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A FACILE CLEAVAGE OF OXIRANE WITH HYDRAZOIC ACID IN DMF
A NEW ROUTE TO CHIRAL β-HYDROXY-α-AMINO ACIDS

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Summary: Chiral β-hydroxy-α-amino acids such as *erythro*-β-hydroxy-L-aspartic acid and *erythro*-β-hydroxymethyl-L-serine derivatives have been synthesized in optically pure form from L- and D-tartaric acids through a novel oxirane ring-opening reaction and a selective reduction of α-hydroxy ester as key steps.

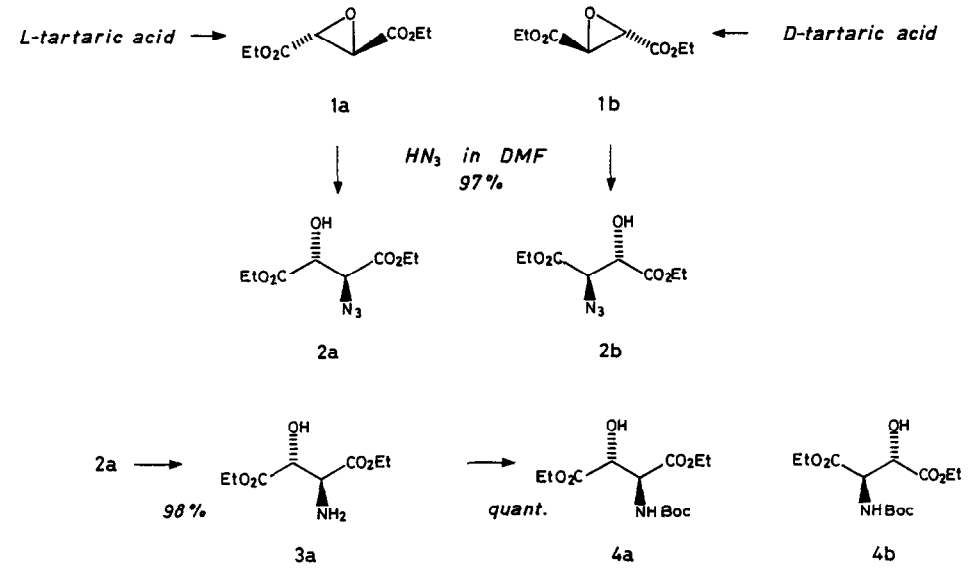
During the last 30 years, many unusual amino acids which are structurally different only slightly from the regular protein amino acids have been found.[1] Among them, such that carries β-hydroxy-α-amino acid functionality in *threo* or *erythro* relationship has drawn attention of those who are interested in biologically directed studies[2] or a developement of the methods for stereocontrolled synthesis of them.[3] With regard to the latter area, various approaches have been exploited so far with moderate to high efficiency in terms of both yield and diastereoselectivity.[3] However, a fertile methodology still seems to be required which is capable of gaining access to possible diastereomers with high optical purity, introducing functional group in the side chain so chosen that they can be easily and mildly elaborated further, and effecting high chemical yield. Unveiled herein is a new avenue to chiral β-hydroxy-α-amino acid derivatives which encompasses these standards and offers potent chiral building blocks for amino polyols or β-lactam framework.

For this purpose, we have envisaged that 1,2-amino alcohol functionality is to be introduced by ring opening of oxiranes with azide nucleophile, wherein, however, the oxiranes should be C_2 symmetrical in nature because of an expected regiochemical problem sometimes encountered in such transformation.[4] This consideration, coupled with above-mentioned objectives, led us necessarily to conclude that (*2R*,*3R*)- or (*2S*,*3S*)-2,3-epoxysuccinic acid ester serves our requirements most eminently. Conveniently, such has been proved to be three short steps away from L- or D-tartaric acid as executed by K. Mori and H. Iwasawa.[5]

Hitherto available protocols for oxirane cleavage by N_3^- have totally thwarted our intention.[6] Our previous finding that the carbon-oxygen bond of cyclic imidates such as 2-methyl-2-oxazoline or 2-methyl-5,6-dihydro-4*H*-1,3-oxazine is readily cleaved with hydrazoic acid (HN_3) generated *in situ* from trimethylsilyl azide ($TMSN_3$) and CH_3OH in DMF[7] prompted us to test the feasibility of this system in the present instance. Fortunately, it turned out that this gave

