An Expeditious and Enantioselective Entry to the *ABC* Ring of the Quassinoid Skeleton

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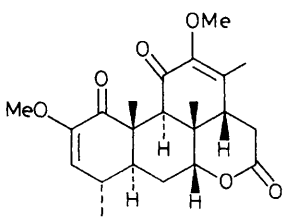
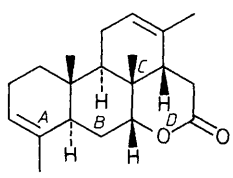
The tricycle (**5**) with two *trans*-fused angular methyl groups is constructed from tiglic aldehyde and (*S*)-carvone involving a stereocontrolled aldol reaction and an *endo*-selective intramolecular Diels–Alder (IMDA) reaction; the stereochemistry was established by an *X*-ray study.

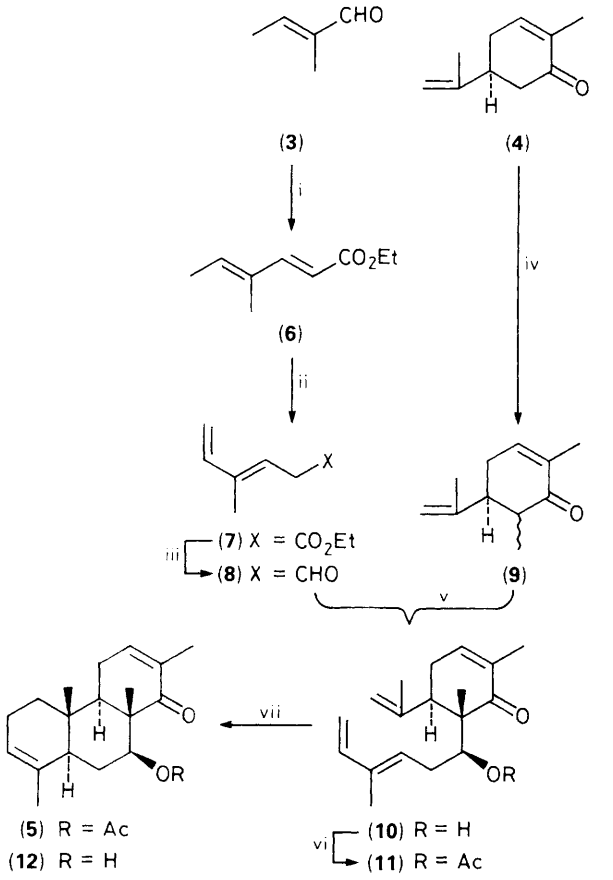
The quassinoids,[1] a large group of triterpenoid bitter principles found in the *Simaroubacea* plant family, have displayed a wide spectrum of biological activities[1,2] and present a significant synthetic challenge. Recently, the total syntheses of (±)-quassin (**1**),[3] (±)-catelanolide,[4] (±)-klaineanone,[5] and (±)-amarolide[6] have been described. All these quassinoids share a basic tetracyclic carbon skeleton (**2**) with common stereochemical features. Substantial differences in the substitution pattern and oxidation level are found in the *A* and the *B* ring.[1] Here we report, starting from commercially available



(**1**)



(**2**)



Scheme 1. *Reagents and conditions*: i, potassium t-butoxide, triethyl phosphonoacetate, tetrahydrofuran (THF), 20 °C, (90%); ii, lithium di-isopropylamide (LDA), THF, then 10% aq. AcOH, −78 °C (85%); iii, DIBAL-H, toluene, −100 °C; iv, LDA, MeI, THF, −10 °C (88%); v, LDA, then followed by aldehyde (**8**), THF; −100 °C (60%); vi, Et_3N, *N*,*N*-dimethylaminopyridine, Ac_2O, CH_2Cl_2, (100%); vii, toluene, Methylene Blue, 220 °C, 110 h, sealed tube, (80%).

tiglic aldehyde (**3**) and (*S*)-carvone (**4**), rapid access to the *ABC* ring of the quassinoid skeleton, *i.e.* optically active tricycle (**5**), in which the two angular methyl groups are fabricated with excellent stereocontrol.

