Pergamon

Tetrahedron, Vol. 53, No. 26, pp. 8779-8794, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00568-1

Aldol Reactions of Ketal-Protected Tartrate Ester Enolates. Asymmetric Syntheses and Absolute Stereochemical Assignments of Phospholipase A_2 Inhibitors Cinatrin C_1 and C_3

David A. Evans,* B. Wesley Trotter, and James C. Barrow

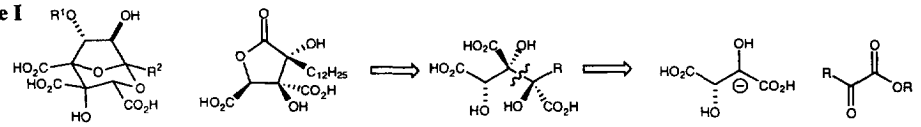
Department of Chemistry & Chemical Biology, Harvard University, Cambridge, MA 02138, USA

Abstract: An efficient approach to the syntheses of cinatrins C_1 and C_3 has been developed and used to establish the absolute configurations of these natural products. The construction of each molecule has been achieved in a five-step reaction sequence (overall yield 43% for cinatrin C_1, 33% for cinatrin C_3) from the di-*tert*-butyl ester of (*R,R*)-tartaric acid. The two contiguous, quaternary chiral centers in the cinatrin skeleton are constructed via a diastereoselective, titanium-mediated aldol coupling of a tartrate-derived silylketene acetal and an achiral α-ketoester. This bond construction proceeds with excellent diastereoselectivity for a variety of aldehyde and α-ketoester substrates. © 1997 Elsevier Science Ltd.

Introduction

The natural abundance of tartaric acid in both of its enantiomeric forms has insured its popularity as a chiral building block[1] and as a useful chiral ligand in asymmetric catalytic processes.[2] We have recently investigated tartaric acid as a chiral synthon because of its potential utility in the construction of densely oxygenated natural products such as the zaragozic acids and cinatrins (Scheme I). The purpose of this investigation is to demonstrate that tartrate-derived silylketene acetals undergo diastereoselective addition reactions with both aldehydes and α-ketoesters and that this reaction may be employed in the efficient synthesis of the phospholipase inhibitors cinatrin C_1 and C_3.[3] As a consequence of this exercise we have corrected the absolute configuration of the cinatrins reported by Itazaki[3] to that illustrated below.

Scheme I

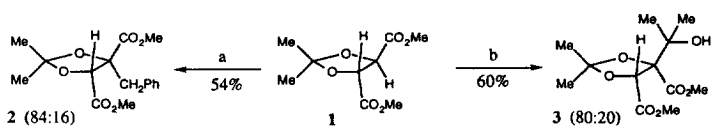


Zaragozic Acid Cinatrin C_3

Tartrate Enolate-Derived Aldol Reactions

In 1981, Seebach demonstrated that dimethyl tartrate acetonide **1** formed a stable lithium enolate that could be trapped stereoselectively with electrophiles (Scheme II).[4] Treatment of this enolate with benzyl bromide provided adduct **2**, which resulted from "contrasteric" alkylation of the more hindered enolate diastereoface. In contrast, an aldol reaction with acetone proceeded with the sense of induction expected on steric grounds to furnish **3**. The latter mode of reactivity was exploited in our recently reported syntheses of

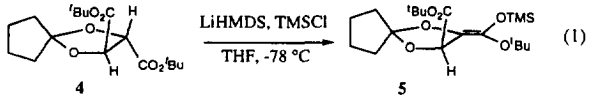
Scheme II



2 (84:16) 1 3 (80:20)

(a) LDA, HMPA/THF, benzyl bromide, -70 °→-10 °C; (b) LDA, HMPA/THF, acetone.

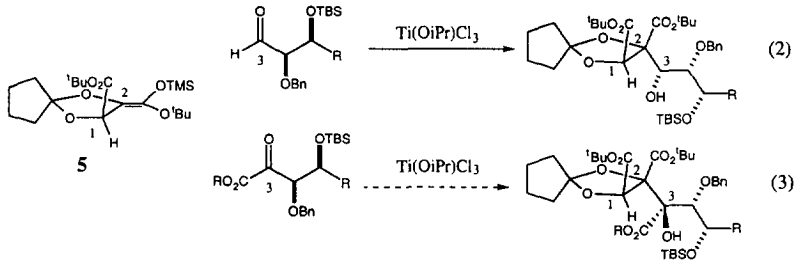
zaragozic acids A and C.[5] During the course of these studies we found that the di-*tert*-butyl tartrate variant **4**, in comparison with its methyl ester analogue, furnished a more reliable enolate (via silylketene acetal **5**) for these types of aldol bond constructions (eq. 1).[6] We report here that tartrate equivalent **5** undergoes highly diastereoselective aldol reactions with a variety of prochiral aldehydes and activated ketones.



(1)

4 **5**

By way of precedent, our zaragozic acid synthesis utilized silylketene acetal **5** to establish a core quaternary center (denoted C_2, eq 2) via the illustrated stereoselective titanium-mediated aldol reaction. A more aggressive approach to the synthesis of the zaragozic acid skeleton was envisaged via the related α-ketoester (eq 3). At that time, the stereochemical outcome of this projected process had not been investigated.



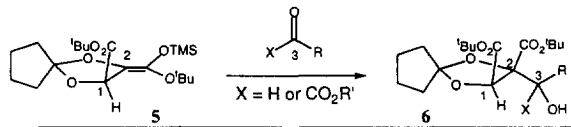
(2)

(3)

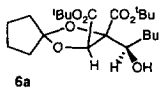
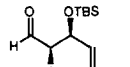
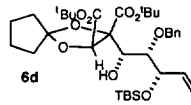
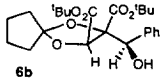
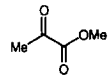
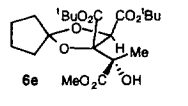
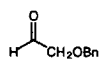
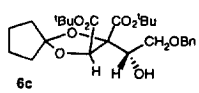
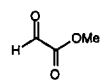
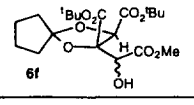
5

The preceding involvement with these aldol processes has led to the present investigation that has examined the scope of this aldol process with a representative set of aldehydes and α-ketoester substrates (Table 1). From the data, it is evident that the aldol process proceeds with good levels of stereocontrol at both of the newly formed stereocenters. In all cases, the C_2 stereocenter is established with >95:5 diastereoselectivity in accord with the steric bias imposed by the tartrate C_1 stereocenter. In contrast, the sense of induction obtained at the C_3 stereocenter exhibits a marked dependence on aldehyde structure. The same sense of induction at C_3 is observed for both alkyl and aryl aldehydes (entries 1 and 2). α-Heteroatom-substituted aldehydes (entries 3

Table 1. Titanium-mediated aldol reactions of silyl ketene acetal **5**[a]



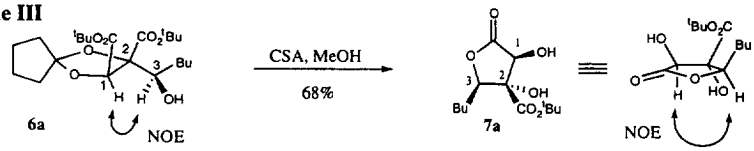
5 **6**

entry	substrate	adduct	C_3 selectivity (yield, %)[b]	entry	substrate	adduct	C_3 selectivity (yield, %)[b]
1		 **6a**	91:9 (48%)	4		 **6d**	>95:5 (80%)
2		 **6b**	88:12 (67%)	5		 **6e**	>95:5 (66%)
3		 **6c**	91:9 (64%)	6		 **6f**	50:50 (44%)

[a]Conditions: $Ti(OiPr)Cl_3$, CH_2Cl_2, -78 °C→-40 °C. [b]Ratios determined by ^1H NMR analysis of the unpurified products.

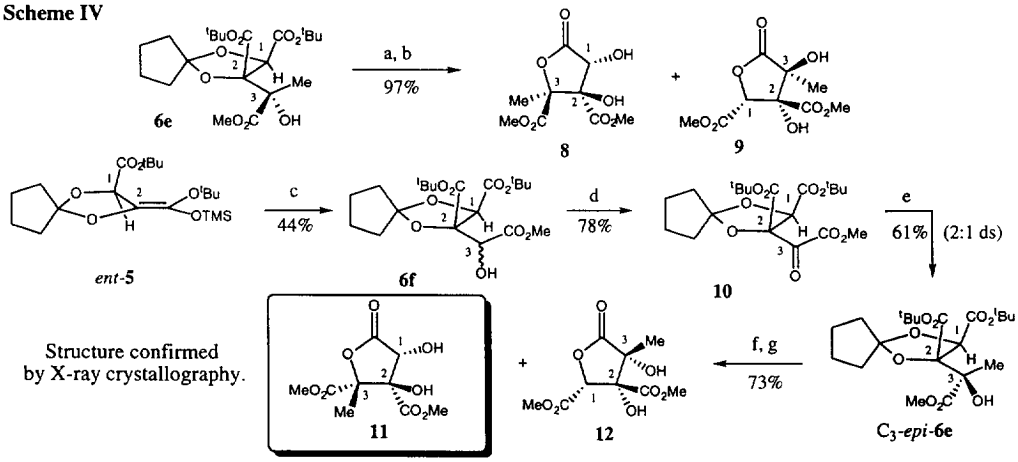
and 4) exhibit the opposite sense of induction. The stereochemical outcome of each these reactions was inferred on the basis of NOE data (Scheme III). NOE enhancements between C_1H and C_3H establish the stereochemistry at C_2, as shown for aldol adduct **6a**. Treatment of **6a** with camphorsulfonic acid (CSA) effects removal of the cyclopentylidene ketal and lactonization to give **7a**. The observed NOE enhancements between C_1H and C_3H in the rigid system **7a** establish the stereochemistry at C_3. This strategy was also employed to assign stereochemistry for adducts **6b** and **6c**.[7]

Scheme III



α-Ketoesters (entry 5) also afford high diastereoselectivity at the hydroxyl-bearing stereocenter. Methyl glyoxylate (entry 6) is one of the few substrates examined that provides poor selectivity. The configurations of adducts **6e** and **6f** were determined indirectly by X-ray crystallographic analysis of a derivative of C_3-*epi*-**6e** (Scheme IV). Removal of the cyclopentylidene ketal in **6f** required the use of trifluoroacetic acid/water; the resulting carboxylic acid lactones were then treated with diazomethane to provide **8** and **9**. Unfortunately, NOE data obtained for these compounds did not unambiguously confirm the stereochemical assignment. However, we found that we could access C_3-*epi*-**6e** via oxidation of **6f** followed by addition of methylmagnesium bromide (2:1 C_3-*epi*-**6e**:**6e**). This unoptimized reaction sequence could provide a general entry to C_3 epimers of this type. Deketalization and esterification gave lactones **11** and **12** (Scheme IV). The structure of the crystalline lactone **11** was assigned by X-ray crystallography, thus confirming the assignments of both **6e** and **6f**.[8] Consistent NOE data were obtained for both **11** and **12**.

