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Synthetic Studies towards Pentacyclic Quassinoids: Facile and Stereocontrolled Construction of the E Ring

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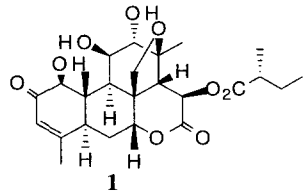
Abstract: The CE ring **15** of the pentacyclic quassinoid skeleton is fabricated from (*S*)-carvone involving regioselective bishydroxylmethylation, acetonation, stereocontrolled epoxidation and epoxymethano-bridge formation, selective protection, deprotection, and oxidation.

The quassinoids[1] constitute a constantly expanding group of terpenoid bitter principles isolated from the plant *Simaroubaceae*.[2] The biological properties[1,3] of the quassinoids and the highly oxygenated tetracyclic/pentacyclic carbon frameworks of the C_{20} picrasane family, comprising a number of contiguous stereocenters, pose a formidable synthetic challenge and therefore have stimulated massive synthetic efforts from many research teams.[4] The pioneer and the major contributor in this area of research has been the Grieco group, producing elegant total syntheses of a number of tetracyclic and pentacyclic members. Among the quassinoids, simalikalactone D **1**[5] and quassimarin **2**,[6] having a common pentacyclic skeleton **3**, are of considerable interest because they are cytotoxic and display potent activity *in vivo* against the P-388 lymphocytic leukemia in mice (PS).[4i,g] Also, recent findings have indicated that **1** and **2** possess marked differential solid tumour selectivity.[4i,g] In our own quest for an enantiospecific entry to optically active quassinoids, we recently reported the construction of a tetracyclic quassinoid skeleton **4** that has the general ABCD ring system with six stereogenic centres common to numerous quassinoids *via* a series of regioselective and stereocontrolled reactions from (+)-carvone with one stereogenic center (Scheme 1).[7] Our synthetic strategy for its fabrication is based on the C → ABC → ABCD ring annulation sequence and the major hurdle in the synthesis of quassinoids is the stereocontrolled construction of the angular methyl groups. We described two solutions to this problem employing an aldol reaction {**5** (R = CH_3) + **6** → **7**} and an intramolecular Diels-Alder (IMDA) reaction (**7** → **8**), leading to a *trans,anti,trans*-perhydrophenanthrene nucleus **8** with excellent stereocontrol.[7c] Now, we would like to exploit this developed approach to construct optically active pentacyclic simalikalactone D **1** and quassimarin **2** and this paper describes our effort in the construction of the epoxymethano-bridge (ring E) as a suitable intermediate for further elaboration into the target molecules.



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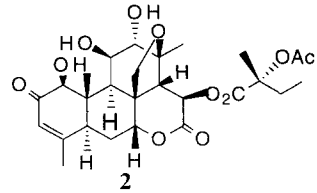

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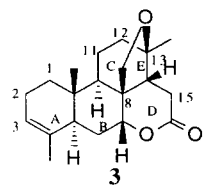
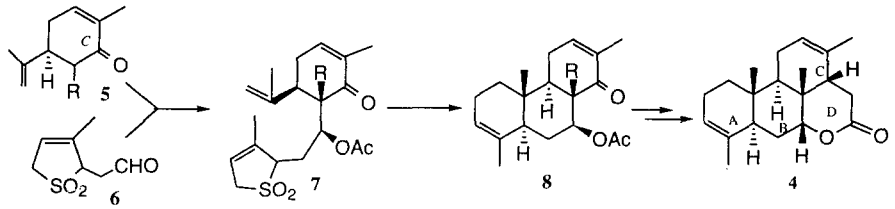


3

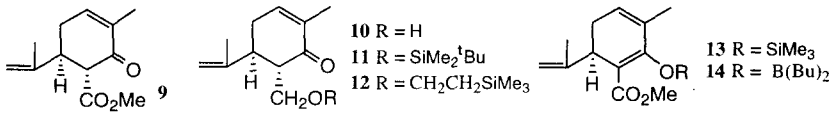
On the basis of the synthetic strategy shown in Scheme 1, we reasoned that substitution of the methyl group in **5** with a hydroxymethyl group or a suitable synthetic equivalent and taking it (**5**, R = CH_2OH or its

equivalent) through the same sequence of reactions as in the preparation of tricycle **8** would allow formation of the ring E at a later stage. This task appeared trivial in principle, but proved troublesome in practice. Our first assignment was the introduction of a suitable functional group at C-2 of (+)-carvone (**5**, R = H) and several different hydroxymethyl equivalents could be attached to that position.

