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Aromatic Enamide/Ene Metathesis toward Substituted Indoles and Its Application to the Synthesis of Indomethacins

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A steric and electronic effect on enamide/ene metathesis, a novel preparation of 2-substituted indoles and 3-substituted indoles using enamide-ene metathesis as a key reaction, and its application to the synthesis of indomethacin are described.

Introduction

Over the past 10 years, diene and enyne metathesis, such as ring-closing metathesis (RCM), ring-opening metathesis (ROM), and cross metathesis (CM) have been major tools for the synthesis of complex molecules.[1] The product of widely used diene metathesis is an olefin, which can be further modified but only to a limited extent. Since the regioselective transformation of the newly formed double bond is generally difficult, the resulting olefin moiety usually either remains in the final product without modification or undergoes only simple chemical transformations in which regioselectivity is not required (e.g. epoxidation, hydrogenation, and dihydroxylation).

On the other hand, carbon–carbon double bonds substituted by a heteroatom, such as Si, O, N, P, S, B, or a halogen, offer vast functionalization possibilities, and regioselectivity in the transformation is no longer a problem.

Therefore, the metathesis of heteroatom-substituted olefins, where the newly formed double bond can undergo versatile chemical transformations, is a valuable process in organic synthesis.[2] We have been exploring a method for the synthesis of N-containing heterocycles using RCM and then applying them to the synthesis of biologically active natural products.[3] In the course of our research, we have reported several novel examples of heteroatom-substituted olefin metathesis such as silyl enol ether/ene metathesis[3a] and aromatic enamide/ene metathesis.[3b] These led to novel methods for preparing 4-siloxy-1,2-dihydroquinolines and indoles, which are key compounds for the synthesis of biologically active natural products and important pharmaceuticals.

Indole is a prominent and privileged structure widely found in naturally occurring substances and biologically active molecules of pharmaceutical importance.[4,5] Progress in indole chemistry depends on efficient synthetic routes to indole derivatives with various substitution patterns.[5] Although many methodologies have been developed, the synthesis of 2,3-disubstituted indoles with a substituent at a desired position remains challenging. We previously developed an aromatic enamide/ene metathesis induced synthesis of substituted indoles without a substituent at the 2- and/or 3-positions on the indole ring.[3b,3d] However, enamide/ene metathesis is in the middle of development,[3b,3f,6] and has recently been highlighted.[7] An isomerization/RCM-based strategy[8] and RCM/isomerization[9] have also been reported. Therefore, we decided to explore our enamide/ene metathesis in much more detail and establish a flexible method for the synthesis of 2,3-disubstituted indoles with a variety of substituents under mild conditions. In this article, we report a novel method for preparing 2,3-disubstituted indoles, including 2-substituted indoles and 3-substituted indoles using enamide/ene metathesis as a key reaction, and its application to the synthesis of indomethacin, a non-steroid anti-inflammatory drug (NSAID), and its derivative. We also describe steric and electronic effects in enamide/ene metathesis.

Results and Discussion

Our one-pot method for preparing substituted indoles consists of two reactions: the selective isomerization of an *N*-allyl-amide to the corresponding aromatic enamide and subsequent aromatic enamide/ene metathesis.

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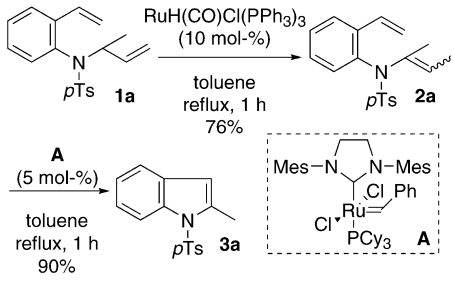
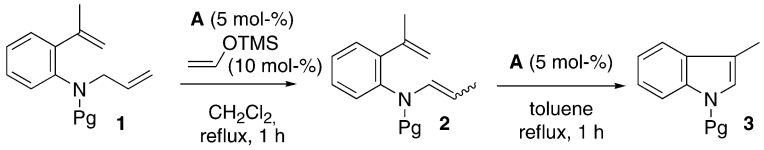
Before we investigated a novel synthetic method for preparing 2,3-disubstituted indoles, we examined the preparation of 2- or 3-monosubstituted indoles by our indole synthesis procedure. We refluxed the 2nd-generation Grubbs catalyst (**A**, 5 mol-%) and enamide **2a**, *N*-(but-2-en-2-yl)-*N*-(tolylsulfonyl)-2-vinylaniline (which was prepared in the same flask by the $RuH(CO)Cl(PPh_3)_3$-induced[3f] isomerization of **1a** and subsequent concentration in 76% yield) in toluene for 1 h, and obtained the corresponding 2-methylindole derivative **3a** in 90% yield (Scheme 1), which was comparable to a simple indole synthesis.[3b] On the other hand, the selective isomerization of *N*-allyl-2-isopropenyl-*N*-(tolylsulfonyl)aniline (**1b**) to give **2b** proceeded quantitatively. However, the subsequent aromatic enamide/ene metathesis to form the 3-methylindole derivative **3b** did not proceed at all. In this reaction, we isolated the corresponding enamide intermediate **2b** in 59% yield instead (Table 1, Entry 1). If we consider the reactivity of monosubstituted terminal olefins, it is reasonable that the enamide/ene metathesis between a 1-monosubstituted olefin and a 1,1,2-trisubstituted olefin to form a 2-substituted indole derivative such as **3a** proceeded much better than that of a 1,1-disubstituted olefin and a 1,2-disubstituted olefin to form a 3-substituted indole derivative like **3b**. Based on these results, since we sought to establish a method for preparing 3-substituted indole derivatives by our indole synthesis procedure, we continued experiments by changing the N substituent and prepared *N*-substituted 2-isopropenylaniline derivatives **1c**–**g**. The same one-pot reaction of the less hindered *N*-(methylsulfonyl) substrate **1c** gave the cyclized product **3c** and the intermediate **2c** in yields of 13% and 78%, respectively (Table 1, Entry 2). We converted the *N*-(*tert*-butoxycarbonyl) substrate **1d** and the methoxycarbonyl substrate **1e** into the cyclized products **3d** and **3e** in yields of 23% and 64%, respectively (Table 1, Entries 3 and 4). These results suggest that there is a steric effect on the aromatic enamide/ene metathesis; a bulky N substituent on the substrate may suppress the cyclization. These results also seem to indicate the existence of an electronic effect on this reaction, since substrates with a less electron-withdrawing alkoxycarbonyl substituent on the aromatic amine formed the corresponding RCM products in higher yields (Table 1, Entries 3 and 4) compared to the substrates with an electron-withdrawing sulfonyl substituent (Table 1, Entries 1 and 2). To confirm these suppositions, we prepared the acetyl and trifluoroacetyl substrates **1f** and **1g** and subjected them to the same one-pot reaction. As expected, we converted these into the desired cyclized products, **3f** and **3g**, in yields of 83% and 21%, respectively (Table 1, Entries 5 and 6). Thus, it became clear that there is an electronic effect on aromatic enamide/ene metathesis. For the preparation of 3-substituted indole derivatives, an N substituent is very important, and acetyl gave the best results among all of the protecting groups we examined.



Scheme 1. Synthesis of 2-methylindole.

