

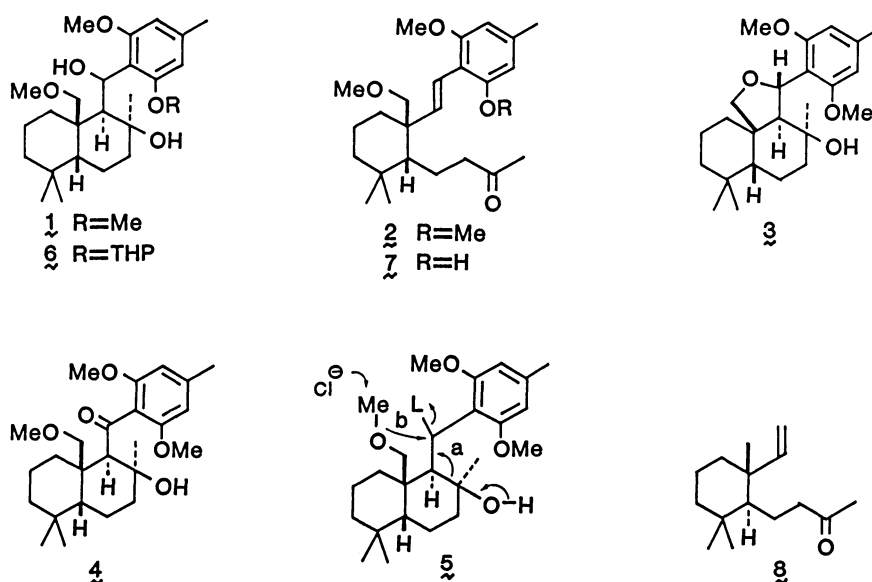
Remarkably Facile 1,3-Diol Fragmentation.
 Synthesis of a Seco-sesquiterpene of Tobacco

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A benzylic hydroxyl group activated by the 2,6-dimethoxy-4-methylphenyl group was proved to be a remarkably reactive nucleofuge in 1,3-diol fragmentation under mild conditions. 4-(2,2,6-Trimethyl-6-vinylcyclohexyl)-2-butanone, a seco-sesquiterpene, was synthesized by using a fragmentation product thereby obtained.

Fragmentation reactions¹⁾ are useful in degradative C-C bond cleavages and have been extensively utilized in structural and synthetic studies of natural products.

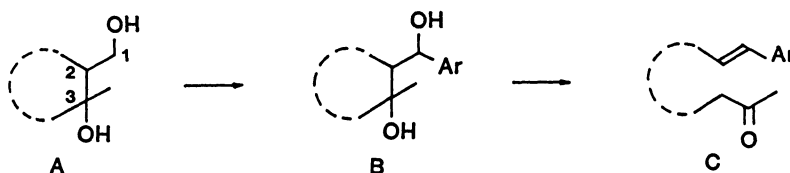
In the course of our synthetic study on siccanin,²⁾ an antibiotic mold metabolite, we have encountered with a remarkably facile 1,3-diol fragmentation. Exposure of 1,3-diol **1** to pyridinium chlorochromate in CH₂Cl₂ afforded ketone **2** and tetrahydrofuran **3** in 24% and 28% yields, respectively, along with a very minor amount of the expected ketone **4**. This result would be rationalized by presuming that a chromate ester group (L in **5**) initially formed at the benzylic position that was activated by the phenyl group substituted with three electron donating groups at ortho and para positions would act as a nucleofuge¹⁾ under acidic conditions to afford **2** and **3** in the fragmentation (path a) and neighbor-



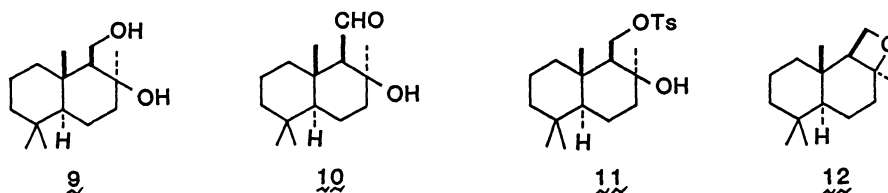
ing participation (path b)³⁾ modes, respectively.⁴⁾

