Synthesis of carboxylic amides by ring-opening of oxazolidinones with Grignard reagents

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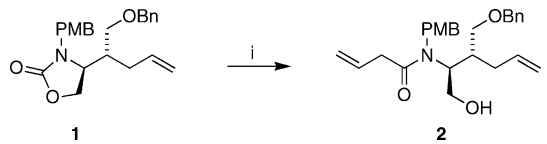
Treatment of *N*-alkyl-oxazolidin-2-ones with Grignard reagents gives tertiary carboxylic amide products. Various substituted oxazolidinones can be used as illustrated with phenyl, benzyl or isopropyl groups on the 4-position, and methyl, benzyl or *p*-methoxybenzyl groups on the 3-position (the nitrogen atom). A selection of Grignard reagents were successful, including allyl, benzyl, alkyl and phenyl magnesium halides. The organomagnesium species attacks the carbonyl group and promotes ring-opening of the oxazolidinone. The product tertiary amides are useful substrates for stereoselective transformations and were applied to a highly selective enolate alkylation and to a ring-closing metathesis reaction to a six-membered lactam and hence a formal synthesis of the alkaloids (−)-coniine and (+)-stenusine.

Introduction

Oxazolidin-2-ones are very important in synthetic chemistry. They form the basis of some antibacterial agents,[1] and have played a crucial role as chiral auxiliaries in asymmetric synthesis.[2] The oxazolidin-2-one ring can act as a masked β-amino-alcohol and has been used for the synthesis of a variety of different ring-opened products.[3,4] Typically the oxazolidin-2-one is hydrolysed to a β-amino-alcohol using forcing conditions such as by refluxing with excess hydroxide ions.[3] Alternatively, but less commonly, strong acids, trimethylsilanolate or diamines such as ethylene diamine can be used.[4] As far as we are aware, there is only a single publication of the ring-opening of oxazolidin-2-ones with alkyllithiums,[5] together with an isolated example of the use of methyllithium to open a hindered oxazolidin-2-one.[6] These methods make use of the (weak) electrophilicity of the carbonyl group. The carbon atom at C-5 is also electrophilic and ring-opening of oxazolidin-2-ones at C-5 with a nucleophile is possible.[7]

During research on the synthesis of some alkaloids, we had recourse to investigate the ring-opening of the oxazolidin-2-one **1** (Scheme 1).[8] Treatment of this oxazolidin-2-one with allyl magnesium bromide gave the tertiary carboxylic amide **2**. To our knowledge this is the first example of the ring-opening of an oxazolidin-2-one with a Grignard reagent, although there is a report of the use of a Grignard reagent to open a 6-membered cyclic carbamate (a benzoxazinone).[9] This chemistry could provide a useful method of wide generality for ring-opening of oxazolidin-2-ones that expands the range of carbon-based nucleophiles in comparison to the addition of the more reactive organolithium species.[5] We therefore decided to investigate the reaction further and report here a range of examples of this methodology.

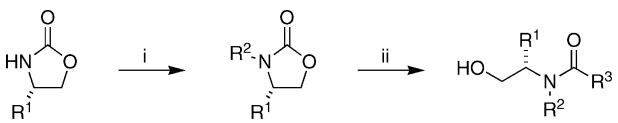


1 **2**

Scheme 1 *Reagents and conditions*: i, 2 equiv. allyl magnesium bromide, THF, −78 °C, 2.5 h, 63%; PMB = *p*-methoxybenzyl.

Results and discussion

The *N*-alkyl oxazolidin-2-ones **4a–f** used in this chemistry were prepared from their corresponding *N*-unsubstituted analogues **3a–c** (Schemes 2 and 3), themselves prepared using standard methods as reported previously.[10] The *N*-alkylations were performed using sodium or potassium hydride in THF together with iodomethane, benzyl bromide or *p*-methoxybenzyl chloride.[11] This led to a selection of different substrates **4a–f**, including *N*-alkyl and *N*-benzyl compounds with either alkyl (isopropyl), benzyl or phenyl substituents at the 4-position of the oxazolidin-2-one ring. This range of substrates was used to probe the scope of the subsequent ring-opening reaction.



3a $R^1 = {}^iPr$
3b $R^1 = CH_2Ph$

4a $R^1 = {}^iPr$, $R^2 = CH_2Ph$
4b $R^1 = {}^iPr$, $R^2 = PMB$
4c $R^1 = CH_2Ph$, $R^2 = Me$
4d $R^1 = CH_2Ph$, $R^2 = PMB$

5a–h

Scheme 2 Ring-opening of oxazolidinones **4a–d** (see Table 1). *Reagents and conditions*: i, NaH, THF, BnBr or PMBCl or MeI; ii, R^3MgX, THF, −78 °C.

