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A Novel Sequential Aminodiene Diels–Alder Strategy for the Rapid Construction of Substituted Analogues of Kornfeld's Ketone

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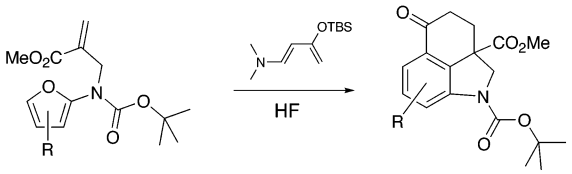
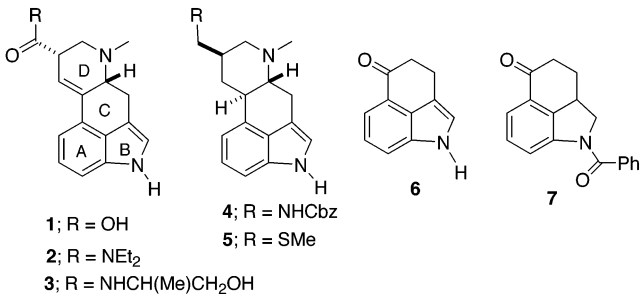
ABSTRACT



Through a novel sequence of aminodiene Diels–Alder reactions, amidofurans 18a–c were converted to tricyclic ketones 21a–c in moderate to good yields. Ketone 21a could be converted to Uhlé's ketone (6) by cleaving the *tert*-butyl carbamate and oxidatively removing the methyl ester. Tricycle 21a readily underwent bromination to give 22. Formation of the corresponding enol triflate 25 followed by carbonylation gave ester 27, which was then coupled with *N*-methyl propriolamide to furnish 26.

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, of which lysergic acid (**1**) is representative, are particularly important as they possess the widest spectrum of biological activity found in any family of natural products.[2] Small variations in the substituents present on the core tetracycle change the biological response from psychotropic (LSD, **2**) to oxytocic (ergonovine, **3**). Several synthetic derivatives are used clinically as antimigrain (lisuride), analgesic (metergoline, **4**), and anti-Parkinsonian (pergolide, **5**) therapeutics, to name just a few.[3]

The clinical success of these synthetic derivatives has prompted keen interest in indoles that are substituted around the aryl A ring. For example, compounds with the general structure **8** have antihypertensive, antiparkinson, and prolactin-inhibiting activities,[4] while compounds represented by



1; R = OH
2; R = NEt_2
3; R = $NHCH(Me)CH_2OH$
4; R = NHCbz
5; R = SMe

9 are analgesic and cell protective agents.[5] The position of the *tert*-butyl group (R) in indole **10** strongly impacts on the selectivity of these molecules for 5-HT_{1A} vs 5-HT_2 receptors.[6]

Many of the synthetic studies dealing with ergot structures focus on Uhlé's (**6**)[7,8] and Kornfeld's (**7**)[9−11] ketones, and methodologies that efficiently construct these tricycles have been important tools for medicinal chemists. Consequently,

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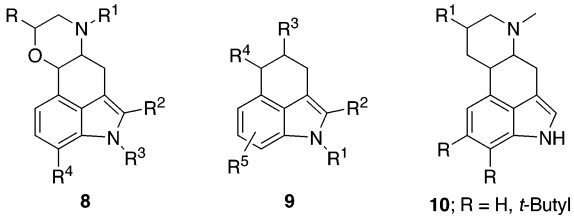
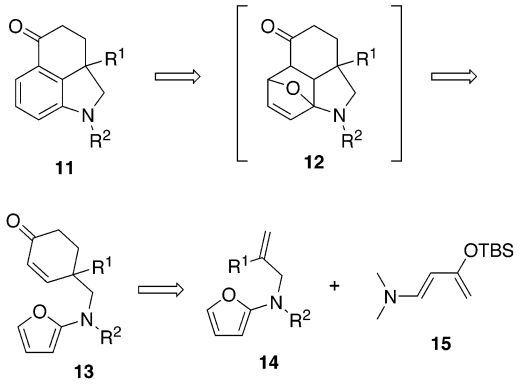


much attention has been centered on synthetic methods that construct indoles, particularly 3,4-disubstituted indoles.[12] New procedures that can selectively generate polysubstituted indoles and also allow for the rapid construction of substituted analogues such as **6** or **7** would be of particular use to the medicinal community.

