Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 31 Oct 2008.

To cite this article: Rajendra K. Kharul, Archana Gite, Amitgiri Goswami, Mukul Jain, Bipin Pandey & Pankaj R. Patel (2008) Efficient Synthesis of Structurally Novel Diaryl Ethers by Regioselective Functionalization, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:23, 4282-4294, DOI: 10.1080/00397910802326547

To link to this article: http://dx.doi.org/10.1080/00397910802326547

Synthetic Communications®, 38: 4282–4294, 2008

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802326547

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Efficient Synthesis of Structurally Novel Diaryl Ethers by Regioselective Functionalization

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Abstract: Synthesis of structurally novel and biologically useful 3′-substituted diaryl ethers employing Cu(0) as a catalyst, followed by regioselective either sulfonylation or carbonylation, is described.

Keywords: Chlorosulfonic acid, diaryl ether, hexamethylene tetraamine, regioselective sulfonylation and carbonylation

INTRODUCTION

Diaryl ether linkage is present in many important classes of organic molecules (e.g., ligands for inorganic complexes and polyphenylene oxide polymer). Diaryl ether motif is also present in a number of natural compounds as well as biologically active compounds.[1]

RESULTS AND DISCUSSION

In continuation of our efforts to synthesize biologically active diaryl ethers[2] for a new drug discovery program supported by molecular modeling studies, we required 3′-substituted diaryl ethers (**1** and **2**). Although simple diaryl ethers can be obtained by coupling the suitable fragments,

Received May 4, 2008.
ZRC Communication No. 243.
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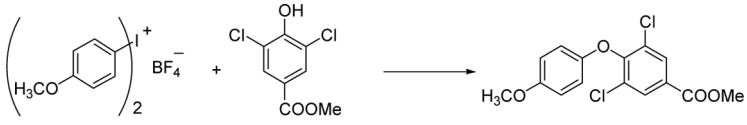


3 **4** **5**

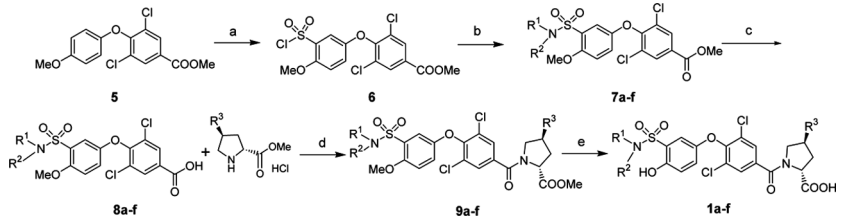
Scheme 1. Reagents and conditions: a) Cu, Et_3N, CH_2Cl_2, rt, 4 days, 80%.

there are few reports related to regioselective electrophilic substitution at the 3′-position.[3] The present communication describes regioselective functionalization at the 3′-position by using simpler reaction conditions and readily available reagents, which makes the approach scalable. To execute this, we needed various diaryl ethers. The literature describes various ways to assemble the ether backbone,[4] of which the Cu(0)-catalyzed reaction[5] appeared to be the most effective.

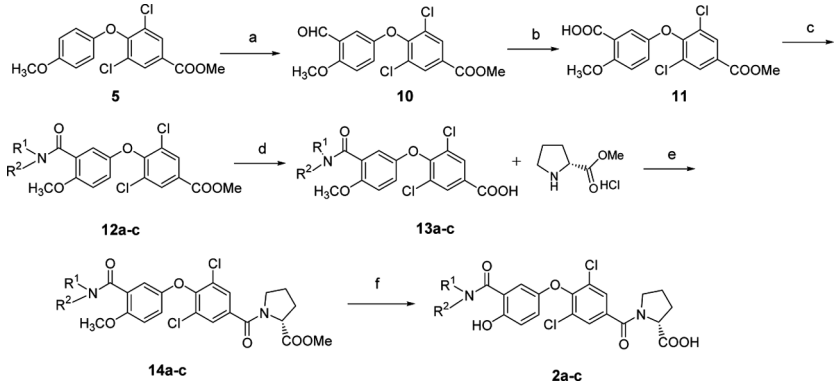
Initially, bis-(4-methoxyphenyl) iodoniumtetrafluoroborate (**3**) was coupled with methyl 3,5-dichloro-4-hydroxybenzoate (**4**) by using Cu(0) as catalyst to get coupled product (**5**) (Scheme 1).[6] Subsequent regioselective functionalization of (**5**) followed by functional group transformations furnished **1** and **2** (Schemes 2 and 3).

hus, diaryl ether (**5**) was sulfonylated at 0 °C by using chlorosulfonic acid to furnish corresponding arylsulfonyl chloride, which was obtained by carefully quenching the excess of chlorosulfonic acid present in the reaction mixture by slow addition of water at −5 to 0 °C. The spectral analysis indicated monosulfonylation in the prime ring (^{1}H NMR, electrospray ionization-mass spectrometry [ESI-MS]). It is important and interesting to note that the 3′-position was regioselectively sulfonylated.

