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An efficient synthesis of Ecopladib

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This paper is dedicated with respect to the memory of Hassan Elokdah and Ronald L. Magolda.

ABSTRACT

An efficient synthesis of Ecopladib, an indole inhibitor of cytosolic phospholipase $A_2\alpha$, is described. A new reaction involving indole C3 reductive alkylation using an acetal in the absence of water and a novel transformation of the C2 methyl to an aldehyde via dimethyl sulfoxide-mediated oxygen-transfer reaction are used in the present synthesis, which dramatically increased the synthetic efficiency.

1. Introduction

Cytosolic phospholipase $A_2\alpha$ ($cPLA_2\alpha$) catalyzes the selective release of arachidonic acid to initiate the production of leukotrienes, prostaglandins, thromboxanes and the downstream generation of platelet-activating factor (PAF).[1] As part of a program at Wyeth directed toward the development of orally active small molecule inhibitors for this enzyme, Ecopladib **1** (Fig. 1) was advanced to clinical trials.[2] We report herein an efficient synthesis of **1** developed to support the preclinical studies.

Ecopladib **1** is a tetrasubstituted indole derivative. The indole scaffold is common for known $cPLA_2\alpha$ inhibitors, such as compounds **2a–c**,[3] and offers a pharmacophore with favorable properties and viability for derivatization.

2. Results and discussion

The proposed synthesis of **1** consisted of three stepwise stages (Scheme 1):[2] the C3 alkylation of the commercially available 5-chloro-2-methylindole **5** to form **4**, the transformation of the 2-methyl group to the corresponding aldehyde **3**, and the final stage including C2 homologation of **3** to the corresponding C2-ethylamine for the final derivatization to **1**. Installation of the *N*-benzhydryl group would be optional at various points in the synthesis. The exploration and development of new reaction protocols were emphasized in this synthesis.

Among available literature protocols for indole C3 alkylations, reductive alkylation appeared the most attractive. For this application, preparation of the alkylation precursor **7** was required (Scheme 2). Initially, a common literature protocol was utilized to carry out the O-alkylation of **6** using K_2CO_3 in DMF near reflux.[2b] Under these conditions, the reaction required 2–3 days at one mole scale, and a large excess of K_2CO_3 was added in portions to drive the reaction to completion. Alternative procedures were investigated to improve the reaction. The best results were obtained using Cs_2CO_3 in DMSO at 95 °C for 5 h, furnishing **7** in 90% yield.

The procedures reported for indole C3 reductive alkylation are based on nucleophilic addition of the indole C3 carbon to an aldehyde in the presence of TFA and triethylsilane (TES).[4] TFA is used to activate the carbonyl through protonation for the formation of intermediate **8c** (Scheme 3). Elimination of water from **8c** under acidic conditions sets the stage for ionic hydrogenation[5] to generate the desired product **8** (Schemes 2 and 3).

2.1. The one-pot acetal–indole reductive alkylation

For our synthesis, it would be advantageous to use acetal **7** directly for the alkylation. This objective should be achieved by addition of water to the reaction medium to generate **7c** in situ via acid hydrolysis of **7**. Indeed, treatment of **7** and indole **5** with TFA/

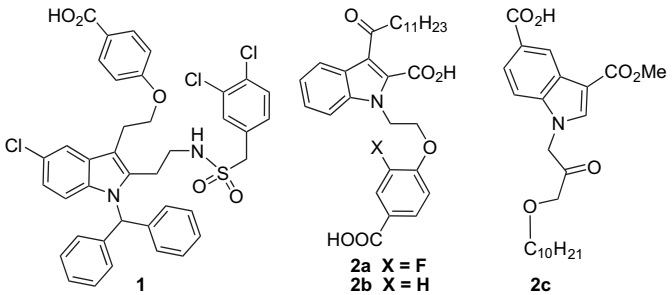

Figure 1. $cPLA_2\alpha$ indole inhibitors.

