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SYNTHESIS OF 5S-(1-OXOALKYL AND ARYL)-2-PYRROLIDINONE DERIVATIVES[1]

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Abstract: N-Benzyl pyroglutamate esters react with aryllithium reagents and methyllithium to give moderate to good yields of 5-(1-oxoaryl) or 5-(1-oxoalkyl)-2-pyrrolidinone derivatives. The reaction proceeds without racemization, but is accompanied by formation of 5-(1-hydroxy-1-alkyl)-2-pyrrolidinone derivatives. This reaction gives very poor yields of ketone products with most other alkyl organolithium reagents such as *n*-butyllithium. Grignard reagents react to give primarily the alcohol.

Our recent work has focused on using ethyl pyroglutamate as a chiral template in various synthetic projects. As part of this ongoing study, we looked at the reaction of ethyl pyroglutamate with a variety of organometallic reagents, including enolate anions, Grignard reagents, and organolithium reagents. We found that the reaction with organolithium reagents is promising since the ester group of ethyl pyroglutamate is converted to a ketone moiety in many cases, although there is also a significant amount of over-alkylation to the disubstituted alcohol.

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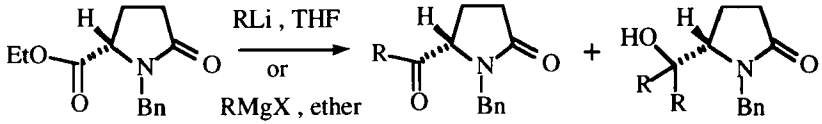

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The reaction of pyroglutamic acid derivatives with organolithium reagents and with Grignard reagents has been reported previously in the literature. Corey reacted pyroglutamic acid derivatives with phenylmagnesium chloride, and the product was a diphenyl tertiary alcohol.[3a] Campaigne reacted *N*-benzyl pyroglutamate with two equivalents of phenylmagnesium bromide, but the product was the corresponding phenyl ketone in 40% yield.[3b] Kolocouris used the acid chloride of pyroglutamic acid to form methyl, ethyl, and butyl ketones from the appropriate Grignard reagent at -80 °C.[3c] In a separate approach to the same compounds, Kokai prepared several ketones by reaction of the acid chloride of pyroglutamic acid with several benzene derivatives in the presence of aluminum chloride by a Friedel-Crafts reaction.[3c] Most of this previous work involved reaction with pyroglutamic acid rather than the ester. This includes the work of Soai,[4] who found that reaction of (*S*)-pyroglutamic acid and three equivalents of phenyllithium gave ketone **1a**, but as a racemate. This racemization led Soai to prepare the ketone derived from an *N*-protected (*S*)-proline anhydride (synthesized via a Friedel-Crafts reaction) by reaction with phenylmagnesium bromide.

We prepared ethyl pyroglutamate from commercially available *L*-glutamic acid using known procedures.[5,6] Subsequent reaction with sodium hydride and either benzyl bromide or iodomethane gave the N-phenylmethyl (benzyl) ester (**1**) in 73% yield, or the N-methyl ester in 71% yield. Since **1** showed the best reactivity, we focused our attention of that derivative. Initial work reacted one equivalent of commercially available phenyllithium with **1** in THF (-78°C, 2h) and we isolated the phenyl ketone (**2a**) in 40% yield. We also observed that about 10% of diphenyl alcohol **3** was formed along with some unreacted **1**. Reaction of **1** with two equivalents of phenyllithium improved yields of **2a** to 63%, but in several cases we obtained 30-40% of **2a** along with up to 36% of **3**. The reaction is very sensitive to temperature control and how fast the reagents are added. The 63% yield of **2a** represents the optimal conditions, whereas the 32:36% mixture of **2a**:**3** was obtained in our initial studies. We observed similar results in the reaction of **1** with methyllithium. Reaction with one equivalent of methyllithium gave a 28% yield of **2b** along with a 7% yield of **4**. Similar reaction with two

Table 1. Reaction of N-benzyl 5-oxoproline ethyl esters with organometallic reagents

