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Authors: Ben Schurgers, Johan Wouters, An De Blieck, Christel Menet, Guy Van Lommen, and Guido Verniest

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Regio- and diastereoselective functionalization of 3-amino-hexahydrooxazoninones


Abstract: The regio- and diastereoselectivity of transformations of nine-membered lactams with a Z-double bond in the cyclic tether towards novel building blocks for medicinal chemistry was evaluated. To this end, 3-amino-hexahydrooxazoninones were synthesized using a standard ring closing metathesis (RCM) approach of easily available O,N-bisallylated serine derivatives. The obtained Z-double bond in the medium sized lactam was used as a handle to evaluate the stereoselectivity of electrophile induced transformations. It was shown that dibromination and electrophilic activation by NBS followed by attack of O-nucleophiles proceeded in a diastereoselective manner. Cyclization of obtained bromohydrins and face-selective epoxidation gave access to both diastereomers of the epoxidized lactams. Finally, a Heck-reaction of a bromobenzyl moiety at the lactam N-atom with the Z-double bond resulted in the diastereoselective formation of novel bicyclic bridged 9-membered lactams.

Introduction

The use of medium-sized ring structures, in particular nine-membered heterocycles, is not very widespread in medicinal chemistry. Although these types of substituted ring systems can offer additional value in terms of conformational orientation of key substituents as well as in terms of creating novel IP space, the chemistry of nine-membered lactams is still underdeveloped.[1,2] This is partly because of an often difficult synthesis due to entropically disfavoured ring closure reactions and the relatively high Prelog, Baeyer and Pitzer strain,[3] and also because the limited amount of experimental data that demonstrate post-cyclization modifications of nine-membered ring systems.[4] However, some examples of beautiful syntheses and selective transformations have shown the synthetic potential of such strained rings.[5] As examples, azoninones bearing E-olefins have been synthesized viaaza-Claisen rearrangements and display planar chirality which was used to transfer chirality in transannular reactions.[6] Also nine-membered lactams with a Z-double bond have been synthesized[7] and used in diastereoselective transannular cyclizations towards bicyclic amino acid derivatives.[8] The often observed high stereoselectivity in functionalizations of nine-membered ring systems (including carbocycles or lactones) arises from the specific conformational preferences of the intermediate transition states, directed by both steric and electronic factors.[8,9] With respect to electrophilic additions to double bonds, reaction generally occurs at the most exposed face of the double bond as depicted in Figure 1.[10] For planar chiral E-norones as well as for Z-isomers, both diastereomeric reaction products are possible but highly selective transformations have been described as exemplified in Figure 1.[10-12] The difficulty in predicting the stereochemical outcome with nine-membered rings lies in the fact that subtle changes in the ring substituents can alter significantly the reactive conformation and hence reaction outcome.[3] For instance, it has been shown that a change from a N-acyl to an N-benzoyl amide substituent changes the cis-trans geometry of the amide moiety in nine-membered lactams[11] and that diastereoselective dihydroxylation of substituted 3-propylcycloclonon-1-enes occurs at the opposite side (cis to the propyl, see Fig 1.) as initially assumed.[12] These examples highlight that, while the stereoselectivity of reactions with 8- and 10-membered rings can often be predicted in a reliable manner,[13] this is less general for substituted nine-membered rings. Therefore, the experimental exploration of double bond transformations in unsaturated nine-membered amides can deliver new insights for the development of diastereoselective methods towards novel nine-membered ring compounds.

Figure 1. Selected examples of diastereoselective double bond transformations in unsaturated 9-membered rings.

Results and Discussion

For the preparation of novel 3-amino-oxazoninones 3 (scheme 1) via RCM, α,ω-dienic amides 2 were synthesized by coupling of O-allylserines 1 with amines using (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo-
[4,5]-bipyridinum-3-oxide hexafluorophosphate (HATU) as reported coupling agent. Optimal conditions included the treatment of the serine derivatives 1 with HATU and Et3N in DMF at 0°C before adding amines. Next, the evaluation of the ring closing metathesis towards 9-membered lactams 3 using diene 2c (Table 1) was performed. The use of 10 mol% of either Grubbs 2nd generation (GII) or Grubbs–Hoveyda 2nd generation (G-HII) catalyst in refluxing CH2Cl2 (entry 1 and 3) resulted in poor conversion or in the formation of side products when the reaction times were increased (entry 2 and 4). According to LCMS-analysis, the formation of oligomers and structural isomers of 2c and 3b was observed but these side products could not be isolated. Heating the reaction mixture to 70°C in 1,2-dichloroethane (entry 6) gave higher conversions, but still a considerable amount of oligomers was formed. Again, also at these temperatures, longer reaction times resulted in the formation of more side products (entry 7). To maximize the formation of 3b, a limited reaction time combined with 2 subsequent additions of 5 mol% G-H II catalyst was required (entry 8). It should be noted that after the reaction was completed, a catalyst denaturated step was required to avoid metathesis side reactions during concentration and work-up. This was done by adding 10 equiv of Et3N before extractive work-up and concentration. Attempts to lower the reaction temperature resulted in poor conversion (entry 9), or an increase in side products (entry 10).

