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A Ring-Closing Metathesis Approach to Cyclic α,β-Dehydroamino Acids

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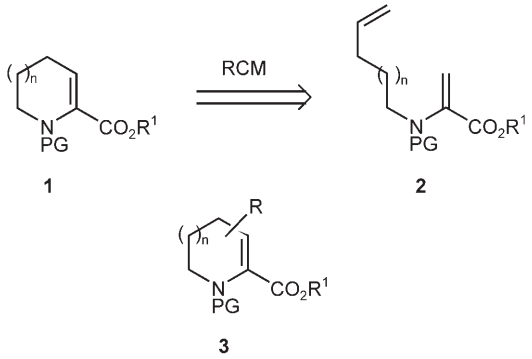
Abstract: A comprehensive study on the synthesis and ring-closing metathesis (RCM) of α,β-dehydroamino acids is described. This sequence has led to the formation of a range of biologically relevant functionalized nitrogen heterocycles. The incorporation of chiral building blocks in the RCM precursors eventually resulted in the formation of optically active 4-substituted cyclic dehydroamino acids. In addition, olefin isomerization under metathesis conditions was observed for a number of compounds, which could be successfully inhibited either by the introduction of allylic substituents or by the addition of a ruthenium hydride scavenger.

Keywords: 1,4-benzoquinone; enamides; isomerization; nitrogen heterocycles; olefin metathesis

Introduction

Non-proteinogenic α,β-dehydroamino acids are encountered in a range of natural products with important biological activities.[1] Their occurrence in nature, in combination with their interesting and diverse reactivity, has inspired many chemists to develop methodology to synthesize dehydroamino acids and study their behaviour.[2] Conceptually, a dehydroalanine fragment consists of a double bond substituted with both an electron-donating and an electron-withdrawing group, similar to the α-alkoxyacrylate systems that have previously been reported by us.[3] Since ring-closing metathesis (RCM) of the latter systems appeared to be a particularly versatile process and successful RCM of regular enamides had already been developed by our group,[4] we also set out to investigate the metathesis behaviour of dehydroamino acids.[5] Initially, our efforts were focused on the generation of nitrogen heterocycles **1** from the corresponding precursors **2** *via* RCM. If the formation of such model systems would be successful, this methodology could be applied to more complex systems, eventually resulting in functionalized cyclic dehydroamino acids **3** (Scheme 1).



Scheme 1. Ring-closing metathesis of dehydroamino acids.

Besides the introduction of R substituents, building blocks of type **3** possess a double bond representing a useful handle for further functionalization. First of all, hydrogenation leads to the corresponding pipecolic acid derivatives, which are key structural elements in a range of natural products and pharmaceutically active compounds.[6] One of the most relevant classes is the family of 4-substituted pipecolic acids, which constitute key structural elements in a number of pharmaceutically relevant compounds (Figure 1). For instance, 4-alkyl-substituted pipecolic acids are constituents of Argatroban, a potent inhibitor of the enzyme thrombin,[7] and the selective trypsin inhibitor MNAPPA.[8] Moreover, 4-*O*-substituted pipecolic acids have been applied in a number of biologically active compounds, such as the potent HIV-1 protease

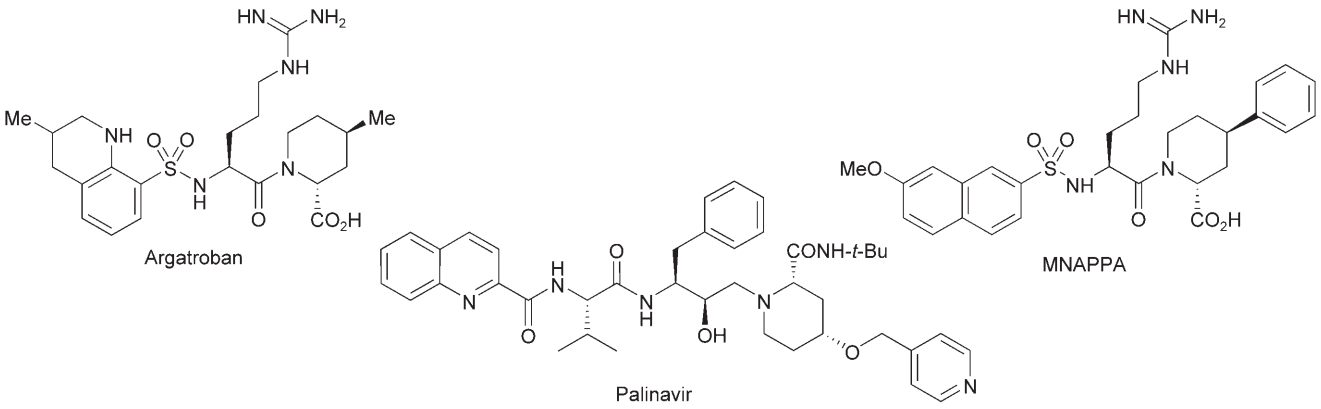


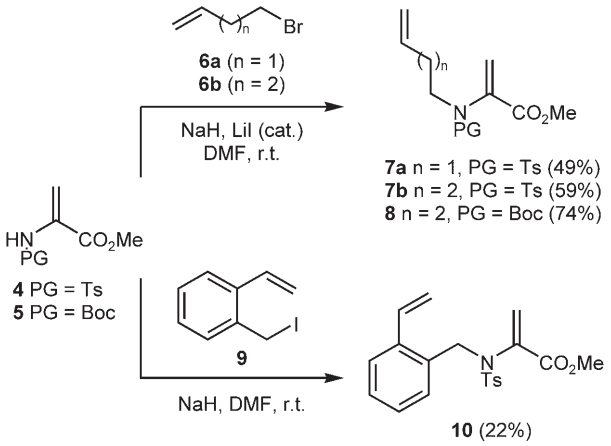
Figure 1. Therapeutically relevant agents incorporating a 4-substituted pipecolic acid moiety.

inhibitors Palinavir[9] and analogues thereof.[10] Finally, dehydroamino acids are reasonably reactive in, for instance, Michael additions, radical additions and cycloadditions, opening up possibilities for further functionalization at the 2- and 3-positions.[2]

