Stereocontrolled 5-*Exo-Trig* Cyclization of Imidoyl Radicals in the Synthesis of Substituted (Alkylthio)pyrrolines, Pyroglutamates, and Thiopyroglutamates

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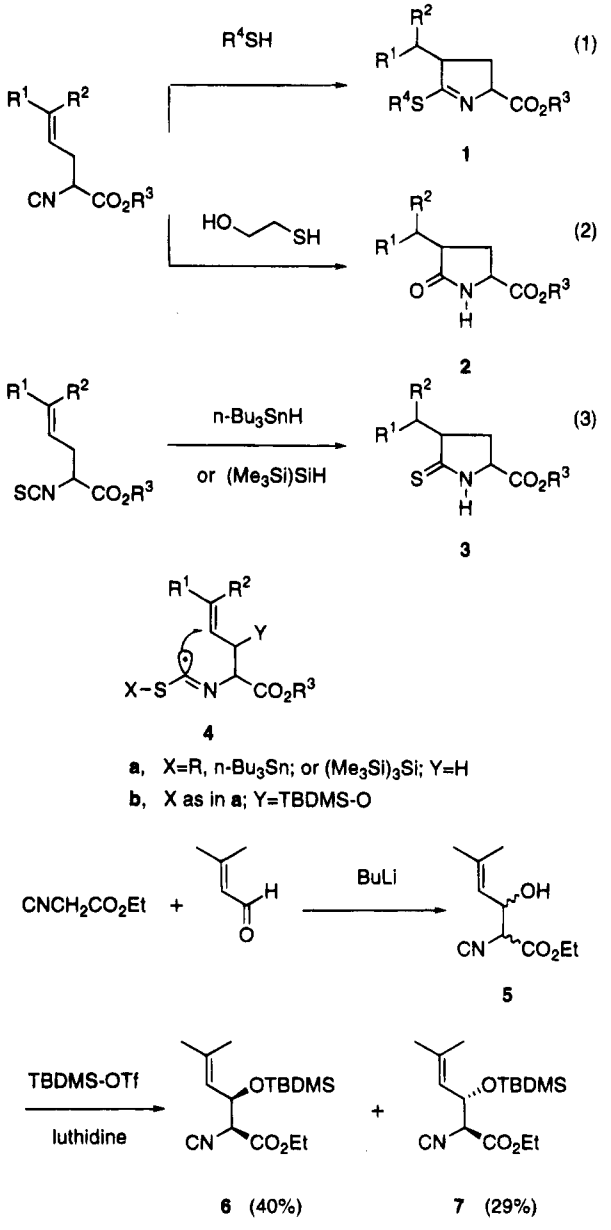
In recent papers we described the synthesis of esters of 4-alkyl-5-(alkylthio)dihydropyrrole-2-carboxylic acid of type **1**, 4-alkylpyroglutamic acid of type **2**, and 4-alkylthiopyroglutamic acid of type **3**.[1-3] The synthesis of these five-membered-ring heterocycles is based on the homolytic cyclization of isocyanides and of isothiocyanates deriving from substituted α-allylglycine. Cyclization of isocyanides is mediated by thiols (eqs 1 and 2) while cyclization of isothiocyanates can be mediated by either *n*-Bu_3SnH or $(Me_3Si)_3SiH$ (eq 3). All these cyclizations involve a 5-*exo-trig* addition of a carbon centered imidoyl radical of type **4a**. Compounds structurally related to heterocycles **1**–**3** have been used as building blocks in the synthesis of bicyclic β-lactams,[4,5] anatoxin a,[6] angiotensin-converting enzyme inhibitor,[7] and domoic acid.[8] Application of the method used for the preparation of heterocycles **1**–**3** to the synthesis of biologically active compounds of the types outlined above is hampered by the lack of diastereoselectivity.

In the present paper we describe an improved method that allows an efficient stereocontrol of the key cyclization step, thus leading to diastereomerically pure esters of 4-alkylpyroglutamic acid, 4-alkylthiopyroglutamic acid, and 4-alkyl-5-(alkylthio)dihydropyrrole-2-carboxylic acid.[9] For this purpose we designed starting materials that allow the generation of imidoyl radicals of type **4b** which carry a bulky TBDMS-O group vicinal to the site of radical addition. *Syn* and *anti* substituted alkenoyl esters **6** and **7** may be prepared using advanced methodologies developed for diastereo- and enantioselective synthesis of either *syn* or *anti*-β-hydroxy-α-amino acids.[10] However, since both diastereomers were required they were prepared by simple condensation of the lithium enolate of ethyl isocyanoacetate with dimethylacrylaldehyde. The resulting hydroxy esters **5** were silylated with TBDMS-OTf and separated chromatographically.[9] The relative *syn*/*anti* configuration of **6**/**7** was assigned by correlation to the respective cyclization products **9**/**15**. Diastereomeric purity of all title compounds is at least 98% (determined by ^1H NMR).



