Turk J Chem
29 (2005) , 199 – 205.
© TÜBİTAK

A Concise Synthesis and the Antibacterial Activity of 5,6-Dimethoxynaphthalene-2-carboxylic Acid

Süleyman GÖKSU[1*], Metin Tansu UĞUZ[2], Hasan ÖZDEMİR[1], Hasan SEÇEN[1]
[1] *Department of Chemistry, Faculty of Arts and Sciences, Atatürk University, 25240 Erzurum-TURKEY*
e-mail: sgoksu@atauni.edu.tr
[2] *Department of Microbiology, Faculty of Medicine, Atatürk University, 25240 Erzurum-TURKEY*

Received 25.05.2004

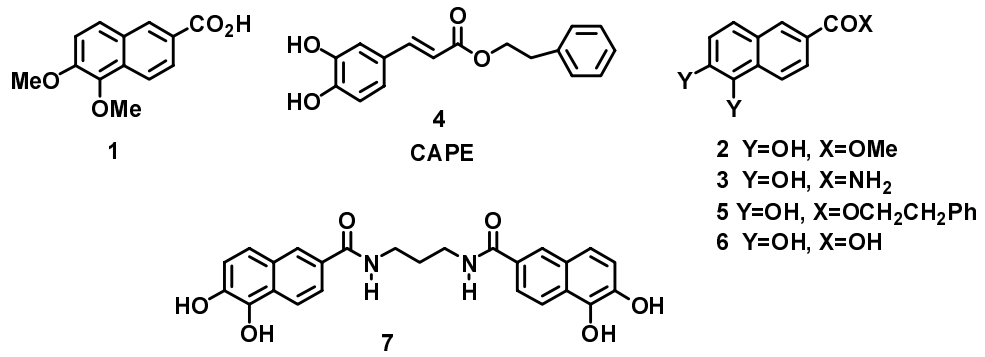
5,6-Dimethoxynaphthalene-2-carboxylic acid was synthesized in 7 steps and with an overall yield of 46%. Bromination of 2-naphthol, and methylation with dimethyl sulfate followed by Friedel-Crafts acylation with AcCl gave 2-acetyl-5-bromo-6-methoxynaphthalene. 2-Acetyl-5-bromo-6-methoxynaphthalene was converted to 5-bromo-6-methoxynaphthalene-2-carboxylic acid by a haloform reaction. The esterification of the acid with methanol, methoxylation with $NaOCH_3$ in the presence of CuI and subsequent de-esterification with NaOH afforded 5,6-dimethoxynaphthalene-2-carboxylic acid. The 5-bromo-6-methoxynaphthalene-2-carboxylic acid and 5,6-dimethoxynaphthalene-2-carboxylic acid were found to have in vitro antibacterial activity against some pathogenic bacteria.

Key Words: Naphthalene-2-carboxylic acids, 2-naphthol, bromination, haloform, antibacterial activity.

Introduction

5,6-Dimethoxynaphthalene-2-carboxylic acid (**1**), demethylated ester (**2**) and amide (**3**) analogues have moderate inhibitory activity for protein-tyrosine kinases (PTKs)[1]. Caffeic acid phenylethyl ester (CAPE) (**4**) has been reported to have HIV-1 integrase inhibitory activity[2]. Demethylated phenylethyl ester analogue (**5**), having constrained CAPE moiety, also shows HIV-1 integrase inhibitory activity and it is somewhat similar in potency to CAPE. 5,6-Dihydroxynaphthalene-2-carboxylic acid methyl ester (**2**) is equipotent to CAPE. Even though its demethylated acid analogue (**6**) is less potent, its demethylated dimeric amide form (**7**) is the most potent for HIV-1 integrase inhibitory activity[3].

*Corresponding author



Scheme 1

To our knowledge, the synthesis of 5,6-dimethoxynaphthalene-2-carboxylic acid has only been performed by Burke et al.[1] from 6-bromo-2-naphthol. In the literature synthesis, oxidation of 6-bromo-2-naphthol with potassium nitrosodisulfonate gives 6-bromo-1,2-naphthalenedione[4]. The reduction of 6-bromo-1,2-naphthalenedione with $Na_2S_2O_4$ gives 6-bromo-1,2-naphthalenediol, from which 6-bromo-1,2-dimethoxynaphthalene is prepared by methylation with dimethyl sulfate[5]. Metalation of 6-bromo-1,2-dimethoxynaphthalene with n-BuLi and then treatment with CO_2 gives 5,6-dimethoxynaphthalene-2-carboxylic acid[1]. The overall yield of this reaction sequence is 34%.

