Direct Asymmetric Entry into the Cytotoxic 8,9-Secokaurene Diterpenoids. Total Synthesis of (−)-*O*-Methylshikoccin and (+)-*O*-(Methylepoxy)shikoccin

Leo A. Paquette,* Dirk Backhaus, and Ralf Braun

Evans Chemical Laboratories, The Ohio State University Columbus, Ohio 43210

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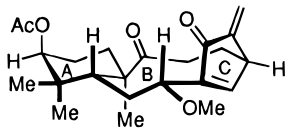
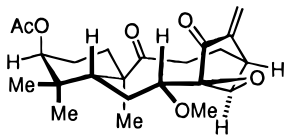
Plants of the genus *Rabdosia* (Labiatae) are well recognized to produce structurally unusual diterpenoids which exhibit potent cytotoxicity against HeLa, KB, and FM 3A/B cells, Ehrlich ascites and Walker intramuscular carcinomas, and P388 lymphocytic leukemia.[1] In large part, these properties are concentrated within a small group of 8,9-seco-*ent*-kaurenes typified by shikodomedin,[2] shikoccin,[3] rabdoshikoccin A and B,[4] rabdolatifolin,[5] rabdoumbrosanin,[6] and *O*-methylshikoccin (**1**).[7] In a number of these cases, the corresponding epoxides such as



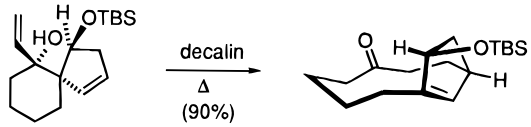
1



2

O-(methylepoxy)shikoccin (**2**) co-occur as equally potent antitumor constituents.[1] The potential of these agents as biological probes and the bridgehead olefinic nature of **1** and its analogs provided the incentive for this synthetic undertaking. We report here the first successful entry to this compound class in the form of **1** and **2**.

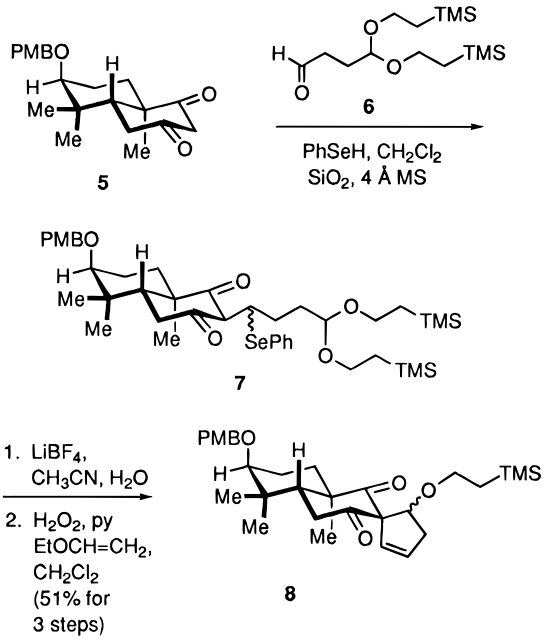
The strategy is based on the recognition that the oxygenated bicyclo[7.2.1]dodecene subunit which is embodied within the B/C rings of **1** can be quickly elaborated via oxy-Cope rearrangement of a spirocyclopentenol. In the model reaction previously reported,[8] **3** was transformed in 90% yield into **4**



3 **4**

when heated in decalin solution. Despite the success of this sigmatropic reaction, a concern regarding its adaptability to the proposed syntheses arose because of the conformational flexibility of **3**, a property which is not shared by any required transfused decalin homolog. This appreciably reduced structural mobility did indeed prove to be troublesome. In fact, early studies quickly revealed that the spiroalkylation technology

Scheme 1



which had served so very well for the preparation of **3**[8] was not serviceable in more highly functionalized and more rigid carbocyclic networks.

