HETEROCYCLES, Vol. 75, No. 3, 2008, pp. 599 - 609. © The Japan Institute of Heterocyclic Chemistry
Received, 15th October, 2007, Accepted, 21st November, 2007, Published online, 22nd November, 2007. COM-07-11244

A FACILE SYNTHESIS OF 1,3-DIHYDROISOBENZOFURANS USING IODOCYLIZATION OF 2-VINYLBENZYL ALCOHOLS

Kazuhiro Kobayashi,* Kazuaki Shikata, Shuhei Fukamachi, and Hisatoshi Konishi

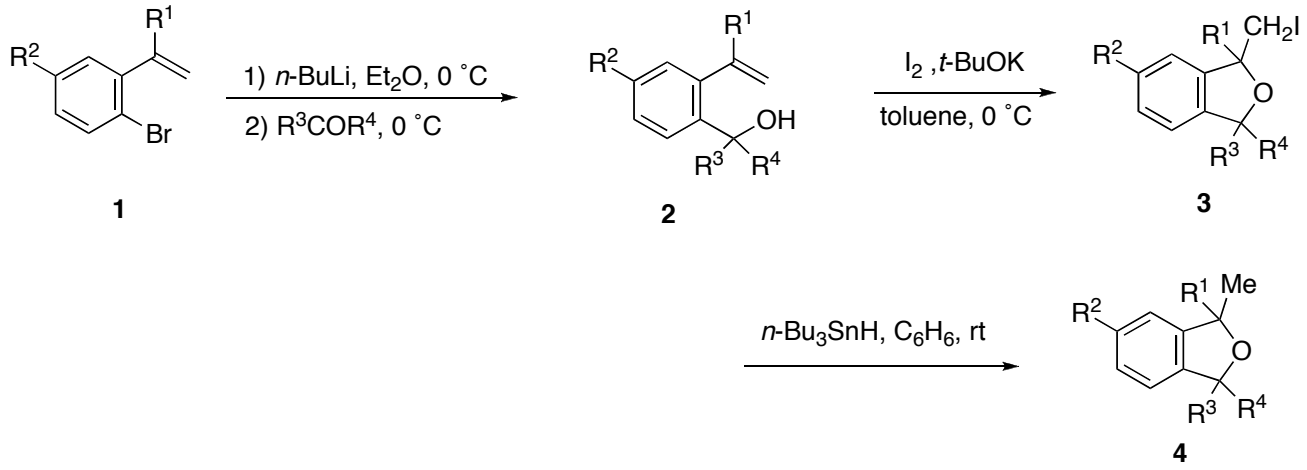
Department of Materials Science, Faculty of Engineering, Tottori University, 4-101 Koyama-minami, Tottori 680-8552, Japan

Abstract - An efficient route for the preparation of 1,3-dihydroisobenzofurans based on the iodine-mediated cyclization of 2-vinylbenzyl alcohols, which can be prepared feasibly by reactions of 2-vinylphenyllithiums with carbonyl compounds, is reported. Substitution reactions of the iodo moiety of the resulting 1-(iodomethyl)-1,3-dihydroisobenzofurans with tributyltin hydride and sodium thiolates are also described.

Iodocyclization is one of the most useful operations in organic synthesis. Recently, it has been reported to be very effective in the synthesis of benzene-fused heterocyclic compounds from appropriate *o*-substituted styrene derivatives.[1] In this paper, we wish to report a simple approach to 1,3-dihydroisobenzofuran (phthalane) derivatives, which involves the conversion of 2-vinylbenzyl alcohols (**2**) to 1-(iodomethyl)-1,3-dihydroisobenzofurans (**3**) on treatment with iodine in the presence of potassium *t*-butoxide. 1,3-Dihydroisobenzofuran derivatives are of biological interest.[2] Moreover, a natural product having this system has recently been isolated from the nature.[3] A few methods for the preparation of this class of molecules have been reported.[4] However, these suffer from limited generality and troublesome preparation of the precursors. We also report on substitution reactions of the iodo moiety of **3** with tributyltin hydride and sodium thiolates.

The synthesis of 1,3-dihydroisobenzofurans was conducted as shown in Scheme 1. The starting 2-vinylbenzyl alcohols (**2**) were obtained by reactions of 2-vinylphenyllithium derivatives, generated from 2-bromostyrene derivatives **1** by bromine-lithium exchange with butyllithium in diethyl ether at 0 ˚C, with carbonyl compounds in fair yields, as summarized in Table 1. These alcohols were subsequently transformed into the corresponding 1-(iodomethyl)-1,3-dihydroisobenzofurans (**3**) in generally good yields on treatment with iodine in the presence of potassium *t*-butoxide at 0 ˚C in toluene. These results are also listed in Table 1. Entry 11 shows that, when compound (**2k**) carring a methoxy substituent on benzene ring was used, the corresponding desired product **3k** was obtained in somewhat

lower yield from a complicated mixture of products. The use of sodium hydrogencarbonate in place of potassium *t*-butoxide gave rather intractable mixture of products, from which only lower yields of the desired products were isolated. Unfortunately, however, we have no explicit explanation for these.



1 **2** **3** **4**

Scheme 1

Table 1. Preparation of 1,3-Dihydroisobenzofuran Derivatives (**3**) and (**4**), via **2**

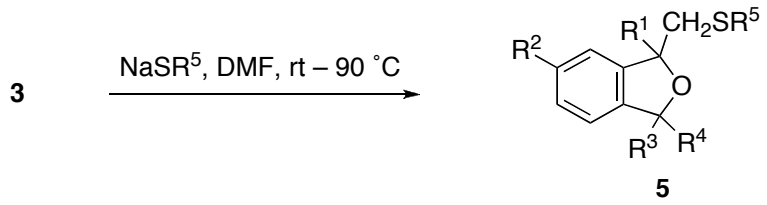
Entry	*o*-Bromostyrene **1**	R^3COR^4	**2** (Yield/%)[a]	**3** (Yield/%)[a]	**4** (Yield/%)[a]
1	**1a** (R^1 = Ph, R^2 = H)	cyclopentanone	**2a** (57)	**3a** (88)	**4a** (60)
2	**1a**	cyclohexanone	**2b** (67)	**3b** (72)	**4b** (56)
3	**1b** (R^1 = 4-ClC_6H_4, R^2 = H)	benzaldehyde	**2c** (61)	**3c** (70)[b),c)]	**4c** (72)[c),d)]
4	**1b**	acetone	**2d** (63)	**3d** (72)	**4d** (60)
5	**1b**	cyclopentanone	**2e** (64)	**3e** (66)	**4e** (63)
6	**1b**	cyclohexanone	**2f** (61)	**3f** (70)	**4f** (73)
7	**1c** (R^1 = Me, R^2 = H)	acetone	**2g** (64)	**3g** (79)	**4g** (71)
8	**1c**	cyclopentanone	**2h** (63)	**3h** (73)	**4h** (61)
9	**1c**	cyclohexanone	**2i** (64)	**3i** (70)	**4i** (68)
10	**1c**	cyclooctanone	**2j** (65)	**3j** (78)	**4j** (58)
11	**1d** (R^1 = Me, R^2 = OMe)	cyclohexanone	**2k** (61)	**3k** (49)	e)

