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Syntheses of *trans*- and *cis*-3-Methoxy-4-methylthio-2-piperidinethiones. Previously Proposed Structures for Raphanusanins, Structural Revision, and Biological Activities of Their Congeners

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Related to raphanusanins, light-induced growth inhibitors of radish seedlings, syntheses of *trans*- and *cis*-3-methoxy-4-methylthio-2-piperidinethiones provided the structural revision of the natural products. During syntheses of several piperidinethione derivatives, the dihydropyridinethione derivative was found to possess twentyfold stronger inhibitory activity than the natural products.

Raphanusanins A and B were isolated as light-induced plant growth inhibitors from the light-exposed Sakurajima radish seedlings (*Raphanus sativus* L. var. *hortensis* f. *gigantissimus* Makino).[1] The amount of these inhibitors increased apparently under red light, but decreased or maintained the initial level in the dark, suggesting that they may play an important role in phytochrome-mediated light inhibition.[1] Recently, it has been reported that the raphanusanins are not only concerned in the light growth inhibition but also in phototropism of radish seedlings; these substances increased in the illuminated sides during phototropic curvature proportional to light intensities, and their unilateral application caused the hypocotyl to bend toward the site of application.[2] It was also reported that auxin was evenly distributed over the illuminated and shaded sides during phototropic curvature.[3] Furthermore, Sakoda et al. found that the raphanusanins induce growth inhibition through interference with the auxin-mediated microtubule orientation.[4] These data indicate that phototropism is not regulated by a lateral auxin gradient, but instead unilateral illumination induces the unequal distribution of the substances inhibiting auxin activity.[5] Hasegawa et al. have proposed the structures of raphanusanins A and B, or previously named *trans*- and *cis*-raphanusanins to be **1** and **2**, respectively.[1]

The prominent biological activities of raphanusanins prompted us to initiate synthesis of *trans*- and *cis*-3-methoxy-4-methylthio-2-piperidinethiones (**1** and **2**).

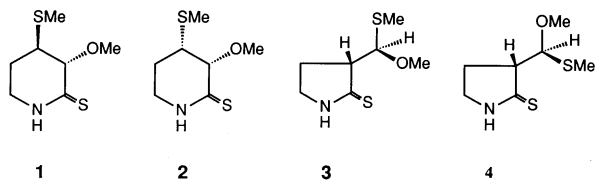
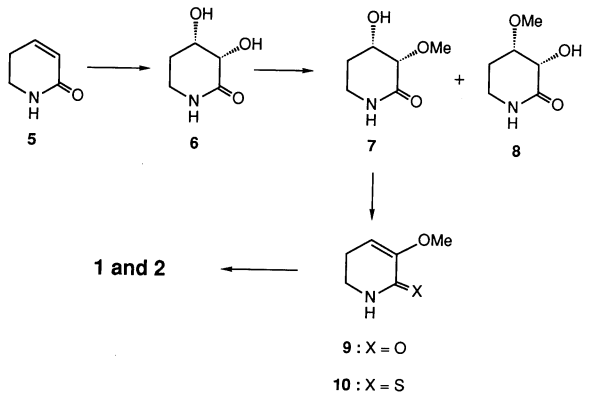


Fig. 1. Structures of the proposed (**1** and **2**) and the newly determined (**3** and **4**) raphanusanins.

We describe herein our research process.[6]

Results and Discussion

When the known 5,6-dihydro-2(1*H*)-pyridinone (**5**)[7] was oxidized under OsO_4–*N*-methylmorpholine *N*-oxide conditions, the corresponding *cis*-diol (**6**) was obtained in high yield. Selective methylation of **6** was undertaken by reaction with *n*-Bu_2SnO, followed by addition of CsF and MeI[8] to provide an approximately 1 : 2 mixture of **7** and **8**. Their structures could be determined by comparison of the ^1H NMR spectra, where the H-3 and 4 protons appeared at δ=3.65 (as a sharp doublet) and 4.27 (as a broad ddd) in **7**, and at δ=4.10 (as a broad doublet) and 3.95 (as a multiplet) in **8**. Upon irradiation of each OH signal (δ=2.79 in **7**; δ=3.75 in **8**), the resonance ascribed to the H-4 proton of **7** changed into a sharp ddd, whereas the broad doublet in the spectrum of **8** sharpened. Accordingly, the OH groups of **7** and **8** should be located as depicted in Scheme 1. Conversion of **7** into the enone (**9**) was effected by *p*-toluenesulfonylation of the OH group, followed by β-elimination under basic conditions. Any Michael-type additions made to introduce a methylthio function to the



