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Design of a depside with a lipophilic adamantane moiety: Synthesis, crystal structure and molecular conformation

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Abstract

New adamantane depsides, ethyl 2-(1-adamantyl)-3-*O*-[(*S*)-Boc-Phe]butanoate (*R*,*R*,*S*)-**1a** and (*S*,*S*,*S*)-**1b** were prepared and characterized by spectroscopic data. The crystal structures and the stereochemistry of *rac*-(*R*,*R*,*S*)-**1a** and *threo*-2-(1-adamantyl)-3-hydroxy-butanoic acid *rac*-(*R*,*R*)-**4a** were determined by X-ray structure analysis. In the racemic crystal, the molecules of **1a** form centrosymmetric dimers through hydrogen bonds involving a double acceptor function of the depside carbonyl oxygen, and donors of the amino group and aromatic C–H atoms. The dimers are connected through an infinite chain of C–H···O interactions, where C–H is an aromatic donor and the ester carbonyl oxygen is an acceptor. In the solid state, amphiphilic molecules **1a** and **4a** exhibit pronounced hydrophilic and hydrophobic bilayers.

Keywords: Depside design; Adamantyl hydroxybutanoic acid; Conformation; X-ray structure analysis

1. Introduction

Cyclic peptides and depsipeptides have been characterized from many natural environments, and show a wide spectrum of biological activity. Depsipeptides are therefore promising lead compounds for drug discovery. Depsipeptides are heterodetic peptides in which at least one amide bond has been replaced with an ester bond [1]. The best known cyclodepsipeptide structures are the ion-selective antibiotics such as valinomicyne [2] and closely related molecules [3]. The design and synthesis of novel macrocyclic depsipeptides with potential bioactivity continue to attract the attention of synthetic chemists [4].

The use of unnatural amino acids has a broad application in structure–function studies [5a]. The incorporation of unnatural amino or hydroxy acids into peptides and depsides induces particular steric properties to the rest of the molecule and expands the scope of structural perturbation [5].

Modifications of depsides and depsipeptides using lipophilic moieties may be of particular interest because of the increase of hydrophobicity. The enhancement of hydrophobicity via the incorporation of an adamantane moiety opens up new possibilities in terms of the chemical structure and activity relationship. As a part of the project directed towards the synthesis of cyclic depsipeptides we wish to report the synthesis and structural characterization of a new linear adamantane-containing depside fragment **1** and the adamantane precursor, 2-(1-adamantyl)-3-hydroxy-butanoic acid (**4a**). The charaterization of both compounds (**1** and **4a**) by X-ray analysis and spectroscopic methods is described.

2. Experimental

2.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded on 300 MHz and 600 MHz spectrometers using TMS as the

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internal standard. IR spectra were recorded on a FT-IR ABB Bomem MB 102 spectrophotometer and elemental analyses were performed at the Central Analytical Laboratory, Ruđer Bošković Institute. HPLC analyses were performed on a Varian ProStar instrument equipped with a UV detector operated at $\lambda = 230$ nm. Ethyl keto ester **2** [6] and (*S*)-Boc-PheOH [7] were prepared according to established procedures. Unless stated otherwise, reagent grade solvents were used.

