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Dynamic Kinetic Resolution of Epichlorohydrin via Enantioselective Catalytic Ring Opening with $TMSN_3$. Practical Synthesis of Aryl Oxazolidinone Antibacterial Agents

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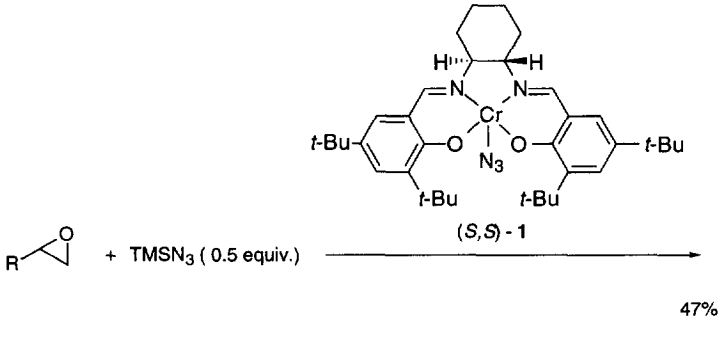
Abstract: The dynamic kinetic resolution of racemic epichlorohydrin has been achieved via enantioselective asymmetric ring opening with $TMSN_3$ catalyzed by the (salen)Cr(III)N_3 complex **1**. The resulting 3-azido-1-chloro-2-trimethylsiloxypropane product was obtained in high enantiomeric purity and incorporated into the synthesis of U-100592, a representative from a class of highly-promising aryl oxazolidinone antibacterial agents.

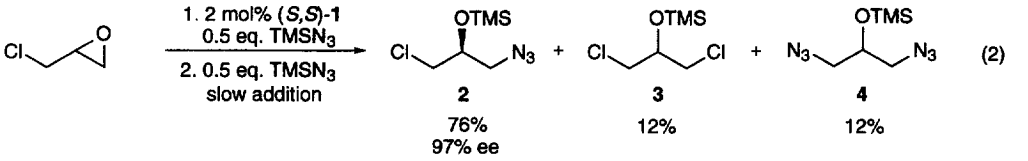
Dynamic kinetic resolution serves as an attractive strategy for the generation of enantiomerically enriched compounds for organic synthesis.[1] Such a process requires the *in situ* racemization of the slower reacting enantiomer under conditions compatible with a kinetic resolution reaction. The kinetic resolution of (±)-epichlorohydrin catalyzed by (*S*,*S*)-**1** with $TMSN_3$ recently reported from our laboratory was shown to yield the ring opened product (*S*)- 3-azido-1-chloro-2-trimethylsiloxypropane **2** with a k_{rel} exceeding 100 (eq. 1).[2] This particular substrate proved unusual, in that the unreacted epichlorohydrin was found to undergo racemization under the reaction conditions. In a separate control experiment, we found that treatment of highly enantioenriched (*R*)-epichlorohydrin (97% ee) with (*S*,*S*)-**1** (2 mol%) at room temperature led to nearly racemic epoxide (20% ee) within 24 h.



(1)

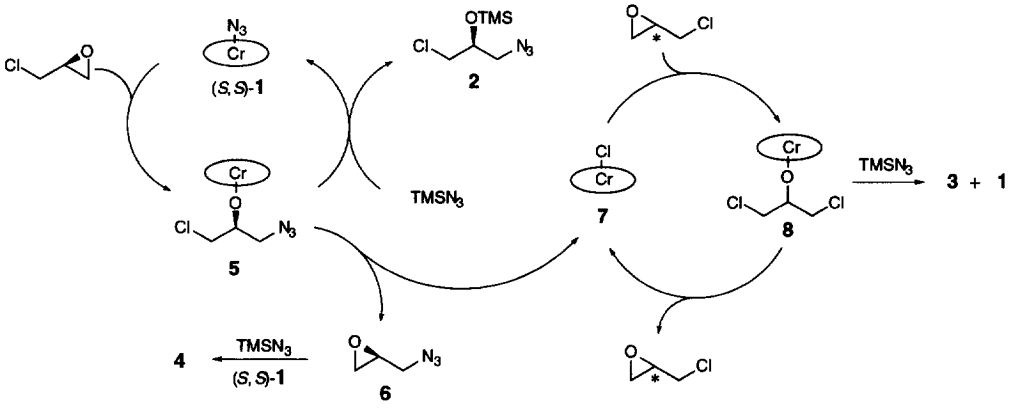
This suggested that under the appropriate conditions, it may be possible to effect the dynamic kinetic resolution of epichlorohydrin to give the product **2** in highly enantiomerically enriched form. Indeed, treatment of (±)-epichlorohydrin with one equivalent of $TMSN_3$ in the presence of 2 mole % (*S*,*S*)-**1** yielded **2** in 40% ee with complete consumption of the epoxide. Clearly, dynamic kinetic resolution was occurring to some extent, but a more controlled addition of the $TMSN_3$ was warranted in

