Journal of Labelled Compounds and Radiopharmaceuticals
J Label Compd Radiopharm 2007; **50**: 706–710.
Published online in Wiley InterScience
(www.interscience.wiley.com). DOI: 10.1002/jlcr.1403

JLCR

Research Article

Synthesis of carbon-14-labeled isotopomer of 6-(4-methanesulfonylphenyl)-5-[4-(2-piperidin-1-yl-ethoxy) phenoxy]-naphthalen-2-ol HCL salt (LY2066948-[^{14}C] HCL salt)

FENGJIUN KUO*, DEAN K. CLODFELTER and TAMARA R. PRIEST

Lilly Research Laboratories, Division of Eli Lilly and Company Lilly Corporate Center, Indianapolis, IN 46285, USA

Received 12 January 2007; Accepted 12 May 2007

Abstract: Carbon-14-labeled 6-(4-methanesulfonylphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)phenoxy]naphthalen-2-ol, a novel selective estrogen receptor modulator (SERM) was synthesized. The key component, 6-methoxy-1-tetralone-[carbonyl-^{14}C], was synthesized from 3-(3-methoxyphenyl)-propionic acid via an intra-molecular Friedel–Crafts acylation of 4-(3-methoxyphenyl)butanoic acid-[carboxy-^{14}C]. A palladium catalyzed alpha-keto arylation of 6-methoxy-1-tetralone with 4-methanesulfonyl-phenyl bromide, followed by a sequence of bromination, DDQ dehydrogenation, aryl Ullmann reaction, and demethylation with BBr_3 gave the desired product LY2066948-[^{14}C]. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: 6-methoxy-1-tetralone-[1-^{14}C]; LY2066948-[^{14}C]; SERM GYN

Introduction

The HCl salt of compound 6-(4-methanesulfonylphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)phenoxy]naphthalen-2-ol (**1**, LY2066948 HCl) is a novel selective estrogen receptor modulator (SERM) for the potential treatment of uterine leiomyoma. It binds with high affinity to estrogen receptors α and β (ERα and ERβ, respectively) and is a potent uterine antagonist with minimal effects on the ovaries as determined by serum biomarkers and histologic evaluation.[1] To support the studies on metabolism and disposition of the compound in a number of animal species it was necessary to have its carbon-14-labeled isotopomer synthesized. The chemistry for the preparation of this compound will be presented here.

Discussion

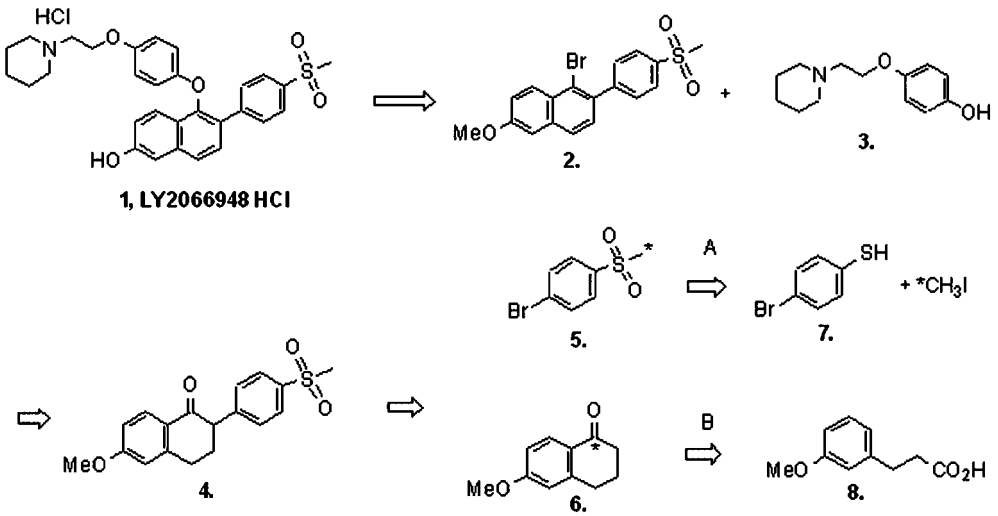
Retrosynthetic analysis of the target compound **1**[2] gave two possible approaches to introduce the carbon-14 labeling (Scheme 1).

