Total Synthesis of (+)-Albicanol and (+)-Albicanyl Acetate *via* a Highly Diastereoselective Intramolecular [3 + 2] Cycloaddition†

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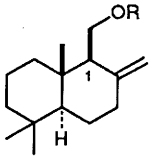
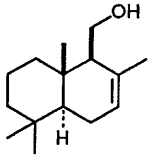
The enantioselective total syntheses of the drimane-type sesquiterpenes albicanol (**1**) and albicanyl acetate(**2**) starting from (+)-Wieland–Miescher ketone (**8**) have been accomplished. The key step in the synthetic strategy involves a highly diastereoselective intramolecular [3 + 2] dipolar cycloaddition reaction of the nitrile oxide (**6**), which affords the isoxazoline (**5**) as the sole product in high yield. Reductive hydrolysis of compound (**5**) followed by methylenation of the resulting β-hydroxy ketone (**4**) by application of the Nozaki–Lombardo procedure provides (+)-albicanol (**1**), which is then converted into (+)-albicanyl acetate (**2**) by acetylation. The olefinic acetal (**15**), an intermediate of the present total synthesis, has been transformed by sequential Jones oxidation and methylation into a secosesquiterpene (**17**), one of the components of sun-cured Greek tobacco.

The drimane-type sesquiterpene albicanol (**1**) was first isolated[1] by N. H. Andersen in 1977 from steam distillates of the liverwort *Diplophyllum albicans*. In 1982 albicanol was also isolated from methanol extracts of intact specimens of *Cadlina luteomarginata*, together with its acetate, albicanyl acetate (**2**), which appears to have potent fish antifeedant activity, by R. J. Andersen.[2] Albicanol thus obtained was completely identical with the liverwort-derived product (**1**). The structure of compound (**1**) was determined mainly from a ^{1}H NMR analysis[1] and the stereochemical assignment, including the absolute configurations,[1,2] was confirmed by comparison of the hydrogenation products of compound (**1**) and authentic (−)-drimenol (**3**), and by other chemical correlations.



(**1**) R = H
(**2**) R = Ac

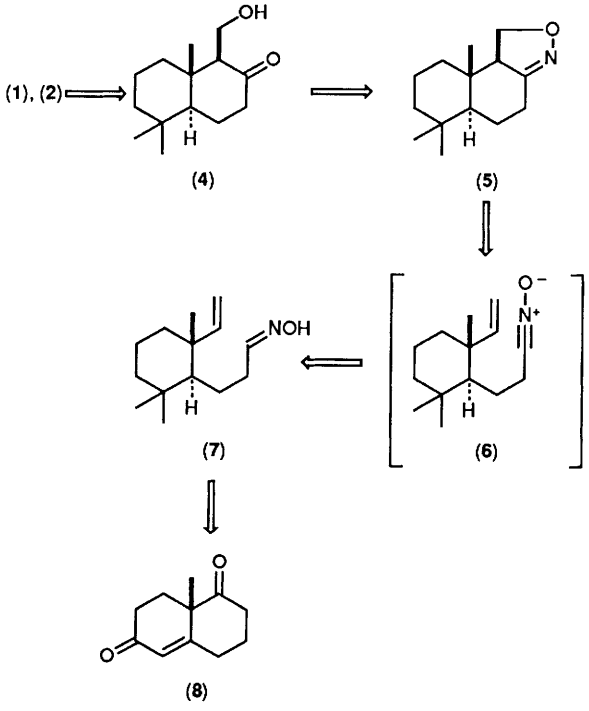


(**3**)

Although the total syntheses of racemic albicanol and albicanyl acetate have already been accomplished by Armstrong,[3] who employed the electrophilic cyclisation of olefinic allylsilanes as the key step, crucial problems associated with the stereochemical control at C-1[4] and the separation of stereoisomers still remain. Owing to the simple and promising structure of albicanol as an intermediate for the construction of a variety of biologically important terpenes, such as warburganal,[5] galanolactone,[6] ambrein,[7] cryptoporic acid A,[8] *etc.*, it seemed to us attractive to establish an efficient synthetic route to optically active albicanol (**1**). In this article we report the details of total syntheses[9] of (+)-albicanol (**1**) and (+)-albicanyl acetate (**2**) starting from (+)-Wieland–Miescher ketone (**8**),[10] which features the successful use of a highly diastereoselective intramolecular [3 + 2] dipolar cycloaddition reaction[11] to overcome the problem of stereochemical control at C-1.

Results and Discussion

Scheme 1 outlines the key features of our strategy for the total synthesis. The pivotal step in this approach is the intramolecular [3 + 2] dipolar cycloaddition reaction of nitrile



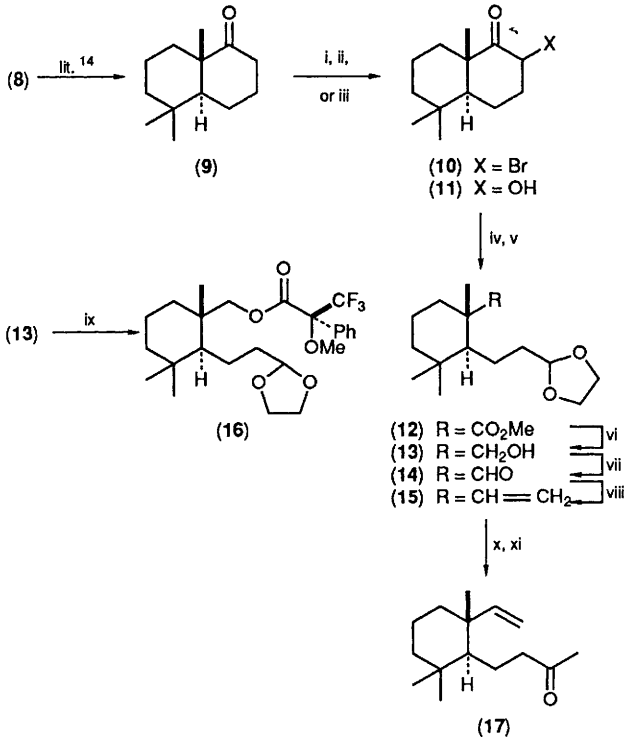
Scheme 1.

