# Efficient Enantioselective Synthesis of Methyl Esters of α-Unsubstituted β-Hydroxy Acids via Asymmetric Aldol-Type Addition of Chiral Boron Enolates of (Methylthio)acetic Acid to Aldehydes

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The aldol-type addition of chiral boron enolates of (methylthio)-acetic acid to various aldehydes gives α-(methylthio)-β-hydroxy acids stereoselectively and with good yields. The desulfenylation of methyl esters of the condensation adducts allows methyl esters of α-unsubstituted β-hydroxy acids to be obtained with high ee. Derivatives of (+)-2- and (+)-3-carene were used as chiral inducers. The enantioselectivity and diastereoselectivity of the aldol-type addition are efficaciously controlled by the SMe group in the α-position of the enolate and by the type of chiral ligand used.

Chiral boron enolates[1] of ketones,[2] carboxylic acids,[3] esters,[4,5b] thioesters,[5] tertiary amides[2e,6] and oxazolines[7] are largely employed in asymmetric aldol-type additions for the construction of simple and complex acyclic molecules.[2g,8] The enantioselectivity of the reaction is strongly controlled by the presence of substituents in the α-position of the boron enolate. Whereas α-mono- and α,α′-disubstituted enolates exhibit high enantioselectivity, the aldol-type additions of α-unsubstituted enolates give low levels of asymmetric induction.[3,6a,g,h] To date, an efficient synthesis of chiral α-unsubstituted β-hydroxy acids via enol boration reaction remains a challenge for the organic chemist. Progress in this area has been made using chiral acetates such as *N*-acetyloxazolidinethione[6g] and *N*-acetyloxazolidinone,[6h] chiral organoborane reagents such as 2,5-dimethylborolane trifluoromethanesulfonate[5a] and bis[3,5-(trifluoromethyl)]benzenesulfonamide bromoborane[5b] and by making use of chiral boron Lewis catalysts.[9]

In continuation of our studies on the enantioselectivity of the aldol-type reaction of boron and titanium enolates,[3,4e] we recently reported[3b] the first asymmetric aldol addition of chiral boron enolates of carboxylic acids to prochiral faces of carbonyl compounds. Enolates of carboxylic acids have some advantages with respect to the analogous enolates of esters and amides because they do not require either a stereoselective synthesis of *E* and *Z* enols or the hydrolysis of the condensation products to obtain the corresponding β-hydroxy acids. Using derivatives of (+)-2- and (+)-3-carene as chiral inducers, a notable reversal of the diastereofacial selectivity of boron-mediated aldol addition was observed and the synthesis of α-mono and α,α′-disubstituted β-hydroxy carboxylic acids with high enantiomeric excess was achieved.[3b]

In this paper, we describe an efficient asymmetric synthesis of methyl esters of α-unsubstituted β-hydroxy acids[10] via aldol-type addition of chiral boron enolates of (methylthio)acetic acid to aldehydes which takes advantage of enantiocontrol of the methylthio group[15] in the α-position and the ease of the desulfenylation reaction.

To our knowledge, the only known examples of this strategy in this area use chiral boron enolates derived from 3-(thiomethylacetyl)-2-oxazolidone[6a] and from *tert*-butyl bromoacetate.[4c]

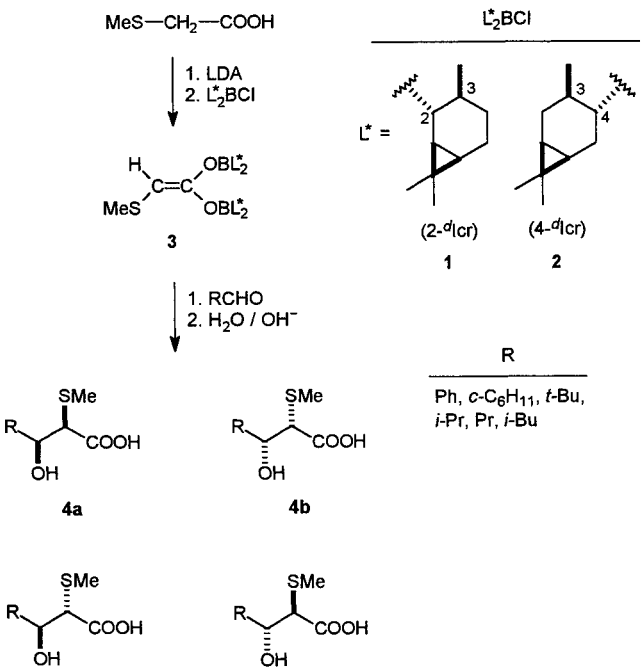
Transmetallation of the dilithiated (methylthio)acetic acid with (−)-di-2- and (−)-di-4-isocaranylchloroborane (**1** and **2**) in THF at −78 °C gives the boron enolates **3** which, when condensed with representative aldehydes, afford *syn* and *anti* 3-substituted 3-hydroxy-2-(methylthio)propionic acids **4** and **5** in good yield (Scheme 1).

