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A Synthesis of (–)-Tashiromine and Formal Synthesis of (+)-Tashiromine Utilizing a Highly Enantioselective Pyrrole/Cobaloxime π-Cation Cyclization

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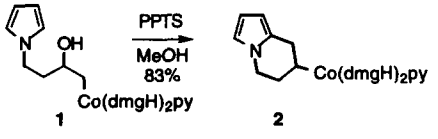
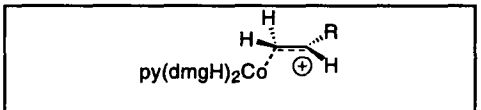
Abstract: Cyclization of (5-*N*-pyrrolyl-2-hydroxypentyl)cobaloxime (**13**) proceeds by intramolecular electrophilic aromatic substitution of a cobaloxime π-cation onto the pyrrole ring to provide 6-exo cyclization product (**14**) in 95% yield. This cyclization is highly enantioselective. It is applied to a synthesis of highly enantioenriched (–)-tashiromine, (–)-**21**, and a formal synthesis of (+)-tashiromine.

Cobaloxime π-cations have been known as reactive intermediates since 1972.[1] We recently reported the first examples of C-C bond formation by nucleophilic substitution of cobaloxime π-cations with allylsilane and pyrrole C-nucleophiles.[2] We also demonstrated that the reaction with an alcohol oxygen nucleophile to form an ether proceeds with retention of configuration.[3] Allylsilane cyclizations of cobaloxime π-cations were reported recently.[4]

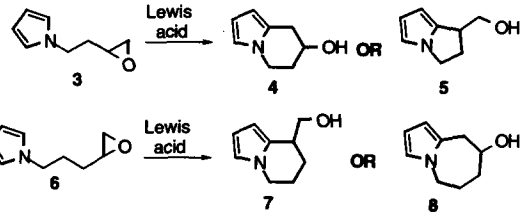


1 2



Unsymmetrical Hyperconjugated Cobaloxime π-Cation
The large δ+ on the most substituted carbon directs nucleophilic attack to the most substituted carbon.

In our previous work we found that β-hydroxyalkylcobaloxime **1** underwent 6-endo cyclization to provide **2**. This reaction is unusual in that nucleophilic attack occurred at the least substituted carbon. In all other known reactions to date nucleophilic attack occurs exclusively at the most substituted carbon, presumably due to the unsymmetrical structure of cobaloxime π-cations.[5] The Lewis acid mediated cyclization of the analogous pyrrole epoxide **3** provided 6-endo cyclization product **4** as the exclusive cyclization product.[6] Cyclization of the homolog **6** gave a mixture of 6-exo and 7-endo cyclization under most conditions. Compared to the relatively symmetrical structure of Lewis acid complexed epoxides, the unsymmetrical structure of cobaloxime π-cations should provide a stronger preference for 6-exo cyclization.



3 4 5

6 7 8

Lewis Acid Mediated Epoxide/Pyrrole Cyclizations (ref. 6)

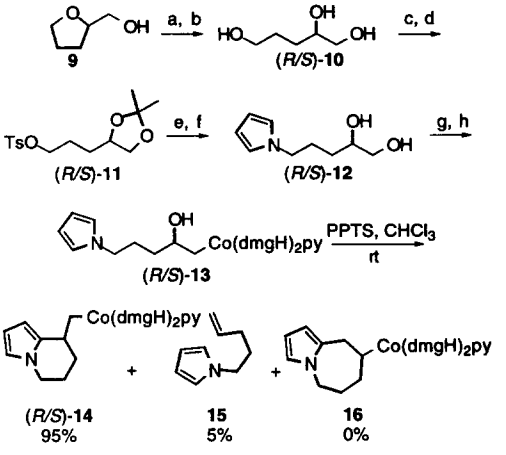
N-(epoxy-alkyl pyrrole)	BF_3•Et_2O (1 equiv)	$EtAlCl_2$ (2 equiv)	Et_2AlCl (2 equiv)	Ti(O-*i*-Pr)$_3$Cl (3 equiv)	ZnI_2 (3 equiv)
3	**4** (70%)	**4** (23%)	**4** (32%)	**4** (45%)	**4** (33%)
6	**7** (20%)	**7** (35%) **8** (45%)	**7** (37%) **8** (48%)	**7** (64%)	**7** (21%) **8** (30%)