oxide (**6**) generated *in situ* by oxidation of the oxime (**7**). This process would be predicted to occur further through the chair-like transition state to give the isoxazoline (**5**) diastereo-

† This is considered as Part 1 201 of the series 'Studies on The Syntheses of Heterocyclic and Natural Compounds' by Tetsuji Kametami. Part 1 200, T. Honda, T. Kametani, K. Kanai, Y. Tatsuzaki, and M. Tsubuki, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1733.

selectively.[12] The isoxazoline would then be transformed into the target molecule by sequential reductive hydrolysis and methylenation. The oxime (**7**), substrate for the cycloaddition reaction, might, in turn, be prepared from (+)-Wieland–Miescher ketone (**8**).

Treatment of ketone (**9**),[13] one of the versatile synthetic intermediates for several terpenes and derived from (+)-Wieland–Miescher ketone {$[\alpha]_D^{25}$ +99.7° (lit.,[10] $[\alpha]_D^{25}$ +100°)} *via* the known six-step sequence,[14] with pyridinium hydrobromide perbromide provided the α-bromo ketone (**10**), which was then exposed to aqueous sodium hydroxide to afford the α-hydroxy ketone (**11**)[14] in 88% overall yield. The conversion was also achieved in one step by the method of Davis.[15] Thus, treatment of ketone (**9**) with lithium di-isopropylamide (LDA) and 2-sulphonyloxaziridine led directly to the acyloin (**11**) in 72% yield. Oxidative cleavage of compound (**11**) with lead tetra-acetate (LTA) in the presence of methanol followed by immediate acetalisation of the resulting crude formyl ester produced the ester (**12**), which was then reduced with lithium aluminium hydride to provide the alcohol (**13**) in 84% overall yield from acyloin (**11**). At this point, the optical purity of compound (**13**) was examined by conversion into the corresponding methoxy(trifluoromethyl)phenyl acetate (MTPA ester) (**16**).[16] The ester was shown to be isomerically pure on comparison with the MTPA ester prepared from racemic alcohol (**13**) (500 MHz ^{1}H NMR spectra). Transformation of the alcohol moiety in compound (**13**) into the olefin was performed by sequential Swern oxidation and Wittig reaction of the resulting aldehyde (**14**) to afford the alkene (**15**) in 79% yield from the alcohol (**13**). The olefinic acetal (**15**) was then exposed to Jones oxidation, followed by treatment with methyl-lithium to provide the secosesquiterpene (**17**),[4b,17,18] {$[\alpha]_D^{25}$ −0.86° (*c* 1.54 in $CHCl_3$); lit.,[17] $[\alpha]_D^{20}$ −0.5° (*c* 0.2 in $CHCl_3$); lit.,[18] $[\alpha]_D^{26}$ −10.4° (*c* 1.06)}, one of the components of sun-cured Greek tobacco *Nicotiana tabacum*, in 62% overall yield (Scheme 2).



Scheme 2. *Reagents:* i, $Py^+ \cdot HBr_3^-$; ii, NaOH; iii, LDA, $PhSO_2\overline{NCH(Ph)O}$; iv, LTA, MeOH; v, $HO[CH_2]_2OH$, PTSA; vi, $LiAlH_4$; vii, $(COCl)_2$, DMSO, Et_3N; viii, $Ph_3P{=}CH_2$; ix, MTPACl, Et_3N, 4-DMAP (cat.); x, Jones' reagent; xi, MeLi.

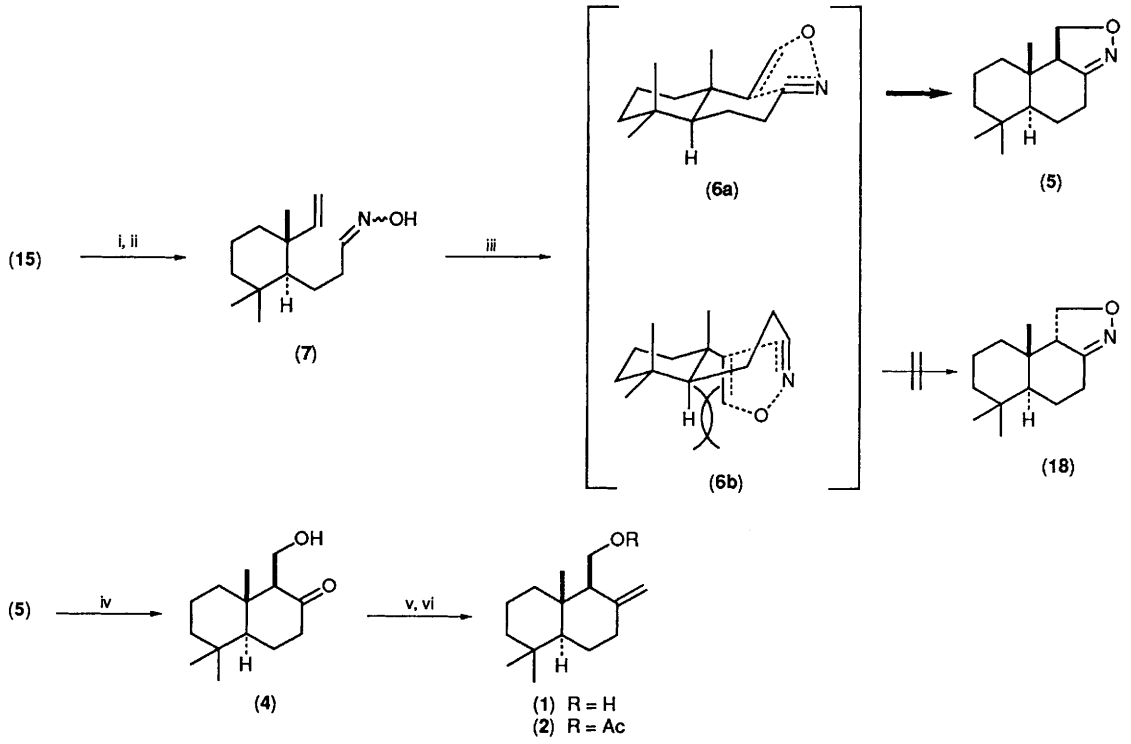
The prepared compound (**17**) was shown to be identical with authentic material by comparison of the reported spectral data (^{1}H NMR, IR, and mass).

