Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 63 (2007) 1610–1616
Tetrahedron

One-pot regioselective synthesis of dihydronaphthofurans and dibenzofurans☆

Manish Dixit,[a] Resmi Raghunandan,[b] Brijesh Kumar,[c] P. R. Maulik[b,†] and Atul Goel[a,*]

[a]*Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow 226001, UP, India*
[b]*Molecular and Structural Biology Division, Central Drug Research Institute, Lucknow 226001, UP, India*
[c]*Sophisticated Analytical Instrument Facility, Central Drug Research Institute, Lucknow 226001, UP, India*

Received 23 August 2006; revised 17 November 2006; accepted 7 December 2006
Available online 8 January 2007

Abstract—A regioselective approach for the synthesis of substituted naphthofurans and dibenzofurans has been demonstrated through a ring transformation reaction of suitably functionalized 2*H*-pyran-2-ones by reaction with 6,7-dihydro-5*H*-benzofuran-4-one and 7-methoxybenzofuran-3-one, respectively, in high yields. The novelty of the procedure lies in the creation of an aromatic ring transformed by 2*H*-pyran-2-one involving the $-COCH_2-$ moiety of a cyclic ketone.

1. Introduction

The chemical and biological potentials of five-membered heterocyclic compounds fused with aromatic nuclei such as indole, benzofuran and their annulated derivatives have attracted the attention of organic and medicinal chemists for several years. Amongst them, the dihydronaphthofuran and dibenzofuran ring systems occupy an important place because they constitute the core skeleton of a family of structurally unique and medicinally important natural products.[1] These natural products mainly belong to sesquiterpene and arylquinone classes of aromatic compounds.[2] Due to the pronounced biological activities of many of the natural 4,5-dihydronaphthofurans such as (±)-laevigatin[3] (**1**), balsaminone[4] A (**2**) and dibenzofurans such as cannabifuran[5] **3**, ruscodibenzofuran[6] **4**, this class of compounds continues to attract the interest of researchers of both academic and pharmaceutical fields (Fig. 1).

Recently, two novel dibenzofurans, karnatakafurans A (**5**) and B (**6**) have been isolated from Novum *Aspergillus karnatakaensis* Frisvad, which were found active against *Plasmodium falciparum*.[7] A new prenylated dibenzofuran, achyrofuran[8] (**7**) was isolated from an extract of *Achyrocline satureioides*, which exhibited glucose lowering activity in *db*/*db* mouse at oral dose of 20 mg/kg q.d. Several synthetic compounds bearing this ring skeleton are associated with diverse biological activities such as antifungal,[9] antibacterial,[10] antiviral,[11] β-adrenolytic,[12] antitumor[13] and anthelmintic.[14]

Common approaches for the synthesis of naphthofurans and dibenzofurans have been reported in the literature.[1] Among them, the metal-assisted Dötz benzannulation reaction has received a great deal of attention for preparing diversely functionalized arenes and heteroarenes.[15] Many examples

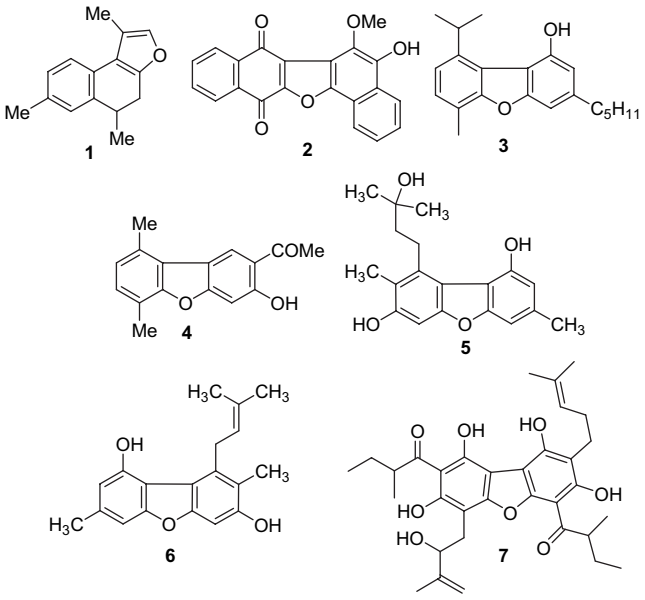


Figure 1. Naturally occurring naphthofurans and dibenzofurans.

☆ CDRI communication number: 7052.
* Corresponding author. Tel.: +91 522 2612411; fax: +91 522 2623405; e-mail: agoel13@yahoo.com
† For crystallographic enquiries.

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.12.017

of benzannulation using an array of α,β-unsaturated chromium–carbene complexes and suitably functionalized alkynes have been reported in recent years. Unfortunately the scope of these reactions suffers due to the difficulty in obtaining suitably functionalized organometallic reagents and/or the formation of undesired byproducts.

Several synthetic methodologies[16] are available for the synthesis of 1,2-substituted-naphtho[2,1-*b*]furans but access to 1,2-unsubstituted-naphthofurans is only by a paucity of methods. The general approaches for the synthesis of 1,2-substituted-naphtho[2,1-*b*]furans include reaction of 1-substituted-2-naphthol with either chloroacetone or chloroacetate esters or phenacyl bromides. But the applications of these procedures limit the scope of derivatization simply because of the need for functionalized naphthols such as 1-substituted-2-naphthols, which are not always easily available.

Various methods are available in the literature for the synthesis of dibenzofuran skeleton, which include intramolecular cyclization of 2-phenoxybenzene diazonium salt,[17] the acid-catalyzed dehydration of 2,2′-dihydroxybiphenyls or their methyl ethers,[1b] photochemical cyclization of 2-phenoxyphenols[18] and the thermal rearrangement of diquinones.[19] Despite various modifications of the reaction conditions, these cyclization reactions produced low yields of desired compounds, which restricted the applicability of these reactions.[20] Recent approaches to access dibenzofuran ring system include the flash vacuum pyrolysis of 3-(2-furoyl)cinnoline at high temperature,[21] gas-phase condensation of phenoxy radicals at moderately elevated temperature[22] and the Diels–Alder type cycloaddition of 2-isopropenyl-3-methoxybenzofuran with DMAD.[23]

The chemical and the pharmacological potentials of substituted naphthofurans and dibenzofurans and the limitations of existing procedures prompted us to develop an expeditious route to their synthesis that could offer flexibility of substituent variations on their molecular scaffold. Herein, we report an elegant route for preparing substituted naphthofurans and dibenzofurans through carbanion-induced ring transformation of 2*H*-pyran-2-ones by 6,7-dihydro-5*H*-benzofuran-4-one and benzofuran-3-one, respectively, in high yields. The advantage of the procedure lies in the construction of a phenyl ring from a lactone in a single step under mild conditions without using any organometallic reagents.