In our ongoing synthesis of biologically active naphthalene compounds[6], in the present study we performed an easy alternative synthesis of 5,6-dimethoxynaphthalene-2-carboxylic acid (**1**) starting from 2-naphthol (**8**) in 7 steps with a 46% total yield. As there has been no detailed study regarding the antibacterial properties of 5,6-dimethoxynaphthalene-2-carboxylic acid (**1**) and 5-bromo-6-methoxynaphthalene-2-carboxylic acid (**12**), in this study we investigated the in vitro antibacterial activities of these compounds against 17 pathogenic bacteria

Experimental

The ^{1}H and ^{13}C-NMR spectra were recorded on 200 (50) MHz Varian spectrometers. Column chromatography experiments were performed on silica gel 60 (70-230 mesh ASTM). TLC was carried out on Merck 2.0 mm silica gel and 60 F_{254} analytical aluminum plates. Melting points were determined on a Buchi 530 apparatus, and are uncorrected.

1-Bromo-naphthalene-2-ol (**9**)**.** To a stirred solution of 2-naphthol (**8**) (30.00 g, 208.3 mmol) in acetic acid (100 mL) was added dropwise a solution of bromine (36.70 g, 229.4 mmol) in acetic acid (20 mL) over 30 min at 18 °C. The reaction mixture was stirred at room temperature for 2 h and poured into 1000 mL of water. The precipitated product was isolated with suction and washed with 100 mL of water. Drying of the crude product at 30 °C and recrystalization from ethanol gave bromonaphthol **9** (37.20 g, 80%). White crystals. M.p. 81-83 °C (from EtOH). Lit.[7] M.p. 83 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 8.05 (dm, 1H, H_5 or H_8, J=8.5 Hz), 7.80 (dm, 1H, H_5 or H_8, J=7.4 Hz), 7.76 (bd, 1H, H_4, $J_{3,4}$=8.9 Hz), 7.59 (ddd, 1H, H_6 or H_7, J=8.3, 6.9, 1.3 Hz), 7.41 (ddd, 1H, H_6 or H_7, J=8.1, 6.9, 1.1 Hz), 7.28 (bd, 1H, H_3, $J_{3,4}$=8.9 Hz), 5.95 (bs, 1H, OH). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 150.6, 129.7, 129.3, 128.2, 127.8, 125.3, 124.2, 117.2, 106.2.

1-Bromo-2-methoxy-naphthalene (10). A 500 mL, 3-necked flask fitted with a condenser and a 50 mL dropping funnel was charged with anhydrose K_2CO_3 (17.30 g, 125.4 mmol), 200 mL of acetone and bromonaphthol **9** (20.00 g, 89.7 mmol). Me_2SO_4 (14.70 g, 11.3 mL, 116.7 mmol) was added under stirring from the dropping funnel to the mixture over 2 min. The stirred mixture was heated gently under reflux for 12 h. The precipitate was filtered off and the acetone was evaporated. The residue was dissolved in $CHCl_3$ (150 mL) and the solution was washed with water (2 x 60 mL) and dried (Na_2SO_4). Removal of the solvent gave **10** (20.20 g, 95%). White solid. M.p. 81-83 °C (from CH_2Cl_2/hexane). Lit.[8] M.p. 82-83 °C. ^{1}H and ^{13}C-NMR are in agreement with the data given in the literature[8].

