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SYNTHETIC ENTRY INTO THE *ent*-KAURENE FRAMEWORK. APPLICATION OF AN UNPRECEDENTED TRANSANNULAR CYCLIZATION FOR FORMING THE CENTRAL BOND COMMON TO THE B AND C RINGS

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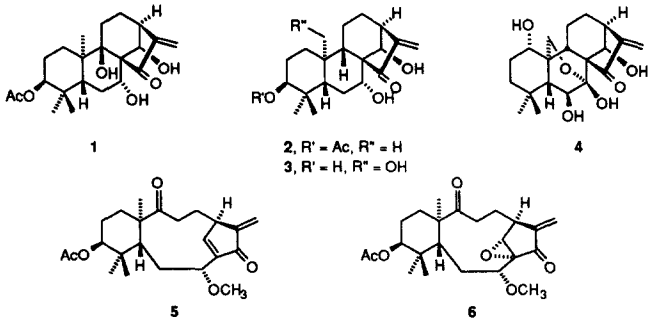
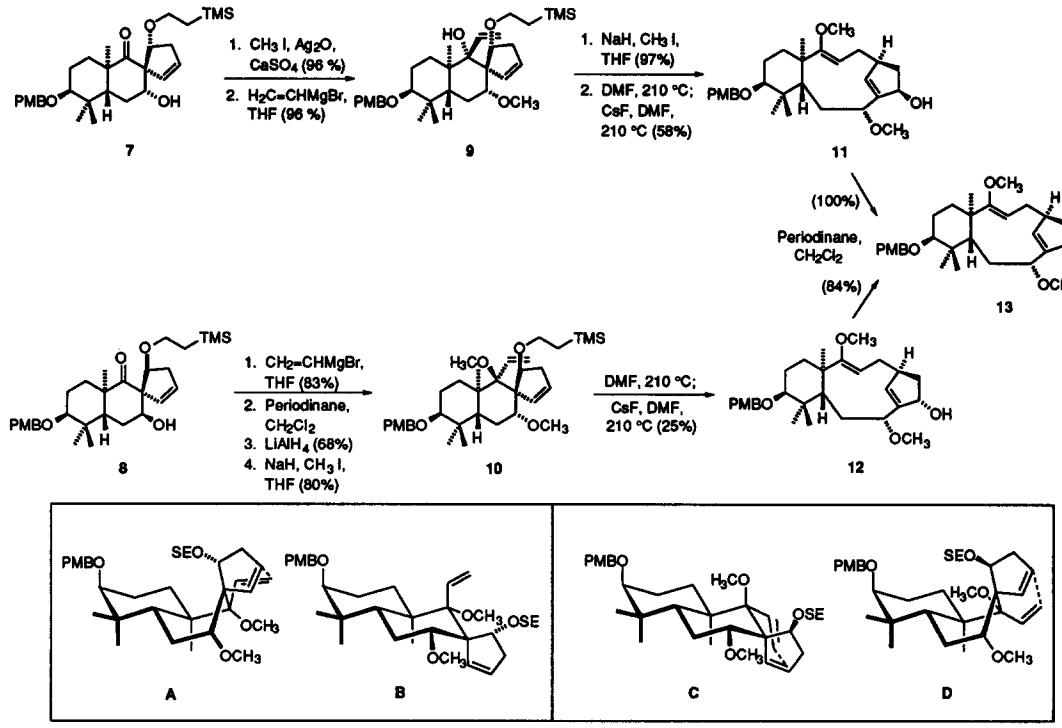
Abstract: A stereocontrolled means for constructing the *ent*-kaurene framework is described. The key transformation involves transannular ring closure of an 8,9-seco precursor with migration of an interstitial methoxyl group. Copyright © 1996 Elsevier Science Ltd

