Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 7112–7119

# Synthesis of (+)-7a-*epi*-7-deoxycasuarine via cross metathesis

David Koch, Simon Maechling and Siegfried Blechert*

*Institute of Chemistry, TU Berlin—Berlin University of Technology, Str. d. 17. Juni 115, 10623 Berlin, Germany*

Received 14 February 2007; revised 12 April 2007; accepted 1 May 2007
Available online 6 May 2007

**Abstract**—Olefin cross metathesis of vinyl pyrrolidine derivatives has been explored, culminating in a concise synthesis of (+)-7a-*epi*-7-deoxycasuarine in nine steps, from commercially available starting materials.


## 1. Introduction

Polyhydroxylated pyrrolizidine alkaloids constitute an important class of molecules, which possess biological activity. Alexine (**1**), first isolated from *Alexa liopetala*,[1] has been shown to exhibit antiviral and anti-HIV activity.[2] Other members of the family that have attracted interest include hyacinthacine $A_2$ (**2**) and casuarine (**3**) (Fig. 1). Acting as sugar mimics, many of these alkaloids possess glycosidase inhibition activity, which makes them and their analogues potential drug candidates against viral infections, cancer and diabetes.[3] For example, **2** was found to be a selective inhibitor of amyloglucosidase (*Aspergillus niger*) with an $IC_{50}$=8.6 μM,[4] and 7-deoxycasuarine (**4**) has also shown to be a potent, specific and competitive inhibitor of amyloglucosidase (*Rhizopus* mould) with an $IC_{50}$=4.2 μM.[5]

It has been well documented that the biological activity exhibited by these polyhydroxylated alkaloids varies with the position and stereochemistry of the hydroxy groups on the pyrrolizidine skeleton.[6] For biological evaluation of members of this class we were interested in exploring a simple, rapid and straightforward route to these molecules and novel congeners. In this communication we report our progress towards the synthesis of 3-(hydroxymethyl)pyrrolizidine alkaloids from vinyl pyrrolidine derivatives, including the synthesis of (+)-7a-*epi*-7-deoxycasuarine. A variety of approaches towards 3-(hydroxymethyl)pyrrolizidine alkaloids have so far been disclosed,[7] including the only previous synthesis of **5**, a carbohydrate based approach, that utilised L-xylose as a chiral starting material.[8]

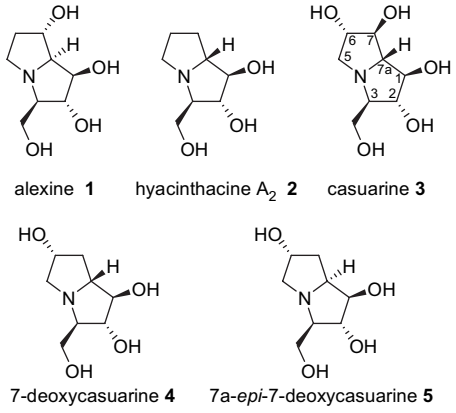
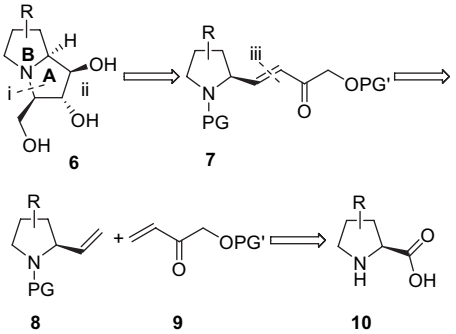



**Figure 1**. Structures of selected polyhydroxylated pyrrolizidine alkaloids.

We were interested in developing a flexible synthesis of 3-(hydroxymethyl)pyrrolizidine alkaloids and their congeners, in few synthetic steps from readily available chiral starting materials. In our analysis of the target molecule (Scheme 1), the key retrosynthetic steps are (i) reductive cyclisation followed by (ii) dihydroxylation of the internal C–C double bond, installing the **A** ring, and its appropriate stereochemistry. This will enable key intermediate **7** to be synthesised by (iii) olefin cross metathesis (CM) with enone **9** (PG′=Bn). The CM precursor **8** was planned to be prepared by simple functional group interconversions from commercially available proline derivatives **10**. We anticipated that this approach would allow access to the target compound **5** and a variety of analogues.



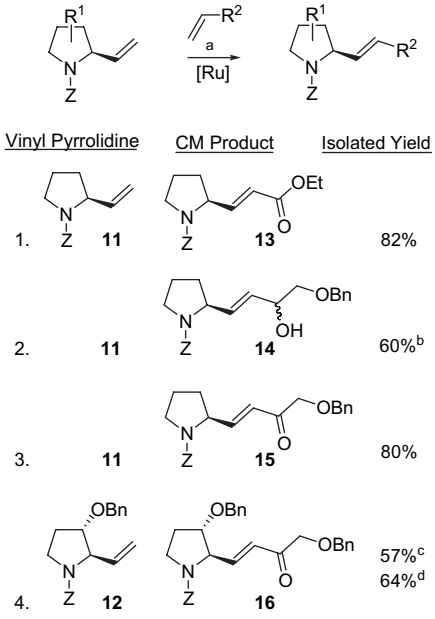

**Scheme 1**. General retrosynthesis.

*Keywords*: Cross metathesis; Deoxycasuarine; Alkaloids; Pyrrolizidines.
* Corresponding author. E-mail: blechert@chem.tu-berlin.de

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.05.007

## 2. Results and discussion

Our initial investigations were aimed at scrutinising the feasibility of vinyl pyrrolidines such as **8**, to undergo successful cross metathesis. Intrigued by previous reports regarding the cross metathesis of vinyl pyrrolidine derivatives,[9] where an excess of the vinyl pyrrolidine was needed to achieve good yields of the cross metathesis product,[9b] we investigated the reactivity of **11**[10] in representative cross metathesis reactions. Our initial results with **11**, a type II olefin, according to Grubbs' classification were promising (Scheme 2).[11] We were pleased to find that **11** reacted efficiently with ethyl acrylate (also a type II olefin) utilising the Hoveyda–Grubbs second generation catalyst [Ru],[12] and **13** was isolated in high yield (Scheme 2, entry 1). CM was also successful with a racemic allylic alcohol (a type I olefin) affording **14** in good isolated yield (Scheme 2, entry 2). When we reacted **11** with enone **9** (PG′=Bn)[13] (Scheme 2, entry 3), according to our retrosynthetic scheme, we were delighted to find that **15** could be isolated in a high yield of 80%. Vinyl pyrrolidine **12** also reacted efficiently with **9** affording the desired CM product **16** in a yield of 64%. The reduced yield compared to **15** was presumably a result of increased steric hindrance in the vicinity of the reacting olefin.



