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Development of a Practical, Asymmetric Synthesis of the Hepatitis C Virus Protease Inhibitor MK-5172

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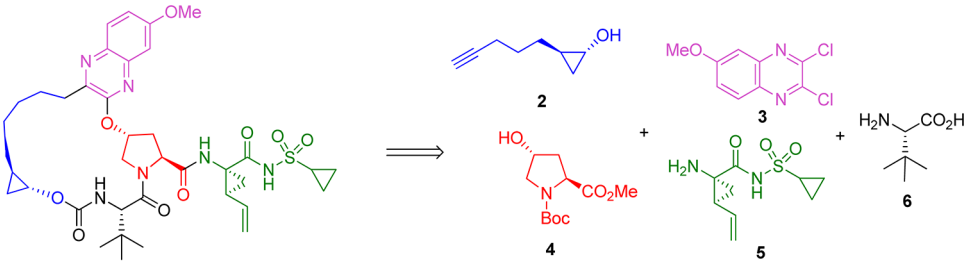
ABSTRACT



The development of a practical, asymmetric synthesis of the hepatitis C virus (HCV) protease inhibitor MK-5172 (1), an 18-membered macrocycle, is described.

Affecting an estimated 130−170 million people worldwide, the hepatitis C virus (HCV) is the leading cause of chronic liver infection and transplants.[1] Therapy for chronic HCV infection consists of a regimen of pegylated interferon-α and ribavirin (P/R).[2] These agents provide nonspecific immunostimulatory and antiviral effects. A virologic cure is achieved in only 40 to 75% of patients, depending on the virus genotype, patient characteristics, and the severity of liver damage at the time of treatment. Therapy may be accompanied by significant side effects.

Recently, compounds that directly target key HCV proteins such as HCV NS3/4A protease have been discovered. The first generation of such agents, including Merck's boceprevir,[3,4] have substantially improved the probability of a cure among patients with HCV G1 infection when added to P/R. Despite this advance, patients continue to experience treatment related failure, often due to emergence of a resistant virus. Efficacy in genotypes other than G1 has not been defined. Therapy requires three-time daily administration, with food, and the total duration of therapy typically ranges from 24 to 48 weeks.

Seeking to further optimize the pharmacokinetic profile and offer broader activity across genotypes and resistant HCV variants, medicinal chemists at Merck have discovered MK-5172 (**1**) which has the potential to be the cornerstone of an all-oral treatment for HCV (Figure 1).[5] In this Letter we describe the development of a practical and highly efficient asymmetric synthesis of MK-5172 (**1**).

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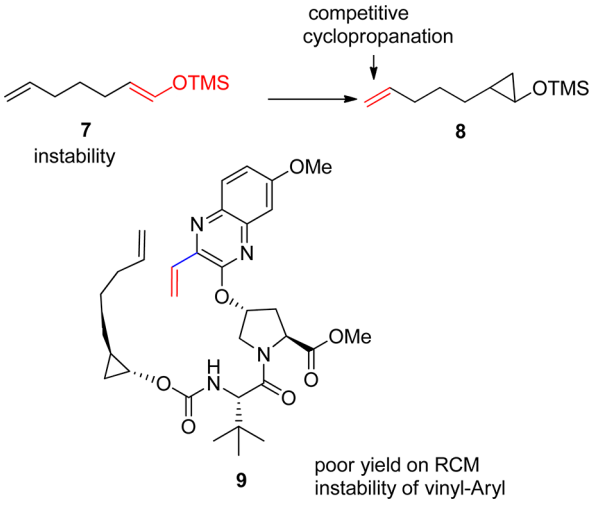
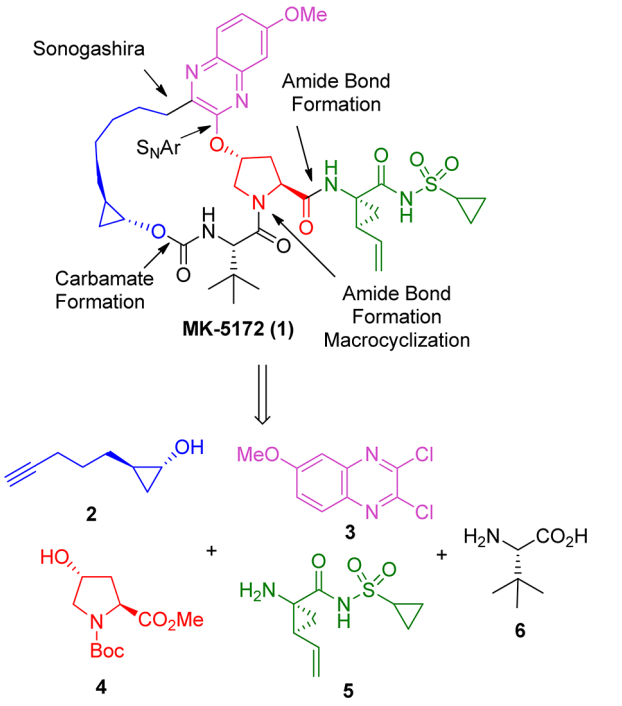


