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ACYCLIC STEREOSELECTION—13

ARYL ESTERS: REAGENTS FOR *THREO*-ALDOLIZATION[1,2]

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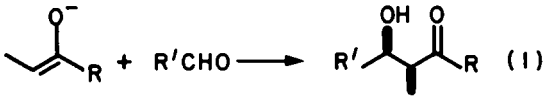
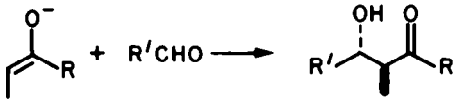
Abstract—Preformed Li enolates of hindered aryl esters condense with aldehydes to give predominantly *threo* aldols. The method has been explored with esters **3** (DMP propionate), **4** (BHT propionate), and **5** (DBHA propionate). DMP propionate reacts with benzaldehyde and α-unbranched aliphatic aldehydes to give *threo*:*erythro* ratios of about 6.5 : 1. However, with α-branched aliphatic aldehydes, ester **3** gives only *threo*-aldols. BHT propionate and DBHA propionate give only *threo*-aldols with all aldehydes studied. The DMP aldols may be converted into β-hydroxy acids by simple hydrolysis with KOH in aqueous methanol. BHT aldols cannot be hydrolyzed without retroaldolization. However, these aldols can be reduced to diastereomerically pure 1,3-diols. The DBHA aldols can be converted into β-hydroxy acids by a method involving oxidation with ceric ammonium nitrate (CAN) in aqueous acetonitrile. *Threo*-selectivity is also seen in the condensations of DMP butyrate (**15**), DBHA butyrate (**16**), DMP pentenoate (**17**), and BHT pentenoate (**18**). The approach has been utilized in a stereoselective synthesis of racemic methyl corynomycolate (**30**).

It has been established that there is a mechanistic relationship between the stereostructure of an enolate and the stereostructure of the kinetic aldol it produces upon reaction with an aldehyde, such that *cis*-enolates lead predominantly to *erythro*-aldols and *trans*-enolates give mainly *threo*-aldols (eqns 1 and 2).[3-5] When the R group

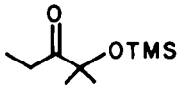


(1)



(2)

is large, the stereoselectivity of these reactions can be quite high.[5] In previous papers in this series, we have introduced reagents (**1** and **2**) which yield *cis*-enolates and therefore *erythro*-aldols.[1,5]



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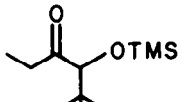
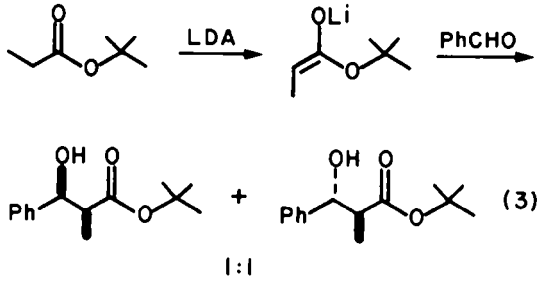


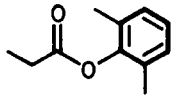
2

In a search for suitable *threo*-selective reagents, we noticed that esters give nearly pure *trans*-enolates upon deprotonation by lithium diisopropylamide (LDA) in ethereal solvents.[5] However, aldol stereoselectivity is not generally observed, even with t-butyl propionate (eqn 3). We reasoned that esters of more bulky alcohols might show the desired stereoselectivity in aldolization and therefore open a simple path to *threo*-aldols. To test this hypothesis we prepared propionate esters **3** (DMP propionate), **4** (BHT propionate) and **5** (DBHA propionate). Esters **3–5** are conveniently prepared by addition of



(3)

propionyl chloride to a cold THF solution of the Li salt of 2,6-dimethylphenol (DMP), 2,6-di-t-butyl-4-methylphenol ("butylated hydroxytoluene", BHT), or 2,6-di-t-butyl-4-methoxyphenol ("dibutylated hydroxyanisole", DBHA).



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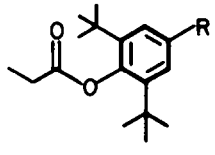
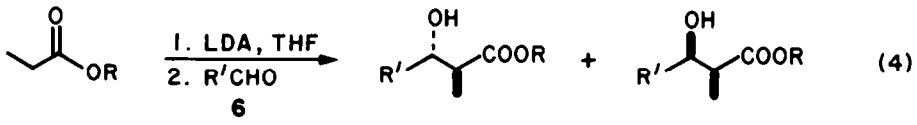


4: R = Me
5: R = OMe

As aldehydes for this study, we used benzaldehyde (**6a**), propionaldehyde (**6b**), hexanal (**6c**), isobutyraldehyde (**6d**), pivaldehyde (**6e**), and α-phenylpropionaldehyde (**6f**). Aldol condensations were carried out in the normal manner.[5] Enolates were formed by treating ester **3**, **4** or **5** with a THF solution of LDA at −78° for 45 min. After addition of the appropriate aldehyde, reaction was allowed to proceed for 5 min at −78° before workup (eqn 4). In most cases, the crude yield is nearly quantitative, The only significant contaminants are recovered aldehyde and ester. In many cases, particularly with the BHT and DBHA esters, the aldols show a pronounced tendency toward retroaldolization, and some retroaldolization often occurs upon chromatography.

Nevertheless, for cases in which the aldol is not crystalline, purification is conveniently accomplished by this technique if the contact time of the aldol with the silica gel is minimized (high pressure LC, flash chromatography).

equilibration or retroaldolization, by treatment with potassium hydroxide in aqueous methanol at 25° (eqn 5). *Threo*-β-hydroxy acids **11** are obtained in 85–99% yield. Stereostructures of aldols **7** and β-hydroxy acids **11** were



(4)

3: R = DMP
4: R = BHT
5: R = DBHA

7: R = DMP
9: R = BHT
10: R = DBHA

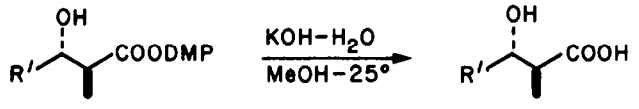
8: R = DMP

(a) $R' = C_6H_5$ (b) $R' = C_2H_5$ (c) $R' = n\text{-}C_5H_{11}$ (d) $R' = i\text{-}C_3H_7$ (e) $R' = t\text{-}C_4H_9$
(f) $R' = C_6H_5(CH_3)CH$

The results of this preliminary investigation are summarized in Table 1. With DMP propionate, benzaldehyde and hexanal give rise to *threo*:*erythro* ratios of about 6.5 : 1. However, with aldehydes which are branched at the α-carbon, this reagent gives solely the *threo*-aldols, within our analytical limits (stereoselectivity ≥ 98 : 2). Hydroxy esters **7** are conveniently hydrolyzed, without

assigned on the basis of their ^{13}C-NMR spectra.[6] In addition, hydroxy acids **11a**, **11d**, and **11f** are different from the known *erythro*-diastereomers.[5]

With BHT propionate (**4**) only *threo*-aldols are formed, even with benzaldehyde. Unfortunately, it is not possible to hydrolyze β-hydroxy esters **9**. Compound **9a** is inert to 1 M lithium hydroxide in refluxing methanol. With



(5)

7 **11**

(a) $R' = C_6H_5$ (c) $R' = n\text{-}C_5H_{11}$ (d) $R' = i\text{-}C_3H_7$ (e) $R' = t\text{-}C_4H_9$
(f) $R' = C_6H_5(CH_3)CH$

Table 1. Condensation of esters **3**–**5** with various aldehydes (eqn 4).