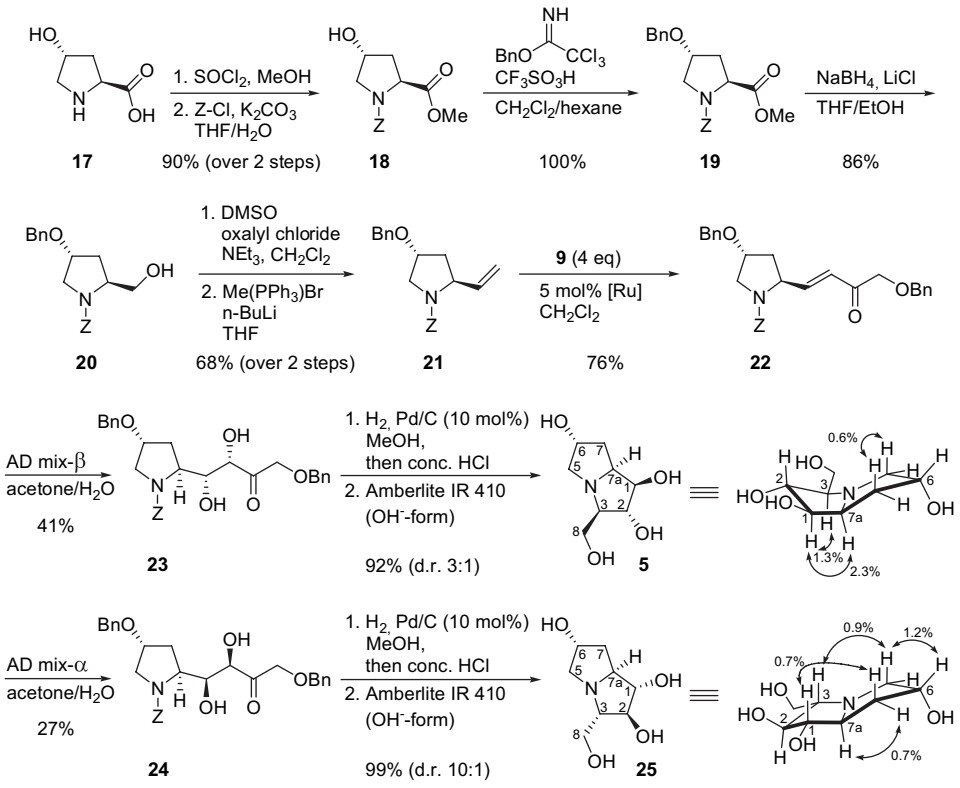

**Scheme 2**. Cross metathesis of vinyl pyrrolidines. [a]Standard reaction conditions: 0.1 M, 2 equiv cross partner, $CH_2Cl_2$, 5 mol % [Ru],[12] 40°C, 60 h; [b]1:1 mixture of diastereoisomers; [c]4 equiv cross partner; [d]0.2 M, 4 equiv cross partner.

These results highlight the importance of choosing a proper cross partner for a particular CM reaction and the high reactivity of the catalyst [Ru]. It is worth to mention that **15** and **16** constitute key retrosynthetic intermediates of our proposed route towards the synthesis of (−)-hyacinthacine $A_2$ and alexine (**1**). With these results in hand, we embarked on the synthesis of the target molecule (+)-7a-*epi*-7-deoxycasuarine.

Commercially available [2*S*,4*R*]-(−)-4-hydroxypyrrolidine-2-carboxylic acid (**17**) was first esterified by reaction with thionyl chloride in methanol, followed by smooth benzyloxycarbonyl (Z) protection using $K_2CO_3$ in THF/$H_2O$ to afford **18** in excellent yield over two steps (Scheme 3). This protocol was found to be vital for high yields, as standard conditions for Z protection involving DCM and $Et_3N$ as base consistently led to lower isolated yields (~60%). *O*-Benzyl protection was achieved with benzyl trichloroacetimidate and catalytic triflic acid, affording **19** in quantitative yield. Reduction of ester **19** gave **20** in high isolated yield. Alcohol **20** was converted via Swern oxidation to the corresponding aldehyde, followed immediately by Wittig olefination to yield **21** without epimerisation in good yield (over two steps). The vinyl pyrrolidine derivative **21** was subjected to the previously optimised CM conditions with enone **9** allowing key intermediate **22** to be isolated in high yield. With a reliable synthesis of **22** in hand the dihydroxylation reaction was attempted. Initial investigations probed the use of sequential catalysis to install the cis diol moiety, utilising recently developed methodology from our group,[14] and others.[15] After completion of CM the solvent was removed in vacuo and $YbCl_3$ (10 mol %) was added followed by EtOAc/$CH_3CN$/$H_2O$ 3:3:1, after cooling to 0 °C solid $NaIO_4$ (1.2 equiv) was added. However, although complete consumption of the starting material was observed, no diastereoselective induction from the remote chiral centre took place as determined by $^1H$ NMR of the crude reaction mixture, therefore other methods of dihydroxylation were pursued. Utilisation of $OsO_4$ in acetone/$H_2O$ on purified **22** also led to the formation of a 1:1 mixture of **23**:**24**. By employing commercially available AD-mix-β the desired diastereoisomer **23** could be isolated in acceptable yield. Switching to AD-mix-α furnished diastereoisomer **24** as anticipated. Diol **24** was treated with Pd/C under 1 atm of $H_2$. After Z-group deprotection and reductive cyclisation, HCl was added to ensure quantitative reduction of the benzyl ethers. To liberate the free amine, we used Amberlite IR 410 to afford **25** in excellent yield and good diastereoselectivity. Following the same procedure **23** was smoothly transformed into **5** whose optical rotation $[\alpha]_D^{20}$ +15.0 (*c* 0.12, $H_2O$) closely matches that of previously synthesised material $[\alpha]_D^{20}$ +15.8 (*c* 0.92, $H_2O$).[8]

Proof of the stereochemistry of **5** came from NOE experiments (Scheme 3) and the relative stereochemistry of C-1, C-2 and C-3 was determined starting from the known stereochemistry on C-7a (given by [2*S*,4*R*]-(−)-4-hydroxypyrrolidine-2-carboxylic acid). The observation of a large NOE between H-7a and H-1 indicates a cis orientation. The observed NOE between H-1 and H-3, indicates both protons being pseudoaxial. Furthermore the NOE between H-5α and H-7α indicates both protons being pseudoaxial. There was also a large NOE observed between H-7a and H-7β (not shown). Interestingly, the NMR chemical shifts of **5** did not match the previously reported data. A similar observation was recently reported by Donohoe et al.,[16] whereby the chemical shifts of the atoms in the direct environment of the nitrogen became shifted (Table 1). Wormald et al. described that $^3J_{HH}$ coupling constants remain unchanged between different samples,[17] even if NMR chemical shifts differed.

The *J* values of our sample were consistent with that of previously synthesised **5**.[8] The coupling constant $^3J$ (4.1 Hz)




**Scheme 3**. Synthesis of 7a-*epi*-7-deoxycasuarine.

between H-5α and H-6 indicates a cis relationship, $^{3}J$ (8.1, 4.1 Hz) of H-7α indicates a cis relationship to H-6 and a trans-diaxial to H-7a. $^{3}J$ (1.7 Hz) between H-5β and H-6 indicates trans, but not trans-diaxial arrangement and finally $^{3}J$ (7.9, 1.7 Hz) of H-7β indicates cis relationship to H-7a and a trans, but not trans-diaxial to H-6. Therefore H-5α and H-7α are pseudoaxial, H-5β and H-7β are pseudoequatorial and in a W-geometry, both showing a long range coupling of $^{4}J$=1.7 Hz. It is also known that variation in solvent (ionic strength, hydrogen bonding, metal ion chelation) can exert discrepancies in NMR spectra of polyhydroxylated alkaloids.[17] The stereochemistry of **25** was also determined in a similar manner by NOE studies starting from known stereochemistry on C-6 (given by [2*S*,4*R*]-(−)-4-hydroxypyrrolidine-2-carboxylic acid) and by coupling constant analysis. The observed NOE between H-5α and H-6 indicate both protons to be cis, along with the NOE between H-5α and H-3, indicating a pseudoaxial orientation for both protons and confirming the stereochemistry at C-3.

**Table 1**. NMR data for **5** in $D_2O$

| Label[a] | Ref. 8 (ppm) | This work (ppm) |
|---|---|---|
| H-6 | 4.63 | 4.54 |
| H-7a | 4.23 | 3.85 |
| H-1 | 4.20 | 4.16 |
| H-2 | 3.98 | 3.89 |
| H-8 | 3.90 | 3.87 |
| H-8′ | 3.80 | 3.87 |
| H-3 | 3.45 | 3.07 |
| H-5α | 3.26 | 3.11 |
| H-5β | 3.24 | 2.93 |
| H-7α | 2.22 | 2.13 |
| H-7β | 1.95 | 1.84 |
| C-7a | 68.2 | 64.0 |
| C-3 | 67.5 | 65.3 |
| C-5 | 58.5 | 55.7 |

[a] α: topside; β: bottom side.

