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SYNTHESIS OF (+)-GALANTINIC ACID, A CONSTITUENT AMINO ACID IN THE PEPTIDE ANTIBIOTIC GALANTIN I, *via* THE STEREOSELECTIVE EPOXIDATION OF A CHIRAL SERINE EQUIVALENT

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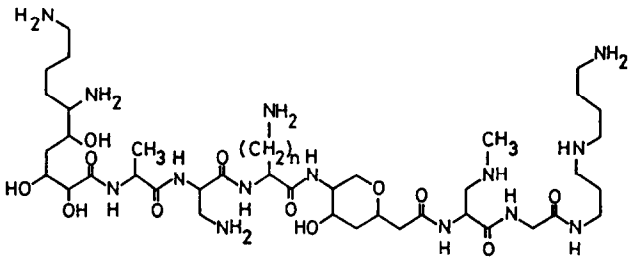
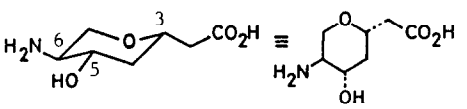
SUMMARY: Epoxidation of (2R)-t-butoxycarbonylamino-3-butenol afforded, in a highly stereoselective manner, a *threo*-3,4-epoxy-2-aminobutanol derivative which was successfully converted to the unusual amino acid (+)-galantinic acid in 8 steps *via* regiospecific epoxide ring opening with divinyl cuprate.

Unusual amino acids possessing *threo* or *erythro* β-hydroxy-α-amino acid moieties are widely distributed in biologically important peptides. However, only few stereocontrolled synthetic methods are available for these types of systems.[1] We have recently developed the chiral 2-amino-3-butenol derivatives as a useful synthon for the synthesis of such unusual amino acids.[2] We chose to employ this synthon in the synthesis of galantinic acid (2),[3] a unique pyran containing amino acid in the peptide antibiotic galantin I (1).[4]

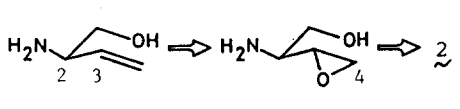
Since the absolute configuration of 2 was shown to be (3S,5S,6S) 2 from its CD studies of derivative 2a,[3b] (2R)-t-butoxycarbonylamino-3-butenol 3a was employed as starting material. The synthesis requires the introduction of a hydroxyl group at C-3 followed by coupling to a three carbon unit at C-4. Conversion of 3 into epoxide 4 was the first problem to be considered.



Galantin I (1)

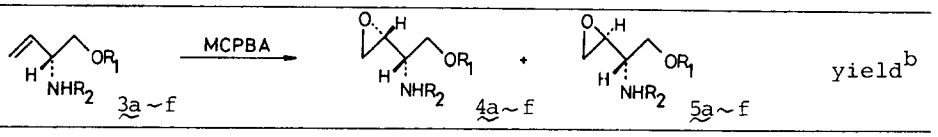


Galantinic acid (2)



3 4 2

Table I. Reactions of 2-amino-3-butenol derivatives with m-chloroperbenzoic acid[a]



