Synthesis of Enantiomerically Pure Bicyclic Lactams

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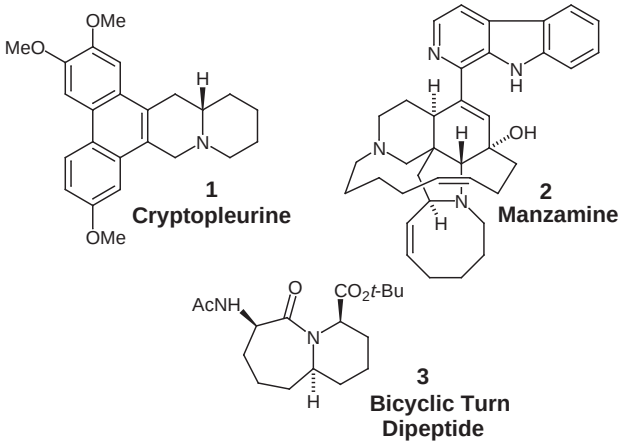
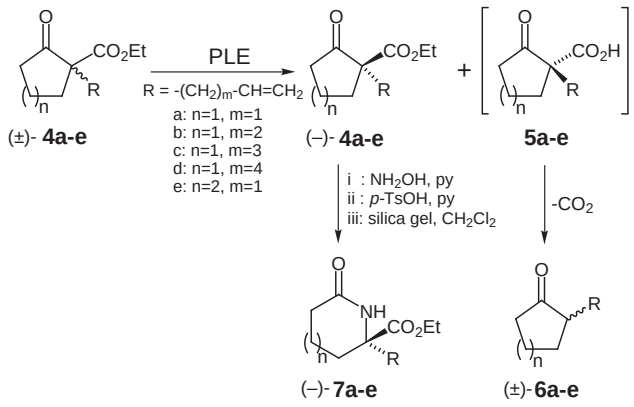
Abstract: Enantiomerically pure homologous 1-azabicyclo-[x.y.0]alkanones (x = 4-5, y = 4-7) can be synthesized by ring closing olefin metathesis using Grubbs' ruthenium catalyst. By starting from monocyclic lactams, the bicyclic products, even eight- and nine-membered rings, are formed in high yields. The monocyclic lactames can be obtained enantiomerically pure by enzyme-catalyzed kinetic resolution.

Key words: Grubbs' catalyst, ring-closing olefin metathesis, PLE, lactams, natural products

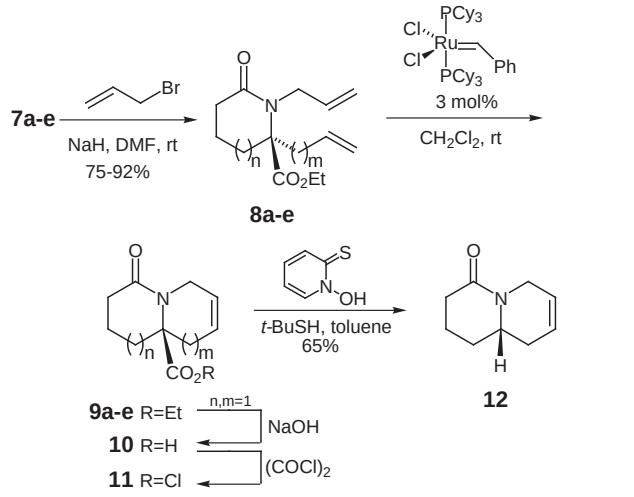
Due to their ubiquity as frameworks in natural products, the synthesis of 1-azabicyclo[x.y.0]alkane-alkaloids such as **1** [4.4.0] or **2** [6.3.0] and [10.3.1] has attracted considerable attention.[1,2] In addition, these heterocycles **3** [5.4.0] are useful candidates for the incorporation into small peptides to induce certain secondary structural elements, e. g. β turns.[3] In retrospect, most of the numerous synthetic strategies towards enantiomerically pure products reported so far start from building blocks provided by the *chiral pool*.[4,5] By starting from naturally occurring and easily available amino acids the number of derivatives allowing the synthesis of a broad variety of differing ring sizes is limited. Therefore, there is still need for a method by which homologues can be prepared following a common synthetic route.