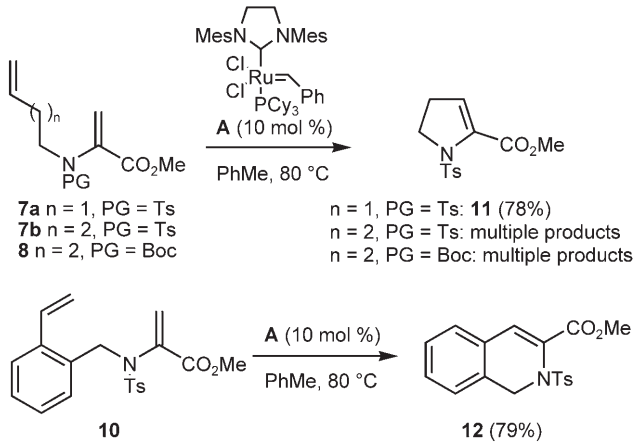
Results and Discussion

We envisaged that the preparation of dehydroamino acid-based RCM precursors could in principle be carried out using a protected dehydroalanine fragment as building block. Conversion into an RCM precursor is then performed through *N*-alkylation of the dehydroalanine with, for instance, an alkyl halide. Regarding the dehydroalanine building blocks, we focused our attention on a Ts- as well as a Boc-protected scaffold (i.e., **4**[11] and **5**,[12] Scheme 2). The *N*-alkylations of **4** and **5** were performed at room temperature in DMF, using NaH as a base. Reactions with K_2CO_3/acetone and Et_3N/DMF did not show any conversion, illustrating the somewhat reduced nucleophilicity of the nitrogen in these dehydroamino acids, as compared to regular protected amines. Reacting **4** with 4-bromo-1-butene (**6a**) and 5-bromo-1-pentene (**6b**) resulted in the formation of RCM precursors **7a** and **7b** in yields of 49 and 59%, respectively. Alkylation of Boc-protected **5** with **6b** proceeded slightly better and the corresponding product **8** was isolated in 74% yield. In addition, the aromatic iodide **9**[13] was coupled with **4**, resulting in precursor **10** (Scheme 2).

With four precursors in hand, the stage was set for investigation of the behaviour of these systems under metathesis conditions. The RCM reactions were performed in toluene at 80 °C, using 10 mol% of the 2nd generation Grubbs catalyst (**A**, Scheme 3). Gratifyingly, cyclization of **7a** proceeded smoothly, resulting in the formation of five-membered heterocycle **11** in a yield of 78%. In contrast, in the reaction of **7b** and **8** under identical conditions multiple products were formed, none of which could be separated by column chromatography. According to LC-MS measurements on the crude mixture the desired six-membered rings had not been formed. The analyses did, however, show masses corresponding to dimeric species of different lengths, as well as masses that corresponded to



Scheme 2. Synthesis of RCM precursors *via* alkylation of protected dehydroalanine methyl esters.



Scheme 3. RCM-mediated generation of five- and six-membered ring heterocycles.

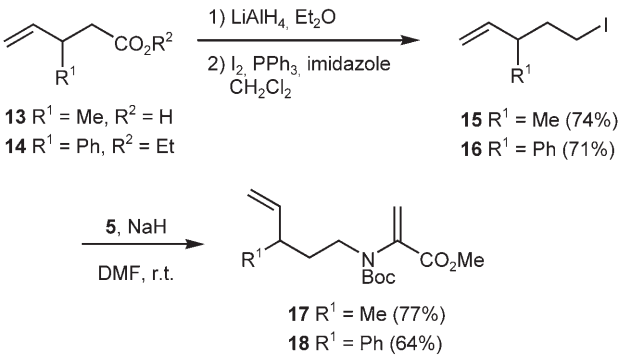
the five-membered ring analogues. This suggests that olefin isomerization had taken place, followed by cyclization, resulting in the formation of a smaller ring. Furthermore, homodimerization/cross-metathesis between **7b** or **8** and their isomerized forms probably explains the observation of several dimers. In addition, reaction of **8** with the first generation Grubbs catalyst [$(PCy_3)_2Cl_2Ru=CHPh$] yielded exclusively the corresponding homodimer. This behaviour, including the isomerization, is comparable to that observed during earlier work by our group on the RCM of α-alkoxyacrylates.[3]

Interestingly, ring-closing metathesis of **10** proceeded without problems in a yield of 79%. Apparently, the impossibility of isomerization of **10** in combination with a constrained geometry eliminates all side reactions. Thus, formation of six-membered cyclic dehydroamino acids by RCM can indeed occur, if undesired side reactions can be overcome.

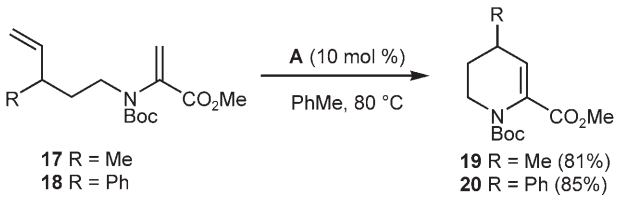
During our work on the ring-closing metathesis of carbohydrate-derived α-alkoxyacrylates, we found that the presence of allylic substituents in the substrate completely inhibited olefin isomerization.[3] In view of the disappointing metathesis behaviour of compounds **7b** and **8**, we decided to investigate the influence of allylic methyl and phenyl substituents on the formation of six-membered cyclic dehydroamino acids *via* RCM. This required the synthesis of substituted halides **15** and **16**, which can then be used in the alkylation of the protected dehydroalanine derivative (Scheme 4).

Methyl-substituted **15** was prepared from commercially available carboxylic acid **13** by reduction with $LiAlH_4$ and subsequent iodination. Ester **14** – obtained by Claisen rearrangement of cinnamyl alcohol[14] – was transformed into the corresponding iodide **16** by the same reduction/iodination procedure. The alkylation of **5** was performed under the same conditions as described earlier, using DMF and NaH. Thus, RCM precursors **17** and **18** were synthesized in yields of 77 and 64% (Scheme 4).

In sharp contrast to the metathesis behaviour of **7b** and **8**, the cyclization of substituted precursors **17** and **18** proceeded smoothly and six-membered heterocycles **19** and **20** could be isolated in yields of 81 and 85% (Scheme 5). No traces of side products were observed, which is surprising in both cases. First of all, it is striking that a single methyl substituent in **17** is apparently sufficient to prevent side reactions. Furthermore, **18** was expected to be prone to olefin isomerization due to the position of the phenyl substituent, however, this is clearly not the case. Finally, it should be mentioned that compound **19** appeared to be fairly labile. We found that degradation was caused by ruthenium residues, which remained in the product, even after careful column chromatography. Additional work-up procedures prior to column chromatography – for example, flushing over silica and stirring with activated carbon[15] – solved this problem and resulted in the isolation of a stable product.



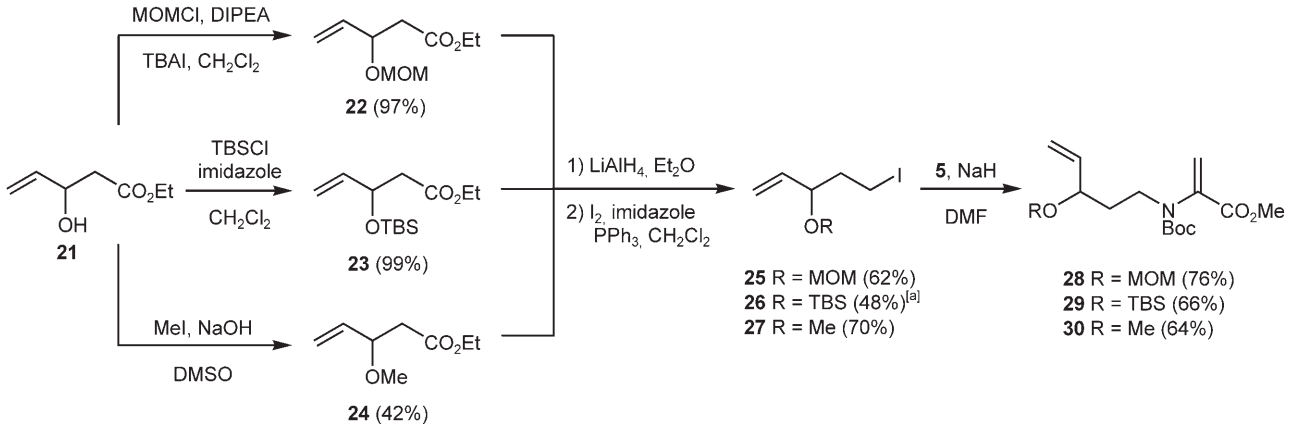
Scheme 4. Synthesis of allylically substituted RCM precursors.