**Table 1.** Enantio- and Diastereoselectivity in the Aldol-Type Addition of Boron Enolates of (Methylthio)acetic Acid to Aldehydes

| | | | | *syn* | | *anti* | | |
|---|---|---|---|---|---|---|---|---|
| Entry | R | L*[a] | *syn/anti* | Product | ee(%) | Product | ee(%) | Yield[b] (%) |
| 1 | Ph | 2-$^d$Icr | 90/10 | (+)-**4a** | >99[3b] | – | – | 85 |
| 2 | Ph | 4-$^d$Icr | 8/92 | – | – | (+)-**5b** | 61[3b] | 82 |
| 3 | *c*-$C_6H_{11}$ | 2-$^d$Icr | 87/13 | (+)-**4a** | >99 | (+)-**5b** | 12 | 76 |
| 4 | *c*-$C_6H_{11}$ | 4-$^d$Icr | 7/93 | – | – | (+)-**5b** | 66 | 62 |
| 5 | *t*-Bu | 2-$^d$Icr | 80/20 | (+)-**4a** | 97 | (−)-**5a** | 7 | 72 |
| 6 | *t*-Bu | 4-$^d$Icr | 25/75 | (−)-**4b** | 87 | (+)-**5b** | 14 | 67 |
| 7 | *i*-Pr | 2-$^d$Icr | 88/12 | (+)-**4a** | 98 | (+)-**5b** | 7 | 75 |
| 8 | *i*-Pr | 4-$^d$Icr | 9/91 | (−)-**4b** | 78 | (+)-**5b** | 78 | 62 |
| 9 | Pr | 2-$^d$Icr | 90/10 | (+)-**4a** | 96 | (−)-**5a** | 4 | 82 |
| 10 | Pr | 4-$^d$Icr | 10/90 | – | – | (+)-**5b** | 83 | 60 |
| 11 | *i*-Bu | 2-$^d$Icr | 91/9 | (+)-**4a** | 93 | (+)-**5b** | 8 | 76 |
| 12 | *i*-Bu | 4-$^d$Icr | 10/90 | (−)-**4b** | 86 | (+)-**5b** | 86 | 70 |

[a] The symbols 2-$^d$Icr and 4-$^d$Icr signify that the isocaranyl moiety comes from (+) isomer of 2- and 3-carene, respectively.[17]
[b] Yield of isolated products.

Aliphatic aldehydes react about five-times faster than benzaldehyde.[3b] The results are reported in Table 1.




**Scheme 1**

After chromatographic purification, the *syn* and *anti* adducts **4** and **5** were converted to the corresponding methyl esters and then desulfenylated with Raney nickel to give the known methyl esters **6**, in good yield. The enantiomers **6a** were obtained in excellent ee, while those of the opposite configuration **6b** had a lower ee level (Table 2).

The SMe group significantly affects the enantioselectivity of the process. While di-2- and di-4-isocaranylboron enolates of acetic acid react with benzaldehyde to give (+)-**6a** (R = Ph) in 72% ee and (−)-**6b** (R = Ph) in 42% ee, respectively,[3a] the same enantiomers were obtained using (methylthio)acetic acid, with ee values > 99% and 61%, respectively.

A remarkable reversal of the diastereoselectivity of the addition of enolates **3** to the enantiotopic faces of aldehydes was observed depending on the type of chiral ligand used. When L* = 2-$^d$Icr, the *unlike* approach[20] of the reactants is prevalent which produces the *syn*-3-hydroxy-2-(methylthio)carboxylic acids **4** (80–90%); when L* = 4-$^d$Icr, the *like* approach is prevalent and gives the *anti*-3-hydroxy-2-(methylthio)carboxylic acids **5** as the main reaction products (75–93%).