Treatment of the oxazolidin-2-ones **4a–d** with allyl, methyl, ethyl or phenyl magnesium bromide or with benzyl magnesium chloride gave the desired tertiary amides **5a–h** (Scheme 2, Table 1). Best yields were normally obtained by using an excess of the Grignard

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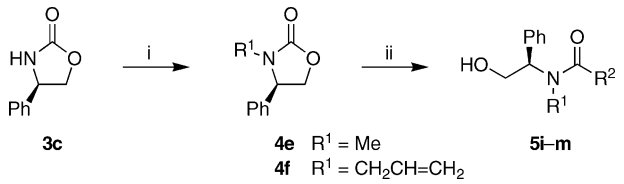


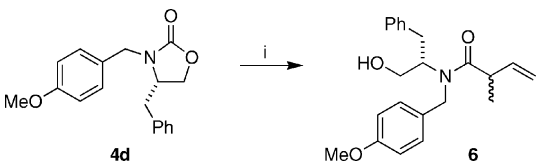
Scheme 3 Ring-opening of oxazolidinones **4e–f** (see Table 2). *Reagents and conditions*: i, NaH, THF, MeI or allyl bromide; ii, R^2MgX, THF, −78 °C.

reagent (1.5–3 equiv.) in THF at low temperature (−78 °C), although in some cases it was beneficial to allow the reaction mixture to warm to room temperature slowly. The products were purified by column chromatography and NMR spectroscopy revealed a mixture of rotamers in all cases. The oxazolidin-2-ones **4e–f** were treated with allyl, ethyl or *n*-hexyl magnesium bromide or with benzyl magnesium chloride to give the related tertiary amides **5i–m** (Scheme 3, Table 2).

Some comments on the ring-opening reaction are worthy of mention. Allyl magnesium bromide was a good nucleophile and good yields of the products **5a**, **5c**, **5d**, **5h** and **5i** were obtained. The product **5c** appeared to be unstable and visible discolouration was observed over several hours at room temperature. Addition of allyl magnesium bromide to the oxazolidinone **4f** was more sluggish but was improved by the addition of further excess of the Grignard reagent (3 equiv. gave 20% yield of **5m**, with 60% recovered oxazolidin-2-one **4f** but 7 equiv. of allyl magnesium bromide gave up to 60% yield of **5m**). The addition of magnesium bromide as an alternative to activate the oxazolidinone was ineffective in this case but did improve the yields in the reactions of alkyl magnesium bromides. Hence MeMgBr and EtMgBr gave only low yields (< 20%) of the products **5e**, **5f** and **5k** in the absence of $MgBr_2$, but significant improvements were obtained in its presence (Table 1, entries 5 and 6 and Table 2, entry 3). The longer chain *n*-hexyl magnesium bromide was successful in the absence of $MgBr_2$ to give the product **5l**. We were pleased to find that the chemistry was also amenable to benzyl Grignard reagents (to give the tertiary amides **5b** and **5j**) and with phenyl magnesium bromide (to give **5g**).

The addition of the Grignard reagent to the oxazolidin-2-one requires several hours at −78 °C and this presumably reflects the poor electrophilicity of the carbonyl group. We propose that the addition provides a tetrahedral intermediate that is relatively stable at low temperature. This intermediate is then hydrolysed on work up to give the desired tertiary carboxylic amide. If the temperature of the mixture is allowed to rise then this should enhance the rate of addition, however it also enhances the breakdown of the tetrahedral intermediate. For example, addition of allyl magnesium bromide at 0 °C gave lower yields of the products **5**, together with, in some cases, the 2,2-diallyl-oxazolidine product (corresponding to the complete replacement of the carbonyl oxygen of **4** by two allyl units).

Allyl magnesium bromide is a good nucleophile for this ring-opening reaction. Insight into the mechanism of the reaction was obtained by studying the related crotyl (but-2-enyl) magnesium bromide as the nucleophile. The addition of this reagent to the oxazolidin-2-one **4d** gave a mixture of products, from which the tertiary amides **6** were isolated as the major components (Scheme 4). These products represent addition of the allyl unit at the γ- position. There was no stereoselectivity in the process and the products **6** were formed as a mixture of stereoisomers.



Scheme 4 Ring-opening of oxazolidinone **4d** with crotyl magnesium bromide. *Reagents and conditions*: i, $MeCH{=}CHCH_2MgBr$, THF, −78 °C, 32%, dr 1:1.

Table 1 Ring-opening of oxazolidinones **4a–d**

Entry	Starting material	Product	R^1	R^2	R^3	Yield **5** (%)
1	**4a**	**5a**	^{i}Pr	CH_2Ph	$CH_2CH{=}CH_2$	69
2	**4a**	**5b**	^{i}Pr	CH_2Ph	CH_2Ph	53
3	**4b**	**5c**	^{i}Pr	PMB	$CH_2CH{=}CH_2$	68
4	**4c**	**5d**	CH_2Ph	Me	$CH_2CH{=}CH_2$	72
5[a]	**4c**	**5e**	CH_2Ph	Me	Me	39
6[a]	**4c**	**5f**	CH_2Ph	Me	Et	44
7	**4c**	**5g**	CH_2Ph	Me	Ph	65
8	**4d**	**5h**	CH_2Ph	PMB	$CH_2CH{=}CH_2$	82

[a] With added $MgBr_2$.