The regioselectivity was conceptualized and established based on enhanced inductive effect of OMe group vis-à-vis OAr group for ortho substitution followed by spectroscopic evidence. Thus, $H^{2'}$ proton (7.33



Scheme 2. Reagents and conditions: (a) $ClSO_3H$, −10 to 0 °C, 30 min; (b) R^1R^2NH, CH_2Cl_2, 0 °C to rt, 2 h, 70–80% (combined yield for two steps); (c) KOH, MeOH:H_2O (1:1), rt, 90–94%; (d) EDCI, HOBT, Et_3N, CH_2Cl_2, 0 °C to rt, 15 h, 72–75%; (e) BBr_3, $CHCl_3$, −78 °C, 58–75%.



Scheme 3. Reagents and conditions: (a) HMTA, TFA, 80%; (b) Jones reagent, acetone, 0 °C, 30 min, 70%; (c) i) $(COCl)_2$, cat. DMF, CH_2Cl_2, 0 °C to rt, 2 h; ii) R^1R^2NH, Et_3N, CH_2Cl_2, 0 °C to rt, 30 min, 75–85%; (d) KOH, MeOH:H_2O (1:1), rt, 85–90%; (e) EDCI, HOBT, Et_3N, CH_2Cl_2, 0 °C to rt, 15 h, 50–60%; (f) BBr_3, $CHCl_3$, −78 °C, 53–80%.

δ, d, $J = 3$ Hz) was flanked by sulfonyl and aryloxy groups and deshielded as compared to $H^{5'}$ and $H^{6'}$ proton (Fig. 2). $H^{5'}$ and $H^{6'}$ appear at 6.95 δ (d, $J = 9$ Hz) and 7.02 δ (dd, $J = 3$, 9 Hz) respectively. The reason for exclusive monosubstitution at the 3′-position can also be attributed to the steric hindrance at either 2′ or 6′ position.

The sulfonyl chloride thus obtained was treated either with primary or secondary amine to yield sulfonamides esters (**7a–f**). The sulfonamide ester (**7**) was hydrolyzed to the corresponding acids (**8a–f**), and the acids were coupled with (L)-proline by using 3-ethyl-1(*N*,*N*-dimethyl)amino-propylcarbodiimide (EDCI).[7] The aryl ethers (**9a–f**) thus obtained, when subjected to demethylation with BBr_3,[8] furnished the desired diaryl ethers (**1a–f**) in one pot (Fig. 1 and Table 1).

To synthesize caboxamides (**2a–c**), the diaryl ether (**5**) was regioselectively carbonylated at the 3′-position with hexamethylene tetraamine[9] (HMTA) to furnish aldehyde (**10**). The aldehyde thus obtained was oxidized with Jones reagent[10] to give the corresponding acid (**11**). The

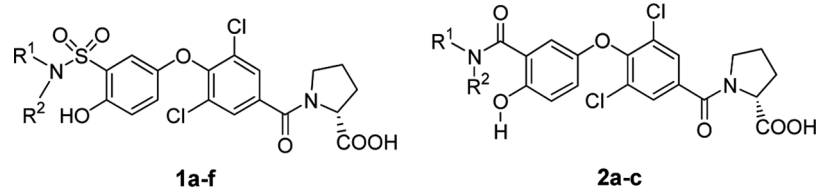


Figure 1. Various sulfonamides (**1a–f**) and carboxamides (**2a–c**).

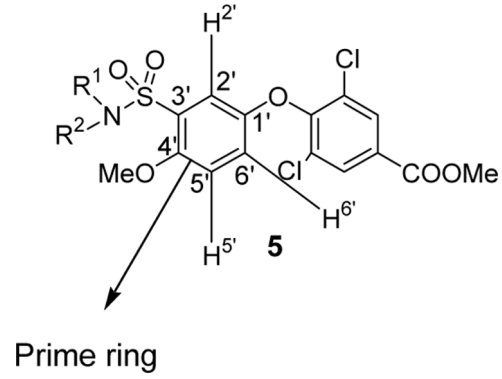
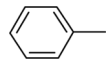
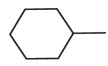
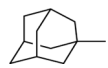


Figure 2.

carboxylic acid was converted to the amides (**12a–c**) via its acid chlorides, which were prepared using oxalyl chloride. The amides (**12**) were regioselectively hydrolyzed to the acid and then coupled with (L)-proline using

Table 1. Different substituents, absolute configuration, melting point, and yields for products (**1a–f**) and (**2a–c**)

