Synthesis of Single-Enantiomer 6-Hydroxy-7-phenyl-1,4-oxazepan-5-ones

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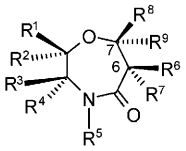
Abstract: An efficient two-step preparation of (6*R*,7*R*)-6-hydroxy-7-phenyl-1,4-oxazepan-5-ones (**1**) starting from aminoethanols and (2*R*,3*S*)-3-phenyloxirane-2-carboxylic ethyl ester or potassium salt has been described. The most efficient catalyst identified for the ring closure of the resulting intermediate epoxyamides was $Sc(OTf)_3$. By choice of appropriate chiral starting substituted aminoethanol and 3-phenyloxirane-2-carboxylic derivatives, the procedure allows facile synthesis of other single enantiomer 6-hydroxy-7-phenyl-1,4-oxazepan-5-ones.

Key words: heterocycles, ring closure, epoxides, scandium, magnesium

We wished to develop a synthesis of (6*R*,7*R*)-6-hydroxy-7-phenyl-1,4-oxazepan-5-one (**1**) (Figure 1) that would allow facile access for mono-, di- and tri-substitution at R^1, R^2, R^3, R^4 and R^5.

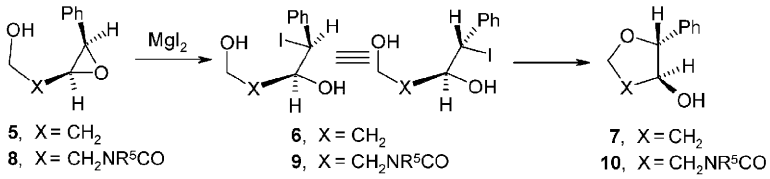


	R^6	R^7	R^8	R^9	
1	OH	H	H	Ph	6*R*,7*R*
2	H	OH	Ph	H	6*S*,7*S*
3	OH	H	Ph	H	6*R*,7*S*
4	H	OH	H	Ph	6*S*,7*R*

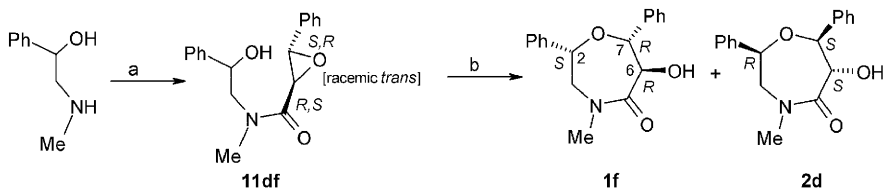
Figure 1 6-Hydroxy-7-phenyl-1,4-oxazepan-5-one diastereomers **1**–**4**. See Table 2 for the letter assignment of R^1–R^5 combinations prepared in this paper.

A report[1] on the cyclization of the racemic *cis*-epoxide (**5**, *cis*-racemate, Scheme 1) with MgI_2 to yield racemic *trans*-2-phenyltetrahydrofuran-3-ol (**7**, *trans*-racemate) led us to speculate whether a similar transformation would be possible with epoxyamide **8**. We anticipated that as with **5** and other similar alcohols, esters, and aldehydes,[2] the epoxyamide **8** would exhibit chelation-controlled epoxide opening with MgI_2 to yield the iodohydrin **9**. A 7-*exo*-tet displacement of the iodide would theoretically control the oxazepine versus pyran issue.

In order to rapidly test this approach we examined the reaction of *N*-(2-hydroxy-2-phenylethyl)-*N*-methyl-3-phenyloxirane-2-carboxamide (**11df**, Scheme 2) with MgI_2 under the conditions employed by Karikomi.[1] A 43% yield of a 1:1 mixture of the 6-hydroxy-4-methyl-2,7-diphenyl-1,4-oxazepan-5-ones **1f** and **2d** was obtained. The relative stereochemistry of the substituents of the product was determined by a NMR NOE study. The material used in the study was prepared in 46% yield by the method of Huang[3] from commercial ethyl phenylglycidate (90% *trans* by ^{1}H NMR) and DL-α-(methylaminomethyl)benzylalcohol. NMR spectral analysis of **11df** confirmed that the material consisted only of *trans*-epoxyamide. We did not further examine the diastereomeric balance of **11df**. Diastereomeric enrichment in the preparation of **11df** would compromise a rigorous mechanistic



Scheme 1



Scheme 2 *Reagents and conditions:* a) Ethyl 3-phenyloxirane-2-carboxylate, MeOH, cat. NaOMe, –20 °C; b) 10 mol% MgI_2, refluxing THF.

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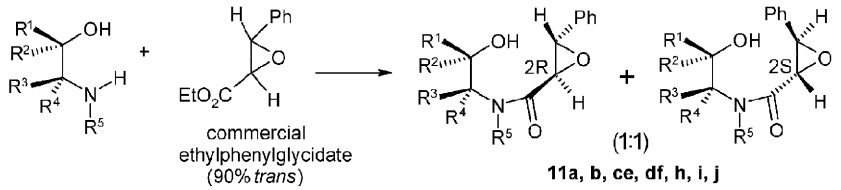
analysis of the results of the ring closure. However, it is distinctly clear that *trans*-epoxide, such as **11df**, should yield 6-hydroxy-7-phenyl-1,4-oxazepan-5-ones with *cis*-6-hydroxy and 7-phenyl groups if the speculated double inversion mechanism of Scheme 1 (starting with *cis*-epoxide; yielding *trans* products) is operational. At that point in time, we felt that we were unable to distinguish between two of the most likely alternative mechanisms, a carbonium ion intermediate or a concerted attack of the alcohol moiety on the epoxide. A direct epoxide opening would be a 7-*endo*-tet ring closure. While 5-*endo*-tet ring and 6-*endo*-tet ring closures are disfavored[4] 7-*endo*-tet ring closures are allowed and can even be facile under conditions of chelation control,[5] a condition, in this case, possibly provided by the magnesium ion. The uncertainty around the diastereomeric purity of **11df** prevented accurately deducing why only the two *cis* oriented 2,7-diphenyl derivatives **1f** and **2d** were obtained.

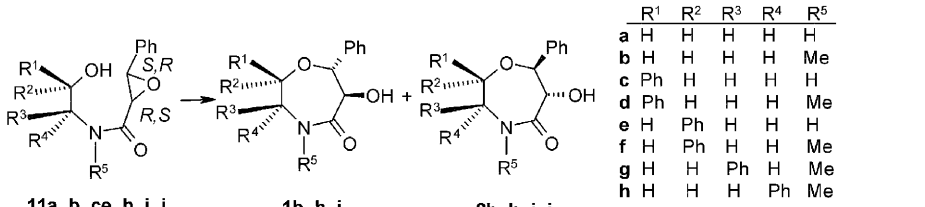
Table 1 Synthesis of Racemic *trans*-Epoxyamides



Mixture	R^1	R^2	R^3	R^4	R^5	Method	Yield (%)
11a	H	H	H	H	H	B	27
11b	H	H	H	H	Me	A	84
11ce	C_6H_5 or (H)[a]	H or (C_6H_5)[a]	H	H	H	B	40
11df	C_6H_5 or (H)[a]	H or (C_6H_5)[a]	H	H	Me	A	46
11h	H	H	H	Ph	Me	A	59
11i	R^1R^4 = -$(CH_2)_4$-, R^2,R^3 = H				Me	A	69
11j	R^2R^3 = -$(CH_2)_4$-, R^1,R^4 = H				Me	A	60

[a] Mono-phenyl racemate

Table 2 Initial Scope-Determining Reactions with MgI_2



Epoxyamide	R^1	R^2	R^3	R^4	R^5	Oxazepanone (yield)[a]
11a[b]	H	H	H	H	H	No cyclized products
11b[c]	H	H	H	H	Me	**1b/2b** (1:1) (50%)
11ce[c]	C_6H_5 or (H)[d]	H or (C_6H_5)[d]	H	H	H	No cyclized products
11h[c]	H	H	H	C_6H_5	Me	**1h**[e] (9%), **2h**[e](30%)
11i[b]	R^1R^4 = -$(CH_2)_4$-, R^2 = R^3 = H				Me	**1i** (0%), **2i** (34%)
11j[b]	R^2R^3 = -$(CH_2)_4$-, R^1 = R^4 = H				Me	**1j**[f] (33%), **2j**[f] (5%)

[a] Isolated yields.
[b] Reaction conditions: 20 mol% MgI_2 in THF, overnight reflux.
[c] Reaction conditions: 10 mol% MgI_2 in THF, overnight reflux.
[d] Mono phenyl racemate.
[e] Separated by flash column chromatography (hexanes–Et_2O, 2:1).
[f] Separated as **e**, then crystallization from Et_2O.

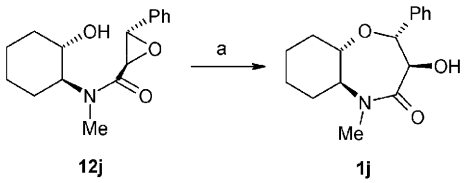
As **1f** has the desired stereochemistry of **1**, the utility of this ring closure reaction in the context of our program was first investigated using additional racemic *trans*-epoxyamides (Tables 1 and 2). As in the synthesis of **11df** we employed the method of Huang[3] (General Method A) to prepare the *N*-methyl substituted epoxyamides and an adaptation of the method of Baldas and Porter[6] (General Method B) to prepare the secondary amides. The diastereomeric makeup of **11ce**, **11h–j** was determined to be 1:1 (NMR or NMR and HPLC analysis).

There are several intriguing observations that can be made concerning the cyclization results presented in Table 2. The secondary amides **11a** or **11ce** did not yield ring closed products. Our working hypothesis was that amide N-substitution is necessary to 'pre-organize' the ring closure (*Z* amide versus *E* amide). In support of the hypothesis, the ^{1}H NMR spectra of the *N*-methyl amides all show two conformations (twinned resonances) while the NH amides show only a single set of resonances that can be assigned to the *E* conformation. The R^1–R^4 unsubstituted **11b** underwent facile ring closure to a 1:1 mixture of **1b** and **2b.** The use of chiral epoxide in the synthesis of **11b** would be expected to allow the synthesis of either pure **1b** or **2b**. As with **11df** and **11b** the ring closure of the epoxyamide **11h** gave a mixture of **1h** and **2h**, however the undesired diastereomer **2h** predominated in a 3.3:1 ratio. The cyclohexyl derivative **11i** gave only the undesired **2i** while the other *trans*-cyclohexyl derivative **11j** gave the desired fused cyclohexyl **1j** in 33% yield.

In order to: 1) expedite preparation of our targeted oxazepanones **1**, 2) elucidate some mechanistic features of the ring closure and 3) examine the influence of possible steric factors in the ring closure we decided to use only optically pure starting epoxides in further syntheses.

