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STEREOSELECTIVE SYNTHESIS OF SUBSTITUTED PIPECOLIC ACIDS

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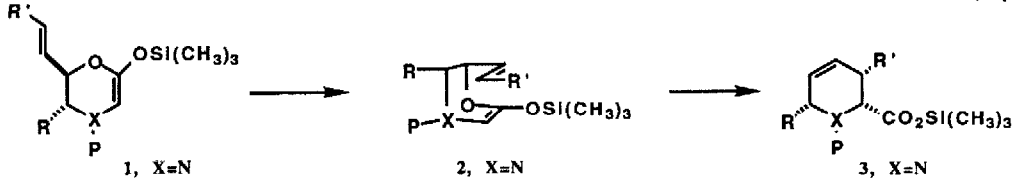
ABSTRACT: The stereoselective synthesis of $\Delta^{4,5}$-pipecolic acid derivatives is described. The key step in the sequence is a [3,3] sigmatropic rearrangement.

The tetrahydropyridine nucleus is a structural subunit found in numerous alkaloids.[1] In addition, it has served as a key intermediate in the synthesis of other azacyclic systems.[2] We report herein the stereocontrolled synthesis of substituted pipecolic acid derivatives[3,4] via a short sequence of reactions which should prove to be a general method for the synthesis of 1,2,5,6-tetrahydropyridines from α-amino carbonyl compounds. The major advantage of this new methodology is the high degree of stereochemical control. The key reaction in the sequence is a conformationally restricted ketene-acetal Claisen [3,3] sigmatropic rearrangement (X=N, equation 1). This type of conformationally restricted Claisen rearrangement has been studied by Danishefsky[5] ($X=CH_2$), Burke[6] (X=O), and others[7] (eq 1). The reaction is restricted to a boat like transition state,[5-7] and the stereochemistry of the products can be predicted with certainty. The nitrogen analog of this Claisen rearrangement (X=N), which has not previously been reported, should provide a short route to $\Delta^{4,5}$-pipecolic acids **3**, with complete stereochemical control at all three stereogenic centers.

(eq. 1)

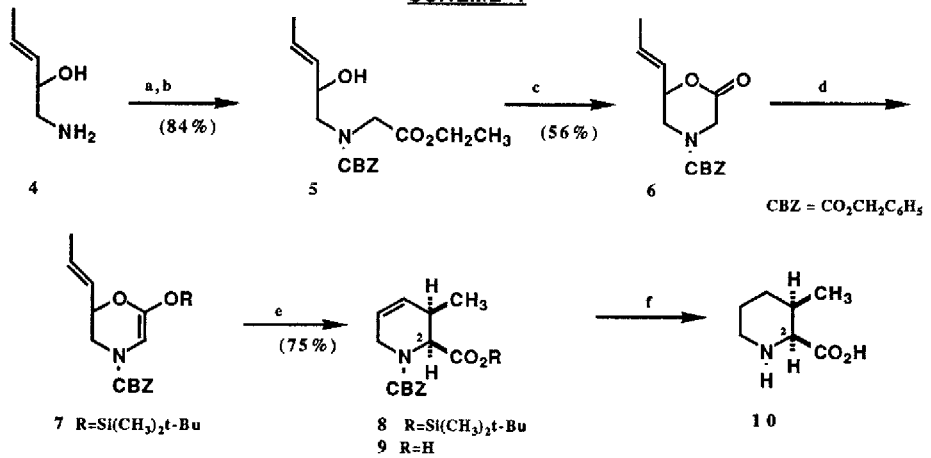


We chose to first explore the viability of this Claisen rearrangement (X=N) in a readily available system. The known[8] amino alcohol **4** was alkylated with ethyl bromoacetate (THF, Et_3N, 2h) and the resulting secondary amine was protected as the carbobenzyloxy carbamate (CBZ-Cl, CH_2Cl_2, aq $NaHCO_3$, 1h, 25°C) to afford hydroxy ester **5** (scheme 1).[9] Heating a benzene solution of **5** with a catalytic amount of acid (0.05eq TsOH, reflux) gave lactone **6** in 47% overall yield.