We now report a general method for the preparation of bicyclic lactams using δ- and ε-lactams as conformational constraint precursors in the ring closing olefin metathesis employing the Grubbs' catalyst [Ru = $CHPh(Cl)_2(PCy_3)_2$].[6] Enantiomerically pure monocyclic lactams can be prepared as we previously described.[7] Starting from β-keto esters **4a-e** bearing an ω-olefinic side chain at the quaternary carbon center, kinetic resolution was carried out with pig liver esterase (PLE) (Scheme 1). The products were isolated in high enantiomeric purities (ee > 98%). Subsequently, treatment of (–)-**4a-e** with hydroxylamine afforded the corresponding *E*-oximes in almost quantitative yield (*E*:*Z* ≥ 50:1). Consequently, lactams (–)-**7a-e** were obtained via a stereospecific Beckmann-rearrangement. No racemization took place during the Beckmann-rearrangement as determined by ^{1}H NMR employing chiral shift reagent $Eu(tfc)_3$.[8]



Scheme 1

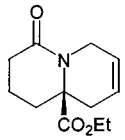
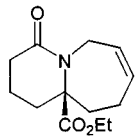
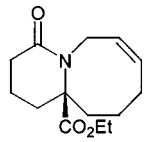
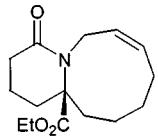
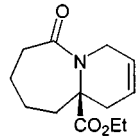


Scheme 2

Transformation of **7** into the diolefinic compounds **8** was carried out with allyl bromide after deprotonation with NaH (Scheme 2). The intramolecular ring closing metathesis reaction to form **9** was performed using 3 mol% of Grubbs' ruthenium catalyst. After stirring in CH_2Cl_2 at room temperature, the cyclized products were isolated in high yields (see Table 1). Starting from valerolactams (n = 1), the reaction was completed after 1 – 12 hours. The yields of isolated products ranged from 67% – 95%.[9] These high yields were especially remarkable for the formation of 9-membered rings, which, in general, are not easy to obtain.[10] In addition, the formation of the new double bond, which can be *cis*- or *trans* configurated for **9d** was highly selective. Indeed, the bicyclic product contained only a *cis*-double bond.

By starting from caprolactam **7e** (n = 2), the yield of cyclized product **9e** was 77%, the reaction time was prolonged in comparison with the valerolactam derivatives.

Table 1 Synthesis of bicyclic lactams **9** by ring closing olefin metathesis of **8**.

8	9	time [h]	yield [%]
a (m=1, n=1)		1	95
b (m=2, n=1)		3	90
c (m=3, n=1)		12	83
d (m=4, n=1)		12	67
e (m=1, n=2)		24	77

We also showed that lactam **9a** can be decarboxylated using the Barton protocol, which is known to be stereoselective in rigid bicycles.[11,12] Cleavage of the ethyl ester (NaOH) of **9a** afforded acid **10** in essentially quantitative yield. After treatment with oxalyl chloride, the acid chloride **11** was directly coupled with *N*-hydroxy pyridine-2-thione, which was exposed to *t*-butyl sulfide in toluene (80 °C). Enantiomerically pure **12** was obtained in 65% yield (**9a** → **12**).

The results presented above show the power of the ring-closing metathesis by using Grubbs' ruthenium catalyst. To the best of our knowledge, these results are among the highest reported so far for the formation of 8- and 9-membered rings. Due to the high degree of functionalization these bicyclic lactams offer the possibility to be employed in natural product synthesis.