Occurrence of such a facile fragmentation was also observed on the attempted deprotection of tetrahydropyranyl (THP) ether **6**. Under mild acidic conditions (AcOH-THF-H₂O or pyridinium *p*-toluenesulfonate (PPTS)),⁵⁾ not only deprotection but also concomitant fragmentation proceeded smoothly to give olefinic phenol **7** in quantitative yield.

For the C(2)-C(3) bond cleavage of 1,3-diol **A**, its primary hydroxyl is usually less effective as a nucleofuge than a secondary or tertiary one. The above findings indicate that in the corresponding secondary benzyl alcohol **B** readily derivable from **A**, its benzylic hydroxyl is readily activated by an electron donating aromatic group (Ar), and the fragmentation product **C** would be led from **B** without difficulty even under mild conditions. We wish to describe here our investigation on this methodology and an application to the synthesis of ()-4-(2,2,6-trimethyl-6-vinylcyclohexyl)-2-butanone (**8**), a seco-sesquiterpene isolated from sun-cured Greek tobacco.⁶⁾

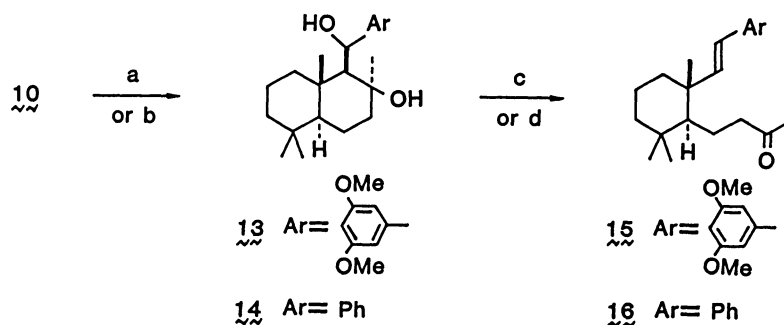


We selected drimanic 1,3-diol **9** and aldehyde **10** as substrates in this study.⁷⁾ When **9** was treated with pyridinium chloride or PPTS, it was completely recovered unchanged. On the other hand, treatment of its tosylate **11** with sodium hydride in 1,2-dimethoxyethane turned out formation of oxetane **12** in 30% yield along with unchanged **11** (65%). No formation of **8** was found on the careful inspection of the above reaction mixture. We then prepared benzyl alcohol **13** by condensation of **10** with the lithium salt of orcinol dimethyl ether.⁸⁾ For comparison, benzyl alcohol **14** was also prepared by treatment of **10** with phenyllithium.



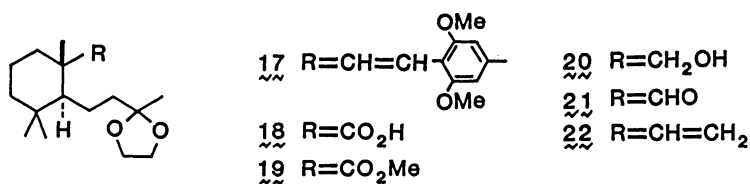
On exposure to pyridinium chloride or PPTS⁵⁾ in CH₂Cl₂ at room temperature, **13** underwent the fragmentation within a few minutes to give olefinic ketone **15** in almost quantitative yield, whereas under the same reaction conditions **14** was recovered unchanged. On long heating **14** with *p*-toluenesulfonyl chloride in pyridine, fragmentation product **16** was obtained in moderate yield. Obviously unsubstituted phenyl group was insufficient to cause the fragmentation under the above mild conditions. The above findings indicate that the 2,6-dimethoxy-4-methylphenyl group acted as a remarkably reactive nucleofuge in the 1,3-diol

fragmentation even under mild conditions.