2-Acetyl-5-bromo-6-methoxy-naphthalene (11). To a stirred solution of **10** (20.00 g, 84.4 mmol) in 300 mL of dry 1,2-dichloroethane were added freshly distillated AcCl (8.00 g, 101.9 mmol) in 1 portion and $AlCl_3$ (33.80 g, 253.2 mmol) in small portions over 1 h at 0 °C. The mixture was stirred at 0 °C for 12 h and monitored by TLC. After the completion of the reaction, the mixture was poured into 250 g of ice and 100 mL of conc. HCl. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 120 mL). The organic phases were combined and washed with 100 mL of dilute Na_2CO_3 and 100 mL of H_2O. Drying of the organic phase (Na_2SO_4), evaporation of the solvent and then chromatography of the residue through a short silica-gel column (15 g, CH_2Cl_2) afforded **11** (20.20 g, 86%). Yellowish crystals. M.p. 125-127 °C (from CH_2Cl_2/hexane). Lit.[9] M.p. 128 °C (from EtOH). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 8.32 (d, 1H, H_1, $J_{1,3}$=1.6 Hz), 8.18 (A part of AB system, d, 1H, H_4, $J_{3,4}$=9.0 Hz), 8.03 (B part of AB system, dd, 1H, H_3, $J_{3,4}$=9.0 Hz, $J_{1,3}$=1.6 Hz), 7.88 (A part of AB system, d, 1H, H_8, $J_{7,8}$=9.0 Hz), 7.53 (B part of AB system, d, 1H, H_7, $J_{7,8}$=9.0 Hz), 4.03 (s, 3H, OCH_3), 2.68 (s, 3H, $C(O)CH_3$). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 197.3, 155.6, 135.2, 132.8, 130.6, 130.1, 128.5, 126.4, 125.6, 113.8, 108.4, 55.8, 26.5.

5-Bromo-6-methoxy-naphthalene-2-carboxylic acid (12). To a stirred solution of NaOH (21.60 g, 539.4 mmol) in 75 mL of H_2O was added dropwise Br_2 (28.40 g, 177.5 mmol) over 25-30 min at 0 °C. A solution of **11** (15.00 g, 53.8 mmol) in 100 mL of THF was added to the reaction mixture in 1 portion at 0-5 °C. The mixture was stirred at room temp. for 12 h and the organic phase was dispatched from the separatory funnel. To the aqueous solution were added ice (100 g) and a 20% aqueous solution of $NaHSO_3$ (100 mL). After acidification with 37% HCl (pH $\leq$2) the solidified acid was filtered with suction and dried at 50 °C (13.30 g, 88%). White crystals. Solidified. M.p. 284 $\geq$ decomposition. Lit.[10] M.p. 290-291 °C. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 8.60 (bs, 1H, H_1), 8.19 (A part of AB system, d, 1H, H_8, $J_{7,8}$=9.2 Hz), 8.09 (A part of AB system, d, 1H, H_3 or H_4, $J_{3,4}$=8.5 Hz), 8.06 (B part of AB system, d, 1H, H_3 or H_4, $J_{3,4}$=8.5 Hz), 7.59 (B part of AB system, d, 1H, H_7, $J_{7,8}$=9.2 Hz), 4.03 (s, 3H, OCH_3). ^{13}C-NMR (50 MHz, DMSO-d_6): δ 168.9, 157.2, 136.1, 132.9, 132.8, 130.1, 129.0, 128.2, 127.3, 116.6, 108.5, 58.7.

Methyl 5-bromo-6-methoxy-naphthalene-2-carboxylate (13). To a stirred solution of **12** (10.00 g, 35.6 mmol) in 100 mL of MeOH was added TsOH (100 mg) followed by refluxing for 12 h. MeOH was evaporated and the residue was dissolved in 100 mL of EtOAc and washed with a solution of Na_2CO_3 (2 x 50 mL). Drying of the solution (Na_2SO_4) and evaporation of the solvent gave **13** (10.30 g, 98%). White solid. M.p. 164-166 °C (from MeOH). Lit.[10] M.p. 162-163 °C, lit.[11] 164 °C (from acetone/H_2O). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 8.40 (bs, 1H, H_1), 8.12 (A part of AB system, d, 1H, H_3 or H_4, $J_{3,4}$=9.0 Hz), 8.03 (B part of AB system, d, 1H, H_3 or H_4, $J_{3,4}$=9.0 Hz), 7.78 (A part of AB system, d, 1H, H_8, $J_{7,8}$=9.2 Hz), 7.18 (B part of AB system, d, 1H, H_7, $J_{7,8}$=9.2 Hz), 3.98 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3). ^{13}C-NMR

(50 MHz, $CDCl_3$): δ 166.8, 155.4, 135.1, 131.1, 130.4, 128.4, 126.8, 126.2, 125.6, 113.7, 108.2, 56.6, 52.1.

