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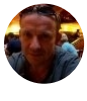

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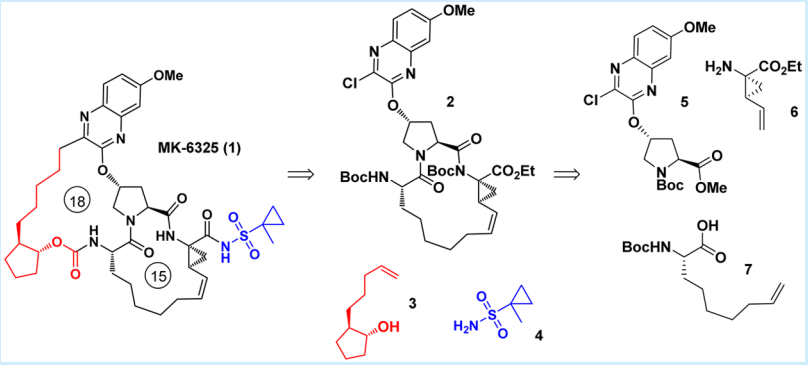
Synthesis of Bis-Macrocyclic HCV Protease Inhibitor MK-6325 via Intramolecular sp^2–sp^3 Suzuki–Miyaura Coupling and Ring Closing Metathesis

Hongmei Li,*[,†] Jeremy P. Scott,*[,‡] Cheng-yi Chen,[†] Michel Journet,[†] Kevin Belyk,[†] Jaume Balsells,[†] Birgit Kosjek,[†] Carl A. Baxter,[‡] Gavin W. Stewart,[‡] Christopher Wise,[‡] Mahbub Alam,[‡] Zhiguo Jake Song,[†] and Lushi Tan[†]

[†]Department of Process Chemistry, Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065, United States

[‡]Department of Process Chemistry, Merck Sharp & Dohme Research Laboratories, Hertford Road, Hoddesdon, Hertfordshire, EN11 9BU, U.K.

Supporting Information

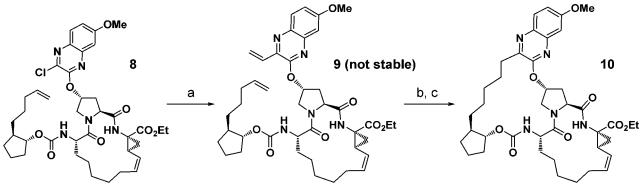


ABSTRACT: A practical asymmetric synthesis of the complex fused bis-macrocyclic HCV protease inhibitor MK-6325 (**1**) is described. Through the combination of a high yielding and low catalyst loading ring-closing metathesis (RCM) to forge the 15-membered macrocycle with an intramolecular sp^2–sp^3 Suzuki–Miyaura cross-coupling to append the 18-membered macrocycle, multikilogram access to the unique and challenging architecture of MK-6325 (**1**) has been achieved.

Infection with the Hepatitis C virus (HCV) is a worldwide epidemic, affecting approximately 170 million individuals.[1,2] The chymotrypsin-like NS3/4A serine protease plays an essential role in the HCV viral replication process and has proven a viable target for intervention. In 2011, the first-generation direct acting NS3/4A antivirals boceprevir[3] and telaprevir[4] were approved by the FDA. Vaniprevir (MK-7009)[5] has subsequently been approved in Japan, and grazoprevir (MK-5172)[6] is currently in phase III clinical trials. As part of efforts to discover an enhanced therapeutic profile, MK-6325 (**1**) was recently identified as a potent HCV NS3/4A protease inhibitor with improved genotype and mutant coverage.[7] To support clinical evaluation, a practical and efficient synthesis of this unique bis-macrocyclic compound was needed. The synthesis of MK-6325 (**1**) represents a substantial development challenge due to the high complexity of the molecule which contains not one but two fused macrocyclic rings. In this letter, we describe the development of a practical asymmetric synthesis of MK-6325 (**1**).

