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Enantioselective Synthesis of an HCV NS5a Antagonist

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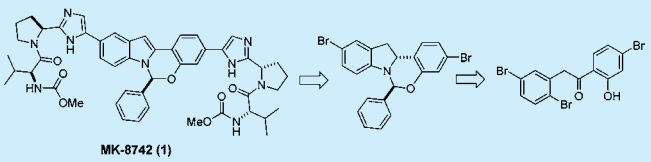
Supporting Information

ABSTRACT: A concise, enantioselective synthesis of the HCV NS5a inhibitor MK-8742 (**1**) is reported. The features of the synthesis include a highly enantioselective transfer hydrogenation of an NH imine and a dynamic diastereoselective transformation. The synthesis of this complex target requires simple starting materials and nine linear steps for completion.



Chronic hepatitis C virus (HCV) infection is estimated to afflict over 170 million people worldwide.[1] Untreated chronic HCV patients are at high risk of succumbing to cirrhosis, liver cancer, or liver failure.[2] Standard of care for HCV patients has generally been a combination of pegylated interferon-α and ribavirin; unfortunately, this combination has been shown to have limited efficacy and tolerability.[3] Moreover, achieving sustained virologic response is dependent upon the genotype of the virus and the duration of treatment. There has been considerable interest in the development of direct-acting antiviral agents[4] to treat HCV in order to provide an interferon-free regimen with efficacy for a broader population of patients while improving tolerability.

One of the most promising new targets for development of direct-acting HCV therapies is the nonstructural viral protein 5a (NS5a).[5] A recent clinical study provided validation of NS5a as a therapeutic target, during which a single dose of a NS5a inhibitor resulted in significant viral load reduction.[5a] Although the NS5a protein has no known enzymatic function, it has been shown to serve a number of functions in the life cycle of the virus, including viral replication.[5c] MK-8742 (**1**) is a potent and selective NS5a inhibitor recently disclosed by Merck & Co.[6] Herein is described a concise, enantioselective synthesis of MK-8742.

The critical and most challenging structural feature of MK-8742 from a synthetic perspective is the remote hemiaminal stereocenter. We were attracted by the intriguing possibility of using stereochemical relay to introduce the hemiaminal stereoselectively (Figure 1).[7] In this approach, introduction of the symmetrical heterocyclic fragments (**2**) at a late stage via cross-coupling reactions places pentacyclic indole **3** as a retrosynthetic target. Indole **3** could then be derived from the corresponding indoline (**4**) via a net dehydrogenation.

We anticipated that chiral indoline **5** could condense diastereoselectively with benzaldehyde, installing the hemiaminal stereocenter. We reasoned that iminium **6** would preferentially adopt an (*E*)-geometry to minimize van der Waals interactions between the phenyl ring and the proximal

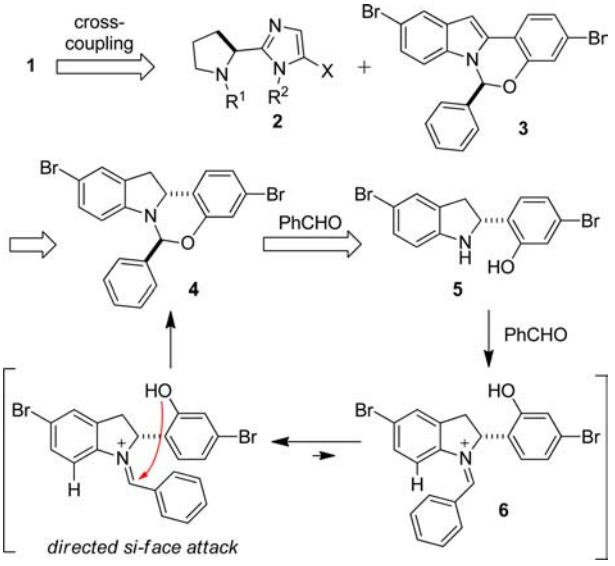


Figure 1. Retrosynthesis and stereochemical relay strategy.

aryl hydrogen of the indoline.[8] As a result, the resident stereochemistry of the indoline would then direct the attack of the phenol selectively to the *Si* face of the iminium, ensuring stereocontrol. We further envisioned that indoline **4** could be derived from an acyclic amine via an intramolecular C−N aryl bond coupling.

