DOI: 10.1002/ejoc.201000587

Expedient Pathway into Optically Active 2-Oxopiperidines

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Keywords: Nitrogen heterocycles / Alkaloids / Ring-closing metathesis / Amino acids / Dehydroamino acids

The piperidine ring system is one of the most common structural subunits and is found in many natural products. Moreover, piperidine alkaloids and derivatives thereof are of great interest for the pharmaceutical industry since they exhibit a wide range of biological activities. Consequently, short and valuable routes to highly functionalized building blocks for this important ring system are of general interest. A ring-closing metathesis (RCM)-mediated approach based on linear (substituted) dehydroamino esters was developed to provide cyclic dehydroamino esters. These structures represent valuable intermediates en route to highly substituted pipecolic acids as well as more elaborate heterocycles.

Introduction

The 2-oxopiperidine ring structure is encountered in many biologically active products (e.g., HIV protease inhibitors,[1] glycosidase inhibitors,[2] thrombin inhibitors,[3] antagonists of the neurokinin-2 receptor,[4] and fibrinogen receptor antagonists),[5] but is also a common structural feature of peptidomimetics.[6,7,8] In addition, functionalized 2-oxopiperidines have served as key building block in the synthesis of various natural products including piperidines,[9] indolizidines,[10] and quinolizidines[11] (Figure 1). As a result, the development of new methodology for enantiopure 2-oxopiperidines remains of general interest for organic and medicinal chemists.

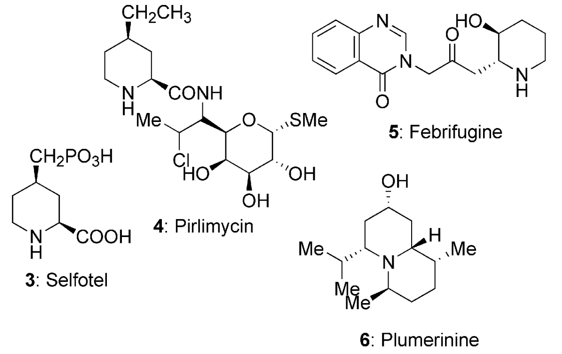

Figure 1. Natural products synthesized via 2-oxopiperidines.

First examples of the synthesis of nitrogen heterocycles involving ring-closing metathesis (RCM) of terminal alkenes, appeared already in the literature in 1992.[12] Since then, the development of more reactive ruthenium-based catalysts[13] tremendously broadened the scope of this reaction, thereby allowing cyclization of highly substituted alkenes, including trisubstituted enamides.[14]

Among various applications of the metathesis reaction, ring-closing metathesis (RCM) has emerged as one of the most powerful tools for construction cyclic compounds.[15,16] Following up on recent research developed in our own group demonstrating the opportunities of RCM of a,β-unsaturated dehydroamino esters,[17] we now wish to report further exploration of this methodology leading to optically active heterocyclic systems of type **1**. Synthesis of these compounds was anticipated to proceed via initial condensation of unsaturated amides with ethyl pyruvate to yield enamides **2**. Subsequently, RCM would provide the 2-oxopiperidine carboxylic esters **1** (Scheme 1). In addition, we reasoned that once developed this methodology could also be applied to more complex systems. For example, condensation of functionalized unsaturated amides (R ≠ H) would provide excellent precursors for 4- and 5-substituted pipecolic acids, representing key elements in a variety of natural products.[18] Furthermore, the double bond provides ample opportunities for introduction of substituents at C5 to further diversify the cyclic structures **1**.

Results and Discussion

We envisaged that formation of linear α,β-unsaturated dehydroamino esters **2** (PG = H) could in principle be carried out in a single transformation via condensation of unsaturated amides with pyruvate.[19] This requires the unsaturated amides **8**, which are readily obtained via acid chloride formation of the corresponding carboxylic acids with oxalyl

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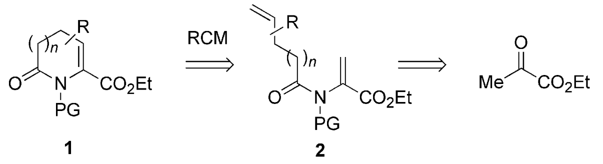
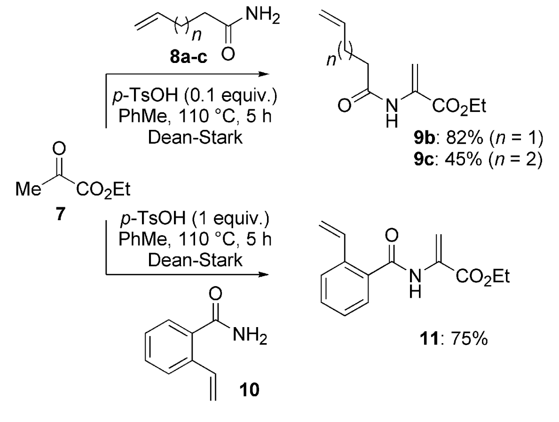
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000587.



