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
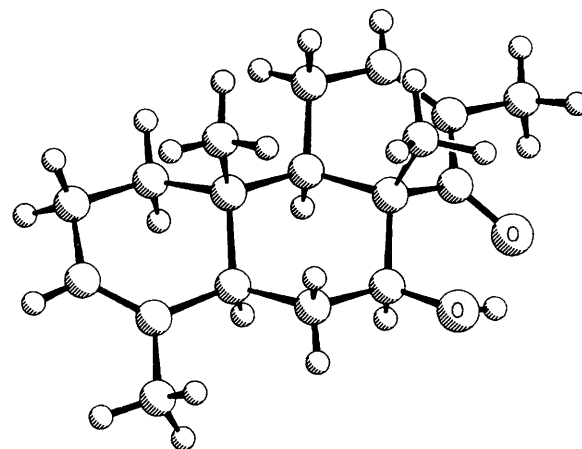

(1)

(2)
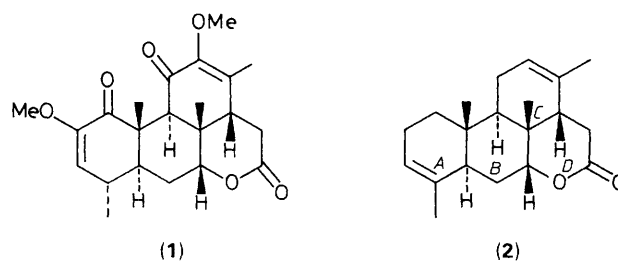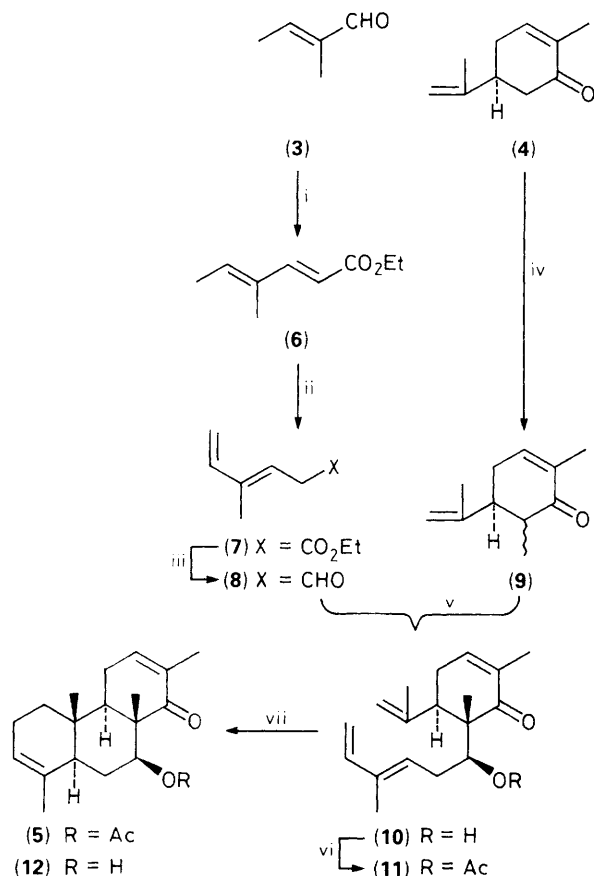
Scheme 1. *Reagents and conditions*: i, potassium t-butoxide, triethyl phosphonoacetate, tetrahydrofuran (THF), 20 °C, (90%); ii, lithium di-isopropylamide (LDA), THF, then 10% aq. AcOH, −78 °C (85%); iii, DIBAL-H, toluene, −100 °C; iv, LDA, MeI, THF, −10 °C (88%); v, LDA, then followed by aldehyde (8), THF, −100 °C (60%); vi, Et$_3$N, N,N-dimethylaminopyridine, Ac$_2$O, CH$_2$Cl$_2$, (100%); vii, toluene, Methylene Blue, 220 °C, 110 h, sealed tube, (80%).

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

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; [α]$_D$ +89.8° (*c* 0.61, EtOH). Since detailed spectroscopic studies of (5) failed to indicate un-ambiguously 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.

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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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),† [α]$_D$ −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), [α]$_D$ +17.1° (*c*

† All new compounds gave satisfactory analytical and spectral data.