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The synthesis of 12-membered macrocycles containing a C1–C8 alkene unit via ring-closing metathesis

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This work is dedicated to Professor Dr. Christian Bruneau on the occasion of his 60th birthday

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1. Introduction

The renin-angiotensin system,¹ known to regulate blood pressure, has been the target of studies leading to the discovery of angiotensinconverting enzyme inhibitors² and angiotensin II receptor blockers.³ Due to its role in the enzymatic cascade, leading to the ultimate release of vasoconstricting peptides, renin was considered as an important target to prevent hypertension. Thorough, structure-based design research revealed a number of potent inhibitors of renin.⁴ However, because none of the peptide-like renin inhibitors survived all the stages of drug development, there was a need for new classes of nonpeptide renin inhibitors that fulfill all the criteria for becoming a successful drug. Researchers designed a new class of hydroxyethylene-based renin inhibitors that lack the peptide backbone.⁵ From this research, the nonpeptide compound, [2(S),4(S),5(S),7(S)-N-(carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropiyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl] octanamide] (aliskiren)⁶ emerged as a potent renin modulator, exhibiting a sub-nanomolar binding affinity to human renin and oral

ABSTRACT

Model cross and ring-closing metathesis strategies toward the C1–C8-linear carbon skeleton are presented. The introduction of a four-atom tether enables the formation of 12-membered rings in good-toexcellent yields and stereoselectivity. Furthermore, the study revealed that the cross-metathesis approach and the formation of medium ring sizes via ring-closing metathesis are much less favorable. © 2012 Elsevier Ltd. All rights reserved.

> administration properties. The first synthesis toward renin inhibitors applied a convergent synthetic strategy via coupling of the enantiopure Grignard reagent and diastereomerically pure γ -lactone.⁷ Dondoni et al. described the synthesis of the renin inhibitor SPP-100 involving the addition of the Grignard reagent to a nitrone intermediate.⁸ Furthermore, Hanessian et al. developed a stereocontrolled approach to CGP-60536B, a potent renin inhibitor, in which the entire carbon skeleton of the target molecule was incorporated in a partially functionalized bicyclic indolizidinone precursor.⁹ Later on Skrydstrup et al. explored an alternative coupling strategy for the preparation of the hydroxyethylene isostere-based class of protease inhibitors.¹⁰ A similar methodology was applied for a SmI₂-promoted acyl-like radical addition reaction between an amino acid^{11a} or *N*-acyl oxazolidinones^{11b} with substituted acrylates and acrylamides as a key step to the synthesis of the potent renin inhibitor, aliskiren. An asymmetric hydrogenation process for the preparation of the aliskiren intermediate has been developed using ligated rhodium and ruthenium catalysts.¹² Recently, Hanessian et al. described a total synthesis of aliskiren, a strategy relying on the ring-closing metathesis reaction, producing the nine-membered lactone as a key intermediate in an excellent yield.¹³ Furthermore, novel nonpeptide small-molecule renin inhibitors bearing an N-isopropyl P₁ motif were discovered based on an initial lead structure and aliskiren.¹⁴





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We now report a model study to generate 12-membered macrocycles containing an unsaturated C1–C8 unit by ring-closing metathesis.

2. Results and discussion

As a part of our efforts toward the synthesis of aliskiren analogues, we envisioned that their C8-linear carbon skeleton **A** could be assembled via the metathesis synthetic step due to the existing symmetry in the chain structure (Scheme 1).



Scheme 1. Retrosynthetic pathway for the construction of the C8-linear carbon framework A.

Initially, the cross-metathesis reaction (CM) of two differently functionalized pentenes was undertaken. Thus, reacting the ketone **1** and alcohol **2** (in a 2-fold excess) in the presence of the H-G(II) catalyst in refluxing dichloromethane resulted in the formation of the asymmetric dimer **3** in a disappointing yield of 36%, mostly at the expense of side products arising from isomerization and homocoupling of the starting materials (Scheme 2).



As the above described metathesis reaction led to the low yield of the cross-coupling product, an alternative approach to the construction of the C1-C8-carbon unit, being incorporated in a cyclic structure, by employing a ring-closing (RC) metathesis reaction was attempted. We started our metathesis approach from readily available anhydrides 4 (Scheme 3) that were prepared from the corresponding pent-4-enoic acids in good yields. Once formed, the cyclic anhydrides 5 would be suitable for further desymmetrization with different nucleophiles, thus directly leading to the C1-C8 fragment. However, attempted RCM reactions of 4, employing different reaction conditions and ruthenium catalysts (Grubbs catalyst second generation, Hoveyda-Grubbs second generation, and tricyclohexylphosphine[3phenyl-1*H*-inden-1-ylidene][1,3-bis(2,4,6trimethylphenyl)-4-5dihydroimidazol-2-ylidene]ruthenium(II) dichloride), did not produce the desired cyclic anhydrides 5. The reaction led to dimeric, cyclicdimeric, and oligomeric species as indicated by the mass spectrometry. Upon hydrolysis of the crude metathesis reaction mixture we were able to isolate the dicarboxylic acids **6a** and **6b** in reasonable vields and satisfactory stereoselectivity regarding the newly formed carbon-carbon double bond.