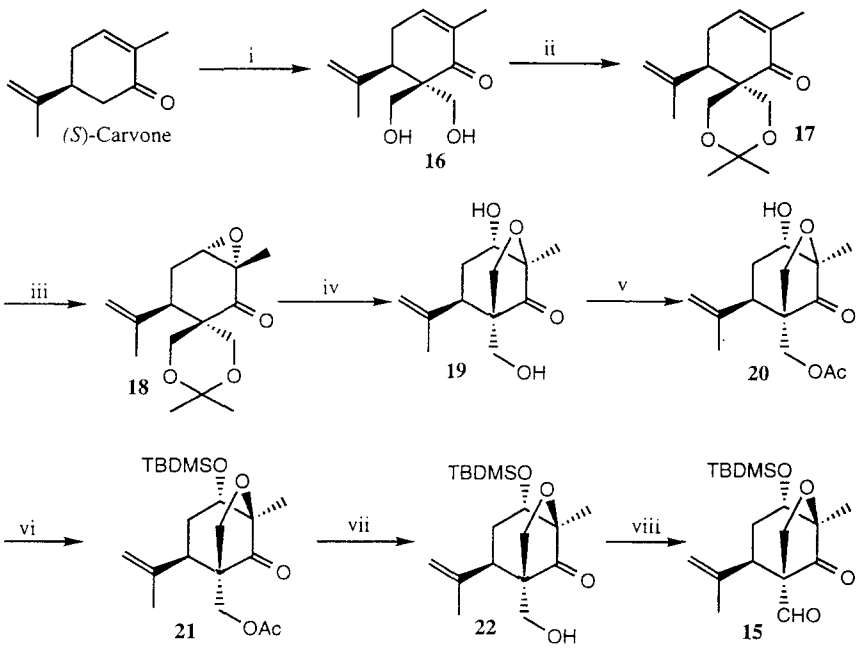


Scheme 1

Thus enolisation of (+)-carvone (**5**, R = H) with LDA in THF-*N,N'*-dimethylpropyleneurea (DMPU) (3:1) at – 78 °C followed by the addition of Mander's reagent (MeO_2CCN),[8] gaseous methanal, TBDMSCl, or 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl), afforded β-ketoester **9** (95%), β-hydoxyketone **10** (90%), silyl ether **11** (85%), or 2-SEM-carvone **12** (82%), respectively. At this stage, we had high hopes that one of these derivatives would react with an aldehyde (benzaldehyde, hexanal or aldehyde **6**) to furnish an aldol product {c.f. the conversion of **5** (R = CH_3) + **6** → **7** in Scheme 1}. Unfortunately, under a variety of basic reaction conditions for the aldolisation, all the compounds failed to furnish any aldols. Attempts to stabilise the aldol product via metal chelation by conducting Lewis acid ($TiCl_4$ or $ZnCl_2$) catalyzed aldolisation of silyl enol ether **13** or by reaction with boron enolate[9] **14** were also unsuccessful.



In view of the failures, we had to revise our synthetic approach and attempted to construct first an E ring **15** with reversed polarity so that a nucleophilic diene equivalent could be introduced to set up the IMDA precursor similar to **7**. This change of strategy proved successful and now we describe a simple solution to the fabrication of epoxymethano-bridge in pentacyclic quassinoids. Thus reaction of (+)-carvone with an excess of methanal from – 40 °C to room temperature gave 6,6-bishydroxymethylated carvone **16** in 75% yield (Scheme 2).[10] We envisaged that formation of an oxirane across the electrophilic alkene moiety in **16** would allow one of the primary alcohols to ring open the epoxide, leading to an epoxymethano-bridge. By analogy with the reactivity of α-halo-ketones, the epoxide ring opening was expected to proceed at the alpha position regioselectively. However, exposure of enone **16** to alkaline *tert*-butylhydroperoxide caused retro-aldol reaction and hence the primary alcohols had to be blocked first. These alcohols were best and conveniently protected as an acetonide. Thus the diol **16** was isopropylidenated under standard conditions to give the spiral compound **17**. Epoxidation of the electrophilic alkene in **17** with alkaline *tert*-butylhydroperoxide occurred smoothly at the less hindered alpha face to give the α-epoxide **18** in 95% yield. The alternative β-epoxide was not detectable by NMR or TLC. Acidic hydrolysis of the acetonide blocking group proceeded with concomitant ring-opening reaction by the liberated alcohol to form the THF ring **19**.



