^{1}H NMR ($CDCl_3$) δ 3.80 (m, 2 H), 3.26 (m, 1 H), 2.05 (m, 1 H), 1.77 (m, H), 1.53-1.25 (m, 17 H), 1.01 (d, J = 6.6 Hz, 3 H), 0.86 (t, J = 6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 86.0, 66.6, 39.0, 34.8, 34.4, 31.9, 29.9, 29.7, 29.6, 29.5, 26.6, 22.7, 17.3, 14.1; HRMS calcd for $C_{14}H_{28}O - H^+$ 211.2062, found 211.2053.

The major (trans) stereoisomer could not be effectively separated from the minor product, *cis*-**6**. The ratio between them was therefore estimated from the relative sizes of the ^{13}C signals at 66.6 and 86.0 ppm and the much smaller signals at 66.7 and 81.8 ppm. The latter signals corresponded to carbon resonances present in the spectrum of **6** prepared from **14b**.

Also prepared in this manner was **8**: IR (neat) 2922, 2853, 1464, 912 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.64 (m, 1 H), 5.04 (m, 2 H), 3.84 (m, 2 H), 3.43 (m, 1 H), 2.35 (m, 1 H), 2.10 (m, 1 H), 1.77-1.25 (m, 17 H), 0.87 (t, J = 6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 139.1, 115.5, 83.7, 67.0, 49.8, 33.9, 33.2, 31.9, 29.7, 29.5, 29.3, 26.47, 22.7, 14.1 (one peak, probably 29.7, 29.5, or 29.3, corresponds to two carbon resonances); HRMS calcd for $C_{15}H_{28}O$ 224.2140, found 224.2140. (Note: Occasionally the green color of LN faded partway through the reaction, perhaps due to reaction of the excess LN with the Teflon-covered stirring bar. In these cases an additional portion of LN was added, after which the reactions proceeded normally.)

2-*n*-Hexyl-4-methyl-*N*-butylpyrrolidine (10). 4-(*n*-Butylamino)-1-decane was prepared, at 0 °C in Et_2O, by the reaction of the appropriate imine with allylmagnesium bromide and purified by Kugelrohr distillation (75 °C, 5 mm): IR (neat) 2957, 2924, 2856, 1466 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.76 (m, 1 H), 5.05 (m, 2 H), 2.54 (m, 2 H), 2.19 (m, 4 H), 1.25 (m, 12 H), 0.87 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 135.8, 116.8, 56.9, 46.7, 38.3, 33.9, 32.4, 31.7, 29.4, 25.6, 22.5, 20.4, 13.9, 13.8. Anal. Calcd for $C_{14}H_{29}N$: C, 79.55; H, 13.83; N, 6.63. Found: C, 79.20; H, 13.69; N, 6.53.

A solution of the above-prepared amine (402 mg, 1.9 mmol) in 5 mL of toluene was treated with PhSH (212 μL, 2.1 mmol), paraformaldehyde (74 mg, 2.4 mmol), and a few crystals of 4,4'-methylenebis(2,6-di-*tert*-butylphenol). The mixture was stirred overnight at 100 °C. The volatiles were removed under reduced pressure, leaving the crude *N,S*-acetal **9**: ^{1}H NMR ($CDCl_3$) δ 7.48-7.17 (m, 5 H), 5.77 (m, 1 H), 4.97 (m, 2 H), 4.58 (s, 2 H), 2.69-2.53 (m, 4 H), 2.11 (m, 2 H), 1.27 (m, 12 H), 0.85 (m, 6 H).

The *N,S*-acetal **9** was taken up in 10 mL of THF and added to 11 mL of 0.5 M LN in THF at 0 °C. After 1.5 h at 0 °C, the mixture was poured into dilute HCl and the nonbasic material was removed by Et_2O extraction. The solution was basified with NaOH and then extracted with CH_2Cl_2. The organic extracts were dried (K_2CO_3) and concentrated, and the product was purified on silica gel with a 0-3% gradient of methanolic ammonia in CH_2Cl_2 to give **10** (143 mg, 56% for two steps): IR (neat) 2957, 2928, 2859, 1458 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.73 (m, 1 H), 2.32-1.98 (m, 4 H), 1.45-1.24 (m, 17 H), 1.00 (d, J = 6 Hz, 3 H), 0.85 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 6.66, 61.0, 54.3, 40.2, 33.5, 31.8, 30.2, 29.9, 29.5, 26.7, 22.5, 20.8, 20.7, 14.0, 13.9; HRMS calcd for $C_{15}H_{31}N$ 225.2456, found 225.2451.

Sigmatropic Rearrangements of 11, 13a,b. These reactions were carried out by using the same reductive-lithiation protocol employed for **5** and **7**. The rearrangements were allowed to proceed for 1.5 h at 0 °C. Workup and product isolation was performed as in the case of **6** and **8**. The resulting alcohols were identified by comparison with authentic samples prepared by using established methods (see ref 6).

Amines 16 and 17. *N,S*-Acetal **15** was prepared in the same manner as was **9** from allyl heptylamine (bp 170 °C/5 mm): IR (neat) 2955, 2928, 2855, 742, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45 (m, 2 H), 7.25 (m, 3 H), 5.73 (m, 1 H), 5.05 (m, 2 H), 4.55 (s, 2 H), 3.16 (d, J = 6 Hz, 2 H), 2.54 (t, J = 6 Hz, 2 H), 1.21 (m, 10 H), 0.87 (t, J = 6 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 138.5, 135.2, 132.3, 128.6, 126.2, 117.7, 63.9, 55.9, 52.0, 31.7, 29.0, 27.2, 27.1, 22.5, 14.0. Anal. Calcd for $C_{17}H_{27}NS$: C, 73.58; H, 9.81; N, 5.05; S, 11.55. Found: C, 73.48; H, 9.90; N, 5.14; S, 11.68.

A solution of 0.5 M LN in THF (10 mL) was cooled to 0 °C and a solution of **15** (280 g, 1.0 mmol) in 5 mL of THF was added slowly. After stirring for 2 h, the reaction was worked up in the manner described for the cyclization leading to **10**. Purification of the products on silica gel (eluting with 3% methanolic ammonia in CH_2Cl_2) gave **17** and **16** (130 mg, 76%). Their ratio was determined to be 4:1 by NMR. (The minor product **16** was identified by comparison with a nearly pure sample prepared by quenching a reaction similar to the above but conducted at -78 °C immediately after reductive lithiation). **17**: IR (neat) ^{1}H NMR ($CDCl_3$) δ 5.76 (m, 1 H), 5.04 (m, 2 H), 2.60 (t, J = 6 Hz, 2 H), 2.52 (t, J = 6 Hz, 2 H), 2.19 (m, 2 H), 1.20 (m, 11 H), 0.79 (t, J = 6 Hz, 3 H). **16**: IR (neat) 2955, 2928, 916, 1458 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.82 (m, 1 H), 5.15 (m, 2 H), 2.95 (d, J = 6 Hz, 2 H), 2.28 (t, J = 7 Hz, 2 H), 2.17 (s, 3 H), 1.48-1.25 (m, 10 H), 0.85 (t, J = 6 Hz, 3 H).

Acknowledgment. We thank the Research Board of the University of Illinois and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their support of this work.

Registry No. 1, 113352-43-5; *cis*-**2**, 113352-45-7; *trans*-**2**, 113352-46-8; **3**, 113352-55-9; *cis*-**4**, 113352-60-6; *trans*-**4**, 113352-61-7; **5**, 119010-67-2; *trans*-**6**, 119010-68-3; *cis*-**6**, 119010-80-9; **7**, 119010-69-4; *trans*-**8**, 119010-70-7; *cis*-**8**, 119010-81-0; **9**, 119010-71-8; *cis*-**10**, 119010-72-9; *trans*-**10**, 119010-83-2; **11**, 119010-73-0; **12**, 117951-87-8; **13a**, 119010-74-1; **13b**, 119010-84-3; **14a**, 94453-48-2; **14b**, 94453-47-1; **15**, 119010-75-2; **16**, 119010-76-3; **17**, 119010-77-4; $CH_3(CH_2)_5CH(OH)CH_2CH{=}CHC(CH_3)_2OCH_3$, 119010-78-5; (*E*)-$CH_3CH{=}CHCH_2OH$, 504-61-0; (*Z*)-$CH_3CH{=}CHCH_2OH$, 4088-60-2; $CH_2{=}CHCH_2CH_2OH$, 627-27-0; $CH_3(CH_2)_5OCH_2CH{=}CHCH_2CH_2OH$, 119010-79-6; PhSH, 108-98-5; 1-decen-4-ol, 36971-14-9; (iodomethyl)-tributyltin, 66222-29-5; decyl phenyl sulfide, 13910-18-4; allyl alcohol, 107-18-6; 4-(*n*-butylamino)-1-decene, 119010-82-1; 1-(butylimino)heptane, 6898-76-6; allyl heptylamine, 91342-40-4.

A Highly Stereoselective Synthesis of (+)-Olivin, the Aglycon of Olivomycin A

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Abstract: The first total synthesis of (+)-olivin (**1**), the naturally occurring enantiomer of the aglycon of olivomycin A, is described. The synthesis is highly stereoselective, featuring the reaction of (γ-methoxyallyl)boronate **21** with chiral aldehyde **17** and the addition of lithiodivinylcuprate to unsaturated aldehyde **40** as the key diastereoselective transformations. The anthracenone nucleus of **1** was constructed beginning with the coupling of unsaturated ester **42** and phthalide **46**. The vinyl unit of naphthoate **48** was oxidized to the acetic ester appendage in **53**, and then the final C-C bond of anthracenone **54** was established by a Dieckmann cyclization. The C(2') hydroxyl group of **57** was oxidized to the necessary side-chain carbonyl function, and then the C(2) hydroxyl group was introduced stereoselectively by the *m*CPBA epoxidation of the mono TBDMS enol ether prepared from **58**. All five acid-labile protecting groups were removed in a single operation to complete the synthesis.

Olivin (**1**) is the aglycon of olivomycin A (**2**), a member of the aureolic acid family of antitumor antibiotics.[2] Also included in this group are the chromomycins and the mithramycins [e.g., aureolic acid (**4**)]. Several of these antibiotics have undergone

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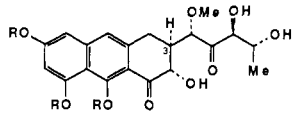
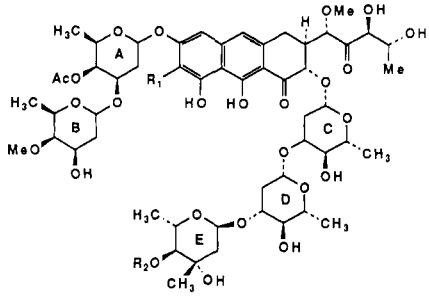
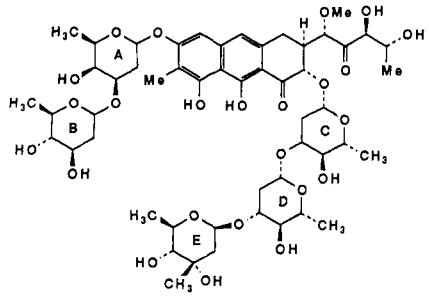
successful clinical trials as anticancer drugs.[2,3] Olivomycin A has been used in the Soviet Union for the treatment of testicular and tonsilar tumors, while chromomycin A_3 (**3**) and aureolic acid (**4**) have been approved for clinical use in Japan and the United States, respectively. These compounds are inhibitors of DNA-dependent RNA polymerase,[4] but the exact site of binding to DNA is still unclear.[4] The binding to DNA affects both normal and cancerous cells, resulting in acute toxicity and side effects such as anorexia, internal bleeding, and anemia among others.[2] Consequently, the development of synthetic routes to analogues with improved therapeutic efficacy is highly desirable.



1, olivin (R = H)
5, trimethyl olivin (R = Me)



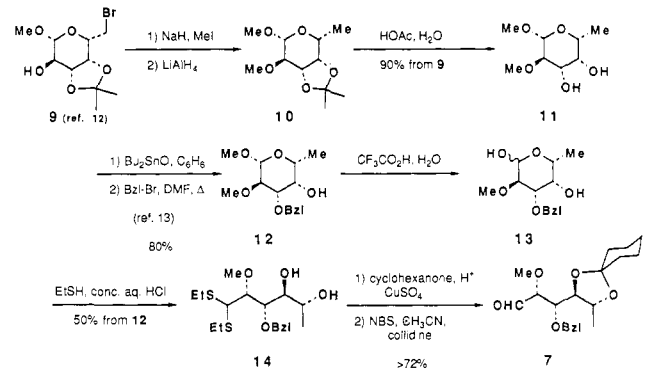
2, R_1 = H, R_2 = $(CH_3)_2CHCO$-, olivomycin A
3, R_1 = CH_3, R_2 = CH_3CO-, chromomycin A_3



4, aureolic acid

The total synthesis of the aureolic acid antibiotics has been the focus of attention of several research groups.[5] The bulk of the work thus far has been devoted to the synthesis of olivin. Weinreb reported a synthesis of racemic tri-*O*-methylolivin (**5**) in 1984,[6] and 2 years later Franck reported an efficient total synthesis of the natural enantiomer of **5**.[7] Several additional reports have appeared describing studies related to the synthesis of the anthracenone nucleus and the carbohydrate-like side chain.[8] We have completed the first synthesis of olivin in the naturally occurring enantiomeric form and provide here a full account of this work.[9]

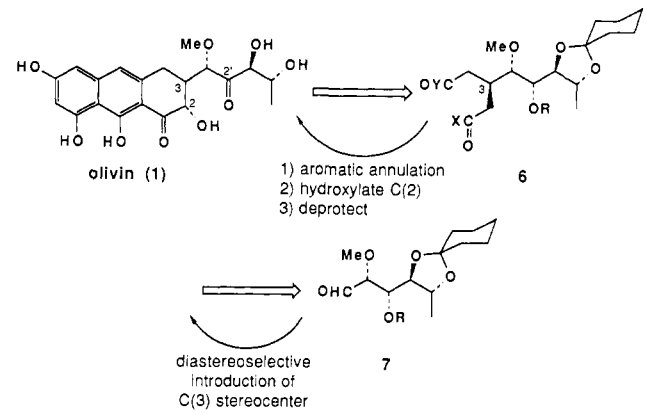
Scheme I



Synthetic Considerations

Our strategy called for the carbohydrate-like side chain of olivin to be assembled in the form of a differentially protected D-fucose derivative **7**, the resident chirality of which would be used to induce the correct stereochemistry at C(3) of **6** in a subsequent C–C bond forming reaction. Because the C(3) side chain of **1** would be carried through a major portion of the synthesis, we decided to mask the potentially sensitive C(2′) carbonyl unit as an alcohol derivative in **7**. The anthracenone nucleus of **1** would be assembled from **6** by an aromatic annulation sequence, the specific tactics for which would depend on the functionality X and Y.[6b,10] The critical final steps of the synthesis would involve introduction of a hydroxyl group at C(2) followed by deprotection. The hydroxylation step was not regarded to be strategically significant

