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A Tactically Novel Alternative to Acyclic Stereoselection Based on the Concept of a Replicating Chiron — Access to 1,3-Polyols†

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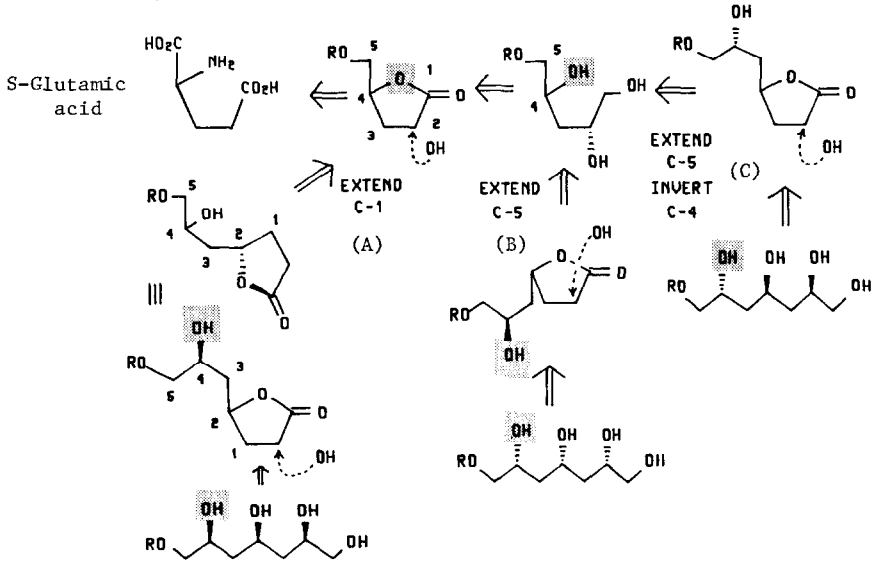
Summary - (S)-Glutamic acid is used as a chiral template to construct seven carbon subunits containing alternating hydroxyl groups with stereochemical control. Enantiomeric and/or diastereomeric 3,5-dideoxy-heptitols are thus obtained.

Access to acyclic polyols, long considered the domaine of carbohydrate chemists has recently become possible through diverse strategies.[1] The attraction of a carbohydrate approach resides in its predictive power,[2] and the flexibility in the length of carbon chains (usually 3-7 carbon atoms). However, the necessity to manipulate hydroxyl and other functionality in order to achieve the desired level of deoxygenation and/or stereochemical convergence with an intended target structure has fostered renewed interest in preparing

Scheme 1

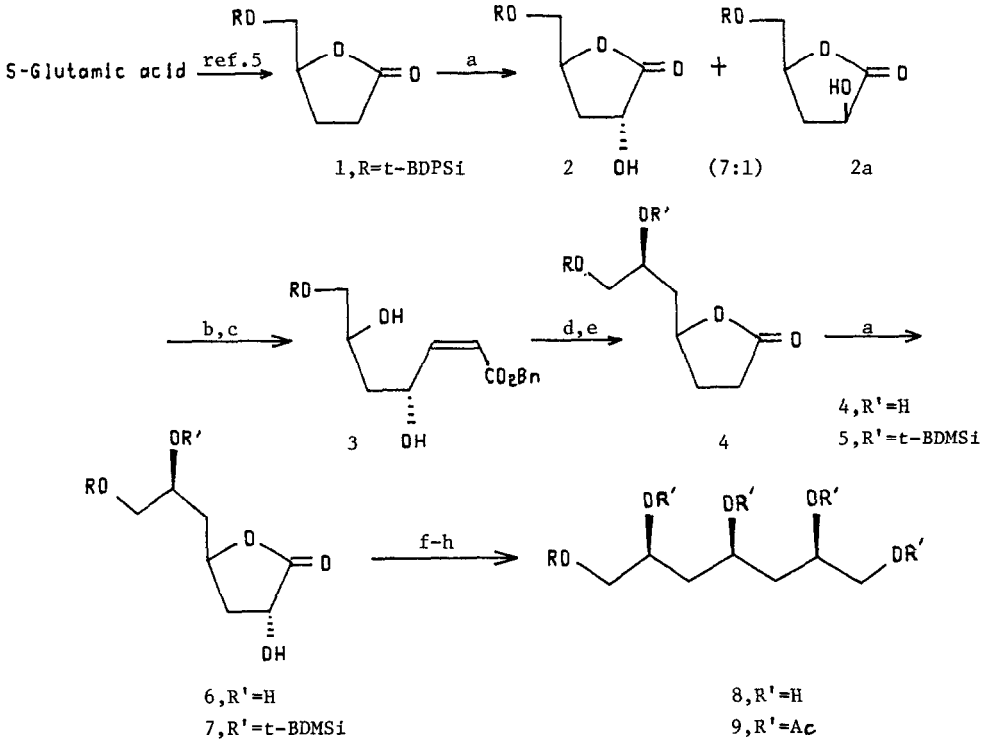


† Dedicated to Prof. H.H. Wasserman on the occasion of his 65th birthday.

