A New Access to Kainoids via a Tandem Aza-Cope/Mannich Reaction. Application to the Enantioselective Synthesis of (−)-α-Allokainic Acid

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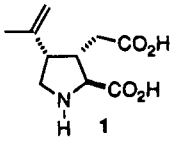
Kainoids belong to a family of non-proteinogenic amino acids structurally related to proline. Owing to their potent neuroexcitatory properties,[1] these compounds are of considerable interest. The pyrrolidine ring of these bioactive molecules bears three contiguous stereocenters and this represents an interesting problem solved by numerous syntheses[2] of (+)-α-kainic acid **1** and its C-4 epimer (+)-α-allokainic acid **2**. These complex amino acids have been constructed from various chiral starting materials including proteinogenic amino acids,[3] diethyl tartrate,[4] or chiral building blocks prepared by Sharpless asymmetric epoxidation.[5] These syntheses were based upon transformation of the above substrates and it is worthy to note that, to our knowledge, the only work which did not follow this strategy was reported by Oppolzer[6] who made use of (−)-8-phenylmenthol as a chiral auxiliary.



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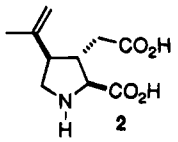

2

We wish to report here a new enantioselective entry to kainoid compounds which is based on the use of (*R*)-phenylglycinol as a chiral inductor. Since both enantiomeric forms of this amino alcohol are available, it is not surprising that it has been taken as the basis of an increasing number of published asymmetric syntheses.[7] Our approach is based on a tandem aza-Cope/Mannich reaction which was first discovered by Overman *et al.*[8] Such processes have found widespread use in the construction of complex functionalized pyrrolidines, culminating in a recent total synthesis of strychnine.[9]

Recent work from our laboratory[10] has shown that this tandem reaction can be used for constructing of an enantiopure *cis*-4-substituted proline derivative **7** (R = H) as shown in Scheme 1.

Bicyclic hemiacetal **6** was produced in a totally stereoselective manner from amino alcohol **3** and glyoxal via a tandem aza-Cope/Mannich reaction. This process occurs in aqueous medium and consists of three consecutive reactions: (i) iminium ion **4** formation from condensation of **3** and glyoxal, (ii) aza-Cope rearrangement and (iii) Mannich reaction. Our synthesis starts from aminodiol **8** whose ethylenic double bound is now properly designed to generate the third stereogenic center of (−)-α-allokainic acid **2**. In this way, the three contiguous stereocenters will be set up in a one-pot reaction. The amino alcohol **8** required for this strategy was synthesized as depicted in Scheme 2.

The lithium salt of alkyne **12**, prepared[11] from the commercially available corresponding alcohol, was reacted with ethyl pyruvate. The resulting ester **13** was condensed with (*R*)-phenylglycinol and furnished amide **14** as a mixture of epimers which were treated with $LiAlH_4$. (*E*)-Alkene **8** was thus prepared on a multigram scale. Reaction of **8** with glyoxal in a slightly acidic (pH 4–5) aqueous medium gave the expected bicyclic hemiacetal **11** along with tricyclic compound **15** (relative ratio: 70/30) which were readily separated by flash chromatography. Isolated **15** gave another crop of **11** when it was allowed to stand in the same acidic medium as above (Scheme 3).

Transformation of **11** to *ent*-**2** was realized as displayed in Scheme 4. Compound **17** was obtained via Wittig olefination of the silyl ether protected derivative **16**. Debenzylation of morpholine **17** by vinylchloroformate, followed by Jones oxidation, yielded a mixture of ester **19** and acid **20** which was simply transformed into methyl ester **21**. Diester **23** was obtained from compound **21** using a three-step sequence: (i) $TiCl_4$-mediated cleavage[12] of the *t*-butoxy moiety of **21**, (ii) Jones oxidation of the resulting alcohol **22**, and (iii) final esterification yielding the dimethyl ester. Ultimately, a basic treatment of the N-protected pyrrolidine diester **23** afforded the desired *ent*-**2**. Spectroscopical data of *ent*-**2** fitted perfectly with literature values[6b] and showed an optical rotation opposite to that shown by natural (+)-α-allokainic acid **2**.

Three stereocenters are created during the key-step of this synthesis (see the formation of compound **11** from substrate **8** in Scheme 1). The observed complete stereoselectivity is the result of three factors, each one governing the formation of a specific stereocenter. First, as previously evidenced by many other nucleophilic additions[10,13] on cyclic iminium ions related to intermediate **9**, an axial attack by the olefinic double bond is responsible for the stereochemistry of the C-2 center (see

