# 5(R)-Methyl-1-(chloromethyl)-2-pyrrolidinone: A New Reagent for the Determination of Enantiomeric Composition of Alcohols[1]

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We have prepared a new chiral nonracemic reagent (5(*R*)-methyl-1-(chloromethyl)-2-pyrrolidinone) in enantiopure form that reacts with alcohols containing a stereogenic center to produce diastereomeric *N*-(alkoxymethyl)-2-pyrrolidinone derivatives. These derivatives exhibit large and easily observed diastereotopic signals in the proton NMR that allow direct determination of diastereomeric ratio (% dr) for the product.

Asymmetric synthesis is an integral part of organic chemistry, and the use and formation of chiral nonracemic alcohols remains an important component of asymmetric systems. Prochiral ketones are reduced or react with various organometallic reagents to produce alcohols with a stereogenic center. Reactions of epoxides can also generate chiral nonracemic alcohols. In all cases, it is important to determine the diastereoselectivity and, where appropriate, the enantioselectivity of the reaction. One of the most useful methods for determining enantiomeric composition is to derivatize the alcohol with a chiral nonracemic reagent and examine the ratio of resulting diastereomers by gas chromatography.[2] Several reagents have been developed for this purpose, including α-(alkanoyloxy)propanoic acid,[3] α-hydroxy- and α-acetoxyalkanoic acids,[4] halogen-substituted α-(alkanoyloxy)alkanoic acids,[5] and (*S*)-α-acetoxypropionic acids ((*S*)-lactic or -mandelic).[2b,6] Other reagents used to prepare diastereomeric esters include *N*-(trifluoroacetyl)-L-alanine,[7] drimanoyl, and *trans*-chrysanthemoyl derivatives,[8] 3β-acetoxy-Δ⁵-etienoyl esters,[9] and esters derived from 2-phenylpropanoyl acid chlorides.[10] Other derivatizing agents are commonly used, including menthyl chloroformate[11] and (*R*)-(+)-1-phenylethyl isocyanate.[12] The half esters of succinic and phthalic acids have also been used for this purpose.[13] Of the currently available methods, making derivatives of α-methoxy-α-(trifluoromethyl)-phenylacetic acid (MTPA, Mosher's acid, 1)[14] is probably the most widely used.[2] When treated with a chiral nonracemic alcohol, a so-called Mosher's ester (2) is formed that can be analyzed for diastereomeric composition by $^1$H NMR as well as by chromatographic techniques.[15] Analysis by $^1$H NMR is often less useful since the signals for the OMe group and the α-proton of the alcohol can overlap other signals. The signals arising from the alcohol may be coupled with protons elsewhere in the molecule. In those cases, however, $^{19}$F NMR can be used. Alternatively, lanthanide shift reagents allow the signals of the MTPA ester to be resolved and used to determine enantiomeric composition.[16]

We have an ongoing program to use pyroglutamate **3** as a chiral nonracemic starting material for a variety of synthetic applications, including asymmetric Diels–Alder reactions[17] and radical cyclizations.[18] Pyroglutamate offered three distinct advantages as a potential auxiliary to be used for determining the composition of enantiomeric alcohols: (1) the ester moiety a $C_5$ could be easily refunctionalized, (2) the nitrogen is internally protected as the lactam, and (3) the nitrogen could be functionalized. In other work, 1-(chloromethyl)-2-pyrrolidinone (4), first prepared by Böhme by reaction of 2-pyrrolidinone with formaldehyde and thionyl chloride,[19] was used to prepare alkoxymethyl lactams such as **5**. Böhme[19] and others[20] had previously prepared compounds of this type. A suitable chiral nonracemic analog of **5** might allow the determination of the enantiomeric composition of a chiral nonracemic alcohol, if the chiral nonracemic lactam produced a suitable diastereomer (7). Recognition of the

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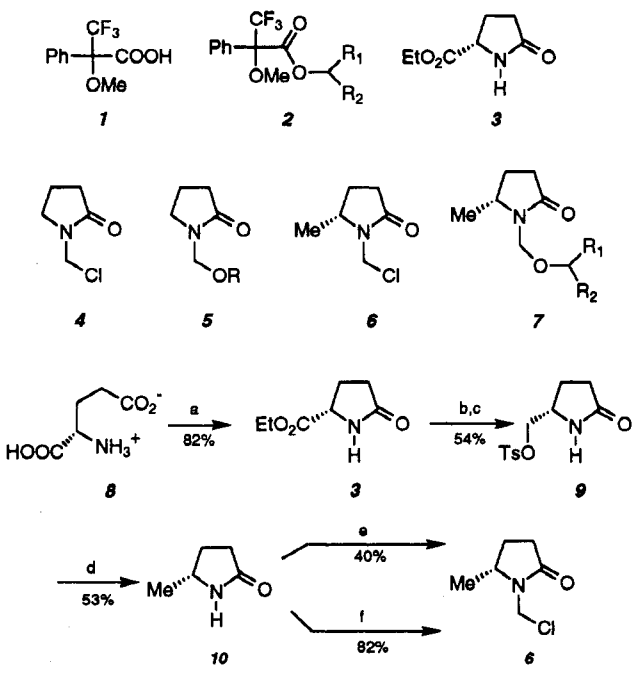
**Scheme 1**[a]

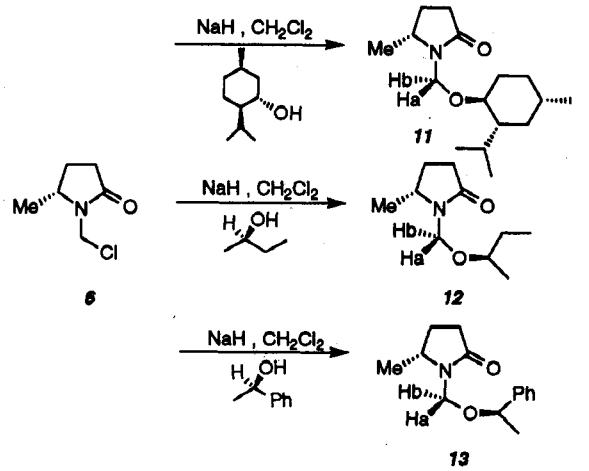


[a] Key: (a) $SOCl_2$, EtOH; (b) $NaBH_4$, $H_2O$; (c) KOH, *p*-TsCl, $Bu_4NHSO_4$, $CHCl_3$, 48 h; (d) $Bu_3SnH$, AIBN, NaI, DME; (e) $(HCHO)_n$, $SOCl_2$; (f) $(HCHO)_n$, $Me_3SiCl$.

facile reactivity of **4** with alkoxide reagents and the presence of the stereogenic center in **3** led us to target 1-(chloromethyl)-5(*R*)-methyl-2-pyrrolidinone (**6**) as a prototype reagent, derived from the known 5(*R*)-methyl-2-pyrrolidinone.[15b,16] Lactam **6** would offer at least four possible signals in the $^1H$ NMR spectrum of an alkoxymethyl derivative resulting from reaction with a chiral nonracemic alcohol that could be used to determine diastereomeric excess. The first is the downfield doublet of doublets (an AB quartet) observed for the diastereotopic $NCH_2OR$ signals (at 4.3–5.2 ppm), and the second is the signal for the proton adjacent to the oxygen in the chiral nonracemic alcohol (typically 3.3–4.0 ppm). A third possibility is the proton at $C_5$ of the lactam, which typically appears at 3.5–3.8 ppm, and the fourth is the methyl signal for the $C_5$ methyl group at about 1.3 ppm. The latter two signals will likely be masked or partially observed in many samples due to the "backbone" of the chiral nonracemic alcohol, so the first two signals are excellent candidates for our purpose. Only the $NCH_2O$ signals at 4.3–5.2 ppm, however, are not coupled with other protons of the lactam or the alcohol and appear in a region of the $^1H$ NMR spectrum that makes them ideal for analysis.

