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A New Retro-Aza-Ene Reaction: Formal Reductive Amination of an α-Keto Acid to an α-Amino Acid

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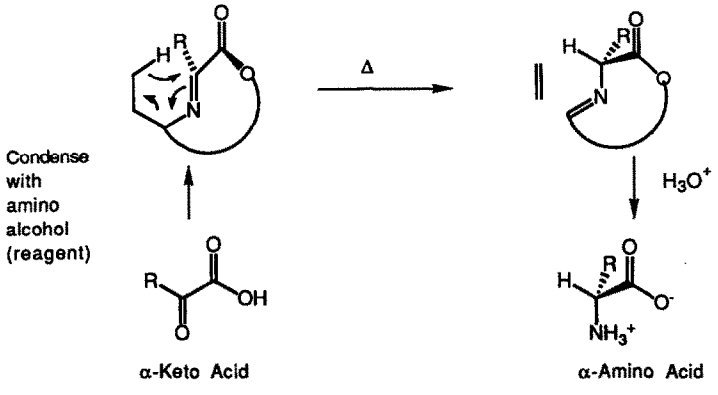
Key Words: retro-ene reaction; reductive amination; α-amino acid; α-keto acid; *exo* transition state.

Abstract: Two diastereomeric reductive amination reagents, **1a** and **1b**, were synthesized. Each reagent was condensed with ethyl pyruvate as a model α-keto acid. Flash vacuum pyrolysis of the pyruvate adducts, **10a** and **10b**, results in cheleotropic elimination of CO, followed by a new type of retro-aza-ene reaction. A molecule of benzene and a protected alanine derivative, **11**, are produced in the retro-ene reaction. This sequence constitutes the first formal reductive amination of an α-keto acid via a thermal rearrangement. Diastereomer **10b** undergoes the rearrangement more readily than diastereomer **10a**, indicating that an *exo* transition state is preferred over an *endo* transition state for this particular retro-aza-ene reaction.

In 1927, Knoop and Oesterlin first reported the nonenzymatic reductive amination of an α-keto acid to an α-amino acid.[1] Since that time, a myriad of chemical[2] and biomimetic[3] reductive aminations of α-keto acids have been disclosed. In the former approaches, an azomethine intermediate (imine, hydrazone, oxime) is generated and then chemically reduced. The biomimetic procedures employ modified pyridoxamines as both amino donor and reducing agent. In both of these approaches a hydrogen equivalent (proton, radical or hydride ion) is delivered *intermolecularly* to the α-center of an aminated α-keto acid.

In this work, a mechanistically distinct approach to the same overall transformation is examined. An α-keto acid would be tethered to an appropriate amino alcohol in an iminolactone linkage. Upon heating, an α-hydrogen equivalent would be delivered to the imino center via a retro-aza-ene reaction (see Scheme 1). This would be the first instance of a formal reductive amination of an α-keto acid via a thermal rearrangement. Moreover, hydrogen delivery would be mechanistically constrained to be *intramolecular* and geometrically con-



Scheme 1. Formal Reductive Amination via a Retro-Ene Reaction

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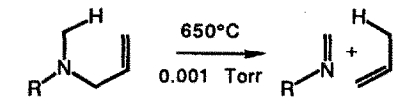
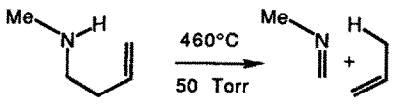
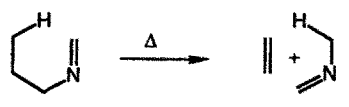
strained to occur from only one face of the imine. This approach was seen to hold promise for the absolute control of face selectivity in reductive amination.

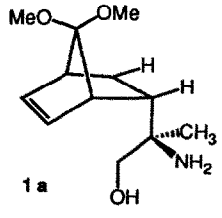
An inspection of the literature reveals no known retro-aza-ene reaction of this class. Rough estimates of the enthalpy of reaction for these transformations suggest an explanation for this situation. Whereas the two heretofore reported retro-aza-ene reactions are either exothermic[4] (Table 1, entry 1), or approximately isoenthalpic[5] (Table 1, entry 2), the desired retro-aza-ene rearrangement (Table 1, entry 3a) is clearly endothermic. However, if this retro-ene reaction could be coupled to the aromatization of a benzene ring, then the overall process would be enthalpically favorable (Table 1, entry 3b).

Table 1. Retro-Ene Reactions Involving a Single Nitrogen Heteroatom

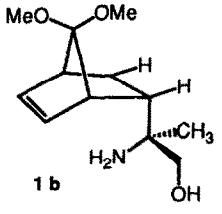
		$^{*}\Delta H^{est}$ (kcal/mole)	Ref.
(1)		- 7	4
(2)		0	5
(3a)		+19	unknown
(3b)		-17	this work

* Calculated using average bond energies from ref. 6. The resonance stabilization energy of benzene is taken as 36 kcal/mole.[7]

The required 1,3-cyclohexadiene moiety might be prone to oxidation and could therefore be unmasked "at the last second," thermally, via a cheleotropic elimination of CO from a suitable norbornen-7-one system.[8] These considerations led to the design of retro-ene reductive amination "reagents" **1a** and **1b**. To test the feasibility of this retro-ene approach to reductive amination, a synthesis of the racemic reagents, **1a** and **1b**, was undertaken.



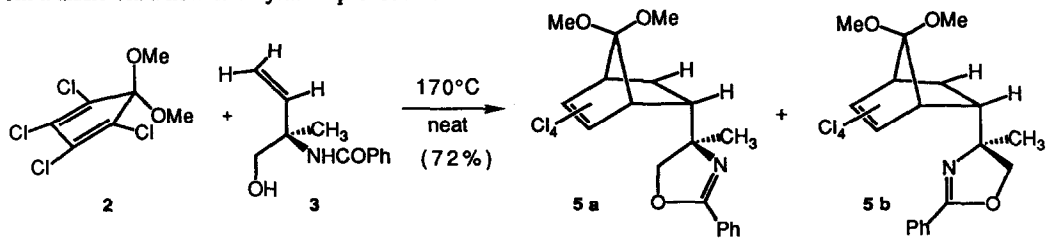
1a



1b

In retrosynthetic terms, the target molecules, **1a** and **1b**, may be disconnected to cyclopentadienone dimethyl ketal and α-vinylalaninol by a Diels-Alder transform. Although ketals of cyclopentadiene are known,

they dimerize rapidly even at room temperature.[9] On the other hand, the commercially available diene **2** may be heated to high temperatures without dimerizing and is known to react with a wide variety of dienophiles.[8,10] The dienophile **3** could be obtained in 87% yield from the reduction of N-benzoyl-α-vinylalanine methyl ester, **4**, with ethanolic sodium borohydride. Vinylalanine derivative **4**, in turn, was available in multigram quantities from alanine via a new α-vinylation procedure.[11]

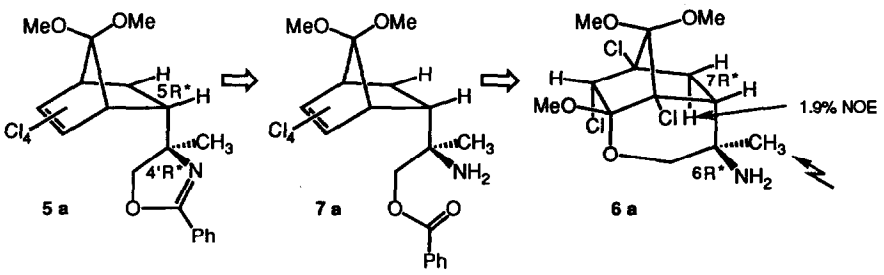


(**5a**:**5b** = 1.3:1.0)

Scheme 2.

The Diels-Alder reaction of protected vinylalaninol **3** and diene **2** proceeded smoothly. Interestingly, under the conditions of the Diels-Alder reaction, the β-hydroxybenzamide **3** cyclizes--either before or after undergoing cycloaddition--to an oxazoline, with concomitant loss of water. The diastereomeric *endo* Diels-Alder adducts obtained, **5a** and **5b**, were separable by conventional chromatography.

The *endo* stereochemistry was assigned to the adducts, **5a** and **5b**, on the basis of NOE experiments. Thus irradiation of the *anti* methoxy group gives NOE's at both the C_5 methine proton, and the C_6 *exo* proton, for each diastereomer. The C_5 protons must then be *exo* in both **5a** and **5b**, and so the adducts have the *endo* stereochemistry. A high *endo* bias for the diene **2** has been noted by others,[10c] and is probably due to an effective screening of the *exo* face by the methoxy groups.



Scheme 3. Assignment of the Relative Stereochemistry at C_5 and $C_{4'}$ in Adduct 5a by NOE

It remained to establish the relative stereochemistry at C_5 and $C_{4'}$ for each *endo* diastereomer. Thus **5a** could be converted to the tricyclic *bis*-ketal **6a** in two steps via a curious cyclization reaction first noted by Hoch and coworkers[12] (See Experimental for details). Observation of an NOE at the *endo* C_{10}-proton in **6a** upon irradiation of the C_6-methyl group (see Scheme 3) established that **6a** has the ($6R^*$,$7R^*$) stereochemistry, and hence **5a** must have the ($5R^*$,$4'R^*$) stereochemistry. It follows that **5b** has the ($5R^*$,$4'S^*$) stereochemistry.

The relative stereochemistry at C_5 and $C_{4'}$ in **5a** and **5b** eventually manifests itself in differential reactivities of the corresponding pyruvate adducts **10a** and **10b** toward the desired thermal rearrangement.

Therefore, it was deemed appropriate to rigorously confirm the NMR-based assignment of relative stereochemistry by means of X-ray diffraction. Accordingly, crystals of the retro-ene reductive amination reagent **1a** (*vide infra*), derived from **5a**, were grown and a single crystal X-ray structure determination performed. A schematic representation of **1a** is displayed in Figure 1. The results of X-ray crystallography unambiguously demonstrate that **1a** has the (5*R**,2'*S**) stereochemistry. By direct correlation then, **5a** must have the (5*R**,4'*R**) stereochemistry, in agreement with the assignment based on NOE.