Treatment of *syn*-isocyanide **6** with EtSH (1.1 equiv) and AIBN (0.25 equiv) at 80 °C in toluene afforded the 2β,3β,4α-substituted dihydropyrrole derivative **8** (Scheme 1). Excellent stereocontrol and high yield was observed also in the reaction of isocyanide **6** with β-mercaptoethanol which gave the pyroglutamate **9**. In line with previous reports[1] treatment of isocyanide **6** with a tertiary thiol gave the isothiocyanate **10**. *n*-Bu_3SnH/AIBN-mediated cyclization of **10** afforded tin thioimidate **11** which hydrolyzed during chromatography to give the thiopyroglutamate **12**.

High diastereoselectivity was observed also in the EtSH/AIBN-mediated cyclization of *anti*-isocyanide **7** to the 2β,3α,4β-substituted dihydropyrrole **13**. In this case the NMR spectrum of the crude product indicated the presence of diastereomer **14** (*ca.* 6%).[11] Likewise the β-mercaptoethanol/AIBN-induced cyclization yielded pyroglutamate **15** as the major product with a small quantity of **16** (*ca.* 7%) (Scheme 2).[11] The relative configuration at positions 2, 3, and 4 in pyroglutamates **9** and **15**

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(9) All chiral compounds in this work are racemic; only one enantiomer of each pair is addressed to in the text and displayed in the structural formulas.
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(11) Compounds **14** and **16** were not isolated.

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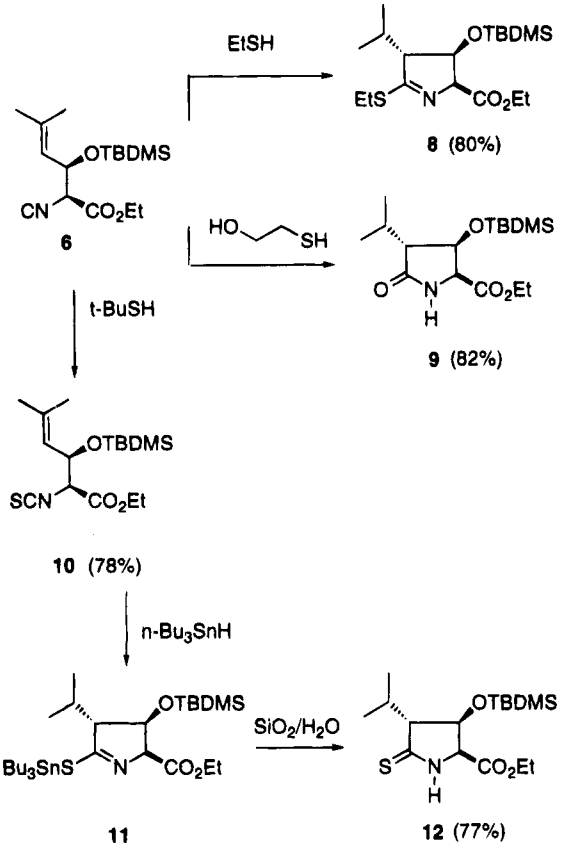
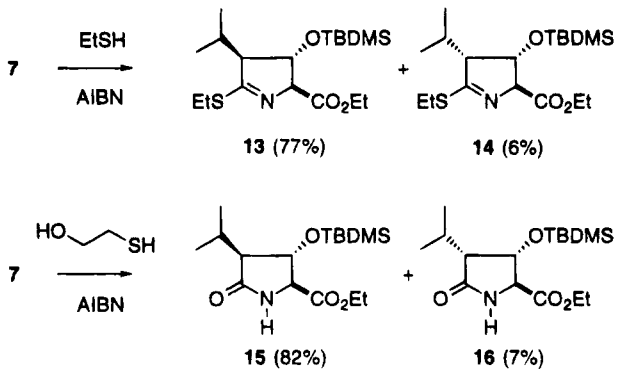
Scheme 1



