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Sequential Aminodiene Diels–Alder Approach to the Ergoline Skeleton

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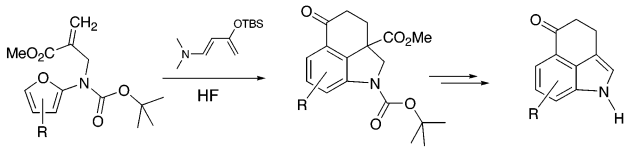
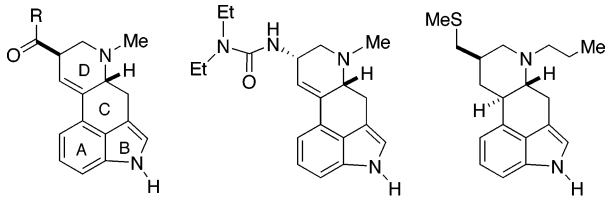


Through a novel sequence of aminodiene Diels–Alder reactions, several substituted amidofurans were readily converted to tricyclic ketones in good yield. The formation of the tricyclic ketone system is the result of a ring opening and dehydration of a transient oxabicyclic adduct formed by an intramolecular Diels–Alder cycloaddition of an amidofuran with a cyclohexenone moiety tethered such that it participates in the cycloaddition as the 2π component. A convenient way to construct the cyclohexenone is to make use of some aminodiene chemistry developed by Rawal. An angular carbomethoxy group is required in order to activate the olefin toward cycloaddition with Rawal's diene. The presence of this activating group not only prevents the isomerization of the advanced ergoline intermediate to a naphthalene but can also be leveraged for an oxidation to provide Uhle's ketone (**13**). The easily formed Kornfeld ketone analogue **25** was readily transformed into the corresponding triflate **41** by the action of triflic anhydride and a base. Oxidative addition of vinyl triflate **41** to Pd(0) and the ability of the resulting vinyl palladium species to undergo cross-coupling with terminal alkynes prompted us to devise an expeditious route to lysergic acid. Unfortunately, our inability to carry out a regioselective Heck reaction using vinyl triflate **41** and the methylene amino acrylate ester **48** thwarted the completion of the synthesis of lysergic acid.

Introduction

Indole alkaloids constitute a major family of natural products whose structural diversity and broad pharmacological activity have made them both synthetically interesting and medicinally important.[1] The ergot alkaloids have also attracted a great deal of interest, in part because they possess the widest spectrum of biological activity found in any family of natural products.[2–4]



1; R = OH (Lysergic Acid) **4**; Lisuride **5**; Pergolide

2; R = NEt_2

3; R = $NHCH(Me)CH_2OH$

FIGURE 1. Some typical ergot alkaloids.

Lysergic acid (**1**) has been a major synthetic target, since it possesses the fundamental nucleus of this class of alkaloids, as do the analogous derivatives Lisuride (**4**) (an anti-prolactin drug) and Pergolide (**5**) (an anti-Parkinson's drug) (Figure 1).

The substituents present on the core tetracycle of the ergots change the biological response from psychotropic (LSD, **2**) to oxytocic (ergonovine, **3**).[5] Several derivatives in which the D ring is variably substituted are used clinically as labor-inducing agents as well as anti-

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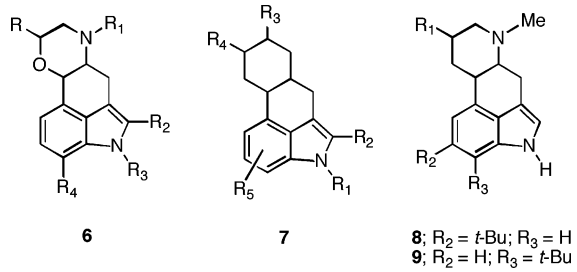


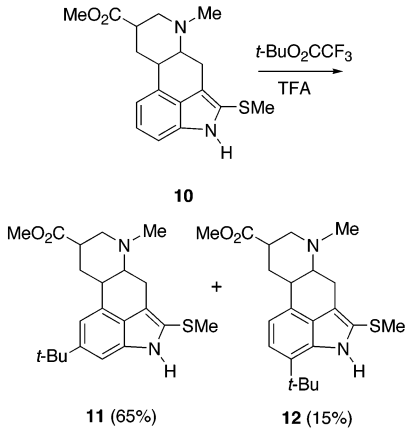
FIGURE 2. Biological properties of ergot structures.

migraine, analgesic, and anti-Parkinson's therapeutics.[5] The clinical success of these synthetic derivatives has prompted keen interest in derivatives that are substituted around the aryl A ring, though little has been reported in terms of general synthetic strategies to access these structures. For example, compounds with the general structure **6** have antihypertensive, anti-Parkinson, and prolactin-inhibiting activities, while compounds represented by **7** are analgesic and cell protective agents (Figure 2).[6] One particularly interesting example that illustrates the potential of A ring derivatives is the difference in 5-hydroxytryptamine (5-HT, serotonin) receptor selectivities for compounds **8** and **9**.[7] Compounds of type **8**, which contain a *tert*-butyl group on C(13), exhibit a selectivity for the 5-HT_{IA} receptor. Molecules of type **9**, on the other hand, which possess a *tert*-butyl group on C(14), show selectivity for the 5-HT_2 family of receptors. Without any substitution on the A ring, there is little selectivity between the two classes of receptors.

Selective synthesis of A ring derivatives requires either a regioselective modification of an indole core or de novo construction of the indole moiety. Methods for the modification of indoles are complicated by the inherent regiochemical preferences dictated by electronic factors. For example, the synthesis of **8** and **9** was accomplished by electrophilic alkylation of the aryl ring by exposing a synthetic intermediate to *tert*-butyl cation, followed by separation of the regioisomers (Scheme 1).[7] When the methyl lysergate derivative **10**, which contains a thiomethyl residue to protect the more electrophilic 2-position of the indole, was exposed to a mixture of *tert*-butyl acetate and trifluoroacetic acid, it gave rise to **11** (65%) and **12** (15%). A strategy in which the indole is constructed with the appropriate substitution would offer an advantage in the synthesis of compounds containing substituents on C(12)−C(14).

This existence of useful drugs and the potential for discovery of new therapeutics has sustained much interest in the synthesis of the ergot template. The majority of synthetic approaches have utilized the method first developed by Uhle to effect an intramolecular Friedel−Crafts cyclization, in which the indole was masked as an indoline moiety.[8] This strategy imposes the necessity of reoxidizing the indoline to an indole at a later stage of the synthesis,[3] usually a difficult and inefficient process.

SCHEME 1. Selective Synthesis of A Ring Derivatives



Several groups attempted to avoid the problems associated with the reoxidation of an advanced indoline intermediate by maintaining the indole moiety while effecting the formation of the tricyclic system through intramolecular cyclizations employing a Diels−Alder reaction,[9] an electrophilic cyclization,[10] or a tandem radical reaction.[11]

The first total synthesis of lysergic acid (**1**) was published by Kornfeld, Woodward, and colleagues in 1954.[12] Since the original synthesis, racemic lysergic acid ((±)-**1**) has been prepared by 10 different groups,[13] but the number of publications dealing with the synthetic efforts toward (±)-**1** is much higher. Among these approaches one can find about a dozen methods attempting to construct the ergoline ring, some of which were successful and others remaining at the level of attempt.[4,14] A critical intermediate in the Kornfeld−Woodward synthesis was a compound that became affectionately known as Kornfeld's ketone (**14**).[12] Over the past several decades many of the synthetic studies dealing with ergot structures focus on both Uhle's (**13**)[8,15] and Kornfeld's (**14**) ketones[16] as convenient synthetic intermediates (Figure 3). Methodologies that conveniently

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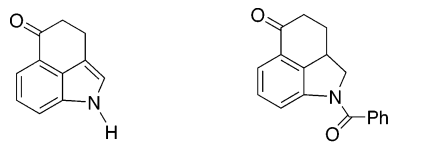
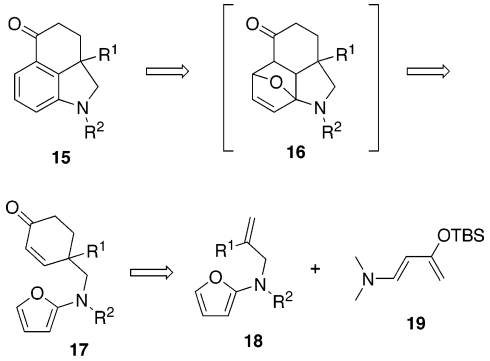


FIGURE 3. Uhle's and Kornfeld's ketones.

