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An Efficient Synthesis of Polyoxamic Acid Utilizing the Aryl Group as the Carboxyl Synthon. A New Approach to Polyhydroxyamino Acids.

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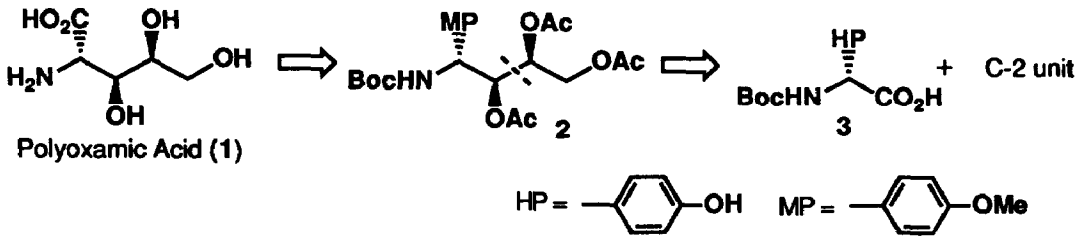
Abstract: Polyoxamic acid (**1**), an amino acid moiety of antifungal antibiotics polyoxins, has been efficiently synthesized from Boc-(R)-4-hydroxyphenylglycine (**3**) utilizing its aryl group as the carboxyl synthon.

A wide range of synthetic approaches to polyhydroxyamino acids and related compounds has been recently reported.[1] We have already accomplished efficient syntheses of phytosiderophores having the polyhydroxyamino acid skeleton: mugineic acid,[2] 3-epi-hydroxymugineic acid,[3] and distichonic acid A.[3] The key feature of these syntheses has been the use of the phenyl group as the carboxyl synthon. The former can be easily converted to the latter by oxidation with ruthenium trichloride ($RuCl_3$) - sodium metaperiodate ($NaIO_4$).[4] As an extension of this methodology, we now wish to report an efficient synthesis of polyoxamic acid (**1**),[5] the unique polyhydroxyamino acid constructing the side chain moiety of the antifungal antibiotics polyoxins.[6] The retrosynthetic analysis is shown in Scheme 1.

