Design, Development, and Scale-Up of a Selective *meso*-Epoxide Desymmetrization Process

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Abstract:

A pilot-plant scale desymmetrization of the cyclic *meso*-epoxide 4b, using a chiral lithium amide prepared from symmetrical diamine 17, was designed and implemented to provide allylic alcohol 3b in high yield and greater than 99% ee. This chiral alcohol was converted to ketone 2b, a key intermediate in a new asymmetric synthesis of LY459477. Chiral diamine 17 was prepared from a readily available chiral precursor, (*R*)- α -methylbenzylamine, and could be recovered from the reaction mixture and reused. Studies performed to probe the mechanism of the rearrangement reaction of epoxide 4b showed that diamine 17 provided an optimal combination of selectivity and scaleability for this process.

Introduction

The preparation of enantiomerically enriched allylic alcohols via desymmetrization of *meso*-epoxides with chiral lithium amide reagents is a well-studied asymmetric rearrangement.¹ In the course of designing an asymmetric synthesis of the metabatropic glutamate (mGlu2/3) receptor agonist LY459477 (1),² this transformation was evaluated as a key element of a potential commercial synthesis for this stereochemically dense glutamic acid analogue. Shown retrosynthetically in Scheme 1, we envisioned the synthesis of cyclopentene *meso*-epoxide **4** from a protected glycine equivalent followed by a desymmetrization of **4** with a chiral lithium amide. Simple oxidation would then provide the key intermediate, cyclopentenone **2**.

This report describes the pilot-scale synthesis of epoxide 4, design and scale-up of the process for the conversion of 4 to enantiomerically enriched allylic alcohol 3, and the preparation of the key intermediate cyclopentenone 2. The

subsequent diastereoselective reactions to convert 2 to the drug substance 1 will be described in a separate report.

Results and Discussion

At the outset of this work we were encouraged by the report of Hodgson³ on the conversion of cyclopentene epoxide 4a to alcohol 3a with 33% ee using n-BuLi/(-)sparteine, albeit in low yield (Scheme 2). Several reports of the preparation of enantioenriched cyclopentenols using lithium amides derived from chiral diamines led us to initiate screening studies with epoxide 4a.4 To evaluate the rearrangement in a racemic case, we treated epoxide 4a with 3 equiv of LDA in THF at 0 °C/2 h. The desired allylic alcohol **3a** was isolated in 37% yield. Amide **6**, resulting from reaction of the ester with LDA, was also obtained in 25% yield (Scheme 3). To limit this undesired displacement reaction we prepared tert-butyl ester 4b (vide infra) and again treated it with LDA under the same conditions. Alcohol 3b was obtained in 81% crystallized yield; no formation of amide 6 was observed. Thus, epoxide 4b, with a *tert*-butoxy carbonyl (Boc) amine protecting group and the tert-butyl ester, was used in subsequent studies.

An initial screen of 25 chiral amines, 1,2-diamines, and 1,2-amino alcohols, was performed as follows. Epoxide **4b** in THF was added to a 0 °C THF solution containing three equivalents of the lithium amide, diamide, or amide/alkoxide (prepared by treating the chiral amine with one or two equivalents of *n*-BuLi/equivalent of amine). The reaction mixtures were allowed to warm to room temperature and were stirred 18 h. Alcohol **3b** was isolated by an aqueous HCl/MTBE workup and purified via chromatography on

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(1) For reviews see: (a) O'Brien, P. J. Chem. Soc., Perkin Trans. 1 1998, 1439.
(b) Cox, P. J.; Simpkins, N. S. Tetrahedron: Asymmetry 1991, 2, 1. (c) Eames, J. Eur. J. Org. Chem. 2002, 393. (d) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. Tetrahedron 1996, 52, 14361. (e) Magnus, A.; Bertilsson, S. K.; Andersson, P. G. Chem. Soc. Rev. 2002, 31, 223. For general reviews see also: (f) Crandall, J. K.; Apparu, M. Org. React. 1983, 29, 245. (g) Satoh, T. Chem Rev. 1996, 96, 3303.

^{(2) (}a) Moher, E. D.; Monn, J. A.; Pedregal-Tercero, C.; Collado, C. I.; Blanco-Urgoiti, J. G. PCT Int. Appl. WO 2003104217, 2003. (b) Massey, S. M.; Monn, J. A.; Valli, M. J. Eur. Pat. Appl. 878463, 1998.

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⁽³⁾ Hodgson, D. M.; Thompson, A. J.; Wadman, S.; Keats, C. J. *Tetrahedron* 1999, 55, 10815.

⁽⁴⁾ For example see: (a) Asami, M.; Ogawa, M.; Inoue, S. Tetrahedron Lett. 1999, 40, 1563. (b) O'Brien, P.; Towers, T. T.; Voith, M. Tetrahedron Lett. 1998, 39, 8175. (c) Hodgson, D. M.; Gibbs, A. R. Tetrahedron: Asymmetry 1996, 7, 407. (d) Bhuniya, D.; DattaGupta, A.; Singh V. K. J. Org. Chem. 1996, 61, 6108. (e) Hodgson, D. M.; Gibbs, A. R.; Drew, M. G. B. J. Chem. Soc., Perkin Trans. I 1999, 3579. (f) Milne, M.; Murphy, P. J. J. Chem. Soc., Chem. Commun. 1993, 884. (g) Hodgson, D. M.; Witherington, J. Moloney, B. A. J. Chem. Soc., Perkin Trans. I 1994, 3373. (h) Asami, M.; Takahashi, J.; Inoue, S. Tetrahedron: Asymmetry 1994, 5, 1649. (i) Sodergen, M. K.; Bertilsson, S. K.; Andersson, P. G. J. Am. Chem. Soc. 2000, 122, 6610.



Scheme 2. Rearrangement of epoxide 4a with *n*-BuLi/(-)-sparteine³



Scheme 3. Rearrangement of epoxides 4a,b with LDA



silica gel. A subset of the screening results is shown in Table 1.

Notably, the best enantioselectivities were obtained with the symmetrical diamines **13** and **14**, which gave alcohol **3b** with 93 and 78% ee, respectively. Both diamines were prepared from readily available (*R*)- α -methylbenzylamine using modified literature procedures (Scheme 4).^{7,8}

Thus, further optimization work was focused on this series of symmetrical diamines. While the simpler diamine **14** was easier to prepare, it is an oil at room temperature. Diamine **13** is highly crystalline, provides higher enantioselectivity, and was therefore studied first. Reducing the amount of dilithium-**13** to 2.2 equiv and maintaining the reaction temperature at 0 °C provided crude alcohol **3b** with 97% ee. Crystallization of the crude product from heptane/MTBE gave **3b** of 99.8% ee in 64% yield at 250-g scale (Scheme 5). Diamine **13** dihydrochloride salt was recovered from the reaction mixture by filtration following the quench of the reaction with aqueous HCl. This salt was converted to the free base and crystallized from ethanol to yield diamine **13** in 80% overall yield.

This process provided intermediates for the study of downstream chemistry, but it was not initially viewed as ideal for commercial development. Although diamine 13 could be recovered from the reaction and reused, its preparation required a low-yielding, cryogenic Grignard reaction (Scheme 4).9 In addition the rearrangement reaction required a relatively large mass of diamine 13 (3.5 kg/kg of epoxide 4b). However, attempts to reduce the amount of 13 needed, potentially to catalytic amounts,¹⁰ provided valuable insight into the reaction. Data to accompany the following discussion is presented in Table 2. In principle, only one equivalent of lithium diamide should be required to both deprotonate the NHBoc group and effect the rearrangement of 4b. In the event, adding epoxide 4b to 1.2 equiv of dilithium-13 at 0 °C gave incomplete conversion (after 21 h) and produced alcohol 3b with diminished (83%) enantiomeric excess (entry 2). Pretreatment of epoxide 4b with 1.2 equiv of LDA at -10 °C followed by reaction with 1.2 equiv of dilithium-13 did consume all epoxide starting material but still provided 3b with decreased enantiomeric purity (89% ee). This was presumably due to a competing background rearrangement reaction with LDA. Attempts to deprotonate the NHBoc of epoxide 4b with one equivalent of lithium reagents (n-BuLi, s-BuLi, or PhLi) at -78 °C resulted in substantial formation of the expected ketone and carbinol products resulting from alkyl/aryl lithium addition to the tert-butyl ester. However, reaction of 3.3 equiv of 2-lithio-1,3-dimethoxybenzene¹¹ with 1.1 equiv of diamine 13, followed by addition of a THF solution of epoxide 4b provided a 70% yield of alcohol 3b with 90% ee (entry 5). No products resulting from addition of the aryl lithium to the ester were observed. An attempted catalytic reaction, in which epoxide 4b was treated with 0.2 equiv of dilithium-13 followed by 2.2 equiv of LDA, gave essentially racemic **3b** (entry 4). Again, this is presumably

⁽⁵⁾ Commercially available from Sigma-Aldrich Chemical Company, Milwaukee, WI.

