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Accidental discovery of a 'longer-range' vinylogous Pummerer-type lactonization: formation of sulindac sulfide lactone from sulindac

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ABSTRACT

Unexpected formation of sulindac sulfide lactone occurred when sulindac was treated with oxalyl chloride and triethylamine. Structurally analogous sulindac sulfide and indomethacin did not undergo such lactonization under similar reaction conditions. We believe that the sulfoxide function in sulindac plays a pivotal role possibly via a 'longer-range' vinylogous Pummerer-type reaction as a driving force for the observed lactonization. The structure of the lactone was confirmed by single crystal X-ray analysis.

As an extension of our mission to discover new gastric-sparing nitric oxide-releasing non-steroidal anti-inflammatory drugs (NO-NSAIDs) as potentially 'safe NSAIDs',[1,2] we wanted to synthesize and evaluate the NO-sulindac (**3a**) from sulindac (**1**), which is a widely used non-steroidal anti-inflammatory drug for acute or long term treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute painful shoulder, and acute gouty arthritis.[3] When we attempted to synthesize NO-sulindac (**3a**) from sulindac (**1**) by an established method as shown in Scheme 1 for the synthesis of such NO-NSAIDs,[1] the desired ester compound **3a** was not obtained. However, to our surprise, the major product isolated from the above reaction was found to be the sulindac sulfide lactone (**4**) on the basis of its analytical and spectroscopic data. To rule out any ambiguity associated with the structural assignment, we have further confirmed the structure of lactone **4** by single crystal X-ray analysis (Fig. 1).

Obviously, the reduction of sulindac sulfoxide to sulindac sulfide along with concomitant lactonization has occurred in the above reaction. Surprised by the non-participation of 2-((2-hydroxyethyl)disulfanyl)ethyl nitrate (**L1**) in the above reaction, we have repeated the above reaction twice with slight modifications as stated below to verify whether the formation of anticipated sulindac acid chloride (**2**) has really occurred: using ethanol in place of 2-((2-hydroxyethyl)disulfanyl)ethyl nitrate (**L1**) in the first reaction and in the absence of any alcoholic reactant in the second reaction. In both the experiments, lactone **4** was obtained as the major product and the expected ethyl ester of sulindac (**3b**) was not formed in the first reaction. These results confirmed our doubt that the formation of sulindac acid chloride (**2**) is indeed not occurring under the reaction conditions.

Intrigued by the above unique transformation, we have subjected structurally analogous compounds, such as sulindac sulfide (**5**) and indomethacin (**6**) to similar reaction conditions, but this time in the presence of ethanol as alcoholic reactant and observed that the respective sulindac sulfide lactone (**4**) and indomethacin lactone (**9**) were not formed (Schemes 2 and 3, respectively).

However, the corresponding sulindac sulfide ethyl ester (**10**) and indomethacin ethyl ester (**11**) were obtained as major products from the above reactions thereby confirming the formation of acid chlorides (**7**) and (**8**), respectively, in these reactions (Schemes 2 and 3, respectively).

The above results clearly demonstrate that the sulfoxide present in sulindac (**1**) plays a pivotal role in this unique transformation probably via a plausible mechanism, as depicted in Scheme 4, involving a 'longer-range' vinylogous Pummerer-type thionium ion-assisted lactonization.[4] Thus, in the initial step, the oxalyl chloride is expected to preferentially acylate the sulfoxide oxygen in sulindac to give an acyloxysulfonium salt (**A**). In the second step, the base is expected to abstract an acidic methylene proton, which is connected to the sulfonium group via a conjugated chain of 'nine-carbon atoms' (marked in blue) consisting of a phenyl ring and two indene double bonds, to yield a carbanion, which passes through the said conjugated nine carbon atom chain to assist the cleavage of sulfur-oxygen bond to yield a thionium ion (**B**). In the third step, the thionium ion (**B**) pulls the electrons through the conjugated chain of 'seven carbon atoms' (marked in blue) consisting

