

Molecular Rearrangements During Terpene Syntheses[†]

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[†] To Mr. Victor Marcos Simon, a beloved gardner of 90 years old.

Abstract

Rearrangements of several organic compounds with acids, iodine, boron trifluoride etherate, thionyl chloride-pyridine, manganese(III) acetate and silicon dioxide have been discussed. These rearrangements were observed during our studies on the synthesis of natural products related to diterpenes and triterpenes. The mechanism of these molecular rearrangements has been suggested in order to explain the formation of the obtained structures.

Key words: rearrangement, terpenes, natural products

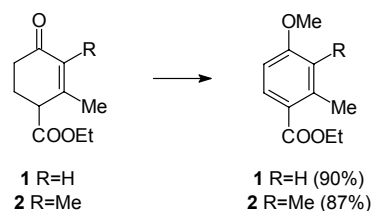
Introduction

Molecular rearrangements are frequently associated with undesired skeletal transformations leading to totally unexpected products. These rearrangements have provided many of the keys which have opened the doors to our understanding of organic chemistry.

As the title implies we have not tried to include all recorded rearrangements of terpenoid chemistry.¹ In relation with our studies on terpenoid compounds we have observed the molecular transformation of several organic compounds (ketones, dienones, alcohols) leading to the formation of unexpected products. This information which remained scattered in several journals is brought together now in the form of a short review article. This review also includes a brief description of similar transformations observed by other authors. The majority of the rearrangements reported are somewhat related to the well-known Grob-type fragmentation particularly those in the first part.

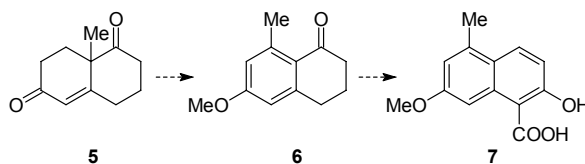
Rearrangement of bicyclic diones with iodine and methanol

Several unsaturated ketones and esters undergo aromatization with iodine. Kotnis² reported the aromatization of a variety of Hagemann's esters **1–2** to the corresponding p-methoxybenzoate derivatives **3–4** (Scheme 1). Tamura and Yoshimoto³ have observed the aromatization of cyclohexenone with iodine and methanol at reflux.



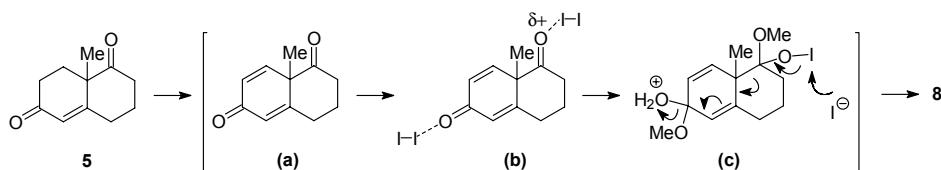
Scheme 1

These interesting observations gave us the impetus to study⁴ the rearrangement of the commercially available dione **5** expecting its transformation to tetralone **6** which may prove to be a potential intermediate for the synthesis of the naphthoic acid **7**⁵ (Scheme 2).

