

Synthetic studies towards anti-SARS agents: application of an indium-mediated allylation of α -aminoaldehydes as the key step towards an intermediate

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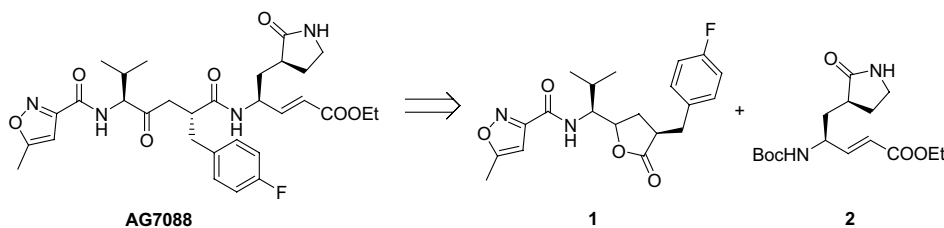
Abstract—AG7088 was identified as a good starting point for modification, leading to an efficient and bio-available inhibitor for the SARS coronavirus main proteinase (SARS-CoV M^{Pro}). Synthesis of intermediate **1** and analogues proceeded via a highly diastereoselective indium-mediated allylation of α -aminoaldehydes.

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Severe acute respiratory syndrome (SARS) was first reported in Asia in February 2003. Over a few months, the disease spread from its likely origin in Southern China to more than two dozen countries in North America, South America, Europe and Asia with more than 8400 cases of infection.¹ SARS is characterized by high fever, malaise, rigor, headache and nonproductive cough or dyspnoea and may progress to generalized interstitial infiltrates in the lung. The fatality rate among people with the illness is around 15% (calculated as deaths/(deaths + surviving patients)).^{1a}

A novel coronavirus has been identified as the causative agent of SARS.^{2,3} In order to find an efficient therapy for SARS, many scientists are now focusing on the development of drugs that inhibit the viral main prote-

inase (SARS-CoV M^{Pro}) and disrupt the replication cycle of the virus. In May 2003, Hilgenfeld and co-workers showed that the substrate-binding site in SARS-CoV M^{Pro} is well conserved compared to those in two other coronavirus main proteinases (HCoV 229E and TGEV M^{Pro}).⁴ In addition, they reported similarities between substrate/inhibitor-binding modes of SARS-CoV M^{Pro} and the distantly related human rhinovirus 3C proteinase (HRV 3C^{Pro}). Based on these findings, it was suggested that the HRV 3C^{Pro} inhibitor, AG7088, could serve as a good starting point for modifications leading to an efficient and bio-available inhibitor for the SARS-CoV M^{Pro} and other coronavirus main proteinases. AG7088 is currently under clinical trial for treatment of the ‘common cold’ caused by HRV



Scheme 1.

Keywords: Anti-SARS agents; AG7088; Indium-mediated allylation; Diastereoselective.

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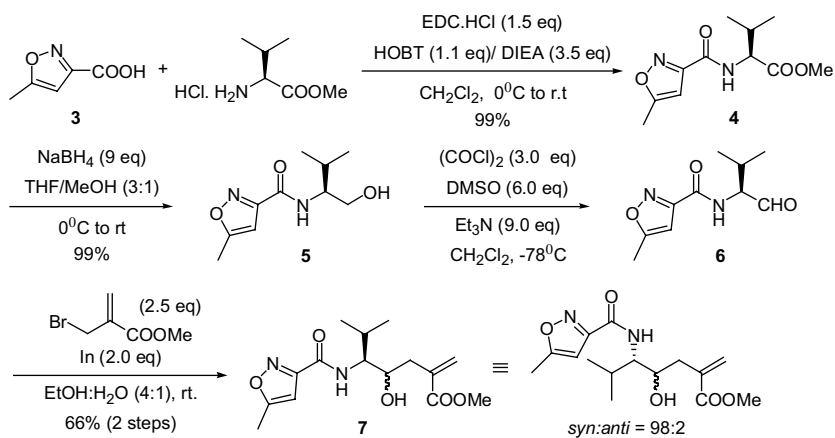
Retrosynthetic analysis of **AG7088** led us to two key intermediates, lactone **1** and lactam **2**. The synthesis of **1** in our group has proceeded via the highly stereoselective indium-mediated allylation reaction of *N*-protected valinal as illustrated in Scheme 2. Although syntheses of fragments similar to **1** have previously been reported, the synthetic strategy presented herein has two major advantages.⁵ Firstly, the incorporation of the 5-methylisoxazole-3-carbonyl group in the first step of the synthesis increases the efficiency by doing away with the protection and de-protection of the amino group. In addition, our synthetic strategy easily allows us to make modifications to **AG7088**. Hilgenfeld and co-workers suggested that most parts of **AG7088** could be accommodated by the active site of SARS-CoV M^{pro}.⁴ Based on molecular modeling, only the *p*-fluorobenzyl group might be too long to fit into the pocket. In our synthesis of **1**, the *p*-fluorobenzyl group is introduced in the final step, allowing us to generate analogues of **AG7088** by simply changing the organocuprate reagent employed.

