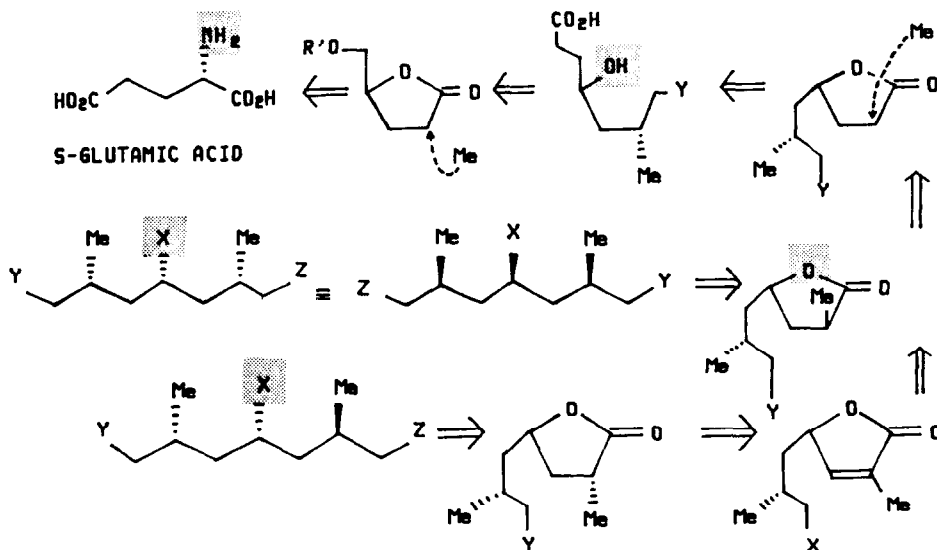


**A Tactically Novel Alternative to Acyclic Stereoselection Based on
 the Concept of a Replicating Chiron – 1,5-C-Methyl Substitution†**

Stephen Hanessian*, Peter J. Murray, Soumya P. Sahoo
 Department of Chemistry, Université de Montréal
 Montréal, Québec, Canada H3C 3V1

Summary – A synthetic sequence is described wherein a chiral butyrolactone is used as a template to control the stereochemistry of a C-methylation process on the corresponding enolate. A sequential two-carbon homologation and replication of the butyrolactone template allows a second stereocontrolled C-methylation. The ultimate outcome is a seven carbon acyclic chain with a predictable 1,5-substitution pattern of C-methyl groups with or without an intervening hydroxyl group.

Among the numerous ways in which Nature chooses to display her prowess in assembling complex natural products, is one where several asymmetric centers bearing C-methyl and hydroxyl groups adopt vicinal, alternating or remote patterns of substitution on a mainframe carbon chain. Much innovation has come forth in an effort to achieve the synthesis of such subunits based on various methods of stereocontrol.^{1,2} We wish to report a versatile protocol that allows the construction of acyclic chains of seven carbons (or more), with predisposed, alternating, and/or remote C-methyl substitution patterns of the 1,5-type with or without an intervening hydroxyl group as shown in Scheme 1.



