hydrochloride and 2 equiv of potassium carbonate. This mixture is refluxed overnight and allowed to cool and collect precipitate.

Compound **22**: mp 198–200 °C; NMR ($Me_2SO$-$d_6$) δ 8.40–7.20 (m, 4, Ar), 3.57–3.07 (m, 1, NOH), 2.37 (s, 3, $CH_3$); IR (KBr) 3500–2500 (br), 1500, 1322, 921 $cm^{-1}$. Anal. Calcd for $C_9H_8N_2SO$: C, 56.33; H, 4.19; N, 14.58. Found: C, 56.02; H, 4.11; N, 14.43.

Compound **23**: mp 118–123 °C; NMR ($CDCl_3$) δ 8.30–7.20 (m, 4, Ar), 3.85 (septet, 1, $J$ = 7 Hz), 1.51 (d, 3, $J$ = 7 Hz), 1.40 (d, 3, $J$ = 7 Hz); IR ($CH_2Cl_2$) 3525, 3250 (br), 2940, 1440, 955 $cm^{-1}$. Anal. Calcd for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72. Found: C, 60.00; H, 5.50; N, 12.62.

Compound **28**: mp 215–218 °C; NMR ($Me_2SO$-$d_6$) δ 7.83–7.07 (m, 4, Ar), 5.40–3.23 (4, br singlet for NOH and singlet at 4.00 for $NCH_3$), 2.37 (s, 3, $CH_3$); IR (KBr) 3700–2100, 1550–1410, 1362, 1325, 1262, 1020, 930 $cm^{-1}$. Anal. Calcd for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86; N, 22.21. Found: C, 62.76; H, 5.64 N, 21.75.

Compound **29**: mp 165–168 °C; NMR ($CDCl_3$/$Me_2SO$-$d_6$) δ 8.03–7.00 (m, 4, Ar), 6.03–5.23 (m, 1, CH), 4.03–2.73 (m, 3, ($H_2O$), s, 3.35 NOH), 2.47 (s, 3, $CCH_3$), 1.65 (d, 6, dimethyl multi, $J$ = 6): IR (KBr) 3500–2400 (br), 1400, 1362, 1290, 1020, 745 $cm^{-1}$. Anal. Calcd for $C_{12}H_{15}N_3O{\cdot}H_2O$: C, 61.28; H, 7.29; N, 17.88. Found: C, 61.13; H, 7.29; N, 17.65.

**Preparation of Phosphates 24, 25, 30, and 31.** These phosphates were prepared by the standard phosphorylating procedure described above. The final organic solutions were not washed with base and were not chromatographed so as not to effect the isomer ratio. The impurities were of a small proportion that it did not interfere with $^{13}C$ NMR interpretation of the condensed oxime phosphate. Elemental analyses of the crude products were all equally low (2.5%) in carbon, correct for hydrogen, and ~1% low in nitrogen. Subsequent attempts at chromatography led to considerable decomposition on the column.

Compound **24**: NMR ($CDCl_3$) δ 8.33–7.00 (m, 4, Ar), 4.80–3.97 (m, 2, -$POCH_2CH_3$), 3.37–2.67 (m, 2, $SCH_2CH_2CH_3$), 2.63 (s, 3, $CH_3$), 2.20–1.62 (m, 2, $SCH_2CH_2CH_3$), 1.47 (t, 3, $OCH_2CH_3$, $J$ = 4 Hz), 1.07 (t, 3, $SCH_2CH_2CH_3$, $J$ = 5 Hz); IR ($CH_2Cl_2$) 3100–2700 (br), 1370, 1332, 910 $cm^{-1}$.

Compound **25**: NMR ($CDCl_3$) δ 8.30–7.20 (m, 4, Ar), 4.73–3.60 (m, 2, $OCH_2CH_3$), 3.47–2.63 (m, 1, CH), 3.96–0.63 (m, 8): IR (neat) 3700–2500 (br), 1798, 1710, 1558, 1462, 1395, 1163, 1100, 660, 620 $cm^{-1}$.

Compound **30**: NMR ($CDCl_3$) δ 8.00–7.10 (m, 4, Ar), 4.67–3.90 (m, 5, $NCH_3$ singlet at 4.07), 2.95 (m, 2, $SCH_2$), 2.63 (s, 3, $CH_3$), 2.27–1.20 (m, 2), 1.42 (t, 3, $OCH_2CH_3$, $J$ = 5 Hz), 1.00 (t, 3, $SCH_2CH_2CH_3$, $J$ = 4 Hz); IR (neat) 3700–2000, 2000–1700 (br), 1609 $cm^{-1}$.

Compound **31**: NMR ($CDCl_3$) δ 8.00–7.00 (m, 4, Ar), 6.00–5.37 (m, 1, CH), 4.67–3.93 (m, 2, -$OCH_2$-), 3.33–2.75 (m, 2, -$SCH_2$-), 2.63 (s, 3, $CH_3$), 2.17–1.53 (m, 8), 1.38 (t, 3, -$OCH_2CH_3$, $J$ = 6 Hz), 1.00 (t, 3, -$SCH_2CH_2CH_3$, $J$ = 6 Hz); IR (neat) 3600–2200 (br), 1610, 1340, 1200, 1140, 680 $cm^{-1}$.

**Acknowledgment.** We thank Stephanie Dunlap and Florence Hoover for their synthetic efforts and Dr. Paul Bartlett for his assistance in both mechanistic and structural consultation.

**Registry No.** **1**, 70510-23-5; **2**, 96327-78-5; **3a**, 1498-51-7; **3b**, 7651-98-1; **4**, 814-49-3; **6**, 96327-79-6; **7**, 96327-80-9; **8**, 1565-39-5; **9**, 96327-81-0; **10**, 96327-82-1; **11**, 96327-83-2; **12**, 52755-90-5; **13**, 96327-84-3; **14**, 96327-85-4; **15**, 96327-86-5; **16**, 89204-68-2; **17**, 96327-87-6; **18**, 89204-57-9; **19**, 89204-65-9; **20**, 1629-78-3; **21**, 96327-88-7; **22**, 1629-79-4; **23**, 96327-89-8; **24**, 96327-90-1; (*E*)-**25**, 96327-95-6; (*Z*)-**25**, 96327-91-2; **26**, 942-25-6; **27**, 31539-67-0; **28**, 945-78-8; **29**, 96327-92-3; (*E*)-**30**, 96327-93-4; (*Z*)-**30**, 96327-96-7; (*E*)-**31**, 96327-94-5; (*Z*)-**31**, 96327-97-8; $Me_2NCOCl$, 79-44-7; 2,4-dichlorobenzaldehyde, 874-42-0; *N*-methylbenzimidazole, 1632-83-3; benzoxazole, 273-53-0; benzothiazole, 95-16-9.

# Acyclic Stereoselection. 25. Stereoselective Synthesis of the C-1 to C-7 Moiety of Erythronolide A[1,2]

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*Received October 22, 1984*

A stereoselective synthesis of aldehyde ester **1**, a synthon for the C-1 to C-7 section of erythronolide A, is reported. The synthesis begins with β,γ-unsaturated aldehyde **12**, which is prepared from mesityl oxide as shown in eq 2. Aldehyde **12** reacts with the preformed lithium enolates of reagents **13** and **5** to give, in each case, a 15:1 mixture of two aldols (eq 3 and 4). Reduction of the major isomer **16** from the reaction of **5** with **12** with lithium aluminum hydride followed by periodate cleavage of the resulting vicinal diol provides β-hydroxy aldehyde **20**. This material is protected as the triethylsilyl derivative **21**, which is treated with the lithium enolate of BHT *O*-benzyllactate (**22c**). The resulting 5:1 mixture of aldols is converted into acetonides **27c** and **28c**, which are separated by chromatography. The stereostructure of the major acetonide **27c** was elucidated by single-crystal X-ray analysis (Figure 1). Lithium aluminum hydride reduction of **27c** gives alcohol **29**, which is converted into acetate **34**. Ozonolysis of this material gives aldehyde **35**, which is oxidized by pyridinium dichromate in DMF. Diazomethane esterification provides diester **36**, which is methanolized to hydroxy ester **37**. Swern oxidation of **35** provides racemic ester aldehyde **1**. Enantiomerically homogeneous **1** is obtained in a similar sequence, via the *O*-methylmandelates **39a** and **39b**.

In previous papers in this series, we have reported the development of useful strategies and reagents for the stereorational synthesis of complex organic molecules having many stereocenters. In this paper, we report the application of two of these reagents in a synthesis of **1**, the

(1) For part 24, see: Heathcock, C. H.; Hagen, J. P.; Young, S. D.; Pilli, R.; Bai, D. L.; Märki, H.-P.; Kees, K.; Badertscher, U. *Chim. Scr.*, in press.

(2) The work reported in this paper was reported in preliminary form at the Fourth International Conference on Organic Synthesis, Tokyo, Japan, August 22–27, 1982. Heathcock, C. H. In "Current Trends in Organic Synthesis"; Nozaki, H., Ed.; Pergamon Press: Oxford and New York, 1983.

(3) Present address: (a) Research Laboratories, Merck Sharp & Dohme, West Point, PA 19486. (b) Department of Chemistry, University of Nebraska, Omaha, NE 68182. (c) Universidade Estandual de Campinas, Barao Geraldo, Campinas S.P., Brasil 13.100. (d) Lonza, Inc., P.O. Box 1400, La Porte, TX 77571.

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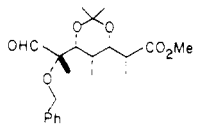
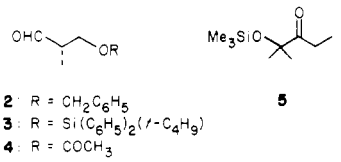
C-1 to C-7 moiety of the macrolide antibiotic erythromycin A.



1

As a synthon for the C-1 to C-3 portion of **1**, containing the C-2 stereocenter, we first examined (*S*)-3-(benzyloxy)-2-methylpropanal (**2**)[4] and the related derivatives **3** and **4**. For the syn-selective[5] propionaldehyde enolate equivalent, we employed the keto ether **5**.[6]

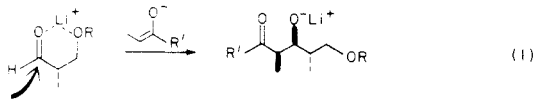


**2**: R = $CH_2C_6H_5$
**3**: R = $Si(C_6H_5)_2(t\text{-}C_4H_9)$
**4**: R = $COCH_3$

**5**

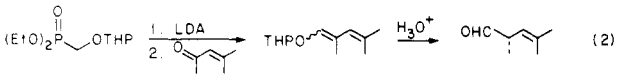
Addition of the preformed lithium enolate of ketone **5** to aldehydes **2–4** gives, in each case, a mixture of diastereomeric aldols, the ratio being 2:1 in the case of **2**, 3.7:1 in the case of **3**, and 3.4:1 in the case of **4** (Scheme I). The stereostructures of aldols **6a/7a**, **6b/7b**, and **6c/7c** were established as shown in Scheme I; $^{13}C$ NMR spectra of the final triacetates showed in each case that the chiral isomer **8** is the major product.[7]

Although the simple diastereoselectivity of ketone **5** is good in these reactions, the diastereofacial preferences shown by aldehydes **2–4** are not what would be predicted on the basis of the various empirical models for asymmetric induction[8] and are opposite to that required for application in the erythronolide A synthesis. The reason for the unexpected behavior of these β-alkoxy aldehydes is not clear. One possibility is that a lithium cation is chelated between the aldehyde and β-alkoxy oxygens. This would give a structured substrate that would be expected to suffer addition trans to the methyl substituent, thus leading to the observed major aldol (eq 1). However, if this hypothesis were correct, one would expect acetoxy aldehyde **4** to show this behavior to a lesser degree, since the electron-withdrawing effect of the acyl group should render the β-oxygen less basic. However, the **6c/7c** ratio is *greater* than the **6a/6b** ratio.



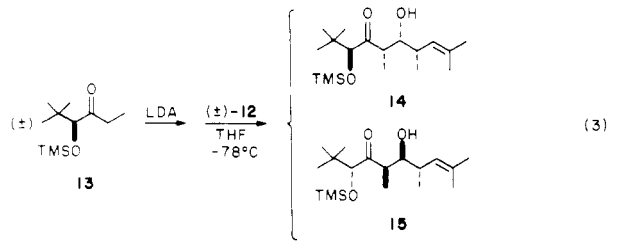
(1)

Since the aberrant diastereofacial preference of aldehydes **2–4** seems to be associated with the β-alkoxy group, we prepared β,γ-unsaturated aldehyde **12**, as shown in eq 2.[9] Reaction of mesityl oxide with the Kluge reagent (**10**)[13] gives a stereoisomeric mixture of dienes **11**, which is hydrolyzed in a two-phase mixture of aqueous HCl and tetrahydrofuran to give aldehyde **12**, accompanied by 8–10% of its conjugated isomer.



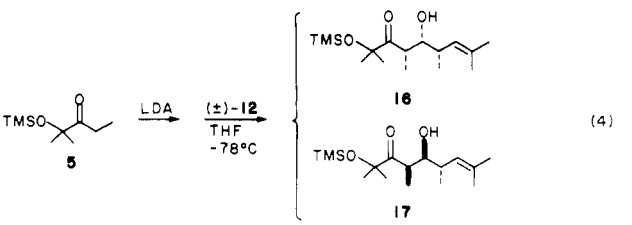
**10** **11** **12** (2)

Treatment of **12** with the enolate of the racemic α-(trimethylsilyl)oxy ketone **13**[14] affords aldols **14** and **15** in a ratio of 15:1 and in a yield of about 60% (eq 3). It is noteworthy that, of the eight racemates that could result from this reaction, only two are formed, and these in a ratio of 93:7! Thus, not only does the enolate of ketone **13** show the expected high simple diastereoselectivity,[15] but it also exhibits mutual kinetic resolution[14] in its reaction with racemic **12**.



