Graphical Abstract

Catalytic Enantioselective Alkene Epoxidation using Novel Spirocyclic *N*-Carbethoxy-Azabicyclo[3.2.1]Octanones

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Catalytic Enantioselective Alkene Epoxidation using Novel Spirocyclic *N*-Carbethoxy- Azabicyclo[3.2.1]Octanones[†]

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Abstract: A general synthetic route allowing access to several spirocyclic *N*-carbethoxy-azabicyclo[3.2.1]octanones is developed. These novel ketones efficiently catalyse alkene epoxidation using Oxone[®] with up to 91.5% ee.

Keywords: Epoxidation, asymmetric, ketone, dioxirane

1. Introduction

Enantioselective alkene epoxidation catalyzed by chiral ketones, using Oxone as stoichiometric oxidant, has been intensively studied over the past decade and has resulted in the design of several effective novel ketone architectures.^{1,2} In particular, a comprehensive series of inventive contributions from Shi and co-workers has demonstrated chiral ketones derived from carbohydrates to be exceptionally selective and practical members of the asymmetric synthesis toolbox.^{1,3-5} The fructose-derived ketone **1** is now widely employed for the epoxidation of trans- and trisubstituted alkenes. Interestingly, Shi has extended the applicability of his catalysts to a wide range of alkene substitution patterns, including challenging terminal olefins,⁵ by modifying the catalyst structure. Catalysts **2** incorporating a fused spirocyclic oxazolidinone moiety have been especially effective for this purpose, and several interesting electronic effects have been noted upon variation of the oxazolidinone *N*-substituent.⁴ As well as their synthetic utility, chiral ketone catalysts have provided outstanding insights into the mechanisms of asymmetric induction with computational studies providing satisfying agreement with experimental data.⁶

[†] With congratulations to Prof. Steve Ley on the award of the Tetrahedron Prize.

In our own work, we have introduced 2-substituted-bicyclo[3.2.1]octanones **3** as a family of chiral catalysts which are generally stable to Baeyer-Villiger reaction,⁷ allowing the development of solid supported variants.^{7c} Good-to-excellent enantioselectivities (up to 98% ee) have been obtained for trans- and trisubstituted olefins, but generally poor results for terminal alkenes. Nevertheless, the enantioselectivities afforded are notable given the simple nature of the ketone alpha-substituents (*e.g.* Y=F or OAc). In view of the remarkable effectiveness and tunability of the alpha-oxazolidinone-bearing spirocyclic systems developed by Shi, we were keen to incorporate this more complex motif onto our own bicyclic system. In addition, we reasoned that the markedly different synthetic routes available for catalyst synthesis from non-carbohydrate precursors might allow access to novel spirocyclic moieties that have not previously been explored. The synthesis of several novel catalysts of this type (**4-6**) and their effectiveness for enantioselective epoxidation of a range of alkenes is reported herein. A new alternative spirocycle, the sulfamidate unit, is also prepared and tested.

2. Results and Discussion

2.1 Catalyst synthesis

Our previous studies on bicyclo[3.2.1]octanone catalysts⁷ employed chiral base-mediated desymmetrisation of the parent ketone **7** to access enantiomerically enriched material. This approach relied on enantiomeric enrichment by recrystallisation for access to enantiomerically pure catalysts. In the present study, we prepared catalysts initially in

racemic form and resolved them on a chiral stationary phase (*vide infra*) to facilitate catalyst screening. We identified enone **8** as a key potential intermediate for the synthesis of a wide range of our target spirocyclic ketones. We have previously reported a synthesis of **8** from commercially available **7**.^{7d} However, we were keen to develop a superior route since the earlier approach, involving cyclopropanation of the trimethylsilyl enol ether of **7**, was quite lengthy and low yielding (33% from **7**). A better approach was found to involve silyl enol ether formation and reaction with Eschenmoser's salt, followed by N-quaternization and base-mediated elimination (Scheme 1).⁸ After some experimentation to identify optimal conditions, the process provided reproducible yields of *ca.* 60% of **8**, with the main side-product (10-20%) being dienone. We have previously reported^{7d} dihydroxylation of **8** to give diol **9**; the derived acetonide was found to be a poor epoxidation catalyst, undergoing decomposition by Baeyer-Villiger reaction. We reasoned that the corresponding carbonate **4** would be less susceptible to this side-reaction, and would present a novel spirocyclic motif not tested in the Shi systems. Treatment of **9** with triphosgene yielded racemic **4** (Scheme 1).

Scheme 1: (a) (i) LiHMDS, THF, -78 °C; (ii) TMSCl, -78 °C; (b) (i) Eschenmoser's salt (Me₂NCH₂I), DMF, RT, 1.5 h; (ii) MeI, 50 °C, sealed tube; (iii) NaHCO₃, DMF, 95 °C, 60-65%. (c) K₂OsO₄·2H₂O, quinuclidine, NMO, acetone / H₂O, 86%; (d) triphosgene, pyridine, DCM, 60%.

For the synthesis of further fused heterocycles including oxazolidinones, epoxidation of **8** followed by ring opening with an appropriate nucleophile was an attractive strategy. However, attempts to effect direct epoxidation of **8** were generally low yielding and afforded mixtures of diastereomers. While diol **9** could be converted cleanly to the diastereomerically pure ketoepoxide, exploratory experiments indicated that some of the later ketone

intermediates in this synthetic route were unstable. The ketone was therefore temporarily reduced by Luche reduction⁹ of **8** to give the allylic alcohol followed by epoxidation with *m*-CPBA; the sequence occurred stereoselectively to afford **10** as confirmed by nOe studies. Epoxide **10** could then be opened by nucleophilic addition of several primary amines at the less hindered carbon to give amino alcohols **11** (Scheme 2). The regiochemical outcome of the epoxide opening was confirmed in one case (**11d**, R=Bn) by HMBC studies, notably a 3-bond correlation between the benzylic protons and the CH₂ carbon of the amino alcohol moiety. The other examples were assumed to follow the same regiochemical outcome. Since attempts to selectively engage the tertiary alcohol and amine in oxazolidinone formation with triphosgene proved problematic, we sought to oxidize the secondary alcohol group first. Several common methods (TPAP, PCC, Jones or Dess-Martin reagents) proved unsuccessful. An effective method was eventually found to be the use of IBX in the presence of acid (TFA),¹⁰ under which conditions protonation of the amino group is presumed to protect it from oxidation. Attempts to use this route to prepare **5g** (R = Ph) failed at the IBX oxidation step: as an alternative, the Swern oxidation was successful in this case. Finally, cyclisation with triphosgene in pyridine afforded ketones **5**. Where a chiral, enantiomerically pure amine (*S*- α -methyl benzylamine) was used in the epoxide opening step, the final product was obtained as a mixture of two separable diastereomers, the configuration of one of which (**5e**) was determined by X-ray crystallography (*vide infra*).

*derived from **ent-11**

Scheme 2 (a) NaBH₄, CeCl₃·7H₂O, MeOH, 0 °C, 95%; (b) *m*-CPBA, DCM, 0 °C, 70%; (c) RNH₂ (1 eq), EtOH, 80 °C; (d) For **11a-f**: IBX, TFA, DMSO. For **11g**: (COCl)₂, DMSO, then Et₃N; (e) triphosgene, pyridine, DCM.

We wished to evaluate the steric and electronic effects of replacing the oxazolidinone nitrogen with a tetrahedral carbon atom. The required lactone was prepared as shown in Scheme 3. Silylation of epoxy alcohol **10** was followed by epoxide opening with the anion of diethyl malonate and concomitant lactonization and desilylation. Krapcho decarboxylation followed by TPAP oxidation¹² of the secondary alcohol **12** delivered the target racemic ketone **6**.

Scheme 3: (a) Et₃N, TMSOTf, DCM, -78 °C→-30 °C, quantitative. (b) (i) NaH, diethyl malonate, THF; (ii) NaCl, DMSO, H₂O, 150 °C, 35%. (c) TPAP, NMO, DCM, 53%.

Finally, we decided to investigate the effect of replacing the oxazolidinone carbonyl with SO₂. To the best of our knowledge, ketones bearing the spirocyclic cyclic sulfate or sulfamidate motif have not previously been tested in asymmetric epoxidation. The former was found to be too unstable under the Oxone epoxidation conditions to allow proper evaluation. The cyclic sulfamidate **14** was prepared from the amino alcohol **13**, an intermediate in the synthesis of oxazolidinone **5a**, by reaction with thionyl chloride followed by oxidation (Scheme 4).

Scheme 4: (a) SOCl₂, pyridine, DCM, 48%; (b) RuCl₃·xH₂O, NaIO₄, CH₃CN, H₂O, 55%.

With the exception of **5e/5f** derived from α -methyl benzylamine, all catalysts in Schemes 1-4 were prepared as racemates. These were resolved by supercritical fluid chromatography (SFC) on chiral stationary phases to give enantiomerically pure catalysts for testing. The relative configuration of **5e** was confirmed by X-ray crystallography (*vide infra*), and the absolute configuration for the other ketones was assigned based on correlation of the results for asymmetric epoxidation of *E*-stilbene (see later discussion). Overall, we have developed a versatile, 6-step approach from commercially available *N*-carbethoxytropinone **7** which offers the great advantage of reacting the advanced intermediate epoxide **10** with various nucleophiles at a late stage, thus allowing ready access to a wide range of substituted derivatives. The route could potentially be rendered enantioselective by desymmetrisation of **7** using, for example, deprotonation with chiral bases, as in our earlier work.⁷

2.2 Catalyst Evaluation

Catalyst screening under standard Oxone/NaHCO₃/CH₃CN/H₂O conditions¹³ began with *E*-stilbene as test substrate, since this would allow comparison to results with our earlier catalysts. As a benchmark, the fluoroketone **3** (X=NCO₂Et, Y=F) has been reported to epoxidize *E*-stilbene with 76% ee.^{7d} The carbonate **4** was screened first (Table 1, entry 1). Complete conversion was observed using 10 mol% of **4**, and the epoxide was obtained in excellent ee (87%). Similar results were obtained with the opposite catalyst enantiomer (entry 2). Turning to the oxazolidinone catalysts, the NMe derivative **5a** was screened first. Although a small decrease in conversion was noted, this catalyst displayed a slightly higher enantioselectivity (91.5% ee, entries 3 and 4). The effect of increased steric hindrance in the N-substituent was now probed. Moving to N=iPr derivative **5b** resulted in a slight drop in conversion and enantioselectivity (entry 5), while the N^tBu analog **5c** performed more poorly in both regards (entry 6). The NBn counterpart **5d** provided similar results (entry 7), with incomplete conversion even at 20 mol% loading, suggesting that this substituent does not provide beneficial aromatic-aromatic interactions with the alkene substrate. The related catalysts **5e** and **5f** provided an interesting test of the effect of an additional element of central chirality. The former performed better both in terms of conversion and enantioselectivity (87 vs 69% ee, entries 9 and 10). The final derivatives tested in Table 1 (entries 11-14), whilst showing variations in reactivity, displayed remarkably similar levels of enantioselectivity. Indeed, the five catalysts **4**, **5a**, **5g**, **6**, **14**, with cyclic carbonate, N-methyl- and N-phenyl oxazolidinone, lactone and sulfamidate spiro systems all afforded *E*-stilbene oxide in the

narrow range of 87-91.5% ee. This suggests that in this catalyst family, specific interactions with particular elements of the spirocycle are not significant factors in controlling enantioselectivity.

In each case, the enantiomer of the ketone catalyst that afforded (*R,R*)-stilbene oxide was assigned the configuration depicted in the Schemes based on the well established spiro-TS model^{1, 6} in Figure 1 which has been found to operate with our previous related catalysts.⁷ In the case of **5e**, the catalyst configuration was confirmed by X-ray crystallography. In this crystal structure (Figure 2), **5e** adopts a conformation in which the benzylic hydrogen almost eclipses the oxazolidinone carbonyl. This places the Me-substituent towards the catalyst region approached by the olefin in the epoxidation TS. If the diastereomer **5f** adopts a similar conformation, this would place the Ph-substituent in this position, with a resulting steric clash with the incoming olefin, offering a possible explanation for the lower reactivity and enantioselectivity observed for this catalyst. Similar steric interactions may account for the slightly lower ee value obtained with the *N*^tBu catalyst *ent*-**5c** (entry 6).

Figure 1: Epoxidation TS model

Figure 2: The molecular structure of one of the two crystallographically independent molecules present in the crystals of **5e**.¹¹

Table 1: Catalytic Asymmetric Epoxidation of *E*-Stilbene^a

Entry	Catalyst	X	t(h)	Conversion (%) ^c	Yield (%)	ee (%) ^d	Epoxide Configuration ^d
1	4	O	18	100	85	87	(<i>R,R</i>)
2	<i>ent</i> -4	O	18	100	83	89	(<i>S,S</i>)
3	5a	N-Me	12	87	85	91.5	(<i>R,R</i>)
4	<i>ent</i> -5a	N-Me	12	86.5	85	91.5	(<i>S,S</i>)
5	5b	N- ⁱ Pr	18	90	90	87	(<i>R,R</i>)
6	<i>ent</i> -5c	N- ^t Bu	18	41	41	79	(<i>S,S</i>)
7	<i>ent</i> -5d	N-Bn	24	37	17	82	(<i>S,S</i>)
8	<i>ent</i> -5d ^b	N-Bn	18	50	50	82	(<i>S,S</i>)
9	5e	(<i>S</i>)-NCH(CH ₃)Ph	12	52	50	87	(<i>R,R</i>)
10	5f	(<i>S</i>)-NCH(CH ₃)Ph	12	24	20	69	(<i>S,S</i>)
11	5g	N-Ph	12	76	74	87	(<i>R,R</i>)
12	<i>ent</i> -5g	N-Ph	12	69	68	88	(<i>S,S</i>)
13	6	CH ₂	24	95	nd	90	(<i>R,R</i>)
14	14	SO ₂	8	95	nd	87	(<i>R,R</i>)

^aConditions: alkene (0.1 mmol), Oxone[®] (1.0 mmol KHSO₅), NaHCO₃ (1.55 mmol), CH₃CN (1.5 ml), aq. Na₂EDTA (1 ml of 0.4 mM solution), catalyst (10 mol%). ^b catalyst (20% mol). ^cEstimated from the ¹H NMR spectrum of the crude reaction mixture. ^d Product ee and configuration determined by chiral HPLC analysis.

A selection of the catalysts was screened with two other *trans*-disubstituted olefins. With *E*-β-methyl styrene (Table 2), the NMe-derivative **5a** afforded best results (73.5% ee, entry 2). Catalysts with distinct cyclic motifs were again found to afford epoxides in a narrow range of enantioselectivity (compare entries 1, 3, 6 and 7). Cinnamate esters represent more challenging, less reactive substrates, the epoxides of which are synthetically useful. While moderate conversions were obtained, promising levels of enantioselectivity were observed (up to 82% ee, Table 3). For both of these *trans*-disubstituted substrates, the major epoxide enantiomer obtained is again consistent with the model in Figure 1.