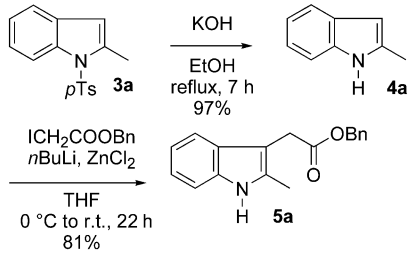
Based on these results and with the goal of establishing a novel method for the synthesis of 2,3-disubstituted indoles with a variety of substituents on the benzene moiety (positions 4–7), we next designed a stepwise method, in which we introduced a substituent at position 3 by alkylation of a 2-substituted indole, which would be prepared by our indole synthesis procedure. Thus, we found that Bach's method is useful for the 3-alkylation of 2-substituted indoles by treating the zinc salt of the indole with a primary alkyl halide.[10] When we stirred 2-methylindole (**4a**) and ICH_2CO_2Bn at 0 °C to r.t. for 22 h in the presence of *n*BuLi and $ZnCl_2$ in THF, we isolated the desired 2,3-disubstituted product **5a** in 81% yield (Scheme 2). Therefore, 2,3-disubstituted indoles can be prepared by this stepwise method, a combination of aromatic enamide/ene metathesis to form 2-substituted indoles and subsequent 3-alkylation.

Table 1. Synthesis of 3-methylindole.



Entry	Substrate		Yield [%, 2 steps][a]	
	1	Protecting group (Pg)	**2**	**3**
1	**b**	*p*Ts	59	0
2	**c**	Ms	78	13
3	**d**	Boc	62	23
4	**e**	MeOCO	23	64
5	**f**	Ac	11	83
6	**g**	CF_3CO	44	21

[a] Isolated yields.



Scheme 2. 3-Alkylation of 2-methylindole.

We next sought to confirm that a variety of 2-substituted indoles could be prepared by our method. Thus, we prepared *N*-(alk-2-en-2-yl)-*N*-(tolylsulfonyl)-2-vinylanilines **1i** and **1j** with a substituent at the allylic carbon atom and subjected them to our two-step reaction (Table 2, Entries 1–4). The results show that the 2-substituent of the resulting indole had an effect on the reaction. We obtained the 2-ethyl and -phenyl derivatives **3i** and **3j** from **1i** and **1j** in yields of 91% and 84%, respectively.

We next examined a substituent effect on the benzene ring in the resulting indole with the substrates **1k**–**1n**, and the results are shown in Table 2, Entries 5–8. The reactions of **1k**–**1n**, under the optimized conditions, gave the corresponding enamides quantitatively. However, substitution at the 3-position of the substrate **1k** prevented cyclization to give the corresponding indole (Table 2, Entry 2), probably due to steric hindrance or chelation in the transition state. We transformed other substrates, including the 4-methoxy substrate **1l**, the 5-methoxy substrate **1m**, and the 6-methoxy substrate **1n**, into the corresponding indoles (i.e. the RCM product) in good to excellent yields. Based on our previous results,[3f] various 2-substituted indoles with a substituent on the aromatic ring, such as methyl or halogen, can be prepared by this method.

Indomethacin (**6**) is a clinically useful non-steroid anti-inflammatory drug (NSAID) with an indole structure. Although it has been reported that the bioactive conformations of indomethacin in complexes with cyclooxygenase-1 (COX-1) and COX-2 are the *s-trans*[11] and *s-cis* forms,[12] respectively (Figure 1), the introduction of substituents at the 2- or 7-position of indomethacin may restrict its conformation in the *s-trans* or *s-cis* form due to steric repulsion of the substituent at the 2- or 7-position relative to the *N*-acyl side chain. These conformationally restricted analogues may be selectively active toward COX-1 or COX-2. Thus, we set out to synthesize these indomethacin analogues, which could not be prepared previously, because methods for preparing substituted indomethacins has been limited for these purposes.[13] Before such a medicinal chemical study, we applied our method for preparing 2,3-disubstituted indoles to the synthesis of indomethacin (**6**). The removal of the *p*-tolylsulfonyl group on the N atom of **3l**, the 3-alkylation of **4l**, the *N*-acylation of **5l**, and the debenzylation by using Pd/C led to **6** in 51% yield (4 steps, Scheme 3). This new method can be applied to the synthesis of a variety of indomethacin derivatives. One synthetic example was shown in Scheme 3.

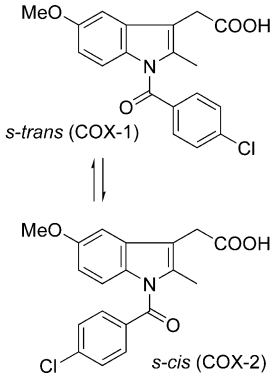
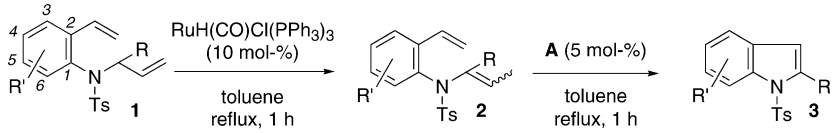


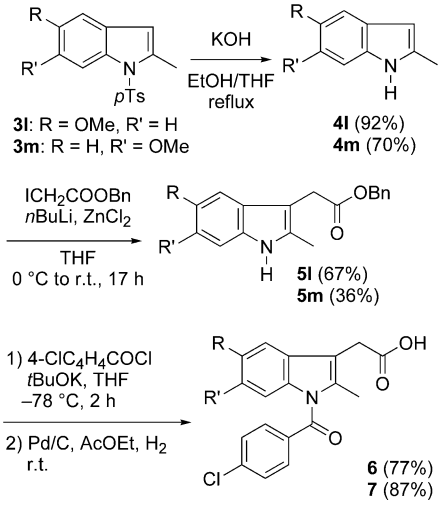
Figure 1. Bioactive conformations of indomethacin (**6**).

Table 2. Scope and limitations of the two-step preparation of substituted indoles.



Entry	Substrate			Yield [%, 2 steps][a]
	1	R	R′	**3**
1	**a**	Me	H	68[b]
2	**h**	H	H	94[c]
3	**i**	Et	H	91
4	**j**	Ph	H	84
5	**k**	Me	3-MeO	11 (55)[d]
6	**l**	Me	4-MeO	73
7	**m**	Me	5-MeO	98
8	**n**	Me	6-MeO	92

[a] Isolated yields. [b] The same data is seen in Scheme 1. [c] Ref.[3c,3d] [d] 20 mol-% of **A** was used; 80% of **1k** was recovered. The yield in parentheses indicates the yield based on the recovered starting material.



Scheme 3. Novel method for the synthesis of indomethacin (**6**) and derivative **7**.

Conclusions

We found that steric hindrance and an electron-withdrawing effect influence aromatic enamide/ene metathesis and developed a novel method for preparing 2-substituted indoles and 3-substituted indoles, using enamide/ene metathesis as a key reaction, which led to a novel synthetic method of preparing substituted indomethacin derivatives.

Experimental Section

General: ^{1}H NMR spectra were recorded in $CDCl_3$ at 25 °C, unless otherwise noted, at 400 or 500 MHz, with TMS as an internal standard. ^{13}C NMR spectra were recorded in $CDCl_3$ at 25 °C, unless otherwise noted, at 400 or 500 MHz. Flash column chromatography was performed with silica gel 60 (spherical, neutral, 40–50 μm, Kanto Chemical Co., Inc.). **A** and $RuH(CO)Cl(PPh_3)_3$ were obtained commercially. Compounds **1f**,[3d] **1h**,[3b] and **3h**[3b] were prepared according to reported procedures.

