Natural Product Total Synthesis

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Pyrone Diels–Alder Routes to Indolines and Hydroindolines: Syntheses of Gracilamine, Mesembrine, and Δ^7-Mesembrenone

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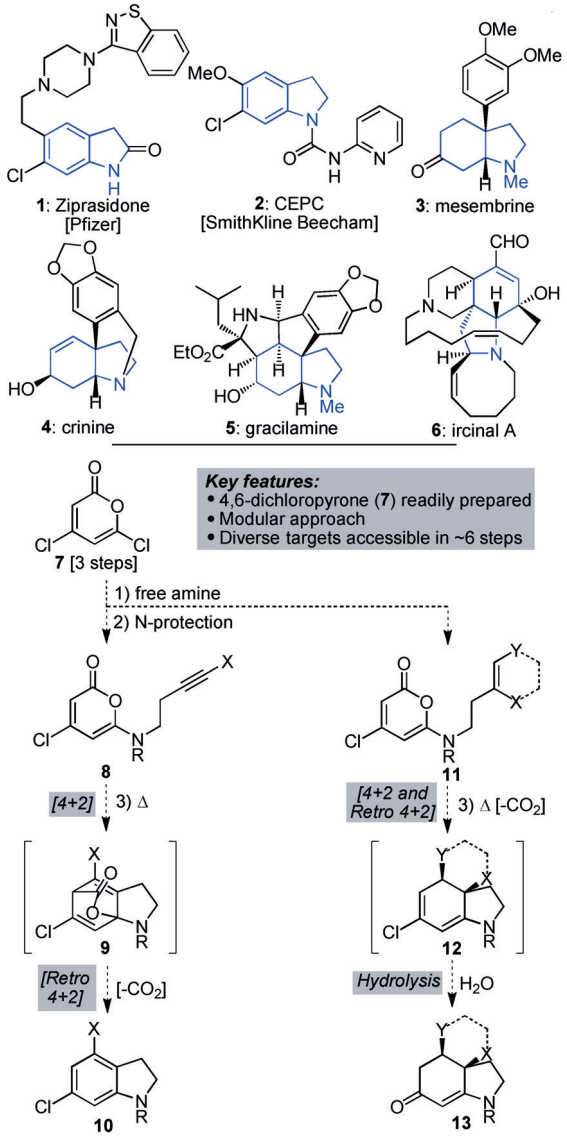
Abstract: *Although the Diels–Alder reaction has long been utilized for the preparation of numerous heterocycles, opportunities to extend its power remain. Herein, we detail a simple, modular, and robust approach that combines various amines regioselectively with 4,6-dichloropyrone to create substrates 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 amaryllidaceae 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.[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**)[2] and crinine (**4**)[3] achieved to date, two recent elegant total syntheses of gracilamine (**5**),[4] and creative solutions leading to ircinal A (**6**) and the manzamine alkaloids.[5] As an outgrowth of programs seeking to prepare entire natural product families from common intermediates,[6] 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. That compound is 4,6-dichloropyrone (**7**), readily prepared on a multigram scale in three steps with one chromatographic purification.[7] 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[8,9] followed by in situ retro-[4+2] loss of CO_2 could directly afford indolines with 4,6-substitution.[10] Alternatively, 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-



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**).

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coupling reactions,[10a,b] 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,[10c] and that example involved a constrained, polycylic framework that could not afford the more versatile bicyclic products targeted here, compounds with patterning not readily prepared through other Diels–Alder processes.[11a,c] 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 hydroindoline structures, including formal syntheses of both mesembrine (**3**) and gracilamine (**5**), with the latter sequence being the shortest to date in terms of step count.

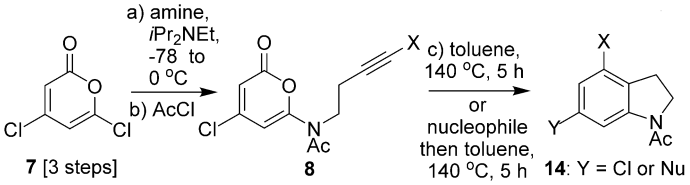
Our efforts began by probing substrates of type **8**, readily prepared from 4,6-dichloropyrone (**7**) by adding a primary amine and stirring them with *i*Pr_2NEt from −78 to 0 °C, followed by protection of the nitrogen atom with an acetyl group (see the Supporting Information for details).[12] Subsequent 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.[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).