2. Results and discussion

During studies on the chemistry of 2*H*-pyran-2-ones, we found that 4-methylsulfanyl-2-oxo-6-phenyl-2*H*-pyran-3-carboxylic acid methyl esters are susceptible to carbanion attack at position 6 leading to the formation of a benzene ring under mild basic conditions at room temperature.[24] This novel conversion of an α-pyranone ring to a benzene ring (recently termed[25] as 'Lactone Methodology') utilizing methylenecarbonyl compounds under mild basic conditions encouraged us to explore this methodology for preparing various arenes and heteroarenes of particular importance.[26] The unique feature of 2*H*-pyran-2-ones **1** is the presence of three electrophilic centres: C-2, C-4 and C-6, which can be exploited regioselectively by reacting with various C-, N- and S-nucleophiles to generate molecular diversity.[27]

2.1. Synthesis of substituted naphthofurans

The 2*H*-pyran-2-ones (**1a**–**n**) used as parent precursors have been conveniently prepared by the reaction of methyl 2-carbomethoxy/cyano-3,3-dimethylsulfanylacrylate with acetophenone in high yield as described earlier.[28] There are three electrophilic centres C-2, C-4 and C-6 in lactone **1**, the latter is highly susceptible to nucleophiles due to the extended conjugation and the presence of the electron withdrawing substitutent at position 3 of the pyranone ring. The synthesis of naphtho[2,1-*b*]furans (**3a**–**n**) was achieved (Table 1) by stirring an equimolar mixture of 2*H*-pyran-2-one **1**, 6,7-dihydro-5*H*-benzofuran-4-one **2** and powdered KOH in dry DMF at room temperature for 24–30 h as shown in Scheme 1.

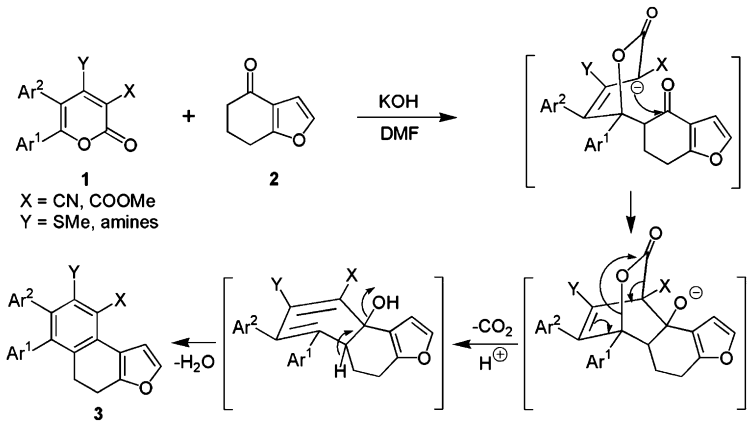
The reaction is initiated by attack of the carbanion generated in situ from 6,7-dihydro-5*H*-benzofuran-4-one **2** at position C-6 of the pyran-2-one, followed by cyclization involving the carbonyl group and C-3 of the pyran ring to form a bicyclic intermediate. This intermediate on decarboxylation, protonation and dehydration furnished naphtho[2,1-*b*]furans in good yields. The beauty of the reaction lies in the insertion of two carbon atoms of methylenecarbonyl group of **2** into cyclic dienone **1** without affecting any functional groups present on the substrate. Due to the flexibility of substituent variation, this methodology can be applied to the synthesis of various natural products bearing dihydronaphtho[2,1-*b*]furan ring skeleton. It is worth mentioning that among the three electrophilic positions on 2*H*-pyran-2-one, the reaction took place predominantly at position 6 and no side products were obtained.

The ^{1}H NMR spectrum of **3a** showed two sharp singlets at δ 2.46 and 7.11 for a methylsulfanyl group and a C-7 proton, respectively. Two multiplets at δ 2.75–2.79 and 2.86–2.92 for two methylene groups and two multiplets at δ 7.26–7.32 and 7.40–7.45 for six aromatic protons and a singlet at δ 3.99 for a methoxycarbonyl group protons were in agreement with the proposed structure. The presence of the carbonyl peak at ν_{max} 1720 cm^{-1} in the IR spectrum and the molecular ion peak *m*/*z* at 351 in the mass spectrum confirmed the structure as 8-methylsulfanyl-6-phenyl-4,5-dihydro-naphtho[2,1-*b*]furan-9-carboxylic acid methyl ester.

Table 1

1,3	Ar^1	Ar^2	X	Y	Yield[a] (%)
a	C_6H_5	H	COOMe	SMe	68
b	4-ClC_6H_4	H	COOMe	SMe	64
c	4-FC_6H_4	H	COOMe	SMe	69
d	4-BrC_6H_4	H	COOMe	SMe	71
e	3,4-$Cl_2C_6H_4$	H	COOMe	SMe	68
f	2-Thienyl	H	COOMe	SMe	63
g	4-ClC_6H_4	H	CN	SMe	54
h	4-BrC_6H_4	H	CN	SMe	59
i	2-Thienyl	H	CN	SMe	53
j	4-$OMeC_6H_4$	H	CN	SMe	51
k	4-MeC_6H_4	H	CN	SMe	48
l	4-ClC_6H_4	H	CN	4-Methyl-piperidine	82
m	3,4-$CH_2O_2C_6H_3$	H	CN	Piperidine	73
n	C_6H_5	C_6H_5	COOMe	SMe	28

[a] For naphthofurans **3a**–**n**.



Scheme 1.

Similarly, all the synthesized compounds were characterized by spectroscopic analysis. The structure of one of the naphthofurans **3b** was unambiguously confirmed by a single crystal X-ray diffraction analysis (CCDC No. 627559). The conformation of **3b** along with the atom-numbering scheme is shown in Figure 2.