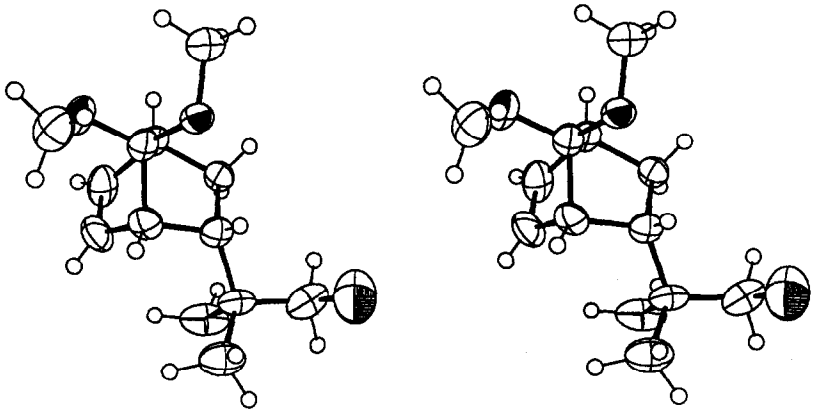
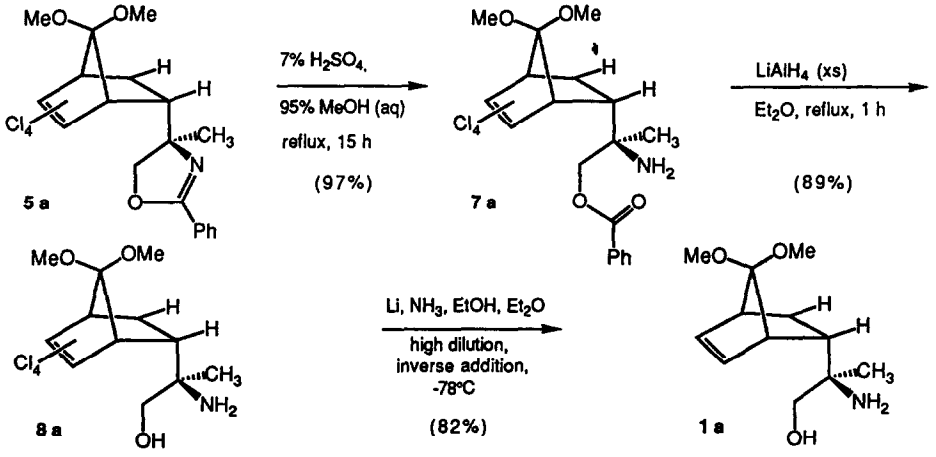


Figure 1. Perspective Drawing of the X-Ray Crystal Structure for Compound 1a: Vibrational ellipsoids of C, N and O are drawn at the 50% probability level (C = solid ellipse; N = solid ellipse with one octant cut out; O = solid ellipse with one octant cut out and shaded).

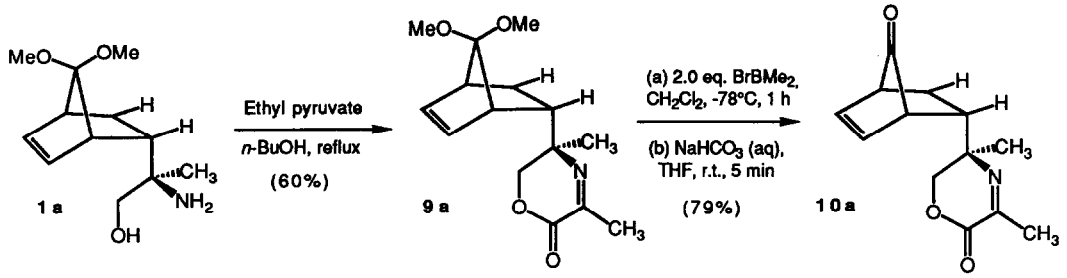
The oxazoline ring in **5a** and **5b** could be cleaved by heating in acidic aqueous methanol (shown for the a series in Scheme 4). Reductive cleavage of the resulting benzoates, **7a** and **7b**, could be effected with lithium



Scheme 4. Synthesis of Retro-Ene Reductive Amination Reagent 1a

aluminium hydride, without attending benzoyl migration or Hoch cyclization.[12] To prevent undesirable side reactions from interceding at a later stage,[13] the dechlorination of **8a** and **8b** was undertaken. Traditional

dehalogenation methods[14] failed, or proceeded with accompanying double bond reduction.[10a-c] A new method for the reductive dechlorination of tetrachloronorbornenone ketals was developed.[15] If the reductant, lithium in liquid ammonia, is added inversely to a dilute solution of the tetrachloride, **8a** or **8b**, at -78°C in ether, then **1a** or **1b**, respectively, is obtained in good yield, and completely free of contaminating saturated byproduct.

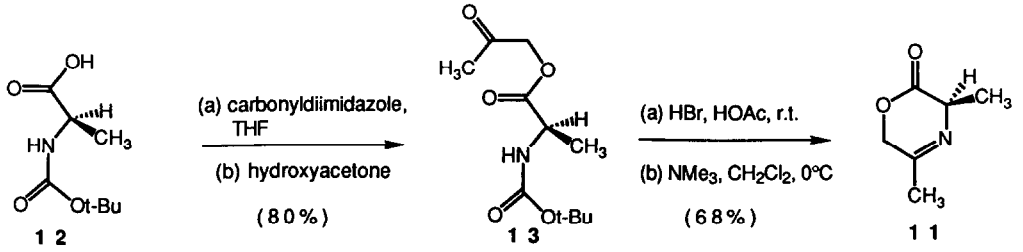


Scheme 5. Condensation of the Reductive Amination Reagent 1a with Ethyl Pyruvate

The two diastereomeric reductive amination reagents, **1a** and **1b**, could now be evaluated by condensing them with pyruvate as a model α-keto acid. Upon refluxing **1a** with ethyl pyruvate in *n*-butyl alcohol, the desired iminolactone, **9a**, was obtained (see Scheme 5 and Experimental for **9b**). These conditions are an adaptation of those of Koch and coworkers for the synthesis of simple 5,6-dihydro-1,4-oxazin-2-ones.[16]

It remained only to unveil the bridging ketone functionality. This transformation demands a high degree of chemoselectivity as the iminolactone moiety in compounds **9a** and **9b** could easily be cleaved under the aqueous acidic conditions normally employed for ketal hydrolysis. The dimethylboron bromide reagent of Guindon[17] performed admirably in this regard. Using two equivalents of this reagent, the dimethyl ketal functionality in **9a** and **9b** could be selectively cleaved to yield the desired rearrangement precursors **10a** and **10b**, respectively.

To have a standard for comparison, the desired rearrangement product, **11**,was first prepared by an independent route. Indeed, **11**, a protected alanine derivative, had been synthesized by Schultz and Steglich.[18] In this work, **11** was obtained from alanine and acetol by a similar procedure (see Scheme 6).



Scheme 6. Independent Synthesis of the Rearrangement Product

Armed with an authentic sample of the rearrangement product **11**, the proposed cheleotropic elimination/retro-ene rearrangement of diastereomers **10a** and **10b** was examined. Both the cheleotropic

elimination of carbon monoxide and the subsequent retro-ene reaction could be observed when the pyrolysis was carried out directly in the injector of the GC-MS (gas chromatograph with mass spectral detector). At an injector temperature of 210°C, both **10a** and **10b** gave single peaks with mass spectra indicative of loss of carbon monoxide (**14a** and **14b**, respectively; m/e = 205). Thus, under these conditions the initial extrusion of carbon monoxide apparently does take place, but the subsequent retro-ene reaction does not.

As the temperature of the injector was raised, small amounts of both the rearrangement product **11** and benzene were observed in the GC, in addition to **14a** and **14b**, indicating that the desired retro-ene reaction does take place. However, whereas the initial cheleotropic elimination goes to completion for both diastereomers **10a** and **10b** at 210°C, the progress of the subsequent retro-ene reaction differs for the two diastereomers. For **10a**, retro-ene rearrangement product (m/e = 127; retention time and mass spectrum identical to those of authentic **11**) first appears at an injector temperature of 300°-350°C. For **10b**, on the other hand, retro-ene rearrangement product is clearly visible at an injector temperature of 250°C.

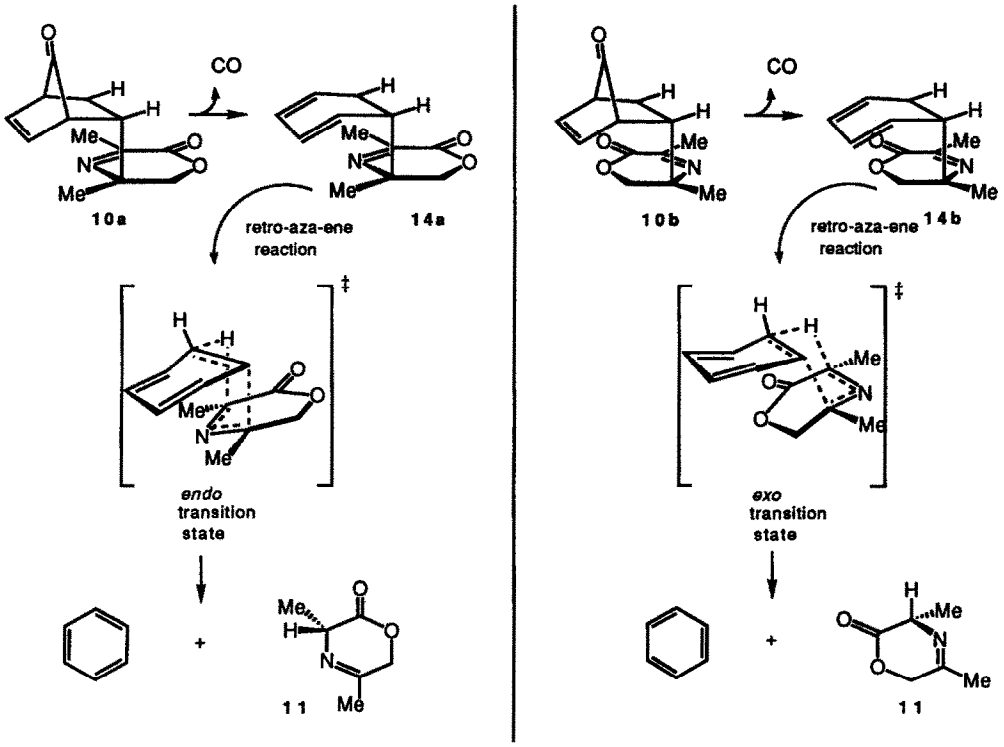
The thermal rearrangement could be carried out under flash vacuum pyrolytic conditions and sufficient material obtained to permit ^{1}H-NMR spectral analysis. The ^{1}H-NMR spectrum, the mass spectrum and the GC-trace of the product isolated from these pyrolyses were superimposable upon those of authentic **11**, prepared by an independent synthesis (*vide supra*). The results of a series of flash vacuum pyrolyses of diastereomers **10a** and **10b** are shown in Table 2. By filling the pyrolysis tube with quartz Raschig rings to increase contact time, the temperature necessary to effect the retro-ene rearrrangement could be effectively lowered by ca. 100°C (Compare entries 6 and 10). On the other hand, use of a carrier gas resulted in slightly decreased product yields (Compare entries 4 and 5). In the best case, a modest 25% yield of the desired alanine derivative **11** was obtained.