Scheme IV

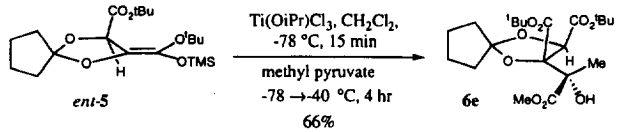


(a) CH_2Cl_2:TFA:H_2O, 20:10:1, 14 h; (b) CH_2N_2, CH_2Cl_2/MeOH; **8:9** = 10:1; (c) $Ti(OiPr)Cl_3$, methyl glyoxylate, CH_2Cl_2, -78→ -40 °C; (d) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, then Et_3N, 0 °C; (e) MeMgBr, THF, -78 °C, 2:1 at C_3; (f) CH_2Cl_2:TFA:H_2O, 20:10:1, 14 h; (g) CH_2N_2, CH_2Cl_2/MeOH.

Stereochemical Model for the Aldol Reaction

Our initial attempts to couple silylketene acetal *ent*-**5**, subsequently used in the cinatrin synthesis (*vide infra*), and methyl pyruvate utilized an electrophile-Lewis acid pre-complexation protocol optimized for our zaragozic acid project (eq 2). This procedure provided the desired aldol adduct as a single diastereomer in modest yield. However, we found that a permuted order of addition provided higher yields of the desired adduct with identical selectivity. When silylketene acetal *ent*-**5** and $Ti(OiPr)Cl_3$ were premixed at -78 °C to afford a dark green-brown solution, the addition of the α-ketoester provided adduct **6e** in 66% isolated yield (Scheme V).

Scheme V



These observations suggest that the aldol reaction could be proceeding through the intermediacy of a titanium enolate rather than via addition of the silylketene acetal to the Lewis acid-activated carbonyl. No obvious model incorporating an open transition state explains the strong sense of induction obtained at the C_3 stereocenter; accordingly, the prospect of a closed transition state involving a titanium enolate is proposed. The chair-like transition state (A) shown in Figure 1 orients the α-ketoester on the face of the tartrate enolate opposite the *tert*-butyl ester and positions the methyl ester of the electrophile in a pseudo axial orientation, allowing chelation to titanium.[9] This model predicts the induction observed experimentally at both of the newly formed stereocenters.[10] Evidence for the formation of a titanium enolate is provided by NMR data obtained for an equimolar mixture of silylketene acetal *ent*-**5** and $Ti(OiPr)Cl_3$ in CD_2Cl_2 at -78 °C. Upon addition of the titanium Lewis acid, the singlets at 0.17 and 0.19 ppm (trimethylsilyl resonances due to the (*E*) and (*Z*) isomers of the silylketene acetal) are diminished in intensity, and a new singlet at 0.37 ppm (trimethylsilyl chloride) is observed. Integration of these signals indicates that approximately 30% of the material is converted to the putative titanium enolate; the ratio of the signals does not change with time. No change is observed in this ratio in the temperature range -78→-40 °C. The observed spectrum may depict an equilibrium between a titanium enolate, which is the reactive species in the aldol, and the silylketene acetal. We cannot rule out the possibility that the appearance of the trimethylsilyl chloride resonance indicates nonproductive decomposition of the silylketene acetal, but the invariance of the spectrum with time and temperature suggests that decomposition is not occurring.

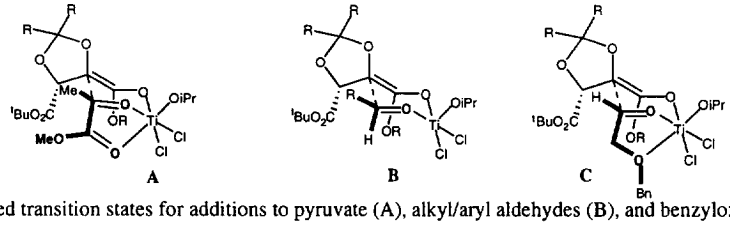


Figure 1. Proposed transition states for additions to pyruvate (A), alkyl/aryl aldehydes (B), and benzyloxyacetaldehyde.

The results reported in Table 1 may be rationalized by invoking the proposed transition state model. The stereoinduction observed for unfunctionalized aldehydes (entries 1 and 2) may be rationalized when these substrates are oriented such that the alkyl or aryl group occupies a pseudo equatorial position in the closed transition state (B). Benzyloxyacetaldehyde, on the other hand, realizes its chelate potential via pseudo axial orientation of the benzyl ether (C). An identical arrangement leads to the selectivity observed with a more highly functionalized aldehyde (entry 4).[5] The only substrate to exhibit no induction at the C_3 stereocenter was methyl glyoxylate (entry 6); the highly activated nature of this aldehyde may lead to a less rigid transition state in which the preference for a chelating ester group over a sterically undemanding proton in the pseudo axial position is diminished.

Syntheses of Cinatrins C_1 and C_3

Cinatrins C_1 and C_3 are members of a family of phospholipase inhibitors recently isolated from the fermentation broth of *Circinotrichum falcatisporum*.[3] Cinatrin C_3 is a Ca(2+)-independent, noncompetitive inhibitor of rat platelet phospholipase A_2 (PLA_2). It is believed to be unique in its ability to inhibit PLA_2 via direct interaction with the enzyme rather than via interactions with PLA_2 substrates. The cinatrins may consequently prove useful as probes for further elucidation of the biological role of PLA_2.[11] Itazaki and coworkers have reported the relative and absolute stereochemical assignments of these lactones using X-ray crystallogra-

phy and CD spectroscopy (Figure 2).[3] Cinatrins C_1 and C_3 are isomeric γ-lactones derived from seco acid **15**, which bears a striking resemblance to the zaragozic acid core functionality (Scheme VI).

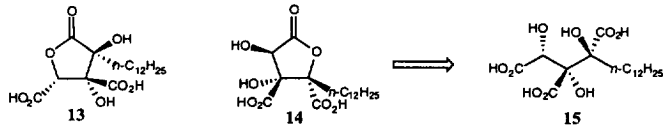
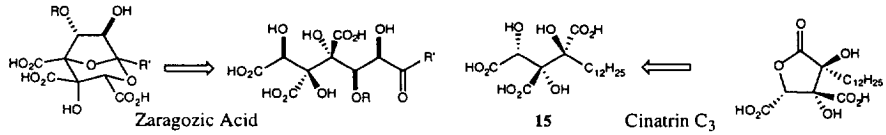


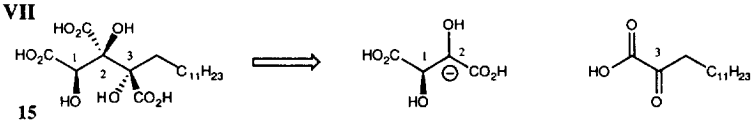
Figure 2. Structures of cinatrin C_3 (**13**) and cinatrin C_1 (**14**) as assigned by Itazaki (ref. 3) and their common precursor (**15**).

Scheme VI



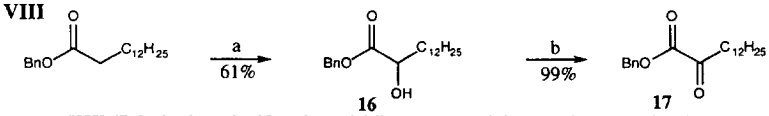
We were interested by the fact that the assigned cinatrin structure was enantiomeric to the relevant zaragozic acid fragment and by the potential to rapidly access the complete cinatrin skeleton via a single aldol coupling in which both contiguous quaternary stereocenters were established (Scheme VII).

Scheme VII



The sense of induction observed in the aldol reaction of silylketene acetal *ent*-**5** (derived from (*R*,*R*)-tartaric acid) and methyl pyruvate (Scheme V) provided the same stereochemical array present in the cinatrin skeleton. Application of this highly selective aldol reaction to the cinatrin synthesis therefore required only the substitution of an appropriate α-ketoester for methyl pyruvate. We chose to employ a benzyl ester, which could be easily removed in the final steps of the synthesis. The required α-ketoester was prepared in two steps via oxidation of benzyl myristate[12] (Scheme VIII). Treatment of the potassium enolate of benzyl myristate with 2-phenylsulfonyloxaziridine[13] provided α-hydroxy ester **16** in 61% isolated yield after flash chromatography. Further oxidation under Swern conditions furnished benzyl α-ketoester **17** in 99% yield after a mild aqueous workup.[14]

Scheme VIII

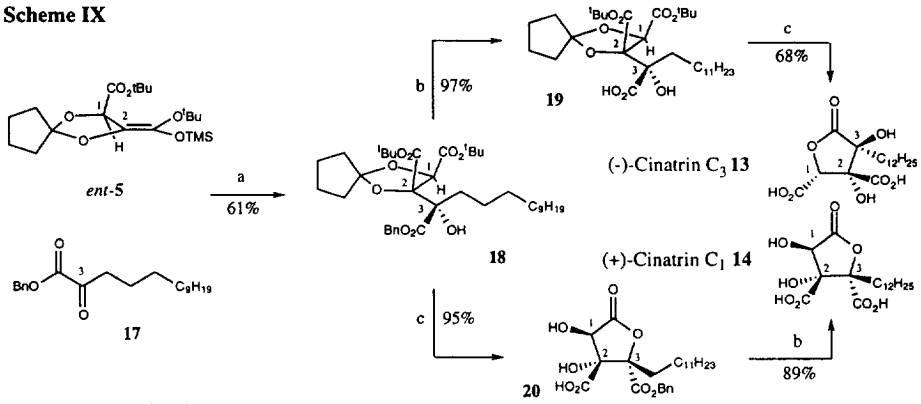


(a) KHMDS, 2-phenylsulfonyloxaziridine, THF, -78 °C; (b) Swern oxidation

The crucial aldol coupling was achieved by addition of α-ketoester **17** to a premixed solution of silylketene acetal *ent*-**5** and $Ti(OiPr)Cl_3$ (Scheme IX); this provided the desired adduct **18** in 61% isolated yield as a single diastereomer (>95:5 by ^1H NMR). With the complete skeleton assembled, a pair of facile deprotection steps completed the total syntheses of cinatrins C_1 and C_3 and confirmed the stereochemical outcome of the aldol. Hydrogenolysis of the benzyl ester (Scheme IX) provided the monoacid **19**, which was then treated with trifluoroacetic acid/water[5] to provide a 3:1 mixture of cinatrin C_3 and C_1 in 90% yield. Cinatrin C_3 was isolated by crystallization (68% yield) and was spectroscopically identical to a natural sample (^1H NMR, ^{13}C NMR, mass spec., IR, HPLC). The synthetic material exhibited an optical rotation approximately equal in magnitude but *opposite in sign* to that of the natural sample (synthetic $[\alpha]_D^{23}$ -76.3 ° (*c* 0.170, MeOH), natural $[\alpha]_D^{23}$ +73.2 ° (*c* 0.168, MeOH)).[15] Reversal of the final deprotection steps provided selective access to cinatrin C_1 (Scheme IX). When aldol adduct **18** was treated with trifluoroacetic acid/water, the benzyl moiety effectively blocked one of the two lactonization-prone carbonyls; cyclization onto the remaining carboxylic acid furnished monobenzyl cinatrin C_1 (**20**) in 95% yield. Hydrogenolysis of the benzyl ester then provided cinatrin C_1 in 89% yield.[16] Synthetic cinatrin C_1 exhibited spectral and physical properties identical

to those of the natural material, with an approximately equal but opposite optical rotation (synthetic $[\alpha]_D^{23}$ +9.7 ° (*c* 0.314, MeOH), *lit.* $[\alpha]_D^{23}$ -11.7 ° (*c* 0.314, MeOH)).[17]

Scheme IX



(a) $Ti(OiPr)Cl_3$, CH_2Cl_2, -78 →-40 °C; (b) H_2, 10% Pd-C, ethanol, 30 min; (c) 20:10:1 CH_2Cl_2:TFA:H_2O, 14 h.