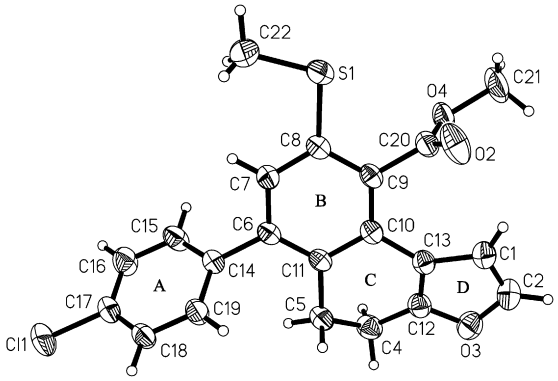
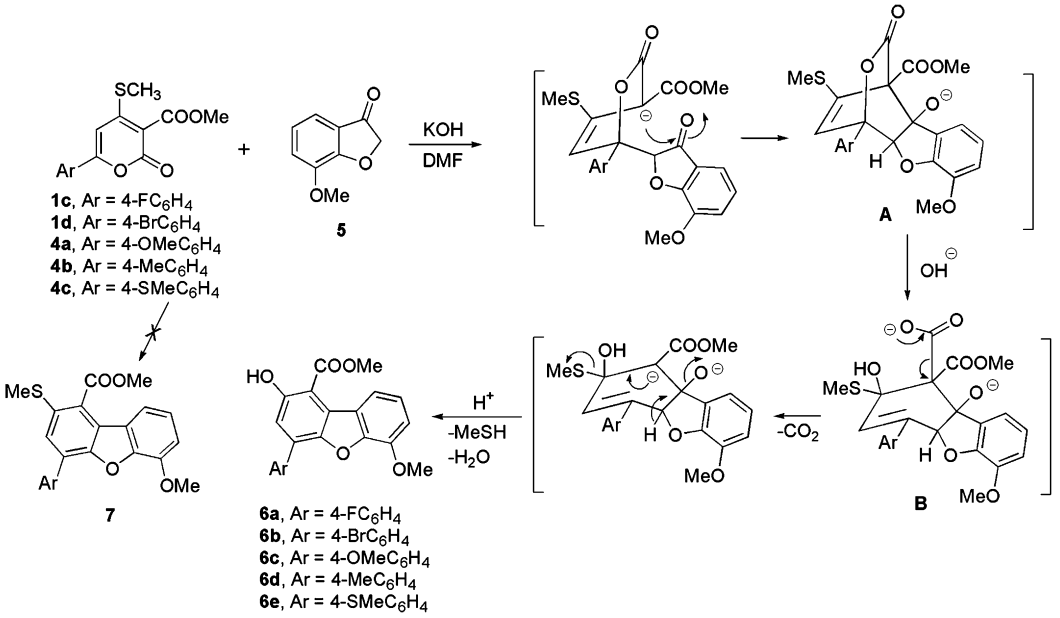


Figure 2. ORTEP diagram of **3b** with 50% probability.

2.2. Synthesis of substituted dibenzofurans

It was envisaged that the reaction of 2*H*-pyran-2-one with benzofuran-3-one would analogously furnish dibenzofurans following same reaction mechanism as described for the synthesis of naphtho[2,1-*b*]furans. Thus, diversely substituted dibenzofurans (**6a**–**e**) were prepared by stirring an equimolar mixture of the 2*H*-pyran-2-one (**1c**,**d**, **4a**–**c**), 7-methoxybenzofuran-3-one **5** and powdered KOH in dry DMF under an inert atmosphere at ambient temperature for 4–6 h as shown in Scheme 2. The spectroscopic analysis of a ring-transformed product **6a** revealed that the reaction of 6-(4-fluorophenyl)-3-methoxycarbonyl-4-methylsulfanyl-2*H*-pyran-2-one (**1c**) with 7-methoxybenzofuran-3-one **5** afforded 2-hydroxy-6-methoxy-4-aryl-dibenzofuran-1-carboxylic acid methyl ester (**6a**) instead of the corresponding 2-methylsulfanyl derivatives (**7**). The ^{1}H NMR spectrum of **6a** showed two sharp singlets at δ 4.02 and 4.19 for a methoxy group and the methoxycarbonyl group protons, respectively. Two multiplets in the range of δ 7.22–7.28 and 7.86–7.94 for six protons were assigned for methine



Scheme 2.

protons. The absence of a singlet in the range of δ 2.4–2.6 for a methylsulfanyl group and the presence of a peak at δ 11.29 for a hydroxyl group were in agreement with the proposed structure. The presence of the carbonyl peak at ν_{max} 1653 cm^{-1} and hydroxyl peak at 3436 cm^{-1} in the IR spectrum and the molecular ion peak *m*/*z* at 367 in the mass spectrum confirmed the proposed structure as 4-(4-fluorophenyl)-2-hydroxy-6-methoxy-dibenzofuran-1-carboxylic acid methyl ester. The mechanism, depicted in Scheme 2, implies that the reaction is initiated by attack of the carbanion generated in situ from benzofuran-3-one **5** at position C-6 of the 2*H*-pyran-2-one, followed by intramolecular cyclization involving the carbonyl group of benzofuran-3-one and C-3 of the pyranone to form a diene intermediate **A**. The intermediate **A** is electrophilic in nature and hydroxide may attack at this position to form intermediate **B**, followed by decarboxylation, protonation and elimination of methyl mercaptan and water yielding **6a–e** in high yields. All the synthesized compounds were similarly characterized by spectroscopic analyses. The structure of the compound **6d** was further unambiguously confirmed by a single X-ray diffraction analysis (CCDC No. 627558) (Fig. 3).

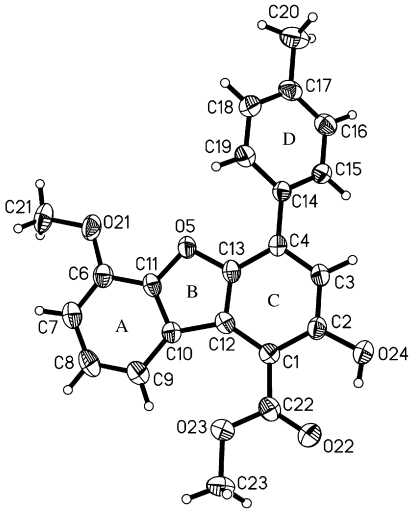


Figure 3. ORTEP diagram of **6d** with 50% probability.

3. Conclusion

In summary, we have developed a one-pot regioselective synthesis of diversely functionalized naphtho[2,1-*b*]furans and substituted dibenzofurans in high yields. The reaction of 2*H*-pyran-2-one with 6,7-dihydrobenzofuran-4-one afforded naphtho[2,1-*b*]furans while reaction with 7-methoxy-benzofuran-3-one furnished dibenzofurans in high yields. These dibenzofurans and naphthofurans with hydroxyl, methoxy and ester functionalities are structurally similar to naturally occurring ruscodibenzofurans and achyrofurans. Therefore, this methodology can be applied to the synthesis of benzofuran-based natural products. The potential of the procedure lies in the creation of C–C bond through carbanion-induced ring transformation of 2*H*-pyran-2-one in a single step from easily accessible precursors without using any organometallic reagents.

4. Experimental

4.1. General

^{1}H NMR spectra were taken on a Bruker WM-200 at 200 MHz. $CDCl_3$ was used as the solvent. Chemical shifts are reported in parts per million shift (δ-value) from Me_4Si (δ 0 ppm for ^{1}H) as an internal standard. Signal patterns are indicated as s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet. Coupling constants (*J*) are given in hertz. Infrared (IR) spectra were recorded on a Perkin–Elmer AX-1 spectrophotometer in KBr disc and reported in wave number (cm^{-1}). Fast-atomic bombardment (FAB) spectrometer was used for mass spectra analysis. HRMS spectra were recorded on JEOL-MSroute JMS-600H spectrometer. Melting points were measured with Buchi-530 melting point apparatus and are uncorrected. All the reactions were carried out under nitrogen atmosphere conditions and were monitored by TLC; visualization was done with UV-light (254 nm).

