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Stereoselective Organocatalytic Approach to α,β-Disubstituted-β-amino Acids: A Short Enantioselective Synthesis of Cispentacin

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α-Branched α,β-unsaturated aldehydes have been tested in the organocatalytic tandem Michael addition/cyclization with *N*-(benzyloxycarbonyl)hydroxylamine, a reaction which until now has been restricted to α-unsubstituted enals. Starting from cyclopentene-2-carbaldehyde, and using diphenylprolinol trimethylsilyl ether as a chiral amine catalyst, this approach has led to the development of a practical, high yielding (93–98 % overall yield, three steps), and highly enantioselective (up to 98:2 *er*) route to the cyclic β-amino acid cispentacin, which compares favourably with previously described asymmetric syntheses of this biologically active natural product. When using acyclic α-branched α,β-unsaturated aldehydes as substrates, the reaction yields depend on the substitution pattern of the aldehydes, and mixtures of *cis*- and *trans*-isomers are obtained. Nevertheless, this strategy has proved to be successful in some instances, and (3*R*,4*R*)-benzyl 3-ethyl-4-methyl-5-oxoisoxazolidin-2-carboxylate could be obtained in 70 % overall yield (two steps) from the reaction of 2-ethylcrotonaldehyde and *N*-(benzyloxycarbonyl)hydroxylamine under catalysis with diphenylprolinol trimethylsilyl ether, and with high enantiomeric purity (99:1 *er*).

Introduction

Acyclic and alicyclic β-amino acids are important compounds from both chemical and biological points of view.[1] Although less abundant than α-amino acids, they are found in peptides and in other types of natural products; they are useful precursors of β-lactams;[2] they can be incorporated into synthetic peptides to give well-defined three-dimensional structures and with improved stability;[3] and some of them have significant pharmacological properties.[4]

An especially relevant alicyclic β-amino acid is *cis*-2-aminocyclopentane-1-carboxylic acid, cispentacin (**1**). The (1*R*,2*S*) enantiomer of cispentacin was isolated in 1989 as an antifungal antibiotic from the culture broth of a *Bacillus cereus* strain (L450–B2).[5] The same compound was independently isolated from the culture broth of *Streptomyces setonii*,[6] and was found to have a potent therapeutic effect against *Candida albicans*.[5–7] On the other hand, the non-natural (1*S*,2*R*) enantiomer of **1** is devoid of biological activity.[5] The interesting pharmacological activity, together with the relative structural simplicity of cispentacin, has stimulated the search for practical enantioselective syntheses of this compound.

Until now, most approaches to the preparation of **1** in optically active form have relied on resolution of racemic cispentacin by crystallization of diastereomeric salts,[5,8] or by enzymatic hydrolysis, either of cispentacin derivatives or of synthetic precursors.[9] However, Davies[10] and Aggarwal[11] have achieved asymmetric syntheses of cispentacin using chiral auxiliaries, and Bolm and co-workers have developed a three-step sequence relying on the quinidine-promoted asymmetric desymmetrization of the *meso*-anhydride of *cis*-1,2-cyclopentanedicarboxylic acid, followed by Curtius degradation of the acyl azide derived from the optically active hemiester.[12]

A retrosynthetic analysis of cispentacin (Scheme 1) showed that a potentially attractive synthesis of this compound could be based on the stereocontrolled tandem aza-Michael/cyclization reaction of cyclopentene-1-carbaldehyde (**2**) with *N*-(benzyloxycarbonyl)hydroxylamine (**3**), followed by oxidation of intermediate 5-hydroxyisoxazolidine **4** to isoxazolidinone **5** and then hydrogenolysis. In fact, the chiral-secondary-amine-catalysed tandem aza-Michael/cyclization reaction of α-unsubstituted enals with **3**, reported by Córdova and co-workers a few years ago, constitutes a highly enantioselective route for the synthesis of 2-substituted 5-hydroxyisoxazolidines, which can be converted in two steps into the corresponding acyclic β-amino acids.[13]

It is worth noting that until now, the substrate scope of asymmetric organocatalytic aza-Michael additions to unsaturated aldehydes has been mainly restricted to simple β-substituted enals,[13,14] since the use of α-branched α,β-unsaturated aldehydes in these reactions is plagued by very

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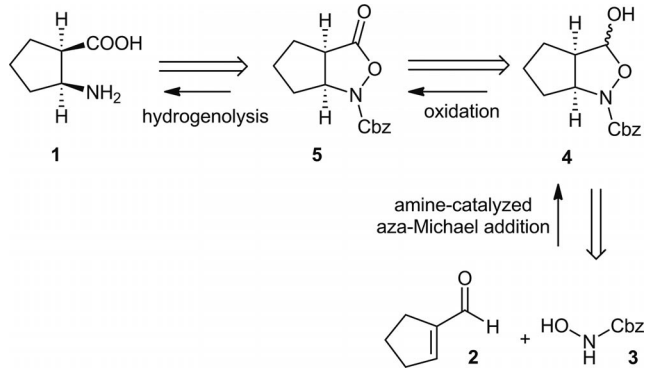


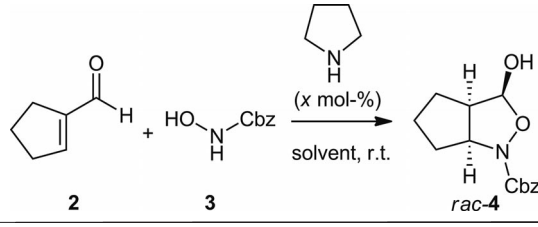
Scheme 1. Retrosynthetic analysis of cispentacin.

low rates and/or stereoselectivities, due to steric hindrance for the formation of the enamine intermediate.[15] As a result of these limitations, there are very few examples describing successful amine-catalysed Michael additions to cyclopentene-1-carbaldehyde (**2**).[16,17] In particular, to the best of our knowledge, there are no reports concerning aza-Michael additions with this compound. In light of these precedents, we decided to investigate in some depth the amine-catalysed Michael additions of *N*-(benzyloxycarbonyl)hydroxylamine (**3**) with α-branched α,β-unsaturated aldehydes, and in particular with cyclopentene-1-carbaldehyde (**2**).

Results and Discussion

We initiated our study by choosing as a benchmark reaction the addition of *N*-(benzyloxycarbonyl)hydroxylamine (**3**) to cyclopentene-1-carbaldehyde (**2**)[18] using pyrrolidine as the amine promoter. We were confident that although the primary product of the Michael addition would be presumably obtained as a *cis*/*trans* diastereomeric mixture, amine-catalysed epimerization of the exocyclic carbaldehyde moiety would lead to the selective formation of the desired isoxazolidine (i.e., **4**), given the greater thermodynamic stability of *cis*-1-aza-2-oxabicyclo[3.3.0]octane systems relative to the *trans* isomers. This expectation turned out to be right, and we found that in a variety of solvents, racemic bicyclic isoxazolidine **4** was isolated as a single diastereomer[19] in moderate to good yields (Table 1).

Table 1. Pyrrolidine-promoted aza-Michael/cyclization reaction of cyclopentene-1-carbaldehyde (**2**) with *N*-Cbz-hydroxylamine (**3**).