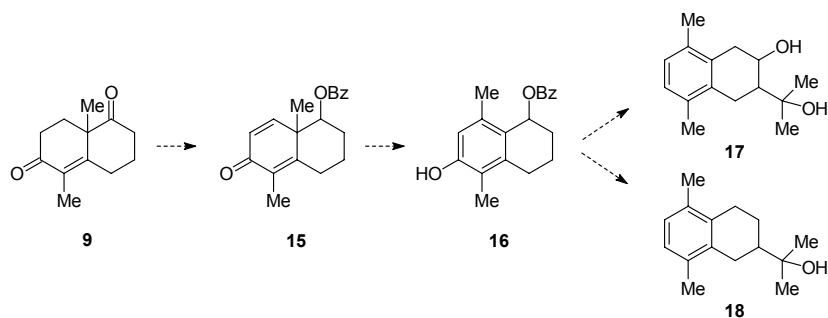


Scheme 2

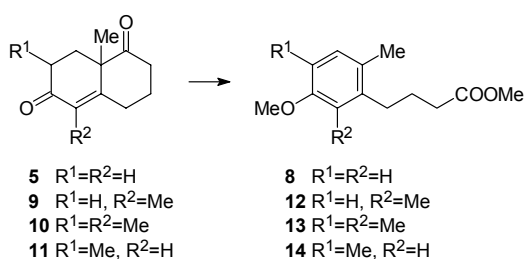
We observed that dione **5** on heating with iodine and methanol afforded a product (70%) which was assigned to structure **8** on the basis of spectral data (Scheme 3). The diones **9**, **10** and **11** under similar conditions afforded anisole derivatives **12** (65%), **13** (70%) and **14** (68%) respectively (Scheme 3).



Scheme 4



Scheme 5



Scheme 3

The above mentioned observations may lead one to think that hydroiodic acid produced by the reaction of iodine caused aromatization and fragmentation. This assumption proved incorrect on finding that diones on heating with hydroiodic acid and methanol were recovered unchanged. On heating with iodine and methanol diones **5**, **9**, **10**, **11** did not generate practically any acid (litmus paper test). A reasonable mechanism of the transformation of dione **5** to anisole derivative **8** is depicted in Scheme 4. Probably the iodine activates the carbonyl groups of the dienone (a) formed by halogenation and dehydrohalogenation of the dione **5** yielding intermediate (b) and this by the nucleophilic attack of methanol suffered cleavage to the anisole derivative **8**.

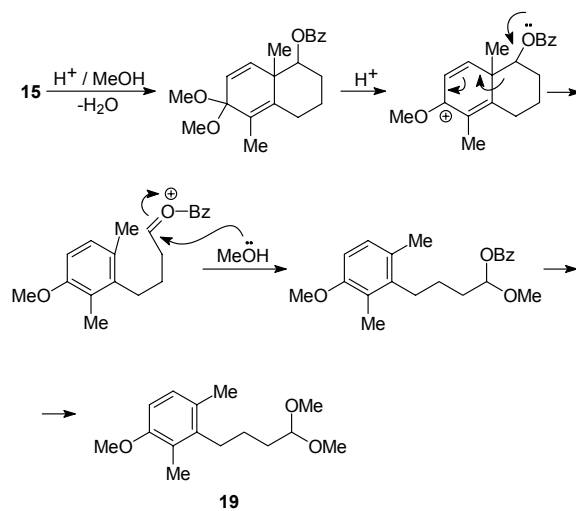
To the best of our knowledge this is the first report of aromatization and fragmentation of the cyclic diones with iodine and methanol.

Rearrangement of dienone with acids

The acid catalyzed rearrangement of cyclohexadienone to phenol is a well known reaction^{6,7}

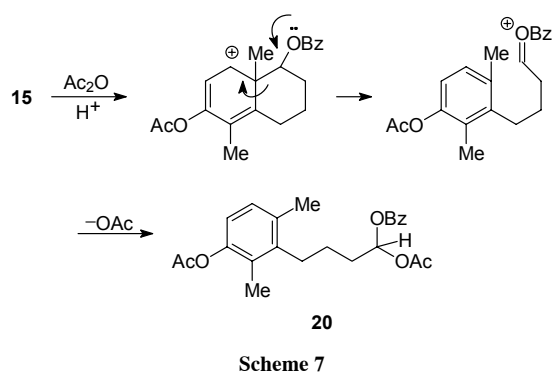
and has been applied to the conversion of steroidal dienones to aromatic steroids.⁸

This finding encouraged us to study the transformation of dienone **15** to phenol **16** which can be of considerable utility in synthesis of rishitinol⁹ and occidol¹⁰ **18** (Scheme 5). Dienone **15** was synthesized¹¹ from dione **9** but on heating with hydrochloric acid in methanol it did not yield the expected phenol **16**. Aromatization followed by ring cleavage provided ketal **19** whose formation has been explained in Scheme 6.