The syntheses of (-)-cinatrin C_3 and (+)-cinatrin C_1 establish the structures of the natural compounds as enantiomeric to those proposed by Itazaki and coworkers (Figure 3). This structural assignment reveals that the cinatrin skeleton actually maps onto both the relative *and* absolute stereostructure of the corresponding zaragozic acid fragment. The natural enantiomer (+)-cinatrin C_3 was easily synthesized by use of the (*S*,*S*)-tartrate-derived ketal **4**. The synthetic material thus obtained ($[\alpha]_D^{23}$ +84.2 ° (*c* 0.170, MeOH)) was spectroscopically identical to a natural sample, confirming our stereochemical assignment.

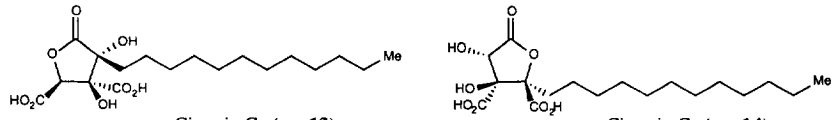
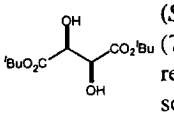


Figure 3. Revised absolute configurations of cinatrins C_1 and C_3.

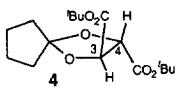
Experimental Section.

General Information. Melting points are uncorrected. Optical rotations were measured on a Jasco DIP-0181 digital polarimeter with a sodium or mercury lamp and reported as follows: $[\alpha]^{t°C}_{\lambda}$ (*c* g/100 ml, solvent). Infrared spectra were recorded on a Perkin Elmer model 1600 FT-IR spectrometer. ^1H NMR spectra were recorded on Bruker AM-500 (500 MHz) or AM-400 (400 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: δ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), integration, and assignment. Cinatrin numbering is used for assignments of all intermediates. ^{13}C NMR spectra were recorded on Bruker AM-500 (125 MHz) or AM-400 (100 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (deuterochloroform: δ 77.0 ppm). Mass spectra were obtained on a JEOL AX-505 or SX-102 high resolution magnetic sector mass spectrometer by the Harvard University Mass Spectrometry Laboratory. Combustion analyses were performed by Atlantic Microlab (Norcross, GA). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Flash chromatography was performed using EM silica gel 60 (230-240 mesh). Solvents for extraction and chromatography were HPLC grade. Unless otherwise noted, all reactions were conducted in oven (80 °C) or flame-dried glassware with magnetic stirring under an inert atmosphere of dry nitrogen. When necessary, solvents and reagents were dried prior to use. Deuterochloroform was stored over 4 Å molecular sieves. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium or potassium

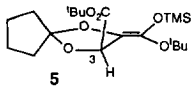
metal/benzophenone ketyl. Dichloromethane (CH_2Cl_2), benzene, trimethylchlorosilane, triethylamine, and 1,1,1,3,3,3-hexamethyldisilazane were distilled from calcium hydride. Dimethylsulfoxide (DMSO) was distilled under reduced pressure from calcium hydride and stored over 4 Å molecular sieves. Titanium tetraisopropoxide, titanium tetrachloride and oxalyl chloride were distilled prior to use. Ti(O*i*Pr)Cl_3 was prepared as a 1 M solution in CH_2Cl_2 by mixing $TiCl_4$ (3 equiv) and Ti(O*i*Pr)$_4$ (1 equiv) in CH_2Cl_2 at room temperature. Methyl glyoxylate,[18] 2-(phenylsulfonyl)-3-phenyloxaziridine,[14] and benzyl myristate[13] were prepared as described. All other commercially obtained reagents were used as received.



(*S,S*)-Di-*tert*-butyl tartrate. To a mixture of 31 g (207 mmol) of (*S,S*)-tartaric acid and 58 ml (728 mmol) of chloroacetyl chloride was added 0.5 ml (9 mmol) of conc. H_2SO_4, and the resulting slurry was heated to 74 °C whereupon the solid slowly dissolved to give a brown solution. After 24 h at 74 °C, the reaction was allowed to cool, then poured into a mixture of 1.5 L of brine and 1.5 L of EtOAc and vigorously shaken for 10 min. The layers were partitioned and the aqueous extracted with EtOAc (4 x 500 ml). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The resulting residue was then added to a -78 °C solution of approx. 60 ml isobutylene in 1 L of CH_2Cl_2. To this was added 1 ml (18 mmol) of H_2SO_4 and the reaction allowed to warm to room temperature and stir 24 h. The reaction was diluted with 500 ml of CH_2Cl_2 and washed with 1.5 L of brine. The organic layer was concentrated and redissolved in 1.5 L of a 1:1 EtOAc:hexane mixture, then washed with 1 L of water and 1 L of brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was then dissolved in 1 L of MeOH and cooled to 0 °C. To this was added 4.0 g (29 mmol) of K_2CO_3. The reaction was stirred for 17 min at 0 °C, then quenched by pouring into 1 L of a 1 M pH 7 aqueous phosphate buffer and the volatiles removed *in vacuo*. The resulting mixture was extracted with EtOAc (3 x 600 ml), and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Recrystallization from hexanes provided 30.5 g (56% from tartaric acid) of the title compound which gave spectral data identical to those reported by Uray.[19]

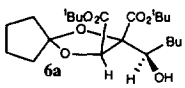


Di-*tert*-butyl-(2*S*, 3*S*)-1,4-dioxaspiro[4.4]nonane-2,3-dicarboxylate (4). To a solution of 23.4 g (89 mmol) of (*S,S*)-di-*tert*-butyl tartrate in 300 ml benzene was added 33.5 g (258 mmol) of cyclopentanone dimethylketal and 0.2350 g (1.2 mmol) of *p*-toluenesulfonic acid monohydrate. The flask was fitted with a Soxhlet extractor and reflux condenser, and a thimble containing freshly activated 4Å sieves was placed in the Soxhlet extractor. The reaction mixture was then heated to 60 °C under slight (approx. 200 torr) vacuum (so as to maintain gentle reflux at 60 °C) for 6 h. The thimble was recharged with fresh sieves, 0.05 g more *p*-toluenesulfonic acid monohydrate was added, and the reaction was heated under vacuum as before for 5 h. The reaction flask was cooled, diluted with 700 ml of ether, and washed with 600 ml of saturated $NaHCO_3$ solution and 600 ml of brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (11.5 x 22 cm, linear gradient 5 to 10% EtOAc:hexane) afforded 25.0 g (85%) **4** as a white solid. mp 64 - 65 °C, $[\alpha]^{24}_D$ +36°(*c* 1.39, CH_2Cl_2); IR (KBr) 2980, 1758, 1734, 1458, 1370, 1251, 1167, 1113, 990, 963, 839; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.50 (s, 2H, OC*H*C*H*O); 1.95 (m, 2H, C(C*H*$_2$CH$_2$CH$_2$CH$_2$); 1.85 (m, 2H, C(C*H*$_2$CH$_2$CH$_2$CH$_2$); 1.70 (m, 4H, C(CH$_2$C*H*$_2$C*H*$_2$CH$_2$) 1.49 (s, 18H, $CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.8, 123.0, 82.5, 77.7, 36.7, 36.7, 27.9, 23.4; TLC R_f = 0.5 (20% EtOAc:hexane); Exact mass calcd for $C_{17}H_{28}O_6$: 328.1886 Found: 328.1884 (EI).

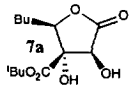


***tert*-butyl - (2*S*, 3*S*)- 1,4-dioxaspiro [4.4] nonane - 3 - (1-*tert*butoxy-1-trimethylsilyloxymethylenyl)-2-carboxylate (5).** To a 0°C solution of 2.26 ml (10.7 mmol) of hexamethyldisilazane in 15 ml of THF was slowly added 7.0 ml (10.7 mmol) of *n*-butyllithium (1.53 M in hexanes). The reaction was stirred 5 min at 0°C and 10 min. at -78°C, then added via cannula to a -78°C solution of 2.70 g (8.23 mmol) **8** and 1.36 ml (10.7 mmol) TMSCl in 45 ml of THF. After stirring for 30 min at -78 °C, the dry ice bath was removed and the reaction allowed to warm for 30 min. The stir bar was removed and the reaction concentrated until almost all of the THF was removed, then 20 ml pentane added. The remainder of the solvent was then removed and the residue taken up in 40 ml pentane and filtered through celite. The filtercake was washed with 30 ml of pentane, and the filtrate

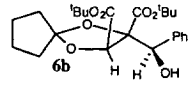
was concentrated, redissolved in 30 ml of pentane, and filtered again through celite. The filtercake was washed with 20 ml of pentane, and the filtrate was concentrated to give 3.21 g (97%) of **5** as an amber oil that was used immediately. ^{1}H NMR ($CDCl_3$, 400 MHz) 2:1 ratio of silylketene acetal isomers. δ 4.86 (s, 1H, major C*H*); 4.82 (s, 1H, minor C*H*); 2.00 (m, 2H, C(C*H*$_2$CH$_2$CH$_2$CH$_2$); 1.83 (m, 2H, C(C*H*$_2$CH$_2$CH$_2$CH$_2$); 1.70 (m, 4H, C(CH$_2$C*H*$_2$C*H*$_2$CH$_2$); 1.48 (s, 9H, major CO$_2$C(C*H*$_3$)$_3$); 1.33 (s, 9H, minor CO$_2$C(C*H*$_3$)$_3$); 1.30 (s, 9H, major CO(OSi(CH$_3$)$_3$)OC(C*H*$_3$)$_3$); 1.29 (s, 9H, minor CO(OSi(CH$_3$)$_3$)OC(C*H*$_3$)$_3$); 0.24 (s, 9H, major CO(OSi(C*H*$_3$)$_3$)OC(CH$_3$)$_3$); 0.18 (s, 9H, minor CO(OSi(C*H*$_3$)$_3$)OC(CH$_3$)$_3$).