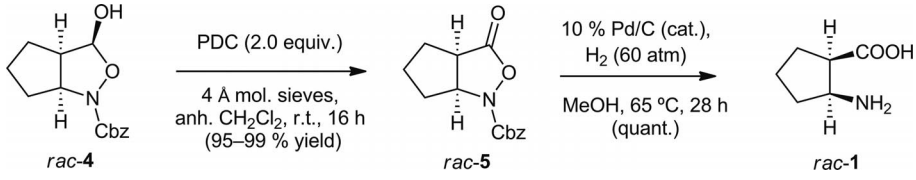
Entry	Solvent	**2**/**3** ratio	Pyrrolidine [mol-%]	Time [d][a]	Yield [%][b]
1	$CHCl_3$	1.0	100	2	47
2	MeOH	1.0	100	2	24
3	EtOH	1.0	100	2	34
4	toluene	1.0	100	2	42
5	CH_3CN	1.0	100	2	32
6	$CHCl_3$	2.0	100	1	60
7	$CHCl_3$	2.0	20	4	56
8	toluene	2.0	20	4	80

[a] Time necessary for consumption of **3**, as monitored by ^{1}H NMR spectroscopy. [b] Yield of isolated *rac*-**4** after chromatographic purification.

As can be seen from the results shown in Table 1, the best yields were obtained in relatively non-polar solvents such as chloroform (Table 1, entry 1) and toluene (Table 1, entry 4), although these yields are still relatively low due to the consumption of **3** in the formation of *N*-Cbz-pyrrolidine. This side-reaction could be minimized by using an excess of the aldehyde, and by reducing the concentration of pyrrolidine in the reaction mixture. Thus, using the conditions of Table 1, entry 8, *rac*-**4** could be isolated in 80% yield after 4 d of reaction at room temperature in toluene.

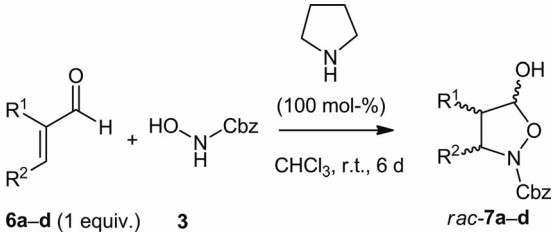
We then proceeded with the conversion of *rac*-**4** into racemic cispentacin. In contrast to the behaviour of monocyclic 5-hydroxyisoxazolidines, the oxidation of this compound to the corresponding isoxazolidinone (i.e., *rac*-**5**) did not take place with sodium chlorite,[13a] but the transformation could be efficiently brought about using pyridinium dichromate (PDC) in the presence of 4 Å molecular sieves.[20] Finally, medium-pressure catalytic hydrogenation of *rac*-**5** effected both the cleavage of the N–O bond and of the Cbz amine-protecting group to give racemic cispentacin (**1**) in quantitative yield (Scheme 2).

We next examined the pyrrolidine-promoted Michael addition/cyclization of **3** to a set of acyclic α,β-unsaturated, α-branched aldehydes **6a**–**d** (Table 2).



Scheme 2. Synthesis of racemic cispentacin (**1**).

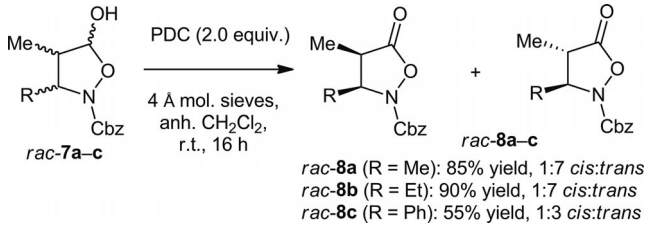
Table 2. Pyrrolidine-promoted aza-Michael/cyclization reaction of α-branched enals **6a**–**d** with *N*-Cbz-hydroxylamine (**3**).



Entry[a]	Enal	R^1, R^2	Product	Yield [%][a]	*dr*[b]
1	**6a**	Me, Me	**7a**	96	7:1
2	**6b**	Me, Et	**7b**	82	3:1
3	**6c**	Me, Ph	**7c**	35[c]	3:1
4	**6d**	*n*Pr, *n*Bu	**7d**	0[d]	–

[a] Yield of isolated product after chromatographic purification. [b] Determined by ^{1}H NMR of the reaction product before chromatographic purification. [c] *N*-Cbz-pyrrolidine isolated in 44% yield, together with an 11% of **3**. [d] *N*-Cbz-pyrrolidine isolated in 18% yield, together with unreacted **3**.

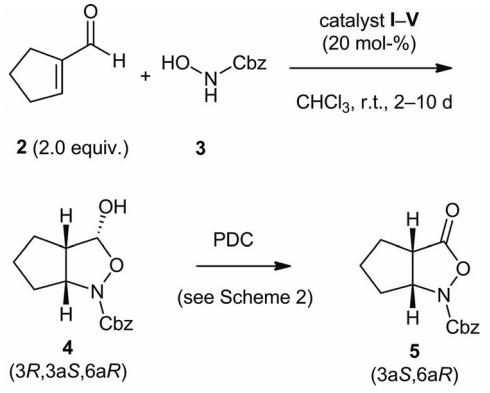
The reaction yields were heavily dependent on the substitution pattern of the enal. Good yields were obtained both with tiglic aldehyde (**6a**; Table 2, entry 1) and with **6b** (Table 2, entry 2). With α-methylcinnamaldehyde (**6c**), the reaction was not complete after 6 d at room temperature, and consumption of *N*-Cbz-hydroxylamine (**3**) to form *N*-Cbz-pyrrolidine took place (Table 2, entry 3). On the other hand, enal **6d** failed to give any addition product (Table 2, entry 4). Isoxazolidines **7a**–**c** were obtained as inseparable mixtures of diastereomers. Subsequent oxidation with PDC gave racemic isoxazolidinones **8a**–**c** in moderate to good yields, also as diastereomeric mixtures (Scheme 3). In this case, however, the two diastereomers could be readily separated by column chromatography on silica gel, and the relative stereochemistry was established by means of NOESY experiments on compounds **8a**-*trans*, **8b**-*cis*, and **8c**-*cis* (see Supporting Information). As expected, the *trans* isomers were the major isomers in all instances.

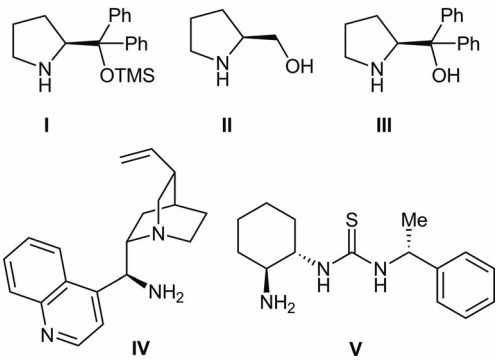


Scheme 3. Synthesis of 4,5-disubstituted *N*-Cbz-isoxazolidinones **8a**–**c**.