Synthetic Strategy



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since the C(2) center is trans to the C(3) side chain, a relationship we presumed could be controlled by either kinetic or thermodynamic experimental conditions. It seemed prudent, however, to design the synthesis such that acid-labile protecting groups would be used with all advanced intermediates, since olivin and chromomycinone (the aglycon of the chromomycins) are known to be base sensitive.[2b]

Synthesis of the D-Fucose Derivative 7

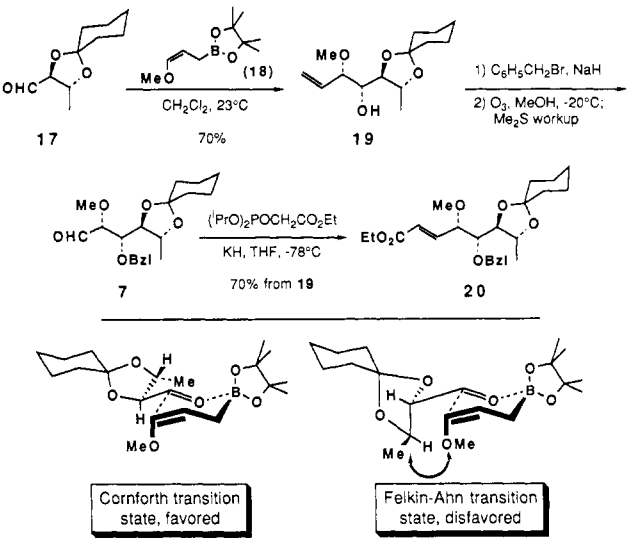
At the inception of this synthesis, D-galactose appeared to be an ideal starting material because each of the six carbon atoms and four chiral centers mapped directly into **7** and only the hydroxyl group at C(6) would need to be removed.[11] Thus, commercially available β-D-galactopyranoside (**8**) was converted into **9** by using slight modifications of a two-step literature procedure,[12] and then **9** was elaborated to D-fucose derivative **7** by using the nine-step sequence summarized in Scheme I; a more detailed discussion of this sequence appears elsewhere.[9c]

Although the desired subgoal had been reached, we were not satisfied with what had been accomplished. First of all, this synthesis required 11 steps from D-galactose and was not nearly so efficient as we would have liked (14% yield overall from **8**). Second, no new chemistry had been developed. And, finally, the brutally harsh conditions[14] required for the conversion of **13** to **14** precluded the use of more desirable protecting groups for C(3)–OH (e.g., silyl ethers). Intermediates containing C(3)–TBDMS ethers ultimately were used in completing this synthesis.

These shortcomings prompted us to begin exploratory studies of diastereoselective approaches for the synthesis of carbohydrate-like molecules from acyclic precursors. The idea that carbohydrates could be constructed via the reaction of an allyl ether anion and an α-alkoxy aldehyde was particularly attractive. For this approach to be successful, however, it would be necessary to control (i) the regioselectivity of the reaction of the allyl ether anion,[15] (ii) the syn (threo) or anti (erythro) relationship at C(3) and C(4) generated in concert with the new C–C bond, and (iii) the diastereofacial selectivity of the addition of the allyl ether anion to the electrophilic chiral aldehyde [e.g., C(3)–C(4) relative to C(5)].

Solutions to issues i and ii were available by virtue of studies by Hoffmann and Wuts on the reactions of (γ-alkoxyallyl)boronates with achiral aldehydes.[16–18] Relatively little information was available in 1982 when our studies were initiated, however, regarding the stereochemistry of such reactions with chiral aldehydes. Hoffmann had reported several examples of reactions of (*E*)- and (*Z*)-crotylboronates with chiral aldehydes such as 2-methylbutanal, but the best diastereofacial selectivity that had been reported was only 83:17.[19] In fact, the reaction of 2-methylbutanal and (*Z*)-crotylboronate, the closest analogy to the reaction we hoped to achieve, provided the 3,4-syn-4,5-anti diastereomer with only 70:30 selectivity.[19]

Aldehyde **17** was prepared by a four-step synthesis from L-threonine (ca. 50% yield overall)[9b,20] and was treated with the known reagent **18**[17a,c] in CH_2Cl_2. This reaction was relatively slow and required 24–48 h at room temperature to go to completion. It was, however, extremely selective and provided homoallyl alcohol **19** in 70% yield with greater than 95% diastereoselectivity. The stereochemistry of **19** was quickly verified as the desired 3,4-syn (threo)-4,5-anti (erythro) diastereomer by conversion to **7** and **20**, both of which had already been prepared from D-galactose.



The stereochemistry of **19** is superficially consistent with the reaction of **17** and **18** proceeding by way of a Felkin–Ahn transition state, as suggested in our preliminary account.[9b] On the basis of our results with the reactions of **17** and D-glyceraldehyde acetonide with the pinacol (*E*)- and (*Z*)-crotylboronates (methyl replacing methoxyl in **18**) however, we now believe the reaction of **17** and **18** proceeds by way of the Cornforth transition state since a serious nonbonded interaction exists between the (*Z*)-methoxyl substituent and the C(3) substituents of **17** in the Felkin–Ahn arrangement. A detailed discussion of these arguments is presented elsewhere.[21]

The synthesis of **7** is relatively brief (seven steps from L-threonine) and considerably more efficient (25% overall) than the D-galactose-based synthesis. One problem, however, concerned the preparation of **18** which, in our hands, was low yielding, tedious, and not readily amenable to scale-up.[17a,c] These problems were solved by using dimethyl [(*Z*)-γ-methoxyallyl]boronate (**21**), which is extremely easy to generate and use in situ.[17b,22] This modified procedure provided **19** in slightly higher yield (75–83%) than the method involving **18** and was used for all large-scale work.

Introduction of the C(3) Stereocenter in Olivin Precursors

The next stage of the synthesis involved devising a diastereoselective method for introducing the C(3) stereocenter in intermediates suitably functionalized for elaboration to olivin. Our original intention was to proceed by way of a cyclohexenone

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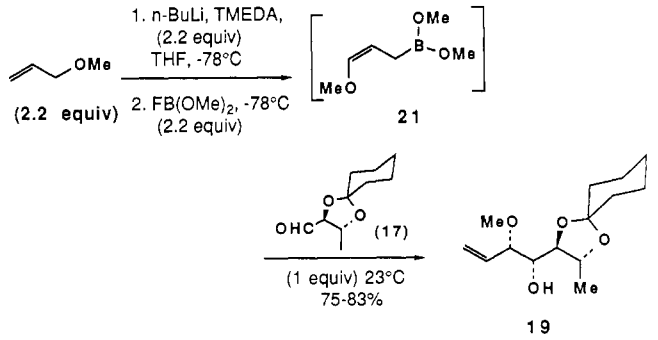
(19) Hoffmann, R. W.; Zeiss, H. J.; Ladner, W.; Tabche, S. *Chem. Ber.* **1982**, *115*, 2357.

(20) Servi, S. *J. Org. Chem.* **1985**, *50*, 5865.

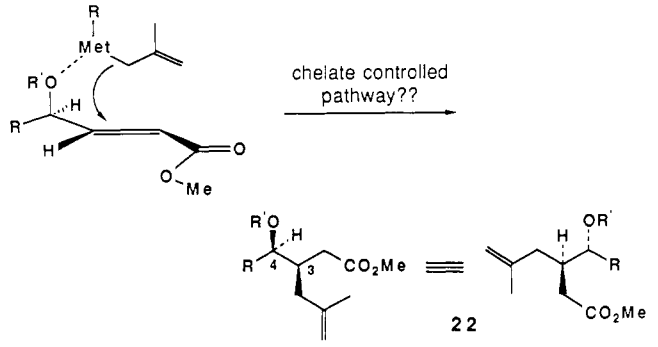
(21) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422.

(22) Fujita, K.; Schlosser, M. *Helv. Chim. Acta* **1982**, *65*, 1258.



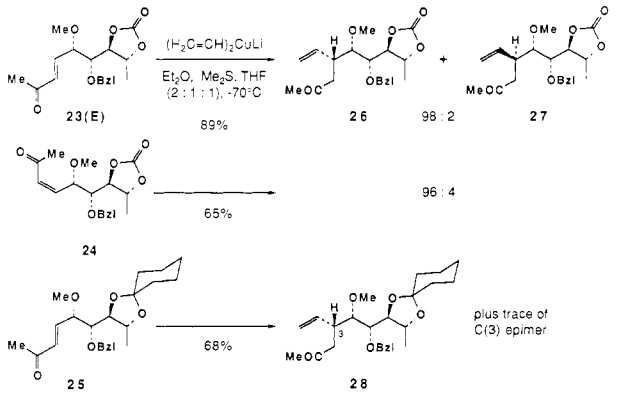
intermediate that would be prepared by an aldol cyclization of **6** (X = Me, Y = H). The critical steps in the synthesis of **6** thus would involve a Wittig olefination to α,β-unsaturated methyl ketone followed by a diastereoselective 1,4-addition of an acetaldehyde equivalent.[23]

Relatively little was known about the diastereoselectivity of the 1,4-additions of organometallic reagents to γ-alkoxy-α,β-unsaturated carbonyl systems when this research was initiated. Isobe had reported several examples of highly diastereoselective additions of alkyllithium reagents to γ-alkoxy-α-trimethylsilyl-α,β-unsaturated sulfones that apparently proceed by way of chelated intermediates,[24] and Nicolaou had shown that dimethallylcuprate reacted with carbohydrate-derived enoates with very high selectivity that also could be rationalized by invoking chelated reaction intermediates.[25] These results were very interesting for our purposes since the stereochemical relationship between C(3) and C(4) of **22** is exactly that needed for C(3) and C(1′) of **6** (X = Me, Y = H). On the other hand, it was unclear as to the generality of this process, since Ziegler reported that the stereochemistry of the Nicolaou cuprate reaction is completely reversed when Bu_2CuLi is used.[26]

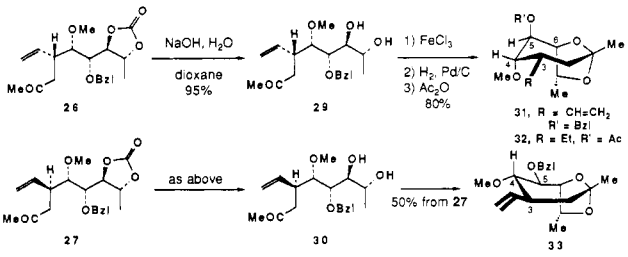


Attempts to condense enone **23** (prepared from **14**) and diallylcuprate were unsuccessful,[27] and when CH_2=$CHCH_2MgBr$ and CuBr–Me_2S were employed only products of 1,2-addition were detected. We also briefly examined the applicability of the Sakurai reaction to this problem.[28] No reaction occurred when enone **23** was treated with 1–2 equiv of $TiCl_4$ and allyltrimethylsilane at −78 °C. We assumed that the Lewis acid was binding preferentially to the ethereal or carbonate carbonyl oxygen atoms, thereby precluding reaction at the enone. When a much greater excess of reagents was used (5 equiv each), a mixture of products was obtained including compounds resulting from 1,2-carbonyl addition and benzyl ether cleavage.

A successful 1,4-addition reaction was realized when **23** was treated with excess divinylcuprate in an Et_2O, Me_2S, and THF solvent mixture.[29] Only one product (**26**) was detected by NMR analysis of the crude reaction product, but a second diastereomer (**27**) was isolated in low yield by chromatography. Similar results were subsequently achieved with enone **25**. Interestingly, the stereochemistry of this reaction is insensitive to the geometry of the enone [compare results with **23**(*E*) and **24**(*Z*)], an important observation since mixtures of enone and enoate isomers frequently are obtained in the reactions of carbohydrate-derived aldehydes and stabilized phosphoranes (Ph_3P=CHCOR).



The stereochemistry of adducts **26**–**28** was assigned following conversion to bicyclic ketals **32** and **33**. Thus, treatment of **26** and **27** with NaOH in aqueous dioxane afforded diols **29** and **30**, which cyclized under acidic conditions to give bicyclic ketals **31** and **33**. Best results were obtained by using $FeCl_3$ in CH_2Cl_2.[30] Ketal **31**, which was also obtained directly from **28** upon exposure to 98:2 TFA–H_2O (77% yield), was converted to **32** by hydrogenolysis and acylation in order to ensure first-order behavior of the H(4)–H(5) and H(5)–H(6) spin systems. The presence of *w* coupling ($J_{4,6}$ = 1.7 Hz) in **32** and its absence in **33**, together with the presence of two large coupling constants for H(4) in **33** ($J_{3,4}$ = 10.2 Hz, $J_{4,5}$ = 7.5 Hz; in addition, $J_{5,6}$ = 0 Hz) versus very small values in **32** ($J_{3,4}$ = 0 Hz, $J_{4,5}$ = 3.5 Hz, and $J_{5,6}$ = 1.7 Hz) enables the conformations and stereochemistry of **32** and **33** to be assigned as indicated in the accompanying diagrams.



These results clearly showed that **26** and **28** possess the wrong stereochemistry at C(3) for use in this approach to olivin since cyclohexenone **35** would be produced if a bond were constructed between C(4a) and C(9a) of **28** (olivin numbering). It was apparent, however, that 1,4-adducts **34** prepared from enoate **20** could be used if the roles of the vinyl and acetic ester appendages in subsequent C–C bond forming reactions were reversed. That is, reduction of the ester unit in **34** to the corresponding aldehyde followed by a Wittig olefination would give **36**. The unsaturated ester unit would provide a handle for constructing the naphthalene core of the aglycon, while the vinyl appendage would contribute C(2) of the natural product skeleton.

The stereochemistry of the reactions of vinylcuprates with enoates such as **20** proved to be the same as with enones **23** and **25**.[29a,31] For example, the reaction of either **20a** or **20b** and

(23) An alternative strategy for constructing the desired cyclohexenone intermediate via Diels–Alder methodology is discussed in ref 9c.

(24) Isobe, M.; Kitamura, M.; Goto, T. *Tetrahedron Lett.* **1979**, 3465; **1980**, *21*, 4727.

(25) (a) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1981**, *103*, 1224; *Tetrahedron Lett.* **1979**, 2327. (b) See also: Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1982**, *104*, 2027. (c) Tatsuta, K.; Amemiya, Y.; Kanemura, Y.; Kinoshita, M. *Tetrahedron Lett.* **1981**, *22*, 3997.

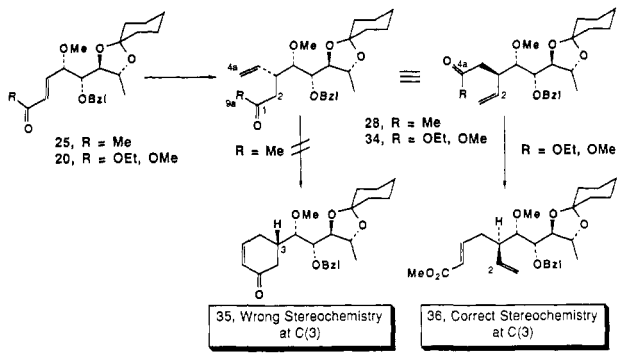
(26) Ziegler, F. E.; Gilligan, P. J. *J. Org. Chem.* **1981**, *46*, 3874.

(27) House, H. O.; Wilkins, J. M. *J. Org. Chem.* **1978**, *43*, 2443.

(28) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673.