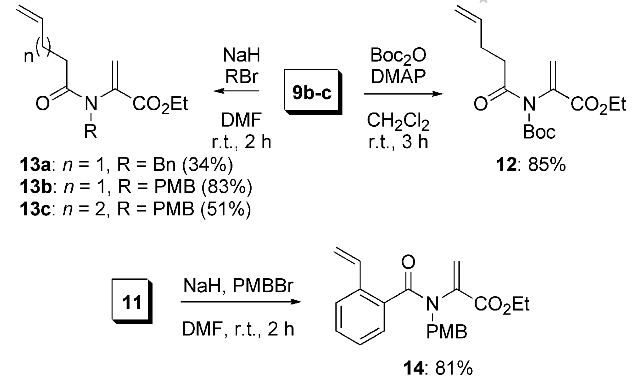
Scheme 1. Ring-closing metathesis approach to dehydroamino esters **1**.

chloride and subsequent reaction with ammonia.[20] Condensation of **8b** ($n = 1$) and **8c** ($n = 2$) with ethyl pyruvate under Dean–Stark conditions in the presence of *p*-toluenesulfonic acid (10 mol-%) afforded initial imine formation followed into the more stable α,β-unsaturated dehydroamino esters **9b** and **c** in 82 and 45% yield, respectively (Scheme 2). Interestingly, condensation of **8a** ($n = 0$) led to isomerization of the terminal alkene to the corresponding crotyl amide. Furthermore, the aromatic amide **10** was prepared from a Wittig reaction with 2-formylbenzoic acid[21] followed by amidation of the carboxylic acid via the aforementioned procedure. Subsequent condensation with ethyl pyruvate provided **11** in 75% yield. With these three precursors in hand, initial attempts to effect ring closure were undertaken. Reactions involved use of the first generation Grubbs catalyst (**G1**) in toluene at 80 °C. However, according to mass spectroscopic analysis, no cyclization took place and only dimerization was observed. Disappointingly, reactions in the presence of the second-generation Grubbs' catalyst (**G2**) led to similar results.



Scheme 2. Condensation of unsaturated amides with ethyl pyruvate.

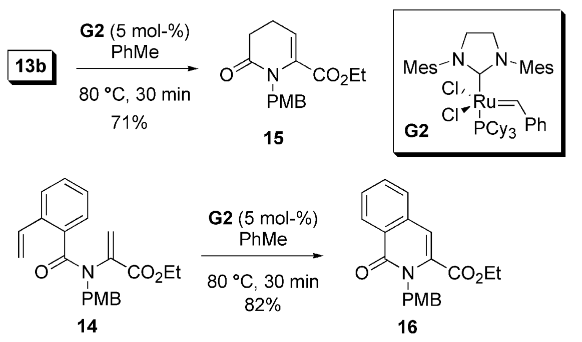
The reluctance of the amides to undergo ring closure[22] could be due to the energetically favored *s-trans* conformation of the amide bond. This situation may be altered by introduction of a protecting group on the nitrogen,[22b,23] which lowers the *s-cis*/*trans* rotation barrier. Attempts to Cbz-protect the nitrogen in the presence of DMAP resulted in the recovery of starting material, while deprotonation with LHMDS followed by addition of CBz-OSu at low temperatures only led to decomposition. Interestingly, reaction of the amide with Boc anhydride (CH_2Cl_2, DMAP, room temp.) led to the formation of the desired Boc-protected dehydroamino ester **12** in 85% yield (Scheme 3).



Scheme 3. Protection of the dehydroamino esters.

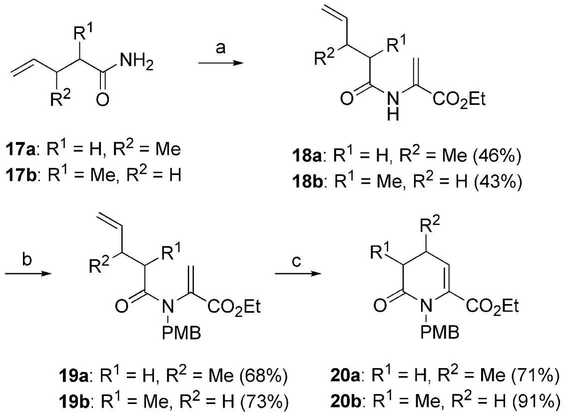
Unfortunately, the dehydroamino ester **12** remained unreactive toward RCM upon treatment with **G1** and **G2** (10 mol-%) and only led to multiple products after extended reaction times. While the energetically unfavored *s-cis* conformation of the dehydroamino ester is required for cyclization to proceed, carbamate-protection of the amide probably renders s-*cis*/*trans* isomerization sterically impossible.

Next, *N*-alkylation was pursued to enhance rotational freedom. First, **9b** was treated with benzyl bromide in the presence of LHMDS at temperatures ranging from –78 °C to room temp. However, this attempt led to decomposition of the starting material. Therefore **9b** was treated with benzyl bromide in the presence of sodium hydride. Although this resulted in the desired compound **13a**, the yield was rather low (34%). Addition of the more reactive *p*-methoxybenzyl bromide (PMBBr) on the other hand yielded **13b** in 56%. In addition, portionwise addition of sodium hydride increased the yield to 83%. Gratifyingly, subsequent RCM in the presence of **G2** (toluene, 80 °C) proceeded smoothly to give compound **15** in a yield of 71%. In sharp contrast, cyclization of **13c** under similar conditions led to homodimeric species. Finally, PMB-protection and ring closure of **11** yielded the isoquinoline derivative **16** in 82% yield (Scheme 4).



Scheme 4. RCM-mediated synthesis of 2-oxopiperidine and 2-oxoisoquinazolone carboxylic esters **15** and **16**.

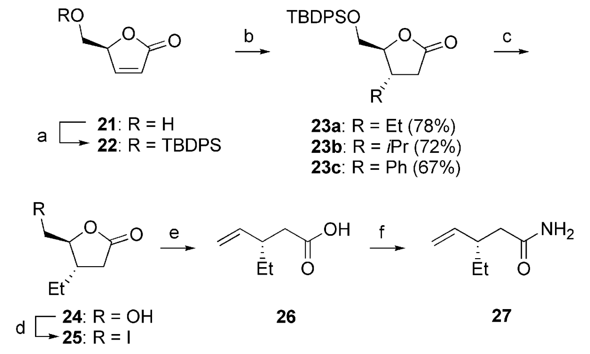
Encouraged by these results we decided to investigate the influence of substituted amides on the condensation reaction. To this end, methyl-substituted amides **17a** and **b** were prepared from the corresponding commercially available carboxylic acids. First, 2-methyl-substituted **17a** was condensed with ethyl pyruvate (Scheme 5). Subsequent *N*-alkylation (68%), followed by RCM provided **20a** in 71% yield. Exposed reaction times for cyclization of the sterically more demanded precursors **19a**–**b** slow down *s-cis*/*trans* isomerization thereby increasing reaction times. Synthesis of the 3-methyl-substituted derivative **20b** gave similar results.