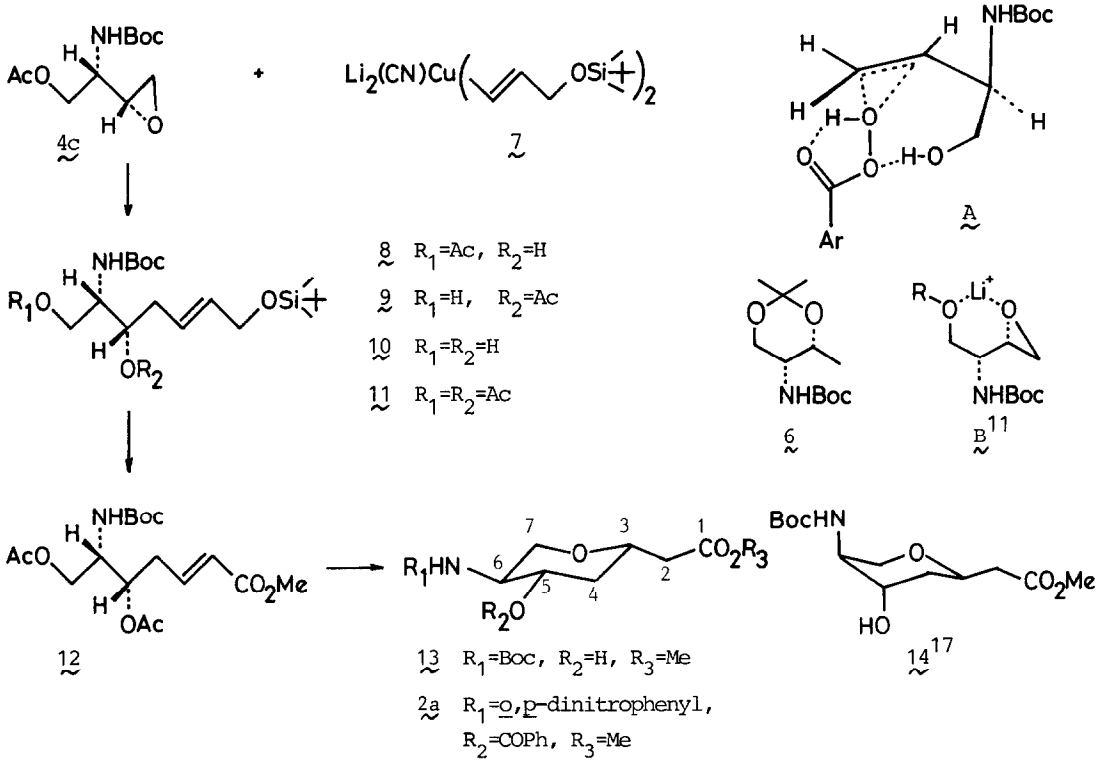
								yield[b]
Entry 1.	R_1=H,	R_2=Boc	(3a)	40	:	1	(4a : 5a)[c]	60%
2.	R_1=CH_2Ph,	R_2=Boc	(3b)[d]	5[e]	:	2	(4b : 5b)	62%
3.	R_1=Ac,	R_2=Boc	(3c)[d]	7.5[e]	:	1	(4c : 5c)	60%
4.	R_1=H,	R_2=Z	(3d)[2]	4[f]	:	1	(4d : 5d)	70%
5.	R_1=H,	R_2=Ts	(3e)[g]	3.2[f]	:	2	(4e : 5e)	89%
6.	R_1=H,	R_2=$COCF_3$	(3f)[g]	5	:	4[h]	(4f : 5f)	60%

[a]All reactions were carried out at room temperature in CH_2Cl_2 as solvent. [b]Chromatographically isolated yield. [c]The ratio determined by the integration of 360MHz ^1H NMR. [d]Synthesized from 3a. Details for the preparation of these compounds will be described elswhere. [e]The major isomer was identical in all respect with those derived from 4a. [f]Threo relationship for this compound was confirmed by the conversion to the corresponding acetonide using the same manner as ref 6. [g]Synthesized from 2-amino-3-butenol, see ref 2. [h]Threo or erythro isomers have not been determined.

Epoxidation of (2R)-N-t-butoxycarbonyl(Boc)-amino-3-butenol with m-chloroperbenzoic acid (MCPBA)[5] (CH_2Cl_2, room temperature, 20 h) proceeded smoothly and provided a mixture of epoxides 4a and 5a in a 40 : 1 ratio (60% yield): 4a; mp 60~61.5°C, $[\alpha]_D^{26}$ +17.8° (c 1.5, $CHCl_3$). The configuration of the major isomer 4a at C-3 was determined to be S as shown by the conversion of 4a into acetonide 6, which was identical with those derived from D-threonine in all respects.[6] Since a decrease in the selectivity of epoxidation (Table I, entry 1~3) was observed when the hydroxyl group was blocked, the reaction presumably proceeds via transition state A.[7] In addition , an increase in the electronegativity of the N-protecting group also led to a decrease in selectivity; this is probably due to interaction between the amide proton and the reagent (Table I, entry 4~6).[8]