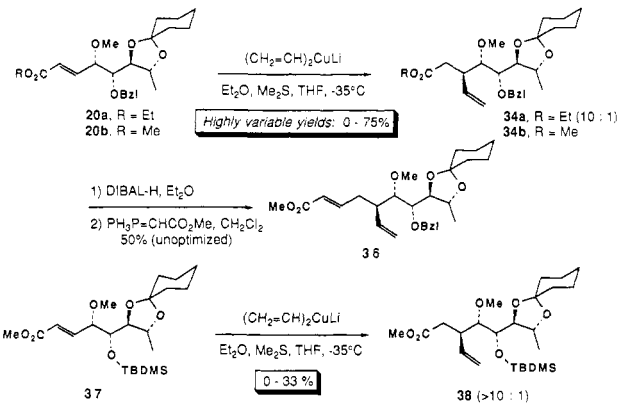
(29) (a) Roush, W. R.; Lesur, B. M. *Tetrahedron Lett.* **1983**, *24*, 2231. (b) House, H. O.; Chu, C. Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460.

(30) Singh, P. P.; Gharia, M. M.; Dasgupta, F.; Srivastava, H. C. *Tetrahedron Lett.* **1977**, 439.



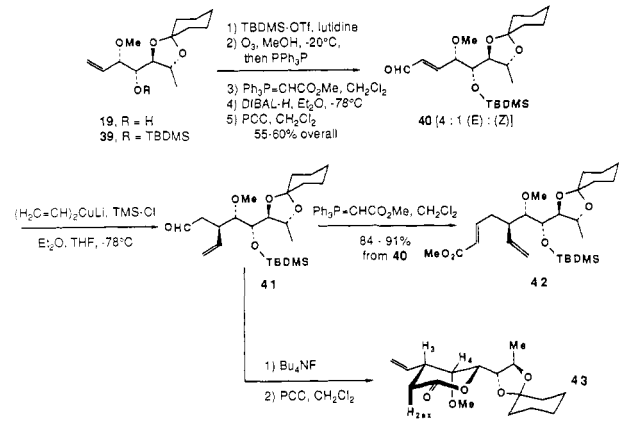
$(CH_2{=}CH)_2CuLi$ at −35 °C yielded **34a** and **34b** as 10:1 mixtures of C(3) epimers. Here again the stereochemistry of the reaction was independent of the enoate olefin geometry.[29a]

While this reaction appeared to solve the C(3) stereochemical problem, it was unsatisfactory for two reasons. First, the yield of **34** was highly variable (0–75%) and very poor results were obtained on attempted scale-up. Second, the benzyl ether protecting group, an artifact of the original galactose-based synthesis of aldehyde **7**, was unattractive for later stages of the synthesis. In a parallel series of experiments, therefore, TBDMS ether **37** was prepared (vide infra). While **37** also displayed useful diastereoselectivity (≥10:1) in the reaction with $(CH_2{=}CH)_2CuLi$, **37** was even less reactive than **20** and the best yield of **38** ever obtained was 33%.



The poor reactivity of **20** and **37** as cuprate acceptors[29b] together with the sensitivity of the vinylcuprate toward O_2 and Cu^{2+} impurities presumably contributed to these poor results. The reagent rapidly decomposed (visual evidence) when the reactions were attempted at temperatures above −35 °C, and enoates **20**/**37** were too unreactive for the experiments to be performed at temperatures below −40 °C. Poor results also were obtained in initial attempts to apply $(CH_2{=}CH)_2CuLi$–BF_3,[32] $CH_2{=}CHCu$–BF_3,[33] and $(CH_2{=}CH)_2Cu(CN)Li_2$[34] to this problem. Efforts to prepare **36** directly by the addition of vinylcuprates to the corresponding diene esters also were unpromising.

A highly effective solution to this phase of the synthesis ultimately was achieved by using unsaturated aldehyde **40** as the electrophilic component in this reaction.[35] The greater reactivity of the enal permitted this step to be performed at −78 °C, conditions under which $(CH_2{=}CH)_2CuLi$ was stable. This reaction is highly stereoselective (a single diastereomer was observed), high yielding (>84–91%), and highly reproducible. The reaction is successful if performed in the absence of TMS-Cl, albeit somewhat lower yielding (75%).[36] Here again, the stereoselectivity was not influenced by the isomeric purity of **40**, which was used in most cases as a mixture of olefin isomers.

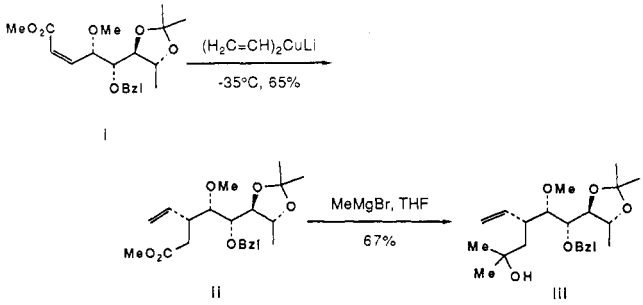


The stereochemistry of 1,4-adduct **41** was assigned following conversion to lactone **43**. In particular, the multiplicity of H(4) (br t, J = 2 Hz) and the diaxial coupling constant (J = 10 Hz) between H(3) and $H(2_{ax})$ are uniquely consistent with this structure.

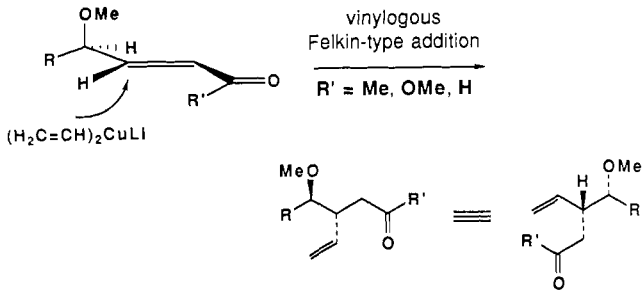
Aldehyde **40** was synthesized from **19** in excellent overall yield via a sequence involving (i) protection of the free alcohol as the TBDMS ether **39** (82%), (ii) ozonolysis to the corresponding aldehyde, (iii) Wittig olefination to give α,β-unsaturated ester **37** (70%), and (iv) reduction of **37** to the allylic alcohol followed by PCC oxidation (90%). Preparation of **40** directly from **39** by using $Ph_3P{=}CHCHO$ in the olefination step was less efficient (up to 55% following recycle of recovered saturated aldehyde), as some dienal (6–25%) was also produced. This method, however, provided (*E*)-**40** as a single olefin isomer.

It is interesting that the stereochemical outcome of the vinylcuprate additions to enones **23** and **25**, enoates **20** and **37**, and enal **40** are the same. In each case it is consistent with addition of the organometallic reagent anti to the allylic C–O bond from a rotamer in which the smallest allylic substituent, H, lies in the plane of the C–C double bond. We describe this as a "vinylogous Felkin-type addition" to reflect the absence of chelation in the reaction transition state and to emphasize the role that stereoelectronics presumably play.[37,38] The alternative allylic rotamer

(31) The assignment of stereochemistry to the enoate adducts rests on the correlation of ii, the major product of vinylcuprate addition to i, with tertiary alcohol iii, which was also prepared from enone adduct **26** [(i) ethylene glycol, *p*-TsOH, C_6H_6; (ii) NaOH, H_2O, dioxane; (iii) 2,2-dimethoxypropane, *p*-TsOH; (iv) MeMgCl, Et_2O; 51% overall yield].



(32) Smith, A. B., III; Jerris, P. J. *J. Am. Chem. Soc.* **1981**, *103*, 194.
(33) Yamamoto, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1978**, *100*, 3240.
(34) Lipshutz, B. H.; Kozlowski, J. A.; Parker, D. A.; Nguyen, S. L.; McCarthy, K. E. *J. Organomet. Chem.* **1985**, *285*, 437.
(35) For studies of the reactions of enals and organocuprates, see: (a) Liu, H. J.; Browne, E. N. C. *Can. J. Chem.* **1978**, *56*, 306. (b) Chuit, C.; Foulon, J. P.; Normant, J. F. *Tetrahedron* **1981**, *37*, 1385.
(36) For recent studies on the use of TMS-Cl in organocuprate conjugate additions, see: (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015, 6019. (b) Alexakis, A.; Berlan, J.; Besace, Y. *Ibid.* **1986**, *27*, 1047. (c) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Ibid.* **1986**, *27*, 4025. (d) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Ibid.* **1986**, *27*, 4029.
(37) (a) Che'rest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Ahn, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.
(38) This transition-state paradigm differs from the Felkin transition state for carbonyl addition in that C=C is aligned with the smaller (H) rather than the larger (R) substituent. The mechanism of the vinylcuprate conjugate additions is also undoubtedly different from a carbonyl addition. See, for example: (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015; **1984**, *25*, 3063. (b) Hallnemo, B.; Ullenius, C. *Ibid.* **1986**, *27*, 395, and references therein.

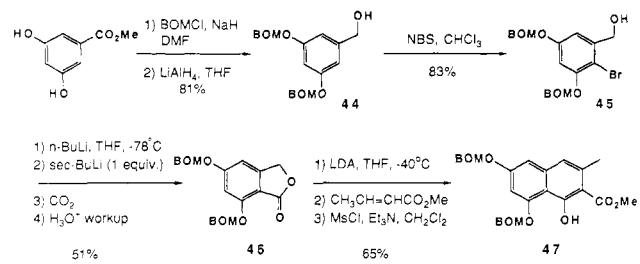


in which R eclipses the double bond is undoubtedly disfavored for steric reasons and is especially bad when the double bond is (*Z*). While we recognize that the allylic rotamer we invoke is reflective of the energetically favored ground-state conformation and may not actually be the reactive species in the transition state,[39] this picture is consistent with our observation that both olefin isomers of enone **23**, enoate **20**, and enal **40** give rise to the same (anti) diastereomer in the 1,4-addition reactions. Additional examples have been published that are consistent with this model.[40] The only organometallic 1,4-addition reactions that deviate markedly from the results reported here involve allylic cuprates,[25,26] allyllithium reagents,[25c,26,40a] and the additions of $RCu-BF_3$ to (*Z*)-enoates.[39] In each of these cases, the diastereoselectivity is consistent with a chelated reaction pathway (vide supra). Further experimentation is clearly called for to resolve the differences that exist, for example, in the behavior of allylic vs vinylic cuprates.

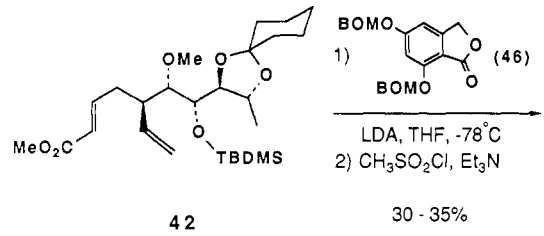
Completion of the Olivin Synthesis

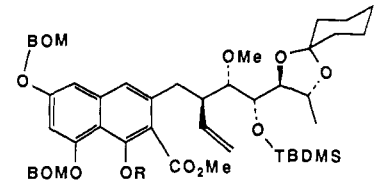
With a highly selective and efficient solution to the major stereochemical issues in hand, we turned to the problem of the construction of the anthracenone nucleus of **1**. Given the functionality established in intermediate **42**, we intended to proceed by synthesizing naphthoate **48** before the final ring was closed. Of several methods that were considered (and explored),[9c] the only one that proved useful in this context was the phthalide annulation protocol reported originally by Sammes.[10c]

Thus, phthalide **46** was prepared by a four-step sequence starting from methyl 3,5-dihydroxybenzoate.[41] As a test of this procedure, phthalide **46** was treated with LDA in THF at −40 °C and the resulting lithium anion condensed with methyl crotonate (excess) to give an intermediate hydroxytetralone that smoothly aromatized upon exposure to methanesulfonyl chloride (1.1 equiv based on **46**) and Et_3N (65% yield of naphthoate **47**). We did not use the aromatization conditions described by Sammes (CF_3CO_2H or BF_3-Et_2O),[10c] since we were concerned that the acid-labile protecting groups of **46** and enoate **42** might not survive.



The same protocol was used for the coupling of phthalide **46** and enoate **42**, with the exception that they were used in equimolar amounts. This reaction provided naphthoate **48** in 30–35% yield together with 5–10% of the corresponding phenolic mesylate **49**. Numerous attempts to improve this reaction by modifying the base, solvent, and reaction stoichiometry have been unsuccessful. Attempts to regenerate phenol **48** from mesylate **49** were also unsuccessful. Although the efficiency of this step was considerably lower than we had hoped for, sufficient quantities of **48** were prepared to complete the synthesis.

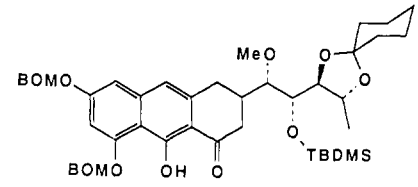




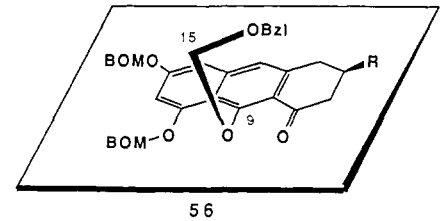
48, R = H
49, R = Ms

Protection of **48** by treatment with BOM-Cl and NaH in DMF proceeded smoothly to provide the fully protected naphthoate **50** in 91% yield (Scheme II). The vinyl appendage was then oxidized via a hydroboration sequence with 9-BBN to give alcohol **51**, which was oxidized to aldehyde **52** by using a Swern procedure.[42] Further oxidation of the aldehyde **52** to diester **53** proved to be nontrivial, as a variety of standard procedures for the oxidation of aldehydes to carboxylic acids, including PDC in DMF, Jones' reagent, mCPBA, and $AgCO_3$–Celite were very inefficient. Fortunately, use of Masamune's recently introduced method ($KMnO_4$, KH_2PO_4)[43] followed by CH_2N_2 esterification provided **53** in excellent yield (90%).

The final C–C bond was established by a Dieckmann cyclization. Thus, treatment of **53** with excess of KO^{t}Bu in benzene at room temperature afforded the corresponding β-keto ester. Subsequent exposure of the crude product to 0.4 M NaOH in aqueous EtOH at reflux for 2 h effected decarbomethoxylation, thereby providing anthracenone **54** in 60% overall yield. If longer reaction periods were employed phenol **55**, along with other side



55



56

products resulting from air oxidation of **55**, was isolated in variable amounts. Products arising from clevage of the C(9) BOM group were also the major products if the Dieckmann cyclization was

(39) For cases in which stereoselectivity is dependent on the double bond geometry, see: Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 464.