Accordingly, the assembly of **8** was accomplished by application of a modified Knoevenagel procedure.[9] This convenient three-step maneuver (Scheme 1) features condensation of enantiopure 1,3-dione **5**[10] with aldehyde **6**[11] under conditions where the 2-alkylidene adduct is intercepted with phenylselenol as in **7**. The selection of **6** from among a host of related acetals was predicated on the facility of the subsequent spirocyclization and the feasibility of diastereomer separation at the stage of **9**−**11**. Exposure of **7** to $LiBF_4$ in moist acetonitrile[12] resulted in ready ring closure. Without purification, selenoxide elimination was undertaken to provide **8** as a 1:1 mixture of epimers in 51% overall yield. That these two products differ in stereochemistry uniquely at the site of the protected hydroxyl became quite apparent from those chemical interconversions described in Scheme 2 and ultimately by virtue of X-ray crystallographic analysis of **12**. Consequently, ring closure had necessarily to occur totally via generation of an *equatorial* carbon−carbon bond, thereby guaranteeing proper absolute configuration at the bridgehead stereogenic center subsequent to the impending Cope rearrangement.

Since the two carbonyl groups in **8** experience widely different steric shielding, it was anticipated that chemoselectivity would be reliably achieved during Dibal reduction. Indeed, three alcohols were formed (Scheme 2) and these could be obtained in individually pure condition by chromatography on silica gel when the 2-(trimethylsilyl)ethyl protecting group was in place. It is noteworthy that hydride delivery occurred only from below when the C-ring oxygen was projected toward the reaction center (see **9**), a consequence of steric approach control. In contrast, the α-isomer gave rise to both **10** and **11**. Further experimentation revealed that, while **9** is surprisingly resistant to epimerization by retroaldol ring opening, **10** and **11** are slowly

(1) (a) Fuji, K.; Xu, H.-J.; Tatsumi, H.; Imahori, H.; Ito, N.; Node, M.; Inaba, M. *Chem. Pharm. Bull.* **1991**, *39*, 685 and relevant references cited therein. (b) Nagao, Y.; Ito, N.; Kohno, T.; Kuroda, H.; Fujita, E. *Chem. Pharm. Bull.* **1982**, *30*, 727. (c) Fuji, K.; Node, M.; Ito, N.; Fujita, E.; Takada, S.; Unemi, N. *Chem. Pharm. Bull.* **1985**, *33*, 1038.

(2) Fujita, T.; Takeda, Y.; Shingu, T.; Kido, M.; Taira, Z. *J. Chem. Soc., Chem. Commun.* **1982**, 162.

(3) Fujita, E.; Ito, N.; Uchida, I.; Fuji, K.; Taga, T.; Osaki, K. *J. Chem. Soc., Chem. Commun.* **1979**, 806.

(4) Takeda, Y.; Futatsuishi, Y.; Matsumoto, T.; Terada, H.; Otsuka, H. *Phytochemistry* **1994**, *35*, 1289.

(5) Takeda, Y.; Fujita, T.; Ueno, A. *Phytochemistry* **1983**, *22*, 2531.

(6) Takeda, Y.; Ichihara, T.; Fujita, Y.; Ueno, A. *Chem. Pharm. Bull.* **1989**, *37*, 1213.

(7) (a) Node, M.; Ito, N.; Fuji, K.; Fujita, E. *Chem. Pharm. Bull.* **1982**, *30*, 2639. (b) Node, M.; Ito, N.; Uchida, I.; Fujita, E.; Fuji, K. *Chem. Pharm. Bull.* **1985**, *33*, 1029.

(8) (a) Ladouceur, G.; Paquette, L. A. *Synthesis* **1992**, 185. (b) Paquette, L. A.; Ladouceur, G. *J. Org. Chem.* **1989**, *54*, 4278.

(9) Fuchs, K.; Paquette, L. A. *J. Org. Chem.* **1994**, *59*, 528.