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(9) General procedure for the preparation of lactams **9a-e**: To a solution of lactam **8a** (550 mg, 2.2 mmol) in dry CH_2Cl_2 (200 ml) was added Ru = $CHPh(Cl)_2(PCy_3)_2$ (52 mg, 0.07 mmol) and the reaction mixture was stirred at rt (time see Table 1). After evaporation of the solvent at reduced pressure, the residue was purified by chromatography on silica gel. **9a**: TLC (petroleum/AcOEt, 1:1) R_F = 0.10. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.23 (t, ^3J 7.1 Hz, 3H, CH_3), 1.59 – 1.91 (m, 3H, CH_2), 2.18 – 2.56 (m, 4H, CH_2), 2.76 – 2.88 (m, 1H, CH_2), 3.65 – 3.75 (m, 1H, NCH_2), 4.17 (q, ^3J 7.1 Hz, 2H, OCH_2), 4.38 – 4.49 (m, 1H, NCH_2), 5.63 – 5.71 (m, 2H, CH = CH). – ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.6, 17.9, 32.9, 34.6, 35.9, 42.4, 62.1, 63.9, 122.4, 124.8, 170.9, 173.4. – HR-MS (EI): $C_{12}H_{17}NO_3$: calcd. 223.1209 found 223.1214. **9b**: TLC (petroleum/AcOEt, 1:1) R_F = 0.13. – ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.24 (t, ^3J 7.1 Hz, 3H; CH_3), 1.60 – 2.50 (m, 10H, CH_2), 3.27 – 3.35 (m, 1H, NCH_2), 4.18 (q, ^3J 7.1 Hz, 2H, OCH_2), 4.61 – 4.80 (m, 1H, NCH_2), 5.63 – 5.73 (m, 2H, CH = CH). – ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.6, 17.9, 24.4, 31.8, 32.3, 36.2 41.9, 62.0, 68.0, 128.0, 130.7, 170.0, 174.4. – HR-MS (EI): $C_{13}H_{19}NO_3$: calcd. 237.1365 found 237.1363. **9c**: TLC (petroleum/AcOEt, 1:1) R_F = 0.16. – ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.24 (t, ^3J 7.1 Hz, 3H, CH_3), 1.49 – 2.56 (m, 12 H, CH_2), 3.19 – 3.30 (m, 1H, NCH_2), 4.17 (q, ^3J 7.1 Hz, 2H, OCH_2), 4.84 – 4.95 (m, 1H, NCH_2), 5.46 – 5.66 (m, 2H, CH = CH). – ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.6, 17.9, 22.1, 24.0, 30.3, 30.8, 32.6, 46.2, 62.1, 68.4, 126.6, 128.7, 170.9,

174.3. – HR-MS (EI): $C_{14}H_{21}NO_3$: calcd. 251.1521 found 251.1524.
9d: TLC (petroleum/AcOEt, 1:1) R_F = 0.24. – ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, ^3J 7.1 Hz, 3H, CH_3), 1.37 – 2.62 (m, 10H, CH_2), 3.48 (dd, *J* 10.9, 13.6 Hz, 1H, NCH_2), 4.12 – 4.33 (m, 3H, OCH_2, NCH_2), 5.49 (ddd, *J* 6.8 Hz, 10.3 Hz, 1H, CH = CH) 6.18 (ddd, *J* 6.2 Hz, 10.8 Hz, 1H, CH = CH). – ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.7, 17.6, 18.4, 22.8, 23.9, 31.4, 32.2, 32.5, 41.5, 62.1, 70.9, 128.7, 130.2, 171.8, 174.8. – HR-MS (EI): $C_{15}H_{23}NO_3$: calcd. 265.1678 found 265.1685.
9e: TLC (petroleum/AcOEt, 1:1) R_F = 0.27. – ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.24 (t, ^3J 7.1 Hz, 3H, CH_3), 1.60 – 1.81 (m, 4H, CH_2), 1.96 – 2.70 (m, 6H, CH_2), 3.80 – 3.89 (m, 1H, NCH_2), 4.18 (q, ^3J 7.1, 2H, OCH_2), 4.39 (m, 1H, NCH_2) 5.71 – 5.78 (m, 2H, CH = CH). – ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.6, 21.3, 22.7, 36.5, 36.6, 37.9, 44.3, 62.0, 65.3, 123.5, 126.3, 173.6, 175.6. – HR-MS (EI): $C_{13}H_{19}NO_3$: calcd. 237.1364 found 237.1362.

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