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TETRAHEDRON

An Efficient Synthesis of 4-Ethyl-4-[(3-Hydroxycarbonyl)propyl]dihydro-2(3*H*)-Furanone And Its Use In A Formal Total Synthesis of (±)-Quebrachamine.

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Abstract: The $Rh_2(OAc)_4$-catalyzed reaction of diazoacetate **5** provides ready access to the pivotal cyclic acetal **13** that undergoes Pictet-Spengler-type condensation with tryptamine to directly afford an epimeric mixture of the tetracyclic lactam **17a,b**. Lithium aluminum hydride reduction of **17a,b** provides the known tetracyclic amino alcohol **18a,b** which, overall, constitutes a formal synthesis of (±)-quebrachamine.

INTRODUCTION

γ-Lactone derivatives are synthetically useful intermediates[1] and much interest has been directed toward the development of new methods for their preparation. Geminally substituted γ-lactones have proven useful in the synthesis of natural products that possess a quaternary carbon centre.[2] In particular, the C-3 geminally substituted γ-lactones have received the most attention and have been effectively utilized for the synthesis of indole alkaloids,[3] in particular alkaloids belonging to the genuses *Aspidosperma* and *Hunteria* alkaloids. In contrast, C-4 geminally substituted γ-lactones have not recieved the same attention and one possible reason for this is the lack of general methods for their preparation.[4]

Recently we showed that the Rh(II)-catalyzed tertiary C-H insertion in β' branched O-alkyl α-(alkoxycarbonyl)-α-diazoacetates provides a useful method for the preparation of 4,4-disubstituted γ-lactones.[5] We demonstrate in this report the preparation and use of the 4,4-disubstituted γ-lactone **12** in a formal synthesis

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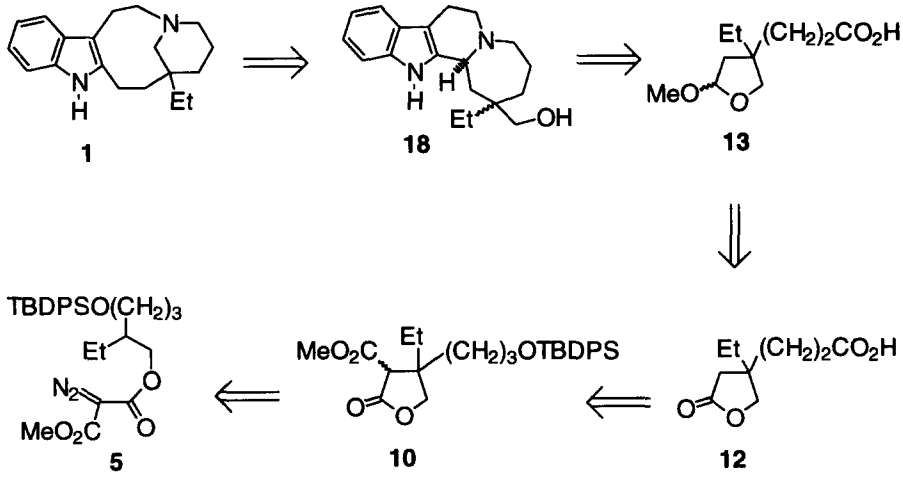


Chart 1

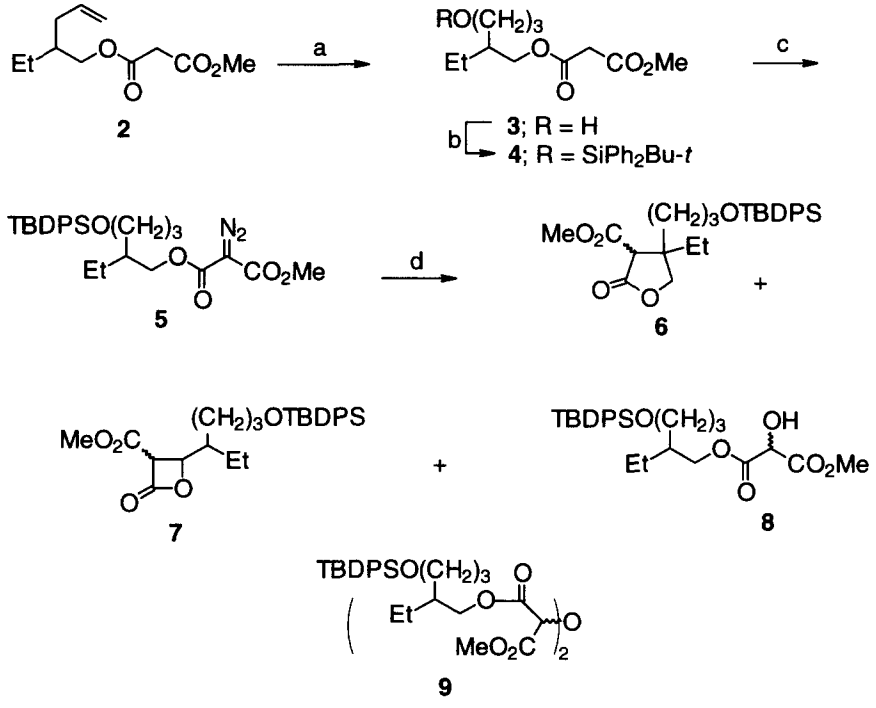
of (±)-quebrachamine **1**. Quebrachamine has been prepared from the tetracyclic amino alcohol **18** by Takano and coworkers.[6] and this study reports the synthesis of **18**. Our retrosynthetic analysis of **18**, as shown in Chart 1, differs from the published route.[6] We envisage that compound **18** should be accessible through the condensation of the pivotal intermediate **13** and tryptamine. Compound **13** is obtained from the γ-lactone **12** that is derived from **10**. γ-Lactone **10** is prepared via the Rh(II)-catalyzed tertiary C-H insertion of diazoacetate **5**.

RESULTS AND DISCUSSION.

The double bond moiety in the known[5] β-keto ester **2** was hydrated[7] using disiamylborane followed by oxidation with alkaline hydrogen peroxide to give a good yield of the primary alcohol **7** (Scheme 1). Reaction of **7** with *t*-$BuPh_2SiCl$[8] proceeded efficiently to afford the silyl ether **8**, which was diazotized[9] with mesyl azide[10] to give the diazo compound **5**.

