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A new process for the synthesis of nafoxidene as a key intermediate of lasofoxifene

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Abstract A novel brief process for the synthesis of nafoxidene has been developed. The epoxidation of 6-methoxy-1-{4-[2-(pyrrolin-1-yl)ethoxy)]phenyl}-3,4-dihydronaphthalene by m-CPBA directly gave the ketone 6-methoxy-1-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-3,4-dihydronaphthalen-2(1H)-one, which was subject to phenyl magnesium bromide/cerium chloride and subsequently treated with an acid to yield nafoxidene. In addition, the preparation of the starting naphthalene was also optimized by replacing the aromatic lithium at low temperature with its Grignard reagent at refluxing THF. This mild process, without the use of toxic or noble metals, was more cost-efficient and easily worked up.

Keywords Lasofoxifene · Nafoxidene · Synthesis · Pinacol rearrangement

Introduction

Lasofoxifene (**1**), a third-generation selective estrogen receptor modulator for the prevention and treatment of osteoporosis, was approved in the EU under the brand name Fablyn by the EMEA in March 2009 [1, 2]. For preparation of lasofoxifene, the reduction of a double bond of nafoxidene (**2**), followed by demethylation is an essential pathway (Scheme 1) [3–6]. As a key intermediate of lasofoxifene, synthetic exploration for nafoxidene, a non-marketed drug, has attracted the chemist's interest again.

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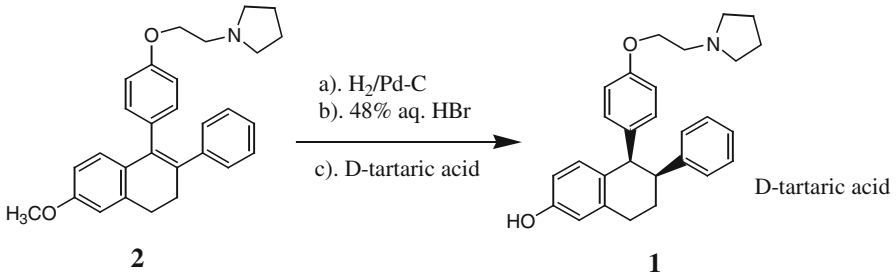


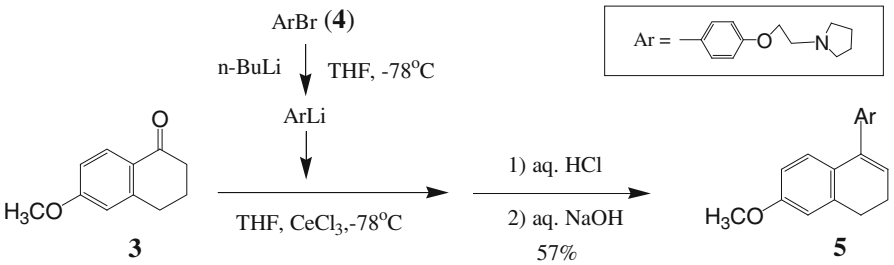
Scheme 1 The synthetic route of lasofoxifene D-tartrate from nafoxidene

Among the reported literatures, there are four representative processes: (a) commercially bulky 6-methoxy-1-tetralone (**3**) for the synthesis of methylnorethindrone was used as a starting material (Scheme 2), and addition of 4-(2-pyrrolidin-1-yl-ethoxy)phenyl lithium [ArLi prepared from ArBr (**4**) and nBuLi] in the presence of cerium chloride at −78 °C and subsequent acid treatment afforded compound **5**. Bromination of the double bond of **5** and Suzuki coupling with phenylboronic acid gave nafoxidene [4]; (b) addition of ArLi (Scheme 2) to 6-methoxy-2-phenyl-1-tetralone, followed by dehydration by treatment of hydrochloric acid yielded nafoxidene [3, 7]; (c) five steps starting from 2-bromo-5-methoxytoluene and 4-benzyloxybenzonitrile were described for the synthesis of nafoxidene via a key coupling reaction catalyzed by $TiCl_3$ [5]; (d) recently, a novel procedure was presented via $HfCl_4$-mediated three-component coupling reaction to construct the major skeleton of nafoxidene in one pot [6]. Unfortunately, all these methods are involved in one or more of the following drawbacks: tedious procedures [4, 6], rare raw materials [3, 5, 7], a noble metal [4, 5], harsh conditions, or low yield [3–5, 7].