Ester	Aldehyde	Aldol R	Aldol R'	Aldol Yield,[a] %	*Threo*: *Erythro*	mp, °C
3	6a	C_6H_5	DMP	72	88/12	62–63[c]
	6c	$n\text{-}C_5H_{11}$	DMP	70	86/14	oil[c]
	6d	$i\text{-}C_3H_7$	DMP	78	>98/2	77
	6e	$t\text{-}C_4H_9$	DMP	82	>98/2	70–71
	6f	$C_6H_5(CH_3)CH$	DMP	81	>98/2	oil[d]
4	6a	C_6H_5	BHT	96	>98/2	oil
	6d	$i\text{-}C_3H_7$	BHT	100[b]	>98/2	105–106
	6f	$C_6H_5(CH_3)CH$	BHT	100[b]	>98/2	oil[d]
5	6b	C_2H_5	DBHA	75	>98/2	59–61
	6c	$n\text{-}C_5H_{11}$	DBHA	70	>98/2	oil
	6d	$i\text{-}C_3H_7$	DBHA	79	>98/2	91–93
	6e	$t\text{-}C_4H_9$	DBHA	77	>98/2	88–89

a. Unless otherwise indicated, high pressure LC purified yield.

b. Crude yield of product; these products were not purified by chromatography.

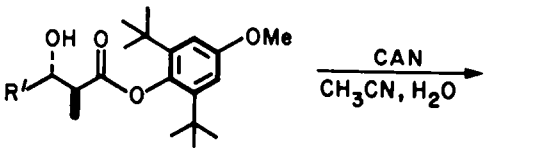
c. Major diastereomer.

d. Mixture of Cram's rule and anti-Cram's rule diastereomers: ratio = 4:1.

potassium hydroxide in hot methanol, **9a** undergoes retroaldolization giving ester **4** and benzaldehyde. However, lithium aluminum hydride reduction of **9a** provides the known diol **12**[7] in 77% yield.

9a **12**

The DBHA ester **5** was introduced as a surrogate for ester **4**. Not surprisingly, it gives the same high *threo*-selectivity as does **4**, even with the unbranched aldehydes propionaldehyde and hexanal. However, in this case the aryl group can be removed under oxidative, rather than hydrolytic conditions. Thus, treatment of aldols **10** with ceric ammonium nitrate (CAN) in aqueous acetonitrile[8] effects oxidation, yielding quinone **13** and hydroxy acids **11**. However, the yields of β-hydroxy acid



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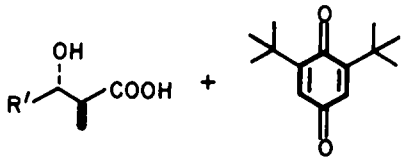
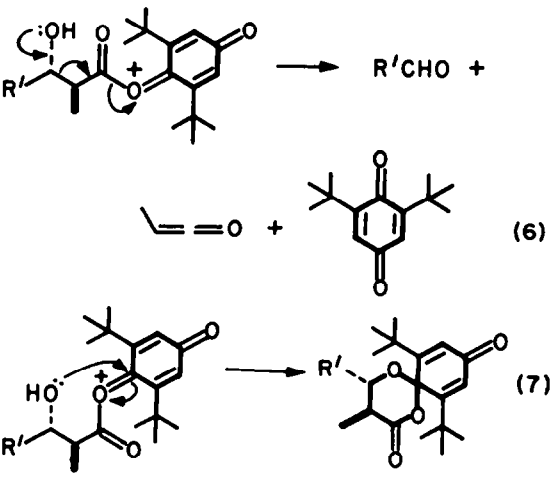


11 **13**

(b) $R' = C_2H_5$ (c) $R' = n\text{-}C_5H_{11}$
(d) $R' = i\text{-}C_3H_7$ (e) $R' = t\text{-}C_4H_9$

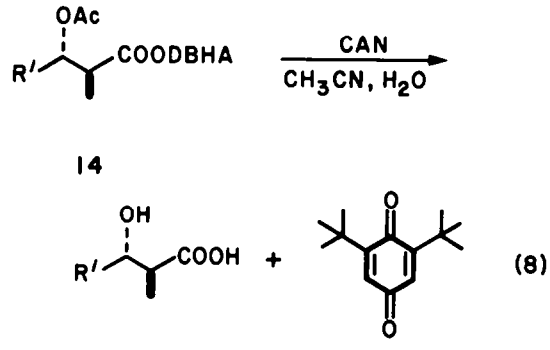
which are obtained in this oxidative process are highly variable (18–67%). The problem clearly lies with the β-hydroxy group, since ester **5** itself gives 2,6-di-t-butylbenzoquinone in virtually quantitative yield under the same conditions. Althouth no tractable side-products could be isolated, two reasonable side-reactions, both involving the β-OH group, may be responsible for the low yields of β-hydroxy acids (eqns 6 and 7). Although



(6)

(7)

eqns (6) and (7) are pure speculation, we were encouraged to carry out the CAN oxidation on the acetates of the β-hydroxy DBHA esters. These acetates may be conveniently prepared by adding acetic anhydride to the lithium aldolate resulting from the initial aldol condensation; the resulting β-acetoxy esters are obtained in 60–73% yield.[9] Oxidation of β-acetoxy esters **14** provides the corresponding β-hydroxy acids **11** in 46–81% yield (eqn 8).

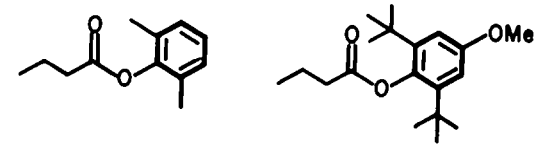


14

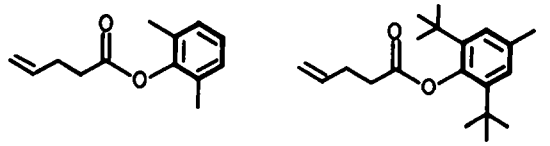
11 **13** (8)

(b) $R = C_2H_5$ (d) $R = i\text{-}C_3H_7$ (e) $R = t\text{-}C_4H_9$

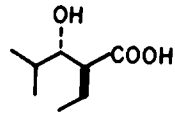
In order to further explore the scope and utility of these *threo*-selective reagents, we have also prepared esters **15–18**. Butyrate esters **15** and **16** were used to convert isobutyraldehyde into β-hydroxy acid **19** (69% overall from **15**, 51% overall from **16**). Reagents **17** and **18** were each allowed to condense with benzaldehyde (**6a**), propionaldehyde (**6b**), and isobutyraldehyde (**6d**,



15 **16**



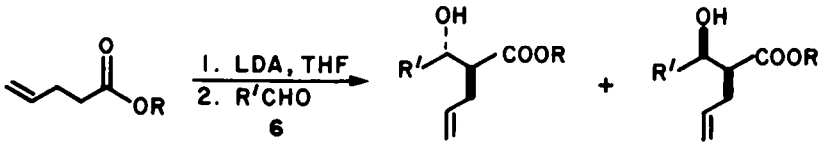
17 **18**



19

eqn 9). Data are summarized in Table 2. The observed stereoselectivity is generally good, but lower than expected with the BHT ester **18** in its reactions with propionaldehyde and isobutyraldehyde.

As a final application of the aryl ester method, we have synthesized esters **24** (DMP palmitate), and **25** (DIPP palmitate) from palmitoyl chloride and 2,6-dimethylphenol (DMP) and 2,6-diisopropylphenol (DIPP), res-



(9)

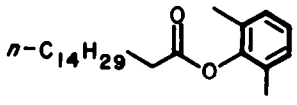
18: R = DMP
19: R = BHT

20: R = DMP
22: R = BHT

21: R = DMP
23: R = BHT

(a) $R' = C_6H_5$ (b) $R' = C_2H_5$ (d) $R' = i\text{-}C_3H_7$

pectively. The enolates of esters **24** and **25** were condensed with palmitaldehyde to give β-hydroxy esters



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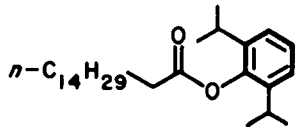
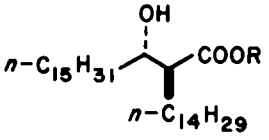
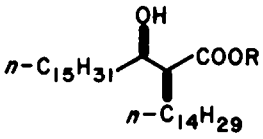


25

26+**27** and **28**+**29**, respectively. Although the *threo*-aldol is favored in each case, the *threo*:*erythro* ratio is



26: R = DMP
28: R = DIPP
30: R = Me
32: R = H



27: R = DMP
29: R = DIPP
31: R = Me

only 60:40 with reagent **24** and 67:33 with ester **25**. Methanolysis of either mixture provides methyl esters **30** (m.p. 56.5–58°) and **31** (m.p. 70–71°). Compound **30** is the methyl ester of the naturally-occurring corynomycolic acid (**32**).[10]

In summary, aryl esters having substituents at C-2 and C-6 of the benzene ring are good reagents for *threo*-aldolization. If the substrate aldehyde is aliphatic and branched at the α-carbon the DMP esters are the reagents of choice, since they show good *threo*-selectivity and the resulting aldols are easily hydroxyzed to the corresponding β-hydroxy acids. With aromatic aldehydes and unbranched aliphatic aldehydes, the DMP esters show only modest diastereoselectivity. In these cases either the BHT or DBHA esters may be used. The BHT aldols may be reduced to provide 1,3-diols. The DBHA esters may be converted to β-hydroxy acids by a mild oxidative process.

