Synthesis and structural aspects of some intermediates in furofuran lignan synthesis

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The synthesis of some intermediates of furofuran lignans was accomplished by a chemical cyclisation reaction using *N*-ethylpiperidine hypophosphite and azobisisobutyronitrile. This reaction afforded the 5-*exo*-dig cyclic compound as the major product along with another isomeric cyclic compound which possess an endocyclic double bond. A brief discussion is presented to explain the formation of these isomeric cyclic compounds by a base-catalysed tautomerism mechanism. Some structural aspects are discussed based on nuclear magnetic resonance data.

Keywords: radical cyclisation, hypophosphite salt, furofuran lignans

Biologically-active naturally occurring lignans have attracted considerable attention from organic chemists.[1] Radical cyclisation continues to be a method for the preparation of natural products containing heterocyclic rings.[2,3] Most radical cyclisations in heterocyclic chemistry are still accomplished using tri-*n*-butyltin hydride, Bu_3SnH.[3-5] Such syntheses involve the use of an excess of Bu_3SnH in the presence of a small amount of radical initiator, usually azobisisobutyronitrile (AIBN).

To avoid the problems associated with the use of Bu_3SnH, such as, product purification, high cost and toxicity, considerable effort has been aimed at the development of more user- and environmentally-friendly reagents for the generation of reactive radicals.[6,7] For example, C–C bond formation by radical cyclisation has been performed using hypophosphite salts (*e.g. N*-ethylpiperidine hypophosphite, EPHP) acting on alkyl bromide substrates with alkyne[8,9] or alkene[10] side chains.

A convenient alternative to synthetic methods involving organometallic hydrides is the use of electrogenerated nickel(I) complexes as mediators for reductive intramolecular cyclisations.[11-17] This methodology proved to be successful in the formation of carbocyclic products from various organic halides.[11-13] Olivero *et al.*[13] have employed electrogenerated Ni(I) species to catalyse the intramolecular cyclisation of 2-haloaryl ethers containing unsaturated side chains.

Over the past few years we have focused our attention on electroreductive intramolecular cyclisation using macrocyclic Ni(II) complexes in order to synthesise carbocyclic products[17] and substituted tetrahydrofurans.[18,19] Bromopropargyloxy substrates and cyclic products were prepared as starting materials and standard samples for GC analysis, respectively, as shown in Scheme 1.

In this paper we present a brief discussion of the stereochemical outcome of the bromoalkoxylation and cyclisation reactions based on NMR spectroscopic analysis. The bromoalkoxylation reactions were carried out by two different methods in order to improve the yields.[20,21]

Results and discussion

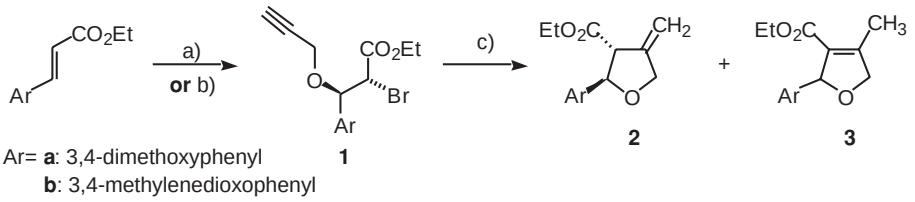
Our chemical cyclisation reactions afforded **2** along with another product, isomeric with **2** (**a** and **b**) and identified as **3** (**a** and **b**). To the best of our knowledge this is the first time that compound **3** has been obtained. The formation of **3a** was corroborated by our studies on electroreductive intramolecular cyclisation. Indeed, this compound was one of the two major products recovered from the electrolysis medium.[19]

Based on Baldwin's rules[22] it might be predicted that compound **2** would be the only cyclic substrate formed. The radical obtained from **1** by abstraction of Br• cyclises preferentially in a 5-*exo*-dig manner. We believe that compound **3** is formed *via* a base-catalysed isomerisation of **2**. The proton adjacent to the carboxylic ester group in **2** is strongly acidic. If the $(HPO_2Br)^-$ anion, present in the reaction medium of chemical cyclisation, acts as a base for compound **2**, a stabilised carbanion is formed which can add a proton affording **3**. Moreover, it is well-established in the literature[23] that unconjugated β,γ-unsaturated carbonyl compounds readily rearrange to their thermodynamically more stable conjugated isomers. In these base-catalysed reactions, the intermediate is a conjugated dienolate ion, which is reprotonated at the γ-carbon. We have also proposed a similar mechanism for the formation of **3** under electrochemical cyclisation conditions.[19] Changing the ester group to a moderate electron-withdrawing group (phenyl), the cyclisation reaction afforded exclusively a product of type 2.[22]

