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LETTERS

Stereo- and regiocontrolled hydroxylation of oxyallyl [4+3] cycloadducts. A concise synthesis of hinokitiol

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Abstract

Stereo- and regioselective hydroxylation of 8-oxabicyclo[3.2.1]oct-6-en-3-ones was achieved by the action of (diacetoxyiodo)benzene in methanolic potassium hydroxide (the Moriarty oxidation). Subsequent double elimination afforded a convenient preparation of substituted tropolones, as exemplified in a three-step synthesis of hinokitiol (**1**). © 1999 Elsevier Science Ltd. All rights reserved.

Tropones and tropolones (2-hydroxytropones) attracted considerable interest as 'non-benzenoid aromatic compounds'.[1] Very recently, their elegant uses in so-called higher-order cycloaddition reactions have been demonstrated under thermal and metal-mediated conditions.[2] Consequently, their utility as synthetic intermediates has been greatly enhanced. Interesting biological activity was also reported for several naturally occurring tropolones, ranging from structurally simple monocyclic compounds such as hinokitiol (also called β-thujaplicin; 4-isopropyltropolone) (**1**) which exhibits antibacterial and antifungal activity to the tricyclic alkaloid, colchicine (**2**) which is well-known for antimitotic effects. We recently developed an efficient synthesis of **2**, in which the central features involve an intramolecular Diels–Alder reaction of an acetylenic oxazole and subsequent [4+3] cycloaddition of an alkoxy-substituted oxyallyl.[3] This little-explored utilization of the [4+3] cycloaddition of oxyallyls and furans should provide a general method for the regiocontrolled syntheses of a wide range of tropones, tropolones, and tropoloisoquinoline alkaloids,[4] in addition to synthetically useful oxabicyclo[3.2.1] compounds. Herein we report stereo- and regiocontrolled hydroxylation of the oxyallyl [4+3] cycloadducts and subsequent elaboration to tropones and tropolones. A concise synthesis of hinokitiol (**1**) is also included.[5]

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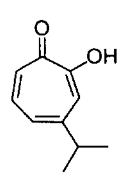
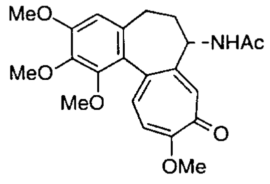
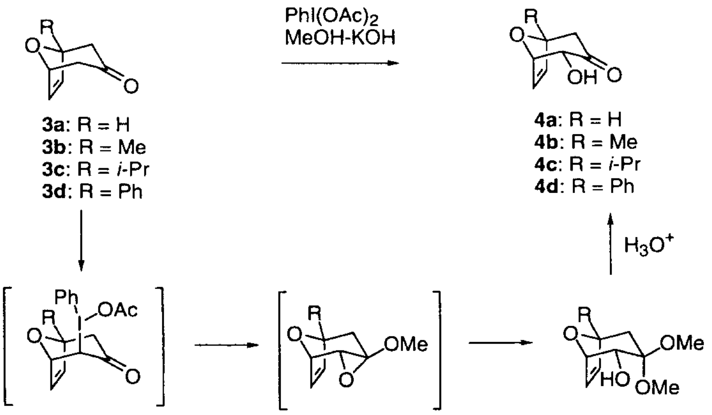


hinokitiol (**1**)



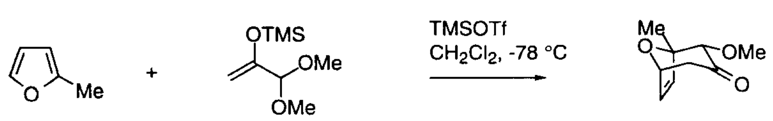
colchicine (**2**)

