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, polycyclic 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 iPr$_2$NEt 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

Table 1: Initial exploration of the scope of indoline synthesis using tethered alkynes.[a]
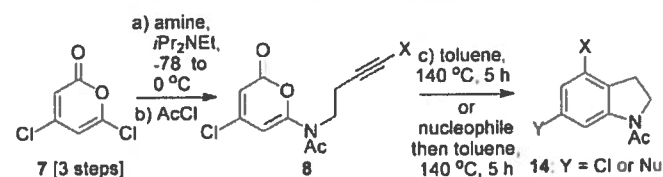
Entry	Starting Material	Product	Yield [%][b]
1	**15**	**16**	97
2	**17**	**18**	91
3	**19**	**20**	86
4	**21**	**22**	98
5	**23**	**24**	93

[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.

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**

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Pyrone Diels–Alder Routes to Indolines and Hydroindolines: Syntheses of Gracilamine, Mesembrine, and Δ7-Mesembrenone

Pei Gan, Myles W. Smith, Nathaniel R. Braffman, and Scott A. Snyder*

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 CO₂ could directly afford indolines with 4,6-substitution.[10] Alter-
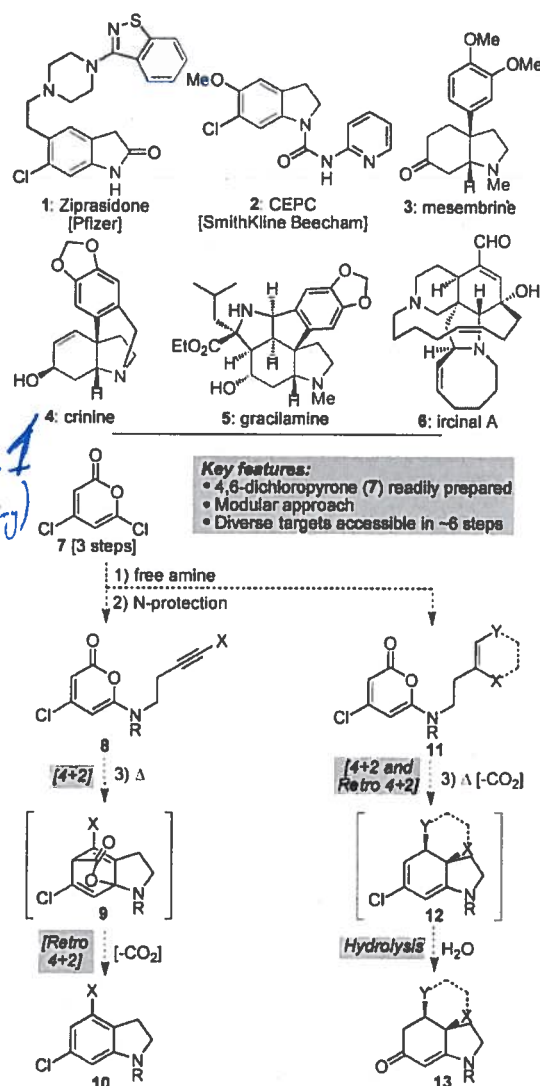
Scheme 1. A proposal for modular and concise access to indolines and their derivatives through pyrone Diels–Alder reactions starting from 4,6-dichloropyrone (**7**).

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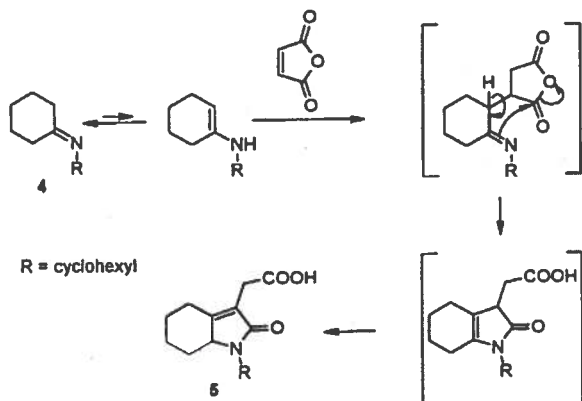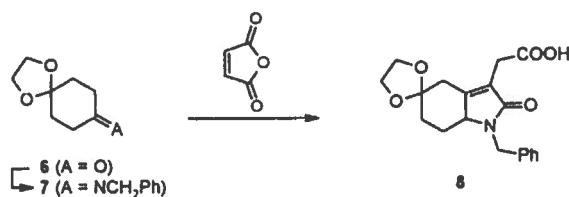   article are available on the WWW under http://dx.doi.org/10.1002/
    anie.201510520.