The enantiomerically pure starting epoxyamides (Table 3) used in further studies were all prepared by a EDCI, HOBt coupling of the enantiomerically pure potassium 3-phenyloxirane-2-carboxylate (Table 4) with the appropriate (chiral) amine.

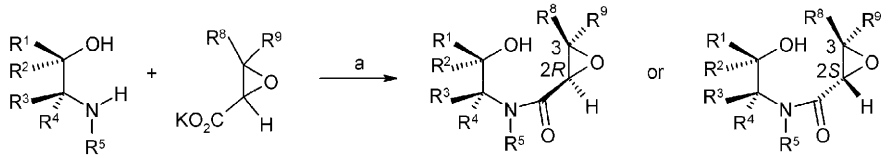
Our initial study using enantiomerically pure starting epoxyamide was to be a repeat of the ring closure of **11j** (Table 2) using a single diastereomer **12j** (Scheme 3). However as we purified **12j** by reversed phase chromatography we discovered that a solution of purified **12j** in 90% MeCN–water containing 0.1% TFA on standing overnight at room temperature gave a 90% yield (HPLC) of **1j**.



12j **1j**

Scheme 3 *Reagents and conditions:* a) 90% MeCN–H_2O, 0.1% TFA 16 h, 90%.

Table 3 Synthesis of Single-Enantiomer Epoxyamides



16 or **17** or **18** or **19**

12 R^8 = H, R^9 = Ph
14 R^8 = Ph, R^9 = H

13 R^8 = Ph, R^9 = H
15 R^8 = H, R^9 = Ph

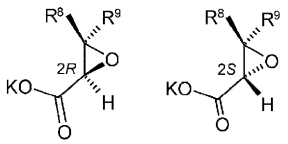
Epoxyamide	Starting Epoxide	R^1	R^2	R^3	R^4	R^5		R^8	R^9	Yield (%)
12a	**16**	H	H	H	H	H	2*R*,3*S*	H	Ph	44
12b	**16**	H	H	H	H	Me	2*R*,3*S*	H	Ph	68
12f	**16**	H	Ph	H	H	Me	2*R*,3*S*	H	Ph	85
13f	**17**	H	Ph	H	H	Me	2*S*,3*R*	Ph	H	63
14f	**18**	H	Ph	H	H	Me	2*R*,3*R*	Ph	H	59
15f	**19**	H	Ph	H	H	Me	2*S*,3*S*	H	Ph	96
12h	**16**	H	H	H	Ph	Me	2*R*,3*S*	H	Ph	45
13h	**17**	H	H	H	Ph	Me	2*S*,3*R*	Ph	H	74
12i	**16**	R^1R^4 = $(CH_2)_4$ R^2,R^3 = H, R^5 = Me					2*R*,3*S*	H	Ph	60
12j	**16**	R^2R^3 = $(CH_2)_4$ R^1,R^4 = H, R^5 = Me					2*R*,3*S*	H	Ph	69

[a] EDCI, HOBt, NMM, CH_2Cl_2 (General method C) 0 °C → r.t.

The results of a study on the ring closure of the four (*S*)-2′-phenyl epoxyamides **12f, 13f, 14f** and **15f** are presented in Table 5. TFA, as well as $Sc(OTf)_3$, a reagent we had found to be very useful in a synthesis of 3-hydroxy-2-phenyl-2,3-dihydro-1,5-benzoxazepin-4(5*H*)-ones[7] were also employed as ring closure catalysts.

MgI_2 conditions were successful only with the 2*R*,3*S*-*trans*-epoxyamide **12f** (Table 5). This result as well as the yield of **1f** are consistent with that predicted from Scheme 2 with the assumption that **11df** consisted of a 1:1 diastereomeric mixture of **12f** and **13d**. Acid catalyst was facile with the two 2*R*-epoxyamides (**12f** and **14f**) but required longer reaction times and gave lower yields with the two 2*S*-epoxyamides (**13f** and **15f**). $Sc(OTf)_3$ was efficient with all enantiomers but the relative sluggishness of the 2*S*,3*S*-*cis*-epoxyamide **15f** is evident.

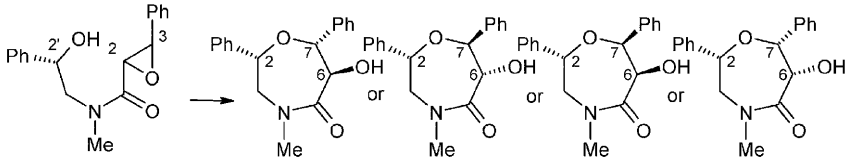
Table 4 Potassium 3-Phenyloxirane-2-carboxylates



	R^8	R^9		R^8	R^9
16	H	Ph	**17**	Ph	H
18	Ph	H	**19**	H	Ph

To exemplify a ring closure with a substituent in the 3-position, we chose epoxyamides **12h** and **13h** (Table 6) containing the 3′-phenyl (*S*)-conformation and *trans* configurations on the epoxide ring.

Table 5 Ring Closure of the (*S*)-2′-Phenyl Epoxyamides

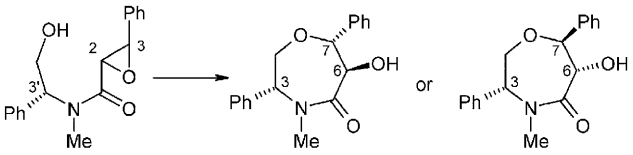


12f or **13f** or **14f** or **15f** **1f** **2f** **3f** **4f**

Starting Epoxyamide	Oxazepinone	Reagent, yield,[a] reaction time[b] MgI_2 (Method D)	TFA (Method E)	$Sc(OTf)_3$ (Method F)
12f 2*R*,3*S*	**1f** 2*S*,6*R*,7*R*	87%, 3 h	84%, 3 h	97%, 10 min
13f 2*S*,3*R*	**2f** 2*S*,6*S*,7*S*	0%, 40 h	50%, 48 h	89%, 60 min
14f 2*R*,3*R*	**3f** 2*S*,6*R*,7*S*	0%, 40 h	90%, 1 h	73%, 60 min
15f 2*S*,3*S*	**4f** 2*S*,6*S*,7*R*	0%, 40 h	56%, 240 h	75%, 18 h[b]

[a] Typical reaction conditions: MgI_2: 10 mol% MgI_2 in THF under N_2 at reflux, TFA: 10 mol% TFA in MeCN (0.4% TFA–MeCN by volume) at r.t., $Sc(OTf)_3$: 10 mol% $Sc(OTf)_3$ in MeCN at r.t.
[b] Estimated (HPLC) 60% at 45 min.

Table 6 Ring Closure of Epoxyamides with a Substituent in the 3-Position



12h or **13h** **1h** **2h**

Starting Epoxyamide	Oxazepanone	Reagent, yield[a] MgI_2[b] (Method D)	TFA[c] (Method E)	$Sc(OTf)_3$[d] (Method F)
12h. 3′*R*,2*R*,3*S*	**1h** 3*R*,6*R*,7*R*	35%	10%	76%
13h. 3′*R*,2*S*,3*R*	**2h** 3*R*,6*S*,7*S*	29%[e]	68%	85%

[a] Isolated yield.
[b] MgI_2 (10 mol%) in THF under nitrogen at reflux overnight
[c] TFA (10 mol%) in MeCN (0.4% TFA–MeCN) at r.t. 24 h
[d] $Sc(OTf)_3$ (10 mol%) in MeCN at r.t., 10 min.
[e] Yield determined by HPLC; addition of an additional 20 mol% MgI_2 and 2 h additional reflux gave 85% isolated yield.

Cyclization of **12h** was sluggish compared to **13h**. While the overnight MgI_2 reaction of both **12h** and **13h** appear equivalent, **12h** did not proceed further with additional catalyst. Unidentified iodinated and elimination products predominated. With TFA, elimination products predominated with **12h**.

In an effort to resolve some of the questions generated by our initial scope-finding ring closure reactions (Table 2) and to selectively prepare derivatives with the proper stereochemistry for our program we undertook the series of reactions shown in Table 7.

As is illustrated in Table 7, we were able to obtain the desired pure enantiomers **1a**, **1b** and **1i** employing scandium triflate as the catalyst. Consistent with our scope determining reactions of Table 2 only **1b** was prepared successfully with MgI_2 catalyst. TFA was also only successful in the synthesis of **1b**.

The TFA (4.5 mol%) catalyzed ring closure of 0.093 M **12f** in MeCN, was followed by Raman spectroscopy (Figure 2). The disappearance of starting material was followed using the very strong epoxide band at 1238 cm^{-1}. The appearance of product was followed by using the band at 1198 cm^{-1}. The aromatic band at 1011.3–972.6 cm^{-1} was used as an internal standard to account for differences in spectrometer alignment, temperature effects, etc. The starting material and product band intensity profiles are covariant within the time resolution of the Raman experiment. There is no evidence of a two-step reaction in which the starting material was first complexed by the acid and then later reacted to effect ring closure.

A similar experiment carried out with 0.7 mol% scandium triflate was complete in about 30 minutes. A 4.5 mol% scandium triflate reaction was virtually instantaneous.

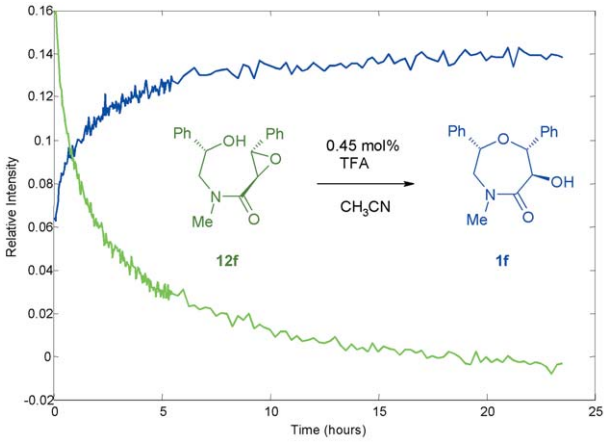
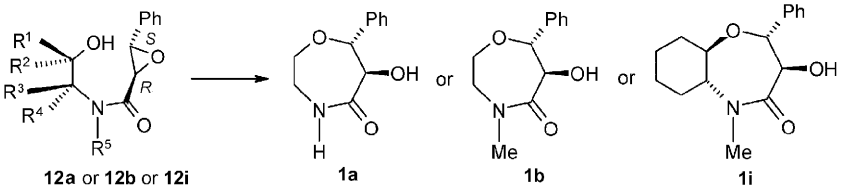


Figure 2 Raman intensity vs. time profiles for reaction of **12f** (green line) with TFA to yield **1f** (blue line).

