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Potent thrombin inhibitors via a 20-membered ring olefin metathesis macrocyclization

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Abstract—Twenty-membered ring pyrazinone derived macrocycles were prepared as a means to enhance the potency of existing thrombin inhibitors. Macrocyclization was accomplished via Grubbs olefin metathesis of a highly functionalized allyl-alloc scaffold, thus further confirming the power of such methodology.

The search for orally active, direct thrombin inhibitors[1] has lead our laboratories to the discovery of pyrazinone[2] based small molecules which inhibit thrombin with a high degree of potency and selectivity. Studies with proline[3] and pyrazinone[4] (**1**, Fig. 1) based thrombin inhibitors have shown that access to the S_4 affinity pocket of the enzyme both from a P_1 phenoxy group or by branching off the P_3 group results in potency enhancement. Examination of X-ray data[3] revealed the close spatial proximity of both P_4 groups derived from either P_1 or P_3. The lure of enhanced potency by conformational preorganization[5] and potential added metabolic stability[6] directed us toward the design of macrocycles of type **2** which would tether the P_3-branched aminomethyl group and the P_4 phenoxy substituent. We anticipated that the Grubbs olefin metathesis[7] might be an efficient method for the macrocyclization of such densely functionalized molecules, and herein we report on the superiority of such methodology versus standard macrolactamization protocols.

The application of the proposed strategy is outlined in Scheme 1. Starting from commercially available (*S*)-Boc-phenylalaninol **3**, we could prepare the corresponding azide under Mitsunobu conditions.[8] Removal of the Boc protecting group with anhydrous HCl provided aminoazide **4**. Reaction between bromopyrazinone **5**[2] and amine **4** in EtOH at 100°C in a sealed tube lead to the formation of aminopyrazinone **6** in 73% isolated yield. Chlorination with *N*-chlorosuccinimde and reduction of the azide to the corresponding amine **7**, followed by installation of an allyl carbamate and hydrolysis of the ethyl ester with 1N LiOH in THF lead to the alloc-carboxylic acid **8**. A P1 substituent bearing an allyl substituent was then installed via the EDC/HOAt coupling of benzyl amine **9**.[9] Exposure of **10** to a catalytic amount of Grubbs catalyst[10] in

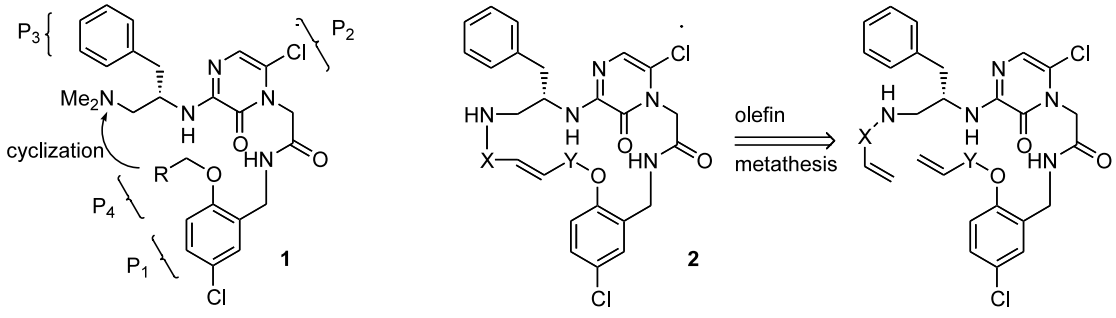

Figure 1.

