sion[8] was shaken at 45 °C and 250 rpm. After 48 h, when virtually all sugar substrate had reacted, the enzyme was filtered out, and the remaining solution was added to a mixture of 25 mL of *n*-butanol and 8 mL of trifluoroacetic acid to remove the trityl moiety.[12] After a 10-min incubation at room temperature the mixture was evaporated to dryness under vacuum, and the residue was washed with 100 mL of toluene, dissolved in ethyl acetate, and applied to a silica gel column equilibrated with the same solvent. The column was thoroughly washed with ethyl acetate, and then the product was eluted with a mixture of ethyl acetate, methanol, and water (100:10:1). As a result, 0.75 g (88% isolated yield) of pure (by TLC, GC, and NMR) crystalline 3-*O*-butyrylglucose (identical to that prepared in (i)) was obtained. ^{13}C NMR (67.9 MHz, acetone) δ 97.4, 93.1, 78.3, 77.1, 76.3, 73.8, 72.5, 71.4, 69.2, 61.9 (a mixture of α and β anomers) (C1, β) (C1, α) (C3, β) (C5, β) (C3, α) (C2, β) (C5, α) (C2, α) (C4, α,β) (C6, α,β). These data are in agreement with those reported for 3-*O*-acetylglucose.[22] Anal. Calcd for $C_{10}H_{18}O_7$·EtOAc: C, 49.68; H, 7.69; O, 42.51. Found: C, 49.53; H, 7.62; O, 42.43.

Enzymatic Synthesis of 2-*O*-Butyrylglucose. We dissolved 2 g of 6-*O*-(*tert*-butyldiphenylsilyl)glucose (prepared chemically[13]) and 5 mL of **4** in 20 mL of methylene chloride. Then 5 g of *Candida cylindracea* lipase was added, and the suspension[8] was shaken at 45 °C and 250 rpm. After 60 h, when 60% of the glucose substrate had reacted, the enzyme was removed by filtration and the solvent and unreacted **4** were evaporated at 100 °C under vacuum. The residue was dissolved in CH_2Cl_2, applied on a silica gel column equilibrated with the same solvent, and thoroughly washed with it. Then the product was eluted with methylene chloride containing 4% (v/v) of methanol, and consequently 1.1 g (75% isolated yield) of light yellow oil was obtained which was determined to be pure (GC, NMR, and TLC) 2-*O*-butyryl-6-*O*-(*tert*-butyldiphenylsilyl)glucose. To remove the protective group in the C-6 position with a minimal migration of the butyryl moiety we followed the procedure kindly suggested to us by Professor Stephen Hanessian of Universite de Montreal. The enzymatically formed product (2 mmol) was dissolved in 60 mL of dry tetrahydrofuran, and the solution was cooled to −50 °C. A solution of 2 mmol of tetrabutylammonium fluoride and 10 mmol of acetic acid in 25 mL of tetrahydrofuran was then added dropwise, and the temperature of the mixture was allowed to reach 25 °C and remain at that temperature overnight. Following evaporation of the solvent under vacuum at room temperature, the residue was purified by a silica gel column chromatography with use of a mixture of ethyl acetate, methanol, and water (100:10:1) as a solvent. As a result, we obtained 0.41 g (75% isolated yield) of 2-*O*-butyrylglucose which contained about 10% of the 3-O-isomer (as determined by GC and NMR). This contamination was presumably due to migration of the acyl moiety, also observed in other systems.[13] The 2-O-isomer: ^{13}C NMR (67.9 MHz, acetone) δ 95.7, 90.5, 77.3, 75.9, 75.4, 74.7, 72.3, 71.5, 71.4, 71.2, 62.2 (a mixture of α and β anomers) (C1, β) (C1, α) (C5, β) (C2, β) (C3, β) (C2, α) (C5, α) (C3, α) (C4, α) (C4, β) (C6, α,β). These data are in agreement with those reported for 2-*O*-myristoylglucose.[22] Anal. Calcd for $C_{10}H_{18}O_7$: C, 49.74; H, 7.70; O, 42.49. Found: C, 49.82; H, 7.61; O, 42.33.

Enzymatic Hydrolysis of Di-*O*-butyryl Sugars. The procedure described above for 3,6-di-*O*-butyrylglucose did not afford a satisfactory selectivity when applied to the other diesters. Therefore, the following protocol was employed instead. A diester (0.1 g) was dissolved in 5 mL of a CH_2Cl_2–acetone–water (8:5:0.4) mixture, and then 0.1 g of *Candida cylindracea* lipase was added. The suspension was shaken at 25 °C and 250 rpm for 24–48 h, after which time the enzyme was removed by filtration and the solvent evaporated. The residue was subjected to silica gel column chromatography with an ethyl acetate–methanol–water mixture (100:10:1) as solvent.

A General Method for the Synthesis of Chiral Multifunctional Chain Compounds Incorporating Pentitol Fragments[1]

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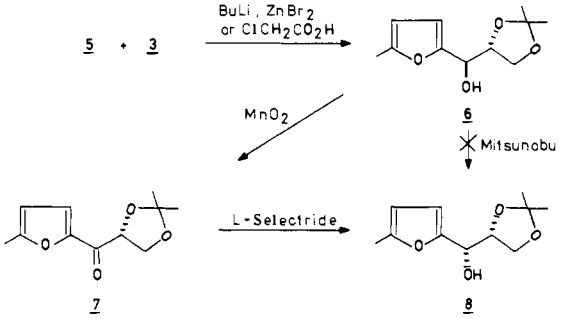
Abstract: A new method for the synthesis of pentitol derivatives **21–32** of all possible configurations is described. The method is based on the use of 2,3-*O*-isopropylidene-D-glyceraldehyde (**3**) as a chiral starting material. Compound *anti*-**6** is obtained by the zinc bromide mediated addition of furyllithium to **3**, while *syn*-**8** is prepared by L-Selectride reductrion of ketone **7**; in both cases the diastereoselectivity is at least 20:1. It is shown that the furan ring is a very convenient precursor of the enedione system. The regioselective protection of one of the carbonyl groups of enedione allows for stereoselective reduction of ketones **15**, **16**, **19**, and **20**. Syn selectivity greater than 14:1 is observed for **15** and **19** when diisobutylaluminum hydride is used as reducing agent. In contrast, the reduction of **16** and **20** with zinc borohydride is 20:1 antiselective. Stereochemical assignments for **23**, **26**, and **29** were established by unambigous chemical correlations with compounds synthesized from natural D-arabinose, D-xylose, and D-ribose, respectively.

In recent years there has been a growing interest in the synthesis of natural products possessing a dense array of chiral centers bearing hydroxy groups. These structure types are characteristic not only of carbohydrates but also of other highly important, biologically active compounds such as macrolides[4] and antitumor antibiotics[5] as well as some marine toxins, e.g., palitoxin.[6] Significant advances in syntheses of such compounds have recently occurred.[7] Among many methodologies developed, those leading in an acyclic manner and with higher selectivity to the 1,3-dimethyl-2-hydroxy unit (A) have attracted great attention.[7,8] On the other hand, methodologies for the steroselective construction

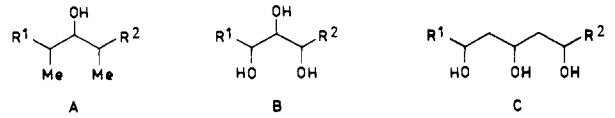
(1) Taken in part from the Ph.D. Thesis of S.P., Institute of Organic Chemistry, Polish Academy of Sciences, Warszawa, 1986.
(2) Institute of Organic Chemistry, Poish Academy of Sciences.
(3) AB Hässle.
(4) *Macrolide Antibiotics*; Omura, S., Ed.; Academic Press: Orlando, 1984.
(5) *The Chemistry of Antitumor Antibiotics*; Remers, W. A., Ed.; Wiley: New York, 1979.
(6) Cha, I. K.; Christ, W. J.; Finan, J. M.; Fujioka, H.; Kishi, Y.; Klein, L. L.; Ko, S. S.; Leder, J.; McWhorther, W. W., Jr.; Pfaff, K.-P.; Yonaga, M.; Uemura, D.; Hirata, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7369 and references cited therein.
(7) For example: Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569.
(8) (a) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 111. (b) Evans, D. A.; Nelson, J. U.; Taber, T. R. *Top Stereochem.* **1982**, *13*, 1. (c) Mukaiyama, T. *Org. React. (N.Y.)* **1982**, *28*, 203.

0002-7863/87/1509-3981$01.50/0

Scheme I



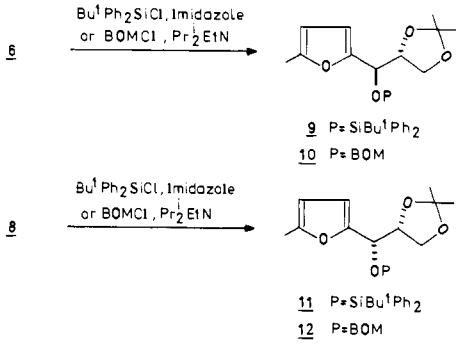
of the 1,2,3 polyol unit (B)[9] as well as the 1,3,5 analogue (C)[10] are much less common.



