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# Approaches to the Total Synthesis of Natural Products Using "Chiral Templates" Derived from Carbohydrates

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The concept of asymmetric synthesis[1] has been known since 1894, when Emil Fischer outlined its potential based upon the cyanohydrin reaction in the sugar series.[2] Since then, asymmetric synthesis has been ingeniously and widely used in the creation of C–C bonds in organic molecules. In spite of these developments, the control of absolute stereochemistry and the regiospecific introduction of functionality at predetermined sites remain as crucial problems in the construction of even moderately functionalized chiral compounds. This in fact has been one of the major problems in total synthesis[3] over the years, and we have almost grown accustomed to *dl* or (±) prefixes. The planning and execution of a synthetic scheme in which *optically active* chiral intermediates can be produced and efficiently utilized has enormous advantages and is unquestionably a most desirable commodity in the quest for optically pure compounds.[4]

## The Concept of "Chiral Templates" Derived from Carbohydrates

Historically, much of the synthetic efforts in carbohydrate chemistry have been inspired by biochemical events, and the knowledge gained from such studies has been useful in advancing many frontier areas in the biological sciences. Let us, however, look at carbohydrates in a different perspective. In them, we have a relatively cheap and replenishable source of chiral carbon compounds, available in a variety of chain lengths and endowed with a plethora of functional, stereochemical, and conformational features. On a per-carbon basis, carbohydrates are unmatched in chirality and functionality, and in this context they are also ideally suited for chemical manipulations and the exploration of novel synthetic methods. It is therefore obvious that the most useful role of carbohydrates in organic synthesis in general, and natural product chemistry in particular, should be one that capitalizes on their inherent molecular features and transforms them into chiral synthetic intermediates.[5] It should, in fact, be possible to construct a number of multifunctional and chiral acyclic, carbocyclic, and heterocyclic compounds from carbohydrate derivatives based on the concept of "chiral templates". In essence, this involves scrutinizing the molecular architecture of a target compound to locate elements of hidden or apparent symmetry, decoding the stereochemical information, and transposing it, partially or totally, onto the carbon framework of a suitable sugar derivative. The latter is then used as a "chiral template" and is asymmetrically modified to achieve the desired level of functional and chiral overlap.[6] The carbohydrate backbone is therefore used to prepare prefabricated chiral intermediates carrying the stereochemical and functional code of the intended synthetic target. The combination of natural chirality, conformational bias, and the inherent topology of a cyclic sugar derivative should provide a high degree of regio- and stereocontrol for the systematic functionalization of predetermined sites in the molecule. Such carbohydrate-derived "chiral templates" can then be further modified, and eventually integrated into the structural framework of the synthetic target. The concept is schematically illustrated taking α-D-glucose as a chiral building block (Scheme I). In operational terms, this approach is fundamentally different from other, more routinely used and "accepted" ones, and it offers an alternative strategy in total synthesis which can be applied to a wide variety of synthetic objectives. Two very broad

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(1) D. Valentine, Jr., and J. W. Scott, *Synthesis*, 329 (1978); "Asymmetric Organic Reactions", J. D. Morrison and H. S. Mosher, Prentice-Hall, Englewood Cliffs, N.J., 1972; see also J. W. Scott and D. Valentine, Jr., *Science*, **184**, 943 (1974); N. Cohen, *Acc. Chem. Res.*, **9**, 412 (1976).

(2) For a summary see K. Freudenberg, *Adv. Carbohydr. Chem.*, **21**, 1 (1960).

(3) See, for example, "Organic Synthesis", R. E. Ireland, Prentice-Hall, N.J., 1969; "Creativity in Organic Synthesis", J. S. Bindra and R. Bindra, Vol. I, Academic Press, New York, 1975.

(4) The total synthesis of chiral molecules from optically active compounds (chiral pool) and by asymmetric substitution with a chiral reagent or by microbiological transformations (chiral economy) is well-known; see, for example, D. Seebach and H.-O. Kalinowski, *Nachr. Chem. Tech.*, **24**, 415 (1976); B. Seuring and D. Seebach, *Helv. Chim. Acta*, **60**, 1175 (1977); A. Fischli, *Chimia*, **30**, 4 (1976); Q. Branca and A. Fischli, *Helv. Chim. Acta*, **60**, 925 (1977). For other elegant approaches, see R. V. Stevens and F. C. A. Gaeta, *J. Am. Chem. Soc.*, **99**, 1016 (1977).

(5) See also, for example, T. D. Inch, *Adv. Carbohydr. Chem. Biochem.*, **27**, 191 (1972); B. Fraser-Reid, *Acc. Chem. Res.*, **8**, 192 (1975).

(6) J. B. Hendrickson, *Top. Curr. Chem.*, **62**, 49 (1976).

