Aza-Reformatsky Reaction Promoted by Catalytic Samarium Diiodide: Synthesis of β-Amino Esters or Amides

Humberto Rodríguez-Solla,* Ainhoa Díaz-Pardo, Carmen Concellón, Vicente del Amo

Dpto. Química Orgánica e Inorgánica, Universidad de Oviedo, C/ Julián Clavería 8, 33006 Oviedo, Spain
E-mail: hrsolla@uniovi.es

Received: 31.03.2014; Accepted after revision: 05.05.2014

Abstract: The synthesis of β-amino esters or amides has been achieved from moderate to high yields from the reaction of imines and α-halo esters or amides promoted by catalytic amounts of samarium diiodide in the presence of magnesium turnings as co-reductant. A mechanism is proposed to explain this catalytic samarium(II)-promoted aza-Reformatsky reaction.

Key words: amino esters, catalytic reactions, enolates, Reformatsky reaction, samarium

Several syntheses of β-amino acids and their derivatives have been reported to date.[1] β-Amino acid derivatives[2] are relevant starting materials in organic synthesis,[3] as this functionality is present in compounds with biological[4] or pharmacological[5] activity. In addition, their peptides[6] are also featured in several active drugs.[7]

Previously, we have reported a synthetic protocol to carry out aza-Reformatsky reactions using samarium enolates, derived from different α-amino esters or amides, and a number of imines.[8] In those cases, stoichiometric amounts of samarium diiodide were required for the samarium enolate generation.

Samarium diiodide[9] is a very important reagent as it can mediate reactions that other reagents cannot, however, one of the main drawbacks of SmI_2 chemistry is its relatively high cost, moreover when it has been generally employed in stoichiometric amounts. For this reason, methods to carry out transformations using this salt in catalytic amounts would be desirable.

Several systems for the regeneration of Sm(II) from Sm(III) species have been reported to date: the use of catalytic amounts of samarium diiodide and different co-reductants such as Zn(Hg) amalgams,[10] Ce-mischmetal,[11] and magnesium turnings (with different additives: 1,2-dibromoethane,[12] trimethylsilyl chloride,[13] dimethylsilyl dichloride),[14] or electrochemical techniques employing magnesium[15] or samarium[16] cathodes. As part of our research program concerned with the use catalytic amounts of samarium diiodide in organic synthesis, we have also reported the use of a mixture of catalytic SmI_2/Mg/$ZnCl_2$ in β-elimination reactions of α-halo-β-hydroxy esters affording (*E*)-α,β-unsaturated esters in a totally stereoselective manner.[17]

In this communication, we report a new and easy access to β-amino esters or amides by treatment of α-halo esters or amides with our previously developed $SmI_{2\ cat.}$/Mg/$ZnCl_2$ system. A mechanism to explain this catalytic samarium(II)-promoted aza-Reformatsky process is also proposed.

Imines **1**, derived from *p*-toluenesulfonamide and used as starting materials, were prepared in high yields according to a method previously reported in the literature.[18,19]

Initially, we studied the addition reaction of ethyl bromoacetate **2a** to the *N*-tosylimine **1a** derived from octanal according to the same reaction conditions, previously reported by our group for the SmI_2-catalyzed β-elimination reaction.[16] So, when 0.4 equivalents of SmI_2 and six equivalents of the mixture Mg/$ZnCl_2$ were added to **1a** and **2a** in THF, β-amino ester **3a** was isolated in 83% yield after chromatography.[20]

We have also tested different amounts of SmI_2 (0.05, 0.1 equiv) and reaction times. In all cases, the yields of the isolated products were lower than when the reaction was performed with 0.4 equivalents used in our previous contribution.[16] When the reaction was carried out in the absence of SmI_2 no reaction took place and compound **1a** was isolated unaltered.

