

0040-4020(95)01114-5

Cyclic Imidate Salts in Acyclic Stereochemistry: Diastereoselective *Syn*-Epoxidation of 2-Alkyl-4-Enamides to Epoxyamides

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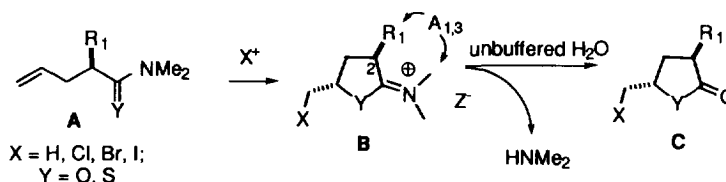
Keywords: Enamide; Epoxidation; Imidate; Indinavir; Iodohydrin.

Abstract: Reaction of 2-alkyl-4-enamides with I^+ and aqueous sodium bicarbonate results in the diastereoselective formation of the corresponding iodohydrins with essentially no iodolactone by-product. The reaction appears to proceed through a cyclic imidate type intermediate. This methodology has been successfully employed for the synthesis of the epoxide intermediate of the orally active HIV-1 protease inhibitor MK-639 (indinavir sulfate).

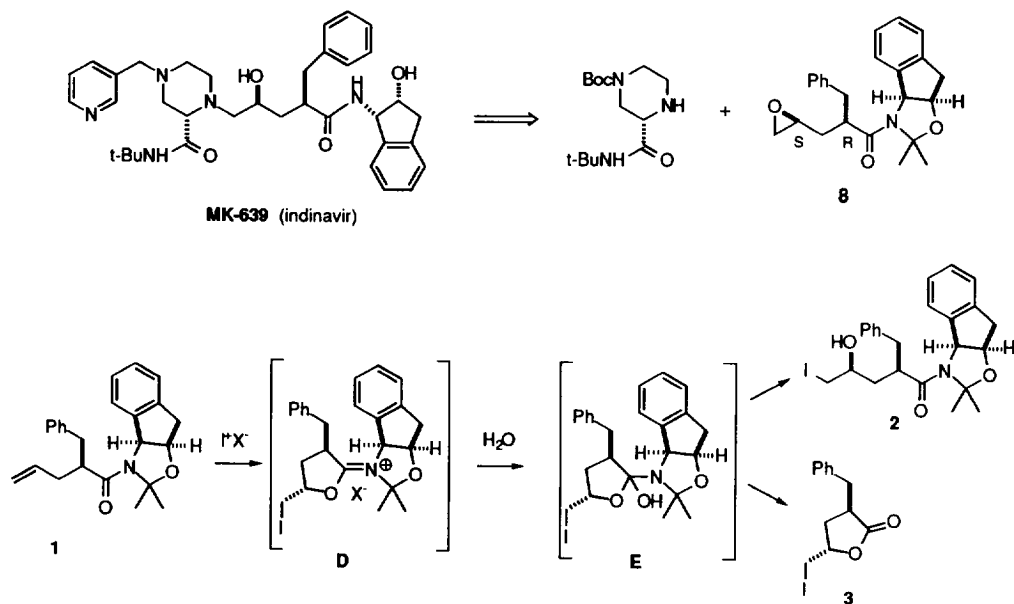
INTRODUCTION

In 1984, Yoshida *et al* reported a highly diastereoselective process for the synthesis of 2,4-disubstituted γ -butyrolactones and γ -butyrothiolactones via halo- (and protio) lactonization of 2-substituted-4-ene-dimethyl-amides **A** and the corresponding thioamides.¹ Very efficient 1,3-chirality transfer was noted with this process; diastereomer ratios in excess of 97:3 for the *trans*:*cis* lactone mixtures were obtained for many substrates. The high selectivity obtained in the dimethylamide-based cases was not observed with the corresponding unsaturated carboxylic acids, which gave only moderate and reversed (about 2:1 *cis*:*trans*) selectivity in the cyclization. The efficient chirality transfer is consistent with a highly ordered, cyclic imidate transition state **B** wherein non-bonded $A_{1,3}$ interactions shift the 2-substituent to a pseudoaxial conformation, which results in high preference for the 2,4 *trans*-relationship in the lactone products **C** ($R_1 = \text{Me, Bn}$).

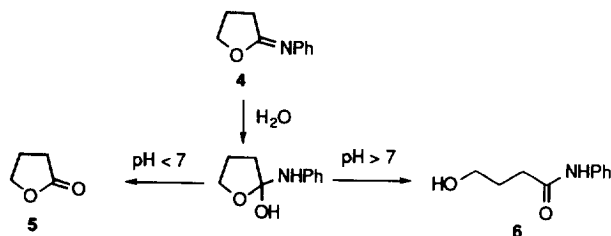
More recently, Kurth *et al*² have employed the Yoshida method with chiral amine auxiliaries to prepare chiral 2,4-disubstituted γ -butyroidolactone derivatives (**C**, $X = \text{I}$; $R_1 = \text{Me}$) after cyclization with I_2 in aqueous THF.



The epoxide **8** is a key intermediate for the preparation of the HIV-1 protease inhibitor MK-639 (indinavir sulfate).³ For a process to prepare **8**, we became interested in the possibility that the cyclic iodoimide salt intermediate **D** derived from ene-amide **1** could be selectively hydrolyzed to the corresponding acyclic (iodomethyl)-hydroxyamide **2**, without accompanying loss of the amide linkage to form the undesired iodolactone **3**.⁴ To effect this conversion, control of the breakdown of the presumed tetrahedral intermediate **E** was necessary.

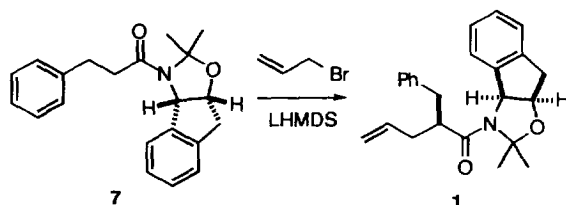


Generally speaking, it appears well precedented that imide hydrolysis affords lactones (or esters) and amines at low pH, and amides at high pH.⁵ Thus, hydrolysis of iminolactone **4** at pH < 7 affords the lactone **5** and aniline, while hydrolysis at pH > 7 affords hydroxybutyranilide **6**.⁶ In the case of tetrahedral intermediate **E**, it was anticipated that the electron-withdrawing iodomethyl group would assist in stabilizing the developing alkoxide leading to iodohydrin **2**.^{5c,d}



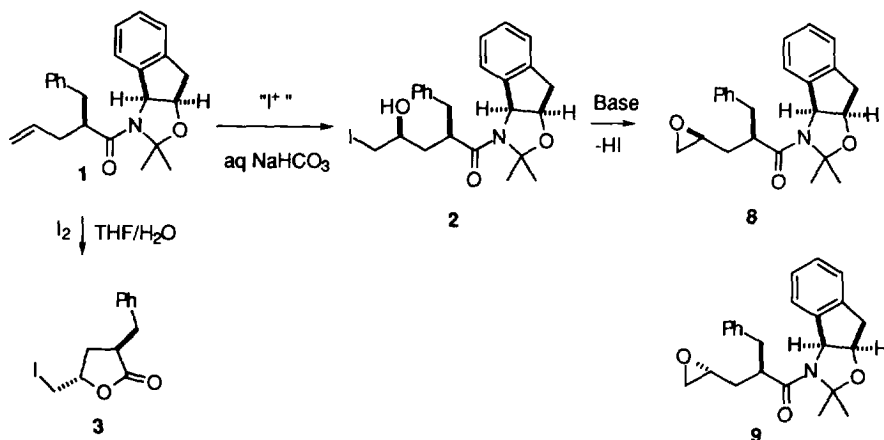
RESULTS AND DISCUSSION

The effect of pH on the Yoshida process with olefin **1** was investigated. Preparation of **1** was achieved in 97:3 diastereoselectivity (**1**:**12**) from amide **7** by allylation with lithium hexamethyldisilazide (LHMDS)/allyl bromide (**7**→**1**, 95%) at -35°C in THF.