Table 2: Catalytic Asymmetric Epoxidation of *E*- β -Methylstyrene^a

Entry	Catalyst	X	t(h)	Conversion (%) ^c	Yield (%)	ee (%) ^d	Epoxide Configuration ^d
1	<i>ent</i> -4	O	1	100	25	63	(<i>S,S</i>)
2	5a ^b	N-Me	18	100	71	73.5	(<i>R,R</i>)
3	5b ^b	N- ⁱ Pr	18	95	53	62	(<i>R,R</i>)
4	<i>ent</i> -5d ^b	N-Bn	15	83	69	45	(<i>S,S</i>)
5	5e ^b	(<i>S</i>)-NCH(CH ₃)Ph	18	85	70	57	(<i>R,R</i>)
6	<i>ent</i> -5g ^b	N-Ph	18	96	90	64	(<i>S,S</i>)
7	<i>ent</i> -6	CH ₂	8	100	nd	67	(<i>S,S</i>)

^a Conditions: alkene (0.1 mmol), Oxone[®] (1.0 mmol KHSO₅), NaHCO₃ (1.55 mmol), CH₃CN (1.5 ml), aq. Na₂EDTA (1 ml of 0.4 mM solution), catalyst (10% mol). ^b Reaction conditions: alkene (0.2 mmol), Oxone[®] (2.0 mmol KHSO₅), ketone (10 mol%), NaHCO₃ (3.01 mmol), CH₃CN (3 ml), aq. Na₂EDTA (2 ml of 0.4 mM solution). ^c Estimated from the ¹H NMR spectrum of the crude reaction mixture. ^d Product ee and configuration determined by chiral HPLC analysis.

Table 3. Catalytic Asymmetric Epoxidation of *E*-Ethyl Cinnamate^a

Entry	Catalyst	X	t(h)	Conversion (%) ^c	Yield (%)	ee (%) ^d	Epoxide Configuration ^d
1	<i>ent</i> -4	O	18	55	48	74	(<i>2R,3S</i>)
2	5a ^b	N-Me	18	44	41	80	(<i>2S,3R</i>)
3	<i>ent</i> -5a	N-Bn	15	20	17	61	(<i>2R,3S</i>)
4	5b	(<i>S</i>)-NCH(CH ₃)Ph	18	28	21	73	(<i>2S,3R</i>)
5	<i>ent</i> -5d ^b	N-Ph	18	40	35	82	(<i>2R,3S</i>)
6	<i>ent</i> -6	CH ₂	18	23	nd	78	(<i>2R,3S</i>)
7	<i>ent</i> -14	SO ₂	18	17	nd	81	(<i>2R, 3S</i>)

^a Conditions: alkene (0.1 mmol), Oxone[®] (1.0 mmol KHSO₅), NaHCO₃ (1.55 mmol), CH₃CN (1.5 ml), aq. Na₂EDTA (1 ml of 0.4 mM solution), catalyst (10% mol). ^b Reaction conditions: alkene (0.2 mmol), Oxone[®] (2.0 mmol KHSO₅), ketone (10 mol%), NaHCO₃ (3.01 mmol), CH₃CN (3 ml), aq. Na₂EDTA (2 ml of 0.4 mM solution). ^c Estimated from the ¹H NMR spectrum of the crude reaction mixture. ^d Product ee and configuration determined by chiral HPLC analysis.

Phenylcyclohexene has proved to be a particularly interesting substrate in epoxidation reactions with Shi's carbohydrate-derived catalysts. The first generation catalyst **1** afforded (*R,R*)-phenyl cyclohexene oxide in excellent ee. This sense of selectivity is in accord with the

spiro-TS model similar to that shown in Figure 1. However, Shi has reported a reversal of enantioselectivity for some N-aryl- and N-Boc-oxazolidinone-containing spirocyclic ketones (*e.g.* **15**, Figure 3).⁴ This was attributed to an attractive interaction between the oxazolidinone N-substituent and the phenyl ring on the alkene, resulting in predominant reaction *via* a planar-TS. With our own catalysts (Table 4), the major enantiomer was in all cases in accord with the spiro-TS-model (*cf.* Figure 1), suggesting that attractive interactions between the substrate-phenyl and our own spirocyclic substituents do not exert a significant influence.

Figure 3: Enantiomeric excesses for epoxidation of phenyl cyclohexene with ketones **1** and **15**

Table 4: Catalytic Asymmetric Epoxidation of 1-Phenylcyclohexene^a

Entry	Catalyst	X	t(h)	Conversion (%) ^c	Yield (%)	ee (%) ^d	Epoxide Configuration ^d
1	ent-4	O	1	98	63	73	(<i>S,S</i>)
2	5a^b	N-Me	18	100	65	74	(<i>R,R</i>)
3	5b^b	N- ^{<i>i</i>} Pr	1	95	54	71	(<i>R,R</i>)
4	ent-5d^b	N-Bn	15	100	58	51	(<i>S,S</i>)
5	5e^b	(<i>S</i>)-NCH(CH ₃)Ph	18	100	69	64	(<i>R,R</i>)
6	ent-5g^b	N-Ph	18	100	86	58	(<i>S,S</i>)
7	6	CH ₂	8	88	nd	45	(<i>R,R</i>)
8	14	SO ₂	8	65	nd	69	(<i>R,R</i>)

^a Conditions: alkene (0.1 mmol), Oxone[®] (1.0 mmol KHSO₅), NaHCO₃ (1.55 mmol), CH₃CN (1.5 ml), aq. Na₂EDTA (1 ml of 0.4 mM solution), catalyst (10% mol). ^b Reaction conditions: alkene (0.2 mmol), Oxone[®] (2.0 mmol KHSO₅), ketone (10 mol%), NaHCO₃ (3.01 mmol), CH₃CN (3 ml), aq. Na₂EDTA (2 ml of 0.4 mM solution). ^c Estimated from the ¹H NMR spectrum of the crude reaction mixture. ^d Product ee and configuration determined by chiral HPLC analysis.

Direct enantioselective epoxidation of terminal alkenes remains an important challenge, and the highly encouraging results reported by Shi with his spirocyclic ketones⁵ prompted us to

screen our own catalysts. Epoxidation of styrene with fluoroketone **3** (X=NCO₂Et, Y=F) affords styrene oxide in poor ee (29%).^{7d} The majority of the new catalysts improve on this (Table 5), with **5f** again affording lower enantioselectivity than its diastereomer **5e** (entries 6 and 7). The best result (59% ee) was with the NPh-derivative **5g** (entry 8), suggesting that exploration of the effect of substituents on the catalyst's aromatic ring may be worthwhile. Finally, the particularly challenging 1,1-disubstituted alkene class was examined (Table 6), but enantioselectivities were poor, and again within a relatively narrow range, suggesting an absence of specific TS-interactions between the various spirocyclic substituents and the alkene.

Table 5: Catalytic Asymmetric Epoxidation of Styrene^a

Entry	Catalyst	X	t(h)	Conversion (%) ^c	Yield (%)	ee (%) ^d	Epoxide Configuration ^d
1	ent-4	O	1	100	nd	46	(<i>S</i>)
2	5a^b	N-Me	12	100	79	58	(<i>R</i>)
3	5b^b	N- ⁱ Pr	18	88	35	54	(<i>R</i>)
4	ent-5c^b	N- ^t Bu	18	>30	8	43	(<i>S</i>)
5	ent-5d^b	N-Bn	24	89	68	43	(<i>S</i>)
6	5e^b	(<i>S</i>)-NCH(CH ₃)Ph	12	94	66	55	(<i>R</i>)
7	5f^b	(<i>S</i>)-NCH(CH ₃)Ph	12	63	40	27	(<i>S</i>)
8	ent-5g^b	N-Ph	24	93	29	59	(<i>S</i>)
9	ent-6	CH ₂	18	100	nd	50	(<i>S</i>)

^a Conditions: alkene (0.1 mmol), Oxone[®] (1.0 mmol KHSO₅), NaHCO₃ (1.55 mmol), CH₃CN (1.5 ml), aq. Na₂EDTA (1 ml of 0.4 mM solution), catalyst (10% mol). ^b Reaction conditions: alkene (0.2 mmol), Oxone[®] (2.0 mmol KHSO₅), ketone (10 mol%), NaHCO₃ (3.01 mmol), CH₃CN (3 ml), aq. Na₂EDTA (2 ml of 0.4 mM solution). ^c Estimated from the ¹H NMR spectrum of the crude reaction mixture. ^d Product ee and configuration determined by chiral HPLC analysis.

Table 6. Catalytic Asymmetric Epoxidation of α -Methylstyrene^a

Entry	Catalyst	X	t(h)	Conversion (%) ^c	Yield (%)	ee (%) ^d	Epoxide Configuration ^d
1	<i>ent</i> - 4 ^b	O	1	100	30	19	(<i>S</i>)
2	5a ^b	N-Me	12	100	90	17	(<i>R</i>)
3	5b ^b	N- ^{<i>i</i>} Pr	10	100	27	15	(<i>R</i>)
4	<i>ent</i> - 5c ^b	N- ^{<i>i</i>} Bu	18	55	45	16	(<i>S</i>)
5	<i>ent</i> - 5d ^b	N-Bn	18	81	49	6	(<i>S</i>)
6	5e ^b	(<i>S</i>)-NCH(CH ₃)Ph	24	69	67	13	(<i>R</i>)
7	<i>ent</i> - 5g ^b	N-Ph	24	97	52	12	(<i>S</i>)
8	6	CH ₂	8	81	nd	13	(<i>R</i>)

^a Conditions: alkene (0.1 mmol), Oxone[®] (1.0 mmol KHSO₅), NaHCO₃ (1.55 mmol), CH₃CN (1.5 ml), aq. Na₂EDTA (1 ml of 0.4 mM solution), catalyst (10% mol). ^b Reaction conditions: alkene (0.2 mmol), Oxone[®] (2.0 mmol KHSO₅), ketone (10 mol%), NaHCO₃ (3.01 mmol), CH₃CN (3 ml), aq. Na₂EDTA (2 ml of 0.4 mM solution). ^c Estimated from the ¹H NMR spectrum of the crude reaction mixture. ^d Product ee and configuration determined by chiral HPLC analysis.

3. Conclusions

We have developed an efficient synthetic approach to a range of spirocyclic ketones which has allowed access to a several novel derivatives from a common synthetic intermediate. These new ketones are efficient catalysts for alkene epoxidation using Oxone, and can be used at low loadings (10 mol%). Enantioselectivities are very good for epoxidation of *E*-stilbene, and the new spirocyclic catalysts afford higher ee for epoxidation of styrene than does the simpler ketone **3**. The results for epoxidation of phenylcyclohexene, and the generally low variation of product ee with catalyst substitution, suggest that specific interactions with the spirocyclic substituents are not significant contributors to the observed enantioselectivities. Synthesis of a wider range of ketones, including more highly substituted variants, are ongoing and will be reported in due course.

4. Experimental

4.1 General details

All reactions requiring dry or inert conditions were conducted in oven-dried equipment under an atmosphere of nitrogen. Syringes and needles were oven-dried. Anhydrous THF, DMF, Et₂O and MeOH were purchased from Aldrich Chemical Co. All commercially reagents were used without further purification. Flash chromatography was performed on silica gel Merck Kieselgel (230-400) mesh or on Varian Mega Be-Si pre-packed cartridges or on pre-packed Biotage silica cartridges. In a number of preparations, purification was performed using either Biotage manual flash chromatography (Flash+) or automatic flash chromatography (Horizon, SP1) systems. All these instruments work with Biotage Silica cartridges.

SPE-SCX cartridges are ion exchange solid phase extraction columns supplied by Varian. The eluent used with SPE-SCX cartridges is methanol followed by 2 M ammonia solution in methanol.

In a number of preparations, “dried” refers to a solution dried over anhydrous sodium sulfate (when organic solvents as diethyl ether or ethyl acetate are used) or by phase separator cartridge (when DCM is used). Phase separation cartridges were supplied by Whatman (PTFE, 5 µm pore size).

Thin layer chromatography (TLC) was carried out on Merck 5×10 cm plates with silica gel 60 F₂₅₄ as sorbant. Visualisation of reaction components was achieved with UV lamp (254 nm) and with ceric ammonium nitrate or potassium permanganate stains. Preparative thin layer chromatography was carried out using 20×20 cm silica gel GF tapered plates supplied by Analtech Inc, Newark. IR spectra were recorded on a Perkin-Elmer FT-IR spectrometer, Spectrum 1000 or on Nicolet FT-IR Magna 760 spectrometer. Samples were run as thin films (produced by the evaporation of chloroform or DCM) on aluminium oxide plates or on nujol. Absorption maxima are reported in wavenumber (cm⁻¹).

¹H and ¹³C NMR spectra were recorded in CDCl₃ unless stated otherwise on either a Bruker spectrometer at 500, 400 or 360 MHz, or on Varian instruments at 300, 400 or 500 MHz. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as internal standard and coupling constants are quoted in Hertz (Hz). Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br) and combinations of the above. The NMR spectra were recorded at a temperature ranging from 25 to 90°C.

Mass spectra were recorded using a HP1100 flow inject system (50:50 1% formic acid-H₂O:CH₃CN) into an electrospray source of a Waters ZMD2000 or on a 4 II triple quadrupole Mass Spectrometer (Micromass UK) or on a Agilent MSD 1100 Mass Spectrometer, operating in ES (+) and ES (-) ionization mode. Accurate mass was recorded using a HP1100 flow injection into an electrospray source of a Waters Q-Tof micro or a Waters LCT Premier mass spectrometer equipped with a Z-spray source and coupled to a Waters UPLC (Ultra Performance Liquid Chromatography). Leucine Enkephalin was used as external standard and infused with a reference probe. Optical rotations were recorded on a Perkin-Elmer Polarimeter 241, with a path length of 5 cm or on a Optical-Activity AA-5 Polarimeter with a path length of 5 cm, in chloroform or methanol. $[\alpha]_D$ values are given in 10⁻¹ deg cm² g⁻¹. Concentrations (c) are given in grams per 100 cm³. Melting points were obtained using a Buchi melting point B-540 hot stage apparatus or a Gallenkamp melting point apparatus and are quoted as uncorrected.

Separations of racemic ketones into single enantiomers were performed using Supercritical Fluid Chromatography (Chiralpak IA, Chiralpak AS or AS-H, Chiralpak AD-H column) on a Berger Minigram system with UV/VIS detector at 220 nm using CO₂/methanol as mobile phase. Alternatively, they were performed by chiral chromatography (Chiralpak AS-H, ACE C8, Chiralpak AD-H or Chiralcel OJ-H column) on an Agilent HP1100 system with UV/VIS detector at 254 or 220 nm using *iso*-propanol/*n*-hexane or methanol/*n*-hexane as eluent; retention times are quoted in minutes. The absolute configuration of the ketones was assumed based on the observed major enantiomer of *E*-stilbene oxide obtained when they were used as catalysts, *i.e.* the catalyst enantiomers depicted in the Schemes give (*R,R*)-stilbene oxide, whilst the *ent*-series gives (*S,S*)-stilbene oxide. This is consistent with the *spiro*-TS model in Figure 1, with the results for earlier catalysts,⁷ and was confirmed by X-ray crystallography in the case of **5e**.¹¹

Epoxide enantiomeric excesses (ee) were determined by chiral HPLC HP 1100 (Chiralpak AS, Chiralcel OD or Chiralcel OJ-H column) on an Agilent HP1100 system with UV/VIS detector at 254 or 220 nm using *iso*-propanol/*n*-hexane or methanol/*n*-hexane as eluent.