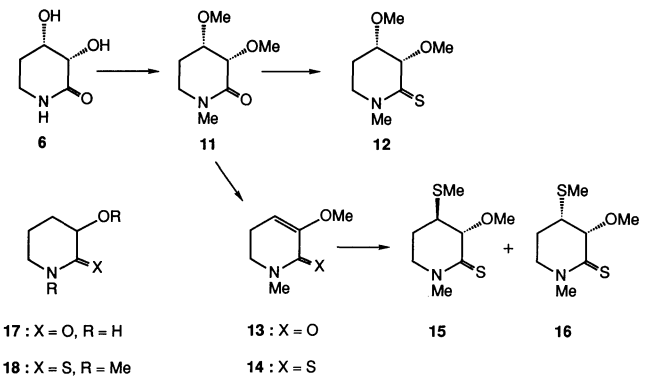
Scheme 1.

C-4 position of **9** were unsuccessful, probably due to ready β-elimination process under the reaction conditions. Therefore, **9** was further transformed into the corresponding enethione (**10**) by $(MeOC_6H_4)_2P_2S_4$ (Lowesson's reagent). Upon treatment of **10** with MeSH in the presence of catalytic amounts of K_2CO_3, the desired Michael reaction proceeded smoothyl to provide **1** and **2**. Although the spectral data of both compounds agreed with the expected structures, they were entirely different from the published data.[1] Therefore we reexamined the ^1H and ^{13}C NMR spectral data of raphanusanins in detail by comparing with those of synthetic **1** and **2**. The apparent difference could be found in the ^1H NMR spectra, where the proton resonances of the C-3 position bearing a MeO group of **1** and **2** were observed at δ=4.00 and 4.12, while the corresponding signals appeared in the lower magnetic fields [δ=5.04 in raphanusanin A; δ=5.11 in raphanusanin B], indicating that they should bear one more electron-withdrawing group. Thus, the signals in natural raphanusanins indicated the presence of such acetal as (MeO)(MeS)CH group. Ultimately, the stereostructures of raphanusanins A and B were unambiguously determined by an X-ray crystallographic analysis, as shown in **3** and **4**,[9,10] which were identical with those of raphantins.[11] Interestingly, however, a 1 : 1 mixture of the synthetic piperidinethiones (**1** and **2**) inhibited the hypocotyl growth of etiolated lettuce seedling, and their biological activities were not significantly different from those of natural raphanusanins (**3** and **4**), although the activities of the synthetic compounds were slightly lower, as seen in Table 1.

Table 1. The Biological Activities[a] of Natural Raphanusanins A and B (**3** and **4**) and the Synthesized 2-Piperidinethione Derivatives (**1**+**2**, **12**, **14**, **15**, **16**, and **18**)

Compounds	1+2	3	4	12	14	15	16	18
I_{50} ($\times 10^{-3}$ M)	5.2	3.2	2.6	0.95	0.12	1.1	4.9	3.5

a) Lettuce hypocotyl length.



Scheme 2.

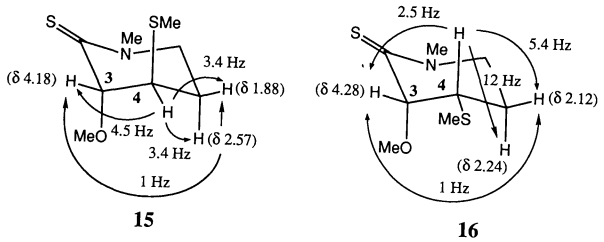


Fig. 2. The reasonable conformations of **15** and **16**.

In the light of these results, we further synthesized several 2-piperidinethiones to evaluate their activities, as follows.