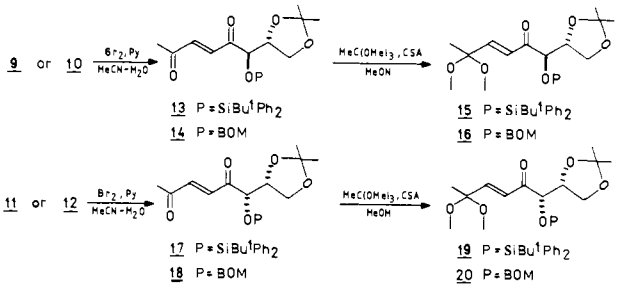
In the case of the synthesis of B-type units, it was not until the development of the efficient method for the asymmetric epoxidation of allylic alcohols[11] that a general approach could be formulated and successfully realized.[9ab] Another general solution of the problem has very recently been given by Japanese chemists.[9c] In contrast, other methods leading to the construction of B-type units[9d-h] have not been developed to the level that would allow general access to all possible stereoisomers, although several recent results show promise in addressing this problem.[12] In a preliminary report[13] we presented an alternative method for the preparation of tetraol units with *arabino* or *ribo* configurations. Herein, we present a full account of this subject as well as an extention of the method which yields the remaining *xylo* and *lyxo* stereoisomers.

For the construction of polyhydroxylated open-chain compounds (e.g., **1**) we decided to use 2,3-*O*-isopropylidene-D-glyceraldehyde (**3**)[14] as an optically pure starting material. This aldehyde is characterized by the ready availability of both enantiomers from natural sources and by a pronounced versatility in reactivity due to the presence of the aldehyde and protected diol functionalities. It is well-suited for the synthesis of polyol chains. Since **3** possesses only one chiral center, it will be necessary to introduce two additional chiral centers before the pentose chiral core is realized. We thought that this could be carried out in a stepwise manner, namely: (1) addition of a proper nucleophile **2** to the carbonyl group of **3**, thus creating a second chiral center in the chain, and (2) introduction of the third chiral center through the reduction

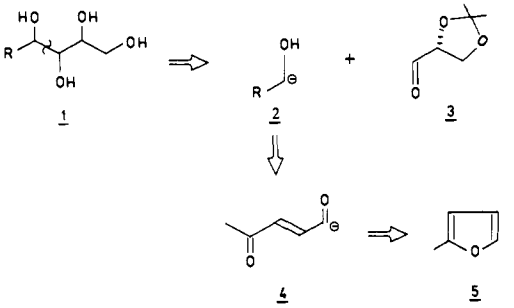
Scheme II



Scheme III



of the ketone functionality newly introduced in the previous step. Subsequently, we considered the enedione system **4** as a potential precursor of **1**. The great advantage of **4** is that it bears two carbonyl groups, one of which can be reduced to generate a new chiral center, while the second can be incorporated into the α,β-unsaturated ketone functionality. The enedione **4**, in turn, can be masked as a nucleophile in the form of the furan **5**.



The diastereoisomeric furans **6** and **8** were prepared as outlined in Scheme I. Compound **6** is readily available in large quantities from **3**. Of the three methods given in our previous paper,[13] the two suitable for large scale preparation are the following: (1) the reaction of lithiated 2-methylfuran (**5**) with **3** carried out in the presence of $ZnBr_2$ according to Mukaiyama et al.[15] and (2) chloroacetic acid catalyzed reaction of **5** and **3** according to Zamojski et al.[16] (Scheme I). Both methods afforded **6** in reasonably good yield (60–70%) and with high *anti* selectivity (95:5[17] in the case of the organometallic addition, and 93:7 in the case of the acid catalyzed one).[18] Alcohol **6** can easily be purified by a single crystallization from hexane–diethyl ether giving material of >99% diastereoisomeric purity.[17]

The preparation of the second diastereoisomer *syn*-**8** was not straightforward due to the profound anti-facial selectivity of **3**[14] and other similarly protected α,β-dialkoxyaldehydes[19] in reactions

(9) (a) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373. Lee, A. W. M.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Walker, F. J. *J. Am. Chem. Soc.* **1982**, *104*, 3515. Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Science* **1983**, *220*, 949. (b) Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109. (c) Sato, F.; Kobayashi, Y.; Takahashi, O.; Chiba, T.; Takeda, Y.; Kusakabe, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1636. Kusabe, M.; Sato, F. *Ibid.* **1986**, 989. (d) Yamaguchi, M.; Mukaiyama, T. *Chem. Lett.* **1981**, 1005. (e) Raush, W. R.; Harris, D. J.; Lesur, B. M. *Tetrahedron Lett.* **1983**, *24*, 2227. (f) David, S.; Lepine, M.-C. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1262. (g) Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, *24*, 3951. (h), Cha, I. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247.

(10) Based on acyclic control: (a) Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Vitti, S. M. *J. Org. Chem.* **1982**, *47*, 1378. (b) Nicolaou, K. C.; Uenishi, J. *J. Chem. Soc., Chem. Commun.* **1982**, 1292. (c) Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833. (d) Lipshutz, B. H.; Kozlowski, J. A. *J. Org. Chem.* **1984**, *49*, 1147. Based on cyclic control: (e) Nakata, T.; Takao, S.; Fukui, M.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 3873. Nakata, T.; Nagao, S.; Takao, S.; Tanaka, T.; Oishi, T. *Ibid.* **1985**, *26*, 73. Nakata, T.; Nagao, S.; Oishi, T. *Ibid.* **1985**, *26*, 75.

(11) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

(12) (a) Overman, L. E.; McCready, R. J. *Tetrahedron Lett.* **1982**, *23*, 2355. (b) Nakata, T.; Tanaka, T.; Oishi, T. *Ibid.* **1983**, *24*, 2653. (c) Fujita, M.; Hiyama, T. *J. Am. Chem. Soc.* **1984**, *106*, 4629. (d) Mead, K.; Macdonald, T. L. *J. Org. Chem.* **1985**, *50*, 422.

(13) Jurczak, J.; Pikul, S.; Ankner, K. *Tetrahedron Lett.* **1986**, *27*, 1711.

(14) Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron*, **1986**, *42*, 447.

(15) Suzuki, K.; Yuki, Y.; Mukaiyama, T. *Chem. Lett.* **1981**, 1529.

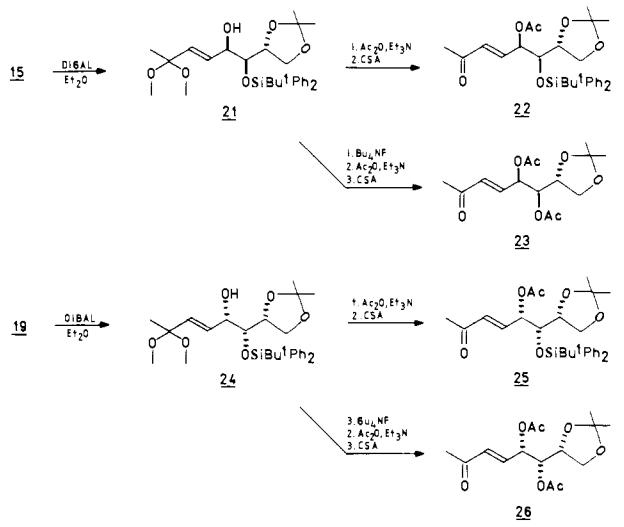
(16) Grzeszczyk, B.; Dziewiszek, K.; Jarosz, S.; Zamojski, A. *Carbohydr. Res.* **1985**, *145*, 145.

(17) Determined by HPLC analysis of the *tert*-butyldiphenylsilyl derivatives, cf. Experimental Section.

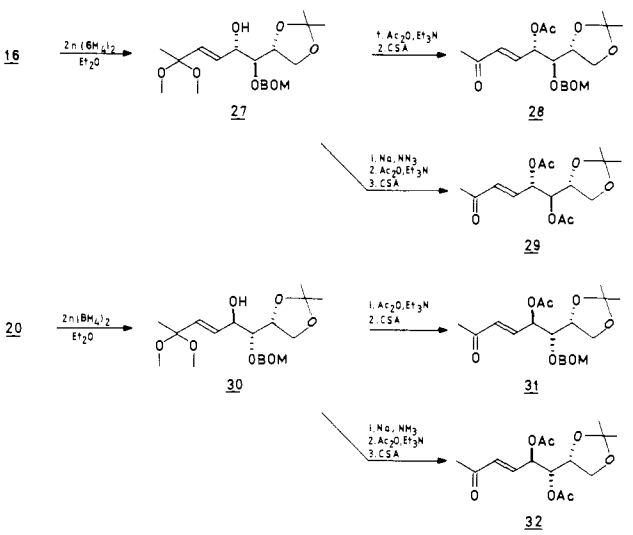
(18) Compare: Pikul, S.; Jurczak, J. *Tetrahedron Lett.* **1985**, *26*, 4145.

(19) McGarvey, G. J.; Kimura, M.; Oh, Y.; Williams, J. M. *J. Carbohydr. Chem.* **1984**, *3*, 125.

