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# Synthesis and Crystal Structure of (4S,5R)-5-[3,5-*Bis*(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one

HONG CUI†, QING JIE ZHAO†, FA PU CHEN, XIAO YUN CHAI, YAN ZOU, HONG GANG HU, YONG SHENG JIN* and SHI CHONG YU*

Department of Organic Chemistry, School of Pharmacy, Second Military Medical University, Shanghai 200433, P.R. China

*Corresponding authors: Fax: +86 21 81871225; Tel : + 86 21 81871228-17; E-mail: yuscc@hotmail.com; ysjin@smmu.edu.cn
†Contributed equally to this work

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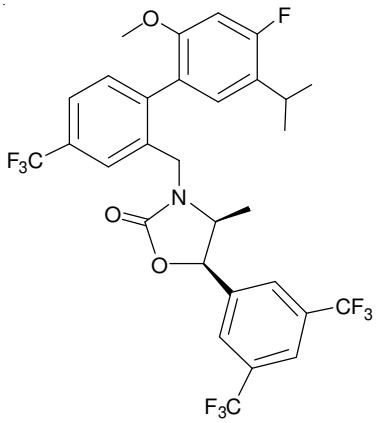
The crystal structure of the (4S,5R)-5-[3,5-*bis*(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one has been determined by single crystal X-ray diffraction method. The compound crystallizes in the monoclinic system, space group P2(1) with a = 11.867(4) Å, b = 5.6968(19) Å, c = 20.258(7) Å, α = 90.00º, β = 91.866(4)º, γ = 90.00º, Z = 4 , V = 1368.8(8) Å$^3$, Dx = 1.520 Mg/m$^3$, $F_{(000)}$ = 632, μ(MoK$_\alpha$) = 0.157 mm$^{-1}$, R = 0.0562 and wR = 0.1744 for 3675 reflections with I > 2σ(I). X-Ray analysis reveals that the benzene and oxazolidin rings are non-coplanar. The oxazolidin ring displays a twist conformation. The two molecules interact with each other by two strong N-H···O hydrogen bonds. Herein, we report the synthesis and crystal structure of (4S,5R)-5-[3,5-*bis*(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one.

**Key Words: Synthesis, Crystal structure, Anacetrapib, (4S,5R)-5-[3,5-*Bis*(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one.**

## INTRODUCTION

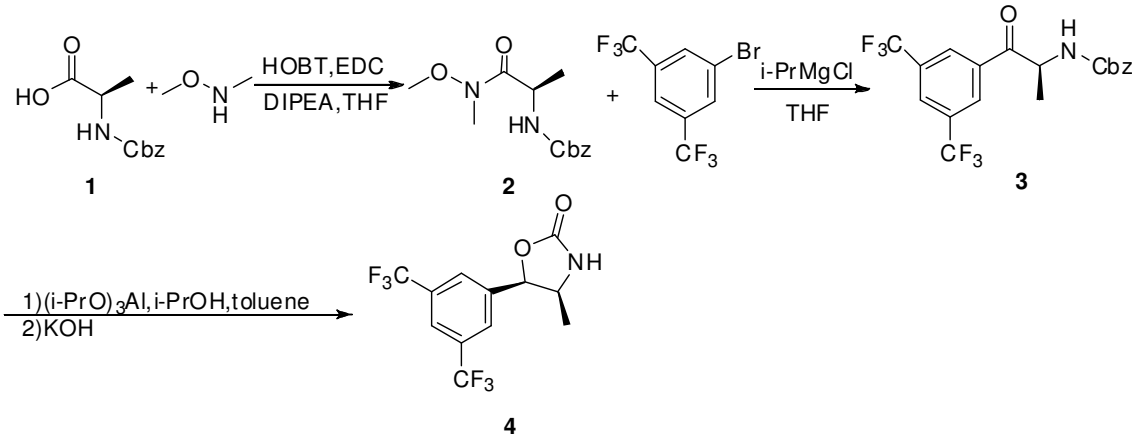
Cardiovascular disease (CVD) continues to be a leading cause of morbidity and mortality among adults in Europe and North America. Rising levels of low density lipoprotein-cholesterol (LDL-C) are considered to be a major risk factor for coronary heart disease (CHD), as one of CVD[1]. Inhibition of cholesteryl ester transfer protein (CETP) is considered as a new approach to coronary heart disease. Cholesteryl ester transfer protein is hydrophobic glycoprotein that is mainly from the liver and that circulates in plasma. The most important effect of CETP is keeping balance of high density lipoprotein-cholesterol (HDL-C) and LDL-C *in vivo*. Inhibition of CETP raises HDL-C and reduces LDC-C. Stains have an ability of reducing LDL-C but are ineffective raising HDL-C. The therapy of combination of a CETP inhibitor and a statin may be valuable for treating and preventing coronary heart disease[2]. But pharmaceuticals containing CETP inhibitors are not available. Anacetrapib researched by Merck in phase III clinical trial at present has a prospect of becoming a pharmaceutical[3] (**Scheme-I**). (4S,5R)-5-[3,5-*bis*(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one is an important intermediate for anacetrapib. It has two chiral centers and usually is synthesized by the method of asymmetric synthesis. We use achiral reactions to construct chiral centers and certify the absolute configuration through X-ray.




