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Efficient Construction of Cyclopenta[*b*]quinoline Core of Isoschizozygane Alkaloids via Intramolecular Formal Hetero-Diels−Alder Reaction

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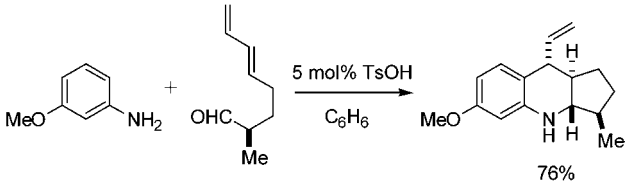
ABSTRACT



Acid-catalyzed condensation of aromatic amines with δ,ϵ-unsaturated aldehydes, followed by intramolecular formal hetero Diels−Alder reaction, is described as a potential route to the cyclopenta[*b*]quinoline substructure of isoschizozygane alkaloids. Reactions are highly diastereoselective and produce adducts with up to four contiguous stereocenters.

Isoschizogaline (**1**) and isoschizogamine (**2**) were first isolated in 1963 from the leaves of *Schizozygia coffaeoides*, a plant used in Kenyan traditional medicine for treatment of skin diseases (Figure 1).[1] The structures of the two alkaloids were initially reported to contain a vicinal diamino unit that is also present in schizozygine (**3**), a major constituent of *Schizozygia coffaeoides*.[2] However, the structure of isoschizogamine was subsequently revised to be **2** on the basis of extensive NMR studies.[3] Recently, bioassay-guided analysis of the extracts from the roots of the same plant led to the isolation of isoschizogaline that was shown to display antibacterial properties.[4] The structure of isoschizogaline was also revised to possess an interesting polycyclic structure (**1**) containing an aminal moiety. The architecturally unique structures of isoschizozygane alkaloids, as well as ambiguity surrounding their structure elucidation, make these natural products attractive targets for synthesis. This paper describes the results of a model study toward the construction of cyclopenta[*b*]quinoline core of isoschizogaline by an intramolecular formal hetero-Diels−Alder reaction.

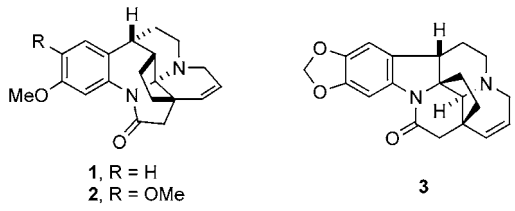


Figure 1. Structures of isoschizogaline (**1**), isoschizogamine (**2**), and schizozygine (**3**).

The general synthetic strategy to be followed in the assemblage of isoschizogaline is illustrated in Scheme 1. The polycyclic skeleton of isoschizogaline can be formed from

(1) Renner, U.; Kernweisz, P. *Experientia* **1963**, *19*, 244−246.
(2) Renner, U. *Lloydia* **1964**, *27*, 406−415.
(3) Hajiček, J.; Taimr, J.; Budešinsky, M. *Tetrahedron Lett.* **1998**, *39*, 505−508.
(4) Kariba, R. M.; Houghton, P. J.; Yenesew, A. *J. Nat. Prod.* **2002**, *65*, 566−569.

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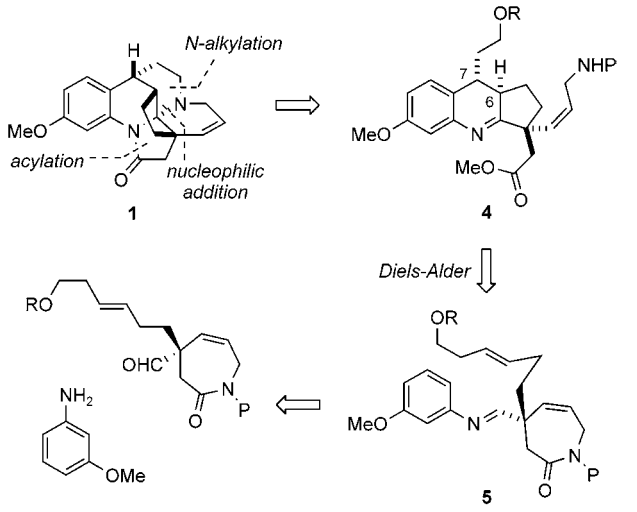
Scheme 1

