

The synthesis of polyoxygenated natural products via fully synthetic branched pyranose derivatives: application to the erythronolide problem

David C. Myles and Samuel J. Danishefsky

Department of Chemistry, Yale University, New Haven, Connecticut 06511 U.S.A.

Abstract - Reiterative cyclocondensation reactions and highly stereoselective functionalization reactions have been coordinated to reach a derivatized version (5b) of the seco acid of 6-deoxyerythronolide B (1).

BACKGROUND

In 1983 our laboratory began to explore some new possibilities for synthesizing extensively oxygenated natural products with a particular focus on polypropionates and polyols (ref. 1). The polypropionate pattern is readily identified in the backbone functionality of the macrolide aglycones (ref. 2). This pattern is also encountered, though in a less regular fashion, in various ionophores bearing pyranoid and furanoid substructures (ref. 3). The polyol functionality is widely encountered in carbohydrates. While the most common of the polyol arrangements are found in the pentoses and hexoses, we have been particularly concerned with the longer ensembles found in the complex higher order monosaccharides (ref. 4).

The "carbohydrate-connection" in our synthesis of polypropionates is only slightly less obvious than is its involvement in our higher order monosaccharide efforts. Indeed, we treat the polypropionate targets in the context of more general issues in the synthesis of C-alkylated sugars. Our emphasis is on elaborating, by total synthesis, branched pyranose rings. For long chain polypropionate ensembles, the pyranose rings are disconnected at the O-C₁ (anomeric carbon) bond. *An aldehyde function, fashioned from C₁, becomes the device for chain elongation.*

In the case of the complex monosaccharides again an aldehyde is employed for major extension. In these cases the aldehyde projects from the pyranose or furanose matrix (either with or without an intervening spacer). The strategies for these two synthetic goals are summarized in Fig. 1. In this lecture we will describe our progress in using this type of generalized protocol toward the synthesis of 6-deoxyerythronolide B (1) (ref. 5).

As matters transpired, we focused on the tetra-protected seco ester 5b corresponding in its array of relative stereogenic centers to macrolide 1. The identification of this particular compound as a target was not based on any prior knowledge that it would be an ideal or even workable substrate for lactonization (ref. 6). Our objective was to demonstrate the feasibility of our strategy for dealing with the eleven stereogenic centers contained in this macrolide system. Presumably the synthesis could be modified toward products with other protective arrangements which might be more suitable for macrolactonization.

During our efforts it was found that the series of compounds 3-5 could be prepared from the natural product itself. Reduction of 6-deoxyerythronolide B (1) with sodium borohydride in the presence of alumina afforded the crystalline dihydro compound 2.