a) Isolated yields. b) An inseparable mixture of diastereomers (ca. 3:1). c) Stereochemistry of each isomer was not determined yet. d) A separable mixture of diastereomers (ca. 3:1). e) The reduction of **3k** was not carried out.

We then proceeded to study the replacement of iodine of 1-iodomethyl-1,3-dihydroisobenzofurans (**3**) with hydrogen. The compound (**3**) were treated with tributyltin hydride in benzene at room temperature. The reactions were completed within 2 h to give the corresponding 1-methyl derivatives (**4**) in fair to good yields, as summarized in Table 1.

We next proceeded to explore the nucleophilic substitution of **3** with sodium thiolates. The procedure is outlined in Scheme 2. The reactions were conducted in DMF at the temperature indicated in the Table 2, in which reaction times and yields of the products were also summarized. Phenylmethanethiolate (entries

1 and 3), 2-hydroxyethanethiolate (entry 4), and benzenethiolate (entry 6) reacted smoothly with **3** at room temperature to give the corresponding sulfenylated 1,3-dihydroisobenzofurans (**5**) in fair yields. It was also found that heterocyclic thiols, such as pyridine-2-thiol and 4,6-dimethylpirimidine-2-thiol, could be successfully employed in this substitution reaction, but elevated reaction temperatures were required for satisfactory production of the desired products (**5b**), (**5e**), and (**5g**) (entries 2, 5, and 7).



Scheme 2

Table 2. Reactions of **3** with Sodium Thiolates

Entry	**3**	R^5 in $NaSR^5$	Temp	Time/h	Product (Yield/%) [a)]
1	**3b**	Bn	rt	4	**5a** (70)
2	**3f**	4,6-dimethylpyrimidin-2-yl	90 ˚C	7	**5b** (51)
3	**3g**	Bn	rt	2	**5c** (60)
4	**3g**	$(CH_2)_2OH$	rt	20	**5d** (67)
5	**3h**	pyridin-2-yl	65 ˚C	18	**5e** (48)
6	**3i**	Ph	rt	24	**5f** (64)
7	**3k**	4,6-dimethylpyrimidin-2-yl	70 ˚C	9	**5g** (51)

a) Isolated yields.

In conclusion, the present study has led to the development of a novel and convenient method for the preparation of 1,1,4,4-tetrasubstituted 1,3-dihydroisobenzofurans. The present method has advantages over the previous methods of 1,3-dihydroisobenzofuran synthesis: simple manipulations as well as the ready availability of the starting materials. Applications of the present procedure to the preparation of related heterocycle systems are presently under investigation and will be reported at a later date.

EXPERIMENTAL

The melting points were determined on a Laboratory Devices MEL-TEMP II melting-point apparatus and are uncorrected. The IR spectra were recorded on a Shimadzu FTIR-8300 spectrometer. ^1H NMR spectra were determined using $SiMe_4$ as an internal reference in $CDCl_3$ with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz or a JEOL LA400 FT NMR spectrometer operating at 400 MHz. Low-resolution mass spectra (EI) were recorded on a JEOL AUTOMASS 20 spectrometer. Low-resolution mass spectra (CI) were recorded on a JEOL JMS AX505 HA spectrometer. Thin-layer chromatography (TLC) was carried out using Merck Kieselgel 60 PF_{254}. Column chromatography was

performed using Merck Kieselgel 60 (0.063–0.200 mm). All of the solvents used were dried over the appropriate drying agents and distilled under argon prior to use.

Starting Materials 1-Bromo-2-(1-phenylethenyl)benzene (**1a**),[5] 1-bromo-2-[1-(4-chlorophenyl)ethenyl]benzene (**1b**),[1d] and 1-bromo-2-(methylethenyl)benzene (**1c**)[6] were prepared by appropriated reported methods. All other chemicals used in this study were commercially available.

Typical Procedure for the Preparation of 2-Vinylbenzyl Alcohol Derivatives (2). 1-[2-(2-Phenylethenyl)phenyl]cyclopentanol (2a): To a stirred solution of **1a** (0.96 g, 3.7 mmol) in Et_2O (10 mL) at 0 °C was added dropwise *n*-BuLi (1.6 M in hexane; 3.7 mmol); the mixture was stirred for 1 h at the same temperature. Cyclopentanone (0.31 g, 3.7 mmol) was added and stirring was continued for an additional 30 min. The reaction was quenched by adding saturated aqueous NH_4Cl (15 mL) and extracted with Et_2O three times (10 mL each). The combined extracts were washed with brine and dried over anhydrous Na_2SO_4, and the solvent was evaporated. The residue was purified by preparative TLC on silica gel to give **2a** (0.56 g, 57%); a yellow oil; R_f 0.24 (1:9 AcOEt–hexane); IR (neat) 3570, 3458, 1612 cm^{-1}; ^1H NMR (400 MHz) δ 1.65–1.82 (4H, m), 1.88 (1H, s), 1.95–1.97 (4H, m), 5.27 (1H, d, *J* = 1.1 Hz), 5.89 (1H, d, *J* = 1.1 Hz), 7.14 (1H, dd, *J* = 7.7, 1.8 Hz), 7.24–7.34 (7H, m), 7.50 (1H, dd, *J* = 8.0, 1.4 Hz). Anal. Calcd for $C_{19}H_{20}O$: C, 86.32; H, 7.63. Found: C, 86.05; H, 7.63.

