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COMMUNICATION

A facile synthetic route to diazepinone derivatives *via* ring closing metathesis and its application for human cytidine deaminase inhibitors†

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A variety of diazepinone derivatives were prepared from α-amino acids and amino alcohols by a new synthetic methodology based on ring closing metathesis as a key step. The diazepinones were coupled with ribose derivatives to afford novel diazepinone nucleosides. Among them, (4*R*)-1-ribosyl-4-methyl-3,4-dihydro-1*H*-1,3-diazepin-2(7*H*)-one (3) showed a potent inhibitory effect (K_i = 145.97 ± 4.87 nM) against human cytidine deaminase.

Human cytidine deaminase (hCDA) is a key enzyme to metabolize cytidine analogues used in anticancer and antiviral agents *via* a hydrated transition-state intermediate that results from the nucleophilic attack of zinc-bound water at the active site.[1] hCDA thus catalyses the irreversible deamination of cytidine and deoxycytidine to uridine and deoxyuridine analogues and leads to loss of their biological activity or possession of undesirable side-effects. Moreover, it is generally overexpressed in cancers resistant to cytidine analogues and has been considered as an attractive target for the development of anticancer adjuvants.[2] The crystal structure of hCDA bound to diazepinone-1-ribose (**1**) showed a CH–π interaction as a key binding interaction, which is distinguished from that of other CDA inhibitors.[4] The structure revealed a canonical CH–π-interaction between inhibitor **1** and Phe 137 in the active site.[3] To evaluate the substitution effect of the diazepinone ring on its binding affinity, it was necessary to develop a versatile synthetic route to generate a new class of diazepinone derivatives (Fig. 1).

Moreover, the cyclic urea moiety in the diazepinone ring is found in many biologically active natural products and pharmaceutically relevant compounds, and plays a key role in the activity.[5] Therefore, development of a synthetic methodology for symmetrical and unsymmetrical diazepinone derivatives is of enormous significance in medicinal chemistry.[6] Hanson *et al.* demonstrated the synthesis of unsymmetrical urea compounds from *cis*-1,4-diamines and *N*,*N*′-carbonyldiimidazole (CDI).[7] They used an indirect method involving a temporary organophosphorus reagent for making cyclic phosphorus tethers using ring closing metathesis (RCM) reaction, which might be limited for the synthesis of various cyclic urea compounds due to the strong binding character of the organophosphorus reagent. In this communication, we have developed a simple, efficient, and direct method for these seven-membered heterocyclic compounds *via* addition of allyl isocyanate to protected amino alcohol and subsequent RCM reaction with Grubb's 2nd generation catalyst under mild conditions to achieve the desired 1,3-diazepinone derivatives.

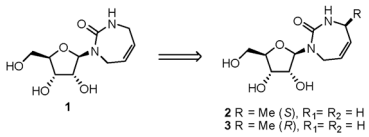

Fig. 1 Methyl substituted diazepinone nucleoside analogues.

The synthesis of various substituted 1,3-diazepinones was accomplished from commercially available natural and unnatural amino acids or amino alcohols. Initially, L-alanine was converted to the corresponding *p*-methoxybenzaldehyde (PMB)-protected amino alcohol **5**, which was reacted with isocyanate to produce an inseparable mixture of the desired urea **7** and allylcarbamate **8** in a 9 : 1 ratio. Hence, the hydroxyl group was protected with a *tert*-butyldimethylsilyl (TBS) group to give compound **6**. The amine **6** was then treated with allyl isocyanate to afford a urea compound **9** in an excellent yield. The TBS group was then deprotected followed by oxidation and Wittig reaction to furnish a diallyl urea intermediate **10**. Our initial attempts to cyclize **10** by RCM reaction under various conditions *i.e.* change of solvents (CH_2Cl_2, benzene, and toluene) and/or temperature (room temperature and heating) were not successful as shown in Scheme 1.[8] This may be due to the unfavourable orientation of the allyl groups. It is well documented in the literature that *trans*-substituted cyclohexane derivatives undergo RCM reaction under rigorous conditions and lower yield than the corresponding *cis*-isomers is obtained.[9] Thus, the NH group of the urea

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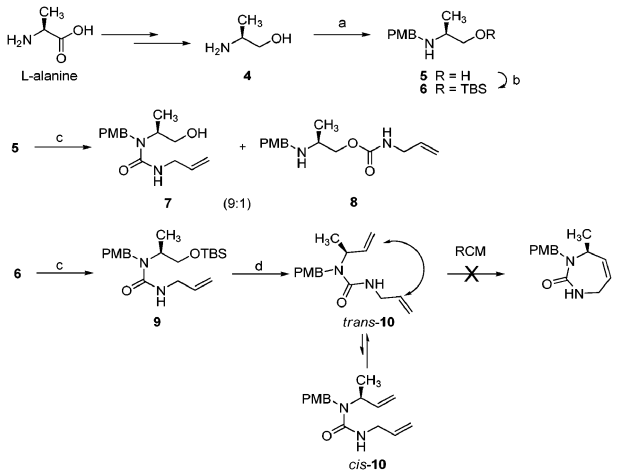
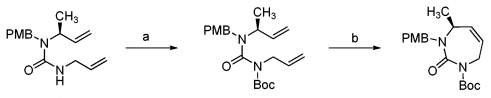


