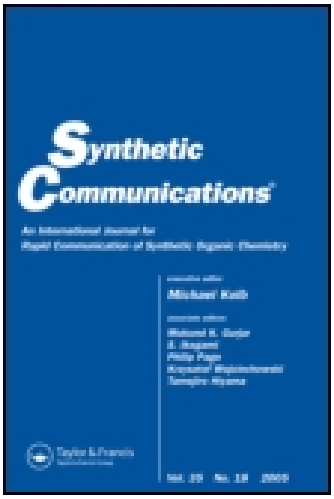

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DIASTEREOSELECTIVE APPROACH TO *cis*-4-METHYL/THIOL-PIPECOLIC ESTERS BASED ON RCM REACTION AND CONJUGATE MICHAEL ADDITION

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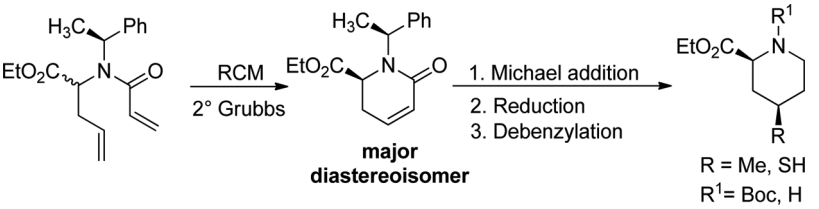
GRAPHICAL ABSTRACT



Abstract *A synthetic route for the access to enantiopure* cis*-4-methyl/thiol-pipecolic esters is presented. It is based on the ring-closing metathesis reaction to build the* α,β*-unsaturated piperidin-2-one derived from (*S*)-(−)-phenylethylamine, followed by either diastereoselective conjugate addition of methylorganocuprate allowing access to* cis*-4-methyl pipecolic ester or by tandem diastereoselective hydrosulforization–thionization reaction providing access to* cis*-4-thiol pipecolic ethyl esters.*

Keywords Diastereoselective Michael addition; hydrosulforization; pipecolic esters; ring-closing metathesis

INTRODUCTION

Cyclic α-amino acids are present in many biologically important compounds.[1] Specifically, 4-substituted pipecolic acids (4-substituted piperidine-2-carboxylic acid) and their derivatives are key fragments of compounds of pharmacological interest.

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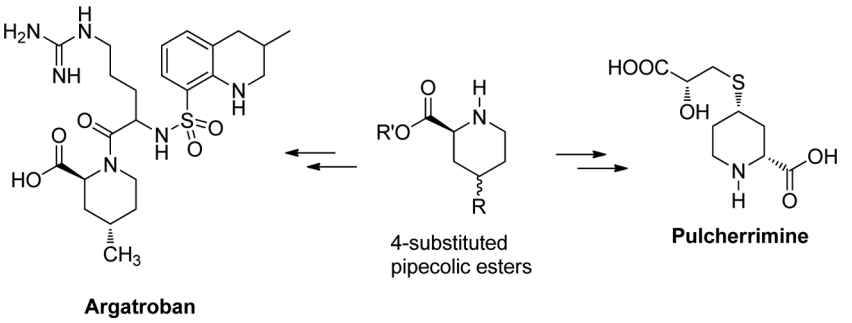


Scheme 1. Compounds containing 4-substituted pipecolic acids.

For example, argatroban, an important anticoagulant, is a small molecule direct thrombin inhibitor.[2] Sulfur-containing amino acids include pulcherrimine, from the ovaries of the sea urchin *Hemicentrotus pulcherrimus.*[3] Consequently, enantiopure 4-substituted-pipecolic esters, their acids, and their salts are, in general, important synthetic intermediates (Scheme 1).