Treatment of lactone **6** with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMS-OTf, 1.1eq; Et_3N, 1.1eq, 0.9M in C_6D_6) resulted in smooth conversion to ketene acetal **7**.[10] This extremely sensitive com-pound was purified by chromatographic filtration through silylated silica gel.[11] The 300 MHz ^{1}H-NMR spec-trum of **7** showed it to be a mixture of carbamate isomers at room temperature, each displaying a characteristic singlet for the new alkene hydrogen (δ6.4 and δ6.1, 23°C). At 65°C the carbamate isomers rapidly interconvert and the two singlets coalesce, simplifing the ^{1}H-NMR spectrum.

Heating a toluene solution of purified **7** (0.2M, reflux, 2h) resulted in smooth conversion to ester **8** as a single diastereomer. Lactone **6** could be easily converted to **8** upon treatment with TBDMS-OTf (1.5 eq; Et_3N, 2.1eq; toluene, reflux 2h) in 75% yield. Cleavage of the silyl ester (ether, aq NaOH) afforded the free acid **9** in 71% overall yield from lactone **6**. The 300 MHz ^{1}H-NMR spectrum (65°C) of **9** showed H(2) as a 6 Hz doublet indicative of the assigned stereochemistry. To prove the structure of **9** unequivocally , the carbobenzyloxy group was removed with concomitant hydrogenation of the alkene (H_2, 1 atm, EtOH, Pd/C) to afford amino acid **10**.[12] Acid **10** could also be obtained from crude silyl ester **8** upon hydrogenation, followed by hydrolysis, indicating that no epimerization had occurred during the saponification of silyl ester **9**. The 300 MHz ^{1}H-NMR spectrum of **10** shows H(2) as a doublet (J = 3.8 Hz) at δ3.69, consistent only with a *cis*-orientation between the methyl and carboxyl groups. This stereochemical outcome is also consistent with the predicted boat like transition state for the sigmatropic rearrangement.[5-7]

SCHEME 1



4 5 6

7 R=Si(CH$_3$)$_2$t-Bu

8 R=Si(CH$_3$)$_2$t-Bu
9 R=H

10

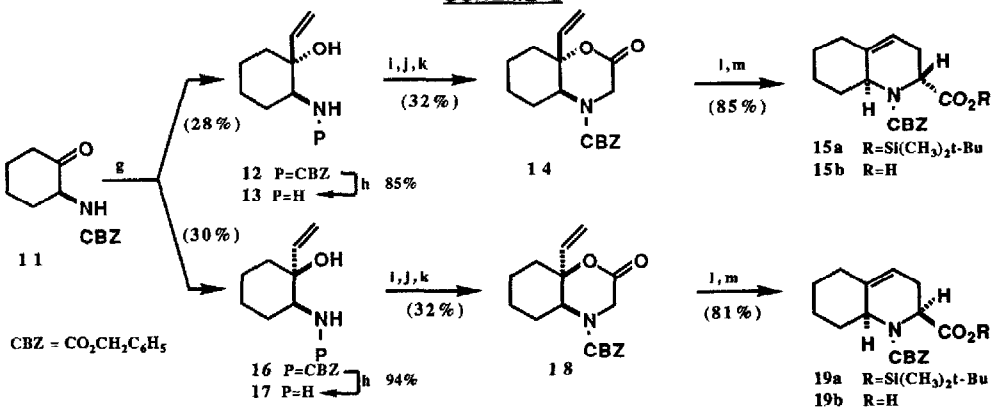
a) $BrCH_2CO_2Et$, Et_3N, THF
b) $ClCO_2CH_2Ph$, aq $NaHCO_3$, CH_2Cl_2
c) cat. *p*-TsOH, C_6H_6, reflux
d) *t*-Bu$(CH_3)_2$SiOTf, Et_3N, C_6D_6
e) toluene, reflux
f) H_2, Pd/C, EtOH

The viability of this sequence as a general method for the annulation of a tetrahydropyridine onto an α-aminoketone was also examined. Treatment of α-aminoketone **13**[13] with vinylmagnesium bromide (2.1 eq, THF, -78 to 25°C) afforded a 1:1 mixture of diastereomeric alcohols, **12** and **16** in 28% and 30% yields respectively (scheme 2). Each diastereomer was separately hydrolyzed (40% KOH, CH_3OH, 100°C) to afford amino alcohols **13** and **17** (85% and 94% yields).[14]