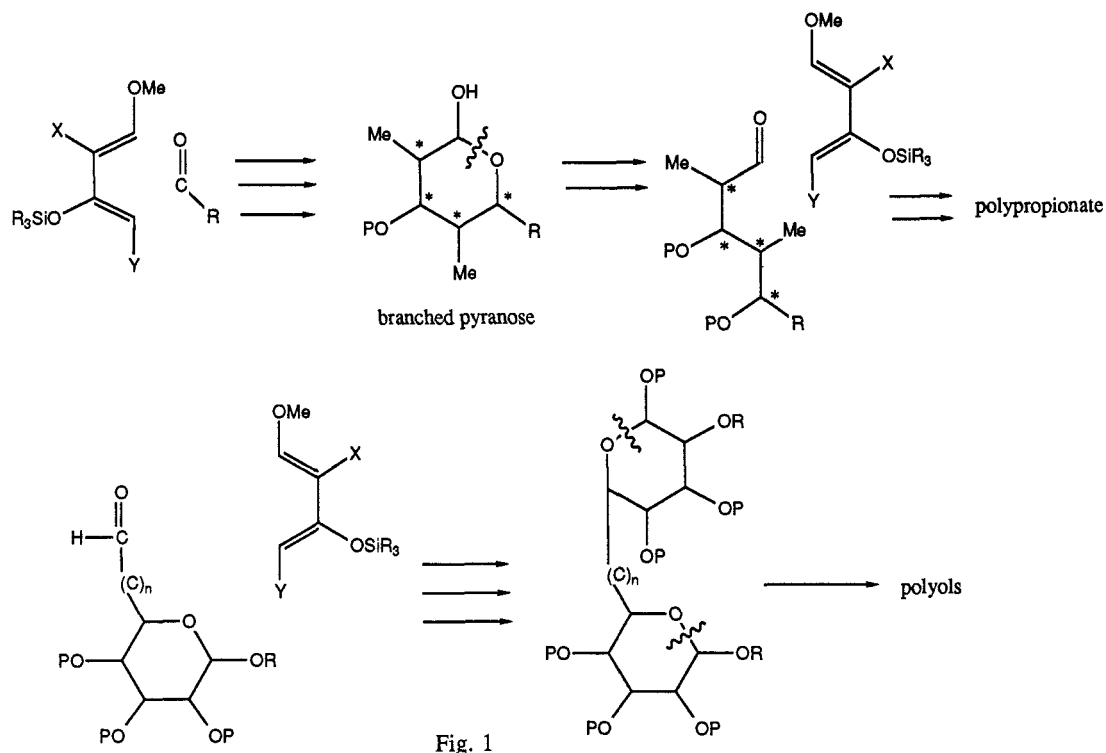


Fig. 1

The configuration at C_9 was proven by a single crystal X-ray determination (ref. 7). Tetra-benzylation was achieved, though with some difficulty, through the reaction of **2a** with benzyltrichloroacetimidate. Reduction of **2b** with lithium aluminumhydride (LAH) gave diol **3**. Selective oxidation of the primary alcohol by the method of Nozaki (ref. 8) afforded **4** which upon Lingren oxidation (ref. 9) gave **5a**. Esterification with diazomethane led to the easily characterizable **5b**.

In this investigation it was our intention to use a single stereogenic center to dictate in a serial fashion the required configurations at the ten new centers required in the seco ester, **5b**. Elsewhere (ref. 1) we have described this type of approach as being one of "stereochemical communication" and have distinguished it from that of "stereochemical correlation" where suitably matched chiral subunits are merged. Since at no stage would we be linking chiral fragments, we could carry out our explorations with racemic materials. The lessons learned in creating, manipulating, and disconnecting these branched pyranose ensembles, in the racemic series, could be confidently transmitted to enantiomerically homogeneous substances.