2.2. Synthesis

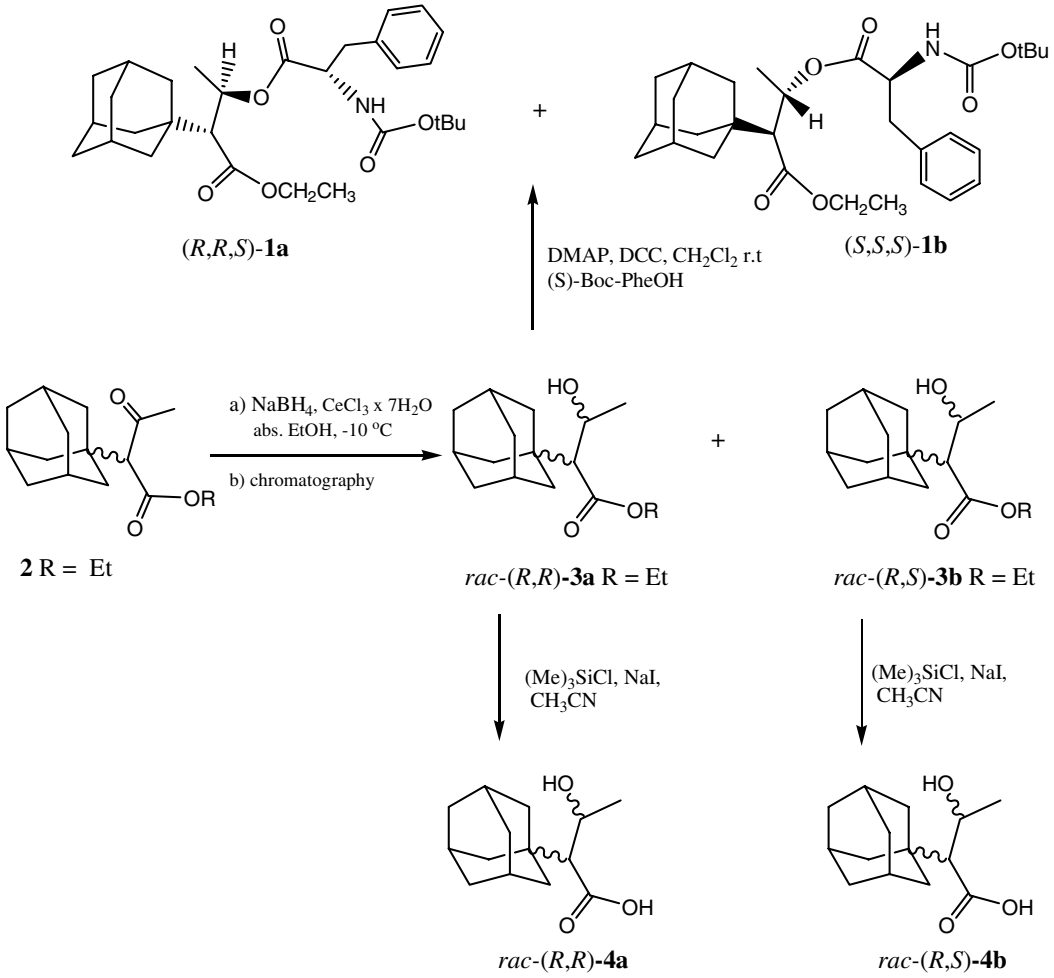
The key intermediate for the synthesis of target depsides **1a** and **1b** was the ethyl 2-(1-adamantyl)-3-oxobutanoate (**2**), Scheme 1.

2.2.1. Preparation of a diastereomeric mixture of ethyl 2-(1-adamantyl)-3-hydroxybutanoate (*3a* and *3b*)

To a stirred solution of keto ester **2** (4.9 g, 19 mmol) in abs. ethanol (180 mL), under N_2 atmosphere, crystals of $CeCl_3{\cdot}7H_2O$ (8.9 g, 24 mmol) were added. The reaction mixture was then cooled to −10 °C and $NaBH_4$ (1.3 g, 35 mmol) was added in several portions during 2.5 h, so that the temperature of the reaction mixture did not exceed −5 °C. The reaction mixture was then stirred for another 1.5 h at +8 °C after which the reaction was quenched by adding acetone (500 mL). After 30 min of stirring at room temperature, the solvent was removed under reduced pressure and the residue suspended in $CHCl_3/CH_2Cl_2$ (3:1, 400 mL), washed with water (250 mL), saturated $NaHCO_3$ (2× 50 mL) and brine (2× 80 mL). The organic phase was dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure to afford the mixture of products (4.6 g, 93%). Products **3a** and **3b** were formed in a 1:1.3 ratio according to HPLC analysis. [OmniSpher C18, 250 × 10 mm, solvent $CH_3CN/H_2O = 90{:}10$, 1 mL/min, $t_R = 4.86$ and 6.41 min, respectively].

The mixture of diastereoisomers **3a** and **3b** (4.6 g) was chromatographed on silica gel (70–230 mesh) by eluting with 0 → 1% methanol in CH_2Cl_2 to afford the diastereoisomer **3a** (1.84 g), a mixture of **3a** and **3b** (1.3 g) and **3b** (1.45 g) as oily substances.

Product **3a**: ^{1}H NMR (300 MHz, C_6D_6): $\delta = 4.09$–4.23 (m, 1H), 3.96 (q, $J = 7.1$ Hz, 2H), 3.59 (d, $J = 9.6$ Hz, 1H, OH), 1.95 (d, $J = 2.1$ Hz, 1H), 1.91 (br s, 3H), 1.81 (d, $J = 12.6$ Hz, 3H), 1.74 (d, $J = 12.6$ Hz, 3H), 1.53–1.69



Scheme 1.