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Diastereoselective Alkylation of 1-Benzyl-(5S)-Substituted 2-Pyrrolidinones.

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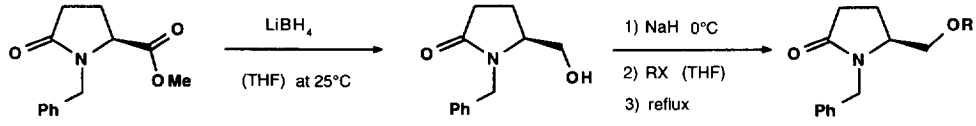
Abstract: The (S)-glutamic acid derivatives, (5S)-Methoxymethyl- and (5S)-Benzyloxymethyl-N-Benzyl-2-Pyrrolidinones, compounds **3a** and **3b** respectively, exhibit good to excellent diastereoselection upon alkylation with primary alkyl bromides or iodides. Copyright © 1996 Elsevier Science Ltd

Introduction

Due to their presence in alkaloids and other bioactive compounds, chiral pyrrolidines have been starting materials for natural,[1a] as well as nonnatural[1b] compounds or targets of enantiomerically pure compound (EPC) synthesis.[2] Molecules containing an (S)-proline derived pyrrolidine ring have long been used as chiral auxiliaries.[3] On the other hand, (S)-glutamic acid has been the source of optically active 4-hydroxy-γ-butyrolactone, on which diastereoselective reactions have been carried out.[4] However, diastereoselective alkylations on lactams similar to those employed in the present work have been studied only fairly recently.[5]

We are currently interested in preparing new pyrrolidines in order to test them as chiral auxiliaries. While studying the reactivity of the carbonyl moiety in compound **3a** towards organometallic reagents, we found that its enolate was diastereoselectively benzylated. This fact prompted us to study the reaction with other alkylating agents. We wish to disclose here our findings on this matter.

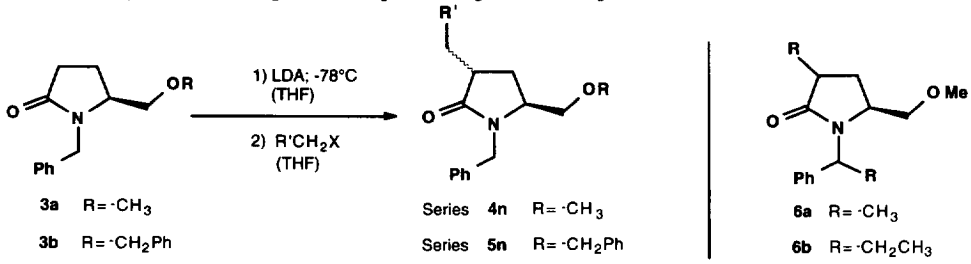
Results and Discussion



1 **2** **3a** R= -CH_3 **3b** R= -CH_2Ph

The preparation of amidoethers **3** proceeded as shown in the reaction sequence above. The ester **1**[6] was obtained from (S)-glutamic acid *via* N-benzyl (S)-glutamic acid.[7] On addition of compounds **3** to n-BuLi, MeLi or LDA in THF at -78°C the mixture turned immediately yellow indicating the formation of the corresponding enolates. Because of n-BuLi promoted formation of product mixtures due to Li/halogen exchange,[8] especially with alkyl iodides, we employed one equivalent of freshly prepared LDA to carry out the enolization. Experiments were performed initially on the enolate of **3a**; it was allowed to react at -78°C with the alkylating agents listed in the table. The bromides gave only the desired products **4**: no other product could be detected by TLC

or in the spectra of crude products. However, the corresponding iodides (entries 1 and 3) afforded an additional product in varying yields (see experimental part) along with the expected one.



3a R= -CH_3

3b R= -CH_2Ph

Series **4n** R= -CH_3

Series **5n** R= -CH_2Ph

6a R= -CH_3

6b R= -CH_2CH_3

Entry	Product	Alkyl residue R'	hal. X	Ether group R	Chem. yld. (%)	Ratio trans/cis
1	**4a**	H	I	-CH_3	60[b]	91 : 9
2	**4a**	H	Br	-CH_3	92[a]	90 : 10
3	**4b**	Me	I	-CH_3	25[b]	92 : 8
4	**4b**	Me	Br	-CH_3	89[a]	86 : 14
5	**4c**	Ph	Br	-CH_3	75[b]	>97 : 3
6	**4d**	CH_2=CH	Br	-CH_3	95[a]	94 : 6
7	**4e**	$(Me)_2C$=CH	Br	-CH_3	96[a]	97 : 3
8	**4f**	HC≡C	Br	-CH_3	60[b]	84 : 16
9	**5a**	H	I	-CH_2Ph	45[b]	90 : 10
10	**5b**	Me	Br	-CH_2Ph	55[b]	80 : 20
11	**5c**	Ph	Br	-CH_2Ph	63[b]	85 : 15
12	**5d**	CH_2=CH	Br	-CH_2Ph	40[b]	87 : 13
13	**5e**	$(Me)_2C$=CH	Br	-CH_2Ph	49[b]	89 : 11
14	**5f**	HC≡C	Br	-CH_2Ph	53[b]	81 : 19

[a] Yield of crude product. [b] Yield after passing crude product through a short silica gel column to separate unreacted starting material or side-product; in the case of **4c**, after recrystallization.

