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1,2-Dihydroisoquinolines as Templates for Cascade Reactions To Access Isoquinoline Alkaloid Frameworks

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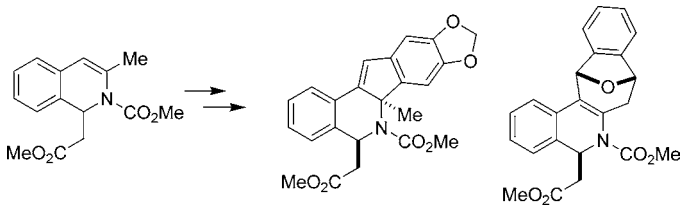
ABSTRACT



The synthesis of isoquinoline alkaloid frameworks has been achieved via a series of cascade reactions identified through reaction discovery utilizing 1,2-dihydroisoquinoline scaffolds.

Tetrahydroisoquinolines are found abundantly in Nature and comprise the largest family of alkaloids.[1] Their structural novelty and diverse biological activities inspired us to undertake preparation of tetrahydroisoquinoline-based small molecule libraries.[2,3] In an effort to identify novel reactions leading to the production of highly functionalized, alkaloidal structures, we considered 1,2-dihydroisoquinoline scaffolds **1** (Figure 1)[2b,4,5] as templates for reaction discovery.[6] As outlined in Figure 1, we anticipated that treatment of **1** with electrophiles would lead to dihydroisoquinolinium intermediates **2** which could provide access to alkaloidal frameworks after subsequent reaction processes. Herein, we report the discovery of a series of cascade reactions to produce novel isoquinoline alkaloid frameworks from diverse 1,2-dihydroisoquinolines generated via cycloisomerization−addition of alkynylacylimines.[7]

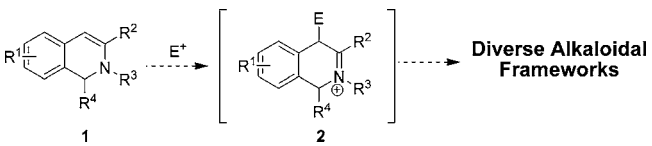


Figure 1. Synthesis of diverse isoquinoline alkaloid frameworks using dihydroisoquinoline scaffolds.

In order to efficiently access the requisite 1,2-dihydroisoquinoline scaffolds, we first evaluated cycloisomerization−addition of alkynylacylimine **3** (Table 1) using select carbon nucleophiles and alkynophilic transition metals.[8] Reaction screening led to the identification of $AgSbF_6$ as the most

(1) Phillipson, J. D.; Roberts, M. F.; Zenk, M. H. *The Chemistry and Biology of Isoquinoline Alkaloids*; Springer-Verlag: New York, 1985.

(2) For recent examples of isoquinoline-based chemical libraries, see: (a) Gracias, V.; Moore, J. D.; Djuric, S. W. *Tetrahedron Lett.* **2004**, *45*, 417. (b) Taylor, S. J.; Taylor, A. M.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1681. (c) Pla, D.; Marchal, A.; Olsen, C. A.; Francesch, A.; Cuevas, C.; Albericio, F.; Alvarez, M. *J. Med. Chem.* **2006**, *49*, 3257.

(3) For reviews concerning diversity-oriented synthesis (DOS), see: (a) Schreiber, S. L. *Science* **2000**, *287*, 1964. (b) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46.

(4) For reactions of enamines, see: Dyke, S. F. *Adv. Heterocycl. Chem.* **1972**, *14*, 279.

(5) For seminal work concerning preparation of polycyclic, alkaloid-like libraries, see: (a) Gan, Z.; Reddy, P. T.; Quevillon, S.; Couve-Bonnaire, S.; Arya, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 1366. (b) Reayi, A.; Arya, P. *Curr. Opin. Chem. Biol.* **2005**, *9*, 240.

(6) Beeler, A. B.; Su, S.; Singleton, C. A.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 1413.