^{(6) (}a) Reference 4i. (b) Modin, S. A.; Andersson, P. G. J. Org. Chem. 2000, 65, 6736. (c) Andersson, P. G.; Sodergen, M. K.; Bertilsson, S. K.; Andersson, P. G. J. Org. Chem. 2002, 67, 1567.

⁽⁷⁾ Bambridge, K.; Begley, M. J.; Simpkins, N. S. *Tetrahedron Lett.* **1994**, *35*, 3391. For an example of asymmetric deprotonation of a sulfonium salt using the lithium amide of **13**, see: McComas, C. C.; Van Vranken, D. L. *Tetrahedron Lett.* **2003**, *44*, 8203.

^{(8) (}a) Mimoun, H.; de saint Laumer, J. Y.; Giannini, L.; Scopelliti, R.; Floriani, C. J. Am. Chem. Soc. **1999**, *121*, 6158. (b) Horner, L.; Dickerhof, K. Liebigs Ann. Chem. **1984**, 1240.

⁽⁹⁾ The estimated cost to prepare diamine 13 on large scale was >\$365/kg.

⁽¹⁰⁾ Several systems for the asymmetric rearrangement of *meso*-epoxides using a catalytic amount of a chiral lithium amide and an achiral stoichiometric base (e.g., LDA with DBU or lithiated imidazoles) have been reported. For leading references, see: (a) Reference 1c. (b) Oxenford, S. J.; Wright, J. M.; O'Brien, P.; Panday, N.; Shipton, M. R. *Tetrahedron Lett.* 2005, 46, 8315 and references therein.

⁽¹¹⁾ Prepared by reaction of 1,3-dimethoxybenzene with n-BuLi in diethyl ether.

Table 1. Screening results for conversion of epoxide 4b to alcohol 3b



^a Reaction performed at 0 °C with 2 equiv of Li-12.

Scheme 4. Preparation of diamines 13 and 14



due to a substantially faster background reaction rate of epoxide **4b** with LDA, relative to the rate of reaction with dilithium-**13**.

Another outcome of these studies was the finding that crude alcohol **3b** of <93% ee could not be reliably upgraded by crystallization using the standard heptane/MTBE crystallization process.¹² With this target in mind, attention was focused on optimizing the selectivity of the simpler diamine, **14**. Using diamine **14** and decreasing the reaction temperature

to -55 °C provided alcohol **3b** with 97% ee, the same selectivity achieved with diamine **13** (entry 9). However, the low solubility of dilithium-**14** at this temperature resulted in very thick, poorly agitated mixtures at desirable reaction volumes.¹³

As observed with diamine **13**, maximum selectivity required two equivalents of the lithium <u>diamide</u> of **14** (compare entries 6 and 7).¹⁴ Entry 12 of Table 2 is also illustrative. In this experiment, 2.2 equiv of **14** were reacted with 3.3 (rather than the standard 4.4) equiv of *n*-BuLi to presumably produce 1.1 equiv of dilithium-**14** and 1.1 equiv

⁽¹²⁾ Racemic and enantiomerically pure alcohol **3b** have different crystal forms, based on X-ray powder diffraction patterns and melting points (122–124. °C and 112–112. °C, respectively). In addition, the racemate is significantly less soluble in the 65:35 heptane/MTBE crystallization solvent: 3 mg/mL vs 15 mg/mL for the single enantiomer (at 22 °C).

⁽¹³⁾ On laboratory scale, using a mechanical paddle stirrer, the maximum final concentration of 4b that enabled agitation of the lithium diamide was 0.25 M.

Table 2. Comparison studies of rearrangement reactions using diamines 13 and 14



Entry	Diamide	Equiv	Reaction	Base additive	Reaction	%ee	% V:-14	%
			Temp (°C)	(equiv)	Time (n)	30	3b ^b	4b ^b
1	13	2.2	0		18	97	75	
2	13	1.1	0		21	83	46	38
3	13	1.1	0	LDA (1.1)	22	89	64	
4	13	0.2	0	LDA (2.2)	21	6	66	15
5	13	1.1	0	MeO OMe (1.1)°	19	90	70	3
6	14	2.2	0		4	86	66	
7	14	1.1	0		18	75	40	30
8	14	2.2	-40		14	95	79	
9	14	2.2	-55		18	97	80	
10	14	2.2	-78		7	98	76	18
11	14	1.1	0	NaH (1.5) ^d	7	32	61	19
12	14	1.1°	0		7	62	75	4

^{*a*} Measured on sample of **3b** obtained after chromatography. ^{*b*} Yield after chromatography on silica gel. ^{*c*} 1.1 equiv diamine **13** was added to 3.3 equiv 2-lithio-1,3-dimethoxybenzene ^{*d*} Epoxide **4b** treated with 1.5 equiv NaH in THF at 22 °C for 1 h. ^{*e*} 2.2 equiv of diamine **14** treated with 3.3 equiv *n*-BuLi rather than the standard 4.4 equiv *n*-BuLi.

Scheme 5. Epoxide rearrangement process using diamine 13



of monolithium-14. Epoxide 4b was added, and the reaction mixture was stirred 7 h at 0 °C. Alcohol 3b was obtained with significantly reduced enantiomeric purity (62% ee), compared to the analogous reaction utilizing 2.2 equiv of dilithium-14 (86% ee, entry 6).

The use of inexpensive NaH for deprotonation of the carbamate nitrogen followed by reaction of the resulting Na-

4b with 1.1 equiv of dilithium-**14** was also studied. Unfortunately, this protocol gave **3b** in 61% yield and only 32% ee (entry 11). Assuming that the poor enantioselectivity might be related to the presence of sodium counterions, LiH was also evaluated. However, deprotonation of the carbamate nitrogen of **4b** with LiH in THF was not successful.¹⁵

One additional observation from these data is worth noting. Total accountable mass balance (% product + % recovered starting material) appeared to increase with

⁽¹⁴⁾ Aliquots of the reaction of 4b with 1.1 equiv dilthium-14 (entry 7) were quenched and assayed by NMR for conversion. After the 2 h, the ratio of starting material/product was 40:60 and remained constant thereafter. This suggests that the reaction may have occurred substantially during the addition of the epoxide solution, when the epoxide would be exposed to excess dilthium-14. After addition of one-half of the epoxide solution, only monolithium-14 would remain.

⁽¹⁵⁾ For example, reaction of 4b with 1.5 equiv of LiH in THF for 76 h at 22 °C, followed by quenching with CD₃CO₂D gave 4b (89% recovery) with no measurable incorporation of deuterium, based on integration of the NH signal in the NMR spectrum.

Scheme 6. Proposed decomposition pathway for alcohol 3



decreasing reaction temperature (compare entries 6 and 8–10 in Table 2.) No other organic solvent–soluble byproducts were isolated via extraction of the aqueous layer (even after adjusting the pH to 13), suggesting a decomposition pathway of the product and/or starting material to water-soluble byproducts. Indeed, when alcohol **3b** was treated with 2.2 equiv of dilithium-**14** at 23 °C for 18 h, **3b** was recovered in only 45% yield and was the only identifiable product-like fragment observed. The mass loss in this reaction *may* be attributed to the proposed pathway shown in Scheme 6, resulting in the presumably highly water-soluble amino acid **16**, derived from the cyclic oxazolidinone **15**.¹⁶

In total, the studies with diamines **13** and **14** led to the hypothesis that chelation of the dilithium amide to *both* the carbamate oxygen and the epoxide may be necessary for optimum selectivity.¹⁷ This resulted in a rationale for the stereochemical outcome of the reaction as shown in Scheme 7.