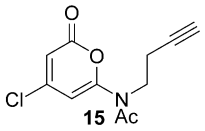
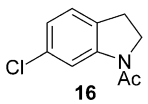
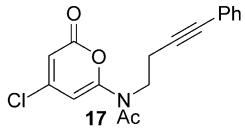
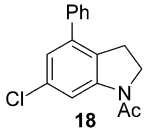
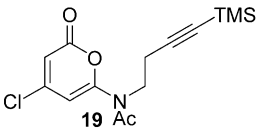
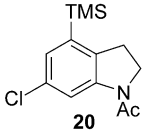
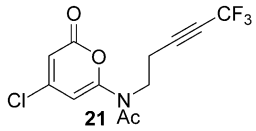
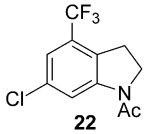
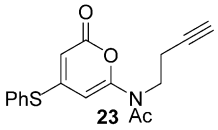
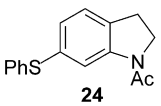
In addition, with the exception of product **16**, none of these materials or their deprotected counterparts are known molecular entities based on standard search engines; **16** in its deprotected form (as a free indoline or HCl salt) is commercially available from several suppliers.[14] This finding 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.[11] 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 alkene dienophiles is arguably of greater value. Its success would generate hydroindoline structures bearing a quaternary center at a ring junction, a possible second chiral center, and a vinylogous 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 manzamine 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 alkene and group X being an aromatic ring.

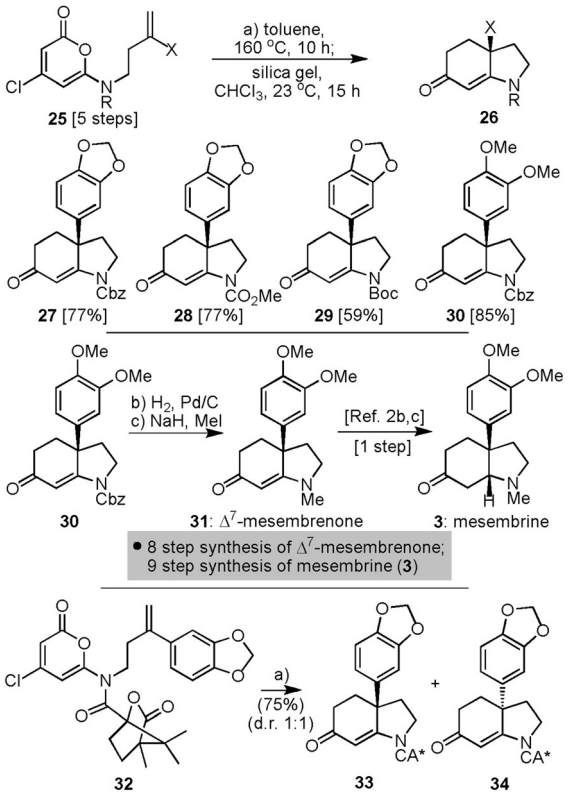
Pleasingly, four initial examples, in which both the carbamate protecting group and aryl ring were varied (to match those of natural products **3** and **4**), were readily converted into **27**–**30** using similar microwave conditions. Treatment of the intermediate Diels–Alder products with silica 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.[15] Importantly, compound **30** (X-ray structure of acetate derivative obtained) could be converted into Δ^7-mesembrenone (**31**)[16] through a two-step sequence, thereby completing an eight-step preparation of a minor constituent of *Sceletium namaquense*[17] and a known synthetic precursor for mesembrine (**3**).[2b,c] Furthermore, although **27**–**30** were produced racemically,[18] 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**

Table 1: Initial exploration of the scope of indoline synthesis using tethered alkynes.[a]



Entry	Starting Material	Product	Yield [%][b]
1	 **15**	 **16**	97
2	 **17**	 **18**	91
3	 **19**	 **20**	86
4	 **21**	 **22**	98
5	 **23**	 **24**	93

[a] General conditions: substrate dissolved in toluene and solution degassed with bubbling argon for 5 min. The reaction mixture was then heated under microwave irradiation at 140 °C for 5 h, cooled, concentrated, and purified. [b] Yield of Diels–Alder step only. TMS = trimethylsilyl.