**Scheme-I:** Construction of anacetrapib

## EXPERIMENTAL

The melting point was determined on a Yamato MP-21 meltingpoint apparatus and the thermometer was uncorrected. $^1$H spectra were measured on a Varian InNova 500 MHz instrument with $CDCl_3$ as the solvent. LC MS was recorded on an Agilent 1260 Infinity instrument. The single-crystal structure was determined on a Rigaku Saturn CCD area detector. All chemicals were of analytical reagent grade and purchased from commercial sources, which were used directly without further purification.




**Scheme-II:** Procedure of preparing the title compound (**4**)

**Synthesis and characterization:** The (4S,5R)-5-[3,5-*bis* (trifluoromethyl) phenyl]-4-methyl-1,3-oxazolidin-2-one (**4**) was prepared following **Scheme-II**.

**Synthesis of compound 2:** A mixture of compound **1** (0.65 g, 2.5 mmol), HOBT (0.48 g, 3.48 mmol), N,O-dimethylhydroxylamine hydrochloride (0.34 g, 3.62 mmol), THF (10 mL) was stirred at ice bath under an inert atmosphere of argon. DIPEA (0.92 g, 7.1 mmol) and EDC·HCl (0.70 g, 3.62 mmol) was added to the mixture keeping the temperature = 20 ºC. The mixture was stirred at room temperature overnight. The mixture was diluted with DCM, washed with HCl (1 N), $NaHCO_3$ twice, dried over $Na_2SO_4$, concentrated *in vacuo* and purified by column chromatography to give the product as white solid (0.56 g, 79.2 %). m.p. 88.7-92.1 ºC. LCMS calcd. (%) = 267.13; found (%) = 267.3 $(M + H)^+$. $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.36-7.28 (m, 5H), 5.59 (d, *J* = 8.5 Hz, 1H), 5.12 (d, *J* = 12.2 Hz, 1H), 5.07 (d, *J* = 12.3 Hz,1H), 4.74 (t, *J* = 7.8 Hz, 1H), 3.77 (s, 3H), 3.20 (s, 3H), 1.34 (d, *J* = 6.9 Hz, 3H).

**Synthesis of compound 3:** A mixture of compound **2** (2.01 g, 7.5 mmol), 1-bromo-3,5-*bis*(trifluoromethyl)benzene (18.2 mL, 9.37 mmol) and THF (20 mL) was stirred at -10 ºC under an inert atmosphere of argon. *i*-PrMgCl in THF (10 mL, 15 mmol) was slowly added to the mixture keeping the temperature ≤ -5 ºC. The mixture was stirred at room temperature overnight. HCl (4.6 mL, 5N) was added to the mixture keeping the temperature ≤ 5 ºC. The mixture was extracted with DCM, washed with $NaHCO_3$ twice, dried over $Na_2SO_4$, concentrated *in vacuo* and purified by column chromatography to give the product as white solid (0.56 g, 79.2 %). m.p. 105.5-106.9 ºC. LC-MS calcd. (%) 420.10; found (%) 420.2 $(M + H)^+$. $^1H$ NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 2H), 8.12 (s, 1H), 7.38-7.30 (m, 5H), 5.79 (d, *J* = 7.6 Hz, 1H), 5.42-5.33 (m, 1H), 5.15 (s, 2H), 1.48 (d, *J* = 7.2 Hz, 3H).

**Synthesis of compound 4:** A mixture of compound **3** (2.02 g, 4.78 mmol), $(i\text{-PrO})_3Al$ (0.39 g, 1.91 mmol), *i*-PrOH (4 mL), toluene (6 mL) was stirred at 50 ºC overnight under an inert atmosphere of argon. KOH (0.48 g, 8.57 mmol) was added to the mixture slowly maintaining temperature ≤ 25 ºC. After about 2 h, the reaction was complete. 1 N HCl was added to the mixture to quench the reaction. The organic layer was washed with sat. aq. $NaHCO_3$ twice, brine and dried over $Na_2SO_4$. Then the solution was concentrated *in vacuo* to give crude product and the crude product was washed with petroleum ether twice to give product (1.43 g, 95.3 %) as white solid. m.p. 132.6-133.7 ºC. LC-MS calcd. (%) = 314.06; found (%) = 314.2 $(M + H)^+$. $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.78 (s, 2H), 6.33 (s, 1H), 5.82 (d, *J* = 8.0Hz, 1H), 4.36-4.27 (m, 1H), 0.83 (d, *J* = 6.6 Hz, 3H).

