Pergamon

Tetrahedron Letters 42 (2001) 5271–5273

TETRAHEDRON LETTERS

Synthetic studies on quassimarin and simalikalactone D: functionalization of ring C

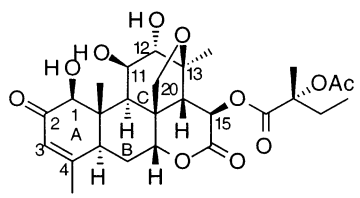
Qin Jiang and Tony K. M. Shing*

Department of Chemistry, The Chinese University of Hong Kong, Hong Kong, China

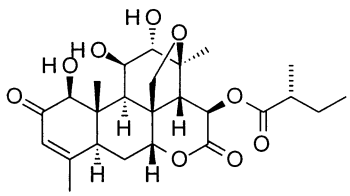
Received 3 April 2001; accepted 1 June 2001

Abstract—The tricycle **18** containing the oxygenated ring C is constructed from (*S*)-carvone in 14 steps involving a Shapiro reaction and a selective acylation as the key steps.

Among the pentacyclic quassinoids,[1] quassimarin (**1**) and simalikalactone D (**2**) are important synthetic targets because of their potent activity in vivo against the P-388 lymphocytic leukemia in mice and in vitro against human carcinoma of the nasopharynx at the 10^{-3} mg/mL level.[2] They have also been shown to possess marked differential solid tumor selectivity.[3] Both quassimarin (**1**) and simalikalactone D (**2**) possess a C_{20} picrasane carbon framework, but have a different butyrate ester at C(15).



Quassimarin (**1**)

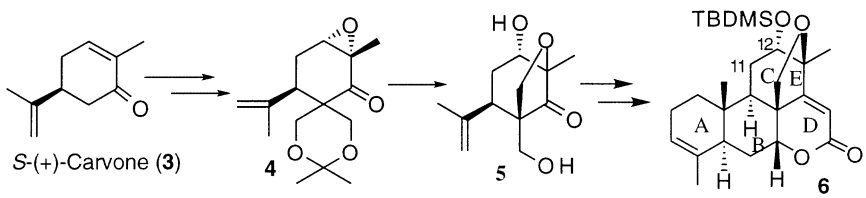


Simalikalactone D (**2**)

In our quest for the first enantiospecific entry to quassimarin **1** and simalikalactone D **2**, we have reported that (*S*)-(+)-carvone **3** could be transformed into diol **5**, and then into a pentacyclic quassinoid skeleton **6** in 18 steps with an overall yield of 22%.[4]

Functionalization of ring C in **6** by installing a *trans*-diaxial diol at C(11) and C(12) has been unsuccessful, attributable to the sensitive lactone D ring. We reasoned that construction of the diol moiety at an early stage should solve the problem. This letter describes our endeavors in the preparation of a functionalized ring C intermediate that could be transformed into the target molecules.

Our initial attempt was to protect the isopropenyl group and the primary alcohol in **5** in one-pot so that the remaining secondary alcohol could be eliminated. Towards this end, bromocyclization of diol **5** with *N*-bromosuccinimide (NBS) caused the formation of

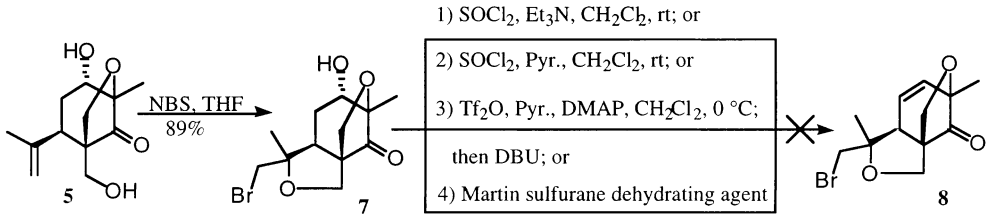


S-(+)-Carvone (**3**) **4** **5** **6**

Keywords: quassinoids; antitumour compounds; elimination reactions.

* Corresponding author. Tel.: +852 2609 6367; fax: +852 2603 5057; e-mail: tonyshing@cuhk.edu.hk