Scheme 2

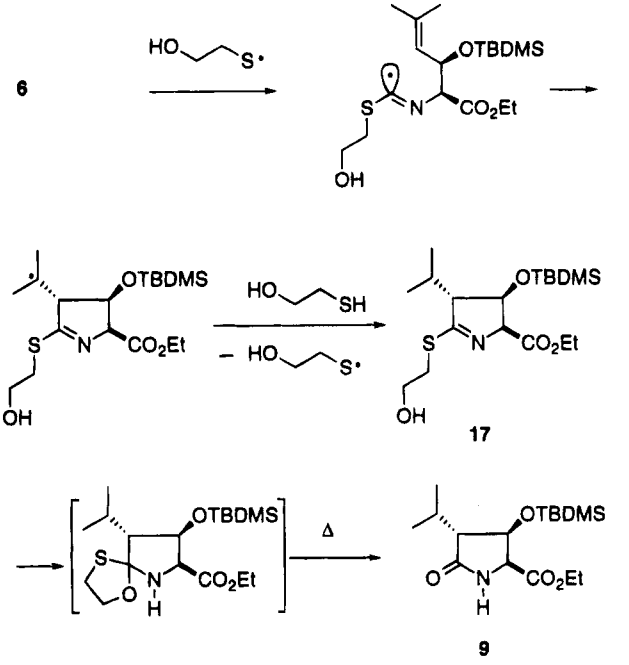


was assigned using NOE (see Experimental Section). From this data the relative configurations of the other chiral compounds were deduced.[9]

It was postulated that lactam formation in the β-mercaptoethanol/AIBN-mediated cyclizations proceeds through the sequence of radical, polar, and thermal steps shown in Scheme 3. [1] This was corroborated by identification of NMR signals attributed to intermediate **17** in a reaction performed in the NMR tube (C_6D_9, 80 °C), under strictly anhydrous oxygen-free conditions (see Experimental Section).

Compounds **6**, **7**, and **10** used in the cyclization reactions are highly functionalized derivatives of racemic α-amino acids. In view of the diastereomeric purity of the products and the mild reaction conditions employed, we expect that the use of enantiomerically pure α-amino acid derivatives[10] will allow the enantioselective synthesis of a variety of substituted (alkylthio)pyrrolines, pyroglutamates, and thiopyroglutamates. These compounds contain functionalities like thioimidate, amide,

Scheme 3



thioamide, TBDMS-O, and CO_2R which lend themselves to selective transformations. They were purposely designed to serve as intermediates for the synthesis of more elaborated heterocycles, including biologically active compounds of the type referred to in the introduction. Work along this line is in course.

Experimental Section

General Procedures. Solvents and glassware were dried by conventional methods, and the reactions were performed in atmosphere of argon. MPLC (medium-pressure liquid chromatography) was performed on silica gel 60 40–63 μm (Merck). Unless otherwise stated NMR spectra were recorded in $CDCl_3$ at 400 MHz. All chiral compounds in this work are racemic; only one enantiomer of each pair is displayed.

Ethyl 2-Isocyano-3-(*tert*-butyldimethylsiloxy)-5-methylhex-4-eneoates 6 and 7. To a solution of phenanthroline (approximately 1 mg) in dry THF (20 mL) at −30 °C was added *n*-BuLi (2 mL of 1.6 M solution in hexane). The resulting solution was cooled to −72 °C and neat ethyl isocyanoacetate (0.34 g, 3 mmol) was added dropwise while temperature was maintained below −65 °C. A small quantity of *n*-BuLi was subsequently added to preserve the pink color of phenanthroline. The reaction mixture was then cooled to −74 °C, and 3-methyl-2-butenal (0.25 mL, 3 mmol) was added in one portion. The reaction mixture was stirred 5 min at −74 °C, quenched with 0.5 mL of acetic acid, and poured into 5% aqueous $NaHCO_3$. The emulsion was extracted with 50 mL of hexane, dried with $NaHCO_3 + Na_2SO_4$, and evaporated. The residue (hydroxy ester **5**) was dissolved in dry methylene chloride (2 mL) and cooled to −60 °C, and 2,6-lutidine (0.53 mL, 4.5 mmol) and *tert*-butyldimethylsilyl triflate (0.87 g, 0.33 mmol) were added at −60 °C. The reaction mixture was stirred 1 h at −60 °C and 50 min at −10 °C, the solvent was evapotated, and the residue was separated by MPLC (EtOAc–hexane 1:20) affording title *syn*-isocyanide **6** (isomer with lower R_f, 370 mg, 40%):[9] IR (neat) 1754, 2150 cm^{-1}; ^1H NMR (δ) 0.02, 0.03 (2 × s, 6H), 0.86 (s, 9H), 1.32 (t, J = 7.2 Hz, 3H), 1.70, 1.75 (2 × d, J = 1.4 Hz, 6H), 4.10 (d, J = 4.1 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2H), 4.85 (dd, J = 4.1, 9.1 Hz, 1H), 5.28 (d of quintet, J = 9.1, 1.4 Hz, 1H). Anal. Calcd for $C_{16}H_{29}NO_3Si$: C, 61.69; H, 9.38; N, 4.50. Found: C, 61.73; H, 9.43; N, 4.80; and *anti* isocyanide **7** (isomer of higher R_f, 274 mg, 29%): IR (neat) 1756, 2150 cm^{-1}. ^1H NMR (δ) 0.02, 0.05 (2 × s, 6H), 0.86 (s, 9H), 1.31 (t, J = 7.2 Hz, 3H), 1.73, 1.77 (2 × d, J = 1.4 Hz, 6H), 4.10 (d, J = 4.1 Hz, 1H), 4.22, 4.25 (2 × dq, J = 7.2, 10.8 Hz, 2H), 4.79 (dd, J = 4.1, 9.4 Hz, 1H), 5.28 (d of quintet,