4.1.1. 8-Methylsulfanyl-6-phenyl-4,5-dihydro-naphtho[2,1-*b*]furan-9-carboxylic acid methyl ester (3a). A mixture of 2*H*-pyran-2-one **1a** (276 mg, 1 mmol), 6,7-dihydro-5*H*-benzofuran-4-one **2** (140 mg, 1 mmol) and powdered KOH (84 mg, 1.5 mmol) in dry DMF (7 mL) was stirred at room temperature for 24–26 h. After completion of reaction, the mixture was poured onto crushed ice with vigorous stirring, then neutralized with 10% HCl. The precipitate thus obtained was filtered off, washed with water, dried and purified by silica gel column chromatography (11% $CHCl_3$/hexane), which gave the title compound **3a** (236 mg, 68%) as a white solid; mp 123–124 °C; R_f ($CHCl_3$) 0.91; ν_{max} (KBr) 1720 cm^{-1} (CO); δ_H (200 MHz, $CDCl_3$): 7.40–7.45 (3H, m, *H*-3′, *H*-4′, *H*-5′), 7.26–7.32 (3H, m, *H*-2′, *H*-6′, *H*-2), 7.11 (1H, s, *H*-7), 6.44 (1H, d, *J* 2.0 Hz, *H*-1), 3.99 (3H, s, OCH_3), 2.86–2.92 (2H, m, CH_2CH_2C–O–), 2.75–2.79 (2H, m, CH_2CH_2C–O–), 2.46 (3H, s, SCH_3); *m*/*z* 351 $(M+H)^+$; HRMS (EI): M^+, found 350.0975. $C_{21}H_{18}O_3S$ requires 350.0977.

4.1.2. 6-(4-Chlorophenyl)-8-methylsulfanyl-4,5-dihydro-naphtho[2,1-*b*]furan-9-carboxylic acid methyl ester (3b). A procedure similar to the one described above for the preparation of **3a** starting from **1b** (310 mg, 1 mmol), **2** (140 mg, 1 mmol) and chromatography (13% $CHCl_3$/hexane) gave the title compound **3b** (242 mg, 64%) as a white solid, mp 141–142 °C; R_f ($CHCl_3$) 0.87; ν_{max} (KBr) 1728 cm^{-1} (CO); δ_H (200 MHz, $CDCl_3$): 7.44 (2H, d, *J* 8.4 Hz, *H*-2′, *H*-6′), 7.31 (1H, d, *J* 2.0 Hz, *H*-1), 7.22 (2H, d, *J* 8.4 Hz, *H*-3′, *H*-5′), 7.07 (1H, s, *H*-7), 6.44 (1H, d, *J* 2.0 Hz, *H*-2), 3.99 (3H, s, OCH_3), 2.86–2.93 (2H, m, CH_2CH_2C–O–), 2.72–2.79 (2H, m, CH_2CH_2C–O–), 2.46 (3H, s, SCH_3); *m*/*z* 385 $(M+H)^+$; HRMS (EI): M^+, found 384.0588. $C_{21}H_{17}O_3SCl$ requires 384.0587.

4.1.3. 6-(4-Fluorophenyl)-8-methylsulfanyl-4,5-dihydro-naphtho[2,1-*b*]furan-9-carboxylic acid methyl ester (3c).[27f] A procedure similar to the one described above for the preparation of **3a** starting from **1c** (294 mg, 1 mmol), **2** (140 mg, 1 mmol) and chromatography (14% $CHCl_3$/hexane) gave the title compound **3c** (258 mg, 69%) as a white solid; mp 147–148 °C; R_f ($CHCl_3$) 0.86; ν_{max} (KBr)

1726 cm^{-1} (CO); δ_H (200 MHz, $CDCl_3$): 7.31 (1H, d, *J* 2.0 Hz, *H*-2), 7.21–7.26 (2H, m, *H*-2′, *H*-6′), 7.12–7.17 (2H, m, *H*-3′, *H*-5′), 7.08 (1H, s, *H*-7), 6.44 (1H, d, *J* 2.0 Hz, *H*-1), 3.99 (3H, s, OCH_3), 2.85–2.90 (2H, m, CH_2CH_2C–O–), 2.74–2.79 (2H, m, CH_2CH_2C–O–), 2.46 (3H, s, SCH_3); *m*/*z* 369 $(M+H)^+$.

4.1.4. 6-(4-Bromophenyl)-8-methylsulfanyl-4,5-dihydronaphtho[2,1-*b*]furan-9-carboxylic acid methyl ester (3d). A procedure similar to the one described above for the preparation of **3a** starting from **1d** (354 mg, 1 mmol), **2** (140 mg, 1 mmol) and chromatography (15% $CHCl_3$/hexane) gave the title compound **3d** (304 mg, 71%) as a white solid; mp 138–140 °C; R_f ($CHCl_3$) 0.85; ν_{max} (KBr) 1728 cm^{-1} (CO); δ_H (200 MHz, $CDCl_3$): 7.57 (2H, d, *J* 8.4 Hz, *H*-3′, *H*-5′), 7.31 (1H, d, *J* 2.0 Hz, *H*-2), 7.16 (2H, d, *J* 8.4 Hz, *H*-2′, *H*-6′), 7.06 (s, 1H, *H*-7), 6.44 (1H, d, *J* 2.0 Hz, *H*-1), 3.99 (3H, s, OCH_3), 2.85–2.90 (2H, m, CH_2CH_2C–O–), 2.74–2.79 (2H, m, CH_2CH_2C–O–), 2.45 (3H, s, SCH_3); *m*/*z* 429 $(M+H)^+$; HRMS (EI): M^+, found 428.0099. $C_{21}H_{17}O_3SBr$ requires 428.0082.

4.1.5. 6-(3,4-Dichlorophenyl)-8-methylsulfanyl-4,5-dihydronaphtho[2,1-*b*]furan-9-carboxylic acid methyl ester (3e).[27f] A procedure similar to the one described above for the preparation of **3a** starting from **1e** (344 mg, 1 mmol), **2** (140 mg, 1 mmol) and chromatography (15% $CHCl_3$/hexane) gave the title compound **3e** (284 mg, 68%) as a white solid; mp 176–177 °C; R_f ($CHCl_3$) 0.85; ν_{max} (KBr) 1719 cm^{-1} (CO); δ_H (200 MHz, $CDCl_3$): 7.51 (1H, d, *J* 8.4 Hz, *H*-6′), 7.39 (s, 1H, *H*-2′), 7.32 (1H, d, *J* 2.0 Hz, *H*-2), 7.12 (1H, dd, *J* 8.4, 2.0 Hz, *H*-5′), 7.05 (s, 1H, *H*-7), 6.44 (1H, d, *J* 2.0 Hz, *H*-1), 3.99 (3H, s, OCH_3), 2.85–2.87 (2H, m, CH_2CH_2C–O–), 2.77–2.80 (2H, m, CH_2CH_2C–O–), 2.46 (3H, s, SCH_3); *m*/*z* 419 $(M+H)^+$.