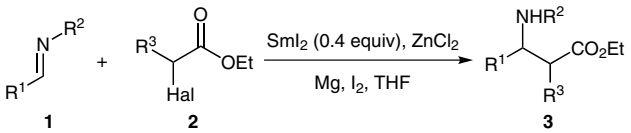
After several tests, we found that ideal reaction conditions utilizing a mixture composed of one equivalent of *N*-tosyl imine **1a**, one equivalent of α-halo ester **2**, 0.4 equivalents of SmI_2, 6.0 equivalents of magnesium turnings,[21] and 6.0 equivalents of $ZnCl_2$, for 3.5 hours at room temperature.[22] With this set of conditions in hand, we performed the aza-Reformatsky reaction with a range of imines **1** as it is shown in Table 1.

Table 1 reveals that, according to our methodology, the synthesis of β-amino esters is general. It has been possible to use linear, cyclic, branched, or aromatic *N*-tosyl imines **1**. Moreover, this reaction has been also carried out using imines containing readily enolizable protons, such as **1d** (Table 1, entry 5). It is noteworthy that other protecting group such as *tert*-butoxycarbonyl[23] can be used in this process (Table 1, entry 8). Also, no differences were observed on the reaction outcome when this process was carried out on bromo or chloro derivatives **2** (Table 1, entries 1 and 2).

As a logical extension, we have also studied the synthesis of β-amino amides. So, the reaction of imines **1c** with the samarium enolate generated from *N*,*N*-diethyl chloroacet-

SYNLETT 2014, 25, 1709–1712
Advanced online publication: 24.06.2014
DOI: 10.1055/s-0034-1378229; Art ID: st-2014-d0273-l

Table 1 Synthesis of β-Amino Esters **3** by Using Catalytic SmI_2

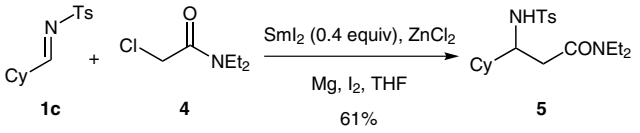


1 2 3

Entry	1	2	3	R^1	R^2	R^3	Hal	Yield (%)[a]
1	**1a**	**2a**	**3a**	*n*-C_7H_{15}	Ts	H	Br	83
2	**1a**	**2b**	**3b**	*n*-C_7H_{15}	Ts	Me	Cl	64
3	**1b**	**2a**	**3c**	*s*-Bu	Ts	H	Br	68
4	**1c**	**2a**	**3d**	Cy	Ts	H	Br	71
5	**1d**	**2a**	**3e**	Bn	Ts	H	Br	54
6	**1e**	**2a**	**3f**	$BnCH_2$	Ts	H	Br	60
7	**1f**	**2a**	**3g**	Ph	Ts	H	Br	66
8	**1g**	**2a**	**3h**	Ph	Boc	H	Br	74

[a] Isolated yield of pure compounds **3** after column chromatography based on compounds **1**.

amide (**4**) afforded the corresponding β-amino amide **5** in similar yield to that obtained when ester functionalities were used (Scheme 1).



1c 4 5

Scheme 1 Synthesis of β-amino amide **5**

The structure of β-amino esters **3** and amide **5** were established by comparison with the NMR data of these compounds previously reported in the literature (**3b–d**,[8] **3f**,[8] **3g**,[24] **3h**,[22] and **5**[8b]). The structure of compounds **3a**[19] and **3e**[25] were assigned by ^1H NMR, ^{13}C NMR, and IR spectroscopy, and HRMS.

