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Stereoselective synthesis of a conformationally restricted β-hydroxy-γ-amino acid

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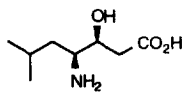
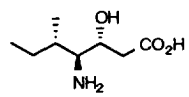
Abstract: β-Hydroxy-γ-amino acids are a class of non-proteinogenic amino acids present in many important biologically active natural products. In conjunction with our research on didemnins, we designed and synthesized a sterically constrained β-hydroxy-γ-amino acid in which the requisite carboxyl, hydroxyl and amino groups are positioned on a conformationally stable 6-membered ring. © 1997 Elsevier Science Ltd

β-Hydroxy-γ-amino acids are a class of non-proteinogenic amino acids present in many important biologically active natural products.[1] The representative member, statine **1**,[2] is the key amino acid in the acidic protease inhibitor pepstatine. Statine has been shown to mimic the transition state of the enzymatic hydrolysis of the scissile dipeptide bond[3] and this concept eventually led to the development of some anti-HIV drugs on the market. Another interesting β-hydroxy-γ-amino acid, isostatine **2**,[4] is a component of the didemnins, a family of cyclodepsipeptides which exhibits a broad spectrum of biological activities. In conjunction with our research on didemnins, we designed a β-hydroxy-γ-amino acid **3** in which the requisite hydroxyl and amino groups are positioned on a conformationally stable 6-membered ring.[5] Conformational constraint of amino acids is an important tool to improve the properties of bioactive peptidal agents.[6–8] This approach also proves valuable in investigating the bioactive conformation of drugs and receptors.[9–11]



1



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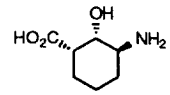

3

We now report the synthesis of an enantiomerically pure cyclohexane β-hydroxy-γ-amino acid **3** which has evaded our previous synthetic endeavors.[12] The particular (*S,S,S*)-isomer was designed by molecular modelling studies.[5] Synthesis of the designed cyclohexane amino acid began with an auxiliary type Diels–Alder reaction. Thus, the camphorsultam derived dienophile **4**[13] was reacted with 1-acetoxy-1,3-diene in 4 M lithium perchlorate in ether.[14] Two products were obtained in a ratio of 96:4, in which the desired *endo* product **5** predominated. No *exo* product was detected but a 1,3-regioisomer **6** was isolated and both structures were identified with the aid of X-ray crystal analysis (Equation 1).

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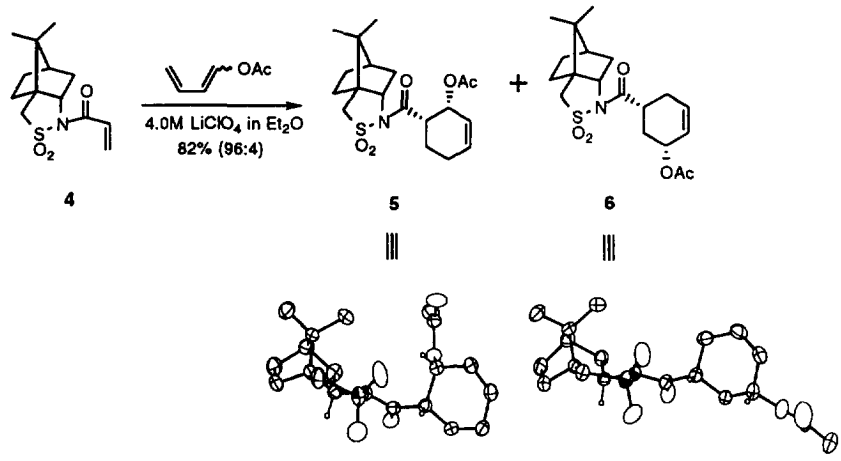
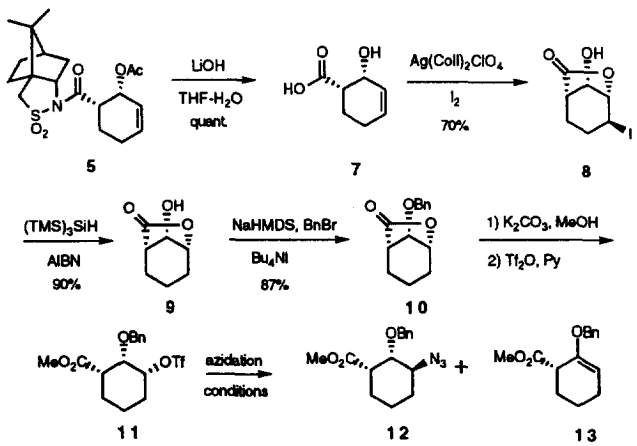
Equation 1:



After the asymmetric Diels–Alder reaction was completed, the major product **5** was hydrolyzed to give the intermediate hydroxy acid **7** in nearly quantitative yield. Introduction of the amino group was envisioned by an azide displacement at the γ-position, which in turn could be functionalized by iodolactonization. Although initial attempts employing I_2-Na_2CO_3 or NaH failed, we later found that iodonium biscollidine perchlorate[15] effected the desired transformation and gave iodolactone **8** in 70% yield. The iodine was removed under radical conditions using tris(trimethylsilyl)silane and the β-hydroxyl group in the resulting hydroxylactone **9** was then protected as its benzyl ether **10** in 87% yield. This lactone, **10**, was subjected to transesterification with methanol and K_2CO_3 to free the γ-hydroxyl group. However, two problems were encountered. Firstly, very dilute K_2CO_3 was used to prevent the epimerization of the ester, but these conditions resulted in incomplete methanolysis. Secondly, the resulting hydroxyester was unstable on silica gel and readily recyclized to the precursor lactone. Therefore, we carried the intermediate with a small amount of starting material through the next two steps without purification. Inversion of the γ-hydroxyl group with azide was the next step. Unfortunately, inversion of the γ-hydroxyl group using DPPA[16] or $Zn(N_3)_2Py_2$[17] as azide sources, under Mitsunobu conditions, did not afford a product. The mesylate was also not effectively displaced by azide ion even at elevated temperature. Eventually, the triflate derivative **11** afforded a mixture of the desired azide **12** and an elimination product **13** (Scheme 1).



Scheme 1.

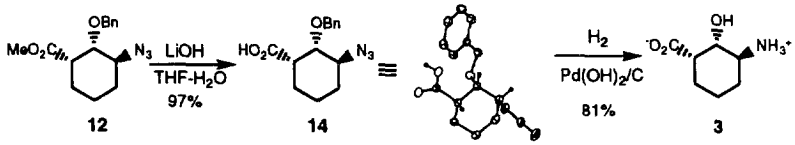
Table 1. Optimization of the azidation reaction conditions

Nucleophile	Solvent	Selectivity (12:13)	yield (12+13)[a]
NaN_3	DMF	4:1	56% + 14%
NaN_3	DMF-MeCN	4.5:1	33% + 7%
$Zn(N_3)_2Py_2$	DMF	no reaction	----------
Bu_4NN_3	C_6H_6	13 only	0% + 60%
$TMSN_3$	MeCN	complex mixture	----------
$TMGN_3$	CH_2Cl_2	7:1	62% + 7.5%

[a] based on the recovered starting material over 3 steps.

Considerable efforts were directed to optimize the azidation reaction conditions and the results are summarized in Table 1. The alkaline metal azides such as NaN_3, LiN_3 and $TMSN_3$–CsF[18] in DMF all gave the same results (only the representative results with NaN_3 are shown in Table 1). The azide concentration proved to be a critical factor because at lower concentration less product from elimination was formed. Although lowering the polarity of the solvent was thought to yield less eliminated product[19] as in the case of 1:1 DMF:MeCN, this protocol also retarded the reaction rate and resulted in a low overall yield. When the reaction was run in benzene under phase transfer conditions using tetrabutylammonium chloride and sodium azide,[19] only **13** was obtained. Other azides also proved unsatisfactory. Eventually, when buffered tetramethylguanidinium azide[20] was used, the desired product **12** was isolated in 62% yield, based on the recovered starting material, along with 7.5% elimination product **13**.

With the functionalities and desired stereochemistries secured, the methyl ester **12** was hydrolyzed to afford the corresponding free acid **14**, whose relative configuration was confirmed by X-ray crystal analysis. The azido acid **14** was then hydrogenated to afford the targeted amino acid **3** in zwitterionic form (Scheme 2).[21]



Scheme 2.

Acknowledgements

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21. All new compounds were characterized by ^{1}H and ^{13}C NMR, IR and HRMS. Data for compound **3**: off-white powder, mp: 242°C (dec.); $[\alpha]_D$=+72.5 (c=1.22, H_2O); IR (KBr), 3380, 3306, 2965 (broad), 1580 cm^{-1}; ^{1}H NMR (D_2O): δ 3.54 (1H, b), 3.29 (1H, b), 2.77 (1H, b), 2.26-1.97 (2H, m), 1.56 (1H, b), 1.38-1.23 (3H, m); ^{13}C NMR: δ 183.70, 74.59, 56.11, 48.26, 31.31, 29.51, 23.17; HRMS (EI): calcd for $C_7H_{14}NO_3$ 160.0973 (MH), found 160.0967.

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