The cyclisation reactions afforded an excellent *trans* selectivity which can be properly interpreted within the stereoinduction Beckwith-Houk model.[25] The cyclisation must occur by way of the resonance stabilised radical **4** (Fig. 1) in which the hydrogen atom, geminal with the aryl group, is *syn* to the olefinic bond of the delocalised radical.

This radical may be drawn in a "chair-like" conformation **5a** and **5b** (Fig. 2) although the reaction occurred by form **5a**.

The *trans*-configuration is confirmed by the ^1H NMR data for compounds **2a** and **2b**. In fact, the coupling constants between 2-H and 3-H are about 9 Hz. Based on the Karplus



Scheme 1 Reagents and conditions: (a) *N*-bromosuccinimide, propargyl alcohol, –15°C → R.T.; (b) LiBr, cerium ammonium nitrate, propargyl alcohol, N_2, R.T.; (c) EPHP, AIBN, toluene, reflux.

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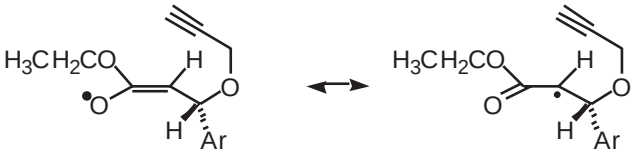

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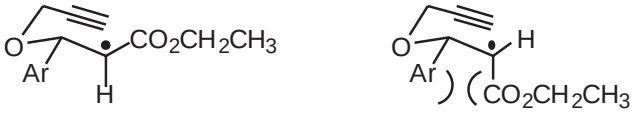
Fig. 1 Resonance forms of radical **4**.



5a **5b**

Fig. 2 Conformations of radical **4**.

equation this value for coupling constant between two vicinal protons is associated with a torsion angle approximately 180°. The value of J_{H2H3} analysed by this equation leads to an estimated H2–C2–C3–H3 dihedral angle of 166.5˚. The molecular conformation proposed for these compounds, as well as for bromoalkoxylated substrates of type **1**, was corroborated through a geometry optimisation by molecular mechanics calculations using the Hyperchem 7.0 molecular modeling software. In fact, the values calculated by this approach were 158° and 167° for **2a** and **2b**, respectively. The corresponding torsion angles for **1a** and **1b** were found to be 178° and 179°, respectively.

The ^{1}H NMR spectrum of compound **1a** was run in $CDCl_3$ and C_6D_6 to clarify some coupling patterns. In fact, the signal centred at 4.29 ppm was better resolved in C_6D_6, showing 12 lines and coupling constants of 7.2 and 10.8 Hz. The signal at 4.00 ppm was well defined appearing as a doublet of AB quartets with coupling constants of 2.4 and 15.6 Hz.

The ^{1}H NMR spectra for all compounds show some complexity of the signals due to direct and long-range couplings. Complete assignment of proton and carbon spectra was achieved by double resonance, DEPT, HMQC and HMBC techniques. None of the spectra of these compounds shows evidence of mixtures of isomers as was inferred by the appearance of only one set of signals in the ^{1}H NMR spectrum. For all compounds a common splitting pattern for the ester methylene protons was found and described as a quartet of AB quartets (although partially superimposed) with coupling constants of about 7 and 11 Hz. In our opinion the complex signal observed for the ester methylene protons of **1a**–**b** could not be attributed to a mixture of *threo* and *erythro* isomers as reported in the literature.[20] We believe that only the more stable *threo* isomer was formed as a racemic mixture. For compounds **1a** and **1b** the two methylene protons next to the triple bond are diastereotopic and are coupled to each other and also with the methyne proton. The signal in the ^{1}H NMR spectrum is in fact a doublet of AB quartets (*J* 2.4 and 15.6 Hz). This splitting could not be attributed to a 1:1 mixture of *threo* and *erythro* isomers as was claimed by Roy *et al*.[26] The data obtained from ^{1}H and ^{13}C spectra do not show duplication of any other peaks which excludes the presence of a mixture of isomers.