The sequential implementation of the oxyallyl [4+3] cycloaddition[6] and double elimination[7] has been demonstrated by Mann,[7b] Albizati,[8] and our[3] groups to provide facile preparation of tropones, *O*-methyltropolone, and tropoloisoquinolines, respectively.[9] It occurred to us that hydroxylaton of the initial [4+3] cycloadduct prior to the elimination step would afford rapid access to tropolones; hence there was an attractive possibility of preparing both tropones and tropolones from the common intermediates. A convenient method for the requisite oxidation was found in Moriarty's procedure employing (diacetoxyiodo)benzene.[10] Thus, treatment of the ketone **3a**, which is readily available by the [4+3] cycloaddition methodology developed by Noyori,[6a] Hoffmann,[6b] or Föhlisch,[11] with (diacetoxyiodo)benzene in methanolic potassium hydroxide, followed by acid hydrolysis of the resulting acetal, gave the α-hydroxy ketone **4a** (61% yield) in excellent (>10:1) diastereoselectivity (Scheme 1). The stereochemistry of the α-hydroxyl group was predicated on the well-known diastereofacial bias present in the oxabicyclo[3.2.1] system and confirmed by the presence of the characteristic vicinal coupling (J=5.0 Hz) of the exo methine and the bridgehead protons.[12] It should be noted that the stereochemical outcome of the Moriarty oxidation complements that of Rubottom oxidation of the corresponding silyl enol ether or related direct hydroxylation of the enolate.



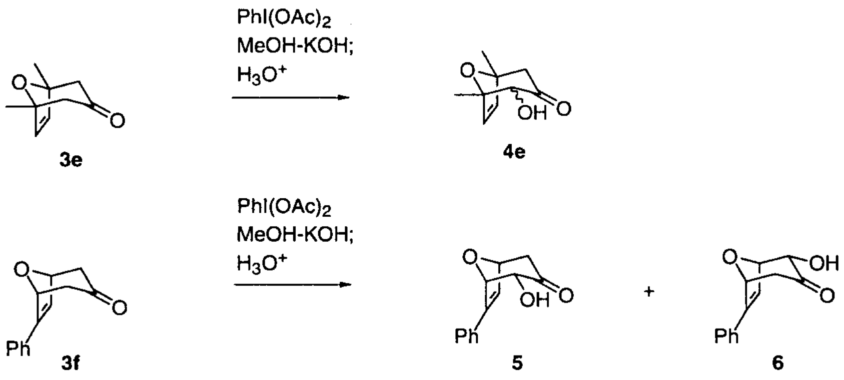
Scheme 1.

Exceptional regioselectivity was found for the Moriarty oxidation of the ketone **3b** bearing the methyl substituent at the bridgehead, which afforded **4b** (68%) in 12:1 diastereoselectivity. Similarly, **4c** and **4d** were obtained as the only detectable isomers in 59% and 55% yields, respectively, from **3c** and **3d** under identical conditions. Particularly useful is the regioselectivity of the cycloaddition–oxidation sequence which is opposite to that of the [4+3] cycloaddition of a trialkylsiloxyallyl cation and 2-methylfuran as described by Albizati (Eq. 1).[8]



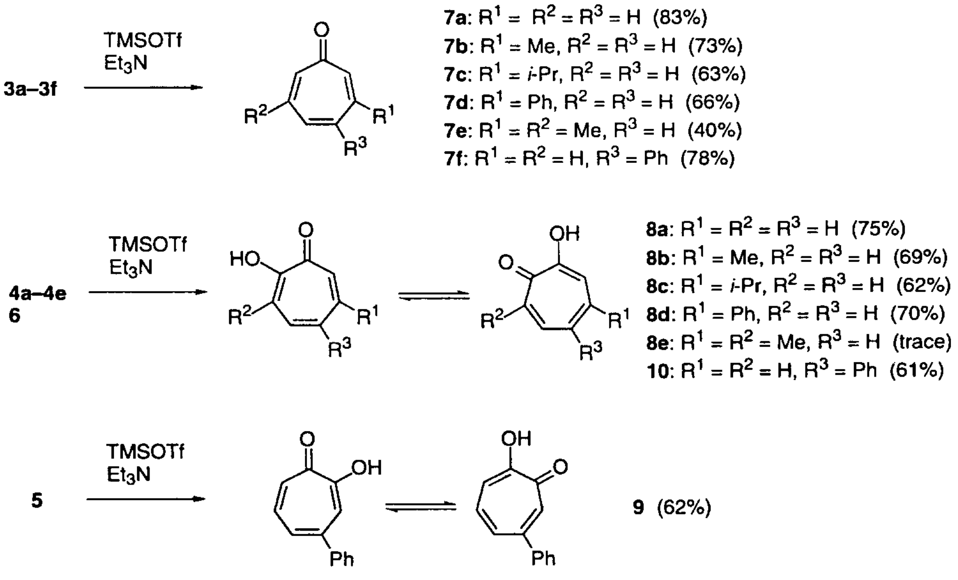
(1)