4.1.6. 8-Methylsulfanyl-6-thiophen-2-yl-4,5-dihydronaphtho[2,1-*b*]furan-9-carboxylic acid methyl ester (3f).[27f] A procedure similar to the one described above for the preparation of **3a** starting from **1f** (282 mg, 1 mmol), **2** (140 mg, 1 mmol) and chromatography (12% $CHCl_3$/hexane) gave the title compound **3f** (225 mg, 63%) as a white solid; mp 139–140 °C; R_f ($CHCl_3$) 0.88; ν_{max} (KBr) 1729 cm^{-1} (CO); δ_H (200 MHz, $CDCl_3$): 7.39–7.46 (2H, m, *H*-3′, *H*-4′), 7.26–7.31 (2H, m, *H*-2, *H*-5′), 7.12 (s, 1H, *H*-7), 6.45 (1H, d, *J* 2.0 Hz, *H*-1), 3.99 (3H, s, OCH_3), 2.87–2.91 (2H, m, CH_2CH_2C–O–), 2.74–2.78 (2H, m, CH_2CH_2C–O–), 2.46 (3H, s, SCH_3); *m*/*z* 357 $(M+H)^+$.

4.1.7. 6-(4-Chlorophenyl)-8-methylsulfanyl-4,5-dihydronaphtho[2,1-*b*]furan-9-carbonitrile (3g).[27f] A procedure similar to the one described above for the preparation of **3a** starting from **1g** (277 mg, 1 mmol), **2** (140 mg, 1 mmol) and chromatography (13% $CHCl_3$/hexane) gave the title compound **3g** (179 mg, 54%) as a white solid; mp 181–182 °C; R_f ($CHCl_3$) 0.87; ν_{max} (KBr) 2228 cm^{-1} (CN); δ_H (200 MHz, $CDCl_3$): 7.36–7.41 (3H, m, *H*-2′, *H*-6′, *H*-2), 7.33 (1H, d, *J* 2.0 Hz, *H*-1), 7.15 (2H, d, *J* 8.6 Hz, *H*-3′, *H*-5′), 6.84 (1H, s, *H*-7), 2.74–2.84 (4H, m, CH_2CH_2C–O–, CH_2CH_2C–O–), 2.46 (3H, s, SCH_3); *m*/*z* 351 $(M+H)^+$.

4.1.8. 6-(4-Bromophenyl)-8-methylsulfanyl-4,5-dihydronaphtho[2,1-*b*]furan-9-carbonitrile (3h). A procedure similar to the one described above for the preparation of **3a** starting from **1h** (321 mg, 1 mmol), **2** (140 mg, 1 mmol) and chromatography (12% $CHCl_3$/hexane) gave the title compound **3h** (232 mg, 59%) as a white solid; mp 204–206 °C; R_f ($CHCl_3$) 0.88; ν_{max} (KBr) 2230 cm^{-1} (CN); δ_H (200 MHz, $CDCl_3$): 7.60 (2H, d, *J* 8.4 Hz, *H*-3′, *H*-5′), 7.47 (1H, d, *J* 2.0 Hz, *H*-2), 7.40 (1H, d, *J* 2.0 Hz, *H*-1), 7.16 (2H, d, *J* 8.4 Hz, *H*-2′, *H*-6′), 6.91 (1H, s, *H*-7), 2.79–2.88 (4H, m, CH_2CH_2C–O–, CH_2CH_2C–O–), 2.53 (3H, s, SCH_3), *m*/*z* 397, 395 $(M+H)^+$; HRMS (EI): M^+, found 394.9982. $C_{20}H_{14}NOSBr$ requires 394.9979.

4.1.9. 8-Methylsulfanyl-6-thiophen-2-yl-4,5-dihydronaphtho[2,1-*b*]furan-9-carbonitrile (3i).[27f] A procedure similar to the one described above for the preparation of **3a** starting from **1i** (249 mg, 1 mmol), **2** (140 mg, 1 mmol) and chromatography (11% $CHCl_3$/hexane) gave the title compound **3i** (172 mg, 53%) as a white solid; mp 177–176 °C; R_f ($CHCl_3$) 0.89; ν_{max} (KBr) 2213 cm^{-1} (CN); δ_H (200 MHz, $CDCl_3$): 7.39–7.46 (3H, m, *H*-5′, *H*-1, *H*-2), 7.04–7.15 (3H, m, *H*-7, *H*-3′, *H*-4′), 3.10 (2H, t, *J* 7.8 Hz, CH_2CH_2C–O–), 2.83 (2H, t, *J* 7.8 Hz, CH_2CH_2C–O–), 2.54 (3H, s, SCH_3); *m*/*z* 323 $(M+H)^+$.

4.1.10. 6-(4-Methoxyphenyl)-8-methylsulfanyl-4,5-dihydronaphtho[2,1-*b*]furan-9-carbonitrile (3j).[27f] A procedure similar to the one described above for the preparation of **3a** starting from **1j** (273 mg, 1 mmol), **2** (140 mg, 1 mmol) and chromatography (11% $CHCl_3$/hexane) gave the title compound **3j** (177 mg, 51%) as a white solid; mp 154–156 °C; R_f ($CHCl_3$) 0.89; ν_{max} (KBr) 2215 cm^{-1} (CN); δ_H (200 MHz, $CDCl_3$): 7.47 (1H, d, *J* 2.0 Hz, *H*-2), 7.39 (1H, d, *J* 2.0 Hz, *H*-1), 7.22 (2H, d, *J* 8.9 Hz, *H*-2′, *H*-6′), 6.99 (2H, d, *J* 8.9 Hz, *H*-3′, *H*-5′), 6.96 (1H, s, *H*-7), 3.87 (3H, s, OCH_3), 2.97 (2H, t, *J* 7.6 Hz, CH_2CH_2C–O–), 2.80 (2H, t, *J* 7.6 Hz, CH_2CH_2C–O–), 2.53 (3H, s, SCH_3); *m*/*z* 347 $(M+H)^+$.

4.1.11. 8-Methylsulfanyl-6-*p*-tolyl-4,5-dihydro-naphtho[2,1-*b*]furan-9-carbonitrile (3k). A procedure similar to the one described above for the preparation of **3a** starting from **1k** (257 mg, 1 mmol), **2** (140 mg, 1 mmol) and chromatography (10% $CHCl_3$/hexane) gave the title compound **3k** (160 mg, 48%) as a white solid; mp 182–184 °C; R_f ($CHCl_3$) 0.90; ν_{max} (KBr) 2215 cm^{-1} (CN); δ_H (200 MHz, $CDCl_3$): 7.48 (1H, d, *J* 2.0 Hz, *H*-2), 7.39 (1H, d, *J* 2.0 Hz, *H*-1), 7.29 (2H, d, *J* 7.0 Hz, *H*-2′, *H*-6′), 7.16–7.30 (2H, m, *H*-3′, *H*-5′), 6.96 (1H, s, *H*-7), 2.94 (2H, t, *J* 7.6 Hz, CH_2CH_2C–O–), 2.79 (2H, t, *J* 7.6 Hz, CH_2CH_2C–O–), 2.53 (3H, s, SCH_3), 2.43 (3H, s, CH_3); *m*/*z* 332 $(M+H)^+$; HRMS (EI): M^+, found 331.1038. $C_{21}H_{17}NOS$ requires 331.1031.