4.2 Synthesis of Ketone Catalysts

(1*R,5*S**)-Ethyl 2-methylene-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (±8).** Under a nitrogen atmosphere, LiHMDS 1.0 M in THF (83 ml, 0.08 mol) was added dropwise to a stirred solution of ketone **7** (15.0 g, 0.08 mol) in THF (150 ml) cooled at -78 °C. After stirring

at -78 °C for 30 minutes, Me₃SiCl (14.4 ml, 0.11 mol) was added, and stirring was continued for ½ hour. The reaction mixture was quenched with a saturated solution of NH₄Cl (50 ml) at 0 °C; then the organic layer was diluted with EtOAc (100 ml) and extracted with EtOAc (3× 20 ml). The combined organics were washed with a saturated solution of NaHCO₃ (50 ml), dried over MgSO₄ and concentrated. The crude silyl enol ether intermediate was dissolved in DMF (150 ml), under a nitrogen atmosphere, and Eschenmoser's salt (15.4 g, 0.08 mol) was added. The reaction mixture was stirred at room temperature for 1.5 hour and then MeI (23 ml, 0.38 mol) was added. After stirring at 50 °C overnight in a sealed tube, NaHCO₃ (47.0 g, 0.56 mol) was added and the reaction mixture diluted with DMF (100 ml). It was heated to 95 °C overnight and then cooled to room temperature, diluted with EtOAc (100 ml), washed with H₂O (50 ml), extracted with EtOAc (3× 30 ml) and separated. The combined organics were dried over MgSO₄ and concentrated. The residue was purified by flash chromatography over silica gel eluting with 25% EtOAc in *n*-hexane to give (±)-**8** as a colourless oil (10.1 g, 63%); $\nu_{\text{max}}/\text{cm}^{-1}$ (CHCl₃): 2977, 1693, 1622, 1410, 1380, 1106, 946, 768; ¹H NMR δ_{H} (ppm) (CDCl₃, 500 MHz): 5.91 (1 H, s, C=CH₂), 5.24 (1 H, br s, C=CH₂), 4.91 (1 H, br s, NCHC), 4.57 (1 H, br s, NCHCH₂CO), 4.18-4.14 (2 H, q, J = 7.1 Hz, OCH₂CH₃), 2.78 (1 H, br s, CHCH_{2ax}CO), 2.46 (1 H, d, J = 18.0 Hz, CHCH_{2eq}CO), 2.29-2.17 (2 H, m, CHCH_{2exo}CH_{2exo}CH), 1.80-1.68 (2 H, m, CHCH_{2endo}CH_{2endo}CH), 1.26 (3 H, t, J = 7.1 Hz, OCH₂CH₃); ¹³C NMR δ_{C} (ppm) (CDCl₃, 91 MHz): 198.5 (C, C=O_{ketone}), 154.0 (C, C=O_{carbamate}), 146.8 (C, C=CH₂), 119.6 (CH₂, C=CH₂), 61.8 (CH₂, OCH₂CH₃), 58.6 (CH, NCHC), 52.8 (CH, NCHCH₂CO), 47.9 (CH₂, CHCH₂CO), 31.4 (CH₂, CHCH₂CH₂CH), 29.5 (CH₂, CHCH₂CH₂CH), 15.0 (CH₃, OCH₂CH₃); *m/z* (ES+) 210 ([M+H]⁺, 100%); *m/z* (ES+) found: [M+H]⁺, 210.1138. C₁₁H₁₆NO₃ requires: [M+H]⁺, 210.1130.

(1R*,2S*,5S*)-Ethyl 2-hydroxy-2-(hydroxymethyl)-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (±9). To a stirred suspension of K₂OsO₄·2H₂O (5.2 mg, 0.01 mmol), quinuclidine (7.8 mg, 0.07 mmol) and *N*-methylmorpholine-*N*-oxide (336 mg, 2.87 mmol) in H₂O (0.64 ml) a solution of enone (±)-**8** (300 mg, 1.40 mmol) in acetone (3.36 ml) was added. The reaction mixture was stirred vigorously at room temperature for 3 days, then solid sodium metabisulfite (~1.5 g) was added and vigorous stirring was continued for a further hour. The reaction mixture was diluted with DCM (10 ml). The solid was removed by filtration through a pad of Celite™ and washed with DCM (20 ml). The combined filtrate and washings were dried and evaporated to dryness and the residue purified by flash chromatography on silica gel eluting with 3% MeOH in DCM to give (±)-**9** as a pale yellow

oil (300 mg, 86%); $\nu_{\max}/\text{cm}^{-1}$ (CHCl_3): 3526, 3410, 2978, 1726, 1676, 1115, 1068; ^1H NMR δ_{H} (ppm) (CDCl_3 , 500 MHz): 4.61 (1 H, br s, NCHCH_2CO), 4.50 (1 H, br s, NCHC), 4.22 (2 H, m, OCH_2CH_3), 4.06 (1 H, dd, $J = 18.5$ and 5.5 Hz, CCH_2OH), 3.56-3.54 (1 H, m, CCH_2OH), 3.15 (1 H, d, $J = 20.6$ Hz, $\text{CHCH}_{2\text{ax}}\text{CO}$), 2.41 (1 H, br s, COH), 2.22 (1 H, d, $J = 20.6$ Hz, $\text{CHCH}_{2\text{eq}}\text{CO}$), 2.05-2.00 (2 H, m, $\text{CHCH}_{2\text{exo}}\text{CH}_{2\text{exo}}\text{CH}$), 1.64 (1 H, br s, CH_2OH), 1.61-1.57 (2 H, m, $\text{CHCH}_{2\text{endo}}\text{CH}_{2\text{endo}}\text{CH}$), 1.31 (3 H, m, OCH_2CH_3); ^{13}C NMR δ_{C} (ppm) (CDCl_3 , 91 MHz): 208.4 (C, $\text{C}=\text{O}_{\text{ketone}}$), 155.7 (C, $\text{C}=\text{O}_{\text{carbamate}}$), 80.0 (C, CCH_2OH), 62.9 (CH_2 , CCH_2OH), 62.2 (CH_2 , OCH_2CH_3), 59.4 (CH, NCHC), 54.1 (CH, NCHCH_2CO), 46.4 (CH_2 , CHCH_2CO), 28.3 (CH_2 , $\text{CHCH}_2\text{CH}_2\text{CHCH}_2$), 23.9 (CH_2 , $\text{CHCH}_2\text{CH}_2\text{CHCH}_2$), 15.0 (CH_3 , OCH_2CH_3); m/z (ES+) 244 ($[\text{M}+\text{H}]^+$, 100%); m/z (ES+) found: $[\text{M}+\text{H}]^+$, 244.1189. $\text{C}_{11}\text{H}_{18}\text{NO}_5$ requires: $[\text{M}+\text{H}]^+$, 244.1185.

(1R*,2S*,5S*)-Ethyl 2',3-dioxo-8-2',3-dioxo-8H-spiro[8-azabicyclo[3.2.1]octane-2,4'-[1,3]dioxolane]-8-carboxylate ($\pm$)-4, and resolution to give **4** and *ent*-**4**. To a stirred solution of diol ($\pm$)-**9** (150 mg, 6.15 mmol) and pyridine (0.5 ml, 6.15 mmol) in DCM (3 ml) a solution of triphosgene (0.182 mg, 6.15 mmol) in DCM (0.4 ml) was added at 0 °C under a nitrogen atmosphere. The mixture was stirred between 0 °C and room temperature for 8 hours. It was then quenched with H_2O (2 ml). The organic phase was diluted with DCM (20 ml), separated, dried over MgSO_4 and concentrated. The residue was purified by flash chromatography on silica gel eluting with 50% EtOAc in *n*-hexane to give ($\pm$)-**4** as a colourless solid (100 mg, 60%); m.p.: 113.4-114.3 °C; $\nu_{\max}/\text{cm}^{-1}$ (CHCl_3): 1806, 1692, 1426, 1335, 1047; ^1H NMR δ_{H} (ppm) (CDCl_3 , 500 MHz): 5.04-4.99 (1 H, m, CCH_2O), 4.85-4.64 (2 H, m, NCHC and NCHCH_2CO), 4.27-4.18 (2 H, m, OCH_2CH_3), 4.00 (1 H, d, $J = 8.8$ Hz, CCH_2O), 3.15-3.01 (1 H, br m, $\text{CHCH}_{2\text{ax}}\text{CO}$), 2.52 (1 H, dd, $J = 15.2$ and 2.2 Hz, $\text{CHCH}_{2\text{eq}}\text{CO}$), 2.16-2.08 (2 H, m, $\text{CHCH}_{2\text{exo}}\text{CH}_{2\text{exo}}\text{CH}$), 1.63-1.61 (1 H, m, $\text{CHCH}_{2\text{endo}}\text{CH}_{2\text{endo}}\text{CHCH}_2$), 1.33-1.24 (4 H, m, OCH_2CH_3 and $\text{CHCH}_{2\text{endo}}\text{CH}_{2\text{endo}}\text{CHCH}_2$); ^{13}C NMR δ_{C} (ppm) (CDCl_3 , 91 MHz): 199.6 (C, $\text{C}=\text{O}_{\text{ketone}}$), 154.4 (C, $\text{C}=\text{O}_{\text{carbamate}}$), 152.6 (C, $\text{C}=\text{O}_{\text{carbonate}}$), 85.2 (C, CCH_2O), 65.8 (CH_2 , CCH_2O), 62.4 (CH_2 , OCH_2CH_3), 59.4 (CH, NCHC), 54.0 (CH, NCHCH_2CO), 47.1 (CH_2 , CHCH_2CO), 27.9 (CH_2 , $\text{CHCH}_2\text{CH}_2\text{CHCH}_2$), 23.8 (CH_2 , $\text{CHCH}_2\text{CH}_2\text{CHCH}_2$), 14.9 (CH_3 , OCH_2CH_3); m/z (ES+) 270 ($[\text{M}+\text{H}]^+$, 100%); m/z (ES+) found: $[\text{M}+\text{H}]^+$, 270.0976. $\text{C}_{12}\text{H}_{16}\text{NO}_6$ requires: $[\text{M}+\text{H}]^+$, 270.0978.

The racemic compound was separated into single enantiomers by SFC (Chiralpak AD-H column, 220 nm, 90/10 CO_2 /*iso*-propanol, 10 ml/min, 35 °C, Outlet P=100 bar):

ent-4: enantiomer 1, Rt = 5.20 min, colourless solid., m.p.: 126.5-128.1 °C; $[\alpha]_{\text{D}}^{20}$ -25.2 (c 1, CHCl₃); 99% ee.

4: enantiomer 2, Rt = 6.35 min, colourless solid, m.p.: 116.1-120.2 °C; $[\alpha]_{\text{D}}^{20}$ +21.0 (c 0.3, CHCl₃); 97% ee.

(1R*,2S*,3S*,5S*)-Ethyl 3-hydroxy-8H-spiro[8-azabicyclo[3.2.1]octane-2,2'-oxirane]-8-carboxylate (±)-10. CeCl₃·7H₂O (7.8 g, 0.02 mol) was added to a solution of enone (**±**)-**8** (4.0 g, 0.02 mol) in MeOH (30 ml). The mixture was cooled to 0 °C and then NaBH₄ (0.79 g, 0.02 mol) was added portionwise. After stirring at 0 °C for 1 hour, the mixture was quenched with water (3 ml). The organic solvent was evaporated *in vacuo* and the residue diluted with EtOAc (30 ml), washed with 0.1 M HCl (10 ml), brine (10 ml), dried over MgSO₄ and concentrated. It was then purified by flash chromatography on silica gel eluting with 50% EtOAc in *n*-hexane and then with 5% MeOH in DCM to yield the allylic alcohol as a colourless oil (3.8 g, 95%); $\nu_{\text{max}}/\text{cm}^{-1}$ (CHCl₃): 3518, 1697, 908; ¹H NMR δ_{H} (ppm) (DMSO-*d*₆, 500 MHz): 4.92 (1 H, d, J = 6.5 Hz, OH), 4.90-4.89 (1 H, m, C=CH₂), 4.80 (1 H, br s, C=CH₂), 4.46 (1 H, d, J = 6.3 Hz, NCHC), 4.32-4.29 (1 H, m, CHCH₂CHOH), 4.16 (1 H, br s, NCHCH₂CHOH), 4.01 (2 H, q, J = 7.0 Hz, OCH₂CH₃), 1.91-1.87 (3 H, m, CHCH₂CHOH and CHCH₂_{exo}CH₂_{exo}CH), 1.76-1.67 (1 H, m, CHCH₂_{endo}CH₂_{endo}CHCH₂), 1.66-1.57 (1 H, m, CHCH₂_{endo}CH₂_{endo}CHCH₂), 1.55-1.40 (1 H, m, CHCH₂CHOH), 1.16 (3 H, t, J = 7.1 Hz, OCH₂CH₃); ¹H NMR δ_{H} (ppm) (CDCl₃, 500 MHz): 5.08-4.79 (2 H, br m, C=CH₂), 4.75-4.51 (1 H, br m, NCHC), 4.50-4.40 (1 H, br s, CHCH₂CHOH), 4.39-4.28 (1 H, br s, NCHCH₂CHOH), 4.15-4.02 (2 H, m, OCH₂CH₃), 2.65-1.97 (4 H, br m, OH, CHCH₂CHOH and CHCH₂_{exo}CH₂_{exo}CH), 1.76-1.52 (3 H, br m, CHCH₂_{endo}CH₂_{endo}CH and CHCH₂CHOH), 1.25-1.20 (3 H, m, OCH₂CH₃); ¹³C NMR δ_{C} (ppm) (CDCl₃, 91 MHz): 154.5 (C, C=O_{carbamate}), 150.4 (C, C=CH₂), 106.3 (CH₂, C=CH₂), 66.5 (CH, CHCH₂CHOH), 61.4 (CH₂, OCH₂CH₃), 60.3 (CH, NCHC), 53.9 (CH, NCHCH₂CHOH), 43.1 (CH₂, CHCH₂CHOH), 29.4 (CH₂, CHCH₂CH₂CHCH₂), 28.1 (CH₂, CHCH₂CH₂CHCH₂), 15.1 (CH₃, OCH₂CH₃); *m/z* (ES+) 166 ([M+H] (-OH and -C₂H₅))+ 100%; *m/z* (ES+) found: [M+H]⁺, 212.1287. C₁₁H₁₈NO₃ requires: [M+H]⁺, 212.1287.