**Crystallography studies:** The title compound was dissolved in DCM and white transparent crystals suitable for X-ray analysis grew over a period of two week when the solution was exposed to air at room temperature. A white single crystal of title compound with dimensions of 0.15 mm × 0.05 mm × 0.04 mm was chosen for X-ray diffraction analysis performed on a BRUCKER SMART APEX-CCD diffractometer equipped with a graphite- monochromatic $MoK_\alpha$ radiation (λ = 0.71073 Å) radiation at 293(2) K. A total of 6243 reflections were collected in the range of $1.72° < \theta < 26.01°$ by using a ψ-ω scan mode with 4472 independent ones ($R_{int}$ = 0.0294), of which 3675 with $I > 2\sigma(I)$ were observed and used in the succeeding refinements. The data set was corrected by SADABS program; the structure was solved by direct methods with SHELXS-97[4] and refined by full-matrix least-squares method on $F^2$ with SHELXL-97[5]. The non-hydrogen atoms were refined anisotropically and the hydrogen atoms were added according to theoretical models. The structure was refined by full-matrix least-squares method on $F^2$ with SHELXT-97[5]. The final refinement gave R = 0.0562, wR = 0.1744 ($w = 1/[s^2(Fo^2) + (0.1124P)^2 + 0.0230P]$, where $P = (Fo^2 + 2Fc^2)/3$), S = 1.062, $(\Delta/\sigma)_{max} = 0.001$, $(\Delta\rho)_{max} = 0.332$ e/Å$^3$ and $(\Delta\rho)_{min} = -0.218$ e/Å$^3$.

## RESULTS AND DISCUSSION

**Crystal structure description:** The title compound was prepared according to **Scheme-II**. The $^1H$ NMR, LC-MS and m.p. for the product are in good agreement with the title compound. In order to confirm the configuration of the product, a single crystal of the title compound was cultured for X-ray diffraction analysis. The crystal belongs to monoclinic with space group P2(1). The molecular structure with atomic labeling scheme and perspective view of the crystal packing in a unit cell of the title compound are shown in Figs. 1 and 2, respectively. The selected bond lengths are listed in Table-1 and the bond angles in Table-2.

TABLE-1
SELECTED BOND LENGTHS (Å) FOR THE TITLE COMPOUND

| Bond | Length | Bond | Length | Bond | Length |
|---|---|---|---|---|---|
| O(1)-C(1) | 1.201(4) | O(2)-C(1) | 1.369(4) | O(2)-C(2) | 1.439(4) |
| N(1)-C(1) | 1.342(5) | N(1)-C(3) | 1.459(5) | C(2)-C(5)c | 1.494(4) |
| C(2)-C(3) | 1.530(5) | C(3)-C(4) | 1.501(6) | C(5)-C(10) | 1.383(5) |
| C(5)-C(6) | 1.386(5) | C(6)-C(7) | 1.389(5) | C(7)-C(8) | 1.369(5) |
| C(7)-C(11) | 1.480(5) | C(8)-C(9) | 1.373(6) | C(9)-C(10) | 1.380(5) |
| C(9)-C(12) | 1.497(5) | – | – | – | – |
| O(1)-C(1) | 1.201(4) | O(2)-C(1) | 1.369(4) | O(2)-C(2) | 1.439(4) |
| N(1)-C(1) | 1.342(5) | N(1)-C(3) | 1.459(5) | C(2)-C(5)c | 1.494(4) |
| C(2)-C(3) | 1.530(5) | C(3)-C(4) | 1.501(6) | C(5)-C(10) | 1.383(5) |
| C(5)-C(6) | 1.386(5) | C(6)-C(7) | 1.389(5) | C(7)-C(8) | 1.369(5) |
| C(7)-C(11) | 1.480(5) | C(8)-C(9) | 1.373(6) | C(9)-C(10) | 1.380(5) |

