A CONCISE SYNTHESIS OF (+)-α-ALLOKAINIC ACID *VIA* SITE- AND DIASTEREOSELECTIVE INTRAMOLECULAR C-H INSERTION PROCESS

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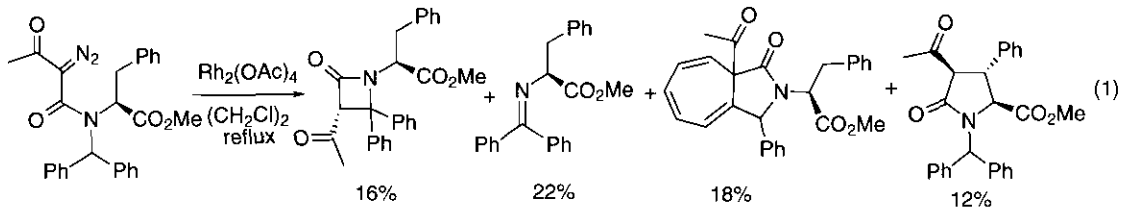
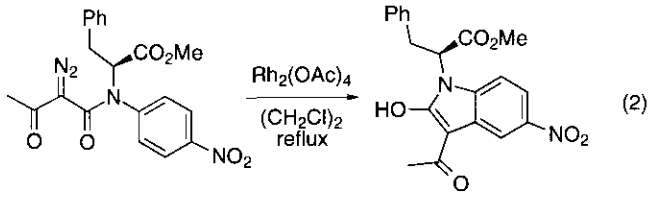
Abstract – A new route to (+)-α-allokainic acid commencing with L-serine has been established, wherein the key step involves a C3-C4 bond formation with a simultaneous creation of a C2, C3-*trans* and C3, C4-*trans* arrangement of substituents by $Rh_2(OAc)_4$-catalyzed C-H insertion reaction of α-diazoacetoacetamide tethered to (*S*)-4-(3-butenyl)-2,2-dimethyl-1,3-oxazolidine system. Taber's computational model confirms the observed diastereomer preference.

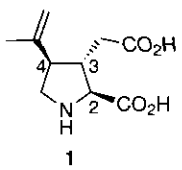
With the advent of dirhodium(II) carboxylate catalysts, intramolecular C-H insertion reactions of α-diazocarbonyl compounds, featuring C-C bond formation at an unactivated carbon atom, have been recognized as a potentially powerful means for the construction of both carbocycles, especially cyclopentanones, and heterocycles.[1] While an enormous amount of effort is being devoted to the realization of their enantioselective version by devising dirhodium(II) catalysts of rationally designed chiral ligands,[2,3] there still exists a continuing demand for appreciable developments in terms of site- and diastereocontrol.[1g,4] In the system where competing C-H insertions are possible, less reliable prediction of the insertion site as well as the stereochemistry of the stereogenic center installed appears to preclude their application to the natural product synthesis.[5] In this context, our interest was centered on the synthesis of naturally occurring nitrogen-containing heterocycles by intramolecular C-H insertion of α-diazo amides derived from L-amino acids. Surprisingly, there is only one precedent in the literature for a related transformation; Zaragoza[6] attempted to develop a practical method for *C*-alkylation of L-amino acids by intramolecular C-H insertion, wherein $Rh_2(OAc)_4$-catalyzed decomposition of *N*-diarylmethyl-*N*-(2-diazo-3-oxobutyryl)-L-phenylalanine esters gave the desired pyrrolidinone in low yield together with the azetidinone, imine, and cycloheptapyrrolidinone derivatives [eqn. (1)]. Since cyclization of the *N*-(4-nitrophenyl) diazoacetoacetamide afforded exclusively the corresponding nitroindole *via* aromatic C-H insertion [eqn. (2)], installation of practically unremovable *tert*-alkyl groups as the *N*-substituents on the amide moiety was considered to be indispensable for a predominant formation of the desired





pyrrolidinone as Doyle pointed out in his pioneering work on rhodium(II)-catalyzed transformations of α-diazo amides.[7] With such a background information, we addressed this problem by exploiting α-diazoacetoacetamide tethered to a 2,2-dimethyl-1,3-oxazolidine system derived from L-amino acid, where the *N,O*-acetal moiety was expected to function as a substitute for the *tert*-butyl group.[3i] Herein we report a new route to (+)-α-allokainic acid from L-serine, incorporating site- and diastereoselective intramolecular C-H insertion reaction as a key step.

The term kainoid refers to a group of naturally occurring non-proteinogenic amino acids possessing a 4-substituted pyrrolidinedicarboxylic acid structure, which has attracted considerable interest owing to their pronounced insecticidal, anthelmintic and principally neuroexcitatory properties.[8,9] Whereas most members of the kainoid family (e.g., (-)-α-kainic acid, domoic acid, acromelic acids) possess the three contiguous stereogenic centers in a C2, C3-*trans*- and C3, C4-*cis*-arrangement of substituents, (+)-α-allokainic acid (**1**), C4-epimer of (-)-α-kainic acid, features all-*trans* relationship coupled with less biological activity. While the non-stereoselective synthetic procedures for (-)-α-kainic acid have also led to the synthesis of **1**,[10] several groups have accomplished the stereocontrolled synthesis of **1** by devising innovative strategies and tactics since the pioneering work of Oppolzer and coworkers employing a Lewis acid-promoted intramolecular ene-type reaction.[11]



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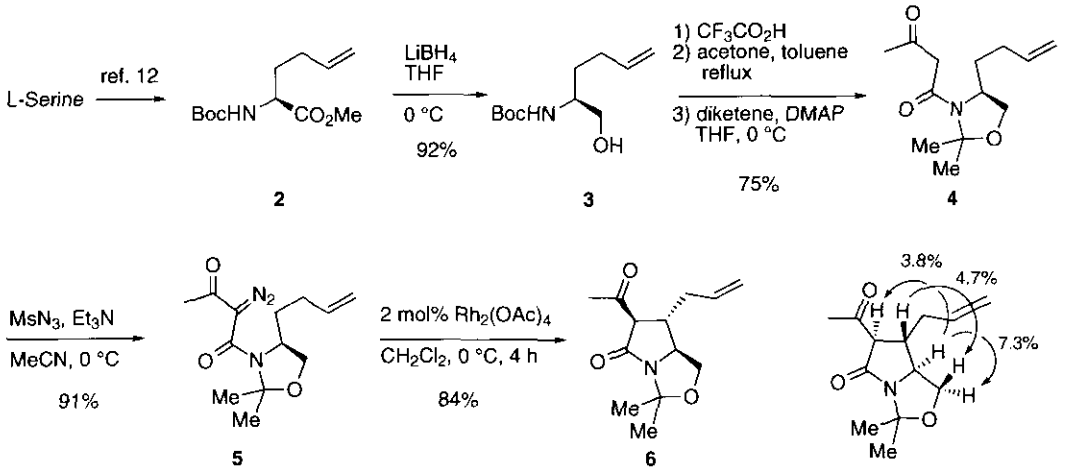
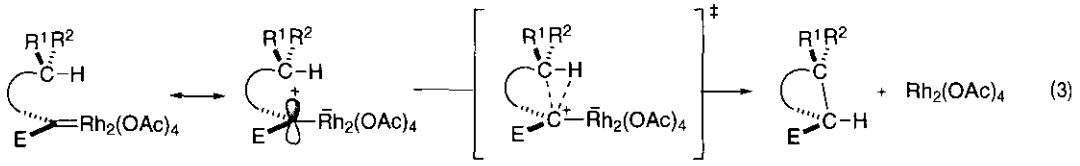
Standard retrosynthetic manipulation of (+)-α-allokainic acid (**1**) based on our intramolecular C-H insertion approach dictated the disconnection of the C3-C4 bond to furnish α-diazoacetoacetamide (**5**) as a potential carbene precursor. The synthesis of **5** was uneventfully implemented as shown in Scheme 1. The *N*-Boc protected amino ester (**2**), readily prepared from L-serine according to literature procedures,[12] was reduced with $LiBH_4$ to give alcohol (**3**) in 92% yield. Deblocking of the Boc group in **3** with TFA was followed by sequential condensation with acetone and diketene to furnish 1,3-oxazolidine (**4**) in 75% overall yield, which, upon diazo transfer with methanesulfonyl azide, produced α-diazoacetoacetamide (**5**) in 91% yield. The stage was now set for the key C-H insertion reaction. To our delightful surprise, cyclization of **5** with the aid of 2 mol % of $Rh_2(OAc)_4$ proceeded smoothly at 0 °C to give the desired pyrrolidinone (**6**) as the sole product in 84% yield, no trace of 2-azetidinone derivative being detected