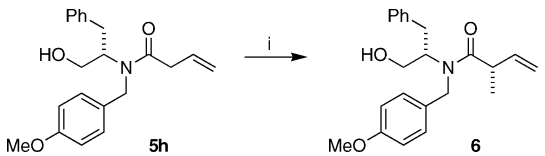
Table 2 Ring-opening of oxazolidinones **4e–f**

Entry	Starting material	Product	R^1	R^2	Yield **5** (%)
1	**4e**	**5i**	Me	$CH_2CH{=}CH_2$	86
2	**4e**	**5j**	Me	CH_2Ph	70
3[a]	**4e**	**5k**	Me	Et	30
4	**4e**	**5l**	Me	$(CH_2)_5CH_3$	52
5	**4f**	**5m**	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	60

[a] With added $MgBr_2$.

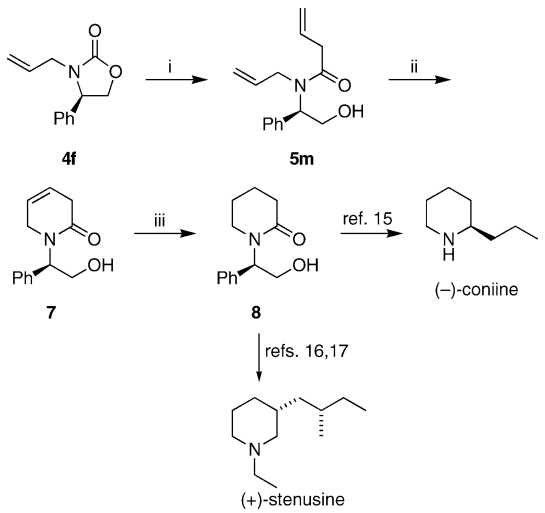
The ability of allyl Grignard reagents to add at the γ- position may contribute to the enhanced reactivity of these nucleophiles, although even simple alkyl Grignard reagents can be successful (Tables 1 and 2).

Tertiary carboxylic amides of β-amino-alcohols have been found to be excellent substrates for asymmetric alkylation reactions. This has been demonstrated using enolates of amides derived from, for example, pseudoephedrine or phenylglycinol.[12] To illustrate this chemistry, the tertiary carboxylic amide **5h** was treated with two equivalents of LDA and LiCl, followed by alkylation with iodomethane (Scheme 5). This gave the alkylated product **6**. The diastereoselectivity in the reaction was high (dr 97:3) and was determined by HPLC. The configuration of the major diastereomer is expected to be that shown in structure **6**, based on related alkylations of other tertiary carboxylic amides.[12]



Scheme 5 Asymmetric alkylation of the amide **5h**. *Reagents and conditions*: i, LDA, LiCl, THF, −78 °C, then MeI, 72%, dr 97:3.

To further illustrate the use of this chemistry, ring-closing metathesis using Grubbs' second generation catalyst[13] with the product **5m** gave the novel 6-membered lactam **7** (Scheme 6).[14] Reduction of the alkene gave the known compound **8**, and this completes a formal synthesis of the alkaloids (−)-coniine[15] and (+)-stenusine.[16,17]



Scheme 6 Formal synthesis of (−)-coniine. *Reagents and conditions*: i, CH_2=$CHCH_2MgBr$, THF, −78 °C, 60%; ii, Grubbs II, CH_2Cl_2, heat, 1.5 h, 94%; iii, H_2, 5% Pd/C, MeOH, room temp., 87%.

Conclusions

The ring-opening of *N*-alkyl-oxazolidin-2-ones is possible using Grignard reagents. A variety of substituted oxazolidin-2-ones and different Grignard reagents can be used. In cases that give low yields, some enhancement can be achieved by using excess Grignard reagent or by conducting the reaction in the presence of $MgBr_2$. The products are tertiary carboxylic amides. These compounds are useful in synthesis, for example as substrates for stereoselective alkylation or for conversion to alkaloids, as demonstrated by ring-closing metathesis to lactam products.

Experimental

General methods

For general experimental details, including information on solvent purifications and the spectrometers used in this research, see previous descriptions.[18]

General method for the ring-opening of *N*-alkyl-oxazolidin-2-ones

The Grignard reagent (3 mmol) was added to the oxazolidinone (1 mmol) in THF (5 mL) at −78 °C. After 3 h, aqueous NH_4Cl (5 mL) was added, the mixture was warmed to room temperature and was extracted with Et_2O (3 × 20 mL), dried (Na_2SO_4) and evaporated. Purification by column chromatography on silica, eluting with petrol–EtOAc, gave the tertiary amide product.