General Procedure for the Preparation of Dienes 1a,i–n

1a: To a solution of 2-ethenyl-*N*-(*p*-tolylsulfonyl)aniline[3e] (1.00 mmol, 273 mg), 3-buten-2-ol (1.00 mmol, 79.3 mg), and triphenylphosphane (1.10 mmol, 289 mg) in THF (1.0 mL) was added dropwise a solution of diethyl azodicarboxylate (1.10 mmol, 0.17 mL) in THF (5.0 mL), and the mixture was stirred at r.t. for 2.5 h. After the solvent was removed, the residue was subjected to column chromatography (hexane/AcOEt, 20:1) to give **1a** (242 mg, 74%) as a colorless oil. ^{1}H NMR ([D$_6$]DMSO, 150 °C): δ = 7.67 (d, J = 6.8 Hz, 1 H, aromatic), 7.59 (d, J = 8.2 Hz, 2 H, aromatic), 7.39–7.37 (m, 1 H, aromatic), 7.36 (d, J = 8.4 Hz, 2 H, aromatic), 7.23 (dd, J = 7.7, 7.7 Hz, 1 H, aromatic), 7.00–6.83 (m, 2 H, Ar-C*H*=CH$_2$, aromatic), 5.76–5.69 (m, 1 H, NCHC*H*), 5.69 (d, J = 17.4 Hz, 1 H, Ar-CH=C*H*$_2$), 5.22 (d, J = 1.7 Hz, 1 H, Ar-CH=C*H*$_2$), 5.03 (d, J = 17.2 Hz, 1 H, NCHCH=C*H*$_2$), 4.98 (d, J = 10.4 Hz, 1 H, NCHCH=C*H*$_2$), 4.77 (dq, J = 6.6, 6.6 Hz, 0.66 H, NC*H*), 4.04 (d, J = 6.4 Hz, 0.34 H, NC*H*), 2.42 (s, 0.51 H, *p*Ts 4-C*H*$_3$), 2.41 (s, 2.49 H, *p*Ts 4-C*H*$_3$), 1.49 (d, J = 5.9 Hz, 0.51 H, NCHC*H*$_3$), 1.13 (d, J = 6.7 Hz, 2.49 H, NCHC*H*$_3$) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 143.35, 134.18, 143.14, 140.35, 139.90, 138.66, 138.07, 137.75, 137.68, 137.64, 133.85, 133.63, 133.56, 132.82, 131.95, 131.90, 130.61, 29.39, 129.20, 129.10, 128.71, 128.84, 128.35, 128.00, 127.85, 127.80, 127.65, 127.48, 127.39, 125.96, 125.86, 124.88, 116.89, 116.47, 115.67, 115.19, 58.40, 58.32, 54.10, 21.51, 18.80, 18.69, 17.54 ppm. IR (neat): $\tilde{\nu}$ = 2980, 1598, 1342, 1162 cm^{-1}. LRMS (EI): m/z (%) = 172 (100), 327 (35) [M]$^+$. HRMS (FAB): calcd. for $C_{19}H_{22}NO_2S$ [M$^+$ + H]$^+$ 328.1371, found 328.1385.

1i: 95% yield from 2-ethenyl-*N*-(*p*-tolylsulfonyl)aniline[3e] and 1-penten-3-ol as an inseparable mixture of **1i** and 2-ethenyl-*N*-(pent-2-en-1-yl)-*N*-(*p*-tolylsulfonyl)aniline (7:3); colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (dd, J = 1.4, 7.8 Hz, 0.5 H, aromatic), 7.63–7.67 (m, 0.5 H, aromatic), 7.59 (d, J = 8.2 Hz, 1 H, aromatic), 7.56 (d, J = 8.7 Hz, 1 H, aromatic), 7.09–7.34 (m, 4 H, aromatic), 7.06 (dd, J = 10.9, 17.8 Hz, 0.6 H, Ar-C*H*), 6.91 (dd, J = 10.9, 17.9 Hz, 0.4 H, Ar-C*H*), 6.63–6.67 (m, 1 H, aromatic), 5.74 (dd, J = 0.9, 18.0 Hz, 0.6 H, Ar-CH=C*H*$_2$), 5.64 (dd, J = 0.9, 17.8 Hz, 0.4 H, Ar-CH=C*H*$_2$), 5.26–5.42 (m, 2 H, Ar-CH=C*H*$_2$, NCHC*H*), 5.05–5.21 (m, 2 H, NCHCH=C*H*$_2$), 4.52–4.28 (m, 0.6 H, NC*H*), 4.46–4.52 (m, 0.4 H, NC*H*), 2.40–2.42 (m, 3 H, *p*Ts 4-C*H*$_3$), 1.70–1.80 (m, 0.6 H, NCHC*H*$_2$), 1.56–1.66 (m, 0.4 H, NCHC*H*$_2$), 1.31–1.43 (m, 0.4 H, NCHC*H*$_2$), 1.07–1.19 (m, 0.6 H, NCHC*H*$_2$), 0.75–0.82 (m, 3 H, CHC*H*$_3$) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 143.29, 143.03, 140.39, 139.70, 138.72, 138.25, 137.79, 137.42, 136.67, 136.36, 135.79, 135.45, 134.17, 133.77, 133.65, 132.90, 132.15, 132.05, 129.37, 129.30, 129.11, 129.01, 128.81, 128.73, 128.31, 128.14, 127.80, 127.77, 127.52, 127.28, 125.91, 125.84, 125.79, 122.56, 118.95, 118.57, 115.39, 114.86, 65.90, 65.58, 54.12, 26.34, 26.26, 25.00, 21.46, 13.00, 11.01, 10.94 ppm. LRMS (EI): m/z (%) = 341 [M]$^+$. HR-MS (EI): calcd. for $C_{20}H_{23}NO_2S$ 341.1449, found 341.1447 [M]$^+$.

1j: 66% yield from 2-ethenyl-*N*-(*p*-tolylsulfonyl)aniline[3e] and 1-phenyl-2-propenol as an inseparable mixture of **1j** and 2-ethenyl-*N*-(3-phenylprop-2-en-1-yl)-*N*-(*p*-tolylsulfonyl)aniline (7:3); colorless oil. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.60–7.66 (m, 2 H, aromatic), 7.19–7.49 (m, 9 H, aromatic), 6.98–7.03 (m, 2 H, aromatic, Ar-C*H*=CH$_2$), 6.81 (d, J = 6.8 Hz, 1 H, aromatic), 6.16–6.26 (m, 1 H, Ar-CH=C*H*$_2$), 6.00–6.09 (m, 1 H, NCHC*H*), 5.78–5.91 (m, 1 H, NC*H*), 5.26–5.45 (m, 2 H, Ar-CH=C*H*$_2$, NCHCH=C*H*$_2$), 5.12–5.16 (m, 1 H, NCHCH=C*H*$_2$), 2.42–2.45 (m, 3 H, *p*Ts 4-C*H*$_3$) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 143.20, 143.05, 140.78, 136.86, 138.97, 137.75, 137.69, 137.61, 135.41, 134.88, 134.43, 133.69, 133.48, 133.04, 132.10, 131.93. 129.22, 129.08, 128.95, 128.88, 128.82, 128.19, 128.14, 128.00, 127.95, 127.85, 127.79, 127.32, 127.29, 125.72, 125.64, 118.88, 118.13, 115.24, 114.39, 67.43, 66.58, 21.54, 21.48 ppm. LRMS (EI): m/z = 389 [M]$^+$. HR-MS (EI): calcd. for $C_{24}H_{23}NO_2S$ 389.1449, found 389.1448 [M]$^+$.