The olefinic oxime (**7**), substrate for the [3 + 2] cycloaddition reaction, was prepared from compound (**15**) by sequential acid hydrolysis and oxime formation[19] in 96% yield as an inseparable mixture of two isomers (*syn*:*anti* 1:1 from ^{1}H NMR analysis). Having the desired oxime (**7**) in hand, we proceeded to examine the key transformation of the synthetic sequence. When an isomeric mixture of oxime (**7**) with 7% aq. sodium hypochlorite[20] in methylene dichloride was stirred at room temperature for 1.5 h, the reaction cleanly proceeded to provide the isoxazoline (**5**) [*m*/*z* 221 (M^+)] as the sole product in 90% yield. The isoxazoline was shown to be homogeneous by the gamut of analytical and spectroscopic techniques. However, the exact absolute configuration of the newly formed chiral centre of the isoxazoline could not be determined from the spectral properties at this stage. Examination of the transition state during the cycloaddition revealed that non-bonding interactions develop in the boat-like transition state (**6b**), which will form the isomer (**18**), whereas the interactions are absent altogether in the chair-like transition state (**6a**).[12b] From these considerations, the exclusive product, generated from the conformer (**6a**), was tentatively assigned as having structure (**5**) with the desired stereochemistry. Although the conversion of compound (**5**) into the β-hydroxy ketone (**4**)[21] by reductive hydrolysis with Raney nickel and boron trichloride[22] under hydrogen resulted in a poor yield of product, a trimethyl borate modification of the reaction reported by Curran[23] gave a greatly improved yield. Attempted methylenation of compound (**4**) by employing either a Wittig reaction or a Peterson olefination[24] of the corresponding silyl ether proved unsuccessful or met with only limited success. Completion of the synthesis of (+)-albicanol (**1**) was accomplished by application of the method of Nozaki and Lombardo.[25] Thus, treatment a solution of compound (**4**) in methylene dichloride with a suspension of the reagent prepared from zinc, methylene dibromide, and titanium tetrachloride in tetrahydrofuran (THF) at room temperature produced albicanol (**1**) in 48% yield (Scheme 3). The identity of the synthetic material (**1**) {m.p. 71–72 °C (lit.,[2] 68–69 °C); $[\alpha]_D^{22}$ +13.6° (*c* 0.56 in $CHCl_3$) {lit.,[2] $[\alpha]_D^{20}$ +13° (*c* 0.6 in $CHCl_3$)} was confirmed by careful comparison of the ^{1}H NMR, IR, and mass spectroscopic properties with those of an authentic sample. Albicanol thus synthesized was then acetylated with acetic anhydride in pyridine to provide (+)-albicanyl acetate (**2**), $[\alpha]_D^{26}$ +21.9° (*c* 0.37 in $CHCl_3$) {lit.,[2] $[\alpha]_D^{20}$ +24° (*c* 0.5 in $CHCl_3$)}, which also exhibited spectral characteristics fully consistent with those of natural compound (**2**).

In conclusion, efficient and enantioselective total syntheses of two drimane-type sesquiterpenes, (+)-albicanol and (+)-albicanyl acetate, have been achieved starting from (+)-Wieland–Miescher ketone. The crucial role which an intramolecular [3 + 2] dipolar cycloaddition reaction of a nitrile oxide played in the stereoselection in this synthesis is certainly worthy of note.

Experimental

M.p.s were determined on a Yanagimoto MP-22 apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-10 spectrophotometer. ^{1}H NMR spectra were recorded at 90 MHz on a JEOL JNM-FX-90A or at 500 MHz on a JEOL JNM-GX500 spectrometer, and all samples for NMR analyses were dilute solutions in deuteriochloroform. Mass spectra were recorded on a JEOL JMS-01SG-2 spectrometer, and high-resolution mass spectroscopy was performed on a JEOL JMS-DX-303 spectrometer. Optical rotations were determined on a



Scheme 3. *Reagents*: i, H_3O^+; ii, NH_2OH·HCl, NaOAc; iii, 7% aq. NaOCl; iv, H_2, Raney-Ni, $B(OMe)_3$; v, Zn–CH_2Br_2–$TiCl_4$; vi, Ac_2O, Py.

JASCO-DIP-340 polarimeter. All reactions were carried out under dry argon or nitrogen. Column chromatography was carried out with silica gel (Kieselgel 60, 70–230 mesh, Merck). TLC was carried out with E. Merck Silica gel 60F-254 (0.25 mm thickness) pre-coated TLC plates. The phrase 'residue upon work-up' refers to the residue when the organic layer was separated, dried over magnesium sulphate ($MgSO_4$), and evaporated under reduced pressure. All new compounds described in this Experimental section were homogeneous on TLC.

