coupling reactions \cite{10,11} direct nucleophilic displacement by an amine of the type required for 8 or 11 is unknown. Similarly, only one case employing an amide-tethered alkyne in an intramolecular pyrone Diels–Alder reaction has been reported, \cite{12} and that example involved a constrained, polycyclic framework that could not afford the more versatile bicyclic products targeted here, compounds with patterning not readily prepared through other Diels–Alder processes \cite{13-15}.

Herein, we demonstrate that both of the pathways outlined in Scheme 1 are viable, and afford building blocks that are not commercially available or are expensive. In addition, they have led to a range of hydroindolone structures, including formal syntheses of both mesembrine (3) and gracilamine (5), with the latter sequence being the shortest to date in terms of steps count.

Our efforts began by probing substrates of type 8, readily prepared from 4,6-dichloropyrone (7) by adding a primary amine and stirring them with \( n \)-Pr\(_3\)NEt from −78 to 0°C, followed by protection of the nitrogen atom with an acetyl group (see the Supporting Information for details). \cite{12} Subsequent dissolution of the mixture in toluene and microwave irradiation at 140°C for 5 h smoothly effected conversion of the five substrates shown in Table 1 into the expected indolines, typically in excellent yields for the Diels–Alder step and irrespective of the group attached to the terminal end of the alkyne; thermal conditions also worked, albeit with longer reaction times \cite{13}. Of note, replacement of the remaining 4-chloro motif within the starting pyrone can be achieved prior to cycloaddition, with phenylsulfide used for purposes of illustration (entry 5).

In addition, with the exception of product 16, none of these materials or their deprotected counterparts are known molecular entities based on standard search engines; 16 in its unprotected form (as a free indoline or HCl salt) is commercially available from several suppliers \cite{14}. This finding highlights, in general terms, that 4,6-substituted indoline building blocks are relatively scarce, particularly in comparison to their 5,7-substituted counterparts. As such, we believe that this approach is complementary to other methods for indoline/indole synthesis, including those based on Diels–Alder reactions and C–H functionalization \cite{15}. It also affords an overall ease of variability using simple starting materials.

From the standpoint of generating complexity, however, the process of converting 7 into 13 (see Scheme 1) using tethered alkenediones is arguably of greater value. Its success would generate hydroindolone structures bearing a quaternary center at a ring junction, a possible second chiral center, and a vinyllogous amide in a single reaction. Not only is the connection of these final products to a Diels–Alder process more challenging to discern, but if there was broad ability to vary groups X and Y along with additional ring sizes through their linking tether, then products of direct relevance to the amaryllidaceae, sceletium, and zamianthe families of alkaloids (such as 3–6) should be accessible in short order.

We began by utilizing substrates of general type 25 (Scheme 2), materials bearing a disubstituted alkenedione and group X being an aromatic ring.

Pleasingly, four initial examples, in which both the carbamate protecting group and aryl ring were varied (to match those of natural products 3 and 4), were readily converted into 27–30 using similar microwave conditions. Treatment of the intermediate Diels–Alder products with silica gel in CHCl\(_3\) in the same pot (open to air) effected mild hydrolysis of the vinyl chloride. We ascribe the lower yield observed for the formation of compound 29 (59\%) to the thermal lability of its Boc protecting group during the Diels–Alder step \cite{16}. Importantly, compound 30 (X-ray structure of acetate derivative obtained) could be converted into \( \Delta^2 \)-mesembrone (31) \cite{17} through a two-step sequence, thereby completing an eight-step preparation of a minor constituent of \textit{Sceletium ramosissimum} \cite{17} and a known synthetic precursor for mesembrine (3). \cite{18,19}

Furthermore, although 27–30 were produced racemically, \cite{20} access to enantiopure materials could be achieved in a preliminary study by adding a chiral auxiliary onto the nitrogen tether. As shown at the bottom of Scheme 2, these efforts afforded a 1:1 separable mixture of 33.
Pyrone Diels–Alder Routes to Indolines and Hydroindolines: Syntheses of Gracilamine, Mesembrine, and Δ7-Mesembrenone

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Abstract: Although the Diels–Alder reaction has long been utilized for the preparation of numerous heterocycles, opportunities to extend its power remain. Herein, we detail a simple, modular, and robust approach that combines various annulenes regioselectively with 4,6-dichloropyrone to create substrates which, under appropriate conditions, can directly deliver varied indolines and hydroindolines through [4+2] cycloadditions with substitution patterns difficult to access otherwise. As an initial demonstration of the power of the strategy, several different natural products have been obtained either formally or by direct total synthesis, with efforts toward one of these—the complex arylusilicaceae alkaloid gracilamine—affording the shortest route to date in terms of linear step count.