Scheme IV



Scheme V



with organometallic reagents.[20] For this reason and because the Mitsunobu reaction failed, we resorted to a two-step oxidation–reduction sequence.[21] Oxidation of **6** with manganese dioxide gave cleanly ketone **7** which was subsequently reduced by L-Selectride to give alcohol **8** in 87% yield with 50:1 syn selectivity. The stereochemical outcome of the reduction is in good agreement with the results obtained by Mead and Macdonald for similar model compounds.[12d,22] The hydroxy funtionalities of **6** and **8** were then protected as silyl ethers through the reaction with *tert*-butyldiphenylsilyl chloride[23] to give **9** and **11**, respectively, in greater than 90% yield (Scheme II). Alternatively, the benzyloxymethylene (BOM) protecting group[24] was introduced to give **10** and **12** in 90 and 88% yield, respectively.

Compounds **9**, **10**, **11**, and **12** were subjected to a furan ring opening transformation with bromine in aqueous acetone.[25] However, even though the reaction worked well for many furan derivatives, it had a drawback in that small amounts of the lachrymatory bromoacetone side product made the workup unpleasent particularly in large-scale experiments. Fortunately, use of acetonitrile in place of acetone solved the problem and, in several cases, we found to give better yields. Such modified conditions were applied for the transformations of **9**, **10**, **11**, and **12** to the enediones **13**, **14**, **17**, and **18**, respectively (Scheme III). In every case, the reaction led cleanly to the desired product in greater than 80% yield.

Compounds with the enedione system are very attractive candidates for further functionalization; however, to take a full advantage of the enedione functionality, it is desirable to find a way to regioselectively protect one of the carbonyl groups. We decided that the most convenient method would be the selective ketalization of the "terminal" carbonyl group. After many experiments employing ethylene glycol, 1,3-propanediol, trimethyl orthoformate, trimethyl orthoacetate, and acid catalysts like *p*-toleuensulfonic acid, camphorsulfonic acid (CSA), pyridinium *p*-toluenesulfonate, and zinc chloride, we found the system trimethyl orthoacetate/CSA/methanol to be the most efficient in the realization of the intended process. Under these conditions compounds **13**, **14**, **17**, and **18** were transformed to monoketones **15**, **16**, **19**, and **20**, respectively, in high yields only when the temperature of the reaction mixture was kept at 0 °C or below. Higher temperatures resulted in the formation of other products, probably due to the loss of the isopropylidene protecting group and/or the addition of methanol to the double bond. In every case, the reaction was clean and was complete after 2–6 h. The only exception was compound **13** which resisted complete protection, and after about 6 h, an equilibrium was reached with the ratio of **15** to **13** being 10:1; a chromatographic separation was necessary in this case.

The last chiral center could now be introduced by the stereoselective reduction of any of the four diastereoisomeric α,β-unsaturated ketones **15**, **16**, **19**, or **20**. Ketones **15** and **19** bear the α-*tert*-butyldiphenylsilyloxy group which because of its bulk might be expected to give rise to high diastereoselectivity in the reduction of the adjacent carbonyl site. In fact, reduction of ketones **15** and **19** with diisobutylaluminum hydride (DIBAL) afforded alcohols **21**[26] and **24** in 75 and 77% yield, after chromatography, respectively (Scheme IV).

Compounds **21** and **24** were subsequently transformed to monoacetates **22** (82% yield) and **25** (80% yield), respectively, through acetylation of the newly formed hydroxy functions and subsequent deprotection of the carbonyl groups. Although these α,β-unsaturated ketones gave appropriate ^{1}H (500 MHz) NMR, IR, and MS spectra, it was difficult to establish the extent of asymmetric induction occurring in the reduction process through the analysis of either alcohols **21** and **24** or their derivatives **22** and **25**. However, compounds **21** and **24** could be converted to diacetates **23** (79% yield) and **26** (75% yield), respectively, in a three-step sequence: (1) removal of the silyl protection by means of tetrabutylammonium fluoride, (2) acetylation of the intermediate diol, (3) hydrolysis of the dimethyl ketal. At this stage it was possible to determine the asymmetric induction in both cases by analyzing without chromatographic separation the region of the vinyl protons in the ^{1}H (500 MHz) NMR spectra of the crude diacetates **23** and **26** obtained from **15** and **19**, respectively. In this manner, it was shown that **23** was a 20:1 mixture of two diastereoisomers while **26** was 14:1 mixture of diastereoisomers.

The reduction of the α,β-unsaturated ketones **16** and **20**, in which the α-hydroxy groups were protected as the benzyloxymethylene ethers (BOM), with zinc borohydride[27] cleanly afforded alcohols **27** (97% yield) and **30** (95% yield), respectively (Scheme V). This change in the stereochemistry of the reduction of the carbonyl group (cf. Scheme IV) employing the mild and very

(20) The only exceptions are ((trimethylsilyl)vinyl)copper and phenyltriisopropoxytitanium which in reactions with **3** showed 99:1 (cf. ref 9c) and 91:9 (cf.: Mulzer, J.; Angermann, A. *Tetrahedron Lett.* **1983**, *24*, 2849.) syn selectivity, respectively.

(21) Jurczak, J.; Pikul, S.; Raczko, J., submitted for publication.

(22) An alternative solution of the problem may be the use of 2,3-di-*O*-benzyl-D-glyceraldehyde. For this aldehyde the reaction conditions for α- or β-chelate-controlled pathways have recently been developed; this makes possible direct and highly stereoselective preparation of either anti or syn diastereoisomer, cf. ref 12d.

(23) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975; **1977**, *55*, 562.

(24) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 6260.

(25) Jurczak, J.; Pikul, S. *Tetrahedron Lett.* **1985**, *26*, 3039.

(26) Partial migration (8%) of the silyl group to the allylic position was observed for this compound; the migration was found to be dependent on the solvent and reducing agent used: Jurczak, J.; Pikul, S.; Ankner, K., submitted for publication.

(27) Gensler, W. J.; Johnson, F.; Sloan, A. D. B. *J. Am. Chem. Soc.* **1960**, *82*, 6074.

Scheme VI

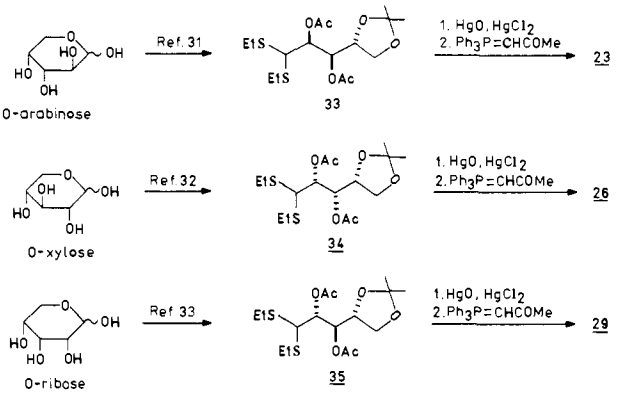


Table I. Specific Rotations of Compounds **23**, **26**, **29**, and **32** in $CHCl_3$

compd	prepared from **3**	prepared from the natural sugar
23	+32.5° (*c* 0.90)	+34.5° (*c* 1.28)
26	−18.5° (*c* 0.83)	−19.7° (*c* 0.75)
29	+14.6° (*c* 0.60)	+13.0° (*c* 1.51)
30	−10.0° (*c* 0.60)	

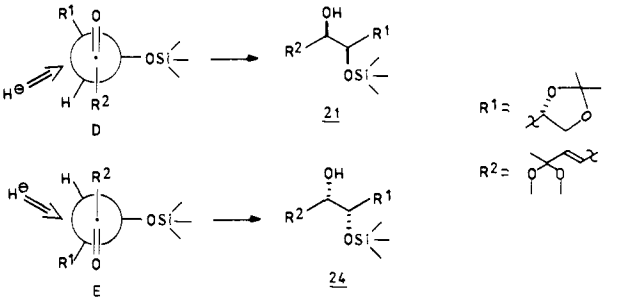
selective zinc borohydride[12b,28,29] was anticipated, based on the chelating ability of the neighboring BOM group.[12a,b,30]

Enones **28** (85% yield) and **31** (86% yield) were obtained from **27** and **30**, respectively. However, as in the case of the silyl counterparts, the determination of the asymmetric induction at this stage was beyond the analytical methods at our disposal. Once again, we decided to transform the products of zinc borohydride reduction to diacetates **29** and **32**, respectively. The three-step sequence adapted for this purpose was analogous to that used previously for the silyl derivatives except that the BOM protecting group was removed with sodium in liquid ammonia. Compounds **29** and **32**, obtained in this way in 81 and 75% yield, respectively, were shown by ^1H NMR spectroscopy to each be diastereoisomeric mixtures in the ratio of 20:1.