Lactam **6** can be prepared from a chiral nonracemic lactam precursor [5(*R*)-methyl-2-pyrrolidinone, **10**] by standard methods. A modification of Silverman's[21] procedure was used to convert L-glutamic acid (**8**) to ethyl 2-pyrrolidinone-5(*S*)-carboxylate (**3**) in 82% yield. The ester moiety of **3** was reduced to the corresponding hydroxymethyl derivative using sodium borohydride and then converted to the *O*-tosyl derivative **9** in 54% overall yield from **3**. The most convenient method for the reduction of the tosyl group involved Finkelstein exchange with sodium iodide and *in situ* reduction of the resulting iodide by tri-*n*-butyltin hydride (with AIBN and NaI in benzene). This procedure gave **10** in 53% yield. We initially converted **10** to **6** in 40% yield using Böhme's conditions,[22] which entailed treating **6** with paraformaldehyde and thionyl chloride. The low yield of this procedure was further complicated by our inability to isolate a pure sample of **6** without extensive manipulation of the product. Orlova and Shipov reported the preparation of **4** from 2-pyrrolidinone using paraformaldehyde and chlorotrimethylsilane.[23] When we used this procedure, **10** was converted to **6** in 82% yield (95% purity) after simple Kugelrohr distillation.

Our first criterion for enantiopurity of **6** was the specific rotation initially based on the reported specific rotation of the L-glutamic acid precursor $[(\alpha]^{23}_D = +29°)$.[26] The specific rotation of all intermediate products as well as **6** suggested retention of stereochemistry during the synthetic sequence. The most important criterion of optical purity, however, was the preparation, isolation, and analysis of the diastereomer resulting from the reaction of **6** with (±)-menthol along with both (+)-menthol (to give **11a**) and (−)-menthol (to give **11b**). These diastereomers were



analyzed by GC–mass spectrometry and by proton and carbon NMR, as well as by reversed-phase ($C_{18}$) analytical HPLC. The ether products **11** derived from (+)-menthol and (−)-menthol were isolated and purified and showed no contaminating diastereomers within the limits of detectability of these techniques. In addition, analysis of the initial reaction mixtures showed less than 1% contamination from diastereomeric products. On the basis of these analyses, we conclude that, at worst, **6** prepared by our synthesis contains less than 1% of the contaminating enantiomer (the 5(*S*)-methyl analog).

When **6** was treated with chiral nonracemic alcohols, ether **7** was produced in near-quantitative yield, and this "crude" mixture[24] was used to determine % dr. All yields reported are of isolated and fully characterized pure **7**. The data reported by the manufacturer were used as the initial criterion of optical purity for the alcohols used to prepare **7**. In most cases, prolonged (or meticulous) silica gel chromatography led to partial decomposition of **7** (usually by acid-catalyzed hydrolysis of the $NCH_2OR$ moiety) and lower isolated yields. When we treated **6** with the sodium salt of (±)-menthol (NaH, menthol, $CH_2Cl_2$)

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(24) The term "crude" refers to an extractive workup of the reaction (usually with $CH_2Cl_2$) followed by chromatographic filtration through a short plug of silica gel and removal of solvents.

**Table 1. Reaction of Standard Mixtures of (+)- and (−)-Antipodes of Selected Alcohols with *6* and Analysis by $^1$H NMR**

| | actual | | found | |
|---|---|---|---|---|
| alcohol | % (+) | % (−) | % (+) | % (−) |
| menthol | 50[a] | 50[a] | 50.3 | 49.7 |
| | 11.3 | 88.7 | 11.9 | 88.1 |
| | 28.6 | 71.9 | 29.0 | 71.0 |
| | 40.3 | 59.7 | 35.6 | 64.4 |
| | 62.0 | 38.0 | 61.6 | 38.4 |
| | 73.5 | 26.5 | 78.1 | 21.9 |
| | 88.4 | 11.6 | 89.7 | 10.3 |
| 2-butanol | 50[b] | 50[b] | 49.9 | 50.1 |
| | 13.4 | 86.6 | 6.6 | 93.4 |
| | 27.8 | 72.2 | 26.6 | 73.4 |
| | 38.8 | 61.2 | 36.0 | 64.0 |
| | 57.2 | 42.8 | 57.6 | 42.4 |
| | 76.7 | 23.3 | 68.1 | 31.9 |
| | 90.2 | 9.8 | 85.4 | 14.6 |
| 1-phenylethanol | 50[b] | 50[b] | 49.9 | 50.1 |
| | 10.5 | 89.5 | 5.0 | 95.0 |
| | 26.5 | 73.5 | 25.2 | 74.8 |
| | 41.1 | 58.9 | 43.9 | 56.1 |
| | 60.0 | 40.0 | 69.2 | 30.8 |
| | 75.7 | 24.3 | 77.6 | 22.4 |
| | 90.0 | 10.0 | 90.9 | 9.1 |

[a] Commercially available (±)-menthol. [b] The commercially available racemate.

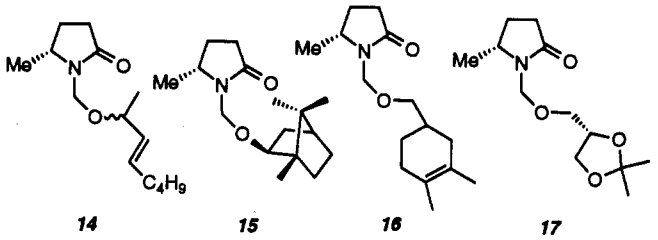
we obtained a 64% isolated yield of **11**. Examination of the doublet of doublets for the $H_a/H_b$ protons of the "crude" product[24] revealed the signals for each diastereomeric product were cleanly resolved in the proton NMR spectrum at 270 MHz. Integration allowed direct determination of the relative composition of the diastereomeric mixture. We next treated **6** with 2-butanol to produce **12** (67% isolated yield) and with 1-phenylethanol to give **13** (64% yield). Both **12** and **13** showed signals for $H_a/H_b$ that allowed direct determination of the diastereomeric composition (% de) at 270 MHz. It is noted that the signals for **11** could be distinguished even at 60 MHz. These three alcohols have been examined by others as the MTPA ester, but analysis by $^1$H NMR was possible only with the use of lanthanide shift reagents (Eu[fod]$_3$ for 2-butanol, 1-phenylethanol, and menthol).[16] Analysis by $^{19}$F NMR is possible, but $^1$H NMR analysis required extensive decoupling. An advantage of **6** is the ability to directly determine the enantiomeric composition without decoupling experiments or the use of shift reagents.