Scheme 5. Conditions: (a) ethyl pyruvate, *p*TsOH (10 mol-%), Dean–Stark, PhMe, 110 °C, 2 h; (b) NaH, PMBBr, DMF, room temp., 1 h; (c) **G2** (5 mol-%), PhMe, 80 °C, 2 h.

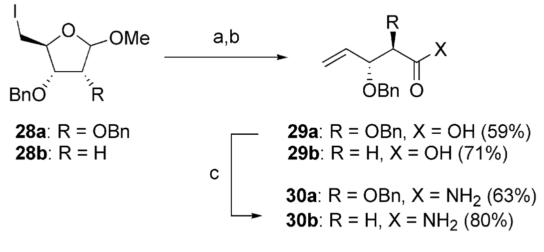
As mentioned in the introduction, substituted 2- and 3-oxopiperidines may represent useful intermediates for the construction of highly functionalized *N*-heterocyclic building blocks. While the cyclic dehydroamino esters prepared so far were racemic, the enantiomerically pure variants would be more valuable. In order to achieve this, synthesis of enantiopure allylic amides would be a prerequisite. Literature examples showing the accessibility of enantiopure oxygen-substituted pentenoic acids upon zinc-mediated ring opening of substituted pentoses,[24] prompted us to probe the generality of this procedure to prepare the aforementioned allylic amides.

The synthesis of enantiopure amide **27** involved TBDPS-protection of commercially available furanone **21** yielding **22** in 85% yield, followed by diastereoselective 1,4-addition using Grignard reagents in the presence of copperthiophenolate to give lactones **23a** and **b** (Scheme 6).[25] While reaction with aliphatic Grignard reagents went smoothly, reaction with aromatic ones appeared to be more problematic leading to multiple products. Treatment of furanone **22** with phenyllithium in the presence of copper iodide and TMSCl on the other hand, resulted in a high conversion into lactone **23c**. In the next steps, the ethyl-substituted furanone **23a** was converted into iodide **25** by deprotection with tetrabutylammonium fluoride and iodination with I_2/PPh_3/imidazole. Next, Zn-mediated ring opening of iodolactone **25** at elevated temperatures afforded the carboxylic acid **26** in 86% yield. Finally, the carboxylate was readily converted into amide **27** via acid chloride formation, followed by reaction with ammonia as described previously.



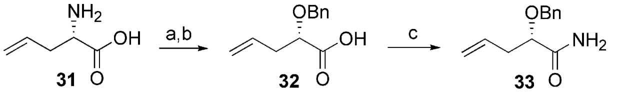
Scheme 6. Conditions: (a) TBDPSCl, imidazole, DMF, room temp., 2 h, 85%; (b) R = Et, *i*Pr: RMgBr, PhSCu, THF, –30 °C, 10 min; R = Ph: PhLi, CuI, TMSCl, Et_2O, –78 °C, 1 h; (c) TBAF, THF, 0 °C, 1 h, 76%; (d) PPh_3, I_2, imidazole, THF, room temp., 1 h, 74%; (e) Zn, AcOH, MeOH, room temp., 15 min, 86%; (f) i: oxalyl chloride, CH_2Cl_2, room temp., 1 h, ii: NH_3, THF, room temp., 2 h, 67%.

In order to prepare hydroxylated derivatives, ribolactonic acids were considered suitable precursors. Extensive research proved that protection of the alcohols was not straightforward. While silyl ethers were hydrolyzed during the condensation reaction, *O*-alkylation on the other hand led to multiple products. Gratifyingly, 1-*O*-methyl-D-ribofuranoside derivative **28a**, readily obtained via literature procedures,[26] afforded the iodinated precursor for ring opening. Although reduction of **28a** with zinc in MeOH proceeded slowly at 70 °C, resulting in multiple products, addition of acetic acid in a THF/H_2O mixture at room temperature afforded the carboxylic acid **29a** in 89% yield. In the next step, oxidation of the aldehyde into the carboxylic acid should lead to the carboxylic acid which was then transformed into the amide precursor for condensation via described procedures (Scheme 7). Where both Pinnick and Jones oxidation appeared to be too harsh resulting in decomposition, treatment with the fairly mild oxidant pyridinium dichromate (PDC) gave the carboxylic acid in 80% yield. Finally, conversion into the ester and quenching with ammonia provided **30a**. With the synthesis of **30a** completed, the same procedure was applied to the 2-deoxy variant **30b** which proceeded in a similar fashion.



Scheme 7. Conditions: (a) Zn, AcOH, THF/H_2O (4:1), 70 °C, 30 min; (b) PDC, DMF, room temp., 16 h; (c) For R = H: a. oxalyl chloride, CH_2Cl_2, room temp., 1 h; b. NH_3, THF, room temp., 2 h; for R = OBn: a. $TMSCHN_2$, MeOH, room temp., 15 min; b. 7 M NH_3, MeOH, room temp., 48 h.