4.1.12. 6-(4-Chlorophenyl)-8-(4-methyl-piperidin-1-yl)-4,5-dihydronaphtho[2,1-*b*]furan-9-carbonitrile (3l). A procedure similar to the one described above for the preparation of **3a** starting from **1l** (328 mg, 1 mmol), **2** (140 mg, 1 mmol) and chromatography (12% $CHCl_3$/hexane) gave the title compound **3l** (330 mg, 82%) as a white solid, mp 166–168 °C; R_f ($CHCl_3$) 0.88; ν_{max} (KBr) 2215 cm^{-1} (CN); δ_H (300 MHz, $CDCl_3$): 7.48 (1H, d, *J* 2.0 Hz, *H*-2), 7.42 (2H, d, *J* 8.4 Hz, *H*-2′, *H*-6′), 7.38 (1H, d, *J* 2.0 Hz, *H*-1), 7.22 (2H, d, *J* 8.4 Hz, *H*-3′, *H*-5′), 6.64 (1H, s, *H*-7),

3.45–3.58 (2H, m, CH_2NCH_2), 2.70–2.86 (6H, m, CH_2NCH_2, CH_2CH_2C–O–), 1.70–1.81 (2H, m, $CHCH_2CH_2$), 1.47–1.60 (3H, m, $CHCH_2CH_2$), 1.01 (3H, s, $CHCH_3$); *m/z* 403 $(M+H)^+$; HRMS (EI): M^+, found 402.1492. $C_{25}H_{23}N_2OCl$ requires 402.1499.

4.1.13. 6-Benzo[1,3]dioxol-5-yl-8-piperidin-1-yl-4,5-dihydronaphtho[2,1-*b*]furan-9-carbonitrile (3m). A procedure similar to the one described above for the preparation of **3a** starting from **1m** (324 mg, 1 mmol), **2** (140 mg, 1 mmol) and chromatography (13% $CHCl_3$/hexane) gave the title compound **3m** (292 mg, 73%) as a white solid, mp 185–187 °C; R_f ($CHCl_3$) 0.87; ν_{max} (KBr) 2207 cm^{-1} (CN); δ_H (200 MHz, $CDCl_3$): 7.48 (1H, d, *J* 2.0 Hz, *H*-2), 7.38 (1H, d, *J* 2.0 Hz, *H*-1), 6.88 (1H, d, *J* 7.8 Hz, *H*-6′), 6.70–6.76 (2H, m, *H*-2′, *H*-5′), 6.67 (s, 1H, *H*-7), 6.02 (s, 2H, OCH_2O), 3.04–3.14 (4H, m, CH_2NCH_2), 2.83–2.96 (2H, m, CH_2CH_2C–O–), 2.70–2.81 (2H, m, CH_2CH_2C–O–), 1.72–1.81 (4H, m, $CH_2CH_2CH_2$), 1.54–1.62 (2H, m, $CH_2CH_2CH_2$); *m/z* 399 $(M+H)^+$; HRMS (EI): M^+, found 398.1610. $C_{25}H_{22}N_2O_3$ requires 398.1631.

4.1.14. 8-Methylsulfanyl-6,7-diphenyl-4,5-dihydronaphtho[2,1-*b*]furan-9-carboxylic acid methyl ester (3n). A procedure similar to the one described above for the preparation of **3a** starting from **1n** (352 mg, 1 mmol), **2** (140 mg, 1 mmol) and chromatography (17% $CHCl_3$/hexane) gave the title compound **3n** (120 mg, 28%) as a white solid, mp 222–224 °C; R_f ($CHCl_3$) 0.83; ν_{max} (KBr) 1733 cm^{-1} (CO); δ_H (200 MHz, $CDCl_3$): 7.29 (1H, d, *J* 2.0 Hz, *H*-2), 7.03–7.15 (6H, m, *Ph*), 6.85–7.01 (4H, m, *Ph*), 6.47 (1H, d, *J* 2.0 Hz, *H*-1), 3.99 (3H, s, OCH_3), 2.75 (4H, s, CH_2CH_2C–O–, CH_2CH_2C–O–), 1.98 (3H, s, SCH_3); *m/z* 426 $(M+H)^+$; HRMS (EI): M^+, found 426.1272. $C_{27}H_{22}O_3S$ requires 426.1290.

4.2. Synthesis of 4-(aryl)-2-hydroxy-6-methoxy-dibenzofuran-1-carboxylic acid methyl ester compounds (6a–e)

4.2.1. 4-(4-Fluorophenyl)-2-hydroxy-6-methoxy-dibenzofuran-1-carboxylic acid methyl ester (6a). A mixture of 2*H*-pyran-2-one **1c** (294 mg, 1 mmol), 7-methoxybenzofuran-3-one **5** (152 mg, 1 mmol) and powdered KOH (84 mg, 1.5 mmol) in dry DMF (7 mL) was stirred at room temperature for 2–4 h. After completion of reaction, the mixture was poured onto crushed ice with vigorous stirring, and then neutralized with 10% HCl. The precipitate thus obtained was filtered off, washed with water, dried and purified by silica gel column chromatography (13% $CHCl_3$/hexane) to give the title compound **6a** (317 mg, 87%) as a white solid; mp 214–215 °C; R_f ($CHCl_3$) 0.87; ν_{max} (KBr) 1653 (CO), 3436 cm^{-1} (OH); δ_H (200 MHz, $CDCl_3$): 11.29 (1H, s, O*H*), 7.86–7.94 (3H, m, *H*-9, *H*-2′, *H*-6′), 7.22–7.28 (3H, m, *H*-8, *H*-7, *H*-3), 7.02 (2H, d, *J* 8.0 Hz, *H*-3′, *H*-5′), 4.19 (3H, s, $COOCH_3$), 4.02 (3H, s, OCH_3); *m/z* 367 $(M+H)^+$; HRMS (EI): M^+, found 366.0897. $C_{21}H_{15}FO_5$ requires 366.0903.