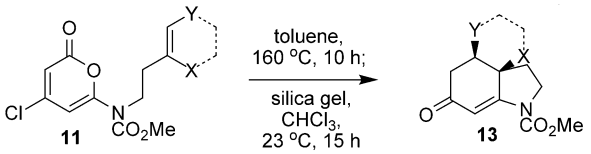
Scheme 2. Demonstration of the pyrone Diels–Alder approach through a total synthesis of Δ^7-mesembrenone (**31**), formal total synthesis of mesembrine (**3**), and a means to access enantiopure materials through a chiral auxiliary: a) toluene (0.02 M), 160 °C using microwave irradiation, 10 h, then $CHCl_3$, silica gel, 23 °C, 15 h; b) 10% Pd/C (2.0 equiv), EtOAc, H_2 (1 atm), 23 °C, 3 h, quantitative; c) NaH (2.2 equiv), MeI (1.5 equiv), 23 °C, 45 min, 75% over two steps. Boc = *tert*-butoxycarbonyl, Cbz = carbobenzyloxy, CA* = chiral auxiliary; (1*S*)-(−)-camphanoyl.

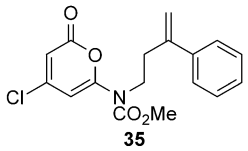
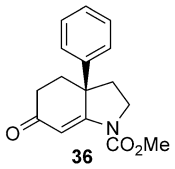
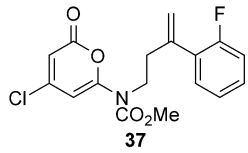
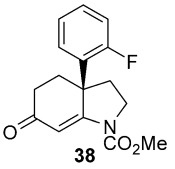
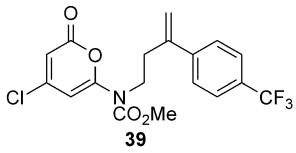
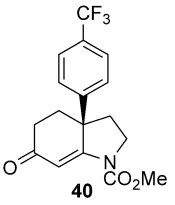
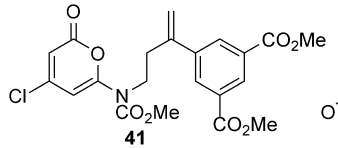
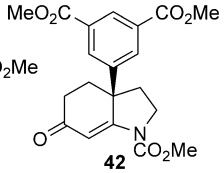
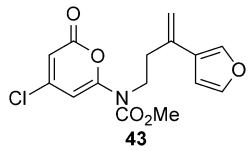
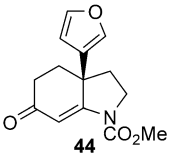
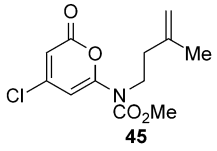
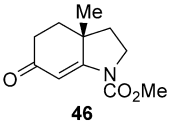
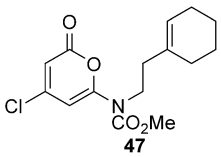
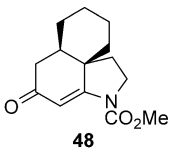
and **34** in 75% yield, with the implanted chirality proving too remote to control stereoinduction.

In an effort to evaluate the substrate scope of this variant of the design more fully, a range of alkene dienophiles with different substitution patterns and electronic properties were probed (Table 2). Pleasingly, highly electron-deficient aryl rings, heteroaromatic motifs, and even simple alkanes were tolerated as substituents within the core Diels–Alder/retro-[4+2]/hydrolysis sequence (entries 1–6), thereby leading to products in good to excellent yield despite the number of processes achieved in a single pot. Of particular importance, a cyclic alkene (**47**) could be converted into a polycyclic product (entry 7). This example, in particular, suggested to us that targets such as gracilamine (**5**) and ircinal A (**6**, see Scheme 1) could likely be accessed through the method.

