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Synthesis and resolution of diethyl (1*S*,2*S*)-1-amino-2-vinylcyclopropane-1-phosphonate for HCV NS3 protease inhibitors

Hyung-Jung Pyun *, Kleem Chaudhary †, John R. Somoza, X. Christopher Sheng, Choung U. Kim

Gilead Sciences, 333 Lakeside Drive, Foster City, CA 94404, USA

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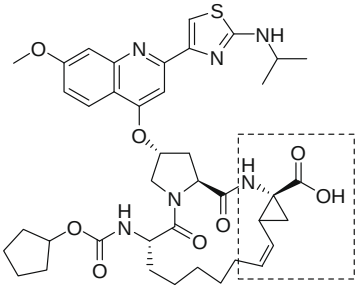
ABSTRACT

We herein describe an efficient synthesis of optically active diethyl 1-amino-2-vinylcyclopropane-1-phosphonate (analogous to 1-amino-2-vinylcyclopropane-1-carboxylate). The racemic phosphonate diethyl ester was obtained from an imine derived from aminomethylphosphonate diester and *trans*-1,4-dibromo-2-butene. Crystallizations of the dibenzoyl-L-tartaric acid salt allowed for separation of enantiomers. The enantiomerically pure material was used to synthesize an extremely potent tripeptide phosphonate inhibitor of HCV NS3 protease. X-ray crystal structure of the inhibitor bound to the HCV NS3 protease confirmed the absolute stereochemistry of the title compound.

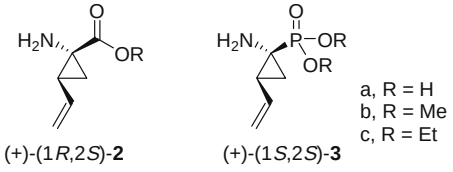
One of the approaches to discovering promising drug candidates is the use of a bio-isostere, which utilizes a new functional group to replace a pharmacophore from a known biologically active molecule, with the expectation of maintaining or improving the activity and pharmaceutical properties.[1] The phosphonic acid moiety is considered to be an isostere of the carboxylic acid, especially in α-amino acids and their derivatives. Thus, α-aminophosphonic acids and/or their derivatives have been studied extensively as inhibitors and pharmacological agents.[2]

Hepatitis C virus (HCV) infection is a serious chronic liver disease which has been known to be linked to liver cirrhosis and hepatocellular carcinoma.[3] It is estimated that over 170 million people are currently infected with HCV.[4] Current standard of therapy is based on α-interferon (Peg-Intron® and Pegasus®) in combination with ribavirin but it is only partially effective and exhibits severe side effects.[5] Recently, HCV NS3 protease has been proven to be a promising target for antiviral therapy for HCV. Since the discovery of BI-2061 (**1**)[6] several other promising drug candidates targeting this enzyme have advanced to human clinical trials.[7] Among these candidates, several are mimics of the N-terminal cleavage product and contain either (+)-(1*R*,2*S*)-1-amino-2-vinylcyclopropane-1-carboxylic acid ((+)-**2a**) moiety or the acylsulfonamide derivative.[8,9]

Based on molecular modeling studies, the phosphonic acid analog **5** was designed as a possible isostere for the carboxylic acid **4** for HCV NS3 protease inhibitors. We report herein the synthesis



1 (BI-2061)



(+)-(1*R*,2*S*)-**2** (+)-(1*S*,2*S*)-**3**

of 1-amino-2-vinylcyclopropane-1-phosphonic acid diethyl ester (**3c**) and its resolution.

Previous reports describe the synthesis of racemic carboxylate methyl ester, **2b**, by alkylation of the imine derived from glycine methyl ester.[10] Similarly, the racemic diethyl phosphonate **3c**, was prepared by the alkylation of commercially available imine **6** as shown in Scheme 1. Thus, imine **6** was treated with *trans*-1,4-dibromo-2-butene (**7**), in the presence of cesium hydroxide and phase transfer catalyst.[11] After hydrolysis of the imine **8** under acidic conditions, the racemic diethyl 1-amino-2-vinylcyclopropane-1-phosphonate, (±)-**3c**, was obtained. An impurity, which

* Corresponding author. Tel.: +1 650 522 5437; fax: +1 650 522 5169.
E-mail addresses: peter.pyun@gilead.com, peterpyun@yahoo.com (H.-J. Pyun).
† Present address: Novartis Institutes for BioMedical Research, Inc., 220 Massachusetts Avenue, Cambridge, MA 02139, USA.

