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ENANTIOSELECTIVE SYNTHESIS OF NATURAL (+)-DACTYLOXENE-B AND -C BY ACTUATION OF OXONIUM ION-INITIATED PINACOL REARRANGEMENT

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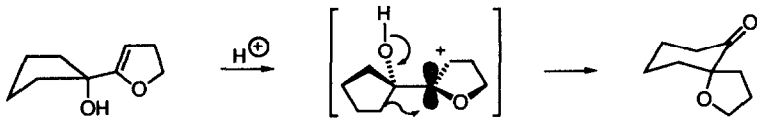
Abstract: A direct route is described for assembling the spirocyclic framework of two sesquiterpene ethers derived biogenetically from the cyclization of farnesol with rearrangement of a methyl group.

Tertiary allylic alcohols derived from the 1,2-addition of α-lithiated vinyl ethers to ketones are now recognized to undergo acid-catalyzed conversion to oxonium intermediates typified by **1** rather than S_N1 ionization to allyl cations.[1] When ring strain relief can be accommodated, a pinacol-like rearrangement ensues to give α-alkoxy ketones such as **2**.[2] The recent discovery of this reaction has



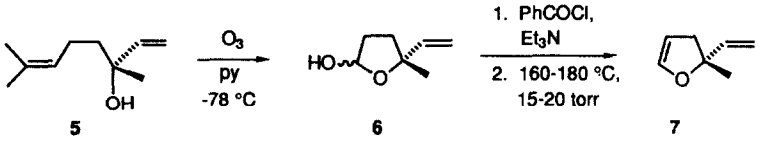
1 **2**

3 **4**

ignited an interest in its deployment in the context of enantiocontrolled natural products synthesis. To this end, we embarked on a convergent approach to both (+)-dactyloxene-B (**3**) and (+)-dactyloxene-C (**4**) in which the 2,3-dihydrofuran and cyclopentanone building blocks have been prefabricated in enantioenriched condition and subsequently amalgamated. These sesquiterpene ethers, originally isolated from the sea hare *Aplysia dactylomella*,[3] possess a close structural relationship to the widely distributed theaspiranes, agents valued for their flavoring and organoleptic properties.[4] Both classes of compounds have previously been the subject of successful synthetic undertakings.[5-7] The absolute configurations of **3** and **4** have earlier been assigned on the basis of a *de novo* total synthesis.[5b]

Our initial focus was placed on acquiring **7** having the requisite *R* configuration. As seen in Scheme I, this objective was realized without event by ozonolysis of commercialy available (*R*)-(-)-linalool (**5**)[8] in a CH_2Cl_2-pyridine solvent system at -78 °C.[9] Under these conditions, the more

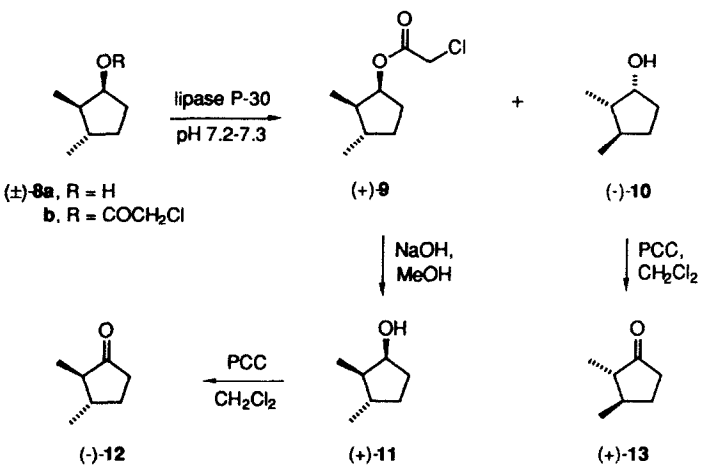
Scheme I



electron-rich double bond is attacked regioselectively to deliver **6** as a 1:1 diastereomeric mixture. Maximized yields were realized if this oxidative cleavage was carried forward to approximately 65-70% consumption of **5**. In this way, unwanted by-product formation was circumvented and the unreacted linalool could be recovered quantitatively for recycling. To reach **7**, **6** was converted to its benzoate ester and heated to 160-180 °C under vacuum (15-20 torr)[10] in a Kugelrohr apparatus. As a consequence of the high volatility of **7**, $[\alpha]_D^{20}$ +0.42° (*c* 0.74, $CHCl_3$), losses were incurred in its recovery (unoptimized yields averaging ca 50%).