1k: 80% yield from 2-ethenyl-3-methoxy-*N*-(*p*-tolylsulfonyl)aniline[3f] and 1-buten-3-ol as an inseparable mixture of **1k** and *N*-(but-2-en-1-yl)-2-ethenyl-3-methoxy-*N*-(*p*-tolylsulfonyl)aniline (4:1); colorless oil. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.67 (d, J = 8.0 Hz, 0.8 H, aromatic), 7.63 (d, J = 8.0 Hz, 1.2 H, aromatic), 7.46 (d, J = 8.0 Hz, 0.8 H, aromatic), 7.43 (d, J = 8.0 Hz, 1.2 H, aromatic), 7.25–7.17 (m, 1 H, aromatic), 7.14 (d, J = 8.6 Hz, 1 H, aromatic), 6.95 (dd, J = 18.0, 12.6 Hz, 0.6 H, Ar-C*H*), 6.83 (dd, J = 18.0, 12.6 Hz, 0.4 H, Ar-C*H*), 6.43 (d, J = 8.0 Hz, 0.4 H, aromatic), 6.31 (d, J = 8.0 Hz, 0.6 H, aromatic), 6.15 (dd, J = 18.0, 2.2 Hz, 0.6 H, Ar-CH=C*H*$_2$), 6.10 (dd, J = 18.0, 2.2 Hz, 0.4 H, Ar-CH=C*H*$_2$), 5.66–5.73 (m, 0.4 H, NCHC*H*), 5.47–5.56 (m, 0.6 H, NCHC*H*), 5.49 (dd, J = 12.3, 2.2 Hz, 0.6 H, Ar-CH=C*H*$_2$), 5.41 (dd, J = 12.3, 2.2 Hz, 0.4 H, Ar-CH=C*H*$_2$), 4.98–5.08 (m, 2 H, NCHCH=C*H*$_2$), 4.81–4.87 (m, 1 H, NC*H*), 3.89 (s, 1.8 H, OC*H*$_3$),

3.88 (s, 1.2 H, OCH_3), 2.45 (s, 1.8 H, *p*Ts 4-CH_3), 2.44 (s, 1.2 H, *p*Ts 4-CH_3), 1.07 (d, *J* = 6.9 Hz, 1.8 H, NCHCH_3), 1.00 (d, *J* = 6.9 Hz, 1.8 H, NCHCH_3) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 159.21, 159.14, 158.88, 143.22, 143.13, 143.07, 138.45, 138.12, 137.81, 173.71, 136.57, 135.82, 135.57, 130.60, 130.39, 130.34, 129.36, 129.33, 129.11, 128.79, 123.38, 128.15, 127.89, 127.86, 127.79, 127.58, 127.47, 127.27, 126.82, 126.71, 124.92, 124.08, 124.03, 121.32, 120.75, 120.43, 120.22, 116.68, 116.21, 111.61, 111.57, 111.01, 110.95, 58.74, 58.72, 55.52, 55.49, 54.05, 21.49, 18.79, 18.72, 17.54, 13.43 ppm. LRMS (EI): *m*/*z* = 357 [M]$^+$. HR-MS (EI): calcd. for $C_{20}H_{23}NO_3S$ 357.1399, found 357.1400 [M]$^+$.

1l: 100% yield from 2-ethenyl-4-methoxy-*N*-(*p*-tolylsulfonyl)aniline[3f] and 1-buten-3-ol; colorless oil. ^{1}H NMR (500 MHz, [D$_6$]-DMSO): δ = 7.64 (d, *J* = 8.0 Hz, 0.8 H, aromatic), 7.61 (d, *J* = 8.0 Hz, 1.2 H, aromatic), 7.45 (d, *J* = 8.0 Hz, 0.8 H, aromatic), 7.43 (d, *J* = 8.0 Hz, 1.2 H, aromatic), 7.30 (d, *J* = 2.9 Hz, 0.6 H, aromatic), 7.28 (d, *J* = 2.9 Hz, 0.4 H, aromatic), 7.01 (dd, *J* = 11.5, 17.8 Hz, 0.6 H, Ar-C*H*), 6.91–6.82 (m, 1.4 H, Ar-C*H*, aromatic), 6.72 (d, *J* = 8.6 Hz, 0.4 H, aromatic), 6.59 (d, *J* = 9.2 Hz, 0.6 H, aromatic), 5.92 (d, *J* = 17.8 Hz, 0.6 H, Ar-CH=CH_2), 5.86 (d, *J* = 11.5 Hz, 0.4 H, Ar-CH=CH_2), 5.69–5.62 (m, 0.4 H, NCHC*H*), 5.58–5.51 (m, 0.6 H, NCHC*H*), 5.37 (d, *J* = 11.5 Hz, 0.6 H, Ar-CH=CH_2), 5.29 (d, *J* = 12.0 Hz, 0.4 H, Ar-CH=CH_2), 5.09 (m, 2 H, NCHCH=CH_2), 4.90–4.88 (m, 1 H, NC*H*), 3.82 (s, 3 H, OCH_3), 2.45 (s, 1.2 H, *p*Ts 4-CH_3), 2.44 (s, 1.8 H, *p*Ts 4-CH_3), 1.05 (d, *J* = 6.9 Hz, 1.8 H, NCHCH_3), 1.02 (d, *J* = 6.9 Hz, 1.2 H, NCHCH_3) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 159.43, 159.40, 143.08, 143.04, 141.41, 140.95, 138.05, 137.80, 137.75, 137.64, 133.73, 132.93, 132.87, 129.35, 129.16, 127.93, 127.73, 127.57, 126.40, 126.40, 126.23, 116.78, 116.33, 115.44, 115.15, 113.32, 113.22, 110.32, 110.25, 58.22, 58.10, 55.28, 21.46, 18.71, 18.64 ppm. LRMS (EI): *m*/*z* = 357 [M]$^+$. $C_{20}H_{23}NO_3S$ (357.47): calcd. C 67.20, H 6.49, N 3.92; found C 66.91, H 6.42, N 3.99.