The allylic alcohol (4.9 g, 0.02 mol) was dissolved in DCM (60 ml) and cooled to 0 °C. Then *m*-CPBA 75% w (6.2 g, 0.03 mol) was added portionwise and the mixture stirred at 0 °C for 3 h. A white solid formed during the reaction. The suspension was diluted with DCM (20 ml); it was washed with a 10% solution of sodium tiosulfate (40 ml), then with 1.0 M NaOH (40

ml) and finally with brine (40 ml). The organic layer was dried over MgSO_4 and then concentrated *under vacuum*. The residue was purified by flash chromatography on silica gel eluting with 50% EtOAc in *n*-hexane and then with 5% MeOH in DCM to yield ($\pm$)-**10** as a colourless oil (3.7 g, 70%); $\nu_{\text{max}}/\text{cm}^{-1}$ (CHCl_3): 3525, 1707, 1487, 1123; ^1H NMR δ_{H} (ppm) ($\text{DMSO}-d_6$, 500 MHz): 4.33 (1 H, d, $J = 9.0$ Hz, OH), 4.26 (1 H, br s, $\text{NCHCH}_2\text{CHOH}$), 4.08-4.00 (3 H, m, OCH_2CH_3 and CHCH_2CHOH), 3.78 (1 H, br s, NCHC), 2.82 (1 H, d, $J = 5.3$ Hz, CCH_2O), 2.66 (1 H, d, $J = 5.3$ Hz, CCH_2O), 1.92-1.86 (3 H, m, CHCH_2CHOH and $\text{CHCH}_{2\text{exo}}\text{CH}_{2\text{exo}}\text{CH}$), 1.76-1.69 (2 H, m, $\text{CHCH}_{2\text{endo}}\text{CH}_{2\text{endo}}\text{CH}$), 1.59 (1 H, m, CHCH_2CHOH), 1.17 (3 H, br t, OCH_2CH_3); ^1H NMR δ_{H} (ppm) (CDCl_3 , 500 MHz): 4.44 (1 H, br s, $\text{NCHCH}_2\text{CHOH}$), 4.17-4.10 (3 H, m, OCH_2CH_3 and CHCH_2CHOH), 4.09-3.90 (1 H, m, NCHC), 3.04 (1 H, d, $J = 5.3$ Hz, CCH_2O), 2.76 (1 H, br s, CCH_2O), 2.16-2.12 (1 H, m, $J = 13.0, 6.1$ and 2.9 Hz, $\text{CHCH}_{2\text{eq}}\text{CHOH}$), 2.08-1.96 (2 H, m, $\text{CHCH}_{2\text{exo}}\text{CH}_{2\text{exo}}\text{CH}$), 1.84-1.76 (2 H, m, $\text{CHCH}_{2\text{endo}}\text{CH}_{2\text{endo}}\text{CH}$ and CHCH_2CHOH), 1.74-1.70 (2 H, m, $\text{CHCH}_{2\text{ax}}\text{CHOH}$ and $\text{CHCH}_{2\text{endo}}\text{CH}_{2\text{endo}}\text{CH}$), 1.26 (3 H, t, $J = 7.1$ Hz, OCH_2CH_3); ^{13}C NMR δ_{C} (ppm) (CDCl_3 , 91 MHz): 154.3 (C, $\text{C}=\text{O}_{\text{carbamate}}$), 61.9 (CH, CHCH_2CHOH), 61.6 (CH_2 , OCH_2CH_3), 61.2 (C, CCH_2O), 58.8 (CH, NCHC), 52.7 (CH, $\text{NCHCH}_2\text{CHOH}$), 48.8 (CH_2 , CCH_2O), 40.2 (CH_2 , CHCH_2CHOH), 26.6 (CH_2 , $\text{CHCH}_2\text{CH}_2\text{CH}$), 26.4 (CH_2 , $\text{CHCH}_2\text{CH}_2\text{CH}$), 14.7 (CH_3 , OCH_2CH_3); m/z (ES+) 250 ($[\text{M}+\text{Na}]^+$, 100%); m/z (ES+) found: $[\text{M}+\text{H}]^+$, 228.1247. $\text{C}_{11}\text{H}_{18}\text{NO}_4$ requires: $[\text{M}+\text{H}]^+$, 228.1236.

(1R*,2R*,5S*)-Ethyl 3'-methyl-2',3-dioxo-8H-spiro[8-azabicyclo[3.2.1]octane-2,5'-[1,3]oxazolidine]-8-carboxylate ($\pm$)-**5a**, and resolution to give **5a** and *ent*-**5a**. Epoxide ($\pm$)-**10** (500 mg, 2.2 mmol) was dissolved in EtOH (5 ml) and then methylamine 33% wt in EtOH (0.27 ml, 2.2 mmol) was added. The solution was heated to 70 °C overnight in a sealed tube. The reaction mixture was cooled to RT and concentrated under reduced pressure. The residue was purified by SCX cartridge eluting first with MeOH and then with 2.0 M NH_3 in MeOH to yield ($\pm$)-**11a** as a colourless oil. It was dissolved in DMSO (20 ml) and TFA (180 μl , 2.39 mmol) was added followed by IBX (1.82 g, 6.5 mmol). The reaction mixture was stirred at RT overnight. Then 3 ml of water were added and after 20 minutes stirring a white solid was filtered. The filtrate was diluted with EtOAc (15 ml) and purified by SCX cartridge eluting first with MeOH and then with 2.0 M NH_3 in MeOH. The ammonia fractions were further purified by flash chromatography on silica gel eluting with 5% MeOH in DCM to yield the ketone **a** as a colourless oil (0.4 g, 72% slightly impure).

A small portion was further purified by chromatography on silica gel eluting with 5% MeOH in DCM to get full characterization data while all the rest of the material was taken through the next step: $\nu_{\max}/\text{cm}^{-1}$ (CHCl_3): 2981, 1697, 1430, 1332, 1108, 1034, 765; ^1H NMR δ_{H} (ppm) (CDCl_3 , 500 MHz): 4.57 (1 H, br s, NCHCH_2CO), 4.48-4.26 (1 H, br s, NCHC), 4.25-4.18 (2 H, m, OCH_2CH_3), 3.24 (1 H, d, $J = 12.2$ Hz, CCH_2NH), 3.18 (1 H, br d, $J = 14.6$, $\text{CHCH}_{2\text{ax}}\text{CO}$), 3.00 (2 H, br s, OH and NH), 2.49 (3 H, s, NHCH_3), 2.30-2.24 (1 H, br s, CCH_2NH), 2.17 (1 H, dd, $J = 14.6$ Hz and 1.9, $\text{CHCH}_{2\text{eq}}\text{CO}$), 1.99-1.96 (2 H, m, $\text{CHCH}_{2\text{exo}}\text{CH}_{2\text{exo}}\text{CH}$), 1.55-1.49 (2 H, m, $\text{CHCH}_{2\text{endo}}\text{CH}_{2\text{endo}}\text{CH}$), 1.30 (3 H, t, $J = 7.1$ Hz, OCH_2CH_3); ^{13}C NMR δ_{C} (ppm) (CDCl_3 , 91 MHz): 209.3 (C, $\text{C}=\text{O}_{\text{ketone}}$), 155.2 (C, $\text{C}=\text{O}_{\text{carbamate}}$), 78.3 (C, CCH_2NH), 61.8 (CH_2 , OCH_2CH_3), 61.4 (CH, NCHC), 53.7 (CH, NCHCH_2CO), 52.8 (CH_2 , CCH_2NH), 46.2 (CH_2 , CHCH_2CO), 37.3 (CH_3 , NHCH_3), 28.2 (CH_2 , $\text{CHCH}_2\text{CH}_2\text{CH}$), 23.5 (CH_2 , $\text{CHCH}_2\text{CH}_2\text{CH}$), 15.0 (CH_3 , OCH_2CH_3); m/z (ES+) 257 ($[\text{M}+\text{H}]^+$, 100%); m/z (ES+) found: $[\text{M}+\text{H}]^+$, 257.1494. $\text{C}_{12}\text{H}_{21}\text{N}_2\text{O}_4$ requires: $[\text{M}+\text{H}]^+$, 257.1501.

The ketone (0.4 g, 1.56 mmol) was dissolved in DCM (20 ml); pyridine (1.6 ml, 0.02 mol) was added and the mixture cooled to 0 °C. Triphosgene (0.51 g, 1.72 mmol) was subsequently added portionwise and the final mixture was stirred at RT for 6 h. It was then diluted with DCM (20 ml), washed with 0.1 M HCl (20 ml), H_2O (20 ml), brine (20 ml), dried over MgSO_4 and concentrated. The residue was purified by flash chromatography on silica gel eluting with EtOAc to yield ($\pm$)-**5a** as a pale yellow oil that solidified at room temperature (210 mg, 48%); m.p.: 110.3-113.2 °C; $\nu_{\max}/\text{cm}^{-1}$ (CHCl_3): 2981, 1784, 1716, 1695, 1441, 1337, 1122, 1037, 934, 755; ^1H NMR δ_{H} (ppm) (CDCl_3 , 500 MHz): 4.76-4.48 (2 H, m, NCHCH_2CO and NCHC), 4.33-4.14 (3 H, m, OCH_2CH_3 and CCH_2N), 3.17-3.02 (2 H, m, $\text{CHCH}_{2\text{ax}}\text{CO}$ and CCH_2N), 2.91 (3 H, s, NCH_3), 2.45 (1 H, dd, $J = 14.8$ and 1.6 Hz, $\text{CHCH}_{2\text{eq}}\text{CO}$), 2.18-2.00 (2 H, m, $\text{CHCH}_{2\text{exo}}\text{CH}_{2\text{exo}}\text{CH}$), 1.63-1.55 (1 H, m, $\text{CHCH}_{2\text{endo}}\text{CH}_{2\text{endo}}\text{CHCH}_2$), 1.36-1.25 (4 H, m, $\text{CHCH}_{2\text{endo}}\text{CH}_{2\text{endo}}\text{CHCH}_2$ and OCH_2CH_3); ^1H NMR δ_{H} (ppm) (CDCl_3 , 360 MHz, 56 °C): 4.75-4.55 (2 H, m, NCHCH_2CO and NCHC), 4.34-4.20 (2 H, m, OCH_2CH_3), 4.17 (1 H, d, $J = 8.9$ Hz, CCH_2N), 3.16 (1 H, br d, $J = 14.8$ Hz, $\text{CHCH}_{2\text{ax}}\text{CO}$), 3.04 (1 H, d, $J = 8.9$ Hz, CCH_2N), 2.92 (3 H, s, NCH_3), 2.46 (1 H, dd, $J = 14.8$ and 1.9 Hz, $\text{CHCH}_{2\text{eq}}\text{CO}$), 2.19-2.03 (2 H, m, $\text{CHCH}_{2\text{exo}}\text{CH}_{2\text{exo}}\text{CH}$), 1.68-1.60 (1 H, m, $\text{CHCH}_{2\text{endo}}\text{CH}_{2\text{endo}}\text{CHCH}_2$), 1.36-1.27 (4 H, m, $\text{CHCH}_{2\text{endo}}\text{CH}_{2\text{endo}}\text{CHCH}_2$ and OCH_2CH_3); ^{13}C NMR δ_{C} (ppm) (CDCl_3 , 91 MHz): 201.0 (C, $\text{C}=\text{O}_{\text{ketone}}$), 155.8 (C, $\text{C}=\text{O}_{\text{cyclic carbamate}}$), 154.6 (C, $\text{C}=\text{O}_{\text{carbamate}}$), 82.3 (C, CCH_2N), 62.3 (CH_2 , OCH_2CH_3), 60.2 (CH, NCHC), 54.0

(CH, NCHCH₂CO), 47.9 (CH₂, CCH₂N), 46.8 (CH₂, CHCH₂CO), 31.5 (CH₃, NCH₃), 27.9 (CH₂, CHCH₂CH₂CHCH₂), 23.8 (CH₂, CHCH₂CH₂CHCH₂), 15.0 (CH₃, OCH₂CH₃); *m/z* (ES+) 283 ([M+H]⁺, 100%); *m/z* (ES+) found: [M+H]⁺, 283.1292. C₁₃H₁₉N₂O₅ requires: [M+H]⁺, 283.1294.

The racemic compound was then separated into single enantiomers by SFC (Chiralpak AD-H column, 220 nm, 85/15 CO₂/MeOH, 10 ml/min, 35 °C, Outlet P=100 bar):

5a: enantiomer 1, Rt = 3.74 min; 70 mg, colourless solid, m.p. 119.1-120.0 °C; [α]_D²⁰ -49.3 (c 1, CHCl₃); >99% enantiomeric excess,

ent-5a: enantiomer 2, Rt = 4.31 min; 70 mg, colourless solid, m.p. 119.1-120.0 °C; [α]_D²⁰ +49.2 (c 1, CHCl₃); >99% enantiomeric excess.

(1R*,2R*,5S*)-Ethyl 3'-iso-propyl-2',3-dioxo-8H-spiro[8-azabicyclo[3.2.1]octane-2,5'-[1,3]oxazolidine]-8-carboxylate (±)-5b and resolution to give **5b** and **ent-5b**. Epoxide (±)-**10** (0.4 g, 1.76 mmol) was dissolved in EtOH (7 ml) and then *iso*-propylamine (0.12 ml, 1.41 mmol) was added. The solution was heated to reflux temperature overnight. The reaction mixture was cooled to RT and concentrated under reduced pressure. The residue was purified by SCX cartridge eluting first with MeOH and then with 2.0 M NH₃ in MeOH to yield the amino alcohol (±)-**11b** as a colourless oil. It was then dissolved in DMSO (10 ml) and TFA (0.1 ml, 1.35 mmol) was added followed by IBX (1.03 g, 3.70 mmol). The reaction mixture was stirred at RT overnight. Then 3 ml of water were added and after 10 minutes stirring a white solid was filtered. The solid was washed with further EtOAc and then volatiles were concentrated under reduced pressure. The residue was purified by SCX cartridge eluting first with MeOH and then with 2.0 M NH₃ in MeOH. The ammonia fractions were concentrated, diluted with EtOAc (20 ml), washed with water (20 ml), dried over Na₂SO₄ and concentrated. They were further purified by flash chromatography on silica gel eluting with 5% MeOH in DCM to yield the ketone as a colourless oil (210 mg, 60%); *v*_{max}/cm⁻¹ (CHCl₃): 3316, 2966, 1697, 1424, 1382, 1314, 1106, 1022, 765; ¹H NMR δ_H (ppm) (CDCl₃, 500 MHz): 4.56 (1 H, br s, NCHCH₂CO), 4.42-4.18 (3 H, m, NCHC and OCH₂CH₃), 3.24-3.17 (2 H, m, CCH₂NH and CHCH_{2ax}CO), 2.82-2.74 (1 H, m, J = 6.3 Hz, NHCH(CH₃)₂), 2.21-2.14 (2 H, m, CCH₂NH and CHCH_{2eq}CO), 1.97-1.91 (2 H, m, CHCH_{2exo}CH_{2exo}CH), 1.54-1.46 (2 H, m, CHCH_{2endo}CH_{2endo}CH), 1.28 (3 H, t, J = 7.1 Hz, OCH₂CH₃), 1.09 (3 H, d, J = 6.3 Hz, NHCH(CH₃)₂), 1.05 (3 H, d, J = 6.3 Hz, NHCH(CH₃)₂); ¹H NMR δ_H (ppm) (CDCl₃, 360 MHz, 56 °C): 4.55 (1 H, br s, NCHCH₂CO), 4.33 (1 H, br s, NCHC), 4.27-3.80 (4 H, m,

OCH₂CH₃, NH and OH), 3.27-3.17 (2 H, m, CCH₂NH and CHCH_{2ax}CO), 2.82-2.74 (1 H, m, J = 6.3 Hz, NHCH(CH₃)₂), 2.34 (1 H, d, J = 12.3 Hz, CCH₂NH), 2.15 (1 H, dd, J = 11.6 and 1.8 Hz, CHCH_{2eq}CO), 2.06-1.87 (2 H, m, CHCH_{2exo}CH_{2exo}CH), 1.58-1.44 (2 H, m, CHCH_{2endo}CH_{2endo}CH), 1.28 (3 H, t, J = 7.1 Hz, OCH₂CH₃), 1.54-1.08 (6 H, m, NHCH(CH₃)₂); ¹³C NMR δ_c (ppm) (CDCl₃, 91 MHz): 209.4 (C, C=O_{ketone}), 154.7 (C, C=O_{carbamate}), 77.8 (C, CCH₂NH), 61.4 (CH₂, OCH₂CH₃), 61.1 (CH, NCHC), 53.4 (CH, NCHCH₂CO), 49.9 (CH, NHCH(CH₃)₂), 47.2 (CH₂, CCH₂NH), 45.9 (CH₂, CHCH₂CO), 27.8 (CH₂, CHCH₂CH₂CH), 23.3 (CH₂, CHCH₂CH₂CH), 22.2 (CH₃, NHCH(CH₃)₂), 22.0 (CH₃, NHCH(CH₃)₂), 14.7 (CH₃, OCH₂CH₃); *m/z* (ES+) 285 ([M+H]⁺, 100%); *m/z* (ES+) found: [M+H]⁺, 285.1822. C₁₄H₂₅N₂O₄ requires: [M+H]⁺, 285.1814.