(10) Prepared from a Wieland−Mischer ketone of >99% enantiomeric purity by the following sequence: (a) ethylene glycol, H^+. (b) CH_3I, KO*t*-Bu, *t*-BuOH. (c) L-Selectride. (d) TMSCl, imid; CrO_3, 3,5-Me_2-pyrazole; H_3O^+. (e) Li, NH_3. (f) NaH, PMBCl, DMF; H_3O^+.

(11) Prepared from β-bromoacetaldehyde dimethyl acetal by displacement with cyanide ion, acetal exchange with β-trimethylsilyl ethanol (TsOH, toluene, heat), and Dibal-H reduction.

(12) Lisphutz, B. H.; Harvey, D. F. *Synth. Commun.* **1982**, *12*, 267.

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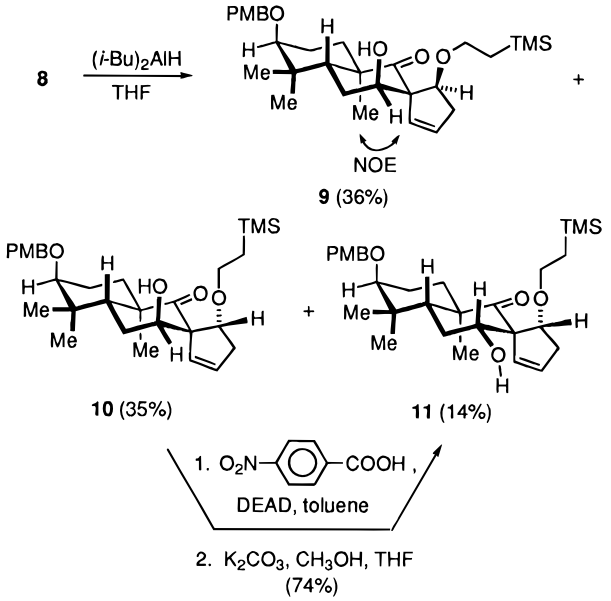
Scheme 2