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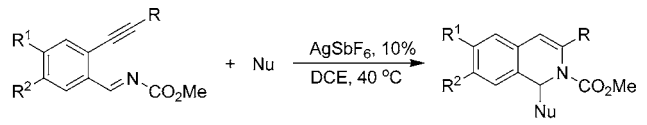
Table 1



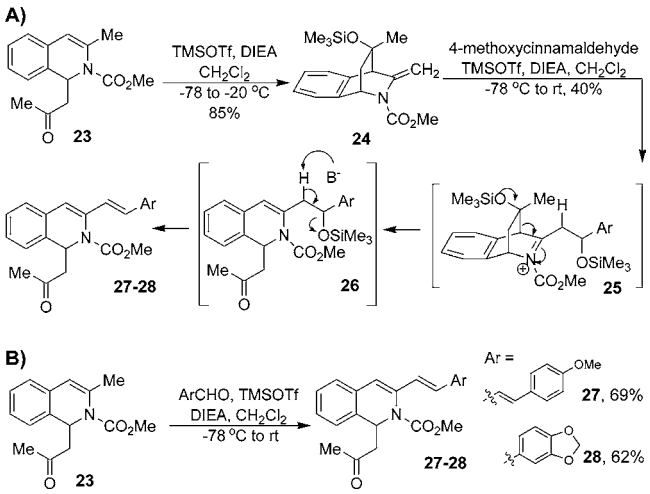
entry	R	R_1, R_2	Nu	product	yield (%)[a]
1	$(CH_2)_6Me$	H, H	9	15 d.r.=1:1	91
2	$(CH_2)_6Me$	H, F	10	16	72
3	Me	H, H	10	17	76[b]
4	OMe	OCH_2O	10	18	61[b]
5	$(CH_2)_6Me$	H, H	11	19	76
6		H, H	12	20	74[c]
7	Me	H, H	13 Z/E=1:3	21 d.r.=1:1	72[c]
8	Me	H, H	14	22 Z:E =1:3	62[c]

[a] Isolated yields based on alkynylacylimine. [b] 1.0 equiv of MgO was added as base. [c] Reaction employing bis(2,4,6-trimethylpyridine)silver(I) hexafluorophosphate (10 mol %) and *t*-BuOH (1.0 equiv); alkynylacylimine and nucleophile were added via syringe pump simultaneously over 15 min.[8]

effective catalyst for the transformation. Further reaction optimization revealed that reactions conducted at 40 °C in 1,2-dichloroethane (DCE) ($AgSbF_6$, 10 mol %) afforded optimal results. Bis(2,4,6-trimethylpyridine)silver(I) hexafluorophosphate[9] was found to be superior to $AgSbF_6$ when employing silyl enol ether **11** as nucleophile. Using $AgSbF_6$ and bis(2,4,6-trimethylpyridine)silver(I) hexafluorophosphate, select nucleophiles were reacted with various alkynylacylimines to generate a number of dihydroisoquinoline scaffolds **15**−**22** (Table 1). Silver-mediated dihydroisoquinoline formation was found to be workable with *o*-alkynylacylimines **5**−**8** bearing enyne, propargyl ether, and cyclopropane functionality, as well as substrates with electron-withdrawing and -donating substituents on the aromatic backbone (cf. entries **2** and **4**). In addition to β-keto esters **9** and dimethyl malonate **10**, silyl ketene acetals **12** and **13** were found to cleanly generate dihydroisoquinolines **20**−**21**. Notably, dihydroisoquinoline **21** mimics the skeleton of the bisbenzylisoquinoline alkaloids.[10] Furthermore, reaction of alkynyl acylimine **8** and *O*-silylated dienolate **14**[11] provided dihydroisoquinoline **22** with complete γ selectivity.[12]

