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Synthesis of 1,2-Dithiolane Analogues of Leucine for Potential Use in Peptide Chemistry

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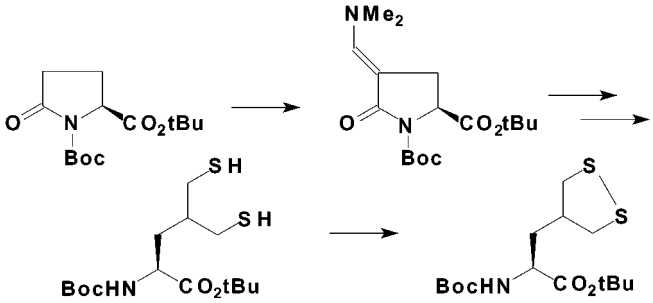
ABSTRACT



1,2-Dithiolanes present several points of interest for both peptide and medicinal chemistry, yet no chiral α-amino acids containing this five-membered heterocyclic system are available. We report here the first synthesis of *N*- and *C*-protected derivative of (*S*)-2-amino-3-(1,2-dithiolan-4-yl)propionic acid (Adp) and its 1,3-dithiolic form.

Proteinogenic α-amino acids represent an exceptionally rich source of chiral building blocks and synthons to be used in both organic and medicinal chemistry.[1] Nonproteinogenic and synthetic amino acids are, however, becoming increasingly important for the design of peptidomimetics endowed with improved specific properties.[2] It is well-known in fact that, although native biologically active peptides have a great potential as therapeutic agents, they need to be modified to overcome problems connected with metabolic stability, appropriate bioavailability, and receptor selectivity.

Among nonproteinogenic α-amino acids, particular attention is being devoted to models whose side chain bears a heterocyclic ring system;[3] these compounds present in fact a variety of chemical structures and, when appropriately inserted into peptide backbones, offer the opportunity to establish efficient interactions with the biomolecular targets.

In this context, the heterocyclic five-membered ring of 1,2-dithiolanes should represent an interesting molecular fragment to be introduced into α-amino acid side chains. Due to the stereoelectronic effects involving the sulfur lone pairs and the small dihedral angle around the S−S bond,[4,5] the chemical and physical properties of 1,2-dithiolanes, which represent the oxidized form of 1,3-dithiols, are very distinct from those of open chain and large ring disulfides; of particular relevance, in the field of peptidomimetics, are the fast rate of ring opening by nucleophiles,[6,7] the activity as

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(1) (a) Barrett, G. C. *Chemistry and Biochemistry of the Amino Acids*; Chapman and Hall: London, 1985. (b) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539.

(2) (a) Hruby, V. J.; Balse, P. M. *Curr. Med. Chem.* **2000**, *7*, 945. (b) Williams, R. M. *Organic Chemistry Series Volume 7: Synthesis of Optically Active a-Amino Acids*; Baldwin, J. E., Magnus, P. D., Eds.: Pergamon Press: Oxford, 1989.

(3) Adlington, R. M.; Baldwin, J. E.; Catterick, D.; Pritchard, G. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 668 and references therein.

(4) (a) Bock, H.; Wagner, G. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 150. (b) Bock, H.; Stein, U.; Semkov, A. *Chem. Ber.* **1980**, *113*, 3208.

(5) (a) Breslow, D. S.; Skolnik, H. Multi-sulfur and Sulfur and Oxygen Five- and Six-Membered Heterocycles, Part One; *The Chemistry of Heterocyclic Compounds*, Vol. 21; Weissberger, A., Ed.; Interscience Publ.: New York, 1966. (b) Teuber, L. *Sulfur Rep.* **1990**, *9*, 257.