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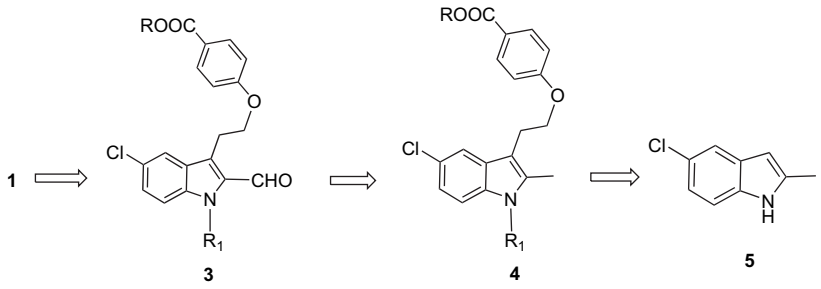
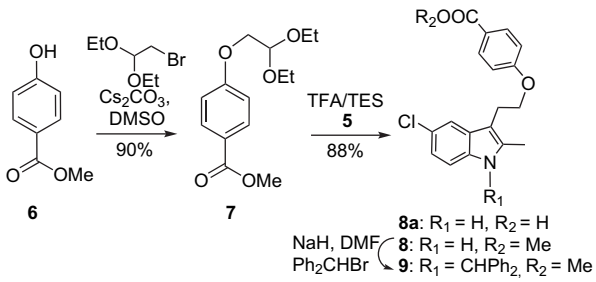
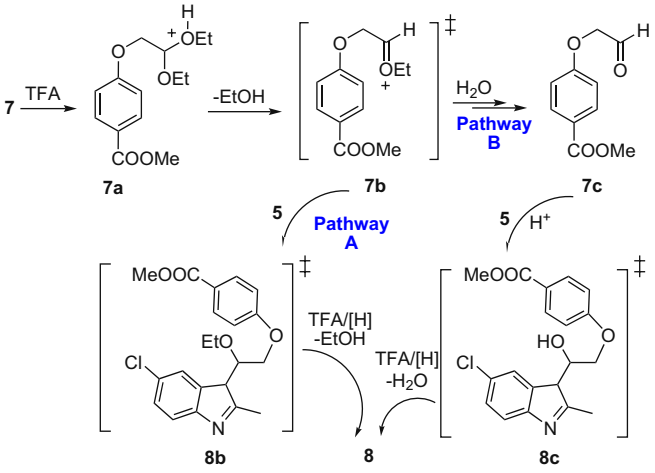


Scheme 1. Retrosynthetic analysis.



Scheme 2. Synthesis of compound **9**.



Scheme 3. Active intermediate **7b** in the indole C3 alkylation.

TES/water resulted in the desired product **8** in good yield, which also suggests that aldehyde **7c** is generated under the aqueous acidic conditions[6] during the course of the reaction.

However, benzoic acid byproduct **8a** (Scheme 2) was detected following the alkylation, contaminating the desired product **8**. The byproduct **8a** could be generated from hydrolysis of the desired methyl ester **8** under the reaction conditions or from the hydrolysis of **7**, with the resulting acid carried on to **8a** in the C3 alkylation. Nonetheless, this outcome led us to question the function of water in the reaction. Based on the proposed reaction mechanism (Scheme 3), the presence of water might not be necessary if indole **5** could capture the active intermediate **7b** (pathway A), which has been widely accepted as the first step of acetal hydrolysis under acidic conditions.[7] In this case, the reductive alkylation would then be accomplished without going through the generation of aldehyde **7c** (pathway B), a step that requires the presence of water.

To our delight, the test reaction of indole **5** with **7** worked perfectly without water to afford **8** in high yield, while the byproduct **8a** was not detected. The reaction outcome supports our hypothesis that the C3 alkylation could happen on an earlier active intermediate, the *O*-alkyl oxonium **7b** and indicated that there are two different pathways in the C3 alkylation between the acetal and aldehyde. To the best of our knowledge, this is the first example of an acetal being directly employed in an indole C3 reductive alkylation under anhydrous conditions and the absence of water may render acetals potentially more useful. We are currently investigating its synthetic implications.

