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LETTERS

# Fe(III)/Cu(II) mediated 5- and 6-*exo* oxidative ring expansion/cyclisation of cyclopropyl ethers: studies towards dictyol C and α-eudesmol

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**Abstract**

The outcome of oxidative ring expansion/cyclisation of cyclopropanes with a mixed Fe(III)/Cu(II) system was found to be dependent on the mode of cyclisation. When 6-*exo* cyclisation was attempted unusual products resulting from oxidation of ring opened primary radicals were obtained. © 2000 Elsevier Science Ltd. All rights reserved.

For a number of years we have been studying the oxidative cyclisation of cyclopropanes with Fe(III) salts and have developed this chemistry to provide a new method for the rapid synthesis of [*n*.3.0] carbocycles[1] ($n=4,5,6$) as well as highly functionalised cyclopentanes.[2] Present studies involve the evaluation of our tandem ring expansion/cyclisation methodology in the synthesis of natural products. In this letter we discuss our preliminary results towards the natural products dictyol C **1**[3] and α-eudesmol **2**[4] which possess antimicrobial and potent calcium channel blocking activities, respectively. The schemes illustrate how our previous chemistry could be used to enable rapid access to these systems (Scheme 1). An initial common strategy was to generate the *exo*-cyclic products **5** and **8** by ring expansion of cyclopropanes **3** and **6**, followed by 5-*exo* and 6-*exo* radical cyclisation, respectively. Subsequent alkene isomerisation[5] would then give the endocyclic isomers with the correct geometry for the respective natural products.

**Dictyol C**: We had previously shown[1] that the chemistry in Scheme 1 was suitable for the formation of 7,5-systems by ring expansion and 5-*exo* radical cyclisation onto both alkenes and alkynes. Conjugate addition of both butenyl- and butynyl-magnesium bromides onto mono-protected enone **9** gave the corresponding enol ethers, which, upon treatment with diethylzinc/diiodomethane,

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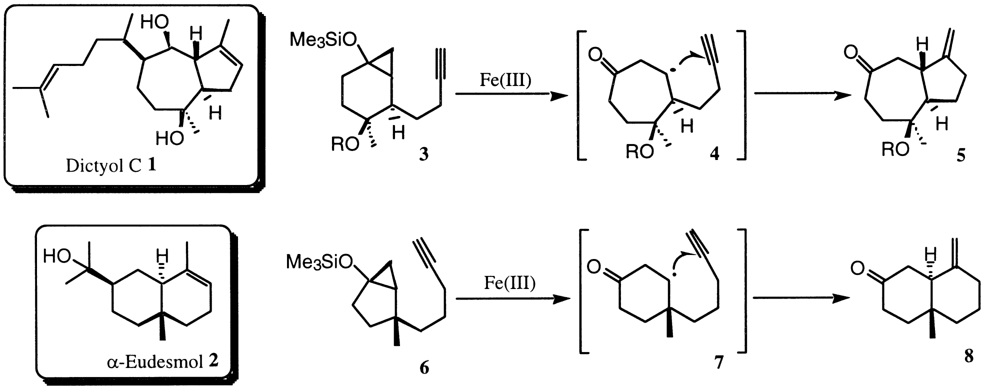
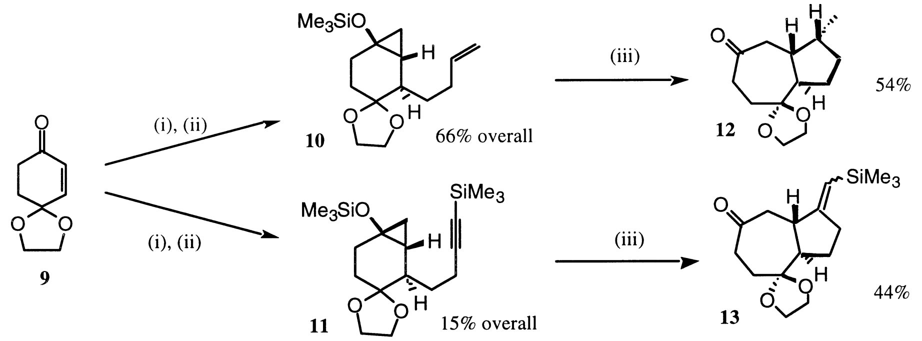


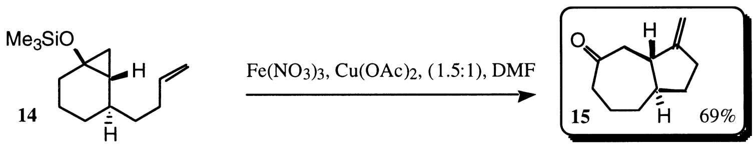
Scheme 1.

gave cyclopropyl ethers **10** and **11** in good and low overall yields, respectively (4:1 ratio of diastereomers). Oxidative cyclisation with $Fe(NO_3)_3$ using our previously optimised conditions gave bicyclic-ketones **12** and **13** in moderate yields. It was pleasing to observe that the acid labile acetal group remained intact upon exposure to the Lewis acidic conditions (Scheme 2).