Selectivity is achieved via coordination of the dilithium-**14** with the epoxide oxygen and the carbamate oxygen, followed by the known removal of a *syn-β*-hydrogen.¹⁸ In this model, the minor enantiomer is derived from chelated structure **B**, in which a methyl group of the chiral diamine occupies a space above the five-membered ring. The major enantiomer is derived from chelated structure **A** in which a hydrogen can occupy this space above the ring. The reaction of epoxide **4b** with the magnesium amide of **14** may offer support for this chelate model. Diamine **14** was treated with Bu₂Mg in refluxing THF¹⁹ presumably to provide the cyclic Mg-**14** amide (Scheme 8), which would be less likely to

(16) Amino acid 16 has been prepared, as the trifluoroacetate salt, via reaction of 3b with neat trifluoroacetic acid. Further studies to confirm the presence of 16 in the aqueous layers of quenched reaction mixtures are in progress. No amide products, resulting from the reaction of chiral lithium amides with the ester of 4b, have been observed.

(17) The reaction of epoxide diastereomer 4c with dilithium-13 provided alcohol 3c with only 61% ee.



In this substrate simultaneous chelation with the epoxide and carbamate oxygens is not possible. A carbamate anion may be not be essential for bidentate coordination, however. Reaction of the *N*-Me epoxide \mathbf{i} with dilithium-13 yielded alcohol \mathbf{ii} with 85% ee (see Supporting Information).



participate in bidentate coordination with the carbamate and epoxide oxygens. Epoxide **4b** was added to the resulting solution at 0 °C, and the reaction mixture was stirred for 6 h. Alcohol **3b** was isolated in 21% yield (along with 58% recovered epoxide **4b**) and was essentially racemic (4% ee).

Further studies will certainly be required to establish the kinetically relevant amide species in the rearrangement reaction. The simple rationale proposed does not account for the potential impact of reactive lithium amide dimers or aggregates. In addition to solvent effects, the lithium amide environment may be substantially impacted by the buildup of lithium alkoxide and the monolithium amides as the reaction proceeds. However, this model led to the study of additional diamines to optimize the tether length between the chiral amine fragments. Longer carbon chain tethers in the diamine were attractive as they might provide for higher selectivity and possibly more soluble lithium diamides, thus solving a critical processing problem.

Results of comparative rearrangement reactions performed with diamines having modified carbon chain tethers and substituents (diamines 17-21) are shown in Table 3.^{20,21} In summary, diamine 17 having a *three* carbon linker, provided **3b** with the highest enantiomeric excess. The findings that the enantioselectivity could be optimized by changing the size of the carbon chain linker and that the replacement of one secondary amine of the diamine with a tertiary amine (diamine 19) gave essentially racemic **3b** are consistent with the bidentate chelation model shown in Scheme 7.

With project timing dictating pilot-plant processing, we focused on developing the process using the simplest

⁽¹⁸⁾ Examples of epoxide rearrangements via removal of syn-β, α-, and anti-β hydrogen have been demonstrated via deuterium labeling and other studies. See for example (a) Thummel, R. P.; Rickborn, B. J. Am. Chem. Soc. 1970, 92, 2064 (syn-β elimination pathway). (b) Morgan, K. M.; Gajewski, J. J. J. Org. Chem. 1996, 61, 820. (c) Hodgson, D. M.; Gibbs, A. R. Tetrahedron Lett. 1997, 51, 8907. (d) Hodgson, D. M.; Gibbs, A. R. J. Chem. Soc., Perkin Trans. 1 1999, 3679. (e) Ramirez, A.; Collum, D. B. J. Am. Chem. Soc. 1999, 121, 11114. (f) Morgan, K. M.; Gronert, S. J. Org. Chem. 2000, 65, 1461 (anti-β elimination pathway). Both solvent and conformational effects have been reported to impact the site of deprotonation. 3-Substituted cyclopentene oxides have been reported to show a preference for the syn-β-deprotonation pathway in the presence of chiral lithium amides. Based on the retention of deuterium labels in the α-positions of epoxide 4b (below), there is indication that the often observed syn-β elimination mechanism may be operating in this substrate.



- (19) For an asymmetric deprotonation of meso ketones with chiral magnesium amides, see for example: Anderson, J. D.; Garcia Garcia, P.; Hayes, D.; Henderson, K. W.; Kerr, W. J.; Moir, J. H.; Fondekar, K. P. *Tetrahedron Lett.* **2001**, *42*, 7111.
- (20) Diamine 17 was originally prepared from dibromopropane as described in reference 8b. For a recent use of catalytic dilithium-17 in the rearrangement of cyclcohexene oxide see: Equuey, O.; Alexakis, A. *Tetrahedron Asymmetry* 2004, 15, 1069.
- (21) Diamine 18: Kobayashi, Y.; Hayashi, N.; Kishi, Y. Org. Lett. 2002, 4, 411. The preparations of diamines 19–21 are described in the Supporting Information.





 $\begin{array}{ccc} & & & & & \\ & & & & \\ & & & & \\ & & & & \\ &$

(although noncrystalline) diamine, **17**. As shown in Table 4, reducing the reaction temperature below -25 °C did provide **3b** with >95% ee. Importantly, dilithium-**17** did not precipitate at the lower reaction temperatures. For pilot-plant processing, -45 °C was selected as the reaction temperature.

One added challenge to pilot-plant processing was the use of diamine **17** as an oil. The free base was conveniently prepared by adding 1,3-dibromopropane to 4 equiv of (*R*)- α -methylbenzylamine at 100 °C. Upon reaction completion, the mixture was partitioned between aqueous NaOH and MTBE. MTBE was removed, and excess (*R*)- α -methylbenzylamine was recovered via vacuum distillation. The product could be easily separated from higher-boiling byproducts²² by further vacuum distillation. A more practical purification process was designed in which crude **17** was treated with aq HCl in ethanol, and the dihydrochloride salt of **17** was





^a Isolated yield after column chromatography.



isolated as shown in Scheme 9. Commercially available (R)- α -methylbenzylamine of 98.2% ee provided the dihydrochloride salt of **17** in 85% yield (35-kg scale) with an isomer ratio R,R/meso of 98.1:1.9. The *S*,*S*-enantiomer was not detected by capillary electrophoresis assay.

It was most desirable to integrate the free basing of 17dihydrochloride and the rearrangement reaction into a telescoped process. Thus, we evaluated the impact of potential water-immiscible organic solvents for free basing that would be carried into the rearrangement reaction. Under model laboratory reaction conditions, the final reaction mixture solvent contained 6:1 (v:v) THF/hexanes (the latter derived from *n*-BuLi solution). As shown in Table 5, performing the reaction in 6:1 MTBE/hexanes reduced the % ee of the crude product 3b by approximately 10%. In toluene the enantioselectivity was reversed, providing the undesired enantiomer of 3b with 35% ee. However, adding 2 or 10 equiv of THF/equivalent of diamine to either MTBE or toluene nearly restored the selectivity to that observed with THF as solvent. Thus, MTBE solutions of the free base 17 were used for pilot-plant processing.

Two additional studies were performed prior to scale-up of the rearrangement reaction. One set of experiments probed the stability of dilithium-17. This study was prompted by the observation of acetophenone in the crude organic extracts from the epoxide rearrangements using diamines 13, 14, or 17. Acetophenone presumably is formed via hydrolysis of imine 22 resulting from β -hydride elimination of the lithium amide (Scheme 10). This reaction was of potential concern for larger-scale processing in which the likely longer addition times would require longer solution lifetimes for the diamide. Laboratory studies were conducted in which the dilithium-17 solution was aged 30 min, 2 and 5 h prior to addition of the epoxide solution. These studies showed no change in yield or enantiomeric purity of isolated 3b. The amount of acetophenone observed in the crude product was not substantially different (<10%, relative to **3b**) in these three reactions.

A second screening study examined the impact of inorganic cations or anions that might be carried into the rearrangement reaction from the free basing of diamine **17**-

(22) Crude reaction mixtures typically contained a 96:4 ratio of **17** and tertiary amine **iii**. The latter was removed by isolation of **17**-dihydrochloride salt.





^a Crude **3b** was crystallized from 13 mL of 65:35 hexanes/MTBE/g. ^b Isolated by silica gel chromatography. ^c Unseeded crystallizations. ^d Crystallization seeded with 99% ee **3b**.