due probably to its high strain energy. The all-*trans* relationship of the C2, C3, and C4 hydrogens was rigorously established by ^{1}H NOE experiment.



Scheme 1

The virtually complete diastereoselection in the present C-H insertion can be explained by the mechanistic hypothesis proposed originally by Doyle[13] and refined later by Taber,[14] wherein it is requisite that the rhodium(II)-carbene bond is in parallel with the target C-H bond in a three-centered, *two electron transition state via* overlap of the empty *p*-orbital of the carbene's carbon with the σ-orbital of the reacting C-H bond [eqn. (3)]. Assuming that overlap of the nitrogen nonbonded electrons with the



(3)

carbonyl π-system fixes the amide conformation, two competing transition states (**A**) and (**B**) can be presented (Figure 1). In this regard, plausible cyclizations *via* the rhodium(II)-carbene intermediates (**C**) and (**D**) can be disregarded due to little overlap between the Rh-C bond and the target C-H bond. The high preference for the transition state (**A**) over the transition state (**B**) is understandable by considering the severe steric repulsion between the allyl substituent at the insertion site and the acetyl and methyl groups, leading to the predominant formation of pyrrolidinone (**6**) in accord with the observed diastereoselection. It is noteworthy that the computational method developed by Taber[14] estimates the transition state (**A**) to be favored by 3.8 kcal/mol compared to the transition state (**B**).

With an efficient access to the pyrrolidinone (**6**) secured, we then proceeded to the elaboration of the target molecule (Scheme 2). Protection of **6** as an ethylene acetal was accompanied by deprotection of the isopropylidene group to give alcohol (**7**) in 95% yield. Reduction of **7** with $LiAlH_4$ followed by protection with methyl chloroformate afforded *N*-methoxycarbonyl protected pyrrolidine (**8**) in 87%

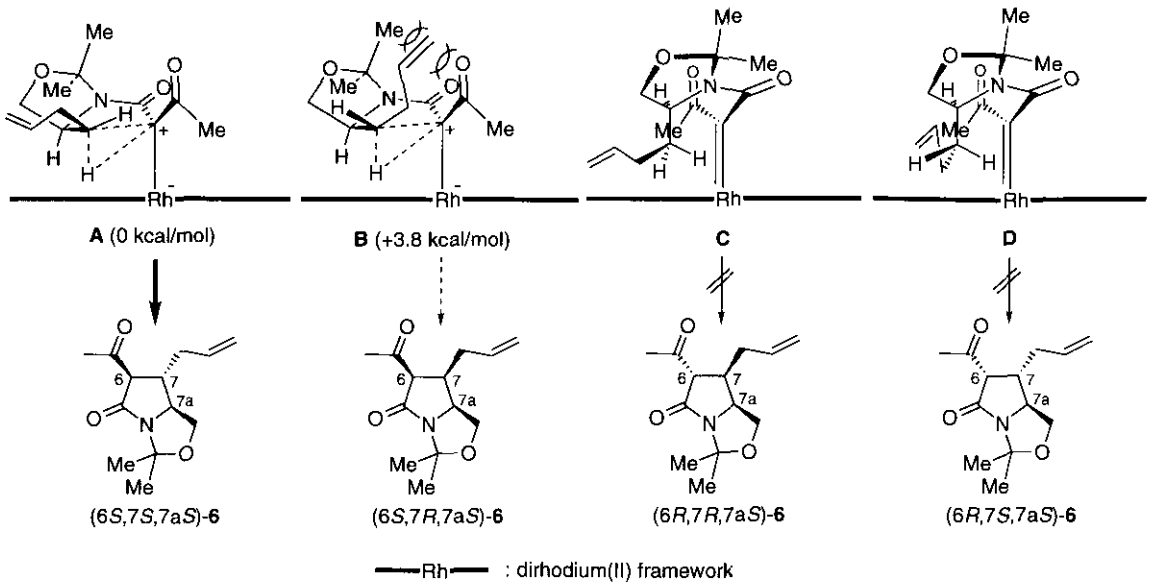
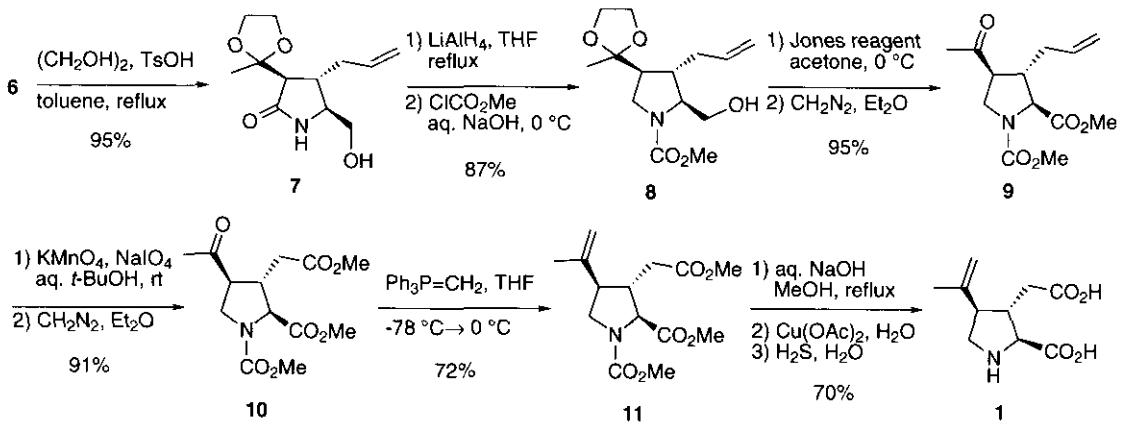