order to increase the rate of racemization relative to the rate of ring-opening. In fact, reaction of 0.50 equivalent $TMSN_3$ with (±)-epichlorohydrin at 4 °C for 16 h followed by addition of a second 0.50 equivalent added over 16 h afforded the desired product **2** in 76% yield and in 97% ee.[3] Analysis of the products obtained from the reaction showed that small amounts of the 1,3-dichloro compound **3** and 1,3-diazide **4** were formed as well (equation 2).



The identity of these byproducts provides an indication as to the mechanism of racemization (Scheme 1). It has been established that reaction of **1** with epoxide leads initially to the formation of a Cr-alkoxide intermediate **5**.[4] This intermediate can either undergo silylation with $TMSN_3$ to form **2** and regenerate **1**, or decomposition with chloride displacement to generate the epoxide **6** and the (salen)CrCl complex **7**.

Scheme 1

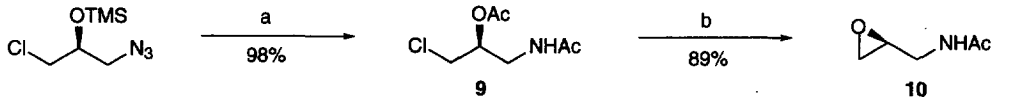


Epoxide **6** undergoes ring opening with (*S*,*S*)-**1** to yield the achiral diazide **4** [CAUTION!].[5] Complex **7** can then nonselectively deliver chloride to epichlorohydrin[6] producing the Cr-alkoxide **8**, which can regenerate **7** and either enantiomer of epichlorohydrin, or undergo silylation to form **3** and (salen)CrN_3 **1**. It is important to note that the ability of complex **7** to deliver chloride to the slow-reacting enantiomer of epichlorohydrin is essential for the dynamic kinetic resolution to occur. Unfortunately, the formation of small amounts of **3** and **4** as by-products is intrinsically tied to this mechanism, and has proven difficult to suppress. However, this procedure still provides an exceptionally attractive method for generating the desired product **2** in good yield and highly enantioenriched form.

The densely functionalized product **2** obtained from the dynamic kinetic resolution is readily applied to the synthesis of a variety of interesting compounds. One such target is the oxazolidinone U-100592, a highly-promising antibacterial agent recently developed by scientists at Upjohn.[7] Elaboration of

2 to the *O*-acetyl acetamide **9** was accomplished by sequential desilylation, azide reduction by catalytic hydrogenation, and acetylation (Scheme 2).[8] Treatment of **9** with methanolic K_2CO_3 served both to deprotect the acetate and to effect ring closure to form epoxide **10**.[9]

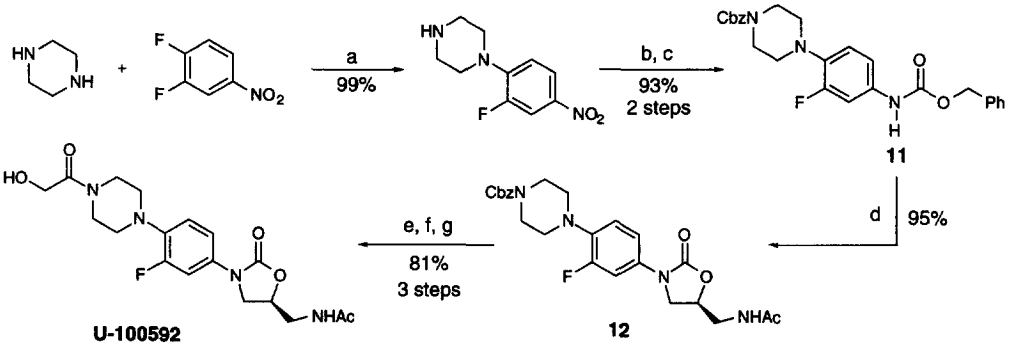
Scheme 2[a]



Legend.[a] (a) i. MeOH, catalytic TFA, rt, 30 min.; ii. 2 mol% PtO_2, H_2(1 atm), THF, rt, 6 h; iii. Ac_2O, TEA, 0 °C → rt, 4 h; (b) K_2CO_3, MeOH, rt, 2 h.