Scheme 9. Preparation of diamine 17-dihydrochloride salt



Scheme 10. Possible decomposition pathway of dilithium-17



dihydrochloride (sodium and/or chloride) or from the presence of adventitious water during processing (e.g., LiOH). As shown in Table 6, the presence five equivalents of LiOH did not impact the yield or enantioselectivity of the reaction (performed -5 °C in this screening study). Addition of five

Table 5. Impact of solvent on selectivity of the rearrangement reaction

0,	Ph N Li 2.	N P Li 2 equiv	h	OH
BocHNC	O ₂ t-Bu solvent/h -5 °l	exanes (6/1) C/1.5 h		BOCHN CO2t-BL
4b				3b
solvent	equiv THF added/ equiv diamine	% ee 3b (HPLC)	% yield 3b ^a	% recovered $4\mathbf{b}^a$
THF	_	94	64	_
MTBE	-	84	73	5
MTBE	2	88	73	1
MTBE	10	88	77	4
PhCH ₃	_	-35	39	20
PhCH ₃	2	90	53	3
PhCH ₃	10	92	65	_

^a Isolated yields after purification by column chromatography.

equivalents of LiCl resulted in an 8% ee decrease, while the more soluble lithium *tert*-butoxide²³ caused a 17% reduction in ee, relative to the control reaction. Addition of 5 equiv of sodium *tert*-butoxide gave essentially racemic product (12% ee). As seen previously with diamine **14**, soluble sodium cations have a substantial deleterious impact on the enanti-oselectivity of the reaction.

Pilot-Scale Preparation of Epoxide 4b. The synthesis of the ethyl ester epoxide **4a** from diethyl malonate was previously reported by Hodgson.³ Syntheses of epoxide **4b** were demonstrated in the laboratory using this strategy and a variety of strategies based on the alkylation of *tert*-butyl glycine imines²⁴ with 1,4-disubstituted-*cis*-2-butene derivatives to form the cyclopentene ring. Due to ready commercial

Table 6. Impact of additives on the epoxide rearrangement reaction

BocHN BocHN	-Bu THF/hexa 5 equiv of	N Li equiv nes (6/1) 1.5 h "additive"	
additive	% ee 3b (HPLC)	% yield 3b ^a	% recovered $4\mathbf{b}^a$
none LiOH LiCl LiOt-Bu NaOt-Bu	92 91 84 75 12	75 77 76 69 39	1 2 1 9 21

^{*a*} Isolated yields after purification by column chromatography.

Scheme 11. Pilot-plant preparation of epoxide 4b



access, *tert*-butyl methylmalonate²⁵ was selected as the starting material in preference to *tert*-butyl glycine. *cis*-1,4-Dichloro-2-butene was selected as the alkylating agent.

The pilot-plant process used to prepare epoxide **4b** (Scheme 11) began with the alkylation of *tert*-butyl methylmalonate with *cis*-1,4-dichloro-2-butene²⁶ using LiH in THF/ DMPU.²⁷ The resulting solution of cyclopentene diester **23** was hydrolyzed directly with aqueous NaOH to give the mono ester acid **24** in 79% overall yield (5-kg scale).

Acid **24** was converted to the Boc-protected amine **5b** via a four-step sequence of acid chloride (**25**) formation with thionyl chloride, phase transfer-catalyzed preparation of the acylazide **26**, Curtius rearrangement of **26**, and trapping of the isocyanate **27** with potassium *tert*-butoxide/*tert*-BuOH.

⁽²⁶⁾ The *cis*-1,4-dichloro-2-butene used contained 3.9% *trans*-1,4-dichloro-2butene and 1.0% 3,4-dicihloro-1-butene. In the preparation of 24, *trans*-1,4,dichloro-2-butene reacts with *tert*-butyl methylmalonate to give vinyl cyclopropane diastereomers iv and subsequently acids v, which are removed in the crystallization of 24.



(27) (a) Depres, J. P.; Greene, A. E. Org. Synth. 1997, 75, 195. (b) Depres, J. P.; Greene, A. E. J. Org. Chem. 1984, 49, 928.

Crystallization from MTBE/heptane provided cyclopentene **5b** in 71% overall yield from **24** on 6-kg scale.

Under a variety of oxidizing conditions, epoxidation of **5b** preferentially gave epoxide diastereomer **4b** in which the epoxide oxygen occupies the same face of the ring as the NHBoc group.²⁸ Magnesium monoperoxyphthalate, available in commercial quantities, was used in a biphasic water/ethyl acetate mixture with *n*-Bu₄NHSO₄ phase transfer catalyst to afford a 93:7 mixture of epoxide diastereomers (**4b:4c**). The crude product was crystallized from EtOAc/heptane to give a 71% yield of **4b**, containing 3% of the minor diastereomer (on 10-kg scale).

Scale-Up of the Epoxide Rearrangement. The rearrangement of epoxide 4b was performed in pilot-plant equipment using diamine 17 via the process shown in Scheme 12. The free base diamine 17 was prepared from the dihydrochloride salt in a mixture of aqueous NaOH and MTBE. The MTBE layer was azeotropically dried and diluted with THF. The solution was cooled to -45 °C, and 2.5 M *n*-BuLi in hexanes was added to form the dilithium amide. A solution of epoxide 4b was then added, and the reaction was stirred at -45 °C. Upon reaction completion (approximately 16 h),²⁹ the reaction was quenched with aqueous sulfuric acid.³⁰ After layer separation, a brine wash, and concentration of the organic layer, alcohol 3b was

⁽²³⁾ For a study of achiral rearrangements of epoxides with lithium *tert*-butoxide and lithium amide bases see: Saravanan, P.; DattaGupta, A.; Bhuniya, D.; Singh, V. K. *Tetrahedron* 1997, 53, 1855.

⁽²⁴⁾ Park, K. H.; Olmstead, M. M.; Kurth, M. J. J. Org. Chem. 1998, 63, 113.

⁽²⁵⁾ tert-Butyl methylmalonate was purchased in bulk quantities from Tateyama Kasei Co., Ltd, Toyama, Japan. A synthesis of **5b** starting with *tert*-butyl acetoacetate has been reported: Larionov, O. L.; Kozhushkov, S. I.; de Meijere, A. Synthesis **2005**, 158.

⁽²⁸⁾ Characterization data for major/minor epoxide diastereomers 4b and 4c were consistent with that reported for the analogous ethyl ester epoxides (ref 3). The observed epoxidation facial preference has been reported for several other 3-amide cyclopentene substrates. See, for example, refs 4a,b and O'Brien, P. O.; Childs, A. C.; Ensor, G. J.; Hill, C. L.; Kirby, J. P.; Dearden, M. J.; Oxenford, S. J.; Rosser, C. M. *Org. Lett.* 2003, *26*, 4955.



Scheme 13. Comparison of rearrangement reaction of epoxide diastereomers



crystallized form heptane/MTBE. In two runs at 3-kg scale, alcohol **3b** was obtained in 79 and 74% (assay-corrected) yields, each lot with 99.6% ee. Diamine **17**-dihydrochloride was subsequently recovered from the combined aqueous acid extracts in 80% overall yield via free-basing and re-forming the HCl salt (see Experimental Section). Recovered diamine **17**-dihydrochloride showed the same stereoisomeric purity as the starting lot and was successfully reused in the rearrangement reaction.³¹

Both of the above lots of **3b** contained approximately 0.5% of alcohol **3c**, derived from the rearrangement of the minor epoxide diastereomer **4c** (Scheme 13). By virtue of the subsequent oxidation step, this alcohol is also converted to the desired ketone **2b**. However, the presence of alcohol **3c** could potentially have a minor impact on the enantiomeric purity of ketone **2b** if the rearrangement of epoxide **4c** proceeds with opposite or less enantioselectivity relative to that observed for epoxide **4b**. In a laboratory reaction comparison, epoxides **4b** and **4c** were reacted with lithium dilithium-**17** under standard pilot-plant reaction conditions, and the reactions were quenched after 1.25 h. Interestingly,

the rearrangement reaction of the minor epoxide 4c is much slower (3% yield vs 72% yield) and less selective (48% ee vs 99.8% ee product) than the reaction of epoxide 4b. Oxidation of alcohols 3b and 3c provided samples of ketone 2b with the same sign of optical rotation, which indicates that the deprotonation occurs with the same relative enantiomeric preference for both epoxides.³²

Oxidation Reaction. The final conversion to the key intermediate **2b** was accomplished in the pilot plant in a biphasic mixture of MTBE and aqueous NaOCl containing 8 mol % of the TEMPO radical.³³ This process provided the key API intermediate, ketone **2b**, in 81% assay corrected yield on 3-kg scale (Scheme 14).

Conclusion

The desymmetrization of epoxide **4b** was accomplished on pilot-plant scale to provide high yields of allylic alcohol



(33) Anneli, P. L.; Montanari, F.; Quici, S. Org. Synth. 1990, 69, 212 and references therein.