The unexpected product featured in its ^{1}H-NMR spectrum a multiplet, either a quartet or a triplet above 5 ppm, depending on the alkylating agent used, that integrated for one proton. Conversely, starting material and expected product characteristically displayed a pair of doublets (J=15 Hz) due to the N-benzylic protons, one close to 4.9 ppm and the other around 4.1 ppm. Evidently the unexpected products had lost an N-benzylic proton to give way to an alkyl group. Noteworthy is the fact that in the absence of the neighboring ether group on a five-membered ring like this, no alkylation at the benzylic position has been observed.[9] On the other hand, we could not detect in our experiments any product of alkylation solely at the benzylic position. The spectral data allowed us to assign structures **6** to these by-products. When **3a** was subjected to a tandem dialkylation procedure with methyl bromide, the isolated product was **6a**. Unsuccessful were several attempts to incorporate deuterium on the benzylic position of **3a**, **4a** and **4c** using our standard alkylation conditions as well as one equivalent of n-BuLi or t-BuLi or even an excess of base. Complete monodeuteration alpha to the lactam carbonyl occurred only in **3a** with t-BuLi. According to these facts we could draw the following conclusions:

Alkylation alpha to the carbonyl moiety precedes alkylation of the benzylic methylene group. Complexation of the base by the ether oxygen may play a role in the benzylic methylene alkylation. It is noteworthy that alkylation of the benzylic methylene group is observed with alkyl iodides even when only a slight excess of base is used.

In order to study the effect of changing the ether grouping on the diastereoselectivity of the reaction, the enolate of **3b** was reacted with the same alkylating agents as **3a**. The corresponding side-product due to methylation at the benzylic position was also detected in this case. The alkylations were generally less clean with **3b** and some starting material was usually recovered.

Products **4** and **5** showed in their 300 MHz ^{1}H-NMR spectra several signals that enabled us to determine the degree of diastereoselection. In most examples the pair of doublets in the 4 to 5 ppm region was quite useful towards this end: at least one of the doublets corresponding to the major diastereomer did not overlap with the one due to the minor isomer thus showing the ratio of major to minor product clearly. As can be seen from the table, good levels of diastereoselection were attained throughout. This compares favorably with the first alkylation of other systems that particularly with small alkyl groups has been less stereoselective.[10] The R at the ether grouping seemed not to influence greatly the degree of diastereoselection; with R=Me (entries 1-8) better results were usually obtained. The reaction of ether **3a** with benzyl bromide afforded product **4c**; it could be crystallized as a single enantiomer and was subjected to X-ray crystallography, whereby the configuration of the newly created stereocenter turned out to be as expected, the one resulting from *trans* attack. Differential NOESY experiments on compound **4a** purified by silica gel chromatography established the same configuration for the predominant diastereomer. Due to similar signal displacements and coupling patterns on all the other compounds, it can be assumed that their configuration is *trans* as well. To our knowledge, alkylated compounds **4** and **5** have not been previously reported.[11]

Conclusions

Compounds **3** are suitable substrates for stereoselective alkylation alpha to the carbonyl group. Better results are obtained using **3a** with a methyl ether at the biasing group, but care must be taken regarding the halide on the alkylating agent to be employed.[16]

Experimental Section

Commercial THF was distilled under an inert atmosphere from sodium benzophenone ketyl prior to use. Other reagents and solvents were purchased and used without further purification unless stated otherwise. Work up as usual means separating the organic phase, drying over Na_2SO_4 and concentrating on a rotary evaporator. Melting points were taken on a Fisher-Johns apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR data were recorded on a Varian Gemini 200 (200 MHz) and Varian Unity Plus (300 MHz) and are given as δ ppm displacements from TMS as internal standard; coupling constants (J) are expressed in Hertz. IR spectra were obtained on a Nicolet 55-XFT and a Perkin Elmer 283B. Mass Spectra were measured on a Hewlett Packard 5985B. Optical rotations were taken on a Jasco DIP-60 polarimeter. Analytical TLC was performed on Macherey-Nagel aluminum foils coated with F_{254} silica gel cut in 7 × 2-3 cm pieces and viewed with UV light and/or ethanolic 10% phosphomolybdic acid solution. Column chromatography was carried out using 70-230 mesh silica gel from Merck.

