JOC*Article*

Stereodivergent Process for the Synthesis of the Decahydroquinoline Type of Dendrobatid Alkaloids

Naoki Toyooka,* Maiko Okumura, and Hideo Nemoto*

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930-0194, Japan

toyooka@ms.toyama-mpu.ac.jp

Received May 13, 2002

A flexible and stereodivergent synthesis of the *cis*- and *trans*-fused 2,5-disubstituted octahydroquinolinone ring systems bearing all four stereogenic centers for the synthesis of the decahydroquinoline type of dendrobatid alkaloids has been achieved. The strategy involves stereoselective and stereodivergent construction of 2,3,6-trisubstituted piperidine ring systems using the Michael type of conjugate addition reaction to the enaminoesters **1** and **3**, the intramolecular aldol type of cyclization reaction of keto aldehydes **11** and **12**, and ring-closing metathesis of **21** as key steps.

Introduction

The neotropical dart poison frogs contain a remarkable diversity of alkaloids, and the 2,5-disubstituted decahydroquinolines represent one of the major classes of these amphibian alkaloids.[1] Isolation of these alkaloids from some ants strengthens a dietary hypothesis for the origin of the above alkaloids that have been detected in extracts of frog skin.[2] In addition, these alkaloids contain both *cis* and *trans* ring fusions, which have been identified as well as diastereomers at C-2 and C-5 positions (Figure 1).

The structural diversity and pharmacological activity associated with this class of alkaloids have stimulated synthetic activity in numerous groups.[3] However, the route which can be applicable to the synthesis of both *cis*- and *trans*-fused ring systems has been reported only to a small extent.[4] Moreover, no methodology for the

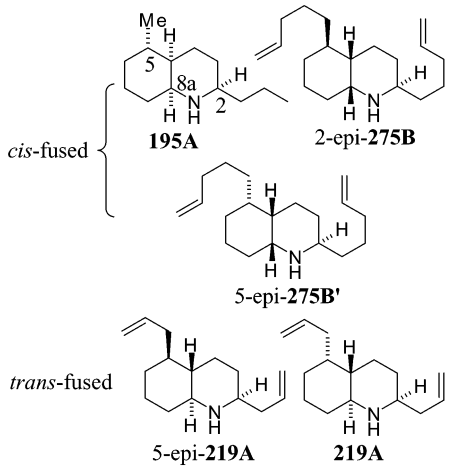


FIGURE 1.

divergent synthesis of the 2,8a-*cis*- and -*trans*-substituted ring systems has been reported to date.

Here, we wish to describe the flexible and stereodivergent route to the octahydroquinolinone ring core, which contains all four stereogenic centers of target alkaloids. The basic strategy we used involves three key reactions (Figure 2).

The first key step is the highly stereoselective and stereodivergent construction of a 2,3,6-trisubstituted piperidine ring system using the Michael type of conjugate addition reaction of the cyclic enaminoesters (steps A and B).[5] The second key step is an intramolecular aldol type of cyclization reaction[6] of the keto aldehydes (steps C and D) or ring-closing metathesis reaction[7] of the vinyl ketone (step E) derived from the above adducts, respectively. The final key step is the stereoselective installa-

(1) (a) Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *Alkaloids*: *Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon Press: New York, 1999; Vol. 13, pp 1−161. (b) Daly, J. W. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 50, pp 141−169.

(2) Spande, T. F.; Jain, P.; Garraffo, H. M.; Pannell, L. K.; Yeh, H. J. C.; Daly, J. W.; Fukumoto, S.; Imamura, K.; Tokuyama, T.; Torres, J. A.; Snelling, R. R.; Jones, T. H. *J. Nat. Prod*. **1999**, *62*, 5−21.