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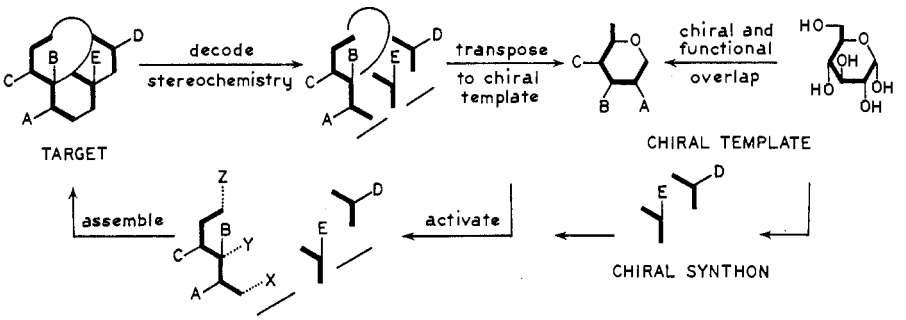
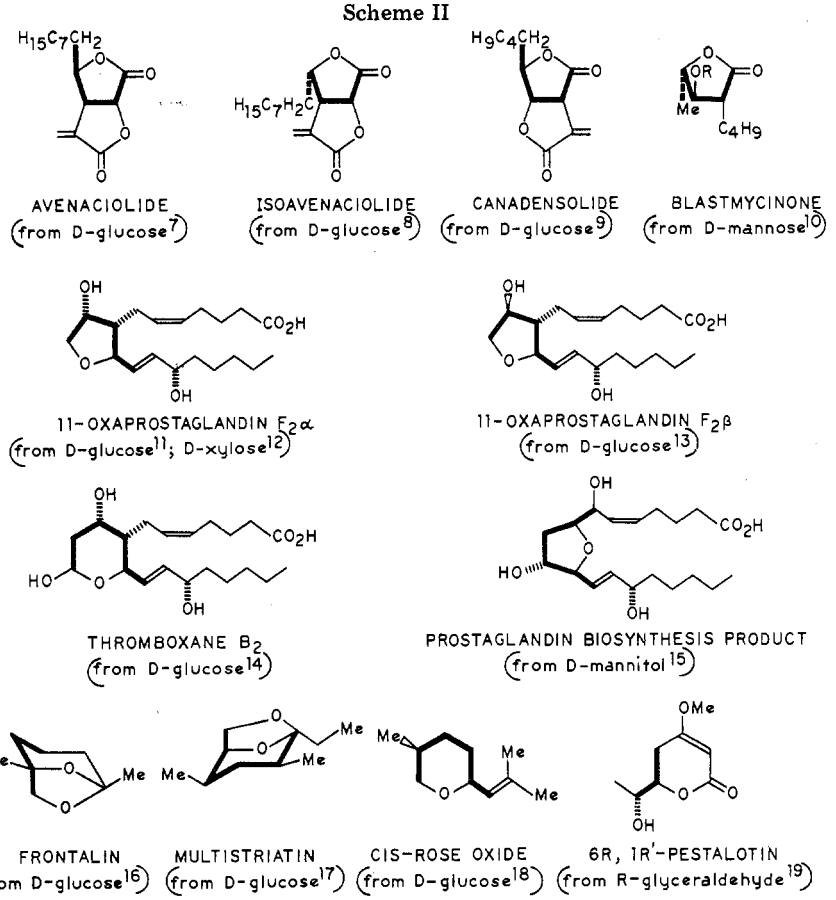
Scheme I




Scheme II

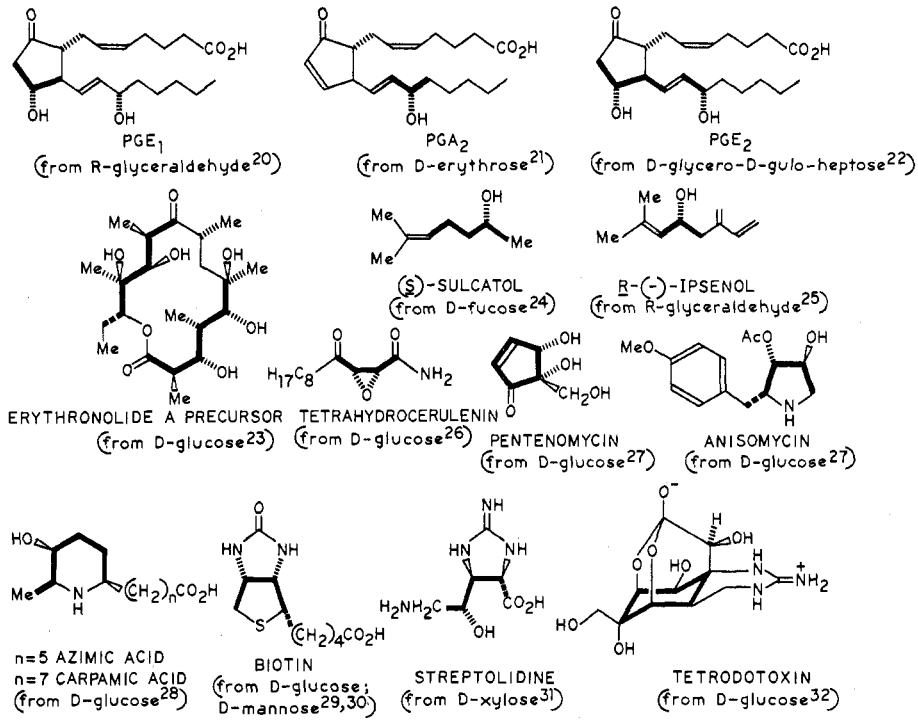



divisions can be made in the area of natural products:

(*a*) *Compounds in which the "sugar" portion is apparent and can be singled out by an examination of the structure in question.* This category includes a large number of compounds that comprise chiral tetrahydrofuran and tetrahydropyran rings such as polyether antibiotics (ionophores), certain terpenes, metabolites, and toxins derived from marine and other natural sources, *C*-nucleosides and *C*-glycosides, biosynthetic byproducts of prostaglandins (oxaprostaglandins, thromboxanes), pheromones and insect poisons, as well as other biologically interesting groups of compounds. Also included in this category are chiral monocyclic and bicyclic lactones (antifungal agents, antitumor agents, etc.). The examples chosen in Scheme II[7-19] illustrate the diversity in the structures of compounds that have been synthesized by these approaches. The bold lines show the remaining carbon atoms of the original sugar precursor after appropriate modification. (*b*) *Compounds in which the "sugar" portion is part of a hidden symmetry, hence, not immediately apparent from an examination of the structure in question.* For the purpose of synthetic