Rao et al.¹⁵ reported an elegant synthesis of topsentolide B_3 involving an RCM synthetic step for the formation of the substituted nine-membered lactone ring, having a carbon–carbon double bond at position 5. Encouraged by these results we first tested the cyclization of model diene **7** (Scheme 4) catalyzed by the Hoveyda–Grubbs second-generation catalyst (H–G(II), 2.5 mol % in refluxing dichloromethane). The corresponding nonalactone **8** was



isolated in a modest yield of 43%.¹⁶ It is worth mentioning that applying the first-generation Grubbs catalyst did not result in the formation of nonalactone **8**. It has been noted that the site of the ring closure in the formation of 12- to 21-membered macrocycles by the RCM reaction may influence the reaction outcome.¹⁷ We speculated that a low yield of the cyclization reaction affording the nonalactone **8** might be due to the formation of a regioisomer having a carbon-carbon double bond at position 4 instead of 5, if compared to the successful formation of topsentolide B₃. To investigate this hypothesis we evaluated the cyclization formpound **9** (Scheme 4), applying the same reaction conditions. The isomeric nonanolactone **10** was isolated in a similar yield of 32%.



Scheme 4. RCM of simple nonanolactone ring precursors.

According to the results of Rao et al., and Hernández-Galán et al.,¹⁸ and our own observations we can conclude that highyielding cyclization in the synthesis of topsentolide B₃ most probably results from the conformational restraints, the Thorpe–Ingold effect,¹⁹ originating in the side chain of topsentolide B₃ and is apparently not related to the position of the carbon–carbon double bond in the final lactone ring.

However, the concept of tethering in intermolecular olefin metathesis (i.e., CM) has proved to be beneficial and is a wellestablished synthetic strategy. This approach also addresses two major drawbacks of the CM strategy, i.e., E/Z stereoselectivity and an excess of one of the reaction partners in the process. A temporarily installed unit connecting two fragments enables the formation of different ring sizes and can be disposed of from the system after the completion of the desired transformation. The selection of a disposable unit is based on the nature of the substrates and the applied reaction conditions in the specific transformation. The tethering unit should be stable during the synthetic operations and should be a functional group that is compatible with the catalytic system.

In due course we oriented toward the RCM for the preparation of larger ring systems and subsequently synthesized dihydrazide **11** (Scheme 5) in which two identical five-carbon units are tethered via 1,2-dimethylhydrazine, which served as a model substrate for the formation of the 10-membered ring.



Scheme 5. RCM reaction forming 10-membered heterocycle 12.

Three different ruthenium metathesis catalysts (Grubbs' catalyst second generation, Hoveyda–Grubbs second generation, and tricyclohexylphosphine[3-phenyl-1*H*-inden-1-ylidene][1,3-bis(2,4,6trimethylphenyl)-4-5dihydroimidazol-2-ylidene]ruthenium(II) dichloride) were examined in the cyclization of **11** to **12**. Among them, the Hoveyda–Grubbs second generation catalyst (2.5 mol %) proved to be the most efficient, but still the product **12** was isolated in a low yield (Scheme 5). However, not every ring size is accessible with the same efficiency because of enthalpic (increasing strain in the transition state) and entropic influences (probability of the chain ends meeting) on the cyclization process. Consequently, medium-sized rings are generally difficult to prepare.²⁰

Next we considered a complementary route to a subunit of type **A** (Scheme 1), starting from acyclic diester or amido-ester precursors **13**. The RCM reaction of dienes **13** containing a four-atom tether would afford 12-membered rings for the control of the *E*-configuration of the newly formed double bond. Disposal of a tethering unit from the RCM generated rings would directly lead to framework **A**.

Using glycol as a tether made it possible to test whether the approach to the C1-C8-linear carbon framework through 12membered rings is more feasible. Apart from the glycol and aminoethanol tether-based RCM we introduced a 1,2-dihydroxybenzene (catechol) tether to assist the RCM strategy. Thus, the unsubstituted dienes **13a–c** smoothly underwent the RCM in the presence of the H-G(II) catalyst (2.5 mol%, CH₂Cl₂, 40 °C) and the corresponding unsaturated 12-membered heterocyclic rings were formed in goodto-excellent yields (Table 1, entries 1-3). Additionally, o-aminophenol and o-phenylenediamine were introduced as a link to expand the tethering options in the studied system. The substrates 13d and 13e were also successfully cyclized to the 12-membered rings in a 90% isolated yield for 14d and 94% for 14e, respectively (Table 1, entries 4 and 5). Similar results were obtained using the iso-propyl substituted analogues 13f and 13g. In all cases the mixtures of E/Z-isomers in a ratio of 10:1 were observed.