The test run protocol followed a procedure developed for the indole/aldehyde conditions with a typical concentration of 0.1 M of **5** in dichloromethane and an average yield of 60%.[4] The low concentration limited the synthetic efficiency of our preparation. Thus, modifying the protocol to increase throughput was crucial. It was found that the reaction gave better yields at higher concentrations. The optimal conditions involved conducting the reaction at room temperature with a concentration of 1 mol of **5** in 1.3 L of dichloromethane, which afforded **8** in 88% yield. This was a 10-fold increase over the indole concentration reported in the literature[4] and seemed to be the limit—a 15-fold concentration resulted in a reduced yield (71%).

Since high concentrations and large scale often bring unpredictable events to reactions, the reaction was further tested on one mole scale in a 5 L flask (165.6 g of **5**, 0.96 L of DCM). After the addition of TFA, a temperature increase from 25 to 29 °C was observed. In our previous smaller scale reactions, no exotherm had been detected. In addition, in contrast to the earlier studies under dilute conditions, a white solid slowly precipitated out of the reaction medium. The white solid, upon analysis, turned out to be the desired product **8** with 99.2% purity. Therefore, isolation and purification of **8** became straightforward. A simple filtration of the reaction mixture afforded **8** as a white powder in 61% yield for the first crop. The rest of the product in the filtrate was easily recovered through recrystallization (CH_2Cl_2/CH_3OH) to get an additional 27% yield. The ease of isolation, high yield, and the superior quality of the product rendered this procedure as the best protocol for the indole C3 reductive alkylation.

Several unique features of this acetal–indole reductive alkylation are worth further discussion. First, this is a multi-step cascade reaction initiated by a Friedel–Crafts alkylation[8] on an indole aromatic ring via an active oxonium intermediate generated by reaction of the acetal and TFA under anhydrous conditions. This is the first example successfully employing an acetal for the regio-selective indole C3 alkylation. Second, the Friedel–Crafts alkylation did not stop after the alkylation, rather proceeded to subsequent in situ reduction of the resulting 3-alkoxymethylindole intermediate (**8b**) through ionic hydrogenation.[9] Therefore, the novelty of the water-free reductive alkylation conditions lies in the ability to conduct both the Friedel–Crafts reaction and subsequent Si–H reduction in *one-pot* simultaneously.

Dialkylation[10] and reduction of indole to indoline[11] are possible byproducts in indole C3 alkylations. Under the reaction conditions here, byproducts such as **8d** and **8e** (Fig. 2) were not detected (by HPLC/MS).

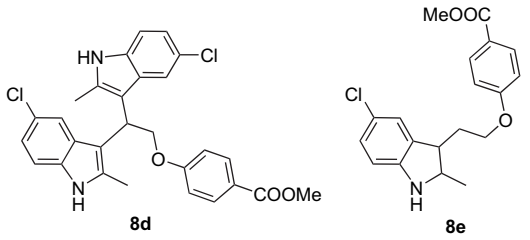
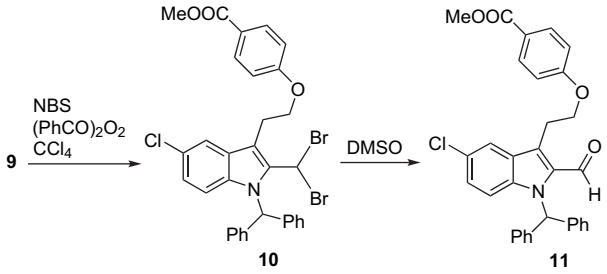


Figure 2. Possible byproducts.

The indole N-alkylation of **8** was carried out using NaH in DMF and benzhydryl bromide (Scheme 2). After completion, the reaction mixture was slowly poured into water, and desired product **9** precipitated and was collected by filtration and used directly in the subsequent bromination step.

Early attempts to prepare the monobrominated intermediate for homologation at C2 failed due to the heavy contamination from side products resulting from competitive dibromination. The manipulation of the C2 substituent therefore commenced with the dibromination of **9**, which was conducted using NBS (2 equiv) in the presence of a radical initiator (Scheme 4). After completion, the reaction mixture was filtered to remove the succinimide. The filtrate was concentrated to afford **10** as a thick oil.



Scheme 4. Synthesis of compound **11**.

