Pergamon

Tetrahedron Letters 40 (1999) 7431–7433

TETRAHEDRON LETTERS

A formal synthesis of (±) parvifoline by manganese(III)-based oxidative arylation of ketones †

Dipal Ranjan Bhowmik and Ramanathapuram V. Venkateswaran *

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta 700 032, India

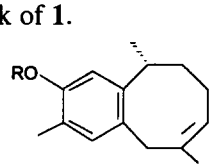
Received 29 June 1999; accepted 10 August 1999

Abstract

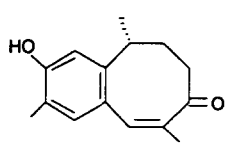
A short, formal synthesis of the phenolic sesquiterpene (±) parvifoline **1** is described involving manganese(III)-based oxidative arylation of the ketone **9** as the key step. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Keywords: oxidative free-radical cyclization; Grob fragmentation; benzocyclooctene.

The sesquiterpenes parvifoline **1**, isoparvifolinone **2** and parvifoline isovalerate **3**, isolated from the species *Coreopsis* and *Perezia*, constitute the only examples of naturally occurring compounds containing a trimethyl benzocyclooctane structural unit.[1] Efforts leading to the synthesis of **1** and **2** have been reported.[2–4] We report a facile, formal synthesis of **1**, employing a manganese(III)-based oxidative cyclisation of a ketone onto an aromatic ring to furnish a benzobicyclo[3.3.1]nonane system followed by a Grob fragmentation to generate the benzocyclooctene core. Manganese(III)-based oxidative cyclisations and annulations involving relatively acidic compounds such as 1,3-diones, acetoacetates, malonates, α-sulfinyl ketones etc. and unsaturated ketones have been extensively studied and their synthetic utility demonstrated.[5] However, there has been only one report on the manganese(III)-catalysed oxidative cyclisation of a ketone onto an aromatic ring leading to a new arylation process.[6] We have employed this protocol to prepare a benzobicyclo[3.3.1]nonane system which was fragmented to reveal the benzocyclooctene framework of **1**.



1, R=H
3, R=i val



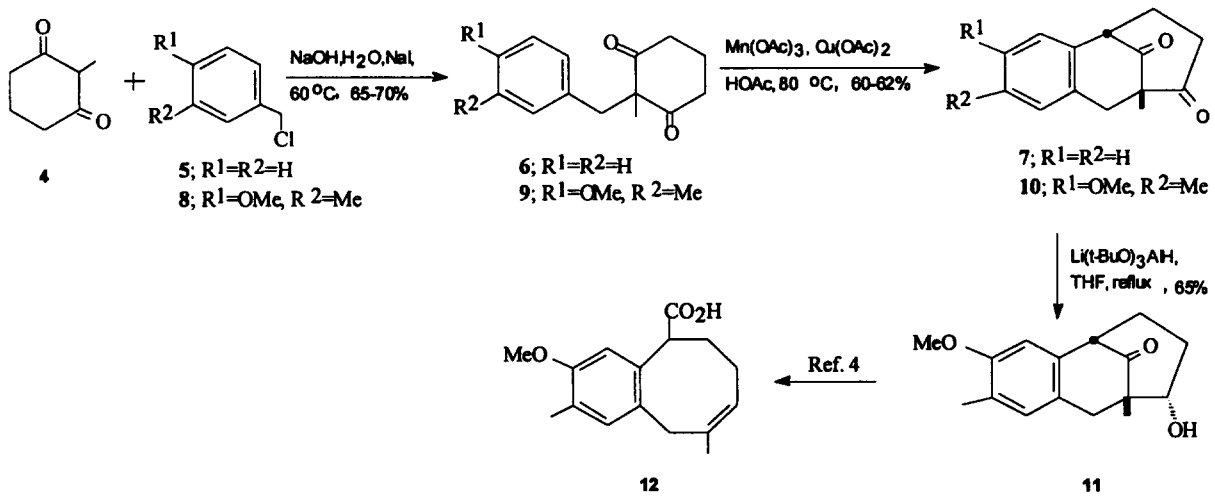
2

* Corresponding author. Tel: (91) 33 473 4971; fax: (91) 33 473 2805; e-mail: ocrvv@mahendra.iacs.res.in

† Dedicated to the memory of Professor R. A. Raphael.

