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

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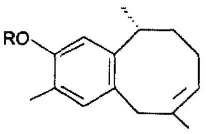
Abstract

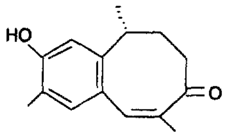
A short, formal synthesis of the phenolic sesquiterpene (±) parvifoline **1** is described involving manganese(III)-based oxidative arylation of the ketone **9** as the key step. © 1999 Published by Elsevier Science Ltd. All rights reserved.

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



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

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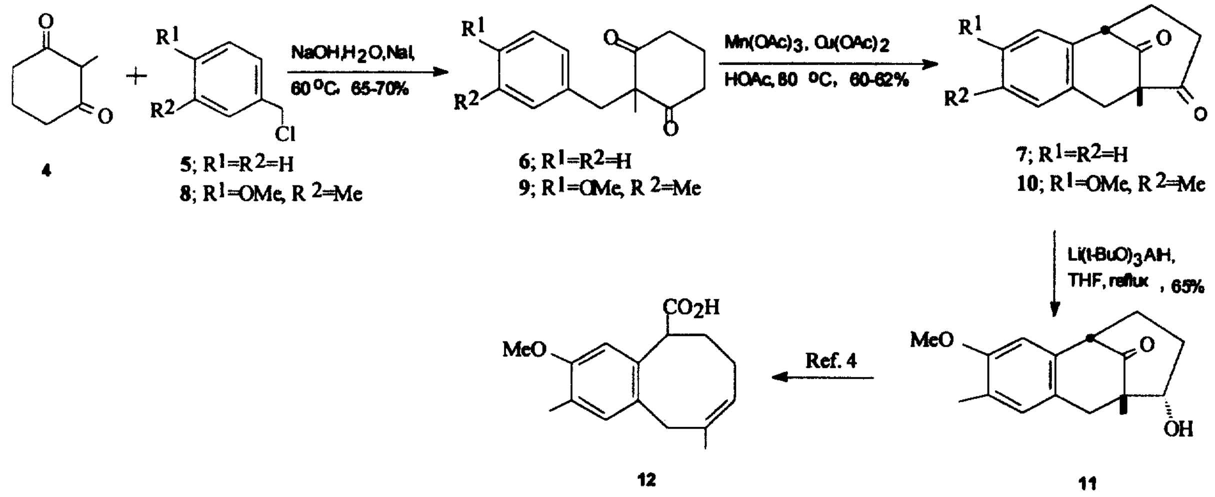
Alkylation[7] of 2-methylcyclohexane-1,3-dione **4** with benzyl chloride **5** afforded the *C*-alkylated product **6** in 70% yield (Scheme 1). Reaction of **6** in acetic acid with 2.5 equivalents of $Mn(OAc)_3$ and 1 equivalent of $Cu(OAc)_2 \cdot H_2O$ at 80°C for 5 h furnished the bridged bicyclo[3.3.1]nonandione **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

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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}; ^{1}H 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}; ^{1}H 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).
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