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Efficient enantioselective synthesis of 2-substituted thiomorpholin-3-ones

Nicolas Franceschini, Sophie Da Nascimento, Pascal Sonnet and Dominique Guillaume*

Laboratoire de Chimie Thérapeutique, EA 2629, 1 rue des Louvels, 80000 Amiens, France

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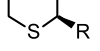
Abstract—The synthesis of enantiomerically pure 4-(2-hydroxy-(1*R*)-phenylethyl)-thiomorpholin-3-one **2** from (*R*)-phenylglycine methyl ester, *S*-benzylthioglycolic acid and bromoacetic acid is reported. Stereoselective C-2 alkylation of **2**, performed using various electrophiles, leads to enantiomerically pure 2-substituted thiomorpholin-3-ones after *N*-deprotection.

1. Introduction

2-Substituted thiomorpholin-3-one (2-STMO) **1** is a pharmacophore of great interest and derivatives containing such a sub-unit have already been prepared and evaluated in various biological fields.[1,2] Compounds accessible by taking advantage of the chemical potential of 2-STMOs have also been reported as pharmacologically relevant[3–5] or as chemically peculiar.[6] However the proliferation of 2-STMOs in medicinal chemistry is undoubtedly hampered by the small number of enantioselective methods available. Indeed, whereas several racemic syntheses of 2-STMO derivatives have been described in the liquid[1–15] or solid phase[16] only two methods affording enantiomerically pure 2-STMOs have been reported so far.[17,18] However, in both cases, the diversity for the C_2-substituting chain is severely limited by the availability of the corresponding enantiomerically pure starting material (aminoacid,[17] or alkylglycidic ester[18]) and in one case,[18] the enantiomeric purity is unsatisfactory. Consequently, although chemically efficient, these methodologies can hardly be considered as general. Facing a recent crucial need to have access to a synthetic method that would quickly afford a large variety of enantiomerically pure 2-STMOs we have studied different approaches and finally designed a strategy leading to the required derivatives with a very high enantioselectivity. Since 1,2-amino alcohols are chiral auxiliaries often used in asymmetric synthesis[19] and phenylglycinol has already been successfully used to obtain different kinds of enantiomerically pure substituted heterocycles,[20–23] we consequently considered the novel thialactam **2** as a key intermediate for our synthesis.

Herein we describe the first, efficient synthesis of **2** in an enantiomerically pure form together with its stereoselective C-2 alkylation. *N*-Deprotection of the alkylated adducts finally opens the field to a large diversity of 2-STMOs.



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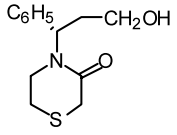

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2. Results and discussion

2.1. Preparation of 4-(2-hydroxy-(1*R*)-phenylethyl)-thiomorpholin-3-one 2

While morpholin-3-ones, piperazin-2-ones, and δ-lactams having a nitrogen atom substituted with a chiral appendage are known,[20–23] the corresponding thiomorpholin-3-ones have not been described to date. We prepared **2** from (*S*)-phenylglycine methyl ester **3**. Condensation between **3** and *S*-benzylthioglycolic acid in the presence of 1,3-dicyclohexylcarbodiimide (DCC) afforded **4** in quantitative yield. Simultaneous reduction

* Corresponding author. Tel.: (33) 322 827 785; fax: (33) 322 827 469; e-mail: dominique.guillaume@sa.u-picardie.fr

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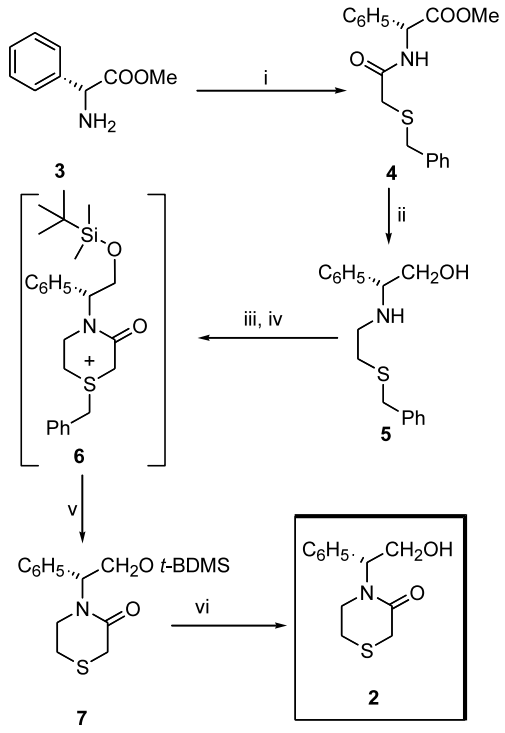


