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ELECTROPHILIC AMINATION: ENANTIOSELECTIVE SYNTHESES OF D-ALLOTHREONINE AND L-THREONINE[§]

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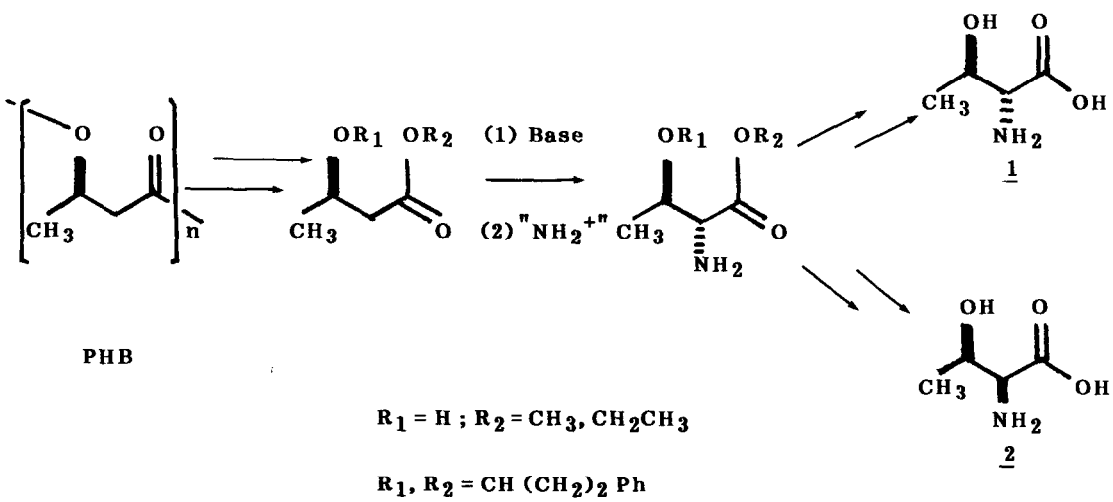
Abstract: Starting from inexpensive polyhydroxybutanoate (PHB), D-allothreonine **1** and L-threonine **2** were synthetized by a sequence involving a diastereoselective electrophilic amination. When (R) 3-hydroxybutanoic acid was protected as dioxanone **9** very good yield (>95 %) and high diastereomeric excess (>99 %) were obtained in the amination step.

α-Amino- β -hydroxyacids are of major importance as chiral intermediates and biologically active compounds (1). Although much work has been done on their enantioselective synthesis by C-C bong forming (2), to our knowledge, syntheses based on enantioselective C-N bond forming are much less documented(3b). This is probably due to the fact that few efficient electrophilic aminating reagents are known (4, 5).
Polyhydroxy butanoate (PHB) is an inexpensive source of chiral (R) 3-hydroxybutanoic acid (6) and extensive work has been done on this useful compound (7). We report here syntheses of D-allothreonine **1** and L-threonine **2** whose strategy relies on the recognition that these aminoacids have the same C-3 configuration as PHB.



The key step of this strategy required an efficient electrophilic aminating synthon "NH_2^+". We first investigated several reagents derived from hydroxylamine (4). But these did not react with hydroxybutanoates **3** and **4** (entries 1-2). We turned then our efforts to di-t-butyl azodicarboxylate (DBAD) (5) ; this reagent gave modest to good yields of aminated products as shown in the table.

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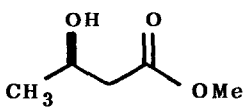
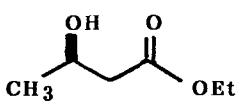
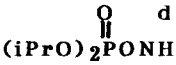
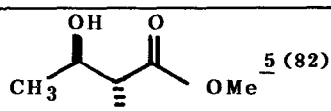
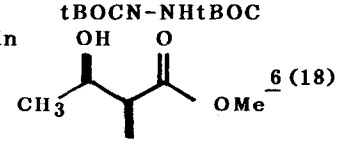
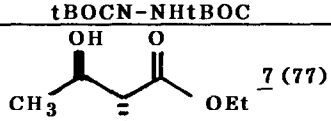
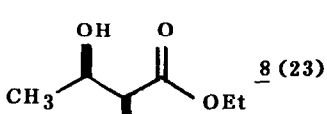
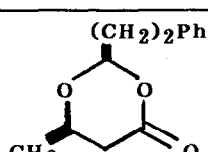
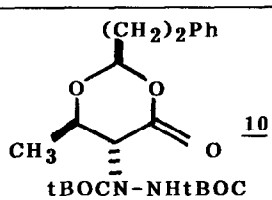
We then examined the reaction of the dianions of methyl and ethyl (R)3-hydroxybutanoates 3 and 4 on DBAD (entry 3-4). Under the conditions indicated in the table (N, N') di-Boc-hydrazino derivatives 5 and 7 were obtained in 58% yield with 64 and 54 % diastereomeric excess respectively. The desired diastereomer could be obtained either by flash chromatography on silica gel or recrystallization from pentane for 5 (9) and by flash chromatography on silica gel for 7 (10). Upon deprotection and hydrogenation, 5 gave D- allothreonine in 50% yield and 95% diastereomeric excess (11). Derivative 7 was converted into L-threonine 2 through a known procedure (12, 13).