A comparable result was also obtained for the disubstituted cycloadduct **3e** (Scheme 2), oxidation of which gave **4e–α** (60%) and **4e–β** (34%). Not surprisingly, C-6 substituents of 8-oxabicyclo[3.2.1]oct-6-en-3-ones exert little regiocontrol during the Moriarty oxidation. For example, treatment of **3f** with (diacetoxyiodo)benzene in methanolic potassium hydroxide, followed by subsequent acid hydrolysis, furnished a mixture of two regioisomers **5** (31%) and **6** (18%).



Scheme 2.

Finally, the ketones **3a–3f** and the respective α-hydroxy ketones **4a–4d**, **5**, and **6** were subjected to double elimination according to the procedures of Föhlisch^{7a} and Mann^{7b} to produce tropones **7a–7f** and tropolones **8a–8d**, **9**, and **10**; the tropolones were also isolated as the acetates for ease of handling (Scheme 3). Compound **4e** was the sole example which failed to afford the elimination product.



7a: R^1 = R^2 = R^3 = H (83%)
7b: R^1 = Me, R^2 = R^3 = H (73%)
7c: R^1 = *i*-Pr, R^2 = R^3 = H (63%)
7d: R^1 = Ph, R^2 = R^3 = H (66%)
7e: R^1 = R^2 = Me, R^3 = H (40%)
7f: R^1 = R^2 = H, R^3 = Ph (78%)

8a: R^1 = R^2 = R^3 = H (75%)
8b: R^1 = Me, R^2 = R^3 = H (69%)
8c: R^1 = *i*-Pr, R^2 = R^3 = H (62%)
8d: R^1 = Ph, R^2 = R^3 = H (70%)
8e: R^1 = R^2 = Me, R^3 = H (trace)
10: R^1 = R^2 = H, R^3 = Ph (61%)

9 (62%)

Scheme 3.

In summary, excellent stereo- and regioselective hydroxylation of the oxyallyl [4+3] cycloadducts was achieved by use of (diacetoxyiodo)benzene in methanolic potassium hydroxide (the Moriarty oxidation). Subsequent double elimination led to a convenient preparation of substituted tropolones, as exemplified in a three-step synthesis of hinokitiol (**8c**) starting from 2-isopropylfuran. Moreover, as 8-

oxabicyclo[3.2.1]oct-6-en-3-ones have been demonstrated to serve as useful synthetic intermediates, the Moriarty oxidation of these cycloadducts broadens the scope of the oxyallyl [4+3] cycloaddition.