NMR Studies. Structural Assignment as Oxazapinones

Structural assignment of **1f** and **2d** (Scheme 2) serves to exemplify NMR studies carried out to establish structures. The 300 MHz ^1H NMR spectrum of the mixture is shown in Figure 3. An oxazepanone versus morpholinone ring was confirmed based on a 2D HMBC spectrum optimized for two and three-bond carbon–proton couplings [delays set for $J_{(C,H)}$ = 10 Hz]. In this spectrum (Figure 4), the proton attached to C7 (oxazepanone) had two long-range coupling correlations to carbons 8 and 9 in the phenyl A ring. Only in the seven-membered oxazepanone ring is this proton within three bonds of the two carbons. In the morpholinone, H7 is four bonds from carbon 9 and a coupling correlation would not be expected in this experiment.

Table 7 Preparation of Pure Enantiomers **1a**, **1b** and **1i** Using Scandium Triflate as the Catalyst



Starting Epoxyamide	Oxazepanone	R^1	R^2	R^3	R^4	R^5	Reagent yield[a] MgI_2[b]	TFA[b]	$Sc(OTf)_3$
12a	**1a**	H	H	H	H	H	0%	0%	29%[c]
12b	**1b**	H	H	H	H	CH_3	56%	50%	82%
12i	**1i**	R^1–R^4 = -$(CH_2)_4$-, R^2 = R^3 = H				CH_3	0%	trace[d]	61%[e]

[a] Isolated yield.
[b] See Table 3 for reaction conditions.
[c] $Sc(OTf)_3$ (10 mol%), MeCN, 24 h at r.t.
[d] Presence by HPLC.
[e] $Sc(OTf)_3$ (10 mol%), MeCN, 1 h at r.t. Real-time Raman spectroscopy analysis of epoxide reactivity.

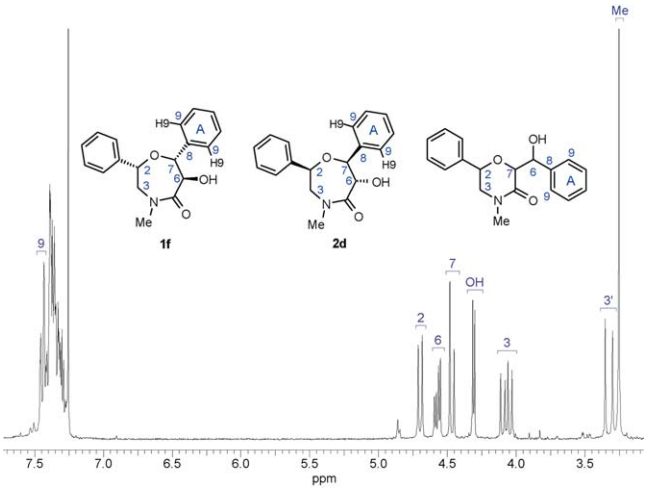


Figure 3 ^{1}H NMR spectrum (300 MHz) of the mixture of **1f** and **2d**.

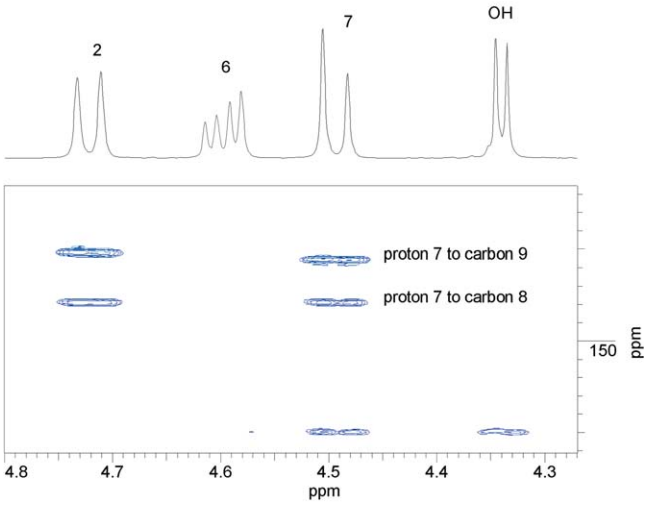


Figure 4 A portion of the contour plot of the HMBC spectrum of **1f** and **2d** mixture in $CDCl_3$.

The protons attached to C6 and C7 (H6 and H7) are in a *trans* configuration as based on a 2D NOESY experiment (Figure 5), which showed NOE's between H6 and the A phenyl ring *ortho* protons H9. This would only be expected if H6 and the A phenyl ring were in a *cis* configuration relative to each other, which necessitates H6 and H7 being *trans* to one another. There was very little NOE observed between H6 and H7, which indicated that they are on opposite sides of the ring. The coupling constant between H6 and H7 was measured to be 9.1 Hz. This value also supports a *trans* configuration.

NMR Studies: Study of Epoxy Amide *E*/*Z* Conformations

The epoxyamides of Table 3 were used in this study. As the secondary amide **12a** exists in solution as one conformer, there was a single set of resonances for all protons in the sample (Figure 6). A 2D NOESY spectrum shows NOEs between the NH proton and the protons of the epoxy ring whereas there is no NOE to the epoxy protons

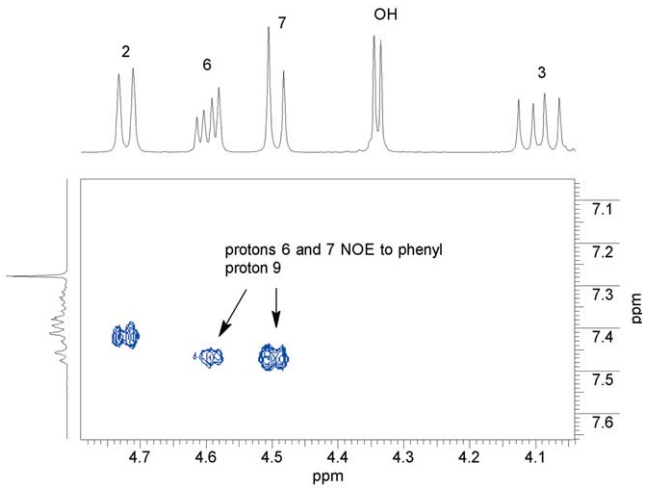


Figure 5 A portion of the contour plot of the NOESY spectrum of **1f** and **2d** mixture in $CDCl_3$.

and the ethane protons. That data is consistent with an *E* amide conformation (**12a-*E***, Figure 7).

In the *N*-methyl amides (**12b** exemplifies the NMR data), the ^{1}H spectra consisted of two sets of resonances that could be assigned to each conformer (Figure 8). The temperature was lowered to –10 °C for acquisition of the NMR spectra for the *N*-methyl amides because there was better resolution of the resonances for the two conformers at the lower temperature. As shown in Figure 9, the *N*-methyl group of the *E* conformer displayed NOE to the

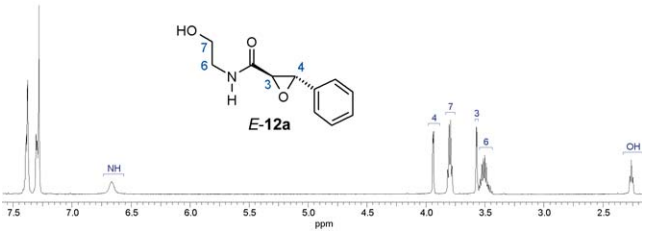


Figure 6 ^{1}H NMR spectrum (400 MHz) of **12a** in $CDCl_3$ at 27 °C.

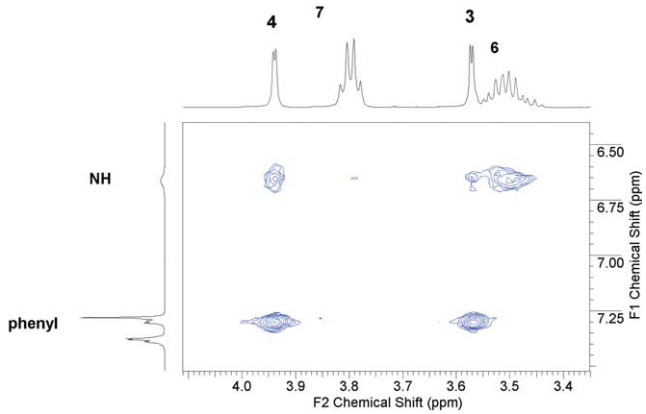


Figure 7 A portion of the contour plot of the NOESY spectrum of **12a-*E*** in $CDCl_3$ at 27 °C.

epoxy ring H3 proton 2. For the *Z* conformer, there was NOE observed between ethane H6 and the epoxy ring. Quite similar and consistent results were observed for the other *N*-methyl amides. Thus, the NOE data could be used to assign the *E* and *Z* resonances in each spectrum for each compound in the series.

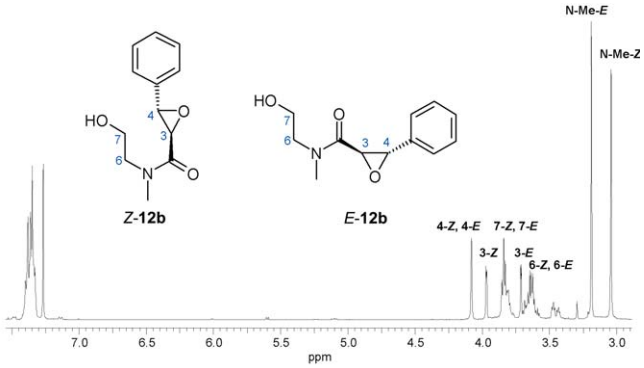


Figure 8 ^{1}H NMR (400 MHz) spectrum of **12b** in $CDCl_3$ at –10 °C.

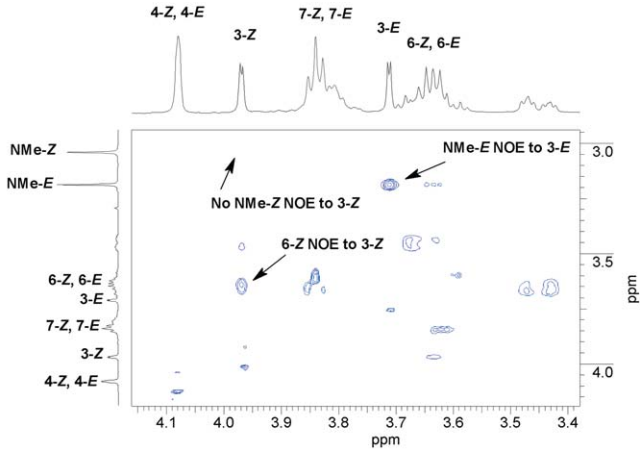


Figure 9 A portion of the contour plot of the NOESY spectrum of **12b** in $CDCl_3$ at –10 °C.