1-[2-(2-Phenylethenyl)phenyl]cyclohexanol (2b): a yellow oil; R_f 0.39 (1:9 AcOEt–hexane); IR (neat) 3572, 3466, 1612 cm^{-1}; ^1H NMR (500 MHz) δ 1.11–1.20 (1H, m), 1.46–1.88 (9H, m), 1.98 (1H, s), 5.19 (1H, s), 5.83 (1H, s), 7.08 (1H, d, *J* = 7.3 Hz), 7.21–7.35 (7H, m), 7.50 (1H, d, *J* = 8.2 Hz). Anal. Calcd for $C_{20}H_{22}O$: C, 86.29; H, 7.97. Found: C, 86.24; H, 7.84.

{2-[2-(4-Chlorophenyl)ethenyl]phenyl}phenylmethanol (2c): a pale-yellow oil; R_f 0.33 (1:7 Et_2O–hexane); IR (neat) 3404, 1601 cm^{-1}; ^1H NMR (500 MHz) δ 1.93 (1H, d, *J* = 3.7 Hz), 5.17 (1H, d, *J* = 1.4 Hz), 5.789 (1H, d, *J* = 1.4 Hz), 5.790 (1H, d, *J* = 3.7 Hz),7.16–7.25 (10H, m), 7.31 (1H, td, *J* = 7.8, 1.4 Hz), 7.39 (1H, td, *J* = 7.8, 1.4 Hz), 7.53 (1H, dd, *J* = 7.8, 1.4 Hz). Anal. Calcd for $C_{21}H_{17}ClO$: C, 78.62; H, 5.34. Found: C, 78.71; H, 5.50.

2-[2-(4-Chlorophenyl)ethenyl]phenylpropan-2-ol (2d): a pale-yellow oil; R_f 0.22 (1:3 Et_2O–hexane); IR (neat) 3568, 3412, 1614 cm^{-1}; ^1H NMR (500 MHz) δ 1.49 (6H, s), 2.14 (1H, s), 5.22 (1H, d, *J* = 0.9 Hz), 5.84 (1H, d, *J* = 0.9 Hz), 7.07 (1H, dd, *J* = 7.8, 1.4 Hz), 7.23 (2H, d, *J* = 9.2 Hz), 7.24 (2H, d, *J* = 9.2 Hz), 7.26 (1H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.34 (1H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.50 (1H, dd, *J* = 7.8, 1.4 Hz). Anal. Calcd for $C_{17}H_{17}ClO$: C, 74.86; H, 6.28. Found: C, 74.90; H, 6.21.

1-[2-(4-Chlorophenyl)ethenyl]phenylcycopentanol (2e): a pale-yellow oil; R_f 0.40 (1:2 CH_2Cl_2–hexane); IR (neat) 3576, 3458, 1614 cm^{-1}; ^1H NMR (500 MHz) δ 1.65–1.72 (2H, m), 1.78–1.86 (3H, m), 1.91–1.98 (4H, m), 5.27 (1H, s), 5.87 (1H, s), 7.10 (1H, d, *J* = 7.8 Hz), 7.23–7.29 (5H, m), 7.33 (1H, dd, *J* = 7.8, 7.3 Hz), 7.49 (1H, d, *J* = 7.8 Hz). Anal. Calcd for $C_{19}H_{19}ClO$: C, 76.37; H, 6.41. Found: C, 76.21; H, 6.80.

1-[2-(4-Chlorophenyl)ethenyl]phenylcycohexanol (2f): a pale-yellow oil; R_f 0.40 (1:2 Et_2O–hexane); IR (neat) 3580, 3468, 1612 cm^{-1}; ^1H NMR (500 MHz) δ 1.16–1.20 (1H, m), 1.47–1.52 (2H, m), 1.61–1.74 (5H, m), 1.80–1.87 (2H, m), 1.88 (1H, s), 5.18 (1H, d, *J* = 0.9 Hz), 5.81 (1H, d, *J* = 0.9 Hz), 7.04 (1H, dd, *J* = 7.8, 1.4 Hz), 7.22–7.30 (5H, m), 7.34 (1H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.49 (1H, d, *J* = 8.2 Hz). Anal. Calcd for $C_{20}H_{21}ClO$: C, 76.79; H, 6.77. Found: C, 76.76; H, 6.84.

2-[2-(1-Methylethenyl)phenyl]propan-2-ol (2g): a yellow oil; R_f 0.25 (1:10 AcOEt–hexane); IR (neat) 3566, 3452, 1635 cm^{-1}; ^1H NMR (500 MHz) δ 1.62 (6H, s), 2.17 (3H, d, *J* = 1.4 Hz), 2.97 (1H, s), 4.89 (1H, d, *J* = 0.9 Hz), 5.21 (1H, qd, *J* = 1.4, 0.9 Hz), 7.01 (1H, dd, *J* = 7.8, 1.4 Hz), 7.18 (1H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.23 (1H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.36 (1H, dd, *J* = 7.8, 1.4 Hz). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.75; H, 9.24.

1-[2-(1-Methylethenyl)phenyl]cyclopentanol (2h): a white solid; mp 42–44 °C (hexane); IR (KBr) 3560, 3452, 1634 cm^{-1}; ^1H NMR (500 MHz) δ 1.75–1.82 (2H, m), 1.90–1.99 (2H, m), 2.02–2.12 (4H, m), 2.18 (3H, s), 2.56 (1H, s), 4.92 (1H, d, *J* = 1.4 Hz), 5.22 (1H, d, *J* = 1.4 Hz), 7.05 (1H, dd, *J* = 7.8, 1.4 Hz), 7.18–7.24 (2H, m), 7.37 (1H, dd, *J* = 7.8, 1.4 Hz). Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.84; H, 9.13.

1-[2-(1-Methylethenyl)phenyl]cyclohexanol (2i): a yellow oil; R_f 0.40 (1:5 AcOEt–hexane); IR (neat) 3568, 3454, 1633 cm^{-1}; ^1H NMR (500 MHz) δ 1.21–1.30 (1H, m), 1.55–1.60 (2H, m), 1.71–1.93 (7H. m), 2.18 (3H, t, *J* = 1.4 Hz), 2.70 (1H, s), 4.85 (1H, quint, *J* = 1.4 Hz), 5.16 (1H, q, *J* = 1.4 Hz), 7.00 (1H, dd, *J* = 7.3, 1.8 Hz), 7.17 (1H, td, *J* = 7.3, 1.4 Hz), 7.23 (1H, ddd, *J* = 7.8, 7.3, 1.8 Hz), 7.36 (1H, dd, *J* = 7.8, 1.4 Hz). Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 82.98; H, 9.46.