We selected **5** for an initial proof-of-principle study. This material, isolated in Turkey from *Galanthus gracilus*,[19] was recently synthesized in racemic form by the Ma research group through an inventive biomimetic [3+2] approach in 17 steps,[4a] and by the Gao research group through a creative photo-Nazarov reaction, Michael addition, and intramolecular Mannich sequence in 19 steps.[4b] In particular, we noted within these studies that Gao and co-workers had utilized

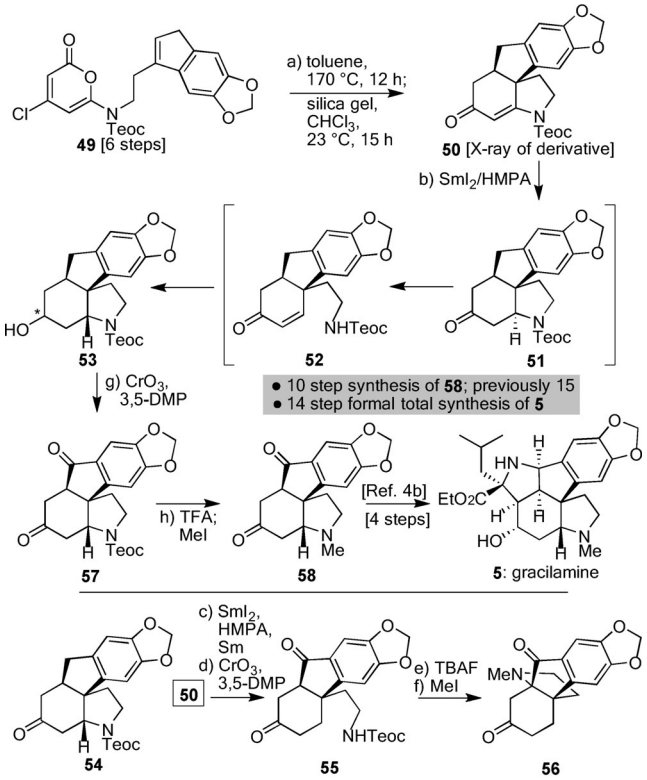
Table 2: Further exploration of the scope of indoline synthesis using tethered alkenes with varied substitution patterning.[a]



Entry	Starting Material	Product	Yield [%]
1	 **35**	 **36**	75
2	 **37**	 **38**	73
3	 **39**	 **40**	79
4	 **41**	 **42**	64
5	 **43**	 **44**	86
6	 **45**	 **46**	76
7[b]	 **47**	 **48**	66

[a] General conditions: substrate dissolved in toluene and solution degassed with bubbling argon for 5 min. The reaction mixture was then heated under microwave irradiation at 160 °C for 10 h, cooled, diluted with $CHCl_3$, treated with silica gel, and stirred at 23 °C for 15 h.
[b] Performed in toluene with microwave irradiation at 170 °C for 10 h.

diketone **58** (prepared in 15 steps) as one of their intermediates. We hoped to forge the same compound in a more expeditious manner using our pyrone Diels–Alder reaction to thus achieve a formal total synthesis of the target. As shown in Scheme 3, following an efficient preparation of **49**, we believed that subsequent use of our cascade strategy could afford **50**, which would need two subsequent changes in oxidation state and an installation of the required *N*-methyl group to complete the target diketone. As matters transpired, this hypothesis proved true, although the final tailoring of the structure required specific ordering of events and careful control of reaction conditions.



Scheme 3. Concise, formal total synthesis of gracilamine (**5**) through a 10-step synthesis of ketone **58**: a) toluene, 170 °C under microwave irradiation, 12 h, then silica gel, $CHCl_3$, 23 °C, 5 h, 83 %; b) SmI_2 (0.1 M in THF, 6.0 equiv), HMPA (24 equiv), *t*BuOH (2.0 equiv), THF, 23 °C, 5 h; c) Sm metal (6.0 equiv), SmI_2 (0.1 M in THF, 6.0 equiv), HMPA (24 equiv), *t*BuOH (2.0 equiv), THF, 23 °C, 10 h; d) CrO_3 (20 equiv), 3,5-DMP (20 equiv), CH_2Cl_2, −40 to 23 °C, 4 h, 15 % over two steps; e) TBAF (20.0 equiv), THF, 0 °C, 1 h; f) K_2CO_3 (20 equiv), MeI (6.4 equiv), MeCN, 40 °C, 3 h, 54 % over two steps; g) CrO_3 (20 equiv), 3,5-DMP (20 equiv), CH_2Cl_2, −40 to 23 °C, 4 h, 20 % over two steps; similar oxidation from **54** proceeded in 51 % yield; h) TFA/CH_2Cl_2 (1:1), 23 °C, 10 min, then K_2CO_3 (100 equiv), MeI (20 equiv), MeCN, 23 °C, 3 h, 85 %. HMPA = hexamethylphosphoramide, DMP = dimethylpyrazole, TBAF = tetra-*n*-butylammonium fluoride, Teoc = 2-(trimethylsilyl)ethoxycarbonyl, TFA = trifluoroacetic acid.