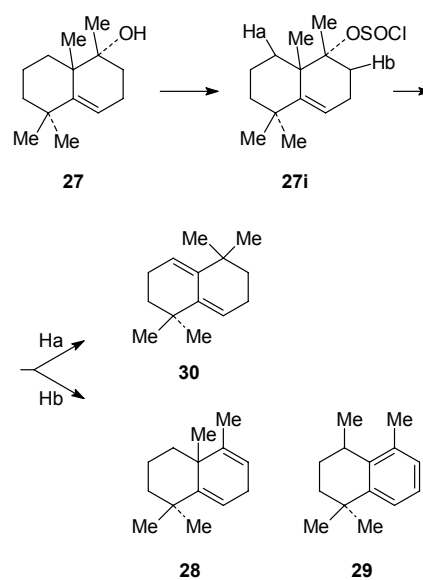
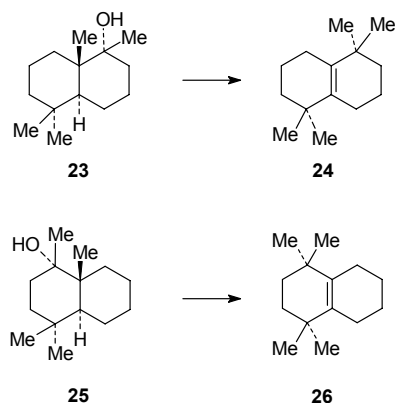
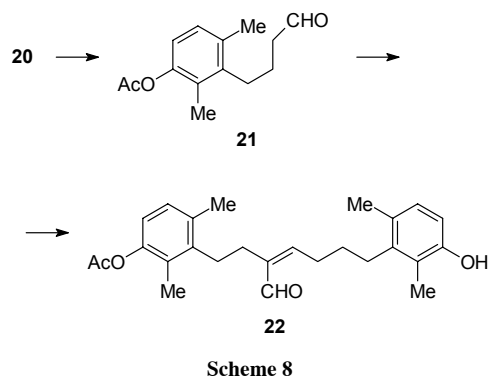


Scheme 6

Heating the dienone **15** with acetic anhydride and *p*-toluene-sulphonic acid yielded compound **20** by a mechanism illustrated in Scheme 7.



Alkaline hydrolysis of ester **20** did not give the expected aldehyde **21** but afforded a dimeric product **22** instead. We assume that aldehyde **21** formed during alkaline hydrolysis yielded via aldol condensation the dimeric adduct **22** (Scheme 8). The above mentioned observations support the previous finding that the rearrangement of dienone depends upon the structural features,⁶ nature of the substituent and the reaction condition.¹²



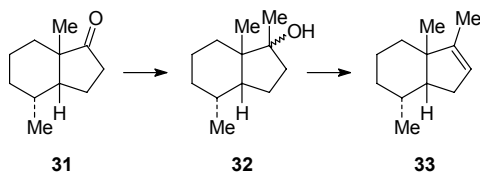
Rearrangement of alcohols with thionyl chloride

Thionyl chloride, a valuable synthetic reagent in preparative organic chemistry has been frequently utilized for the dehydration¹³ of tertiary alcohols for the preparation of alkenes but does not always produce¹⁴ the desired result. Thionyl chloride-pyridine mediated rearrangement of tertiary alcohols **23** and **25** to olefins **24** and **26** respectively has been reported (Scheme 9).^{15,16}

Alcohol **27** upon treatment with thionyl chloride and pyridine yielded a mixture of tetrahydronaphthalene **29** and diene **30** (Scheme 10). The formation of hexahydronaphthalene **30** which occurred through the intermediate **27i** (**Ha**) was expected on the basis of published result.¹⁶ The origin of tetrahydronaphthalene **29** involves dehydration of alcohol **27** to diene **28** via the intermediate **27i** (**Hb**), followed by aromatization.