Our next task was to demonstrate that **11**–**13** could be used to determine the actual % dr of a mixture of (+)- and (−)-enantiomers of menthol, 2-butanol, and 1-phenylethanol. We were also concerned that the reaction of **6** with the various alcohols might have proceeded with kinetic resolution of the enantiomeric alcohols. Lastly, we wanted to apply this reagent to other alcohols, especially to an alcohol obtained by a chemical reaction known to be highly enantioselective.

We prepared mixtures of both enantiopure antipodes of menthol, 2-butanol, and 1-phenylethanol (see Table 1) of known composition and also used the racemate of each alcohol. We then converted them into **11**, **12**, or **13**, respectively, and used $^1$H NMR (at 270 MHz) to determine the relative compositions of each mixture. The crude reaction product[24] was used in each case. We examined the signals at 4.3–5.2 ppm for **11**, at 4.0–5.1 ppm for **12**, and at 4.3–5.1 ppm (alternatively 3.4–4.0 ppm could be used) for **13**. As shown in Table 1 for these three representative cases, integration of the proton NMR signals gave percentages in generally good agreement with the actual composition of each mixture. In the worst case, the integrated value was 9% in error from the actual value (actual, 60:40; found, 69.2:30.8). We repeated this experiment and enlarged the signals of interest. Integration of this enlarged spectrum led to a calculated mixture of 60.8:39.2, in good agreement with the standard. A limiting factor in this analysis is, therefore, the relative intensity of the signal being integrated. We have retained the original 69.2:30.8 value in Table 1 to show "worst case" variations in the experimental data.

To further probe the possibility of kinetic resolution, we treated **6** with a 30:70 mixture of *R*/*S* phenylethanol using a 1:2 ratio of lactam to alcohol. Analysis of **11** showed a 29:71 ratio, in agreement with the actual composition. We conclude from Table 1 and this latter experiment that kinetic resolution is not a problem in the cases examined and the stereogenic centers of the respective alcohols do not undergo racemization under the reaction conditions. Menthol is representative of chiral nonracemic alcohols containing several stereogenic centers. A different representative example is 1-phenylethanol, where the benzylic chiral nonracemic position is subject to racemization but survived all steps of this sequence. 2-Butanol is a small molecule (small differences in the chemical shift of diastereomeric derivatives usually make small molecules such as this difficult to analyze), but reaction with **6** generated a derivative allowing direct determination of the enantiomeric composition. Figure 1 shows an enlarged proton NMR spectrum for the derivative **12**, which is derived from a 28:72 mixture of (+)-2-butanol and (−)-2-butanol. The signals of interest are well resolved and appear in a "clean" region of the NMR (5.5–4.0 ppm).

We also prepared several other derivatives of **6** from both racemic and chiral nonracemic alcohols. We treated **6** with *trans*-2-octen-4-ol to give **14**, with isoborneol to give **15**, with 1,2-dimethyl-1-cyclohexenyl-4-methanol to give **16** and with 2,2-dimethyl-1,3-dioxolane-4-methanol to give **17**. The proton NMR of **14** clearly showed the 1:1




**14** **15** **16** **17**

mixture of diastereomers expected from the racemate by analysis of signals in the 4.0–5.3 ppm region (the alkenyl signals appeared at 5.1–5.7 ppm and did not interfere with the analysis). The doublet of doublets for compounds **15** and **17** was more complex than observed in other derivatives analyzed at 270 MHz. The $H_a/H_b$ signal of the diastereotopic methylene for **16** was not resolved.

The apparent complexity of the signals for compounds **15** and **17** prompted us to examine these compounds in optically pure form. Reduction of (1*R*)-(+)-camphor with lithium aluminum hydride in ether followed by chromatographic separation of the *endo* and *exo* isomers afforded isoborneol (*exo*-(2*R*)-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-ol). Optically active 2,2-dimethyl-1,3-dioxolane-4-methanol is commercially available. The spectrum of **15** derived from optically active isoborneol was compared with the spectrum derived from racemic

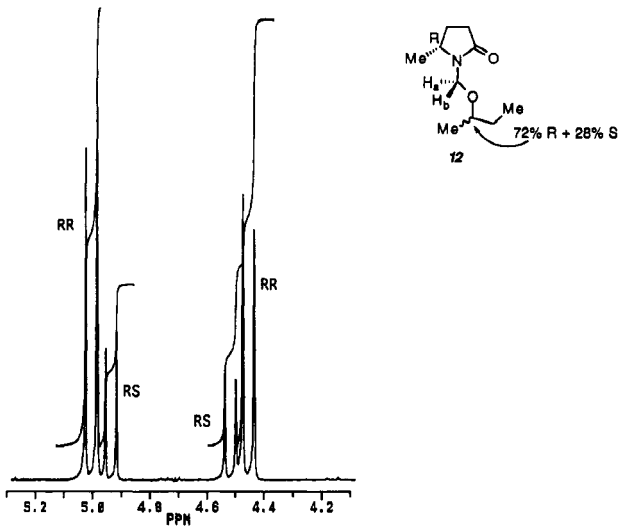
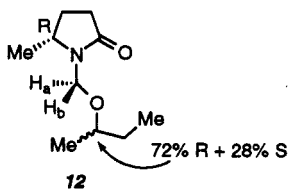



**Figure 1.** Region of analysis in the $^1$H NMR of **12**, derived from reaction of **6** with a mixture of 72% (*R*)- and 28% (*S*)-2-butanol.

isoborneol. It was immediately obvious that the apparent complexity in the spectrum of racemic **15** was due to overlapping doublet of doublets since the optically pure material showed only the characteristic single set of doublet of doublets. Similar results were observed with **17**. Interestingly, $H_a/H_b$ for **17** was cleanly resolved whereas $H_a/H_b$ for **16** was not. In both cases the stereogenic carbon in the alcohol is not directly attached to the oxygen (as is the case in all other examples). Presumably, the $C_2$ oxygen in **17** is responsible for this difference. The inability to resolve signals in systems such as **16** is clearly a limitation to this method. Despite this limitation, we believe that ether derivatives of **6** will be extremely valuable for the determination of % dr (and thereby the ee of the chiral nonracemic alcohol precursor) for both structurally simple alcohol precursors as well as those with more complex substitution patterns.

A synthetically derived example was obtained when acetophenone was reduced with (+)-*B*-chlorodiisopinocamphenylborane [(+)-Ipc$_2$BCl] to produce optically active 1-phenylethanol. Brown reported[25] that 1-phenylethanol was produced by reaction of acetophenone with (−)-Ipc$_2$BCl with 98% ee, based upon optical rotation, or 97.4% based upon capillary GC analysis of the Mosher's esters. We reacted this product with **6** to produce **13**. Examination of the proton NMR spectrum indicated 91% ee for the major enantiomer produced by our reduction. Similar reduction of 2-butanone gave 0% ee according to $^1$H NMR analysis of **12**, in general agreement with Brown's




**12**

observation that the reduction proceeded with only 4% ee (based upon optical rotation). The lower limit of detectability by this $^1$H NMR technique is the usual 2%, but 3–5% is probably a more reliable lower limit (see Table 1). The signals used for determination of enantiomeric composition, the specific rotation data for the enantiopure alcohols, and the observed $\Delta\delta$ (ppm) are presented in Table 2.

