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Stereoselective Δ^4-Pipecolic Acid Synthesis *via* Alkylation of a Vinyl *N*-Boc-iminium Ion Derived from Baikiain

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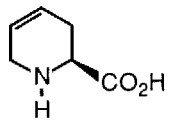
Summary: *Stereoselective functionalization of Boc-(±)-Baikiain was demonstrated via seleno- and iodolactonization to afford lactones* **5**. *These were converted to enecarbamate* **7**, *which undergoes regio- and stereoselective alkylation at C-6 upon treatment with organoaluminum reagents.*

The stereoselective synthesis of substituted pipecolic acids[1] is a subject of much current investigation. As part of a program to develop our own stereocontrolled pipecolic acid synthesis, a member of the chiral pool, α-amino acid baikiain **1**, was chosen as the starting material.[2] We postulated that by using the carboxyl and olefinic groups of *baikiain* in tandem transformations, a variety of heteroatomic arrays might be stereoselectively constructed. Baikiain is a natural product extracted from hardwood,[3] and has been relatively unexplored as a chiral building block for nitrogen heterocycle synthesis. We began by showing, using literature precedent,[4] that *iodolactonization* is a convenient regio- and stereoselective operation. Thus, synthetic (±)-baikiain hydrochloride **3**[5], protected as the easily removable *N*-*t*-butyloxycarbonyl (Boc) derivative **4**, was iodolactonized[6] (I_2, KI, H_2O, $NaHCO_3$, rt) providing **5a** as a crystalline substance (Scheme 1): mp 89-90°; IR($CHCl_3$): 1799, 1703 cm^{-1}; 60% yield. Alternatively, selenolactonization can be carried out (phenylselenenyl chloride, Et_3N, CH_2Cl_2, 0°) to afford **5b**: mp 88-89°; IR($CHCl_3$): 1795, 1775 cm^{-1}; 40% yield.



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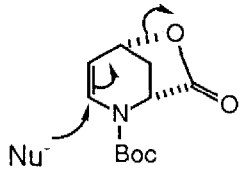
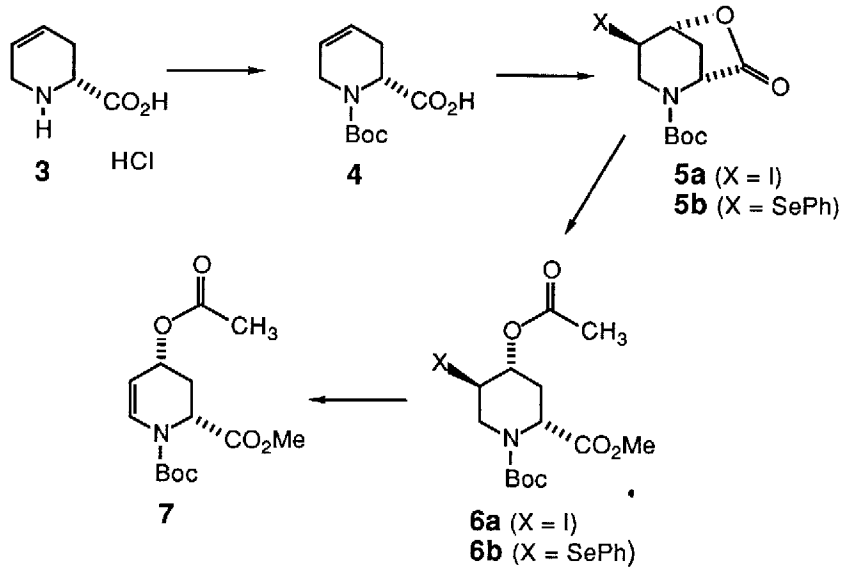


2

Having readily introduced reactive functionality at C-4 and C-5, we realized that if a double bond were introduced at the 5th position (as in **2**), the carbon α- to nitrogen (C-6) could be alkylated in an S_N2' fashion; this operation would regenerate the baikiain functionality and permit a repeat of iodolactonization. Because initial attempts at preparing the strained, labile lactones **2** were unpromising, ring-opened compounds were chosen for further elaboration. Lactones **5** were subjected to methanolysis (**5a**: MeOH, rt, TFA; **5b**: MeOH, cat. *t*-BuOK, rt, 5min), followed by acetylation (Ac_2O, DMAP) to produce acetates **6a** (mp 114.3-116°) and **6b** (mp 106-107°). Iodoacetate **6a** was smoothly eliminated (3eq DBU; DMF; 80-90°; 25min; argon atm.; 90% yield; suitable for use without further purification) to provide the oily enecarbamate **7**. **6b** was also eliminated *via* selenoxide formation (*m*CPBA, 0° to rt) to provide **7**: 67% yield after SiO_2 chromatography.