Ketone	R	Reagent (eq.)	Yield 2a-2f	3-9 (%)
2a	Ph	PhLi (1)	40%	**3** (10%)[a]
	Ph	PhLi (1)	32%	**3** (36%)
	Ph	PhLi (2)	63%	**3** (8%)
	Ph	PhMgBr (1)	40%	**3** (<5%)[a]
2b	Me	MeLi (1)	28-60%	**4** (7%)[a]
	Me	MeLi (2)	29%	**4** (21%)
	Me	MeLi (2)	62%	**4** (10%)
2c	*n*-Bu	*n*-BuLi (1)	12%[a]	**5**[b]
	n-Bu	*n*-BuLi (2)	29%	**5**[b]
	n-Bu	*n*-BuMgBr (3)	29%	**5** (7%)[a]
2d	*o*-$MeOC_6H_4$	*o*-$MeOC_6H_4Li$ (2)	66%	**6**[b]
	o-$MeOC_6H_4$	*o*-$MeOC_6H_4MgBr$ (3)	8%[a]	**6**[b]
	Et	EtMgBr (-)	-	**7** (26%)
	$CH_2CH=CH_2$	$CH_2=CHCH_2MgBr$ (-)	-	**8** (41%)
	$CH=CH_2$	$CH_2=CHMgCl$	-	**9** (39%)

[a] Not isolated; yield estimated by GC/MS [b] Not detected

equivalents of methyllithium gave 29% of **2b** and 21% of **4**. In one case we obtained a 62% yield of **2b** using two equivalents of methyllithium. In no case did we detect racemization of the chiral center at C_5 of the lactam, and both ketone **2a** and ketone **2b** were determined to be chiral, non-racemic at C_5 when the carbonyl unit was reduced to a diastereomeric mixture of alcohols with $NaBH_4$, reacted with N-chloromethyl-5R-methyl-2-pyrrolidinone,[7] and then examined by proton NMR.

We next reacted several commercially available organolithium reagents with ester **1** to examine the scope of the ketone-forming reaction. Butyl ketone **2c** was prepared in poor yield (12%) and many side products were observed. In order to optimize this clearly inferior reaction, three different sets of conditions were examined, all with one equivalent of **1**. First, the reaction was run at -100 °C (ether/CO_2 bath) in THF, but this gave only a 12% yield of **2c**, as mentioned. Secondly, the reaction was run in anhydrous ether at -78 °C, and this gave a 25% yield of **2c**. Finally, very slow

addition of *n*-butyllithium (-78°C, THF) gave a 29% yield of **2c**. Using a greater excess of *n*-butyllithium only increased the number and amount of unwanted side products. *t*-Butyllithium was also used as a reagent , but the reaction produced a complex mixture of products of which less than 5% might be the desired ketone, although the starting ester was completely consumed. We were not able to isolate this ketone in pure form to verify the structure. A functionalized organolithium reagent was prepared from *o*-bromoanisole by reaction with 2.2 equivalents of *t*-butyllithium (ether, -78°C).[8] After 15 minutes, ester **1** was added and ketone **2d** was isolated in 66% yield. We did not detect any alcohol (**6**) in this experiment. The results of our study with these organolithium reagents are found in Table 1.

The reaction of **1** with organolithium reagents gave good results in a few cases, and we next examined the reaction of Grignard reagents with this pyroglutamate ester. As with the organolithium reagents, Grignard reagents generally add to an ester to initially give a reactive ketone, but this reacts further to give a tertiary alcohol. However, Fuson demonstrated that addition of Grignard reagents to highly hindered esters often gave the ketones.[9] Using an excess of reagent with simple esters almost always gives the tertiary alcohol as the only product.[10] In our study, pyroglutamate ester **1** reacted with Grignard reagents to give an interesting mixture of products, as shown in Table 1. Phenylmagnesium bromide reacted with ester **1** to give a 40% yield of phenyl ketone **2a**, and no alcohol product was observed. This is in sharp contrast to the reaction of ethylmagnesium bromide, commercially available vinylmagnesium chloride, or allylmagnesium bromide. These reagents reacted with **1** but gave no ketone at all, only tertiary alcohols **7**, **8**, and **9** in yields ranging from 21-41%. In each case, mixtures of products were obtained that contained a significant amount of unreacted ester, the tertiary alcohol, and small amounts of unidentifiable side products. In the reaction with ethylmagnesium bromide, we modified the reaction conditions to include low temperature reactions, a change in solvent from ether to THF, and inverse addition of one equivalent of the Grignard reagent to the ester. These modifications failed to give the desired ketone, and alcohol **7** was isolated in each case.