(5S)-1-Benzyl-5-carbomethoxy-2-pyrrolidinone (1).

In a 500 mL two-necked round bottom flask provided with a reflux condenser and an addition funnel N-benzyl-(S)-pyroglutamic acid[7] (50.8 g; 232 mmol) was dissolved in 250 mL MeOH. The solution was cooled in an ice/salt bath and $SOCl_2$ (25 mL; 343 mmol) was added dropwise with stirring. After the addition was complete, the reaction mixture was refluxed 2h and monitored by TLC. Upon completion of the reaction, the mixture was allowed to cool down to room temperature. It was then cooled in an ice bath

and 95-100 mL Et_3N was added carefully through the addition funnel until production of fumes ceased. If necessary, at the end of the addition the mixture was vacuum filtered. The residue left after concentrating the clear solution on a rotary evaporator was taken up in ethyl ether (300 mL). The resulting suspension was vacuum filtered and the filter cake was washed several times with ethyl ether. The filtrate and washings were worked up as usual. The slightly yellow oil left after ether evaporation was used in the next step without further purification. Yield: 52 g (96%). $[\alpha]_D$ = +31.1 (c=1.06; $CHCl_3$).

IR (film, cm^{-1}): 3030, 2953, 1742, 1695, 1438, 1205. **^{1}H-NMR** ($CDCl_3$): 7.15-7.36 (m, 5H), 4.98 (d, H_A, J=14.8), 4.0 (d, $2H_B$, J=14.8), 3.93-4.01 (m, 1H), 3.65 (s, 3H), 2.35-2.64 (m, 2H), 1.96-2.34 (m, 2H). **^{13}C-NMR** ($CDCl_3$): 174.5, 171.7, 135.3, 128.2, 127.9, 127.2, 58.2, 51.8, 45.0, 29.0, 22.2. **MS** m/z (%): 233 (M^+ 4), 174 (25), 146 (10), 91 (100), 65 (18), 39 (15). Anal. calcd for $C_{13}H_{15}NO_3$ C: 66.92 H: 6.49; N: 6.01 Found C: 66.75; H: 6.33; N: 6.19.

(5S)-1-Benzyl-5-hydroxymethyl-2-pyrrolidinone (2).

In a two-necked round bottom flask equipped with an addition funnel and a reflux condenser (Ar atmosphere) commercial[12] $LiBH_4$ (4.73 g; 215 mmol) was dissolved in 75 mL anhydrous THF. Next, a solution of compound **1** (50 g; 215 mmol) in 100 mL anhydrous THF was added dropwise at room temperature to the stirred solution in the flask. A slightly exothermic reaction ensued and towards the end of the addition a sticky precipitate made the stirring difficult. The reaction was monitored by TLC and quenched at 0°C by the addition of aqueous 20% AcOH (200 mL) until the mixture became clear and the bubbling subsided, then it was neutralized with solid Na_2CO_3. The mixture was transferred to a separatory funnel and after extraction with ethyl acetate (3×100 mL), worked up as usual. The residue crystallized slowly on standing or after being covered with ethyl ether. Recrystallization from ether afforded 39.6 g (90% yield) of white crystalline **2**; m.p.= 85°C. $[\alpha]_D$ = +115.1 (c=1.09; MeOH).

IR (KBr, cm^{-1}): 3240, 3060, 3020, 2950, 2910, 2860, 1655, 1495, 1465, 1435, 1410, 1060, 700. **^{1}H-NMR** ($CDCl_3$): 7.18 (m, 5H), 4.97 (d, H_A, J=15), 4.11 (d, H_B, J=15), 3.89-3.95 (t, 1H), 3.7-3.88 (m, 1H), 3.4-3.58 (m, 2H), 2.27-2.7 (m, 2H), 1.92-2.14 (m, 2H). **^{13}C-NMR** ($CDCl_3$): 176.1, 136.5, 128.6, 127.8, 127.4, 61.9, 58.5, 44.3, 30.4, 20.9. **MS** m/z (%): 205 (M^+ 10), 174 (85), 146 (8), 91 (100), 65 (9). Anal. calcd for $C_{12}H_{15}NO_2$ C: 70.21; H: 7.37; N: 6.83 Found C: 70.39; H: 7.57; N: 6.67.

General procedure for the preparation of compounds 3.