Figure 1. Putative rhodium(II) carbene intermediates leading to pyrrolidinone **6**

yield. Jones oxidation[15] of the hydroxy group in **8** with concomitant unmasking of the ketone carbonyl group was followed by treatment with diazomethane to furnish methyl ester (**9**) in 95% yield. Oxidative cleavage of the vinyl group in **9** under Lemieux-von Rudloff conditions[16] followed by esterification with diazomethane produced dimethyl ester (**10**) in 91% yield, which, upon Wittig methylenation, furnished the protected α-allokainic acid (**11**), $[\alpha]_D^{22}$ -34.6° (c=1.45, $CHCl_3$) {lit.,[11e] $[\alpha]_D^{24}$ -34.5° (c=1.33, $CHCl_3$)}, in 72% yield. Finally, following literature precedent,[11b] **11** was hydrolyzed to give (+)-α-allokainic acid (**1**), mp 230-237 °C (decomp), $[\alpha]_D^{24}$ +7.5° (c=1.22, H_2O) {lit.,[11b] mp 238-242 °C (decomp), $[\alpha]_D^{23}$ +7.4° (c=0.7, H_2O)}, in 70% yield, which exhibited identical spectroscopic data with those reported for **1** (IR, ^1H NMR, ^{13}C NMR, HRMS).[11f]

In conclusion, we have developed a new route to (+)-α-allokainic acid from L-serine, wherein the 1,3-oxazolidine ring tethered to α-diazoacetoacetamide group plays a role not only as a protecting group for



Scheme 2

amino and hydroxyl groups but more importantly as a rigid template for controlling site-selectivity and diastereoselectivity during the key $Rh_2(OAc)_4$-catalyzed intramolecular C-H insertion. It is also noteworthy that the present finding represents the first successful example of *C*-alkylation of α-amino acid derivatives by the C-H insertion methodology.

EXPERIMENTAL

General. Melting points were determined on a Büchi 535 digital melting apparatus and are uncorrected. IR spectra were recorded on a Jasco FT/IR-5300 spectrophotometer. NMR spectra were measured with JEOL JNM-EX 270 (^{1}H at 270 MHz and ^{13}C at 67.8 MHz) or JEOL JNM-AL 400 (^{1}H at 400 MHz and ^{13}C at 100 MHz) spectrometer, with tetramethylsilane (δ 0.0, ^{1}H) or chloroform-d_1 (δ 77.0, ^{13}C) as an internal standard. Electron impact MS spectra (EIMS) were obtained on a JEOL JMS-DX 303 spectrometer, operating with an ionization energy of 70 eV. Fast atom bombardment MS spectra (FABMS) were obtained on a JEOL JMS-HX 110 spectrometer. Optical rotations were measured on a Jasco DIP-370 digital polarimeter. THF and toluene were distilled from sodium/benzophenone. Dichloromethane and acetonitrile were distilled from CaH_2. Column chromatography was performed on Merck silica gel 60, 70-230 mesh.

(*S*)-2-(*tert*-Butoxycarbonyl)amino-5-hexen-1-ol (3). A solution of methyl (*S*)-2-(*tert*-butoxycarbonyl)amino-5-hexenoate[12] {**2**, $[\alpha]_D^{23}$ -18.9° (c=1.13, $CHCl_3$), 6.80 g, 28 mmol} in THF (10 mL) was added dropwise to a solution of $LiBH_4$ (588 mg, 28 mmol) in THF (10 mL) at 0 °C. After 6 h of stirring at this temperature, the reaction was quenched with water (1 mL). The whole mixture was poured into an ice-cooled, two-layer mixture of AcOEt (100 mL) and water (30 mL), and layers were separated. The organic layer was washed successively with water (2 x 30 mL), and brine (2 x 30 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* furnished the crude product (7.2 g of colorless oil), which was purified by column chromatography on silica gel (60 g) with AcOEt-hexane (3:1) to give **3** (5.55 g, 92%) as a colorless oil; IR νmax (film): 3364, 3078, 2978, 1694, 1526, 1171, 912 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.41 (s, 9H, ^{t}Bu), 1.45-1.64 (m, 2H, C3-*H*), 2.09 (br q, *J* = 7.0 Hz, 2H, C4-*H*), 3.03 (br s, 1H, O*H*), 3.51-3.63 (m, 3H, C1-*H* and C2-*H*), 4.82 (br s, 1H, N*H*), 4.93 (d, *J* = 10.3 Hz, 1H, C6-*H*), 5.01 (d, *J* = 18.6 Hz, 1H, C6-*H*), 5.77 (ddt, *J* = 10.3, 18.6, 7.0 Hz, 1H, C5-*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 28.3 (CH_3), 30.1 (CH_2), 30.6 (CH_2), 52.2 (CH), 65.3 (CH_2), 79.5 (C), 115.0 (CH_2), 137.7 (CH), 156.4 (C); FABMS *m/z* : 216 (M^++1); HRMS (FAB) *m/z*: Calcd for $C_{11}H_{22}NO_3$, 216.1608. Found 216.1604; $[\alpha]_D^{23}$ -11.8° (c=2.00, $CHCl_3$) .

(*S*)-4-(3-Butenyl)-2,2-dimethyl-3-(1,3-dioxobutyl)-1,3-oxazolidine (4). A solution of **3** (5.50 g, 25 mmol) in CH_2Cl_2 (10 mL) was added to TFA (10 mL) at 0 °C. After 4 h of stirring at this temperature, the mixture was concentrated under reduced pressure. The residue was subjected to ion-exchange resin (Amberlite IRA-400, 30 g, water as eluent) to afford (*S*)-2-amino-5-hexen-1-ol (3.01 g of colorless syrup), which was used without further purification; IR νmax (film): 3347, 3077, 2926, 1642, 1575, 1059, 912 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.25-1.59 (m, 2H, C3-*H*), 2.01-2.25 (m, 2H, C4-*H*), 2.84 (dddd, *J* = 3.6, 8.0, 8.0, 12.1 Hz, 1H, C2-*H*), 3.27 (dd, *J* = 8.0, 11.2 Hz, 1H, C1-*H*), 3.48 (s, 1H, O*H*), 3.58 (dd, *J* = 4.0, 11.2 Hz, 1H, C1-*H*), 4.96 (d, *J* = 10.2 Hz, 1H, C6-*H*), 5.06 (d, *J* = 18.6 Hz, 1H, C6-*H*), 5.80 (ddt, *J* = 10.2, 18.6, 6.8 Hz, 1H, C5-*H*).