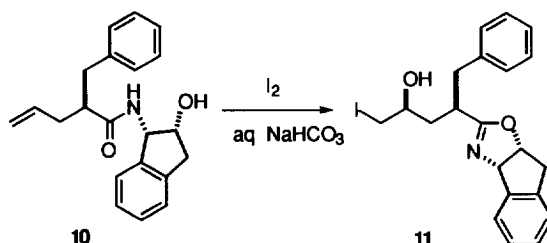


Subjection of **1** to the unbuffered Yoshida conditions (3 equiv I_2 , THF/ H_2O) resulted in the formation of iodolactone **3** with high *trans* selectivity, as expected. However, treatment of **1** with I_2 in aqueous THF in the presence of $NaHCO_3$ led to a 77% yield of the desired iodohydrin **2**. Conversion of the iodohydrin **2** to the desired MK-639 intermediate epoxide **8** was then effected with NaOMe (99%).

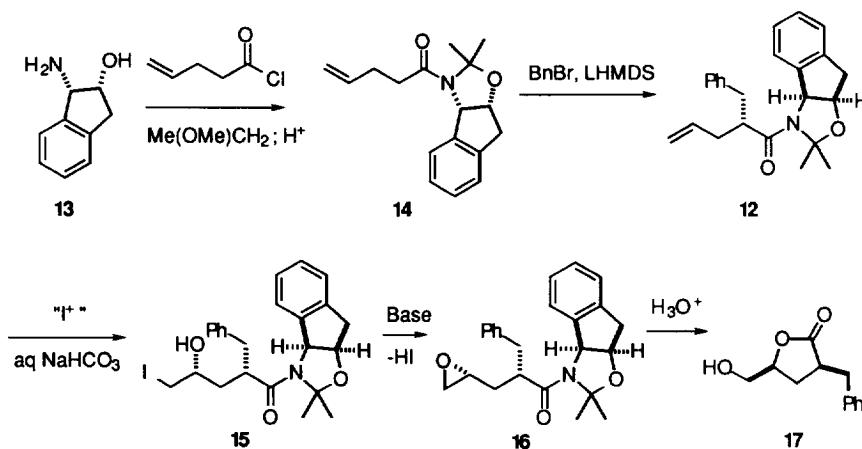
A higher yielding transformation was achieved with the more reactive *N*-iodosuccinimide (NIS) in a two phase isopropyl acetate/aqueous $NaHCO_3$ mixture. The iodohydrin **2** was obtained in 92% yield from **1** in this system; the iodolactone **3** was present at very low levels (< 1% by HPLC) in the crude reaction mixture.⁸ Treatment of the crude mixture with NaOMe produced a 97:3 mixture of epoxide **8** and diastereomer **9**, the latter of which was independently prepared from the condensation of amide **7** and (R)-glycidyl tosylate.⁹ Since olefin **1** was unreactive towards *N*-chlorosuccinimide (NCS), the NIS could be generated *in situ* by addition of a solution of NaI to an olefin/NCS¹⁰ mixture in the presence of aqueous $NaHCO_3$. Similarly, the inexpensive 1,3-dichloro-5,5-dimethylhydantoin functioned as a source of the corresponding diiodohydantoin¹¹ to afford iodohydrin **2** in 96% yield from **1**.



Interestingly, reaction of the unprotected olefin **10** under the iodohydroxylation conditions afforded unstable oxazoline **11**¹² as the major product.¹³



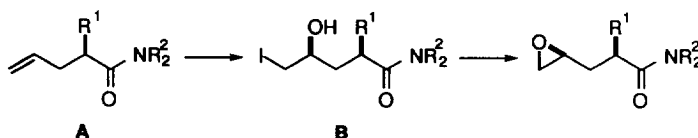
The pro-(2*S*) diastereomer **12** was prepared by reversal of the order of introduction of the benzyl and allyl groups. Thus, acylation of (-)-*cis*-aminoindanol¹⁴ **13** with 4-pentenoyl chloride and acetonide formation gave **14**. Diastereoselective alkylation of **14** gave olefin **12**. Subjection of **12** to the iodohydrin formation resulted in formation of the 2,4-*syn* product **15** with 97% diastereoselectivity. This result indicates that the stereochemistry of the 2-alkyl substituent completely overrides any double diastereoselection from the amine moiety, since similar 2,4-*syn* diastereoselectivity was observed with olefin **1**. Confirmation of the 2,4-*syn* stereochemistry of the derived epoxide **16** was carried out by acid catalyzed lactonization to *cis* lactone **17**. NOE difference spectroscopy was used to rigorously confirm the stereochemistry of **17**.



To further examine the scope of the biphasic iodohydrin formation process, a series of *N,N*-dialkyl-2-substituted-4-enamides **18-23** (Table I) were prepared. The corresponding iodohydrins **25-30** were formed in high yields with excellent diastereoselectivities in the 2-alkyl substituted cases **18-21**, but moderated selectivities in the 2-oxygenated cases (**22** and **23**). The stereochemistry of the major product **29** from the 2-benzyloxy substrate **22** was confirmed by conversion to the derived epoxide followed by acid catalyzed lactonization to the *cis*-disubstituted lactone **32** (NOE difference studies). The 2-*t*-butyldiphenylsiloxy (2-

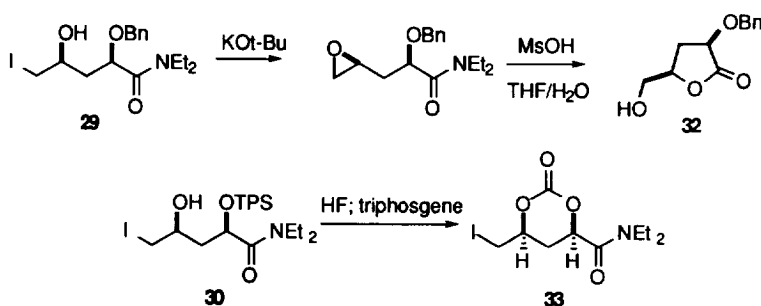
OTPS) substrate **23** afforded enhanced 1,3-*syn* diastereoselectivity (9:1) in the iodohydroxylation reaction. In this case, the *syn* stereochemistry of the major iodohydrin **30** was confirmed by desilylation followed by formation of the cyclic carbonate **33**. NOE difference spectroscopy once again confirmed the 1,3-*cis* substituted carbonate stereochemistry.