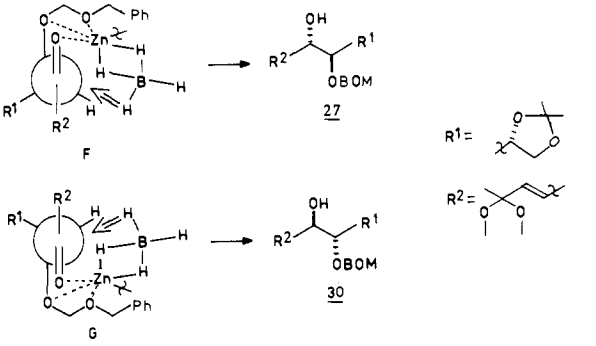
At this point, it was necessary to establish the absolute configurations of the four diacetates **23**, **26**, **29**, and **32** and prove that we were able to synthesize compounds incorporating the fragments of all the pentoses. To establish these points we prepared the three diacetates **23**, **26**, and **29** starting from the natural pentoses: D-arabinose, D-xyloe, and D-ribose, respectively (Scheme VI).

The protected dithioacetals **33**,[31] **34**,[32] and **35**[33] were synthesized according to the literature procedures via the monoisopropylidene derivatives of the corresponding tetrahydroxydithioacetals. However, it is important to note that while the introduction of the terminal 1,2-acetonide protecting group is very efficient for arabinose, this is not the case for xylose or ribose in which the yields of the proper regioisomer do not exceed 40% and problems arise in the isolation of the desired regioisomers.[32,33] The dithioacetal protections in **33**, **34**, and **35** were subsequently removed by using the mercury oxide/mercury chloride method[34] and the aldehydes released were allowed to react with acetonyltriphosphorane to give **23**, **26**, and **29**, respectively, in 60–70% yield. ^1H (500 MHz) and ^{13}C (125 MHz) NMR spectra of these compounds were superimposable with those obtained from ketones **15**, **19**, and **16**, respectively, but different from the spectra recorded for **32**. Furthermore, comparison of the specific rotations of all the diacetates prepared gave additional stereochemical proof (Table I) and ultimately established the absolute configuration of all compounds detailed in this paper.

While formation of the C3 chiral center was straightforward due to the substantial knowledge accumulated for reactions of **3**[12d,14] the reductions of the C4 carbonyl group deserve comment. The reduction of simple hydroxy and alkoxy ketones has been investigated by several groups,[12a,b] and based on these results it was anticipated that the bulky silyl and the BOM protecting grooups would influence the reduction of the neighboring carbonyl group in a divergent fashion. From the results presented above, it can be seen that these two protecting groups, combined with the proper reducing agent, are very efficient in directing the stereochemical course of the reductions of adjacent ketone groups and also in case of more complex molecules. Reduction of the silyl protected ketones **15** and **18** led consistently to products with the 3,4-syn relative configuration. This suggests that conformations D and E of **15** and **18**, respectively, are the most stable ones, thus leading to **21** and **24** in agreement with the Felkin steric model.[35]



In contrast, conformations F and G of ketones **16** and **20**, respectively, appear to be stabilized by the chelating interactions between the C4 carbonyl group, the BOM group, and Zn-$(BH_4)_2$.[12b,30] This has a profound stereochemical effect since the hydride addition occurs from the opposite face of the carbonyl group giving rise to compounds **27** and **30** with 3,4-anti relative configuration. Furthermore, on the grounds of the very high anti selectivity observed, one can say that the chelating ability of the BOM protecting group seems to be much higher than that of the acetonide group since complexation of $Zn(BH_4)_2$ with the two isopropylidene oxygens and C=O group would facilitate 3,4-syn diastereoisomer formation.



In summary, a versatile and highly stereoselective method for the synthesis of open-chain compounds bearing chiral fragments related to all the pentoses has been developed. The method, based on the use of 2,3-*O*-isopropylidene-D-glyceraldehyde (**3**) as the starting chiral material and of 2-methylfuran (**5**) as the source of the carbon chain, enables the synthesis of target compounds with a very high degree of acyclic stereocontrol and in very good yields. The pattern of protection of the pentitol fragments, achieved in the synthesis, is very convenient for deprotection on any of the C1–C4 hydroxy groups, this being of value for further transformations. Furthermore, the α,β-unsaturated ketone system offers wide possibilities for the introduction of subsequent chiral centers, owing to the directing ability of the C3/C4 hydroxy or

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alkoxy groups.[36] The method can also be considered a general one since—on account of the ready availability of 2,3-*O*-isopropylidene-L-glyceraldehyde[14,37]—the synthesis of all stereisomers of the pentitol is possible.

Experimental Section

Preparative flash chromatography was performed on Merck Kieselgel 60 (230–400 mesh), according to Still's procedure[38] with use of different systems of hexane (H)–ethyl acetate (EA) as eluents. 2,3-*O*-Isopropylidene-D-glyceraldehyde (**3**) was prepared from D-mannitol according to Kierstead's modification[39] of the known procedure.[40]

(2*R*,3*R*)-1,2-*O*-Isopropylidene-3-[2-(5-methylfuryl)]-1,2,3-propanetriol (6). To a solution of 2-methylfuran (**5**, 15 mL, 166 mmol) in THF (160 mL) cooled to −30 °C, butyllithium (100 mL of a 1.6 M solution in hexane, 160 mmol) was added and the reaction mixture was stirred for 4 h while the temperature was gradually raised to 10 °C. Anhydrous $ZnBr_2$ (36 g, 160 mmol) was then added and stirring was continued for an additional 15 min. After being cooled to −40 °C, a solution of freshly prepared **3** (20.8 g, 160 mmol) in THF (160 mL) was added dropwise. The resulting mixture was stirred at this temperature for 4 h and then warmed to 0 °C within 3 h, whereupon it was quenched with saturated aqueous NH_4Cl and worked up. The crude product[41] was purified by crystallization from hexane–ethyl ether to give 22.1 g (65% yield) of **6** as colorless crystals: mp 63–64 °C; $[\alpha]_D$ +29.5° (*c* 1.07);[42] IR (KBr) 3270, 2980, 1560, 1440, 1380, 1260, 1220, 1150, 1070 cm^{-1}; ^1H NMR (500 MHz) δ 6.19 (d, *J* = 3.0 Hz, 1 H), 5.92 (m, 1 H), 4.77 (d, *J* = 4.8 Hz, 1 H), 4.37 (ddd, *J* = 4.8, 6.3, 6.6 Hz, 1 H), 4.13 (dd, *J* = 6.3, 8.4 Hz, 1 H), 4.05 (dd, *J* = 6.6, 8.4 Hz, 1 H), 2.32 (br s, 1 H), 2.27 (s, 3 H), 1.45 (s, 3 H), 1.37 (s, 3 H). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.10; H, 7.66.

(2*R*,3*R*)-3-*O*-(*tert*-Butyldiphenylsilyl)-1,2-*O*-isopropylidene-3-[2-(5-methylfuryl)]-1,2,3-propanetriol (9). To a solution of **6** (2.12 g, 10 mmol) in DMF (10 mL) imidazole (1.02 g, 15 mmol) and *tert*-butyldiphenylsilyl chloride (2.86 mL, 11 mmol) were added and the reaction mixture was stirred at 80 °C for 5 h. After being cooled to room temperature, the mixture was diluted with pentane–ethyl ether (3:1 v/v) and worked up. The crude product was purified by crystallization from ethanol to give 4.15 g (92% yield) of 9 as colorless crystals: mp 74–75 °C; $[\alpha]_D$ +91.3° (*c* 1.04); IR (KBr) 2920, 2840, 1565, 1430, 1370, 1220, 1120, 1050 cm^{-1}; ^1H NMR (500 MHz) δ 7.70–7.65 (m, 4 H), 7.42–7.38 (m, 6 H), 5.66 (m, 2 H), 4.59 (d, *J* = 6.4 Hz, 1 H), 4.41 (ddd, *J* = 6.0, 6.0, 6.4 Hz, 1 H), 4.15 (m, 2 H), 1.318 (s, 3 H), 1.316 (s, 3 H), 1.01 (s, 9 H); ^{13}C NMR δ 151.40, 151.36, 136.01, 135.88, 133.51, 133.32, 129.61, 129.22, 127.49, 127.07, 109.40, 108.29, 105.97, 77.77, 69.51, 66.69, 26.91, 26.57, 25.42, 19.40, 13.40. Anal. Calcd for $C_{27}H_{34}O_4Si$: C, 71.95; H, 7.61. Found: C, 71.77; H, 7.71.

(2*R*,3*R*)-3-*O*-(Benzyloxymethylene)-1,2-*O*-isopropylidene-3-[2-(5-methylfuryl)]-1,2,3-propanetriol (10). A mixture of **6** (2.12 g, 10 mmol), diisopropylethylamine (1.6 mL, 15 mmol), and benzyl chloromethyl ether (2.0 mL, 13 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 24 h. The mixture was diluted with CH_2Cl_2 and worked up. The crude product was purified by crystallization from hexane to give 3.0 g (90% yield) of **10** as colorless crystals: mp 67–68 °C; $[\alpha]_D$ +142.9° (*c* 0.98); IR (KBr) 2980, 2880, 1565, 1450, 1380, 1370, 1225, 1090, 1010 cm^{-1}; ^1H NMR (500 MHz) δ 7.33 (m, 5 H), 6.24 (d, *J* = 3.1 Hz, 1 H), 5.92 (m, 1 H), 4.73 ($^1/_2$AB q, *J* = 7.0 Hz, 1 H), 4.72 ($^1/_2$AB q, *J* = 7.0 Hz, 1 H), 4.69 ($^1/_2$AB q, *J* = 11.8 Hz, 1 H), 4.687 (d, *J* = 6.2 Hz, 1 H), 4.52 ($^1/_2$AB q, *J* = 11.8 Hz, 1 H), 4.47 (ddd, *J* = 6.1, 6.2, 6.4 Hz, 1 H), 4.14 (dd, *J* = 6.4, 8.5 Hz, 1 H), 4.09 (dd, *J* = 6.1, 8.5 Hz, 1 H), 2.27 (s, 3 H), 1.42 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR δ 152.63, 149.19, 137.71, 128.39, 127.97, 127.71, 110.91, 109.48, 106.20, 92.23, 78.60, 71.57, 69.74, 66.43, 26.54, 25.43, 13.59. Anal. Calcd for $C_{19}H_{24}O_5$: C, 68.65; H, 7.28. Found: C, 68.51; H, 7.17.