Di-*tert*-butyl-(2*R*,3*S*)-2[(1*S*)-(1-hydroxypentyl)]-1,4-dioxaspiro[4.4]nonane-2,3-dicarboxylate (6a). To a solution of **5** (174 mg, 0.44 mmol) in 3 ml of CH_2Cl_2 at -78 °C was added a solution of Ti(OiPr)Cl$_3$ (0.47 mmol) in 1 ml of CH_2Cl_2. After 15 min, valeraldehyde (0.049 ml, 0.47 mmol) was added via syringe. The reaction was stirred for 3 h at -78 °C, then warmed to -40 °C and stirred overnight. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate, warmed to ambient temperature, and partitioned between EtOAc and water. The aqueous extracts were washed twice with EtOAc. The combined organic layers were washed with saturated brine, dried over sodium sulfate, and concentrated to give 150 mg of a yellow oil (91:9 mixture of diastereomers by ^{1}H NMR). Purification by flash chromatography (linear gradient 0-10% EtOAc/hexanes) afforded 87 mg (48%) of the major diastereomer **6a** as a clear oil. $[\alpha]_D^{23}$ +9.2 ° (*c* 1.35, CH_2Cl_2); IR (neat) 3509, 2959, 2934, 2874, 1740, 1700, 1458, 1394, 1369, 1336, 1257, 1225, 1159, 1120, 994 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49 (s, 1H, C$_1$*H*), 3.77 (ddd, *J* = 9.9, 8.3, 1.9 Hz, 1H, C$_3$*H*), 2.71 (d, *J* = 8.1 Hz, 1H, C$_3$O*H*), 2.06 (m, 2H, C(C*H*$_2$CH$_2$CH$_2$CH$_2$)), 1.80-1.31 (m, 12H, C(CH$_2$C*H*$_2$C*H*$_2$C*H*$_2$), HOCHC*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.48 (s, 9H, CO$_2$C(C*H*$_3$)$_3$), 1.47 (s, 9H, CO$_2$C(C*H*$_3$)$_3$), 0.89 (app. t, *J* = 7.1 Hz, 3H, -CH$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.3, 167.0, 121.9, 87.6, 83.2, 82.5, 79.9, 74.8, 37.7, 36.8, 31.3, 28.2, 27.9, 23.3, 22.4, 13.9; Anal. calcd. for NaC$_{22}$H$_{38}$O$_7$: C, 63.73; H, 9.24. Found: C, 63.84; H, 9.24. Exact mass calcd. for C$_{22}$H$_{38}$O$_7$Na: 437.2515; found: 437.2500 (EI).



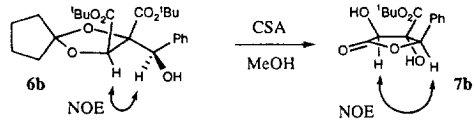
***Tert*-butyl-(3*S*,4*R*, 5*R*)-4-carboxy-3,4-dihydroxytetrahydro-2-oxo-5-butylfuran (7a).** To a solution of **6a** (36 mg, 0.09 mmol) in 2 ml of 1:1 CH_2Cl_2:MeOH was added camphorsulfonic acid (20 mg, 0.08 mmol). The resulting solution stirred 48 h at ambient temperature and an additional 24 h at reflux. The reaction was then cooled to ambient temperature, diluted with EtOAc, and washed with saturated aqueous solutions of sodium bicarbonate and sodium chloride. The organic layer was dried over sodium sulfate and concentrated. The residue was purified by flash chromatography (0-30% EtOAc:hexanes) to give 16 mg (68%) of a white, crystalline solid. m.p. 78-79 °C. $[\alpha]_D^{23}$ +54.4 ° (*c* 0.58, CH_2Cl_2); IR (KBr) 3474, 2951, 2872, 1779, 1742, 1471, 1369, 1229, 1152, 1097, 1006, 890, 848 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59 (d, *J* = 4.2 Hz, 1H, C$_1$*H*), 4.27 (t, *J* = 6.7 Hz, 1H, C$_3$*H*), 3.87 (s, 1H, C$_2$O*H*), 2.58 (d, *J* = 4.3 Hz, C$_1$O*H*), 1.66-1.55 (m, 2H, C$_4$*H*$_2$), 1.55-1.49 (m, 2H, C$_5$*H*$_2$), 1.51 (s, 9H, CO$_2$C(C*H*$_3$)$_3$), 1.38-1.35 (m, 2H, C*H*$_2$CH$_3$), 0.91 (t, *J* = 7.2 Hz, 3H, C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.6, 168.8, 85.9, 82.6, 81.0, 75.4, 28.3, 27.9, 22.3, 13.7; Anal. calcd. for C$_{13}$H$_{22}$O$_6$: C, 56.90; H, 8.09. Found: C, 57.15; H, 8.03. Exact mass calcd. for C$_{13}$H$_{26}$O$_6$N (M + NH$_4^+$): 292.1760; found: 292.1750 (CI).

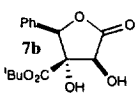


Di-*tert*-butyl-(2*R*,3*S*)-2-[(1*R*)-(hydroxyphenylmethyl)]-1,4-dioxaspiro[4.4]nonane-2,3-dicarboxylate (6b) To a -78 °C solution of benzaldehyde (0.025 ml, 0.25 mmol) in 1 ml of CH_2Cl_2 was added 0.23 ml (0.23 mmol) of Ti(O*i*Pr)Cl$_3$ (1 M sol'n in CH_2Cl_2). The reaction was stirred for 10 min at -78 °C, then a solution of 0.0871g (0.22 mmol) silylketene acetal **5** in 0.5 ml of CH_2Cl_2 was added. The reaction was allowed to stir at -78 °C for 1 h, then quenched by pouring into a vigorously stirred mixture of 10 ml of EtOAc and 10 ml of saturated aqueous NaHCO$_3$. The layers were mixed and separated and the aqueous layer extracted again with 10 ml of EtOAc. The combined organic layers were washed with 20 ml of brine, dried over MgSO$_4$, and concentrated to give di-*tert*-butyl-(2*R*,3*S*)-2-[(1*R*)-(hydroxyphenylmethyl)]-1,4-dioxaspiro[4.4]nonane-2,3-dicarboxylate as an 88:12 mixture of diastereomers at C$_3$. Flash chromatography (1.75 x 15 cm silica gel, linear gradient 7 - 30% EtOAc:hexane afforded 0.0073 g of the minor diastereomer (8%) and 0.0561 g of the major diastereomer **6b**

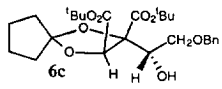
(59%). $[\alpha]_D^{23}$ +11°(*c* 3.51, CH_2Cl_2); IR (film) 3497, 2974, 1759, 1728, 1456, 1400, 1369, 1328, 1261, 1164, 1123, 1082, 1051, 995, 846, 702; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54 (m, 2H, Ar*H*); 7.38 - 7.30 (m, 3H, Ar*H*); 5.32 (d, *J* = 6.16 Hz, 1H, ArC*H*OH); 4.05 (s, 1H, *t*-BuO_2CC*H*); 2.88 (d, *J* = 6.18 Hz, 1H, ArCHO*H*); 2.24 (m, 1H, C(CH*H*$CH_2CH_2CH_2$)); 2.05 (m, 1H, C(CH*H*$CH_2CH_2CH_2$)); 1.65 (m, 3H, C(CH_2C*H*HC*H*$_2CH_2$)); 1.57 (s, 9H, $CO_2C(CH_3)_3$); 1.49 (s, 9H, $CO_2C(CH_3)_3$); 1.48 (m, 1H, C(CH_2C*H*HCH_2CH_2)); 1.28 (m, 1H, C(C*H*HC$H_2CH_2CH_2$)); 1.07 (m, 1H, C(C*H*HC$H_2CH_2CH_2$)); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.5, 165.7, 138.4, 128.7, 128.4, 127.9, 121.7, 87.7, 83.4, 83.0, 79.5, 75.5, 37.3, 36.2, 28.1, 28.0, 23.5, 23.0; TLC R_f = 0.33 (20% EtOAc:hexane); HRMS (*m*-nitrobenzylalcohol, added NaI) exact mass calcd for $C_{24}H_{34}O_7Na$: 457.2202 Found: 457.2217.

The stereochemical outcome of the aldol reaction was inferred following the method employed for **6a**:



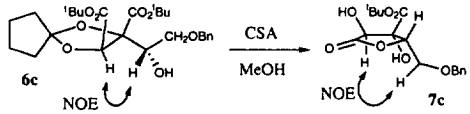


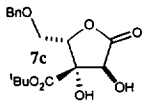
(3*S*,4*R*,5*R*)-4-carboxy-3,4-dihydrotetrahydro-2-oxo-5-phenylfuran, *tert*-butyl ester (7b). To a solution of 0.0507 g (0.12 mmol) **6b** in 1 ml of MeOH was added 0.005 g (0.02 mmol) CSA. After 46 h at room temperature, the reaction was diluted with 15 ml of EtOAc, washed with 10 ml of saturated $NaHCO_3$ solution and 10 ml of brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. Flash chromatography (1 x 14 cm silica gel, linear gradient 25 - 50% EtOAc:hexane afforded 0.0197 g **7b** (57%). $[\alpha]_D^{23}$ +10 °(*c* 1.23, CH_2Cl_2); IR (film) 3429, 2984, 2932, 1767, 1746, 1455, 1370, 1264, 1233, 1159, 1021, 841, 751, 703; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46 - 7.44 (m, 2H, Ar*H*); 7.39 - 7.33 (m, 3H, Ar*H*); 5.50 (s, 1H, ArC*H*); 4.80 (d, *J* = 4.22 Hz, 1H, O=CC*H*OH); 4.20 (s, 1H, CO*H*); 2.73 (d, *J* = 4.21 Hz, 1H, O=CHO*H*); 1.19 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.9, 167.8, 133.5, 128.6, 128.3, 124.8, 85.8, 84.1, 80.2, 75.6, 60.4, 27.4; TLC R_f = 0.03 (20% EtOAc:hexane); HRMS (EI) exact mass calcd for $C_{15}H_{18}O_6$: 294.1094, Found: 294.1103.



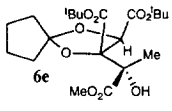
Di-*tert*-butyl-(2*R*,3*S*)-2-[(1*S*)-(2-benzyloxy-1-hydroxyethyl)]-1,4-dioxaspiro[4.4]nonane-2,3-dicarboxylate (6c) To a -78 °C solution of 0.0407g (0.271 mmol) benzyloxyacetaldehyde in 1.5 ml of CH_2Cl_2 was added 0.029 ml (0.264 mmol) of $TiCl_4$. The reaction was stirred 1 min at -78 °C, then added via cannula to 0.1278g (0.32 mmol) silylketene acetal **5** in 1.5 ml of CH_2Cl_2. The reaction was allowed to stir at -78 °C for 1 h, then quenched by pouring into a vigorously stirred mixture of 10 ml of EtOAc and 10 ml of saturated aqueous $NaHCO_3$. The layers were separated and the aqueous extracted again with 10 ml of EtOAc. The combined organic layers were washed with 20 ml of brine, dried over $MgSO_4$, and concentrated to give **6c** as a 91:9 mixture of diastereomers at C_3. Flash chromatography (1.75 x 15 cm silica gel, linear gradient 7 - 30% EtOAc:hexanes) afforded 0.0832 g of the major diastereomer (64%). $[\alpha]_D^{23}$ -1.3°(*c* 2.74, CH_2Cl_2); IR (film) 3499, 2976, 2940, 2874, 1755, 1719, 1457, 1370, 1334, 1254, 1225, 1162, 1123, 999, 847, 738; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 - 7.27 (m, 5H, Ar*H*); 4.81 (s, 1H, *t*-BuO_2CC*H*); 4.58 (d, *J* = 12.0 Hz, 1H, ArC*H*HO); 4.54 (d, *J* = 12.0 Hz, 1H, ArC*H*HO); 4.34 (ddd, *J* = 7.40, 7.40, 3.36 Hz, 1H, C*H*OH); 3.62 (dd, *J* = 10.1, 3.40 Hz, 1H, HOCHC*H*HOBn); 3.57 (dd, *J* = 10.0, 7.20 Hz, 1H, HOCHC*H*HOBn); 2.51 (d, *J* = 7.63 Hz, 1H, CHO*H*); 2.13 (m, 2H, C(C$H_2CH_2CH_2CH_2$)); 1.71 (m, 2H, C(CH_2C$H_2CH_2CH_2$)); 1.67 (m, 4H, C($CH_2CH_2CH_2CH_2$); 1.49 (s, 9H, $CO_2C(CH_3)_3$); 1.43 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.2, 166.2, 137.8, 128.3, 127.7, 121.4, 86.1, 82.9, 82.6, 78.1, 73.3, 70.8, 69.9, 37.8, 36.5, 27.9, 27.8, 23.6, 23.3; TLC R_f = 0.30 (20% EtOAc:hexane); HRMS (FAB *m*-nitrobenzylalcohol, added NaI) exact mass calcd for $C_{26}H_{38}O_8Na$: 501.2465 Found: 501.2444.

