A Simple and Enantioselective Synthesis of (+)-Albicanol

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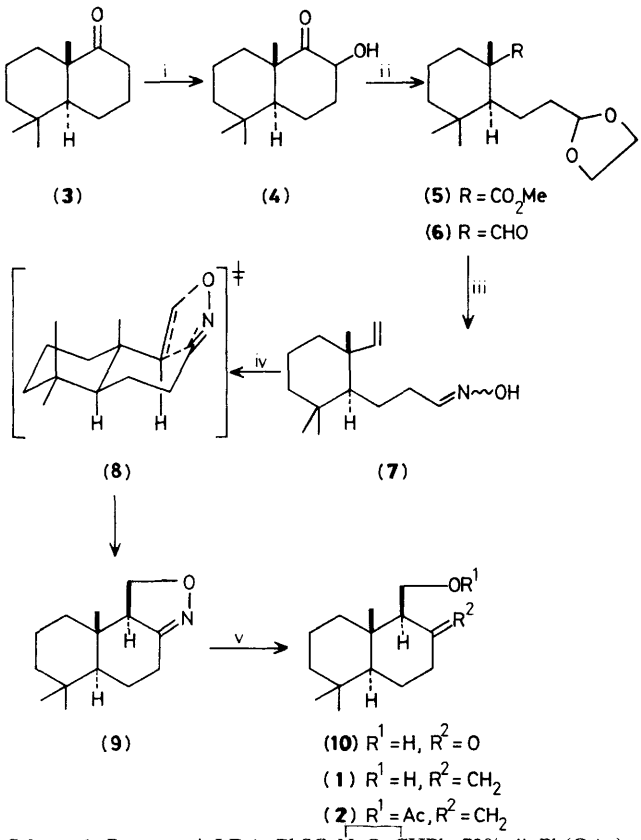
An efficient synthesis of sesquiterpenes (+)-albicanol (**1**) and (+)-albicanyl acetate (**2**) is described that employs a highly diastereoselective intramolecular nitrile oxide cycloaddition as the key step.

The drimane-type sesquiterpene albicanol (**1**) was isolated from the liverworts *Diplophyllum albicans*[1] and also from the dorid nudibranch *Cadlina luteomarginata*[2] together with its acetate (**2**), which has a potent fish antifeedant activity. The structure of (**1**) was elucidated by its ^{1}H n.m.r. spectrum and chemical correlations.[1] Its absolute configuration was ascertained by conversion to (+)-drimanol, whose absolute configuration had been established, employing a stereoselective catalytic hydrogenation.[2] Although the total synthesis[3] of the racemic (**1**) and (**2**) has already been accomplished by Armstrong utilising the electrophilic cyclisation of alkenic allylsilanes, a crucial problem of the stereochemical control at C–1 still remains. In this Communication, we report an efficient total synthesis of (+)-albicanol (**1**) and (+)-albicanyl acetate (**2**) from (−)-5,5,9-trimethyl-*trans*-1-decalone (**3**),[4] a readily available and versatile synthetic intermediate[5] for several terpenes, which features the use of a highly diastereoselective intramolecular nitrile oxide cycloaddition reaction.[6]

Oxidation of (**3**), derived from the (+)-Wieland–Miescher ketone[7] *via* the known six-step sequence,[4] with lithium di-isopropylamide (LDA) and 2-sulphonyloxaziridine[8] provided the hydroxy ketone (**4**) in 72% yield. Oxidative cleavage of (**4**) with lead tetra-acetate in methanol followed by immediate acetalisation produced the methyl ester (**5**) which was converted to the aldehyde (**6**) by successive $LiAlH_4$ reduction and Swern oxidation. Transformation of (**6**) into the alkenic oxime (**7**) was achieved by sequential Wittig reaction, acid hydrolysis, and a standard oxime formation to give (**7**), as a mixture of *E* and *Z* isomers, in 61% overall yield from (**4**). Treatment of (**7**) with a solution of 7% sodium hypochlorite in dichloromethane at room temperature provided the single isoxazoline (**9**)† {$[\alpha]_D$ −160° (*c* 0.79, $CHCl_3$)} in 90% yield.



Scheme 1. *Reagents*: i, LDA, $PhSO_2N$–O–CHPh, 72%; ii, $Pb(OAc)_4$, MeOH, followed by *p*-$MeC_6H_4SO_3H$, $HO(CH_2)_2OH$, 92%, and $LiAlH_4$, 85%, and $(COCl)_2$, dimethyl sulphoxide, NEt_3; iii, $Ph_3P{=}CH_2$, 81%, followed by H_3O^+, and $NH_2OH{\cdot}HCl$, NaOAc, 96%; iv, NaOCl, CH_2Cl_2, 90%; v, H_2 Raney Ni, $B(OMe)_3$, 100%, followed by Zn–CH_2Br_2–$TiCl_4$, CH_2Cl_2, tetrahydrofuran, 60%, and Ac_2O, pyridine, 100%.

† *Spectral data* for (**9**): m.p. 94.5—96.5 °C; i.r. ($CHCl_3$, cm^{-1}) 1630; δ_H (500 MHz, $CDCl_3$) 0.79, 0.85, and 0.92 (3H each, s), 1.86 (1H, ddt, *J* 13.4, 6.1, and 2.3 Hz), 2.12 (1H, td, *J* 13.4 and 6.7 Hz), 2.80—2.83 (2H, m), 4.07 (1H, dd, *J* 8.5 and 6.7 Hz), 4.12 (1H, dd, *J* 11.0 and 8.5 Hz); *m/z* 221 (M^+, 100%).

Although the absolute configuration of the newly formed chiral centre in (**9**) could not be determined from the spectral properties at this stage, it was suggested the cycloaddition proceeded through the chair-like transition state (**8**)[9] to afford the desired isomer shown in Scheme 1. Reductive hydrolysis of (**9**) with Raney nickel in the presence of trimethyl borate in aqueous methanol[10] gave the β-hydroxy ketone (**10**) quantitatively. Attempted methylenation of (**10**) using either the Wittig reaction or Peterson alkenation of the corresponding silyl ether met with little or no success. The problem was solved by exposure of (**10**) to the conditions used by Lombardo[11] to provide (+)-albicanol (**1**) {m.p. 71—72 °C, lit[2]; m.p. 68—69 °C; $[\alpha]_D$ + 14° (*c* 0.56, $CHCl_3$), lit[2]; $[\alpha]_D$ + 13° (*c* 0.6, $CHCl_3$)} in 48% yield. The i.r., ^1H n.m.r., and mass spectra of synthetic and authentic samples of albicanol were indistinguishable. Furthermore, (**1**) was converted by standard acetylation conditions to albicanyl acetate (**2**) {$[\alpha]_D$ + 22° (*c* 0.37, $CHCl_3$), lit[2]; $[\alpha]_D$ +24° (c 0.5, $CHCl_3$)}, which was also identical to an authentic sample.‡

The synthesis of sesquiterpenes (**1**) and (**2**) reported herein appears to be not only a simple and practical one, but also represents rigorous confirmation of the absolute structures of both compounds.

‡ All compounds reported gave ^1H n.m.r., i.r., and mass spectra in accord with the structure given. Analytical (combustion and/or high resolution mass spectral) data were obtained for all new compounds.

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