TABLE I
Syn-Epoxidation of 2-Alkyl-4-Enamides with NIS



entry	A	B	R ¹	NR ₂ ²	yield ^a	ratio (syn:anti) ^b
1	18	25	Bn	NMe ₂	94 ^e	19:1 (95:5) ^{e,f}
2	19	26	Bn	NEt ₂	94 ^e	32:1 (97:3) ^{e,f}
3	20	27	Cy-C ₆ H ₁₁ CH ₂	NMe ₂	95 ^e	15:1 ^{e,g}
4	21	28	Me	NEt ₂	96 ^c	20:1 ^{c,g}
5	22	29	OBn	NEt ₂	90 ^d	2:1 ^{d,g}
6	23	30	OTPS	NEt ₂	90 ^d	9:1 ^{d,g}
7	24	31	H	NEt ₂	55 ^c	-

a) All reactions were run with solid NIS (1.3 equiv) and 2.0 equiv NaHCO₃ 0.3 M in biphasic organic/aqueous mixtures. Yields represent chromatographically and spectroscopically homogeneous (¹³C and ¹H NMR) material isolated by silica gel flash chromatography unless otherwise stated. b) Ratio determined on crude reaction mixture (organic phase of iodohydrin formation reaction or organic phase after addition of water to the epoxide formation reaction mixture). c) Iodohydrin formation performed in EtOAc (0.3 M, 20 °C) d) Iodohydrin formation in EtOAc (0.3 M, 0 °C) e) Iodohydrin formation in dichloromethane (0.3 M, 20 °C) f) Ratio determined by HPLC analysis; (150 × 4.6 mm YMC-Pack C-8 column at 40 °C, 0.1M NH₄H₂PO₄/methanol, gradient 60/40-20/80 (v/v) over 40 min, 220 nm detection. g) Ratio determined by integration of resolved peaks in ¹³C and ¹H NMR spectra.



In summary, we have discovered an efficient *syn*-epoxidation of 2-substituted-4-enamides to the corresponding epoxy-amides via iodohydrin intermediates. This method provided an efficient route to the HIV-1 protease inhibitor, MK-639 (indinavir sulfate).

Acknowledgment: Fruitful discussions with Professor Barry M. Trost are gratefully acknowledged. We wish to acknowledge Dr. Tom Novak and Ms. Amy Bernick for obtaining mass spectral data, and Ms. Lorrie Berwick for HPLC studies.

EXPERIMENTAL

General

¹H NMR chemical shifts are reported in ppm from the residual CDCl₃ (7.27 ppm) peak, coupling constants are reported in Hz; ¹³C chemical shifts are reported in ppm from the center peak of CDCl₃ (77.0 ppm) and were recorded on Bruker AM and AMX systems. Reagents were used as received unless otherwise stated; 3A molecular sieves were used to dry solvents for anhydrous reactions. Unless otherwise noted, all manipulations were carried out under an inert atmosphere of nitrogen gas. In general, glassware was not specially dried prior to use. Analytical TLC was performed using Merck silica gel 60 F₂₅₄ precoated plates (0.25 mm) followed by visualization with UV light (254 nm), staining with iodine vapor or staining with aq phosphomolybdic acid-ceric sulfate. Flash column chromatography was performed using silica gel (Merck, 70-230 mesh ASTM). Elemental Analysis was obtained at Robertson Microlit Laboratories, Inc, Madison, NJ. IR spectra were recorded on a Nicolet Magna-IR 550.

Preparation of Olefin 1

The amide **7**⁷ (32.1 g, 100 mmol) was dissolved in 200 mL sieve-dried THF in a 1000 mL 3 neck flask equipped with an addition funnel and degassed by bubbling in nitrogen for 20 min. The mixture was cooled to -25 °C, and allyl bromide (12.7 g, 105 mmol) was added via a weighed syringe. Lithium hexamethyl-disilazide (LHMDS, 1.0 M in THF, 105 mL, 105 mmol) was allowed to slowly drop into the stirred reaction mixture over 20 min. The internal temperature was kept below -15 °C. The mixture was aged at -20 to -15 °C for 30 min. Water (100 mL) and isopropyl acetate (IPAC, 100 mL) were added and the temperature rose to 5 °C. The lower aqueous phase was discarded and the organic phase was washed with 100 mL of 0.2 M HCl in 3% aq. NaCl, 30 mL brine, and 30 mL 0.5 M sodium bicarbonate. The organic phase was evaporated (55 °C, 100 Torr) to an oil, another 40 mL of IPAC were added, and the mixture was again evaporated to an oil. The assay yield of the desired diastereomer **1** by HPLC was 34.0 g, 94%: YMC Pack C8 150 × 4.6 mm, S 3_μ, 120 Å, mobile phase: 75% MeOH/25% 10 mmol KH₂PO₄, flow = 1.0 mL/min, 25 °C, detection = 220 nm; approx. retention times: **1** = 11.8 min, **12** = 13.3 min. The diastereomer ratio of **1** to **12** was 96:4 by HPLC. The crude allylated product was taken directly on to the next step. Amide **1** could be isolated by crystallization from 30:1 hexane-IPAC in 87% yield: mp 101-102 °C; ¹³C NMR data for major rotamer (62.9 MHz, CDCl₃) δ 171.0, 140.4, 140.2, 134.8, 129.6, 128.6, 128.2, 127.1, 126.6, 125.6, 124.0, 117.9, 96.8, 78.9, 65.6, 47.5, 38.6, 38.0, 36.1, 26.6, 24.1. FTIR (thin film) ν_{max} 2926, 1645, 1420 cm⁻¹; m/z 362 (M+H)⁺. Anal. Calcd. for C₂₄H₂₇NO₂: C, 79.74; H, 7.53; N, 3.87. Found: C, 79.91; H, 7.49; N, 3.80.

Preparation of Iodohydrin 2 with NCS/NaI

To the allyl amide **1** (211.4 g, 585 mmol) in IPAC at 25 °C was added a solution of sodium bicarbonate (36.6 g, 435 mmol) in 1.03 L of distilled water and the biphasic mixture was cooled to 5 °C. *N*-chlorosuccinimide (141.2 g, 1.06 mol) was added. To this mixture was added an aqueous solution of sodium iodide (159 g, 1.06 mol in 121 mL of water) while maintaining the reaction mixture at 6-11 °C. The mixture was warmed to 25 °C and aged with vigorous stirring for 2.25 h. The agitation was discontinued and the layers were separated. To the organic phase was added aqueous sodium sulfite (80 g, 0.635 mol in 400 mL). The mixture was agitated for 40 min at 25 °C. The layers were separated. Quantitative analysis of the mixture by HPLC (same system as above) indicated 272 g (92% yield) of iodohydrin **2** (approximate retention time = 8.1 min). An analytical sample of iodohydrin **2** was prepared by crystallization of the crude mixture from IPAC. mp 148-149 °C dec. ¹³C NMR (62.9 MHz, CDCl₃, major rotamer) δ 172.2, 140.6, 140.4, 139.3, 129.5, 128.8, 128.2, 127.2, 126.8, 125.7, 124.0, 96.9, 79.1, 68.7, 65.8, 43.7, 40.6, 39.0, 36.6, 26.5, 24.3, 16.3. FTIR (thin film) ν_{max} 3383, 2926, 1616, 1442 cm⁻¹; m/z 506 (M+H)⁺. Anal. Calcd for C₂₄H₂₈NO₃I: C, 57.04; H, 5.58; N, 2.77; I, 25.11. Found: C, 56.88; H, 5.59; N, 2.67; I, 25.60.