To begin investigations into the stereochemical relay strategy, we first sought an efficient synthesis of indoline **4**. In the first step, 2,5-dibromophenylacetic acid was converted to its corresponding acid chloride and coupled with 3-bromophenol to provide crystalline ester **7** in 91% yield (Scheme 1). Ester **7** then underwent a Fries rearrangement mediated by neat methanesulfonic acid desiccated by Ms_2O to

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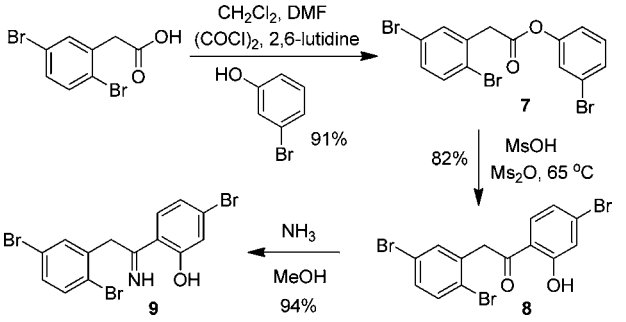
Scheme 1. Synthesis of *o*-Hydroxyaryl Imine 9



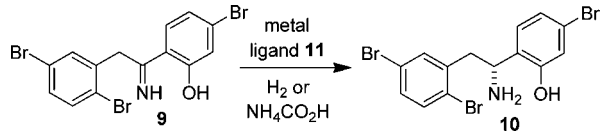
furnish ketone **8** as a crystalline intermediate in 82% yield.[9] Condensing ketone **8** with dry ammonia in methanol provided crystalline *o*-hydroxyaryl imine **9** (94% yield), a potential substrate for asymmetric reduction.

A number of reports have described asymmetric hydrogenations of imines,[10] and a recent study from Merck detailed the success of iridium catalysis for the enantioselective hydrogenation of unprotected N−H imines.[10c] However, we anticipated that the *o*-phenol functional group of imine **9** might stabilize the imine by hydrogen bonding, reducing its affinity for transition metals and therefore attenuating its reactivity. Nevertheless, we began surveying the reduction of imine **9** with catalytic $[Ir(COD)Cl]_2$ in conjunction with a range of bisphosphine ligands (Table 1).[11] To our delight, we found that amine **10** could be accessed in enantiomeric excesses as great as 87% with select ligands (Table 1, entries 1−2); however, yields were modest due to competing hydrolysis of the imine back to the ketone, and subsequent reduction of the ketone to the corresponding alcohol.[12] Rhodium catalysts[13] and traditional Noyori-type Ru transfer hydrogenation catalysts[14] were also evaluated, with promising enantioselectivities, but, unfortunately, the same limitations in yield (entries 3−5). However, it was found that structurally related "tethered" TsDPEN catalysts pioneered by Wills[15] provided not only superior enantioselectivity, but also significantly improved the yield of amine **10** (entries 6−10). Although the magnitude of improvement provided by the Wills catalyst was surprising, it is consistent with studies suggesting a role for the tethered ligand in stabilizing the catalyst and providing faster Ru hydride regeneration, and perhaps providing a stabilizing interaction in the transition state of the reduction that aids selectivity.[17c]

Several solvents, including MeOH and iPrOH, provided good yields but only moderate enantioselecitvity (entries 6 and 7, 78−85% ee). Subsequently, it was found that THF (entry 8, 94% ee) provided improved reactivity and selectivity. Our best results were achieved with 0.3 mol % (*R*,*R*) Teth-TsDPEN-RuCl in CH_2Cl_2 using ammonium formate as the hydrogen source (entry 9, 98% ee). This catalyst system ultimately afforded chiral amine **10** in a crude 96% yield and 98% ee, which upon crystallization increased to 99% ee (88% isolated yield). A mixture of Et_3N and formic acid can be used as an alternative hydrogen source, but we found that the yield was diminished with hydrolysis of the imine becoming more prevalent (entry 10).[16]