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-

Ex. 2

Scheme 1

Scheme 2

6 (A = O)
7 (A = NCH₂Ph)

intermediate suitable to synthesize either serotonin and melatonin or bufotenin.

Scheme 3

an oxindole, such a process can occur with compound **10**[12] since a CH₂CH₂ moiety is present in the six-atom ring, thus avoiding a hydrogenolysis step.

Further standard reactions from indole **11** led to serotonin **1** and melatonin **2**, as well as to bufotenin **3** (Scheme 5).
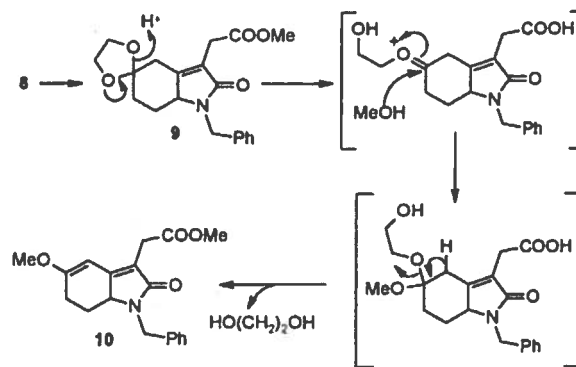
Results and Discussion

The benzyl imine (**7**) of commercial monoprotected 1,4-cyclohexanedione **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**.[10] The reaction of POCl₃ is known to transform oxindoles into 2-chloroindoles which in turn can lead to indoles by hydrogenolysis.[11] 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 intermediates.

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

Conclusion

We have thus shown that key-intermediate **11**, suited for the preparation of 5-alkoxytryptamine derivatives, can be readily synthesized through a novel aromatization process, in good yield from commercially available ketone **6**.
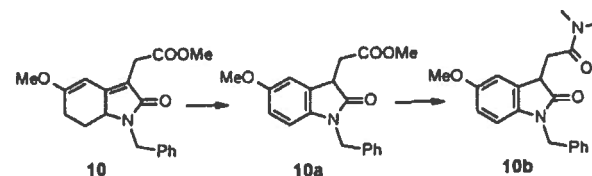
Experimental Section

General. TLC was performed with glass plates (0.25 mm) precoated with silica gel, and flash chromatography (FC) was carried out with silica gel (200–450 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 □ 0.20 mm dimethylpolysiloxane capillary column) linked to a HP 5971 EIMS. ¹H and ¹³C NMR spectra of CDCl₃ solutions were respectively recorded at 300 and 75.5 MHz. Anhydrous solvents were freshly distilled under argon, CH₂Cl₂ 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-idene)benzylamine (**7**). A solution of 3.90 g (25.0 mmol) of commercial 1,4-cyclohexanedione mono-ethylene ketal **6** and 3.00 mL (27.5 mmol) 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. An analytical 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

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(10) To this end, a preliminary attempt was tried with a first step involving *O*-alkylation of compound 10 with Me₂SO₄ but aromatization of the six-atom ring was observed instead, giving oxindole **10a**, the amidation of which with Me₂NH afforded **10b**.
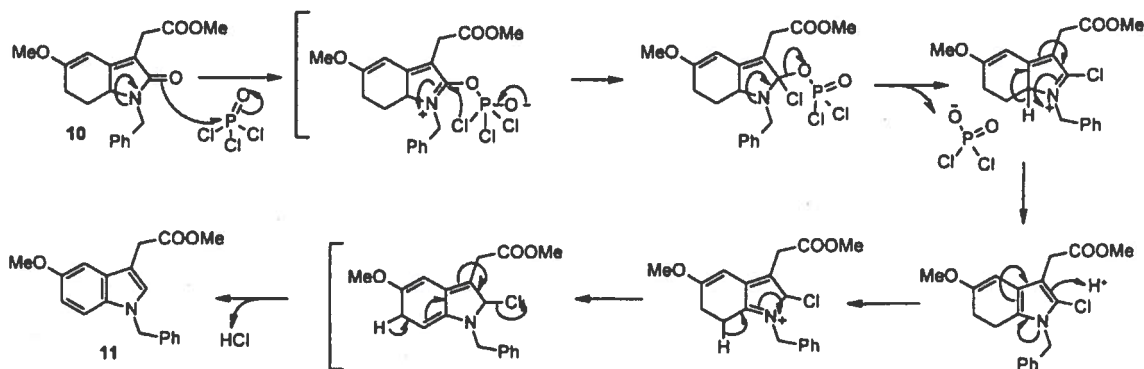