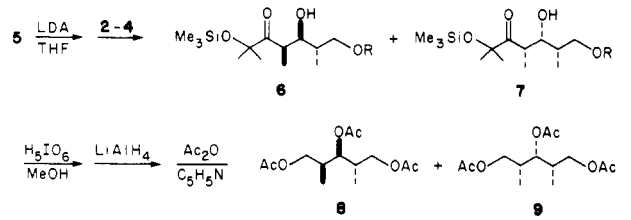
**13** **14** **15** (3)

We also examined the reaction of **12** with the simpler propionaldehyde synthon, ketone **5**. Somewhat surprisingly, the reaction of **12** with **5** also gives the two syn aldols **16** and **17** in a ratio of 15:1 (eq 4).



**5** **16** **17** (4)

Scheme I[a]



[a] (a) R = $CH_2C_6H_5$, (b) R = $Si(C_6H_5)_2(t\text{-}C_4H_9)$, (c) R = OAc.

(4) An ether analogous to **2**, except that the hydroxy group is protected as the (benzyloxy)methyl ether, was employed by Still and co-workers in their monensin synthesis: Collum, D. H.; MacDonald, J. H., III; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2117.

(5) In this paper, the qualitative stereochemical descriptors syn and anti are employed, as defined by Masamune and co-workers: Masamune, S.; Ali, Sk. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557. For a full discussion of various other systems that have been used for describing the stereostructures of aldols, see: Heathcock, C. H. In "Asymmetric Synthesis"; Morrison, J. D., Ed., Academic Press: New York, 1984; Vol. 3, 112–115.

(6) (a) Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 2337. (b) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066. (c) Young, S. D.; Buse, C. T.; Heathcock, C. H. *Org. Synth.*, in press.

(7) Of course, this analysis involves the tacit assumption that aldols of ketone **5** have only the syn relative configuration at the two new stereocenters. However, this assumption is well-founded on a wealth of precedent.[8]

(8) (a) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. (b) Karabatsos, G. J. *Ibid.* **1967**, *89*, 1367. (c) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. See also (d) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.

(9) Aldehyde **12** has been reported in the literature several times.[10-12] The most attractive of these procedures is that of Matteson and coworkers.[12] However, it did not appear to us that the Matteson procedure was suitable for the scale we envisioned. Therefore, we developed the synthesis of **12** that is reported herein.

(10) Heilbron, I. M.; Johnson, A. W.; Jones, E. R. H.; Spinks, A. *J. Chem. Soc.* **1942**, 727.

(11) de Botton, M.; Normant, H. *C. R. Acad. Sci. Paris, Ser. C* **1967**, *264*, 399.

(12) (a) Matteson, D. S.; Moody, R. J.; Jesthi, P. K. *J. Am. Chem. Soc.* **1975**, *97*, 5608. (b) Matteson, D. S.; Moody, R. J. *J. Org. Chem.* **1980**, *45*, 1091.

(13) (a) Kluge, A. F.; Cloudsdale, I. S. *J. Org. Chem.* **1979**, *44*, 4847. (b) Kluge, A. F. *Org. Synth.*, in press.

(14) Heathcock, C. H.; Pirrung, M. C.; Lampe, J.; Buse, C. T.; Young, S. D. *J. Org. Chem.* **1981**, *46*, 2290.

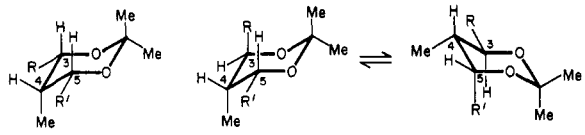
(15) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.

**Table I. Simple Diastereoselection in Reactions of Aryl Esters 22a–c with Aldehydes (eq 6)[a]**

| | | isomer ratio, 24/23 | | |
|---|---|---|---|---|
| ester | EtCHO | $i$-$C_3H_7$CHO | $t$-BuCHO | PhCHO |
| **22a** | 22:78 | 17:83 | >97:3 | 75:25 |
| **22b** | | 47:53 | | 90:10 |
| **22c** | 87:17 | >97:3 | | >97:3 |

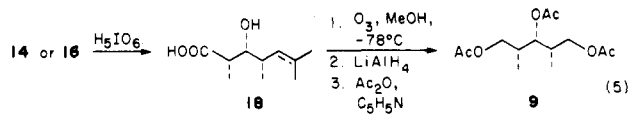
[a] For more details, see ref 16.

**Scheme II**



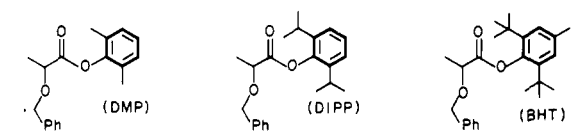
**27** **28x** **28y**

The stereostructures of the major isomers in the reactions of aldehyde **12** with ketones **13** and **5** were established as shown in eq 5. Periodic acid oxidation of the major isomer in each case provides a β-hydroxy acid (**18**), which was subjected to the three-step sequence shown to obtain the *meso*-triacetate **9**.[7]



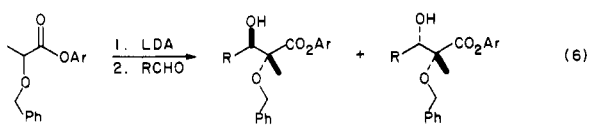
**18** **9** (5)

Having a viable route to a synthon representing the C-1 to C-5 segment of erythronolide A and containing three stereocenters, we addressed the issue of adding a lactaldehyde synthon in order to introduce C-6 (with its tertiary hydroxy group) and C-7. In a recent paper, we have discussed the development of a series of such reagents, hindered aryl esters **22a–c**.[16]



**22a** **22b** **22c**

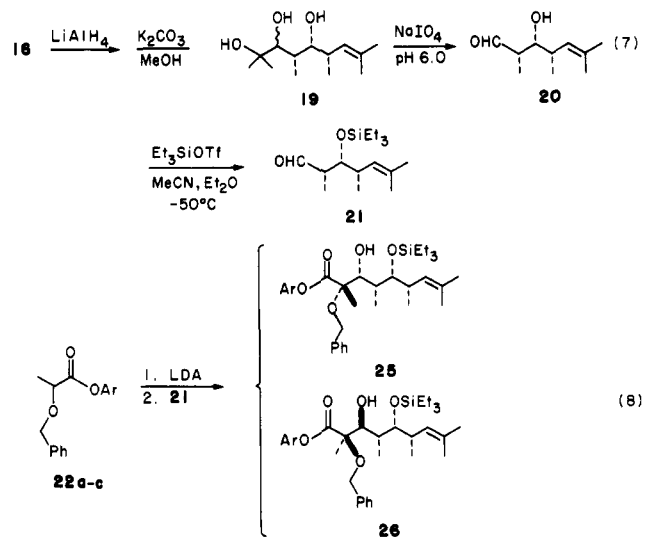
In the previous work, aldol additions of **22a–c** with various aldehydes were examined, and it was found that simple diastereoselection, both in sense and in magnitude, is related to the size of the R group of the aldehyde, RCHO (eq 6).



**22a–c** **23a–c** **24a–c** (6)

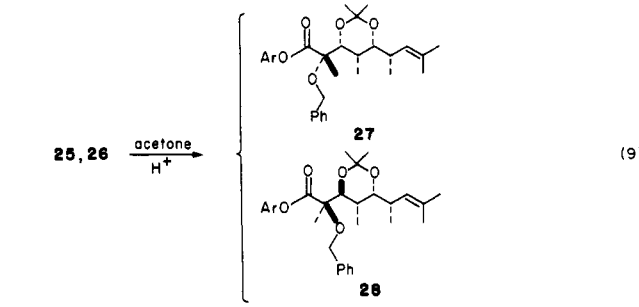
Selected data from this study (eq 6) are summarized in Table I. Note that simple diastereoselection in the sense of **24** (2*RS*,3*SR*) is greater for larger Ar and also for larger R in RCHO. However, with pivaldehyde, even DMP *O*-benzyllactate shows virtually complete simple diastereoselection in the sense of **24**.

With this background, we examined the reactions of esters **22a–c** with the protected β-hydroxy aldehyde **21**, as shown in eq 7. In the event, all three reagents provided mixtures of diastereomeric aldols (eq 8). In the case of diastereomeric pairs **25a/26a** and **25c/26c**, the isomers have been separated and converted individually into 3,5-*O*-isopropylidene derivatives **27a/28a** and **27c/28c**, respectively; with **25b/26b**, the mixture of aldols was not separated but was converted into a mixture of acetonides **27b/28b** (eq 9). The diastereomeric ratios in these three reactions are 35:65, 50:50, and 85:15, respectively, for esters **22a**, **22b**, and **22c**.



**19** **20** **21** **22a–c** **25** **26** (7) (8)

a: Ar = DMP, b: Ar = DIPP, c: Ar = BHT



**27** **28** (9)

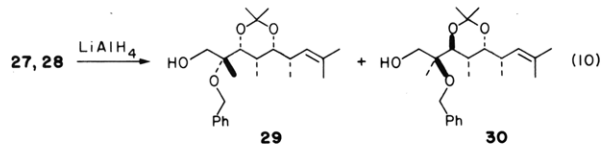
a: Ar = DMP, b: Ar = DIPP, c: Ar = BHT

With our previous study in mind (Table I), and with the assumption that isobutyraldehyde is a reasonable model for aldehyde **21**, we first believed that the two isomers in each case differed in the sense of their simple diastereoselection and that aldehyde **21** was therefore showing an unexpectedly high diastereofacial preference with all three reagents. The first indication that this simple assumption is incorrect came from careful scrutiny of the $^1H$ NMR spectra of the three pairs of isomeric acetonides. In each case, the C-3 proton in **27** appears as a sharp doublet, with $J \cong 2$ Hz. However, in isomer **28**, the C-3 proton resonance appears as a doublet with $J \cong 6$ Hz. If the two isomers resulted from the same diastereofacial preference at the chiral aldehyde **21**, they would have the same stereochemistry at C-3, C-4, C-5, and C-6, and we would expect the C-3 proton to show similar coupling to the C-4 proton in the two acetonides. The fact that this is not observed suggests that a situation such as is outlined in Scheme II exists. That is, if isomer **27**, the major product from ester **22c**, has the expected structure, then the axial proton at C-3 would be expected to have a rather small coupling to the equatorial proton at C-4. On the other hand, if the minor isomers **28a–c** result from the *same* sense of simple diastereoselection but differ in the sense of diastereofacial selectivity in reactions of **22a–c** with **21**, the acetonide ring of **28** would be as diagrammed in Scheme II. In this case, either R or R′ must be axial and experience a 1:3 interaction with one of the isopropylidine methyl groups. Since R is a quaternary atom, and R′ is not, one might expect conformation **28y** to predominate. In this conformer, both

(16) Heathcock, C. H.; Pirrung, M. C.; Young, S. D.; Hagen, J. P.; Jarvi, E. T.; Badertscher, U.; Märki, H.-P.; Montgomery, S. *J. Am. Chem. Soc.*, in press.

the C-3 and C-4 protons are axial, and a larger vicinal coupling constant is expected, as is observed.

For these reasons, it seemed important to fully elucidate the stereostructures of aldols **25a–c** and **26a–c**. The first step was to show that the two isomers in each case differ in the same manner. This was easily accomplished by reduction of acetonides **27/28** in each series with lithium aluminum hydride to a mixture of diols, **29** and **30** (eq 10).



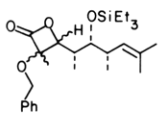

(10)

The next step was to carry out rigorous identification of one aldol of structure **25** and one of **26**. For the **25** series, the nicely crystalline acetonide **27** was selected. Its structure was found by single-crystal X-ray analysis to be as has been indicated heretofore, and an ORTEP representation is shown in Figure 1.

The stereostructure of aldol **26a** was also elucidated by single-crystal X-ray analysis, albeit in a somewhat convoluted manner. As shown in Scheme III, oxidation of alcohol **30** with pyridinium chlorochromate[17] gives an aldehyde (**31**), which is allowed to condense with the preformed lithium enolate of the chiral, racemic $\alpha$-(trimethylsilyl)oxy ketone **13**. The resulting crystalline aldol **32** was subjected to single-crystal X-ray analysis and found to have the structure indicated in Scheme III; an ORTEP representation is shown in Figure 2.

Although only incidental to the subject of the present paper, the chemistry summarized in Scheme III shows several features of interest. First, the reaction of racemic **13** with racemic **31** is a further example of double stereodifferentiation with mutual kinetic resolution. Second, ketone **13** once again reacts in the *ul* mode (reaction occurs on the *re* face of the *S* enantiomer and on the *si* face of the *R* enantiomer).[18,19] Finally, the diastereofacial preference of aldehyde **31** is also *ul* (relative to the stereocenter at C-2). That is, the facial preference of **31** in its reaction with the lithium enolate of **13** is that predicted by application of the Felkin model,[8c] assuming $OCH_2Ph$ to be the large group (Anh effect).[8d] On the other hand, chelation of a lithium cation by the $\beta$-alkoxy group could dictate the facial sense observed with **31**. However, since chelation-controlled facial selection has not generally been observed in reactions of other $\beta$-alkoxy or $\alpha,\beta$-dialkoxy aldehydes,[20] it is probably safe to assume that it is not involved in the case of **31**, either.