5,6-Dimethoxy-naphthalene-2-carboxylic acid (1). To refluxing MeOH (60 mL) was added Na (1.20 g, 52.2 mmol) in small pieces over 1 h under N_2. To this solution was added a solution of **13** (5.00 g, 16.9 mmol) in freshly distillated DMF (25-30 mL). While the reaction mixture was being refluxed, CuI (approximately 100-150 mg) was added. After refluxing for 12 h, the reaction mixture was cooled to room temp. and MeOH was evaporated. Then 100 mL of CH_2Cl_2 and 50 mL of H_2O were added and the organic phase was separated. The organic phase was washed with H_2O (4 x 50 mL). After evaporation of the solvent, the residue was hydrolyzed with 2 M NaOH in MeOH/H_2O at room temp. over 12 h. Then MeOH was evaporated. To the residue were added H_2O (50 mL) and CH_2Cl_2 (70 mL). The organic phase was dispatched and the aqueous phase was acidified with 37% HCl (pH $\leq$2). The solidified acid **1** was filtered with suction (or workups with EtOAc) and dried at 40 °C (3.20 g, 82%). White crystals. M.p. 213-215 °C (from MeOH). Lit.[1] M.p. 209-211 °C. ^{1}H-NMR is in agreement with the data given in the literature[1]. ^{13}C-NMR (50 MHz, DMSO-d_6): δ 169.2, 151.8, 143.6, 132.5, 132.1, 129.8, 128.0, 127.7, 127.2, 122.8, 118.0, 62.4, 58.3.

Measurement of in vitro antibacterial activity. The antibacterial activity of naphthalene carboxylic acid **1** and **12** was determined by the disk diffusion method of Bauer-Kirby using Mueller-Hinton agar medium with a slight modification[12]and compared with well known antibacterial substances such as tetracycline and netilmicin.

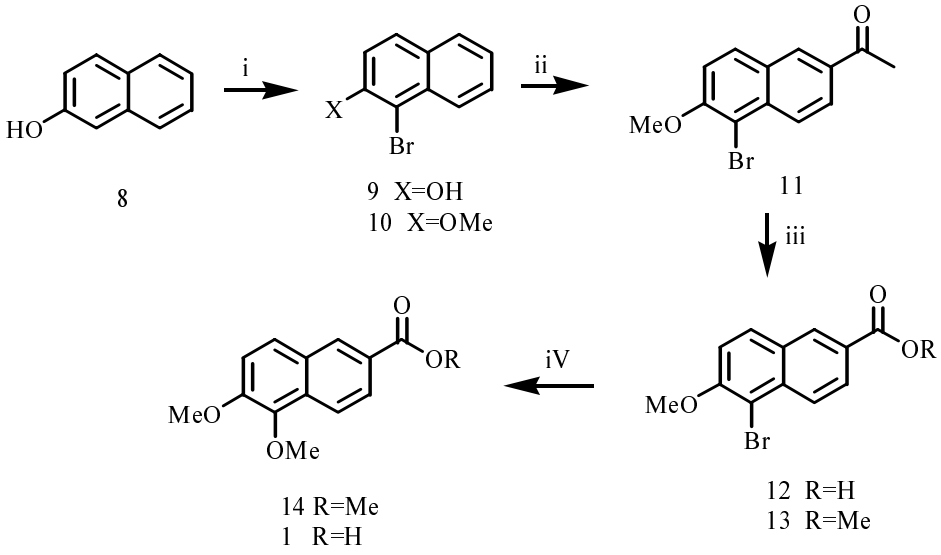
Mueller-Hinton agar medium (prepared in sterile conditions) was cooled to 40-45 °C and each 10 mL portion of it was added to Petri dishes. The organic compounds were dissolved in DMSO (10 mg/2 mL). Then 20 μL solutions of the compounds (ca. 100 μg) were applied to the sterile disks. Bacteria suspensions (prepared in McFarland standard 0.5) were applied to the Mueller-Hinton agar medium by the spread plate technique. The prepared sterile disks were placed in bacteria-culture spread Petri dishes using a sterile needle. The Petri dishes were left at +4 °C for 1 h and then incubated in an incubator at 37 °C for 18-24 h.

