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Benzothienyloxy phenylpropanamines, novel dual inhibitors of serotonin and norepinephrine reuptake

J. R. Boot,[a] G. Brace,[a] C. L. Delatour,[b] N. Dezutter,[b] J. Fairhurst,[a] J. Findlay,[a] P. T. Gallagher,[a,*] I. Hoes,[b] S. Mahadevan,[b] S. N. Mitchell,[a] R. E. Rathmell,[a] S. J. Richards,[a] R. G. Simmonds,[a] L. Wallace[a] and M. A. Whatton[a]

[a]*Eli Lilly and Company, Ltd, Lilly Research Centre, Windlesham, Surrey, GU20 UK 6PH*
[b]*Lilly Development Centre, Parc Scientifique de Louvain-la-Neuve, Rue Granbonpré 11, 1348 Mont-Saint-Guibert, Belgium*

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Abstract—A series of benzothienyloxy propylamines have been prepared and are demonstrated to be inhibitors of both serotonin and norepinephrine reuptake.

Major depressive disorder is currently the fourth leading cause of disease or disability world wide and is projected to rise to second by 2020.[1] Furthermore it has been suggested that dual serotonin (5-HT) and norepinephrine (NE) reuptake inhibitors offer the potential for superior anti-depressant activity.[2] That enhancing both serotonergic and noradrenergic neurotransmission results in anti-depressant efficacy is now supported by clinical experience with duloxetine (Cymbalta™) (**1**), a dual 5-HT and NE uptake inhibitor.[3,4]

Prior to the development of duloxetine, exploration of the aryloxypropanamine SAR had resulted in the identification of fluoxetine (Prozac™) (**2**) and atomoxetine (Straterra™) (**3**) (Fig. 1).

Herein we report on the activity of a series of heterocyclic phenylpropylamines that extend the exploration of the duloxetine SAR. As part of continuing investigation into the diverse pharmacology mediated by the monoaminergic transporters, we wished to identify additional agents that could be used to address emerging clinical targets with dual NE and 5-HT reuptake inhibitors.

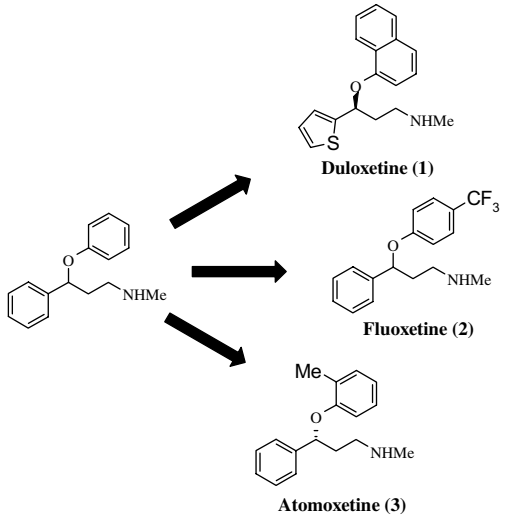

Figure 1.

In parallel with the search for new dual reuptake inhibitors it was decided to address the stability in acid medium of the new analogues. Early clinical development showed that it was advisable to formulate duloxetine in enteric coated tablets, due to its stability characteristics in acid solutions.[5]

Thus three molecules (**4**–**6**) (Fig. 2) were targeted in order to gauge, which fragments were responsible for

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* Corresponding author. Tel.: +44 (0)1276 483536; fax: +44 (0)1276 483525; e-mail: gallagher_p@lilly.com

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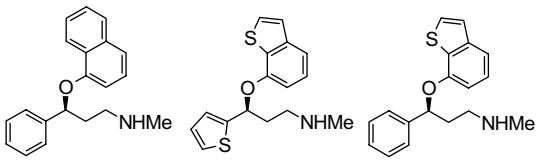
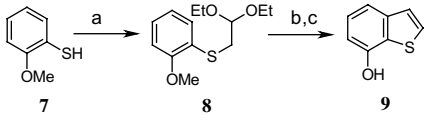
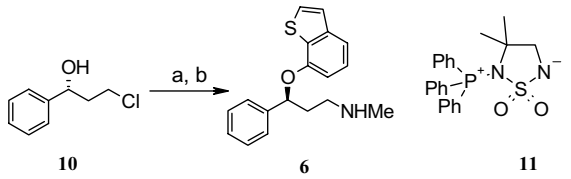


Figure 2.