The stereochemical outcome of the aldol reaction was inferred following the method employed for **6a**:

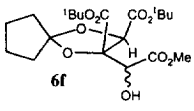




(3*S*,4*R*,5*S*)-5-benzyloxymethyl-4-carboxy-3,4-dihydro-2-oxo-tetrahydrofuran, *tert*-butyl ester (7c). To a solution of 0.0416 g (0.087 mmol) **6c** in 1 ml of MeOH was added 0.005 g (0.02 mmol) CSA. After 28 h at room temperature, the reaction was diluted with 15 ml of EtOAc, washed with 10 ml of saturated $NaHCO_3$ solution, and 10 ml of brine. The organic layer was dried over $MgSO_4$, filtered and concentrated.. Flash chromatography (1 x 14 cm silica gel, linear gradient 25 - 50% EtOAc:hexane) afforded 0.0148 g **7c** (50%). $[\alpha]_D^{23}$ -37 °(*c* 0.89, CH_2Cl_2); IR (film) 3489, 3404, 2977, 2935, 2870, 1775, 1721, 1369, 1311, 1220, 1161, 1135, 1103, 1055, 847, 730 ^1H NMR ($CDCl_3$, 400 MHz) δ 7.36 - 7.27 (m, 5H, Ar*H*); 4.88 (d, *J* = 4.09 Hz, 1H, O=CC*H*OH); 4.60 (d, *J* = 11.9 Hz, 1H, ArC*H*HO); 4.56 (d, *J* = 11.9 Hz, 1H, ArC*H*HO); 4.47 (t, *J* = 2.61 Hz, C*H*CH$_2$OBn); 3.96 (s, 1H, CO*H*); 3.84 (dd, 1H, *J* = 11.1, 2.37 Hz, CHCH_2OBn); 3.78 (dd, 1H, *J* = 11.1, 2.85 Hz, 1H, CHCH_2OBn); 2.83 (br d, *J* = 4 Hz, 1H, O=CHO*H*); 1.50 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.7, 170.1, 137.4, 128.5, 127.9, 127.7, 85.7, 80.0, 79.6, 73.8, 73.6, 67.3, 27.8 TLC R_f = 0.21 (30% EtOAc:hexane); HRMS (FAB, *m*-nitrobenzyl alcohol, added NaI) exact mass calcd for $C_{17}H_{22}O_7Na$: 361.1263, Found: 361.1262.



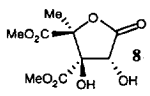
Di-*tert*-butyl-(2*S*,3*R*)-2[(1*S*)-methyl-1-carboxy-1-hydroxyethyl]-1,4-dioxaspiro[4.4]nonane-2,3-dicarboxylate (6e). To a solution of *ent*-**5** (174 mg, 0.44 mmol) in 2 ml of CH_2Cl_2 at -78 °C was added a solution of $Ti(OiPr)Cl_3$ (0.47 mmol) in 1 ml of CH_2Cl_2. After 15 min, methyl pyruvate (0.042 ml, 0.466 mmol) was added to the reaction via syringe. The resulting solution stirred at -78 °C for 2 h and was then stirred 12h at -40 °C. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate, warmed to ambient temperature, and partitioned between EtOAc and water. The aqueous extracts were washed twice with EtOAc. The combined organic layers were washed with saturated brine, dried over sodium sulfate, and concentrated to give 160 mg of a yellow oil. Purification by flash chromatography (linear gradient 0-10% EtOAc/hexanes) afforded 123 mg (66%) of a clear oil. $[\alpha]_D^{23}$ +22.2 ° (*c* 0.33, CH_2Cl_2); IR (neat) 3504, 2979, 2978, 2876, 1746, 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.86 (s, 1H, C$_1$*H*), 3.80 (s, 3H, CO_2CH_3), 3.70 (s, 1H, C$_3$O*H*), 2.21-1.99 (m, 4H, C(CH_2CH$_2$CH$_2$CH_2)), 1.83 (apparent t, *J* = 7.0 Hz, 2H, C(CH$_2$CH_2CH$_2$CH$_2$)), 1.69 (m, 2H, CCH$_2$CH$_2$CH_2CH$_2$)), 1.66 (s, 3H, C$_3$(OH)CH_3), 1.50 (s, 9H, $CO_2C(CH_3)_3$), 1.47 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.9, 168.4, 167.4, 122.8, 89.6, 82.88, 82.5, 79.4, 76.9, 53.0, 37.5, 36.7, 27.97, 27.91, 23.5, 23.0, 21.0; Anal. calcd. for $C_{21}H_{34}O_9$: C, 58.57; H, 7.96. Found: C, 58.75; H, 8.09. Exact mass calcd. for $C_{21}H_{34}O_9$: 430.2203; found: 430.2222 (EI)



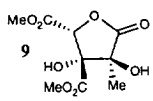
Di-*tert*-butyl-(2*S*,3*R*)-2[methyl-1-carboxy-1-hydroxyethyl]-1,4-dioxaspiro-[4.4]nonane-2,3-dicarboxylate (6f). To a -78 °C solution of 0.192 g (0.48 mmol) *ent*-**5** in 0.5 ml of CH_2Cl_2 was added freshly distilled methyl glyoxylate (0.042 g, 0.48 mmol). A solution of 0.48 mmol $Ti(OiPr)Cl_3$ in 0.5 ml of CH_2Cl_2 was then added via cannula to give a dark green-brown solution. After 90 min stirring at -78 °C, the reaction was quenched by the addition of saturated aqueous sodium bicarbonate, warmed to ambient temperature, and partitioned between EtOAc and water. The aqueous extracts were washed twice with EtOAc. The combined organic layers were washed with saturated brine, dried over sodium sulfate, and concentrated to give a yellow oil. Purification by flash chromatography (linear gradient 5-20% EtOAc/hexanes) gave 0.088 g (44%) of a clear oil. IR (neat) 3496, 2979, 1746, 1729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.83 (s, 1H, C*H*-CO$_2$tBu), 4.80 (s, 1H, C*H*-CO$_2$tBu), 4.80 (d, *J* = 7.7 Hz, 1H, C*H*OH), 4.68 (d, *J* = 8.6 Hz, 1H, C*H*OH), 3.83 (s, 3H, CO_2CH_3), 3.80 (s, 3H, CO_2CH_3), 3.44 (d, *J* = 8.6 Hz, CHO*H*), 3.25 (d, *J* = 8.6 Hz, CHO*H*), 2.20-2.10 (m, 2H, C(CH*H*CH$_2$CH$_2$CH$_2$)), 2.10-2.00 (m, 2H, C(CH*H*CH$_2$CH$_2$CH$_2$)), 1.80-1.55 (m, 12H, C(CH$_2$CH_2CH$_2$CH_2)), 1.502 (s, 9H, $CO_2C(CH_3)_3$), 1.497 (s, 9H, $CO_2C(CH_3)_3$), 1.49 (s, 9H, $CO_2C(CH_3)_3$), 1.48 (s, 9H,

$CO_2C(CH_3)_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.9, 171.0, 168.7, 168.5, 166.1, 165.8, 122.4, 121.7, 86.5, 86.3, 83.7, 83.0, 82.8, 79.0, 78.2, 73.8, 70.4, 53.1, 52.9, 38.0, 37.9, 36.8, 36.4, 28.01, 27.97, 27.92, 23.7, 23.6, 23.5, 23.4; Anal. calcd. for $C_{20}H_{32}O_9$: C, 57.66; H, 7.75. Found: C, 57.79; H, 8.13. Exact mass calcd. for $C_{20}H_{32}O_9$: 416.2047; found: 416.2044 (EI).

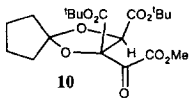
Lactones 8 and **9.** To a solution of **6e** (467 mg, 1.09 mmol) in 10 ml CH_2Cl_2 were added 5 ml of a 10:1 TFA:water solution. The resulting solution stirred at ambient temperature for 12 h. The reaction was concentrated; water and TFA were removed by coevaporation with toluene. The residue was dissolved in $MeOH/CH_2Cl_2$ and cooled to 0 °C. Diazomethane in ether was added dropwise until a yellow color persisted. The reaction was warmed to room temperature, concentrated, and purified by flash chromatography (0-2% $MeOH/CH_2Cl_2$) to give 236 mg (88%) **8** and 23 mg (8.5%) **9** as clear oils.



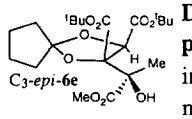
Dimethyl-(3*S*,4*R*,5*S*)-4,5-dicarboxy-2-oxo-5-methyl-3,4-dihydroxytetrahydrofuran (8). $[\alpha]_D^{23}$ +34.8 ° (*c* 0.465, CH_2Cl_2); IR (neat) 3448, 2961, 1801, 1749, 1636, 1282, 1221, 1155, 1101, 1057, 973, 800 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.07 (d, *J* = 4.4 Hz, 1H, C_1H), 3.97 (s, 1H, C_2OH), 3.93 (s, 3H, CO_2CH_3), 3.84 (s, 3H, CO_2CH_3), 2.70 (d, *J* = 4.4 Hz, 1H, C_1OH), 1.56 (s, 3H, C_3CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.8, 169.5, 169.1, 84.6, 83.9, 73.1, 53.8, 53.4, 17.4; Anal. calcd. for $C_9H_{12}O_8$: C, 43.54; H, 4.88. Found: C, 43.63; H, 5.00. Exact mass calcd. for $C_9H_{12}O_8$: 248.0532; found: 248.0540 (EI).



Dimethyl-(3*S*,4*R*,5*R*)-4,5-dicarboxy-2-oxo-3-methyl-3,4-dihydroxytetrahydrofuran (9). $[\alpha]_D^{23}$ -76.3 ° (*c* 0.563, CH_2Cl_2); IR (neat) 3462, 2960, 2924, 2853, 1800, 1750, 1438, 1374, 1283, 1223, 1125, 1098, 1022, 932, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.26 (s, 1H, C_1H), 3.92 (s, 3H, CO_2CH_3), 3.88 (s, 1H, O*H*), 3.83 (s, 3H, CO_2CH_3), 3.00 (s, 1H, O*H*), 1.56 (s, 3H, C_3CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.7, 170.3, 166.4, 80.8, 78.2, 54.1, 52.9,19.7; Anal. calcd. for $C_9H_{12}O_8$: C, 43.54; H, 4.88. Found: C, 43.26; H, 5.06. Exact mass calcd. for $C_9H_{16}NO_8$ (M + NH_4^+): 266.0876; found: 266.0862 (CI).