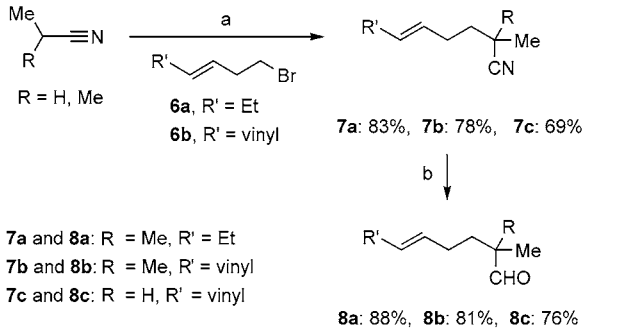


the compound of type **4** by a sequence of intramolecular nucleophilic addition, *N*-acylation, and *N*-alkylation reactions. Taking into account that the imine group in **4** can be formed by oxidation of the corresponding aniline, the tetrahydroquinoline ring with trans substituents at C-6 and C-7 may be generated by an intramolecular Diels−Alder reaction of imine **5**, itself formed by condensation of the corresponding aldehyde and *m*-anisidine.

The Diels−Alder reactions of aryl imines typically require both acidic catalysts and electron-rich dienophiles and are believed to proceed either by a concerted inverse electron demand Diels−Alder mechanism, or by a stepwise mechanism involving iminium ion attack on a dienophile π-bond followed by an electrophilic aromatic substitution.[5] Although intermolecular reactions of aryl imines with olefins are well documented,[6] the intramolecular variant of the reaction has received only scarce attention.[7] To investigate the possibility of using this strategy for the synthesis of isoschizogaline, several model aldehydes were prepared as outlined in Scheme 2. Because conjugated dienes are significantly more π-nucleophilic than disubstituted alkenes,[8] the reactions of dienyl aldehydes **8b** and **8c** were expected to proceed under milder conditions.

Initial experiments demonstrated that treatment of an equimolar mixture of *m*-anisidine and **8b** with 10 mol % of trifluoroacetic acid in CH_2Cl_2 at room temperature provided

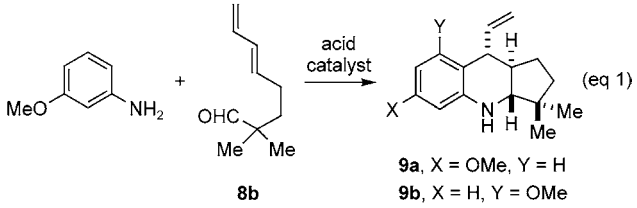
Scheme 2[a]



[a] Reaction conditions: (a) LDA, THF, −78 °C, then **6a** or **6b**; (b) DIBAL-H, PhMe, −78 °C.

54% yield of a 62:38 mixture of the desired cyclization product **9a** and its regioisomer **9b** (Table 1, entry 1). The

Table 1. Acid-Catalyzed Reaction of **8b** with *m*-Anisidine



entry	acid	solvent[a]	yield,[b] (%)	ratio **9a**/**9b**[c]
1	TFA	CH_2Cl_2	54	62:38
2	AcOH	CH_2Cl_2	0	
3	CSA	CH_2Cl_2	40	68:32
4	TsOH	CH_2Cl_2	64	68:32
5	$Zn(OTf)_2$	CH_2Cl_2	73	65:35
6	BF_3	CH_2Cl_2	80	66:34
7	$Sc(OTf)_3$	CH_2Cl_2	75	65:35
8	$Yb(OTf)_3$	CH_2Cl_2	82	62:38
9	TsOH	PhH	89	86:14

[a] Reactions conducted at 23 °C for 24 h, except for reaction in entry 9 performed under reflux for 1 h. [b] Isolated yields for entries 1 and 9, estimated NMR yields for entries 2−8. [c] Ratios determined by ^{1}H NMR analysis of the unpurified product mixtures.

structure of **9a** was unambiguously established by a single-crystal X-ray analysis of the corresponding hydrochloride salt (Figure 2). Importantly, the reaction proceeded with a high degree of stereochemical fidelity leading to single diastereomers of **9a** and **9b**. A survey of acid catalysts revealed that the regioselectivity of substitution in the aromatic ring was nearly insensitive to the nature of Lewis

(5) Povarov, L. S.; Mikhailov, B. M. *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* **1963**, 955−956. For a review, see: Povarov, L. S. *Russ. Chem. Rev.* **1967**, *36*, 656−670.