1m: 85% yield from 2-ethenyl-5-methoxy-*N*-(*p*-tolylsulfonyl)aniline[3f] and 1-buten-3-ol as an inseparable mixture of **1m** and *N*-(but-2-en-1-yl)-2-ethenyl-5-methoxy-*N*-(*p*-tolylsulfonyl)aniline (6:1); colorless oil. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.76 (d, *J* = 9.2 Hz, 0.6 H, aromatic), 7.74 (d, *J* = 8.6 Hz, 0.4 H, aromatic), 7.68 (d, *J* = 8.0 Hz, 0.8 H, aromatic), 7.65 (d, *J* = 8.0 Hz, 1.2 H, aromatic), 7.47 (d, *J* = 8.0 Hz, 1.2 H, aromatic), 7.45 (d, *J* = 8.0 Hz, 0.8 H, aromatic), 7.04 (d, *J* = 9.2 Hz, 1 H, aromatic), 7.00 (dd, *J* = 11.4, 17.8 Hz, 0.6 H, Ar-C*H*), 6.90 (dd, *J* = 11.4, 17.4 Hz, 0.4 H, Ar-C*H*), 6.26 (d, *J* = 2.3 Hz, 0.4 H, aromatic), 6.15 (d, *J* = 2.9 Hz, 0.6 H, aromatic), 5.74 (d, *J* = 17.8 Hz, 0.6 H, Ar-CH=CH_2), 5.69 (d, *J* = 17.1 Hz, 0.4 H, Ar-CH=CH_2), 5.71–5.64 (m, 0.4 H, NCHC*H*), 5.61–5.54 (m, 0.6 H, NCHC*H*), 5.24 (d, *J* = 10.9 Hz, 0.6 H, Ar-CH=CH_2), 5.16 (d, *J* = 12.0 Hz, 0.4 H, Ar-CH=CH_2), 5.11–5.01 (m, 2 H, NCHCH=CH_2), 4.91–4.85 (m, 1 H, NCHCH=CH_2), 3.69 (s, 1.2 H, OCH_3), 3.65 (s, 1.8 H, OCH_3), 2.46 (s, 1.2 H, *p*Ts 4-CH_3), 2.44 (s, 1.8 H, *p*Ts 4-CH_3), 1.07 (d, *J* = 6.9 Hz, 1.8 H, NCHCH_3), 1.04 (d, *J* = 6.9 Hz, 1.2 H, NCHCH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 158.59, 158.47, 143.36, 143.23, 143.20, 138.01, 137.73, 137.62, 137.60, 134.67, 134.40, 133.03, 132.99, 132.93, 132.44, 132.20, 131.23, 130.71, 129.37, 129.16, 128.02, 127.82, 127.66, 126.61, 126.56, 126.46, 124.86, 117.13, 117.09, 116.96, 116.43, 114.79, 114.77, 114.59, 114.04, 113.25, 112.97, 58.41, 58.34, 55.23, 55.18, 54.08, 21.47, 18.88, 18.60, 17.54 ppm. LRMS (EI): *m*/*z* = 357 [M]$^+$. HR-MS (EI): calcd. for $C_{20}H_{23}NO_3S$ 357.1399, found 357.1399 [M]$^+$.

1n: 100% yield from 2-ethenyl-6-methoxy-*N*-(*p*-tolylsulfonyl)aniline[3f] and 1-buten-3-ol; yellow powder, m.p. 72.5–74.0 °C (hexane/AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.6 Hz, 1.2 H, aromatic), 7.66 (d, *J* = 8.6 Hz, 0.8 H, aromatic), 7.29–7.17 (m, 4.4 H, aromatic), 7.07 (dd, *J* = 10.9, 17.8 Hz, 0.6 H, aromatic), 6.77–6.73 (m, 0.6 H, Ar-C*H*), 6.70 (dd, *J* = 2.3, 7.3 Hz, 0.4 H, Ar-C*H*), 5.87–5.70 (m, 2 H, NCHC*H*, Ar-CH=CH_2), 5.34 (dd, *J* = 1.4, 11.2 Hz, 0.4 H, Ar-CH=CH_2), 5.26 (dd, *J* = 1.4, 11.2 Hz, 0.6 H, Ar-CH=CH_2), 5.11 (d, *J* = 17.2 Hz, 0.6 H, NCHCH=CH_2), 4.99–4.95 (m, 1 H, NCHCH=CH_2), 4.86 (d, *J* = 10.0 Hz, 0.4 H, NCHCH=CH_2), 4.73–4.60 (m, 1 H, NC*H*), 3.47 (s, 1.8 H, OCH_3), 3.33 (s, 1.2 H, OCH_3), 2.42 (s, 1.8 H, *p*Ts 4-CH_3), 2.41 (s, 1.2 H, *p*Ts 4-CH_3), 1.17 (d, *J* = 6.8 Hz, 1.2 H, NCHCH_3), 1.08 (d, *J* = 6.8 Hz, 1.8 H, NCHCH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 158.00, 157.68, 142.41, 142.30, 141.51, 141.17, 139.04, 138.98, 138.97, 134.18, 134.11, 129.23, 128.65, 128.49, 128.02 127.91, 124.00, 123.82, 117.36, 117.31, 115.66, 115.59, 115.47, 114.77, 110.20, 110.16, 60.22, 59.44, 54.55, 54.21, 21.34, 20.91, 18.88, 14.06 ppm. LRMS (EI): *m*/*z* = 357 [M]$^+$. $C_{20}H_{23}NO_3S$ (357.47): calcd. C 67.20, H 6.49, N 3.92; found C 67.21, H 6.40, N 3.94.

General Procedure for the Isomerization of Terminal Olefins and Subsequent RCM: To a solution of diene in toluene (0.04 M) was added Ru(CO)HCl(PPh$_3$)$_3$ (10 mol-%) or 2nd-generation Grubbs catalyst **A** (5 mol-%) and trimethyl(vinyloxy)silane (10 mol-%), and the mixture was refluxed for 1 h. The reaction mixture was cooled, more **A** (5 mol-%) was added, and the mixture was refluxed for 1 h. The residue was subjected to column chromatography to give the corresponding indole.

3a:[14] 68% from **1a**; colorless prisms, m.p. 63–64 °C (MeOH), ref.[14] 66–67 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.2 Hz, 1 H, indole), 7.66 (d, *J* = 8.4 Hz, 2 H, aromatic), 7.40 (d, *J* = 7.3 Hz, 1 H), 7.26 (ddd, *J* = 7.8, 7.8, 1.3 Hz, 1 H, indole), 7.20 (dd, *J* = 7.3, 1.3 Hz, 1 H, indole), 7.20 (d, *J* = 8.4 Hz, 2 H, aromatic), 6.34 (d, *J* = 0.9 Hz, 1 H, indole), 2.60 (s, 3 H, *p*Ts 4-CH_3), 2.34 (s, 3 H, indole-CH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 144.65, 137.26, 136.91, 136.20, 129.80, 129.60, 126.24, 13.65, 123.33, 119.90, 114.40, 109.51, 21.48, 15.72 ppm. LRMS (EI): *m*/*z* (%)= 130 (100), 285 (96) [M]$^+$.

3f:[15] 83% from **1f**; colorless prisms, m.p. 64–65 °C (EtOH), ref.[15] 66–67 °C (hexane/AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (br., 1 H, indole), 7.49 (d, *J* = 7.7 Hz, 1 H, indole), 7.27–7.37 (m, 2 H, indole), 7.17 (br., 1 H, indole), 2.59 (s, 3 H, COCH_3), 2.28 (d, *J* = 1.4 Hz, 3 H, indole-CH_3) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 168.22, 135.73, 131.32, 125.04, 123.28, 122.13, 118.72, 118.26, 116.48, 23.88, 9.60 ppm. LRMS (EI): *m*/*z* = 173 [M]$^+$.