In a two-necked round bottom flask enough 60% NaH in oil was weighed to leave 1-1.5 eq of dry, oil free reagent. After washing 3 times with dry hexane and vacuum-drying it was suspended in anhydrous THF under an Ar atmosphere. The flask was fitted with an addition funnel and a reflux condenser and placed in an ice bath. The suspension was stirred magnetically and a solution of compound **2** and the corresponding alkyl halide in anhydrous THF was added at such a rate through the addition funnel, that the mixture began to froth and a slight reflux was observed. After completing the addition, the ice bath was removed to allow the mixture to reach room temperature. If the color of the mixture had not by then changed from gray to milky white, the reaction was refluxed for 1h or until no starting material showed on TLC. Upon reaction completion and after the mixture had reached room temperature it was placed again in an ice bath and quenched by the dropwise addition of a saturated NH_4Cl aqueous solution until gas evolution subsided and two clear phases could be observed. The mixture was transferred to a separatory funnel and worked up as usual. The crude oils obtained were suitable for the alkylation reactions.

(5S)-1-Benzyl-5-methoxymethyl-2-pyrrolidinone (3a).[13]

This compound was prepared employing **2** (12 g; 58.5 mmol) dissolved in 100 mL anhydrous THF, 3.51 g of 60% NaH in oil, suspended after oil removal in 50 mL anhydrous THF and methyl iodide (7.3 mL; 2 eq). Yield: 13.08 g (96%) of a yellow oil.

$[\alpha]_D$ = +65.3 (c=0.33; MeOH). **IR** (film, cm^{-1}): 3050, 3020, 2920, 1680, 1490, 1445, 1415, 1250, 1110, 700. **^{1}H-NMR** ($CDCl_3$): 7.18-7.37 (m, 5H), 4.85 (d, H_A, J=15), 4.18 (d, H_B, J=15), 3.59 (m, 1H), 3.38 (dd, 1H, J_1=10; J_2=4), 3.29 (dd, 1H, J_1=10; J_2=5), 3.1 (s, 3H), 2.26-2.62 (m, 2H), 1.74-2.15 (m, 2H). **^{13}C-NMR** ($CDCl_3$): 174.9, 136.5, 127.9, 127.3, 126.7, 72.9, 58.4, 56.5, 44.2, 29.7,

21.0. **MS** m/z (%): 219 (M^+ 3), 91 (100), 71 (25), 41 (27). Anal. calcd for $C_{13}H_{17}NO_2$ C: 71.19; H: 7.82; N: 6.39 Found C: 71.01; H: 7.49; N: 6.07.

(5S)-1-Benzyl-5-benzyloxymethyl-2-pyrrolidinone (3b).[14]

This compound was prepared employing **2** (13.08 g; 63.8 mmol) dissolved in 150 mL anhydrous THF, 60% NaH in oil (3.8 g), suspended after oil removal in 80 mL anhydrous THF and benzyl bromide (7.6 mL; 1 eq). Yield: 18.2 g (97%) of a light yellow oil. $[\alpha]_D$ = +14.8 (c=0.8; MeOH). **IR** (film, cm^{-1}): 3061, 3027, 2925, 2860, 1685, 1495, 1450, 1417, 1251, 1113, 701.

^{1}H-NMR ($CDCl_3$): 7.18-7.37 (m, 10H), 4.92 (d, H_A, J=15), 4.40 (s, 2H), 4.10 (d, H_B, J=15), 3.57-3.68 (m, H), 3.44 (ddd, 2H, J_1=14; J_2=10; J_3=4), 2.49-2.67 (m, 1H), 2.3-2.46 (m, 1H), 2.0-2.16 (m, 1H), 1.8-1.97 (m, 1H). **^{13}C-NMR** ($CDCl_3$): 175.5, 137.7, 136.9, 128.5, 128.4, 127.9, 127.7, 127.6, 127.3, 73.2, 70.8, 56.9, 44.7, 30.2, 21.7. **MS** m/z (%): 295 (M^+ 4), 174 (99), 91 (100), 65 (9). Anal. calcd for $C_{19}H_{21}NO_2$ C: 77.25; H: 7.17; N: 4.74 Found C: 77.56; H: 7.39; N: 4.98.

General procedure for the alkylation of compounds 3. Preparation of compounds 4 or 5.

A solution of 5 mmol of compound **3a** or **3b** in 5 mL THF was added via syringe to a vigorously stirred, freshly prepared solution of 5.5 mmol (1.1 eq) LDA (1.1 eq n-BuLi in hexane added to 0.85 mL (1.2 eq) diisopropylamine in 10 mL THF at 0°C; ½-1h stirring) in a septum provided 50 mL flask under an Ar atmosphere, cooled at -78°C in a dry ice/acetone bath. Upon addition of the first drops of substrate, the reaction mixture turned immediately yellow; it was stirred for a total of 2h at -78°C. Next, while keeping the mixture at this temperature, one molar equivalent of the alkyl halide was added dropwise via syringe whereby the deep color of the solution faded, usually very rapidly. The mixture was stirred for 1h, not allowing the bath temperature to rise above -20°C; it was quenched by addition of 10 mL of a saturated NH_4Cl aqueous solution at -78°C. The liquid in the still partially frozen mixture was decanted and the afterwards molten aqueous phase was extracted with ethyl ether (3×20 mL). The decanted THF and ether extracts were combined and worked up as usual. The eluent is indicated in those cases where the oily crude product was passed through a short silica gel column.