To return to the main theme of the paper, the synthesis of **1**, it is clear that the reagent of choice is **22c**, which gives the two diastereomeric aldols in a ratio of 85:15. In most preparations, the crude aldol product contains an infrared absorption band at 1825 $cm^{-1}$. From one run, careful chromatography of the aldols, before conversion to acetonides, allowed us to isolate the $\beta$-lactone **33**, as a dia-




**33**

stereomeric mixture, in 9% yield. Normally, however, the crude aldol product is converted into the 3,5-*O*-iso-

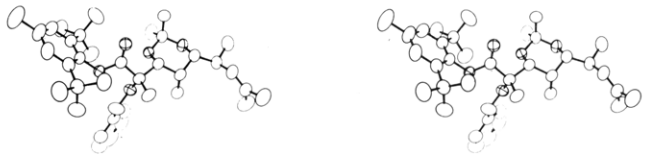


**Figure 1.** ORTEP representation of acetonide **27**.

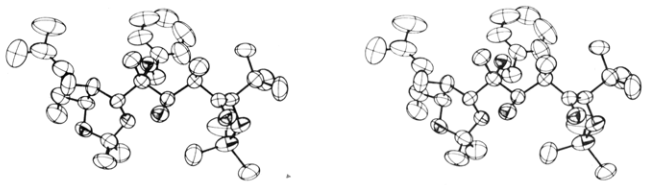
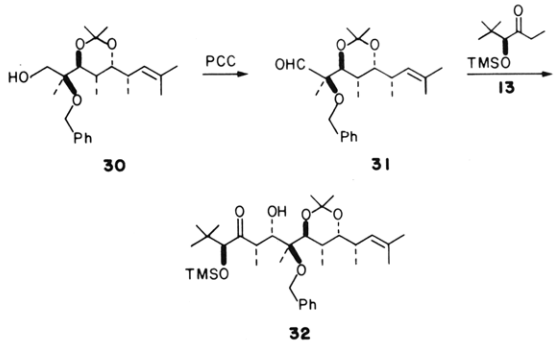
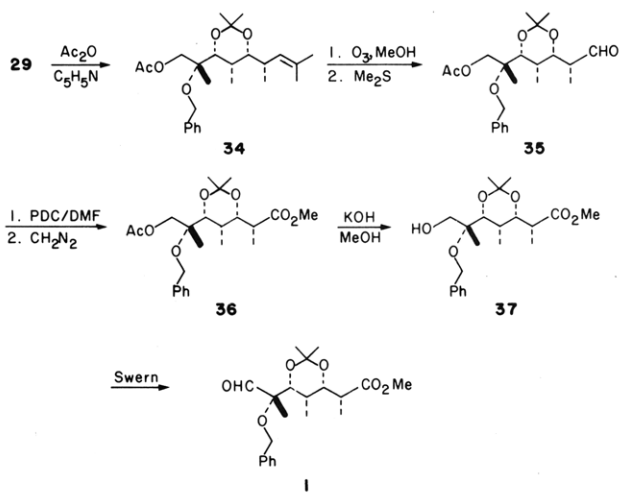


**Figure 2.** ORTEP representation of aldol **32**.

**Scheme III**

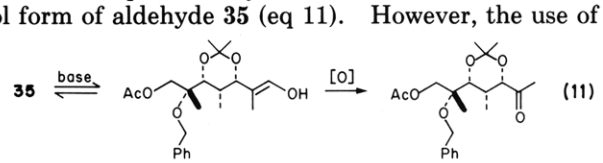



**Scheme IV**




propylidene derivatives **27c** and **28c**, which are readily separated by silica gel chromatography.

The final steps of the synthesis of synthon **1** are summarized in Scheme IV. Acetylation of alcohol **29** provides **34**, which is ozonized in methanol to obtain aldehyde **35**. The oxidation of this substance proved to be an unexpected problem. With many oxidants, including argentic oxide,[21] methyl ketone **38** was a major reaction product. This material presumably results from oxidation of the enol form of aldehyde **35** (eq 11). However, the use of

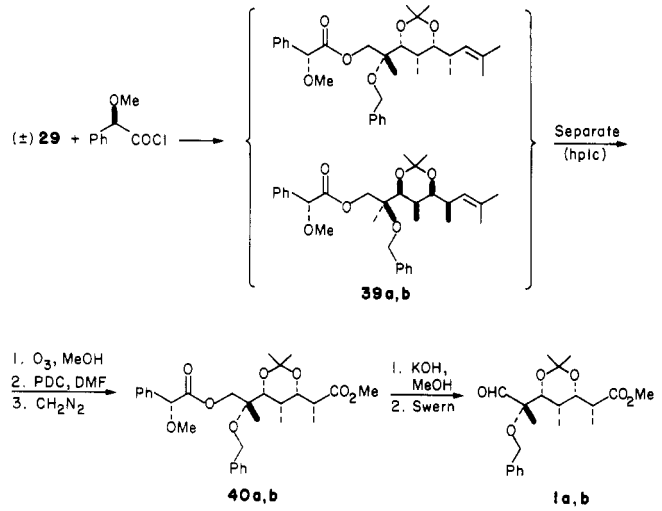



(11)

pyridinium dichromate in DMF[22] completely obviates the

(17) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(18) For a definition of *ul*, see: Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 385.
(19) For another case in which the enolate of **13** shows *ul* diastereofacial preference, see ref 14.
(20) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, M. C.; White, C. T.; VanDerveer, D. *J. Org.* Chem. **1980**, *45*, 3846.
(21) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.

**Scheme V**




problem. The resulting carboxylic acid is esterified with diazomethane to obtain diester **36**. Methanolysis of this material provides hydroxy ester **37**, which is subjected to Swern oxidation[23] to obtain the racemic version of ester aldehyde **1**.

The separate enantiomers of **1** may be obtained by the resolution summarized in Scheme V. Racemic alcohol **29** is esterified with (*R*)-*O*-methylmandelyl chloride to obtain the diastereomeric esters **39a** and **39b**. These diastereomers are separated by preparative HPLC, and the separated isomers are each subjected to the previously described sequence of reactions to obtain (+)-**1** and (−)-**1**. Absolute configurations of the enantiomers of **1** have not yet been elucidated.

In summary, aldehyde ester **1**, representing the C-1 to C-7 segment of erythronolide A, has been synthesized, both in racemic and in enantiomerically homogeneous form. The synthesis of (±)-**1** requires 14 steps from mesityl oxide and proceeds in 80% stereochemical yield and 0.7–1.0% chemical yield.

## Experimental Section

**General Methods.** Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran (THF) was distilled from sodium benzophenone immediately prior to use. Methylene chloride and diisopropylamine were distilled from calcium hydride prior to use. All reactions involving organometallic reagents were conducted under a nitrogen atmosphere. Upon workup, solvents were evaporated by using a Büchi rotary evaporator, unless otherwise indicated. Boiling points and melting points (Pyrex capillary) are uncorrected. Infrared spectra (IR) were determined with a Perkin-Elmer 297 infrared recording spectrophotometer. $^1$H NMR spectra were determined with superconducting, FT instruments operating at 200 and 250 MHz. $^{13}$C NMR spectra were measured at 62.89 Hz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Significant $^1$H NMR data are tabulated in order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, coupling constant(s) in hertz. Data for AB systems are given in the format suggested by Jackman and Sternhell.[24] High-performance liquid chromatography (HPLC) was done with a Waters Model ALC/GPC-244 liquid chromatograph. "Flash chromatography" refers to the procedure of Still, Kahn, and Mitra.[25] Elemental analyses were performed by the Microanalytical Laboratory, University of California, Berkeley.

**3-(Benzyloxy)-2-methyl-1-propanol.** To 5.2 g (50 mmol) of (*S*)-(+)-3-hydroxy-2-methylpropanoic acid[26] was added 100 mL of a 3:1 DME/HMPA mixture and a trace of triphenylmethane. The mixture was cooled to −10 °C and 66.7 mL (100 mmol) of a 1.5 M solution of *n*-butyllithium in hexane was added dropwise to give a persistent endpoint. Benzyl bromide (9 mL, 75 mmol) was added; the resulting mixture was stirred overnight and was then poured into 300 mL of $H_2O$ and 200 mL of ether. The aqueous phase was acidified with 150 mL of 1.2 M HCl and extracted twice with equal volumes of ether. The ether fractions were combined, washed with brine, and dried over $MgSO_4$. Removal of solvent gave 10.02 g of an oil which was dissolved in 50 mL of ether and added to a suspension of 2.67 g (70 mmol) of $LiAlH_4$ in ether. After 1 h, the mixture was quenched by successive additions of 2.6 mL of $H_2O$, 2.6 mL of 3.75 N NaOH, and 7.5 mL of water. The foul-smelling mixture was filtered and the solvent was removed to produce 6.43 g (71%) of alcohol, which was carried on without further purification. An analytical sample was prepared by TLC ($SiO_2$, $R_f$ 0.24, eluant 1:1 $Et_2O$/hexane): $^1$H NMR ($CDCl_3$) δ 7.5 (s, 5 H), 4.25 (s, 2 H), 3.45 (m, 4 H), 2.55 (bs, 1 H), 2.00 (sextet, 1 H, $J$ = 6), 0.85 (d, 3 H, $J$ = 7). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.15; H, 8.92.

**(*S*)-3-(Benzyloxy)-2-methylpropanal (2).** To 15.0 g (69.7 mmol) of pyridinium chlorochromate in 100 mL of $CH_2Cl_2$ was added 6.27 g (34.8 mmol) of crude alcohol in 75 mL of $CH_2Cl_2$. After 1 h, the mixture was diluted with 200 mL of ether and 200 mL of pentane and filtered through a short plug of silica gel (60–200 mesh). Preparative HPLC (eluant 1:4 ether/hexane) gave 3.09 g (35%) of aldehyde **2**: $^1$H NMR ($CDCl_3$) δ 9.63 (d, 1 H, $J$ = 2), 7.27 (s, 5 H), 4.43 (s, 2 H), 3.60 (s, 2 H, $J$ = 7), 2.57 (m, 1 H), 1.10 (d, 3 H, $J$ = 7). $[\alpha]^{25}_D$ +27.6° (*c* 4.9, $CHCl_3$). Satisfactory analytical data were not obtained for this material.

**(*S*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-2-methylpropanoic Acid.** To 1.1 g (10.6 mmol) of (*S*)-(+)-3-hydroxy-2-methylpropanoic acid[26] were added 3 mL of dry DMF, 1.44 g (21.2 mmol) of imidazole, and 2.75 mL (10.6 mmol) of chloro-*tert*-butyldiphenylsilane. The mixture was stirred overnight and poured into 50 mL of 1.2 M HCl. The aqueous phase was extracted with ether (3 × 50 mL), and the ether was washed with brine, dried over $MgSO_4$, and evaporated to obtain 3.35 g of crude product. Preparative HPLC (eluant 1:4 ether/hexane) gave 2.49 g (67%) of pure acid: IR (film) 3500–2300, 1700, 1585 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 10.65 (s, 1 H), 7.55 (m, 4 H), 7.28 (m, 6 H), 3.7 (m, 2 H), 2.68 (sextet, 1 H, $J$ = 6), 1.15 (d, 3 H, $J$ = 7), 1.05 (s, 9 H). Anal. Calcd for $C_{20}H_{26}O_3Si$: C, 70.14; H, 7.65. Found: C, 70.35; H, 7.59.

**Methyl (*S*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-2-methylpropanoate.** To a mixture of 17.6 g of KOH in 30 mL of $H_2O$ and 30 mL of ether at 0 °C was added 1.24 g (12 mmol) of *N*-nitrosomethylurea. After 10 min at 0 °C, the mixture was warmed to room temperature and the ether was decanted to a 50-mL Erlenmeyer flask containing KOH pellets as a drying agent. The ether solution of diazomethane was then added to 2.27 g (6.64 mmol) of the foregoing protected hydroxy acid in 5 mL of ether. After 2 h at room temperature, 360 μL of acetic acid was added to the solution to remove the yellow color. The ether was evaporated, the residue was dissolved in hexane, and the mixture was filtered. Evaporation of solvent gave 2.238 g (95%) of protected hydroxy ester. An analytical sample was obtained by preparative TLC ($SiO_2$, eluant 1:14 ether/hexane, $R_f$ 0.41): IR (film) 1738, 1585 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.58 (m, 4 H), 7.30 (m, 6 H), 3.65 (m, 2 H), 3.60 (s, 3 H), 2.68 (sextet, 1 H, $J$ = 6), 1.13 (d, 3 H, $J$ = 7), 1.02 (s, 9 H). Anal. Calcd for $C_{21}H_{28}O_3Si$: C, 70.74; H, 7.92. Found: C, 70.39; H, 7.85.

**(*S*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-2-methylpropanal (3).** A 100-mL three-necked flask fitted with a mechanical stirrer, nitrogen inlet, and addition funnel was charged with 2.081 g (5.85 mmol) of the foregoing ester in 50 mL of ether. This solution was cooled to below −100 °C with an ether–methanol–liquid

(22) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.
(23) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(24) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry"; Pergamon Press: New York, 1969; p 129.
(25) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(26) Goodhue, C. T.; Schaeffer, J. R. *Biotechnol. Bioeng.* **1965**, *13*, 203. We thank Dr. Noal Cohen of Hoffmann-La Roche Inc. for a generous gift of this material.

nitrogen slush, and 124.6 mL (14.6 mmol) of a 1 M solution of diisobutylaluminum hydride in hexane was added dropwise over a 6-min period. After 1 h, the mixture was poured (cold!) all at once into a rapidly stirring room-temperature mixture of 100 mL of 1.2 M aqueous HCl and 100 mL of hexane. When hydrolysis was complete (usually less than 5 min was required), the mixture was clear. The aqueous phase was extracted with hexane (2 × 50 mL), and the combined hexane fractions were dried over $MgSO_4$ and filtered. Removal of solvent gave 1.98 g of a colorless oil. Preparative HPLC ($SiO_2$, eluant 1:4 ether/hexane) gave 0.41 g (21%) of alcohol ($R_f$ 0.1), 0.163 g of a mixture of product aldehyde and hydroxy-*tert*-butyldiphenylsilane ($R_f$ 0.2), and pure aldehyde **3** (1.218 g, 64%, $R_f$ 0.42): mp 51–61 °C (hexane); IR (film) 2710, 1725, 1585 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 9.65 (d, 1 H, $J$ = 2), 7.55 (m, 4 H), 7.28 (m, 6 H), 3.78 (d, 2 H, $J$ = 6), 2.50 (sextet, 1 H, $J$ = 6), 1.05 (m, 3 H), 1.03 (s, 9 H). Anal. Calcd for $C_{20}H_{26}O_2Si$: C, 73.57; H, 8.03. Found: C, 73.73; H, 8.05.

