1 PERKIN

Chemo-enzymatic preparation of hydroxymethyl ketones

Csaba Paizs,[a] Monica Toşa,[a] Cornelia Majdik,[a] Viktória Bódai,[b] Lajos Novák,[b] Florin-Dan Irimie *[a] and László Poppe *[b]

[a] *Department of Biochemistry and Biochemical Engineering, Babes-Bolyai University, Arany János 11, RO-3400 Cluj-Napoca, Romania. E-mail: irimie@chem.ubbcluj.ro; Fax: (+40-64) 190 818; Tel: (+40-64) 193 833*

[b] *Institute for Organic Chemistry and Research Group for Alkaloid Chemistry of the Hungarian Academy of Sciences, Budapest University of Technology and Economics, Gellért tér 4, H-1111 Budapest, Hungary. E-mail: poppe@mail.bme.hu; Fax: (+36-1) 463 3297; Tel: (+36-1) 463 2229*

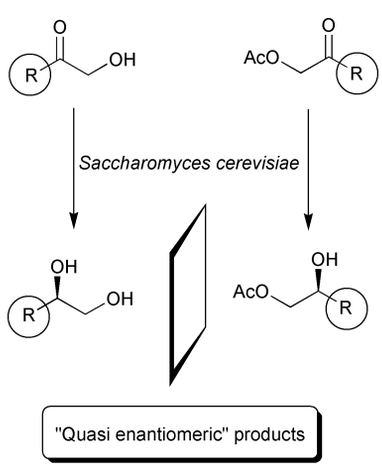
Received (in Cambridge, UK) 12th July 2002, Accepted 27th August 2002
First published as an Advance Article on the web 27th September 2002

A series of hydroxymethyl ketones **4a**–**g** were obtained from the corresponding halogenomethyl ketones **2a**–**g** *via* their transformation into acetoxymethyl ketones **3a**–**g** by 18-crown-6 catalysed substitution with NaOAc followed by Novozyme 435™ catalysed ethanolysis. This convenient chemo-enzymatic route provides a mild, heavy-metal-free alternative to the direct α-hydroxylations of methyl ketones **1a**–**g**.

Introduction

The two main reasons for which organic chemists use enzymatic methods are selectivity and mild reaction conditions. We have previously investigated the stereoselective reductions with baker's yeast of 1-aryloxypropan-2-ones[1] and 3-*O*-protected dihydroxyacetone derivatives.[2] In order to explore the scope of these mild and effective stereoselective bioreductions, we set out to develop a mild, efficient and generally applicable method for the preparation of similar hydroxymethyl ketones and their acetates.

The known examples for enantiotope selective reduction of hydroxymethyl ketones[2–10] or acetoxymethyl ketones[1,2,7,8] with baker's yeast showed that ketones with a relatively small and hydrophilic hydroxymethyl group were all attacked from the same face, although as a result of the sequence rules, the products may have different configuration labels. On the other hand, acetoxymethyl ketones were reduced with the opposite preference.



This inversion in the sense of enantiomeric preference was demonstrated by baker's yeast reductions of phenacyl alcohols and their acetates[8,11] or of 3-*O*-protected dihydroxyacetone derivatives.[2] A similar reduction of hydroxymethyl ketones and their acetates by *Geotrichum* sp., however, proceeded without inversion of the sense of the enantiotope selectivity.[12]

Several systems were developed for the direct oxidation of enolizable ketones. For example, oxidations with several reagents based on iodosylbenzene derivatives were reported such as iodosylbenzene, NaOH in MeOH;[13] $PhI(OAc)_2$–CF_3CO_2H in MeCN–H_2O;[14] polymer supported $PhI(OAc)_2$–CF_3CO_2H system.[15] $PhI(OCOCF_3)_2$ was also applied for direct oxidation of aromatic,[16] aliphatic[17] or heteroaromatic[17] methyl ketones.

Another approach is the base mediated conversion of the ketone into an enolate followed by oxidation. This way, hydroxylation of a methyl ketone was performed with LDA in THF and subsequent treatment with dimethyldioxirane.[18] Methods based on oxidation of silylated enols have also been reported. The LDA–TMSCl or KH–TMSCl silylation of enolizable precursors followed by NMO–cat. OsO_4 oxidation[19] or the LDA–TMSCl treatment and subsequent oxidation with MCPBA[20] resulted in the formation of the corresponding hydroxy derivatives.