Scheme 1. Reagents and conditions: (a) $BrCH_2CH(OEt)_2$, K_2CO_3, DMF, 98%, (b) PPA, 145 °C, 45%, (c) BBr_3, DCM, 38%.



Scheme 2. Reagents: (a) **9**, **11**, THF, 37%, (b) $MeNH_2$, H_2O, EtOH, 66%.

Table 1. Acid stability of compounds **4**–**6** in acid medium

Compd	Acid stability (% parent remaining @ 2 h and 37 °C)
1 (duloxetine)	18
4	99
5	40
6	99

the observed acid instability. The synthesis of **4** required the commercially available 1-naphthol, while that of **5** and **6** required 7-hydroxybenzothiophene (**9**).[6] Thus thiophenol **7** was alkylated with bromoacetaldehyde diethyl acetal to give **8**, which was cyclised with PPA and demethylated with boron tribromide in DCM to give **9** (Scheme 1).

Table 2. Binding affinities at the serotonin, norepinephrine and dopamine transporters for duloxetine (**1**) and compounds **4**–**6**

Compd	5-HT[a]	NE[a]	DA
1 (duloxetine)	0.8 ± 0.04	7.5 ± 0.3	240 ± 23
4	1.0 ± 0.1	6.1 ± 0.25	190 ± 3
5	1.5 ± 0.1	1.4 ± 0.3	120 ± 10
6	8.2 ± 1.3	2.2 ± 0.1	220 ± 5

[a] K_i, nM. Binding affinities and displacement measurements were done in triplicate.[4]

The synthesis of **6** was achieved by taking the commercially available (1*R*)-3-chloro-1-phenyl-1-propanol (**10**) and converting with 4,4-(dimethyl-1,1-dioxido-1,2,5-thiadiazolidin-2-yl)-triphenyl phosphonium (**11**) and phenol **9** (under Mitsunobu conditions) to give the intermediate chloro-ether, which was subsequently converted to **6** with aqueous methylamine (Scheme 2).[7,8]

Compound **5** was synthesised in an analogous manner to **6** but using (1*R*)-3-chloro-1-(2-thienyl)-1-propanol while **4** was synthesised analogously to **6** but with the replacement of 1-naphthol for **9**.[9]

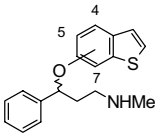
The acid stability of compounds **4**–**6** was compared with duloxetine (**1**) in 0.1 M HCl solution at 37 °C for 2 h and the percentage of parent remaining was determined (Table 1).

The acid stability was reduced when the electron rich thiophene susbtituent was present, so the SAR focused on maintaining the phenyl ring of **4** and **6** and in finding alternatives to 1-naphthalene and 7-benzothiophene.

Products of acid mediated decomposition were not identified. Compounds **4**–**6** were also assessed for their ability to inhibit the binding to transporter receptors (Table 2).

The activity of compounds **4**–**6** was comparable to **1** but as **4** and **6** demonstrated greater acid stability and **6**

Table 3. Binding affinities at the serotonin, norepinephrine and dopamine transporters for **6**, **12**–**18**