Incorporation of **10** into the synthesis of U-100592 provided a concise alternative to the published route which employs (*R*)-glycidyl butyrate.[7] The requisite carbamate **11** was prepared by nucleophilic aromatic substitution of 3,4-difluoro-nitrobenzene by piperazine, nitro group reduction, and subsequent Cbz protection of both the secondary and aryl amines.[7a] *N*-Lithiation followed by addition of excess **10** effects both epoxide opening and oxazolidone formation to give the aryl oxazolidone **12** directly and in excellent overall yield.[10] Finally, elaboration of the Cbz-protected secondary amine was accomplished by Pd catalyzed deprotection, acetylation with benzyloxyacetyl chloride, and debenzylation to yield U-100592.

Scheme 3[a]



Legend.[a] (a) CH_3CN, 80 °C, 2 h; (b) 1 mol% PtO_2, H_2 (1 atm), EtOH, rt, 8 h; (c) CbzCl, 10% Na_2CO_3, acetone, 0 °C → rt, 18 h; (d) i. *n*-BuLi, THF, -78 °C, 1.5 h; ii. 2.0 eq. **10**, THF, 0 → 60 °C, 2 h; (e) 10% Pd/C, H_2(1 atm), CH_2Cl_2, MeOH, rt; (f) benzyl-oxyacetyl chloride, TEA, CH_2Cl_2, 0 °C; (g) 10% Pd/C, H_2(1 atm), CH_2Cl_2, MeOH, rt.

The dynamic kinetic resolution of epichlorohydrin provides a straightforward method for converting a commodity chemical to a valuable enantiomerically enriched synthetic building block. Application towards the practical synthesis of biologically interesting targets such as U-100592 illustrate an immediate useful application of this efficient reaction methodology.

Acknowledgments: This work was supported by the National Institutes of Health (GM-43214) and by a generous gift from Versicor, Inc.

Notes and References

(1) For a timely review, see: Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.*, **1995**, *68*, 36.

(2) (a) Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420. (b) Martínez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897.

(3) An oven dried 10 mL flask equipped with a stir bar was charged with 64 mg (0.10 mmol) of (*S,S*) **-1**. The flask was sealed, purged with N_2, and cooled to 0 °C in an ice bath. This was followed by the sequential addition of (±)-epichlrohydrin (390 μL, 5.0 mmol, 99% Aldrich, distilled from CaH_2) and $TMSN_3$ (330 μL, 2.5 mmol, Lancaster, distilled from CaH_2). The mixture was allowed to stir at 0-4 °C for 16 h, at which time the reaction was allowed to warm to rt. The remaining $TMSN_3$ (330 μL, 2.5 mmol) was added over the next 16 h at rt, and the reaction was allowed to stir an additional 24 h. Product was isolated by vacuum distillation (50 °C / 0.5 mm Hg) into a cooled collection flask to yield 1.04 g (76% by GC analysis) of **2** as a colorless oil. Chiral GC analysis of the corresponding azido alcohol (γ-TA, 80 °C for 19 min, 1 °C / min to 95 °C) indicated that **2** was produced in 97% ee.

(4) Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. *J. Am. Chem. Soc.*, in press.

(5) CAUTION: Although problems have never been encountered in our labs in experiments carried out at multigram scale, low molecular weight organic azide compounds should be handled with extreme caution due to their possible shock sensitivity.

(6) The (salen)CrCl complex **7** has been shown to transfer chloride to epoxides with low enantioselectivity. See ref 3.

(7) (a) Brickner, S. J.; Hutchinson, D. K.; Barbachyn, M. R.; Manninen, P. R.; Ulanowicz, D. A.; Garmon, S. A.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 673. (b) Barbachyn, M. R.; Hutchinson, D. K.; Brickner, S. J.; Cynamon, M. H.; Kilburn, J. O.; Klemens, S. P.; Glickman, S. E.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 680.