1-[2-(1-Methylethenyl)phenyl]cyclooctanol (2j): a yellow oil; R_f 0.30 (1:2 CH_2Cl_2–hexane); IR (neat) 3501, 3385, 1636 cm^{-1}; ^1H NMR (500 MHz) δ 1.35–1.40 (1H, m), 1.48–2.10 (13H, m), 2.18 (3H, s), 2.83 (1H, s), 4.84 (1H, d, *J* = 1.8 Hz), 5.17 (1H, d, *J* = 1.8 Hz), 7.00 (1H, dd, *J* = 7.3, 1.8 Hz), 7.18 (1H, td, *J* = 7.3, 1.4 Hz), 7.22 (1H, ddd, *J* = 7.8, 7.3, 1.8 Hz), 7.33 (1H, dd, *J* = 7.8, 1.4 Hz). Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.41; H, 10.01.

1-[4-Methoxy-2-(1-methylethenyl)phenyl]cyclohexanol (2k): a colorless oil; R_f 0.33 (1:9 EtOAc–hexane); IR (neat) 3564, 1634, 1605 cm^{-1}; ^1H NMR (500 MHz) δ 1.19–1.28 (1H, m), 1.54–1.59 (2H, m), 1.69–1.90 (7H, m), 2.18 (3H, s), 2.59 (1H, s), 3.79 (3H, s), 4.87 (1H, s), 5.16 (1H, s), 6.54 (1H, d, *J* = 2.8 Hz), 6.78 (1H, dd, *J* = 8.7, 2.8 Hz), 7.29 (1H, d, *J* = 8.7 Hz). Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.85; H, 9.14.

Typical Procedure for the Preparation of 1-(Iodomethyl)-1,3-dihydroisobenzofuran Derivatives (3)

3'-Iodomethyl-3'-phenyl-3'*H*-spiro[cyclopentane-1,1'-(1',3'-dihydroisobenzofuran)] (3a): To a stirred solution of **2a** (0.31 g, 1.2 mmol) in toluene (15 mL) containing *t*-BuOK (0.40 g, 3.6 mmol) at 0 °C was added I_2 (0.96 g, 3.6 mmol) in several portions; stirring was continued for 15 min. Ten percent aqueous $Na_2S_2O_3$ was added until the color of iodine disappeared, and the organic materials were

extracted with Et_2O three times (10 mL each). The combined extracts were washed with saturated aqueous NH_4Cl and then brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by preparative TLC on silica gel (1:9 CH_2Cl_2–hexane) to give **3a** (0.41g, 88%); a pale-yellow solid; mp 109–114 °C (hexane–Et_2O); IR (KBr) 1040 cm^{-1}; ^1H NMR (500 MHz) δ 1.68–1.81 (1H, m), 1.83–1.85 (2H, m), 1.93–2.09 (4H, m), 2.37–2.41 (1H, m), 3.76 (1H, d, *J* = 11.0 Hz), 3.83 (1H, d, *J* = 11.0 Hz), 7.14 (1H, d, *J* = 7.3 Hz), 7.25 (1H, t, *J* = 7.3 Hz), 7.31–7.36 (5H, m), 7.58 (2H, d, *J* = 7.3 Hz); MS (EI) *m/z* 390 (M^+, 0.2), 263 (1.1), 249 (100). Anal. Calcd for $C_{19}H_{19}IO$: C, 58.47; H, 4.91. Found: C, 58.42; H, 4.89.

3'-Iodomethyl-3'-phenyl-3'*H*-spiro[cyclohexane-1,1'-(1',3'-dihydroisobenzofuran)] (3b): a pale-yellow solid; mp 88–90 °C (hexane–Et_2O); IR (KBr) 1040 cm^{-1}; ^1H NMR (500 MHz) δ 1.47–1.65 (5H, m), 1.73–1.99 (4H, m), 2.10–2.13 (1H, m), 3.72 (1H, d, *J* = 10.5 Hz), 3.85 (1H, d, *J* = 10.5 Hz), 7.10 (1H, dd, *J* = 7.3, 2.2 Hz), 7.25 (1H, t, *J* = 7.3 Hz), 7.31–7.35 (5H, m), 7.62 (2H, d, *J* = 7.8 Hz); MS (EI) *m/z* 404 (M^+, 1.2), 263 (100). Anal. Calcd for $C_{20}H_{21}IO$: C, 59.42; H, 5.24. Found: C, 59.27; H, 4.96.

1-(4-Chlorophenyl)-1-iodomethyl-3-phenyl-1,3-dihydroisobenzofuran (3c): a mixture of diastereoisomers (*ca*. 3:1); a pale-yellow solid; mp 109–114 °C; IR (KBr) 1601, 1092 cm^{-1}; ^1H NMR (500 MHz) δ 3.87 (0.75H, d, *J* = 11.0 Hz), 3.88 (0.25H, d, *J* = 11.0 Hz), 3.91 (0.75H, d, *J* = 11.0Hz), 3.93 (0.25H, d, *J* = 11.0 Hz), 6.02 (0.25H, s), 6.40 (0.75H, s), 6.93 (0.25H, d, *J* = 7.8 Hz), 7.03 (0.75H, dd, *J* = 7.8, 0.9 Hz), 7.16–7.18 (1.5H, m), 7.28–7.42 (7.5H, m), 7.46–7.58 (3H, m); MS (EI) *m/z* 446 (M^+, 0.02), 305 (100). Anal. Calcd for $C_{21}H_{16}ClIO$: C, 56.46; H, 3.61. Found: C, 56.15; H, 3.61.

1-(4-Chlorophenyl)-1-iodomethyl-3,3-dimethyl-1,3-dihydroisobenzofuran (3d): a pale-yellow solid; mp 108–110 °C (hexane–Et_2O); IR (KBr) 1069 cm^{-1}; ^1H NMR (500 MHz) δ 1.40 (3H, s), 1.72 (3H, s), 3.71 (1H, d, *J* = 11.0 Hz), 3.79 (1H, d, *J* = 11.0 Hz), 7.11–7.14 (1H, m), 7.30 (2H, d, *J* = 8.7 Hz), 7.35–7.39 (3H, m), 7.53 (2H, d, *J* = 8.7 Hz); MS (EI) *m/z* 398 (M^+, 0.19), 257 (100). Anal. Calcd for $C_{17}H_{16}ClIO$: C, 51.22; H, 4.05. Found: C, 51.08; H, 4.27.