Compound 4a. Prepared with **3a** and methyl iodide. Yield: 0.7 g (60%) + product **6a.** Column elution: Hexane/Ethyl acetate 3:2. Prepared also with methyl bromide.[15] Crude yield: 1.08 g (92%). **IR** (film, cm^{-1}): 3063, 3031, 2930, 2874, 2831, 1686, 1605, 1496, 1454, 1425, 1115, 703. **^{1}H-NMR** ($CDCl_3$): 7.20-7.37 (m, 5H), 4.91 (d, H_A, J=15), 4.16 (d, H_B, J=15), 3.46-3.57 (m, 1H), 3.30-3.38 (m, 2H), 3.24 (s, 3H), 2.55-2.78 (m, 1H), 2.09 (ddd, 1H, J_1=13; J_2=9; J_3=3), 1.67 (dt, 1H, J_1=13; J_2=8.6), 1.22 (d, 3H, J=7). **^{13}C-NMR** ($CDCl_3$): 177.9, 137.2, 128.5, 127.9, 127.3, 73.6, 58.9, 54.9, 45.0, 35.4, 31.1, 16.7. **MS** m/z (%): 233 (M^+ 3.3), 188 (40), 91 (100), 45 (10). Anal. calcd for $C_{14}H_{19}NO_2$ C: 72.06; H: 8.21; N: 6.01 Found C: 71.71; H: 8.47; N: 6.32.

Product 6a. Yield: 0.33 g (28%). **IR** (film, cm^{-1}): 3060, 3030, 2971, 2928, 2875, 1684, 1456, 1417, 1116, 700. **^{1}H-NMR** ($CDCl_3$): 7.22-7.40 (m, 5H), 5.40 (q, 1H, J=7.2), 3.20-3.38 (m, 3H), 3.26 (s,3H), 1.59 (d, 3H, J=7.2), 1.18 (d, 3H, J=7.2). **MS** m/z (%): 247 (M^+ 10), 202 (53), 105 (100), 98 (77), 91 (16).

Compound 4b. Prepared with **3a** and ethyl iodide. Yield: 0.31 g (25%) + product **6b.** Column elution: Hexane/Ethyl acetate 1:1. Prepared also with ethyl bromide. Crude yield: 1.1 g (89%). **IR** (film, cm^{-1}): 3059, 3031, 2930, 2875, 2828, 1685, 1601, 1496, 1448, 1426, 1118, 703. **^{1}H-NMR** ($CDCl_3$): 7.20-7.37 (m, 5H), 4.94 (d, H_A, J=15), 4.14 (d, H_B, J=15), 3.46-3.58 (m, 1H), 3.31-3.40 (m, 2H), 3.26 (s, 3H), 2.55 (dq, 1H, J_1=9; J_2=4), 1.81-2.10 (m, 2H), 1.73 (dt, 1H, J_1=13; J_2=J_3=8.6), 1.31-1.53 (m, 1H), 0.96 (t, 3H, J=7.4). **^{13}C-NMR** ($CDCl_3$): 177.2, 137.2, 128.5, 127.9, 127.3, 73.8, 59.0, 55.1, 44.9, 42.0, 28.2, 24.5, 11.3. **MS** m/z (%): 247 (M^+ 1.2), 202 (33), 91 (100), 65 (12). Anal. calcd for $C_{15}H_{21}NO_2$ C: 72.83; H: 8.56; N: 5.67 Found C: 73.19; H: 8.85; N: 5.99.

Product 6b. Yield: 0.77 g (62%). **IR** (film, cm^{-1}): 3061, 3027, 2963, 2930, 2874, 1683, 1456, 1412, 1120, 701. **^{1}H-NMR** ($CDCl_3$): 7.2-7.45 (m, 5H), 5.05 (t, 1H), 3.22-3.35 (m, 2H), 3.25 (s, 3H), 1.85-2.15 (m, 4H), 1.26-1.63 (m, 2H), 0.99 (t, 3H), 0.93 (t, 3H). **^{13}C-NMR** ($CDCl_3$): 177.6, 139.6, 128.5, 127.9, 127.4, 74.7, 58.6, 58.1, 55.4, 42.1, 29.6, 25.5, 24.3, 11.4. **MS** m/z (%): 275 (M^+ 18), 246 (53), 230 (98), 119 (100), 112 (95), 91 (98).