Compound	R^1	R^2	R^3	Absolute configuration of –COOH[a]	Mp (°C)	Yield (%)
1a	H		H	(*S*)	147–148	58
1b		$-(CH_2)_5-$	H	(*S*)	121–122	75
1c		$-(CH_2)_5-$	H	(*R*)	122–124	72
1d	H		H	(*S*)	147–148	61
1e	H		H	(*S*)	139–140	66
1f		$-(CH_2)_5-$	OH (*R*)	(*S*)	163–165	60
2a		$-(CH_2)_5-$	H	(*S*)	145–146	80
2b	H		H	(*S*)	210–212	53
2c		$-(CH_2)_5-$	H	(*R*)	122–123	66

Note. We have used L- and D-proline as well as *trans*-3-hydroxy-(L)-proline as obtained from Aldrich & Co. We did not determine specific optical rotation of the final compounds though they are chiral.

EDCI to furnish diaryl ethers (**14a–c**). After demethylation with BBr_3, diaryl ether (**14**) furnished the desired polysubstituted diaryl ethers (**2a–c**).

CONCLUSION

Thus, a successful methodology for regioselective sulfonylation as well as carbonylation at the 3′-position of the polysubstituted diaryl ether has been established. The further exploration of this methodology to prepare differently functionalized complex diaryl ethers is under way.

EXPERIMENTAL

General Methods

^{1}H NMR was recorded on the NMR spectrometer (M-300) at 300 MHz in $CDCl_3$ or DMSO-d_6 solvent. Chemical shifts were reported as parts per million downfield from an internal tetramethylsilane standard ($\delta = 0.00$ for ^{1}H NMR). Mass spectra were recorded on a Perkin-Elmer Sciex API 3000. IR spectra were recorded on FT-IR 8300 Shimadzu in KBr pellets or $CHCl_3$ or CCl_4 as solvent. The compounds were analyzed for purity by analytical HPLC at λ_{max} 220 nm using column ODS C-18, 150 mm × 4.6 mm × 4 µ on an Agilent 100 series. Melting points were taken on a Scientific melting-point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed by using 25 DC-Alufolien 20 × 20 cm Kieselgel 60 F_{254} Merck plates.

Glassware was oven or flame dried prior to use. Reactions were performed under an argon or nitrogen inert atmosphere whenever needed. Crude products were purified by flash chromatography using 100- to 200-mesh silica gel, 230- to 400-mesh silica gel, or neutral aluminum oxide.

Preparation of 3,5-Dichloro-4-(4-methoxy-phenoxy)-benzoic Acid, Methyl Ester (5)

To a stirred solution of bis-(4-methoxyphenyl) iodoniumtetrafluoroborate (**3**) (20 g, 46.72 mmol, 1.5 equiv.) in dry dichloromethane (40 mL), copper bronze (3.95 g, 62.30 mmol, 2 equiv.) was added at 0–5 °C. To this solution, a mixture of methyl 3,5-dichloro-4-hydroxybenzoate (**4**) (6.88 g, 31.15 mmol, 1.0 equiv.) and triethyl amine (3.46 g, 34.26 mmol, 1.1 equiv.) in dichloromethane (60 mL) was added dropwise over a period of 1 h. The resulting mixture was warmed to room temperature, stirred for 96 h, and filtered through Celite®, and the residual copper bronze was washed thoroughly

with dichloromethane. The combined organic extracts were concentrated in vacuo to obtain a crude, brown, thick liquid. The crude product was purified by flash-column chromatography using (100- to 200-mesh) silica gel as stationary phase and ethyl acetate and n-hexane (2:98) as mobile phase to obtain methyl ester (**5**) as white solid (8.3 g, 82%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.06 (s, 2H), 6.83 (dd, $J = 9$, 3 Hz, 2H), 6.76 (dd, $J = 9$, 3 Hz, 2H), 3.94 (s, 3H), 3.77 (s, 3H); mp: 67–68 °C; HPLC purity: 99.33%.

General Procedure for Preparation of 7a–7f

3,5-Dichloro-4-[4-methoxy-3-(piperidine-1-sulfonyl)-phenoxy]-benzoic Acid, Methyl Ester (7b)