Indolines, oxindoles, and other variants of differential oxidation state are found in a plethora of pharmaceutical agents and natural products, a small selection of which is shown in the top part of Scheme 1. Such ubiquity has induced the development of myriad synthetic approaches for such domains, as evidenced in part by the more than 50 total syntheses of mesembrine (3) and cinerine (4) achieved to date, two recent elegant total syntheses of gracilamine (5) and creative solutions leading to icerinal A (6) and the manzamine alkaloids. As an outgrowth of programs seeking to prepare entire natural product families from common intermediates, we wondered if the range of oxidation states and functional patterning of the materials in Scheme 1 could arise through a single, cohesive strategy starting from a key building block. This compound is 4,6-dichloropyrone (7), readily prepared on a multigram scale in three steps with one chromatographic purification. If its 6-chloro substituent could be chemoselectively displaced by an amine with a pendant alkyne to generate 8 following N-protection (Scheme 1), then a subsequent intramolecular pyrone Diels–Alder reaction followed by in situ retro-[4+2] loss of CO₂ could directly afford indolines with 4,6-substitution.  

Scheme 1. A proposal for modular and concise access to indolines and their derivatives through pyrone Diels–Alder reactions starting from 4,6-dichloropyrone (7).

natively, if an amine with an alkene and a group at position X (and/or Y) was used instead, then a similar sequence would afford 12, a molecule whose vinyl chloride could potentially be hydrolyzed upon work-up to generate vinylogous amide 13 in a single pot. In both cases, these key steps appear to constitute unique reactions. Indeed, although extremely limited precedent for selective tertiary amine addition to 7 was provided during studies on its metal-based C–C cross-

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Aromatization of 1,6,7,7a-Tetrahydro-2H-indol-2-ones

Scheme 1

Scheme 2

intermediate suitable to synthesize either serotonin and melatonin or bufotenin.

Results and Discussion

The benzyl imine (7) of commercial monoprotected 1,4-cyclohexanedicarboxylic acid ester 6 was reacted with maleic anhydride to afford the crystalline adduct 8 in 96% yield from 6 (Scheme 2).

Ester 9 was readily obtained from acid 8 (90% yield), and it was observed that if the esterification time was extended from 0.5 to 4 h, a transacetalization followed, leading directly to the desired compound 10 in 91% yield from ketone 6 (Scheme 3).

The next step was the aromatization of compound 10. The reaction of POCl₃ is known to transform oxindoles into 2-chloroindoles which in turn can lead to indoles by hydrogenolysis. Thus, ester 10 was reacted with POCl₃ and, to our delight, indole 11 was directly obtained in 77% yield. Key-intermediate 11 was also obtained in 74% yield from ketone 6 without purification of the intermediate.

The mechanism proposed for this novel type of aromatization is shown in Scheme 4. Indeed, while HCl elimination is not possible in the case reported above with

Experimental Section

General. TLC was performed with glass plates (0.25 mm) precoated with silica gel, and fast chromatography (F2) was carried out with silica gel (200-400 mesh), using EtOAc/hexanes as eluents (proportions given) unless otherwise stated. GC-MS was performed with a HP 5890 GC apparatus (equipped with a 12 m x 0.20 mm dimethyl polysiloxane capillary column) linked to a HP 5971 EIMS. ¹H and ¹³C NMR spectra of CDC₃ solutions were respectively recorded at 300 and 75.5 MHz. Anhydrous solvents were freshly distilled under argon, CH₃Cl over CaCl₂, ether and THF over Na/benzophenone. All reactions were performed under a nitrogen atmosphere. Unless otherwise indicated, after extractions, organic phases were washed with water and brine, dried over MgSO₄, filtered, and evaporated under reduced pressure.

