# Total Synthesis of (+)-Quassin from (+)-Carvone†

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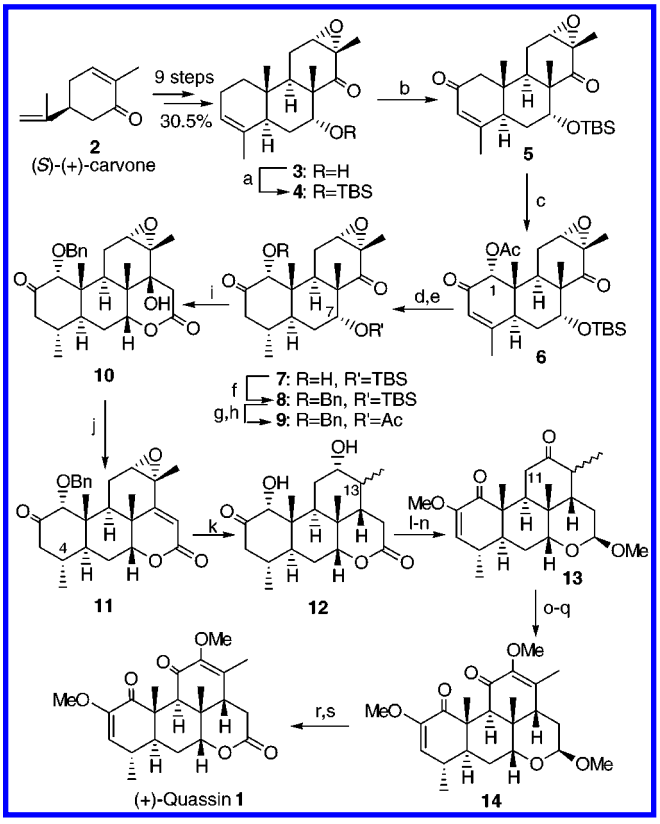
Quassin (**1**) belongs to a large and constantly expanding family of terpenoid bitter principles,[1] extracted from the plant species *Simaroubaceae*[2] and named collectively as quassinoids. The quassinoids have been demonstrated to exhibit a wide spectrum of biological properties.[1a,3] Their highly oxygenated tetracyclic/pentacyclic carbon frameworks, comprising a number of contiguous stereocenters, pose a formidable synthetic challenge and have attracted immense interest from synthetic chemists.[4]

The constitution of quassin (**1**) was established by Valenta and co-workers in the early 1960s,[5] and the same group subsequently reported its racemic total synthesis in 1991.[6] However, the first total synthesis of (±)-quassin was only realized in 1980 by the impressive Grieco group.[7] To date, there is only one report on the synthesis of optically active (+)-quassin, which was addressed by the Watt group using the (−)-enantiomer of the Wieland−Miescher ketone as the starting material.[8] In our own quest for an enantiospecific avenue toward tetracyclic quassinoids such as (+)-quassin (**1**), we already disclosed the construction of a partial quassinoid skeleton **3** that has the general ABC ring system with five stereogenic centers common to numerous quassinoids, based on a C → ABC → ABCD ring annulation strategy.[9] As an extension of this approach, we now report our successful elaboration of **3** into the target molecule (+)-quassin (**1**).

**Scheme 1**[a]




[a] Key: (a) TBSOTf, 2-6-lutidine, rt, 5 days (98% yield based on 75% conversion); (b) $Cr(CO)_6$, *t*-BuOOH, $CH_3CN$, reflux (78% yield based on 84% conversion); (c) $Mn(OAc)_3$, $C_6H_6$, reflux (84%); (d) $K_2CO_3$, MeOH, rt (87%); (e) $H_2$, 10% Pd/C, EtOH, rt (99%); (f) NaH, BnBr, THF, TBAI (cat.), 0 °C to rt (85%); (g) $Et_2O{\cdot}BF_3$, $CH_2Cl_2$, 0 °C to 10 °C (92%); (h) $Ac_2O$, DMAP, $CH_2Cl_2$, rt (94%); (i) LDA, THF, −78 °C (90%); (j) $SOCl_2$, pyridine, 0 °C (94%); (k) $H_2$, 10% Pd/C, EtOH, rt (92%); (l) DIBAL-H, THF, −78 °C then concd HCl (cat.), MeOH, 0 °C; (m) DMSO, TFAA, $CH_2Cl_2$, −78 °C then $Et_3N$, −78 °C to rt; (n) NaH, $CH_3I$, DMF, −20 °C (65% for steps l to n); (o) LDA, THF, −78 °C then MoOPH, −78 to 0 °C; (p) DMSO, TFAA, $CH_2Cl_2$, −78 °C then $Et_3N$, −78 °C to rt; (q) NaH, $CH_3I$, DMF, −20 °C (53% for steps o to q); (r) HOAc/$H_2O$ (3:2 v/v), reflux; (s) Fetizon's reagent, $C_6H_6$, reflux (79% for steps r and s).

Our recent endeavor[9d] has shown that (+)-carvone (**2**) could be readily converted into tricycle **3**, involving an aldol reaction and an intramolecular Diels−Alder reaction to create the quaternary centers in **1** (Scheme 1).