We next evaluated a number of transformations of the enecarbamate moiety of the 1,2-dihydroisoquinoline scaffolds.[2b] Initial studies were focused on intramolecular condensation of the ketone and enecarbamate of substrate **23** in an effort to generate an *aza*-tricyclic framework (Scheme 1).[13] After

Scheme 1



evaluation of Lewis acid promoters, we found that the bridged, exocyclic enecarbamate **24** was formed in 84% yield when scaffold **23** was treated with TMSOTf/*N*,*N*-diisopropylethylamine (DIEA) (CH_2Cl_2, −78 → −20 °C).[14] Subsequent reaction of **24** with 4-methoxycinnamaldehyde and TMSOTf unexpectedly provided diene **27**, likely through fragmentation of the intermediate dihydroisoquinolinium species **25** and subsequent elimination of the derived dihydroisoquinoline **26**. After further reaction optimization,

(7) For cycloisomerization of alkynyl imines and related derivatives, see: (a) Huang, Q.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 980. (b) Dai, G.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 920. (c) Ohtaka, M.; Nakamura, H.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 7339. (d) Asao, N.; Yudha, S.; Nogami, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 5526. (e) Yanada, R.; Obika, S.; Kono, H.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3822. (f) Sromek, A. W.; Rheingold, A. L.; Wink, D. J.; Gevorgyan, V. *Synlett.* **2006**, 2325. (g) Obika, S.; Kono, H.; Yasui, Y.; Yanada, R.; Takemoto, Y. *J. Org. Chem.* **2007**, *72*, 4462. (h) Su, S.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 7744.

(8) See the Supporting Information for complete experimental details.

(9) Brunel, Y.; Rousseau, G. *J. Org. Chem.* **1996**, *61*, 5793.

(10) Curcumelli-Rodostamo, M. *Alkaloids*; Academic Press: New York, 1971; Vol. 13, p 303.

(11) Gaudemar, M.; Bellassoued, M. *Tetrahedron Lett.* **1989**, *30*, 2229.

(12) (a) Fleming, I.; Lee, T. V. *Tetrahedron Lett.* **1981**, *22*, 705. (b) Denmark, S. E.; Heemstra, J. R., Jr. *Synlett* **2004**, 2411.

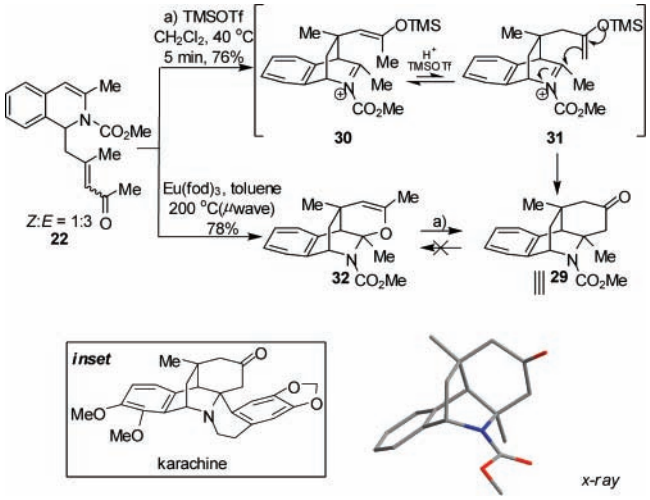
(13) (a) Gupta, R. B.; Franck, R. W. *J. Am. Chem. Soc.* **1987**, *109*, 5393. (b) Yadav, J. S.; Reddy, B. V. S.; Srinivas, M.; Sathaiah, K. *Tetrahedron Lett.* **2005**, *46*, 3489.

(14) For isomerization of bicyclic iminium ions to exocyclic enamines, see: (a) Walker, G. N.; Alkalay, D. *J. Org. Chem.* **1967**, *32*, 2213. (b) Quast, U.; Schneider, W. *Liebigs Ann. Chem.* **1982**, *8*, 1501.

a one-pot procedure was developed to generate **27**−**28** (69 and 62% yields, respectively) directly from **23** and aromatic aldehydes.

