cdot}$, <1%), 567 [$(M-H_3C\cdot)^+$, <1], 525 {[$M-(CH_3)_3C\cdot]^+$, 1}, 73 (100).

HRMS Found: $(M-H_3C\cdot)^+$, 567.3911. $C_{32}H_{62}O_5Si_2$ requires $(M-H_3C\cdot)^+$, 567.3901.

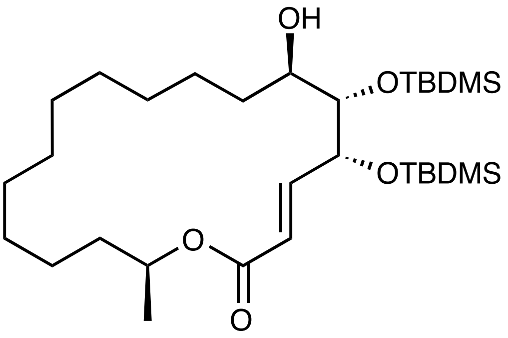
Specific Rotation $[\alpha]_D$ +12 (*c* 1.1, $CHCl_3$).

Compound 18



A solution of Grubbs' catalyst [(PCy$_3$)$_2$Cl$_2$Ru=CHPh] (118 mg, 0.13 mmol) in dichloromethane (20 mL) was added, dropwise and *via* cannula, to a magnetically stirred solution of compound **17** (379 mg, 0.65 mmol) in dichloromethane (650 mL) maintained at 18 °C under an atmosphere of nitrogen. The reaction mixture was stirred for a further 14 h after which time TLC analysis indicated that no starting material remained. The reaction mixture was concentrated under reduced pressure to afford a dark oil which was then subjected to flash chromatography (silica, 1-5% v/v ethyl acetate/petrol elution). Concentration of the appropriate fractions (R_f 0.5, 5% v/v ethyl acetate/petrol) then provided an inseparable and 3:1 mixture (as judged by ^{1}H NMR analysis) of the E/Z isomers associated with the *title compound **18*** (252 mg, 70%) as a clear, colourless oil. This material was immediately subjected to the next step in the reaction sequence.

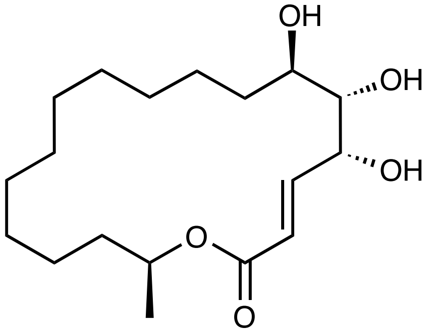
(+)-Aspicilin *bis*-TBDMS-ether



A magnetically stirred solution of compound **18** (100 mg, 0.18 mmol) in ethyl acetate (8 mL) containing 5% Pd on $BaSO_4$ (80 mg) was placed under a hydrogen atmosphere at 18 °C for 25 min. The reaction mixture was then filtered through a short pad of Celite^{TM} which was washed with ethyl acetate (20 mL). The combined filtrates were concentrated under reduced pressure to afford a light-yellow oil (*ca*. 100 mg) which was subjected to flash chromatography (silica, 5% v/v ethyl acetate/petrol elution). Concentration of the appropriate fractions (R_f 0.6), then provided the *title compound* (92 mg, 92%) as a microcrystalline solid, m.p. 78-81 °C.

^{1}H NMR (300 MHz) δ 6.87 (dd, *J* 16 and 7 Hz, 1H), 5.87 (d, *J* 16 Hz, 1H), 5.02 (m, 1H), 4.38 (br d, *J* 7 Hz, 1H), 3.53 (m, 2H), 2.83 (br s, 1H), 1.54-1.19 (m, 20H), 1.25 (d, *J* 6 Hz, 3H), 0.93 (s, 9H), 0.91 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H), 0.09 (s, 3H), 0.06 (s, 3H).
^{13}C NMR (75 MHz) δ 165.4 (C), 146.3 (CH), 122.9 (CH), 71.1 (CH), 69.6 (CH), 35.4 (CH_2), 32.0 (CH_2), 28.7 (CH_2), 27.8 (CH_2), 27.5 (CH_2), 27.2 (CH_2), 26.8 (CH_2), 26.2 (CH_2), 26.1 (3 x CH_3), 26.0 (3 x CH_3), 24.7 (CH_2), 23.3 (CH_2), 20.5 (CH_3), 18.4(1) (C), 18.3(5) (C), -3.6 (CH_3), -4.3 (CH_3), -4.6 (CH_3), -4.9 (CH_3) (two signals due oxy-methine carbons not observed).
IR (KBr) ν_{max} 3532, 2929, 1722, 1656, 1462, 1253, 1122, 1063 cm^{-1}.
Mass Spectrum (70 eV) *m/z* 556 ($M^{+\cdot}$, 14%), 499 {$[M-(CH_3)_3C\cdot]^+$, 15}, 367 (46), 73 (100).
HRMS Found: $M^{+\cdot}$, 556.3976. $C_{30}H_{60}O_5Si_2$ requires $M^{+\cdot}$, 556.3979.
Elemental Analysis Found: C, 64.58; H, 10.75. $C_{30}H_{60}O_5Si_2$ requires C, 64.69; H, 10.86%.
Specific Rotation $[\alpha]_D$ +19 (*c* 0.8, CH_3OH).