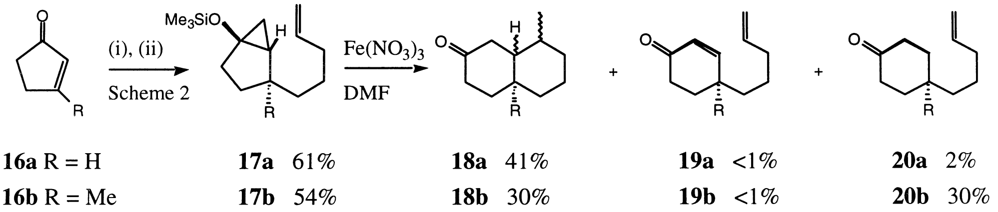
Scheme 2. *Reagents*: (i) RMgBr, $Me_3SiCl$, CuI, HMPA, THF; (ii) $Et_2Zn$, $CH_2I_2$; (iii) $Fe(NO_3)_3$, 1,4-cyclohexadiene, DMF

Unfortunately, the conversion of protected dione **9** to bicyclic ketone **13** was simply too inefficient to be used in a practical synthesis of dictyol C and an alternative method of introducing the exocyclic alkene was sought. Our attention was drawn to the pioneering work of Kochi[6] from the early 1960s which involved the oxidation of primary radicals with Cu(II) salts to yield alkenes. The synthetic potential of this chemistry has been realised by Snider[7] in his elegant and comprehensive work with Mn(III)/Cu(II) mediated radical cyclisations. We were therefore pleased to find that, in a model study, treatment of cyclopropane **14** with a $Fe(NO_3)_3/Cu(OAc)_2$ mixture (1.5:1) in DMF gave only the *trans*-fused exocyclic alkene **15**, in good yield (Scheme 3). Present studies are concerned with the total synthesis of dictyol C by the application of this strategy to enone **9** and derivatives. The key benefit of the Fe(III)/Cu(II) system is the reduction in the number of steps in the synthesis of **5**, as cumbersome manipulation of protected alkynyl side chains will be unnecessary.



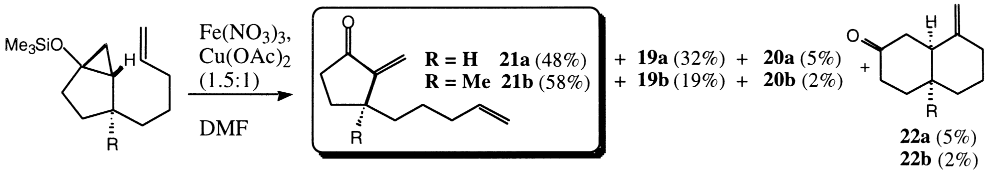
Scheme 3.

**α-Eudesmol**: Previously, we and others[8a,c] have found that Fe(III)- and Mn(III)-mediated ring expansion chemistry could be used to form six-membered rings by 6-*exo* cyclisation; although, in the one transannular example we studied, problems arose through competitive 1,5-hydrogen atom abstraction.[8b] Our initial approach was to consider the 6-*exo-dig* radical cyclisation as outlined in Scheme 1. However, in light of the good results obtained with the dictyol C synthesis, it became apparent that the mixed Fe(III)/Cu(II) oxidative cyclisation onto an alkene should provide a more practical synthesis of exocyclic alkene **8**. Conjugate addition of pentenylmagnesium bromide to the cyclopentenones **16a/b** followed by cyclopropanation gave ethers **17a/b** in good overall yield (**17b** as a 2:1 mixture of diastereoisomers). Oxidative ring expansion–cyclisation with $Fe(NO_3)_3$ alone gave mixed results. With R = H the 6-*exo* product **18a** predominated with trace amounts of the uncyclised products **19a** and **20a** formed from oxidation and hydrogen atom abstraction of the uncyclised radicals, respectively. Where R = Me oxidation gave an equal mixture of **18b** and **20b**. In both cases, the cyclised products were obtained as a complex mixture of diastereoisomers, with two major isomers predominating in a ratio of 3:2. The higher amount of uncyclised material observed with R = Me clearly indicated that the methyl group has an unfavourable influence on the rate of 6-*exo* cyclisation (Scheme 4).



Scheme 4.