In conclusion, the bromoalkoxylation reaction, as well as the formation of compounds **2**, were stereoselective affording the more stable *threo* isomers as shown by nuclear magnetic resonance data. Furthermore, cyclisation reactions afforded an unexpected product **3**.

Experimental

All melting points were measured on a Gallenkamp apparatus and are uncorrected. NMR spectra were run at 25 °C. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were determined at 75.4 MHz on a Varian Unity Plus Spectrometer. In the NMR spectra was used the solvent peak as internal reference. Elemental analyses were obtained on a Leco CHNS-932. Column chromatography was performed on silica gel (230–400 mesh) under conditions that are described below. Light petroleum refers to the fraction boiling in the range 40–60 °C.

Experimental procedure for bromoalkoxylation reactions

Method A[20]*:* A solution (0.30–0.40 M) of alkene (commercial) in dry dichloromethane was added dropwise to another solution of recrystallised *N*-bromosuccinimide (1.5 equiv.) in propargyl alcohol (5 equiv.) at –15°C (salt-ice bath). The resulting mixture was stirred at this temperature for two hours followed by 24 h at room temperature. The reaction mixture was diluted with dichloromethane and successively washed with 1% aqueous sodium metabissulfite, 5% aqueous sodium thiosulfate, water and dried ($MgSO_4$). The residue was purified by flash chromatography using ethyl acetate–light petroleum 2:1 (for **1a**) or dichloromethane-diethyl ether–light petroleum 1:1:4 (for **1b**) as eluant. Recrystallisation from methanol afforded the pure **1a** in 36% yield, m.p. 79–80°C. Compound **1b** was isolated as an oil in 20% yield.

Method B[21]: To a solution of alkene (1 mmol) in dry acetonitrile (5 ml) under nitrogen it was successively added dry lithium bromide (2 equiv.), propargyl alcohol (12.4 equiv.) and a solution of cerium ammonium nitrate (1.8 equiv.) in dry acetonitrile (5 ml) at room temperature. The resulting mixture was stirred under nitrogen for 24 h. Then it was diluted with diethyl ether and washed with saturated sodium bicarbonate, water, brine, water and dried (MgSO4). The residue was purified by recrystallisation from MeOH (for **1a**) or by flash cromatography (ethyl acetate–light petroleum 1:4) (for **1b**). The yields obtained were 70 (**1a**) and 57% (**1b**); m.p. 80–81.5°C for **1a**.

Ethyl 2-bromo-3-(3',4'-dimethoxyphenyl)-3-(propargyloxy) propanoate (**1a**): δ_H ($CDCl_3$) 1.33 (3H, t *J* 7.2 Hz, OCH_2CH_3), 2.43 (1H, t *J* 2.4 Hz, $OCH_2C{\equiv}CH$), 3.88 (6H, s, 2xOCH_3), 4.00 (2H, dABq *J* 2.4 and 15.6 Hz, $OCH_2C{\equiv}CH$), 4.24 (1H, d *J* 10.0 Hz, 3-*H*), 4.29 (2H, qABq *J* 7.2 and 10.8 Hz, OCH_2CH_3), 4.93 (1H, d *J* 10.0 Hz, 2-*H*), 6.85 (1H, d *J* 8.4 Hz, 5'-*H*), 6.88 (1H, d *J* 1.8 Hz, 2'-*H*), 6.94 (1H, dd *J* 8.4 and 1.8 Hz, 6'-*H*). δ_C ($CDCl_3$) 13.88 (OCH_2CH_3), 47.48 (C-3); 55.73 and 55.82 (2xOCH_3), 56.16 ($OCH_2C{\equiv}CH$), 62.05 (OCH_2CH_3), 74.93 ($OCH_2C{\equiv}CH$), 78.58 ($OCH_2C{\equiv}CH$), 80.73 (C-2), 109.91 (C-2'), 110.44 (C-5'), 121.48 (C-6'), 128.09 (C-1'), 149.03 (C-4') or (C-3') and 149.51 (C-3') or (C-4'), 168.44 (C=O).