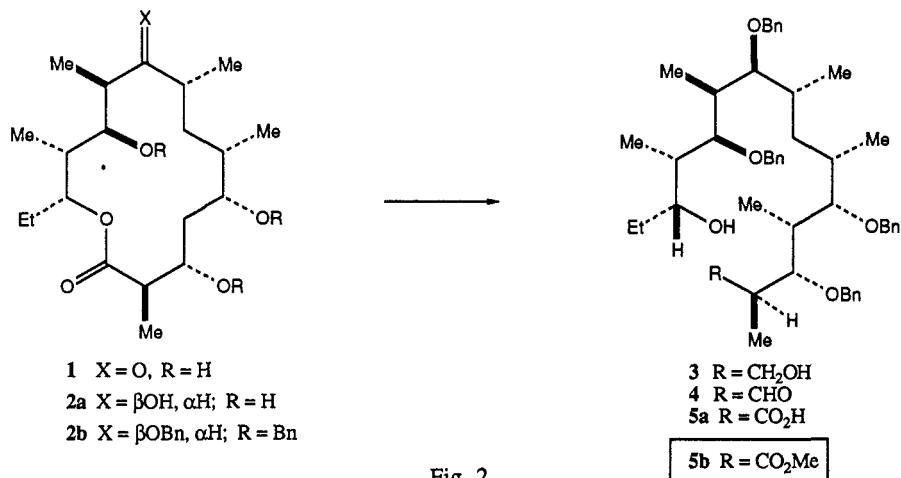


Fig. 2

DISCUSSION OF RESULTS

Construction and disconnection of the 'first' pyranose

In Fig. 3 we begin describing the process by which the branched pyranose concept was used. Formaldehyde (which was envisioned to become C₁ of the seco ester **5b**) underwent cyclocondensation with diene **6** in the presence of zinc chloride-THF, to produce racemic dihydropyrone **7** in 70-78% yield. *It was the configuration at C₂ (arbitrarily drawn) which would dictate the rest of the stereochemistry.* Treatment of **7** with sodium borohydride/CeCl₃·7H₂O followed by solvolysis of the resulting carbinol (glycal) with methanol/p-TsOH (ref. 10) afforded the ene-pyranoside **8** (83-88%). Given the absence of a conformationally defining substituent at C₅, it is not surprising that the methyl glycoside emerged as an anomeric mixture. From previous studies in the zincophorin area we had come to learn that very high margins of stereoselectivity were available through hydroboration of such systems, and that the facial sense of the hydroboration would be *anti* to the C₄-methyl group (ref. 11). Indeed, reaction of **8** with borane-DMS followed by oxidation with hydrogen peroxide gave alcohol **9** as substantially the only product (78-85%). The pyranose ring was now opened through the action of 1,3-propanedithiol in the presence of titanium tetrachloride. A unique blocking group, the *t*-butyldiphenylsilyl function, was appended selectively on the primary alcohol. The secondary alcohol was then protected as its benzyl ether (see compound **10**, 76-81% from **9**). The stage was now set for exposure of the "second" aldehyde. This was accomplished by treatment of **10** with *N*-bromosuccinimide in aqueous acetone. Aldehyde **11** was thus in hand. With the stereogenic centers at carbons 2, 3, and 4 properly mounted, our attentions were directed to the next elongation cycle.

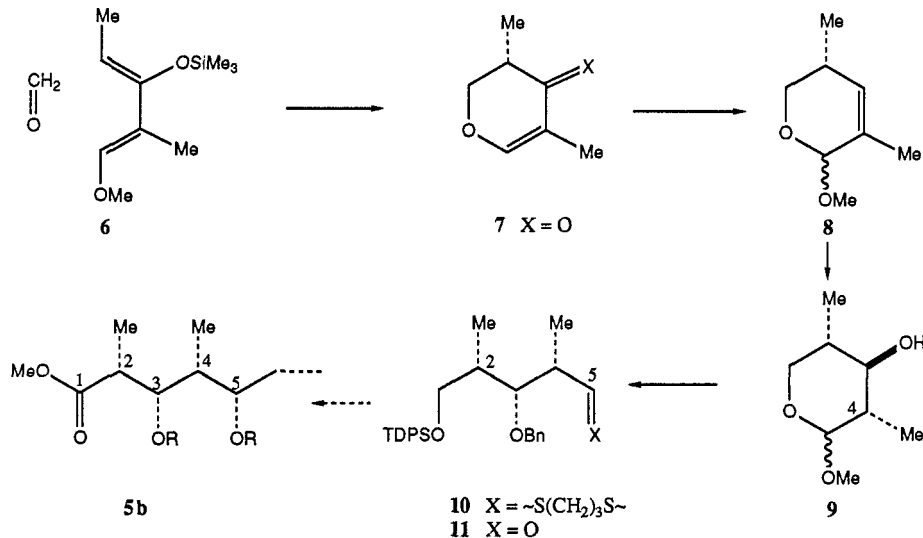


Fig. 3

The problem of the intervening methylene group at C₇

Our focus turned to carbons 5, 6, and 8 of our target. The results are summarized in Fig. 4. Cyclocondensation of aldehyde **11** was carried out with diene **6**, this time under mediation by BF₃-etherate, in methylene chloride at -78° C. Following this reaction, the crude extract was treated with pyridinium *p*-toluenesulfonate (PPTS) in benzene, affording, after chromatography, dihydropyrone **12** as the major product (51-60% from **10**).

Elsewhere (ref. 1) we have formulated a set of stereochemical descriptor terms for dealing with the diastereofacial issues of the cyclocondensation reaction. As expected with this catalyst, with a β-oxygenated aldehyde substrate, the Cram-Felkin mode of attack (ref. 12, 13, 14) had dominated the facial sense of attack, while *exo* addition (equivalent to a threo aldol reaction) prevailed at the topographic level.

At this juncture we faced the requirement of reduction of the future carbon 7 to the CH_2 level with introduction of the desired stereochemistry at the carbon destined to become C_8 . Analysis of the stereochemistry required at C_8 in **5b**, in the context of the pyranoside matrix which we have constructed, reveals that the methyl group must emerge equatorial, analogous to the future C_4 -methyl group in the previously encountered **9**. *In this case the requirements at both C_7 and C_8 might be served simultaneously by catalytic hydrogenation of a C_7 - C_8 double bond.* To direct hydrogenation in the α -sense, we would install a large axial (β) glycosidic alkoxy group at the future C_9 (ref. 15). In practice, reduction of **12** with sodium borohydride- $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ afforded **13**, bearing an equatorial alcohol at C_7 . Another Ferrier rearrangement (ref. 10), this time using isopropanol as the solvent/nucleophile, afforded cleanly the axial branched pyranose glycoside **14** (87-92% from **12**). Indeed, catalytic hydrogenation $\text{H}_2/\text{PdAl}_2\text{O}_3$ afforded **15** as substantially the only product (78-81%).