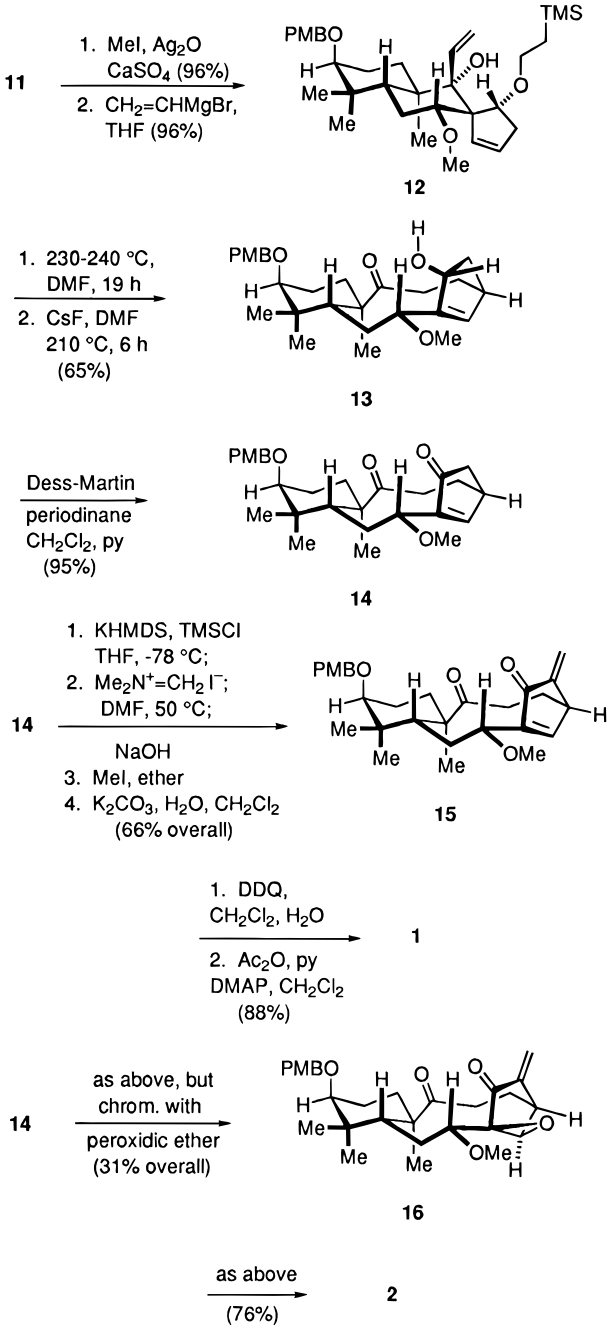


interconverted in methanol containing K_2CO_3. On this basis, it is difficult to assess the degree of stereoselectivity with which their ketone precursor is reduced. Application of the Mitsunobu protocol to **10** provided additional **11**, such that the net proportion of **9** to **11** ultimately approximated 1:1.

Although the ensuing documentation focuses only on the further use of **11**, suffice it to say that **9** can also be transformed into **1** and **2**.[13] Following the O-methylation of **11**, the resultant methoxy ketone was reacted with vinylmagnesium bromide. This two-step process gave rise exclusively to **12** (Scheme 3). The time had now come to evaluate the oxy-Cope rearrangement. On the basis of several exploratory experiments, the decision was made to proceed with DMF as the solvent of choice. When heated to 230−240 °C for 19 h in this medium, **12** was transformed into a single detectable isomer (TLC and NMR analysis). At this point, cesium fluoride was introduced and the DMF solution was brought back to 210 °C in order to effect hydroxyl deprotection directly. Subsequent workup afforded **13** in 65% yield and set the stage for oxidation to diketone **14** with the Dess−Martin periodinane reagent.[14] Extensive COSY and NOE studies on **14** confirmed the indicated stereochemistry.

The highly regioselective transformation of **14** into its *exo*-methylene derivative was very efficiently accomplished by use of the Eschenmoser salt.[15] If the product of the Mannich reaction is chromatographed on silica gel with ether that contains peroxides, epoxidation occurs to deliver **16** ultimately two steps later. Although Bredt's rule is not at all violated in **15**, sufficient ring strain evidently resides in its bridgehead double bond to endow this site with heightened reactivity. This phenomenon proved to be nicely conducive to our goal, as deprotection[16]/acetylation of **15** and **16** afforded high-quality samples of **1** and **2**, respectively.[17] That (−)-*O*-methylshikoccin and (+)-*O*-(methylepoxy)shikoccin were indeed in hand derived from careful direct comparison of ^1H and ^{13}C NMR data with those recorded on authentic samples of **1** and **2**.[18]

Scheme 3



In summary, we have achieved a total synthesis of **1** in 15 steps and in 6.7% overall yield from **5** via only **11**. Efficiency is further heightened when **9** is also included. The route also allows convenient access to the epoxy derivative **2**.

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Supporting Information Available: Text describing spectral characterization of key compounds (5 pages). See any current masthead page for ordering and Internet access instructions.

JA962799D

(13) Backhaus, D. Unpublished results. This information will be included in the full paper.

(14) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(15) (a) Holy, N.; Fowler, R.; Burnett, E.; Lorenz, R. *Tetrahedron* **1979**, *35*, 613. (b) Caputo, R.; Ferreri, C.; Mastroianni, D.; Palumbo, G.; Wenkert, E. *Synth. Commun.* **1992**, *22*, 2305.

(16) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.

(17) Yields are reported for isolated compounds purified by flash chromatography on silica gel. All new compounds exhibited IR, $^1H/^{13}C$ NMR, and high-resolution mass spectra in complete accord with their assigned structures. Elemental analyses were also obtained in many cases.

(18) In the original report,[7b] the signals due to H-13 (δ 3.20) and OCH_3 (δ 3.26) were erroneously claimed to appear at δ 3.34 and 3.18, respectively. The spectra graciously provided to us by the original authors immediately revealed the source of confusion to be typographical.