Oxidations with 4-nitrobenzenesulfonic acid–$Tl(OAc)_3$ in refluxing MeCN followed by treatment with DMSO–H_2O[21] or with $Mn(OAc)_3$ in refluxing benzene[22] were also reported.

Although these direct oxidations of the enolizable methyl ketones are well established methods, they suffer often from several drawbacks (*i.e.* expensive, toxic reagents, over-oxidized by-products and low yield).

In this paper we report a convenient, three-step chemo-enzymatic sequence (Table 1, Scheme 1) for indirect conversion of methyl ketones **1a**–**g** into hydroxymethyl ketones **4a**–**g** *via* acetates **3a**–**g** obtained by 18-crown-6 catalyzed substitution of the corresponding halogenomethyl ketones **2a**–**g** with NaOAc, followed, as the final step, by a mild and efficient lipase-catalyzed ethanolysis.

To evaluate the scope and limitations of our method, two aromatic, three heteroaromatic and two aliphatic methyl ketones were chosen as test compounds (Scheme 1).

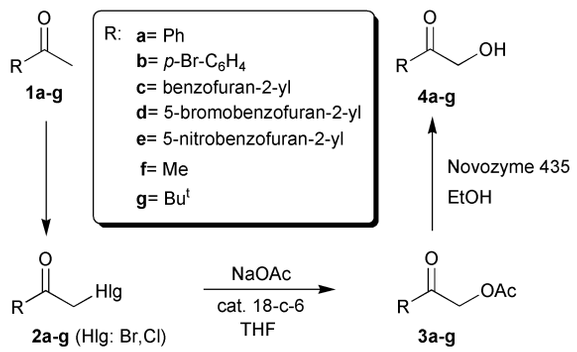
Halogenation, especially bromination at the α-position of the methyl ketones – the first step of this sequence – is a well established process. For this purpose, Br_2 in various solvents such as AcOH[23] or Et_2O,[24] tetrabutylammonium tribromide in

 DOI: 10.1039/b206851f

Table 1 Preparation of hydroxymethyl ketones **4a**–**g**

1–4	Halogen in **2a**–**g**	**3a**–**g** Yield (%)	**4a**–**g** Yield (%)
a	Br	93	92
b	Br	95	95
c	Br	92	91
d	Br	88	93
e	Br	91	89
f	Cl	92	60[a]
g	Br	89	75

[a] Calculated yield. Based on the ^{1}H-NMR spectrum of the reaction mixture in MeOH-d_4.



Scheme 1 Preparation of hydroxymethyl ketones **4a**–**g**.

CH_2Cl_2–MeOH,[25] polymer-supported pyridinium bromide perbromide in toluene,[26] 5,5-dibromobarbituric acid in Et_2O[27] or 2-pyrrolidinone hydrotribromide in 2-pyrrolidinone[28] have been successfully applied. By using $CuBr_2$, side chain bromination can be performed even in the presence of an electron rich aromatic ring.[29] Halogenomethyl ketones **2a**,**b**,**f**,**g** are commercially available, **2c**[30] and **2d**[31] are also known compounds. Because the halogenation is a well established process and only the 2-bromo-1-(5-nitrobenzofuran-2-yl)ethanone (**2e**) was newly synthesized, we did not refine this step.

Substitution of the halogen by an acetoxy group – the second step – has also been reported many times. Substitution of bromine has been carried out with AcOH in the presence of a base such as Na_2CO_3 in refluxing EtOH–H_2O,[32] Et_3N[33] or $KHCO_3$[34] in acetone; or with AcOH and KF in DMF.[35] Salts of acetic acid such as NaOAc in AcOH,[36] KOAc–KI in acetone–AcOH[37] can also be applied. Interestingly, only one example of phase transfer catalysis by 18-crown-6 for acceleration of the AcOH–0.1 M KOH reaction in acetonitrile was found.[38] Although some of these methods – such as the fluoride promoted substitution of bromomethyl ketones with AcOH in DMF[35] – gave excellent yields, we have developed another efficient method in a lower temperature boiling solvent. Thus, halides **2a**–**g** were transformed into acetates **3a**–**g** in good yields by solid–liquid phase-transfer catalysis with NaOAc–18-crown-6 in dry THF.