In order to establish the configuration of the major isomer in products **14** we prepared a single crystal of compound **14b** suitable for X-ray analysis,²¹ which together with ¹H, ¹³C, and NOESY NMR spectroscopy confirmed the *E*-isomer to be the major one in all cases. Different shieldings of the allylic carbons in the olefin structures could be significant for trans and cis isomers, as is evident in linear structures.²² Namely, we have observed a systematic upfield shift for the allylic carbons in cis isomers **14** compared to *trans*-**14**.

Finally, we validated the ring opening reaction of the macrocycles **14**. Thus, the ester functionality of **14d** was selectively hydrolyzed by using LiOH in ethanol/water mixture leading to the bifunctional C1–C8-linear alkene **15** in an excellent yield of 96% (Scheme 6).

Table 1

Synthesis of 12-membered rings 14 with a C8 unit A^a



^a Reaction conditions: Hoveyda–Grubbs second-generation catalyst (2.5 mol %), DCM, reflux, 5–25 h.

 $^{\rm b}$ The ratio of E/Z was determined by ^{1}H NMR spectroscopy and was found to be 10:1 in all cases.

^c Yields of pure isolated products are given.

In conclusion, model ring-closing metathesis strategies toward the C1–C8-carbon skeleton have been presented. The introduction of a four-atom tether enables the formation of 12-membered rings in good yields and stereoselectivity with E-isomer being the major



Scheme 6. Opening of macrocycle 14d.

one. Furthermore, the presented study revealed that the CM approach and the formation of medium ring sizes via RCM are much less favorable, compared to the formation of 12-membered systems **14**. The selective base hydrolysis of the macrocycle **14** led to the asymmetric C1–C8-linear alkene skeleton.

3. Experimental section

3.1. General information

All non-aqueous reactions were run in flame-dried glassware under a positive pressure of argon with exclusion of the moisture from reagents and glassware using standard techniques for manipulating air-sensitive compounds. Anhydrous solvents were obtained using standard drying techniques. Unless stated otherwise, commercial-grade reagents were used without further purification. Reactions were monitored by analytical thin-laver chromatography (TLC) or reverse-phase HPLC. Visualization of the developed TLC chromatogram was performed by UV absorbance or aqueous potassium permanganate. Flash chromatography was performed on 230-400-mesh silica gel with the indicated solvent system. Yields refer to chromatographically and spectroscopically (¹H and ¹³C NMR) homogenous materials. Reverse-phase HPLC analyses were performed using C18 column (60×4.6 mm, 2 μ M) and water/acetonitrile gradient; UV detection at 254 nm. Melting points are uncorrected. Infrared spectra were recorded on an FTIR spectrometer and are reported in reciprocal centimeters (cm⁻¹) Routine nuclear magnetic resonance spectra were recorded either on a Bruker Avance DPX 300 or Avance III 500 MHz spectrometer. Chemical shifts for ¹H NMR spectra are recorded in parts per million (ppm) from tetramethylsilane as an internal standard. Data are reported as follows: chemical shift, number of equivalent nuclei (by integration), multiplicity, (s=singlet, d=doublet, t=triplet, q=quartet, qn=quintet, sext=sextet, sept=septet, m=multiplet, and br=broad), coupling constants (J) quoted in hertz to the nearest 0.25 Hz. Chemical shifts for the ¹³C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of the solvent resonance as an internal standard. All spectra were obtained with complete proton decoupling. High-resolution mass spectra were recorded on an Agilent 6224 Accurate Mass TOF LC/ MS instrument by electrospray ionization operating at a resolution of 15,000 full widths at half height.

3.2. Experimental procedures

3.2.1. 8-Hydroxy-1,2,7-triphenyloct-4-en-1-one (**3**). To the solution of ketone **1** (169 mg, 0.72 mmol) and alcohol **2** (233 mg, 1.44 mmol) in dichloromethane (10 mL) the Hoveyda–Grubbs second-generation catalyst (11 mg, 2.5 mol %) was added. The reaction mixture was refluxed for 24 h and then evaporated under reduced pressure. The residue, yellow oil, was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=20:1) yielding 96 mg (36%) of **3**; colorless oil, mixture of isomers=1:4; IR (NaCl, cm⁻¹) 3425, 3061, 3027, 2920, 1681, 1598, 1494, 1449, 699; ¹H NMR (300 MHz, CDCl₃) minor isomer: δ 1.54 (br s, 1H, OH), 2.19–2.48 (m,

3H, CH_2CH = in $CHCH_2OH$), 2.65–2.88 (m, 2H, CH_2CH =CH), 3.58–3.70 (m, 2H, H_2COH), 4.34 (t, J=7.3 Hz, 1H, CHCOPh), 5.26–5.30 (m, 2H, CH=CH), 7.09–7.48 (m, 13H, Ar), 7.88–7.91 (m, 2H, Ar); ¹H NMR (300 MHz, CDCl₃) major isomer: δ 1.54 (rs, 1H, OH), 2.19–2.48 (m, 3H, CH_2CH = and $CHCH_2OH$), 2.65–2.88 (m, 2H, CH_2CH =CH), 3.58–3.70 (m, 2H, H_2COH), 4.47 (t, J=7.3 Hz, 1H, CHCOPh), 5.34–5.38 (m, 2H, CH=CH), 7.09–7.48 (m, 13H, Ar), 7.88–7.91 (m, 2H, Ar); ¹³C NMR (75.5 MHz, CDCl₃) major isomer: δ 35.3, 37.0, 48.3, 54.0, 66.6, 126.6, 127.0, 127.9, 128.1, 128.42, 128.44, 128.6, 128.8, 129.4, 130.0, 132.8, 136.7, 139.1, 142.0, 199.3; m/z (EI⁻) 371 (MH⁺); HRMS (EI⁻): MH⁺, found 371.2014. C₂₆H₂₇O₂ requires 371.2011.