**(*RS*)-3-Acetoxy-2-methylpropanol.** To 4.0 g (14.4 mmol) of 2-methylpropane-1,3-diol in 35 mL of THF was added dropwise at −10 °C 29.6 mL (44.4 mmol) of a 1.5 M hexane solution of *n*-butyllithium. After 10 min the mixture was transferred in small portions by metal cannula to a rapidly stirring room-temperature solution of 4.2 mL (44.4 mmol) of acetic anhydride in 30 mL of THF. The thick mixture obtained was stirred vigorously for 15 min, and 10 mL of $H_2O$ was added. Stirring was continued for an additional 10 min, and the mixture was then poured into $H_2O$ (100 mL) and extracted with ether (2 × 50 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated to obtain 5.32 g of an oil. Preparative HPLC ($SiO_2$, eluant 45:55 ether/hexane) gave diacetate ($R_f$ 0.36, 0.88 g, 11%) and monoacetate ($R_f$ 0.13, 3.07 g, 52%).

**Diacetate**: $^1H$ NMR ($CDCl_3$) $\delta$ 3.95 (d, 4 H, $J$ = 6), 2.03 (m, 1 H), 2.00 (s, 6 H), 0.95 (d, 3 H, $J$ = 7). Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.27; H, 8.42.

**Monoacetate**: $^1H$ NMR ($CDCl_3$) $\delta$ 3.98 (d, 2 H, $J$ = 6), 3.45 (d, 2 H, $J$ = 6), 2.15 (bs, 1 H), 2.00 (s, 3 H), 2.00 (m, 1 H), 0.95 (d, 3 H, $J$ = 7). Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.48; H, 9.07.

**(*SR*)-3-Acetoxy-2-methylpropanal (4).** A 100-mL three-necked flask fitted with an addition funnel, nitrogen inlet, thermometer, and mechanical stirrer was charged with 1.08 mL (12.43 mmol) of oxalyl chloride in 25 mL of dry $CH_2Cl_2$. The solution was cooled to −60 °C, and 1.76 mL of $CH_2Cl_2$ was added over a 5-min period. The temperature was kept below −50 °C during the addition. After an additional 2 min, the foregoing alcohol (1.493 g, 11.3 mmol) in 11 mL of $CH_2Cl_2$ was added over a 5-min period, whereupon a white precipitate formed. This mixture was stirred for 15 min and triethylamine (7.88 mL, 56.5 mmol) was added in portions. After 5 min the solution was allowed to warm to room temperature and partitioned between water and $CH_2Cl_2$. The aqueous phase was extracted with $CH_2Cl_2$ (2 × 25 mL). The combined organic fractions were washed with 1 M HCl and saturated $NaHCO_3$ and dried over $MgSO_4$. Filtration and solvent removal gave 946 mg of an oil. Flash distillation at room temperature (0.15 mm) gave 844 mg (57%) of aldehyde **4**: IR (film) 2730, 1735 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 9.58 (d, 1 H, $J$ = 2), 4.18 (d, 2 H, $J$ = 6), 2.65 (m, 1 H), 2.00 (s, 3, H), 1.15 (d, 3 H, $J$ = 7). Anal. Calcd for $C_6H_{16}O_3$: C, 55.36; H, 7.74. Found: C, 55.33; H, 7.73.

**(4*R*,5*S*,6*S*)-7-*O*-Benzyl-2-*O*-(trimethylsilyl)-2,4,6-trimethyl-2,5,7-trihydroxyheptan-3-one (6a).** Standard aldol condensation of 1.5 mmol each of ketone **5** (331.5 μL) and aldehyde **2** (262.5 μL) followed by a saturated $NH_4Cl$ quench and normal workup gave 533 mg of an oil. Purification by preparative TLC ($SiO_2$, eluant 1:5 ether/hexane, $R_f$ 0.13) gave 348 mg (63%) of a 1:2 mixture of isomers in which the title compound predominated: IR (film) 3500, 1705 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.28 (s, 5 H), 4.40 (m, 2 H), 3.8–3.0 (m, 4 H), 1.75 (m, 1 H), 1.35 (s, 6 H), 1.10 (m, 7 H), 0.18 (s, 9 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 2.1, 9.7, 11.7 (minor), 13.0 (minor), 13.9, 27.1, 27.3, 27.7, 35.6 (minor), 35.8 (minor), 36.2, 40.9, 41.7 (minor), 71.9 (minor), 72.3 (minor), 72.4 (minor), 73.1, 73.4, 73.5, 73.9, 74.3, 80.5, 126.1, 126.7, 127.3, 128.1, 128.7, 138.2, 219.1. Anal. Calcd for $C_{20}H_{34}O_4Si$: C, 65.53; H, 9.35. Found: C, 65.56; H, 9.15.

**(4*R*,5*S*,6*S*)-7-*O*-(*tert*-Butyldiphenylsilyl)-2-*O*-(trimethylsilyl)-2,4,6-trimethyl-2,5,7-trihydroxyheptan-3-one (6b).** Standard aldol condensation of ketone **5** (221 μL, 1 mmol) and aldehyde **3** (327 mg, 1 mmol) gave 504 mg of an oil. Purification by TLC ($SiO_2$, eluant 1:9 ether/hexane) gave 295 mg (57%) of a 3.7:1 mixture of aldols ($R_f$ 0.19, 0.27) with the title compound predominating: IR (film) 3500, 1703 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.55 (m, 4 H), 7.25 (m, 6 H), 3.8–3.2 (m, 5 H), 1.60 (m, 1 H), 1.30 (s, 6 H), 1.00 (s, 9 H), 0.98 (m, 6 H), 0.15 (s, 9 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 2.3, 9.6, 11.3 (minor), 13.3 (minor), 13.7, 19.2, 26.9, 27.5, 27.8, 38.0, 40.8, 42.0 (minor), 66.9, 68.1 (minor), 73.1, 74.1 (minor), 80.7, 127.6, 129.5, 135.6, 219.3. Anal. Calcd for $C_{29}H_{46}O_4Si_2$: C, 67.65; H, 9.01. Found: C, 67.75; H, 8.89.

**(4*RS*,5*SR*,6*SR*)-7-*O*-Acetyl-2-*O*-(trimethylsilyl)-2,4,6-trimethyl-2,5,7-trihydroxyheptan-3-one (6c).** Standard aldol condensation of ketone **5** (340 μL, 1.54 mmol) with aldehyde **4** (200 mg, 1.54 mmol) gave 505 mg of an oil. Purification by column chromatography ($SiO_2$, eluant 1:2 ether/hexane) gave 233 mg (42%) of a 3.4:1 mixture of aldols ($R_f$ 0.41) in which the title compound predominated. The product was characterized as the 5,7-*O*-diacetyl compound, obtained by treatment of the crude aldol mixture with acetic anhydride: IR (film) 3550, 1740, 1712 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.23 (dd, 1 H, $J$ = 9, 4), 4.0–3.4 (m, 3 H), 2.00 (m, 1 H), 2.00 (m, 6 H), 1.33 (s, 3 H), 1.25 (s, 3 H), 1.00 (d, 3 H, $J$ = 7), 0.98 (d, 3 H, $J$ = 7), 0.20 (s, 9 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 2.2, 10.4, 10.9 (minor), 13.5 (minor), 14.2, 20.5, 26.6, 27.1 (minor), 27.9 (minor), 28.2, 31.3 (minor), 34.6, 37.2 (minor), 39.6, 40.8 (minor), 64.9 (minor), 65.4, 65.9 (minor), 73.3, 80.0, 169.7, 170.5, 215.3. Anal. Calcd for $C_{17}H_{32}O_6Si$: C, 56.64; H, 8.95. Found: C, 56.99; H, 9.01.

**General Procedure for the Conversion of Aldols 6 and 7 to the Triacetates 8 and 9.** To 497.5 mg (2.18 mmol) of $H_5IO_6$ in 25 mL of methanol was added 0.546 mmol of aldol in 1 mL of methanol. After 5 h at room temperature the solvent was removed (aspirator) and the residue was diluted with 5 mL of THF and added dropwise to 311 mg (8.19 mmol) of $LiAlH_4$ at room temperature. After 1 h, the excess $LiAlH_4$ was quenched by successive additions of 0.3 mL of $H_2O$, 0.3 mL of 3.75 M NaOH, and 0.9 mL of water. When the precipitate had become white, it was removed by filtration, and the filter cake was washed with ether and ethyl acetate. Solvent removal by aspirator gave a yellow oil: IR (film) 3350, 1460, 1030, 980, 910, 730 $cm^{-1}$; $^{13}C$ NMR ($CDCl_3$) $\delta$ (major isomer) 8.8, 13.2, 36.5, 37.4, 67.2, 68.3, 78.7. Without further purification, this oil was dissolved in 2.6 mL of pyridine, and acetic anhydride (1.03 mL, 10.92 mmol) was added. After being stirred overnight at room temperature, the mixture was poured into 10 g of ice, and the resulting mixture was stirred for 1 h. The aqueous phase was extracted with ether (3 × 30 mL), and the ether phase was washed with saturated $CuSO_4$, water, and brine and dried over $MgSO_4$. Filtration and solvent removal gave 119 mg (80%) of triacetate. Purification by column chromatography ($SiO_2$, eluant 40% ether/hexane) gave 69 mg of a mixture of triacetates. The major component showed no plane of symmetry (analysis by $^{13}C$ NMR before and after chromatography). Aldols **6a**/**7a**, **6b**/**7b**, and **6c**/**7c** all gave identical results when subjected to this sequence. The spectral properties of the major isomer are as follows: $^1H$ NMR ($CDCl_3$) $\delta$ 4.96 (dd, 1 H, $J$ = 8.6, 3.6), 3.96 (m, 4 H), 2.10 (m, 2 H), 2.00 (s, 9 H), 0.98 (d, 3 H, $J$ = 6.9), 0.91 (d, 3 H, $J$ = 6.9); $^{13}C$ NMR ($CDCl_3$) $\delta$ 10.39, 14.15, 20.79 (triple height), 33.64, 34.21, 65.72, 66.01, 73.70, 170.31, 170.86, 170.91. Anal. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08. Found: C, 56.54; H, 8.13.

**1-[(2-Tetrahydropyranyl)oxy]-2,4-dimethyl-1,3-pentadiene (11).** Into a 5-L, three-necked, round-bottomed flask equipped with a low-temperature thermometer, argon inlet, mechanical stirrer, and 1-L pressure-equalizing dropping funnel was placed 2.70 L of dry tetrahydrofuran. The flask and its contents were cooled to 0 °C, and 187.8 g (260 mL, 1.86 mol) of diisopropylamine was added in one portion. To this solution was added 1.86 mol of *n*-butyllithium (1230 mL of a 1.5 M solution in hexane) over a 1-h period by means of a cannula inserted through a rubber septum in the top of the dropping funnel. The resulting solution was cooled to −78 °C, and 446 g (1.77 mol) of diethyl [[(2-tetrahydropyranyl)oxy]methyl]phosphonate[13] was added dropwise with vigorous stirring over a 1-h period, taking care that the temperature did not rise above −60 °C. When the addition was complete, the mixture was stirred for an additional 10 min and 173.5 g (202 mL, 1.77 mol) of mesityl oxide was added dropwise over 45 min. When this addition was complete, the dropping

funnel and the thermometer were replaced with reflux condensers and the cooling bath was replaced with a heating mantle. The mixture was refluxed for 6 h, during which time the color changed from light yellow to burgundy. The mixture was allowed to cool to room temperature and was divided into two portions. Each portion was worked up as follows: the mixture was diluted with 1.5 L of hexanes and washed with 1.5 L of 5% aqueous HCl, 1.0 L of saturated aqueous $NaHCO_3$ solution, and 1.0 L of brine. The solution was then dried over 200 g of anhydrous $K_2CO_3$, filtered, and concentrated with a rotary evaporator at 25 °C (30 min). Distillation of the residue through a 25-cm Vigreux column gave 210–228 g (61–66%) of a 1:1 mixture of *E* and *Z* dienes as a light yellow oil: bp 65–75 °C (0.3 mm); IR (film) 1760, 1725 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.40–1.70 (m, 6 H), 1.72 (s, 3 H), 1.75 (s, 3 H), 1.78 (s, 3 H), 3.30–3.90 (m, 2 H), 4.75 (m, 1 H); in addition to the foregoing, several resonances of individual isomers are discernable, isomer A, 5.43 (s, 1 H), 5.96 (s, 1 H); isomer B, 5.62 (s, 1 H), 6.10 (s, 1 H). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.63; H, 10.31.

**(*SR*)-2,4-Dimethylpent-3-enal (12).** To a 5-L, three-necked, round-bottomed flask equipped with a mechanical stirrer and an argon inlet was added 227 g (1.16 mol) of a 1:1 mixture of (*E*)- and (*Z*)-1-[(2-tetrahydropyranyl)oxy]-2,4-dimethoxy-1,3-pentadiene, 2.26 L of tetrahydrofuran, and 1.36 L of water. The mechanical stirrer was started and 73 mL of a 12.4 N aqueous solution of hydrochloric acid was added in one portion. The mixture was stirred vigorously for 12 h at room temperature, during which time the two-phase mixture became homogeneous. The mixture was diluted with 2 L of diethyl ether, resulting in a phase separation. The layers were separated and the aqueous phase was extracted with two 1-L portions of ether. The combined organic layers were then washed with 1 L of saturated aqueous $NaHCO_3$ solution and 1 L of brine and dried over 100 g of anhydrous $MgSO_4$ for 12 h. Filtration, removal of the solvents with a rotary evaporator, and distillation gave 48–60 g (37–46%) of 2,4-dimethylpent-3-enal: bp 55–65 °C (25 mm); IR (film) 1720 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.11 (d, 3 H, *J* = 7), 1.68 (s, 3 H), 1.72 (s, 3 H), 3.22 (m, 1 H), 4.98 (br d, 1 H, *J* = 10), 9.55 (d, 1 H, *J* = 1.8). Material prepared in this manner is contaminated with 7–10% of the α,β-unsaturated isomer, which has $^1H$ NMR resonances at 6.30 (d, *J* = 10) and 9.38 (s). Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 75.02; H, 10.91.