(8) A 100 mL oven-dried flask equipped with a stir bar was charged with 950 mg (4.60 mmol) of **2**. The flask was sealed and purged with N_2. Methanol (4.6 mL, 1.0 M) and one drop of TFA were sequentially added at rt and the solution was allowed to stir for 30 min. The solvent was removed in vacuo and the clear residue was taken up in THF (6.6 mL, 0.70 M). PtO_2 (22 mg, 0.092 mmol) was added to the solution and the reduction was effected at rt under H_2 atmosphere (1 atm) for 6 hr. The flask was then purged with N_2, cooled to 0 °C, and sequentially charged with Ac_2O (1.30 mL, 13.8 mmol) and Et_3N (1.70 mL, 14.7 mmol). The reaction flask was allowed to warm to rt over 4 h at which time the solution was filtered through Celite, diluted with H_2O and saturated NaCl solution, and extracted 3 X 1:1 EtOAc:THF. The combined organic extracts were dried over Na_2SO_4, filtered, concentrated in vacuo to produce a viscous oil. The material was dissolved in Et_2O and treated with an equal volume of hexanes. The resulting mixture was heated until homogeneity was achieved and allowed to cool to rt. Filtration yielded 870 mg (4.51 mmol, 98%) of **9** as clear white crystals. $[\alpha]_D^{25}$ -2.2 (*c* 0.865, CH_2Cl_2); IR (KBr) 3267, 3088, 1741, 1641, 1571, 1439, 1371, 1297, 1236, 1047, 935; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.74 (s(br), 1H, NHAc), 5.06-5.12 (m, 1H, CH_2CHOAc), 3.69 (dd, 1H, *J* = 1.3 and 4.7 Hz, $ClCH_2CH$), 3.47-3.64 (m, 3H, $ClCH_2CH$ and CH_2NHAc), 2.10 (s, 3H, $OCOCH_3$), 2.00 (s, 3H, $NHCOCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.44, 170.40, 72.0, 43.4, 40.6, 23.1, 20.9.

(9) A 100 mL flask equipped with a stir bar was treated with 317 mg (1.60 mmol) of **9**. The material was dissolved in methanol (5.5 mL, 0.30 M) and treated with 442 mg K_2CO_3. The heterogenous mixture was allowed to stir at rt for 2 h at which time the reaction was diluted with EtOAc, rinsed sequentially with saturated NH_4Cl and NaCl solutions and dried over Na_2SO_4. The solution was filtered, concentrated in vacuo, and purified by flash chromatography (MeOH 1 - 5% MeOH:CH_2Cl_2 1:99 - 5:95 to yield 164 mg (1.42 mmol, 89%) of **10** as a clear oil. $[\alpha]_D^{25}$ -15.8 (*c* 2.40, CH_2Cl_2); IR (thin film) 3209, 2931, 1658, 1553, 1374, 1291; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.71 (s(br), 1H, NHAc), 3.71-3.77 (m, 1H, CH_2NHAc), 3.24-3.30 (m, 1H, CH_2NHAc), 3.09-3.13 (m, 1H, CH_2OCH), 2.80 (t, 1H, *J* = 4.5 Hz, CH_2OCH), 2.58 (dd, 1H, *J* = 2.7 and 4.5 Hz, CH_2OCH), 2.00 (s, 3H, $NHCOCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4, 50.5, 45.1, 40.5, 22.9; Exact mass (CI) calcd for $C_5H_{10}NO_2$ [M + H]$^+$: 116.0711; found: 116.0714.

(10) A 10 mL oven-dried flask was charged with 156 mg (0.337 mmol) **11**. The flask was sealed and flushed with N_2. The material was taken up in THF (1.7 mL, 0.2 M), cooled to –78 °C in a methanol-dry ice bath, and 2.5 M *n*-BuLi (150 μL, 0.371 mmol) was added dropwise. The light yellow solution was allowed to stir at –78 °C for 1.5 h and then placed in an ice bath. A solution of epoxide **10** (77.6 mg, 0.675 mmol) in THF (200 μL) was added and the resulting mixture allowed to warm to rt over 30 min. Gentle heating to 60 °C for 2 h resulted in the mixture turning heterogeneous. The reaction was allowed to cool to rt over an hour and quenched with a saturated solution of NH_4Cl. The resulting emulsion was rendered basic by addition of $NaHCO_3$ (satd.) and extracted 3 X 1:1 EtOAc:THF. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The resulting solid was triturated with warm 30% EtOAc in hexanes and collected to yield 151 mg (0.322 mmol, 95%) of **12**[7a] as an off white solid.

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