Scheme 5. RCM of allylically substituted dehydroamino acid-based precursors.

Since a small allylic substituent is apparently sufficient to facilitate the ring-closing metathesis of dehydroamino acids and to prevent olefin isomerization, we decided to investigate whether the scope of this reaction could be extended to *O*-substituted substrates. These allylic ethers are notorious for their isomerization behaviour, because they can easily form the corresponding enol ether, or, in case of allylic alcohols, the ketone or aldehyde.[16] We decided to focus on substrates containing three protected alcohols as substituents, all possessing distinct differences in steric bulk. The mutual starting point for the three RCM-precursors was hydroxy ester **21**.[17] The alcohol function in **21** was transformed into three different side groups, using standard procedures, resulting in the MOMO-, TBSO- and MeO-substituted esters **22**–**24** (Scheme 6).

Conversion of the esters into the corresponding iodides was performed using the same conditions as described earlier, involving sequential reduction/iodination. The reduction of **23** with $LiAlH_4$ was accompanied by removal of the TBS group, which is a known problem for TBS-protected β-hydroxy esters.[18] Using DIBALH as a reducing agent left the OTBS group intact, but resulted in a somewhat lower overall yield of **26** (48%), compared to those of **25** (62%) and **27** (70%). Finally, the coupling of **25**–**27** to **5** using NaH/

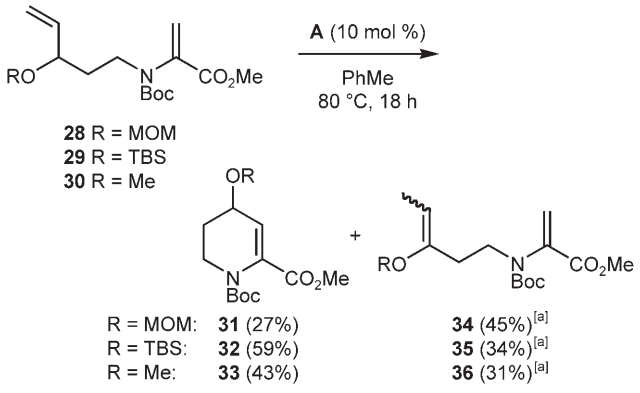


Scheme 6. Synthesis of *O*-substituted RCM precursors;[a] DIBALH was used for the reduction instead of $LiAlH_4$.

DMF proceeded as expected, yielding the RCM precursors **28**–**30** in 64–76% (Scheme 6).

The ring-closing metathesis was again carried out in toluene at 80 °C, using 10 mol% of catalyst **A**. In all cases the expected cyclic products (**31**–**33**) were formed in yields of 27–59%, however, together with significant amounts of non-cyclic isomerized starting material (**34**–**36**, Scheme 7). The resulting enol ethers are apparently not cyclized by the catalyst, judging from the absence of smaller ring products. Although the isolated amount of isomerized product was comparable (31–45%) for all three substrates, the yield of cyclized product varied considerably. The TBSO-functionalized heterocycle **32** was isolated in an acceptable yield of 59%, whereas **31** and **33** were formed in yields of 27 and 43%, respectively.

In order to gain more insight into the underlying mechanism for the observed isomerization of allylic ethers, we decided to monitor the conversion in time by ^{1}H NMR. A 5.0 μM solution of the MeO-substituted precursor **30** and catalyst **A** (10 mol%) in C_6D_6 was heated to 70 °C and a sample was measured every 20 min (Figure 2).



Scheme 7. RCM and isomerization of allylic ether fragments;[a] mixture of *E*/*Z*-isomers.

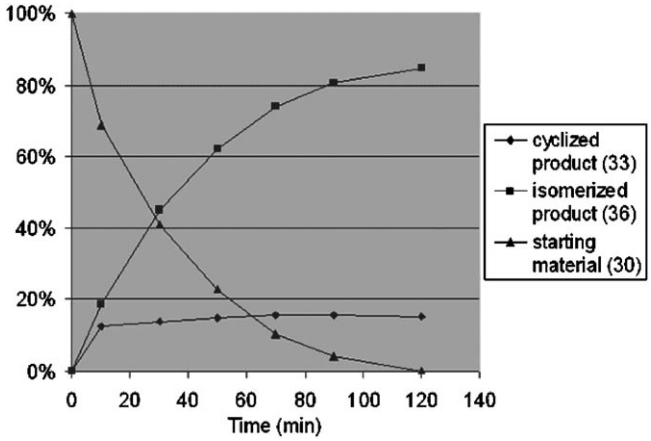
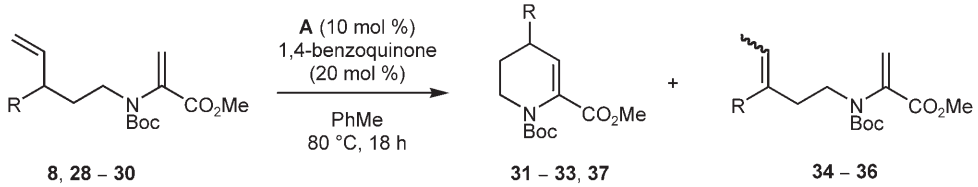


Figure 2. Conditions: **30** in C_6D_6 (5 μM), **A** (10 mol%), 70 °C. Values are based on ^{1}H NMR.

Figure 2 clearly shows that the formation of the intended product **33** stops at a certain point in time, while the formation of **36** continues until all starting material has been consumed. This observation clearly points to a hydride-based mechanism, suggesting that the metathesis catalyst decomposes quickly, resulting in a ruthenium hydride species.[16a,c,19] This compound is presumably responsible for converting the remaining starting material into the isomerized side-product. Furthermore, it is important to note that the isomerization is apparently more favoured in deuterated benzene than in toluene. The final ratio between **33** and **36** was 1:5.7 in benzene-d_6, whereas it was only 1:0.7 in toluene. This is not completely unexpected, since it is known that the generation of a ruthenium hydride species from catalyst **A** occurs readily in benzene.[19] The use of a number of different solvents and additives that have been reported to influence isomerization during olefin metathesis[20] was not particularly successful. THF[21a] and $CHCl_3$[21b] as a solvent completely inhibited metathesis, as did adding $Ph_3P{=}O$[22a] and $(PhO)P(O)(OH)_2$.[22b] Ring-closing metathesis in

Table 1. RCM in the presence of 1,4-benzoquinone.