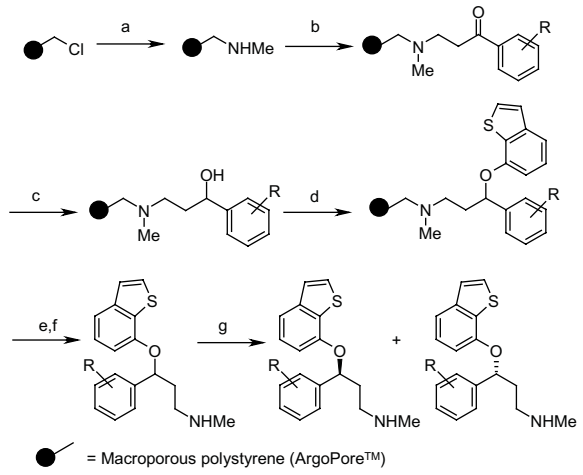


Compd	Subs.	Stereo.	5-HT[a]	NE[a]	DA
6	7	*S*	8.2 ± 1.3	2.2 ± 0.1	220 ± 5[a]
12	7	*R*	1.9 ± 0.15	1.8 ± 0.3	270 ± 20[a]
13	4	*R*	5.4 ± 1.5	10 ± 1	930 ± 15[a]
14	4	*S*	0.5 ± 0.1	4.4 ± 0.25	440 ± 10[a]
15	5	*R*	1.2 ± 0.05	47 ± 3	260 ± 16[a]
16	5	*S*	1.7 ± 0.1	300 ± 16	480 ± 10[a]
17	6	*R*	1.9 ± 0.1	24 ± 0.3	−68 ± 0.5%[b]
18	6	*S*	0.5 ± 0.3	62 ± 2	260 ± 8[a]

[a] K_i, nM.
[b] % Inhibition @ 1 μM. Binding affinities and displacement measurements were done in triplicate.

more diverse SAR possibilities **6** formed the basis of further SAR.

After demonstrating dual 5-HT and NE uptake activity with **6** it was decided to explore if the dual uptake activity could be extended to either the 4-, 5- or 6-substitution of benzothiophene. The three phenols needed to initiate this exercise were reported in the literature.[10–12] The Mitsunobu route using (1*R*)-3-chloro-1-phenyl-1-propanol was used to provide the three (*S*)-enantiomers while, (1*R*)-3-chloro-1-phenyl-1-propanol was used to provide the four (*R*)-enantiomers (Table 3). Thus the yield of the intermediate chloro-ethers from the Mitsunobu reaction ranged from 37% to 89%, the chloro-ethers were then converted to compounds **12**–**18** (Table 3) in yields ranging from 52% to 98%. From Table 3 it can be seen that the 5- and 6-substitution patterns have markedly reduced NE uptake activity but still retain 5-HT uptake activity.



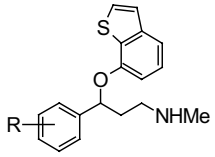
Scheme 3. Reagents and conditions: (a) $MeNH_2$, THF, (b) $ArCOCH_3$, HCHO, HCl, THF, H_2O, (c) $NaBH_4$, EtOH, tri(ethyleneglycol) dimethyl ether, (d) **9**, PPh_3, t-$BuO_2CN{=}NCO_2t$-Bu, (e) $ClCO_2CHClCH_3$, Hunig's base, THF, (f) MeOH, reflux, (g) Chiral chromatography on 5 M Chiracel-OD, 20% heptane/20% ethanol/0.2% dimethylethylamine, 0.5 mL/min.

Having prioritised the 4- and 7-linked benzothiophenes for further investigation we next sought to understand the contribution to activity that phenyl ring substitution could make. To do this a rapid parallel Mannich reaction was developed (Scheme 3) to provide racemic aminoethers that were subsequently separated by chiral chromatography.

From the substituents (Table 4) examined the influence on 5-HT and NE uptake inhibition is negligible. The notable exception being compound **29** the 3-trifluoromethyl substituent phenyl analogue (isomer 1), which had reduced affinity for both 5-HT and NE transporter.

As substitution in the phenyl ring offered no significant enhancement in activity it was decided to progress the (*R*)-enantiomer of the 7-benzothienyl propanamine bearing no substituent on the phenyl ring (**12**). On further development the metabolic profile of **12** was examined. Thus human liver microsomes were incubated with **12** and the resultant oxidative products identified (Fig. 3). Of the metabolites identified the dihydrodiol (**31**), and the phenolic metabolites **32** and **33** were the most prevalent. Of particular concern is the presence of the dihydrodiol metabolites that occur through the hydration of intermediate epoxides. As epoxides are known to form adducts that could lead to toxicity in vivo, the development of **12** was halted.[13] Metabolic profiling of the 4-linked benzothiophene indicated no dihydrodiol

Table 4. Binding affinities at the serotonin, norepinephrine and dopamine transporters for compounds **19**–**30**