Ethyl 2-bromo-3-(3',4'-methylenedioxophenyl)-3-(propargyl oxy) propanoate (**1b**): δ_H ($CDCl_3$) 1.35 (3H, t *J* 7.0 Hz, OCH_2CH_3), 2.44 (1H, t *J* 2.4 Hz, $OCH_2C{\equiv}CH$), 4.00 (2H, dABq *J* 2.4 and 15.6 Hz, $OCH_2C{\equiv}CH$), 4.21 (1H, d *J* 10.2 Hz, 3-*H*), 4.31 (2H, qABq *J* 7.0 and 11.0 Hz, OCH_2CH_3), 4.87 (1H, d *J* 10.2 Hz, 2-*H*), 6.01 (2H, s, OCH_2O), 6.82 (1H, d *J* 8.4 Hz, 5'-*H*), 6.86–6.90 (2H, m, 2'-*H* and 6'-*H*). δ_C ($CDCl_3$) 13.89 (OCH_2CH_3), 47.40 (C-3), 56.14 ($OCH_2C{\equiv}CH$), 62.06 (OCH_2CH_3), 75.04 ($OCH_2C{\equiv}CH$), 78.50 ($OCH_2C{\equiv}CH$), 80.56 (C-2), 101.24 (OCH_2O), 107.56 (C-2'), 107.94 (C-5'), 122.69 (C-6'), 129.63 (C-1'), 147.92 (C-4') or (C-3') and 148.23 (C-3') or (C-4'), 168.36 (C=O).

Experimental procedure for intramolecular cyclisation reactions[9,19]

To a stirred solution of the bromoalkoxylated substrates (**1a**, **1b**; 1 mmol) in toluene (0.066 M), EPHP (5 equiv.) and AIBN (0.2 equiv.) were added. The resulting mixture was refluxed for 4 h and concentrated. The residue was taken up in dichloromethane and the solution obtained was filtered over a pad of Celite, washed with brine and water. Dried ($MgSO_4$) organic phase was concentrated and purified by flash chromatography using dichloromethane-diethyl ether-light petroleum 1:1:1 (for **2a** and **3a**) or diethyl ether-light petroleum 1:2 (for **2b** and **3b**). In both cases the first eluted material was identified as **2a** or **2b** and the second eluted material as **3a** or **3b**. Compounds **2a**–**b** and **3a**–**b** were obtained as light yellow oils, in yields (%) as follows: **2a**: 40; **2b**: 37; **3a**: 25; **3b**: 30.

2-(3',4'-Dimethoxyphenyl)-3-(ethoxycarbonyl)-4-methylene tetrahydrofuran **(2a)**: δ_H ($CDCl_3$) 1.28 (3H, t *J* 7.2 Hz, OCH_2CH_3), 3.49 (1H, apparent ddd *J* 8.7, 2.4 and 2.4 Hz, 3-*H*), 3.88 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.22 (2H, qABq *J* 7.2 and 11.0 Hz, OCH_2CH_3), 4.50 (1H, apparent dq *J* 13.2 and 2.4 Hz, 5-*H*), 4.65 (1H, br apparent d *J* 13.2 Hz, 5-*H*), 5.11 (1H, apparent q *J* 2.4 Hz, C=CH*H*), 5.19 (1H, d *J* 8.7 Hz, 2-*H*), 5.20 (1H, apparent q *J* 2.4 Hz, C=C*H*H), 6.84 (1H, d *J* 8.7 Hz, 5'-*H*), 6.90 (1H, d *J* 1.8 Hz, 2'-*H*),

6.91 (1H, dd *J* 8.7 and 1.8 Hz, 6'-*H*). δ_C ($CDCl_3$) 14.11 (OCH_2CH_3), 55.70 (OCH_3), 55.74 (OCH_3), 56.94 (C-3), 61.00 (OCH_2CH_3), 71.36 (C-5), 83.23 (C-2), 106.14 (C=CH_2), 108.86 (C-2'), 110.76 (C-5'), 118.48 (C-6'), 132.15 (C-1'), 146.44 (C-4), 148.71 (C-3') and (C-4'), 170.60 (C=O). Calc. for $C_{16}H_{20}O_5$ C, 65.73; H, 6.91. Found C, 65.64; H, 6.86.

