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A HIGHLY STEREOSELECTIVE SYNTHESIS OF DAVANONE

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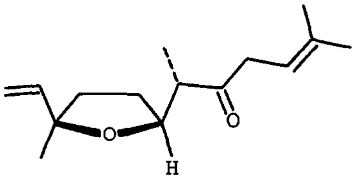
Iodocyclization of the anti 4-bromobenzyl ether acetate 4f is a key step in the first stereocontrolled synthesis of the trisubstituted tetrahydrofuran davanone.

Davanone (1), a sesquiterpene isolated from the flowering herb *Artemesia pallens*, was first characterized in 1968 by Sipma and van der Wal.[1] The relative stereochemistry was proposed independently by Naegeli[2] and Birch,[3] and proven by Ohloff and Giersch[4] in 1970. During the past decade there have been several syntheses of davanone and related compounds[2,3,5,6]; however, in each case a mixture of the four possible diastereomers was produced. In connection with our study of the stereocontrolled formation of substituted tetrahydrofurans,[7,8] we have developed a stereoselective synthesis of davanone, which we report here.

The substrate we required for application of our cis-2,5-substituted tetrahydrofuran synthesis[7] was a substituted benzyl ether derivative of diol 4a. This material was obtained by lithium aluminum hydride reduction of β-hydroxy ester 3,[10a] which in turn was produced from (E)-4-methyl-4-hexenal (2)[7] and the propanoate ester of BHT, using the anti-selective aldol condensation developed by Heathcock.[11] Diol 4a[10a] was obtained in 76% overall yield, with a stereochemical purity of 97.6%.

Our initial studies focussed only on the stereoselectivity of the tetrahydrofuran synthesis, hence no attempt was made at first to differentiate between the primary and secondary hydroxyl groups of 4a. Three bis(benzyl) ethers (4b-4d) were prepared and, along with the diol 4a itself, subjected to iodocyclization and potassium t-butoxide-induced elimination.[12] As expected,[7] the diol affords the trans compound 5a predominantly, while benzyl ethers 4b and 4c give the cis



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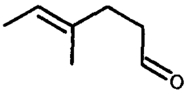

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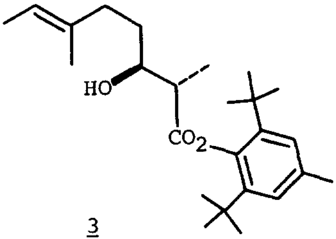

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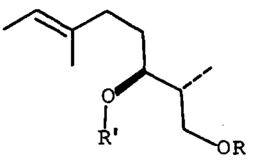

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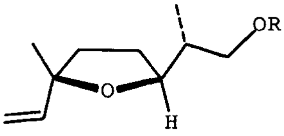

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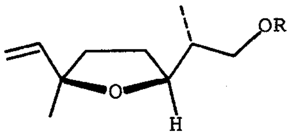

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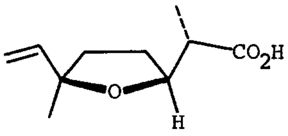

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a: R = R' = H
b: R = R' = $PhCH_2$
c: R = R' = $4\text{-}BrPhCH_2$
d: R = R' = $2,6\text{-}Cl_2PhCH_2$
e: R = Ph_3C, R' = $4\text{-}BrPhCH_2$
f: R = Ac, R' = $4\text{-}BrPhCH_2$

TABLE. Stereochemical Course of Cyclizations

Substrate	Solvent[a]	Ratio, **6**/**5**[b]
4a	MeCN	1:5
4a	CH_2Cl_2	1:1.5
4b	CH_2Cl_2	6:1
4c	CH_2Cl_2	16:1

[a] See footnote 12 for representative reaction conditions.
[b] Determined by 250-MHz ^1H-NMR.

isomers **6b** and **6c** with varying degrees of stereoselectivity, as indicated in the Table. The 2,6-dichlorobenzyl derivative **4d** does not react.

Although the 4-bromobenzyl derivative **6c** is formed with a high degree of selectivity, not surprisingly removal of the benzyl group is impractical in the presence of the allylic ether. However, the two hydroxyl groups of **4a** can readily be distinguished by selective protection of the primary one with trityl chloride. Subsequent alkylation with 4-bromobenzyl bromide then affords **4e** in 89% overall yield.[10a] Conversion of this material to the acetate **4f**,[10a,13] iodocyclization,[12] elimination, and hydrolysis provide the desired alcohol **6a**[10b] in 50% overall yield from **4e**. High-field ^{1}H-NMR analysis indicated that this material is comprised of a major and two minor diastereomers, presumably the *cis*-*anti*, *trans*-*anti*, and *cis*-*syn* compounds.

Jones oxidation of **6a** affords the acid **7**[10a] in 74% yield. Using the method of Birch et al.,[3] this compound is then converted to racemic davanone **1** in 39% yield by condensation with excess dimethallyllithium.[14] The spectral characteristics (^{1}H- and ^{13}C-NMR, IR, MS) of our synthetic material proved to be identical with those reported for natural davanone, and significantly different from those reported for its diastereomers.[2] Capillary GC analysis (12.5-m × 0.2-mm dimethylsilicone column, temp 50 → 250 °C) indicated that the ratio of diastereomers observed for the alcohol **6a** (above) is preserved in our final product, which consists of 2% of the *cis*-*syn*, 6% of the *trans*-*anti*, and 92% of the desired *cis*-*anti* davanone isomers.[16]

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10. The ^{1}H- and ^{13}C-NMR and IR spectra and (a) combustion or (b) high-resolution mass spectral analysis of this compound were fully consistent with the structure assigned.
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12. Representative cyclization/elimination conditions: substrate, 2.5 eq of I_2, and 0.1 eq of $NaHCO_3$ in CH_2Cl_2 stirred at 0°C for 1.5 hr; partitioned between aq. $Na_2S_2O_3$ and ether, dried and concentrated; treated with 6 eq of KO*t*-Bu in THF for 2 hr at 25°C.
13. Direct cyclization of the trityl benzyl ether **4e** was not successful, because of loss of the labile trityl ether during the reaction.
14. Dimethallyllithium was prepared from dimethallyl phenyl ether, using lithium-1% sodium dispersion in ether/THF.[15]
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16. The stereochemical assignments were confirmed by epimerization studies, which afforded all four davanone diastereomers as previously reported.[6a]

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