A Synthesis of N–Substituted β–Alanines: Michael Addition of Amines to Trimethylsilyl Acrylate

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Abstract

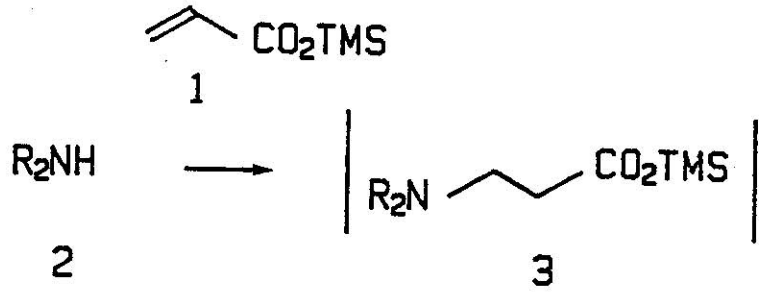
The Michael addition of primary and secondary amines to trimethylsilyl acrylate afforded β–(alkylamino)– and β–(dialkylamino)propionic acids, respectively, in good yield.

In connection with the production of haptens of various pharmaceuticals and drugs of abuse, we required a convenient procedure for the modification of primary and secondary amines in order to attach a carboxylic acid functional group suitable for conjugation to bovine serum albumin. Although this type of modification[3,4] often involves the treatment of amines with succinic anhydride or methyl succinyl chloride, these procedures are not always compatible with functionality elsewhere in the substrate and in some cases, afford antibodies with reduced specificity in comparison with antibodies produced from β–alanine derivatives. We report that the reactions of trimethylsilyl acrylate (**1**) with various amines **2** provide convenient access to N–substituted β–alanines **4**.

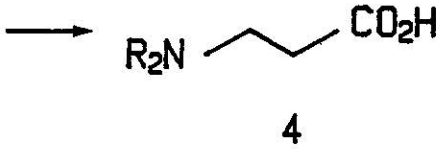
Although the Michael addition of amines **2** to acrylonitrile,[5] methyl acrylate, or ethyl acrylate[3,4] was known, the use of these methods for the synthesis of N–substituted β–alanines **4** required basic or acidic hydrolysis in order to liberate the free carboxylic acid. Procedures that avoided this hydrolysis step employed the addition of secondary N–(trimethylsilyl)amines to β–propiolactone[6,7] to give β–(dialkylamino)propionic acids, but this route required the synthesis of N–(trimethylsilyl)amines and the use of the carcinogenic β–propiolactone. Although the direct addition of amines to acrylic acid failed,[5] the addition of amines to trimethylsilyl acrylate[8] (**1**) provided the intermediate β–alanine trimethylsilyl esters **3** that were readily solvolyzed in methanol to N–substituted β–alanines **4** in good yield (Tables 1-2).

This new approach was particularly useful in the synthesis of new haptens for cocaine and acetylcodeine. Norcocaine[9] (**2h**), for example, was treated with 1.2 equivalents of trimethylsilyl acrylate[8] (**1**) to afford the trimethylsilyl ester of norcocaine–8–propionic acid (**3h**) which was directly hydrolyzed to **4h**. As shown in Scheme 2, conversion[10] of the 6–acetate derivative **6** of codeine (**5**) to the vinyl urethane **7** and selective hydrolysis afforded the N–demethylated derivative **2k**. Subsequent treatment of **2k** with **1** and hydrolysis furnished the acid **4k** that was saponified to afford **8**. As indicated in Table 1, the process accommodated a variety of primary and secondary amines having pK_b values in the range of 3 to 4 and accommodated the synthesis of haptens of a variety of bioactive compounds.

Scheme 1.

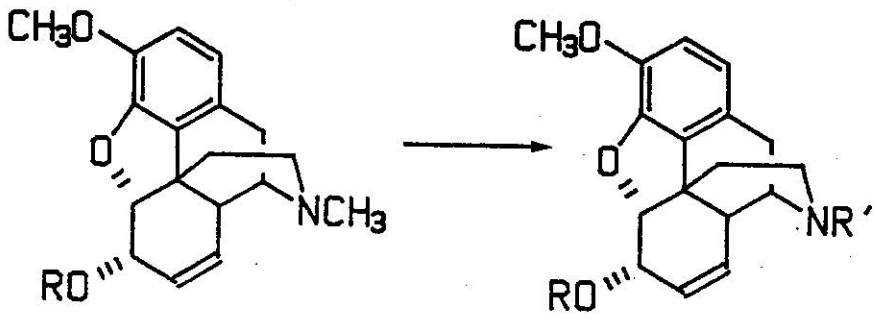


CH_3OH, 25°, 4 h



Scheme 2.