For the compounds, microorganisms that showed zones of inhibition <10 mm were considered resistant, between 10 and 15 were considered weakly sensitive, and >15 were considered sensitive[12]. According to NCCLS (1999), zones of inhibition for tetracycline <14 mm were considered resistant, between 15 and 18 mm were considered weakly sensitive, and >19 were considered sensitive. Zones of inhibition for netilmicin of <12 mm were considered resistant, between 13 and 14 mm were considered weakly sensitive, and >15 were considered sensitive.

Results and Discussion

By a known literature procedure[13] applied to 2-methoxynaphthalene, the bromination of 2-naphthol (**8**) in acetic acid gave 1-bromo-2-naphthol (**9**). Methylation of 1-bromo-2-naphthol (**9**) with dimethyl sulfate and K_2CO_3 gave 1-bromo-2-methoxynaphthalene (**10**)[13]. Friedel-Crafts acylation with acetyl chloride in the presence of $AlCl_3$ performed in 1,2-dichloroethane gave 2-acetyl-5-bromo-6-methoxynaphthalene (**11**)[9]. Acetyl compound **11** was converted to carboxylic acid **12**[10] by a haloform reaction (Br_2/NaOH). The acid **12** was converted to ester derivative **13**[10,11] with the treatment of a catalytic amount of TsOH (p-toluenesulfonic acid) in methanol. The most critical step of our synthesis was the substitution of bromine in compound **13** with NaOMe. Copper-assisted nucleophilic substitutions of aryl halogens are reported in the literature[14].

Considering the applicability of the reaction, we assume that the methoxylation of **13** proceeded with the substitution of methoxide with bromine. Indeed, the reaction of bromoester **13** with NaOMe in the presence of CuI in methanol and DMF afforded methyl 5,6-dimethoxynaphthalene-2-carboxylate (**14**), from which the corresponding carboxylic acid **1** was prepared by NaOH-assisted hydrolysis followed by acidification.



Scheme 2. Reagents and Conditions: (**i**) a) Br_2, AcOH, 88% b) Me_2SO_4/K_2CO_3, acetone, 95% (**ii**) AcCl /$AlCl_3$, 1,2-dichloroethane, 86% (**iii**) a) Br_2/NaOH, HCl, 88% b) MeOH/TsOH, 98% (**iv**) a) NaOMe/MeOH, DMF, CuI b) NaOH/MeOH-H_2O, then HCl, 82%.

As there has been no detailed study regarding the antibacterial properties of carboxylic acids **1** and **12**, in this study we investigated the antibacterial activities of these compounds. As can be seen in the Table**,** for carboxylic acid **1**, *Aeromonas hydrophila ATCC 7966, Micrococcus luteus LA 2971, Bacillus subtilis* var. *niger ATCC 10, Klebsiella pneumoniae FMC 5, Pseudomonas pyocyanea*, *Bacillus megaterium EU*, *Staphylococcus aerogenes, Streptococcus faecalis, Bacillus megaterium DSM32* and *Mycobacterium smegmatis RUT* showed inhibition zones >14-26 mm in size and were sensitive. *Bacillus megaterium NRS, Bacillus brevis FMC, Pseudomonas aeroginosa ATCC 2785, Enterococcus faecalis ATCC 15753 and Mycobacterium smegmatis CCM 2067* were weakly sensitive (11-14 mm). *Corynebacterium xerosis UC 9165* and *Klebsiella oxytocica* showed inhibition zones 0 mm in size and were resistant.

For carboxylic acid **12**, *Pseudomonas pyocyanea, Mycobacterium smegmatis RUT* and *Bacillus megaterium DSM32* showed inhibition zones 16-24 mm in size and were sensitive. *Aeromonas hydrophila ATCC 7966, Micrococcus luteus LA 2971, Bacillus subtilis* var. *niger ATCC 10, Pseudomonas aeroginosa ATCC 27853, Enterococcus faecalis ATCC 15753, Bacillus brevis FMC3, Klebsiella pneumoniae FMC 5, Bacillus megaterium NRS, Bacillus megaterium EU, Staphylococcus aerogenes, Streptococcus faecalis* and *Mycobacterium smegmatis CCM 2067* showed inhibition zones >10-14 mm in size and were weakly sensitive. *Corynebacterium xerosis UC 9165* and *Klebsiella oxytocica* showed inhibition zones 0 mm in size and were resistant. Tetracycline and netilmicin are well known as antibacterial substances and showed very large inhibition zones (all >17 mm radius) for the same pathogenic bacteria.

