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UTILIZATION OF THE ANTIAROMATIC 2*H*-INDOL-2-ONE RING SYSTEM FOR THE SYNTHESIS OF SUBSTITUTED SPIRO-OXINDOLES†

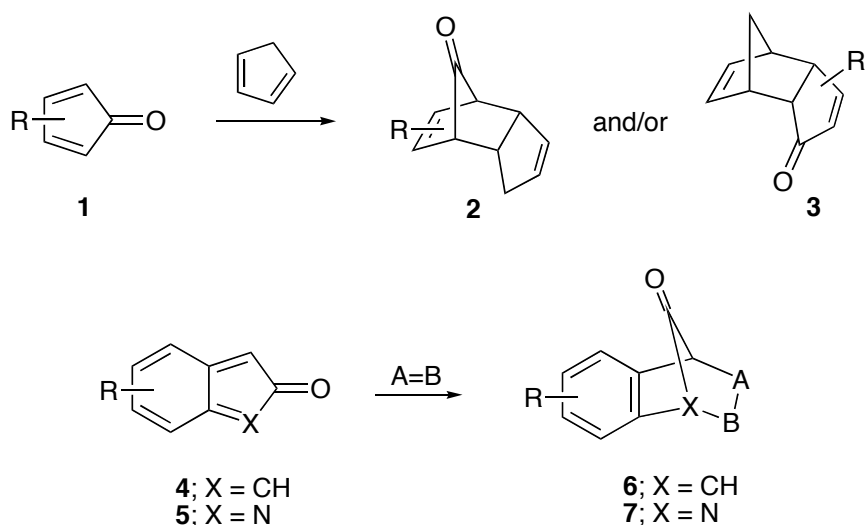
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Abstract – The utility of the quasi-antiaromatic 2*H*-indol-2-one system for the synthesis of substituted oxindoles and spiro-oxindoles was investigated. The highly reactive 2*H*-indol-2-one could be readily generated by treating a 3-hydroxy substituted 1,3-dihydroindol-2-one with a Lewis acid. Stepwise addition of various π -substrates such as styrene, furan and thiophene to the 2*H*-indol-2-one system occurs smoothly to produce a carbocation intermediate which subsequently undergoes proton loss to afford substituted oxindoles. The cyclization was also carried out in an intramolecular fashion to give spiro-substituted oxindoles in good yield.

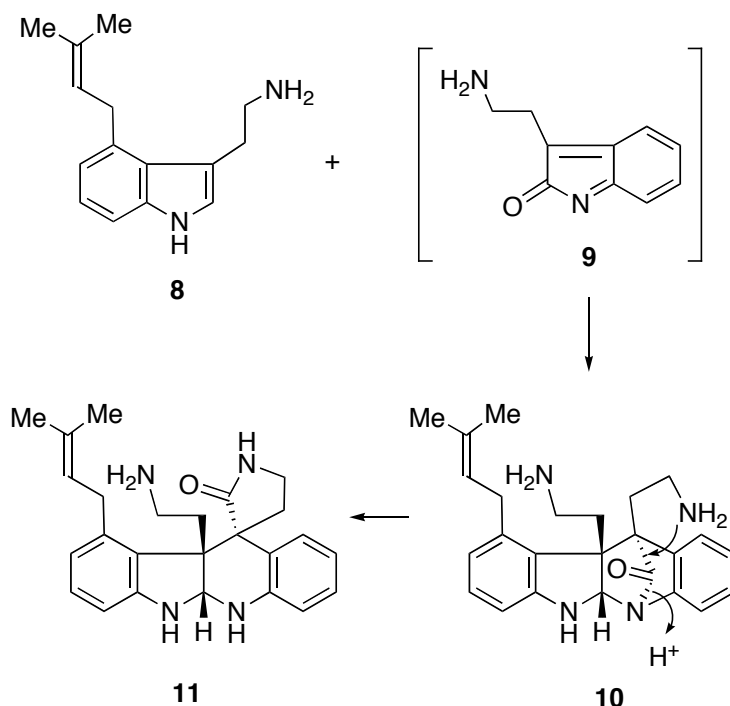
The Diels-Alder cycloaddition is recognized as one of the most powerful carbon-carbon bond forming reactions in organic synthesis.¹ Cyclopentadienones **1** have emerged as one of the more interesting components for the Diels-Alder reaction and these compounds react readily with many different unsaturated π -systems (Scheme 1).² Cyclopentadienones may behave as either the diene or dienophile to give the adducts of type **2** and/or **3**, respectively when reacted with other dienes, such as cyclopentadiene.³ The pericyclic reaction behavior of **1** has been rationalized in terms of frontier molecular orbital (FMO) interactions.⁴ FMO analysis predicts that **1** and its substituted derivatives should behave exclusively as dienophiles toward both cyclopentadiene and the related 6-substituted fulvenes. Although the cycloaddition chemistry of cyclopentadienones has attracted much attention in recent years, the related inden-2-one system **4** has not been as thoroughly explored.⁵ Nevertheless, there are quite a number of examples where this highly reactive intermediate has been generated and trapped with various dienophiles in a [4+2] manner to yield cycloadducts such as **6**.⁶ On the other hand, the analogous aza antiaromatic indol-2-one **5** has rarely been reported in the literature. Few examples exist in the chemical literature for generating and trapping this reactive intermediate.⁷ It has recently been suggested that a [4+2]-cycloaddition of the quasi-antiaromatic 2*H*-indol-2-one **5** might be involved in the biosynthesis of the alkaloid communesin B.^{8,9}

