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

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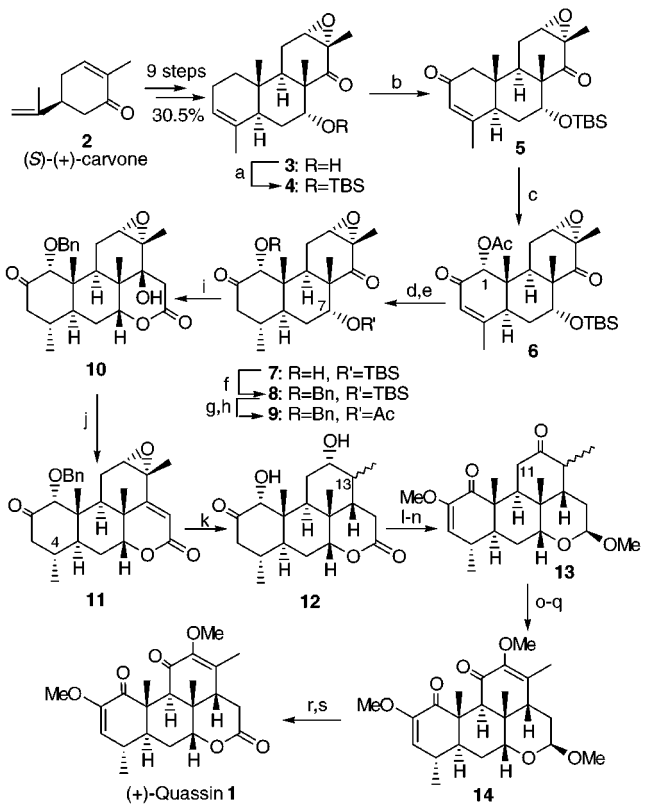
Received December 10, 1997

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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(1) (a) Polonsky, J. *Fortschr. Chem. Org. Naturst.* **1985**, *47*, 221; **1973**, *30*, 101. (b) London, E.; Robertson, A.; Worthington, H. *J. Chem. Soc.* **1950**, 3431. (c) Beer, R. J. S.; Jaquiss, D. B. G.; Robertson, A.; Savige, W. E. *J. Chem. Soc.* **1954**, 3672. (d) Hanson, K. R.; Jaquiss, D. B.; Lamberton, J. A.; Robertson, A.; Savige, W. E. *J. Chem. Soc.* **1954**, 4238. (e) Beer, R. J. S.; Hanson, K. R.; Robertson, A. *J. Chem. Soc.* **1956**, 3280. (f) Beer, R. J. S.; Dutton, B. G.; Jaquiss, D. B.; Robertson, A.; Savige, W. E. *J. Chem. Soc.* **1956**, 4850. (g) Carman, R. M.; Ward, A. D. *Aust. J. Chem.* **1962**, *15*, 807.

(2) For examples of some recently isolated quassinoids, see: Koike, K.; Yokoh, M.; Furukawa, M.; Ishii, S.; Ohmoto, T. *Phytochemistry* **1995**, *40*, 233. Grieco, P. A.; VanderRoest, J. M.; Pineironunez, M. M.; Campaigne, E. E.; Carmack, M. *Phytochemistry* **1995**, *38*, 1463. Ouyang, Y.; Mitsunaga, K.; Koike, K.; Ohmoto, T. *Phytochemistry* **1995**, *39*, 911.

(3) Grosvenor, P. W.; Gothard, P. K.; Mcwilliam, N. C.; Supriono, A.; Gray, D. O. J. *Ethnopharmacol.* **1995**, *45*, 75. Lidert, Z.; Wing, K.; Polonsky, J.; Imakurra, Y.; Okano, M.; Tani, S.; Lin, Y.-M.; Kiyokawa, H.; Lee, K.-H. *J. Nat. Prod.* **1987**, *50*, 442. Polonsky, J. In *The Chemistry and Chemical Taxonomy of the Rutales*; Waterman, P. G., Grandon, M. F., Eds.; Academic Press: New York, 1983; p 247.