Racemic 1,2,5-pentanetriol [(*R/S*)-**10**] was prepared from tetrahydrofurfuryl alcohol (**9**) according to a literature procedure.[7] Introduction of an acetonide group with acetone and *p*-toluenesulfonic acid monohydrate (TsOH•H_2O)[8] followed by tosylate formation (TsCl, Et_3N, DMAP/ CH_2Cl_2) produced (*R/S*)-**11**. Alkylation of pyrrole anion (KOH/DMSO) with (*R/S*)-**11** and removal of the acetonide protecting group (0.1 M HCl/MeOH) provided (*R/S*)-**12**. Selective tosylation of (*R/S*)-**12** at the primary hydroxyl position (TsCl, Et_3N, DMAP/CH_2Cl_2) followed by reaction with NaCo(dmgH)2py/MeOH (formed in situ from $CoCl_2$•$6H_2O$, dimethylglyoxime, NaOH, pyridine, and $NaBH_4$) produced cobaloxime (*R/S*)-**13**. Cyclization of (*R/S*)-**13** [1.2

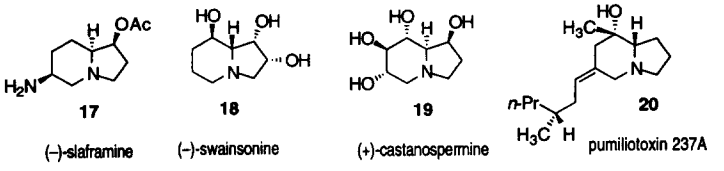
equiv PPTS/$CDCl_3$, rt, 17-47 min] produced only the 6-exo cyclization product (*R/S*)-**14** in 95% yield along with the eliminated alkene (**15**) in 5% yield; none of the 7-endo cyclization product **16** was detected.[9]

Although the reaction of a cobaloxime π-cation with an oxygen nucleophile is known to be highly enantioselective, and most probably enantiospecific, there have been no previous studies on the stereoselectivity of C–C bond formation. Therefore we undertook to examine this question and to do so in the context of the synthesis of an indolizidine alkaloid. Indolizidine alkaloids possess diverse structures and important biological activities.[10] Representative indolizidine alkaloids include (–)-slaframine (**17**), a causative agent in "slobbers syndrome" in livestock that graze on crops contaminated with the fungus *Rhizoctonia leguminicola*, (–)-swainsonine (**18**), an anticancer agent, (+)-castanospermine (**19**), an anti-HIV agent, and frog toxins such as the pumiliotoxins, with pumiliotoxin 237A (**20**) as an example.

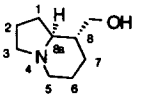
Scheme 1



Reagents and conditions: (a) Ac_2O, $ZnCl_2$, reflux (27-56%), (b) 0.1 M HCl, reflux (94% crude), (c) $TsOH{\cdot}H_2O$, acetone (61%), (d) TsCl, Et_3N, DMAP, CH_2Cl_2 (53%), (e) KOH, pyrrole, DMSO (92% crude), (f) 0.1 M HCl, MeOH (94% crude), (g) TsCl, Et_3N, DMAP, CH_2Cl_2 (89% crude), (h) Na[Co(dmgH)$_2$py], MeOH (55%).