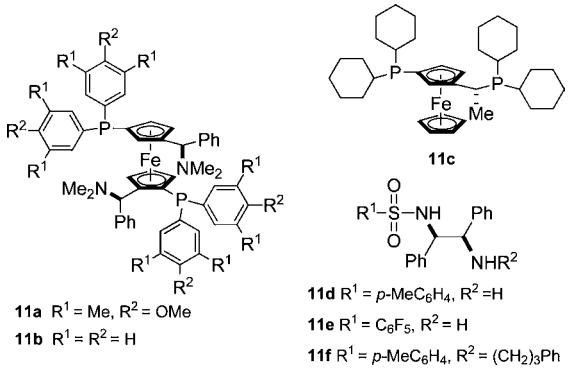
With a reliable synthesis of amine **10** in hand, we then sought to complete the indoline ring system by way of an intramolecular aryl C−N bond coupling (Scheme 2). Although **10** features three aryl bromides that could participate in a transition metal insertion, we found that catalytic CuI smoothly

Table 1. Asymmetric Reduction Optimization



entry	metal	ligand	solvent	yield[a] (%)	ee[b] (%)
1[c]	Ir	**11a**	MeOH	13	87
2[c]	Ir	**11b**	MeOH	22	80
3[d]	Rh	**11c**	MeOH	30	80
4[e]	Ru	**11d**	MeOH	19	56
5	Ru	**11e**	MeOH	15	78
6	Ru	**11f**	MeOH	81	78
7	Ru	**11f**	*i*-PrOH	83	85
8	Ru	**11f**	THF	95	94
9	Ru	**11f**	CH_2Cl_2	96	98
10[f]	Ru	**11f**	CH_2Cl_2	82	95

[a]Assay yield of **12** as determined by HPLC. [b]Enantiomeric excess determined by HPLC. [c]4 mol % of $[Ir(COD)Cl]_2$, 500 psi H_2, 25 °C. [d]4 mol % of $[Rh(COD)Cl]_2$, 500 psi H_2, 50 °C. [e]Commercially available DPEN-RuCl catalysts used at 0.3 mol % loading, 2.0 equiv of NH_4CO_2H, 70 °C. [f]1:1 Et_3N:HCO_2H used as the hydrogen source.



mediated the C−N bond coupling selectively to provide indoline **5** in 91% yield.[17] There was no evidence of competing intramolecular C−N bond coupling products, though indoline **5** can eventually proceed to react intermolecularly to form dimeric species if the reaction is not quenched. A number of ligands for Cu were evaluated but found to have no impact on reactivity or yield, perhaps indicating that amine **10** is itself precoordinating the Cu catalyst.

We then surveyed reaction conditions for the proposed stereochemical relay by condensing benzaldehyde with indoline **5**. Gratifyingly, it was found that the pentacyclic hemiaminal **4** could be formed in the presence of a mild acid catalyst, with diastereoselectivity on the order of 7:1. Unfortunately, the diastereomeric ratio and yield degraded on prolonged reaction times due to reversibility of the hemiaminal formation. However, by carefully optimizing solvent and temperature to favor crystallization during the course of the reaction, we were able to promote a dynamic diastereoselective transformation.[18] That is, by taking advantage of the reversibility of the hemiaminal formation in solution and the greater stability of the crystalline phase of **4** relative to its diastereomer, we could drive the isolated dr of **4** from 7:1 to >99:1 in 93% yield using acetonitrile as the solvent and TFA as the acid catalyst.

We began to look extensively at conditions for effecting a net dehydrogenation of hemiaminal **4** to access indole **3**.[19] Various low-valent transition metals known to mediate dehydrogenation of unsaturated systems were evaluated, but provided only