## 3. Conclusions

In conclusion we present the CM of vinyl pyrrolidine derivatives, culminating in the synthesis of polyhydroxylated pyrrolizidine **25** in nine steps and 11% overall yield, and the synthesis of 7a-*epi*-7-deoxycasuarine (**5**) in nine steps and 15% overall yield. Further applications of this methodology and the synthesis of other polyhydroxylated pyrrolizidines will be reported in due course.

## 4. Experimental section

### 4.1. General

All experiments were carried out in oven-dried glassware and under an atmosphere of nitrogen. Reagents were supplied from Aldrich Chemical Company, Fluka, Acros or Lancaster Synthesis and used without any further purification. All solvents were distilled or dried prior to use. THF and $Et_2O$ were distilled from sodium/benzophenone. $CH_2Cl_2$ was distilled from $P_2O_5$. Hexane was distilled from $CaH_2$. MeOH and EtOH were dried over 3 Å molecular sieves. Analytical thin layer chromatography was performed on precoated Merck silica gel 60 $F_{254}$ plates and preparative chromatography was performed on ICN silica gel 60 (0.040–0.063 mm). $^{1}H$ NMR and $^{13}C$ NMR spectra were recorded

on a Bruker DRX-500 spectrometer. All chemical shifts are reported in parts per million relative to the internal solvent peak. IR spectra were measured on a Nicolet FTIR 750 spectrometer. Mass spectra were recorded on a Finnigan MAT 95 SQ spectrometer and for ESI-MS on a Bruker-Daltonics esquire 2000. Elemental analyses were obtained on an Analytic Jena Elementar Vario El. Optical rotations were measured on a Perkin–Elmer polarimeter 341 in a 1 dm cell at 20 °C and at a wavelength of 589 nm.

### 4.2. Experimental procedures

**4.2.1. 1-(Benzyloxy)but-3-en-2-one (9) via the Weinreb amide.** To a stirred solution of benzyloxyacetylchloride (1.00 g, 5.42 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (528 mg, 5.42 mmol) in $CH_2Cl_2$ (35 mL) at 0 °C was added dropwise triethylamine (1.51 mL, 10.8 mmol), and stirring was continued for 4 h at this temperature. After this time MeOH was added before concentration in vacuo. Purification by column chromatography (2:3 hexanes/MTBE) afforded the Weinreb amide as a colourless oil (1.05 g, 93%). $R_f$=0.33 (1:2 hexanes/MTBE); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.44–7.28 (m, 5H), 4.68 (s, 2H), 4.28 (s, 2H), 3.64 (s, 3H), 3.20 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 137.6 ($C_q$), 128.5 (CH), 128.1 (CH), 127.9 (CH), 73.3 ($CH_2$), 67.1 ($CH_2$), 61.5 ($CH_3$), 32.4 ($CH_3$); IR (ATR) cm$^{-1}$ 3063, 3030, 2938, 2900, 1677, 1454, 1140, 1087, 993, 739, 698; MS (EI, 70 eV) *m*/*z* (%) 210 ($M^+$, <1), 103 (48), 91 (100), 73 (13), 65 (12); HRMS (EI) calcd for $C_{11}H_{15}NO_3$ ($MH^+$) 210.1130, found 210.1130. To a stirred solution of the Weinreb amide (710 mg, 3.39 mmol) in absolute $Et_2O$ (15 mL) at 0 °C was added dropwise a 1.0 M solution of vinyl magnesiumbromide in THF (8.5 mL, 8.5 mmol) and stirred at 0 °C for 30 min and then for 1.5 h at room temperature before cooling to 0 °C, and acetone (1.3 mL) was added. After stirring for 15 min the solution was quenched by addition of ice-cold 1 M HCl (20 mL). The mixture was extracted with MTBE (3×60 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (20:1 hexanes/MTBE) gave the title compound as a colourless oil (505 mg, 85%). $R_f$=0.21 (9:1 hexanes/MTBE); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.45–7.29 (m, 5H), 6.55 (dd, *J*=17.6, 10.8 Hz, 1H), 6.35 (dd, *J*=17.6, 1.1 Hz, 1H), 5.83 (dd, *J*=10.8, 1.1 Hz, 1H), 4.62 (s, 2H), 4.28 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 197.2 ($C_q$), 137.2 ($C_q$), 132.5 (CH), 129.3 ($CH_2$), 128.6 (CH), 128.1 (CH), 128.0 (CH), 73.9 ($CH_2$), 73.4 ($CH_2$). IR (ATR) cm$^{-1}$ 3064, 3031, 2954, 2924, 1728, 1699, 1454, 1102, 741, 698; MS (EI, 70 eV) *m*/*z* (%) 107 (10), 91 (100), 70 (26), 55 (34).

**4.2.2. (2*R*,3*S*)-Benzyl 3-(benzyloxy)-2-vinylpyrrolidine-1-carboxylate (12).** DCM (30 mL) was cooled to −78 °C under $N_2$ and DMSO (0.51 mL, 7.24 mmol) was added dropwise followed by oxalyl chloride (0.31 mL, 3.62 mmol). After 45 min (2*R*,3*S*)-benzyl 3-(benzyloxy)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (618 mg, 1.81 mmol) was added in DCM (5 mL) and stirring continued for 60 min. $Et_3N$ (2.5 mL, 18 mmol) was then added and the reaction mixture allowed to warm to room temperature over 45 min. HCl (1 N, 50 mL) was then added and the solution extracted with DCM (3×50 mL), washed with satd $NaHCO_3$ (60 mL) and satd NaCl (50 mL), dried ($MgSO_4$) and concentrated in vacuo to afford the crude aldehyde in quantitative yield. Meanwhile *n*-BuLi (2.5 M in hexane, 1.99 mmol) was added to a suspension of methyl triphenylphosphoniumbromide (776 mg, 2.17 mmol) in THF (25 mL) at −78 °C under $N_2$ and stirred for 30 min before a solution of the aldehyde in THF (5 mL) was added dropwise to the bright yellow suspension. The reaction mixture was allowed to warm to room temperature and stirred overnight. Satd $NH_4Cl$ (120 mL) was added and the mixture extracted with MTBE (3×90 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (4:1 hexanes/MTBE) gave the title compound as a colourless oil (377 mg, 62%). $R_f$=0.24 (3:1 hexanes/MTBE); $[\alpha]_D^{20}$ +3.9 (*c* 1.2, $CHCl_3$); $^1$H NMR (500 MHz, DMSO-$d_6$, 373 K) $\delta$ 7.38–7.23 (m, 10H), 5.78 (m, 1H), 5.13–5.00 (m, 4H), 4.55 (s, 2H), 4.40 (br d, *J*=5.4 Hz, 1H), 3.93 (m, 1H), 3.58–3.50 (m, 1H), 3.49–3.42 (m, 1H), 1.99 (m, 2H); $^{13}$C NMR (125 MHz, DMSO-$d_6$, 373 K) $\delta$ 154.3 ($C_q$), 138.5 ($C_q$), 137.3 ($C_q$), 136.5 (CH), 128.2 (CH), 128.1 (CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 127.2 (CH), 115.1 ($CH_2$), 82.4 (CH), 70.1 ($CH_2$), 65.9 ($CH_2$), 64.9 (CH), 44.5 ($CH_2$), 28.4 ($CH_2$); IR (ATR) cm$^{-1}$ 3062, 3031, 2948, 2893, 1699, 1409, 1343, 1203, 1096, 1065, 922, 734, 697; MS (EI, 70 eV) *m*/*z* (%) 337 ($M^+$, <1), 246 (6), 202 (43), 91 (100), 69 (6); HRMS (EI) calcd for $C_{21}H_{23}NO_3$ ($M^+$) 337.1678, found 337.1680. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.97; H, 6.68; N, 4.15.