**Table 2.** Desulfenylation of the Methyl Esters of Carboxylic Acids **4** and **5**

| Entry | R | Substrate | Product[a] | ee(%) | Yield (%) | Ref. |
|---|---|---|---|---|---|---|
| 1 | Ph | (+)-**4a** | (+)-**6a** | > 99 | 72 | 6a, 14b, 18 |
| 2 | Ph | (+)-**5a** | (−)-**6b** | 61 | 71 | 6a, 14b, 18 |
| 3 | $c$-$C_6H_{11}$ | (+)-**4a** | (+)-**6a** | > 99 | 75 | 14b |
| 4 | $c$-$C_6H_{11}$ | (+)-**5b** | (−)-**6b** | 66 | 70 | 14b |
| 5 | $t$-Bu | (+)-**4a** | (+)-**6a** | 97 | 73 | 18 |
| 6 | $t$-Bu | (+)-**5b** | (−)-**6b** | 14 | 75 | 18 |
| 7 | $i$-Pr | (+)-**4a** | (+)-**6a** | 98 | 74 | 18 |
| 8 | $i$-Pr | (+)-**5b** | (−)-**6b** | 78 | 73 | 18 |
| 9 | Pr | (+)-**4a** | (+)-**6a** | 96 | 72 | 18 |
| 10 | Pr | (+)-**5b** | (−)-**6b** | 83 | 70 | 18 |
| 11 | $i$-Bu | (+)-**4a** | (+)-**6a** | 93 | 74 | 19 |
| 12 | $i$-Bu | (+)-**5b** | (−)-**6b** | 86 | 75 | 19 |

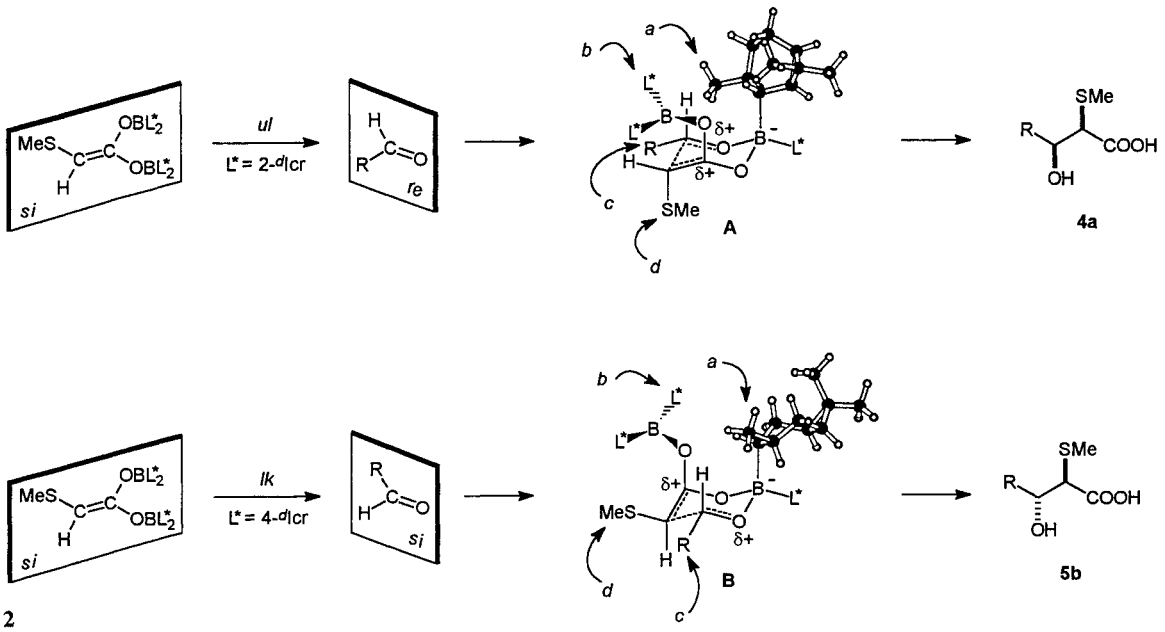
[a] The products **6a** and **6b** were identified by comparison with authentic samples reported in references 6a, 14b, 18, 19.

The two chiral ligands also control the enantioselectivity of the aldol addition differently. With L* = 2-$^d$Icr, the *si*(enol)-*re*(aldehyde) *unlike* approach[20] is almost exclusive and the *syn* enantiomers **4a** are obtained in high ee (93–99%). With L* = 4-$^d$Icr, the *si-si like* approach is prevalent and the *anti* enantiomers **5b** are the main reaction products, but they are obtained with less enantioselectivity (14–86%).

The *syn* and *anti* adducts **4** and **5** were separated by column chromatography (silica gel 230–400 mesh) eluting with hexane/ethyl acetate (1 : 1). The *syn-anti* stereochemistry of the unknown compounds **4** and **5** was determined by $^1$H and $^{13}$C NMR spectroscopy. The coupling constants $J_{H-2,H-3}$ of α-(methylthio)-β-hydroxy carboxylic acids and $J_{H-2,H-3}$ and $J_{H-3,OH}$ of the corresponding methyl esters are known[16] to exhibit higher values in the *anti* than in the *syn* diastereoisomers, but the small observed differences ($\Delta J$ = 0.2–0.9 Hz) can leave some doubt. The $^{13}$C NMR chemical shifts of C-3 of methyl esters of **4** and **5** are higher for *anti* than for the *syn* as expected[16] and are certainly diagnostic ($\Delta\delta$ = 1.7–7.1).