A stirred solution of (*S*)-2-amino-5-hexen-1-ol (3.01 g, 26 mmol) and acetone (1.74g, 30 mmol) in toluene (50 mL) was refluxed for 6 h under azeotropic removal of water. The solution was cooled to rt, and DMAP (20 mg, 0.16 mmol) was added. A solution of diketene (2.52 g, 30 mmol) in toluene (10 mL) was added to the mixture at 0 °C. After 1.5 h of stirring at this temperature, the reaction was quenched by addition of four pieces of crushed ice (*ca.* 5 x 5 x 5 mm), and the whole was stirred vigorously for 0.5 h, and partitioned between AcOEt (100 mL) and water (50 mL). The separated organic layer was washed successively with saturated $NaHCO_3$ solution (3 x 20 mL), water (2 x 20 mL), and brine (2 x 20 mL), and dried over anhydrous Na_2SO_4. Filtration and concentration *in vacuo* furnished the crude product (7.3 g of dark orange oil), which was purified by column chromatography on silica gel (80 g) with hexane-AcOEt (2:1) to afford **4** (4.54 g, 75%) as a light-brown viscous oil; IR νmax (film): 3079, 2984, 1721, 1642, 1591 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, *ca.* 1:1 mixture of keto/enol tautomers) δ: 1.52 and 1.53 (s, 3H, C2-C*H*$_3$), 1.62 (s, 2.2H, C2-C*H*$_3$), 1.65 (s, 0.8H, C2-C*H*$_3$), 1.69-1.89 (m, 2H, CH_2=CHCH$_2$C*H*$_2$), 1.92 (s, 0.8H, C*H*$_3$-C=), 1.97-2.21 (m, 2H, CH_2=CHC*H*$_2$CH$_2$), 2.27 (s, 2.2H, C*H*$_3$CO), 3.43 (s, 1H, CH_3COC*H*$_2$), 3.70-3.95 (m, 3H, C4-*H* and C5-*H*), 4.86 (s, 0.5H, CH_3C=C*H*CO), 5.02 (d, *J* = 10.5 Hz, 1H, C*H*$_2$=CH), 5.08 (d, *J* = 19.8 Hz, 1H, C*H*$_2$=CH), 5.79 (ddt, *J* = 10.5, 19.8, 6.8 Hz, 1H, CH_2=C*H*), 14.7 (s, 0.5H, enol); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 21.9 (CH_3), 22.7 (CH_3), 23.3 (CH_3), 26.4 (CH_3), 26.8 (CH_3), 30.3 (CH_2), 30.4 (CH_3), 32.5 (CH_2), 33.4 (CH_2), 51.7 (CH_2), 56.7 (CH), 57.6 (CH), 66.6 (CH_2), 89.4 (CH), 95.1 (C), 95.2 (C), 115.9 (CH_2), 116.2 (CH_2), 136.5 (CH), 136.8 (CH), 163.1 (C), 175.1 (C), 202.3 (C); EIMS *m/z* (rel. int. %): 239 (M^+, 1.5), 224 (39), 181 (13), 140 (100); HRMS (EI) *m/z*: Calcd for $C_{13}H_{21}NO_3$, 239.1522. Found 239.1523; $[\alpha]_D^{25}$ -31.9° (c=0.85, $CHCl_3$).

(*S*)-4-(3-Butenyl)-3-(2-diazo-1,3-dioxobutyl)-2,2-dimethyl-1,3-oxazolidine (5). A solution of methanesulfonyl azide (2.57 g, 20 mmol) in MeCN (5 mL) was added to a stirred solution of **4** (4.25 g, 18 mmol) and triethylamine (2.73 g, 27 mmol) in MeCN (10 mL) at 0 °C. After 3 h of stirring at this temperature, the whole mixture was diluted with AcOEt (50 mL). The dark-red solution was washed successively with 10% NaOH solution (3 x 20 mL), water (3 x 20 mL), and brine (2 x 15 mL), and then dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* furnished the crude product (5.7 g of dark orange half solid), which was purified by column chromatography on silica gel (40 g) with hexane-AcOEt (4:1) to afford **5** (4.31 g, 91%) as a pale yellow viscous oil; IR νmax (film): 3079, 2984, 2105, 1721, 1645 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 1.55 (s, 6H, C2-C*H*$_3$), 1.64-1.79 (m, 2H, CH_2=CHCH$_2$C*H*$_2$), 1.95-2.10 (m, 2H, CH_2=CHC*H*$_2$CH$_2$), 2.34 (s, 3H, C*H*$_3$CO), 3.82 (dd, *J* =2.6, 8.6 Hz, 1H, C5-*H*), 3.96 (m, 1H, C4-*H*), 4.08 (dd, *J* = 5.6, 8.6 Hz, 1H, C5-*H*), 5.02 (d, *J* = 10.2 Hz, 1H, (*Z*)-C*H*$_2$=CH), 5.03 (d, *J* = 16.8 Hz, 1H, (*E*)-C*H*$_2$=CH), 5.66-5.81 (ddt, *J* = 10.2, 16.8, 6.3 Hz, 1H, CH_2=C*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 23.6 (CH_3), 26.6 (CH_3) 27.2 (CH_3), 30.1 (CH_2), 33.4 (CH_2), 56.9 (CH), 67.7 (CH_2), 74.7 (C, very weak), 96.2 (C), 115.9 (CH_2), 136.4 (CH), 156.4 (C), 188.7 (C, very weak); FABMS *m/z* : 266 (M^++1); HRMS (FAB) *m/z*: Calcd for $C_{13}H_{20}N_3O_3$, 266.1505. Found 266.1486; $[\alpha]_D^{25}$ +275° (c=1.26, $CHCl_3$); Anal. Calcd for $C_{13}H_{19}N_3O_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 59.06; H, 7.28; N, 15.37.

(6*S*,7*S*,7a*S*)-6-Acetyl-5,6,7,7a-tetrahydro-3,3-dimethyl-7-(2-propenyl)-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-5-one (6). Bis(methanol) adduct of dirhodium(II) tetraacetate (32 mg, 0.062 mmol) was added in one

portion to a stirred solution of **5** (830 mg, 3.1 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The mixture was stirred at this temperature for 4 h, and the solvent was removed *in vacuo*. The residue (920 mg of greenish viscous oil) was purified by column chromatography on silica gel (15 g) with hexane-AcOEt (3:1) to provide **6** (615 mg, 84%) as a colorless viscous oil; IR νmax (film): 3079, 2984, 1694, 1641, 1400, 1356, 1242, 1034, 922 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.44 (s, 3H, C3-C*H*$_3$), 1.56 (s, 3H, C3-C*H*$_3$), 2.05 (dt, *J* = 16.8, 8.0 Hz, 1H, CH_2=CHC*H*$_2$), 2.26 (dt, *J* = 16.8, 7.6 Hz, 1H, CH_2=CHC*H*$_2$), 2.39 (s, 3H, C*H*$_3$CO), 2.75 (dddd, *J* = 7.6, 8.0, 8.5, 10.8 Hz, 1H, C7-*H*), 3.47 (t, *J* = 8.5 Hz, 1H, C1-*H*), 3.64 (d, *J* = 10.8 Hz, 1H, C6-*H*), 3.78 (dt, *J* = 5.6, 8.5 Hz, 1H, C7a-*H*), 4.06 (dd, *J* = 5.6, 8.5 Hz, 1H, C1-*H*), 5.03 (d, *J* = 11.2 Hz, 1H, CH=C*H*$_2$), 5.08 (d, *J* = 18.0 Hz, 1H, CH=C*H*$_2$), 5.63 (dddd, *J* = 7.6, 8.0, 11.2, 18.0 Hz, 1H, C*H*=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.7 (CH_3), 26.5 (CH_3), 30.9 (CH_3), 36.6 (CH_2), 40.0 (CH), 63.7 (CH), 65.8 (CH), 69.3 (CH_2), 91.4 (C), 117.6 (CH_2), 134.8 (CH), 165.6 (C), 202.6 (C); EIMS *m/z* (rel. int. %): 237 (M^+, 1.0), 222 (62), 180 (19), 138 (73), 43 (100); HRMS (EI) *m/z*: Calcd for $C_{13}H_{19}NO_3$, 237.1365. Found 237.1356; $[\alpha]_D^{25}$ +26.2° (c=1.34, $CHCl_3$); Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.41; H, 8.03; N, 5.90.