Lactone **1** was synthesized in six steps from *L*-valine methyl ester hydrochloride. The hydrochloride salt was first coupled with 5-methylisoxazole-3-carboxylic acid **3** to give methyl ester **4** in almost quantitative yield. Subsequently, NaBH₄ reduction of **4** in THF/methanol afforded β -aminoalcohol **5** in 99% yield. Alcohol **5** was then oxidized to α -aminoaldehyde **6** under Swern conditions. As α -aminoaldehydes are particularly prone to epimerization, no purification was performed on **6**.⁶ In-

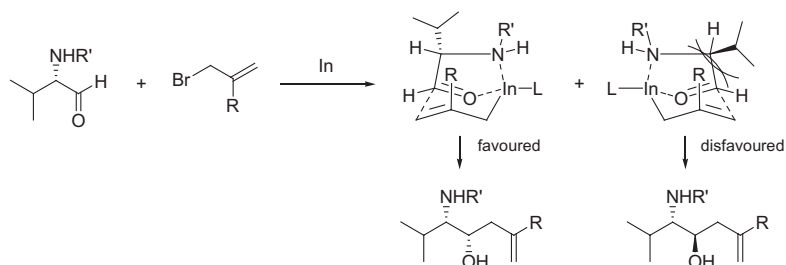
stead, the crude product from the Swern oxidation was used directly in the subsequent indium-mediated allylation reaction. Thus, crude aldehyde **6** was reacted with methyl 2-(bromomethyl)acrylate in the presence of indium metal to furnish homoallylic alcohol **7** in overall 66% yield (from **5**) with almost complete *syn* diastereoselectivity (*syn/anti* = 98:2).

The unusually high diastereoselectivity for the indium-mediated allylation might be explained based on the Felkin-Anh chelation model.⁷ As shown in Scheme 3, the α -nitrogen atom can coordinate to the indium metal to form a five-membered chelation ring. We can see in the transition state leading to the *anti*-isomer that there is more pronounced steric repulsion between the *i*-propyl group and the R group in the axial position (R = COOMe). As a result, the *syn*-isomer is favoured.

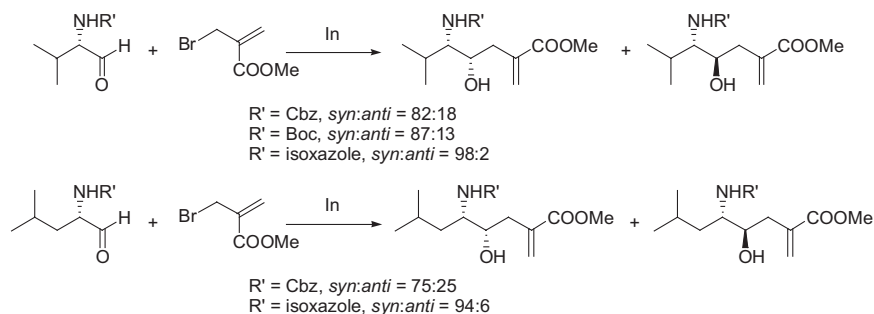
However, it has been reported by Steurer and Podlech that when the α -amino group was protected using benzyloxycarbonyl (Cbz), the indium-mediated allylation of the corresponding *L*-valinal gave a *syn/anti* diastereoisomeric ratio of only 82:18.⁸ In addition, when we performed the same indium-mediated allylation reaction on *N*-*t*-butyloxycarbonyl-*L*-valinal, we obtained the homoallylic alcohol as an 87:13 mixture of *syn/anti* isomers (Scheme 4). Clearly, chelation of the α -nitrogen atom and the steric bulkiness of the *i*-propyl group cannot totally account for the observed selectivity in our reaction. This suggests that the isoxazole group could have been involved.



Scheme 2.



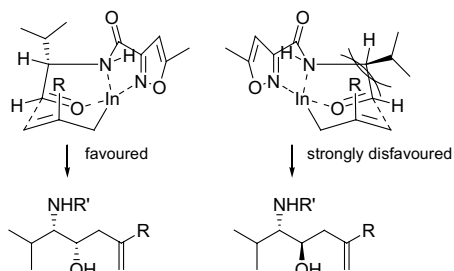
Scheme 3.



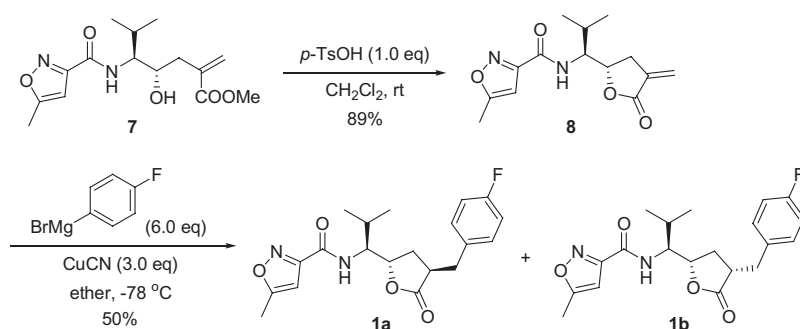
Scheme 4.