The aryl esters introduced here appear to offer advantages over the other methods which have been suggested for *threo*-aldolization. Masamune[11] and Evans[12] have used the dialkylboron enolate of S-t-butyl propanethioate, which shows very good *threo*-selectivity. However, it is clear that it is more convenient to prepare and handle Li enolates. Meyers found that the preformed Li enolates of certain alkoxy-alkyl propionates give *threo*;*erythro* ratios as high as 10:1 with isobutyraldehyde.[13] However, with other aldehydes, stereoselectivity is not as high.[5,13] *Threo*-stereoselection has also been realized under conditions of thermodynamic control. In many cases the zinc and magnesium enolates of ketones appear to give mainly *threo*-aldols, but *threo*;*erythro* ratios are modest at best and the method has not been extended to the enolates of esters.[5,14] *Threo*-stereoselection is also observed in equilibration of the Li aldoloxides arising from the condensation of carboxylic acid dianions with some aldehydes and in the condensation of potassium carboxylic acid dianions with certain aldehydes.[15] Finally, *threo*-β-hydroxy carbonyl compounds may be obtained by an indirect method utilizing an (*E*)-2-butenylchromium reagent[16] or an (*E*)-2-butenylborane.[17]

Table 2. Condensation of esters **17** and **18** with various aldehydes (eqn 9).

Ester	Aldehyde	Aldol R	Aldol R'	Aldol yield,[a] %	*Threo*: *Erythro*	mp, °C[b]
17	6a	C_6H_5	DMP	87	91:9	74–75
	6b	C_2H_5	DMP	67	84:16	33–35
	6d	$i\text{-}C_3H_7$	DMP	77	≥98:2	44
18	6a	C_6H_5	BHT	76	≥94:6	100–101
	6b	C_2H_5	BHT	60	≥98:2	oil
	6c	$i\text{-}C_3H_7$	BHT	81	≥96:4	oil

a. Yield of high-pressure LC or flash chromatography purified product.

b. Melting point of major diastereomer, isolated by crystallization from pentane.

EXPERIMENTAL

General. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. THF was distilled from LAH or Na/benzophenone immediately prior to use. All enolate reactions were conducted under N_2. B.ps and m.ps (pyrex capillary) are uncorrected. IR spectra were determined with a Perkin–Elmer Model 297 infrared recording spectrophotometer. ^{1}H-NMR spectra were determined on the following spectrometers: varian EM 390, UCB 180, UCB 200, or UCB 250 (super-conducting 180 MHz, 200 MHz and 250 MHz FT instruments). ^{13}C-NMR spectra were measured at 25.14 MHz with a Nicolet TT-23 spectrometer, at 45.28 MHz on the UCB 180, or at 62.89 MHz on the UCB 250 ($CDCl_3$ unless otherwise stated). Chemical shifts are expressed in ppm downfield from internal TMS. Significant ^{1}H-NMR data are tabulated in order: number of protons, multiplicity (s, singlet; d, double; t, triplet; q, quartet; m, multiple), coupling constant(s) in Hertz. Mass spectra were obtained with Atlas MS-12 and Consolidated 12-110B mass spectrometers. Mass spectral data are tabulated as *m/e* (intensity expressed as per cent of total ion current). Gas–liquid partition chromatography (glpc) was done with Varian Aerograph A-90P, 920 and 940 gas chromatographs. High pressure liquid chromatography (hplc) was done with a Waters Model ALC/GPC-244 liquid chromatograph (analytical) or a Waters PrepLC/system 500 (preparative). μPorasil columns were used unless otherwise indicated. Elemental analyses were performed by the Microanalytical Laboratory, operated by the College of Chemistry, University of California, Berkeley, California.

Illustrative procedure for the preparation of aryl esters

2′,6′-Bis(1″,1″-*Dimethylethyl*)-4′-*methylphenyl propanoate*, (*BHT propionate*, **4**). In a 50 mL, 3-neck round-bottom flask under N_2 was placed 2,6-di-t-butyl-4-methylphenol (2.60 g, 11.8 mmol). The phenol was dissolved in dry THF (12 mL) and the soln was cooled to 0°. A soln of n-BuLi (7.90 mL of a 1.5 M soln in hexane, 11.85 mmol) was added at this temp. (exotherm), and after the soln had returned to 0°, propionyl chloride (1.54 mL, 17.7 mmol) was added. The soln was stirred overnight, poured into NH_4Cl aq, and extracted with ether. The combined organic phases were washed with $NaHCO_3$ aq and NaCl aq, dried ($MgSO_4$), filtered, and evaporated. Distillation (Kugelrohr, 120°, 0.5 torr) gave 3.12 g (96%) of **4**. Glpc analysis (10′ × 1/4″ 8% Se-30, 130°) showed a single peak with retention time = 13 min. IR (film): 3070, 2950, 2870, 1760, 1600, 1480, 1460, 1420, 1395, 1360, 1345, 1270, 1220, 1200, 1185, 1145, 1110, 1075, 980, 890, 860, 800 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.00 (18H, s), 1.30 (3H, t, J = 7), 2.28 (3H, s), 2.63 (2H, q, J = 7), 7.03 (2H, s). (Found: C, 78.34; H, 10.15. Calc. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21%).

2′,6′,-Bis(1″,1″-*Dimethylethyl*)-4′-*methoxyphenyl propanoate* (*DBHA propionate*, **5**). After reaction and workup as described above, distillation (Kugelrohr, 150°, 0.6 torr) provided a viscous, colorless liquid in 93% yield. After prolonged standing, this material crystallized, m.p. 45° (hexane). IR (film): 2950, 1760, 1590, 1480, 1450, 1420, 1360, 1300, 1180, 1145, 1105, 1060 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.00 (18H, s), 1.30 (3H, t, J = 7), 2.60 (2H, q, J = 7), 3.77 (3H, s), 6.80 (2H, s). (Found: C, 73.57; H, 9.38. Calc. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65%).

2′,6′-*Dimethylphenyl propanoate* (*DMP propionate*, **3**). Reaction and workup as described above gave a crude product which was distilled (Kugelrohr, 100°, 0.7 torr) to give a liquid in 94% yield. IR (film): 2950, 1755, 1475, 1460, 1350, 1265, 1145, 980, 885, 770 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.27 (3H, t, J = 7), 2.43 (6H, s), 2.55 (2H, q, J = 7), 6.90 (3H, s). (Found: C, 73.88; H, 8.16. Calc. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92%).

2′,6′-Bis(1″,1″-*Dimethylethyl*)-4′-*methoxyphenyl butanoate* (*DBHA butryate*, **16**). The standard procedure was followed to give the ester in 92% distilled yield (Kugelrohr, 160°, 0.6 torr). IR (film): 1760, 1595, 1415, 1360, 1300, 1145, 1060 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.00 (3H, t, J = 7), 1.33 (18H, s), 2.10 (2H, q, J = 7), 3.70 (3H, s), 6.80 (2H, s). (Found: C, 74.16; H, 9.77. Calc. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87%).