SCHEME 2. Strategic Diels–Alder Disconnections



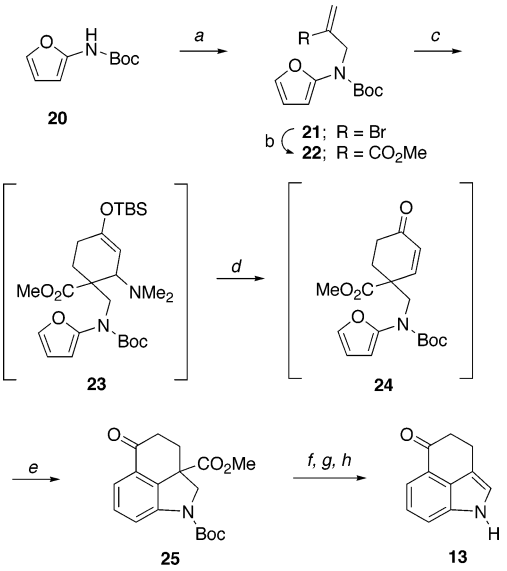
synthesize these tricycles have become important tools for medicinal chemists. Consequently, much attention has been centered on approaches that construct indoles, particularly 3,4-disubstituted indoles.[17] Because of the potential presented by A ring ergot analogues, new tactical strategies that can selectively generate polysubstituted indoles and also allow for the rapid construction of substituted analogues of **13** and **14** would be of particular use to the medicinal community.

Results and Discussion

As part of our ongoing program dealing with the intramolecular Diels–Alder reaction of 2-amidofurans,[18] we had previously noted that polysubstituted dihydroindoles could easily be prepared.[19] It occurred to us that the strategic deployment of this methodology could furnish a tricyclic ketone similar to Kornfeld's ketone **14** in relatively few steps and in a manner that would form the aromatic moiety in a particularly novel way. To demonstrate the feasibility of such an approach to the ergot core, a model study was initiated.[20]

The formation of tricyclic ketone **15** was envisioned to come about from a ring opening and dehydration of the oxabicyclic **16** (Scheme 2). In turn, this oxabicycle is the result of an intramolecular Diels–Alder reaction of amidofuran **17** with a cyclohexenone moiety tethered such that it participates in the cycloaddition as the 2π component. A convenient way to construct the cyclohexenone is to make use of some aminodiene chemistry

SCHEME 3. Consecutive [4 + 2] Cycloadditions[a]



[a] Reagents: (a) NaH, 2,3-dibromopropene, DMF, 0 °C; 70%; (b) $Pd(PPh_3)_4$, CO, *i*-Pr_2EtN, MeOH, 100 °C; 70%; (c) **19**, CH_3CN, heat; (d) HF·pyr, 25 °C; (e) PhMe, heat; 60%; (f) TFA, CH_2Cl_2, room temperature; (g) KOTMS, Et_2O, room temperature; (h) $Pb(OAc)_4$, DMF, 0 °C; 58%.

developed by Rawal and co-workers.[21] Consequently, the key amidofuran **17** was imagined to be derived from an appropriately substituted furan **18** and diene **19**[22] via an intermolecular [4 + 2] cycloaddition.

Initial studies on the simple allyl system **18** (R_1 = H; R_2 = CO_2-*t*-Bu) confirmed that an electron-withdrawing group was necessary to activate the olefin toward cycloaddition with Rawal's diene. Unfortunately, attempts to acylate the (*tert*-butyloxy)carbonyl-protected 2-amidofuran **18**[23] with acryloyl chloride failed to provide useful material. Furan **20** could, however, be alkylated with 2,3-dibromopropene to give the vinyl bromide **21** in 83% yield (Scheme 3). Palladium-catalyzed carbonylation of **21** in the presence of methanol provided the acrylate derivative **22** (68%), which was required for the intermolecular aminodiene cycloaddition reaction. Heating a mixture of Rawal's diene **19** and **22** in anhydrous CH_3CN at reflux for 2 h furnished a separable 2:1 mixture of diastereomeric amines **23** in 70% yield. The use of anhydrous CH_3CN was critical to the yield, as wet CH_3CN led to significant decomposition of both reactants. Exposing the mixture of **23** to HF at 0 °C unmasked the enone functionality to give **24**. Because furan **24** slowly underwent an intramolecular Diels–Alder reaction during isolation attempts, the crude furan was simply heated at reflux in toluene for 30 min to effect the cycloaddition, ring opening, and dehydration cascade that provides the desired tricyclic ketone **25** in 80% yield from **23**. Alternatively, a protocol in which the intermolecular Diels–Alder reaction is followed by immediate addition of HF to the reaction mixture at 0 °C furnished **25** in 60%

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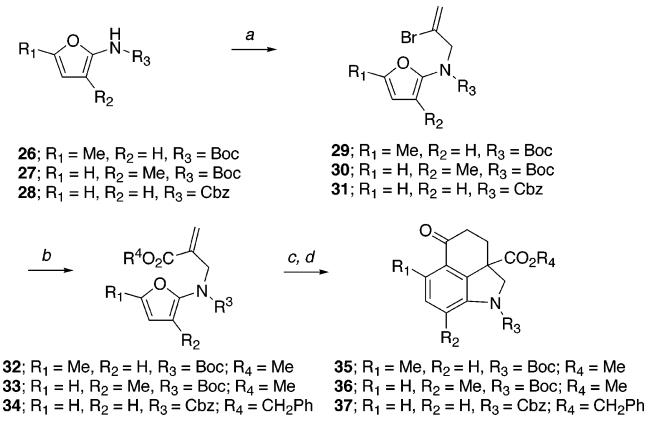
(21) (a) Janey, J. M.; Iwama, T.; Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **2000**, *65*, 9059. (b) Kozmin, S. A.; Janey, J. M.; Rawal, V. H. *J. Org. Chem.* **1999**, *64,* 3039.
(22) Kozmin, S. A.; He, S.; Rawal, V. *Org. Synth.* **2001**, *78*, 152. This reagent has recently become commercially available.
(23) Padwa, A.; Brodney, M. A.; Lynch, S. M. *Org. Synth.* **2001**, *78*, 202.

SCHEME 4. Intramolecular Amino Furan Cycloadditions[a]



[a] Reagents: (a) NaH, 2,3-dibromopropene, DMF, 0 °C; (b) $Pd(PPh_3)_4$, CO, *i*-Pr_2EtN, MeOH, 10 °C; (c) **19**, CH_3CN, heat; HF, −20 °C; (d) PhMe, heat.

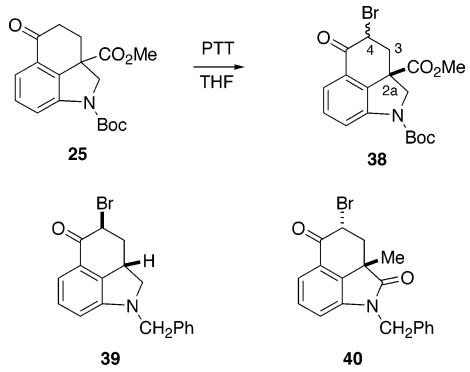
overall yield from **22**. Although Danishefsky's diene also participates in this sequence of events, higher temperatures (150 °C, sealed tube) and longer reaction times (12 h) were necessary in order to induce the intermolecular cycloaddition, and lower overall yields (30%) of **25** were obtained from **22** on employing this diene.