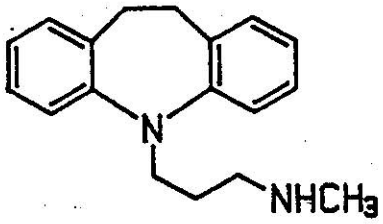
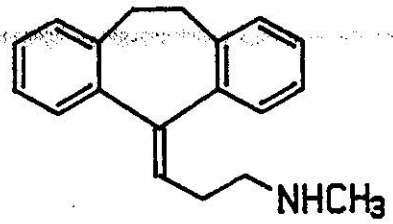
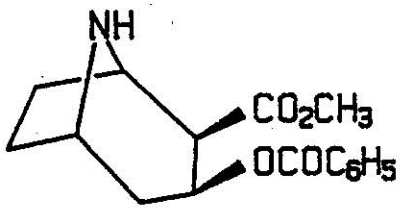
1. CH_2=CHOCOCl
2. HOAc, HCl; Na_2CO_3
3. CH_2=$CHCO_2TMS$; MeOH
4. KOH; HCl

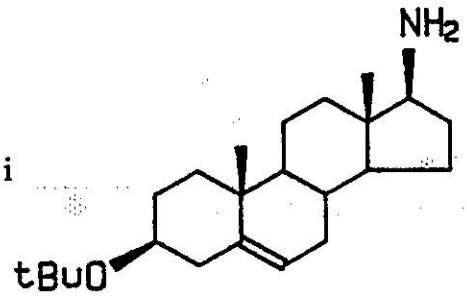
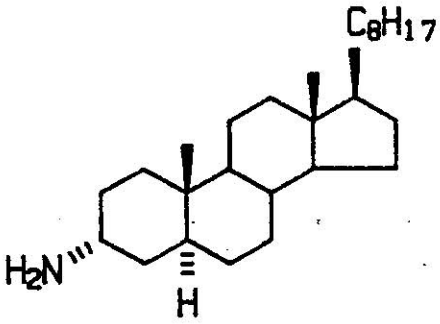
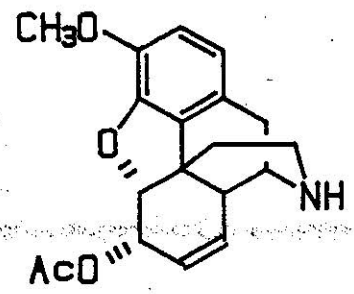
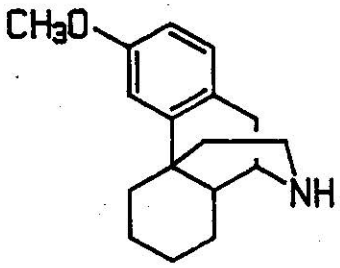
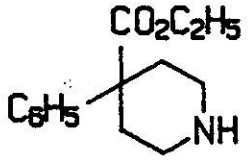


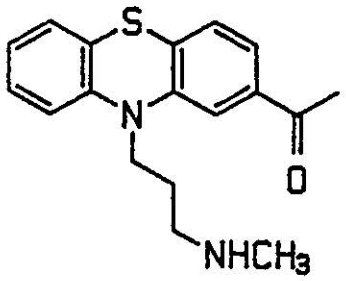
	R
5	H
6	Ac

	R	R´
7	Ac	CO_2CH=CH_2
2k	Ac	H
4k	Ac	$CH_2CH_2CO_2H$
8	H	$CH_2CH_2CO_2H$

Table 1. The Addition of Amines 2 to Trimethylsilyl Acrylate (1).

