A Stereocontrolled and Enantioselective Synthesis of the Tetracyclic Quassinoid Skeleton

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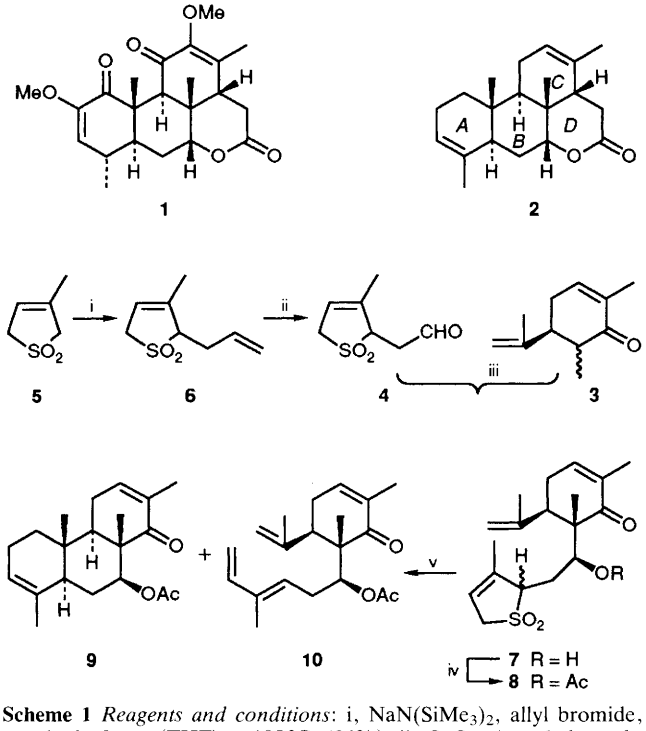
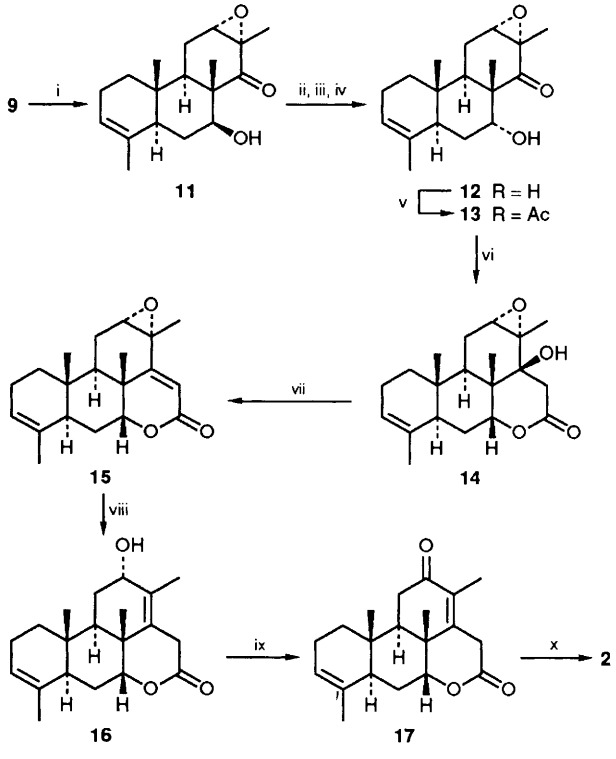
The optically active tetracycle **2** with six correct chiral centres common to numerous quassinoids is constructed from (*S*)-carvone and 3-methyl-2,5-dihydrothiophene *S,S*-dioxide involving highly regioselective and stereocontrolled reactions.

The quassinoids represent a large group of terpenoid bitter principles from the *Simaroubacea* plant family.[1] Their biological activities[1,2] and intriguing structures have attracted considerable attention from synthetic chemists.[3,4] The pioneering work of Grieco and his coworkers is impressive, although the target molecules were obtained in racemic forms.[5] In our own quest for an enantioselective entry to tetracyclic quassinoids such as (+)-quassin **1**, we are interested in the construction of the quassinoid skeleton **2** which has the general *ABCD* ring system with six chiral centres common to numerous quassinoids.[1] Our synthetic strategy for its fabrication is based on the *C*→*ABC*→*ABCD* ring annulation sequence and we recently reported the convergent synthesis of the *ABC* ring of **2**.[6] We now describe an improvement of our previous effort and also report the successful synthesis of **2**.