Several analogues of **25** were prepared using differently substituted furyl carbamates. Following the same general sequence of reactions, the sodium salts of furans **26**−**28** were first alkylated with 2,3-dibromopropene to give **29**−**31** in moderate to good yields (43−97%). Palladium-mediated carbonylation of **29** and **30** in methanol provided **32** and **33** in ca. 60% yield (Scheme 4). When the (benzyloxy)carbonyl-substituted derivative **31** was subjected to similar conditions, but using a toluene/benzyl alcohol solvent mixture instead of methanol, the benzyl ester **34** was obtained in 40% yield. In the key reaction sequence, **32**−**34** were converted to **35**−**37** by reaction with Rawal's diene **19** followed by exposure to HF and thermolysis of the intermediate enones (e.g. **24**). The substitution pattern of **35** and **36** is significant in that ergot derivatives based upon **35** are not available through electrophilic alkylation, and those based upon **36** are the minor isomers of electrophililc alkylation (vide supra).

Several features of the cascade sequence outlined in Scheme 3 are worth noting. (1) The use of the aminodiene chemistry developed by Rawal and co-workers allows for the enantioselective synthesis of these ketones by selecting a chiral amine for the formation of a diene reactant analogous to **19**.[21a] (2) The carbomethoxy functionality, required to activate the olefin toward cycloaddition with diene **19**, also serves as a protecting group that prevents the known aromatization of advanced ergoline intermediates to a naphthalene system.[12b] (3) This sequence also allows for independent substitution of the aryl ring as in ketones **35** and **36**, a feature rarely exploited by other methodologies.

With a successful procedure for the formation of a Kornfeld's ketone analogue (i.e., **25**), we next examined the conversion of dihydroindole **25** to Uhle's ketone (**13**). The angular carbomethoxy group, required to activate the olefin toward cycloaddition with diene **19**, was seen to fulfill two functions. It would not only prevent the

SCHEME 5. Bromination of a Kornfeld's Ketone Analog



isomerization of advanced ergoline intermediates to a naphthalene system but could also be leveraged for an oxidation to provide Uhle's ketone (**13**). Accordingly, we developed a three-step protocol to convert **25** to **13**. First, treatment of **25** with trifluoroacetic acid cleaved the carbamate group. This was followed by hydrolysis of the methyl ester with potassium trimethylsilanolate to provide the potassium salt of the carboxylic acid.[24] Finally, exposure of the crude salt to lead tetraacetate in wet DMF effected an oxidative decarboxylation[25] without purifying any of the intermediates.

The reactivity of **25** appears to be similar to that of Kornfeld's ketone **14**. For example, when **25** was treated with phenyltrimethylammonium tribromide (PTT) in THF, bromide **38** was isolated as a separable mixture (7:1) of diastereomers favoring the equatorial bromide in 85% yield (Scheme 5).[26] Interestingly, the bromide derived from Kornfeld's ketone **14** is exclusively isolated as the axial isomer **39**,[12b] while **40**, a similar substrate that possesses an angular methyl group, is only isolated as the equatorial bromide.[16]

With a viable approach to substituted derivatives of Kornfeld's ketone established, we next turned our attention to the elaboration of these derivatives toward ergot natural products. In our initial studies, we found that ketone **25** could be easily transformed into triflate **41** in 89% yield by the action of triflic anhydride in the presence of 4-methyl-2,6-di-*tert*-butylpyridine (Scheme 6). Subsequent cross coupling of **41** with *N*-methylpropriolamide[27] could be accomplished via palladium catalysis to afford **42** in 87% yield. Alternatively, **41** could be carbonylated under a CO atmosphere in the presence of methanol to provide the diester **43** in good yield. Cis hydrogenation of the alkynyl group present in **42** was expected to give the (*Z*)-dienamide **44**, which we hoped would undergo cyclization to furnish the ergoline skeleton **45**. Hydrogenation of **42** over palladium on carbon poisoned with quinoline provided **44** in 56% yield, but unfortunately we could not find any conditions to effect the cyclization of **44** to give **45**. Exposure of **44** to various bases, for example, produced an intractable mixture whose ^1H NMR spectra lacked resonances attributable

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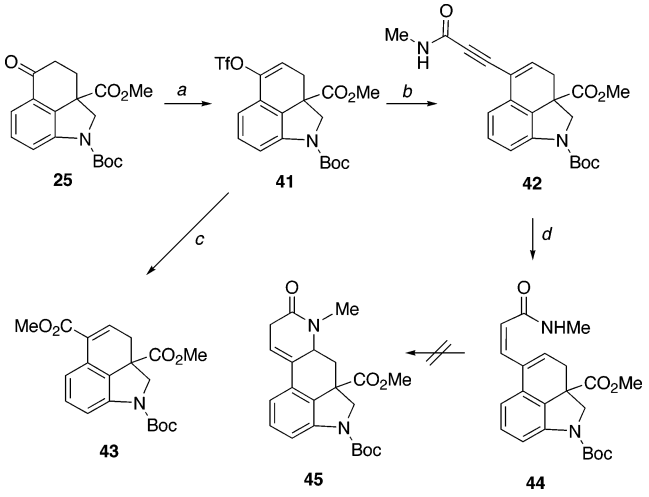
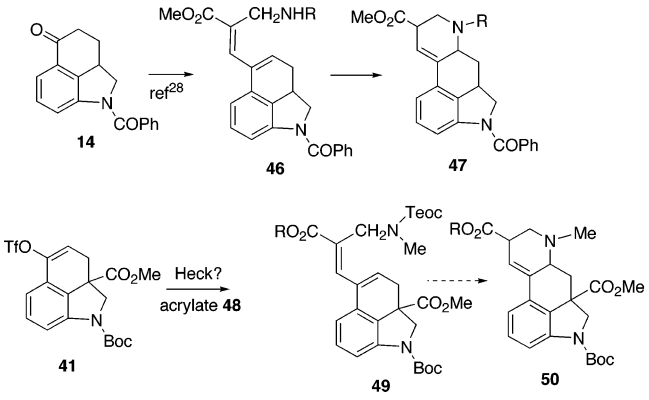
(26) Stereochemical assignments are based upon coupling constants for the C(4) proton in each diastereomer.
(27) Hay, L. A.; Koenig, T. M.; Ginah, F. O.; Copp, J. D.; Mitchell, D. *J. Org. Chem.* **1998**, *63*, 5050.

SCHEME 6. Cross-Coupling of Ketone 25 with *N*-Methylpropriolamide[a]



[a] Reagents and yields: (a) Tf_2O, 4-methyl-2,6-di-*tert*-butylpyridine, CH_2Cl_2, −78 °C → −20 °C, 48 h, 89%; (b) $(PPh_3)_2Pd(OAc)_2$, NaOAc, *N*-methylpropiolamide, DMF, 60 °C, 90 min, 87%; (c) $Pd(PPh_3)_4$, CO, *i*-Pr_2EtN, MeOH, 50 °C, 3 h; (d) H_2, Pd(C), quinoline, 25 °C, 56%.

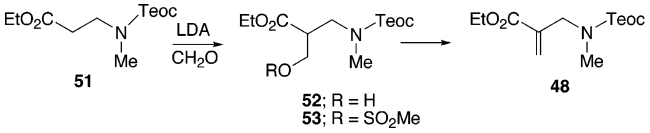
SCHEME 7. Synthesis of Modified Lysergic Systems by Intramolecular Conjugate Addition Reactions



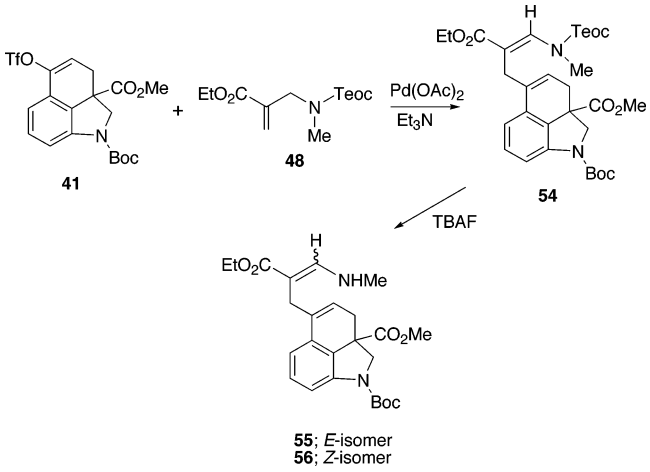
to **45**. Irradiation with a medium-pressure Hg lamp returned the starting materials, and reaction with $Me_3O^{\cdot}BF_4$ led to extensive decomposition. A literature search failed to disclose any related cyclizations of dienamides; therefore, we decided to change our approach to the ergoline skeleton.