Scheme 1 *Reagents and conditions*: (a) *p*-methoxybenzaldehyde, 4 Å molecular sieves, CH_2Cl_2, then EtOH, $NaBH_4$, 93% (over two steps); (b) TBSCl, Et_3N, CH_2Cl_2, 99%; (c) allyl isocyanate, THF, 0 °C, 12 h, 78%; (d) (i) HF–pyridine, pyridine, THF or PTSA, MeOH, 3 h, 62%, (ii) DMP, CH_2Cl_2, 86%, (iii) $CH_3{}^+PPh_3I^-$, NaHMDS, 0 °C, dry ether, 86%.



Scheme 2 *Reagents and conditions*: (a) $(Boc)_2O$, Et_3N, DMAP, THF, reflux, 24 h, 96%; (b) 10 mol% Grubb's 2nd generation catalyst, CH_2Cl_2, rt, 3 h, 99%.

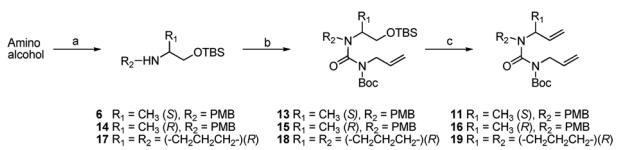
derivative **10** was protected with *tert*-butyloxycarbonyl (Boc) to afford **11**, which was then subjected to RCM reaction by using Grubb's 2nd-generation catalyst to obtain the desired seven-membered ring **12** in a quantitative yield (Scheme 2).

After optimization of the conditions for RCM reaction, compound **11** was obtained from the corresponding amino alcohol. Diallyl urea analogues **16** and **19** were also prepared from the corresponding amino alcohols following a similar method to that employed for **11**, respectively (Scheme 3).

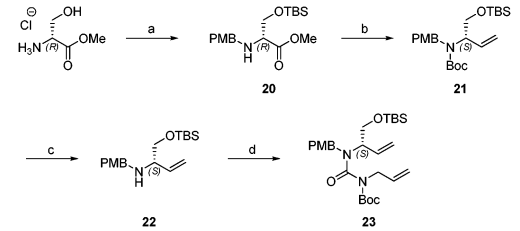
As shown in Scheme 4, L-serine ester was converted to an allyl amine **21**, which was also reacted with isocyanate to afford compound **23**.

For the preparation of the reference compound **1**, allyl amine was coupled with allyl isocyanate followed by RCM reaction to afford compound **25**. Compound **27** was also obtained from methylallyl amine with the same method (Scheme 5).

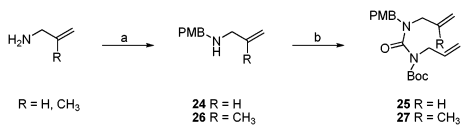
The prepared diallyl urea analogues shown in Schemes 3–5 were subjected to RCM reactions to afford the cyclic urea



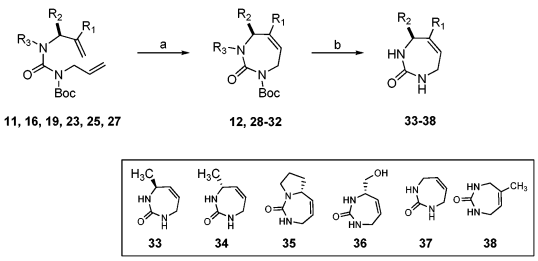
Scheme 3 *Reagents and conditions*: (a) *p*-methoxybenzaldehyde, CH_2Cl_2, Et_3N, 4 Å molecular sieves, for 3 h, then $NaBH_4$, EtOH, 92–98%; (b) (i) allyl isocyanate, THF, 0 °C, 12 h, 78–80% and (ii) $(Boc)_2O$, Et_3N, DMAP, THF, reflux, 24 h, 90–97%; (c) (i) HF–pyridine, pyridine, THF or PTSA, MeOH, 3 h, 62–75%, (ii) DMP, CH_2Cl_2, 85–90%, (iii) $CH_3{}^+PPh_3I^-$, NaHMDS, 0 °C, dry ether, 70–78%.