At this point, having successfully realized the synthesis of the 3-*O*- and 2,3-*O*-(di)substituted unsaturated dehydroamino esters **30a**–**b**, we aimed to synthesize the 2-*O*-substituted variant at the α-position. The unnatural amino acid L-allylglycine (**31**) was thought to be a suitable precursor. At first, a diazotization reaction introduced the hydroxy group with full retention of stereochemistry. Then, *O*-alkylation using benzyl bromide with a large excess of NaH provided **32** in a yield of 41% as a single enantiomer. Carboxylic acid **32** was successively treated with oxalyl chloride and ammonia to form the amide **33** (Scheme 8). Disappointingly, HPLC measurements showed complete racemization. Probably, ammonia acts as a base resulting in ketene formation, thereby leading to the racemic amide **33**. To avoid racemization, the amide was successfully synthesized via treatment of the corresponding methyl ester with ammonia, which is not prone to ketene formation.

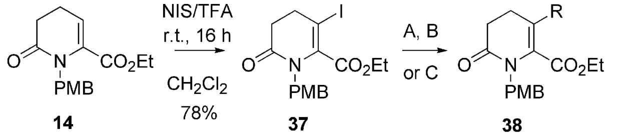


Scheme 8. Conditions: (a) $NaNO_2$, H_2O/AcOH (4:1), 70 °C, 3 h; (b) BnBr, NaH, DMF, room temp., 2 h (41%, 2 steps); (c) $TMSCHN_2$, MeOH, room temp., 15 min, then 7 M NH_3, MeOH, room temp., 48 h (59%).

With the four unsaturated amides in hand, the stage was set for condensation with ethyl pyruvate as described above (Table 1). Indeed, formation of the dehydroamino esters **34** proceeded as anticipated. Next, alkylation of **34** with PMBBr provided the α,β-unsaturated dehydro-amino esters ready for RCM. Finally, we were pleased that RCM of both oxygen- and C3-substituted dehydroamino esters **35b** and **35d** proceeded smoothly with **G2** in toluene at 80 °C. Cyclization of the 2-*O*-substituted precursor **35a** also proceeded well in 58% yield. This in sharp contrast to the 2,3-disubstituted product **35c**, which did not lead to any cyclization, probably due to steric hindrance.

With the synthesis of the functionalized α,β-substituted cyclic dehydroamino esters completed, we envisioned that incorporation of β-substituents onto the heterocycle would enlarge the diversity of the heterocycle. Thus, the enamide was iodinated to give a new key intermediate enabling introduction of a variety of substituents via cross-coupling methodology. Indeed, when **14** was subjected to NIS at elevated temperatures, the iodinated **37** was isolated, albeit in a yield of only 6%. This might be due to electrophilic aromatic substitution onto the PMB group. Gratifyingly, treatment of **14** at room temperature in the presence of TFA to increase the electrophilicity of the iodonium ion, resulted in **37** in a good yield of 78%. Iodide **37** was then subjected to a range of cross-couplings for the formation of C–C bonds as depicted in Table 2. Finally, an Ullmann-type addition/elimination protocol led to the successful introduction of aromatic/aliphatic alcohols, aromatic thiols, amides and carbamates in moderate to good yields.[27]

Table 2. Synthesis of 5-substituted cyclic dehydroamino esters.



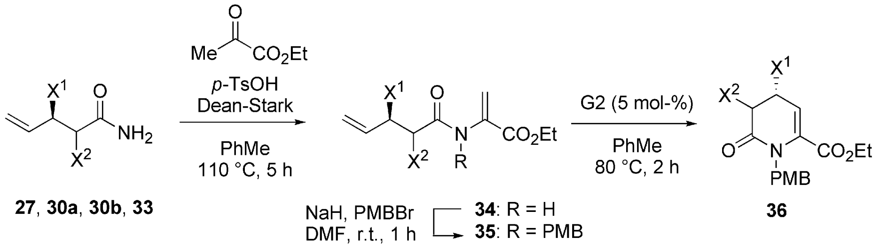
Entry	R	Method[a]	Product	Yield (%)
1	Ph	A	**38a**	70
2	3-FC_6H_4	A	**38b**	78
3	PhCH=CH	A	**38c**	86
4	EtO_2CCH=CH	B	**38d**	79
5	CH_2=CH	C	**38e**	74
6	PhS	D	**38f**	49
7	BnO	D	**38g**	73
8	BzHN	D	**38h**	75
9	CbzHN	D	**38i**	85

[a] A: 10 mol-% $Pd(OAc)_2$, $PhB(OH)_2$, Na_2CO_3, EtOH, 55 °C, $RB(OH)_2$; B: DIPEA, $Pd(OAc)_2$, 80 °C, ethyl acrylate; C: 5 mol-% CuI (cat.), 10 mol-% $Pd(PPh_3)_4$, CsF, DMF, 45 °C, $\mathrm{RS}n\mathrm{Bu}_3$; D: 10 mol-% CuI, 10 mol-% 1,10-phenanthroline, PhMe, 110 °C, RSH/ROH/RCO_2NH_2.

Conclusions

In conclusion, we have developed a short route for the synthesis of 2-oxopiperidine carboxylic esters via condensation of pyruvate with olefinic amides, followed by *N*-alk-

Table 1. RCM of optically active dehydroamino esters.



Entry	Substrate	X^1	X^2	Yield (%)	Yield (%)	Yield (%)
1	**33**	H	OBn (*S*)	**34a**: 59% (R = H)	**35a**: 52% (R = PMB)	**36a**: 58% (R = PMB)
2	**30a**	OBn	H	**34b**: 38% (R = H)	**35b**: 78% (R = PMB)	**36b**: 91% (R = PMB)
3	**30b**	OBn	OBn (*R*)	**34c**: 73% (R = H)	**35c**: 66% (R = PMB)	**36c**: 0% (R = PMB)
4	**27**	Et	H	**34d**: 57% (R = H)	**35d**: 77% (R = PMB)	**36d**: 88% (R = PMB)

ylation and ring closure to obtain the targeted heterocycles. Furthermore, both oxygen- and carbon-substituted amides at the allylic position were readily incorporated via the newly developed method. Finally, cross-coupling reactions applied onto iodinated cyclic dehydroamino esters led to the introduction of both carbon- and hetero-substituents at C5.

