Total synthesis of lasofoxifene and nafinoxidine
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**ABSTRACT**

An intramolecular reductive coupling process of diketone with low-valent titanium species to form a dihydronapthalene skeleton was an important step in the synthesis of nafinoxidine (1) and lasofoxifene (2). Diketone 6 was prepared in a convenient, three-step sequence starting from 3-methoxy benzaldehyde in good yields.

**GRAPHICAL ABSTRACT**

**ARTICLE HISTORY**

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**KEYWORDS**

Diketone; lasofoxifene; low-valent titanium; nafinoxidine; reductive coupling process

**Introduction**

Nafinoxidine 1 and Lasofoxifene 2 are nonsteroidal selective estrogen receptor modulators (SERM). Lasofoxifene was approved in the European Union under the brand name Fablyn in March 2009.

Lasofoxifene was tested also for the prevention of osteoporosis and for the treatment of vaginal atrophy. Both 1 and 2 were also studied for their anti-breast-cancer properties. Osteoporosis is one of the most common disorders in elderly subjects and represents a major public health problem, affecting up to 50% of postmenopausal women and 20%...
of men older than 50 years. Lasofoxifene 0.5 mg/day significantly increased bone mineral density (BMD) and decreased bone turnover compared to a placebo.

After lasofoxifene showed promise for osteoporosis, a few improved methods were reported and patented. All protocols for the generation of lasofoxifene 2 utilized nafoxidine 1 or its derivatives as a precursor. Lednicer et al.\cite{3} reported a method for the synthesis of 1 via the dehydration of the tertiary alcohol obtained from the Grignard reaction of 6-methoxy-2-phenyl-1-tetralone with appropriate reagent. Cameron et al.\cite{4} at Pfizer used the methodology of Suzuki reaction to add aromatic nucleus at the 2-position to 1-aryl-2-bromo-3,4-dihydronaphthalene with phenyl bromide. Chiu\cite{5} at Pfizer also showed an alternative route to 1 and 2 via the intermolecular reductive coupling process of a diketone using a titanium species to form the desired nucleus. Isamu et al.\cite{6} prepared 1 and 2 via a three-component coupling process of 4-pivaloyloxy benzaldehyde, cinnamoyl trimethyl silane, and anisole in the presence of HfCl\textsubscript{4} to give a coupling product, which on routine transformations gave 1. Other researchers\cite{7} used palladium chemistry to prepare 2-aryl-6-methoxy-1-tetralone from bromo benzene and 6-methoxy-1-tetralone, and another team\cite{8} also started with 6-methoxy-1-tetralone and did a Grignard reaction with 1-[2-(4-bromophenoxy)ethyl] pyrrolidine, followed by bromination and Suzuki reaction with phenyl boronic acid to give 1.

**Results and discussion**

Our synthetic strategy for nafoxidine 1 and lasofoxifene 2 is described in Scheme 1.

![Scheme 1](image)

**Scheme 1.** Synthesis of nafoxidine. (a) KOH, MeOH, rt, 2 h, 88%; (b) EtOH, 5% Pd/C, rt, 3 h, 95%; (c) DCM, AlCl\textsubscript{3}, 0–5 °C, 30 min; (d) Cu-Zn comp, TiCl\textsubscript{3}, DME, 70–75 °C, 35%; (e) pyrrolidine, EtOAC, HCl, 80–85 °C, 88%.
Compared to the reported methods, our methodology is simple and practical. In this methodology, the first step is a known aldol condensation between 3-methoxy benzaldehyde 3 and acetophenone to give compound chalcone[9] 4. Compound 4 on hydrogenation gave 3-(3-methoxyphenyl)-1-phenyl propane-1-one[9] 5. Compound 5 on Friedel–Crafts benzylation with 4-(2-chloro ethoxy)benzoyl chloride[10] 8 gave compound 6a and a cyclized product 6. Both compounds can be separated on column chromatography, but we found it better to separate them after the titanium chloride reaction. The crude mixture 6 and 6a were subjected to reductive cyclization with titanium trichloride and Zn-Cu couple[5] reaction to give a mixture of 6 and 7. The diaryl dihydronaphthalene compound 7 was separated. Compound 7 was reacted with pyrrolidine to give compound[4] 1 in an overall yield of 26%.

Compound 1 is converted to lasofoxifene 2 in a reported way and was compared with the reported material[4] (Scheme 2).

In conclusion we have reported a practical and simple total synthesis of nafoxidine and lasofoxifene.

