Alkaloid Synthesis

Highly Enantioselective Construction of Fused Pyrrolidine Systems That Contain a Quaternary Stereocenter: Concise Formal Synthesis of (+)-Conessine**

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The construction of organic molecules with stereogenic quaternary carbon centers by stereoselective reactions is a very challenging task in organic synthesis.[1] A diverse array of steroidal alkaloids and natural products derived from benzohydrindan (**21**) feature quaternary stereocenters in the ring-fused pyrrolidine system.[2] Although significant progress has been made in the development of strategies for the enantioselective synthesis of such compounds, there remains a need for alternative approaches.

Tetracyclic pyrrolidines **C**, which contain the key BCDE ring system of (+)-conessine (Scheme 1), have four contiguous stereogenic centers, one of which is a quaternary carbon atom. In early reports, the synthesis of racemic steroidal alkaloids from racemic **C** was an efficient pathway.[3] The

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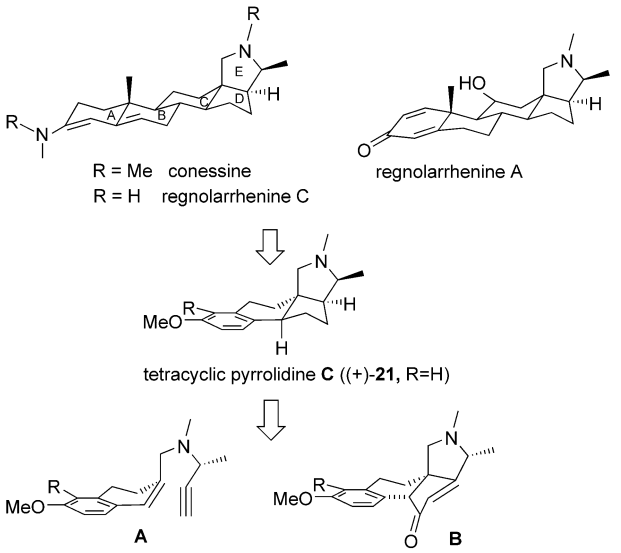
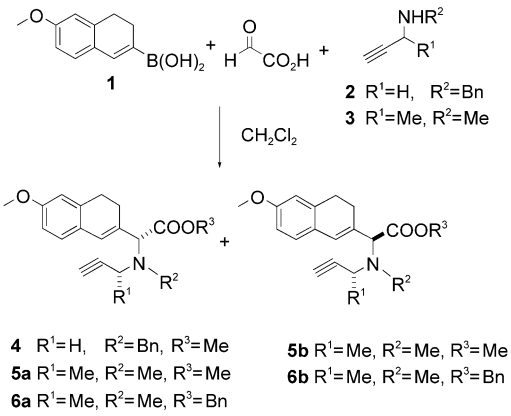


Scheme 1. Structures of the conessine family and retrosynthetic analysis of the BCDE ring system of (+)-conessine.

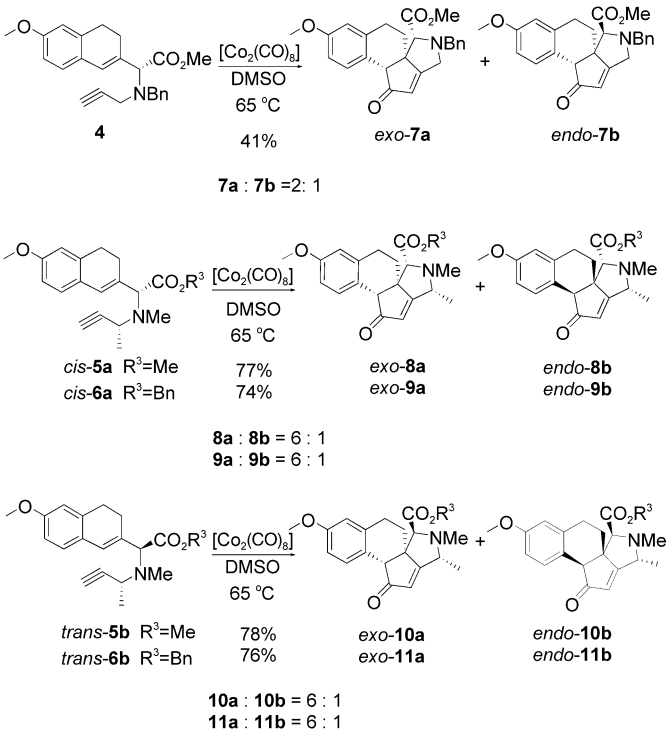
enantioselective synthesis of (+)-**21** was demonstrated by the Meyers research group from a chiral nonracemic lactam in 13 steps. The key transformation was a diastereoselective [3+2] cycloaddition with an azomethine ylide under pressure to construct the pyrrolidine ring system, followed by intramolecular addition of an aryl lithium and an aldol reaction to afford the tetracyclic cyclopentenone skeleton of the tetracyclic pyrrolidine enantioselectively.[4] Based on our recent studies towards the convergent assembly of the cyclopenta[*c*]proline ring system in an efficient and stereoselective manner by an intramolecular Pauson–Khand reaction of a chiral enyne amino acid,[5] it was envisaged that the tetracyclic pyrrolidine **21** of (+)-conessine could be accessed by an asymmetric Pauson–Khand reaction in a single step. The installation of the stereogenic quaternary carbon center would also be possible if the substrates possessed a dihydronaphthalenyl group (Scheme 1).