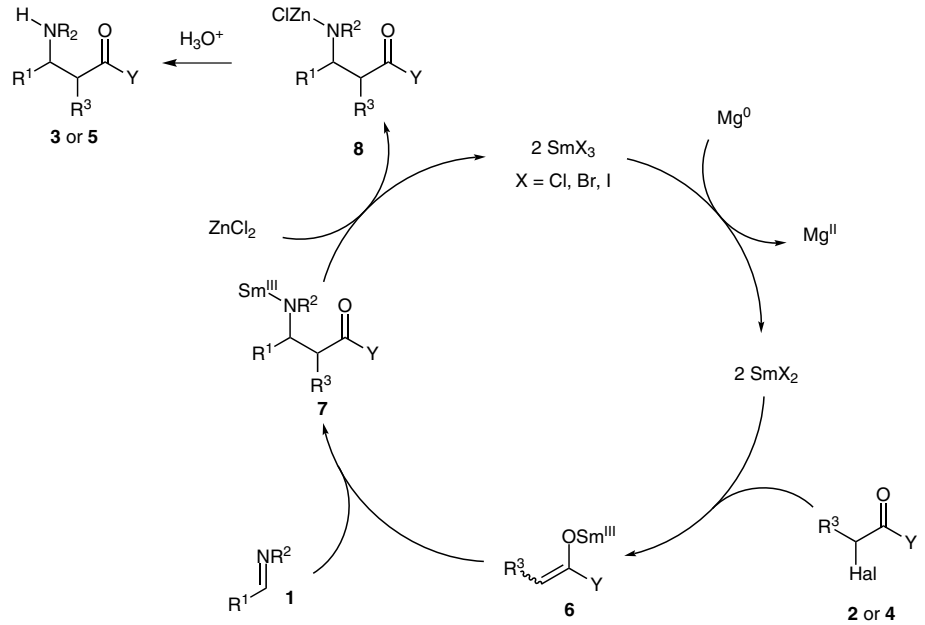
A mechanistic proposal is described in Scheme 2. Thus, the formation of β-amino esters **3** or amides **5** might be explained assuming the generation of the samarium enolate **6** after metalation, by SmI_2, of the C–Hal bond in esters **2** or amides **4**.

Reaction between the enolate **6** and imines **1** would afford the samarium(III) amide **7** which, after transmetalation with $ZnCl_2$, would generate a Zn(II) amide **8**. The use of $ZnCl_2$ allowed the release of the samarium(III) species from the amide group. Samarium(III) is further reduced by magnesium turnings to generate samarium(II) species, which are again involved in the catalytic cycle to promote the formation of enolates **6** from esters **2** or amides **4**. Finally, hydrolysis of Zn(II) amides **8** would afford β-amino esters or amides **3**, and **5**, respectively.

In conclusion, an efficient, general, and very cheap methodology has been developed for the synthesis of β-amino esters from easily available *N*-tosyl or *N*-Boc imines and commercial α-halo esters or amides with catalytic amounts of SmI_2. Attempts to carry out other processes with catalytic samarium diiodide, including an asymmetric version of the aza-Reformatsky reaction, are currently under investigation within our laboratory.

Acknowledgment

We thank to Ministerio de Economía y Competitividad for financial support. V.d A. and A. D. -P. thank MINECO (Spain), and University of Oviedo, for a Ramón y Cajal contract and a predoctoral fellowship, respectively.



Scheme 2 Mechanistic proposal for the conversion of **1** into **3** or **5**

References and Notes

(1) For reviews on the synthesis of β-amino acids, see: (a) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517. (b) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, **1997**. (c) Juaristi, E.; López-Ruiz, H. *Curr. Med. Chem.* **1999**, *6*, 983. (d) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1. (e) Lui, M.; Sibi, M. *Tetrahedron* **2002**, *58*, 7991. (f) Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833. (g) Sleebs, B. E.; Van Nguyen, T. T.; Hughes, A. B. *Org. Prep. Proced. Int.* **2009**, *41*, 429. For recent papers on the synthesis of β-amino acids, see: (h) Shen, B.; Johnston, J. N. *Org. Lett.* **2008**, *10*, 4397. (i) Yang, J. W.; Chandler, C.; Stadler, M.; Kampen, D.; List, B. *Nature (London, U.K.)* **2008**, *452*, 453. (j) Seayad, J.; Patra, P. K.; Zhang, Y.; Ying, J. Y. *Org. Lett.* **2008**, *10*, 953. (k) Lu, X.; Deng, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 7710. (l) Martin, N. J. A.; Cheng, X.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 13862. (m) Malkov, A. V.; Stončius, S.; Vranková, K.; Arndt, M.; Kočovský, P. *Chem. Eur. J.* **2008**, *14*, 8082. (n) Nolte, G. T.; Baxter, Vu. J. M.; Leighton, J. L. *Org. Lett.* **2011**, *13*, 816. (o) Bea, S.-H.; Park, H.-J.; Lee, S.-H.; Yun, H. *Chem. Commun.* **2011**, *47*, 5894. (p) Wang, Q.; Leutzsch, M.; van Gemmeren, M.; List, B. *J. Am. Chem. Soc.* **2013**, *135*, 15334.