(4) For examples of some recent synthetic work, see: Chiu, C. K.-F.; Govindan, S. V.; Fuchs, P. L. *J. Org. Chem.* **1994**, *59*, 311. Spino, C.; Liu, G.; Tu, N.; Girard, S. *J. Org. Chem.* **1994**, *59*, 5596. Spino, C.; Tu, N. *Tetrahedron Lett.* **1994**, *35*, 3683. Grieco, P. A.; Piñeiro-Nuñez, M. M. *J. Am. Chem. Soc.* **1994**, *116*, 7606. Grieco, P. A.; Collins, J. L.; Moher, E. D.; Fleck, T. J.; Gross, R. S. *J. Am. Chem. Soc.* **1993**, *115*, 6078. Grieco, P. A.; VanderRoest, J. M. *J. Am. Chem. Soc.* **1993**, *115*, 5841. Spino, C.; Liu, G. *J. Org. Chem.* **1993**, *58*, 817. Fleck, T. J.; Grieco, P. A. *Tetrahedron Lett.* **1992**, *33*, 1813. Sasaki, M.; Murae, T.; Takahashi, T. *J. Org. Chem.* **1990**, *55*, 528. Kim, M.; Applegate, L. A.; Kawada, K.; Watt, D. S. *Synth. Commun.* **1990**, *20*, 989. Kawada, K.; Kim, M.; Watt, D. S. *Tetrahedron Lett.* **1989**, *30*, 5985. Earlier synthetic efforts are described in Professor Watt's excellent review; see: Kawada, K.; Kim, M.; Watt, D. S. *Org. Prep. Proc. Int.* **1989**, *21*, 521.

(5) (a) Valenta, Z.; Papadopoulos, S.; Podesva, C. *Tetrahedron* **1961**, *15*, 100. (b) Valenta, Z.; Gray, A. H.; Orr, D. E.; Papadopoulos, S.; Podesva, C. *Tetrahedron* **1962**, *18*, 1433.

(6) Stojanac, H.; Valenta, Z. *Can. J. Chem.* **1991**, *69*, 853.

(7) Grieco, P. A.; Ferriño, S.; Vidari, G. *J. Am. Chem. Soc.* **1980**, *102*, 7587. Vidari, G.; Ferriño, S.; Grieco, P. A. *J. Am. Chem. Soc.* **1984**, *106*, 3539.

(8) Kim, M.; Kawada, K.; Gross, R. S.; Watt, D. S. *J. Org. Chem.* **1990**, *55*, 504.

(9) (a) Shing, T. K. M.; Tang, Y.; Malone, J. F. *J. Chem. Soc., Chem. Commun.* **1989**, 1294. (b) Shing, T. K. M.; Tang, Y. *Tetrahedron* **1990**, *46*, 2187. (c) Shing, T. K. M.; Tang, Y. *J. Chem. Soc., Chem. Commun.* **1992**, 341. (d) Shing, T. K. M.; Tang, Y. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1625.

(10) (a) Pearson, A. J.; Chen, Y.-S.; Hsu, S.-Y.; Ray, T. *Tetrahedron Lett.* **1984**, *25*, 1235. (b) Pearson, A. J.; Han, G. R. *J. Org. Chem.* **1985**, *50*, 2791. (c) Pearson, A. J.; Chen, Y.-S.; Han, G. R.; Hsu, S.-Y.; Ray, T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 267.

S0022-3263(97)01896-3 CCC: $15.00
Published on Web 03/06/1998

$Cr(CO)_6$ 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.

Acknowledgment. This work was partially supported by the RGC Earmarked Grant (Ref. No. CUHK303/94P).

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).

JO9718962

(11) All new compounds gave satisfactry elemental analysis or HRMS spectra.

(12) (a) Williams, G. J.; Hunter, N. R. *Can. J. Chem.* **1976**, *54*, 3830. (b) Dunlap, N. K.; Sabol, M. R.; Watt, D. S. *Tetrahedron Lett.* **1984**, *25*, 5839.

(13) Crystal structure data have been deposited at the Cambridge Crystallographic Data Centre.

(14) (a) Accrombessi, G. C.; Geneste, P.; Olivé, J.-L. *J. Org. Chem.* **1980**, *45*, 4139. (b) Accrombessi, G. C.; Geneste, P.; Olivé, J.-L.; Pavia, A. A. *Tetrahedron* **1981**, *37*, 3135. (c) Confalone, P. N.; Pizzolato, G. *J. Am. Chem. Soc.* **1981**, *103*, 4251. (d) Notheisz, F.; Zsigmond, Á. G.; Bartók, M.; Smith, G. V. *J. Chem. Soc., Faraday Trans. 1* **1987**, *83*, 2359.

(15) Mancuso, A. J.; Brownfair, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148.

(16) (a) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188. (b) Mimoun, H.; Seree de Roch, I.; Sajus, L. *Bull. Soc. Chim. Fr.* **1969**, 1481. (c) Vidari, G.; Ferriño, S.; Grieco, P. A. *J. Am. Chem. Soc.* **1984**, *106*, 3539.

(17) Fetizon, M.; Golfier, M. *C. R. Acad. Sci., Ser. C* **1968**, *267*, 900.

(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%.