Powdered 3,5-dichloro-4-(4-methoxy-phenoxy)-benzoic acid, methyl ester (**5**) (1 g, 3.06 mmol, 1.0 equiv.) was taken in a round-bottomed flask, and chlorosulfonic acid (1.78 g, 15.3 mmol, 5 equiv.) was carefully added drop wise at 0–5 °C. The resulting mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was cooled to 0–5 °C, and excess chlorosulfonic acid was carefully quenched by dropping cold water along the walls of the flask. The white precipitate obtained was extracted with ethyl acetate (2 × 25 mL). The combined organic phase was washed with brine (25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to furnish methyl ester (**6**) (1.1 g, crude). To the stirred solution of methyl ester (**6**) (1.08 g, 2.55 mmol, 1 equiv.) in dichloromethane (20 mL), piperidine (0.54 g, 6.37 mmol, 2.5 equiv.) was added at 0–5 °C dropwise. The resulting mixture was warmed to room temperature and stirred for 2 h. The solvent was removed in vacuo, to give a light yellow solid (1.12 g, 93% crude). The crude solid was treated with methanol (10 mL) and stirred at room temperature for 10 min. The obtained white solid was filtered in vacuo, to give methyl ester (**7b**) (0.87 g, 72%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.07 (s, 2H), 7.33 (d, $J = 3$ Hz, 1H), 7.01 (dd, $J = 9$, 3 Hz, 1H), 6.94 (d, $J = 9$ Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 3.20–3.17 (m, 4H), 1.64–1.55 (m, 4H), 1.54–1.50 (m, 2H); ESI-MS: 497 $[M + Na]^+$; mp 139–140 °C; HPLC purity: 94.25%.

General Procedure for Preparation of 8a–8f

3,5-Dichloro-4-[4-methoxy-3-(piperidine-1-sulfonyl)-phenoxy]-benzoic Acid (8b)

NaOH (0.14 g, 3.65 mmol, 5 equiv.) dissolved in water (3 mL) was added to a stirred solution of methyl ester (**7b**) (0.34 g, 0.73 mmol, 1.0 equiv.) in

methanol (3 mL) at 26 °C. The resulting mixture was stirred at room temperature for 6 h. The reaction mixture was concentrated in vacuo. The residue was dissolved in water (10 mL) and washed with ethyl acetate (2 × 10 mL); the aqueous layer was acidified using 10% HCl solution (5 mL) to furnish a white solid product. The white solid product was filtered under suction, washed with n-hexane (20 mL), and dried in vacuo to obtain acid (**8b**) (0.27 g, 82%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.11 (s, 2H), 7.50 (d, $J = 3$ Hz, 1H), 7.02 (dd, $J = 9$, 3 Hz, 1H), 6.94 (d, $J = 9$ Hz, Hz, 1H), 3.96 (s, 3H), 3.20–3.12 (m, 4H), 1.60–1.50 (m, 6H); ESI-MS: 459 [M−1]; mp: 206–207 °C; HPLC purity: 96.66%.

General Procedure for Preparation of 9a–9f

1-{3,5-Dichloro-4-[4-methoxy-3-(piperidine-1-sulfonyl)-phenoxy]-benzoyl}-pyrrolidine-2-carboxylic Acid, Methyl Ester (9b)

EDC · HCl (0.216 g, 1.13 mmol, 2 equiv.) and HOBT (0.076 g, 0.565 mmol, 1 equiv.) were added to a stirred solution of acid (**8b**) (0.26 g, 0.56 mmol, 1.0 equiv.) in dichloromethane (10 mL) at 0–5 °C. L-Proline methyl ester hydrochloride (0.108 g, 0.565 mmol, 1 equiv.) was added followed by addition of triethyl amine (0.058 g, 0.565 mmol, 1 equiv.), and the resulting mixture was stirred at 26 °C for 24 h. The reaction mixture was diluted with dichloromethane (10 mL), washed with water (2 × 10 mL) and brine (1 × 10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to obtain the crude product. The crude product was purified by flash-column chromatography using alumina as stationary phase and ethyl acetate in n-hexane (4:6) as mobile phase to obtain the methyl ester (**9b**) (0.186 g, 58%) as low melting solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.62 (s, 2H), 7.41 (d, $J = 3$ Hz, 1H), 7.01 (dd, $J = 9$, 3 Hz, 1H), 6.94 (d, $J = 9$ Hz, 1H), 4.68–4.64 (m, 1H), 3.89 (s, 3H), 3.79 (s, 3H), 3.73–3.60 (m, 2H), 3.21–3.12 (m, 4H), 2.38–2.35 (m, 1H), 2.09–1.99 (m, 3H), 1.60–1.50 (m, 6H); ESI-MS: 571.6 $[M + H]^+$; mp: 62–64 °C; HPLC purity: 98.14%.