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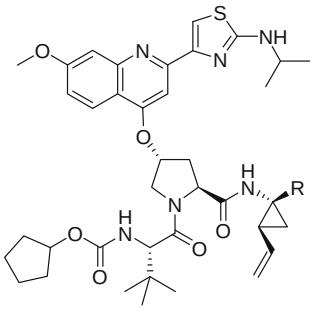
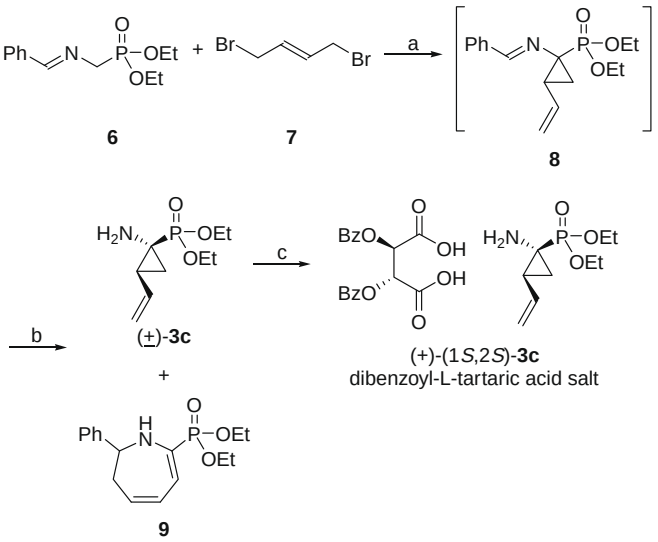


4; R = COOH
5; R = $PO(OH)_2$

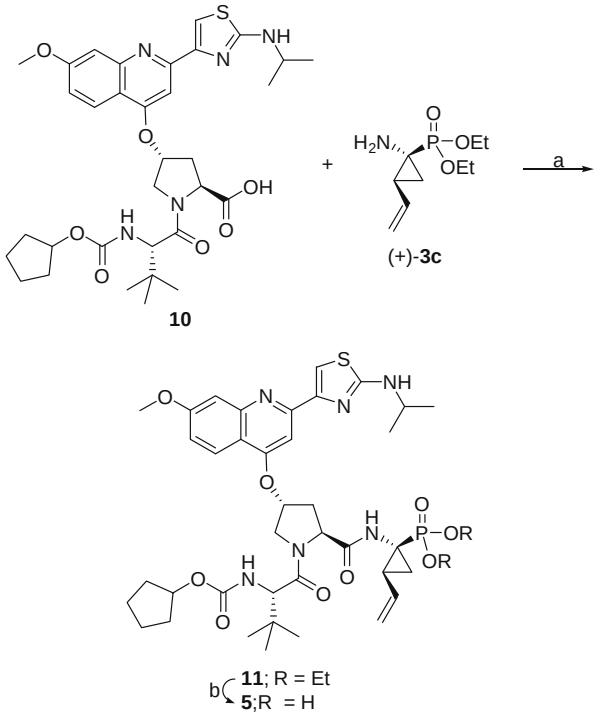
was identified as the seven-membered ring **9**, was found to have formed during the reaction. Fortunately, the impurity **9** could be easily removed by simple acid–base extractions. A subsequent filtration through silica gel provided (±)-**3c** in 27% yield. It is noteworthy that only the *Z*-diastereomer, between phosphonate and vinyl groups, was isolated in this reaction. A similar seven-membered ring impurity was also reported in the synthesis of (±)-**2b**.[10b] We speculate that this byproduct **9** is formed via an aza-Cope rearrangement of the undesired *E*-diastereomer of the imine **8**, which has the *cis*-vinyl-imine functionality on the strained cyclopropane ring.