Many reports have documented the fact that plants of the genus *Rabdosia* (Labiatae) constitute a veritable treasure trove of biologically active 8,9-seco-*ent*-kaurenes and their tetracyclic (*ent*-kaurene) counterparts. Representative examples in the latter category include the antitumor agent shikoccidin (**1**),[1] its 9-deoxy analog known as leukamenin E (**2**),[2] and the side-chain oxygenated systems coestinol (**3**)[3] and oridonin (**4**).[4] As a sequel to our recently completed asymmetric syntheses of (-)-O-methylshikoccin (**5**) and (+)-O-methylepoxyshikoccin (**6**),[5] we have now developed an unusual transannular cyclization process that constitutes a uniquely different synthetic entry to the *ent*-kaurene framework.[6]



We chose initially to transform the hydroxy ketones **7** and **8** available from our earlier study into the single advanced tricyclic intermediate **13** (Scheme 1). For the α-hydroxy diastereomer, the most satisfactory pathway involved O-methylation and subsequent stereocontrolled addition of vinylmagnesium bromide to provide **9**. A second O-methylation was followed by thermal oxy-Cope rearrangement[7] and removal of the β-(trimethylsilyl)ethyl (SE) group. The last two steps leading to **11** could be accomplished in a one-pot procedure by heating a DMF solution at 210 °C (sealed

Scheme 1



tube) for 4.5 h, cooling, adding CsF, and returning to 210 °C for another 6.5 h. The overall yield was 58%. From **8**, the conversion could be accomplished by sequential vinylation, periodinane oxidation,[8] hydride reduction, and O-methylation. Once **10** had been produced, treatment in the predescribed manner afforded **12**. The deprotection step was not as effective in this instance, giving rise to the desired alcohol in 25% yield alongside 37% of the product resulting from loss of only the TMS group. In turn, **11** and **12** were oxidized smoothly to **13**, $[\alpha]_D^{23}$ -46.4° (*c* 1.21, $CHCl_3$).

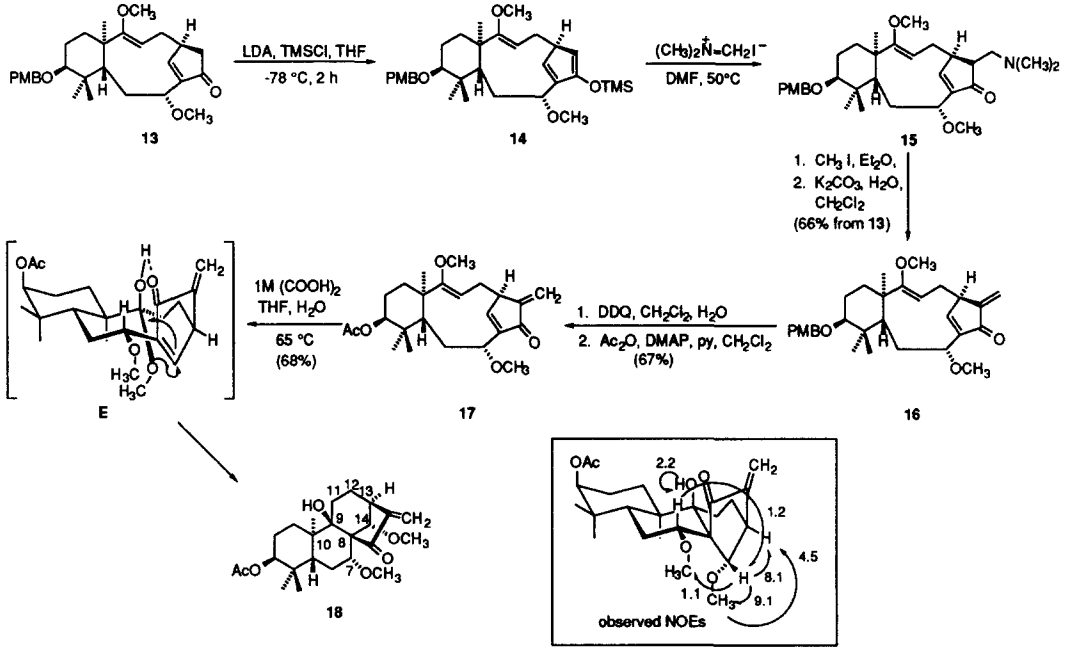
The mechanistic details of the pair of [3,3] sigmatropic shifts are worthy of comment. Alcohol **11** proved to be sufficiently crystalline to permit X-ray crystallographic analysis. The depicted stereochemistry was thereby confirmed. In view of the common linkup to **13**, alcohol **12** must share the analogous *Z*-configured enol ether and trans relationship between the OPMB substituent and bridgehead cyclopentenyl proton. When the double bonds in the precursor are arranged trans as in **9**, only in the chair-boat-chair arrangement **A** is proximity realized and rearrangement likely to proceed (compare **B**). The evolution of a (*Z*)-configured enol ether is in accordance with this transition state model. For **10**, on the other hand, the same eventuality requires either passage through a chair-chair-chair arrangement (**C**) to furnish the *E* product, which subsequently isomerizes at the elevated temperatures, or involvement of the higher energy chair-boat-boat construct **D** which would lead directly to the *Z* geometry. *It is important to note that the absolute*