an expeditious solution to the problem. Thus, to a solution of diethyl (*2R,3R*)-2,3-epoxysuccinate (**1a**)[5] in dry DMF was added a mixture of $TMSN_3$ (1.5-2.0 eq) and CH_3OH (mole eq to $TMSN_3$) in dry DMF and the whole was warmed up to 60°C, the reaction being continued at that temperature for 10-12 h to give desired azidoalcohol (**2a**) in 97% yield after purification (SiO_2). For this transformation, DMF seems essential because the reaction was not effected at all if CH_3OH was employed in place of DMF.[8] The azido-group of **2a** was reduced (H_2/10% Pd-C/EtOAc/rt, 6 h) to leave behind the corresponding amine (**3a**),[9] which, without purification, was protected with *t*-butoxycarbonyl group (*t*-Boc) [(*t*-Boc)$_2$O/$CHCl_3$/refl, 1 h], giving rise to diethyl (*2R,3S*)-2-hydroxy-3-(*N*-*t*-Boc-amino)butanedioate (**4a**) in 98% yield after purification (SiO_2): $[\alpha]_D^{21}$ +22.5° (c 1.91, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 5.56 (1H, d, *J*=8.3 Hz, NH), 4.83 (1H, dd, *J*= 8.3, 2.2 Hz, NCH), 4.50 (1H, dd, *J*=4.2, 2.2 Hz, OCH), 4.30 (2H, q, *J*=7.3 Hz), 3.54 (1H, d, *J*= 4.2 Hz), 1.47 (9H, s), 1.33 (3H, t, *J*=7.3 Hz), and 1.25 (3H, t, *J*=7.3 Hz); IR (CH_2Cl_2) 3540, 3450, 1740, 1719 cm^{-1}; ^{13}C NMR analysis revealed that **4a** is diastereomerically homogeneous. An overall efficiency for a series of reactions is highly gratifying and this constitutes a straightforward route to **4a** or **4b**, equivalent to *erythro*-β-hydroxy-L-aspartic acid and its antipode (Scheme 1).[10]

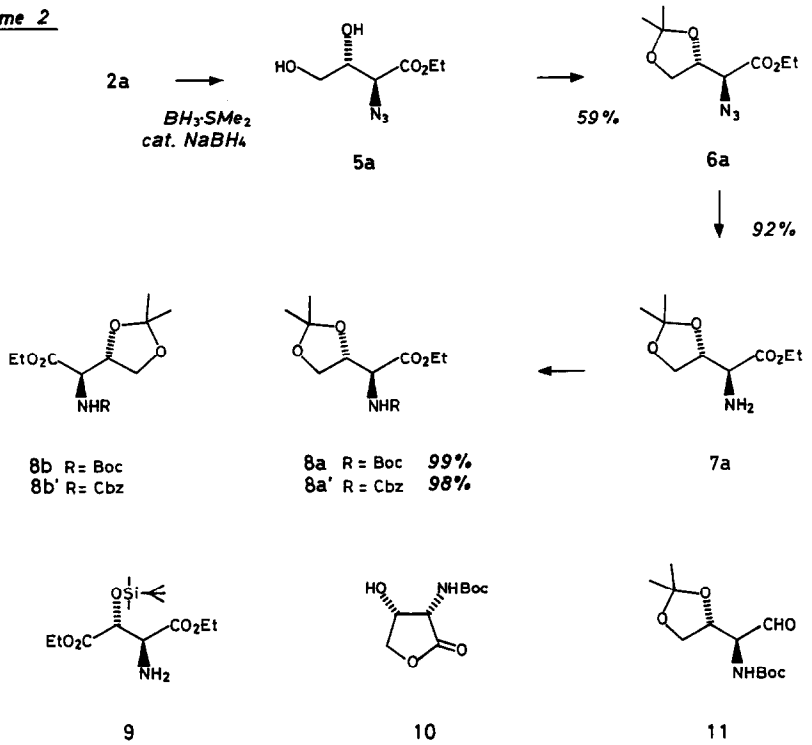
Scheme 1



With secure supplies of **2a** or **2b** in hand, we proceeded to elaborate the side chain of these molecules of amino acid equivalent. The task associated with this idea is to reduce the ester group α to the hydroxyl group. For this regioselective transformation, $BH_3 \cdot SMe_2$-catalytic $NaBH_4$ reducing system[11] was applied. Thus, to a solution of **2a** in THF was added $BH_3 \cdot SMe_2$ (1.05 eq) at room temperature and the mixture was stirred at that temperature for 2 h. Then, $NaBH_4$ (5 mol%) was thrown into the reaction and resulting mixture was stirred during 2 h, followed by the addition of CH_3OH, leading to dihydroxy-azidoester (**5a**), which proved to be highly labile on chromatographical purification. Accordingly, the product was quickly treated with