8, **28** – **30** **31** – **33**, **37** **34** – **36**

Entry	Substrate	R	Cyclized product	Yield [%][a]	Isomerized product	Yield [%][a]	Starting material [%][a]
1	**28**	OMOM	**31**	75	**34**[b]	3	22
2	**29**	OTBS	**32**	58	**35**[b]	1	41
3	**30**	OMe	**33**	62	**36**[b]	0	38
4	**8**[c]	H	**37**	98[d]	n.a.	n.a.	2

[a] Yields based on ^{1}H NMR.
[b] Mixture of *E*/*Z*-isomers.
[c] Reaction time was 1 h.
[d] Isolated yield was 94%.

the presence of Ti(*i*-OPr)$_4$[23] did proceed, but unfortunately the outcome was not influenced in a positive manner: **33** and **36** were formed in yields of 37 and 42%, respectively.

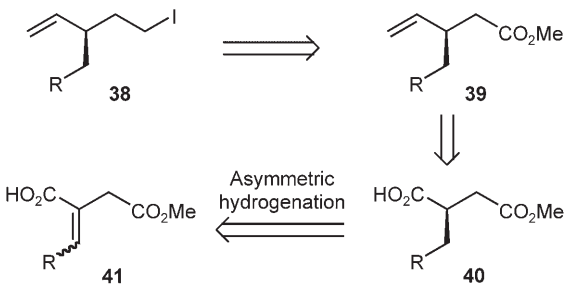
Very recently, Grubbs and co-workers reported that the addition of certain metal hydride scavengers can prevent isomerization during olefin metathesis. For instance, catalytic amounts of benzoquinones or organic acids completely inhibited olefin isomerization during the RCM of diallyl ether in CD_2Cl_2 at 40 °C.[24] Despite the fact that the RCM of dehydroamino acids is typically carried out in toluene and at elevated temperatures, we decided to investigate the influence of 1,4-benzoquinone on the isomerization of the allylic ether moieties under these circumstances.

Entries 1–3 in Table 1 clearly show that the addition of 20 mol% of 1,4-benzoquinone almost completely inhibited isomerization of the allylic ether fragments of all three substrates. Cyclic products **31**–**33** were formed in yields of 58–75%, according to ^{1}H NMR. It should be noted that the addition of the quinone does not necessarily increase the absolute yield, as is illustrated by the yield of 58% for **32**, compared to 59% in the absence of the quinone (Scheme 7). This can be explained by the fact that the additive scavenges the decomposition product (e.g., the ruthenium hydride), but does not inhibit catalyst decomposition itself. Possibly, both cyclization and catalyst decomposition are relatively fast for the reaction of **29**, meaning that a certain amount of substrate is rapidly cyclized anyway, before isomerization gets the upper hand.

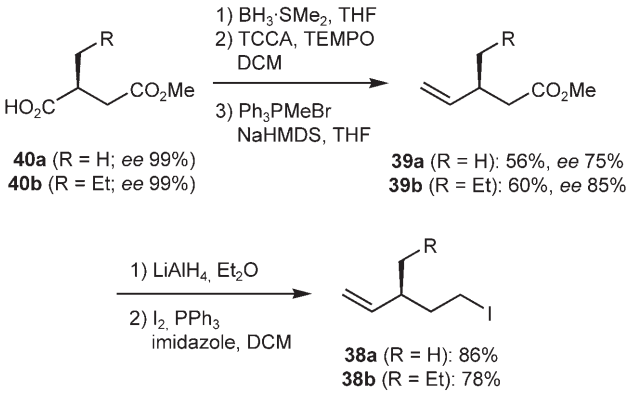
The encouraging results of these experiments prompted us to test the unsubstituted precursor **8** under the same conditions. Surprisingly, reaction of **8** with **A** in the presence of 1,4-benzoquinone resulted in a nearly quantitative conversion into the desired six-membered ring **37** (entry 4), whereas without 1,4-benzoquinone no trace of this product was observed (Scheme 3). Although a complex mixture of products was formed in that original attempt, the current results suggest that the cause for those observations is probably hydride-based.

As already pointed out in the introduction, cyclic dehydroamino acids substituted at the allylic position may represent valuable intermediates en route to 4-substituted pipecolic acid derivatives. While the heterocyclic products prepared so far are racemic, the enantiomerically pure analogues would be more useful as synthetic building blocks. If a similar RCM-based retrosynthetic approach to these compounds is to be followed – that is, alkylation of a protected dehydroalanine and subsequent cyclization by RCM – a general procedure for the synthesis of enantiomerically pure iodides **38** is required. We envisioned that carboxylic acids **40** are useful precursors for these iodides. Because carboxylic acids can be selectively reduced in the presence of esters, it should be possible to convert the carboxylic acid function of **40** into a double bond prior to transforming the methyl ester into the corresponding iodide **38** (Scheme 8).

The carboxylic acids **40** were available *via* asymmetric hydrogenation of functionalized itaconic acid monoesters **41**. Four carboxylic acids (**40a–d**; R = H, Et, Ph, *p*-MeOC$_6$H$_4$) were synthesized on a preparative scale *via* this method, details on these investigations are reported separately in the preceding paper in this issue.[25] The selected route from the monoacids **40a–d** to the corresponding olefinic iodides **38a–d** involved selective reduction of the carboxylic acids with $BH_3 \cdot SMe_2$, followed by oxidation to the aldehyde using trichloroisocyanuric acid (TCCA) and TEMPO.[26] Subsequent Wittig reaction of the crude aldehydes resulted in the olefinic esters **39**, which were purified by column chromatography. Next, the ester groups were converted into the corresponding iodides by subsequent reduction with $LiAlH_4$ and io-



Scheme 8. Retrosynthetic approach to optically active iodide building blocks.