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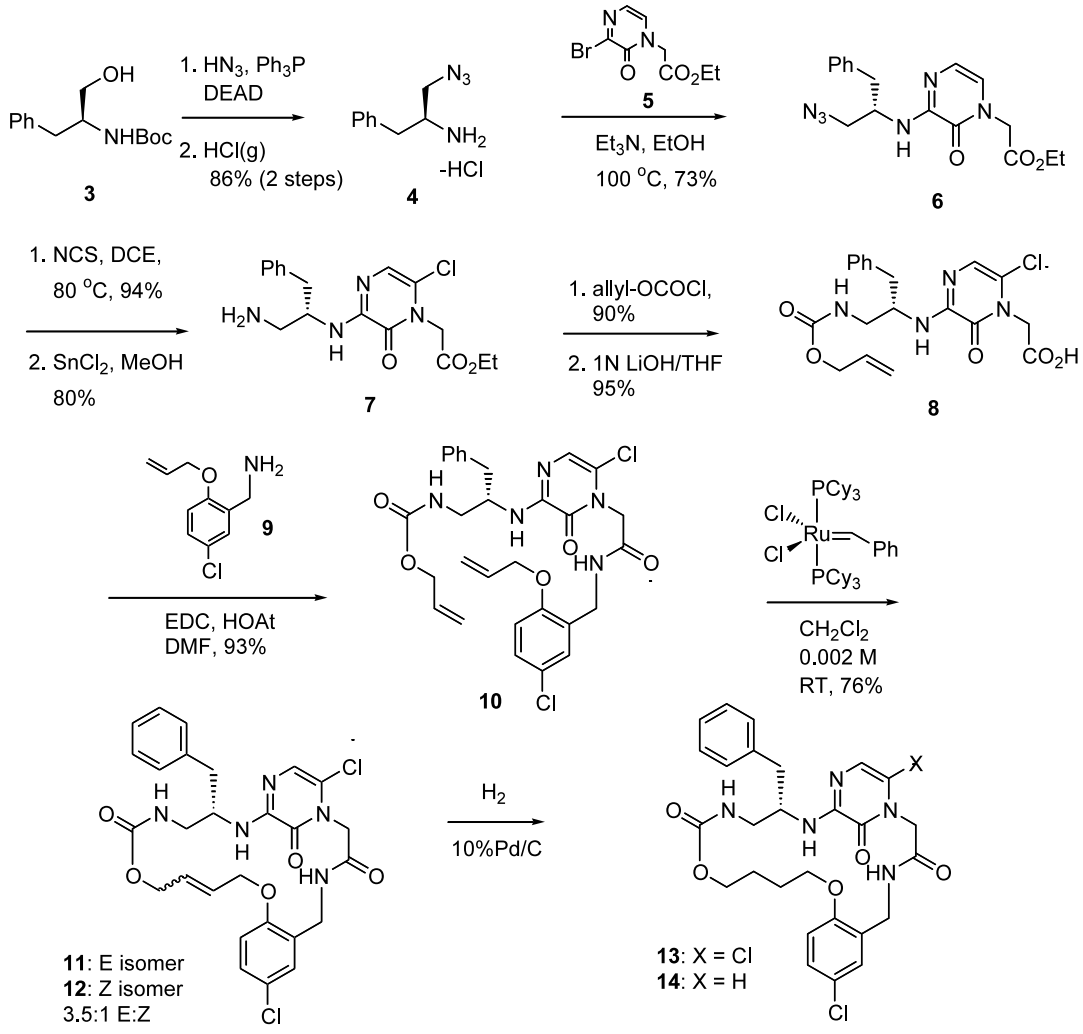