As part of our ongoing program dealing with the intramolecular Diels−Alder reaction of 2-amidofurans,[13] we had previously noted that polysubstituted dihydroindoles could easily be prepared.[14] It occurred to us that the strategic deployment of this methodology could fashion a tricyclic ketone similar to Kornfeld's ketone **7** 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.

The formation of tricyclic ketone **11** was envisioned to come about from a ring opening and dehydration of an oxabicycle **12** (Scheme 1). In turn, this oxabicycle is the

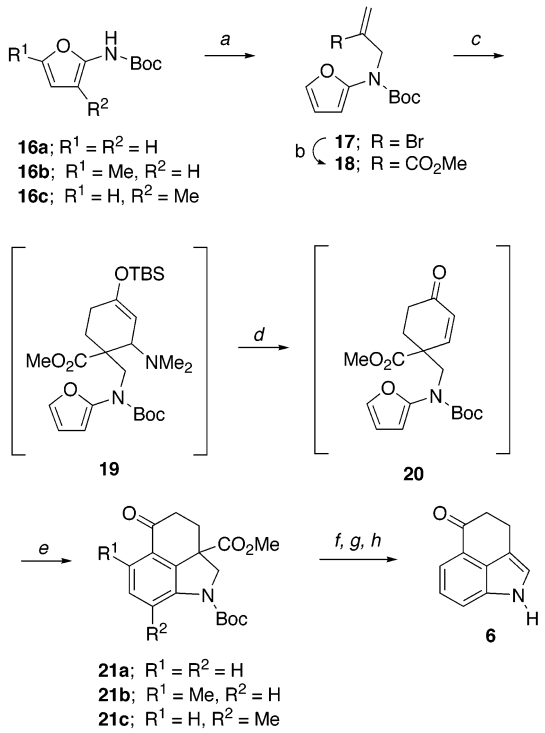
Scheme 1. Strategic Sequential Diels−Alder Disconnections



result of an intramolecular Diels−Alder reaction of amidofuran **13** 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 recently developed by Rawal.[15] Consequently, the key amidofuran **13** was imagined to be derived from an appropriately substituted furan **14** and diene **15**[16] via an intermolecular [4+2]-cycloaddition.

Accordingly, the *tert*-butyloxycarbonyl protected 2-amidofuran **16a** (R^1, R^2 = H)[17] was first alkylated with 2,3-dibromopropene to give vinyl bromide **17** (Scheme 2).

Scheme 2[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) **15**, CH_3CN, △; (d) HF, 25 °C; (e) PhMe △; 60% (f) TFA, CH_2Cl_2, rt; (g) KOTMS, Et_2O, rt; (h) $Pb(OAc)_4$, DMF, 0 °C, 58%.

Palladium-catalyzed carbonylation of **17** in the presence of methanol provided the acrylate derivative **18** that was required for the intermolecular aminodiene cycloaddition reaction. Heating a mixture of **15** and **18** in CH_3CN at reflux for 2 h furnished a 2:1 mixture of diastereomeric amines **19**

