Synthetic Studies Targeted at the Cytotoxic 8,9-Seco-*ent*-kaurene Diterpenes. Concise Complementary Stereocontrolled Construction of the Bridgehead Olefin Core

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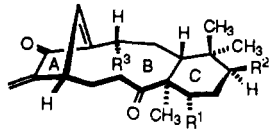
Summary: Methodology for rapid construction of the A/B subunit of the 8,9-seco-*ent*-kaurenes is described that takes advantage of complementary stereocontrol in consecutive intramolecular Claisen rearrangement, allylsilane–carboxaldehyde cyclization, and oxy-Cope sigmatropic steps.

Sir: Shikodomedin (**1a**),[1] a potent inhibitor of cultured FM 3A/B rat mammary cancer cells,[2] has attracted interest because of its cytotoxic activity. More recently,

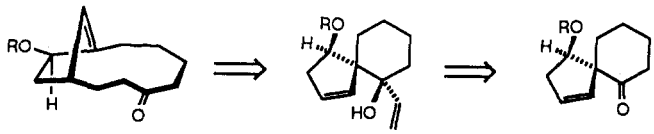


1a, R^1=OAc, R^2=OAc, R^3=OH
b, R^1=OH, R^2=H, R^3=OH
c, R^1=H, R^2=OAc, R^3=OH
d, R^1=H, R^2=OAc, R^3=OMe

rabdolatifolin (**1b**),[3] shikoccin (**1c**),[4] and *O*-methylshikoccin (**1d**)[4] have been isolated from related *Rabdosia* plant sources to join **1a** as the few existing members of the previously unknown 8,9-seco-*ent*-kaurene class of diterpenes. This small, but biologically potent group of tricyclic natural products are uniformly characterized by a 5-methylene-2-cyclopentenone part structure, the intracyclic double bond of which is positioned at a bridgehead site within a bicyclo[7.2.1]dodec-1,12-ene-6,11-dione framework. X-ray confirmation of this fascinating structural feature is available in the case of **1a**.[1]

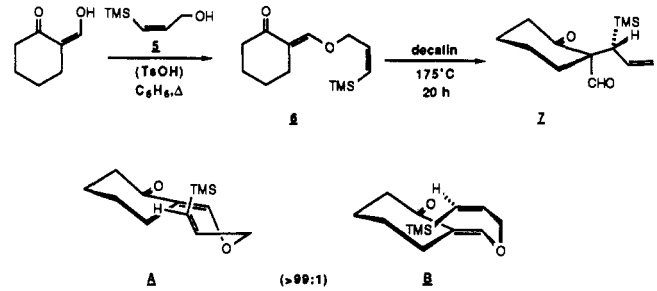
In this communication, we describe the successful development of a route that concisely elaborates the unusual A/B subunit of these substances. The protocol takes advantage of complementary stereocontrol at several steps and makes provision for incorporation of the appropriately functionalized C ring and the hydroxyl (or methoxyl) C-2 substituent.

Careful analysis of the target ring system revealed that **2** bears an oxy-Cope relationship to **3**. Also recognized in the arrangement of atoms found in **3** was the potential for its direct preparation from **4**. From the retrosynthetic



2 **3** **4**

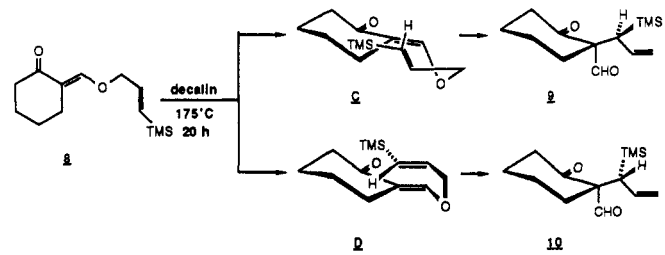
perspective, therefore, this spirocyclic ketone gave indication of being the key intermediate. With this goal in mind, (*Z*)-3-(trimethylsilyl)-2-propen-1-ol (**5**)[5,6] was dehydratively coupled[7] with 2-(hydroxymethylene)cyclohexanone to give **6**. This adaptation of the Kuwajima procedure[8] was necessary to realize enol ether formation in reasonable (61%) yield.[9] The Claisen rearrangement of **6** was expected to adhere strictly to a chair transition-state geometry (A) because of the highly adverse steric congestion attending the boat conformer alternative (B).[10]



5 **6** **7**

A (>99:1) **B**

This course of events transforms the olefinic geometry localized in both double bonds of **6** into two unequivocally defined stereogenic centers in **7** (68% isolated). The importance of the favorable steric control elements found in A to the excellent stereochemical complementary can best be underscored by comparison with the response of **8** (from the *E* allylic alcohol[11]) to the identical reaction conditions. In the case of the isomer, 25% of the aldehydic product mixture arises by way of boat transition state D because it is rather less crowded than C.