The convergent synthesis of the tricycle (**5**) is shown in Scheme 1. Tiglic aldehyde (**3**) was alkenated with the potassium salt of triethyl phosphonoacetate into ethyl dienoate (**6**) which was deconjugated to the diene (**7**).[3] The corresponding aldehyde (**8**), which proved to be unstable on isolation, was best prepared by partial reduction of the ester (**7**) with di-isobutylaluminium hydride (DIBAL-H) at −100 °C and used *in situ*. A stereocontrolled aldol reaction proceeded smoothly between the aldehyde (**8**) and the kinetic enolate derived from methyl carvone (**9**) [prepared from methylation[7] of (*S*)-carvone (**4**)]. The resultant aldol (**10**),† $[\alpha]_D$ −4.4° (*c* 1.9, EtOH) with two new chiral centres was isolated as a single diastereoisomer in an overall yield of 60% from (**7**) and (**9**). Presumably, the approach of the aldehyde to the less hindered α-face of the enolate secured the desired stereochemistry of the angular methyl moiety and the stereochemical outcome of the hydroxy group in (**10**) was then as expected from a six-centre chair-type transition state. The alcohol (**10**) underwent a reto-aldol reaction on heating and was therefore protected as the acetate (**11**), $[\alpha]_D$ +17.1° (*c* 1.31, EtOH). IMDA reaction[8] of (**11**) in a sealed tube furnished the tricyclic ketone (**5**) as the sole product in 80% yield, m.p. 138—140 °C; $[\alpha]_D$ +89.8° (*c* 0.61, EtOH). Since detailed spectroscopic studies of (**5**) failed to indicate unambiguously the stereochemistry of the newly formed ring junction, a single crystal *X*-ray analysis‡ was performed on the alcohol (**12**) derived from the Diels–Alder adduct (**5**). This *X*-ray result, shown in Figure 1, demonstrated that the IMDA reaction proceeded *via* a chair-like transition state and was *endo*-selective.

† All new compounds gave satisfactory analytical and spectral data.

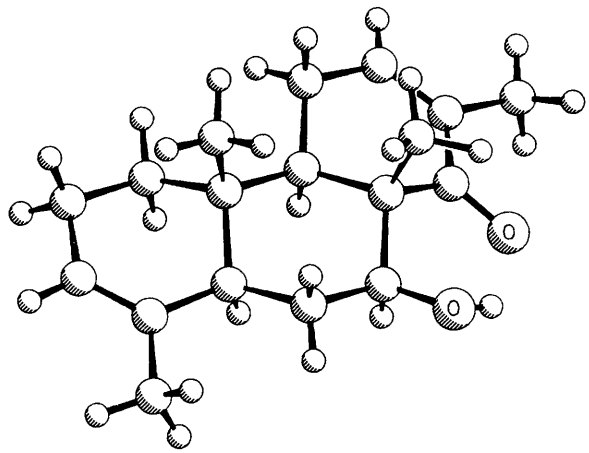


Figure 1. *X*-Ray crystal structure of the alcohol (**12**).

In conclusion, we have described a short, convergent, stereocontrolled, and enantioselective synthesis of the tricycle (**5**) with functionalities suitable for further elaboration to optically active quassinoids and analogues.

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‡ *Crystal data* for (**12**): $C_{18}H_{26}O_2$, M = 274.4, monoclinic, a = 10.050(2), b = 14.284(2), c = 10.440(2) Å, β = 92.40(2)°, U = 1497.5(5) Å^3, Z = 4, D_x = 1.22 g cm^{-3}, $F(000)$ = 600, space group $P2_1/c$, Mo-K_α radiation, λ = 0.71073 Å, μ(Mo-K_α) = 0.42 cm^{-1}, Nicolet P3/V2000 diffractometer, $3.0 \leq 2\theta \leq 55°$, θ—2θ scans, 3486 unique measured data, non-hydrogen atoms anisotropic, all hydrogens located in a difference Fourier synthesis and refined freely with isotropic vibration parameters. Final R = 0.049, R_w = 0.056 for 1490 reflections with $F > 6\sigma(F)$. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.