Compound 1 [(+)-aspicilin]



A magnetically stirred solution of (+)-aspicilin-*bis*-TBDMS-ether (174 mg, 0.31 mmol) in HCl (5 mL of a 2 M solution in MeOH) was maintained at 0 °C under an atmosphere of nitrogen. After 3 h the reaction mixture was concentrated under reduced pressure to afford a white solid which was subjected to flash chromatography (silica, ethyl acetate elution). Concentration of the appropriate fractions (R_f 0.4) then provided the title compound **1** (78 mg, 76%) as a white solid. Recrystallisation ($CHCl_3$/hexane) of a portion of this material afforded an analytically pure sample of (+)-aspicilin as fine white crystals, m.p. 152-154 °C (lit.[18] m.p. 153-154 °C).

^{1}H NMR (300 MHz) δ 6.90 (dd, *J* 15.9 and 4.9 Hz, 1H), 6.12 (dd, *J* 15.9 and 1.7 Hz, 1H), 5.05 (app sext, *J* 6 Hz, 1H), 4.56 (m, 1H), 3.76 (m, 1H), 3.57 (m, 1H), 3.27 (d, *J* 6.8 Hz, 1H), 3.05 (d, *J* 7.6 Hz, 1H), 2.50 (d, *J* 3.5 Hz, 1H), 1.59-1.52 (complex m, 4H), 1.45-1.17 (complex m, 16H), 1.25 (d, *J* 6 Hz, 3H).

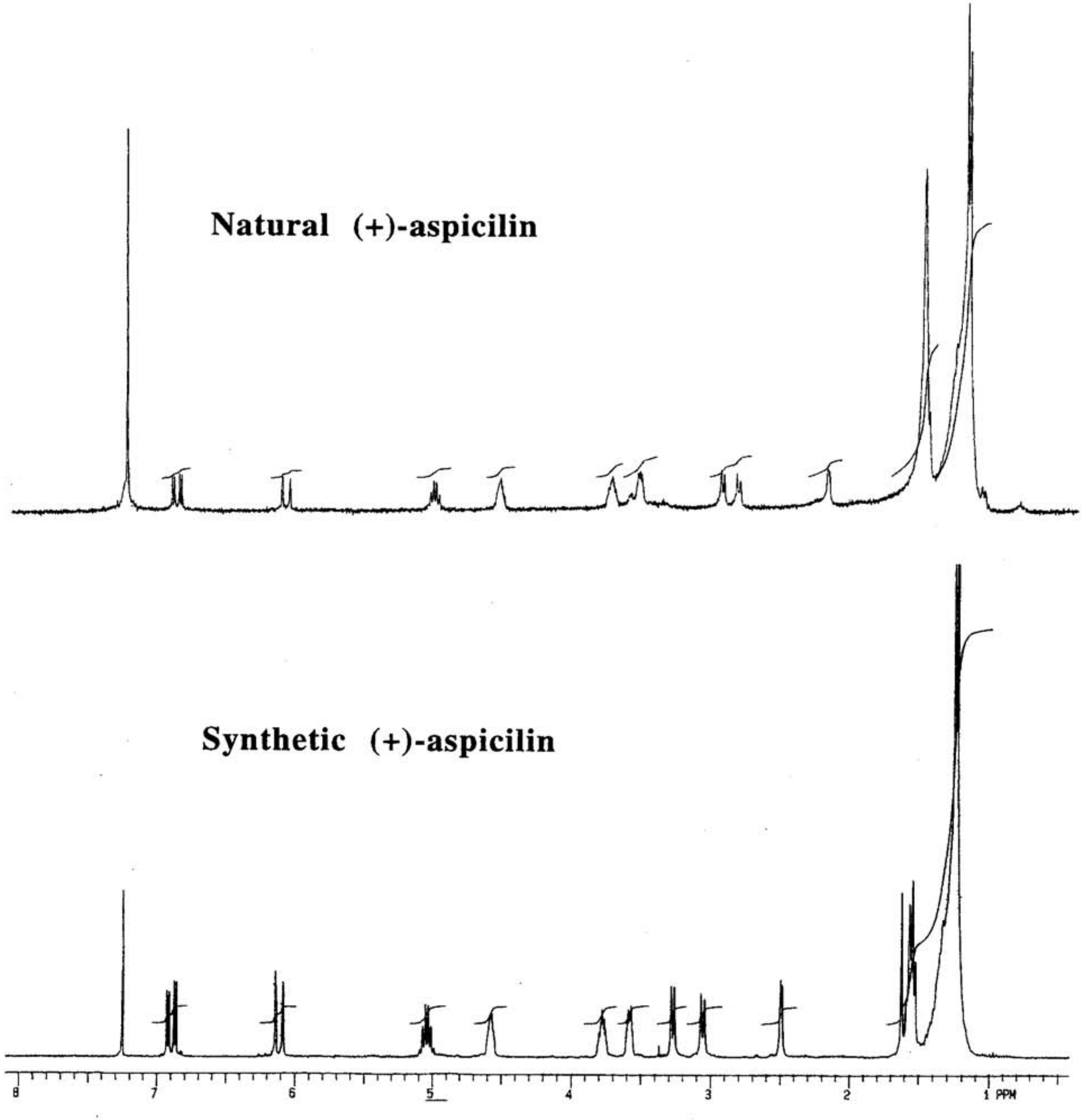
^{13}C NMR (75 MHz) δ 165.7 (C), 144.8 (CH), 123.0 (CH), 74.7 (CH), 73.4 (CH), 71.2 (CH), 69.9 (CH), 35.6 (CH_2), 31.9 (CH_2), 28.3 (CH_2), 27.7 (CH_2), 27.5 (CH_2), 27.2 (CH_2), 27.1 (CH_2), 26.3 (CH_2), 24.3 (CH_2), 23.5 (CH_2), 20.4 (CH_3).