**Experimental**

**Materials and instruments**

Most of the reagents used in this work were obtained from commercial suppliers and were of laboratory-reagent or analytical-reagent (LR/AR) grade. Solvents were purified before use by standard procedures. Melting points were determined using open capillary tubes on a Polmon melting-point apparatus (model 96) and are uncorrected. ¹H (400 MHz) and ¹³C (100 MHz) NMR spectra were recorded by using a Bruker 400 spectrometer with tetramethylsilane (TMS) as an internal standard. Infrared (IR) spectra were recorded on a Perkin-Elmer Spectrum 100 FTIR spectrophotometer as KBr pellets or with the neat products. Mass spectra were recorded on an API 2000 LCMS/MS Applied Bio Systems MDS Sciex spectrometer. Microanalysis was performed on a Perkin-Elmer 240CHN elemental analyzer. Analytical thin-layer chromatography (TLC) was conducted on E-Merck 60F254 aluminium-packed plates of silica gel (0.2 mm). Developed plates were visualized by using ultraviolet (UV) light or in an iodine chamber. High-performance liquid chromatography (HPLC) was performed by using a Shimadzu 2010 instrument.
Synthesis of \(3-[4-(2\text{-chloro-ethoxy})-phenyl]-6\text{-methoxy-1H-inden-2-yl} \) \(-\) \( \text{-phenyl-methanone (6)} \) and \(3-[2-[4-(2\text{-chloro-ethoxy})-benzoyl]-5\text{-methoxy-phenyl}]-1\text{-phenyl-propan-1-one (6a)} \)

To a stirred solution of aluminum chloride (4.23 g, 0.031 mol) and dichloromethane (DCM) (30 mL) at 0–5 °C 4-(2-chloro-ethoxy)-benzoyl chloride \(\text{(8)}\) in DCM (5.5 g, 0.031 mol in 25 mL DCM) was added over 20 min, and after 10 min compound 4 in DCM \(\text{(3-[3\text{-methoxy-phenyl}]-1\text{-phenyl-propan-1-one, 5 g, 0.020 mol in 20 mL DCM\)}}\) was added at 0–5 °C. After 1 h the reaction mixture was quenched in to 10% aqueous HCl solution (100 mL) and extracted with DCM (2⋅100 mL). The organic layer was washed with demineralized (DM) water (200 mL), dried over sodium sulfate, and concentrated under vacuum to get the crude product. This crude product, which is unstable to silica gel, was used to next step without further purification.

For conformation of the product, 2 g of crude product was purified quickly using column chromatography.

The first compound on elution with 10% ethyl acetate in hexane gave a cyclization product whose structure 6 was confirmed on the basis of spectral data. Description: yellow color solid; mp: 100.2–101.6 °C; IR (in KBr, cm\(^{-1}\)): 2835, 1603, 1359, 1244, 1028, 817, 711, 541; \(^1\)H NMR (400 MHz, CDCl\(_3\)) (δ ppm): 7.49 (d, \(J = 7.58\) Hz, 2H), 7.38 (d, \(J = 8.42\) Hz, 1H), 7.24 (m, 1H), 7.16–7.08 (m, 5H), 6.92 (t, \(J = 6.2\) Hz, 1H), 6.69 (d, \(J = 8.5\) Hz, 2H), 4.14 (t, \(J = 6.0\) Hz, 2H), 3.99 (s, 2H), 3.89 (s, 3H, OCH\(_3\)), 3.74 (t, \(J = 6.0\) Hz, 2H) \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) (δ ppm): 195.22, 160.26, 157.94, 150.42, 146.07, 138.48, 137.69, 137.43, 131.40, 130.81, 129.19, 127.62, 127.50, 123.54, 114.48, 113.41, 109.93, 68.01, 55.64, 41.70, 40.31. Anal. calcd. for C\(_{25}\)H\(_{21}\)ClO\(_3\): C, 74.16; H, 5.23. Found: C, 74.12; H, 5.26.

On further elution with 10% ethyl acetate in hexane the second compound (required) was obtained. Its structure 6a was confirmed on the basis of spectral data. Description: White color solid; mp: 93–95.2 °C; IR (in KBr, cm\(^{-1}\)): 2021, 1708, 1608, 1563, 1506, 1489, 1462, 1428, 1280, 1240, 1175; \(^1\)H NMR (400 MHz, CDCl\(_3\)) (δ ppm): 7.97 (d, \(J = 7.32\) Hz, 2H), 7.78 (d, \(J = 8.28\) Hz, 2H), 7.57 (t, \(J = 6.78\) Hz, 1H), 7.48–7.44 (m, 2H), 7.26 (d, \(J = 7.8\) Hz, 1H), 6.99–6.87 (m, 4H), 4.27 (t, \(J = 5.20\) Hz, 2H), 3.82 (t, \(J = 5.15\) Hz, 2H), 3.71 (s, 3H), 3.35 (t, \(J = 7.20\) Hz, 2H), 3.13 (t, \(J = 7.0\) Hz, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) (δ ppm): 198.97, 194.89, 161.97, 157.36, 145.69, 136.78, 132.24, 131.47, 129.75, 128.69, 128.05, 126.99, 120.39, 113.98, 111.82, 68.02, 55.63, 41.70, 40.08, 30.38. Anal. calcd. for C\(_{25}\)H\(_{23}\)ClO\(_4\): C, 71.0; H, 5.48. Found: C, 71.4; H, 5.52.

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