3.2.2. (2S)-2-Isopropylpent-4-enoic anhydride (4b). To the solution of (S)-2-isopropylpent-4-enoic acid²³ (**4a**) (1.0 g, 7.04 mmol) in dry dichloromethane (17 mL) the solution of N,N'-dicyclohexylcarbodiimide (0.747 g, 3.62 mmol) in dry dichloromethane (8 mL) was added over a period of 6 h. The reaction mixture was allowed to stir for an additional hour at room temperature. After the reaction was completed the reaction mixture was filtered and the solvent evaporated at 40 °C under reduced pressure. The residue was suspended in petroleum ether (30 mL) and cooled to -20 °C for 8 h. The precipitated material was filtered off and washed with petroleum ether (10 mL). The solvent was removed by evaporation under a reduced pressure at 40 $^\circ\text{C}$ and a colorless oily residue was distilled under vacuum. Yield 824 mg (88%). $[\alpha]^{25}_{Hg}$ +12.6 (c 5.0, CH₂Cl₂); IR (NaCl, cm⁻¹) 2965, 1811, 1744, 1643, 1466, 1371, 1032; ¹H NMR (300 MHz, CDCl₃) δ 1.00 (d, 6H, *I*=7.0 Hz, $-CH(Me)_2$), 1.01 (d, 6H, J=7.0, -CH(Me)₂), 1.97 (sym 7-line m, 2H, J=7.0 Hz, -CH(Me)₂). 2.25-2.41 (m, 6H, H₂C=CH-CH₂CH), 5.03-5.14 (m, 4H, H₂C= CH-), 5.71-5.85 (m, 2H, H₂C=CH-); ¹³C NMR (126 MHz, DMSO d_6) δ 19.3, 28.1, 30.4, 54.9, 115.6, 138.1, 170.9; m/z (EI⁺) 267 (MH⁺); HRMS (EI⁺): MH⁺, found 267.1963. C₁₆H₂₇O₃ requires 267.1960.

3.2.3. Oct-4-enedioic acid (6a). To the solution of pent-4-enoic anhydride (4b) (547 mg, 3.0 mmol) in dichloromethane (150 mL) the Hoveyda–Grubbs second generation catalyst (47 mg, 0.075 mmol, 2.5 mol %) was added. The reaction mixture was refluxed for 12 h and then evaporated at 25 °C. The residue was dissolved in tetrahydrofuran (15 mL) and NaOH (2 M, 3 mL) was added. The reaction mixture was stirred at room temperature for 24 h. After the reaction was completed the reaction mixture was evaporated under reduced pressure and the residue dissolved in dichloromethane (20 mL) and washed with NaOH solution (2 M, 30 mL). The water layer was acidified with HCl (1:1, v/v) to pH=1 and the product was extracted with ethyl acetate (3×30 mL). The combined organic phases were dried over anhydrous Na₂SO₄, filtered, and evaporated, yielding 280 mg (54%) of product. White crystals. Mp=151-154 °C; IR (NaCl, cm⁻¹) 3477, 1689, 1432, 1430, 1328, 1276, 1208, 984, 935, 685; ¹H NMR (300 MHz, DMSO-*d*₆) δ 2.28–2.35 (m, 4H, –CHCH₂CH₂–), 2.39–2.45 (m, 4H, -CH₂CH₂CO₂H), 5.40-5.554 (m, 2H, -CH=CH-); ¹³C NMR (126 MHz, DMSO-*d*₆) δ 173.9, 129.3, 33.6, 27.4; *m*/*z* (EI⁻) 171 (MH⁻); HRMS (EI⁻): MH⁻, found 171.0657. C₈H₁₁O₄ requires 171.0657. Found: C, 55.88; H, 7.06%. C₈H₁₂O₄ requires C, 55.81; H, 7.02%.