After considerable experimentation, we realized that the sensitive ring D could not survive the conditions for the functionalization of ring A. Consequently, oxygenation of ring A had to be executed first before assembly of the D ring. Toward this end, silylation of **3**[9d] afforded alkene **4**, which was subjected to a regioselective allylic oxidation[10] with

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$Cr(CO)_6$ to give enone **5**[11] as the major product: mp 89−90 °C; $[\alpha]^{20}_D$ −51.3 ($c$ = 4.4 in $CHCl_3$). Regioselective acetoxylation with manganic acetate[12] at C-1 of enone **5** furnished α′-acetate **6** as the sole product: mp 119−120 °C; $[\alpha]^{20}_D$ +31.5 ($c$ = 6.6 in $CHCl_3$). The approach of the acetate group to the β-face was believed to be hindered by the C-10 angular methyl group. The structure and stereochemistry of **6** was confirmed by an X-ray crystallographic analysis.[13] Deacetylation of **6** followed by catalytic hydrogenation of the alkene moiety of the enone gave stereoselectively keto alcohol **7** [mp 166−167 °C; $[\alpha]^{20}_D$ −65.1 ($c$ = 4.4 in $CHCl_3$)] in essentially quantitative yield. Hydrogen was delivered to the β-face of the alkene moiety because the α-face was probably hindered more by the C-1 acetate and the C-7 OTBS group. The A ring was now functionalized, and assembly of the D ring would be the new mission. Toward this end, the C-1 oxygen functionality needed to be protected as a benzyl ether while an acetate group was required at C-7 for subsequent internal cyclization to form the D ring. Thus, benzylation of **7** afforded benzyl ether **8** from which the silyl blocking group was replaced by an acetyl group under standard conditions, giving C-7 acetate **9** [mp 173−174 °C; $[\alpha]^{20}_D$ −66.0 ($c$ = 1.5 in $CHCl_3$)] in excellent overall yield. The ester **9** was treated with lithium diisopropylamide (LDA) at −78 °C to induce an intramolecular aldol addition. Indeed, the lactone **10** [mp 187−188 °C; $[\alpha]^{20}_D$ +10.8 ($c$ = 1.6 in $CHCl_3$)] was isolated in 90% yield as a single diastereoisomer. Dehydration of the β-hydroxylactone **10** using thionyl chloride in pyridine proceeded smoothly to give α,β-unsaturated lactone **11** in 94% yield: mp 193−194 °C; $[\alpha]^{20}_D$ −82.8 ($c$ = 1.1 in $CHCl_3$). The structure of **11** and especially the stereochemistry of the C-4 methyl group were confirmed by an X-ray crystallographic analysis.[13] Catalytic hydrogenation of **11** over palladium caused debenzylation, saturation of the alkene moiety, and ring opening of the epoxide functionality,[14] producing the crystalline diol **12** in 92% yield as a single compound: mp 215 °C dec; $[\alpha]^{20}_D$ +23.3 ($c$ = 0.5 in $CHCl_3$). The stereochemistry of the C-13 methyl group was not determined because it would be lost in the target molecule.

The lactone carbonyl needed to be protected as a mixed acetal before the enone units in ring A and C could be established. Thus, keto lactone **12** was transformed into **13** [mp 198−200 °C; $[\alpha]^{20}_D$ +77.2 ($c$ = 1.3 in $CHCl_3$)] by DIBAL-H reduction of the two carbonyl groups into an alcohol and a lactol, acetalization of the lactol moiety with acidic methanol to a mixed acetal, Swern oxidation[15] of all the alcohols to ketones, and *O*-methylation[8] of the α-hydroxy enone to the α-methoxy enone unit in ring A. The next objective would be the formation of an α-methoxy enone unit in ring C and hence completion of the synthesis. Kinetic deprotonation of **13** with LDA occurred at the C-11 methylene, and treatment of the resulting enolate with HMPA−$MoO_5$−pyridine complex (MoOPH)[16] gave the corresponding α-hydroxy ketone, which underwent Swern oxidation and *O*-methylation as above to the desired bis-α-methoxy enone **14**: mp 218 °C dec; $[\alpha]^{20}_D$ +62.4 ($c$ = 0.5 in $CHCl_3$). Selective hydrolysis of the acetal moiety in **14** with aqueous acetic acid followed by mild oxidation with Fetizon's reagent[17] ($Ag_2CO_3$ on Celite) afforded the target molecule (+)-quassin, mp 219−220 °C, undepressed with an authentic sample (lit.[5a] mp 221 °C): $[\alpha]^{20}_D$ +33.8 ($c$ = 0.5 in $CHCl_3$) [lit.[1b] $[\alpha]^{20}_D$ +34.5 ($c$ = 5.1 in $CHCl_3$)]. The synthetic quassin, the structure of which was confirmed by a X-ray crystallographic analysis,[13] was also identical to the purified commercial material purchased from Apin Chemicals Ltd by TLC, MS, IR, and $^1H$ and $^{13}C$ NMR.

In summary, we have presented a stereoselective and enantiospecific synthesis of tetracyclic quassin (**1**).[18] Application of the established strategy to the syntheses of other tetracyclic members as well as pentacyclic quassinoids is under active investigation.

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**Supporting Information Available:** Experimental procedures and characterization data, copies of the $^1H$ NMR spectra for compounds **4**−**14**, and X-ray structural data for compounds **1**, **6**, and **11** (48 pages).

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(18) In the present synthesis, (+)-quassin was harvested from (*S*)-carvone in 28 steps with an overall yield of about 2.6%. In Watt's synthesis,[8] 35 steps were required to obtain (+)-quassin from (*R*)-Wieland−Miescher ketone with an overall yield of less than 0.02%.