Scheme 1



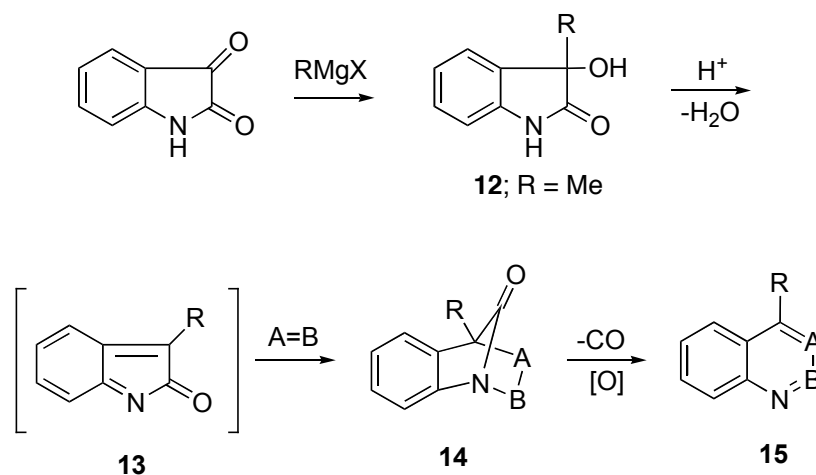
Biogenetically, the communesins can be thought of as arising *via* an oxidative union of the prenylated tryptamine **8** with 3-(2-aminoethyl)indol-2-one (**9**). The resulting cycloadduct **10** was suggested to undergo a rapid transamidation reaction with the strained bridged bicyclic lactam to afford the spiro lactam **11** (Scheme 2). Since there have been few examples of the Diels-Alder reaction of *2H*-indol-2-ones in the literature, we thought it would be worthwhile to study this intriguing cycloaddition reaction. Our approach to synthesizing and trapping such a reactive species is shown in Scheme 3. We envisioned oxindole **12** being prepared *via* a Grignard reaction with isatin, and we expected that further treatment of **12** with a Lewis acid

Scheme 2



would result in the loss of H₂O to generate the highly reactive antiaromatic intermediate **13**. Trapping **13** with various alkenes in a [4+2] sense should generate cycloadduct **14**, which could possibly lose carbon monoxide and then be readily oxidized to produce compounds such as quinoline **15**.

Scheme 3



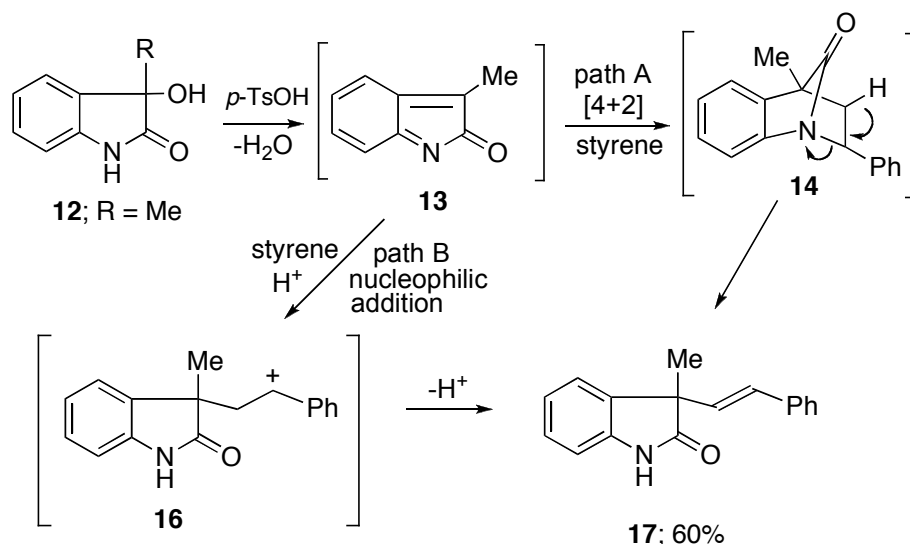
To test the feasibility of this type of cycloaddition, we first prepared oxindole **12** (R = Me) *via* a methyl magnesium bromide addition to isatin which proceeded in 98% yield.¹⁰ Functionalized 1,3-dihydroindol-2-ones (oxindoles) represent the core structure of many important pharmacological agents and natural products.¹¹ For example, the oxindole motif is present in the anti-Parkinson's drug ropinirole,¹² in non-opioid nociceptin receptor ligands,¹³ and in the growth hormone secretagogues.¹⁴ In addition, the oxindole moiety constitutes a key structural element in several natural products¹⁵ including the antibiotic speradine¹⁶ and the cytostatic welwistatin.¹⁷ Consequently, the development of novel synthetic strategies leading to 3,3-disubstituted oxindole derivatives is of paramount importance. Various methods have been developed for the construction of this ring system. Among the techniques commonly used in their synthesis are derivatization of other heterocycles,¹⁸ intramolecular Heck reactions,¹⁹ arylation of amides²⁰ and variants of the Stolle reaction.²¹ The synthesis of oxindoles has also been carried out using the Friedel-Crafts reaction,²² the Gassman sulfonium ylide reaction,²³ photoinduced²⁴ and radical cyclizations²⁵ as well as transition-metal catalyzed reactions.²⁶ Even though a variety of methods are available, simple and efficient approaches toward 3,3-disubstituted oxindoles still remain scarce. In connection with our current studies dealing with the synthesis of indole alkaloids, we describe herein an approach to diversely functionalized oxindoles starting from the commercially available isatin.²⁷

RESULTS AND DISCUSSION

3-Substituted 3-hydroxyindolin-2-ones are important substrates for studies of biological activity

as well as useful synthetic intermediates for drug candidates and alkaloids.²⁸ Their construction has stimulated the interest of synthetic chemists, and the challenging absolute control of the quaternary center has recently been achieved.²⁹ These compounds can readily be prepared by treating 2,3-indolinediones (isatins) with a variety of organometallic reagents.³⁰ Our initial investigations involved the use of several electron rich π -bonds as possible dienophiles. Thus, treatment of **12** with various Lewis acids in the presence of commercially available trapping agents such as 1-morpholino-1-cyclohexene or 1-morpholino-1-cyclopentene failed to yield a cycloadduct and only led to recovered starting material. On the other hand, heating a sample of **12** with a 10 molar excess of styrene in toluene at reflux in the presence of *p*-toluenesulfonic acid afforded 3-methyl-3-styryl-1,3-dihydro-indol-2-one (**17**) in 60% yield as the only isolable product (Scheme 4). Two possible reactions paths may account for the observed product. Path A involves a [4+2]-cycloaddition of the isoindol-2-one intermediate **13** with styrene giving rise to cycloadduct **14** which then undergoes simultaneous proton loss and ring opening to generate product **17**. Path B has styrene reacting with **13** in a nucleophilic addition manner producing carbocation **16**, which then suffers a subsequent proton loss to produce **17**. It would appear as though the reaction actually takes place *via* path B as we were unable to detect the