J = 9.4, 1.4 Hz, 1H). Anal. Calcd for $C_{16}H_{29}NO_3Si$: C, 61.69; H, 9.38; N, 4.50. Found: C, 62.01; H, 9.53; N, 4.66.

2β-(Ethoxycarbonyl)-3β-(*tert*-butyldimethylsiloxy)-4α-isopropyl-5-(ethylthio)-4*H*-2,3-dihydropyrrole (8). *syn*-Isocyanide **6** (860 mg, 2.8 mmol), AIBN (114 mg, 0.7 mmol), ethanethiol (240 mg 3.1 mmol), and toluene (60 mL) were stirred under argon for 3 h at 70 °C. The solvent was evaporated, and MPLC chromatography (EtOAc–hexane 2:10) of the residue afforded the dihydropyrrole **8** (842 mg, 80%): IR (neat) 1586,-1733 cm^{-1}; ^1H NMR (δ) 0.06, 0.08 (s, 6H), 0.83 (s, 9H), 0.87, 1.05 (2 × d, J = 6.9 Hz, 6H), 1.30 (t, J = 7.4 Hz, 3H), 1.36 (t, J = 7.4 Hz, 3H), 2.10 (d of septets, J = 6.9 Hz, 3.6 Hz, 1H), 2.78 (dd, J = 1.6, 3.6 Hz, 1H), 3.13, 3.14 (2 × dq, J = 7.4, 1.1 Hz, 2H), 4.05, 4.27(2 × dq, J = 7.4, 10 Hz, 2H), 4.53 (dd, J = 1.6, 5.3 Hz, 1H), 4.57 (d, J = 5.3 Hz). Anal. Calcd for $C_{18}H_{35}NO_3SSi$: C, 57.86; H, 9.44; N, 3.75; S, 8.58. Found: C, 57.89; H, 9.47; N, 3.71; S, 8.19.

2β-(Ethoxycarbonyl)-3β-(*tert*-butyldimethylsiloxy)-4α-isopropyl-4-pyrrolidone (9). *syn*-Isocyanide **6** (220 mg, 0.72 mmol), AIBN (20 mg, 0.12 mmol), mercaptoethanol (66 mg, 0.83 mmol), and toluene (50 mL) were stirred under argon for 4 h at 100 °C. The solvent was evaporated, and MPLC chromatography (EtOAc–hexane 1:4) of the residue afforded the pyroglutamate **9** (0.186 g, 82%): IR (neat) 1710, 1716, 1743, 3250 cm^{-1}. ^1H NMR (δ) 0.09, 0.11 (s, 6H), 0.85 (s, 9H), 1.06 (d, J = 7.1 Hz, 6H), 1.31 (t, J = 7.1 Hz, 3H), 2.05 (d of septets, J = 7.1, 5.2 Hz, 1H), 2.32 (dd, J = 5.2, 3.2 Hz, 1H), 4.10, 4.31 (2 × dq, J = 7.1, 10.9 Hz, 2H), 4.26 (d, J = 5.8 Hz, 1H), 4.52 (dd, J = 3.3, 5.8 Hz, 1H), 5.7 (s, 1H). Anal. Calcd for $C_{16}H_{31}NO_4Si$: C, 58.32; H, 9.48; N, 4.25. Found: C, 58.07; H, 9.78; N, 4.43.

