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A Tactically Novel Alternative to Acyclic Stereoselection Based on the Concept of a Replicating Chiron — 1,3- and 1,4-C-Methyl Substitution†

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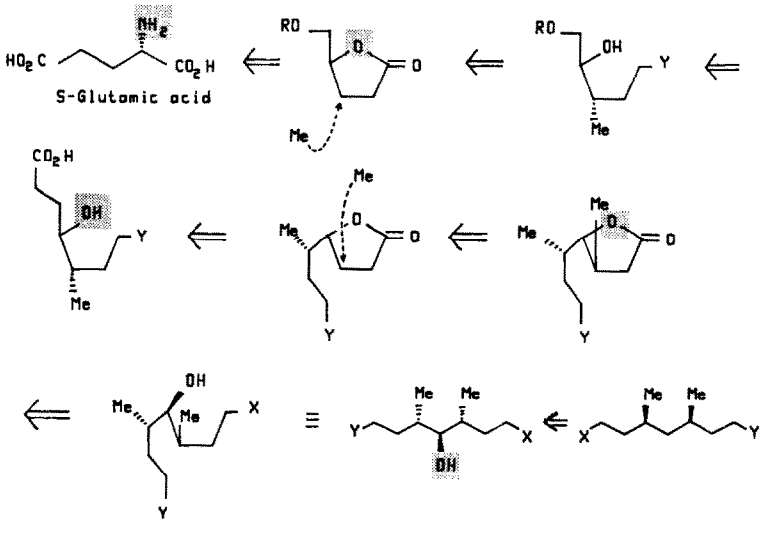
Summary - A chiral 4-hydroxymethyl butenolide is used as a template for the stereocontrolled conjugate addition of a C-methyl group. A sequential two-carbon extension and reformation of a lactone with the new side-chain leads to a "replicated" butenolide, which is subjected to a second conjugate addition. This process leads to a seven-carbon chain with a predictable 1,3-C-methyl substitution pattern.

In the preceeding paper[1], we demonstrated the utility of a chiral butyrolactone derivative prepared from (S)-glutamic acid as a template for the stereocontrolled introduction of C-methyl substituents having a 1,5-relative disposition on a seven-carbon framework. The operational basis for such a strategy was predicated upon the concept of a replicating chiron, generated as a result of the inherent symmetrical disposition of a pivotal functional group (hydroxyl) with regard to other flanking substituents.

Scheme 1



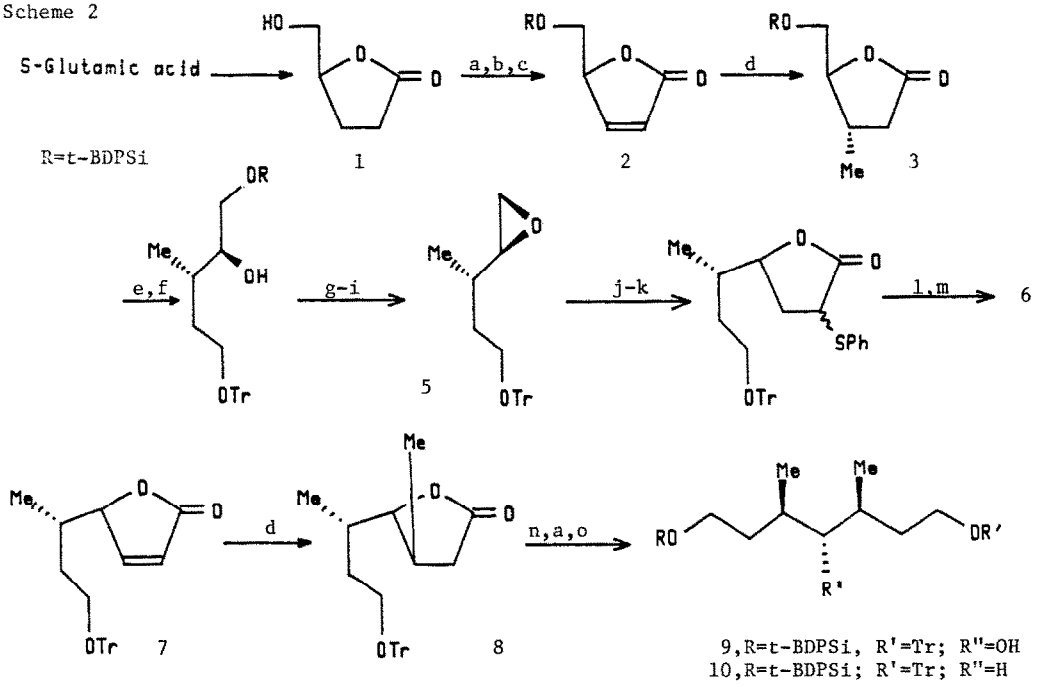
† Dedicated to Prof. H.H. Wasserman on the occasion of his 65th birthday.