We next examined the regiospecific epoxide ring opening of epoxide 4 with divinyl cuprate 7, prepared from propargyl alcohol [(i) t-butyldimethylsilyl chloride (TBDMSCl)/imidazole/DMF; (ii) n-Bu_3SnH,[9] 100°C; (iii) n-BuLi/CuCN/THF,[10] -78°C]. The reaction was dependent on the hydroxyl protecting groups of both reactants,[11] and proceeded smoothly when the epoxide and cuprate were masked with acetyl and TBDMS groups, respectively (-78°C, 30 min, -45°C, 30 min, 0°C, 14 h), to provide a mixture of the desired adducts 8, 9, and 10 in 51% yield (8:9:10= 5:1:2.5).[12] The mixture, without separation, was converted (Ac_2O/pyridine) to the diacetate 11: oil, $[\alpha]_D^{26}$ -3.9 (c 3.0, $CHCl_3$). Removal of silyl group of 11 (p-TsOH/MeOH, 88%), followed by oxidation of the allylic alcohol using a method developed by Corey and Wollenberg[13] [(i) pyridinium chlorochromate/CH_2Cl_2; (ii) MnO_2/NaCN/AcOH-MeOH, room temperature, 5 h, 75% yield)], gave rise to the ester 12: oil, $[\alpha]_D^{26}$

-8.3°(c 2.3, $CHCl_3$). Deprotection of the acetate (MeOH/0.1 equiv K_2CO_3, room temperature, 14 h) led to spontaneous cyclization[14] to afford a 1:1 mixture of 13 [39%; R_f=0.51, Et_2O/AcOEt=1/1; mp 104.5~106°C; $[\alpha]_D^{26}$ -4.4°(c 1.2, $CHCl_3$)] and its C-3 epimer 14 [38% ; R_f=0.62, Et_2O/AcOEt=1/1; oil; $[\alpha]_D^{26}$ +20.8°(c 1.5, MeOH)]. The 300MHz ^1H NMR($CDCl_3$) data of 13 [δ1.42(4αH, dd, $J_{4\alpha-5}$=$J_{4\alpha-3}$=12.0, $J_{4\alpha-4\beta}$=13.0 Hz), 1.44(t-Bu, s), 2.09(4βH, dd, $J_{4\beta-3}$=2.0, $J_{4\beta-5}$=4.8Hz, $J_{4\alpha-4\beta}$=13.0Hz), 2.425(2α or 2βH, dd, $J_{2\alpha \text{ or } 2\beta-3}$=5.0, $J_{2\alpha-2\beta}$=16Hz), 2.60(2α or 2βH, dd, $J_{2\alpha \text{ or } 2\beta-3}$=7.2, $J_{2\alpha-2\beta}$=16Hz), 3.08(7βH, dd, $J_{7\beta-6}$=$J_{7\beta-7\alpha}$=11.0Hz), 3.45(6-H, m), 3.56(5-H, dt, $J_{5-4\beta}$=4.8, $J_{5-4\alpha}$=J_{5-6}=12.0Hz), 3.70(OMe, s), 3.80(3-H, dddd, $J_{3-4\alpha}$=12.0, $J_{3-4\beta}$=2.0, $J_{3-2\alpha \text{ or } 2\beta}$=5.0, $J_{3-2\alpha \text{ or } 2\beta}$=7.2Hz), 4.00(7αH, dd, $J_{7\alpha-6}$=5.0, $J_{7\alpha-7\beta}$=11.0Hz), 4.44(NH, d, J=7.2Hz)] indicated it to possess the desired stereochemistry.[15] The ^1H NMR data of 3-epimer 14 is shown in ref 17. The protecting groups were removed in two steps: (i) KOH/MeOH; (ii) CF_3CO_2H/CH_2Cl_2. Treatment of the resultant trifluoroacetate with Dowex 50W x 4(H^+ form), and elution with 1N NH_3 yielded (+)-galantinic acid (2) as white crystals, mp 230°C(decomp), $[\alpha]_D^{26}$ +2.64°(c 1.1, H_2O). The ^1H NMR data of the synthetic material was identical with those reported.[3a,18] Since the $[\alpha]_D$ value of the natural product was not reported, product 2 was converted into the 2,4-DNP derivative 2a, of which the CD spectrum was identical with the natural product derivative.[3b]