### 4.3. General procedure for cross metathesis

To a stirring solution of the vinyl pyrrolidine in DCM (0.1 M) was added the freshly prepared cross partner (2–4 equiv) and the solution was heated to reflux under $N_2$ before the catalyst [Ru] was added (5 mol %). The mixture was heated at reflux for 60 h, before concentration and purification by flash chromatography. In order to remove all ruthenium residue following metathesis the chromatographed product was stirred in DCM with 10 parts (w/w) of activated charcoal (6–12 h) before a second purification by flash chromatography.

**4.3.1. Benzyl 2-((*E*)-2-(ethoxycarbonyl)vinyl)pyrrolidine-1-carboxylate (13).** Following the general procedure for cross metathesis, and purification by column chromatography (7:3 hexanes/MTBE) afforded the title compound as a colourless oil (143 mg, 82%). $R_f$=0.35 (1:1 hexanes/MTBE); $^1$H NMR (500 MHz, $CDCl_3$)* $\delta$ 7.37–7.22 (m, 5H), 6.80 (m, 1H), 5.85 (d, *J*=15.5 Hz, 0.5H), 5.76 (d, *J*=15.5 Hz, 0.5H), 5.15–5.03 (m, 2H), 4.53 (m, 0.5H), 4.46 (m, 0.5H), 4.15 (m, 2H), 3.51–3.39 (m, 2H), 2.10–1.99 (m, 1H), 1.89–1.80 (m, 2H), 1.80–1.70 (m, 1H), 1.29–1.20 (m, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$)* $\delta$ 166.3 ($C_q$), 154.8 ($C_q$), 148.0 (CH), 147.5 (CH), 136.8 ($C_q$), 136.7 ($C_q$), 128.5 (CH), 128.4 (CH), 128.0 (CH), 127.9 (CH), 121.0 (CH), 67.0 ($CH_2$), 66.9 ($CH_2$), 60.4 ($CH_2$), 58.1 (CH), 57.8 (CH), 46.9 ($CH_2$), 46.5 ($CH_2$), 31.7 ($CH_2$), 30.8 ($CH_2$), 23.6 ($CH_2$), 22.8 ($CH_2$), 14.3 ($CH_3$); MS (EI, 70 eV) *m*/*z* (%) 303 ($M^+$, 1), 189 (12), 168 (13), 140 (3), 114 (3), 91 (100), 65 (5); HRMS (EI) calcd for $C_{17}H_{21}NO_4$ ($M^+$) 303.1471, found 303.1476. (*1:1 Mixture of rotamers.)

**4.3.2. Benzyl 2-((*E*)-4-(benzyloxy)-3-hydroxybut-1-enyl)-pyrrolidine-1-carboxylate (14).** Following the general

procedure for cross metathesis, and purification by column chromatography (1:2 hexanes/MTBE) afforded the title compound as a colourless oil (404 mg, 60%). $R_f$=0.41 (MTBE); $^1$H NMR (500 MHz, $CDCl_3$)* $\delta$ 7.40–7.23 (m, 10H), 5.78–5.64 (m, 1H), 5.65 (m, 0.5H), 5.42 (m, 0.5H), 5.19–5.13 (m, 1H), 5.11–4.99 (m, 1H), 4.57–4.47 (m, 2H), 4.47–4.23 (m, 2H), 3.54–3.30 (m, 3.5H), 3.24–3.17 (m, 0.5H), 2.92 (m, 0.5H), 2.75 (m, 0.5H), 1.98 (m, 1H), 1.91–1.80 (m, 2H), 1.80–1.68 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$)* $\delta$ 155.1 ($C_q$), 154.8 ($C_q$), 138.0 ($C_q$), 137.1 ($C_q$), 132.6 (CH), 132.4 (CH), 132.0 (CH), 128.9 (CH), 128.7 (CH), 128.52 (CH), 128.46 (CH), 127.9 (CH), 127.8 (CH), 74.3 ($CH_2$), 73.3 ($CH_2$), 70.7 (CH), 66.7 ($CH_2$), 58.6 (CH), 58.5 (CH), 58.4 (CH), 58.3 (CH), 53.6 ($CH_2$), 49.5 (CH), 46.8 ($CH_2$), 46.4 ($CH_2$), 32.4 ($CH_2$), 32.3 ($CH_2$), 31.4 ($CH_2$), 31.3 ($CH_2$), 27.1 (CH), 27.0 (CH), 23.6 ($CH_2$), 23.5 ($CH_2$), 22.84 ($CH_2$), 22.75 ($CH_2$); MS (EI, 70 eV) *m/z* (%) 381 ($M^+$, <1), 260 (3), 204 (13), 160 (6), 108 (17), 91 (100), 65 (6), 57 (8). HRMS (EI) calcd for $C_{23}H_{27}NO_4$ ($M^+$) 381.1940, found 381.1945. (*1:1 Mixture of rotamers, and each rotamer is a 1:1 mixture of diastereoisomers.)

**4.3.3. Benzyl 2-((*E*)-4-(benzyloxy)-3-oxobut-1-enyl)-pyrrolidine-1-carboxylate (15).** Following the general procedure for cross metathesis, and purification by column chromatography (7:3 hexanes/MTBE) afforded the title compound as a colourless oil (26 mg, 80%). $R_f$=0.27 (1:1 hexanes/MTBE); $^1$H NMR (500 MHz, $CDCl_3$)* $\delta$ 7.45–7.20 (m, 10H), 6.83 (m, 1H), 6.31 (d, *J*=15.7 Hz, 0.5H), 6.18 (d, *J*=15.7 Hz, 0.5H), 5.20–4.98 (m, 2H), 4.67–4.43 (m, 3H), 4.23 (s, 1H), 4.08 (s, 1H), 3.59–3.40 (m, 2H), 2.18–2.01 (m, 1H), 1.94–1.74 (m, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$)* $\delta$ 196.8 ($C_q$), 196.7 ($C_q$), 154.9 ($C_q$), 147.1 (CH), 146.7 (CH), 137.3 ($C_q$), 137.2 ($C_q$), 136.8 ($C_q$), 136.6 ($C_q$), 128.6 (CH), 128.1 (CH), 128.0 (CH), 124.8 (CH), 124.6 (CH), 74.3 ($CH_2$), 73.4 ($CH_2$), 67.0 ($CH_2$), 58.4 (CH), 58.1 (CH), 47.0 ($CH_2$), 46.6 ($CH_2$), 31.8 ($CH_2$), 30.9 ($CH_2$), 23.8 ($CH_2$), 23.0 ($CH_2$); MS (EI, 70 eV) *m/z* (%) 397 ($M^+$, 1), 273 (14), 248 (8), 204 (9), 160 (13), 138 (18), 91 (100), 65 (16), 57 (9); HRMS (EI) calcd for $C_{23}H_{25}NO_4$ ($M^+$) 379.1784, found 379.1780. (*1:1 Mixture of rotamers.)