With compound **5** in hand we investigated its Rh(II)-catalyzed tertiary C–H insertion reaction to give **6** (Scheme 1). In our previous study,[5] we employed diazo substrates that possessed a methine centre and an olefinic double bond functionality. We found that Rh(II)-carbenoid cycloaddition to the double bond is competitive with γ-lactone formation (from tertiary C–H insertion) but β-lactone formation is a minor pathway. In particular, the results from the comparison between $Rh_2(OAc)_4$ and the "electronically selective"[10] $Rh_2(acam)_4$ revealed that the latter catalyst promotes Rh(II)-carbenoid cycloaddition. In **5**, however, the abovementioned competition is absent

and this prompted us to examine the relative effectiveness of $Rh_2(OAc)_4$ to $Rh_2(acam)_4$ in promoting tertiary C–H insertion under reaction conditions (Methods A and B) that were previously developed. It was expected that the



Scheme 1

Reagents: a) $(Sia)_2BH$, THF, 0 °C; H_2O_2, NaOH, b) *t*-$BuPh_2SiCl$, pyridine, 0 °C, c) MsN_3, Et_3N, MeCN, 0 °C, d) Rh_2L_4, CH_2Cl_2 (0.01 M), T °C.

$Rh_2(acam)_4$-derived carbenoid should favour insertion into the more electron-rich methine C-H over the less electron-rich methylene C-H bond resulting in an increased preference for formation of γ-lactone.

It turned out that when we carried out the Rh(II)-catalyzed reactions using either Method A or B, a mixture of products comprising of the γ-lactone **6**, β-lactone **7**, water-insertion **8**, and dimer **9** were obtained. A brief study of reaction conditions was therefore conducted to determine the best conditions for the formation of **6** and the results are summarized in Table 1.

It is clear that, in Method A, water-insertion and dimer formation to give **8** and **9** are competitive with tertiary C–H insertion and this is especially marked in the $Rh_2(acam)_4$-catalyzed reaction (entries 1 and 4). Whereas β-lactone formation is a minor reaction for the $Rh_2(acam)_4$ reaction, it is a significant pathway with $Rh_2(OAc)_4$. This may likely be associated with the higher reactivity (lower selectivity) of the carbenoid

intermediate. As well, these reactions are characterized by the low chemical yields of the desired **6**; 39% and 24% with $Rh_2(OAc)_4$ and $Rh_2(acam)_4$, respectively. In Method B, there was a substantial decrease in the amounts of the byproducts that were formed and a marked increase in the yield of **6** when $Rh_2(OAc)_4$ was used as the catalyst (compare entries 1 and 2). This was not the case with $Rh_2(acam)_4$ wherein byproducts **8** and **9** were still produced as main products and only a slight improvement in the yield of **6** was obtained (compare entries 4 and 5). However, β-lactone was now obtained as a minor product with $Rh_2(OAc)_4$, but was not detected with

Table 1. Product Distribution In The Rh(II)-catalyzed Reaction of Diazoacetate **6**.

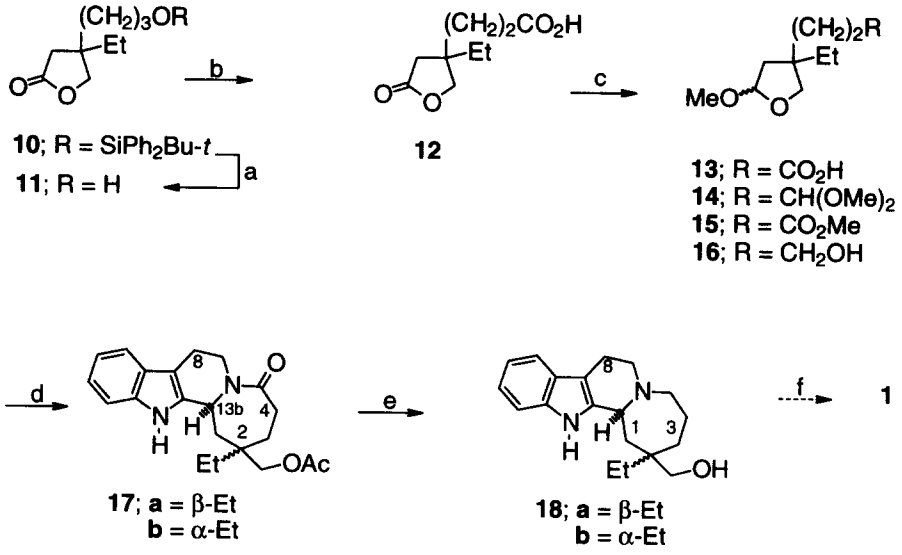
entry	method	catalyst[a]	**6**[b] (%[c])	**7**[b]	**8/9**[b] (ratio[d])
1	A	$Rh_2(OAc)_4$	50 (39)	17	33 (1.5:1)
2	B	$Rh_2(OAc)_4$	81 (74)	8	11 (2:1)
3	C	$Rh_2(OAc)_4$	90 (90)	8	2 (2.4:1)
4	A	$Rh_2(acam)_4$	25 (24)	6	69 (3:1)
5	B	$Rh_2(acam)_4$	37 (33)	0	63 (2.3:1)
6	C	$Rh_2(acam)_4$	73 (67)	0	27 (1:1)

Method A: Compound **5** in CH_2Cl_2 (0.01 M), rt. Method B: **5** in CH_2Cl_2 was added slowly (over 5 h) to a suspension of the Rh(II) catalyst in refluxing CH_2Cl_2 The final concentration of **5** in CH_2Cl_2 was 0.01 M. Method C: Same as Method B but used flame-dried reaction apparatus. a) 2 mol % of catalyst was used. b) Product ratio is based on the weight of the individual isolated products divided by the total weight. c) Chemical yield of **6** d) Ratio of **8**:**9** is based on the integration of the α–H in **8** (δ 4.70) and **9** (δ 4.92 and 4.94) in the ^1H NMR spectrum.

$Rh_2(acam)_4$. It is obvious that adventitious water is somehow getting into the reaction and trapping out the reactive Rh(II)-carbenoid. This led to the development of Method C which gave the highest yield of γ-lactone **6** (entries 3 and 6). In particular, the amount of byproducts formed in the $Rh_2(acam)_4$-catalyzed reaction was drastically curtailed (compare entries 5 and 6).

The γ-lactone **6** was then decarboxylated by heating in wet DMSO containing NaCl at 110 °C to give an 84% yield of **10** (Scheme 2). Compound **10** was efficiently desilylated with Bu_4N F in THF to give **11** which was subjected to Jones' oxidation to yield the carboxylic acid **12** in 97% yield.

We found that when the decarboxylation was conducted at 160 °C, an unexpected desilylation[12] of the *t*-$BuPh_2Si$ group occurred resulting in a 1:1 mixture of **10**:**11**. Although this step could, in principle, be exploited for the direct conversion of **6** to **11**, we found that the very polar primary alcohol **11** is somewhat soluble in aqueous mixtures which meant that there is a potential loss in the yield of **11**. Therefore, the decarboxylation-desilylation protocol described above, for the conversion of **6** to **11**, was judged to be more efficient, overall.