To check the viability of intramolecular Pauson–Khand reactions of *N*-propargyl dihydronaphthalenyl amino acid derivatives, the model 1,6-enyne **4** was readily prepared in 92% yield by treating the dihydronaphthalenyl boronic acid **1** with the propargyl amine **2** and glyoxylic acid.[6] To study the steric effects of the propargylic amine substituent on the efficiency and stereoselectivity of the cyclization, the *cis* and *trans* isomers **5a**, **6a** and **5b**, **6b**, respectively, were prepared from *N*-methyl-*N*-(1-methyl-2-propynyl)amine (**3**) in a ratio of 1:1, and separated by flash chromatography (Scheme 2). With this series of enynes in hand, we proceeded to study their reactivity under typical Pauson–Khand reaction conditions.

Initially, the Pauson–Khand reaction was carried out under catalytic conditions, as described previously.[5] However, the reaction gave a complex mixture of products. Gratifyingly, the treatment of the enyne **4** with $[Co_2(CO)_8]$ (1.1 equiv) at 65 °C for 6 h in the presence of DMSO (6 equiv) as an oxidant afforded the desired compact tetracyclic pyrrolidine in 41% yield (Scheme 3). Two diastereomers, *exo*-**7a** and *endo*-**7b**, were isolated in a ratio of 2:1. To



Scheme 2. Synthesis of the 1,6-enyne amino esters **4**–**6b**.



Scheme 3. Studies on the stereochemical effects of the α methyl group in the propargylic moiety.

examine the influence of the substituent on the propargylic moiety on the stereochemical outcome of the reaction, the enynes **5** and **6** were treated under the same Pauson–Khand reaction conditions. All the reactions proceeded in good yields, and the ratio of diastereomers reached 6:1. It was found that the methyl group α to the N atom in the propargylic moiety played the main role in controlling the stereochemistry of the product. Irrespective of the nature of the ester group and of whether it was oriented *cis* or *trans* with respect to the methyl group α to N, the *exo* products (**8a**, **9a**, **10a**, **11a**) were isolated as the major diastereomers (Scheme 3). The stereochemistry of the products was readily established by NMR spectroscopic studies. The NOESY spectrum of **8a** showed an NOE between H_a and the methyl group α to the N atom in the pyrrolidine ring, thus indicating

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a *cis* relationship between this methyl group and the cyclohexyl ring, and confirming that the major product had an *exo* configuration (Figure 1).[7]

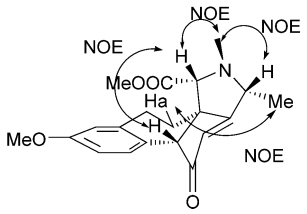
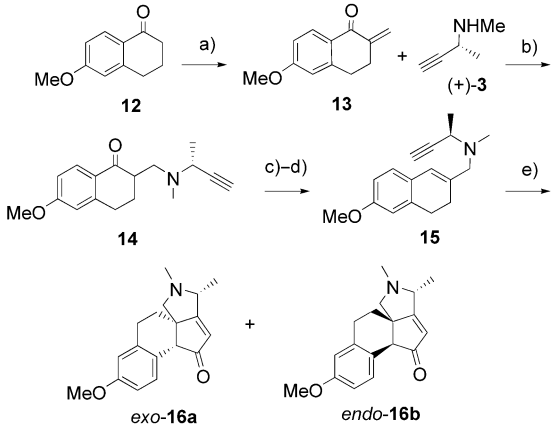


Figure 1. NOEs observed for compound **8a**.