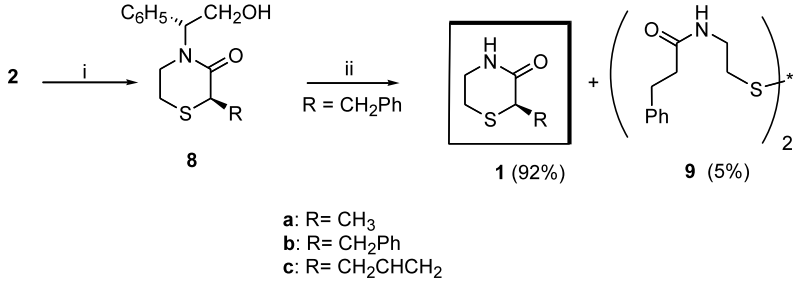
Scheme 1. *Reagents and conditions*: (i) DCC, NMM, $PhCH_2SCH_2COOH$; (ii) LAH, Et_2O, 30 h; (iii) *t*-BDMSCl, imidazole, 0°C; (iv) DCC, NMM, $BrCH_2COOH$; (v) KBr; (vi) Bu_4NF, 0°C.

of the ester and amide function of **4** was achieved using a suspension of $LiAlH_4$ in ether as a reducting agent, affording **5** in 95% yield. Protection of the primary alcohol of **5** was achieved in 95% yield using *tert*-butyldimethylsilyl chloride (*t*-BDMSCl) in the presence of imidazole and condensation of the resulting adduct with bromoacetic acid in the presence of DCC and 4-methylmorpholine (NMM) allowed the simultaneous amide bond formation and cyclisation, leading, to the thiomorpholin-3-one **7** in 85% yield (two steps). Cyclisation reasonably occured through the sulfonium intermediate **6** that underwent spontaneous debenzylation in the presence of bromide ions. Deprotection of **7** (Bu_4NF) led to the key synthon **2** in 80% yield (Scheme 1).

2.2. Reaction of compound 2 with various electrophiles and synthesis of 2-substituted-thiomorpholines

Being able to prepare **2** in satisfactory yields and enantiomerically pure, we then studied its C_2-substitution. Stereoselective alkylation of **2** was achieved in THF in the presence of HMPA (a co-solvent generally permitting the alkylation step to proceed in better yields[22]), using LDA as a strong base and methyl iodide, benzyl bromide, and allyl bromide as model electrophiles (Scheme 2). Chemical yields were between 91 and 96% and only one diastereomer was observed on the ^1H NMR spectrum (500 MHz) of the alkylation products demonstrating their high diastereomeric purity (above 96%) (Table 1). We also prepared an equimolar mixture of **8b** and its C_2-epimer by alkylating **7** (LDA/HMPA, $PhCH_2Br$) which shared no asymmetric induction followed by the *O*-deprotection step. Having in hands the necessary isomers in pure form and as a racemic mixture, we finally performed a HPLC analysis that demonstrated the enantiomeric purity of **8b** to be above 99% (only one diastereomer was detected).

Unfortunately none of the alkylated compounds **8** afforded crystals suitable for X-ray analysis precluding the unambiguous determination of the C_2-configuration in this series. Hence, we decided to demonstrate the C_2-configuration in the *N*-deprotected series and chose **1b** as an example. Whereas hydrogenolysis has always been the method of choice to remove the chiral appendage in the previously studied series,[20–23] **8b** remained unreactive in the presence of hydrogen and various Pt- or Pd-derived catalysts. However, debenzylation of **8b** was successfully achieved using lithium in ammonia/THF (−78°C, 10 min)[24] and **1b** was isolated



a: R= CH_3
b: R= CH_2Ph
c: R= CH_2CHCH_2

Scheme 2. *Reagents and conditions*: (i) LDA, HMPA, RX, −78°C; (ii) NH_3, Li, −78°C, 10 min.