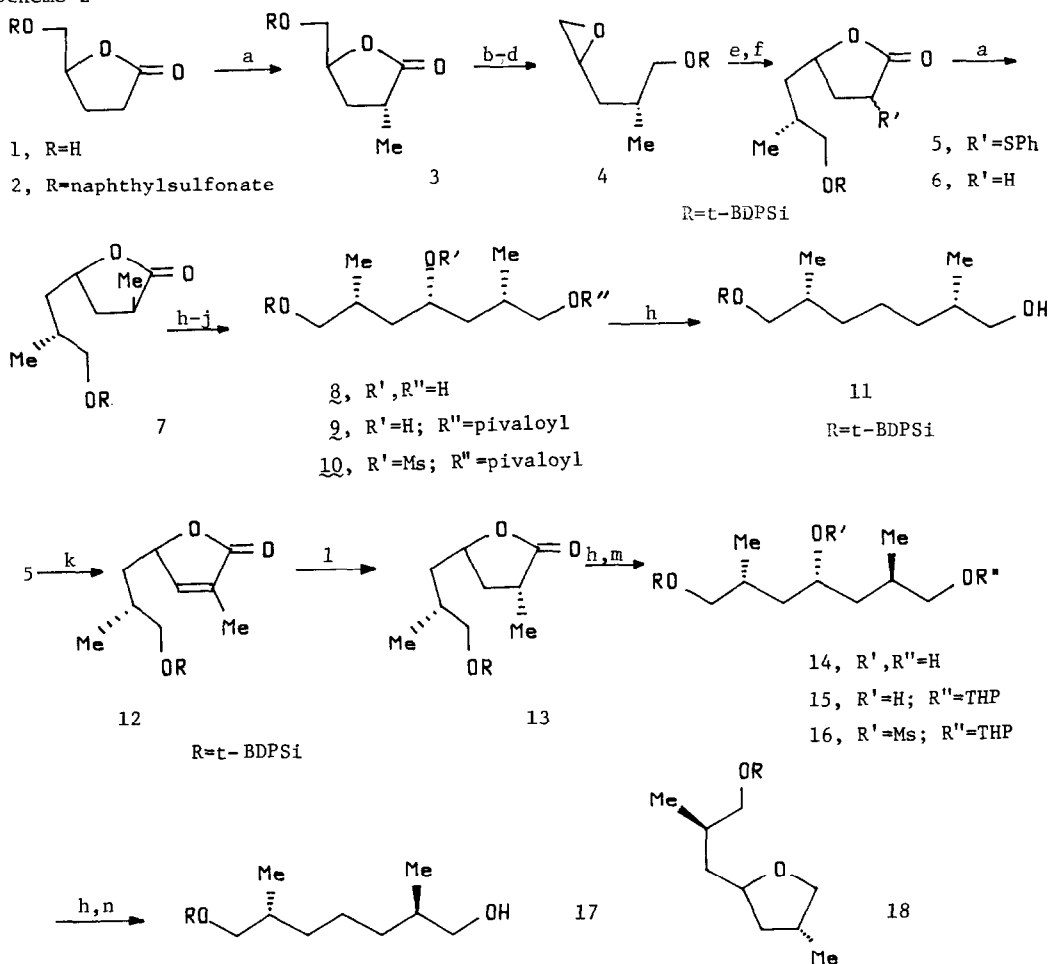
† Dedicated to Prof. H.H. Wasserman on the occasion of his 65th birthday.

Our strategy is based on the exploitation of template³ properties as well as symmetry elements presented by a chiral (S)-4-hydroxymethyl butyrolactone derivative^{4,5}, readily available from (S)-glutamic acid^{4,5}, D-mannitol⁷ or D-ribonolactone⁸. Thus, by virtue of the steric effect of an anchored hydroxymethyl substituent, alkylation of the corresponding enolate is expected to occur predominantly in the anti-mode⁹. A two-carbon (acetic acid) extension provides an intermediate in which the pivotal C-4 OH has a symmetrical disposition with regard to the carbon chains on either side. Lactonization provides a new "replicated" butyrolactone. Alkylation of the corresponding enolate should once again be highly stereoselective to give another anti-relationship, giving rise to acyclic carbon chains containing a predetermined array of alternating C-methyl and hydroxyl groups. The intermediates could also be amenable to functional and configurational change thus producing stereoisomeric compounds.

Treatment of the naphthylsulfonate **2**, m.p. 90.5-91°; $[\alpha]_D +58.3^\circ$ (CHCl₃), readily available from **1** with lithium hexamethyldisilazide followed by methyl iodide, and chromatographic purification of the mixture of isomers (>11:1), gave **3** as the major product (82%), mp 95-96°; $[\alpha]_D +65.6^\circ$ (CHCl₃) (Scheme 2). It is noteworthy that successful alkylation can be effected in the presence of the sulfonate group, since this obviates the exchange of protecting groups later in the sequence.¹⁰ Reduction of the lactone, preferential silylation, and treatment with sodium methoxide gave the epoxide **4** in excellent overall yield, (syrup), $[\alpha]_D 0^\circ \pm 2^\circ$ (CHCl₃). A two-carbon extension by treatment with dilithio 2-phenylthioacetate, followed by lactonization led to **5** as a mixture of isomers at C-2. Raney-nickel desulfurization readily afforded the "replicated" lactone **6**, which was poised for a second cycle of alkylation. Indeed, similar treatment as for **2**, led to the new lactone **7** as the major product (>11:1), $[\alpha]_D -13.3^\circ$ (CHCl₃). With both C-methyl groups introduced with predictable stereocontrol, there remained to unfold the lactone template now that it had served its intended purpose. Reduction led to the selectively protected triol **8**, (syrup); $[\alpha]_D -1.4^\circ$ (CHCl₃). Sequential esterification with pivaloyl chloride, then with methanesulfonyl chloride gave the diester **10** which, upon reduction with LAH, gave the desired seven-carbon unit **11** (syrup), $[\alpha]_D -3.6^\circ$ (CHCl₃), accompanied by a small amount of the corresponding tetrahydrofuran derivative, $[\alpha]_D -11.1^\circ$ (CHCl₃). Compound **11**, available in optically pure form, represents a well known chiral subunit in a number of natural products, including vitamins¹¹ and pheromones¹².