**Table 2. Correlation of $^1$H NMR Signals in *11–18* with Determination of Their Diastereomeric Ratios**

| alcohol precursor | [α] (deg) | signals of interest | Δδ (ppm) |
|---|---|---|---|
| (1*S*,2*R*,5*S*)-menthol | +48 | 4.99, 4.55 | 0.19, 0.17 |
| (1*R*,2*S*,5*R*)-menthol | −50 | 5.18, 4.38 | |
| (*R*)-2-butanol | −12.6 | 5.04, 4.50 | |
| | | | 0.06, 0.05 |
| (*S*)-2-butanol | +13.0 | 4.98, 4.55 | |
| (*R*)-1-phenylethanol | +42 | 5.02, 4.50 | |
| | | | 0.10, 0.02 |
| (*S*)-1-phenylethanol | −41.3 | 4.92, 4.52 | |
| *trans*-2-octen-4-ol | | 5.30, 4.57 | |
| | | | 0.24, 0.15 |
| | | 5.06, 4.72 | |
| *exo*-1,7,7-trimethyl[2.2.1]-heptan-2-ol | | 4.93, 4.72 | |
| | | | 0.02, 0.06 |
| | | 4.91, 4.52 | |
| 2,2-dimethyl-1,3-dioxolane-4-methanol | | 4.95, 3.68 | |
| | | | 0.02, 0.02 |
| | | 4.94, 4.66 | |

We believe that **6** will be a valuable addition to the synthetic chemist who is involved in the synthesis of molecules containing stereogenic centers. The overall yield of **6** from glutamic acid is 19% for four steps. All of the compounds used in this synthesis are readily available, and the reactions proceed in a straightforward manner. Lactam **6** can be prepared in multigram quantities and is quite stable. It has been stored at temperatures below 0 °C for up to 3 months without observable decomposition when moisture is excluded. The coupling reaction with chiral nonracemic alcohols generally gave 65–85% isolated yields of the diastereomeric product **7** but is nearly quantitative when done on small scale and analyzed directly by $^1$H NMR after removal of dichloromethane and filtering the byproducts.[24] The reaction proceeded without kinetic resolution or racemization in all cases examined. Perhaps the most attractive feature of **6** is the ability to use $^1$H NMR to directly measure the % dr (due to the lack of coupling with other signals and the chemical shift) and, thereby, the ee of the alcohol of interest. The 4.3–5.2 ppm region of the proton NMR is most commonly used in our analyses, and this region is usually uncluttered in a variety of systems. The results are obtained quickly and easily and with small quantities of material. We believe that **6** is a very useful and attractive alternative to using Mosher's acid **1** for determination of the composition of chiral nonracemic alcohols.

## Experimental Section

$^1$H and $^{13}$C NMR were recorded at 270.13 and 67.3 MHz, respectively, and reported in ppm downfield from tetramethylsilane (TMS) as an internal standard. High-resolution mass spectra were obtained by electron impact at 70 eV. Melting points are uncorrected.

Dichloromethane was distilled from calcium hydride, and 1,2-dimethoxyethane was distilled from lithium aluminum hydride under argon just prior to use. Anhydrous, reagent-grade ethanol and sodium iodide were used. The L-glutamic acid was purchased from Janssen Chemical Co., and 2,2-dimethyl-1,3-dioxolane-4(*S*)-methanol was purchased from Lancaster Chemical Co. All other reagents were purchased from the Aldrich Chemical Co. and used as received. Glassware for anhydrous reactions was dried in an oven at 120 °C overnight and cooled under a stream of dry argon.

**Ethyl 2-Pyrrolidinone-5(*S*)-carboxylate (3).** This was prepared by modification of the procedure of Silverman and

(25) Chandrasekharan, J.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.*, **1986**, *51*, 3394.

Levy.[21] Thionyl chloride (16.2 g, 136.2 mmol) was added dropwise to a well-stirred suspension of L-glutamic acid (8, 10.0 g, 68.0 mmol, lit.[26] $[\alpha]^{23}_D = +29°$, $c = 1$, 6 N HCl) in 100 mL of absolute ethanol at 0 °C. After the addition was complete the mixture was stirred at room temperature for 30 min and then refluxed for 90 min. Excess ethanol was removed and the residue heated at 130 °C under aspirator vacuum until the evolution of HCl gas ceased. The residue was purified by Kugelrohr distillation (oven temp. 160 °C, 3 mmHg), and 3 was collected after a brief forerun to give 8.75 g (55.7, mmol, 82%) of a white solid: bp 152–153 °C/3 mmHg (lit.[21] bp 159–162 °C/2 mmHg); $^1$H NMR ($CDCl_3$) $\delta$ 7.10 (br, 1H), 4.24 (m, 3H), 2.40 (m, 4H), and 1.30 ppm (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 178.50, 172.00, 61.70, 55.70, 29.35, 24.78, and 14.15 ppm; IR (neat) 1740 and 1700 cm$^{-1}$.

**5(*S*)-(Hydroxymethyl)-2-pyrrolidinone *p*-Toluenesulfonate (9).** To a solution of ethyl 2-pyrrolidinone-5(*S*)-carboxylate (3, 15.7 g, 100.0 mmol) dissolved in water (50 mL) was added sodium borohydride (2.20 g, 58.2 mmol) in water (50 mL) slowly at 0 °C. The mixture was warmed to room temperature and stirred for 90 min. Acetone (10 mL) was added slowly at 0 °C, and the reaction was warmed to room temperature and stirred for 40 min. The solution was then concentrated to a volume of approximately 50 mL. Potassium hydroxide (7.00 g, 125.0 mmol), toluenesulfonyl chloride (19.10 g, 100.2 mmol), tetra-*n*-butylammonium hydrogen sulfate (1.0 g, 2.94 mmol), and chloroform (150 mL) were added.[27] The reaction was vigorously stirred for 48 h with sonication (provided by immersion of the reaction flask in the center of an ultrasonic cleaning bath). The organic layer was separated and the aqueous phase extracted with dichloromethane (3 × 100 mL). The organic extracts were combined and dried over $Na_2SO_4$. Evaporation of the solvent gave a white solid which was recrystallized from toluene, collected by suction filtration, and washed on the filter with diethyl ether. The yield was 14.5 g (53.9 mmol, 54%) of 5(*S*)-(hydroxymethyl)-2-pyrrolidinone *p*-toluenesulfonate (9) obtained as a white solid: mp 129–130 °C (lit.[24] mp 128.5–130 °C); $^1$H NMR ($CDCl_3$) $\delta$ 7.79 (d, $J$ = 8.4 Hz, 2H), 7.30 (d, $J$ = 8.4 Hz, 2H), 6.20 (br, 1H), 4.00 (m, 3H), 2.46 (s, 3H), 2.32 (m, 3H), and 1.80 ppm (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 177.96, 145.17, 132.28, 129.92, 127.78, 71.82, 52.51, 29.20, 22.68, and 21.52 ppm; IR (neat) 1705 cm$^{-1}$; $[\alpha]^{20}_D$ −7.1° ($c$ = 0.10, EtOH) [lit.[27] $[\alpha]^{20}_D = -7.1°$, $c$ = 1.0, EtOH).[27]