Once again, disconnection of the branched pyranoside was accomplished through the action of 1,3-propanedithiol and titanium tetrachloride on **15**. The alcohol destined to become C_5 was protected as a benzyl ether (70-74% from **16**). The dithiane linkage of **16** was cleaved through the action of NBS in aqueous acetone. Aldehyde **17**, destined to service the next cyclocondensation reaction, was now in hand.

It was not without some apprehensions, at the stereochemical level, that we approached the cyclocondensation of aldehyde **17** with stereogenic centers 9 and 10 as our targets. Needless to say, our primary concern was the diastereofacial outcome of this reaction. Previous studies in the cyclocondensation program with chiral aldehydes had disclosed major opportunities for facial selectivity (ref. 16). However, those investigations were directed to systems with stereogenic centers bearing hetero substituents at the α - or β -carbons of the formyl group. It is such hetero-substituted centers which we had exploited. Since carbon 7 is not oxygenated, we would be confronting a situation

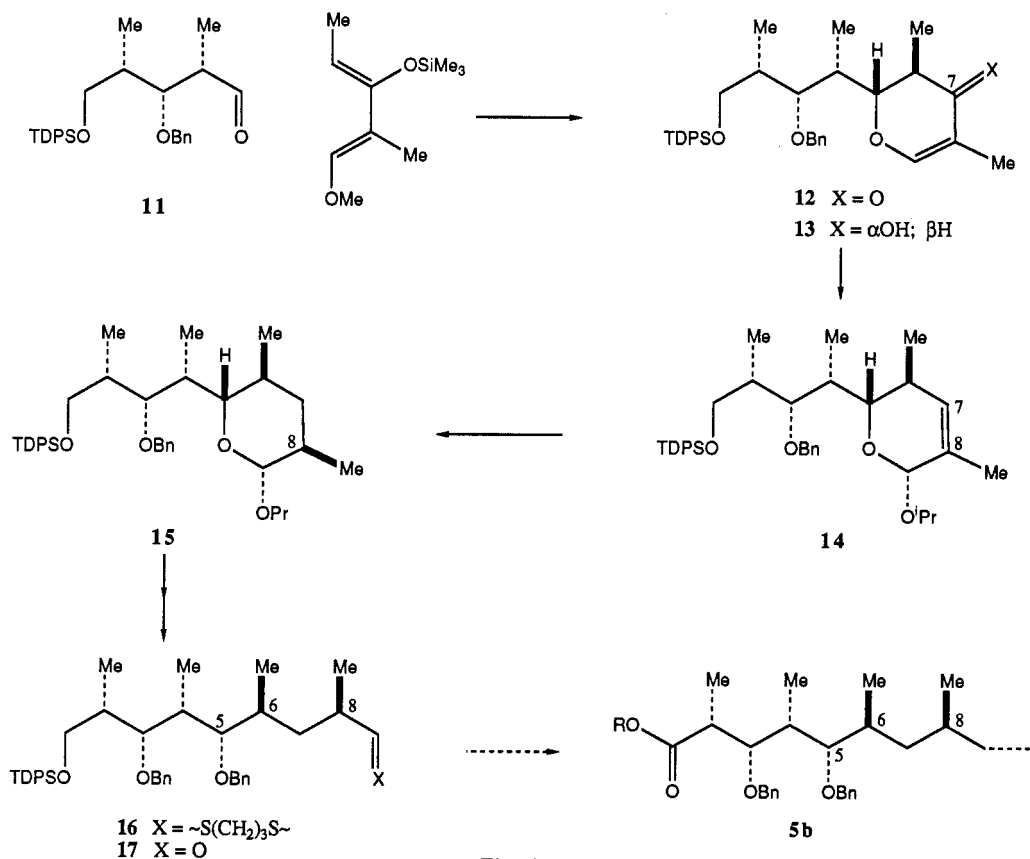


Fig. 4

wherein the closest hetero functionality with obvious potential for conformational or electronic perturbation was δ - to the carbonyl function.