Our efforts began by evaluating the approach used to discover MK-6325 (**1**) which employed a ring-closing metathesis (RCM) strategy to construct the 18-membered ring (Scheme 1).[7,8] We quickly recognized that the vinylation, RCM, and reduction sequence to the key intermediate **10** had a number of liabilities for large-scale production. Specifically, (1) vinylation via Stille coupling was undesirable due to the generation of toxic Sn residues whereas the alternative vinylation via Suzuki–Miyaura coupling with vinyl boronic acid gave very low yields; (2) the

Scheme 1. Discovery Chemistry Approach to Key Bis(Macrocyclic) Intermediate 10[a]



[a]Conditions: (a) $VinylSnBu_3$, $(tBu_3P)_2Pd$, BHT, CsF, dioxane, 90% yield. (b) RCM, 6 mol % Zhan-1B (see Scheme 3 for structure), 180 mL/g CH_2Cl_2, 40 °C, 67% yield. (c) $BiCl_3$, KBH_4, 68% yield.

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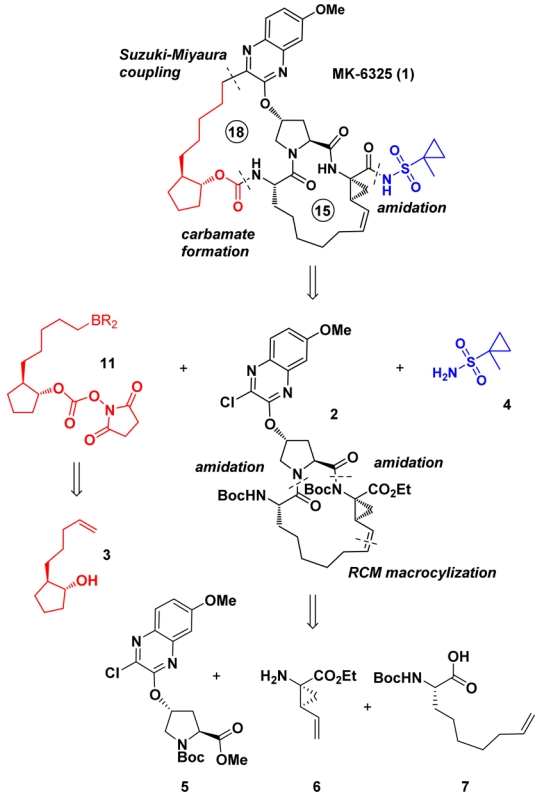
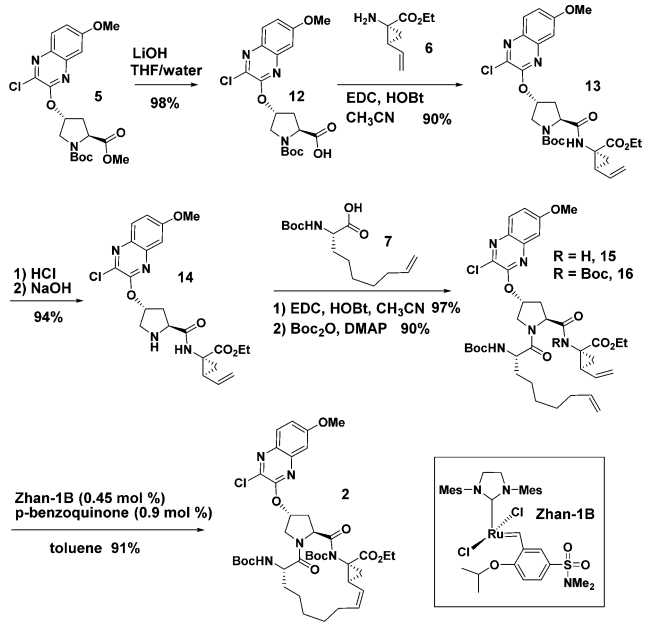
vinyl quinoxaline RCM precursor **9** is unstable; (3) the RCM reaction required a high catalyst loading and high dilution conditions and only proceeded in moderate yields; and (4) selective reduction of the alkene isomers with $BiCl_3/KBH_4$ was unscalable with lower yields of the desired product **10** at increasing scale. Macrocyclization through intramolecular Heck coupling of an analogue of **8** to form the 18-membered ring was also investigated;[5b,9] however, extensive screening of a variety of Pd sources and phosphine ligands only provided <20% conversion to a mixture of 18- and 17-membered macrocycles.