Based on the above results, a practical synthesis of the tetracyclic pyrrolidine (+)-**21** was attempted. Starting from commercially available 6-methoxy-1-tetralone (**12**), the enyne **15** was readily prepared (Scheme 4). A direct methylene-transfer reaction by a general synthetic method produced the



Scheme 4. Synthesis of the key intermediate *exo*-**16a**: a) $CF_3CO_2^-$ $Ph(CH_3)NH_2^+$, $(HCHO)_n$, THF, 65 °C, 4 h, 73 %; b) Al_2O_3/toluene, room temperature, 24 h, 95 %; c) $NaBH_4$, MeOH, 0 °C, 1 h; d) *p*-TsOH·H_2O, benzene, reflux, 91 % (two steps); e) $[Co_2(CO)_8]$ (1.1 equiv), DMSO (6 equiv), THF, 65 °C, 6 h, **16a**/**16b** (6:1), 67 %. DMSO = dimethyl sulfoxide, Ts = toluenesulfonyl.

α-methylene enone **13** from **12**.[8] The Michael addition of (*R*)-(+)-*N*-methyl-*N*-(1-methyl-2-propynyl)amine (**3**) to the enone **13** catalyzed by activated alumina[9] gave the adduct **14** in 95 % yield. Reduction of the ketone group in **14** with sodium borohydride, followed by dehydration, delivered the required enyne **15** in 91 % yield with 98.2 % *ee* ($[\alpha]_D^{25} = +166.7$ ($c = 1.275$, $CHCl_3$)). The treatment of the enyne **15** with $[Co_2(CO)_8]$ in the presence of DMSO as an oxidant at 65 °C for 6 h afforded the desired fused cyclopentenones **16a** ($[\alpha]_D^{25} = +252.6$ ($c = 0.67$, $CHCl_3$)) and **16b** ($[\alpha]_D^{25} = -306.7$ ($c = 0.60$, $CHCl_3$)) in a ratio of 6:1 in 67 % yield. The configuration of **16a** was determined by X-ray crystallographic analysis, which further supported the assignment of the *exo* configuration to the major product of the Pauson–Khand reaction (Figure 2).[10] A possible mechanism for the observed *exo* selectivity is shown in Scheme 5.

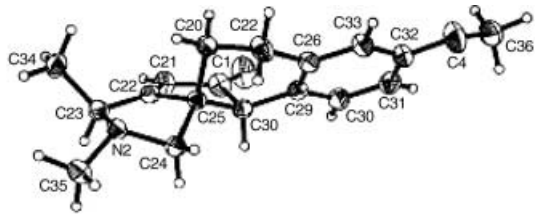
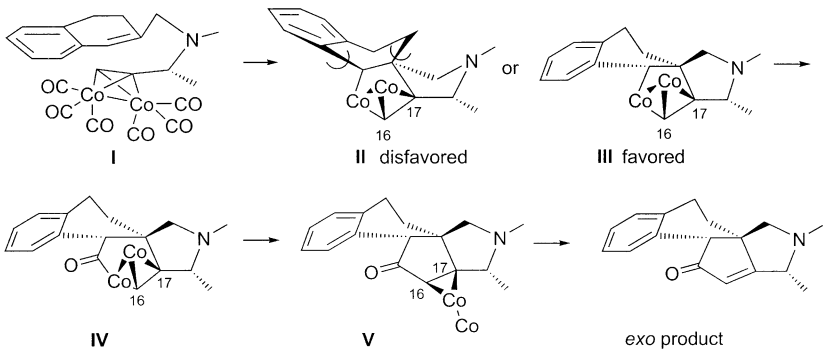


Figure 2. X-ray crystal structure of compound **16a**.

Complex **I** can form two plausible diastereomeric *cis* cobaltacycles **II** and **III** upon alkene insertion into the internal Co–C bond. Because of the bulky tetrahydronaphthalene group on the convex face, the upper side of newly formed *cis* cobaltacycle is quite congested. In the *cis* cobaltacycle **III**, which would lead to the *exo* product, the steric interactions between the methyl group α to the N atom and the C16–C17 bond in the cobaltacycle might be minimized, whereas in **II** a strong steric interaction exists between the methyl group on the *endo* face and the C16–C17 bond. Thus, *exo* selectivity is observed.

At this stage, the scaffold of the tetracyclic pyrrolidine (+)-**21** had been constructed, and the quaternary carbon center had been generated with the desired configuration. Emphasis was then given to the establishment of the correct configuration at C14 and C20 (conessine numbering; Scheme 6). The hydrogenation of the adduct **16a** in the presence of palladium on activated carbon gave the product **17** as a mixture of diastereomers in a ratio of 23:1. The stereoselectivity of the reaction was governed by the relative steric inaccessibility of the concave β face, thus leading to the attack of hydrogen from the α face. We hoped to take advantage of the carbonyl group adjacent to the C14 center and initially attempted to invert the configuration at C14 by the conventional method with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene). However, the inversion product was obtained in less than 35 % yield, and a significant amount of the starting material was recovered (> 50 %). We then attempted to obtain the desired product through hydrogenation of the corresponding olefin **18**. It was anticipated that hydrogenation would occur from the α face on the basis of molecular modeling analysis. The successive treatment of the ketone **17** with sodium borohydride then methanesulfonyl chloride (MsCl) was followed by elimination of methanesulfonic acid by treatment with potassium *tert*-butoxide, to give the olefin **18** in 79 % yield. Unexpectedly, hydrogenation of



Scheme 5. A possible mechanism for the observed *exo* selectivity.