(3*S*,4*S*,5*S*)-5-Hydroxymethyl-3-(2-methyl-1,3-dioxolan-2-yl)-4-(2-propenyl)-2-pyrrolidinone (7). A stirred solution of **6** (600 mg, 2.5 mmol), ethylene glycol (310 mg, 5.0 mmol) and *p*-toluenesulfonic acid (10 mg, 0.058 mmol) in toluene (30 mL) was refluxed for 2 h under azeotropic removal of water. The solution was cooled to rt, and triethylamine (0.02 mL) was added. Concentration *in vacuo* afforded the crude product (1.02 g of pale brown viscous oil), which was purified by column chromatography on silica gel (15 g) with CH_2Cl_2-MeOH (10:1) to provide **7** (570 mg, 95%) as a colorless viscous oil; IR νmax (neat): 3380, 2936, 1682, 1445, 1044 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 1.52 (s, 3H, C*H*$_3$), 2.12-2.47 (m, 3H, C*H*$_2$CH=CH_2 and C4-*H*), 2.52 (d, *J* = 6.0 Hz, 1H, C3-*H*), 3.31 (br-s, 1H, O*H*), 3.38-3.49 (m, 2H, C*H*$_2$OH), 3.65-3.72 (m, 1H, C5-*H*), 3.94-4.05 (m, 4H, OC*H*$_2$C*H*$_2$O), 5.10 (d, *J* = 10.4 Hz, CH=C*H*$_2$), 5.12 (d, *J* = 17.1 Hz, 1H, CH=C*H*$_2$), 5.74 (ddt, *J* = 10.4, 17.1, 6.2 Hz, 1H, C*H*=CH_2), 6.99 (br s, 1H, N*H*); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 22.3 (CH_3), 36.6 (CH), 39.4 (CH_2), 54.4 (CH), 59.1 (CH), 64.6 (CH_2), 64.7 (CH_2), 65.2 (CH_2), 109.6 (C), 117.7 (CH_2), 134.9 (CH), 175.9 (C); EIMS *m/z* (rel. int. %): 241 (M^+, 0.04), 226 (5.9), 210 (11), 124 (2.7), 87 (100); HRMS (EI) *m/z*: Calcd for $C_{12}H_{19}NO_4$, 241.1315. Found 241.1319; $[\alpha]_D^{21}$ +24.6° (c=1.66, $CHCl_3$); Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.80. Found: C, 59.23; H, 7.77; N, 5.73.

(2*S*,3*S*,4*S*)-1-(Methoxycarbonyl)-4-(2-methyl-1,3-dioxolan-2-yl)-3-(2-propenyl)pyrrolidine-2-methanol (8). A solution of **7** (550 mg, 2.3 mmol) in THF (5 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (171 mg, 4.5 mmol) in THF (10 mL) at 0 °C. The mixture was refluxed for 12 h, and then cooled to 0 °C. The reaction was quenched by sequential addition of water (0.17 mL), 15% NaOH solution (0.17 mL), and water (0.5 mL), and the mixture was stirred at rt until the gray color has completely disappeared. The suspension was filtered through a Celite pad and the residue was washed with ether-THF (1:1, 2 x 20 mL). The combined filtrates were concentrated *in vacuo* and the residue (560 mg of colorless oil) was mixed with 10% NaOH soluiton (5 mL). A solution of methyl chloroformate (250 mg, 2.6 mmol) in dichloromethane (2 mL) was added dropwise to the mixture at 0 °C. After 1.5 h of stirring at this temperature, the mixture was partitioned between AcOEt (30 mL) and

water (10 mL). The separated organic layer was washed successively with water (2 x 5 mL), and brine (5 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* furnished the crude product (620 mg of colorless oil), which was purified by column chromatography on silica gel (10 g) with AcOEt-hexane (5:1) to afford **8** as a colorless viscous oil (473 mg, 87%); IR νmax (film): 3439, 3076, 2957, 1752, 1698, 1454, 1267, 1161, 756 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 1.25 (s, 3H, C*H*$_3$), 1.60-1.80 (m, 1H, C3-*H*), 1.95 (br s, 1H, O*H*), 2.18-2.38 (m, 3H, CH_2=CHC*H*$_2$ and C4-*H*), 3.22 (t, *J* = 8.1 Hz, 1H, C5-*H*), 3.38-3.49 (m, 3H, HOC*H*$_2$, C2-*H* and C5-*H*), 3.68 (s, 3H, C*H*$_3$O$_2$C), 3.94-4.05 (m, 4H, OC*H*$_2$C*H*$_2$O), 4.28 (br, 1H, O*H*), 5.08 (d, *J* = 10.1 Hz, 1H, C*H*$_2$=CH), 5.11 (d, *J* = 17.4 Hz, 1H, C*H*$_2$=CH), 5.78 (ddt, *J* = 10.1, 17.4, 6.2 Hz, 1H, CH_2=C*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ: 22.3 and 22.5 (CH_3), 37.1 and 41.2 (CH), 37.3 and 39.6 (CH_2), 48.1 (CH_2), 48.8 and 54.1 (CH), 52.5 and 55.2 (CH_3), 54.9 and 65.2 (CH), 64.4 (CH_2), 64.7 (CH_2), 66.1 (CH_2), 70.3 (CH_2), 109.3 and 109.7 (C), 117.8 and 118.1 (CH_2), 134.5 and 134.9 (CH), 155,3 and 157.1 (C); EIMS *m/z* (rel. int. %): 285 (M^+, 0.3), 270 (2.0), 254 (47), 87 (100); HRMS (EI) *m/z*: Calcd for $C_{14}H_{23}NO_5$, 285.1576. Found 285.1605; $[\alpha]_D^{25}$ -8.65° (c=1.03, $CHCl_3$); Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 58.53; H, 8.08; N, 4.99.