**5(*R*)-Methyl-2-pyrrolidinone (10).** This was prepared by modification of the procedure of Ringdahl and co-workers.[28] To 100 mL of dry 1,2-dimethoxyethane were added 5(*S*)-(hydroxymethyl)-2-pyrrolidinone *p*-toluenesulfonate (9, 3.0 g, 11.2 mmol), sodium iodide (3.3 g, 22.3 mmol), tributyltin hydride (3.5 g, 12.0 mmol), and 50 mg of azobisisobutyronitrile (AIBN) were added, under argon. The mixture was refluxed for 12 h, and the precipitated solid was filtered and then washed with diethyl ether. Concentration of the solution gave an oil which was chromatographed on silica gel, eluting first with diethyl ether to remove tributyltin iodide and then with 9:1 diethyl ether–2-propanol. The yield was 0.586 g (5.9 mmol, 53%) of purified 10 obtained as a colorless liquid: bp 68 °C/5 mmHg (lit.[27] bp 66 °C/3 mmHg); $R_f$ 0.19 (diethyl ether, silica gel); $^1$H NMR ($CDCl_3$) $\delta$ 7.66 (br, 1H), 3.77 (m, 1H), 2.26 (m, 3H), 1.66 (m, 1H), and 1.23 ppm (d, $J$ = 5.7 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 178.77, 50.30, 30.82, 29.13, and 22.16 ppm; IR (neat) 3417, 2972, 1667, 1423, 1381, 1340, 1282, and 1139 cm$^{-1}$; mass spectrum $m/z$ (rel intensity) 54 (5), 55 (17), 56 (28), 57 (2), 66 (1), 70 (2), 82 (1), 84 (100), 85 (5), 98 (4), 99 (30), and 100 (2); $[\alpha]^{20}_D$ +16.0° ($c$ = 1, EtOH).

**1-(Chloromethyl)-5(*R*)-methyl-2-pyrrolidinone (6).** 5(*R*)-methyl-2-pyrrolidinone (10, 1.10 g, 11.1 mmol) and paraformaldehyde (0.37 g, 12.2 mmol) were combined in trimethylsilyl chloride (5 mL) and heated at reflux for 2 h. The excess trimethylsilyl chloride and hexamethyldisiloxane were removed *in vacuo*, and the resulting oil was purified by Kugelrohr distillation (2 mmHg, oven temp 120 °C) to yield 0.90 g (9.1 mmol, 82%) of 6 as a colorless liquid: bp 99 °C/6 mmHg; $^1$H NMR ($CDCl_3$) $\delta$ 5.62 (d, $J$ = 10.0 Hz, 1H), 4.86 (d, $J$ = 10.0 Hz, 1H), 3.88 (m, 1H), 2.36 (m, 3H), 1.64 (m, 1H), and 1.31 ppm (d, $J$ = 6.0 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 177.00, 52.03, 51.31, 30.30, 26.72, and 19.34 ppm; IR (neat) 1676, 1419, 1381, and 1315 cm$^{-1}$; mass spectrum $m/z$ (rel intensity) 53 (20), 55 (37), 56 (25), 67 (10), 68 (13), 83 (19), 84 (13), 112 (100), 132 (15), 147 (3), and 149 (1); HRMS calcd for $C_6H_{10}NOCl$ $m/z$ 147.0451, found 147.0447; $[\alpha]^{20}_D$ +109.9° ($c$ = 0.032, $CHCl_3$).

**General Procedure for the Preparation of *N*-(Alkoxymethyl)-5(*R*)-methyl-2-pyrrolidinones.** A suspension of sodium hydride (1.1 equiv) in dry dichloromethane (10 mL/mmol alcohol) cooled to 0 °C under argon was treated with alcohol (1.0 equiv) dropwise with stirring. The reaction was maintained at that temperature for 30 min. 1-(Chloromethyl)-5(*R*)-methyl-2-pyrrolidinone (1.1 equiv) was added as a solution in about 5 mL of dichloromethane, and the reaction was allowed to warm to room temperature and stirred for 12–24 h. The reaction was cooled to 0 °C and quenched with water to destroy excess sodium hydride. The organic layer was separated and the aqueous phase extracted with diethyl ether. Organic extracts were combined, washed with brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by chromatography on silica gel eluting with an ethyl ether–hexanes solvent system.

**1-[(1*S*,2*R*,5*S*)-Menthoxymethyl]-5(*R*)-methyl-2-pyrrolidinone (11a).** (+)-(1*S*,2*R*,5*S*)-Menthol (0.160 g, 1.0 mmol, lit.[29] $[\alpha]^{23}_D = +48°$, $c$ = 10, EtOH), sodium hydride (60% in mineral oil, 0.046 g, 1.2 mmol), and 1-(chloromethyl)-5(*R*)-methyl-2-pyrrolidinone (6, 0.161 g, 1.1 mmol) were reacted, and the crude material was purified as described in the general procedure to yield 0.176 g (0.66 mmol, 64%) of 11a as a colorless liquid: $R_f$ 0.40 (ethyl ether, silica gel); $^1$H NMR ($CDCl_3$) $\delta$ 4.99 (d, $J$ = 10.0 Hz, 1H), 4.55 (d, $J$ = 10.0 Hz, 1H), 3.84 (m, 1H), 3.28 (m, 1H), 2.38 (m, 2H), 2.22 (m, 3H), 1.65 (m, 3H), 1.26 (m, 4H), 0.88 (m, 10 H), and 0.78 ppm (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 175.65, 78.38, 69.58, 52.85, 48.54, 41.48, 34.43, 31.48, 30.64, 26.99, 25.48, 23.09, 22.33, 21.10, 19.75, and 16.10 ppm; IR (neat) 2925, 1702, 1456, 1415, 1382, and 1312 cm$^{-1}$; mass spectrum $m/z$ (rel intensity) 41 (20), 43 (11), 70 (16), 98 (100), 99 (60), 100 (6), 112 (1), 114 (7), 116 (2), 210 (1), and 238 (1, $M^+ - CH_3$); HRMS calcd for $C_{16}H_{29}NO_2$ $m/z$ 267.2198, found 267.2191; $[\alpha]^{20}_D$ +10.1° ($c$ = 0.148, $CHCl_3$).