Experimental Section

Ethyl 2-(Pent-4-enoyl)aminoacrylate (9b): To a solution of **8b** (515 mg, 5.2 mmol) in PhMe (50 mL) were added hydroquinone (57.2 mg, 10 mol-%), *p*TsOH (98.8 mg, 10 mol-%) and ethyl pyruvate (1.14 mL, 10.4 mmol). The reaction mixture was stirred using Dean–Stark conditions under slightly reduced pressure. After 3 h the reaction was cooled to room temperature and filtered through a plug of neutral Al_2O_3. The Al_2O_3 was washed with PhMe (2 × 50 mL) and the organic layer was concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane, 1:1) to give ester **9b** (594 mg, 3.02 mmol, 82%) as a colorless oil. R_f = 0.75 (EtOAc/heptane, 1:1). FTIR (ATR): $\tilde{\nu}$ = 1187, 1314, 1512, 1683, 2980, 3355 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.82 (br. s, 1 H, N*H*), 6.60 (s, 1 H, C=C*H*$_2$), 5.88 (d, *J* = 1.5 Hz, 1 H, C=C*H*$_2$), 5.77–5.88 (m, 1 H, CH=C*H*$_2$), 5.01–5.11 (m, 2 H, C*H*$_2$), 4.29 (q, *J* = 7.1 Hz, 2 H, C*H*$_2$), 2.40–2.46 (m, 4 H, 2 × C*H*$_2$), 1.34 (t, *J* = 7.1 Hz, 3 H, C*H*$_3$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.54, 163.61, 136.07, 130.56, 115.29, 107.62, 61.65, 36.24, 28.61, 13.56 ppm. HRMS (ESI) *m/z* calcd. for $C_{10}H_{15}INO_4Na$ [M + Na]$^+$: 220.09496, found: 220.09528.

Ethyl 2-[(4-Methoxybenzyl)pent-4-enoylamino]acrylate (13b): To a solution of **9b** (187 mg, 0.88 mmol) in dry DMF (9 mL), were added at 0 °C NaH (40 mg, 1.1 equiv.) and then PMBBr (190 µL, 1.5 equiv.). The reaction mixture was stirred for 1 h and then another portion of NaH (18 mg, 0.97 mmol) was added. After stirring for another hour, the reaction was quenched with H_2O (10 mL) and extracted with a mixture of EtOAc/heptane (1:1) (3 × 25 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane, 1:2) to give **13b** (248 mg, 0.73 mmol, 83%) as a colorless oil. R_f = 0.48 (EtOAc/heptane, 1:1). FTIR (ATR): $\tilde{\nu}$ = 1175, 1246, 1511, 1663, 1723, 2936 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.09 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.91 (d, *J* = 8.2 Hz, 2 H, Ar*H*), 6.33 (s, 1 H, C=C*H*$_2$), 5.81 (m, 1 H, C*H*=CH$_2$), 5.29 (s, 1 H, C=C*H*$_2$), 4.89–4.96 (m, 2 H, CH=C*H*$_2$), 4.56 (s, 2 H, C*H*$_2$Ar), 4.12 (q, *J* = 7.0 Hz, 2 H, C*H*$_2$), 3.87 (s, 3 H, C*H*$_3$Ar), 1.94–2.11 (m, 4 H, 2 × C*H*$_2$), 1.27 (t, *J* = 7.0 Hz, 3 H, C*H*$_3$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.94, 163.33, 158.50, 138.32, 137.55, 129.85, 129.75, 127.29, 114.55, 113.25, 61.28, 54.72, 49.73, 32.72, 32.64, 23.88, 13.09 ppm. HRMS (ESI) *m/z* calcd. for $C_{19}H_{25}INO_4Na$ [M + Na]$^+$: 354.1681, found: 354.1694.

Ethyl 1-(4-Methoxybenzyl)-6-oxo-1,4,5,6-tetrahydropyridine-2-carboxylate (15): A solution of **13b** (170 mg, 0.54 mmol) in dry PhMe (25 mL) was flushed with nitrogen for 15 min after which the temperature was raised to 80 °C. At 80 °C **G2** (23 mg, 5 mol-%) was added and the reaction was stirred for 1 h. After 1 h the organic layer was concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane, 1:2) to give **15** (111 mg, 0.38 mmol, 71%) as a brown oil. R_f = 0.34 (EtOAc/heptane, 1:1). FTIR (ATR): $\tilde{\nu}$ = 1249, 1513, 1677, 1720 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.12 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.85 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.31 (t, *J* = 2.6 Hz, 1 H, C=C*H*), 5.06 (s, 2 H, C*H*$_2$Ar), 4.17 (q, *J* = 7.2 Hz, 2 H, C*H*$_2$), 3.82 (s, 3 H, C*H*$_3$Ar), 2.68–2.77 (m, 2 H, C*H*$_2$), 2.35–2.43 (m, 2 H, C*H*$_2$), 1.25 (t, *J* = 7.0 Hz, 3 H, C*H*$_3$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.04, 158.32, 133.98, 129.91, 128.77, 120.76, 113.40, 60.83, 54.74, 44.07, 30.55, 19.32, 13.59 ppm. HRMS (ESI) *m/z* calcd. for $C_{16}H_{19}NO_4Na$ [M + Na]$^+$: 312.1212, found: 312.1204.