Tashiromine (**21**) was chosen as a target molecule to address the stereochemistry question. Tashiromine was recently isolated from the Asian deciduous shrub, *Maackia tashiroi*. The optical rotation of natural tashiromine remains unknown due to a shortage of material.[11] Racemic tashiromine has been synthesized several times.[12] (–)-Tashiromine [(–)-**21**] has been synthesized by Nagao, therefore the absolute configuration of the (–)-stereoisomer is known.[13]



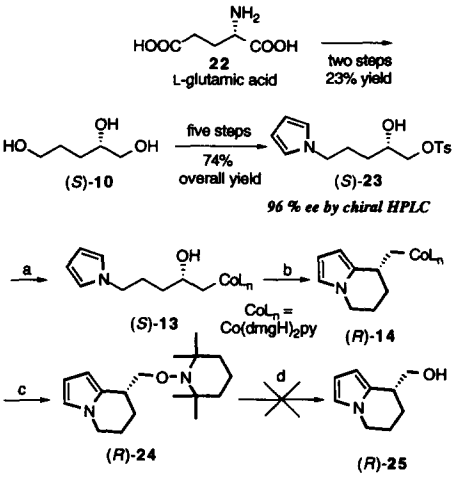
L-glutamic acid (**22**) was used to synthesize enantiomerically enriched (*S*)-1,2,5-pentanetriol [(*S*)-**10**] in 23% yield over two steps.[14] The preparation of monotosylate (*S*)-**23** from (*S*)-**10** was accomplished in five steps in 74% overall yield by the same synthetic sequence shown in Scheme 1 for the conversion of (*R/S*)-**10** to racemic (*R/S*)-**23** (structure of (*R/S*)-**23** not shown in Scheme 1). The preparation of acid-sensitive cobaloxime (*S*)-**13** from tosylate (*S*)-**23** was done using Schrauzer's original method,[15] which involves precipitation instead of silica gel chromatography. Cyclization of (*S*)-**13** provided cobaloxime (*R*)-**14**, isolated as a thermally unstable crude reaction product which was immediately taken on to the next step. Two major modifications of (*R*)-**14** remained before the synthesis of (–)-tashiromine could be completed: oxygenative cleavage of the Co-C bond, and reduction of the pyrrole ring. Alcohols can be synthesized directly from alkylcobaloximes by photochemical insertion of oxygen into the C-Co bond to provide a peroxyalkylcobaloxime, followed by reduction with sodium borohydride.[16] This method could not be used here due to the high photochemical reactivity of pyrroles with oxygen. An anaerobic homolytic cleavage and trapping method was chosen instead. Photolysis of cobaloxime (*R*)-**14** with visible light in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) provided (*R*)-**24**.[17]

Direct transformation of (*R*)-**24** to the corresponding alcohol (*R*)-**25** using zinc dust in acetic acid-water[17] was unsuccessful and resulted in destruction of the pyrrole. Instead, (*R*)-**24** was hydrogenated over 5% Rh/Al_2O_3[18] to provide a mixture of two diastereomers, **28** and **29**. These diastereomers were readily separable by chromatography, but direct chromatography of these two compounds resulted in considerable N-oxide formation. Thus, the mixture of diastereomers, **28** and **29**, was protected from N-oxidation by the formation of borane complexes **26** and **27**.[19] These complexes were separated by careful chromatography, then deprotected by refluxing in ethanol to provide a 2:1 ratio of **28** : **29** in 37% overall yield from (*S*)-**13**.