Based on the successful intramolecular condensation of ketone-substituted dihydroisoquinoline **23**, related reactions of α,β-unsaturated ketone-containing substrate **22** (Table 1) were investigated with the anticipation of forming a protoberberine alkaloid[15] core structure (cf. karachine, inset, Scheme 2). After investigation of various Lewis acids, the

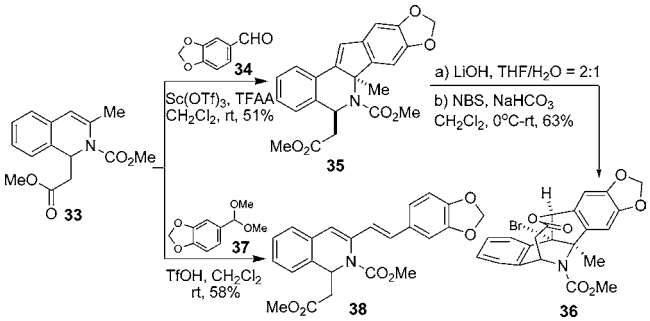
Scheme 2



aza-tetracyclic structure **29** was generated from enone **22** using TMSOTf (CH_2Cl_2, 40 °C, 76%) via a tandem Michael addition−Mannich reaction process likely involving intermediates **30** and **31**. The structure of **29** was confirmed by X-ray crystal structure analysis.[8] Interestingly, treatment of **22** with Eu(fod)$_3$ under thermal conditions (200 °C, toluene, microwave 300 W) led to the production of the formal hetero-Diels−Alder product **32**.[16] Further studies revealed that dihydropyran **32** could be converted to ketone **29** in the presence of TMSOTf. However, transformation of **29** to **32** was not observed under various reaction conditions.

In order to evaluate intermolecular condensation of the enecarbamate moiety with electrophiles followed by further annulation, the ester-substituted dihydroisoquinoline **33** was condensed with electron-rich aromatic aldehydes and aldehyde equivalents using Lewis acids. For example, treatment of **33** and piperonal **34** with Sc(OTf)$_3$ and TFAA[17] produced the novel indenoisoquinoline[18] **35** (Scheme 3). To determine the relative stereochemistry of **35**, saponification and sub-

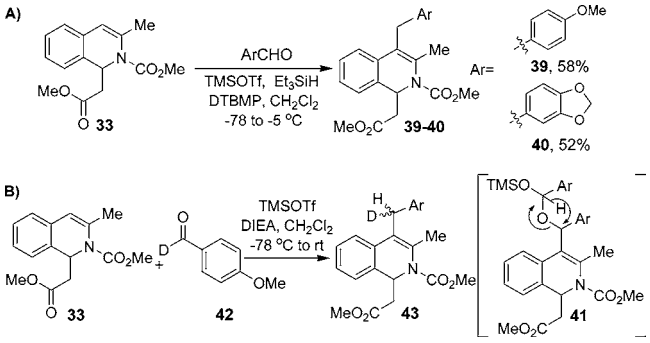
Scheme 3



sequent NBS-mediated bromo-lactonization was conducted and was found to selectively produce compound **36** as determined by X-ray crystallography.[8] In contrast, treatment of **33** with dimethoxyacetal **37** and triflic acid (0.5 equiv) afforded diene **38** as the major product along with a trace amount of annulation product **35**. The formation of **38** may proceed through a similar pathway to that of **27** and **28** (Scheme 1) in which enecarbamate **33** first condenses at its β-carbon with acetal **37**.