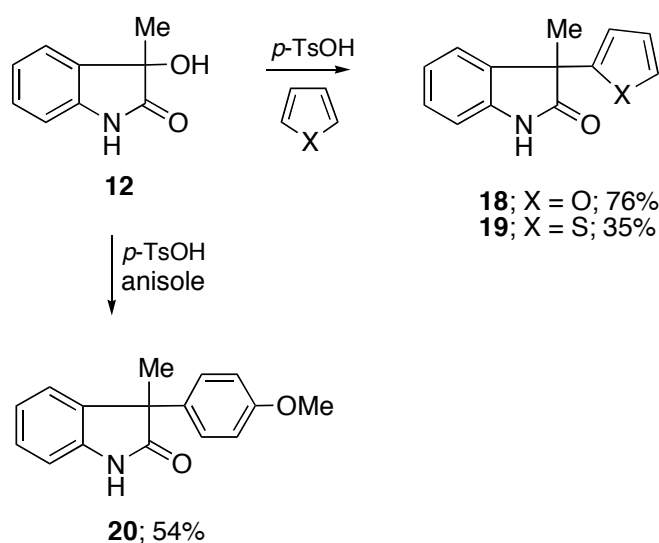
Scheme 4



presence of cycloadduct **14**, even when the reaction was carefully monitored by NMR spectroscopy. Apparently, stepwise addition to the quasi-antiaromatic *2H*-indol-2-one species is preferred over the [4+2]-cycloaddition reaction. It should be noted that while the mechanism shown in Scheme 4 is not unreasonable, there is no real evidence for the proposed electrophilic addition of **13** to styrene. An alternative possibility could involve an initial dehydration of **12** with acid to produce a reactive benzylic cation which would then undergo stepwise addition of styrene to eventually give **17**. We found however, that the *N*-methyl analog of **12** did not undergo the substitution reaction with styrene and this observation provides good support for the requirement

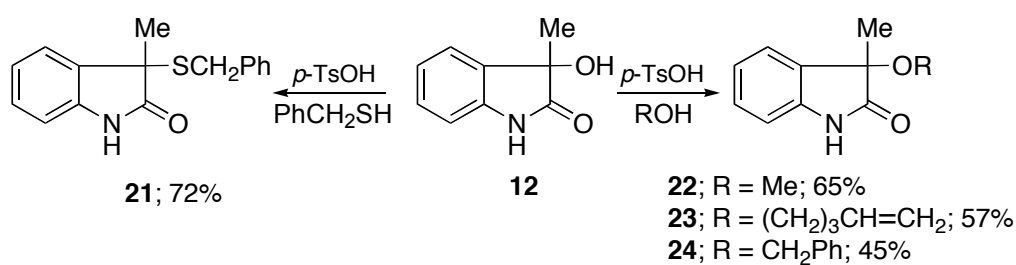
of a 2*H*-indol-2-one intermediate (*i.e.* **13**). A series of additional experiments showed that this electrophilic induced substitution reaction proceeds with a variety of substrates containing activated π -bonds. Thus, we were pleased to find that an analogous substitution reaction occurred using furan, thiophene and anisole as added nucleophilic π -substrates.³¹ Oxindoles **18**, **19** and **20** were isolated in good yields for these three systems (Scheme 5).

Scheme 5



Because all of the above examples involve nucleophilic reagents possessing π -bonds, we decided to study the substitution reaction using an alcohol or a mercaptan as the nucleophilic partner. We found that treatment of **12** with benzyl mercaptan afforded sulfide **21** in 72% yield. Similarly, the reaction of **12** with methanol, 4-penten-1-ol, and benzyl alcohol gave rise to ethers **22** (65%), **23** (57%), and **24** (45%) as the exclusive products (Scheme 6).

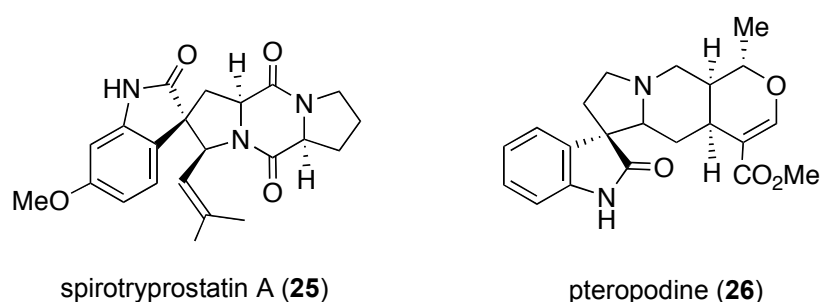
Scheme 6



Spirocyclic compounds correspond to systems containing one carbon atom common to two rings and are structurally quite interesting entities.³² Among them, the heterocyclic spiro-oxindole framework is an important structural motif in biologically relevant compounds as both natural products and pharmaceuticals.³³ For example, spirotryprostatin A (**25**), a natural product

isolated from the fermentation broth of *Aspergillus fumigatus*, has been identified as a novel inhibitor of microtubule assemble,³⁴ and pteropodine (**26**) has been shown to modulate the function of muscarinic and serotonin receptors³⁵ (Figure 1). Because of their remarkable biological activity, a reasonable amount of effort has been devoted to the stereoselective synthesis of substituted spiro-oxindole derivatives.³⁶ Due to our ongoing interest in indole alkaloids, we decided to expand the scope of the synthetic methodology outlined above and apply the method toward the cyclization of several 3-hydroxy substituted oxindoles bearing unsaturated side chains.