General Procedure for Preparation of 1a–1f

1-{3,5-Dichloro-4-[4-hydroxy-3-(piperidine-1-sulfonyl)-phenoxy]-benzoyl}-pyrrolidine-2-carboxylic Acid (1b)

To a stirred solution of methyl ester (**9b**) (0.206 g, 0.36 mmol, 1.0 equiv.) in chloroform (8 mL) at −78 °C, BBr_3 (0.541 g, 2.16 mmol, 6 equiv., 1 M solution in $CHCl_3$) were added. The resulting brown-colored reaction mixture was stirred at 26 °C for 16 h. The reaction mixture was quenched

with water (10 mL) and stirred at room temperature for 1 h. The organic layer was separated and washed with saturated NH_4Cl solution (1×10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to obtain crude product. The crude product was purified by treating it with saturated solution of $NaHCO_3$, washing the aqueous layer with ethyl acetate (2×10 mL), and acidifying the aqueous layer with 10% HCl solution (5 mL). The aqueous layer was extracted with ethyl acetate (2×20 mL); the chloroform layer was washed with water (2×20 mL) and brine (1×20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to obtain acid (**1b**) (0.16 g, 95%). Compound **(1a)**: 58% yield; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.65 (br s, 1H), 7.73 (s, 2H), 7.05–6.92 (m, 3H), 4.39–4.25 (m, 1H), 3.55–3.50 (m, 3H), 2.26–2.16 (m, 1H), 2.06–1.86 (m, 3H), 0.94 (d, $J = 6.51$ Hz, 6H); ESI-MS: 516 [M − 1]; mp: 147–148 °C; HPLC purity: 97.80%. **(1b)**: 95% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.60 (br s, 1H), 7.65 (s, 2H), 7.09–7.03 (m, 2H), 6.94 (d, $J = 9$ Hz, 1H), 4.74 (t, $J = 6.7$ Hz, 1H), 3.69–3.63 (m, 2H), 3.06–3.02 (m, 4H), 2.36–2.29 (m, 2H), 2.14–1.97 (m, 3H), 1.64–1.56 (m, 4H), 1.48–1.42 (m, 2H); ESI-MS: 507.1 $[M + H]^+$; mp: 121–122 °C; HPLC purity: 97.28%. **(1c)**: 72% yield; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.66 (br s, 1H), 10.46 (s, 1H), 7.74 (s, 2H), 7.08–6.97 (m, 3H), 4.44–4.35 (m, 1H), 3.58–3.56 (m, 2H), 3.05 (s, 4H), 2.28–2.24 (m, 1H), 2.04–1.82 (m, 3H), 1.49–1.40 (m, 6H); ESI-MS: 543.5 $[M + H]^+$; mp: 122–124 °C; HPLC purity: 97.18%. **(1d)**: 61% yield: ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.64 (br s, 1H), 10.72 (s, 1H), 10.1 (s, 1H), 7.72 (s, 2H), 7.15 (t, $J = 8.0$ Hz, 2H), 7.04–6.89 (m, 6H), 4.43–4.36 (m, 1H), 3.59–3.56 (m, 2H), 2.28–2.26 (m, 1H), 2.06–1.86 (m, 3H); ESI-MS: 551 [M − 1]; mp: 147–148 °C; HPLC purity: 98.73%. **(1e)**: 66% yield; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.66 (br s, 1H), 10.45 (s, 1H), 7.72 (s, 2H), 7.27–7.24 (m, 1H), 7.09–6.95 (m, 3H), 4.38–4.36 (m, 1H), 3.59–3.56 (m, 2H), 3.16–3.14 (m, 1H), 2.28–2.26 (m, 1H), 2.06–1.86 (m, 3H), 1.60–1.56 (m, 3H), 1.44–1.42 (m, 1H), 1.18–1.09 (m, 6H); ESI-MS: 557 $[M]^+$; mp 139–140 °C; HPLC purity: 96.46%. **(1f)**: 60% yield; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.73 (br s, 1H), 10.45 (s, 1H), 7.75–7.64 (m, 2H), 7.08–6.97 (m, 3H), 5.20–5.14 (m, 1H), 4.47 (t, $J = 8.1$ Hz, 1H), 4.29–4.26 (m, 1H), 3.89–3.79 (m, 1H), 3.05 (s, 4H), 2.26–2.15 (m, 1H), 2.06–1.96 (m, 1H), 1.47–1.42 (m, 6H); ESI-MS: 557 $[M]^-$; mp: 163–165 °C; HPLC purity: 97.34%.

Preparation of 3,5-Dichloro-4-(3-formyl-4-methoxy-phenoxy)-benzoic Acid, Methyl Ester (**10**)

To a stirred solution of methyl ester (**5**) (4.0 g, 12.23 mmol, 1.0 equiv.) in trifluoroacetic acid (40 mL), hexamethyl tetramine (4.28 g, 30.58 mmol,

2.5 equiv.) was added at 26 °C. The resulting brown-colored reaction mixture was heated at 70–80 °C and stirred for 4 h. Trifluoroacetic acid was removed in vacuo, and the resulting solid residue was stirred with water (60 mL) for 16 h. The aqueous solution was carefully neutralized using solid sodium bicarbonate, and pH was adjusted to 8. The aqueous layer was extracted with dichloromethane (3 × 40 mL). The combined organic extracts were washed with water (2 × 40 mL) and brine (1 × 40 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to obtain a crude yellow solid (4.2 g, 100%). The crude product was purified by flash column chromatography using silica gel (100–200 mesh size), and the pure product was eluted using ethyl acetate and n-hexane (7:93) to obtain methyl ester (**10**) (3.4 g, 78%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.27 (s, 1H), 8.12 (s, 2H), 7.34 (dd, $J = 9.12$ and 3 Hz, 1H), 7.27 (d, $J = 9.15$ Hz, 1H), 6.95 (d, $J = 3$ Hz, 1H), 3.91 (s, 3H), 3.9 (s, 3H); mp: 145–147 °C; HPLC purity: 96.12%.