Scheme 2 *Reagents and conditions*: i, LDA, THF, HCHO, - 78°C to - 40°C then rt (75%); ii, $(MeO)_2CMe_2$, PPTS, CH_2Cl_2, rt, 2 h (100%); iii, *t*-BuOOH, 2N NaOH, MeOH, 45 °C, 24 h (95%); iv, CF_3COOH, EtOH, H_2O, 50 °C, 48 h, (85%); v, AcCl, $(iPr)_2EtN$, CH_2Cl_2, 0 °C to rt, 4 h (97%); vi, TBDMSOTf, 2,6-lutidine, CH_2Cl_2, rt, 2 h (100%); vii, NaOH, MeOH, THF, rt, 4 h (96%); viii, TPAP, NMO, CH_2Cl_2, rt, 4 h (84%).

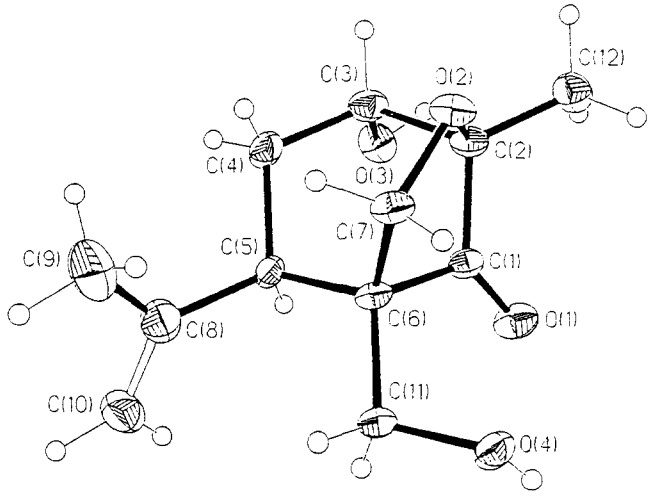


Fig. 1 Perspective view of the molecular structure of compound **19**. The thermal ellipsoids are drawn at the 50% probability level.

Again there was no other isomer isolable or detected. The structure **19** was confirmed by an X-ray study (Fig. 1) which demonstrated the nucleophilic opening of the oxirane did proceed as anticipated.

Now the secondary alcohol in **19** has to be blocked for further synthetic manipulation. This could be achieved by a selective protection and deprotection sequence. Thus selective acylation of the primary alcohol in diol **19** with acetyl chloride in the presence of diisopropylethylamine according to the Yamamoto protocol[11] gave the monoacetate **20** in an excellent yield. The silylation of the free alcohol in **20** was best effected with TBDMS-Otriflate, affording the silyl ether **21** in a quantitative yield. The ester grouping in **21** was hydrolysed under basic conditions without incident to give alcohol **22** that was subjected to a number of oxidation protocols {(PDC, PCC, Swern, tetrapropylammonium perruthenate (TPAP)}. The most efficient transformation was achieved using TPAP,[12] leading to aldehyde **15** in 84% yield.

With an efficient and facile approach to the optically active aldehyde **15** available, the stage was set for the IMDA reaction and for the fabrication of the pentacyclic skeleton **3** subsequently. This research is currently under active investigation.