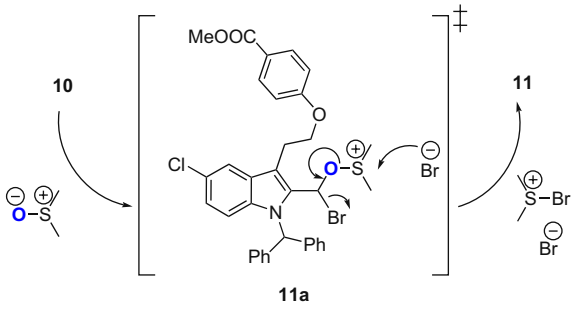


Figure 3. Oxygen-transfer from DMSO.

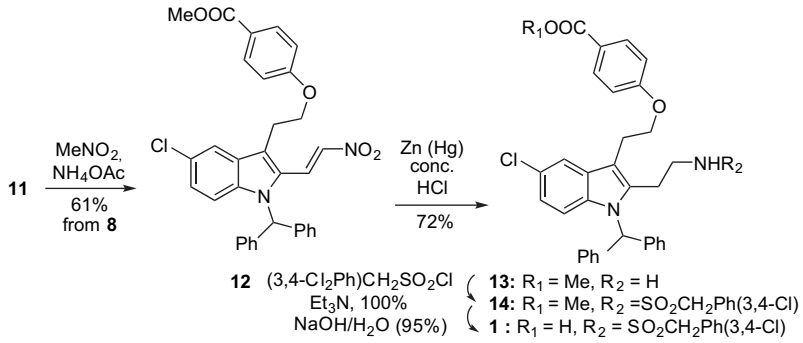
2.2. Formation of aldehyde via DMSO-mediated oxygen-transfer

Conversion of *gem*-dihalo compound **10** to aldehyde **11** was carried out using the DMSO-mediated oxygen-transfer protocol developed in our laboratory.[12] Thus, DMSO was poured into the concentrated filtrate with stirring, and the resulting solution was poured into water. The solid that formed was filtered to afford the desired aldehyde **11** (Scheme 4). This reaction is not only straightforward (incorporating a reaction into a work-up operation), but also trims one step from the original synthetic sequence. Prior to this discovery, the aldehyde **11** had been obtained[2a] via Ag^{+} mediated hydrolysis of the *gem*-dibromo species **10**.[13]

Sulfoxides have the ability to either accept or donate oxygen in organic reactions, but the majority of synthetic applications are associated with its oxygen-donating property, although exceptions exist.[14] One widely used reaction is the conversion of structurally diverse alcohols into their corresponding carbonyl compounds by DMSO in the presence of activating agents. In these reactions, the original oxygen atom in DMSO is not directly donated to form the carbonyl oxygen during the oxidative process, but rather is donated to the activating agents.[15] What we have described here is a unique example in which the sulfoxide serves as a direct oxygen donor in the absence of activating agents. It should also be pointed out that unlike the Kornblum reaction,[16] this is not an oxidative process: the oxidation states of both starting material and product remain the same. Therefore, this oxygen-transfer from sulfoxide occurs in a non-oxidative reaction.

Mechanistically, the alkoxysulfonium species **11a**[17] (Fig. 3) appears to be the active intermediate, which undergoes a 1,2-elimination to give the desired aldehyde **11**. However, the alkoxysulfonium **11a** was not detected when the reaction was monitored by ^{1}H NMR. This observation suggests that the displacement of the first bromine atom is slow, and the 1,2-elimination occurs rapidly following the first displacement.

Condensation of the aldehyde **11** and nitromethane in the presence of ammonium acetate provided the desired nitroethene **12** as a pale yellow solid (Scheme 5, 61% overall yield from **8**). The choices for reduction of **12** to the ethylamine species **13** are very limited due to the presence of the C5-chlorine and the methyl ester. Hydride reducing agents such as $LiAlH_4$ would reduce the methyl ester, and hydrogenolysis would generate impurities from the reduction of the aromatic chlorine, or deprotection of the *N*-benzhydryl group. It appears that the Zn(Hg)/HCl reduction[18] of nitro olefin **12** is the only viable option for the preparation of **13**. Indeed, reduction of **12** by Zn/HCl afforded the desired ethylamine **13** as a white powder.