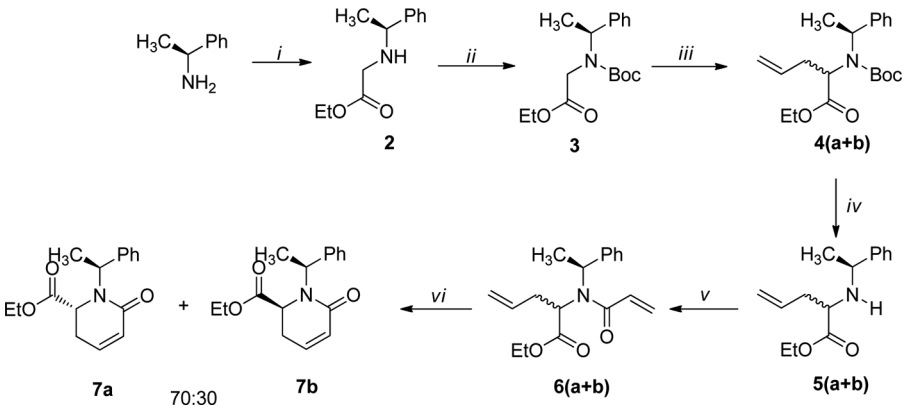
In this sense, approaches toward the synthesis of racemic or *cis-trans*-4-substituted mixture are known,[4] and several methodologies to the synthesis of *trans*-4-substituted pipecolic acids[5] and processes for the synthesis of *cis*-4-substituted pipecolic acid have been also disclosed.[6]

In this article, we describe a diastereoselective synthetic route to *cis*-4-methyl/thiol pipecolic ethyl esters based on the ring-closing methathesis reaction followed by either diastereoespecific conjugate addition of methylorganocuprate or by tandem diastereospecific hydrosulforization/thionization reaction. Interestingly, the presence of the ester function located at C-6 on the piperidine ring directs the nucleophilic attack on the Michael addition reaction.

DISCUSSION

The separable diastereomeric mixture of the α,β-unsaturated piperidin-2-ones **7a** + **7b** in six steps was prepared. First, (*S*)-(–)-phenylethylamine was treated with ethyl 2-bromoacetate, giving the corresponding chiral glycine **2,** which was treated with di-*tert*-butyl dicarbonate, affording the *N*-Boc protected glycine **3**. Next, the compound **3** was reacted with lithium diisopropylamide (LDA) and allyl iodide at −78 °C providing the unseparable diastereomeric mixture of alkylated adducts **4(a+b),**[7] which was reacted with trifluoroacetic acid (TFA) to deliver the deprotected diastereomeric mixture **5(a+b)**. These compounds were condensed with acryloyl chloride affording the unsaturated mixture **6(a+b)**. Finally, **6(a+b)** were subjected to a ring-closing metathesis reaction giving access to α,β-unsaturated diastereomeric mixture of **7a** + **7b** in 70:30 dr, determined by ^{1}H NMR from the crude reaction mixture (Scheme 2).[8]

The diastereomeric mixture of **7(a+b)** was separated, and then **7a** and **7b** were crystallized. The absolute configuration at C-6 was determined by X-ray diffraction analysis as (*R*) and (*S*) respectively (Fig. 1).[9]



Scheme 2. Reagents and conditions: (i) ethyl 2-bromoacetate, K_2CO_3(2 eq), CH_3CN, rt, 1.45 h, 90%. (ii) $(Boc)_2O$ (1.5 eq), H_2O, rt, 5 h, 98%. (iii) LDA (1.5 eq), THF, −78 °C, 3 h, then allyl iodide, −20 °C 8 h. (iv) TFA (5 eq), CH_2Cl_2, rt, 2 h. (v) Acryloyl chloride, K_2CO_3 (2 eq), CH_2Cl_2/H_2O 70% after three steps. (vi) Grubbs's second-generation (5 mol%), CH_2Cl_2, rt, 6 h, quantitative.

With the α,β-unsaturated piperidin-2-one in our hands, we started to explore the conjugate addition of methylcuprate to the α,β-unsaturated lactam **7a**. In this sense, Hanessian[10] reported that the conjugate addition of organocuprates to *N*-Boc unsaturated lactams delivers a mixture of *cis* and *trans* diastereoisomers. After testing various reaction conditions, the best result was obtained by the use of chlorotrimethylsilane (TMSCl), which accelerates copper-mediated conjugate addition reaction in THF.[11] This procedure afforded the desired 4-methyl piperidin-2-one **8a** as a mayor diastereoisomer (determined direct from the ^{1}H NMR spectra of the crude reaction mixture), in 80% yield. The analysis of two-dimensional nuclear Overhauser spectroscopy (2D-NOESY) experiments of lactam **8a** indicates that both substituents are *cis*-oriented for the lactam ring (Scheme 3). It is worth noting that Antoni et al.[12] reported a highly diastereoselective conjugate addition of methylorganocuprate to enantiopure *N*-Boc pipecolic α,β-unsaturated esters; however, in this case only the *trans*-4-methyl pipecolic ester was obtained.