Table 2. Flash Vacuum Pyrolysis Experiments

	Diast.	Temp.	Quartz Raschig Rings? (diam.)	Pyrolysis Tube (length)	Product(s)
(1)	**10a**	400°C	No	22 cm	recovered **10a**
(2)	**10a**	800°C	No	22 cm	7% **11**
(3)	**10a**	400°C	Yes, 3 mm	22 cm	intermediate **14a**
(4)*	**10a**	600°C	Yes, 3 mm	22 cm	12% **11**; 5% **14a**
(5)	**10a**	600°C, N_2 carrier gas	Yes, 3 mm	22 cm	10% **11**
(6)	**10b**	350°C	No	30 cm	25% **11**
(7)	**10b**	400°C	No	30 cm	20% **11**
(8)*	**10b**	400°C	Yes, 3 mm	22 cm	18% **11**; 4% **14b**
(9)	**10b**	210°C	Yes, 2 mm	30 cm	65% **14b**
(10)	**10b**	250°C	Yes, 2 mm	30 cm	21% **11**; 13% **14b**
(11)	**10b**	300°C	Yes, 2 mm	30 cm	10% **11**
(12)	**10b**	350°C	Yes, 2 mm	30 cm	10% **11**

* See Experimental for a detailed description of this experiment.

Interestingly, just as in the GC-MS experiments, the rearrangement of diastereomer **10b** is clearly more facile than the rearrangement of diastereomer **10a** (compare entries 3 and 8). Diastereomer **10a** leads to a retro-aza-ene reaction with an *endo* transition state, whereas diastereomer **10b** leads to a retro-aza-ene reaction with an *exo* transition state (see Scheme 7).[19]



Scheme 7. The Cheleotropic Elimination/Retro-Ene Sequence for 10a and 10b

CONCLUSIONS

Flash vacuum pyrolysis of the pyruvate derived adduct **10a** gave alanine derivative **11**, in modest yield. This is the first instance of the formal reductive amination of an α-keto acid to an α-amino acid via a thermal rearrangement. The rearrangement consists of a cheleotropic elimination of CO, followed by a new type of retro-aza-ene reaction. The results of the GC-MS experiments and the flash vacuum pyrolyses indicate that, for this type of retro-aza-ene reaction, an *exo* transition state (from diastereomer **10b**) is more favorable than an *endo* transition state (from diastereomer **10a**).

EXPERIMENTAL

All chemicals were of reagent grade unless otherwise stated. All melting points were measured on a Büchi 510 melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 983G spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker WM-300, Bruker AM-400 or a Varian XL-300 spectrometer. ^{13}C NMR spectra (broad-band and DEPT) were recorded on a Varian XL-300 or a Bruker AM-400 spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane. Electron impact mass spectra were obtained on a Hitachi-Perkin-Elmer RMU-6M and FAB mass spectra on a Kratos AEI MS-5 mass spectrometer. Mass spectral peaks are given in units of mass/charge followed by relative peak intensity in

parentheses. Analytical gas chromatography was performed using a Hewlett Packard 5890 GC with mass spectral detector (GC-MS). The column was cross-linked methyl silicone (film thickness: 0.33 μ; interior diameter: 0.020 mm; length: 12 m). Elemental analyses were carried out in the microanalytical laboratory at the ETH Zürich.

(±)-Methyl 2-benzamido-2-methylbut-3-enoate [(±)-N-Benzoyl-α-vinylalanine methyl ester] (4) was synthesized as previously reported.[11]

(±)-2-Benzamido-2-methylbut-3-enol [(±)-N-Benzoyl-α-vinylalaninol] (3). Modest yields (ca. 60 %) had been reported[20] for the reduction of an N-benzoyl-α-amino ester using $NaBH_4$ in aqueous ethanol. The following procedure, using absolute ethanol to eliminate possible competing ester hydrolysis, would appear to be a significant improvement.
Methyl ester **4** (12.1 g, 51.9 mmol) was dissolved in absolute ethanol (distilled from Na-diethyl phthalate, 120 ml) and the resulting solution cooled to 4°C. Sodium borohydride (9.82 g, 260 mmol) was added and the reaction mixture stirred for 19 h at room temperature with exclusion of moisture. The reaction was quenched by pouring on to ice-ethyl acetate and acidifying to pH 6.5 with HCl (initially conc. HCl, then 2 N HCl). The two-phase mixture was let stand in a separatory funnel until hydrogen gas evolution subsided. After a second extraction of the aqueous layer, the organic layers were combined and dried over $MgSO_4$. The solvent was evaporated in vacuo and the crude product purified by flash chromatography [7:3 petroleum ether (40-70°C)-ethyl acetate] to yield 8.73 g (87%) of **3**, as a colorless oil which solidified upon storage at -20°C: bp(0.02 torr) 128-129°C; IR ($CHCl_3$): 3430 (s, NH), 3150-3450 (br, OH), 3000 (sh), 1660 (s, C=O), 1515 (s), 1485 (s), 1460, 1290, 1060, 995, 925, 870 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.50 (s, 3H, CH_3), 3.65-3.71 (dd, 1H, J = 7.0 Hz, 11.6 Hz, C_1-H), 3.73-3.79 (dd, 1H, J = 5.9 Hz, 11.6 Hz, 1H, C_1-H), 4.52-4.57 (apparent t, J = 6.1 Hz, 6.9 Hz, 1H, OH), 5.21-5.27 (m, 2H, C=CH_2), 5.96-6.05 (dd, J_{cis} = 10.6 Hz, J_{trans} = 17.6 Hz, 1H, HC=CH_2), 6.4-6.5 (s, br, 1H, NH), 7.40-7.54 (m, 3H, *m*-, *p*-ArH), 7.75-7.78 (m, 2H, *o*-ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.69 (CH_3), 60.27 (C_2), 69.34 (CH_2O), 114.5 (C=CH_2); 127.0, 128.7, 131.7 (Ar CH); 134.8 (*ipso*-Ar), 140.1 (HC=CH_2), 168.1 (C=O); MS (EI): 205 (M^+, 0.4), 190 (M^+ - CH_3, 0.5), 174 (M^+ - CH_2OH, 18), 122 (8.1), 105 (COPh, 100), 77 (Ph, 46), 51 (14); Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.08; H, 7.49; N, 6.76.