***N*-Benzyl-*N*-[(*S*)-1-hydroxy-3-methylbutan-2-yl]-but-3-enamide 5a.** Using the general method, allyl magnesium bromide and the oxazolidinone **4a** gave the amide **5a** (0.18 g, 69%) as an oil as a mixture of rotamers (ratio 3:1); R_f 0.42 [CH_2Cl_2–EtOAc (4:1)]; $[\alpha]_D^{20}$ +29.1 (1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3395, 2965, 1620; δ_H(250 MHz, $CDCl_3$) 7.42-7.25 (5H, m, ArH), 6.14-5.89 (1H, m, CH=), 5.32-5.08 (2H, m, =CH_2), 4.76 (0.75H, d, *J* 16.5, CH), 4.28 (0.75H, d, *J* 16.5, CH), 4.22-4.16 (0.75H, m, CH), 3.83 (0.25H, d, *J* 16, CH), 3.75-3.54 (1.75H, m, CH + minor rotamer CH peaks), 3.39-3.23 (0.75H, m, CH), 3.22-3.08 (2H, m, CH_2), 2.57-2.43 (0.75H, m, CH), 1.98-1.83 (0.25H, m, CH), 0.99 (0.8H, d, *J* 6.5, CH_3), 0.97 (2.2H, d, *J* 6.5, CH_3), 0.93 (2.2H, d, *J* 6.5, CH_3), 0.90 (0.8H, d, *J* 6.5, CH_3); δ_C(125 MHz, $CDCl_3$) 173.5, 173.4, 139.5, 136.6, 132.1, 131.4, 129.0, 127.9, 127.6, 127.5, 126.8, 118.4, 118.0, 69.1, 66.3, 63.4, 61.6, 54.0, 44.3, 39.9, 39.4, 27.7, 26.1, 20.4, 20.1; HRMS (EI) found: M^+, 261.1739, $C_{16}H_{23}NO_2$ requires M^+, 261.1729; LRMS *m*/*z* (EI) 260 (7%, M^+), 230 (22), 162 (49), 150 (20), 91 (100).

***N*-Benzyl-*N*-[(*S*)-1-hydroxy-3-methylbutan-2-yl]-phenylacetamide 5b.** Using the general method, benzyl magnesium chloride and the oxazolidinone **4a** gave the amide **5b** (0.16 g, 53%) as an oil as a mixture of rotamers (ratio 3:1); R_f 0.38 [petrol–EtOAc (3:2)]; $[\alpha]_D^{20}$ +19.6 (1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3370, 2960, 1620; δ_H(250 MHz, $CDCl_3$) 7.39-7.18 (10H, m, ArH), 5.25 (0.25H, d, *J* 15, CH), 4.77 (0.75H, d, *J* 16.5, CH), 4.37-4.22 (0.75H, m, CH), 4.22 (0.75H, d, *J* 16.5, CH), 3.92-3.53 (3.5H, m, 3 × CH + minor rotamer CH peaks), 3.34-3.23 (0.25H, m, CH), 3.08 (0.75H, dt, *J* 10.5, 4, CH), 2.60-2.45 (0.75H, m, CH), 1.93-1.77 (0.25H, m, CH), 0.97 (0.8H, d, *J* 6.5, CH_3), 0.91 (2.2H, d, *J* 6.5, CH_3), 0.84 (2.2H, d, *J* 6.5, CH_3), 0.59 (0.8H, d, *J* 6.5, CH_3); δ_C(125 MHz, $CDCl_3$) 173.6, 139.5, 136.6, 135.4, 134.6, 129.2, 129.0, 128.9, 128.85, 128.75, 128.7, 127.9, 127.6, 127.4, 127.1, 126.9, 126.6, 69.2, 66.2, 63.5, 61.7, 54.3, 42.2, 41.7, 27.6, 26.1, 20.3, 20.0, 19.6; HRMS (EI) found: M^+, 311.1883, $C_{20}H_{25}NO_2$ requires M^+, 311.1885; LRMS *m*/*z* (EI) 311 (9%, M^+), 162 (37), 91 (100).

***N*-*p*-Methoxybenzyl-*N*-[(*S*)-1-hydroxy-3-methylbutan-2-yl]-but-3-enamide 5c.** Using the general method, allyl magnesium

bromide and the oxazolidinone **4b** gave the amide **5c** (0.2 g, 68%) as an oil as a mixture of rotamers (ratio 2.3:1); R_f 0.2 [petrol–EtOAc (3:2)]; $[\alpha]_D^{20}$ 19.6 (c 1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3370, 2960, 1610; δ_H(250 MHz, $CDCl_3$) 7.32-6.80 (4H, m, ArH), 6.12-5.88 (1H, m, CH=), 5.15-4.93 (2H, m, $=CH_2$), 4.67 (1H, d, *J* 16.5, CH), 4.32 (1H, br t, *J* 5, OH), 4.20 (1H, d, *J* 16.5, CH), 3.79 (2.1H, s, CH_3), 3.76 (0.9H, s, CH_3), 3.71-3.65 (2H, m, CH_2), 3.33-3.05 (3H, m, CH and CH_2), 2.56-2.38 (0.7H, m, CH), 1.93-1.80 (0.3H, m, CH), 0.99-0.85 (6H, m, 2 × CH_3); δ_C(125 MHz, $CDCl_3$) 173.4, 159.3, 158.8, 132.2, 131.5, 131.4, 129.0, 128.4, 128.2, 118.3, 117.9, 114.4, 114.3, 68.8, 66.3, 63.4, 61.5, 55.3, 55.2, 53.4, 39.9, 39.3, 27.8, 26.0, 20.3, 20.2, 20.1; HRMS (ES) found: MH^+, 292.1918, $C_{17}H_{26}NO_3$ requires MH^+, 292.1913; LRMS *m*/*z* (ES) 314 (72%, MNa^+), 292 (100, MH^+).