Other Grignard reagents were prepared, and in the reaction of **1** with *n*-butylmagnesium bromide, we detected what appeared to be alcohol **5** in about 7% yield (as estimated by GC/MS), and 29% of ketone **2c** was isolated. Although *o*-bromoanisole generated an organolithium reagent that reacted with **1** to give **2d** in 66% yield, the analogous Grignard reagent gave ketone **2d** in only 8% yield, with large amounts of unreacted ester.

Some general conclusions can be drawn from this study. 1-Phenylmethyl-5-oxoproline ethyl ester (N-benzyl pyroglutamate ethyl ester) reacts with an excess of organolithium reagents to give ketones in moderate to good yields, but only with the aryllithium reagents and with methyllithium. This ester reacts with an excess of alkylmagnesium halides (C_4 and larger) or arylmagnesium halides to give ketones in poor yield. This ester reacts with "small" alkylmagnesium halides (C_3 and smaller) to give only tertiary alcohols. The chiral center at C_5 of the lactam ring appears to be uncompromised during these reactions.

EXPERIMENTAL

All melting points were taken on a Mel-Temp apparatus and are uncorrected. All boiling points listed are also uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded in deutero-chloroform at 270.1 MHz and 67.9 MHz receptively, on a Brüker AC-270 with tetramethylsilane (TMS) as an internal standard, and with chemical shifts given in ppm. Infrared spectra recorded on a Perkin-Elmer 1600 Series FT-IR and given in reciprocal centimeters. GC spectra were obtained on a Hewlett-Packard 5890 GC with a HP-1 methyl silicone column and detected by a low resolution 5970 series mass selective detector. High resolution electron impact mass spectra were collected at 70 eV using a Kratos MS-50 instrument and are accurate to ± 5 mmu. Specific rotations determined with an O.C. Rudolph polarimeter with a sodium D line with concentrations given in g/mL. Column chromatography performed with EM Science Silica Gel 60; 70-230 mesh. Thin layer chromatography performed with silica gel IB-F pre-coated plates from J.T. Baker. All reaction glassware was oven dried, and most procedures were performed under an argon atmosphere as listed. 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, absolute ethanol, ethyl acetate, magnesium turnings, ammonium chloride, and tetrahydrofuran were obtained from J.T. Baker. Thionyl chloride, *L*-glutamic acid, sodium borohydride, 60% sodium hydride, benzyl bromide, benzyl chloride, allyl bromide, bromoethane, bromopentane, bromobutane, iodomethane, vinylmagnesium chloride, diisobutylaluminum hydride, potassium *tert*-butoxide, *n*-butyllithium, *t*-butyllithium, methyllithium and lithium tri-*tert*-butoxide aluminum hydride were purchased from the Janssen Chemical Company. Barium oxide, 4Å molecular sieves, 50% sodium hydride, lithium aluminum hydride, *o*-bromoanisole, sodium iodide, 5-bromo-1-propene, phenyllithium, and diethylamine were obtained from the Aldrich Chemical Company. Ethyl pyroglutamate (5-oxoproline ethyl ester)[5,6] was prepared by previously established procedures.

1-Phenylmethyl-(*S*)-(-)-5-oxoproline ethyl ester, 1

(*S*)-(+)-5-Oxoproline ethyl ester (2.5 g, 15.92 mmol) was dissolved in 30 mL of dry THF (from sodium/benzophenone) and stirred at ambient temperature for 0.25 h prior to addition of 0.76 g (15.92 mmol) of 50% NaH in mineral oil, added in one portion. Evolution of hydrogen ceased after stirring for 0.25 h, 1.75 mL (2.72 g, 15.92 mmol, ρ= 1.44 g/mL) of distilled benzyl bromide was added, and the solution was stirred for 2h at ambient temperature. Washing with water and extraction with 3 x 25 mL of ether was followed by drying over $MgSO_4$. Filtration and concentration in vacuo gave a crude brown oil that was purified by column chromatography (SiO_2, Et_2O, R_f= 0.45) to give 2.86 g (11.56 mmol, 73%) of **1**:[11] ^1H NMR ($CDCl_3$): δ 1.2 (3H, t), 2.3 (4H, m), 3.7 (1H, m) 4.0 (1H, m), 4.1 (2H, q), 5.0 (1H, d), and 7.2 ppm (5H, m); ^{13}C NMR ($CDCl_3$): δ 14.2, 22.9, 29.6, 45.7, 58.9, 61.5, 127.9, 128.6, 128.8, 135.9, 171.8, and 175.1 ppm; IR (neat): 3006 (w), 2977 (m), 1739 (s), 1695 (s), 1413 (m), 1375 (m) 1198 (m) 1030 (m), and 750 (m) cm^{-1}; mass spectrum (*m/z*, relative intensity): P^+ 247 (15), 219 (3), 191 (2), 175 (9), 174 (57), 146 (11), 117 (4), 92 (10), 91 (100), and 65 (11); HRMS Calcd. for $C_{14}H_{17}NO_3$, 247.1208; Found 247.1208 (± 1.2 mmu); $[\alpha]_D^{25}$= -5.7 ° (c=0.014; CH_2Cl_2).