Although the last step – transformation of the acetates **3a**–**g** into hydroxymethyl ketones **4a**–**g** – seems to be easy, this reaction is not trivial because the simple α-keto alcohols are known to be unstable due to the formation of enols, hemiacetals, cyclic dimers or to other isomerization–disproportion processes. Accordingly, only a single example describing the liberation of the hydroxymethyl ketone from its acetate by solvolysis in refluxing MeOH[39] has been found. It is worth mentioning that all of our efforts failed for efficient chemical deacetylation of 1-acetoxy-3-aryloxypropan-2-ones.[1] To overcome this problem, an enzymatic method was developed for mild and effective conversion of the acetates **3a**–**g** into the parent alcohols **4a**–**g**. Screening of a dozen commercially available lipases using 2-acetoxy-1-phenylethanone (**3a**) as a substrate in ethanol revealed that Novozyme 435™ is particularly convenient in the last step. Deacetylation of further substrates **3a**–**g** (Scheme 1, Table 1) confirmed the general applicability of this enzyme for the liberation of alcohols **4a**–**g** by mild alcoholysis in EtOH or MeOH.

In conclusion, a novel, generally applicable three-step conversion of methyl ketones **1a**–**g** into hydroxymethyl ketones **4a**–**g** has been elaborated. The key step in this sequence is a clean and mild lipase catalyzed alcoholysis of the acetoxymethyl ketone intermediates **3a**–**g**.

Experimental

NMR spectra were recorded on a Bruker DRX-500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C; $CDCl_3$; TMS). IR spectra were taken on a Specord 2000 spectrometer.

Halogenomethyl ketones, 2a–g

The halogenomethyl ketones **2a**,**b**,**f**,**g** were products of Fluka. The bromomethyl ketones **2c**[30] and **2d**[31] were prepared according to the published procedures.

2-Bromo-1-(5-nitrobenzofuran-2-yl)ethanone, 2e

Br_2 (19.4 mmol, 3.11 g, 1 ml) dissolved in CH_2Cl_2 (10 ml) was added dropwise to a solution of 1-(5-nitrobenzofuran-2-yl)ethanone (**1e**, 19.4 mmol) in CH_2Cl_2 (30 ml) at room temperature over 30 min. After the reaction was complete (about 20 min, checked by TLC), the mixture was washed with 10% $NaHCO_3$ solution (2 × 25 ml) and brine (25 ml). The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was recrystallized from ethanol yielding **2e** (73%) as white crystals (Found: C, 42.18; H, 2.18; Br, 28.18; N, 4.88. Calc. for $C_{10}H_6BrNO_4$: C, 42.28; H, 2.13; Br, 28.13; N, 4.93%); mp 126–127 °C (from EtOH); ν_{max}(KBr)/cm^{-1} 1688, 1624, 1552, 1520, 1344, 1144, 1012, 820, 752, 680; δ_H 4.46 (2H, s), 7.73 (1H, d), 7.92 (1H, s), 8.43 (1H, dd), 8.70 (1H, d); δ_C 29.97, 113.45, 114.90, 120.35, 124.18, 127.33, 145.23, 152.82, 158.16, 182.10.

Acetoxymethyl ketones, 3a–g

To the corresponding halogenomethyl ketone (**2a**–**g**, 5 mmol) dissolved in anhydrous THF (10 ml), NaOAc (10 mmol, 0.85 g) and 18-crown-6 (0.19 mmol, 50 mg) were added and the mixture was stirred under reflux for 2 h. After cooling, the reaction mixture was filtered and the solvent was distilled off from the filtrate *in vacuo*. The crude product was extracted from the residue with CH_2Cl_2–acetone (1 : $1_{v/v}$, 50 ml), the organic extract dried and evaporated under reduced pressure. The residue was purified by column chromatography on silica using CH_2Cl_2–acetone 10 : $1_{v/v}$ as eluent to give **3a**–**e** as white crystals or **3f**,**g** as colorless oils in the yields shown in Table 1.

All data of the known compounds [**3a** (mp, IR, ^{1}H NMR and ^{13}C NMR);[40] **3b** mp,[41] IR[42] and ^{1}H NMR;[11] **3c** mp;[43] **3f** (IR, ^{1}H NMR and ^{13}C NMR);[44] **3g** (IR, ^{1}H NMR and ^{13}C NMR)[45]] agreed with the published results.