Scheme 1

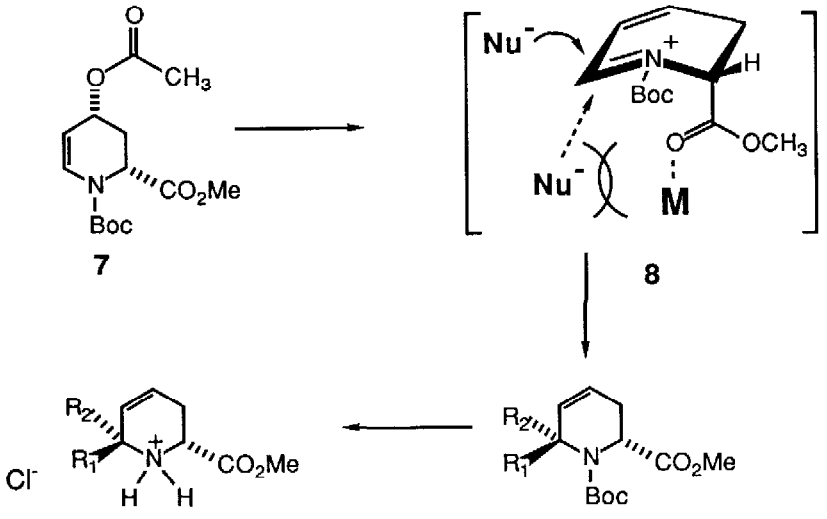


Enecarbamates (*N*-carbalkoxyl-4-alkoxy-$\Delta^{5,6}$-piperidines) have been proposed as vinyl *N*-acyliminium ion precursors that α-alkylate with soft nucleophiles such as allylsilanes as shown by Kozikowski[7] and with organozinc reagents as shown by Comins.[8] Because organoaluminum reagents react sequentially as Lewis acids then as nucleophiles,[9] we were attracted by the possibility that these reagents might alkylate **7** via nucleophilic addition to a vinyl N-Boc-iminium ion. By forming the organoaluminum reagent *in situ* from a Grignard reagent and aluminum chloride, we envisioned the introduction of a wide variety of alkyl groups. In particular, *benzyl* might be introduced (for which no "soft" form is available), thus effecting the addition of a hard nucleophile to a vinyl acyliminium ion.

Enecarbamate **7** was treated[10] (Scheme 2) with an organo- Al-Mg reagent formed from aluminum chloride and benzylmagnesium chloride to give predominantly the **trans** 6-benzyl-Δ^4-pipecolate **9a** (trans/cis ratio[11] = 25:1; 92% combined isolated yield after SiO_2 chromatography). *This* **trans** *mode of addition is* opposite *to the* cis *addition reported*[8] *for the reaction of organozinc reagents with an encarbamate containing a 2-methyl substituent in place of the 2-carbomethoxy of* **7**. The mechanism of stereoselective trans addition may involve initial complexation of a bulky Al-Mg species to the carbomethoxy group of **7**, followed by generation of vinyl Boc-iminium ion **8** (**M** = organometallic complex) with subsequent nucleophilic attack by benzyl from the least hindered side. This view is consistent with the expected *axial* conformation of the -CO_2Me in **8**, as predicted by $A^{(1,3)}$ strain theory.[12] That steric effects are important is supported by an experiment in which enecarbamate **7** was added to a mixture of *methyl*magnesium bromide and aluminum chloride (reagent formed from $AlCl_3$-MeMgBr (molar ratio = 1:3) as described,[10] CH_2Cl_2, -15°, 20min) to give the *cis* α-alkylated product **9b** as the predominant diastereomer (cis/trans[11] = >10:1; the **9b**/epi-**9b** mixture was deblocked as described below to give hydrochlorides **10b**/epi-**10b** in 86% combined isolated yield); this stereochemical result is *similar* to that reported in the literature.[8] In the case of cis delivery (ie. when **M** is small), the reaction may proceed through an

energetically more favorable "half-chair" transition state; in the trans case (when M is large), steric hindrance may preclude this stereoelectronically favored attack. Enecarbamate **7** was also treated with trimethylaluminum (5eq $Al(Me)_3$, 10eq THF, CH_2Cl_2, -15°, 50min) to give the cis product **9b** (cis/trans ratio[11] = >10:1; after deblocking, a mixture of hydrochlorides **10b**/epi-**10b** was isolated in 87% combined yield).[13]