(2*R*,3*S*)-3-*O*-(*tert*-Butyldiphenylsilyl)-1,2-*O*-isopropylidene-3-[2-(5-methylfuryl)]-1,2,3-propanetriol (11). Under the reaction conditions identical with those used for the preparation of 9, compound **8**[21] afforded **11** (91% yield) as a colorless oil: $[\alpha]_D$ −25.3° (*c* 1.75); IR (film) 2960, 2920, 2860, 1560, 1430, 1380, 1220, 1115, 1055 cm^{-1}; ^1H NMR (500 MHz) δ 7.72–7.67 (m, 4 H), 7.40–7.36 (m, 6 H), 5.84 (d, *J* = 3.0 Hz, 1 H), 5.75 (m, 1 H), 4.58 (d, *J* = 7.2 Hz, 1 H), 4.45 (ddd, *J* = 6.3, 6.7, 7.2 Hz, 1 H), 3.86 (dd, *J* = 6.7, 8.6 Hz, 1 H), 3.70 (dd, *J* = 6.3, 8.6 Hz, 1 H), 2.17 (s, 3 H), 1.32 (s, 3 H), 1.21 (s, 3 H), 1.05 (s, 9 H); mass spectrum, *m/z* 393 ($M^+ - C_4H_9$), 349, 335, 255.

(2*R*,3*S*)-3-*O*-(Benzyloxymethylene)-1,2-*O*-isopropylidene-3-[2-(5-methylfuryl)]-1,2,3-propanetriol (12). Under the reaction conditions identical with those used for the preparation of **10**, compound **8**[21] afforded **12** (88% yield) as a colorless oil: $[\alpha]_D$ −135.0° (*c* 1.27); IR (film) 2980, 1560, 1455, 1380, 1365, 1220, 1090, 1010 cm^{-1}; ^1H NMR (500 MHz) δ 7.31 (m, 5 H), 6.24 (d, *J* = 3.0 Hz, 1 H), 5.91 (m, 1 H), 4.82 ($^1/_2$AB q, *J* = 7.0 Hz, 1 H), 4.78 ($^1/_2$AB q, *J* = 7.0 Hz 1 H), 4.77 ($^1/_2$AB q, *J* = 11.5 Hz, 1 H), 4.65 (d, *J* = 8.6 Hz, 1 H), 4.57 (ddd, *J* = 6.4, 6.6, 8.6 Hz, 1 H), 4.53 ($^1/_2$AB q, *J* = 11.5 Hz, 1 H), 3.89 (dd, *J* = 6.6, 8.6 Hz, 1 H), 3.62 (dd, *J* 6.4, 8.6 Hz, 1 H), 2.26 (s, 3 H), 1.42 (s, 3 H), 1.40 (s, 3 H). Anal. Calcd for $C_{19}H_{24}O_5$: C, 68.65; H, 7.28. Found: C, 68.47; H, 7.56.

General Procedure for Oxidation of 9, 10, 11, and 12 to Enediones 13, 14, 17, and 18. The oxidation of 9 is described as an illustrative case. To a solution of 9 (2.25 g, 5 mmol) and pyridine (1.61 mL, 20 mmol) in an acetonitrile–water mixture (50 mL, 85:15 v/v) cooled to −20 °C, bromine [6.25 mL of a 0.8 M solution in an acetonitrile–water mixture (4:1 v/v)] was added with vigorous stirring. The resulting solution was allowed to warm gradually to room temperature and was stirred for an additional 2 h. When the more polar *Z*-isomer was no longer detected by TLC analysis, the mixture was diluted with ethyl ether and worked up. The crude products were purified by flash chromatography (H-EA 4:1 v/v) for **13** and **17** and (H-EA 7:3 v/v) for **14** and **18**.

(*E*)-(2*R*,3*R*)-3-*O*-(*tert*-Butyldiphenylsilyl)-1,2-*O*-isopropylidene-5-octene-4,7-dione-1,2,3-triol (13): a yellow oil (85% yield); $[\alpha]_D$ +38.5° (*c* 2.01); IR (film) 2940, 2860, 1690, 1660, 1430, 1380, 1260, 1220, 1160, 1120 cm^{-1}; ^1H NMR (500 MHz) δ 7.65–7.56 (m, 4 H), 7.45–7.33 (m, 6 H), 7.05 (d, *J* = 16.2 Hz, 1 H), 6.57 (d, *J* = 16.2 Hz, 1 H), 4.32 (d, *J* = 5.2 Hz, 1 H), 4.23 (ddd, *J* = 5.2, 6.2, 6.3 Hz, 1 H), 3.91 (dd, *J* = 6.2, 8.8 Hz, 1 H), 3.83 (dd, *J* = 6.3, 8.8 Hz, 1 H), 2.26 (s, 3 H), 1.31 (s, 3 H), 1.29 (s, 3 H), 1.12 (s, 9 H); mass spectrum, *m/z* 451 ($M^+ - CH_3$), 409, 366, 351.

(*E*)-(2*R*,3*R*)-3-*O*-(Benzyloxymethylene)-1,2-*O*-isopropylidene-5-octene-4,7-dione-1,2,3-triol (14): yellow crystals (80% yield); mp 52–53 °C (hexane–ethyl ether); $[\alpha]_D$ +0.6° (*c* 1.40); IR (KBr) 2970, 2900, 1690, 1465, 1400, 1380, 1310, 1290, 1090 cm^{-1}; ^1H NMR (500 MHz) δ 7.30 (m, 5 H), 7.19 (d, *J* = 16.1 Hz, 1 H), 6.89 (d, *J* = 16.1 Hz, 1 H), 4.85 ($^1/_2$AB q, *J* = 6.9 Hz, 1 H), 4.81 ($^1/_2$AB q, *J* = 6.9 Hz, 1 H), 4.60 ($^1/_2$AB q, *J* = 10.8 Hz, 1 H), 4.57 ($^1/_2$AB q, *J* = 10.8 Hz, 1 H), 4.33 (ddd, *J* = 5.3, 6.2, 6.3 Hz, 1 H), 4.25 (d, *J* = 6.2 Hz, 1 H), 4.09 (dd, *J* = 6.3, 8.7 Hz, 1 H), 3.95 (dd, *J* = 5.3, 8.7 Hz, 1 H), 2.29 (s, 3 H), 1.40 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR δ 198.26, 197.76, 137.29, 137.03, 133.78, 128.45, 127.88, 127.64, 110.22, 95.23, 82.22, 75.74, 70.44, 66.34, 28.40, 26.37, 25.02. Anal. Calcd for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.73; H, 7.08.

(*E*)-(2*R*,3*S*)-3-*O*-(*tert*-Butyldiphenylsilyl)-1,2-*O*-isopropylidene-5-octene-4,7-dione-1,2,3-triol (17): a yellow oil (82% yield); $[\alpha]_D$ −77.5° (*c* 2.40); IR (film) 2930, 2860, 1690, 1430, 1375, 1260, 1115 cm^{-1}; ^1H NMR (500 MHz) δ 7.61–7.56 (m, 4 H), 7.45–7.31 (m, 6 H), 7.04 (d, *J* = 16.2 Hz, 1 H), 6.52 (d, *J* = 16.2 Hz, 1 H), 4.42 (d, *J* = 4.5 Hz, 1 H), 4.26 (dt, *J* = 4.5, 6.6 Hz, 1 H), 3.94 (d, *J* = 6.6 Hz, 2 H), 2.22 (s, 3 H), 1.37 (s, 3 H), 1.28 (s, 3 H), 1.13 (s, 9 H); ^{13}C NMR δ 199.48, 197.88, 136.33, 136.02, 135.92, 133.98, 132.49, 132.41, 130.27, 130.20, 127.84, 127.80, 109.90, 78.28, 65.04, 27.89, 26.96, 26.08, 25.13, 19.39; mass spectrum, *m/z* 451 ($M^+ - CH_3$), 409, 366, 351.