**4.3.4. (3*S*)-Benzyl 3-(benzyloxy)-2-((*E*)-4-(benzyloxy)-3-oxobut-1-enyl)pyrrolidine-1-carboxylate (16).** Following the general procedure for cross metathesis, and purification by column chromatography (7:3 hexanes/MTBE) afforded the title compound as a colourless oil (101 mg, 64%). $R_f$= 0.21 (7:3 hexanes/MTBE); $[\alpha]_D^{20}$ −24.6 (*c* 0.78, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$)* $\delta$ 7.40–7.10 (m, 15H), 6.79 (m, 1H), 6.35 (d, *J*=15.7 Hz, 0.5H), 6.23 (d, *J*=15.7 Hz, 0.5H), 5.20–5.10 (m, 1.5H), 5.00 (d, *J*=12.4 Hz, 0.5H), 4.70 (br d, *J*=4.9 Hz, 0.5H), 4.63–4.47 (m, 4.5H), 4.21 (s, 1H), 4.07 (s, 1H), 3.92 (m, 1H), 3.69 (m, 1H), 3.59 (m, 1H), 2.06 (m, 1H), 1.92 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$)* $\delta$ 196.6 ($C_q$), 196.4 ($C_q$), 155.1 ($C_q$), 155.0 ($C_q$), 144.2, 143.9, 137.5 ($C_q$), 137.3 ($C_q$), 137.2 ($C_q$), 137.0 ($C_q$), 136.6 ($C_q$), 128.65 (CH), 128.57 (CH), 128.51 (CH), 128.17 (CH), 128.10 (CH), 128.04 (CH), 127.97 (CH), 127.8 (CH), 127.7 (CH), 125.7 (CH), 125.6 (CH), 82.2 (CH), 81.2 (CH), 74.4 ($CH_2$), 73.4 ($CH_2$), 71.1 ($CH_2$), 67.14 ($CH_2$), 67.08 ($CH_2$), 64.10 (CH), 64.06 (CH), 45.2 ($CH_2$), 44.9 ($CH_2$), 29.6 ($CH_2$), 28.5 ($CH_2$); IR (ATR) $cm^{-1}$ 3063, 3031, 2945, 2894, 1703, 1634, 1412, 1346, 1099, 739, 698; MS (EI, 70 eV) *m/z* (%) 394 ($M^+-C_7H_7$, 4), 350 (10), 244 (2), 188 (2), 91 (100), 65 (2); HRMS (EI) calcd for $C_{23}H_{24}NO_5$ ($M^+-C_7H_7$) 394.1654, found 394.1655. (*1:1 Mixture of rotamers.)

**4.3.5. (2*S*,4*R*)-1-Benzyl 2-methyl-4-hydroxypyrrolidine-1,2-dicarboxylate (18).** To (2*S*,4*R*)-4-hydroxypyrrolidine-2-carboxylic acid (1.44 g, 11.0 mmol) in MeOH (60 mL) at 0 °C was added dropwise thionyl chloride (4.0 g, 33 mmol) and stirred for 18 h overnight at room temperature. Co-evaporation with toluene afforded quantitatively the methyl ester hydrochloride. The methyl ester hydrochloride was added directly to a vigorously stirred suspension of $K_2CO_3$ (6.84 g, 49.5 mmol) and benzyl chloroformate (2.82 g, 16.5 mmol) in THF (60 mL)/water (10 mL). Stirring was continued under $N_2$ for 4 h before water (10 mL) was added. The resultant biphasic solution was allowed to stir under air overnight. The solution was acidified with 1 N HCl (100 mL) before being extracted with EtOAc (3×100 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to leave a pale yellow residue. Flash chromatography (1:3 hexanes/EtOAc) afforded the title compound as a colourless oil (2.76 g, 90%). $R_f$=0.39 (1:3 hexanes/EtOAc); $[\alpha]_D^{20}$ −62.6 (*c* 1.0, $CHCl_3$); $^1$H NMR (500 MHz, DMSO-$d_6$, 378 K) $\delta$ 7.33–7.25 (m, 5H), 5.10 (d, *J*=12.7 Hz, 1H), 5.06 (d, *J*=12.7 Hz, 1H), 4.69 (br d, *J*=3.4 Hz, 1H), 4.40 (dd, *J*=7.7, 7.4 Hz, 1H), 4.33 (m, 1H), 3.60 (s, 3H), 3.52 (dd, *J*=11.0, 4.7 Hz, 1H), 3.41 (ddd, *J*=11.0, 2.6, 1.4 Hz, 1H), 2.18 (m, 1H), 2.01 (m, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$, 378 K) $\delta$ 172.6 ($C_q$), 154.2 ($C_q$), 136.9 ($C_q$), 128.2 (CH), 127.6 (CH), 127.3 (CH), 68.3 (CH), 66.3 ($CH_2$), 57.9 (CH), 54.8 ($CH_2$), 51.5 ($CH_3$), 38.6 ($CH_2$); IR (ATR) $cm^{-1}$ 3443, 3064, 3033, 2952, 2885, 1744, 1681, 1416, 1202, 1167, 1119, 1082, 769, 697; MS (EI, 70 eV) *m/z* (%) 279 ($M^+$, 10), 234 (8), 220 (68), 192 (40), 176 (74), 144 (15), 121 (25), 91 (100), 65 (22). HRMS (EI) calcd for $C_{14}H_{17}NO_5$ ($M^+$) 279.1107, found 279.1109.

**4.3.6. (2*S*,4*R*)-2-Methyl 1-phenyl-4-(benzyloxy)pyrrolidine-1,2-dicarboxylate (19).** Alcohol **18** (2.75 g, 9.85 mmol) was dissolved in DCM (20 mL) and hexane (40 mL) was added followed by benzyl trichloroacetimidate (2.98 g, 11.8 mmol). After stirring for 5 min 15 drops of triflic acid were added and a white precipitate was formed immediately. Stirring was continued for 8 h before the suspension was filtered and the filter cake washed with hexanes (3×10 mL). The solvent was removed in vacuo and the residue taken up in MTBE (150 mL) and washed with 1 N HCl (3×50 mL) and satd $NaHCO_3$ (3×50 mL). The combined ethereal extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (2:1 hexanes/MTBE) gave the title compound as a colourless oil (3.66 g, 100%). $R_f$=0.34 (1:1 hexanes/MTBE); $[\alpha]_D^{20}$ −36.1 (*c* 1.5, $CHCl_3$); $^1$H NMR (500 MHz, DMSO-$d_6$, 373 K) $\delta$ 7.38–7.23 (m, 10H), 5.11 (d, *J*=12.7 Hz, 1H), 5.07 (d, *J*=12.7 Hz, 1H), 4.53 (d, *J*=12.1 Hz, 1H), 4.50 (d, *J*=12.1 Hz, 1H), 4.39 (dd, *J*=8.3, 6.9 Hz, 1H), 4.24 (m, 1H), 3.64–3.55 (m, 5H), 2.38 (dddd, *J*=13.5, 8.3, 3.8, 1.3 Hz, 1H), 2.10 (ddd, *J*=13.5, 6.9, 5.4 Hz, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$, 373 K) $\delta$ 172.3 ($C_q$), 154.1 ($C_q$), 138.4 ($C_q$), 136.8 ($C_q$), 128.2 (CH), 128.1 (CH),

127.7 (CH), 127.4 (CH), 127.34 (CH), 127.29 (CH), 76.3 (CH), 70.4 ($CH_2$), 66.4 ($CH_2$), 57.8 (CH), 52.0 ($CH_2$), 51.6 ($CH_3$), 35.7 ($CH_2$); IR (ATR) $cm^{-1}$ 3063, 3031, 2951, 2884, 1747, 1705, 1415, 1204, 1118, 736, 697; MS (EI, 70 eV) *m/z* (%) 369 ($M^+$, 3), 310 (41), 266 (73), 234 (8), 181 (10), 158 (5), 144 (7), 128 (10), 91 (100), 65 (16). HRMS (EI) calcd for $C_{21}H_{23}NO_5$ ($M^+$) 369.1576, found 369.1569. Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 67.64; H, 6.12; N, 4.32.