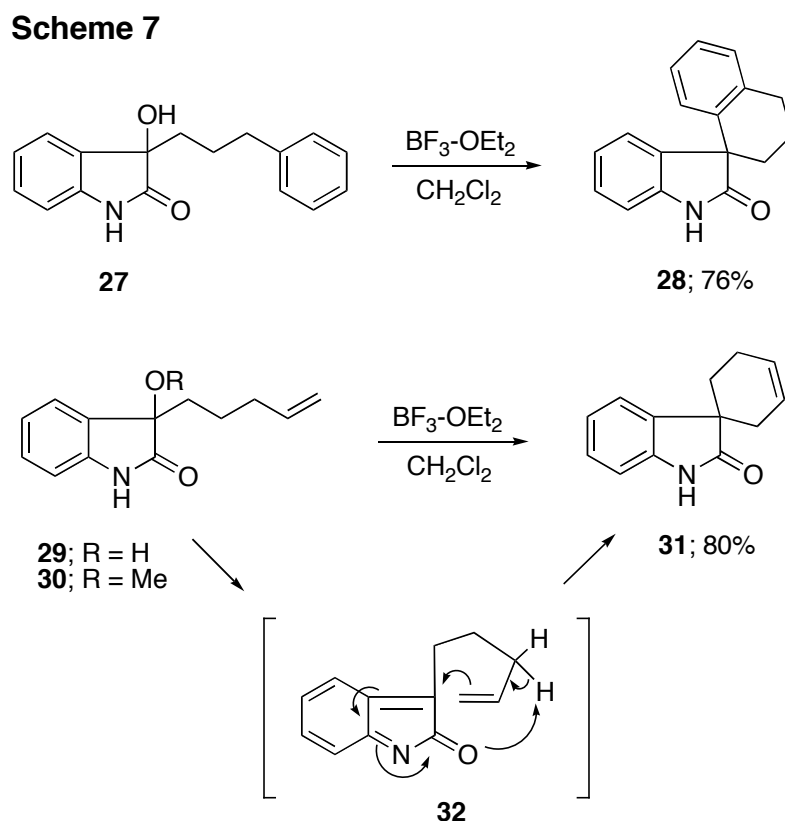
Figure 1



The exploitation of cationic π -cyclizations for the construction of polycyclic ring systems has been the object of intense study since the early 1950s.³⁷ Initial forays into this arena demonstrated the syntheses of fused ring terpenoid-type systems, and later efforts were carried out for the syntheses of spiro and bridged ring carbocyclic systems.³⁸ These studies showed that a wide variety of terminating moieties can be incorporated into the cyclization substrate and this resulted in the easy construction of terpenoids as well as alkaloids. For our methodological studies into the formation of spiro-oxindoles, we selected to investigate some very simple core systems. Our initial inquiry involved a study of the cyclization reaction of 3-hydroxy-3-(3-phenylpropyl)-1,3-dihydro-indol-2-one (**27**). We found that **27** could be converted into spiro-oxindole **28** in 76% yield upon heating with $\text{BF}_3 \cdot \text{OEt}_2$ in CH_2Cl_2 at reflux. A related acid-catalyzed cyclization using 3-hydroxy-3-pent-4-enyl-1,3-dihydroindole-2-one (**29**) also occurred under similar conditions. Most interestingly, a single cyclized product was generated in 80% isolated yield.³⁹ Extensive NMR studies showed that the product corresponded to spiro-oxindole **31** (Scheme 7). One possibility to account for the high specificity associated with this particular cyclization is that the reaction proceeds *via* a pseudo-ene type process that involves 2*H*-indol-2-one **32**. This pathway avoids the formation of a highly reactive secondary carbocation intermediate. Such an intermediate would have been expected to produce a mixture of regioisomeric spiro-oxindoles (*vide infra*). The identical cyclized product (*i.e.*, **31**) was also formed from the acid-catalyzed reaction of the corresponding methyl ether **30**.

Interestingly, the reaction of (4-methylpent-4-enyl)indolone **33** with $\text{BF}_3 \cdot \text{OEt}_2$ failed to produce the expected spirocyclic oxindole **36**, giving instead the cyclic tetrahydro-2*H*-pyran **35** in 81%

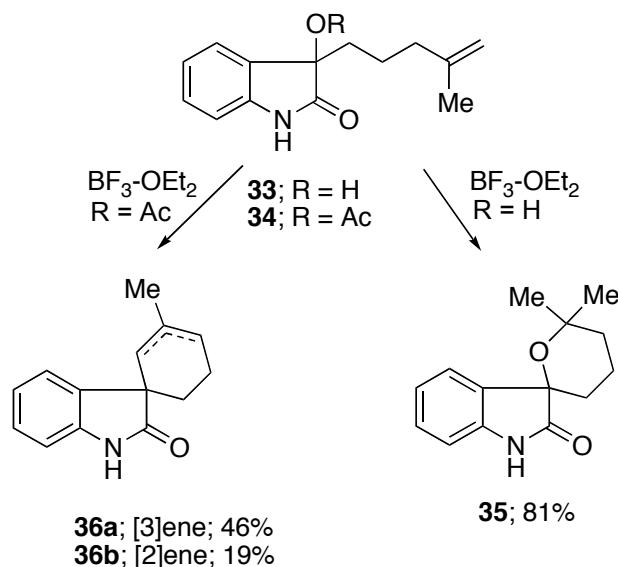
yield as the exclusive product. In retrospect, this result is not totally unexpected as protonation of the activated olefinic π -bond leads to a more stable tertiary carbocation and this path occurs in preference to formation of the *2H*-indolone intermediate. However, if **33** is first converted into



the corresponding acetate **34**, the spiro-substituted oxindole **36** is indeed formed (65%) by a pathway involving attack of the alkene π -bond onto a transient indol-2-one intermediate (Scheme 8). In this case, a 2.5:1-mixture of regioisomer alkenes (**36a/36b**) is produced and this is consistent with a mechanism for cyclization that proceeds *via* a distinct tertiary carbocation intermediate.

In summary, we have demonstrated the utility of the quasi-antiaromatic *2H*-indol-2-one system for the synthesis of substituted oxindole derivatives. The highly reactive indolone behaves more like an electrophilic π -acceptor than as a reactive diene. The formation of several cyclized spiro-oxindoles is the result of an initial loss of water from a 3-hydroxy substituted 1,3-dihydroindol-2-one followed by nucleophilic addition of a tethered alkenyl π -bond. The mechanistic details of the cyclization reaction seem to depend on the nucleophilicity of the attacking olefin. When a 4-pentenyl group is attached to the lactam ring, the reaction seemingly proceeds in an ene-like process, with assistance from the amide carbonyl group and this leads to a single cyclized product.