The absolute configurations of acids **4** and **5** were established from the known sign of the specific rotations of desulfenylated methyl esters **6** (Table 2) and by observing the proton shifts of the OMe group of methyl esters of **4** and **5** after complexation with Eu(hfc)$_3$ (see experimental).

The diastereo- and enantioselectivity of the addition of diisocaranylboron enolates of (methylthio)acetic acid to aldehydes can be justified on the basis of the Zimmerman-Traxler chairlike transition state model. Molecular models and computational analysis with the ALCHEMY III program, show that the main factors (Scheme 2[20]) that affect the stability of transition state of the reaction are (a) the methyl of the isocaranyl group in the axial position, (b) the ligand of the quasi axial OBL$_2^*$ group, (c) the R group of aldehyde and (d) the SMe group.




**Scheme 2**

The transition states **A** and **B**, depicted in Scheme 2, that give the enantiomers **4a** and **5b**, are those that account for the smaller steric interactions in the approach of di-2- and di-4-isocaranylboron enolates, respectively, to enantiotopic faces of the aldehydes.

In conclusion, the methylthio group can be used to control the enantioselectivity of the aldol-type addition. Desulfenylation of methyl esters of condensation adducts allows methyl esters of α-unsubstituted β-hydroxy acids with high ee to be prepared. By using derivatives of (+)-2- and (+)-3-carene as chiral ligands of boron enolates, it is possible to control the stereoselectivity of aldol-type addition. The 2-isocaranyl ligand allows *syn* adducts with high ee to be prepared, while the 4-isocaranyl ligand gives *anti* adducts but with less enantioselectivity.

For instruments and materials, see our previous paper.[3b] Melting points are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded at 200 MHz in $CDCl_3$ solution. Optical rotations were measured in $CHCl_3$ solution. Aldol additions with aliphatic aldehydes were carried out according to the previously described procedure,[3b] except that the condensation time at 0 °C was 3 h. The *syn* and *anti* adducts **4** and **5** were separated by column chromatography (silica gel 230–400 mesh) eluting with hexane/EtOAc (1 : 1). The ee were determined on methyl esters of **4** and **5** by $^1$H NMR chiral shift experiments using Eu(hfc)$_3$.[3b] The absolute configurations of acids **4** and **5** were assigned from the known sign of the specific rotations of the esters **6** (references in Table 2) and by Eu(hfc)$_3$ proton shifts experiments conducted on the methyl esters of **4** and **5**. The $OCH_3$ protons of the methyl esters of the enantiomers **5a** were shifted to low field with respect to those of the corresponding esters of opposite absolute configuration **5b**, on the contrary the $OCH_3$ protons of the methyl esters of enantiomers **4a** were shifted to high field with respect those of corresponding enantiomers **4b**.[3b]

**3-Substituted 3-Hydroxypropionic Acids 6a, b**

The acids **4** or **5** were first esterified with $CH_2N_2$ in the conventional manner to afford the corresponding esters. To a solution of the ester (1 mmol) in acetone (10 mL) was added Raney nickel W-2 (1 g) and the mixture stirred for 20 min at 60 °C. The mixture was decanted and the catalyst washed with acetone (2 × 5 mL). The organic phase was evaporated and the residue dissolved in $Et_2O$. The $Et_2O$ solution was dried ($Na_2SO_4$) and evaporated under reduced pressure. Yield and ee of esters **6a** and **6b** are reported in Table 2.

*(+)-(2R,3S)-3-Cyclohexyl-3-hydroxy-2-(methylthio)propionic Acid* (**4a**, R = *c*-$C_6H_{11}$): mp 93–95 °C; $[\alpha]_D$ + 47.0 (*c* = 1.1).

$^1$H NMR: δ = 1.05–1.95 (m, 11 H, *c*-$C_6H_{11}$), 2.24 (s, 3 H, $SCH_3$), 3.36 (d, 1 H, *CH*$SCH_3$, *J* = 6 Hz), 3.73 (t, 1 H, *CH*OH, *J* = 6 Hz).

Anal. Calcd for $C_{10}H_{18}O_3S$ (218.3): C, 55.02; H, 8.32.Found: C, 55.09; H, 8.28.

*Methyl ester:* $[\alpha]_D$ + 57.8 (*c* = 1.7).