General procedure for reaction of 5-oxoproline ethyl esters with organolithium reagents

The 1-phenylmethyl or 1-methyl-5-oxoproline ethyl ester was dissolved in 10 mL of dry THF (distilled from sodium and benzophenone) and then cooled to -78°C, under an argon atmosphere. This solution was stirred for 0.5 h and then treated with two equivalents of the organolithium reagent via syringe, stirred at -78°C for 2 h, and then quenched by addition of 25 mL of saturated ammonium chloride solution. Warming to ambient temperature was followed by extraction with ether, washing the ether extracts with saturated sodium chloride solution. The ether extracts were dried ($MgSO_4$), and removal of solvent *in vacuo* to give the ketone.

(-)-1-Phenylmethyl-[(5*S*)-(1-oxo-1-phenyl)]-2-pyrrolidinone, 2a

A solution **1** (0.2 g, 0.95 mmol) in 10 mL of dry THF was treated with 2 equivalents of 1.8M phenyllithium in 70% cyclohexane/30% ethyl ether (1.03 mL, 1.90 mmol) via syringe. Reaction for 2 h and the standard workup gave a brown oil and column chromatography (SiO_2/Et_2O, R_f=0.35) gave 0.17 g (0.61 mmol, 63%) of **2a** as a pale yellow oil: ^1H NMR ($CDCl_3$): δ 2.0 (2H, m), 2.5 (2H, m), 3.7 (1H, dd, J = 11.8 Hz), 4.9 (1H, t), 5.2 (1H, dd, J= 11.8 Hz), 7.2-7.8 ppm (10H, m); ^{13}C NMR ($CDCl_3$): δ 23.3, 29.7, 45.6, 80.6, 126.3, 127.8, 127.9, 128.4, 128.7, 128.9,

129.1, 134.1, 134.4, 136.3, 175.3, and 197.1 ppm; IR (neat): 3056(m), 2967 (s), 1681 (b), 1448 (s), 1233 (s), 1083 (m), 1044 (m), and 701 (s) cm^{-1}; mass spectrum (*m/z*, relative intensity): P^+ 279 (1), 174 (66), 144 (1), 105 (6), 92 (7), 91 (100), 77 (11), 65 (12), and 51 (6); HRMS Calcd. for $C_{18}H_{17}NO$, 279.1259; Found 279.1251 (± 1.4 mmu); $[\alpha]_D^{25}$= -10.0 ° (c=0.018; CH_2Cl_2).

(-)-1-Phenylmethyl-[(5*S*)-(1-oxo-1-methyl)]-2-pyrrolidinone, 2b

A solution of 2.0 g (8.10 mmol) of **1** in 10 mL of dry THF (distilled from sodium/benzophenone) was treated with 5.06 mL (8.09 mmol) of 1.6M methyllithium (in diethyl ether) via syringe. Reaction for 2 h and the standard workup gave a yellow-brown oil. Purification by column chromatography ($SiO_2/CH_2Cl_2/Et_2O$ (75:25), R_f= 0.38) gave 1.05 g (4.83 mmol, 60%) of **2b**: ^1H NMR ($CDCl_3$): δ 1.8 (1H, m), 2.0 (3H, s), 2.2 (1H, m), 2.4 (2H, m), 3.8 (1H, dd, J = 11.8 Hz), 4.0 (1H, dd, J = 12.8, 2.1 Hz), 5.2 (1H, dd, J = 11.8 Hz), 7.1 (2H, m), and 7.3 ppm (3H, m); ^{13}C NMR ($CDCl_3$): δ 21.7, 26.3, 29.5, 45.7, 64.8, 127.9, 128.7, 128.9, 135.9, 174.9, and 206.0 ppm; IR (neat): 3034 (m), 2974 (m), 2928 (m), 1719 (s), 1684 (s), 1415 (m), 1163 (m), 905 (s), 729 (s), and 647 (s) cm^{-1}; mass spectrum (*m/z*, relative intensity): P^+ 217 (1), 175 (5), 174 (43), 144 (1), 117 (1), 92 (7), 91 (100), 65 (13), and 51 (1); HRMS Calcd. for $C_{13}H_{15}NO$ 217.1103 ; Found 217.1105 (±1.1 mmu); $[\alpha]_D^{25}$= -18.8 ° (c=0.016; CH_2Cl_2).