(2R,4aS,8aS)-(−)-1,2,3,4,4a,5,6,7,8,8a-*Decahydro*-2α-*hydroxy*-5,5,8aβ-*trimethyl*-1-*oxonaphthalene* (**11**).—Butyl-lithium (1.60M in hexane; 2.3 ml, 3.68 mmol) was added dropwise to a stirred solution of di-isopropylamine (0.39 g, 3.86 mmol) in dry THF (9 ml) at −78 °C. After the mixture had been stirred at the same temperature for 20 min, a solution of the ketone (**9**) (0.44 g, 2.27 mmol) in dry THF (6 ml) was added dropwise and the mixture was stirred for a further 30 min at −78 °C. To this solution was added a solution of 2-phenylsulphonyloxaziridine (0.95 g, 3.6 mmol) in dry THF (7 ml) and the mixture was stirred for 45 min at −78 °C. The reaction mixture was then quenched by addition of saturated aq. ammonium chloride and the solvent was evaporated off. The residue was extracted with chloroform, the extracts were washed with saturated brine, and the residue upon work-up was chromatographed with hexane–ethyl acetate (19:1, v/v) as eluant to afford the recovered starting ketone (**9**) (0.13 g). From the later fractions, the α-hydroxy ketone (**11**)[14] (0.24 g, 72% based on consumed starting ketone) was obtained as an oil, $[\alpha]_D^{26}$ −31.2° (*c* 0.72 in $CHCl_3$) {lit.,[14] $[\alpha]_D^{17}$ −28.9° (*c* 0.28 in $CHCl_3$)}; $\nu_{max.}(CHCl_3)$ 3 450 (OH) and 1 710 cm^{-1} (C=O); δ_H (500 MHz) 0.89 (3 H, s, Me), 0.92 (3 H, s, Me), 1.15 (3 H, s, Me), 2.45 (1 H, dddd, *J* 12.4, 7.4, 3.5, and 3.5 Hz, 4-H_{eq}), 3.61 (1 H, d, *J* 4.2 Hz, OH; disappeared on D_2O shake), and 4.38 (1 H, ddd, *J* 12.0, 7.4, and 4.2 Hz, 2-H).

(1S,2S)-*Methyl*-(+)-2β-[2-(1,3-*Dioxolan*-2-*yl*)*ethyl*]-1β,3,3-*trimethylcyclohexanecarboxylate* (**12**).—LTA (6.65 g, 15.0 mmol) was added portionwise to a stirred solution of the α-hydroxy ketone (**11**) (3.00 g, 14.3 mmol) in methanol–hexane (1:3; 100 ml) at 0 °C. After being stirred at 0 °C for 20 min, and then at room temperature for 30 min, the reaction mixture was treated with saturated aq. sodium hydrogen carbonate (84 ml). After filtration through a pad of Celite, the filtrate was extracted with diethyl ether after salting out, and the combined extracts were washed with saturated brine. The residue upon work-up was dissolved in benzene (170 ml), to which were added ethylene glycol (1.30 g, 21.5 mmol) and a catalytic amount of toluene-*p*-sulphonic acid (PTSA). The resulting mixture was refluxed using a Dean–Stark water separator for 1.5 h, and the organic phase was washed successively with saturated aq. sodium hydrogen carbonate and saturated brine. The residue upon work-up was chromatographed with hexane–ethyl acetate (4:1, v/v) as eluant to afford the *ester* (**12**) (3.74 g, 92%) as an oil (Found: C, 67.4; H, 9.55. $C_{16}H_{28}O_4$ requires C, 67.55; H, 9.95%); $[\alpha]_D^{26}$ +0.89° (*c* 3.19 in $CHCl_3$); $\nu_{max}(CHCl_3)$ 1 700 cm^{-1} (C=O); δ_H (90 MHz) 0.89 (3 H, s, Me), 0.91 (3 H, s, Me), 1.17 (3 H, s, Me), 3.63 (3 H, s, OMe), 3.84 (4 H, m, OCH_2CH_2O), and 4.76 (1 H, t, *J* 8.6 Hz, OCHO); *m*/*z* 284 (M^+).

(1S,2S)-(−)-{2β-[2-(1,3-*Dioxolan*-2-*yl*)*ethyl*]-1β,3,3-*trimethylcyclohexyl*}*methanol* (**13**).—A solution of the ester (**12**) (1.17 g, 4.11 mmol) in dry THF (8 ml) was added dropwise to a suspension of lithium aluminium hydride (0.31 g, 8.22 mmol) in dry THF (5 ml) at 0 °C. After being stirred at 0 °C for 30 min, the mixture was treated successively with water-saturated diethyl ether and water, then filtered through a pad of Celite. The filtrate was dried over magnesium sulphate and evaporated to give a residue, which was chromatographed with hexane–ethyl acetate (7:3, v/v) as eluant to provide the *alcohol* (**13**) (0.96 g, 91%) as an oil; $[\alpha]_D^{21}$ −6.15° (*c* 0.61 in $CHCl_3$); $\nu_{max}(CHCl_3)$ 3 640 cm^{-1} (OH); δ_H (90 MHz) 0.78 (3 H, s, Me), 0.88 (6 H, s, Me × 2), 2.09 (1 H, br s, OH, D_2O-labile), 3.05 (1 H, d, *J* 11.1 Hz, CH*H*OH), 3.43 (1 H, d, *J* 11.1 Hz, C*H*HOH), 3.92 (4 H, m,

OCH_2CH_2O), and 4.83 (1 H, t, *J* 4.5 Hz, OCHO); *m/z* 256 (M^+) (Found: M^+, 256.2031. $C_{15}H_{28}O_3$ requires *M*, 256.2039).