Unsaturated esters of type **46** have previously been obtained by Ramage[28] in nine steps from Kornfeld's ketone (**14**) and were shown to constitute promising intermediates in the synthesis of modified lysergic systems (**47**) via intramolecular conjugate addition reactions (Scheme 7). Given the success of the palladium-catalyzed transformations of the vinyl triflate **41**, we chose to examine an alternate method to prepare the related compound **49** by using a sequence similar to that employed by Cacchi for establishing the D ring of the ergoline skeleton.[16e] The envisaged building block **49** was to be obtained from a palladium-catalyzed reaction

SCHEME 8. Synthesis of Acrylic Acid Ethyl Ester 48



SCHEME 9. Palladium-Mediated Heck Coupling of Triflate 41



between **41** and acrylate derivative **48**, since a related transformation had been described in the literature.[16e] Our intention was to cleave the [2-(trimethylsilyl)ethoxy]-carbonyl (Teoc) group[29] and cyclize the resulting secondary amine to the desired ergoline core **50**. The required acrylate derivative **48** for the Heck reaction was obtained by a three-step sequence comprising the trapping of the anion of **51** with formaldehyde to give the hydroxymethyl derivative **52**, conversion of **52** into the mesylate **53**, and an elimination reaction on crude **53** to give **48** (Scheme 8).

Unfortunately, the palladium-mediated Heck coupling of **41** and acrylate **48** in the presence of Et_3N delivered the isomeric vinylogous enamido ester **54** in yields comparable to that obtained by Cacchi.[16e] When **54** was treated with TBAF, it afforded a 1.5:1 mixture of the *E* (**55**) and *Z* (**56**) stereoisomers of the deprotected enamino ester in good yield. The structure of **55** was unequivocally established by an X-ray crystal structure. Apparently, the presence of the angular carbomethoxy group affects the regioselectivity of the reductive elimination step so that the vinylogous enamido ester **54** is the preferred olefin formed (Scheme 9).

In conclusion, while we were ultimately thwarted at the last stage of our ergoline synthesis by an uncooperative Heck reaction, there is no question that the sequential aminodiene Diels–Alder cycloaddition method has shown its potential for the preparation of various ergot alkaloids. In one operation, the ABC core skeleton is assembled and the method also allows for the independent substitution on the aryl A ring, a feature rarely exploited by other methodologies. Investigation into the range of substituents that are allowed as well as the

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application of the method to the synthesis of several ergot alkaloids is currently being explored.

Experimental Section

General Procedure for the Alkylation of Furyl Carbamates. To a solution of furan-2-yl carbamate (10 mmol) in DMF (20 mL) at 0 °C was added NaH (60% dispersion, 0.44 g, 11 mmol). The mixture was stirred at 0 °C for 1 h, and then 2,3-dibromopropene (2.6 g, 13 mmol) was added. Stirring was continued for 1 h, and the reaction mixture was partitioned between H_2O (50 mL) and ether (50 mL). The layers were separated, and the aqueous layer was extracted with ether. The combined organic layer was washed with H_2O, dried over $MgSO_4$, and concentrated under reduced pressure. The resultant oil was subjected to flash silica gel chromatography using an EtOAc/hexane mixture as the eluent.

***tert*-Butyl *N*-(2-Bromo-2-propenyl)-*N*-(2-furyl)carbamate (21).** By the general experimental procedure, the reaction of furanyl carbamate **20** (14.6 g, 80.0 mmol), NaH (60% dispersion, 3.5 g, 88 mmol), and 2,3-dibromopropene (20.8 g, 104 mmol) in DMF (160 mL) gave **21** (20 g, 83%). IR (neat): 2978, 2932, 1720, and 1613 cm^{-1}. ^1H NMR (300 MHz): δ 1.46 (s, 9H), 4.39 (s, 2H), 5.55 (d, 1H, J = 1.7 Hz), 5.77 (dd, 1H, J = 3.2 and 1.7 Hz) 6.09 (brs, 1H), 6.33 (dd, 1H, J = 3.1 and 2.2 Hz), and 7.17 (d, 1H, J = 1.7 Hz). ^{13}C NMR (75 MHz): δ 28.3, 56.0, 82.1, 101.8, 109.6, 111.1, 117.5, 128.9, 138.5, and 147.8. Anal. Calcd for $C_{12}H_{16}NO_3Br$: C, 47.84; H, 5.36; N, 4.65. Found: C, 47.71; H, 5.30; N, 4.52.

***tert*-Butyl *N*-(2-Bromo-2-propenyl)-*N*-(5-methylfur-2-yl)carbamate (29).** By the general experimental procedure, the reaction of furanyl carbamate **26**[30] (1.9 g, 9.4 mmol), NaH (60% dispersion, 0.4 g, 10.3 mmol), and 2,3-dibromopropene (2.4 g, 12.2 mmol) in DMF (20 mL) gave **29** (1.4 g, 47%). IR (neat): 2979, 2928, 1721, 1628, and 1575 cm^{-1}. ^1H NMR (300 MHz): δ 1.45 (s, 9H), 2.21 (s, 3H), 4.34 (s, 2H), 5.54 (dd, 1H, J = 1.9 and 1.0 Hz), 5.78 (d, 1H, J = 1.4 Hz), 5.89 (dd, 1H, J = 1.9 and 0.7 Hz), and 5.94 (brs, 1H). ^{13}C NMR (75 MHz): δ 13.8, 28.3, 56.4, 81.9, 103.2, 106.8, 117.4, 129.0, 145.9, 148.3, and 153.8. Anal. Calcd for $C_{13}H_{18}NO_3Br$: C, 49.52; H, 5.76; N, 4.44. Found: C, 49.28; H, 5.80; N, 4.19.

***tert*-Butyl *N*-(2-Bromo-2-propenyl)-*N*-(3-methylfur-2-yl)carbamate (30).** By the general experimental procedure, the reaction of furanyl carbamate **27**[31] (1.5 g, 7.5 mmol), NaH (60% dispersion, 0.33 g, 8.3 mmol), and 2,3-dibromopropene (2.0 g, 9.8 mmol) in DMF (25 mL) gave **30** (1.2 g, 52%). IR (neat): 2976, 2920, 1713, and 1641 cm^{-1}. ^1H NMR (300 MHz): δ 1.40 (brs, 9H), 1.92 (s, 3H), 4.33 (brs, 2H), 5.52 (s, 1H), 5.81 (s, 1H), 6.18 (d, 1H, J = 1.8 Hz), and 7.11 (d, 1H, J = 1.7 Hz). ^{13}C NMR (75 MHz): δ 10.0, 28.3, 56.1, 81.5, 112.7, 113.3, 118.5, 128.8, 138.6, 143.7, and 154.1. Anal. Calcd for $C_{13}H_{18}NO_3Br$: C, 49.52; H, 5.76; N, 4.44. Found: C, 49.35; H, 5.61; N, 4.36.

Benzyl *N*-(2-Bromo-2-propenyl)-*N*-(fur-2-yl)carbamate (31). By the general experimental procedure, the reaction of furanyl carbamate **28** (1.0 g, 4.6 mmol), NaH (60% dispersion, 0.13 g, 5.5 mmol), and 2,3-dibromopropene (1.1 g, 5.5 mmol) in DMF (10 mL) gave **31** (1.5 g, 97%). IR (neat): 2959, 1719, 1612, and 1504 cm^{-1}. ^1H NMR (300 MHz): δ 4.48 (s, 2H), 5.22 (s, 2H), 5.57 (m, 1H), 5.79 (s, 1H), 6.30 (s, 1H), 6.37 (dd, 1H, J = 3.4 and 2.0 Hz), and 7.33 (s, 5H). ^{13}C NMR (75 MHz): δ 56.6, 68.3, 103.4, 11.3, 118.6, 127.9, 128.3, 128.4, 128.7, 130.7, 132.5, 136.1, 139.3, 147.1, and 155.0. Anal. Calcd for $C_{15}H_{14}NO_3Br$: C, 53.73; H, 4.21; N, 4.18. Found: C, 53.59; H, 4.07; N, 4.31.