4.2.2. 4-(4-Bromophenyl)-2-hydroxy-6-methoxy-dibenzofuran-1-carboxylic acid methyl ester (6b). A procedure similar to the one described above for the preparation of **6a** starting from **1d** (354 mg, 1 mmol), **5** (152 mg, 1 mmol) and chromatography (14% $CHCl_3$/hexane) gave the title compound **6b** (355 mg, 83%) as a white solid; mp 226–227 °C; R_f ($CHCl_3$) 0.86; ν_{max} (KBr) 1654 (CO), 3428 cm^{-1} (OH); δ_H (200 MHz, $CDCl_3$): 11.29 (s, 1H, O*H*), 7.98 (1H, d, *J* 8.0 Hz, *H*-9), 7.80 (2H, d, *J* 8.6 Hz, *H*-3′, *H*-5′), 7.68 (2H, d, *J* 8.6 Hz, *H*-2′, *H*-6′), 7.23–7.26 (2H, m, *H*-3, *H*-8), 7.03 (1H, d, *J* 8.0 Hz, *H*-7), 4.20 (3H, s, $COOCH_3$), 4.03 (3H, s, OCH_3); *m/z* 427 $(M+H)^+$; HRMS (EI): M^+, found 426.0113, $C_{21}H_{15}BrO_5$ requires 426.0103.

4.2.3. 2-Hydroxy-6-methoxy-4-(4-methoxyphenyl)-dibenzofuran-1-carboxylic acid methyl ester (6c). A procedure similar to the one described above for the preparation of **6a** starting from **4a** (306 mg, 1 mmol), **5** (152 mg, 1 mmol) and chromatography (11% $CHCl_3$/hexane) gave the title compound **6c** (352 mg, 93%) as a white solid; mp 168–169 °C; R_f ($CHCl_3$) 0.89; ν_{max} (KBr) 1658 cm^{-1} (CO); δ_H (200 MHz, $CDCl_3$) 11.31 (1H, s, O*H*), 7.98 (1H, d, *J* 8.0 Hz, *H*-9), 7.90 (2H, d, *J* 8.8 Hz, *H*-3′, *H*-5′), 7.21–7.30 (2H, m, *H*-3, *H*-8), 7.08 (2H, d, *J* 8.8 Hz, *H*-2′, *H*-6′), 7.01 (1H, d, *J* 8.0 Hz, *H*-7), 4.18 (3H, s, OCH_3), 4.03 (3H, s, $COOCH_3$), 3.90 (3H, s, OCH_3); *m/z* 379 $(M+H)^+$; HRMS (EI): M^+, found 378.1103. $C_{22}H_{18}O_6$ requires 378.1103.

4.2.4. 2-Hydroxy-6-methoxy-4-*p*-tolyl-dibenzofuran-1-carboxylic acid methyl ester (6d). A procedure similar to the one described above for the preparation of **6a** starting from **4b** (290 mg, 1 mmol), **5** (152 mg, 1 mmol) and chromatography (11% $CHCl_3$/hexane) gave the title compound **6d** (326 mg, 90%) as a white solid; mp 164–165 °C; R_f ($CHCl_3$) 0.89; ν_{max} (KBr) 1663 cm^{-1} (CO); δ_H (200 MHz, $CDCl_3$) 11.30 (1H, s, O*H*), 8.00 (1H, d, *J* 8.0 Hz, *H*-9), 7.83 (2H, d, *J* 8.1 Hz, *H*-2′, *H*-6′), 7.36 (2H, d, *J* 8.1 Hz, *H*-3′, *H*-5′), 7.21–7.31 (2H, m, *H*-3, *H*-8), 7.01 (1H, d, *J* 8.0 Hz, *H*-7), 4.19 (3H, s, $COOCH_3$), 4.03 (3H, s, OCH_3), 2.45 (3H, s, CH_3); *m/z* 362 $(M+H)^+$; HRMS (EI): M^+, found 362.1149. $C_{22}H_{18}O_5$ requires 362.1154.

4.2.5. 2-Hydroxy-6-methoxy-4-(4-methylsulfanyl-phenyl)-dibenzofuran-1-carboxylic acid methyl ester (6e). A procedure similar to the one described above for the preparation of **6a** starting from **4c** (322 mg, 1 mmol), **5** (152 mg, 1 mmol) and chromatography (12% $CHCl_3$/hexane) gave the title compound **6e** (324 mg, 82%) as a white solid, mp 123–124 °C; R_f ($CHCl_3$) 0.88; white solid; mp 163–164 °C; ν_{max} (KBr) 1663 cm^{-1} (CO); δ_H (200 MHz, $CDCl_3$) 11.30 (1H, s, O*H*), 7.98 (1H, d, *J* 8.0 Hz, *H*-9), 7.87 (2H, d, *J* 8.6 Hz, *H*-2′, *H*-6′), 7.42 (2H, d, *J* 8.6 Hz, *H*-3′, *H*-5′), 7.21–7.31 (2H, m, *H*-8, *H*-3), 7.02 (1H, d, *J* 8.0 Hz, *H*-7), 4.19 (3H, s, $COOCH_3$), 4.03 (3H, s, OCH_3), 2.56 (3H, s, SCH_3); *m/z* 394 $(M+H)^+$; HRMS (EI): M^+, found 394.0873. $C_{22}H_{18}O_5S$ requires 394.0875.

Acknowledgements

The authors thank Sophisticated Analytical Instrument Facility (SAIF), Central Drug Research Institute, Lucknow for providing spectroscopic data for the synthesized compounds. Financial assistance by DST and CSIR, New Delhi is gratefully acknowledged.