⁽²⁹⁾ The reaction was typically >80% complete 1 h after addition of the epoxide solution. For pilot-plant processing, end of reaction was defined as less than 2% epoxide 4b remaining. Levels of 4b greater than 2% were not substantially reduced in the crystallization of 3b or the subsequent intermediate 2b. As the reaction proceeds, it is possible that the effective concentration of epoxide is further reduced by nonproductive coordination with monolithium-17, which is present at substantially higher concentration than dilithium-17.

⁽³⁰⁾ Sulfuric acid was used in preference to aqueous HCl, as the former salt does not precipitate from the reaction mixture, resulting in simpler layer separations.

⁽³¹⁾ Recovered 17-dihydrochloride used in a laboratory test provided alcohol 3b in 72% yield and 99.9% ee.



3b, with >99% ee. This provided a key chiral intermediate, ketone **2b**, for the synthesis of LY459477. The chiral diamine **17** used is easily prepared from commercially available (*R*)- α -methyl benzylamine and was recovered in 80% yield from the pilot-plant reaction mixtures. This reagent was designed by balancing ease of preparation, enantioselectivity, and operational requirements in the rearrangement reaction. Study of a variety of diamine analogues provided insight into the possible mechanism of the reaction but more importantly led to the design of a scaleable reaction. Results of studies to make this transformation more practical (e.g., reducing the amount of diamine required) will be reported in due course.

Experimental Section

General. Melting points were obtained using a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR data were obtained using a Varian instrument at 300 or 500 MHz for ¹H and 125 MHz for ¹³C. Unless otherwise stated, reagents were commercially available and used without further purification. Reaction completion for compounds 23, 25, 26, and 27 was monitored using an Agilent 5890 GC equipped with a 15 m \times 0.25 mm DB1701 column and a flame ionization detector using the following conditions: flow, 1.5 mL/min; temperature gradient, 60 °C for 2 min, 18 °C/min to 280 °C, 280 °C for 5 min. Reaction completion for compounds 24, 3b, 4b, 5b, and 2b was monitored by HPLC using an Agilent 1100 series instrument equipped with a UV detector and a Zorbax SB-Phenyl 25 cm \times 4.5 mm column using the following conditions: eluents, acetonitrile and 0.1% aqueous H₃PO₄; eluent gradient, 40:60 acetonitrile/0.1% aq H₃PO₄ to 80:20 acetonitrile/0.1% H₃- PO_4 from 1 to 21 min; flow = 1 mL/min; detector = 200 nm; column temperature = $25 \, ^{\circ}$ C. Chiral assays for compounds 4a-c were performed using an Agilent 1100 series HPLC equipped with a Chiralpak 5 μ m, 4.6 mm \times 250 mm column and a UV detector using the following conditions: column temperature, 30 °C; eluent, isocratic 90:10 hexane/isopropyl alcohol; flow rate, 1 mL/min; detector, 210 nm. Reaction completion for compound 17 was monitored using an Agilent 5890 GC equipped with a 30 m \times 0.25 mm DB-1 column and a flame ionization detector using the following conditions: flow = 1 mL/min, temperature gradient, 60 °C for 2 min, 18 °C/min to 300 °C. Chiral assays for diamine 17 were obtained with a Hewlett-Packard 3D capillary electrophoresis instrument equipped with an uncoated capillary and a UV detector using the following conditions: buffer, 25 mM NaH_2PO_4 (pH 7.0) + 15 mM SBE-B-CD; preconditioning, 0.1 N H₃PO₄ for 3 min; voltage, +25 kV; column temperature, 15 °C; detection: 195 nM; pressure injection (50 mbar, 4 s); capillary: 50 μ m i.d. \times 64.5 cm (56 cm to detector). For small-scale and screening epoxide rearrangement reactions, compounds **3a,b** were purified via column chromatography using silica gel (EMD silica gel 60), eluting with 1:1 hexanes/MTBE. (R_f for compound **3b** = 0.15; compound **4b** = 0.33). Magnesium monoperoxy phthalate was obtained from DeGussa, Peroxid-Chemie GmbH & Co., Germany. *tert*-Butyl methylmalonate was obtained from Tateyama Kasei Co., Ltd, Toyama, Japan. *cis*-1,4-Dichloro-2-butene was obtained form Alfa Aesar, Ward Hill, MA. (R)- α -Methylbenzylamine was obtained from Zeeland Chemicals, Zeeland, MI.

3-Cyclopenetene-1,1-dicarboxylic Acid, Mono(1,1-dimethylethyl) Ester (24). To a 30-gal glass-lined reactor under N₂, were added *N*,*N*-dimethylpropyleneurea (DMPU, 16 kg) followed by a slurry of LiH (0.605 kg, 75.5 mol) in 10 L of THF. The slurry was heated to 40-45 °C and (neat) tert-butyl methylmalonate (5.0 kg, 28.7 mol) was added over 30 min, maintaining the temperature at 40–45 °C. (Hydrogen was evolved.) A solution of cis-1,4-dichloro-2-butene (4.10 kg, 31.8 mol) in 10 L of THF was then added over 3.8 h, maintaining the temperature at 40 °C. Hydrogen was evolved throughout the addition. The reaction was stirred at 40 °C and monitored by GC assay. After 1.5 h, the reaction mixture was cooled to room temperature and added over 25 min to 40 L of water in a 50-gal glass-lined reactor. The temperature was maintained below 30 °C; hydrogen was evolved. Aqueous NaOH (5 M, 10 L, 50 mol, 1.75 equiv) was added over 5 min, and the resulting homogeneous mixture was stirred at 25 °C for 2 h, at which time HPLC assay showed no 23 remained. MTBE (25 L) was added to the reaction mixture, and the layers were separated. The aqueous layer was transferred to a 50-gal Hastelloy C reactor containing 25 L of MTBE. The pH of the aqueous layer was adjusted to 2.8 by the addition of 46 L of 2 M NaHSO₄ over 16 min. The layers were separated, and the aqueous layer was extracted with 25 L of MTBE. The combined organic layers were extracted with 2×50 L of 5% LiCl solution (to remove DMPU), and filtered through a 5 micron cartridge filter into a 30-gal glass-lined tank. The solution was concentrated under vacuum (160 mmHg, solution temperature of 20-25 °C) to approximately 20 L. Heptane (70 L) was added, and the solution was concentrated to 30-35 L under vacuum; crystals formed. The slurry was stirred 1.5 h at 20-25 °C and filtered. The solid was washed with 20 L of heptane and vacuum-dried 24 h at 45 °C to obtain 4.98 kg (81% yield) of 625222 as a white solid, mp 119-122 °C. HPLC assay showed 0.7% of the cyclopenetene dicarboxylic acid and 1.45% residual DMPU. Corrected yield = 79%. ¹H NMR (300 MHz, CDCl₃): δ 5.61 (s, 2H), 3.00 (s, 4H), 1.46 (s, 9H). ¹³C NMR (125 MHz, CDCl₃): δ 178.8, 178.8, 127.8, 82.1, 59.6, 40.9, 27.7. IR (CHCl₃): 3800-3000 (br, COOH), 1741, 1705, 1283, and 1149 cm⁻¹.

1-[[(1,1)-Dimethylethoxy]carbonyl]amino]-3-cyclopentene-1-carboxylic Acid, 1,1-Dimethylethyl Ester (5b). Preparation of acid chloride **25**. Compound **24** (6.0 kg, 28.27 mol) was dissolved in 100 L of 70:30 toluene/MTBE in a 200-gal glass-lined tank. Thionyl chloride (4.0 kg, 33.6 mol, 1.2 equiv) was added to the stirred reaction mixture

(maintaining the temperature at 23 °C), followed by a toluene rinse (1-2 L) of the SOCl₂ container. The reaction solution was cooled to 0-10 °C and a solution of triethylamine (3.83 kg, 37.85 mol, 1.34 equiv) in 15 L of toluene was added over 1.75 h. The reaction mixture was warmed to 20-23 °C over 10 min. GC assay of the reaction showed that 0.85% of the starting material remained. The reaction mixture was transferred over 25 min to a 200-gal glass-lined tank containing deionized water (75 L), while maintaining the temperature at 20-25 °C. The tank containing the reaction mixture was rinsed with toluene (20 L), and the rinse was added to the aqueous reaction mixture. The solution was stirred for 10 min, and the layers were separated. To the organic layer was added 1 M NaHCO₃ (60 L), and the mixture was stirred for 10 min. The layers were allowed to settle over 10 min and then were separated. The acid chloride 25 contained in the organic (toluene/MTBE) layer was taken directly into the next reaction. Acid chloride 25 could be isolated as an oil by concentration of the organic layer. ¹H NMR (300 MHz, CDCl₃): δ 5.61 (s, 2H), 3.04 (quartet, J_{AB} = 15.1 Hz, 4H), 1.49 (s, 9H). IR (film): 1796, 1743, 1274, 1233, 1158 cm⁻¹.