(-)-1-Phenylmethyl-[(5*S*)-(1-oxo-1-butyl)]-2-pyrrolidinone, 2c

A solution of **1** (1.0 g, 4.05 mmol) in 15 mL of dry THF was treated with 2.45 mL of 1.65M *n*-butyllithium in hexane via syringe. Reaction for 2 h and the standard workup gave 1.54 g of a crude oil. Purification by column chromatography (SiO_2/ether, R_f= 0.23) gave 0.29 g (1.12 mmol, 28%) of **2c** as a pale yellow oil: ^1H NMR ($CDCl_3$): δ 0.9 (3H, t), 1.2 (2H, m), 1.5 (2H, m), 2.0-2.5 (6H, m), 3.8 (1H, dd, J = 16.0 Hz), 4.0 (1H, m), 5.1 (1H, dd, J = 16.0 Hz), and 7.2-7.3 (5H, m) ppm; ^{13}C NMR ($CDCl_3$): δ 13.9, 21.9, 22.4, 25.6, 29.6, 39.0, 45.9, 84.2, 127.9, 128.7, 128.9, 136.0, 175.1, and 208.2 ppm; IR (neat): 3146 (m), 2958 (m), 2927 (m), 1717 (m), 1681 (s), 1535 (m), 1457 (s), 1378 (m), and 1092 (m) cm^{-1}; mass spectrum (*m/z*, relative intensity): P^+ 259 (1), 175 (9), 174 (80), 144 (1), 117 (2), 92 (7), 91 (100), and 65 (11); HRMS Calcd. for $C_{16}H_{21}NO_2$ 259.1572; Found 259.1569 (±1.3 mmu); $[\alpha]_D^{25}$= -5.0 ° (c=0.002; CH_2Cl_2).

(-)-1-Phenylmethyl-[(5*S*)-(1-oxo-1-(2-methoxyphenyl))]-2-pyrrolidinone, 2d

Two equivalents of *ortho*-bromoanisole (0.53 g, 2.82 mmol) were dissolved in 15 mL of anhydrous ether and cooled to -78 °C under argon. This solution was treated

with 4.4 equivalents of 1.5 M *t*-BuLi in pentane (4.17 mL) via syringe and the mixture was stirred at -78 °C for 0.25 h. This solution was treated with of 0.35 g (1.42 mmol) of **1** dissolved in 5 mL of anhydrous ether. The solution was stirred for 0.5 h and the standard workup gave a crude yellow oil that was purified by column chromatography (SiO_2, Et_2O, R_f= 0.20) to give 0.29 g (0.94 mmol, 66%) of **2d** as a cloudy white oil: ^1H NMR ($CDCl_3$): δ 1.9-2.4 (4H, m), 3.7 (3H, s), 3.8 (1H, dd, J = 12.8 Hz), 4.9 (1H, dd, J = 9.6, 2.1 Hz), 5.1 (1H, dd, J = 12.8 Hz), and 6.9-7.7 (9H, m) ppm; ^{13}C NMR ($CDCl_3$): δ 22.7, 29.4, 45.6, 55.6, 64.5, 111.8, 121.2, 127.5, 128.5, 128.6, 131.2, 134.7, 136.8, 158.8, and 175.7 ppm; IR (neat): 3017 (s), 2960 (s), 1701 (br), 1593 (s), 1486 (s), 1356 (m), 1283 (s), 1108 (s), 1017 (s), 842 (m), 758 (s), and 622 (s) cm^{-1}; mass spectrum (*m/z*, relative intensity): P^+ 309 (7), 175 (11), 174 (93), 135 (12), 92 (12), 91 (100), 72 (12), and 65 (10); HRMS Calcd. for $C_{19}H_{19}NO_3$ 309.1365; Found 309.1365 (± 1.5 mmu); $[\alpha]_D^{25}$= -17.5 ° (c=0.012; CH_2Cl_2).