In this paper we show the flexibility of this approach in the construction of acyclic carbon chains bearing C-methyl substituents with 1,3- and 1,4- disposition, with and without an intervening hydroxyl group. Such patterns of substitution are present in the segments of a number of natural products of relevance as well as in the structures of an important class of enzyme inhibitors.[2] Several studies have addressed this problem and a number of innovative approaches have been reported.[3]

Based on previous experience[4] and our own studies, it was reasoned that the general retrosynthetic analysis shown in Scheme 1 might be successfully realized, leading to several combinations of 1,3-situated C-methyl substituents on a seven carbon framework. Thus, stereocontrolled conjugate addition, chain-extension, and repetition of the cycle on a replicated butenolide-type chiron would be expected to provide a chiral butyrolactone with two C-methyl substituents flanking the pivotal ring oxygen. These operations were successfully accomplished with virtually complete stereoselection.

The butenolide **2**, mp 83-84°, $[\alpha]_D$ -83.2°,[5] obtained from the known lactone **1**[6] or from D-ribonolactone[7] (Scheme 2), was treated with lithium dimethyl cuprate to give the C-methyl derivative **3**, $[\alpha]_D$ +30.5° in 87% yield. Transformation of **3** via acyclic intermediates led to the epoxide **5**, mp 62-63°, $[\alpha]_D$ -9°, in excellent overall yield.

Scheme 2

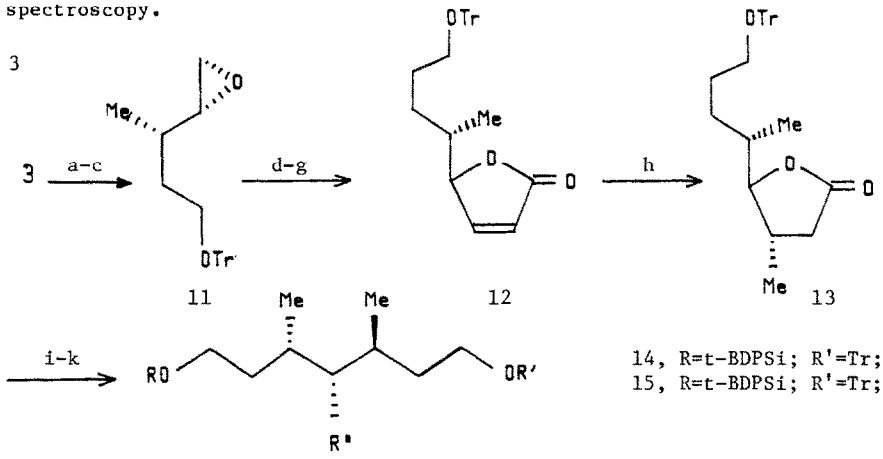


a. t-butyldiphenylsilyl chloride, CH_2Cl_2 pyr., DMAP, 18h, (85%); b. $LiN(TMS)_2$, THF, 20 min.; then PhSeCl; c. H_2O_2, CH_2Cl_2, 0°, 30 min., (50%, 2 steps); d. Me_2CuLi, Et_2O, -20°, 30 min., (87%); e. $BH_3.Me_2S$, THF, 18h, (quant.); f. Ph_3CCl, pyr., DMAP, 18h, (quant.); f. Ph_3CCl, pyr., DMAP, 18h, (92%); g. $(n\text{-}Bu)_4N^+F^-$, THF, 2h, (92%); h. 2,4,6-triisopropyl benzenesulphonyl chloride, pyr., 0°, 24h; i. NaOMe, MeOH, 0°, 30 min., (75%, 2 steps); j. $PhSCH_2CO_2H$, $LiN(TMS)_2$, THF, 0° to 25°; add epoxide, 18h; k. ethyl (dimethylaminoethyl) carbodiimide HCl, DMAP, Et_2O, (85%, 2 steps); l. mCPBA, CH_2Cl_2, -23°, 30 min.; m. toluene, $CaCO_3$, reflux, 45 min., (81%, 2 steps); n. LAH, Et_2O, 1h, (94%); o. MsCl, pyr., CH_2Cl_2, then repeat n, (73%, 2 steps).

Chain-extension[1] with dilithio phenylthioacetic acid,[8] followed by lactonization, oxidation and elimination gave the replicated chiral butenolide **7**, $[\alpha]_D$ +54.5°. With the bulky side-chain effectively shielding the α-face of the α,β-unsaturated lactone **7**. A second cuprate addition gave the crystalline chiral lactone **8**, mp 122-123°; $[\alpha]_D$ -34.3° as the sole product in 93% yield. Now that the cyclic lactone templates had served their purpose, acyclic equivalent structures could be considered. Thus, reduction of **8**, followed by selective substitution of the primary hydroxyl group led to **9**, $[\alpha]_D$ -4.4°. Deoxygenation was easily achieved by reductive desulfonylation of the corresponding mesylate to give the (3R,5S)-dimethyl-1,7-heptanediol derivative **10**, $[\alpha]_D$ -3.6°, in high yield.