**(3*SR*,5*SR*,6*RS*,7*SR*)- and (3*RS*,5*RS*,6*SR*,7*SR*)-6-Hydroxy-2,2,5,7,9-pentamethyl-3-[(trimethylsilyl)oxy]dec-8-en-4-one (14 and 15).** To a 25-mL, three-necked, round-bottomed flask equipped with nitrogen inlet, septum, and low-temperature thermometer were added THF (5 mL) and diisopropylamine (106 mg, 0.15 mL, 1.05 mmol). The mixture was cooled to 0 °C and *n*-butyllithium (1.05 mmol, 0.67 mL of a 1.55 M solution in hexanes) was added. The resulting mixture was cooled to −78 °C and racemic ketone **13** (216 mg, 1.0 mmol) was added. After the reaction mixture was stirred for 2 h at −78 °C, TMEDA (238 mg, 0.31 mL, 2.10 mmol) was added and the mixture was stirred for 1 min. Racemic aldehyde **12** (112 mg, 1.00 mmol) was added, and the mixture was stirred for 20 min. Reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution, and the resulting mixture was allowed to warm to room temperature with stirring. The layers were separated, the aqueous phase was extracted with ether, and the combined organic phases were washed with cold 1% HCl, saturated $NaHCO_3$, and brine. Drying ($MgSO_4$), filtration, and removal of the solvent in vacuo left 334 mg of the crude aldol mixture, which was chromatographed on 20 g of silica gel with 1:4 ether/hexanes as the eluant to give 200 mg (61%) of a 15:1 mixture of **14** and **15** (61%): IR (film) 3500, 1690 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.10 (s, 9 H), 0.85 (s, 9 H), 1.00 (d, 5 H, *J* = 6), 1.60 (s, 3 H), 1.65 (s, 3 H), 2.40 (m, 1 H), 3.00–3.40 (m, 3 H), 3.55 (s, 1 H), 4.60 (br d, 1 H, *J* = 10); $^{13}C$ NMR ($CDCl_3$) δ 0.3, 10.3, 17.7, 17.9, 25.6, 26.6, 36.0, 42.3, 74.4, 86.1, 127.5. Anal. Calcd for $C_{18}H_{36}O_3Si$: C, 65.80; H, 11.04. Found: C, 65.49; H, 11.00.

**(4*SR*,5*RS*,6*SR*)- and (4*RS*,5*SR*,6*SR*)-5-Hydroxy-2,4,6,8-tetramethyl-2-[(trimethylsilyl)oxy]non-7-en-3-one (16 and 17).** To a 25-mL, three-necked, round-bottomed flask equipped with stirring bar, nitrogen inlet, septum, and low-temperature thermometer were added THF (5 mL) and diisopropylamine (1.05 mmol, 106 mg, 0.15 mL). The mixture was cooled to 0 °C and *n*-butyllithium (1.05 mmol, 0.67 mL of a 1.55 M solution in hexanes) was added. The mixture was cooled to −78 °C and ketone **5** (188 mg, 1.00 mmol) was added. The resulting mixture was stirred for 1 h and aldehyde **12** (112 mg, 1.00 mmol) was added. After being stirred for 20 min, reaction was quenched by addition of saturated aqueous $NaHCO_3$. The resulting mixture was allowed to warm to room temperature with stirring, the layers were separated, and the aqueous phase was extracted with ether. The combined organic phases were washed with cold 1% HCl, saturated aqueous $NaHCO_3$, and brine. Drying ($MgSO_4$), filtration, and removal of the solvent in vacuo left 250 mg of crude aldols. This mixture was chromatographed on 20 g of silica gel with 15% ether in hexanes as the eluant to give 127 mg (42%) of a 15:1 mixture of **16** and **17**: IR (film) 3520, 1700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.20 (s, 9 H), 1.05 (d, 3 H, *J* = 6), 1.06 (d, 3 H, *J* = 6), 1.35 (s, 3 H), 1.37 (s, 3 H), 1.66 (br s, 3 H), 1.72 (br s, 3 H), 2.50 (m, 1 H), 3.08 (d, 1 H, *J* = 1), 3.50 (m, 2 H), 4.87 (br d, 1 H, *J* = 10); $^{13}C$ NMR ($CDCl_3$) δ 2.2, 9.9, 17.6, 17.9, 25.7, 27.4, 27.6, 36.1, 40.7, 75.5, 127.5. Anal. Calcd for $C_{16}H_{32}O_3Si$: C, 63.95; H, 10.73. Found: C, 64.18; H, 10.66. This procedure has been carried out many times on a scale of 0.1–0.5 mol, with yields of 42–55%.

**(2*SR*,3*RS*,4*SR*)-3-Hydroxy-2,4,6-trimethylhept-5-enoic Acid (18). Method A. From Aldols 14 and 15.** To a solution of a 15:1 mixture of aldols **14** and **15** (200 mg, 0.61 mmol) in methanol (10 mL) was added a solution of $H_5IO_6$ (2.44 mL, 555 mg) in water (0.5 mL). This mixture was stirred at room temperature for 16 h and concentrated in vacuo. The residue was partitioned between ether (60 mL) and water (20 mL). The layers were separated, and the ether layer was washed with water (10 mL) and was extracted with 5% aqueous NaOH (3 × 15 mL). The NaOH extracts were combined and acidified to pH 2 with concentrated HCl and then extracted with ether (3 × 40 mL). The combined ether extracts were washed with water (20 mL) and brine (20 mL). Drying ($MgSO_4$), filtration, and removal of the solvent in vacuo gave 96 mg (84%) of acid **18** as white crystals: mp 91–95 °C (from ether); IR (Nujol) 3350, 1710 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.00 (d, 3 H, *J* = 6), 1.15 (d, 3 H, *J* = 7), 1.60 (s, 3 H), 2.50 (m, 2 H), 3.65 (dd, 1 H, *J* = 2, 9), 4.75 (d, 1 H, *J* = 10), 6.90 (br s, 2 H); $^{13}C$ NMR ($CDCl_3$) δ 9.3, 17.6, 17.8, 25.7, 35.8, 41.8, 75.4, 126.3, 131.9, 181.5. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.35; H, 9.52.

**Method B. From Aldols 16 and 17.** A similar oxidation of 127 mg of a 15:1 mixture of **16** and **17** gave 66 mg (84%) of acid **18** as white crystals. The spectral and physical properties of the material prepared in this manner were identical with those of the material obtained by method A.

**(2*RS*,3*RS*,4*SR*)-2,4-Dimethylpentane-1,3,5-triol Triacetate (9).** Into a solution of acid **18** (175 mg, 0.94 mmol) in methanol (30 mL), cooled to −78 °C, was bubbled ozone at the rate of 1 mmol $min^{-1}$ for 5 min. The excess ozone was removed by passing oxygen through the solution for 10 min. Dimethyl sulfide (4.23 g, 5 mL, 68.1 mmol) was added, and the mixture was allowed to warm to room temperature with stirring. The solvent was removed in vacuo and the residue was taken up in dry THF (20 mL). To this mixture was added lithium aluminum hydride (5 mmol, 190 mg) under nitrogen, and the mixture was heated under reflux for 2 h. After being cooled to room temperature, the reaction was quenched by addition of water (0.19 mL), 15% aqueous NaOH (0.19 mL), and water (0.57 mL). The mixture was dried ($MgSO_4$) and filtered. After removal of solvent in vacuo, the residue was dissolved in pyridine (5 mL). To this solution was added acetic anhydride (2.04 g, 1.88 mL, 20 mmol). The mixture was stirred for 12 h at room temperature and poured onto 5 g of ice. The resulting mixture was diluted with ether, the layers were separated, and the organic phase was washed with saturated aqueous $CuSO_4$, $NaHCO_3$, and brine. Drying ($MgSO_4$), filtration, removal of solvent in vacuo, and column chromatography on 10 g of silica gel with 2:3 ether/hexanes as eluant gave 80 mg (31%) of triacetate **9**: IR (film) 1735 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.85 (d, 6 H, *J* = 6.5), 1.95 (s, 9 H), 2.05 (m, 2 H), 3.75 (dd, 4 H, *J* = 2, 6), 4.86 (t, 1 H, *J* = 6); $^{13}C$ NMR ($CDCl_3$) δ 11.9, 20.6, 34.0, 65.8, 73.3, 170.3, 170.7. Anal. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08. Found: C, 56.67; H, 8.09.

**(3*RS*,4*SR*,5*RS*,6*SR*)- and (3*SR*,4*SR*,5*RS*,6*SR*)-2,4,6,8-Tetramethylnon-7-ene-2,3,5-triol (19).** Aldol **16** was prepared on a 148-mmol scale (vide supra) and purified by distillation

through a 13-cm Vigreux column (bp 89–99 °C at 0.020 torr) to give 20.48 g (46%) of product as a colorless oil. To a solution of lithium aluminum hydride (6.47 g, 170 mmol) in anhydrous ether (300 mL) was added the foregoing aldol (20.48 g, 68 mmol) in 50 mL of ether dropwise over a 1-h period. The reaction mixture was stirred for 3 h at room temperature, cooled to 0 °C, and quenched by dropwise addition of water (6.5 mL), 15% aqueous NaOH solution (6.5 mL), and water (19.5 mL). This mixture was stirred for 12 h and then dried ($MgSO_4$). Filtration and removal of the solvent in vacuo gave a colorless syrup. This material was taken up in methanol (350 mL), anhydrous potassium carbonate (6.8 mmol, 940 mg) was added, and the mixture was refluxed for 30 min. Upon cooling, the mixture was filtered through a pad of Celite and the methanol was removed in vacuo to give 15.65 g (100%) of triol **19**. An analytical sample was obtained by distillation (Kugelrohr, 0.15 mm, <90 °C): IR (film) 3400, 1660 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 4.70 (1 H, d, $J$ = 9), 4.30 (1 H, br s), 3.70 (1 H, m), 3.30 (2 H, m), 2.80 (1 H, br s), 2.35 (1 H, m), 1.80 (1 H, m), 1.63 (3 H, s), 1.60 (3 H, s), 1.20 (3 H, s), 1.15 (3 H, s), 0.95 (3 H, t, $J$ = 6), 0.95 (3 H, m). Anal. Calcd for $C_{13}H_{26}O_3$: C, 67.79; H, 11.38. Found: C, 67.70; H, 11.20.

**(2*SR*,3*RS*,4*SR*)-3-Hydroxy-2,4,6-trimethylhept-5-enal (20).** To a cold (0 °C) stirring solution of triol **19** (16.31 g, 71 mmol) in absolute ethanol (480 mL) was added a solution of sodium periodate (45.6 g, 213 mmol) and sodium hydroxide (1.07 g, 2.67 mmol) in 10 mL of ice-cold water. The reaction mixture was stirred for 30 min at 0 °C (during which time a white precipitate formed) and was partitioned between water (1 L) and chloroform (1 L). The layers were separated and the aqueous phase was extracted with chloroform (2 × 400 mL). The combined organic fractions were washed with water (400 mL) and dried ($MgSO_4$). Filtration and removal of the solvent in vacuo gave 11.92 g (99%) of aldehyde **20**: IR (film) 3450, 2700, 1715 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.05 (d, 3 H, $J$ = 5.4), 1.13 (d, 3 H, $J$ = 5), 1.60 (d, 3 H, $J$ = 1.3), 1.63 (d, 3 H, $J$ = 1.3), 1.90 (d, 1 H, $J$ = 5.4), 2.45 (m, 2 H), 3.75 (ddd, 1 H, $J$ = 9.6, 5.4, 3.0), 4.65 (d, 1 H, $J$ = 9), 9.55 (s, 1 H). An acceptable elemental analysis could not be obtained for this sensitive compound.

**(2*SR*,3*RS*,4*SR*)-3-[(Triethylsilyl)oxy]-2,4,6-trimethylhept-5-enal (21).** To a three-necked, 500-mL, round-bottomed flask equipped with low-temperature thermometer, stirring bar, argon inlet, and septum was added ether (117 mL) and acetonitrile (82 mL). This mixture was cooled to −20 °C and triethylsilyl triflate[27] (15.15 g, 57.4 mmol) and pyridine (5.23 g, 5.35 mL, 66.1 mmol) were added. The resulting mixture was cooled to −50 °C and a solution of aldehyde **20** (8.78 g, 51.6 mmol) in acetonitrile (10 mL) was added in one portion. This reaction mixture was stirred for 10 min at −50 °C, during which time a white precipitate formed. The cold reaction mixture was poured into 400 mL of saturated aqueous $NaHCO_3$ solution layered with 400 mL of pentane, and the resulting mixture was shaken. The layers were separated and the pentane layer was washed with water (200 mL) and dried ($MgSO_4$). Filtration, removal of the solvent in vacuo, and distillation with a Kugelrohr apparatus (bath temperature 70–100 °C; 0.01 torr) gave 11.41 g (79%) of aldehyde **21**: IR (film) 3500, 2700, 1725 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.60 (m, 6 H), 0.95 (m, 15 H), 1.57 (d, 3 H, $J$ = 2), 1.65 (d, 3 H, $J$ = 2), 2.45 (m, 2 H), 4.75 (d, 1 H, $J$ = 10), 4.83 (dd, 1 H, $J$ = 3, 8), 9.57 (s, 1 H); mass spectrum, $m/e$ 275 (0.10), 256 (0.16), 255 (0.72), 243 (0.14), 115 (5.83); HRMS, calcd for $C_{14}H_{27}O_2Si$ 255.1781, found 255.1786. A satisfactory elemental analysis could not be obtained.