We envisaged an alternative approach to construct the 18-membered ring macrocyclization of **1** through Pd-catalyzed intramolecular sp^2–sp^3 Suzuki–Miyaura coupling.[10] The use of such an sp^2–sp^3 coupling would directly set the required oxidation state without need for a subsequent selective alkene reduction step. Retrosynthetically, MK-6325 (**1**) could be assembled from cyclopropane sulfonamide side chain **4**, 15-membered macrocycle **2**, and the cyclopentyl building block **11** (Scheme 2). The 15-membered macrocycle **2** could in turn be constructed from commercially available amino ester **6**, amino acid **7**, and quinoxaline derivative **5** via an RCM approach.

Scheme 2. Retrosynthesis Analysis of MK-6325 (1)



Scheme 3. Preparation of 15-Membered Macrocycle 2

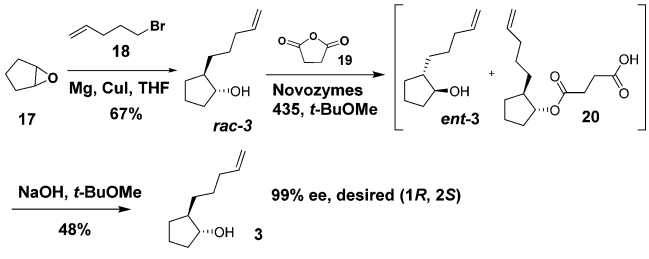


heptane to afford RCM precursor **16** in 87% isolated yield over the two steps.

The RCM of **16** to form 15-membered macrocycle **2** proved robust and scalable and could be performed at low catalyst loadings. For example, metathesis of diene **16** proceeded efficiently with 0.75 mol % Zhan-1B catalyst[11] and 1.5 mol % *p*-benzoquinone in $ClCH_2CH_2Cl$ (50 mL/g) at 60 °C. When toluene was used as solvent, the RCM reaction could be carried out with as low as just 0.45 mol % of Zhan-1B catalyst at a concentration of 20 mL/g with full conversion within 1 h at 80 °C. The macrocycle **2** was isolated in 91% yield as a crystalline solid.

For the preparation of the cyclopentanol **3** we envisioned an enzymatic resolution of the corresponding racemic alcohol (Scheme 4).[12] Racemic cyclopentanol **3** was prepared in 67%

Scheme 4. Preparation of (1*R*,2*S*)-Cyclopentanol 3 *via* Enzymatic Resolution



Our synthesis of the 15-membered macrocycle **2** started with quinoxaline derivative **5** (Scheme 3), a known intermediate in the synthesis of grazoprevir (MK-5172).[6b] Treatment of **5** with lithium hydroxide in THF and water afforded acid **12** in 98% yield. Acid **12** and amino ester **6** were then coupled using 1.25 equiv of EDC in the presence of 0.1 equiv of HOBt, and the product **13** was isolated in 90% yield after crystallization. Deprotection of **13** with HCl followed by neutralization with a base afforded crude **14**, which was subsequently coupled with amino acid **7** followed by Boc protection and crystallization in yield through copper-catalyzed epoxide opening of 1,2-epoxycyclopentane **17** with a Grignard reagent freshly prepared from magnesium turnings and 5-bromopent-1-ene **18**. The crude racemic cyclopentanol was then enzymatically resolved using Novozymes 435 and succinic anhydride in *t*-BuOMe to give the undesired *ent*-**3** and succinic acid derivative **20**, both with >98% ee. Upon basification with aqueous Na_2CO_3, the undesired alcohol *ent*-**3** and other neutral organic impurities were readily removed with a *t*BuOMe wash. The aqueous layer containing **20** was then hydrolyzed with NaOH, and the product was extracted

