

Short Note

## Improved Synthesis and Crystal Structure of Dalcetrapib

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**Abstract:** An improved synthesis of the Cholesteryl Ester Transfer Protein inhibitor dalcetrapib is reported. The precursor disulfide was reduced (a) by Mg/MeOH or (b) by EtSH/DBU/THF. The resulting thiol was acylated (a) by a known procedure or (b) in a one-pot process. Impurities were removed (a) by dithiothreitol (DTT) or (b) by oxidation using H<sub>2</sub>O<sub>2</sub>. Dalcetrapib crystallized in space group *P*2<sub>1</sub>/*c*.

**Keywords:** CETP inhibitor; dalcetrapib; disulfide; thioester

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### 1. Introduction

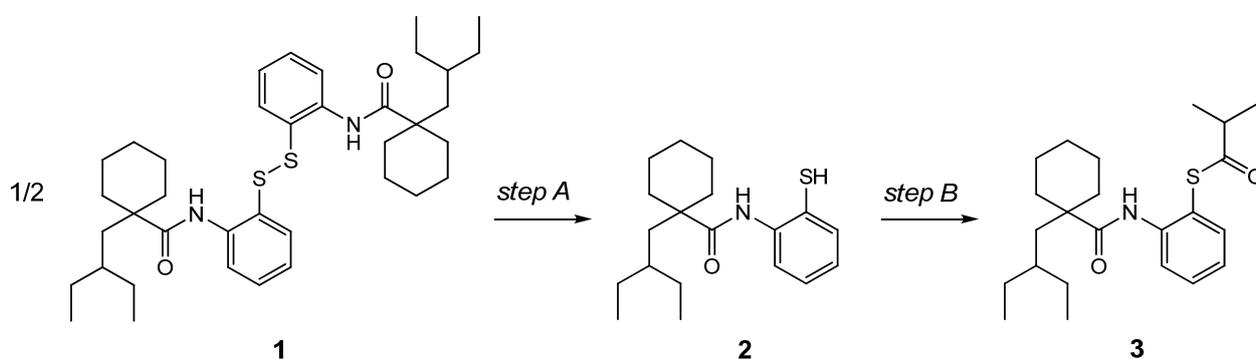
Cholesteryl Ester Transfer Protein (CETP) inhibitors [1] are investigated as high density lipoprotein-cholesterol (HDL-C) raising agents with beneficial effects on atherosclerosis. A series of *S*-(2-(acylamino)phenyl) alkanethioates was evaluated, and *S*-(2-((1-(2-ethylbutyl)cyclohexane)carbonyl-amino)phenyl) 2-methylpropanethioate was found to exhibit significant inhibition of CETP activity in animals [2,3] and clinical trials [4,5]. It was first synthesized by reduction of the disulfide **1** using triphenylphosphine and subsequent acylation of the resulting thiol **2** to give the title compound,

dalcetrapib **3** (Figure 1) [2]. A one-pot process for the preparation of **3** comprising acylation in the presence of a reducing agent such as phosphine, phosphinite, phosphonite, or phosphite was patented [6].

## 2. Results and Discussion

The synthesis of dalcetrapib involves two key steps (Figure 1): Reduction and acylation. The patented use of phosphorus(III) compounds as reducing agents [6] showed several disadvantages. The excess phosphines and resulting phosphine oxides are difficult to remove, and we intended to avoid chromatography. Methyl or ethyl phosphites (and the resulting phosphates) are alkylating agents giving rise to thioether byproducts. In addition, a patent-free synthesis was desired.

**Figure 1.** Synthesis of dalcetrapib (**3**). Step A: reduction; Step B: acylation (see text).



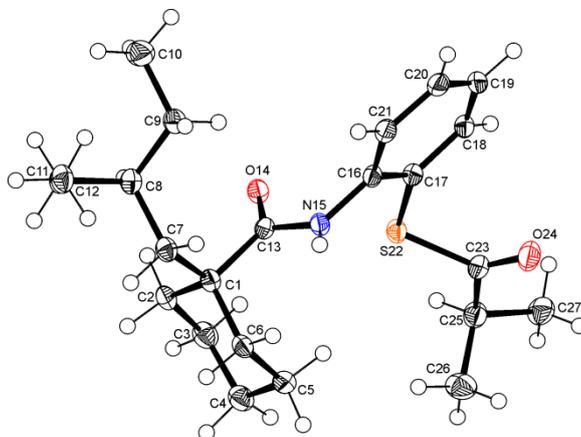
The reduction of disulfide **1** to thiol **2** using magnesium in methanol [7] seemed to be a good option for the first step and proceeded smoothly. The thiol is, however, very sensitive to oxygen. The final product dalcetrapib was therefore always contaminated by a few percent of the corresponding disulfide. Purification was effected by treatment with dithiothreitol (DTT), a reagent capable of reducing disulfides and maintaining thiols in the reduced state [8]. The use of this reagent gave a perfectly pure product. It is, however, rather expensive. Water-soluble phosphines, such as tris(2-carboxyethyl)-phosphine or trisodium tris(3-sulfonatophenyl)phosphine, also worked well for this purpose, but they carry an even steeper price. Consequently, a process was sought which did not require the isolation of the sensitive intermediate **2**.