***N*-[(*S*)-1-Hydroxy-3-phenylpropan-2-yl]-*N*-methyl-but-3-enamide 5d.** Using the general method, allyl magnesium bromide and the oxazolidinone **4c** gave the amide **5d** (0.23 g, 72%) as an oil as a mixture of rotamers (ratio 3:1); R_f 0.15 [petrol–EtOAc (3:7)]; $[\alpha]_D^{20}$ −67.0 (1.1, $CHCl_3$), −27.9 (10.7, $CHCl_3$), lit.[19] −7.4 (10.7, $CHCl_3$); HRMS (EI) found: M^+, 233.1413, $C_{14}H_{19}NO_2$ requires M^+, 233.1416. Spectroscopic data consistent with literature.[19]

***N*-[(*S*)-1-Hydroxy-3-phenylpropan-2-yl]-*N*-methyl-acetamide 5e.** Methyl magnesium bromide (0.5 mL, 1.5 mmol, 3 M in Et_2O) and magnesium bromide (0.28 g, 1.5 mmol) were added to the oxazolidinone **4c** (0.2 g, 1.0 mmol) in THF (5 mL) at −78 °C. The mixture was allowed to warm to room temperature over 16 h. Aqueous NH_4Cl (5 mL) was added and the mixture was extracted with Et_2O (3 × 20 mL), dried (Na_2SO_4) and evaporated. Purification by column chromatography on silica, eluting with petrol–EtOAc (1:3), gave the amide **5e** (0.08 g, 39%) as an oil as a mixture of rotamers (ratio 2:1); R_f 0.04 [petrol–EtOAc (1:3)]; $[\alpha]_D^{20}$ −50.0 (1.0, $CHCl_3$), lit.[5] −36.0 (3.9, $CHCl_3$), no spectroscopic data reported; ν_{max}(neat)/cm^{-1} 3355, 2925, 1615; δ_H(250 MHz, $CDCl_3$) 7.32-7.11 (5H, m, ArH), 4.54-4.43 (0.7H, m, CH), 4.16-4.01 (0.3H, m, CH), 3.82-3.65 (2H, m, CH_2), 2.96-2.66 (5H, m, CH_2 and CH_3), 2.03 (2H, s, CH_3), 1.79 (1H, m, CH_3); δ_C(125 MHz, $CDCl_3$) 172.4, 172.2, 138.0, 137.6, 128.7, 128.7, 128.7, 128.4, 126.7, 126.4, 62.9, 62.3, 62.2, 58.8, 35.1, 34.4, 33.1, 26.5, 22.4, 21.4; HRMS (ES) found: MNa^+, 230.1151, $C_{12}H_{17}NO_2Na$ requires MNa^+, 230.1157; LRMS *m*/*z* (ES) 230 (5%, MNa^+), 208 (100, MH^+).

***N*-[(*S*)-1-Hydroxy-3-phenylpropan-2-yl]-*N*-methyl-propionamide 5f.** In the same way as the amide **5e**, ethyl magnesium bromide (2.6 mL, 2 mmol, 0.8 M in THF), magnesium bromide (0.19 g, 1 mmol) and the oxazolidinone **4c** (0.2 g, 1.0 mmol) gave, after purification by column chromatography on silica, eluting with CH_2Cl_2–Et_2O (7:3), the amide **5f** (0.1 g, 44%) as an oil as a mixture of rotamers (ratio 2.6:1); R_f 0.22 [CH_2Cl_2–Et_2O (7:3)]; $[\alpha]_D^{20}$ −28.0 (1.1, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3375, 2940, 1615; δ_H(250 MHz, $CDCl_3$) 7.31-7.11 (5H, m, ArH), 4.54-4.43 (0.7H, m, CH), 4.18-4.06 (0.3H, m, CH), 3.81-3.65 (2H, m, CH_2), 3.17-3.08 (0.7H, m, OH), 2.94-2.70 (5.3H, m, OH, CH_2 and CH_3), 2.26 (2H, q, *J* 7.5, CH_2), 1.07 (2.1H, t, *J* 7.5, CH_3), 0.92 (0.9H, t, *J* 7.5, CH_3); δ_C(100 MHz, $CDCl_3$) 176.2, 175.6, 138.6, 138.0, 129.3, 129.25, 129.2, 128.9, 127.2, 126.9, 63.9, 62.8, 61.2, 60.5, 35.8, 34.8, 33.5, 27.9, 27.1, 26.6, 9.8, 9.6; HRMS (ES) found: M^+, 222.1501, $C_{13}H_{19}NO_2$ requires M^+, 222.1494; LRMS *m*/*z* (ES) 244 (9%, MNa^+), 222 (100, MH^+).