10   10a   10b
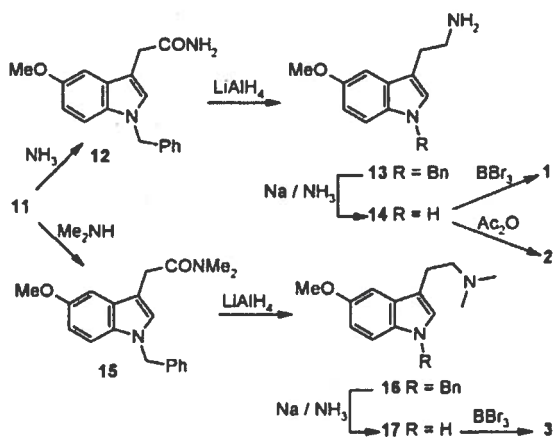
(11) Kubo, A.; Nakai, T. *Synthesis* **1980**, 365–366.

*Ex. 2
(following)*

Scheme 4

Scheme 5

(base); ^{1}H NMR (C_6D_6) %d.68- 1.76 (m, 2H), 1.83- 1.90 (m, 2H), 2.32 (dd, J) 7.0, 6.6 Hz. 2H), 2.71 (dd. J) 7.0, 6.6 Hz. 2H), 3.52- 3.57 (m, 4H), 4.46 (s, 2H), 7.00- 7.47 (m, 5H); ^{13}C NMR (C_6D_6) %25.8, 35.2, 35.9, 37.1, 55.1, 64.9 (2C), 108.8, 127- 129 (5C), 142.0, 170.7.

1'-Benzyl-2'-oxo-1',2',4',6',7',7a'-hexahydrospiro[1,3-di-oxolane-2,5'-[5H]indole]-3'-acetic Acid (8). A solution of 3.00 g (30.0 mmol, 1.2 equiv) of maleic anhydride in 12 mL of THF was added dropwise to a solution of the crude imine **7** above. in 10 mL of THF at 0 °C. After stirring for 1 h, the crystalline adduct **8** was filtered. Evaporation of the solvent gave a residue which was purified by FC (80:20, then 100:0) affording additional adduct **8**, for a total of 8.25 g (96% yield from **6**). An analytical sample was obtained by recrystalliza-tion: mp 199- 201 °C (EtOAc/MeOH); calcd for $C_{19}H_{21}NO_5$. C 66.46, H 6.16, N 4.08; found C 66.4, H 6.2, N 4.0; EIMS *m/z* (rel int) 299 (M⁺ - 44, 10), 297 (25), 210 (13), 99 (38), 91 (base), 65 (14); IR (Nujol) 1715, 1645 cm⁻¹; ^{1}H NMR %l.29 (qd, J) 12, 4 Hz, 1H), 1.69 (dt. J) 14, 3.7 Hz, 1H), 1.81 (qd, J) 12, 3 Hz, 1H), 2.18- 2.27 (m, 1H), 2.43 (d, J) 14 Hz, 1H), 2.88 (dd, J) 14, 2.6 Hz, 1H), 3.40 (d, J) 15.5 Hz, 1H), 3.47 (d, J) 15.5 Hz, 1H), 3.73 (dd, J) 11.5, 5.8 Hz, 1H), 3.84- 4.04 (m, 4H), 4.29 (d, J) 15.1 Hz, 1H), 4.99 (d, J) 15.1 Hz, 1H), 7.30-7.37 (m, 5H), carboxylic H not observed; ^{13}C NMR %27.7, 31.9, 32.0, 36.2, 44.5, 60.6, 64.6, 64.9, 109.5, 123.3, 127.9, 128.0 (2C), 128.9 (2C), 136.6, 154.6, 170.7, 172.6.