The above ketone (0.21 g, 0.74 mmol) was dissolved in DCM (10 ml); pyridine (0.75 ml, 7.4 mmol) was added and the mixture cooled to 0 °C. Triphosgene (241 mg, 0.81 mmol) was slowly added portionwise and the final mixture was stirred at RT for 7 h. It was then diluted with DCM (10 ml), washed with 0.1 M HCl (10 ml), H₂O (20 ml), brine (20 ml), dried over MgSO₄ and concentrated. The residue was purified by flash chromatography on silica gel eluting with 3% MeOH in DCM and, after evaporation of the volatiles, was triturated with Et₂O to yield (**±**)-**5b** as a colourless solid (180 mg, 78%); m.p.: 148.5-150.0 °C; ν_{max}/cm⁻¹ (CHCl₃): 2974, 2364, 1750, 1695, 1412, 1332, 1275, 1101, 1034, 930, 755; ¹H NMR δ_H (ppm) (DMSO-*d*₆, 360 MHz): 4.70-4.41 (2 H, br m, NCHCH₂CO and NCHC), 4.19-4.01 (2 H, m, OCH₂CH₃), 3.96-3.81 (2 H, m, CCH₂N and NCH(CH₃)₂), 3.23 (1 H, d, J = 9.3 Hz, CCH₂N), 2.90 (1 H, dd, J = 15.3 Hz and 4.0, CHCH_{2ax}CO), 2.44 (1 H, dd, J = 15.3 Hz and 1.8, CHCH_{2eq}CO), 2.15-1.95 (2 H, m, CHCH_{2exo}CH_{2exo}CH), 1.57-1.45 (1 H, m, CHCH_{2endo}CH_{2endo}CHCH₂), 1.40-1.28 (1 H, m, CHCH_{2endo}CH_{2endo}CHCH₂), 1.22 (3 H, t, J = 7.3 Hz, OCH₂CH₃), 1.16 (3 H, d, J = 6.7 Hz, NCH(CH₃)₂), 1.13 (3 H, d, J = 6.7 Hz, NCH(CH₃)₂); ¹³C NMR δ_c (ppm) (DMSO-*d*₆, 91 MHz): 201.9 (C, C=O_{ketone}), 154.1 (C, C=O_{carbamate} and C=O_{cyclic carbamate}), 82.1 (C, CCH₂N), 61.2 (CH₂, OCH₂CH₃), 59.5 (CH, NCHC), 53.6 (CH, NCHCH₂CO), 45.8 (CH₂, CHCH₂CO), 45.0 (CH, NCH(CH₃)₂), 40.8 (CH₂, CCH₂N), 27.6 (CH₂, CHCH₂CH₂CHCH₂), 23.2 (CH₂, CHCH₂CH₂CHCH₂), 19.8 (CH₃, NCH(CH₃)₂), 19.7 (CH₃, NCH(CH₃)₂), 14.8 (CH₃, OCH₂CH₃); *m/z* (ES+) 311 ([M+H]⁺, 100%); *m/z* (ES+) found: [M+H]⁺, 311.1600. C₁₅H₂₃N₂O₅ requires: [M+H]⁺, 311.1607.

The racemic compound was then separated into single enantiomers by SFC (Chiralpak AD-H column, 220 nm, 80/20 CO₂/MeOH, 10 ml/min, 35 °C, Outlet P=100 bar):

5b: enantiomer 1, Rt = 2.38 min; 50 mg, colourless solid, m.p. 147.4-148.1 °C; $[\alpha]_D^{20} +125.5$ (c 1, CHCl₃); >99% enantiomeric excess.

ent-5b: enantiomer 2, Rt = 3.16 min; 50 mg, colourless solid, m.p. 147.4-148.1 °C; $[\alpha]_D^{20} -125.6$ (c 1, CHCl₃); >99% enantiomeric excess.

(1S*,2S*,5R*)-Ethyl 3'-tert-butyl-2',3-dioxo-8H-spiro[8-azabicyclo[3.2.1]octane-2,5'-[1,3]oxazolidine]-8-carboxylate (±)-5c and resolution to give **ent-5c**. Epoxide (**±**)-**10** (0.6 g, 2.64 mmol) was dissolved in EtOH (5 ml) and then *t*-butylamine (0.28 ml, 2.64 mmol) was added. The solution was heated to 70 °C overnight in a sealed tube. The reaction mixture was cooled to RT and concentrated under reduced pressure. The residue was purified by SCX cartridge eluting first with MeOH and then with 2.0 M NH₃ in MeOH to yield (**±**)-**11c** as a colourless oil (0.79 g, quantitative yield); $\nu_{\max}/\text{cm}^{-1}$ (CHCl₃): 3374, 2964, 1688, 1434, 1314, 1109, 764; ¹H NMR δ_{H} (ppm) (CDCl₃, 500 MHz): 4.38-4.26 (1 H, br s, NCHCH₂CHOH), 4.24-3.98 (3 H, m, NCHC and OCH₂CH₃), 3.88-3.75 (1 H, m, CHCH₂CH_{ax}OH), 2.78-2.68 (2 H, m, CCH₂NH), 1.99-1.84 (2 H, m, CHCH_{2exo}CH_{2exo}CH), 1.83-1.65 (2 H, m, CHCH₂CHOH), 1.65-1.49 (2 H, m, CHCH_{2endo}CH_{2endo}CH), 1.31-1.16 (3 H, m, OCH₂CH₃), 1.13-0.95 (9 H, m, NHC(CH₃)₃); ¹³C NMR δ_{C} (ppm) (CDCl₃, 91 MHz): 155.6 (C, C=O_{carbamate}), 73.8 (C, CCH₂NH), 69.5 (CH, CHCH₂CHOH), 61.5 (CH₂, OCH₂CH₃), 59.9 (CH, NCHC), 52.4 (CH, NCHCH₂CHOH), 50.8 (C, NHC(CH₃)₃), 49.1 (CH₂, CCH₂NH), 36.4 (CH₂, CHCH₂CHOH), 29.3 (CH₃, NHC(CH₃)₃), 27.8 (CH₂, CHCH₂CH₂CH), 25.1 (CH₂, CHCH₂CH₂CH), 15.1 (CH₃, OCH₂CH₃); *m/z* (ES+) 301 ([M+H]⁺, 100%); *m/z* (ES+) found: [M+H]⁺, 301.2125. C₁₅H₂₉N₂O₄ requires: [M+H]⁺, 301.2127.

Intermediate (**±**)-**11c** (0.69 g, 2.3 mmol) was dissolved in DMSO (30 ml) and TFA (0.2 ml, 2.53 mmol) was added followed by IBX (1.9 g, 6.9 mmol). The reaction mixture was stirred at RT overnight. Then 5 ml of water were added and after 10 minutes stirring a white solid was filtered. The solid was washed with further EtOAc and then volatiles were concentrated under reduced pressure. The residue was purified by SCX cartridge eluting first with MeOH and then with 2.0 M NH₃ in MeOH to yield the ketone as a yellow oil (0.6 g, 88%); $\nu_{\max}/\text{cm}^{-1}$ (CHCl₃): 3327, 2964, 1694, 1425, 1313, 1108, 1022, 748; ¹H NMR δ_{H} (ppm) (CDCl₃, 500 MHz): 4.56 (1 H, br s, NCHCH₂CO), 4.37 (1 H, br s, NCHC), 4.24-4.20 (2 H, m, OCH₂CH₃), 3.27-3.02 (2 H, m, CHCH_{2ax}CO and CCH₂NH), 2.30-2.19 (1 H, br d, CCH₂NH), 2.16 (1 H, dd, *J* = 20.0 and 3.6 Hz, CHCH_{2eq}CO), 1.98-1.96 (2 H, m, CHCH_{2exo}CH_{2exo}CH), 1.51-1.49 (2 H, m, CHCH_{2endo}CH_{2endo}CH), 1.29 (3 H, m, *J* = 7.1 Hz, OCH₂CH₃), 1.1 (9 H, s, NHC(CH₃)₃),

^{13}C NMR δ_{c} (ppm) (CDCl_3 , 91 MHz): 210.0 (C, $\text{C}=\text{O}_{\text{ketone}}$), 155.1 (C, $\text{C}=\text{O}_{\text{carbamate}}$), 77.4 (C, CCH_2NH from HMBC), 61.7 (CH_2 , OCH_2CH_3 and CH, NCHC), 53.7 (CH, NCHCH $_2$ CO), 51.1 (C, NHC(CH_3) $_3$), 46.3 (CH_2 , CHCH $_2$ CO), 43.7 (CH_2 , CCH $_2$ NH), 29.4 (CH_3 , NHC(CH_3) $_3$), 28.3 (CH_2 , CHCH $_2$ CH $_2$ CHCH $_2$), 23.0 (CH_2 , CHCH $_2$ CH $_2$ CHCH $_2$), 15.1 (CH_3 , OCH_2CH_3); m/z (ES+) 299 ([M+H] $^+$, 100%); m/z (ES+) found: [M+H] $^+$, 299.1966. $\text{C}_{15}\text{H}_{27}\text{N}_2\text{O}_4$ requires: [M+H] $^+$, 299.1971.

The ketone (0.6 g, 2.02 mmol) was dissolved in DCM (20 ml); pyridine (2 ml, 0.02 mol) was added and the mixture cooled to 0 °C. Triphosgene (660 mg, 2.2 mmol) was subsequently added portionwise and the final mixture was stirred at RT for 2 h. It was then diluted with DCM (10 ml), washed with 0.1 M HCl, H_2O (20 ml), brine (20 ml), dried over MgSO_4 and concentrated. The residue was purified by flash chromatography on silica gel eluting with 50% EtOAc in *n*-hexane to yield ($\pm$)-**5c** as a colourless oil (250 mg, 38%); $\nu_{\text{max}}/\text{cm}^{-1}$ (CHCl_3): 2978, 1760, 1704, 1408, 750; ^1H NMR δ_{H} (ppm) (CDCl_3 , 360 MHz, 56 °C): 4.70-4.52 (2 H, br m, NCHCH $_2$ CO and NCHC), 4.26-4.17 (3 H, m, OCH_2CH_3 and CCH $_2$ N), 3.12 (1 H, br dd, $J = 14.7$ and 1.9 Hz, CHCH $_{2\text{ax}}$ CO), 3.05 (1 H, d, $J = 9.1$ Hz, CCH $_2$ N), 2.41 (1 H, dd, $J = 14.7$ and 1.9 Hz, CHCH $_{2\text{eq}}$ CO), 2.10-2.00 (2 H, m, CHCH $_{2\text{exo}}$ CH $_{2\text{exo}}$ CH), 1.68-1.52 (1 H, m, CHCH $_{2\text{endo}}$ CH $_{2\text{endo}}$ CHCH $_2$), 1.40 (9 H, s, NC(CH_3) $_3$), 1.35-1.26 (4 H, m, CHCH $_{2\text{endo}}$ CH $_{2\text{endo}}$ CHCH $_2$ and OCH_2CH_3); ^{13}C NMR δ_{c} (ppm) (CDCl_3 , 91 MHz): 201.4 (C, $\text{C}=\text{O}_{\text{ketone}}$), 154.8 (C, $\text{C}=\text{O}_{\text{carbamate}}$), 154.0 (C, $\text{C}=\text{O}_{\text{carbamate}}$), 81.3 (C, CCH $_2$ N), 62.1 (CH_2 , OCH_2CH_3), 60.1 (CH, NCHC), 54.3 (C, NC(CH_3) $_3$), 54.0 (CH, NCHCH $_2$ CO), 46.7 (CH_2 , CCH $_2$ N), 44.4 (CH_2 , CHCH $_2$ CO), 28.0 (CH_2 , CHCH $_2$ CH $_2$ CHCH $_2$), 27.8 (CH_3 , NC(CH_3) $_3$), 23.8 (CH_2 , CHCH $_2$ CH $_2$ CHCH $_2$), 14.9 (CH_3 , OCH_2CH_3); m/z (ES+) 325 ([M+H] $^+$, 100%); m/z (ES+) found: [M+H] $^+$, 325.1764. $\text{C}_{16}\text{H}_{25}\text{N}_2\text{O}_5$ requires: [M+H] $^+$, 325.1763.

The racemic compound was then separated into single enantiomers by SFC (Chiralpak IA column, 220 nm, 87/13 CO_2 /*iso*-propanol, 10 ml/min, 35 °C, Outlet P=100 bar).

ent-5c: enantiomer 1, $R_t = 3.45$ min; colourless oil, $[\alpha]_{\text{D}}^{20} -35.3$ (c 1, CHCl_3); >99% ee.

(1R*,2R*,5S*)-ethyl 3'-benzyl-2',3-dioxo-8H-spiro[8-azabicyclo[3.2.1]octane-2,5'-[1,3]oxazolidine]-8-carboxylate ($\pm$)-5d and resolution to give **5d** and **ent-5d**.

Epoxide ($\pm$)-**10** (0.5 g, 2.2 mmol) was dissolved in EtOH (5 ml) and benzylamine (0.24 ml, 2.2 mmol) was added. The solution was heated to reflux temperature overnight. The reaction mixture was cooled to RT and concentrated under reduced pressure. The residue was purified by SCX cartridge eluting first with MeOH and then with 2.0 M NH_3 in MeOH to yield ($\pm$)-

11d as a colourless oil (0.73 g, quantitative yield); $\nu_{\max}/\text{cm}^{-1}$ (CHCl_3): 3405, 1690, 1113; ^1H NMR δ_{H} (ppm) (CDCl_3 , 500 MHz): 7.34-7.25 (5 H, m, CH_{Ar}), 4.31 (1 H, br s, $\text{NCHCH}_2\text{CHOH}$), 4.19-4.09 (3 H, m, OCH_2CH_3 and NCHC), 3.85-3.77 (3 H, m, NCH_2Ar and CHCH_2CHOH), 3.19 (3 H, br s, OH , OH , NH), 2.82 (1 H, d, $J = 12.1$ Hz, CCH_2NH), 2.78 (1 H, d, $J = 12.1$ Hz, CCH_2NH), 1.92-1.69 (4 H, m, $\text{CHCH}_{2\text{exo}}\text{CH}_{2\text{exo}}\text{CH}$ and CHCH_2CHOH), 1.57-1.49 (2 H, m, $\text{CHCH}_{2\text{endo}}\text{CH}_{2\text{endo}}\text{CH}$), 1.26 (3 H, t, $J = 7.1$ Hz, OCH_2CH_3); ^{13}C NMR δ_{C} (ppm) (CDCl_3 , 91 MHz): 155.6 (C, $\text{C}=\text{O}_{\text{carbamate}}$), 139.6 (C, C_{Ar}), 129.0 (CH, CH_{Ar}), 128.5 (CH, CH_{Ar}), 127.8 (CH, CH_{Ar}), 74.6 (C, CCH_2NH), 69.4 (CH, CHCH_2CHOH), 61.6 (CH_2 , OCH_2CH_3), 59.9 (CH, NCHC), 55.5 (CH_2 , CCH_2NH), 54.6 (CH_2 , NHCH_2Ar), 52.5 (CH, $\text{NCHCH}_2\text{CHOH}$), 36.5 (CH_2 , CHCH_2CHOH), 27.7 (CH_2 , $\text{CHCH}_2\text{CH}_2\text{CH}$), 25.0 (CH_2 , $\text{CHCH}_2\text{CH}_2\text{CH}$), 15.1 (CH_3 , OCH_2CH_3); m/z (ES+) 335 ($[\text{M}+\text{H}]^+$, 100%); m/z (ES+) found: $[\text{M}+\text{H}]^+$, 335.1974. $\text{C}_{18}\text{H}_{27}\text{N}_2\text{O}_4$ requires: $[\text{M}+\text{H}]^+$, 335.1971.