Then, compound **7b** (minor diastereoisomer) was treated with methylcuprate following the optimized conditions described. 4-Methyl piperidin-2-one **8b** was obtained in 80% yield. The relative configuration at C-4 as (*S*) was confirmed from the X-ray analysis diffraction of compound **8b** (Fig. 2).[13]

Next, diastereoisomers **8a** and **8b** were treated with BH_3 SMe_2 giving the corresponding piperidines **9a** and **9b** in 95% yield, which were subject to hydrogenolysis

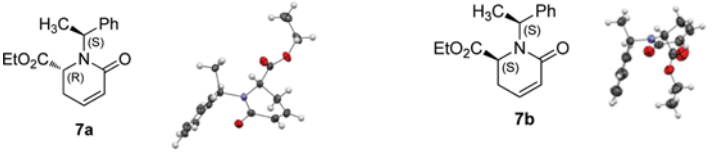
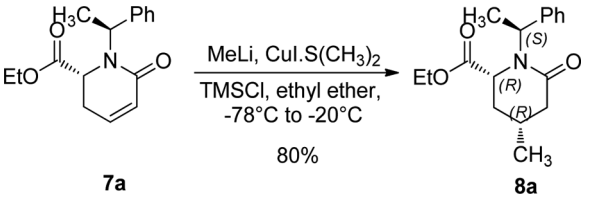


Figure 1. X-ray ORTEP diagram of compounds **7a** and **7b**.



Scheme 3. Diastereoselective conjugate addition of methyl cuprate to α,β-unsaturated lactam **7a**.

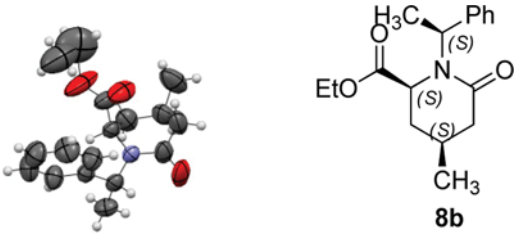
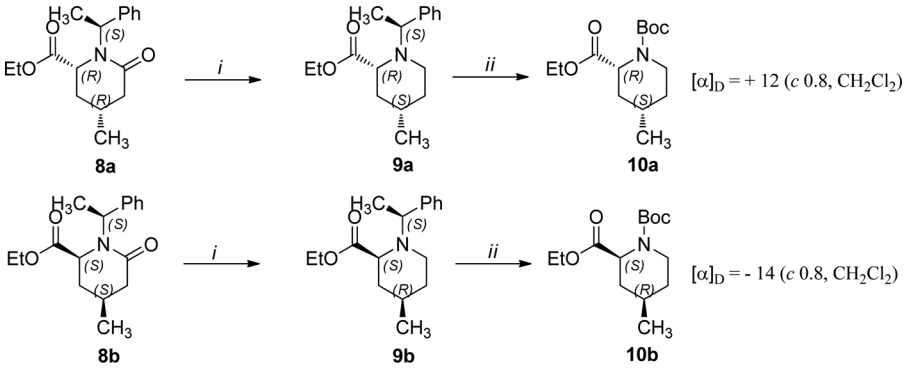


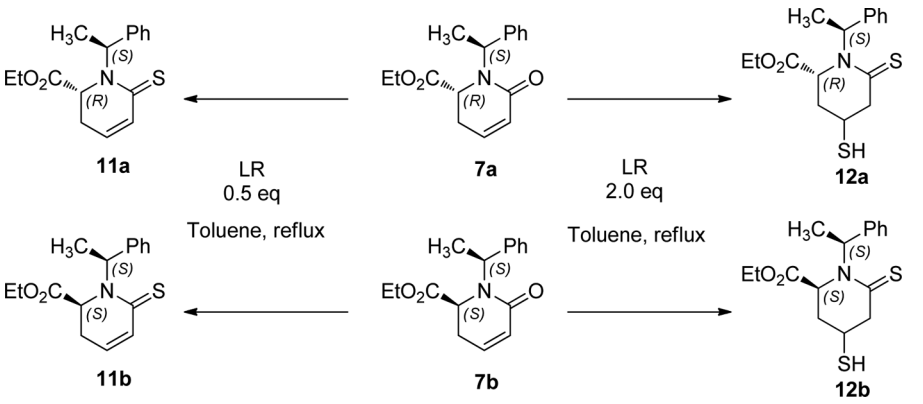
Figure 2. X-ray ORTEP diagram of compound **8b**.