Compd	R	Isomer	5-HT[a]	NE[a]	DA
19	3-Me	1	2.2 ± 0.4	2.2 ± 0.5	114 ± 4[a]
20	3-Me	2	2.4 ± 0.1	0.6 ± 0.1	147 ± 2[a]
21	2-F	1	0.4 ± 0.05	1 ± 0.1	−61.4 ± 1%[b]
22	2-F	2	1.5 ± 0.1	1.1 ± 0.1	−55.0 ± 1%[b]
23	3-F	1	1.4 ± 0.1	0.7 ± 0.1	100 ± 3[a]
24	3-F	2	1.1 ± 0.1	0.4 ± 0.05	134 ± 2[a]
25	4-F	1	1.1 ± 0.05	2 ± 0.1	164 ± 7[a]
26	4-F	2	0.5 ± 0.1	0.6 ± 0.1	176 ± 9[a]
27	3-MeO	1	2.2 ± 0.3	4.6 ± 0.2	196 ± 4[a]
28	3-MeO	2	2.4 ± 0.3	0.9 ± 0.1	177 ± 11[a]
29	3-CF_3	1	13 ± 1	23 ± 2	−54.2 ± 0.1%[b]
30	3-CF_3	2	3.2 ± 0.1	0.5 ± 0.05	208 ± 3[a]

[a] K_i, nM.
[b] % Inhibition @ 1 μM. Binding affinities and displacement measurements were done in triplicate.

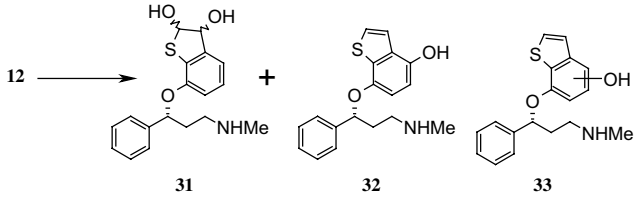


Figure 3.

formation and this series was then exemplified further by selected substitution on the benzothiophene ring. For the synthesis of the 4-linked analogues substituted 4-hydroxybenzothiophenes were needed and the syntheses are exemplified in Scheme 4.

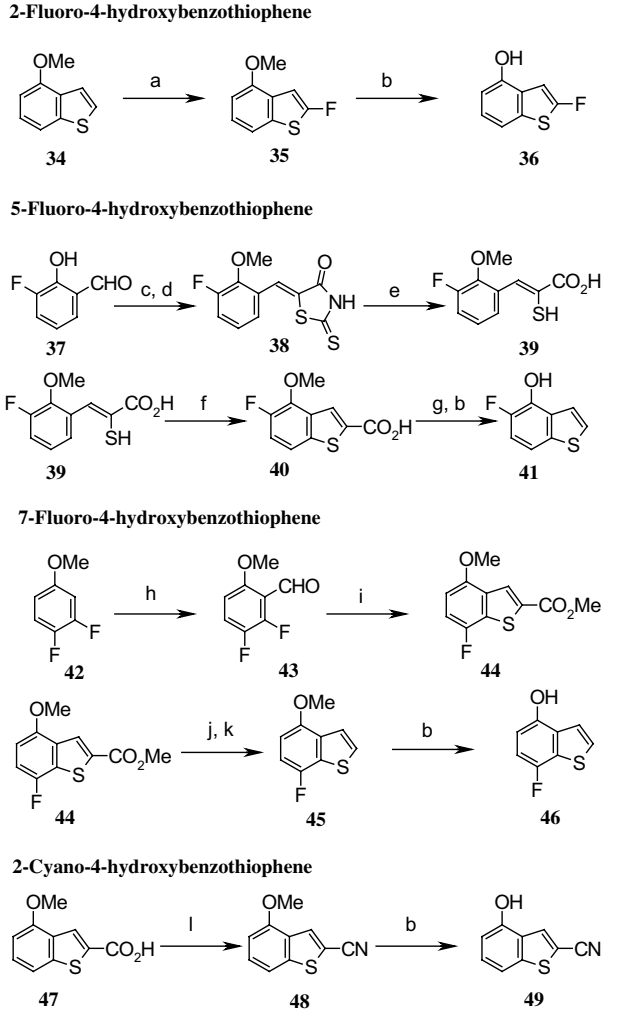
Thus taking 4-methoxy benzothiophene[14] (**34**) and fluorinating with perchloryl fluoride gave ether **35** and subsequent demethylation with boron tribromide gave 2-fluoro-4-hydroxybenzothiophene (**36**) in 26% yield for the two steps. For 5-fluoro-4-hydroxybenzothiophene (**41**) a ring closure of a mercaptocinammic acid was used to give the benzothiophene.[15] Thus commercially available 3-fluorosalicylaldehyde (**37**) was methylated with dimethylsulfate and condensed with rhodanine to give the thiazolidinone (**38**) in 78% for the two steps. The thiazolidinone (**38**) was hydrolysed under basic conditions to give 2-mercapto-3-phenylpropenoic acid (**39**) that in turn was cyclised with iodine in the microwave at 120 °C to give 5-fluoro-4-hydroxybenzothiophenecarboxylic acid (**40**) in 63% yield from the thiazolidinone. Decarboxylation of **40** was achieved with DBU and microwave heating. Subsequent demethylation of **40** to give **41** was effected with boron tribromide in a low yield of 5% for the two steps.