Scheme 2

Reagents: (a) Bu_4N F, THF, 0 °C, (b) CrO_3, H_2SO_4, H_2O, (c) DIBAL-H, PhMe-Et_2O -78 °C then MeOH, TsOH, (d) tryptamine, glacial AcOH-PhMe (2:1 v/v), 80 °C (24 h) and then reflux (24 h), (e) $LiAlH_4$, THF, reflux, (f) *Ref.* 6

Next we investigated the preparation of **13** via selective reduction of the lactone carbonyl in **12**. Fuji and coworkers have described[3b] a useful and very efficient "one-pot" DIBAL-H reduction-acetal formation of a related carboxylic acid γ-lactone to the corrresponding cyclic acetal carboxylic acid. A very small amount (6%) of a side product which was identified as the methyl ester derivative of the desired product was also isolated. We therefore applied Fuji's procedure to the reduction of γ-lactone **12** and this led to a 65% yield of the desired compound **13**. However, three other minor products, identified as the diacetal **14**, the acetal ester **15**, and the acetal alcohol **16** on the basis of their spectral data, were also isolated. The ratio of **13**:**14**:**15**:**16** is 72:21:4:3.

The stage is set for a Pictet-Spengler[13]-type condensation of **13** with tryptamine.[14] We first examined the condensation in hot acetic acid, a reaction condition that is commonly employed for similar types of reaction.[3] We were pleased to find that, the condensation of **13** and tryptamine (1.1 eq) in refluxing acetic acid led directly to the tetracylic O-acetate lactam **17a,b** albeit in 40% yield. No unreacted starting **13** was recovered even when the aqueous extracts were carefully acidified and reextracted. Although it may be possible to improve on the yield of **17** by using a larger excess of tryptamine in the condensation, we decided to investigate whether a mixture of toluene-acetic acid would be a suitable medium for the condensation. We reasoned that the addition of toluene would serve to lower the acidity of the reaction medium (through dilution) which, in turn, would slow down the

(possible) decomposition of **13**. First we examined the reaction of **13** and tryptamine (1.1 equiv.) in a 2:1 v/v mixture of acetic acid-toluene at 110 °C (oil bath). This led to a disappointingly low yield of **17** (34%). We also obtained an equal amount of N_b-acetyl tryptamine, a product that was not detected when the reaction was conducted in only acetic acid. This result suggests that tryptamine was being consumed by an unanticipated N_b-acylation pathway that is competitive with the desired Pictet-Spengler reaction. Replacement of acetic acid with the more hindered pivalic acid did not suppress the undesired N_b-acylation pathway; in fact N_b-pivalyltryptamine was the only product isolated and the desired **17** was not detected at all. After several variations on reaction parameters, such as the amount of tryptamine and reaction temperature, we finally found that a good yield of **17** (52–57%) was obtained when the condensation was conducted in acetic acid-toluene (2:1) using three equivalents of tryptamine and at a reaction temperature of 80 °C for 24 h and then raising the temperature to 100 °C for an additional 24 h.

It is useful to note that under both cyclization reaction conditions (AcOH and AcOH:PhMe) the tetracycle **17** was obtained as a 1.3:1 mixture of readily separable epimers **17a** and **b**. Their structures are in full accord with their ^1H and ^{13}C NMR (including COSY and HETCOR) data as well as high resolution mass spectral data. The relative stereochemistry between the C(13b)-H and the ethyl and CH_2OAc groups was assigned on the basis of NOE experiments (*vide infra*). The salient features in the ^1H and ^{13}C NMR spectra are collected in Table 2.

Table 2. Selected ^1H and ^{13}C NMR Data For **17a** and **17b**.

	17a (β-Et)	**17b** (α-Et)		**17a** (β-Et)	**17b** (α-Et)
^1H	δ; m; *J* (Hz)	δ, m, *J* (Hz)	^{13}C	δ	δ
C(4)-H	2.46; dd; 14.6, 7.3	2.48; dd; 13.8, 6.9	C(8)	20.7	20.7
C(7)-H	3.10; dq; 13.4, 10.9, 5.5	3.04; dq; 12.6, 10.3, 4.3	C(3)	30.6	24.7
CHOAc	3.80; d; 12.2	3.81; d; 11.5	C(4)	31.9	31.2
CHOAc	4.99; d; 12.2	3.87; d; 11.5	CH_2Me	32.7	28.3
C(7)-H'	4.78; dq; 13.4, 4.5, 2.9	4.85; dq; 12.5, 4.6, 2.3	C(7)	37.6	38.0
C(13b)-H	5.20; d; 9.6	5.05; d; 8.6	C(2)	38.9	37.7
			C(1)	39.8	40.1
			C(13b)	49.4	48.7
			CH_2OAc	66.4	70.5

It can be seen that the C(13b)-H in **17a** resonated at lower field than in **17b**; however, both appeared as a broad doublet indicating that C(13b)-H is only strongly coupled to one of the vicinal C(1)-methylene hydrogens. Interestingly, the chemical shifts of the doublets due to each of the methylene hydrogens in the CH_2OAc group in

17a are well separated by 1.1 ppm, whereas the separation is smaller (0.06 ppm) in **17b**. In the ^{13}C NMR spectra of **17a,b** the methylene carbons of the ethyl and CH_2OAc groups, in particular, showed a marked difference in their chemical shifts. For the β-ethyl group, the methylene carbon is deshielded (δ 32.7) whereas in the α-ethyl, the methylene carbon is shielded (δ 24.7). The opposite trend is observed for the CH_2OAc methylene carbon.

The *syn* relative stereochemistry between the C(13b)-H and the CH_2OAc unit in **17a** was established by NOE experiments. Specifically, irradiation of the low field doublet of the CH_2OAc group centred at δ 4.99 resulted in a 4.7% enhancement in the C(13b)-H doublet centred at δ 5.20. No enhancement, however, was observed when the higher field doublet at δ 3.80 was irradiated.

Standard reduction of **17a** and **b** with $LiAlH_4$ in refluxing THF proceeded eficiently to furnish the known key tetracyclic amino alcohols **18a** (mp. 215°C, lit.[6] 219-221 °C) and **18b** (mp. 230-232 °C, lit.[6] 232.5-235°C), whose ^1H NMR data are in accord with those obtained for the authentic samples. Since Takano and coworkers[6] have converted **18a** and **b** to (±)-quebrachamine **1**, this constitutes a formal synthesis of **1**.