(3) (a) Oppolzer, W.; Flaskamp, E.; Bieber, L. W. *Helv. Chim. Acta* **2001**, *84*, 141−145. (b) Akashi, M.; Sato, Y.; Mori, M. *J. Org. Chem*. **2001**, *66*, 7873−7874. (c) Riechers, T.; Krebs, H. C.; Wartchow, R.; Habermehl, G. *Eur. J. Org. Chem*. **1998**, 2641−2646. (d) Toyota, M.; Asoh, T.; Fukumoto, K. *Tetrahedron Lett*. **1996**, *37*, 4401−4404. (e) Davies, S. G.; Bhalay, G. *Tetrahedron: Asymmetry* **1996**, *7*, 1595−1596. (f) Naruse, M.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett*. **1994**, *35*, 9213−9216. (g) Naruse, M.; Aoyagi, S.; Kibayashi, C. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1113−1124. (h) Murahashi, S.; Sasao, S.; Saito, E.; Naota, E. *J. Org. Chem*. **1992**, *57*, 2521−2523. (i) Murahashi, S.; Sasao, S.; Saito, E.; Naota, E. *Tetrahedron* **1993**, *49*, 8805−8826 and references therein.

(4) Comins', Schultz's, and Kunz's approach could be applicable to the divergent synthesis of *cis*- and *trans*-fused decahydroquinoline ring systems. See: (a) Comins, D. L.; Dehghani, A. *J. Chem. Soc., Chem. Commun*. **1993**, 1838−1839. (b) Comins, D. L.; Dehghani, A. *J. Org. Chem*. **1995**, *60*, 794−795. (c) Schultz, A. G.; McCloskey, P. J.; Court, J. J. *J. Am. Chem. Soc*. **1987**, *109*, 6493−6502. (d) McCloskey, P. J.; Schultz, A. G. *J. Org. Chem*. **1988**, *53*, 1380−1383. (e) Weymann, M.; Schultz-Kukula, M.; Kunz, H. *Tetrahedron Lett*. **1998**, *39*, 7835−7838.

(5) (a) Momose, T.; Toyooka, N. *J. Org. Chem*. **1994**, *59*, 943−945. (b) Toyooka, N.; Tanaka, K.; Momose, T.; Daly, J. W.; Garraffo, H. M. *Tetrahedron* **1997**, *53*, 9553−9574. (c) Toyooka, N.; Fukutome, A.; Nemoto, H.; Daly, J. W.; Spande, T. F.; Garraffo, H. M.; Kaneko, T. *Org. Lett*. **2002**, *4*, 1715−1717.