2′,6′-*Dimethylphenyl butanoate* (*DMP butryate*, **15**). The ester was obtained in 96% yield after distillation (Kugelrohr, 100°, 0.6 torr) after following the standard procedure. IR (film): 1760, 1480, 1250, 760 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.07 (3H, t, J = 7), 1.80 (2H, m), 2.13 (6H, s), 2.57 (2H, t, J = 6), 7.00 (3H, s). (Found: C, 75.05; H, 8.43. Calc. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39%).

2′,6′-*Dimethylphenyl 4-pentenoate* (*DMP pentenoate*, **17**). After reaction and workup as described above, distillation (Kugelrohr, 90°, 0.05 torr) gave 2.06 g (93%) of **17**. IR (film): 1755, 1645, 1475, 1420, 1170, 1140, 995, 920 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.13 (6H, s), 2.60 (4H, t, J = 7), 5.02 (1H, d, J = 10), 5.06 (1H, d, J = 16), 5.8 (1H, m), 6.98 (3H, s). (Found: C, 76.54; H, 7.98. Calc. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90%).

2′,6′-Bis(1″,1″-*Dimethylethyl*)-4′-*methylphenyl 4-pentenoate* (*BHT pentenoate*, **18**). The ester was obtained as above in 85% yield after preparative hplc (2% ether/hexane). This material crystallized. Recrystallization from pentane gave material with m.p. 54–55°. IR ($CHCl_3$): 2950, 1750, 1640, 1600, 1420, 1365, 1270, 1180, 1140, 1100, 1025, 915, 860, 705 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.33 (18H, s), 2.30 (3H, s), 2.50 (2H, m), 2.70 (2H, m), 5.10 (2H, m), 5.90 (1H, m), 7.12 (2H, s); ^{13}C-NMR: δ 21.3, 28.2, 30.3, 31.5, 35.0, 115.7, 126.9, 134.3, 136.5, 142.0, 145.9, 172.7, 182.9. (Found: C, 79.45; H, 10.20. Calc. for $C_{20}H_{30}O_2$: C, 79.42; H. 10.00%).

2′,6′-*Dimethylphenyl hexadecanoate* (*DMP palmitate*, **24**). A soln of 2,6-dimethylphenol (3.67 g, 30.0 mmol) in 30 mL THF at −78° was treated with a 1.50 M soln of n-BuLi in hexane (20.0 mL, 30.0 mmol). To resulting soln of phenoxide ion was added a soln of hexadecanoyl chloride [prepared by heating a soln of hexadecanoic acid (7.68 g; 30.0 mmol) in 20 mL $SOCl_2$ at reflux for 30 min, followed by removal of excess $SOCl_2$ by distillation] in 20 mL THF. The mixture was stirred at room temp. for 16 hr, after which it was taken up in ether, washed with 10% NaOH aq and brine, and dried ($MgSO_4$). Evaporation of the solvent left 11.3 g of crude yellow solid, which was purified by recrystallization from EtOH followed by chromatography on silica gel eluting with 5% ether/hexane to yield 4.40 g (41%) of the desired ester as a white solid, m.p. 50–51°. IR (CCl_4): 1750 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.97 (3H, s), 2.52 (2H, t, J = 8), 2.13 (6H, s), 1.67–1.07 (26H, br s), 0.87 (3H, m). (Found: C, 79.99; H, 10.96. Calc. for $C_{24}H_{40}O_2$: C, 79.94; H, 11.18%).

2′,6′-Bis(1″-*Methylethyl*)*phenyl hexadecanoate* (*DIPP palmitate*, **25**). A soln of 2,6-*bis*(1′-methylethyl)phenol (5.35 g, 30.0 mmol) in 30 mL THF at −78° was treated with a 1.50 M soln of n-BuLi (20.0 mL, 30.0 mmol) in hexane. To the resulting soln of phenoxide ion was added a soln of hexadecanoyl chloride [prepared by heating a soln of hexadecanoic acid (7.68 g; 30.0 mmol) in 20 mL $SOCl_2$ at reflux for 30 min, followed by removal of excess $SOCl_2$ by distillation] in 20 mL THF. The mixture was stirred at room temp. for 18 hr, after which it was taken up in ether, washed with 10% NaOH aq and brine, and dried ($MgSO_4$). Evaporation of the solvent left 12.45 g of the crude ester as a yellow oil. Purification of 6.00 g of the crude product by hplc, eluting with 3% ether/hexane gave 5.15 g (86%) of the desired ester as a clear colorless oil. IR (film): 1750 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.03 (3H, s), 3.10–2.47 (4H, m), 1.53–1.00 (26H, br s), 1.20 (12H, d, J = 8), 0.93 (3H, m). (Found: C, 80.89; H, 11.56. Calc. for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61%).

Illustrative procedure for aldol condensations of aryl esters

Procedure for the condensation of **4** *with aldehydes.* In a 50 mL, 3-neck, round-bottom flask under N_2 was placed 7 mL THF. After LDA was prepared in this solvent, the soln was cooled to −70°. Compound **4** (0.30 mL, 1.10 mmol) was dissolved in 2 mL of THF and added slowly. The flask containing the ester was rinsed with an additional 2 mL THF. After 45 min at −70°, an aldehyde (1.10 mmol) was added, the soln was stirred for 5 min, and the reaction was quenched with sat NH_4Cl aq. Workup consisted of warming, separation of phases, ether extraction, washing with 1% HCl and NaCl, drying and evaporation.

2′,6′-Bis(1″,1″-*Dimethylethyl*)-4′-*methylphenyl* (2SR, 3RS)-2-*methyl*-3-*hydroxybenzenepropanoate* (**9a**). The crude aldol was obtained in 98% yield. Column chromatography (10% ether/hexane) gave the pure material (R_f = 0.27) as a highly viscous oil in 96% yield. IR (film): 3500, 3050, 2950, 2870, 1740, 1600, 1480, 1450, 1420, 1395, 1360, 1270, 1200, 1180, 1105, 1080, 1050, 910,

860, 760, 740, 700 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.90 (3H, d, J = 7), 1.06 (18H, s), 2.32 (3H, s), 3.06 (1H, m), 4.06 (1H, br d), 4.86 (1H, dd, J = 3, 9), 7.10 (2H, s), 7.33 (5H, s); ^{13}C-NMR: δ 13.7, 21.3, 31.5, 47.7, 76.0, 125.4, 126.9, 127.2, 128.0, 128.3, 128.9; mass spectrum *m/e*, 57 (7.71), 107 (5.92), 191 (1.73), 205 (7.25), 220 (7.30), 367 (M-15, 0.06). HRMS on M-15 ion: (Found: 367.22580. Calc. for $C_{24}H_{31}O_3$: 367.22595).

2′,6′-Bis(1″,1″-*Dimethylethyl*)-4′-*methylphenyl* (2SR, 3SR)-2,4-*dimethyl*-3-*hydroxypentanoate* (**9d**). An oil was obtained in 100% crude yield after following the standard procedure. This material crystallized. Recrystallization from hexane gave material with m.p. 105–106°. IR (film): 3500, 2950, 2870, 1730, 1600, 1480, 1460, 1420, 1360, 1320, 1290, 1270, 1200, 1180, 1120, 1100, 1030, 1000, 860 cm^{-1}; ^{1}H-NMR ($CDCl_3$ and trace HCO_2H): δ 0.90 (3H, d, J = 7), 1.10 (3H, d, J = 7), 1.32 (18H, s), 2.63 (3H, s), 7.10 (2H, s); ^{13}C-NMR: δ 13.4, 14.7, 20.2, 21.3, 29.6, 31.5, 44.0, 76.9, 127.0, 127.2. (Found: C, 76.09; H, 10.28. Calc. for $C_{22}H_{36}O_3$: C, 75.82; H, 10.41%).