In conclusion, we have developed a facile method of preparation of single enantiomer 6-hydroxy-7-phenyl-1,4-oxazepan-5-ones. The method was largely exemplified with 6*R*,7*R*-enantiomers required for our program but can readily be applied to other single enantiomers. We examined three catalysts in the ring closure of the intermediate epoxyamides and in all cases where a comparison was carried out $Sc(OTf)_3$ was superior to MgI_2 or TFA. These results raise interesting questions about the stereochemical and electronic factors that influence the selectivities evidenced by our synthetic results. Additional studies would be required to fully elucidate the mechanistic details of the ring closure reaction.

Potassium (2*R*,3*S*)-3-Phenyloxirane-2-carboxylate (16)

This material was prepared essentially by a method reported by Harada[8] for the preparation of potassium (2,3-*trans*)-3-phenyloxirane-2-carboxylate. To a stirred mixture of (1*S*)-1-phenylethanaminium (2*R*,3*S*)-3-phenyloxirane-2-carboxylate[9] (28.54 g, 0.10 mol), EtOH (65 mL) and H_2O (15 mL) was added a warm (35 °C) solution of KOH (6.7 g, 0.12 mol) in EtOH (50 mL). After stirring for 20 min at ambient temperature, Et_2O (200 mL) was added, stirring was continued for an additional 10 min, the white solid collected by filtration and washed with Et_2O. The yield of dried white solid was 17.9 g (89%); $[\alpha]_D^{25}$ –145.7 (*c* = 1.1, H_2O).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.34–7.22 (m, 5 H), 3.67 (d, *J* = 1.7 Hz, 1 H), 2.98 (d, *J* = 1.7 Hz, 1 H).

Potassium (2*S*,3*R*)-3-Phenyloxirane-2-carboxylate (17)

Using the procedure described for **16** except using (1*R*)-1-phenylethanaminium (2*S*,3*R*)-3-phenyloxirane-2-carboxylate[9] (5.24 g, 0.184 mol), returned the title compound (2.2 g, 60%) as a white solid; $[\alpha]_D^{25}$ +143.5 (*c* = 1.47, H_2O).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.35–7.22 (m, 5 H), 3.68 (d, *J* = 2 Hz, 1 H), 2.99 (d, *J* = 2 Hz, 1 H).

Potassium (2*R*,3*R*)-3-Phenyloxirane-2-carboxylate (18)

Using a procedure similar to that described for **16** except using ethyl (2*R*,3*R*)-3-phenyloxirane-2-carboxylate[10] (0.934 g, 4.9 mmol) returned the title compound (0.793 g, 80%) as a white solid; $[\alpha]_D^{25}$ –6 (*c* = 1.05, H_2O).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.49–7.46 (m, 2 H), 7.26–7.19 (m, 3 H), 3.84 (d, *J* = 5 Hz, 1 H), 3.32 (d, *J* = 5 Hz, 1 H).

Potassium (2*S*,3*S*)-3-Phenyloxirane-2-carboxylate (19)

Using a procedure similar to that described for **16** except using ethyl (2*S*,3*S*)-3-phenyloxirane-2-carboxylate[10] (0.753 g, 3.9 mmol) returned the title compound (0.635 g, 80%) as a white solid; $[\alpha]_D^{25}$ +6 (*c* = 1.05, H_2O).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.49–7.46 (m, 2 H), 7.26–7.20 (m, 3 H), 3.84 (d, *J* = 5 Hz, 1 H), 3.32 (d, *J* = 5 Hz, 1 H).

(1*S*,2*S*)-2-(Methylamino)cyclohexanol (20)

Oil.

$[\alpha]_D^{23}$ +73.3 (*c* = 0.9, H_2O); Lit.[11] $[\alpha]_D^{20}$ +86.3 (*c* = 5, H_2O), Lit.[12] $[\alpha]_D^{20}$ +92.5 (*c* = 5, H_2O).

(1*R*,2*R*)-2-(Methylamino)cyclohexanol (21)

Oil; bp 85–95 °C (kugelrohr bulb temperature)/2 torr; $[\alpha]_D^{24}$ –84.1 (*c* = 5, H_2O); Lit.[11] $[\alpha]_D^{20}$ –84.4 (*c* = 5, H_2O), Lit.[12] $[\alpha]_D^{20}$ –91.5 (*c* = 5, H_2O).

Compounds **20** and **21** were obtained via resolution of (1*RS*,2*RS*)-2-(methylamino)cyclohexanol[13] employing (+)-di-*para*-toluoyltartaric acid[13] and (–)-di-*para*-toluoyltartaric acid, respectively. [Note that the stereochemistry of the enantiomers are misdrawn in ref.[13]]

(2*R*)-2-(Methylamino)-2-phenylethanol (22)

To a stirred cooled (0 °C) mixture of $LiAlH_4$ (6.11 g, 40 mmol) and THF (100 mL) under a N_2 atmosphere was added dropwise a solution of (2*R*)-[(ethoxycarbonyl)amino](phenyl)acetic acid[14] {mp 143–145°, $[\alpha]_D^{25}$ –154.4 (*c* = 1.036, MeOH); Lit.[15] $[\alpha]_D^{20}$ –158 (*c* = 1, MeOH)} (8.93 g, 40 mmol) keeping the temperature between 0–5 °C. The mixture was stirred at ambient temperature for 15 min and then stirred at reflux overnight. The mixture was cooled in an ice bath and 15% NaOH solution (20 mL) was added cautiously dropwise. When approximately half had been added the reaction became a gel-like mass. THF (200 mL) was added, the mixture was swirled and the 15% NaOH addition was completed. After stirring for 1 h the solid was filtered off and the filter cake washed well with EtOAc. The solvent was the removed from the filtrate to yield a clear oil which was placed under vacuum where it solidified, (5.91 g, 98%); mp 53–56 °C (Lit.[16] 62 °C); $[\alpha]_D^{24}$ –84.5 (*c* = 1.018, EtOH); Lit.[17] $[\alpha]_D^{20}$ –79.6 (*c* = 1.0, EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27–7.38 (m, 5 H), 3.70–3.75 (m, 1 H), 3.63–3.67 (m, 1 H), 3.52–3.58 (m, 1 H), 2.35 (s, 3 H), 1.8 (br s, 2 H, exchangeable). NMR analysis using the chiral shift reagent TBPTA[18] gave an ee of > 99%.

(1*S*)-2-(Methylamino)-1-phenylethanol (23)

A stirred mixture of (1*RS*)-2-(methylamino)-1-phenylethanol (31.24 g, 206.6 mmol) and acetone (250 mL) was heated to near reflux to dissolve all the solid and a solution of dibenzoyl-D-tartaric acid (18.51 g, 51.7 mmol) in acetone (100 mL) was added in one portion. After a few minutes a precipitate appeared. The mixture was stirred for 2 h at ambient temperature, the solid collected by filtration, washed with acetone (100 mL) and Et_2O (100 mL) and dried in vacuo at 35 °C to yield bis[(2*S*)-2-hydroxy-*N*-methyl-2-phenylethanaminium]dibenzoyl-D-tartrate as a white solid (30.71 g, 90%); mp 162–163 °C; $[\alpha]_D^{24}$ +100.0 (*c* = 1.035, H_2O).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.96 (d, *J* = 7.0 Hz, 4 H), 7.58–7.63 (t, 2 H), 7.45–7.50 (t, 4 H), 7.22–7.34, (m, 10 H), 5.63 (s, 2 H), 4.79 (dd, *J* = 9.7, 3.1 Hz, 2 H), 2.92 (dd, *J* = 3.3, 12.5 Hz, 2 H), 2.75–2.82 (m, 2 H), 2.44 (s, 6 H), plus 6 exchangeable protons.

Anal. Calcd for $C_{36}H_{40}N_2O_{10}$ (660.73): C, 65.44; H, 6.10; N, 4.24. Found: C, 65.15; H, 5.97; N, 4.16.

A sample of the salt, freed as described below, gave title compound; $[\alpha]_D^{24}$ +41.0 (*c* = 1.024, EtOH); Lit.[19] $[\alpha]_D^{24}$ +40.41 (*c* = 1.89, EtOH). NMR analysis using the chiral shift reagent TBPTA[18] gave an ee of 92.6%.

A portion (15.63 g) of the above salt was dissolved in refluxing 95% EtOH (250 mL) and treated warm with sufficient Et_2O to bring the volume of the solution to 400 mL. After standing in a freezer for 2 h, the solid was collected, washed with Et_2O and dried in vacuo at 35 °C to return 12.52 g (80% recovery) of purified bis[(2*S*)-2-hydroxy-*N*-methyl-2-phenylethanaminium] dibenzoyl-D-tartrate; mp 172–173 °C; $[\alpha]_D^{25}$ +103.3 (*c* = 1.045, H_2O).

To a mixture of the purified bis[(2*S*)-2-hydroxy-*N*-methyl-2-phenylethanaminium] dibenzoyl-D-tartrate (12.5 g, 18.9 mmol) and H_2O (125 mL) in a separatory funnel were added 28% ammonium hydroxide (12.5 mL, 90 mmol) and EtOAc (75 mL) and the mixture was shaken until no solid remained. The aqueous phase was extracted with EtOAc (5 × 75 mL) and the combined EtOAc extracts were stripped in vacuo. The residual oil was treated with Et_2O and a small amount of Celite, swirled and filtered. The solvent was removed and the colorless oil placed under high vacuum where it solidified. The yield of the white solid title compound was 5.7 g [100% from the salt, 72% overall from starting racemic 2-(methylamino)-1-phenylethanol]; mp 45–47 °C (Lit.[19] 39–40 °C, Lit[20,21] 43–45 °C); $[\alpha]_D^{23}$ +42.0 (*c* = 1.012, EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25–7.38 (m, 5 H), 4.73 (dd, *J* = 4.0, 8.8 Hz, 1 H), 2.82 (dd, *J* = 4.0, 11.8 Hz, 1 H), 2.72 (dd, *J* = 8.8, 11.8 Hz, 1 H), 2.46 (s, 3 H), 2.40 (br s, 2 H, exchangeable). NMR analysis using the chiral shift reagent TBPTA[18] gave an ee of >99%.

Preparation of Epoxyamides by the Method of Huang;[3] General Method A

***N*-(2-Hydroxy-2-phenylethyl)-*N*-methyl-(2,3-*trans*)-3-phenyloxirane-2-carboxamide (11df)**

To a solution of ethyl 3-phenyloxirane-2-carboxylate (5.0 g, 26.0 mmol) in MeOH (10 mL) at –20 °C was added 2-(methylamino)-1-phenylethanol (4.29 g, 28.4 mmol) followed by catalytic NaOMe (25%, 10 drops). The reaction was placed in a freezer (ca –20 °C) for 2 d, filtered and washed with cold MeOH to afford the title mixture as a white solid (3.3 g, 46%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 10 H), 5.08–4.88 (m, 0.9 H), 4.08–4.04 (m, 0.8 H), 3.85–3.44 (m, 3.3 H), 3.07, 3.06 (s, 2 H), 2.98 (s, 1 H).