We then turned our attention to the possibility of using chiral amine catalysts to develop a catalytic asymmetric version of this methodology. As a benchmark reaction, we chose again the addition of *N*-(benzyloxycarbonyl)hydroxylamine (**3**) to cyclopentene-1-carbaldehyde (**2**), using chloroform as solvent at room temperature. The enantiomeric purity of the product was established after its essentially quantitative conversion into isoxazolidinone **5** under the conditions of Scheme 2. We initially screened a set of chiral primary and secondary amine catalysts **I**–**V** (Table 3).

Table 3. Catalyst screening for the asymmetric aza-Michael/cyclization reaction of cyclopentene-1-carbaldehyde (**2**) with *N*-Cbz-hydroxylamine (**3**).





Entry	Catalyst	Time [d][a]	Yield [%][b]	*er*[c]
1	**I**	10	73	91:9
2	**II**	5[d]	16	38:62[e]
3	**III**	6[f]	0	–
4	**IV**	4	73	38:62[e]
5	**V**	8	84	26:74[e]
6[g]	**V**	2	80	33:67[e]

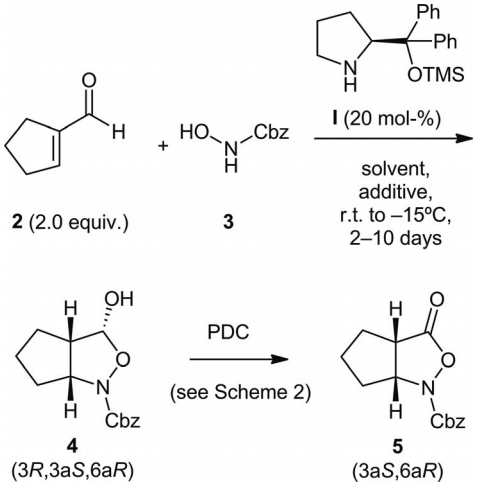
[a] Time necessary for consumption of **3**, monitored by ^{1}H NMR spectroscopy. [b] Yield of isolated **4** after chromatographic purification. [c] Determined by chiral HPLC analysis of **5**. [d] Reaction stopped before completion. [e] The major enantiomer had the configuration (3a*R*,6a*S*). [f] No reaction was observed after 6 d at room temp. [g] Reaction performed in toluene in the presence of water (2.0 equiv.) and acetic acid (0.15 equiv.).

We were pleased to find that the reaction could be catalysed by the commercially available diphenylprolinol trimethylsilyl ether (**I**), giving bicyclic isoxazolidine **4** in 73% yield and with good enantiomeric purity, although the reaction rate was much lower than that observed when pyrrolidine was used as a catalyst under the same conditions (Table 3, entry 1). Prolinol (**II**) showed very poor catalytic activity (Table 3, entry 2), and in the presence of diphenylprolinol (**III**; Table 3, entry 3), no reaction was observed after 6 d. Primary amine catalyst **IV**, derived from

cinchonidine,[21] led to the preferential formation of the (3*S*,3a*R*,6a*S*) enantiomer of **4**, in good yield but with poor enantioselectivity (Table 3, entry 4). Better results were obtained with Tsogoeva's amine-thiourea catalyst **V**,[22] although the enantiomeric purity of **4** was only moderate (Table 3, entry 5). With this catalyst, the reaction was also performed in toluene, with acetic acid as co-catalyst and in the presence of water;[22] these conditions increased the reaction rate, but **4** was obtained in a lower yield and with a lower enantioselectivity (Table 3, entry 6).

Having thus selected **I** as the most enantioselective catalyst, we proceeded to optimize the reaction conditions (solvent, temperature, acidic co-catalysts) for the formation of **4** (Table 4).

Table 4. Optimization studies for the asymmetric aza-Michael/cyclization reaction of cyclopentene-1-carbaldehyde (**2**) with *N*-Cbz-hydroxylamine (**3**) using catalyst **I**.



Entry	Solvent	Additive [mol-%]	*T* [°C]	Time[a] [d]	Yield[b] [%]	*er*[c]
1	$CHCl_3$	–	r.t.	10	73	91:9
2	toluene	–	r.t.	6	73	92:8
3	CH_3CN	–	r.t.	6	56	91:9
4	EtOH	–	r.t.	6	63	86:14
5	THF	–	r.t.	6	0[d]	–
6	toluene	BzOH (20)	r.t.	2	86	91:9
7	toluene	BzOH (40)	r.t.	2	99	87:13
8	toluene	BzOH (80)	r.t.	2	98	86:14
9	toluene	BzOH (20)	4	3	98	98:2
10	toluene	BzOH (20)	–15	10	80	86:14

[a] Time necessary for consumption of **3**, monitored by ^1H NMR spectroscopy. [b] Yield of isolated **4** after chromatographic purification. [c] Determined by chiral HPLC analysis of **5**. [d] No reaction was observed after 6 d at room temp.

A solvent screening at room temp. (Table 4, entries 1–5) showed that the best results were obtained in toluene (Table 4, entry 2). We therefore investigated the effect of acid co-catalysts in this solvent. After some trials with different carboxylic acids, we found that an equimolar amount of benzoic acid (with respect to **I**) reduced the reaction time from 6 to 2 d, and increased the yield of **4** to 86%, essentially maintaining the enantioselectivity (Table 4, entry 6). Further increases in the quantity of benzoic acid gave very high yields of **4**, but eroded its enantiomeric purity (Table 4, entries 7 and 8). Lowering the reaction temperature to 4 °C (fridge) somewhat reduced the reaction rate, but gave **4** in high yields and with excellent enantioselectivity (Table 4, entry 9); finally, further lowering of the reaction temperature to –15 °C greatly diminished the speed of the reaction and did not improve the performance of the process (Table 4, entry 10). The conditions of entry 9 (toluene as a solvent, 20 mol-% of both catalyst **I** and benzoic acid, 4 °C) appear to be the optimal conditions for the aza-Michael/cyclization reaction between **2** and **3**.

Oxidation of the resulting non-racemic product **4** to isoxazolidinone **5**, and catalytic hydrogenation under the conditions of Scheme 2 above, gave dextrorotatory cispentacin (**1**), with a known (1*S*,2*R*) configuration,[11a] establishing the (3*R*,3a*S*,6a*R*) stereochemistry of the major enantiomer of **4** obtained with catalyst **I**, derived from L-proline. This stereochemical sense of induction is the one expected for iminium-catalysed Michael additions to enals with **I**.[23] Thus, attack of the *N*-Cbz-hydroxylamine (**3**) to the less-hindered *Re*-face of the β-carbon of the unsaturated iminium ion derived from **2** and **I** gives rise to an (*R*) absolute configuration at the newly created stereogenic centre in the resulting exocyclic enamine, which ultimately leads to the (1*S*,2*R*) enantiomer of cispentacin (Figure 1).