(7) R. C. Anderson and B. Fraser-Reid, *J. Am. Chem. Soc.*, **97**, 3870 (1975); H. Ohrui and S. Emoto, *Tetrahedron Lett.*, 3657 (1975).
(8) R. C. Anderson and B. Fraser-Reid, *Tetrahedron Lett.*, 2865 (1977).
(9) R. C. Anderson and B. Fraser-Reid, *Tetrahedron Lett.*, 3233 (1978).
(10) S. Aburaki, N. Konishi, and M. Konoshita, *Bull. Chem. Soc. Jpn.*, **48**, 1254 (1975).
(11) Unpublished results, S. Hanessian and Y. Guindon; G. J. Lourens and J. M. Koekemoer, *Tetrahedron Lett.*, 3719 (1975); for a synthesis of (±)-11-oxa-$PGF_2$ via a nonchiral route, see I. Vlattas and A. O. Lee, *Tetrahedron Lett.*, 4451 (1974).
(12) G. J. Lourens and J. M. Koekemoer, *Tetrahedron Lett.*, 3715 (1975).
(13) S. Hanessian, P. Dextraze, A. Fougerousse and Y. Guindon, *Tetrahedron Lett.*, 3983 (1974); unpublished results, S. Hanessian, P. Lavallée and Y. Guindon; P. Lavallée, Ph.D. Thesis, University of Montreal, 1977.
(14) S. Hanessian and P. Lavallée, *Can. J. Chem.*, **55**, 562 (1977); see also ref 49.
(15) S. Hanessian and G. Rancourt, 169th National Meeting of the American Chemical Society, Philadelphia, Pa., 1975, Abstr. CARB 26.
(16) D. R. Hicks and B. Fraser-Reid, *J. Chem. Soc., Chem. Commun.*, 869 (1976).
(17) P. Sum and L. Weiler, *Can. J. Chem.*, **56**, 2700 (1978).
(18) T. Ogawa, M. Takasaka, and M. Matsui, *Carbohydr. Res.*, **60**, C4 (1978).
(19) K. Mori, M. Oda, and M. Matsui, *Tetrahedron Lett.*, 3173 (1976).

**Scheme III**



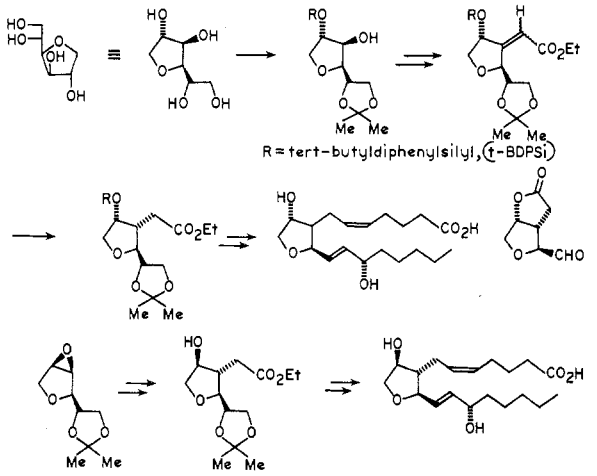

design, the chiral segment in such a molecule has to be "located", then transposed onto the carbon framework of a chiral precursor derived from a cyclic or acyclic carbohydrate. Examples in this category are more difficult to define, although certain alkaloids, other heterocyclic compounds, amino acids, chiral acyclic, carbocyclic, and macrocyclic compounds, as well as the "polyoxo" macrolide aglycones can be mentioned. The structures of a variety of natural products that have been synthesized, totally or partially, based on this approach are shown in Scheme III.[20-32] Again, the heavy lines indicate the carbon atoms that remain after asymmetric modification of the original sugar precursor.

## Stereocontrolled Syntheses of *C*-Glycosides. Access to Chiral Tetrahydrofurans and Tetrahydropyrans

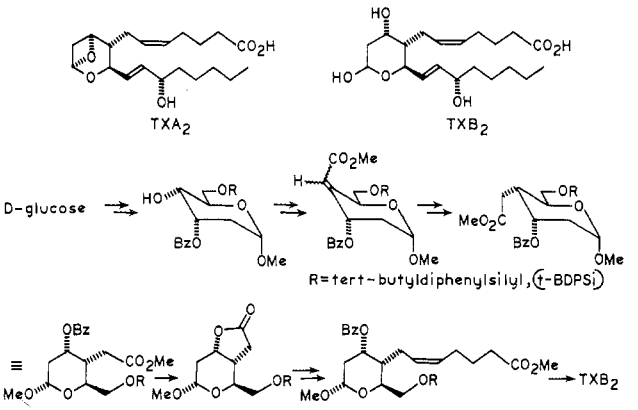
During the last decade or so, the discovery of a number of naturally occurring *C*-nucleosides,[33,34] a class of biologically important compounds in which the anomeric carbon is attached to a heterocyclic moiety via a C–C bond, prompted us to explore stereocontrolled syntheses of functionalized β-D-*C*-glycosides. We concerned ourselves mainly with two approaches,[33] namely, the intramolecular cyclization of an acyclic compound and C–C bond formation at the anomeric center of suitably protected sugar derivatives. In the first instance, use was made of a well-known dehydrative cyclization[35] of 1,6-di-*O*-benzoyl-D-mannitol to give 2,5-anhydro-D-mannitol, which after inversion at C-3 and preferential oxidation at C-1 led to an efficient and simple synthesis of a *C*-nucleoside precursor having the natural D-*ribo* configuration.[15,33] In a more exploratory approach, stereocontrolled glycosidation was achieved by allowing anomerically activated sugar derivatives to react with carbanions[36] or their synthetic equivalents,[37] thus providing α- and β-*C*-glycosyl compounds with a functionalized appendage at the original anomeric carbon atom. A highly efficient route to β-D-*C*-ribofuranosyl acetates consists in the treatment of ester[38] and acetal[38,39] derivatives in the D-ribofuranose series with stabilized phosphoranes. Related reactions