Compound 4c. Prepared with **3a** and benzyl bromide. Yield: 1.16 g (75%) of a crystalline compound after recrystallization from ethyl ether; m.p. = 67°C. **IR** ($CHCl_3$, cm^{-1}): 3064, 3031, 2928, 2873, 2830, 1674, 1601, 1496, 1450, 1248, 1121. **^{1}H-NMR** ($CDCl_3$): 7.12-7.36 (m, 10H), 4.93 (d, H_A, J=15), 4.14 (d, H_B, J=15), 3.32-4.46 (m, 1H), 3.16-3.32 (m, 3H), 3.21 (s, 3H), 2.94 (m, 1H), 2.70 (dd, H, J_1=13.5; J_2=9.3) 1.70-1.96 (m, 2H). **^{13}C-NMR** ($CDCl_3$): δ 176.3, 139.3, 136.9, 129.2, 128.5, 128.4, 127.9, 127.3, 126.2, 73.5, 58.9, 54.9, 44.9, 42.4, 37.1, 27.9. **MS** m/z (%): 309 (M^+ 0.5), 264 (14), 91 (100), 65 (10), 45 (18). Anal. calcd for $C_{20}H_{23}NO_2$ C: 77.63; H: 7.50; N: 4.53 Found C: 77.39; H: 7.21; N: 4.25.

Compound 4d. Prepared with **3a** and allyl bromide. Crude yield: 1.24 g (95%). **IR** (film, cm^{-1}): 3069, 3028, 2924, 2829, 1686, 1602, 1496, 1435, 1119, 702. **^{1}H-NMR** ($CDCl_3$): 7.21-7.35 (m, 5H), 5.71-5.85 (m, 1H), 5.02-5.13 (m, 2H), 4.93 (d, H_A, J=15), 4.15 (d, H_B, J=15), 3.46-3.55 (m, 1H), 3.28-3.39 (m, 2H), 3.25 (s, 3H), 2.55-2.77 (m, 2H), 2.11-2.25 (m, 1H) 1.99 (ddd, 1H, J_1=13; J_2=9; J_3=3), 1.78 (dt, 1H, J_1=13; J_2=J_3=8.6). **^{13}C-NMR** ($CDCl_3$): 176.3, 136.9, 135.4, 128.4, 127.9, 127.2, 116.8, 73.6, 58.9, 55.0, 44.8, 40.2, 35.7, 27.9. **MS** m/z (%): 259 (M^+ 4), 214 (59), 91 (100), 65 (8). Anal. calcd for $C_{16}H_{21}NO_2$ C: 74.09; H: 8.17; N: 5.40 Found C: 74.45; H: 8.54; N: 5.18.

Compound 4e. Prepared with **3a** and prenyl bromide. Crude yield: 1.38 g (96%). **IR** (film, cm^{-1}): 3061, 3028, 2923, 2880, 1688, 1604, 1496, 1443, 1381, 1357, 1120, 703. **^{1}H-NMR** ($CDCl_3$): 7.21-7.35 (m, 5H), 5.10 (t, 1H), 4.95 (d, H_A, J=15), 4.13 (d, H_B, J=15), 3.44-3.56 (m, 1H), 3.29-3.40 (m, 2H), 3.25 (s, 3H), 2.6-2.72 (m, 1H), 2.44-2.57 (bm, 1H), 2.12-2.25 (m, 1H), 1.92-2.01 (m, 1H), 1.70-1.80 (m, 1H), 1.69 (bs, 3H), 1.63 (bs, 3H). **^{13}C-NMR** ($CDCl_3$): 176.7, 137.1, 133.7, 128.4, 127.9, 127.2, 120.8, 73.7, 58.9, 55.0, 44.8, 40.8, 29.6, 27.8, 25.7, 17.8. **MS** m/z (%): 287 (M^+ 3), 242 (50), 91 (100), 65 (11). Anal. calcd for $C_{18}H_{25}NO_2$ C: 75.21; H: 8.77; N: 4.88 Found C: 75.02; H: 8.44; N: 4.51.

Compound 4f. Prepared with **3a** and propargyl bromide. Column elution: Hexane/Ethyl acetate 7:3. Yield: 0.77 g (60%). **IR** (film, cm^{-1}): 3290, 3240, 3063, 3030, 2925, 2118, 1683, 1605, 1496, 1452, 1120, 704. **^{1}H-NMR** ($CDCl_3$): 7.2-7.4 (m, 5H), 4.97 (d, H_A, J=15), 4.12 (d, H_B, J=15), 3.51-3.6 (m, H), 3.4 (dd, 1H, J_1=9.9; J_2=3.7), 3.32 (dd, 1H, J_1=9.9; J_2=4.4), 3.25 (s, 3H), 2.8-2.9 (m, 1H), 2.45-2.62 (m, 2H), 1.99-2.14 (m, 2H), 1.95 (t, 1H, J=2.6). **^{13}C-NMR** ($CDCl_3$): 175.2, 136.8, 128.5, 128.0, 127.4, 81.5, 73.4, 69.9, 59.1, 55.1, 45.0, 39.7, 27.7, 20.6. **MS** m/z (%): 257 (M^+ 2.7), 212 (100), 91 (81), 65 (10). Anal. calcd for $C_{16}H_{19}NO_2$ C: 74.67; H: 7.45; N: 5.45 Found C: 74.31; H: 7.18; N: 5.81.