Scheme 5. Synthesis of Ecopladib (**1**).

The remaining synthesis was accomplished in two steps. Reaction of the amine **13** with the corresponding sulfonyl chloride furnished the desired sulfonamide **14**, and the methyl ester was hydrolyzed under standard saponification conditions to afford **1** as a white powder.

3. Conclusions

In conclusion, Ecopladib was synthesized in a three-stage, nine-step process in 32% overall yield from indole **5**. This process is characterized by a novel C3 indole alkylation using acetal in the absence of water and a unique oxygen-transfer reaction between DMSO and a *gem*-dibromomethyl group for the transformation of a methyl group to the corresponding aldehyde.

4. Experimental section

4.1. General

All reagents and solvents were purchased from commercial sources and used as received. All products were characterized by ^{1}H and ^{13}C NMR, and MS if ionization was detectable. Mass spectrometers used were the Micromass LCT (ESI or APCI) with an Agilent 1100 LC Pump (for LCMS). Gilson reversed-phase preparatory HPLC (pump models of 331 and 332 and UV detector wave length: 254 nm) was used for separation with a Phenomenex Gemini column (5u C18 110A, 150×30 mm) gradient solvent program (solvent A: H_2O, solvent B: acetonitrile) from 10 to 50% solvent B for 10 min at 40 mL/min flow rate. NMR experiments were performed on a Bruker AVANCE 400 MHz spectrometer equipped with a 5 mm broadband probe. The following abbreviations are used to designate the multiplicity: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. ^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million with the solvent resonance as the internal standard ($CDCl_3$: δ 77.0 ppm).

4.2. Methyl 4-(2,2-diethoxyethoxy)benzoate (7)

A three-necked 5 L r.b. flask with an overhead mechanical stirrer was charged with methyl 4-hydroxybenzoate (**6**) (169.10 g, 1.10 mol) and DMSO (2 L). After flushing with nitrogen for 30 min, cesium carbonate (550.0 g, 1.69 mol) and bromoacetaldehyde diethylacetal (222.90 g, 1.10 mol) were added. The resulting suspension was heated at 95 °C for 12 h under nitrogen. After completion of the reaction, the reaction mixture was poured into cold water (3 L) and extracted with ethyl acetate (3 L×2). The organic layers were combined and dried over $MgSO_4$. Removal of the solvent yielded the desired product **7** as a colorless oil (268.3 g, 90% yield), which was directly used without further purification. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 1.13–1.29 (m, 6H), 3.54–3.69 (m, 2H), 3.68–3.81 (m, 2H), 3.85 (s, 3H), 4.02 (d, *J*=5.3 Hz, 2H), 4.81 (t, *J*=5.2 Hz, 1H), 6.85–7.08 (m, 2H), 7.87–8.08 (m, 2H).

4.3. Methyl 4-(2-(5-chloro-2-methyl-1*H*-indol-3-yl)ethoxy) benzoate (8)

A three-necked 3 L r.b. flask was charged with the methyl 4-(2,2-diethoxyethoxy)benzoate (**7**) (205.50 g, 0.758 mol), DCM (0.940 L), and 5-chloro-2-methylindole (**5**) (122.57 g, 0.731 mol). To this solution was added TFA (247.17 g, 2.168 mol), followed by triethylsilane (250.42 g, 2.32 mol). The solution turned red, and the reaction temperature rose from 24 to 29 °C within 1 h. Precipitation of a white solid started after 3 h and the reaction mixture was stirred at room temperature for an additional 24–48 h until TLC showed completion of the reaction. The reaction mixture was filtered. The filter cake was washed with MeOH (300 mL×2) and hexane (300 mL×2), and dried to give 153.56 g of white solid. The filtrate was concentrated to 150 mL, and MeOH was added until no further precipitation was observed. White solid (62.70 g) was obtained after filtration as the second crop with equal quality. Further recovery of the desired product from the mother liquor by repeating the same procedure described above afforded 4.14 g of desired product. The combined yield of **8** was 220.40 g (88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 3.15 (t, *J*=7.0 Hz, 2H), 3.87 (s, 3H), 4.15 (t, *J*=7.0 Hz, 2H), 6.81–6.91 (m, 2H), 7.07 (dd, *J*=8.6, 2.0 Hz, 1H), 7.18 (d, *J*=8.3 Hz, 1H), 7.50 (d, *J*=2.0 Hz, 1H), 7.86 (s, 1H), 7.91–8.03 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 11.9, 24.3, 51.9, 68.0, 107.6, 111.3, 114.0, 117.4, 121.3, 122.4, 125.1, 129.8, 131.6, 133.5, 133.9, 162.6, 167.0. HRMS (ES-MS) [$(M+H)^+$]: for $C_{19}H_{18}ClNO_3$ 344.1048. Found 344.1045.