IR (KBr) ν_{max} 3444, 3286, 1715, 1662, 1458, 1235, 1215, 1181, 1074 cm^{-1}.

Mass Spectrum (70 eV) *m/z* 328 ($M^{+\cdot}$, 2%], 310 [($M-H_2O\cdot)^+$, 2], 102 (100).

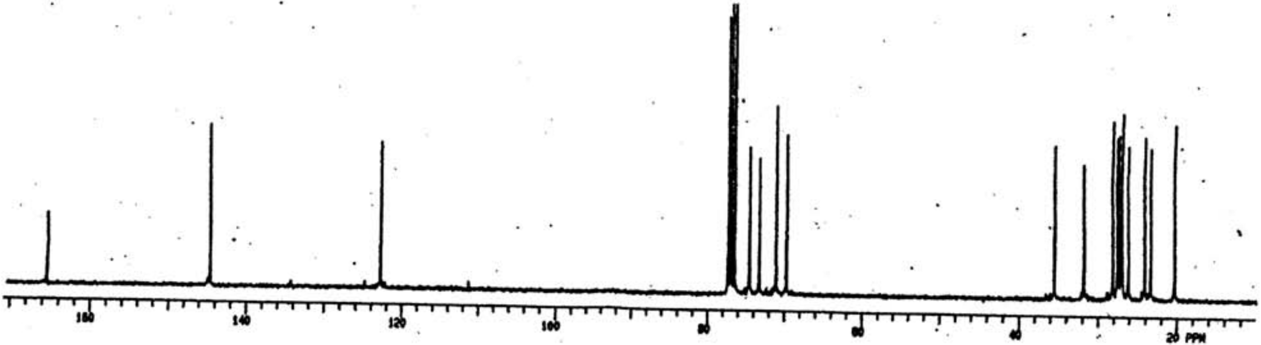
HRMS Found: $M^{+\cdot}$, 328.2253. $C_{18}H_{32}O_5$ requires $M^{+\cdot}$, 328.2250.

Specific Rotation $[\alpha]_D$ +39 (*c* 1.10, $CHCl_3$), {lit.[18] $[\alpha]_D$ +32 (*c* 2.31, $CHCl_3$)}.



Natural (+)-aspicilin

Synthetic (+)-aspicilin



^{13}C NMR (75 MHz) spectrum of synthetic (+)-aspicilin.