(1) Johnson, R.;Koerner, J. F. *J. Med. Chem.* **1988**, *31*, 2057.
(2) For a recent synthesis of (±)-**1** and a review of prior work, see: Monn, J. A.; Valli, J. M. *J. Org. Chem.* **1994**, *59*, 2773 and references cited therein. See also: Williams, R. M. *Synthesis of Optically Active α-Amino acids*; Pergamon Press: Oxford, 1989; pp 306–320.
(3) From glutamic acid, see: Oppolzer, W.; Thirring, K. *J. Am. Chem. Soc.* **1982**, *104*, 4978. From aspartic acid, see: Cooper, J.; Knight, D. W.; Gallagher, P. T. *J. Chem. Soc., Chem. Commun.* **1987**, 1220. From serine, see: Barco, A.; Benetti, S.; Spalluto, G. *J. Org. Chem.* **1992**, *57*, 6279.
(4) Takano, S.; Sugihara, T.; Satoh, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1988**, *110*, 6467.
(5) (a) Baldwin, J. E.; Li, C. S. *J. Chem. Soc., Chem. Commun.* **1987**, 166. (b) Takano, S.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1992**, 169. (c) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1204.
(6) (a) Oppolzer, W.; Robbiani, C.; Bättig, K. *Helv. Chim. Acta* **1980**, *63*, 2015. (b) Oppolzer, W.; Robbiani, C.; Bättig, K. *Tetrahedron* **1984**, *40*, 1391.
(7) For recent uses of phenylglycinol in asymmetric synthesis, see *inter alia*: (a) Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1993**, *58*, 36. (b) Baussanne, I.; Chiaroni, A.; Husson, H. P.; Riche, C.; Royer, J. *Tetrahedron Lett.* **1994**, *35*, 3931.
(8) Overman, L. E.; Kakimoto, M. A. *J. Am. Chem. Soc.* **1979**, *101*, 1310.
(9) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1993**, *115*, 9293.
(10) Agami, C.; Couty, F.; Lin, J.; Mikaeloff, A.; Poursoulis, M. *Tetrahedron* **1993**, *49*, 7239.
(11) Alexakis, A.; Duffault, J. M. *Tetrahedron Lett.* **1988**, *29*, 6243.
(12) Schlessinger, R. H.; Nugent, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 1116.
(13) (a) Agami, C.; Couty, F.; Prince, B.; Puchot, C. *Tetrahedron* **1991**, *47*, 4343. (b) Agami, C.; Couty, F.; Poursoulis, M.; Vaissermann, J. *Tetrahedron* **1992**, *48*, 431.

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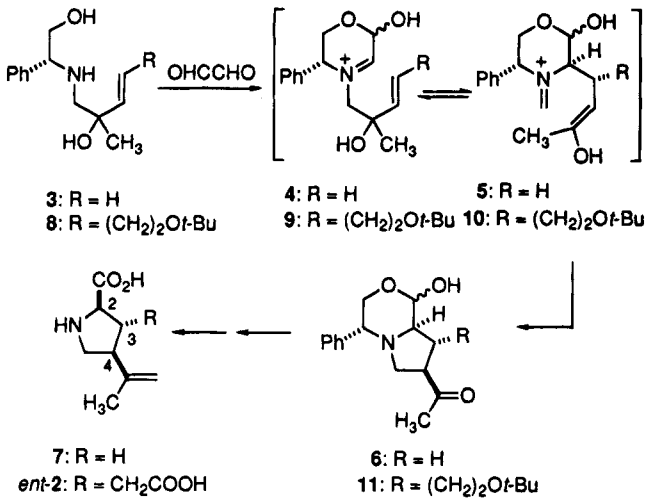
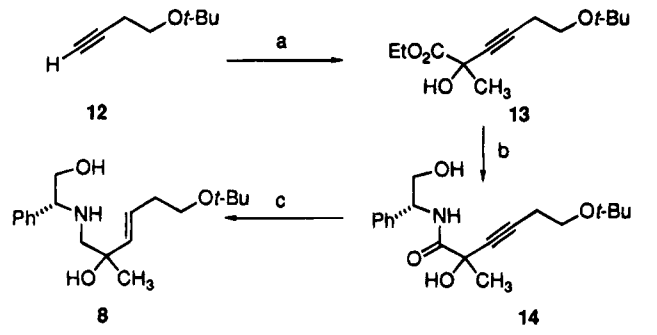
Scheme 1

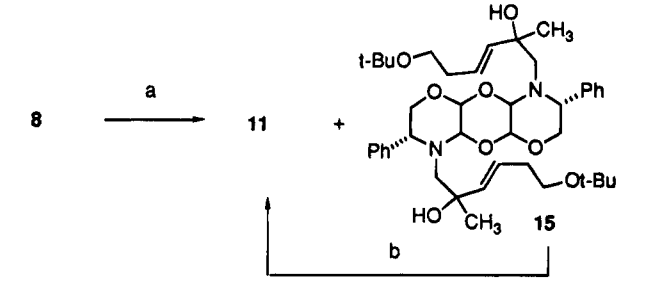


Scheme 2[a]



[a] Reaction conditions: (a) BuLi, THF; ethyl pyruvate, −78 °C, 86%; (b) (*R*)-phenylglycinol, toluene, reflux, 77%; (c) LiAlH4, THF, reflux, 94%.