Preparation of Epoxide 8 from Iodohydrin 2

The crude solution from the previous step containing iodohydrin **2** (272 g, 538 mmol) in IPAC was concentrated in vacuo (28" Hg) to azeotropically dry the solution. A total of 700 mL of distillate was collected while maintaining a batch temperature of 22-28 °C. The distillate was replaced with 500 mL of IPAC. The solution was cooled to 26 °C and 25% NaOMe/MeOH solution (168.1 g, 777 mmol) was added

over a 10 min period. The mixture was aged for 1 h at 25 °C. The reaction was quenched by the addition of 366 mL of water at 25 °C and the layers were separated. The organic phase was washed with 3% aqueous sodium sulfate (2 × 750 mL). HPLC analysis (same conditions as above) indicated 201 g (99% yield) of epoxide **8** at this point. The diastereomeric ratio of **8**:**9** was 97:3 (approximate retention times: epoxide **9** = 6.5 min, epoxide **8** = 7.1 min). Crystallization of the crude mixture from IPAC gave isolated **8**: mp 141-142 °C. ¹³C NMR (62.9 MHz, CDCl₃) δ 171.1, 140.6, 140.5, 139.6, 129.6, 128.8, 128.2, 127.2, 126.8, 125.6, 124.1, 96.8, 79.2, 65.8, 50.0, 48.0, 44.8, 39.2, 37.4, 36.2, 26.6, 24.1. FTIR (thin film) ν_{\max} 2933, 1639, 1424 cm⁻¹. m/z 378 (M+ H⁺). Anal. Calcd for C₂₄H₂₇NO₃: C, 76.37; H, 7.21; N, 3.71. Found: C, 76.26; H, 7.30; N, 3.48. For **9**: mp 118-119 °C. ¹³C NMR (62.9 MHz, CDCl₃) δ 171.0, 140.5, 139.9, 129.7, 128.8, 128.2, 127.2, 126.8, 125.6, 124.1, 96.8, 79.1, 65.5, 50.5, 47.7, 45.9, 37.8, 37.1, 36.2, 26.6, 23.8. FTIR (thin film) ν_{\max} 3080, 1640, 1421 cm⁻¹; m/z 378 (M+ H⁺). Anal. Calcd for C₂₄H₂₇NO₃: C, 76.37; H, 7.21; N, 3.71. Found: C, 76.23; H, 7.28; N, 3.68.

Preparation of Iodohydrin **2** with 1,3-Dichloro-5,5-dimethylhydantoin (DCDMH)/NaI

To a solution of olefin **1** (200 g, 553 mmol) in 1.3 mL IPAC was added aqueous sodium bicarbonate solution (32.5 g in 929 ml water; 387 mmol) and dichlorodimethylhydantoin (92.6 g; 470 mmol). The resulting reaction mixture was cooled to 5 °C and aqueous sodium iodide (141 g in 109 ml water; 940 mmol) was added dropwise over 50 min during which time the reaction temp did not exceed 10 °C. The batch was then warmed to 25 °C over 75 min and aged for 2.5 h. Aqueous sodium sulfite (83 g in 330 ml water; 658 mmol) was added dropwise over 10 min, the mixture was agitated for 15 min and the layers separated. Analysis of the IPAC solution by HPLC (same conditions as above) indicated 267.4 g (96%) of iodohydrin **2** which was identical to the material prepared previously.

Preparation of Iodohydrin **2** with Iodine

Olefin **1** (5.0 g; 13.8 mmol) was dissolved in 28 mL THF at 18 °C, followed by the addition of 6% aqueous sodium bicarbonate (28 ml; 20 mmol) and iodine (10.5 g; 41.5 mmol). The reaction mixture was aged at room temperature for 4.5 h, then quenched with aqueous sodium sulfite (5 g in 20 ml water). The pH was adjusted to 6.7 with solid sodium bicarbonate. The volatiles were removed *in vacuo* at 25-27 °C and the residue dissolved in 50 mL IPAC. Analysis of the IPAC solution by HPLC (same conditions as above) indicated 5.4 g (76%) of iodohydrin **2**.

Preparation of Hydroxy-Amide **10**

A solution of **1** in IPAC (150 ml @ 148 g/l; 22.2 g, 61.4 mmols) was charged to a round-bottom flask and cooled to 5 °C. Aqueous hydrochloric acid (50 ml of 12N solution diluted with 30 ml water; 600 mmols) was added dropwise while keeping the internal temperature < 20 °C. The reaction mixture was warmed to 28 °C and aged for 3 h. The reaction mixture was neutralized with 25 % NaOH while keeping internal temperature below 35 °C. EtOAc (75 ml) was added to aid in dissolution of the solids. The layers were separated and the organic layer washed with saturated brine (1 × 25 mL). CHCl₃ (25 mL) was added to dissolve the remaining product. The solution was dried over Na₂SO₄ and concentrated *in vacuo* until a heavy slurry had developed. The slurry was filtered and the flask and cake washed with hexanes. The product was dried *in vacuo* at 30 °C for 18 h to give 14.3 g (73%) of hydroxy-amide **10**: mp = 157-8 °C. ¹H NMR (300.1 MHz, CDCl₃) δ 7.32(m, 2H), 7.26(m, 3H), 7.17(m, 3H), 7.08(m, 1H), 5.89(m, 1H), 5.65(br d, J=8.8, 1H), 5.28(dd, J=8.8, 4.9, 1H), 5.20(m, 1H), 5.14(m, 1H), 4.20(td, J=4.9, 1.0, 1H), 3.08(dd, J=16.6, 4.9, 1H), 2.89(m, 2H), 2.79(d, J=16.6, 1H), 2.62(m, 1H), 2.46(m, 1H), 2.35(m, 1H); ¹³C NMR (75.5 MHz, CDCl₃) δ 174.2, 140.2₉, 140.2₅, 140.1₇, 135.6, 129.2, 128.6, 128.1, 127.0, 126.6, 125.2, 124.1, 117.3, 73.1, 57.3, 51.0, 39.3, 39.2, 36.9. FTIR (thin film) ν_{\max} 3030, 1670, 1510, 1215 cm⁻¹. m/z 322 (M+ H⁺). Anal. C₂₁H₂₃NO₂: C, 78.47; H, 7.21; N, 4.35. Found: C, 78.67; H, 7.27; N, 4.21.

Preparation of Oxazoline **11**

The hydroxyamide **10** (1.0 g, 3.1 mmols) was combined with THF (8 mL) and aqueous sodium bicarbonate (3.5% solution; 8 mL) at 18 °C. Iodine (2.35 g; 9.3 mmols) was added in one portion to the flask and the reaction aged at 18 °C for 3 h, followed quenching with aqueous sodium sulfite. The pH of the reaction mixture was adjusted to 6.9 with aqueous sodium bicarbonate. The product was extracted into CHCl₃ (1 × 20 mL). The aqueous layer was concentrated *in vacuo* to remove the volatiles and again extracted with CHCl₃ (1 × 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to provide 1.15 g (83%) of crude oxazoline **11** as a yellow solid: ¹H NMR (400.1 MHz, CDCl₃) δ 7.38(d, J=7.1, 1H), 7.26(m, 3H), 7.13(m, 3H), 7.04(m, 2H), 5.50(d, J=7.5, 1H), 5.28(t, J=7.5, 1H), 3.65(m, 1H), 3.41(dd, J=17.8, 6.7, 1H), 3.23(d, J=17.8, 1H), 3.12(d, J=5.6, 2H), 2.99(m 2H), 2.77(m, 1H), 1.88(m, 1H), 1.72(m, 1H); ¹³C NMR (100.6 MHz, CDCl₃) δ 170.1, 141.6, 139.3, 138.3, 128.8, 128.5, 128.3, 127.5,

126.4, 125.4, 125.2, 83.4, 75.7, 68.4, 39.5, 38.5, 37.6, 37.5, 14.2. FTIR (thin film) ν_{\max} 3366, 2921, 1719, 1649, 1454. m/z 320 ($M^+ - 1$).