in the presence of di-*tert*-butyl dicarbonate to give the *N*-Boc-protected piperidines **10a** and **10b**. The comparison of its optical rotation confirmed that **10a** and **10b** are enantiomers and as a correlation compound **8a** have the (*R*) configuration at C-4 (Scheme 4).

We then oriented our attention to the reactivity of **7a** (major diastereoisomer) toward Lawesson's reagent (LR), taking into account our previous report.[14] When compound **7a** was treated with 0.5 equivalents of LR in boiling toluene, the expected unsaturated thioamide **11a** was obtained in 70% yield. Interestingly, the treatment of **7a** with an equimolar amount of LR gave a mixture of compound **11a** and the unexpected 4-mercapto-substituted thioamide **12a** as a single diastereoisomer. The use of 2 equivalents of LR resulted in exclusive formation of compound **12a** in 73% yield. Finally, compound **7b** showed the same behavior toward LR (Scheme 5).



Scheme 4. Reagents and conditions: (i) BH_3 SMe_2, THF, 25 °C, 95%. (ii) H_2, $(Boc)_2O$, $Pd(OH)_2$, AcOEt, 25 °C, 90%.



Scheme 5. Reactivity of α,β-unsaturated lactam **7a** toward the Lawesson's reagent.

Compounds **12a** and **12b** were crystallized and the absolute configuration at C-4 was determined by x-ray analysis diffraction as (*R*) for **12a** and (*S*) for **12b**, and the presence of the thiol function was also confirmed (Fig. 3).[15]

To obtain the corresponding pipecolic ethyl ester, compound **12b** was treated with BH_3 SMe_2, affording the desired reduced compound **13b** in 95% yield. Debenzylation of **13b** was performed under Birch conditions to give the desired piperidine **14b** in 43% yield (Scheme 6).

In conclusion, an efficient method for the diastereoselective synthesis of *cis*-4-methyl/thiol-pipecolic ethyl esters from (*S*)-phenylethylamine has been developed.

The stereochemical outcome showed that the conjugate addition occurs from the same side of the ester function located at C-6 on the piperidine ring. Expansion of the protocol scope and application of this methodology to the total synthesis are currently under way in our group.

EXPERIMENTAL

(*R*)-Ethyl-1,2,3,6-tetrahydro-6-oxo-1-((*S*)-1-phenylethyl)pyridine-2-carboxylate, 7a

$[\alpha]_D^{20} = +18.45$ (*c* 1.0, CH_2Cl_2); bp = 96–98 °C. IR (film) 2964, 2924, 1738, 1659, 1429, 1018, 809, 707, 536 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, $J = 7.2$ Hz, 3H), 1.45 (d, $J = 7.2$ Hz, 3H), 2.50 (AB, $J = 1.6$, 6.0, 2.3, 2.9, 7.0, 18.1 Hz, *2*H), 3.86

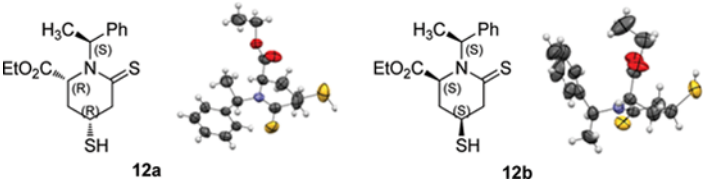
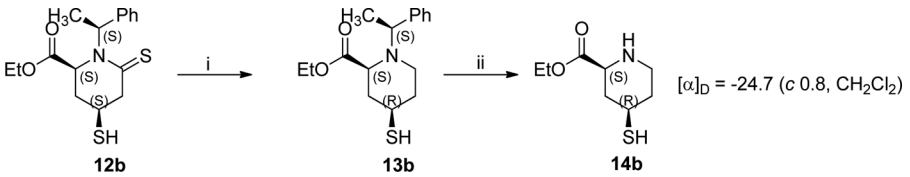


Figure 3. X-ray ORTEP diagram of compounds **12a** and **12b**.