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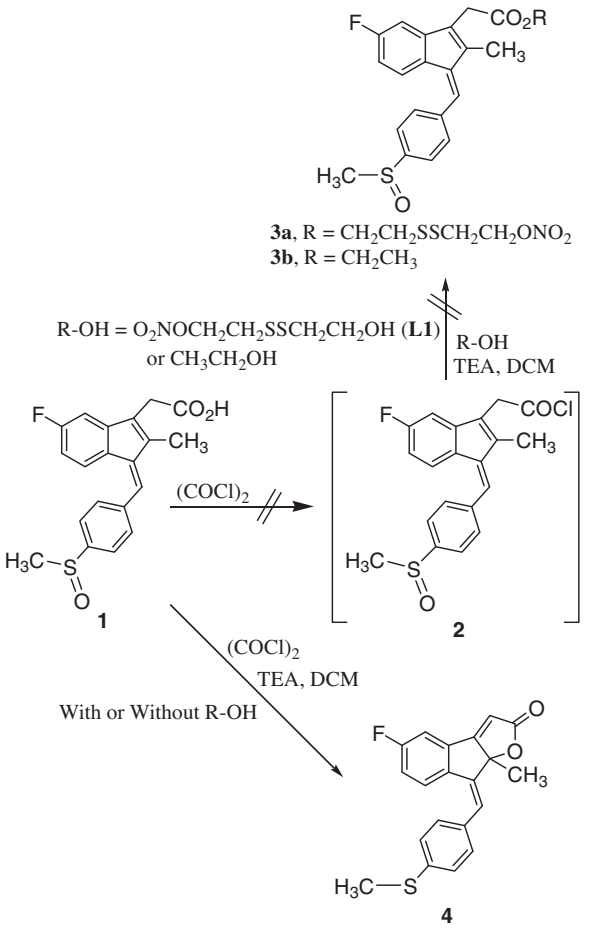


Scheme 1. Formation of sulindac sulfide lactone (**4**) from sulindac (**1**).

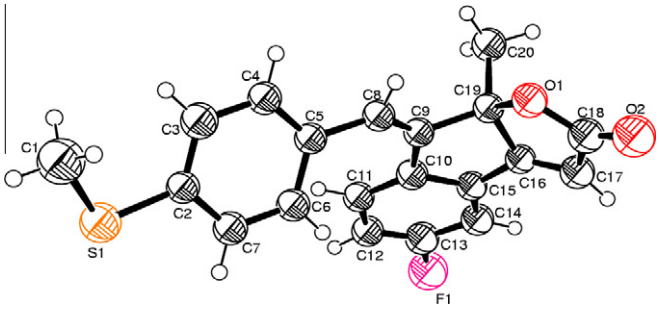
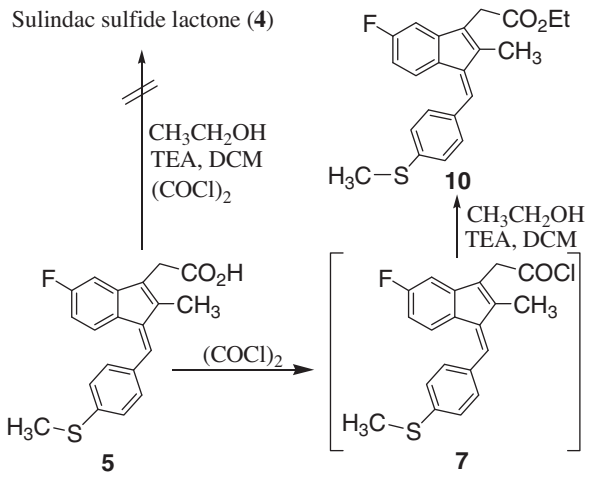
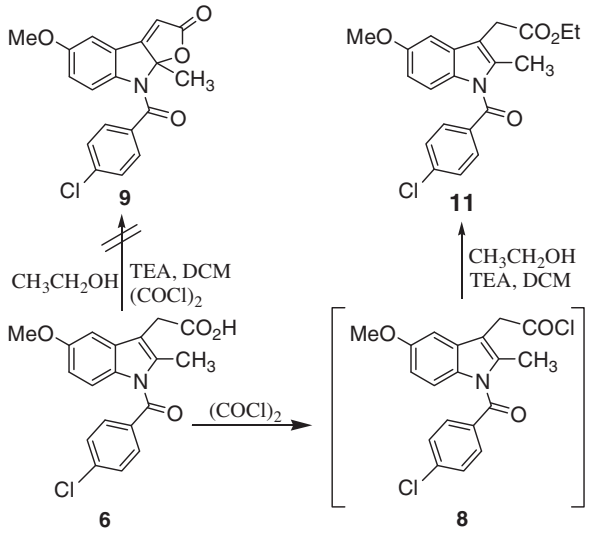


Figure 1. X-ray structure of sulindac sulfide lactone (**4**).