**4.3.7. (2*S*,4*R*)-Benzyl 4-(benzyloxy)-2-(hydroxymethyl)-pyrrolidine-1-carboxylate (20).** To a stirred solution of ester **19** (2.89 g, 7.82 mmol) under $N_2$ in THF (20 mL)/EtOH (30 mL) at 0 °C were added $NaBH_4$ (657 mg, 17.4 mmol) and LiCl (738 mg, 17.4 mmol). The suspension was allowed to warm to room temperature and stirring was continued for 3 days under $N_2$. To the resultant thick white suspension was added 1 N HCl (100 mL), and the solution extracted with EtOAc (5×50 mL). The organic layer was dried ($MgSO_4$), and concentrated in vacuo to leave a pale yellow residue. Flash chromatography (1:2 hexanes/MTBE) afforded the title compound as a milky oil (2.30 g, 86%). $R_f$=0.23 (1:2 hexanes/MTBE); $[\alpha]_D^{20}$ −35.6 (*c* 2.5, $CHCl_3$); $^1$H NMR (500 MHz, DMSO-$d_6$, 373 K) $\delta$ 7.38–7.22 (m, 10H), 5.12 (d, *J*=12.7 Hz, 1H), 5.09 (d, *J*=12.7 Hz, 1H), 4.50 (d, *J*=12.1 Hz, 1H), 4.48 (d, *J*=12.1 Hz, 1H), 4.22 (m, 2H), 3.97 (m, 1H), 3.60 (br d, *J*=11.5 Hz, 1H), 3.54 (m, 2H), 3.45 (dd, *J*=11.5, 5.0 Hz, 1H), 2.15–2.03 (m, 2H); $^{13}$C NMR (DMSO-$d_6$, 125 MHz, 373 K) $\delta$ 154.6 ($C_q$), 138.7 ($C_q$), 137.3 ($C_q$), 128.2 (CH), 128.1 (CH), 127.5 (CH), 127.31 (CH), 127.28 (CH), 127.2 (CH), 76.6 (CH), 70.3 ($CH_2$), 66.0 ($CH_2$), 62.5 ($CH_2$), 58.0 (CH), 52.2 ($CH_2$), 34.3 ($CH_2$); IR (ATR) $cm^{-1}$ 3441, 3063, 3031, 2942, 2880, 1699, 1680, 1418, 1355, 1115, 1083, 735, 697; MS (EI, 70 eV) *m/z* (%) 341 ($M^+$, <1), 310 (57), 266 (47), 158 (3), 91 (100), 65 (8); HRMS (EI) calcd for $C_{20}H_{23}NO_4$ ($M^+$) 341.1627, found 341.1621. Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.27; H, 6.59; N, 4.62.

**4.3.8. (2*S*,4*R*)-Benzyl 4-(benzyloxy)-2-vinylpyrrolidine-1-carboxylate (21).** A solution of the alcohol **20** (978 mg, 2.87 mmol) in DCM was cooled to −78 °C under $N_2$ and DMSO (0.82 mL, 11.5 mmol) was added dropwise followed by oxalyl chloride (0.49 mL, 5.73 mmol). Stirring was continued for 60 min. $Et_3N$ (4.0 mL, 29 mmol) was then added dropwise and the reaction mixture allowed to warm to room temperature for over 60 min. HCl (1 N, 80 mL) was then added and the solution extracted with DCM (3×80 mL), washed with satd $NaHCO_3$ (100 mL) and satd NaCl (100 mL), dried ($MgSO_4$) and concentrated in vacuo to afford the crude aldehyde in quantitative yield. Meanwhile *n*-BuLi (2.5 M in hexane, 3.16 mmol) was added to a suspension of methyl triphenylphosphoniumbromide (1.23 g, 3.44 mmol) in THF (40 mL) at −78 °C under $N_2$ and stirred for 30 min before a solution of the aldehyde in THF (8 mL) was added dropwise to the bright yellow suspension. The reaction mixture was allowed to warm to room temperature and stirred overnight. Satd $NH_4Cl$ (120 mL) was added and the mixture extracted with MTBE (3×90 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (6:1 hexanes/MTBE) gave the title compound as a colourless oil (662 mg, 68%). $R_f$=0.33 (2:1 hexanes/MTBE); $[\alpha]_D^{20}$ +8.0 (*c* 0.50, $CHCl_3$); $^1$H NMR (500 MHz, DMSO-$d_6$, 373 K) $\delta$ 7.38–7.22 (m, 10H), 5.82 (ddd, *J*=17.1, 10.3, 6.0 Hz, 1H), 5.12–5.04 (m, 3H), 5.01 (d, *J*=10.3 Hz, 1H), 4.51 (d, *J*=12.2 Hz, 1H), 4.48 (d, *J*=12.2 Hz, 1H), 4.42 (m, 1H), 4.17 (m, 1H), 3.61 (br d, *J*=11.6 Hz, 1H), 3.48 (dd, *J*=11.6, 4.9 Hz, 1H), 2.20 (m, 1H), 1.91 (ddd, *J*=13.0, 5.8, 5.8 Hz, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$, 373 K) $\delta$ 154.5 ($C_q$), 139.1 (CH), 138.6 ($C_q$), 137.2 ($C_q$), 128.6 (CH), 128.2 (CH), 128.1 (CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 113.9 ($CH_2$), 76.3 (CH), 70.3 ($CH_2$), 66.0 ($CH_2$), 57.9 (CH), 51.7 ($CH_2$), 37.7 ($CH_2$); IR (ATR) $cm^{-1}$ 3064, 3031, 2941, 2881, 1700, 1410, 1354, 1111, 917, 734, 696; MS (EI, 70 eV) *m/z* (%) 337 ($M^+$, <1), 246 (10), 202 (3), 170 (4), 91 (100), 65 (6); HRMS (EI) *m/z* calcd for $C_{21}H_{23}NO_3$ ($M^+$) 337.1678, found 337.1679. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.98; H, 6.93; N, 4.19.

**4.3.9. (2*S*,4*R*)-Benzyl 4-(benzyloxy)-2-((*E*)-4-(benzyloxy)-3-oxobut-1-enyl)pyrrolidine-1-carboxylate (22).** To a stirring solution of the vinyl pyrrolidine **21** (192 mg, 0.570 mmol) in DCM (2.9 mL, 0.2 M) was added freshly prepared enone **9** (402 mg, 2.28 mmol), and the solution heated to reflux before the catalyst [Ru] (18 mg, 5 mol %) was added. The green solution was heated to reflux for 60 h, before purification by column chromatography (2:1 hexanes/EtOAc). Second flash chromatography (3:1 hexanes/EtOAc) afforded the title compound as a colourless oil (211 mg, 76%). $R_f$=0.18 (3:1 hexanes/EtOAc); $[\alpha]_D^{20}$ −24.7 (*c* 0.70, $CHCl_3$); $^1$H NMR (500 MHz, DMSO-$d_6$, 373 K) $\delta$ 7.32–7.21 (m, 15H), 6.80 (dd, *J*=15.9, 6.3 Hz, 1H), 6.25 (dd, *J*=15.9, 0.9 Hz, 1H), 5.09 (d, *J*=12.7 Hz, 1H), 5.04 (d, *J*=12.7 Hz, 1H), 4.58–4.50 (m, 4H), 4.48 (d, *J*=12.2 Hz, 1H), 4.22 (s, 2H), 4.18 (m, 1H), 3.65 (ddd, *J*=11.8, 2.3, 1.7 Hz, 1H), 3.52 (dd, *J*=11.8, 4.8 Hz, 1H), 2.29 (dddd, *J*=13.3, 7.9, 3.9, 1.5 Hz, 1H), 1.93 (ddd, *J*=13.3, 7.1, 5.1 Hz, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$, 373 K) $\delta$ 196.5 ($C_q$), 154.5 ($C_q$), 146.7 (CH), 138.5 ($C_q$), 138.0 ($C_q$), 137.0 ($C_q$), 128.2 (CH), 128.14 (CH), 128.13 (CH), 127.61 (CH), 128.55 (CH), 127.5 (CH), 127.4 (CH), 127.32 (CH), 127.30 (CH), 125.3 (CH), 76.2 (CH), 74.1 ($CH_2$), 72.7 ($CH_2$), 70.3 ($CH_2$), 66.2 ($CH_2$), 57.0 (CH), 51.9 ($CH_2$), 37.5 ($CH_2$); IR (ATR) $cm^{-1}$ 3063, 3031, 2936, 2877, 1703, 1632, 1412, 1355, 1113, 739, 698; MS (EI, 70 eV) *m/z* (%) 485 ($M^+$, 1), 244 (5), 181 (2), 91 (100), 65 (6). HRMS (EI) calcd for $C_{30}H_{31}NO_5$ ($M^+$) 485.2202, found 485.2210. Anal. Calcd for $C_{30}H_{31}NO_5$: C, 74.21; H, 6.43; N, 2.88. Found: C, 74.38; H, 6.33; N, 2.97.