Methyl 1'-Benzyl-2'-oxo-1',2',4',6',7',7a'-hexahydrospiro-[1,3-dioxolane-2,5'-[5H]indole]-3'-acetate (9). A mixture of 1.00 g (2.90 mmol) of acid **8**, 3 mL of methanol, 1 mL (3 equiv) of 2,2-dimethoxypropane, and a catalytic amount of PTSA was heated at reflux temperature for 30 min. After evaporation of the solvent and FC (40:60, then 100:0), 0.97 g (90% yield) of oily ester **9** was obtained: HRMS (EI) calcd for $C_{20}H_{23}NO_5$ *m/z* 357.1576, found *m/z* 357.1579; EIMS *m/z* (rel int) 357 (M⁺, 7), 326 (2), 312 (1), 297 (1), 99 (base), 91 (34); IR (film) 1736, 1670
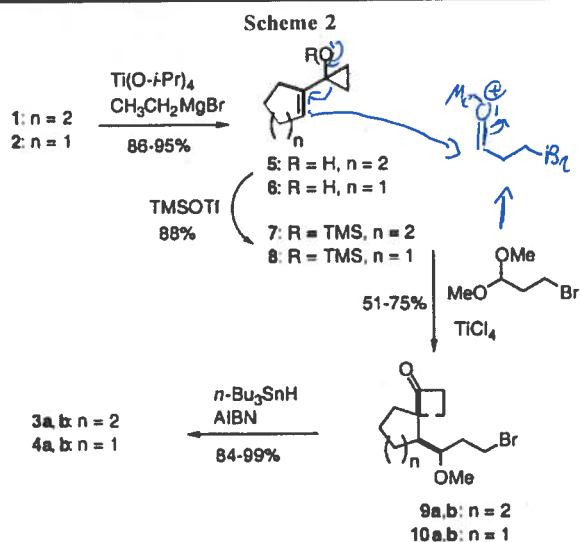
cm⁻¹; ^{1}H NMR %d.18- 1.34 (m, 1H), 1.67 (td, J) 13.6, 3.7 Hz, 1H), 1.74- 1.83 (m, 1H), 2.12- 2.22 (m, 1H), 2.45 (d, J) 14.3 Hz, 1H), 2.85 (dd, J) 14.3, 2.7 Hz, 1H), 3.31 (d, J) 16.3 Hz, 1H), 3.43 (d, J) 16.3 Hz, 1H), 3.62- 3.72 (m, 4H), 3.85- 4.02 (m, 4H), 4.26 (d, J) 15.1 Hz, 1H), 4.96 (d, J) 15.1 Hz, 1H), 7.15- 7.35 (m, 5H); ^{13}C NMR %27.8, 28.7, 32.0, 36.3, 44.1, 51.9, 59.4, 64.4, 64.6, 109.5, 124.3, 127.3, 127.8 (2C), 128.5 (2C), 137.5, 153.2, 170.61, 170.64.

Methyl 1-Benzyl-5-methoxy-2-oxo-2,6,7,7a-tetrahydro-1H-indole-3-acetate (10). Crude imine **7** was obtained as above, using in this instance 10.1 g (65.0 mmol) of **6** and 8.00 mL (73.3 mmol) of benzylamine. Its reaction performed as above with maleic 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 **10**: HRMS (EI) calcd for $C_{19}H_{21}NO_4$ *m/z* 327.1471, found *m/z* 327.1468; EIMS *m/z* (rel int) 327 (M⁺, 51), 312 (5), 296 (5), 268 (21), 267 (29), 252 (13), 195 (11), 194 (14), 176 (20), 91 (base), 77 (7); IR (film) 1735, 1660, 1600 cm⁻¹; ^{1}H NMR %l.33- 1.50 (m, 1H), 2.11- 2.21 (m, 1H), 2.32 (dd, J) 8.5, 3.3 Hz, 2H), 3.33 (d, J) 16.3 Hz, 1H), 3.43 (d, J) 16.3 Hz, 1H), 3.65 (s, 3H), 3.70 (s, 3H), 3.78 (dd, J) 13.0, 4.6 Hz, 1H), 4.39 (d, J) 15.4 Hz, 1H), 4.85 (d, J) 15.4 Hz, 1H), 5.56 (s, 1H), 7.19- 7.38 (m, 5H); ^{13}C NMR %27.4, 27.7, 28.8, 44.5, 51.9, 55.2, 58.3, 90.7, 116.2, 127.2, 127.7 (2C), 128.4 (2C), 137.9, 152.4, 164.2, 171.1, 172.2.