Scheme 1

A route to label the carbon-14 on the 4-[2-piperidinylethoxy]phenol **3** was ruled out considering the cost and the possible metabolic instability of the molecule at that location. In order to put the labeling on intermediate **4**, two possible approaches, path A and B, were considered. Methylation of a commercially available 4-bromobenzenethiol **7** with a volatile carbon-14-labeled methyliodide, followed by an oxidation of the thiol ether will give the corresponding methylsulfone, **5**. Alternatively, the carbon chain on a commercially available 3-[3-methoxylphenyl]propionic acid, **8**, can be extended by one carbon unit using a carbon-14-labeled potassium cyanide. Hydrolysis of the nitrile to the corresponding carboxylic acid, followed by an intramolecular Friedel–Crafts acylation should give the desired compound 6-methoxy-1-tetralone, **6**. Although route B will take three radiosynthetic steps to give the desired intermediate, considering the cost and the availability of the reagents, it was decided to take route B to pursuit the synthesis.

A tosylate **9** was prepared in two steps from carboxylic acid **8** by a borane reduction followed by a tosylation of the resulting alcohol. Treatment of the tosylate **9** with a carbon-14-labeled potassium cyanide,

*Correspondence to: Fengjiun Kuo, Eli Lilly and Company, Lilly Corporate Center, DC0734, Indianapolis, IN 46285, USA.
E-mail: kuo_fengjiun@lilly.com



Scheme 1

followed by a hydrolysis in 1 N NaOH gave a carbon-14-labeled carboxylic acid **11**. Conversion of the acid **11** to the corresponding acyl chloride followed by an intramolecular Friedel–Crafts acylation with $AlCl_3$ in benzene gave the key intermediate 6-methoxy-1-tetralone-[carbonyl-^{14}C], **6** (Scheme 2).

The coupling of keto-enolates with aryl halides is a very important and useful transformation in organic synthesis, but has been difficult to achieve until recently when Hartwig and Buchwald[3,4] discovered the highly active and selective palladium catalysts for the formation of α-aryl ketones. Thus, the treatment of 6-methoxy-1-tetralone **6** with 4-methanesulfonylphenyl bromide **5** under the conditions described by Buchward gave a coupling product **4**.[2] This aryl ketone **4** was then converted to a vinyl bromide **12** with phosphorus tribromide[5] in toluene, followed by dehydrogenation with DDQ[6] to give the 2-aryl-1-bromonaphthalene **2**.

Scheme 2

An Ullmann diaryl ether formation[7] was carried out by heating a degassed solution of aryl bromide **2** and 4-(2-piperidinylethoxy)phenol **14** in diglyme in the presence of cuprous chloride and cesium carbonate[2] to afford a free base of compound **13**. The free base was then converted to its hydrochloric acid salt **13** before it was demethylated with boron trichloride[8] to give the desired final product **1**, **LY2066948** HCl salt.

Conclusions

A general and simple method has been developed for the synthesis of a carbon-14-labeled LY2066948, a novel selective estrogen receptor modulator (SERM). The key component, 6-methoxy-1-tetralone-[1-^{14}C] **6-[^{14}C]** was synthesized by intramolecular Friedel–Crafts acylation on 4-[3-methoxyphenyl]butanoic acyl chloride-[carboxy-^{14}C], which was synthesized in five steps (three radioactive steps) from 3-[3-methoxylphenyl]propionic acid using potassium cyanide-[^{14}C] to introduce the labeling.