4.4. Methyl 4-(2-(1-benzhydryl-5-chloro-2-methyl-1*H*-indol-3-yl)ethoxy)benzoate (9)

To a 2 L three-necked r.b. flask containing a solution of methyl 4-(2-(5-chloro-2-methyl-1*H*-indol-3-yl)ethoxy)benzoate (**8**) (68.76 g, 0.2 mol) in DMF (0.3 L) was added sodium hydride suspension (9.90 g, 0.246 mol) slowly in portions. The temperature of the resulting mixture rose to 40 °C after completion of the addition. The mixture was stirred for an additional 30 min. Bromodiphenylmethane (62.36 g, 0.239 mol) in 100 mL of DMF was added slowly, and the reaction temperature was kept below 60 °C by adjusting the rate of addition. The reaction mixture was slowly poured into 1 L of stirred ice-water. The crude **9** precipitated as a pale yellow solid and was used directly after filtration. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29 (s, 3H), 3.19 (t, *J*=7.1 Hz, 2H), 3.88 (s, 3H), 4.17 (t, *J*=7.1 Hz, 2H), 6.54 (d, *J*=8.8 Hz, 1H), 6.81 (dd, *J*=8.8, 2.0 Hz, 1H), 6.83–6.90 (m, 3H), 7.03–7.13 (m, 4H), 7.28–7.34 (m, 6H), 7.51 (d, *J*=2.0 Hz, 1H), 7.89–8.02 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 11.6, 24.7, 51.8, 62.7, 68.0, 107.9, 112.7, 114.1, 117.2, 120.9, 122.5, 124.9, 127.9, 128.2, 128.7, 129.6, 131.6, 134.8, 136.4, 139.0, 162.7, 166.9. HRMS (ES-MS) [$(M+H)^+$]: for $C_{32}H_{28}ClNO_3$ 510.1830. Found 510.1824. Anal. Calcd for $C_{32}H_{28}ClNO_3$: C, 75.36; H, 5.53; N, 2.75. Found: C, 75.69; H, 5.26; N, 2.63.

4.5. Methyl 4-(2-(1-benzhydryl-5-chloro-2-formyl-1*H*-indol-3-yl)ethoxy)benzoate (11)

To a solution of methyl 4-(2-(1-benzhydryl-5-chloro-2-methyl-1*H*-indol-3-yl)ethoxy)benzoate (**9**) (114.84 g, 225 mmol) in CCl_4 (900 mL) were added NBS (80.2 g, 450 mmol) and benzoylperoxide (0.050 g). The resulting mixture was heated to reflux for 2.5 h. The mixture was cooled to room temperature and filtered to remove the succinimide. The filtrate was concentrated, and the crude product **10** (300.0 g) was obtained as a thick oil, which was dissolved in DMSO (600 mL). The resulting solution was stirred at room temperature for 30 min. An indication of the conversion of the dibromide to above aldehyde is the smell of dimethyl sulfide. After completion of the reaction, the reaction mixture was poured into water (4 L). The resulting suspension was filtered. The filter cake was washed with water. The product **11** (220.0 g) was used directly for the next step. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.58 (t, *J*=6.6 Hz, 2H), 3.90 (s, 3H), 4.19–4.50 (m, 2H), 6.69 (d, *J*=9.2 Hz, 1H), 6.86 (d, *J*=8.9 Hz, 2H), 6.97–7.51 (m, 10H), 7.76 (d, *J*=2.0 Hz, 1H), 7.97 (d, *J*=8.9 Hz, 2H), 8.23 (s, 1H), 10.22 (s, 1H). HRMS (ES-MS) [$(M+H)^+$]: for $C_{32}H_{26}ClNO_4$ 524.1550. Found 524.1553.