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 (65.7 mmol, 3 equiv) of pyridine was added dropwise 4.10 mL (44.0 mmol, 2 equiv) 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 NaH-CO₃, followed by the usual workup. A FC (20:80) afforded 5.03 g of oily indole **11** in 82% yield (75% from ketone **6**): HRMS (CI, NH₃) calcd for $C_{19}H_{19}NO_3$ *m/z* 309.1365. found *m/z* 309.1360; EIMS *m/z* (rel int) 309 (M⁺ 63), 250 (base), 159 (19), 144 (20), 91 (99); IR (film) 2940, 1740 cm⁻¹; ^{1}H NMR %3.68 (s, 3H), 3.73 (d, J) 0.7 Hz, 2H), 3.84 (s, 3H), 5.19 (s, 2H), 6.82 (dd, J) 8.8, 2.2 Hz, 1H), 7.04- 7.30 (m, 8H); ^{13}C NMR %31.2, 50.2, 51.9, 55.8, 100.9, 106.9, 110.6, 112.2, 126.8 (2C), 127.6, 127.7, 128.3, 128.7 (2C), 131.8, 137.5, 154.1, 172.4.

1-Benzyl-5-methoxy-1H-indole-3-acetamide (12). A so-lution of 6.70 g (21.7 mmol) of indole **11** in 100 mL of MeOH saturated with NH₃ was stirred at room temperature for 8 days. leading to crystalline amide **8**. The suspension was flushed with nitrogen to remove NH₃ and filtered. After washing with MeOH, the crystals were dried over P₂O₅, affording 5.29 g of pure **12** (83% yield[13]): mp 157 °C (MeOH) [lit.[14] 156- 157 °C (EtOH)]; calcd for $C_{18}H_{18}N_2O_2$, C 73.45, H 6.16, N 9.52; found C 73.3, H 6.1, N 9.5; EIMS *m/z* (rel int) 294 (M⁺ 42), 276 (20), 250 (93), 91 (base); IR (CDCl₃) 3380,

Scheme 2

1: n = 2
2: n = 1

Ti(O-*i*-Pr)$_4$
CH$_3$CH$_2$MgBr
——————
88-95%

5: R = H, n = 2
6: R = H, n = 1

TMSOTf
88%

7: R = TMS, n = 2
8: R = TMS, n = 1

OMe
MeO⎓⎓Br

51-75%
TiCl$_4$

3a,b: n = 2
4a,b: n = 1

n-Bu$_3$SnH
AIBN
——————
84-99%

OMe

9a,b: n = 2
10a,b: n = 1

presence of titanium isopropoxide afforded the corresponding cyclopropanols **5** and **6** in 95 and 86% yields, respectively.[6] Vinyl cyclopropanols and silyl ethers can be viewed as vinylogous enols and enol silyl ethers, and their synthetic utility in electrophilic addition reactions was first demonstrated by the Wasserman and Trost groups and, more recently, in our laboratory.[7-9] Following standard silylation (88% yield), a vinylogous Mukaiyama condensation[10] of **7** with 3-bromopropionaldehyde dimethylacetal by the action of TiCl$_4$ gave a 5:3 mixture of **9a** and **9b** (71% yield) that were epimeric at the methoxy stereocenter. The ring junction stereochemistry of **9a** and **9b** was assigned on the basis of the stereoelectronic requirements for electrophilic addition,[8] whereas the relative configuration of the methoxy substituent could not be ascertained. Other Lewis acids such as TMSOTf, BF$_3$·Et$_2$O, and Et$_2$AlCl were ineffective in effecting coupling with an acetal.

Slow addition of *n*-tributyltin hydride and AIBN to a solution (14 M) of **9a** in refluxing benzene afforded cyclooctenone **3a** as a single isomer in 99% yield. Similarly, free radical-mediated cyclization- fragmentation of **9b** also proceeded efficiently to provide **3b** in 91% yield. The identical annulation sequence was also evaluated by starting with **6**, especially because the resultant bicyclo[6.3.0]-undecane skeleton is commonly found in an increasing number of bioactive natural products.[11] In parallel to the

(6) For a previous synthesis of **5** and **6**, see: Salaun, J.; Garnier, B.; Conia, J. M. *Tetrahedron* **1974**, *30*, 1413.

