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

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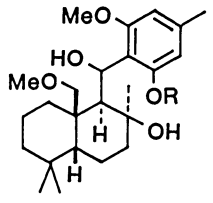
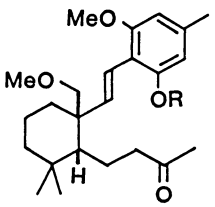
A benzylic hydroxyl group activated by the 2,6-dimethoxy-4-methylphenyl group was proved to be a remarkably reactive nucleofuge in 1,3-diol fragmentation under mild conditions. 4-(2,2,6-Trimethyl-6-vinylcyclohexyl)-2-butanone, a seco-sesquiterpene, was synthesized by using a fragmentation product thereby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

Fragmentation reactions[1] are useful in degradative C-C bond cleavages and have been extensively utilized in structural and synthetic studies of natural products.

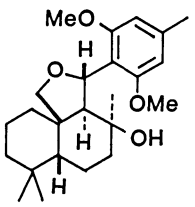
In the course of our synthetic study on siccanin,[2] an antibiotic mold metabolite, we have encountered with a remarkably facile 1,3-diol fragmentation. Exposure of 1,3-diol **1** to pyridinium chlorochromate in CH_2Cl_2 afforded ketone **2** and tetrahydrofuran **3** in 24% and 28% yields, respectively, 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 nucleofuge[1] under acidic conditions to afford **2** and **3** in the fragmentation (path a) and neighbor-



1 R=Me
6 R=THP



2 R=Me
7 R=H



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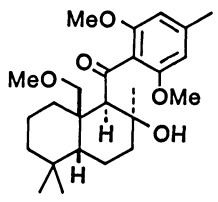

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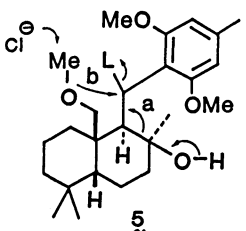

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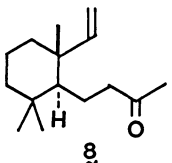

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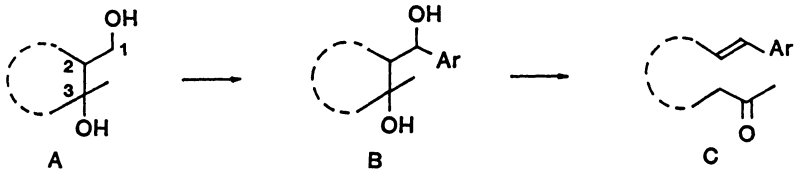
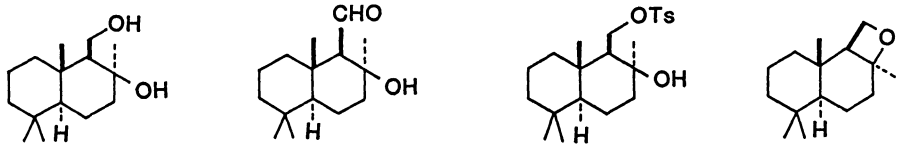
ing participation (path b)[3] modes, respectively.[4]

Occurrence of such a facile fragmentation was also observed on the attempted deprotection of tetrahydropyranyl (THP) ether **6**. Under mild acidic conditions (AcOH-THF-H_2O 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]

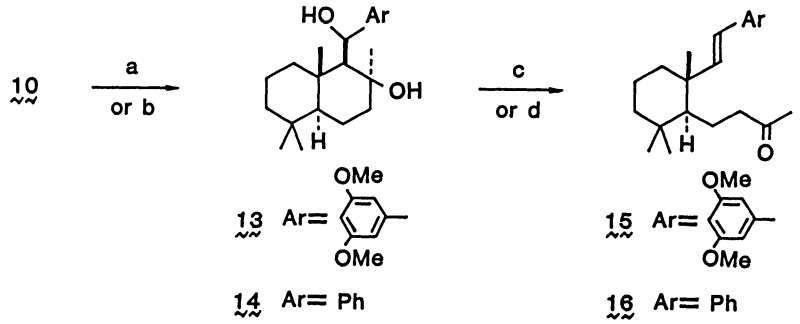


We selected drimanic 1,3-diol **9** and aldehyde **10** as substrates in this study.[7] When **9** was treated with pyridinium chloride or PPTS, it was completely recovered unchanged. On the other hand, treatment of its tosylate **11** with sodium hydride in 1,2-dimethoxyethane turned out formation of 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.