Following a six-step synthesis of **49** (see the Supporting Information),[20] the use of our cascade reaction conditions, albeit at 170 °C for 10 h, afforded polycycle **50** in 83 % yield. Its connectivities were confirmed by X-ray analysis of a related compound. The reaction itself proved robust, proceeding smoothly on gram scale. From here, our next goal was to reduce the olefinic portion of the vinylogous amide. Unfortunately, as observed by others,[21] this operation proved challenging, with several conditions such as catalytic hydrogenation failing to deliver anything other than recovered starting material.[22] Radical reduction conditions such as $[Mn(dpm)_3]$ (dpm = dipivaloylmethane), $PhSiH_3$, and *tert*-butyl hydroperoxide (TBHP) in *i*PrOH,[23] by contrast, did afford the reduced product in low conversion (ca. 5 %), but resulted in the incorrect configuration at the ring junction in the form of **51**, presumably because of the steric bulk of the adjacent aromatic ring. Pleasingly, however, use of conditions deployed by Rigby et al. on a related system,[21a] and originally pioneered by Molander and McKie,[24] provided a solution.

In that key event, vinylogous amide **50** was treated with 6 equiv of SmI_2, activated with 24 equiv of HMPA, and stirred in THF at 23 °C for 5 h; those conditions delivered **53** as a single, unassigned diastereomer about the starred carbon atom with the correct ring junction configuration. In this process we believe that **51** is initially formed, with subsequent elimination and reattack of the amine onto the resultant Michael system of **52** affording the needed *cis*-fusion in the hydroindoline core;[25] over the time course of the reaction, the resultant ketone is then reduced to afford **53**, a material which, for purposes of full characterization, was oxidized with pyridinium dichromate (PDC) to afford **54** in 39 % yield. In support of this proposal, a short reaction time of only 15 min affords isolable quantities of **51**. By contrast, the use of additional equivalents of SmI_2 or adding Sm metal to the original mixture afforded **55** after subjecting the crude reaction products to a Salmond oxidation (CrO_3, 3,5-dimethylpyrazole).[26] This outcome suggests that the α,β-unsaturated system of putative intermediate **52** had been reduced prior to reclosure of the ring. The identity of **55** was confirmed by its conversion, in two further steps, into **56**,[27] a side product Gao and co-workers had also prepared and whose ^{1}H NMR data[4b] were in full agreement with our synthetic material.

Nevertheless, from **53** the target molecule was readily completed by use of a Salmond oxidation[26] to effect oxidation of both the alcohol and the lone benzylic position to deliver **57** (20 % overall from **50**),[28] and a one-pot Teoc cleavage/methylation[29] to afford **58** (in 85 % yield from **57**). In total, only 10 steps were required to prepare **58** from commercial materials, thereby affording a formal total synthesis of (±)-gracilamine (**5**) in 14 steps overall.

In summary, a modular and procedurally simple sequence from 4,6-dichloropyrone (**7**) and a range of readily prepared amines has afforded diverse indoline and hydroindoline frameworks. These materials are of pertinence to pharmaceuticals as well as natural products, with three total or formal syntheses—including the shortest route to gracilamine in terms of step count—being achieved as a result. Although the core reactions rely upon the venerable Diels–Alder reaction,[30] the particular variant deployed here has not, to the best of our knowledge, been explored in any depth. Numerous opportunities for the construction of novel heterocycles and asymmetric variants are apparent, and are the subject of current investigations.

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