Preparation of Amide 14

Oxalyl chloride (69.7 g, 550 mmol) was added dropwise to a stirred solution of 50 g (500 mmol) of 4-pentenol acid in 60 mL of CH_2Cl_2 with 0.5 mL of DMF at 0 °C. The reaction was aged for 2.5 h, during which time it was allowed to warm to room temperature. The reaction mixture was distilled at atmospheric pressure first to remove the solvent (~70 °C pot temp), and then to collect the 4-pentenoyl chloride (115-125 °C, 27.2 g, 46%) as a clear liquid. A solution of (-) *cis*-aminoindanol **13** (34.2 g, 230 mmol) in 540 mL IPAC was added to a 1.1 M solution of sodium carbonate in H_2O (250 mL). The two-phase mixture was heated to 60 °C and stirred vigorously, and 27.2 g (230 mmol) 4-pentenoyl chloride was added dropwise. The organic phase was washed at 70 °C with 125 mL each of water, saturated sodium bicarbonate, brine, and finally water (2×125 mL). Cooling to room temperature and addition of hexanes gave 45.6 g (86%) of crude hydroxyamide after filtration and drying which was resuspended in 500 mL IPAC at 35 °C and treated with methanesulfonic acid (0.9 g, 10 mmol) and 2-methoxypropene (30.0 g, 428 mmol). The mixture was warmed to 40 °C and aged for 1.5 h, the solution was cooled to 25 °C and washed with 5% sodium bicarbonate (2×150 mL), water (1×150 mL) saturated NaCl (1×150 mL) and water (1×150 mL). The organic phase was dried with magnesium sulfate and concentrated in vacuo to afford 49 g (93%) of acetamide-amide **14** as a low melting solid: ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 168.9, 140.9, 140.8, 137.0, 128.5, 127.2, 125.9, 124.3, 115.7, 96.6, 78.7, 66.0, 36.3, 35.6, 29.5, 26.6, 24.2; FTIR (thin film) ν_{\max} 2990, 2933, 1647, 1410 cm^{-1} .

Preparation of Olefin 12

A solution of 44 g (162 mmol) of amide **14** in 360 mL sieve dried THF was degassed by sparging with nitrogen. Benzyl bromide (30.5g, 178 mmol) was added, and the solution was cooled to -20 °C. Lithium hexamethyldisilazide (1 M in THF, 195 mL) was added over 0.5 h, and the reaction mixture was allowed to warm to room temperature. After 1 h, the reaction was quenched with 250 mL of water and diluted with 500 mL of EtOAc. The organic phase was washed with 250 mL each of saturated sodium bicarbonate, saturated brine and water, then dried over MgSO_4 . Crystals formed on concentration from EtOAc, and the crystallization was completed with the addition of hexanes, affording 47.2 g (81%) of olefin **12**: mp 126-129 °C. ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 171.5, 140.8, 140.7, 139.4, 136.0, 129.4, 128.5, 128.4, 127.0, 126.7, 125.8, 124.2, 117.7, 96.7, 78.5, 65.4, 47.3, 39.9, 37.8, 36.0, 26.6, 24.0. FTIR (thin film) ν_{\max} 2975, 2933, 1644, 1418.

Preparation of Iodohydrin 15 and Epoxide 16

Sodium bicarbonate (16.7 g, 199 mmol), water (36 mL), EtOAc (550 mL), and olefin **12** (36.0 g, 100 mmol) were combined and cooled to 0 °C. *N*-Iodosuccinimide (29.1g, 130 mmol) was added over 1 h. After 3 h, the reaction mixture was washed with aqueous sodium bisulfite (~0.5 M, 155 mL), saturated aqueous sodium bicarbonate (180 mL), and aqueous sodium chloride (180 mL), and dried (MgSO_4). Filtration and concentration afforded ~50 g, 99 mmol of crude iodohydrin **15** which was analysed by HPLC as a 97:3 mixture of **15**:4-*epi*-**15** (YMC OCTYL-C8 column 4.6×100 mm, A = 0.01 M $\text{NH}_4\text{H}_2\text{PO}_4$, B = MeOH, A:B, 33:67 to 28:72 over 22 min, 220 nm, 1.2 mL/min); for **15**: ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 172.3, 140.6, 140.3, 138.7, 129.3, 128.7, 128.5, 127.3, 127.0, 125.8, 124.2, 97.0, 78.7, 67.8, 65.8, 44.4, 39.6, 39.1, 36.0, 26.6, 24.0, 16.3. FTIR (thin film) ν_{\max} 3490, 2926, 1618, 1427 cm^{-1} . The crude iodohydrin **15** was directly dissolved in 360 mL dry THF and cooled to 0 °C and treated over 15 min with potassium *tert*-butoxide (1.7M in THF, 116.4 mL). The reaction was quenched by pouring into 900 mL EtOAc and 180 mL of water. The layers were separated and the organic phase was washed with 180 mL of water and 180 mL of saturated aq NaCl and dried (MgSO_4). Chromatography of the crude product on 750 g silica gel (15% EtOAc in hexanes to 30% EtOAc in hexanes) gave enriched fractions which were crystallized from hexanes/ethyl acetate to afford 29.4 g (78% from olefin **12**) of crystalline epoxide **16** after filtration: mp 150-152 °C. ^{13}C NMR (CDCl_3 , 75.5 MHz) δ 170.9, 140.6, 140.5, 138.8, 129.4, 128.5, 128.3, 127.3, 126.8, 125.6, 124.3, 96.7, 78.7, 65.4, 50.6, 47.4, 45.2, 41.0, 36.9, 35.9, 26.6, 24.0. FTIR (thin film) ν_{\max} 3020, 1636, 1428. m/z 378 ($M^+ - \text{H}^+$). Anal. Calcd for $\text{C}_{24}\text{H}_{27}\text{NO}_3$: C, 76.37; H, 7.21; N, 3.71. Found: C, 76.40; H, 7.28; N, 3.72.