It should be noted that RCM did not work in our hands using dienes and 4-membered lactams – although free amine to give 3 in the presence of HATU was observed but merely highlight the observed trends.

Applying the optimized RCM reaction conditions to diene precursors 2 gave rise to a collection of 9-membered rings 3a-g in low to moderate yields over 7–9 h (Scheme 1). It should be noted that RCM did not work in our hands using dienes 2b and 2e where X = Cl or X = Me. Reactions at elevated temperatures in toluene (110°C) and/or using higher catalyst loadings only resulted in starting material and side products. Because of these results and the results obtained from earlier work on RCM towards related 7-membered lactams, it is suggested that the presence of a vinylic substituent in these kinds of substrates creates to much steric congestion for RCM to proceed. The Z-stereochmistry of the double bond was proven via X-ray analysis. Chiral derivatization of the resulting 9-membered rings followed by HPLC-MS analysis indicated that racemization occurred during RCM. N-Deprotection and coupling of the resulting free amine of 2c to Marfey’s reagent (1-fluoro-2,4-dinitrophenyl-5-L-alanine amide, FDAA) resulted in the corresponding diastereomer and giving one signal in HPLC, while a similar FDA coupling to a mixture of 2c and 2d gave two separate signals. In contrast, after the ring closure, an analogous LC-MS analysis of the FDAA coupled 3b showed the presence of two diastereomers and indicated that racemization occurred during RCM and not during synthesis of compounds 2. The racemisation is the result from either the instability of the starting substrates, of the end product or the combination of both under the used conditions. Because attempts to decrease the reaction temperature unfortunately resulted in low conversions (Table 1, entries 9 and 10), no further studies were performed and following reactions using the lactams were performed on the racemic mixtures.

To demonstrate the potential use as building block for medicinal chemistry purposes, additional functionalisations of 3c were performed using the 3-aminogroup as a handle. At first, TFA mediated N-Boc deprotection was followed by acylation of the resulting free amine to give 3-(acylamino)oxazinones in moderate to good yields via treatment with the corresponding acid in the presence of HATU. Next, functionalization of the double bond in oxazinones was explored to provide an extra

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**Scheme 1. Synthesis of (Z)-3-aminohydroxyoxazinones 3a-j via RCM.**

**Table 1. Evaluation of RCM of 2c to 3b.**

<table>
<thead>
<tr>
<th>Cat.</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>Conv. (%)</th>
<th>3b</th>
<th>2e</th>
<th>3b</th>
<th>3b isomer</th>
<th>Oligomers</th>
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<tr>
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<td>GII&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Δ</td>
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<tr>
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<td>GII&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>23</td>
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<td>51</td>
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<tr>
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</table>

Reactions performed in dichloroethane (entries 6-10) or CH2Cl2 (for entries 1-5) at 2.10<sup>3</sup> mol L<sup>-1</sup>, [10 mol%], [25 mol%] x 5 mol%, <sup>4</sup> percentages are given as area% based on UV response (HPLC) and are therefore not actual molar distributions but merely highlight the observed trends.
derivatisation handle. It should be noted that (diastereoselective) functionalisations of double bonds in nine-membered rings are not widespread and that extra experimental data can give further insight in the reactivity profile of such compounds. Treatment of oxazoninone 3c with N-bromosuccinimide (NBS) in MeOH at 0°C and stirring at room temperature for two hours resulted in the formation of two isomers (ratio 4:1) of which only the major isomer was isolated by crystallization to give methoxyminated nine-membered lactam 7a in 68% yield. X-Ray analysis of crystals unambiguously demonstrated the diastereoselectivity of the reaction.\(^{15}\) Apparently, the Boc-amino substituent forces the nine-membered ring in a conformation in which the initial bromonium complex is formed at opposite side of the Boc-amino substituent (possibly as chair-boat conformation as shown in Scheme 2) and where subsequent attack of the nucleophile occurs remotely from the N-Bn substituent. A related reaction using NBS in dioxane/H\(_2\)O resulted in bromohydrins 7b,c in good yield. Again, good regional and diastereoselectivity was obtained as the isolated products represented more than 80% of the reaction mixture as indicated by HPLC/MS. Also, a direct bromination of the double bond of 3b using Br\(_2\) yielded dibrominated compound 4 as a single diastereomer. To obtain both diastereomeric epoxides 6 and 8 (Scheme 2), direct epoxidation and ring closure from bromohydrins were evaluated. Whereas the reaction of 3b,c with meta-chloroperbenzoic acid (mCPBA) in CH\(_2\)Cl\(_2\) was low yielding, the treatment with Oxone® in a H\(_2\)O/acetone mixture at 0°C nicely gave rise to only one (racemic) diastereomer in good isolated yields. Prolonged reaction times resulted in the formation of the corresponding diols via attack of water. To prepare the other epoxide diastereomer, bromohydrin 7c was treated with K\(_2\)CO\(_3\) in CH\(_3\)CN at 60°C for 4 h. This resulted in a clean conversion to epoxide 8 in very good yield.