General Procedure for Carbonylation of Vinyl Bromide. A mixture of vinyl bromide (1 mmol), $Pd(PPh_3)_4$ (0.023 g, 0.02 mmol), and *N,N*-diisopropylethylamine (0.26 g, 2 mmol) in MeOH (1 mL) was heated at 100 °C under a CO atmosphere (250 psi) for 18 h. The mixture was cooled to room temperature, diluted with ether (10 mL), and washed with a saturated aqueous $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash silica gel chromatography using an EtOAc/hexane (1:19) mixture as the eluent afforded the desired ester.

***tert*-Butyl *N*-[2-(Carboxymethyl)-2-propenyl]-*N*-(2-furyl)carbamate (22).** By the general procedure, the reaction of furanyl carbamate **21** (13.7 g, 45.0 mmol), $Pd(PPh_3)_4$ (1.0 g, 0.9 mmol), and *N,N*-diisopropylethylamine (11.6 g, 90 mmol) in MeOH (45 mL) gave **22** (8.6 g, 68%). IR (neat): 1716, 1639, and 1614 cm^{-1}. ^1H NMR (300 MHz): δ 1.43 (s, 9H), 3.72 (s, 3H), 4.43 (t, 1H, J = 1.6 Hz), 5.71−5.72 (m, 1H), 5.99 (brs, 1H), 6.25−6.32 (m, 2H), and 7.12 (dd, 1H, J = 1.9 and 1.0 Hz). ^{13}C NMR (75 MHz): δ 28.3, 49.3, 52.1, 81.8, 101.1, 111.1, 125.5, 136.3, 138.2, 148.5, 153.7, and 166.5. HRMS: calcd for $C_{14}H_{19}NO_5$, 281.126 32; found, 281.126 07.

***tert*-Butyl *N*-[2-(Carboxymethyl)-2-propenyl]-*N*-(5-methylfur-2-yl)carbamate (32).** By the general procedure, the reaction of furanyl carbamate **29** (1.4 g, 4.4 mmol), $Pd(PPh_3)_4$ (0.1 g, 0.09 mmol), and *N,N*-diisopropylethylamine (1.1 g, 8.8 mmol) in MeOH (5 mL) gave **32** (0.75 g, 58%). IR (neat): 1720, 1625, 1575, and 1476 cm^{-1}. ^1H NMR (300 MHz): δ 1.43 (s, 9H), 2.20 (s, 3H), 3.73 (s, 3H), 4.39 (t, 2H, J = 1.6 Hz), 5.74 (m, 1H), 5.82−5.90 (m, 2H), and 6.29 (m, 1H). ^{13}C NMR (75 MHz): δ 13.8, 28.3, 49.6, 52.1, 81.6, 102.5, 106.7, 125.5, 136.3, 146.6, 148.0, 154.1, and 166.6. HRMS: calcd for $C_{15}H_{21}NO_5$, 295.141 97; found, 295.140 69.

***tert*-Butyl *N*-[2-(Carboxymethyl)-2-propenyl]-*N*-(3-methylfur-2-yl)carbamate (33).** By the general procedure, the reaction of furanyl carbamate **30** (0.35 g, 1.1 mmol), $Pd(PPh_3)_4$ (0.03 g, 0.02 mmol), and *N,N*-diisopropylethylamine (0.28 g, 2.2 mmol) in MeOH (1 mL) gave **33** (0.19 g, 59%). IR (neat): 1719, 1646, 1508, and 1475 cm^{-1}. ^1H NMR (300 MHz): δ 1.40 (s, 9H), 1.86 (s, 3H), 3.71 (s, 3H), 4.37 (brs, 2H), 5.83 (s, 1H), 6.16 (d, 1H, J = 1.9 Hz), 6.28 (d, 1H, J = 1.0 Hz), and 7.09 (d, 1H, J = 1.9 Hz). ^{13}C NMR (75 MHz): δ 9.7, 28.3, 49.2, 52.0, 81.2, 112.1, 113.2, 126.8, 136.2, 138.4, 144.3, 154.2, and 166.5. HRMS: calcd for $C_{15}H_{21}NO_5$: 295.141 97. Found: 295.142 42.

Benzyl *N*-(2-(Carboxybenzyl)-2-propenyl)-*N*-(fur-2-yl)carbamate (34). A mixture of furanyl carbamate **31** (1.6 g, 4.6 mmol), $Pd(PPh_3)_4$ (0.11 g, 0.09 mmol), benzyl alcohol (1.5 g, 13.8 mmol), and *N,N*-diisopropylethylamine (1.2 g, 9.2 mmol) in toluene (4 mL) was heated to 100 °C under a CO atmosphere (1 atm) for 18 h. The mixture was cooled to room temperature, diluted with ether, and washed with a saturated aqueous $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$, and the mixture was concentrated under reduced pressure. Purification of the residue by flash silica gel chromatography using an EtOAc/hexane (1:19) mixture as the eluent afforded **34** (0.7 g, 39%). IR (neat): 3033, 2954, 1720, 1612, and 1499 cm^{-1}. ^1H NMR (300 MHz): δ 4.57 (s, 2H), 5.19 (s, 2H), 5.20 (s, 2H), 5.79 (s, 1H), 6.05 (s, 1H), 6.33−6.34 (m, 1H), 6.38 (s, 1H), 7.18 (m, 1H), and 7.32−7.35 (m, 10H). ^{13}C NMR (75 MHz): δ 49.9, 66.9, 68.2, 101.5, 102.8, 106.3, 111.3, 126.7, 128.0, 128.5, 128.8, 132.6, 136.0, 136.9, 139.1, 140.4, 147.7, 154.9, and 165.7. HRMS: calcd for $C_{23}H_{21}NO_5$, 391.141 97; found, 391.142 18.

General Procedure for the Sequential Diels−Alder Cascade. A mixture of furyl acrylate (1 mmol), Rawals' diene **19** (0.27 g, 1.2 mmol), and CH_3CN (1 mL) was heated at reflux for 2 h. The mixture was cooled to 0 °C, and then a solution of HF·pyr (0.09 g, 3.0 mmol) in CH_3CN (3 mL) was added. The reaction mixture was stirred at 0 °C for 2 h and then partitioned between a saturated aqueous $NaHCO_3$ solution and EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, and the mixture was concentrated under reduced pressure. The crude residue was dissolved in toluene and the solution heated at reflux for 2 h. The mixture was cooled to

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room temperature and concentrated under reduced pressure. Purification by flash silica gel chromatography using an EtOAc/hexane (2:8) mixture as the eluent afforded the pure product.

1-[(*tert*-Butyloxy)carbonyl]-2*a*-carbomethoxy-5-keto-1,2,2*a*,3,4,5-hexahydrobenz[*cd*]indole (25). By the general procedure, furanyl carbamate **22** (0.28 g, 1.0 mmol) was reacted with Rawal's diene **19** (0.27 g, 1.2 mmol), followed by exposure to HF·pyr (0.09 g, 3.0 mmol) in 3 mL of CH_3CN to give **25** (0.2 g, 60%). Mp: 166−167 °C. IR (film): 1733, 1706, 1689, 1614, and 1596 cm^{-1}. ^1H NMR (300 MHz): δ 1.79 (s, 9H), 2.12−2.24 (m, 1H), 2.63−2.71 (m, 3H), 3.67 (s, 3H), 3.76 (d, 1H, J = 11.1 Hz), 4.62 (brd, J = 11.1 Hz), 7.34 (t, 1H, J = 7.9 Hz), 7.47 (dd, 1H, J = 7.9 and 0.8 Hz), and 7.89 (brs, 1H). ^{13}C NMR (75 MHz): δ 28.6, 32.3, 35.8, 49.6, 53.3, 59.8, 81.9, 119.3, 119.5, 130.2, 136.5, 141.9, 152.2, 173.3, and 195.9. Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.02; H, 6.44; N, 4.12.