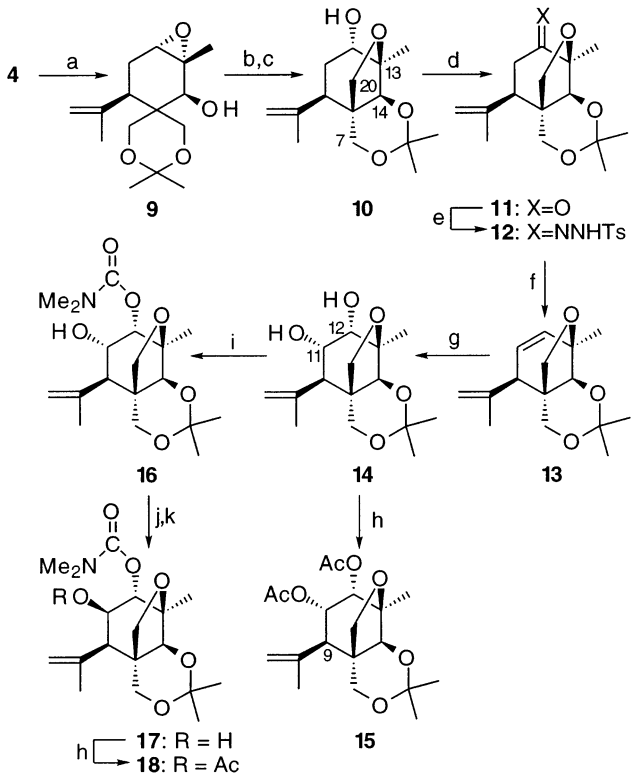
0040-4039/01/$ - see front matter
PII: S0040-4039(01)00964-9



Scheme 1.

bromo-tetrahydrofuran **7** in a good yield (Scheme 1). However, the free secondary alcohol could not be eliminated to give the corresponding alkene **8** under a number of reaction conditions. We speculated that the rigid tricycle **8** might not be flexible enough to accommodate three sp^2 carbons in ring C.

In view of these failures, we revised our approach by reducing the ketone moiety first before attempting the elimination of the secondary alcohol. Hence, stereoselective reduction of the ketone group in **4** with $NaBH_4$ in the presence of $CeCl_3{\cdot}7H_2O$ gave a quantitative yield of β-alcohol **9** (Scheme 2). Exposure of β-alcohol **9** to trifluoroacetic acid (TFA) in ethanol at about 50°C



Scheme 2. (a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0°C (100%); (b) TFA, EtOH, 50°C; (c) $(MeO)_2CMe_2$, *p*TsOH (cat.), CH_2Cl_2, rt (40% overall yield); (d) Dess–Martin periodinane, CH_2Cl_2, rt (93%); (e) *p*TsNHNH$_2$, *p*TsOH (cat.), $MgSO_4$, THF, rt (100%); (f) *t*-BuLi, THF 0°C to rt (73%, 86% conversion); (g) NMO·H_2O, OsO_4 (cat.), acetone/H_2O (5:1, v/v), rt (86%); (h) DMAP, Ac_2O, CH_2Cl_2, rt (94%); (i) phosgene iminium chloride, Et_3N, CH_2Cl_2, reflux (82%); (j) DMSO, TFAA, CH_2Cl_2, −78°C then Et_3N −78°C to rt; (k) $NaBH_4$, MeOH, rt (overall 90%).

followed by protection of the diol at C(7) and C(14) (quassimarin numbering) with 2,2-dimethoxypropane afforded the acetonide **10** in a moderate yield. The constitution of the acetonide **10**, especially the stereochemistry of the α-proton at C(14) and the epoxy bridge between C(13) and C(20), was confirmed by an X-ray crystallographic analysis.[5] Oxidation of the acetonide **10** with Dess–Martin periodinane[6] yielded ketone **11** in an excellent yield. Exposure of ketone **11** to tosylhydrazine in the presence of a catalytic amount of tosic acid afforded a quantitative yield of hydrazone **12**. Shapiro reaction[7] of the hydrazone **12** with *tert*-butyllithium in THF resulted in a 73% yield of alkene **13** (86% conversion). Stereoselective dihydroxylation of alkene **13** with a catalytic amount of OsO_4 furnished *cis*-diol **14** in 86% yield. The stereochemistry of the β-protons at C(11) and C(12) in diol **14** was confirmed by ^{1}H NMR spectral analysis of its corresponding diacetate **15**. The ^{1}H NMR spectrum of **15** showed that H_{12} appeared at δ 5.19 ppm as a doublet ($J_{12,11}=4.5$ Hz), H_{11} appeared at δ 5.48 ppm as a doublet of doublets ($J_{11,12}=4.5$ Hz and $J_{11,9}=12$ Hz), and H_9 appeared at δ 2.44 ppm as a doublet ($J_{9,11}=12$ Hz). The small coupling constant of 4.5 Hz was consistent with H_{12} occupying the equatorial position (β-face) and the large coupling constant of 12 Hz was consistent with both H_{11} and H_9 being in the axial position which supported our assignment of the stereochemistry of the C(11α) and C(12α) diacetate unit in **15** (Fig. 1). Regioselective protection of the C(12α) hydroxy group with phosgene iminium chloride in the presence of triethylamine produced the α-hydroxy carbamate **16** in 82% yield.[8] A plausible mechanism is shown in Fig. 2. The favorable protonation of the less hindered equatorial alkoxy moiety in the cyclic intermediate led to the selective protection of the axial hydroxy group at the C(12) position.