Compound 5a. Prepared with **3b** and methyl iodide. Column elution: Hexane/Ethyl acetate 3:1. Yield: 0.69 g (45%). **IR** (film, cm^{-1}): 3023, 2930, 1687, 1453, 1359, 1250, 1113, 699. **^{1}H-NMR** ($CDCl_3$): 7.15-7.4 (m, 10H), 4.89 (d, H_A, J=15), 4.44 (s, 2H), 4.08 (d, H_B, J=15), 3.49-3.6 (m, 1H), 3.32-3.47 (m, 2H), 2.69 (m, 1H), 2.12 (ddd, 1H, J_1=12.8; J_2= 8.8; J_3=2.6), 1.67 (dt, 1H, J_1= 12.8; J_2=8.8), 1.21 (d, 3H, J=7.2). **^{13}C-NMR** ($CDCl_3$): 177.9, 137.8, 137.1, 128.7, 128.5, 128.4, 127.9, 127.7, 127.5, 127.3, 73.2, 70.7, 54.9, 44.9, 35.5, 31.2, 16.8. **MS** m/z (%): 309 (M^+ 15), 188 (100), 91 (93), 65 (6). Anal. calcd for $C_{20}H_{23}NO_2$ C: 77.63; H: 7.50; N: 4.53 Found C: 77.14; H: 7.85; N: 4.97.

Compound 5b. Prepared with **3b** and ethyl bromide. Column elution: Hexane/Ethyl acetate 3:1. Yield: 0.89 g (55%).

IR (film, cm^{-1}): 3029, 2926, 2865, 1688, 1453, 1266, 1124, 697. **^{1}H-NMR** ($CDCl_3$): 7.14-7.39 (m, 10H), 4.93 (d, H_A, J=15), 4.43 (d, H_A, J=12), 4.39 (d, H_B, J=12), 4.06 (d, H_B, J=15), 3.49-3.58 (m, 1H), 3.35-3.48 (m, 2H), 2.57 (dq, 1H, J=9; J=4.5), 2.05 (ddd, 1H, J_1=13; J_2=9; J_3=3), 1.84-1.98 (m, 1H), 1.72 (dt, 1H, J_1=13; J_2=J_3=9), 1.28-1.53 (m, 1H), 0.95 (t, 3H, J=7.5). **^{13}C-NMR** ($CDCl_3$): 177.1, 137.8, 137.1, 128.5, 127.9, 127.7, 127.5, 127.3, 73.2, 70.9, 55.1, 44.80, 42.1, 28.3, 24.5, 11.3. **MS** m/z (%): 323 (M^+ 15), 202 (100), 91 (93), 65 (6). Anal. calcd for $C_{21}H_{25}NO_2$ C: 77.97; H: 7.80; N: 4.33 Found C: 78.34; H: 8.05; N: 4.61.

Compound 5c. Prepared with **3b** and benzyl bromide. Column elution: Hexane/Ethyl acetate 3:1. Yield: 1.22 g (63%). **IR** (film, cm^{-1}): 3062, 3029, 2922, 2860, 1693, 1453, 1253, 1114, 739, 700. **^{1}H-NMR** ($CDCl_3$): 7.07-7.33 (m, 15H), 4.93 (d, H_A, J=15), 4.38 (d, H_A, J=12), 4.35 (d, H_B, J=12), 4.06 (d, H_B, J=15), 3.37-3.43 (m, 2H), 3.29-3.36 (m, 1H), 3.24 (dd, H_A, J_{AX}=14; J_{AM}=4), 2.97 (dq, H_M, J_{MX}=9; J_{AM}=4), 2.71 (dd, H_X, J_{AX}=14; J_{MX}=9), 1.908 (ddd, 1H, J_1=13; J_2=9; J_3=3), 1.79 (dt, 1H, J_1=13; J_2=J_3=9). **^{13}C-NMR** ($CDCl_3$): 176.3, 139.3, 137.7, 136.8, 129.2, 129.0, 128.4, 127.9, 127.7, 127.5, 127.3, 127.2, 126.2, 73.2, 70.6, 55.0, 44.9, 42.5, 37.1, 28.1. **MS** m/z (%): 385 (M^+ 40), 264 (100), 91 (94), 65 (4). Anal. calcd for $C_{26}H_{27}NO_2$ C: 81.00; H: 7.06; N: 3.64 Found C: 80.72; H: 6.84; N: 3.33.