(20) G. Stork and T. Takahashi, *J. Am. Chem. Soc.*, **99**, 1275 (1977).
(21) G. Stork and S. Raucher, *J. Am. Chem. Soc.*, **98**, 1583 (1976).
(22) G. Stork, T. Takahashi, I. Kawamoto, and T. Suzuki, *J. Am. Chem. Soc.*, **100**, 8272 (1978).
(23) S. Hanessian and G. Rancourt, *Pure Appl. Chem.*, **49**, 1201 (1977). See Also Centennial Meeting of the American Chemical Society, New York, 1976, Abstr. CARB 32; G. Rancourt, Ph.D. Thesis, University of Montreal, 1978.
(24) H. R. Schuler and K. N. Slessor, *Can. J. Chem.*, **55**, 3280 (1977).
(25) K. Mori, *Tetrahedron Lett.*, 1609 (1976).
(26) H. Ohrui and S. Emoto, *Tetrahedron Lett.*, 2095 (1978); J.-R. Pougny and P. Sinaÿ, *Tetrahedron Lett.*, **3**, 301 (1978).
(27) J. P. H. Verheyden, A. C. Richardson, R. S. Bhatt, B. D. Grant, W. L. Fitch, and J. G. Moffatt, *Pure Appl. Chem.*, **50**, 1363 (1978).
(28) S. Hanessian and R. Frenette, M.Sc. Thesis, University of Montreal, 1979.
(29) T. Ogawa, T. Kawano, and M. Matsui, *Carbohydr. Res.*, C31 (1977).
(30) H. Ohrui and S. Emoto, *Tetrahedron Lett.*, 2765 (1975).
(31) S. Kusumoto, S. Tsuji, K. Shima, and T. Shiba, *Bull. Chem. Soc. Jpn.*, **49**, 3611 (1976).
(32) M. Funabashi, J. Wakai, K. Sato, and J. Yoshimura, Abstracts, IXth International Symposium on Carbohydrate Chemistry, Kyoto, Japan, SD-5, 1976; see also Ph.D. Theses, Harvard University, E. Vieira, Jr., 1969; R. D. Sitrin, 1972; J. Upeslācis, 1975.
(33) S. Hanessian and A. G. Pernet, *Adv. Carbohydr. Chem. Biochem.*, **33**, 111 (1976).
(34) "Nucleoside Antibiotics", R. J. Suhadolnik, Wiley-Interscience, New York, 1970; G. Doyle and C. C. Cheng, *Prog. Med. Chem.*, **13**, 304 (1976).
(35) R. C. Hockett, H. G. Fletcher, Jr., E. L. Sheffield, R. M. Goepp, Jr., and S. Soltzberg, *J. Am. Chem. Soc.*, **68**, 927 (1946); P. Brigl and H. Gruner, *Ber.*, **66**, 1945 (1933); **67**, 1582 (1934).
(36) S. Hanessian and A. G. Pernet, *Can. J. Chem.*, **52**, 1266, 1280 (1974); *Chem. Commun.*, 755 (1971); A. G. Pernet, T. Ogawa, and S. Hanessian, *Tetrahedron Lett.*, 3547 (1974); A. G. Pernet, Ph.D. Thesis, University of Montreal, 1973.
(37) T. Ogawa, A. G. Pernet, and S. Hanessian, *Tetrahedron Lett.*, 3543 (1974).
(38) S. Hanessian, T. Ogawa, and Y. Guindon, *Carbohydr. Res.*, **38**, C12 (1974).
(39) H. Ohrui, G. H. Jones, J. G. Moffatt, M. L. Maddox, A. T. Christensen, and S. K. Byram, *J. Am. Chem. Soc.*, **97**, 4602 (1975); see also H. Ohrui and S. Emoto, *J. Org. Chem.*, **42**, 1951 (1977); F. G. De Las Heras, C. K. Chu, S. Y. K. Tam, T. S. Klein, K. A. Watanabe, and J. J. Fox, *J. Heterocycl. Chem.*, **13**, 175 (1976), and previous references; T. J. Cousineau and J. A. Secrist III, *J. Carbohydr. Nucleosides, Nucleotides*, **3**, 185 (1976).

Scheme IV




Scheme V




in which *C*-ribofuranosyl acetic acid derivatives are produced[40] have also been reported. The functionalized *C*-glycosides, and related ones prepared by other methods,[41] constitute valuable starting materials not only for the preparation of *C*-nucleosides but also for a variety of substituted tetrahydrofurans, and tetrahydropyrans with predetermined centers of chirality.[11-15] Several years ago, we initiated a program aimed at the synthesis of 11-oxaprostaglandins from chiral precursors.[11,13] Our interest in this class of synthetic compounds was motivated by the close structural resemblance between $PGF_{2}\alpha$ and, for example, its 11-oxa analogue, the premise being that such a functional modification could bring about subtle conformational changes which, in turn, could be reflected at the molecular level. The synthetic plan for 11-oxa-$PGF_{2}\alpha$ called for the utilization of the side-chain in 1,4-anhydro-D-glucitol as the origin of the "C-15" side chain in the intended target and the application of regiospecific and stereocontrolled chain branching at C-3 to introduce the "acid" side chain. The *O*-(*tert*-butyldiphenylsilyl) protecting group[42] played an important role in this synthesis, since it provided the selectivity, compatibility, and possibly the steric environment needed in subsequent transformations. Elaboration of the PG side chains was effected in the normal way to give the 15*R* and -*S* epimers of 11-oxa-$PGF_{2}\alpha$ in good overall yield (Scheme IV). The chiral oxa analogue of the well-known Corey aldehyde[43] was also readily available by this route. The 11-oxa-$PGF_{2}\beta$ analogue was prepared from the same readily available starting material, utilizing a different C–C bond forming reaction, involving a stereocontrolled but nonregiospecific opening of an epoxide with diethyl sodiomalonate.[13] Since procedures are available for the replacement of the oxygen atom in a sugar ring by other heteroatoms,[44] the approach described here could be potentially applicable to the chiral synthesis of aza-, thia- and related prostaglandins. Several ring-oxygenated products have been isolated during studies on the biosynthesis of prostaglandins from arachidonic acid.[45] Among these are oxaprostanoids which can be regarded as derivatives of chiral $\alpha,\alpha$-disubstituted tetrahydrofurans[46] and tetrahydropyrans.[47] Access to the former class of compounds has been possible[15] based on the chemical modification of 2,5-anhydro-D-mannitol.

Endoperoxide intermediates arising from arachidonic acids can, under certain conditions, produce significant amounts of a biologically important substance called thromboxane $A_2$ ($TXA_2$),[48] which in turn is transformed into thromboxane $B_2$ ($TXB_2$) (Scheme V). From a synthetic point of view, these intriguing substances can be regarded as 2,4,6-trideoxy-D-*ribo*-hexoses in which positions 4 and 6 are the sites of C-branching and chain extension, respectively. Our synthesis of thromboxane $B_2$[14] consisted in the systematic and stereospecific introduction of substituents using the chiral framework of a 2-deoxy sugar derivative which is readily available from D-glucose. Stereospecific chain branching at C-4 of the sugar derivative was achieved via a Wittig–Horner reaction to introduce the intended acetic acid side chain, followed by catalytic hydrogenation, which was predictably stereospecific, no doubt because of the favorable steric environment provided by the $\beta$ side of the molecule. Our chiral route to thromboxane $B_2$ is also ideally suited for the preparation of analogues from common intermediates. Thromboxane $B_2$ has also been synthesized from prostanoid precursors[49] and directly.[50] Noteworthy among other syntheses is the Corey chiral approach,[51] which utilizes a Claisen rearrangement for transfering chirality from O to C in a sugar derivative and leads to a chiral *cis*-lactone precursor to thromboxane $B_2$.