**4.3.10. (2*S*,4*R*)-Benzyl 4-(benzyloxy)-2-((1*R*,2*S*)-4-(benzyloxy)-1,2-dihydroxy-3-oxobutyl)pyrrolidine-1-carboxylate (23).** To a stirred solution of the enone **22** (55 mg, 0.113 mmol) in acetone (1.5 mL) and water (0.8 mL) at 0 °C were added sodium bicarbonate (29 mg, 0.339 mmol), methylsulfonamide (11 mg, 0.113 mmol) and 317 mg of modified AD-mix-β (contains additional $K_2Os_4(OH)_4$ to raise the total to 1 mol %). The mixture was stirred overnight at room temperature. At 0 °C satd $NaHSO_3$ (5 mL) was added and the mixture extracted with ethyl acetate (5×8 mL), the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was chromatographed (2:1 hexanes/EtOAc) to afford the title compound as a colourless oil (24 mg, 41%). $R_f$=0.40 (1:1 hexanes/EtOAc); $[\alpha]_D^{20}$ −25.5 (*c* 0.55, $CHCl_3$); $^1$H NMR

(500 MHz, DMSO-$d_6$, 373 K) $\delta$ 7.35–7.23 (m, 15H), 5.09 (s, 2H), 4.76 (br d, $J$=4.9 Hz, 1H), 4.57 (m, 1H), 4.51 (s, 2H), 4.46 (d, $J$=12.0 Hz, 1H), 4.44 (d, $J$=12.0 Hz, 1H), 4.39 (s, 2H), 4.24–4.15 (m, 2H), 4.11 (m, 1H), 3.93 (m, 1H), 3.76 (m, 1H), 3.37 (dd, $J$=12.0, 4.6 Hz, 1H), 2.16 (m, 1H), 2.07 (m, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$, 373 K) $\delta$ 208.3 ($C_q$), 156.8 ($C_q$), 138.6 ($C_q$), 138.2 ($C_q$), 137.0 ($C_q$), 128.2 (CH), 128.1 (CH), 127.9 (CH), 127.6 (CH), 127.51 (CH), 127.49, 127.4 (CH), 127.3 (CH), 127.2 (CH), 76.8 (CH), 75.7 (CH), 73.3 ($CH_2$), 73.0 (CH), 72.6 ($CH_2$), 70.1 ($CH_2$), 66.4 ($CH_2$), 59.1 (CH), 52.2 ($CH_2$), 33.9 ($CH_2$); IR (ATR) cm$^{-1}$ 3425, 3063, 3031, 2926, 2871, 1727, 1671, 1420, 1356, 1103, 738, 698; MS (EI, 70 eV) *m/z* (%) 520 ($MH^+$, 6), 386 (10), 370 (3), 340 (16), 310 (40), 296 (7), 266 (40), 181 (8), 149 (15), 107 (5), 91 (100), 65 (10); HRMS (EI) calcd for $C_{30}H_{34}NO_7$ ($MH^+$) 520.2335, found 520.2343. Anal. Calcd for $C_{30}H_{33}NO_7$: C, 69.35; H, 6.40; N, 2.70. Found: C, 69.04; H, 6.38; N, 2.52.

**4.3.11. (2*S*,4*R*)-Benzyl 4-(benzyloxy)-2-((1*S*,2*R*)-4-(benzyloxy)-1,2-dihydroxy-3-oxobutyl)pyrrolidine-1-carboxylate (24).** To a stirred solution of the enone **22** (65 mg, 0.134 mmol) in acetone (1.8 mL) and water (0.9 mL) at 0 °C were added sodium bicarbonate (34 mg, 0.402 mmol), methylsulfonamide (13 mg, 0.134 mmol) and 375 mg of modified AD-mix-$\alpha$ (contains additional $K_2Os_4(OH)_4$ to raise the total to 1 mol %). The mixture was stirred overnight at room temperature. At 0 °C satd $NaHSO_3$ (6 mL) was added and the mixture extracted with ethyl acetate (5×8 mL), the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was chromatographed (2:1 hexanes/EtOAc) to afford the title compound as a colourless oil (19 mg, 27%). $R_f$=0.32 (1:1 hexanes/EtOAc); $[\alpha]_D^{20}$ −13.1 (*c* 0.35, $CHCl_3$); $^1$H NMR (500 MHz, DMSO-$d_6$, 373 K) $\delta$ 7.37–7.22 (m, 15H), 5.11 (d, $J$=12.8 Hz, 1H), 5.08 (d, $J$=12.8 Hz, 1H), 4.74 (br d, $J$=6.2 Hz, 1H), 4.67 (br d, $J$=6.7 Hz, 1H), 4.51 (d, $J$=12.0 Hz, 1H), 4.50 (d, $J$=12.0 Hz, 1H), 4.47 (d, $J$=12.0 Hz, 1H), 4.45 (d, $J$=12.0 Hz, 1H), 4.42 (d, $J$=18.0 Hz, 1H), 4.37 (d, $J$=18.0 Hz, 1H), 4.22–4.12 (m, 2H), 4.08–4.02 (m, 2H), 3.65 (ddd, $J$=11.7, 2.1, 2.1 Hz, 1H), 3.35 (dd, $J$=11.7, 4.7 Hz, 1H), 2.34 (ddd, $J$=13.7, 5.8, 5.8 Hz, 1H), 1.98 (dddd, $J$=13.7, 8.3, 3.6, 1.5 Hz, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$, 373 K) $\delta$ 208.5 ($C_q$), 138.7 ($C_q$), 138.2 ($C_q$), 137.1 ($C_q$), 128.2 (CH), 128.10 (CH), 128.09 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 127.31 (CH), 127.28 (CH), 127.20 (CH), 77.3 (CH), 77.1 (CH), 73.2 ($CH_2$), 72.5 ($CH_2$), 71.1 (CH), 70.1 ($CH_2$), 66.1 ($CH_2$), 59.3 (CH), 52.0 ($CH_2$), 32.1 ($CH_2$); IR (ATR) cm$^{-1}$ 3424, 3063, 3031, 2916, 2849, 1728, 1674, 1418, 1356, 1103, 737, 697; MS (EI, 70 eV) *m/z* (%) 520 ($MH^+$, 5), 386 (19), 356 (3), 340 (8), 310 (40), 296 (9), 266 (47), 181 (21), 158 (5), 107 (7), 91 (100), 65 (9); HRMS (EI) calcd for $C_{30}H_{34}NO_7$ ($MH^+$) 520.2335, found 520.2337. Anal. Calcd for $C_{30}H_{33}NO_7$: C, 69.35; H, 6.40; N, 2.70. Found: C, 69.40; H, 6.24; N, 2.87.