2′,6′-Bis(1″,1″-*Dimethylethyl*)-4′-*methylphenyl* (2SR, 3SR, 4RS *and* SR)-2,4-*dimethyl*-3-*hydroxybenzenebutanoate* (**9f**). The aldol was obtained in quantitative crude yield by following the standard procedure. Preparative hplc (10% ether/hexane) gave the adduct in 50% yield as an 82 : 18 mixture of Cram and *anti*-Cram products. IR (film): 3550, 3055, 2960, 2870, 1725, 1680, 1600, 1495, 1490, 1480, 1420, 1360, 1270, 1200, 1180, 1130, 1105, 1050, 1040, 1015, 980, 910, 890, 860, 760, 740, 700 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.00 (18H, s), 2.28 (3H, s), 7.06 (2H, s), 7.20 (5H, s); ^{13}C-NMR: δ 14.8, (15.2), 15.7, 21.3, 31.5, 35.2, (42.4), 42.7, 43.6, (44.1), (76.0), 78.0, 126.4, 127.0, 127.1, 127.9, 128.4, 128.8, 129.0, 134.6, 141.9, 142.2, 145.0, 175.6. Satisfactory analytical data could not be obtained for this compound. HRMS on M-15 ion: (Found: 395.2596. Calc. for $C_{26}H_{35}O_3$: 395.2595).

(2RS, 3RS)-2-*Methyl*-3-*phenyl*-1,3-*propanediol* (**12**). To a soln of LAH (81 mg, 2.13 mmol) in 15 mL THF was added **9a** (237 mg, 0.62 mmol) in 3 mL THF. The soln was heated at reflux for 5 hr, cooled, and quenched by the N,N,3N method. Drying, filtering, and evaporation gave the crude mixture of diol and phenol which was purified by preparative tlc to give **12** (77 mg, 77%) as indicated by ^{1}H-NMR spectroscopy.[7]

2′,6′-*Dimethylphenyl* (2SR, 3RS)-2-*methyl*-3-*hydroxybenzenepropanoate* (**7a**). Aldol condensation under standard conditions provided in 72% yield an 88 : 12 mixture of *threo*- and *erythro*-diastereomers **7a** and **8a** after preparative hplc (25% ether/hexane, R_f = 0.22). After prolonged standing, the *threo*-isomer crystallized, and was recrystallized from hexane, m.p. 62–63°. IR (film): 3500, 1750, 1450, 1375, 1270, 1240, 760 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.20 (3H, d, J = 7), 2.10 (6H, s), 3.06 (1H, m), 4.83 (1H, d, J = 8), 7.00 (3H, s), 7.33 (5H, s); ^{13}C-NMR: δ 130.2, 128.5, 128.1, 126.7, 125.8, 76.2, (74.1), 47.3, (46.8), 16.1, 14.9, (10.1). (Found: C, 76.17; H, 7.19. (*threo*) Calc. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09%).

2′,6′-Dimethylphenyl (2SR, 3SR)-2-*methyl*-3-*hydroxyoctanoate* (**9c**). The aldol was prepared following the standard procedure in 70% yield after preparative hplc (15% ether/hexane, R_f = 0.10). This material was an 86 : 14 mixture of *threo*- and *erythro*-diastereomers. IR (film): 3500, 1750, 1460, 1380, 1260, 765 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.87 (3H, br t), 1.06 (3H, d, J = 7), 2.10 (6H, s), 2.65 (1H, m), 7.00 (3H, s); ^{13}C-NMR: δ 128.4, 125.7, 73.1, (71.6), 45.6, (44.5), 34.4, 31.6, 25.0, 22.3, 16.2, 14.3, 13.8, (10.9). (Found: C, 73.49; H, 9.34. Calc. for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41%).

2′,6′ - *Dimethylphenyl* (2SR, 3SR) - 2,4 - *dimethyl* - 3 - *hydroxypentanoate* (**7d**). The aldol was obtained in 78% yield after preparative hplc (20% ether/hexane) under the standard conditions. This material crystallized after prolonged standing. Recrystallization from hexane gave material with m.p. 77°; IR (film): 3500, 1735, 1455, 1250, 770 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.00 (3H, d, J = 7), 1.07 (3H, d, J = 7), 1.40 (3H, d, J = 7), 2.20 (6H, s), 2.93 (1H, quintet, J = 7), 3.50 (2H, m), 7.03 (3H, s); ^{13}C-NMR: δ 128.5, 125.7, 77.9, 43.0, 30.5, 19.7, 16.2, 15.9, 14.9. (Found: C, 71.69; H, 9.06. Calc. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86%).

2′,6′ - *Dimethylphenyl* (2SR, 3RS) - 2,4,4 - *trimethyl* - 3 - *hydroxypentanoate* (**7e**). Aldol condensation under standard conditions provided the aldol in 82% yield after column chromatography (15% ether/hexane, R_f = 0.38). This material crystallized. Recrystallization from hexane gave material with m.p. 70–71°; IR (CCl_4): 3520, 1735, 1470, 1460, 1375, 1365, 1260, 1165, 1135, 995, 715 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.00 (9H, s), 1.53 (3H, d, J = 7), 2.13 (6H, s), 3.00 (1H, dq, J = 3,7), 3.40 (1H, d, J = 3), 6.97 (3H, s); ^{13}C-NMR: δ 128.8, 126.0, 82.7, 39.4, 35.9, 26.5, 19.0, 16.6. (Found: C, 72.90; H, 9.09. Calc. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15%).

2′,6′ - *Dimethylphenyl* (2SR, 3SR, 4RS *and* SR) - 2,4 - *dimethyl* - 3 - *hydroxybenzenebutanoate* (**7f**). The aldol was obtained following the standard procedure in 81% yield after preparative hplc (20% ether/hexane). IR (film): 3500, 1740, 1450, 1380, 1250, 770, 705 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.27 (3H, d, J = 7), 1.43 (3H, d, J = 7), 2.13 (6H, s), 6.97 (3H, s), 7.20 (5H, s); ^{13}C-NMR: δ 128.5, 127.6, 126.5, 125.7, 78.1, (77.4), 43.0, 42.3, 16.3, 15.6, 14.8. (Found: C, 76.69; H, 7.92. Calc. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74%).

2′,6′ - Bis(1″,1″ - *Dimethylethyl*) - 4′ - *methoxyphenyl* (2SR, 3SR) - 2 - *methyl* - 3 - *hydroxypentanoate* (**10a**). The aldol was obtained in 74% yield after preparative hplc (20% ether/hexane, R_f = 0.09). IR (CCl_4): 3550, 1735, 1415, 1365, 1305, 1270, 1220, 1060 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.00 (3H, t, J = 7), 1.33 (18H, s), 1.43 (3H, d, J = 7), 2.73 (1H, quintet, J = 7), 3.73 (3H, s), 6.80 (2H, s); ^{13}C-NMR: δ 179.9, 160.2, 147.2, 147.0, 115.4, 77.4, 58.8, 49.8, 39.2, 35.0, 30.3, 16.7, 13.4. (Found: C, 72.36; H, 9.79. Calc. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78%). Acetate ^{1}H-NMR ($CDCl_3$): δ 0.90 (3H, br t, J = 7), 1.27 (18H, br s), 1.35 (3H, d, J = 7), 1.67 (2H, m), 2.00 (3H, s), 3.03 (1H, m), 3.67 (3H, s), 5.17 (1H, m), 6.75 (2H, s).

2′,6′ - Bis(1″,1″ - *Dimethylethyl*) - 4′ - *methoxyphenyl* (2SR, 3SR) - 2 - *methyl* - 3 - *hydroxyoctanoate* (**10c**). The aldol was obtained in 70% yield after preparative hplc (10% ether/hexane, R_f = 0.24). IR (film): 3500, 1740, 1590, 1410, 1385, 1360, 1300, 1165, 1060 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.90 (3H, br t, J = 6), 1.34 (18H, s), 1.47 (3H, d, J = 7), 2.73 (1H, quintet, J = 7), 3.73 (3H, s), 6.82 (2H, s); ^{13}C-NMR: δ 176.4, 156.5, 143.6, 111.8, 72.7, 55.2, 46.3, 35.6, 33.0, 32.3, 31.8, 31.4, 25.0, 22.5, 13.2, 13.0. (Found: C, 73.30; H, 10.08. Calc. for $C_{24}H_{40}O_4$: C, 73.43; H, 10.27%).