***N*-[(*S*)-1-Hydroxy-3-phenylpropan-2-yl]-*N*-methyl-benzamide 5g.** Using the general method, phenyl magnesium bromide and the oxazolidinone **4c** gave the amide **5g** (0.17 g, 65%) as needles as a mixture of rotamers (ratio 3:2); R_f 0.17 [petrol–EtOAc (2:3)]; m.p. 103–104 °C; $[\alpha]_D^{20}$ −79.5 (0.4, $CHCl_3$), lit.[5] −75.4 (0.4, $CHCl_3$), no spectroscopic data reported; ν_{max}(neat)/cm^{-1} 3355, 1605, 1590; δ_H(250 MHz, $CDCl_3$) 7.35-6.84 (10H, m, ArH), 4.74-4.61 (0.6H, m, CH), 4.11-3.56 (2.8H, m, $CHCH_2OH$), 3.36-3.27 (0.6H, m, CH), 3.15-2.60 (4.6H, m, CH_2 and CH_3), 1.80-1.68 (0.4H, m, CH); δ_C(125 MHz, $CDCl_3$) 173.6, 137.9, 137.3, 136.55, 136.5, 129.7, 129.1, 128.9, 128.8, 128.65, 128.6, 128.4, 128.0, 126.9, 126.7, 126.6, 63.1, 62.3, 62.0, 59.1, 35.1, 34.8, 34.2, 27.0; HRMS (ES) found: MH^+, 270.1488, $C_{17}H_{20}NO_2$ requires MH^+, 270.1494; LRMS *m*/*z* (ES) 270 (100, MH^+).

***N*-*p*-Methoxybenzyl-*N*-[(*S*)-1-hydroxy-3-phenylpropan-2-yl]-but-3-enamide 5h.** Using the general method, allyl magnesium bromide and the oxazolidinone **4d** gave the amide **5h** (0.28 g, 82%) as an oil as a mixture of rotamers (ratio 4:1); R_f 0.21 [petrol–EtOAc (3:2)]; $[\alpha]_D^{20}$ 29.5 (c 1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3375, 2930, 1610; δ_H(500 MHz, $CDCl_3$) 7.31-7.09 (5.4H, m, ArH), 7.03 (1.6H, d, *J* 8.5, ArH), 6.84 (2H, d, *J* 8.5, ArH), 5.98-5.81 (1H, m, CH=), 5.19-4.97 (2H, m, $=CH_2$), 4.37 (1H, d, *J* 16, CH), 4.21-4.10 (1H, m, CH), 3.82-3.47 (3H, m, $CHCH_2$), 3.79 (2.4H, s, CH_3), 3.77 (0.6H, s, CH_3), 3.16-3.01 (3.6H, m, 2 × CH_2), 2.84-2.72 (0.4H, m, CH_2); δ_C(125 MHz, $CDCl_3$, major rotamer) 173.2, 159.2, 138.7, 131.3, 129.2, 128.5, 128.2, 128.1, 126.5, 118.2, 114.3, 64.3, 63.9, 55.3, 52.7, 39.9, 34.3; HRMS (EI) found: M^+, 339.1823, $C_{21}H_{25}NO_3$ requires M^+, 339.1834; LRMS *m*/*z* (ES) 362 (30%, MNa^+), 340 (100, MH^+).

***N*-[(*R*)-2-Hydroxy-1-phenylethyl]-*N*-methyl-but-3-enamide 5i.** Using the general method, allyl magnesium bromide and the oxazolidinone **4e** gave the amide **5i** (0.21 g, 86%) as needles as a mixture of rotamers (ratio 3:1); R_f 0.29 [petrol–EtOAc (3:7)]; m.p. 37–38 °C; $[\alpha]_D^{20}$ −118.0 (1.4, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3405, 1615; δ_H(250 MHz, $CDCl_3$) 7.40-7.20 (5H, m, ArH), 6.13-5.92 (1H, m, CH=), 5.85 (1H, dd, *J* 9.5, 5, CH), 5.23-5.12 (2H, m, $=CH_2$), 4.22-4.02 (2H, m, CH_2), 3.37 (0.5H, br d, *J* 7, CH_2), 3.23 (1.5H, dt, *J* 7, 1.5, CH_2), 2.77 (3H, s, CH_3), 2.55 (1H, br s, OH); δ_C(62 MHz, $CDCl_3$) 172.9, 172.8, 137.1, 136.7, 131.9, 131.1, 128.9, 128.7, 127.9, 127.7, 127.7, 126.9, 118.0, 61.6, 61.4, 61.3, 58.1, 39.4, 39.0, 31.0, 28.3; HRMS (ES) found: MH^+, 220.1327, $C_{13}H_{18}NO_2$ requires MH^+, 220.1338; LRMS *m*/*z* (ES) 242 (18%, MNa^+), 220 (100, MH^+); Anal. calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: 71.15; H, 7.88; N, 6.20%.

***N*-[(*R*)-2-Hydroxy-1-phenylethyl]-*N*-methyl-2-phenylacetamide 5j.** Using the general method, benzyl magnesium chloride and the oxazolidinone **4e** gave the amide **5j** (0.19 g, 70%) as needles as a mixture of rotamers (ratio 2.5:1); R_f 0.22 [petrol–EtOAc (2:3)]; m.p. 73–74 °C, lit.[18] 75–77 °C; $[\alpha]_D^{20}$ −113.0 (1.1, $CHCl_3$), lit.[20] −117 (1.25, $CHCl_3$); HRMS (ES) found: MH^+, 270.1496, $C_{17}H_{20}NO_2$ requires MH^+, 270.1494. Spectroscopic data consistent with literature.[20]

***N*-[(*R*)-2-Hydroxy-1-phenylethyl]-*N*-methyl-propionamide 5k.** In the same way as the amide **5e**, ethyl magnesium bromide

