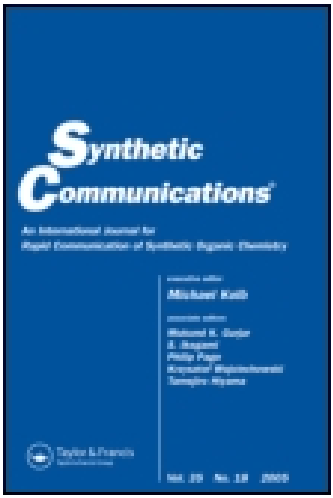

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Synthetic Approaches to 2-Pyrrolidinone-5-carboxaldehyde

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SYNTHETIC APPROACHES TO 2-PYRROLIDINONE-5-CARBOXALDEHYDE

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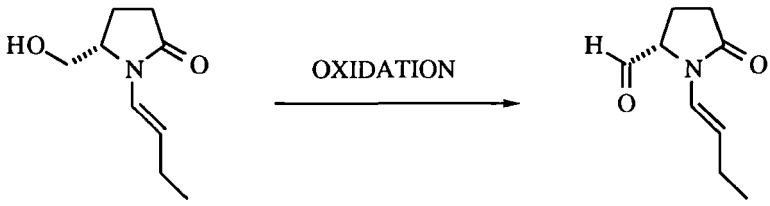
Abstract: We have examined routes for the preparation of 2-pyrrolidinone-5S-carboxaldehyde which include oxidation of 5-hydroxymethyl-2-pyrrolidinone and reduction of 5-oxoproline ethyl ester. Only the oxidation route proved satisfactory. Moffatt oxidation was most efficient but PCC oxidation gave modest yields of the desired aldehyde.

We have a vigorous program designed to exploit the readily available chiral, nonracemic lactam, ethyl pyroglutamate (5-oxoproline ethyl ester), in organic synthesis. We have previously converted pyroglutamate to asymmetric pyrrolizidine



1 **2**

alkaloids via a radical cyclization strategy.[1] We have also prepared the anti-epileptic agent 4S-aminohex-5-enoic acid,[2] and we have converted pyroglutamate to dienyl

derivatives[3] and examined their role in asymmetric Diels-Alder reactions.[4] We have also converted pyroglutamate to 5R-methyl-1-chloromethyl-2-pyrrolidi-none, a new reagent for the determination of enantiomeric composition of alcohols and amines via proton NMR.[5] In connection with this work, N-butenyl-2-pyrroli-dinone-5-carbox-aldehyde (**2**)[3,6] has played a key role in many of the above-mentioned syntheses. In all of this work, we used a Moffatt oxidation but this procedure suffered from the use of DMSO and the removal of the dicyclohexyl urea by-product. We therefore wanted to explore alternative methods in the hope we would discover a procedure more amenable to 'scale-up' work. We have attempted to oxidize alcohol (**1**) to (**2**) using a variety of oxidizing agents and the results are presented in Table 1. We have also examined the possibility of reducing the ester group of pyroglutamate (**3**) to aldehyde (**2**) and these results are presented in Table 2. Our work clearly demonstrates that the only good method for the preparation of (**2**) is via Moffatt oxidation of (**1**).

We first prepared N-butenyl-5S-carboethoxy-2-pyrrolidinone (**3**) from *L*-glutamic acid by literature tested methods,[5,7,1] and then reacted the lactam with butanal and a catalytic amount of *p*-toluenesulfonic acid or P_2O_5 to give **3**.[1-3,8] Reduction of **3** with sodium borohydride in ethanol or water gave **1**.[1-3] We then treated **1** with several different oxidizing reagents, under a variety of conditions shown in Table 1. Collins' oxidation (CrO_3, pyridine)[9] gave aldehyde **2**, but in very poor yield. Surprisingly, the reaction of **1** with PCC[10] and PDC[11] also gave very poor yields of **2**. The desired aldehyde was obtained with PCC, but five equivalents of reagent were required to give a 45% yield of **2**. Longer reaction times under identical conditions gave diminished yields and many by-products. It appeared that the poor reactivity of alcohol **1** was due to steric hindrance. The lactam ring is rather flat, and the environment for generating a chromate ester and removal of the requisite proton is congested. In an attempt to alleviate this problem, a number of DMSO-based oxidizing methods were examined, but only Moffatt oxidation[12] and variations of it[13] gave good yields (75-80% of **2**).