(1R*,4S*,5S*,4'S*)-7,7-Dimethoxy-1,2,3,4-tetrachloro-5-[4'-(4'-methyl-2'-phenyl-2'-oxazolinyl)]-bicyclo[2.2.1]hept-2-ene (5a).
(1R*,4S*,5S*,4'R*)-7,7-Dimethoxy-1,2,3,4-tetrachloro-5-[4'-(4'-methyl-2'-phenyl-2'-oxazolinyl)]-bicyclo[2.2.1]hept-2-ene (5b). A mixture of **3** (478 mg, 2.33 mmol) and 7,7-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene **2** (Fluka, 3.08 g, 11.7 mmol) was placed under Ar atmosphere by carrying out twenty cycles of: (a) evacuation with a high vacuum pump, followed by (b) purging with Ar. The stopcock was closed and the reaction mixture heated at 170°C for 60 h. After cooling to room temperature, the crude product was taken up in ethyl acetate, adsorbed on to silica gel, and chromatographed directly. Two fractions were obtained, each of which was subjected to another round of flash chromatography [R_f(**5a**) 0.27; R_f(**5b**) 0.21, 9:1 petroleum ether (40-70°C)-ethyl acetate] to obtain complete separation. The total yield was 72%, consisting of 431 mg (41%) of **5a**, and 324 mg (31%) of **5b**, both as glassy light orange solids which could be distilled on a kugelrohr apparatus.
For **5a**: bp(0.03 torr) 210°C; IR ($CHCl_3$): 2980, 2960, 1650 (s, C=N), 1610, 1580, 1495, 1450, 1360, 1300, 1195 (s), 1120 (s), 1100, 1065, 1025, 990, 890 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.53 (s, 3H, 4'-CH_3), 1.73-1.78 (dd, J_{trans} = 4.8 Hz, J_{gem} = 11.6 Hz, 1H, *endo* C_6-H), 2.42-2.49 (dd, J_{cis} = 9.2 Hz, J_{gem} = 11.5 Hz, 1H, *exo* C_6-H), 2.87-2.92 (dd, J_{trans} = 4.8 Hz, J_{cis} = 9.2 Hz, 1H, C_5-H), 3.56 (s, 3H, *syn* OCH_3), 3.61 (s, 3H, *anti* OCH_3), 4.00-4.04 (d, J = 8.6 Hz, 1H, C_5'-H), 4.07-4.10 (d, J = 8.6 Hz, 1H, C_5'-H), 7.36-7.49 (m, 3H, *m*-, *p*-ArH), 7.93-7.96 (m, 2H, *o*-ArH); ^1H NMR NOE experiments (300 MHz, $CDCl_3$): (a) Irradiation of the *syn* OCH_3 (3.56 ppm) showed no enhancement; (b) Irradiation of the *anti* OCH_3 (3.61 ppm) gave a 0.92% NOE at the C_5 proton and a 0.31% NOE at the *exo* C_6 proton; ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.97 (4'-CH_3), 38.53 (C_6); 51.66, 52.86 (ketal OCH_3); 53.74 (C_5), 72.39 (C_4'); 73.85, 77.96 (C_1, C_4); 78.73 (CH_2O), 112.6 (C_7); 127.5, 130.0 (C_2, C_3); 128.2 (*ipso*-Ar); 128.2, 128.5, 131.4 (Ar CH); 162.8 (C=N); MS (FAB, 3-NOBA matrix): 454 (60), 452 (MH^+ for 3 x ^{35}Cl, 1 x ^{37}Cl, 96), 450 (81), 418 (15), 416 (M^+ - Cl, 17), 414 (15), 256 (44), 254 (45), 219 (7.2), 188 (10), 160 (100), 105 (COPh, 65), 104 (33), 77 (Ph, 26), 59 (14); Anal. Calcd for $C_{19}H_{19}NO_3Cl_4$: C, 50.58; H, 4.24; N, 3.10; Cl, 31.43. Found: C, 50.29; H, 4.23; N, 3.13; Cl, 31.61.
For **5b**: bp(0.03 torr) 210°C; IR ($CHCl_3$): 2980, 2960, 2850, 1650 (s, C=N), 1603, 1580, 1495, 1450, 1360, 1280, 1195 (s), 1120, 1100, 1065, 990, 885 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.49 (s, 3H, 4'-CH_3), 1.99-2.04 (dd, J_{trans} = 4.6 Hz, J_{gem} = 12.0 Hz, 1H, *endo* C_6-H), 2.49-2.56 (dd, J_{cis} = 9.2 Hz, J_{gem} = 12.0 Hz, 1H, *exo* C_6-H), 3.09-3.13 (dd, J_{trans} = 4.6 Hz, J_{cis} = 9.2 Hz, 1H, C_5-H), 3.55 (s, 3H, *syn* OCH_3), 3.61 (s, 3H, *anti* OCH_3), 3.99-4.02 (d, J = 9.2 Hz, 1H, C_5'-H), 4.38-4.42 (d, J = 9.2 Hz, 1H, C_5'-H), 7.36-7.49 (m, 3H, *m*-, *p*-ArH), 7.87-7.91 (m, 2H, *o*-ArH); ^1H NMR NOE experiments (300 MHz, $CDCl_3$): (a) Irradiation of the *syn* OCH_3 (3.55 ppm) showed no enhancement; (b) Irradiation of the *anti* OCH_3 (3.61 ppm) gave a 0.97% NOE at the C_5 proton and a 0.36% NOE at the *exo* C_6 proton; ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.02 (4'-CH_3), 38.98 (C_6); 51.73, 52.82 (ketal OCH_3); 52.73 (C_5), 72.61 (C_4'), 73.58 (CH_2O); 74.03, 77.95 (C_1, C_4); 112.4 (C_7); 127.6, 129.5 (C_2, C_3); 128.3, 128.4, 131.4 (Ar CH); 128.6 (*ipso*-Ar), 162.7 (C=N); MS (FAB, 3-NOBA matrix): 454 (60), 452 (MH^+ for 3 x ^{35}Cl, 1 x ^{37}Cl, 100), 450 (82), 418 (13), 416 (M^+ - Cl, 17), 414 (17), 256 (29), 254 (27), 219 (6.5), 188 (9.0), 172 (7.0), 160 (84), 105 (COPh, 55), 104 (32), 77 (Ph, 25), 59 (12); Anal. Calcd for $C_{19}H_{19}NO_3Cl_4$: C, 50.58; H, 4.24; N, 3.10; Cl, 31.43. Found: C, 50.35; H, 4.10; N, 3.11; Cl, 31.63.

(1R*,4S*,5S*,2'S*)-7,7-Dimethoxy-1,2,3,4-tetrachloro-5-[2'-(2'-amino-1'-benzoyloxy)-propyl]-bicyclo[2.2.1]hept-2-ene (7a). A solution of 7% H_2SO_4 (w/v) in 95 % aqueous methanol was prepared as follows: To methanol (50 ml) was added conc. H_2SO_4 (Merck, 4 ml), H_2O (5 ml), and then methanol to a total volume of 100 ml. To solid **5a** (625 mg, 1.39 mmol) was added 7% H_2SO_4 in 95% MeOH(aq) (25 ml). The reaction mixture was refluxed for 15.5 h, allowed to cool to room temperature, and then brought to pH 8 with 1 N NaOH. Following addition of ether (150 ml), more base was added (to ca. pH 11) and the aqueous layer extracted (2 x 150 ml ether). The combined ether portions were dried ($MgSO_4$) and the volatiles removed in vacuo. Thorough drying on a high vacuum pump at room temperature gave 629 mg (97%) of **7a** as a light orange oil which displayed a satisfactory ^1H NMR spectrum. An analytical sample could be obtained by flash chromatography (R_f 0.22, methylene chloride-petroleum ether (40-70°C)-methanol, 60:40:1): IR ($CHCl_3$): 3400 (w, NH_2), 2990, 2955, 2850, 1720 (s, C=O), 1605 (sh, C=C), 1450, 1275 (s), 1190, 1120, 1030, 990, 910 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.33 (s, 3H, 3'-CH_3), 1.3-1.5 (s, br, D_2O exchangeable, 2H, NH_2), 2.11-2.15 (dd, J_{trans} = 5.0 Hz, J_{gem} = 11.8 Hz, 1H, *endo* C_6-H), 2.46-2.51 (dd, J_{cis} = 9.4 Hz, J_{gem} = 11.8 Hz, 1H, *exo* C_6-H), 2.90-2.93 (dd, J_{trans} = 4.9 HZ, J_{cis} = 9.4 Hz, 1H, C_5-H), 3.55 (s, 3H, *syn* OCH_3), 3.60 (s, 3H, *anti* OCH_3), 4.06-4.09 (d, J = 11.0 Hz, 1H, C_1'-H), 4.11-4.14 (d, J = 11.0 Hz, 1H, C_1'-H), 7.45-7.49 (m, 2H, *m*-ArH), 7.57-7.61 (m, 1H, *p*-ArH), 8.04-8.06 (m, 2H, *o*-ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.34 (3'-CH_3), 38.10 (C_6); 51.62, 52.87 (ketal OCH_3); 51.76 (C_5), 53.80 (C_2'), 72.16 (CH_2O); 73.94, 77.93 (C_1, C_4); 112.8 (C_7); 128.5, 129.6, 133.2 (Ar CH); 128.5, 129.9 (C_2, C_3); 129.4 (*ipso*-Ar), 166.2 (C=O); MS (FAB, 3-NOBA matrix): 472 (11), 470 (MH^+ for 3 x ^{35}Cl, 1 x ^{37}Cl, 22), 468 (17), 255 (5.4), 253 (6.2), 105 (COPh, 100), 77 (8.7); Anal. Calcd for $C_{19}H_{21}NO_4Cl_4$: C, 48.64; H, 4.51; N, 2.99; Cl, 30.22. Found: C, 48.98; H, 4.69; N, 2.88; Cl, 30.31.

(1R*,4S*,5S*,2'R*)-7,7-Dimethoxy-1,2,3,4-tetrachloro-5-[2'-(2'-amino-1'-benzoyloxy)-propyl]-bicyclo[2.2.1]hept-2-ene (7b).
To solid **5b** (10.8 g, 23.9 mmol), was added 7% H_2SO_4 in 95% MeOH(aq) (60 ml, prepared as for the hydrolysis of **5a**, *vide supra*). After refluxing for 4 h, the reaction was worked up in the same manner as for **7a**. In this case the crude product was purified by flash chromatography (eluant: CH_2Cl_2-petroleum ether (40-70°C)-MeOH-NH_3(aq), 50:50:2.5:0.5) to give 11.0 g (98%) of **7b** as a light orange oil: IR ($CHCl_3$): 3400 (w, NH_2), 2980, 2960, 2850, 1720 (s, C=O), 1605 (sh, C=C), 1450, 1320, 1275 (s), 1195, 1120, 1030, 990 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.11 (s, 3H, 3'-CH_3), 1.2-1.5 (s, br, 2H, NH_2), 2.20-2.26 (dd, J_{trans} = 5.1 Hz, J_{gem} = 11.4 Hz, 1H, *endo* C_6-H), 2.41-2.48 (dd, J_{cis} = 9.3 Hz, J_{gem} = 11.3 Hz, 1H, *exo* C_6-H), 2.92-2.97 (dd, J_{trans} = 5.1 Hz, J_{cis} = 9.3 Hz, 1H, C_5-H), 3.55 (s, 3H, *syn* OCH_3), 3.60 (s, 3H, *anti* OCH_3), 4.25-4.29 (d, J = 11.1 Hz, 1H, C_1'-H), 4.37-4.40 (d, J = 11.0 Hz, 1H, C_1'-H), 7.44-7.50 (m, 2H, *m*-ArH), 7.56-7.62 (m, 1H, *p*-ArH), 8.05-8.08 (m, 2H, *o*-ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.70 (3'-CH_3), 37.78 (C_6); 51.57, 52.83 (ketal OCH_3); 51.57 (C_5), 53.86 (C_2'), 71.96 (CH_2O); 74.00, 77.88 (C_1, C_4), 112.9 (C_7); 127.8, 128.5, 130.1 (C_2, C_3, *ipso*-Ar); 128.5, 130.1, 133.1 (Ar CH); 166.1 (C=O); MS (FAB, 3-NOBA matrix): 470 (MH^+ for 3 x ^{35}Cl, 1 x ^{37}Cl, 47), 468 (37), 253 (8.1), 178 (24), 105 (COPh, 100), 77 (Ph, 22), 70 (15); Anal. Calcd for $C_{19}H_{21}NO_4Cl_4$: C, 48.64; H, 4.51; N, 2.99; Cl, 30.22. Found: C, 49.06; H, 4.77; N, 2.80; Cl, 29.94.