N-(1,4-Dioxaspiro[4,5]decyl-7(1H)-idene)benzylamine (7). A solution of 3.70 g (25.9 mol%) of commercial 1,4-cyclohexanedione mono-ethylene ketal 6 and 3.00 mL (27.5 mol%) of benzylamine in 25 mL of toluene was heated under reflux in a Dean-Stark apparatus for 6 h. The solvent was removed under reduced pressure affording the crude imine 7 which was directly used for the next step. A sample was obtained by molecular distillation: EIMS m/z (rel int) 245 (M⁺, 18), 173 (6), 159 (17), 158 (14), 154 (11), 126 (9), 101 (52), 91

References


(10) To this end, a preliminary attempt was tried with a first step involving O-alkylation of compound 10 with MeSO₃ but aromatization of the six-atom ring was observed instead, giving oxindole 10a, the amartiation of which with Me₂NH afforded 10b.

Scheme 4

Scheme 5

Methyl 1-Benzyl-5-methoxy-2-oxo-2,6,7,8-tetrahydro-1H-indole-3-acetate (10). Crude imine 7 was obtained above, in using this instance 10.1 g (65.0 mmol) of 6 and 8.00 mL (73.3 mmol) of benzylamine. Its reaction performed above with malonic anhydride (7.32 g, 74.7 mmol) in 20 mL of THF led to crude acid 8 which was dissolved in a mixture of 200 mL of MeOH, 20 mL of 2.2-dimethoxypropane, and 3.00 g of PTSA. The solution was heated at reflux temperature for 4 h and evaporated. The residue was diluted with EtOAc and washed with a saturated solution of NaHCO₃. A FC (80:20) afforded 80 mg of oxindole 10a (vide infra) and 19.3 g (91% yield from ketone 6) of viscous ester 10b. HRMS (El) calculated for C₂₉H₂₇NO₄ [M+H]⁺ 471.1921, found 471.1903 (1%); [M+Na]⁺ 493.1921, found 493.1919 (1%).

Methyl 1-Benzyl-5-methoxy-1H-indole-3-acetate (11). To a solution of 6.50 g (19.9 mmol) of ester 10 in 22 mL of acetonitrile and 5.3 mL (56.7 mmol, 3 eq) of pyridine was added dropwise 4.10 mL (44.0 mmol, 2 eq) of POCl₃, and the mixture was stirred at 60 °C for 1 h. After cooling, water was added, and the mixture was extracted with ether. The organic layer was washed with a saturated solution of NaHCO₃, followed by the usual workup. A FC (20:80) afforded 5.0 g of oily indole 11 in 82% yield (75% from ketone 6): HRMS (Cl⁻, N(CH₃)₂⁺) calculated for C₂₉H₂₇NO₄ [M⁺] - 1HNMR δ 8.09-8.18 (m, H1), 7.17-7.19 (m, H4), 7.12-7.53 (m, H7, H8, H9, H10), 6.95-6.96 (d, J = 8.0 Hz, H1), 4.96 (s, H2), 3.92-3.94 (m, H5), 3.80-3.82 (m, H6), 3.78 (d, J = 8.0 Hz, H3).
above-mentioned results, **10a** and **10b** were obtained in 51% yield in a 1:3:1 ratio from condensation of **8** with 3-bromo-propanaldehyde dimethylacetal. Again, free radical-mediated cyclization-fragmentation of **10a** and **10b** took place smoothly to afford **4a** and **4b** (84% (93%) yield), respectively, as the sole product in each case.