dimethoxypropane in acetone (p-TsOH/rt, 3 h), which afforded isolable ethyl 2-azido-3,4-*O*-isopropylidene-3,4-dihydroxybutanoate (**6a**) in 59% yield (for two steps) after purification (SiO_2): $[\alpha]_D^{26}$ -3.1° (c 1.64, Et_2O); ^1H NMR ($CDCl_3$) δ 4.45 (1H, m, OCH), 4.28 (2H, q, *J*=7.1 Hz, OCH_2C), 3.91-4.09 (3H, m, OCH_2, CHN_3), 1.47 (3H, s, CCH_3), 1.36 (3H, s, CCH_3), 1.32 (3H, t, *J*=7.1 Hz, $CH_2\underline{CH_3}$); ^{13}C NMR ($CDCl_3$) δ 167.90 (s), 110.34 (s), 75.35 (d), 65.70 (t), 63.26 (d), 62.09 (t), 26.32 (q), 25.05 (q), 14.13 (q); IR (CH_2Cl_2) 2120, 1745 cm^{-1}. Then, a series of reactions from **6a**, involving reduction (H_2/10% Pd-C/AcOEt/rt, 3 h) and *N*-protection [$(t\text{-Boc})_2O/CHCl_3$/rt, 10 h or $ClCO_2Bn/NaHCO_3/H_2O$/0°C, 2 h], delivered (*2S,3R*)-2-(*N*-R-amino)-3,4-*O*-isopropylidene-3,4-dihydroxybutanoate (**8a** or **8a'**) in 91% or 90% yield (for two steps), respectively, equivalent to *erythro*-β-hydroxymethyl-L-serine (Scheme 2).[12]

Scheme 2



Thus, L- or D-tartaric acid has been conveniently led to β-hydroxy-α-amino acid derivatives relying on the newly developed oxirane ring-cleavage reaction by HN_3 generated *in situ* from $TMSN_3$ and CH_3OH in DMF or $TMSN_3$ itself in DMF,[8] which is highly efficient and mild, and seems to be crucial in the present synthetic pathway.[13] Successful application of $BH_3\cdot SMe_2$-catalytic $NaBH_4$ system[11] to the regiocontrolled reduction of α-hydroxy ester as recorded above, is suggestive of its potential utility in related synthetic transformations.

Further elaboration of the chiral substances furnished as above provided, for example, **9**, **10**, or **11**, on the reactions of **2a** with TBDMS-Cl (imidazole/DMF/rt, 6 h), followed by reduction (H_2/10% Pd-C/EtOAc/rt, 6h), of **8a** with p-TsOH in CH_3OH (rt, 12 h) and, subsequently, in CH_2Cl_2 (rt, 6 h), and of **8a** with DIBAL-H in toluene (-78°C, 1 h), respectively. Synthetic efforts

directed to β-lactams, aminoglycosides, or other β-hydroxy-α-amino acids using these chiral building blocks are currently our major concern.

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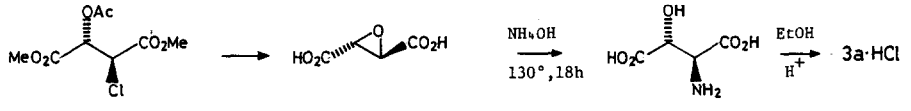
8) Reaction of **1a** with $TMSN_3$ (2 eq) in DMF at 60°C for 24 h gave the corresponding *O*-$SiMe_3$-**2a** in a comparable yield.
9) *N*-benzoyl derivative of **3a**: mp 99-100°C; $[\alpha]_D^{30}$ +26.0° (c 3.32, EtOH) [Lit (ref.(3f)): mp 99-100°C; $[\alpha]_D^{16}$ +27.9° (c 4.52, EtOH); the earlier synthesis of **3a**·HCl appeared in ref. (3f) is outlined below:



10) The diastereomer nomenclature conventions in the context of the definition proposed by Prof. R. Noyori are employed in this communication: R. Noyori, I. Nishida, and J. Sakata, J. Am. Chem. Soc., 103, 2106 (1981) and 105, 1598 (1983).
11) S. Saito, T. Hasegawa, M. Inaba, R. Nishida, T. Fujii, S. Nomizu, and T. Moriwake, Chem. Lett., 1984, 1389.
12) For the earlier synthesis of β-hydroxymethyl-D-serine from D-mannitol *via* Strecker reaction, see ref. (3a and 3b).
13) Specific rotations (589 nm), not appeared in the text, are as follows (in CH_2Cl_2 unless otherwise noted): **2a**; $[\alpha]^{18}$ +16.5° (c 1.47), **2b**; $[\alpha]^{26}$ -15.4° (c 1.26), **4b**; $[\alpha]^{26}$ -23.4° (c 1.13), **6b**; $[\alpha]^{30}$ +3.2° (c 2.29, Et_2O), **7a**; $[\alpha]^{25}$ +30.3 (c 2.00), **7b**; $[\alpha]^{26}$ -28.8° (c 1.50), **8a**; $[\alpha]^{21}$ +30.0° (c 1.14), **8a'**; $[\alpha]^{17}$ +29.4° (c 0.53), **8b**; $[\alpha]^{31}$ -30.8° (c 0.61), **8b'**; $[\alpha]^{31}$ -30.2° (c 1.14), **10**; $[\alpha]^{30}$ +39.7° (c 0.65).

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