CONCLUSIONS

We have shown the the Rh(II)-catalyzed tertiary C-H insertion of the β-branched O-alkyl α-(methoxycarbonyl)-α-diazoacetate **5** provides ready access to the pivotal cyclic acetal carboxylic acid **13** and thence to the known tetracylic amino alcohols **18**. This method for the formation of 4,4-disubstituted γ-lactones should prove useful in natural product synthesis. Its application to the asymmetric synthesis of (+)-eburnamonine and (+)-aspidospermine will be reported in future.

EXPERIMENTAL SECTION

General: Melting points are uncorrected and were measured on a Kofler hot-stage melting point apparatus. Infra-red spectra were recorded using a Perkin Elmer 1600FT spectrophotometer: only diagnostic absorptions in the infra-red spectrum are reported. ^1H (200 MHz) and ^{13}C (50.3 MHz) N.M.R. spectra were recorded in $CDCl_3$ (unless otherwise stated), using a Bruker 200QNP spectrometer. Tetramethylsilane (δ_H = 0.00) and the $CDCl_3$ resonance (δ_C = 77.0) were used as references. Where applicable, the signals of minor diastereomers are given within square brackets. Proton assignments were made using double irradiation experiments and confirmed, where necessary, by 2D-COSY-45 experiments. ^{13}C assignments were made using DEPT and HETCOR experiments. Elemental analyses and high resolution electron impact (70 eV) and chemical ionization mass spectral analyses were performed at the Chemistry Department, University of Saskatchewan, Canada.

The Rh(II)-catalyzed reaction of **5** was performed in CH_2Cl_2 using 2 mol % of the catalyst. Methods A and B are basically those described in reference (5), but differ only in total reaction times: Method A, the total

reaction was 4 h; Method B, the total reaction time was 10 h. Method C is similar to Method B except that the reaction apparatus was flame dried under a stream of Ar before use. $Rh_2(acam)_4$ is rhodium(II) acetamide.

(2-Ethyl-5-hydroxypentyl)-α-(methoxycarbonyl)acetate (3). Compound **2**[5] (214 mg, 1 mmol) in dry THF was added dropwise to a mixture of disiamylborane (prepared in situ using 1.2 mL of 1M BH_3 inTHF and 1.2 mL 2M 2-methyl-2-butene in THF) at 0 °C. After stirring for 30 min at 0 °C and 30 min at rt, the solution was recooled to 0 °C. Water (0.1 mL), 30% H_2O_2 (0.5 mL, 4.2 mmol) and 1M aqueous NaOH (0.43 mL, 0.43 mmol) were added sequentially. The mixture was stirred for 20 min at 10-20 °C and then ether (2 mL) was added and the layers separated. The aqueous layer was extracted twice with ether (5 mL) and the combined ethereal layers were washed with saturated $NaHSO_3$, dried, filtered and concentrated to give an oil. Chromatographic purification (2:1 pet. ether:EtOAc) gave 170 mg (74%) of **3**. IR (neat): 3418, 1756, 1732 cm^{-1}. ^1H NMR, δ: 0.88 (t, 3H, J = 8 Hz, Me), 1.26–1.43 (m, 4H, CH_2), 1.46–1.70 (m, 4H, CH, CH_2, OH), 3.37 (s, 2H, CH_2C=O), 3.62 (t, 2H, J = 6.9 Hz, CH_2O), 3.71 (s, 3H, OMe), 4.60 (d, 1H, J = 5.7 Hz, OCH), 4.70 (d, 1H, J = 5.7 Hz, OCH). ^{13}C NMR, δ: 10.9, 23.6 (-), 26.7 (-), 29.7 (-), 38.5, 41.4 (-), 52.5, 63.0 (-), 67.6 (-), 166.6, 167.1. Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.73; H, 8.78.

[5-(*t*-Butyldiphenylsilyloxy)-2-ethylpentyl]-α-(methoxycarbonyl)acetate (4). *t*-Butyldiphenlsilyl chloride (4 mL, 15 mmol) was added to the mixture of alcohol **3** (3.5 g, 15 mmol) in dry pyridine (35 mL) at 0 °C. The mixture was stirred at 0 °C to rt over a period of 12 h, water (50 mL) and EtOAc (50 mL) were added and the organic layer was separated. The aqueous phase was reextracted with EtOAc (30 mL) and the combined organic layers were washed with saturated $CuSO_4$, water, brine and dried. The filtered solution was evaporated to give a crude oil which was chromatographed (7:1 and then 2:1 pet. ether:Et_2O) to afford **4** as a thick oil. Yield was 6.4 g, 89%. IR ν_{max} (film): 1754, 1738 cm^{-1}. ^1H NMR, δ: 0.88 (t, 3H, J = 7.4 Hz, Me), 1.05 (s, 9H, *t*-Bu), 1.27–1.70 (m, 7H, CH, $(CH_2)_2$, CH_2Me), 3.38 (s, 2H, CH_2C=O), 3.65 (t, 2H, J = 6.3 hz, CH_2OSi), 3.72 (s, 3H, OMe), 4.06 (d, 2H, J = 5.7 Hz, CH_2O), 7.32–7.40 (m, 6H, PhH), 7.60–7.73 (m, 4H, PhH). ^{13}C NMR, δ: 10.8, 19.2, 23.5 (-), 26.7 (-), 26.8, 29.6 (-), 38.4, 41.4 (-), 52.4, 64.0 (-), 67.8 (-), 127.6, 129.5, 134.0, 135.5, 166.6, 167.0. Anal. Calcd for $C_{27}H_{38}O_5Si$: C, 68.90; H, 8.14. Found: C, 69.19; H, 7.89.

[5-(*t*-Butyldiphenylsilyloxy)-2-ethylpentyl]-α-diazo-α-(methoxycarbonyl)acetate (5). Compound **4** (4.3 g, 9.1 mmol) was dissolved in dry MeCN (30 mL) and the solution was cooled to 0 °C. Mesyl azide (1.3 mL, 14 mmol) was added followed by dry Et_3N (2.5 mL, 18 mmol). The mixture was stirred at 0 °C for 30 min and then at rt for 10 h. The mixture was diluted with CH_2Cl_2 (100 mL) and washed with 10% aqueous NaOH (20 mL) and water (30 mL). The aqueous layer was reextracted with more CH_2Cl_2 (2 X 30 mL). The combined organic layers were dried, filtered and evaporated. The crude product was chromatographed (7:1 and then 2:1 pet. ether:Et_2O) to give

5.9g (88%) of the diazo product **5**. IR ν_{max} (neat): 2135, 1761, 1737, 1695 cm^{-1}. ^1H NMR, δ: 0.89 (t, 3H, J = 7.2 Hz, Me), 1.05 (s, 9H, *t*-Bu), 1.27–1.70 (m, 7H, $(CH_2)_2$, CH_2Me, CH), 3.64 (t, 2H, J = 6.0 Hz, CH_2OSi), 3.83 (s, 3H, OMe), 4.15 (d, 2H, J = 5.8 Hz, CH_2O), 7.30–7.40 (m, 6H, PhH), 7.60 –7.75 (m, 4H, PhH). ^{13}C NMR, δ: 10.9, 19.2, 23.6 (-), 26.7 (-), 26.8, 29.6 (-), 38.6, 52.5, 63.9 (-), 67.7 (-), 127.6, 129.5, 133.9, 135.5, 160.9, 161.6. Anal. Calcd for $C_{27}H_{36}N_2O_5Si$: C, 65.29; H, 7.31; N, 5.64. Found: C, 65.34; H, 7.29; N, 5.54.