As outlined in Scheme 3, the reaction sequence is likely to involve 6-exo-cyclization of the initially formed primary radical B to the cyclobutanone functionality to generate the

alkoxy radical B. Ring opening, which is driven by the relief of strain in the four-membered ring, affords the fused bicyclic radical C. The ring-annulated radical C is anticipated to suffer 1,5-hydrogen transfer leading to the stabilized R-acyl radical D, which finally undergoes hydrogen abstraction from tributyltin hydride to furnish the bicyclic ketone products **3a.b and 4a.b**. By analogy to a related system examined by Dowd, the preferential formation of the trans isomers would seem more favorable than the alternate cis ring junction isomers, arising from 1,5-hydrogen transfer of **H₄** (vs **H₅**) (i.e., C over C'). Apparently, the methoxy configuration exerted negligible influences on the stereochemical course, which might be attributable to its small A value.

To confirm the presumed reaction mechanism involving 1,5-hydrogen transfer, the deuterium labeling experiment using tributyltin deuteride and also the radical allylation reaction by allyltributyltin were undertaken next (Scheme 4). Reduction of **9a** with tributyltin deuteride afforded **11** having the deuterium R to the carbonyl group as a 4:1 diastereomeric mixture (94%). Similarly, separate treatment of **9a** and **9b** with allyltributyltin resulted in grafting an allyl group adjacent to the carboxyl group to give **12 and 13** in 96 and 95% yields, respectively; in both cases, two diastereomers were obtained in a 1:3:1 ratio. The stereochemistry of **9a,b and 11-13** was tentatively assigned as shown in Scheme 4 primarily by analogy to **10a,b** and **14-16** (vide

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**Scheme 2**

**Scheme 3**

**Figure**

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In this remarkable reaction, the relative stereochemistry of the C12 quaternary center and vicinal chlorine are simultaneously set with excellent stereocontrol. Analysis of the $^1$H NMR spectrum of the crude product mixture indicated that the mass balance was a mixture of several minor byproducts (<2% yield per byproduct); the major and only cleanly isolable byproduct was olefin 59 (<5% yield), resulting from competitive deprotonation α to the chloronium ion.36

With chloroketone 56 in hand, attention turned to accessing fully functionalized reductive cyclization substrate 45 (see Scheme 9) by converting the C20 ketone to the requisite vinyl functionality. Disappointingly, all attempts to reduce ketone 56 resulted in recovery of starting material. Reasoning that the TIPS protecting group was blocking access to the C20 ketone, 56 was destylated by treatment with fluorosilicic acid in warm acetonitrile to give hydroxy ketone 60 (Scheme 14).37 Interestingly, prolonged heating (>12 h) resulted in formation of cyclobutane quinolone 62.38 This unanticipated byproduct likely arises by acid-mediated retro-alkoxy chloride elimination to give putative intermediate 61, followed by CO$_2$ extrusion and intramolecular condensation.

To avoid complications that could arise by the retro-aldol pathway illustrated in Scheme 14, hydroxy ketone 60 was reduced with Me$_2$NHBr(OAc)$_2$, to give diol 63 (Scheme 15). Fortuitously, diol 63 crystallized from CDCl$_3$, and single-crystal X-ray diffraction provided definitive proof of the assigned stereochemistry at C12 and C13 set by the semipinacol rearrangement. Exposure of diol 63 to Martin sulfurane39 resulted in selective dehydration of the C20 alcohol, furnishing the required vinyl moiety of 1. Subsequent oxidation of alcohol 64 using Dess–Martin periodinane39 furnished ketone 45 and set the stage for the previously developed SmI$_2$/LiCl-mediated reductive cyclization.

In the event, we were gratified to find that treatment of ketone 45 with DBU smoothly effected the elimination of CO$_2$ and provided the corresponding aniline, which was converted in situ to isocyanate 31 (Et$_3$N/COCl$_2$). Upon removal of the triethylamine salts, cooling to −78 °C and subjection to a preformed mixture of SmI$_2$/LiCl, spiro-oxindole 11 was isolated in 75% yield as a single diastereomer. The stereochemical assignment of oxindole 11 was confirmed by X-ray crystallographic analysis and is consistent with bond formation at C3 occurring on the less hindered, convex face of the bicyclic molecule. Importantly, there was no detection of products wherein the C13 chlorine had been reduced under the reaction conditions; an observation which is consistent with literature reports that SmI$_2$/LiCl mixtures reduce enones significantly faster than alkyl chlorides.37