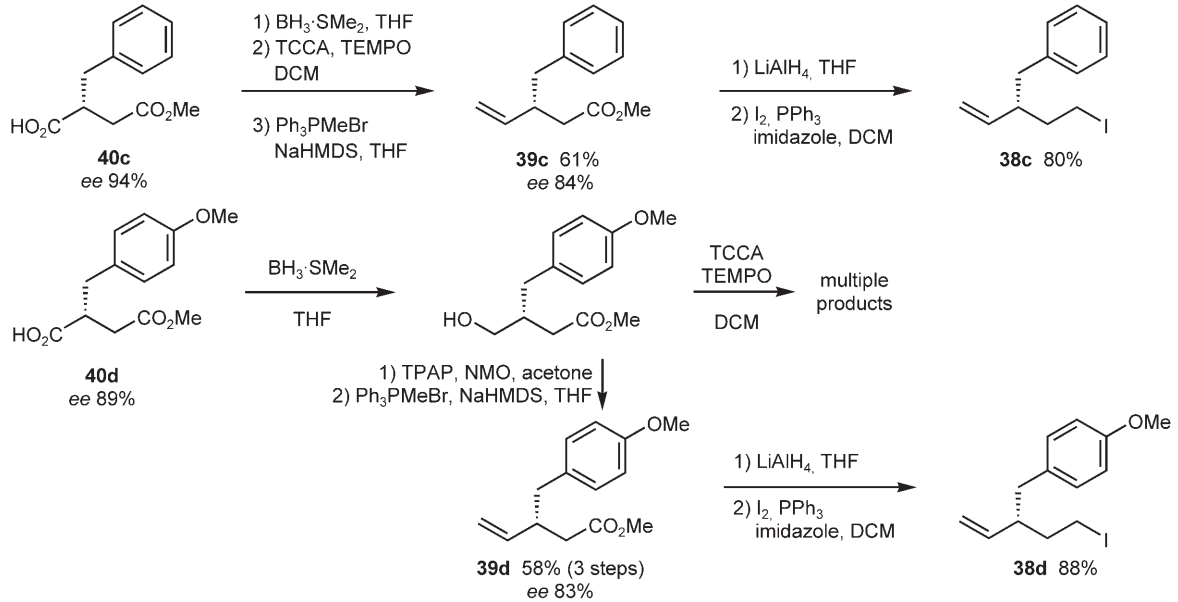


Scheme 9. Transformation of hydrogenation products into unsaturated iodides.

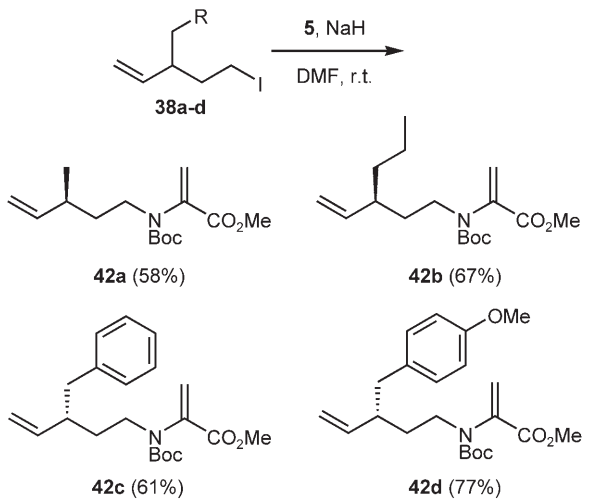
dination of the crude alcohol with I_2/PPh_3/imidazole. The syntheses of **39a** and **b** *via* this route proceeded well, resulting in isolation of the two products in 56 and 60% yields over three steps (Scheme 9). However, a setback was that the *ee* dropped to 75 and 85% for **39a** and **b**, respectively. This partial racemization possibly occurs in the Wittig reaction, due to the basicity of the phosphonium ylide. Finally, **39a** and **b** were reduced with $LiAlH_4$ in THF followed by iodination with I_2/PPh_3, resulting in iodides **38a** and **b** in yields of 86 and 78% over two steps.

The synthesis of **39c** from **40c** proceeded in a similar yield as observed for **39a** and **b** (61% over 3 steps), however, application of this synthetic route to **40d** proved to be problematic (Scheme 10). After reduction of the carboxylic acid function of **40d**, oxidation of the alcohol to the corresponding aldehyde with TCCA/TEMPO resulted in multiple products, presumably due to overoxidation at, for instance, the benzylic position. Thus, we were forced to apply a different oxidation method. Reaction of the alcohol with TPAP/NMO in acetone produced a single aldehyde and subsequent Wittig olefination resulted in **39d** in an overall yield of 58%. Moreover, a small amount of racemization was again observed for both **39c** and **d** and the compounds were isolated with *ee*s of 84 and 83%, respectively. Finally, transformation of **39c** and **d** into the corresponding olefinic iodides proceeded as expected, resulting in the isolation of **38c** and **d** in 80 and 88% yields over two steps.

With the four desired unsaturated iodides in hand, the stage was set for the synthesis of the corresponding RCM precursors. Similar to the synthesis of the racemic precursors (see above) **42a–d** were prepared by alkylation of protected dehydroalanine **5** (Scheme 11).



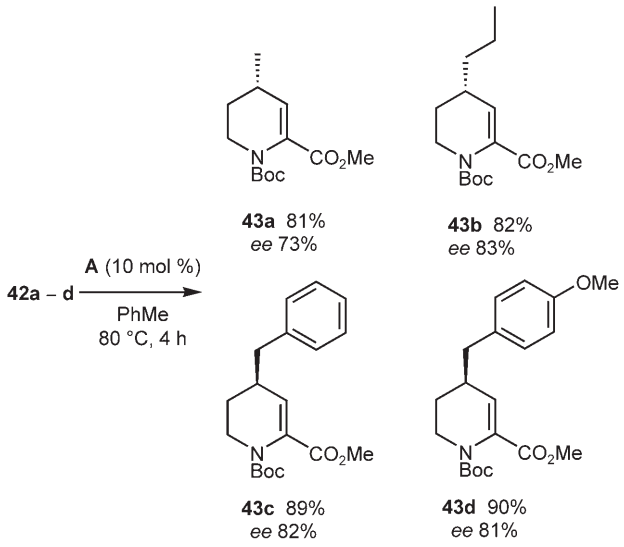
Scheme 10. Synthesis of aryl-substituted iodides.



Scheme 11. Preparation of optically active RCM precursors.

The alkylations were performed using the optimized conditions described above. Deprotonation of **5** at room temperature in DMF using NaH as a base and subsequent addition of the appropriate iodide resulted in the formation of RCM precursors **42a–d** in satisfactory yields of 58–77%.

Finally, we were pleased to find that ring-closing metathesis of olefins **42a–d** proceeded readily. Reaction of these compounds with the second generation Grubbs catalyst (**A**) in toluene at 80 °C for 4 h resulted in the formation of the functionalized cyclic dehydroamino acids **43a–d** in excellent yields of 81–90% (Scheme 12). Determination of the *ee*s of the heterocyclic products by chiral HPLC led to the conclusion that no significant racemization had taken place in the four-step conversions of **39a–d** to **43a–d**.



Scheme 12. Ring-closing metathesis of optically active dehydroamino acids.

Conclusions

Ring-closing metathesis of dehydroamino acids was found to proceed readily and therefore represents a suitable method for the preparation of a range of five- and six-membered nitrogen heterocycles. Olefin isomerization of allylic ether fragments in the starting materials initially gave considerable problems in the formation of 4-*O*-substituted cyclic dehydroamino acids. However, the addition of a catalytic amount of 1,4-benzoquinone as a hydride scavenger almost completely inhibited this side reaction. Even an attempted cyclization in which a complex mixture of products was formed could be optimized by the addition of 1,4-benzoquinone, suggesting that ruthenium hydrides are indeed responsible for most, if not all of the observed side products.

Finally, the use of enantiomerically enriched building blocks – obtained by asymmetric hydrogenation of itaconic acid monoesters – resulted in the formation of optically active 4-substituted cyclic dehydroamino acids. These substituted heterocycles present a useful class of synthetic building blocks, given that the dehydroamino acid double bond opens up possibilities for further functionalization and thereby the generation of highly functionalized, biologically relevant products.