Scheme 3[a]



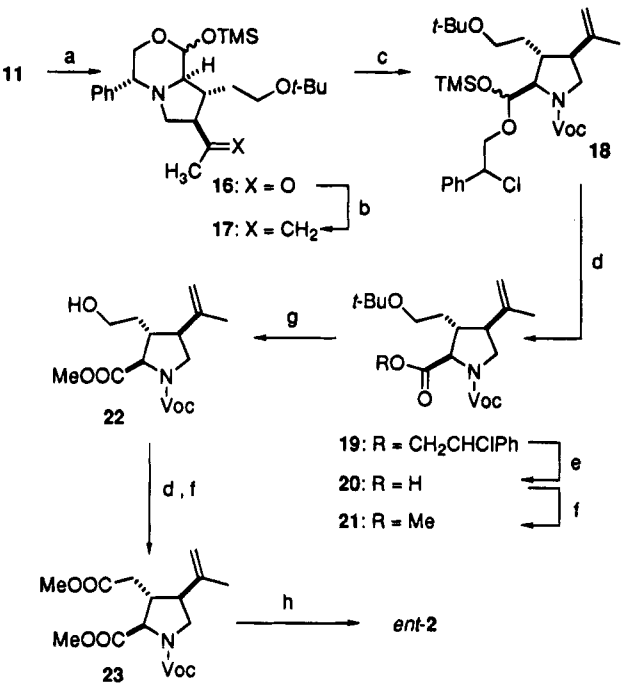
[a] Reaction conditions: (a) OHCCHO, 2 equiv HCl 1 N, 1 equiv, THF:H_2O (50:50), rt, 72 h, 65%; (b) HCl 1 N, 2 equiv, THF:H_2O (50:50), rt, 72 h, 37%.

the kainate numbering of *ent*-**2**). The second element is the *E* stereochemistry of the ethylenic linkage in aminodiol **8** which accounts for the stereospecific formation of the C-3 center. Finally, the relative configuration of the C-2 and C-4 centers was precedented by the clear outcome of similar aza-Cope/Mannich tandem reactions.[14] This method should provide access to a large array of kainoid analogs.

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra ($CDCl_3$ solutions unless otherwise stated) were respectively carried out at 200 and 50 MHz. Melting points are uncorrected. All reactions were run under nitrogen. Column chromatography was performed on silica gel, 230–400 mesh. THF was distilled from benzophenone ketyl; CH_2Cl_2 was distilled from CaH_2. Mention of "usual workup" means (i) decantation of the organic layer, (ii) extraction of the aqueous layer with ether, (iii) drying of the combined organic layers over $MgSO_4$, (iv) solvent evaporation under reduced pressure. Compositions of stereoisomeric mixtures were determined by NMR analysis on crude products before any purification.

Scheme 4[a]



[a] Reaction conditions: (a) TMSCl, DMAP, CH_2Cl_2, 98%; (b) $CH_3P(C_6H_5)_3Br$, BuLi, THF, 85%; (c) vinyl chloroformate (VocCl), CH_2Cl_2, 81%; (d) Jones reagent, 50% (**19**) and 44% (**20**, crude yield); (e) LiOH, THF:EtOH:H_2O (2:2:1); (f) K_2CO_3, MeI, DMF, **21**: 71% overall yield from **18**, **23**: 51% overall yield from **21**; (g) $TiCl_4$, CH_2Cl_2; (h) NaOH, EtOH:H_2O (50:50), purification via the Cu^{2+} salt,[6b] 75%.

Ethyl 6-*tert*-Butoxy-2-hydroxy-2-methylhex-3-ynoate (13). To a solution of *tert*-butyl ether **12** (12.4 g, 98 mmol) in dry THF (200 mL) was added dropwise at 0 °C a solution of *n*-butyllithium in hexane (1.6 N solution, 60 mL, 98 mmol). After being stirred for 0.25 h at 0 °C, the solution was cooled at −78 °C and transferred dropwise (1h) by cannulation into a solution of ethyl pyruvate (11.3 g, 98 mmol) in dry THF (100 mL) at −78 °C. The resulting solution was stirred at −78 °C for 0.5 h and hydrolyzed by addition of a saturated aqueous solution of NH_4Cl (50 mL). The usual workup gave **13** as a clear oil (20.4 g, 86%). ^1H NMR: 1.12 (s, 9H), 1.46 (t, J = 7 Hz, 3H), 1.58 (s, 3H), 2.34 (t, J = 7 Hz, 2H), 3.38 (t, J = 7 Hz, 2H), 3.45 (bs, 1H), 4.21 (q, J = 7 Hz, 2H); ^{13}C NMR: 14, 21.1, 27.3, 27.5, 60.2, 62.6, 68, 73.1, 82, 84.3, 171.8; IR ($CHCl_3$): 3680, 3500, 2140, 1730 cm^{-1}. Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.43; H, 9.15. Found: C, 64.49; H, 9.14.

(2*RS*)-6-*tert*-Butoxy-2-hydroxy-2-methylhex-3-ynoic Acid (1*R*)-2-Hydroxy-1-phenyl-1-ethylamide (14). A suspension of (*R*)-phenylglycinol (11.6 g, 85 mmol) and ester **13** (20.4 g, 85 mmol) in toluene (200 mL) was refluxed in a Dean-Stark apparatus filled with $CaCl_2$ for 2h. Evaporation of the solvent gave a residue which was subjected to flash chromatography (E/EP: 75/25, then E/EP: 100/0). The two diastereoisomers were obtained as a clear oil in a 1 : 1 ratio (21.4 g, 77%).