(1R*,2R*,3S*,6S*,7S*,8S*)-6-Amino-6-methyl-1,2,8-trichloro-3,9,9-trimethoxy-4-oxatricyclo[5.2.1.$0^{3,8}$]decane (6a).
(1R*,2R*,3S*,6S*,7S*,8S*)-6-Benzamido-6-methyl-1,2,8-trichloro-3,9,9-trimethoxy-4-oxatricyclo[5.2.1.$0^{3,8}$]decane (15a). To a solution of benzoate **7a** (629 mg, 1.34 mmol) in THF (2 ml) were added 6 N KOH (2 ml, 12 mmol) and methanol (4 ml). The resulting yellow emulsion was stirred vigorously at room temperature for 5 h and then brought to pH 4 with 2 N HCl. The mixture was partitioned between ether (100 ml) and H_2O (100 ml). The organic layer was extracted with a second portion of H_2O and conversely, the aqueous layer extracted with a second portion of ether. The combined aqueous layers were lyophilized. The combined ether extracts were dried over $MgSO_4$ and then adsorbed directly on to silica gel and subjected to flash chromatography [eluant: 50:50:0.5 CH_2Cl_2-petroleum ether (40-70°C)-MeOH]. This procedure afforded 54.3 mg (8.7%) of **15a** as a white solid which could be recrystallized from ether-hexane to give a white powder: mp 160-161°C. The residue obtained from lyophilization of the aqueous extracts was taken up in CH_2Cl_2 (200 ml) to which Na_2CO_3 (530 mg, 5.0 mmol) and H_2O (4 ml) were added. The resulting suspension was stirred vigorously at room temperature for 2 h and then dried over Na_2SO_4. The solvent was removed in vacuo and the residue purified by flash chromatography [eluant: 57:38:5:1 CH_2Cl_2-petroleum ether (40-70°C)-MeOH-NH_3(aq)] to give a first fraction (R_f 0.46) containing 90.5 mg (18.7%) of **6a** as a white crystalline solid: mp 83-85°C. A second fraction (R_f 0.20) afforded 299 mg (61.1%) of amino alcohol **8a** (*vide infra*).
For compound **6a**: IR (KBr): 3375 (sh, NH_2), 3000, 2970, 2950, 2840, 1470, 1445, 1320, 1220, 1130, 1085, 1045, 830, 810, 760, 700, 650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): d 1.09 (s, 3H, CH_3), 1.72 (s, br, 2H, NH_2), 2.15-2.20 (dd, J_{trans} = 5.4 Hz, J_{gem} = 13.1 Hz, 1H, *endo* C_{10}-H), 2.22-2.29 (ddd, $^4J_{10x,2}$ = 2.4 Hz, J_{cis} = 11.7 Hz, J_{gem} = 13.1 Hz, 1H, *exo* C_{10}-H), 2.54-2.59 (ddd, $^4J_{7,5}$ = 1.0 Hz, J_{trans} = 5.5 Hz, J_{cis} = 11.7 Hz, 1H, C_7-H), 3.49 (s, 3H, *exo* OCH_3), 3.64 (s, 3H, ketal OCH_3), 3.66 (s, 3H, ketal OCH_3), 3.62-3.66 (dd, $^4J_{5,7}$ = 1.0 Hz, 1H, C_5-H_R), 4.07-4.10 (d, J =12.1 Hz, 1H, C_5-H_S), 4.66-4.67 (d, $^4J_{2,10x}$ = 2.4 Hz, 1H, C_2-H); NOE experiments (300 MHz, $CDCl_3$): (a) Irradiation of the C_6 methyl group gave enhancements at *endo* C_{10}-H (1.9%), C_5-H_S (1.2%), C_7-H (0.76%) and at the NH_2 (0.26%). [The NOE observed for the *endo* C_{10} proton establishes the relative stereochemistry at C_6 and C_7 as (6R,7R).]; (b) Irradiation of the C_6 amino group showed enhancements at C_7-H (2.7%), C_5-H_R (2.4%) and at the C_6 methyl group (1.9%); (c) Irradiation of the C_3 OCH_3 group gave a single NOE at the C_2-H (3.1%); ^{13}C NMR (100 MHz, $CDCl_3$): d 24.66 (CH_3), 33.85 (C_{10}), 48.39 (C_7), 48.97 (C_6); 50.09, 51.42, 51.78 (3 x OCH_3); 71.14 (CHCl),

71.28 (CH_2O); 71.14, 72.98 (C_1, C_8); 97.02, 103.0 (C_3, C_9); MS (FAB, 3-NOBA matrix): 364 (26), 362 (78), 360 (MH^+ for 3 x ^{35}Cl, 83), 345 (6.1), 343 (6.5), 330 (6.5), 328 (M^+ - OCH_3, 9.4), 289 (8.5), 287 (8.1), 273 (11), 271 (13), 215 (18), 154 (24), 147 (28), 137 (29), 136 (46), 135 (26), 109 (23), 91 (31), 73 (100); Anal. Calcd for $C_{13}H_{20}NO_4Cl_3$: C, 43.29; H, 5.59; N, 3.88; Cl, 29.49. Found: C, 43.19; H, 5.64; N, 3.65; Cl, 29.05.

For compound **15a**: IR (KBr): 3430, 3310 (NH), 2975, 2950, 2840, 1635 (s, C=O), 1550, 1480, 1320, 1280, 1265, 1215, 1120 , 1090, 1050 ,1040, 830, 815, 710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): d 1.51 (3, 3H, CH_3), 2.14-2.19 (dd, J_{trans} = 4.8 Hz, J_{gem} = 13.2 Hz, 1H, *endo* C_{10}-H), 2.34-2.41 (ddd, $^4J_{10x,2}$ = 2.6 Hz, J_{cis} = 12.2 Hz, J_{gem} = 13.2 Hz, 1H, *exo* C_{10}-H), 3.43-3.48 (ddd, $^4J_{7,5}$ = 1.6 Hz, J_{trans} = 4.8 Hz, J_{cis} = 12.1 Hz, 1H, C_7-H), 3.50 (s, 3H, *exo* OCH_3), 3.61 (s, 3H, ketal OCH_3), 3.65 (s, 3H, ketal OCH_3), 4.02-4.06 (dd, $^4J_{5,7}$ = 1.7 Hz, J = 13.1 Hz, 1H, C_5-H_R), 4.41-4.44 (d, J = 13.1 Hz, 1H, C_5-H_S), 4.74-4.75 (d, $^4J_{2,10x}$ = 2.6 Hz, 1H, C_2-H), 6.53 (s, br, 1H, NH), 7.38-7.42 (m, 2H, *m*-ArH), 7.45-7.49 (m, 1H, *p*-ArH), 7.73-7.76 (m, 2H, *o*-ArH); ^{13}C NMR (100 MHz, $CDCl_3$): d 19.83 (CH_3), 32.50 (C_{10}), 42.43 (C_7), 50.14 (*exo* OCH_3); 51.41, 51.89 (ketal OCH_3); 51.87 (C_6), 68.50 (CH_2O), 70.09 (CHCl); 71.26, 72.13 (C_1, C_8); 97.37, 102.9 (C_3, C_9); 127.0, 128.5, 131.3 (Ar CH); 135.3 (*ipso*-Ar), 167.6 (C=O); MS (FAB, 3-NOBA matrix): 466 (33), 464 (MH^+ for 3 x ^{35}Cl, 34), 434 (9.9), 432 (M^+ - OCH_3, 10), 215 (5.9), 160 (12), 154 (23), 137 (25), 136 (25), 105 (COPh, 100), 79 (33), 77 (Ph, 23); Anal. Calcd for $C_{20}H_{24}NO_5Cl_3$: C, 51.69; H, 5.20; N, 3.01; Cl, 22.88. Found: C, 51.91; H, 5.39; N, 2.80; Cl, 22.85.

(1R*,4S*,5S*,2'S*)-7,7-Dimethoxy-1,2,3,4-tetrachloro-5-[2'-(2'-amino-1'-hydroxy)-propyl]-bicyclo[2.2.1]hept-2-ene (8a).
Lithium aluminium hydride (50.3 mg, 1.32 mmol) was suspended in ether (distilled from Na-benzophenone, 8 ml) and brought to reflux. A solution of **7a** (270 mg, 0.576 mmol) in dry ether (2 ml) was added by syringe and refluxing continued for 1 h. After cooling to room temperature, the reaction was quenched with H_2O (300 µl) and let stir 1.5 h, whereupon a generous white precipitate formed. The ether was decanted and the precipitate extracted thoroughly with ether (9 x 20 ml). The combined ether portions were dried over Na_2SO_4. The solvent was evaporated in vacuo and the residue purified by flash chromatography [eluant: CH_2Cl_2-petroleum ether (40-70°C)-MeOH-NH_3(aq), 50:50:2.5:0.5] to yield 187 mg (89%) of **8a** as a slightly yellow oil: IR ($CHCl_3$): 3630 (br, OH), 3300-3500 (br, NH_2), 2990, 2950, 2850, 1605 (sh, C=C), 1460, 1280, 1195, 1125, 1045, 990, 910, 885 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.16 (s, 3H, 3'-CH_3), 1.45-1.85 (s, br, 3H, NH_2, OH), 1.93-1.98 (dd, J_{trans} = 4.9 Hz, J_{gem} = 11.9 Hz, 1H, *endo* C_6-H), 2.42-2.47 (dd, J_{cis} = 9.5 Hz, J_{gem} = 11.8 Hz, 1H, *exo* C_6-H), 2.77-2.80 (dd, J_{trans} = 4.9 Hz, J_{cis} = 9.4 Hz, 1H, C_5-H), 3.24-3.27 (d, J = 10.7 Hz, 1H, C_1'-H), 3.37-3.40 (d, J = 10.7 Hz, 1H, C_1'-H), 3.55 (s, 3H, *syn* OCH_3), 3.61 (s, 3H, *anti* OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.11 (3'-CH_3), 37.98 (C_6); 51.70, 52.86 (ketal OCH_3); 52.01 (C_5), 54.91 (C_2'), 69.86 (CH_2O); 73.95, 78.10 (C_1, C_4); 112.8 (C_7); 128.5, 129.4 (C_2, C_3); MS (FAB, 3-NOBA): 368 (56), 366 (MH^+ for 3 x ^{35}Cl, 1 x ^{37}Cl, 100), 364 (86), 334 (18), 332 (18), 255 (18), 253 (17), 219 (10), 74 (63), 70 (37), 59 (16); Anal. Calcd for $C_{12}H_{17}NO_3Cl_4$: C, 39.48; H, 4.69; N, 3.84; Cl, 38.84. Found: C, 39.94; H, 4.84; N, 3.62; Cl, 38.49.

