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Stereoselective synthesis of the *cis*-275B decahydroquinoline ring system ☆

Edith J. Banner, Edwin D. Stevens and Mark L. Trudell*

Department of Chemistry, University of New Orleans, New Orleans, LA 70148, USA

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Abstract—The Diels–Alder precursor was constructed from readily available D-glutamic acid utilizing a series of functional group transformations. The stereocenter of the amino acid provided the desired stereochemistry at C2 and diastereoselectively directed the intramolecular Diels–Alder cyclization. This simultaneously generated the three remaining stereocenters and yielded a bicyclic intermediate with all four stereocenters of the target decahydroquinoline 275B.

The first decahydroquinoline found in nature, *cis*-**195A** (Pumiliotoxin C, **1**), was isolated in 1968 by Daly et al. from skin extracts of the neotropical frog *Dendrobates pumilio*.[1] Since the discovery of **1**, about 40 decahydroquinoline alkaloids have been isolated from frog skin extracts.[2] In general, these amphibian alkaloids are bicyclic secondary amines substituted at C2 and C5 with various relative stereochemical arrangements and possess *cis*- or *trans*-ring fusions. The side chains vary in length and can contain diene, acetylene, and allene subunits (Fig. 1).[3]

Decahydroquinolines were initially believed to be unique to amphibians until recently when two isomers of *cis*-**275B** (**2**), were detected in extracts of myrmicine ants [*Solenopsis* (*Diplorhoptrum*) *azteca*] collected in Puerto Rico (**3**, **4**).[4] These novel alkaloids have been found to be potent non-competitive inhibitors at nicotinic acetylcholine receptor-ion channels.[5] As such, the decahydroquinolines are attractive targets for the development of therapeutics aimed at disease states and disorders that can be remedied via nicotinic acetylcholine receptor-ion channels.[6]

To date, synthetic efforts have been primarily focused on the preparation of **1**. Various synthetic routes have exploited intramolecular Diels–Alder chemistry to obtain the desired *cis*-ring fusion and C5 stereochemistry.[7] Other approaches have included intermolecular Diels–Alder reactions,[8] Beckmann rearrangements of tetrahydroindanones,[9] intramolecular enamine cyclizations,[10] and [3,3]-sigmatropic rearrangements.[11] More recent syntheses of **1** have employed regioselective Haller–Bauer cleavage,[12] chiral auxiliaries,[13] aza-annulation,[14] mediation by amine protecting groups,[15] and biomimetic approaches.[16] It was of interest to develop a general stereoselective synthesis of the *cis*-2,5-disubstituted decahydroquinoline ring system with variable

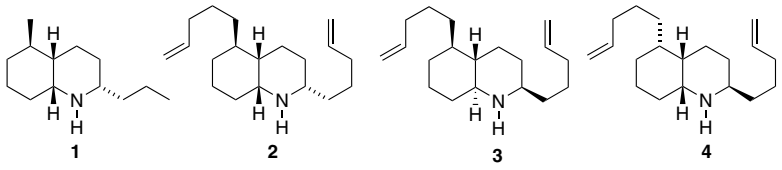

Figure 1. Decahydroquinoline alkaloids.

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* Corresponding author. Tel.: +1-504-580-7337; fax: +1-504-280-6860; e-mail: mtrudell@uno.edu

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functionality at the 2- and 5- positions. This could then serve as a common intermediate for the preparation of a variety of more highly functionalized natural decahydroquinoline alkaloids. In addition, the availability of a *cis*-2,5-disubstituted decahydroquinoline with variable functionality would be useful for the synthesis of non-natural alkaloids for structure–activity studies and drug discovery.