	Amine 2	Ratio of 1 to 2	Time (hr)	Temperature	Yield of 4 (%)
a	$(CH_3CH_2)_2NH$	1.2	17	25	99[a]
b	piperidine	1.2	17	25	99[a]
c	$C_6H_5CH_2NH_2$	1.0	9	50	37[a]
d	$C_6H_5CH_2CH(CH_3)NH_2$	1.2	44	50	53
e	$C_6H_5CH_2CH(CH_3)NHCH_3$	1.2	17	50	83
f		1.2	17	50	82[b,c]
g		1.2	17	50	95[b,c]
h		1.2	17	50	88

i		1.1	40	65	83
j		1.1	40	65	82
k[d]		1.2	48	22	92
l		1.2	25	60	59
m		2.0	24	20	76

n		2.0	48	20	55

a, Gresham, T. L.; Jansen, J. E.; Shaver, F. W.; Bankert, R. A.; Fiedorek, F. T. *J. Am. Chem. Soc.* 1951, 73, 3168; b, Hubbard, J. W.; Midha, K. K.; McGilveray, I. J.; Cooper, J. K. *J. Pharm. Sci.* 1978, 67, 1563; c, Hubbard, J. W.; Midha, K. K.; Cooper, J. K.; Charette, C. *J. Pharm. Sci.* 1978, 67, 1571; d, Olofson, R. A.; Martz, J. T.; Senet, J. P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* 1984, 49, 2061.

Table 2. Physical and Spectral Data for β–Alanine Derivatives **4**. [a]

	mp	IR (cm^{-1})	^1H NMR Data	^{13}C NMR Data
4d	181–182.5°	1580	1.27 (d, J = 6.4 Hz, 3), 2.57 (t, J = 5.5 Hz, 2), 2.78 (dd, J = 15.8 Hz, J = 7.8 Hz, 1), 3.0–3.39 (m, 4), 7.16–7.33 (m, 5), 7.0–8.0 (br s, 2)	16.38, 32.32, 40.24, 42.37, 55.30, 127.52, 129.31, 129.88, 137.15, 177.56
4e	oil	1710, 1600	1.1 (d, J = 6.4 Hz, 3), 2.56 (s, 3), 2.44–2.62 (m, 3), 3.05–3.45 (m, 4), 7.15–7.35 (m, 5), 12.58 (br s, 1)	13.16, 31.59, 35.36, 38.34, 50.07 61.34, 127.21, 129.16, 129.72, 138.16, 175.70
4f	105–107° (dp)	1710, 1590	1.78–1.95 (m, 2), 2.31 (s, 3), 2.30–2.40 (m, 2), 2.70–2.82 (m, 4), 3.12 (s, 4), 3.73 (t, J = 5.5 Hz, 2), 6.85–7.12 (m, 8), 11.72 (br s, 1)	23.31, 31.08, 32.36, 40.04, 48.14, 53.03, 54.37, 120.23, 123.42, 127.09, 130.54, 134.70, 148.25, 175.25
4g	121–123° (dp)	1705, 1600	2.37 (s, 3), 2.35–2.50 (m, 4), 2.70–2.98 (m, 6), 3.17–3.40 (m, 2), 5.76 (t, J = 7.0 Hz, 1), 6.97–7.24 (m, 8), 9.70 (br s, 1)	24.70, 30.38, 31.77, 33.54, 39.33, 52.54, 55.25, 125.75, 126.17, 126.26, 127.56, 127.85, 128.03, 128.42, 128.67, 130.26. 137.18, 139.44, 139.52, 140.57, 146.13, 174.80
4h	oil	1735, 1720, 1625	1.86–2.30 (m, 5), 2.40–2.60 (m, 3) 2.67 (t, J = 6.4 Hz, 2), 3.16–3.24 (m, 1), 3.60 (br s, 1), 3.74 (s, 4), 5.30–5.42 (m, 1), 7.40–7.60 (m, 3) 7.95–8.05 (m, 2), 12.70 (br s, 1)	25.19, 26.10, 31.58, 35.40, 48.63, 50.17, 52.41, 59.04, 63.27, 66.24, 128.96, 128.99, 130.16, 133.83, 166.52, 171.05, 173.87
4i	166–167°	1585	0.83 (s, 3), 0.99 (s, 3), 1.18 (s, 9), 2.40–2.53 (m, 2), 2.82–3.02 (m, 3), 3.18–3.35 (m, 2), 5.27–5.32 (m, 1), 11.57 (br s, 1, OH)	18.62, 19.47, 21.04, 25.96, 26.48, 28.7, 31.25, 31.64, 32.06, 32.3, 32.47, 36.9, 38.17, 42.32, 44.11, 44.51, 39.52, 50.2, 60.6, 71.76, 73.84, 121.34, 142.27, 177.82