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References and Notes

(1) (a) Polonsky, J. *Fortschr. Chem. Org. Naturst.* **1985**, *47*, 221. (b) **1973**, *30*, 101.
(2) Fernando E. S.; Gadek P. A.; Quinn, C. *Am. J. Bot.* **1995**, *82*, 92.
(3) (a) Grosvenor, P. W.; Gothard, P. K.; Mcwilliam, N. C.; Supriono, A.; Gray, D. O. J. *Ethnopharmacol.* **1995**, *45*, 75. (b) Lidert, Z.; Wing, K.; Polonsky, J.; Imakurra, Y.; Okano, M.; Tani, S.; Lin, Y.-M.; Kiyokawa, H.; Lee, K.-H. *J. Nat. Product.*, 1987, **50**, 442. (c) Polonsky, J. Chemistry and Biological Activity of the Quassinoids. In *The Chemistry and Chemical Taxonomy of the Rutales*; Waterman, P. G., Grandon, M. F., Eds.; Academic Press: New York, 1983; p 247. (d) Wall, M. E.; Wani, M. International Symposium on the Chemistry of Natural Products, Riga, USSR, IUPAC 7th, 1970; Abstracts E 138, 614.
(4) (a) Grieco, P. A.; Piñeiro-Nuñez, M. M. *J. Am. Chem. Soc.* **1994**, *116*, 7606. (b) Chiu, C. K.-F.; Govindan, S. V.; Fuchs, P. L. *J. Org. Chem.* **1994**, *59*, 311. (c) Spino, C; Liu, G.; Tu, N.; Girard, S. *J. Org. Chem.* **1994**, *59*, 5596. (d) Spino, C; Tu, N. *Tetrahedron Lett.* **1994**, *35*, 3683. (e) Grieco, P. A.; Collins, J. L.; Moher, E. D.; Fleck, T. J.; Gross, R. S. *J. Am. Chem. Soc.* **1993**, *115*, 6078. (f) Grieco, P. A.; VanderRoest, J. M. *J. Am. Chem. Soc.* **1993**, *115*, 5841. (g) Moher, E. D.; Grieco, P. A.; Collins, J. L. *J. Org. Chem.* **1993**, *58*, 3789. (h) Spino, C; Liu, G. *J. Org. Chem.* **1993**, *58*, 817. (i) Moher, E. D.; Collins, J. L.; Grieco, P. A. *J. Am. Chem. Soc.* **1992**, *114*, 2764. (j) Fleck, T. J.; Grieco, P. A. *Tetrahedron Lett.* **1992**, *33*, 1813. (k) Stojanac, H.; Valenta, Z. *Can. J. Chem.* **1991**, *69*, 853. (l) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595. (m) Sasaki, M.; Murae, T.; Takahashi, T. *J. Org. Chem.* **1990**, *55*, 528. (n) Kim, M.; Kawada, K.; Gross, R. S.; Watt, D. S. *J. Org. Chem.*, **1990**, *55*, 504. (o) Collins, J. L.; Grieco, P. A.; Gross, R. S. *J. Org. Chem.*, **1990**, *55*, 5816. (p) Gross, R. S.; Grieco, P. A., Collins, J. L.; *J. Am. Chem. Soc.* **1990**, *112*, 9436. (q) Grieco, P. A., Nunes, J. J.; Gaul, M. D.; *J. Am. Chem. Soc.* **1990**, *112*, 4595. (r) Kim, M.; Applegate, L. A.; Kawada, K.; Watt, D. S. *Synth. Commun.* **1990**, *20*, 989. (s) Kawada, K.; Kim, M.; Watt, D. S. *Tetrahedron lett.*, **1989**, 30, 5989. (r) Grieco, P. A.; Nargund, R. P.; Parker, D. T. *J. Am. Chem. Soc.* **1989**, *111*, 6287. Earlier synthetic efforts are described by Watt's excellent review, see Kawada, K.; Kim, M.; Watt, D. S. *Org. Prep. Proc. Int.*, **1989**, *21*, 521.
(5) Tresa, J.-P.; Alais, L.; Polonsky, J. *C. R. Seances Acad. Sci., Ser. C* **1971**, *273*, 601.
(6) Kupchan, S. M.; Streelman, D. R. *J. Org. Chem.*, **1976**, *41*, 3481.
(7) (a) Shing, T. K. M.; Tang, Y.*J. Chem. Soc., Perkin Trans 1* **1994**, 1625. (b) *Idem. J. Chem. Soc., Chem. Commun.* **1992**, 341. (c) *Idem. Tetrahedron,* **1990**, *46*, 2187. (d) Shing, T. K. M.; Tang, Y.; Malone, J. F. *J. Chem. Soc. Chem. Commun.*, **1989**, 1294.
(8) Mander, L. N.; Sethi, P. *Tetrahedron Lett.* **1983**, *24*, 5425.
(9) Masamune, S.; Sato, T.; Kim , B.; Wollmann, T. A.; *J. Am. Chem. Soc.***1986**, *108*, 8279.
(10) All new compounds gave satisfatory spectral and analytical data.
(11) Ishihara K.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 3791.
(12) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

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