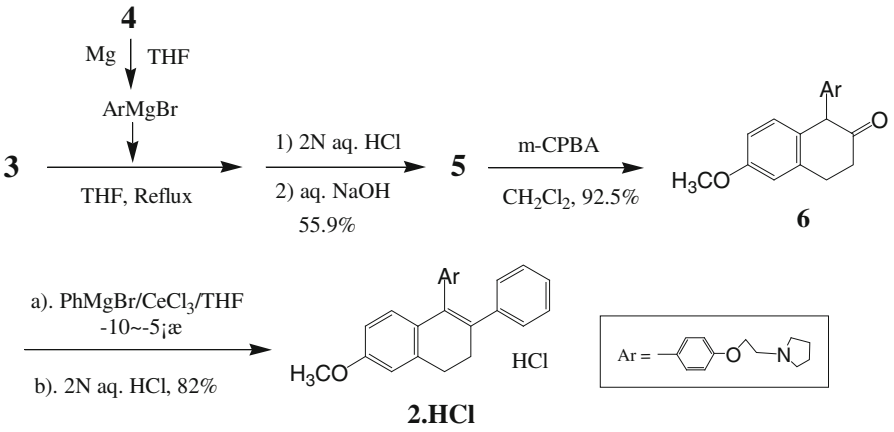
Herein, we present a novel brief process for the synthesis of nafoxidene under mild conditions without the use of toxic and noble metals: epoxidation and simultaneous pinacol rearrangement of compound **5** afforded the ketone **6**, which was subject to phenyl magnesium bromide/$CeCl_3$ and then treated with hydrochloric acid to give nafoxidene in good yields (Scheme 3). The preparation of **5** was also optimized.

Results and discussion

It is well known that the addition of Grignard or lithium reagents to ketones is significantly enhanced by cerium trichloride with remarkable suppression of side reaction, particularly enolization [8–10], but in our case, the application of cerium chloride to ArMgBr failed to yield the desired product. Referred to the preparation of similar compounds [11], the Grignard reagent, freshly prepared from **4** and magnesium turnings was added to refluxing THF solution of **3** to give **5** in a moderate yield (55.9 %) similar to how the corresponding lithium was used at low temperature.



Scheme 2 The synthetic route of intermediate **5**



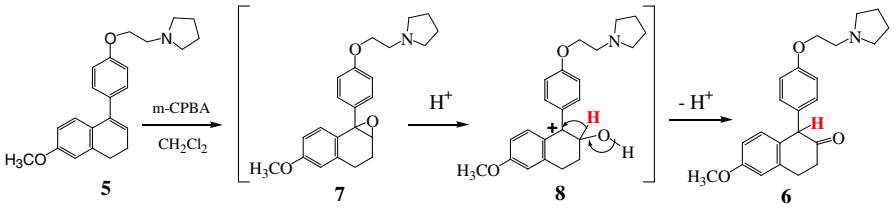
Scheme 3 The synthetic route of nafoxidene hydrochloride

Epoxidation of **5**, subsequent addition of PhMgBr in the presence of CuI, and final acidification were our initial imagination for the synthesis of nafoxidene. However, epoxidation of **5** by m-CPBA in CH_2Cl_2 at 0–5 °C failed to give the desired epoxide **7** but the ketone **6** in a yield of 92.5 %. It was proposed that after the formation of the epoxy **7**, the epoxy ring was immediately opened and rearranged to the ketone **6** under the acidic condition (Scheme 4).

With the ketone **6** in hand, the addition of phenyl magnesium bromide/cerium chloride to **6** at −10 to −5 °C and acidic treatment readily gave **2 HCl** (nafoxidene) in a yield of 82 %.