10.1021/jo025929b CCC: $22.00
Published on Web 07/20/2002

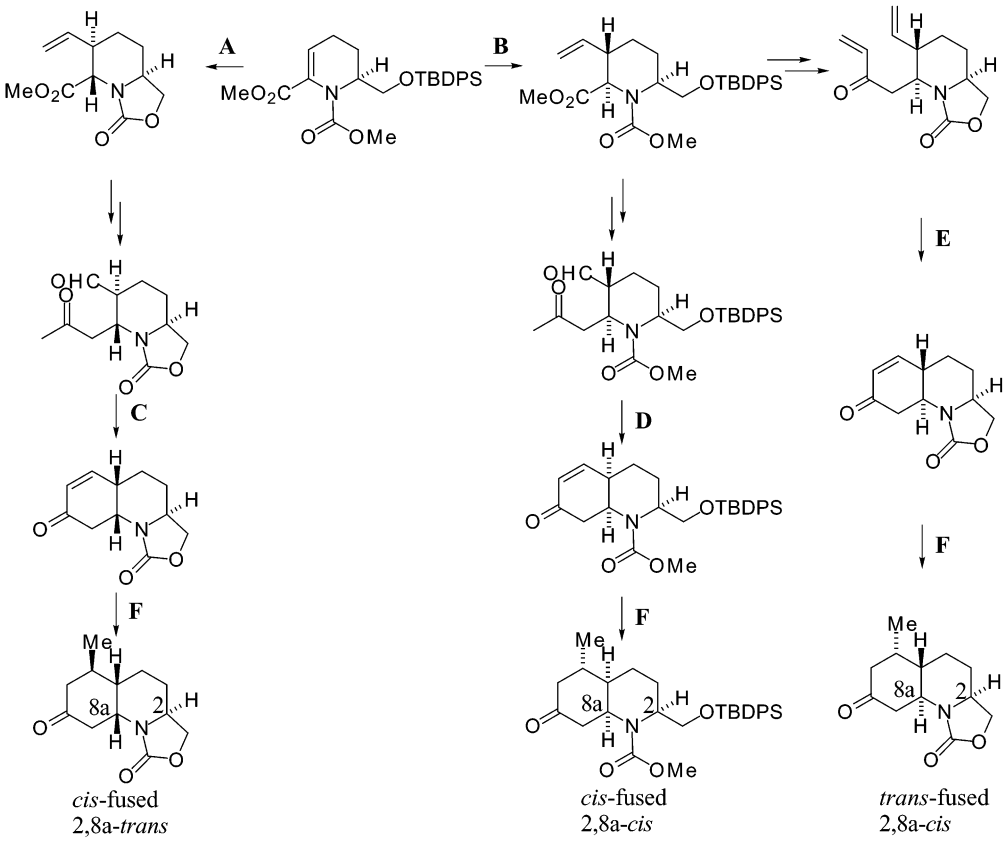


FIGURE 2.

tion of the alkyl side chain at the C-5 position (step F) by the conjugate addition reaction to the enone moiety.

Results and Discussion

The common starting material **1**[5c] was treated with divinyllithium cuprate to afford the adduct **2** as a single isomer. The stereoselectivity of this addition reaction can be explained by $A^{(1,3)}$ strain[8] and stereoelectronic effect,[9] similar to the case for our recent investigations.[5] On the other hand, deprotection of the *tert*-butyldiphenylsilyl group with tetrabutylammonium fluoride followed by oxazolizinone ring formation using sodium hydride as a base afforded the oxazolizinone **3**. The conjugate addition reaction of **3** proceeded smoothly to provide the adduct **4** as a single isomer again. The stereochemistry of **4** was determined by the NOE between H_a and H_b and the half-height width ($W_{1/2}$, 11.5 Hz) of H_c in **4**, as shown in Scheme 1.

The stereoselectivity of this conjugate addition reaction can be rationalized as follows. The conformation of **3** is restricted to **3-A** by the oxazolizinone ring, and the vinyl anion attacks from the stereoelectronically preferred β-axial direction[9] to give rise to the adduct **4** exclusively (Figure 3).

The carbon chain at the α-positions on both adducts **2** and **4** was elongated by the Arndt−Eistert sequence to provide the homologated esters **5** and **6**. The esters **5** and **6** were transformed into the methyl ketones **9** and **10** via the Weinreb's amides[10] **7** and **8**.

Oxidative cleavage of the terminal olefins in **9** and **10** gave the keto aldehydes **11** and **12**, which were subjected to an intramolecular aldol type of cyclization to afford the *cis*-fused quinolinone **13** selectively (*cis*/*trans* = 6.5:1, 52% isolated yield) or **14** exclusively (51% yield). The stereochemistry of **13** and **14** was determined by NOE experiments, as shown in Scheme 2.

Next, we examined the synthesis of a 4a,8a-*trans*-fused ring system such as **18** using the same aldol type of cyclization reaction of **17**. The methyl ketone **9** was converted to alcohol **15**, which was treated with sodium hydride to afford the oxazolizinone **16**. The terminal olefin in **16** was cleaved oxidatively to give rise to the keto aldehyde **17** (Scheme 3). However, the aldol type of cyclization reaction of **17** under the same reaction conditions as those for **11** or **12** was very messy, and no cyclized product was isolated.

According to the above observation, we anticipate that the aldol type of cyclization reaction of **11** should proceed via aldehyde **11-E** rather than *trans*-enone **13-T**, as shown in Figure 4.

(6) (a) Toyooka, N.; Okumura, M.; Takahata, H. *J. Org. Chem*. **1999**, *64*, 2182−2183. (b) Toyooka, N.; Okumura, M.; Takahata, H.; Nemoto, H. *Tetrahedron* **1999**, *55*, 10673−10684.