(1R*,4S*,5S*,2'R*)-7,7-Dimethoxy-1,2,3,4-tetrachloro-5-[2'-(2'-amino-1'-hydroxy)-propyl]-bicyclo[2.2.1]hept-2-ene (8b). To a refluxing suspension of $LiAlH_4$ (1.38 g, 36.3 mmol) in ether (distilled from Na-benzophenone, 100 ml) was added via syringe a solution of **7b** (7.40 g, 15.8 mmol) in dry ether (50 ml). After refluxing for 0.5 h, the reaction mixture was cooled to 0°C, carefully quenched with H_2O (7.5 ml), and then stirred at room temperature for 1 h. After decanting the ether, the white precipitate was extracted once more with ether and then allowed to stir overnight with a third portion (100 ml each). The combined organic extracts were dried over Na_2SO_4, and the solvent removed in vacuo. Flash chromatography [R_f 0.24, CH_2Cl_2-petroleum ether(40-70°C)-MeOH-NH_3(aq), 56:38:5:1] afforded 4.52 g (79%) of **8b** as a white solid which could be recrystallized from ether-hexane: (white needles) mp 112°C; IR (KBr): 3380, 3305 (both sh, NH_2); 3050-3500 (br, OH), 2995, 2950, 2825, 1605 (sh, C=C), 1580, 1465, 1290, 1210, 1195, 1120, 1035, 995, 905, 885, 785, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.98 (s, 3H, 3'-CH_3), 1.4-1.85 (br, 3H, NH_2, OH), 1.94-2.00 (dd, J_{trans} = 5.1 Hz, J_{gem} = 11.5 Hz, 1H, *endo* C_6-H), 2.41-2.47 (dd, J_{cis} = 9.4 Hz, J_{gem} = 11.5 Hz, 1H, *exo* C_6-H), 2.83-2.88 (dd, J_{trans} = 5.1 Hz, J_{cis} = 9.4 Hz, 1H, C_6-H), 3.36-3.40 (d, J = 11.0 Hz, 1H, C_1'-H), 3.45-3.49 (d, J = 11.0 Hz, 1H, C_1'-H), 3.55 (s, 3H, *syn* OCH_3), 3.61 (s, 3H, *anti* OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.76 (3'-CH_3), 38.17 (C_6), 51.44 (C_5); 51.66, 52.86 (ketal OCH_3); 55.25 (C_2'), 70.11 (CH_2O); 73.90, 78.31 (C_1, C_4); 113.0 (C_7); 128.1, 129.6 (C_2, C_3); MS (FAB, 3-NOBA matrix): 368 (48), 366 (MH^+ for 3 x ^{35}Cl, 1 x ^{37}Cl, 100), 364 (77), 334 (15), 332 (13), 255 (8.9), 253 (8.7), 74 (61), 70 (43); Anal. Calcd for $C_{12}H_{17}NO_3Cl_4$: C, 39.48; H, 4.69; N, 3.84; Cl, 38.84. Found: C, 39.43; H, 4.56; N, 3.80; Cl, 39.19.

(1R*,4R*,5R*,2'S*)-7,7-Dimethoxy-5-[2'-(2'-amino-1'-hydroxy)-propyl]-bicyclo[2.2.1]-hept-2-ene (1a) and **(1R*,4R*,5R*,2'R*)-7,7-Dimethoxy-5-[2'-(2'-amino-1'-hydroxy)-propyl]-bicyclo[2.2.1]hept-2-ene (1b)** were synthesized by reductive dechlorination of **8a** and **8b**, respectively, as previously reported.[15]

(1R*,4R*,5R*,5'S*)-7,7-Dimethoxy-5-[5'-(3',5'-dimethyl-5',6'-dihydro-2'*H*-1',4'-oxazin-2'-onyl)]-bicyclo[2.2.1]hept-2-ene (9a). The condensation conditions used here are similar to those employed by Koch et al.[16] to generate simple 5,6-dihydro-2*H*-1,4-oxazin-2-ones. To a solution of amino alcohol **1a** (992 mg, 4.37 mmol) in refluxing *n*-butyl alcohol (distilled from Na-diethyl phthalate, 22 ml) under Ar was added dropwise, via syringe, freshly distilled ethyl pyruvate [Fluka, bp(35 torr) 63-64°C, 488 µl, 4.37 mmol]. A Dean Stark trap containing activated 4 Å molecular sieves was used to remove H_2O

and EtOH formed in the reaction. The reaction mixture was allowed to reflux for 12 h and then cooled to room temperature. The solvent was removed under reduced pressure and the crude product purified by flash chromatography (eluant: 1:1 ethyl acetate-pentane) to yield 725 mg (59.5%) of **9a** as a white solid (R_f 0.74, 95:5 CH_2Cl_2-MeOH). Recrystallization from ether-hexane gave transparent prisms: mp 110°C; IR (KBr): 2990, 2960, 2940, 2830, 1735 (s, C=O), 1640 (m, C=N), 1575 (w), 1479, 1450, 1410, 1290, 1250, 1115 (s), 1100, 1085, 1035, 1010, 795, 755 (sh), 660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.92-0.97 (dd, J_{trans} = 5.6 Hz, J_{gem} = 11.9 Hz, 1H, *endo* C_6-H), 1.14 (s, 3H, 5'-CH_3), 2.02-2.08 (ddd, $J_{6x,1}$ = 4.1 Hz, J_{cis} = 8.9 Hz, J_{gem} = 11.9 Hz, 1H, *exo* C_6-H), 2.23 (s, 3H, 3'-CH_3), 2.56-2.60 (ddd, $J_{5,4}$ = 3.2 Hz, J_{trans} = 5.6 Hz, J_{cis} = 8.9 Hz, 1H, C_5-H), 2.79-2.82 (m, 1H, C_1-H), 2.91-2.93 (m, 1H, C_4-H), 3.13 (s, 3H, *syn* OCH_3), 3.20 (s, 3H, *anti* OCH_3), 4.09-4.11 (d, J = 11.5 Hz, 1H, C_6'-H), 4.20-4.23 (d, J = 11.5 Hz, 1H, C_6'-H), 6.02-6.05 (ddd, $^4J_{3,1}$ = 0.94 Hz, $J_{3,4}$ = 3.2 Hz, J_{cis} = 6.2 Hz, 1H, C_3-H), 6.12-6.14 (ddd, $^4J_{2,4}$ = 0.95 Hz, $J_{2,1}$ = 3.5 Hz, J_{cis} = 6.2 Hz, 1H, C_2-H); ^1H NMR decoupling experiments (300 MHz, $CDCl_3$): (a) Irradiation of C_1-H gave decoupling at C_2-H and *exo* C_6-H, as well as allylic decoupling at C_3-H; (b) Irradiation of C_4-H showed decoupling at C_3-H and C_5-H, as well as allylic decoupling at C_2-H; ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.57 (5'-CH_3), 22.71 (3'-CH_3), 26.91 (C_6); 44.04, 44.70, 47.02 (C_1, C_4, C_5); 49.70, 51.98 (ketal OCH_3); 58.16 (C_5'), 73.84 (CH_2O), 119.0 (C_7); 131.2, 133.2 (C_2, C_3); 155.8 (C=N), 156.6 (C=O); MS (FAB, 3-NOBA matrix): 280 (MH^+, 57), 279 (M^+, 53), 264 (M^+ - CH_3, 33), 248 (M^+ - OCH_3, 100), 232 (12), 193 (14), 154 (66), 153 (66), 137 (54), 136 (52), 128 (37), 79 (41); Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.18; H, 7.53; N, 4.83.

(1R*,4R*,5R*,5'R*)-7,7-Dimethoxy-5-[5'-(3',5'-dimethyl-5',6'-dihydro-2'*H*-1',4'-oxazin-2'-onyl)]-bicyclo[2.2.1]hept-2-ene (9b). To a refluxing solution of amino alcohol **1b** (1.48 g, 6.52 mmol) in *n*-butyl alcohol (distilled from Na-dibutyl phthalate, 32.6 ml) under Ar was added dropwise, via syringe, freshly distilled ethyl pyruvate [Fluka, bp(35 torr) 62-64°C, 728 µl, 6.52 mmol]. and refluxing continued for 12 h. Reaction, work up and flash chromatography (R_f 0.35, 1:1 ethyl acetate-pentane) were carried out in the same manner as for the synthesis of **9a** (*vide supra*) to give 1.16 g (64%) of **9b** as a slightly yellow oil: IR ($CHCl_3$): 2980, 2940, 2840, 1735 (s, C=O), 1640 (m, C=N), 1575 (very w), 1465, 1450, 1400, 1370, 1310, 1290, 1120 (s), 1080, 1050, 870 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.05-1.11 (dd, J_{trans} = 5.4 Hz, J_{gem} = 11.7 Hz, 1H, *endo* C_6-H), 1.16 (s, 3H, 5'-CH_3), 2.01-2.09 (ddd, $J_{6x,1}$ = 4.1 Hz, J_{cis} = 8.9 Hz, J_{gem} = 11.8 Hz, 1H, *exo* C_6-H), 2.23 (s, 3H, 3'-CH_3), 2.63-2.68 (ddd, $J_{5,4}$ = 3.3 Hz, J_{trans} = 5.4 Hz, J_{cis} = 8.9 Hz, 1H, C_5-H), 2.82-2.84 (m, 1H, C_1-H), 2.93-2.96 (m, 1H, C_4-H), 3.13 (s, 3H, *syn* OCH_3), 3.20 (s, 3H, *anti* OCH_3), 4.04-4.08 (d, J = 11.5 Hz, 1H, C_6'-H), 4.16-4.20 (d, J = 11.5 Hz, 1H, C_6'-H), 5.90-5.93 (ddd, $^4J_{3,1}$ = 0.94 Hz, $J_{3,4}$ = 3.2 Hz, J_{cis} = 6.2 Hz, 1H, C_3-H), 6.14-6.17 (ddd, $^4J_{2,4}$ = 0.97 Hz, $J_{2,1}$ = 3.6 Hz, J_{cis} = 6.2 Hz, 1H, C_2-H); ^1H NMR decoupling experiments (300 MHz, $CDCl_3$): (a) Irradiation of C_1-H gave decoupling at C_2-H and *exo* C_6-H, as well as allylic decoupling at C_3-H; (b) Irradiation of C_4-H showed decoupling at C_3-H and C_5-H, as well as allylic decoupling at C_2-H; ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.55 (5'-CH_3), 22.80 (3'-CH_3), 26.26 (C_6); 44.50, 44.69, 46.68 (C_1, C_4, C_5); 49.70, 51.97 (ketal OCH_3); 58.28 (C_5'), 73.87 (CH_2O), 119.3 (C_7); 130.7, 133.7 (C_2, C_3); 155.9 (C=N), 156.8 (C=O); MS (FAB, 3-NOBA matrix): 280 (MH^+, 60), 279 (M^+, 53), 264 (M^+ - CH_3, 69), 252 (49), 248 (M^+ - OCH_3, 100), 153 (97), 128 (71), 121 (48), 105 (37), 95 (49), 91 (45), 79 (38), 77 (36), 75 (38); Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.37; H, 7.69; N, 4.78.