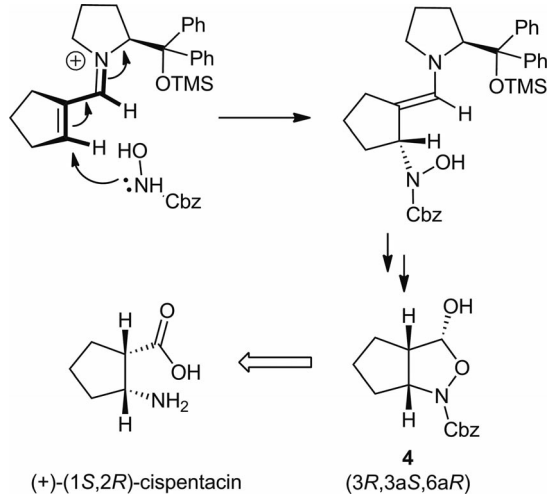
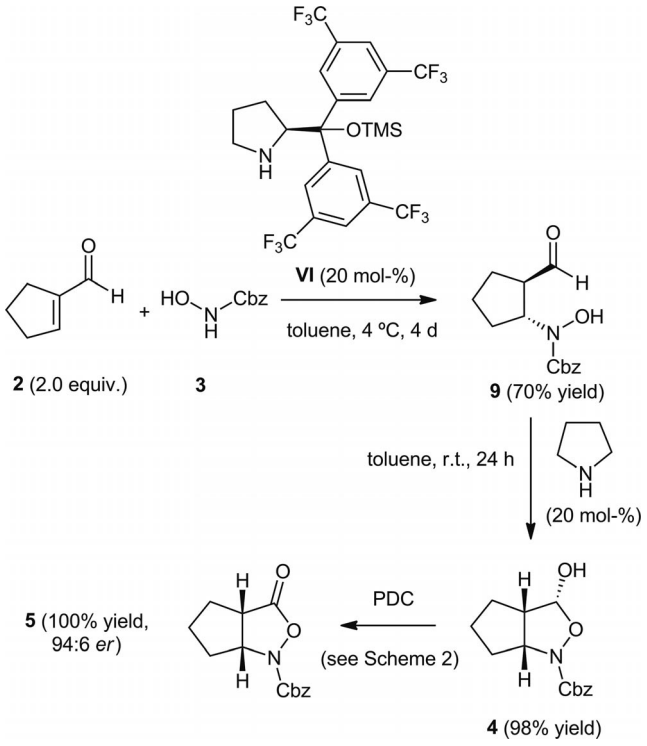


Figure 1. Rationalization of the absolute configuration of the major enantiomer of compound **4** under catalysis by **I**.

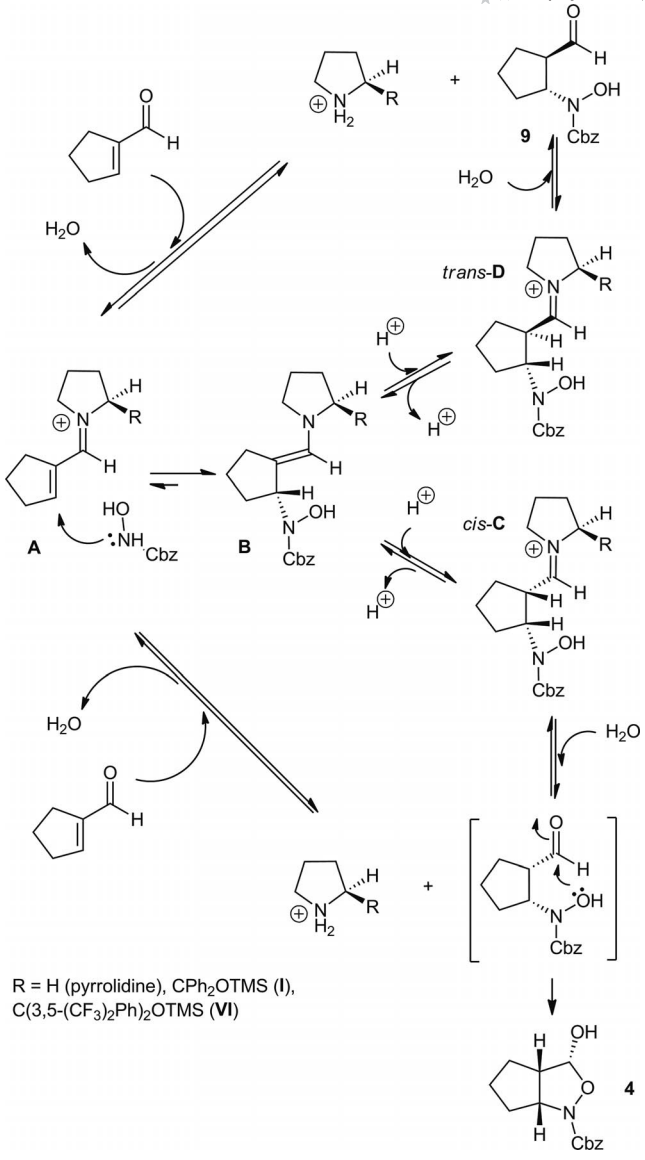
Since the D-proline-derived catalyst *ent*-**I** is also commercially available, these findings constitute a practical, high yielding (93–98% global yield, three steps) and highly enantioselective (up to 98:2 *er*) route to both enantiomers of cispentacin (**1**), which compares favourably with previously described asymmetric syntheses of this compound.[10–12]

When we used the bis(3,5-trifluoromethylphenyl)prolinol trimethylsilyl ether (**VI**) as the catalyst, the reaction between **2** and **3** (toluene, 4 d at 4 °C) unexpectedly gave a new compound **9** instead of bicyclic isoxazolidine **4**. Analysis of the spectroscopic data (HRMS, IR, ^1H and ^{13}C NMR) of this compound strongly suggested that we had in fact obtained, as the sole reaction product, the *trans* Michael adduct **9** in

70% yield after chromatographic purification (Scheme 4). This structural assignment was confirmed when, in the presence of a 20 mol-% of pyrrolidine, a toluene solution of **9** was almost quantitatively converted into **4**, for which an enantiomeric ratio of 94:6 was found after oxidation to isoxazolidinone **5**.



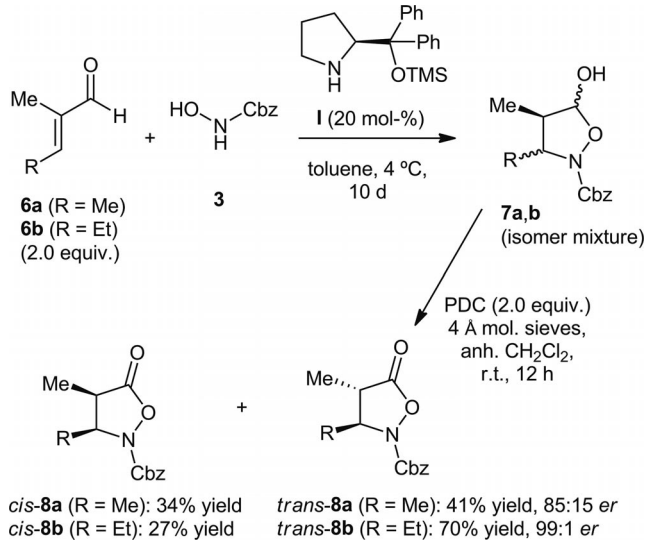
Scheme 4. Asymmetric aza-Michael addition of *N*-Cbz-hydroxylamine (**3**) to cyclopentene-1-carbaldehyde (**2**) using catalyst **VI**.