2β-(Ethoxycarbonyl)-3β-(*tert*-butyldimethylsiloxy)-4α-isopropylpyrrolidine-5-thione (12). *syn*-Isocyanide **6** (190 mg, 0.62 mmol), *tert*-butylmercaptan (63 mg, 0.68 mmol), AIBN (20 mg, 0.12 mmol) and toluene (20 mL) were heated at 90 °C for 3 h. The solvent was evaporated, and the residue was purified by MPLC chromatography (EtOAc–hexane 1:20) to afford 165 mg (78%) of *syn*-ethyl 2-isothiocyano-3-(*tert*-butyldimethylsiloxy)-5-methylhex-4-enoate (**10**). Isothiocyanate **10** (143 mg, 0.42 mmol), AIBN (14 mg, 0.85 mmol), tributyltin hydride (200 mg, 0.66 mmol), and toluene (20 mL) were stirred for 3 h at 100 °C. The solvent was evaporated, and the residue was separated by flash-chromatography (EtOAc–hexane 1:4) affording title thiopyroglutamate **12** (110 mg, 60% from **6**): IR (neat) 1111, 1744, 3159, 3176 cm^{-1}; ^1H NMR (δ) 0.07, 0.10 (s, 6H), 0.83 (s, 9H), 0.90, 1.16 (2 × d, J = 7.0 Hz, 6H), 1.32 (t, J = 7.2 Hz, 3H), 2.37 (d of septets, J = 7.0, 4.1 Hz, 1H), 2.81 (dd, J = 4.1, 0.9 Hz, 1H), 4.14, 4.30 (2 × dq, J = 7.2, 10.8 Hz, 2H), 4.46 (d, J = 4.8 Hz, 1H), 4.66 (dd, J = 0.9, 4.8 Hz, 1H), 7.8 (br s, 1H). Anal. Calcd for $C_{16}H_{31}NO_3SSi$: C, 55.65; H, 8.79; N, 4.06; S, 9.28. Found: C, 55.47; H, 9.00; N, 4.00; S, 8.88.

2β-(Ethoxycarbonyl)-3α-(*tert*-butyldimethylsiloxy)-4β-isopropyl-5-(ethylthio)-4*H*-2,3-dihydropyrrole (13). *anti*-Isocyanide **7** (479 mg, 1.54 mmol), AIBN (50 mg, 0.31 mmol), ethanethiol (143 mg, 2.31 mmol), and toluene (40 mL) were stirred under argon for 3 h at 70 °C. Evaporation of the solvent followed by chromatography afforded a product (475 mg, 83%) which consisted of a 14:1 mixture of dihydropyrrole **13** and dihydropyrrole **14** (based on NMR). In a second experiment MPLC afforded analytically pure **13**: IR (neat) 1588, 1739 cm^{-1}; ^1H NMR (δ) 0.12, 0.13 (2 × s, 6H), 0.77, 1.02 (2 × d, J = 6.9 Hz, 6H), 0.88 (s, 9H), 1.31 (t, J = 7.2 Hz, 3H), 1.36 (t, J = 7.4 Hz, 3H), 2.10 (d of septets, J = 6.9, 3.0 Hz, 1H), 2.86 (t, J = 2.9, 3.0 Hz, 1H), 3.01, 3.19 (2 × dq, J = 7.4, 13 Hz, 2H), 4.26, 4.28 (2 × dq, J = 7.4 Hz, 10.8 Hz, 2H), 4.49 (d, J = 2.8 Hz), 4.51 (t, J = 2.8 Hz, 1H). Anal. Calcd for $C_{18}H_{35}NO_3SSi$: C, 57.86; H, 9.44; N; 3.75; S, 8.58. Found: C, 57.99; H, 9.37; N, 3.49; S, 8.28.