The MTPA Ester (**16**) *of the Alcohol* (**13**).—A solution of the alcohol (**13**) (11.9 mg, 0.046 mmol) in dry methylene dichloride (0.5 ml), triethylamine (18.8 mg, 0.19 mmol), and a catalytic amount of 4-dimethylaminopyridine (DMAP) were successively added to a solution of (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (35.2 mg, 0.14 mmol) in dry methylene dichloride (0.7 ml) at 0 °C. After being stirred for 10 min at 0 °C, and then for 4 h at room temperature, the reaction mixture was diluted with chloroform, and washed successively with 5% aq. hydrochloric acid, saturated aq. sodium hydrogen carbonate, and saturated brine. The residue upon work-up was chromatographed with hexane–ethyl acetate (9:1, v/v) as eluant to provide the MTPA ester (**16**) (13.9 mg, 63%) as an oil; δ_H (500 MHz) 0.82 (3 H, s, Me), 0.83 (3 H, s, Me), 0.84 (3 H, s, Me), 3.53 (3 H, s, OMe), 3.87 (1 H, d, *J* 11.3 Hz, C*H*HOMTPA), 4.07 (1 H, d, *J* 11.3 Hz, CH*H*OMTPA), 4.75 (1 H, t, *J* 4.8 Hz, OCHO), and 7.35–7.56 (5 H, m, Ph).

(2S,3R)-(−)-Sβ-[2-(1,3-*Dioxolan*-2-*yl*)*ethyl*]-1,1,3β-*trimethyl*-3α-*vinylcyclohexane** (**15**).—A solution of dimethyl sulphoxide (DMSO) (0.60 g, 7.69 mmol) in dry methylene dichloride (4 ml) was added to a stirred solution of oxalyl dichloride (0.49 g, 3.84 mmol) in dry methylene dichloride (5 ml) at −78 °C, and the mixture was stirred for a further 5 min. A solution of the alcohol (**13**) (0.82 g, 3.20 mmol) in dry methylene dichloride (7.5 ml) was then added dropwise to the solution at −78 °C. After the solution had been stirred at the same temperature for 15 min, triethylamine (1.62 g, 16.0 mmol) was added dropwise and the resulting mixture was allowed to warm to room temperature during 30 min, and was then diluted with water, extracted (CH_2Cl_2), and the extracts were washed with saturated brine. The residue, the crude, oily aldehyde (**14**) (0.82 g), obtained upon work-up was taken up in dry THF (13 ml). Butyl-lithium (1.22M in hexane; 10.5 ml, 12.8 mmol) was added to a stirred suspension of methyltriphenylphosphonium bromide (5.15 g, 14.4 mmol) in dry THF (20 ml) at 0 °C and the resulting mixture was stirred at the same temperature for 30 min, to which (at 0 °C) was added dropwise the solution of aldehyde in THF. After being stirred at 0 °C for 3 h, the reaction mixture was quenched with saturated aq. ammonium chloride, the solvent was evaporated off, and the residue was extracted with chloroform. The extracts were washed with saturated brine and the residue upon work-up was chromatographed with hexane–ethyl acetate (9:1, v/v)as eluant to afford the *olefinic acetal* (**15**) [0.64 g, 79% from (**13**)] as an oil (Found: C, 75.95; H, 11.5. $C_{16}H_{28}O_2$ requires C, 76.15; H, 11.2%); $[\alpha]_D^{20}$ −5.47° (*c* 0.42 in $CHCl_3$); $\nu_{max}(CHCl_3)$ 1 640 cm^{-1} (C=C); δ_H (90 MHz) 0.90 (6 H, s, Me × 2), 0.99 (3 H, s, Me), 3.87 (4 H, m, OCH_2CH_2O), 4.74 (1 H, t, *J* 4.9 Hz, OCHO), 4.87 (1 H, dd, *J* 17.1 and 1.5 Hz, HC=C*H*H), 4.90 (1 H, dd, *J* 10.7 and 1.5 Hz, HC=CH*H*), and 5.67 (1 H, dd, *J* 17.1 and 10.7 Hz, *H*C=CH_2); *m/z* 252 (M^+).

(−)-4-[(1S,6R)-2,2,6-*Trimethyl*-6-*vinylcyclohexyl*]*butan*-2-*one* (**17**).—Jones' reagent, prepared from chromium trioxide (261 mg, 2.61 mmol), conc. sulphuric acid (0.25 ml), and water (1.5 ml), was added dropwise to a stirred solution of the acetal (**15**) (110 mg, 0.43 mmol) in acetone (5 ml) at 0 °C, and the mixture was stirred for 1 h at room temperature. After the reaction mixture had been cooled to 0 °C, isopropyl alcohol was added and the resulting solution was stirred for 20 min at room temperature. After removal of the solvent, the residue was extracted with diethyl ether, and the extracts were washed with saturated brine, dried over magnesium sulphate, and evaporated to give the corresponding carboxylic acid (109 mg, 100%) as an oil, $\nu_{max}(CHCl_3)$ 3 400–2 500 (OH), 1 710 (C=O), and 1 635 cm^{-1} (C=C); δ_H (90 MHz) 0.90 (6 H, s, Me × 2), 1.01 (3 H, s, Me), 4.89 (1 H, br d, *J* 17.4 Hz, HC=C*H*H), 4.93 (1 H, br d, *J* 10.3 Hz, HC=CH*H*), 5.65 (1 H, dd, *J* 17.4 and 10.3 Hz, *H*C=CH_2), and 10.8 (1 H, br s, CO_2H; D_2O-labile); *m/z* 224 (M^+), which was used to the next reaction without further purification.