Faster eluting diastereoisomer (oil) ^1H NMR: 1.20 (s, 9H), 1.69 (s, 3H), 2.1 (bs, 1H), 2.45 (t, J = 7 Hz, 2H), 2.8 (bs, 1H), 3.45 (t, J = 7 Hz, 2H), 3.8–4.0 (m, 2H), 4.95–5.1 (m, 1H), 7.25–7.5 (m, 6H); ^{13}C NMR: 21.1, 27.4, 29.3, 56.9, 60.2, 65.9, 69.2, 73.5, 81, 83.9, 126.5, 127.8, 128.8, 138.6, 172.8; $[\alpha]^{20}_D$: −1.1 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$): 3600, 3400, 2250, 1675 cm^{-1}; mass

(14) Jacobsen, E. J.; Levin, J.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4329.

spectrum m/e 303 (10), 261 (10), 113 (100), 57 (85); exact mass calcd for $C_{19}H_{27}O_3N$ (M^+-OH) m/z = 316.1912, found m/z = 316.1911.

Slower eluting diastereoisomer (oil): ^1H NMR: 1.18 (s, 9H), 1.67 (s, 3H), 2.42 (t, J = 7 Hz, 2H), 3.45 (bs, 1H), 3.46 (t, J = 7 Hz, 2H), 3.75–3.9 (m, 2H), 4.25 (bs, 1H), 4.95–5.1 (m, 1H), 7.25–7.5 (m, 6H); ^{13}C NMR: 21.0, 27.5, 29.2, 55.9, 60.1, 65.9, 69.1, 73.4, 80.9, 83.7, 126.5, 127.8, 128.7, 138.5, 172.7; $[\alpha]^{20}_D$: −23.5 (c 1.1, $CHCl_3$).

(*E*)-(2*RS*)-6-*tert*-Butoxy-1[(1*R*)-2-hydroxy-1-phenylethylamino]-2-methylhex-3-en-2-ol (8). A mixture of the two amide epimers **14** (11 g, 33 mmol) in dry THF (75 mL) was added dropwise into a suspension of $LiAlH_4$ (10 g, 0.26 mol) in THF (600 mL). The resulting mixture was refluxed for 20 h and hydrolyzed by successive addition of water (10 mL), 15% aqueous NaOH (10 mL), and water (30 mL). The resulting suspension was stirred vigorously for 1h and filtrated over a pad of Celite. Evaporation of the solvent gave crude amino alcohol **8** (10 g, 94%, 1:1 mixture of stereoisomers at the tertiary alcohol moiety). This crude mixture was used without further purification in the next step. An analytical sample was purified by flash chromatography (EP/E : 0/100) and displayed the following analytical data:

Faster eluting diastereoisomer (oil) ^1H NMR: 1.19 (s, 12H), 2.24 and 2.31 (AB, J = 6.8 Hz, 2H), 2.45 and 2.52 (AB, J = 11.6 Hz, 2H), 2.71 (bs, 3H), 3.38 (dd, J = 7.1 and 8.5 Hz, 2H), 3.5–3.8 (m, 3H), 5.51 (d, J = 15.6 Hz, 1H), 5.73 (td, J = 5.9 and 15.6 Hz, 1H), 7.2–7.4 (m, 5H); ^{13}C NMR: 26.1, 27.5, 33.6, 56.6, 61.4, 64.7, 67.1, 71.6, 73, 126.1, 127.3, 127.6, 128.6, 137, 140.3; IR ($CHCl_3$): 3600, 2920, 2860, 1665, 1600, 1360 cm-1; $[\alpha]^{20}_D$ −50.8 (c 0.9, $CHCl_3$); exact mass calcd for $C_{19}H_{31}O_3N$ (M^+) m/z = 321.2304, found m/z = 321.2306.

Slower eluting diastereoisomer (oil) ^1H NMR: 1.10 (s, 12H), 2.15 and 2.21 (AB, J = 6.6 Hz, 2H), 2.33 and 2.47 (AB, J = 10.2 Hz, 2H), 3.2–3.7 (m, 5H), 5.38 (d, J = 15 Hz, 1H), 5.61 (td, J = 6 and 15 Hz, 1H), 7.1–7.3 (m, 5H); ^{13}C NMR: 26.3, 27.5, 33.5, 57.1, 61.3, 65, 66.8, 72, 72.9, 126.1, 127.1, 127.5, 128.6, 136.9, 140.7. $[\alpha]^{20}_D$ −1.1 (c 1.2, $CHCl_3$).

(1*R*)-1-[(1*RS*,4*R*,8*R*)-8-(2-*tert*-Butoxyethyl)-1-hydroxy-4-phenylhexahydropyrrolo[2,1-c][1,4] oxazin-7-yl]ethanone (11) and Tricyclic Compound 15. To a solution of the above crude amino alcohol **8** (10.4 g, 32.3 mmol) in THF (60 mL) and water (30 mL) cooled at 0 °C was added successively an aqueous solution of HCl (1N solution, 32.3 mL, 32.3 mmol) and an aqueous solution of glyoxal (40% wt, 9.54 mL, 64.6 mmol). The resulting solution was stirred at rt for 72 h and neutralized by addition of 50 mL of a saturated aqueous solution of $NaHCO_3$. Addition of water (150 mL) followed by the usual workup gave a residue which was subjected to flash chromatography (E/EP: 70/30, then E/EP: 100/0). The following compounds were obtained by order of elution:

(i) Tricyclic compound **15**, mixture of stereoisomers (2.2 g, 20%), oil: ^1H NMR: 1.1–1.3 (m, 2H), 2.05–2.25 (m, 2H), 2.65–3 (m, 2H), 3.2–3.6 (m, 4H), 3.6–4.1 (m, 2H), 4.69 (bs, 1H), 5.53 (bs, 1H), 5.55–5.8 (m, 2H), 7.1–7.4 (m, 5H); ^{13}C NMR (major stereoisomer): 15.4, 26.7, 27.7, 33.8, 59.4, 61.5, 66, 73, 78.9, 88.8, 89.8, 124.8, 128.3, 128.4, 137.9, 139; mass spectrum m/e 315 (10), 229 (25), 191(20), 104 (100).