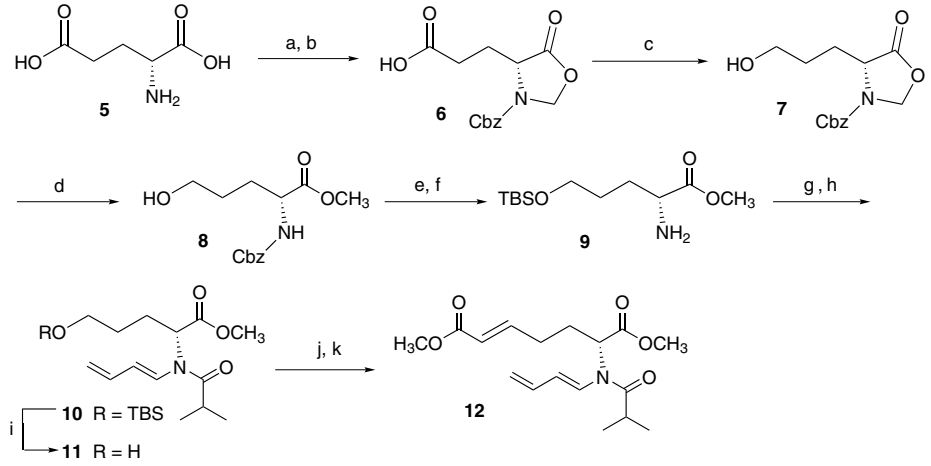
The intramolecular Diels–Alder approach previously utilized by Oppolzer and co-workers[7,17] for the construction of **1** seemed to offer the greatest synthetic flexibility for introduction of more diverse functionality with adequate stereochemical control for the preparation of a *cis*-2,5-difunctionalized decahydroquinoline. Since the stereogenic center of the Diels–Alder precursor (**12**) would ultimately provide the C2 stereochemistry of the decahydroquinoline, D-glutamic acid (**5**) was selected as the starting material for the construction of the Diels–Alder precursor (Scheme 1). Initially, the α-amino group of **5** was protected as the benzyloxy carbamate (Cbz). Subsequent differentiation between the two carboxylic acid residues was achieved by conversion of the α-carboxyl group into the oxazolidinone **6** using methodology developed by Ben-Ishai.[18] This afforded the oxazolidinone **6** in 91% yield and was routinely carried out on a 15 g scale. Finally, the γ-carboxylic acid residue was selectively reduced to the alcohol with BH_3·THF to furnish **7** in 75% overall yield from **5**.

Initial attempts to construct the dienophile fragment of the Diels–Alder precursor were unsuccessful. Oxidation of the hydroxyl moiety of **7** was difficult due to competing side reactions. Despite using a variety of oxidizing reagents and conditions only low yields of the corresponding aldehyde were obtained. As an alternative, our attention turned toward the addition of the diene fragment of the molecule. In order to pursue this approach it was necessary to release the secondary Cbz-amine from the oxazolidinone moiety. This was achieved by sodium methoxide catalyzed methanolysis of **7** to furnish the corresponding methyl ester **8** in 99% yield. Careful control of the methoxide stoichiometry, temperature, and reaction time was found to be critical to maintain enantiopurity. In our hands we found that excess methoxide (>10%), elevated temperatures (>25 °C), or extended reaction times led to significant C2 epimerization and gave scalemic to racemic mixtures of **8**.

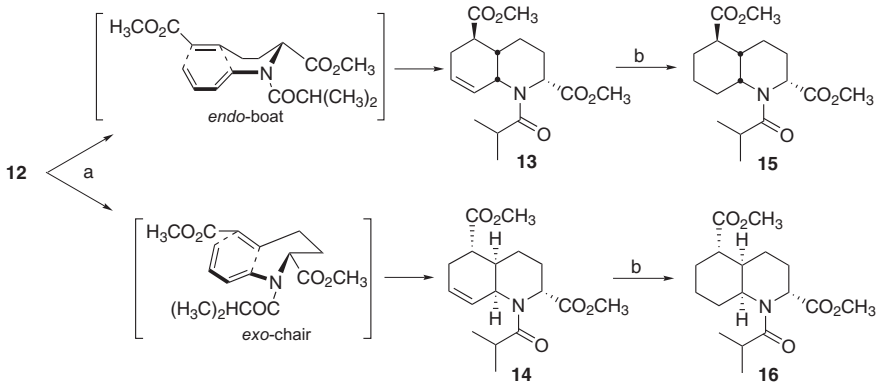
Protection of the hydroxyl group as the TBS ether and hydrogenolysis of the Cbz moiety then furnished the amine **9** in 81% yield over the two steps. Introduction of the diene was then achieved using the crotonaldehyde condensation method developed by Oppolzer.[7] Treatment of **9** with crotonaldehyde and molecular sieves for 11 days followed by concomitant addition of isobutyryl chloride provided the diene **10** in 65% overall yield.

