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Chloroperoxidase-mediated asymmetric epoxidation. Synthesis of (*R*)-dimethyl 2-methylaziridine-1,2-dicarboxylate — a potential α-methylamino acid synthon

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Abstract: Methoxycarbonyl-protected methallyl amine serves as an excellent substrate for chloroperoxidase-mediated asymmetric epoxidation. The resulting (*R*)-epoxide (94% ee) was converted to the title compound in three steps with nearly complete maintenance of stereochemical integrity. Titanium tetrachloride ring-opening of the epoxide provided the chlorohydrin with excellent selectivity and inversion of the stereogenic center. Oxidation with pyridinium dichromate was followed by ring-closure to the aziridine which was esterified *in situ* with methyl iodide. © 1997 Elsevier Science Ltd

α-Methylamino acids are intriguing peptide building blocks because of their complete resistance to α-epimerization, and once incorporated they may impart conformational rigidity[1] and a reduced tendency toward proteolysis. Furthermore, α-methylamino acids of both optical antipodes, particularly α-methylcysteines, have been converted to biologically active natural products.[2]

Aziridinecarboxylates have increasingly been demonstrated as viable precursors to amino acids in general. Both heteroatom nucleophiles[3] and carbon nucleophiles[4] have been shown to react with aziridinecarboxylates stereo- and regioselectively. Thus, we have sought a short and simple route to a protected 2-methylaziridinecarboxylate which could be elaborated to a variety of α-methylamino acids and natural products.

Chloroperoxidase (CPO), isolated from *Caldariomyces fumago*, is an efficient and versatile catalyst that has successfully transformed a number of prochiral alkenes to optically active epoxides in the presence of a stoichiometric oxidant.[5] An efficient synthesis of (*R*)-(−)-mevalonolactone[5d] serves as an example of its utility. Herein, we report that protected methallylamine[6] is epoxidized in high yield and excellent enantioselectivity when catalyzed by CPO. The resultant product is converted to (*R*)-dimethyl 2-methylaziridine-1,2-dicarboxylate (**1**) in only three additional steps (Scheme 1).

Carbamate **2** was dissolved as a 50 mM solution in 10 mM Na citrate buffer (pH=5.5) and treated with 2.0 equiv. of *t*-butylhydroperoxide, followed by 1.9×10^{-4} equiv. of purified chloroperoxidase[7] (8.0 mg CPO/mmol substrate). After 1.5 h, extraction and flash chromatography provided an 82% yield of (*R*)-epoxide **3**[8] with 94% ee. Results were quite similar when *C. fumago* culture medium supernatant[9] was used instead of purified enzyme. 2-Methyl-1-alkenes similar to **2** have always given *R*-configuration epoxides[5c] (barring a priority change), but the configuration in this case was proven by correlation to (*S*)-methylglycidol.[10]

An aza-Payne type reaction[11] would have been convenient at this point, but all attempts to form the hydroxy aziridine by this direct method failed.[12] Instead, acid-promoted epoxide ring opening of *rac*-**3**[13] was investigated and a wide range of regioselectivities[14] was observed (Table 1). Titanium tetrachloride proved to be the most useful Lewis acid for our purposes providing chlorohydrin **4**[15] in 92% yield. Regioselectivity was high (96:4) and inversion of stereochemistry appeared to be complete: Treating chlorohydrin (*S*)-**4** with NaH in THF regenerated (*R*)-**3** with the original ee.