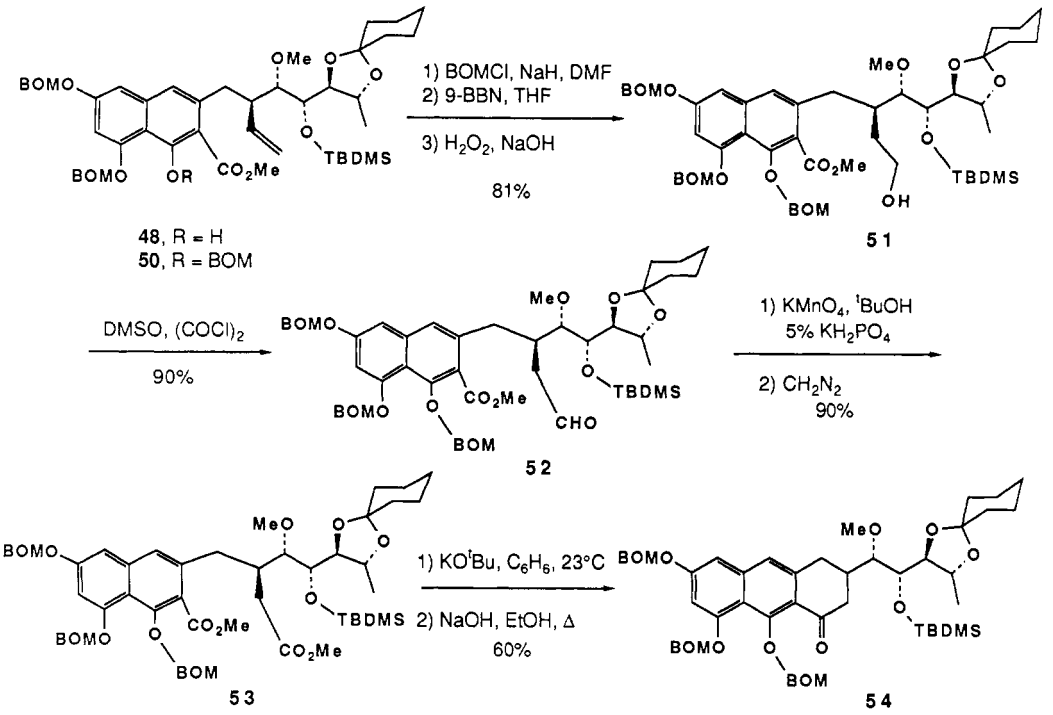
(40) (a) Lenord, J.; Ryan, G. *Tetrahedron Lett.* **1987**, *28*, 2525. (b) Cha, J. K.; Lewis, S. C. *Ibid.* **1984**, *25*, 5263. (c) Salomon, R. G.; Miller, D. B.; Raychaudhuri, S. R.; Avasthi, K.; Lal, K.; Levison, B. S. *J. Am. Chem. Soc.* **1984**, *106*, 8296. (d) Heathcock, C. H.; Kiyooka, S.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, *49*, 4214; **1986**, *51*, 3252.

(41) The corresponding bis-MOM and dimethyl ethers have been prepared by related procedures: (a) Townsend, C. A.; Davis, S. G.; Christensen, S. B.; Link, J. C.; Lewis, C. P. *J. Am. Chem. Soc.* **1981**, *103*, 6885. (b) Noire, P. D.; Franck, R. W. *Synthesis* **1980**, 882.

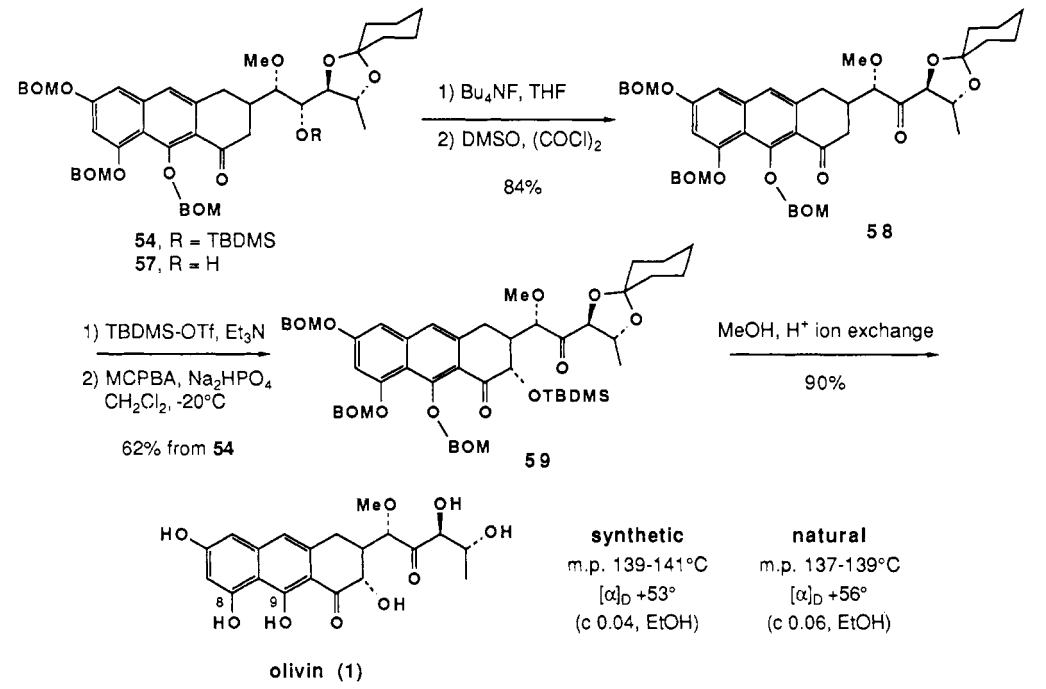
(42) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

(43) Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4537.

Scheme II



Scheme III



carried out at reflux. The sensitivity of the C(9) BOM group is attributed to the conformation indicated in **56** that places the C(15)–O bond parallel to the aromatic π-system and effectively activates the C(9) phenol as a leaving group. This conformation is favorable as it alleviates steric interactions between the C-(9)-OBOM unit and the flanking C(8)-OBOM and the C(1) ketone functionality. It should be noted further that attempts to affect an anionic cyclization of aldehyde ester **52** were not successful.

Next, the side-chain TBDMS ether of **54** was cleaved by treatment with Bu_4NF in THF (93%) and then the resulting hydroxyl group of **57** was oxidized to the C(2′) ketone in **58** via a standard Swern procedure (90%)[42] (Scheme III). Diketone **58** is very similar to an intermediate in Frank's synthesis of tri-*O*-methylolivin (**5**), and our efforts to convert **58** to **59** closely paralleled this earlier work.[7a] Selective conversion of the C(1) carbonyl to the corresponding TBDMS enol ether was smoothly accomplished according to Mander's method,[44] thereby setting the stage for the oxidative introduction of the C(2) hydroxyl group. Initial attempts using both catalytic and stoichiometric amounts of OsO_4[6a,45] generated a multitude of products. Mixtures of products also were obtained when we first attempted a Rubottom oxidation using *m*CPBA.[46] When this reaction was performed in the presence of solid Na_2HPO_4 as buffer at −20 °C, however, protected olivin **59** was obtained in 76% overall yield. The success of this last step was also dependent on the purity of the TBDMS

(44) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1984**, *25*, 5953.
(45) McCormick, J. P.; Tomasik, W.; Johnson, M. W. *Tetrahedron Lett.* **1981**, *22*, 607.
(46) (a) Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599. (b) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319.

enol ether, and it proved necessary to filter this intermediate through silica gel before exposure to *m*CPBA.

The final step in the synthesis was the deprotection of **59**. All protecting groups were chosen to be acid labile in order to avoid use of basic conditions to which olivin is known to be unstable.[2b] Olivin is, however, stable to relatively vigorous acidic conditions (e.g., 0.1 N MeOH, H_2SO_4, reflux, 3 h or 2 M HCl, MeOH, 23 °C).[47] Initial attempts to deprotect **59** by using *p*-TsOH in MeOH were disappointing as even after 4 days only a small amount of olivin was obtained. The major compound produced under these conditions is what we believe to be the C(8)–C(9) methylene acetal. Formation of this intermediate was troublesome because bisphenolic methylene acetals are among the most acid-stable protecting groups.[48] An additional complication was the anticipated difficulty of isolating olivin. Olivin, present in very small amounts, could not be separated from Et_3NH^+-p-TsO^- (Et_3N was used to quench the reaction; we were reluctant to subject small samples to an extractive workup owing to the potential water solubility of olivin) even after repeated chromatographic purification. Attempted deprotection of **59** with BCl_3 at −78 °C results in extensive decomposition. The reaction of chromomycinone, the C(7)-methylated analogue of olivin, with BCl_3 has previously been reported to result in cleavage of the methyl ether.[49]

Fortunately use of an acidic ion-exchange resin solved these problems. Thus, all five protecting groups were removed very efficiently (90%) by treatment of **59** with Dowex 50W-X8 H^+ resin in MeOH at room temperature for 5–6 days. Removal of the resin by filtration followed by crystallization of the crude product from ether–hexane provided synthetic olivin [mp 139–141 °C; $[\alpha]^{25}_D$ + 53° (*c* 0.04, EtOH)], which by all the usual criteria was identical with an authentic sample [mp 137–139 °C; $[\alpha]^{25}_D$ + 56° (*c* 0.05, EtOH)] prepared by acidic methanolysis of olivomycin A.[47b] It is noteworthy that olivin, both synthetic and natural, decomposed rapidly even upon storage at −20 °C, presumably due to air oxidation. The measurement of the optical rotation proved to be indicative of the rapid rate of decomposition. For example, a crystalline sample that was stored for 2 weeks had a rotation of $[\alpha]^{25}_D$ −20° (*c* 0.04, EtOH), with the sign reversed relative to olivin. Examination of this material by TLC revealed that a mixture of materials had formed. It is recommended, therefore, that intermediates be stored at the stage of **59** if synthetic olivin is to be used in glycosidation studies.

In summary, a highly stereoselective synthesis of the natural enantiomer of olivin has been accomplished. Future reports will detail our progress toward completion of a synthesis of olivomycin A.

Experimental Section

D-*galacto*-3-Methoxyhept-1-ene-4,5,6-triol 5,6-Cyclohexyl Ketal (19). A mixture of TMEDA (19.6 g, 160 mmol) in 100 mL of THF at −78 °C was treated successively with 80 mL of *n*-BuLi (2.0 M solution in hexane, 160 mmol) and 11.5 g (160 mmol) of methyl allyl ether. The resulting yellow solution was stirred at −78 °C for 1 h and then treated with 27.5 g (160 mmol) of freshly distilled fluorodimethoxyborane. The reaction mixture was allowed to warm over 1 h to 0 °C, stirred at this temperature for another hour, and then recooled to −78 °C. A solution of 13.0 g (70 mmol) of aldehyde **17** in 5 mL of dry THF was then added, and the resulting mixture was allowed to warm slowly to 23 °C. After being stirred overnight, the reaction mixture was poured into saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), concentrated in vacuo, and purified by flash chromatography (silica gel, 20% ether–hexane) to afford 27.0 g (75%) of **19** as white needles: R_f 0.15 (20% ether–hexane); mp 61–62 °C; $[\alpha]^{18}_D$ +32.0° (*c* 0.30, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 5.81 (ddd, *J* = 2.3, 6.1, 12.2 Hz, 1 H), 5.34 (d, *J* = 2.3 Hz, 1 H), 5.30 (d, *J* = 12.2 Hz, 1 H), 4.11 (m, 1 H), 3.78 (dd, *J* = 2.9, 7.2 Hz, 1 H), 3.58 (t, *J* = 7.7 Hz, 1 H), 3.45 (dt, *J* = 2.9, 7.7 Hz, 1 H), 3.33 (s, 3 H), 2.30 (d, *J* = 7.7 Hz, 1 H), 1.68–1.43 (m, 10 H), 1.34 (d, *J* = 7.4 Hz, 3 H); IR (CH_2Cl_2) 3560, 2920, 1450, 1370, 1110, 1095, 940 cm^{-1}; mass spectrum *m/e* 256 (parent ion). Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.45; H, 9.35.

Ethyl D-*galacto*-5-(Benzyloxy)-6,7-dihydroxy-4-methoxyoct-2(*E*)-enoate 6,7-Cyclohexyl Ketal (20). To a stirred suspension of NaH (hexane washed; 339 mg of a 50% by weight dispersion in oil, 7.0 mmol) in DME (10 mL) was added dropwise a solution of alcohol **19** (0.90 g, 3.5 mmol) in DME (25 mL). The resulting orange suspension was heated to reflux for 30 min, treated with benzyl bromide (0.84 mL, 7.0 mmol, 2 equiv), refluxed for another 30 min, and then allowed to cool to 23 °C. The mixture was partitioned between Et_2O (50 mL) and saturated aqueous NH_4Cl (50 mL). The aqueous layer was separated and extracted with Et_2O (25 mL). The combined ethereal layers were washed with brine (35 mL), diluted with CH_2Cl_2 (100 mL), dried over Na_2SO_4, and evaporated to give a yellow-orange oil that was purified by Kugelrohr distillation. The desired benzyl ether was isolated as a pale yellow oil: 1.16 g (95% yield); bp 140–146 °C (1.7 Torr); $[\alpha]^{25}_D$ +2.2 (*c* 0.78, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 7.93–7.65 (m, 5 H), 5.32 (d, *J* = 15.6 Hz, 1 H), 5.27 (d, *J* = 9.2 Hz, 1 H), 4.72 (d, *J* = 11.1 Hz, 1 H), 4.58 (d, *J* = 11.1 Hz, 1 H), 4.04 (m, 1 H), 3.78 (m, 2 H), 3.52 (dd, *J* = 3.6, 6.4 Hz, 1 H), 3.32 (s, 3 H), 1.93–1.48 (m, 10 H), 1.28 (d, *J* = 6.0 Hz, 3 H); IR (neat) 2950, 2890, 1445, 1360, 1275, 1160, 1090 cm^{-1}; mass spectrum *m/e* 346 (parent ion).

A −20 °C solution of the benzyl ether (300 mg, 0.79 mmol) and a drop of 0.1% Sudan III in dry CH_2Cl_2 (10 mL) was treated with a stream of ozone (0.9 mmol/min) until no color remained. The reaction mixture was allowed to warm to room temperature, and the ozonide was carefully quenched by dropwise addition of Me_2S (10 mL). After 6.5 h at room temperature, the solution was concentrated in vacuo to a red oil, which was further dried by concentration from benzene. Crude D-fucose derivative **7** so obtained was used directly in the next step without purification: ^1H NMR (270 MHz, $CDCl_3$) δ 9.85 (s, 1 H), 7.45–7.22 (m, 5 H), 4.58 (d, *J* = 11.5 Hz, 1 H), 4.46 (d, *J* = 11.5 Hz, 1 H), 4.05 (m, 1 H), 3.95–3.75 (m, 3 H), 3.58 (s, 3 H), 1.72–1.53 (m, 10 H), 1.32 (d, *J* = 5.5 Hz, 1 H).