Scheme 8



However, attachment of a 4-methyl-pent-4-enyl group to the indolone ring afforded a 2.5:1-mixture of cyclized products. The formation of a mixture of regioisomeric products is consistent with a distinct tertiary carbocation intermediate being involved with this system. Further investigations are currently underway to exploit 2*H*-indol-2-ones as useful substrates for alkaloid synthesis and our future findings will be reported in due course.

EXPERIMENTAL SECTION

Melting points are uncorrected. MS spectra were determined at an ionizing voltage of 70eV. Unless otherwise noted, all reactions were performed in flame dried glassware under an atmosphere of dry argon. Solutions were evaporated under reduced pressure with a rotary evaporator and the residue was chromatographed on a silica gel column using an ethyl acetate/hexane mixture as the eluent unless specified otherwise.

3-Hydroxy-3-methyl-1,3-dihydroindol-2-one (12). To a solution of 3.0 g (20.4 mmol) of isatin in 50 mL of THF was added 20.4 mL (61 mmol) of MeMgBr (3M solution in Et₂O) at -78 °C. After stirring for 2 h, the mixture was quenched with a saturated aqueous solution of NH₄Cl and extracted with EtOAc. The combined organic extracts were washed with H₂O, brine, dried over Na₂SO₄, and concentrated under reduced pressure to give 3.3 g (98%) of **12** as a yellow solid: mp 154-156 °C (lit.,¹⁰ mp 160-161 °C); IR (neat) 3270, 1716, 1623, 1472, 1334, and 1193 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.62 (s, 3H), 3.15 (brs, 1H), 6.90 (d, 1H, *J* = 7.6 Hz), 7.10 (dt, 1H, *J* = 7.6 and 1.0 Hz), 7.27 (dt, 1H, *J* = 7.8 and 1.3 Hz), 7.41 (d, 1H, *J* = 7.3 Hz), and 8.22 (brs, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 25.0, 74.2, 110.6, 123.5, 124.1, 129.9, 131.9, 139.9, and 186.4.

General Experimental Procedure for the Acid-Catalyzed Substitution Reactions of Oxindole 12. To a solution of oxindole **12** in 10 mL of toluene was added the appropriate nucleophile together with a catalytic amount of *p*-toluenesulfonic acid (20 mol%). The reaction

mixture was heated at reflux for 48 h. After cooling to rt, the mixture was extracted with EtOAc. The combined organic extracts were washed with a NaHCO₃ solution, H₂O, brine, dried over Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography to give the pure product.

3-Methyl-3-styryl-1,3-dihydroindol-2-one (17). Following the general procedure described above, 0.2 g (1.2 mmol) of oxindole **12** and 1.4 mL (12 mmol) of styrene in 20 mL of toluene was heated for 48 h. The crude residue obtained after solvent removal was subjected to flash silica gel chromatography to give 0.18 g (60%) of **17** as a light tan solid: mp 116-118 °C; IR (neat) 3242, 3028, 2971, 2927, 2870, 1710, 1619, and 1472 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.63 (s, 3H), 6.35 (d, 1H, *J* = 16.2 Hz), 6.46 (d, 1H, *J* = 16.2 Hz), 6.99 (d, 1H, *J* = 7.6 Hz), 7.11 (t, 1H, *J* = 7.3 Hz), 7.21-7.35 (m, 7H), and 8.65 (brs, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 23.0, 51.1, 110.1, 122.6, 124.3, 126.5, 127.7, 128.2, 128.5, 129.5, 130.3, 133.4, 136.5, 140.1, and 181.2.

3-Furan-2-yl-3-methyl-1,3-dihydroindol-2-one (18). The general procedure described above was followed using 0.1 g (0.6 mmol) of oxindole **12** and 0.9 mL (12.3 mmol) of furan in 10 mL of toluene. The crude residue was subjected to flash silica gel chromatography after solvent removal to give 0.1 g (76%) of **18** as an off-white solid: mp 162-164 °C; IR (neat) 3219, 2980, 2873, 2833, 1714, 1620, and 1472 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.79 (s, 3H), 6.22 (d, 1H, *J* = 3.2 Hz), 6.30-6.32 (m, 1H), 6.96 (d, 1H, *J* = 7.6 Hz), 7.06 (t, 1H, *J* = 7.3 Hz), 7.22-7.26 (m, 2H), 7.35 (s, 1H), and 8.48 (brs, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 22.2, 49.4, 106.7, 110.2 (2 carbons), 122.8, 124.0, 128.5, 132.9, 140.1, 142.7, 153.0, and 179.5; HRMS Calcd. for [C₁₃H₁₁NO₂ + H⁺]: 214.0863. Found 214.0860.

3-Methyl-3-thiophen-2-yl-1,3-dihydroindol-2-one (19). Following the general procedure described above, 0.2 g (1.2 mmol) of oxindole **12** and 0.5 mL (6 mmol) of thiophene in 15 mL of toluene was heated at reflux for 48 h. Removal of the solvent under reduced pressure followed by flash silica gel chromatography gave 0.1 g (35%) of **19** as a light pink solid: mp 170-172 °C; IR (neat) 3215, 2973, 1711, 1618, and 1472 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.85 (s, 3H), 6.92-6.98 (m, 3H), 7.07-7.12 (m, 1H), 7.21-7.32 (m, 3H), and 8.56 (brs, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 25.6, 50.6, 110.4, 122.8, 124.3, 124.9, 124.95, 126.8, 128.5, 134.5, 140.1, 144.5, and 180.6.