Scheme 2. Attempted synthesis of sulindac sulfide lactone (**4**) from sulindac sulfide (**5**) and formation of sulindac sulfide ethyl ester (**10**).



Scheme 3. Attempted synthesis of indomethacin lactone (**9**) from indomethacin (**6**) and formation of indomethacin ethyl ester (**11**).

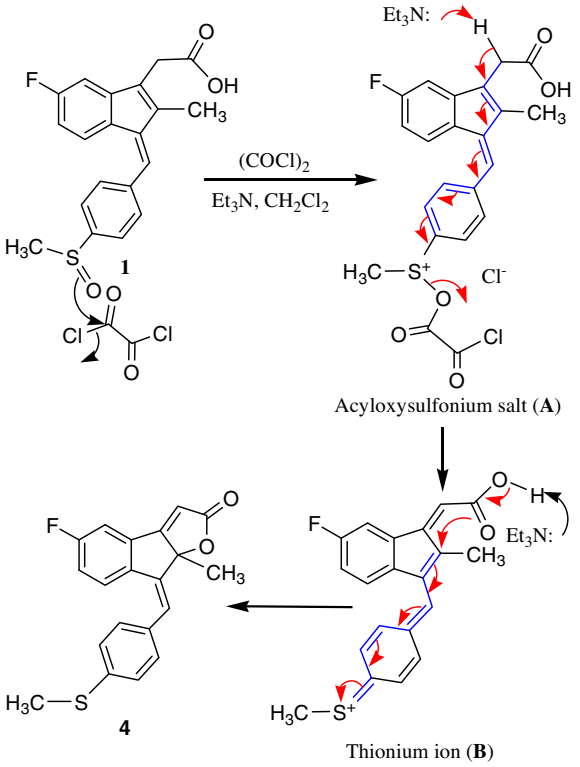
of an indene double bond and the sulfonium quinone methide probably via a 'longer-range' vinylogous Pummerer-type lactonization of carboxylic acid and gets reduced to sulfide thereby yielding the sulindac sulfide lactone (**4**).

Literature survey on Pummerer-type reactions[5] revealed the following known examples involving such extended or long range (i.e., consisting of a conjugated chain of 3–5 atoms) vinylogous Pummerer-type reactions (Scheme 5): (1) Feldman et al. reported the synthesis of spirocyclic indole compounds (**15**) from indole-2-sulfoxides and proposed the intermediate thionium ion (**14**), which undergoes vinylogous extended Pummerer-type reaction;[6] (2) Zhou and co-workers synthesized 5-phenylthiovinyl-1,3-oxazoles (**17**) via the application of 'long-range' Pummerer-type cyclization of thionium ion intermediate (**16**);[7] (3) Wang and co-workers reported the synthesis of unsaturated δ-lactones (**19**) via the application of vinylogous Pummerer-type lactonization of the thionium ion intermediate (**18**).[8]

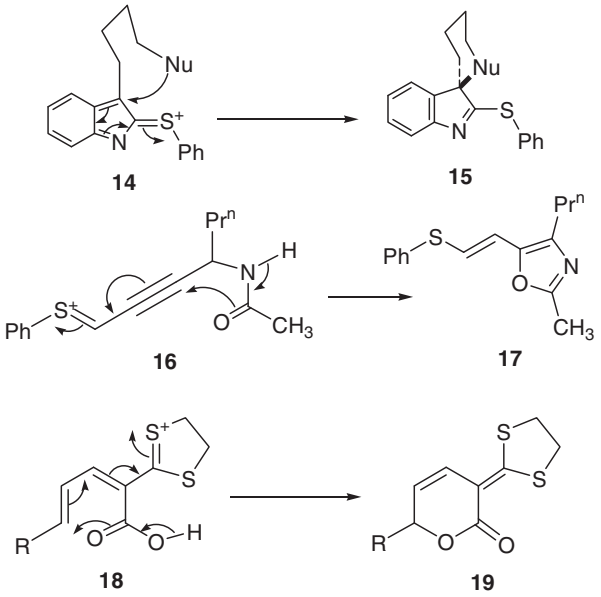
However, we have not come across any known example involving such a 'longer-range' (i.e., consisting of a conjugated chain of 7 or 9 carbon atoms) vinylogous Pummerer-type cyclization. We, therefore, believe that ours is the first example of its kind.