3i: 91% from **1i**; colorless needles, m.p. 68–69 °C (EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 8.2 Hz, 1 H, indole), 7.62 (d, *J* = 8.6 Hz, 2 H, aromatic), 7.41 (d, *J* = 7.2 Hz, 1 H, indole), 7.27–7.20 (m, 2 H, indole), 7.18 (d, *J* = 8.0 Hz, 2 H, aromatic), 6.39 (s, 1 H, indole), 3.02 (q, *J* = 7.4 Hz, 2 H, indole-CH_2), 2.33 (s, 3 H, *p*Ts 4-CH_3), 1.34 (t, *J* = 7.4 Hz, 3 H, CH$_2$CH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 144.58, 143.78, 137.16, 136.18, 129.76, 129.73, 126.19, 123.74, 123.35, 120.04, 114.61, 107.65, 22.29, 21.49, 12.86 ppm. LRMS (EI): *m*/*z* = 299 [M]$^+$. $C_{17}H_{17}NO_2S$ (299.39): calcd. C 68.20, H 5.72, N 4.68; found C 67.96, H 5.74, N 4.66.

3j:[16] 84% from **1j**; colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 8.2 Hz, 1 H, aromatic), 7.52–7.49 (m, 2 H, aromatic), 7.43–7.42 (m, 4 H, aromatic), 7.38–7.33 (m, 1 H, aromatic), 7.28–7.25 (m, 3 H, aromatic), 7.04 (d, *J* = 8.2 Hz, 2 H, aromatic), 6.54 (s, 1 H, aromatic), 2.28 (s, 3 H, *p*Ts 4-CH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 144.50, 142.10, 138.23, 134.58, 132.38, 130.53, 130.30, 1229.17, 128.63, 127.48, 126.77, 124.76, 124.29, 120.66, 116.64, 113.62, 21.51 ppm. LRMS (EI): *m*/*z* = 347 [M]$^+$.

3k:[17] 11% from **1k**, 80% of **1k** was recovered; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.2 Hz, 1 H, indole),

7.66 (d, J = 8.2 Hz, 2 H, aromatic), 7.15–7.21 (m, 3 H, indole, aromatic), 6.65 (d, J = 7.7 Hz, 1 H, indole), 6.45 (s, 1 H, indole), 3.88 (s, 3 H, OCH_3), 2.58 (s, 3 H, pTs 4-CH_3), 2.34 (s, 3 H, indole-CH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 152.07, 144.63, 138.15, 136.27, 135.77, 129.82, 126.30, 124.50, 119.79, 107.60, 106.30, 103.69, 55.36, 21.54, 15.78 ppm. LRMS (EI): m/z = 315 $[M]^+$.

3l: 73% from **1l**; colorless prisms, m.p. 80–82 °C (MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, J = 10.4 Hz, 1 H, indole), 7.62 (d, J = 8.2 Hz, 2 H, aromatic), 7.18 (d, J = 8.2 Hz, 2 H, aromatic), 6.84–6.87 (m, 2 H, indole), 6.26 (s, 1 H, indole), 3.81 (s, 3 H, OCH_3), 2.57 (d, J = 0.9 Hz, 3 H, pTs 4-CH_3), 2.33 (s, 3 H, indole-CH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 156.33, 144.57, 138.05, 136.07, 131.50, 130.64, 29.77, 126.18, 115.28, 112.12, 109.72, 102.61, 55.50, 21.49, 15.75 ppm. LRMS (EI): m/z = 315 $[M]^+$. $C_{17}H_{17}NO_3S$ (315.38): calcd. C 64.74, H 5.43, N 4.44; found C 64.40, H 5.44, N 4.35.

3m:[17] 98% from **1m**; colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.74 (d, J = 1.7 Hz, 1 H, indole H-7), 7.64 (d, J = 8.6 Hz, 2 H, aromatic), 7.26 (d, J = 8.6 Hz, 1 H, indole H-4), 7.20 (d, J = 8.0 Hz, 2 H, aromatic), 6.79 (dd, J = 8.0, 2.3 Hz, 1 H, indole H-5), 6.25 (s, 1 H, indole H-3), 3.88 (s, 3 H, OCH_3), 2.55 (d, J = 1.1 Hz, 3 H, pTs 4-CH_3), 2.34 (s, 3 H, indole-CH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 157.17, 144.64, 137.91, 136.24, 135.96, 129.82, 126.19, 123.37, 120.24, 112.14, 109.25, 99.30, 55.74, 21.52, 15.75 ppm. LRMS (EI): m/z = 315 $[M]^+$. $C_{17}H_{17}NO_3S$ (315.39): calcd. C 64.74, H 5.43, N 4.44; found C 64.58, H 5.47, N 4.35.

3n: 92% from **1n**; colorless prisms, m.p. 108.0–109.5 °C (MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, J = 8.6 Hz, 2 H, aromatic), 7.26 (d, J = 8.2 Hz, 2 H, aromatic), 7.10–7.01 (m, 2 H, indole), 6.63 (d, J = 7.7 Hz, 1 H, indole), 6.37 (d, J = 0.9 Hz, 1 H, indole H-3), 3.61 (s, 3 H, OCH_3), 2.73 (d, J = 0.9 Hz, 3 H, pTs 4-CH_3), 2.39 (s, 3 H, indole-CH_3) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 147.36, 143.46, 140.58, 138.95, 132.1, 129.20, 126.53, 126.32, 124.14, 112.77, 109.40, 107.22, 55.52, 21.54, 17.14 ppm. LRMS (EI): m/z = 315 $[M]^+$. $C_{17}H_{17}NO_3S$ (315.39): calcd. C 64.74, H 5.43, N 4.44; found C 64.91, H 5.40, N 4.43.

Preparation of 4a: To a solution of **3a** (28 mg, 0.098 mmol) in EtOH (1.0 mL) was added KOH (56 mg, 1.0 mmol), and the mixture was refluxed for 7 h. The mixture was cooled and partitioned between HCl (1 N) and Et_2O. The aqueous layers were combined with saturated aqueous $NaHCO_3$, and the organic compounds were extracted with AcOEt. The AcOEt layers were washed with brine and dried with Na_2SO_4. After the solvent was removed, the residue was purified by column chromatography (hexane/AcOEt, 24:1) to give **4a** (12 mg, 90%); red prisms, m.p. 55–56 °C (EtOH/H_2O), ref.[18] 59–60 °C (EtOH/H_2O). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.82 (br., 1 H, NH), 7.51 (d, J = 8.0 Hz, 1 H, indole), 7.27 (d, J = 8.0 Hz, 1 H, indole), 7.04–7.12 (m, 2 H, indole), 6.21 (d, J = 1.1 Hz, 1 H, indole 3-H), 2.44 (d, J = 1.1 Hz, 3 H, indole) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 135.81, 135.17, 128.76, 120.68, 119.44, 110.32, 99.94, 13.27 ppm. LRMS (EI): m/z = 131 $[M]^+$.