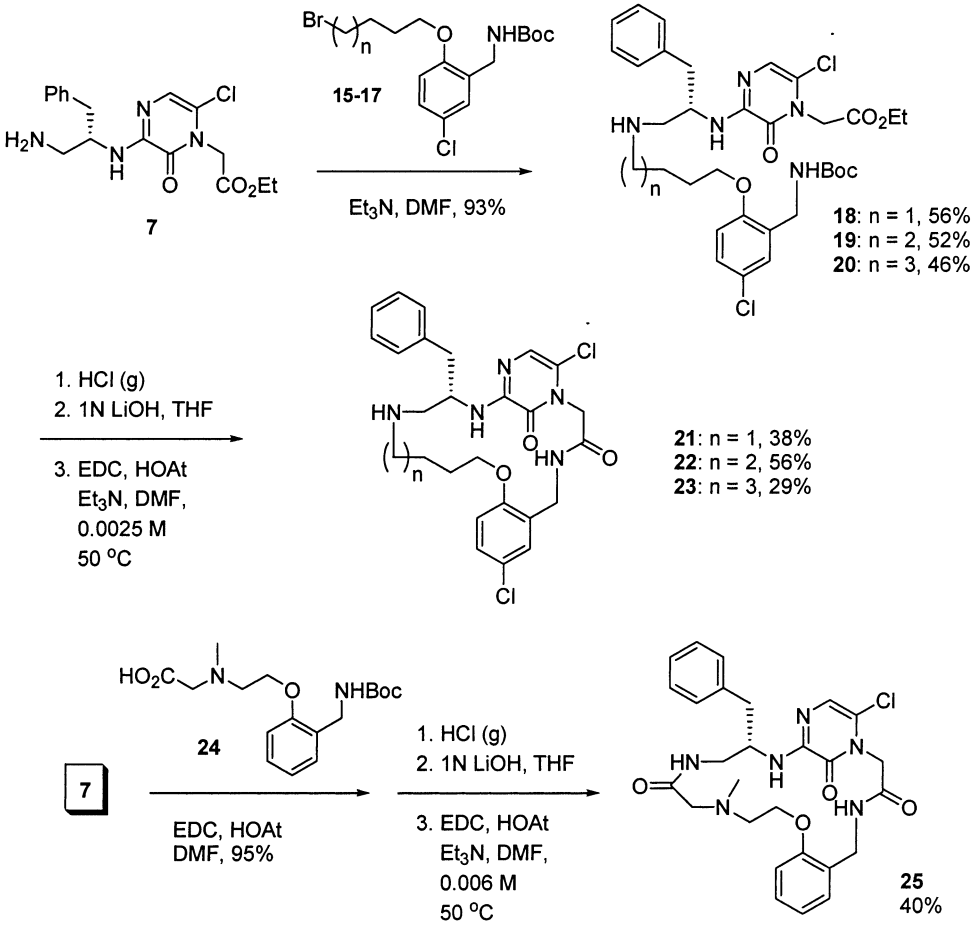
Scheme 1.

dichloromethane (0.002 M) at room temperature, overnight, resulted in the formation of macrocycles **11** and **12** in a 3.5:1 *E*:*Z* ratio and in 76% isolated yield.[11] This amounts to a fairly impressive result considering the functional complexity of the system and the presence on the substrate of various chelating and basic groups which could immobilize the metal–substrate complex in a non-productive conformation. The ease of cyclization could, however, be in part due to substrate preorganization via internal H-bonding. Catalytic hydrogenation with Pd/C under 1 atm hydrogen allowed for the preparation of the saturated macrocycles **13** and **14**.[12]

As a comparison to the metathesis strategy, Scheme 2 illustrates a more conventional mode of macrocyclization via the formation of an amide bond. Amine **7** was coupled to bromides **15**–**17**[9] to provide intermediates **18**–**20** which display tethers of 4–6 carbons length. Boc removal, ester hydrolysis and macrolactamization using EDC/HOAt conditions in DMF (0.0025 M) at 50°C, overnight, lead to the formation of macrocycles **21**–**23** in 38, 56 and 29%, respective isolated yields.[13] In a similar system, attachment of the sarcosine containing P_1–P_4 group **24**[9] to **7** followed by deprotection and macrolactamization under similar conditions as for compounds **21**–**23**, provided macrocycle **25** in 40% isolated yield. Assuming that both the Boc removal and ester hydrolysis steps were nearly quantitative in each of these examples, macrolactamizations occurred in 29–56% yield suggesting that the more traditional macrolactamization strategy is less efficient than the olefin metathesis approach, at least in this case.

Macrocycles **11**–**14**, **21**–**23** and **25** were found to be potent and selective thrombin inhibitors with K_i against the enzyme in the single digit nanomolar to subnanomolar range.[14]

The results shown in this letter suggest that the Grubbs olefin metathesis ring closure strategy is more efficient than the conventional macrolactamization approach. The facility by which this 20-membered ring cyclization of a rather densely functionalized molecule occurs is yet another tribute to the synthetic utility of the olefin metathesis reaction.