A one-pot method to obtain thiol esters directly from disulfides and acyl chlorides in the presence of zinc and aluminum trichloride [9] was tried, but a new byproduct was observed. Therefore, this route was not pursued further. A thiol-disulfide interchange reaction employing inexpensive ethanethiol in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was found to produce thiols in a very short time [10]. This concept has been successfully applied to the one-pot synthesis of dalcetrapib and has been reported by an anonymous author in an online journal [11]. In our hands, however, a much higher yield was obtained (reported 52%, found 82%). A modified workup was necessary to remove an unidentified impurity beyond the limit of detection.

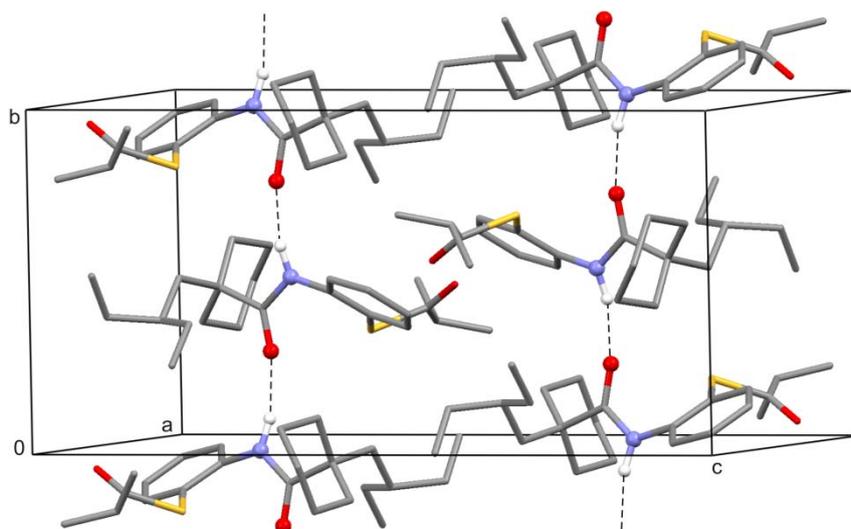
In the search for polymorphs, crystalline dalcetrapib was obtained from several solvents (ethanol, heptane, tetrahydrofuran). Powder X-ray diffraction showed that they were identical crystalline forms. The molecular structure is shown in Figure 2. The cyclohexane ring adopts a typical chair conformation. The molecules are arranged in chains by N-H...O=C hydrogen bonds in the

direction of the crystallographic *b* axis (Figure 3). The pertinent distances are H···O 2.02(2) Å and N···O 2.905(2) Å. The N···H···O angle is 159(2)°.

**Figure 2.** ORTEP plot of dalcetrapib (thermal ellipsoids drawn at the 50% level).



**Figure 3.** Packing diagram of dalcetrapib (3). Atoms engaged in hydrogen bonding are drawn as balls, and all other hydrogen atoms are omitted for clarity.



### 3. Experimental Section

The disulfide **1** [211513-15-4] has been prepared according to the literature [2]. <sup>1</sup>H NMR spectra of thiol **2** [211513-21-2] and dalcetrapib **3** [211513-37-0] have been previously published [2].

#### 3.1. Two-Step Synthesis of Dalcetrapib (3)

Mg turnings (1.1 g) were added to a solution of the disulfide **1** (10.0 g) in MeOH (100 mL). The reaction mixture was stirred under argon for 9 h in a water bath to keep the temperature below 50 °C. The solvent was removed and the residue partitioned between 1M HCl (100 mL) and EtOAc (100 mL). The organic phase was washed with brine (60 mL), then dried over MgSO<sub>4</sub>, and taken to dryness to give the thiol **2** as a foul-smelling oil, which solidified overnight (yield 98%). This intermediate was dissolved in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (70 mL). Pyridine (6 mL) was added and, dropwise, isobutyryl

chloride (3.4 mL). The mixture was stirred at room temperature for 3 h. After removal of the solvent, the residue was redissolved in EtOAc (100 mL) and washed with H<sub>2</sub>O (100 mL), 1M HCl (100 mL), 1M NaOH (100 mL), and brine (100 mL). The solvent was evaporated, and the crude product was dissolved in Et<sub>2</sub>O (200 mL) and vigorously stirred with a solution of DTT (0.8 g) and NaHCO<sub>3</sub> (0.5 g) in H<sub>2</sub>O (40 mL) at room temperature for 45 min. The organic phase was separated, washed with 1M NaOH (140 mL) and H<sub>2</sub>O (100 mL), and the solvent was evaporated. The residue was dissolved in EtOH (40 mL) and precipitated by slow addition of H<sub>2</sub>O (40 mL) with stirring for 1 h. The crystalline product **3** was filtered off, washed with H<sub>2</sub>O (40 mL), and dried over P<sub>2</sub>O<sub>5</sub> in vacuum. Yield: 77%. The single crystals were obtained by cooling of a hot solution in EtOH (from 80 °C to 20 °C in 3 h).