Exhaustive methylation of **6** provided the trimethyl derivative (**11**) in 65% yield, which on exposure to Lowesson's reagent furnished the corresponding **12** in 76% yield. As an alternative manipulation of **11**, basic treatment effected β-elimination to give the enone (**13**). After conversion of the carbonyl oxygen of **13** into a sulfur atom, the resulting **14** was submitted to the Michael addition as described in the case of **10**, leading to the methylated derivatives of **1** and **2** (**15** and **16**). Their stereostructures including the reasonable conformations were determined based on their ^1H NMR spectral data, where the characteristic difference appeared in the resonances of the methine proton at the C-4 position bearing a MeS group [**15**: δ=3.14 (dt, J=3.4, 4.5 Hz); **16**: δ=2.88 (ddd, J=2.5, 5.4, 12 Hz)]. As depicted in Fig. 2, an equatorial orientation of the proton of **15** was indicated by the small eq-ax and eq-eq coupling constants, whereas that of **16** was assigned as an axial orientation. Long range couplings [J=1 Hz] between H-3 and 5eq protones [**15**: δ=4.18 (H-3) and 1.88 (H-5eq); **16**: δ=4.28 (H-3) and 2.12 (H-5eq)] supported that both derivatives bear an axial MeO group at the C-3 position.

Additionally, the demethylthio derivative (**18**) was also synthesized in two steps [1. MeI–NaH; 2. Lowesson's reagent] starting from commercially available 3-hydroxyl-2-piperidinone (**17**).

Biological Activities.[12] As shown in Table 1, apparently, the newly synthesized derivatives (**1**, **2**, **12**, **14**, **15**, **16**, and **18**) exhibited potent inhibitory activities against the lettuce hypocotyl growth. Amongst them, the α,β-unsaturated thiolactam (**14**) had approximately twentyfold stronger activity than those of natural raphanusanins. In the present study, it was found out that the thiolactam functions are an indispensable function for the inhibitory activity, since a lactam derivative did not show the inhibitory activity. In addition, it would be suggested that such α,β-unsaturated function might play an important role, whereas a MeS group at the C-4 position of 2-piperidinones was not a crucial factor. Further extensive studies on structure–activity relationships are in progress.

Experimental

All the melting points were obtained on a Mitamura Riken melting point apparatus and uncorrected. IR spectra were recorded on a JASCO Model A-202 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were obtained on a JEOL FX-90 A or JEOL JNM GX-400 NMR spectrometer in deuteriochloroform ($CDCl_3$) solution using tetramethylsilane as an internal standard, unless otherwise stated. High-resolution mass spectra were obtained on a Hitachi M-80 GC-MS spectrometer operating with an ionization energy (70 eV). Preparative and analytical TLC were carried out on silica-gel plates (Kieselgel 60 F254, E. Merck. A. G., Germany) using UV light and/or 5% molybdophosphoric acid in ethanol for detection. Katayama silica gel (K 070) was used for column chromatography.

***cis*-3,4-Dihydroxy-2-piperidinone (6).** A mixture of **5** (45 mg) and *N*-methylmorpholine *N*-oxide (70 mg) in *t*-BuOH (1.5 ml) in the presence of catalytic amounts of OsO_4 was stirred at room temperature for 27 h. To the reaction mixture was added $Na_2S_2O_4$ (200 mg) and H_2O (0.05 ml), and the resulting suspension was kept at room temperature overnight. After removal of the solvents, the syrup obtained was diluted with MeOH and filtered. The filtrate was concentrated in vacuo to give a residue, which was submitted to silica-gel column chromatography (gradient elution from $CHCl_3$ to $CHCl_3$–MeOH=4 : 1) to give 64 mg of **6** as crystals: Mp 138—140 °C (from $CHCl_3$–MeOH); IR (film) 3250 and 1665 cm^{-1}; ^1H NMR (CD_3OD) δ=2.00 (2H, complex), 3.05—3.67 (2H, overlapped with solvent signal), 3.99 (1H, broad d, J=4 Hz), and 4.20 (1H, broad q, J=4 Hz); ^{13}C NMR (CD_3OD) δ=28.9 (t), 39.3 (t), 68.9 (d), 72.1 (d), and 175.8 (s). Found: m/z 132.0660. Calcd for $C_5H_{10}NO_3$: M+1, 132.0660.

***cis*-4-Hydroxy-3-methoxy-2-piperidinone (7) and *cis*-3-Hydroxy-4-methoxy-2-piperidinone (8).** A suspension of **6** (2.39 g) and *n*-Bu_2SnO (3.06 g) in benzene (30 ml) and MeOH (2 ml) was heated at refluxing temperature for 20 h, while removing water formed as the azeotropic mixture. The reaction mixture was evaporated to dryness, and a mixture of the residue, CsF (3.06 g), and MeI (4 ml) in DMF (35 ml) was stirred at room temperature for 12 h. Precipitates were filtered off, and the filtrate was evaporated to give a white solid, which was separated by a silica-gel column ($CHCl_3$–MeOH=7 : 1) to give crystalline **7** (0.15 g) and **8** (0.32 g).