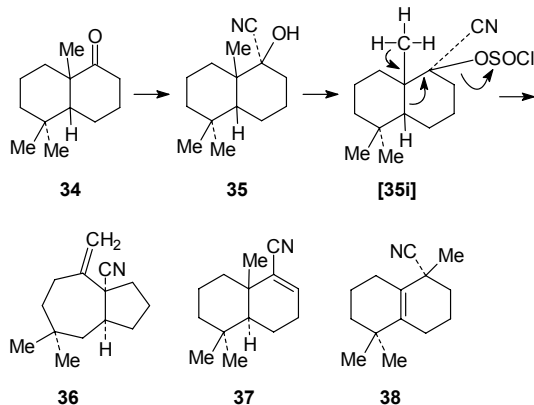
It is only too obvious that **29** would be far more stable than **28** by virtue of aromaticity. This transformation can also be explained on the basis of computational calculation.¹⁷

Octahydroindenol **32**,¹⁶ prepared from ketone **31** by Grignard reaction afforded **33** (Scheme 11) with thionyl chloride and pyridine. This appeared strange from past experience^{15,16} but the phenomenon may be explained by analyzing the orientations of the various bonds involved in the rearrangement. The trans ring juncture of alcohols **23** and **25** permits an antiperiplanar rearrangement of the migrating methyl group and the hydrogen at a bridgehead position, thus fulfilling the stereoelectronic requirement for a more or less synchronous elimination rearrangement reaction. As a result of the cis juncture a similar rearrangement cannot be expected in alcohol **32**.



Scheme 11

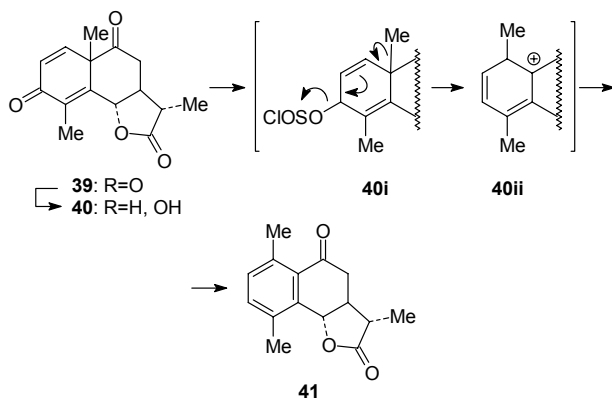
Tertiary alcohol **35**, prepared from ketone **34** by treatment with potassium cyanide and alcohol, afforded via intermediate (**35i**) the product **36** in major yield.¹⁷ (Scheme 12). The unsaturated nitrile **37** was obtained in inferior yield and the formation of the expected¹⁶ rearrangement product **38** could not be detected.



Scheme 12

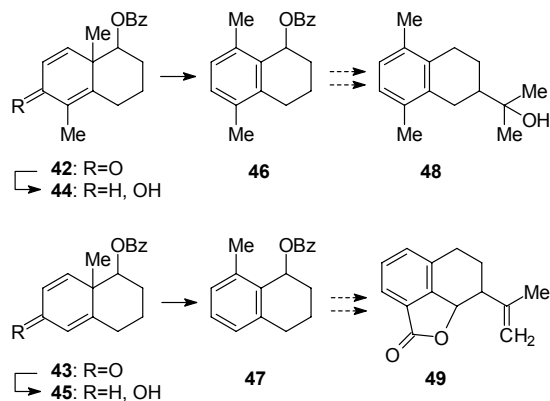
It can be seen that the mentioned rearrangement opened an efficient route for the construction of the fundamental ring skeleton of cis-fused perhydroazulenes.

During our studies on the synthesis of sesquiterpenes, the rearrangement of several cyclohexadienyl alcohols with thionyl chloride and pyridine has been observed. The alcohol **40**, obtained from α -santonine **39**, underwent aromatization¹⁸ with thionyl chloride and pyridine and yielded hyposantonin **41** via the intermediates **40i** and **40ii** (Scheme 13).