such polyols in stereocontrolled fashion from non-carbohydrate precursors. A great impetus in pursueing such studies arises from the occurrence of a number of natural products in which a 1,3-polyol substitution pattern is an important structural and functional feature.[3] We describe in this paper a strategy that addresses this problem, based on the concept of a replicating chiron.[4] Thus, as illustrated in Scheme 1, an enolate derived from a chiral butyrolactone derivative is used as a template for the stereocontrolled introduction of a hydroxyl group. A two-carbon chain-extension is now possible from either extremity to give diastereomeric or enantiomeric lactones respectively. Hydroxylation of the "replicated" lactones leads to heptitols having a predictable 1,3-substitution pattern.

The crystalline lactone **1**,[4-6] readily available from (S)-glutamic acid,[7] among other sources[8] was converted into its enolate, then treated with 1.1 equiv. of MoOPH[9] to give the desired hydroxy derivative **2**, mp 79-80°, $[\alpha]_D$ + 62.8°, easily separable from its epimer **2a** (oil), in 80% yield (7:1 ratio respectively) (Scheme 2). The stereochemical integrity of **2a** was ascertained by comparison with the product obtained from D-ribonolactone by an

Scheme 2



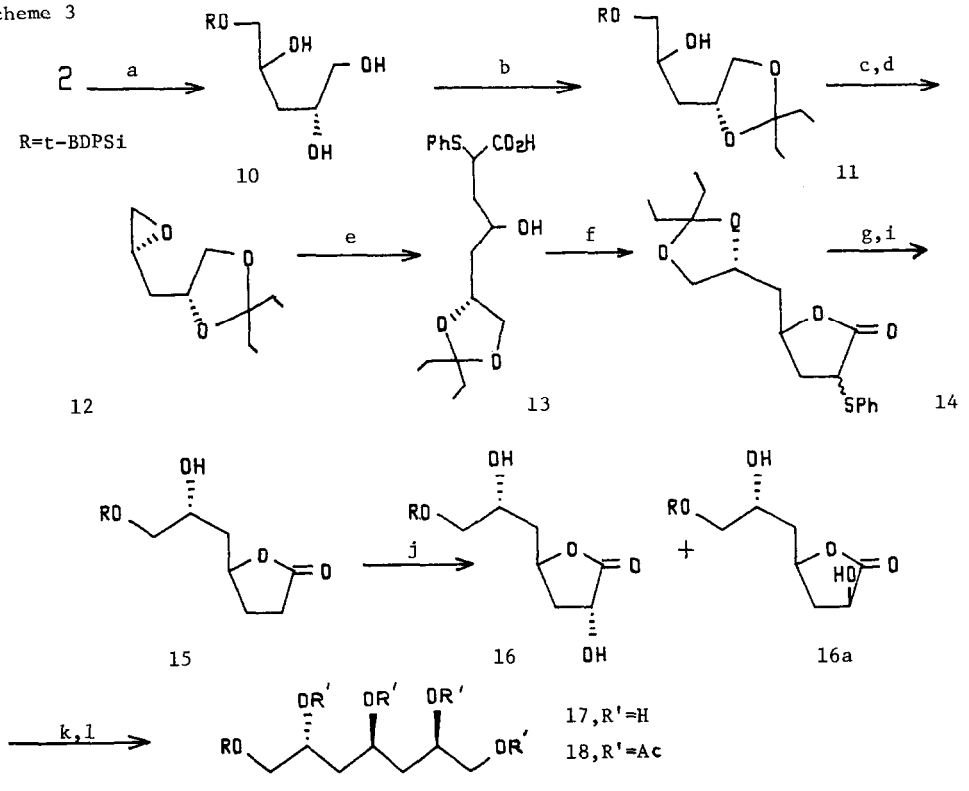
a. $LiN(TMS)_2$, THF, -78°, 30 min; then MoOPH, 1h (80%); b. DIBAL, toluene, -78°, 3h, (88%); c. Ph_3P=CHCOOBn, cat C_6H_5COOH, CH_3CN, 12h, (80%); d. Pd/C, H_2, EtOAc, 1h; then ethyl(dimethylaminoethyl)carbodiimide HCl, DMAP, Et_2O (87%, 2 steps); e. t-butyldimethyl silyl chloride, pyridine, DMAP, 36h, (82%); f. $NaBH_4$, 0°-R.T, THF/H_2O (3:1), 1h, (88%); g. Ac_2O, pyr., DMAP, (90%); h. NaOMe/MeOH, 0°, (quant.).