Amino alcohol ($\pm$)-**11d** (0.73 g, 2.2 mmol) was dissolved in DMSO (20 ml) and TFA (0.18 ml, 2.3 mmol) was added followed by IBX (1.85 g, 6.6 mmol). The reaction mixture was stirred at RT overnight. Then 3 ml of water were added and after 10 minutes of stirring a white solid was filtered. The filtrate was diluted with EtOAc (30 ml), washed with water, dried over Na_2SO_4 and concentrated. It was then purified by SCX cartridge eluting first with MeOH and then with 2.0 M NH_3 in MeOH. The ammonia fractions were further purified by flash chromatography on silica gel eluting with 3% MeOH in DCM to yield the ketone as a yellow oil (0.44 g, 63%); $\nu_{\max}/\text{cm}^{-1}$ (CHCl_3): 3404, 2978, 1681, 1422, 1314, 1105, 747; ^1H NMR δ_{H} (ppm) (CDCl_3 , 500 MHz): 7.34-7.25 (5 H, m, CH_{Ar}), 4.56 (1 H, br s, NCHCH_2CO), 4.45-4.18 (3 H, m, OCH_2CH_3 and NCHC), 3.84 (1 H, d, $J = 13.4$ Hz, NCH_2Ar), 3.80 (1 H, d, $J = 13.4$ Hz, NCH_2Ar), 3.25 (1 H, d, $J = 12.2$ Hz, CCH_2N), 3.17 (1 H, br d, $\text{CHCH}_{2\text{ax}}\text{CO}$), 2.28 (1 H, d, $J = 12.2$ Hz, CCH_2NH), 2.16 (1 H, dd, $J = 14.6$ and 1.7 Hz, $\text{CHCH}_{2\text{eq}}\text{CO}$), 1.97-1.89 (2 H, m, $\text{CHCH}_{2\text{exo}}\text{CH}_{2\text{exo}}\text{CH}$), 1.52-1.42 (2 H, m, $\text{CHCH}_{2\text{endo}}\text{CH}_{2\text{endo}}\text{CH}$), 1.30 (3 H, t, $J = 7.1$ Hz, OCH_2CH_3); ^{13}C NMR δ_{C} (ppm) (CDCl_3 , 91 MHz): 209.5 (C, $\text{C}=\text{O}_{\text{ketone}}$), 155.2 (C, $\text{C}=\text{O}_{\text{carbamate}}$), 140.0 (C, C_{Ar}), 128.9 (CH, CH_{Ar}), 128.4 (CH, CH_{Ar}), 127.6 (CH, CH_{Ar}), 77.7 (C, CCH_2NH), 61.8 (CH_2 , OCH_2CH_3), 61.4 (CH, NCHC), 54.6 (CH_2 , NCH_2Ar), 53.7 (CH, NCHCH_2CO), 50.3 (CH_2 , CCH_2NH), 46.2 (CH_2 , CHCH_2CO), 28.3 (CH_2 , $\text{CHCH}_2\text{CH}_2\text{CHCH}_2$), 23.4 (CH_2 , $\text{CHCH}_2\text{CH}_2\text{CHCH}_2$), 15.1 (CH_3 , OCH_2CH_3); m/z (ES+) 333 ($[\text{M}+\text{H}]^+$, 100%); m/z (ES+) found: $[\text{M}+\text{H}]^+$, 333.1820. $\text{C}_{18}\text{H}_{25}\text{N}_2\text{O}_4$ requires: $[\text{M}+\text{H}]^+$, 333.1814.

The ketone (0.44 g, 1.35 mmol) was dissolved in DCM (20 ml); pyridine (1.3 ml, 0.01 mol) was added and the mixture cooled to 0 °C. Triphosgene (432 mg, 1.46 mmol) was subsequently added portionwise and the final mixture was stirred at RT for 7 h. It was then diluted with DCM (10 ml), washed with 0.1 M HCl (10 ml), H₂O (20 ml), brine (20 ml), dried over MgSO₄ and concentrated. The residue was purified by flash chromatography on silica gel eluting with 50% EtOAc in *n*-hexane to yield 330 mg (70%) of (**±**)-**11d** as a pale yellow solid; m.p.: 123.0-123.9 °C; $\nu_{\max}$ /cm⁻¹ (CHCl₃): 2968, 1760, 1698, 1418, 1332, 1106; ¹H NMR δ_{H} (ppm) (CDCl₃, 500 MHz): 7.40-7.26 (5 H, m, CH_{Ar}), 4.65 (1 H, br s, NCHCH₂CO), 4.51-4.47 (2 H, m, NCH₂Ar and NCHC), 4.39 (1 H, d, J = 15.0 Hz, NCH₂Ar), 4.30-4.21 (2 H, m, OCH₂CH₃), 4.03 (1 H, d, J = 8.8 Hz, CCH₂N), 3.21-3.07 (1 H, br d, J = 14.8 Hz, CHCH_{2ax}CO), 2.86 (1 H, br d, J = 8.8 Hz, CCH₂N), 2.43 (1 H, d, J = 14.8 Hz, CHCH_{2eq}CO), 2.08-1.98 (2 H, m, CHCH_{2exo}CH_{2exo}CH), 1.53 (1 H, m, CH₂CHCH_{2endo}CH_{2endo}CH), 1.37-1.27 (3 H, m, OCH₂CH₃), 1.26-1.20 (1 H, m, CH₂CHCH_{2endo}CH_{2endo}CH); ¹³C NMR δ_{C} (ppm) (91 MHz, CDCl₃): 200.8 (C, C=O_{ketone}), 155.7 (C, C=O), 154.7 (C, C=O), 135.8 (C, C_{Ar}), 129.4 (CH, CH_{Ar}), 128.6 (CH, CH_{Ar}), 128.4 (CH, CH_{Ar}), 82.7 (C, CCH₂N), 62.3 (CH₂, OCH₂CH₃), 60.2 (CH, NCHC), 54.0 (CH, NCHCH₂CO), 48.8 (CH₂, NCH₂Ar), 46.8 (CH₂, CHCH₂CO), 45.3 (CH₂, NCH₂C), 27.9 (CH₂, CH₂CHCH₂CH₂CH), 23.9 (CH₂, CH₂CHCH₂CH₂CH), 15.0 (CH₃, OCH₂CH₃); *m/z* (ES⁺) 359 ([M+H]⁺, 100%); *m/z* (ES⁺) found: [M+H]⁺, 359.1619. C₁₉H₂₃N₂O₅ requires: [M+H]⁺, 359.1607.

The racemic compound was then separated into single enantiomers by SFC (Chiralpak AS-H column, 220 nm, 85/15 CO₂/MeOH, 10 ml/min, 40 °C, Outlet P=100 bar):

ent-11d: enantiomer 1; Rt = 3.60 min; colourless solid, 80 mg, m.p. 82.5-88.3 °C; [α]_D²⁰ -5.0 (c 1, CHCl₃); >99% ee.

11d enantiomer 2, Rt = 4.19 min, colourless solid, 80 mg, m.p. 88.5-90.7 °C [α]_D²⁰ +4.6 (c 1, CHCl₃); >99% ee.

(1R,2R,5S)-(-)-ethyl 2',3-dioxo-3'-[(1S)-1-phenylethyl]-8H-spiro[8-azabicyclo[3.2.1]octane-2,5'-[1,3]oxazolidine]-8-carboxylate **5e** and (1S,2S,5R)-(-)-ethyl 2',3-dioxo-3'-[(1S)-1-phenylethyl]-8H-spiro[8-azabicyclo[3.2.1]octane-2,5'-[1,3]oxazolidine]-8-carboxylate **5f**.

Epoxide (**±**)-**10** (0.5 g, 2.2 mmol) was dissolved in EtOH (5 ml) and then (S)-(-)- α -methyl benzylamine (0.24 ml, 2.2 mmol) was added. The solution was heated to 70 °C overnight in a

sealed tube. The reaction mixture was cooled to RT and concentrated under reduced pressure. The residue was purified by SCX cartridge eluting first with MeOH and then with 2.0 M NH₃ in MeOH to yield a mixture of **11e** and **11f** as a colourless oil. The crude reaction was used immediately in the following step. It was dissolved in DMSO (20 ml) and TFA (0.18 ml, 2.3 mmol) was added followed by IBX (1.85 g, 6.6 mmol). The reaction mixture was stirred at RT overnight. Then 5 ml of water were added; after 10 minutes of stirring a white solid was filtered. The filtrate was diluted with EtOAc (30 ml), washed with water, dried over MgSO₄ and concentrated. The residue was purified by SCX cartridge eluting first with MeOH and then with 2.0 M NH₃ in MeOH. The ammonia fractions were further purified by flash chromatography on silica gel eluting with 5% MeOH in DCM to yield the ketone (0.4 g, 53%) as a yellow oil and as a 0.8:1 mixture of diastereoisomers A:B; $\nu_{\max}/\text{cm}^{-1}$ (CHCl₃): 3328, 2977, 1699, 1432, 1186, 1112, 762; ¹H NMR δ_{H} (ppm) (CDCl₃, 500 MHz): 7.36-2.24 (10 H, m, CH_{Ar} A+B), 5.54 (2 H, br s, NCHCH₂CO A+B), 4.38-4.10 (6 H, m, NCHC and OCH₂CH₃ A+B), 3.88-3.77 (1 H, q, J = 6.6 Hz, NCHCH₃ B), 3.75-3.64 (1 H, q, J = 6.6 Hz, NCHCH₃ A), 3.25-3.07 (3 H, m, CHCH₂CO A+B and CCH₂NH B), 3.02 (1 H, d, J = 12.2 Hz, CCH₂NH A), 2.25-2.02 (4 H, m, CHCH₂CO A+B and CCH₂NH A+B), 2.00-1.77 (4 H, m, CHCH₂_{exo}CH₂_{exo}CH A+B), 1.52-1.41 (2 H, m, CHCH₂_{endo}CH₂_{endo}CHCH₂ A+B), 1.40-1.19 (14 H, m, NCHCH₃ A+B, OCH₂CH₃ A+B and CHCH₂_{endo}CH₂_{endo}CHCH₂ A+B); ¹³C NMR δ_{C} (ppm) (CDCl₃, 91 MHz): 209.5 (C, C=O_{ketone} A+B), 155.3 (C, C=O_{carbamate} A+B), 145.4 (C, C_{Ar} A/B), 145.0 (C, C_{Ar} A/B), 129.1 (CH, CH_{Ar} A/B), 129.0 (CH, CH_{Ar} A/B), 127.6 (CH, CH_{Ar} A/B), 127.5 (CH, CH_{Ar} A/B), 127.2 (CH, CH_{Ar} A/B), 126.5 (CH, CH_{Ar} A/B), 78.5 (C, CCH₂NH A+B), 61.8 (CH₂, OCH₂CH₃ A+B), 61.2 (CH, NCHC A+B), 59.5 (CH, NCHCH₃ A), 58.6 (CH, NCHCH₃ B), 53.8 (CH, NCHCH₂CO A/B), 53.6 (CH, NCHCH₂CO A/B), 49.3 (CH₂, CCH₂NH A), 48.4 (CH₂, CCH₂NH B), 46.2 (CH₂, CHCH₂CO A+B), 28.2 (CH₂, CHCH₂CH₂CHCH₂ A+B), 24.9 (CH₃, NCHCH₃ A/B), 24.7 (CH₃, NCHCH₃ A/B), 23.4 (CH₂, CHCH₂CH₂CHCH₂ A+B), 15.1 (CH₃, OCH₂CH₃ A/B), 15.0 (CH₃, OCH₂CH₃ A/B); *m/z* (ES+) 347 ([M+H]⁺, 100%); *m/z* (ES+) found: [M+H]⁺, 347.1976. C₁₉H₂₇N₂O₄ requires: [M+H]⁺, 347.1971.

The mixture of ketone diastereomers (0.4 g, 1.16 mmol) was dissolved in DCM (20 ml); pyridine (1.2 ml, 0.016 mol) was added and the mixture cooled to 0 °C. Triphosgene (0.38 g, 1.27 mmol) was subsequently added portionwise and the final mixture was stirred at RT for 4 hours. It was then diluted with DCM (10 ml), washed with 0.1 M HCl (10 ml), H₂O (20 ml), brine (20 ml), dried over MgSO₄ and concentrated. The residue was purified by flash

chromatography on silica gel eluting with 40% EtOAc in *n*-hexane to yield the two single diastereoisomers **5e** and **5f** as pale yellow solids.

Less polar **5e**, pale yellow solid (100 mg, 23% of the overall yield); m.p. 91.8-92.4 °C; $[\alpha]_D^{20}$ -120.0 (c 1, CHCl₃); Rt = 5.47 min; $\nu_{\max}/\text{cm}^{-1}$ (CHCl₃) 2981, 1769, 1731, 1713, 1417, 1334, 1220, 1113, 1022, 702; ¹H NMR δ_H (ppm) (CDCl₃, 500 MHz): 7.41-7.32 (5 H, m, CH_{Ar}), 5.22-5.17 (1 H, q, J = 7.1 Hz, NCHCH₃), 4.63 (1 H, br s, NCHCH₂CO), 4.58-4.19 (3 H, m, NCHC and OCH₂CH₃), 4.09 (1 H, br d, J = 8.5 Hz, CCH₂N), 3.17-3.05 (1 H, m, CHCH_{2ax}CO), 2.56 (1 H, br d, J = 8.5 Hz, CCH₂N), 2.42 (1 H, d, J = 14.9 Hz, CHCH_{2eq}CO), 2.04-1.98 (2 H, m, CHCH_{2exo}CH_{2exo}CH), 1.66-1.53 (4 H, m, NCHCH₃ and CHCH_{2endo}CH_{2endo}CHCH₂), 1.32-1.27 (3 H, m, OCH₂CH₃), 1.16-1.14 (1 H, m, CHCH_{2endo}CH_{2endo}CHCH₂); ¹H NMR δ_H (ppm) (CDCl₃, 360 MHz, 55 °C): 7.40-7.13 (5 H, m, CH_{Ar}), 5.21-5.15 (1 H, q, J = 7.1 Hz, NCHCH₃), 4.67 (1 H, br s, NCHCH₂CO), 4.46-4.15 (3 H, m, NCHC and OCH₂CH₃), 4.09 (1 H, d, J = 9.0 Hz, CCH₂N), 3.13 (1 H, br d, J = 15.0 Hz, CHCH_{2ax}CO), 2.56 (1 H, d, J = 9.0 Hz, CCH₂N), 2.39 (1 H, d, J = 15.0 Hz, CHCH_{2eq}CO), 2.14-1.88 (2 H, m, CHCH_{2exo}CH_{2exo}CH), 1.61-1.48 (4 H, m, NCHCH₃ and CHCH_{2endo}CH_{2endo}CHCH₂), 1.32-1.27 (3 H, t, J = 7.1 Hz, OCH₂CH₃), 1.18-1.12 (1 H, m, CHCH_{2endo}CH_{2endo}CHCH₂); ¹³C NMR δ_C (ppm) (CDCl₃, 91 MHz): 201.0 (C, C=O_{ketone}), 155.0 (C, C=O), 154.8 (C, C=O), 139.7 (C, C_{Ar}), 129.3 (CH, CH_{Ar}), 128.5 (CH, CH_{Ar}), 127.3 (CH, CH_{Ar}), 82.8 (C, CCH₂N), 62.2 (CH₂, OCH₂CH₃), 60.1 (CH, NCHC), 54.0 (CH, NCHCH₂CO), 52.0 (CH, NCHCH₃), 46.7 (CH₂, CHCH₂CO), 41.4 (CH₂, CCH₂N), 27.9 (CH₂, CHCH₂CH₂CHC), 23.8 (CH₂, CHCH₂CH₂CHC), 16.5 (CH₃, NCHCH₃), 14.9 (CH₃, OCH₂CH₃); *m/z* (ES+) 373 ([M+H]⁺, 100%); *m/z* (ES+) found: [M+H]⁺, 373.1772. C₂₀H₂₅N₂O₅ requires: [M+H]⁺, 373.1763. Structure and absolute configuration confirmed by X-ray of a sample obtained by crystallisation from ether.