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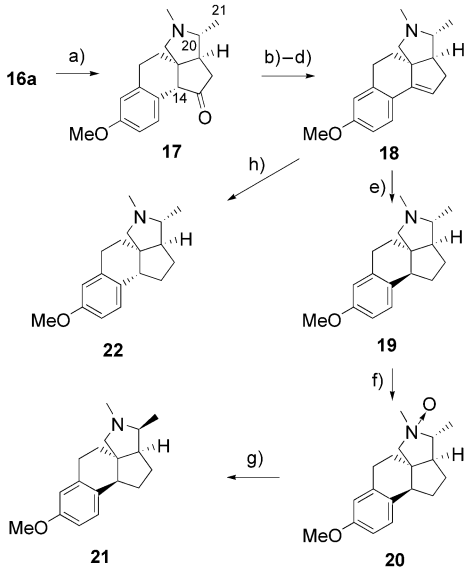

Scheme 6. Completion of the synthesis of the tetracyclic pyrrolidine (+)-**21**: a) Pd/C (10%), MeOH, H_2 (20 atm), 24 h, 92%; b) $NaBH_4$, MeOH, 0°C, 1 h; c) MsCl (2 equiv), pyridine, 0°C, 3 h; d) KO*t*Bu (10 equiv), THF, room temperature, 24 h, 79% (three steps); e) Et_3SiH (20 equiv), TFA, room temperature, 24 h, 88%; f) MCPBA (2 equiv), CH_2Cl_2, 0°C, 1 h; g) TFAA (2.5 equiv), −30°C; then $NaBH(OAc)_3$, 93% (two steps); h) Pd/C (10%), H_2 (1 atm), 2 h, 78%.

the olefin **18** in the presence of palladium on activated carbon gave inseparable products in a ratio of 8:1. ^{1}H NMR spectroscopic analysis revealed that the major product was the undesired product **22** of addition to the β face. This disappointing result led us to investigate other conditions for alkene reduction. To our delight, the treatment of the olefin **18** with triethylsilane[11] in trifluoroacetic acid (TFA) as the solvent afforded exclusively the required α adduct **19** in 88% yield.

The last challenge was to invert the configuration of the C20 center adjacent to the nitrogen atom. It is well-documented that the Polonovski reaction[12] is suitable for this transformation. The oxidation of **19** with *m*-chloroperbenzoic acid (MCPBA) gave the *N*-oxide derivative **20**, which was treated directly with trifluoroacetic anhydride (TFAA) at −30°C. Reduction with sodium triacetoxyl borohydride then provided (+)-**21** as a single isomer in 93% yield ($[\alpha]_D^{25} = +51$ ($c = 0.21$, benzene)). The optical rotation of the product was in agreement with that reported by Meyers and co-workers for the same compound,[4] and the configuration of the product was further confirmed by X-ray crystallographic analysis.[13] The steric hindrance at the concave α face of the tetracyclic molecule **20** may explain the excellent stereoselectivity observed.

In summary, we have described a concise and efficient synthesis of the optically active tetracyclic pyrrolidine (+)-**21** under mild conditions. We have demonstrated a highly diastereoselective method for the construction of the compact tetracycle in the fused pyrrolidine system, which bears a quaternary stereocenter. The stereochemistry of the product was affected by the substituent on the starting propargylic amine. No protecting groups were used in the synthesis, and the entire chiral tetracyclic framework was created in one step by a Pauson–Khand reaction. Thus, the synthesis was efficient in terms of atom economy.

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[10] X-ray crystallographic data for compound **16a**: $C_{18}H_{21}NO_2$, $M_r = 283.36$, monoclinic, space group $P2(1)/n$, $a = 15.5826(10)$, $b = 10.7104(7)$, $c = 19.0881(12)$ Å, $V = 3008.7(3)$ Å^3, $\alpha = 90.00°$, $\beta = 109.1930(10)°$, $\gamma = 90.00°$; $T = 20.0$°C, $Z = 8$, $\mu(Mo_{K\alpha}) = 0.081$ mm^{-1}, reflections collected: 17600 (unique 6948), number of data with $I > 2.00\sigma(I)$: 3824, parameters: 547, $R_1 = 0.0462$, $R_w = 0.0923$, $R_{int} = 0.0459$. CCDC 230574 (**16a**) and CCDC 230573 (**21**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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