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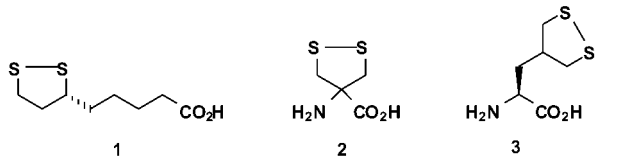
antioxidant and free-radical scavengers,[8] and the efficient metal-ion coordinating properties.[9] It should be remembered here that the 1,2-dithiolane ring system represents the key structural feature on which the reactivity of relevant biomolecules such as that of lipoic acid (**1**, Figure 1), the



1 2 3

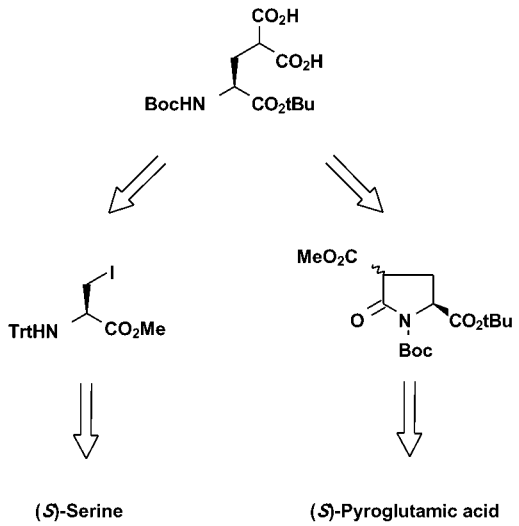
Figure 1. Structure of 1,2-dithiolane derivatives: naturally occurring *R*-enantiomer of 1,2-dithiolane-3-pentanoic acid (lipoic acid, **1**); 4-amino-1,2-dithiolan-4-carboxylic acid (Adt, **2**); (*S*)-2-amino-3-(1,2-dithiolan-4-yl)-propionic acid (Adp, **3**).

essential cofactor in the oxidative decarboxylation of α-ketoacids, is based.[9,10]

On the basis of the above-reported considerations and by considering the absence of information on the chemistry of peptidomimetics incorporating 1,2-dithiolane heterocyclics, we recently began a research program centered on the study of this topic. The $C^{\alpha,\alpha}$-tetrasubstituted and achiral residue of 4-amino-1,2-dithiolane-4-carboxylic acid (Adt, **2**) was chosen as an initial model and the conformational and biochemical consequences of its insertion into bioactive oligopeptides have been described.[11,12] As a continuation of these studies we report here the stereocontrolled synthesis of the *N*- and *C*-protected derivatives of (*S*)-2-amino-3-(1,2-dithiolan-4-yl)propionic acid (Adp, **3)** and its 1,3-dithiolic form **14**. The Adp molecule represents the first example of chiral an α-amino acid containing a cyclic disulfide in its side chain.

The use of the malonic precursor, obtained from (*S*)-pyroglutamic acid or (*S*)-serine derivatives, as depicted in Scheme 1, was initially considered a suitable approach to prepare **3**. However, the regioselective reduction of this compound was found to be sluggish and gave complex reaction mixtures. Difficulties during the reduction of *N*-protected γ-carboxy glutamyl derivatives analogous to that reported in Scheme 1 have already been noted by Dubois et al.[13] and are attributable, at least in part, to the participation of the urethane NH and formation of pyrrolidine derivatives.

Scheme 1



An alternative approach (see Scheme 2), which follows in part the route previously used to prepare (*S*)-5,5′-dihydroxyleucine,[14] was then adopted.

tert-Butyl (*S*)-*N*-*tert*-butoxycarbonylpyroglutamate **6** was used as the starting material.[15] This was converted in high yield into the enaminone **7** by using *tert*-butoxy-bis(dimethylamino)methane (Bredereck's reagent).[16] The $NaBH_3$-CN reduction of the intermediate aldehyde **8**, obtained by acidic hydrolysis of **7**, at a pH value between 3.5 and 4.0, afforded a diastereoisomeric mixture of *cis* and *trans* alcohols **9** with improvement of the yield and shortening of the reaction time as compared with the original protocol.[14] The mixture of the alcohols was then hydrolyzed using aqueous LiOH in THF, and the resulting hydroxy acid **10** was regioselectively reduced after conversion into the corresponding mixed anhydride and in situ treatment with $NaBH_4$. The synthesis of the dimesylate **12** was followed by treatment with potassium thiolacetate to give the bis-mercaptoacetyl derivative **13** in 85% combined yields. Aqueous alkaline hydrolysis of **13** at 0 °C afforded the (*S*)-5,5′-dimercaptoleucine derivative **14**[17] whose iodine oxidation furnished

(6) Concerning nucleophilic reactions at the sulfur atoms, it should be noted (see: Schmidt, U.; Grafen, P.; Goedde, H. W. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 846) that the ground state of the1,2-dithiolane ring system (valence angle at the S atom, 92°; S−S bond length, 2.1 Å) is much more similar geometrically to the transition state than is the ground state of an open chain disulfide (valence angle at S, 107°; S−S distance, 2.05 Å).