Methyl-lithium (1.50M in diethyl ether; 0.29 ml, 0.43 mmol) was added to a stirred solution of the above carboxylic acid (109 mg, 0.43 mmol) in dry THF (4 ml) at 0 °C. After the mixture had been stirred at 0 °C for 30 min, further methyl-lithium (1.50M in diethyl ether; 0.29 ml, 0.43 mmol) was added at the same temperature, and the resulting solution was stirred for a further 30 min. Chlorotrimethylsilane (472 mg, 4.43 mmol) was added in portions to the reaction mixture at 0 °C, which was then allowed to warm to room temperature during 2.5 h. The reaction mixture was then treated with 5% aq. hydrochloric acid and the solvent was evaporated off to give a residue, which was extracted with chloroform, and the extracts were washed with saturated brine. The residue upon work-up was chromatographed with hexane–ethyl acetate (95:5, v/v) as eluant to afford the methyl ketone (**17**)[4b,17,18] [60 mg, 62% from (**15**)] as an oil; $[\alpha]_D^{25}$ −0.86° (*c* 1.54 in $CHCl_3$) {lit.,[17] $[\alpha]_D^{20}$ −0.5° (*c* 0.2 in $CHCl_3$); lit.,[18] $[\alpha]_D^{26}$ −10.4° (*c* 1.06)}; $\nu_{max}(CHCl_3)$ 1 710 (C=O) and 1 630 cm^{-1} (C=C); δ_H (500 MHz) 0.86 (3 H, s, Me), 0.88 (3 H, s, Me), 0.99 (3 H, s, Me), 1.10–1.63 (9 H, m, CH_2 × 4 and CH), 2.06 (3 H, s, COMe) 2.36 (1 H, ddd, *J* 16.9, 11.4, and 5.5 Hz, $CH_2CHHCOMe$), 2.44 (1 H, ddd, *J* 16.9, 11.4, and 5.5 Hz, $CH_2CHHCOMe$), 4.88 (1 H, br d, *J* 17.7 Hz, HC=C*H*H), 4.88 (1 H, br d, *J* 10.4 Hz, HC=CH*H*), and 5.60 (1 H, dd, *J* 17.7 and 10.4 Hz, *H*C=CH_2); *m/z* 222 (M^+) and 95 (100%).

(2S,3R)-(+)-2β-(3-*Hydroxyiminopropyl*)-1,1,3β-*trimethyl*-3α-*vinylcyclohexane* (**7**).—5% Aq. hydrochloric acid (10.4 ml) was added to a solution of the acetal (**15**) (0.52 g, 2.06 mmol) in THF (16 ml), and the mixture was stirred at room temperature for 14 h. After removal of the solvent, the residue was extracted with methylene dichloride, and the extracts were washed successively with saturated aq. sodium hydrogen carbonate and brine. The residue, a yellow oil (0.45 g), upon work-up was taken up into methanol (16 ml), to which were added hydroxylamine hydrochloride (0.22 g, 3.17 mmol) and sodium acetate (0.29 g, 3.54 mmol), and the resulting mixture was stirred at room temperature for 9 h. After evaporation of the solvent, the residue was extracted with chloroform. The combined extracts were washed with saturated brine and the residue upon work-up was then chromatographed with hexane–ethyl acetate (19:1, v/v) as eluant to give the recovered starting acetal (**15**) (43 mg). From the fractions obtained using hexane–ethyl acetate (9:1, v/v) as eluant, the *oxime* (**7**) [405 mg, 96% based on the consumed starting acetal (**15**)], an inseparable mixture of two isomers (*syn*:*anti* 1:1), was obtained as an oil; $[\alpha]_D^{21}$ −16.2° (*c* 2.18 in $CHCl_3$); $\nu_{max}(CHCl_3)$ 3 550 (OH) and 1 630 cm^{-1} (C=N and C=C); δ_H (500 MHz) 0.90 (6 H, s, Me × 2), 1.01 (3 H, s, Me), 2.03–2.51 (2 H, m, H_2CCH=NOH), 4.89 (1 H, dd, *J* 17.4 and 1.3 Hz, HC=CH*H*), 4.92 (1 H, dd, *J* 10.8 and 1.3 Hz, HC=C*H*H), 5.47–5.86 (1 H, m, *H*C=CH_2), 6.68 (0.5 H, t, *J* 5.5 Hz, *H*C=NOH), and 7.35 (0.5 H, t, *J* 6.1 Hz, *H*C=NOH); *m/z* 223 (M^+) (Found: M^+, 223.1937. $C_{14}H_{25}NO$ requires *M*, 223.1936).

(5aS,9aS,9bR)-(−)-1,4,5,5aα,6,7,8,9,9aα,9b-*Decahydro*-6,6,9aβ-*trimethylnaphth*[2,1-c]*isoxazole* (**5**).—7% Aq. sodium hypochlorite (3.5 ml) was added dropwise to a stirred solution of the oxime (**7**) (489 mg, 2.19 mmol) in methylene dichloride

* *Systematic name:* 2-{2-[(1*S*,6*R*)-2,2,6-trimethyl-6-vinylcyclohexyl]-ethyl}-1,3-dioxolane.

(39 ml) at room temperature. After being stirred for 1.5 h the solution was treated with water, the organic phase was separated, and the aq. phase was extracted with chloroform. The combined organic phases were washed with saturated brine and the residue upon work-up was chromatographed with hexane–ethyl acetate (4:1, v/v) as eluant to afford the *dihydroisoxazole* (**5**) (437 mg, 90%) as needles after recrystallisation from hexane, m.p. 94.5–96.5 °C; $[\alpha]_D^{24}$ −160° (*c* 0.79 in $CHCl_3$); $\nu_{max}(CHCl_3)$ 1 635 cm^{-1} (C=N); δ_H (500 MHz) 0.82 (3 H, s, Me), 0.84 (3 H, s, Me), 0.91 (3 H, s, Me), 1.86 (1 H, ddt, *J* 13.4, 6.1, and 2.3 Hz, $CH_{eq}H$CH$_2$C=N), 2.12 (1 H, ddd, *J* 13.4, 6.7, and 6.7 Hz, CH_{ax}HC=N), 2.80 (2 H, m, CCHC=N and CH_{eq}HC=N), 4.07 (1 H, dd, *J* 8.5 and 6.7 Hz, CHHO), and 4.12 (1 H, dd, *J* 11.0 and 8.5 Hz, CHHO); *m/z* 221 (M^+) (Found: M^+, 221.1773. $C_{14}H_{23}NO$ requires *M*, 221.1780).