3.2.4. (2S,7S)-2,7-Diisopropyloct-4-enedioic acid (**6b**). To the solution of (2S)-2-isopropylpent-4-enoic anhydride (1.0 g, 3.76 mmol) in dichloromethane (150 mL) the Hoveyda–Grubbs second generation catalyst (59 mg, 0.095 mmol, 2.5 mol%) was added. The reaction mixture was refluxed for 12 h and then evaporated at 25 °C. The residue was dissolved in tetrahydrofuran (15 mL) and NaOH (2 M, 6 mL) was added. The reaction mixture was stirred at room temperature for 24 h. After the reaction was completed the reaction mixture was evaporated under reduced pressure and the residue dissolved in dichloromethane (20 mL) and washed with NaOH solution (2 M, 30 mL). The water layer was acidified with HCl (1:1,

v/v) to pH=1 and the product was extracted with ethyl acetate (3×30 mL). The combined organic phases were dried over anhydrous Na₂SO₄, filtered, and evaporated, yielding 900 mg of the crude product. The purification by column chromatography (SiO₂, petroleum ether/ethyl acetate=10:1+2% CH₃CO₂H) yielded 703 mg (73%) of pure product as colorless oil; IR (NaCl, cm⁻¹) 2965 (br), 2650, 1702, 1466; ¹H NMR (300 MHz, CDCl₃) δ major isomer: 0.94 (d, *J*=6.0 Hz, 12H, 2×Me), 1.86 (sym 6-line m, *J*=6.0 Hz, 2H), 2.10–2.26 (m, 6H), 5.45 (m, 2H); minor isomer: 0.98 (d, *J*=6.0 Hz, 12H, 2×Me), 1.89 (sym 6-line m, *J*=6.0 Hz, 2H), 2.2–2.40 (m, 6H), 5.44 (m, 2H), 10.80 (br s, 2H); ¹³C NMR (75 MHz, CDCl₃) major isomer: δ 20.0, 20.5, 30.3, 32.4, 52.4, 129.5, 180.9; minor isomer: 19.9, 20.4, 27.0, 30.1, 52.9, 128.4, 181.6. MS-ESI *m/z* (%): 279 (100, M+Na⁺); HRMS calculated for C₁₄H₂₄O₄Na: 279.1572; found: 279.1570.

3.2.5. Oxacyclonon-5-en-2-one (**8**). To a solution of pent-4-en-1-yl pent-4-enoate (**7**) (168 mg, 1.0 mmol) in dichloromethane (50 mL), the Hoveyda–Grubbs second generation catalyst (16 mg, 0.025 mmol, 2.5 mol%) was added. The reaction mixture was heated at 40 °C for 5 h. After the reaction was completed the reaction mixture was evaporated under reduced pressure and the residue chromatographed (SiO₂, dichloromethane) to give 61 mg (43%) colorless oil; IR (NaCl, cm⁻¹) 2953, 2926, 1734, 1436, 1347, 1254, 1159, 972; ¹H NMR (300 MHz, CDCl₃): δ =1.59–1.74 (m, 2H, –CH₂CH₂CH₂-), 2.00–2.20 (m, 2H, –CH₂CH₂CH=CH₂), 2.29–2.44 (m, 4H, –CH₂CH₂COO–), 4.04–4.15 (m, 2H, –CH₂O–), 5.34–5.51 (m, 2H, –CH=CH–); ¹³C NMR (75 MHz, CDCl₃): δ =173.4, 131.2, 128.9, 63.7, 34.7, 29.0, 28.9, 28.7; *m/z* (El⁺) 141 (MH⁺); HRMS (El⁺): MH⁺, found 141.0912. C₈H₁₃O₂ requires 141.0916.

3.2.6. *Oxacyclonon-6-en-2-one* (**10**). To a solution of but-3-en-1-yl hex-5-enoate (**9**) (178 mg, 1.06 mmol) in dichloromethane (50 mL), the Hoveyda-Grubbs second generation catalyst (17 mg, 0.027 mmol, 2.5 mol %) was added. The reaction mixture was heated at 40 °C for 12 h. After the reaction was completed the reaction mixture was evaporated under reduced pressure and the residue chromatographed (SiO₂, petroleum ether/ethyl acetate=10:1) to give 48 mg (32%), colorless oil; IR (NaCl, cm⁻¹) 2951, 2934, 1726, 1311, 1224, 1159, 1020, 962, 926; ¹H NMR (500 MHz, CDCl₃): δ =1.66–1.73 (m, 2H, –CH₂CH₂CH₂—), 2.03–2.09 (m, 2H, –CH₂CH₂CH=CH–), 2.24–2.29 (m, 2H, –CH₂COO–), 2.30–2.35 (m, 2H, =CH–CH₂-CH₂O–), 4.11–4.15 (m, 2H, –CH₂CH₂O–), 5.29–5.50 (m, 2H, –CH=CH–); ¹³C NMR (126 MHz, CDCl₃): δ =173.7, 132.0, 127.5, 62.9, 33.4, 32.0, 31.7, 24.5; *m*/*z* (El⁺) 141 (MH⁺); HRMS (El⁺): MH⁺, found 141.0908. C₈H₁₃O₂ requires 141.0916.