**2,6-Dimethylphenyl (2*SR*,3*RS*,4*RS*,5*RS*,6*SR*)- and (2*RS*,3*SR*,4*RS*,5*RS*,6*SR*)-2-*O*-Benzyl-5-*O*-(triethylsilyl)-2,3,5-trihydroxy-2,4,6,8-tetramethylnon-7-enoate (25a and 26a).** To a 100-mL, three-necked, round-bottomed flask equipped with stirring bar, argon inlet, septum, and low-temperature thermometer were added THF (15 mL) and diisopropylamine (0.72 g, 1.00 mL, 7.15 mmol). This solution was cooled to 0 °C, and $n$-butyllithium (4.32 mL of a 1.58 M solution in hexanes, 6.83 mmol) was added in one portion. The resulting LDA solution was cooled to −78 °C and a solution of ester **22a** (1.85 g, 6.50 mmol) in THF (5.0 mL) was added dropwise. After the reaction mixture was stirred for 1-h, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (1.51 g, 2.01 mL, 13.0 mmol) was added, followed by aldehyde **21** (1.85 g, 6.5 mmol), neat, dropwise. This mixture was allowed to stir for 20 min at −78 °C, and the reaction was quenched by rapid addition of saturated aqueous $NaHCO_3$ (5.0 mL). The mixture was allowed to warm to room temperature with stirring, the layers were separated, and the aqueous phase was extracted with ether (3 × 50 mL). The combined organic fractions were washed with 1% aqueous HCl, saturated aqueous $NaHCO_3$, and brine. Drying ($MgSO_4$), filtration, and removal of the solvent in vacuo left 3.61 g of a yellow oil, which was purified by preparative HPLC with 1:19 ether/hexanes as eluant to obtain 400 mg (11%) of aldol **25a** and 800 mg (27%) of aldol **26a**.[16] In several other runs, the isolated yields of **25a** and **26a** were 21% and 40%, respectively.

Compound **25a**: TLC $R_f$ 0.30 (1:9 ether/hexanes); IR (film) 3555, 1760 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.65 (m, 6 H), 0.95 (m, 15 H), 1.65 (s, 3 H), 1.68 (s, 3 H), 1.70 (s, 3 H), 2.21 (s, 6 H), 2.49 (d, 1 H, $J$ = 10), 2.59 (m, 1 H), 3.56 (m, 1 H), 4.20 (dd, 1 H, $J$ = 2, 10), 4.71 (AB, 2 H, $J$ = 11 $\nu_{AB}$ = 60), 5.01 (d, 1 H, $J$ = 9), 7.03 (s, 3 H), 7.36 (m, 5 H). Anal. Calcd for $C_{34}H_{52}O_5Si$: C, 71.79; H, 9.21. Found: C, 71.69; H, 9.01.

Compound **26a**: TLC $R_f$ 0.35 (1:9 ether/hexanes); IR (film) 3550, 1760 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.65 (m, 6 H), 0.98 (m, 15 H), 1.61 (s, 3 H), 1.65 (s, 3 H), 1.76 (s, 3 H), 2.12 (m, 1 H), 2.23 (s, 6 H), 2.58 (m, 1 H), 2.82 (m, 1 H), 3.90 (m, 2 H), 4.75 (AB, 2 H, $J$ = 17, $\nu_{AB}$ = 57.5), 4.80 (d, 1 H, $J$ = 10), 7.08 (s, 3 H), 7.39 (m, 5 H). Anal. Calcd for $C_{34}H_{52}O_5Si$: C, 71.79; H, 9.21. Found: C, 71.91; H, 9.32.

**2,6-Diisopropylphenyl (2*SR*,3*RS*,4*RS*,5*RS*,6*SR*)- and (2*RS*,3*SR*,4*RS*,5*RS*,6*SR*)-2-*O*-Benzyl-5-*O*-(triethylsilyl)-2,3,5-trihydroxy-2,4,6,8-tetramethylnon-7-enoate (25b and 26b).** To a 25-mL, three-necked, round-bottomed flask equipped with stirring bar, nitrogen inlet, low-temperature thermometer, and septum were added THF (3.0 mL) and diisopropylamine (648 mg, 0.90 mL, 6.40 mmol). The mixture was cooled to 0 °C and $n$-butyllithium (5.80 mmol, 3.67 mL of a 1.58 M solution in hexanes) was added. The resulting LDA solution was cooled to −78 °C and a solution of ester **22b**[16] (1.80 g, 5.30 mmol) in THF (3.0 mL) was added dropwise. This mixture was stirred for 1 h at −78 °C, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (1.35 g, 1.79 mL, 11.60 mol) was added, and the mixture was stirred for 1 min. Aldehyde **21** (1.50 g, 5.30 mmol) was added, neat, dropwise. After stirring for 20 min at −78 °C, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution (1.0 mL), and the mixture was allowed to warm to room temperature with stirring. The mixture was diluted with ether and the layers were separated. The organic phase was washed with cold aqueous 1% HCl, saturated aqueous $NaHCO_3$, and brine. Drying ($MgSO_4$), filtration, and removal of the solvent in vacuo left 3.30 g of yellow oil. This material was purified by preparative HPLC with 5% ether in hexanes as eluant to obtain 1.60 g (48%) of a 1:1 mixture of aldols **25b** and **26b**: IR (film) 3550, 1760 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.65 (m, 6 H), 0.98 (m, 15 H), 1.20 (m, 12 H), 1.80 (m, 11 H), 2.08 (m, 1 H), 2.50 (m, 1 H), 3.0–3.21 (m, 1 H), 3.50–3.60 (m, 1 H), 3.85–4.20 (m, 1 H), 4.60–5.05 (m, 3 H), 7.30 (m, 8 H). Anal. Calcd for $C_{38}H_{60}O_5Si$: C, 73.03; H, 9.68. Found: C, 72.63; H. 9.58.

**2,6-Di-*tert*-butyl-4-methylphenyl (2*SR*,3*RS*,4*RS*,5*RS*,6*SR*)- and (2*RS*,3*SR*,4*RS*,5*RS*,6*SR*)-2-*O*-Benzyl-5-*O*-(triethylsilyl)-2,3,5-trihydroxy-2,4,6,8-tetramethylnon-7-enoate (25c and 26c).** To a 100-mL, round-bottomed, three-necked flask equipped with a low-temperature thermometer, stirring bar, septum, and argon inlet were added THF (35 mL) and diisopropylamine (3.08 g, 4.3 mL, 30.5 mmol). The solution was cooled to 0 °C and $n$-butyllithium (30.5 mmol, 19.0 mL of a 7.6 M solution in hexane) was added. The temperature was lowered to −78 °C and a solution of ester **22c**[16] (8.98 g, 23.5 mmol) in 15 mL of THF was added dropwise at such a rate as to keep the temperature below −50 °C. The pale yellow solution was stirred 45 min at −78 °C and *N*′,*N*′,*N*,*N*-tetramethylethylenediamine (8.18 g, 10.9 mL, 70.5 mmol) was added. Aldehyde **21** (4.46 g, 15.7 mmol) was added neat, and the mixture was stirred for 20 min at −78 °C and quenched with 15 mL of saturated aqueous $NH_4Cl$. The mixture was allowed to warm to room temperature while stirring and was diluted with 200 mL of ether. The organic phase was washed with cold 1% HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (2 × 30 mL) and dried over $MgSO_4$. Filtration and removal

(27) Triethylsilyl triflate was prepared by the procedure of Corey et al.: Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1961**, *22*, 3455.

of the solvent under reduced pressure afforded 13.20 g of a pale yellow oil which was purified by preparative HPLC (1:49 ether/hexanes) to obtain 5.44 g (8.16 mmol, 52% yield) of a mixture of aldols, 4.74 g (12.4 mmol) of ester **25c**, and 0.63 g (1.41 mmol, 9% yield) of a mixture of β-lactones **33**.

Compound **33**: IR ($CHCl_3$) 1825 $cm^{-1}$. Anal. Calcd for $C_{26}H_{42}O_4Si$: C, 69.91; H, 9.48. Found: C, 69.90; H, 9.29.

Compound **25c**. An analytical sample of the major aldol was obtained by TLC ($SiO_2$, eluant 1:19 ether/hexane, $R_f$ 0.28); IR (film) 3600, 1755 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.20 (m, 5 H), 7.03 (s, 2 H), 4.70 (m, 3 H), 4.20 (m, 1 H), 3.45 (m, 1 H), 2.65 (d, 1 H, $J$ = 10), 2.50 (m, 1 H), 2.23 (s, 3 H), 2.03 (m, 1 H), 1.73 (s, 3 H), 1.58 (s, 3 H), 1.53 (s, 3 H), 1.33 (s, 9 H), 1.30 (s, 9 H), 0.90 (m, 15 H), 0.63 (m, 6 H). Anal. Calcd for $C_{41}H_{66}O_5Si$: C, 73.82; H, 9.97. Found: C, 73.47; H, 9.97.

**2,6-Dimethylphenyl (2*SR*,3*RS*,4*SR*,5*RS*,6*SR*)-2-*O*-Benzyl-3,5-*O*-isopropylidene-2,3,5-trihydroxy-2,4,6,8-tetramethylnon-7-enoate (27a).** A solution of aldol **25a** (93 mg, 0.16 mmol) in anhydrous acetone (50 mL) containing concentrated $H_2SO_4$ (100 μL) was stirred for 15 min at room temperature. Reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution (5 mL). The acetone was removed in vacuo and the aqueous residue was extracted with ether (3 × 30 mL). The combined ether extracts were washed with brine and dried ($MgSO_4$). Filtration, removal of the solvent in vacuo, and preparative TLC on a 1-mm silica gel plate with 1:9 ether/hexanes as the eluant gave 42 mg (53%) of pure acetonide **27a**: IR (film) 1750 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.96 (d, 3 H, $J$ = 6), 1.70 (d, 3 H, $J$ = 7), 1.43 (s, 3 H), 1.49 (s, 3 H), 1.63 (s, 3 H), 1.70 (s, 3 H), 1.82 (m, 1 H), 2.21 (s, 6 H), 2.52 (m, 1 H), 3.54 (dd, 1 H, $J$ = 1.6, 9.8), 4.55 (d, 1 H, $J$ = 2.1), 4.82 (d, 1 H, $J$ = 10), 4.90 (AB, 2 H, $J$ = 16, $\nu_{AB}$ = 21.8), 7.60 (s, 3 H), 7.29 (m, 5 H). Anal. Calcd for $C_{31}H_{42}O_5$: C, 75.27; H, 8.56. Found: C, 75.32; H, 8.91.

**2,6-Dimethylphenyl (2*RS*,3*SR*,4*SR*,5*RS*,6*SR*)-2-*O*-Benzyl-3,5-*O*-isopropylidene-2,3,5-trihydroxy-2,4,6,8-tetramethylnon-7-enoate (28a).** A solution of aldol **26a** (1.62 mmol, 922 mg) in anhydrous acetone (150 mL) containing concentrated $H_2SO_4$ (100 μL) was stirred for 12 h at room temperature. Reaction was quenched by addition of saturated aqueous $NaHCO_3$ (10 mL). The acetone was removd in vacuo and the aqueous residue was extracted with ether (3 × 75 mL). The combined ether extracts were washed with brine and dried ($MgSO_4$). Filtration and removal of the solvent in vacuo gave 630 mg (79%) of nearly pure acetonide **28a**. An analytical sample was obtained by preparative TLC with 1:9 ether/hexanes as eluant: IR (film) 1755 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.93 (d, 3 H, $J$ = 6), 0.94 (d, 3 H, $J$ = 7), 1.36 (s, 3 H), 1.38 (s, 3 H), 1.64 (s, 6 H), 1.68 (s, 3 H), 2.23 (s, 6 H), 2.41 (m, 1 H), 3.53 (dd, 1 H, $J$ = 3.6, 10.5), 3.93 (d, 1 H, $J$ = 6.4), 4.73 (d, 1 H, $J$ = 10), 4.98 (s, 2 H), 7.07 (s, 3 H), 7.38 (m, 5 H). Anal. Calcd for $C_{31}H_{43}O_5$: C, 75.27; H, 8.56. Found: C, 75.54; H, 8.84.

**2,6-Di-*tert*-butyl-4-methylphenyl (2*SR*,3*RS*,4*SR*,5*RS*,6*SR*)- and (2*RS*,3*SR*,4*SR*,5*RS*,6*SR*)-2-*O*-Benzyl-3,5-*O*-isopropylidene-2,3,5-trihydroxy-2,4,6,8-tetramethylnon-7-enoate (27c and 28c).** Aldols **25c** and **26c** (5.44 g, 8.16 mmol) were dissolved in acetone (700 mL) and 0.1 mL of concentrated $H_2SO_4$ was added. The solution was stirred for 5 h at room temperature and was quenched with 100 mL of saturated aqueous $NaHCO_3$. The solvent was removed under reduced pressure and the aqueous phase was extracted with ether (4 × 150 mL). The combined organic extracts were washed with brine (2 × 100 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Purification of the crude product by preparative HPLC (1:49 ether/hexanes) afforded 3.14 g (65%) of acetonide **27c**, mp 128–130 °C.

Compound **27c**: IR (film) 1735, 1595 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.93 (d, 3 H, $J$ = 6.4), 0.98 (d, 3 H, $J$ = 6.7), 1.31 (s, 9 H), 1.36 (s, 3 H), 1.38 (s, 9 H), 1.45 (s, 3 H), 1.62 (s, 3 H), 1.67 (s, 3 H), 1.69 (s, 3 H), 2.30 (s, 3 H), 2.50 (m, 2 H), 3.49 (dd, 1 H, $J$ = 9.5, 1.4), 4.56 (d, 1 H, $J$ = 1.8), 4.77 (d, 1 H, $J$ = 10.0), 5.00 (d, 1 H, $J$ = 11.4), 7.14 (br s, 2 H), 7.25 (br t, 1 H, $J$ = 6.6), 7.29 (br d, 2 H, $J$ = 6.6), 7.38 (br d, 2 H, $J$ = 6.7). Anal. Calcd for $C_{38}H_{56}O_5$: C, 76.99; H, 9.52. Found: C, 77.11; H, 9.56.