Scheme 2.

Acknowledgements

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9. Obtained from the alkylation of the corresponding phenol. US Patent, US 5,792,779, issued Jun. 8, 1998.
10. Bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride, 20 mol%, 0.002 M.
11. Compound **11**: ^{1}H NMR (CD_3OD+$CDCl_3$, 400 MHz): δ 7.83 (bt, $J=5.2$ Hz, 1H); 7.36–7.10 (m, 7H); 6.83 (s, 1H); 6.82 (d, $J=9.2$ Hz, 1H); 5.89 (A of ABX, dt, $J=16$, 4 Hz, 1H); 5.80 (B of ABX, dt, $J=16$, 4.5 Hz, 1H); 5.16 (A of AB, d, $J=16$ Hz, 1H); 4.56–4.29 (m, 6H); 4.29 (B of AB, d, $J=16$ Hz, 1H); 3.60 (A of ABX, dd, $J=14$, 3.6 Hz, 1H); 3.11 (B of ABX, dd, $J=14$, 8.4 Hz, 1H); 2.99–2.82 (m, 2H). HRMS ES calculated for $C_{27}H_{27}Cl_2N_5O_5$: 572.1462, found 572.1471. Compound **12**: ^{1}H NMR (CD_3OD+$CDCl_3$, 400 MHz): δ 7.32–7.12 (m, 7H); 6.89 (d, $J=7.8$ Hz, 1H); 6.85 (s, 1H); 5.80 (dt, $J=11$, 5.2 Hz, 1H); 5.64 (dt, $J=11$, 6.7 Hz, 1H); 4.96 (A of AB, d, $J=16.3$ Hz, 1H); 4.69–4.52 (m, 3H); 4.46 (B of AB, d, $J=16.3$ Hz, 1H); 4.29–4.20 (m, 1H); 4.16–4.07 (m, 1H); 3.50–3.41 (m, 1H); 3.21–3.12 (m, 1H); 2.96 (A of ABX, dd, $J=14$, 7.4 Hz, 1H); 2.79 (B of ABX, dd, $J=14$, 7 Hz, 1H). HRMS ES calculated for $C_{27}H_{27}Cl_2N_5O_5$: 572.1462, found 572.1469.
12. Compounds **13** and **14** were isolated in a 1:1 ratio. It should, however, be possible to alter this ratio and perhaps eliminate the formation of **14** by modifying the reaction parameters such as the nature of the catalyst (rhodium for example) and reaction time.
13. Compound **21** (dihydrochloride): ^{1}H NMR (d_6-DMSO, 400 MHz): δ 8.78 (bs, 2H); 7.82 (bs, 1H); 7.68 (d, $J=8.5$ Hz, 1H); 7.40–7.15 (m, 7H); 7.00 (d, $J=7.9$ Hz, 1H); 6.92 (s, 1H); 4.85 (bd, $J=15$ Hz, 1H); 4.60 (bs, 2H); 4.40 (bd, $J=15$ Hz, 1H); 4.05–3.95 (m, 1H); 3.95–3.60 (m, H count obliterated by residual water); 3.42–3.28 (m, 1H); 3.05–3.15 (m, 1H); 3.15–2.80 (m, 3H); 2.80–2.65 (m, 1H); 1.80–1.55 (m, 2H); 1.55–1.45 (m, 1H); 1.45–1.30 (m, 1H). HRMS ES calculated for $C_{26}H_{29}Cl_2N_5O_3$: 530.1720, found: 530.1737. CHN calculated for $C_{26}H_{29}Cl_2N_5O_3$+ $0.4H_2O$+2HCl: C, 51.14; H, 5.25; N, 11.47; found: C, 51.13; H, 5.34; N, 11.13%. Rotation: $[\alpha]_d=-15.4°$ (c 0.21, MeOH).
14. Full details to be published elsewhere in due time.