3.2.7. N,N'-Dimethyl-1,2-diazacyclodec-5-en-3,10-dione (12). To a solution of N,N'-dimethyl-N'-(pent-4-enoyl)pent-4-enehydrazide (11) (224 mg, 1.0 mmol) in dichloromethane (50 mL), the Hoveyda–Grubbs second generation catalyst (16 mg, 0.025 mmol, 2.5 mol %) was added. The reaction mixture was heated at 40 °C for 20 h. After the reaction was completed the reaction mixture was evaporated under reduced pressure and the residue chromatographed (SiO₂, dichloromethane/methanol=20:1) to give 50 mg (26%) white solid. Mp=207-209 °C; IR (NaCl, cm⁻¹) 2918, 1658, 1432, 1379, 1277, 1149, 978; ¹H NMR (300 MHz, CDCl₃): δ=2.20-2.45 (m, 8H, -CH₂CH₂-), 3.09 (s, 3H, -CH₃), 3.12 (s, 3H, -CH₃), 5.46-5.50 (m, 2H, -CH=CH-); ¹³C NMR (75 MHz, CDCl₃): δ =174.0, 173.9, 129.7, 129.4, 33.5, 33.2, 31.8, 31.1, 27.0, 26.7; *m*/*z*(EI⁺) 197 (MH⁺); HRMS (EI⁺): MH⁺, found 197.1295. C10H17N2O2 requires 197.1290. Found: C, 60.89; H, 8.58; N, 13.90%. C₁₀H₁₆N₂O₂ requires C, 61.20; H, 8.22; N, 14.27%.

3.2.8. General procedure for the synthesis of 12-membered heterocycles (**14a**–**g**). To a solution of olefin **13** (1.0 mmol) in dichloromethane (50 mL), the Hoveyda–Grubbs second generation catalyst (16 mg, 0.025 mmol, 2.5 mol%) was added. The reaction mixture was heated at 40 °C for 5–24 h. After the reaction was completed (monitored by TLC or HPLC) the reaction mixture was evaporated under reduced pressure and the residue chromatographed on SiO₂.

3.2.8.1. 1,4-Dioxacyclododec-8-ene-5,12-dione (**14a**). After the chromatography (using dichloromethane as an eluent), the title compound **14a** was isolated, colorless oil, 180 mg (87%); IR (NaCl, cm⁻¹): 2946, 1736, 1443, 1346, 1240, 1176, 1131, 1053, 974, 857; ¹H NMR (300 MHz, CDCl₃): δ =2.29–2.31 (m, 8H, –CH₂CH₂–), 4.35 (s, 4H, –OCH₂CH₂O–), 5.39–5.41 (m, 2H, –CH=CH–); ¹³C NMR (75 MHz, CDCl₃): δ =172.9, 129.9, 60.8, 34.7, 29.2; *m*/*z* (EI⁺) 199 (MH⁺); HRMS (EI⁺): MH⁺, found 199.0976. C₁₀H₁₅O₄ requires 199.0970.

3.2.8.2. 1-0xa-4-azacyclododec-8-ene-5,12-dione (14b). After the chromatography (using dichloromethane/methanol=20:1 as an eluent), the title compound 14b was isolated as a mixture of isomers E/Z=10:1, white solid, 145 mg (74%). Mp=144–145 °C; IR (KBr, cm⁻¹): 3281, 3098, 2936, 2849, 1719, 1641, 1566, 1439, 1346, 1263, 1181, 1040, 980, 955, 713; ¹H NMR (300 MHz, CDCl₃): δ =2.17–2.46 (m, 8H, $-CH_2CH_2-$), 3.55 (dt, J=5.5, 5.5 Hz, 2H, $-CH_2CH_2NH-$), 4.29 (t, J=5.0 Hz, 2H, $-OCH_2CH_2-$), 5.37–5.47 (m, 2H, -CH=CH-), 7.26 (s, 1H, -NHCO-); ¹³C NMR (75 MHz, DMSO): δ =173.8, 172.4, 130.6, 130.2, 60.6, 38.4, 37.1, 34.5, 29.1, 29.0; m/z (EI⁺) 198 (MH⁺); HRMS (EI⁺): MH⁺, found 198.1125. C₁₀H₁₆NO₃ requires 198.1130. Found: C, 60.61; H, 7.68; N, 7.08%. C₁₀H₁₅N₂O₂ requires C, 60.90; H, 7.67; N, 7.10%.

3.2.8.3. 3,4,7,8-Tetrahydrobenzo[b][1,4]dioxacyclododecine-2,9dione (**14c**). After the chromatography (using petroleum ether/ ethyl acetate=7:1 as an eluent), the title compound **14c** was isolated as a mixture of isomers *E*/*Z*=10:1, white solid, 200 mg (81%). Mp=143-145 °C; IR (KBr, cm⁻¹): 3065, 2951, 1755, 1493, 1345, 1238, 1151, 1119, 1097, 945, 840, 762; ¹H NMR (300 MHz, CDCl₃): δ =2.42-2.48 (m, 4H, -CH₂CH₂-), 2.63-2.67 (m, 4H, -CH₂CH₂-), 5.61-5.65 (m, 2H, -CH=CH-), 7.08-7.14 (m, 2H, Ar), 7.22-7.26 (m, 2H, Ar); ¹³C NMR (75 MHz, CDCl₃): δ =170.8, 142.4, 130.0, 126.9, 123.8, 43.7, 28.9; *m*/*z* (EI⁺) 247 (MH⁺); HRMS (EI⁺): MH⁺, found 247.0977. C₁₄H₁₅O₄ requires 247.0970. Found: C, 68.36; H, 5.83. C₁₄H₁₄O₄ requires C, 68.36; H, 5.83%.