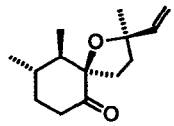
The second building block, (2*R*,3*S*)-2,3-dimethylcyclopentanone (**12**), was produced from the known racemic ketone[11] by L-Selectride reduction[12] to **8a**, formation of the (±)-chloroacetate **8b**, and enantioselective hydrolysis of this ester with lipase P-30[13] (Scheme II). When the enzymatic reaction

Scheme II



was allowed to proceed to the 54% level, the slower reacting ester **9** was enantioenriched to the extent of 79% ee, as established by Mosher ester analysis[14] of the corresponding alcohol **11**. The absolute configurations of the alcohols and ketones were assigned on the basis of data earlier published by Varech and co-workers.[15]

Coupling was satisfactorily realized by first treating **7** with *tert*-butyllithium to give the 5-lithio derivative, which was transmetalated with anhydrous $CeCl_3$ to provide the less basic vinyl cerate.[16,17] Following upon the introduction of **12**, the resulting alcohol was directly subjected to acid-catalyzed ring expansion in the presence of Dowex 50x4-400 resin in CH_2Cl_2 as solvent at room temperature. The four chromatographically separable major products obtained from this reaction in a combined



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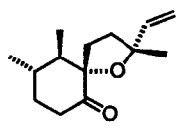

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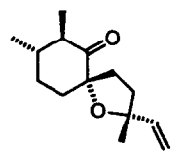

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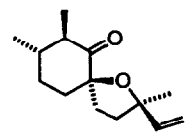

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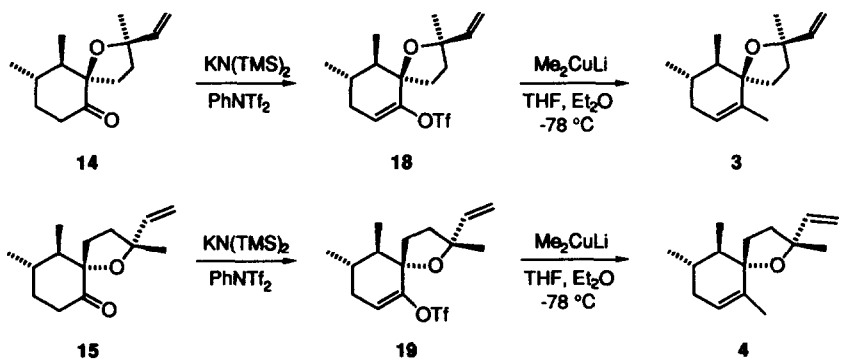
yield of 61-63% were assigned the structures shown on the basis of extensive nOe studies[18] and the subsequent conversion of **14** and **15** into **3** and **4**, respectively. The relative proportions of **14** (44%) and **15** (18%) indicate that Wagner-Meerwein shifting of the secondary carbon is the predominant rearrangement pathway, as expected.[19] The competing formation of **16** (15%) and **17** (23%) obviously signals that 1,2-migration of the primary carbon is reasonably competitive, presumably as a consequence of steric factors operating in the several available transition states.[20]

With quantities of **14** and **15** in hand, progression to the dactyloxenes was realized according to Scheme III. Each spirocyclic ketone was smoothly converted to its enol triflate by condensation of the enolate anions with N-phenyltriflimide.[21] The action of lithium dimethylcuprate[22] on these enol triflates afforded the targeted spirocyclic ethers.[23] The $[\alpha]_D$ values determined for **3**, +105.6° (*c* 0.65, $CHCl_3$), and **4**, +42.6° (*c* 0.72, $CHCl_3$) compare closely to prerecorded literature values,[3,5b]

Scheme III



In summary, the oxonium ion-initiated pinacol protocol has served to produce natural (+)-dactyloxene-B and -C from (*R*)-(-)-linalool in seven steps via a common intermediate.

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(18) These studies will be detailed in the full paper concerned with this investigation.

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(23) The steric congestion in the vicinity of the reactive center in both **18** and **19** was conducive to competing reduction of the C-OTf bond.

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