(*E*)-(2*R*,3*S*)-3-*O*-(Benzyloxymethylene)-1,2-*O*-isopropylidene-5-octene-4,7-dione-1,2,3-triol (18): yellow crystals (80% yield); mp 40–41 °C (hexane–ethyl ether); $[\alpha]_D$ −76.2° (*c* 1.05); IR (KBr) 3000, 2920, 1695, 1460, 1390, 1380, 1300, 1050 cm^{-1}; ^1H NMR (500 MHz) δ 7.30 (m, 5 H), 7.22 (d, *J* = 16.1 Hz, 1 H), 6.90 (d, *J* = 16.1 Hz, 1 H), 4.90 ($^1/_2$AB q, *J* = 7.0 Hz, 1 H), 4.85 ($^1/_2$AB q, *J* = 7.0 Hz, 1 H), 4.62 (s, 2 H), 4.38 (ddd, *J* = 5.5, 6.1, 6.6 Hz, 1 H), 4.30 (d, *J* = 5.5 Hz, 1 H), 4.04 (dd, *J* = 6.6, 8.7 Hz, 1 H), 3.90 (dd, *J* = 6.1, 8.7 Hz, 1 H), 2.30 (s, 3 H), 1.42 (s, 3 H), 1.34 (s, 3 H); ^{13}C NMR δ 198.69, 197.71, 137.35, 137.16, 133.76, 128.48, 127.88, 127.59, 110.10, 95.35, 82.44, 75.88, 70.54, 65.48, 28.44, 26.15, 25.12. Anal. Calcd for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.73; H, 7.08.

General procedure for Selective Ketalization of 13, 14, 17, and 18 To Form 15, 16, 19, and 20. The reaction of **13** is described as an illustrative case. To a solution of **13** (932 mg, 2 mmol) in anhydrous methanol (6 mL) at 0 °C were added trimethyl orthoacetate (252 μL, 2 mmol) and camphorsulfonic acid (30 mg). The mixture was stirred at 0 °C and the

(36) For example: cis hydroxylation (*N*-methylmorpholine *N*-oxide, OsO_4 catalyst) of **28** to a 12:1 mixture of two possible diastereoisomers with that of the C4–C5 anti relationship (overall D-*glycero*-D-*galacto* configuration) predominating (Jurczak, J.; Pikul, S., unpublished results).

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(41) HPLC analysis (heptane–ethyl ether, 97.5:2.5 (v/v); *V* = 1.2 mL/min, t_R syn = 10′35″, t_R anti = 13′36″) of this material showed a 95:5 anti:syn ratio.

(42) All optical rotations were measured for $CHCl_3$ solutions.

reaction was monitored by TLC; when no further progress could be detected, triethylamine (25 μL) was added and after 10 min the mixture was diluted with ethyl ether and worked up with Na_2SO_4 as a drying agent. The crude products were purified by flash chromatography (H-EA 4:1 v/v) for **15** and **19** and (H-EA 7:3 v/v) for **16** and **20**.

(*E*)-(2*R*,3*R*)-3-*O*-(*tert*-Butyldiphenylsilyl)-1,2-*O*-isopropylidene-5-octene-4,7-dione-1,2,3-triol, 7-dimethyl ketal (15): colorless oil (77% yield); $[\alpha]_D$ +20.4° (*c* 1.30); IR (film) 2940, 1700, 1640, 1475, 1430, 1375, 1115, 1050 cm^{-1}; ^1H NMR (100 MHz) δ 7.80–7.50 (m, 4 H), 7.50–7.25 (m, 6 H), 6.73 (d, *J* = 15.5 Hz, 1 H), 6.48 (d, *J* = 15.5 Hz, 1 H), 4.73 (d, *J* = 5.1 Hz, 1 H), 4.32–4.14 (m, 1 H), 4.00–3.80 (m, 2 H), 3.14 (s, 6 H), 1.32 (s, 9 H), 1.14 (s, 9 H); mass spectrum, *m/z* 497 ($M^+ - CH_3$), 455, 423, 412.

(*E*)-(2*R*,3*R*)-3-*O*-(Benzyloxymethylene)-1,2-*O*-isopropylidene-5-octene-4,7-dione-1,2,3-triol, 7-dimethyl ketal (16): colorless oil (92% yield); $[\alpha]_D$ −18.0° (*c* 1.66); IR (film) 2980, 2930, 1685, 1640, 1455, 1375, 1220, 1050 cm^{-1}; ^1H NMR (100 MHz) δ 7.50 (br s, 5 H), 6.90 (s, 2 H), 4.93 (s, 2 H), 4.70 (s, 2 H), 4.65–4.05 (m, 4 H), 3.23 (s, 6 H), 1.45 (s, 3 H), 1.36 (s, 6 H); mass spectrum, *m/z* 394 (M^+), 379, 294, 264, 262.

(*E*)-(2*R*,3*S*)-3-*O*-(*tert*-Butyldiphenylsilyl)-1,2-*O*-isopropylidene-5-octene-4,7-dione-1,2,3-triol, 7-dimethyl ketal (19): colorless oil (82% yield); $[\alpha]_D$ −23.8° (*c* 1.60); IR (film) 2940, 1700, 1640, 1470, 1430, 1375, 1115, 1060 cm^{-1}; ^1H NMR (100 MHz) δ 7.80–7.50 (m, 4 H), 7.50–7.25 (m, 6 H), 6.74 (d, *J* = 15.5 Hz, 1 H), 6.48 (d, *J* = 15.5 Hz, 1 H), 4.40–4.15 (m, 2 H), 3.90–3.70 (m, 2 H), 3.10 (s, 6 H), 1.30–0.90 (complex, 18 H); mass spectrum, *m/z* 455 ($M^+ - C_4H_9$), 423, 392, 323.

(*E*)-(2*R*,3*S*)-3-*O*-(Benzyloxymethylene)-1,2-*O*-isopropylidene-5-octene-4,7-dione-1,2,3-triol, 7-dimethyl ketal (20): colorless oil (90% yield); $[\alpha]_D$ −24.0° (*c* 1.60); IR (film) 2940, 1690, 1640, 1460, 1370, 1210, 1045 cm^{-1}; ^1H NMR (100 MHz) δ 7.32 (s, 5 H), 6.78 (s, 2 H), 4.90–4.75 (m, 2 H), 4.65 (s, 2 H), 4.35–4.25 (m, 2 H), 4.10–3.70 (m, 2 H), 3.17 (s, 3 H), 1.45–1.25 (complex, 9 H); mass spectrum, *m/z* 379 ($M^+ - CH_3$), 294, 264, 262.

(*E*)-(2*R*,3*R*,4*R*)-4-*O*-Acetyl-3-*O*-(*tert*-butyldiphenylsilyl)-1,2-*O*-isopropylidene-5-octene-7-one-1,2,3,4-tetraol (22). To a solution of **15** (364 mg, 0.71 mmol) in ethyl ether (15 mL) at −78 °C, DIBAL (0.75 mL of a 1 M solution in ethyl ether, 0.75 mmol) was added, and the resulting solution was stirred for 0.5 h. Then, methanol (0.6 mL) was added and the cooling bath was removed. At 0 °C, brine (0.5 mL), ethyl ether (50 mL), and anhydrous Na_2SO_4 (5 g) were added, and the mixture was stirred at room temperature for 1.5 h. Filtration and evaporation of solvents gave 365 mg (100% yield) of crude **21** [flash chromatography (H-EA 7:3 v/v) afforded pure **21** (75% yield) as a colorless oil] which was immediately used for further reactions. Alcohol **21** was subsequently dissolved in CH_2Cl_2 (5 mL), and triethylamine (137 μL, 1 mmol), acetic anhydride (51 μL, 0.8 mmol), and a crystal of 4-(dimethylamino)pyridine (DMAP) were added. After 3 h of being stirred at room temperature, the reaction mixture was diluted with ethyl ether and worked up. The crude product was dissolved in wet acetone (5 mL) and CSA (20 mg) was added. After 1 h of stirring at room temperature, Et_3N (16 μL) was added and the solvent was evaporated at reduced pressure. The residue was subjected to flash chromatography (H-EA 7:3 v/v) to give 232 mg (64% overall yield) of **22** as a colorless oil: $[\alpha]_D$ +30.6° (*c* 0.63); IR (film) 1940, 1750, 1680, 1640, 1430, 1230, 1115, 1060 cm^{-1}; ^1H NMR (500 MHz) δ 7.72–7.67 (m, 4 H), 7.46–7.37 (m, 6 H), 6.56 (dd, *J* = 5.1, 16.2 Hz, 1 H), 5.94 (dd, *J* = 0.8, 16.2 Hz, 1 H), 5.33 (ddd, *J* = 0.8, 4.0, 5.1 Hz, 1 H), 4.13 (ddd, *J* = 5.3, 5.9, 6.2 Hz, 1 H), 4.02 (dd, *J* = 4.0, 5.3 Hz, 1 H), 3.88–3.62 (m, 2 H), 2.07 (s, 3 H), 1.92 (s, 3 H), 1.29 (s, 3 H), 1.17 (s, 3 H), 1.05 (s, 9 H); mass spectrum, *m/z* 495 ($M^+ - CH_3$), 453, 395, 353.