Demonstration of the relative stereochemistry of epoxide **16**: A solution of epoxide **16** (1.0 mmol, 233 mg) in 3:1 THF-water (2 mL) was treated with MsOH (4.0 mmol, 384 mg) for 16 h at 25 °C. The mixture was diluted with MTBE (5 mL) and washed with saturated aqueous NaHCO_3 (5 mL). The organic phase was dried over MgSO_4 and evaporated in vacuo to provide the *syn*-lactone **17** as a viscous oil (170 mg, 83%): ^1H NMR (400.1 MHz, CDCl_3) δ 7.31(m, 2H), 7.22(m, 3H), 4.47(m, 4.47), 3.85(dd, $J=12.7$, 2.8, 1H), 3.55(dd, $J=12.7$, 5.2, 1H), 3.29(dd, $J=13.9$, 4.0, 1H), 2.98(m, 1H), 2.74(dd, $J=13.9$, 9.9, 1H), 2.52(br s, 1H), 2.19(ddd,

$J=12.7, 9.1, 6.3, 1\text{H}$), 1.87(ddd, $J=12.7, 11.5, 8.9, 1\text{H}$); ^{13}C NMR (CDCl_3 , 100.6 MHz) δ 178.1, 138.5, 128.7, 128.6, 126.6, 78.9, 63.5, 42.5, 36.2, 29.2 FTIR (thin film) ν_{max} 3430, 2933, 1766, 1178 cm^{-1} .

General experimental for the preparation of 2-substituted-4-enamides 18-22, 24: The 2-substituted-4-enamides **18-22** and **24** were prepared by alkylation of the appropriate tertiary amides with allyl bromide in the presence of LHMDS in THF at $-20\text{ }^\circ\text{C}$. The starting tertiary amides, where not commercially available, were prepared from the corresponding acid chlorides by treatment of a solution of the acid chloride (0.1 mol) in diethyl ether (400 mL) with the appropriate dialkyl amine (0.25 mol) for 1h maintaining a temperature $<-20\text{ }^\circ\text{C}$. The suspension was filtered, and the filtrate was washed with 5 M aq NaOH (50 mL). The organic phase was dried over MgSO_4 and evaporated to afford the desired tertiary amides in 90-98% yields. The tertiary amides (10 mmol) were dissolved in 30 mL dry THF, the solution was degassed by bubbling in nitrogen for 5 min, allyl bromide (12 mmol 1.45 g) was added via a weighed syringe, and the mixture was cooled to $-20\text{ }^\circ\text{C}$. A solution of 1M LHMDS in THF (12 mmol, 12 mL) was added dropwise to the stirred mixture over 30 min maintaining the temperature at $-20\text{ }^\circ\text{C}$. After the reaction mixture was aged at $-20\text{ }^\circ\text{C}$ for 1 h, the mixture was warmed to $10\text{ }^\circ\text{C}$ over 1 h. The mixture was diluted with MTBE (30 mL) and washed with 30 mL each of 10% aqueous NaCl, 1 M aqueous HCl, 10% aqueous NaCl, 5% aqueous NaHCO_3 , and saturated aqueous NaCl. The organic phase was dried over MgSO_4 and evaporated in vacuo. The residue was chromatographed (SiO_2) using a gradient elution with 5 \rightarrow 30% MTBE in hexanes to afford the allylated products.

***N,N*-Dimethyl-2-benzyl-4-pentenamide (18):** $R_f = 0.14$ (4:1 hexane-MTBE). ^1H NMR (250.1 MHz, CDCl_3) δ 7.21(m, 3H), 7.14(m, 2H), 5.74(m, 1H), 5.05(m, 1H), 5.00(m, 1H), 2.93(m, 2H), 2.82(s, 3H), 2.72(dd, $J=12.0, 4.6, 1\text{H}$), 2.61(s, 3H), 2.46(m, 1H), 2.21(m, 1H); ^{13}C NMR (62.9 MHz, CDCl_3) δ 174.4, 139.8, 135.8, 128.8, 128.2, 126.1, 116.6, 43.5, 38.9, 36.9(2 Carbons), 35.4; FTIR (thin film) ν_{max} 2926, 1630, 1494 cm^{-1} .

***N,N*-Diethyl-2-benzyl-4-pentenamide (19):** $R_f = 0.27$ (4:1 hexane-MTBE). ^{13}C NMR (62.9 MHz, CDCl_3) δ 173.6, 140.0, 135.9, 129.1, 128.2, 126.2, 116.8, 43.9, 41.6, 40.5, 39.3, 37.7, 14.4, 12.9; FTIR (thin film) ν_{max} 2976, 2932, 1630, 1452 cm^{-1} .

***N,N*-Dimethyl-2-cyclohexylmethyl-4-pentenamide (20):** $R_f = 0.24$ (4:1 hexane-MTBE). ^{13}C NMR (62.9 MHz, CDCl_3) δ 175.7, 136.2, 116.2, 40.2, 38.2, 37.3, 35.6, 35.3, 33.6, 33.5, 26.5, 26.2, 26.1; FTIR (thin film) ν_{max} 2934, 2851, 1644, 1446 cm^{-1} .

***N,N*-Diethyl-2-methyl-4-pentenamide (21):** $R_f = 0.27$ (4:1 hexane-MTBE). ^{13}C NMR (62.9 MHz, CDCl_3) δ 175.4, 136.2, 116.3, 41.8, 40.3, 38.6, 35.6; FTIR (thin film) ν_{max} 2974, 2934, 1639, 1432 cm^{-1} .

***N,N*-Diethyl-2-benzyl-4-pentenamide (22):** $R_f = 0.18$ (4:1 hexane-MTBE). ^{13}C NMR (62.9 MHz, CDCl_3) δ 169.9, 137.7, 133.8, 128.3, 127.7, 117.5, 76.9, 70.6, 40.9, 40.2, 36.8, 14.4, 12.9; FTIR (thin film) ν_{max} 2975, 2934, 1647, 1455 cm^{-1} .

***N,N*-Diethyl-4-pentenamide (24):** $R_f = 0.20$ (4:1 hexane-MTBE). ^{13}C NMR (62.9 MHz, CDCl_3) δ 171.1, 137.6, 114.8, 41.8, 39.9, 32.2, 29.3, 14.2, 13.0; FTIR (thin film) ν_{max} 2975, 2934, 1641, 1431 cm^{-1} .

Preparation of *N,N*-Diethyl-2-*t*-butyldiphenylsilyloxy-4-pentenamide (23)

Glycolic acid (0.500 mol, 38.03 g) and 2-methoxypropene (1.50 mol, 108.2 g) were combined with ice cooling, and after the initial exotherm had subsided (30 min) the solution was aged at $45\text{ }^\circ\text{C}$ for 30 min. The mixture was vacuum distilled, collecting the forerun of 2-methoxypropene and 2,2-dimethoxypropane followed by the acetone (10 Torr, $60-65\text{ }^\circ\text{C}$). The distillate was treated with Et_2NH (1.00 mol, 103.5 g) and DMAP (0.1 mmol, 12 mg) at $55\text{ }^\circ\text{C}$ for 18 h. The mixture was vacuum distilled collecting the 2-hydroxy-*N,N*-diethylacetamide at 0.5 Torr, $80-85\text{ }^\circ\text{C}$ (40.7 g, 67% from glycolic acid). The 2-hydroxy-*N,N*-diethylacetamide (0.300 mol, 39.35 g) was dissolved in dihydropyran (0.33 mol, 27.76 g) and TsOH (1 mmol, 190 mg) was added. After the initial exotherm the mixture was aged at $45\text{ }^\circ\text{C}$ for 2h. The mixture was diluted with diethyl ether (100 mL) and washed with satd aqueous NaHCO_3 (50 mL). The organic phase was dried over MgSO_4 and filtered through a plug of neutral alumina (10 g). The filtrate was evaporated ($60\text{ }^\circ\text{C}$, 20 Torr) leaving the crude THP ether as a viscous oil (65 g). The crude THP ether was dissolved in 600 mL dry THF, the solution was degassed by bubbling in nitrogen for 5 min, allyl bromide (0.36 mol 43.6 g) was added via a weighed syringe, and the mixture was cooled to $-35\text{ }^\circ\text{C}$. A solution of 1 M LHMDS in THF (0.360 mol, 360 mL) was added dropwise to the stirred mixture over 90 min maintaining the temperature