Earlier, Sperl et al. reported the synthesis of sulindac sulfide lactone (**4**) form sulindac sulfide (**5**) and used the same as an intermediate for the synthesis of ^{14}C-labeled compounds.[9] However, its structure was not fully established and its biological activity was not evaluated. We have now evaluated the anti-inflammatory and anti-cancer activities of sulindac sulfide lactone **4** as well as its sulfoxide (**12**) and sulfone (**13**) derivatives (Fig. 2) and those results will be reported elsewhere in due course.

In summary, we have accidentally discovered an interesting 'longer-range' vinylogous Pummerer-type lactonization process wherein we obtained the sulindac sulfide lactone (**4**) as the major product when sulindac (**1**) was treated with oxalyl chloride and triethylamine. Although a few examples of extended or 'long-range'



Scheme 4. A plausible mechanism for the formation of sulindac sulfide lactone (**4**) from sulindac (**1**) via a longer-range vinylogous Pummerer-type thionium ion-induced lactonization.



Scheme 5. Some known examples of extended or 'long-range' vinylogous Pummerer-type thionium ion-triggered cyclizations.

(i.e., involving a conjugated chain of 3–5 atoms) vinylogous Pummerer-type cyclizations are reported in the literature, as far as we know, ours is the first example of a vinylogous Pummerer-type lactonization wherein such a 'longer-range' (i.e., consisting of a conjugated chain of 7 or 9 carbon atoms) process is involved. We have also confirmed the structure of lactone **4** by a single crystal X-ray analysis.[10]

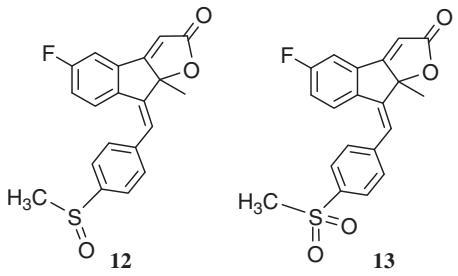


Figure 2. Structures of sulindac sulfoxide lactone (**12**) and sulindac sulfone lactone (**13**).

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Supplementary data

X-ray crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary Publication No. CCDC 742703. Supplementary data (scanned copies of spectral data and HPLC chromatograms for all the reported compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.008.

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10. Experimental procedures and compound characterization data for all the compounds reported in this article are presented below: Synthesis of (E)-5-fluoro-8a-methyl-8-(4-(methylthio)benzylidene)-8,8a-dihydro-2*H*-indeno-[2,1-*b*]furan-2-one (sulindac sulfide lactone **4**) in the presence of $HOCH_2CH_2SSCH_2CH_2ONO_2$ (**LI**): To a solution of sulindac (**1**) (2 g, 5.61 mmol) in dichloromethane (15 mL) at room temperature was added oxalyl chloride (0.58 mL, 6.71 mmol) and the mixture was stirred for 2 h. The solvent was removed under reduced pressure and the residue was re-dissolved in dichloromethane (15 mL). A solution of 2-((2-hydroxyethyl)disulfanyl)ethyl nitrate (**L1**, 1.5 gm, 7.50 mmol) and triethylamine (1 mL, 7.20 mmol) in dichloromethane (10 mL) was added drop-wise and the solution was stirred at RT for 4 h. The solvent was evaporated and the residue was extracted with ethyl acetate (3 × 25 mL), washed with water (2 × 25 mL) and brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude material was purified by silica gel column chromatography using 5–10% ethyl acetate/petroleum ether as eluent to afford lactone **4** (400 mg, 21%) as a yellow solid. Formation of the expected NO-sulindac (**3a**) was not observed. Mp 148 °C. IR (KBr): 1759, 1658, 1471, 1202 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.67 (s, 3H),