To a suspension of KH (0.14 g of a 35% by weight dispersion, 1.2 mmol) in THF (5 mL) at 0 °C was added a solution of diisopropyl [(ethoxycarbonyl)methyl]phosphonate (496 mg, 1.96 mmol) in THF (5 mL). After 1 h at 0 °C, the red solution was cooled to −78 °C and added via cannula to a −78 °C solution of the above aldehyde in THF (15 mL). The mixture was allowed to warm slowly to room temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and extracted into Et_2O (3 × 15 mL). The combined ethereal layers were washed with 1 M NaOH (2 × 15 mL) and brine (3 × 10 mL) and dried over Na_2SO_4. After removal of solvent in vacuo the residue was purified by flash chromatography (silica gel, 20% ether–hexane) to yield 270 mg (68%) of (*E*)-α,β-unsaturated ester **20** as a single olefin isomer. Enoate **20** so obtained was in all respects identical with material prepared from diol **14** (Scheme I): R_f 0.26 (20% ether–hexane); $[\alpha]^{25}_D$ +21.5° (*c* 0.77, CH_2Cl_2); ^1H NMR (270 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5 H), 6.99 (dd, *J* = 5.6, 15.7 Hz, 1 H), 6.12 (dd, *J* = 1.6, 15.7 Hz, 1 H), 4.67 (d, *J* = 11.0 Hz, 1 H), 4.53 (d, *J* = 11.0 Hz, 1 H), 4.25 (q, *J* = 7.3 Hz, 2 H), 4.09–3.98 (m, 2 H), 3.76 (t, *J* = 7.7 Hz, 1 H), 3.52 (dd, *J* = 3.2, 7.7 Hz, 1 H), 3.40 (s, 3 H), 1.70–1.20 (m, 10 H), 1.32 (t, *J* = 7.3 Hz, 3 H), 1.30 (d, *J* = 7.7 Hz, 3 H); IR (neat) 2935, 2850, 1720, 1450, 1365, 1275, 1165, 1100 cm^{-1}; mass spectrum *m/e* 418 (parent ion). Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.18. Found: C, 68.88; H, 8.48.

D-*galacto*-6-(Benzyloxy)-7,8-dihydroxy-5-methoxynon-3(*E*)-en-2-one 7,8-Cyclohexyl Ketal (25). A −20 °C solution of the benzyl ether prepared from **19** (2.0 g, 5.77 mmol) and a catalytic amount of Sudan III in CH_2Cl_2 (25 mL) was treated with a stream of ozone until no color remained. Triphenylphosphine (2.0 g, 7.6 mmol) was then added, and the mixture was allowed to warm to 23 °C over a period of 30 min. This solution was then treated with 1-(triphenylphosphoranylidene)-2-propanone (3.7 g, 11.5 mmol) and benzoic acid (50 mg). After a reaction time of 24 h, the mixture was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The organic layer was washed with saturated aqueous NH_4Cl, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, 15% EtOAc–hexane), giving 1.45 g (65%) of geometrically pure enone (*E*)-**25**: R_f 0.18 (15% EtOAc–hexane); $[\alpha]^{25}_D$ +25.9° (*c* 1.20, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 7.40–7.20 (m, 5 H), 6.79 (dd, *J* = 6.4, 17.0 Hz, 1 H), 6.33 (dd, *J* = 1.0, 17.0 Hz, 1 H), 4.67 (d, *J* = 10.5 Hz, 1 H), 4.58 (d, *J* = 10.5 Hz, 1 H), 4.12–3.99 (m, 2 H), 3.78 (t, *J* = 7.8 Hz, 1 H), 3.56 (dd, *J* = 3.5, 7.8 Hz, 1 H), 3.41 (s, 3 H), 2.26 (s, 3 H),

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1.78–1.50 (m, 10 H), 1.33 (d, J = 7.8 Hz, 3 H); IR (neat) 2945, 2865, 1680, 1625, 1445, 1355, 1265, 975, 940 cm^{-1}; mass spectrum m/e 388 (parent ion).

Reaction of Enone 23 with $(H_2C{=}CH)_2CuLi$: Synthesis of 4(*R*),5-(*S*),6(*R*),7(*S*),8(*R*)-6-(Benzyloxy)-5-methoxy-7,8-dihydroxy-4-vinylnonan-2-one 7,8-Carbonate (26). To a −65 °C solution of CuBr–Me_2S (0.20 g, 0.99 mmol) in ether (5 mL) and Me_2S (5 mL) was added vinyllithium (5 mL, 0.36 M in THF, 1.8 mmol). The mixture was stirred at −65 to −70 °C for 0.75 h and then treated with a solution of enone **23**(*E*) (0.15 g, 0.45 mmol) in ether (5 mL). After being stirred at −65 °C for 1 h and an additional 0.5 h at −45 °C, the reaction mixture was poured into a cold mixture of ether and saturated aqueous NH_4Cl. Aqueous NH_4OH was then added, and the resulting mixture was stirred until a homogeneous organic phase and a dark blue aqueous layer were obtained. The two layers were separated, and the aqueous phase was further extracted with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, concentrated, and purified by column chromatography (silica gel, 40% EtOAc–hexane) to provide 140 mg (86%) of **26** and 3 mg (2%) of **27**.

A sample of **24**(*Z*) (39 mg, 0.12 mmol) was treated with divinylcuprate as described for **23**(*E*). The reaction afforded 26 mg (65%) of **26** and 1.5 mg (3%) of **27** following chromatographic purification.

Data for **26**: R_f 0.25 (30% EtOAc–hexane); $[\alpha]^{25}_D$ −15.6° (c 1.01, CH_2Cl_2); ^1H NMR (270 MHz, $CDCl_3$) δ 7.45–7.30 (m, 5 H), 5.76 (ddd, J = 8.6, 10.6, 17.0 Hz, 1 H), 5.3–5.08 (m, 2 H), 4.74 (d, J = 11.0 Hz, 1 H), 4.66 (d, J = 11.0 Hz, 1 H), 4.65 (m, 1 H), 4.35 (dd, J = 5.4, 5.4 Hz, 1 H), 3.80 (dd, J = 3.5, 5.9 Hz, 1 H), 3.23 (dd, J = 3.4, 7.8 Hz, 1 H), 3.09 (m, 1 H), 2.74 (dd, J = 4.9, 16.6 Hz, 1 H), 2.53 (dd, J = 8.3, 16.6 Hz, 1 H), 2.13 (s, 3 H), 1.46 (d, J = 6.0 Hz, 3 H); IR (CH_2Cl_2) 3060, 2920, 1800, 1710, 1635, 1495, 1450, 1370, 1360 cm^{-1}. Anal. Calcd for $C_{20}H_{20}O_6$: C, 66.27; H, 7.23. Found: C, 66.04; H, 7.32.

Data for **27**: R_f 0.35 (30% EtOAc–hexane); $[\alpha]^{25}_D$ +23.2 (c 0.41, CH_2Cl_2); ^1H NMR (270 MHz, $CDCl_3$) δ 7.42–7.30 (m, 5 H), 5.80 (ddd, J = 8.7, 10.1, 17.5 Hz, 1 H), 5.15 (m, 2 H), 4.93 (dq, J = 6.4, 6.4 Hz, 1 H), 4.70 (s, 2 H), 4.36 (dd, J = 2.4, 5.3 Hz, 1 H), 3.84 (dd, J = 2.4, 7.4 Hz, 1 H), 3.44 (s, 3 H), 3.21 (dd, J = 3.0, 7.4 Hz, 1 H), 2.90 (dd, J = 7.7, 17.1 Hz, 1 H), 2.75 (m, 1 H), 2.51 (dd, J = 4.4, 17.1 Hz, 1 H), 2.12 (s, 3 H), 1.55 (d, J = 6.4 Hz, 3 H).

Reaction of Enone 25 and $(H_2C{=}CH)_2CuLi$: Synthesis of 4(*R*),5-(*S*),6(*R*),7(*S*),8(*R*)-6-(Benzyloxy)-5-methoxy-7,8-dihydroxy-4-vinylnonan-2-one 7,8-Cyclohexyl Ketal (28). To a −55 °C suspension of CuBr–Me_2S (1.53 g, 7.5 mmol) in Et_2O (10 mL) and Me_2S (10 mL) was added vinyllithium (8.3 mL, 1.80 M in THF, 14.9 mmol) over a period of 0.5 h. This mixture was treated with a solution of enone **25** (1.44 g, 3.7 mmol) in Et_2O (40 mL) and stirred at −50 to −30 °C for 1 h. The reaction was worked up by the procedure described for the preparation of **26** from **23**(*E*). The crude product was purified by column chromatography (silica gel, 8–15% EtOAc–hexane) to yield 1.04 g of **28** (68% yield) plus a very small amount of the C(3) epimer: R_f 0.54 (40% EtOAc–hexane); $[\alpha]^{25}_D$ −24.5° (c 1.11, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 7.56–7.25 (m, 5 H), 5.73 (ddd, J = 8.6, 10.3, 18.8 Hz, 1 H), 5.11 (d, J = 10.3 Hz, 1 H), 5.06 (d, J = 18.8 Hz, 1 H), 4.70 (d, J = 11.2 Hz, 1 H), 4.62 (d, J = 11.2 Hz, 1 H), 4.07 (m, 1 H), 3.76 (t, J = 6.1 Hz, 1 H), 3.57 (dd, J = 2.7, 6.1 Hz, 1 H), 3.49 (s, 3 H), 3.12 (dq, J = 2.7, 6.1 Hz, 1 H), 2.76 (dd, J = 5.0, 15.9 Hz, 1 H), 2.51 (dd, J = 8.6, 15.9 Hz, 1 H), 2.12 (s, 3 H), 1.82–1.47 (m, 10 H), 1.34 (d, J = 6.1 Hz, 3 H); IR (neat) 2885, 2810, 1715, 1440, 1355, 1270, 1090, cm^{-1}; mass spectrum m/e 416 (parent ion).

Stereochemical Assignment for 26: Preparation of Bicyclic Ketal 31. A 0 °C solution of **26** (80 mg, 0.22 mmol) in water (0.3 mL) and dioxane (0.3 mL) was treated with 0.5 M aqueous NaOH (1 mL). The resulting mixture was stirred for 1 h, then neutralized with 5 N HCl, and partitioned between $CHCl_3$ and H_2O. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 73 mg (quantitative yield) of diol **29**, which was used in the following step without any further purification: ^1H NMR (250 MHz, $CDCl_3$) δ 7.42–7.30 (m, 5 H), 5.77 (m, 1 H), 5.04 (m, 2 H), 4.66 (s, 2 H), 3.97 (m, 1 H), 3.70–3.60 (m, 2 H), 3.42 (s, 3 H), 3.45 (m, 1 H), 3.11 (m, 1 H), 3.00 (m, 1 H), 2.75 (dd, J = 5.5, 16.2 Hz, 1 H), 2.50 (dd, J = 8.1, 15.8 Hz, 1 H), 2.23 (m, 1 H), 2.11 (s, 3 H), 1.24 (d, J = 6.8 Hz, 3 H).

A solution of diol **29** (61 mg, 0.19 mmol) in CH_2Cl_2 (2 mL) containing $FeCl_3$ (20 mg) was stirred at room temperature for 20 min. The mixture was then diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$, filtered, and concentrated to give the crude product that was purified via preparative TLC (15% EtOAc–hexane) giving 48 mg (84%) of ketal **31**: R_f 0.65 (20% EtOAc–hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 7.45–7.25 (m, 5 H), 5.97 (ddd, J = 8.0, 9.9, 17.0 Hz, 1 H), 5.12 (d, J = 17.0 Hz, 1 H), 5.03 (d, J = 9.9 Hz, 1 H), 4.67 (s, 2 H), 4.30 (dq, J = 2.3, 6.3 Hz, 1 H), 4.17 (dd, J = 1.6, 3.5 Hz, 1 H), 3.53 (dd, J = 1.6, 3.5 Hz, 1 H), 3.46 (m, 1 H), 3.34 (s, 3 H), 2.97 (m, 1 H), 2.10 (dd, J = 11.0, 14.6 Hz, 1 H), 1.85 (dd, J = 5.3, 14.6 Hz, 1 H), 1.48 (s, 3 H), 1.18 (d, J = 6.3 Hz, 1 H); IR (CH_2Cl_2) 3070, 3030, 1450, 1375, 1230, 1200, 1030 cm^{-1}; mass spectrum m/e 318 (parent ion).

Preparation of Ketal 31 from 28. Cyclohexyl ketal **28** (830 mg, 2.0 mmol) was dissolved in a 98:2 mixture of TFA–H_2O (10 mL) at 0 °C. After 45 min the resultant yellow solution was carefully poured into saturated aqueous $NaHCO_3$ (200 mL) and extracted with Et_2O (3 × 30 mL). The combined ethereal layers were diluted with CH_2Cl_2 (50 mL), dried over Na_2SO_4, and evaporated to give a green oil. Pure ketal **31** was obtained after two successive flash column chromatographic separations, with 5% EtOAc–benzene and CH_2Cl_2, respectively. In this manner, 460 mg (77% yield) of **31** was isolated as a pale yellow oil.

Bicyclic Ketal 32. A mixture of **31** (37 mg, 0.12 mmol), 20% Pd-$(OH)_2$/C(8 mg) and absolute EtOH (2 mL) was shaken under a hydrogen atmosphere (40 psi) for 3.5 h. After the catalyst was removed via filtration through Celite, the filtrate was concentrated to give 28 mg (98%) of the corresponding alcohol: R_f 0.30 (20% EtOAc–hexane); mp 95.5–96.5 °C; $[\alpha]^{25}_D$ +65.9° (c 0.47, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 4.35 (dq, J = 3.9, 6.0 Hz, 1 H), 4.12 (m, 1 H), 3.82 (m, 1 H), 3.42 (s, 3 H), 3.41 (m, 1 H), 2.38 (m, 1 H), 1.99–1.68 (m, 3 H), 1.48 (s, 3 H), 1.42–1.36 (m, 2 H), 1.24 (d, J = 6.1 Hz, 3 H), 0.92 (t, J = 7.3 Hz, 3 H); IR 3570, 2930, 1750, 1600, 1460, 1375 cm^{-1}; mass spectrum m/e 230 (parent ion).

A mixture of the above alcohol (9 mg, 0.04 mmol), Ac_2O (0.1 mL), and pyridine (0.1 mL) was stirred at 23 °C for 5.5 h. After removal of all volatile materials, the residue was purified by preparative TLC (15% EtOAc–hexane) to give 7 mg (65%) of acetate **32**: R_f 0.57 (20% EtOAc–hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 5.06 (dq, J = 1.7, 3.5 Hz, 1 H, H_5), 4.40 (dq, J = 2.3, 6.3 Hz, 1 H), 4.08 (m, 1 H, H_6), 3.42 (s, 3 H), 3.33 (dd, J = 1.7, 3.5 Hz, 1 H, H_4), 2.13 (s, 3 H), 2.10–1.75 (m, 3 H), 1.50 (s, 3 H), 1.39 (d, J = 6.3 Hz, 3 H), 1.48–1.15 (m, 2 H), 0.9 (t, J = 7.4 Hz, 3 H).

Structure Proof for 27: Preparation of Bicyclic Ketal 33. A sample of **27** (6.8 mg, 0.02 mmol) was hydrolyzed to diol **30** as described for the preparation of **33**. The diol underwent intramolecular ketalization upon treatment with $FeCl_3$ in CH_2Cl_2 to give 3.0 mg (50%) of ketal **39** following chromatographic purification: R_f 0.56 (20% EtOAc–hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 7.40–7.28 (m, 5 H), 5.75 (ddd, J = 8.5, 10.2, 17.1 Hz, 1 H), 5.07–5.00 (m, 2 H), 4.72 (d, J = 11.7 Hz, 1 H), 4.61 (d, J = 11.7 Hz, 1 H), 4.15 (dq, J = 3.0, 6.1 Hz, 1 H), 4.02 (d, J = 2.9 Hz, 1 H, H_6), 3.50 (s, 3 H), 3.46 (d, J = 7.5 Hz, 1 H, H_5), 3.37 (dd, J = 7.5, 10.2 Hz, 1 H, H_4), 2.56 (m, 1 H), 1.82 (dd, J = 3.4, 14.2 Hz, 1 H), 1.68 (m, 1 H), 1.45 (s, 3 H), 1.16 (d, J = 6.1 Hz, 3 H); mass spectrum m/e 318 (parent ion).