below -20 °C. After the reaction mixture was aged at -20 °C for 1 h, the mixture was warmed to 10 °C over 1 h. The mixture was diluted with diethyl ether (500 mL) and washed with 10 % aq NaCl (500 mL). The organic phase was evaporated down to ca 100 mL, redissolved in diethyl ether (500 mL) and dried over MgSO₄. The solution was filtered through a plug of silica (10 g), and the filtrate was evaporated. The residue was dissolved in MeOH (200 mL) and conc aqueous HCl (0.12 mol, 10 mL) was added so that the pH was < 1. The mixture was aged for 2 h, solid NaHCO₃ (0.3 mol, 25.2 g) was added, and aged for 1 h. The mixture was evaporated to an oil (<100 mL). The residue was dissolved in 3:1 diethyl ether-CH₂Cl₂ (200 mL), dried over MgSO₄, and filtered through a plug of silica (10 g) and basic alumina (10 g). The filtrate was evaporated leaving the *N,N*-diethyl 2-hydroxy-4-enamide as a pale amber oil (30.7 g of ca 90% pure material, 92% from 2-hydroxy-*N,N*-diethylacetamide). The crude hydroxyamide (6.00 g) was chromatographed (silica) using a gradient elution with 50 → 100% MTBE in hexane giving the pure *N,N*-Diethyl 2-hydroxy-4-pentamide (5.38 g): *R*_f = 0.54 (MTBE); FTIR (thin film) ν_{\max} 3400, 2976, 2937, 1636 cm⁻¹. A mixture of 2-hydroxy-*N,N*-diethyl-4-pentamide (30 mmol, 5.14 g), *t*-BuPh₂SiCl (33 mmol, 6.07 g), imidazole (45 mmol, 3.06 g) and DMF (5 g) was stirred for 18 h at 20 °C. The mixture was diluted with diethyl ether (50 mL) and washed with 3 × 50 mL of water and 20 mL of satd aqueous NaCl. The organic phase was dried over MgSO₄ and evaporated. The residue was chromatographed (silica) using a gradient elution with 5 → 25% MTBE in hexane to provide the TPS ether **23** as a viscous oil (12.2 g, 99 %) *R*_f = 0.30 (4:1 hexane-MTBE). ¹³C NMR (62.9 MHz, CDCl₃) δ 170.4, 135.7, 133.4, 133.2, 133.0, 129.5, 129.4, 127.3, 127.2, 117.5, 71.1, 40.7, 39.9, 39.8, 26.6, 19.0, 13.9, 12.4; IR (thin film) ν_{\max} 2964, 2932, 2858, 1654, 1428, 1112 cm⁻¹.

General experimental for the preparation of iodohydrins 25-31

The iodohydrins **25-31** were prepared by the reaction of the 2-substituted-4-enamides **18-24** with NIS in biphasic mixtures of aq NaHCO₃ and an organic solvent such as CH₂Cl₂, EtOAc or IPAC. The 2-substituted-4-enamides **18-24** (10 mmol) were dissolved in the appropriate solvent (30 mL, Table I), 0.5 M aq NaHCO₃ (20 mmol, 40 mL) was added, and after cooling the mixture to 0 °C, solid NIS (13 mmol, 2.925 g) was added in 3 equal portions over 10 min to the well agitated mixture. The mixture was aged at 0-5 °C for 15 min and allowed to warm to 20 °C over 15 min. The brown color was discharged by the addition of several drops of 40 % aqueous NaHSO₃, the organic phase was separated, dried over MgSO₄ and evaporated *in vacuo*. The residue was chromatographed (silica) using a gradient elution with 50 → 100% MTBE in hexane to afford the iodohydrins **25-31**.

2,4-Syn-*N,N*-dimethyl-2-benzyl-4-hydroxy-5-iodo-pentanamide (25): *R*_f = 0.42 (MTBE). mp 79-80 °C; ¹H NMR (250.1 MHz, CDCl₃) δ 7.25(m, 3H), 7.15(m, 1H), 3.51(m, 1H), 3.31(dd, *J*=10.2, 3.7, 1H), 3.18(dd, *J*=10.2, 6.9, 1H), 2.91(dd, *J*=13.0, 9.3, 1H), 2.84(s, 3H), 2.70(dd, *J*=13.0, 5.6, 1H), 2.63(s, 3H), 2.08(m, 1H), 1.60(m, 1H); ¹³C NMR (62.9 MHz, CDCl₃) δ 175.1, 139.1, 128.8, 128.2, 126.4, 68.3, 40.1, 39.6, 39.1, 37.1, 35.6, 16.7; FTIR (thin film) ν_{\max} 3359, 2905, 1618, 1494 cm⁻¹. *m/z* 361 (M⁺).

2,4-Syn-*N,N*-diethyl-2-benzyl-4-hydroxy-5-iodo-pentanamide (26): *R*_f = 0.48 (MTBE). ¹³C NMR (62.9 MHz, CDCl₃) δ 174.2, 139.2, 129.0, 128.3, 126.4, 68.3, 41.7, 40.7, 40.3, 39.7, 39.5, 16.8, 14.1, 12.8; FTIR (thin film) ν_{\max} 3354, 2974, 2931, 1611, 1454 cm⁻¹. *m/z* 390 (M+ H)⁺. Anal. Calcd for C₁₆H₂₄NO₂I: C, 49.37; H, 6.21; N, 3.60; I, 32.60. Found: C, 49.57; H, 6.13; N, 3.58; I, 32.72. The stereochemistry of iodohydrin **26** was confirmed by conversion to the corresponding epoxide (*N,N*-Diethyl-2-Benzyl-4,5-epoxy-pentanamide) and lactonization by the following procedure: the iodohydrin **26** (10 mmol) in dry THF (25 mL) was cooled to -20 °C, and a solution of 1.78 M KOt-Bu in THF (11 mmol, 6.18 mL) was added dropwise by syringe over 10 min. The mixture was aged at -15 °C for 15 min and warmed to 10 °C over 15 min. The mixture was diluted with MTBE (50 mL) and washed with 2 × 100 mL 5% Na₂SO₄ and 50 mL satd aqueous Na₂SO₄. The organic phase was dried over MgSO₄ and evaporated. The residue was chromatographed (silica) using a gradient elution with 50 → 100% MTBE in hexane to afford the derived epoxide: *R*_f = 0.36 (MTBE). ¹³C NMR (62.9 MHz, CDCl₃) δ 173.1, 139.1, 128.9, 128.1, 126.1, 50.2, 47.4, 41.4, 41.0, 40.4, 40.0, 36.5, 14.0, 12.7; FTIR (thin film) ν_{\max} 2974, 2936, 1616, 1456 cm⁻¹. Anal. Calc'd for C₁₆H₂₃NO₂: C, 73.53; H, 8.87; N, 5.36. Found: C, 72.98; H, 8.81; N, 5.30. A solution of the epoxide (0.13 mmol, 50 mg) in 3:1 THF-water (1 mL) was treated with MsOH (0.53 mmol, 51 mg) for 16 h at 25 °C. The mixture was diluted with MTBE (5 mL) and washed with satd aqueous NaHCO₃ (5 mL). The organic phase was dried over MgSO₄ and evaporated *in vacuo* to provide the *syn*-lactone **17** as a viscous oil (25 mg, 92%).