2.50 (s, 3H), 5.99 (s, 1H), 6.71 (s, 1H), 6.95–7.43 (m, 7H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 15.4, 27.2, 94.7, 108.8, 111.6, 111.8, 118.6, 118.8, 123.8, 126.2, 127.6, 128.4, 134.9, 137.9, 138.4, 138.8, 161.9, 163.9, 173.0, 173.8. HRMS ESI (*m*/*z*): $[M+Na]^+$ calculated for $C_{20}H_{15}FNaO_2S$: 361.0669; found: 361.0660 (mass accuracy: 2.49 ppm). *Synthesis of (E)-5-fluoro-8a-methyl-8-(4-(methylthio)benzylidene)-8,8a-dihydro-2H-indeno[2,1-b]furan-2-one (sulindac sulfide lactone* ***4****) in presence of alcohol (EtOH)*: To a solution of sulindac (**1**) (357 mg, 1 mmol) in dichloromethane (5 mL) at room temperature was added oxalyl chloride (0.12 mL, 1.38 mmol) and the mixture was stirred for 2 h. The solvent was removed under reduced pressure and the residue was re-dissolved in dichloromethane (5 mL). A solution of absolute EtOH (0.08 mL, 1.37 mmol) and triethylamine (0.19 mL, 1.37 mmol) in dichloromethane (2 mL) was added drop-wise and the solution was stirred at rt for 4 h. The reaction mixture was washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude material was purified by silica gel column chromatography using 40% dichloromethane/petroleum ether as eluent to afford the lactone **4** (222 mg, 65.5%) as a yellow solid. The formation of expected ester compound **3b** was not observed. Analytical and spectral data of the product are identical to those reported above. *Synthesis of (E)-5-fluoro-8a-methyl-8-(4-(methylthio)benzylidene)-8,8a-dihydro-2H-indeno[2,1-b]furan-2-one (sulindac sulfide lactone* ***4****) in absence of an alcoholic reactant*: To a solution of sulindac (**1**) (5 g, 14.02 mmol) in dichloromethane (50 mL) at room temperature was added oxalyl chloride (1.45 mL, 16.79 mmol) and the mixture was stirred for 2 h. The solvent was removed under reduced pressure and the residue was re-dissolved in dichloromethane (50 mL). Triethylamine (3.5 mL, 25.8 mmol) was added drop-wise and the solution was stirred for 4 h. The reaction mixture was washed with water (2 × 50 mL) and brine (2 × 50 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude material was purified by silica gel column chromatography using 50% dichloromethane/petroleum ether as eluent to afford lactone **4** (3.2 g, 67%) as a yellow solid, which was recrystallized from methanol to get yellow crystals for X-ray analysis. Analytical and spectral data are identical to those obtained above. X-ray analysis for compound **4**: Formula $C_{20}H_{15}FO_2S$, unit cell parameters *a* 7.317(5) *b* 18.346(5) *c* 12.347(5), α 90, β 107.07(5), γ 90, space group P21/a monoclinic, CCDC No. 742703. *Synthesis of (E)-ethyl 2-((Z)-6-fluoro-2-methyl-3-(4-(methylthio)benzylidene)-2,3-dihydro-1H-inden-1-ylidene)-acetate (Sulindac sulfide ethyl ester) (****10****)*: Sulindac sulfide **5** (50 mg, 0.147 mmol) was dissolved in dichloromethane (5 mL) by warming on a hot water bath. Oxalyl chloride (0.018 mL, 0.20 mmol) was added at room temperature under nitrogen and the reaction mixture was stirred for 2 h. The solvent was removed under reduced pressure. The crude material was re-dissolved in dichloromethane (5 mL) and a solution of absolute EtOH (0.012 mL, 0.20 mmol) and triethylamine (0.028 mL, 0.20 mmol) in dichloromethane (2 mL) was added drop-wise. The reaction mixture was stirred at rt for 30 min, diluted with dichloromethane (25 mL), washed with water (25 mL) and brine (25 mL), and dried over anhydrous Na_2SO_4 and concentrated. The crude material was purified by silica gel column chromatography using 5% ethyl acetate/petroleum ether as eluent to obtain ester **10** (48 mg, 89%) as a yellow solid. Mp 95–97 °C. IR (KBr): 1722, 1605, 1465, 1166 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.2 Hz, 3H), 2.22 (s, 3H), 2.56 (s, 3H), 3.57 (s, 2H), 4.19 (t, *J* = 7.2 Hz, 2H), 6.60 (dt, J_1 = 3.0 Hz, J_2 = 8.85 Hz, 1H), 6.90 (dd, J_1 = 2.4 Hz, J_2 = 9.1 Hz, 1H), 7.15 (s, 1H), 7.29–7.47 (m, 5H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 10.9, 14.5, 15.7, 32.2, 61.4, 105.9, 106.3, 110.7, 110.9, 123.9, 124.0, 126.2, 130.1, 130.2, 131.2, 133.3, 138.7, 139.4, 140.5, 146.8, 170.7; HRMS, ESI (*m*/*z*): $[M+H]^+$ calculated for $C_{22}H_{22}FO_2S$ 369.1319, found 369.1319. *Synthesis of ethyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetate (Indomethacin ethyl ester) (****11****)*: To a solution of indomethacin (**6**) (500 mg, 1.39 mmol) in dichloromethane (8 mL) was added oxalyl chloride (0.144 mL, 1.67 mmol) and the solution was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the crude material was re-dissolved in dichloromethane (8 mL). A solution of absolute EtOH (0.098 mL, 1.67 mmol) and triethylamine (0.23 mL, 1.67 mmol) in dichloromethane (1 mL) was added drop-wise, and the reaction mixture was stirred for 30 min. The reaction mixture was diluted with dichloromethane (25 mL), washed with water (2 × 25 mL) and brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated to afford ester **11** (500 mg, 93%) as a white solid. Mp 85–87 °C (lit.[11] mp 82–83 °C). IR (KBr): 1728, 1680, 1602, 1467, 1183 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (t, *J* = 6.9 Hz, 3H), 2.40 (s, 3H), 3.67 (s, 2H), 3.85 (s, 3H), 4.16 (q, *J* = 7.2 Hz, 2H), 6.67 (dd, J_1 = 2.4 Hz, J_2 = 9.0 Hz, 1H), 6.87 (d, *J* = 9 Hz, 1H), 6.97 (d, *J* = 2.4 Hz, 1H) 7.45–7.50 (m, 2H), 7.63–7.69 (m, 2H). MS *m*/*z* ESI (+ve): 386.1 $[M+H]^+$, 408.1 $[M+Na]^+$. *Synthesis of (E)-5-fluoro-8a-methyl-8-(4-(methylsulfinyl)benzylidene)-8,8a-dihydro-2H-indeno[2,1-b]furan-2-one (sulindac sulfoxide lactone) (****12****)*: The lactone **4** (500 mg, 1.47 mmol) was dissolved in a mixture of methanol (35 mL) and acetone (16 mL). A solution of sodium periodate (650 mg, 3.03 mmol) in water (9 mL) was added and the mixture was stirred for 40 h. The solvent was removed under reduced pressure and the white precipitate obtained was filtered, washed with water, and dried to afford the corresponding sulfoxide **12** (370 mg, 70%) as a white solid. Mp 83–84 °C (lit.[12] mp 84 °C). IR (KBr): 1763, 1661, 1471, 1205, 1048 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.71 (s, 3H), 2.79 (s, 3H), 6.04 (s,1H), 6.80 (s, 1H), 7.00 - 7.73 (m, 7H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 26.6, 43.9, 93.9, 108.8, 111.4, 111.7, 118.4, 118.7, 121.2, 127.3, 128.5, 134.8, 134.9, 139.4, 140.3, 140.8, 161.2, 164.6, 172.1, 172.4. HRMS ESI (*m*/*z*): $[M+Na]^+$ calculated for $C_{20}H_{15}FNaO_3S$: 377.0618; found: 377.0602 (mass accuracy: 4.24 ppm). *Synthesis of (E)-5-fluoro-8a-methyl-8-(4-(methylsulfonyl)-benzylidene)-8,8a-dihydro-2H-indeno[2,1-b]furan-2-one (sulindac sulfone lactone) (****13****)*: The lactone **4** (100 mg, 0.29 mmol) was dissolved in THF (5 mL) and cooled to 0 °C. A solution of oxone (218 mg, 0.35 mmol) in water (4 mL) was added drop-wise and the reaction mixture was stirred at room temperature for 20 h. The solvent was removed under reduced pressure and the white precipitate obtained was filtered, washed with water, and dried to afford the corresponding sulfone **13** (90 mg, 82%) as a white solid. Mp: 191–192 °C (lit.[12] mp 193 °C). IR (KBr): 1762, 1591, 1468, 1311, 1144 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.69 (s, 3H), 3.09 (s, 3H), 6.04 (s,1H), 6.77 (s, 1H), 6.98–7.94 (m, 7H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 26.6, 43.9, 93.9, 108.8, 111.4, 111.8, 118.4, 118.7, 121.2, 127.3, 128.5, 134.8, 136.7, 139.3, 140.3, 140.7, 161.2, 164.6, 172.1, 172.4. HRMS ESI (*m*/*z*): $[M+Na]^+$ calculated for $C_{20}H_{15}FNaO_4S$: 393.0567; found: 393.0553 (mass accuracy: 3.56 ppm).

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