2-(3', 4'-Methylenedioxophenyl)-3-(ethoxycarbonyl)-4-methylenetetrahydrofuran **(2b)**: δ_H ($CDCl_3$) 1.28 (3H, t *J* 7.2 Hz, OCH_2CH_3), 3.42–3.47 (1H, m, 3-*H*), 4.21 (2H, qABq *J* 7.2 and 11.0 Hz, OCH_2CH_3), 4.49 (1H, apparent dq *J* 13.0 and 2.4 Hz, 5-*H*), 4.63 (1 H, br apparent d *J* 13.0 Hz, 5-*H*), 5.10 (1H, apparent q *J* 2.4 Hz, C=CH*H*), 5.15 (1H, d *J* 8.7 Hz, 2-*H*), 5.18 (1H, apparent q *J* 2.4 Hz, C=C*H*H), 5.96 (2H, s, OCH_2O), 6.77 (1H, d *J* 8.0 Hz, 5'-*H*), 6.88 (1H, dd *J* 8.0 and 1.8 Hz, 6'-*H*), 6.90 (1H, d *J* 1.8 Hz, 2'-*H*). δ_C ($CDCl_3$) 14.17 (OCH_2CH_3), 57.12 (C-3), 61.12 (OCH_2CH_3), 71.44 (C-5), 83.28 (C-2), 101.01 (OCH_2O), 106.31 (C=CH_2), 106.51 (C-2'), 108.10 (C-5'), 119.76 (C-6'), 133.69 (C-1'), 146.36 (C-4), 147.37 (C-4') or (C-3') and 147.79 (C-3') or (C-4'), 170.60 (C=O). Calc. for $C_{15}H_{16}O_5$ C, 65.20; H, 5.85. Found C, 65.05; H, 5.69.

2-(3', 4'-Dimethoxyphenyl)-3-(ethoxycarbonyl)-4-methyl-2, 5-dihydrofuran **(3a)**: δ_H ($CDCl_3$) 1.15 (3H, t *J* 7.0 Hz, OCH_2CH_3), 2.19 (3H, apparent d *J* 1.2 Hz, 4-CH_3), 3.87 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.08 (2H, qABq *J* 7.0 and 11.0 Hz, OCH_2CH_3), 4.72 (1H, apparent ddd *J* 15.0, 3.6 and 1.2 Hz, 5-*H*), 4.89 (1H, apparent ddd *J* 15.0, 5.7 and 0.9 Hz, 5-*H*), 5.88-5.92 (1H, m, 2-*H*), 6.83 (1H, d *J* 8.1 Hz, 5'-*H*), 6.84 (1H, br s, 2'-*H*), 6.88 (1H, dd *J* 8.1 and 1.8 Hz, 6'-*H*). δ_C ($CDCl_3$) 11.95 (4-CH_3), 13.99 (OCH_2CH_3), 55.77 (OCH_3), 55.81 (OCH_3), 60.01 (OCH_2CH_3), 79.35 (C-5), 88.66 (C-2), 110.30 (C-5'), 110.73 (C-2'), 119.57 (C-6'), 127.12 (C-4), 134.09 (C-1'), 148.69 (C-3') or (C-4') and 148.73 (C-4') or (C-3'), 150.41 (C-3), 163.39 (C=O). Calc. for $C_{16}H_{20}O_5$ C, 65.73; H, 6.91. Found C, 65.50; H, 6.75.

2-(3', 4'-Methylenedioxophenyl)-3-(ethoxycarbonyl)-4-methyl-2, 5-dihydrofuran **(3b)**: δ_H ($CDCl_3$) 1.16 (3H, t *J* 7.2 Hz, OCH_2CH_3), 2.18 (3H, apparent d *J* 1.2 Hz, 4-CH_3), 4.09 (2H, qABq *J* 7.2 and 10.8 Hz, OCH_2CH_3), 4.71 (1H, apparent ddd *J* 15.0, 3.5 and 1.0 Hz, 5-*H*), 4.87 (1H, apparent ddd *J* 15.0, 5.0 and 1.0 Hz, 5-*H*), 5.83–5.87 (1H, m, 2-*H*), 5.94 (2H, s, OCH_2O), 6.76 (1H, d *J* 8.0 Hz, 5'-*H*), 6.77 (1H, d *J* 1.8 Hz, 2'-*H*), 6.82 (1H, dd *J* 8.0 and 1.8 Hz, 6'-*H*). δ_C ($CDCl_3$) 11.92 (4-CH_3), 13.99 (OCH_2CH_3), 60.03 (OCH_2CH_3), 79.41 (C-5), 88.66 (C-2), 100.95 (OCH_2O), 107.39 (C-2'), 107.88 (C-5'), 121.00 (C-6'), 127.06 (C-4), 135.59 (C-1'), 147.28 (C-4') or (C-3') and 147.56 (C-3') or (C-4'), 150.33 (C-3), 163.26 (C=O). Calc. for $C_{15}H_{16}O_5$ C, 65.20; H, 5.85. Found C, 65.10; H, 5.70.