Conclusions

A novel synthetic route for nafoxidene has been developed. The oxidation of 6-methoxy-1-{4-[2-(pyrrolin-1-yl)ethoxy)]phenyl}-3,4-dihydronaphthalene by m-CPBA readily gave the ketone 6-methoxy-1-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-3,4-dihydronaphthalen-2(1H)-one in a high yield. The subsequent addition of phenyl



Scheme 4 Mechanism of the rearrangement

magnesium bromide in the presence of cerium chloride followed by treatment with an acid yielded nafoxidene in a good yield. The process of starting naphthalene was optimized 1-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl magnesium bromide in place of its lithium at low temperature was added to refluxing THF solution of 6-methoxy-1-tetralone to give an approximate yield. This process was more cost-efficient and easily worked up.

Experimental

IR spectra were acquired on a Bruker Vector 22 spectrometer and are expressed in cm^{-1} (KBr), ^{1}HNMR spectra on a Bruker DRX300 (500 MHz) spectrometer, ^{13}CNMR spectra on a Bruker DRX300 (75.5 MHz) spectrometer, and mass spectra with an automated Finnigan TSQ QuantumUltra AM (Thermal) LC–MS spectrometer. All commercial chemicals (AR grade) were used without further purification. THF was distilled from Na under nitrogen. m-CPBA: meta-chloroperoxybenzoic acid.

6-Methoxy-1-{4-[2-(pyrrolidin-1-yl)ethoxy)]phenyl}-3,4-dihydronaphthalene (**5**)

To the mixture of flame-dried magnesium turnings (5.83 g, 240 mmol) and 50 ml of absolute THF, a small amount of I_2 was added in a 500-ml three-necked flask, and several minutes later about 0.5 ml of **4** was injected in. After the reaction was initiated by heat, the rest of **4** (62.1 g, 230 mmol) and THF (350 ml) were added slowly between 20 and 30 °C to give the Grignard reagent as a gray solution.

To the refluxing solution of **3** (23.9 g, 136 mmol) in absolute THF (120 ml) was the above Grignard reagent added within 30 min. The resulting mixture continued to reflux for 30 min, and then cooled down to room temperature and quenched with aqueous saturated NH_4Cl (400 ml). The mixture was extracted with ethyl acetate (160 ml × 2), and the combined extracts were washed with water (20 ml × 2), dried with anhydrous Na_2SO_4, and finally evaporated. The residue was dissolved in 2 M aq. HCl, and extracted with isopropyl ether (120 ml × 2) (discarded). The aqueous phase was adjusted to pH 11–12 with 2 M aq. NaOH (21 ml), then extracted with ethyl acetate (160 ml × 2). The organic layer was washed with saturated brine (200 ml) and dried over anhydrous Na_2SO_4, and evaporated to leave

5 as a brown oil (26.6 g, 55.9 %). ^{1}H-NMR (500 MHz, $CDCl_3$) δ:7.29 (d, $J = 5.2$ Hz, 2H), 7.02–6.94 (m, 3H), 6.79 (s, 1H), 6.7 (d, $J = 7.5$ Hz, 1H), 5.94 (t, $J = 2.5$ Hz, 1H), 4.18 (t, $J = 2.5$ Hz, 3H), 3.82 (s, 3H), 2.96 (t, $J = 5.1$ Hz, 2H), 2.83 (t, $J = 2.5$ Hz, 2H), 2.70 (s, 4H), 2.42–2.37 (m, 2H), 1.86 (s, 4H); IR (KBr): 3,463.2, 2,920.8, 2,952.3, 1,608.3, 1,569.2, 1,455.2, 1,356.3, 907.8, 805.4, 790.7, 747.3, 647, 557.3 cm^{-1} (identical to the literature [4]).