Each diastereomer was then carried through the sequence of alkylation with ethyl bromoacetate, protection with benzyl chloroformate, and lactonization to give **14** and **18** in 32% yields in both cases. Treatment of **14** with TBDMS-OTf (1.5eq; Et_3N, 2.0eq; 0.2M toluene, reflux 2h) afforded tetrahydropyridine ester **15a** as a single diastereomer by ^{1}H-NMR spectroscopy (300 MHz, 65°C). Cleavage of the silyl ester (NaOH, H_2O, THF) followed by base extraction afforded acid **15b** in 85% yield from lactone **14**. Treatment of lactone **18** as above

gave acid **19b**, as a single diastereomer by ^{1}H-NMR spectroscopy (300 MHz, 65°C), in 81% overall yield. Thus, the stereochemistry about the tetrahydropyridine can easily be controlled by establishing the required relative orientation of the amino and alcohol functionalities in the starting amino alcohols, **13** and **17**. The stereochemical assignments of **15** and **19** are based upon the required boat topology in the Claisen rearrangement.[5-7]

SCHEME 2



g) H_2C=CHMgBr, THF
h) 40% KOH, CH_3OH, H_2O
i) $BrCH_2CO_2Et$, Et_3N, THF
j) $ClCO_2CH_2Ph$, aq $NaHCO_3$, CH_2Cl_2
k) cat. *p*-TsOH, C_6H_6, reflux
l) *t*-Bu$(CH_3)_2SiOTf$, Et_3N, C_6H_6
m) toluene, reflux

This general synthetic route should find broad application in the stereoselective synthesis of substituted $\Delta^{4,5}$-pipecolic acids. Current research efforts are directed toward the application of this methodology to the synthesis of natural products using readily available α-amino acids as starting materials.

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9. All new compounds showed satisfactory 300 MHz ^{1}H-NMR, ^{13}C NMR, IR, low resolution MS and either HRMS or elemental analysis.

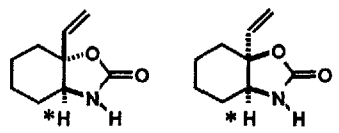
10. The procedure used was a modification of: Emde, H.; Gotz, A.; Hofmann, K.; Simchen, G. **Liebigs Ann. Chem.** *1981*, 1643.

11. Standard methods for the purification of ketene acetals (distillation and precipitation of salts with pentane) proved inferior. Silylated silica gel: Overman, L.E.; Angle, S.R. **J. Org. Chem.** *1985*, **50**, 4021.

12. The acid substituent in **9** should show a strong tendency for an axial orientation due to an $A^{1,3}$ interaction with the planar N-CBZ carbamate (see reference **4** for an example of this type of allylic strain; for a review on A strain see: Johnson, F. **Chem Rev.** *1968*, **64**, 375). The observed coupling constant is also consistent with an alternative diastereomer in which the methyl and acid groups are both pseudoaxial. Amino acid **10** has no such interaction and the stereochemical assignment was straight forward. Thus, the stereochemistry of **9** must be as shown.

13. Prepared from cyclohexene oxide in 30% overall yield via the following sequence: i) NH_4OH, CH_3OH reflux; ii) $ClCO_2CH_2C_6H_5$, aq $NaHCO_3$, CH_2Cl_2; iii) $(ClCO)_2$, DMSO, Et_3N.

14. The stereochemistry was assigned as follows: treatment of amino alcohols **13** and **17** with carbonyldiimidazole (1.5 eq, Et_2O, toluene; 25°C 18h; 111°C 3h) afforded the corresponding cyclic carbamates **i** and **ii**. In isomer **i** the bridgehead hydrogen (*) appears as a doublet of doublets (J = 3Hz, 13Hz) in the ^{1}H NMR spectrum, indicative of H* in an axial orientation. In isomer **ii**, H* appears as a triplet (J = 4Hz), consistent only with H* in an equatorial orientation.



i **ii**

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