Interestingly, treatment of **33** with 4-methoxy benzylaldehyde, TMSOTf, and DIEA unexpectedly provided the tetrasubstituted dihydroisoquinoline **39** (Scheme 4A). Ini-

Scheme 4



tially, we speculated that a Cannizzaro-type hydrogen-transfer reduction of proposed intermediate **41** (Scheme 4B) may be responsible for the formation of **39**. However, a deuterium-labeling experiment employing deuterated benzaldehyde derivative **42** afforded the monodeuterated product **43** (1:1 dr), which led to the assumption that DIEA may serve as a hydride donor[19] required for the formation of alkylation product **39**. To further investigate the reaction pathway and to improve reproducibility, various hydride sources and bases were evaluated. It was ultimately determined that treatment of **33** with TMSOTf, arylaldehyde, Et_3SiH, and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) afforded tetrasubstituted dihydroisoquinolines **39** and **40** in moderate yields. Using this condition, tetracycle **35** (Scheme 3) was not observed.

(15) (a) Blasko, G.; Murugesan, N.; Freyer, A. J.; Shamma, M.; Ansari, A. A.; Atta, R. *J. Am. Chem. Soc.* **1982**, *104*, 2039. (b) Stevens, R. V.; Pruitt, J. R. *J. Chem. Soc., Chem. Commun.* **1983**, *23*, 1425.

(16) For Eu(fod)$_3$-catalyzed hetero-Diels−Alder cycloaddition of enecarbamates, see: Gaulon, C.; Dhal, R.; Chapin, T.; Maisonneuve, V.; Dujardin, G. *J. Org. Chem.* **2004**, *69*, 4192.

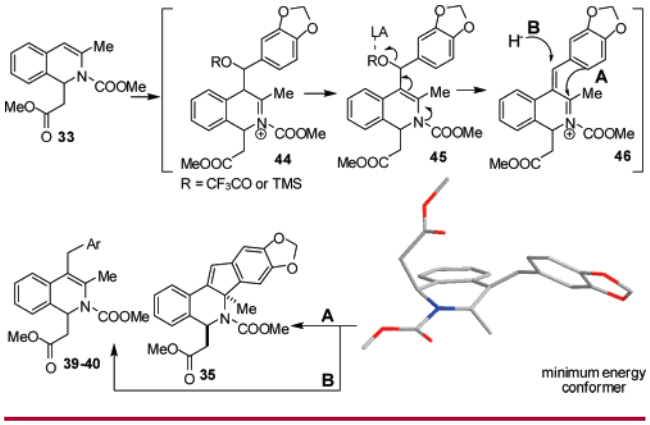
(17) For synthesis of geminal acetates using Sc(OTf)$_3$/TFAA, see: Aggarwal, V. K.; Fonquerna, S.; Vennall, G. P. *Synlett.* **1998**, 849.

(18) Nagarajan, M.; Morrell, A.; Ioanoviciu, A.; Antony, S.; Kohlhagen, G.; Agama, K.; Hollingshead, M.; Pommier, Y.; Cushman, M. *J. Med. Chem.* **2006**, *49*, 6283.

(19) (a) Schreiber, S. L. *Tetrahedron Lett.* **1980**, *21*, 1027. (b) Cheng, Y.; Meth-Cohn, O.; Taylor, D. *J. Chem. Soc., Perkin Trans. 1* **1998**, *7*, 1257.

Based on these results, it is apparent that a common, unsaturated iminium ion **46**[20] (Scheme 5) is likely responsible