4j	182–184°	1580	0.62 (s, 3), 0.78 (s, 3), 0.84 (d, J = 7.5 Hz, 6), 0.87 (d, J = 7.5 Hz, 3), 2.50–2.60 (m, 2), 3.0–3.1 (m, 2), 3.2–3.3 (m, 1), 11.12 (br s, 1)	11.50, 12.25, 18.86, 21.09, 22.86, 23.14, 23.53, 24.19, 28.30, 28.57, 30.12, 31.94, 32.0, 32.34, 35.67, 36.13, 36.5, 39.6, 39.8, 40.2, 42.9, 43.0, 53.8, 54.0, 56.8, 177.8
4k	178–181°	1725, 1705, 1595	1.90–2.02 (m, 1), 2.15 (s, 3), 2.18–2.35 (m, 1), 2.56–2.75 (m, 4), 2.96–3.24 (m, 5), 3.85 (s, 3), 3.85–3.96 (m, 1), 5.10 (d, J = 6.7 Hz, 1) 5.14–5.22 (m, 1), 5.43 (d, J = 8.0 Hz, 1), 5.68 (d, J = 8.0 Hz, 1), 6.60 (d, J = 6.5 Hz, 1) 6.72 (d, J = 6.5 Hz, 1), 10.30 (br s, 1)	20.98, 22.48, 31.28, 33.74, 38.50, 42.28, 44.82, 51.16, 56.95, 58.10, 67.98, 87.77, 114.98, 120.17, 128.05, 129.90, 130.16, 133.74, 143.27 147.28, 171.11, 175.97
4l	oil	1710, 1600	1.03–1.59 (m, 7), 1.64 (d, J = 11.6 Hz, 1), 1.97 (dt, J = 18.8 Hz, J = 5.8 Hz, 1), 2.13 (dt, J = 11.6 Hz, J = 3.0 Hz, 1), 2.36 (d, J = 13.0 Hz, 1), 2.44 (t, J = 7.2 Hz, 2), 3.02 (s, 2), 3.11 (d, J = 11.6 Hz, 1), 3.24 (t, J = 7.2 Hz, 2), 3.47 (s, 1), 3.78 (s, 3), 6.76 (dd, J = 8.0 Hz, J = 2.4 Hz, 1), 6.81 (d, J = 2.4 Hz, 1), 7.07 (d, J = 8.0 Hz, 1), 9.34 (br s, 1)	21.72, 24.52, 25.80, 25.99, 30.50, 34.54, 36.73, 39.40, 42.13, 44.82, 50.65, 55.12, 56.99, 111.0, 111.60, 126.19, 128.75, 139.48, 158.72, 175.08
4m	143–145°	1705, 1605	1.17 (t, J = 7.1 Hz, 3), 2.10–2.30 (m, 2), 2.50–2.70 (m, 6), 2.95 (t, J = 6.0 Hz, 2), 3.15–3.30 (m, 2), 4.14 (q, J = 7.1 Hz, 2), 7.20–7.40 (m, 5), 9.90 (br s, 1)	14.16, 31.86, 48.50, 50.46, 54.12, 61.66, 126.18, 127.96, 129.26, 141.66, 174.11, 176.21
4n	98–100°	1675	1.96–2.12 (m, 2), 2.34 (s, 3), 2.40 (t, J = 6.8 Hz, 2), 2.56 (s, 3), 2.76 t, J = 6.8 Hz, 4), 3.96 (t, J = 6.8 Hz, 2), 6.87–7.50 (m, 7)	22.75, 26.43, 30.68, 40.30, 44.60, 52.89, 53.44, 114.17, 116.11, 123.33, 123.53, 124.40, 127.34, 127.74, 127.99, 132.80, 136.43, 144.25, 145.34, 174.96, 197.77

a, all compounds exhibited satisfactory high resolution mass spectral data.

General Procedure for the Addition of Amines 2 to Trimethylsilyl Acrylate (1) and Methanolysis of β–Alanine Trimethylsilyl Esters 3 to β–Alanines 4. To a solution of 0.3 mmol of amine 2 in 0.6 mL of chloroform (or $CDCl_3$ in cases where the reaction was monitored by ^1H NMR) was added 0.35 mmol (1.2 eq) of trimethylsilyl acrylate[8] (1) (or the amount indicated in Table 1), and the mixture was heated for the time period and temperature specified in Table 1. Disappearance of starting amine was monitored by tlc or ^1H NMR. After the addition was complete, 1 mL of methanol was added. The resulting clear solution was stored at 22°C for 4 h and concentrated to afford crude 4. Purification of the β–alanine derivatives 4 by silica gel chromatography using 4:1 chloroform–methanol afforded the N–substituted β–alanines 4.