Experimental Section

General

All reactions were carried out under an atmosphere of dry argon, unless stated otherwise. Argon was dried over SICAPENT®, $CaCl_2$ and KOH. Infrared (IR) spectra were obtained using an ATI Mattison Genesis Series FTIR spectrometer and wavelengths (ν) are reported in cm^{-1}. Optical rotations were measured on a Perkin–Elmer 241 polarimeter, using concentrations (*c*) in g/100 mL in the indicated solvents. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were determined in $CDCl_3$, unless indicated otherwise, using a Bruker DMX200 (200 MHz) or a Bruker DMX300 (300 MHz) spectrometer. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane. HR-MS measurements were carried out using a Fisons (VG) Micromass 7070E or a Finnigan MAT900S instrument. Column chromatography was performed with Acros Organics silica gel (0.035 ± 0.070 nm) or Merck silica gel 60 (0.040–0.063 mm). THF and Et_2O were distilled over sodium. Toluene was distilled before use and deoxygenated using the freeze-pump-thaw method. Et_3N was distilled and stored over KOH. Unless stated otherwise, all commercially available reagents were used as received. Compounds **4**,[11] **5**,[12] **9**,[13] **16**[14] and **21**[17] were synthesized according to literature procedures. Analytical and spectroscopic data can be found in the Supporting Information.

General Procedure A for the Alkylation of *N*-Ts-Protected Dehydroalanine Methyl Ester 4

A solution of **4** in DMF (~0.03 M) was cooled to 0 °C and NaH (60% dispersion in mineral oil, 1.5 equivs.) was added. The resulting solution was stirred at 0 °C for 15 min. Next, the alkyl halide (2 equivs.) was added, the solution was warmed to 60 °C and stirred for 3 h. Saturated NH_4Cl was added and the mixture was extracted with pentane (3×). The organic layers were dried ($MgSO_4$) and concentrated under vacuum. The product was purified by column chromatography (EtOAc/heptane/Et_3N, 10:90:1).

General Procedure B for the Alkylation of *N*-Boc-Protected Dehydroalanine Methyl Ester 5

A solution of **5** in DMF (~0.1 M) was cooled to 0 °C and NaH (60% dispersion in mineral oil, 1.3 equivs.) was added. The resulting solution was stirred at 0 °C for 15 min and at room temperature for 30 min. Next, the reaction was cooled to 0 °C, followed by addition of the alkyl halide (2 equivs.). The solution was allowed to warm to room temperature and stirred for 2 h. Saturated NH_4Cl was added and the mixture was extracted with pentane (3×). The organic layers were dried (Na_2SO_4) and concentrated under vacuum. The crude product was purified by column chromatography (EtOAc/heptane, 1:10).

Methyl 2-[*N*-(but-3-enyl)-4-methylphenylsulfonamido]-acrylate (7a): This compound was synthesized from **4** and bromo-1-butene, following general procedure A; yield: 29.4 mg (49%).

Methyl 2-[4-methyl-*N*-(pent-4-enyl)phenylsulfonamido]-acrylate (7b): This compound was synthesized from **4** and 5-bromo-1-pentene, following general procedure A; yield: 37.5 mg (59%).

Methyl 2-[*tert*-butoxycarbonyl(pent-4-enyl)amino]acrylate (8): This compound was synthesized from **5** and 5-bromo-1-pentene, following general procedure C. A catalytic amount of LiI (5 mg, 0.037 mmol) was used as an additive; pale yellow oil; yield: 122 mg (74%).

Methyl 2-[4-methyl-*N*-(2-vinylbenzyl)phenylsulfonamido]acrylate (10): This compound was synthesized from **4** and **9**, following general procedure A; yield: 13.8 mg (22%).

General Procedure C for Ring-Closing Metathesis of Dehydroamino Acids

A solution of the substrate in toluene (~5 μM) was stirred under an inert atmosphere. Catalyst **A** (10 mol%) was added and the reaction mixture was stirred at the specified temperature. When TLC indicated that the reaction was complete, the mixture was concentrated under vacuum. The product was purified by column chromatography (EtOAc/heptane, 1:10).

Methyl 1-tosyl-4,5-dihydro-1*H*-pyrrole-2-carboxylate (11): This compound was prepared from **7a**, following general procedure B, at 80 °C; yield: 20.7 mg (78%).

Methyl 2-tosyl-1,2-dihydroisoquinoline-3-carboxylate (12): This compound was prepared from **10**, following general procedure B, at 80 °C; yield: 7.3 mg (79%).

5-Iodo-3-methylpent-1-ene (15)

To a cooled (0 °C) suspension of $LiAlH_4$ (1.00 g, 26,3 mmol) in Et_2O (60 mL), was added a solution of methyl 3-methylpent-4-enoic acid (**13**) in Et_2O (15 mL). After stirring at room temperature for 24 h, the reaction mixture was poured over ice and the remaining salts were dissolved with H_2SO_4 (5 M, 15 mL). The layers were separated and the organic layer washed with H_2O (15 mL). The combined aqueous layers were washed with Et_2O (2×20 mL). The solvents were evaporated, yielding the corresponding alcohol as a colorless liquid; yield: 1.20 g (90%). Analytical data were agreement with reported values.[27]

Next, the reaction mixture was cooled to 0 °C and a solution of iodine (2.64 g, 10.4 mmol) in CH_2Cl_2 (60 mL) was added. The reaction mixture was stirred at room temperature for 45 min. The mixture was washed with a 10% Na_2SO_3 solution (3×20 mL), H_2O (20 mL) and brine (20 mL). The organic layer was dried with Na_2SO_4 and the solvents were removed under vacuum. The crude product was purified by column chromatography (100% pentane) to give **15** as a colorless liquid; yield: 1.38 g (82%). Analytical data agreed with those reported in the literature.[28]

Methyl 2-[*tert*-butoxycarbonyl(3-methylpent-4-enyl)amino]acrylate (17): This compound was synthesized from **5** and **15**, following general procedure B; colorless oil; yield: 553 mg (77%).

Methyl 2-[*tert*-butoxycarbonyl(3-phenylpent-4-enyl)amino]acrylate (18): This compound was synthesized from **5** and **16**, following general procedure B; colorless oil; yield: 281 mg (64%).

1-*tert*-Butyl 2-methyl 4-methyl-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate (19): This compound was prepared from **17**, following general procedure C, at 60 °C; yield: 22.2 mg (81%). Additional work-up was required in order to prevent degradation of the product over time. The product was stirred overnight with activated carbon to remove any ruthenium residues, after which the solvent was evaporated and the product purified by column chromatography (EtOAc/heptane, 1:40) to give **19**; yield: 18.4 mg (67%).

1-*tert*-Butyl 2-methyl 4-phenyl-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate (20): This compound was prepared from **18**, following general procedure C, at 80 °C; colorless oil; yield: 11.3 mg (85%).