Compound **28c**. From a similar experiment, there was also isolated 14% of the isomeric acetonide **28c**: mp 49–51 °C; IR (film) 1740, 1600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.94 (d, 3 H, $J$ = 5), 0.94 (d, 3 H, $J$ = 4), 1.32 (s, 3 H), 1.33 (s, 3 H), 1.36 (s, 9 H), 1.39 (s, 9 H), 1.61 (s, 3 H), 1.66 (s, 3 H), 1.71 (s, 3 H), 2.23 (m, 1 H), 2.31 (s, 3 H), 2.40 (m, 1 H), 3.56 (dd, 1 H, $J$ = 3.3, 10.4), 3.98 (d, 1 H, $J$ = 6.1), 4.73 (d, 1 H, $J$ = 10), 5.05 (2 H, AB, $\nu_{AB}$ = 20.8, $J$ = 12), 7.18 (m, 2 H), 7.32 (m, 5 H). Anal. Calcd for $C_{38}H_{56}O_5$: C, 76.99; H, 9.52. Found: C, 77.00; H, 9.50.

**(2*RS*,3*RS*,4*SR*,5*RS*,6*SR*)-2-*O*-Benzyl-3,5-*O*-isopropylidene-2,4,6,8-tetramethylnon-7-ene-1,2,3,5-tetrol (29).** To a solution of $LiAlH_4$ (7.28 g, 192 mmol) in THF (100 mL) was added a solution of acetonide ester **27c** (5.69 g, 9.60 mmol) in 100 mL of THF. The mixture was heated at reflux under argon for 72 h. After being cooled to room temperature the excess $LiAlH_4$ was quenched by cautious addition of water (7.3 mL), 15% aqueous NaOH (7.3 mL), and water (21.9 mL). (NOTE: External cooling of the mixture with ice/salt may be necessary during the initial addition of water.) This mixture was stirred for 12 h at room temperature and then dried ($MgSO_4$). Filtration, removal of the solvent in vacuo, and preparative HPLC with 1:6 ether/hexanes as eluant gave 2.93 g (81%) of alcohol **29**: IR (film) 3450 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.85 (d, 6 H, $J$ = 6), 1.22 (s, 3 H), 1.42 (s, 6 H), 1.55 (s, 3 H), 1.59 (d, 3 H, $J$ = 6), 3.52 (1 H, br s), 3.84 (d, 1 H, $J$ = 2), 4.44 (s, 2 H), 4.62 (d, 1 H, $J$ = 10), 7.10 (s, 5 H). Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64. Found: C, 73.46; H, 9.84.

Alcohol **29** was also prepared by the reduction of aldol **27a**. In this case, the reaction was carried out with 3.55 mmol of $LiAlH_4$ and 0.48 mmol of ester **27a** in 30 mL of THF. Workup after 1.5 h at 25 °C gave **29** in 48% yield.

**(2*SR*,3*SR*,4*SR*,5*RS*,6*SR*)-2-*O*-Benzyl-3,5-*O*-isopropylidene-2,4,6,8-tetramethylnon-7-ene-1,2,3,5-tetrol (30).** To a solution of $LiAlH_4$ (349 mg, 9.20 mmol) in THF (50 mL) was added a solution of acetonide **28a** (630 mg, 1.27 mmol) in THF (50 mL). The mixture was heated at reflux under argon for 5 h and cooled. Reaction was quenched by addition of water (0.35 mL), 15% aqueous NaOH (0.36 mL), and water (1.00 mL). The resulting mixture was stirred for 12 h, then dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo. The residue was chromatographed on 50 g of silica gel with 20% ether in hexanes as the eluant to give 200 mg (42%) of alcohol **30**: IR (film) 3460 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.85 (d, 3 H, $J$ = 6), 0.91 (d, 3 H, $J$ = 6), 1.28 (s, 3 H), 1.33 (s, 3 H), 1.38 (s, 3 H), 1.62 (s, 3 H), 1.68 (s, 3 H), 2.18 (m, 1 H), 2.41 (m, 1 H), 2.72 (t, 1 H, $J$ = 5), 3.50 (m, 2 H), 3.71 (d, 2 H, $J$ = 5), 4.63 (s, 2 H), 4.81 (d, 1 H, $J$ = 10), 7.30 (m, 5 H). Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64. Found: C, 73.43; H, 9.67.

Alcohol **30** was also prepared from ester **28c**. The reduction was carried out with 24.63 mmol of $LiAlH_4$ and 1.23 mmol of **28c** in 20 mL of THF at reflux for 72 h; alcohol **30** was obtained in 32% yield.

A similar reduction of a 1:1 mixture of acetonides **27b** and **28b** was carried out with 5.0 mmol of $LiAlH_4$ and 0.99 mmol of the mixture of esters (vide supra) in 10 mL of THF for 24 h at 25 °C; a 1:1 mixture of alcohols **29** and **30** was obtained in 81% yield. The alcohols were separated by analytical HPLC with 1:10 ethyl acetate/hexanes as eluant. The separated alcohols were shown by $^1H$ NMR to be identical with samples of **29** and **30**, prepared as described in the foregoing procedures.

**(2*RS*,3*SR*,4*SR*,5*RS*,6*SR*)-2-*O*-Benzyl-3,5-*O*-isopropylidene-2,4,6,8-tetramethyl-2,3,5-trihydroxynon-7-enal (31).** A solution of alcohol **30** (26 mg, 0.069 mmol) in dry $CH_2Cl_2$ (3.0 mL) was treated with pyridinium chlorochromate (23 mg, 0.104 mmol), and the resulting mixture was stirred under argon at room temperature for 30 min. Analysis by TLC indicated that the reaction was slow. An additional 30 mg of pyridinium chlorochromate was added in 10-mg portions at 30-min intervals. After addition of the last 10 mg, the mixture was stirred for an additional 30 min (total time, 2 h). The solution was filtered through a pad of silica gel, the brown residue was triturated with ether, and the ether solution was filtered through the silica gel. The combined filtrates were concentrated in vacuo to give 26 mg (100%) of pure aldehyde **31**: IR (film) 2710, 1730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.91 (m, 6 H), 1.31 (s, 3 H), 1.34 (m, 6 H), 3.50 (dd, 1 H, $J$ = 4, 10), 3.63 (d, 1 H, $J$ = 7), 4.71 (s, 2 H), 4.75 (d, 1 H, $J$ = 9), 7.40 (m, 5 H), 9.77 (s, 1 H). Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.82; H, 9.17.

**(3*SR*,5*SR*,6*SR*,7*SR*,8*SR*,9*SR*,10*RS*,11*SR*)-3-*O*-(Tri-**

**methylsilyl)-7-*O*-benzyl-8,10-*O*-isopropylidene-2,2,5,7,9,11,13-heptamethyl-3,6,7,8,10-pentahydroxytetradec-12-en-4-one (32).** To a 25-mL, three-necked, round-bottom flask equipped with stirring bar, argon inlet, low-temperature thermometer, and septum were added THF (5.0 mL) and diisopropylamine (111 mg, 0.15 mL, 1.10 mmol). The solution was cooled to 0 °C, and *n*-butyllithium (1.05 mmol, 0.66 mL of a 1.58 M solution in hexanes) was added. The resulting LDA solution was cooled to −78 °C and ketone **13** (216 mg, 0.25 mL, 1.00 mmol) was added neat, dropwise. After 2 h of stirring at −78 °C, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (232 mg, 0.31 mL, 2.00 mmol) was added and the mixture was stirred for 1 min longer. To this solution was added a solution of aldehyde **31** (150 mg, 0.40 mmol) in THF (2.0 mL). The reaction mixture was stirred for 20 min at −78 °C, and reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution (1.0 mL). The mixture was allowed to warm to room temperature with stirring, the layers were separated, and the aqueous phase was extracted with ether. The combined organic phases were washed with cold 1% HCl, saturated aqueous $NaHCO_3$, and brine. Drying ($MgSO_4$), filtration, and removal of the solvent in vacuo gave 310 mg of an oil. This material was chromatographed on two 100-$\mu$m silica gel preparative TLC plates with 1:10 ether/hexanes as eluant to obtain 42 mg (18%) of aldol **32**. An analytical sample and a crystal suitable for single-crystal X-ray analysis, mp 60–62 °C, were obtained by recrystallization from hexanes: IR ($CHCl_3$) 3460, 1710 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.10 (s, 9 H), 0.87 (s, 9 H), 0.90 (d, 3 H, $J$ = 7), 1.13 (d, 3 H, $J$ = 7), 1.33 (s, 3 H), 1.36 (s, 6 H), 1.62 (s, 3 H), 1.65 (s, 3 H), 2.32 (m, 1 H), 2.42 (m, 1 H), 3.17 (d, 1 H, $J$ = 2.5), 3.40 (d, 1 H, $J$ = 6), 3.46 (dd, 1 H, $J$ = 4, 10), 3.66 (d, 1 H, $J$ = 7), 3.94 (s, 1 H), 4.25 (br s, 1 H), 4.67 (AB, 2 H, $J$ = 11, $\nu_{AB}$ = 43.6), 4.74 (d, 1 H, $J$ = 9.5), 7.34 (m, 5 H). Anal. Calcd for $C_{34}H_{58}O_6Si$: C, 69.11; H, 9.89. Found: C, 69.22; H, 9.88.

**(2*RS*,3*RS*,4*SR*,5*RS*,6*SR*)-2-*O*-Benzyl-3,5-*O*-isopropylidene-2,3,5-trihydroxy-2,4,6,8-tetramethylnon-7-enyl Acetate (34).** A solution of alcohol **29** (0.200 g, 0.53 mmol) and pyridine (0.047 g, 0.048 mL, 0.60 mmol) in acetic anhydride (1.71 g, 1.58 mL, 16.7 mmol) was stirred for 14 h at room temperature under nitrogen. The reaction mixture was then diluted with ether (100 mL) and washed with 5% HCl (30 mL), water (30 mL), and brine. After drying over $MgSO_4$ and evaporation of the solvent under reduced pressure, the crude acetate was chromatographed on silica gel (1:6 ether/hexanes) to afford 0.210 g (95%) of acetate **34**: IR ($CHCl_3$) 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.94 (3 H, d, $J$ =7), 0.99 (d, 3 H, $J$ = 7), 1.28 (s, 3 H), 1.39 (s, 3 H), 1.46 (s, 3 H), 1.64 (s, 3 H), 1.69 (s, 3 H), 2.05 (m, 1 H), 2.07 (s, 3 H), 2.48 (m, 1 H), 3.43 (dd, 1 H, $J$ = 10, 2), 3.88 (d, 1 H, $J$ = 2), 4.29 (AB, 2 H, $J$ = 12, $\nu_{AB}$ = 35.6), 4.69 (AB, 2 H, $J$ = 12, $\nu_{AB}$ = 50.8), 4.78 (d, 1 H, $J$ = 12), 7.31 (m, 5 H). Anal. Calcd for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.58; H, 9.09.

**(2*RS*,3*SR*,4*SR*,5*RS*,6*RS*)-7-*O*-Acetyl-6-*O*-benzyl-3,5-*O*-isopropylidene-3,5,6,7-tetrahydroxy-2,4,6-trimethylheptanal (35).** A solution of acetate **34** (0.209 g, 0.50 mmol) in methanol (25 mL) containing the red dye no. 23 (0.05 mL of a 0.1% solution in a 2:1 mixture of $CH_2Cl_2$–ethanol) was cooled to −78 °C and ozone was bubbled through until the color of the dye faded. Dimethyl sulfide (0.34 g, 0.40 mL, 5.4 mmol) was then added and the solution was allowed to warm to room temperature. After removing the solvent under reduced pressure, the residue was chromatographed on silica gel (1:4 ethyl acetate/hexanes) to afford 0.145 g (74%) of aldehyde **35**: IR ($CHCl_3$) 2745, 1745 (sh), 1730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.11 (d, 3 H, $J$ = 7), 1.14 (d, 3 H, $J$ = 7), 1.27 (s, 3 H), 1.41 (s, 3 H), 1.45 (s, 3 H), 1.84 (1 H, m), 2.07 (3 H, s), 2.70 (7 H, m), 3.92 (d, 1 H, $J$ = 2), 3.98 (d, 1 H, $J$ = 7), 4.29 (AB, 2 H, $J$ = 12, $\nu_{AB}$ = 18.4), 4.69 (AB, 2 H, $J$ = 12, $\nu_{AB}$ = 41.3), 7.30 (m, 5 H), 9.73 (d, 1 H, $J$ = 2). Anal. Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.48; H, 8.20.

**Methyl (2*RS*,3*SR*,4*SR*,5*RS*,6*RS*)-7-*O*-Acetyl-6-*O*-benzyl-3,5-*O*-isopropylidene-3,5,6,7-tetrahydroxy-2,4,6-trimethylheptanoate (36).** To a solution of aldehyde **35** (0.180 g, 0.46 mmol) in DMF (2.0 mL) was added pyridinium dichromate (1.13 g, 3.0 mmol). The mixture was stirred for 16 h at room temperature and was diluted with water (40 mL) and extracted with ether (2 × 30 mL). The aqueous phase was acidified with concentrated HCl (pH 4) and further extracted with ether (30 mL). The combined organic extracts were washed with water (2 × 20 mL) and brine (20 mL) and dried over $MgSO_4$. After removing the solvent at reduced pressure, the crude residue (0.165 g) was dissolved in ether (10 mL) and treated with excess $CH_2N_2$ at room temperature. The solvent was removed at reduced pressure and the residue was chromatographed on silica gel (1:3 ethyl acetate/hexanes) to afford 0.151 g (78%) of methyl ester **36**: IR ($CHCl_3$) 1735 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.10 (d, 3 H, $J$ = 7), 1.22 (d, 3 H, $J$ = 7), 1.26 (s, 3 H), 1.40 (s, 3 H), 1.44 (s, 3 H), 1.72 (m, 1 H), 2.07 (s, 3 H), 2.65 (m, 1 H), 3.67 (s, 3 H), 3.85 (dd, 1 H, $J$ = 10, 2), 3.92 (d, 1 H, $J$ = 2), 4.28 (AB, 2 H, $J$ = 12, $\nu_{AB}$ = 22.3), 4.68 (AB, 2 H, $J$ = 12, $\nu_{AB}$ = 40.6), 7.30 (5 H, m). Anal. Calcd for $C_{23}H_{34}O_7$: C, 65.38; H, 8.11. Found: C, 65.53; H, 8.17.