**1-[(1*R*,2*S*,5*R*)-Menthoxymethyl]-5(*R*)-methyl-2-pyrrolidinone (11b).** (−)-(1*R*,2*S*,5*R*)-Menthol (0.172 g, 1.10 mmol, lit.[29] $[\alpha]^{20}_D = -50°$, $c$ = 10, EtOH), sodium hydride (60% in mineral oil, 0.050 g, 1.25 mmol), and 1-(chloromethyl)-5(*R*)-methyl-2-pyrrolidinone (6, 0.177 g, 1.20 mmol) were reacted and the crude material was purified as described in the general procedure to yield 0.179 g (0.670 mmol, 61%) of 11b as a colorless liquid: $R_f$ 0.40 (ethyl ether, silica gel); $^1$H NMR ($CDCl_3$) $\delta$ 5.18 (d, $J$ = 11.0 Hz, 1H), 4.38 (d, $J$ = 11.0 Hz, 1H), 3.87 (m, 1H), 3.20 (m, 1H), 2.39 (m, 2H), 2.22 (m, 3H), 1.65 (m, 3H), 1.23 (m, 4H), 0.90 (m, 10 H), and 0.71 ppm (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 175.70, 76.27, 66.80, 51.94, 48.20, 40.36, 34.44, 31.33, 30.35, 26.74, 25.34, 22.96, 22.27, 21.10, 19.36, and 5.18 ppm; IR (neat) 2925, 1702, 1456, 1415, 1382, and 1312 cm$^{-1}$; mass spectrum $m/z$ (rel intensity) 41 (20), 43 (11), 70 (16), 98 (100), 99 (60), 100 (6), 112 (1), 114 (7), 116 (2), 210 (1), and 238 (1); HRMS calcd for $C_{16}H_{29}NO_2$ $m/z$ 267.2198, found 267.2191; $[\alpha]^{20}_D$ −72.5° ($c$ = 0.147, $CHCl_3$).

**1-[2(*R*)-Butoxymethyl]-5(*R*)-methyl-2-pyrrolidinone (12a).** (*R*)-2-Butanol (0.100 g, 1.35 mmol), sodium hydride (60% in mineral oil, 0.060 g, 1.5 mmol), and 1-(chloromethyl)-5(*R*)-methyl-2-pyrrolidinone (6, 0.222 g, 1.50 mmol, lit.[29] $[\alpha]^{22}_D = -12.6°$, $c$ = neat) were reacted, and the crude material was purified as described in the general procedure to yield 0.170 g (0.910 mmol, 67%) of 12a as a colorless liquid: $R_f$ 0.40 (ethyl ether, silica gel); $^1$H NMR ($CDCl_3$) $\delta$ 5.04 (d, $J$ = 10.8 Hz, 1H), 4.50 (d, $J$ = 10.8 Hz, $^1$H), 3.83 (m, 1H), 3.43 (m, 1H), 2.42 (m, 2H), 2.20 (m, 1H), 1.48 (m, 3H), 1.26 (d, $J$ = 5.9 Hz, 3H), 1.15 (d, $J$ = 6.0 Hz, 3H), and 0.88 ppm (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 175.76, 74.06, 67.82, 52.30, 30.43, 29.52, 26.85, 19.58, 19.08, and 9.93 ppm; IR (neat) 3460, 2969, 1702, 1458, 1410, 1377, and 1316 cm$^{-1}$; mass spectrum $m/z$ (rel intensity) 55 (21), 56 (14), 57 (13), 83 (21), 84

(26) Reported by the Janssen, Chemical Co.

(27) Ackermann, J.; Matthes, M.; Tamm, C. *Helv. Chim. Acta* **1990**, *73*, 122.

(28) Ringdahl, B.; Amstutz, R.; Karlen, B.; Roch, M.; Jenden, D. J. *J. Med. Chem.* **1985**, *28*, 1760.

(29) Reported by the Aldrich Chemical Co.

(27), 98 (15), 100 (8), 112 (100), 113 (12), 128 (13), and 156 (0.1, $M^+ - C_2H_5$); HRMS calcd for $C_8H_{14}NO_2$ $m/z$ 156.1023, found 156.1024; $[\alpha]^{20}_D$ -29.1° ($c$ = 0.086, $CHCl_3$).

**1-[2(*S*)-Butoxymethyl]-5(*R*)-methyl-2-pyrrolidinone (12b).** (*S*)-2-Butanol (0.100 g, 1.35 mmol, lit.[29] $[\alpha]^{20}_D$ = +13°, $c$ = neat), sodium hydride (60% in mineral oil, 0.060 g, 1.5 mmol), and 1-(chloromethyl)-5(*R*)-methyl-2-pyrrolidinone (**6**, 0.222 g, 1.50 mmol) were reacted, and the crude material was purified as described in the general procedure to yield 0.176 g (0.95 mmol, 70%) of **12b** as a colorless liquid: $R_f$ 0.43 (ethyl ether, silica gel); $^1$H NMR ($CDCl_3$) δ 4.98 (d, $J$ = 10.6 Hz, 1H), 4.55 (d, $J$ = 10.6 Hz, 1H), 3.81 (m, 1H), 3.46 (m, 1H), 1.50 (m, 3H), 1.26 (d, $J$ = 6.4 Hz, 3H), 1.15 (d, $J$ = 6.0 Hz, 3H), and 0.88 ppm (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR ($CDCl_3$) δ 175.77, 74.80, 68.90, 52.70, 30.55, 29.05, 26.92, 19.86, 19.73, and 9.65 ppm; IR (neat) 3460, 2969, 1702, 1458, 1410, 1377, and 1316 cm$^{-1}$; mass spectrum $m/z$ (rel intensity) 55 (21), 56 (14), 57 (13), 83 (21), 84 (27), 98 (15), 100 (8), 112 (100), 113 (12), 128 (13), and 156 (0.1, $M^+ - C_2H_5$); HRMS calcd for $C_8H_{14}NO_2$ $m/z$ 156.1023, found 156.1024; $[\alpha]^{20}_D$ +5.4° ($c$ 0.093, $CHCl_3$).

**1-[1(*R*)-Phenethoxymethyl]-5(*R*)-methyl-2-pyrrolidinone (13a).** (*R*)-1-Phenylethanol (0.120 g, 0.98 mmol, lit.[29] $[\alpha]^{22}_D$ = +42°, $c$ = neat), sodium hydride (60% in mineral oil, 0.045 g, 1.12 mmol), and 1-(chloromethyl)-5(*R*)-methyl-2-pyrrolidinone (**6**, 0.168 g, 1.14 mmol) were reacted, and the crude material was purified as described in the general procedure to yield 0.146 g (0.63 mmol, 64%) of **13a** as a colorless liquid: $R_f$ 0.45 (ethyl ether, silica gel); $^1$H NMR ($CDCl_3$) δ 7.31 (m, 5H), 5.02 (d, $J$ = 10.8 Hz, 1H), 4.52 (m, 2H), 3.50 (m, 1H), 2.23 (m, 1H), 1.95 (m, 1H), 1.71 (m, 1H), 1.42 (m, 4H), and 1.18 ppm (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR ($CDCl_3$) δ 175.70, 143.95, 128.25, 127.38, 125.96, 77.00, 69.72, 52.40, 30.13, 26.34, 23.95, and 19.77 ppm; IR (neat) 2972, 1698, 1451, 1415, 1313, and 1263 cm$^{-1}$; mass spectrum $m/z$ (rel intensity) 55 (26), 77 (23), 84 (21), 98 (46), 105 (39), 112 (70), 113 (100), 121 (21), and 233 (0.1); HRMS calcd for $C_{14}H_{19}NO_2$ $m/z$ 233.1416, found 233.1406; $[\alpha]^{20}_D$ +90.6° ($c$ = 0.112, $CHCl_3$).