(ii) Ketone **11**, 70/30 mixture of epimers (5.21 g, 45%), amorphous solid, ^1H NMR: 1.04 and 1.07 (two s, 9H), 1.1–1.9 (m, 3H), 2.09 and 2.1 (two s,3H), 2.5–2.9 (m, 5H), 3.2–3.4 (m, 2H), 3.6–3.8 (m, 2H), 3.95–4.1 (m, 1H), 4.87 (d, J = 4.5 Hz, 0.7H), 5.18 (d, J = 2 Hz, 0.3H), 7.2–7.4 (m, 5H); ^{13}C NMR (signals belonging to the major stereoisomer are italicized): *27.5, 28.9*, 29.1, *33.4*, 34.5, 37.7, *40, 52.5, 56.4*, 57, *59.3, 60*, 60.4, 65, 65.2, *65.6, 66.6*, 73.2, *73.4*, 93.3, *95.6, 127.6, 128.3, 129.2*, 137.3, *137.9, 209.3*, 209.5; IR ($CHCl_3$): 3600, 3300, 2870, 1710 cm^{-1}; mass spectrum m/e 343 (15), 332 (15), 258 (16), 104 (100); exact mass calcd. for $C_{21}H_{31}NO_4$ (M^+) m/z = 361.2253, found m/z = 361.2254.

Ketone 11 from Tricyclic Compound 15. A solution of the above tricyclic compound (1.67g, 2.32 mmol) in THF (20 mL), water (15 mL) and aqueous solution of HCl (1N solution, 4.6 mL, 4.6 mmol) was stirred at rt for 72 h. Treatment as described above gave, after flash chromatography, ketone **4** (601 mg, 37%).

(1*R*)-1-[(1*RS*,4*R*,8*R*)-8-(2-*tert*-Butoxyethyl)-4-phenyl-1-[(trimethylsilyl)oxy]hexahydropyrrolo[2,1-c][1,4]oxazin-7-yl]ethanone (16). Trimethylchlorosilane (3.7 mL, 34 mmol) was added dropwise at 0 °C into a solution of hemiacetal **11** (3.5 g, 9.69 mmol) and DMAP (4.15 g, 34 mmol) in dry dichloromethane (350 mL). The resulting suspension was stirred at rt for 0.25 h, and water (200 mL) was added. Usual workup gave an oily residue which was chromatographied (E/EP: 50/50) over a column of neutral alumina (50 g). Silylated hemiacetal **16** was obtained as a clear oil (4.1 g, 98%), 80/20 mixture of epimers at C-1. ^1H NMR: 0.16 and 0.19 (two s, 9H), 1.09 and 1.11 (two s, 9H), 1.1–1.9 (m, 3H), 2.12 and 2.13 (two s, 3H), 2.5–3 (m, 4H), 3.2–3.45 (m, 2H), 3.5–3.7 (m, 2H), 3.9–4.1(m, 1H), 4.95 (d, J = 3.2 Hz, 0.8H), 5.25 d, J = 2.1 Hz, 0.2H), 7.2–7.5 (m, 5H); ^{13}C NMR (signals belonging to the major stereoisomer are italicized): *0.1, 27.4*, 28.3, *29.1, 34.4*, 35, 38.5, *39.2, 53.1*, 54.5, *56.7*, 57.3, *59.3*, 60, *60.2*, 60.6, 65.3, *66.1*, 66.3, *67.4, 72.5*, 94.3, *95.1, 127.4, 128.1, 128.8, 138.4*, 139.2, 209, *209.2*; IR ($CHCl_3$): 2860, 1705, 1600, 1360 cm^{-1}; exact mass calcd. for $C_{24}H_{39}O_4NSi$ (M^+) m/z = 433.2648, found m/z = 433.2647.

(1*RS*,4*R*,7*R*,8*R*)-8-(2-*tert*-Butoxyethyl)-7-isopropenyl-4-phenyl-1-[(trimethylsilyl)oxy]hexahydropyrrolo[2, 1-c][1, 4]oxazine (17). To a suspension of methyltriphenylphosphonium bromide (8.9 g, 25 mmol) in dry THF (150 mL) was added dropwise at 0 °C a solution of n-butyllithium in hexane (1.6N solution, 15.6 mL, 25 mmol). The orange slurry was stirred at 0 °C for 0.25 h and a solution of **16** (4.1 g, 9.4 mmol) in THF (50 mL) was then added dropwise at 0 °C. The yellow suspension was stirred for 0.5 h and a saturated aqueous solution of NH_4Cl was added until the yellow color faded. Addition of water (150 mL) and usual workup gave a semi solid residue which was washed with small portions of E/EP: 50/50. Evaporation of the combined organic layers gave an oily residue which was chromatographied over a column of neutral alumina (50 g). Elution with E/EP: 20/80 gave **17** as a clear oil (3.44 g, 85%), 88/12 mixture of epimers. ^1H NMR: 0.24 and 0.25 (two s, 9H), 1.17 and 1.19 (two s, 9H), 1.2–1.9 (m, 3H), 1.72 and 1.77 (two s, 3H), 1.75–2.15 (m, 1H), 2.3–2.5 (m, 1H), 2.6–2.9 (m, 2H), 3.38 (t, J = 7.3 Hz, 2H), 3.6–3.9 (m, 2H), 4.06 (dd, J = 5.2 and 12.1 Hz, 0.88H), 4.1–4.25 (m, 0.12H), 4.73 (bs, 1H), 4.82 (bs, 1H), 4.97 (d, J = 5.5 Hz, 0.88H), 5.32 (d, J = 2Hs, 0.12H), 7.2–7.5 (m, 5H); ^{13}C NMR (major stereoisomer): 0.25, 20.1, 27.5, 35.2, 40.8, 51.8, 55.8, 59.8, 60.5, 66.2, 72.3, 96.6, 110.6, 127.1, 127.8, 128.6, 139.2, 147; IR ($CHCl_3$): 1640, 1600, 1450 cm^{-1}; exact mass calcd for $C_{25}H_{41}O_3NSi$ (M^+) m/z = 431.2856, found m/z = 431.2853.