**4.3.12. (+)-7a-*epi*-7-Deoxycasuarine (5).** To a solution of ketodiol **23** (15 mg, 0.0289 mmol) in MeOH (3 mL) was added 5% Pd/C (12 mg, 50 wt % $H_2O$), and the heterogeneous mixture was stirred under 1 atm of $H_2$ at room temperature for 24 h. Concentrated HCl (3 drops) was added and the suspension stirred for additional 24 h. The solution was filtered (Celite) and lyophilised. The residue was dissolved in MeOH (3 mL), and stirred with strong basic ion-exchange resin (200 mg Amberlite IR 410, $OH^-$-form) for 30 min. Filtration and evaporation afforded 5 mg (92%) of a 3:1 diastereomeric mixture with the title compound as the major component. Purification on silica (98:2 MeOH/$NH_4OH$) gave 3.5 mg of the title compound. $R_f$=0.21 (98:2 MeOH/$NH_4OH$); $[\alpha]_D^{20}$ +15.0 (*c* 0.12, $H_2O$); $^1$H NMR (500 MHz, $D_2O$) $\delta$ 4.54 (m, 1H, H-6), 4.16 (dd, $J$=7.5, 6.2 Hz, 1H, H-1), 3.92–3.81 (m, 4H, H-8, H-8′, H-7a, H-2), 3.11 (dd, $J$=11.1, 4.1 Hz, 1H, H-5$\alpha$), 3.07 (m, 1H, H-3), 2.93 (ddd, $J$=11.1, 1.7, 1.7 Hz, 1H, H-5$\beta$), 2.13 (ddd, $J$=13.9, 8.1, 5.6 Hz, 1H, H-7$\alpha$), 1.84 (dddd, $J$=13.9, 7.9, 1.7, 1.7 Hz, 1H, H-7$\beta$); $^{13}$C NMR (125 MHz, $D_2O$) $\delta$ 77.3 (C-1), 76.9 (C-2), 72.6 (C-6), 65.3 (C-3), 64.0 (C-7a), 59.9 (C-8), 55.7 (C-5), 33.7 (C-7); IR (ATR) cm$^{-1}$ 3323, 2925, 2853, 2715, 1576, 1411, 1341, 1122, 1044, 985; MS (ESI) *m/z* 190.1 ($MH^+$), and 1.3 mg of the epimer at C-3 compound **5a**. $R_f$=0.30 (98:2 MeOH/$NH_4OH$); $^1$H NMR (500 MHz, $D_2O$) $\delta$ 4.57 (m, 1H, H-6), 4.28 (m, 1H, H-2), 4.05 (m, 1H, H-1), 3.94 (m, 1H, H-7a), 3.80 (m, 1H, H-8), 3.68 (dd, $J$=11, 6 Hz, 1H, H-8′), 2.99–2.92 (m, 2H, H-3 and H-5), 2.81 (dd, $J$=11, 5 Hz, 1H, H-5′), 2.16 (m, 1H, H-7), 1.74 (m, 1H, H-7′). MS (ESI): *m/z* 190.1 ($MH^+$).

**4.3.13. Compound 25.** To a solution of ketodiol **24** (5 mg, 0.00962 mmol) in MeOH (1 mL) was added 5% Pd/C (4 mg, 50 wt % $H_2O$), and the heterogeneous mixture was stirred under 1 atm of $H_2$ at room temperature for 24 h. Concentrated HCl (1 drop) was added and the suspension stirred for additional 24 h. The solution was filtered (Celite) and lyophilised. The residue was dissolved in MeOH (1 mL), and stirred with strong basic ion-exchange resin (100 mg Amberlite IR 410, $OH^-$-form) for 30 min. Filtration and evaporation afforded 1.8 mg (99%) of 10:1 diastereomeric mixture with the title compound as the major component. $R_f$=0.50 (98:2 MeOH/$NH_4OH$); $[\alpha]_D^{20}$ −5.8 (*c* 0.18, $H_2O$); $^1$H NMR (500 MHz, $D_2O$) $\delta$ 4.58 (m, 1H, H-6), 3.88–3.83 (m, 2H, H-1, H-2), 3.79 (dd, $J$=11.8, 3.6 Hz, 1H, H-8), 3.64 (dd, $J$=11.8, 6.6 Hz, 1H, H-8′), 3.38 (m, 1H, H-7a), 2.99 (dd, $J$=11.8, 3.6 Hz, 1H, H-5$\beta$), 2.93 (dd, $J$=11.8, 4.7 Hz, 1H, H-5$\alpha$), 2.76 (m, 1H, H-3), 2.07 (ddd, $J$=13.5, 7.3, 3.9 Hz, 1H, H-7$\beta$), 1.99 (ddd, $J$=13.5, 7.3, 5.3 Hz, 1H, H-7$\alpha$); $^{13}$C NMR (125 MHz, $D_2O$) $\delta$ 81.4 (CH), 78.6 (CH), 72.9 (C-6), 70.8 (C-3), 66.0 (C-7a), 63.5 (C-8), 62.3 (C-5), 38.6 (C-7); IR (ATR) cm$^{-1}$ 3323, 2916, 2848, 1573, 1408, 1337, 1098, 1067, 1039, 963; MS (ESI) *m/z* 190.1 ($MH^+$).

## Acknowledgements

We are grateful to the Fonds der Chemischen Industrie, and the Graduiertenkolleg ‘Synthetische, mechanistische und reaktionstechnische Aspekte von Metallkatalysatoren’ for financial support.

## References and notes

1. Nash, R. J.; Fellows, L. E.; Dring, J. V.; Fleet, G. W. J.; Derome, A. E.; Hamor, T. A.; Scofield, A. M.; Watkin, D. J. *Tetrahedron Lett.* **1988**, *29*, 2487.

2. Taylor, D. L.; Nash, R. J.; Fellows, L. E.; Kang, M. S.; Tyms, A. S. *Antiviral Chem. Chemother.* **1992**, *3*, 273.
3. (a) Pearson, M. S. M.; Mathé-Allainmat, M.; Fargeas, J.; Lebreton, J. *Eur. J. Org. Chem.* **2005**, *11*, 2159; (b) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265; (c) Asano, N.; Kato, A.; Watson, A. A. *Mini Rev. Med. Chem.* **2001**, *1*, 145.
4. Asano, N.; Kuroi, H.; Ikeda, K.; Kizu, H.; Kameda, Y.; Kato, A.; Adachi, I.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1.
5. Carmona, A. T.; Whigtman, R. H.; Robina, I.; Vogel, P. *Helv. Chim. Acta* **2003**, *86*, 3066.
6. *Imino Sugars as Glycosidase Inhibitors: Norjirmycin and Beyond*; Stuetz, A. E., Ed.; Wiley-VCH: Weinheim, 1999.
7. For recent examples see: (a) Denmark, S. E.; Hurd, A. R. *Org. Lett.* **1999**, *1*, 1311; (b) Chabaud, L.; Landais, Y.; Renaud, P. *Org. Lett.* **2005**, *7*, 2587; (c) Donohoe, T. J.; Sintim, H. O. *Org. Lett.* **2004**, *6*, 2003; (d) Tang, M.; Pyne, S. G. *J. Org. Chem.* **2003**, *68*, 7818; (e) Yoda, H. *Curr. Org. Chem.* **2002**, *6*, 223; (f) Dewi-Wuelfing, P.; Blechert, S. *Eur. J. Org. Chem.* **2006**, 1852; (g) Cardona, F.; Faggi, E.; Liguori, F.; Cacciarini, M.; Goti, A. *Tetrahedron Lett.* **2003**, *44*, 2315; (h) Izquerdo, I.; Plaza, M. T.; Tamayo, J. A. *Tetrahedron* **2005**, *61*, 6527; (i) van Ameijde, J.; Horne, G.; Wormald, M. R.; Dwek, R. A.; Nash, R. J.; Jones, P. W.; Evinson, E. L.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2006**, *17*, 2702.
8. Behr, J.-B.; Erard, A.; Guillerm, G. *Eur. J. Org. Chem.* **2002**, 1256.
9. (a) Romyr, D.; Das, S. K.; Liu, B.; Nahra, J.; Schmor, B.; Gan, Z.; Roy, R. *Methods Enzymol.* **2003**, *362*, 17; (b) Vasbinder, M. M.; Miller, S. J. *J. Org. Chem.* **2002**, *67*, 6240.
10. Takeuchi, Y.; Yamada, A.; Suzuki, T.; Koizumi, T. *Tetrahedron* **1996**, *52*, 225.
11. Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, G. H. *J. Am. Chem. Soc.* **2003**, *123*, 11360.
12. [Ru] refers to ruthenium, [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro[[2-(1-methylethoxy)phenyl]-methylene].
13. See Section 4 for synthesis.
14. Beligny, S.; Eibauer, S.; Maechling, S.; Blechert, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 1900.
15. Scholte, A. A.; An, M. H.; Snapper, M. L. *Org. Lett.* **2006**, *8*, 4759.
16. Donohoe, T. J.; Sintim, H. O.; Hollinshead, J. *J. Org. Chem.* **2005**, *70*, 7297.
17. Wormald, M. R.; Nash, R. J.; Hrnciar, P.; White, J. D.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2549.