Table 1. Chemical yield and diastereomeric purity of the compounds obtained by enantioselective alkylation of **2**

Electrophile used	Chemical yield (%)	De (method)	Isolated adduct ($[\alpha]_D^{18}$)
CH_3I	93	>96% (NMR)	**8a** [−97 (*c* 0.1, EtOH)]
$PhCH_2Br$	96	>99% (NMR, HPLC)	**8b** [−99 (*c* 0.1, EtOH)]
CH_2CHCH_2Br	91	>96% (NMR)	**8c** [−97 (*c* 0.1, EtOH)]

in 92% yield. Dimer **9** was isolated as a minor adduct (5%) but longer debenzylation time led to its exclusive obtention.

To study the configuration of the created stereogenic center, we also prepared **1b** according to the previously known aminoacid route.[17] We separately used L- and D-phenylalanine as starting material in order to obtain, individually, **1b** and its enantiomer $\mathbf{1b}_{(S)}$ and, as expected **1b** and $\mathbf{1b}_{(S)}$ displayed specific rotations of identical absolute value but opposite sign (+34.8, *c* 0.05, EtOH, −32.9, *c* 0.05, EtOH; respectively). Optical rotation observed for **1b** obtained by our alkylation route was found to be +33.9 (*c* 0.05, EtOH) demonstrating the anticipated (*R*)-configuration of C_2 and evidencing the lack of racemization during the debenzylation step and consequently the high enantiomeric purity of **1b**.

The origin of the diastereoselectivity during the alkylation reaction of lactams has been previously investigated[25] and it is very likely that the high diastereoselectivity observed in our study follows the suggested models.

3. Conclusion

In summary, we have been able to prepare synthon **2** following a short and efficient route and have demonstrated that its stereoselective C_2-alkylation by various electrophiles is possible. This shows that the sulfur atom lone pairs do not modify the chemistry and stereoselectivity of the alkylation reaction observed in other series. Our strategy will permit the preparation of thiomorpholin-3-ones stereoselectively substituted at their 2-position by non proteogenic side-chains. The allyl side chain will permit an entry to a variety of derivatives design to mimic Asn, Gln, Glu, and Arg side chains and since the phenyl group is not specifically necessary for the asymmetric induction[26] various 4-substituted-2-STMOs can be easily reached. Biological properties of selected derivatives obtained from **8** are currently being investigated.

4. Experimental

4.1. General

Infrared spectra were recorded on a Nicolet 210 spectrometer using film KBr pellet techniques. ^{1}H and ^{13}C NMR spectra were recorded at 500 and 125 MHz; respectively, residual solvent traces being used as internal standard. Mass spectra were obtained in chemical ionization mode by direct insertion (ionizing gas NH_3). Diisopropylamine was dried over CaH_2 and distilled prior to use. Et_2O and THF were dried over sodium/benzophenone before distillation. Alkylation reactions were carried out under nitrogen atmosphere condition. Thin layer chromatography was performed on precoated silica gel plates (60-F_{254}, 0.2 mm) and revealed by spraying with phosphomolybdic acid the heating. Silica gel (grade 60, 230–400 mesh) was used for column chromatography. Diastereomeric excesses (de) were determined by NMR and HPLC using a chirobiotic 18 mm column eluted with an isopropanol/cyclohexane system. Optical rotations were taken at 18°C with a Perkin Elmer 241 polarimeter.

4.2. (2*R*)-(2-Benzylsulfanylacetylamino)-phenylacetic acid methyl ester, 4

A solution of *S*-benzylthioglycolic acid (5 g, 26.25 mmol) and DCC (6.1 g, 29.61 mmol) in CH_2Cl_2 (80 mL) was stirred at rt for 1 h. An ice-cooled solution of **3** (5.54 g, 29.61 mmol) and *N*-methylmorpholine (6 mL, 53.81 mmol) in CH_2Cl_2 (80 mL) was added. The reaction was stirred overnight at rt. The precipitate was filtered and washed with CH_2Cl_2. The filtrate was dried over $MgSO_4$, evaporated and compound **4** was obtained as a white solid in quantitative yield after silica gel chromatography (EtOAc, C_6H_{12}): mp 86°C; $[\alpha]_D^{18} = -86$ (*c* 0.1, EtOH); ^{1}H NMR δ ($CDCl_3$) 7.81 (d, 1H, $J = 7.3$ Hz), 7.6–7.3 (m, 10H), 5.72 (d, 1H, $J = 7.3$ Hz), 3.78 (s, 3H), 3.75 (s, 2H), 3.20 (d, 1H, $J = 16.4$ Hz), 3.14 (d, 1H, $J = 16.4$ Hz); ^{13}C NMR δ ($CDCl_3$) 171.5, 168.5, 137.2, 136.6, 129.5, 129.4, 129.1, 129.0, 127.8, 127.7, 57.0, 53.2, 37.2, 35.3; IR (cm^{-1}) 3348, 1737, 1666, 1516, 1325, 1172, 711.