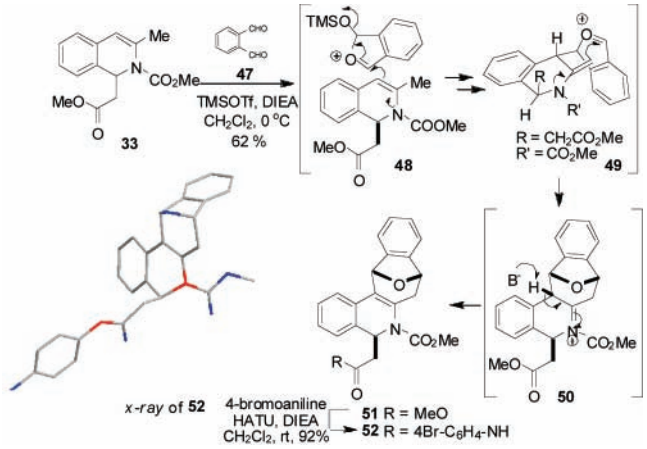
Scheme 5



for the formation of products **35** and **39**−**40**. In the absence of hydride, intramolecular Friedel−Crafts cyclization[21] leads to indenoisoquinoline product **35** (route A). Alternatively, conjugate hydride addition[22] to iminium **46** affords dihydroisoquinolines **39**−**40** (route B). In order to understand the stereochemical outcome leading to the production of **35**, a conformer search[23] was conducted on the putative iminium intermediate **46**. The minimum energy conformer of **46** (Scheme 5) shows a boat conformation and a pseudoaxial orientation of the ester substituent which minimizes *peri* strain with the neighboring aryl hydrogen. As a result, the subsequent Friedel−Crafts reaction generates **35** with the methyl group at *C*2 position *anti* to the ester group at C4 as revealed by X-ray crystal structure analysis of **36**.[8] Transformations to prepare **35**, and **38**−**40** thus illustrate access to diverse frameworks using reagent-controlled diversity generation.[2b]

As previously described, dihydroisoquinolinium intermediates generated from condensation of the dihydroisoquinoline and suitable electrophiles may lead to the formation of exocyclic enecarbamates (cf. **23** → **24**, Scheme 1). Tandem transformations utilizing this enecarbamate transposition strategy were therefore investigated with bis-electrophiles including phthaldialdehyde **47** (Scheme 6). Accordingly, treatment of **33** and **47** with TMSOTf/DIEA (CH_2Cl_2, −78 → 0 °C) led to the production of the highly complex isobenzofuran **51** (63%). The relative stereochemistry of **51** was determined by X-ray crystal structure analysis of the

Scheme 6



derived anilide **52**.[8] Formation of **51** may be initiated by facially selective condensation of **33** and an isobenzofuranylium species generated from phthaldialdehyde **47** and TMSOTf.[24] Subsequent generation of isobenzofuranylium enecarbamate **49**, followed by intramolecular cyclization, affords dihydroisoquinolinium **50**, which may undergo further isomerization to dihydroisoquinoline **51**.

In summary, 1,2-dihydroisoquinoline scaffolds obtained via cycloisomerization of alkynylacylimines have been utilized as templates for discovery of novel transformations of the enecarbamate moiety. Using this approach, a number of cascade reaction processes to access diverse isoquinoline alkaloid frameworks have been identified including an *aza*-tetracyclic structure via a tandem Michael−Mannich reaction process and intermolecular condensation/annulations with benzaldehydes and phthaldialdehyde to construct indenoisoquinolines and polycyclic isobenzofurans, respectively. Further studies, including syntheses of tetrahydroisoquinoline alkaloids based on adaptations of the methodology described herein, are currently in progress and will be reported in due course.

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Supporting Information Available: General experimental procedures, X-ray crystallographic data, and selected NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) For a related unsaturated iminium ion, see: Rivas, L.; Quintero, L.; Fourrey, L-L.; Benhida, R. *Tetrahedron Lett.* **2002**, *43*, 7639.

(21) For intramolecular Friedel−Crafts cyclization of dihydroisoquinolinium ions, see: Diaz, J. L.; Miguel, M. L.; Lavilla, R. *J. Org. Chem.* **2004**, *69*, 3550.

(22) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32.

(23) Low energy conformations were generated through a stochastic conformational search using MOE (molecular operating environment).

(24) For generation of isobenzofurans from phthaldialdehyde, see: Yasuda, M.; Fujibayashi, T.; Shibata, I.; Baba, A.; Matsuda, H.; Sonoda, N. *Chem. Lett.* **1995**, *3*, 167.