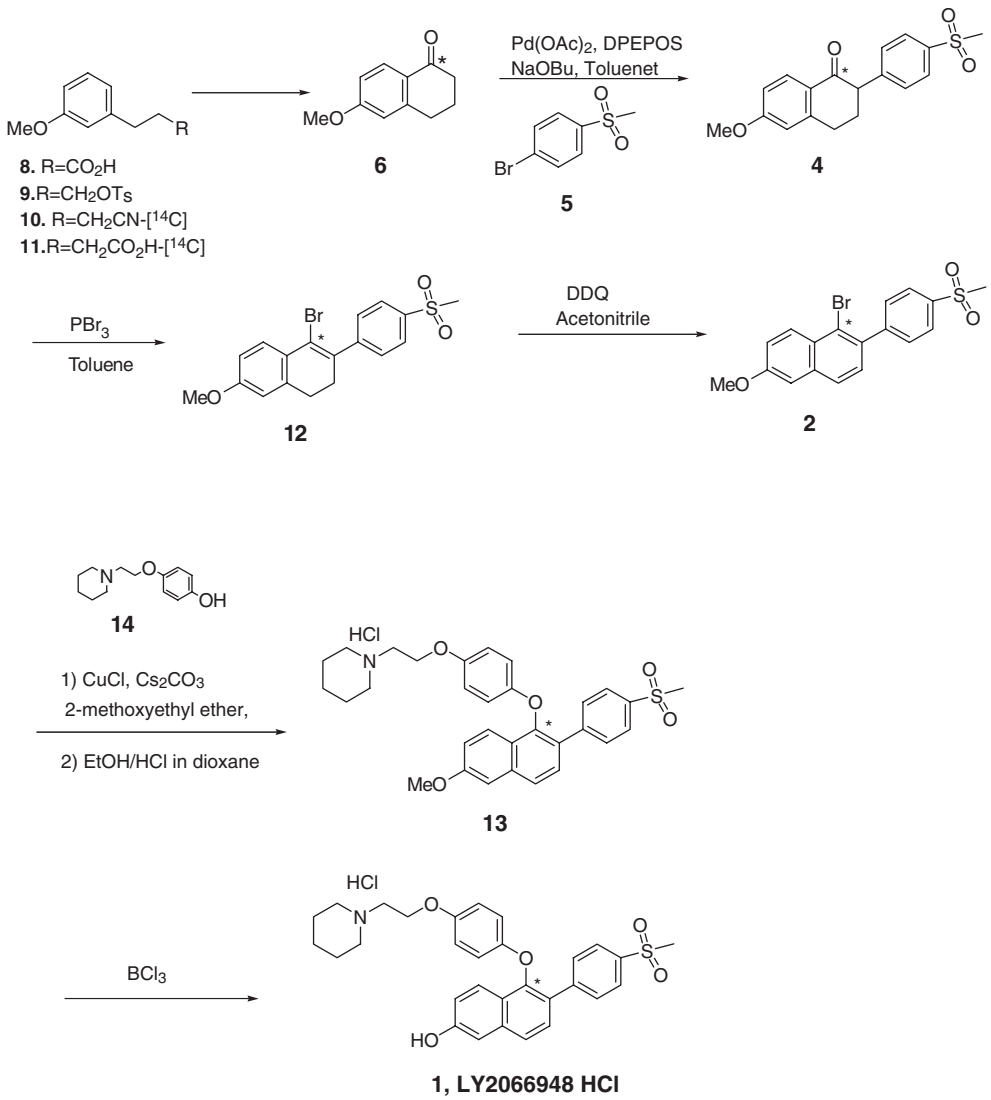
Experimental

The H-NMR spectra were obtained on a Varian Mercury-400 spectrometer at 400 (^{1}H). Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. Electrospray mass spectra were obtained on a Waters Micromass ZQ single quadropole mass spectrometer. Flash chromatography was performed on Biotage™ system. Unless otherwise noted, the organic extracts were dried over anhydrous magnesium sulfate. Thin-layer chromatography was performed on E. Merck silica gel F-254 plates. All carbon-14-labeled compounds were identified by TLC and or radio-HPLC comparison with the corresponding non-labeled isotopomers. Radiochemical purity (RCP) was assessed by radio-HPLC.

Synthesis of 6-methoxy-1-tetralone-[carbonyl-^{14}C], 6

To the solution of a compound tosylate **9** (1.25 g, 4 mmol, prepared from the corresponding alcohol, which was prepared from the corresponding acid **9** by borane reduction) in 5 mL of anhydrous DMF was added potassium cyanide (143 mg, 2.2 mmol) and carbon-14-labeled potassium cyanide (1.71 mmol, 94.6 mCi at 55.1 mCi/mmol) with stirring. The resulting mixture was

DOI: 10.1002.jlcr



Scheme 2

heated gradually to about 80°C, and was stirred at that temperature for about 22 h under argon atmosphere. After cooling to room temperature, the solution was diluted with 100 mL of water, and the resulting aqueous solution was extracted three times with EtOAc/hexanes (3:1). The combined extracts were washed twice with water and concentrated with ethanol to give a light brown residue. After briefly drying *in vacuo*, this light brown residue was taken into 10 mL of ethanol and 10 mL of 1 N NaOH solution. To the solution was added 0.5 mL of 30% H_2O_2, and the resulting solution was stirred at 40–50°C for about 2.5 h. The color faded and the solution turned colorless. This clear colorless solution was then heated to reflux overnight (about 17 h). TLC (SiO_2, 1:1 hexanes/CH_2Cl_2) indicated no starting material remained. After cooling to room temperature, the ethanol was removed under reduced pressure. The remaining aqueous solution was diluted with 10 mL of 1 N NaOH, and extracted twice with ethyl ether to remove any remaining neutral components. The solution was then adjusted to about pH 1.0 by adding 6 mL of 5 N HCl, and extracted once with ethyl acetate. The extract was washed twice with water, concentrated with ethanol, and then with toluene/EtOAc, to give the desired acid **11** as a light brown viscous oil (636 mg, 3.24 mmol, 80.9% from tosylate **9**).