With the diene fragment in place, attention returned to the construction of the dienophile portion of the Diels–Alder precursor. Deprotection of the hydroxyl group was performed with acetic acid in aqueous THF to furnish the alcohol **11** in 88% yield. This method of deprotection was superior to fluoride-mediated reactions, which gave low yields presumably due to competing reactions at the diene residue. The oxidation of the alcohol **11** to the corresponding aldehyde was achieved in high yield (84%) by utilizing DIPEA as the base under Swern reaction conditions. Finally, olefination of the aldehyde gave the Diels–Alder precursor **12** in 69% yield from **11**.

The Diels–Alder cyclization (Scheme 2) was achieved by refluxing **12** in toluene with a mild Lewis acid, bis(trimethylsilyl)acetamide (BSA), for 7 days. This afforded a mixture of octahydroquinoline diastereomers **13**:**14** (70:30) in 89% yield. The diastereomers were easily separated by column chromatography. Subsequent hydrogenation (50 psi) of the individual diastereomers,



Scheme 1. Reagents and conditions: (a) CbzCl, $NaHCO_3$, H_2O, 20 °C, 16 h. (b) $(CH_2O)_n$, TsOH, toluene, reflux, 20 min. (c) BH_3·THF, THF, −30 to 20 °C, 16 h. (d) $NaOCH_3$ (cat), CH_3OH, 20 °C, 30 min. (e) TBSCl, imidazole, DMF, 20 °C, 24 h. (f) H_2, Pd/C, CH_3OH, 20 °C, 16 h. (g) crotonaldehyde, mol. sieves, Et_2O, 20 °C, 11 d. (h) $(CH_3)_2CHCOCl$, Et_3N, CH_2Cl_2, −78 to 0 °C, 16 h. (i) AcOH, H_2O, THF, 0 to 20 °C, 2 h. (j) $(COCl)_2$, DMSO, DIPEA, CH_2Cl_2, −78 to 20 °C, 5 h. (k) $(CH_3O)_2POCH_2CO_2CH_3$, LiCl, CH_3CN, DIPEA, 20 °C, 16 h.



Scheme 2. Reagents and conditions: (a) BSA, toluene, reflux, 7 d. (b) H_2, 10% Pd/C, CH_3OH.

13, and **14**, over 10% palladium on carbon in methanol for 7 h provided the decahydroquinolines, **15**, and **16**, respectively, each in 92% yield. The structures of decahydroquinolines **15** and **16** were both unequivocally confirmed by X-ray crystallography.[19] The crystal structures showed the two diastereomers to be enantiomerically pure with the four stereocenters of the major product **15** corresponding to the stereochemistry of *cis*-**275B**.

As predicted, the major diastereomer of the intramolecular Diels–Alder cyclization was the (2*R*)-(2α, 4aβ, 5β, 8aβ) *cis*-fused octahydroquinoline **13**. The transition state of this reaction for related triene systems has been well studied.[7,17] Presumably, **13** is formed via an *endo*-stabilized boat transition-state (Scheme 2) in which the pseudo-equatorial orientation of the C2 carbomethoxy group provides the desired asymmetric induction at the newly developing stereocenters at C4a, C5, and C8a. The minor diastereomer **14** is believed to be formed via an *exo*-chair transition-state. The equatorial orientation of the C2 carbomethoxy group in the transition state then leads to the observed chirality induced at C4a, C5, and C8a.

This synthesis provides a versatile approach for the construction of the 2,5-difunctional decahydroquinoline ring system. The overall approach can be easily modified to access the different stereoisomers of the decahydroquinoline *cis*-**275B** series of frog and ant alkaloids. Studies directed toward the total synthesis of these natural products and evaluation of their biological activity are ongoing and will be reported in due course.

Supplementary Data: Experimental procedures, spectral data and elemental analyses are available for compounds **9**–**16**. The supplementary data is available online with the paper in ScienceDirect.

Acknowledgements

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19. Crystallographic data (excluding structure factors) for **15** and **16**, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 230111 & 230112. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-0-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).