D-*galacto*-3-Methoxy-4-[(*tert*-butyldimethylsilyl)oxy]hept-1-ene-5,6-diol 5,6-Cyclohexyl Ketal (39). To a solution of 25.6 g (100 mmol) of alcohol **19** and 26.8 mL (250 mmol) of 2,6-lutidine in 150 mL of dry CH_2Cl_2 was added 31.7 mL (120 mmol) of TBDMS-OTf. After being stirred at room temperature overnight, the solvent was removed in vacuo and the residue was purified by flash chromatography (silica gel, 10% ether–hexane) to afford 30.2 g (82%) of **39**: R_f 0.38 (10% ether–hexane); $[\alpha]^{22}_D$ +1.8° (c 1.7, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 5.81 (m, 1 H), 5.23 (m, 2 H), 4.14 (dq, J = 7.2, 7.2 Hz, 1 H), 3.82 (dd, J = 5.6, 7.2 Hz, 1 H), 3.67 (dd, J = 5.6, 7.6 Hz, 1 H), 3.47 (t, J = 7.6 Hz, 1 H), 3.24 (s, 3 H), 1.56 (s, 10 H), 1.27 (d, J = 7.2 Hz, 3 H), 0.88 (s, 9 H), 0.07 (s, 6 H); IR ($CHCl_3$) 3000, 2915, 2850, 1470, 1460, 1445, 1360, 1250 cm^{-1}; high-resolution mass spectrum for $C_{20}H_{38}O_4Si$ calcd 370.2539, found 370.2538. Anal. Calcd for $C_{20}H_{38}O_4Si$: C, 64.82; H, 10.33. Found: C, 64.84; H, 10.56.

Methyl D-*galacto*-4-Methoxy-6,7-dihydroxy-5-[(*tert*-butyldimethylsilyl)oxy]oct-2(*E*)-enoate 6,7-Cyclohexyl Ketal (37). Ozone was bubbled into a −20 °C solution of **39** (11 g, 30 mmol) in MeOH (200 mL), and the reaction was monitored by TLC. Upon consumption of all starting material, triphenylphosphine (8 g, 30 mmol) was added. The resulting mixture was stirred for 1 h at −20 °C and then allowed to warm to room temperature over a period of 2 h. MeOH was then removed, and the crude product was filtered through a short silica gel column using CH_2Cl_2 as eluent. The filtrate was concentrated in vacuo and the crude aldehyde [R_f 0.17 (10% ether–hexane); $[\alpha]^{22}_D$ +4.6° (c 0.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 9.65 (d, J = 1.9 Hz, 1 H), 4.08 (m, 1 H), 3.94 (dd, J = 5.0, 7.0 Hz, 1 H), 3.64 (t, J = 7.0 Hz, 1 H), 3.57 (dd, J = 2.0, 5.0 Hz, 1 H), 3.42 (s, 3 H), 1.6–1.4 (br, 10 H), 1.30 (d, J = 2.0 Hz, 3 H), 0.86 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H); IR ($CDCl_3$) 2940, 2860, 2250, 1730, 1445, 1365 cm^{-1}; mass spectrum m/e 372 (parent ion); high-resolution mass spectrum for $C_{19}H_{36}O_5Si$ calcd 372.2332, found 372.2335] was redissolved in CH_2Cl_2 (100 mL) and treated with methyl (triphenylphosphoranylidine)acetate (15 g, 45 mmol). The mixture was stirred overnight at room temperature and then concentrated in vacuo. The residue was purified by column chromatography (silica gel, 20%

ether–hexane) to yield 8.9 g (70% for two steps) of **37** as a ~4:1 mixture of (*E*)- and (*Z*)-olefin isomers. For preparative purposes this mixture was not separated. A sample of **37**(*E*) was purified for characterization purposes: R_f 0.48 (20% ether–hexane); $[\alpha]^{25}_D$ +7.4° (*c* 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 6.86 (dd, *J* = 5.8, 15.8 Hz, 1 H), 6.00 (d, *J* = 15.8 Hz, 1 H), 4.07 (m, 1 H), 3.75 (m, 5 H), 3.61 (dd, *J* = 5.6, 7.2 Hz, 1 H), 3.30 (s, 3 H), 1.61–1.40 (br, 10 H), 1.28 (d, *J* = 6.0 Hz, 3 H), 0.87 (s, 9 H), 0.55 (s, 6 H); IR ($CHCl_3$) 3005, 2930, 2850, 1720, 1470, 1460, 1450, 1435, 1280, 1250 cm^{-1}; mass spectrum *m/e* 428 (parent ion), 385 (13), 299 (25), 281 (25), 273 (20), 255 (62), 241 (44), 201 (20), 155 (100); high-resolution mass spectrum for $C_{22}H_{40}O_6Si$ calcd 428.2595, found 428.2597. Anal. Calcd for $C_{22}H_{40}O_6Si$: C, 61.64; H, 9.41. Found: C, 61.62; H, 9.32.

D-*galacto*-4-Methoxy-6,7-dihydroxy-5-[(*tert*-butyldimethylsilyl)oxy]-oct-2(*E*)-enal 6,7-Cyclohexyl Ketal (40). To a −78 °C solution of a mixture of cis and trans unsaturated esters **37** (9.5 g, 22.0 mmol) in dry ether (80 mL) was added DIBAL-H (60 mL, 1 M in THF, 60 mmol). The mixture was stirred for 1 h, MeOH (50 mL) was added dropwise, and the resulting solution was slowly poured into cold (0 °C) 1 N HCl. The aqueous phase was extracted with CH_2Cl_2, and the combined extracts were dried over $MgSO_4$. Filtration and removal of solvent afforded 8.4 g (95%) of crude alcohol that was used without purification in the following reaction: R_f 0.20 (20% ether–hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (m, 1 H), 5.65 (m, 1 H), 4.20–4.05 (m, 3 H), 3.78 (t, *J* = 5.9 Hz, 1 H), 3.64 (dd, *J* = 5.0, 7.4 Hz, 1 H), 3.54 (t, *J* = 6.8 Hz, 1 H), 3.27 (s, 3 H), 1.57 (m, 10 H), 1.29 (d, *J* = 6.3 Hz, 3 H), 0.90 (s, 9 H), 0.09 (s, 6 H); IR (neat) 3420, 2930, 2850, 1470, 1460, 1450, 1360, 1250 cm^{-1}; mass spectrum *m/e* 400 (parent ion). Anal. Calcd for $C_{21}H_{40}O_5Si$: C, 62.95; H, 10.07. Found: C, 62.90; H, 10.34.

PCC (15 g, 69.0 mmol) was added to a solution of the above allylic alcohol (8.4 g, 21.0 mmol) in CH_2Cl_2 (150 mL), and the reaction mixture was stirred at room temperature for 15 h. The mixture was then filtered, and the solids were washed with ether. The filtrate was concentrated, and crude **40** was directly purified by flash chromatography (silica gel, 20% ethyl acetate–hexane) to give 7.5 g (90%) of aldehyde **40** as a mixture of olefin isomers. This mixture was used as such in the following experiment.

Data for **40**(*E*): R_f 0.45 (20% ether–hexane); $[\alpha]^{25}_D$ −4.2° (*c* 1.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 9.61 (d, *J* = 7.9 Hz, 1 H), 6.80 (dd, *J* = 6.0, 15.8 Hz, 1 H), 6.27 (dd, *J* = 7.0, 15.8 Hz, 1 H), 4.07 (m, 1 H), 3.87 (dt, *J* = 5.6, 6.6 Hz, 1 H), 3.79 (t, *J* = 5.8 Hz, 1 H), 3.58 (t, *J* = 6.6 Hz, 1 H), 3.32 (s, 3 H), 1.56 (s, 10 H), 1.29 (d, *J* = 6.1 Hz, 3 H), 0.87 (s, 9 H), 0.07 (s, 6 H); IR ($CHCl_3$) 2940, 2860, 1680 cm^{-1}; high-resolution mass spectrum for $C_{21}H_{38}O_5Si$ calcd 398.2489, found 398.2490.

Reaction of 40 with Divinylcuprate: Synthesis of 3(*R*),4(*S*),5(*R*),6(*S*),7(*R*)-4-Methoxy-6,7-dihydroxy-5-[(*tert*-butyldimethylsilyl)oxy]-3-vinyloctanal 6,7-Cyclohexyl Ketal (41). To a −78 °C solution of CuI (1.52 g, 8.0 mmol) in ether (60 mL) under argon were added vinyllithium (10 mL, 2.2 M in THF, 22.0 mmol) and an additional 10 mL of THF. The mixture was allowed to warm to −35 to −40 °C, held at that temperature for 15 min, and then recooled to −78 °C. This mixture was then treated with TMS-Cl (0.3 mL, 2.3 mmol) followed by a solution of aldehyde **40** (1.0 g, 2.5 mmol) in ether (10 mL). The reaction mixture was stirred at −78 °C for 10 min and then poured into saturated aqueous NH_4Cl solution. The resulting mixture was stirred for 2 h and then extracted with CH_2Cl_2. The organic extracts were eluted (1:1 ether–hexane) through a silica gel column and concentrated to afford 1.0 g (91%) of aldehyde **41**, which was pure enough to be used in the next step without any further purification. Only a single stereoisomer of **41** was observed and comparable results were obtained whether isomerically pure (*E*)-**40** or mixtures of enal olefin isomers were used: R_f 0.65 (1:1 ether–hexane); $[\alpha]^{25}_D$ −16.1° (*c* 1.20, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 9.58 (t, *J* = 2.0 Hz, 1 H), 5.75 (m, 1 H), 5.07 (d, *J* = 7.4 Hz, 1 H), 5.01 (s, 1 H), 4.04 (m, 1 H), 3.72 (dd, *J* = 3.7, 7.4 Hz, 1 H), 3.60 (t, *J* = 7.0 Hz, 1 H), 3.32 (s, 3 H), 3.13 (dd, *J* = 3.7, 6.3 Hz, 1 H), 3.04 (m, 1 H), 2.46 (m, 2 H), 1.49 (br, 10 H), 1.27 (d, *J* = 6.1 Hz, 3 H), 0.84 (s, 3 H), 0.05 (s, 3 H), 0.03 (s, 3 H); IR ($CDCl_3$) 2950, 2840, 1730, 1640 cm^{-1}; mass spectrum *m/e* (rel intensity) 426 (parent ion, 1), 398 (5), 299 (25), 271 (30), 255 (35), 239 (44), 155 (91), 73 (100).

Methyl 5(*R*),6(*S*),7(*R*),8(*S*),9(*R*)-6-Methoxy-8,9-dihydroxy-7-[(*tert*-butyldimethylsilyl)oxy]-5-vinyldec-2(*E*)-enoate 8,9-Cyclohexyl Ketal (42). A solution of aldehyde **41** (1.0 g, 2.3 mmol) and methyl (triphenylphosphoranylidine)acetate (1.0 g, 3.0 mmol) in CH_2Cl_2 (10 mL) was stirred overnight at room temperature. Workup consisted of filtering the mixture through a silica gel column (100 g of silica gel, 1:1 ether–hexane) and removal of solvent in vacuo. This gave 1.1 g (91%) of **42**(*E*) as a >9:1 mixture of olefin isomers: R_f 0.70 (1:1 ether–hexane); $[\alpha]^{22}_D$ +8.9° (*c* 3.7, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 6.88 (m, 1 H), 5.80 (d, *J* = 15.4 Hz, 1 H), 5.63 (m, 1 H), 5.03 (m, 2 H), 4.09 (m, 1 H), 3.80 (dd, *J* = 5.3, 6.3 Hz, 1 H), 3.70 (s, 3 H), 3.60 (t, *J* = 6.7 Hz, 1 H), 3.43 (s, 3 H), 3.13 (t, *J* = 5.3 Hz, 1 H), 2.56 (m, 2 H), 2.25 (m, 1 H), 1.56 (m, 10 H), 1.31 (d, *J* = 6.1 Hz, 3 H), 0.88 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 3 H); IR (neat) 2930, 2850, 1725, 1655, 1470, 1460, 1445, 1435, cm^{-1}; mass spectrum *m/e* 482 (parent ion); high-resolution mass spectrum for $C_{26}H_{46}O_6Si$ calcd 482.3064, found 482.3068. Anal. Calcd for $C_{26}H_{46}O_6Si$: C, 64.69; H, 9.60. Found: C, 64.83; H, 9.48.

Stereochemical Assignment for 41: Preparation of Lactone 43. To a solution of aldehyde **41** (10 mg, 0.023 mmol) in THF (1 mL) was added *n*-Bu_4NF (8 drops, 1 M in THF). After being stirred at room temperature for 1 h, the mixture was partitioned between water and CH_2Cl_2. The organic layer was dried over $MgSO_4$, and the solvent was removed in vacuo. The crude alcohol so obtained was dissolved in CH_2Cl_2 (2 mL) and treated with excess PCC (120 mg, 0.56 mmol). The mixture was stirred at room temperature overnight and then filtered. The solvent was removed in vacuo, and the residue was directly purified by preparative TLC (1:1 ether–hexane) to afford 5 mg (70%) of lactone **43**: R_f 0.15 (1:1 ether–hexane); $[\alpha]^{22}_D$ −60° (*c* 0.09, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 5.89 (m, 1 H), 5.17 (d, *J* = 10 Hz, 1 H), 5.15 (d, *J* = 16.2 Hz, 1 H), 4.12 (m, 2 H), 3.76 (dd, *J* = 7.5, 9.1 Hz, 1 H), 3.67 (br t, *J* = 2 Hz, H_4), 3.53 (s, 3 H), 2.71 (dd, *J* = 10, 10 Hz, H_{2ax}), 2.63 (m, H_3), 2.50 (br d, *J* = 10 Hz, H_{2eq}), 1.65 (m, 10 H), 1.45 (d, *J* = 7.0 Hz, 3 H); IR ($CHCl_3$) 2930, 2850, 1745, 1450, 1365 cm^{-1}; mass spectrum *m/e* 312 (parent ion).

3,5-Bis[(benzyloxy)methoxy]benzyl Alcohol (44). To a 0 °C suspension of NaH (5.5 g, 60% dispersion in oil, 137 mmol) in dry DMF (100 mL) was added dropwise a solution of methyl 3,5-dihydroxybenzoate (10 g, 59.6 mmol) in DMF (30 mL). After being stirred at 23 °C for 60 min, the mixture was treated with (benzyloxy)methyl chloride (18.5 mL, 126 mmol) and stirred for 30 min. The suspension was then poured into water, acidified with 1 N HCl, and extracted three times with benzene. The combined extracts were washed with brine, dried (K_2CO_3), and concentrated in vacuo to give 21.9 g (90%) of protected benzoate which was used in the next step without purification: R_f 0.54 (1:1 ether–hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 7.45 (d, *J* = 2.9 Hz, 2 H), 7.36 (m, 10 H), 7.03 (t, *J* = 2.9 Hz, 1 H), 5.33 (s, 4 H), 4.76 (s, 4 H), 3.93 (s, 3 H); IR (neat) 3050, 2940, 2875, 1780, 1600, 1455, 1300, 1160, 1020 cm^{-1}; mass spectrum *m/e* 408 (parent ion).