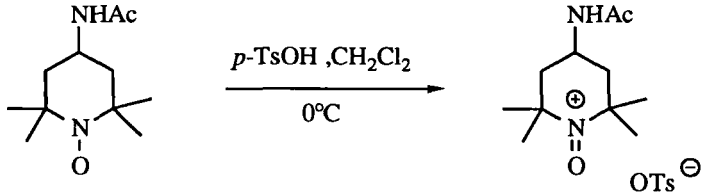
Table 1. Oxidation of N-butenyl-5-hydroxymethyl-2-pyrrolidinone, **1**.

Reagent (solvent)	Time (h)	Temp.	% **2***
6 CrO_3/12 Py (CH_2Cl_2)	0.25	RT	0%
3 CrO_3/6 Py (CH_2Cl_2)	2.0	0 °C to RT	< 1%
1.5 CrO_3/3 Py (CH_2Cl_2)	0.5	0 °C	2%
1.5 CrO_3/3 Py (CH_2Cl_2)	0.75	0 °C	4%
1.5 CrO_3/3 Py (CH_2Cl_2)	2.0	0 °C	4%
2 CrO_3/4 Py (CH_2Cl_2)	10.0	RT	15%
2 CrO_3/4 Py (CH_2Cl_2)	48	RT	13%
1.5 PCC	0.75	RT	23%
1.5 PCC	2.0	RT	8%
1.5 PCC	24.0	RT	6%
3 PCC	0.25	RT	29%
3 PCC	1.0	RT	23%
3 PCC	24.0	RT	17%
5 PCC	1.0	RT	43%
5 PCC	24.0	RT	30%
1.5 PDC	0.5	RT	3%
2 DMSO/1 oxalyl chloride/5 Et_3N	1.0	-78 °C	0%
2 DMSO/0.6 P_2O_5	24.0	RT	0%
36 DMSO/1 Ac_2O	0.5	-5 °C	0%
42 DMSO/5 Ac_2O	20.0	RT	3%
42 DMSO/5 Ac_2O	0.25	0 °C	2%
42 DMSO/5 Ac_2O	0.5	0 °C	3%
50 DMSO/25 Ac_2O	48.0	RT	5%
excess DMSO/3 DCC/0.5 TFA/1 Py	24.0	RT	80%
excess DMSO/3 DCC/0.5 DCA	24.0	RT	75%
1.5 NCS/2 Me_2S (toluene)	2.0	-25°C	<25%
5 (CH_2Cl_2)	20.0	0°C	0%
CrO_3/Amberlite IRA-400 (toluene)	5.0	RT	0%

* Yields less than 40% were determined by GC integration

Oxidation with DMSO admixed with oxalyl chloride (Swern oxidation),[14] phosphorus pentoxide,[15] or acetic anhydride[16] all gave less than 5% yield of **2**. In several instances, the starting material was recovered unchanged and when the reaction was "pushed," decomposition occurred. These results are surprising, since the Swern oxidation is the reagent of choice for hindered alcohols,[14a] and the DMSO/DCC reagent required for Moffatt oxidation is presumably rather bulky. The other DMSO-based reagents mentioned above have been used successfully in the literature for oxidation of sterically congested alcohols. Nonetheless, only Moffatt oxidation provided **2** in good yield. We explored three additional oxidation methods: N-chlorosuccinimide[17] mixed with dimethyl sulfide, the nitrosonium salts developed by Bobbitt (reagent **5**),[18] and a polymer-bound chromium trioxide reagent.[19] It is noted that **5** was prepared *in situ* by treating **4** with *p*-toluenesulfonic acid.[12] This reagent was also reported to oxidize hindered alcohols in excellent yield. No oxidation was observed, however, with **1** and it was recovered unchanged. We also used the perchlorate and tetrafluoroborate salts of **5**.[13] From these results, it is clear that **2** can be obtained in modest yield by PCC oxidation and in good yield by Moffatt oxidation.