As was the case with aldehyde **12** (see Figure 4), the cyclocondensation of aldehyde **17** was carried out with diene **6** in the presence of BF_3 -etherate at -78°C . We were both pleased and surprised to find the emergence, after treatment with PPTS in benzene, of a predominant dihydropyrone in 72-78% yield from the dithiane. In the light of subsequent findings we now know (*vide infra*) this compound to be the *trans* product corresponding to the formal Cram sense of addition. A second product is a *cis* disubstituted dihydropyrone of undetermined stereochemical connectivity. It is natural to suppose that since the *trans* dihydropyrone (see **18**) was generated specifically in the Cram sense (ref. 1, 12), that the same is true of the *cis* product but at present there is no experimental basis to distinguish between **19** and **20**. Nonetheless, we can already assert the surprising result that the minimum facial selectivity is 6:1 in the classical Cram sense and possibly significantly greater. At the present writing we have not yet sorted out whether this selectivity arises from specific features of aldehyde **17** or is indicative of generally high facial selectivity in Lewis acid catalyzed cyclocondensations reactions of C_2 - C_4 branched alkanals.

The problem of the C_{12} center

It will be noted that to reach the *seco* system **5b** it would be necessary to install an equatorial hydroxyl group at the carbon atom destined to become C_{11} , and an axial methyl group at the future C_{12} . The former goal was easily accomplished by reduction of **18** with sodium borohydride-cerium(III) chloride to afford **21**. A variety of methods were investigated starting with either compound **21** or derivatives of the C_{11} hydroxyl. Among the many approaches that were examined were oxymercuration-demercuration, hydroxyselenation-reduction, and various halohydrin combinations followed by reduction. The overall stereochemical outcome of such reaction sequences either ran counter to our needs or were unacceptably non-selective. It was often unclear whether the difficulties were being encountered in the introduction of the various hetero atoms at C_{12} or in their reductive cleavage (ref. 17).