6-Methoxy-1-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-3,4-dihydronaphthalen-2(1H)-one (**6**)

To the solution of **5** (25.2 g, 72.1 mmol) in CH_2Cl_2 (100 ml), a solution of m-CPBA (18.6 g, 108 mmol) in CH_2Cl_2 (186 ml) was added at 0–5 °C for 1 h and stirred for 1.5 h. The reaction was terminated with aqueous solution of Na_2SO_3 (5.12 g, 40.6 mmol), and basified by 2 M aq. NaOH (21 ml) to pH 10–11. The two layers were partitioned and the organic layer was washed with brine (50 ml × 2), dried over anhydrous Na_2SO_4 (12.1 g), and evaporated to afford **6** as a white power (24.4 g, 92.5 %). ^{1}H-NMR (500 MHz, $CDCl_3$) Naphthalene–Carbon: *abbrev*. n–C; 1-phenyl carbon: p–C. δ 7.66 (d, $J = 5.3$ Hz, 1H, n–C7–H), 6.93–6.96 (m, 3H, n–C5–H; p–C2–H; p–C5–H), 6.82 (d, $J = 5.1$ Hz, 2H, p–C3–H; p–C4–H), 6.75 (d, $J = 1.2$ Hz, 1H, n–C8–H), 4.67 (s, 1H, n–C1–H), 4.18 (t, $J = 2.5$ Hz, 2H, $OC\underline{H}_2CH_2$), 3.86 (s, 3H, $OC\underline{H}_3$), 3.02 (t, $J = 5.1$ Hz, 2H, $O{=}CC\underline{H}_2$), 2.79 (m, 7H, 3 × CH_2 of N and 1H of $O{=}CCH_2C\underline{H}_2$), 2.57 (dt, $J = 10.1/2.5$ Hz, 2H, 1H of $O{=}CCH_2C\underline{H}_2$), 1.89 (s, $NCH_2C\underline{H}_2C\underline{H}_2$, 4H); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 210.0, 159.6, 158.2, 136.7, 132.7, 130.2, 128.4, 128.2, 114.9, 112.9, 80.2, 66.3, 55.4, 54.4, 33.3, 27.7, 23.5; IR (KBr): 3,035.6, 2,929.4, 1,691.3, 1,605.4, 1,511.5, 1,462.4, 1,421.6, 1,282.6, 1,245.8, 1,172.3, 1,119.1, 829.0 cm^{-1}.

6-Methoxy-2-phenyl-1-{4-[2-(pyrrolin-1-yl)ethoxy)]phenyl}-3,4-dihydronaphthalene hydrochloride (**2**, nafoxidene hydrochloride)

To a suspension of cerium chloride (12.3 g, 33.0 mmol) in THF (80 ml) was added a solution of compound **6** (11.0 g, 30.1 mmol) in THF (45 ml) at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred for 1.5 h at that temperature, and further cooled down to −10 to −5 °C. A solution of phenyl magnesium bromide, freshly prepared from bromobenzene (5.21 g, 33.2 mmol) and magnesium turnings (0.820 g, 33.7 mmol) in THF (40 ml), was added. The mixture was stirred for 2 h and quenched with aqueous aq. NH_4Cl (80 ml). Cerium chloride was discarded by suction filtration and the filtrate was extracted with CH_2Cl_2 (120 ml × 2), and the combined organic layers were washed with brine. The extract was evaporated to leave a yellowish oil, which was treated with 2 M aq. HCl to yield **2** HCl as white crystals (10.5 g, 82.0 %). Mp: 164–167 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.16–7.12 (t, $J = 7.4$ Hz, 2H), 7.09–7.03 (m, 3H), 6.99 (d, $J = 8.5$ Hz, 2H), 6.80 (m, 4H), 6.63 (dd, $J = 8.6/2.7$ Hz, 1H), 4.10 (t, $J = 6.0$ Hz, 2H), 3.82 (s, 3H), 2.99–2.95 (m, 2H), 2.92 (t, $J = 6.0$ Hz, 2H), 2.81 (dd, $J = 9.2/6.3$ Hz, 2H), 2.66 (b.s, 4H), 1.87–1.82 (m, 4H) (identical to the literature [4]).

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