To provide an example of a saturated nine-membered analogue, the double bond was hydrogenated easily without removal of the benzyl protecting group.

In a next approach, an intramolecular Heck reaction was envisaged using bromoarylated structures 3c and 3f towards bridged oxazoninones. Treatment of 3c with Pd(PPh\(_3\))\(_4\) in the presence of K\(_2\)CO\(_3\) in DMF at 150°C (µ-wave) resulted in the clean formation of 10a after 90 minutes. The position of the resulting double bond originates form the β-hydride elimination step, which can only occur with a proton next to the oxygen in the 9-membered ring due to the cis-requirement (see intermediate 9). When applying similar reaction conditions on 3f almost no reaction was observed. It was found that the use of dioxane greatly improved the reaction outcome, leading to the respective oxazinonones 10. Because of possible stability problems of the enol ether, it was decided to not isolate and purify the formed compounds 10, but reduce the double bond directly. Gratifyingly, treatment of 10 with H\(_2\) in the presence of Pd on carbon cleanly transformed the enol ether into the saturated fused oxazoninones 11. Cyclizations of this type are rare, but are have been used before on related structures to synthesize the natural product cleavamine, which also contains a bridged nine-membered azaheterocycle core structure.\(^{17}\)

**Conclusions**

In conclusion it can be stated that a successful synthesis was developed towards 3-aminohexahydrooxazinones containing a Z-double bond using a standard ring closing metathesis (RCM) approach of easily available O,N-bisallylated serine derivatives. These compounds proved useful in electrophile induced transformations of the double bond showing high regio- and diastereoselectivity. Cyclization of obtained bromohydrins and face-selective epoxidation gave access to both diastereomers of the epoxidized lactams. Finally, a Heck-reaction of a bromobenzyl moiety at the lactam N-atom with the Z-double bond resulted in the diastereoselective formation of novel...
bicyclic bridged 9-membered heterocycles. Given the rising importance of medium-size ring compounds, the obtained scaffolds are not only of interest as building blocks for medicinal chemistry purposes, but the obtained insights are also of value to further map the reactivity of unsaturated nine-membered ring.

Experimental Section

Column chromatography purifications were conducted on silica gel 60 (40–63 μm; Grace Davison) or with a Grace Reveleris X2 Flash Chromatography System on silica gel (prepacked 40 μm; Grace Reveleris) or C18 silica gel (prepacked 40 μm, Grace Reveleris). TLC was carried out on glass plates precoated with silica gel 60F254 (Merck); the spots were visualized under UV light (λ = 254 nm) and/or KMnO4 (aq.) was used as the revealing system. Preparative HPLC was conducted using a Gilson semi-preparative HPLC equipped with a Supelco Discovery Bio Wide Pore C18 column (250 mm × 10 mm, 5 μm). Samples were analyzed on an Agilent 1100 Series HPLC.

Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (J) are given in Hz (Hz). High resolution mass spectrometry was conducted on a Waters Micromass QToF in ESI mode using as reprecipitate as the reference. Reactions using microwave irradiation were performed in a Biotage Initiator microwave reactor (at 75 W). X-ray diffraction data were collected at room temperature on a Gemini Ultra (Rigaku) diffractometer using Cu Kα (λ = 1.5418 Å) radiation.

