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A Highly Convergent and Efficient Synthesis of a Macrocyclic Hepatitis C Virus Protease Inhibitor BI 201302

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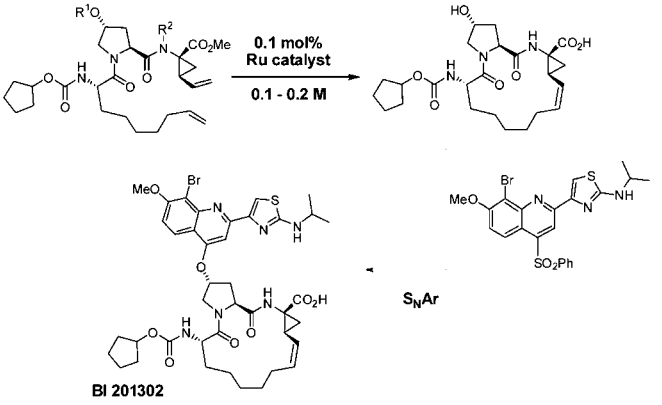
ABSTRACT



A highly convergent large scale synthesis of a 15-membered macrocyclic hepatitis C virus (HCV) protease inhibitor BI 201302 was achieved, in which the key features are the practical macrocyclization by Ru-catalyzed ring-closing metathesis (0.1 mol % Grela catalyst, 0.1−0.2 M concentration) and the efficient sulfone-mediated S_NAr reaction.

Over the past two decades substantial development has been made in novel chemotherapies for chronic type C hepatitis, which aimed to change the dire prognosis of infected patients.[1] In 2002, the first human proof-of-concept for a direct acting antihepatitis C virus (HCV) drug was achieved with the Boehringer-Ingelheim NS3 protease inhibitor Ciluprevir (BILN2061, **1**, Figue 1).[2] Recently, two anti-HCV drugs were approved by the FDA to treat HCV infected patients.[3,4]

The emerging HCV protease inhibitors not only exemplified the power of modern synthetic methods in drug discovery but also posed unique challenges for the development of practical and economical large scale syntheses to support clinical trials and potential market demands. As our continued effort in this area,[5] herein we report a highly convergent and efficient synthesis of the macrocyclic HCV protease inhibitor BI 201302 (**2**).

Our new synthetic strategy (Scheme 1) focuses on tackling several unmet but critical challenges encountered in our initial scale-up work of BILN 2061.[5] At first, the required high dilution (0.01 M) of the ring-closing

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(2) Lamarre, D.; Anderson, P. C.; Bailey, M.; Beaulieu, P.; Bolger, G.; Bonneau, P.; Boes, M.; Cameron, D. R.; Cartier, M.; Cordingley, M. G.; Faucher, A.-M.; Goudreau, N.; Kawai, S. H.; Kukolj, G.; Lagacé, L.; LaPlante, S. R.; Narjes, H.; Poupart, M.-A.; Rancourt, J.; Sentjens, R. E.; St. George, R.; Simoneau, B.; Steinmann, G.; Thibeault, D.; Tsantrizos, Y. S.; Weldon, S. M.; Yong, C.-L.; Llinàs-Brunet, M. *Nature* **2003**, *426*, 314.

(3) Boceprevir/Victrelis was approved by US FDA on May 13th 2011.

(4) Telaprevir/Incivek was approved by US FDA on May 23rd 2011.

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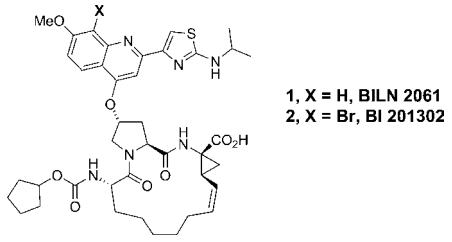


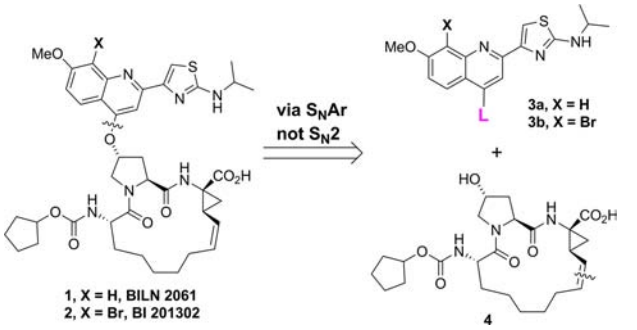
Figure 1. Macrocyclic HCV inhibitors.

metathesis (RCM) reaction must be overcome, which is a typical problem for macrocyclization. The high ruthenium (Ru) catalyst loading (3−5 mol %) for RCM reaction was impractical due to not only its high cost but also the extreme difficulty of removing high levels of residual Ru metal from the Active Pharmaceutical Ingredient (API). Its long reaction time (~24 h) and risk for epimerization[6] were also troublesome for production. Second, the assembly sequence via double S_N2 reactions was lengthy and costly, and a higher level of the assembly convergency called for a direct installation of the quinoline heterocycle to the macrocycle through an S_NAr reaction to avoid the double inversions of the stereocenter at the C-4 position of the hydroxyproline moiety (**4**).