Preparation of Azide 26. A solution of tetrabutyl ammonium hydrogen sulfate (0.105 kg, 0.31 mol, 0.01 equiv) in deionized water (0.5 L) was added to a solution of sodium azide (2.25 kg, 34.61 mol, 1.22 equiv) in deionized H₂O (75 L) in a 100-gal glass-lined tank. The solution containing acid chloride 25 in MTBE/toluene was added to the azide solution over 50 min. The tank containing the acid chloride was rinsed with 10 L of toluene, and the rinse was added to the reaction solution. The reaction mixture was stirred for 2.75 h at 23 °C. GC analysis of the reaction solution showed that the acid chloride was consumed. The layers were separated, and the organic layer was washed with 1 M NaHCO₃ (60 L) and deionized H₂O (60 L, then 30 L). The organic layer was filtered through a 14 kg sodium sulfate filter and collected in a 200-gal glass-lined tank. This solution of acyl azide 26 in MTBE/toluene was used in the next step. Azide 26 could be isolated as an oil by evaporation of the solvent under a stream of nitrogen. ¹H NMR (300 MHz, CDCl₃): δ 5.58 (s, 2H), 2.96 (t, J = 2.3 Hz, 4H), 1.46 (s, 9H). IR (film): 2137 (CON₃), 1720, 1246, 1185, 1136 cm^{-1} .

Preparation of Isocyanate 27. Toluene (30 L) was added to a 100-gal glass-lined tank and was heated to 90–100 °C. The acyl azide **26** solution was transferred slowly over 45 min to the heated toluene solution, maintaining the temperature at 90–100 °C. (Evolution of nitrogen gas was addition-rate controlled under these conditions.) Additionally, MTBE was distilled from the reaction during the addition. The reaction was stirred for 15 min at 95 °C. GC assay showed that 0.8% of the acyl azide remained. The reaction mixture was cooled to 20–25 °C over 30 min. The isocyanate **27** solution was carried forward to the next step. Isocyanate **27** could be isolated as an oil by evaporation of the solvent under vacuum. ¹H NMR (300 MHz, CDCl₃): δ 5.67 (s, 2H), 3.01 (d, J = 15.6 Hz, 2H), 2.61 (d, J = 15.6 Hz, 2H), 1.50 (s, 9H). IR (film): 2258 (–NCO), 1732, 1157 cm⁻¹.

Preparation of 5b. Potassium tert-butoxide (44 kg, 1 M solution in THF, 48.8 mol, 1.7 equiv) was added to a 200gal glass-lined tank. To the KOt-Bu solution was added tertbutanol (5.2 L), and the transfer lines were washed with toluene (2 L). The reaction solution was cooled to 0-5 °C, and the toluene solution containing isocyanate 27 was added over 60 min, maintaining the temperature at 0-10 °C. The reaction was warmed to 23 °C, stirred for 40 min, and assayed by GC for the disappearance of isocyanate. The reaction mixture was then added to a mixture of deionized H₂O (140 L) and MTBE (140 L) over 15 min, maintaining the temperature between 20 and 30 °C. The solution was stirred for 20 min, and the lavers were separated. The aqueous layer was washed with MTBE (70 L), and the combined organic layers were extracted with a 20% brine solution (60 L), stirred for 10 min, and separated. The organic layer was transferred to 100-gal glass-lined tank and concentrated via distillation (45-50 °C, 550 mmHg) to approximately 25 L. A solvent exchange to heptane was accomplished by repeating the following process four times: heptane (50 L) was then added to the distillation tank, and the resulting solution was distilled at 40-50 °C, 60-90 mmHg, until the total volume was 20-30 L. The final distillation concentrated the solution to approximately 10 L. Heptane (20 L) was added and the solution cooled to 20 °C over 3 h. The solution was further cooled to -10 °C over 60 min and stirred for 3.5 h to precipitate the product. The solid was filtered, washed with 20 L of cold heptane, and vacuum-dried at 50 °C for 12 h to yield 5.92 kg (73% yield) of compound **5b** as a white solid, mp 87–89 °C. HPLC assay showed 97.8 area % compound **5b**. Corrected yield = 71.4%. ¹H NMR (500 MHz, CDCl₃): δ 5.63 (s, 2H), 5.1 (bs, 1H, NH), 2.99 (d, *J* = 17.2 Hz, 2H), 2.57 (d, *J* = 16.0 Hz, 2H), 1.46 (s, 9H), 1.44 (s, 9H). ¹³C NMR (CDCl₃): δ 173.3, 154.9, 127.7, 81.1, 64.5, 44.8, 28.3, 27.8. IR (KBr): 3451, 2981, 2932, 1712, 1489, 1369, 1154 cm⁻¹. MS (ES) *m/e* (% relative intensity): 284.2 (M⁺ + 1, 56), 228.2 (73), 172.1 (97), 128.0 (100).

 $(1\alpha, 3\beta, 5\alpha)$ -3-[[(1,1-Dimethylethoxy)carbonyl]amino]-6-oxabicyclo[3.1.0]hexane-3-carboxylic Acid, 1,1-Dimethylethyl Ester (4b). Compound 5b (11.02 kg, 38.89 mol) was dissolved in EtOAc (55 L) in a 100-gal glass-lined carbon steel tank. To this solution was added 60 L of 0.1 N H₂SO₄. The mixture was stirred for 5 min, and the layers were allowed to separate over 25 min³⁴ The lower aqueous layer was removed and neutralized. Tetrabutylammonium hydrogen sulfate (2.20 kg, 6.48 mol, 0.17 equiv) was then added to the EtOAc solution, followed by a solution of magnesium monoperoxyphthalate hydrate (MMPA, 28.80 kg, 4.76% active oxygen = 1.1 equiv) in deionized H_2O (32 L). The tank containing the MMPA solution was rinsed with deionized H₂O (20 L), and the rinse was added to the reaction mixture. The reaction was stirred at 22 °C for 22 h. A sample was analyzed, and the starting material was absent by HPLC

⁽³⁴⁾ The extraction of the solution of 5b with dilute acid prevented the formation of small amounts of two, yet unidentified, non-polar impurities during the reaction.

analysis. A solution of sodium sulfite (9.9 kg) in deionized $H_2O(100 L)$ was added to the reaction mixture over 18 min. The reaction was stirred for 20 min at 22 °C at which point a KI/starch paper test showed no peroxide present. Ethyl acetate (60 L) was added to the reaction, and the mixture was stirred for 5 min. The layers were separated, and the organic layer was washed with deionized H₂O (58 L), 2 N NaOH (60 L), and deionized H₂O (2 \times 60 L). The organic layer was transferred to a clean tank, and the solution was distilled at 75-95 °C at atmospheric pressure until the volume reached 20-25 L. The solution was cooled to 75 °C, and heptane (65 L), heated to 70-80 °C, was added over 13 min, maintaining the reaction solution temperature at 70-80 °C. The solution was cooled to 65-70 °C, and a small portion of the reaction solution was drawn into a tube, allowed to cool and crystallize, and was added back to the reaction mixture as seed crystals. The reaction was stirred at 67 °C for 20 min, cooled to 64 °C over 1 h, cooled to 41 °C over 67 min, cooled to -5 °C over 1.5 h, and stirred for 60 min. The precipitate was filtered, washed with a cold (-5 °C) mixture of heptane (35 L) and EtOAc (10 L), and dried under vacuum for 5 h at 50 °C to give 8.70 kg of epoxide 4b with assay (potency) of 95.9% (HPLC vs a reference standard) and contained 3% of epoxide 4c. A recrystallized sample of 4b (free of diastereomer 4c) had a melting point of 131–33 °C. ¹H NMR (500 MHz, CDCl₃): δ 5.0 (bs, 1H), 3.58 (s, 2H), 2.41 (d, J = 15.3 Hz, 2H), 2.20 (d, J = 15.2 Hz, 2H), 1.43 (s, 9H), 1.40 (s, 9H). ¹³C NMR $(CDCl_3)$: δ 171.3, 154.3, 81.2, 79.5, 62.8, 57.0, 38.6, 28.3, 27.7. IR (KBr): 3453, 2982, 2932, 1726, 1708, 1489, 1369, 1293, 1156, 840 cm⁻¹. MS (ES) *m/e* (% relative intensity): $300.3 (M^+ + 1, 65), 244.4 (68), 188.2 (100), 144.1 (99).$