3-(4-Methoxyphenyl)-3-methyl-1,3-dihydroindol-2-one (20). Following the general procedure described above, 0.2 g (1.2 mmol) of oxindole **12** and 0.65 mL (6 mmol) of anisole in 15 mL of toluene was heated at reflux for 48 h. Removal of the solvent under reduced pressure followed by flash silica gel chromatography gave 0.16 g (54%) of **20** as a clear oil: IR (neat) 3215, 2968, 2836, 1708, 1617, 1511, and 1471 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.79 (s, 3H), 3.77 (s, 3H), 6.84 (d, 2H, *J* = 8.9 Hz), 6.96 (d, 1H, *J* = 7.6 Hz), 7.05 (t, 1H, *J* = 7.3 Hz), 7.13 (d, 1H, *J* = 7.0 Hz), 7.21-7.25 (m, 3H), and 8.79 (brs, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 23.5, 52.0, 55.2, 110.1, 113.9, 122.7, 124.3, 127.8, 128.0, 132.6, 135.7, 140.3, 158.7, and 182.4.

3-Benzylsulfanyl-3-methyl-1,3-dihydroindol-2-one (21). The general procedure described above was followed using 0.2 g (1.2 mmol) of oxindole **12** and 0.7 mL (6 mmol) of benzyl

mercaptan in 15 mL of toluene. The crude residue was subjected to flash silica gel chromatography after solvent removal to give 0.23 g (72%) of **21** as an off-white solid: mp 109-111 °C; IR (neat) 3214, 3029, 2924, 1714, 1618, and 1471 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.70 (s, 3H), 3.56 (d, 1H, $J = 12.1$ Hz), 3.67 (d, 1H, $J = 12.1$ Hz), 6.93 (d, 1H, $J = 7.6$ Hz), 7.08-7.28 (m, 7H), 7.35 (d, 1H, $J = 7.6$ Hz), and 8.65 (brs, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 22.4, 34.1, 51.5, 110.1, 123.0, 124.0, 127.1, 128.3, 128.9, 129.1, 131.5, 136.5, 139.9, and 179.9.

3-Methoxy-3-methyl-1,3-dihydroindol-2-one (22). Following the general procedure described above, 0.2 g (1.2 mmol) of oxindole **12** and 2 mL (50 mmol) of methanol in 20 mL of toluene was heated for 48 h. The crude mixture obtained after removal of the solvent was subjected to flash silica gel chromatography to give 0.14 g (65%) of **22** as an off-white solid: mp 120-122 °C (lit.,⁴⁰ mp 124-124.5 °C); IR (neat) 3252, 2982, 2929, 2826, 1726, 1622, and 1472 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.60 (s, 3H), 3.10 (s, 3H), 6.99 (d, 1H, $J = 7.6$ Hz), 7.11 (dt, 1H, $J = 7.6$ and 1.0 Hz), 7.27-7.33 (m, 2H), and 9.52 (brs, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 23.9, 53.2, 80.2, 110.7, 123.1, 124.1, 128.8, 129.7, 140.7, and 179.7.

3-Methyl-3-pent-4-enyloxy-1,3-dihydroindol-2-one (23). Following the general procedure described above, 0.1 g (0.6 mmol) of oxindole **12** and 0.32 mL (3.1 mmol) of 4-penten-1-ol in 10 mL of toluene was heated for 48 h. Concentration of the reaction mixture under reduced pressure followed by flash silica gel chromatography gave 0.08 g (57%) of **23** as a pale orange oil: IR (neat) 3250, 3079, 2979, 2929, 2871, 1725, 1621, and 1472 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.58 (s, 3H), 1.58-1.68 (m, 2H), 2.03-2.10 (m, 2H), 3.05 (dt, 1H, $J = 8.3$ and 6.4 Hz), 3.23 (dt, 1H, $J = 8.3$ and 6.4 Hz), 4.90 (dd, 1H, $J = 10.2$ and 1.9 Hz), 4.96 (dd, 1H, $J = 17.2$ and 1.9 Hz), 5.68-5.79 (m, 1H), 6.92 (d, 1H, $J = 7.6$ Hz), 7.09 (t, 1H, $J = 7.3$ Hz), 7.25-7.31 (m, 2H), and 8.67 (brs, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 24.2, 29.0, 30.1, 64.9, 79.4, 110.4, 114.7, 123.1, 124.0, 129.5, 129.7, 138.1, 140.3, and 179.3.

3-Benzyloxy-3-methyl-1,3-dihydroindol-2-one (24). The general procedure described above was followed using 0.2 g (1.2 mmol) of oxindole **12** and 0.6 mL (6 mmol) of benzyl alcohol in 15 mL of toluene. The crude residue was subjected to flash silica gel chromatography after solvent removal to give 0.14 g (45%) of **24** as a yellow solid: mp 124-126 °C; IR (neat) 3252, 3032, 2981, 2928, 2868, 1723, 1622, and 1472 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.67 (s, 3H), 4.13 (d, 1H, $J = 10.5$ Hz), 4.30 (d, 1H, $J = 10.5$ Hz), 7.00 (d, 1H, $J = 7.6$ Hz), 7.12 (t, 1H, $J = 7.6$ Hz), 7.24-7.33 (m, 6H), 7.39 (d, 1H, $J = 7.3$ Hz), and 9.33 (brs, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 24.2, 67.9, 79.8, 110.7, 123.2, 124.1, 127.7, 128.0, 128.2, 129.3, 129.8, 137.5, 140.6, and 179.4.

3-Hydroxy-3-(3-phenylpropyl)-1,3-dihydroindol-2-one (27). To a stirred solution of 0.25 g (10.2 mmol) of magnesium turnings in 20 mL of THF was added 1.0 mL (6.8 mmol) of (3-bromopropyl)benzene dropwise. The resulting mixture was heated at reflux for 2 h, after which time the reaction was cooled to -78 °C, and 0.5 g (3.4 mmol) of isatin dissolved in 10 mL of THF was slowly added. The solution was allowed to stir at -78 °C for 30 min, followed by an additional 2 h at rt. The solution was then quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was separated, and the aqueous layer was

extracted with EtOAc. The combined organic layers were washed with H₂O, brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.37 g (41%) of **27** as a pale orange oil: IR (neat) 3263, 3027, 2942, 2859, 1720, 1623, and 1472 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.41-1.58 (m, 2H), 1.93-2.04 (m, 2H), 2.50-2.59 (m, 2H), 3.53 (s, 1H), 6.85 (d, 1H, *J* = 7.6 Hz), 7.03-7.24 (m, 7H), 7.30 (d, 1H, *J* = 7.3 Hz), and 8.63 (brs, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 24.8, 35.7, 37.9, 76.9, 110.5, 123.1, 124.2, 125.8, 128.25, 128.3, 129.6, 130.4, 140.4, 141.6, and 180.9.