Inversion of configuration of the C(11α) hydroxy group in **16** was accomplished via a two-step oxidation–reduction sequence. Swern oxidation[9] of the free alcohol in carbamate **16** followed by reduction with $NaBH_4$ yielded the desired β-hydroxy carbamate **17** and the α-hydroxy carbamate **16**. The ratio of **17** to **16** was

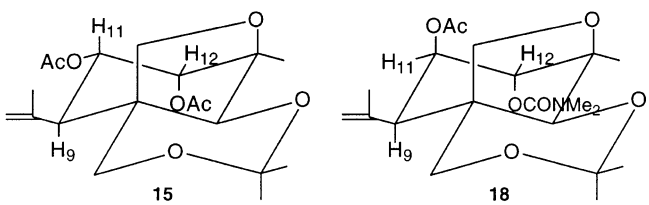


Figure 1.

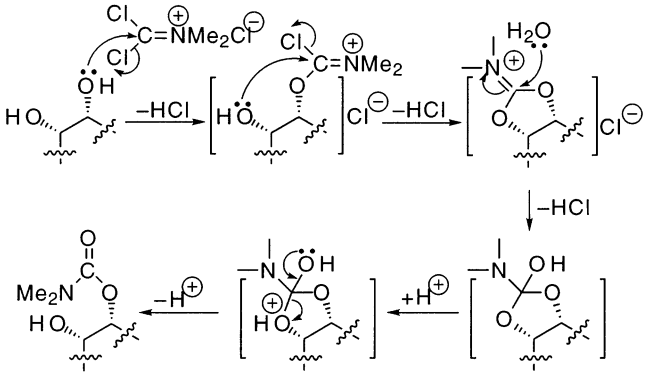


Figure 2.

2.3:1. Acetylation of **17** provided the β-acetate **18**. The ^{1}H NMR spectrum of **18** showed that H_{12} appeared at δ 4.76 ppm as a doublet ($J_{12,11}=1.2$ Hz), H_{11} at δ 5.14 ppm as a doublet of doublets ($J_{11,12}=1.2$ Hz and $J_{11,9}=4.8$ Hz), and H_9 at δ 2.36 ppm as a doublet ($J_{9,11}=4.8$ Hz). The small coupling constants of 4.8 and 1.2 Hz were consistent with both H_{12} and H_{11} being in the equatorial position, which supported our assignment of the stereochemistry of the C(11β) and C(12α) diacetate moiety in **18** (Fig. 1). In summary, we have presented a facile, efficient, and stereocontrolled synthetic avenue for the functionalization of ring C in quassimarin and simalikalactone D. Starting from (*S*)(+)-carvone, the tricycle **18** comprising the functionalized CE ring has been constructed in 14 steps with an overall yield of 12%. Conversion of tricycle **18** into the target molecules quassimarin and simalikalactone D is under investigation.

Acknowledgements

Financial support from Hong Kong RGC (Ref. No. CUHK 4185/97P) is gratefully acknowledged.

References

1. (a) Polonsky, J. *Fortschr. Chem. Org. Naturst.* **1985**, *47*, 221; (b) **1973**, *30*, 101.
2. (a) Kupchan, S. M.; Streelman, D. R. *J. Org. Chem.* **1976**, *41*, 3481; (b) Kupchan, S. M.; Lacadie, J. A.; Howie, G. A.; Sickles, B. R. *J. Med. Chem.* **1976**, *19*, 1130; (c) Liao, L. L.; Kupchan, S. M.; Horowitz, S. B. *Mol. Pharmacol.* **1976**, *12*, 167; (d) Kupchan, S. M.; Lacadie, J. A. *J. Org. Chem.* **1975**, *40*, 654.
3. (a) Moher, E. D.; Collins, J. L.; Grieco, P. A. *J. Am. Chem. Soc.* **1992**, *114*, 2764; (b) Moher, E. D.; Grieco, P. A.; Collins, J. L. *J. Org. Chem.* **1993**, *58*, 3789.
4. (a) Shing, T. K. M.; Zhu, X. Y.; Mak, T. C. W. *Tetrahedron: Asymmetry* **1996**, *7*, 673; (b) Shing, T. K. M.; Zhu, X. Y.; Mak, T. C. W. *Chem. Commun.* **1996**, 2369.
5. Crystal structure data have been deposited at the Cambridge Crystallographic Data Centre.
6. Dess, D. R.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
7. (a) Shapiro, R. H.; Heath, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 5734; (b) Shapiro, R. H. *Tetrahedron Lett.* **1968**, 345.
8. (a) Viehe, H. G.; Janousek, Z. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 573; (b) Copeland, C.; Stick, R. V. *Aust. J. Chem.* **1982**, *35*, 2257; (c) Sunay, U.; Mootoo, D.; Molino, B.; Fraser-Reid, B. *Tetrahedron Lett.* **1986**, *27*, 4697.
9. Mancuso, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148.