Additional spectral data for known compounds: **3b**: δ_C 20.93, 66.23, 129.54, 129.65, 132.63, 133.32, 170.75, 191.73; **3c**: ν_{max}(KBr)/cm^{-1} 1748, 1704, 1560, 1384, 1272, 1228, 1180, 1160, 1136, 1112, 1080, 1008, 832, 752; δ_H 2.24 (3H, s), 5.31 (2H, s), 7.33 (1H, t), 7.50 (1H, m), 7.58 (2H, s), 7.71 (1H, d); δ_C 20.50, 65.79, 112.44, 113.35, 123.47, 124.19, 126.66, 128.70, 150.37, 155.60, 170.29, 183.72.

Data for new compounds: **3d** (Found: C, 48.62; H, 3.08; Br, 25.71. Calc. for $C_{12}H_9BrO_4$: C, 48.51; H, 3.05; Br, 26.89%); mp 81 °C; ν_{max}(KBr)/cm^{-1} 1744, 1696, 1584, 1224, 1072, 1000, 968, 816; δ_H 2.23 (3H, s), 5.28 (2H, s), 7.62–7.64 (2H, d), 7.76–7.79 (2H, d); δ_C 20.69, 66.00, 129.30, 129.42, 132.41, 133.11, 140.02, 144.54, 145.10, 151.29, 170.53, 191.51. **3e** (Found: C, 54.22; H, 3.38; N, 5.38. Calc. for $C_{12}H_9NO_6$: C, 54.76; H, 3.45; N, 5.32%); mp 108 °C; ν_{max}(KBr)/cm^{-1} 1744, 1700, 1520, 1352, 1244, 1072,

1008; δ_H 2.25 (3H, s), 5.32 (2H, s), 7.70 (1H, m), 7.72 (1H, s), 8.41 (1H, dd), 8.69 (1H, d); δ_C 20.61, 65.98, 83.64, 113.36, 113.58, 120.32, 120.62, 124.05, 127.16, 145.23, 153.03, 157.98, 170.41, 183.62.

Hydroxymethyl ketones, 4a–g

(a) Into a solution of 2-acetoxymethyl ketones (**3a**–**e**,**g**, 5 mmol) in ethanol (5 ml), Novozyme 435™ (50 mg) was added. The reaction mixture was shaken (250 rpm) at room temperature (1.5 h for **3a**–**d**, and 32 h for **3g**). The enzyme was filtered off from the reaction mixture and washed with acetone (2 × 5 ml). The combined filtrates were evaporated, and the residue was purified by column chromatography (silica gel, CH_2Cl_2–acetone 9 : $1_{v/v}$) giving **4a**–**e** as white solids or **4g** as a colorless oil in the yields shown in Table 1. *(b)* Into a solution of 1-acetoxypropan-2-one (**3f**, 1 mmol) in MeOH-d_4 (1 ml), Novozyme 435™ (10 mg) was added. The reaction mixture was shaken (250 rpm) at room temperature for 24 h. After removing the enzyme by filtration, the residue was analyzed by NMR as such.

All data of the known hydroxymethyl ketones [**4a** (mp, IR, ^{1}H NMR and ^{13}C NMR);[46] **4b** mp,[47] (IR and ^{1}H NMR);[48] **4c** (mp and ^{1}H NMR);[49] **4f** (^{1}H NMR and ^{13}C NMR);[50] **4g** (IR, ^{1}H NMR and ^{13}C NMR)[51]] agreed with the published results.

Additional spectral data for known compounds: **4b**: δ_C 65.83, 129.53, 129.94, 132.52, 132.76, 197.93; **4c**: ν_{max}(KBr)/cm^{-1} 3424, 1676, 1552, 1288, 1172, 1104, 1008; δ_C 65.79, 112.44, 113.35, 123.47, 124.19, 126.66, 128.70, 150.37, 155.60, 183.72.