3.2.8.4. 3,4,7,8-Tetrahydro-2H-benzo[b][1,4]oxaazacyclododecine-2,9(10H)-dione (14d). After the chromatography (using petroleum ether/ethyl acetate=7:1 as an eluent), the title compound 14d was isolated as a mixture of isomers E/Z=10:1, white solid, 220 mg (90%). Mp=143-146 °C; IR (KBr, cm⁻¹): 3676, 3287, 2963, 1763, 1657, 1526, 1452, 1186, 1096, 990, 915, 752; ¹H NMR (500 MHz, CDCl₃): $\delta = 2.47 - 2.51$ (m, 2H, $-CH_2CH = CH_2$), 2.55 - 2.59 (m, 4H, -CH₂CH₂CO-), 2.74 (t, J=6.0 Hz, 2H, -CH₂CH₂CO-), 5.65-5.71 (m, 1H, -CH=CH-), 5.84-5.90 (m, 1H, -CH=CH-), 7.05 (dd, J=1.5, 8.0 Hz, 1H, Ar), 7.12 (ddd, J=1.5, 8.0, 8.0 Hz, 1H, Ar), 7.24 (ddd, J=1.5, 8.0, 8.0 Hz, 1H, Ar), 7.88 (rs, 1H, Ar-NH-CO-), 8.23 (dd, J=1.5, 8.0 Hz, 1H, Ar); ¹³C NMR (126 MHz, CDCl₃): δ =171.1, 170.7, 140.4, 132.37 (2C), 130.1, 126.8, 124.5, 122.6, 122.2, 36.6, 34.6, 29.6, 28.5; *m*/*z* (EI⁺) 246 (MH⁺); HRMS (EI⁺): MH⁺, found 246.1125. C₁₄H₁₆NO₃ requires 246.1130. Found: C, 68.44; H, 6.06; N, 5.70. C₁₄H₁₅NO₃ requires C, 68.56; H, 6.16; N, 5.77%.

3.2.8.5. 3,4,7,8-Tetrahydrobenzo[b][1,4]diazacyclododecine-2,9(1H,10H)-dione (**14e**). After the reaction was completed the reaction mixture was cooled down to 0 °C and the precipitated material filtered off. White solid, 229 mg (94%). Mp=266–268 °C; IR (KBr, cm⁻¹): 3242, 3028, 1646, 1599, 1531, 1499, 768; ¹H NMR (300 MHz, DMSO): δ =2.27–2.39 (m, 8H, –CH₂CH₂–), 5.50–5.53 (m, 2H, -CH=CH-), 7.18–7.23 (m, 2H, Ar), 7.28–7.34 (m, 2H, Ar), 8.95 ppm (rs, 2H, Ar–N*H*–CO–); ¹³C NMR (75 MHz, DMSO): δ =171.9, 133.5, 132.1, 127.4, 127.1, 37.3, 30.1; *m*/*z* (EI⁺) 245 (MH⁺); HRMS (EI⁺): MH⁺, found 245.1290. C₁₄H₁₇N₂O₂ requires 245.1290.

3.2.8.6. 6.11-Diisopropyl-1-oxa-4-azacyclododec-8-ene-5.12*dione* (**14f**). After the chromatography (using dichloromethane/ methanol=100:1 as an eluent), the title compound **14f** was isolated as a mixture of isomers E/Z=10:1, white solid, 238 mg (85%). Mp=180-185 °C; IR (KBr, cm⁻¹): 3675, 3298, 2987, 2970, 2901, 1712, 1646, 1560, 1405, 1383, 1393, 1241, 1075, 1066, 1056, 959, 892, 764; ¹H NMR (500 MHz, CDCl₃): δ =0.89 (d, *J*=6.5 Hz, 3H, -CH₃), 0.90 (d, J=6.5 Hz, 3H, -CH₃), 0.93 (d, J=7.0 Hz, 3H, -CH₃), 0.94 (d, J=7.0 Hz, 3H, $-CH_3$), 1.59 (ddd, J=3.0, 9.0, 12.0 Hz, 1H, $-CH(CH(CH_3)_2)CH_2-CH=CH-), 1.74-1.81 (m, 1H, -CHCH(CH_3)_2),$ 1.82-1.90 (m, 1H, -CHCH(CH₃)₂), 2.08-2.15 (m, 2H, -CH(CH₃)₂), 2.19-2.26 (m, 3H, -CH₂-CH=CH-CH₂-), 2.91-2.94 (m, 1H, -OCH₂CH₂NH-), 3.61-3.65 (m, 1H, -OCH₂CH₂NH-), 4.19-4.27 (m, -OCH₂CH₂NH-), 4.92-4.97 (m, 1H, -OCH₂CH₂NH-), 1H. 5.27–5.38 (m, 3H, -CH=CH-, -CH₂-NH-CO-); ¹³C NMR $(126 \text{ MHz}, \text{CDCl}_3)$: $\delta = 176.1, 174.8, 130.7, 129.4, 60.0, 56.7, 53.4, 38.3, 120.4,$ 33.8, 33.5, 30.9, 30.1, 21.3, 20.7, 20.3, 20.2; *m*/*z* (EI⁺) 282 (MH⁺); HRMS (EI⁺): MH⁺, found 282.2056. C₁₆H₂₈NO₃ requires 282.2050. Found: C, 68.20; H, 9.51; N, 4.82%. C₁₆H₂₇NO₃ requires C, 68.29; H, 9.67; N, 4.98%.