(−)-(1S,4aS,8aS)-1α,2,3,4,4aα,5,6,7,8,8aα-*Decahydro*-1β-*hydroxymethyl*-5,5,8aβ-*trimethyl*-2-*oxonaphthalene* (**4**).—Trimethyl borate (116 mg, 1.12 mmol) was added to a suspension of a mixture of the dihydroisoxazole (**5**) (24.8 mg, 0.11 mmol) and a catalytic amount of Raney nickel (W-2) in methanol–water (1.2 ml and 0.1 ml respectively), and the resulting mixture was stirred under a hydrogen pressure of 2.0 kg cm^{-2} for 7 h at room temperature. After filtration through a pad of Celite, the filtrate was evaporated to leave a residue, which was extracted with chloroform. The extracts were washed with saturated brine and the residue upon work-up was chromatographed with hexane–ethyl acetate (4:1, v/v) as eluant to give the recovered dihydroisoxazole (**5**) (11 mg). From the fractions obtained using hexane–ethyl acetate (7:3, v/v) as eluant, the hydroxy ketone (**4**)[21] (14 mg, 100% based on the consumed starting material) was obtained as needles after recrystallisation from diethyl ether–hexane, m.p. 69.5–70.5 °C (lit.,[21] 68–69 °C); $[\alpha]_D^{26}$ −38.9° (*c* 1.24 in $CHCl_3$) {lit.,[21] $[\alpha]_D^{25}$ −38.3° (*c* 1)}; $\nu_{max}(CHCl_3)$ 3 575 (OH) and 1 695 cm^{-1} (C=O); δ_H (500 MHz) 0.79 (3 H, s, Me), 0.83 (3 H, s, Me), 0.95 (3 H, s, Me), 3.57 (1 H, dd, *J* 11.5 and 3.2 Hz, CHHOH), and 3.93 (1 H, dd, *J* 11.5 and 9.5 Hz, CHHOH); *m/z* 224 (M^+) (Found: M^+, 224.1791. Calc. for $C_{14}H_{24}O_2$: *M*, 224.1776).

—(+)-*Albicanol* (**1**).—Titanium tetrachloride (15.0 g, 79.3 mmol) was added to a suspension of zinc powder (14.0 g, 214 mg-atom) and methylene dibromide (12.0 g, 68.8 mmol) in dry THF (117 ml) at −40 °C, and the mixture was stirred at 5 °C for 72 h. The resulting suspension was used as the reagent for methylenation.

A solution of the hydroxy ketone (**4**) (9.4 mg, 0.042 mmol) in dry methylene dichloride (2 ml) was added to a suspension of the reagent (0.59M in THF; 0.36 ml, 0.21 mmol) at 0 °C, and the mixture was then stirred at room temperature for 9 h before being treated witn saturated aq. sodium hydrogen carbonate and hexane. The organic phase was separated, the aqueous layer was extracted with hexane, and the combined organic phases were washed with saturated brine. The residue upon work-up was chromatographed with hexane–ethyl acetate (9:1, v/v) as eluant to afford albicanol (**1**)[1,2] [3.6 mg, 48% based on the consumed starting hydroxy ketone (**4**)] as prisms after recrystallisation from hexane, m.p. 71–72 °C (lit.,[2] 68–69 °C); $[\alpha]_D^{22}$ +13.6° (*c* 0.56 in $CHCl_3$) {lit.,[2] $[\alpha]_D^{20}$ +13° (*c* 0.6 in $CHCl_3$)}; $\nu_{max}(CHCl_3)$ 3 610, 3 450 (OH), and 1 650 cm^{-1} (C=C); δ_H (500 MHz) 0.72 (3 H, s, Me), 0.78 (3 H, s, Me), 0.87 (3 H, s, Me), 1.94–2.02 (1 H, m, CHC=C), 2.40 (1 H, ddd, *J* 12.8, 4.3, and 2.4 Hz, CH_{eq}HC=C), 3.75 (1 H, dd, *J* 11.0 and 9.9 Hz, CHHOH), 3.83 (1 H, dd, *J* 11.0 and 3.7 Hz, CHHOH), 4.62 (1 H, d, *J* 1.6 Hz, =CHH), and 4.93 (1 H, d, *J* 1.6 Hz, =CHH); *m/z* 222 (M^+) and 137 (100%) (Found: M^+, 222.1974. Calc. for $C_{15}H_{26}O$: *M*, 222.1982). The starting hydroxy ketone (**4**) (1.8 mg) was recovered from the fractions obtained using hexane–ethyl acetate (7:3, v/v) as eluant.