$^1$H NMR: δ = 1.1–1.9 (m, 11 H, *c*-$C_6H_{11}$), 2.19 (s, 3 H, $SCH_3$), 2.89 (d, 1 H, OH, *J* = 2.3 Hz), 3.32 (d, 1 H, *CH*$SCH_3$, *J* = 6.8 Hz), 3.70 (ddd, 1 H, *CH*OH, *J* = 6.8, 5.1, 2.3 Hz), 3.77 (s, 3 H, $OCH_3$).

$^{13}$C NMR: δ = 13.7, 25.7, 26.0, 26.7, 29.5, 40.3, 51.1, 51.9, 72.9 (C-3), 171.8.

Anal. Calcd for $C_{11}H_{20}O_3S$ (232.3): C, 56.87; H, 8.68. Found: C, 56.92; H, 8.61.

*(+)-(2R,3R)-3-Cyclohexyl-3-hydroxy-2-(methylthio)propionic Acid* (**5b**, R = *c*-$C_6H_{11}$): $[\alpha]_D$ + 23.8 (*c* = 1.0).

$^1$H NMR: δ = 1.0–1.9 (m, 11 H, *c*-$C_6H_{11}$), 2.23 (s, 3 H, $SCH_3$), 3.39 (d, 1 H, *CH*$SCH_3$, *J* = 6.3 Hz), 3.73 (dd, 1 H, *CH*OH, *J* = 6.3, 5.3 Hz).

Anal. Calcd for $C_{10}H_{18}O_3S$ (218.3): C, 55.02; H, 8.32. Found: C, 54.97; H, 8.30.

*Methyl ester:* $[\alpha]_D$ + 38.5 (*c* = 1.8).

$^1$H NMR: δ = 1.1–1.9 (m, 11 H, *c*-$C_6H_{11}$), 2.17 (s, 3 H, $SCH_3$), 2.47 (d, 1 H, OH, *J* = 7.2 Hz), 3.36 (d, 1 H, *CH*$SCH_3$, *J* = 7.3 Hz), 3.71 (ddd, 1 H, *CH*OH, *J* = 7.3, 7.2, 4.5 Hz), 3.78 (s, 3 H, $OCH_3$).

$^{13}$C NMR: δ = 14.1, 25.8, 25.9, 26.1, 29.9, 39.8, 49.6, 52.0, 75.0 (C-3), 172.4.

Anal. Calcd for $C_{11}H_{20}O_3S$ (232.3): C, 56.87; H, 8.68. Found: C, 56.84; H, 8.63.

*(+)-(2R,3S)-3-Hydroxy-4,4-dimethyl-2-(methylthio)pentanoic Acid* (**4a**, R = *t*-Bu): mp 118–120 °C; $[\alpha]_D$ + 68.75 (*c* = 1.3).

$^1$H NMR: δ = 0.99 (s, 9 H, *t*-$C_4H_9$), 2.21 (s, 3 H, $SCH_3$), 3.30 (d, 1 H, *CH*$SCH_3$, *J* = 8.2 Hz) 3.66 (d, 1 H, *CH*OH, *J* = 8.2 Hz).

Anal. Calcd for $C_8H_{16}O_3S$ (192.3): C, 49.98; H, 8.39. Found: C, 50.01; H, 8.36.

*Methyl ester:* $[\alpha]_D$ + 61.6 (*c* = 1.8).

$^1$H NMR: δ = 0.95 (s, 9 H, *t*-$C_4H_9$), 2.17 (s, 3 H, $SCH_3$), 2.94 (d, 1 H, OH, *J* = 2.4 Hz), 3.27 (d, 1 H, *CH*$SCH_3$, *J* = 8.7 Hz), 3.64 (dd, 1 H, *CH*OH, *J* = 8.7, 2.4 Hz), 3.74 (s, 3 H, $OCH_3$).

$^{13}$C NMR: $\delta$ = 13.4, 26.0, 35.3, 50.4, 52.1, 74.5 (C-3), 171.6.

Anal. Calcd for $C_9H_{18}O_3S$ (206.3): C, 52.40; H, 8.80. Found: C, 52.45, H, 8.82.

*(+)-(2R,3R)-3-Hydroxy-4,4-dimethyl-2-(methylthio)pentanoic Acid* (**5b**, R = *t*-Bu): mp 110–112 °C, $[\alpha]_D$ + 6.4 (*c* = 1.1).

$^1$H NMR: $\delta$ = 0.99 (s, 9 H, *t*-$C_4H_9$), 2.27 (s, 3 H, $SCH_3$), 3.46 (d, 1 H, *CH*OH, *J* = 2.0 Hz), 3.68 (d, 1 H, *CH*$SCH_3$, *J* = 2.0 Hz).