To a suspension of $LiAlH_4$ (4.0 g, 105 mmol) in THF (100 mL) was added dropwise a solution of the above benzoate (21.9 g, 53.7 mmol) in THF (50 mL). After being stirred at 23 °C for 2 h, the mixture was treated successively with 4 mL of water, 4 mL of 15% NaOH, and 10 mL of water. The resulting suspension was filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, 40% ethyl acetate–hexane) to afford 18.5 g (90%) of **44**: R_f 0.40 (2:1 ether–hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 7.34 (m, 10 H), 6.77 (s, 3 H), 5.29 (s, 4 H), 4.73 (s, 4 H), 4.64 (s, 2 H), 1.75 (s, 1 H); IR (neat) 3600–3150 (br), 3025, 2790, 1600, 1455, 1170, 1080, 1035 cm^{-1}; mass spectrum *m/e* 381 (M + 1). Anal. Calcd for $C_{23}H_{24}O_5$: C, 72.61; H, 6.36. Found: C, 72.60; H, 6.39.

2-Bromo-3,5-bis[(benzyloxy)methoxy]benzyl Alcohol (45). To a solution of alcohol **44** (16.7 g, 43.8 mmol) in dry $CHCl_3$ (150 mL) was added recrystallized NBS (7.80 g, 43.8 mmol). The solution was heated at reflux for 90 min and then allowed to cool to room temperature. The mixture was diluted with freshly prepared saturated aqueous $Na_2S_2O_3$ (200 mL), and the organic phase was washed with water (2 × 200 mL), dried over K_2CO_3, and concentrated. The residue was purified by column chromatography (silica gel, 30% ethyl acetate–hexane) to yield 16.7 g (83%) of the aryl bromide **45** as a low-melting, yellow solid: R_f 0.29 (1:1 ether–hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 7.50–7.10 (m, 10 H), 6.97 (m, 2 H), 5.38 (s, 2 H), 5.30 (s, 2 H), 4.87 (s, 2 H), 4.73 (s, 2 H), 4.67 (d, *J* = 4.9 Hz, 1 H), 2.65 (s, 1 H); IR ($CHCl_3$) 3400, 2890, 1585, 1450, 1400, 1310, 1165, 1095, 1040, 1015 cm^{-1}.

5,7-Bis[(benzyloxy)methoxy]phthalide (46). To a −78 °C solution of aryl bromide **45** (14.6 g, 32.0 mmol; azeotropically dried from toluene) in THF (150 mL) under nitrogen were added sequentially *n*-BuLi (16.0 mL, 2.0 M in hexane, 32.0 mmol) and *sec*-BuLi (32.0 mL, 1.0 M in cyclohexane, 32.0 mmol). The resulting solution was stirred at −78 °C for 70 min. Dry CO_2 gas was then bubbled through the orange anion solution for ~2.5 h. The solution was allowed to warm to −20 °C and then to 23 °C overnight. The mixture was carefully diluted with water (20 mL), whereupon vigorous gas evolution occurred, then acidified with 10% aqueous HCl (20 mL), saturated with NaCl, and extracted with ether (2 × 150 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, 1:1 ether–hexane) to give 6.62 g (51%) of phthalide **46**. On a 10-mmol scale the yield of **46** was 70%: R_f 0.20 (1:1 ether–hexane); mp 82–83 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 7.50–7.24 (m, 10 H), 6.95 (d, *J* = 1.5 Hz, 1 H), 6.79 (d, *J* = 1.5 Hz, 1 H), 5.49 (s, 2 H), 5.34 (s, 2 H), 5.18 (s, 2 H), 4.80 (s, 2 H), 4.72 (s, 2 H); IR (KBr) 1765, 1610,

1485, 1450, 1385, 1340, 1315, 1285, 1235, 1210, 1175, 1155, 1090, 1045 cm^{-1}; mass spectrum m/e 406 (parent ion). Anal. Calcd for $C_{24}H_{22}O_6$: C, 70.92; H, 5.46. Found: C, 70.88; H, 5.31.

Methyl 6,8-Bis[(benzyloxy)methoxy]-1-hydroxy-3-[1′-[[2′(*R*),3′(*S*),4′(*R*),5′(*S*),6′(*R*)]-3′-methoxy-5′,6′-[cyclohexylidenebis(oxy)]-4′-[(*tert*-butyldimethylsilyl)oxy]-2′-vinylheptyl]]-2-naphthoate (48). A solution of LDA was prepared by the addition of *n*-BuLi (2.0 mL, 2.5 M in hexane, 5.0 mmol) to diisopropylamine (0.5 mL, 3.5 mmol) in THF (5 mL) at 0 °C. This solution was stirred for 15 min, then cooled to −40 °C, and treated with a solution of phthalide **46** (406 mg, 1.0 mmol) in THF (4 mL), resulting in an orange-yellow color. Ten minutes later, a solution of enoate **42** (482 mg, 1.0 mmol) in THF (2 mL) was added dropwise over a period of 20 min. The red solution so obtained was stirred at −40 °C for another 20 min and then was diluted with saturated aqueous NH_4Cl. This mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated in vacuo to give the crude hydroxytetralone. This material was dissolved in CH_2Cl_2 (40 mL) along with triethylamine (5 mL, 36 mmol). Methanesulfonyl chloride was then added dropwise until all the hydroxytetralone [R_f 0.19 (1:1 ether–hexane)] was consumed as evidenced by TLC analysis. The mixture was then treated with 1 N HCl, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated. Purification of the residue by column chromatography (silica gel, 15–25% ether–hexane) afforded 62 mg of an unknown mixture, 342 mg (35%) of naphthol **48**, and 105 mg (10%) of mesylate **49**.

Data for **48**: R_f 0.35 (1:1 ether–hexane); $[\alpha]^{22}_D$ −15.0° (*c* 2.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 10.17 (s, 1 H), 7.4–7.25 (m, 10 H), 6.95 (s, 2 H), 6.88 (d, J = 2.1 Hz, 1 H), 5.68 (m, 1 H), 5.45 (s, 2 H), 5.33 (s, 2 H), 4.90–4.68 (m, 6 H), 4.12 (m, 1 H), 3.97 (s, 3 H), 3.92 (t, J = 5.6 Hz, 1 H), 3.70 (dd, J = 4.7, 6.8 Hz, 1 H), 3.48 (s, 3 H), 3.25 (d, J = 9.6 Hz, 1 H), 3.12 (t, J = 4.8 Hz, 1 H), 2.64 (m, 2 H), 1.56 (m, 10 H), 1.31 (d, J = 5.6 Hz, 3 H), 0.90 (s, 9 H), 0.11 (s, 3 H), 0.07 (s, 3 H); IR ($CDCl_3$) 2940, 2860, 1715, 1660, 1625, 1610, 1590 cm^{-1}; mass spectrum m/e (rel intensity) 870 (parent ion, 2), 621 (1), 531 (2), 479 (3), 155 (17), 91 (100).

Data for **49**: R_f 0.30 (1:1 ether–hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.24 (m, 10 H), 7.06 (d, J = 2.6 Hz, 1 H), 7.03 (d, J = 1.7 Hz, 1 H), 5.63 (m, 1 H), 5.45 (s, 2 H), 5.38 (s, 2 H), 4.87–4.65 (m, 6 H), 4.12 (m, 1 H), 3.96 (s, 3 H), 3.88 (t, J = 6.0 Hz, 1 H), 3.68 (dd, J = 5.9, 7.8 Hz, 1 H), 3.48 (s, 3 H), 3.28 (dd, J = 3.0, 13.9 Hz, 1 H), 3.13 (s, 3 H), 2.68 (m, 2 H), 1.56 (m, 10 H), 1.31 (d, J = 5.7 Hz, 3 H), 0.90 (s, 9 H), 0.10 (s, 3 H), 0.07 (s, 3 H).

Methyl 3-[1′-[[2′(*R*),3′(*S*),4′(*R*),5′(*S*),6′(*R*)]-3′-Methoxy-5′,6′-[cyclohexylidenebis(oxy)]-4′-[(*tert*-butyldimethylsilyl)oxy]-2′-vinylheptyl]]-1,6,8-tris[(benzyloxy)methoxy]-2-naphthoate (50). To 10 mL of dry THF containing 300 mg of NaH was added a solution of naphthol **48** (800 mg, 0.92 mmol) in DMF (2 mL). The mixture was stirred at room temperature for 20 min, treated with (benzyloxy)methyl chloride (1.5 mL, 10.7 mmol) and stirred for an additional 1 h. The reaction was quenched with water and extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 820 mg (91%) of **50**: R_f 0.35 (2:1 hexane–ether); $[\alpha]^{22}_D$ +6.8° (*c* 3.4, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 7.45–7.25 (m, 16 H), 7.03 (d, J = 2.0 Hz, 1 H), 6.95 (d, J = 2.0 Hz, 1 H), 5.70 (m, 1 H), 5.36 (s, 2 H), 5.35 (s, 2 H), 5.22 (s, 2 H), 4.9–4.7 (m, 8 H), 4.14 (m, 1 H), 3.98–3.87 (m, 4 H), 3.72 (t, J = 5.6 Hz, 1 H), 3.49 (s, 3 H), 3.23–3.10 (m, 2 H), 2.74–2.60 (m, 2 H), 1.7–1.5 (m, 10 H), 1.33 (d, J = 6.0 Hz, 3 H), 0.91 (s, 9 H), 0.12 (s, 3 H), 0.09 (s, 3 H); IR ($CDCl_3$) 2950, 2935, 2860, 1725, 1625, 1610, 1575 cm^{-1}; mass spectrum m/e 990 (parent ion). Anal. Calcd for $C_{58}H_{74}O_{12}Si$: C, 70.35; H, 7.43. Found: C, 70.44; H, 7.41.

Methyl 3-[1′-[[2′(*R*),3′(*S*),4′(*R*),5′(*S*),6′(*R*)]-2′-[1″-(2″-Hydroxyethyl)]-3′-methoxy-5′,6′-[cyclohexylidenebis(oxy)]-4′-[(*tert*-butyldimethylsilyl)oxy]heptyl]]-1,6,8-tris[(benzyloxy)methoxy]-2-naphthoate (51). Naphthoate **50** (418 mg, 0.42 mmol) was dissolved in THF (3 mL) under N_2, cooled to 0 °C, and treated with 9-BBN (8.0 mL, 0.5 M in THF, 4.0 mmol). The mixture was allowed to warm slowly to 23 °C (0.5 h), stirred for 2 h, recooled to 0 °C, and quenched with MeOH (3 mL). When gas evolution had subsided, 3 mL each of 3 M aqueous NaOH and 30% aqueous H_2O_2 was added simultaneously dropwise. The solution (containing a white precipitate) was allowed to warm to 23 °C and stirred for 2 h. Workup consisted of partitioning the mixture between water (50 mL) and CH_2Cl_2 (100 mL). The aqueous layer was further extracted with CH_2Cl_2 (100 mL), and the combined organic extracts were washed with aqueous $Na_2S_2O_3$ and dried over Na_2SO_4. After removal of solvent in vacuo the residue was purified by flash chromatography (silica gel, 35% ethyl acetate–hexane) to give 423 mg (89%) of **51**: R_f 0.46 (40% ethyl acetate–hexane); $[\alpha]^{22}_D$ +2.0° (*c* 0.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.55–7.25 (m, 16 H), 7.03 (d, J = 2.0 Hz, 1 H), 6.96 (d, J = 2.0 Hz, 1 H), 5.37 (s, 2 H), 5.35 (s, 2 H), 5.22 (s, 2 H), 4.76 (s, 2 H), 4.75 (s, 2 H), 4.73 (s, 2 H), 4.16 (m, 1 H), 3.99–3.90 (m, 4 H), 3.60 (dd, J = 4.0, 7.9 Hz, 1 H), 3.57–3.48 (m, 4 H), 3.13 (dd, J = 2.0, 7.7 Hz, 1 H), 3.02 (dd, J = 4.0, 14.4 Hz, 1 H), 2.64 (dd, J = 10.0, 14.4 Hz, 1 H), 2.18 (m, 1 H), 1.81–1.43 (m, 10 H), 1.33 (d, J = 5.8 Hz, 3 H), 0.96 (s, 9 H), 0.13 (s, 3 H), 0.06 (s, 3 H); IR ($CDCl_3$) 3605, 3430, 2940, 2880, 1730, 1625, 1610, 1575 cm^{-1}; mass spectrum m/e 1008 (parent ion).

Methyl 3-[1′-[[2′(*R*),3′(*S*),4′(*R*),5′(*S*),6′(*R*)]-3′-Methoxy-5′,6′-[cyclohexylidenebis(oxy)]-2′-(2″-oxoethyl)-4′-[(*tert*-butyldimethylsilyl)oxy]heptyl]]-1,6,8-tris[(benzyloxy)methoxy]-2-naphthoate (52). DMSO (0.75 mL, 10.5 mmol) was added dropwise to a −78 °C solution of oxalyl chloride (0.5 mL, 5.7 mmol) in CH_2Cl_2 (10 mL) under Ar. This mixture was stirred for 10 min and then a solution of alcohol **51** (400 mg, 0.39 mmol) in CH_2Cl_2 (5 mL) was added. The cloudy mixture was stirred at −78 °C for 10 min, treated with triethylamine (4 mL, 28.6 mmol), and then allowed to warm to room temperature. The resulting mixture was partitioned between water and CH_2Cl_2. The organic layer was separated, dried over Na_2SO_4, and then concentrated. The residue was dissolved in ether and filtered through a Kimwipe plug. Removal of solvent in vacuo afforded 360 mg (90%) of aldehyde **52**, which was used without purification in the subsequent reaction: R_f 0.82 (40% ethyl acetate–hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 9.57 (s, 1 H) 7.4–7.24 (m, 16 H), 7.04 (d, J = 2.0 Hz, 1 H), 6.79 (d, J = 2.0 Hz, 1 H), 5.37 (s, 2 H), 5.36 (s, 2 H), 5.21 (m, 2 H), 4.77 (s, 2 H), 4.75 (s, 2 H), 4.73 (s, 2 H), 4.17 (m, 1 H), 4.00 (dd, J = 4.4, 8.0 Hz, 1 H), 3.91 (s, 3 H), 3.68 (dd, J = 4.0, 7.5 Hz, 1 H), 3.49–3.43 (m, 4 H), 3.10 (t, J = 7.5 Hz, 1 H), 2.70–2.30 (m, 4 H), 1.7–1.50 (m, 10 H), 1.36 (d, J = 6.2 Hz, 3 H), 0.91 (s, 9 H), 0.12 (s, 3 H), 0.11 (s, 3 H); IR ($CDCl_3$) 2930, 1720, 1625, 1607, 1580 cm^{-1}.