2β-(Ethoxycarbonyl)-3α-(*tert*-butyldimethylsiloxy)-4β-isopropylpyrrolidone (15). *anti*-Isocyanide **7** (479 mg, 1.54 mmol), AIBN (50 mg, 0.31 mmol), mercaptoethanol (180 mg, 2.31 mmol), and 40 mL of toluene were stirred for 4 h at 100 °C. Evaporation of the solvent followed by chromatographic purification afforded a mixture (450 mg, 89%) which consisted of a 11:1 mixture of pyrrolidone **15** and pyrrolidone **16** (based on NMR). In a second experiment MPLC afforded analytically pure **15**: IR (neat) 1708, 1747, 3250 cm^{-1}; ^1H NMR (δ) 0.143, 0.146 (s, 6H), 0.90 (s, 9H), 0.90, 1.02 (2 × d, J = 6.9 Hz, 6H), 1.32 (t, J = 7.2 Hz, 3H), 2.09 (d of septets, J = 6.9, 2.5 Hz, 1H), 2.28 (ddd, J = 3.5, 2.5, 0.7 Hz, 1H), 3.98 (dd, J = 2.5, 0.7 Hz), 4.25 (quartet, 2H, J = 7.2 Hz), 4.45 (t, J = 2.5 Hz, 1H), 5.76 (s, 1H). Anal. Calcd for $C_{16}H_{31}NO_4Si$: C, 58.32; H, 9.48; N, 4.25. Found: C, 58.60; H, 9.78; N, 4.43.

NOE for Pyroglutamates 9 and 15. Irradiation at H-3 in pyroglutamate **9** resulted in NOE response at H-2 (6.6%) and at H-4 (2.1%). Irradiation at H-3 in pyroglutamate **15** resulted in NOE response at H-2 (1.6%) and at H-4 (1.6%). These data indicate *trans*-configuration of H-3 and H-4 in both isomers, *cis*-configuration of H-2 and H-3 in pyroglutamate **9**, and *trans*-configuration of H-2 and H-3 pyroglutamate **15**.

Cyclization of Isocyanide 6 Monitored by NMR. A solution of *syn*-isocyanide **6** (163 mg, 0.52 mmol), mercaptoethanol (40 mg, 0.52 mmol), and AIBN (16 mg, 0.1 mmol) in C_6D_6 (1mL) in a sealed NMR tube was heated at 80 °C. The sample was periodically cooled to 20 °C, and NMR spectra (C_6D_6, δ) were recorded at the following intervals: (1) starting material, (2) 10 min, (3) 30 min, (4) 2 h, (5) 8 h. Relevant spectra (1, 3, and 5) are reported herein: ^1H NMR of **6** (δ) 0.09, 0.12 (2 × s, 6H), 0.95 (t, J = 7.1 Hz, 3H), 0.98 (t, J = 6.6 Hz, 1H, mercaptoethanol), 1.02 (s, 9H), 1.44 (d, J = 1.3 Hz, 3H), 1.49 (d, J = 1.2 Hz, 3H), 2.23 (dt, J = 6.6, J = 6.0 Hz, 2H, mercaptoethanol), 3.29 (t, J = 6.0 Hz, mercaptoethanol), 3.79 (d, J = 4.1 Hz, 1H), 3.93 (qrt, J = 7.1 Hz, 2H), 4.91 (dd, J = 4.1, J = 9.0 Hz, 1H), 5.39 (d of sept, J = 9.0, J = 1.3 Hz, 1H). (3) ^1H NMR assigned to **17** (δ): 0.05, 0.12 (2 × s, 6H), 0.71, 0.85 (2 × d, J = 6.9 Hz, 6H), 0.93 (s, 9H), 1.14 (t, J = 7.2 Hz, 3H), 1.90 (d of sept, J = 4.0, J = 6.9 Hz, 1H), 2.93 (dd, J = 2.0, J = 4.0 Hz, 1H), (t, J = 5.3 Hz, 2H), (t, J = 5.3 Hz, 2H), 4.07, 4.23 (2 × d of quart, J = 10.8, J = 7.2 Hz, 2H, 4.45 (dd, J = 2.0, J = 5.4 Hz, 1H), 4.54 (d, J = 5.4 Hz, 1H). (5) ^1H NMR of **9** (δ): 0.04, 0.10 (2 × s, 6H), 0.93 (s, 9H), 1.03, 1.09 (2 × d, J = 6.9 Hz, 6H), 1.06 (t, J = 7.1 Hz, 3H), 2.09 (d of sept, J = 4.4, J = 6.9 Hz, 1H), 2.63 (dd, J = 4.4, J = 5.7 Hz, 1H), 3.86 (d, J = 6.6 Hz, 1H), 3.94, 4.14 (2 × d of qrt, J = 10.8 Hz, J = 7.1 Hz, 2H), 4.30 (t, J = 6.2 Hz, 1H). Peaks at 2.23 (3.03), 3.29 (3.87) deriving from mercaptoethanol hydrogen atoms practically disappeared (this excludes an hydrolytic reaction).

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