(6) (a) Nomura, Y.; Kimura, M.; Takeuchi, Y.; Tomoda, S. *Chem. Lett.* **1978**, 267−270. (b) Cheng, Y.-S.; Ho, E.; Mariano, P. S.; Ammon, H. L. *J. Org. Chem.* **1985**, *50*, 5678−5686. (c) Kametani, T.; Takeda, H.; Suzuki, Y.; Kasai, H.; Honda, T. *Heterocycles* **1986**, *24*, 3386-3395. (d) Grieco, P. A.; Bahsas, A. *Tetrahedron Lett.* **1988**, *29*, 5855−5858. (e) Narasaka, K.; Shibata, T. *Heterocycles* **1993**, *35*, 1039−1053. (f) Mellor, J. M.; Merriman, G. D. *Tetrahedron* **1995**, *51*, 6115−6132. (g) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1996**, *118*, 8977−8978. (h) Pearson, W. H.; Fang, W.-K. *Isr. J. Chem.* **1997**, *37*, 39−46. (i) Crousse, B.; Begue, J.-P.; Bonnet-Delpon, D. *J. Org. Chem.* **2000**, *65*, 5009−5013. (j) Sundararajan, G.; Prabagaran, N.; Varghese, B. *Org. Lett.* **2001**, *3*, 1973−1976. (k) Powell, D. A.; Batey, R. A. *Org. Lett.* **2002**, *4*, 2913−2916. (l) Cheng, D.; Zhou, J.; Saiah, E.; Beaton, G. *Org. Lett.* **2002**, *4*, 4411−4414.

(7) The only example of construction of cyclopentaquinoline ring system by intramolecular reaction of aryl imine with olefin was reported by Tietze: Wölfling, J.; Frank, E.; Schneider, G.; Tietze, L. F. *Eur. J. Org. Chem.* **1999**, 3013−3020. For the synthesis of octahydroacridine derivatives see: Laschat, S.; Lauterwein, J. *J. Org. Chem.* **1993**, *58*, 2856−2861.

(8) Nucleophilicity parameters *N* for *trans*-olefin and monosubstituted conjugated diene are −2.45 and 1.49, respectively: Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66−77.

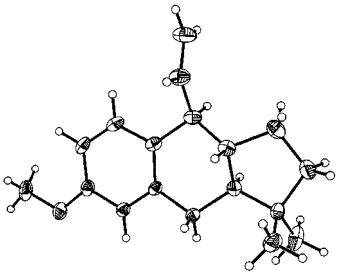
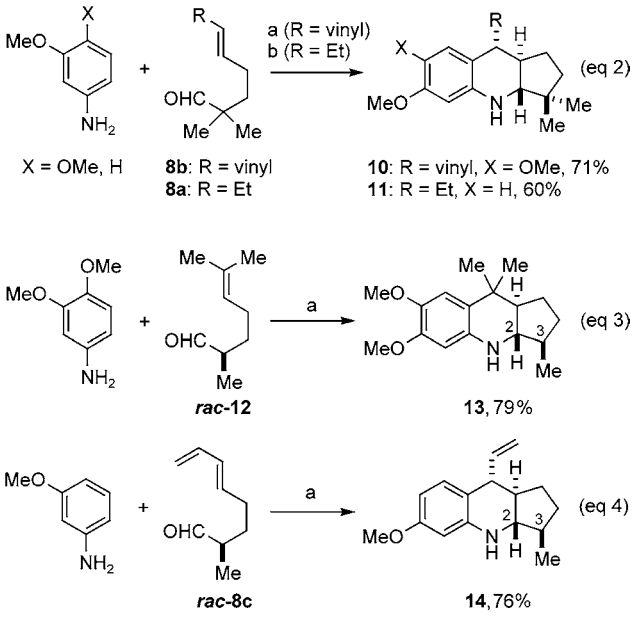


Figure 2. ORTEP drawing of the X-ray structure of hydrochloride salt of **9a** (counterion is omitted).

or Brönsted acid catalysts (Table 1, entries 3−8). After some experimentation, the optimized conditions for this transformation were found to involve refluxing the two components in benzene with azeotropic removal of water. The reaction was catalyzed by 5 mol % of TsOH and provided 89% yield of an 86:14 mixture of **9a** and **9b** that could be readily separated by crystallization or column chromatography (entry 9).

With optimized conditions in hand, reactions of anilines with other model aldehydes were investigated (Scheme 3).