We next turned our attention to the selective reduction of pyroglutamate **3**. The "standard" reagent to convert esters to aldehydes is diisobutylaluminum hydride.[20] As reported in Table 2, no aldehyde **2** was produced. We then tried the reduction

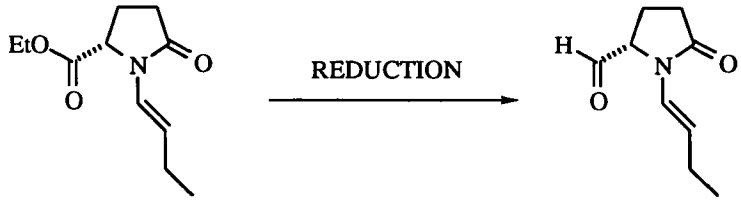


4 **5**

with lithium tri-*t*-butoxyaluminum hydride,[21] but less than 5% of **2** was observed in a mixture of products. Cha recently reported the preparation of lithium *tris*-(diethyl-

amino)aluminum hydride[22] and its ability to selectively reduce esters, amides and nitriles to the corresponding aldehyde. We prepared this reagent and, as seen in Table 2, observed a poor yield (at best 19%) of **2**. It is clear from our study that direct reduction of the ester moiety in pyroglutamate does not yield aldehyde **2** in synthetically useful amounts under the conditions examined in Table 2.

Table 2. Reduction of N-butenyl-5-carboethoxy-2-pyrrolidinone, **3.**



3 **2**

Reagent	Time (h)	Temperature	% 2*
1 $(iBu)_2AlH$ [9]	2	- 78 °C	< 1%
1 $LiAlH(Ot\text{-}Bu)_3$ [10]	2	0 °C	5%
1 $Li(Et_2N)_3AlH$ [11]	2	- 78 °C	4%
1 $Li(Et_2N)_3AlH$	2	0 °C	9%
1 $Li(Et_2N)_3AlH$	1	RT	10%
1 $Li(Et_2N)_3AlH$	12	RT	15%
1 $Li(Et_2N)_3AlH$	24	RT	19%
2 $Li(Et_2N)_3AlH$	1	RT	18%
1 $Li(Et_2N)_3AlH$	3	65 °C	13%

* Conversion to aldehyde determined by GC integration

Our conclusion from this study is that aldehyde **2** is difficult to prepare directly from pyroglutamate (**3**), and only Moffatt oxidation of alcohol **1** provides a synthetically useful route to it. Oxidation with PCC is experimentally easier and the modest yield of

2 may be acceptable in some cases. In none of the cases examined was reduction of the ester group in **3** a viable route to **2**.