(5α,6α)–6–Acetoxy–7,8–didehydro–4,5–epoxy–3–methoxy–17–methylmorphinan (6). To a solution of 317 mg (1 mmol) of codeine monohydrate (5) in 5 mL of anhydrous pyridine was added 314 mg (285 μL, 4 mmol) of acetyl chloride. The solution was stirred under a nitrogen atmosphere for 5 h at 25°C and 17h at 50°C. The pyridine was evaporated under reduced pressure, and semisolid residue was dissolved in 3 mL of water. To this solution was added a solution of 1 g potassium carbonate in 3 mL of water, and an oily product separated. The mixture was extracted with ether and dried to afford 326 mg (91%) of 6 as a yellow solid: mp 132–133°C (lit.[11] 133.5°C); IR ($CDCl_3$) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (s, 3, $COCH_3$), 2.44 (s, 3, NCH_3), 2.70–2.80 (m, 1, H at C–14), 3.05 (d, J = 19 Hz, 1, C–10β H), 3.33–4.02 (m, 1, C–9 H), 3.84 (s, 3, OCH_3), 5.70 (d, J = 7 Hz, 1, C–5 H), 5.15–5.23 (m, 1, C–6 H), 5.44 (d, J = 8 Hz, 1, C–8 H), 5.63 (d, J = 8 Hz, 1; C–7 H), 6.53 (d, J = 6.5 Hz, 1, C–2 H), 6.67 (d, J = 6.5 Hz, 1, C–1 H); ^{13}C NMR ($CDCl_3$) δ 20.50 (C–15), 21.09 ($\underline{CH_3}C{=}O$), 35.68 (C–10), 41.02 (C–14), 42.68 (C–13), 43.36 (NCH_3), 46.91 (C–16), 56.86 (OCH_3), 59.31 (C–9), 68.63 (C–6), 88.51 (C–5), 114.17 (C–8), 119.63 (C–7), 127.54 (C–11), 128.90 (C–1), 131.13 (C–12), 130.20 (C–2), 142.32 (C–3), 146.60 (C–4), 170.94 (C=O).

Vinyl (5α,6α)–6–Acetoxy–7,8–didehydro–4,5–epoxy–3–methoxy–17–morphinan–carboxylate (7). A solution of 320 mg (0.94 mmol) of **6** and 501 mg (400 μL, 4.70 mmol) of vinyl chloroformate in 2 mL of anhydrous dichloromethane was stirred under a nitrogen atmosphere for 48 h at 25°C. The dark brown mixture was evaporated to afford a semisolid residue which was chromatographed on silica gel using 1:1:1 ethyl acetate–hexane–chloroform to afford 305 mg (82%) of **7**: dp 178–181°C; IR ($CDCl_3$) 1725, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.88–2.0 (m, 2, C–15 H), 2.16 (s, 3, $COCH_3$), 3.87 (s, 3, OCH_3), 4.04–4.18 (m, 1, one H at C–16), 4.50 (t, J = 6 Hz, 1, C–9 H), 4.78–5.0 (m, 2, $CH=C\underline{H}_2$), 5.08 (d, J = 7 Hz, C–5 H), 5.12–5.20 (m, 1, C–6 H), 5.47 (d, J = 8 Hz, 1, C–8 H), 5.70 (d, J = 8 Hz, 1, C–7 H), 6.56 (d, J = 6.5 Hz, 1, C–2 H), 6.70 (d, J = 6.5 Hz, 1, C–1 H), 7.20–7.30 (m, 1, vinylic H); ^{13}C NMR ($CDCl_3$) δ 20.98 $CO\underline{C}H_3$), 29.59 (C–10), 35.20 (C–15), 38.39 (C–14), 39.48 (C–16), 43.20 (C–13), 50.94 (C–9), 56.85 (H_3CO), 67.92 (C–6), 88.04 (C–5), 96.14 (C_β–vinyl), 114.75 (C–2), 120.23 (C–1), 125.79 (C–11), 128.51 (C–8), 129.81 (C–12), 130.03 (C–7), 143.02 (C–3, $\underline{C}H=CH_2$), 146.50 (C–4), 153.0 (C=O urethane), 171.14 (C=O acetyl); exact mass spectrum calcd for $C_{22}H_{23}NO_6$ 397.1526, found 397.1525.