(2.6 mL, 2 mmol, 0.8 M in THF), magnesium bromide (0.19 g, 1 mmol) and the oxazolidinone **4e** (0.2 g, 1.0 mmol) gave, after purification by column chromatography on silica, eluting with CH_2Cl_2–Et_2O (7:3), the amide **5k** (0.06 g, 30%) as an oil as a mixture of rotamers (ratio 2.4:1); R_f 0.27 [EtOAc–MeOH (98:2)]; $[\alpha]_D^{20}$ −45.9 (1.1, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3385, 2935, 1615; δ_H(250 MHz, $CDCl_3$) 7.34-7.14 (5H, m, ArH), 5.85 (0.7H, dd, *J* 9, 5, CH), 5.10 (0.3H, dd, *J* 9, 4, CH), 4.15-3.94 (2H, m, CH_2), 3.54 (1H, br s, OH), 2.72 (2.1H, s, CH_3), 2.70 (0.9H, s, CH_3), 2.42 (2H, q, *J* 7.5, CH_2), 1.13 (2.1H, t, *J* 7.5, CH_3), 1.11 (0.9H, t, *J* 7.5, CH_3); δ_C(125 MHz, $CDCl_3$) 175.7, 175.5, 137.3, 137.0, 128.6, 128.4, 127.8, 127.7, 127.6, 126.8, 61.6, 61.4, 61.3, 58.1, 30.7, 28.1, 27.3, 26.7, 9.6, 9.2; HRMS (ES) found: MNa^+, 230.1152, $C_{12}H_{17}NO_2Na$ requires MNa^+, 230.1157; LRMS *m*/*z* (ES) 230 (47%, MNa^+), 208 (100, MH^+).

***N*-[(*R*)-2-Hydroxy-1-phenylethyl]-*N*-methyl-2-heptanamide 5l.** Using the general method, hexyl magnesium bromide and the oxazolidinone **4e** gave the amide **5l** (0.14 g, 52%) as an oil as a mixture of rotamers (ratio 3:1); R_f 0.27 [petrol–EtOAc (1:1)]; $[\alpha]_D^{20}$ −95.3 (1.1, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3385, 2925, 1620; δ_H(250 MHz, $CDCl_3$) 7.37-7.18 (5H, m, ArH), 5.86 (0.75H, dd, *J* 9.5, 5, CH), 5.15 (0.25H, dd, *J* 9.5, 5, CH), 4.15-4.07 (2H, m, CH_2), 2.76 (3H, s, CH_3), 2.39 (2H, t, *J* 7.5, CH_2), 1.71-1.62 (2H, m, CH_2), 1.39-1.26 (6H, m, 3 × CH_2), 0.91-0.86 (3H, m, CH_3); δ_C(125 MHz, $CDCl_3$) 175.4, 174.9, 137.2, 137.0, 128.9, 128.7, 127.9, 127.8, 126.8, 61.9, 61.6, 61.3, 58.3, 34.2, 33.7, 31.6, 31.2, 29.2, 29.1, 28.1, 25.5, 25.1, 22.6, 14.1; HRMS (ES) found: MH^+, 264.1959, $C_{16}H_{26}NO_2$ requires MH^+, 264.1964; LRMS *m*/*z* (ES) 550 (100%, M_2HNa^+), 286 (18, MNa^+), 264 (50, MH^+).

***N*-Allyl-*N*-[(*R*)-2-Hydroxy-1-phenylethyl]-but-3-enamide 5m.** Using the general method, allyl magnesium bromide (7 mmol), and the oxazolidinone **4f** (0.2 g, 1.0 mmol) gave, after purification by column chromatography on silica, eluting with petrol–EtOAc (3:2), the amide **5m** (0.15 g, 60%) as an oil; R_f 0.21 [petrol–EtOAc (3:2)]; $[\alpha]_D^{20}$ −51.0 (1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3395, 2930, 1615; δ_H(250 MHz, $CDCl_3$) 7.37-7.19 (5H, m, ArH), 6.09-5.91 (1H, m, CH=), 5.73-5.58 (1H, m, CH=), 5.54 (1H, t, *J* 6.5, NCH), 5.22-5.07 (4H, m, 2 × $=CH_2$), 4.12 (2H, br d, *J* 6.5, CH_2), 3.84-3.65 (2H, m, CH_2), 3.21 (2H, br d, *J* 6.5, CH_2); δ_C(125 MHz, $CDCl_3$) 173.4, 137.1, 135.0, 134.1, 131.8, 131.6, 129.0, 128.7, 128.5, 128.5, 128.1, 127.9, 127.0, 118.0, 116.9, 63.1, 62.3, 62.1, 62.0, 60.9, 48.2, 45.4, 39.3; HRMS (EI) found: M^+, 245.1413, $C_{15}H_{19}NO_2$ requires M^+, 245.1416; LRMS *m*/*z* (EI) 245 (6%, M^+), 214 (33), 146 (51), 101 (35), 86 (100).