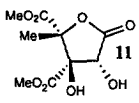
Di-*tert*-butyl-(2*R*,3*S*)-2-(methyl oxalyl)-1,4-dioxaspiro[4.4]nonane-2,3-dicarboxylate (10). To a -78 °C solution of oxalyl chloride (0.053 ml, 0.6 mmol) in 3 ml CH_2Cl_2 was added dimethyl sulfoxide (0.073 ml, 1.03 mmol). After 15 min, a solution of **6f** (177 mg, 0.43 mmol) in 2 ml CH_2Cl_2 was added to the reaction via cannula. The resulting suspension stirred for 30 min, after which triethylamine (0.300 ml, 2.15 mmol) was added via syringe. The reaction was warmed to 0 °C and quenched by addition of saturated aqueous ammonium chloride. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over sodium sulfate. and concentrated to give 175 mg of a yellow oil, which was purified by flash chromatography (0-15% EtOAc/hexanes) to give 138 mg (78%) of a clear oil. $[\alpha]_D^{23}$ -22.3 ° (*c* 0.36, CH_2Cl_2); IR (neat) 2980, 2878, 1743, 1684 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.21 (s, 1H, $CHCO_2(CH_3)_3$), 3.92 (s, 3H, CO_2CH_3), 2.21 (m, 2H, $C(CH_2CH_2CH_2CH_2)$), 1.76-1.62 (m, 6H, $C(CH_2CH_2CH_2CH_2)$), 1.48 (s, 18H, $CO_2C(CH_3)_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 185.1, 166.7, 164.3, 160.5, 124.5, 87.2, 84.7, 83.3, 77.9, 53.2, 37.7, 36.9, 27.9, 27.7, 27.6, 23.5, 23.2; Anal. calcd. for $C_{20}H_{30}O_9$: C, 57.94; H, 7.30. Found: C, 57.61; H, 7.26. Exact mass calcd. for $C_{20}H_{30}O_9$: 432.2234; found: 432.2235 (EI).



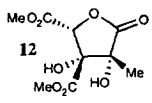
Di-*tert*-butyl-(2*S*,3*R*)-2[(1R)-methyl-1-carboxy-1-hydroxyethyl]-1,4-dioxaspiro[4.4]nonane-2,3-dicarboxylate (C_3-*epi*-**6e**). To a solution of **10** (66 mg, 0.16 mmol) in 3 ml tetrahydrofuran at -78 °C was added methylmagnesium bromide (0.14 μL, 0.40 mmol, 3.0 M solution in Et_2O). After 5 min, the reaction was quenched by addition of saturated aqueous ammonium chloride, warmed to ambient temperature, and partitioned between EtOAc and water. The aqueous layer was washed once with EtOAc. The combined organics were washed with saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated to give 66 mg of a yellow oil. Purification by flash chromatography (0-1% acetone/CH_2Cl_2) afforded 42 mg (61%) of a clear oil as a 2:1 (C_3-*epi*-**6e**:**6e**) mixture of isomers at the newly formed quaternary center. IR (neat) 3524, 2978, 1746, 1456, 1394,

1368, 1257, 1158, 1118, 979, 846 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, Major:minor = 2:1) δ 4.85 (s, 1H, C_1H [major]), 4.84 (s, 1H, C_1H [minor]), 3.95 (s, 1H, C_3OH [major]), 3.78 (s, 3H, CO_2CH_3 [minor]), 3.77 (s, 3H, CO_2CH_3 [major]), 3.67 (s, 1H, C_3OH [minor]), 2.15-2.01 (m, 2H + 4H, $C(CH_2CH_2CH_2CH_2)$ [major], $C(CH_2CH_2CH_2CH_2)$ [minor]), 1.82 (apparent t, J = 7.0 Hz, 2H, $C(CH_2CH_2CH_2CH_2)$ [minor]), 1.76 (apparent t, J = 7.2 Hz, 2H, $C(CH_2CH_2CH_2CH_2)$ [major]), 1.70-1.62 (m, 4H + 2H, $C(CH_2CH_2CH_2CH_2)$ [major], $C(CH_2CH_2CH_2CH_2)$ [minor]), 1.62 (s, 3H, C_3CH_3 [minor]), 1.57 (s, 3H, C_3CH_3 [major]), 1.49 (s, 9H, $CO_2C(CH_3)_3$ [minor]), 1.48 (s, 18H, $CO_2C(CH_3)_3$ [major]), 1.47 (s, 9H, $CO_2C(CH_3)_3$ [minor]); ^{13}C NMR (400 MHz, $CDCl_3$) Major isomer δ 173.9, 170.1, 167.45, 123.6, 88.7, 83.6, 82.6, 79.4, 78.8, 52.8, 37.4, 37.0, 27.9, 23.0, 21.0; Minor isomer δ 173.86, 168.4, 167.4, 122.8, 89.6, 82.8, 82.5, 79.35, 76.8, 52.9, 37.43, 36.7, 27.94, 23.4, 20.93; Anal. calcd. for $C_{21}H_{34}O_9$: C, 58.57; H, 7.96. Found: C, 58.51; H, 7.95. Exact mass calcd. for $C_{21}H_{34}O_9Na$: 453.2101; found: 453.2089 (FAB, *m*-nitrobenzyl alcohol, NaI added).

Lactones 11 and 12. To a solution of C_3-*epi*-**6e**/**6e** (250 mg, 0.58 mmol, 2:1 mixture of diastereomers) in 10 ml CH_2Cl_2 were added 5 ml of a 10:1 trifluoroacetic acid:water solution. The resulting solution stirred at ambient temperature overnight. The reaction was concentrated; water and trifluoroacetic acid were removed by coevaporation with toluene. The residue was dissolved in $MeOH/CH_2Cl_2$ and cooled to 0 °C. Diazomethane in ether was added dropwise until a yellow color persisted. The reaction was warmed to room temperature, concentrated, and purified by flash chromatography (0-2% $MeOH/CH_2Cl_2$) to give 32 mg **12** (22%) as a clear oil and 37 mg **11** (26%) as a crystalline solid. The balance of the material was comprised of lactones **8** (32 mg, 22%) and **9** (3.6 mg, 2.5%), which arose from the minor diastereomer **6e**.

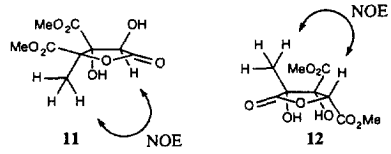


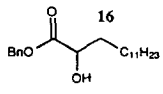
Dimethyl-(3*S*,4*R*,5*R*)-4,5-dicarboxy-2-oxo-5-methyl-3,4-dihydroxytetrahydrofuran (11). m.p. 165-168 °C. $[\alpha]_D^{23}$ -38.8 ° (*c* 0.77, acetone); IR (KBr) 3484, 2965, 1816, 1766, 1744, 1428, 1386, 1294, 1247, 1209, 1164, 1138, 1094, 1063, 975, 957, 778, 744 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 5.73 (d, J = 5.4 Hz, 1H, C_1OH), 5.40 (s, 1H, C_2OH), 4.80 (d, J = 5.1 Hz, 1H, C_1H), 3.71 (s, 3H, CO_2CH_3), 3.68 (s, 3H, CO_2CH_3), 1.65 (s, 3H, C_3CH_3); ^{13}C NMR (100.6 MHz, acetone-d_6) δ 171.0, 85.1, 84.4, 75.0, 53.0, 52.9, 21.8; Anal. calcd. for $C_9H_{12}O_8$: C, 43.54; H, 4.88. Found: C, 43.44; H, 4.94. Exact mass calcd. for $C_9H_{12}O_8$: 248.0532; found: 248.0520 (EI).



Dimethyl-(3*R*,4*R*,5*R*)-4,5-dicarboxy-2-oxo-3-methyl-3,4-dihydroxytetrahydrofuran (12). $[\alpha]_D^{23}$ -63.3 ° (*c* 1.08, CH_2Cl_2); IR (neat) 3460, 2961, 2924, 2854, 1801, 1772, 1744, 1441, 1372, 1283, 1236, 1201, 1114, 1081, 1051, 1019, 950, 855, 789, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.38 (s, 1H, C_1H), 4.39 (s, 1H, O*H*), 4.09 (s, 1H, O*H*), 3.93 (s, 3H, CO_2CH_3), 3.81 (s, 3H, CO_2CH_3), 1.47 (s, 3H, C_3CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.3, 168.5, 165.5, 81.2, 78.0, 76.8, 53.9, 53.1, 20.3; Anal. calcd. for $C_9H_{12}O_8$: C, 43.54; H, 4.88. Found: C, 43.67; H, 4.97. Exact mass calcd. for $C_9H_{16}O_8N$ ($M+NH_4^+$): 266.0876; found: 266.0867 (CI).

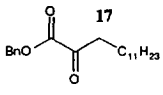
NOE studies corroborated the the information obtained from the X-ray data:



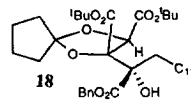


Benzyl-2-hydroxytetradecanoate (16). A solution of potassium hexamethyldisilazane (29 ml, 23.6 mmol, 0.82 M in THF) in 100 ml of THF was cooled to -40 °C. A solution of 5.0 g (15.7 mmol) benzyl myristate in 50 ml of THF was then added via cannula with the reaction temperature maintained below -39 °C. The resulting solution was stirred for 15 min at -40 °C, then cooled to -75 °C. A solution of 5.4 g (23.6 mmol) 2-(phenylsulfonyl)-3-phenyloxaziridine in 50 ml of THF was then added via cannula with the reaction temperature maintained below -69 °C. After 10 min stirring at -75 °C, the reaction was quenched by the addition of saturated aqueous ammonium chloride and allowed to warm to ambient temperature. The mixture was then partitioned between water and CH_2Cl_2. The aqueous

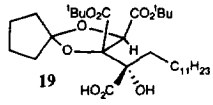
layer was washed once with CH_2Cl_2. The combined organic layers were dried over sodium sulfate and concentrated. Flash chromatography (linear gradient 1:49:50 - 2:48:50 EtOAc:CH_2Cl_2:hexanes) provided 3.2 g (61%) **16** as a clear oil. IR (neat) 3460(br), 2923, 2853, 1736, 1641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 5H, Ar*H*), 5.23 (d, *J* = 12.2 Hz, 1H, Ar-C*H*$_2$), 5.19 (d, *J* = 12.2 Hz, 1H, Ar-C*H*$_2$), 4.22 (ddd, *J* = 7.2, 5.8, 4.4 Hz, 1 H, C*H*OH), 2.75 (d, *J* = 5.8 Hz, 1H, CHO*H*), 1.78 (m, 1H, C*H*$_2$CHOH), 1.65 (m, 1H, C*H*$_2$CHOH), 1.25 (m, 20H, (C*H*$_2$)$_{10}$CH$_3$), 0.88 (t, *J* = 6.8 Hz, 3H, C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.3, 135.2, 128.6, 128.5, 128.3, 70.5, 67.2, 34.4, 31.9, 29.6, 29.5, 29.4, 29.33, 29.28, 24.6, 22.7, 14.1; Anal. calcd. for $C_{21}H_{34}O_3$: C, 75.39; H, 10.25. Found: C, 75.12; H, 10.11. Exact mass calcd. for $C_{21}H_{34}O_3$: 334.2508; found: 334.2495 (EI).