More polar diastereoisomer **5f**, pale yellow solid (135 mg, 31% of the overall yield); m.p. 125.0-126.2 °C; $[\alpha]_D^{20}$ -67.0 (c 1, CHCl₃); Rt = 5.62 min; $\nu_{\max}/\text{cm}^{-1}$ (CHCl₃): 2980, 1728, 1752, 1700, 1420, 1110, 1022, 752, 701; ¹H NMR δ_H (ppm) (CDCl₃, 500 MHz): 7.41-7.28 (5 H, m, CH_{Ar}), 5.21-5.13 (1 H, q, J = 7.1 Hz, NCHCH₃), 4.77-4.44 (2 H, m, NCHCH₂CO and NCHC), 4.35-4.14 (2 H, m, OCH₂CH₃), 3.81 (1 H, br d, J = 9.1 Hz, CCH₂N), 3.20-3.01 (1 H, m, CHCH_{2eq}CO), 3.00-2.85 (1 H, m, CCH₂N), 2.39 (1 H, d, J = 15.7 Hz, CHCH_{2ax}CO), 2.17-1.94 (2 H, m, CHCH_{2exo}CH_{2exo}CH), 1.67-1.49 (4 H, m, NCHCH₃ and CHCH_{2endo}CH_{2endo}CHCH₂), 1.39-1.15 (4 H, m, OCH₂CH₃ and CHCH_{2endo}CH_{2endo}CHCH₂); ¹H NMR δ_H (ppm) (CDCl₃, 360 MHz, 56 °C): 7.38-7.27 (5 H, m, CH_{Ar}), 5.17-5.11 (1 H, q, J =

7.1 Hz, NCHCH_3), 4.62-4.50 (2 H, m, NCHCH_2CO and NCHC), 4.26-4.16 (2 H, m, OCH_2CH_3), 3.81 (1 H, d, $J = 8.9$ Hz, CCH_2N), 3.11 (1 H, br d, $J = 14.7$ Hz, $\text{CHCH}_{2\text{ax}}\text{CO}$), 2.90 (1 H, d, $J = 8.9$ Hz, CCH_2N), 2.36 (1 H, d, $J = 14.7$ Hz, $\text{CHCH}_{2\text{eq}}\text{CO}$), 2.10-1.96 (2 H, m, $\text{CHCH}_{2\text{exo}}\text{CH}_{2\text{exo}}\text{CH}$), 1.61-1.52 (4 H, m, NCHCH_3 and $\text{CHCH}_{2\text{endo}}\text{CH}_{2\text{endo}}\text{CHCH}_2$), 1.34-1.19 (4 H, m, OCH_2CH_3 and $\text{CHCH}_{2\text{endo}}\text{CH}_{2\text{endo}}\text{CHCH}_2$); ^{13}C NMR δ_{c} (ppm) (CDCl_3 , 91 MHz): 200.8 (C, $\text{C}=\text{O}_{\text{ketone}}$), 155.1 (C, $\text{C}=\text{O}$), 154.7 (C, $\text{C}=\text{O}$), 139.3 (C, C_{Ar}), 129.1 (CH, CH_{Ar}), 128.4 (CH, CH_{Ar}), 127.3 (CH, CH_{Ar}), 82.8 (C, CCH_2N), 62.3 (CH_2 , OCH_2CH_3), 60.3 (CH, NCHC), 54.0 (CH, NCHCH_2CO), 52.2 (CH, NCHCH_3), 46.7 (CH_2 , CHCH_2CO), 42.1 (CH_2 , CCH_2N), 27.9 (CH_2 , $\text{CHCH}_2\text{CH}_2\text{CHCH}_2$), 23.9 (CH_2 , $\text{CHCH}_2\text{CH}_2\text{CHCH}_2$), 17.3 (CH_3 , NCHCH_3), 15.0 (CH_3 , OCH_2CH_3); m/z (ES+) 373 ($[\text{M}+\text{H}]^+$, 100%); m/z (ES+) found: $[\text{M}+\text{H}]^+$, 373.1766. $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_5$ requires: $[\text{M}+\text{H}]^+$, 373.1763.

(1R*,2R*,5S*)-Ethyl 2',3-dioxo-3'-phenyl-8H-spiro[8-azabicyclo[3.2.1]octane-2,5'-[1,3]oxazolidine]-8-carboxylate ($\pm$)-5g and resolution to give **5g** and **ent-5g**. Epoxide ($\pm$)-**10** (0.5 g, 2.2 mmol) was dissolved in EtOH (5 ml) and aniline (0.2 ml, 2.2 mmol) was added. The solution was heated to 70 °C overnight in a sealed tube. The reaction mixture was then cooled to RT and concentrated under reduced pressure. The residue was purified by SCX cartridge eluting first with MeOH and then with 2.0 M NH_3 in MeOH to yield ($\pm$)-**11g** as a colourless oil (0.7 g, quantitative yield); $\nu_{\text{max}}/\text{cm}^{-1}$ (CHCl_3): 3370, 2978, 1670, 1603, 1438, 1314, 1115; ^1H NMR δ_{H} (ppm) (CDCl_3 , 500 MHz): 7.19 (2 H, t, $J = 7.9$ Hz, $\text{CH}_{\text{Ar-meta}}$), 6.76 (1 H, t, $J = 7.3$ Hz, $\text{CH}_{\text{Ar-para}}$), 6.71 (2 H, d, $J = 7.9$, $\text{CH}_{\text{Ar-orto}}$), 4.45 (1 H, br d, NCHC), 4.36 (1 H, br s, $\text{NCHCH}_2\text{CHOH}$), 4.20-4.13 (2 H, m, OCH_2CH_3), 3.73-3.70 (1 H, dd, $J = 11.4$ and 6.0 Hz, $\text{CHCH}_2\text{CH}_{\text{ax}}\text{OH}$), 3.49 (1 H, d, $J = 12.8$ Hz, CCH_2NH), 3.20 (1 H, d, $J = 12.8$ Hz, CCH_2NH), 1.97-1.89 (3 H, m, $\text{CHCH}_{2\text{exo}}\text{CH}_{2\text{exo}}\text{CH}$ and CHCH_2CHOH), 1.83-1.65 (2 H, m, CHCH_2CHOH and $\text{CHCH}_{2\text{endo}}\text{CH}_{2\text{endo}}\text{CH}$), 1.65-1.49 (1 H, m, $\text{CHCH}_{2\text{endo}}\text{CH}_{2\text{endo}}\text{CH}$), 1.27 (3 H, t, $J = 7.1$ Hz, OCH_2CH_3); ^{13}C NMR δ_{c} (ppm) (CDCl_3 , 91 MHz): 155.5 (C, $\text{C}=\text{O}_{\text{carbamate}}$), 148.7 (C, C_{Ar}), 129.7 (CH, $\text{CH}_{\text{Ar-meta}}$), 118.9 (CH, $\text{CH}_{\text{Ar-para}}$), 114.4 (CH, $\text{CH}_{\text{Ar-orto}}$), 75.3 (C, CCH_2NH), 67.5 (CH, CHCH_2CHOH), 61.5 (CH_2 , OCH_2CH_3), 58.8 (CH, NCHC), 52.7 (CH, $\text{NCHCH}_2\text{CHOH}$), 48.0 (CH_2 , CCH_2NH), 37.2 (CH_2 , CHCH_2CHOH), 27.3 (CH_2 , $\text{CHCH}_2\text{CH}_2\text{CHCH}_2$), 24.7 (CH_2 , $\text{CHCH}_2\text{CH}_2\text{CHCH}_2$), 14.7 (CH_3 , OCH_2CH_3); m/z (ES+) 321 ($[\text{M}+\text{H}]^+$, 100%); m/z (ES+) found: $[\text{M}+\text{H}]^+$, 321.1824. $\text{C}_{17}\text{H}_{25}\text{N}_2\text{O}_4$ requires: $[\text{M}+\text{H}]^+$, 321.1814.

COCl₂ (0.21 ml, 2.42 mmol) in DCM (17 ml) was cooled to -60 °C; DMSO (0.34 ml, 4.84 mmol) in DCM (1 ml) was added at -60 °C and the mixture stirred for 10 minutes. Then intermediate (**±**)-**11g** (0.7 g, 2.2 mmol) in DCM (2 ml) was added over 5 minutes at -60 °C. After 15 minutes stirring at this temperature, Et₃N (1.5 ml, 0.011 mol) was added. The cooling bath was removed and slowly warmed to RT. Then H₂O (3 ml) was added and the mixture stirred at RT for 10 minutes. The two phases were then separated; the organic layer was dried over Na₂SO₄ and concentrated. Purification by flash chromatography on silica gel eluting with 3% MeOH in DCM yielded a yellow oil that was further purified by SCX cartridge eluting first with MeOH and then with 2.0 M NH₃ in MeOH. The ketone was obtained as a pale yellow oil, (550 mg, 79%); $\nu_{\max}/\text{cm}^{-1}$ (CHCl₃): 3381, 2979, 1684, 1603, 1438, 1112, 748; ¹H NMR δ_{H} (ppm) (CDCl₃, 500 MHz): 7.20 (2 H, t, J = 7.6 Hz, CH_{Ar-meta}), 6.78 (1 H, t, J = 7.3 Hz, CH_{Ar-para}), 6.73 (2 H, d, J = 7.9, CH_{Ar-orto}), 4.63-4.56 (2 H, br m, NCHCH₂CO and NCHC), 4.26-4.20 (2 H, m, OCH₂CH₃), 4.01 (1 H, br s, NH), 3.70 (1 H, br s, OH), 3.58 (1 H, d, J = 13.4 Hz, CCH₂NH), 3.24-3.17 (2 H, m, CCH₂NH and CHCH_{2ax}CO), 2.25 (1 H, dd, J = 14.7 and 2.0 Hz, CHCH_{2eq}CO), 2.04-2.01 (2 H, m, CHCH_{2exo}CH_{2exo}CH), 1.63-1.59 (2 H, m, CHCH_{2endo}CH_{2endo}CH), 1.30 (3 H, t, J = 7.1 Hz, OCH₂CH₃); ¹³C NMR δ_{C} (ppm) (CDCl₃, 91 MHz): 208.1 (C, C=O_{ketone}), 155.8 (C, C=O_{carbamate}), 148.8 (C, C_{Ar}), 129.7 (CH, CH_{Ar}), 119.0 (CH, CH_{Ar}), 114.5 (CH, CH_{Ar}), 79.7 (C, CCH₂NH), 62.2 (CH₂, OCH₂CH₃), 60.5 (CH, NCHC), 54.2 (CH, NCHCH₂CO), 46.3 and 46.2 (CH₂, CCH₂NH and CH₂, CHCH₂CO), 28.4 (CH₂, CHCH₂CH₂CH), 24.0 (CH₂, CHCH₂CH₂CH), 15.1 (CH₃, OCH₂CH₃); *m/z* (ES+) 319 ([M+H]⁺, 100%); *m/z* (ES+) found: [M+H]⁺, 319.1650. C₁₇H₂₃N₂O₄ requires: [M+H]⁺, 319.1658.

The amino alcohol (0.55 g, 1.73 mmol) was dissolved in DCM (10 ml); pyridine (1.76 ml, 0.02 mol) was added and the mixture cooled to 0 °C. Triphosgene (0.56 g, 1.90 mmol) was subsequently added portionwise and the final mixture was stirred at RT for 4 hours. It was then diluted with DCM (20 ml), washed with 0.1 M HCl (10 ml), H₂O (20 ml), brine (20 ml), dried over MgSO₄ and concentrated. The residue was purified by flash chromatography on silica gel eluting with 50% EtOAc in *n*-hexane to yield (**±**)-**5g** as a colourless solid (0.39 g, 66%); m.p.: 169.1-172.4 °C; $\nu_{\max}/\text{cm}^{-1}$ (CHCl₃): 2981, 1759, 1729, 1699, 1403, 1316, 1111, 757; ¹H NMR δ_{H} (ppm) (CDCl₃, 500 MHz): 7.56 (2 H, d, J = 8.1 Hz, CH_{Ar-orto}), 7.39 (2 H, t, J = 8.1 Hz, CH_{Ar-meta}), 7.17 (1 H, t, J = 7.4 Hz, CH_{Ar-para}), 4.90-4.60 (3 H, m, NCHCH₂CO, NCHC and CCH₂N), 4.31-4.20 (2 H, m, OCH₂CH₃), 3.48 (1 H, br d, J = 12.9 Hz, CCH₂N), 3.24-3.20 (1 H, m, CHCH_{2ax}CO), 2.51 (1 H, d, J = 20.5 Hz, CHCH_{2eq}CO), 2.14-2.01 (2 H, m,

CHCH₂exoCH₂exoCH), 1.68-1.56 (1 H, m, CHCH₂endoCH₂endoCHCH₂), 1.45-1.33 (4 H, m, CHCH₂endoCH₂endoCHCH₂ and OCH₂CH₃); ¹³C NMR δ_c (ppm) (CDCl₃, 91 MHz): 200.4 (C, C=O_{ketone}), 154.3 (C, C=O_{carbamate}), 151.7 (C, C=O_{cyclic carbamate}), 137.7 (C, C_{Ar}), 129.2 (CH, CH_{Ar-meta}), 124.6 (CH, CH_{Ar-para}), 118.3 (CH, CH_{Ar-orto}), 81.6 (C, CCH₂N), 62.0 (CH₂, OCH₂CH₃), 60.0 (CH, NCHC), 53.8 (CH, NCHCH₂CO), 46.4 (CH₂, CHCH₂CO), 46.0 (CH₂, CCH₂N), 27.6 (CH₂, CHCH₂CH₂CHCH₂), 25.1 (CH₂, CHCH₂CH₂CHCH₂), 14.6 (CH₃, OCH₂CH₃); *m/z* (ES+) 345 ([M+H]⁺, 100%); *m/z* (ES+) found: [M+H]⁺, 345.1442. C₁₈H₂₁N₂O₅ requires: [M+H]⁺, 345.1450.

The racemic compound was resolved by SFC (Chiralpak AS-H column, 220 nm, 85/15 CO₂/MeOH, 10 ml/min, 35 °C, Outlet P=100 bar):

ent-5g: enantiomer 1, Rt = 3.32 min; colourless solid, 70 mg, m.p. 162.2-163.4 °C; [α]_D²⁰ -53.5 (c 1, CHCl₃); 99% ee.

5g enantiomer 2, Rt = 4.23 min; colourless solid, 70 mg, m.p. 163.8-164.2 °C [α]_D²⁰ +46.5 (c 1, CHCl₃); 98% ee.