8 **C** **9** **D** **10**

Ethylaluminum dichloride smoothly promoted[12] 5-*exo*,*trig* cyclization in **7** to deliver **11a** exclusively (65% after conversion to **11b**). This stereochemical result is consistent only with adoption by the Lewis acid complex of the antiperiplanar transition state *E*, wherein coordination of oxygen to aluminum from that direction anti to the R group of the aldehyde[13] engenders facial selectivity at carbon via the less sterically encumbered orientation of the reacting groups. The alternative option F is seen

(1) Fujita, T.; Takeda, Y.; Shingu, T.; Kido, M.; Taira, Z. *J. Chem. Soc., Chem. Commun.* **1982**, 162.
(2) Fujita, T.; Takeda, Y.; Shingu, T. *Phytochemistry* **1979**, *18*, 299.
(3) Takeda, Y.; Fujita, T.; Yeno, A. *Phytochemistry* **1983**, *22*, 2531.
(4) Node, M.; Ito, N.; Uchida, I.; Fijuta, E.; Fuji, K. *Chem. Pharm. Bull.* **1985**, *33*, 1029.
(5) To our knowledge, this *Z* alcohol has not previously been synthesized in pure form.[11] Our route to stereochemically pure material involved bis-silylation of propargyl alcohol, hydroboration of the triple bond with dicyclohexylborane, and protonolysis with acetic acid. The possibility of a one-pot procedure as devised for the methylstannane analogue[6] exists.
(6) Corey, E. J.; Eckrich, T. M. *Tetrahedron Lett.* **1984**, *25*, 2415.
(7) Seifert, P.; Schinz, H. *Helv. Chim. Acta* **1951**, *34*, 728.
(8) Kuwajima, I.; Tanaka, T.; Atsumi, K. *Chem. Lett.* **1979**, 779.
(9) Use of the ethyl ether of 2-(hydroxymethylene)cyclohexanone resulted in extensive decomposition.
(10) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423.
(11) Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595.
(12) (a) Schinzer, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 308. (b) Denmark, S. E.; Weber, E. J. *J. Am. Chem. Soc.* **1984**, *106*, 7970. (c) Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655.
(13) (a) Itoh, A.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1979**, 1783. (b) Andersen, N. H.; McCrae, D. A.; Grotjohn, D. B.; Gable, S. Y.; Theodore, L. J.; Ippolito, R. M.; Sarkar, T. K. *Tetrahedron* **1981**, *37*, 4069. (c) Schinzer, D. *Synthesis* **1988**, 263. (d) Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React.*, in press.

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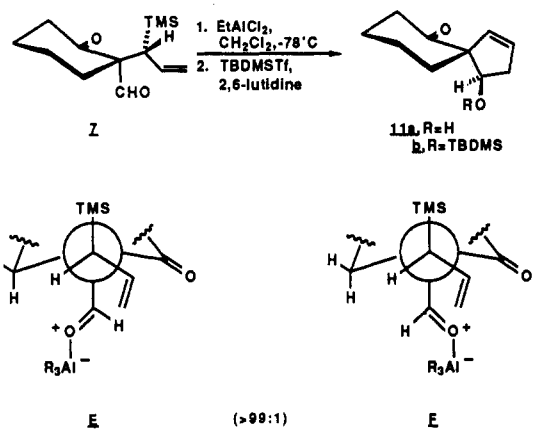
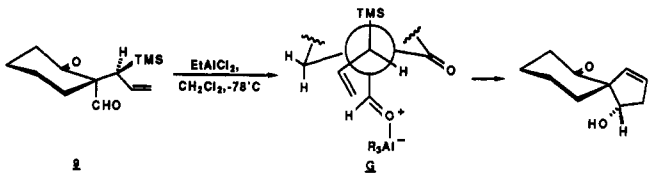
to be significantly more crowded.[14]