Nitrogen-oxygen bond cleavage with zinc dust in acetic acid-water gave (–)-tashiromine [(–)-**21**] from **29** in 67% yield. An X-ray analysis of (*R*)-**14** confirmed the absolute stereochemistry of (–)-**21**.[20] By the same method (zinc dust, acetic acid-water), epitashiromine (**30**) was produced from **28** in 92% crude yield (23% after chromatography). Both (–)-tashiromine and epitashiromine gave ^1H and ^{13}C NMR spectra that were identical to published data.[12,13] The synthesis of enantiomerically enriched epitashiromine represents the formal synthesis of (+)-tashiromine since epimerization of racemic epitashiromine at C-8 to form racemic tashiromine is known.[12b]

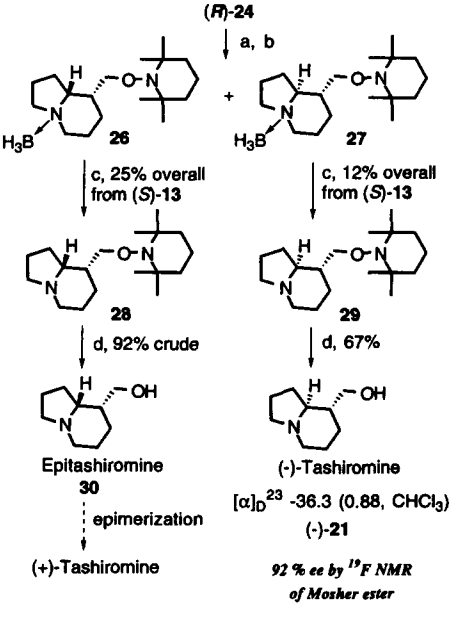
The enantiomeric purity of both monotosylate (*S*)-**23** and (–)-tashiromine [(–)-**21**] were analyzed to determine whether or not the cyclization process had proceeded with full transfer of stereochemical integrity. (*S*)-**23** was analyzed by HPLC on a chiral stationary phase using racemic (*R/S*)-**23** (structure of (*R/S*)-**23** not shown in Scheme 1) as an HPLC standard to establish the retention times of the two enantiomers. (*S*)-**23** was found to be of >98% enantiomeric purity (96+% ee).[21,22] Racemic tashiromine was synthesized from (*R/S*)-**14** (Scheme 1) by the synthetic path shown in Schemes 2 and 3 and a benzoate ester derivative of racemic tashiromine was synthesized for use as a standard for chiral chromatographic analysis. Enantiomers of the benzoate ester of **21** could not be separated on the chiral HPLC or chiral GC systems used.[22] Instead, the enantiomeric purity of (–)-**21** was determined by Mosher ester analysis. A Mosher ester of (–)-**21** with (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride was synthesized for analysis. A Mosher ester of (–)-**21** with (±)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride was synthesized as an ^{19}F NMR standard.[23] The enantiomeric purity of (–)-**21** was found to be 96% (92% ee); the difference in % ee determined for (*S*)-**23** and (–)-**21** is within experimental error. Thus, it has been shown that the cyclization reaction [(*S*)-**13** to (*R*)-**14**] proceeds with very high enantioselectivity, and is most likely enantiospecific. This is the first example of a highly enantioselective formation of a carbon-carbon bond in a cobaloxime π-cation cyclization.

Scheme 2



Reagents and Conditions: (a) Na[Co(dmgH)$_2$py], MeOH, 54-66% crude, (b) PPTS, $CHCl_3$, (c) TEMPO, MeOH, hν, (d) Zn, HOAc-H_2O.

Scheme 3



Reagents and Conditions: (a) H_2, Rh/Al_2O_3, EtOH, (b) BH_3•THF, THF, (c) EtOH, reflux (d) Zn, HOAc-H_2O.

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21. Compound (*S*)-**23** from a previous synthesis was determined to be 97.7% enantiomerically pure (95.4% ee) [(*S*)-pentanetriol produced from L-glutamic acid by the methodology shown has variable optical purity]. The amount of (*R*)-**23** present in the sample from the more recent synthesis was below the detection limit of the chiral HPLC system.
22. (a) HPLC analysis was performed on a Chiralcel OD-H analytical column (0.46 x 25 cm) and monitored at 254 nm. (b) GC analysis on a column containing a chiral stationary phase was performed on a β-Dex 110 capillary column: 30 m x 0.25 mm ID x 0.25 μm film thickness.
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