The synthesis of the 7-fluoro-4-hydroxybenzothiophene (**46**) necessitated the synthesis of a tetra-substituted benzaldehyde intermediate (**43**). This was achieved by the formylation of commercially available 2,4-difluoroanisole (**42**) in 95% yield with LDA and dimethylformamide. Compound **43** was then converted to the benzothiophene ester **44** by nucleophilic displacement of the activated fluorine with thioglycollic acid and triethylamine and subsequent cyclisation in 87% yield.[16] The benzothiophene ester (**44**) was then hydrolysed with aqueous sodium hydroxide (97%) and decarboxylated with copper and quinoline to give (**45**) in 84%. Finally demethylation was effected with boron tribromide to give **46** in 79% yield.

2-Cyano-4-hydroxybenzothiophene (**49**) was synthesised from 4-methoxybenzothiophene-2-carboxylic acid[17] (**47**) via the primary carboxamide with methanesulfonyl chloride and ammonia to give the carbonitrile (**48**) in 74% yield. Demethylation of **48** to give cyanobenzothiophene **49** was effected with boron tribromide in 95% yield.

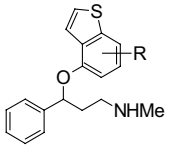
Following the method used for the synthesis of **6** (utilising phenols **36**, **41**, **46** and **49)** the analogues in Table 5 were produced. Thus the yield of the intermediate chloro-ethers from the Mitsunobu reaction ranged from 47% to 95%, the chloro-ethers were then converted to compounds **50**–**55** (Table 5) in yields ranging from 40% to 89%. As amination of the interemediate chloro-nitriles proved low yielding, due to side product formation, a Finkelstein (NaI, acetone, 56 °C) reaction was used to convert the chloro-ethers to iodo-ethers (2-*R* iodide 90%, 2-*S* iodide 80%) prior to amination to provide **56** and **57**.

The impact of fluorination on 5-HT transporter affinity is minimal (Table 5), but inhibition of NE uptake is more variable, in particular 2-fluorination is detrimental to NE uptake. Introducing the polar (and larger than hydrogen or fluorine) electron withdrawing nitrile functionality markedly reduces NE transporter inhibition. In conclusion and considering the increased synthetic complexity of **40**, used in the synthesis of the potent dual inhibitors **52** and **53**, it was decided to advance **14** into in vivo studies. Thus in in vivo microdialysis



Scheme 4. Reagents and conditions: (a) lithium tetramethylpiperidide, THF, perchloryl fluoride, 48%, (b) BBr_3, CH_2Cl_2, 21–95%, (c) K_2CO_3, acetone Me_2SO_4, 100%, (d) rhodanine, H_4NOAc, toluene, 78%, (e) NaOH, H_2O, 94%, (f) I_2, DME, 120 °C, microwave, 67%, (g) DBU, DMA, 200 °C, microwave, 23%, (h) LDA, THF, DMF, 95%, (i) $HSCH_2CO_2Me$, Et_3N, DMF, 87%, (j) NaOH, MeOH, H_2O, 97%, (k) Cu, quinoline, 190 °C, 84%, (l) $MeSO_2Cl$, NH_3, 74%.