Preparation of 3,5-Dichloro-4-(3-carboxy-4-methoxy-phenoxy)-benzoic Acid (11)

Jones reagent (9 mL) was added to a stirred solution of methyl ester (**10**) (3.0 g, 8.45 mmol, 1.0 equiv.) in acetone (50 mL) at 0–5 °C until brown color persisted. The resulting brown-colored reaction mixture was warmed to room temperature and stirred for 4 h. The reaction mixture was quenched with isopropanol (8.0 mL); the green inorganic salts precipitated were removed by filtration under suction. The colored solution was concentrated in vacuo to obtain crude off-white solid, which was stirred with water (50 mL) for 30 min at room temperature and filtered off. Thus the free-flowing acid (**11**) (1.9 g, 61%) was obtained. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.88 (br s, 1H), 8.11 (s, 2H), 7.12–7.04 (m, 3H), 3.89 (s, 3H), 3.78 (s, 3H); ESI-MS: 372.2 $[M + H]^+$; mp: 199–200 °C; HPLC purity: 93.77%.

General Procedure for Preparation of 12a–12c

3,5-Dichloro-4-[4-methoxy-3-(piperidine-1-carbonyl)-phenoxy]-benzoic Acid, Methyl Ester (**12a**)

A catalytic amount of *N,N*-dimethylformamide (2 drops) was added to the stirred solution of methyl ester (**11**) (0.9 g, 2.42 mmol, 1.0 equiv.) in dichloromethane (5 mL) followed by oxalyl chloride (0.64 mL, 7.26 mmol, 3 equiv.) at 0–5 °C. The resulting mixture was warmed to

room temperature and stirred for 1 h. The reaction mixture was concentrated and dried in vacuo to obtain the corresponding acid chloride (0.94 g, crude). To the stirred solution of acid chloride (0.94 g, 2.42 mmol, 1 equiv.) in dichloromethane (10 mL), piperidine (0.41 g, 4.85 mmol, 2.0 equiv.) at 0–5 °C was added dropwise. The resulting mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was diluted with dichloromethane (5 mL), washed with water (1 × 20 mL) and brine (20 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to obtain methyl ester (**12a**) in the form of a light-yellow, thick liquid (1.13 g, 98% crude). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.05 (s, 2H), 6.83–6.82 (m, 2H), 6.68–6.67 (m, 1H), 3.95 (s, 3H), 3.79 (s, 3H), 3.69–3.65 (m, 2H), 3.19–3.16 (m, 2H), 1.64–1.50 (m, 6H); ESI-MS: 437.9 $[M]^+$; HPLC purity: 93.27%.

General Procedure for Preparation of 13a–13f

3,5-Dichloro-4-[4-methoxy-3-(piperidine-1-carbonyl)-phenoxy]-benzoic Acid (**13a**)

To the stirred solution of methyl ester (**12a**) (1.0 g, 2.28 mmol, 1.0 equiv.) in methanol (5 mL), NaOH (0.45 g, 11.41 mmol, 5 equiv.) dissolved in water (5 mL) was added at room temperature. The resulting mixture was stirred at room temperature for 6 h. The reaction mixture was concentrated in vacuo. The residue was dissolved in water (10 mL), washed with ethyl acetate (2 × 10 mL); the water layer was acidified using 10% HCl solution (5 mL) to yield a white solid. The white solid was filtered under suction, washed with n-hexane (20 mL), and dried in vacuo to obtain acid (**13a**) (0.9 g, 93%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 13.65 (br s, 1H), 7.98 (s, 2H), 6.97 (d, $J = 9.12$ Hz, 1H), 6.82 (dd, $J = 9$, 3 Hz, 1H), 6.60 (d, $J = 3.12$ Hz, 1H), 3.68 (s, 3H), 3.47–3.43 (m, 2H), 3.02–2.98 (m, 2H), 1.48–1.29 (m, 6H); ESI-MS: 423.9 $[M]^+$; mp: 147–148 °C; HPLC purity: 95.04%.