4.6. (*E*)-Methyl 4-(2-(1-benzhydryl-5-chloro-2-(2-nitrovinyl)-1*H*-indol-3-yl)ethoxy)benzoate (12)

The aldehyde **11** from the previous step (145 g, 0. 217 mol), NH_4OAc (170.6 g, 2.17 mol), and $MeNO_2$ (1.8 L) were heated to

reflux for 4 h. After completion of the reaction, the solvent was removed by evaporation under reduced pressure. The residue was dissolved in 200 mL of DMF, and the resulting solution was poured into water. The resulting suspension was filtered. The yellow filter cake was washed with water and dried (187 g, crude). Recrystallization of the crude product from EtOAc yielded the desired product with 94% purity, which was further purified by column chromatography (eluting with 1–10% DCM/hexane) to afford pure product (75.05 g, 61% for the last four steps) as a pale yellow solid. Mp 74–75 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.37 (t, J=6.1 Hz, 2H), 3.87 (m, 3H), 4.33 (t, J=6.1 Hz, 2H), 6.82 (m, 3H), 7.06 (m, 6H), 7.34 (m, 6H), 7.57 (d, J=13.6 Hz, 1H), 7.66 (d, J=2.0 Hz, 1H), 7.95 (m, 2H), 8.02 (d, J=13.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 25.5, 51.9, 63.8, 67.6, 113.6, 114.0, 118.8, 119.3, 123.0, 125.6, 126.6, 127.5, 128.0, 128.5, 129.0, 129.0, 130.3, 131.7, 137.1, 137.6, 138.0, 162.1, 166.7. HRMS (ES-MS) [(M+H)$^+$]: for $C_{33}H_{27}ClN_2O_5$ 567.1681. Found 567.1680.

4.7. Methyl 4-(2-(2-(2-aminoethyl)-1-benzhydryl-5-chloro-1*H*-indol-3-yl)ethoxy)benzoate (13)

A three-necked 5 L r.b. flask containing a solution of the nitro olefin **12** (35.0 g, 61.7 mmol) in THF (1450 mL) was charged with concentrated HCl (175 mL) and the freshly prepared Zn(Hg) amalgam[11] (186 g, 2.7 mol). Hydrogen release occurred immediately. The reaction temperature rose from 20 to 52 °C. Color of the reaction mixture turned from yellow to pale green once the reaction was complete (1–3 h, monitored by TLC). The reaction mixture was poured into a mixture containing EtOAc (1.45 L) and concentrated NH_4OH (0.3 L) with efficient agitation for 20 min. The organic layer was separated, washed with aq NH_4OH (200 mL), satd $NaHCO_3$ (500 mL), water (2000 mL×4), and brine (500 mL), and dried over $MgSO_4$. Evaporation of the solvent afforded 34.5 g of crude product. Purification by flash column chromatography (eluting with 0–5% MeOH/DCM) afforded the pure product (24.03 g, 72%) as a pale yellow solid. Mp 121–122 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.81 (t, J=7.3 Hz, 2H), 2.98 (t, J=7.4 Hz, 2H), 3.25 (t, J=7.1 Hz, 2H), 3.88 (s, 3H), 4.22 (t, J=7.0 Hz, 2H), 6.51 (d, J=9.1 Hz, 1H), 6.8 (dd, J=8.9, 2.1 Hz, 1H), 6.9 (d, J=9.1 Hz, 2H), 6.9 (s, 1H), 7.03–7.18 (m, 4H), 7.28–7.38 (m, 6H), 7.54 (d, J=1.9 Hz, 1H), 7.96 (d, J=9.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 24.9, 29.6, 42.3, 51.9, 62.5, 68.1, 109.2, 113.6, 114.1, 117.6, 121.3, 122.6, 125.1, 127.9, 128.1, 128.7, 129.5, 131.6, 134.8, 137.8, 139.0, 162.6, 166.9. HRMS (ES-MS) [(M+H)$^+$]: for $C_{33}H_{31}ClN_2O_3$ 539.2096. Found 539.2096.