(1R*,4R*,5R*,5'S*)-5-[5'-(3',5'-Dimethyl-5',6'-dihydro-2'*H*-1',4'-oxazin-2'-onyl)]-bicyclo[2.2.1]hept-2-en-7-one (10a). Preparation of a solution of dimethylboron bromide: The general ketal deprotection procedure employed here is due to Guindon and coworkers.[17] Dimethylboron bromide was obtained as a neat liquid from Aldrich. A 1.5 M solution of Me_2BBr in CH_2Cl_2 (distilled from CaH_2 and stored over 4 Å molecular sieves) was prepared as follows: To a dry 50 ml round bottom flask was added 23.5 ml of dry CH_2Cl_2. The flask was flushed with Ar and sealed with a septum. A "glove box" constructed from a plastic bag was simultaneously flushed with house nitrogen and evacuated on a house vacuum line for 15 min. The vacuum was then removed and the following operations carried out in the "glove box" under positive nitrogen pressure. An ampule containing the Me_2BBr (5.0 g, 41.4 mmol, 4.0 ml) was cooled for 20 s in liquid nitrogen and then opened. The transparent liquid was transferred via syringe to the CH_2Cl_2-containing flask. The resulting solution was stored dessicated (KOH) at -20°C and showed no appreciable decomposition after 4 months. To a stirred solution of **9a** (590 mg, 2.11 mmol) in dry CH_2Cl_2(18 ml) under Ar at -78°C was added, via syringe, Me_2BBr (4.23 mmol, as 2.82 ml of a 1.5 M solution in CH_2Cl_2). The resulting lemon yellow solution was stirred for 1 h at -78°C and then transferred via cannula to a vigorously stirred suspension of THF (20 ml) and saturated, aqueous $NaHCO_3$ (10 ml) at room temperature. After 5 min, the suspension was poured into a separatory funnel containing ether (80 ml), and enough H_2O was added to dissolve all salts. The aqueous layer was extracted once more (80 ml ether) and the combined organic layers dried over $NaSO_4$. Removal of the solvent in vacuo, and flash chromatography (R_f 0.40, 1:1 ethyl acetate-pentane) gave 393 mg (79%) of **10a** as a yellow solid. Slightly yellow needles were obtained upon recrystallization from ether: mp 73-75°C; IR (KBr): 2980, 2880, 1770 (s, C=O, ketone), 1735 (s, C=O, lactone), 1645 (m, C=N), 1455, 1410, 1370, 1300, 1150, 1120, 1040, 925, 870, 790, 760, 725 (sh), 640, 615, 565 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.12-1.19 (dd, J_{trans} = 7.8 Hz, J_{gem} = 12.1 Hz, 1H, *endo* C_6-H), 1.17 (s, 3H, 5'-CH_3), 2.18-2.27 (ddd, $J_{6x,1}$ = 4.3 Hz, J_{cis} = 9.8 Hz, J_{gem} = 12.1 Hz, 1H, *exo* C_6-H), 2.24 (s, 3H, 3'-CH_3), 2.44-2.51 (ddd, $J_{5,4}$ = 3.1 Hz, J_{trans} = 7.8 Hz, J_{cis} = 9.8 Hz, 1H, C_5-H), 2.93-2.97 (m, 1H, C_1-H), 2.99-3.02 (m, 1H, C_4-H), 4.12-4.16 (d, J = 11.6 Hz, 1H, C_6'-H), 4.19-4.23 (d, J = 11.6 Hz, 1H, C_6'-H), 6.42-6.45 (ddd, $^4J_{3,1}$ = 0.76 Hz, $J_{3,4}$ = 3.1 Hz, J_{cis} = 6.8 Hz, 1H, C_3-H), 6.54 - 6.58 (ddd, $^4J_{2,4}$ = 0.99 Hz, $J_{2,1}$ = 3.8 Hz, J_{cis} = 6.8 Hz, 1H, C_2-H); ^1H NMR decoupling experiments (300 MHz, $CDCl_3$): (a) Irradiation of C_1-H gave decoupling at C_2-H

and *exo* C_6-H, as well as allylic decoupling at C_3-H; (b) Irradiation of C_4-H showed decoupling at C_3-H and C_5-H, as well as allylic decoupling at C_2-H; ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.61 (5'-CH_3), 22.19 (3'-CH_3), 26.38 (C_6), 41.40 (C_5); 46.64, 48.74 (C_1, C_4); 58.45 ($C_{5'}$), 72.87 (CH_2O); 130.4, 132.3 (C_2, C_3); 155.4 (C=N), 157.5 (C=O, lactone), 201.4 (C=O, ketone); MS (FAB, 3-NOBA matrix): 234 (MH^+, 100), 233 (M^+, 25), 205 (M^+ - CO, 45), 165 (12), 154 (99), 137 (77), 127 (54), 91 (44), 79 (65), 77 (50), 69 (32); Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.64; H, 6.65; N, 5.81.

(1R*,4R*,5R*,5'R*)-5-[5'-(3',5'-Dimethyl-5',6'-dihydro-2'*H*-1',4'-oxazin-2'-onyl)]-bicyclo[2.2.1]hept-2-en-7-one (10b). To a stirred solution of dihydrooxazinone **9b** (1.16 g, 4.16 mmol) in CH_2Cl_2 (distilled from CaH_2 and stored over 4 Å molecular sieves, 36.1 ml) under Ar at -78°C was added dropwise via syringe dimethylboron bromide (Aldrich, 8.32 mmol as 5.54 ml of a 1.5 M solution in CH_2Cl_2). After stirring for 1 h at -78°C, the reaction was quenched (20 ml of $NaHCO_3$(aq)-40 ml of THF) and worked up exactly as in the preparation of **10a** (*vide supra*). Flash chromatography (R_f 0.40, 1:1 ethyl acetate-pentane) gave 817 mg (84%) of **10b** as a white solid which readily crystallized from ethyl acetate-ether as transparent, colorless prisms: mp 133-135°C; IR (KBr): 2980, 2960, 2940, 2900, 1765 (s, C=O, ketone), 1735 (s, C=O, lactone), 1640 (m, C=N), 1455, 1430, 1410, 1205, 1155, 1140, 1125 (sh), 1040 (sh), 865, 805, 780, 760, 730 (sh), 550 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.17 (s, 3H, 5'-CH_3), 1.31-1.37 (dd, J_{trans} = 7.4 Hz, J_{gem} = 12.0 Hz, 1H, *endo* C_6-H), 2.17-2.26 (ddd, $J_{6x,1}$ = 4.3 Hz, J_{cis} = 9.8 Hz, J_{gem} = 12.0 Hz, 1H, *exo* C_6-H), 2.23 (s, 3H, 3'-CH_3), 2.43-2.49 (ddd, $J_{5,4}$ = 3.1 Hz, J_{trans} = 7.4 Hz, J_{cis} = 9.7 Hz, 1H, C_5-H), 2.96-2.98 (m, 1H, C_1-H), 3.05-3.08 (m, 1H, C_4-H), 4.10-4.13 (d, J = 11.5 Hz, 1H, $C_{6'}$-H), 4.21-4.25 (d, J = 11.5 Hz, 1H, $C_{6'}$-H), 6.29-6.33 (ddd, $J_{3,4}$ = 3.4 Hz, J_{cis} = 6.8 Hz, 1H, C_3-H), 6.53-6.57 (ddd, $^4J_{2,4}$ = 0.89 Hz, $J_{2,1}$ =3.8 Hz, J_{cis} = 6.8 Hz, 1H, C_2-H); ^1H NMR decoupling experiments (300 MHz, $CDCl_3$): (a) Irradiation of C_1-H gave decoupling at C_2-H and *exo* C_6-H, as well as allylic decoupling at C_3-H; (b) Irradiation of C_4-H showed decoupling at C_3-H and C_5-H, as well as allylic decoupling at C_2-H; ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.58, 22.02 (3'-, 5'-CH_3); 25.46 (C_6), 41.69 (C_5); 46.58, 48.72 (C_1, C_4); 58.45 ($C_{5'}$), 73.36 (CH_2O); 129.8, 132.4 (C_2, C_3); 155.5 (C=N), 157.6 (C=O, lactone), 201.6 (C=O, ketone); MS (FAB, 3-NOBA matrix): 234 (MH^+, 73), 233 (M^+, 36), 205 (M^+ - CO, 39), 154 (100), 137 (89), 136 (85), 127 (59), 107 (44), 79 (64), 77 (42); Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.00; H, 6.41; N, 5.93.