7: Mp 143—145 °C (from hexane–EtOAc); IR (film) 3250 and 1665 cm^{-1}; ^1H NMR δ=1.92 (1H, m), 2.11 (1H, m), 2.79 (1H, broad s), 3.19 (1H, m), 3.56 (1H, m), 3.65 (1H, d, J=3 Hz), 3.68 (3H, s), 4.27 (1H, broad ddd, J=each 3 Hz), and 6.11 (1H, broad s); ^{13}C NMR (CD_3OD) δ=28.6 (t), 39.2 (t), 60.0 (q), 67.1 (d), 81.3 (d), and 174.2 (s). Found: m/z 146.0840. Calcd for $C_6H_{12}NO_3$: M+1, 146.0816.

8: Mp 147—149 °C (from hexane–EtOAc); IR (film) 3250 and 1660 cm^{-1}; ^1H NMR δ=1.92 (1H, m), 2.21 (1H, m), 3.25 (1H, m), 3.51 (3H, s, overlapped with 1H signal), 3.75 (1H, broad s), 3.95 (1H, m), 4.10 (1H, broad d, J=3 Hz), and 6.32 (1H, broad s); ^{13}C NMR (CD_3OD) δ=25.7 (t), 39.3 (t), 58.6 (q), 71.9 (d), 78.7 (d), and 175.6 (s). Found: m/z 146.0821. Calcd for $C_6H_{12}NO_3$: M+1, 146.0816.

5,6-Dihydro-3-methoxy-2(1*H*)-pyridinone (9). A mixture of **7** (17 mg) and TsCl (38 mg) in pyridine (0.7 ml) was kept at room temperature for 17 h. The reaction mixture was partitioned between $CHCl_3$ and 1 M HCl (1 M=1 mol dm^{-3}), and the organic extract was washed with brine, then dried over anhydrous Na_2SO_4. After evaporation, the residue was purified by preparative TLC ($CHCl_3$–MeOH=10 : 1) to yield the corresponding oily tosylate (15 mg).

To a solution of the tosylate (40 mg) in MeOH (5 ml) was added K_2CO_3 (100 mg), and the suspension was stirred at room temperature for 3 h. The resulting mixture was concentrated in vacuo, and the residue was diluted with $CHCl_3$. The suspension was filtered using a Celite pad to remove inorganic salts, and the filtrate was evaporated to give a residue, which on purification by preparative TLC ($CHCl_3$–MeOH=10 : 1) provided **9** (19 mg) as an oil: IR (film) 1665 and 1620 cm^{-1}; ^1H NMR δ=2.41 (2H, complex), 3.38 (2H, t, J=6.8 Hz), 3.64 (3H, s), 5.44 (1H, t, J=4.5 Hz), and 6.63 (1H, broad s); ^{13}C NMR δ=22.7 (t), 39.9 (t), 55.0 (q), 105.1 (d), 147.7 (s), and 163.5 (s). Found: m/z 127.0628. Calcd for $C_6H_9NO_2$: M, 127.0632.

5,6-Dihydro-3-methoxy-2-(1*H*)-pyridinethione (10). A mixture of **9** (19 mg) and Lawesson's reagent (58 mg) in toluene (5 ml) was heated for 2 h at 70 °C. The reaction mixture was evaporated to give a residue, which was purified by preparative TLC ($CHCl_3$–MeOH=5 : 1) to afford **10** (14 mg) as an oil: IR (film) 3220, 1630, and 1510 cm^{-1}; ^1H NMR δ=2.45 (2H, dt, J=4.9, 7.3 Hz), 3.35 (1H, t, J=7.3 Hz), 3.36 (1H, t, J=7.3 Hz), 3.67 (3H, s), 5.31 (1H, t, J=4.9 Hz), and 8.00 (1H, broad s); ^{13}C NMR δ=22.5 (t), 41.4 (t), 55.7 (q), 100.6 (d), 150.4 (s), and 190.4 (s). Found: m/z 143.0396. Calcd for C_6H_9NOS: M, 143.0403.