Rh(II)-catalyzed reaction of diazoacetate 5. The distribution of products is summarized in Table 1 and is calculated based on the weight of the isolated products. Compounds **6**, **7**, are well separated from the mixture of **8/9**. Byproducts **8/9** are very closely moving; however, small amounts of analytically pure samples of each were isolated by careful chromatographic separation.

catalyst	method	diazoacetate **5** (mg)	γ-lactone **6** (mg)	β-lactone **7** (mg)	water insertion **8**/ dimer **9** (mg)
$Rh_2(OAc)_4$	A	296	109	37	74
$Rh_2(acam)_4$	A	288	66	16	182
$Rh_2(OAc)_4$	B	359	254	25	36
$Rh_2(acam)_4$	B	232	87	0	145
$Rh_2(OAc)_4$	C	659	593	11	12
$Rh_2(acam)_4$	C	226	157	0	58

4-[3-(*t*-Butyldiphenylsilyloxypropyl)-4-ethyl-3-(methoxycarbonyl)dihydro-2(3*H*)-furanone (6). Obtained as a 1:1 mixture of diastereomers based on the integration of the ester methoxy singlets. IR ν_{max} (neat): 1787, 1737 cm^{-1}. ^1H NMR, δ: 0.90 and 0.91 (t, 3H, J = 7.2 Hz, Me), 1.04 (s, 9H, *t*-Bu), 1.31–1.70 (m, 6H, $(CH_2)_2$, CH_2Me), 3.27 and 3.28 (s, 1H, H-3), 3.55–3.70 (m, 2H, CH_2), 3.71 and 3.76 (s, 3H, OMe), 4.03 and 4.07 (d, 1H, J = 8.6 Hz, H-5), 4.19 (d, 1H, J = 8.6 Hz, H-5'), 7.35–7.45 (m, 6H, PhH), 7.60–7.70 (m, 4H, PhH). Anal. Calcd for $C_{27}H_{36}O_5Si$: C, 69.20; H, 7.74. Found: C, 69.00; H, 7.92.

4-[4(*t*-Butyldiphenylsilyloxy)-1-ethylbutyl]-3-(methoxycarbonyl)-2-oxooxetane (7). Obtained as a 2.2:1 mixture of major diastereomers on the basis of the integration of the methoxy singlet of the CO_2Me moiety. IR ν_{max} (neat): 1838, 1744 cm^{-1}. ^1H NMR, δ: 0.94 (t, 3H, J = .4 Hz, Me), 1.08 (s, 9H, *t*-Bu), 1.30–1.80 (m, 7H, $(CH_2)_2$, CH, CH_2Me), 3.60–3.73 (m, 2H, CH_2O), 3.76 and 3.80 (s, 3H, OMe), 4.07 (J = 5.7 Hz) and 4.15 (J = 5.1

Hz) (d, 1H, H-3), 4.62 (dd, 1H, J = 8.6, 5.1 Hz, H-4). 7.30–7.60 (m, 6H, PhH), 7.61–7.75 (m, 4H, PhH). Anal. Calcd for $C_{27}H_{36}O_5Si$: C, 69.20; H, 7.74. Found: C, 68.99; H, 7.91.

[5-(*t*-Butyldiphenylsilyloxy)-2-ethylpentyl]-α-hydroxy-α-(methoxycarbonyl)acetate (8). Obtained as one diastereomer. IR ν_{max} (neat): 3575–3225, 1760, 1743 cm^{-1}. ^1H NMR, δ: 0.90 (t, 3H, J = 7.3 Hz, Me), 1.05 (s, 9H, *t*-Bu), 1.23–1.70 (m, 7H, $(CH_2)_2$, CH_2Me, CH), 3.39 (br s, 1H, OH), 3.62 (t, 2H, J = 5.8 Hz, CH_2OSi), 3.79 (s, 3H, OMe), 4.02–4.21 (m, 2H, CH_2O), 4.70 (br s, 1H, CHOH), 7.30–7.45 (m, 6H, PhH), 7.60–7.75 (m,4H, PhH). ^{13}C NMR, δ: 10.9, 19.2, 23.5 (-), 26.6 (-), 26.8, 29.6 (-), 38.5 , 53.2, 64.0 (-), 68.9 (-), 71.4, 127.7, 129.6, 134.0, 135.6, 168.6, 169.0. Anal. Calcd for $C_{27}H_{38}O_6Si$: C, 66.63; H, 7.87. Found: C, 66.60; H, 7.98.

Dimer (9). Obtained as a 1:1 mixture of diastereomer on the basis of the integration of the C(α)-H singlets. IR ν_{max} (neat): 1770, 1743 cm^{-1}. ^1H NMR, δ: 0.88 (t, 6H, J = 7.2 Hz, 2 X Me), 1.05 (s, 18H, 2 X *t*-Bu), 1.21–1.70 (m, 14H, 2 X $(CH_2)_2$, CH_2Me, CH), 3.63 (t, 4H, J = 6.6 Hz, 2 X CH_2OSi), 3.74 (s, 6H, 2 X OMe), 4.00–4.20 (m, 4H, 2 X CH_2O), 4.92 (s, 1H, C(α)-H) and 4.94 (s, 1H, C(α)-H), 7.30–7.58 (m, 12H, PhH), 7.60–7.70 (m, 8H, PhH). Anal. Calcd for $C_{54}H_{74}O_{11}Si_2$: C, 67.89; H, 7.80. Found: C, 67.95; H, 8.01.