(*E*)-(2*R*,3*R*,4*R*)-3,4-Di-*O*-acetyl-1,2-*O*-isopropylidene-5-octen-7-one-1,2,3,4-tetraol (23). To a solution of **21** (prepared as in the previous procedure, 181.5 mg, 0.35 mmol) in THF (2 mL) at 0 °C, tetrabutylammonium fluoride (0.8 mL of 0.5 M solution in THF, 0.4 mmol) was added and the reaction mixture was stirred at room temperature for 3 h, whereupon it was diluted with ethyl ether and worked up. The crude product was dissolved in CH_2Cl_2 (5 mL) and subsequently Et_3N (192 μL, 1.4 mmol), Ac_2O (99 μL, 1.05 mmol), and a crystal of DMAP were added. After 5 h of stirring at room temperature, the reaction mixture was diluted with ethyl ether and worked up. The crude product was dissolved in wet acetone (4 mL) and CSA (10 mg) was added. After 1 h of stirring at room temperature, Et_3N (8 μL) was added and the solvent was evaporated at reduced pressure. The residue was subjected to flash chromatography (H-EA 3:2 v/v) to give 87.6 mg (79% yield) of colorless oil which crystallized upon standing; recrystallization from hexane afforded analytically pure **23** as colorless crystals: mp 52–53 °C; $[\alpha]_D$ cf. Table I; IR (KBr) 2990, 2900, 1755, 1680, 1640, 1375, 1220, 1070 cm^{-1}; ^1H NMR (500 MHz) δ 6.64 (dd, *J* = 4.6, 16.1 Hz, 1 H), 6.12 (dd, *J* = 1.7, 16.1 Hz, 1 H), 5.71 (ddd, *J* = 1.7, 3.1, 4.6 Hz, 1 H), 5.17 (dd, *J* = 3.1, 7.2 Hz, 1 H), 4.22 (ddd, *J* = 5.4, 6.2, 7.2 Hz, 1 H), 4.01 (dd, *J* = 6.2, 8.8 Hz, 1 H), 3.82 (dd, *J* = 5.4, 8.8 Hz, 1 H), 2.25 (s, 3 H), 2.16 (s, 3 H), 2.06 (s, 3 H), 1.41 (s, 3 H), 1.34 (s, 3 H); ^{13}C NMR δ 197.38, 169.75, 169.23, 140.54, 131.41, 109.84, 73.70, 72.71, 71.11, 66.21, 26.91, 26.62, 25.18, 20.62, 20.58. Anal. Calcd for $C_{15}H_{22}O_7$: C, 57.31; H, 7.06. Found: C, 57.03; H, 7.11.

(*E*)-(2*R*,3*S*,4*S*)-4-*O*-Acetyl-3-*O*-(*tert*-butyldiphenylsilyl)-1,2-*O*-isopropylidene-5-octen-7-one-1,2,3,4-tetraol (25). Under the same reaction conditions as for the preparation of **22**, compound **19** afforded alcohol **24** in 77% yield, which was then acetylated to give, after purification by flash chromatography (H-EA 7:3 v/v), the acetate **25** (80% yield) as a colorless oil: $[\alpha]_D$ −10.4° (*c* 1.03); IR (film) 2930, 1750, 1680, 1640, 1430, 1225, 1115, 1060 cm^{-1}; ^1H NMR (500 MHz) δ 7.71–7.65 (m, 4 H), 7.43–7.36 (m, 6 H), 6.67 (dd, *J* = 4.9, 16.2 Hz, 1 H), 6.00 (dd, *J* = 1.6, 16.2 Hz, 1 H), 5.44 (ddd, *J* = 1.6, 4.4, 4.9 Hz, 1 H), 4.06 (m, 1 H), 3.90–3.86 (m, 3 H), 2.12 (s, 3 H), 1.88 (s, 3 H), 1.37 (s, 3 H), 1.24 (s, 3 H), 1.06 (s, 9 H); mass spectrum, *m/z* 495 ($M^+ - CH_3$), 453, 395, 353.

(*E*)-(2*R*,3*S*,4*S*)-3,4-Di-*O*-acetyl-1,2-*O*-isopropylidene-5-octen-7-one-1,2,3,4-tetraol (26). Under the same reaction conditions as for the preparation of **23**, compound **24** afforded diacetate **26** (75% yield) as a colorless oil: $[\alpha]_D$ cf. Table I; IR (film) 2990, 2920, 1750, 1680, 1635, 1380, 1220, 1070 cm^{-1}; ^1H NMR (500 MHz) δ 6.69 (dd, *J* = 5.2, 16.1 Hz, 1 H), 6.24 (dd, *J* = 1.6, 16.1 Hz, 1 H), 5.68 (ddd, *J* = 1.6, 5.2, 5.5 Hz, 1 H), 5.13 (dd, *J* = 4.7, 5.5 Hz, 1 H), 4.22 (ddd, *J* = 4.7, 5.4, 6.7 Hz, 1 H), 4.01 (dd, *J* = 6.7, 8.8 Hz, 1 H), 3.83 (dd, *J* = 5.4, 8.8 Hz, 1 H), 2.27 (s, 3 H), 2.13 (s, 3 H), 2.11 (s, 3 H), 1.42 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR δ 197.25, 170.14, 169.38, 139.66, 132.09, 110.09, 73.97, 72.53, 71.26, 65.59, 27.37, 26.09, 25.24, 2 × 20.70. Anal. Calcd for $C_{15}H_{22}O_7$: C, 57.31; H, 7.06. Found: C, 57.33; H, 7.35.

(*E*)-(2*R*,3*R*,4*S*)-4-*O*-Acetyl-3-*O*-(benzyloxymethylene)-1,2-*O*-isopropylidene-5-octen-7-one-1,2,3,4-tetraol (28). To a solution of **16** (200 mg, 0.507 mmol) in ethyl ether (5 mL) at −20 °C, zinc borohydride (2 mL of a solution in ethyl ether[27]) was added and the resulting solution was stirred for 0.5 h, whereupon brine (0.2 mL) was added and the cooling bath was removed. After 0.5 h of stirring at room temperature, ethyl ether (30 mL) and anhydrous Na_2SO_4 (3 g) were added and the mixture was left for 1 h. Filtration and evaporation of the solvent afforded 195.5 mg (97% yield) of crude **27** which was immediately used for further reactions. Subsequent acetylation, dimethyl ketal hydrolysis, and flash chromatography, carried out in an analogous way as in the case of **22**, gave 164.4 mg (82% overall yield) of **28** as colorless oil: $[\alpha]_D$ +29.8° (*c* 0.81); IR (film) 3000, 2940, 1755, 1690, 1645, 1465, 1380, 1235, 1030 cm^{-1}; ^1H NMR (500 MHz) δ 7.33 (br s, 5 H), 6.77 (dd, *J* = 5.6, 16.1 Hz, 1 H), 6.24 (dd, *J* = 1.5, 16.1 Hz, 1 H), 5.77 (ddd, *J* = 1.5, 2.5, 5.6 Hz, 1 H), 4.90 $^1/_2$AB q, *J* = 7.1 Hz, 1 H), 4.83 ($^1/_2$AB q, *J* = 7.1 Hz, 1 H), 4.65 ($^1/_2$AB q, *J* = 11.9 Hz, 1 H), 4.62 ($^1/_2$AB q, *J* = 11.9 Hz, 1 H), 4.10–3.97 (m, 4 H), 2.27 (s, 3 H), 2.09 (s, 3 H), 1.40 (s, 3 H), 1.35 (s, 3 H); ^{13}C NMR δ 197.51, 169.52, 140.15, 137.35, 131.93, 128.51, 127.88, 127.78, 109.51, 94.89, 78.34, 74.78, 73.05, 70.09, 66.41, 27.32, 26.51, 25.28, 20.87. Anal. Calcd for $C_{21}H_{28}O_7$: C, 64.27; H, 7.19. Found: C, 64.47; H, 7.28.

(*E*)-(2*R*,3*R*,4*S*)-3,4-Di-*O*-acetyl-1,2-*O*-isopropylidene-5-octen-7-one-1,2,3,4-tetraol (29). To a solution of **27** (prepared as in the previous procedure, 96.1 mg, 0.242 mmol) in a mixture of liquid ammonia (3 mL), THF (6 mL), and ethanol (30 μL) at −60 °C, sodium was added in small pieces until the dark blue color persisted for 10 min. Then, a solid NH_4Cl was added and the cooling bath was removed. When all the ammonia evaporated, the reaction mixture was diluted with ethyl ether and warmed to room temperature. Filtration and evaporation of solvents yielded the crude intermediate diol. It was immediately acetylated, dimethyl ketal was hydrolyzed, and the crude product was purified by flash chromatography in an analogous way as in the case of **23** to afford 61.7 mg (81% yield) of **29** as a colorless oil: $[\alpha]_D$ cf. Table I; IR (film) 2990, 2940, 1755, 1685, 1640, 1375, 1070 cm^{-1}; ^1H NMR (500 MHz) δ 6.74 (dd, *J* = 5.8, 16.1 Hz, 1 H), 6.28 (dd, *J* = 1.6, 16.1 Hz, 1 H), 5.77 (ddd, *J* = 1.6, 3.0, 5.8 Hz, 1 H), 5.19 (dd, *J* = 3.0, 6.9 Hz, 1 H), 4.15 (ddd, *J* = 5.1, 6.3, 6.9 Hz, 1 H), 4.03 (dd, *J* = 6.3, 8.6 Hz, 1 H), 3.84 (dd, *J* = 5.1, 8.6 Hz, 1 H), 2.30 (s, 3 H), 2.10 (s, 3 H), 2.09 (s, 3 H), 1.43 (s, 3 H), 1.34 (s, 3 H); ^{13}C NMR δ 197.33, 169.73, 169.39, 138.90, 132.27, 109.90, 73.56, 73.22, 71.62, 66.34, 27.46, 26.46, 25.22, 2 × 20.67. Anal. Calcd for $C_{15}H_{22}O_7$: C, 57.31; H, 7.06. Found: C, 57.50; H, 7.31.