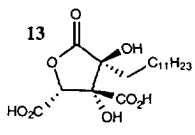
Benzyl-2-oxo-tetradecanoate (17). A solution of 1.12 ml (12.9 mmol) oxalyl chloride in 30 ml of CH_2Cl_2 was cooled to -78 °C. Dimethyl sulfoxide (1.57 ml, 22.1 mmol) was added via syringe; the resulting solution was stirred at -78 °C for 20 min. A solution of 3.1 g (9.2 mmol) **16** in 30 ml of CH_2Cl_2 was then added via cannula. The resulting suspension stirred for 25 min, after which 6.41 ml (46 mmol) triethylamine was added via syringe. The reaction was warmed to 0 °C and stirred for 45 min, then quenched with saturated aqueous ammonium chloride. The mixture was partitioned between water and CH_2Cl_2, and the aqueous layer was washed twice with CH_2Cl_2. The combined organic layers were washed with saturated ammonium chloride and water, then dried over sodium sulfate. Concentration *in vacuo* provided 3.1 g (100%) **17**, which was >95% pure as judged by ^1H NMR. Analytically pure material was obtained by recrystallization from hexanes, which afforded a white, crystalline solid (2.2 g, 72% recovery). The recrystallized material exhibited reactivity in the ensuing aldol identical to that of the quantitative product. m.p. 35-36 °C. IR (film) 2952, 2919, 2850, 1739, 1718, 1462, 1278, 1066, 904 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.35 (m, 5H, Ar*H*), 5.27 (s, 2H, Ar-C*H*$_2$), 2.82 (t, *J* = 7.3 Hz, 2H, BnO-COCO-C*H*$_2$), 1.65-1.58 (m, 2H, BnOCOCO-CH$_2$-C*H*$_2$), 1.26 (m, 18H, (C*H*$_2$)$_9$CH$_3$), 0.88 (t, *J* = 6.8 Hz, 3H, (CH$_2$)$_9$C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 194.3, 161.0, 134.5, 128.72, 128.66, 128.6, 67.8, 39.4, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 28.9, 22.9, 22.6, 14.1; Anal. calcd. for $C_{21}H_{32}O_3$: C, 75.85; H, 9.71. Found: C, 75.77; H, 9.66. Exact mass calcd. for $C_{21}H_{36}O_3N(M+NH_4^+)$: 350.2695; found: 350.2695 (CI).



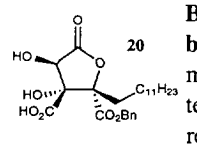
Di-*tert*-butyl-(2*S*,3*R*)-2[(1*S*)-benzyl-1-carboxy-1-hydroxydodecyl]-1,4-dioxaspiro[4.4]nonane-2,3-dicarboxylate (18). To a solution of *ent*-**5** (406 mg, 1.02 mmol) in 5 ml of CH_2Cl_2 at -78 °C was added a solution of $Ti(OiPr)Cl_3$ (1.07 mmol) in 1 ml of CH_2Cl_2. After 15 min, a -40 °C solution of **17** (373 mg, 1.12 mmol) in 5 ml of CH_2Cl_2 was added dropwise via cannula. The reaction was stirred for one hour at -78 °C, then warmed to -40 °C and stirred 12 h. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate, warmed to ambient temperature, and partitioned between EtOAc and water. The aqueous extracts were washed twice with EtOAc. The combined organic layers were washed with saturated brine, dried over sodium sulfate, and concentrated to give 670 mg of a yellow oil. Purification by flash chromatography (linear gradient 0-10% ethyl ether/pentane) afforded 409 mg (61%) of a clear oil. $[\alpha]_D^{23}$ +6.40 ° (*c* 1.05, CH_2Cl_2); IR (neat) 3517, 2926, 2854, 1732, 1730, 1455, 1393, 1368, 1256, 1221, 1159, 1119, 984, 846, 739, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.29 (m, 5H, Ar*H*), 5.46 (d, *J* = 12.3 Hz, 1H, Ar-C*H*$_2$), 5.06 (d, *J* = 12.3 Hz, 1H, Ar-C*H*$_2$), 4.89 (s, 1H, C$_1$*H*), 3.63 (d, *J* = 1.3 Hz, 1H, C$_3$-O*H*), 2.21-2.11 (m, 2H, C(C*H*$_2$CH$_2$CH$_2$CH$_2$)), 2.07-1.91 (m, 2H, C(CH$_2$CH$_2$CH$_2$C*H*$_2$)), 1.82 (t, *J* = 6.9 Hz, 2H, C$_4$*H*$_2$), 1.74-1.64 (m, 4H; C(CH$_2$C*H*$_2$C*H*$_2$CH$_2$)), 1.48 (s, 9H, CO$_2$C(C*H*$_3$)$_3$), 1.41 (s, 9H, CO$_2$C(C*H*$_3$)$_3$), 1.32-1.17 (m, 19H, (C*H*$_2$)$_{10}$CH$_3$), 0.88 (t, *J* = 6.9 Hz, 3H, C*H*$_3$), 0.77-0.74 (m, 1H, (C*H*$_2$)$_{10}$CH$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.9, 168.39, 167.38, 135.2, 128.5, 128.4, 128.2, 122.6, 89.9, 82.8, 82.5, 80.2, 79.4, 67.7, 37.5, 36.7, 32.9, 31.9, 29.7, 29.6, 29.5, 29.44, 29.35, 28.0, 27.9, 23.5, 23.3, 23.0, 22.7, 14.1; Anal. calcd. for $C_{38}H_{60}O_9$: C, 69.05; H, 9.16. Found: C, 69.01; H, 9.20. Exact mass calcd. for $C_{38}H_{60}O_9Na$: 683.4138; found: 683.4152 (FAB, *m*-nitrobenzyl alcohol, added NaI).



Di-*tert*-butyl-(2*S*,3*R*)-2[(1*S*)-1-carboxy-1-hydroxydodecyl]-1,4-dioxaspiro[4.4]nonane-2,3-dicarboxylate (19). To a solution of **18** (350 mg, 0.53 mmol) in 5 ml of absolute ethanol was added a slurry of 10% palladium on carbon (20 mg) in ethanol. The resulting suspension was stirred under a hydrogen balloon for 1 h. The reaction was then filtered through celite and concentrated to give 340 mg of a clear gum. Flash chromatography (20:78:2 EtOAc:hexanes:acetic acid) provided 292 mg (97%) of a clear gum. $[\alpha]_D^{23}$ -1.31 ° (*c* 0.752, CH_2Cl_2); IR (neat) 3502, 3221, 2926, 2854, 1744, 1730, 1458, 1369, 1337, 1256, 1159, 1119, 976, 846 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.83 (s, 1H, C_1H), 4.31 (s, 1H, C_3-O*H*), 2.17-1.99 (m, 3H, $C(CH_2CH_2CH_2CH_2)$), C_4HH), 1.90-1.71 (m, 3H, $C(CH_2CH_2CH_2CH_2)$, C_4HH), 1.69-1.50 (m, 4H; $C(CH_2CH_2CH_2CH_2)$), 1.50 (s, 9H, $CO_2C(CH_3)_3$), 1.49 (s, 9H, $CO_2C(CH_3)_3$), 1.40-1.19 (m, 19H, $(CH_2)_{10}CH_3$), 1.19-1.10 (m, 1H, $(CH_2)_{10}CH_3$), 0.88 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.6, 169.3, 167.3, 122.8, 89.3, 83.85, 82.7, 80.2, 79.4, 37.4, 36.8, 33.3, 31.9, 29.8, 29.62, 29.58, 29.52, 29.3, 29.0, 27.9, 27.8, 23.4, 23.1, 22.7, 14.1; Exact mass calcd. for $C_{31}H_{53}O_9$ ($M-H^-$): 569.3690; found: 569.3673 (FAB, negative ion).

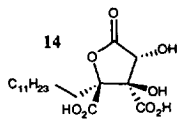


(-)-Cinatrin C_3 (13). To a solution of **19** (254 mg, 0.45 mmol) in 6 ml of CH_2Cl_2 was added 3 ml of a 10:1 trifluoroacetic acid:water solution. The resulting solution was stirred 12 h at ambient temperature. The reaction was concentrated; water and trifluoroacetic acid were removed by coevaporation with toluene. The residue was crystallized from methanol/water to afford 79 mg (47%) cinatrin C_3 as a white, crystalline solid. The mother liquor was concentrated and subjected to preparative HPLC (Zorbax Rx-C8, 21.2 x 250 mm, 50% H_2O/MeCN (0.1% trifluoroacetic acid), 20 ml/min) to afford an additional 35 mg cinatrin C_3 (21%, total 68%). 37 mg cinatrin C_1 (22%) were also isolated. Cinatrin C_3: m.p. 206-209 °C. $[\alpha]_D^{23}$ -84.9 ° (*c* 0.525, MeOH); $[\alpha]_D^{23}$ -76.3 ° (*c* 0.170, MeOH), natural $[\alpha]_D^{23}$ +73.2 ° (*c* 0.168, MeOH); HPLC (Zorbax Rx-C8, 4.6 x 25 mm, 45% H_2O/MeCN (0.1% trifluoroacetic acid), 1 ml/min) retention time 8.4 min, natural 8.4 min, co-injection 8.4 min; IR (KBr) 3530, 3375, 2923, 2852, 1828, 1728, 1697, 1442, 1384, 1257, 1167, 1118, 1062, 810 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 6.22 (s(br), 1H, C_2-O*H*), 5.32 (s, 1H, C_1H), 1.70-1.65 (m, 2H, C_4H_2), 1.40 (m, 2H, C_5H_2), 1.23 (m, 18H, $(CH_2)_9CH_3$), 0.84 (t, *J* = 6.8 Hz, 3H, CH_3); ^1H NMR (400 MHz, CD_3OD) δ 5.40 (s, 1H, C_1H), 1.83 (app. t, *J* = 8.4 Hz, 2H, C_4H_2); 1.55-1.41 (m, 2H, C_5H_2); 1.28 (m, 18H, $(CH_2)_9CH_3$); 0.89 (app. t, *J* = 6.9 Hz, 3H, CH_3); natural ^1H NMR (400 MHz, CD_3OD) δ 5.40 (s, 1H, C_1H), 1.83 (app. t, *J* = 8.4 Hz, 2 H, C_4H_2); 1.55-1.41 (m, 2H, C_5H_2); 1.28 (m, 18H, $(CH_2)_9CH_3$); 0.89 (app. t, *J* = 6.9 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, DMSO) δ 174.6, 170.5, 167.5, 81.3, 79.5, 78.8, 31.3, 30.6, 29.7, 29.1, 29.0, 28.7, 22.1, 21.1, 14.0; ^{13}C NMR (100.6 MHz, CD_3OD) δ 176.3, 172.6, 169.7, 82.5, 81.4, 80.4, 33.1, 32.3, 31.3, 30.8, 30.7, 30.6, 30.5, 23.7, 22.7, 14.4; natural ^{13}C NMR (100.6 MHz, CD_3OD) δ 176.3, 172.6, 169.7, 82.5, 81.4, 80.4, 33.1, 32.3, 31.3, 30.8, 30.7, 30.6, 30.5, 23.7, 22.7, 14.4; Anal. calcd. for $C_{18}H_{30}O_8$: C, 57.72; H, 8.08. Found: C, 57.64; H, 8.00. Exact mass calcd. for $C_{18}H_{29}O_8$: 373.1862; found: 373.1866 (FAB, $[M-H]^-$).