4-[3-(*t*-Butyldiphenylsilyloxypropyl)-4-ethyldihydro-2(3*H*)-furanone (10). γ-Lactone **6** (720 mg, 1.53 mmol) was dissolved in DMSO (2 mL) containing NaCl (90 mg, 1.53 mmol). Water (60 μL, 3.1 mmol) was added and the mixture was heated at 110 °C for 12 h. The mixture was cooled to rt and water (2 mL) was added. The aqueous layer was extracted with Et_2O (3 X 20 mL), the combined organic phases were washed with brine (2 X 20 mL) and then dried. The filtered solution was evaporated and the crude product was purified by chromatography (4:1 and then 2:1 pet. ether:Et_2O) to give **10** (530 mg, 84%). IR ν_{max} (neat): 1778 cm^{-1}. ^1H NMR, δ: 0.87 (t, 3H, J = 7.2 Hz, Me), 1.05 (s, 9H, *t*-Bu), 1.42–1.58 (m, 6H, $(CH_2)_2$, CH_2Me), 2.31 (s, 2H, H-3), 3.65 (t, 2H, J= 5.1 Hz, CH_2OSi), 3.96 (d, 1H, J = 8.6 Hz, H-5), 4.03 (d, 1H, J = 8.6 Hz, H-5), 7.35–7.40 (m, 6H, PhH), 7.60–7.70 (m, 4H, PhH). ^{13}C NMR, δ: 8.4, 19.2, 26.8, 27.3 (-), 29.0 (-), 32.2 (-), 40.0 (-), 42.5, 63.7 (-), 77.1 (-), 127.7, 129.7, 133.7, 135.5, 177.1. Anal. Calcd for $C_{25}H_{34}O_3Si$: C, 73.13; H, 8.35. Found: C, 73.08; H, 8.49.

When **6** (4.9g, 10 mmol) was decarboxylated under identical conditions but at a higher temperature of 160°C, a mixture of compound **10** (2 g) and the desilylated compound **11**, (0.76 g) were obtained.

4-Ethyl-4-(3-hydroxypropyl)dihydro-2(3*H*)-furanone (11). Compound **10** (400 mg, 1mmol) was dissolved in dry THF (5 mL) and the solution was cooled to 0 °C. Bu_4N F (0.51 mL, 0.51 mmol, 1M in THF) was added dropwise and the mixture was stirred at rt for 40 min. Water (1 mL) was added and THF was evaporated. The residual oil was chromatographed (1:1 pet. ether:EtOAc) to give 160 mg (93%) of **11**. IR ν_{max} (neat): 3600–3125, 1770 cm^{-1}. ^1H NMR, δ: 0.88 (t, 3H, J = 7.7 Hz, Me), 1.40–1.60 (m, 6H, $(CH_2)_2$, CH_2Me), 1.60–1.88 (br hump,

1H, OH), 2.35 (s, 2H, H-3), 3.66 (br s, 2H, CH_2OH), 4.03 (s, 2H, H-5). ^{13}C NMR, δ:8.4, 27.2 (-), 29.0 (-), 32.2 (-), 39.8 (-), 42.5, 62.6 (-), 77.0 (-), 177.1. Anal. Calcd for $C_9H_{11}O_3$: C, 62.77; H, 9.36. Found: C, 62.57 H, 9.16.

4-Ethyl-4-[(2-hydroxycarbonyl)ethyl]dihydro-2(3*H*)-furanone (12). Jones reagent was added dropwise to a solution of **11** (620 mg, 3.6 mmol) in acetone (40 mL) at 0 °C until the orange color of the oxidant persisted. A few drops of 2-propanol were added and then followed by water (1 mL). The mixture was evaporated and the resulting mixture was mixed with saturated NaCl. The mixture was extracted with EtOAc (2 X 20 mL), the organic extracts were washed with brine, dried, filtered and evaporated to give a colorless solid **12** (660 mg, 98%). mp 65–67 °C. IR ν_{max} (neat): 3500–2500, 1770, 1710 cm^{-1}. ^1H NMR, δ: 0.90 (t, 3H, J = 7.4 Hz, Me), 1.52 (q, 2H, J = 7.4 Hz, CH_2), 1.78–1.88 (m, 2H, CH_2), 2.20–2.39 (m, 4H, 2 X CH_2C=O), 4.00 (d, 1H, J = 9.2 Hz, CHO), 4.06 (d, 1H, J = 9.2 Hz, CHO). ^{13}C NMR, δ: 8.4, 28.8 (-), 29.1 (-), 30.6 (-), 39.6 (-), 42.4, 76.5 (-), 176.5, 178.4. Anal. Calcd for $C_9H_{14}O_4$: C, 58.05 H, 7.58. Found: C, 58.17; H, 7.59.

4-Ethyl-4-[(2-hydroxycarbonyl)ethyl]-2-methoxytetrahydrofuran (13). The acid **12** (300 mg, 1.6 mmol) was dissolved in dry Et_2O (20 mL) and the solution was cooled to -78 °C. DIBAL-H (3.3 mL, 3.3 mmol, 1M in toluene) was added dropwise to the cold solution. After stirring at -78 °C for 1 h, dry MeOH (10 mL) and *p*-toluenesulfonic acid monohydrate (1.1 g, 5.5 mmol) were added and the mixture was warmed slowly to rt and then was refluxed for 40 min. The solvent was evaporated and water (2 mL) was added and the mixture was extracted twice with EtOAc (20 mL). The organic layers were washed with brine, dried, filtered and evaporated to give an oil. Chromatographic separation (1:1 pet. ether:EtOAc) afforded the desired **13** (200 mg) as well as **14** (60 mg), **15** (10 mg), and **16** (8 mg). All four compounds were obtained as 1:1 mixture of diastereomers on the basis of the integration of the methyl triplet of the ethyl moiety. *Compound 13*. IR ν_{max} (neat): 3500–2500, 1712 cm^{-1}. ^1H NMR, δ: 0.83 and 0.84 (t, 3H, J = 7.4 Hz, Me), 1.31–1.96 (m, 6H, CH_2, C(2)H_2, CH_2Me), 2.21–2.36 (m, 2H, CH_2C=O), 3.32 (s, 3H, OMe), 3.58 (d, 1H, J = 9.2 Hz, C(5)H), 3.63 (d, 1H, J = 9.2 Hz, C(5)H), 4.97–5.03 (m, 1H, C(1)H). Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.42; H, 9.04. *Compound 14*. IR ν_{max} (neat): 1125, 1102, 1054 cm^{-1}. ^1H NMR, δ: 0.84 and 0.85 (t, 3H, J = 7.7 Hz), 1.32–1.68 (m, 7H, $(CH_2)_2$, CH_2Me, C(3)H), 1.91 and 1.93 (dd, 1H, J = 13.7, 2.9 Hz, C(3)H), 3.32 (s, 6H, OMe), 3.33 (s, 3H, OMe), 3.60 (s, 2H, C(5)H_2), 4.33 (t, 1H, J = 5.1 Hz, $CH(OMe)_2$), 4.97–5.03 (m, 1H, C(1)H). Anal. Calcd for $C_{12}H_{24}O_4$: C, 62.04; H, 10.41. Found: C, 62.33; H, 10.43. *Compound 15*. Its infrared spectrum showed the absence of the CO_2H absorptions at 3500–2500 cm^{-1} and at 1712 cm^{-1} but the presence of an ester carbonyl absorption at 1741 cm^{-1}. Its ^1H NMR spectrum is identical to that of **13** with the exception of the methoxy singlet of the ester group at δ 3.37. Base hydrolysis (K_2CO_3, MeOH) of **15** gave **13**. *Compound 16*. IR ν_{max} (CH_2Cl_2): 3424, 1101, 1054 cm^{-1}. ^1H NMR, δ: 0.83 and 0.85 (t, 3H, J = 7.4 Hz, Me), 1.33–1.85 (m, 8H, $(CH_2)_2$, C(3)H, CH_2Me, OH), 1.92 (dd, 1H, J = 13.7, 6.0 Hz, C(3)H), 3.32 (s, 3H, OMe), 3.56–3.71 (m, 4H, C(5)H_2, CH_2OH), 4.99–5.01 (m, 1H, C(1)H).