This acid **11** was dissolved in 15 mL of anhydrous benzene to give a clear pale yellow solution, to which was added 1.5 mL of oxalyl chloride quickly using a syringe. The reaction flask was equipped with a drying tube filled with Drierite®, and the solution was stirred at room temperature overnight. The solution was concentrated under reduced pressure; the residue was taken into 10 mL of anhydrous benzene, and the solution was concentrated again to remove residual

DOI: 10.1002.jlcr

oxalyl chloride. The residue was taken into 16 mL of anhydrous benzene, and cooled in an ice bath. To the solution was added 750 mg of anhydrous $AlCl_3$ powder in one portion with stirring. The solution turned reddish brown immediately and started to freeze after stirring in the ice bath for about 45 min. The cooling bath was removed, and the solution was stirred at room temperature for about 5 h. TLC (SiO_2, 1:1 CH_2Cl_2/EtOAc) indicated that most of the starting material was consumed. The solution was cooled in an ice bath, and the reaction was quenched by adding 10 mL of ethyl ether and 15 mL of 1 N HCl. The color of the solution faded to light greenish yellow. The solution was further diluted with 25 mL of EtOAc to give clear two layers. The organic layer was separated, washed twice with water, and concentrated with ethanol to give a light yellowish solid. The crude material was purified by the Biotage® system eluting with CH_2Cl_2 to give the desired product 6-methoxy-1-tetralone-[^{14}C], **6** as a white solid (493 mg, 2.77 mmol). H-NMR ($CDCl_3$, ppm) of non-labeled analog: 8.0 (d, 1H), 6.81 (d, 1), 6.70 (s, 1H), 3.82 (s, 3H), 2.90 (t, 2H), 2.60 (t, 2H), 2.10 (m, 2H).

Synthesis of 1-bromo-2-(4-methanesulfonyl-phenyl)-6-methoxy-naphthalene-[^{14}C], 2

To a solution of 6 mL of anhydrous toluene containing 6-methoxy-1-tetralone-[^{14}C], **6**, (493 mg, 2.77 mmol) was added in sequence 690 mg of **14**, 35 mg of $Pd(OAc)_2$, and 80 mg of bis[(2-diphenylphosphino)phenyl] ether (DPEPOS) followed by adding 700 mg of *t*-BuONa as a powder in one portion to give a yellow slurry. The flask was rinsed with 1 mL of anhydrous toluene, and the slurry was stirred in an oil bath (80–90°C) for about 90 min. TLC (SiO_2, 1:1 CH_2Cl_2/EtOAc) indicated the disappearance of 1-tetralone **6**. The solution was cooled to room temperature. To this solution was added 1 mL of PBr_3, and the solution was heated at reflux overnight (about 17 h at 135°C) with the condenser equipped with a drying tube filled with Drierite®. After cooling to room temperature, 15 mL of CH_2Cl_2 was added to this dark brown heterogeneous mixture with vigorous stirring. The mixture was filtered, and the solid in the funnel was rinsed with CH_2Cl_2. The combined filtrates were concentrated to remove CH_2Cl_2, and the remaining toluene (heterogeneous) solution was diluted with some ethyl acetate. Some white solid remained, to which about 25 mL of water was added, and the solution was stirred for 2 h. Some of the product, **12**, remained as a white solid in the solution, and was filtered off. The organic layer of the filtrate was separated, washed twice with water, and concentrated with ethanol. The white solid left in the funnel was dissolved in CH_2Cl_2 and combined with the crude product from filtrate. The combined solution was concentrated to give crude **12** as a light yellowish solid. (956 mg, 2.43 mmol). H-NMR ($CDCl_3$, ppm) of non-labeled analog: 7.98 (d, 2H), 7.66 (d, 2H), 7.58 (d, 1H), 6.80 (d, 1H), 6.72 (br 1H), 3.83 (s, 3H), 3.09 (s, 3H), 2.94 (t, 2H), 2.70 (t, 2H).