N,N'-Bis[(1R)-1-phenethyl-1,3-propanediamine]dihydrochloride (17-diHCl). Preparation of Free Base Diamine 17. (R)- α -methylbenzylamine (5.36 kg, 44.23 mol, 3.8 equiv) was heated to 98-105 °C in a 22-L flask, and 1,3-dibromopropane (2.25 kg, 11.14 mol) was added over 110 min, while maintaining the temperature at 100-120 °C. The solution was stirred for 45 min at approximately 100 °C, at which time GC assay of the reaction mixture showed that no 1,3-dibromopropane remained. The solution was cooled to 80 °C, and a 50% NaOH solution (1.4 L) was added over 11 min. The solution was cooled to <50 °C, MTBE (4.45 L) was added, and the mixture was stirred for 15 min. Deionized water (5 L) was added to the reaction, and the layers were separated. To the organic layer was added brine (3 L). The layers were separated, and the organic layer was dried with Na₂SO₄ (1 kg). The solid was removed by filtration, and the filtrate was concentrated under vacuum. This above reaction was duplicated to give two batches of crude diamine 17 (5.61 and 5.21 kg). The oils were combined in a 22-L flask equipped with a mechanical stirrer and a short-path distillation head. The flasks containing the oils were rinsed with 0.1 L of MTBE, and the rinses were added to the oils. Vacuum was slowly applied, and the solution was heated to 35 °C to distill off MTBE. The remaining oil was slowly heated (at 4 mmHg), until the vapor temperature peaked at 75-80 °C, to distill the α -methylbenzylamine away from the product. The solution was cooled under N_2 to give 5.689 kg (94.2% uncorrected yield) of diamine **17** (94.9 area % by GC; α -methylbenzylamine not detected).

Preparation of 17-Dihydrochloride Salt. Crude diamine 17 (32.22 kg, 114.2 mol) was added to ethanol (495 L, denatured with toluene) in a 200-gal, glass-lined stainless steel tank. The containers were rinsed with ethanol (10 L), and the rinse was added to the reaction tank. Aqueous HCl (34 wt %, 29.74 kg, 277.4 mol) was added to the reaction mixture, while maintaining a temperature of 20-30 °C. The HCl container was rinsed with ethanol (10 L), and the rinse was added to the reaction solution. The solution was cooled and stirred for 1 h at -8 °C. The precipitate was filtered, washed with cold (-10 °C) ethanol (67 L), and vacuumdried for 4 days at 70 °C to give 36.83 kg (85.7% yield) of diamine 17-dihydrochloride as a white solid, mp 285 °C. Capillary electrophoresis assay showed this material to contain 98.1% of the (R,R)-isomer and 1.9% of the mesoisomer. ($t_{\rm R} = 25.7, 26.1, \text{ and } 26.8 \text{ min for } (R,R)$ -, meso-, and (S,S)-isomers, respectively.) ¹H NMR (500 MHz, DMSO- d_6): δ 9.93 (bs, 2H), 9.47 (bs, 2H), 7.56 (d, J =7.0 Hz, 4H), 7.37 (m, 6H), 4.27 (m, 2H), 2.84 (m, 2H), 2.48 (m, 2H), 2.1 (m, 2H), 1.56 (d, J = 6.7 Hz, 6H).

(1S,4R)-1-[[(1,1-Dimethylethoxy)carbonyl]amino]-4hydroxy-2-cyclopentene-1-carboxylic acid, 1,1-Dimethylethyl Ester (3b). Diamine 17-dihydrochloride (13.70 kg, 38.55 mol, 2.4 equiv) was added to deionized H₂O (50 L) in a 100-gal, glass-lined stainless steel tank. The solids dissolved after 6 min of stirring. A solution of 2.4 N NaOH (42 L, 102 mol) was added to the reaction solution and stirred for 10 min followed by the addition of MTBE (75 L). The reaction mixture was stirred for 10 min, and the layers were separated. The aqueous layer was extracted with MTBE (25 L, 10 min stir time), and the layers were separated. The organic layers were combined and stirred for 10 min with a 20% NaCl solution (40 L). The layers were allowed to settle for 1 h and then were separated. The organic layer was refluxed for a total of 4 h, and water was periodically drained from the distillate take-off valve. The solution was then concentrated to 30 L by atmospheric distillation of the MTBE. (Karl Fischer titration assay of the solution indicated 0.14% H₂O.) The solution was cooled to 25 °C and diluted with 50 L of MTBE. The reflux and atmospheric distillation operations were repeated, and the solution was concentrated to a volume of 30 L. (KF assay of the solution showed 0.035% water.) The organic solution was transferred to a 50-gal, glass-lined carbon steel tank, the previous tank was rinsed with THF (10 L), and the rinse was added to the 50gal tank. The reaction solution was cooled to -35 to -55 °C over 30 min. A solution of n-BuLi (2.5 M in hexanes, 19.8 kg, 71.1 mol, 4.4 equiv relative to **4b**)³⁵ was added over 70 min, while maintaining the reaction temperature at -35to -55 °C. The solution was stirred for 2.2 h at -45 °C, and then a solution of epoxide 4b (4.80 kg, 16.05 mol) in

⁽³⁵⁾ The yield of the free basing was determined to be 93%, based on gravimetric assay of a sample of the free base 17 solution. This yield was consistent over multiple pilot-plant runs. The stoichiometry of the *n*-BuLi and epoxide 4b were calculated based on this yield.

THF (23 L) was added over 1.75 h, while maintaining the reaction solution at -35 to -55 °C. The tank containing the 4b solution was rinsed with THF (2 L), and the rinse was added to the reaction solution. The reaction solution was stirred at -45 °C for 15 h at which point HPLC assay showed 1.1% of epoxide 4b remained. The reaction solution was then transferred over 1.5 h to a 100-gal, glass-lined stainless steel tank containing a 4 N H₂SO₄ solution (45 L) that was maintained at a temperature below 20 °C. The mixture was stirred for 20 min, and the layers were separated. The aqueous layer was extracted with MTBE (15 L), and the layers were separated. The combined organic layers were washed with water (20 L) and a 20% NaCl solution (25 L). The organic layer was concentrated by distillation at 34-41°C at 350-550 mmHg to a volume of 15 L. The organic layer was then heated at atmospheric pressure to 45-55 °C, and heptane (35 L) was added slowly over 1 h, while maintaining a temperature of 44-55 °C. The solution was cooled to 0-5 °C over 3 h and stirred at 2 °C for 3 h. The solid was filtered, and the tank was rinsed with a cold (5 °C) 3:1 heptane/MTBE solution (20 L). The rinse was filtered over the product cake, and the cake was dried dry under N₂ for 4 h. The cake was transferred to a vacuum dryer and dried for 19 h at 50 °C to give 3.61 kg (76.7% yield) of 578242 as white crystals (97.7% potency). Corrected yield = 74.9%. HPLC assay showed this lot contained 0.59%alcohol 3c and 0.42% epoxide 4b. Chiral HPLC assay: 99.6% ee. ($t_{\rm R} = 10.07$ and 7.10 min for desired and undesired enantiomer, respectively.) An analytically pure sample of compound **3b** had a melting point of 111-112 °C. $[\alpha]^{25}_{D} =$ +114 (c 1, MeOH). ¹H NMR (500 MHz, CDCl₃): δ 6.1 (bs, 1H), 5.9 (bs, 1H), 5.55 (d, J = 5.0 Hz, 1H), 4.8 (m, 1H), 4.44 (d, J = 10.5 Hz, 1H), 2.87 (dd, J = 14.5, 7.5 Hz, 1H), 2.00 (d, J = 14.5 Hz, 1H), 1.45 (s, 9H), 1.42 (s, 9H). IR (KBr): 3413, 2983, 1703, 1491, 1370, 1309, 1255, 1155, 1055 cm⁻¹. MS (ES) *m/e* (% relative intensity): 300.3 (M⁺ + 1, 15), 226.2 (29), 170.1 (100), 126.1 (89), 108.3 (20). Anal. Calcd for C₁₅H₂₅NO₅: C, 60.18; H, 8.41; N, 4.68. Found: C, 60.59; H, 8.58; N, 4.78.