Methyl (2*S*,3*S*,4*S*)-4-acetyl-1-methoxycarbonyl-3-(2-propenyl)pyrrolidine-2-carboxylate (9). Jones reagent[15] (2.67 M, 1.5 mL) was added dropwise to a solution of **8** (460 mg, 1.9 mmol) in acetone (5 mL) at 0 °C. The reaction was quenched with 2-propanol (5 mL), and the whole mixture was poured into an ice-cooled, two-layer mixture of ether (30 mL) and saturated $NaHCO_3$ solution (15 mL). After the organic layer was separated, the aqueous layer was acidified with 10% hydrochloric acid (10 mL), and the whole was extracted with AcOEt (3 x 15 mL). The combined organic layers were washed with water (2 x 10 mL), and brine (2 x 10 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* furnished the crude carboxylic acid (620 mg of colorless oil), which was used without further purification. To a solution of the carboxylic acid in ether (5 mL) was added a solution of diazomethane in ether at 0 °C. Evaporation *in vacuo* afforded the crude product (750 mg of pale brown oil), which was purified by column chromatography on silica gel (10 g) with AcOEt-hexane (1:1) to afford **9** (512 mg, 95%) as a colorless oil; IR νmax (film): 3079, 2957, 1750, 1709, 1641, 1453, 1391, 1200, 1001, 774 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ: 2.08 (s, 3H, C*H*$_3$), 2.06-2.12 (m, 1H, CH_2=CHC*H*$_2$), 2.18-2.32 (m, 1H, CH_2=CHC*H*$_2$), 2.64-2.92 (m, 2H, C3-*H* and C4-*H*), 3.49 (dd, *J* = 7.5, 10.6 Hz, 1H, C5-*H*), 3.56 (s, 1.5H, C*H*$_3$O$_2$C), 3.62 (s, 4.5H, C*H*$_3$O$_2$C), 3.68-3.92 (m, 1H, C5-*H*), 3.98 and 4.02 (d, *J* = 5.2 Hz, 1H, C2-*H*), 5.02 (d, *J* = 10.3 Hz, 1H, C*H*$_2$=CH), 5.06 (d, *J* = 16.8 Hz, 1H, C*H*$_2$=CH), 5.63 (ddt, *J* = 10.3, 16.8, 6.8 Hz, 1H, CH_2=C*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 29.1 and 29.2 (CH_3), 36.4 and 37.0 (CH_2), 43.7 and 44.4 (CH), 47.1 and 48.1 (CH_2), 52.1 and 52.5 (CH_3), 53.7 and 54.5 (CH), 62.6 and 63.1 (CH), 117.9 (CH_2), 134.1 (CH), 154.5 and 154.8 (C), 171.8 and 171.9 (C), 205.5 and 205.6 (C); EIMS *m/z* (rel. int. %): 269 (M^+, 0.9), 254 (1.7), 210 (93), 166 (63), 43(100); HRMS (EI) *m/z*: Calcd for $C_{13}H_{19}NO_5$, 269.1264. Found 269.1255; $[\alpha]_D^{25}$ -6.47° (c=1.16, $CHCl_3$); Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.85; H, 7.17; N, 5.59.

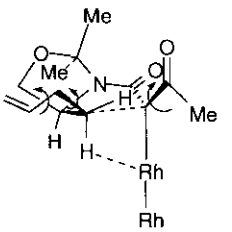
Methyl (2*S*,3*S*,4*S*)-4-acetyl-1,2-bis(methoxycarbonyl)pyrrolidine-3-acetate (10). A solution of **9** (470 mg, 1.6 mmol) in *t*-butyl alcohol (10 mL) was added dropwise to a suspension of $KMnO_4$ (52 mg, 0.33

mmol), $NaIO_4$ (3.8 g, 18.0 mmol) and K_2CO_3 (250 mg, 1.8 mmol) in water (100 mL) and *t*-butyl alcohol (10 mL), and the whole was stirred at room temperature for 1.5 h. The reaction was quenched with ethylene glycol (1.2 g, 20 mmol), and the mixture was filtered through a Celite pad. The filtrate was acidified with 10% hydrochloric acid (10 mL), and extracted with AcOEt (2 x 50 mL). The combined extracts were washed with water (20 mL), and brine (2 x 15 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* furnished the crude carboxylic acid (620 mg of colorless oil), which was used without further purification. To a solution of the carboxylic acid in ether (5 mL) was added a solution of diazomethane in ether at 0 °C. Evaporation *in vacuo* gave the crude product (750 mg of brown oil), which was purified by column chromatography on silica gel (10 g) with AcOEt-hexane (1:1) to afford **10** (450 mg, 91%) as a colorless viscous oil; IR νmax (film): 2957, 1747, 1699, 1454, 1393, 1130, 1017, 756 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 2.11 (s, 3H, CH_3CO), 2.46 (dd, J = 6.9, 15.8 Hz, 1H, MeO_2CCH_2), 2.58 (dd, J = 5.8, 15.8 Hz, 1H, MeO_2CCH_2), 2.91-3.09 (m, 2H, C3-*H* and C4-*H*), 3.41-4.03 (m, 3H, C2-*H* and C5-*H*), 3.63 (s, 6H, CH_3O_2C), 3.74 (s, 3H, CH_3O_2C); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 28.9 and 29.0 (CH_3), 36.3 (CH_2), 40.6 and 41.5 (CH), 47.5 and 48.1 (CH_2), 51.7 (CH_3), 52.2 (CH_3), 52.3 (CH_3), 53.9 and 54.8 (CH), 63.1 and 63.5 (CH), 154.4 and 154.7 (C), 171.2 and 171.4 (C), 171.5 and 171.6 (C), 204.9 and 205.0 (C); EIMS *m/z* (rel. int. %): 301 (M^+, 6.3), 269 (23), 242 (58), 182 (100); HRMS (EI) *m/z*: Calcd for $C_{13}H_{19}NO_7$, 301.1162. Found 301.1147; $[\alpha]_D^{25}$ -12.6° (c=1.53, $CHCl_3$).

Methyl (2*S*,3*S*,4*R*)-1,2-bis(methoxycarbonyl)-4-(1-methylethenyl)pyrrolidine-3-acetate (11). *n*-Butyllithium in hexane (1.5 M, 2.2 mL, 3.3 mmol) was added dropwise to a stirred suspension of methyltriphenylphosphonium bromide (1.25 g, 3.5 mmol) in THF (5 mL) at -78 °C. The suspension was warmed to 0 °C over 0.5 h, and the resultant orange solution was cooled to -78 °C. A solution of **10** (440 mg, 1.5 mmol) in THF (3 mL) was added dropwise to the solution at this temperature, and the whole was warmed to 0 °C over 2 h. The reaction was quenched with saturated NH_4Cl solution (2 mL). The resulting mixture was partitioned between AcOEt (30 mL) and water (10 mL). The organic layer was washed successively with water (2 x 15 mL), and brine (2 x 10 mL), and dried over anhydrous Na_2SO_4. Filtration and concentration *in vacuo* gave the crude product (450 mg of yellow viscous oil), which was purified by column chromatography on silica gel (10 g) with hexane-AcOEt (2:1) to afford **11** (312 mg, 72%) as a colorless caramel; IR νmax (neat): 2957, 1738, 1709, 1454, 1393, 1198 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ: 1.72 (s, 3H, CH_3), 2.48-2.62 (m, 4H, MeO_2CCH_2 , C3-*H* and C4-*H*), 3.36 (t, J = 10.5 Hz, 1H, C5-*H*), 3.65 (s, 4.5H, CH_3O_2C), 3.70 (s, 1.5H, CH_3O_2C), 3.75 (s, 1.5H, CH_3O_2C), 3.77 (s, 1.5H, CH_3O_2C), 3.65-3.78 (m, 1H, C5-*H*), 4.02 and 4.03 (d, J = 7.8 Hz, 1H, C2-*H*), 4.86 and 4.90 (s, 2H, CH_2=); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 18.8 and 18.9 (CH_3), 35.6 and 35.7 (CH_2), 42.5 and 43.5 (CH), 50.0 and 50.4 (CH_2), 50.8 and 51.5 (CH_3), 51.6 (CH_3), 52.3 and 52.6 (CH_3), 63.9 and 64.6 (CH), 114.6 and 114.8 (CH_2), 140.5 (C), 154.9 (C), 171.4 (C), 172.1 and 172.4 (C); EIMS *m/z* (rel. int. %): 299 (M^+, 12), 267 (46), 240 (86), 180 (78), 138 (100); HRMS (EI) *m/z*: Calcd for $C_{14}H_{21}NO_6$, 299.1369. Found 285.1370; $[\alpha]_D^{22}$ -34.6° (c=1.45, $CHCl_3$) {lit.,[11e] $[\alpha]_D^{24}$ -34.5 (c=1.33, $CHCl_3$)}.