The versatility of our method as an alternative approach to acyclic stereoselection can be further demonstrated by the generation of other stereoisomeric units, simply by manipulation of functional groups in some intermediates (Scheme 2). Thus, methylation of the enolate resulting from **5**, gave a mixture of C-methyl derivatives, which was transformed by oxidative elimination to the α,β -unsaturated lactone **12**, mp 65-66°; $[\alpha]_D -27^\circ$ (CHCl₃). Catalytic hydrogenation of **12** led to the lactone **13**, in which the C-2 methyl group now had an α -orientation or syn to the lactone side-chain. Similar treatment as for the diastereomeric **7**, gave the triol derivative **14**, (syrup), $[\alpha]_D +6.4^\circ$ (CHCl₃), which was converted to the diol **17**, (syrup), $[\alpha]_D +7.4^\circ$ (CHCl₃), via a reductive sequence. Interestingly, when the corresponding pivaloyl ester was subjected to LAH reduction as for **10**, the tetrahydrofuran derivative **18**, was the sole product.

Scheme 2



a. $\text{LiN}(\text{TMS})_2$, THF, -78° , 20 min; then MeI, 10 min. (82%); b. $\text{BH}_3 \cdot \text{Me}_2\text{S}$, THF, 1 h; c. *t*-butyldiphenylsilyl chloride, DMF, imidazole (85%, 2 steps); d. NaOMe, MeOH, 0° , 15 min. (quant.); e. $\text{PhSCH}_2\text{CO}_2\text{H}$, $\text{LiN}(\text{TMS})_2$, THF, 0° , then 25° ; add epoxide, 18 h; f. ethyl(dimethylaminoethyl) carbodiimide HCl, DMAP, Et_2O , (75%, 2 steps); g. Raney Ni, MeOH, 30 min, 92%; repeat step a, (83%); h. LAH, THF, -10° , 2 h (70%); i. pivaloyl chloride, pyr., CH_2Cl_2 , (85%); j. MsCl, pyr., CH_2Cl_2 ; then LAH, 0° , 2 h (71%); k. NaIO_4 , aq. MeOH; then toluene containing 1% pyr., reflux 3 h; l. Pd/C, H_2 , EtOAc, (63%, 3 steps); m. dihydropyran, PPTS, CH_2Cl_2 , then mesylation (81%); n. aq. 0.5 M HCl/MeOH, 2 h (67%, 3 steps).

In addition to providing the intended subunits, it should be noted that the acyclic derivatives produced by our method are also endowed with stereochemical duality, by virtue of their inherent symmetry and the substitution pattern. Thus, all the optical isomers of 2,6-dimethyl 1,4,7-heptanetriol, and 2,6-dimethyl heptane 1,7-diol can be obtained from (R)- or (S)-glutamic acid¹³ by application of the methods developed in this work, and by subsequent manipulation of stereocenters and protecting groups. It is also clear that the template effect in related butyrolactone derivatives can be used to generate other acyclic subunits with different patterns of substitution¹⁴ (vicinal and alternating).