(2*R*,3*R*,4*R*)-3-(2-*tert*-Butoxyethyl)-2-[(*RS*,2*S*)-(2-chloro-2-phenylethoxy)[(trimethylsilyl)oxy]methyl]-4-isopropenylpyrrolidine-1-carboxylic Acid Vinyl Ester (18). A solution of **17** (230 mg, 0.53 mmol) in dichloromethane (3 mL) and vinyl chloroformate (1.5 mL) was refluxed for 1h. Evaporation to dryness gave an oily residue which was flash chromatographied over silica gel (E/EP: 10/90). Carbamate **18** was obtained as a clear oil (212 mg, 81%). ^1H NMR (due to the conformational exchange of the carbamate moiety, the ^1H and ^{13}C spectra showed some splitted resonances for compounds **18–23**): 0.1 and 0.25 (two s, 9H), 1.15 and 1.16 (two s, 9H), 1.56 and 1.72 (two s, 3H), 1.6–1.85 (m, 2H), 2.4–2.7 (m, 2H), 2.9–3.1 (m, 1H), 3.25–3.45 (m, 2H), 3.7–4.2 (m, 4H), 4.4–4.5 (m, 1H), 4.7–5.05 (m, 4H), 5.19 (d, J = 2.2 Hz, 0.47 H), 5.32 (d, J = 2.2 Hz, 0.53 H), 7.15–7.45 (m, 6H); ^{13}C NMR: 0.13, 0.26, 19.1, 19.3, 27.5, 34.4, 37, 37.9, 51.2, 52, 59.4, 59.9, 60.7, 61.2, 65, 65.3, 72.1, 72.4, 72.7, 95.2, 96.3, 97.9, 113.4, 127.4, 128.5, 138.6, 142.2, 142.9, 151.4, 151.7; mass spectrum m/e 522 (20), 343 (50), 315 (50), 296 (100); exact mass calcd for $C_{28}H_{43}O_5NSiCl$ (M^+-H) m/z = 536.2599, found m/z = 536.2596.

(2*R*,3*R*,4*R*)-3-(2-*tert*-Butoxyethyl)-4-isopropenylpyrrolidine-1,2-dicarboxylic Acid 2-(2*R*)-(2-Chloro-2-phenylethyl) Ester 1-Vinyl Ester (19) and (2*R*,3*R*,4*R*)-3-(2-*tert*-butoxyethyl)-4-isopropenylpyrrolidine-1,2-dicarboxylic Acid 1-Vinyl Ester (20). Jones reagent (2.67 N, 12 mL, 42 mmol) was added dropwise at 0 °C to a solution of carbamate **18** (1.9 g, 3.86 mmol) in acetone (100 mL). The mixture was allowed to reach 20 °C and water (3.3 mL) was added. After having been stirred for 1 h, the slurry was cooled with an ice bath and isopropanol (3.2 mL) was added dropwise. Stirring was maintained 0.5 h. After addition of water (150 mL), the mixture was extracted with ether (3 × 100 mL), the combined etheral layers were washed with a saturated aqueous solution of $NaHCO_3$ (2 × 30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was flash chromatographied (E/EP: 40/60) to give ester **19** as an oil (821 mg, 50%). The basic aqueous layers were

combined, acidified to pH 1–2 by addition of an aqueous solution of 1N HCl, and extracted with ether (3 × 40 mL). The combined etheral layers were dried over $MgSO_4$ and concentrated under reduced pressure to give crude acid **20** as an oil (560 mg).