V. Attempts to Convert Ketone 11 to Welwitindolinone A Isonitrile (1). Having developed an efficient and stereoselective preparation of highly functionalized spiro-oxindole 11 (17 steps and 10.3% overall yield from cyclohexadiene 14), completion of (±)-welwitindolione A (1) isonitrile required only conversion of the C11 ketone to the corresponding vinyl

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36 Attempts to assign the C12 stereochemistry of byproduct 59 using nOe techniques were inconclusive, and 59 was unstable to reesterification conditions.
38 Compound 62 was isolated as a single olefin isomer; however, the bond geometry was not confirmed.
synthesize a series of strychnoline alkaloids and their derivatives. Retrosynthesis of the lactone moiety would lead to homoenolate 6 that could mediate an intramolecular attack from C9 to the C8 carbonyl moiety and the ensuing cyclization and methylation. The lactam moiety in 6 was deemed equivalent to the oxazolidine in 7 via N–O cleavage and lactamization. The intramolecular 1,3-dipolar cycloaddition reaction of nitrones 8 was thus envisaged as an ideal cyclization strategy for introducing the C–7 stereochemistry.

The route to the pivotal intermediate 5 commenced with the transformation of commercially available (S)-benzyl glycidyl ether (9) to prepare the known terminal olefin 10 (Scheme 2). This olefin was subjected to the Lemieux–Johnson oxidation and Roskamp’s reaction, followed by diazotization to give the corresponding diazoketone 11. Among the known procedures for implementing the N–H insertion reaction, Che’s methodology employing [RuCl₃(pymenene)] as the catalyst followed by the in situ NaBH₄ reduction of ketone proved to give 12 in 70% isolated yield. The secondary alcohol of 12 was then acylated with fumaric acid monomethyl ester 13 to furnish 14. An attempt to remove the Boc group and to transform 14 to a nitro compound was initially hampered by the β-elimination of the fumarate moiety. This seemingly unavoidable elimination was suppressed by first isolating the secondary amine as the trifluoroacetate salt 15. The salt was then subjected to m-CPBA oxidation by means of a slow neutralization with solid NaHCO₃, thereby affording the desired nitro compound selectively in good conversion yield. While the 1,3-dipolar cycloaddition reaction proceeded to some extent during oxidation, it was driven to completion by heating in toluene to give only the desired diastereomer in 17 to 62% overall yield via the arrangement 18. Formation of the undesired isomer 19 via the arrangement 20 was not observed because of the molecular strain which hampered the overlap between the nitro moieties and the double bond in 20. The high selectivity of this cycloaddition allowed the successful construction of the C–7 stereochemistry in the target molecule. The next task was to transform the methoxycarbonyl oxazolidine moiety. Cleavage of the N–O bond in 17 with Mo(CO)₆ gave 21, which was then subjected to cyclization under acidic conditions to afford the α-hydroxy lactam 22. The hydroxy group in 22 was removed by means of the Appel reaction followed by one-pot deiodination of the α-iodo lactam with additional PPh₃. Further transformations were facilitated by reduction of the C3 ethoxycarbonyl group via the mixed anhydride and protection of the resultant alcohol with a TIPS group to afford 23. Preliminary studies focused on the formation of the bond between C8 and C9 suggested that the additional ring strain caused by the amide or a potential enolization of the amide would be a major obstacle. Accordingly, we decided to eliminate these factors by reducing the amide before cyclization. Reduction of the amide in 23 was performed by treatment with Lawesson’s reagent followed by desulfurization of the resultant thio lactam with Raney nickel to give the tertiary amine 24, which was ready for C8–C9 bond formation.

The intended formation of the caged structure concomitant with the γ-lactone formation necessitated the transformation of 24 into a homoenolate equivalent. Among the various candidates, we envisioned utilizing an allylic sulfoxide as a three-carbon homologation substructure. Scheme 3 represents our proposed route to this goal. Inspired by the pioneering work of Evans, the allylic sulfoxide 25 would be treated with LHMDS in the presence of the carbonyl compound 26, followed by addition of TMSCl. If the lithiated allylic sulfoxide were to attack the carbonyl group in 26 from the γ-position...