*configuration of the newly formed stereogenic center in the ten-membered ring depends only on the configuration of the spirocyclic carbon, such that **9** and **10** must respond identically in installing this key element of chirality irrespective of the transition state adopted.*

The Eschenmoser sequence[9] was determined to be most efficient in elaborating the exo-methylene moiety (Scheme 2). The transiently generated silyl enol ether **14** was coupled with dimethyl(methylene)ammonium iodide in DMF[10] at 50 °C to deliver **15** diastereoselectively. Removal of the nitrogen functionality via Hoffmann elimination afforded **16** in 66% yield over four steps. For the purpose of making the cyclization product more directly comparable to shikoccidin (1), the OPMB protecting group in **16** was transformed into an acetate as in **17**. When heated at 65 °C with oxalic acid in aqueous THF for 3 h, **17** was isomerized to **18** (68%).

The structural assignment to **18** is based on extensive NMR analysis. Thus, two new quaternary carbon signals appear at 63.6 and 78.6 ppm (in C_6D_6) and these can be assigned as C-8 and C-9 (compare 66.2 and 81.1 ppm for **1** in $CDCl_3$).[1] COSY experiments clearly defined H-3, H-7, H-13, and H-14, setting the stage for long-range DEPT experiments.[11] Independent irradiation of the two methoxy carbons (3.42 and 3.31 ppm) revealed coupling to the methine carbons C-7 and C-14, respectively, thereby proving that neither resided at C-9. The stereodisposition of H-7 and H-14 was confirmed by taking note of the dihedral angle dependence of $^3J_{C,H}$ couplings (maximum

Scheme 2



values for 0 ° and 180°; vanishing effects for 90°). The most revealing information was derived from the following correlations

–C<u>H</u>OCH$_3$ (H-7, 4.41 ppm): C-8 ($^2J_{C,H}$), O<u>C</u>H$_3$, C-14, C-15;

–C<u>H</u>OCH$_3$ (H-14, 4.13 ppm): C-8 ($^2J_{C,H}$), O<u>C</u>H$_3$, C-9, C-12;

and from ^{1}H,^{1}H NOE effects shown in the inset.

Arrival at **18** can be economically rationalized in terms of exo hydration of the enol ether functionality.[12] With formation of hemiketal **E**, the endo methoxyl group now finds itself thrust well into the interstitial space within the interior of the medium-sized ring and in rather close proximity to C-14. An intramolecular Michael addition is thereby triggered. The rebonding events could occur synchronously as shown, or via an intermediate keto enol which then cyclizes to the observed product. Intermolecular capture of methanol can be excluded because steric factors would regulate approach only to the molecular exterior and this configurational requirement is not seen at C-14. Furthermore, the rearrangement was performed at high dilution (3 x 10^{-6} mol/mL), making recapture of liberated methanol quite unlikely.

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