Ester **19**: ^{1}H NMR: 1.14 (s, 9H), 1.68 (s, 3H), 1.6–1.8 (m, 2H), 2.2–2.4 (m, 1H), 2.5–2.7 (m, 1H), 3.15–3.5 (m, 3H), 3.76 and 3.81 (two dd, J = 2.3 and 7.7 Hz, 1H), 4.08 and 4.13 (two d, J = 8 Hz, 1H), 4.35–4.55 (m, 3H), 4.65 and 4.83 (two dd, J = 8 and 1.5 Hz, 1H), 4.87 (s, 2H), 5.05–5.15 (m, 1H), 7.05–7.25 (m, 1H), 7.25–7.5 (m, 5H); ^{13}C NMR: 19.2, 19.3, 27.5, 32.8, 32.9, 43.2, 44.2, 50.6, 50.8, 51, 51.9, 58.6, 59.2, 59.4, 64.6, 64.8, 68.2, 68.4, 72.7, 95.6, 114.3, 127.5, 128.7, 137.4, 137.6, 141.5, 142, 142.3, 151.1, 151.7, 171.4, 171.8; IR ($CHCl_3$): 2920, 1720, 1740, 1640 cm^{-1}. $[\alpha]^{20}_D$ + 61.4 (c 0.82, $CHCl_3$); mass spectrum m/e 407 (25), 364 (30), 336 (65), 57 (100); exact mass calcd for $C_{25}H_{34}O_4NCl$ (M^+) m/z = 463.2125, found m/z = 463.2124.

Crude acid **20**: ^{1}H NMR: 1.13 and 1.15 (two s, 9H), 1.65 (s, 3H), 1.65–1.9 (m, 2H), 2.15–2.35 (m, 1H), 2.4–2.6 (m, 1H), 3.2–3.6 (m, 3H), 3.77 and 3.81 (two dd, J = 2.3 and 7.7 Hz, 1H), 4.36 (td, J = 6.2 and 1.5 Hz, 1H), 4.69 ((td, J = 14 and 1.5 Hz, 1H), 4.83 and 4.84 (two s, 2H), 6.95–7.2 (m, 1H), 9.58 (bs, 1H); ^{13}C NMR: 19.3, 27.3, 33.4, 44.1, 45.1, 50.1, 51.9, 52.7, 74.6, 74.7, 96, 114.7, 128.1, 128.9, 142, 142.2, 175.1, 175.3.

Saponification of Ester 19. Lithium hydroxyde monohydrate (635 mg, 15.12 mmol) was added at 0 °C to a solution of ester **19** (700 mg, 1.51 mmol) in a EtOH/THF/H_2O: 2/2/1 mixture (15 mL) . The resulting suspension was stirred at rt for 5 h, carefully acidified (pH 1–2) by addition of aqueous 1N HCl and extracted with ether (3 × 30 mL). Usual workup gave crude acid **20** as an oil (740 mg).

(2*R*,3*R*,4*R*)-3-(2-*tert*-Butoxyethyl)-4-isopropenylpyrrolidine-1,2-dicarboxylic Acid 2-Methyl Ester 1-Vinyl Ester (21). Methyl iodide (0.8 mL) was added to a suspension of crude acid **9** (1.57 g) and K_2CO_3 (1.57 g) in DMF (50 mL). The mixture was stirred at rt for 1 h, diluted with water (100 mL) and extracted with ether (3 × 40 mL). Usual workup followed by flash chromatography (E/EP: 70/30) gave ester **21** as an oil (930 mg, 71% overall yield from carbamate **18**). ^{1}H NMR: 1.17 (s, 9H), 1.70 (s, 3H), 1.65–1.75 (m, 2H), 2.15–2.40 (m, 1H), 2.40–2.60 (m, 1H), 3.25–3.45 (m, 3H), 3.73 and 3.74 (two s, 3H), 3.65–3.8 (m, 1H), 4.04 and 4.10 (two d, J = 8.1 Hz, 1H), 4.39 and 4.42 (two dd, J = 4.7 and 1.5 Hz, 1H), 4.61 and 4.85 (two dd, J = 14 and 1.5 Hz, 1H), 4.87 and 4.88 (two s, 2H), 7.05–7.2 (m, 1H); ^{13}C NMR: 19.2, 19.3, 27.5, 33, 43.3, 44.2, 50.6, 50.8, 51.1, 52, 52.2, 58.7, 64.9, 65, 72.7, 95.6, 114.2, 141.5, 142, 142.3, 151.3, 151.8, 172.7, 172.9; IR ($CHCl_3$): 2920, 1710, 1740, 1640 cm^{-1}; $[\alpha]^{20}_D$ + 49.3 (c 1.75, $CHCl_3$). Anal. Calcd for $C_{18}H_{29}NO_5$: C, 63.69; H, 8.61; N, 4.13. Found: C, 63.69; H, 8.61; N, 4.17.

(2*R*,3*R*,4*R*)-3-(2-Hydroxyethyl)-4-isopropenylpyrrolidine-1,2-dicarboxylic Acid 2-Methyl Ester 1-Vinyl Ester (22). To a solution of ester **21** (156 mg, 0.146 mmol) in dry dichloromethane (12 mL) was added dropwise at 0 °C a solution of $TiCl_4$ in dichloromethane (1N solution, 0.78 mL, 0.78 mmol). The resulting solution was stirred at 0 °C for 0.25 h and water (10 mL) was added. Filtration of the mixture through a pad of Celite and usual workup (dichloromethane) gave crude alcohol **22** as an oil (122 mg). This crude compound was used without further purification for the next step. An analytical sample was purified by flash chromatography (E/EP : 60/40). ^{1}H NMR: 1.62 (s, 3H), 1.65–1.95 (m, 2H), 1.96 (bs, 1H), 2.1–2.4 (m, 1H), 2.4–2.6 (m, 1H), 3.2–3.4 (m, 1H), 3.6–3.85 (m, 3H), 3.74 and 3.77 (two s, 3H), 4.07 and 4.12 (two d, J = 8 Hz, 1H), 4.41 (td, J = 4.5 and 1.5 Hz, 1H), 4.65 and 4.75 (two dd, J = 14 and 1.5 Hz, 1H), 4.8–4.9 (m, 2H), 7.0–7.15 (m, 1H); ^{13}C NMR: 19.2, 19.3, 35.2, 35.3, 43.4, 44.4, 50.5, 50.6, 51.6, 52.3, 60.2, 64.4, 64.6, 95.6, 114.2, 141.9, 142.1, 151.4, 174; IR ($CHCl_3$): 3590, 1740, 1640 cm^{-1}. $[\alpha]^{20}_D$+ 50.4 (c 1.6, $CHCl_3$). Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.34; H, 7.47; N, 4.94. Found: C, 59.25; H, 7.59; N, 4.81.