3.2.8.7. 3.8-Diisopropyl-3.4.7.8-tetrahydro-2H-benzolbl[1.4]-oxaazacvclododecine-2.9(10H)-dione (14g). After the chromatography (using dichloromethane/methanol=100:1 as an eluent), the title compound **14f** was isolated as a mixture of isomers E/Z=10:1, white solid, 266 mg (81%). Mp=167–170 °C; ¹H NMR (500 MHz, CDCl₃): $\delta = 0.97$ (d, I = 6.5 Hz, 3H, $-CH_3$), 1.02 (d, I = 6.5 Hz, 3H, $-CH_3$), 1.04 (d, J=7.0 Hz, 3H, -CH₃), 1.06 (d, J=7.0 Hz, 3H, -CH₃), 1.92-1.99 (m, 1H, -CH(CH₃)₂), 2.06-2.10 (m, 1H, -CH₂-CH=CH-), 2.18-2.25 (m, 3H, -CH₂-CH=CH-CH₂-), 2.40-2.43 (m, 1H, -CH(CH₃)₂), 2.48-2.56 (m, 2H, -CHCH(CH₃)₂), 5.54–5.59 (m, 1H, -CH=CH-), 5.65–5.71 (m, 1H, -CH=CH-), 7.01 (dd, *J*=1.5, 8.0 Hz, 1H, Ar), 7.19 (ddd, *J*=1.5, 8.0, 8.0 Hz, 1H, Ar), 7.22 (rs, 1H, Ar-NH-CO-), 7.24 (ddd, J=1.5, 8.0, 8.0 Hz, 1H, Ar), 7.72 (dd, *J*=1.5, 8.0 Hz, 1H, Ar); ¹³C NMR (126 MHz, CDCl₃): *δ*=173.9, 173.0, 143.6, 131.3, 130.8, 130.0, 126.7, 126.5, 126.2, 122.4, 54.4, 53.5, 34.3, 31.6, 30.9, 29.7, 21.1, 21.0, 20.1, 19.2; m/z (EI⁺) 328 (M-H⁻); HRMS (EI⁺): (M-H)⁻, found 328.1920. C₂₀H₂₆NO₃ requires 328.1918. Found: C, 73.11; H, 8.40; N, 4.23%. C₂₀H₂₇NO₃ requires C, 72.92; H, 8.26; N, 4.25%.

3.2.8.8. 8-((2-Hydroxyphenyl)amino)-8-oxooct-4-enoic acid (**15**). To the solution of **14d** (193 mg, 0.79 mmol) in ethanol (2 mL) LiOH·H₂O (100 mg, 2.37 mmol) in water (1 mL) was added. The reaction mixture was stirred at 25 °C for 48 h. The reaction was quenched with HCl (1 M, 10 mL) and the product was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over anhydrous NaSO₄, and evaporated under reduced pressure to give 200 mg (96%) of analytically pure product **15**. Mp=84–86 °C; ¹H NMR (500 MHz, CDCl₃): δ =2.15–2.29 (m, 6H), 2.44 (t, *J*=8.0 Hz, 2H), 5.38–5.55 (m, 2H), 6.73–6.78 (m, 1H), 6.85 (dd, *J*=1.5, 8.0 Hz, 1H), 6.91–6.97 (m, 1H), 7.64–7.68 (m, 1H), 9.23 (br s, 1H), 9.68 (m, 1H), 12.01 (m, 1H); ¹³C NMR (126 MHz, CDCl₃): δ =173.8, 171.2, 147.9, 129.4, 129.2, 126.3, 124.6, 122.4, 118.9, 115.9, 35.7, 33.6, 28.1, 27.4; *m/z* (EI⁺) 264 (MH⁺); HRMS (EI⁺): MH⁺, found 264.1230. C₁₄H₁₈NO₄ requires

264.1228. Found: C, 63.54; H, 6.47; N, 5.23%. C₁₄H₁₇NO₄ requires C, 63.87; H, 6.51; N, 5.32%.

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Supplementary data

Characterization and synthetic procedures for the starting materials **7**, **9** and **13a**–**13g**, as well as ORTEP diagrams of compounds **14b** and **14d**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.04.043.

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