3'-(4-Chlorophenyl)-3'-iodomethyl-3'*H*-spiro[cyclopentane-1,1'-(1',3'-dihydroisobenzofuran)] (3e): a white solid; mp 91–92 °C (hexane–Et_2O); IR (KBr disk) 1091 cm^{-1}; ^1H NMR (500 MHz) δ 1.67–1.73 (1H, m), 1.80–2.08 (6H, m), 2.33–2.39 (1H, m), 3.71 (1H, d, *J* = 10.5 Hz), 3.78 (1H, d, *J* = 10.5 Hz), 7.15 (1H, dd, *J* = 7.8, 0.9 Hz), 7.30 (2H, d, *J* = 8.7 Hz), 7.31–7.38 (3H, m), 7.50 (2H, d, *J* = 8.7 Hz); MS (EI) *m/z* 424 (M^+, 0.29), 283 (100). Anal. Calcd for $C_{19}H_{18}ClIO$: C, 53.73; H, 4.27. Found: C, 53.70; H, 4.18.

3'-(4-Chlorophenyl)-3'-iodomethyl-3'*H*-spiro[cyclohexane-1,1'-(1',3'-dihydroisobenzofuran)] (3f): a pale-yellow solid; mp 110–111 °C (hexane–Et_2O); IR (KBr) 1089 cm^{-1}; ^1H NMR (500 MHz) δ 1.31–1.40 (1H, m), 1.47–1.55 (2H, m), 1.62–1.66 (1H, m), 1.72–2.00 (5H, m), 2.07–2.09 (1H, m), 3.67 (1H, d, *J* = 11.0 Hz), 3.80 (1H, d, *J* = 11.0 Hz), 7.11–7.13 (1H, m), 7.29 (2H, d, *J* = 8.7 Hz), 7.34–7.36 (3H, m), 7.55 (2H, d, *J* = 8.7 Hz); MS (EI) *m/z* 438 (M^+, 2.1), 297 (100). Anal. Calcd for $C_{20}H_{20}ClIO$: C, 54.75; H, 4.59. Found: C, 54.63; H, 4.61.

1-Iodomethyl-1,3,3-trimethyl-1,3-dihydroisobenzofuran (3g): a yellow oil; R_f 0.40 (1:1 AcOEt–hexane); IR (neat) 1067 cm^{-1}; ^1H NMR (500 MHz) δ 1.52 (3H, s), 1.61 (3H, s), 1.69 (3H, s), 3.48 (1H, d, *J* = 10.5 Hz), 3.51 (1H, d, *J* = 10.5 Hz), 7.11 (1H, d, *J* = 7.3 Hz), 7.16 (1H, dd, *J* = 6.9, 1.4 Hz), 7.30 (1H, td, *J* = 7.3, 1.4 Hz), 7.33 (1H, ddd, *J* = 7.3, 6.9, 1.4 Hz); MS (EI) *m/z* 302 (M^+, 0.01), 287 (14), 161 (100). Anal. Calcd for $C_{12}H_{15}IO$: C, 47.70; H, 5.00. Found: C, 47.61; H, 5.01.

3'-Iodomethyl-3'-methyl-3'*H*-spiro[cyclopentane-1,1'-(1',3'-dihydroisobenzofuran)] (3h): a yellow oil; R_f 0.42 (1:2 CH_2Cl_2–hexane); IR (neat) 1032 cm^{-1}; ^1H NMR (500 MHz) δ 1.67 (3H, s), 1.79–2.05 (7H, m), 2.19–2.33 (1H, m), 3.49 (2H, s), 7.12 (1H, dd, *J* = 7.3, 1.4 Hz), 7.14 (1H, d, *J* = 7.3 Hz), 7.29 (1H, td, *J* = 7.3, 0.9 Hz), 7.33 (1H, td, *J* = 7.3, 1.4 Hz); MS (EI) *m/z* 328 (M^+, 1.3), 299 (9.8), 187 (100). Anal. Calcd for $C_{14}H_{17}IO$: C, 51.24; H, 5.22. Found: C, 51.21; H, 5.50.

3'-Iodomethyl-3'-methyl-3'*H*-spiro[cyclohexane-1,1'-(1',3'-dihydroisobenzofuran)] (3i): a yellow oil; R_f 0.29 (1:10 CH_2Cl_2–hexane); IR (neat) 1034 cm^{-1}; ^1H NMR (500 MHz) δ 1.30–1.38 (1H, m), 1.61–1.87 (11H, m including s at 1.67), 1.91–1.95 (1H, m), 3.47 (1H, d, *J* = 10.5 Hz), 3.50 (1H, d, *J* = 10.5 Hz), 7.11 (1H, dd, *J* = 7.8, 1.4 Hz), 7.17 (1H, dd, *J* = 6.9, 1.4 Hz), 7.27–7.33 (2H, m); MS (EI) *m/z* 342 (M^+, 6.7), 299 (32), 201 (100). Anal. Calcd for $C_{15}H_{19}IO$: C, 52.65; H, 5.60. Found: C, 52.48; H, 5.62.

3'-Iodomethyl-3'-methyl-3'*H*-spiro[cyclooctane-1,1'-(1',3'-dihydroisobenzofuran)] (3j): a pale-yellow oil; R_f 0.57 (1:2 CH_2Cl_2–hexane); IR (neat) 1032 cm^{-1}; ^1H NMR (500 MHz) δ 1.56–1.61 (2H, m), 1.66 (3H, s), 1.68–1.86 (9H, m), 1.96–2.06 (2H, m), 2.10–2.16 (1H, m), 3.46 (1H, d, *J* = 10.5 Hz), 3.49 (1H, d, *J* = 10.5 Hz), 7.16–7.18 (2H, m), 7.27–7.32 (2H, m); MS (CI) *m/z* 371 [$(M+1)^+$, 100]. Anal. Calcd for $C_{17}H_{23}IO$: C, 55.14; H, 6.26. Found: C, 54.87; H, 6.47.