Scheme 5. Rationalization of the stereochemical outcome of the amine-catalysed aza-Michael addition of *N*-Cbz-hydroxylamine (**3**) to cyclopentene-1-carbaldehyde (**2**).

This result clearly shows that the stereochemical outcome of the aza-Michael addition of **3** to **2** depends on the structure of the secondary amine catalyst. This behaviour can be tentatively rationalized by assuming that in the catalytic cycle, intermediate enamine **B**, arising from the attack of **3** on unsaturated iminium **A**, is protonated to give a mixture of saturated iminium cation *cis*-**C** and *trans*-**D**, which are subsequently hydrolysed to give the corresponding aldehydes (Scheme 5). When using pyrrolidine or diphenylprolinol trimethylsilyl ether (**I**) as catalysts, intermediates *cis*-**C** and *trans*-**D** are in equilibrium through enamine **B**, and although presumably *trans*-**D** is more thermodynamically stable than *cis*-**C**, its hydrolysis is reversible, so that the subsequent cyclization of the *cis* aldehyde completely shifts the equilibrium to the formation of the isoxazolidine **4**. On the other hand, when bis(3,5-trifluoromethylphenyl)prolinol trimethylsilyl ether (**VI**) is used as the catalyst, *trans*-**D** is much more stable thermodynamically than *cis*-**C**, and its hydrolysis is essentially irreversible. In this way, *trans* aldehyde **9** cannot be equilibrated to **4**.

Finally, we decided to briefly explore the feasibility of using **I** as a catalyst in the addition of **3** to the acyclic α,β-unsaturated aldehydes **6a** and **6b**, which had given good yields of racemic isoxazolidines *rac*-**7a** and *rac*-**7b** when pyrrolidine was used as the promoter. The reactions were run in toluene at 4 °C in the presence of 20 mol-% of **I**, and required 10 d for the total consumption of **3**. After removal of the solvent and filtration through a short pad of silica gel, isoxazolidines **7a** and **7b** were oxidized with pyridinium dichromate, and the resulting products were submitted to column chromatography. The diastereomerically pure *trans* isomers of **8a** and **8b** were obtained with 85:15 and with 99:1 *er*, respectively (Scheme 6).[24] A (4*R*) absolute configuration is assumed for the major enantiomers of both compounds, in accordance with the mechanistic rationalization of the absolute configuration of compound **4** under catalysis by **I**. These isoxazolidinones are immediate precursors of (2*R*,3*R*)-3-amino-2-methylbutanoic acid and of (2*R*,3*R*)-3-amino-2-ethylbutanoic acid, respectively.[25]



Scheme 6. Enantioselective synthesis of isoxazolidinones **8a** and **8b**.

Conclusions

In conclusion, we have demonstrated that the organocatalytic Michael addition of *N*-(benzyloxycarbonyl)hydroxylamine (**3**) to cyclopentene-2-carbaldehyde **2** takes place in good yields to give cyclized isoxazolidine **4** as a diastereomerically pure compound. Racemic **4** can be obtained by using pyrrolidine, and a variety of chiral amino catalysts can be used to obtain non-racemic **4** with variable yields and enantioselectivities. Commercially available (*S*)-diphenylprolinol trimethylsilyl ether (**I**), in the presence of benzoic acid as a co-catalyst, provided **4** in 98% yield (after chromatographic purification) and with an excellent 98:2 *er* when the reaction is run in toluene at 4 °C. Oxidation of **4** with pyridinium dichromate, followed by catalytic hydrogenation, gave (1*S*,2*R*)-cispentacin **1** in essentially quantitative yield. Since the (*R*) enantiomer of **I** is also commercially available, the same synthetic sequence can be applied to the preparation of the (1*R*,2*S*) natural enantiomer of cispentacin, and this demonstrates the utility of organocatalysis in the preparation of medicinally relevant drugs and natural products.[26] Unexpectedly, the bis(3,5-trifluoromethylphenyl)prolinol trimethylsilyl ether catalyst (**VI**) produced the *trans* Michael adduct (i.e., **9**) in 70% yield (94:6 *er*) after chromatographic purification. When using acyclic α-branched α,β-unsaturated aldehydes **6a**–**d** as substrates, the reaction yields depend on the substitution pattern of the aldehydes, and mixtures of *cis*- and *trans*-isomers were obtained. Nevertheless, the present strategy has proved to be successful in some instances, and oxazolidinone *trans*-**8b** could be obtained in 70% overall yield from the reaction of **6b** and **3** under catalysis with **I**, and with high enantiomeric purity (99:1 *er*).

Experimental Section

General Methods: Room-temperature reactions were generally performed with magnetic stirring and open to the air, either in round-bottomed flasks or in loosely stoppered glass vials. Commercially available reagents, catalysts, and solvents were used as received, with the exception of catalyst **VI**, which was chromatographically purified immediately prior to use, and dichloromethane, which was distilled from calcium hydride. Aldehydes **2**,[18] **6b**,[27] and **6d**[27] were prepared according to literature procedures. For thin-layer chromatography, silica gel plates Merck 60 F254 were used, and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (2.5 g), $Ce(SO_4)_2 \cdot 2H_2O$ (1.0 g), conc. H_2SO_4 (1.0 mL), and H_2O (94 mL) followed by heating, or by treatment with a solution of *p*-anisaldehyde (2.3 mL), conc. H_2SO_4 (3.5 mL), acetic acid (1.0 mL), and ethanol (90 mL) followed by heating. Flash column chromatography was performed using silica gel Merck 60 (particle size: 0.040–0.063 mm). IR spectra were obtained with a Nicolet 6700 FTIR apparatus, using ATR techniques. ^{1}H (400 MHz) and ^{13}C (100.6 MHz) NMR spectra were recorded with a Varian Mercury 400 spectrometer. Chemical shifts (δ) are given in ppm relative to tetramethylsilane (TMS), and coupling constants (J) are given in Hz. The spectra were recorded in $CDCl_3$ as solvent at room temperature. TMS served as an internal standard (δ = 0.00 ppm) for ^{1}H NMR spectra, and $CDCl_3$ (δ = 77.0 ppm) for ^{13}C NMR spectra. Data are reported as follows: s, singlet; d, doublet, t, triplet; q, quartet; m, multiplet; br, broad signal. Where appropriate, 2D techniques (COSY, NOESY) were also used to assist in structure elucidation. High-resolution mass spectra (HRMS) were recorded with a Bruker MicrOTOF spectrometer by the Unitat d'Espectrometria de Masses, CCiT-UB. Specific rotations were determined at room temp. with a Perkin–Elmer 241 MC polarimeter. Chiral HPLC analyses were performed with a Shimadzu LC Series 20 apparatus with an M20 diode array UV/Vis detector, using Chiralpak® IA, IB, and IC columns. The homogeneity of the peaks corresponding to the two enantiomers of the product was thoroughly checked by comparison of the UV spectra.