2-(Acetoxymethyl)-2-ethyl-2,3,4,5,7,8,13,13b-octahydro-5-oxo-1H-azepino[1'2':1,2]pyrido[3,4-b]indole (17). A mixture of **13** (140 mg, 0.7 mmol) and tryptamine (400 mg, 2.1 mmol) were dissolved in a mixture toluene (4 mL) and acetic acid (8 mL). The solution was stirred at 80 °C for 24 h and then at reflux for another 24 h. The solution was evaporated and then a mixture of 10% aqueous NaOH (10 mL) and ice-water (10 mL) were added. The aqueous mixture was extracted with CH_2Cl_2 (2 X 20 mL), the organic phases were washed with brine, dried, filtered and evaporated. The crude product was purified by chromatography (2:1 pet. ether:EtOAc) to afford 80 mg of **17a** and 60 mg of **17b**. *Compound 17a*: IR ν_{max} (film): 3384, 1732, 1634 cm^{-1}. ^1H NMR, δ: 0.90 (t, 3H, *J* = 7.5 Hz, Me), 1.30–1.95 (m, 6H, CH_2Me, $C(3)H_2$, $C(1)H_2$), 2.25 (s, 3H, MeC(O)), 2.46 (dd, 1H, *J* = 14.6, 7.3 Hz, C(4)H), 2.65–2.95 (m, 3H, C(4)H', $C(8)H_2$), 3.10 (dq, 1H, *J* = 13.4, 10.9, 5.5 Hz, C(7)H), 3.80 (d, 1H, *J* = 12.2 Hz, CHOAc), 4.78 (dq, 1H, *J* = 13.4, 4.5, 2.9 Hz, C(7)H'), 4.99 (d, 1H, *J* = 12.2 Hz, CHOAc), 5.20 (d, 1H, *J* = 9.6 Hz, C(13b)H), 7.01–7.25 (m, 2H, C(10)H, C(11)H), 7.30 (br d, 1H, *J* = 7.2 Hz, C(12)H, 7.49 (br d, 1H, *J* = 7.2 Hz, C(9)H), 8.75 (br s, 1H, NH). ^{13}C NMR, δ: 7.4, 20.7 (-), 21.4, 30.6 (-), 31.9 (-), 32.7 (-), 37.6 (-), 38.9, 39.8 (-), 49.4, 66.4 (-), 109.9, 111.1, 118.2, 119.5, 121.9, 126.4, 132.7, 136.4, 172.9, 174.8. HRMS Calcd. for $C_{21}H_{26}N_2O_3$: 354.1943. Found: 354.1940. *Compound 17b*: IR ν_{max} (film): 3457, 1732, 1632 cm^{-1}. ^1H NMR, δ: 0.99 (t, 3H, *J* = 7.5 Hz, Me), 1.42–1.95 (m, 6H, $C(1)H_2$, $C(3)H_2$, CH_2Me), 2.05 (s, 3H, MeC(O)), 2.48 (dd, 1H, *J* = 13.8, 6.9 Hz, C(4)H), 2.62–2.93 (m, 3H, C(4)H', $C(8)H_2$), 3.04 (dq, 1H, *J* = 12.6, 10.3, 4.3 Hz, C(7)H), 3.81 (d, 1H, *J* = 11.5 Hz, CHOAc), 3.87 (d, 1H, *J* = 11.5 Hz, CHOAc), 4.85 (dq, 1H, *J* = 12.5, 4.6, 2.3 Hz, C(7)H), 5.05 (d, 1H, *J* = 8.6 Hz, C(13b)H), 7.02–7.26 (m, 2H, C(10)H, C(11)H), 7.30 (br d, 1H, *J* = 7.2 Hz, C(12)H), 7.48 (br d, 1H, *J* = 7.2 Hz, C(9)H), 8.05 (br s, 1H, NH). ^{13}C NMR, δ: 7.9, 20.7 (-), 20.8, 24.7 (-), 28.3 (-), 31.2 (-), 37.7 (-), 38, 40.1 (-), 48.7, 70.5 (-), 110.7, 110.8, 118.3, 119.7, 122.2, 126.5, 132.1, 136.4, 170.9, 174.9. HRMS Calcd. for $C_{21}H_{26}N_2O_3$: 354.1943. Found: 354.1945.

2-Ethyl-2-(hydroxymethyl)-2,3,4,5,7,8,13,13b-octahydro-5-oxo-1H-azepino[1'2':1,2]pyrido[3,4-b]indole (18). The acetate **17a** (40 mg, 0.11 mmol) was dissolved in dry THF (10 mL) at rt and $LiAlH_4$ (40 mg, 0.11 mmol) was added. The mixture was stirred at rt for 30 min and then was refluxed for 20 h. The reaction mixture was cooled to rt and 10% aqueous KOH (50 μL) was added and the mixture was stirred for 30 min. The mixture was filtered through a bed of Celite and the solid residue washed with CH_2Cl_2 (3 X 10 mL). The combined filtrates were dried, filtered and evaporated to leave a semi-solid that was chromatographed (10:1 CH_2Cl_2:MeOH) to give the known **18a** (30 mg, 95%). mp 215 °C (lit.[6] 219–221 °C). IR ν_{max} (film): 3311 cm^{-1}. ^1H NMR, δ: 0.87 (t, 3H, *J* = 8.0 Hz, Me), 1.33 (q, 2H, *J* = 8.0 Hz, CH_2Me), 1.48 (br t, 2H, *J* = 5.7 Hz, $C(3)H_2$), 1.76 (dd, 1H, *J* = 14.9, 9.2 Hz, C(1)H), 1.73–1.96 (m, 2H, $C(4)H_2$), 2.12 (dd, 1H, *J* = 14.9, 2.9 Hz, C(1)H), 2.53–3.18 (m, 7H, $C(5)H_2$, $C(7)H_2$, $C(8)H_2$, OH), 3.61 (s, 2H, CH_2OH), 4.00 (br d, 1H, *J* = 9.2 Hz, C(13b)H), 7.02–7.20 (m, 2H, ArH), 7.22–7.31 (m, 1H, ArH), 7.41–7.50 (m, 1H, ArH), 8.10 (br s, 1H, NH). ^{13}C NMR, δ: 8.1, 20.2 (-), 25.3 (-),