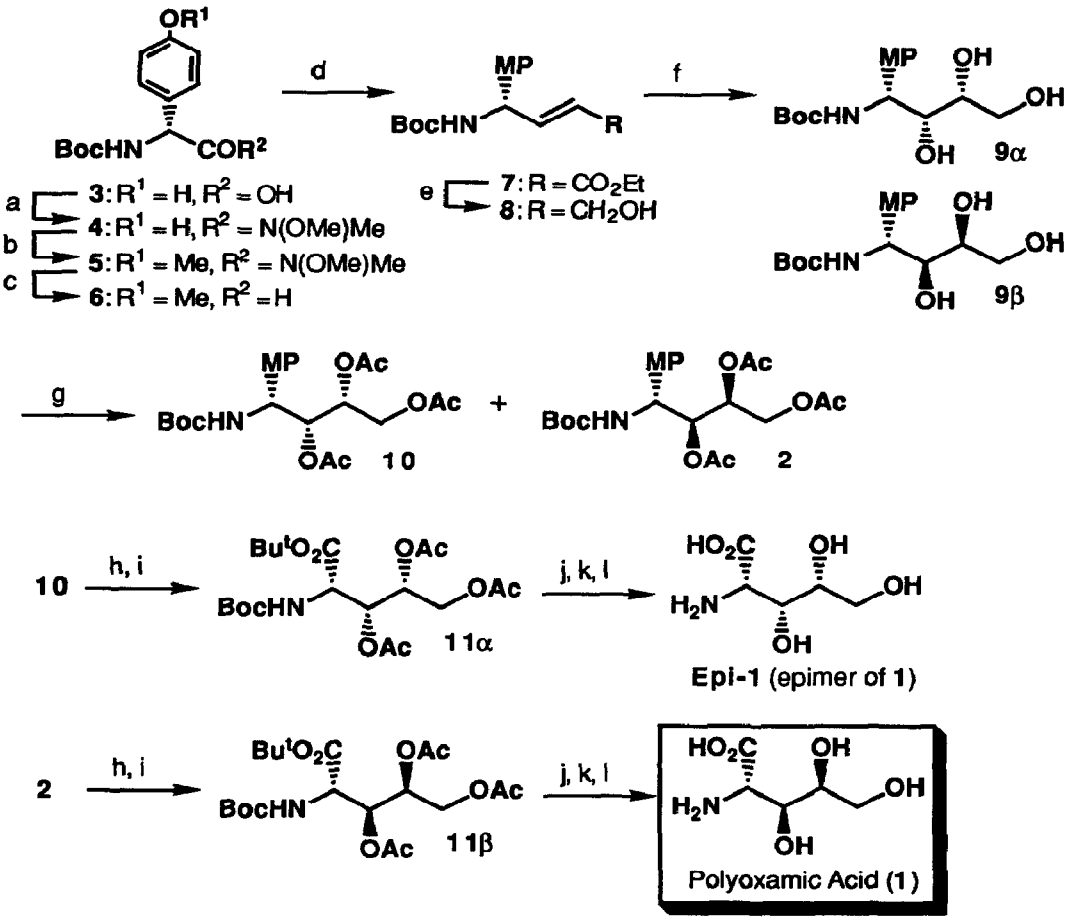
Scheme 1



First, we investigated a synthetic approach through the stereoselective osmylation of the (E)-allyl alcohol **8** as a key step, starting from known N-tert-butoxycarbonyl(Boc)-(R)-4-hydroxyphenylglycine (**3**),[7,8] as shown in Scheme 2. Condensation of **3** with N,O-dimethylhydroxylamine by use of diethyl phosphorocyanidate (DEPC, $(C_2H_5O)_2P(O)CN$),[9] followed by the methylation of the phenol group of the resulting amide **4**, $[\alpha]^{23}_D$ -87.5° (c 0.68, $CHCl_3$) afforded the O-methyl amide **5**, mp 85-86°C, $[\alpha]^{27}_D$ -139.5° (c 1.27, $CHCl_3$), in 74% yield. Reduction of **5** with lithium aluminum hydride (LAH) gave the amino aldehyde **6**,[10,11] which underwent the Wittig reaction with ethyl 2-(triphenylphosphonylidene)acetate to give the (E)-α,β-unsaturated ester **7**, mp 104-107°C, $[\alpha]^{27}_D$ -54.9° (c 0.90, $CHCl_3$), in 75% yield. Reduction of **7** with diisobutylaluminum hydride (DIBAL) in the presence of boron trifluoride etherate (BF_3-Et_2O)[12] furnished the allyl alcohol **8**, mp 81-82°C, $[\alpha]^{28}_D$ -44.7° (c 1.12, $CHCl_3$), in 92% yield. The usual dihydroxylation of **8** with osmium tetroxide and N-methylmorpholine N-oxide yielded a diastereoisomeric mixture of the triols **9α** and **9β**, which were converted to a mixture of the triacetates **10** and **2**. Separation on silica gel column was easily carried out to give the undesired **10**, mp 131-134°C, $[\alpha]^{27}_D$ +2.0° (c 0.77, $CHCl_3$), in 51% yield and the desired **2**, $[\alpha]^{27}_D$ -57.3° (c 1.05, $CHCl_3$), in 45% yield.[13] However, application of the Sharpless asymmetric

dihydroxylation using dihydroquinine 4-chlorobenzoate (DHQ-CLB) as a chiral catalyst[14] produced **10** in 33% yield and **2** in 55% yield, respectively, after acetylation. Transformation of the 4-methoxyphenyl group in both **10** and **2** to the carboxyl one was smoothly achieved by using $RuCl_3$-$NaIO_4$. After esterification of the oxidation products with O-tert-butyl-N,N'-diisopropylisourea, the polyhydroxyamino acid esters **11α**, $[\alpha]^{27}_D$ +1.5° (c 1.71, $CHCl_3$), and **11β**, $[\alpha]^{27}_D$ +14.1° (c 1.12, $CHCl_3$), were obtained in 82 and 80% yields, respectively. Final deprotection of all the protecting groups from **11β** was performed by sequential treatment with conc. hydrochloric acid and 1N aqueous sodium hydroxide to give polyoxamic acid (**1**), mp 170-174°C (dec), $[\alpha]^{27}_D$ +2.4° (c 0.41, H_2O) [lit.[6] mp 171-173°C (dec), $[\alpha]^{23}_D$ +2.8° (c 1.02, H_2O)], in 90% yield. Analogously, **11α** was converted to the epimer of polyoxamic acid (**Epi-1**), mp 148-152°C (dec), $[\alpha]^{27}_D$ -17.9° (c 0.24, H_2O), in 92% yield.[15]