EXPERIMENTAL SECTION

All experimental procedures given are representative of oxidation or reduction methods used and vary in regard to molar ratios, reaction time or reaction temperature as listed in the above tables. All boiling points listed are uncorrected. All reaction glassware was oven dried, and all oxidation and reduction procedures were performed under an argon atmosphere. Reagents or solvents were dried as indicated. Dimethyl sulfoxide was obtained from the Alfa Chemical Company. Methylene chloride, magnesium sulfate, pyridine, acetic anhydride, phosphorous pentoxide, benzene, and tetrahydrofuran were obtained from Baker. Amberlite IRA-400 was obtained from Aldrich. Chromium trioxide, triethylamine, trifluoroacetic acid, N,N'-dicyclohexylcarbodiimide, N-chlorosuccinimide, dimethyl sulfide, *p*-toluenesulfonic acid, dichloroacetic acid, diisobutylaluminum hydride, and lithium tri-*t*-butoxide aluminum hydride were purchased from the Janssen Chemical Company. Barium oxide, 4 Å molecular sieves, oxalyl chloride, lithium aluminum hydride, and diethylamine were obtained from the Aldrich Chemical Company. We prepared ethyl pyroglutamate from *L*-glutamic acid by procedures we described earlier.[1-3] The (S)-(+)-5-(hydroxymethyl)-N-(1-butenyl)-2-pyrrolidinone (**1**) was prepared by procedures described previously.[1-3] Pyridinium chlorochromate (PCC) was prepared as described by Corey.[10] Pyridinium dichromate was prepared as described by Corey.[11] Nitroxide **4** was provided by Professor J.M. Bobbitt from the University of Connecticut.[18]

Gas chromatography-mass spectrometry analyses were done on a Hewlett-Packard 5890 GC/MS system fitted with a HP-1 methyl silicone column (12.0 m x 0.2 m , i.d.) with helium as a carrier gas utilizing a 5970-B mass selective detector. The identity of

the aldehyde, ester, and alcohol components for each reactions was determined by comparison of low resolution mass spectra (70 eV) with an authentic sample of each. All reaction trials gave crude oils after work up, and approximately 50 mg of each oil was diluted in 1 mL of ether or acetone for GC/MS analysis. For those reactions that gave the known (S)-(+)-N-(1-Butenyl)-2-pyrrolidinone-5-carboxaldehyde (**2**)[1] in greater than 40% yield, **2** was isolated by chromatography as described below.

Preparation of (S)-(+)-N-(1-Butenyl)-2-pyrrolidinone-5-carboxaldehyde, 2.

Oxidation of (S)-(+)-5-(hydroxymethyl)-N-(1-butenyl)-2-pyrrolidinone, 1.

With CrO_3/pyridine. A solution of 0.72 mL (0.71g, 9 mmol) of distilled pyridine (stored over molecular sieves) in 30 mL of CH_2Cl_2 was stirred at 0 °C (ice/water) for 0.25 h before addition of 0.45 g of CrO_3 (4.5 mmol) in one portion. The flask was sealed and stirred for 0.25 h under argon and 0.5 g (3 mmol) of previously purified (S)-(+)-5-(hydroxymethyl)-N-(1-butenyl)-2-pyrrolidinone (**1**) in 10 mL of CH_2Cl_2 was injected via syringe. Stirring at 0 °C was continued for an additional 0.75 h. The mixture was allowed to warm to room temperature, and then vacuum filtered to remove chromium salts. The filtrate was washed with 1 x 25 mL of 1N NaOH solution and 1 x 25 mL of saturated NaCl solution. The organic layer was dried over $MgSO_4$, filtered and concentrated by rotary evaporation to give 0.32 g of product, which was analyzed by GC/MS.

Oxidation with PCC: A mixture of 0.38 g of PCC (1.77 mmol) in 5 mL of dry CH_2Cl_2 (stored over molecular sieves) was treated with 0.2 g (1.18 mmol) of (S)-(+)-5-(hydroxy-methyl)-N-(1-butenyl)-2-pyrrolidinone (**1**) in 5 mL of dry CH_2Cl_2, at room temperature, in one portion via syringe. The black mixture was allowed to stir at room temperature (under Ar) for 0.75 h, at which time 20 mL of diethyl ether was

added, and the chromium salts were vacuum filtered. The residue was rinsed with diethyl ether and the combined organic layers were dried ($MgSO_4$). Filtration and concentration by rotary evaporation gave 0.14 g of a dark brown oil, which was analyzed by GC/MS.