Anal. Calcd for $C_8H_{16}O_3S$ (192.3): C, 49.98; H, 8.39. Found: C, 49.95; H, 8.40.

*Methyl ester:* $[\alpha]_D$ + 8.9 (*c* = 1.5).

$^1$H NMR: $\delta$ = 0.93 (s, 9 H, *t*-$C_4H_9$), 2.24 (s, 3 H, $SCH_3$), 3.43 (d, 1 H, OH, *J* = 2.4 Hz), 3.61 (dd, 1 H, *CH*OH, *J* = 8.8, 2.4 Hz), 3.74 (d, 1 H, *CH*$SCH_3$, *J* = 8.8 Hz), 3.77 (s, 3 H, $OCH_3$).

$^{13}$C NMR: $\delta$ = 15.1, 26.0, 36.2, 47.2, 52.1, 81.6 (C-3), 173.2.

Anal. Calcd for $C_9H_{18}O_3S$ (206.3): C, 52.40; H, 8.80. Found: C, 52.43; H, 8.75.

*(+)-(2R,3S)-3-Hydroxy-4-methyl-2-(methylthio)pentanoic Acid* (**4a**, R = *i*-Pr): mp 79–80 °C; $[\alpha]_D$ + 69.4 (*c* = 1.2).

$^1$H NMR: $\delta$ = 1.00 (d, 3 H, $CH_3$CHCH$_3$, *J* = 6.7 Hz), 1.02 (d, 3 H, CH$_3$CH$CH_3$, *J* = 6.8 Hz), 1.93 (m, 1 H, CH$_3$*CH*CH$_3$), 2.25 (s, 3 H, $SCH_3$), 3.31 (d, 1 H, *CH*$SCH_3$, *J* = 6.9 Hz), 3.71 (dd, 1 H, *CH*OH, *J* = 6.9, 5.3 Hz).

Anal. Calcd for $C_7H_{14}O_3S$ (178.3): C, 47.17; H, 7.92. Found: C, 47.21; H, 7.90.

*Methyl ester:* $[\alpha]_D$ + 81.5 (*c* = 1.6).

$^1$H NMR: $\delta$ = 0.96 (d, 3 H, $CH_3$CHCH$_3$, *J* = 6.6 Hz), 1.00 (d, 3 H, CH$_3$CH$CH_3$, *J* = 6.7 Hz), 1.85 (m, 1 H, CH$_3$*CH*CH$_3$), 2.20 (s, 3 H, $SCH_3$), 2.89 (d, 1 H, OH, *J* = 2.3 Hz), 3.28 (d, 1 H, *CH*$SCH_3$, *J* = 7.3 Hz), 3.69 (ddd, 1 H, *CH*OH, *J* = 7.3, 5.0, 2.3 Hz), 3.77 (s, 3 H, $OCH_3$).

$^{13}$C NMR: $\delta$ = 13.8, 16.2, 19.7, 30.7, 51.7, 52.1, 73.4 (C-3), 171.9.

Anal. Calcd for $C_8H_{16}O_3S$ (192.3): C, 49.98; H, 8.39. Found: C, 49.97; H, 8.35.

*(+)-(2R,3R)-3-Hydroxy-4-methyl-2-(methylthio)pentanoic Acid* (**5b**, R = *i*-Pr): mp 78–79 °C; $[\alpha]_D$ + 41.4 (*c* = 1.2)

$^1$H NMR: $\delta$ = 0.97 (d, 3 H, $CH_3$CHCH$_3$, *J* = 6.7 Hz), 1.02 (d, 3 H, CH$_3$CH$CH_3$, *J* = 6.9 Hz), 2.08 (m, 1 H, CH$_3$*CH*CH$_3$), 2.23 (s, 3 H, $SCH_3$), 3.34 (d, 1 H, *CH*$SCH_3$, *J* = 7.1 Hz), 3.74 (dd, 1 H, *CH*OH, *J* = 7.1, 4.9 Hz).

Anal. Calcd for $C_7H_{14}O_3S$ (178.3): C, 47.17; H, 7.92. Found: C, 47.12; H, 7.88.

*Methyl ester:* $[\alpha]_D$ + 60.0 (*c* = 1.2).

$^1$H NMR: $\delta$ = 0.94 (d, 3 H, $CH_3$CHCH$_3$, *J* = 6.7 Hz), 1.00 (d, 3 H, CH$_3$CH$CH_3$, *J* = 6.9 Hz), 2.05 (m, 1 H, CH$_3$*CH*CH$_3$), 2.17 (s, 3 H, $SCH_3$), 2.48 (d, 1 H, OH, *J* = 6.9 Hz), 3.32 (d, 1 H, *CH*$SCH_3$, *J* = 7.6 Hz), 3.73 (ddd, 1 H, *CH*OH, *J* = 7.6, 6.9, 4.5 Hz), 3.77 (s, 3 H, $OCH_3$).