1-[(*tert*-Butyloxy)carbonyl]-2*a*-carbomethoxy-5-keto-8-methyl-1,2,2*a*,3,4,5-hexahydrobenz[*cd*]indole (35). By the general procedure, furanyl carbamate **32** (0.75 g, 2.5 mmol) was reacted with Rawal's diene **19** (0.74 g, 3.3 mmol), followed by exposure to HF·pyr (0.21 g, 7.5 mmol) in 10 mL of CH_3CN to give **35** (0.33 g, 39%). Mp: 133−134 °C. IR (film): 1727, 1712, 1685, 1614, and 1590 cm^{-1}. ^1H NMR (300 MHz): δ 1.50 (s, 9H), 1.88−1.99 (m, 1H), 2.36 (s, 3H), 2.57−2.82 (m, 3H), 3.65 (s, 1H), 3.70 (d, 1H, J = 11.8 Hz), 4.81 (d, 1H, J = 11.8 Hz), 7.18 (dd, 1H, J = 8.2 and 0.5 Hz), and 7.51 (d, 1H, J = 8.2 Hz). ^{13}C NMR (75 MHz): δ 20.1, 28.2, 30.6, 35.6, 50.0, 52.9, 63.2, 81.4, 121.7, 127.5, 132.4, 135.3, 140.9, 141.9, 153.7, 172.5, and 196.0. Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 65.94; H, 6.84; N, 4.24.

1-[(*tert*-Butyloxy)carbonyl]-2*a*-carbomethoxy-5-keto-6-methyl-1,2,2*a*,3,4,5-hexahydrobenz[*cd*]indole (36). By the general procedure, furanyl carbamate **33** (0.19 g, 0.65 mmol) was reacted with Rawal's diene **19** (0.19 g, 0.85 mmol) followed by exposure to HF·pyr (0.06 g, 2 mmol) in 2 mL of CH_3CN to give **36** (0.08 g, 37%). Mp: 127−127.5 °C. IR (neat): 1731, 1705, 1680, 1608, and 1585 cm^{-1}. ^1H NMR (300 MHz): δ 1.54 (s, 9H), 2.11−2.19 (m, 1H), 2.56 (s, 3H), 2.60−2.68 (m, 3H), 3.66 (s, 3H), 3.72 (d, 1H, J = 11.2 Hz), 4.58 (brd, 1H, J = 11.2 Hz), 7.11 (d, 1H, J = 8.2 Hz), and 7.78 (brs, 1H). ^{13}C NMR (75 MHz): δ 20.7, 28.3, 31.5, 36.6, 49.9, 52.9, 59.3, 81.4, 118.9, 127.9, 132.7, 133.6, 137.0, 139.9, 151.9, 173.4, and 196.8. Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.14; H, 6.63; N, 4.05.

1-[(Benzyloxy)carbonyl]-2*a*-carbomethoxy-5-keto-1,2,2*a*,3,4,5-hexahydrobenz[*cd*]indole (37). By the general procedure, furanyl carbamate **34** (0.39 g, 1.0 mmol) was reacted with Rawal's diene **19** (0.29 g, 1.3 mmol) followed by exposure to HF·pyr (0.09 g, 3.0 mmol) in 3 mL of CH_3CN to give **37** (0.17 g, 39%). Mp: 99−99.5 °C. IR (neat): 2953, 1716, 1687, 1596, and 1476 cm^{-1}. ^1H NMR (300 MHz): δ 2.18 (ddd, 1H, J = 12.4, 10.5 and 7.9 Hz), 2.58−2.69 (m, 3H), 3.83 (d, 1H, J = 11.5 Hz), 4.73 (brd, 1H, J = 10.5), 5.12 (s, 2H), 5.12−5.29 (m, 2H), 7.15−7.18 (m, 1H), 7.29 (t, 1H, J = 3.2 Hz), 7.39 (s, 9H), 7.53 (d, 1H, J = 7.7 Hz), and 7.97 (brs, 1H). ^{13}C NMR (75 MHz): δ 32.0, 35.7, 49.9, 59.7, 67.8, 119.8, 128.0, 128.4, 128.7, 128.9, 130.4, 135.3, 136.0, 136.9, 142.3, 152.8, 172.3, and 195.7. Anal. Calcd for $C_{27}H_{23}NO_5$: C, 73.46; H, 5.25; N, 3.17. Found: C, 73.41; H, 5.25; N, 3.13.

4-Bromo-1-[(*tert*-butyloxy)carbonyl]-2*a*-(carboxymethyl)-5-keto-1,2,2*a*,3,4,5-hexahydrobenz[*cd*]indole (38). To a solution of ketone **25** (1.7 g, 5.1 mmol) in dry THF (30 mL) was added a solution of phenyltrimethylammonium tribromide (1.9 g, 5.1 mmol) in THF (30 mL). The mixture was stirred for 2 h at room temperature for 3 h, and then H_2O was added. The layers were separated, and the aqueous layer was extracted with ether. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting solid was subjected to flash silica gel chromatography using EtOAc/hexane (3:15) as the eluent to afford a 7:1 mixture of diastereomers. The major (equatorial) diastereomer (1.2 g, 61%) showed the following spectral properties. IR (neat): 1734, 1705, 1698, 1615, 1596 cm^{-1}. ^1H NMR (300 MHz): δ 1.55 (brs, 9H), 2.66 (t, 1H, J = 12.6 Hz), 1.74 (dd, 1H, J = 12.6 and 5.8 Hz), 3.70 (s, 3H), 3.77 (d, 1H, J = 11.0 Hz), 4.64 (brd, 1H, J = 11 Hz), 4.99 (dd, 1H, J = 12.6 and 5.8 Hz), 7.37 (t, 1H, J = 7.8 Hz), 7.52 (dd, 1H, J = 7.8 and 0.8 Hz), and 7.91 (brs, 1H). ^{13}C NMR (75 MHz): δ 28.5, 43.5, 48.0, 50.6, 53.7, 59.1, 82.3, 119.7, 120.1, 120.4, 128.7, 130.8, 136.0, 142.4, 152.0, 172.3, and 189.5. Anal. Calcd for $C_{18}H_{20}BrNO_5$: C, 52.70; H, 4.91; N, 3.41. Found: C, 52.65; H, 4.77; N, 3.50.

The minor (axial) diastereomer (0.18 g, 9%) exhibited the following spectral properties. Mp: 144−145 °C. IR (film): 1735, 1706, 1694, 1597, 1478, and 1461 cm^{-1}. ^1H NMR (300 MHz): δ 1.56 (s, 9H), 2.76 (dd, 1H, J = 15.1 and 5.2 Hz), 3.26 (d, 1H, J = 15.1 Hz), 3.71 (s, 3H), 3.76 (d, 1H, J = 11.3 Hz), 4.53 (d, 1H, J = 11.3 Hz), 4.70 (dd, 1H, J = 5.2 and 1.7 Hz), 7.41 (t, 1H, J = 7.9 Hz), 7.59 (dd, 1H, J = 7.9 and 0.7 Hz), and 7.96 (brs, 1H). ^{13}C NMR (75 MHz): δ 28.5, 40.6, 44.5, 47.4, 53.7, 61.4, 82.4, 120.2, 120.7, 128.1, 130.7, 136.0, 142.6, 152.1, 174.0, and 188.7. Anal. Calcd for $C_{18}H_{20}BrNO_5$: C, 52.70; H, 4.91; N, 3.41. Found: C, 52.92; H, 4.98; N, 3.43.