(±)-N-*tert*-Butyloxycarbonylalanine (12). The procedure for introduction of the BOC protecting group employed here is essentially that of Bodansky and Bodansky.[21] To a solution of alanine (8.91 g, 100 mmol) in a mixture of aqueous NaOH (100 mmol as 200 ml of a 0.5 M solution) and dioxane (100 ml) at 0°C was added di-*tert*-butyl dicarbonate (24.0 g, 110 mmol) and stirring continued for 30 min at room temperature. The reaction mixture was then concentrated to ca. 150 ml on a rotary evaporator. Ethyl acetate (300 ml) was added and, after being cooled to 0°C, the solution was brought to pH 2.5 with aqueous $KHSO_4$ (300 mM). After separation of the organic layer the aqueous phase was extracted once more with ethyl acetate (300 ml) and the combined extracts dried over Na_2SO_4. Removal of the solvent in vacuo gave 17.1 g (90.5%) of **12** as a white solid which could be recrystallized from hot ether to give transparent, colorless needles: mp 109-111°C (lit.[22] mp 110.5-111.5°C); ^1H NMR (200 MHz, $CDCl_3$): δ 1.44 (s, 9H, *t*-butyl CH_3), 1.40-1.44 (d, 3H, α-CH_3), 4.25-4.40 (apparent quintet, 1H, α-H), 5.0-5.2 (s, br, 1H, NH), 7.6-8.3 (s, br, 1H, CO_2H).

(±)-2'-Oxopropyl N-*tert*-butyloxycarbonylalaninate (13). In contrast to reports in the literature[23] it was found that, at least in this case, esterification via an activated imidazolide intermediate proceeds smoothly at room temperature, and without addition of a strong base. To a solution of **12** (1.38 g, 7.30 mmol) in THF (distilled from Na-benzophenone, 7.3 ml) was added N,N-carbonyldiimidazole (1.19 g, 7.30 mmol) whereupon vigorous CO_2 evolution was observed. Stirring was continued for 30 min at room temperature under exclusion of moisture. Freshly distilled hydroxyacetone (acetol) (509 µl, 7.30 mmol) was then added via syringe and the reaction mixture stirred 9 h at room temperature. The solvent was evaporated in vacuo and the residue partitioned between ether (150 ml) and H_2O (50 ml). The ether layer was washed twice more with H_2O (50 ml each time) to remove imidazole. The organic layer was dried over $NaSO_4$ and then adsorbed directly on to silica gel and flash chromatographed (gradient: 25%-67% ethyl acetate/pentane) to afford 1.43 g (80%) of **13** as a white solid: mp 66-69°C; ^1H NMR (200 MHz, $CDCl_3$): δ 1.44 (s, 9H, *t*-butyl CH_3), 1.45-1.49 (d, J = 7.2 Hz, 3H, α-CH_3), 2.16 (s, 3H, $COCH_3$), 4.33-4.48 (apparent quintet, 1H, α-H), 4.57-4.65 (d, J = 16.9 Hz, 1H, CH_2O), 4.75-4.83 (d, J = 16.8 Hz, 1H, CH_2O), 4.9-5.1 (s, br, 1H, NH).

(±)-3,5-Dimethyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (11). For a similar synthesis of this compound from the N-Cbz protected acetol ester of alanine see ref. 18. To solid **13** (300 mg, 1.22 mmol) was added a solution of 33% HBr in acetic acid (Fluka, 4.1 M, 3 ml, 12.3 mmol). Immediately, vigorous evolution of CO_2 was observed. Stirring was continued for 40 min at room temperature, with exclusion of moisture. Ether (15 ml) was added and the reaction flask cooled to 0°C for 20 min to precipitate the desired ammonium hydrobromide salt. The salt was collected by vacuum filtration, washed with ether and dried on a high vacuum line (0.03 torr, 1.5 h) at 0°C. The crude hydrobromide was suspended in CH_2Cl_2 (distilled from CaH_2, 15 ml) containing 4 Å molecular sieves (Chemische Fabrik, Uetikon, Switzerland) and the suspension cooled to 0°C. Excess trimethylamine [prepared by liberation from the hydrochloride salt (Eastman) with aqueous 5 M NaOH at 70-80°C and condensation of the distillate at -78°C; stored over 4 Å molecular sieves under Ar at -20°C] was added under Ar via cannula and stirring continued for 15 min. Precipitated trimethylammonium hydrobromide was removed by filtration and the solvent evaporated in vacuo at 0°C. The residue was taken up in ether and insoluble salts separated via filtration as before. Removal of the solvent under reduced pressure at 0°C and drying on a high vacuum pump (0.03 torr, 40 min, 0°C) afforded 106 mg (68%) of **11** as a slightly yellow oil: IR ($CHCl_3$): 2960, 2930, 2880,

2860, 1755 (s, C=O), 1675 (w, C=N), 1455, 1380, 1170, 1130, 1100, 1070, 1040 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.56-1.60 (d, J = 7.3 Hz, 3H, 3-CH_3), 2.10-2.11 (d, ^5J = 1.9 Hz, 3H, 5-CH_3), 4.00-4.15 (qqt, ^5J = 1.9 Hz, ^5J = 2.0 Hz, J = 7.3 Hz, 1H, C_3-H), 4.82-4.83 (d, ^5J = 2.0 Hz, 2H, CH_2O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.34 (3-CH_3), 22.55 (5-CH_3), 54.60 (C_3), 69.13 (CH_2O), 164.8 (C=N), 169.7 (C=O); GC-MS: (Injector T: 210°C; T gradient: 50-300°C at a rate of 10°C/min; solvent delay: 0.45 min) retention time: 4.76-4.97 min. (3 runs); MS (EI): 127 (M^+, 13), 84 (31), 83 (M^+ - CO_2, 97), 69 (58), 68 (100), 56 (65).

Flash Vacuum Pyrolysis Experiments.
The apparatus used for the flash vacuum pyrolysis experiments contained a quartz pyrolysis tube (inner diameter = 2 cm, length = 22 cm) and a rotatable cold finger. It was similar to the apparatus displayed in reference 24. In the experiments described here (see Table 2), the pyrolysis tube was stoppered with a small plug of glass wool and filled with quartz Raschig rings (inner diameter = 3 mm, length = 5 mm) and no carrier gas was used. Sample was placed in a magnetic "boat" and introduced directly into the oven, after preheating, by means of an external magnet.

(a) **Diastereomer 10a** (Table 2, entry 4)
A magnetic "boat" containing the rearrangement precursor **10a** (50 mg, 0.21 mmol) was placed in a 10 ml round-bottom flask and the flask was connected directly to the pyrolysis tube. The apparatus was evacuated to 0.005 torr and the oven was preheated to 600°C. The cold finger was cooled with liquid nitrogen and then the sample introduced directly into the oven. During the pyrolysis the 10 ml flask at the entrance to the oven was continuously heated with a hot air blower to prevent condensation in the flask. The pyrolysis was complete after ca. 12 min. A slightly yellow condensate was visible on the cold finger. The valve between the apparatus and the vacuum pump was closed, the cold finger rotated by 180°, and CH_2Cl_2 (2-3 ml) condensed directly on to the cold finger. After allowing the liquid nitrogen to evaporate, luke warm water was poured into the cold finger and the solution of crude product collected in a flask positioned directly below the cold finger. The magnetic "boat" contained a small amount (0.6 mg) of black residue. The Raschig rings in the first third of the oven were visibly discolored (black). The crude product was chromatographed directly (CH_2Cl_2-MeOH 98:2) to yield a compound assigned structure **14a** (2 mg, 5%) in a first fraction (R_f 0.54), and product **11** (3.4 mg, 12%) in a later fraction (R_f 0.14).
For **14a**: GC-MS (Injector T: 210°C; T gradient: 50-300°C at a rate of 10°C/min; solvent delay: 0.45 min) retention time 10.8 min; MS (EI): 205 (M^+, 2.4), 127 (20), 91 (15), 82 (31), 79 (100), 77 (35).
For **11**: GC-MS (conditions as above) retention time 4.94 min; MS (EI): 127 (M^+, 7.1), 84 (17), 83 (M^+ - CO_2, 100), 69 (32), 68 (87), 56 (29); ^1H NMR (200 MHz, $CDCl_3$): spectrum superimposable on the ^1H NMR spectrum of compound **11** obtained by independent synthesis (*vide supra*).

(b) **Diastereomer 10b** (Table 2, entry 8)
The procedure for **10b** (50 mg, 0.21 mmol) was the same as for diastereomer **10a** except that the pyrolysis was carried out at 400°C instead of 600°C. Following the pyrolysis, the magnetic "boat" contained a small amount (0.2 mg) of black residue. As before, the Raschig rings in the first third of the oven were visibly discolored (black). The crude product was chromatographed directly (CH_2Cl_2-MeOH 98:2) to yield a compound assigned structure **14b** (1.9 mg, 4%) in a first fraction (R_f 0.63), and product **11** (5 mg, 18%) in a later fraction (R_f 0.21).
For **14b**: GC-MS (Injector T: 210°C; T gradient: 50-300°C at a rate of 10°C/min; solvent delay: 0.45 min) retention time 10.8 min; MS (EI): 205 (M^+, 3.5), 127 (31), 91 (19), 82 (40), 79 (100), 77 (45).
For **11**: GC-MS (conditions as above) retention time 4.73 min; MS (EI): 127 (M^+, 7.4), 84 (23), 83 (M^+ - CO_2, 100), 69 (44), 68 (93), 56 (39); ^1H NMR (200 MHz, $CDCl_3$): spectrum superimposable on the ^1H NMR spectrum of compound **11** obtained by independent synthesis (*vide supra*).

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Supplementary Data. Tables of atomic coordinates, bond distances, and bond angles, and a summary of the X-ray crystallographic determination for compound **1a** (4 pages) are available on request from the Director of the Cambridge Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this article.

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19. In principle, the *exo* (**14b**) and *endo* (**14a**) diastereomers could be interconverted via a thermally allowed 1,5-hydrogen shift. The fact that the two diastereomers display different behavior with respect to the retro-ene reaction demonstrates that this 1,5-hydrogen shift does not occur faster than the desired retro-ene reaction. One referee has suggested that the observed *exo* preference for this retro-ene reaction may be due to favorable secondary orbital overlap between the lactone functionality and the developing benzenoid π-system in the transition state.
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