Synthesis of (Z)-3-aminohexahydropyrazine 3

A representative procedure is given by the synthesis of 3c. In a flame flask, tert-buty1 1-(allyl(2-bromobenzyl)amino)-3-(allyloxy)-1-oxopropan-2-ylcarbamate (1 equiv., 2.21 mmol, 1.0 g) was dissolved in commercially available dichloromethane (DCM; 2 L [2 mL] and degassed with N2). To this solution was added the Grubbs-Hoveyda II catalyst (0.05 equiv, 0.11 mmol, 70 mg) and the reaction was heated to 65°C under nitrogen atmosphere for 4 h. Another 0.05 equiv of catalyst was added and refluxing was continued for 4 h. The reaction mixture was allowed to cool to room temperature, after which triethylamine (0.8 equiv, 1.10 mmol) (400 μL) was added. This mixture was stirred for 16 h at room temperature and the solvent was removed under reduced pressure. The resulting crude mixture was purified by silica gel chromatography. Purification of the crude was done by silica gel chromatography using petroleum ether/EtOAc (8:1 to 6:1) to yield the title compound as a slightly brown oil, which solidified on standing (45% yield).

Synthesis of bridged compounds 11.

A representative procedure is given for the synthesis of tert-butyl [10-oxo-13-oxa-9-azatricyclo[7.6.1.026]3]hexadeca-2,4,6,8-tetra-11-yl]carbamate 11a. In a microwave vial, bromide 3e (1 equiv., 0.36 mmol, 150 mg) was dissolved in a suspension of K2CO3 (2.5 equiv, 0.911 mmol, 120 mg) in degassed (N2) DMF (20 mL) (0.01 M). Pd(PPh3)4 (0.05 equiv, 0.018 mmol, 20 mg) was added and the vial was sealed under an N2 atmosphere. The reaction mixture was heated in a microwave reactor for 60 minutes at 120°C (75 W). The solvent was evaporated under reduced pressure and the resulting crude mixture was purified by silica gel chromatography using 12% EOA in petroleum ether to give 10a in 60% yield as a slightly brown oil which solidified upon standing. The obtained 10a (1 equiv., 0.382 mmol, 145 mg) was dissolved in MeOH (4 mL, 0.1 M). Palladium on carbon (0.1 equiv, 0.038 mmol, 50 mg) was added and the reaction mixture was brought under 1 atm H2. After stirring for 7 h at room temperature, CH3OH (3 mL) was added and the mixture was filtered over a plug of silica gel using petroleum ether/EtOAc (8:1 to 6:1) to yield the title compound as a transparent oil in 90% yield (126 mg). IR (ATR) 3426, 2944, 1712, 1648, 1416, 1350 and 1156 cm−1; 1H NMR (500 MHz, CDCl3) δ = 1.47 (s, 3H, CH3), 1.46–1.57 (m, 1H, CH2CH2CH2), 1.82–2.18 (m, 1H, CH2CH2CH2CH2), 3.03 (dd, J = 10.7 Hz, J = 12.5 Hz, 2H, OCH2), 3.37 (d, J = 12.8 Hz, 1H, NCH3), 3.39 (d, J = 12.5 Hz, 1H, NCH3), 3.40 (d, J = 12.5 Hz, 1H, NCH3), 3.59 (dbr, J = 15.1 Hz, 1H, OCH3), 3.96 (d, J = 15.1 Hz, 1H, OCH3), 3.97 (d, J = 15.1 Hz, 1H, OCH3), 3.99 (d, J = 13.8 Hz, 1H, OCH3), 4.40 (d, J = 13.8 Hz, 1H, OCH3), 4.89–4.97 (m, 2H, CH2CH2CH2), 4.98 (m, 2H, CH2CH2CH2), 5.07 (m, 2H, CH2CH2CH2), 5.17 (m, 2H, CH2CH2CH2), 5.22 (d, J = 13.8 Hz, 1H, OCH3), 5.25–5.39 (m, 2H, CH2CH2CH2), 7.13–7.33 (m, 3H, CH3, CH2), 7.56 (dd, J = 1.0 and 8.5 Hz, 1H, CH=), ppm; 13C NMR (126 MHz, CDCl3) δ 28.3 (3 CH3), 34.1 (CON-CH2), 48.2 (CON-CH2), 51.9 (Cz), 69.5 (CH=O), 73.1 (CH=O), 77.0 (CCl3), 123.8 (Br-Cz1), 126.7 (CH=CH), 127.8 (CH=CH), 129.0 (CH3), 129.2 (CH3), 132.2 (CH2CH=), 135.6 (CCl3), 155.0 (CCl3), 170.9 (CCl3) ppm; HRMS calculated for [C10H7O2N2] +: 247.0840 and 247.0857.

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Keywords: Medium-ring compounds; Heck reaction; Metathesis; Cyclization; Diastereoselectivity.


Nine-membered 3-aminohexahydrooxazinones containing a Z-double bond in the cyclic tether were prepared via RCM and subjected to electrophile induced transformations, giving rise to diastereoselective bromination, alkoxybromination and epoxidation. These results can give new insights into the influence of nine-membered ring conformation on reaction selectivity.

*one or two words that highlight the emphasis of the paper or the field of the study