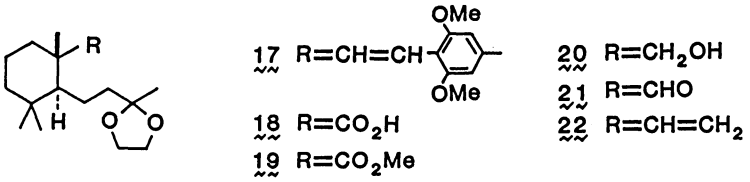
On exposure to pyridinium chloride or PPTS[5] in CH_2Cl_2 at room temperature, **13** underwent the fragmentation within a few minutes to give olefinic ketone **15** in almost quantitative yield, whereas under the same reaction conditions **14** was recovered unchanged. On long heating **14** with p-toluenesulfonyl 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, CH_2Cl_2, 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 CH_2Cl_2 directly provided carboxylic acid **18** (60%). After esterification of the acid with diazomethane, the resulting ester **17** 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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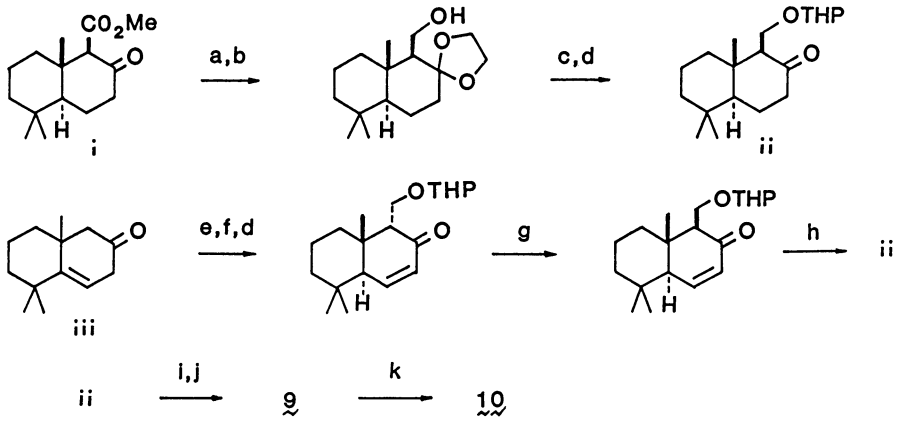
2) M. Kato, Y. Matsumura, K. Heima, N. Fukamiya, C. Kabuto, and A. Yoshikoshi, Tetrahedron, 43, 711 (1987).
3) Treatment of 1 with pyridinium chloride in CH_2Cl_2 afforded 3 in excellent yield (Ref. 2).
4) For an analogous example, see T. F. Tamand and B. J. Fraser-Reid, J. Org. Chem., 45, 1344 (1980).

5) (Review) T. W. Greene, "Protective Group in Organic Synthesis," John Wiley & Sons, New York (1981).
6) J. R. Hlubucek, A. J. Aasen, B. Kimland, and C. R. Enzell, Phytochemistry, 12, 2555 (1973).
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%).

8) R. Adam, H. Wolff, C. K. Cain, and J. H. Clark, J. Am. Chem. Soc., 62, 1779 (1940).
9) Attempted reduction of **19** to **21** with diisobutylaluminium hydride provided **20**.
10) (Other syntheses) J. R. Hlubucek, A. J. Aasen, S-O. Almqvist, and C. R. Enzell, Acta Chem. Scand., Ser. B, 28, 18 (1974); E. J. Corey and R. R. Sauers, J. Am. Chem. Soc., 81, 1743 (1959).
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13) The synthesis of iii and its acid-catalyzed equilibrium will be reported elsewhere.

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