4.3. (2*R*)-(2-Benzylsulfanylethylamino)-phenylethanol, 5

To an ice-cooled solution of **4** (5.57 g, 16.93 mmol) in dry Et_2O (90 mL) was added $LiAlH_4$ (0.64 g, 16.93 mmol). The mixture was stirred for 1 h at rt, and then additional $LiAlH_4$ (1.93 g, 50.8 mmol) was added to the reaction. Stirring was continued for 30 h, and then a 15% aqueous solution of NaOH (0.8 mL) was added dropwise to the reaction cooled at −10°C. After one hour, water (2 mL) was added, and the suspension was stirred overnight at rt. The precipitate was filtered and then washed with CH_2Cl_2. The filtrate was dried over $MgSO_4$, evaporated and a yellow solid was obtained in 95% yield after silica gel chromatography (EtOAc, C_6H_{12}): mp 84°C; $[\alpha]_D^{18} = -50$ (*c* 0.1, EtOH); ^{1}H NMR δ ($CDCl_3$) 7.2–7.5 (m, 10H), 3.7–3.8 (m, 2H), 3.65 (s, 2H), 3.61–3.59 (m, 1H), 2.89 (broad s, 1H), 2.6–2.8 (m, 2H), 2.6–2.65 (m, 2H); ^{13}C NMR δ ($CDCl_3$) 140.9, 138.7, 130.1, 129.3, 128.9, 128.1, 127.7, 127.5, 67.2, 64.8, 45.9, 35.7, 32.1; IR (cm^{-1}) 3252, 1658, 1570, 1043, 769, 698.

4.4. 4-[(2*R*)-[1-(*tert*-Butyldimethylsilanyloxy)]-phenylethyl]thiomorpholin-3-one, 7

To an ice-cooled solution of **5** (3.98 g, 13.86 mmol) were added imidazole (1.89 g, 27.72 mmol) in CH_2Cl_2 (7 mL) and *tert*-butyldimethylsilyl chloride (2.7 g, 18.02 mmol). The solution was stirred for 6 h at rt. The reaction was quenched by addition of H_2O (25 mL) and then made alkaline by addition of a saturated aqueous solution of Na_2CO_3 (100 mL). The aqueous phase was extracted with Et_2O (2×150 mL), which was further washed with H_2O (3×75 mL), dried over $MgSO_4$, and concentrated. An oil was obtained in 95% yield. A solution of bromoacetic acid (8.3 g, 59.51 mmol) and

DCC (6 g, 29.02 mmol) in CH_2Cl_2 (50 mL) was stirred at rt for 1 h. The white precipitate was removed and the filtrate poured into a solution of the previously obtained oil (5.5 g, 13.7 mmol) and *N*-methylmorpholine (4.25 mL, 39.63 mmol) in CH_2Cl_2 (25 mL) cooled at 0°C. The reaction was stirred overnight at rt. The precipitate was filtered and then washed with CH_2Cl_2. The filtrate was dried over $MgSO_4$, evaporated and an oil was obtained in 85% yield after silica gel chromatography (EtOAc, C_6H_{12}): $[\alpha]_D^{18}=-56$ (*c* 0.1, EtOH); ^{1}H NMR δ ($CDCl_3$) 7.2–7.4 (m, 5H), 5.85 (t, 1H, $J=5.5$ Hz), 4.12 (d, 2H, $J=5.5$ Hz), 3.5–3.6 (m, 1H), 3.4–3.45 (m, 1H), 3.35 (s, 2H), 2.82–2.78 (m, 1H), 2.55–2.65 (m, 1H), 0.90 (s, 9H), 0.00 (s, 6H); ^{13}C NMR δ ($CDCl_3$) 168.5, 138.1, 129.4, 128.9, 128.1, 77.5, 62.7, 57.3, 44.4, 30.1, 27.2, 26.5, 0.00; IR (cm^{-1}) 3364, 2957, 2862, 1616, 1475, 1259, 1064, 844, 777.