Scheme 13

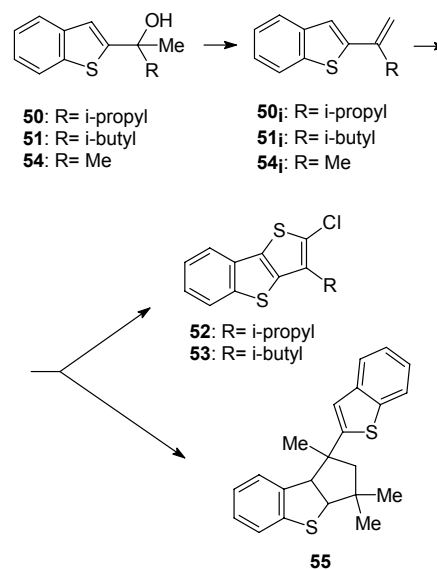
Similarly alcohols **44** and **45** prepared from ketones **42** and **43** respectively experienced aromatization with thionyl chloride and pyridine to afford compounds **46** and **47** respectively.^{18,19} The conversion of compounds **41**, **46** and **47** to the potential intermediates for (+) occidol, (\pm) occidol **48** and (\pm) platphyllide **49** respectively has already been reported (Scheme 14).^{18,19}



Scheme 14

In addition of our above mentioned work, many other interesting rearrangements of tertiary alcohols with thionyl chloride have been reported in a spate of papers. Some selected examples are discussed below.

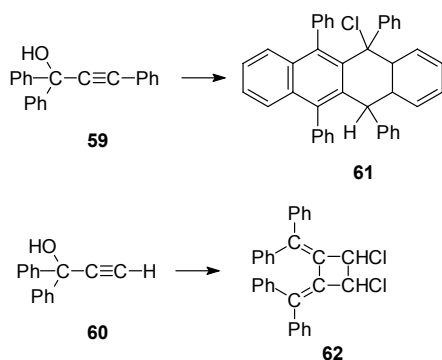
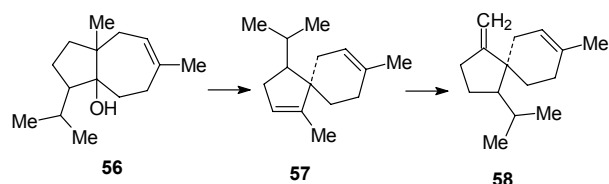
The rearrangement of tertiary alcohols presents in a heterocyclic system has been reported by Jackson.²⁰ On reaction with hot thionyl chloride the alcohols **50** and **51** underwent cyclization yielding the benzothiophenes **52** and **53** but the tertiary alcohol **54** produced a dimeric product **55** (Scheme 15) with thionyl chloride at room temperature. The above mentioned rearrangements are very interesting and permit a new route for the synthesis of various benzothiophenes.



Scheme 15

The transformation of alcohols **50**, **51**, **54** to compounds **52**, **53** and **55** respectively can probably be explained by assuming the formation of intermediates **50i**, **51i**, **54i**. Dimerization of **54i** (R=Me) occurred at room temperature to yield the compound **55**. Such dimerization was not possible with intermediates **50i** and **51i** (R=*i*-propyl, *i*-butyl) probably due to steric repulsion of the bulky groups. Therefore the compounds **50** and **51** did not undergo dimerization.

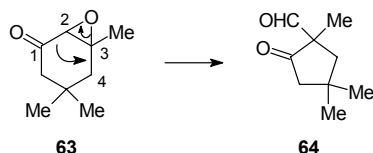
Sesquiterpene cartol **56** with thionyl chloride and pyridine suffered ring contraction²¹, and produced acoradienes **57** and **58** along with other products. The acetylenic carbinols **59** and **60** on similar treatment afforded rearrangements products **61** and **62**, respectively (Scheme 16).²²



Scheme 16

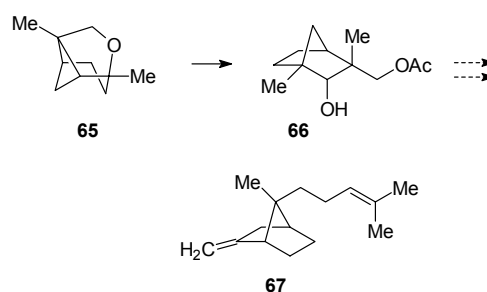
Rearrangement of carbonyl compounds with boron trifluoride etherate

The chemical literature records several interesting rearrangements of organic compounds with boron trifluoride etherate. A few examples are cited below. The conversion of isophorone oxide **63** to **64** was observed²³ (Scheme 17) when treated with boron trifluoride etherate on inert solvent like benzene or dichloromethane.