The crude solid was suspended in 10 mL of anhydrous acetonitrile, and the solution was heated to reflux to give a clear light brown solution. After slightly cooling, DDQ (717 mg, 1.3 eq.) was added as a powder in one portion to the solution. The solution turned dark immediately, and was heated at reflux for about 6 h (110°C bath). After cooling to room temperature, a solution of 10 mL of 1 N NaOH was added, and the resulting mixture, containing some yellowish solid, was stirred for 2.5 h. The solid was filtered off, washed with 50% acetonitrile in water in the funnel until no color was observed in the filtrate. The white solid left in the funnel was dried *in vacuo* for about 3 h. The solid was then dissolved in CH_2Cl_2, and the solution was concentrated with EtOAc to give a beige solid. Further drying in a vacuum oven at 40°C overnight gave a crude desired product **2** (682 mg, 1.73 mmol). Only one spot was observed on TLC (SiO_2, CH_2Cl_2), and the material was used in the next step without further purification. H-NMR (CD_3OD, ppm) of non-labeled analog: 8.24 (d, 1H), 8.04 (d, 2H), 7.85 (d, 1H), 7.70 (d, 2H), 7.35 (d, 1H), 7.30 (m, 2H), 3.95 (s, 3H), 3.18 (s, 3H).

Synthesis of 1-(2-{4-[2-(4-methanesulfonyl-phenyl)-6-methoxyl-naphthalen-1-yloxy]-phenoxy}-ethyl)piperidine-[^{14}C] Hydrochloride salt, 13

A heterogeneous solution of 10 mL of diglyme (2-methoxyethyl ether) containing the crude bromide **2** (682 mg, 1.73 mmol), **14** (765 mg, 2 eq.), CuCl (65 mg) and Cs_2CO_3 (2 g, 3.5 eq.) was degassed and flushed with argon gas five times at room temperature. The resulting solution was then heated to 140°C for about 48 h as the reaction was monitored by TLC (SiO_2, CH_2Cl_2, then 10:1 CH_2Cl_2/MeOH or 10:1 CH_2Cl_2/EtOAc). After cooling to room temperature, the brown heterogeneous solution was purified directly by chromatography by loading and eluting the column initially with CH_2Cl_2, then with 20:1 CH_2Cl_2/MeOH. The desired fractions were collected and concentrated *in vacuo* to give a desired product (a free base of **13)** as a white solid (696 mg, 1.3 mmol). H-NMR (CD_3OD, ppm) of non-labeled analog: 7.88 (m, 3H), 7.78 (m, 3H), 7.55 (d, 1H), 7.35 (s, 1H), 7.10 (d, 1H), 6.68 (d, 2H), 6.52 (d, 2H), 3.92 (t, 2H), 3.90 (s, 3H), 3.70 (s, 3H), 2.65 (t, 2H), 2.50 (br, 4H), 1.58 (m, 4H), 1.45 (br, 2H). The solid was dissolved in a mixed solvent of CH_2Cl_2 and EtOH, to which 0.9 mL of 4 N HCl in dioxane was added. The

DOI: 10.1002.jlcr

resulting clear yellowish solution was concentrated *in vacuo* to give a solid residue. This solid was further dried *in vacuo* at 40°C overnight to give the desired product **13** as a HCl salt (740 mg). H-NMR (CD_3OD, ppm) of non-labeled analog: 7.85 (m, 6H), 7.78 (d, 1H), 7.55 (s, 1H), 7.12 (d, 1H), 6.76 (d, 2H), 6.60 (d, 2H), 4.20 (m, 2H), 3.92 (s, 3H), 3.45 (m, 4H), 3.30 (br, 2H), 3.10 (s, 3H), 1.7–2.0 (br, 6H). Mass: $[M + H]^+ = 532.3$. The material was dissolved in 8 mL of anhydrous CH_2Cl_2, and the resulting solution was divided into two flasks, concentrated, and dried *in vacuo* to give two lots (385 mg in Lot A and 355 mg in Lot B).