(7) Singh, R.; Whitesides, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 6304.

(8) (a) Packer, L.; Witt, E. H.; Tritschler, H. J. *Free Radical Biol. Med.* **1995**, *19*, 227. (b) Haenen, G. R. M. M.; Bast, A. *Biochem. Pharmacol.* **1991**, *42*, 2244.

(9) (a) Sigel, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 389. (b) Lodge, J. K.; Traber, M. G.; Packer, L. *Free Radical Biol. Med.* **1998**, *25*, 287.

(10) Reed, L. J. *Comprehensive Biochemistry* **1966**, *14*, 99.

(11) Morera, E.; Nalli, M.; Pinnen, F.; Rossi, D.; Lucente, G. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1585.

(12) Morera, E.; Lucente, G.; Ortar, G.; Nalli, M.; Mazza, F.; Gavuzzo, E.; Spisani, S. *Bioorg. Med. Chem.* **2002**, *10*, 147.

(13) Dubois, J.; Fourès, C.; Bory, S.; Falcou, S.; Gaudry, M.; Marquet, A. *Tetrahedron* **1991**, *47*, 1001.

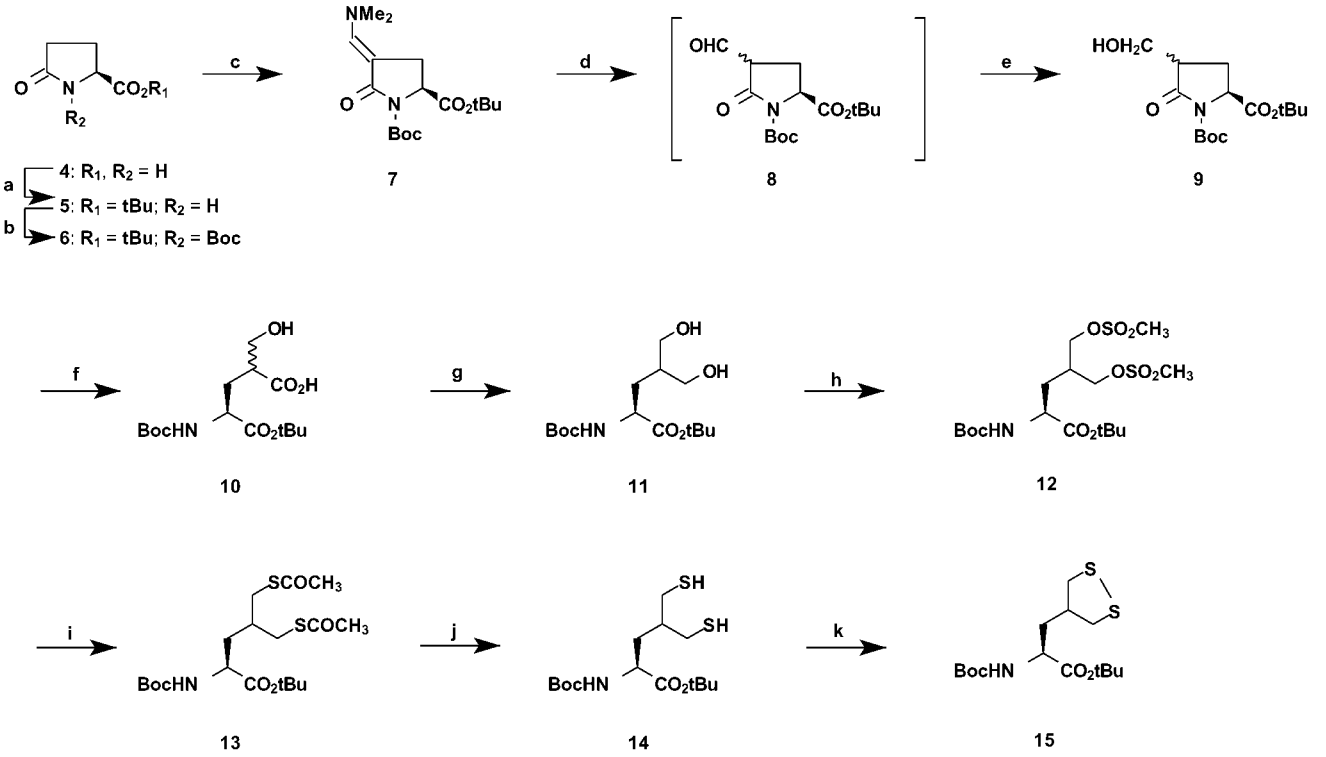
(14) August, R. A.; Khan, J. A.; Moody, C. M.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1996**, 507.