PII: S0040-4039(99)01521-X

Alkylation[7] of 2-methylcyclohexane-1,3-dione **4** with benzyl chloride **5** afforded the *C*-alkylated product **6** in 70% yield (Scheme 1). Reaction of **6** in acetic acid with 2.5 equivalents of $Mn(OAc)_3$ and 1 equivalent of $Cu(OAc)_2 \cdot H_2O$ at 80°C for 5 h furnished the bridged bicyclo[3.3.1]nonandione **7** in 62% yield. The structural assignment was adequately supported by analytical and spectroscopic features.[8] In order to extend this methodology to a formal synthesis of **1**, dione **4** was alkylated with 3-methyl-4-methoxybenzyl chloride **8** to afford **9** in 65% yield. Oxidative cyclisation of **9** initiated by $Mn(OAc)_3$ as for **6** furnished in 60% yield the desired benzobicyclo[3.3.1]nonandione **10**. The two aromatic protons in **10** appeared as two singlets in the ^1H NMR spectrum establishing the regioselectivity of cyclisation. Regio- and stereoselective reduction of the least hindered carbonyl group in **10** was achieved by reaction with lithiumhydridotri *t*-butoxyaluminate[9] to produce the equatorial ketol **11** in 65% yield. Conversion to the corresponding mesylate followed by a Grob fragmentation as reported[4] afforded the benzocyclooctene carboxylic acid **12** in 80% overall yield. The spectroscopic features of the ketol **11** and the acid **12** and the melting point of **12** were in full agreement with those reported previously.[4] Since the acid **12** has been converted to parvifoline **1**[4] the present efforts constituted a formal synthesis of **1**. The synthesis thus demonstrates the versatility of manganese(III)-catalysed oxidative cyclisation of ketones onto aromatic rings to generate synthetically useful ring systems and the synthesis of an advanced intermediate is achieved in a short number of steps and good overall yield.



Scheme 1.

Acknowledgements

We sincerely thank the Department of Science and Technology, New Delhi, Government of India for generous funding of this project.

References

1. Bohlmann, F.; Zdero, Ch. *Chem. Ber.* **1977**, *110*, 468; Joseph-Nathan, P.; Hermandez, J. D.; Roman, L. U.; Garcia, E.; Mendoza, V. *Phytochemistry* **1982**, *21*, 669; Joseph-Nathan, P.; Hernandez, J. D.; Roman, L. U.; Garcia, E.; Mendoza, V.; Mendoza, S. *Phytochemistry* **1982**, *21*, 1129; Garcia, E.; Mendoza, V.; Guzman, J. A. *J. Nat. Prod.* **1988**, *51*, 150.
2. Grimm, E. L.; Levac, S.; Contu, M. L. *Tetrahedron Lett.* **1994**, *35*, 5369.

3. Villagomez-Ibarra, R.; Joseph-Nathan, P. *Tetrahedron Lett.* **1994**, *35*, 4771; Villagomez-Ibarra, R.; Alvarez-Cisneros, C.; Joseph-Nathan, P. *Tetrahedron* **1995**, *51*, 9285.
4. Covarrubias-Zuniga, A.; Cantu, F.; Maldonado, L. A. *J. Org. Chem.* **1998**, *63*, 2918.
5. For a recent review, see: Snider, B. B. *Chem. Rev.* **1996**, *96*, 339.
6. Cole, B. M.; Han, L.; Snider, B. B. *J. Org. Chem.* **1996**, *61*, 7832.
7. Schick, H.; Schwarz, H.; Finger, A. *Tetrahedron* **1982**, *38*, 1279.
8. All compounds reported herein gave analytical and spectral data in agreement with assigned structures. Selected spectral data for **7**: IR 1730, 1700 cm^{-1}; ^1H NMR (300 MHz), δ 1.32 (s, 3H), 3.20 and 3.26 (AB_q, J 17.7 Hz, 2H) 3.84 (t, J 3.3 Hz, 1H); for **10**: IR 1735, 1699 cm^{-1}; ^1H NMR (300 MHz) δ 1.30 (s, 3H), 2.17 (s, 3H), 3.11 and 3.21 (AB_q, J 17.1 Hz, 2H), 3.77 (t, J 3.3 Hz, 1H), 3.82 (s, 3H), 6.49 (s, 1H), 6.84 (s, 1H).
9. Colvin, E. W.; Martin, J.; Parker, W.; Raphael, R. A.; Shroot, B.; Doyle, M. *J. Chem. Soc., Perkin Trans. 1* **1972**, 860.