TABLE-2
SELECTED BOND ANGLES (°) FOR THE TITLE COMPOUND

| Angles | (°) | Angles | (°) | Angles | (°) |
|---|---|---|---|---|---|
| C(1)-O(2)-C(2) | 108.8(3) | C(1)-N(1)-C(3) | 111.3(3) | O(1)-C(1)-N(1) | 129.8(3) |
| O(1)-C(1)-O(2) | 121.4(3) | N(1)-C(2)-O(2) | 108.7(3) | O(2)-C(2)-C(5) | 110.6(3) |
| O(2)-C(2)-C(3) | 103.7(2) | C(5)-C(2)-C(3) | 116.8(3) | N(1)-C(3)-C(4) | 111.3(3) |
| N(1)-C(3)-C(2) | 98.8(3) | C(4)-C(3)-C(2) | 116.3(3) | C(10)-C(5)-C(6) | 118.7(3) |
| C(10)-C(5)-C(2) | 119.5(3) | C(6)-C(5)-C(2) | 121.8(3) | C(5)-C(6)-C(7) | 120.0(3) |
| C(8)-C(7)-C(6) | 121.1(3) | C(8)-C(7)-C(11) | 119.5(3) | C(6)-C(7)-C(11) | 119.4(3) |
| C(7)-C(8)-C(9) | 118.8(3) | C(8)-C(9)-C(10) | 121.1(3) | C(8)-C(9)-C(12) | 120.2(3) |
| C(10)-C(9)-C(12) | 118.7(4) | C(9)-C(10)-C(5) | 120.4(3) | F(3)-C(11)-F(1) | 102.6(4) |
| F(3)-C(11)-F(2) | 107.6(5) | F(1)-C(11)-F(2) | 102.6(5) | F(3)-C(11)-C(7) | 115.4(4) |
| F(1)-C(11)-C(7) | 113.7(5) | F(2)-C(11)-C(7) | 113.7(3) | F(5)-C(12)-F(4) | 104.9(5) |
| F(5)-C(12)-F(6) | 108.0(5) | F(4)-C(12)-F(6) | 104.6(5) | F(5)-C(12)-C(9) | 112.8(4) |
| F(4)-C(12)-C(9) | 112.5(5) | F(6)-C(12)-C(9) | 113.2(4) | – | – |

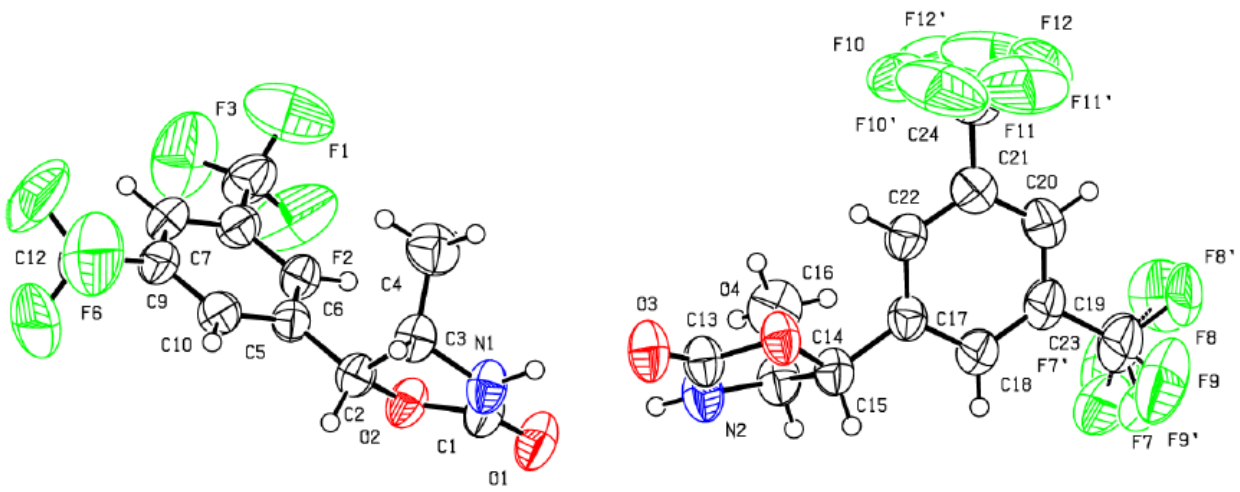



Fig. 1. Molecular structure of the title compound

The asymmetric unit of the title compound contains two molecules. In the molecular structure (Fig. 1), the five-membered ring displays a twist conformation in which atoms O1, O2, N1 and C1 lie in an approximate plane. For molecule 2, the five-membered ring also displays a twist conformation in which atoms O3, O4, N2 and C13 lie in an approximate plane. There are two chiral centers in the molecular. Such as in the molecular structure, (Fig. 1), the chirality of C2 is stationery, so the chirality of the C3 could be defined. Two molecules interact with each other by strong N-H···N and N-H···O hydrogen bonds.