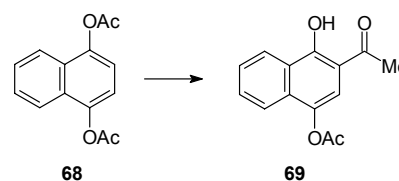
Scheme 17

The coordination between boron trifluoride etherate and the oxygen of the epoxide leads isophorone oxide **63** to attain a transition state geometry²⁴ which facilitates the 1,2 carbonyl migration to give compound **64**. Upon treatment with boron trifluoride etherate in acetic anhydride ether **65** exhibited skeletal rearrangement²⁵ giving alcohol **66** which has turned out to be a potential intermediate in the synthesis of the sesquiterpene sesquifenchene **67** (Scheme 18).



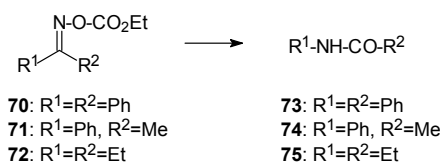
Scheme 18

On treatment with boron trifluoride etherate hydroquinone diester **68** manifested Fries rearrangement²⁶ and yielded **69** (Scheme 19).



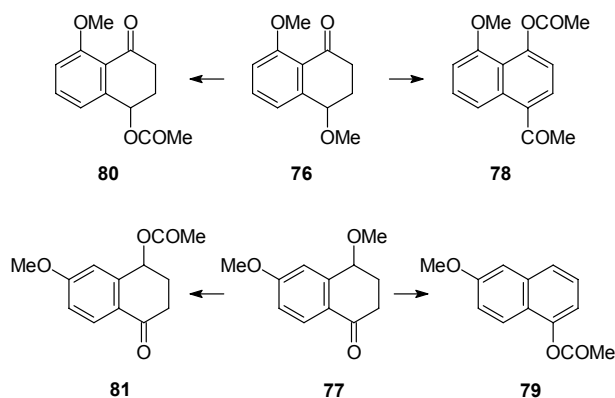
Scheme 19

Upon treatment with boron trifluoride etherate in dichloromethane solution at room temperature a variety of ketoxime ethyl carbonates undergo Beckmann rearrangement²⁷ in excellent yields (generally 75–99%). On treatment with boron trifluoride etherate the ketoxime ethyl carbonates **70–72** yielded amides **73–75** (Scheme 20).

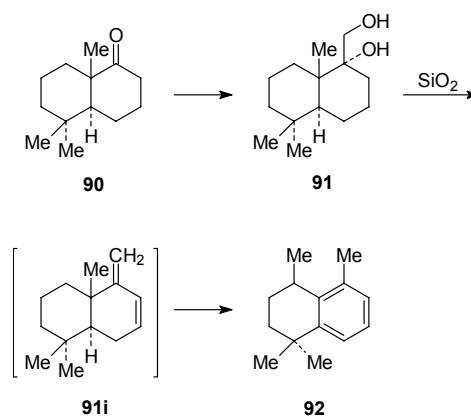


Scheme 20

In contrast to a literature report²⁸ treatment of tetralones **76** and **77** with boron trifluoride etherate and acetic anhydride at 0 °C unexpectedly produced²⁹ compounds **78** and **79** respectively instead of acetates **80** and **81** (Scheme 21).