C-3 Alkylation of 4a To Give 5a: To a solution of **4a** (77 mg, 0.59 mmol) in THF (2.0 mL) was added dropwise a solution of nBuLi in hexane (1.65 M solution, 0.62 mmol, 0.38 mL) at 0 °C. The reaction mixture was stirred at ambient temperature for 30 min, and to the mixture was added a solution of $ZnCl_2$ in Et_2O (1.0 M solution, 0.60 mmol, 0.60 mL). The mixture was stirred at r.t. for 25 min. To the mixture, a solution of benzyl iodoacetate (1.10 mmol, 303 mg) in THF (1.0 mL) was cannulated over 3 min, and the mixture was stirred at r.t. for 22 h. The reaction was quenched with saturated aqueous NH_4Cl. The organic compounds were extracted with AcOEt, and the combined organic layers were washed with HCl (1 N), saturated aqueous $NaHCO_3$ and brine and dried with Na_2SO_4. After the solvent was removed, the residue was purified by column chromatography (hexane/AcOEt, 9:1) to give **5a** (134 mg, 81%); yellow solid, m.p. 84.0–85.0 °C (EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84 (br., 1 H, NH), 7.52 (d, J = 7.4 Hz, 1 H, indole), 7.29–7.34 (m, 5 H, CH_2-Ph), 7.25 (d, J = 7.1 Hz, 1 H, indole), 7.06–7.13 (m, 2 H, indole), 5.11 (s, 2 H, CH_2-Ph), 3.74 (s, 2 H, indole-CH_2-CO), 2.38 (s, 3 H, indole-CH_3) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 171.85, 135.99, 135.03, 132.69, 128.44, 128.40, 128.05, 121.19, 119.50, 118.06, 110.21, 104.35, 66.42, 30.37, 11.66 ppm. HRMS (EI): calcd. for $C_{18}H_{17}NO_2$ $[M]^+$ 279.1259; found 279.1259. $C_{18}H_{17}NO_2 \cdot 0.1H_2O$: calcd. C 76.90, H 6.17, N 4.98; found C 76.70, H 6.14, N 5.01.

Synthesis of Indomethacin (6)

4l: To a solution of **3l** (35 mg, 0.11 mmol) in EtOH (1.0 mL) and THF (0.1 mL) was added KOH (62 mg, 1.1 mmol), and the mixture was refluxed for 6 h. The mixture was cooled and partitioned between HCl (1 N) and Et_2O. The aqueous layers were combined with saturated aqueous $NaHCO_3$, and the organic compounds were extracted with AcOEt. The AcOEt layers were washed with brine and dried with Na_2SO_4. After the solvent was removed, the residue was purified by column chromatography (hexane/AcOEt, 24:1) to give **4l** (16 mg, 92%); colorless prisms, m.p. 84–85 °C (Et_2O/hexane), ref.[19] 86–88 °C (Et_2O/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.74 (br., 1 H, NH), 7.16 (d, J = 9.2 Hz, 1 H, indole 7-H), 6.99 (d, J = 2.3 Hz, 1 H, indole 6-H), 6.76 (dd, J = 8.6, 2.3 Hz, 1 H, indole 5-H), 6.15 (s, 1 H, indole 3-H), 3.84 (s, 3 H, OCH_3), 2.42 (s, 3 H, indole-CH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 153.92, 135.93, 131.06, 129.39, 110.83, 110.52, 101.77, 100.13, 55.79, 13.63 ppm. LRMS (EI): m/z = 161 $[M]^+$.

5l: To a solution of **4l** (430 mg, 2.5 mmol) in THF (15.0 mL) was added dropwise a solution of nBuLi in hexane (1.61 M solution, 3.0 mmol, 1.8 mL) at 0 °C. The reaction mixture was stirred at ambient temperature for 1 h, and to the mixture was added a solution of $ZnCl_2$ in Et_2O (1.0 M solution, 2.5 mmol, 2.5 mL). The mixture was stirred at r.t. for 30 min. To the mixture, a solution of benzyl iodoacetate (3.0 mmol, 828 mg) in THF (3.5 mL) was cannulated, and the mixture was stirred at r.t. for 17 h. The reaction was quenched with saturated aqueous NH_4Cl. The organic compounds were extracted with AcOEt, and the combined organic layers were washed with HCl (1 N), saturated aqueous $NaHCO_3$, and brine and dried with Na_2SO_4. After the solvent was removed, the residue was purified by column chromatography (hexane/AcOEt, 8:1) to give **5l** (510 mg, 67%); yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.77 (br. s, 1 H, NH), 7.21–7.29 (m, 5 H, CH_2-Ph), 7.07 (d, J = 8.6 Hz, 1 H, indole 7-H), 6.95 (d, J = 2.3 Hz, 1 H, indole 4-H), 6.75 (dd, J = 8.6, 2.3 Hz, 1 H, indole 6-H), 5.10 (s, 2 H, CH_2-Ph), 3.76 (s, 3 H, OCH_3), 3.69 (s, 2 H, indole-CH_2CO), 2.30 (s, 3 H, indole-CH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 171.87, 154.00, 135.94, 133.55, 130.06, 128.77, 128.43, 128.07, 128.04, 110.99, 110.96, 104.13, 100.18, 66.43, 55.73, 30.48, 11.69 ppm. LRMS (EI): m/z = 309 $[M]^+$. $C_{19}H_{19}NO_3$ (309.36): calcd. C 73.77, H 6.19, N 4.53; found C 73.63, H 6.29, N 4.53.

6: To a solution of **5l** (51 mg, 0.16 mmol) in THF (1.5 mL) was added a solution of tBuOK in THF (1.0 M solution, 0.2 mL, 0.20 mmol) at –78 °C, and the mixture was stirred for 30 min. To the mixture, a solution of p-chlorobenzoyl chloride (25 μL, 0.20 mmol) in THF (1.0 mL) was added dropwise, and the mixture was stirred for 2 h. The reaction was quenched with saturated aqueous NH_4Cl. The organic compounds were extracted with AcOEt, and the combined organic layers were washed with saturated aque-

ous $NaHCO_3$, H_2O, and brine and dried with Na_2SO_4. After the solvent was removed, the residue was purified by column chromatography (hexane/AcOEt, 24:1) to give indomethacin benzyl ester (66 mg, 92%); colorless needles, m.p. 89–90 °C (EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, J = 8.6 Hz, 2 H, benzoyl), 7.54 (d, J = 8.6 Hz, 2 H, benzoyl), 7.29–7.34 (m, 5 H, CH_2-*Ph*), 6.93 (d, J = 2.3 Hz, 1 H, indole 4-H), 6.67 (dd, J = 9.1, 2.7 Hz, 1 H, indole 7-H), 6.63 (d, J = 9.1 Hz, 1 H, indole 6-H), 5.14 (s, 2 H, C*H*$_2$-Ph), 3.76 (s, 3 H, OC*H*$_3$), 3.71 (s, 2 H, indole-C*H*$_2$CO), 2.36 (s, 3 H, indole-C*H*$_3$) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 170.61, 168.20, 155.93, 139.15, 135.84, 135.64, 133.79, 131.10, 130.68, 130.49, 129.03, 128.48, 128.23, 128.09, 114.90, 112.42, 111.78, 101.03, 66.72, 55.52, 30.32, 13.34, 0.98 ppm. LRMS (EI): m/z = 447 $[M]^+$. $C_{26}H_{22}ClNO_4$ (447.91): calcd. C 69.72, H 4.93, N 3.12; found C 69.43, H 4.93, N 3.12. To a solution of indomethacin benzyl ester (45 mg, 0.10 mmol) in AcOEt (2.0 mL) was added Pd/C (10%, 20 mg), and the mixture was stirred under H_2 for 40 min. The mixture was filtered through Celite 545. After the solvent was removed, the residue was purified by column chromatography ($CHCl_3$) to give **6** (30 mg, 84%); pale yellow solid, m.p. 152–153 °C (50% aq. EtOH), ref.[20] 153–154 °C (50% aq. alcohol). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.66 (d, J = 8.6 Hz, 2 H, benzoyl), 7.46 (d, J = 8.6 Hz, 2 H, benzoyl), 6.94 (d, J = 2.9 Hz, 1 H, indole 4-H), 6.85 (d, J = 9.2 Hz, 1 H, indole 7-H), 6.67 (dd, J = 8.9, 2.9 Hz, 1 H, indole 6-H), 3.82 (s, 3 H, OC*H*$_3$), 3.69 (s, 2 H, indole-C*H*$_2$CO), 2.38 (s, 3 H, indole-C*H*$_3$) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 176.78, 168.28, 156.03, 139.32, 136.24, 133.74, 131.18, 130.74, 130.42, 129.13, 114.99, 111.78, 111.67, 101.19, 55.70, 30.00, 13.29 ppm. LRMS (EI): m/z = 357 $[M]^+$.