The development of a more efficient RCM started from various initial observations on our early RCM process. It was noticed that the remote substituent at the C-4 position of the hydroxyproline moiety in **4** had a small but detectable effect[5] on the RCM rate and therefore on the Effective Molarity[7] (EM = k_{intra}/k_{inter}). This small effect was tentatively ascribed to subtle conformational factors. Also, when the initiation of the reaction was monitored using a substoichiometric amount of Grubbs' catalyst (**7**, Scheme 2), carbene transfer occurred to a large extent (96%) at the vinylcyclopropane moiety **8**, where the Ru may be stabilized by chelation to the carbonyl group. Such stabilization, in turn, may reduce the concentration of the active Ru catalyst in the reaction and negatively affect the rate of the RCM reaction.[6] Guided by these observations, we postulated that substitution on the NH of the P1 amide (vinylcyclopropane amimo acid unit) would change such coordinative stabilization and its conformation in which the Ru-insertion pathway would be altered. A number of derivatives were subsequently prepared, in which the amide bond was protected with various removable groups.[8,9]

As reported in our preliminary studies, the modifications of the RCM substrates **6**, through introducing a substituent on the NH of the P1 amide, led to the

Scheme 1. Retrosynthetic Strategy for BI 201302



profound effects on the efficiency of the RCM reaction. As shown in Scheme 2, the simple N-Boc substrate **6** not only switches the initiation site of the RCM reaction through interrupting the coordinative stabilization by the ester group but also dramatically increase its effective molarity which enables the RCM reaction to be performed at much higher concentrations. As a result, in comparison with the corresponding N−H substrate **5** the desired RCM reaction proceeded 3−4 times faster, and more importantly it could be carried out at a 10−20-fold greater concentration (0.1−0.2 M) which was unprecedented for this type of macrocyclization. In consideration of the reversible nature of the metathesis reaction, the origins of this "N-Boc effect" seem to be grounded in favorable kinetic and thermodynamic effects. The strategic induction of an electron-withdrawing group on the RCM linker can direct the initiation site and have a remarkable effect on the RCM, hence complementing the known relay strategy;[10,11] also it increases the thermodynamic EM, presumably by reducing the ring strain of the macrocyclic product because of its favored conformational characteristics. This hypothesis is supported by theoretical analysis[9,12] through the calculation of the conformational energy change of the macrocycle between the open chain molecules with and without Boc substitution.

With the critical RCM obstacle resolved, the synthesis of BI 201302 used similar building blocks developed for BILN 2061.[5a,13] For preparation of the RCM precursor, (*S*)-2-(*tert*-butyloxycarbonyl)-amino-8-nonenoic acid (**12**) was first coupled with *trans*-hydroxyl-proline ester (**13**)

(6) Zeng, X.; Wei, X.; Farina, V.; Napolitano, E.; Xu, Y.; Zhang, L.; Haddad, N.; Yee, N. K.; Grinberg, N.; Shen, S.; Senanayake, C. H. *J. Org. Chem.* **2006**, *71*, 8864.

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(8) Shu, C. (2007). PCT Int. Appl. WO 2007030656.

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(10) Change of initiation site is known to affect RCM. See: Wallace, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 1912–1915.

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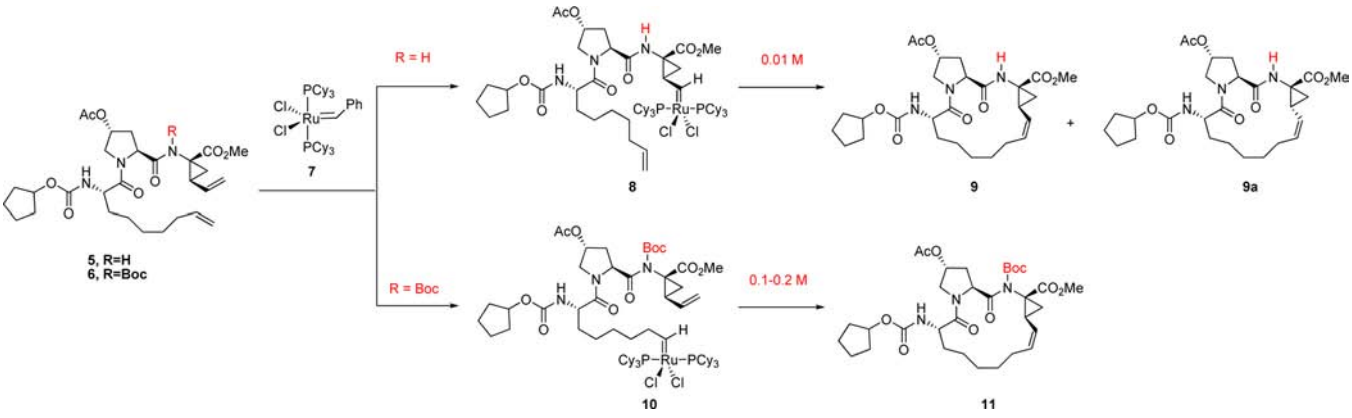
Scheme 2. Ring-Closing Metathesis of **5**/**6**