(2) Sewald, N. *Angew. Chem. Int. Ed.* **2003**, *42*, 5794.

(3) β-Amino acids can be transformed into other compounds. Piperidines: (a) Jefford, C. W.; Wang, J. B. *Tetrahedron Lett.* **1993**, *34*, 2911. (b) Davis, F. A.; Santhanaraman, M. *J. Org. Chem.* **2006**, *71*, 4222. (c) Davies, S. G.; Hughes, D. G.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E.; Williams, O. M. H. *Synlett* **2010**, 567. Indolizidines: (d) Jefford, C. W.; Wang, J. B. *Tetrahedron Lett.* **1993**, *34*, 3119. (e) Davis, F. A.; Yang, B. *Org. Lett.* **2003**, *5*, 5011. (f) Davis, F. A.; Yang, B. *J. Am. Chem. Soc.* **2005**, *127*, 8398. β-Lactams: (g) Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichimica Acta* **1994**, *27*, 3. (h) Tzouvelekis, L. S.; Bonomo, R. A. *Curr. Pharm. Des.* **1999**, *5*, 847. (i) Massova, I.; Mobashery, S. *Curr. Pharm. Des.* **1999**, *5*, 929. (j) Mascaretti, O. A.; Danelon, G. O.; Laborde, M.; Mata, E. G.; Setti, E. L. *Curr. Pharm. Des.* **1999**, *5*, 939. (k) Garau, G.; García-Sáez, I.; Bebrone, C.; Anne, C.; Mercuri, P.; Galleen, M.; Frere, J. M.; Dideberg, O. *Antimicrob. Agents Chemother.* **2004**, *48*, 2347. (l) Ozeki, M.; Ochi, S.; Hayama, N.; Hosoi, S.; Kajimoto, T.; Node, M. *J. Org. Chem.* **2010**, *75*, 4201.

(4) (a) Drey, C. N. C. In *Chemistry and Biochemistry of the Amino Acids*; Barret, G. C., Ed.; Chapman and May: New York, **1985**, Chap. 3. (b) Griffith, O. W. *Annu. Rev. Biochem.* **1986**, *55*, 855.

(5) (a) Tramontini, M.; Angiolini, L. In *Mannich-Bases: Chemistry and Uses*; CRC: Boca Raton, FL, **1994**. (b) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, 117. (c) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E.; Soloshonok, V. A., Eds.; Wiley-VCH: New York, **2005**.

(6) For reviews on β-peptides, see: (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173. (b) Seebach, D.; Abele, S.; Gademann, K.; Jaun, B. *Angew. Chem. Int. Ed.* **1999**, *38*, 1595.

(7) Krauthäuser, S.; Christianson, L. A.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1997**, *119*, 11719.

(8) (a) Concellón, J. M.; Rodríguez-Solla, H.; Simal, C. *Adv. Synth. Catal.* **2009**, *351*, 1238. (b) Concellón, J. M.; Rodríguez-Solla, H.; Simal, C.; del Amo, V.; García-Granda, S.; Díaz, M. R. *Adv. Synth. Catal.* **2009**, *351*, 2991.