Scheme 4 *Reagents and conditions*: (a) (i) *p*-methoxybenzaldehyde, CH_2Cl_2, Et_3N, 4 Å molecular sieves, for 3 h, then $NaBH_4$, EtOH, 99%, (ii) TBSCl, Et_3N, CH_2Cl_2, 93%; (b) (i) $(Boc)_2O$, Et_3N, THF, reflux, 24 h, 97%, (ii) DIBAL-H, toluene, −78 °C, 65%, (iii) Tebbe's reagent, THF, rt, 86%; (c) TMSOTf, TEMDA, CH_2Cl_2, rt, 88%; (d) (i) allyl isocyanate, THF, 0 °C, 12 h, 100%, (ii) $(Boc)_2O$, Et_3N, DMAP, reflux, 24 h, 97%.



Scheme 5 *Reagents and conditions*: (a) *p*-methoxybenzaldehyde, CH_2Cl_2, Et_3N, 4 Å molecular sieves, 3 h, then $NaBH_4$, EtOH, 90–96% (over two steps); (b) (i) allyl isocyanate, THF, 0 °C–rt, 18 h, 78–80%, (ii) $(Boc)_2O$, DMAP, Et_3N, THF, reflux, 24 h, 95–97%.



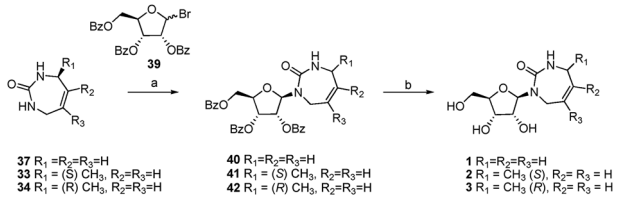
Scheme 6 *Reagents and conditions*: (a) 15 mol% Grubb's 2nd generation catalyst, CH_2Cl_2, rt, 2–3 h; (b) TFA : CH_2Cl_2 (2 : 1), rt, 3–5 h, 80–95%.

analogues, respectively. Finally, PMB and Boc protecting groups were deprotected in a single step using excess TFA to provide the desired unsymmetrical and symmetrical cyclic urea derivatives (Scheme 6).

In hand with diazepinones, novel diazepinone nucleosides were synthesized as potential hCDA inhibitors. Thus, compounds **33**, **34**, and **37** were coupled with bromosugar **39** *via* mercury-catalyzed condensation reaction to produce exclusively single β-isomers **40**, **41**, and **42**, respectively.[10] It was of interest that the coupling reactions produced only 4-methyl diazepinone nucleosides in the case of **41** and **42**, which might be due to the steric hindrance of the methyl substituents. Finally, the diazepinone nucleosides **40**, **41**, and **42** were de-protected with liquid NH_3–MeOH to furnish final compounds **1**, **2**, and **3**, respectively (Scheme 7).

The high regioselectivity for the 4-methyl isomer of **41** was confirmed by its 2D NOESY experiment as shown in Fig. 2. We could observe a correlation between signals of 2′H (5.64 ppm) and 7H_β (3.69 ppm) and no correlation between signals of 2′H (5.48 ppm) and 4H (4.28 ppm).

The newly synthesized compounds **2** and **3** were evaluated for their activities against hCDA in comparison with compound



Scheme 7 *Reagents and conditions*: (a) BSTFA, CH_3CN; **39**, HgO/HgBr, benzene, 40–50%; (b) NH_3, MeOH, RT, 24 h, 95–100%.

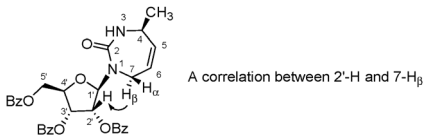


Fig. 2 2D NOESY experiment of **41**.

Table 1 hCDA inhibition assay data[a]

Inhibitor	**1**	**2** (Me, *S*)	**3** (Me, *R*)
K_i	35.3 ± 0.49 (nM)	2.56 ± 0.18 (μM)	146 ± 4.87 (nM)

[a] Human cytidine deaminase activity was determined by a direct spectrophotometric assay based on the decrease in absorbance at 282 nm upon cytidine deamination.

1 (Table 1). Among them, 4*R*-isomer **3** (K_i = 146 nM) was more potent than 4*S*-isomer **2** (K_i = 2.56 μM), which might be due to the stereochemical preference of 4*R*-configuration to 4*S*-configuration in the active site of hCDA. Both isomers were found to show competitive inhibition against cytidine deamination by hCDA, *i.e.* the compounds bind to the active site of hCDA.

In summary, novel diazepinone derivatives were successfully synthesized from the corresponding α-amino acids and amino alcohols by a new and efficient synthetic method using ring closing metathesis. In addition, novel 4-methyl diazepinone derivatives were successfully employed for the synthesis of diazepinone nucleosides, which showed interesting inhibitory activity against hCDA depending on their stereochemistry of 4-methyl substituents. Further work in this regard is underway in our laboratory.

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