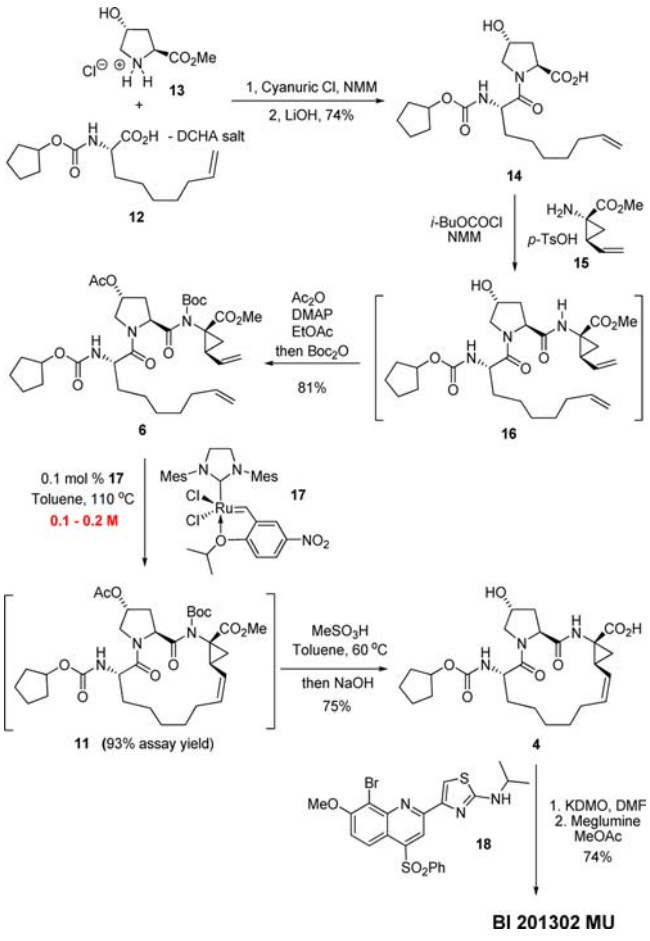
directly using cyanuric chloride as a reagent (Scheme 3). After hydrolysis, the crystalline dipeptide **14** was activated as the mixed anhydride and reacted with the vinylcyclopropane amino acid unit **15** to furnish an unprotected hydroxy tripeptide diene **16**.

A streamlined one-pot preparation of RCM precursor **6** from **16** was then developed, the hydroxyl group of crude intermediate **16** was acetylated with acetic anhydride, and the amide-NH was protected with Boc_2O using DMAP as the catalyst. The tripeptide diene **6** was obtained as a highly crystalline white solid (>99% purity) in 81% overall yield from intermediate **16**, in which the high purity of this diene precursor **6** undoubtedly enabled a very robust RCM process. When a solution of **6** (0.1 M in toluene) was heated to reflux and a solution of Grela catalyst[14] (**17**) (0.1 mol %) was added in portions, the RCM reaction was instantaneously initiated with the immediate release of ethylene gas and completed once all of the catalyst was added to furnish the desired RCM product **11** in excellent 93% assay yield. Again, in the same pot, the crude RCM product **11** was treated with methanesulfonic acid followed by NaOH to sequentially deprotect the Boc group, acetyl group, and ester; the desired hydroxyl acid intermediate **4** was obtained as a highly crystalline solid (75% yield in two steps) in >99% purity.

