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New Strategy for the Synthesis of Tetrahydroisoquinoline Alkaloids

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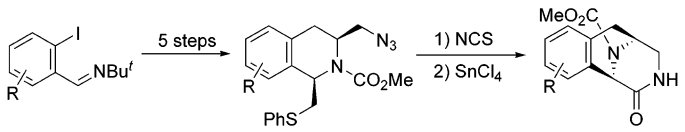
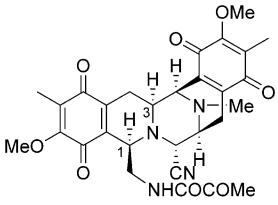
ABSTRACT

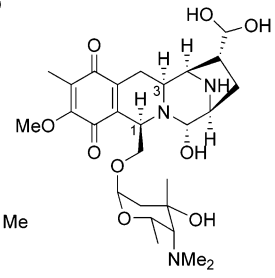


A general strategy for the formation of 1,3-cis-substituted tetrahydroisoquinolines is described from *ortho*-iodo imines involving Larock isoquinoline synthesis, addition of organolithium compounds to unactivated isoquinolines, and ionic hydrogenation. In addition, a new synthesis of lactams via an unprecedented azide cyclization in the presence of a sulfonium ion is described.

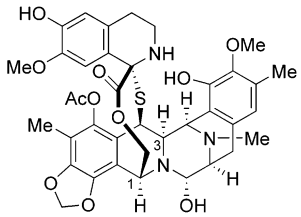
Methods for the stereoselective synthesis of tetrahydroisoquinolines[1] have elicited wide interest because of their potential application to the synthesis of naturally occurring potent antitumor antibiotics such as saframycin A **1**,[2] lemonomycin **2**,[3] and ecteinascidin 743 **3**.[4,5]



1, Saframycin A



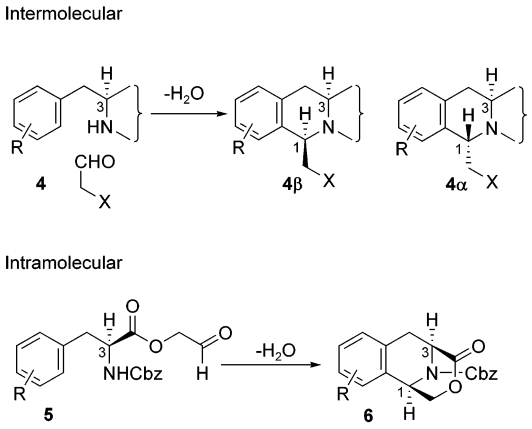
2, Lemonomycin



3, Ecteinascidin 743

One of the key stereochemical issues, which is common to all of these compounds, is the cis relationship between the C1 and C3 positions. The intermolecular Pictet−Spengler reaction depicted in Scheme 1 converts **4** into **4**β- and **4**α-

Scheme 1. Pictet−Spengler Approach



with wide variations in the ratio of the diastereomers, but under mild reaction conditions, **4**β- is the major (but not exclusive) product.[2,5] An elegant solution to this problem was reported by Corey in the course of his synthesis of ecteinascidin 743,[4a] which utilized an intramolecular Pictet−Spengler reaction to convert **5** into **6**, Scheme 1.

[†] Author for inquiries concerning the X-ray data.

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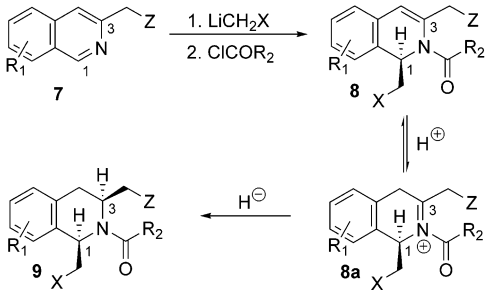
We have examined a new strategy that uses the C1 stereogenic center to induce the required cis relationship between C1 and C3, Scheme 2. The strategy starts with a

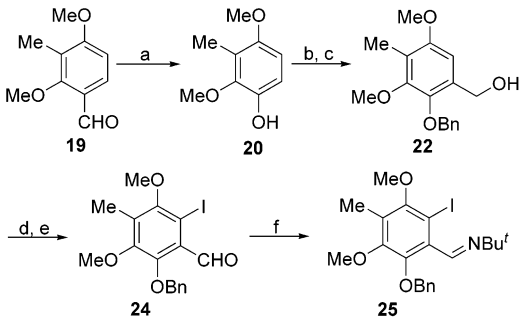
Scheme 2. C1 Nucleophilic Addition Approach