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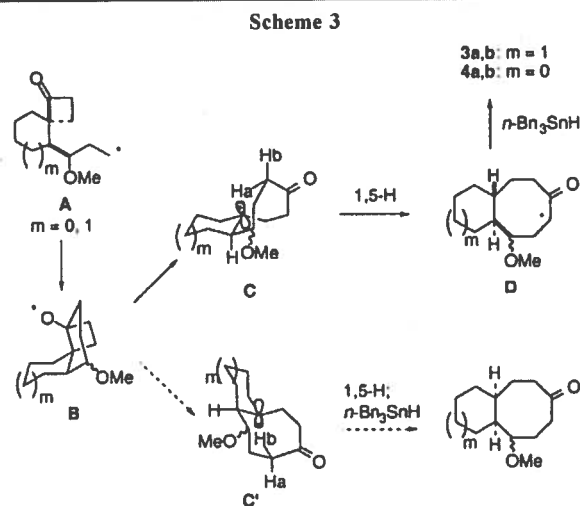
(9) Youn, J.-H.; Lee, J.; Cha, J. K. *Org. Lett.* **2001**, *3*, 2935.

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above-mentioned results, **10a** and **10b** were obtained in 51% yield in a 1.3:1 ratio from condensation of **8** with 3-bromo-propionaldehyde 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 **A** to the cyclobutanone functionality to generate the

Scheme 3

3a,b: m = 1
4a,b: m = 0

A
m = 0, 1

n-Bu$_3$SnH

1,5-H

Hb
Ha
C
D

OMe

B

C'

Ha
Hb
MeO

1,5-H;
n-Bu$_3$SnH

OMe

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,[2c] 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 H$_a$ (vs H$_b$) (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 carbonyl group to give **12** and **13** in 96 and 95% yields, respectively; in both cases, two diastereomers were obtained in a □6:1 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

Scheme 14

Scheme 15
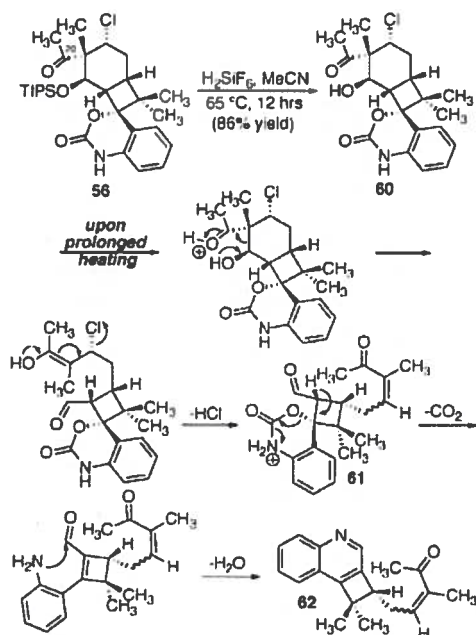
In this remarkable reaction, the relative stereochemistry of the C12 quaternary center and vicinal chlorine are simultaneously set with excellent stereocontrol. Analysis of the ^{1}H NMR spectrum of the crude product mixture indicated that the mass balance was a mixture of several minor byproducts (<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 desilylated 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 quinoline **62**.[38] This unanticipated byproduct likely arises by acid-mediated retro-aldol/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$_4$NHB(OAc)$_3$ 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 sulfurane[39] resulted in selective dehydration of the C20 alcohol, furnishing the required vinyl moiety of **1**. Subsequent oxidation of alcohol
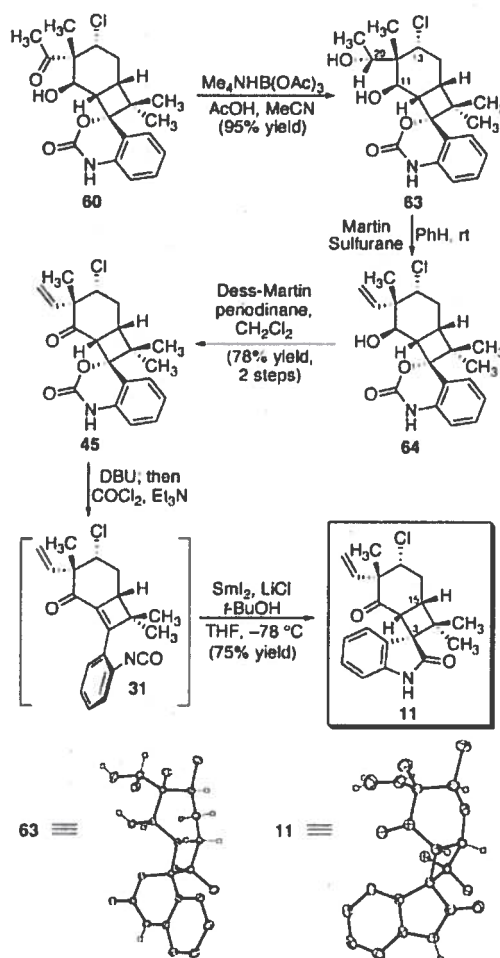
64 using Dess–Martin periodinane[40] furnished ketone **45** and set the stage for the previously developed SmI$_2$/LiCl-mediated reductive cyclization.