***N*-(2-Hydroxyethyl)-*N*-methyl-(2,3-*trans*)-3-phenyloxirane-2-carboxamide (11b)**

To a solution of ethyl 3-phenyloxirane-2-carboxylate (10.0 g, 52.0 mmol) in MeOH (20 mL) at –20 °C was added 2-(methylamino)ethanol (4.6 g, 62.0 mmol) followed by catalytic NaOMe (25%, 20 drops). The reaction was then set in a freezer (ca –20 °C) for 10 d, diluted with 10% HCl (10 drops), H_2O (100 mL), extracted with CH_2Cl_2 (2 ×), and the organic layers combined, dried, filtered and evaporated to afford the title compound (9.7 g, 84%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.31 (m, 5 H), 4.08 (s, 1 H), 3.87–3.79 (m, 2.6 H), 3.67–3.69 (m, 2.4 H), 3.19 (s, 1.7 H), 3.04 (s, 1.3 H), 2.82 (br s, 0.4 H), 2.70 (br s, 0.6 H).

MS (APCI): *m*/*z* = 222 [M + H].

(2*3-trans*)-*N*-[(1*R*)-2-Hydroxy-1-phenylethyl]-*N*-methyl-3-phenyloxirane-2-carboxamide (11h)

Using a procedure similar to that described for **11df** except using (2*R*)-2-(methylamino)-2-phenylethanol (**22**, 12.6 g, 83.4 mmol), a reaction time of 96 h, concentration of the reaction mixture and column chromatography (2% MeOH–$CHCl_3$) yielded pure **11h** (12.2 g, 59%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.16–7.39 (m, 10 H), 5.81 (q, *J* = 7.4 Hz, 0.6 H), 5.31 (q, *J* = 8.1 Hz, 0.4 H), 4.12–4.22 (m, 3 H), 3.99 (d, *J* = 1.3 Hz, 0.2 H), 3.83 (d, *J* = 1.4 Hz, 0.2 H), 3.72 (d, *J* = 1.5 Hz, 0.3 H), 3.70 (d, *J* = 1.3 Hz, 0.3 H), 2.92 (s, 0.6 H), 2.87 (s, 0.6 H), 2.82 (s, 0.8 H), 2.80 (s, 0.8 H), 2.46–2.58 (m, 0.6 H).

MS (APCI): *m*/*z* = 298 [M + H].

(2,3-*trans*)-*N*-[(1*S*,2*S*)-2-Hydroxycyclohexyl]-*N*-methyl-3-phenyloxirane-2-carboxamide (11j)

Using a procedure similar to that described for **11h** except using (1*S*,2*S*)-2-(methylamino)cyclohexanol (**20**, 3.00 g, 21.1 mmol) and a reaction time of 6 d gave pure title compound **11j** (3.5 g, 60%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.41 (m, 5 H), 3.48–4.35 (m, 4 H), 3.04 (s, 0.8 H), 3.01 (s, 0.8 H), 2.92 (s, 1.4 H), 1.90–2.36 (m, 2 H), 1.47–1.93 (m, 3 H), 1.18–1.61 (m, 4 H).

MS (APCI): *m*/*z* = 276 [M + H].

(2,3-*trans*)-*N*-[(1*R*,2*R*)-2-Hydroxycyclohexyl]-*N*-methyl-3-phenyloxirane-2-carboxamide (11i)

Using a procedure similar to that described in **11h** except using (1*R*,2*R*)-2-(methylamino)cyclohexanol (**21**, 4.3 g, 33.3 mmol) and a reaction time of 14 d yielded the pure title compound **11i** (5.7 g, 69%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.44 (m, 5 H), 4.25–4.37 (m, 0.5 H), 4.13 (d, *J* = 2.0 Hz, 0.2 H), 4.07 (m, 0.6 H), 3.82 (d, *J* = 2.0 Hz, 0.2 H), 3.47–3.68 (m, 2.5 H), 3.04 (s, 0.75 H), 3.01 (s, 0.75 H), 2.92 (s, 1.5 H), 2.39 (d, *J* = 5.0 Hz, 0.2 H), 2.06–2.19 (m, 1.3 H), 1.96 (d, *J* = 7.0 Hz, 0.5 H), 1.56–1.78 (m, 3 H), 1.27–1.56 (m, 4 H).

MS (APCI): *m*/*z* = 276 [M + H].

Preparation of Epoxyamides by the Method of Baldas and Porter;[6] General Method B

***N*-(2-Hydroxyethyl)-(2,3-*trans*)-3-phenyloxirane-2-carboxamide (11a)**

To a stirred solution of ethanolamine (3.10 g, 5.1 mmol), MeOH (15 mL) and H_2O (9 mL), under N_2, was added a solution of ethyl-3-phenyloxirane-2-carboxylate (10.0 g, 5.2 mmol) in MeOH (10 mL) and the mixture was stirred at ambient temperature overnight. The solvent was removed in vacuo and the residue was chromatographed on silica gel (2% MeOH–CH_2Cl_2) to yield the solidified impure material (4.50 g, 43%). A second chromatography on silica gel (20% and 40% Et_2O–CH_2Cl_2 followed by 5% MeOH–CH_2Cl_2) and trituration of combined purer fractions (TLC: silica gel, 10%

MeOH–$CHCl_3$) with Et_2O–hexanes, yielded the title epoxyamide as a white solid (2.78 g, 27%); mp 92–94 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.35 (m, 3 H), 7.30–7.25 (m, 2 H), 6.65 (br s, 1 H, exchangeable), 3.91 (d, *J* = 2.0 Hz, 1 H), 3.80–3.75 (m, 2 H), 3.55 (d, *J* = 2.0 Hz, 1 H), 3.57–3.40 (m, 2 H), 2.28 (s, 1 H, exchangeable).

MS (APCI): *m*/*z* = 208 [M + H].

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.72; H, 6.36; N, 6.76.

N-(2-Hydroxy-2-phenylethyl)-(2,3-*trans*)-3-phenyloxirane-2-carboxamide (11ce)

Using a procedure similar to that described for **11a** except using racemic 2-amino-1-phenylethanol (21.6 g, 15.7 mmol) and ethyl 3-phenyloxirane-2-carboxylate (30.8 g, 16.0 mmol) in MeOH (60 mL)–H_2O (30 mL) gave the white title compound (17.95 g, 40%); mp 137–141 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.30 (m, 8 H), 7.25–7.23 (m, 2 H), 6.60 (br m, 1 H), 4.92–4.87 (m, 1 H), 3.81 (d, *J* = 1.8 Hz, 0.5 H), 3.78 (d, *J* = 1.8 Hz, 0.5 H), 3.77–3.68 (m, 1 H), 3.52 (d, *J* = 1.8 Hz, 1 H), 3.47–3.38 (m, 1 H), 2.80 (br s, 1 H).

MS APCI, *m*/*z* = 266 [M + H – H_2O].

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.74; H, 6.02; N, 4.81.

Preparation of Epoxyamides by Carbodiimide Coupling; General Method C

(2*R*,3*S*)-*N*-[(2*S*)-2-Hydroxy-2-phenylethyl]-*N*-methyl-3-phenyloxirane-2-carboxamide (12f)

To a stirred cooled (ice-bath) solution of (1*S*)-2-(methylamino)-1-phenylethanol (**23**, 800 mg, 5.3 mmol) in CH_2Cl_2 (25 mL) was added successively potassium (2*R*,3*S*)-3-phenyloxirane-2-carboxylate (**16**, 711 mg, 3.65 mmol), HOBt (1.2 g, 7.8 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.0 g, 5.3 mmol) and *N*-methylmorpholine (581 μL, 5.3 mmol). After 1.5 h the ice bath was removed and the reaction stirred at ambient temperature. After 2.5 h the volume was reduced to ca. 10 mL and the residue partitioned between H_2O (25 mL) and EtOAc (50 mL). The organic layer was washed successively with 0.5 N HCl (2 × 50 mL), H_2O (2 × 50 mL), sat. $NaHCO_3$ (25 mL), brine (25 mL), dried (Na_2SO_4), filtered and the solvent was removed to yield the crude title compound (1.1 g). Trituration with Et_2O (25 mL) returned pure **12f** (590 mg). Material obtained by evaporation of the filtrate solvent was purified by chromatography (eluent: 50% EtOAc–hexanes) to give an addition 340 mg of pure title compound (85% total yield). The 340 mg was recrystallized from Et_2O (10 mL) to afford the analytically pure title compound (224 mg); mp 99.5–102.5 °C; $[\alpha]_D^{23}$ –26.9 (*c* = 1.08, EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.28 (m, 10 H), 5.06 (m, 0.6 H), 4.98–4.91 (m, 0.4 H), 4.08 (d, *J* = 1.7 Hz, 1 H), 3.85–3.57 (m, 4 H), 3.06 (s, 1.2 H), 2.98 (s, 1.8 H).

MS (APCI): *m*/*z* = 298 [M + H].

Anal. Calcd for $C_{18}H_{19}N_2O_3$ (297.37): C, 72.71; H, 6.44; N, 4.71. Found: C, 72.40; H, 6.42; N, 4.74.

(2*S*,3*R*)-*N*-[(2*S*)-2-Hydroxy-2-phenylethyl]-*N*-methyl-3-phenyloxirane-2-carboxamide (13f)

Using a procedure similar to that described for **12f** except using potassium (2*S*,3*R*)-3-phenyloxirane-2-carboxylate (**17**, 610 mg, 3.2 mmol) yielded **13f** (600 mg, 63%); $[\alpha]_D^{23}$ +104.6 (*c* = 1.09, EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.22 (m, 10 H), 5.07–5.02 (m, 0.67 H), 4.94–4.88 (m, 0.33 H), 4.08 (d, *J* = 1.8 Hz, 0.67 H), 4.04 (d, *J* = 1.8 Hz, 0.33 H), 3.81–3.46 (m, 3.67 H), 3.07 (s, 3 H), 2.67 (d, *J* = 3.9 Hz, 0.33 H).

Anal. Calcd for $C_{18}H_{19}NO_3 \cdot 0.2\ H_2O$ (300.96): C, 71.84; H, 6.50; N, 4.65. Found: C, 71.83; H, 6.31; N, 4.83.