2′,6′ - Bis(1″,1″ - *Dimethylethyl*) - 4′ - *methoxyphenyl* (2SR, 3SR) - 2,4 - *dimethyl* - 3 - *hydroxypentanoate* (**10d**). Aldol condensation under standard conditions gave a material which could be crystallized from the crude mixture in 57% yield. An additional 22% was obtained by column chromatography (10% ether/hexane) of the mother liquors. If this aldol was trapped as its acetate, the yield was 73% after preparative hplc (15% ether/hexane, R_f = 0.27). The aldol itself was recrystallized from hexane, m.p. 91–93°. IR (CCl_4): 3550, 1735, 1460, 1415, 1365, 1300, 1170, 1125, 1100, 1060, 865 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.93 (3H, d, J = 7), 1.00 (3H, d, J = 7), 1.33 (18H, s), 1.43 (3H, d, J = 7), 1.85 (1H, m), 2.80 (1H, quintet, J = 7), 3.45 (1H, m), 3.73 (3H, s), 6.80 (2H, s); ^{13}C-NMR: δ 111.7, 76.7, 55.1, 44.0, 31.7, 31.3, 29.5, 20.2, 14.6, 13.4. (Found: C, 72.84; H, 9.98. Calc. for $C_{22}H_{36}O_4$: C, 72.49; H, 9.95%). Acetate ^{1}H-NMR ($CDCl_3$): δ 0.90 (3H, d, J = 7), 0.97 (3H, d, J = 7), 1.37 (18H, s), 1.43 (3H, d, J = 7), 1.97 (3H, s), 3.00 (1H, quintet, J = 7), 3.70 (3H, s), 5.00 (1H, t, J = 7), 6.78 (2H, s).

2′,6′ - Bis(1″,1″ - *Dimethylethyl*) - 4′ - *methoxyphenyl* (2SR, 3RS) - 2,4,4 - *trimethyl* - 3 - *hydroxypentanoate* (**10e**). The aldol was obtained in 77% yield after preparative hplc (10% ether/hexane, R_f = 0.31). If this aldol was trapped as its acetate, the yield was 64% after preparative hplc (10% ether/hexane, R_f = 0.35). The aldol itself crystallized and was recrystallized from hexane, m.p. 88–89°. IR (CCl_4): 3550, 1730, 1415, 1360, 1300, 1270, 1240, 1200, 1060 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.00 (9H, s), 1.40 (18H, s), 1.62 (3H, d, J = 7), 3.73 (3H, s), 6.80 (2H, s); ^{13}C-NMR: δ 176.0, 156.4, 143.6, 143.2, 111.7, 82.2, 55.0, 41.6, 35.9, 31.3, 26.5, 18.2. (Found: C, 73.28; H, 10.14. Calc. for $C_{23}H_{38}O_4$: C, 72.98; H, 10.12%). Acetate ^{1}H-NMR ($CDCl_3$): δ 1.03 (9H, s), 1.37 (9H, s), 1.40 (9H, s), 1.60 (3H, d, J = 7). 1.97 (3H, s), 3.00 (1H, quintet, J = 7). 4.93 (1H, d, J = 7), 6.80 (2H, s).

2′,6′ - *Dimethylphenyl* (2SR, 3RS) - 2 - *allyl* - 3 - *hydroxybenzenepropanoate* (**20a**). Aldol condensation under the general procedure given above gave a 9 : 1 mixture of diastereomers. Flash chromatography (7% ether/hexane) gave the aldol mixture in 87% yield. Upon standing this material crystallized. The

analytical sample (m.p. 74–75°) was prepared by recrystallization from pentane; IR ($CHCl_3$): 3610, 1755, 1735, 1640, 1145, 990, 910 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.70 (1H, s), 1.94 (6H, s), 2.05 (1H, d, J = 7), 3.05 (1H, q, J = 7), 4.75 (2H, d, J = 8), 4.92 (1H, dd, J = 11,1), 4.97 (1H, dd, J = 18,1), 5.55 (1H, m), 6.86 (3H, s), 7.22 (5H, m); ^{13}C-NMR: δ (16.1), 16.4, (31.5), 33.7, 52.5, (73.6), 74.4, 117.6, 125.7, 126.5, 127.8, 128.4, 130.2, 134.3, 141.8, 148.1, 172.3. (Found: C, 77.10; H, 7.14. Calc. for $C_{20}H_{22}O_3$: C, 77.40; H, 7.14%).

2',6' - *Dimethylphenyl* (2SR,3SR) - 2 - *allyl* - 3 - *hydroxypentanoate* (**20b**). The crude aldol was obtained in 96% yield as a 84 : 16 mixture of *threo*- and *erythro*-diastereomers. Flash chromatography (7% ether/hexane) gave the pure material (R_f = 0.15) as a colorless oil in 66% yield. This material crystallized. Recrystallization from pentane gave material with m.p. 33–35°. IR (film): 3520 (broad), 1755, 1645, 1480, 1445, 1160, 995, 920 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.94 (3H, t, J = 6), 1.53 (2H, t, J = 7), 2.06 (6H, s), 2.49 (2H, m), 2.68 (1H, q, J = 6), 3.10 (1H, broad), 3.63 (1H, q, J = 6), 4.95 (1H, dd, J = 10,1), 5.00 (1H, dd, J = 18,1), 5.75 (1H, m), 6.86 (3H, s); ^{13}C-NMR: δ 9.7, (9.8), 16.5, (27.5), 27.6, 33.0, 50.4, 72.8, (72.9), 115.5, 117.2, 125.5, 128.3, 129.9, 134.8, 163.8. (Found: C, 73.19; H, 8.46. Calc. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45%).

2',6' - *Dimethylphenyl* (2SR,3SR) - 2 - *allyl* - 3 - *hydroxy* - 4 - *methylpentanoate* (**20c**). The crude aldol was obtained in 96% yield as a single diastereomer. This material crystallized after preparative hplc (20% ether/hexane). Recrystallization from hexane gave material with m.p. 44° in 77% yield. IR (film): 3540, 1745, 1645, 1475, 1445, 1150, 995, 920 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.95 (6H, d, J = 6), 1.75 (1H, heptet, J = 6), 2.06 (6H, s), 2.45 (2H, t, J = 7), 2.82 (1H, q, J = 6), 3.35 (1H, t, J = 6), 4.96 (1H, dd, J = 10,1), 5.02 (1H, dd, J = 18,1), 5.75 (1H, m), 6.87 (3H, s); ^{13}C-NMR: δ 16.6, 17.2, 19.6, 31.3, 33.8, 47.9, 77.0, 117.6, 125.7, 128.5, 130.0, 134.7, 148.2, 172.7. (Found: C, 74.04; H, 8.79. Calc. for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75%).

Procedure for the condensation of **18** *with aldehydes.* In a 25 mL round bottom flask under N_2 was placed 2 mL THF. After LDA was prepared in this solvent, the soln was cooled to −70°. Compound **18** (1.0 g, 3.3 mmol) was dissolved in 1 mL THF and added slowly. The flask containing the ester was rinsed with an additional 1 mL of THF. After 6 hr at −70°, the aldehyde (3.6 mmol) was added. After stirring the solution for 30 min the reaction was quenched with sat NH_4Cl aq. Workup consisted of warming, separation of phases, ether extraction, washing with 1% HCl and NaCl aq, drying and evaporation.

2',6' - Bis(1",1" - *Dimethylethyl*) - 4' - *methylphenyl* (2SR,3SR) - 2 - *allyl* - 3 - *hydroxybenzenepropanoate* (**22a**). This material was prepared by the general procedure given above starting with 3.6 mmol of benzaldehyde and **18**. The crude product, 1.35 g was purified by flash chromatography (10% ether/hexane) to obtain 1.02 mg (76%) of pure material (F_f = 0.21) which crystallized upon standing. The material was recrystallized from pentane, m.p. 100–101°; IR ($CHCl_3$): 3500, 2945, 1720, 1640, 1600, 1480, 1415, 1360, 1255, 1140, 1095, 1020, 985, 910, 855 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.10 (9H, s), 1.25 (9H, s), 2.29 (3H, s), 2.74 (1H, m), 2.83 (1H, m), 3.11 (1H, dt, J = 9,5), 4.10 (1H, d, J = 8), 5.00 (1H, dd, J = 8, 5), 5.18 (2H, m), 5.95 (1H, m), 7.12 (2H, m), 7.35, (5H, m); ^{13}C-NMR: δ 21.3, 31.4, 23.3, 35.0, 35.2, 52.7, 73.0, 117.9, 126.7, 126.9, 127.3, 127.5, 128.2, 134.8, 135.1, 141.8, 142.1, 175.0. (Found: C, 79.45; H, 8.90. Calc. for $C_{27}H_{36}O_3$: C, 79.37; H, 8.88%).