### 3.2. One-Pot Synthesis of Dalcetrapib (**3**)

Isobutryl chloride (2.0 mL) was added to a stirred solution of the disulfide **1** (2.0 g), DBU (2.8 mL), and EtSH (0.7 mL) in THF (15 mL) at room temperature. After 10 min, the precipitated DBU hydrochloride was filtered off and washed with Et<sub>2</sub>O (25 mL). The filtrate was stirred with H<sub>2</sub>O (25 mL) for 20 min. The organic phase was shaken with H<sub>2</sub>O (25 mL) and saturated NaHCO<sub>3</sub> solution (25 mL). After removal of the volatiles, the residue was dissolved in heptane/MeOH (20/14 mL) and stirred with 1% H<sub>2</sub>O<sub>2</sub> (6 mL) at 35 °C for 1 h. The organic phase was separated, washed four times with a mixture of MeOH (3 mL) and H<sub>2</sub>O (1 mL), and taken to dryness. The residue was crystallized as described above. Yield: 82%.

### 3.3. Spectroscopic and Crystal Structure Data

Disulfide (**1**): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.70 (t, *J* = 7.3 Hz, 6H), 1.2–1.6 (m, H), 2.0 (m, 2H), 6.91 (Td, *J* = 6.9 Hz, *J* = 1.2 Hz, 1H), 7.12 (dd, *J* = 7.7 Hz, *J* = 1.5 Hz, 1H), 7.41 (Td, *J* = 7.7 Hz, *J* = 1.5 Hz, 1H), 8.48 (dd, *J* = 8.3 Hz, *J* = 1.1 Hz, 1H), 8.59 (br s, 1H) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 11.2, 23.5, 26.4, 27.2, 35.4, 36.2, 45.3, 48.3, 120.9, 122.8, 123.9, 132.6, 136.8, 140.3, 175.4 ppm. IR (neat): ν 3387 w, 2956 m, 2924 m, 2855 m, 1686 m, 1576 m, 1503 s, 1459 m, 1425 s, 1290 m, 753 s cm<sup>-1</sup>.

Thiol (**2**): <sup>1</sup>H NMR, see [2]. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 11.1, 23.5, 26.4, 27.2, 35.5, 36.3, 45.6, 48.2, 116.5, 121.3, 124.1, 129.7, 135.5, 139.6, 175.2 ppm. IR (neat): ν 3377 w, 2957 m, 2927 m, 2869 m, 2850 m, 2507 w, 1644 s, 1507 s, 1459 m, 1439 s, 1287 m, 748 s·cm<sup>-1</sup>.

Dalcetrapib (**3**): <sup>1</sup>H NMR, see [2]. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 11.1, 19.7, 23.4, 26.3, 27.2, 35.6, 36.2, 43.5, 45.7, 48.1, 116.9, 122.1, 124.4, 131.8, 136.4, 140.5, 175.1, 201.5 ppm. IR (neat): ν 3302 w, 2965 m, 2922 m, 2862 m, 1697 s, 1644 m, 1506 m, 1475 s, 959 s, 856 m, 754 s cm<sup>-1</sup>.

Oxford Diffraction Gemini R Ultra diffractometer, Cu-Kα radiation; ω scans; *T* = 100(2) K; θ<sub>max</sub> = 67.2°; indices: -12 ≤ *h* ≤ 12, -11 ≤ *k* ≤ 10, -21 ≤ *l* ≤ 24; *D*<sub>x</sub> = 1.20 g·cm<sup>-3</sup>; 13476 reflections measured, 3624 independent with *R*<sub>int</sub> = 0.048, *F*(000) = 848, μ = 1.46 mm<sup>-1</sup>. Crystal data for C<sub>23</sub>H<sub>35</sub>NO<sub>2</sub>S (*M* = 389.6 g·mol<sup>-1</sup>). Monoclinic, *P*2<sub>1</sub>/*c*, *a* = 10.7572(3), *b* = 9.7154(3), *c* = 20.5873(6) Å, β = 90.003(3)°, *V* = 2151.59(11) Å<sup>3</sup>, *Z* = 4. *R*<sub>1</sub> = 0.039 and *wR*<sub>2</sub> = 0.089 for 2668 reflections with *I* > 2σ(*I*), 251 parameters, *R*<sub>1</sub> = 0.058 and *wR*<sub>2</sub> = 0.094 for all data; *S* = 0.93; Δρ<sub>max</sub> = 0.21 and Δρ<sub>min</sub> = -0.32 e Å<sup>-3</sup>. CCDC reference number: 895592.

#### 4. Conclusions

The new synthetic procedures are superior to the patented processes in terms of purity and yield. Remarkably, the flexible alkyl chains did not exhibit any disorder in the crystal.

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