Oxidations with PDC: A solution of 0.2 g (1.18 mmol) of (S)-(+)-5-(hydroxy-methyl)-N-(1-butenyl)-2-pyrrolidinone (**1**) in 5 mL of dry CH_2Cl_2 (stored over molecular sieves) was added in one portion to a suspension of 0.67 g (1.77 mmol) of PDC in 5 mL of dry CH_2Cl_2, at room temperature. The mixture was stirred at room temperature (under Ar) for 0.5 h, 20 mL of diethyl ether was added, and the chromium salts were removed by vacuum filtration. The residue was washed with additional ether and the combined organic layers were dried over $MgSO_4$. Filtration, then concentration by rotary evaporation gave 0.18 g of a dark brown oil, which was analyzed by GC/MS.

Oxidation with DMSO/Oxalyl Chloride/Triethylamine: A solution of 0.1 mL (0.15 g, 1.18 mmol) of freshly distilled oxalyl chloride in 5 mL of dry CH_2Cl_2 (stored over molecular sieves) was cooled to -78 °C (CO_2/acetone). This was treated with 0.15 mL (0.18 g, 2.36 mmol) of dry DMSO (freshly distilled from BaO) dropwise via syringe. This was followed by addition of 0.2 g (1.18 mmol) of (S)-(+)-5-(hydroxy-methyl)-N-(1-butenyl)-2-pyrrolidinone (**1**) in 5 mL of dry CH_2Cl_2. Triethylamine (0.83 mL, 0.6 g, 5.9 mmol) was then added dropwise via syringe. After addition was complete, the solution was allowed to stir at -78 °C (under Ar) for 1 h, 10 mL of distilled water was added, and the reaction was warmed to room temperature. The aqueous layer was washed with 2 x 25 mL of CH_2Cl_2, and the combined organic layers were dried ($MgSO_4$). Filtration, and concentration by rotary evaporation gave 0.21 g of a yellow oil, which was analyzed by GC/MS

Oxidation with DMSO/P_2O_5: A solution of 0.2 g (1.18 mmol) of (S)-(+)-5-(hydroxy-methyl)-N-(1-butenyl)-2-pyrrolidinone (**1**) in 2 mL of dry DMSO (freshly

distilled from BaO) was treated with 0.1 g (0.71 mmol) of P_2O_5 at room temperature. The mixture was stirred at room temperature (under Ar) for 24 h. The mixture was washed with distilled water (2 x 25 mL) and the remaining organic layer dried over $MgSO_4$. After filtration, 0.10 g of the orange residue was taken up in ether for GC/MS analysis.

Oxidation with DMSO/Acetic Anhydride: A solution of 0.2 g (1.18 mmol) of (S)-(+)-5-(hydroxymethyl)-N-(1-butenyl)-2-pyrrolidinone (**1**) in 3 mL (3.3 g, 49.6 mmol) of dry DMSO (freshly distilled from BaO) was stirred for 0.25 h at 0 °C (ice-water). This was treated with 0.56 mL (0.6 g, 5.9 mmol) of distilled acetic anhydride, added via syringe. The reaction was stirred at 0 °C (under Ar) for 0.5 h. The solution was washed with 3 x 5 mL of distilled water, and the organic layer dried over $MgSO_4$. Vacuum filtration and concentration by rotary evaporation gave 0.12 g of an oily yellow residue, which was analyzed by GC/MS.

Oxidation with DMSO/DCC/TFA-Pyridine: A solution of 0.5 g (3 mmol) of (S)-(+)-5-(hydroxymethyl)-N-(1-butenyl)-2-pyrrolidinone (**1**) in 10 mL of dry benzene (distilled from sodium) was treated with 10 mL of dry DMSO (freshly distilled from BaO). The solution was then treated with 0.2 mL (3 mmol) of dry pyridine (distilled from sodium) and with 0.1 mL (1.5 mmol) of distilled trifluoroacetic acid. To this mixture, 1.7 g (9 mmol) of freshly Kugelrohr distilled dicyclohexylcarbodiimide (140 °C/5 mmHg) was then added. The flask was tightly stoppered, and the cloudy white mixture was allowed to stir at room temperature (under Ar) for 24 h, 30 mL of ether was added, and the white reaction mixture was vacuum filtered to remove dicyclohexyl urea. The solid was washed with addition ether, then the combined filtrates were washed with 3 x 50 mL of distilled water. The organic layer was dried over $MgSO_4$, filtered and concentrated to give a yellow oil. Chromatography of this oil (silica gel: ether) gave 0.40 g (2.4 mmol, 80%) of (S)-N-(1-butenyl)-2-pyrrolidinone-5-carbox-aldehyde (**2**): ^1H NMR ($CDCl_3$): δ 0.99 (3H, t, J = 7.4 Hz), 2.1 (2H, m), 2.3-2.6