(1R*,2R*,3S*,5S*)-Ethyl 3-hydroxy-5'-oxodihydro-3'H,8-azaspiro[bicyclo[3.2.1]octane-2,2'-furan]-8-carboxylate (±)-12. Epoxy alcohol (±)-**10** (0.8 g, 3.5 mmol) was dissolved in DCM (30 ml) and cooled to -78 °C. Et₃N (2.45 ml, 18 mmol) was added followed by TMSOTf (1.6 ml, 8.8 mmol). After stirring at this temperature for 30 min, the reaction mixture was slowly warmed to -30 °C and stirred at this temperature for further 30 min. It was then quenched with a saturated solution of NH₄Cl (10 ml). The organic layer was washed with brine, dried and concentrated *under vacuum*. The crude trimethylsilyl ether, as a colourless oil, was used in the following step without further purification.

NaH (60% dispersed in mineral oil, 87 mg, 2.2 mmol) was suspended in THF (10 ml) and cooled to 0 °C. Diethyl malonate (0.33 ml, 2.2 mmol) in THF (1 ml) was added dropwise and the reaction mixture was stirred at 0 °C for 30 minutes. The silyl ether (540 mg, 1.8 mmol) in THF (2 ml) was added dropwise and then the mixture heated to reflux for 3 hours. The volatiles were evaporated under reduced pressure to give a mixture of diastereomers. This mixture (250 mg) was dissolved in DMSO (5 ml) and water added (0.5 ml) followed by NaCl (56 mg). The mixture was heated to 160 °C for 7 h. After this period of time the mixture was cooled to room temperature and partitioned between DCM and water. The organic layer was washed with brine, dried and concentrated. Purification by chromatography on silica gel eluting with a gradient from 50% to 100% ethyl acetate in cyclohexane afforded (±)-**12** as a

colourless oil (170 mg, 35% over two steps); $\nu_{\max}/\text{cm}^{-1}$ (film): 3440, 1772, 1684, 1437, 1336, 1385, 1217, 1111, 964, 772; ^1H NMR δ_{H} (ppm) (CDCl_3 , 400 MHz): 4.46-4.32 (1 H, br s, $\text{NCHCH}_2\text{CHOH}$), 4.27-4.02 (3 H, m, NCHC and OCH_2CH_3), 3.73 (1 H, dd, $J=11.24$ and 6.06 Hz, CHOH), 2.79-2.53 (2 H, m, CCH_2CH_2), 2.51-2.09 (2 H, m, CCH_2CH_2 and CHOH), 2.08-1.75 (5 H, m, $\text{CHCH}_{2\text{exo}}\text{CH}_{2\text{exo}}\text{CH}$, CCH_2CH_2 , and CHCH_2CHOH), 1.70-1.53 (2 H, m, $\text{CHCH}_{2\text{endo}}\text{CH}_{2\text{endo}}\text{CH}$), 1.32-1.16 (3 H, m, OCH_2CH_3); ^{13}C NMR δ_{C} (ppm) (CDCl_3 , 91 MHz): 176.4 (C, $\text{C}=\text{O}_{\text{lactone}}$), 154.2 (C, $\text{C}=\text{O}_{\text{carbamate}}$), 87.9 (C, CCH_2CH_2), 68.1 (CH, CHCH_2CHOH), 61.3 (CH_2 , OCH_2CH_3), 59.3 (CH, NCHC), 52.3 (CH, $\text{NCHCH}_2\text{CHOH}$), 37.6 (CH_2 , CHCH_2CHOH), 28.8 (CH_2 , CCH_2CH_2), 27.1 (CH_2 , $\text{CHCH}_2\text{CH}_2\text{CH}$), 26.5 (CH_2 , CCH_2CH_2), 24.9 (CH_2 , $\text{CHCH}_2\text{CH}_2\text{CH}$), 14.6 (CH_3 , OCH_2CH_3); m/z (ES+) 270 ($[\text{M}+\text{H}]^+$, 100%), m/z (ES+) found: $[\text{M}+\text{H}]^+$, 270.1337. $\text{C}_{13}\text{H}_{20}\text{NO}_5$ requires: $[\text{M}+\text{H}]^+$, 270.1341.

(1R*,2R*,5S*)-Ethyl 3,5'-dioxodihydro-3'H,8H-spiro[8-azabicyclo[3.2.1]octane-2,2'-3'furan]-8-carboxylate ($\pm$)-6, and resolution to give **6** and *ent*-**6**. Lactone ($\pm$)-**12** (170 mg, 0.63 mmol) was dissolved in DCM (5 ml). NMO (111 mg, 0.95 mmol) was added followed by TPAP (10 mg). The reaction mixture was stirred at RT for 3 h and then was filtered through a pad of CeliteTM. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel eluting with a gradient from 30 to 80% ethyl acetate in cyclohexane to yield ($\pm$)-**6** as a colorless solid (90 mg, 53%); m.p.: 111.5-112.5 °C; $\nu_{\max}/\text{cm}^{-1}$ (nujol): 1795, 1724, 1694, 1113, 1016, 956, 932, 769; ^1H NMR δ_{H} (ppm) (CDCl_3 , 400 MHz): 4.74-4.40 (2 H, m, NCHCH_2CO and NCHC), 4.35-4.14 (2 H, m, OCH_2CH_3), 3.23-2.98 (1 H, m, $\text{CHCH}_{2\text{ax}}\text{CO}$), 2.92-2.80 (1 H, m, CCH_2CH_2), 2.78-2.59 (2 H, m, CCH_2CH_2), 2.46 (1 H, d, $J = 16.0$ Hz, $\text{CHCH}_{2\text{eq}}\text{CO}$), 2.23-1.99 (2 H, m, $\text{CHCH}_{2\text{exo}}\text{CH}_{2\text{exo}}\text{CH}$), 1.86-1.71 (1 H, m, CCH_2CH_2), 1.67-1.57 (1 H, m, $\text{CHCH}_{2\text{endo}}\text{CH}_{2\text{endo}}\text{CHCH}_2$), 1.54-1.42 (1 H, m, $\text{CHCH}_{2\text{endo}}\text{CH}_{2\text{endo}}\text{CHCH}_2$), 1.31 (3 H, t, $J = 7.1$ Hz, OCH_2CH_3); ^{13}C NMR δ_{C} (ppm) (CDCl_3 , 100 MHz): 202.3 (C, $\text{C}=\text{O}_{\text{ketone}}$), 174.4 (C, $\text{C}=\text{O}_{\text{lactone}}$), 154.2 (C, $\text{C}=\text{O}_{\text{carbamate}}$), 88.8 (C, CCH_2CH_2), 61.8 (CH_2 , OCH_2CH_3), 60.4 (CH, NCHC), 53.5 (CH, NCHCH_2CO), 46.4 (CH_2 , CHCH_2CO), 28.5 (CH_2 , CCH_2CH_2), 27.6 (CH_2 , $\text{CHCH}_2\text{CH}_2\text{CH}$), 23.6 and 23.4 (CH_2 , CCH_2CH_2 and $\text{CHCH}_2\text{CH}_2\text{CH}$), 14.6 (CH_3 , OCH_2CH_3); m/z (ES+) 268 ($[\text{M}+\text{H}]^+$, 100%); m/z (ES+) found: $[\text{M}+\text{H}]^+$, 268.1172. $\text{C}_{13}\text{H}_{18}\text{NO}_5$ requires: $[\text{M}+\text{H}]^+$, 268.1185.

Racemate resolved by semi-preparative chiral chromatography (column: Chiralpak AD-H (25 x 2.0 cm); mobile phase: *n*-hexane/ethanol 70/30 % v/v; flow rate: 14.0 ml/min; DAD: 225 nm).

ent-6: enantiomer 1: Rt: 18.75 min; 32 mg, colourless solid, m.p. 145.9-146.7 °C; $[\alpha]_D^{20} +25.0$ (c 0.16, CH₃OH); 100% ee.

6: enantiomer 2: Rt: 22.15 min; 32 mg, colourless solid, m.p.: 145.9-146.7 °C; $[\alpha]_D^{20} -33.3$ (c 0.18, CH₃OH); 100% ee.

(1R*,2R*,5S*)-Ethyl 3'-methyl-3-oxo-8H-spiro[8-azabicyclo[3.2.1]octane-2,5'-[1,2,3]oxathiazolidine]-8-carboxylate 2',2'-dioxide (±)-14, and resolution to give **14** and **ent-14**.

Amino alcohol (±)-**13** was prepared from (±)-**10**, via (±)-**11a**, as described in the procedure for the synthesis of **5a**.

Amino alcohol (±)-**13** (0.7 g, 2.7 mmol) was dissolved in DCM (20 ml) and cooled to 0 °C. Pyridine (2.21 ml, 27 mmol) was added followed by thionyl chloride (0.22 ml, 3 mmol) in DCM (1 ml). The reaction mixture was stirred at 0 °C for 30 min and then slowly warmed to RT. It was stirred at RT for further 48 h and then quenched by addition of a saturated solution of NH₄Cl. The organic phase was diluted with DCM (20 ml), washed with a 0.1 M HCl solution (20 ml), brine (20 ml), dried over MgSO₄ and concentrated. Purification by chromatography on silica gel eluting with a gradient from 50% to 100% EtOAc in cyclohexane delivered the diastereomeric mixture of cyclic sulfamidites as a colorless solid (400 mg, 48%); *m/z* (ES+) 303 ([M+H]⁺ 100%); *m/z* (ES+) found: [M+H]⁺, 303.1003. C₁₂H₁₉N₂O₅S requires: [M+H]⁺, 303.1015. This intermediate (400 mg, 1.32 mmol) was dissolved in CH₃CN (10 ml) and cooled to 0 °C. RuCl₃·xH₂O (catalytic amount) was added followed by NaIO₄ (420 mg, 1.98 mmol) dissolved in H₂O (2 ml). The mixture was stirred at RT for 30 min and then partitioned between DCM (20 ml) and H₂O (20 ml). The organic layer was washed with a saturated solution of NaHCO₃ (20 ml), brine (20 ml), dried over MgSO₄ and concentrated. Purification by chromatography on silica gel eluting with a gradient from 50% to 100% ethyl acetate in cyclohexane delivered a solid that was triturated with diethyl ether to afford (±)-**14** as a colorless solid (230 mg, 55%); m.p.: 127.1-128.2 °C; $\nu_{\max}/\text{cm}^{-1}$ (nujol): 1731, 1689, 1348, 1214, 1178; ¹H NMR δ_{H} (ppm) (CDCl₃, 360 MHz): 4.79-4.77 (1 H, m, NCHC), 4.68-4.66 (1 H, m, NCHCH₂CO), 4.27-4.19 (2 H, m, OCH₂CH₃), 4.10 (1 H, d, *J* = 10.4 Hz, CCH₂N), 3.18-3.09 (2 H, m, CCH₂N and CHCH_{2ax}CO), 2.82 (3 H,

s, NCH_3), 2.50 (1 H, dd, $J = 14.7, 2.1$ Hz, $\text{CHCH}_{2\text{eq}}\text{CO}$), 2.21-1.98 (2 H, m, $\text{CHCH}_{2\text{exo}}\text{CH}_{2\text{exo}}\text{CH}$), 1.62-1.54 (1 H, m, $\text{CHCH}_{2\text{endo}}\text{CH}_{2\text{endo}}\text{CHCH}_2$), 1.35-1.27 (4 H, m, OCH_2CH_3 and $\text{CHCH}_{2\text{endo}}\text{CH}_{2\text{endo}}\text{CHCH}_2$); ^{13}C NMR δ_{c} (ppm) (CDCl_3 , 91 MHz): 199.2 (C, $\text{C}=\text{O}_{\text{ketone}}$), 154.2 (C, $\text{C}=\text{O}_{\text{carbamate}}$), 86.9 (C, CCH_2N), 62.4 (CH_2 , OCH_2CH_3), 60.2 (CH, NCHC), 54.1 (CH, NCHCH_2CO), 50.7 (CH_2 , CCH_2N), 46.9 (CH_2 , CHCH_2CO), 35.6 (CH_3 , NCH_3), 27.7 (CH_2 , $\text{CHCH}_2\text{CH}_2\text{CHCH}_2$), 23.6 (CH_2 , $\text{CHCH}_2\text{CH}_2\text{CHCH}_2$), 14.8 (CH_3 , OCH_2CH_3); m/z (ES+) 319 ($[\text{M}+\text{H}]^+$, 100%); m/z (ES+) found: $[\text{M}+\text{H}]^+$, 319.0970. $\text{C}_{12}\text{H}_{19}\text{N}_2\text{O}_6\text{S}$ requires: $[\text{M}+\text{H}]^+$, 319.0964.

The racemic mixture (110mg) was resolved by semi preparative chiral chromatography, column: Chiralpak AD-H (25 x 0.46 cm); mobile phase: n-hexane/*iso*-propanol 85/15 % v/v; flow rate: 14.0 ml/min; DAD: 225 nm.

ent-14: enantiomer 1: $R_t = 15.23$ min; 40 mg, colourless solid, m.p.: 108.3-110.1 °C; $[\alpha]_{\text{D}}^{20} +40.0$ (c 0.1, CH_3OH); 100% ee.

14: enantiomer 2: $R_t = 18.53$ min; 40 mg, colourless solid, m.p.: 113.5-114.8 °C; $[\alpha]_{\text{D}}^{20} -40.0$ (c 0.1, CH_3OH); 100% ee.

4.3 General procedure for alkene epoxidation¹³

To a solution of ketone and alkene (0.1 mmol) in acetonitrile (1.5 ml) was added aqueous Na_2EDTA solution (1.0 ml of a 0.4 mM aqueous solution). Oxone[®] (307 mg, 1.0 mmol KHSO_5) and NaHCO_3 (130 mg, 1.55 mmol) were added in portions simultaneously over 30 minutes. The reaction was stirred vigorously until completion (by TLC analysis) or for 24 hours, then diluted with water (10 ml).

Two different work-up procedures (A and B) were employed. Work-up B is highly efficient when epoxidation reactions are run in parallel. No difference in the enantioselectivity has been observed for examples where both work-up A and work-up B has been used.

Work-up A (used for Table 1, entries 1, 2, 6, 7, 8; Table 2, entries 2, 4-6; Table 3, entries 1-5; Table 4, entries 2, 4-6; Table 5, entries 4, 5, 8; Table 6, entries 2, 4-7): the reaction mixture was extracted into diethyl ether (3 x 25 ml). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated to dryness under reduced pressure. Flash column chromatography (gradient from 5 to 10% diethyl ether in cyclohexane) on silica or purification by preparative thin layer chromatography afforded the relevant epoxide.

Work-up B (used for Table 1, entries 3, 4, 5, 9-14; Table 2, entries 1, 3, 7; Table 3, entries 6, 7; Table 4, entries 1, 3, 7, 8; Table 5, entries 1-3, 6, 7, 9; Table 6, entries 1, 3, 6): the reaction

mixture was extracted into DCM (25 ml). The organic phase was separated using a phase separation cartridge and evaporated to dryness under reduced pressure or under a stream of nitrogen. Flash column chromatography (gradient from 5 to 10% diethyl ether in cyclohexane) on silica or purification by preparative thin layer chromatography afforded the relevant epoxide.

4.4 Determination of epoxide enantiomeric purity

Epoxides gave ^1H NMR data in accord with literature values.^{7a} Epoxide enantiomeric excesses were determined by HPLC on chiral stationary phases and the absolute configuration of the major products were assigned by comparison with literature retention times or optical rotations, as described previously.^{7a}

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References and Notes

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 11. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 767196. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk). Details are also provided as Supplementary Information to this paper.
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