General Procedure for Preparation of 14a–14c

1-{3,5-Dichloro-4-[4-methoxy-3-(piperidine-1-carbonyl)-phenoxy]-benzoyl}-pyrrolidine-2-carboxylic Acid, Methyl Ester (**14a**)

EDC · HCl (0.76 g, 4.00 mmol, 2 equiv.) and HOBT (0.27 g, 2.00 mmol, 1 equiv.) were added to the stirred solution of acid (**13a**) (0.85 g, 2.00 mmol, 1.0 equiv.) in dichloromethane (10 mL), at 0–5 °C. L-Proline

methyl ester hydrochloride (0.26 g, 2.00 mmol, 1 equiv.) was added followed by addition of triethyl amine (0.20 g, 2.00 mmol, 1 equiv.). The resulting mixture was stirred at room temperature for 24 h and then diluted with dichloromethane (10 mL), washed with water (2×10 mL) and brine (1×10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to obtain crude product. The crude product was purified by flash-column chromatography using silica gel (100–200 mesh) as stationary phase and ethyl acetate in n-hexane (1:1) as mobile phase to obtain methyl ester (**14a**) as a white solid (0.60 g, 60%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.61 (s, 2H), 6.83–6.79 (m, 2H), 6.70–6.69 (m, 1H), 4.68–4.64 (m, 1H), 3.79 (s, 6H), 3.70–3.62 (m, 4H), 3.19–3.16 (m, 2H), 2.40–2.30 (m, 1H), 2.09–1.99 (m, 3H), 1.65–1.60 (m, 4H), 1.52–1.44 (m, 2H); ESI-MS: 557.4 $[M + Na]^+$; mp: 71–73 °C; HPLC purity: 99.32%.

General Procedure for Preparation of 2a–2c

1-{3,5-Dichloro-4-[4-hydroxy-3-(piperidine-1-carbonyl)-phenoxy]-benzoyl}-pyrrolidine-2-carboxylic Acid (**2a**)

To the stirred solution of methyl ester (**14a**) (0.44 g, 0.82 mmol, 1.0 equiv.) in chloroform (8 mL) at −78 °C BBr_3 (1.23 g, 4.93 mmol, 6 equiv. 1 M solution in $CHCl_3$) was added. The resulting brown-colored reaction mixture was stirred at room temperature for 16 h, then quenched with water (10 mL) and stirred at 26 °C for 1 h. The organic layer was separated, washed with saturated NH_4Cl solution (1×10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to obtain crude product. The crude product was purified by treating it with a saturated solution of $NaHCO_3$ and washing the aqueous layer with diethyl ether (2×10 mL). The aqueous layer was acidified with 10% HCl solution (5 mL). The white solid product that precipitated was filtered in vacuo, washed with water (2×25 mL) and n-hexane (2×25 mL), and dried in vacuo to obtain acid (**2a**) (0.35 g, 84%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.19 (br s, 1H), 7.64–7.61 (m, 2H), 6.98–6.90 (m, 2H), 6.62 (d, $J = 2.55$ Hz, 1H), 4.73 (t, $J = 6.64$ Hz, 1H), 3.65–3.57 (m, 6H), 2.35–2.28 (m, 2H), 2.17–2.07 (m, 1H), 2.02–1.94 (m, 1H), 1.68–1.63 (m, 2H), 1.60–1.54, (m, 4H); ESI-MS: 507.0 $[M + H]^+$; mp: 145–146 °C; HPLC purity: 99.12%. **(2b)**: 53% yield; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.62 (br s, 1H), 11.59 (s, 1H), 8.18 (s, 1H), 7.72 (s, 2H), 7.44–7.40 (m, 1H), 6.86–6.73 (m, 2H), 4.44–4.36 (m, 1H), 3.58–3.56 (m, 2H), 2.03 (s, 10H), 1.91–1.83 (m, 3H), 1.64 (s, 6H); ESI-MS: 573.8 $[M + H]^+$; mp: 210–212 °C; HPLC purity: 99.84%. **(2c)**: 66%

yield; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.8 (br s, 1H), 9.56 (s, 1H), 7.70 (s, 1H), 6.82–6.72 (m, 2H), 6.54–6.50 (m, 1H), 4.41–4.35 (m, 1H), 3.57–3.52 (m, 3H), 3.32–3.26 (m, 3H), 1.89–1.85 (m, 4H), 1.53 (s, 2H), 1.43 (s, 4H); ESI-MS: 507.1 $[M + H]^+$; mp: 122–123 °C; HPLC purity: 98.29%.

ACKNOWLEDGMENT

We thank the management of Zydus Cadila Group for encouragement and our analytical department for support.