Scheme 2



10a (R_1 = Benzyl, R_2 = H) **9a** (R_1 =Benzyl, R_2 = H)
10b (R_1 = H, R_2 = Me) **9b** (R_1= H, R_2 = Me)

Direct determination of the stereochemistry of **9a** and **9b** by ^1H NMR was not possible,[14] owing to the presence of the 4,5-double bond and to rotational isomerism of the Boc group. Therefore **9a** was converted by treatment with HCl (6*N* in dioxane, rt, 30min) to crystalline hydrochloride **10a**.[15] The trans configuration of **10a**, shown in the figure, was demonstrated by single crystal X-ray diffraction;[16] in the crystal, this "aza-cyclohexene" **10a** assumes the conformation of the "half-chair" of cyclohexene,[17] with the benzyl group occupying a pseudo-axial position. The stereochemistry of **9b** was determined by conversion to hydrochloride **10b** which, in conjunction with the above X-ray data, was shown by ^1H NMR to have the cis configuration.[16]

The stereoselective reaction sequences described above should prove valuable for the construction of various substituted Δ^4-pipecolic acids. The predominant *trans* alkylation with the benzyl Al-Mg system offers a useful alternative stereochemistry to the reported *cis* alkylations.[8] It has not escaped our attention that the organo-Al-Mg system may be used for the alpha alkylation of saturated cyclic or acyclic α-alkoxyacylamino compounds.[18] We are continuing to define the scope of nucleophilic additions to enecarbamate **7** and α-alkoxycarbamates.

Acknowledgements: We thank Dr. Michael Sabat (Northwestern University) for the X-ray crystallographic determination of the structure of **10a**, and Professor A.G.M. Barrett (Northwestern University) and Lydia Swenton for helpful discussions.

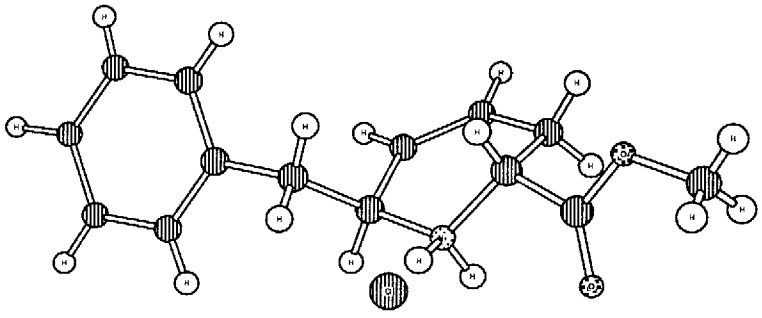


Figure. Structure of **10a** as determined by X-ray crystallography.

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10) To a stirred suspension of $AlCl_3$ (404mg, 3.48mmol) in CH_2Cl_2 at -78°, benzylmagnesium chloride (1M in ether, 10mL, 10mmol) was added. The reaction mixture was allowed to warm to 0°. This reagent was added to a solution of **7** (130mg, 0.435mmol) in CH_2Cl_2 (10mL) at -15°. After 10min the reaction mixture was poured into aqueous citric acid (0.5M) and the product was isolated by ether extraction. Chromatography on SiO_2, eluting with 4:1 petroleum ether-ether gave pure **9a** (oil, 125mg, 92% yield): 400 MHz ^1H NMR ($CDCl_3$): 1.48 (bs, 4.5H), 1.55 (bs, 4.5H), 1.83 (bm, 1H), 2.35 (bm, 1H), 3.05 (m, 2H), 3.65 (s, 3H), 4.54 (m, 2H), 5.70 (bs, 2H), 7.2 (m, 5H); IR($CHCl_3$): 1740, 1685 cm^{-1}; HRMS calcd for $C_{19}H_{26}NO_4$ (M+H): 332.1862; Found: 332.1863.
11) Ratios were determined by 400 MHz ^1H NMR.
12) F. Johnson *Chem. Rev.* (1968) **68**, 375-413.
13) Treatment of **7** with triisobutylaluminum-THF resulted in a complex mixture consisting mainly of Boc baikian methyl ester.
14) Saturation of the double bond of **9a** with Pd-C could complicate structural analysis, owing to the tendency of Pd to isomerize systems of this type: K.T. Wanner, A. Kartner and E. Wadenstorfer *Heterocycles* (1988) **27**, 549-2556.
15) Hydrochloride **10a** was shown to be a single diastereomer by 400 MHz ^1H NMR (deuteriomethanol). All compounds exhibited spectral data (IR, NMR) consistent with their proposed structures. Key compounds gave satisfactory combustion analyses and/or high resolution mass spectra.
16) The complete details of the X-ray and NMR work will be published in a full account of this work.
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