Spiro-oxindole 28. To a stirred solution of 0.05 g (0.19 mmol) of oxindole **27** in 10 mL of CH₂Cl₂ was added 0.07 mL (0.57 mmol) of boron trifluoride etherate at rt. The resulting solution was heated at reflux for 12 h, cooled to rt, and then added to a saturated aqueous solution of NaHCO₃. The organic layer was separated, and the aqueous layer was extracted three times with methylene chloride. The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.036 g (76%) of **28** as a pale yellow solid: mp 213-215 °C; IR (neat) 3197, 3061, 3024, 2938, 1707, 1618, and 1471 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.98-2.09 (m, 2H), 2.23-2.39 (m, 2H), 2.95-3.06 (m, 2H), 6.61 (d, 1H, *J* = 7.6 Hz), 6.95-7.05 (m, 4H), 7.12-7.23 (m, 3H), and 8.64 (brs, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 18.7, 29.2, 34.0, 52.7, 109.9, 122.7, 124.2, 126.4, 127.2, 127.8, 128.1, 129.7, 134.8, 137.7, 137.9, 140.2, and 183.3; HRMS Calcd. for [C₁₇H₁₅NO + H⁺]: 250.1226. Found 250.1223.

3-Hydroxy-3-pent-4-enyl-1,3-dihydroindol-2-one (29). To a stirred solution of 0.37 g (15.2 mmol) of magnesium turnings in 20 mL of THF was added 1.2 mL (10.2 mmol) of 5-bromo-pent-1-ene dropwise. The resulting mixture was heated at reflux for 2 h, after which time the reaction was cooled to -78 °C, and 0.5 g (3.4 mmol) of isatin dissolved in 10 mL of THF was slowly added. The solution was allowed to stir at -78 °C for 30 min, followed by an additional 2 h at rt. The solution was then quenched with a saturated aqueous solution of NH₄Cl and extracted with EtOAc. The organic layer was separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with H₂O, brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.32 g (43%) of **29** as an off-white solid: mp 72-74 °C; IR (neat) 3254, 2939, 1716, 1623, and 1473 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.16-1.37 (m, 2H), 1.93-2.02 (m, 4H), 3.48 (s, 1H), 4.90 (d, 1H, *J* = 9.8 Hz), 4.93 (d, 1H, *J* = 17.2 Hz), 5.62-5.72 (m, 1H), 6.88 (d, 1H, *J* = 7.6 Hz), 7.07 (t, 1H, *J* = 7.6 Hz), 7.24 (t, 1H, *J* = 7.6 Hz), 7.35 (d, 1H, *J* = 7.6 Hz), and 8.64 (brs, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 22.2, 33.5, 37.7, 77.1, 110.6, 115.0, 123.1, 124.1, 129.5, 130.6, 137.9, 140.5, and 181.4.

Spiro-oxindole 31. To a stirred solution of 0.05 g (0.23 mmol) of **29** in 10 mL of CH₂Cl₂ was added 0.09 mL (0.69 mmol) of boron trifluoride etherate at rt. The resulting solution was heated at reflux for 12 h, cooled to rt, and added to a saturated aqueous solution of NaHCO₃. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The

crude residue was subjected to flash silica gel chromatography to give 0.04 g (80%) of **31** as a pale yellow oil: IR (neat) 3215, 3027, 2921, 2838, 1707, 1619, and 1470 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.60-1.64 (m, 1H), 2.00-2.10 (m, 2H), 2.34-2.36 (m, 2H), 2.63-2.70 (m, 1H), 5.86-5.96 (m, 2H), 6.95 (d, 1H, $J=7.6$ Hz), 6.99 (dt, 1H, $J=7.6$ and 1.3 Hz), 7.21 (dt, 1H, $J=7.6$ and 1.3 Hz), 7.31 (d, 1H, $J=7.6$ Hz), and 8.54 (brs, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 21.7, 28.9, 31.5, 46.3, 109.7, 122.3, 124.3, 124.7, 126.8, 127.6, 134.9, 139.8, and 183.1; HRMS Calcd. for $[\text{C}_{13}\text{H}_{13}\text{NO} + \text{H}^+]$: 200.1070. Found 200.1062.

3-Methoxy-3-pent-4-enyl-1,3-dihydroindol-2-one (30). To a stirred solution of 0.2 g (0.92 mmol) of oxindole **29** in 10 mL of toluene was added 0.75 mL (18.4 mmol) of MeOH and 0.035 g (20 mol%) of *p*-toluenesulfonic acid. The resulting mixture was heated at reflux for 12 h, cooled to rt, and the solvent was removed under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.13 g (60%) of **30** as a pale yellow oil: IR (neat) 3251, 3078, 2929, 1721, 1620, and 1471 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.18-1.43 (m, 2H), 1.94-2.02 (m, 4H), 3.09 (s, 3H), 4.89 (d, 1H, $J=9.5$ Hz), 4.93 (d, 1H, $J=17.2$ Hz), 5.63-5.73 (m, 1H), 6.94 (d, 1H, $J=7.6$ Hz), 7.10 (t, 1H, $J=7.3$ Hz), 7.27-7.31 (m, 2H), and 8.97 (brs, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 22.0, 33.6, 37.1, 53.1, 83.4, 110.5, 115.0, 123.0, 124.6, 127.5, 129.7, 138.0, 141.2, and 179.0.

To a stirred solution of 0.05 g (0.22 mmol) of **30** in 10 mL of CH_2Cl_2 was added 0.08 mL (0.66 mmol) of boron trifluoride etherate at rt. The resulting solution was heated at reflux for 12 h, cooled to rt, and the mixture was added to a saturated aqueous solution of NaHCO_3 . The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.035 g (77%) of **31** as a pale yellow oil.