3'-Iodomethyl-5-methoxy-3'-methyl-3'*H*-spiro[cyclohexane-1,1'-(1',3'-dihydroisobenzofuran)] (3k): a white solid; mp 81–83 °C (hexane–Et_2O); IR (KBr) 1614, 1032 cm^{-1}; ^1H NMR (500 MHz) δ 1.30–1.33 (1H, m), 1.57–1.91 (12H, m including s at 1.66), 3.46 (1H, d, *J* = 11.0 Hz), 3.48 (1H, d, *J* = 11.0 Hz), 3.82 (3H, s), 6.69 (1H, d, *J* = 2.3 Hz), 6.85 (1H, dd, *J* = 8.2, 2.3 Hz), 7.01 (1H, d, *J* = 8.2 Hz); MS (EI) *m/z* 372 (M^+, 11) and 329 (100). Anal. Calcd for $C_{16}H_{21}IO$: C, 51.63; H, 5.69. Found: C, 51.43; H, 6.01.

Typical Procedure for the Preparation of 1-Methyl-1,3-dihydroisobenzofuran Derivatives (4)

3'-Methyl-3'-phenyl-3'*H*-spiro[cyclopentane-1,1'-(1',3'-dihydroisobenzofuran)] (4a): A solution of **3a** (0.20 g, 0.52 mmol) in benzene (5 mL) containing *n*-Bu_3SnH (0.30 g, 1.0 mmol) was stirred at rt for 2 h. The solvent was evaporated and the residue was purified by preparative TLC on silica gel to give **4a** (82 mg, 60%); a colorless oil; R_f 0.42 (1:15 THF–hexane); IR (neat) 1072 cm^{-1}; ^1H NMR (400 MHz) δ 1.82–2.14 (11H, m including s at 1.85), 7.13–7.31 (7H, m), 7.49 (2H, d, *J* = 7.3 Hz); MS (EI) *m/z* 264 (M^+, 10), 249 (100). Anal. Calcd for $C_{19}H_{20}O$: C, 86.32; H, 7.63. Found: C, 86.29; H, 7.70.

3'-Methyl-3'-phenyl-3'*H*-spiro[cyclohexane-1,1'-(1',3'-dihydroisobenzofuran)] (4b): a colorless oil; R_f 0.51 (1:10 THF–hexane); IR (neat) 1057 cm^{-1}; ^1H NMR (500 MHz) δ 1.32–1.43 (1H, m), 1.57–1.97 (12H, m including s at 1.84), 7.10–7.12 (1H, m), 7.20 (1H, t, *J* = 7.3 Hz), 7.23–7.27 (3H, m), 7.30 (2H, dd, *J* = 7.8, 7.3 Hz), 7.57 (2H, d, *J* = 7.8 Hz); MS (EI) *m/z* 278 (M^+, 30), 263 (73), 235 (100). Anal.

Calcd for $C_{20}H_{22}O$: C, 86.29; H, 7.97. Found: C, 86.27; H, 8.11.

1-(4-Chlorophenyl)-1-methyl-3-phenyl-1,3-dihydroisobenzofuran (4c): a major diastereomer: a colorless solid; mp 90–92 °C (hexane–Et_2O); IR (KBr) 1094 cm^{-1}; ^1H NMR (500 MHz) δ 1.83 (3H, s), 6.20 (1H, s), 6.95 (1H, dd, *J* = 7.3, 0.9 Hz), 7.09 (1H, d, *J* = 7.3 Hz), 7.16–7.30 (9H, m), 7.42 (2H, d, *J* = 8.7 Hz); MS (EI) *m/z* 320 (M^+, 1.2), 305 (100). Anal. Calcd for $C_{21}H_{17}ClO$: C, 78.62; H, 5.34. Found: C, 78.79; H, 5.67. A minor diastereomer: a colorless solid; mp 68–72 °C (hexane–Et_2O); IR (KBr) 1094 cm^{-1}; ^1H NMR (500 MHz) δ 1.99 (3H, s), 6.07 (1H, s), 6.92 (1H, d, *J* = 7.3 Hz), 7.22–7.39 (10H, m), 7.48 (2H, d, *J* = 8.7 Hz); MS (EI) *m/z* 320 (M^+, 1.6), 305 (100). Anal. Calcd for $C_{21}H_{17}ClO$: C, 78.62; H, 5.34. Found: C, 78.38; H, 4.98.

1-(4-Chlorophenyl)-1,3,3-trimethyl-1,3-dihydroisobenzofuran (4d):[7] a pale-yellow oil; R_f 0.43 (1:10 CH_2Cl_2–hexane); IR (neat) 1096 cm^{-1}; ^1H NMR (500 MHz) δ 1.47 (3H, s), 1.61 (3H, s), 1.84 (3H, s), 7.11–7.13 (1H, m), 7.21–7.22 (1H, m), 7.27 (2H, d, *J* = 8.7 Hz), 7.29–7.32 (2H, m), 7.46 (2H, d, *J* = 8.7 Hz).

3'-(4-Chlorophenyl)-3'-methyl-3'*H*-spiro[cyclopentane-1,1'-(1',3'-dihydroisobenzofuran)] (4e): a colorless oil; R_f 0.70 (1:9 EtOAc–hexane); IR (neat) 1090 cm^{-1}; ^1H NMR (500 MHz) δ 1.77–1.87 (6H, m including s at 1.82), 1.91–2.04 (4H, m), 2.09–2.17 (1H, m), 7.14 (2H, d, *J* = 8.7 Hz), 7.25–7.32 (4H, m), 7.42 (2H, d, *J* = 8.7 Hz); MS (EI) *m/z* 298 (M^+, 10), 283 (100). Anal. Calcd for $C_{19}H_{19}ClO$: C, 76.37; H, 6.41. Found: C, 76.10; H, 6.21.

3'-(4-Chlorophenyl)-3'-methyl-3'*H*-spiro[cyclohexane-1,1'-(1',3'-dihydroisobenzofuran)] (4f): a pale-yellow oil; R_f 0.61 (1:10 THF–hexane); IR (neat) 1094 cm^{-1}; ^1H NMR (500 MHz) δ 1.32–1.41 (1H, m), 1.59–1.92 (12H, m including s at 1.82), 7.10–7.13 (1H, m), 7.19–7.23 (1H, m), 7.25–7.29 (4H, m), 7.49 (2H, d, *J* = 8.7 Hz); MS (EI) *m/z* 312 (M^+, 46), 297 (71), 269 (100). Anal. Calcd for $C_{20}H_{21}ClO$: C, 76.79; H, 6.77. Found: C, 76.77; H, 6.87.