Since the conceptual basis of our strategy is predicated upon the exploitation of the inherent symmetrical disposition of functional groups around a pivotal hydroxyl group such as illustrated in Scheme 1, it is possible to capitalize on their manipulation and to produce stereochemically diverse patterns of substitution. Thus, manipulation of **3** gave the epoxide **11**, mp 62-63°, $[\alpha]_D$ -9° (Scheme 3). Application of the sequence described above for **5**, gave the chiral replicated butenolide **12**, $[\alpha]_D$ -48.4° in high overall yield. Conjugate addition led to the lactone **13**, $[\alpha]_D$ +12.2°, which when reduced and protected as before, gave the acyclic derivative **14** in high overall yield. Reductive removal of the secondary hydroxyl group gave the (3R,5R)-dimethyl-1,7-heptanediol derivative **15**, $[\alpha]_D$ +3.1°, which was easily distinguishable from the diastereoisomeric **10** by high field ^1H n.m.r. spectroscopy.

Scheme 3

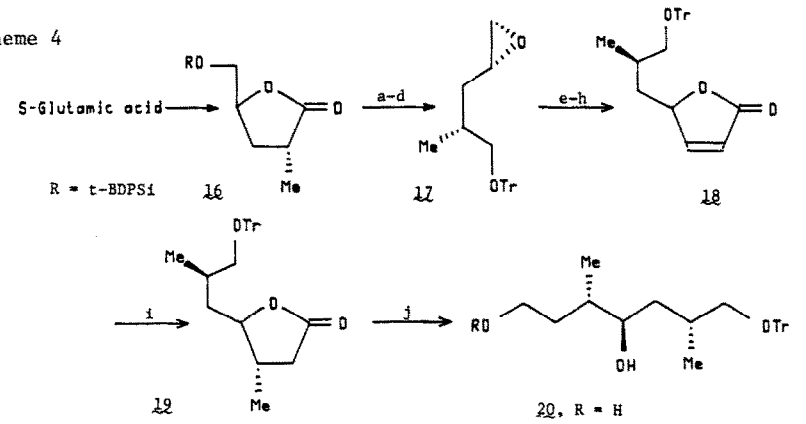


a. $BH_3.Me_2S$, THF, 18h, (quant.); b. MsCl, pyr., DMAP, 2h; c. $(n\text{-}Bu)_4N^+F^-$, THF, 30 min., (71%, 2 steps); d. $PhSCH_2CO_2H$, $LiN(TMS)_2$, THF, 0° to 25°; add epoxide, 18h; e. ethyl (dimethylaminoethyl) carbodiimide HCl, DMAP, Et_2O, (84%, 2 steps); f. mCPBA, CH_2Cl_2, -23°, 30 min.; g. toluene, $CaCO_3$, reflux, 45 min., (92%, 2 steps); h. Me_2CuLi, Et_2O, 45 min.; i.LAH, Et_2O, 45 min., 93%; j. t-butyldiphenylsilyl chloride, CH_2Cl_2, pyr., DMAP, 18h, (98%); k. MsCl, pyr., CH_2Cl_2; then repeat i, (71%, 2 steps).

Finally, access to acyclic chains possessing a 1,4-C-methyl substitution pattern was easily accomplished by a combination of template-controlled lactone enolate alkylation,[1] followed by conjugated addition on a replicated butenolide as shown in Scheme 4. Thus, alkylation of **16** followed by transformation into an acyclic derivative as previously described,[1] then mesylation and treatment with fluoride ion gave the epoxide **17**,

$[\alpha]_D$ +4.1° in good overall yield. Chain-extension and transformation into the chiral butenolide **18**, $[\alpha]_D$ -56.7°, followed by conjugate addition led to the chiral lactone **19**, $[\alpha]_D$ +35.7° in 95% yield. Reduction, followed by silylation of the primary hydroxyl group, then gave the (2R,4R,5S)-2,6-dimethyl-1,4,7-heptanetriol derivative **20** in high yield, $[\alpha]_D$ +19.3°.

Scheme 4



a. $BH_3.Me_2S$, THF, RT, 18h (~quant.); b. Ph_3CCl, pyr., DMAP, RT, 18h, (94%); c. CH_3SO_2Cl, pyr., RT, 2h; d. $Bu_4N^+F^-$, THF, RT, 1h, (69%, 2 steps); e. $PhSCH_2CO_2H$, $LiN(TMS)_2$, THF, 0°, then 25°; add epoxide, 18h; f. ethyl(dimethylaminoethyl)carbodiimide HCl, DMAP, ether, RT, 30 min., (87%, 2 steps); g. m-CPBA, CH_2Cl_2, -23°, 30 min.; h. toluene, $CaCO_3$, reflux, 45 min., (92%, 2 steps); i. Me_2CuLi, Et_2O, -23°, 30 min., (95%); j. LAH, Et_2O, RT, 1h, (91%).

It should be noted that several of the intermediates and/or acyclic products prepared by this strategy, have stereochemical plurality by virtue of the differentiation of the protected hydroxyl groups. Thus, products possessing inherent planes of symmetry (such as in **9,10** can be used as optically active precursors to segments of natural products with substitution patterns that are identical to, or enantiomeric with the precursors in question. The same reasoning applies to products such as **15**, where chain-elongation or shortening can be effected from either extremity at will to give diastereoisomeric compounds.

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