(9) For recent reviews of SmI_2, see: (a) Edmons, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371. (b) Concellón, J. M.; Rodríguez-Solla, H. *Chem. Soc. Rev.* **2004**, *33*, 599. (c) Jung, D.; Kim, Y. H. *Synlett* **2005**, 3019. (d) Concellón, J. M.; Rodríguez-Solla, H. *Eur. J. Org. Chem.* **2006**, 1613. (e) Kagan, H. B.; Gopalaiah, K. *New J. Chem.* **2008**, *32*, 607. (f) Rudkin, I. M.; Miller, L. C.; Procter, D. J. *Organomet. Chem.* **2008**, *34*, 19. (g) Nicolau, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 7140. (h) Concellón, J. M.; Rodríguez-Solla, H.; Concellón, C.; del Amo, V. *Chem. Soc. Rev.* **2010**, *39*, 4103. (i) Procter, D. J.; Flowers, R. A. II.; Skrydstrup, T. *Organic Synthesis Using Samarium Diiodide: A Practical Guide*; Royal Society of Chemistry Publishing: Cambridge, **2010**. (j) Szostak, M.; Spain, M.; Parmar, D.; Procter, D. J. *Chem. Commun.* **2012**, 330. (k) Harb, H. Y.; Procter, D. J. *Synlett* **2012**, *23*, 6. (l) Szostak, M.; Spain, M.; Procter, D. J. *Chem. Soc. Rev.* **2013**, *42*, 9155.

(10) Corey, E. J.; Zheng, G. Z. *Tetrahedron* **1997**, *12*, 2045.

(11) (a) Hélion, F.; Namy, J.-L. *J. Org. Chem.* **1997**, *64*, 2944. (b) Lannon, M.-I.; Hélion, F.; Namy, J.-L. *Tetrahedron* **2003**, *59*, 10551.

(12) Orsini, F.; Lucci, E. M. *Tetrahedron Lett.* **2005**, *46*, 1909.

(13) Nomura, R.; Matsuno, T.; Endo, T. *J. Am. Chem. Soc.* **1996**, *118*, 11666.

(14) Aspinall, H. C.; Greeves, N.; Valla, C. *Org. Lett.* **2005**, *10*, 1919.

(15) Hébri, H.; Dunach, E.; Heintz, M.; Troupel, M.; Périchon, J. *Synlett* **1991**, 901.

(16) Sun, L.; Sahloul, K.; Mellah, M. *ACS Catal.* **2013**, *3*, 2568.

(17) Concellón, J. M.; Rodríguez-Solla, H.; Concellón, C.; Díaz-Pardo, A.; Llavona, R. *Synlett* **2011**, 262.

(18) Wang, Y.; Song, J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156.

(19) **Procedure for the Synthesis of *N*-Tosyloctan-1-imine (1a)**
A mixture of *n*-octanal (10 mmol), *p*-toluenesulfonamide (10 mmol), sodium *p*-toluenesulfinate (10 mmol) in H_2O (15 mL), and formic acid (15 mL) was stirred for 24 h at r.t. The resulting white precipitate was collected by filtration, washed with H_2O (3 × 10 mL) and hexane (2 × 10 mL), then dissolved in CH_2Cl_2 (100 mL), followed by addition of H_2O (35 mL) and sat. aq $NaHCO_3$ (35 mL). The solution was well stirred for 10 min at r.t. The organic phase was collected, the aqueous phase was extracted with CH_2Cl_2 (3 × 70 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to yield *N*-tosyloctan-1-imine (**1a**) as a colorless oil (1.84 g, 65%). This material was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.60 (t, *J* = 4.6 Hz, 1 H), 7.81 (d, *J* = 8.2 Hz, 2 H), 7.34 (d, *J* = 8.2 Hz, 2 H), 2.51 (dt, *J* = 7.4, 4.6 Hz, 2 H), 2.40 (s, 3 H), 1.66–1.57 (m, 2 H), 1.39–1.14 (m, 8 H), 0.86 (t, *J* = 6.8 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.4 (CH), 144.4 (C), 134.4 (C), 129.5 (2 × CH), 127.8 (2 × CH), 35.6 (CH_2), 31.2 (CH_2), 28.7 (CH_2), 28.5 (CH_2), 24.3 (CH_2), 22.2 (CH_2), 21.3 (CH_3), 13.7 (CH_3). IR (neat): ν = 3292, 1629, 1020, 737 cm^{-1}.