A resolution of racemic **3c** was attempted using crystallization with optically pure acids.[12] Our optimized crystallization was achieved with dibenzoyl-L-tartaric acid in acetonitrile. After two crystallizations, (+)-(1*S*,2*S*)-**3c** could be obtained as the dibenzoyl-L-tartaric acid salt in >90% ee.[13–15]

After removing dibenzoyl-L-tartaric acid by acid–base extraction, (+)-**3c** was coupled with the dipeptide precursor **10** as shown in Scheme 2. [16] The diethyl phosphonate ester of the resulting tripeptide analog **11** was hydrolyzed using TMSI in acetonitrile to afford the desired phosphonic acid analog **5**. We were pleased to find that the phosphonic acid analog **5** was a potent HCV NS3 protease inhibitor with IC_{50} of 0.9 nM. This is three-fold more potent compared to the carboxylic acid analog **4** (IC_{50} = 3 nM).[17]



Scheme 1. Synthesis and resolution of diethyl 1-amino-2-vinylcyclopropane-1-phosphonate (**6**). Reagents and conditions: (a) CsOH hydrate, $BnNEt_3Cl$, CH_2Cl_2, rt, 24 h. (b) 1 N HCl, CH_2Cl_2, rt, 3 h. (c) 1 equiv dibenzoyl-L-tartaric acid, MeCN.



Scheme 2. Synthesis of HCV NS3-4A inhibitors **5** from (+)-**3c**. Reagents and conditions: (a) ClCOOEt, NEt_3, THF, −40 °C to rt, 1 h. (b) TMSI, CH_3CN, rt, 30 min.

The absolute stereochemistry of (+)-**3c** was clearly confirmed by X-ray crystal structure of compound **5** bound to the protease. As shown in Figure 1, the crystal structure indicates that the phosphonic acid makes extensive interactions with the oxyanion hole of HCV NS3 protease. Thus, the phosphonate was shown to interact with Ser138, Ser139, and Gly137 backbone amides as well as His57 side chain similarly to BILN 2061 as described in the published crystal structure.[8b] Furthermore, the phosphonic acid was found to make additional H-bonds with the side chains of Ser139 and Lys136 (see Fig. 1).

In summary, a procedure has been developed to synthesize the phosphonic acid analog (±)-**3c** of 1-amino-2-vinylcyclopropane-1-carboxylic acid ((±)-**2**). Resolution of the two enantiomers of **3c** was accomplished by crystallization as dibenzoyl-L-tartaric acid salt. A tripeptide phosphonic acid analog **5** was synthesized from

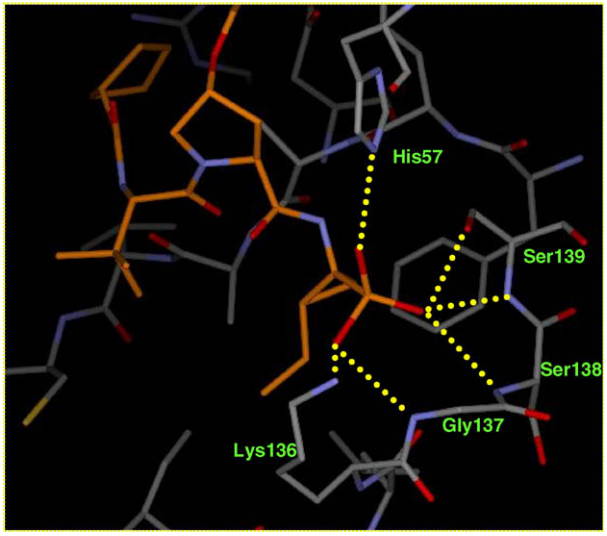


Figure 1. X-ray crystal structure of HCV NS3 protease–compound **5** complex.

(+)-**3c** and was found to be a superior inhibitor of HCV NS3 protease compared to the carboxylic acid analog **4**. Absolute stereochemistry of (+)-**3c** was further proven by X-ray crystal structure of **5** bound to HCV NS3 protease. Further studies on the inhibition of HCV NS3 protease with phosphonic acid analogs will be reported separately.[16]