The authors gratefully acknowledge the financial support from FEDER and Fundação para a Ciência e Tecnologia (POCTI/QUI/37808/2001).

Received 26 April 2004; accepted 10 May 2004
Paper 04/2849

References

1 T.Y. Simpson, *In The Chemistry of Natural Products*, R.H. Thomson, Ed.; Blackie: Glasgow, 1985. pp 123–125.
2 B. Giese, Radicals in Organic Synthesis: Formation of carbon–carbon bonds; Pergamon Press; Oxford, 1986.
3 A.L. Beckwith, *J. Chem. Soc. Rev.*, 1993, 143.
4 B. Venugopalan, P.J. Karnik, S. Shinde, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1015.
5 G. Stork, R. Mook Jr, *J. Am. Chem. Soc*., 1983, **105**, 3720.
6 W.R. Dolbier Jr., X.X. Rong, B.E. Smart, Z.Y. Yang, *J. Org. Chem.*, 1996, **61**, 4824.
7 J. Quirante, C. Escolano, A. Merino, J. Bonjoch, *J. Org. Chem*., 1998, **63**, 968.
8 J.M.B. Calderon, G.J. Chicharro, R.J. Fiandorn, S. Huss, RA. Ward EP 96-500056.
9 R. McCague, R.G. Pritchard, R.J. Stoodley, D. Williamson, *Chem. Commun.*, 1998, 2691.
10 S.R. Graham, J.A. Murphy, D. Coates, *Tetrahedron Lett.*, 1999, **40**, 2415.
11 S. Ozaki, E. Matsui, J. Waku, H. Ohmori, *Tetrahedron Lett.*, 1997, **38**, 2705.
12 M. Ihara, A. Katsumata, F. Setsu, Y. Tokunaga, K. Fukumoto, *J. Org. Chem.*, 1996, **61**, 677.
13 S. Olivero, J.P. Rolland, E. Duñach, *Organometallics*, 1998, **17**, 3747.
14 M.S. Mubarak, D. Peters, *J. Electroanal. Chem.*, 1992, **332**, 127.
15 D.M. Fang, D.J. Peters, M.S. Mubarak, *J. Electrochem. Soc.*, 2001, **148**, E 464-E.
16 A.P. Esteves, A.M. Freitas, M.J. Medeiros, D. Pletcher, *J. Electroanal. Chem.*, 2001, **499**, 95.
17 E. Duñach, A.P. Esteves, A.M. Freitas, M.A. Lemos, M.J. Medeiros, S. Olivero, *Tetrahedron Lett.*, 1999, **40**, 8693.
18 E. Duñach, A.P. Esteves, A.M. Freitas, M.A. Lemos, M.J. Medeiros, S. Olivero, S. *Pure Appl. Chem.*, 2001, **73**, 1941.
19 A.P. Esteves, D.M. Goken, L.J. Klein, M.A. Lemos, M.J. Medeiros, D.G. Peters, *J. Org. Chem*., 2003, **68**, 1024.
20 S.C. Roy, S. Adhikari, *Tetrahedron*, 1993, **49**, 8415.
21 S.C. Roy, C. Guin, K.K. Rana, G. Maiti, *Synlett*, 2001, 226.
22 J.E. Baldwin,. *J. Chem. Soc., Chem. Commun*., 1976, 734.
23 K.P.C. Vollhardt, N.E. Schore, *Organic Chemistry*, 2nd ed.; W. H. Freeman & Co: N. Y., 1994; 675.
24 A.P. Esteves, Unpublished results
25 D.P. Curran, N.A. Porter, B. Giese, *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996, 31.
26 S.C. Roy, C. Guin, K.K. Rana, G. Maiti, *Tetrahedron*, 2002, **58**, 2435.