(40) See, for example, J. G. Buchanan, A. R. Edgar, M. J. Power, and P. D. Theaker, *Carbohydr. Res.*, **38**, C22 (1974); S. De Bernardo and M. Weigele, *J. Org. Chem.*, **42**, 109 (1977).

(41) For some recent examples, see Y. Takamoto, H. Omi, T. Matsizaki, and R. Sudoh, *Carbohydr. Res.*, **60**, 97 (1978); G. Just and M. Lim, *Can. J. Chem.*, **55**, 2993 (1977); J. G. Buchanan, A. D. Dunn, A. R. Edgar, R. J. Hutchinson, M. J. Power, and G. C. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1786 (1977); C. Chang and T. L. Hullar, *Carbohydr. Res.*, **54**, 217 (1977).

(42) S. Hanessian and P. Lavallée, *Can. J. Chem.*, **53**, 2975 (1975).

(43) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Am. Chem. Soc.*, **91**, 5675 (1969).

(44) For reviews, see H. Paulsen and K. Todt, *Adv. Carbohydr. Chem. Biochem.*, **23**, 116 (1968); see also H. El Khadem, *Adv. Carbohydr. Chem. Biochem.*, **25**, 351 (1970).

(45) For recent reviews, see K. H. Gibson, *Chem. Soc. Rev.*, **6**, 489 (1977); K. C. Nicolaou, G. P. Gasic, and W. E. Burnette, *Angew. Chem., Int. Ed. Engl.*, **17**, 293 (1978).

(46) C. Pace-Asciak, *Biochemistry*, **10**, 3664 (1971).

(47) C. Pace-Asciak and L. S. Wolfe, *Chem. Commun.*, 1235 (1970).

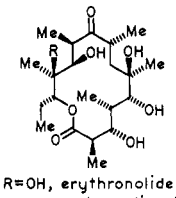
(48) M. Hamberg, J. Svensson, and B. Samuelson, *Proc. Natl. Acad. Sci. U.S.A.*, **72**, 2994 (1975); see also *Science*, **190**, 770 (1975).

(49) N. A. Nelson and R. W. Jackson, *Tetrahedron Lett.*, 3275 (1976); R. C. Kelly, J. Schletter, and S. I. Stein, *Tetrahedron Lett.*, 3279 (1976); W. P. Schneider and R. A. Morge, *ibid.*, 3283 (1976).

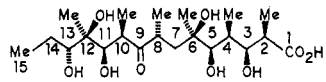
(50) E. J. Corey, M. Shibasaki, J. Knolle, and T. Sugahara, *Tetrahedron Lett.*, 785 (1977).

(51) E. J. Corey, M. Shibasaki, and J. Knolle, *Tetrahedron Lett.*, 1625 (1977); see also, H. Ohrui and S. Emoto, *Agric. Biol. Chem.* 41, 1773, (1977); O. Hernandez, *Tetrahedron Lett.*, 219 (1978).

Scheme VI

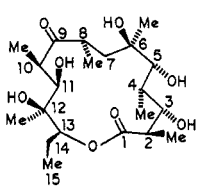


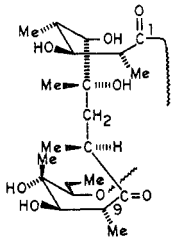
R=OH, erythronolide A
=H, erythronolide B

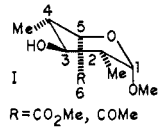


erythronolide A seco-acid

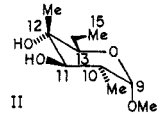
Scheme VII







R=$CO_2$Me, COMe



## Construction of the Chiral Carbon Framework of "Polyoxo" Macrolides and Terpenoids

The constitutional structures and intriguing conformational features of the "polyoxo" macrolide antibiotics have been the subject of elegant studies over the years.[52] Their chemistry has been recently highlighted by the development of ingenious macrolactonization methods[53] and the total synthesis of methymycin[54] and of erythronolide B,[55] which are 12- and 14-membered "polyoxo" macrolides, respectively. These landmark achievements, as well as other important contributions in macrolide chemistry,[52] have been largely responsible for a renewed interest in this general area. It is evident that the multichiral nature of these compounds looms as a major threat to any synthetic approach. The complexity of the problem can be appreciated with an examination of the molecular structure of erythronolide A, for example; it contains 10 asymmetric centers comprising a number of alternating *C*-methyl and hydroxyl groups (Scheme VI). One could, for example, envisage the construction of the corresponding seco acid, by a series of aldol-type condensations, provided that a high degree of regio- and stereocontrol can be achieved in each reaction. Ireland[56] and Heathcock[57] and their respective groups have, in fact, recently reported on their studies in this direction. In a conceptually different approach, Woodward and coworkers[58] have ingeniously shown how a dithiadecalin ring system can be used as a framework for the systematic introduction of the functional groups present in segments of the seco acid. We have viewed the hidden symmetry in macrolide aglycons in another perspective which is the basis of yet a different synthetic approach.[23,59-61] Thus, inspection of the open-chain Celmer model[62] and the hypothetical "folded" model[23] of erythronolide A reveals two six-carbon segments, C-1–C-6 and C-9–C-15, which can be related to two sugar derivatives, precursors I and II, respectively (Scheme VII). The following features are particularly noteworthy in these structures: (a) the absolute configuration and pertinent functionality at C-2, C-3 of each precursor is the same and corresponds to C-2, C-3 and C-10, C-11 of the intended target; (b) the anomeric carbon atoms of I and II correspond to C-1 and C-9 of the target; (c) the ring oxygen atoms in I and II correspond to the C-5 and C-13 hydroxyl groups and they are temporarily protected; (d) the two precursors comprise eight of the ten chiral centers present in erythronolide A. The synthetic strategy for the construction of the macrolide framework consisted therefore in generating two such precursors and exploring methods for their homologation and eventual union through C-6 of precursor I (R = $CO_2$Me or COMe) and C-1 of precursor II. The problem of regio- and stereospecific control in creating the eight chiral centers in I and II was resolved by asymmetrically modifying the readily available methyl α-D-glucopyranoside, based on the notion of "chiral templates". Thus regio- and stereocontrol was achieved in the systematic introduction of functionality at C-2–C-3 and C-2–C-4, as required for precursors I and II, respectively, because of a predictable *conformational bias* provided by the carbohydrate framework.[23,59] Control over the stereochemistry at C-4, C-5 (L sugar!) in precursor I was secured by the original choice of an α orientation of the aglycon, which provides the desired *anomeric stereoselection* in a subsequent step involving stereospecific reduction of an endocyclic double bond. These operations which led to preparatively important quantities of I and II are illustrated in Scheme VIII, and it is particularly interesting that except for C-1 each carbon atom in D-glucose has undergone at least one inversion in the process of converting it into the above-mentioned precursors. The joining of the two precursors through C-6 of I and C-1 of II presented a unique challenge because of the dearth of precedents for C–C bond-forming reactions with such highly functionalized substances. After a number of model studies[23,60] it was found that the phosphonate modification of the Wittig reaction could be admirably adapted to our substrates. The structures of the precursors were such that either one could be converted to a nucleophilic (β-ketophosphonate) or electrophilic (carbonyl) component. In one approach, precursor I was homologated via standard transformations taking advantage of a favorable coordination[63] of the reagent with the ring oxygen to produce a preponderance (6:1) of the desired terminal aldehyde derivative which could be successfully condensed with model β-ketophos-