Data for new compounds: **4d** (Found: C, 47.12; H, 2.67; Br, 31.44. Calc. for $C_{10}H_7BrO_3$: C, 47.09; H, 2.77; Br, 31.33%); mp 156 °C; ν_{max}(KBr)/cm^{-1} 3432, 1680, 1544, 1440, 1292, 1168, 1112, 1008; δ_H (DMSO-d_6) 4.71 (2H, d), 5.43 (1H, t, OH), 7.64 (1H, dd), 7.69 (1H, d), 7.84 (1H, s), 8.04 (1H, d); δ_C (DMSO-d_6) 65.33, 113.00, 114.36, 116.24, 125.98, 128.86, 131.00, 151.22, 153.52, 190.18. **4e**: (Found: C, 54.25; H, 3.18; N, 6.36. Calc. for $C_{10}H_7NO_5$: C, 54.31; H, 3.19; N, 6.33%); mp 160 °C; ν_{max}(KBr)/cm^{-1} 3424, 3104, 1680, 1624, 1528, 1440, 1344, 1264, 1176, 1072, 1008, 832; δ_H (MeOH-d_4) 4.74 (2H, s), 7.97 (1H, d), 8.07 (1H, s), 8.38 (1H, d), 8.81 (1H; s); δ_C (MeOH-d_4) 65.41, 113.36, 114.27, 120.41, 123.44, 127.23, 144.34, 152.64, 157.22, 190.12.

Acknowledgements

The authors thank the Hungarian OTKA (T-033112) for financial support. The Agora Fundation is gratefully acknowledged for short-term fellowships (to Cs. P. and C. M.).