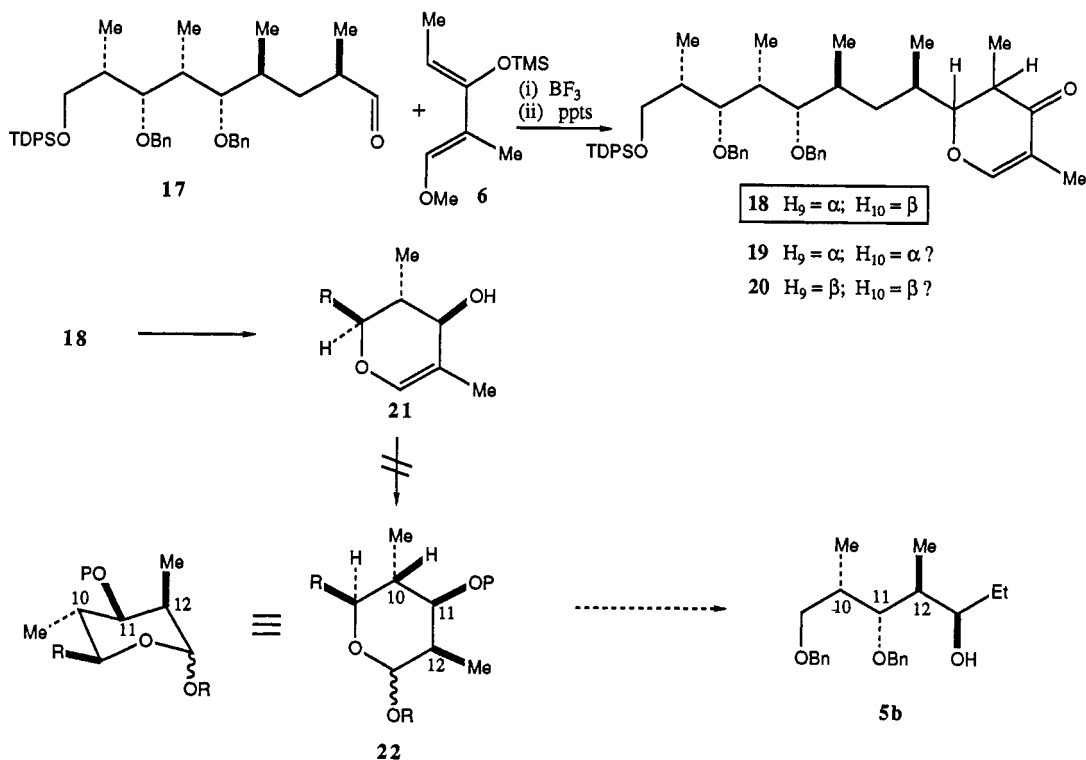


Fig. 5

Of course no *cis* hydroboration-oxidation sequence of starting Ferrier rearrangement product types **23** (readily available from **21**) could provide directly the required C₁₁-methyl C₁₂-hydroxyl relationship. Nonetheless, our goal would have been well served if hydroboration of such pseudo glycols related to **23** would occur from the α - face of the pyranoid ring. In that event, the requisite β (axial) methyl stereochemistry could be secured at C₁₂. Such an outcome could then, in principle, be followed by inversion of configuration of the hydroxyl-bearing carbon at C₁₁ (directly or via oxidation reduction). Unfortunately for our purposes, hydroboration of type **23** model systems occurred primarily from the β - face, presumably under the guidance of the α - disposed C₁₀ methyl group (*vide supra*) (ref. 11). *The lack of capability for installing an axial methyl group at C₁₂ from either 18 or 23 must be seen as a limitation in the scope of our pyranoid matrix protocol.*

Fortunately for the problem at hand, a highly stereoselective, albeit roundabout, solution could be devised starting with **23**, P = H. It had been noted that the NMR spectrum (CDCl₃) of this compound was indicative of the presence of a C₉-hydroxyl-C₁₃ aldehyde tautomer. Not surprisingly, the reduction of **23** with lithium borohydride afforded diol **24** with the presumed *Z*-double bond. Pivaloylation of the primary alcohol benzoylation of the C₉ hydroxyl with benzyltrichloroacetimidate, and deprotection at C₁₃ with lithium aluminum hydride, afforded alcohol **25** (60% yield).

It was now necessary to isomerize the *Z*-double to the *E*-series. This was accomplished by oxidation of **24** with the Dess-Martin periodinane reagent (ref. 18). The *Z*- α,β -unsaturated aldehyde **26** thus produced was isomerized through the action of lithium thiophenoxide to afford the *E*-enal **27**. Finally, reduction of **27** afforded the required *Z*-allylic alcohol **28** (60% from **24**).