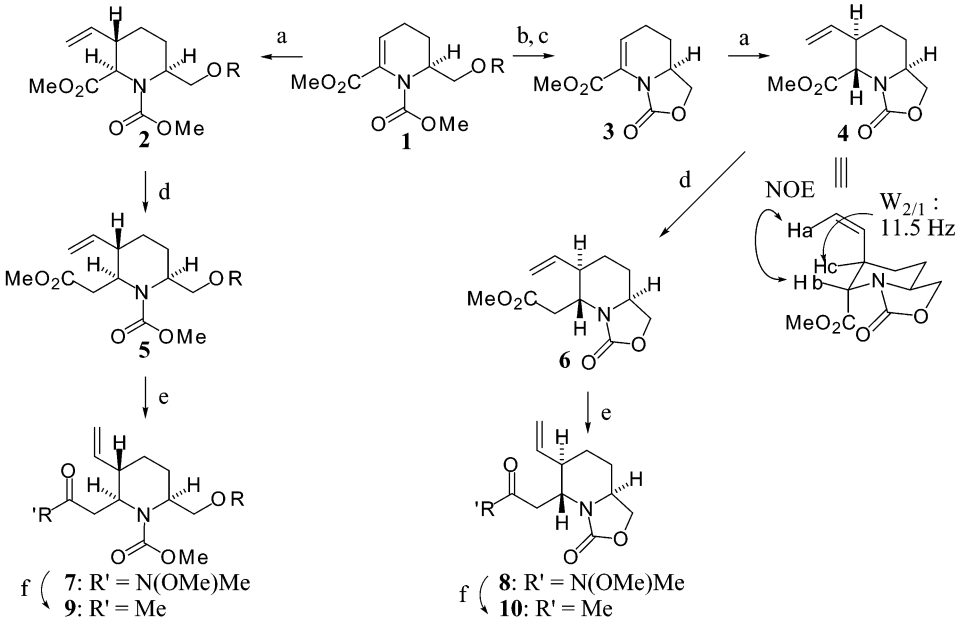
(7) For recent reviews, see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res*. **2001**, *34*, 18−29. (b) Fürstner, A. *Angew. Chem., Int. Ed*. **2000**, *39*, 3013−3043. (c) Wright, D. L. *Curr. Org. Chem*. **1999**, *3*, 211−240. (d) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (e) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. (f) Blechert, S.; Schuster, M. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2036−2056.

(8) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett*. **1981**, *22*, 3815−3818.

(9) Hoffmann, R. W. *Chem. Rev*. **1989**, *89*, 1841−1873.

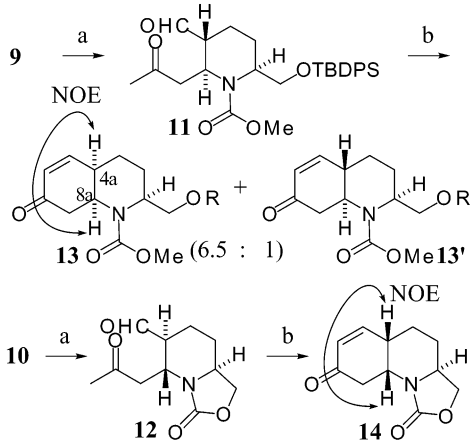
(10) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; pp 209−290.

SCHEME 1[a]



[a] Reagents and conditions: (a) $(vinyl)_2CuLi$, Et_2O, −78 to −30 °C (**2**, 96%; **4**, 78%); (b) TBAF, THF, rt (90%); (c) NaH, THF, 0 °C (95%); (d) LiOH, $MeOH/H_2O$ (3:1), reflux, then $ClCO_2Et$, Et_3N, THF, 0 °C, then CH_2N_2, Et_2O, and then silver benzoate, Et_3N, MeOH, rt (**5**, 80%; **6**, 59%, four steps); (e) LiOH, $MeOH/H_2O$ (3:1), reflux, then 1,1′-carbonyldiimidazole, and then *O*,*N*-dimethylhydroxylamine·HCl, Et_3N, CH_2Cl_2 (**7**, 81%; **8**, 92%, two steps); (f) MeMgBr, THF, rt (**9**, 96%; **10**, 93%); R = TBDPS.

SCHEME 2[a]



[a] Reagents and conditions: (a) OsO_4, $NaIO_4$, 1,4-dioxane/H_2O (1:1), rt (**11**, 79%; **12**, 87%); (b) 4 equiv of DBU, benzene, reflux (**13**, 52%; **14**, 51%); R = TBDPS.