Scheme 6. Reagents and conditions: (i) BH_3 SMe_2, THF, 25 °C, 95%. (ii) Na/NH_3, −78 °C, 43%.

(ddd, $J = 1.1$, 1.6, 7.0 Hz, 1H), 4.17 (q, $J = 7.2$ Hz, 2H), 6.04 (m, 2H), 6.35 (m, 1H), 7.28 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 15.1, 28.3, 50.1, 53.0, 61.6, 126.3–141.0, 163.7, 172.0. HRMS (FAB): Calcd. for $C_{16}H_{19}NO_3$: 273.1365. Found: 273.1368.

(*S*)-Ethyl-1,2,3,6-tetrahydro-6-oxo-1-((*S*)-1-phenylethyl)pyridine-2-carboxylate, 7b

$[\alpha]_D^{20} = -55.73$ (*c* 1.0, CH_2Cl_2); bp = 58–60 °C; IR (film) 2978, 2932, 1744, 1665, 1609, 1433, 1190, 1084, 1033, 813, 702 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.93 (t, $J = 7.1$ Hz, 3H), 1.55 (d, $J = 7.1$ Hz, 3H), 2.60 (ddd, $J = 1.0$, 6.1, 18.1 Hz, 1H), 2.72 (m, 1H), 3.54 (m, 1H), 3.70 (m, 1H), 4.11 (d, $J = 7.4$ Hz, 1H), 6.03 (dd, $J = 3.0$, 9.8 Hz, 1H), 6.06 (q, $J = 7.1$ Hz, 1H), 6.29 (m, 1H), 7.26 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 17.3, 28.7, 50.4, 52.6, 61.0, 126.7–138.2, 163.5, 170.9. HRMS (FAB): calcd. for $C_{16}H_{19}NO_3$: 273.1365. Found: 273.1368.

General Procedure for Conjugate Michael Addition of Organocuprate

Methyl lithium (0.5 M in Et_2O, 5 eq) was added to a suspension of CuBr SMe_2 (5 eq) in Et_2O at −15 °C. The resulting yellow suspension was stirred for 45 min at −15 °C, and then **7a** (0.100 g, 0.183 mmol, 1 eq) in 6 mL of Et_2O and TMSCl (0.148 mL, 0.585 mmol, 3.2 equiv) were successively added. The mixture was warmed to 0 °C and stirred for 18 h. After quenching at 0 °C with saturated NH_4Cl, a few drops of saturated NH_4OH were added until the aqueous layer remained colorless. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography to afford the expected product **8a** as a white solid in 80% yield.

(2*R*,4*R*)-Ethyl-4-methyl-6-oxo-1-((*S*)-1-phenylethyl)piperidine-2-carboxylate, 8a. $[\alpha]_D^{20} = -15.1$ (*c* 1.0, CH_2Cl_2). IR (film) 2950, 2938, 1741, 1654, 1434, 1198, 1029, 922, 732, 691 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, $J = 6.4$ Hz, 3H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.45 (d, $J = 7.2$ Hz, 3H), 1.51 (m, 1H), 1.97 (m, 2H), 2.15 (dd, $J = 12$, 15.6 Hz, 1H), 2.50 (ddd, $J = 1.8$, 4.4, 15.6 Hz, 1H), 3.74 (dd, $J = 4$, 8.7 Hz, 1H), 4.16 (q, $J = 7.1$ Hz, 2H), 5.98 (q, $J = 7.1$ Hz, 1H), 7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 15.7, 21.7, 26.2, 34.1, 40.4, 50.7, 53.4, 61.4, 127.3–128.4, 133.9, 140.1, 172.2, 173.4. HRMS (FAB): calcd. for $C_{17}H_{23}NO_3$: 289.1678. Found: 289.1680.