***trans*-3-Methoxy-4-methylthio-2-piperidinethione (1) and *cis*-3-Methoxy-4-methylthio-2-piperidinethione (2).** A solution of **10** (8 mg) in 30% MeSH in MeOH (1.5 ml) in the presence of catalytic amounts of K_2CO_3 was stirred at room temperature overnight. The resulting mixture was evaporated, and chromatographed using preparative TLC (hexane–EtOAc=1 : 1, three times development) to give oily **1** (2.3 mg) and **2** (2.9 mg).

1: IR (film) 3200 and 1550 cm^{-1}; ^1H NMR δ=2.05 (1H, m), 2.15 (1H, m), 2.19 (3H, s), 2.89 (1H, ddd, J=2.9, 4.9, 11.2 Hz), 3.36 (1H, m), 3.55 (1H, m), 3.70 (3H, s), 4.12 (1H, d, J=2.9 Hz), and 8.17 (1H, broad s); ^{13}C NMR (C_6D_6) δ=14.0 (q), 22.2 (t), 41.0 (t), 43.6 (d), 59.6 (q), 83.8 (d), and 198.9 (s). Found: m/z 191.0440. Calcd for $C_7H_{13}NOS_2$: M, 191.0437.

2: IR (film) 3200 and 1550 cm^{-1}; ^1H NMR δ=1.85 (1H, m), 2.20 (3H, s), 2.43 (1H, m), 3.13 (1H, dt, J=3.9, 4.9 Hz), 3.35 (1H, m), 3.45 (1H, m), 3.68 (3H, s), 4.00 (1H, d, J=3.9 Hz), and 8.16 (1H, broad s); ^{13}C NMR (C_6D_6) δ=14.1 (q), 22.3 (t), 43.5 (t), 44.3 (d), 60.1 (q), 84.0 (d), and 199.5 (s). Found: m/z 191.0436. Calcd for $C_7H_{13}NOS_2$: M, 191.0437.

***cis*-3,4-Dimethoxy-1-methyl-2-piperidinone (11).** To an ice-cooled solution of **6** (167 mg) in DMF (15 ml) was added NaH (120 mg, 60% disperision in mineral oil), and the resulting mixture was stirred at room temperature. After 1 h, methyl iodide (1.5 ml) was added, and the stirring was further continued for 4 h. The reaction was quenched by addition of AcOH, and the mixture was evaporated to dryness. The residue was chromatographed on a silica-gel column ($CHCl_3$–MeOH=20 : 1) to give 144 mg of **11** as an oil; IR (film) 1660 cm^{-1}; ^1H NMR δ=1.93 (1H, m), 2.22 (1H, m), 2.92 (3H, s), 3.17 (1H, dd, J=6.7, 12.2 Hz), 3.39 (1H, dd, J=6.1, 12.2 Hz), 3.45 (3H, s), 3.64 (3H, s), 3.70 (1H, dt, J=8.8, 3 Hz), and 3.79 (1H, d, J=3 Hz); ^{13}C NMR δ=23.5 (t), 34.1 (q), 45.9 (t), 57.0 (q), 59.7 (q), 76.0 (d), 78.5 (d), and 168.2 (s). Found: m/z 174.1109.

Calcd for $C_8H_{16}NO_3$: M, 174.1120.

***cis*-3,4-Dimethoxy-1-methyl-2-piperidinethione (12).** To a solution of **11** (32 mg) in toluene (2 ml) was added Lowesson's reagent (61 mg), and the mixture was stirred at 55°C for 2 h. After evaporation, the residue was purified by preparative TLC (hexane–EtOAc=2:3) to yield **12** (27 mg) as an oil: IR (film) 1535 cm^{-1}; ^1H NMR δ=2.09 (1H, m), 2.25 (1H, m), 3.39 (3H, s), 3.43 (3H, s, overlapped with 1H signal), 3.56 (1H, m), 3.67 (3H, s), 3.74 (1H, m), and 4.38 (1H, broad d, J=2.4 Hz); ^{13}C NMR δ=22.9 (t), 42.7 (q), 51.4 (t), 56.7 (q), 59.6 (q), 75.0 (d), 83.4 (d) and 195.9 (s). Found: m/z 158.0658. Calcd for $C_7H_{12}NOS$: M−OMe, 158.0639.