(4H, m), 4.3 (1H, dd, J = 2.3, 13.7 Hz), 5.1 (1H, dt, J = 6.8, 14.8 Hz), 6.9 (1H, dd, J = 1.1, 14.8 Hz) and 9.60 ppm (1H, d, J = 1.1 Hz); ^{13}C NMR ($CDCl_3$): δ 14.3 (q), 19.9 (t), 23.4 (t), 29.9 (t), 64.0 (d), 115.3 (d), 122.4 (d), 173.0 (s) and 200.0 ppm (s); Infrared (neat): 3100-2800 (s), 1730 (s), 1680 (s), 1410 (s), 1070 (w), and 950 cm^{-1}; Mass Spectrum (m/z, Rel. intensity); P^+ 167 (16), 138 (100), 124 (2), 110 (7), 95 (6), 84 (8), 68 (12) and 55 (21).[1,2]

Oxidation with DMSO/DCC/DCA: A solution of 0.5 g (3 mmol) of (S)-(+)-5-(hydroxy-methyl)-N-(1-butenyl)-2-pyrrolidinone (**1**) in 10 mL of dry benzene (distilled from sodium) was treated with 10 mL of dry DMSO (freshly distilled from BaO). This solution was treated with 0.12 mL (0.19 g, 1.5 mmol) of distilled dichloroacetic acid and then with 1.7 g (9 mmol) of freshly Kugelrohr distilled dicyclohexylcarbodiimide (140°C/5 mmHg). The flask was tightly stoppered, and the cloudy white mixture was allowed to stir at room temperature (under Ar) for 24 h, 30 mL of ether was added, and the white reaction mixture was vacuum filtered to remove dicyclohexyl urea. The solid was washed with addition ether, then the combined filtrates were washed with 3 x 50 mL of distilled water. The organic layer was dried over $MgSO_4$, filtered and concentrated to give a yellow oil. Chromatography, as above, gave 0.38 g (2.3 mmol, 75%) of **2**.

Oxidation with N-chlorosuccinimide: A stirred solution of 0.4 g (3 mmol) of N-chlorosuccinimide in 10 mL of toluene was treated with 0.33 mL (0.25 g, 4.1 mmol) of dimethyl sulfide (under Ar). A white precipitate appeared immediately. This mixture was cooled to -25°C and treated dropwise with a solution of 0.338 g (2 mmol) of (S)-(+)-5-(hydroxymethyl)-N-(1-butenyl)-2-pyrrolidinone (**1**) dissolved in 2 mL of toluene. This mixture was stirred for 2 h at -25°C (under Ar) and then treated with 0.3 mL (3.0 mmol) of triethylamine dissolved in 0.5 mL of toluene. After warming to room temperature, 20 mL of ether was added, the organic layer washed with 5 mL of 1% aq. HCl and then twice with 15 mL of water. The organic layer was separated,

dried ($MgSO_4$), and removed by rotary evaporation to give an oil, which was analyzed by GC/MS.