(52) For recent reviews, see S. Masamune, G. Bates, and J. W. Corcoran, *Angew. Chem., Int. Ed. Engl.*, **16**, 585 (1977); K. C. Nicolaou, *Tetrahedron*, **33**, 683, (1977); T. G. Back, *ibid.*, 33, 3041 (1977).

(53) E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.*, **96**, 5614 (1974); S. Masamune, S. Kamata, and W. Schilling, *ibid.*, **97**, 3515 (1975); E. J. Corey, D. Brunelle, and P. J. Stork, *Tetrahedron Lett.*, 3405 (1976); see also K. Narasaka, K. Murayama, and T. Mukaiyama, *Chem. Lett.*, 885 (1978).

(54) S. Masamune, H. Yamamoto, S. Kamata, and A. Fukugawa, *J. Am. Chem. Soc.*, **97**, 3513 (1975).

(55) E. J. Corey, S. Kim, S. Yoo, K. C. Nicolaou, L. S. Melvin, Jr., D. J. Brunelle, J. R. Falck, E. J. Trybulski, R. Lett, and P. W. Sheldrake, *J. Am. Chem. Soc.*, **100**, 4620 (1978).

(56) R. E. Ireland and C. S. Wilcox, *Tetrahedron Lett.*, 2839 (1977).

(57) C. T. Buse and C. H. Heathcock, *J. Am. Chem. Soc.*, **99**, 8109 (1977).

(58) R. B. Woodward, 25th National Organic Symposium, Morgantown, W.Va., June 19–23, 1977.

(59) S. Hanessian and G. Rancourt, *Can. J. Chem.*, **55**, 1111 (1977).

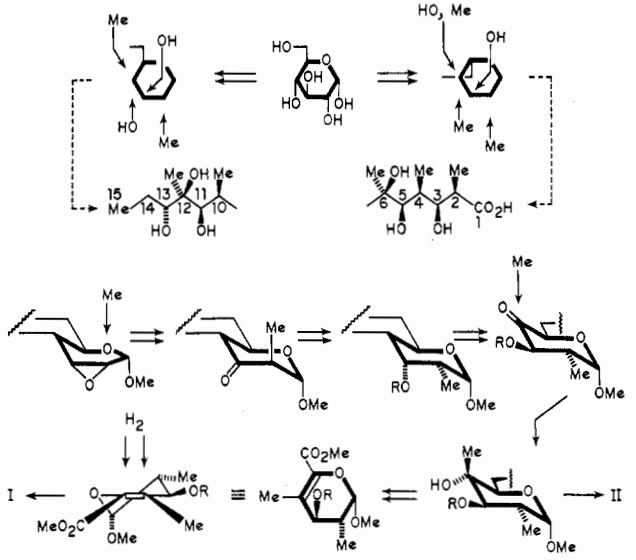
(60) S. Hanessian, G. Rancourt, and Y. Guindon, *Can. J. Chem.*, **56**, 1843 (1978); S. Hanessian and Y. Guindon, unpublished results.

(61) The prospects of using carbohydrate precursors for the synthesis of macrolide aglycons has been alluded to in the literature, but details of the overall strategy are unavailable. Studies directed toward chain-branching reactions in the D-glucose series were reported while our work was in progress; see M. Miljkovic and D. Glisin, *J. Org. Chem.*, **40**, 3357 (1975).

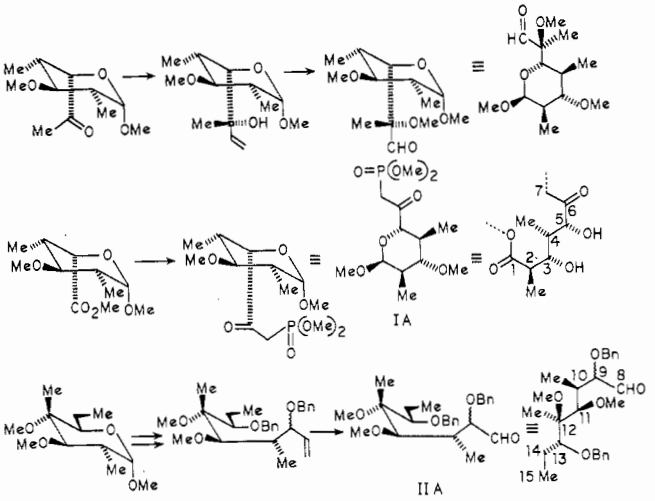
(62) W. D. Celmer, *Pure Appl. Chem.*, 28, 413 (1971).