(2*R*,3*R*,4*R*)-4-Isopropenyl-3-[(methoxycarbonyl)methyl]-pyrrolidine-1,2-dicarboxylic Acid 2-Methyl Ester 1-Vinyl Ester (23). Jones reagent (2.67 N, 1.61 mL, 4.3 mmol) was added dropwise at 0 °C to a solution of crude alcohol **11** (122mg, 0.4 mmol) in acetone (10 mL). The mixture was allowed to reach 20 °C and water (0.37 mL) was added. After having been stirred at rt for 1 h, the slurry was cooled with an ice bath and isopropanol (0.37 mL) was added. After 0.25 h, water (20 mL) and ether (20 mL) were added, and usual workup gave an oil (115 mg) which was dissolved in DMF (5 mL). To this solution were added successively solid K_2CO_3 (160 mg) and methyl iodide (0.095 mL); the suspension was then stirred for 1 h. Addition of water (20 mL) and ether (30 mL) followed by usual workup gave an oily residue which was subjected to flash chromatography (E/EP: 40/60). Diester **23** was obtained as a clear oil (63 mg, 51% overall yield from **21**). ^{1}H NMR: 1.72 (s, 3H), 2.45–2.70 (m, 4H), 3.35–3.50 (m, 1H), 3.64 and 3.65 (two s, 3H), 3.78 (s, 3H), 3.7–3.9 (m, 1H), 4.05 and 4.10 (two d, J = 8.5 Hz, 1H), 4.44 (td, J = 6.4 Hz and 1.5 Hz, 1H), 4.72 and 4.81 (two dd, J = 14 and 1.5 Hz, 1H), 4.87 (s, 1H), 4.91 (s, 1H), 7.0–7.2 (m, 1H); ^{13}C NMR: 18.7, 18.9, 35.4, 42.5, 43.3, 50.1, 50.3, 50.4, 51.3, 51.5, 52.3, 64, 64.2, 95.7, 114.8, 140.6, 141.9, 142.1, 151.6, 171.3; IR ($CHCl_3$): 2920, 1740, 1640, 1400, 1360 cm^{-1}. $[\alpha]^{20}_D$ + 40 (c 1.6, $CHCl_3$). Anal. Calcd for $C_{15}H_{21}NO_6$: C, 57.86; H, 6.80; N, 4.50. Found: C, 57.87; H, 6.74; N, 4.37.

(−)-α-Allokainic Acid (*ent*-2). A solution of diester **23** (70 mg, 0.225 mmol) and NaOH (160 mg) in 1/1 ethanol/water (4 mL) was refluxed for 15 h. The mixture was then concentrated under reduced pressure and water (5 mL) was added. This aqueous solution was washed once with ether (10 mL), neutralized to pH 4–5 by addition of aqueous 1N HCl and filtered through a short pad of Celite. To this clear solution was added $Cu(OAc)_2$ (110 mg) and the solution was heated at 100 °C for 1 h. The resulting suspension was filtrated and the light blue solid was washed successively with an aqueous solution of AcOH (2.5% solution, 1 mL), hot water (3 × 1 mL) and acetone (1 mL). The solid was suspended in water (10 mL) and stirred under H_2S for 2 h. The resulting black suspension of CuS was filtrated through Celite and the filtrate was evaporated under reduced pressure to give (-)-α-allokainic acid *ent*-**2** as a light yellow solid residue (42 mg, 75%): mp (dec): 235–38°C.^{1}H NMR (D_2O): 1.52 (s, 3H), 2.2–2.75 (m, 4H), 3.12 (t, J = 11 Hz, 1H), 3.31 (dd, J = 7.5 and 11 Hz, 1H), 3.70 (d, J = 8.2 Hz, 1H), 4.76 (s, 2H); ^{13}C NMR (D_2O): 16.8, 37.1, 41.4, 47.3, 50.7, 64.3, 114.6, 139.6, 174.8, 177.3; mass spectrum m/e 213 (4) (M^+), 123 (20), 108 (43), 44 (100); IR (KBr): 3410, 2940, 1630, 1710 cm^{-1}. $[\alpha]^{20}_D$ −6.3 (c 0.7, H_2O), $[\alpha]^{20}_{365}$ −36.4 (c 0.7, H_2O) (Lit[6b] $[\alpha]^{20}_D$ +7.4 (c 0.7, H_2O), $[\alpha]^{20}_{365}$ +42 (c 0.7, H_2O) for **2**).

Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for compounds *ent*-**2**, **8**, **11**, **14**, and **16-18** (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.