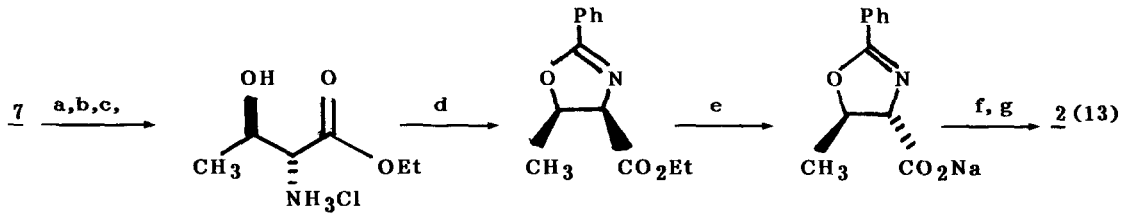
Table: Electrophilic amination of hydroxy butanoates 3 and 4 and dioxanone 9

	Substrate	Reagent	Conditions	Products(%)	Yield (d.e.)[a]
1	 3	 c	THF[e] -78°C - 20°C 16h	—	—
2	 4	 d	"	—	—
3	3	tBOCN=NtBOC (DBAD).1.1 eq	THF[e] -78°C, 3 min	 5 (82) tBOCN-NHtBOC  6 (18) tBOCN-NHtBOC	58 (64)[b]
4	4	"	"	 7 (77) tBOCN-NHtBOC  8 (23) tBOCN-NHtBOC	57 (54)[b]
5	 9	"	THF[f] -78°C, 3 min	 10 tBOCN-NHtBOC	>95 (99)

a) Diastereomeric excess of the crude product was determined by ^{1}H and ^{13}C NMR. b)After flash chromatography on silica gel, 5 and 7 were obtained in 50% yield 95% d.e. and 43% yield 95% d.e. respectively. c) O-(diphenyl phosphinyl) hydroxylamine (4c). d) O-(diisopropyl phosphoryl) hydroxylamine (8). e) 2 equiv. of LDA. f) 1 equiv. of LDA.

We anticipated that the modest yields and diastereoselection obtained in the electrophilic amination of 3 and 4 were due to the acyclic nature of these substrates (14). Indeed, when 3-hydroxybutanoic acid was protected as dioxanone 9 (15b), metallation and reaction with DBAD gave the aminated dioxanone 10 with very high yield and diastereoselection (entry 5) (16). Deprotection and hydrogenation yielded optically pure D-allothreonine 1 in 42% overall yield from 9(17). This is the most efficient and economical synthesis of the very expensive and useful chiral intermediate D-allothreonine 1 (2i).

The optically pure aminated dioxanone 10 is also an efficient derivative for the synthesis of L-threonine. Transesterification of 10 (0.2 equiv. $Ti(OEt)_4$, EtOH, reflux 4 h, 96 % yield) afforded 7 which could be converted into L-threonine 2 through the following sequence (12).



a) CF_3COOH/CH_2Cl_2 1: 1, 0°C, 3h. ; b) HCl 10%, vacuum; c) PtO_2,H_2, 1 atm., $EtOH/CH_3COOH$ 10 : 1;
d) $PhC(=NH)-OCH_2CH_3$, Et_2O/H_2O ; e) EtONa/EtOH, 20°C, 1h, then reflux 1h ; f) HCl 20%, reflux, 4 h ;
g) EtOH/ $CH_3-CH-CH_2$ 2: 1, reflux 15 min.

In summary, anti α-amino- β-hydroxy acids can be easily synthetized from the corresponding hydroxyacids protected as dioxanones. As optically active 3-hydroxyacids are now readily available from enantioselective catalytic reduction of the corresponding 3-oxo esters (18), electrophilic amination provides a general route to this important class of amino acids (19), which are precursors of β-lactam antibiotics.

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