(2*S*,3*S*,4*R*)-2-Carboxy-4-(1-methylethenyl)pyrrolidine-3-acetic acid [α-(+)-Allokainic acid, 1]. The following procedure is similar to the reported procedure.[11b] To a solution of **11** (158 mg, 0.56 mmol) in MeOH (2 mL) was added 40% NaOH solution (2 mL), and the whole was refluxed for 15 h. After the solution was concentrated *in vacuo* to one fourth of the original volume, the resultant solution was partitioned between ether (5 mL) and water (5 mL), and the aqueous layer was separated. The aqueous solution was neutralized to pH 4-5 by addition of 10% hydrochloric acid, and washed with ether (5 mL). $Cu(OAc)_2$ (220 mg) was added to the aqueous layer, and the mixture was stirred at 100 °C for 1 h. The resulting suspension was filtered, and the light blue solid was washed with 2.5% aq. AcOH (2.5 mL), water (2 x 2 mL), and acetone (1 mL) to afford copper complex (210 mg of light blue solid). H_2S was introduced into a suspension of the copper complex in water (5 mL) at rt for 0.5 h. After 2.5 h of stirring at this temperature, the black suspension was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure. The residue (113 mg of pale yellow solid) was recrystallized from aq. MeOH to afford α-(+)-allokainic acid (**1**) (83 mg, 70%) as colorless needles; mp 230-237 °C (decomp) {lit.,[11b] mp 238-242 °C (decomp)}; IR νmax (KBr): 3480, 3036, 1715, 1628, 1404, 1149, 1101 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ: 1.73 (s, 3H, C*H*$_3$), 2.64-2.67 (m, 1H, C*H*$_2CO_2H$), 2.71-2.82 (m, 2H, C*H*$_2CO_2H$ and C3-*H*), 2.86 (br t, *J* = 10 Hz, 1H, C4-*H*), 3.32 (t, *J* = 9.6 Hz, 1H, C5-*H*), 3.53 (dd, *J* = 9.6, 11 Hz, 1H, C5-*H*), 3.91 (d, *J* = 8.0 Hz, 1H, C2-*H*), 4.98 (br s, 2H, C*H*$_2$=); ^{13}C NMR (100 MHz, D_2O) δ: 19.5 (CH_3), 37.7 (CH_2), 43.7 (CH), 50.0 (CH_2), 53.4 (CH), 66.0 (CH), 117.5 (CH_2), 142.0 (C), 175.6 (C), 176.2 (C); FABMS *m/z*: 214 (M^++1); HRMS (FAB) *m/z*: Calcd for $C_{10}H_{16}NO_4$, 214.1079. Found 214.1070; $[\alpha]_D^{24}$ +7.5° (c=1.22, H_2O) {lit.,[11b] $[\alpha]_D^{23}$ +7.4° (c=0.7, H_2O)}.

Molecular Mechanics Calculations. Computational calculations were carried out as reported by Taber[14] using molecular mechanics and ZINDO programs provided in the Sony Tektronics CAChe System, Version 3.8. CAChe uses an augmented version of Allinger's MM2 force field whereby force field parameters are estimated for cases not explicitly addressed by MM2 (i.e., octahedrally disposed nuclei). Initially we minimized $Rh_2(OAc)_4$ with ZINDO and locked the resultant bond lengths and bond angles. To maintain the expected carbene geometry, we locked the Rh-Rh-C bond angle at 180°. To secure overlap between the C-Rh bond and the target C-H bond, we established weak bonds (meaningful in molecular mechanics) between the two incipiently bonding carbons and between the target H and the proximal Rh. We also locked the H-Rh-C-C dihedral angle and C-N-C-O dihedral angle at 0°. The global minima for the Rh(II) carbene intermediates **A** and **B** were determined by a grid search. The minimizations for the intermediates **C** and **D** were not carried out because the target C-H bond can not be aligned with the Rh(II)-carbene bond in these intermediates.