Having arrived at **11a** in only three steps, we prepared for the pivotal [3,3] sigmatropic rearrangement by silylating **11a** and condensing **11b** with vinylcerium dichloride to deter enolization.[15] The complete stereocontrol achieved in this reaction (75% yield of **12**) is believed to stem from axial attack of the organometallic on that conformer of **11b** where the more sterically demanding β-siloxy-substituted carbon is projected equatorially. Heating **12** in decalin at 190 °C for 9 h resulted in its efficient (92%) transformation into **13**.[16,17] The 300-MHz ^{1}H NMR spectrum of **13** (in $CDCl_3$) is characterized by signals at δ 5.17 (s, 1 H) and 4.63 (d, J = 8.6 Hz, 1 H); its IR carbonyl absorption in the same medium appears at 1670 cm^{-1}.

(14) The complementary process, viz. cyclization only to the epimeric keto alcohol, is given by **9** because of the entirely similar steric advantages enjoyed by G:

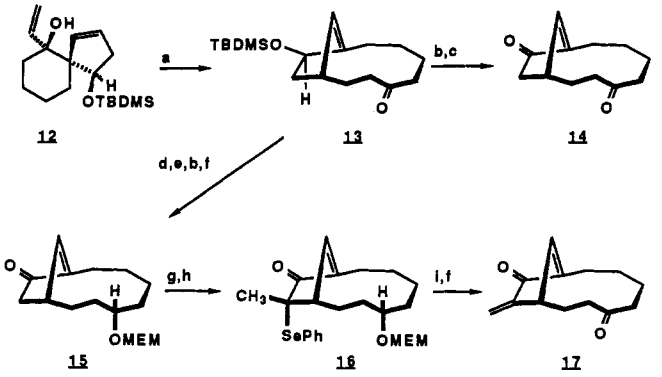


(15) (a) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233. (b) Imamoto, T.; Sugiura, Y. *J. Organomet. Chem.* **1985**, *285*, C21. (c) Imamoto, I.; Takiyama, N.; Nakamura, K. *Tetrahedron Lett.* **1985**, *26*, 4763.

(16) The structure assigned to each new compound was in accord with its infrared, 300 ^{1}H NMR, 75 MHz ^{13}C NMR, and high resolution mass spectra. In addition, analytical samples of new (and stable) compounds gave satisfactory C and H combustion analyses within 0.4%.

(17) The anion-accelerated version of this process resulted in tar formation. This turn of events appears to result from the extreme sensitivity of **13** to base. All attempts to deprotonate this ketone, even under the mildest of conditions, have resulted in similar resinification.

Introduction of a second carbonyl group as in **14** could be accomplished without event, although this macrocyclic diketone proved to be a sensitive compound. More relevant to our synthetic plan at this point, however, was the preparation of **17**. To this end, the existing carbonyl group



[a] decalin,190°C. [b] Bu_4NF. [c] MnO_2. [d] $(i\text{-Bu})_2AlH$. [e] MEMCl, $(i\text{-Pr})_2NEt$. [f] CrO_3·2py. [g] KHMDS; PhSeCl. [h] KH, CH_3I. [i] $TiCl_4$,CH_2Cl_2.

was protected by totally stereoselective reduction (exo hydride delivery assumed) and conversion to the MEM ether (80%).[18] Sequential treatment of this intermediate with tetra-*n*-butylammonium fluoride and CrO_3·2py produced **15** (83% overall). Subsequent studies revealed that the enolate anion derived from this ketone captures electrophiles virtually exclusively from its exo surface. In accord with this strong kinetic bias, it was possible to prepare the α-phenylseleno ketone and to methylate this intermediate, thereby delivering **16** (39%). Following unmasking of the hydroxyl group, recourse to the chromium trioxide dipyridine complex[19] effected concurrent oxidation to the ketone and selenoxide elimination,[20] albeit in low yield (27%). Diene dione **17** exhibited spectral properties fully commensurate with its structural assignment.

Application of the described methodology to the synthesis of 8,9-seco-*ent*-kaurenes **1a–d** beginning with suitably functionalized bicyclic analogues of **6** is currently underway.

Acknowledgment. We thank the National Institutes of Health for support of this research program through Grant CA-12115.

(18) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.

(19) Ratcliffe, R.; Rodehurst, R. *J. Org. Chem.* **1970**, *35*, 4000.

(20) For analogy with sulfone β-eliminations, consult: Mandai, T.; Mori, K.; Hasegawa, K.; Kuwada, M.; Otera, J. *Tetrahedron Lett.* **1984**, *25*, 5225.