***N*-[(*S*)-1-Hydroxy-3-phenylpropan-2-yl]-*N*-*p*-methoxybenzyl-2-methylbut-3-enamide 6.** *n*-Butyllithium (2.5 mL, 6 mmol, 2.5 M) was added to diisopropylamine (0.9 mL, 6.6 mmol) in THF (10 mL) at −78 °C. The mixture was warmed to 0 °C then re-cooled to −78 °C and the amide **5h** (1.0 g, 2.9 mmol) in THF (10 mL) was added. After 1 h, LiCl (0.75 g, 17.4 mmol) was added. After 30 min, iodomethane (0.36 mL, 17.4 mmol) was added. After 30 min, aqueous NH_4Cl (10 mL) was added, the mixture was warmed to room temperature and was extracted with EtOAc (3 × 20 mL), dried (Na_2SO_4) and evaporated. Purification by column chromatography on silica, eluting with petrol–EtOAc (1:1), gave the amide **6** (0.74 g, 72%) as an oil as a mixture of diastereomers (dr 97:3) and a mixture of rotamers (ratio 7:1); R_f 0.55 [petrol–EtOAc (1:1)]; $[\alpha]_D^{20}$ −25.2 (c 1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3400, 2940, 1610; δ_H(400 MHz, $CDCl_3$) 7.21-7.11 (5H, m, ArH), 7.03 (2H, d, *J* 10, ArH), 6.88 (2H, d, *J* 10, ArH), 5.96-5.89 (1H, m, CH=), 5.11-4.91 (2H, m, $=CH_2$), 4.54-4.30 (2H, m, CH_2), 3.82 (3H, s, CH_3), 3.77 (2H, d, *J* 7, CH_2), 3.73-3.68 (1H, m, CH), 3.34-3.29 (1H, m, CH), 3.41-3.06 (2H, m, CH_2), 1.73 (1H, br s, OH), 1.28 (0.4H, s, CH_3), 1.21 (2.6H, s, CH_3); δ_C(100 MHz, $CDCl_3$) 176.1, 159.4, 138.6, 138.4, 138.1, 129.3, 129.2, 129.0, 128.7, 128.5, 128.4, 128.0, 127.7, 126.8, 126.4, 115.8, 115.6, 115.1, 114.3, 114.2, 64.4, 63.9, 63.2, 62.5, 55.2, 52.0, 51.2, 42.1, 34.2, 18.7; HRMS (ES) found: MH^+, 354.2064, $C_{22}H_{28}NO_3$ requires MH^+, 354.2069; LRMS *m*/*z* (ES) 376 (10%, MNa^+), 354 (100, MH^+); Anal. calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: 74.71; H, 7.61; N, 3.99%. The diastereomer ratio was determined by HPLC using an Alltech Alltima ODS 3 μm column, length 150 mm, i.d. 4.6 mm, MeCN–H_2O 40:60, flow rate 1 mL per min, detection at 254 nm, retention times: 17.5 min (minor) and 18.7 min (major).

1,6-Dihydro-1-[(*R*)-2-hydroxy-1-phenylethyl]pyridine-2(3H)-one 7. Grubbs second generation catalyst ($C_{48}H_{65}Cl_2N_2PRu$) (137 mg, 0.16 mmol) was added in two portions to the amide **5m** (1.0 g, 4.07 mmol) in CH_2Cl_2 (30 mL) at 40 °C. After 1.5 h, the mixture was cooled to room temp. After 1 h DMSO (0.5 mL) was added. After 2 h, the solvent was evaporated and the residue was purified by column chromatography on silica, eluting with petrol–EtOAc (1:9), gave the lactam **7** (833 mg, 94%) as an oil; R_f 0.30 [petrol–EtOAc (1:9)]; $[\alpha]_D^{20}$ −65.8 (c 0.8, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3350, 2880, 1615; δ_H(500 MHz, $CDCl_3$) 7.35-7.26 (5H, m, ArH), 5.89-5.86 (1H, m, CH), 5.76-5.62 (2H, m, CH=CH), 4.19-4.12 (2H, m, CH_2), 3.90-3.52 (2H, m, CH_2), 3.07-3.04 (2H, m, CH_2), 2.16 (1H, br s, OH); δ_C(125 MHz, $CDCl_3$) 169.1, 136.4, 127.9, 127.8, 122.0, 121.0, 61.4, 58.5, 44.6, 32.7; HRMS (ES) found: MNa^+, 240.0992, $C_{13}H_{15}NO_2Na$ requires MNa^+, 240.1000; LRMS *m*/*z* (ES) 457 (100%, M_2Na^+), 240 (82, MNa^+), 218 (22, MH^+).

(*R*)-1-(2-Hydroxy-1-phenylethyl)piperidin-2-one 8. The lactam **7** (1.0 g, 4.6 mmol) and palladium on charcoal (100 mg, 5%) in MeOH (20 mL) were stirred under an atmosphere of hydrogen at room temp. After 48 h, the mixture was filtered, the solvent was evaporated and the residue was purified by column chromatography on silica, eluting with CH_2Cl_2–MeOH (95:5), to give the lactam **8** (0.88 g, 87%) as needles; R_f 0.50 [CH_2Cl_2–MeOH (95:5)]; m.p. 112–114 °C, lit.[16] 113–115 °C; $[\alpha]_D^{20}$ −79.8 (c 0.5, $CHCl_3$), lit.[16] −80 (0.5, CH_2Cl_2); Anal. calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: 71.16; H, 7.78; N, 6.43%. NMR spectroscopic data as reported.[16]

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