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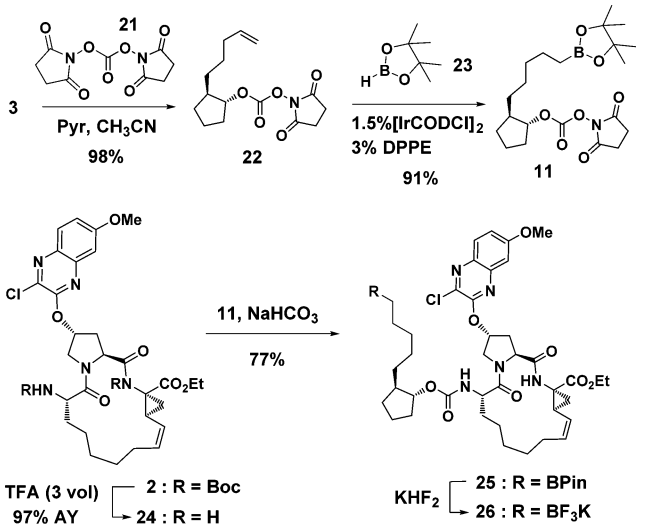
with *t*BuOMe to afford the desired chiral alcohol **3** in 48% yield and 99% ee.

Activation of cyclopentanol **3** with *N,N*-disuccinimidyl carbonate and pyridine as a base at 40 °C afforded intermediate **22** in 98% yield (Scheme 5).[13] Intermediate **22** is stable in weakly

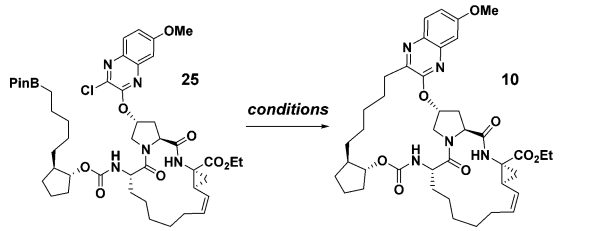
Scheme 5. Preparation of Suzuki–Miyaura Substrate 25



acidic and neutral conditions, and the succinimidyl group in **22** functioned as both an activating and protecting group for the subsequent two transformations. Hydroboration of crude intermediate **22** with 1.5 mol % $[Ir(COD)Cl]_2$ and 3 mol % 1,1-bis(diphenylphosphino)methane (DPPM) in a mixture of CPME and CH_2Cl_2 at 40 °C gave a 91% yield of desired product **11**.[14] The reaction was quenched with water, and the crude product solution was used directly in the formation of carbamate **25**. Deprotection of macrocycle **2** in neat TFA afforded amine **24** in 97% yield which was then combined with **11** in a basic biphasic system to afford BPin Suzuki–Miyaura substrate **25** in 77% yield.

With the BPin compound **25** in hand, we next evaluated the 18-membered macrocyclization through Pd catalyzed intramolecular sp^2–sp^3 Suzuki–Miyaura coupling. Extensive phosphine ligand screening clearly showed that cataCXium A (Ad_2PBu)[15] was superior to all other ligands evaluated (Table 1). After careful evaluation of the reaction parameters including Pd salt, inorganic bases, solvents, temperature, and concentration, the optimized cyclization conditions for **25** were identified as 4 mol % Pd_2dba_3, 16 mol % cataCXium A, and 2.5 equiv of Na_2CO_3 in 30 vol of a 5:1 ratio of CPME/water (0.04 M) at 110 °C. Temperature was found to be crucial to the success of this cyclization, as at a lower temperature of 85–90 °C the reaction produced a large amount of proto-deborylated side product (~50% A%). Practically, the Suzuki–Miyaura coupling was carried out under pressure to enable a reaction temperature of 110 °C to be achieved. Under these conditions, the coupling reaction gave >98% conversion with only 5% proto-deborylation. The macrocyclized product **10** was crystallized and isolated as the *p*-TSA salt from CPME in 70% yield. The use of the potassium trifluoroborate salt **26** for this Suzuki–Miyaura macrocyclization was also investigated.[16] The BF_3K salt **26** was formed when BPin-compound **25** was washed with aqueous KHF_2. While the ligands S-Phos, X-Phos, and RuPhos only produced ~20% of the desired product **10**, cataCXium A with $Pd(OAc)_2$ could efficiently promote the RBF_3K intramolecular

Table 1. Optimization of sp^2–sp^3 Intramolecular Suzuki–Miyaura Coupling of BPin Substrate 25