2,4-Syn-*N,N*-dimethyl-2-cyclohexylmethyl-4-hydroxy-5-iodo-pentanamide (27): mp 103-104 °C. *R*_f = 0.44 (MTBE). ¹³C NMR (62.9 MHz, CDCl₃) δ 176.7, 68.3, 40.2, 38.3, 37.6, 35.9, 35.1, 34.8, 33.9, 33.0, 26.5,

26.2, 26.1, 16.6; FTIR (thin film) ν_{\max} 3367, 2922, 1618, 1448 cm^{-1} . m/z 367 (M^+). Anal. Calcd for $C_{14}H_{26}NO_2$: C, 45.79; H, 7.14; N, 3.81; I, 34.55. Found: C, 46.05; H, 6.99; N, 3.94; I, 33.80.

2,4-Syn-*N,N*-diethyl-2-methyl-4-hydroxy-5-iodo-pentanamide (28): $R_f = 0.50$ (MTBE). ^{13}C NMR (62.9 MHz, CDCl_3) δ 175.7, 68.2, 42.1, 40.6, 40.2, 32.3, 18.2, 16.6, 14.7, 13.0; FTIR (thin film) ν_{\max} 3366, 2972, 2933, 1616, 1448 cm^{-1} .

2,4-Syn-*N,N*-diethyl-2-benzyloxy-4-hydroxy-5-iodo-pentanamide (29): $R_f = 0.52$ (MTBE). ^{13}C NMR (62.9 MHz, CDCl_3) δ 170.0, 136.9, 128.5, 128.0₂, 127.9₉, 74.8, 71.1, 68.3, 41.2, 40.6, 38.3, 14.4, 14.1, 12.8; FTIR (thin film) ν_{\max} 3365, 2973, 2933, 1628, 1454 cm^{-1} . The relative stereochemistry of iodohydrin **29** was demonstrated by conversion to the derived epoxide as described above for **26** and lactonization to lactone **32**: ^1H NMR (250.1 MHz, CDCl_3) δ 7.36(m, 5H), 4.92(d, $J=11.6$, 1H), 4.72(d, $J=11.6$, 1H), 4.42(m, 1H), 4.30(dd, $J=9.7$, 8.3, 1H), 3.84(dd, $J=13.0$, 2.8, 1H), 3.63(dd, $J=13.0$, 5.1, 1H), 3.08(br s, 1H), 2.45(ddd, $J=12.5$, 8.3, 6.0, 1H), 2.13(dt, $J=12.5$, 9.7, 1H); ^{13}C NMR (62.9 MHz, CDCl_3) δ 174.9, 136.8, 128.5, 128.1, 77.3, 73.4, 72.2, 63.4, 30.5.

2,4-Syn-*N,N*-diethyl-2-*t*-butyldiphenylsilyloxy-4-hydroxy-5-iodo-pentanamide (30): $R_f = 0.62$ (MTBE). ^{13}C NMR (62.9 MHz, CDCl_3) δ 172.2, 135.9, 135.7, 133.0, 132.7, 130.0, 129.9, 127.8, 127.6, 67.4, 66.5, 41.4, 41.2, 40.8, 26.8, 19.3, 14.6, 14.0, 12.6; FTIR (thin film) ν_{\max} 3387, 2961, 2931, 2857, 1631, 1111 cm^{-1} . m/z 554 ($M+H$). Anal. Calcd for $\text{C}_{25}\text{H}_{36}\text{NO}_3\text{Si}$: C, 54.25; H, 6.55; N, 2.53; I, 22.92. Found: C, 54.11; H, 6.31; N, 2.19; I, 23.83. Iodohydrin **30** was converted to its corresponding diol by treatment of a solution of crude **30** (600 mg, 1.08 mmol) in MeCN (3 mL) with 48% aqueous HF (1.5 mL) for 10 min at 25 °C followed by the addition of solid Na_2CO_3 (3 g). The mixture was diluted with CH_2Cl_2 (10 mL), filtered and evaporated in vacuo. The residue was washed with hexane (5×30 mL) to provide the crude diol as a gum (280 mg, 82%). A solution of the crude diol (0.50 mmol, 158 mg) and pyridine (0.75 mmol, 60 mg) in CH_2Cl_2 (2 mL) was treated with triphosgene ((0.60 mmol, 60 mg) in CH_2Cl_2 (1 mL). The mixture was diluted with MTBE (10 mL) and washed with satd aqueous NaH_2PO_4 (10 mL), satd aqueous NaCl (10 mL) and satd aqueous NaHCO_3 (10 mL). The organic phase was dried over MgSO_4 , filtered through a plug of silica (1 g) and evaporated in vacuo to provide the carbonate **33** (136 mg, 80%): ^1H NMR (400.1 MHz, CDCl_3) δ 5.21(dd, $J=11.2$, 4.0, 1H), 4.57(m, 1H), 3.50-3.30(om, 6H), 2.47(dt, $J=14.5$, 3.6, 1H), 2.28(dt, $J=14.5$, 11.2, 1H), 1.24(t, $J=7.2$, 3H), 1.13(t, $J=7.2$, 3H).

N,N-diethyl-4-hydroxy-5-iodo-pentanamide (31): $R_f = 0.36$ (MTBE). ^{13}C NMR (62.9 MHz, CDCl_3) δ 172.5, 70.8, 42.2, 40.5, 31.0, 29.4, 14.5, 14.0, 12.9; FTIR (thin film) ν_{\max} 3369, 2973, 2934, 1617, 1453 cm^{-1} . m/z 300 ($M+H$)⁺.

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⁷ Askin, D.; Wallace, M.A.; Vacca, J.P.; Reamer, R.A.; Volante, R.P.; Shinkai, I. *J. Org. Chem.* **1992**, *57*, 2771-2773. The diastereoselectivity is 96:4 (1:12) after allylation at -15°C.

⁸ Interestingly, elimination of the NaHCO₃ buffer in the biphasic system with NIS also afforded the iodohydrin **2** as the predominant product, with only small amounts of iodolactone **3** formed. However, competitive loss of the acetonide protecting group of **2** was observed under the unbuffered conditions. The pH of the mixture without the NaHCO₃ buffering was about 2.5, similar to the pH of the homogeneous iodolactone formation conditions of Yoshida (I₂, aqueous THF). This apparent disparity in product formation at similar pH may be attributed to the biphasic nature of the NIS/IPAc/water system.

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¹² The oxazoline **11** appeared to undergo intramolecular N-alkylation of the iodomethyl group and formation of a 6-membered ring in solution by NMR analysis (¹H, ¹³C). Attempted isolation of this product was not successful. The oxazoline **11** was presumed to bear the 2,4-*syn* stereochemistry; however, this was not confirmed due its instability.

¹³ For a review on the formation and chemistry of 2-oxazolines, see: Grant, T.G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297-2360.

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(Received 14 September 1995; accepted 4 December 1995)