3-Hydroxy-3-(4-methylpent-4-enyl)-1,3-dihydroindol-2-one (33). To a stirred solution of 0.11 g (4.5 mmol) of magnesium turnings in 10 mL of THF was added 0.50 g (3.1 mmol) of 5-bromo-2-methylpent-1-ene dropwise. The resulting mixture was heated at reflux for 2 h, after which time the reaction was cooled to -78 $^\circ\text{C}$, and 0.15 g (1.0 mmol) of isatin dissolved in 5 mL of THF was slowly added. The solution was allowed to stir at -78 $^\circ\text{C}$ for 30 min, followed by an additional 2 h at rt. The solution was then quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with H_2O , brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.18 g (75%) of **33** as an off-white solid: mp $84-86$ $^\circ\text{C}$; IR (neat) 3259, 3075, 2939, 1717, 1623, and 1472 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.21-1.42 (m, 2H), 1.60 (s, 3H), 1.87-2.00 (m, 4H), 3.20 (s, 1H), 4.59 (s, 1H), 4.66 (s, 1H), 6.89 (d, 1H, $J=7.6$ Hz), 7.08 (t, 1H, $J=7.6$ Hz), 7.26 (t, 1H, $J=7.3$ Hz), 7.36 (d, 1H, $J=7.3$ Hz), and 8.39 (brs, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 20.7, 22.1, 37.4, 37.7, 77.1, 110.5 (2 carbons), 123.1, 124.2, 129.5, 130.6, 140.5, 144.8, and 181.2.

Spiro-oxindole 35. To a stirred solution of 0.05 g (0.22 mmol) of oxindole **33** in 10 mL of CH₂Cl₂ was added 0.08 mL (0.66 mmol) of boron trifluoride etherate at rt. The resulting solution was heated at reflux for 12 h, cooled to rt, and the mixture was added to a saturated aqueous solution of NaHCO₃. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.04 g (81%) of **35** as a clear oil: IR (neat) 3223, 2935, 1716, 1622, and 1473 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.32 (s, 3H), 1.53 (s, 3H), 1.60-1.93 (m, 5H), 2.35-2.44 (m, 1H), 6.77 (d, 1H, *J* = 7.6 Hz), 7.02 (dt, 1H, *J* = 7.3 and 1.0 Hz), 7.18 (dt, 1H, *J* = 7.6 and 1.0 Hz), 7.28 (d, 1H, *J* = 7.3 Hz), and 8.27 (brs, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 14.7, 28.0, 32.1, 33.0, 36.3, 74.4, 76.9, 109.6, 122.8, 124.0, 129.1, 133.4, 139.7, and 179.7.

Acetic Acid 3-(4-methylpent-4-enyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl Ester (34). To a stirred solution of 0.14 g (0.6 mmol) of oxindole **33** in 15 mL of CH₂Cl₂ was added 0.15 mL (1.8 mmol) of pyridine, 15 mg (0.12 mmol) of 4-(dimethylamino)pyridine and 0.2 mL (1.8 mmol) of acetic anhydride. The resulting mixture was stirred at rt for 2 h, after which time the reaction mixture was added to H₂O. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with H₂O, brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.13 g (70%) of acetic acid 1-acetyl-3-(4-methyl-pent-4-enyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl ester as a clear oil which was immediately used in the next step.

To a 0.13 g (0.4 mmol) sample of the above compound in 10 mL of methanol was added 8 mg (0.08 mmol) of anhydrous sodium carbonate. After stirring at 0 °C for 30 min, the reaction mixture was quenched with H₂O, and extracted with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.1 g (94%) of **34** as a clear oil: IR (neat) 3389, 2948, 1730, 1623, and 1472 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.32-1.37 (m, 1H), 1.47-1.52 (m, 1H), 1.62 (s, 3H), 1.89-1.99 (m, 4H), 2.07 (s, 3H), 4.62 (s, 1H), 4.69 (s, 1H), 6.85 (d, 1H, *J* = 7.6 Hz), 7.03 (t, 1H, *J* = 7.6 Hz), 7.20 (d, 1H, *J* = 7.6 Hz), 7.25 (t, 1H, *J* = 7.6 Hz), and 7.68 (brs, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 19.7, 20.7, 22.1, 36.0, 37.3, 80.0, 110.1, 110.7, 122.7, 122.9, 128.2, 129.6, 140.7, 144.7, 169.1, and 176.3.

Spiro-oxindole 36. To a stirred solution of 0.05 g (0.18 mmol) of **34** in 10 mL of CH₂Cl₂ was added 0.07 mL (0.55 mmol) of boron trifluoride etherate at rt. The resulting solution was heated at reflux for 12 h, cooled to rt, and the mixture was added to a saturated aqueous solution of NaHCO₃. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.025 g (65%) of an inseparable 2.3:1 mixture of isomers of **36** as a clear oil: IR (neat) 3215, 2968, 2930,

1707, 1620, and 1470 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.12 (s, 2H), 1.56, 1.74 (s, 3H), 1.94-2.01 (m, 2H, minor isomer), 2.26-2.31 (m, 1H), 2.57-2.64 (m, 1H), 2.85-2.95 (m, 2H), 5.64 (brs, 1H, minor isomer), 6.88 (d, 1H, $J = 7.9$ Hz), 6.93-7.00 (m, 1H), 7.04 (t, 1H, $J = 7.6$ Hz), 7.19 (t, 1H, $J = 7.6$ Hz), 7.30 (d, 1H, $J = 7.3$ Hz), and 8.38 (brs, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 17.9, 18.9, 21.9, 23.8, 26.7, 28.1, 28.8, 36.0, 47.1, 56.4, 109.6, 109.8, 120.5, 122.2, 122.5, 123.2, 124.2, 127.6, 127.7, 127.9, 129.9, 131.8, 133.5, 134.9, 139.9, 140.2, 181.3, and 183.6; HRMS Calcd. for $[\text{C}_{14}\text{H}_{15}\text{NO} + \text{H}^+]$: 214.1226. Found 214.1225.

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