∠Rh-Rh-C = 180°
∠H-C-C-Rh = 0 °
∠C-N-C-O = 0 °

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REFERENCES AND NOTES

1. For books and reviews, see: (a) M. P. Doyle, *Acc. Chem. Res.*, 1986, **19**, 348; (b) M. P. Doyle, *Chem. Rev.*, 1986, **86**, 919; (c) G. Maas, *Top. Curr. Chem.*, 1987, **137**, 75; (d) D. F. Taber, 'Comprehensive Organic Synthesis,' Vol. 3, ed. by B. M. Trost and I. Fleming, Pergamon Press, Inc., Oxford, 1991, Chapter 4.2; (e) J. Adams and D. M. Spero, *Tetrahedron*, 1991, **47**, 1765; (f) A. Padwa and K. E. Krumpe, *Tetrahedron*, 1992, **48**, 5385; (g) A. Padwa and D. J. Austin, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1797; (h) T. Ye and M. A. McKervey, *Chem. Rev.*, 1994, **94**, 1091; (i) A. F. Khlebnikov, M. S. Novikov, and R. R. Kostikov, *Adv. Heterocycl. Chem.*, 1996, **65**, 93; (j) M. P. Doyle, M. A. McKervey, and T. Ye, 'Modern Catalytic Methods for Organic Synthesis with Diazo Compounds,' Wiley-Interscience, New York, 1998.
2. For recent reviews, see: (a) M. P. Doyle, *Aldrichimica Acta*, 1996, **29**, 3; (b) S. Hashimoto, N. Watanabe, M. Anada, and S. Ikegami, *J. Synth. Org. Chem., Jpn.*, 1996, **54**, 988; (c) M. P. Doyle and M. A. McKervey, *Chem. Commun.*, 1997, 983; (d) M. P. Doyle and D. C. Forbes, *Chem. Rev.*, 1998, **98**, 911.
3. For our efforts in this area, see: (a) S. Hashimoto, N. Watanabe, and S. Ikegami, *Tetrahedron Lett.*, 1990, **31**, 5173; (b) S. Hashimoto, N. Watanabe, T. Sato, M. Shiro, and S. Ikegami, *Tetrahedron Lett.*, 1993, **34**, 5109; (c) S. Hashimoto, N. Watanabe, and S. Ikegami, *Synlett*, 1994, 353; (d) N. Watanabe, M. Anada, S. Hashimoto, and S. Ikegami, *Synlett*, 1994, 1031; (e) S. Hashimoto, N, Watanabe, K. Kawano, and S. Ikegami, *Synth. Commun.*, 1994, **24**, 3277; (f) N. Watanabe, Y. Ohtake, S. Hashimoto, M. Shiro, and S. Ikegami, *Tetrahedron Lett.*, 1995, **36**, 1491; (g) N. Watanabe, T. Ogawa, Y. Ohtake, S. Ikegami, and S. Hashimoto, *Synlett*, 1996, 85; (h) M. Anada and S. Hashimoto, *Tetrahedron Lett.*, 1998, **39**, 79; (i) M. Anada, N. Watanabe, and S. Hashimoto, *Chem. Commun.*, 1998, 1517.
4. (a) D. F. Taber and R. E. Ruckle, Jr., *J. Am. Chem. Soc.*, 1986, **108**, 7686; (b) S. Hashimoto, N. Watanabe, and S. Ikegami, *Tetrahedron Lett.*, 1992, **33**, 2709; (c) S. Hashimoto, N. Watanabe, and S. Ikegami, *J. Chem. Soc., Chem. Commun.*, 1992, 1508; (d) A. Padwa, D. J. Austin, A. T. Price, M. A. Semones, M. P. Doyle, M. N. Protopopova, W. R. Winchester, and A. Tran, *J. Am. Chem. Soc.*, 1993, **115**, 8669; (e) M. C. Pirrung and A. T. Morehead, Jr., *J. Am. Chem. Soc.*, 1994, **116**, 8991; (f) T. Yakura, S. Yamada, A. Ueki, and M. Ikeda, *Synlett*, 1997, 185; (g) A. G. H. Wee and Q. Yu, *J. Org. Chem.*, 1997, **62**, 3324; (h) F. Estevan, P. Lahuerta, J. Pérez-Prieto, M. Sanaú, S.-E. Stiriba, and M. A. Ubeda, *Organometallics*, 1997, **16**, 880; (i) F. Estevan, P. Lahuerta, J. Pérez-Prieto, I. Pereira, and S.-E. Stiriba, *Organometallics*, 1998, **17**, 3442; (j) C. J. Moody, S. Miah, A. M. Z. Slawin, D. J. Mansfield, and I. C. Richards, *Tetrahedron*, 1998, **54**, 9689; (k) B. S. Balaji and B. M. Chanda, *Tetrahedron Lett.*, 1998, **39**, 6381.
5. (a) D. E. Cane and P. J. Thomas, *J. Am. Chem. Soc.*, 1984, **106**, 5295; (b) S. Hashimoto, T. Shinoda, Y. Shimada, T. Honda, and S. Ikegami, *Tetrahedron Lett.*, 1987, **28**, 637; (c) H. R. Sonawane, N. S. Bellur, J. R. Ahuja, and D. G. Kulkarni, *J. Org. Chem.*, 1991, **56**, 1434; (d) P. Ceccherelli, M. Curini, M. C. Marcotullio, and O. Rosati, *Tetrahedron*, 1991, **47**, 7403;

6. (a) F. Zaragoza and G. Zahn, *J. Prakt. Chem./ Chem.-Ztg.*, 1995, **337**, 292; (b) F. Zaragoza, *Tetrahedron*, 1995, **51**, 8829.
7. (a) M. P. Doyle, M. S. Shanklin, S. Oon, H. Q. Pho, F. R. van der Heide, and W. R. Veal, *J. Org. Chem.*, 1988, **53**, 3384; (b) M. P. Doyle, J. Taunton, and H. Q. Pho, *Tetrahedron Lett.*, 1989, **30**, 5397; (c) M. P. Doyle, M. N. Protopopova, W. R. Winchester, and K. L. Daniel, *Tetrahedron Lett.*, 1992, **33**, 7819.
8. For reviews on syntheses of kainoids, see: (a) R. M. Williams, 'Synthesis of Optically Active α-Amino Acids,' Pergamon Press, Inc., Oxford, 1989, pp. 304-380; (b) K. Hashimoto and H. Shirahama, *Trends Org. Chem.*, 1991, **2**, 1; (c) A. F. Parsons, *Tetrahedron*, 1996, **52**, 4149; (d) M. G. Moloney, *Nat. Prod. Rep.*, 1998, **15**, 205.
9. For recent syntheses of (-)-α-kainic acid, see: (a) M. Kawamura and K. Ogasawara, *Heterocycles*, 1997, **44**, 129; (b) O. Miyata, Y. Ozawa, I. Ninomiya, and T. Naito, *Synlett*, 1997, 275; (c) Y. Nakada, T. Sugahara, and K. Ogasawara, *Tetrahedron Lett.*, 1997, **38**, 857; (d) M. D. Bachi and A. Melman, *J. Org. Chem.*, 1997, **62**, 1896; (e) J. Cossy, M. Cases, and D. G. Pardo, *Synlett*, 1998, 507; (f) A. Rubio, J. Ezquerra, A. Escribano, M. J. Remuiñán, and J. J. Vaquero, *Tetrahedron Lett.*, 1998, **39**, 2171.
10. J. E. Baldwin and C.-S. Li, *J. Chem. Soc., Chem. Commun.*, 1987, 166.
11. (a) W. Oppolzer, C. Robbiani, and K. Bättig, *Helv. Chim. Acta*, 1980, **63**, 2015; (b) W. Oppolzer, C. Robbiani, and K. Bättig, *Tetrahedron*, 1984, **40**, 1391; (c) A. Barco, S. Benetti, A. Casolari, G. P. Pollini, and G. Spalluto, *Tetrahedron Lett.*, 1990, **31**, 4917; (d) A. Barco, S. Benetti, G. Spalluto, A. Casolari, G. P. Pollini, and V. Zanirato, *J. Org. Chem.*, 1992, **57**, 6279; (e) S. Hatakeyama, K. Sugawara, and S. Takano, *J. Chem. Soc., Chem. Commun.*, 1993, 125; (f) S. Hanessian and S. Ninkovic, *J. Org. Chem.*, 1996, **61**, 5418; (g) O. Miyata, Y. Ozawa, I. Ninomiya, K. Aoe, H. Hiramatsu, and T. Naito, *Heterocycles*, 1997, **46**, 321.
12. M. J. Dunn, R. F. W. Jackson, J. Pietruszka, and D. Turner, *J. Org. Chem.*, 1995, **60**, 2210.
13. M. P. Doyle, L. J. Westrum, W. N. E. Wolthuis, M. M. See, W. P. Boone, V. Bagheri, and M. M. Pearson, *J. Am. Chem. Soc.*, 1993, **115**, 958.
14. D. F. Taber, K. K. You, and A. L. Rheingold, *J. Am. Chem. Soc.*, 1996, **118**, 547.
15. C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, 1956, **21**, 1547.
16. (a) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, 1955, **33**, 1701; (b) E. von Rudloff, *Can. J. Chem.*, 1956, **34**, 1413.

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