(4*S*,5*S*)-4-Ethyl-5-(hydroxymethyl)dihydrofuran-2(3*H*)-one (24): To a solution of **23a** (81 mg, 0.21 mmol) in THF (1 mL) at 0 °C was added TBAF (212 µL, 0.21 mmol) and this mixture was stirred for 2 h. The reaction was quenched with aqueous NH_4Cl, extracted with CH_2Cl_2, dried ($MgSO_4$), concentrated in vacuo and purified by column chromatography (EtOAc/heptane, 1:1) to afford **24** (17 mg, 56%) as a colorless oil. R_f = 0.23 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ = +12.1 (*c* 0.09, CH_2Cl_2). FTIR (ATR): $\tilde{\nu}$ = 916, 1709, 2930, 2963 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 4.18–4.16 (m, 1 H, *H*4), 3.89 (d, *J* = 12.6 Hz, 1 H, *H*5α), 3.63 (dd, *J* = 4.2, 12.6 Hz, 1 H, *H*5β), 2.74 (dd, *J* = 8.5, 17.2 Hz, 1 H, *H*2α), 2.65 (s, 1 H, O*H*), 2.31–2.37 (m, 1 H, *H*3), 2.22 (dd, *J* = 8.0, 17.2 Hz, 1 H, *H*2β), 1.38–1.62 (m, 2 H, C*H*$_2$), 0.94 (t, *J* = 7.4 Hz, 3 H, C*H*$_3$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 176.53, 85.42, 62.80, 37.28, 34.42, 25.80, 11.23 ppm. HRMS (ESI) *m/z* calcd. for $C_{17}H_{21}NO_4Na$ [M + Na]$^+$: 167.0684, found: 167.0677.

(4*S*,5*S*)-4-Ethyl-5-(iodomethyl)dihydrofuran-2(3*H*)-one (25): Compound **24** (40 mg, 0.28 mmol) and PPh_3 (88 mg, 0.34 mmol) were dissolved in THF (3 mL). This solution was heated to 70 °C and a solution of imidazole (29 mg, 0.42 mmol), I_2 (85 mg, 0.34 mmol) in CH_2Cl_2 (2 mL) was added. After stirring for 1 h at room temperature, the mixture was diluted with CH_2Cl_2 (15 mL) washed with 10% aqueous $Na_2S_2O_3$ (15 mL), H_2O (20 mL) and brine (15 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and purified using column chromatography (EtOAc/heptane, 1:1) to give furanone **25** (52 mg, 74% yield) as a colorless oil. R_f = 0.81 (EtOAc/heptane, 3:1). $[\alpha]_D^{20}$ = +36.9 (*c* 0.0035, CH_2Cl_2). FTIR (ATR): $\tilde{\nu}$ = 1148, 1170, 1776, 2960 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 4.12 (dd, *J* = 10.2, 5.2 Hz, 1 H, *H*4), 3.30–3.42 (m, 2 H, *H*5), 2.79 (dd, *J* = 19.8, 11.0 Hz, 1 H, *H*2α), 2.22–2.30 (m, 1 H, *H*2β), 1.61–1.69 (m, 1 H, *H*3), 1.40–1.52 (m, 1 H, C*H*$_2$), 0.97 (t, *J* = 7.4 Hz, 3 H, C*H*$_3$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.90, 82.62, 41.87, 34.05, 26.12, 11.12, 6.54 ppm. HRMS (ESI) *m/z* calcd. for $C_{17}H_{22}NO_4$ (M – H)$^-$: 127.0759, found: 127.0759.

(*R*)-3-Ethylpent-4-enoic Acid (26): To a solution of **25** (372 mg, 1.75 mmol) in MeOH (20 mL), zinc (307 mg, 5.25 mmol) and 10 drops of acetic acid were added and the mixture was stirred for 2 h at room temperature. Next, it was filtered through Celite, concentrated in vacuo and purified by column chromatography (EtOAc/heptane, 1:2) to afford carboxylic acid **26** (173 mg, 1.35 mmol, 86%) as a colorless oil. $[\alpha]_D^{20}$ = +7.8 (*c* 0.004, CH_2Cl_2). FTIR (ATR): $\tilde{\nu}$ = 916, 1707, 2924, 2962 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.58–5.68 (m, 1 H, C*H*=CH$_2$), 4.97–5.13 (m, 2 H, CH=C*H*$_2$), 2.37–2.41 (m, 2 H, C*H*$_2$), 2.31–2.40 (m, 1 H, C*H*), 1.41–1.52 (m, 1 H, CH$_2$), 1.35 (m, 1 H, CH$_2$), 0.88 (t, *J* = 7.4 Hz, 3 H, CH$_3$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 177.82, 139.99, 114.90, 41.23, 38.91, 26.76, 10.89 ppm. HRMS (ESI) *m/z* calcd. for $C_{17}H_{20}NO_4$ (M – H)$^-$: 127.0759, found: 127.0759.

3-Ethylpent-4-enamide (27): To a solution of acid **26** (173 mg, 1.37 mmol) in MeOH (4 mL) a 7 M solution of NH_3 in MeOH (3 mL) was added. The mixture was stirred for 4 days at room temperature, concentrated in vacuo and the residue was purified by column chromatography (EtOAc/heptane, 1:1) to afford amide **27** (110 mg, 67%) as a white solid. R_f = 0.08 (EtOAc/heptane, 1:2). $[\alpha]_D^{20}$ = –12.7 (*c* 0.01, CH_2Cl_2). IR (ATR): $\tilde{\nu}$ = 1409, 1631, 1667, 3179, 3351 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz): δ = 5.63 (ddd, *J*

= 17.2, 10.3, 8.3 Hz, 1 H, C*H*=CH$_2$) 5.41 (br. s, 2 H, N*H*$_2$), 5.01–5.12 (m, 2 H, CH=C*H*$_2$), 2.35–2.47 (m, 1 H, CH), 2.23 (dq, *J* = 14.3, 7.1 Hz, 2 H, C*H*$_2$), 1.42–1.57 (m, 1 H, CH$_2$), 1.26–1.36 (m, 1 H, C*H*$_2$), 0.88 (t, *J* = 7.4 Hz, 3 H, C*H*$_3$) ppm. ^{13}C NMR (CD$_3$OD, 75 MHz): δ = 173.93, 140.58, 115.09, 41.86, 41.02, 26.93, 10.97 ppm. HRMS (ESI) *m*/*z* calcd. for $C_{12}H_{15}NO$ [M + H]$^+$: 128.1076, found: 128.1069.