The filtrate was concentrated to approximately 10 L under vacuum to yield a slurry. The solids were filtered, washed with 1 L of hexanes, and vacuum dried at 45 °C to obtain 431 g (12% yield) of **3b**, 86.2% ee by chiral HPLC assay.

Recovery of Diamine 17-Dihydrochloride. To a 100gal glass reactor was charged 150 L of an aqueous sulfuric acid solution containing a maximum of 68.6 mol diamine **17**. The pH was adjusted to 13 with 50% NaOH solution. The mixture was extracted with 2×115 L of MTBE. The combined organic layers were washed with 60 L of deionized water. The organic layer was distilled under atmospheric pressure to a volume of 35 L and subsequently diluted with 250 L of ethanol (denatured with toluene). Hydrochloric acid (32 wt %, 15.5 kg, 136 mol) was then added over 50 min at 15-30 °C. The resulting slurry was cooled to -8 °C, stirred 1 h, and filtered. The filter cake was rinsed with 45 L of ethanol, dried with nitrogen flow for 3 h, and then vacuumdried at 70 °C for 4 days to yield 19.55 kg (55.0 mol, 80% overall recovery) of **17**-dihydrochloride. Capillary electrophoresis assay showed this material to contain 98.5% of the (R,R)-isomer and 1.5% of the *meso*-isomer. The (S,S)-isomer was not detected.

(1S)-1-[[(1,1-Dimethylethoxy)carbonyl]amino]-4-oxo-2-cyclopentene-1-carboxylic Acid, 1,1-Dimethylethyl Ester (2b). Compound 3b (3.10 kg, 10.36 mol) was added to MTBE (31 L) in a 50-gal, glass-lined carbon steel tank. A solution of KBr (100 g, 0.84 mol, 0.08 equiv) in deionized H₂O (0.15 L) was added to the reaction solution followed by the addition of TEMPO (0.13 kg, 0.83 mol, 0.08 equiv). The solution was cooled to 0 °C, and a premixed solution of NaOCl (41.8 kg, 3 wt % solution, 561.5 mol, 1.6 equiv) and NaHCO₃ (1.6 kg, 19.04 mol, 1.84 equiv) was added over 50 min, while maintaining the reaction mixture solution at -5 to 5 °C. The reaction was stirred for 2 h at 0 °C, at which time HPLC assay showed no alcohol 3b remained. The reaction mixture was warmed to 20-25 °C over 20 min, and the layers were separated. The aqueous layer was extracted with MTBE (2 \times 15 L), and the MTBE layers were combined with the original organic layer. A solution of 1 N HCl (30 L) containing KI (0.35 kg, 2.11 mol) was added to the organic layer and stirred. The layers were separated, and the organic layer was washed with Na₂S₂O₃ (3.2 kg dissolved in 30 L of H₂O) and deionized H₂O (2 \times 32 L). The organic layer tested negative for hypochlorite with the use of starch/KI paper. The organic layer was concentrated by vacuum distillation at 50 °C at 550-650 mmHg to a volume of 14 L. Heptane (20 L) was added, and the solution was again concentrated to 14 L. The solution was cooled to 40-50 °C, and heptane (30 L) was added over 60 min, while maintaining the temperature at 45-55 °C. The solution was cooled to 0 °C over 3 h and stirred for 2.5 h. The precipitate was filtered, the tank was rinsed with a cold 3.3:1 heptane/MTBE (13 L) solution, and the rinse was filtered over the product cake. The cake was blown dry under N2 for 2.75 h and then dried under vacuum for 15.5 h at 50 °C to give 2.502 kg (81.2% yield) of ketone 2b as white crystals, mp 116–118 °C. HPLC potency = 99.7%. Corrected yield = 80.9%. $[\alpha]^{25}_{D} = +123$ (c 1, MeOH). ¹H NMR (500 MHz, CDCl₃): δ 7.4 (bs, 1H), 6.32 (d, J = 5.5Hz, 1H), 5.6 (bs, 1H), 2.87 (d, J = 18.2 Hz, 1H), 2.70 (d, J= 18.2 Hz, 1H), 1.43 (s, 18H). ¹³C NMR (CDCl₃): δ 206.1, 170.2, 160.8, 154.9, 136.1, 84.5, 66.1, 46.6, 28.9, 28.4. IR (KBr): 3419, 2983, 1722, 1487, 1730, 1300, 1259, 1151, 1012 cm⁻¹. MS (ES) *m/e* (% relative intensity): 254.2 (M⁺ + 1, 11), 242.3 (18), 228.2 (13), 186.1 (76), 143.2 (11), 242.3 (100). Anal. Calcd for C₁₅H₂₃NO₅: C, 60.59; H, 7.79; N, 4.71. Found: C, 60.57; H, 7.85; N, 4.81.

N,*N*'-Bis-[(*R*)-1-phenethyl]-(*S*,*S*)-1,2-diamino-1,2-diphenylethane (13). This compound was prepared via modification of the literature method.⁷ Sodium sulfate (500 g, 3.5 mol) was stirred in heptane (1.8 L) in a 5-L three-neck flask equipped with mechanical stirrer, nitrogen inlet, and thermocouple. Glyoxal (40 wt/wt % in water, 115 mL, 0.96 mol) was added followed by formic acid (6.0 mL, 0.15 mol). *R*-(+)- α -Methylbenzylamine (274 mL, 2.15 mol) was then added, resulting in a temperature rise to 33 °C. Sodium sulfate (625 g, 4.4 mol) was added, and the reaction mixture was stirred for 3.5 h. The reaction mixture was filtered, and the filter cake was rinsed with heptane (600 mL). The filtrate was concentrated under reduced pressure to obtain *N*,*N'*-bis-[(*R*)-1-phenethyl]ethane diimine as a clear, dark-orange oil (270.4 g, 106% yield) which was used without further purification. ¹H NMR (500 MHz, CDCl₃): δ 1.58 (d, *J* = 6.5 Hz, 6H), 4.5 (q, *J* = 6.5 Hz, 2H), 7.25–7.34 (m, 10H), 8.06 (s, 2H).

A 500-mL three-neck flask equipped with mechanical stirrer, 500 mL addition funnel, and Claisen adapter with septum, nitrogen inlet, and thermocouple was charged with a solution of N, N'-bis-[(R)-1-phenethyl]ethane diimine (30.1 g, 0.114 mol) in anhydrous diethyl ether (150 mL) via cannula under nitrogen. The clear, orange solution was cooled to -78 °C with a dry ice/acetone bath. Phenyl magnesium chloride (2 M in THF, 171 mL, 0.342 mol) was added over 3.5 h, maintaining the temperature below -73 °C. The reaction stirred for 1 h at -78 °C. The ice bath was then removed, and the cloudy mixture was allowed to warm to 0 °C over 45 min. Acetic acid (39 mL, 0.684 mol) in THF (210 mL) was added slowly to the reaction mixture, keeping the temperature below 0 °C by using a dry ice/acetone bath. Deionized water (200 mL) was added to give a clear, biphasic mixture that was allowed to warm to room temperature. The mixture was transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with 2 \times 200 mL of MTBE. The combined organic layers were washed with 1 N NaOH (200 mL), deionized water (200 mL), and then saturated aqueous NaCl (200 mL). The combined organic layers were then dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a clear, orange oil (45.5 g). Ethanol (20 mL) was added to the oil, and the slurry was stirred in an ice/water bath for 30 min. The mixture was filtered and the solid rinsed with cold ethanol and vacuum-dried at 50 °C to give 14.0 g (29% yield) of diamine **13** as a white solid, mp = 110–111 °C. Lit. mp = 119–122 °C. $[\alpha]^{25}_{D} = +196$ (*c* 1, MeOH). ¹H NMR (500 MHz, CDCl₃): δ 1.26 (d, J = 6.5 Hz, 6H), 2.20 (broad singlet, 2H), 3.37 (s, 2H), 3.4 (q, J = 6.5 Hz, 2H), 6.92–7.27 (m, 20H).

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Supporting Information Available

Schemes for the preparation of diamines 19-21; spectral data and experimental procedures for the rearrangement of epoxides 4c and i. This material is available free of charge via the Internet at http://pubs.acs.org.

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