5,6-Dihydro-3-methoxy-1-methyl-2(1*H*)-pyridinone (13). A mixture of **11** (213 mg) and K_2CO_3 (340 mg) in MeOH (6 ml) was heated at 50°C. After 20 h, the reaction mixture was filtered, and the filtrate was concentrated in vacuo to give a residue, which on chromatographic purification yielded **13** (99 mg) as an oil: IR (film) 1680 and 1640 cm^{-1}; ^1H NMR δ=2.39 (2H, complex), 3.02 (3H, s), 3.38 (2H, complex), 3.62 (3H, s), and 5.33 (1H, t, J=4.5 Hz); ^{13}C NMR δ=21.7 (t), 34.8 (q), 47.9 (t), 55.1 (q), 103.0 (d), 148.0 (s), and 162.2 (s). Found: m/z 141.0805. Calcd for $C_7H_{11}NO_2$: M, 141.0789.

5,6-Dihydro-3-methoxy-1-methyl-2(1*H*)-pyridinethione (14). Compound **13** (45 mg) was treated with Lowesson's reagent (130 mg) in toluene (2.5 ml) as described in the case of **12**. Chromatographic purification of the crude product provided **14** (23 mg) as an oil: IR (film) 1630 and 1540 cm^{-1}; ^1H NMR δ=2.43 (2H, complex), 3.55 (3H, s, overlapped with 2H signal), 3.68 (3H, s), and 5.24 (1H, t, J=4.9 Hz); ^{13}C NMR δ=21.4 (t), 43.4 (q), 50.5 (t), 56.0 (q), 97.7 (d), 150.9 (s), and 187.7 (s). Found: m/z 157.0546. Calcd for $C_7H_{11}NOS$: M, 157.0560.

***trans*-3-Methoxy-1-methyl-4-methylthio-2-piperidinethione (15) and *cis*-3-Methoxy-1-methyl-4-methylthio-2-piperidinethione (16).** Treatment of **14** (37 mg) with the same procedure as in the case of **1** and **2** furnished oily **15** (7 mg) and **16** (9 mg).

15: IR (film) 1535 cm^{-1}; ^1H NMR δ=1.88 (1H, m), 2.18 (3H, s), 2.57 (1H, m), 3.14 (1H, dt, J=3.4, 4.5 Hz), 3.42 (3H, s), 3.51 (2H, complex), 3.64 (3H, s), and 4.18 (1H, dd, J=1.0, 3.4 Hz); ^{13}C NMR (C_6D_6) δ=13.9 (q), 23.6 (t), 42.5 (q), 43.4 (d), 48.7 (t), 59.2 (q), 85.5 (d), and 195.5 (s). Found: m/z 189.0234. Calcd for $C_7H_{11}NOS_2$: M−CH_4, 189.0281.

16: IR (film) 1535 cm^{-1}; ^1H NMR δ=2.12 (1H, m), 2.18 (3H, s), 2.24 (1H, m), 2.88 (1H, ddd, J=2.5, 5.4, 12 Hz), 3.40 (3H, s, overlapped with 1H signal), 3.69 (3H, s, overlapped with 1H signal), and 4.28 (1H, dd, J=1, 2.5 Hz); ^{13}C NMR (C_6D_6) δ=14.2 (q), 24.2 (t), 42.0 (q), 44.1 (d), 51.5 (t), 60.1 (q), 85.7 (d) and 196.5 (s). Found: m/z 206.0640. Calcd for $C_8H_{16}NOS_2$: M+1, 206.0671.

3-Methoxy-1-methyl-2-piperidinethione (18). 3-Hydroxy-2-piperidinone (**17**, 96 mg) was methylated according to the same procedure as in the case of **11**, followed by treatment with Lowesson's reagent under the usual conditions to give 107 mg of **18** as an oil: IR (film) 1535 cm^{-1}; ^1H NMR δ=1.80 (2H, complex), 2.05 (1H, m), 2.15 (1H, m), 3.37 (1H, m), 3.43 (3H, s), 3.57 (3H, s), 3.63 (1H, m), and 4.18 (1H, t, J=3.5 Hz); ^{13}C NMR δ=17.9 (t), 25.3 (t), 43.4 (q), 52.2 (t), 58.4 (q), 82.7 (d) and 197.5 (s). Found: m/z 160.0838. Calcd for $C_7H_{14}NOS$: M+1, 160.0795.

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