Methyl 3-[1′-[[2′(*R*),3′(*S*),4′(*R*),5′(*S*),6′(*R*)]-3′-Methoxy-5′,6′-[cyclohexylidenebis(oxy)]-2′-[carbomethoxymethyl)-4′-[(*tert*-butyldimethylsilyl)oxy]heptyl]]-1,6,8-tris[(benzyloxy)methoxy]-2-naphthoate (53). To a solution of aldehyde **52** (360 mg, 0.36 mmol) in DMF (2 mL) were sequentially added *tert*-butyl alcohol (8 mL), $KMnO_4$ (5 mL, 1 M aqueous solution), and KH_2PO_4 (3 mL, 1.25 M aqueous solution). The mixture was stirred for 30 min, treated with 3 mL of saturated aqueous $NaHSO_3$, and acidified to pH 2 with 0.1 N HCl. The clear solution was extracted with CH_2Cl_2, concentrated to ~20 mL, and then treated with excess ethereal diazomethane. About 5 min later the solvent was removed in vacuo to give 325 mg (90%) of diester **53**, which was used in the following experiments without any further purification: R_f 0.38 (20% ethyl acetate–hexane); $[\alpha]^{22}_D$ +12.5° (*c* 1.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.4–7.24 (m, 16 H), 7.03 (d, J = 2.6 Hz, 1 H), 6.97 (d, J = 2.6 Hz, 1 H), 5.36 (s, 2 H), 5.34 (s, 2 H), 5.21 (m, 2 H), 4.76 (s, 2 H), 4.75 (s, 2 H), 4.73 (s, 2 H), 4.20 (m, 1 H), 4.01 (dd, J = 2.8, 8.8 Hz, 1 H), 3.91 (s, 3 H), 3.66 (dd, J = 3.0, 7.5 Hz, 1 H), 3.53 (s, 3 H), 3.44 (s, 3 H), 3.11–3.03 (m, 2 H), 2.60–2.23 (m, 4 H), 1.70–1.45 (m, 10 H), 1.33 (d, J = 6.4 Hz, 3 H), 0.91 (s, 9 H), 0.13 (s, 3 H), 0.11 (s, 3 H); IR ($CDCl_3$) 2950, 2935, 1730, 1625, 1605, 1580 cm^{-1}; mass spectrum m/e 1036 (parent ion). Anal. Calcd for $C_{59}H_{76}O_{14}Si$: C, 68.31; H, 7.38. Found: C, 68.06; H, 7.52.

3-[1′-[[1′(*S*),2′(*R*),3′(*S*),4′(*R*)]-3′,4′-[Cyclohexylidenebis(oxy)]-1′-methoxy-2′-[(*tert*-butyldimethylsilyl)oxy]pentyl]]-6,8,9-tris[(benzyloxy)-methoxy]-1,2,3,4-tetrahydro-1(2*H*)-anthracenone (54). A solution of diester **53** (152 mg, 0.15 mmol) in dry benzene (9 mL) under N_2 was treated with KO^{t}Bu (180 mg, 1.5 mmol). The resulting mixture was stirred at room temperature for 1.5 h, treated with saturated aqueous NH_4Cl, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford a β-keto ester as a mixture of diastereomers. The crude product was dissolved in 30 mL of absolute ethanol and 20 mL of 0.1 N NaOH. The mixture was heated to reflux for 2 h, then cooled to room temperature, poured into aqueous NH_4Cl, and extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated to afford crude **54**. This material was purified by column chromatography (silica gel, 10% ethyl acetate–hexane) to give 83 mg (60%) of **54**: R_f 0.44 (20% ethyl acetate–hexane); $[\alpha]^{22}_D$ +13.5° (*c* 0.17, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.24 (m, 16 H), 7.01 (d, J = 2.0 Hz, 1 H), 6.93 (d, J = 2.0 Hz, 1 H), 5.38 (s, 2 H), 5.36 (s, 2 H), 5.25 (s, 2 H), 4.87 (s, 2 H), 4.86 (s, 2 H), 4.75 (m, 2 H), 4.13 (m, 1 H), 3.90 (t, J = 5.5 Hz, 1 H), 3.59 (t, J = 6.6 Hz, 1 H), 3.47 (s, 3 H), 3.15–2.94 (m, 3 H), 2.63–2.45 (m, 2 H), 1.55 (s, 10 H), 1.30 (d, J = 5.6 Hz, 3 H), 0.89 (s, 9 H), 0.11 (s, 3 H), 0.09 (s, 3 H); IR ($CDCl_3$) 2940, 1675, 1620, 1565 cm^{-1}; mass spectrum m/e 946 (parent ion).

3-[1′-[[1′(*S*),2′(*R*),3′(*S*),4′(*R*)]-3′,4′-[Cyclohexylidenebis(oxy)]-2′-hydroxy-1′-methoxypentyl]]-6,8,9-tris[(benzyloxy)methoxy]-1,2,3,4-tetrahydro-1(2*H*)-anthracenone (57). To a solution of **54** (68 mg, 0.071 mmol) in dry THF (3 mL) under Ar was added *n*-Bu_4NF (0.25 mL, 1 M in THF, 0.25 mmol). After being stirred at 23 °C for 1 h, the mixture was partitioned between water and CH_2Cl_2. The aqueous layer was further extracted with CH_2Cl_2, and the combined extracts were dried

over Na_2SO_4. Removal of solvent in vacuo, followed by column chromatography (silica gel, 40% ethyl acetate–hexane) of the crude product, provided 54 mg (93%) of **57**: R_f 0.07 (20% ethyl acetate–hexane); $[\alpha]^{22}_D$ +41° (*c* 0.24, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.24 (m, 16 H), 7.01 (d, *J* = 2.0 Hz, 1 H), 6.93 (d, *J* = 2.0 Hz, 1 H), 5.38 (s, 2 H), 5.36 (s, 2 H), 5.25 (m, 2 H), 4.86–4.71 (m, 6 H), 4.10 (m, 1 H), 3.58 (s, 3 H), 3.54–3.40 (m, 2 H), 3.22 (d, *J* = 10.0 Hz, 1 H), 2.94 (m, 1 H), 2.63 (d, *J* = 10.0 Hz, 1 H), 2.50 (m, 2 H), 2.21 (d, *J* = 7.0 Hz, 1 H), 1.55 (m, 10 H), 1.38 (d, *J* = 5.6 Hz, 3 H); IR ($CDCl_3$) 3650–3150 (br), 2940, 1675, 1620, 1565 cm^{-1}; mass spectrum *m/e* 832 (parent ion).

3-[1′[[1′(*S*),2′(*R*),3′(*S*),4′(*R*)]-3′,4′-[Cyclohexylidenebis(oxy)]-1′-methoxy-2′-oxopentyl]]-6,8,9-tris[(benzyloxy)methoxy]-1,2,3,4-tetrahydro-1(2*H*)-anthracenone (58). DMSO (0.07 mL, 1.0 mmol) was added dropwise to a −78 °C solution of oxalyl chloride (0.06 mL, 0.74 mmol) in CH_2Cl_2 (3 mL) under Ar. This solution was stirred for 10 min, and then a −78 °C solution of alcohol **57** (52 mg, 0.062 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise via cannula. The cloudy mixture was stirred at −78 °C for 1.25 h, treated with triethylamine (0.21 mL, 1.48 mmol), and then allowed to warm to −5 °C over 2 h. The resulting mixture was poured into water and extracted three times with CH_2Cl_2 (3 × 30 mL). The combined extracts were dried over Na_2SO_4, and the solvent was removed in vacuo. The residue was triturated three times with ether (3 × 15 mL), and the combined triturate was filtered through a Kimwipe plug and then concentrated. The residue was purified by column chromatography (silica gel, 1:1 ether–hexane) to give 47 mg (91%) of diketone **58**: R_f 0.19 (1:1 ether–hexane); $[\alpha]^{22}_D$ −33° (*c* 0.03, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.24 (m, 16 H), 6.99 (d, *J* = 2.0 Hz, 1 H), 6.93 (d, *J* = 2.0 Hz, 1 H), 5.38 (s, 2 H), 5.36 (s, 2 H), 5.23 (m, 2 H), 4.86–4.71 (m, 6 H), 4.10 (m, 3 H), 3.42 (s, 3 H), 3.04–2.60 (m, 5 H), 1.55 (m, 10 H), 1.38 (d, *J* = 8.8 Hz, 3 H); IR ($CDCl_3$) 2940, 1720, 1675, 1618, 1566 cm^{-1}.

3-[1′-[[1′(*S*),2′(*R*),3′(*S*),4′(*R*)]-3′,4′-[Cyclohexylidenebis(oxy)]-1′-methoxy-2′-oxopentyl]]-6,8,9-tris[(benzyloxy)methoxy]-1,2,3,4-tetrahydro-2-[(*tert*-butyldimethylsilyl)oxy]-1(2*H*)-anthracenone, Protected Olivin 59. To a solution of diketone **58** (15.5 mg, 0.018 mmol) in dry CH_2Cl_2 (1.5 mL) under N_2 were added sequentially Et_3N (0.07 mL, 0.50 mmol) and TBDMS-OTf (0.04 mL, 0.17 mmol). After being stirred for 10 min, the reaction was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated, and the residue was purified by column chromatography (silica gel, 50:50:1 ether–hexane–triethylamine). The silyl enol ether [R_f 0.57 (1:1 ether–hexane)] so obtained was immediately dissolved in CH_2Cl_2 (1 mL), cooled to −20 °C, and treated successively with solid NaH_2PO_4 (46 mg, 0.32 mmol) and 97% *m*CPBA (46 mg, 0.32 mmol). The reaction mixture was stirred at −20 °C for 25 min and then quenched with a cold 1:1 mixture of saturated aqueous $NaHSO_3$ and $NaHCO_3$ solutions. The aqueous layer was further extracted with CH_2Cl_2, and the combined extracts were washed with saturated aqueous $NaHCO_3$ and dried over Na_2SO_4. Purification of the crude product by column chromatography (silica gel, 150:50:1 hexane–ether–triethylamine) afforded 11.6 mg (76%) of protected olivin **59**: R_f 0.55 (1:1 ether–hexane); $[\alpha]^{22}_D$ −35° (*c* 0.15, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.26 (m, 15 H), 7.22 (s, 1 H), 6.99 (d, *J* = 2.4 Hz, 1 H), 6.95 (d, *J* = 2.4 Hz, 2 H), 5.41–5.39 (m, 4 H), 5.31 (s, 2 H), 4.95–4.50 (m, 8 H), 4.10 (d, *J* = 8.9 Hz, 1 H), 3.98 (m, 1 H), 3.41 (s, 3 H), 3.32 (m, 1 H), 2.47–2.67 (m, 2 H), 1.61 (m, 10 H), 1.40 (d, *J* = 5.8 Hz, 3 H), 1.03 (s, 9 H), 0.32 (s, 3 H), 0.12 (s, 3 H); IR ($CDCl_3$) 2940, 1715, 1700, 1620, 1565 cm^{-1}; mass spectrum *m/e* 960 (parent ion).

Synthetic Olivin (1). Protected olivin **59** (9.1 mg, 0.008 mmol) was dissolved in dry MeOH (2 mL) and treated with 20 mg of activated Dowex 50W-X8 resin. The resulting mixture was stirred at room temperature for 6 days. Workup consisted of filtering the suspension through a Kimwipe plug and removal of MeOH in vacuo. The residue was crystallized from hexane–ether to afford 3.1 mg (95%) of olivin as a yellow solid. The material so obtained was indistinguishable from natural olivin by all of the usual criteria: R_f 0.15 (94:5:1 CH_2Cl_2–MeOH–HCOOH); mp 139–141 °C; $[\alpha]^{22}_D$ +53° (*c* 0.04, EtOH); ^1H NMR (300 MHz, CD_3CN) δ 6.77 (s, 1 H), 6.50 (d, *J* = 1.1 Hz, 1 H), 6.34 (d, *J* = 1.1 Hz, 1 H), 4.72 (d, *J* = 2.2 Hz, 1 H), 4.39 (d, *J* = 11.4 Hz, 1 H), 4.17–4.13 (m, 2 H), 3.36 (s, 3 H), 2.98–2.93 (m, 1 H) 2.69–2.53 (m, 2 H), 1.20 (d, *J* = 7.0 Hz, 3 H); IR ($CHCl_3$) 3500–3200 (br), 2920, 2850, 1730, 1635 cm^{-1}; mass spectrum *m/e* 406 (parent ion).

Natural Olivin. A solution of olivomycin A (32.9 mg, 0.028 mmol) in 3 mL of 0.05 N methanolic HCl was refluxed under nitrogen for 4 h. After being cooled to room temperature, the reaction mixture was neutralized with Ag_2CO_3. The resulting silver salts were filtered off, and the filtrate was concentrated in vacuo. The residue was then dissolved in 10 mL of water and extracted four times with EtOAc (4 × 5 mL). The combined extracts were concentrated to give a yellow oil which was crystallized from chloroform–ethanol–hexane. The yellow solid so obtained was further purified by column chromatography (silica gel, 94:5:1 CH_2Cl_2–MeOH–HCOOH) to afford 0.7 mg of olivin that was recrystallized from ether–hexane. The yield of olivin could be increased if the mother liquor from the initial crystallization was subjected to additional purification: R_f 0.15 (94:5:1 CH_2Cl_2–MeOH–HCOOH); mp 136–139 °C; $[\alpha]^{22}_D$ +56° (*c* 0.07, EtOH); ^1H NMR (300 MHz, CD_3CN) δ 6.77 (s, 1 H), 6.50 (d, *J* = 1.1 Hz, 1 H), 6.34 (d, *J* = 1.1 Hz, 1 H), 4.72 (d, *J* = 2.2 Hz, 1 H), 4.39 (d, *J* = 11.4 Hz, 1 H), 4.17–4.13 (m, 2 H), 3.36 (s, 3 H), 2.98–2.93 (m, 1 H) 2.69–2.53 (m, 2 H), 1.20 (d, *J* = 7.0 Hz, 3 H); IR ($CHCl_3$) 3500–3200 (br), 2920, 2850, 1730, 1635 cm^{-1}; mass spectrum *m/e* 406 (parent ion).

Acknowledgment. This research was supported by grants from the National Institutes of Health (CA 29847 and AI 20779). We also would like to thank Professor R. W. Franck for a gift of natural olivomycin A used in the preparation of a reference sample of olivin.

Supplementary Material Available: General experimental details and procedures for synthesis of **20** (from **14**), **20b** (from **19**), **23** and **24** (from **14**), and **34b** (from **20b**) (4 pages). Ordering information is given on any current masthead page.

[4 + 2] Cycloaddition Reaction of Dibenzyl Azodicarboxylate and Glycals

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Abstract: The [4 + 2] cycloaddition reaction of dibenzyl azodicarboxylate and glycals allows the stereoselective introduction of an amino function at C-2 of a carbohydrate. Very good results were obtained with both furanoid and pyranoid glycals, except when triacetylglucal (TAG) was used as the substrate. In some instances the course of the reaction was found to be concentration dependent.

Recently, we reported a new and efficient method for the preparation of 2-aminoglycosides.[1,2] This method combines the amination and glycosidation steps into a single strategy, the key step being the highly stereoselective [4 + 2] cycloaddition reaction of dibenzyl azodicarboxylate and glycals (Scheme I). The adducts

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0002-7863/89/1511-2995$01.50/0