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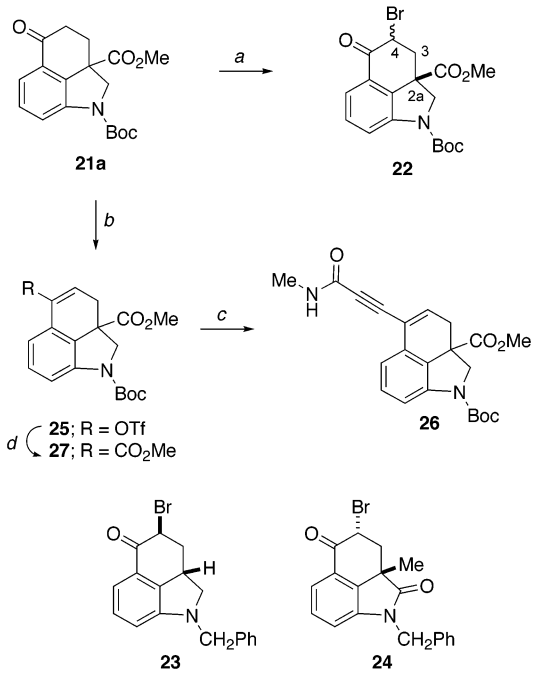
that was immediately treated with HF at room temperature to unmask the enone **20**. Because furan **20** slowly underwent an intramolecular Diels−Alder reaction during isolation attempts, the crude furan was simply heated at reflux in toluene for 30 min to effect the cycloaddition, ring opening, and dehydration cascade that provides the desired tricyclic ketone **21a**. 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 to induce the intermolecular cycloaddition and lower overall yields (30%) of **21a** were obtained from **18** using this diene. In a similar manner, amidofurans **16b**[18] and **16c**[19] were converted to dihydroindoles **21b** and **21c**.

Several features of this sequence are significant: The use of the aminodiene chemistry developed by Rawal and coworkers allows for the enantioselective synthesis of these ketones by selecting a chiral amine for the formation of a diene reactant analogous to **15**.[15a] The carbomethoxy functionality, required to activate the olefin toward cycloaddition with **15**, also serves as a protecting group that prevents the known aromatization of advanced ergoline intermediates to a naphthalene system.[9b] This sequence also allows for independent substitution of the aryl ring as in ketones **21b**,**c**, a feature rarely exploited by other methodologies.

Ketone **21a** was easily converted to Uhlé's ketone (**6**) by a three-step procedure without purifying any of the intermediates. Treatment of **21a** with trifluoroacetic acid cleaved the carbamate group. This was followed by hydrolysis of the methyl ester with potassium trimethylsilylanolate so as to provide the potassium salt of the carboxylic acid.[20] Finally, exposure of the crude salt to lead tetraacetate in wet DMF effected an oxidative decarboxylation to furnish **6** in 60% overall yield from **21a.**[21]

The reactivity of **21a** appears to be similar to that of **7**. For example, when **21a** was treated with phenyl-trimethylammonium tribromide (PTT) in THF,[9f] bromide **22** was isolated as a separable mixture (7:1) of diastereomers favoring the equatorial bromide in 85% yield.[22] Interestingly, the bromide derived from **7** is exclusively isolated as the axial isomer **23**,[9b] while **24**, a similar substrate that possesses an angular methyl group, is only isolated as the equatorial bromide.[11]

Scheme 3[a]



[a] Reagents: (a) PTT, THF, rt; 85%; (b) Tf_2O, 4-methyl-2,6-di-*tert*-butylpyridine, CH_2Cl_2, −78 to −20 °C, 48 h; 89%; (c) $(PPh_3)_2Pd(OAc)_2$, NaOAc, *N*-methylpropriolamide, DMF, 60 °C, 90 min, 87%; (d) $Pd(PPh_3)_4$, CO, *i*-Pr_2EtN, MeOH, 50 °C, 3 h.

Ketone **21a** was also transformed into triflate **25** in 89% yield by the action of triflic anhydride in the presence of 4-methyl-2,6-di-*tert*-butylpyridine. Subsequent cross coupling of **25** with *N*-methylpropriolamide[23] could be accomplished via palladium catalysis to afford **26** in 87% yield. Alternatively, **25** could be carbonylated under a CO atmosphere in the presence of methanol to provide diester **27** in good yield.

In summary, a novel method for constructing analogues of Kornfeld's tricyclic ketone has been developed that relies on two sequential aminodiene Diels−Alder reactions to fashion the aromatic A ring. Investigation into the range of substituents that are allowed as well as the application of this methodology to the synthesis of ergot alkaloids is currently underway, and results will be disclosed in due course.

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Supporting Information Available: Spectral characterization for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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