3-substituted isoquinoline **7** and adds $LiCH_2X$ followed by acylation to give **8**. Ionic hydrogenation (CF_3CO_2H/Et_3SiH) of **8** should give **9**. The C1 substituent in **8** and in the iminium ion **8a** should be in an axial conformation to avoid steric interactions with the -$NCOR_1$ group and the *peri*-H, thus favoring hydride addition from the least sterically encumbered face resulting in **9**.[6]

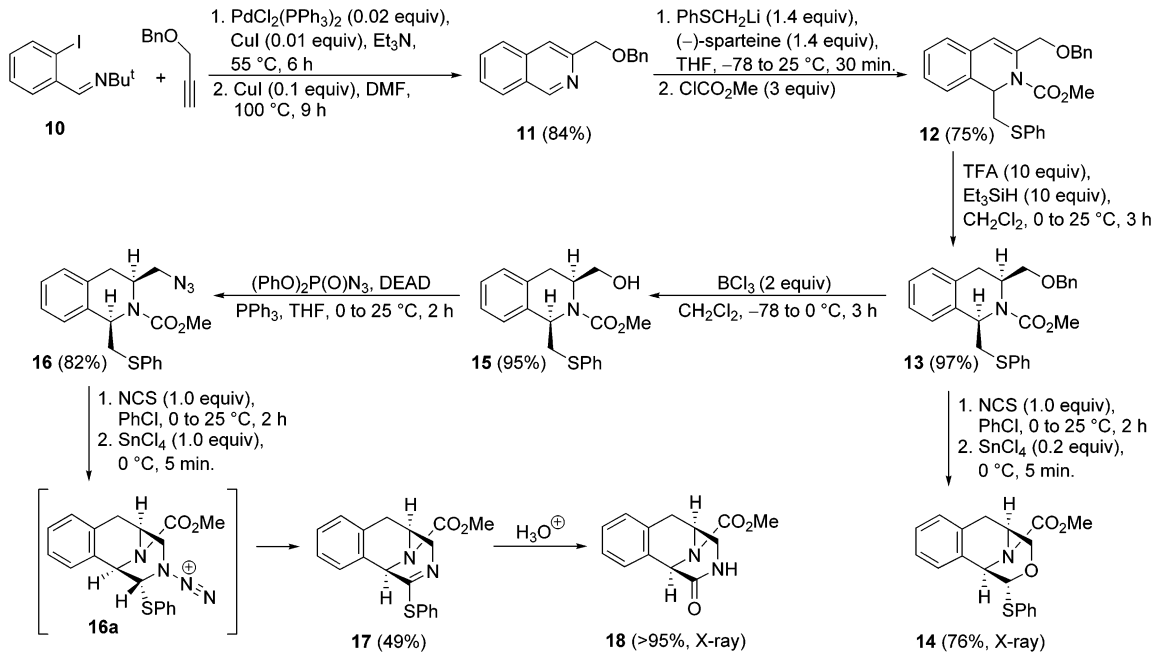
The synthesis of the 3-substituted isoquinoline **11** was readily achieved using the recently reported Larock methodology, Scheme 3.[7] Phenylthiomethyllithium,[8] formed by reacting thioanisole with *n*-BuLi in the presence of a tertiary diamine, was added to a solution of **11** in toluene at −78 °C followed by warming to 25 °C, and quenching with methyl chloroformate gave **12** (75%).[9] Using (−)-sparteine as the tertiary diamine gave the best results when compared to DABCO and TMEDA; however, no enantioselectivity was observed in the formation of **12** under a variety of conditions.[10] Exposure of **12** to trifluoroacetic acid in dichloromethane containing triethylsilane at −10 °C and then warming to 25 °C resulted in the formation of **13** (97%).[11] We could not detect any other stereoisomers (^{1}H NMR). The C1−C3 cis relative stereochemistry of **13** was demonstrated by treatment of **13** with *N*-chlorosuccinimide/PhCl followed by stannic tetrachloride (catalytic) resulting in **14** (76%, structure by X-ray). Treatment of **13** with BCl_3 in dichloromethane at −78 °C followed by warming the solution to 0 °C removed the benzyl protecting group, resulting in **15** (95%). Exposure of **15** to $(PhO)_2P(O)N_3$/DEAD/PPh_3 in THF

Scheme 4. Synthesis of Imine **25**[a]