Table 5. Binding affinities at the serotonin, norepinephrine and dopamine transporters for compounds **13**, **14**, **50**–**57**



Compd	R	Stereo.	5-HT[a]	NE	DA
13	H	*R*	5.4 ± 1.5	10 ± 1[a]	930 ± 15[a]
14	H	*S*	0.5 ± 0.1	4.4 ± 0.25[a]	440 ± 10[a]
50	2-F	*R*	1.95 ± 0.5	32 ± 4[a]	−57 ± 2%[b]
51	2-F	*S*	4.1 ± 1.1	18 ± 1.3[a]	−47 ± 2%[b]
52	5-F	*R*	0.4 ± 0.1	1.4 ± 0.1[a]	−57 ± 1%[b]
53	5-F	*S*	0.4 ± 0.1	0.6 ± 0.05[a]	−57 ± 1 %[b]
54	7-F	*R*	0.7 ± 0.05	11 ± 2[a]	540 ± 20%[a]
55	7-F	*S*	0.9 ± 0.1	12 ± 1[a]	1400 ± 100%[a]
56	2-CN	*R*	13 ± 2	−41 ± 1 %[b]	−58 ± 1%[b]
57	2-CN	*S*	0.25 ± 0.05	−47 ± 1.5%[b]	−22 ± 1%[b]

[a] K_i, nM.
[b] % Inhibition @ 1 μM. Binding affinities and displacement measurements were done in triplicate.

experiments with **14**, increases above basal levels of synaptic 5-HT and NE levels of 222 ± 14% and 215 ± 9% at 3 mg/kg p.o. have been demonstrated. Further in vivo studies will be published elsewhere.

References and notes

1. *The Global Burden of Disease: A comprehensive Assessment of Mortality an Disability from Diseases, Injuries and Risk Factors in 1990 and Projected to 2020*; Murray, C. J. L., Lopez, A. D., Eds.; Harvard University: Cambridge Mass, 1996.
2. Wong, D. T.; Bymaster, F. P. *Prog. Drug Res.* **2002**, *58*, 169.
3. Detke, M. J.; Lu, Y.; Goldstein, D. J.; Hayes, J. R.; Demitrack, M. A. *J. Clin. Psychiat.* **2002**, *63*, 308.
4. Bymaster, F. P.; Beedle, E. E.; Findlay, J.; Gallagher, P. T.; Krushinski, J. H.; Mitchell, S.; Robertson, D. W.; Thompson, D. C.; Wallace, L.; Wong, D. T. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4477.
5. Anderson, N. R.; Oren, P. L.; Ogura, T.; Fujii, T. *Eur. Pat. Appl.* **1996**, *16*, pp EP693282A2. CAN 124:185598.
6. Samanta, S. S.; Ghosh, S. C.; De, A. *JCS Perkin Trans. 1* **1997**, *18*, 2683.
7. Castro, J. L.; Matassa, V. G.; Ball, R. G. *J. Org. Chem.* **1994**, *59*, 2289.
8. Dodge, J. A.; Glasebrook, A. L.; Lugar, C. W. *Eur. Pat. Appl.* **1999**, *35*, pp EP895989A1. CAN 130:168116.
9. Wheeler, W. J.; Kuo, F. *J. Labelled Compd. Radiopharm.* **1995**, *36*, 213.
10. Napier, R. P.; Kaufman, H. A.; Driscoll, P. R.; Glick, L. A.; Chu, C. C.; Foster, H. M. *J. Heterocycl. Chem.* **1970**, *7*, 393.
11. Perez-Silanes, S.; Martinez-Esparza, J.; Oficialdegui, A. M.; Villanueva, H.; Orus, L.; Monge, A. *J. Heterocycl. Chem.* **2001**, *38*, 1025.
12. Hansch, C.; Schmidhalter, B. *J. Org. Chem.* **1955**, *20*, 1056.
13. Pakenham, G.; Lango, J.; Buonarati, M.; Morin, D.; Buckpitt, A. *Drug Metab. Disposition* **2002**, *30*, 247.
14. Campaigne, E.; Dinner, A.; Haseman, M. *J. Heterocycl. Chem.* **1971**, *8*, 755.
15. Campaigne, E.; Abe, A. *J. Heterocycl. Chem.* **1975**, *12*, 889.
16. Bridges, A. J.; Lee, A.; Maduakor, E. C.; Schwartz, A. *Tetrahedron Lett.* **1992**, *33*, 7499.
17. Cheutin, A.; Desvoye, M. L.; Royer, R.; Demerseman, P.; Lechartier, J. P. *C.R. Hebd. Seances Acad. Sci.* **1965**, *261*, 705.