$^{13}$C NMR: $\delta$ = 14.0, 15.3, 19.7, 29.8, 50.1, 52.0, 75.1 (C-3), 172.4.

Anal. Calcd for $C_8H_{16}O_3S$ (192.3): C, 49.98; H, 8.39. Found: C, 49.95; H, 8.42.

*(+)-(2R,3S)-3-Hydroxy-2-(methylthio)hexanoic Acid* (**4a**, R = Pr): mp 70–71 °C; $[\alpha]_D$ + 56.2 (*c* = 1.2).

$^1$H NMR: $\delta$ = 0.95 (t, 3 H, $CH_3CH_2$, *J* = 6.9 Hz), 1.3–1.7 (m, 4 H, $CH_2CH_2$), 2.25 (s, 3 H, $SCH_3$), 3.18 (d, 1 H, *CH*$SCH_3$, *J* = 6.7 Hz), 3.96 (ddd, 1 H, *CH*OH, *J* = 11.4, 6.7, 4.3 Hz).

Anal. Calcd for $C_7H_{14}O_3S$ (178.3): C, 47.17; H, 7.92. Found: C, 47.15; H, 7.93.

*Methyl ester:* $[\alpha]_D$ + 66.5 (*c* = 1.4).

$^1$H NMR: $\delta$ = 0.94 (t, 3 H, $CH_3CH_2$, *J* = 6.9 Hz), 1.35–1.65 (m, 4 H, $CH_2CH_2$), 2.19 (s, 3 H, $SCH_3$), 2.92 (d, 1 H, OH, *J* = 2.1 Hz), 3.15 (d, 1 H, *CH*$SCH_3$, *J* = 7.1 Hz), 3.77 (s, 3 H, $OCH_3$), 3.91 (dddd, 1 H, *CH*OH, *J* = 10.9, 7.1, 3.0, 2.1 Hz).

$^{13}$C NMR: $\delta$ = 13.6, 13.8, 18.6, 36.1, 51.8, 53.8 68.7 (C-3), 171.5.

Anal. Calcd for $C_8H_{16}O_3S$ (192.3): C, 49.98; H, 8.39. Found: C, 50.04; H, 8.37.

*(+)-(2R,3R)-3-Hydroxy-2-(methylthio)hexanoic Acid* (**5b**, R = Pr): mp 67–69 °C; $[\alpha]_D$ + 63.5 (*c* = 1.0).

$^1$H NMR: $\delta$ = 0.96 (t, 3 H, $CH_3CH_2$, *J* = 6.8 Hz), 1.6–1.9 (m, 4 H, $CH_2CH_2$), 2.22 (s, 3 H, $SCH_3$), 3.20 (d, 1 H, *CH*$SCH_3$, *J* = 7.6 Hz), 3.95 (ddd, 1 H, *CH*OH, *J* = 7.8, 7.6, 2.9 Hz).

Anal. Calcd for $C_7H_{14}O_3S$ (178.3): C, 47.17; H, 7.92. Found: C, 47.14; H, 7.88.

*Methyl ester:* $[\alpha]_D$ + 66.7 (*c* = 1.2).

$^1$H NMR: $\delta$ = 0.95 (t, 3 H, $CH_3CH_2$, *J* = 7.0 Hz), 1.35–1.85 (m, 4 H, $CH_2CH_2$), 2.17 (s, 3 H, $SCH_3$), 2.57 (d, 1 H, OH, *J* = 6.5 Hz), 3.19 (d, 1 H, *CH*$SCH_3$, *J* = 7.6 Hz), 3.79 (s, 3 H, $OCH_3$), 3.92 (dddd, 1 H, *CH*OH, *J* = 7.9, 7.6, 6.5, 3.0 Hz).

$^{13}$C NMR: $\delta$ = 13.8, 14.3, 18.6, 36.2, 52.1, 52.8, 70.8 (C-3), 172.2.

Anal. Calcd for $C_8H_{16}O_3S$ (192.3): C, 49.98; H, 8.39. Found: C, 49.94; H, 8.44.

*(+)-(2R,3S)-3-Hydroxy-5-methyl-2-(methylthio)hexanoic Acid* (**4a**, R = *i*-Bu): mp 58–59 °C; $[\alpha]_D$ + 41.7 (*c* = 1.1).