General procedure for reaction of 5-oxoproline ethyl esters with Grignard reagents

Magnesium turnings were placed in an oven-dried roundbottom flask fitted with a reflux condenser. Anhydrous diethyl ether (15 mL) was added via syringe and the mixture was stirred at 0°C under a head of argon. The appropriate halide was added dropwise via syringe over a period of 0.25 h. The resultant solution was warmed to ambient temperature and stirred for 0.5 h. At this time, a solution of **1** in 10 mL of ether was added via syringe, dropwise over a period of 0.25 h. After stirring for 1 h, the reaction was quenched with 25 mL of saturated ammonium chloride solution. Extraction with ether, drying ($MgSO_4$), and removal of solvents *in vacuo* gave the products.

(-)-1-Phenylmethyl-[(5*S*)-(1-oxo-1-phenyl)]-2-pyrrolidinone, 2a

Six equivalents of magnesium turnings (0.6 g, 24.4 mmol) in 15 mL of anhydrous ethyl ether wee stirred at 0 °C with 0.4 mL (0.64 g, 4.05 mmol) of distilled bromobenzene for 0.25 h. The solution was warmed to ambient temperature and then treated with 1.0 g (4.05 mmol) of a solution of **1** in 10 mL of anhydrous ether. The reaction was stirred for 1 h and quenched in the usual manner, but it was stirred for 15 h after hydrolysis. The oil resulting from workup was purified by column chromatography (SiO_2/Et_2O, R_f=0.35) to give 0.45 g (1.61 mmol, 40%) of **2a**.

(-)-1-Phenylmethyl-[(5*S*)-(1-oxo-1-butyl)]-2-pyrrolidinone, 2c

Six equivalents of magnesium turnings (1.16 g, 48.54 mmol) in 30 mL of anhydrous ether were refluxed with three equivalents of bromobutane (3.32 g, 2.59

mL, 24.27 mmol) for 1 h. The resulting slurry was treated with 2.0 g (8.09 mmol) of **1** in 10 mL of anhydrous ether and refluxed for 1.5 h. The standard workup gave a brown oil. Purification by column chromatography (SiO_2/Et_2O, R_f= 0.23) gave 0.27 g (1.04 mmol, 13%) of **2c**.

(-)-1-Phenylmethyl-[(5*S*)-(1-oxo-1-(2-methoxyphenyl))]-2-pyrrolidinone, 2d

Two equivalents of magnesium turnings (0.3 g, 12.4 mmol) in 20 mL of anhydrous ethyl ether were stirred with 0.76 mL of *ortho*-bromoanisole (1.14 g, 6.07 mmol) at ambient temperature for 18h. This slurry was treated with a solution of **1** (1.5 g, 6.07 mmol) in 15 mL of anhydrous ether and stirred at ambient temperature for 1 h. The standard workup gave a crude yellow oil which was purified by column chromatography (SiO_2, Et_2O, R_f= 0.20) to give 0.15 g (0.48 mmol, 8%) of **2d**.

1-Phenylmethyl-(5*S*)-[1,1-diethyl-1-hydroxymethyl]-2-pyrrolidinone, 7

Two equivalents (0.19 g, 8.10 mmol) of magnesium turnings in 20 mL of anhydrous ethyl ether was stirred with 0.30 mL of bromoethane (0.44 g, 4.05 mmol) for 1 h. This slurry was treated with a solution of 1.0 g (4.05 mmol) of **1** in 10 mL of anhydrous ether and stirred at ambient temperature for 2 h. The standard workup gave a dark brown crude oil. Purification gave 0.55 g (2.11 mmol, 26% of **7**: ^1H NMR ($CDCl_3$): δ 0.82 6H, m), 1.30-1.60 (5H, m), 1.76-2.05 (2H, m), 2.21-2.58 (2H, m), 3.52, 3.54, 3.57, 3.58 (1H, dd, J = 9.2 Hz; 3.4 Hz), 4.31/5.13 and 4.38/5.06 (2 H, dd, J = 164.0 Hz; J = 134.8 Hz), and 7.24 ppm (5 H, s); ^{13}C NMR ($CDCl_3$): δ 7.0, 7.1, 20.5, 26.6, 29.6, 30.2, 46.5, 53.4, 62.6, 127.2, 128.2 (2 C), 128.5 (2 C), 137.4, and 176.7 ppm; IR (neat): 3439 and 1670 cm^{-1}; mass spectrum (*m/z*, relative intensity): P+1 262 (1), 232 (2), 176 (5), 175 (34), 174 (41), 146 (2), 104 (2), 92 (16), 91 (100), 84 (39), and 65 (13); HRMS Calcd. for $C_{16}H_{23}NO_2$, 261.1729; Found 261.1721 (±1.3 mmu).