Ethyl 3-(Methoxymethoxy)pent-4-enoate (22)

DIPEA (4.8 mL, 27.6 mmol) was added to a solution of **21**[17] (0.197 g, 1.37 mmol), chloromethyl methyl ether (1.06 mL, 13.96 mmol) and TBAI (51 mg, 0.14 mmol) in CH_2Cl_2 (35 mL) at 0 °C. The reaction mixture was protected from light and allowed to warm to room temperature. After stirring for 18 h, saturated $NaHCO_3$ (10 mL) and Et_2O (5 mL) were added. The organic layer was washed with brine (10 mL) and the aqueous layers were washed with CH_2Cl_2 (2×10 mL). The combined organic layers were dried with $NaSO_4$ and the solvents were evaporated under vacuum. Column chromatography (EtOAc/heptane, 1:10) afforded **22** as a pale yellow liquid; yield: 249 mg (97%).

Ethyl 3-(*tert*-Butyldimethylsilyloxy)pent-4-enoate (23)

To a stirred solution of **21**[17] (1.00 g, 3.87 mmol) and imidazole (527 mg, 7.74 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added TBSCl (1.17 g, 7.74 mmol). After 15 min the reaction mixture was warmed to room temperature and stirred overnight. Saturated $NaHCO_3$ (5 mL) was added and the organic layer was extracted with H_2O (10 mL) and brine (10 mL). After removing the solvent under vacuum, the crude product was purified by Kugelrohr distillation to afford **23** as a colorless liquid; yield: 1.79 g (99 %). Analytical data agreed with those reported in literature.[29]

Ethyl 3-Methoxypent-4-enoate (24)

Powdered NaOH (0.613 g, 15.3 mmol) was added to a solution of **21**[17] (1.49 g, 10.4 mmol) and MeI (1.3 mL, 20.9 mmol) in DMSO (5 mL) at 0 °C. After stirring for 2 h an additional amount of NaOH (0.330 g, 8.45 mmol) and MeI (1.3 mL, 20.9 mmol) were added an the reaction mixture was allowed to warm to room temperature. After 2 h the reaction mixture was diluted with H_2O (20 mL), and extracted with pentane (4×10 mL). The organic layer was dried (Na_2SO_4) and the solvents removed under vacuum. The crude product was purified by column chromatography (100 % pentane→Et_2O/pentane, 1:20) to give **24** as a colorless liquid; yield: 692 mg (42 %).

General Procedure D for the Transformation of Ethyl Esters in Iodides 25–27

To a suspension of $LiAlH_4$ (1.3 equiv's.) in Et_2O at 0 °C was added a solution of the ethyl ester in Et_2O. The reaction mixture was warmed to room temperature and stirred for 15 min, after which it was cooled to 0 °C and H_2O was added. To dissolve the remaining salts H_2SO_4 (1 M) was added and the mixture was stirred for 30 min. The organic layer was separated and the water layer exhaustively extracted with Et_2O. The organic layer was dried with $MgSO_4$ and concentrated under vacuum. The resulting alcohol was purified by column chromatography (Et_2O/pentane). The alcohol was dissolved in CH_2Cl_2 and PPh_3 (1.3 equivs.) and imidazole (1.5 equivs.) were added. The reaction mixture was cooled to 0 °C and a solution of iodine (1.3 equivs.) in CH_2Cl_2 was added. After 30 min the reaction mixture was warmed to room temperature and stirred for 1.5 h. Next, the mixture was extracted with a 10 % Na_2SO_3 solution (3×), H_2O and brine. The organic layer was dried with Na_2SO_4 and the solvents were evaporated under vacuum. The crude product was purified by column chromatography (Et_2O/pentane).

5-Iodo-3-(methoxymethoxy)pent-1-ene (25): This compound was prepared from **22**, following general procedure D; colorless liquid; yield: 469 mg (62 % over 2 steps).

***tert*-Butyl(5-iodopent-1-en-3-yloxy)dimethylsilane (26):** This compound was prepared from **23**, following general procedure D. DIBALH was used instead of $LiAlH_4$ in the reduction step. Work-up after this step was carried out by pouring the mixture into a cold HCl solution, separating the organic phase, extracting the aqueous phase with Et_2O and concentrating the combined organic phases; colorless liquid; yield of **26**: 205 mg (48 % over 2 steps).

5-Iodo-3-methoxypent-1-ene (27): This compound was prepared from **24**, following general procedure D; colorless liquid; yield: 586 mg (70 % over 2 steps).

Methyl 2-{*tert*-butoxycarbonyl[3-(methoxymethoxy)pent-4-enyl]amino}acrylate (28): This compound was synthesized from **5** and **25**, following general procedure B; colorless oil; yield: 157 mg (76 %).

Methyl 2-{*tert*-butoxycarbonyl[3-(*tert*-butyldimethylsilyloxy)pent-4-enyl]amino}acrylate (29): This compound was synthesized from **5** and **26**, following general procedure B; colorless oil; yield: 131 mg (66 %).

Methyl 2-[*tert*-butoxycarbonyl(3-methoxypent-4-enyl)amino]acrylate (30): This compound was synthesized from **5** and **27**, following general procedure B; colorless oil; yield: 394 mg (64 %).

General Procedure E for Ring-Closing Metathesis of 8, 28–30

A solution of the substrate in toluene (~3 μM) was stirred under an inert atmosphere at 80 °C. Catalyst **A** (5 mol %) was added and the reaction mixtuire was stirred at 80 °C for 1 h. Next, a second portion of **A** (5 mol %) was added and the reaction mixture was stirred overnight at 80 °C. The solvent was evaporated and the crude product purified by column chromatography (EtOAc/heptane, 1:20).

1-*tert*-Butyl 2-methyl 4-(methoxymethoxy)-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate (31): This compound was prepared from **28**, following general procedure E. Product **31** was isolated as a colorless oil; yield: 24.4 mg (27 %). Compound **34** (1.4:1) was isolated as a side product; yield: 44.5 mg (45 %).

1-*tert*-Butyl 2-methyl 4-(*tert*-butyldimethylsilyloxy)-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate (32): This compound was prepared from **29**, following general procedure E. Product **32** was isolated as a colorless oil; yield: 6.9 mg (59 %). Compound **35** (2.1:1) was isolated as a side product; yield: 4.3 mg (34 %).

1-*tert*-Butyl 2-methyl 4-methoxy-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate (33): This compound was prepared from **30**, following general procedure E. Product **33** was isolated as a colorless oil; yield: 13.1 mg (43 %). Compound **36** (3.1:1) was isolated as a side product; yield: 10.4 mg (31 %).

1-*tert*-Butyl 2-Methyl 5,6-dihydropyridine-1,2(4*H*)-dicarboxylate (37)

To a solution of **8** (10.1 mg, 37.5 μmol) in toluene (8 mL) and 1,4-benzoquinone (0.8 mg, 20 mol %) was added **A** (3.2 mg, 10 mol %). The reaction mixture was stirred at 80 °C for 1 h, after which ^{1}H NMR of the crude mixture showed a conversion of 98 %. Next, the solvent was evaporated and the product was purified by column chromatography (EtOAc/heptane, 1:10); colorless oil; yield: 8.5 mg (94 %).