1,1,3,3-Tetramethyl-1,3-dihydroisobenzofuran (4g):[4a,8] a pale-yellow liquid; R_f 0.22 (1:2 CH_2Cl_2–hexane). The spectral data for this product were identical to those reported previously.[4a]

3',3'-Dimethyl-3'*H*-spiro[cyclopentane-1,1'-(1',3'-dihydroisobenzofuran)] (4h): a white solid; mp 42–43 °C (hexane–$CHCl_3$); IR (KBr) 1038 cm^{-1}; ^1H NMR (500 MHz) δ 1.50 (6H, s), 1.79–2.06 (8H, m), 7.08 (1H, dd, *J* = 6.9, 1.8 Hz), 7.11 (1H, dd, *J* = 6.9, 1.4 Hz), 7.24–7.29 (2H, m); MS (EI) *m/z* 202 (M^+, 22), 187 (54), 173 (100). Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.07; H, 9.15.

3',3'-Dimethyl-3'*H*-spiro[cyclohexane-1,1'-(1',3'-dihydroisobenzofuran)] (4i):[4a,8] a pale-yellow liquid; R_f 0.34 (1:2 CH_2Cl_2–hexane). The spectral data for this product were identical to those reported previously.[4a]

3',3'-Dimethyl-3'*H*-spiro[cyclooctane-1,1'-(1',3'-dihydroisobenzofuran)] (4j): a colorless oil; R_f 0.29 (1:9 $CHCl_3$–hexane); IR (neat) 1051 cm^{-1}; ^1H NMR (500 MHz) δ 1.49 (6H, s), 1.54–1.61 (2H, m), 1.69–1.79 (8H, m), 1.85–1.90 (2H, m), 2.01–2.06 (2H, m), 7.09 (1H, dd, *J* = 6.9, 1.4 Hz), 7.16 (1H, dd, *J*

= 6.9, 1.4 Hz), 7.23–7.29 (2H, m); MS (EI) *m/z* 244 (M^+, 13), 173 (100). Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.46; H, 10.05.

Typical Procedure for the Preparation of 1-Sulfenylmethyl-1,3-dihydrobenzofuran Derivatives (5)

3'-Benzylthiomethyl-3'-phenyl-3'*H*-spiro[cyclohexane-1,1'-(1',3'-dihydroisobenzofuran)] (5a): To a stirred suspension of NaH (60% in oil; 23 mg, 0.58 mmol) in DMF (4 mL) at 0 ˚C was added dropwise BnSH (72 mg, 0.58 mmol). After 10 min, a solution of **3b** (0.21 g, 0.53 mmol) in DMF (2 mL) was added and the mixture was stirred for at the same temperature for an additional 4 h. Saturated aqueous NH_4Cl (20 mL) was added and the mixture was extracted with Et_2O three times (15 mL each). The combined extracts were washed with water twice and then brine once, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by preparative TLC on silica gel to give **5a** (0.15 g, 70%); a colorless oil; R_f 0.27 (1:5 C_6H_6–hexane); IR (neat) 1040 cm^{-1}; ^1H NMR (500 MHz) δ 1.33–1.63 (4H, m), 1.75–2.05 (6H, m), 3.03 (1H, d, *J* = 13.7 Hz), 3.16 (1H, d, *J* = 13.7 Hz), 3.64 (1H, d, *J* = 13.3 Hz), 3.72 (1H, d, *J* = 13.3 Hz), 7.09–7.11 (1H, m), 7.19–7.36 (11H, m), 7.59 (2H, d, *J* = 8.2 Hz); MS (EI) *m/z* 400 (M^+, 0.04), 262 (100). Anal. Calcd for $C_{27}H_{28}OS$: C, 80.96; H, 7.05. Found: C, 81.04; H, 7.15.

3'-(4-Chlorophenyl)-3'-(4,6-dimethylpyrimidin-2-yl)thiomethyl-3'*H*-spiro[cyclohexane-1,1'-(1',3'-dihydroisobenzofuran)] (5b): a white solid; mp 152–153 ˚C (hexane–Et_2O); IR (KBr) 1088 cm^{-1}; ^1H NMR (500 MHz) δ 1.25–1.36 (1H, m), 1.47–1.87 (8H, m), 2.02–2.06 (1H, m), 2.34 (6H, s), 3.96 (1H, d, *J* = 13.7 Hz), 4.07 (1H, d, *J* = 13.7 Hz), 6.61 (1H, s), 7.07 (1H, d, *J* = 6.9 Hz), 7.21–7.29 (4H, m), 7.45 (1H, dd, *J* = 7.8, 0.9 Hz), 7.63 (2H, d, *J* = 8.7 Hz); MS (EI) *m/z* 450 (M^+, 0.63), 297 (100). Anal. Calcd for $C_{26}H_{27}ClN_2OS$: C, 69.24; H, 6.03; N, 6.21. Found: C, 68.90; H, 6.02; N, 6.08.

1-Benzylthiomethyl-1,3,3-trimethyl-1,3-dihydroisobenzofuran (5c): a colorless oil; R_f 0.28 (1:10 AcOEt–hexane); IR (neat) 1060 cm^{-1}; ^1H NMR (500 MHz) δ 1.51 (3H, s), 1.56 (3H, s), 1.57 (3H, s), 2.81 (2H, s), 3.71 (1H, d, *J* = 13.3 Hz), 3.74 (1H, d, *J* = 13.3 Hz), 7.10 (2H, dd, *J* = 7.8, 1.4 Hz), 7.19–7.32 (7H, m); MS (EI) *m/z* 298 (M^+, 0.11), 283 (0.47), 161 (100). Anal. Calcd for $C_{19}H_{22}OS$: C, 76.46; H, 7.43. Found: C, 76.77; H, 7.49.