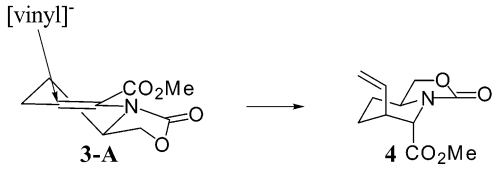


FIGURE 3.

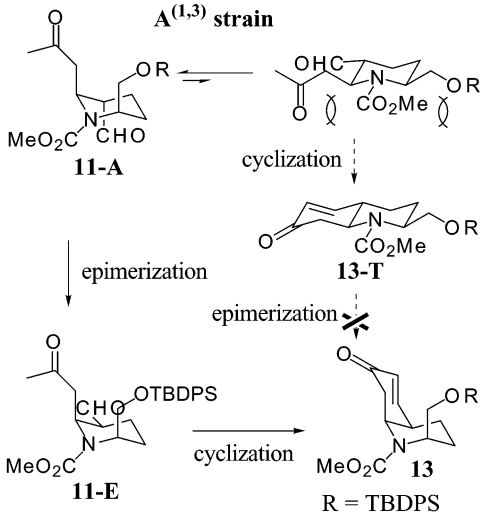


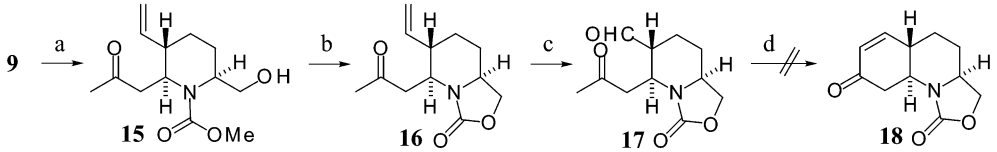
FIGURE 4.

We could not synthesize the 4a,8a-*trans*-fused enone **18** using the aldol type of cyclization reaction of **17**. Thus, we were forced to develop an alternative route to **18**. We designed the ring-closing methathesis reaction of diene **21**. Deprotection of the *tert*-butyldiphenylsilyl (TBDPS) group in **5** with TBAF followed by treatment of the resulting alcohol with sodium hydride gave the oxazolizinone **19**. Reduction of **19** with Super-Hydride provided the alcohol **20**. Swern oxidation of **20** followed by Grignard reaction and PCC oxidation of the resulting secondary alcohol afforded the vinyl ketone **21**. The ring-closing methathesis reaction of **21** using Grubbs' catalyst[11] gave rise to the *trans*-fused quinolinone **18** in good yield (Scheme 4).

With the requisite enones **13**, **14**, and **18** in hand, we next examined the installation of the alkyl side chain at the C-5 position. Thus, treatment of the above enones with dimethyllithium cuprate afforded the adducts **22** and **24** exclusively or **25** selectively (α/β = 3:1). The stereochemistry of the adducts **22** and **24** was determined to be a 4a,5-*cis* relationship by the NOE between H_a and the methyl group on the C-5 position of **23** or between

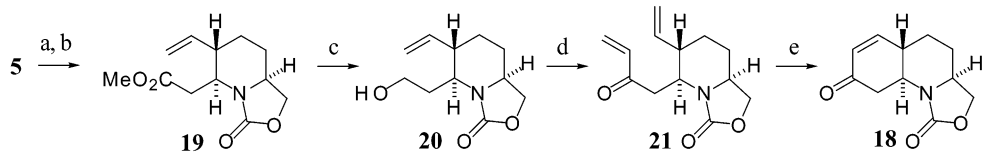
(11) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039−2041.