Benzyl (3*R,3a*S**,6a*R**)-3-Hydroxyhexahydro-1*H*-cyclopenta[*c*]-isoxazole-1-carboxylate (*rac*-4):** Pyrrolidine (from a 10 mg/mL solution in toluene; 0.74 mL, 0.10 mmol) and *N*-Cbz-hydroxylamine (**3**; 87 mg, 0.52 mmol) were added sequentially to a magnetically stirred solution of cyclopentene-1-carbaldehyde (**2**; 100 mg, 1.04 mmol) in toluene (2 mL), and the resulting solution was stirred at room temp. The progress of the reaction was monitored both by ^{1}H NMR spectroscopy and by TLC. When no starting material **3** was detected (4 d), toluene and pyrrolidine were removed in vacuo, and the crude residue was purified by column chromatography (silica gel; 4:1 hexane/ethyl acetate mixtures) to give *rac*-**4** (110 mg, 80%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (m, 5 H), 5.35 (s, 1 H), 5.20 (part A of AB system, J = 12.7 Hz, 1 H), 5.17 (part B of AB system, J = 12.7 Hz, 1 H), 4.78–4.73 (m, 1 H), 2.93–2.86 (m, 1 H), 1.51–1.70 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.2, 135.8, 128.5, 128.2, 128.0, 104.3, 67.8, 63.7, 53.0, 34.2, 29.1, 25.0 ppm. HRMS (ESI): calcd. for $C_{14}H_{17}NNaO_4$ $[M + Na]^+$ 286.1055; found 286.1060.

Benzyl (3a*S,6a*R**)-3-Oxohexahydro-1*H*-cyclopentaisoxazol-1-carboxylate (*rac*-5):** Racemic isoxazolidine **4** (134 mg, 0.50 mmol) and pyridinium dichromate (376 mg, 1.0 mmol) were added sequentially to a stirred suspension of molecular sieves (4 Å, powdered; 750 mg) in anhydrous dichloromethane (4 mL), and the reaction mixture was stirred overnight at room temperature. After the addition of hexane/ethyl acetate (4:1; 10 mL) to precipitate the chromium salts, the solution was decanted and filtered through a short pad of Celite®. After removal of the solvents in vacuo, the reaction product was purified by column chromatography (silica gel, hexane/ethyl acetate mixtures) to give racemic isoxazolidinone

5 (127 mg, 98%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.31 (m, 5 H), 5.25 (part A of AB system, J = 12.5 Hz, 1 H), 5.24 (part B of AB system, J = 12.5 Hz, 1 H), 4.88 (td, J = 8.2, J = 2.5 Hz, 1 H), 3.35 (td, J = 8.2, J = 2.5 Hz, 1 H), 2.26–2.18 (m, 1 H), 2.14–2.06 (m, 1 H), 2.02–1.85 (m, 2 H), 1.84–1.74 (m, 1 H), 1.72–1.60 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.0, 155.7, 135.0, 128.6, 128.3, 68.6, 65.1, 45.1, 34.8, 31.0, 29.6, 24.1 ppm. HRMS (ESI): calcd. for $C_{14}H_{15}NNaO_4$ $[M + Na]^+$ 284.0899; found 284.0897.

General Procedure for the Pyrrolidine-Promoted Michael Addition/Cyclization Reaction Between Aldehydes 6a–d and *N*-Cbz-Hydroxylamine 3: Pyrrolidine (0.10 mL, 1.21 mmol) and *N*-Cbz-hydroxylamine (**3**; 200 mg, 1.22 mmol) were added sequentially to a stirred solution of unsaturated aldehyde **6a**–**d** (1.22 mmol) in chloroform (4 mL). After 6 d at room temperature, the solvent and the pyrrolidine were removed in vacuo, and the resulting product was purified by column chromatography (silica gel, hexane/ethyl acetate mixtures) to give racemic oxazolidines **7a**–**d** as mixtures of diastereomers.

Benzyl 5-Hydroxy-3,4-dimethylisoxazolidin-2-carboxylate (7a): Obtained from **6a** as a 1:7 diastereomeric mixture in 96% yield by the general procedure described above. Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.29 (m, 5 H, both), 5.46 (s, 1 H, major), 5.29 (s, 1 H, minor), 5.24–5.18 (m, 2 H, both), 4.39–4.30 (m, 1 H, minor), 3.79–3.70 (m, 1 H, major), 2.60–2.51 (m, 1 H, minor), 2.16–2.06 (m, 1 H, major), 1.34 (d, J = 6.2 Hz, 3 H, major), 1.25 (d, J = 7.2 Hz, 3 H, minor), 1.09 (d, J = 6.2 Hz, 3 H, major), 0.99 (d, J = 7.2 Hz, 3 H, minor) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 135.8, 128.5, 128.2, 127.9, 103.7 (minor), 99.2 (major), 67.9, 60.5 (major), 56.9 (minor), 48.7 (major), 45.7 (minor), 19.7 (major), 15.4 (minor), 12.0 (minor), 10.8 (major) ppm.

Benzyl 3-Ethyl-5-hydroxy-4-methylisoxazolidin-2-carboxylate (7b): Obtained from **6b** as a 1:3 diastereomeric mixture in 82% yield by the general procedure described above. Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (m, 5 H, both), 5.48 (s, 1 H, both), 5.25–5.12 (m, 2 H, both), 4.17–4.01 (m, 1 H, minor), 3.76–3.67 (m, 1 H, major), 2.27–2.14 (m, 1 H, major), 2.02 (s, 1 H, minor), 1.78–1.43 (m, 2 H, both), 1.11 (d, J = 6.6 Hz, 3 H, both), 0.99–0.91 (m, 3 H, both) ppm.

Benzyl 3-Ethyl-5-hydroxy-4-methylisoxazolidin-2-carboxylate (7c): Obtained from **6c** as a 1:3 diastereomeric mixture in 35% yield by the general procedure described above. Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.08 (m, 10 H, both), 5.65 (s, 1 H, major), 5.46 (d, J = 3.7 Hz, 1 H, minor), 5.15 (s, 2 H, both), 4.67 (d, J = 9.18 Hz, 1 H, major), 2.92–2.84 (m, 1 H, minor), 2.54–2.44 (m, 1 H, major), 1.76 (br., 1 H, OH), 1.15 (d, J = 6.4 Hz, 3 H, major), 0.66 (d, J = 7.0 Hz, 3 H, minor) ppm.

Benzyl 3,4-Dimethyl-5-oxoisoxazolidin-2-carboxylate (8a): Racemic isoxazolidine **7a** (100 mg, 0.40 mmol, diastereomeric mixture) and pyridinium dichromate (300 mg, 0.8 mmol) were added sequentially to a stirred suspension of molecular sieves (4 Å, powdered; 900 mg) in anhydrous dichloromethane (3 mL), and the reaction mixture was stirred overnight at room temperature. After the addition of hexane/ethyl acetate (4:1; 10 mL) to precipitate the chromium salts, the solution was decanted and filtered through a short pad of Celite®. After removal of the solvents in vacuo, **8a** (84 mg, 85%) was obtained as a 7:1 *trans*/*cis* diastereomeric mixture. The two diastereomers were separated by column chromatography (silica gel, hexane/ethyl acetate mixtures).