(5α,6α)–6–Acetoxy–7,8–didehydro–4,5–epoxy–3–methoxymorphinan (17–Norcodeine Acetate) (2k). A solution of 130 mg (0.3 mmol) of **7** in 2 mL of glacial acetic acid containing two drops of concentrated hydrochloric acid was stirred for 22 h at 22°C. The solvents were evaporated under reduced pressure (bath temperature below 50°C), and 3 mL of water was added to the white, crystalline residue. The mixture was filtered to remove insoluble material and the clear filtrate was treated with an excess of solid sodium bicarbonate, causing separation of oily product which was extracted into ether. The combined extracts were dried, filtered and evaporated to afford a crude product. This material was chromatographed on silica gel using 4:1 chloroform–methanol to afford 44 mg (86%) of **2k** as a colorless oil: IR (TF) 3310, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.84–1.96 (m, 2, C–15 H), 2.15 (s, 3, $COCH_3$), 2.18–2.36 (m, 2, NH and C–10α H), 2.60–2.74 (m, 1, C–10β H), 2.80–3.02 (m, 3, C–16, C–14 H), 3.61–3.72 (m, 1, C–9

H), 3.87 (s, 3, OCH_3), 5.05 (d, J = 7 Hz, 1, C–5 H), 5.14–5.23 (m, 1, C–6 H), 5.42 (d, J = 8.2 Hz, 1, C–8 H), 5.65 (d, J = 8.2 Hz, 1, C–7 H), 6.57 (d, J = 6.8 Hz, 1, C–2 H), 6.68 (d, J = 6.8 Hz, 1, C–1 H); ^{13}C NMR ($CDCl_3$) δ 21.10 ($CO\underline{C}H_3$), 31.50 (C–10), 36.30 (C–15), 38.78 (C–14), 41.47 (C–16), 43.95 (C–13), 52.45 C–9), 56.88 (OCH_3), 68.49 (C–6), 89.02 (C–5), 114.20 (C–2), 119.68 (C–1), 127.63 (C–11), 129.04 (C–8), 130.00 (C–7), 131.02 (C–12), 142.52 (C–3), 147.20 (C - 4), 171.27 (C=O); exact mass spectrum calcd for $C_{19}H_{21}NO_4$ 327.1471, found 327.1472.

(5α,6α)–7,8–Didehydro–6–hydroxy–4,5–epoxy–3–methoxy–17–morphinanpropionic Acid (8). A solution of 71.2 mg (0.18 mmol) of **4k** in 1 mL of water and 19.3 mg (0.344 mmol) of potassium hydroxide was stirred at 22°C for 48 h. To this solution was added 345 μL of 1 N hydrochloric acid. The solution was evaporated to dryness under reduced pressure (bath temperature below 50°C) and finally dried under high vacuum to afford white crystals from which the product was extracted with three 5 mL portions of chloroform. Evaporation of the solvent afforded a crude product, which was chromatographed on silica gel using 3:1 chloroform–methanol to afford 36.8 mg (57%) of **8**: dp 110°C; IR ($CDCl_3$) 3500, 3100–2300 (NH+), 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.95–2.07 (m, 1, C–15β H), 2.13–2.32 (m, 1, C–15α H), 2.56–2.77 (m, 4, C–10α H, CH_2CO_2), 2.88–3.16 (m, 5, C–16 H, C–10β H, $NC\underline{H}_2CH_2$), 3.75–3.83 (m, 1, C–9 H), 3.84 (s, 3, OCH_3), 4.18–4.26 (m, 1, C–6 H), 4.95 (d, J = 6 Hz, 1, C–5 H), 5.28 (d, J = 8 Hz, 1, C–8 H), 5.78 (d, J = 8 Hz, 1, C–7 H), 6.62 (d, J = 6.8 Hz, 1, C–2 H), 6.70 (d, J = 6.8 Hz, 1, C–1 H); ^{13}C NMR ($CDCl_3$) δ 22.69 ($\underline{C}H_2CO_2$), 30.07 (C–10), 34.53 (C–15), 39.72 (C–14), 42.95 (C–16), 44.08 (C–13), 51.05 ($N\underline{C}H_2CH_2$), 56.60 (OCH_3), 58.14 (C–9), 66.38 (C–6), 90.98 (C–5), 114.01 (C–2), 120.47 (C–1), 126.55 (C–8), 127.98 (C–11), 131.02 (C–12), 135.24 (C–7), 143.38 (C–3), 147.30 (C–4), 174.49 (C=O); exact mass spectrum calcd for $C_{20}H_{23}NO_5$ 357.1576, found 357.1578.

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References

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