(2*S*,4*S*)-Ethyl-4-methyl-6-oxo-1-((*S*)-1-phenylethyl)piperidine-2-carboxylate, 8b. $[\alpha]_D^{20} = -152$ (*c* 1.0, CH_2Cl_2); bp = 68–70 °C. IR (film) 2949, 2935, 1742, 1651, 1436, 1187, 1029, 733, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, *J* = 6.6 Hz, 3H), 1.0 (t, *J* = 7.1 Hz, 3H), 1.48 (m, 1H), 1.54 (d, *J* = 7.1 Hz, 3H), 1.94 (m, 1H), 2.15 (dd, *J* = 12.1, 15.8 Hz, 1H), 2.26 (m, 1H), 2.48 (ddd, *J* = 2.0, 4.5, 15.8 Hz, 1H), 3.60 (m, 2H), 4.08 (dd, *J* = 5.4, 8.6 Hz, 1H), 5.8 (q, *J* = 7.1 Hz, 1H), 7.25 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 16.1, 21.4, 26.3, 34.7, 40.8, 51.7, 54.7, 61.0, 127.5-128.5, 139.2, 171.8, 172.3. HRMS (FAB): Calcd. for $C_{17}H_{23}NO_3$: 289.1678. Found: 289.1681.

General Procedure for Thionation of α,β-Unsaturated Lactams 7a and 7b

Lawesson's reagent (1.024 mmol, 2.0 eq) was added to a solution of **7a** (0.140 g, 0.512 mmol, 1.0 eq) in 10 mL of dry toluene. The resulting mixture was stirred for 4 h at reflux temperature and then concentrated under reduced pressure. The residue was purified by column chromatography using 80:20 petroleum ether/AcOEt as the eluent to give the compound **12a** as a white solid in 60% yield.

(2*R*,4*R*)-Ethyl-4-mercapto-1-((*S*)-1-phenylethyl)-6-thioxopiperidine-2-carboxylate, 12a. $[\alpha]_D^{20} = -207.4$ (*c* 1.0, CH_2Cl_2). IR (film) 2976, 2926, 1740, 1465, 1311, 1197, 1085, 1023, 801, 700 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.1 Hz, 3H), 1.54 (d, *J* = 7.1 Hz, 3H), 1.84 (d, *J* = 6.5 Hz, 1H), 2.12 (m, 2H), 2.81 (dd, *J* = 11.6, 15.8 Hz, 1H), 3.15 (m, 1H), 3.64, (dd, *J* = 5.5, 15.7 Hz, 1H), 3.98 (dd, *J* = 2.7, 7.4 Hz, 1H), 4.25, (m, 2H), 7.13 (q, *J* = 7.1 Hz, 1H), 7.34 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 14.4, 29.4, 36.3, 52.4, 55.3, 57.8, 62.4, 127.0–128.8, 138.4, 170.3, 201.0. HRMS (FAB): calcd. for $C_{16}H_{21}NO_2S_2$: 323.1014. Found: 323.1016.

(2*S*,4*S*)-Ethyl-4-mercapto-1-((*S*)-1-phenylethyl)-6-thioxopiperidine-2-carboxylate, 12b. $[\alpha]_D^{20} = -348.9$ (*c* 1.0, CH_2Cl_2). IR (film) 2975, 2930, 1736, 1466, 1313, 1199, 1073, 910, 730, 691 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.1 Hz, 3H), 1.52 (d, *J* = 7.0 Hz, 3H), 1.81 (d, *J* = 6.6 Hz, 1H), 2.15 (ddd, *J* = 2.3, 5.9, 14.7 Hz, 1H), 2.56 (m, 1H), 2.96 (dd, *J* = 11.3, 15.6 Hz, 1H), 3.18 (m, 1H), 3.63 (ddd, *J* = 0.8, 5.6, 15.6 Hz, 1H), 3.73, (m, 2H), 4.2 (dd, *J* = 2.3, 8.3 Hz, 1H), 7.14 (q, *J* = 7.1 Hz, 1H) 7.30 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 14.4, 29.7, 37.2, 52.3, 55.3, 58.1, 61.7, 128.2-128.9, 136.8, 169.4, 200.7. HRMS (FAB): Calcd. for $C_{16}H_{21}NO_2S_2$: 323.1014. Found: 323.1017.

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SUPPORTING INFORMATION

Full experimental details and ^1H and ^{13}C NMR spectra for this article can be accessed on the publisher's website.

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