2',6' - Bis(1",1" - *Dimethylethyl*) - 4' - *methylphenyl* (2SR,3SR) - 2 - *allyl* - 3 - *hydroxypentanoate* (**22b**). Aldol condensation using the general procedure for ester **18** and 3.6 mmol propionaldehyde gave 1.20 g of a single diastereomer. Flash chromatography (7% ether/hexane) provided pure adduct in 60% yield. IR ($CHCl_3$): 3540, 2940, 1725, 1640, 1600, 1460, 1415, 1365, 1255, 1150, 1095, 965, 905, 860 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.00 (3H, t, J = 7.4), 1.32 (9H, s), 1.34 (9H, s), 1.68 (2H, m), 2.31 (3H, s), 2.77 (2H, m), 2.90 (2H, m), 3.78 (1H, m), 5.20 (2H, m), 5.85 (1H, m), 7.15 (2H, s); ^{13}C-NMR: δ 10.4, 21.3, 28.0, 31.5, 35.2, 35.3, 50.4, 72.3, 117.6, 127.1, 127.2, 134.7, 135.8, 142.0, 174.7. (Found: C, 76.62; H, 10.32. Calc. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.06%).

2',6' - Bis(1",1" - *Dimethylethyl*) - 4' - *methylphenyl* (2SR,3SR) - 2 - *allyl* - 3 - *hydroxy* - 4 - *methylpentanoate* (**22c**). The crude aldol was obtained in 100% yield as a mixture of *threo*- and *erythro*-diastereomers. Flash chromatography (7% ether/hexane) gave the pure *threo*-material (R_f = 0.15) in 81% yield. IR ($CHCl_3$): 3540, 2925, 1715, 1640, 1595, 1460, 1410, 1360, 1300, 1255, 1150, 970, 905, 860 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.93 (3H, d, J = 6.6), 0.99 (3H, d, J = 6.6), 1.36 (9H, s), 1.38 (9H, s), 2.06 (1H, octet, J = 6.6), 2.32 (2H, s), 2.77 (1H, m), 2.93 (2H, m), 3.03 (1H, m), 3.40 (1H, dt, J = 8,1), 5.20 (2H, m), 5.85 (1H, m), 7.15 (2H, s); ^{13}C-NMR: δ 18.0, 20.0, 21.3, 30.9, 31.5, 32.7, 35.1, 35.2, 47.6, 75.8, 117.7, 127.1, 134.7, 135.6, 141.9, 142.3, 175.0. (Found: C, 76.57; H, 10.34. Calc. for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23%).

General procedure for the hydrolysis of dimethylphenyl esters. The aldol (2.5 mmol) was dissolved in 15 mL of MeOH, and a soln of KOH (20 mmol) was added in 5 mL H_2O and 5 mL MeOH. Analysis by tlc showing only phenol (20% ether/hexane, R_f = 0.27, dark stain with I_2) indicated completion of the reaction (typically 15 min). Solid CO_2 was added cautiously until the soln began to chill. Water and ether were added, the layers were separated, and the aqueous phase was washed with ether. Acidification (3 mL of conc HCl) followed by ether extraction, drying, and evaporation gave the β-hydroxy acid.

(2SR,3SR) - 2,4 - *Dimethyl* - 3 - *hydroxypentanoic acid* (**11d**). The acid was obtained in 91% yield. IR (film): 3450–2500, 1700, 1460, 1385, 1200, 990 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.93 (3H, d, J = 7), 1.00 (3H, d, J = 7), 1.23 (3H, d, J = 7), 1.77 (1H, m), 2.63 (1H, quintet, J = 7), 3.40 (1H, dd, J = 6,7), 6.30 (2H, s); ^{13}C-NMR: δ 180.2, 78.1, 42.7, 30.6, 19.6, 16.0, 14.9, 14.4. (Found: C, 57.26; H, 9.35. Calc. for $C_7H_{14}O_3$: C, 57.51; H, 9.65%).

(2SR,3RS) - 2,4,4 - *Trimethyl* - 3 - *hydroxypentanoic acid* (**11e**). After an 8 hr reaction time, the acid was obtained in 98% yield. This material slowly crystallized and was recrystallized from hexane, m.p. 74.5–76.5°. IR (film): 3400–2500, 1705, 1460, 1190, 980 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.00 (9H, s), 1.37 (3H, d, J = 7), 2.70 (1H, dq, J = 2, 7). 3.15 (1H, d, J = 2), 6.60 (2H, s); ^{13}C-NMR: δ 181.5, 82.5, 38.7, 26.8, 26.4, 26.1, 18.1. (Found: 59.87; H, 9.87. Calc. for $C_8H_{16}O_3$: C, 59.98; H, 10.07%).

(2SR, 3SR, 4SR and RS) - 2,4 - *Dimethyl* - 3 - *hydroxybenzenebutanoic acid* (**11f**). The acid was obtained as a 4:1 mixture of diastereomers in 86% yield. Recrystallization from ether/hexane gave material with m.p. 108–110°. IR (CCl_4): 3500–2500, 1700, 1450, 1400, 1125, 920 cm^{-1}; ^{1}H-NMR (CD_3COCD_3): δ 1.13 (3H, d, J = 7), 1.28 (3H, D, J = 7), 2.36 (1H, m), 2.90 (1H, quintet, J = 7), 3.60 (1H, dd, J = 7,5), 7.20 (5H, s); ^{13}C-NMR (CD_3COCD_3): 180.5, 144.0, 128.4, 127.5, 126.5, 78.2, (77.4), 43.4, (42.9), (42.7), 41.7, 16.1, 15.0. (Found: C, 68.86, H, 7.66. Calc. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%).

General procedure for ceric ammonium nitrate (CAN) oxidations of aldol adducts. The adduct (3 mmol) was dissolved in acetonitrile (6 mL) and ceric ammonium nitrate (6.5 mL of a 1.20 M soln, 7.8 mmol) was added. After stirring for 30 min, mannitol (1.5 g) was added, and the soln was stirred for an additional 30 min. The mixture was diluted with water and ether, the layers were separated, and the aqueous phase was extracted with ether. The combined organic phases were washed with water and extracted with 5% NaOH (2 × 15 mL). If the aldol was protected as its acetate derivative, this basic soln was allowed to stand overnight before acidification. Otherwise, it was acidified with 4 mL of conc HCl and extracted with ether. The combined organic phases where washed with NaCl aq, dried, filtered and evaporated to give the β-hydroxy acid.

(2SR, 3SR) - 2 - *Methyl* - 3 - *hydroxypentanoic acid* (**11b**) was produced in 39% yield from the hydroxy ester and in 46% yield from the acetoxy ester. IR (film): 3400–2500, 1710, 1460, 1200, 980 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.97 (3H, t, J = 7), 1.20 (3H, d, J = 7), 1.50 (2H, m), 2.50 (1H, quintet, J = 7), 3.55 (1H, m), 6.40 (2H, s); ^{13}C-NMR: δ 180.4, 74.6, 44.8, 27.2, 14.0, 9.6. (Found: C, 54.80; H, 8.75. Calc. for $C_6H_{12}O_3$: C, 54.53; H, 9.15%).

(2SR, 3SR) - 2 - *Methyl* - 3 - *hydroxyoctanoic acid* (**11c**) was produced in 67% yield from the hydroxy ester. IR (film): 3400–2500, 1710, 1460, 1200 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.87 (3H, br t, J = 6), 1.20 (3H, d, J = 7), 2.50 (1H, quintet, J = 7), 3.60 (1H, m), 6.80 (2H, s), ^{13}C-NMR: δ 180.2, 73.4, 45.3, 34.4, 33.6, 31.7, 25.0, 22.5, 14.0, 13.9. (Found: C, 61.86; H, 10.26. Calc. for $C_9H_{18}O_3$: C, 62.04; H, 10.41%).