Scheme 21

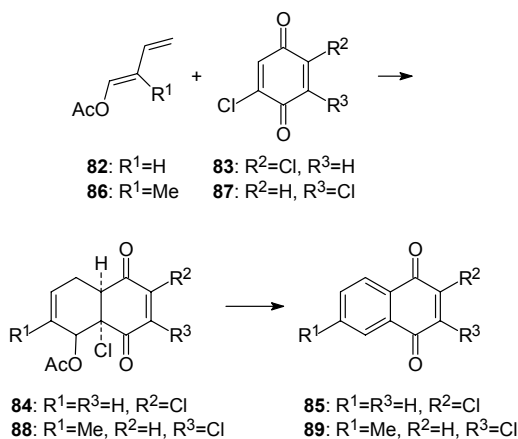


Scheme 23

Rearrangement by silica gel

Many organic compounds undergo diverse molecular rearrangements induced by silica gel. A great variety of interesting rearrangements effected by silica gel have been reviewed by McKillop and Young.³⁰ Therefore for space limitations their discussions have been omitted in this review. We shall confine ourselves to a few cases only.

The addition product **84** of buta-1,3-dien-1-yl acetate **82** and chlorobenzoquinone **83** through a column of silica gel led to rearrangement and concomitant aromatization³¹ affording to naphthoquinone **85** (Scheme 22). Similarly the addition product **88**, of diene **86** and chlorobenzoquinone **87** in a column of silica was transformed into naphthoquinone **89** (Scheme 22).

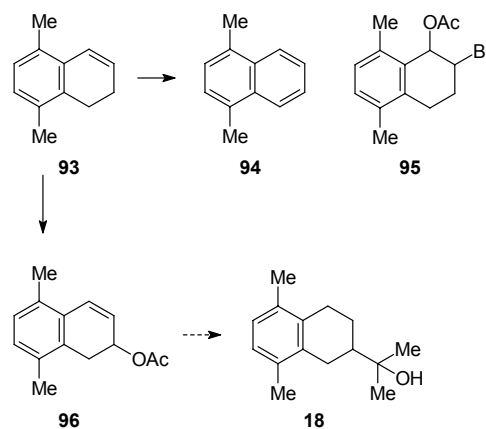


Scheme 22

An attempt to purify the diol **91**, obtained³² from ketone **90** over silica gel afforded tetralin **92** in high yield (Scheme 23). It can be assumed that the dehydration of diol formed the intermediate **91i** which underwent aromatization to afford tetralin **92**.

Rearrangement with Manganese(III) acetate

Oxidation of cyclic olefins with manganese(III) acetate in acetic acid in the presence of a metal halide catalyst (potassium bromide) yields allylic acetates.^{33,34} This method proved unsatisfactory with the compound **93** which yielded tetralin **94** (60%) and compound **95** (40%) instead of expected allylic acetate **96**, which can be of considerable utility in the synthesis¹⁰ of occidol **18** (Scheme 24).



Scheme 24

Concluding remarks

The above mentioned molecular rearrangements have provided some interesting results. Though the desired products were not obtained for their further transformations to terpenoid compounds, the valuable information obtained would definitely constitute an important contribution to organic chemistry.