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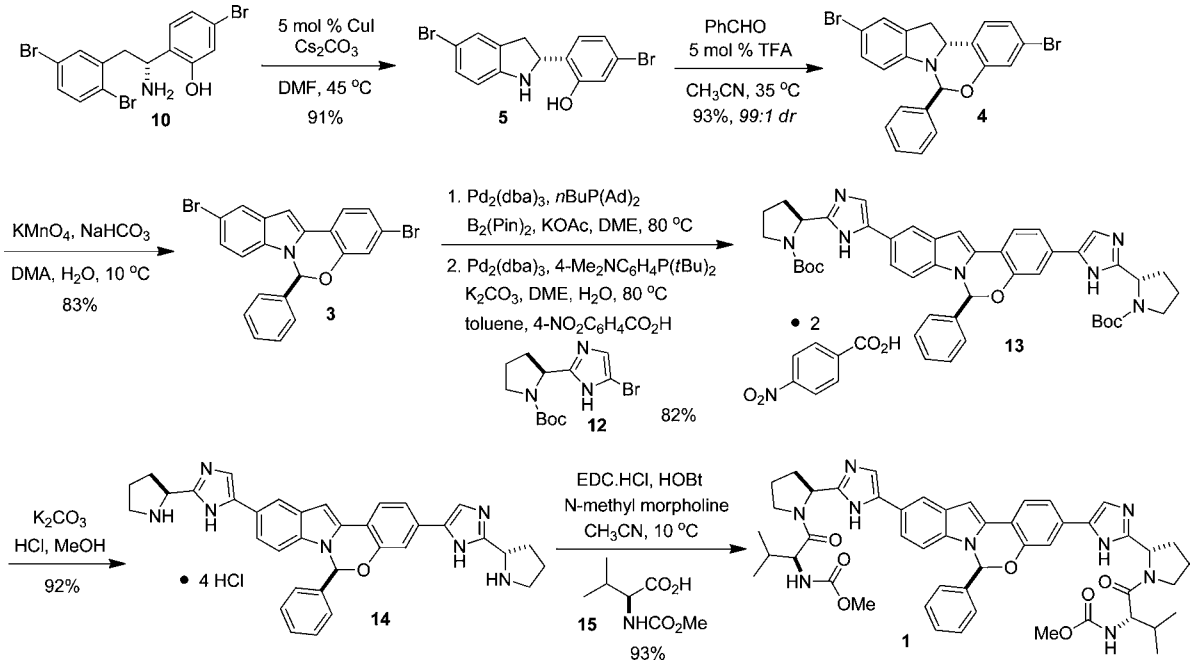
Scheme 2. Completion of the Synthesis of MK-8742 (1)



modest reactivity.[20] A number of conventional oxidants did prove capable of promoting this transformation; however, we observed significant levels of racemization of the hemiaminal stereocenter depending on the nature of the oxidant and the solvent system. Following exhaustive screening efforts, we found $KMnO_4$ effects the desired dehydrogenation without racemization, providing indole **3** in 83% yield and >99% ee.[21]

Indole **3** was then subjected to a palladium mediated bis-borylation and a subsequent bis-Suzuki coupling with imidazole **12**[22] in a through process, after which the product was crystallized as its 4-nitrobenzoic acid salt. Although there are four chemical transformations in this borylation and Suzuki through process, the overall isolated yield of the Suzuki product **13** is 82%, representing an average yield of 95% per transformation. To our surprise, the rate of the Suzuki reaction in the through process is greater than that seen when the steps are decoupled with an intermediate purification, suggesting that one or more components of the borylation reaction stream accelerates the subsequent Suzuki coupling.[23]

Suzuki product **13** was then deprotected with aqueous HCl in MeOH, providing diamine **14** as a crystalline tetra-HCl salt in 92% yield. EDC-mediated coupling of diamine **13** with 2 equiv of L-Moc-valine (**15**) then provided crude MK-8742 (**1**), which was then crystallized from ethanol in 93% overall yield.

In conclusion, a concise, enantioselective synthesis of MK-8742, a potent and selective NS5a inhibitor for the treatment of chronic HCV infection, has been developed. This approach features a highly enantioselective asymmetric hydrogenation and a directed stereochemical relay strategy that leverages a dynamic diastereoselective condensation to produce the challenging hemiaminal stereocenter. The entire synthesis requires only 10 linear steps for completion in the longest linear sequence and proceeds in 30% overall yield without the need for chromatography.

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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(21) DDQ was the best alternative oxidant we found, providing indole **3** in an optimized 91% ee. Catalytic Mn oxidation systems such as $Mn(OAc)_2$ were investigated in conjunction with various oxidants but were found to suffer from significant racemization.
(22) See the Supporting Information for details on the synthesis of imidazole **12**.
(23) A number of additives were evaluated in the Suzuki coupling to mimic the effect of the crude borylation stream, including methanol, pinacol, and inorganic salts; however, no single additive evaluated to date replicates this phenomenon.

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