(2*R*,3*R*)-*N*-[(2*S*)-2-Hydroxy-2-phenylethyl]-*N*-methyl-3-phenyloxirane-2-carboxamide (14f)

Using a procedure similar to that described for **12f** except using potassium (2*R*,3*R*)-3-phenyloxirane-2-carboxylate (**18,** 460 mg, 2.4 mmol) gave the pure **14f** (420 mg, 59%); $[\alpha]_D^{23}$ +18.66 (*c* = 1.34, EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.03 (m, 10 H), 4.81–4.79 (m, 0.2 H), 4.71–4.62 (m, 0.8 H), 4.32 (d, *J* = 4.4 Hz, 0.8 H), 4.19 (d, *J* = 4.4 Hz, 0.2 H), 3.93 (d, *J* = 4.4 Hz, 0.8 H), 3.85–3.42 (m, 1.2 H), 3.02 (dd, *J* = 14.1, 7.2 Hz, 1 H), 2.85 (d, *J* = 4.4 Hz, 0.8 H), 2.75 (s, 0.6 H), 2.74 (s, 2.4 H), 2.04–2.02 (m, 0.2 H).

MS (APCI): *m*/*z* = 298 [M + H].

Anal. Calcd for $C_{18}H_{19}N_2O_3 \cdot (0.1\ C_4H_8O_2)$ (306.17): C, 72.18; H, 6.52; N, 4.58. Found: C, 72.15; H, 6.47; N, 4.67.

(2*S*,3*S*)-*N*-[(2*S*)-2-Hydroxy-2-phenylethyl]-*N*-methyl-3-phenyloxirane-2-carboxamide (15f)

Using a procedure similar to that described for **12f** except using potassium (2*S*,3*S*)-3-phenyloxirane-2-carboxylate (**19,** 390 mg, 2.0 mmol) yielded the pure **15f** (580 mg, 96%); mp 118–119 °C; $[\alpha]_D^{20}$ –88.7 (*c* = 1.16, EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.14 (m, 10 H), 4.88–4.84 (m, 0.25 H), 4.63–4.58 (m, 0.75 H), 4.30 (d, *J* = 4.4 Hz, 0.75 H), 4.24 (d, *J* = 4.4 Hz, 0.25 H), 4.06 (d, *J* = 4.4 Hz, 0.25 H), 3.92 (d, *J* = 4.4 Hz, 0.75 H), 3.72–3.44 (m, 1 H), 3.26 (d, *J* = 4.0 Hz, 0.5 H), 3.21 (d, *J* = 4.0 Hz, 0.5 H), 3.14 (d, *J* = 3.6 Hz, 0.75 H), 2.85 (s, 3 H), 2.47 (d, *J* = 3.4 Hz, 0.25 H).

MS (APCI): *m*/*z* = 298 [M + H].

Anal. Calcd for $C_{18}H_{19}N_2O_3$ (297.35): C, 72.71; H, 6.44; N, 4.71. Found: C, 72.54; H, 6.38; N, 4.75.

(2*R*,3*S*)-*N*-[(1*S*,2*S*)-2-Hydroxycyclohexyl]-*N*-methyl-3-phenyloxirane-2-carboxamide (12j)

Using a procedure similar to that described for **12f** except using (1*S*,2*S*)-2-(methylamino)cyclohexanol (**20**, 1.8 g, 13.9 mmol) yielded the title compound **12j** (2.35 g, 81%). Recrystallization from toluene returned analytically pure **12j** (1.4 g, 60% recovery); mp 119–121 °C; $[\alpha]_D^{23}$ –99.1 (*c* = 1.07, MeCN).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.38 (m, 5 H), 4.30 (m, 0.5 H), 4.13 (d, *J* = 1.9 Hz, 0.5 H), 4.08 (d, *J* = 1.8 Hz, 0.5 H), 3.69 (d, *J* = 1.9 Hz, 0.5 H), 3.51–3.68 (m, 2 H), 3.04 (s, 1.5 H), 2.92 (s, 1.5 H), 2.26 (s, 0.5 H, exchangeable), 2.13 (m, 0.5 H, exchangeable), 1.67–2.00 (m, 4 H), 1.23–1.49 (m, 4 H).

MS (APCI); *m*/*z* = 276 [M + H].

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.52; H, 7.70; N, 5.18

(2*R*,3*S*)-*N*-[(1*R*)-2-Hydroxy-1-phenylethyl]-*N*-methyl-3-phenyloxirane-2-carboxamide (12h)

Using a procedure similar to that described for **12f** except using (2*R*)-2-(methylamino)-2-phenylethanol (**22**, 2.26 g, 15.0 mmol) and a 20 h reaction time gave the pure title compound **12h** (1.34 g, 45%); $[\alpha]_D^{23}$ –212.6 (*c* = 1.03, EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.16 (m, 10 H), 5.83 (dd, *J* = 9.3, 5.1 Hz, 0.6 H), 5.31 (t, *J* = 7.0 Hz, 0.4 H), 4.23– 4.08 (m, 3 H), 3.97 (d, *J* = 1.7 Hz, 0.4 H), 3.69 (d, *J* = 1.7 Hz, 0.6 H), 2.87 (s, 1.8 H), 2.82 (s, 1.2 H), 2.48 (t, *J* = 5.5 Hz, 0.4 H), 2.36 (dd, *J* = 7.3, 4.4 Hz, 0.6 H).

HRMS: *m*/*z* [M + H] calcd for $C_{18}H_{20}NO_3$: 298.1443; found: 298.1432.

(2*S*,3*R*)-*N*-[(1*R*)-2-Hydroxy-1-phenylethyl]-*N*-methyl-3-phenyloxirane-2-carboxamide (13h)

Using a procedure similar to that described for **12f** except using (2*R*)-2-(methylamino)-2-phenylethanol (**22**, 1.24 g, 8.19 mmol), potassium (2*S*,3*R*)-3-phenyloxirane-2-carboxylate (**17**, 1.05 g, 5.46 mmol) and a 5 h reaction time gave the pure title compound **13h** (1.20 g, 74%); $[\alpha]_D^{23}$ –43.0 (*c* = 1.0, EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.26 (m, 10 H), 5.81–5.77 (m, 0.6 H), 5.35–5.30 (m, 0.4 H), 4.20–4.09 (m, 3 H), 3.82 (d, *J* = 1.4 Hz, 0.4 H), 3.72 (d, *J* = 1.4 Hz, 0.6 H), 2.92 (s, 1.8 H), 2.80 (s, 1.2 H), 2.44 (t, *J* = 5.9 Hz, 0.6 H), 2.27 (t, *J* = 5.8 Hz, 0.4 H).

HRMS: *m*/*z* [M + H] calcd for $C_{18}H_{20}NO_3$: 298.1443; found: 298.1439.

(2*R*,3*S*)-*N*-(2-Hydroxyethyl)-3-phenyloxirane-2-carboxamide (12a)

To a stirred, cooled (ice-bath) mixture of potassium (2*R*,3*S*)-3-phenyloxirane-2-carboxylate (**16**, 1.01 g, 5.0 mmol) and CH_2Cl_2 (40 mL) were added successively HOBt (1.67 g, 12.5 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.63 g, 8.5 mmol) and *N*-methylmorpholine (0.86 g, 8.5 mmol) and the mixture was stirred for 10 min. Aminoethanol (0.52 g, 8.5 mmol) was added, the bath was removed and the mixture was stirred at ambient temperature overnight. The reaction mixture containing a white precipitate was added to a 1.5 inch diameter column containing 50 g of silica gel and the column was eluted with 2% MeOH–CH_2Cl_2. Fractions containing the desired material (TLC, silica gel: 2% MeOH–CH_2Cl_2) were combined, the solvent was removed in vacuo and the residual gum was triturated with toluene. The collected white solid was recrystallized from hot toluene (15 mL) to yield the title compound as colorless needles (0.45 g, 44%); mp 102–104 °C; $[\alpha]_D^{23}$ –140.2 (*c* = 1.035, EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.35 (m, 3 H), 7.30–7.26 (m, 2 H), 6.64 (br s, 1 H), 3.91 (d, *J* = 1.9 Hz, 1 H), 3.79–3.76 (m, 2 H), 3.55 (d, *J* = 1.9 Hz, 1 H), 3.57–3.42 (m, 2 H), 2.25 (br s, 1 H).

MS (APCI): *m*/*z* = 208 [M + H].

Anal. Calcd for $C_{11}H_{13}NO_3 \cdot 0.1\ H_2O$ (209.03): C, 63.216; H, 6.37; N, 6.70. Found: C, 63.24; H, 6.28; N, 6.76.

(2*R*,3*S*)-*N*-(2-Hydroxyethyl)-*N*-methyl-3-phenyloxirane-2-carboxamide (12b)

Using a procedure similar to that described for **12a** except using potassium (2*R*,3*S*)-3-phenyloxirane-2-carboxylate (**16**, 0.58 g, 2.9 mmol), 2-(methylamino)ethanol (0.32 g, 4.3 mmol) and the aqueous workup described for **12f** gave the pure **12b** (191 mg). The H_2O layer was re-extracted with EtOAc (3 ×) to yield an additional 312 mg of less-pure product. Column chromatography (eluent: 0–3% MeOH–CH_2Cl_2) returned the title compound (245 mg). Total yield was 436 mg (68%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.29 (m, 5 H), 4.09 (d, *J* = 1.9 Hz, 0.8 H), 3.89–3.76 (m, 2.5 H), 3.71–3.54 (m, 2.6 H), 3.20 (s, 1.7 H), 3.05 (s, 1.3 H), 2.57 (br s, 0.6 H), 2.19 (br s, 0.4 H).

MS (APCI): *m*/*z* = 222 [M + H].

HRMS: *m*/*z* [M + H] calcd for $C_{12}H_{16}NO_3$: 222.1130; found: 222.1129.

(2*R*,3*S*)-*N*-[(1*R*,2*R*)-2-Hydroxycyclohexyl]-*N*-methyl-3-phenyloxirane-2-carboxamide (12i)

Using a procedure similar to that described for **12a** except using potassium (2*R*,3*S*)-3-phenyloxirane-2-carboxylate (**16**, 3.13 g, 24.2 mmol), (1*R*,2*R*)-2-(methylamino)cyclohexanol (**21**, 3.13 g, 24.2 mmol) and the aqueous workup described for **12f** followed by column chromatography of the resulting oil on silica gel (eluent: $CHCl_3$, then 2% MeOH in $CHCl_3$) gave the impure title compound (2.11 g). Further purification by column chromatography on silica gel [eluent: hexanes–CH_2Cl_2 (1:1), CH_2Cl_2 and 5%, 10% and 20% EtOAc–CH_2Cl_2] returned the title compound (0.93 g, 18%) as a hygroscopic tacky solidified white foam; $[\alpha]_D^{23}$ –14.9 (*c* = 1.01, EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.4–7.33 (m, 5 H), 4.36–4.27 (m, 0.55 H), 4.08 (m, 1 H), 3.83 (d, 0.45 H), 3.73–3.48 (m, 2 H), 3.01 (s, 1.65 H), 2.92 (s, 1.35 H), 2.47 (d, 0.45 H, exchangeable), 2.17–2.12 (m, 1.55 H, 0.55 H exchangeable), 1.79–1.22 (m, 7 H).