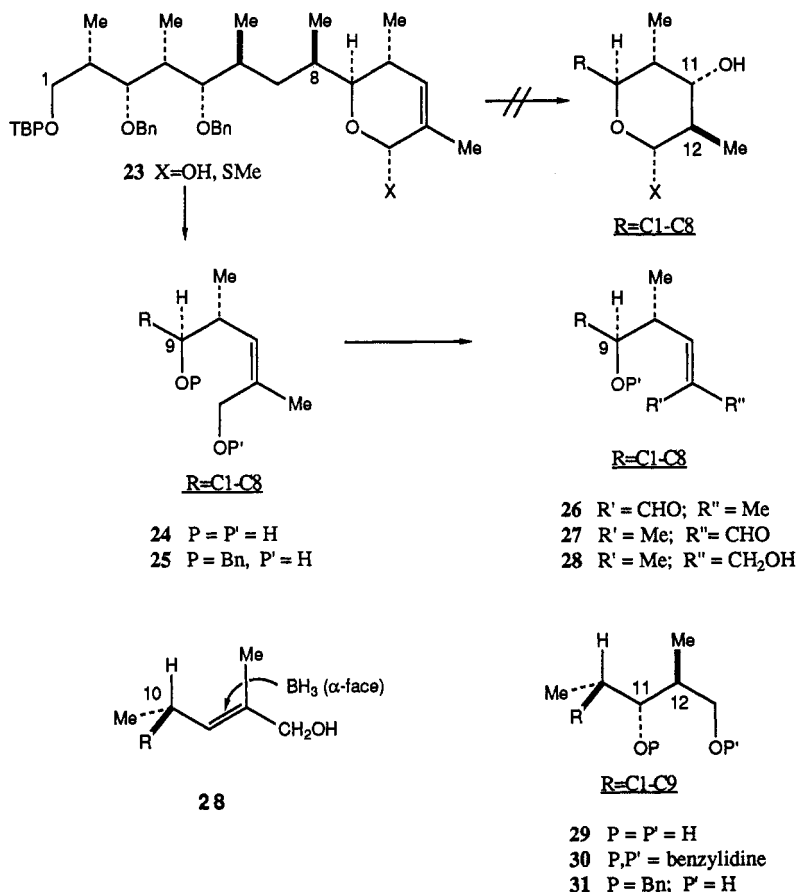


Fig. 6

Precedents from the work of Matsumota and Kishi (ref. 19) suggested the likelihood that reaction of a compound of the type **28** with diborane might occur via the reaction geometry depicted. Hydroboration from the α -face followed by oxidation would indeed provide the required stereochemistry at both carbons 11 and 12. Indeed, this expectation was realized. Reaction of **28** with borane-dimethyl sulfide, followed by oxidation with alkaline hydrogen peroxide, afforded **29** as substantially the only product. The C₁₁ and C₁₃ hydroxyl groups were engaged as the cyclic benzylidene derivative **30**. Selective liberation of the C₁₃-hydroxyl group was accomplished through the action of di-isobutylaluminum hydride on **28** (ref. 20).

Completion of the synthetic goal

Our attentions were now directed toward fashioning the last stereogenic center at carbon 13. Oxidation of **31** with the Dess Martin periodinane (ref. 18) afforded aldehyde **23**. The required relationship of the C₁₂-C₁₄ oxygens would, in principle, be accessible from the chelated conformer **23** (a) with the proviso that the α -disposed R group at C₁₁ would direct attack of the ethyl group to the β -face of the aldehyde. If conformer (a) pertains, the demands of the C₁₁ R group must override those of the methyl group at C₁₂. The same overall outcome could be realized from either a Felkin (b) or Cram (c) type of conformer (ref. 1, 12-14). *Happily, reaction of 32 with ethyl magnesium bromide in THF at -78° C gave 33 as substantially the only isolated product.*

It was now possible to correlate the fully synthetic racemic series with naturally derived material of defined relative configurations. Enantiomerically homogeneous compound **3** (*vide supra*) was converted to its diphenyl-tert-butylsilyl derivative. Comparison of the fully synthetic material with that derived from **1** showed them to be spectroscopically identical. *Since 3 had been converted to seco ester 5b, a fully synthetic route to this compound, albeit not at this writing, has been established. We further note that all stereochemistry has been communicated through a series of highly selective reactions.*