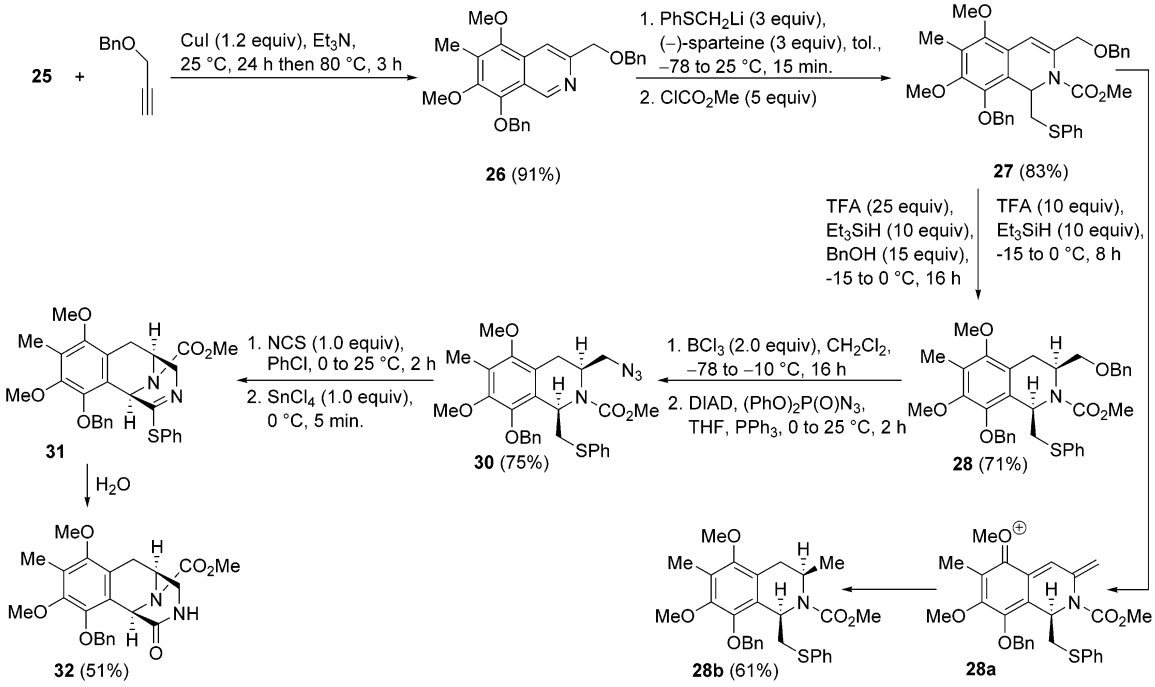


[a] Reaction Conditions: (a) (i) MCPBA; (ii) NaOH, MeOH (94% overall). (b) $(HCHO)_n$, Et_2AlCl, CH_2Cl_2. (c) BnBr, K_2CO_3, acetone (89% over two steps). (d) AgO_2CCF_3, I_2, $CHCl_3$ (82%, **23**). (e) PCC, CH_2Cl_2 (98%). (f) *tert*-butylamine, 4 Å molecular sieves, toluene.

Scheme 3



Scheme 5



at 0−25 °C gave **16** (82%). When **16** was treated with NCS in PhCl followed by $SnCl_4$ (stoichiometric) at 0 °C, the thiophenyl imino ether **17** was rapidly formed (5 min).[12] Mild acid hydrolysis readily converted **17** into the lactam **18**, whose structure was confirmed by X-ray crystallography.

To explore the application of this new strategy to a more highly substituted isoquinoline pertinent to the synthesis of **1** and/or **2** required the synthesis of **25**, Scheme 4. Commercially available **19** was converted into **25** via **20**−**24** using standard procedures.[13]

It was found that treatment of **25** with 2% $PdCl_2(PPh_3)_2$, 1% CuI, benzylpropargyl ether, and TEA/55 °C followed by 10% CuI and DMF/100 °C (Larock isoquinoline synthesis) gave **26** in 38% yield, Scheme 5, whereas treatment of **25** with stoichiometric CuI and Et_3N/benzylpropargyl ether at 25 °C followed by warming to 80 °C gave **26** in 91% yield. Addition of phenylthiomethyllithium in the presence of (−)-sparteine followed by methyl chloroformate gave **27** (83%), but again no enantioselectivity was observed for the addition. Reduction of the enecarbamate double bond in **27** using Et_3SiH/TFA in dichloromethane was complicated by the competitive formation of **28b** (61%) as well as the required product **28** (31%). The formation of **28b** presumably results from the extended oxonium ion **28a** (a pathway not available in the unsubstituted version, Scheme 3). Conducting the above reduction, but now in the presence of benzyl alcohol (15 equiv), increased the yield of **28** to 71%, while **28b** was formed in 22% yield. The primary alcohol benzyl ether protecting group in **28** was selectively removed by