2-(1,3,3-Trimethyl-1,3-dihydroisobenzofuran-1-yl)methylthioethanol (5d): a colorless oil; R_f 0.19 (1:3 AcOEt–hexane); IR (neat) 1063 cm^{-1}; ^1H NMR (500 MHz) δ 1.52 (3H, s), 1.59 (3H, s), 1.62 (3H, s), 2.70 (1H, dt, *J* = 14.2, 5.5 Hz), 2.80 (1H, dt, *J* = 14.2, 6.0 Hz), 2.95–3.01 (3H, m), 3.71–3.74 (2H, m), 7.09–7.12 (2H, m), 7.27–7.33 (2H, m); MS (EI) *m/z* 252 (M^+, 0.02), 237 (0.18), 191 (0.33), 173 (0.75), 161 (100). Anal. Calcd for $C_{14}H_{20}O_2S$: C, 66.63; H, 7.99. Found: C, 66.48; H, 7.83.

3'-Methyl-3'-(pyrydin-2-yl)thiomethyl-3'*H*-spiro[cyclopentane-1,1'-(1',3'-dihydroisobenzofuran)] (5e): a yellow oil; R_f 0.67 (1:7 CH_2Cl_2–hexane); IR (neat) 1061 cm^{-1}; ^1H NMR (500 MHz) δ 1.61 (3H, s), 1.73–1.96 (6H, m), 2.00–2.05 (1H, m), 2.11–2.17 (1H, m), 3.70 (1H, d, *J* = 13.3 Hz), 3.74 (1H, d, *J* = 13.3 Hz), 6.92 (1H, ddd, *J* = 7.3, 5.0, 0.9 Hz), 7.10–7.13 (2H, m), 7.16 (1H, d, *J* = 7.3 Hz), 7.20 (1H, td, *J*

= 7.3, 1.4 Hz), 7.27 (1H, td, *J* = 7.3, 1.4 Hz), 7.39 (1H, ddd, *J* = 8.2, 7.3, 0.9 Hz), 8.38 (1H, ddd, *J* = 7.3, 5.0, 0.9 Hz); MS (EI) *m/z* 311 (M^+, 0.55), 270 (2.8), 191 (3.3), 227 (6.1), 187 (100). Anal. Calcd for $C_{19}H_{21}NOS$: C, 73.27; H, 6.80; N, 4.50. Found: C, 73.19; H, 6.98; N, 4.48.

3'-Methyl-3'-phenylthiomethyl-3'*H*-spiro[cyclohexane-1,1'-(1',3'-dihydroisobenzofuran)] (5f): a pale-yellow oil; R_f 0.19 (1:10 CH_2Cl_2–hexane); IR (neat) 1059 cm^{-1}; ^1H NMR (500 MHz) δ 1.27–1.36 (1H, m), 1.61 (3H, s), 1.62–1.83 (8H, m), 1.90–1.92 (1H, m), 3.36 (1H, d, *J* = 12.8 Hz), 3.39 (1H, d, *J* = 12.8 Hz), 7.10–7.15 (3H, m), 7.20–7.33 (6H, m); MS (EI) *m/z* 324 (M^+, 0.12), 201 (100). Anal. Calcd for $C_{21}H_{24}OS$: C, 77.73; H, 7.46. Found: C, 77.49; H, 7.30.

5-Methoxy-3'-methyl-3'-(4,6-dimethylpirimidin-2-yl)thiomethyl-3'*H*-spiro[cyclohexane-1,1'-(1',3'-dihydroisobenzofuran)] (5g): a white solid; mp 102–103 °C (hexane–Et_2O); IR (KBr) 1614, 1045 cm^{-1}; ^1H NMR (500 MHz) δ 1.25–1.34 (1H, m), 1.58–1.70 (10H, m including s at 1.62), 1.74–1.79 (1H, m), 1.93–1.98 (1H, m), 2.34 (6H, s), 3.67 (1H, d, *J* = 13.7 Hz), 3.73 (3H, s), 3.77 (1H, d, *J* = 13.7 Hz), 6.61 (1H, s), 6.74 (1H, d, *J* = 2.3 Hz), 6.77 (1H, dd, *J* = 8.2, 2.3 Hz), 6.97 (1H, d, *J* = 8.2 Hz); MS (CI) *m/z* 385 [$(M+1)^+$, 100]. Anal. Calcd for $C_{22}H_{28}N_2O_2S$: C, 68.72; H, 7.34; N, 7.29. Found: C, 68.69; H, 7.38; N, 7.09.

ACKNOWLEDGEMENTS

We gratefully acknowledge Mrs. Miyuki Tanmatsu of this Faculty for determining mass spectra and performing combustion analyses.

REFERENCES AND NOTES

1. a) K. Kobayashi, D. Nakamura, K. Miyamoto, O. Morikawa, and H. Konishi, *Bull. Chem. Soc. Jpn.*, 2006, **79**, 489. b) K. Kobayashi, M. Hase, K. Hashimoto, S. Fujita, M. Tanmatsu, O. Morikawa, and H. Konishi, *Synthesis,* 2006, 2493. c) K. Kobayashi, K. Miyamoto, T. Yamase, D. Nakamura, O. Morikawa, and H. Konishi, *Bull. Chem. Soc. Jpn.*, 2006, **79**, 1580. d) K. Kobayashi, S. Fujita, M. Hase, O. Morikawa, and H. Konishi, *Bull. Chem. Soc. Jpn.*, 2007, **80**, 763. e) K. Kobayashi, K. Hashimoto, T. Shiokawa, O. Morikawa, and H. Konishi, *Synthesis,* 2007, 824 and references cited therein.
2. J. Madsen, P. Merachtsaki, P. Davoodpour, M. Bergström, B. Langström, K. Andersen, C. Thomsen, L. Martiny, and G. M. Knudsen, *Bioorg. Med. Chem.*, 2003, **11**, 3447.
3. X. Xu, F. Song, S. Wang, S. Li, F. Xiao, J. Zhao, Y. Yang, S. Shang, L. Yang, and J. Shi, *J. Nat. Prod.*, 2004, **67**, 1661.
4. a) M. Yus, F. Foubelo, and J. V. Ferrández, *Tetrahedron,* 2003, **59**, 2083. b) V. Capriati, S. Florio, R. Luisi, and B. Musio, *Org. Lett.*, 2005, **7**, 3749.
5. M. E. Jason, *Tetrahedron Lett.*, 1982, **23**, 1635.

6. I. Fleming and M. Woolias, *J. Chem. Soc., Perkin Trans. 1,* 1979, 829.
7. A. Fabrycy and H. Glinka, *Rocz. Chem.*, 1967, **41**, 77.
8. E. Baston, R. Maggi, K. Friedrich, and M. Schlosser, *Eur. J. Org. Chem.*, 2001, 3985.