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6. The acetonide 6 was synthesized from D-threonine in 4 steps. (i) Boc-ON/Et_3N; (ii) CH_2N_2; (iii) $LiAlH_4$/THF; (iv) 2,2-dimethoxypropane/p-TsOH: mp 47.5~48.5°C; $[\alpha]_D^{26}$ +26.0°(c 1.0, $CHCl_3$); ^1H NMR($CDCl_3$) δ1.13(3H, d, J=6.0Hz), 1.39(3H, s), 1.46(3H, s), 3.53(1H, ddd, J=2.0, 10.0Hz), 3.77(1H, dd, J=2.0, 12.0Hz), 4.08(1H, dd, J=2.0, 12.0Hz), 4.16(1H,dq, J=2.0, 6.0Hz).
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8. Steric factors of the N-protecting group also appears to be important.
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11. Reactions of epoxide 4, of which hydroxyl group was protected with an ether group such as CH_2Ph, TBDMS, or THP, with cuprate 7 proceeded very slowly to give the desired adduct in poor yield (~5%) and mainly recovery of starting material. It is considered that the formation of cyclic chelate B (depicted in the text), stabilized by the ether oxygen, results in a decrease in reactivity.
12. Acetyl group of 8 might have migrated or been hydrolysed during work-up.
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14. Remarkable stereoselectivity was observed in tetrahydrofuran ring formation, see: S.S.Ko, L.L.Klein, K.-P.Pfaff, and Y.Kishi, Tetrahedron Lett., 4415 (1982).
15. The peaks were fully assigned by an extensive decoupling technique. The large diaxial-like $J_{3-4\alpha}$, $J_{4\alpha-5}$, J_{5-6}, and $J_{6-7\beta}$ values indicate 13 to have the desired stereochemistry.
16. Satisfactory spectroscopic (^1H NMR, IR, MS) data were obtained for all new compounds.
17. 300MHz ^1H NMR($CDCl_3$) data of 3-epimer 14: δ1.45(9H, s), 1.67(1H, dd, J=2.7, 13.2Hz), 1.72(1H, dt, J=2.4, 13.2Hz), 2.39(1H, dd, J=4.8, 14.4Hz), 2.50(1H, dd, J=6.1, 14.4Hz), 3.48(1H, m), 3.66(1H, d, J=12.0Hz), 3.70(3H, s), 4.03(1H, dd, J=2.4, 2.7Hz), 4.07(1H, dd, J=1.5, 12.0Hz), 4.17(1H, ddd, J=4.8, 6.1, 13.2Hz), 5.15(1H, d, J=7.2Hz).
18. 300MHz ^1H NMR(D_2O) data of (+)-galantinic acid (2): δ1.47(1H, dt, J=12.0, 12.5Hz), 2.17(1H, ddd, J=2.4, 5.3, 12.5Hz), 2.38(1H, dd, J=6.2, 16.8Hz), 2.45(1H, dd, J=7.7, 16.8Hz), 3.12(1H, dt, J=5.0, 11.0Hz), 3.47(1H, t, J=11.0Hz), 3.85(1H, dt, J=5.3, 12.0Hz), 3.88(1H, dddd, J=2.4, 6.2, 7.7, 12.0Hz); MS, m/z 175(M^+).

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