4.5. 4-(2-Hydroxy-(1*R*)-phenylethyl)-thiomorpholin-3-one, 2

To an ice-cooled solution of **7** (3.53 g, 10.06 mmol) in THF (130 mL) was added 20 mL of a 1.0 M solution of Bu_4NF in THF. The reaction was stirred for 2 h at rt, and then H_2O (190 mL) was added. The two phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2×250 mL). The combined organic phases were washed with H_2O (4×250 mL), dried, and concentrated, affording a white solid after silica gel chromatography (EtOAc, C_6H_{12}) in 80% yield: mp 88°C; $[\alpha]_D^{18}=-102$ (*c* 1, EtOH); ^{1}H NMR δ ($CDCl_3$) 7.4–7.6 (m, 5H), 5.85 (dd, 1H, $J=8.2$, 5.5 Hz), 4.35 (dd, 1H, $J=8.2$, 6.6 Hz), 4.29 (dd, 1H, $J=6.6$, 5.5 Hz), 3.6–3.7 (m, 2H), 3.57 (s, 2H), 3.0–3.1 (m, 1H), 2.8–2.85 (m, 1H), 2.80 (broad s, 1H); ^{13}C NMR δ ($CDCl_3$) 168.4, 138.5, 129.3, 128.5, 128.2, 62.5, 59.3, 44.5, 30.4, 27.2; IR (cm^{-1}) 3426, 1637, 1450, 1064, 703.

4.6. Alkylated compounds 8a–c, general procedure

A solution of diisopropylamine (1 mL, 7.35 mmol) in dry THF (20 mL) was cooled at −78°C under nitrogen atmosphere. A 1.6 M hexane solution of *n*-BuLi (4 mL, 6.40 mmol) was carefully added and the reaction stirred at −78°C for 15 min. A solution of **2** (0.50 g, 2.13 mmol) and HMPA (1.12 mL, 6.3 mmol) in dry THF (5 mL) was added and the reaction stirred at −78°C for 15 min. A solution of electrophile (6.3 mmol) in dry THF (5 mL) was added and the reaction stirred at −78°C for 45 min, and then at −50°C for 3–5 h, and finally at −15°C for 15 min. At the end of this period, the reaction was quenched by addition of a saturated aqueous solution of ammonium chloride (100 mL). The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×60 mL). The combined organic phases were dried, and concentrated, affording after silica gel chromatography (EtOAc, C_6H_{12}) the alkylated compound.

4.6.1. (2*R*)-Methyl-4-(2-hydroxy-(1′*R*)-phenylethyl)-thiomorpholin-3-one, 8a

Following the general procedure, **8a** was prepared in 93% yield: mp 68°C; $[\alpha]_D^{18}=-97$ (*c* 0.1, EtOH); ^{1}H NMR δ ($CDCl_3$) 7.2–7.4 (m, 5H), 5.82 (dd, 1H, $J=8.8$, 5.2 Hz), 4.10 (dd, 1H, $J=11.4$, 8.8 Hz), 3.95 (dd, 1H, $J=11.4$, 5.2 Hz), 3.6–3.7 (m, 2H), 3.4–3.3 (m, 2H), 2.6–2.7 (m, 1H), 2.2–2.3 (m, 1H), 2.13 (broad s, 1H), 1.19 (s, 3H); ^{13}C NMR δ ($CDCl_3$) 173.5, 137.4, 129.6, 129.2, 128.3, 62.1, 58.5, 42.8, 36.0, 27.8, 15.6; IR (cm^{-1}) 3425, 1659, 1501, 423; HRMS (ESI$^+$) (MH^+): calcd for $C_{13}H_{18}NO_2S$: 252.1058. Found: 252.1046. HPLC analysis: rt = 44.4 min.