1-Phenylmethyl-(5*S*)-[1,1-bis(2-propenyl)-1-hydroxymethyl]-2-pyrrolidinone, 8

A excess of magnesium turnings (0.25 g) in 20 mL of anhydrous ethyl ether was stirred with 0.33 mL of distilled allyl bromide (0.46 g, 3.80 mmol) for 1 h at ambient temperature. This slurry was chilled to 0°C and treated with a solution of 0.46 g (1.90 mmol) of **1** in 10 mL of anhydrous ether an stirred at 0 °C for 2h. The standard workup gave a dark brown crude oil that was purified by column chromatography (SiO_2/Et_2O; R_f= 0.23) to give 0.22 g (0.77 mmol, 41%) of **8**. This product contains a trace of **1**: ^1H NMR ($CDCl_3$) δ 1.8-2.4 (8H, m), 3.6 (1H, m), 4.4 (1H, dd, J = 12.8

Hz), 5.1 (4H, m), 5.2 (1H, dd, J = 12.8 Hz), 5.8 (2H, m), and 7.1-7.2 (5H, m) ppm; ^{13}C NMR ($CDCl_3$): δ 22.9, 30.2, 30.8, 42.8, 43.8, 46.9, 58.5, 63.4, 119.7, 120.1, 127.3, 127.9, 128.8, 132.5, 135.9, 137.7, and 172.6 ppm; IR (neat): 3410 (br), 3069 (s), 2934 (s), 1736 (br), 1659 (br), 1443 (s), 1415 (s), 1249 (s), 1199 (s), 1022 (m), 917 (s), and 729 (s) cm^{-1}; mass spectrum (*m/z*, relative intensity): P^+ 285 (1), 244 (2), 219 (1), 176 (5), 175 (33), 174 (56), 146 (2), 117 (2), 92 (11), 91 (100), 84 (19), 69 (6), and 65 (11); HRMS Calcd. for $C_{18}H_{23}NO_2$, 285.1729; Found 285.1723 (±1.4 mmu).

1-Phenylmethyl-(5*S*)-[1,1-diethenyl-1-hydroxymethyl]-2-pyrrolidinone, 9

A solution of 1.0 g (4.05 mmol) of **1** in 15 mL of dry THF was treated with 2.03 mL (4.05 mmol) of a 15% commercial solution of vinylmagnesium chloride in THF. The reaction was stirred at ambient temperature for 2h. The standard workup gave 1.1 g of crude yellow oil and purification by column chromatography (SiO_2/CH_2Cl_2, R_f=0.41) gave 0.41 g (1.59 mmol, 39%) of **9**: This product contains a small amount of **1**: ^1H NMR ($CDCl_3$): δ 2.1-2.4 (2H, m), 3.5 (2H, m), 3.6 (1H, m), 3.8 (1H, dd), 4.5 (1H, s), 5.1 (1H, dd), 5.8-6.2 (6H, m), 7.1-7.2 (5H, m) ppm; ^{13}C NMR ($CDCl_3$): δ 23.2, 26.7, 51.3, 64.7, 80.6, 115.9, 127.0, 128.2, 129.0, 135.9, 138.5, and 175.2 ppm; IR (neat): 3409 (b), 3060 (m), 2972 (m), 1701 (s), 1415 (s), 1359 (s), 1219 (s), 910 (s), 725 (s), 647 (s), and 535 (s) cm^{-1}; mass spectrum (*m/z*, relative intensity): P^+ 257 (1), 175 (7), 174 (57), 144 (1), 117 (1), 92 (8), 91 (100), 65 (13), and 55 (8); HRMS Calcd. for $C_{16}H_{19}NO_2$ 257.1416; Found 257.1419 (±1.3 mmu).

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