Compound 5d. Prepared with **3b** and allyl bromide. Column elution: Hexane/Ethyl acetate 3:1. Yield: 0.67 g (40%). **IR** (film, cm^{-1}): 3030, 2922, 2861, 1702, 1464, 1253, 1113, 915, 699. **^{1}H-NMR** ($CDCl_3$): 7.16-7.38 (m, 10H), 5.73-5.82 (m, 1H), 5.02-5.12 (m, 2H), 4.92 (d, H_A, J=15), 4.42 (d, H_A, J=12), 4.38 (d, H_B, J=12), 4.07 (d, H_B, J=15), 3.49-3.55 (m, H), 3.35-3.47 (m, 2H), 2.74 (dq, 1H, J=9; J=4), 2.58-2.65 (m, 1H), 2.14-2.22 (m, 1H), 2.02 (ddd, 1H, J_1=13; J_2=9; J_3=3), 1.78 (dt, 1H, J_1=13; J_2=J_3=9). **^{13}C-NMR** ($CDCl_3$): 176.4, 137.7, 136.9, 135.8, 128.5, 128.4, 127.9, 127.7, 127.5, 127.3, 116.8, 73.2, 70.7, 55.1, 44.8, 40.8, 40.3, 35.7, 28.1. **MS** m/z (%): 335 (M^+ 50), 279 (48), 214 (99), 167 (68), 149 (99), 91 (100), 57 (24). Anal. calcd for $C_{22}H_{25}NO_2$ C: 78.76; H: 7.52; N: 4.18 Found C: 78.98; H: 7.78; N: 3.89.

Compound 5e. Prepared with **3b** and prenyl bromide. Column elution: Hexane/Ethyl acetate 3:1. Yield: 0.89 g (49%). **IR** (film, cm^{-1}): 3087, 3063, 3030, 2918, 2858, 1686, 1605, 1496, 1453, 1254, 1113, 738, 700. **^{1}H-NMR** ($CDCl_3$): 7.15-7.38 (m, 10H), 5.05-5.13 (m, 1H), 4.94 (d, H_A, J=15), 4.40 (s, 2H), 4.05 (d, H_B, J=15), 3.45-3.60 (m, 1H), 3.34-3.42 (m, 2H), 2.70 (dq, 1H, J_1=8.8; J_2=4.2), 2.44-2.62 (m, 1H), 2.11-2.26 (m, 1H), 2.00 (ddd, 1H, J_1=13; J_2=9.0; J_3=2.8), 1.74 (dt, 1H, J_1=13; J_2=8.6), 1.69 (s, 3H), 1.62 (s, 3H). **^{13}C-NMR** ($CDCl_3$): 176.82, 137.79, 137.06, 133.80, 128.44, 127.95, 127.70, 127.53, 127.23, 120.85, 73.21, 70.92, 55.11, 44.83, 40.94, 29.65, 27.95t, 25.78, 17.89. **MS** m/z (%): 363 (M^+ 23), 242 (98), 186 (25), 91(100). Anal. calcd for $C_{24}H_{29}NO_2$ C: 79.29; H: 8.05; N: 3.86 Found C: 79.70; H: 8.42; N: 3.47.

Compound 5f. Prepared with **3b** and propargyl bromide. Column elution: Hexane/Ethyl acetate 3:1. Yield: 0.81 g (53%). **IR** (film, cm^{-1}): 3289, 3237, 3031, 2918, 2857, 2118, 1683, 1452, 1605, 1255, 1115, 753, 704. **^{1}H-NMR** ($CDCl_3$): 7.17-7.39 (m, 10H), 4.96 (d, H_A, J=15), 4.41 (s, 2H), 4.03 (d, H_B, J=15), 3.51-3.60 (m, 1H), 3.36-3.49 (m, 2H), 2.80-2.94 (m, 1H), 2.51-2.60 (m, 2H), 2.02-2.21 (m, 2H), 1.88 (t, 1H, J=2.6). **^{13}C-NMR** ($CDCl_3$): 175.2, 137.7, 136.7, 128.4, 128.0, 127.7, 127.5, 127.3, 81.4, 73.2, 70.4, 69.8, 55.1, 44.9, 39.8, 27.8, 20.6. **MS** m/z (%): 333 (M^+ 47), 212 (98), 91 (100), 65 (8). Anal. calcd for $C_{22}H_{23}NO_2$ C: 79.24; H: 6.96; N: 4.20 Found C: 78.86; H: 7.24; N: 3.93.

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References and Notes

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16. This is paper N° 1422 from the Instituto de Química UNAM, México.

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