unambiguous route.[10] The efficient hydroxylation under quasi-stoichiometric conditions is noteworthy, since related reactions have been reported to require excess reagent.[11]

At this point there were three options to consider for the synthesis of diastereomeric or enantiomeric polyols, depending on which extremity of **2** we chose to extend (Scheme 1). Thus, in route A, the lactone **2** was transformed into the lactol, and the corresponding ester **3** by conventional methodology. Hydrogenation and lactonization gave the replicated lactone **4**, $[\alpha]_D$ +14.4° in high overall yield. Initial studies had indicated that the degree of stereoselection in the hydroxylation of lactone enolates was dependent on the steric bulk and nature of the substitutent in the side-chain.[12] Thus, hydroxylation of the dianion of **4** led to the dihydroxy lactone **6**, $[\alpha]$ +29.7° ($CHCl_3$), and its epimer (4:1 ratio respectively, 76 % yield). Hydroxylation of the enolate derived from the disilyl derivative **5**, gave the hydroxy lactone **7** $[\alpha]_D$ +16.2° and its epimer (6:1 ratio respectively, 78%). Reduction of **6** led to the syn, syn-heptitol derivative **8**. The tetraacetate **9** showed $[\alpha]_D$ -15.1° ($CHCl_3$).

Extension and replication through the terminal carbon atom (route B) was studied next. (Scheme 3) Thus, the triol **10** obtained from **2** was selectively protected to give the acetal derivative **11** $[\alpha]_D$ -8.6°.[13] Mesylation, followed by treatment with fluoride ion effected

Scheme 3



a. $NaBH_4$, 0°→R.T, THF/H_2O (3:1), 1h, (76%); b. $(C_2H_5)_2$ CO, CSA, 4h. (82%); c. MsCl, pyridine, DMAP, 12h, (85%); d. $Bu_4N^+F^-$, THF, R.T, 1h (87%); e. $PhSCH_2CO_2H$, $LiN(TMS)_2$, THF, 0°→R.T, add epoxide, 18h; f. ethyl(dimethylaminoethyl)carbodiimide HCl, DMAP, Et_2O (70%, 2 steps); g. Raney-nickel, MeOH; h. AcOH, H_2O (8:2), 4h; i. t-butyldiphenylsilyl chloride, imidazole, DMF, (81%, 3 steps); j. $LiN(TMS)_2$ (4 equiv.); MoOPh (1.2 equiv.), THF, -78° (78%); k. $NaBH_4$, THF-H_2O (3:1), 1h (70%); l. Ac_2O, pyr., DMAP, CH_2Cl_2 (88%).

the expected sequential desilylation and epoxidation to give **12**, $[\alpha]_D$ +11.8°. Opening of the epoxide[4] with dilithiophenylthioacetate,[14] followed by lactonization gave **14**, which after adjustment of protecting groups led to the replicated lactone **15**, $[\alpha]_D$ +24.7° ($CHCl_3$). Hydroxylation of the resulting enolate gave the dihydroxy derivative **16**, $[\alpha]_D$ +44.2° ($CHCl_3$) and its epimer **16a** (2.5:1 ratio respectively, 78%). Finally, reduction of **16** led to the syn, anti-heptitol derivative **18**, $[\alpha]_D$ +18.3° ($CHCl_3$). As in the diastereomeric series (Scheme 2), hydroxylation of the t-butyldimethylsilyl derivative of **15** gave corresponding the 2-hydroxy derivatives (α,β ratio, 8:1); $[\alpha]_D$ +55.2° ($CHCl_3$) for the major isomer.

It is clear from the above results that the strategy for 1,3-polyol formation is versatile and lends itself to stereochemical and structural maneuvrability. For example, application of the epoxide opening sequence via route C (Scheme 1) should give products enantiomeric with those derived from route A. Furthermore, the chain-lengthening process, subsequent lactonization and hydroxylation can, in principle, be reiterated giving replicated lactones to ultimately produce stereoregular $5+2^n$ 1,3 polyol units.

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