**Methyl (2*RS*,3*SR*,4*SR*,5*RS*,6*RS*)-6-*O*-Benzyl-3,5-*O*-isopropylidene-3,5,6,7-tetrahydroxy-2,4,6-trimethylheptanoate (37).** To the diester **36** (0.020 g, 0.047 mmol) was added a methanolic solution of potassium hydroxide (0.14 g of KOH in 2.5 mL of methanol). The solution was stirred for 45 min at room temperature and poured into cold water (10 mL) and extracted with ether (4 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried over $MgSO_4$, and the solvent was removed at reduced pressure to afford 0.017 g (96%) of hydroxy ester **37**: IR ($CHCl_3$) 3550, 1735 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.07 (3 H, d, $J$ = 7), 1.22 (d, 3 H, $J$ = 7), 1.27 (s, 3 H), 1.45 (s, 3 H), 1.46 (s, 3 H), 1.65 (br s, 1 H), 1.74 (m, 1 H), 2.60 (m, 1 H), 3.67 (s, 3 H), 3.87 (dd, 1 H, $J$ = 10, 2), 4.07 (d, 1 H, $J$ = 2), 4.63 (AB, 2 H, $J$ = 12, $\nu_{AB}$ = 13.8), 7.32 (m, 5 H). Anal. Calcd for $C_{21}H_{32}O_6$: C, 66.29; H, 8.48. Found: C, 66.26; H, 8.57.

**Methyl (2*RS*,3*SR*,4*SR*,5*RS*,6*SR*)-6-*O*-Benzyl-3,5-*O*-isopropylidene-7-oxo-3,5,6-trihydroxy-2,4,6-trimethylheptanoate (1).** To a solution of oxalyl chloride (0.044 g, 0.030 mL, 0.035 mmol) in $CH_2Cl_2$ (2.0 mL) under nitrogen and at −60 °C was added $Me_2SO$ (0.055 g, 0.050 mL, 0.70 mmol). The mixture was stirred 10 min at −60 °C and the temperature was adjusted to −50 °C. A solution of hydroxy ester **37** (0.082 g, 0.21 mmol) in $CH_2Cl_2$ (1 mL) was added, and after 45 min the reaction was quenched by adding $Et_3N$ (0.145 g, 0.20 mL, 7.43 mmol). After the solution had warmed to room temperature, it was treated with water (5 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$. After removing the solvent at reduced pressure, the crude product was chromatographed on silica gel (1:3 ethyl acetate/hexanes) to afford 0.069 g (87%) of racemic aldehyde ester **1**: IR ($CHCl_3$) 2875, 1735 (br) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.03 (d, 3 H, $J$ = 7), 1.21 (d, 3 H, $J$ = 7), 1.36 (s, 3 H), 1.47 (s, 3 H), 1.42 (s, 3 H), 1.82 (m, 1 H), 2.64 (m, 1 H), 3.66 (s, 3 H), 3.89 (dd, 1 H, $J$ = 10, 2), 4.14 (1 H, d, $J$ = 2), 4.69 (AB, 2 H, $J$ = 12, $\nu_{AB}$ = 45.8), 7.34 (m, 5 H), 9.78 (s, 1 H). Anal. Calcd for $C_{21}H_{30}O_6$: C, 66.64; H, 7.99. Found: C, 66.36; H, 8.07.

**Mandelates 39a,b.** To a solution of alcohol **29** (0.474 g, 1.1 mmol) in $CH_2Cl_2$ (5 mL) was added 4-(dimethylamino)pyridine (0.024 g, 0.20 mmol) and triethylamine (0.404 g, 4.0 mmol) under argon. The mixture was cooled to 0 °C and a solution of freshly prepared acyl chloride (0.221 g, 1.2 mmol) from (*R*)-(−)-*O*-methylmandelic acid in $CH_2Cl_2$ (5 mL) was added in one portion. The mixture was stirred while the ice bath melted, and after 5 h at room temperature, it was diluted with $CH_2Cl_2$ (200 mL), washed with 5% HCl (50 mL) and saturated $NaHCO_3$ (50 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel (1:4 ether/hexanes) to afford 0.482 g (82%) of esters **39a,b**. Anal. Calcd for $C_{32}H_{44}O_6$: C, 73.25; H, 8.45. Found: C, 73.08; H, 8.25.

The two diastereomers were separated by HPLC with three Waters Associates preparative $\mu$-Porasil columns in series using 1:14 ethyl acetate/hexanes as eluant.

**Faster eluting ester**: $[\alpha]^{20}_D$ −33.6° (*c*, 0.054 in $CHCl_3$); IR ($CHCl_3$) 1750 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.90 (d, 6 H, $J$ = 7), 1.09 (s, 3 H), 1.20 (s, 3 H), 1.40 (s, 3 H), 1.59 (m, 1 H), 1.62 (s, 3 H), 1.68 (s, 3 H), 2.41 (m, 1 H), 3.26 (dd, 1 H, $J$ = 10, 2), 3.40 (s, 3 H), 3.67 (d, 1 H, $J$ = 2), 4.34 (AB, 2 H, $J$ = 12 $\nu_{AB}$ = 30.8), 4.59 (AB, 2 H, $J$ = 12, $\nu_{AB}$ = 45.4), 4.70 (d, 1 H, $J$ = 10), 4.75 (s, 1 H), 7.26 (m, 10 H).

**Slower eluting ester**: $[\alpha]^{20}_D$ −17.8° (*c*, 0.063 in $CHCl_3$); IR ($CHCl_3$) 1750 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.91 (d, 3 H, $J$ = 7), 0.92 (3 H, d, $J$ = 7), 1.17 (s 3 H), 1.33 (s, 3 H), 1.43 (s, 3 H), 1.50 (m, 1 H), 1.62 (d, 3 H, $J$ = 7), 1.68 (d, 3 H, $J$ = 1), 2.42 (m, 1 H), 3.30 (dd, 1 H, $J$ = 10, 2), 3.42 (s, 3 H), 3.76 (d, 1 H, $J$ = 2), 4.32 (AB,

2 H, $J$ = 12, $\nu_{AB}$ = 27.0), 4.51 (AB, 2 H, $J$ = 12, $\nu_{AB}$ = 44.1), 4.67 (d, 1 H, $J$ = 10), 4.80 (s, 1 H), 7.27 (m, 10 H).

**Diesters 40a,b.** These compounds were prepared by the method already described for (±)-**36**.

**From faster eluting ester:** $[\alpha]^{20}_D$ −22.4° ($c$, 0.020 in $CHCl_3$); IR ($CHCl_3$) 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.05 (d, 3 H, $J$ = 7), 1.13 (s, 3 H), 1.18 (s, 3 H), 1.20 (d, 3 H, $J$ =7), 1.32 (s, 3 H), 1.63 (m, 1 H), 2.62 (m, 1 H), 3.40 (s, 3 H), 3.67 (s, 3 H), 3.68 (br s, 1 H), 3.75 (m, 1 H), 4.34 (AB, 2 H, $J$ = 12, $\nu_{AB}$ = 38.8), 4.56 (AB, 2 H, $J$ = 12, $\nu_{AB}$ = 45.9), 4.78 (s, 1 H), 7.2–7.4 (m, 10 H).

**From slower eluting ester:** $[\alpha]^{20}_D$ −12.8° ($c$, 0.018 in $CHCl_3$); IR ($CHCl_3$) 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.04 (d, 3 H, $J$ = 7), 1.09 (3 H, s), 1.21 (d, 3 H, $J$ = 7), 1.38 (s, 3 H), 1.40 (s, 3 H), 1.62 (m, 1 H), 2.61 (m, 1 H), 3.40 (s, 3 H), 3.66 (s, 3 H), 3.69 (br s, 1 H), 3.74 (m, 1 H), 4.34 (AB, 2 H, $J$ = 12, $\nu_{AB}$ = 22.8), 4.48 (AB, 2 H, $J$ = 12, $\nu_{AB}$ = 53.9), 4.75 (1 H, s), 7.2–7.4 (m, 10 H).

**Ester Aldehyde 1.** The same procedure was used as was used to prepare (±)-1.

**From the diester 40 with $[\alpha]^{20}_D$ −22.4°:** (−)-1; $[\alpha]^{20}_D$ −27.0° ($c$, 0.022, in $CHCl_3$).

**From the diester 40 with $[\alpha]^{20}_D$ −12.8°:** (+)-1; $[\alpha]^{20}_D$ +27.0° ($c$, 0.020 in $CHCl_3$).

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**Registry No.** (±)-**1**, 95513-72-7; 1 (enantiomer 1), 95587-20-5; 1 (enantiomer 2), 95587-21-6; **2**, 79027-28-4; **3**, 92817-88-4; **4**, 95513-73-8; **5**, 72507-50-7; **6a**, 95513-74-9; **6b**, 95513-75-0; **6c**, 95513-76-1; **7a**, 95513-77-2; **7b**, 95513-78-3; **7c**, 95513-79-4; **8**, 94942-09-3; **8** triol, 94842-97-4; **9**, 86654-54-8; **9** triol, 95671-21-9; **10**, 71885-51-3; (*E*)-**11**, 95513-80-7; (*Z*)-**11**, 95513-81-8; **12**, 92817-93-1; **13**, 72507-39-2; **14**, 95513-82-9; **15**, 95587-22-7; **16**, 95513-83-0; **17**, 95587-23-8; **18**, 95513-84-1; **19** (isomer 1), 95513-85-2; **19** (isomer 2), 95587-24-9; **20**, 95513-86-3; **21**, 95587-25-0; **22a**, 92817-41-9; **22b**, 92817-42-0; **22c**, 92817-43-1; **25a**, 95513-87-4; **25b**, 95513-88-5; **25c**, 95513-89-6; **26a**, 95587-26-1; **26b**, 95587-27-2; **26c**, 95587-28-3; **27a**, 95513-90-9; **27b**, 95588-26-4; **27c**, 95587-29-4; **28a**, 95587-30-7; **28b**, 95513-91-0; **28c**, 95587-31-8; **29**, 95513-92-1; **30**, 95587-32-9; **31**, 95513-93-2; **32**, 95513-94-3; **33**, 95513-95-4; **34**, 95531-28-5; **35**, 95513-96-5; **36**, 95513-97-6; **36** free acid, 95513-98-7; **37**, 95513-99-8; **39** (isomer 1), 95514-00-4; **39** (isomer 2), 95587-33-0; **40** (isomer 1), 95514-01-5; **40** (isomer 2), 95587-34-1; (*S*)-(+)-3-hydroxy-2-methylpropanoic acid, 26543-05-5; (*R*)-1-(benzyloxy)-2-methyl-3-propanol, 63930-49-4; (*S*)-3-[(*tert*-butyldiphenylsilyl)oxy]-2-methylpropanoic acid, 95514-02-6; methyl (*S*)-3-[(*tert*-butyldiphenylsilyl)oxy]-2-methylpropanoate, 95514-03-7; (*S*)-3-[(*tert*-butyldiphenylsilyl)oxy]-2-methylpropanol, 95514-04-8; 2-methylpropane-1,3-diol, 2163-42-0; 2-methylpropane-1,3-diol diacetate, 55289-53-7; (*RS*)-3-acetoxy-2-methylpropanol, 95514-05-9; mesityl oxide, 141-79-7; 2,4-dimethylpent-2-enal, 623-36-9; (*R*)-(−)-*O*-methylmandelic acid acyl chloride, 34713-98-9; erythronolide A, 26754-37-0.

# Generation, Alkylation, and Silylation of Directed Enolates Formed by Reaction of Ketenes and Organolithium Reagents[1]

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Symmetrical ketenes $R_2C{=}C{=}O$ [$R_2$ = $t$-$Bu_2$ (**1**), $Et_2$ (**2**), $(CH_2)_4$ (**3**), $(CH_2)_5$ (**4**)] were reacted with organolithium reagents R′Li to give directed enolates $R_2C{=}C(OLi)R'$ which were alkylated with MeI or silylated with $Me_3SiCl$. The silylation results for **2–4** were compared to those for reaction of ketones $R_2CHCO$-$n$-Bu (**16–18**) with $Me_3SiCl$ and either $i$-$Pr_2NLi$, KH, or $Et_3N$. These latter conditions usually favored different regioisomers from the ketene route. Reaction of **1** with $t$-BuLi gave the previously inaccessible enolate $t$-$Bu_2C{=}C(OLi)$-$t$-Bu (**25**), which on reaction with MeI gave a mixture of the O-methylation product **27** along with some C-methylation product and with $Me_3SiCl$ gave the silyl enol ether **26**. The vinyl ethers **26** and **27** are among the first substituted tri-*tert*-butylethylenes which have been reported.

The generation of ketone enolates,[2] and their alkylation, silylation,[3] and acylation continue among the most important of synthetic organic transformations. One of the most extensively studied problems in this area concerns the selective generation of specific regioisomeric enolates. In some cases conditions of kinetic or equilibrium control have been found under which there is a significant preference for a particular enolate, and sometimes mixtures of enol acetates or silyl ethers have been prepared and separated into the individual regioisomers as precursors for specific enolates.[2,3]

The reactivity of ketenes has been the object of recent interest in this laboratory,[4] and we were attracted to the possibility that these intermediates might be useful in the generation of specific enolates, particularly species not readily available by other methods.

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