(*E*)-(2*R*,3*S*,4*R*)-4-*O*-Acetyl-3-*O*-(benzyloxymethylene)-1,2-*O*-isopropylidene-5-octen-7-one-1,2,3,4-tetraol (31). Under the same reaction conditions as for the preparation of **28**, compound **20** afforded alcohol **30** in 95% yield (crude) and then, after flash chromatography, acetate **31** (82% overall yield) as a colorless oil: $[\alpha]_D$ −2.2° (*c* 1.00); IR (film) 2940, 2860, 1755, 1690, 1650, 1640, 1380, 1230, 1030; ^1H NMR (500 MHz) δ 7.33 (br s, 5 H), 6.84 (dd, *J* = 5.7, 16.2 Hz, 1 H), 6.21 (dd, *J* = 1.5, 16.2 Hz, 1 H), 5.47 (ddd, *J* = 1.5, 3.4, 5.7 Hz, 1 H), 4.92 $^1/_2$AB

q, J = 7.0 Hz, 1 H), 4.87 ($^1/_2$AB q, J = 7.0 Hz, 1 H), 4.68 (s, 2 H), 4.20 (ddd, J = 6.5, 6.7, 7.1 Hz, 1 H), 4.01 (dd, J = 6.5, 8.4 Hz, 1 H), 3.94 (dd, J = 3.4, 6.7 Hz, 1 H), 3.81 (dd, J = 7.1, 8.4 Hz, 1 H), 2.26 (s, 3 H), 2.04 (s, 3 H), 1.42 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR δ 197.47, 169.47, 140.16, 137.66, 132.15, 128.45, 127.75, 127.65, 109.64, 95.03, 78.70, 76.24, 73.11, 69.96, 65.98, 27.19, 26.35, 25.40, 20.81. Anal. Calcd for $C_{21}H_{28}O_7$: C, 64.27; H, 7.19. Found: C, 64.50; H, 7.30.

(*E*)-(2*R*,3*S*,4*R*)-3,4-Di-*O*-acetyl-1,2-*O*-isopropylidene-5-octen-7-one-1,2,3,4-tetraol (32). Under the same reaction conditions as for the preparation of **29**, compound **30** afforded diacetate **32** (75% yield) as a colorless oil: $[\alpha]_D$ cf. Table I; IR (film) 2980, 2930, 1750, 1685, 1640, 1375, 1220, 1070 cm^{-1}; ^{1}H NMR (500 MHz) δ 6.75 (dd, J = 5.7, 16.1 Hz, 1H), 6.22 (dd, J = 1.4, 16.1 Hz, 1 H), 5.56 (ddd, J = 1.4, 5.0, 5.7 Hz, 1 H), 5.16 (dd, J ; 4.4, 5.0 Hz, 1 H), 4.30 (ddd, J = 4.4, 5.7, 6.8 Hz, 1 H), 4.03 (dd, J = 6.8, 8.6 Hz, 1 H), 3.75 (dd, J = 5.7, 8.6 Hz, 1 H), 2.28 (s, 3 H), 2.11 (s, 3 H), 2.10 (s, 3 H), 1.42 (s, 3 H), 1.35 (s, 3 H; ^{13}C NMR δ 197.35, 170.17, 169.34, 139.66, 132.38, 110,03, 74.14, 72.83, 71.76, 65.83, 27.17, 26.03, 25.39, 2×20.75. Anal. Calcd for $C_{15}H_{22}O_7$: C, 57.31; H, 7.06. Found: C, 57.44; H, 7.25.

General Procedure for Preparation of Reference Compounds 23, 26, and 29 from 33,[29] 34,[30] and 35,[31] Respectively. The preparation of **23** is described as an illustrative case. To a solution of dithioacetal **33** (761 mg, 2 mmol) in a mixture of acetone–water (9 mL, 8:1 v/v), were added yellow mercury oxide (1.0 g, 4.6 mmol) and mercury chloride (1.0 g, 3.7 mmol). The mixture was allowed to stir while the temperature was raised to 60 °C over 3 h. At this moment TLC showed the absence of starting material. Then, the mixture was cooled to room temperature and filtered through a short pad of Celite and the solvents were evaporated. To the residue was added toluene (10 mL), and solids were filtered off. Then, the solution was treated with acetonyltriphenylphosphorane (830 mg, 2.6 mmol), and the reaction mixture was stirred at 60 °C for 4 h. After the mixture was cooled to room temperature, ethyl acetate (10 mL) and hexane (20 mL) were added, the precipitated triphenylphosphine oxide was removed by filtration, and the solvents were evaporated. The crude product was purified by flash chromatography (H-EA 3:2 v/v). When this procedure was used compounds **23**, **26**, and **29** were obtained in 70, 68, and 60% yield, respectively. Optical rotations of these compounds are presented in Table I. All spectral data were superimposable with those obtained for compounds synthesized from ketones **15**, **19**, and **16**, respectively.

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Registry No. 3, 15186-48-8; **5**, 534-22-5; **6**, 103061-82-1; **8**, 103061-83-2; 9, 107941-07-1; **10**, 107941-08-2; **11**, 107941-09-3; **12**, 104731-95-5; **13**, 107941-10-6; **14**, 107959-94-4; **15**, 107941-11-7; **16**, 107941-12-8; **17**, 107941-13-9; **18**, 104731-97-7; **19**, 107941-14-0; **20**, 104731-99-9; **21**, 104732-00-5; **22**, 107941-15-1; **23**, 104732-01-6; **24**, 108031-86-3; **25**, 108031-87-4; **26**, 108031-88-5; **27**, 104732-02-7; **28**, 107941-16-2; **29**, 104760-54-5; **30**, 108031-89-6; **31**, 107941-17-3; **32**, 108031-90-9; **33**, 107941-18-4; **34**, 107941-19-5; **35**, 100423-67-4; Ph_3P=CHCOMe, 1439-36-7.

Synthesis of the 1,3-Dioxolane Ring System of the Trichothecenes Sambucinol and Sporol via a Stereoselective Claisen Rearrangement[1]

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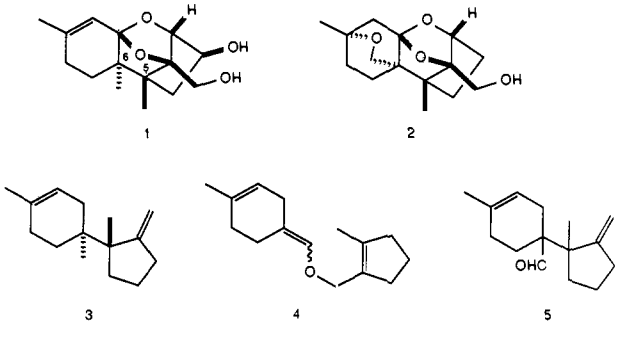
Abstract: The major stereoisomer from the Claisen rearrangement of allyl vinyl ether **10** was shown to be keto nitrile **12** by an X-ray crystallographic analysis on the derived hydroxy nitrile **15**. In a similar fashion, allyl vinyl ether **22** produced keto nitrile **23a**. This substance was converted into hydroxymethyl ketal **25**, which bears the 1,3-dioxolane ring system present in sambucinol **1** and sporol **2**.

Sambucinol **1**[3] and sporol **2**[4] represent recently discovered, unique trichothecenes that are postulated to have trichodiene **3** as their biosynthetic progenitor.[3] While stereocontrolled strategies for the synthesis of trichodiene have been reported,[5] routes employing the Claisen rearrangement for the stereoselective formation of the C_5–C_6 bond bearing the stereogenic centers have been disappointing. Thus, Suda reported[6] that Claisen rearrangement of stereoisomeric vinyl ethers **4** of undefined composition afforded a 1:1 mixture of aldehydes **5**, which, upon Wolff–Kishner reduction gave rise to trichodiene **3** and its stereoisomer, bazzanene. In a reinvestigation of the rearrangement, Gilbert[7] demonstrated that the selectivity for the chair transition state was 85% for vinyl ethers **4**, and that the general lack of stereoselectivity was a result of the inability to control the enol ether double bond stereochemistry. In a related *O*-silyl ester enolate Claisen rearrangement of ester **6**, Kraus[8] realized a 1:1 mixture of carboxyic acids **7**. Finally,



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(1) Dedicated to Professor George Büchi on the occasion of his 65th birthday.
(2) Crystallographer to whom inquires should be addressed concerning the X-ray analysis.
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