Oxidation with nitrosonium salt 5: A solution of 4.47 g (21 mmol) of nitroxide **4** in 30 mL of CH_2Cl_2 was stirred with 4.0 g (21 mmol) of *p*-toluenesulfonic acid at 0°C for 20 min. An intense red color developed and this solution was added dropwise to 0.17 g (10 mmol) of (S)-(+)-5-(hydroxymethyl)-N-(1-butenyl)-2-pyrrolidinone (**1**) in 30 mL of cold CH_2Cl_2 over a period of 30 min. The resulting solution was stirred at room temperature until the orange color had disappeared and a white precipitate formed (16 h). The mixture was cooled (ice), the precipitate filtered, and the solids washed with 10 mL of cold CH_2Cl_2. The organic layer was dried ($MgSO_4$), and solvent removed by rotary evaporation to give an oil that was analyzed by GC/MS.

Oxidation with chromium trioxide bound to Amberlite: A solution of 15 g (150 mmol) of chromium trioxide in 100 mL of water was treated with 35 g of the chloride form of Amberlite IRA-400, with stirring. The slurry was filtered and washed successively with water, acetone and ether. The resin was dried *in vacuo* at 50°C for 5 h. About 10 g of this dried resin was suspended in 40 mL of benzene and then treated with 0.5 g (3 mmol) of (S)-(+)-5-(hydroxymethyl)-N-(1-butenyl)-2-pyrrolidinone (**1**) and then refluxed for 5 h. Filtration and removal of solvents by rotary evaporation gave an oil that was analyzed by GC/MS.

Reduction, (S)-(+)-5-Carboethoxy-N-(1-Butenyl)-2-pyrrolidinone, 3. Reduction with Diisobutylaluminum hydride: A solution of 0.2 g (0.95 mmol) of (S)-(+)-5-carboethoxy-N-(1-butenyl)-2-pyrrolidinone (**3**) in 2 mL of dry toluene (distilled from sodium) was cooled to -78 °C (CO_2/acetone). After 0.5 h, 0.95 mL (0.13 g, 0.95 mmol) of 1M diisobutylaluminum hydride in hexanes was added via syringe. The solution was stirred at -78 °C (under Ar) for 2 h. The mixture was

warmed to room temperature, and concentrated by rotary evaporation to give 0.18 g of a yellow oil which was analyzed by GC/MS.

Reduction with Lithium tri-t-butoxy aluminum hydride: A solution of 0.2 g (0.95 mmol) of (S)-(+)-5-carboethoxy-N-(1-butenyl)-2-pyrrolidinone (**3**) in 2 mL of dry THF (distilled from sodium) was cooled to 0 °C (ice/water). After 0.25 h, a solution of 0.24 g (0.95 mmol) of lithium tri-*t*-butoxyaluminum hydride in 2 mL of dry THF was injected via syringe. The cloudy mixture was stirred at 0 °C (under Ar) for 2 h, warmed to room temperature, and the solids were removed by filtration. Washing with THF and concentration of the combined filtrates was followed by rotary evaporation to give 0.17 g of a pale yellow oil, which was analyzed by GC/MS.

Preparation of Lithium tris-(diethylamino)aluminum hydride (LTDEA).[17] A slurry of 3.8 g (100 mmol) of $LiAlH_4$ in 50 mL of dry THF (distilled from sodium) was cooled to 0°C (ice/water). A total of 32.4 mL (23 g, 315 mmol) of diethylamine was then added (dropwise), and this slurry was stirred vigorously at 0 °C for 3 h to give LTDEA. The resulting product was diluted to 100 mL total volume with dry THF to yield a 1M solution of LTDEA. The solution was stored in a sealed container and refrigerated until use.

Reduction with LTDEA: A solution of 0.2 g (0.95 mmol) of (S)-(+)-5-carboethoxy-N-(1-butenyl)-2-pyrrolidinone (**3**) in 2 mL of dry THF (distilled from sodium) was cooled to -78 °C. Dropwise addition of 1 mL (100 mmol) of 1M LTDEA in THF via syringe with stirring was followed by stirring at -78 °C (under Ar) for 2 h. The solution was warmed to room temperature and concentrated by rotary evaporation to give 0.15 g of a dark yellow oil which was analyzed by GC/MS.

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