SCHEME 3[a]



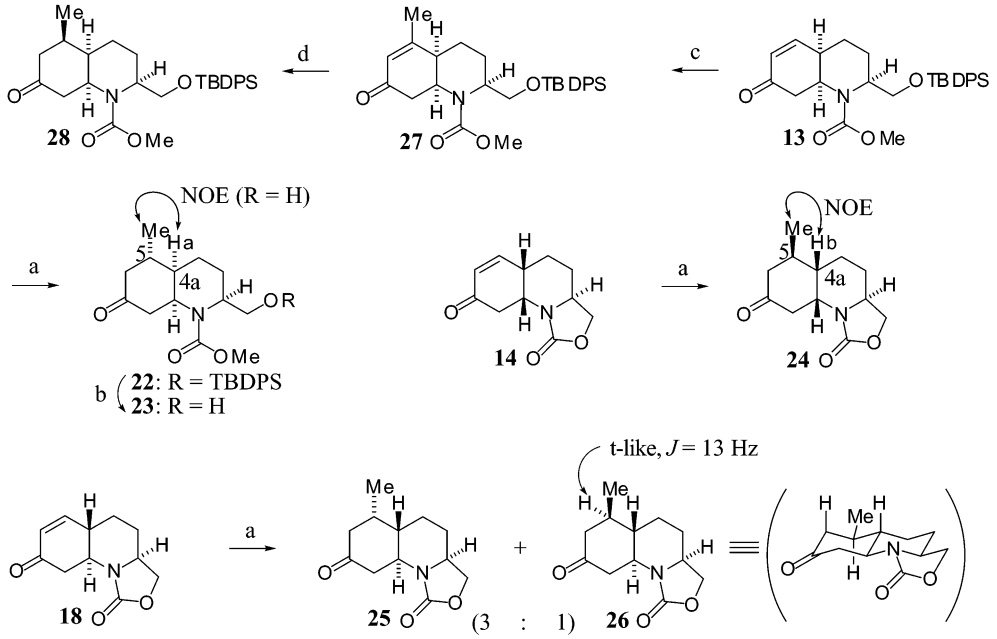
[a] Reagents and conditions: (a) TBAF, THF, rt (86%); (b) NaH, THF, 0 °C (78%); (c) OsO_4, $NaIO_4$, 1,4-dioxane/H_2O (1:1), rt (63%); (d) 4 equiv of DBU, benzene, reflux.

SCHEME 4[a]



[a] Reagents and conditions: (a) TBAF, THF, rt (80%); (b) NaH, THF, 0 °C (85%); (c) Super-Hydride, THF, 0 °C (97%); (d) Swern oxidn, then vinylmagnesium bromide, THF, rt, then PCC, AcONa, CH_2Cl_2 (67%, three steps); (e) benzylidene bis(tricyclohexylphosphine)dichlororuthenium, CH_2Cl_2, rt (96%).

SCHEME 5[a]



[a] Reagents and conditions: (a) Me_2CuLi, Et_2O, −78 to −30 °C (**22**, 96%; **24**, 96%; **25**, 60%; **26**, 20%); (b) TBAF, THF, rt (67%); (c) Me_2CuLi, HMPA, TMSCl, THF, −78 °C then $Pd(OAc)_2$, MeCN, rt (80%, two steps); (d) H_2, $Pd(OH)_2$, MeOH (quant).

H_b and the methyl group on the C-5 position of **24**, respectively. On the other hand, the stereochemistry of the major product of the conjugate addition reaction of **18** was determined to be that of **25** by the large (13 Hz) coupling constant of H-5 in the minor adduct **26**, suggesting the axial (α) position of this proton (Scheme 5).

The C-5 epimer of **22** was synthesized by means of conjugate addition followed by Ito−Saegusa oxidation[12] of the resulting silyl enol ether and catalytic hydrogenation of the enone **27** to give rise to the epimeric octahydroquinolinone **28**.

Conclusions

In summary, we have demonstrated a flexible and stereodivergent route to the 2,5-disubstituted octahydroquinolinone ring core starting from common precursor **1**. In principle, any alkyl chain would be introduced on the C-5 position. In addition, the carbon chain at the 2-position could be elongated by appropriated modification of an oxygenated functional group. This route would be applicable to the divergent synthesis of the *cis*- and *trans*-fused or 2,8a-*cis*- and -*trans*-substituted decahydroquinoline type of dendrobatid alkaloids, shown in Figure 1. Application of this methodology to the synthesis of the above natural products is now under investigation.

Supporting Information Available: Experimental procedures and characterization data for all new compounds, and copies of ^1H and ^{13}C NMR spectra of synthetic compounds **13**, **14**, **18**, **22**, **24**, **25**, **26**, and **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO025929B

(12) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011−1013.