32.4 (-), 34.8 (-), 40.2, 40.5 (-), 52.1 (-), 54.7, 55.3 (-), 68.3 (-), 108.1, 110.7, 118.0, 119.2, 121.3, 127.0, 135.8, 136.1.

Similarly compound **17b** (40 mg, 0.11 mmol) was reduced to afford **18b** (31 mg, 96%). mp. 230–232 °C (lit.[6] 232.5–235 °C). IR ν_{max} (film): 3432 cm^{-1}. ^1H NMR, δ: 0.94 (t, 3H, J = 7.8 Hz, Me), 1.40–1.94 (m, 7H, C(1)H, C(3)H_2, C(4)H_2, CH_2Me), 2.09 (dd, 1H, J = 15.4, 2.3 Hz, C(1)H), 2.47–2.95 (m, 4H, C(5)H, C(7)H, C(8)H_2), 3.00–3.68 (m, 3H, C(5)H, C(7)H, OH), 3.22 (d, 1H, J = 10.5 Hz, CHOH), 3.33 (d, 1H, J = 10.5 Hz, CHOH), 3.75 (br d, 1H, J = 9.2 Hz, C(13b)H), 6.91–7.10 (m, 2H, ArH), 7.23–7.41 (m, 2H, ArH), 9.82 (s, 1H, NH). ^{13}C NMR, δ: 7.0, 19.9 (-), 23.6 (-), 27.7 (-), 32.8 (-), 40.4, 40.8 (-), 51.8 (-), 54.7, 58.2 (-), 66.7 (-), 106.3, 109.8, 116.2, 117.2, 119.3, 125.0, 135.3, 135.9.

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REFERENCES AND NOTES

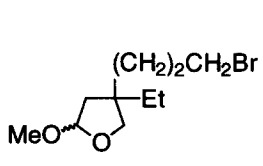
1. Reviews. (a) Collins, I. *Contemp. Org. Syn.* **1997**, *4*, 281. (b) Petragnani, N.; Ferraz, H. M. C.; Silva, G. V. J. *Synthesis* **1986**, 157. (c) Pandey, G. D.; Tiwari, K. P. *Heterocycles* **1981**, *16*, 449. (d) Warnhoff, H.; Korte, F. *Synthesis* **1972**, 151. Some recent examples. (e) Bode, J. W.; Doyle, M. P.; Protopopova, M. N.; Zhou, Q.-L. *J. Org. Chem.* **1996**, *61*, 9146 and references cited (f) Tochtermann, W.; Weidner, F. *Liebigs Ann. Chem.* **1994**, 593 and references cited (g) Sakurai, M.; Hata, T.; Yabe, Y. *Tetrahedron Lett.* **1993**, *34*, 5939. (h) Morimoto, Y.; Iwahashi, M. *SYNLETT* **1995**, 1221. (i) Roder, E.; Krauβ, H. *Liebigs Ann. Chem.* **1992**, 177.

2. Reviews. (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 388. (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (c) Martin, S. F. *Tetrahedron* **1980**, *36*, 419.

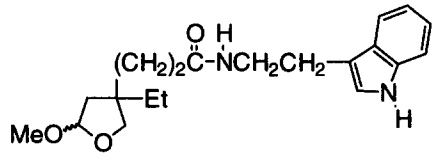
3. (a) Ihara, M.; Takahashi, M.; Taniguchi, N.; Yasui, K.; Niitsuma, H.; Fukumoto, K. *J. Chem. Soc., Perkin Trans* 1 **1991**, 525. (b) Node, M.; Nagasawa, H.; Fuji, K. *J. Org. Chem.* **1990**, *55*, 517 and references cited. (c) Takano, S.; Yonaga, M.; Morimoto, M.; Ogasawara, K. *J. Chem. Soc., Perkin Trans* 1 **1985**, 305 and references cited. For reviews of earlier approaches:(d) Kutney, J. P. The Synthesis of Indole

Alkaloids. In *The Total Synthesis of Natural Products*; Apsimon, J. Ed.; John Wiley and Sons, Inc.: New York, 1977; pp 273-402. (e) Gilbert, B. *The Alkaloids* **1969**, *11*, 205.

4. Wenkert, E.; Halls, T. D. J.; Kwart, L. D.; Manusson, G.; Showalter, H. D. H. *Tetrahedron* **1981**, *37*, 4017. This is the only example of a 4,4-disubstituted γ-lactone that was used in the synthesis of indole alkaloids.
5. Wee, A. G. H.; Yu, Q. *J. Org. Chem.* **1997**, *62*, 3324.
6. Takano, S.; Hatakeyama, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1979**, *101*, 6414.
7. Brown, H. C.; Keblys, K. A. *J. Am. Chem. Soc.* **1964**, *86*, 1795.
8. Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1977**, *55*, 562 and references cited.
9. Regitz, M. *Synthesis* **1972**, 381.
10. Taber, D. F.; Ruckle, R. E., Jr.; Hennessy, M. J. *J. Org. Chem.* **1986**, *51*, 4077.
11. Doyle, M. P.; Bagheri, V.; Pearson, M. M.; Edwards, J. D. *Tetrahedron Lett.* **1989**, *30*, 7001.
12. Cf. Recent reports on the removal of *t*-butyldimethylsilyl ethers, see (a) Farras, J.; Serra, C.; Vilarrasa, J. *Tetrahedron Lett.* **1998**, *39*, 327. (b) Maiti, G.; Roy, S. C. *Tetrahedron Lett.* **1997**, *38*, 495.
13. Review: Cox, E. D.; Cook, J. M. *Chem Rev.* **1995**, *95*, 1797.
14. The feasibility of the cyclization of compound **i** with tryptamine, modelled after the work of Wenkert,[4] and an intramolecular version of the present reaction using **ii** were also investigated. These reactions did not yield the desired **17**.



i



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