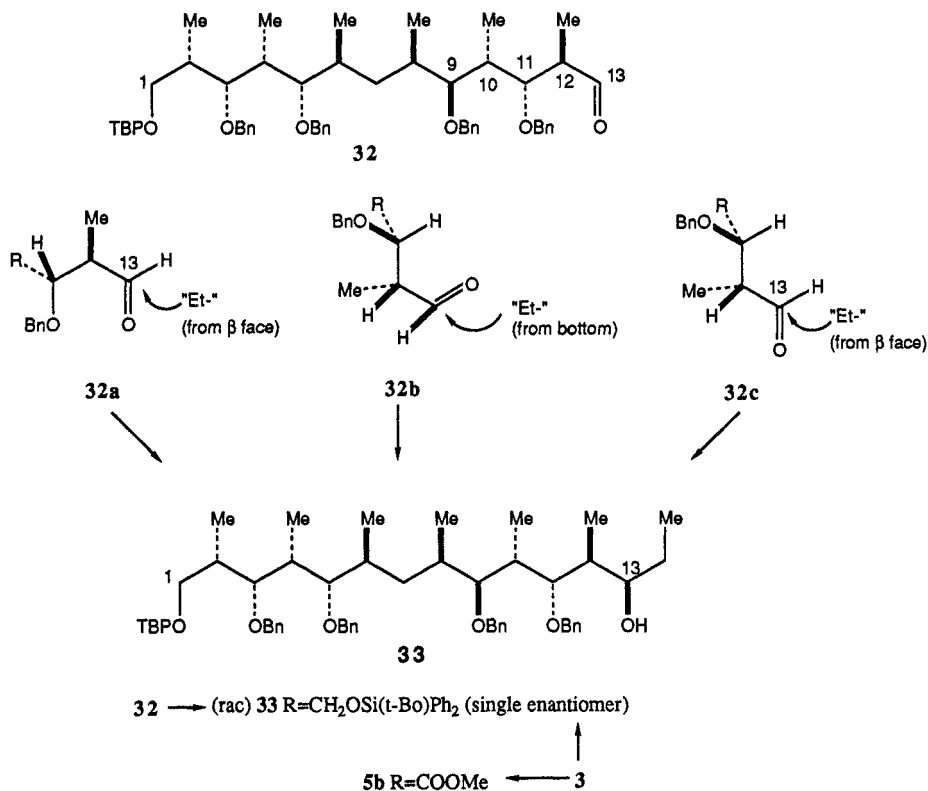


Fig. 7

IMPLICATIONS AND PROSPECTS

Several features of the synthesis warrant special emphasis. The previously formulated concept of building branched pyranoids, using them as matrices for further functionality development, and retrieving an aldehyde for the next elongation cycle had been considerably generalized. A tactic for dealing with a skipped center (carbon 7) had been worked out. Most remarkable in this connection was the high facial selectivity manifested in the cyclocondensation of aldehyde **17**. Remaining at the moment unsolved is the problem of installation of an axial methyl group in a pyranoid setting, such as is present in compound **22** via intermediates derivable from dihydropyrone type **18** or dihydropyrane type **23**.

The nature of our synthesis is such that a variety of differential protecting devices and permutations are accessible in the seco system **5b**. This capability could well be useful in enhancing the opportunities for macrolactonization. With the issues of relativity of stereochemistry well resolved in our favor, an implementable strategy for macrolactonization emerges as our major challenge. Were this realized, opportunities for attainment of enantiomerically homogeneous products (in the desired sense) could also be addressed.

Acknowledgements

This research was supported by PHS Grant AI-16943. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210.

REFERENCES

1. S.J. Danishefsky, *Aldrichimica Acta* **19**, 59-68 (1986).
2. I. Paterson, M.M. Misuri, *Tetrahedron* **41**, 3569-3624 (1985)
3. J.W. Westley, *Polyether Antibiotics*, Marcel Dekker: New York, 1983.
4. S.J. Danishefsky, M.P. DeNinno, *Angew. Chem. Int. Ed. Eng.* **26**, 15-23 (1987).
5. For other approaches to this problem, see S. Masamune, M. Hirama, S. Mori, S.A. Ali, D.S. Garvey, *J. Am. Chem. Soc.* **103**, 1568-1571 (1981). See also ref. 2.
6. K.C. Nicolaou, *Tetrahedron* **33**, 683-710 (1977).
7. G. Schulte, Yale University Chemical Instrumentation Center, unpublished results.
8. H. Tomioka, K. Takai, K. Oshima, H. Nozaki, *Tetrahedron Lett.* **22**, 1605-1608 (1981).
9. B.S. Bal, W.F. Childers, H.W. Pinnick, *Tetrahedron* **37**, 2091-2096 (1981).
10. R.J. Ferrier, *J. Chem. Soc.* 5443-5449 (1964).
11. S.J. Danishefsky, H.G. Selnick, R.E. Zelle, M.P. DeNinno, *J. Am. Chem. Soc.* **110**, 4368-4371 (1988).
12. (a) D.J. Cram, F.A. Elhafez, *J. Am. Chem. Soc.* **74**, 5828-5836 (1952). (b) D.J. Cram, K.R. Kopecky, *Ibid.* **81**, 2748-2755 (1959).
13. D.J. Cram, D.R. Wilson, *J. Am. Chem. Soc.* **85**, 1245-1249 (1963).
14. (a) N.T. Ahn, O. Eisenstein, J.-M. LeFour, M.E. Tran Huu Dau, *J. Am. Chem. Soc.* **95**, 6146-6147 (1973). (b) N.T. Ahn, O. Eisenstein, *Nouv. J. Chim. I.* 61-70 (1977).
15. S.J. Danishefsky, E. Larson, D. Askin, N. Kato, *J. Am. Chem. Soc.* **107**, 1246-1255 (1985).
16. S.J. Danishefsky, W.H. Pearson, D.F. Harvey, C.J. Maring, J.P. Springer, *J. Am. Chem. Soc.* **107**, 1256-1268 (1985).
17. D.C. Myles, doctoral dissertation, Yale University, 1988.
18. D.B. Dess, J.C. Martin, *J. Org. Chem.* **48**, 4156-4157 (1983).
19. (a) T. Matsumoto, Y. Hosoda, K. Mori, K. Fukui, *Bull. Chem. Soc. Jpn.* **45**, 3156-3160 (1972). (b) G. Schmid, T. Fukuyama, K. Akasaka, Y. Kishi, *J. Am. Chem. Soc.* **101**, 259-260.
20. A. Liptak, I. Jodal, P. Nanasi, *Carb. Res.* **44**, 1-11 (1975), and references therein.
21. S.J. Danishefsky, D.C. Myles, D.F. Harvey, *J. Am. Chem. Soc.* **109**, 862-867 (1987).