Benzyl-(3*R*,4*S*,5*S*)-2-oxo-3,4-dihydroxy-4-carboxy-5-dodecyl-tetrahydrofuran-5-carboxylate (20). To a solution of **18** (484 mg, 0.73 mmol) in 10 ml of CH_2Cl_2 were added 5 ml of a 10:1 trifluoroacetic acid:water solution. The resulting solution stirred at ambient temperature overnight. The reaction was concentrated; water and trifluoroacetic acid were removed by coevaporation with toluene. The residue was purified by flash chromatography (linear gradient 5:93:2 - 10:88:2 methanol:CH_2Cl_2:acetic acid) to give 323 mg (95%) of a white powder. $[\alpha]_D^{23}$ +37.9 ° (*c* 1.065, MeOH); IR (KBr) 3448, 2926, 2854, 1793, 1735, 1654, 1618, 1458, 1420, 1274, 1125, 1029, 848, 751, 697, 668 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.37-7.32 (m, 5H, Ar-*H*), 5.25 (d, *J* = 12.5 Hz, 1H, Ar-C*H*$_2$), 5.11 (d, *J* = 12.5 Hz, 1H, Ar-C*H*$_2$), 4.36 (s, 1H, C_1O*H*), 1.99-1.93 (m, 1H, C_4H_2), 1.76-1.70 (m, 1H, C_4H_2), 1.38-0.99 (m, 20H, $(CH_2)_{10}CH_3$), 0.84 (t, *J* = 6.7 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz,

DMSO-d_6) δ 173.6, 169.5, 135.5, 128.4, 128.1, 128.0, 87.2, 83.2, 72.4, 66.7, 31.3, 31.1, 29.2, 29.0, 28.8, 28.7, 23.4, 22.1, 13.9; Exact mass calcd. for $C_{25}H_{35}O_8$ [(M-H)$^-$]: 463.2332; found: 463.2354 (FAB, negative ion).



(+)-Cinatrin C_1 (14). To a solution of 88 mg (0.19 mmol) **20** in 5 ml of absolute ethanol was added a slurry of 10% palladium on carbon (10 mg) in ethanol. The resulting suspension was stirred under a hydrogen balloon for 40 min. The reaction was then filtered through celite and concentrated to give 63 mg (89%) of a white powder. This material was >95% pure by ^{1}H NMR but exhibited an anomalous C_1H chemical shift (δ 4.31; *lit.* δ 4.56). Submission of this material to reverse-phase HPLC (Zorbax Rx-C8, 21.2 x 250 mm, 50% H_2O/MeCN (0.1% trifluoroacetic acid), 20 ml/min) under conditions similar to those reported[11] for isolation of natural cinatrin C_1 provided, in 70% recovery, a white powder which exhibited analytical data comparable to those reported for the natural material. m.p. 164-166 °C. $[\alpha]_D^{23}$ +9.7 ° (*c* 0.319, MeOH); HPLC (Zorbax Rx-C8, 4.6 x 25 mm, 45% H_2O/MeCN (0.1% trifluoroacetic acid), 1 ml/min) retention time 7.6 min, natural 7.6 min, co-injection 7.6 min; IR (KBr) 3452, 2920, 2852, 1797, 1738, 1258, 1171, 1126, 1037, 826, 641 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.37 (br s, 1H, -O*H*), 4,53 (s, 1H, C_1O*H*), 2.02 (m, 1H, C_4*H*), 1.54 (m, 1H, C_4*H*), 1.21 (m, 20H, $(CH_2)_{10}CH_3$), 0.83 (app. t, *J* = 6.2 Hz, CH_3); ^{1}H NMR (400 MHz, CD_3OD) δ 4.71 (s, 1H, C_1*H*), 2.15 (ddd, *J* = 13.3 Hz, 4.2 Hz, 1.7 Hz, 1H, C_4*H*); 1.69 (ddd, *J* = 13.6 Hz, 11.3 Hz, 2.4 Hz, 1H, C_4*H*); 1.51 (m, 1H, C_5*H*); 1.38 (m, 1H, C_5*H*); 1.28 (m, 18H, $(CH_2)_9CH_3$); 0.89 (app. t, *J* = 6.9 Hz, 3H, CH_3); natural ^{1}H NMR (400 MHz, CD_3OD) δ 4.69 (s, 1H, C_1*H*), 2.14 (app. t, *J* = 8.4 Hz, 2 H, C_4H_2); 1.70 (m, 2H, C_5H_2); 1.50 (m, 1H, C_5*H*); 1.39 (m, 1H, C_5*H*); 1.28 (m, 18H, $(CH_2)_9CH_3$); 0.89 (app. t, *J* = 6.9 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 173.3, 170.2, 170.1, 86.4, 83.9, 73.0, 31.3, 30.9, 29.3, 29.1, 29.0, 28.9, 28.7, 23.6, 22.1, 14.0; ^{13}C NMR (100.6 MHz, CD_3OD) δ 175.5, 172.0, 88.4, 85.5, 74.6, 33.1, 32.7, 30.84, 30.75, 30.6, 30.5, 30.4, 25.1, 23.7, 14.4; natural ^{13}C NMR (100.6 MHz, CD_3OD) δ 175.6, 172.0, 74.6, 33.1, 32.7, 30.84, 30.75, 30.6, 30.5, 30.4, 25.1, 23.7, 14.4; Exact mass calcd. for $C_{18}H_{29}O_8$[(M-H)$^-$]: 373.1862; found: 373.1855 (FAB negative ion).

Acknowledgement. Financial support was provided by the NSF and the NIH. Predoctoral fellowships from the NSF (J.C.B. and B.W.T.) and Eli Lilly (J.C.B.) are gratefully acknowledged. We thank Dr. Toshiyuki Kamigauchi of Shionogi Research Laboratories for natural samples of cinatrins C_1 and C_3. We acknowledge the NIH BRS Shared Instrumentation Program 1-S10-RR04870 and the NSF (CHE 88-14019) for providing NMR facilities, Dr. Andrew Tyler of the Harvard Mass Spectrometry Facility for providing mass spectra, and Jeff Long for performing X-ray crystallographic analysis.

References and Footnotes

(1) Seebach, D. In *Modern Synthetic Methods*; R. Scheffold, Ed.; Verlag: Frankfurt, 1980; Vol. 2; pp 93-171.

(2) For examples, see Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; I. Ojima, Ed.; VCH: New York, 1993; pp 103-158 (asymmetric epoxidation) and Maruoka, K.; Yamamoto, H. In *Catalytic Asymmetric Synthesis*; I. Ojima, Ed.; VCH: New York, 1993; pp 413-440 (Lewis acid-mediated reactions).

(3) Itazaki, H.; Nagashima, K.; Kawamura, Y.; Matsumoto, K.; Nakai, H.; Terui, Y. *Journal of Antibiotics* **1992**, *45*, 38-49.

(4) Naef, R.; Seebach, D. *Angew. Chem. Int. Ed. Eng.* **1981**, *20*, 1030-1031. For the related alkylation of threonine-derived ketals see: Seebach, D.; Aebi, J. D.; Gander-Coquoz, M.; Naef, R. *Helv. Chim. Acta* **1987**, *70*, 1194-1216.

(5) (a) Evans, D. A.; Barrow, J. C.; Leighton, J. L.; Robichaud, A. J. *J. Am. Chem. Soc.* **1994**, *116*, 12111-12112. (b) Evans, D. A.; Barrow, J. C.; Leighton, J. L.; Sefkow, M.; Robichaud, A. J. *J. Am. Chem. Soc.* **1997**, manuscript in preparation.

(6) Silylketene acetal **5** is formed as a 2:1 mixture of (*E*) and (*Z*) isomers (reference 5). A single isomer is arbitrarily depicted in the illustrations in this paper.

(7) Proof of stereochemistry for adduct **6d** is detailed in reference 5.

(8) Details of the X-ray crystal structure have been provided.

(9) Similar models have been proposed for aldol reactions of silylketene acetals: (a) Gennari, C.; Bernardi, A.; Colombo, L.; Scolastico, C. *J. Am. Chem. Soc.* **1985**, *107*, 5812-5813 (titanium enolates) and (b) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1992**, *57*, 1324-1326 (tin-mediated aldols).

(10) An analogous chairlike transition state involving the other titanium enolate olefin isomer would provide the opposite C_3 diastereomer. The second enolate isomer may be less reactive due to steric hindrance (by C_1H, for example) of the approach of the electrophile. While we have not rigorously investigated the implication that the titanium enolate isomers can equilibrate under the reaction conditions, work in these laboratories has shown that titanium enolate isomers obtained via transmetallation of silyl enol ethers will equilibrate (Duffy, Joseph L. Ph.D. Thesis, Harvard University, 1996).

(11) Tanaka, K.; Itazaki, H.; Yoshida, T. *Journal of Antibiotics* **1992**, *45*, 50-55.

(12) Williams, K.; Halpern, B. *Synthesis* **1974**, 727-728. We prepared benzyl myristate in 95% yield via acid-catalyzed esterification of myristic acid (benzyl alcohol, *p*-toluenesulfonic acid, refluxing benzene, Dean-Stark apparatus).

(13) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241-3243.

(14) The crystalline α-ketoester **17** is sensitive to silica gel and is therefore used without further purification (>95% pure by ^1H NMR). Analytically pure material (which reproducibly gives yields and selectivities identical to the crude material in the ensuing aldol reaction) can be obtained by recrystallization from hexanes.

(15) There is apparently an error in the sign of the optical rotation of natural cinatrin C_3 reported by Itazaki and coworkers (reported as -86.1 ° in reference 3); our measurements of the natural sample provided by Dr. Kamigauchi gave the positive optical rotation reported here.

(16) The ^1H NMR spectrum of synthetic cinatrin C_1 was highly dependent on the conditions of isolation. Material isolated directly from the hydrogenolysis was >95% pure by ^1H NMR but exhibited an anomalous C_1H chemical shift. Submission of this material to preparative HPLC conditions similar to those of Itazaki (reference 8) provided cinatrin C_1 which exhibited a ^1H NMR spectrum identical to that of the natural sample.

(17) We did not receive a sufficient amount of natural cinatrin C_1 to measure an optical rotation with our instrumentation.

(18) Kelly, T. R.; Schmidt, T. E.; Haggerty, J. G. *Synthesis* **1972**, 544-545.

(19) Uray, G.; Lindner, W. *Tetrahedron* **1988**, *44*, 4357-4362.

(*Received* 31 *January* 1997; *accepted* 18 *March* 1997)