(*R*)-Ethyl 2-(3-Ethylpent-4-enamido)acrylate (34d): To a solution of amide **27** (52 mg, 0.41 mmol) in PhMe (3 mL), *p*TsOH (7.9 mg, 0.041 mmol) and ethyl pyruvate (90 µL, 0.82 mmol) were added. The reaction mixture was stirred under Dean–Stark conditions applying vacuum for regulation. After 3 h the reaction was cooled to room temperature and poured over a plug of neutral Al_2O_3. The Al_2O_3 was washed with PhMe (2 × 25 mL). The organic layer was concentrated in vacuo to give acrylate **34d** (52 mg, 0.23 mmol, 57%). R_f = 0.66 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ = +10.3 (*c* 0.01, CH$_2$Cl$_2$). IR (ATR): $\tilde{\nu}$ = 1188, 1316, 1514, 1686, 2950, 3360 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.75 (s, 1 H, N*H*), 6.60 (s, 1 H, C=C*H*$_2$), 5.87 (d, *J* = 1.4 Hz, 1 H, C=C*H*$_2$), 5.64 (ddd, *J* = 17.2, 10.3, 8.3 Hz, 1 H, CH=C*H*$_2$), 5.01–5.13 (m, 2 H, CH=C*H*$_2$), 4.29 (q, *J* = 7.1 Hz, 2 H, C*H*$_2$), 2.42–2.56 (m, 1 H, C*H*), 2.39 (dd, *J* = 5.8, 14.4 Hz, 1 H, C*H*), 2.29 (dd, *J* = 14.4, 8.4 Hz, 1 H, C*H*), 1.32–1.44 (m, 1 H, C*H*$_2$), 1.34 (t, *J* = 7.1 Hz, 3 H, C*H*$_3$), 1.21–1.39 (m, 1 H, CH$_2$), 0.89 (t, *J* = 7.4 Hz, 3 H, C*H*$_3$) ppm. ^{13}C NMR (MeOD, 75 MHz): δ = 170.24, 163.71, 140.16, 130.50, 115.31, 107.86, 61.70, 42.82, 41.83, 26.92, 13.63, 10.97 ppm. HRMS (ESI) *m*/*z* calcd. for $C_{12}H_{19}NO_3Na$ [M + Na]$^+$: 248.1363, found: 248.1270.

(*R*)-Ethyl 2-[3-Ethyl-*N*-(4-methoxybenzyl)pent-4-enamido]acrylate (35d): To a solution of acrylate **34d** (26 mg, 0.116 mmol) in dry DMF (2 mL) were added at 0 °C NaH (11.4 mg, 0.232 mmol) and then PMBBr (33.2 µL, 0.232 mmol). The reaction mixture was stirred for 1 h, quenched with H$_2$O (10 mL) and extracted with a mixture of EtOAc/heptane (1:1) (3 × 10 mL). The organic layer was dried (MgSO$_4$) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane, 1:2) to give acrylate **35d** (31 mg, 0.090 mmol, 77%) as a colorless oil. R_f = 0.59 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ = +5.6 (*c* 0.056, CH$_2$Cl$_2$). IR (ATR): $\tilde{\nu}$ = 1177, 1248, 1512, 1724 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.17 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 6.81 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 6.32 (s, 1 H, C=C*H*$_2$), 5.51–5.64 (m, 1 H, C*H*=CH$_2$), 5.31 (s, 1 H, C=C*H*$_2$), 4.96–5.08 (m, 2 H, C*H*=CH$_2$), 4.69 (d, *J* = 15.2 Hz, 1 H, C*H*$_2$Ar), 4.57 (d, *J* = 15.2 Hz, 1 H, C*H*$_2$Ar), 4.22 (q, *J* = 7.2 Hz, 2 H, C*H*$_2$), 3.78 (s, 3 H, C*H*$_3$Ar), 2.44–2.57 (m, 1 H, C*H*), 2.21 (d, *J* = 7.3 Hz, 2 H, C*H*$_2$), 1.28 (t, *J* = 7.1 Hz, 3 H, C*H*$_3$), 0.85 (t, *J* = 7.4 Hz, 3 H, C*H*$_3$) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 172.31, 171.14, 158.49, 140.78, 138.34, 135.10, 129.90, 127.54, 114.35, 113.22, 61.34, 54.76, 49.72, 41.57, 38.57, 26.73, 13.64, 11.06 ppm. HRMS (ESI) *m*/*z* calcd. for $C_{20}H_{27}NO_4Na$ [M + Na]$^+$: 368.1838, found: 368.1838.