1-[(*tert*-Butyloxy)carbonyl]-2*a*-(carboxymethyl)-5-[(trifluoromethyl)sulfonyl]-1,2,2*a*,3-tetrahydrobenz[*cd*]indole (41). To a solution of ketone **25** (0.5 g, 1.5 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (0.37 g, 1.8 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added triflic anhydride (0.5 g, 1.8 mmol). The mixture was stirred at −78 °C for 30 min, and it was then warmed to −20 °C. After it was stirred at −20 °C for 48 h, the solution was quenched with a saturated aqueous $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting solid was subjected to flash silica gel chromatography using an EtOAc/hexane (1:9) mixture as the eluent to give triflate **41** as a white solid (0.56 g, 89%). Mp: 132−133 °C. IR (film): 1736, 1706, 1634, 1619, and 1583 cm^{-1}. ^1H NMR (300 MHz): δ 1.55 (s, 9H), 2.64 (dd, 1H, J = 16.8 and 2.2 Hz), 3.14−3.28 (m, 1H), 3.62 (s, 3H), 3.80 (d, 1H, J = 11.5 Hz), 4.49 (brs, 1H), 5.91 (brd, 1H, J = 5.0 Hz), 6.95 (d, 1H, J = 7.9 Hz), 7.29 (t, 1H, J = 7.9 Hz), and 7.70 (brs, 1H). ^{13}C (75 MHz): δ 28.5, 32.0, 47.5, 53.2, 60.1, 82.1, 114.7, 116.1, 117.1, 118.8 (q, J = 320.7), 126.7, 128.6, 130.5, 141.9, 146.5, 152.2, and 173.8. ^{19}F NMR (282 MHz): δ −74.58 (s, 3F). Anal. Calcd for $C_{19}H_{20}F_3NO_7S$: C, 49.24; H, 4.35; N, 3.02. Found: C, 49.23; H, 4.31; N, 2.96.

1-[(*tert*-Butyloxy)carbonyl]-2*a*-(carboxymethyl)-5-(*N*-methylpropriolamid-3-yl)-1,2,2*a*,3-tetrahydrobenz[*cd*]indole (42). A solution of triflate **41** (0.25 g, 0.5 mmol), *N*-methylpropriolamide (0.06 g, 0.7 mmol), NaOAc (0.18 g, 2.2 mmol), and $Pd(OAc)_2(PPh_3)_2$ (8 mg) in DMF (2 mL) was stirred for 90 min. The reaction mixture was cooled to room temperature and was partitioned between H_2O and ether. The layers were separated, and the aqueous layer was extracted with ether. The combined organic layer was successively washed with H_2O and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting solid was subjected to flash silica gel chromatography using an EtOAc/hexane (3:7) mixture as the eluent to give **42** (0.19 g, 88%) as a white foam. IR (film): 3295, 2215, 1733, 1701, 1652, 1568, and 1538 cm^{-1}. ^1H NMR (300 MHz): δ 1.53 (brs, 9H), 2.43 (dd, 1H, J = 17.5 and 2.6 Hz), 2.85 (d, 3H, J = 4.8 Hz), 3.18 (dd, 1H, J = 17.5 and 6.4 Hz), 3.58 (s, 3H), 3.76 (d, 1H, J = 11.5 Hz), 4.43 (brs, 1H), 6.43 (dd, 1H, J = 6.4 and 2.6 Hz), 6.45−6.49 (m, 1H), 7.02 (d, 1H, J = 8.2 Hz), 7.21 (t, 1H, J = 7.7 Hz), 7.62 (brs, 1H). ^{13}C NMR (75 MHz): δ 26.8, 28.6, 32.9, 47.2, 53.1, 60.6, 81.2, 81.9, 85.3, 115.1, 117.9, 119.5, 126.7, 129.3, 130.3, 137.6, 141.5, 152.4, 154.2, and 173.7. Anal. Calcd for $C_{22}H_{24}N_2O_5$: C, 66.64; H, 6.11; N, 7.87. Found: C, 66.51; H, 5.87; N, 7.93.

1-[(*tert*-Butyloxy)carbonyl]-2*a*,5-(dicarboxymethyl)-1,2,2*a*,3-tetrahydrobenz[*cd*]indole (43). A mixture of triflate **41** (0.1 g, 0.22 mmol), $Pd(PPh_3)_4$ (0.005 g, 0.004 mmol),

and *N*,*N*-diisopropylethylamine (0.06 g, 0.4 mmol) in MeOH (1 mL) was heated at 50 °C for 3 h. The reaction mixture was cooled, filtered, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography using EtOAc/hexane (1:9) as the eluent to give **43** (0.06 g, 73%) as a white solid. Mp: 145−146 °C. ^{1}H NMR (300 MHz): δ 1.56 (brs, 9H), 2.46 (dd, 1H, J = 17.3 and 2.4 Hz), 3.30 (dd, 1H, J = 17.3 and 5.4 Hz), 3.60 (s, 3H), 3.79 (d, 1H, J = 11.5 Hz), 3.81 (s, 3H), 4.33−4.54 (m, 1H), 7.13 (d, J = 4.8 Hz), 7.26 (t, 1H, J = 7.8 Hz), 7.54 (d, 1H, J = 7.8 Hz), and 7.67 (brs, 1H). ^{13}C NMR (75 MHz; two rotamers): δ 28.6, 29.9, 32.6, 47.1, 47.9, 52.1, 53.1, 59.9, 60.4, 77.4, 81.3, 82.2, 114.8, 119.7, 128.4, 128.7, 130.0, 138.9, 139.3, 141.1, 141.9, 152.2, 152.6, 165.9, 173.4, and 173.8. Anal. Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.22; H, 6.31; N, 3.69.

1-[(*tert*-Butyloxy)carbonyl]-2*a*-(carboxymethyl)-5-(*N*-methylpropenamid-3-yl)-1,2,2*a*,3-tetrahydrobenz[*cd*]indole (44). A mixture of alkyne **42** (0.17 g, 0.4 mmol), quinoline (0.22 g, 1.7 mmol), and 10% Pd/C (0.05 g) in EtOAc (4 mL) was stirred at room temperature under a hydrogen blanket (1 atm) for 1 h. The mixture was filtered through Celite, washed with aqueous HCl (1 M), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was subjected to flash silica gel chromatography using an EtOAc/hexane (7:3) mixture as the eluent to give **44** (0.1 g, 56%) as a yellow foam. IR (film): 3307, 2975, 1726, 1703, 1652, 1614, and 1568 cm^{-1}. ^{1}H NMR (300 MHz): δ 1.56 (s, 9H), 2.46−2.54 (m, 4H), 3.04 (dd, 1H, J = 17.2 and 6.4 Hz), 3.70 (s, 3H), 3.80 (d, 1H, J = 11.8 Hz), 4.57 (brs, 1H), 6.00−6.04 (m, 1H), 6.02 (d, 1H, J = 12.5 Hz), 6.56−6.60 (m, 1H), 6.83 (d, 1H, J = 8.0 Hz), 7.23 (t, 1H, J = 8.0 Hz), and 7.62 (brs, 1H). ^{13}C NMR (75 MHz): δ 26.2, 28.6, 33.4, 47.4, 53.1, 59.7, 82.1, 114.6, 117.4, 127.7, 128.0, 130.3, 132.0, 134.1, 141.5, 150.4, 152.4, 156.8, 167.3, and 174.4. HRMS: calcd for $C_{22}H_{26}N_2O_5$, 398.184 17; found, 398.183 37.

3-{Methyl[(2-(trimethylsilanyl)ethoxy)carbonyl]amino}-propionic Acid Ethyl Ester (51). To a solution containing 2.0 g (15 mmol) of 3-(methylamino)propionic acid ethyl ester[32] and 4.2 mL (30 mmol) of Et_3N in 10 mL of CH_2Cl_2 at 25 °C was added dropwise a solution of 2-(trimethylsilyl)ethyl carbonochloridate[33] in 5 mL of CH_2Cl_2. After it was stirred at room temperature for 2 h, the reaction mixture was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with H_2O and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude residue was subjected to flash silica gel chromatography to give 2.9 g (71%) of **51** as a colorless oil. IR (neat): 1735, 1698, 1250, 1180, 861, and 839 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.02 (s, 9H), 0.98 (t, 2H, J = 8.1 Hz), 1.24 (t, 3H, J = 6.9 Hz), 2.53 (brt, 2H, J = 8.4 Hz), 2.89 (brd, 3H, J = 7.2 Hz), 3.51 (brd, 2H, J = 7.2 Hz), 4.10 (q, 2H, J = 6.9 Hz), and 4.14 (t, 2H, J = 8.1 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz): δ −1.3, 14.3, 17.9, 18.1, 33.2, 33.6, 34.9, 35.1, 44.9, 45.5, 60.7, 63.7, 63.8, 156.7, 171.9, and 172.2.