(15) Protection as the *N*-Boc *tert*-butyl ester allows a regioselective hydrolysis during the ring-opening step and preserves the stereochemical integrity of the α-center (see: August, R. A.; Khan, J. A.; Moody, C. M.; Young, D. W. *Tetrahedron Lett.* **1992**, *33*, 4617).

(16) Bredereck, H.; Simchen, G.; Rebsdat, S.; Kantlehner, W.; Horn, P.; Wahl, R.; Hoffmann, H.; Grieshaber, P. *Chem. Ber.* **1968**, *101*, 41.

(17) **(*S*)-*N*-Boc-5,5′-dimercaptoleucine *tert*-Butyl Ester (14).** A solution of bis-thioacetate derivative **13** (0.135 g, 0.31 mmol) in degassed EtOH (2 mL) was treated with 0.93 mL of aqueous 1 N NaOH at 0 °C for 1 h. The mixture was neutralized with 2 N HCl and extracted with CH_2Cl_2. The organic phase, washed with water, dried, and evaporated at room temperature, gave an oily residue of pure **14** (0.108 g, 99%). $[\alpha]_D$ +9° (c = 2.0; $CHCl_3$); IR ($CHCl_3$) 3434, 2981, 1706, 1501, 1369, 1236, 1153 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (m, 1H, SH_A), 1.32 (t, 1H, J = 8.5 Hz, SH_B), 1.44 and 1.47 (2 × s, 18H, 2 × *tert*-butyl), 1.65 (m, 1H, β-CH_A), 1.87 (m, 2H, β-CH_B and γ-CH), 2.70 and 2.82 (2 × m, 4H, 2 × CH_2S),

Scheme 2[a]

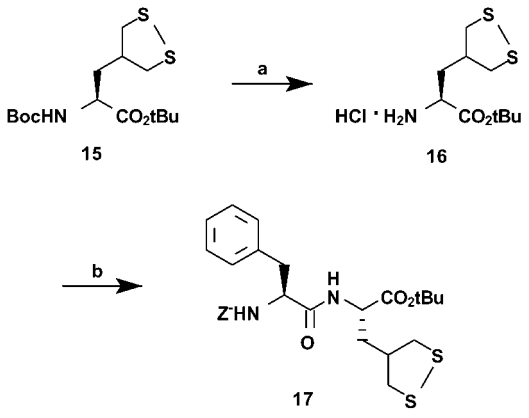


[a] $HClO_4$ 70%, CH_3CO_2tBu, 76%; (b) $(Boc)_2O$, DMAP, 94%; (c) Bredereck's reagent, DME, 75 °C, 88%; (d) aqueous 0.2 N HCl, MeOH; (e) $NaBH_3CN$, 4 h, 56% from **7**; (f) aqueous 1 M LiOH, THF, 0 °C, 95%; (g) *i*BuOCOCl, NMM, THF, −15 °C, then $NaBH_4$ at 0 °C, 79%; (h) CH_3SO_2Cl, TEA, CH_2Cl_2 dry, 0 °C, 94%; (i) CH_3COSK, DMF, 91%; (j) aqueous 1 N NaOH, EtOH, 0 °C, 99%; (k) $CHCl_3$, AcONa, aqueous 0.1 M I_2, 98%.

eventually the desired Adp derivative **15**[18] in almost quantitative yield; this latter compound was also obtained by a *one-pot* procedure starting from **13** (72%). As expected, and in accordance with the chemistry of 1,2-dithiolanes,[5] the new α-amino acid derivative **15** can be easily reduced to regenerate the 5,5′-dimercaptoleucine **14**.

