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

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Abstract – The utility of the quasi-antiaromatic 2H-indol-2-one system for the synthesis of substituted oxindoles and spiro-oxindoles was investigated. The highly reactive 2H-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 2H-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 2H-indol-2-one 5 might be involved in the biosynthesis of the alkaloid communesin B.8,9
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 spirolactam 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 $\text{H}_2\text{O}$ 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 ($R = \text{Me}$) via a methyl magnesium bromide addition to isatin which proceeded in 98% yield. Functionalized 1,3-dihydroindol-2-ones (oxindoles) represent the core structure of many important pharmacological agents and natural products. For example, the oxindole motif is present in the anti-Parkinson’s drug ropinirole, in non-opioid nociceptin receptor ligands, and in the growth hormone secretagogues. In addition, the oxindole moiety constitutes a key structural element in several natural products including the antibiotic speradine and the cytostatic welwistatin. 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, intramolecular Heck reactions, arylation of amides and variants of the Stolle reaction. The synthesis of oxindoles has also been carried out using the Friedel-Crafts reaction, the Gassman sulfonium ylide reaction, photoinduced and radical cyclizations as well as transition-metal catalyzed reactions. 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.

**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.\textsuperscript{28} Their construction has stimulated the interest of synthetic chemists, and the challenging absolute control of the quaternary center has recently been achieved.\textsuperscript{29} These compounds can readily be prepared by treating 2,3-indolinediones (isatins) with a variety of organometallic reagents.\textsuperscript{30} Our initial investigations involved the use of several electron rich $\pi$-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 \textbf{[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 \emph{via} path B as we were unable to detect the presence of cycloadduct 14, even when the reaction was carefully monitored by NMR spectroscopy. Apparently, stepwise addition to the quasi-antiaromatic 2$H$-indol-2-one species is preferred over the \textbf{[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 2H-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 \(\pi\)-bonds. Thus, we were pleased to find that an analogous substitution reaction occurred using furan, thiophene and anisole as added nucleophilic \(\pi\)-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 \(\pi\)-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**

Spiro cyclic 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, and pteropodine (26) has been shown to modulate the function of muscarinic and serotonin receptors (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. 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**

![Spirotryprostatin A (25)](image)

![Pteropodine (26)](image)

The exploitation of cationic \( \pi \)-cyclizations for the construction of polycyclic ring systems has been the object of intense study since the early 1950s. Initial forays into this arena demonstrated the syntheses of fused ring terpenoid-type systems, and later efforts were carried out for the syntheses of spirole and bridged ring carbocyclic systems. 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 BF\(_3\)•OEt\(_2\) in CH\(_2\)Cl\(_2\) 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. 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 2H-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 BF\(_3\)•OEt\(_2\) failed to produce the expected spirocyclic oxindole 36, giving instead the cyclic tetrahydro-2H-pyran 35 in 81%
yield as the exclusive product. In retrospect, this result is not totally unexpected as protonation of the activated olefinic \( \pi \)-bond leads to a more stable tertiary carbocation and this path occurs in preference to formation of the 2\( H \)-indolone intermediate. However, if 33 is first converted into

![Scheme 7](image)

the corresponding acetate 34, the spiro-substituted oxindole 36 is indeed formed (65\%) by a pathway involving attack of the alkene \( \pi \)-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 2\( H \)-indol-2-one system for the synthesis of substituted oxindole derivatives. The highly reactive indolone behaves more like an electrophilic \( \pi \)-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 \( \pi \)-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.
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 2H-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 and gave 0.1 g (35%) of 17 as a light tan solid: mp 122-124 °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-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 0.16 g (54%) of 18 as a light tan 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), 2.92 (m, 3H), 7.12 (m, 1H), 7.21 (ms, 7H), and 8.79 (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
mercaptopan 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\(^{-1}\); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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); \(^13\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) 22.4, 34.1, 51.5, 110.1, 123.0, 124.0, 127.1, 128.3, 128.9, 129.1, 131.7, 136.5, 139.9, and 179.5.

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\(^{-1}\); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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); \(^13\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) 23.9, 53.2, 60.2, 110.7, 123.1, 124.1, 128.8, 129.7, 140.7, and 179.7.

3-Methyl-3-pent-4-enloyloxy-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\(^{-1}\); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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); \(^13\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) 23.9, 53.2, 80.2, 110.7, 123.1, 124.1, 128.8, 129.7, 140.7, and 179.7.

3-Benzylxy-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\(^{-1}\); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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); \(^13\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) 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\(_4\)Cl 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 0.32 g (43%) of 28 as a pale yellow solid: mp 213-215 °C; IR (neat) 3197, 3061, 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+]2: 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; ¹H-NMR (400 MHz, CDCl₃) 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); ¹³C-NMR (100 MHz, CDCl₃) 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 [C₁₃H₁₃NO + 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, 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 CH₂Cl₂ was added 0.08 mL (0.66 mmol) of boron trifluoride etherate at rt. The resulting solution was heated at reflux for 2 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 0.035 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-enone dropwise. The resulting mixture was heated at reflux for 2 h, after which time the reaction was cooled to -78 °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 °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 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 0.18 g (75%) of 33 as an off-white solid: mp 84-86 °C; IR (neat) 3259, 3075, 2939, 1717, 1623, and 1472 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) 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); ¹³C-NMR (100 MHz, CDCl₃) 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 0.025 g (65%) of an inseparable 2.3:1 mixture of isomers 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 = 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-1H-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-1H-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 1.47-1.52 (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\(^{-1}\); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) 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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REFERENCES AND NOTES

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31. An earlier report by Funk and Fuchs described the formation of 3,3-disubstituted 2-indolinones from the reaction of 3-bromo-3-alkyl-2-indolinones with base. The reaction was proposed to proceed by way of a 2H-indol-2-one intermediate which could be trapped by various π-nucleophiles as well as by a [4+2]-cycloaddition with a tethered alkyne, see: J. R. Fuchs and R. L. Funk, *Org. Lett.*, 2005, 7, 677.


39. Attempts to induce a related cyclization using the homologous 3-hydroxy-3-but-3-enyl-1,3-dihydroindol-2-one system failed to produce a spiro cyclopentene derivative and only starting material was recovered.