2-(Hydroxymethyl)-3-{methyl[(2-(trimethylsilanyl)-ethoxy)carbonyl]amino}propionic Acid Ethyl Ester (52). To a solution of 9.8 mmol of freshly prepared LDA in 20 mL of THF at −78 °C was added dropwise a solution of 2.5 g (8.9 mmol) of the Teoc-protected propionic acid ethyl ester **51** in 10 mL of THF. After the mixture was stirred at −78 °C for 45 min, formaldehyde gas (20 equiv), generated by heating dry paraformaldehyde at 150 °C, was added to the enolate solution. The reaction mixture was warmed to room temperature, quenched with a saturated NH_4Cl solution, and extracted with EtOAc. The combined organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 2.5 g (92%) of **52** as a colorless oil. IR (neat): 1733, 1701, 1683, 1250, and 839 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.02 (s, 9H), 0.95 (dd, 2H, J = 9.2 and 8.0 Hz), 1.22 (t, 3H, J = 7.0 Hz), 2.66−2.92 (m, 4H), 3.42−3.81 (m, 5H), and 4.07−4.14 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −1.4, 14.2, 17.8, 35.1, 45.8, 46.9, 59.6, 60.9, 64.3, 158.0, and 172.7.

2-{[Methyl((2-(trimethylsilanyl)ethoxy)carbonyl)amino]-ethyl}acrylic Acid Ethyl Ester (48). To a solution of 2.5 g (8.2 mmol) of alcohol **52** and 2.6 mL (18.0 mmol) of Et_3N at 0 °C was added 1.0 g (9.0 mmol) of mesyl chloride. After it was stirred at room temperature for 1 h, the reaction mixture was quenched with a saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organic layer was washed with H_2O and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the resultant residue was dissolved into 20 mL of benzene, followed by the addition of 1.2 mL (9.0 mmol) of DBU. After it was stirred at room temperature for 30 min, the reaction mixture was quenched with a saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organic layer was washed with H_2O and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 1.5 g (64%) of **48** as a colorless oil. IR (neat): 1705, 1299, 1249, 1151, and 839 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.02 (brs, 5H), 0.02 (brs, 4H), 0.93−1.02 (m, 2H), 1.29 (t, 3H, J = 7.2 Hz), 2.88 (brd, 3H, J = 6.8 Hz), 4.08−4.23 (m, 6H), 5.52 (brs, 0.55H), 5.58 (brs, 0.45H), and 6.27 (brs, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −1.3, 14.3, 18.0, 34.7, 35.0, 49.3, 49.7, 61.0, 63.9, 124.6, 125.3, 136.1, 136.3, 157.0, and 166.4. HRMS: calcd for $C_{13}H_{25}NO_4Si$, 287.1553; found, 287.1550.

5-{2-(Ethoxycarbonyl)-3-[methyl-((2-(trimethylsilanyl)-ethoxy)carbonyl)amino]allyl}-3*H*-benzo[*cd*]indole-1,2*a*-dicarboxylic Acid 1-*tert*-Butyl Ester 2*a*-Methyl Ester (54). To a solution of 0.47 g (1.0 mmol) of triflate **41** and 0.3 g (1.1 mmol) of the Teoc-protected acrylic acid ethyl ester **48** in 6 mL of DMF was added 24 mg (0.1 mmol) of $Pd(OAc)_2$, 53 mg (0.2 mmol) of PPh_3, and 0.35 mL (2.5 mmol) of Et_3N. The reaction mixture was heated to 65 °C for 12 h, quenched with H_2O, and extracted with ether. The combined organic layer was washed with H_2O and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.12 g (21%) of **54** as a yellow oil. IR (neat): 1731, 1701, 1386, 1331, 1250, 1203, and 1160 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.06 (s, 9H), 1.05−1.09 (m, 3H), 1.25 (t, 3H, J = 7.2 Hz), 1.55 (brd, 9H), 2.36 (brd, 1H, J = 16.8 Hz), 3.01−3.10 (m, 1H), 3.13 (s, 3H), 3.38 (brd, 1H, J = 18.4 Hz), 3.56 (s, 3H), 3.72 (brd, 1H, J = 16.8 Hz), 3.77 (brd, 1H, J = 11.6 Hz), 4.17 (q, 2H, J = 7.2 Hz), 4.28−4.32 (m, 2H), 4.36−4.50 (m, 1H), 5.53 (brs, 1H), 6.94 (d, 1H, J = 8.0 Hz), 7.20−7.32 (m, 1.5H), 7.65 (brs, 0.5H), and 8.20 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −1.3, 14.5, 15.5, 17.8, 28.0, 28.6, 32.6, 33.9, 47.4, 48.2, 52.8, 53.2, 59.9, 60.6, 65.8, 66.1, 77.4, 81.2, 82.0, 110.3, 114.3, 115.8, 122.4, 122.8, 128.7, 129.9, 132.9, 135.7, 141.1, 152.3, 155.1, 168.8, and 174.2. HRMS: calcd for [$C_{31}H_{44}N_2O_8Si$ + H^+], 601.2840; found, 601.2943.

(*E*)- and (*Z*)-5-[2-(Ethoxycarbonyl)-3-(methylamino)-allyl]-3*H*-benzo[*cd*]indole-1,2*a*-dicarboxylic Acid 1-*tert*-Butyl Ester 2*a*-Methyl Ester (55 and 56). To a solution of 0.08 g (0.13 mmol) of ester **54** in 4 mL of THF was added 0.8 g of dry 4 Å sieves, followed by the dropwise addition of 0.2 mL (0.2 mmol) of TBAF (1.0 M in THF) at 0 °C. After it was stirred for 30 min, the reaction mixture was quenched with a saturated $NaHCO_3$ solution and extracted with ether. The organic layer was washed with H_2O and brine and dried over $MgSO_4$. The NMR spectrum of the crude residue showed that it contained a 1.5:1 mixture of compounds **55** and **56**. An analytical sample of the *E* isomer **55** was obtained by recrystallization from CH_2Cl_2/MeOH and corresponded to a white solid. Mp: 190−192 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.26 (t, 3H, J = 7.2 Hz), 1.56 (m, 9H), 2.36 (dd, 1H, J = 16.0 and 3.2 Hz), 2.87 (d, 1H, J = 4.8 Hz), 3.02 (brd, 1H, J = 13.2 Hz), 3.30 (brd, 1H, J = 16.8 Hz), 3.54 (m, 1H), 3.59 (s, 3H), 3.76 (d,

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1H, J = 16.0 Hz), 4.09–4.22 (m, 2H), 4.41 (m, 2H), 5.76 (brs, 1H), 6.99 (d, 1H, J = 8.0 Hz), 7.22 (m, 1.5H), 7.39 (d, 1H, J = 13.6 Hz), and 7.60 (brs, 0.5H).

The minor *Z* isomer **56** was obtained as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25 (t, 3H, J = 7.2 Hz), 1.57 (m, 9H), 2.37 (brd, 1H, J = 14.4 Hz), 2.88 (d, 3H, J = 4.8 Hz), 3.06 (brd, 1H, J = 16.0 Hz), 3.05 (brd, 1H, J = 16.0 Hz), 3.36 (brd, 1H, J = 16.0 Hz), 3.62 (s, 3H), 3.78 (brd, 1H, J = 12.0 Hz), 4.10–4.20 (m, 2H), 4.42 (m, 2H), 5.68 (brs, 1H), 6.45 (brd, 1H, J = 13.2 Hz), 6.89 (brd, 1H, J = 7.6 Hz), 7.21 (brs, 1H), and 7.63 (brs, 1H).

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Supporting Information Available: Figures giving an Ortep drawing for **55** and NMR spectra for **22**, **32**–**34**, **44**, **48**, **51**, **52**, and **54**–**56** and a CIF file giving crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org. The authors have also deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre.

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