Therefore, we propose that the nitrogen atom of the isoxazole ring coordinates to the indium atom, forming a second five-membered chelated ring (Scheme 5). The interaction of the isoxazole ring with indium metal causes the transition state to be more rigid (compare Schemes 3 and 5). Less puckering of the transition state ($R' = \text{isoxazole}$) is now possible (compared to $R' = \text{Cbz}$ or Boc) to minimize the steric repulsion between the *i*-propyl group and the COOMe group. The transition state leading to the *anti* product is therefore further destabilized, resulting in the increase in the *syn/anti* selectivity from 82:18 and 87:13 to 98:2, respectively. In our synthesis of the L-leucine analogue of lactone **1**, an improvement in the *syn/anti* selectivity was also clearly demonstrated (Scheme 4). The excellent diastereoselectivity in the allylation step makes our synthetic strategy of **1** very efficient and paves the way for controlling the second stereogenic centre in the molecule.

Upon accomplishing this critical step, homoallylic alcohol **7**⁹ was cyclized using *p*-toluenesulfonic acid in



Scheme 5.



Scheme 6.

dichloromethane to afford α,β -unsaturated lactone **8** in high yield (89%), (Scheme 6). Conjugate addition of the organocuprate reagent (formed in situ from *p*-fluorobenzylmagnesium bromide and copper(I) cyanide) to **8** finally provided key intermediate lactone **1** in 50% yield as a mixture of isomers (*cis/trans* = 39:61). The desired *trans*-isomer **1a**⁹ was obtained as the major product (confirmed by NOE experiments).

Herein, we have reported the asymmetric synthesis of a key intermediate in our synthetic approach towards **AG7088** and its analogues. The critical step in the synthesis involved a highly diastereoselective indium-mediated allylation reaction. Syntheses of the second key intermediate and analogues of **AG7088** are now underway in our laboratory, and the compounds obtained will be tested to examine their inhibitory abilities on the replication and spread of the SARS coronavirus.

Acknowledgements

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9. Data for molecule **7**: ^1H NMR (300 MHz, CDCl_3) δ 7.14 (d, $J = 10.03$ Hz, 1H), 6.39 (s, 1H), 6.18 (s, 1H), 5.66 (s, 1H), 4.01 (ddd, $J = 1.60, 4.32, 8.13$ Hz, 1H), 3.73–3.67 (m, 1H), 3.69 (s, 3H); 2.48 (dd, $J = 4.22, 13.85$ Hz, 1H), 2.42 (s, 3H), 2.39 (dd, $J = 8.03, 14.05$ Hz, 1H), 2.00–1.88 (m, 1H), 0.96 (d, $J = 6.83$ Hz, 3H), 0.92 (d, $J = 6.82$ Hz, 3H). ^{13}C NMR (300 MHz, CDCl_3) δ 171.0, 168.2, 159.4, 158.6, 136.8, 128.6, 101.4, 69.5, 58.5, 52.0, 38.6, 30.2, 19.6, 19.3, 12.1. FTIR (neat): 3404, 2959, 1720, 1666, 1543, 1440, 1209, 1155, 1059, 950, 818 cm^{-1} . HRMS Calcd for $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_5$ [M^+]: 310.1529. Found: 310.1516.
Data for molecule **1a**: ^1H NMR (300 MHz, CDCl_3) δ 7.14–7.08 (m, 2H), 7.00–6.94 (m, 2H), 6.74 (d, $J = 10.04$ Hz, 1H), 6.40 (d, $J = 0.80$ Hz, 1H), 4.47 (ddd, $J = 2.01, 6.32, 8.13$ Hz, 1H), 3.91 (ddd, $J = 2.01, 8.33, 10.14$ Hz, 1H), 3.04–2.80 (m, 3H); 2.47 (s, 3H), 2.19–2.01 (m, 2H), 1.93 (d (hept), $J = 6.83, 8.03$ Hz, 1H), 0.98 (d, $J = 6.83$ Hz, 3H), 0.95 (d, $J = 6.82$ Hz, 3H). ^{13}C NMR (300 MHz, CDCl_3) δ 178.4, 171.6, 161.9, 160.0, 158.1, 133.3, 130.5, 115.6, 101.4, 77.6, 57.3, 41.0, 35.8, 30.6, 29.4, 19.7, 19.2, 12.3. ^{19}F NMR (300 MHz, CDCl_3) δ -40.36 (s, 1F). FTIR (KBr): 3391, 3328, 2928, 2851, 2360, 1771, 1682, 1627, 1536, 1509, 1219, 1154, 1020, 805 cm^{-1} . Norminal MS(EI) for $\text{C}_{20}\text{H}_{23}\text{FN}_2\text{O}_4$ [M^+]: 374.1 (100%), 375.1 (41%).