Figure 1. Major liabilities on the Med Chem Route.[5]

Our initial efforts began by examining the medicinal chemistry approach which utilized an ring-closing metathesis (RCM) strategy to construct the challenging 18-membered ring of **1**.[5] It was recognized that this approach had a number of liabilities. Major liabilities included instability of TMS enol ether **7**, poor regioselectivity during the cyclopropanation of **7** (separation of double cyclopropanated byproducts from the desired intermediate **8** was only accomplished after the RCM step), and the instability of vinyl quinoxaline **9** that resulted in poor yields for the RCM reaction. Therefore, we proposed an alternative approach centered on construction of the macrocycle via macrolactamization (Scheme 1). Retrosynthetically, we envisioned appending the western cyclopropyl side chain through a Sonogashira coupling. Deconstruction of the rest of the molecule leads to a regioselective S_NAr reaction to install the hydroxyproline moiety and two amide bond-forming reactions. The requisite building blocks would include cyclopropanol **2**,[6] dichloroquinoxaline **3**,[7] commercially available hydroxyproline **4**, and amine **5**.[8]

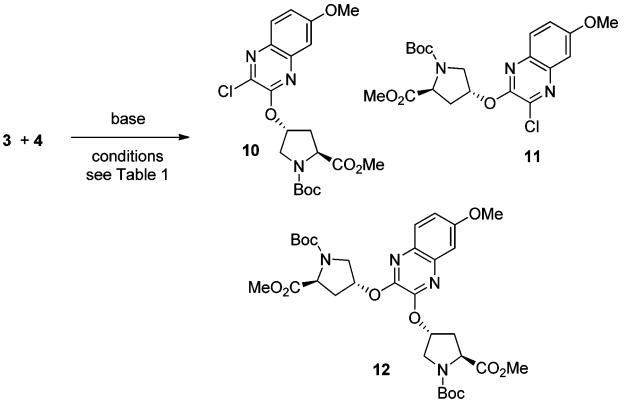
Our investigations began by examining the S_NAr reaction between **3** and **4** (Scheme 2).[9] For example, reaction of **3** and **4** in the presence of Cs_2CO_3 in DMF at room temperature afforded primarily the desired product **10** (Table 1, entry 1). Also detected in the crude reaction mixture was the corresponding regioisomer **11** and double addition product **12**.[10] The high regioselectivity (17:1) favoring the desired product was encouraging, but the high

Scheme 1. Retrosynthesis of **1**



levels of **12** proved problematic during the isolation of **10** without recourse to chromatography. We then set out to fully optimize the reaction in terms of solvent, temperature, and base and discovered that a combination of DBU in either DMSO, NMP, or dimethylacetamide (DMAc) routinely gave the highest level of regioselectivity between **10**:**11** (~20:1) with minimal formation of **12** when conducted at 50 °C (Table 1, entries 7–9). The final conditions selected involved reaction of **3** with 1.05 equiv of **4** in the presence of 1.5 equiv of DBU at 50 °C in DMAc giving **10** in 88% HPLC assay yield.[11] It should also be pointed out that no detectable epimerization of the proline ester was detected in the HPLC analysis of any of the crude reaction mixtures as confirmed by comparison to an authentic sample. Compound **10** was isolated by crystallization from

Scheme 2. Preparation of Heterocyclic Core



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(9) There is precedence for regioselective displacement of **3** with methoxide; see ref 8.

(10) Compounds **11** and **12** were observed spectroscopically (HPLC, LCMS, and NMR) but were not isolated.

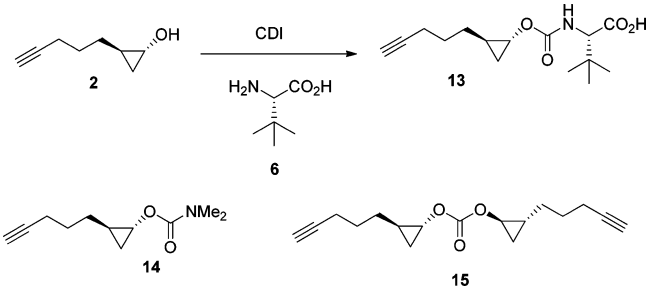
MTBE/heptanes in 71% yield and in analytically pure form.