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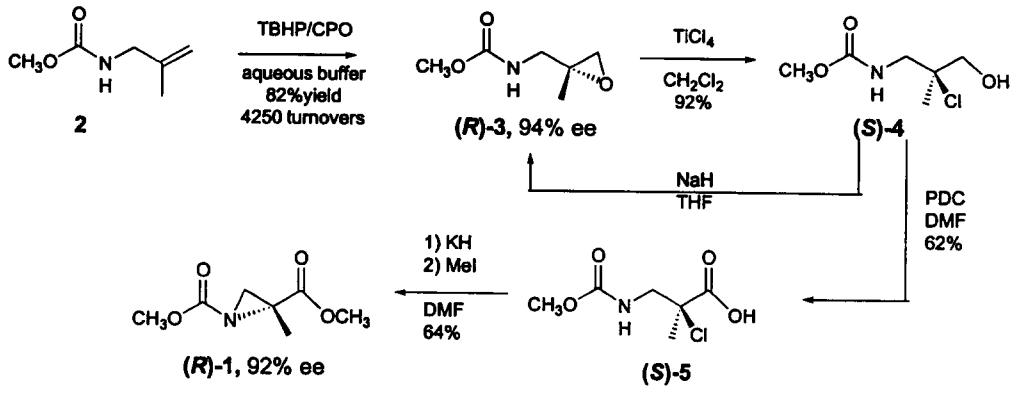
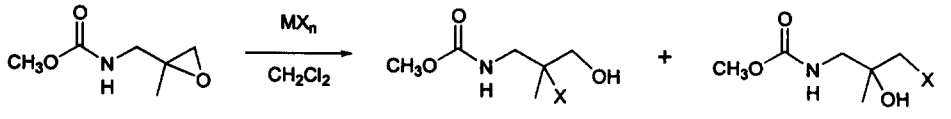


Scheme 1.

Table 1. Acidic ring opening of racemic epoxide 3[a]



MX_n (equiv.)	Temp, Time	Yield (A+B)	A/B[b]
$MgBr_2$ (1.1)	0 °C, 1.0 h	> 98 %	2/98
CatacholBBr (1.1)	0 °C, 2.0 h	> 98 %	11/89
HCl (1.2)[c]	0 °C, 0.5 h	> 98 %	11/89
BBr_3 (1.1)	0 °C, 0.5 h	83 %	31/69
$AlCl_3$ (1.1)	0 °C, 0.5 h	> 98 %	42/58
$TiCl_4$ (1.1)	0 °C, 0.8 h	> 98 %	84/16
$TiCl_4$ (1.5)	–78 °C, 2.0 h	92 %	96/4

[a] Epoxide (200 mg) in 0.5 mL CH_2Cl_2 was added dropwise to the acid dissolved in 4.5 mL CH_2Cl_2, unless otherwise indicated. [b] Determined by GC analysis and confirmed by ^{1}H-NMR integration. [c] ether solvent.

Chlorohydrin (*S*)-**4** could be separated from its regioisomer by chromatography but it was simpler to oxidize both together with pyridinium dichromate in dimethylformamide[16] and separate the acid (*S*)-**5**[17] from the unreacted tertiary alcohol by extraction. Strangely, pure acid (*S*)-**5** possessed no optical rotation either in ethanol or CH_2Cl_2. Also, NMR spectra of this acid in $CDCl_3$ solvent showed apparently two compounds in a ratio of 2:1. Dissolution in D_2O remedied the problem, presumably by disrupting intramolecular hydrogen bonding. Finally, a DMF solution of (*S*)-**5** was added to 2.2 equiv. of pentane-washed KH suspended in DMF. Once H_2 evolution ceased, the mixture was treated with 4.0 equiv. of methyl iodide and was stirred overnight. Workup and flash chromatography resulted in a 64% yield of protected aziridine (*R*)-**1**.[18] Enantiomeric excess was only slightly diminished (92% ee) during this step.

Having established an efficient synthesis of (*R*)-dimethyl 2-methylaziridine-1,2-dicarboxylate (**1**), we would like to elaborate on its synthetic utility. Epoxide (*R*)-**3**, difficult to obtain in high ee by other methods, will be a matter of investigation, also. Base-promoted aza-Payne type reaction with (*R*)-**3** would lead to the aziridinecarboxylate of the other enantiomer since only a single inversion of configuration would occur in that case, presenting another synthetic challenge.