(3*R,4*R**)-Benzyl 3,4-Dimethyl-5-oxoisoxazolidin-2-carboxylate (*rac-trans*-8a):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.14 (m, 5 H), 5.26 (part A of AB system, J = 12.3 Hz, 1 H), 5.25 (part B of AB system, J = 12.3 Hz, 1 H), 4.06–3.99 (m, 1 H), 2.65–2.56 (m, 1 H), 1.51 (d, J = 5.8 Hz, 3 H), 1.28 (d, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8, 156.8, 134.9, 128.6, 128.3, 128.2, 68.7, 43.1, 29.5, 19.4, 9.23 ppm. HRMS (ESI): calcd. for $C_{13}H_{16}NO_4$ $[M + H]^+$ 250.1079; found 250.1075.

(3*S,4*R**)-Benzyl 3,4-Dimethyl-5-oxoisoxazolidin-2-carboxylate (*rac-cis*-8a):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.42 (m, 2 H), 7.40–7.31 (m, 3 H), 5.34 (s, 2 H), 4.80–4.72 (m, 1 H), 3.02–2.94 (m, 1 H), 1.32 (d, J = 6.0 Hz, 3 H), 1.22 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 134.6, 128.6, 128.4, 114.0, 68.8, 42.9, 29.7, 13.7, 9.3 ppm. HRMS (ESI): calcd. for $C_{13}H_{16}NO_4$ $[M + H]^+$ 250.1079; found 250.1077.

Benzyl 3-Ethyl-4-methyl-5-oxoisoxazolidin-2-carboxylate (8b): Racemic isoxazolidine **7b** (100 mg, 0.38 mmol, diastereomeric mixture) and pyridinium dichromate (300 mg, 0.8 mmol) were added sequentially to a stirred suspension of molecular sieves (4 Å, powdered; 900 mg) in anhydrous dichloromethane (3 mL), and the reaction mixture was stirred overnight at room temperature. After the addition of hexane/ethyl acetate (4:1; 10 mL) to precipitate the chromium salts, the solution was decanted and filtered through a short pad of Celite®. After removal of the solvents in vacuo, **8b** (90 mg, 90%) was obtained as a 7:1 *trans*/*cis* diastereomeric mixture. The two diastereomers were separated by column chromatography (silica gel, hexane/ethyl acetate mixtures).

(3*R,4*R**)-Benzyl 3-Ethyl-4-methyl-5-oxoisoxazolidin-2-carboxylate (*rac-trans*-8b):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.34 (m, 5 H), 5.27 (part A of AB system, J = 12.3 Hz, 1 H), 5.26 (part B of AB system, J = 12.3 Hz, 1 H), 4.11–4.06 (m, 1 H), 2.67–2.58 (m, 1 H), 1.87–1.69 (m, 2 H), 1.27 (d, J = 8.0 Hz, 3 H), 1.00 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.3, 157.2, 135.0, 128.7, 128.6, 128.3, 68.8, 68.7, 40.4, 26.5, 15.1, 9.3 ppm. HRMS (ESI): calcd. for $C_{14}H_{18}NO_4$ $[M + H]^+$ 264.1236; found 264.1235.

(3*S,4*R**)-Benzyl 3-Ethyl-4-methyl-5-oxoisoxazolidin-2-carboxylate (*rac-cis*-8b):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.42 (m, 3 H), 7.41–7.31 (m, 2 H), 5.35 (part A of AB system, J = 12.3 Hz, 1 H), 5.34 (part B of AB system, J = 12.3 Hz, 1 H), 4.51–4.44 (m, 1 H), 3.04–2.95 (m, 1 H), 1.76–1.52 (m, 2 H), 1.23 (d, J = 6.8 Hz, 3 H), 1.03 (t, J = 8.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 147.9, 134.7, 128.6, 128.4, 83.8, 68.7, 42.4, 29.7, 21.1, 9.6, 9.2 ppm. HRMS (ESI): calcd. for $C_{14}H_{18}NO_4$ $[M + H]^+$ 264.1236; found 264.1232.

Benzyl 4-Methyl-5-oxo-3-phenylisoxazolidin-2-carboxylate (8c): Racemic isoxazolidine **7c** (40 mg, 0.13 mmol, diastereomeric mixture) and pyridinium dichromate (100 mg, 0.25 mmol) were added sequentially to a stirred suspension of molecular sieves (4 Å, powdered; 360 mg) in anhydrous dichloromethane (1 mL), and the reaction mixture was stirred overnight at room temperature. Following the addition of hexane/ethyl acetate (4:1; 5 mL) to precipitate the chromium salts, the solution was decanted and filtered through a short pad of Celite®. After removal of the solvents in vacuo, **8c** (22 mg, 55%) was obtained as a 3:1 *trans*/*cis* diastereomeric mixture. The two diastereomers were separated by column chromatography (silica gel, hexane/ethyl acetate mixtures).

(3*S,4*R**)-Benzyl 4-Methyl-5-oxo-3-phenylisoxazolidin-2-carboxylate (*rac-trans*-8c):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.18 (m, 10 H), 5.18 (s, 2 H), 4.90 (d, J = 8.6 Hz, 1 H), 3.02–2.93 (m, 1 H), 1.35 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 156.4, 137.8, 134.7, 129.1, 128.7, 128.5, 128.1, 126.0, 109.9, 71.1, 68.8, 45.2, 13.1 ppm. HRMS (ESI): calcd. for $C_{18}H_{18}NO_4$ $[M + H]^+$ 312.1236; found 312.1233.

(3*R,4*R**)-Benzyl 4-Methyl-5-oxo-3-phenylisoxazolidin-2-carboxylate (*rac*-*cis*-8c):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 8 H), 7.23–7.19 (m, 2 H), 5.62 (d, J = 9.2 Hz, 1 H), 5.21 (part A of AB system, J = 12.1 Hz, 1 H), 5.20 (part B of AB system, J = 12.1 Hz, 1 H), 3.40–3.32 (m, 1 H), 0.92 (d, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.6, 156.7, 134.7, 129.0, 128.7, 128.6, 128.2, 126.6, 68.9, 67.1, 29.7, 10.6 ppm. HRMS (ESI): calcd. for $C_{18}H_{18}NO_4$ $[M + H]^+$ 312.1236; found 312.1231.

Benzyl (3*R*,3a*S*,6a*R*)-3-Hydroxyhexahydro-1*H*-cyclopenta[*c*]isoxazole-1-carboxylate (4): Diphenylprolinol trimethylsilyl ether (**I**; 26 mg, 0.10 mmol), benzoic acid (12.8 mg, 0.10 mmol), and *N*-Cbz-hydroxylamine (**3**; 87 mg, 0.52 mmol) were added sequentially to a magnetically stirred solution of cyclopentene-1-carbaldehyde (**2**; 100 mg, 1.04 mmol) in toluene (2 mL), and the resulting solution was stirred at 4 °C. The progress of the reaction was monitored both by ^{1}H NMR spectroscopy and by TLC. When no starting material **3** was detected (3 d), toluene and pyrrolidine were removed in vacuo, and the crude residue was purified by column chromatography (silica gel; 4:1 hexane/ethyl acetate mixture) to give **4** (183 mg, 98%) as a colourless oil.