Synthesis of 6-(4-methanesulfonyl-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-ol-[^{14}C] HCl Salt, 1. LY2066948-[^{14}C] HCl Salt

The aryl methyl ether **13** (Lot A 385 mg, 0.67 mmol) in the flask was cooled in a dry ice/acetone bath (about −50°C), to which 4 mL of 1 M solution of BCl_3 in CH_2Cl_2 was quickly added using a syringe. The solution turned dark brown quickly and was warmed up slowly to room temperature. The reaction was monitored by TLC (SiO_2, 6:1 CH_2Cl_2/MeOH). After stirring for about 64 h, the solution was cooled to 5°C in an ice bath, and the reaction was quenched by adding 4 mL of anhydrous MeOH using a syringe. The solution turned light brown and was concentrated *in vacuo* to give a residue as a yellowish solid. The solid residue was suspended in CH_2Cl_2, to which a saturated solution of $NaHCO_3$ wad added slowly with stirring. The solid dissolved slowly to give a clear two-layer solution. The organic layer was separated and concentrated *in vacuo*. The resulting residue was purified by the Biotage® system (SiO_2, CH_2Cl_2, then 10:1 CH_2Cl_2/MeOH) to give the desired product as a free base (290 mg, 0.56 mmol). The free base was suspended in 5 mL of absolute EtOH and cooled in an ice bath. To this solution was added dropwise a solution of 0.25 mL of 4 N HCl in dioxane. The solid dissolved initially to give a clear solution and then more solid formed again while stirring in the ice bath. To the heterogeneous solution was added 9 mL of MTBE to cause the precipitation of the product. After stirring in an ice bath for about 30 min and at room temperature for additional 90 min, the solution was filtered, and the solid was rinsed with MTBE. Further drying *in vacuo* at room temperature gave a product (293 mg) as a milk-white solid. Analysis by radio-HPLC indicated RCP = 97.5%, but containing two impurities at 0.6 and 1.0%. To further purify the product, the material was suspended in 4 mL of absolute EtOH and 0.55 mL of water, and the slurry was heated in an oil bath at about 89°C for 30 min to give a yellowish clear solution. After cooling to room temperature, a white crystalline solid formed. The solution was stirred for another 30 min. The white solid was filtered off, rinsed with 95% EtOH, and dried *in vacuo* at room temperature overnight to give the desired product **1**, **LY2066948-[^{14}C]** (191 mg, 0.344 mmol) as an off-white powder. RCP = 98.8%. Specific activity = 43.1 μCi/mg. H-NMR (CD_3OD, ppm) of free base of non-labeled analog: 7.78–7.90 (m, 5H), 7.69 (d, 1H), 7.52 (d, 1H), 7.20 (s, 1H), 7.05 (d, 1H), 6.70 (d, 2H), 6.55 (d, 2H), 3.96 (t, 2H), 3.10 (s, 3H), 2.70 (t, 2H), 2.50 (br, 4H), 1.60 (Br, 4H), 1.45 (br, 2H). Mass: $[M + H]^+ = 518.20$.

Acknowledgements

The authors would like to thank the support from the colleagues of Department of Isotopic Chemistry and the colleagues from CPR&D of LRL for providing compound **14**.

REFERENCES

1. Hummel CW, Geiser AG, Bryant HU, Cohen IR, Dally RD, Fong KC, Frank SA, Hinklin R, Jones SA, Lewis G, McCann DJ, Rudmann DG, Shepherd TA, Tian H, Wallace OB, Wang M, Wang Y, Dodge JA. *J Med Chem* 2005; **48**: 6772–6775.
2. Dally RD, Dodge JA, Frank SA, Jones SA, Shepherd TA, Wallace OB, Fong KC, Hummel CW, Lewis GS. (Eli Lilly and Company, USA). *PCT Int Appl* 2004; WO 2004009086 A1 20040129, WO 2004075894 A1.
3. Fox JM, Huang X, Chieffi A, Buchwald SL. *J Am Chem Soc* 2000; **122**: 1360.
4. Kawatsura M, Hartwig JF. *J Am Chem Soc* 1999; **121**: 1473.
5. Walker D, Hiebert JD. *Chem Rev* 1967; **67**: 153.
6. Shagufta, Raghunandan R, Maulik PR, Panda G. *Tetrahedron Lett* 2005; **46**: 5337–5341.
7. Buck E, Song ZK, Tschaen D, Dormer PG, Volante RP, Reider PJ. *Organic Lett* 2002; **4**: 1623–1626.
8. (a) Aikins JA, Miller RS, Zhang TY (Eli Lilly and Company, USA). *PCT Int Appl* 1996; WO 9640691 A1 19961219; (b) Brooks PR, Wirtz MC, Vetelino MG, Rescek DM, Woodworth GF, Morgan BP, Coe JW. *J Org Chem* 1999; **64**: 9719–9721.