(*R*)-Ethyl 4-Ethyl-1-(4-methoxybenzyl)-6-oxo-1,4,5,6-tetrahydropyridine-2-carboxylate (36d): A solution of acrylate **35d** (31 mg, 0.090 mmol) in dry PhMe (2 mL) was flushed with nitrogen for 15 min after which the temperature was raised to 80 °C. At 80 °C catalyst **G2** (8.5 mg, 10 mol-%) was added and the reaction was stirred for 1 h. Then the organic layer was concentrated in vacuo and the residue was purified by column chromatography (EtOAc/heptane, 1:2) to give tetrahydropyridine **36d** (26 mg, 0.082 mmol, 91%) as a brown oil. R_f = 0.41 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ = –16.7 (*c* 0.02, CH$_2$Cl$_2$). FTIR (ATR): $\tilde{\nu}$ = 1255, 1507, 1683, 1714, 2950 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.07 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 6.79 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 6.20 (dd, *J* = 0.8, 4.1 Hz, 1 H, C=C*H*), 5.22 (d, *J* = 14.9 Hz, 1 H, C*H*$_2$Ar), 4.86 (d, *J* = 14.9 Hz, 1 H, C*H*$_2$Ar), 4.12–4.21 (m, 2 H, C*H*$_2$), 3.77 (s, 3 H, C*H*$_3$Ar), 2.61 (ddd, *J* = 14.6, 5.0, 1.0 Hz, 1 H, C*H*$_2$), 2.38–2.48 (m, 1 H, C*H*), 2.33 (dd, *J* = 14.6, 10.6 Hz, 1 H, C*H*$_2$), 1.40–1.46 (m, 2 H, C*H*$_2$), 1.24 (t, *J* = 7.1 Hz, 3 H, C*H*$_3$), 0.93 (t, *J* = 7.4 Hz, 3 H, C*H*$_3$) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 170.00, 158.33, 128.99, 125.36, 113.35, 60.88, 54.73, 44.05, 36.27, 32.62, 25.63, 13.62, 10.71 ppm. HRMS (ESI) *m*/*z* calcd. for $C_{18}H_{23}NO_4Na$ [M + Na]$^+$: 340.1525, found: 340.1523.

Ethyl 3-Iodo-1-(4-methoxybenzyl)-6-oxo-1,4,5,6-tetrahydropyridine-2-carboxylate (37): To a solution of **14** (50 mg, 0.173 mmol) in CH$_2$Cl$_2$ (2 mL) was added dropwise a mixture of NIS (43 mg, 0.190 mmol) and TFA (13 mL, 0.173 mmol) in CH$_2$Cl$_2$ (2 mL). The reaction mixture was stirred at room temperature and after 12 h another equivalent of NIS/TFA mixture was added, after which the reaction was stirred for three hours. Upon quenching with aqueous NaHCO$_3$, the layers were separated. The organic layer was washed with H$_2$O (50 mL) and brine (50 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane, 1:2) to give tetrahydropyridine **37** (57 mg, 0.137 mmol, 78%) as a colorless oil. R_f = 0.67 (EtOAc/heptane, 1:1). FTIR (ATR): $\tilde{\nu}$ = 1247, 1681, 1727, 2980 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.09 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 6.82 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 4.75 (s, 2 H, C*H*$_2$Ar), 4.14 (q, *J* = 7.2 Hz, 2 H, C*H*$_2$), 3.78 (s, 3 H, C*H*$_3$Ar), 2.84 (t, *J* = 7.6 Hz, 3 H, C*H*$_3$) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 168.4, 162.9, 158.6, 137.1, 128.5, 128.3, 113.4, 74.2, 61.6, 54.8, 46.1, 34.6, 31.7, 13.3 ppm. HRMS (ESI) *m*/*z* calcd. for $C_{16}H_{18}INO_4Na$ [M + Na]$^+$: 438.0178, found: 438.0172.

Ethyl 1-(4-Methoxybenzyl)-6-oxo-3-phenyl-1,4,5,6-tetrahydropyridine-2-carboxylate (38a): To a solution of **37** (17.5 mg, 0.042 mmol) in EtOH (1 mL) were added PhB(OH)$_2$ (7.2 mg, 0.063 mmol), Pd(OAc)$_2$ (1 mg, 10 mol-%) and Na$_2$CO$_3$ (8.3 mg, 0.084 mmol). The reaction mixture was stirred at 55 °C for 1 h, after which H$_2$O (10 mL) was added and the mixture was extracted with CH$_2$Cl$_2$ (2 × 10 mL). The organic layer was dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/heptane, 1:2) to give tetrahydropyridine **38a** (10 mg, 0.026 mmol, 70%) as a colorless oil. R_f = 0.42 (EtOAc/heptane, 1:1). FTIR (ATR): $\tilde{\nu}$ = 1248, 1678, 2976 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.21–7.31 (m, 4 H, Ar*H*), 7.11–7.15 (m, 3 H, Ar*H*), 6.81 (d, *J* = 8.8 Hz, 1 H, ArH), 4.87 (s, 3 H, CH$_2$Ar), 3.79 (q, *J* = 7.2 Hz, 2 H, CH$_2$), 3.77 (s, 3 H, CH$_3$Ar), 2.67–2.74 (m, 4 H, 2 × C*H*$_2$), 0.74 (t, *J* = 7.2 Hz, 3 H, CH$_3$) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 169.27, 163.76, 158.40, 138.75, 128.83, 128.76, 128.51, 127.74, 126.95, 126.55, 125.49, 113.377, 60.80, 54.76, 44.82, 30.58, 26.92, 12.72 ppm. HRMS (ESI) *m*/*z* calcd. for $C_{22}H_{23}NO_4Na$ [M + Na]$^+$: 388.1525, found: 388.1538.

Supporting Information (see also the footnote on the first page of this article): General experimental and ^{1}H and ^{13}C NMR spectra of selected compounds.

Acknowledgments

This research has been financially supported (in part) by the Council for Chemical Sciences of The Netherlands Organization for Scientific Research (NWO-CW). Chiralix B.V. (Nijmegen, The Netherlands) is kindly acknowledged for generously providing L-allylglycine.

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Received: April 27, 2010