4.8. Methyl 4-(2-(1-benzhydryl-5-chloro-2-(2-((3,4-dichlorophenyl)methylsulfonamido)ethyl)-1*H*-indol-3-yl)ethoxy)benzoate (14)

To a solution of the amine **13** from the previous step (5.39 g, 10 mmol) in CH_2Cl_2 (100 mL) were added (3,4-dichlorophenyl)methanesulfonyl chloride (3.1 g, 12 mmol) and triethylamine (2.024 g, 20 mmol). The resulting suspension was stirred until the amine was consumed. The mixture was washed with H_2O (80 mL×2) and brine (50 mL×2), dried, and concentrated to afford the product (7.62 g, 100% yield) as white solid, which was directly used in the next step. Mp 94–95 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.89 (m, 2H), 3.09 (t, 2H), 3.19 (t, J=6.6 Hz, 2H), 3.86 (s, 3H), 3.92 (s, 2H), 4.22 (t, J=6.6 Hz, 2H), 4.32 (t, J=6.2 Hz, 1H), 6.54 (d, J=9.1 Hz, 1H), 6.82 (m, 3H), 6.90 (s, 1H), 6.98 (dd, J=8.2, 2.2 Hz, 1H), 7.07 (dd, J=6.6, 2.8 Hz, 4H), 7.30 (m, 8H), 7.54 (d, J=2.1 Hz, 1H), 7.94 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 24.8, 27.5, 43.0, 51.9, 57.6, 60.4, 62.5, 68.0, 110.3, 113.7, 114.1, 117.8, 121.9, 122.7, 125.3, 128.1, 128.9, 129.2, 129.2, 129.7, 130.8, 131.6, 132.3, 132.9, 133.3, 135.1, 135.6, 138.9, 162.5, 166.8.

4.9. Ecopladib (1)

To a solution of the methyl ester **13** (7.62 g, 10 mmol) in inhibitor free THF (150 mL) were added 2 N aq NaOH (15.0 mL, 30.0 mmol) and MeOH (100 mL). The mixture was heated at 55 °C until the ester starting material was consumed. THF was removed and the aqueous residue was acidified to pH 1 using 2 N HCl. The desired product **1** precipitated as a white solid and was collected via filtration (7.10 g, 95%). Mp 124–125 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.97–3.06 (m, 2H), 3.06–3.14 (m, 2H), 3.17 (t, J=6.7 Hz, 2H), 4.22 (t, J=6.7 Hz, 2H), 4.35 (s, 2H), 6.46 (d, J=8.8 Hz, 1H), 6.80 (dd, J=8.8, 2.0 Hz, 1H), 6.91–7.00 (m, 2H), 7.04–7.14 (m, 5H), 7.26 (dd, J=8.3, 2.0 Hz, 1H), 7.33–7.40 (m, 6H), 7.50 (t, 1H), 7.53 (d, J=8.3 Hz, 1H), 7.56 (d, J=2.0 Hz, 1H), 7.67 (d, J=2.3 Hz, 1H), 7.79–7.89 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 23.8, 26.0, 42.6, 55.4, 61.4, 67.7, 109.1, 109.1, 113.1, 113.9, 122.6, 123.4, 127.6, 128.5, 129.2, 130.1, 130.6, 130.7, 130.7, 131.1, 131.2, 132.3, 134.1, 137.3, 138.8, 161.9, 166.7. HRMS (ES-MS) [(M+H)$^+$]: for $C_{39}H_{33}Cl_3N_2O_5S$ 747.1249. Found 747.1241. Anal. Calcd for $C_{39}H_{33}Cl_3N_2O_5S$: C, 62.61; H, 4.45; N, 3.74. Found: C, 62.34; H, 4.28; N, 3.60.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.06.045.

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