(1) (a) *The Chemistry of Heterocyclic Compounds. Isoquinolines*; Grethe, G., Ed.; John Wiley: New York, 1981; Part 1. *The Chemistry of Heterocyclic Compounds. Isoquinolines*; Kathawala, F. G., Coppola, G. M., Schuster, H. F., Eds.; John Wiley, New York, 1990; Part 2. *The Chemistry of Heterocyclic Compounds. Isoquinolines*; Coppola, G. M., Schuster, H. F., Eds.; John Wiley, New York, 1995; Part 3. (b) For a recent review of these alkaloids, see: Ozturk, T. *The Alkaloids.* Cordell, G. A., Ed.; Academic Press, San Diego, 2000; Vol. 53, p 120.

(2) For a comprehensive account of the chemistry and biology of these compounds, see: (a) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669. (b) Myers, A. G.; Kung, D. W. *J. Am. Chem. Soc.* **1999**, *121*, 10828. (c) Myers, A. G.; Kung, D. W.; Zhong, B.; Movassaghi, M.; Kwon, S. *J. Am. Chem. Soc.* **1999**, *121*, 8401. (d) Kubo, A.; Saito, N.; Yamato, H.; Masubuchi, K.; Nakamura, M. *J. Org. Chem.* **1988**, *53*, 4295. (e) Saito, N.; Harada, S.; Yamashita, M.; Saito, T.; Yamaguchi, K.; Kubo, A. *Tetrahedron* **1995**, *51*, 8213. (f) Fukuyama, T.; Sachleben, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 4957. (g) Fukuyama, T.; Yang, L.; Ajeck, K. L.; Sachleben, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 3712. (h) Zhou, B.; Edmondson, S.; Padron, J.; Danishefsky, S. J. *Tetrahedron Lett.* **2000**, *41*, 2039. (i) Zhou, B.; Guo, J.; Danishefsky, S. J. *Tetrahedron Lett.* **2000**, *41*, 2043. (j) Zhou, B.; Guo, J.; Danishefsky, S. J. *Org. Lett.* **2002**, *4*, 43.

(3) He, H.; Shen, B.; Carter, G. T. *Tetrahedron Lett.* **2000**, *41*, 2067.

(4) (a) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202. (b) Martinez, E. J.; Corey, E. J. *Org. Lett.* **1999**, *1*, 75. (c) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552.

(5) Herberich, B.; Kinugawa, M.; Vazquez, A.; Williams, R. M. *Tetrahedron Lett.* **2001**, *42*, 543.

(6) Deslongchamps, P. *Stereoelectronic Effects in Organic Synthesis*; Pergamon Press: Elmsford, NY, 1983; p 211 and references therein.

(7) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 86. In this paper, the yield of 3-hydroxymethylisoquinoline was 0% when propargyl alcohol was used (Table 3, entry 5 in the above reference). Simply using protected derivatives as in Scheme 3 works well.

(8) Corey, E. J.; Seebach, D. *J. Org. Chem.* **1966**, *31*, 4097.

(9) For the addition of organolithium reagents to isoquinoline, see: Alexakis, A.; Amiot, F. *Tetrahedron: Asymmetry* **2002**, *13*, 2117.

(10) Enantiomers were separated using chiral HPLC.

(11) For ionic hydrogenation of aryleneamides, see: Molinksi, T. F.; Masuno, M. N. *Tetrahedron Lett.* **2001**, *42*, 8263.

(12) Closest analogy to the type of reaction is the intramolecular Schmidt rearrangement. (a) Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449. (b) Mossman, C. J.; Aubé, J. *Tetrahedron* **1996**, *52*, 3403.

(13) Saito, D. T.; Morimoto, M.; Akiyama, C.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1995**, *117*, 10757.

treatment with BCl_3 in dichloromethane at −78 °C to −20 °C, and the resulting alcohol **29** was converted into the azide **30**. Treatment of **30** with NCS followed by $SnCl_4$ (stoichiometric) gave **31**, which was directly hydrolyzed to the lactam **32** (51% from **30**).

In summary, a new strategy for the synthesis of 1,3-cis-substituted tetrahydroisoquinolines has been developed that relies on the stereoselctive reduction of 1,2-dihydroisoquinolines under ionic hydrogenation conditions. The [3.3.1] ring system present in **1** and **3** was made by an unprecedented intramolecular trapping of a sulfonium ion with an alkyl azide.

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Supporting Information Available: Experimental procedures and characterization data for compounds **11**−**18**, **22**−**24**, **26**−**30**, and **32** and X-ray data (CIF) for compounds **14** and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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