Benzyl (*3aS,6aR*)-3-Oxohexahydro-1*H*-cyclopentaisoxazole-1-carboxylate (5): Oxidation of (3*R*,3a*S*,6a*R*)-**4** with pyridinium dichromate (0.50 mmol scale) under the conditions described above for the racemic compound gave (*3aS,6aR*)-**5** in essentially quantitative yield and with 98:2 *er*. $[\alpha]_D^{25}$ = –45 (c = 2.3, CH_2Cl_2). HPLC (Chiralpak® IA column, 90:10 hexane/isopropyl alcohol, 1.0 mL/min, λ = 220 nm, 25 °C): t_R = 11.2 min (minor), 13.5 min (major).

(1*S*,2*R*)-Cispentacin (1): A stirred solution of (*3aS,6aR*)-**5** (118 mg, 0.45 mmol, 98:2 *er*) in MeOH (4 mL) was hydrogenated at 60 atm using Pd/C (10%; 11.8 mg) as the catalyst in a medium-pressure reactor. After 24 h at 65 °C, the reaction mixture was filtered through a short pad of Celite®, which was washed with ethyl acetate (2× 5 mL). Evaporation of the solvents in vacuo gave cispentacin **1** (54 mg, 93%) as a colourless crystalline solid, m.p. 199–202 °C. [ref.[11a] m.p. 198–200 °C]. $[\alpha]_D^{25}$ = +6 (c = 1.1, H_2O). {ref.[11a] $[\alpha]_D^{22}$ = +9 (c = 1.1, H_2O)}. ^{1}H and ^{13}C NMR spectra (see Supporting Information) were identical to those described in the literature.

(1*R*,2*S*)-Benzyl 2-Formylcyclopentyl-*N*-hydroxycarbamate (9): Catalyst **VI** (62 mg, 0.10 mmol) and *N*-Cbz-hydroxylamine (**3**; 87 mg, 0.52 mmol) were added sequentially to a magnetically stirred solution of cyclopentene-1-carbaldehyde (**2**; 100 mg, 1.04 mmol) in toluene (2 mL), and the resulting solution was stirred at 4 °C (fridge). The progress of the reaction was monitored both by ^{1}H NMR spectroscopy and by TLC. When no starting material **3** was detected (4 d), the solvent was removed in vacuo, and the crude residue was purified by column chromatography (silica gel; 4:1 hexane/ethyl acetate mixtures) to give uncyclized Michael adduct **9** (96 mg, 70%) as a colourless oil. IR (ATR): $\tilde{\nu}$ = 3300 (broad), 3032, 2954, 2873, 1695, 1425, 1401, 1295, 1075, 735, 690 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.64 (d, J = 2.5 Hz, 1 H), 7.35 (m, 5 H), 5.17 (part A of AB system, J = 12.4 Hz, 1 H), 5.16 (part B of AB system, J = 12.4 Hz, 1 H), 4.81 (m, 1 H), 3.11 (m, 1 H), 1.95 (m, 4 H), 1.83 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.2, 157.1, 135.6, 128.6, 128.5, 128.3, 68.3, 59.8, 53.8, 28.6, 25.8, 23.8 ppm. HRMS (ESI): calcd. for $C_{14}H_{18}NO_4$ $[M + H]^+$ 264.1236; found 264.1231.

A solution of this compound (0.70 mmol) in toluene (1 mL) was treated with pyrrolidine (from a 10 mg/mL solution in toluene; 0.74 mL, 0.10 mmol), and the resulting solution was magnetically stirred overnight at room temperature. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography (silica gel; 4:1 hexane/ethyl acetate mixture) to give **4** (94 mg, 98%). Oxidation of **4** to the oxazolidinone under the conditions described above gave (3a*S*,6a*R*)-**5** in essentially quantitative yield and with 94:6 *er*.

General Procedure for the Reaction of Aldehydes 6a and 6b with *N*-Cbz-hydroxylamine 3 Catalysed by I: Diphenylprolinol trimethylsilyl ether (**I**; 20 mg, 0.12 mmol) and *N*-Cbz-hydroxylamine (**3**; 100 mg, 0.60 mmol) were added sequentially to a magnetically stirred solution of unsaturated aldehyde **6a** or **6b** (1.18 mmol) in toluene (2 mL), and the resulting solution was stirred at 4 °C. The progress of the reaction was monitored both by ^{1}H NMR spectroscopy and by TLC. When no starting material **3** was detected (10 d), toluene was removed in vacuo, and the crude residue was filtered through a short pad of silica gel, washing with a 4:1 hexane/ethyl acetate mixture, to give crude isoxazolidines **7a** and **7b** as colourless oils. Without further purification, the isoxazolidine was dissolved in anhydrous dichloromethane (3 mL). After the addition of molecular sieves (4 Å, powdered; 900 mg) and pyridinium dichromate (330 mg, 0.90 mmol), the resulting suspension was magnetically stirred overnight at room temperature. Following the addition of hexane/ethyl acetate (4:1; 10 mL) to precipitate the chromium salts, the solution was decanted and filtered through a short pad of Celite®. The solvents were removed in vacuo, and the crude residue was purified by column chromatography (silica gel; hexane/ethyl acetate mixtures) to give isoxazolidinones **8a** and **8b**.

(3*R*,4*R*)-Benzyl 3,4-Dimethyl-5-oxoisoxazolidin-2-carboxylate (*trans*-8a): 59 mg, 41% yield, 85:15 *er*. $[\alpha]_D^{25}$ = –9.1 (c = 0.33, CH_2Cl_2). HPLC (Chiralpak® IA column, 95:5 hexane/isopropyl alcohol, 1.0 mL/min, λ = 220 nm, 25 °C): t_R = 9.6 min (major), 11.2 min (minor).

(3*S*,4*R*)-Benzyl 3,4-Dimethyl-5-oxoisoxazolidin-2-carboxylate (*cis*-8a): 48 mg, 34% yield, *er* not determined. $[\alpha]_D^{25}$ = –1.9 (c = 0.53, CH_2Cl_2).

(3*R*,4*R*)-Benzyl 3-Ethyl-4-methyl-5-oxoisoxazolidin-2-carboxylate (*trans*-8b): 86 mg, 70% yield, 99:1 *er*. $[\alpha]_D^{25}$ = –10.6 (c = 0.47, CH_2Cl_2). HPLC (Chiralpak® IC column, 93:7 hexane/isopropyl alcohol, 0.8 mL/min, λ = 220 nm, 25 °C): t_R = 27.4 min (minor), 28.5 min (major).

(3*S*,4*R*)-Benzyl 3-Ethyl-4-methyl-5-oxoisoxazolidin-2-carboxylate (*cis*-8b): 34 mg, 27% yield.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra of compounds **1**, **4**, **5**, **7a**–**c**, *cis*-**8a**–**c**, *trans*-**8a**–**c**, and **9**. NOESY spectra of compounds *trans*-**8a**, *cis*-**8b**, and *cis*-**8c**. HPLC traces of compounds **5**, *trans*-**8a**, and *trans*-**8b**.

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