4.6.2. (2*R*)-Benzyl-4-(2-hydroxy-(1′*R*)-phenylethyl)-thiomorpholin-3-one, 8b

Following the general procedure, **8b** was prepared in 96% yield: $[\alpha]_D^{18}=-99$ (*c* 0.1, EtOH); ^{1}H NMR δ ($CDCl_3$) 7.4–7.6 (m, 10H), 6.13 (dd, 1H, $J=8.2$, 5.5 Hz), 4.01 (dd, 1H, $J=11.5$, 8.2 Hz), 3.91 (dd, 1H, $J=11.5$, 5.5 Hz), 3.74 (dd, 1H, $J=9.2$, 4.6 Hz), 3.41 (dd, 1H, $J=14.3$, 4.6 Hz), 3.4–3.45 (m, 2H), 3.08 (dd, 1H, $J=14.3$, 9.2 Hz), 2.5–2.55 (m, 1H), 2.42 (broad s, 1H), 2.1–2.2 (m, 1H); ^{13}C NMR δ ($CDCl_3$) 172.3, 138.9, 137.2, 129.7, 129.2, 128.8, 128.5, 128.3, 127.1, 62.3, 58.6, 43.6, 43.0, 36.9, 27.6; IR (cm^{-1}) 3413, 2930, 1655, 1627, 1465, 704; HRMS (ESI$^+$) $(MH)^+$: calcd for $C_{19}H_{22}NO_2S$: 328.1371. Found: 328.1375. HPLC analysis: rt = 39.1 min.

4.6.3. (2*R*)-Allyl-4-(2-hydroxy-(1′*R*)-phenylethyl)-thiomorpholin-3-one, 8c

Following the general procedure, **8c** was prepared in 91% yield: $[\alpha]_D^{18}=-97$ (*c* 0.1, EtOH); ^{1}H NMR δ ($CDCl_3$) 7.4–7.2 (m, 5H), 5.82 (dd, 1H, $J=9.6$, 4.8 Hz), 5.81 (m, 1H), 5.1 (d, 1H, $J=17.0$ Hz), 5.0 (d, 1H, $J=10.1$ Hz), 4.10 (dd, 1H, $J=11.3$, 4.8 Hz), 3.96 (dd, 1H, $J=11.3$, 9.8 Hz), 3.5–3.6 (m, 1H), 3.3–3.43 (m, 2H), 3.19 (broad s, 1H), 2.75–2.8 (m, 1H), 2.6–2.7 (m, 1H), 2.3–2.4 (m, 1H), 2.25–2.3 (m, 1H); ^{13}C NMR δ ($CDCl_3$) 172.2, 137.4, 135.3, 129.2, 128.5, 128.3, 117.9, 62.2, 58.5, 42.9, 41.4, 35.1, 27.5; IR (cm^{-1}) 3401, 2974, 1651, 1437, 712; HRMS (ESI$^+$) (MH^+): calcd for $C_{15}H_{20}NO_2S$: 278.1215. Found: 278.1211. HPLC analysis: rt = 38.3 min.

4.7. (2*R*)-Benzylthiomorpholin-3-one, 1b

Anhydrous ammonia (20 mL) was condensed at −78°C under a nitrogen atmosphere. Lithium (3 equiv.) was added. A solution of alkylated compound **8b** (32.7 mg, 1 mmol) in THF (10 mL) was added slowly. The solution was stirred at −78°C for 10 min under nitrogen atmosphere. Then the reaction was quenched by addition of water (0.1 mL) and the mixture stirred at rt for 3 h. The solution was filtered and concentrated under reduced pressure. Purification was achieved by silica gel chromatography (EtOAc, C_6H_{12}) affording **1b** in 92% yield: $[\alpha]_D^{19}=+33.9$ (*c* 0.05, EtOH); ^{1}H NMR δ ($CDCl_3$) 7.2–7.3 (m, 5H), 7.05–7.15 (m, 1H), 3.62 (dd, 1H, $J=10.8$, 5.5 Hz), 3.5–3.55 (m, 1H), 3.4–3.5 (m, 2H), 2.86 (dd, 1H, $J=13.1$, 10.8 Hz), 2.65–2.7 (m, 2H); ^{13}C NMR δ ($CDCl_3$) 171.2, 138.6, 129.4, 128.8, 127.3, 44.1, 43.7, 37.7, 26.3; IR (cm^{-1}) 3460, 3190, 1741, 1662, 1458, 1346, 711; HRMS (ESI$^+$) $(MH)^+$: calcd for $C_{11}H_{14}NOS$: 208.0796. Found: 208.0804.

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