Anal. Calcd for $C_{16}H_{21}NO_3 \cdot 0.1\ H_2O$ (277.15): C, 69.34; H, 7.71; N, 5.05. Found: C, 69.34; H, 7.76; N, 4.85.

MgI_2 Ring Closures; General Method D

(2*S*,6*R*,7*R*)- and (2*R*,6*S*,7*S*)-6-Hydroxy-4-methyl-2,7-diphenyl-1,4-oxazepan-5-one (1:1 mixture of 1f and 2d)

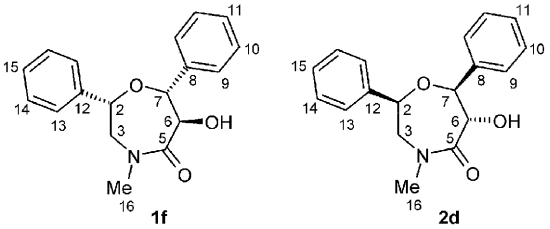


Figure 10 Numbering of **1f**:**2d** for ^{13}C NMR spectra.

To a stirred solution of (2,3-*trans*)-*N*-(2-hydroxy-2-phenylethyl)-*N*-methyl-3-phenyloxirane-2-carboxamide (**11df**, 2.1 g, 7.6 mmol) in anhyd THF (300 mL) was added 10 mol% of MgI_2 (215 mg, 0.76 mmol, 98% purity) and the mixture was heated at reflux over a weekend, cooled, and evaporated to an orange oil. Column chromatography (1% MeOH–CH_2Cl_2) afforded the title mixture of **1f** and **2d** (900 mg, 43%; Figure 10).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.46 (m, 10 H), 4.70 (d, *J* = 8.7 Hz, 1 H), 4.57 (dd, *J* = 9.1, 4.1 Hz, 1 H), 4.47 (d, *J* = 9.1 Hz, 1 H), 4.31 (d, *J* = 4.1 Hz, 1 H), 4.07 (dd, *J* = 15.9, 9.1 Hz, 1 H) 3.33 (d, *J* = 15.9 Hz, 1 H), 3.26 (s, 3 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 174.61 (C5), 139.43 (C8), 139.39 (C12), 128.69 (C10), 128.25 (C15), 128.14 (C14), 128.11 (C11), 127.64 (C9), 125.81 (C13), 82.07 (C7), 81.19 (C2), 73.94 (C6), 59.59 (C3), 37.45 (C16).

MS (APCI): *m*/*z* = 298 [M + Na].

(6*R*,7*R*)- and (6*S*,7*S*)-6-Hydroxy-4-methyl-7-phenyl-1,4-oxazepan-5-one (1:1 mixture of 1b and 2b)

To a stirred solution of (2,3-*trans*)-*N*-(2-hydroxyethyl)-*N*-methyl-3-phenyloxirane-2-carboxamide (**11b**, 5.4 g, 24.4 mmol) in anhyd THF (300 mL) was added 10 mol% of MgI_2 (670 mg, 2.44 mmol, 98% purity) and the mixture was heated to reflux overnight, cooled, and evaporated to a crude orange oil. Column chromatography (1% MeOH–CH_2Cl_2) returned the title mixture (2.7 g, 50%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.29 (m, 5 H), 4.49–4.44 (q, 1 H), 4.30 (d, *J* = 4 Hz, 1 H), 4.23 (d, *J* = 9 Hz, 1 H), 4.14–3.97 (m, 2 H), 3.70–3.63 (q, 1 H), 3.27–3.21 (q, 1 H), 3.19 (s, 3 H).

MS (APCI): *m*/*z* = 222 [M + H].

(6*R*,7*R*)-6-Hydroxy-4-methyl-7-phenyl-1,4-oxazepan-5-one (1b)

Anhydrous MgI_2 (26 mg, 0.095 mmol) was added in one portion to a stirred solution of (2*R*,3*S*)-*N*-(2-hydroxyethyl)-*N*-methyl-3-phe-

nyloxirane-2-carboxamide (**12b**, 105 mg, 0.47 mmol) in anhyd THF (25 mL) and the mixture was stirred at reflux overnight. The reaction was cooled, partitioned between EtOAc (50 mL) and sat. aq NH_4Cl (25 mL) and stirred for 15 min. The layers were separated and the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to a crude oil. Chromatography [eluent: 1% MeOH–CH_2Cl_2] returned the pure product (59 mg, 56% yield), which was identical to **1b** obtained by Method F; $[\alpha]_D^{20}$ +35.4 (*c* = 0.96, EtOH).

MS (APCI): *m*/*z* = 222 [M + H].

The MgI_2 preparation of compounds **1f**, **1h**, and **2h** in Tables 5 and 6 was carried out using the procedure described for **1b** and all compounds were identical to material prepared using method F.

TFA Ring Closures; General Method E

(2*R*,3*S*)-*N*-[(1*S*,2*S*)-2-Hydroxycyclohexyl]-*N*-methyl-3-phenyloxirane-2-carboxamide (1j, Scheme 3)

To an ice cooled suspension of potassium (2*R*,3*S*)-3-phenyloxirane-2-carboxylate (**16**, 220 mg, 1.1 mmol) in CH_2Cl_2 (15 mL) were added successively (1*S*,2*S*)-2-(methylamino)cyclohexanol (**20**, 281 mg, 2.2 mmol), HOBt (281 mg, 2.0 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (271 mg, 1.4 mmol) and *N*-methylmorpholine (153 μL, 1.4 mmol) and the mixture was stirred for 15 min. The ice bath was removed and the mixture was stirred at r.t. overnight. The reaction volume was reduced to ca 5 mL, partitioned between EtOAc (75 mL) and 5% citric acid (30 mL), washed with 5% citric acid, H_2O, sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure to give slightly impure **12j** (300 mg).

A 150 mg sample of this material was purified by reverse phase chromatography (C18 column eluting with 15–90% MeCN–H_2O–0.1%TFA over 20 min). The purest fractions, as determined by the chromatographic trace, were combined and allowed to stand in the MeCN–H_2O–0.1% TFA eluent (estimated as ca 90% MeCN) overnight. Over this time period the eluted compound **12j** was converted to nearly pure ring-closed oxazepinone **1j**. The volume was reduced under reduced pressure, the residue made basic with sat. $NaHCO_3$, extracted into CH_2Cl_2, the organic layer washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield **1j** (100 mg, 67%) which was identical spectrographically to material prepared by Method F.

The remaining 150 mg of **12j** was purified as above and monitored for conversion to **1j**. Immediately after chromatography was complete the ratio of isolated material was 9:1 (**12j**/**1j**). After 7 h the ratio was 1:3 (**12j**/**1j**) with small amounts of elimination products. After 20 h conversion to **1j** was ca 90%.

(6*R*,7*R*)-6-Hydroxy-4-methyl-7-phenyl-1,4-oxazepan-5-one (1b)

To a stirred cooled (ice-bath) solution of (2*R*,3*S*)-*N*-(2-hydroxyethyl)-*N*-methyl-3-phenyloxirane-2-carboxamide (**12b**, 90 mg, 0.41 mmol) in MeCN (2 mL) was added TFA (3.3 μL, 0.041 mmol), the ice bath was removed and the mixture was stirred at ambient temperature for 40 h. Purification by reverse phase chromatography (Rainin–Dynamax 60 Å C-18 21 × 250 mm column, 20–95% MeCN–H_2O over 20 min), combination of the proper fractions and freeze drying returned 45 mg (50% yield) of ca 95% pure product. The material was analytically identical to **1b** from Method F; $[\alpha]_D^{20}$ +34.4 (*c* = 0.90, EtOH).

The TFA preparation of compounds **1f**, **2f**, **3f**, **4f**, **1h**, and **2h** in Tables 5 and 6 was carried out using the procedure described for **1b** and all compounds were identical to material prepared using method F.

$Sc(OTf)_3$ Ring Closures; General Method F

(6*R*,7*R*)-6-Hydroxy-7-phenyl-1,4-oxazepan-5-one (1a)

To a stirred solution of (2*R*,3*S*)-*N*-(2-hydroxyethyl)-3-phenyloxirane-2-carboxamide (**12a**, 0.2072 g, 1.0 mmol) in MeCN (5 mL) was added scandium triflate (0.0492 g, 0.10 mmol) and the mixture was stirred at ambient temperature for 24 h. The solvent was removed in vacuo and the residue added to a silica gel column with CH_2Cl_2. Elution with CH_2Cl_2 returned the crude title compound (0.0755 g, 36%). The material was dissolved in refluxing toluene (5 mL), treated hot with hexanes (2 mL), scratched with a spatula to initiate crystal formation and allowed to stand at ambient temperature overnight. Filtration returned the white title compound (0.0595 g, 29%); mp 150–152 °C; $[\alpha]_D^{23}$ +32.3 (*c* = 1.02, EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.32 (m, 5 H), 6.39 (br s, 1 H), 4.44 (dd, *J* = 3.7, 9.2 MHz, 1 H), 4.27 (d, *J* = 9.1 MHz, 1 H), 4.19–4.13 (q, 1 H), 4.02 (d, exchangeable, *J* = 3.7 MHz, 1 H), 3.81–3.62 (m, 2 H) 3.31–3.23 (m, 1 H).

MS (APCI): *m*/*z* = 208 [M + H].

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.54; H, 6.16; N, 6.69.

(6*R*,7*R*)-6-Hydroxy-4-methyl-7-phenyl-1,4-oxazepan-5-one (1b)

To a cooled (ice-bath) solution of (2*R*,3*S*)-*N*-(2-hydroxyethyl)-*N*-methyl-3-phenyloxirane-2-carboxamide (**12b**, 81 mg, 0.366 mmol) in MeCN (2 mL) was added scandium triflate (18 mg, 0.037 mmol) in one portion. After 5 min no starting material remained. The mixture was concentrated under reduced pressure and purified by column chromatography (eluent: 1% MeOH–$CHCl_3$) to give the title compound (67 mg, 82%). A sample (61 mg) was triturated with Et_2O, filtered and vacuum dried at r.t. overnight to give the analytically pure **1b** (22 mg); mp 70–73 °C; $[\alpha]_D^{23}$ +35.6 (*c* = 1.18, EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.29 (m, 5 H), 4.47 (d, *J* = 9.1 Hz, 1 H), 4.31 (s, 1 H), 4.23 (d, *J* = 9.1 Hz, 1 H), 4.14–3.98 (m, 2 H), 3.68 (d, *J* = 13.0 Hz, 0.5 H), 3.65 (d, *J* = 13.0 Hz, 0.5 H), 3.27 (d, *J* = 4.1 Hz, 0.5 H), 3.22 (d, *J* = 4.1 Hz, 0.5 H), 3.20 (s, 3 H).