Table 1. Optimization of the Regioselective S_NAr Displacement

entry	base	**4** (equiv)	solvent	*t* (°C)	conv (%)	ratio[12] (**10**:**11**:**12**)
1	Cs_2CO_3	1.25	DMSO	rt	100	85:5:10
2	Cs_2CO_3	1.25	DMSO	35	100	85:4:11
3	Cs_2CO_3	1.25	DMAc	rt	<5	NA
4	Cs_2CO_3	1.05	NMP	50	89	91:7:2
5	Cs_2CO_3	1.05	DMSO	50	90	85:8:7
6	DABCO	1.25	DMSO	rt	0	NA
7	DBU	1.05	DMSO	50	91	92:6:2
8	DBU	1.05	NMP	50	100	93:5:2
9	DBU	1.05	DMAc	50	100	94:4:2

With a suitable method in hand for the preparation of **10**, the construction of the macrocyclic ring of **1** was next investigated. Our strategy centered on a Sonogashira/macrolactamization approach and required the preparation of the acetylene precursor **13** (Scheme 3). The synthesis of **13** was extensively examined. Initial experiments involved reaction of **2** with CDI in DMF followed by addition of L-*tert*-leucine **6** and heating to 90 °C for 12 h. Under these conditions, **13** could be isolated routinely in 60−65% yield after an extractive workup. However, also detected in the crude product were carbamate **14** and dimer **15** in varying levels which were extremely difficult to remove.[13] Carbamate **14** arises from hydrolysis of DMF and subsequent reaction with the intermediate acylimidazole with dimethylamine.

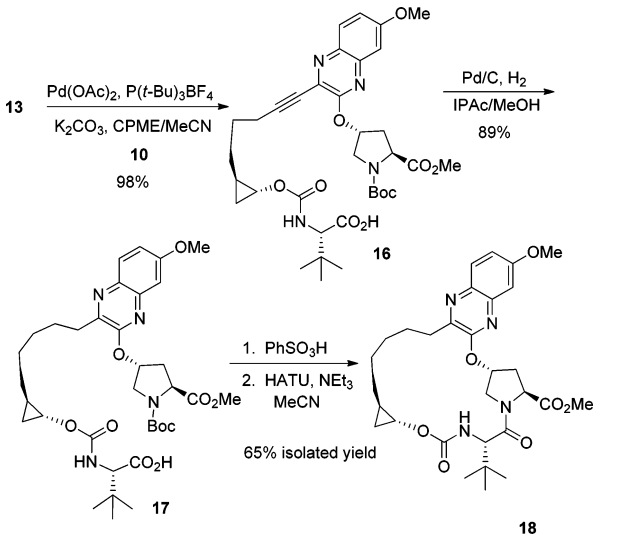
Scheme 3. L-*tert*-Butyl Leucine Carbamate



Attempted activation of **2** with phosgene or triphosgene followed by reaction with **6** in a number of solvent systems led to unsatisfactory results, presumably due to the insolubility of **6** in all solvents other than water. It was discovered that activation of **2** with CDI employing Hünig's base as the reaction solvent followed by the slow addition of **6** and heating to 95 °C for 2.5 h resulted in a much cleaner reaction profile. After an extractive workup, the desired carbamate **13** was isolated as a solution in cyclopentyl methyl ether (CPME) in 70% HPLC assay yield. There was no detectable amounts of dimer **15** formed under these reaction conditions, and the product was sufficiently pure for use in the next transformation without further purification.

The Sonogashira cross-coupling between chloride **10** and carbamate **13** was extensively investigated with the aid of high throughput experimentation where catalyst/ligand combinations, solvent, temperature, and base were explored (Scheme 4). The optimal conditions that were selected involved addition of **10** and crude **13** to a slurry of $Pd(OAc)_2$ (3 mol %), $P(t\text{-}Bu)_3BF_4$ (6 mol %), and K_2CO_3 (2.5 equiv) in a solvent mixture of CPME/MeCN (2.4:1) and heating at 85 °C for 2.5 h. After an aqueous workup, product **16** was obtained in 98% HPLC assay yield. Compound **16** was sufficiently pure for use in the next step without the need for purification. Catalytic hydrogenation of **16** was conducted with Pd/C in IPAc/MeOH and gave the reduced product **17**, which was not isolated, in 89% HPLC assay yield.