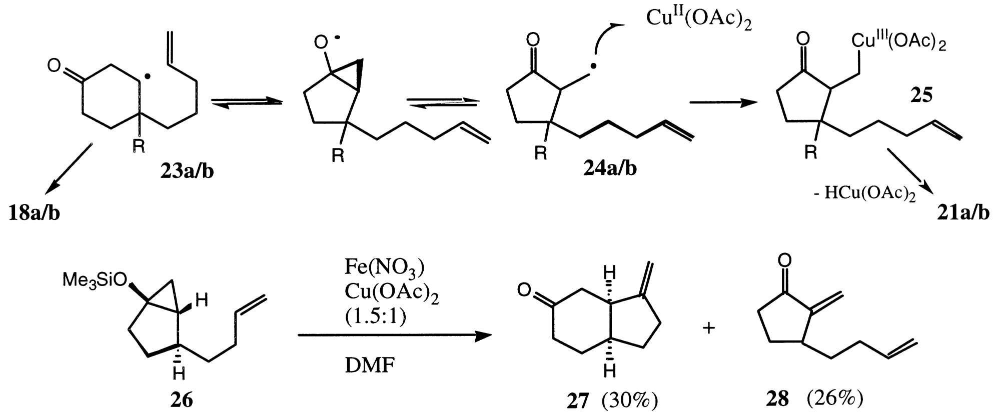
When the same reactions were repeated with the Fe(III)/Cu(II) mix described above a rather startling result was obtained. Only trace amounts of the expected exocyclic alkenes **22a/b** were formed (> 19:1 stereoselectivity) and the major products in both cases were the α-methylene cyclopentanones **21a/b** (Scheme 5).



Scheme 5.

The formation of the α-methylene cyclopentanone can be explained by assuming that initial oxidation of the cyclopropane gives a rapidly equilibrating mixture (via the cyclopropyl alkoxy radical) of the ring opened and ring expanded radicals **24a/b** and **23a/b**. Reaction of the primary radicals **24a/b** with Cu(II) then gives the Cu(III) species **25a/b** which undergoes β-elimination to the alkene according to the mechanism of Kochi. The enones **19a/b** are either formed similarly or are simply a result of SET oxidation of the secondary radical with Fe(III). In the whole history of this work this is the first time that we have observed products resulting from reactions of primary radicals such as **24a/b**. This unusual result gives several important insights into the mechanism of these ring expansions. Most importantly, this result clearly shows that the ring opened primary radicals **24a/b** are true reaction intermediates in equilibrium with the ring expanded secondary radicals. Obviously, the slower rate of 6-*exo* cyclisation allows the other observed pathways to proceed within the reaction timescale. Treatment of the cyclopropanes **17a/b** with $Cu(OAc)_2$ alone gave no reaction. This clearly indicates that Cu(II) is only involved once the radical species have been formed, and no oxidative cleavage of the cyclopropane ring can occur until Fe(III) is present.[9]

Finally, treatment of cyclopropane **26** with the Fe(III)/Cu(II) mix gave the 6,5-bicyclic ketone **27** with the exocyclic double bond, along with the α-methylene cyclopentanone **28** (Scheme 6). As expected, due to the faster rate of cyclisation, the 5-*exo* product was formed. Surprisingly perhaps, was the formation of **28**, which would suggest that 5-*exo* cyclisation of the six-membered β-keto radical is slower than the analogous seven-membered case (**14**→**15**), thus allowing time for the intermediate primary radical to react with the Cu(II).



Scheme 6.

In summary, these results provide the first evidence of the existence of equilibrating primary radicals in the oxidation of cyclopropylsilyl ethers with Fe(III). Further progress on the synthesis of dictyol C and α-eudesmol will be reported in due course.

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## References

1. Booker-Milburn, K. I.; Thompson, D. F. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2315.
2. Booker-Milburn, K. I.; Barker, A.; Brailsford, W.; Cox, B.; Mansley, T. E. *Tetrahedron* **1998**, *54*, 15321.
3. Enoki, N.; Tsuzuki, K.; Omura, S.; Ishida, R. *Chem. Lett.* **1983**, 1627.
4. (a) Humber, D. C.; Pinder, A. R. *Tetrahedron Lett.* **1966**, *41*, 4985; (b) Frey, B.; Hunig, S.; Koch, M.; Reissig, H. *Synlett* **1991**, 854.
5. Rigby, J. H.; Wilson, J. Z. *J. Am. Chem. Soc.* **1984**, *106*, 8217.
6. (a) de la Mare, H. E.; Kochi, J. K.; Rust, F. F. *J. Am. Chem. Soc.* **1963**, *85*, 1437; (b) Kochi, J. K. *Acc. Chem. Res.* **1974**, *7*, 351.
7. Snider, B. B.; Vo, N. H.; Foxman, B. M. *Chem. Rev.* **1996**, *96*, 339.
8. For previous examples of 6-*exo* cyclisations of cyclopropane derived radicals, see: (a) Iwasawa, N.; Funahashi, M.; Hayakawa, S.; Narasaka, K. *Chem. Lett.* **1993**, 545; (b) Booker-Milburn, K. I.; Dainty, R. F. *Tetrahedron Lett.* **1998**, *39*, 5097; (c) Blake, A. J.; Highton, A. J.; Majid, T. N.; Simpkins, N. J. *Org. Lett.* **1999**, *1*, 1787.
9. Ryu has demonstrated that cyclopropylsilyl ethers undergo cleavage to β-Cu(II) ketones using $Cu(BF_4)_2$. Evidence was given in support of a non-radical mechanism in these cases: Ryu, I.; Matsumoto, K.; Kameyama, Y.; Ando, M.; Kusumoto, N.; Ogawa, A.; Kambe, N.; Murai, S.; Sonoda, N. *J. Am. Chem. Soc.* **1993**, *115*, 12330.