The first problem in our previous work[6] was the synthesis of the unstable *E*-4-methylhexa-3,5-dienal. Although this β,γ-unsaturated aldehyde could be generated *in situ* and used directly in the subsequent adolisation reaction with methylcarvone **3**, good yields of the corresponding aldol product were sporadic. We envisaged that masking of the diene moiety as a dihydrothiophene *S,S*-dioxide (sulfolene) derivative[7] would afford a relatively stable aldehyde **4** amenable for high-yielding aldolisation reactions. Thus regioselective deprotonation–alkylation[7] of 3-methylsulfolene **5** gave the alkene **6** as the sole product in 96% yield (Scheme 1). The terminal double bond in **6** was selectively hydroxylated and the resulting glycol cleaved to form the masked diene aldehyde **4**.† This aldehyde **4** gratifyingly gave reproducible yields in aldolisation with methylcarvone **3**. Thus treatment of **4** with the enolised **3** furnished the aldols **7** as a 1 : 1 mixture of diastereoisomers which did not need to be fractionated. The alcohol in **7** was then protected as the acetate **8**. Boiling a dilute solution of **8** in benzonitrile provided the tricyclic keto-ester **9** in 62% yield as a single diastereoisomer. A small amount of the triene **10** was also isolated. Both **9** and **10** were identical to samples reported previously.[6] It therefore appears that, under these conditions, the sulfolene **8** underwent a stereospecific SO_2 extrusion and an *endo*-selective intramolecular Diels–Alder reaction[8] to give the *trans*-fused *AB* ring system **9**.



Scheme 1 *Reagents and conditions*: i, $NaN(SiMe_3)_2$, allyl bromide, tetrahydrofuran (THF), −105 °C, (96%); ii, OsO_4, 4-methylmorpholine *N*-oxide, Bu^tOH, H_2O, then $NaIO_4$, aq. dioxane, (60%); iii, lithium diisopropylamide (LDA), then followed by aldehyde **4**, THF, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), −78 °C, (87%); iv, Ac_2O, pyridine, *N,N*-dimethylaminopyridine (DMAP), CH_2Cl_2, room temp., (89%); v, PhCN, Methylene Blue, 190 °C, 110 h, (62%)



Scheme 2 *Reagents and conditions*: i, Bu^tO_2H, Triton B, MeOH, then KOH, MeOH, (85%); ii, $(CF_3SO_2)_2O$, pyridine, DMAP, CH_2Cl_2, 0 °C; iii, wet dimethylformamide, room temp., 48 h; iv, K_2CO_3, MeOH, room temp., 4 h, (60%); v, Ac_2O, pyridine, DMAP, CH_2Cl_2, room temp., (100%); vi, LDA, THF, DMPU, −78 → 0 °C, (98%); vii, $SOCl_2$, pyridine, 0 °C, 1 h, (98%); viii, Zn, AcOH, (60%); ix, pyridinium chlorochromate, 3 Å molecular sieves, CH_2Cl_2, room temp., (96%); x, (*p*-tosylsulfonyl)hydrazine, EtOH, reflux, then $NaB(CN)BH_3$, AcOH, 70 °C, (50%)

† All new compounds gave satisfactory analytical and spectra data.

With an efficient and expeditious route to the optically active tricycle **9** available, we set to tackle the second problem in our previous work,[6] *i.e.* the assembly of the *D* ring to complete the construction of the quassinoid skeleton **2** (Scheme 2). Thus epoxidation of **9** followed by deacetylation as described previously gave the known alcohol **11**.[6] The configuration of the alcohol in **11** was inverted, *via* a three-step sequence involving trifluoromethanesulfonylation, nucleophilic displacement, and deformylation, into the desired α-alcohol **12**, m.p. 105–106 °C; $[\alpha]_D$ − 72.0 (*c* 0.45, $CHCl_3$). The ^1H NMR spectrum of **12** showed that the 7-H appeared at δ 4.19 as a triplet ($J_{7,6\alpha} = J_{7,6\beta} = 3.9$ Hz); the small coupling constant is consistent with the 7-H being in the equatorial position. The alcohol **12** was then esterified into the acetate **13** in quantitative yield, m.p. 149–150 °C; $[\alpha]_D$ −54.9 (*c* 0.43, CH_2Cl_2). Treatment of **13** with LDA caused an intramolecular aldolisation to occur, giving the aldol **14** which underwent smooth β-elimination to the unsaturated lactone **15**, m.p. 145–156 °C; $[\alpha]_D$ −105.7 (*c* 0.28, CH_2Cl_2).‡ Epoxide opening reaction of **15** with zinc in acetic acid afforded the allylic alcohol **16** which was oxidised to the enone **17**, m.p. 230–231 °C; $[\alpha]_D$ + 89.1 (*c* 0.22, CH_2Cl_2). Finally, the enone carbonyl group in **17** was removed using a modified Wolf–Kishner deoxygenation[9] to yield the quassinoid skeleton **2** as a single diastereoisomer, $[\alpha]_D$ −39.6 (*c* 0.9, CH_2Cl_2).

In summary, we have described a novel synthesis of the optically active quassinoid skeleton **2**, which has the *ABCD* ring system with six correct chiral centres, *via* a series of regioselective and stereocontrolled reactions from (*S*)-carvone with one chiral centre.

‡ Treatment of the acetyl derivative of **11** with LDA led to no reaction.

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