Scheme 4. Sonogashira/Macrolactamization



Perhaps the single most challenging aspect of the synthesis involved the formation of the 18-membered ring system of **1** via macrolactamization. In addition, control of the impurity profile was critical considering the fact that macrolactam **18** was the first isolated crystalline intermediate after 10 steps from commercially available 5-chloropropyne, the starting material for cyclopropanol **2**. We devised a very effective and highly productive procedure for the deprotection, macrolactamization, and isolation of **18** (Scheme 4). Removal of the Boc-protecting group was accomplished by treating crude **17** with $PhSO_3H$ in 8 mL/g of MeCN at 50 °C for 3 h to give the corresponding benzenesulfonate salt. All attempts to crystallize this salt were unsuccessful. Direct addition of Hünig's base

(11) HPLC assay yield refers to quantitative HPLC analysis employing an analytical standard.

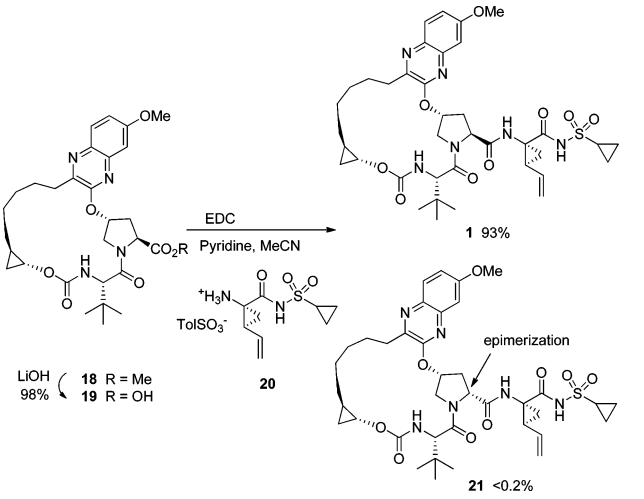
(12) Ratio was determined by HPLC at a wavelength detection of 210 nm.

(13) Compounds **14** and **15** were identified in the NMR of the crude isolated product and were not isolated.

(4.6 equiv) was followed by slow addition of the reaction mixture to a solution of HATU[14] (1.25 equiv)[15] in 7 mL/g of MeCN (based on the amount of **17**). Slow addition to HATU was required in order to minimize dimerization and maintain high productivity. The HPLC assay yield of **18** was 76% for the two-step protocol with dimer formation being controlled to $<2\%$.[16] Concentration of the reaction mixture to 4 mL/g, based on the amount of **18**, resulted in crystallization of **18** which was isolated in analytically pure form in 65% overall yield.[17]

The preparation of MK-5172 is illustrated in Scheme 5. Saponification of **18** with LiOH in aqueous THF furnished the corresponding acid **19** as a crystalline solid in 98% isolated yield. The final coupling with side chain **20** required a degree of reaction optimization. For example, the coupling was effective and gave high conversions when EDC was employed by itself; however, significant amounts of epimerization adjacent to the proline carboxylic acid was observed leading to the formation of **21** (up to 10%). The removal of **21** to acceptable levels during the crystallization of **1** proved to be challenging, and the use of additional additives was explored in order to suppress the formation of **21**. After examining a number of solvents (DCM, EtOAc, MeCN, DMF, DMAc, DMSO, and NMP) and additives (HOBT, 2-hydroxypyridine *N*-oxide, *N*-hydroxysuccinamide, and $CuCl_2$) and the effect of base loading,[18] we found better conditions to minimize the formation of **21**. Thus, EDC coupling in MeCN with an excess of pyridine gave full conversion of acid **19** to the desired product **1** with $<0.2\%$ of isomer **21** observed. After an

Scheme 5. End Game



acidic quench, compound **1** was obtained in 93% yield and with $>99.7\%$ purity.

In conclusion, we have outlined a highly efficient asymmetric synthesis of **1** that centered on a Sonogashira/macrolactamization approach for construction of a challenging 18-membered macrocycle. Key transformations included a regioselective S_NAr reaction for the formation of core heterocycle **10** and a volume efficient macrolactamization protocol leading to **16**. The synthesis proceeded in 42% overall yield from **3**, required no chromatographic purifications, and was amenable to the kilogram scale production of **1**.

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Supporting Information Available. Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(14) *O*-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphase; CAS [148893-10-1].

(15) Other common amide coupling reagents such as EDC, EDC/HOBt, EDC/HOAt, EDC/HOPO, EDC/pyridine, pivolate mixed anhydride, etc. resulted in lower conversion and generated a large amount of the dimerization byproduct.

(16) Dimerization of des-Boc of **17** was observed under various other conditions, but was effectively controlled under the described reaction conditions.

(17) There was no detectable amounts of epimerization at any of the stereogenic centers during macrolactamization as confirmed by HPLC analysis versus previously prepared reference standards.

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