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.[27]

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 (±)-welwitindolinone A (**1**) isonitrile required only conversion of the C11 ketone to the corresponding vinyl

(36) Attempts to assign the C12 stereochemistry of byproduct **59** using nOe techniques were inconclusive, and **59** was unstable to recrystallization conditions.
(37) Pilcher, A. S.; Deshong, P. *J. Org. Chem.* **1993**, *58*, 5130.
(38) Compound **62** was isolated as a single olefin isomer, however the bond geometry was not confirmed.
(39) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327.
(40) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

synthesize a series of stemofoline 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 nitrone 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).[16] This olefin was subjected to the Lemieux−Johnson oxidation and Roskamp's reaction,[17] followed by diazotization to give the corresponding diazoketoester 11. Among the known procedures for implementing the N−H insertion reaction, Che's methodology[18] employing [RuCl$_2$(p-cymene)]$_2$ as the catalyst followed by the in situ NaBH$_4$ reduction of ketone
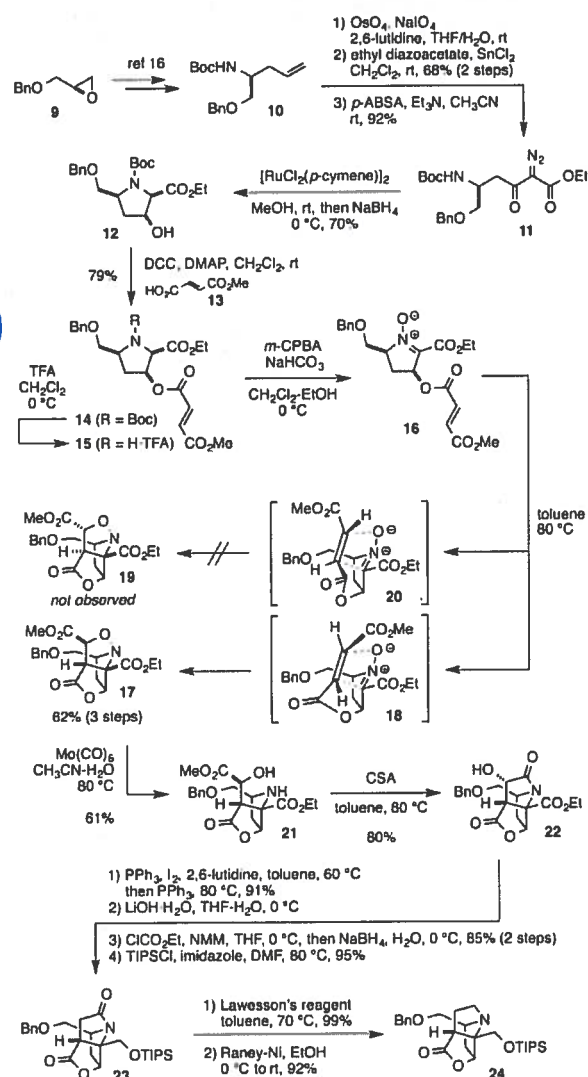
proved to give 12 in 70% isolated yield. The secondary alcohol of 12 was then acylated with fumaric acid monomethyl ester 13 to furnish 14. An attempt to remove the Boc group and to transform 14 to a nitrone was initially hampered by the β-elimination of the fumarate moiety. This seemingly unavoidable 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 NaHCO$_3$, thereby affording the desired nitrone 16 regioselectively 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 17 in a 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 nitrone moiety and the double bond in 20. The high selectivity of this cycloaddition allowed the successful construction of the C7 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)$_6$[19] 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 PPh$_3$. 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 thiolactam 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.[20] 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,[21] 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[22] in 26 from the γ-position

Scheme 2. Construction of the Core Structure via an Intramolecular 1,3-Dipolar Cycloaddition Reaction

Scheme 3. Allylic Sulfoxide as a Potential Equivalent to the Homoenolate Unit