(63) T. D. Inch, *Carbohydr. Res.*, **5**, 45 (1967); see also M. L. Wolfrom and S. Hanessian, *J. Org. Chem.*, **27**, 1800 (1962).

**Scheme VIII**

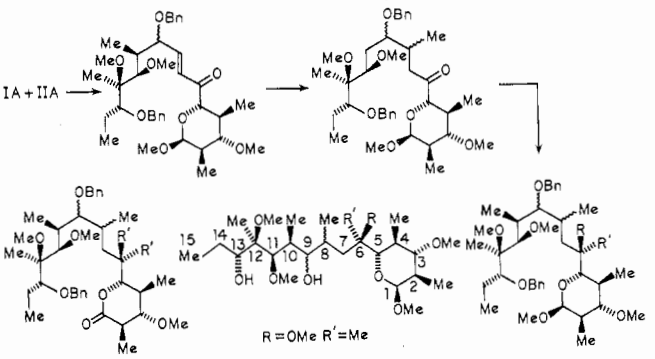


**Scheme IX**

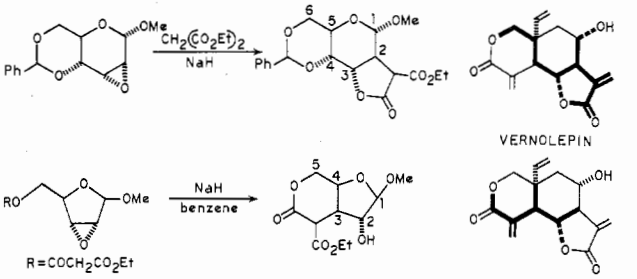


phonates simulating precursor II. In an alternate approach,[60] the synthetic capabilities of precursors I and II were reversed. Thus, each was homologated to produce nucleophilic and electrophilic counterparts IA and IIA corresponding respectively to C-1–C-7 and C-8–C-15 of the target (Scheme IX). Condensation of IA and IIA led to a mixture of the chromatographically discernible epimeric enones, which underwent 1,4-conjugate addition with lithium dimethylcuprate to introduce the methyl group at C-8. That the L-*ido* stereochemistry was still intact in these compounds as would be required for C-2–C-5 of the target compound was ascertained by spectroscopic and chemical studies. Thus treatment of the enone with base (NaOMe, MeOH) resulted in virtually complete epimerization at C-5, leading to the thermodynamically more stable D-*gluco* isomer. The last step in the functionalization of the ketone derivative consisted in the introduction of the tertiary center at C-6, which was done with methyllithium. Conversion of the glycoside derivative to the cyclic hemiacetal and to the corresponding lactone followed established methodology (Scheme X). The stereochemical purity at C-9 and C-8 is unimportant at this stage since the former is the site of the carbonyl group in erythronolide A and the latter can be epimerized to give the desired configuration. Only

**Scheme X**



**Scheme XI**



the stereochemistry at C-6 is the cause of some uncertainty; however, since the tertiary center at C-6 is the last to be introduced, it is possible to study the stereochemical aspects of this reaction under a variety of conditions with no loss of chiral efficiency at other centers. Thus, based on the notion of "chiral templates" derived from carbohydrates, it has been possible to assemble the entire carbon skeletal framework of erythronolide A and its 9-dihydro derivative in the form of an isomeric 1,5-lactone structure. All the hydroxyl and methyl groups have been introduced regiospecifically, and the absolute configuration of at least eight chiral centers has been secured. Although the hydroxyl groups in the above intermediates have been protected as *O*-methyl ethers, it is possible to prepare precursors I and II in their *O*-demethyl forms,[60] thus offering other options for temporary protection in synthetic schemes analogous to the one presented here.

It is evident from these studies that the easy access to unusual branched-chain sugars[64] could, in principle, be of potential utility in the synthesis of chiral tetrahydrofuran and tetrahydropyran rings such as in some ionophores and terpenoids. In a program concerned with C–C bond-forming reactions of the types discussed above,[65] it was found that regio- and stereospecific, inter- and intramolecular ring opening of readily available carbohydrate epoxides could be achieved with malonic esters, giving highly functionalized lactone derivatives[66,67] (Scheme XI). If these structures are

(64) For examples in antibiotics, see H. Grisebach and R. Schmid, *Angew. Chem., Int. Ed. Engl.*, 11, 159 (1972); see also S. Hanessian and T. H. Haskell, in "The Carbohydrates", Vol. IIA, Academic Press, New York, 1970, p 139; J. S. Brimacombe, *Angew. Chem., Int. Ed. Engl.*, 10, 236 (1971).

(65) H. Paulsen, and W. Koebernick, *Carbohydr. Res.*, **56**, 53 (1977), and references cited therein; A. M. Sepulchre, G. Lukacs, G. Vass, and S. D. Gero, *Bull. Soc. Chim. Fr.*, 4000 (1972); T. D. Inch and G. J. Lewis, *Carbohydr. Res.*, **15**, 1 (1970).

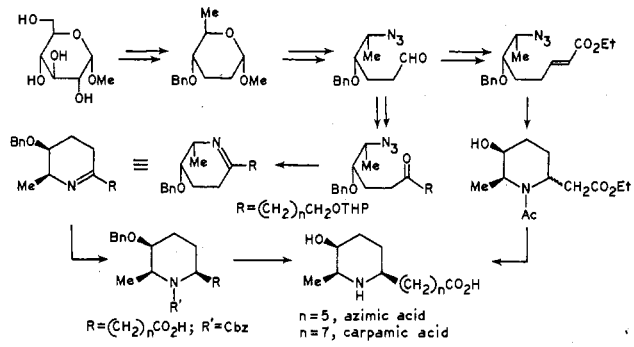
(66) S. Hanessian and P. Dextraze, *Can. J. Chem.*, **50**, 226 (1972); *Chem. Ind. (London)*, 958 (1971); P. Dextraze, Ph.D. Thesis, University of Montreal, 1973.

viewed in a different perspective, there emerge some remarkable structural and functional similarities with the sesquiterpene antitumor compound vernolepin[68] where it can be seen that significant chiral and functional overlap has been attained. In this regard, the concept of "chiral templates" presents definite operational and practical advantages as an approach to the synthesis of a vernolepin-like structure, particularly since the crucial C–C bonds required to construct the remaining rings and the necessary carbon appendages could, in principle, be generated from already existing functionality.