(+)-*Albicanyl Acetate* (**2**).—Acetic anhydride (21.6 mg, 2.12 mmol) was added to a stirred solution of (+)-albicanol (**1**) (6.7 mg, 0.03 mmol) in pyridine (0.5 ml) at 0 °C. After being stirred at room temperature for 12 h, the reaction mixture was diluted with diethyl ether, and the organic phase was washed successively with 3% aq. hydrochloric acid and saturated brine. The residue upon work-up was chromatographed with hexane–ethyl acetate (9:1, v/v) as eluant to afford albicanyl acetate (**2**)[2] (8.0 mg, 100%) as an oil; $[\alpha]_D^{26}$ +21.9° (*c* 0.37 in $CHCl_3$) {lit.,[2] $[\alpha]_D^{20}$ +24° (*c* 0.5 in $CHCl_3$)}; $\nu_{max}(CHCl_3)$ 1 710 (C=O) and 1 630 cm^{-1} (C=C); δ_H (500 MHz) 0.73 (3 H, s, Me), 0.79 (3 H, s, Me), 0.86 (3 H, s, Me), 1.96–2.04 (2 H, m, CHC=C and CH_{ax}-C=C), 2.00 (3 H, s, COMe), 2.38 (1 H, ddd, *J* 12.6, 4.3, and 2.3 Hz, CH_{eq}C=C), 4.17 (1 H, dd, *J* 11.1 and 9.2 Hz, CHHOAc), 4.31 (1 H, dd, *J* 11.1 and 3.4 Hz, CHHOAc), 4.49 (1 H, br s, =CHH), and 4.83 (1 H, br s, =CHH); *m/z* 264 (M^+) and 204 (100%) (Found: M^+, 264.1867. Calc. for $C_{17}H_{28}O_2$: *M*, 264.1878).

Acknowledgements

This work was supported in part by a Grant in Aid for Scientific Research to K. H. (No. 62790301) from the Ministry of Education, Science and Culture of Japan, which is gratefully acknowledged. We are grateful to Professor R. J. Andersen, University of British Columbia, for providing comparison spectra (IR, ^{1}H NMR, and mass) of albicanol and albicanyl acetate. We thank Dr. M. Takeshita, Tohoku College of Pharmacy, for the use of a polarimeter. We are also indebted to Mr. K. Kawamura, Miss K. Mushiake, Miss M. Inada, Mrs. A. Sato, and Miss N. Oikawa of this Institute for spectral measurements and for the preparation of the manuscript.

References

1 Y. Ohta, N. H. Andersen, and C. B. Liu, *Tetrahedron*, 1977, **33**, 617.
2 J. Hellou, R. J. Andersen, and J. E. Thompson, *Tetrahedron*, 1982, **38**, 1875.
3 R. J. Armstrong, F. L. Harris, and L. Weiler, *Can. J. Chem.*, 1986, **64**, 1002.
4 (*a*) R. F. Church, R. E. Ireland, and J. A. Marshall, *J. Org. Chem.*, 1962, **27**, 1118; (*b*) M. Kato, Y. Tooyama, and A. Yoshikoshi, *Chem. Lett.*, 1989, 61.
5 I. Kubo, Y. W. Lee, M. J. Pettei, F. Pilkiewicz, and K. Nakanishi, *J. Chem. Soc., Chem. Commun.*, 1976, 1013.
6 H. Morita and H. Itokawa, *Planta Med.*, 1988, **54**, 117.
7 L. Ruzicka and F. Lardon, *Helv. Chim. Acta*, 1946, **29**, 912.
8 T. Hashimoto, M. Tori, Y. Mizuno, and Y. Asakawa, *Tetrahedron Lett.*, 1987, **28**, 6303.
9 Preliminary communication: K. Shishido, Y. Tokunaga, N. Omachi, K. Hiroya, K. Fukumoto, and T. Kametani, *J. Chem. Soc., Chem. Commun.*, 1989, 1093.
10 J. Gutzwiller, P. Buchschacher, and A. Furst, *Synthesis*, 1977, 167.
11 For reviews, see A. P. Kozikowski, *Acc. Chem. Res.*, 1984, **17**, 410; S. Kanemasa and O. Tsuge, *Heterocycles*, 1990, **30**, 719.
12 (*a*) A. P. Kozikowski and Y. Y. Chen, *Tetrahedron Lett.*, 1982, **23**, 2081; (*b*) K. S. K. Murthy and A. Hassner, *ibid.*, 1987, **28**, 719.
13 S. V. Ley and M. Mahon, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1379; A. B. Smith, III, and R. Mewshaw, *J. Org. Chem.*, 1984, **49**, 3685.
14 M. Ihara, M. Toyota, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1986, 2151.
15 F. A. Davis, L. C. Vishwakarma, J. M. Billmers, and F. Finn, *J. Org. Chem.*, 1984, **49**, 3241.
16 J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.
17 J. R. Hlubucek, A. J. Aasen, S. O. Almqvist, and C. R. Enzell, *Acta Chem. Scand., Ser. B*, 1974, **28**, 18.
18 E. J. Corey and R. R. Sauers, *J. Am. Chem. Soc.*, 1959, **81**, 1743.
19 K. Maruoka, T. Miyazaki, M. Ando, Y. Matsumura, S. Sakane, K. Hattori, and H. Yamamoto, *J. Am. Chem. Soc.*, 1983, **105**, 2831.
20 S. Okamoto, Y. Kobayashi, H. Kato, K. Hori, T. Takahashi, J. Tsuji, and F. Sato, *J. Org. Chem.*, 1988, **53**, 5590.

21 W. Pena, J. T. Lopez, and M. Cortes, *Synth. Commun.*, 1989, **19**, 2841.
22 R. H. Wollenberg and J. E. Goldstein, *Synthesis*, 1980, 757; A. P. Kozikowski and M. Adamczyk, *Tetrahedron Lett.*, 1982, **23**, 3123; G. A. Lee, *Synthesis*, 1982, 508.
23 D. P. Curran, *J. Am. Chem. Soc.*, 1982, **104**, 4024.
24 P. F. Hudrick and D. Peterson, *J. Am. Chem. Soc.*, 1975, **97**, 1464.
25 K. Takai, Y. Hotta, K. Oshima, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 1698; L. Lombardo, *Org. Synth.*, 1987, **65**, 81.

Paper 0/01073A
Received 9*th March*, 1990
Accepted 25*th April* 1990