MS (APCI): *m*/*z* = 222 [M + H].

Anal. Calcd for $C_{12}H_{15}NO_3$ (221.26): C, 65.15; H, 6.83; N, 6.33. Found: C, 64.74; H, 6.68; N, 6.36.

(3*R*,6*R*,7*R*)-6-Hydroxy-4-methyl-3,7-diphenyl-1,4-oxazepan-5-one (1h)

Using a procedure similar to that described for **1b** except using (2*R*,3*S*)-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]-*N*-methyl-3-phenyloxirane-2-carboxamide (**12h**, 170 mg, 0.57 mmol) yielded the pure title compound **1h** (130 mg, 76%); mp 136–137 °C; $[\alpha]_D^{23}$ +29.0 (*c* = 1.07, EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.20 (m, 10 H), 4.74 (dd, *J* = 13.7, 4.7 Hz, 1 H), 4.59 (d, *J* = 4.4 Hz, 1 H), 4.34–4.28 (m, 2 H), 4.17–4.09 (m, 2 H), 3.39 (s, 3 H).

MS (APCI): *m*/*z* = 298 [M + H].

Anal. Calcd for $C_{18}H_{19}N_2O_3 \cdot 0.25\ H_2O$ (301.86): C, 71.62; H, 6.51; N, 4.64. Found: C, 71.87; H, 6.26; N, 4.72.

(2*R*,3*R*,5a*S*,9a*S*)-3-Hydroxy-5-methyl-2-phenyloctahydro-1,5-benzoxazepin-4(5*H*)-one (1j)

Using a procedure similar to that described for **1b** except using (2*R*,3*S*)-*N*-[(1*S*,2*S*)-2-hydroxycyclohexyl]-*N*-methyl-3-phenyloxirane-2-carboxamide (**12j**, 208 mg, 0.756 mmol) yielded the pure title compound **1j** (191 mg, 92%); mp 200–201 °C; $[\alpha]_D^{23}$ –37.1 (*c* = 1.51, MeCN).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26–7.38 (m, 5 H), 4.55 (d, *J* = 8.7 Hz, 1 H), 4.32 (d, *J* = 8.8 Hz, 1 H), 4.29 (br s, 1 H), 3.69–3.77

(m, 1 H), 3.42–3.50 (m, 1 H), 3.16 (s, 3 H), 2.06–2.15 (m, 2 H), 1.82–1.87 (m, 1 H), 1.60–1.75 (m, 2 H), 1.17–1.53 (m, 3 H).

MS (APCI): *m*/*z* = 276 [M + H].

Anal. Calcd for $C_{16}H_{21}NO_3$ (275.35): C, 69.79; H, 7.69; N, 5.09. Found: C, 69.49; H, 7.46; N, 4.95.

(2*R*,3*R*,5a*R*,9a*R*)-3-Hydroxy-5-methyl-2-phenyloctahydro-1,5-benzoxazepin-4(5*H*)-one (1i)

To a stirred solution of (2*R*,3*S*)-*N*-[(1*R*,2*R*)-2-hydroxycyclohexyl]-*N*-methyl-3-phenyloxirane-2-carboxamide (**12i**, 0.2754 g, 1.0 mmol) in MeCN (5 mL) was added scandium triflate (0.0492 g, 0.10 mmol) and the mixture was stirred at ambient temperature for 1 h. The solvent was removed in vacuo and the residue in $CHCl_3$ was added to a silica gel column. Elution with $CHCl_3$ returned the title compound as a white solid (0.1998 g, 73%); mp 143–154 °C. Recrystallization from toluene–hexanes (1:2, 25 mL) returned the white title compound (0.1692 g, 61%); mp 157–159 °C; $[\alpha]_D^{23}$ –29.6 (*c* = 1.015, EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 7.1 Hz, 2 H), 7.41–7.29 (m, 3 H), 4.84 (d, *J* = 10 Hz, 1 H), 4.63 (d, *J* = 10 Hz, 1 H), 4.60 (br s, 1 H, exchangeable), 3.94–3.86 (m, 1 H), 3.12–3.04 (m, 1 H), 3.08 (s, 3 H), 2.23–2.17 (m, 1 H), 2.01–1.96 (m, 1 H), 1.79–1.73 (m, 2 H), 1.46–1.24 (m, 4 H).

MS (APCI): *m*/*z* = 276 [M + H].

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.58; H, 7.62; N, 5.05.

(2*S*,6*R*,7*R*)-6-Hydroxy-4-methyl-2,7-diphenyl-1,4-oxazepan-5-one (1f)

Using a procedure similar to that described for **1b** except using (2*R*,3*S*)-*N*-[(2*S*)-2-hydroxy-2-phenylethyl]-*N*-methyl-3-phenyloxirane-2-carboxamide (**12f**, 103 mg, 0.347 mmol) yielded the pure title compound **1f** (100 mg, 97%). An analytical sample was obtained by recrystallization from Et_2O–hexanes; mp 120–121 °C; $[\alpha]_D^{23}$ +52.5 (*c* = 0.97, EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.27 (m, 10 H), 4.70 (d, *J* = 8.8 Hz, 1 H), 4.58 (dd, *J* = 9.1, 4.1 Hz, 1 H), 4.47 (d, *J* = 9.1 Hz, 1 H), 4.32 (d, *J* = 4.1 Hz, 1 H), 4.07 (dd, *J* = 15.9, 8.8 Hz, 1 H), 3.30 (d, 1 H), 3.25 (s, 3 H).

MS (APCI): *m*/*z* = 298 [M + H].

Anal. Calcd for $C_{18}H_{19}N_2O_3 \cdot 0.15\ H_2O$ (300.06): C, 72.05; H, 6.48; N, 4.67. Found: C, 71.87; H, 6.26; N, 4.72.

(2*S*,6*S*,7*S*)-6-Hydroxy-4-methyl-2,7-diphenyl-1,4-oxazepan-5-one (2f)

Using a procedure similar to that described for **1b** except using (2*S*,3*R*)-*N*-[(2*S*)-2-hydroxy-2-phenylethyl]-*N*-methyl-3-phenyloxirane-2-carboxamide (**13f**, 89 mg, 0.30 mmol) yielded the pure title compound **2f** (80 mg, 89%). An analytical sample was prepared by recrystallization from Et_2O; mp 129–130 °C; $[\alpha]_D^{23}$ +65.7 (*c* = 0.78, EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53–7.28 (m, 10 H), 4.89–4.82 (m, 3 H), 4.32 (d, *J* = 4.4 Hz, 1 H), 4.05 (dd, *J* = 4.4, 15.8 Hz, 1 H), 3.50 (dd, *J* = 2.2, 15.8 Hz, 1 H), 2.98 (s, 3 H).

MS (APCI): *m*/*z* = 298 [M + H].

Anal. Calcd for $C_{18}H_{19}NO_3$ (297.35): C, 72.71; H, 6.44; N, 4.71. Found: C, 72.39; H, 6.47; N, 4.73.

(2*S*,6*R*,7*S*)-6-Hydroxy-4-methyl-2,7-diphenyl-1,4-oxazepan-5-one (3f)

Using a procedure similar to that described for **1b** except using (2*R*,3*R*)-*N*-[(2*S*)-2-hydroxy-2-phenylethyl]-*N*-methyl-3-phenyloxirane-2-carboxamide (**14f**, 131 mg, 0.44 mmol) yielded the pure title compound **3f** (95 mg, 73%); mp 126–128 °C; $[\alpha]_D^{23}$ –39.5 (*c* = 0.78, EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.28 (m, 10 H), 5.41 (d, *J* = 4.1 Hz, 1 H), 4.98 (t, *J* = 3.6 Hz, 1 H), 4.62 (d, *J* = 9.0 Hz, 1 H), 4.38 (d, *J* = 3.1 Hz, 1 H), 3.99 (dd, *J* = 15.7, 9.1 Hz, 1 H), 3.24 (d, *J* = 15.7 Hz, 1 H), 3.10 (s, 3 H).

MS (APCI): *m*/*z* = 298 [M + H].

Anal. Calcd for $C_{18}H_{19}NO_3 \cdot 0.35\ H_2O$ (303.66): C, 71.20; H, 6.54; N, 4.61. Found: C, 71.13; H, 6.42; N, 4.63.

(2*S*,6*S*,7*R*)-6-Hydroxy-4-methyl-2,7-diphenyl-1,4-oxazepan-5-one (4f)

Using a procedure similar to that described for **1b** except using (2*S*,3*S*)-*N*-[(2*S*)-2-hydroxy-2-phenylethyl]-*N*-methyl-3-phenyloxirane-2-carboxamide (**15f**, 100 mg, 0.34 mmol) and a 18 h reaction time yielded the pure title compound **4f** (75 mg, 75%) as a non-crystalline solid; mp 53–58 °C; $[\alpha]_D^{23}$ +24.9 (*c* = 0.72, EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.30 (m, 10 H), 5.02 (d, *J* = 4.1 Hz, 1 H), 4.86–4.79 (m, 2 H), 3.97 (d, *J* = 15.7 Hz, 1 H), 3.68 (d, *J* = 14.9 Hz, 1 H), 3.11 (br s, 1 H), 3.11 (s, 3 H).

MS (APCI): *m*/*z* = 298 [M + H].

Anal. Calcd for $C_{18}H_{19}NO_3 \cdot 0.1\ H_2O$ (300.965): C, 71.84; H, 6.50; N, 4.65. Found: C, 71.73; H, 6.32; N, 4.64.

(3*R*,6*S*,7*S*)-6-Hydroxy-4-methyl-3,7-diphenyl-1,4-oxazepan-5-one (2h)

Using a procedure similar to that described for **1b** except using (2*S*,3*R*)-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]-*N*-methyl-3-phenyloxirane-2-carboxamide (**13h**, 175 mg, 0.59 mmol) yielded the pure title compound **2h** (149 mg, 85%); mp 129–132 °C ; $[\alpha]_D^{23}$ +9.4 (*c* = 1.06, EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.30 (m, 8 H), 7.26–7.22 (m, 2 H), 5.05 (dd, *J* = 8.6, 1.0 Hz, 1 H), 4.81 (d, *J* = 8.9 Hz, 1 H), 4.50 (br s, 1 H), 4.47 (d, *J* = 8.9 Hz, 1 H), 4.29 (dd, *J* = 12.6, 1.5 Hz, 1 H), 4.08 (dd, *J* = 12.6, 8.6 Hz, 1 H), 2.74 (s, 3 H).

MS (APCI): *m*/*z* = 298 [M + H].

Anal. Calcd for $C_{18}H_{19}NO_3 \cdot 0.1\ H_2O$ (299.16): C, 72.27; H, 6.47; N, 4.68. Found: C, 72.10; H, 6.40; N, 5.00.

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