## Chiral Nitrogen Heterocycles from Carbohydrates

Well over a decade ago, a new class of sugar derivative in which the ring oxygen atom was replaced by nitrogen was discovered. Concurrent with the first announced synthesis of 5-acetamido-5-deoxy-α-D-xylopyranose,[69] its enantiomer was isolated from the degradation of paromose, the diamino sugar in the antibiotic paromomycin.[70] Other syntheses of sugars containing nitrogen and sulfur in the ring have appeared since then.[44] In connection with these studies, it was found that upon hydrogenation ω-azidodeoxypentoses gave the corresponding trihydroxypiperidines.[71] This in fact proved to be a general reaction, and a number of chiral and asymmetrically substituted hydroxypiperidines could be prepared from appropriate azido sugars. Likewise, reduction of ω-azido aldonolactones led to ring expansion to give the corresponding polyhydroxy lactams.[72] In this context, Moffatt and co-workers[27] have recently disclosed a synthesis of the antibiotic anisomycin by a route which called for an intramolecular formation of a chiral pyrrolidine ring from an amino sugar derivative. Work in our laboratory has shown that the chiral piperidine ring of macrodilactone alkaloids such as carpaine[73] and azimine,[74] as well as of other piperidine alkaloids such as cassine,[75] can be constructed from carbohydrate precursors.[28] In one of the synthetic routes employed, D-glucose was asymmetrically modified to give an aldehyde precursor which in a model reaction was chain-extended via a Wittig reaction. Reduction of the azide function led to an intramolecular addition reaction and the formation of the 2,3,6-trisubstituted piperidine structure, presumably as a mixture of two isomers at C-6. The chirality of the carbon atoms bearing the methyl and hydroxyl groups corresponds to those in carpamic and azimic acids. Another approach was based on the reductive cyclization[71] of the azido ketone derived from the same

**Scheme XII**




aldehyde derivative by sequential chain extension and oxidation (Scheme XII). Catalytic reduction of the azido ketone derivative led to a α-*cis*-piperidine derivative which was transformed into (+)-azimic acid. The notion of "chiral templates" derived from branched-chain amino sugar derivatives could therefore be applicable to the construction of more elaborate alkaloidal structures, containing a chiral piperidine or pyrrolidine ring as well as their bicyclic variants, and it offers a novel entry into this class of compounds.

## Conclusion

In the preceding pages of this Account, I have attempted to show a different strategy in synthetic design for organic natural products based on our own experiences and those of others. As one can be seen from Schemes II and III, chiral synthesis with carbohydrates does not boast many examples as yet; it is, however, rapidly gaining momentum, and the coming years will witness competitive and highly efficient synthetic approaches to a wide variety of complex, noncarbohydrate substances based on the notion of "chiral templates". "Polyoxo" macrolide aglycons, other multifunctional macrocyclic compounds such as the maytansins and ansa antibiotics, ionophores,[76,77] alkaloids, and terpenes are but a few challenging synthetic targets whose conquests may be greatly aided by considering carbohydrate derivatives as sources of their chiral, polyfunctional segments. *In this regard, our synthetic approach to erythronolide A clearly shows that the chiral carbon atom framework of a large number of organic natural products that are biosynthetically derived from propionate, butyrate, and related patways can, in principle, be constructed from carbohydrate precursors.* It is also clear that the approach could be useful in the construction of acyclic carbon chains containing multiple chiral centers, as it offers a practical alternative to the operationally different aldol condensation,[56,57,77] and other procedures relying on the stereocontrolled generation of cyclic intermediates.[78]

*It is a pleasure to acknowledge the invaluable efforts of a number of my collaborators, past and present, who have been part of the "chiral team" and whose names are cited in the references. The financial support of the National Research Council of Canada and le Ministère de l'Education du Québec is gratefully acknowledged.*

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(68) For some recent elegant syntheses, see G. R. Kieczykowski and R. H. Schlessinger, *J. Am. Chem. Soc.*, **100**, 1978 (1978); M. Isobe, H. Iio, T. Kanai, and T. Goto, *ibid.*, **100**, 1940 (1978); S. Danishefsky, P. F. Schada, T. Kitahara, and S. J. Etheredge, *J. Am. Chem. Soc.*, **99**, 6066 (1977); for the first total synthesis, see P. A. Grieco, N. Nishizawa, S. D. Burke, and N. Maronovic, *J. Am. Chem. Soc.*, **98**, 1612 (1976).

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(71) S. Hanessian, *Chem. Ind. (London)*, 2126 (1966).

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(73) J. L. Coke and W. Y. Rice, Jr., *J. Org. Chem.*, **30**, 3420 (1965).

(74) T. M. Smalberger, G. J. H. Rall, H. L. de Waal, and R. R. Arndt, *Tetrahedron*, **24**, 6417 (1968); for a synthesis of (±)-azimic acid, see E. Brown and R. Dhal, *Tetrahedron Lett.*, 1032 (1974).

(75) W. Y. Rice, Jr., and J. L. Coke, *J. Org. Chem.*, **31**, 1010 (1966); for a synthesis of (±)-cassine, see E. Brown and A. Bonte, *Tetrahedron Lett.*, 2881 (1975).

(76) For an elegant synthesis of the ionophore lasalocid A, see T. Nakata, G. Schmid, B. Vranesic, M. Okizawa, T. Smith-Palmer, and Y. Kishi, *J. Am. Chem. Soc.*, **100**, 2933 (1978).

(77) T. Fukuyama, K. Akasaka, D. S. Karanewsky, C.-L. Wang, G. Schmid, and Y. Kishi, *J. Am. Chem. Soc.*, **101**, 262 (1979).

(78) See, for example, P. A. Bartlett and J. Myerson, *J. Am. Chem. Soc.*, **100**, 2933 (1978); J. D. White and Y. Fukuyama, *ibid.*, **101**, 226 (1979).