Table. Inhibition zones of the naphthalene carboxylic acid **1** and **12** against some bacteria by the disk diffusion method.

Pathogenic bacteria	**12** (mm)	**1** (mm)	**Control** DMSO
Corynebacterium xerosis UC 9165	-	-	-
Klebsiella pneumoniae FMC 5	12	16	-
Bacillus megaterium NRS	13	14	-
Bacillus brevis FMC3	10	11	-
Pseudomonas aeroginosa	12	13	-
Bacillus subtilis var. niger	13	17	-
Aeromonas hydrophila ATCC 7966	14	15	-
Enterococcus faecalis ATCC 15753	12	14	-
Pseudomonas pyocyanea	16	17	-
Bacillus megaterium EU	10	18	-
Mycobacterium smegmatis RUT	17	21	-
Bacillus megaterium DSM32	24	26	-
Klebsiella oxytocica	-	-	-
Staphylococcus aerogenes	12	16	-
Streptococcus faecalis	11	15	-
Mycobacterium smegmatis CCM 2067	14	14	-
Micrococcus luteus LA 2971	11	18	-

In summary, with relatively little synthetic effort, we have achieved a concise and alternative synthesis of 5,6-dimethoxynaphthalene-2-carboxylic acid (**1**) in 7 steps starting from 2-naphthol (**8**) (overall yield of 46%) and we have also shown the considerable antibacterial effects of 5,6-dimethoxynaphthalene-2-carboxylic acid (**1**) and 5-bromo-6-methoxynaphthalene-2-carboxylic acid (**12**) against 15 bacteria.

Acknowledgments

We thank the State Planning Organization (Grant no: 2004K/02) and Ataturk University for their financial support of this work.

References

1. T.R. Burke, B. Lim, V.E. Marquez, Z.H. Li, J.B. Bolen, I. Stefanova and I.D. Horak, **J. Med. Chem., 36**, 425-432 (1993).
2. T.R. Burke, M. Fesen, A. Mazumder, J. Yung, J. Wang, A.M. Carothers, D. Grunberger, J. Driscoll, Y. Pommier and K. Kohn, **J. Med. Chem., 38**, 4171-4178 (1995).
3. H. Zhao, N. Neamati, A. Mazumder, S. Sunder, Y. Pommier and T.R. Burke, **J. Med. Chem., 40**, 1186-1194 (1997).
4. R.W.A. Oliver, R.M. Rashman and A.W. Somerville, **Tetrahedron, 24**, 4067-4072 (1968).
5. S. Archer, P. Osei-Gyimah and S. Silbering, **J. Med. Chem., 23**, 516-519 (1980).
6. S. Goksu, C. Kazaz, Y. Sutbeyaz and H. Secen, **Helv. Chim. Acta, 86**, 3310-3313 (2003).
7. S.E. Hazlet, **J. Am. Chem. Soc., 62**, 2156-2157 (1940).

8. A.S. Castanet, F. Colobert, P.E. Broutin and M. Obringer, **Tetrahedron: Asymmetry, 13**, 659-665 (2002).
9. P. Cagniant, P. Faller and M.P. Cagniant, **Bull. Soc. Chim. Fr.,** 1938-1941 (1961).
10. R.D. Haworth and G. Sheldrick, **J. Chem. Soc.,** 864-867 (1934); **Chem Abstr.** 28, 44950 (1934).
11. S.M. Huh and J.I. Jin, **Macromol., 30**, 3005-3013 (1997).
12. B.M. Jacob, E. Antony, B. Sreekumar and M. Haridas, **Life Sciences, 66**, 2433-2439 (2000).
13. S. Vyskocil, L. Meca, I. Tislerova, I. Cisarova, M. Polasek, S.R. Harutyunyan, Y.N. Belokon, R.M.J. Stead, L. Farrugia, S.C. Lockhart, W.L. Mitchell and P. Kocovsky, **Chem. Eur. J., 8**, 4633-4648 (2002).
14. J. Lindley, **Tetrahedron, 40**, 1433-1456 (1984).