(2SR, 3SR) - 2,4 - *Dimethyl* - 3 - *hydroxypentanoic acid* (**11d**) was produced in 57% yield from the hydroxy ester, and in 81% yield from the acetoxy ester.

(2SR, 3RS) - 2,4,4 - *Trimethyl* - 3 - *hydroxypentanoic acid* (**11e**) was produced in 18% yield from the hydroxy ester, and in 79% yield from the acetoxy ester.

(2SR, 3RS)-2-*Ethyl*-3-*hydroxy*-4-*methylpentanoic acid* (**19**)

(a) Using DMP butyrate (**15**), aldol condensation under standard conditions provided the aldol in 93% yield after preparative hplc (20% ether/hexane, $R_f = 0.33$). ^{1}H-NMR ($CDCl_3$): δ 1.07 (9H, m), 2.17 (6H, s), 3.50 (2H, m), 7.00 (3H, s). This ester was hydrolyzed using the standard conditions to give acid **19** in 74% yield. IR (film): 3400–2500, 1700, 1460, 1200, 990 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.00 (9H, m), 1.65 (2H, m), 2.50 (1H, br q, J = 7), 3.40 (1H, t, J = 6), 5.30 (2H, m); ^{13}C-NMR: δ 179.9, 76.9, 49.7, 31.6, 22.0, 19.4, 17.1, 11.6. (Found: C, 59.68; H, 10.35. Calc. for $C_8H_{16}O_3$: C, 59.98; H, 10.07%).

(b) Using DBHA butyrate (**16**) the aldol was obtained in 68% yield after preparative hplc (20% ether/hexane, $R_f = 0.29$). This material crystallized and was recrystallized from hexane, m.p. 75–76°. If this aldol was trapped as its acetate, the yield was 60% after preparative hplc (10% ether/hexane, $R_f = 0.17$). IR (film): 3550, 1730, 1600, 1415, 1360, 1300, 1260, 1200, 1069 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.97 (3H, d, J = 7), 1.00 (3H, d, J = 7), 1.10 (3H, t, J = 7), 1.34 (18H, s), 2.00 (2H, m), 2.80 (1H, m), 3.45 (1H, m), 3.73 (3H, s), 6.80 (2H, s); ^{13}C-NMR: δ 175.8, 111.7, 75.3, 59.4, 55.0, 31.3, 21.1, 20.1, 17.6, 12.3 (Found: C, 72.81; H, 9.87. Calc. for $C_{21}H_{38}O_4$: C, 72.98; H, 10.11%). Acetate ^{1}H-NMR ($CDCl_3$): δ 0.93 (3H, t, J = 7). 1.13 (6H, d, J = 7), 1.34 (18H, s), 2.00 (3H, s), 2.75 (1H, m), 3.72 (3H, s), 5.00 (1H, dd, J = 4,8), 6.78 (2H, s).

The hydroxy acid was obtained by CAN oxidation under the standard conditions in 35% yield from the hydroxy ester and in 85% yield from the acetoxy ester.

2',6' - *Dimethylphenyl* (2SR, 3SR) - *and* (2SR, 3RS) - 3 - *hydroxy* - 2 - *tetradecyloctadecanoate* (**26** *and* **27**): To a soln of diisopropylamine (0.37 mL, 0.27 g, 2.6 mmol) in 2 mL of THF at −20° was added 1.47 mL (2.21 mmol) of a 1.50 M soln of n-BuLi in hexane. The soln was cooled to −78°, a soln of 2',6'-dimethylphenyl hexadecanoate (0.721 g, 2.00 mmol) in 3 mL THF was added, and the mixture was stirred for 10 1/2 hr. A soln of hexadecanal (0.471 g, 1.96 mmol) in 2 mL THF was added, and the mixture was stirred for 1 hr. The reaction was quenched with 5 mL sat NH_4Cl aq and taken up in 2:1 ether/hexane. The organic phase was washed with water, dried over $MgSO_4$, and the solvents evaporated to give 0.977 g of the crude aldol product as a yellow oil. The crude product was purified by hplc, eluting with 5% ether/hexane, to give the aldols (0.509 g, 43%) as a pale yellow oil. The product was shown by analytical hplc to be a 1.5 : 1 mixture of *threo*- and *erythro*-isomers **26** and **27**. IR (film): 3500, 1750 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.90 (3H, s), 3.83 (1H, br s), 2.87–2.03 (2H, m), 2.13 (6H, s), 1.60–1.03 (54H, br s), 0.87 (6H, m). (Found: C, 79.85; H, 11.96. Calc. for $C_{40}H_{72}O_3$: C, 79.94; H, 12.08%).

(2',6' - Bis(1" - *Methylethyl*)*phenyl* (2SR, 3SR) - *and* (2SR, 3RS) - 3 - *hydroxy* - 2 - *tetradecyloctadecanoate* (**28** *and* **29**): To a soln of diisopropylamine (0.16 mL, 0.11 g, 1.1 mmol) in 2 mL THF at −10° was added a 1.50 M soln of n-BuLi (0.74 mL, 1.1 mmol) in hexane. The soln was cooled to −78°, 2',6'-*Bis*(1"-methylethyl)phenyl hexadecanoate (0.419 g, 1.01 mmol) was added, and the mixture was stirred for 7 hr. A soln of hexadecanal (0.240 g, 1.00 mmol) in 2 mL THF was added, and the mixture was stirred for 30 min. The reaction was quenched with 65 μL glacial AcOH (one equiv) and the resulting mixture was taken up in ether. The mixture was washed with water and brine, dried over $MgSO_4$, and the solvents evaporated to give 0.630 g of the crude aldols as a yellow oil, the ^{1}H-NMR spectrum of which indicated that it was 50% condensed products. The crude material was shown by analytical hplc to be a 2.0 : 1 *threo* : *erythro* mixture. Preparative tlc on 0.542 g of the crude material, eluting with 10% ether/hexane, gave 0.106 (19%) of a pure sample. IR (CCl_4): 3550, 1740 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.13 (3H, s), 3.93 (1H, br s), 3.07–2.13 (4H, m), 1.70–1.03 (54H, br s), 1.27 (12H, d, J = 7), 0.87 (6H, m). (Found: C, 80.26; H, 12.26. Calc. for $C_{44}H_{80}O_3$: C, 80.42; H, 12.27%).

Methyl corynomycolate (**30**)

(A) *From dimethylphenyl esters.* A soln of a 1.5 : 1 mixture of DMP esters **26** and **27** (0.103 g, 0.172 mmol), prepared as described above and NaOMe (98.7 mg, 0.183 mmol) in 10 mL of 1:1 THF : MeOH was stirred at room temp. for 24 hr. The mixture was then taken up in ether, washed with water, and dried over $MgSO_4$. Evaporation of the solvent left 76.0 mg of a white solid, which was purified by preparative tlc, eluting with 10% ether/hexane, to give 20.0 mg (23%) of *epi*-methyl corynomycolate, m.p. 70–71° (Lit. m.p. 68–70°)[18] and 40.2 mg (46%) of methyl corynomycolate, m.p. 56–58° (Lit. m.p. 57–59°).[18]

(B) *From* Bis(1'-*Methylethyl*)*phenyl esters.* A soln of a 2 : 1 mixture of DIPP esters **28** and **29** (19.3 mg, 0.029 mmol), prepared as described above and NaOMe (15.7 mg, 0.029 mmol), in 6 mL of 1 : 1 THF : MeOH was stirred at room temp. for 2 days. Additional NaOMe (10.0 mg, 0.019 mmol) was added to the mixture, and this was stirred for 1 day. The mixture was taken up in water and extracted twice with ether. The ether extracts were washed with brine, dried over $MgSO_4$, and evaporated to yield 18.6 mg of crude product. Chromatography of the crude material on silica gel, eluting with 10% ether/hexane, afforded 13.4 mg (69%) of recovered starting material, and 4.8 mg (31%) of a mixture of methyl corynomycolate and methyl *epi*-corynomycolate, identical with material obtained from the dimethylphenyl esters.

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