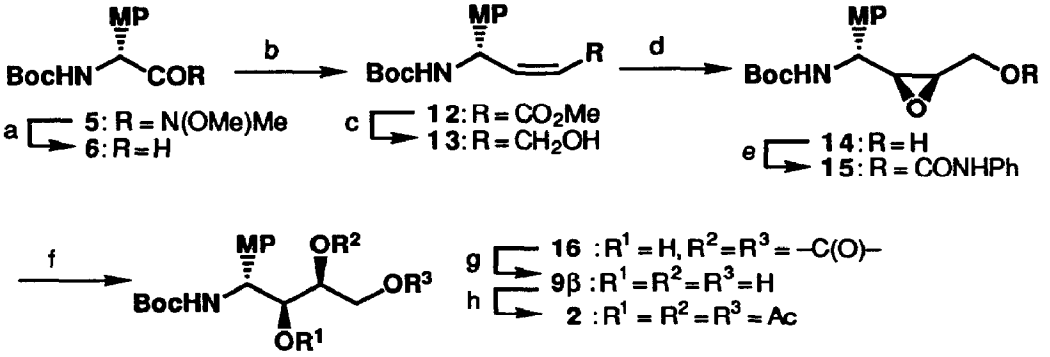
Scheme 2



(a) MeNH(OMe)·HCl, DEPC, Et_3N, DMF, 4°C, 18h. (b) MeI, K_2CO_3, DMF, rt, 7h. (c) 1M LAH (in Et_2O), -15°C→-7°C, 30min. (d) Ph_3PCHCO_2Et, CH_2Cl_2, 0°C, 1h. (e) 1M DIBAL (in hexane), BF_3·OEt_2, CH_2Cl_2, -78°C, 30min. (f) 0.1M OsO_4 (in toluene), DHQ-CLB, K_3FeCN_6, K_2CO_3, t-BuOH, H_2O, 4°C, 34h. (g) Ac_2O, Pyridine, rt, 20h. (h) $RuCl_3$, $NaIO_4$, EtOAc, CH_3CN, H_2O, rt, 4h. (i) O-tert-butyl-N,N'-diisopropylisourea, CH_2Cl_2, 40°C, 6~15h. (j) 35% aqueous HCl, MeOH, rt, 3~4h. (k) 1N aqueous NaOH, rt, 2~3h. (l) Dowex 50W x 4 (H_2O then 15% aqueous NH_3).

Since the stereoselectivity of the osmium-mediated dihydroxylation was not superior in the above synthesis, the alternative route to **1** was explored by using the (Z)-allyl alcohol instead of the (E)-isomer, shown in Scheme 3. The (Z)-selective olefination of the amino aldehyde **6** with methyl (2-trifluoroethoxy)phosphonoacetate under the Still's conditions[16] afforded the (Z)-α,β-unsaturated ester **12**, mp 168-169°C, $[\alpha]^{23}_D$ +79.9° (c 0.54, $CHCl_3$), in 82% yield. Reduction of **12** with DIBAL followed by epoxidation with m-chloroperbenzoic acid (m-CPBA) stereoselectively proceeded[12b,17] to give the (Z)-epoxyalcohol **14**,[18] $[\alpha]^{23}_D$ -12.2° (c 1.12, $CHCl_3$), in 92% yield. Although the direct opening of the epoxide ring in **14** by the Payne rearrangement failed to produce the triol 9β under alkaline conditions (0.5N NaOH aq, t-BuOH, H_2O, 60°C),[19] transformation of **14** to **2** was smoothly accomplished in 4 steps through the phenylurethane-promoted epoxide ring opening reaction.[20] Treatment of **14** with phenyl isocyanate in the presence of catalytic amounts of triethylamine gave the phenylurethane **15**, mp 149-150°C, $[\alpha]^{23}_D$ +13.2° (c 0.79, EtOH), which underwent the epoxide ring opening reaction with BF_3-Et_2O followed by the acidic hydrolysis of the intermediate iminocarbonate to yield the cyclic carbonate **16**,[18] mp 143-145°C, $[\alpha]^{23}_D$ +42.9° (c 0.36, $CHCl_3$), in 81% yield. Alkaline hydrolysis of **16** followed by the acetylation of the resulting triol 9β afforded the triacetate **2** as a single product in 91% yield.

Scheme 3



(a) 1M LAH (in Et_2O), -15°C, 30min. (b) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, 18-crown-6, 0.5M $KN(TMS)_2$ (in toluene), THF, 0°C, 30min→-78°C, 4h. (c) 1M DIBAL (in hexane), BF_3·OEt_2, CH_2Cl_2, -78°C, 30min. (d) 80% m-CPBA, CH_2Cl_2, 0°C, 7h. (e) PhNCO, Et_3N (0.05 eq), CH_2Cl_2, rt, 2h. (f) BF_3·OEt_2 (1 eq), THF, 0°C, 5h. (g) KOH, MeOH, H_2O, 0°C, 1h. (h) Ac_2O, Pyridine, rt, 20h.

Thus, we have accomplished an efficient synthesis of polyoxamic acid (**1**) from Boc-(R)-4-hydroxyphenylglycine (**3**) in 13 steps in an overall yield of 30%. This synthesis will well demonstrate the utility of the aryl group as the carboxyl synthon. The methodology adopted here will be quite useful for the efficient synthesis of the other polyhydroxyamino acids.

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