(a) orcinol dimethyl ether, BuLi, DME (92%); (b) PhLi, DME (90%); (c) Py·HCl or PPTS, CH₂Cl₂, rt (98%); (d) p-TsCl, Py, 60 °C, 2 d (58%).

The fragmentation product 15 was employed as the synthetic precursor of seco-sesquiterpene 8.⁶⁾ Protection of the carbonyl group in 15 by the usual procedure afforded acetal 17 (91%), whose ozonolysis in CH₂Cl₂ directly provided carboxylic acid 18 (60%). After esterification of the acid with diazomethane, the resulting ester 19 was reduced with lithium aluminium hydride in THF to afford alcohol 20,⁹⁾ which was then oxidized with Collins reagent to give aldehyde 21 in 95% overall yield from 19. The Wittig reaction of 21 with methylenetriphenylphosphorane gave olefin 22 (72%), and finally, deprotection of the latter compound provided the target molecule, ()-4-(2,2,6-trimethyl-6-vinylcyclohexyl)-2-butanone (8), in quantitative yield. On spectral comparison (IR and ¹H NMR), the synthetic product was proved to be identical with the natural product.¹⁰⁾

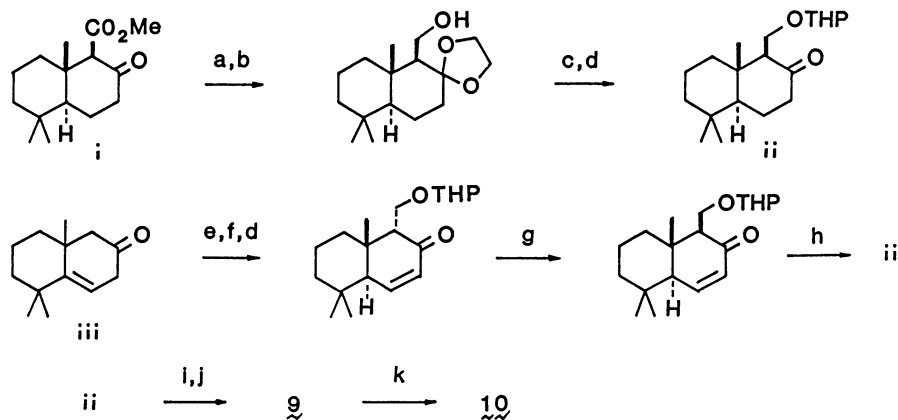


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References

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- 3) Treatment of 1 with pyridinium chloride in CH₂Cl₂ afforded 3 in excellent yield (Ref. 2).
- 4) For an analogous example, see T. F. Tamand and B. J. Fraser-Reid, *J. Org. Chem.*, **45**, 1344 (1980).

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- 7) The diol **9** was prepared on the Grignard reaction of bicyclic ketone **ii** followed by deprotection, and oxidation of **9** provided the aldehyde **10**.¹¹⁾ The ketone **ii** was derived from the known keto ester **i**¹²⁾ or enone **iii**¹³⁾ as shown below.



(a) ethylene glycol, *p*-TsOH, PhH (99%); (b) LiAlH_4 , THF (70%); (c) PPTS, acetone (96%);
 (d) DHP, PPTS (quant); (e) *p*-TsOH, MeOH, 60 °C (47%); (f) LDA, THF, -78 °C, then CH_2O (g)
 (80%), (g) LDA, THF, -78 °C, then 10% citric acid (45%); (h) H_2 , 10% Pd-C, dioxane (95%);
 i) MeMgI , Et_2O , -60 °C (94%); (j) PPTS, MeOH (91%); (k) NCS, Me_2S , toluene (53%).

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- 9) Attempted reduction of **19** to **21** with diisobutylaluminum hydride provided **20**.
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