Acknowledgments

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11. *Procedure for the synthesis of racemic 1-amino-2-vinyl-cyclopropane-1-phosphonic acid diethyl ester (**3c**) is as follows*: A mixture of diethyl (*N*-benzylideneaminomethyl)-phosphonate (**6**, 50 g, 196 mmol), *trans*-1,4-dibromo-2-butene (**7**, 50 g, 235 mmol), and benzyltriethylammonium chloride (4.5 g, 19.6 mmol) in dichloromethane (1.0 L) was stirred at rt with cesium hydroxide monohydrate (82 g, 490 mmol) using a mechanical stirrer for 18 h after which another portion of cesium hydroxide monohydrate (82 g, 490 mmol) was added. After stirring for 24 h more, the solids were then filtered off through Celite pad and the filtrate was allowed to stir with 1 N aq HCl (500 mL) at rt for 3 h. The resulting mixture was filtered again through Celite pad and the two phases of the filtrate were separated. The organic phase was extracted with 1 N aq HCl (250 mL × 1). The two aqueous phases were washed with dichloromethane (250 mL × 1) and were combined. The combined aq. solution was stirred with ethyl acetate (500 mL) while 84 g (1 mol) of $NaHCO_3$ was added cautiously. After the aqueous layer was saturated with NaCl, two layers were separated and the aqueous layer was extracted further with ethyl acetate (250 mL × 2). The organic phases were washed with saturated NaCl solution (250 mL × 1), combined, dried ($MgSO_4$), and concentrated to obtain 16.5–17 g of the crude amine. The crude amine was purified by column chromatography using 165–170 g of silica gel by eluting ethyl acetate (100%, ~500 mL) followed by 5% methanol in ethyl acetate (~1200 mL) to afford 11.5–12 g of (±)-**3c**.
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13. *Resolution procedure of **3c** is as follows*: To the purified (±)-**3c** (11.5–12 g) was added a solution of 18.8–19.6 g (1 mol equiv) of dibenzoyl-L-tartaric acid in 152–158 mL of acetonitrile and the resulting salt was crystallized twice at rt to obtain 11.5 g of the dibenzoyl-L-tartaric acid salt of (+)-(1*S*,2*S*)-**3c** in >90% ee. ^{1}H NMR (300 MHz, CD_3OD) δ 8.14 (br, 2H), 8.11 (d, J = 1.2 Hz, 2H), 7.64 (tt, J = 7.5 and 1.2 Hz, 2H), 7.51 (br t, J = 7.5 Hz, 4H), 5.94 (s, 2H), 5.82 (dt, J = 17.1 and 9.9 Hz, 1H), 5.32 (dd, J = 17.1 and 1.2 Hz, 1H), 5.13 (dd, J = 10.5 and 1.2 Hz, 1H), 4.11–4.26 (m, 4H), 2.11 (m, 1H), 1.33–1.47 (m, 2H), 1.37 (dt, J = 10.2 and 7.2 Hz, 6H); ^{31}P NMR (75 MHz, CD_3OD) δ 22.55.
14. Analytical sample of (+)-**3c** was obtained by basic extraction of the salt. The dibenzoyl-L-tartaric acid salt of (+)-(1*S*,2*S*)-**3c** (10 g) was dissolved in a mixture of saturated aq. $NaHCO_3$ (200 mL) and saturated aq. NaCl (200 mL), and the free amine was extracted by dichloromethane (100 mL × 2). The extracts were washed once with a mixture of saturated aq $NaHCO_3$ (200 mL) and saturated aq NaCl (200 mL), dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography by eluting ethyl acetate to obtain 3.36 g of pure (+)-**3c** as an oil. $[\alpha]_D$ = +26.6 (c 1, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (dt, J = 16.8 and 10.0 Hz, 1H), 5.24 (dd, J = 16.8 and 1.6 Hz, 1H), 5.04 (dd, J = 10.0 and 1.6 Hz, 1H), 4.05–4.19 (m, 4H), 1.82–1.92 (m, 1H), 1.81 (br, 2H), 1.33 (dt, J = 14.0 and 6.8 Hz, 6H); 1.26–1.36 (m, 2H), 1.17 (ddd, J = 9.2, 6.0, and 5.2 Hz, 6H); ^{31}P NMR (100 MHz, $CDCl_3$) δ 27.15.
15. Enantiomeric purity of (+)-**3c** was determined by NMR analysis of the Mosher amide.[18] Among the various deuterated solvents investigated, DMSO-d_6 exhibited the best separation of the ^{31}P signals of the two diastereomers.
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