## Conclusion

The compound (4S,5R)-5-[3,5-*bis* (trifluoromethyl)-phenyl]-4-methyl-1,3-oxazolidin-2-one, was synthesized and characterized by means of $^1$H NMR, LC-MS and X-ray diffraction. The crystal belongs to monoclinic with space group P2(1) and the crystal structure is stabilized by intermolecular hydrogen bonds.

## ACKNOWLEDGEMENTS

The full crystallographic information has been deposited with the Cambridge Crystallographic Data Center, CCDC No.

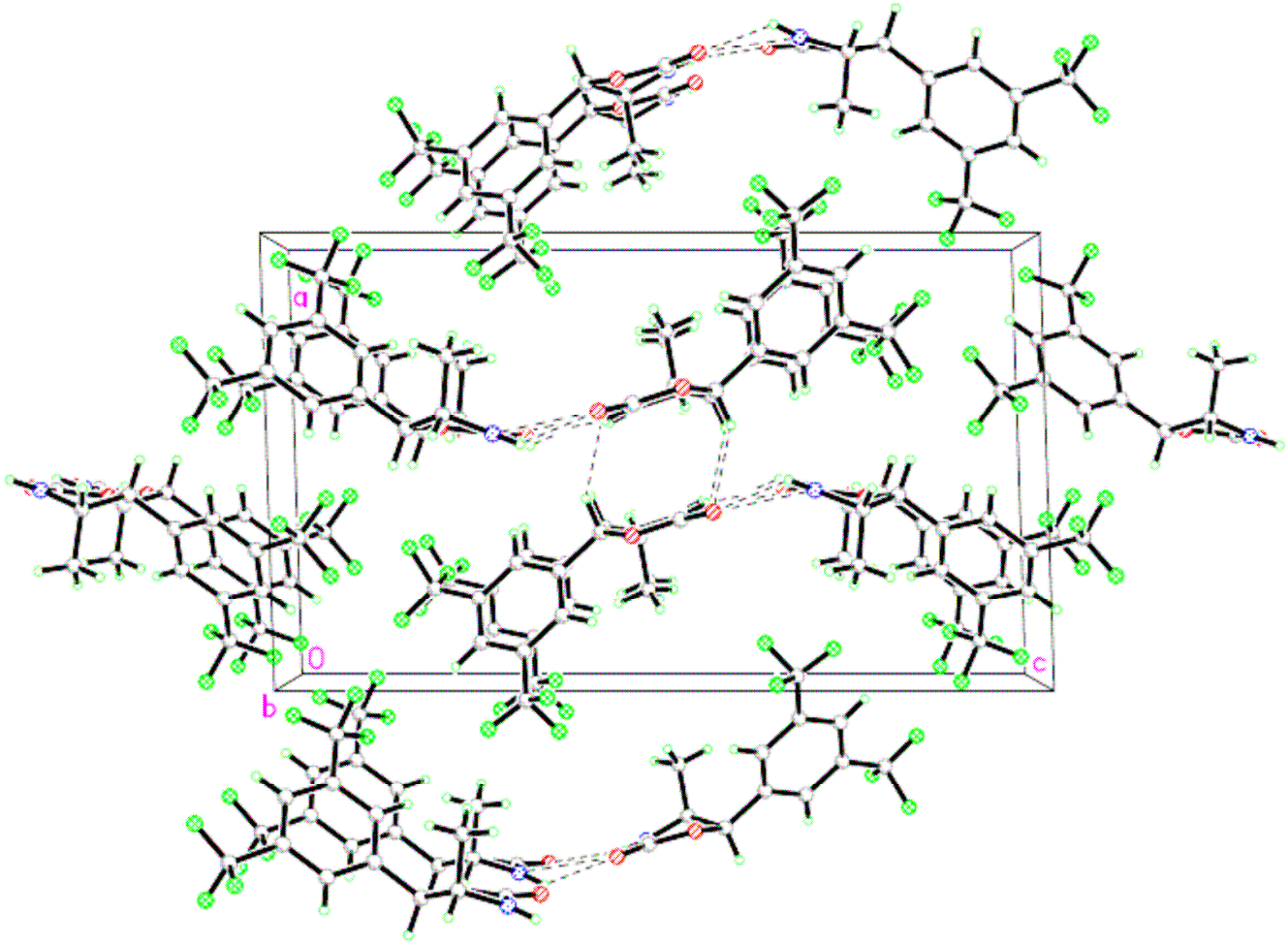



Fig. 2. Crystal packing of the title compound

913698. Copies of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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