**1-[1(*S*)-Phenethoxymethyl]-5(*R*)-methyl-2-pyrrolidinone (13b).** (*S*)-1-Phenylethanol (0.124 g, 1.02 mmol, lit.[29] $[\alpha]^{23}_D$ = -41.3°, $c$ = neat), sodium hydride (60% in mineral oil, 0.045 g, 1.12 mmol), and 1-(chloromethyl)-5(*R*)-methyl-2-pyrrolidinone (**6**, 0.170 g, 1.15 mmol) were reacted, and the crude material was purified as described in the general procedure to yield 0.156 g (0.63 mmol, 61%) of **13b** as a colorless liquid: $R_f$ 0.45 (ethyl ether, silica gel); $^1$H NMR ($CDCl_3$) δ 7.34 (m, 5H), 4.92 (d, $J$ = 10.5 Hz, 1H), 4.50 (m, 1H), 4.35 (d, $J$ = 10.5 Hz, 1H), 3.84 (m, 1H), 2.40 (m, 2H), 2.19 (m, $^1$H), 1.53 (m, 1H), 1.43 (d, $J$ = 6.5 Hz, 3H), and 1.15 ppm (d, $J$ = 6.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$): δ 175.83, 143.25, 128.44, 127.66, 126.41, 75.46, 68.34, 52.26, 30.50, 26.90, 23.79, and 19.54 ppm; IR (neat) 2972, 1698, 1451, 1415, 1313, and 1263 cm$^{-1}$; mass spectrum $m/z$ (rel intensity) 55 (26), 77 (23), 84 (21), 98 (46), 105 (39), 112 (70), 113 (100), 121 (21), and 233 (0.1); HRMS calcd for $C_{14}H_{19}NO_2$ $m/z$ 233.1416, found 233.1406; $[\alpha]^{20}_D$ -99.8° ($c$ = 0.127, $CHCl_3$).

**1-(*trans*-2-Octen-4-oxymethyl)-5(*R*)-methyl-2-pyrrolidinone (14).** *trans*-2-Octen-4-ol (0.055 g, 0.43 mmol), sodium hydride (60% in mineral oil, 0.020 g, 0.50 mmol), and 1-(chloromethyl)-5(*R*)-methyl-2-pyrrolidinone (**6**, 0.060 g, 0.41 mmol) were reacted, and the crude material was purified as described in the general procedure to yield 0.053 g (0.22 mmol, 55%) of **14** as a colorless liquid: $R_f$ 0.65 (ethyl ether, silica gel); $^1$H NMR ($CDCl_3$) δ 5.69 (m, 2H), 5.30 (m, 2H), 5.06 (d, $J$ = 10.6 Hz, 1H), 4.72 (d, $J$ = 10.6 Hz, 1H), 4.57 (d, $J$ = 10.6 Hz, 1H), 4.33 (d, $J$ = 10.6 Hz, 1H), 3.77 (m, 3H), 3.61 (m, 1H), 2.36 (m, 6H), 1.71 (m, 6H), 1.54 (m, 4H), 1.25 (m, 16H), and 0.88 ppm (m, 6H); $^{13}$C NMR ($CDCl_3$) δ 175.65, 175.55, 131.94, 131.01, 129.55, 128.04, 79.61, 78.02, 69.39, 67.08, 53.06, 51.92, 35.39, 35.32, 30.56, 30.54, 27.74, 27.54, 26.90, 26.87, 22.61, 22.56, 20.12, 19.32, 17.81, 17.77, and 14.02 ppm; IR (neat) 2933, 1704, 1409, 1262, 1054, and 968 cm$^{-1}$; mass spectrum $m/z$ (rel intensity): 55 (21), 84 (11), 98 (12), 112 (100), 113 (29), 128 (3), and 197 (0.1); HRMS calcd for $C_{14}H_{25}NO_2$ $m/z$ 239.1885, found 239.1890.

**1-[(*exo*-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-oxy)methyl]-5(*R*)-methyl-2-pyrrolidinone (15).** *exo*-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ol (0.530 g, 3.44 mmol), sodium hydride (60% in mineral oil, 0.140 g, 3.50 mmol), and 1-(chloromethyl)-5(*R*)-methyl-2-pyrrolidinone (**6**, 0.500, g, 3.39 mmol) were reacted, and the crude material was purified as described in the general procedure to yield 0.720 g (2.72 mmol, 80%) of **15** as a colorless liquid: $R_f$ 0.46 (ethyl ether, silica gel); $^1$H NMR ($CDCl_3$) δ 4.93 (d, $J$ = 10.5 Hz, 1H), 4.91 (d, $J$ = 10.5 Hz, 1H), 4.52 (d, $J$ = 10.5 Hz, 1H), 4.46 (d, $J$ = 10.5 Hz, 1H), 3.78 (m, 2H), 3.34 (m, 1H), 3.26 (m, 1H), 2.55–2.10 (m, 6H), 1.75–1.40 (m, 12H), 1.25 (d, $J$ = 6.3 Hz, 6H), 1.00 (m, 4H), 0.95 (s, 6H), 0.88 (s, 3H), 0.85 (s, 3H), and 0.80 ppm (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 175.67, 85.98, 84.32, 70.42, 68.76, 52.77, 52.56, 49.20, 38.96, 46.60, 45.19, 39.07, 38.49, 34.56, 34.38, 30.67, 30.54, 27.14, 26.90, 20.20, 19.82, 19.77, and 11.84 ppm; IR (neat) 2950, 2876, 1701, 1455, 1415, and 1387 cm$^{-1}$; mass spectrum $m/z$ (rel intensity) 55 (22), 67 (01), 83 (10), 84 (12), 98 (10), 112 (100), 113 (16), 114 (19), 153 (3), and 265 (0.1); HRMS calcd for $C_{16}H_{27}NO_2$ $m/z$ 265.2042, found 265.2043.