General Procedure F for the Preparation of Olefins 39a–d

To a cooled (−20 °C) solution of carboxylic acid **40** in THF was added $BH_3{\cdot}Me_2S$ (2 equivs.). The mixture was stirred at room temperature for 3 h and MeOH was added. The solvents were removed under vacuum and this procedure was

repeated twice. The resulting crude alcohol was dissolved in CH_2Cl_2 and cooled to 0 °C. Next, trichloroisocyanuric acid (1 equiv.) and TEMPO (0.01 equiv.) were added and the reaction mixture was stirred while warming to room temperature. After 30 min the mixture was filtered over Celite and washed with H_2O and 1 N HCl. The organic layer was concentrated, yielding the crude aldehyde. Next, Ph_3PMeBr (1.1 equivs.) was suspended in THF and cooled to −78 °C. NaHMDS (2 M solution, 1.0 equiv.) was added and the mixture was stirred while warming to room temperature. After 1 h the solution was again cooled to −78 °C and a solution of the aldehyde was added. The reaction mixture was stirred at room temperature for 18 h, after which saturated NH_4Cl was added. The aqueous layer was extracted with pentane and the organic layer was dried with $NaSO_4$ and concentrated. The resulting olefinic product **39** was purified by column chromatography (Et_2O/pentane, 1:20).

(*S*)-Methyl 3-methylpent-4-enoate (39a): This compound was prepared from **40a** according to general procedure F; yield: 270 mg (56 %). The *ee* was determined by GC to be 75 % (Supelco GammaDEX 120 column; 50 °C isothermal). The analytical data agreed with those reported in the literature.[30]

(*S*)-Methyl 3-vinylhexanoate (39b): This compound was prepared from **40b** according to general procedure F; yield: 101 mg (60 %). The *ee* was determined by GC to be 85 % (Chiraldex G-TA column; 65 °C isothermal).

(*R*)-Methyl 3-benzylpent-4-enoate (39c): This compound was prepared from **40c** according to general procedure F; yield: 76 mg (61 %). The *ee* was determined by HPLC to be 84 % (Chiralcel OD-H column; hexane/2-propanol, 97:3). The analytical data agreed with those reported in the literature.[31]

(*R*)-Methyl 3-(4-methoxybenzyl)pent-4-enoate (39d): This compound was prepared from **40d** according to general procedure F, using modified oxidation conditions. The crude alcohol was dissolved in acetone and NMO (1.1 equivs.) and TPAP (1 mol %) were added. The reaction mixture was stirred at room temperature for 2 h, after which it was filtered over Celite and flushed over a short silica column. The solvent was evaporated, yielding the crude aldehyde, which was used in the next step: overall yield of **39d**: 62 mg (58 %). The *ee* was determined by HPLC to be 83 % (Chiralcel OD-H column; hexane/2-propanol, 99.6:0.4).

General Procedure G for the Preparation of Iodides 38a–d

To a solution of **39** in Et_2O at −78 °C was added $LiAlH_4$ (1.1 equivs.). The reaction mixture was gradually warmed to room temperature and stirred for 1 h, after which H_2O was added. To dissolve the remaining salts HCl (1 M) was added and the mixture was extracted with Et_2O. The organic layers were dried (Na_2SO_4) and concentrated under vacuum. The crude alcohol was dissolved in CH_2Cl_2 and PPh_3 (1.3 equivs.) and imidazole (1.5 equivs.) were added. The reaction mixture was cooled to 0 °C and a solution of iodine (1.3 equivs.) in CH_2Cl_2 was added. After 30 min the reaction was warmed to room temperature and stirred for 2 h. Next, the mixture was extracted with H_2O and brine. The organic layer was dried (Na_2SO_4) and the solvents were evaporated under vacuum. The product was purified by column chromatography (100 % pentane).

(*S*)-5-Iodo-3-methylpent-1-ene (38a): This compound was prepared from **39a** according to general procedure G; yield: 74 mg (86 %) The analytical data agreed with those reported in the literature.[28]

(*S*)-3-(2-Iodoethyl)hex-1-ene (38b): This compound was prepared from **39b** according to general procedure G; yield: 91 mg (78 %).

(*R*)-[2-(2-Iodoethyl)but-3-enyl]benzene (38c): This compound was prepared from **39c** according to general procedure G; yield: 37 mg (80 %).

(*R*)-1-[2-(2-Iodoethyl)but-3-enyl]-4-methoxybenzene (38d): This compound was prepared from **39d** according to general procedure G; yield: 45 mg (88 %).

(*S*)-Methyl 2-[*tert*-butoxycarbonyl(3-methylpent-4-enyl)-amino]acrylate (42a): This compound was prepared from **38a** and **5** following general procedure B; yield: 23 mg (58 %).

(*S*)-Methyl 2-[*tert*-butoxycarbonyl(3-vinylhexyl)amino]-acrylate (42b): This compound was prepared from **38b** and **5** following general procedure B; yield: 18 mg (67 %).

(*R*)-Methyl 2-[(3-benzylpent-4-enyl)(*tert*-butoxycarbonyl)-amino]acrylate (42c): This compound was prepared from **38c** and **5** following general procedure B; yield: 16 mg (61 %).

(*R*)-Methyl 2-[(3-benzylpent-4-enyl)(*tert*-butoxycarbonyl)-amino]acrylate (42d): This compound was prepared from **38d** and **5** following general procedure B; yield: 24 mg (77 %).

General Procedure H for Ring-Closing Metathesis of Dehydroamino Acids 42a–d

A solution of **42** in toluene (~2 μM) was stirred under an inert atmosphere at 80 °C. Catalyst **A** (5 mol %) was added and the reaction mixture was stirred at 80 °C for 1 h. Next, a second portion of **A** (5 mol %) was added and the reaction mixture was stirred for an additional 3 h. The mixture was cooled to room temperature and silica gel was added. The solvent was removed and the crude product, adsorbed to silica, was purified by column chromatography (EtOAc/heptane, 1:20). The *ee* of the product was determined by chiral HPLC.

(*S*)-1-*tert*-Butyl 2-methyl 4-methyl-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate (43a): This compound was prepared from **42a** following general procedure H; yield: 6.0 mg (81 %). The *ee* was determined by HPLC to be 73 % (Chiralcel AD-H column; hexane/2-propanol, 98:2).

(*S*)-1-*tert*-Butyl 2-methyl 4-propyl-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate (43b): This compound was prepared from **42b** following general procedure H; yield: 3.0 mg (82 %). The *ee* was determined by HPLC to be 83 % (Chiralcel AD-H column; hexane/2-propanol, 98:2).

(*R*)-1-*tert*-Butyl 2-methyl 4-benzyl-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate (43c): This compound was prepared from **42c** following general procedure H; yield: 6.5 mg (89 %). The *ee* was determined by HPLC to be 82 % (Chiralcel AD-H column; hexane/2-propanol, 98:2).

(*R*)-1-*tert*-Butyl 2-methyl 4-(4-methoxybenzyl)-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate (43d): This compound was prepared from **42d** and following general procedure H;

yield: 17.5 mg (90%). The *ee* was determined by HPLC to be 81% (Chiralcel AD-H column; hexane/2-propanol, 98:2).

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