(20) Please note that a minimum of 2.0 equiv of SmI_2 are required to carry out this transformation in a stoichiometric manner.

(21) Since magnesium is normally coated with a layer of MgO, we have previously treated the magnesium turnings with a few crystals of iodine to activate its surface.

(22) **Procedure for the Synthesis of Ethyl 3-(Tosylamino)-decanoate (3a)**
A solution of *N*-tosyloctan-1-imine (**1a**, 0.2 mmol) and ethyl bromoacetate (**2a**, 0.2 mmol) in THF (2.5 mL) was added dropwise at r.t. and vigorous stirring to a mixture of SmI_2 (0.1 M in THF, 0.8 mL) and activated Mg (1.2 mmol) with iodine and $ZnCl_2$ (1.2 mmol) in THF (2.5 mL). After stirring at the same temperature 3.5 h, the mixture was hydrolyzed with an aq solution of HCl (0.1 M, 10 mL). The aqueous phase was filtered through a pad of Celite® and extracted

with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography on silica gel (hexane–EtOAc, 5:1) provided pure ethyl 3-(tosylamino)decanoate (**3a**) as a yellow oil (62 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.0 Hz, 2 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 5.22 (d, *J* = 9.0 Hz, 1 H), 4.09–3.92 (m, 2 H), 3.50–3.38 (m, 1 H), 2.51 (ddd, *J* = 3.0, 15.0, 30.0 Hz, 2 H), 2.35 (s, 3 H), 1.47–1.06 (m, 12 H), 1.15 (t, *J* = 7.0 Hz, 3 H), 0.79 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.3 (C), 143.1 (C), 138.1 (C), 129.5 (2 × CH), 126.8 (2 × CH), 60.5 (CH_2), 50.6 (CH), 41.2 (CH_2), 38.8 (CH_2), 34.6 (CH_2), 31.6 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 25.6 (CH_2), 22.5 (CH_3), 21.4 (CH_3), 13.9 (CH_3). IR (neat): ν = 1747, 1331, 1160, 1094 cm^{-1}. HRMS: *m/z* calcd for $C_{19}H_{32}NO_4S$ $[M + H]^+$: 370.2052; found: 370.2049.

(23) For the synthesis of *N*-Boc imine **1g**, see: Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964.
(24) Molander, G. A.; Stengel, P. J. *J. Org. Chem.* **1995**, *60*, 6660.
(25) **Spectroscopic Data of Compound 3e**
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 8.2 Hz, 2 H), 7.14–7.10 (m, 5 H), 6.93 (d, *J* = 8.2 Hz, 2 H), 5.21 (d, *J* = 8.2 Hz, 1 H), 4.08–3.92 (m, 2 H), 3.74–3.63 (m, 1 H), 2.72 (d, *J* = 6.0 Hz, 1 H), 2.71 (d, *J* = 6.0 Hz, 1 H), 2.37 (d, *J* = 5.2 Hz, 2 H), 2.32 (s, 3 H), 1.15 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.6 (C), 143.5 (C), 137.8 (C), 137.1 (C), 129.9 (2 × CH), 129.6 (2 × CH), 128.9 (2 × CH), 127.3 (2 × CH), 127.0 (CH), 61.0 (CH_2), 52.2 (CH), 41.0 (CH_2), 38.3 (CH_2), 21.8 (CH_3), 14.4 (CH_3). IR (neat): ν = 2929, 1740, 1265, 1160, 738 cm^{-1}. HRMS: *m/z* calcd for $C_{19}H_{24}NO_4S$ $[M + H]^+$: 362.1426; found: 362.1428.