Scheme 3[a]

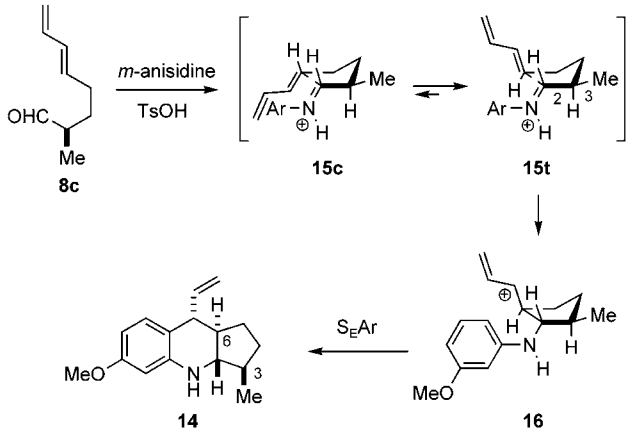


[a] Reaction conditions: (a) *m*-anisidine or 3,4-dimethoxyaniline, 5 mol % of TsOH, C_6H_6, 80 °C, 1 h; (b) *m*-anisidine, PhMe, 110 °C, 24 h.

Contrary to the reaction of *m*-anisidine, condensation of 3,4-dimethoxyaniline with **8b** furnished 1,2,4,5-tetrasubstituted arene **10** as the only product (eq 2). Cyclization efficacy was greatly influenced by nucleophilicity of the pendant alkene group. Aldehyde **8a** bearing a disubstituted olefin provided only traces of the desired product when reacted with *m*-anisidine in refluxing benzene for 5 h. However, changing the reaction medium to refluxing toluene provided the adduct **11** in 60% yield in addition to 8% yield of the corresponding 1,2,3-substituted arene (eq 2). That *gem*-disubstitution was not required for the process to occur was exemplified by reactions of 2,6-dimethylhept-5-enal[9] (**12**) and **8c** (eqs 3 and 4). Moreover, the reactions of these aldehydes were found to be highly diastereoselective. The reaction of **8c** was of particular interest, as it stereoselectively forms tricycle **14** containing four contiguous stereogenic centers.[10] The stereochemical relationship between the proton at C-2 and the methyl group at C-3 in **13** and **14** was established on the basis of NOE experiments. In addition, a large vicinal coupling (J = 10.1 Hz) between protons at C-2 and C-3 indicates that the protons are in a trans relationship to one another.

The stereochemical rationale for the reaction of **8c** is presented in Scheme 4. The diastereoselectivity in the

Scheme 4



formation of a C-2 stereocenter is a function of the facial selectivity of nucleophilic attack of diene to iminium ion and is dictated by a C-3 stereocenter. The exclusive formation of a *trans*-bicyclic system is of interest because the corresponding *cis*-isomer is expected to be of comparable energy. Indeed, semiempirical calculations indicate that the C-6-epimer of **14** is only 0.75 kcal/mol less stable than **14**.[11] Analysis of diastereomeric transition states **15** suggests that the cyclopentane ring closure will occur through a more stable **15t** leading to **16** with a trans arrangement of allylic cation and an amine. An alternative transition state **15c** is destabilized by torsional interaction of dienyl and imino moieties. The electrophilic aromatic substitution reaction between allylic cation and aniline in **16** will then lead to the more stable 1,2,4-trisubstituted arene. This step appears to

(9) Commercially available from Alfa Aesar.

(10) Reaction also yields 11% of the corresponding 1,2,3-substituted arene.

(11) PM3 geometry optimization was conducted using Spartan SGI Version 5.1.1.

be irreversible, as a 50:50 mixture of **9a** and **9b** remained unchanged when submitted to the reaction conditions.

In summary, an efficient assemblage of the cyclopenta-[*b*]quinoline core of isoschizozygane alkaloids was accomplished by an intramolecular formal hetero-Diels−Alder reaction. The use of aldehydes bearing a dienyl side chain furnishes adducts under particularly mild conditions. The diastereoselective reactions of aldehydes bearing α-stereocenters support the projected synthesis of isoschizozygane alkaloids. Application of this strategy to the synthesis of the target molecules is currently under way and will be reported in due course.

Acknowledgment. This paper is dedicated to Professor D. J. Hart on the occasion of his 55th birthday. This work was supported by the University of Rochester. I thank Dr. Rene Lachicotte for performing an X-ray analysis of hydrochloride salt of **9a**.

Supporting Information Available: Experimental procedures and full characterization data for all new compounds. This information is available free of charge via the Internet on http://www.acs.org.

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