Acknowledgements

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References

1. J. F. King, P. de Mayo, "Terpenoid Rearrangements in Molecular Rearrangements", (ed. de Mayo, P.), Interscience Publishers, New York, 1964, 771–840.
2. A. S. Kotnis, *Tetrahedron Lett.* **1990**, 31, 481–484.
3. Y. Tamura, Y. Yoshimoto, *Chem. Ind.* **1980**, 888–889.
4. A. K. Banerjee, E. V. Cabrera, J. A. Azocar, *Synth. Commun.* **2000**, 30, 3815–3821.
5. A. G. Myers, V. Subramanian, M. Hammond, *Tetrahedron Lett.* **1996**, 37, 587–590.
6. R. B. Woodward, T. Singh, *J. Am. Chem. Soc.* **1950**, 72, 494–500.
7. J. Berson, "The Dienone-Phenol Mysteries", in "Chemical Creativity", Wiley-VCH, Weinheim, Germany, 1999, 77–107.
8. R. Shopiro, in "Steroid Reactions", (Edit. Djerassi), Holden-Day, San Francisco, 1963, 371–402.
9. N. Katsui, A. Matsunaga, K. Imaizumi, T. Masamune, K. Tomiyama, *Bull. Chem. Soc. Jpn.* **1972**, 45, 2871–2877.
10. T.-L. Ho, *J. Chem. Soc., Perkin I.* **1973**, 2579–2582 and related references.
11. A. K. Banerjee, H. Hurtado, *Tetrahedron* **1985**, 41, 3029–3032.
12. B. P. J. Kropp, *J. Am. Chem. Soc.* **1965**, 87, 3914–3921.
13. J. D. Roberts, W. G. Young, S. Winstein, *J. Am. Chem. Soc.* **1942**, 64, 2157–2164.
14. J. W. ApSimon, K. Yamasaki, *Chem. Lett.* **1977**, 1453–1456.
15. S. C. Welch, A. S. C. Prakasa Rao, *J. Org. Chem.* **1978**, 43, 1957–1961.
16. A. K. Banerjee, W. Vera, *Rec. Trav. Chim., Pays-Bas* **1995**, 114, 87–90.
17. A. K. Banerjee, W. Vera, *Rec. Trav. Chim., Pays-Bas* **1993**, 112, 259–261.
18. A. K. Banerjee, W. Vera, *Synth. Commun.* **1996**, 26, 4641–464.
19. A. K. Banerjee, J. A. Azocar, W. Vera, *Synth. Commun.* **1999**, 29, 2995–3001.
20. J. L. Jackson, *J. Heterocyclic Chem.* **1991**, 28, 109–112.
21. A. Lardan, T. Reichstern, *Helv. Chim. Acta* **1962**, 45, 943–962.
22. P. D. Landor, S. R. Landor, *J. Chem. Soc.* **1963**, 2707–2711.
23. F. Kunisch, K. Hobert, P. Welzel, *Tetrahedron Lett.* **1985**, 26, 6039–6042.
24. R. D. Bach, R. C. Klix, *Tetrahedron Lett.* **1985**, 26, 985–988.
25. Y. Bessiere-chreiten, C. Grisan, *C.R. Acad. Sci. Ser C.* **1972**, 275, 503–504.
26. J. Boyer, J. Krum, M. Myers, A. Fazal, C. Wigal, *J. Org. Chem.* **2000**, 65, 4712–4714.
27. R. Anilkumar, S. Chandrasekhar, *Tetrahedron Lett.* **2000**, 41, 5427–5429.
28. C. R. Narayanan, K. N. Iyer, *J. Org. Chem.* **1965**, 30, 1734–1736.
29. A. K. Banerjee, L. Bedoya, W. J. Vera, C. Melean, H. Mora, M. S. Laya, M. Alonso, *Synth. Commun.* **2004**, 34, 3399–3408.
30. A. McKillop, D. W. Young, *Synthesis*, **1979**, 401–422.
31. I. Boisvert, P. Brassard, *Tetrahedron Lett.* **1983**, 24, 2453–2456.
32. A. K. Banerjee, V. E. Khalil, W. Vera, *Synth. Commun.* **2000**, 30, 4375–4385.
33. J. R. Gilmore, J. R. Mellor, *J. Chem. Soc.* **1971**, 2355–2357.
34. A. K. Banerjee, W. Vera, M. S. Laya, *Russ. J. Org. Chem.* **2002**, 38, 855–859.
35. A. K. Banerjee, W. Vera, M. S. Laya, *Synth. Comm.* **2004**, 34, 2301–2308.

Povzetek

Opisane so molekulske premestitve nekaterih organskih spojin z reagenti, kot so kisline, jod, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, tionil klorid-piridin, magnezijev(III) acetat in silicijev dioksid. Te premestitve so bile opažene pri sintezi naravnih produktov sorodnih diterpenom in triterpenom. Predlagani so mehanizmi reakcij.