Acknowledgements

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References

1. For general reviews, see: (a) Pauson, P. L. *Chem. Rev.* **1955**, *55*, 9. (b) Nozoe, T. *Pure Appl. Chem.* **1971**, *28*, 239. (c) Pietra, F. *Chem. Rev.* **1973**, *73*, 293. (d) Pietra, F. *Acc. Chem. Res.* **1979**, *12*, 132.
2. (a) Rigby, J. H. *Acc. Chem. Res.* **1993**, *26*, 579. (b) Rigby, J. H. *Tetrahedron* **1999**, *55*, 4521.
3. Lee, J. C.; Jin, S.-j.; Cha, J. K. *J. Org. Chem.* **1998**, *63*, 2804.
4. For a compilation of known synthetic methods for tropones and tropolones, see: (a) Minns, R. A. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p. 1037, and references cited therein. (b) Brady, W. T. *Tetrahedron* **1981**, *37*, 2949. (c) Mak, C.-P.; Büchi, G. *J. Org. Chem.* **1981**, *46*, 1.
5. For previous syntheses of **1**, see: (a) Nozoe, T.; Mukai, T.; Asao, T. *Bull. Chem. Soc. Jpn.* **1960**, *33*, 1452. (b) Tanaka, K.; Yoshikoshi, A. *Tetrahedron* **1971**, *27*, 4889. (c) Takaya, H.; Hayakawa, Y.; Makino, S.; Noyori, R. *J. Am. Chem. Soc.* **1978**, *100*, 1778. (d) Franck-Neumann, M.; Brion, F.; Martina, D. *Tetrahedron Lett.* **1978**, 5033. (e) Banwell, M. G.; Cameron, J. M.; Collis, M. P.; Crisp, G. T.; Gable, R. W.; Hamel, E.; Lambert, J. N.; Mackay, M. F.; Reum, M. E.; Scoble, J. A. *Aust. J. Chem.* **1991**, *44*, 705, and references cited therein.
6. For reviews on oxyallyls, see: (a) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163. (b) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1. (c) Mann, J. *Tetrahedron* **1986**, *42*, 4611. (d) Rigby, J. H.; Pigge, F. C. *Org. React.* **1997**, *51*, 351. (e) Harmata, M. *Tetrahedron* **1997**, *53*, 6235.
7. (a) Föhlisch, B.; Sendelbach, S.; Bauer, H. *Liebigs Ann. Chem.* **1987**, 1. (b) Barbosa, L.-C. A.; Mann, J.; Wilde, P. D. *Tetrahedron* **1989**, *45*, 4619. (c) For an excellent review on ring-opening reactions of oxabicylic compounds, see also: Chiu, P.; Lautens, M. *Top. Curr. Chem.* **1997**, *190*, 1.
8. Murray, D. H.; Albizati, K. F. *Tetrahedron Lett.* **1990**, *31*, 4109.
9. For a conceptually related process involving 2-oxidopyridinium betains, see: Tamura, Y.; Saito, T.; Kiyokawa, H.; Chen, L.-C.; Ishibashi, H. *Tetrahedron Lett.* **1977**, 4075.
10. Although oxidation of ketones with (diacetoxyiodo)benzene is well-known, not a single example has appeared on its application to oxabicyclo[3.2.1]octanones. See: (a) Moriarty, R. M.; Hu, H.; Gupta, S. C. *Tetrahedron Lett.* **1981**, *22*, 1283. (b) Moriarty, R. M.; Prakash, O.; Vavilikolanu, P. R.; Vaid, R. K.; Freeman, W. A. *J. Org. Chem.* **1989**, *54*, 4008. (c) Moriarty, R. M.; Berglund, B. A.; Penmasta, R. *Tetrahedron Lett.* **1992**, *33*, 6065.
11. (a) In this work, the Föhlisch procedure was chosen because of convenient execution and also the commercial availability of 1,1,3-trichloroacetone, from which oxyallyl can be easily generated by treatment with triethylamine in CF_3CH_2OH. Subsequent reduction of the resulting α,α'-dichloro ketones with zinc afforded the desired bicyclic ketones in good yields. (b) Sendelbach, S.; Schwetzler-Raschke, R.; Radl, A.; Kaiser, R.; Hendle, G. H.; Korfant, H.; Reiner, S.; Föhlisch, B. *J. Org. Chem.* **1999**, *64*, 3398, and references cited therein.
12. (a) Hoffmann, H. M. R.; Clemens, K. E.; Smithers, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 3940. (b) Takaya, H.; Makino, S.; Hayakawa, Y.; Noyori, R. *J. Am. Chem. Soc.* *1978*, **100**, 1765.