When **4** was subjected to various S_NAr reaction conditions with the bromochloroquinoline **19**[15] (Scheme 4), a sluggish reaction (<40% assay yield) was typically obtained regardless of the bases used (*t*-BuOK, KHMDS, or NaH). Such a low yield was obviously unacceptable for the final synthetic step of the targeted molecule. Similar observations were also reported by others in literature.[16]

In order to improve this S_NAr reaction, we investigated the reactivity of the quinoline electrophile by evaluating its leaving group effect. It appeared to us that sulfonyl substituted pyridines and quinolines are known substrates for S_NAr reactions,[17] although synthetic applications[18] were quite limited possibly due to the lack of an easy access

Scheme 3. Synthesis of **BI 201302**



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(15) The bromochloroquinoline fragment **19** was synthesized by a similar approach used for BILN2061.[15d]

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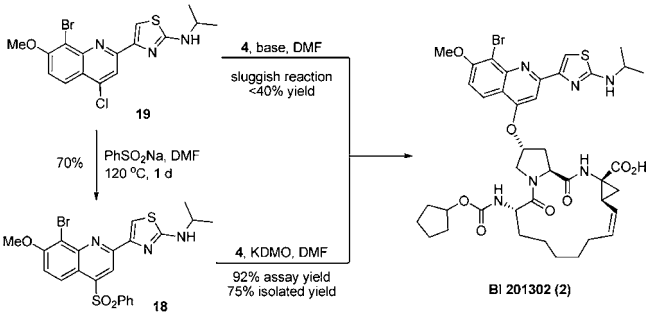
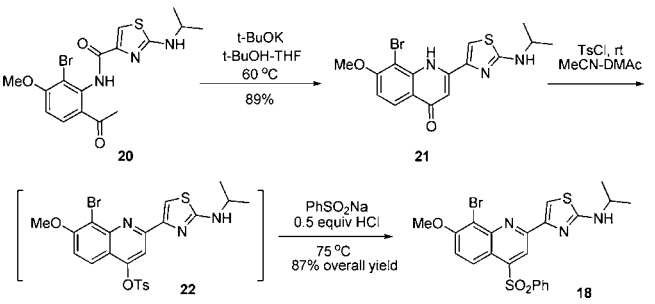
Scheme 4. S_NAr Reactions



to sulfonyl substituted heterocycles.[19] Nevertheless, we converted chloroquinoline **19** to the corresponding sulfone **18** by heating with $PhSO_2Na$ in DMF and then tested **18** for the desired S_NAr reaction (Scheme 3). Gratifyingly, it was found that the reaction of **18** and **4** prompted by *t*-BuOK went to completion in less than 5 h with excellent yield (91−93% by assay). We found the only significant impurity (1−2%) was the *tert*-butyl carbamate analogue of BI201302, which was obviously generated from the trans-carbamoylation to replace the cyclopentyloxy group by *tert*-butoxide. This impurity was difficult to remove from the final API because it had very similar physicochemical properties. In this regard, potassium 3,7-dimethyl-3-octylate (KDMO) was found to be a superior reagent, because the corresponding DMO-carbamate was much more soluble in the solvent and could be removed easily by crystallization. Thus this final step proceeded smoothly to produce BI201302 as a meglumine (MU) salt in 74% isolated yield with >99% purity (single individual impurity <0.3%).

The above-mentioned highly efficient S_NAr reaction called for a more practical and environmentally benign synthesis of the key intermediate **18**. In literature sulfonylquinolines are normally prepared by the reaction of chloroquinoline with $PhSO_2Na$ at high temperature or of chloroquinoline with a thiol to obtain the thio-ether followed by oxidation to the sulfone.[19] We envisioned that a readily accessible tosylate **22** (Scheme 5) would react with $PhSO_2Na$ similarly which would avoid the use of an excess amount of corrosive reagent $POCl_3$. However, initial experiments failed until a critical observation was made in which a small amount of protic acid could greatly accelerate the reaction rate possibly via a more reactive pyridinium species. Thus, a facile alternative synthesis of **18** via a tosylate intermediate was developed as shown in Scheme 5. At first *t*-BuOK promoted cyclization of **20** afforded the quinolone **21** in 89% yield, which was then tosylated at room temperature and then treated with $PhSO_2Na$ and 1.0 equiv of benzenesulfonic acid to convert the tosylate **22** to sulfone **18** smoothly at 75 °C in 8 h. After a simple workup, the desired sulfone **18** was isolated as a solid in an excellent overall yield.

Scheme 5. Alternative Synthesis of **18**



In summary, the development of an efficient and scalable chemical process for a macrocyclic HCV protease inhibitor such as BI 201302 presented unique synthetic challenges for process chemists, particularly for the scale-up of the RCM reaction for macrocycle formation. During the course of these studies, a number of critical parameters for the RCM reaction, such as the initiation site, conformations of substrate/products, and substrate quality, were studied which led to the successful development of a practical process for scaling up (0.1 mol % Ru catalyst, 0.1−0.2 M concentration). Also, the synthesis herein described represents the optimal convergent strategy for the assembly of macrocyclic BI 201302 amenable for its potential commercialization.

Supporting Information Available. Experimental procedures, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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