Synthesis of Indomethacin Derivative 7

4m: To a solution of **3m** (424 mg, 1.34 mmol) in EtOH (13 mL) was added KOH (2.3 g, 40.3 mmol), and the mixture was refluxed for 4 h. The mixture was cooled and partitioned between water and CH_2Cl_2. The combined organic layers were washed with water and dried with Na_2SO_4. After the solvent was removed, the residue was purified by column chromatography (hexane/AcOEt, 15:1) to give **4m** (151 mg, 70%); colorless prisms, m.p. 100–101 °C (Et_2O/hexane), ref.[21] 103–104 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72 (br., 1 H, N*H*), 7.37 (d, J = 8.6 Hz, 1 H, indole 4-H), 6.80 (d, J = 2.3 Hz, 1 H, indole 7-H), 6.74 (dd, J = 8.6, 2.3 Hz, 1 H, indole 5-H), 6.13 (s, 1 H, indole 3-H), 3.83 (s, 3 H, OC*H*$_3$), 2.40 (s, 3 H, indole-C*H*$_3$) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 155.58, 136.67, 133.80, 123.23, 120.03, 108.93, 99.93, 94.40, 55.68, 13.64 ppm. LRMS (EI): m/z = 161 $[M]^+$.

5m: To a solution of **4m** (70 mg, 0.43 mmol) in THF (2.0 mL) was added dropwise a solution of *n*BuLi in hexane (1.59 M solution, 0.65 mmol, 0.41 mL) at 0 °C. The reaction mixture was stirred at ambient temperature for 50 min, and to the mixture was added a solution of $ZnCl_2$ in Et_2O (1.0 M solution, 0.52 mmol, 0.52 mL). The mixture was stirred at r.t. for 50 min. To the mixture, a solution of benzyl iodoacetate (178 mg, 0.65 mmol) in THF (1.5 mL) was cannulated over 3 min, and the mixture was stirred at r.t. for 17 h. The reaction was quenched with saturated aqueous NH_4Cl. The organic compounds were extracted with AcOEt, and the combined organic layers were washed with saturated aqueous NH_4Cl and brine and dried with Na_2SO_4. After the solvent was removed, the residue was purified by column chromatography (hexane/AcOEt, 5:1) to give **5m** (48 mg, 36%); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (br., 1 H, N*H*), 7.54 (d, J = 8.6 Hz, 1 H, indole 4-H), 7.26–7.34 (m, 5 H, CH_2-*Ph*), 6.73 (dd, J = 8.6, 2.3 Hz, 1 H, indole 5-H), 6.67 (d, J = 2.3 Hz, 1 H, indole 7-H), 5.09 (s, 2 H, C*H*$_2$-Ph), 3.78 (s, 3 H, OC*H*$_3$), 3.68 (s, 2 H, indole-C*H*$_2$CO), 2.25 (s, 3 H, indole-C*H*$_3$) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 171.90, 155.82, 135.95, 135.74, 131.34, 128.42, 128.04, 122.79, 118.62, 108.82, 103.97, 94.46, 66.39, 55.66, 30.42, 11.52 ppm. HRMS (EI): calcd. for $C_{19}H_{19}NO_3$ $[M]^+$ 309.1365; found 309.1365. $C_{19}H_{19}NO_3 \cdot 0.1H_2O$: calcd. C 73.34, H 6.22, N 4.50; found C 73.25, H 6.48, N 4.40.

7: To a solution of **5m** (40 mg, 0.13 mmol) in THF (1.0 mL) was added a solution of *t*BuOK in THF (1.0 M solution, 156 µL, 0.16 mmol) at –78 °C, and the mixture was stirred for 30 min. To the mixture, a solution of *p*-chlorobenzoyl chloride (20 µL, 0.16 mmol) in THF (1.0 mL) was added dropwise, and the mixture was stirred for 2 h. The reaction was quenched with saturated aqueous NH_4Cl. The organic compounds were extracted with AcOEt, and the combined organic layers were washed with brine and dried with Na_2SO_4. After the solvent was removed, the residue was purified by column chromatography (hexane/AcOEt, 20:1) to give an *N*-acylated compound (56 mg, 97%); yellow needles, m.p. 92–93 °C (EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65 (d, J = 8.3 Hz, 2 H, benzoyl), 7.46 (d, J = 8.3 Hz, 2 H, benzoyl), 7.29–7.37 (m, 6 H, CH_2-*Ph*, indole 4-H), 6.82 (dd, J = 8.6, 2.0 Hz, 1 H, indole 5-H), 6.72 (d, J = 2.0 Hz, 1 H, indole 7-H), 5.13 (s, 2 H, C*H*$_2$-Ph), 3.70 (s, 3 H, OC*H*$_3$), 3.67 (s, 2 H, indole-C*H*$_2$CO), 2.26 (s, 3 H, indole-C*H*$_3$) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 170.69, 168.58, 156.99, 139.27, 137.05, 135.70, 133.82, 133.30, 131.13, 129.08, 128.50, 128.23, 128.11, 123.51, 118.81, 112.33, 111.35, 99.21, 66.71, 55.49, 30.38, 13.40 ppm. HRMS (EI): calcd. for $C_{26}H_{22}ClNO_4$ $[M]^+$ 447.1237; found 447.1238. To a solution of the above *N*-acylated compound (39 mg, 87 µmol) in AcOEt (1.0 mL) was added Pd/C (10%, 13 mg), and the mixture was stirred under H_2 for 3 h. The mixture was filtered through Celite 545. After the solvent was removed, the residue was purified by column chromatography (hexane/AcOEt, 2:1) to give **7** (78 mg, 90%); pale yellow solid, m.p. 145–146 °C (50% aq. EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (d, 2 H, J = 8.6 Hz, benzoyl): δ = 7.45 (d, J = 8.6 Hz, 2 H, benzoyl), 7.37 (d, J = 8.6 Hz, 1 H, indole 4-H), 6.85 (dd, J = 8.6, 2.3 Hz, 1 H, indole 5-H), 6.68 (d, J = 2.3 Hz, 1 H, indole 7-H), 3.68 (s, 3 H, OC*H*$_3$), 3.66 (s, 2 H, indole-C*H*$_2$CO), 2.29 (s, 3 H, indole-C*H*$_3$) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 176.61, 168.61, 157.05, 139.41, 137.05, 133.73, 133.63, 131.18, 129.15, 123.38, 118.69, 111.67, 111.40, 99.33, 55.53, 30.00, 13.30 ppm. HRMS (EI): calcd. for $C_{19}H_{16}ClNO_4$ $[M]^+$ 357.0768; found 357.0768.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of **1a**,**i**–**n**, **3a**, **3f**,**i**–**n**, **4a**, **4l**, **4m**, **5a**, **5l**, **5m**, **6**, and **7**.

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