References

1 G. Egri, A. Kolbert, J. Bálint, E. Fogassy, L. Novák and L. Poppe, *Tetrahedron: Asymmetry*, 1998, **9**, 271.
2 J. Bálint, G. Egri, A. Kolbert, Cs. Dianóczky, E. Fogassy, L. Novák and L. Poppe, *Tetrahedron: Asymmetry*, 1999, **10**, 4017.
3 P. A. Levene and A. Walti, *Org. Synth., Coll. Vol. 2*, 1943, 545.
4 J. P. Guette and N. Spassky, *Bull. Soc. Chim. Fr.*, 1972, 4217.
5 D. D. Ridley and M. Stralow, *J. Chem. Soc., Chem. Commun.*, 1975, 400.
6 J. Barry and H. B. Kagan, *Synthesis*, 1981, 453.
7 F. Aragozzini, E. Maconi, C. Potenza and C. Scolastico, *Synthesis*, 1989, 225.
8 A. Manzocchi, A. Fiecchi and E. Santaniello, *J. Org. Chem.*, 1988, **53**, 4405.
9 V. Waagen, V. Partali, I. Hollingsaeter, M. S. S. Huang and T. Anthonsen, *Acta Chem. Scand.*, 1994, **48**, 506.
10 C. Y. Watson, W. J. D. Whish and M. D. Threadgill, *Bioorg. Med. Chem.*, 1998, **6**, 721.
11 (*a*) P. Ferraboschi, P. Grisenti, A. Manzocchi and E. Santaniello, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2469; (*b*) P. Ferraboschi, P. Grisenti, A. Manzocchi and E. Santaniello, *Tetrahedron*, 1994, **50**, 10539.
12 Z.-L. Wei, Z.-Y. Li and G.-Q. Lin, *Tetrahedron*, 1998, **54**, 13059.
13 R. M. Moriarty, H. Hu and S. C. Gupta, *Tetrahedron Lett.*, 1981, **22**, 1283.
14 C. Y. Watson, W. J. D. Whish and M. D. Threadgill, *Bioorg. Med. Chem.*, 1998, **6**, 721.
15 S. V. Ley, A. W. Thomas and H. Finch, *J. Chem. Soc., Perkin Trans. 1*, 1999, 669.
16 O. Prakash and V. Sharma, *Ind. J. Chem., Sect. B*, 1999, **38**, 229.
17 R. M. Moriarty, B. A. Berglund and R. Penmasta, *Tetrahedron Lett.*, 1992, **33**, 6065.
18 K. R. Guertin and T.-H. Chan, *Tetrahedron Lett.*, 1991, **32**, 715.
19 J. P. McCormick, W. Tomasik and M. W. Johnson, *Tetrahedron Lett.*, 1981, **22**, 607.
20 I. S. Marcos, J. L. Gonzalez, M. J. Sexmero, D. Díez, P. Basabe, D. J. Williams, M. S. J. Simmonds and J. G. Urones, *Tetrahedron Lett.*, 2000, **41**, 2553.
21 J. C. Lee, C. Park and Y. Choi, *Synth. Commun.*, 1997, **27**, 4079.
22 A. S. Demir, N. Camkerten, H. Akgun, C. Tanyeli, A. S. Mahashneh and D. S. Watt, *Synth. Commun.*, 1990, **20**, 2279.
23 T. Ganesh, Ch. H. Kumar and G. L. D. Krupadanam, *Synth. Commun.*, 1999, **29**, 2069.
24 C.-H. Park and R. S. Givens, *J. Am. Chem. Soc.*, 1997, **119**, 2453.
25 S. Kajigaeshi, T. Kakinami, T. Okamoto and S. Fujisaki, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 1159.
26 J. Habermann, S. V. Ley and R. Smits, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2421.
27 G. Grundke, W. Keese and M. Rimpler, *Chem. Ber.*, 1985, **118**, 4288.
28 H.-C. Zhang, B. D. Harris, M. J. Costanzo, E. C. Lawson, C. A. Maryanoff and B. E. Maryanoff, *J. Org. Chem.*, 1998, **63**, 7964.
29 (*a*) L. C. King and G. K. Ostrum, *J. Org. Chem.*, 1964, **29**, 3459; (*b*) D. S. C. Black, N. Kumar and D. B. McConnell, *Tetrahedron*, 2001, **57**, 2203.
30 S. Laufer, H.-G. Striegel, K. Neher, P. Zechmeister, C. Donat, K. Stolingwa, S. Baur, S. Tries, T. Kammermeier, G. Dannhardt and W. Kiefer, *Arch. Pharm. (Weinheim, Ger.)*, 1997, **330**, 307.
31 H. S. Bevinakatti and V. V. Badiger, *J. Heterocycl. Chem.*, 1982, **19**, 69.
32 W. Pei, S. Li, X. Nie, Y. Li, J. Pei, B. Chen, J. Wu and X. Ye, *Synthesis*, 1998, 1298.
33 H. Sakuragi, T. Koyama, M. Sakurazawa, N. Yasui, K. Tokumaru and K. Ueno, *Bull. Chem. Soc. Jpn.*, 1994, **67**, 1769.
34 A. Takadate, T. Masuda, C. Murata, T. Tanaka and S. Goya, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 3105.
35 J. M. Miller, I. D. Brindle, S. R. Cater, K.-H. So and J. H. Clark, *Anal. Chem.*, 1980, **52**, 2430.
36 J. I. DeGraw, *Tetrahedron*, 1972, **28**, 967.
37 R. H. Levin, B. J. Magerlin, A. V. Jr. McIntosh, A. R. Hanze, G. S. Fonken, J. L. Thompson, A. M Searcy, M. A. Scheri and E. S. Gutsell, *J. Am. Chem. Soc.*, 1954, **76**, 546.
38 D. E. Cane, H. Hasler, P. B. Taylor and T.-C. Liang, *Tetrahedron*, 1983, **39**, 3449.
39 A. Grün, W. Stoll and A. G. Geigy, USP 2 374 283/1945 (*Chem. Abstr.*, 1945, **39**, p35366).
40 M. Goodall, P. M. Kelly, D. Parker, K. Gloe and H. Stephan, *J. Chem. Soc., Perkin Trans. 2*, 1997, 59.
41 Y. G. Ballon, *Zh. Org. Khim.*, 1979, 2351.
42 R. J. Copeland, R. A. Hill, D. J. Hinchcliffe and J. Staunton, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1013.
43 W. Shriner and B. Anderson, *J. Am. Chem. Soc.*, 1939, **61**, 2705.
44 M. Singh and R. W. Murray, *J. Org. Chem.*, 1992, **57**, 4263.
45 K. Griesbaum and R. Greinert, *Chem. Ber.*, 1990, **123**, 391.
46 S. Muthusamy, S. A. Babu, C. Gunananthan and R. V. Jasra, *Tetrahedron Lett.*, 2001, **42**, 5113.
47 C. Brindle and A. Gibbson, *J. Chem. Soc., Perkin Trans. 1*, 1979, 517.
48 B. Plesnicar, J. Smolikova, V. Jehlicka and O. Exner, *Collect. Czech. Chem. Commun.*, 1978, **43**, 2754.
49 R. M. Moriarty, M. P. Duncan and O. Prakash, *J. Chem. Soc., Perkin Trans.1*, 1987, 1781.
50 A. G. Blackman, D. A. Buckingham, C. R. Clark and J. Simpson, *J. Chem. Soc., Dalton Trans.*, 1991, 3031.
51 T. Matsumoto, M. Ohishi and S. Inoue, *J. Org. Chem.*, 1985, **50**, 603.