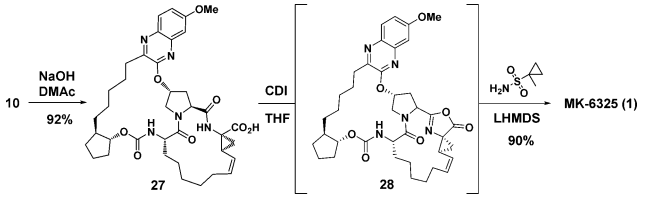
entry	ligand	solvent	efficiency[a]
1	X-Phos	toluene	0
2	JohnPhos	toluene	0
3	RuPhos	toluene	0
4	BrettPhos	toluene	0
5	dtbpf	toluene	0
6	Q-Phos	toluene	0.08
7	S-Phos	toluene	0.13
8	DavePhos	toluene	0.15
9	$(tBu)_3P{\cdot}HBF_4$	toluene	0.19
10	AmPhos	toluene	1.37
11	cataCXium A	toluene	3.18
12	cataCXium A	DMAc	0.73
13	cataCXium A	CPME	3.47

[a]Conditions: **25**, 8 mol % $Pd(OAc)_2$, 16 mol % ligand, 2.0 equiv of aq K_3PO_4, 100 °C. Ligand to Pd = 2:1. Efficiency reflects the A% ratio by HPLC at 254 nm of the product **10** vs biphenyl internal standard. dtbpf = 1,1′-Bis(di-*tert*-butylphosphino)ferrocene.

Suzuki–Miyaura coupling with high conversion at 90 °C, obviating the need to operate under pressure. Optimization led to the use of 4 mol % $Pd(OAc)_2$ and 8 mol % cataCXium A with 3 equiv of K_2CO_3 in a 30 vol solvent mix containing a toluene/DMAc/water ratio of 20:7:3 (0.04 M). Interesting, the presence of DMAc was observed to suppress dimer formation and the desired product **10** could be obtained in 77% yield. The intramolecular sp^2–sp^3 Suzuki–Miyaura 18-membered macrocyclizations of RBPin **25** and RBF_3K **26** have both been successfully demonstrated on multikilogram scale and, to the best of our knowledge, represent the largest ring size to date forged in this way.

Completion of the synthesis of MK-6325 (**1**) required the installation of the cyclopropylsulfonamide side chain (Scheme 6). Saponification of the *p*-TSA salt of **10** with NaOH in DMAc

Scheme 6. Final Amidation To Form MK-6325 (1)



at 50 °C for 2 h produced acid **27** quantitatively, which was isolated in 92% yield through direct crystallization from the reaction mixture by addition of aqueous HCl. Activation of acid **27** with EDC or PivCl gave exclusively intermediate **28**, whereas activation with CDI gave a mixture of the CDI adduct and intermediate **28**. The subsequent ring opening of azlactone **28** with sulfonamide **4** proved to be challenging, as the reaction was plagued by the formation of acid **27** as well as the desired product

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1. We speculated that the lactone ring opening could be facilitated by identification of a suitable base to deprotonate **4**. After screening, we were delighted to find that LHMDS proved to be optimal and afforded >98% of desired **1** with <1% of acid **27**. Compound **1** was then crystallized from *i*PrOH/water as a white solid in 90% yield and >99% purity.

In summary, we have developed a practical asymmetric synthesis of the bis-macrocyclic HCV protease inhibitor candidate MK-6325 (**1**) which has been used to produce multikilogram quantities. A high yielding 15-membered RCM macrocyclization of **16** together with an intramolecular sp^2–sp^3 Suzuki–Miyaura cross-coupling of **25** or **26** to form the 18-membered macrocycle are the key carbon–carbon bond-forming steps. The latter transformation showcases the power of this bond formation for large ring formation in the context of complex molecule total synthesis and represents the largest sp^2–sp^3 Suzuki–Miyaura macrocyclization disclosed to date.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compound characterization, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: hongmei06@gmail.com.
*E-mail: jeremy_scott@merck.com.

Notes

The authors declare no competing financial interest.

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