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References

- For some recent representative methods excluding polyol systems, see, a. Heathcock, C.H.; Jarvi, E.T.; Rosen, T. Tetrahedron Lett., 1984, 25, 243; b. Fujiwara, J.; Fukutani, Y.; Hasegawa, M.; Maruoka, K.; Yamamoto, H. J. Am. Chem. Soc., 1984, 106, 5004; c. Bérubé, G.; Deslongchamps, P. Can. J. Chem., 1984, 62, 1558; d. Koreeda, M.; Brown, L. J. Org. Chem., 1983, 48, 2122; e. Nakata, T.; Fukui, M.; Ohtsuka, H.; Oishi, T. Tetrahedron Lett., 1983, 24, 2661; f. Williams, D.R.; Phillips, J.G.; Huffman, J.C. J. Org. Chem., 1981, 46, 4103; g. Still, W.C.; Darst, K.P. J. Am. Chem. Soc., 1980, 102, 7387; h. Trost, B.M.; Klum, T.P. J. Am. Chem. Soc., 1979, 101, 6756; i. Cohen, N.; Eichel, W.F.; Lopresti, R.J.; Neukom, C.; Saucy, G. J. Org. Chem., 1976, 41, 3512.
- For selected reviews, see Bartlett, P.A. Tetrahedron, 1980, 36, 3; Heathcock, C.H. Science, 1981, 214, 395; Masamune, S.; Choy, W. Aldrichimica Acta, 1982, 15, 47.
- Hanessian, S. "Total Synthesis of Natural Products - The 'Chiron' Approach", J.E. Baldwin, ed., Pergamon, Oxford, 1983.
- See for example, Kano, S.; Shibuya, S.; Ebata, T. Heterocycles, 1980, 14, 661; Vigneron, J.P.; Méric, R.; Larcheveque, M.; Debal, A.; Lallemand, J.Y.; Junesch, G.; Tagatti, P.; Gallois, M. Tetrahedron, 1984, 40, 3521; Ravid, U.; Silverstein, R.M.; Smith, R.M. Tetrahedron, 1978, 34, 1449; Taniguchi, M.; Koga, K.; Yamada, S. Tetrahedron, 1974, 30, 3547.
- For the utilization of optically active 4-hydroxymethyl- γ -butyrolactone as a starting material in the synthesis of a variety of natural products, see Koga, K.; Taniguchi, M.; Yamada, S. Tetrahedron Lett., 1971, 263; Mori, K. Tetrahedron, 1975, 31, 3011; Smith, L.R.; Williams, H.J.; and Silverstein, R.M. Tetrahedron Lett., 1978, 3231; Robin, J.P.; Gringore, O.; Brown, E. Tetrahedron Lett., 1980, 21, 2709, see also ref. 9 and references cited therein.
- Smith, L.R.; Williams, H.J. J. Chem. Ed., 1979, 56, 696.
- Takano, S.; Goto, E.; Hiram, M.; Ogasawara, K. Heterocycles, 1981, 16, 951.
- Camps, P.; Cardellach, J.; Font, J.; Ortuno, R.M.; Ponsati, O. Tetrahedron, 38, 2395 (1982).
- Tomloka, K.; Koga, K. Tetrahedron Lett., 1979, 3315; Prestwich, G.D.; Shieh, H. J. Org. Chem., 1981, 46, 4319; Takamo, S.; Kasahara, C.; Ogasawara, K. Chem. Lett., 1982, 631; Chen, S.Y.; Jouillé, M.M. J. Org. Chem., 49, 2168 (1984).
- Lower diastereoselection ($\sim 7:1$) was observed with the corresponding tosyloxy derivative corresponding to 2.
- For some recent syntheses of Vitamin E side chains, for example see ref. l,c,d,g,h,i; see also Fuganti, C.; Grasselli, P. J. Chem. Soc., Chem. Commun., 1979, 995; Zell, R. Helv. Chim. Acta, 1979, 62, 474; Takahashi, J.; Mori, K.; Matsui, M. Agric. Biol. Chem., 1979, 43, 1605; Fujisawa, T.; Sato, T.; Kawara, T.; Ohashi, K. Tetrahedron Lett., 1981, 22, 4723; Trost, B.M.; Klum, T.P. J. Am. Chem. Soc., 1981, 103, 1864; Leuenberger, H.G.W.; Boguth, W.; Barner, R.; Schmid, M.; Zell, R. Helv. Chim. Acta, 1979 62, 455; Heathcock, C.H. Jarvi, E.T. Tetrahedron Lett., 1982, 23, 2825; and references cited therein.
- Jewett, D. Matsumura, F.; Coppel, H.C. J. Chem. Ecol., 1978, 4, 277; Baker, R.; Winton, P.; Turner, R.W. Tetrahedron Lett., 1980, 21, 1175; Byström, S.; Höggberg, H.-E.; Norin, T. Tetrahedron, 1981, 37, 2554; Sonnet, P.E.; Uebel, E.C.; Harris, R.L.; Miller, R.W. J. Chem. Ecol. 1977, 3, 245; Carbon, D.A.; Langley, P.A.; Huyton, P. Science (Washington, D.C.), 1978, 201, 750, and references cited therein.
- For the synthesis of the (R)-4-hydroxymethyl- γ -butyrolactone from (S)-glutamic acid, see Ho, P.-T.; Davies, N. Synthesis, 1983, 462.
- Hanessian, S.; Murray, P.J.; Sahoo, S.P., see following paper.

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