REFERENCES

1. (a) Nicolaou, K. C.; Takayanagi, M.; Jain, N. F.; Natarajan, S.; Koumbis, A. E.; Bandi, T.; Ramanjulu, J. M. Total synthesis of vancomycin aglycon, part 3: Final stages. *Angew Chem. Int. Ed.* **1998**, *37*, 2717; (b) Bogar, D. L.; Miyazaki, S.; Loiseleur, O. L.; Beresis, R. T.; Castle, S. L.; Wu, J. H.; Jin, Q. *J. Am. Chem. Soc.* **1998**, *120*, 8920; (c) Evans, D. A.; Dinsmore, C. J.; Watson, P. S.; Wood, M. R.; Richardson, T. I.; Trotter, B. W.; Katz, J. L. Nonconventional stereochemical issues in the design of the synthesis of the vancomycin antibiotics: Challenges imposed by axial and nonplanar chiral elements in the heptapeptide aglycons. *Angew. Chem. Int. Ed.* **1998**, *37*, 2704.
2. Kharul, R. K.; Goswami, A.; Gite, A.; Bandyopadhyay, D.; Kumar, J.; Kalpatapu, S.; Modi, H.; Thorave, A. A.; Prajapati, P. N.; Jain, M.; Patel, P. R. Unpublished results.
3. (a) Ryono, D. E.; Hangeland, J. J.; Friends, T. J.; Dejneka, T.; Devasthale, P.; Caringal, Y. V.; Zhang, M.; Doweyko, Arthur, M. P.; Malm, J.; Sanin, A. Thyroid receptor ligands. WO 93799, **2004**. *Chem. Abstr.* **2004**, *141*, 395288; (b) Zhang, M.; Hangeland, J.; Caringal, Y. J.; Friends, T. Pyridine-based thyroid receptor ligands. WO 94845, **2003**, *Chem. Abstr.* **2003**, *139*, 395820; (c) Cremlyn, R. J.; Swinbourne, F. J.; Fitzgerald, P.; Godfrey, N.; Hedges, P.; Lapthorne, J.; Mizon, C. Chlorosulfonation of some aromatic compounds. *Ind. J. Chem. Sect. B* **1984**, *23*, 962.
4. For a recent review, see Sawyer, J. S. Recent advances in diaryl ether synthesis. *Tetrahedron* **2000**, *56*, 5045.
5. (a) Theil, F. Synthesis of diaryl ethers: A long-standing problem has been solved. *Angew. Chem. Int. Ed.* **1999**, *38*, 2345; (b) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. Formation of aryl-nitrogen, aryl-oxygen, and aryl-carbon bonds using well-defined copper(I)-based catalysts. *Org Lett.* **2001**, *3*, 4315; (c) Elizabeth, B.; Zhiguo, J. S.; David, T.; Peter, G. D. Ullmann diaryl ether synthesis: Rate acceleration by 2,2,6,6-tetramethylheptane-3,5-dione. *Org. Lett.* **2002**, *4*, 1623; (d) Simon, J.; Salzbrunn, S.; Surya Prakash, G. K.; Petasis, N. A.; Olah, G. A. Regioselective conversion of arylboronic acids to phenols and subsequent coupling to symmetrical diaryl ethers. *J. Org. Chem.* **2001**, *66*, 633.

6. Yokoyama, N.; Walker, G. N.; Main, A. J.; Stanton, J. L.; Morrissey, M. M.; Boehm, C.; Engle, A.; Neubert, A. D.; Wasvary, J. M.; Stephan, Z. F.; Steele, R. E. Synthesis and structure–activity relationships of oxamic acid and acetic acid derivatives related to L-thyronine. *J. Med. Chem.* **1995**, *38*, 695.
7. (a) Newman, M. S.; Boden, H. *N*-Methylpyrrolidone as solvent for reaction of aryl halides with cuprous cyanide. *J. Org. Chem.* **1961**, *26*, 2525; (b) For a recent review, see Christian, A. G.; Virginie, F. Amide bond formation and peptide coupling. *Tetrahedron* **2005**, *61*, 10827.
8. (a) Mcomie, J. F. W.; Watts, M. L.; West, D. E. Demethylation of aryl methyl ethers by boron tribromide. *Tetrahedron* **1968**, *24*, 2289; (b) Benton, F. L.; Dillon, T. E. The cleavage of ethers with boron bromide. *J. Am. Chem. Soc.* **1942**, *64*, 1128.
9. Chatterjee, A.; Biswas, K. M. Acylation of indoles by Duff reaction and Vilsmeier–Hack formylation and conformation of *N*-formylindoles. *J. Org. Chem.* **1973**, *38*, 4002.
10. (a) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. Researches on acetylenic compounds: The preparation of acetylenic ketones by oxidation of acetylenic carbinols and glycols. *J. Chem. Soc.* **1946**, *39*; (b) Ersenbraun, E. J. Cyclooctanone. *Org. Syn.* **1965**, *45*, 28.