**1-[*exo*-[1(*R*),7,7-Trimethylbicyclo[2.2.1]heptan-2(*R*)-oxy)methyl]]-5(*R*)-methyl-2-pyrrolidinone (15a).** *exo*-1(*R*),7,7-Trimethylbicyclo[2.2.1]heptan-2(*R*)-ol (0.133 g, 0.50 mmol), sodium hydride (60% in mineral oil, 0.020 g, 0.50 mmol), and 1-(chloromethyl)-5(*R*)-methyl-2-pyrrolidinone (**6**, 0.060 g, 0.41 mmol) were reacted, and the crude material was purified as described in the general procedure to yield 0.088 g (0.33 mmol, 82%) of **15a** as a colorless liquid: $R_f$ 0.46 (ethyl ether, silica gel); $^1$H NMR ($CDCl_3$) δ 4.93 (d, $J$ = 10.6 Hz, 1H), 4.46 (d, $J$ = 10.6 Hz, 1H), 3.77 (m, 1H), 3.26 (m, 1H), 2.50–2.10 (m, 3H), 1.75–1.40 (m, 6H), 1.25 (d, $J$ = 6.3 Hz, 3H), 1.00 (m, 2H), 0.95 (s, 3H), 0.85 (s, 3H), and 0.80 ppm (s, 3H), $^{13}$C NMR ($CDCl_3$) δ 175.72, 84.34, 68.77, 52.55, 48.96, 46.63, 45.17, 38.49, 34.56, 34.40, 30.54, 27.15, 26.91, 20.20, 19.76, and 11.81 ppm; IR (neat) 2950, 2876, 1701, 1455, 1415, and 1387 cm$^{-1}$; mass spectrum $m/z$ (rel intensity) 55 (22), 67 (01), 83 (10), 84 (12), 98 (10), 112 (100), 113 (16), 114 (19), 153 (3), and 265 (0.1); HRMS calcd for $C_{16}H_{27}NO_2$ $m/z$ 265.2042, found 265.2043; $[\alpha]^{20}_D$ -22.3° ($c$ = 0.066, $CHCl_3$).

**1-[[(3,4-Dimethyl-3-cyclohexenyl)methoxy]methyl]-5(*R*)-methyl-2-pyrrolidinone (16).** 3,4-Dimethyl-3-cyclohexenylmethanol (0.570 g, 4.07 mmol), sodium hydride (60% in mineral oil, 0.180 g, 4.50 mmol), and 1-(chloromethyl)-5(*R*)-methyl-2-pyrrolidinone (**6**, 0.500 g, 3.39 mmol) were reacted, and the crude material was purified as described in the general procedure to yield 0.762 g (3.04 mmol, 90%) of **16** as a colorless liquid: $R_f$ 0.10 (70:30 pentane/ethyl ether, silica gel); $^1$H NMR ($CDCl_3$) δ 4.92 (d, $J$ = 10.6 Hz, 1H), 4.60 (d, $J$ = 10.6 Hz, 1H), 3.79 (m, 1H), 3.29 (m, 2H), 2.41 (m, 2H), 2.30–1.60 (m, 11H), 1.60 (s, 6H), and 1.27 ppm (d, $J$ = 6.3 Hz, 3H); $^{13}$C NMR ($CDCl_3$) δ 175.81, 125.37, 125.33, 124.20, 73.24, 73.21, 70.60, 52.59, 34.96, 34.93, 34.55, 31.04, 30.31, 26.75, 26.30, 19.76, 19.98, and 18.78 ppm; IR (neat) 2968, 1698, 1453, 1415, and 1379 cm$^{-1}$; mass spectrum $m/z$ (rel intensity) 41 (22), 55 (17), 67 (11), 84 (16), 112 (100), 113 (14), 121 (10), 152 (7), and 151 (1); HRMS calcd for $C_{15}H_{25}NO_2$ $m/z$ 251.1885, found 251.1880.

**1-[[(2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy]methyl]-5-(*R*)-methyl-2-pyrrolidinone (17).** 2,2-Dimethyl-1,3-dioxolane-4-methanol (0.050 g, 0.378 mmol), sodium hydride (60% in mineral oil, 0.020 g, 0.500 mmol), and 1-(chloromethyl)-5(*R*)-methyl-2-pyrrolidinone (**6**, 0.060 g, 0.407 mmol) were reacted, and the crude material was purified as described in the general procedure to yield 0.074 g (0.304 mmol, 80%) of **17** as a colorless liquid: $R_f$ 0.28 (ethyl ether, silica gel); $^1$H NMR ($CDCl_3$) δ 4.95 (d, $J$ = 10.8 Hz, 1H), 4.94 (d, $J$ = 10.8 Hz, 1H), 4.68 (d, $J$ = 10.8 Hz, 1H), 4.66 (d, $J$ = 10.8 Hz, 1H), 4.25 (m, 2H), 4.04 (m, 2H), 3.81 (m, 2H), 3.67 (m, 2H), 3.49 (m, 4H), 2.41 (m, 4H), 2.24 (m, 2H), 1.65 (m, 2H), 1.42 (s, 6H), 1.36 (s, 6H), and 1.27 ppm (d, $J$ = 6.3 Hz, 6H); $^{13}$C NMR ($CDCl_3$) δ 176.14, 109.52, 74.57, 70.94, 69.56, 69.44, 66.55, 66.48, 52.83, 30.34, 26.84, 26.77, 26.72, 25.40, 19.98, and 19.90 ppm; IR (neat) 29.79, 1704, 1408, 1381, 1262, 1212, and 1073 cm$^{-1}$; mass spectrum $m/z$ (rel intensity) 41 (16), 43 (46), 55 (16), 84 (14), 101 (15), 112 (100), 130 (3), 143 (3), 228 (6), and 230 (0.1); HRMS calcd for $C_{12}H_{21}NO_4$ $m/z$ 243.1470, found 243.1461.

**1-[[(2,2-Dimethyl-1,3-dioxolan-4(*S*)-yl)methoxy]methyl]-5(*R*)-methyl-2-pyrrolidinone (17a).** 2,2-Dimethyl-1,3-dioxolane-4(*S*)-methanol (0.050 g, 0.38 mmol, lit.[30] $[\alpha]^{25}_D$ = +15.2°, $c$ = neat), sodium hydride (60% in mineral oil, 0.020 g, 0.50 mmol),

(30) Reported by the Lancaster Chemical Co.

and 1-(chloromethyl)-5(*R*)-methyl-2-pyrrolidinone (**6**, 0.060 g, 0.41 mmol) were reacted, and the crude material was purified as described in the general procedure to yield 0.068 g (0.28 mmol, 74%) of **17a** as a colorless liquid: $R_f$ 0.28 (ethyl ether, silica gel); $^1$H NMR ($CDCl_3$) $\delta$ 4.88 (d, $J$ = 10.8 Hz, 1H), 4.60 (d, $J$ = 10.8 Hz, 1H), 4.20 (m, 1H), 3.98 (m, 1H), 3.76 (m, 1H), 3.60 (m, 1H), 3.43 (d, $J$ = 5.6 Hz, 2H), 2.47–2.18 (m, 3H), 1.62 (m, 1H), 1.42 (s, 3H), 1.36 (s, 3H), and 1.27 ppm (d, $J$ = 4.4 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 176.13, 109.51, 74.55, 70.93, 69.53, 66.53, 52.82, 30.34, 26.84, 26.76, 25.38, and 19.98 ppm; IR (neat) 2979, 1704, 1408, 1381, 1262, 1212, and 1073 cm$^{-1}$; mass spectrum $m/z$ (rel intensity) 41 (16), 43 (46), 55 (16), 84 (14), 101 (15), 112 (100), 130 (3), 143 (3), 228 (6), and 230 (0.1); $[\alpha]^{20}_D$ +12.8° ($c$ = 0.042, $CHCl_3$).

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**Supplementary Material Available:** $^1$H and $^{13}$C NMR spectra for **6**, **9**, **10**, **11a,b**, **12a,b**, **13a,b**, **14**, **15**, **15a**, **16**, **17**, and **17a** (36 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.