Although the Adp derivative **15** contains two *tert*-butyl protecting groups, it was possible, by adopting the procedure described by Rapoport et al.,[19] to selectively remove the *N*-Boc protection in the presence of the *tert*-butyl ester; Scheme 3 reports an application of this procedure together with the synthesis of the dipeptide Z-Phe-Adp-O*t*Bu.

Scheme 3[a]



[a] 1 M HCl in EtOAc, rt, 4 h, 69%; (b) HOBt, EDC, Z-Phe-OH, TEA, DMF, 79%.

4.15 (m, 1H, α-CH), 5.09 (d, 1H, J = 8.4 Hz, NH); ^{13}C NMR (75.43 MHz, $CDCl_3$) δ 26.3 and 27.0 (2 × CH_2S), 27.9 and 28.2 [2 × C(CH_3)$_3$], 35.0 (β-CH_2), 39.5 (γ-CH), 51.8 (α-CH), 79.7 and 82.0 [2 × C(CH_3)$_3$] 155.1 and 171.4 (2 × CO).

(18) ***N*-Boc-Adp *tert*-Butyl Ester (15).** An aqueous solution of 0.1 M iodine was added dropwise at 0 °C to a solution of **14** (0.096 g, 0.273 mmol) and AcONa (0.067 g, 0.820 mmol) in $CHCl_3$ (8 mL) until a persistent pale yellow color appeared (2.9 mL). The mixture was decolorized with 1 M $Na_2S_2O_3$ and the organic phase was separated, washed with water, dried, and evaporated at room temperature. The crude (0.101 g) was cromatographed on silica gel (4 g) using $CHCl_3$ as eluent to give 0.093 g of **15** (98%). Mp 61−61.5 °C (hexane); $[\alpha]_D$ +21° (c = 1.0; $CHCl_3$); IR ($CHCl_3$) 3434, 2982, 1707, 1500, 1369, 1153 cm^{-1}; UV ($CHCl_3$) λ_{max} 332 (152); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 and 1.47 (2 × s, 18H, 2 × *tert*-butyl), 1.71 (m, 1H, β-CH_A), 1.97 (m, 1H, β-CH_B) 2.68 (m, 1H, γ-CH), 2.86 and 3.31 (2 × m, 4H, 2 × CH_2S), 4.19 (m, 1H, α-CH), 5.10 (d, 1H, J = 8.1 Hz, NH); ^{13}C NMR (75.43 MHz, $CDCl_3$) δ 27.9 and 28.3 [2 × C(CH_3)$_3$], 37.3 (β-CH_2), 43.7 and 44.0 (2 × CH_2−S), 44.1 (γ-CH), 53.1 (α-CH), 79.8 and 82.2 [2 × C(CH_3)$_3$], 155.1 and 171.2 (2 × CO). The Adp derivative **15** could also be prepared by a *one-pot* procedure: thus, a solution of bis-dimercaptoacetyl derivative **13** (0.519 g, 1.19 mmol) in EtOH (8 mL) was treated with 3.56 mL of aqueous 1 N NaOH at 0 °C for 1 h. The mixture was diluted with CH_2Cl_2 (60 mL) and then an aqueous solution of 0.1 M iodine was added dropwise until a persistent pale yellow color appeared. The mixture was decolorized with 1 M $Na_2S_2O_3$ and the organic phase was separated, washed with water, dried, and evaporated at room temperature. The crude (0.385 g) was cromatographed on silica gel (12 g) using $CHCl_3$ as eluent to give 0.299 g of **15** (72%).

In conclusion, we have described the efficient synthesis of a pair of chiral α-amino acids structurally related to the natural residue of leucine and characterized by the presence in its side chain of the 1,2-dithiolane−1,3 dithiol redox system. By considering the relevant biological role played by the lipoic−dihydrolipoic acid system as well as the peculiar reactivity of 1,2-dithiolanes, the incorporation of these new residues into bioactive peptides should represent a new and promising approach.

Supporting Information Available: Experimental procedures and characterization data for compounds **12**, **13**, **16**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Gibson, F. S.; Bergmeier, S. C.; Rapoport, H. *J. Org. Chem*. **1994**, *59*, 3216.