$^1$H NMR: $\delta$ = 0.94 (d, 3 H, $CH_3$CHCH$_3$, *J* = 6.5 Hz), 0.96 (d, 3 H, CH$_3$CH$CH_3$, *J* = 6.7 Hz), 1.31 (ddd, 1 H, *CH*H, *J* = 13.8, 9.2, 3.1 Hz), 1.62 (ddd, 1 H, CH*H*, *J* = 13.8, 9.4, 4.7 Hz), 1.88 (m, 1 H, CH$_3$*CH*CH$_3$), 2.25 (s, 3 H, $SCH_3$), 3.15 (d, 1 H, *CH*$SCH_3$, *J* = 6.6 Hz), 4.02 (ddd, 1 H, *CH*OH, *J* = 9.4, 6.6, 3.1 Hz).

Anal. Calcd for $C_8H_{16}O_3S$ (192.3): C, 49.48; H, 8.39. Found: C 49.52; H, 8.41.

*Methyl ester:* $[\alpha]_D$ + 48.9 (*c* = 1.4).

$^1$H NMR: $\delta$ = 0.93 (d, 3 H, $CH_3$CHCH$_3$, *J* = 6.5 Hz), 0.94 (d, 3 H, CH$_3$CH$CH_3$, *J* = 6.6 Hz), 1.21 (dddd, 1 H, *CH*H, *J* = 13.6, 9.3, 3.0, 1.6 Hz), 1.56 (ddd, 1 H, CH*H*, *J* = 13.6, 9.4, 4.7 Hz), 1.87 (m, 1 H, CH$_3$*CH*CH$_3$), 2.19 (s, 3 H, $SCH_3$), 2.89 (dd, 1 H, OH, *J* = 2.7, 1.6 Hz), 3.11 (d, 1 H, *CH*$SCH_3$, *J* = 7.0 Hz), 3.77 (s, 3 H, $OCH_3$), 3.98 (dddd, 1 H, *CH*OH, *J* = 9.4, 7.0, 3.0, 2.7 Hz).

$^{13}$C NMR: $\delta$ = 14.1, 21.5, 23.4, 24.7, 43.2, 52.0, 54.5, 67.4 (C-3), 171.7.

Anal. Calcd for $C_9H_{18}O_3S$ (206.3): C, 52.40; H, 8.80. Found: C, 52.36; H, 8.83.

*(+)-(2R,3R)-3-Hydroxy-5-methyl-2-(methylthio)hexanoic Acid* (**5b**, R = *i*-Bu): mp 113–114 °C; $[\alpha]_D$ + 92.1 (*c* = 1.3).

$^1$H NMR: $\delta$ = 0.94 (d, 3 H, $CH_3$CHCH$_3$, *J* = 6.3 Hz), 0.97 (d, 3 H, CH$_3$CH$CH_3$, *J* = 6.2 Hz), 1.4–1.7 (m, 2 H, $CH_2$), 1.88 (m, 1 H, CH$_3$*CH*CH$_3$), 2.23 (s, 3 H, $SCH_3$), 3.18 (d, 1 H, *CH*$SCH_3$, *J* = 7.2 Hz), 4.01 (ddd, 1 H, CH–OH, *J* = 9.6, 7.2, 3.2 Hz).

Anal. Calcd for $C_8H_{16}O_3S$ (192.3): C, 49.48; H, 8.39. Found: C, 49.51; H, 8.35.

*Methyl ester:* $[\alpha]_D$ + 91.8 (*c* = 1.3).

$^1$H NMR: $\delta$ = 0.93 (d, 3 H, $CH_3$CHCH$_3$, *J* = 6.5 Hz), 0.96 (d, 3 H, CH$_3$CH$CH_3$, *J* = 6.6 Hz), 1.41 (ddd, 1 H, *CH*H, *J* = 14.0, 9.8, 4.5 Hz), 1.60 (ddd, 1 H, CH*H*, *J* = 14.0, 9.4, 3.0 Hz), 1.86 (m, 1 H, CH$_3$*CH*CH$_3$), 2.17 (s, 3 H, $SCH_3$), 2.52 (d, 1 H, OH, *J* = 6.6 Hz), 3.15 (d, 1 H, *CH*$SCH_3$, *J* = 7.4 Hz), 3.79 (s, 3 H, $OCH_3$), 3.99 (dddd, 1 H, *CH*OH, *J* = 9.8, 7.4, 6.6, 3.0 Hz).

$^{13}$C NMR: $\delta$ = 14.0, 21.3, 23.5, 24.3, 43.1, 51.9, 53.2, 69.1 (C-3), 172.1.

Anal. Calcd for $C_9H_{18}O_3S$: C, 52.40; H, 8.80. Found: C, 52.42; H, 8.86.

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