Acknowledgements

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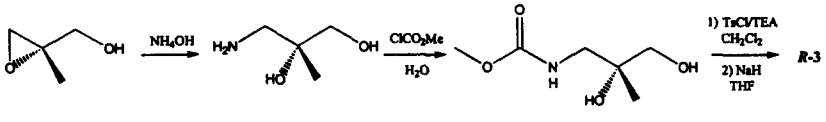
6. Of the protecting groups for methallylamine that were investigated—formyl, acetyl, trifluoroacetyl, *t*-butoxycarbonyl, and methoxycarbonyl—the latter was determined to be the most efficiently epoxidized by CPO.
7. Obtained from Chirazyme Laboratories, 2004 S. Wright St., Urbana, IL 61801, USA.
8. **(*R*)-Epoxide 3**: $[\alpha]_D=-11.4$ (c=1.17, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 3H), 2.55 (d, *J*=4.4 Hz, 1H), 2.66 (d, *J*=4.4 Hz, 1H), 3.31 (d, *J*=6.0 Hz, 2H) 3.59 (s, 3H), 5.15 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 44.8, 51.3, 52.0, 55.9, 157.1; FTIR (film) 3350 (br), 1715, 1540, 1261 cm^{-1}. HRMS Calcd for $C_6H_{11}NO_3$: 145.07389. Found: 145.07385.
9. Since the fungus cements itself to the sides of the roller flasks and secretes CPO, the supernatant is virtually cell-free and possesses good CPO activity.
10. (*R*)-Epoxide **3** was prepared in poor yield by an alternative route in which (*S*)-methylglycidol was aminated, the aminodiol was *N*-protected, tosylated and the monotosylate was treated with NaH in THF. Chiral GC analysis confirmed the *R*-configuration for CPO-generated **3**.



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12. The potassium salt of *rac*-**3** was stable for hours at rt in DMF. Quenching with electrophiles (MeI, $PhCH_2Br$, $ClCO_2Me$, Boc_2O) gave excellent yields of *N*-substituted epoxy carbamates.
13. Conveniently prepared using aqueous bicarbonate-buffered Oxone®: Zhu, W.; Ford, W. T. *J. Org. Chem.* **1991**, *56*, 7022–26.
14. For another study involving regioselective ring-opening of epoxides with Lewis acids see: Eisch, J. J.; Liu, Z.-R.; Ma, X.; Zheng, G.-X. *J. Org. Chem.* **1992**, *57*, 5140–44.
15. **(*S*)-Chlorohydrin 4**: m.p. 47–49°C; $[\alpha]_D=-4.0$ (c=0.84, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (s, 3H), 3.18 (dd, *J*=5.6, 15.2 Hz, 1H), 3.44 (br dd, *J*=6.4, 11.6 Hz, 1H), 3.61 (br d, *J*=16.0 Hz, 1H), 3.68 (d, *J*=15.2 Hz, 1H), 3.68 (s, 3H), 3.93 (br s, 1H), 5.45 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 48.0, 52.8, 67.0, 71.8, 158.6; FTIR (thin film) 3340 (br), 1705, 1540, 1262 cm^{-1}; Anal. Calcd for $C_6H_{12}ClNO_3$: C, 39.68%; H, 6.66%; Cl, 19.52%; N, 7.71%. Found: C, 39.68%; H, 6.85%; Cl, 19.27%; N, 8.11%.
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17. **(*S*)-Acid 5**: m.p. 109–111°C; $[\alpha]_D$=0.0 (EtOH or CH_2Cl_2); ^1H NMR (400 MHz, D_2O) δ 1.54 (s, 3H), 3.45 (d, *J*=15.0 Hz, 1H), 3.47 (s, 3H), 3.55 (d, *J*=15.0 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 24.7, 49.2, 52.4, 68.7, 159.0, 173.6; FTIR (thin film) 3350 (br), 1717, 1535, 1260 cm^{-1}; Anal. Calcd for $C_6H_{10}ClNO_4$: C, 36.84%; H, 5.15%; Cl, 18.12%; N, 7.16%. Found: C, 36.74%; H, 5.18%; 18.21%; N, 7.45%.
18. **(*R*)-Aziridine 1**: $[\alpha]_D$=−55.3 (c=1.91, EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 3H), 2.24 (d, *J*=1.0 Hz, 1H), 2.76 (d, *J*=1.0 Hz, 1H), 3.72 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 37.8, 41.3, 52.8, 53.5, 160.9, 169.9; FTIR (thin film) 1740, 1440, 1252 cm^{-1}; Anal. Calcd. for $C_6H_9NO_4$: C, 48.55%; H, 6.40%; N, 8.09%. Found: C, 48.30%; H, 6.44%; N, 8.16%.

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