References and notes

1. (a) Simpson, T. J. Aromatic Compounds. In *The Chemistry of Natural Products*; Thomson, R. H., Ed.; Blackie: London, 1985; (b) Sargent, M. V.; Stransky, P. O. *Dibenzofurans*; Katritzky, A. R., Ed.; Advances in Heterocyclic Chemistry; Academic: London, 1984; Vol. 35, pp 2–81.
2. (a) Neelakantan, S.; Rajagopalan, V.; Raman, P. V. *Indian J. Chem.* **1983**, *22B*, 95–96; (b) Jakupovic, J.; Schuster, A.; Ganzer, U.; Bohlmann, F.; Boldt, P. E. *Phytochemistry* **1990**, *29*, 2217–2222; (c) Miles, D. H.; Chittawong, V.; Lho, D. S.; Payen, A. M.; De la Cruz, A. A.; Gomez, E. D.; Weeks, J. A.; Atwood, J. L. *J. Nat. Prod.* **1991**, *54*, 286–289.
3. (a) Bohlmann, F.; Zdero, C. *Chem. Ber.* **1977**, *110*, 487–490; (b) de Oliveira, A. B.; De Oliveira, G. G.; Carazza, F.; Braz Filho, R.; Moreira Bacha, C. T.; Bauer, L.; Silva, G.A. de, A. B.; Siqueira, N. C. S. *Tetrahedron Lett.* **1978**, *30*, 2653–2654.
4. Ishiguro, K.; Ohira, Y.; Oku, H. *J. Nat. Prod.* **1998**, *61*, 1126–1129.
5. (a) Friedrich-Fiechtl, J.; Spiteller, G. *Tetrahedron* **1975**, *31*, 479–487; (b) Novak, J.; Salemink, C. A. *Tetrahedron Lett.* **1983**, *24*, 101–102.
6. ElSohly, M. A.; Slatkin, D. J.; Knapp, J. E.; Doorenbos, N. J.; Quimby, M. W.; Schiff, P. L., Jr. *Tetrahedron* **1977**, *33*, 1711–1715.
7. Manniche, S.; Sprogøe, K.; Dalsgaard, P. W.; Christophersen, C.; Larsen, T. O. *J. Nat. Prod.* **2004**, *67*, 2111–2112.
8. Carney, R. J.; Krenisky, M. J.; Williamson, T. R.; Luo, J. *J. Nat. Prod.* **2002**, *65*, 203–205.
9. Qian, X.; Zhang, Y.; Ni, C. *Huadong Ligong Daxue Xuebao* **1994**, *20*, 336–341.
10. Einhorn, J.; Demerseman, P.; Royer, R.; Cavier, R.; Gayral, P. *Eur. J. Med. Chem.* **1984**, *19*, 405–410.
11. Giovanninetti, G.; Cavrini, V.; Chiarini, A.; Garuti, L.; Mannini-Palenzona, A. *Farmaco. Ediz. Scientifica* **1974**, *29*, 375–385.
12. Gaggi, R.; Giovanninetti, G.; Garuti, L. *Farmaco. Ediz. Scientifica* **1982**, *37*, 149–150.
13. Hranjec, M.; Grdisa, M.; Pavelic, K.; Boykin, D. W.; Karminski-Zamola, G. *Il Farmaco* **2003**, *58*, 1319–1324.
14. (a) Mahadevan, K. M.; Padmashali, B.; Vaidya, V. P. *Indian J. Heterocycl. Chem.* **2001**, *11*, 15–20; (b) Mahadevan, K. M.; Vaidya, V. P. *Indian J. Pharm. Sci.* **2003**, *65*, 128–134.
15. (a) Dötz, K. H.; Tomuschat, P. *Chem. Soc. Rev.* **1999**, *28*, 187–198; (b) Herndon, J. W. *Coord. Chem. Rev.* **2004**, *248*, 3–79; (c) Anderson, J. C.; Denton, R. M.; Hickin, H. G.; Wilson, C. *Tetrahedron* **2004**, *60*, 2327–2335; (d) Jahr, H. C.; Nieger, M.; Dötz, K. H. *J. Organomet. Chem.* **2002**, *641*, 185–194; (e) Merlic, C. A.; Roberts, W. M. *Tetrahedron Lett.* **1993**, *34*, 7379–7382.
16. (a) Arrault, A.; Touzeau, F.; Guillaumet, G.; Merour, J.-Y. *Synthesis* **1999**, 1241–1245; (b) Chavan, S. P.; Rao, Y.; Tripura, S.; Govande, C. A.; Zubaidha, P. K.; Dhondge, V. D. *Tetrahedron Lett.* **1997**, *38*, 7633–7634; (c) Arcadi, A.; Rossi, E. *Tetrahedron* **1998**, *54*, 15253–15272; (d) Satoh, T.; Tsuda, T.; Kushino, Y.; Miura, M.; Nomura, M. *J. Org. Chem.* **1996**, *61*, 6476–6477; (e) Karminski-Zamola, G.; Bajic, M. *Synth. Commun.* **1989**, *19*, 1325–1333; (f) Kano, S.; Ebata, T.; Shibuya, S. *Heterocycles* **1980**, *14*, 43–46; (g) Chatterjea, J. N.; Mehrotra, V. N.; Roy, S. K. *Ber.* **1963**, *96*, 1167–1176.
17. (a) Graebe, C.; Ullmann, F. *Chem. Ber.* **1896**, *29*, 1876–1880; (b) De Tar, D. F. *Org. React.* **1957**, *9*, 409–412.
18. Chang, Y.-S.; Jang, J.-S.; Deinzer, M. L. *Tetrahedron* **1990**, *46*, 4161–4164.
19. (a) Erdtman, H. G. H. *Proc. R. Soc. London, Ser. A* **1934**, *143*, 223–227; (b) Shand, A. J.; Thomson, R. H. *Tetrahedron* **1963**, *19*, 1919–1937.
20. Wassmundt, F. W.; Pedemonte, R. P. *J. Org. Chem.* **1995**, *60*, 4991–4994.
21. Ibrahim, Y. A.; Al-Awadi, N. A.; Kaul, K. *Tetrahedron* **2001**, *57*, 7377–7381.
22. Wiater, I.; Born, J. G. P.; Louw, R. *Eur. J. Org. Chem.* **2000**, 921–928.
23. (a) Brewer, J. D.; Davidson, W. J.; Elix, J. A.; Leppik, R. A. *Aust. J. Chem.* **1971**, *24*, 1883–1898; (b) Sha, C.-K.; Lee, R.-S.; Wang, Y. *Tetrahedron* **1995**, *51*, 193–202.
24. Ram, V. J.; Goel, A. *Tetrahedron Lett.* **1996**, *37*, 93–96.
25. Dixit, M.; Goel, A. *Tetrahedron Lett.* **2006**, *47*, 3557–3560.
26. (a) Goel, A.; Singh, F. V. *Tetrahedron Lett.* **2005**, *46*, 5585–5587; (b) Goel, A.; Verma, D.; Dixit, M.; Raghunandan, R.; Maulik, P. R. *J. Org. Chem.* **2006**, *71*, 804–807.
27. (a) Ram, V. J.; Goel, A. *Chem. Lett.* **1997**, 1021–1022; (b) Ram, V. J.; Goel, A. *J. Org. Chem.* **1999**, *64*, 2387–2390; (c) Ram, V. J.; Goel, A. *Synthesis* **1999**, 467–470; (d) Ram, V. J.; Srivastava, P.; Saxena, A. S. *J. Org. Chem.* **2001**, *66*, 5333–5337; (e) Ram, V. J.; Agarwal, N.; Farhanullah. *Tetrahedron Lett.* **2002**, *43*, 3281–3283; (f) Goel, A.; Dixit, M. *Tetrahedron Lett.* **2004**, *45*, 8819–8821; (g) Goel, A.; Dixit, M.; Verma, D. *Tetrahedron Lett.* **2005**, *46*, 491–493; (h) Goel, A.; Singh, F. V.; Sharon, A.; Maulik, P. R. *Synlett* **2005**, 623–626; (i) Goel, A.; Singh, F. V.; Verma, D. *Synlett* **2005**, 2027–2030.
28. (a) Tominaga, Y.; Ushirogouchi, A.; Matsuda, Y.; Kobayashi, G. *Chem. Pharm. Bull.* **1984**, *32*, 3384–3395; (b) Tominaga, Y.; Ushirogouchi, A.; Matsuda, Y. *J. Heterocycl. Chem.* **1987**, *24*, 1557–1567.