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Acylketene Acetals in Organic Synthesis.

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Abstract: The preparation and reactivity of achiral and enantiomerically pure acylketene acetals are described. The key reactions of these substrates involve facile conjugate hydroboration and organolithium addition. Enantiomerically pure acylketene acetals were employed to generate a homochiral β-keto ketal through a highly diastereoselective lithium enolate quench. This β-keto ketal, which was also prepared through a desymmetrization ketalization reaction on a meso dione, was employed in the synthesis of the insect pheromone sitophilure.

Recently, this laboratory has been engaged in the study of enantiomerically pure ketene acetals.[2] Herein are described, in full detail, our efforts in the area of acylketene acetal chemistry (*i* in Figure 1).[3]

Literature suggests that the chemical investigation of acylketene acetals is limited.[4] Considerably more attention has been spent on related compounds, such as acylketene dithioacetals,[5] mono- and bis-silylketene acetals,[6] and enaminoesters.[7] The preparation of simple acylketene acetals, in generally poor yield, by McElvain and coworkers in the early 1950's appears as the first example of these molecules in organic synthesis.[8] Parker[9] prepared simple acylketene acetals by treating the corresponding 3-oxo-(2-haloethyl)-esters with base. This same reaction was employed later by Broadhurst.[10]

Acylketene acetals have found use as dienes[11] and diene precursers[12] in Diels-Alder reactions, while Vandewalle and coworkers have investigated acylketene acetals in [$_{\pi}2$ + $_{\pi}2$] photocycloadditions.[13] The regioselectivity in these latter reactions was excellent owing to the electron donation from the β-ethoxy groups. Raucher, *et al.*, reacted ethyl β,β-diethoxyacrylate with allylic alcohols to produce allylmalonate esters through a [3,3] sigmatropic rearrangement.[14]

Acylketene acetals are highly polarized because of the electron donation to the enone's π-system from the acetal oxygens. As a consequence, the three carbon unit of the enone should function effectively, as either an electrophile (at the carbonyl carbon and β-position) or as a nucleophile (at the α-position).

As depicted below in Figure 1, the possibility of a stereoselective approach to β-hydroxy carbonyl compounds from acylketene acetals seemed attractive for a number of reasons. First, development of this methodology would provide for a unified approach to aldol-type products in two oxidation states; that is, β-hydroxy ketones/aldehydes and β-hydroxy acids. To the best of our knowledge, no other route to the array of aldol products, from a single substrate, is currently available. Second, the asymmetric syntheses of β-hydroxy ketones are few in comparison to the number developed for β-hydroxy acids.[15,16] Our methodology would provide a new route to these substrates. Finally, our proposed approach to β-hydroxy carbonyls does not involve the formation of the "aldol" bond in the key stereochemistry-generating step.[17] Thus, there was the anticipation that different modes of stereochemical manipulation would be possible as compared to the conventional aldol reaction.

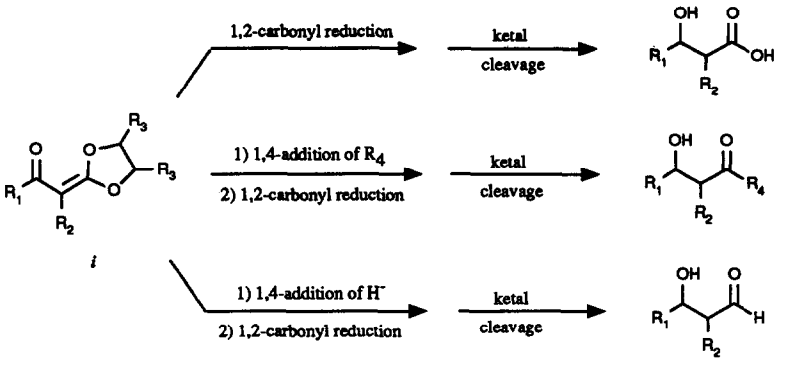
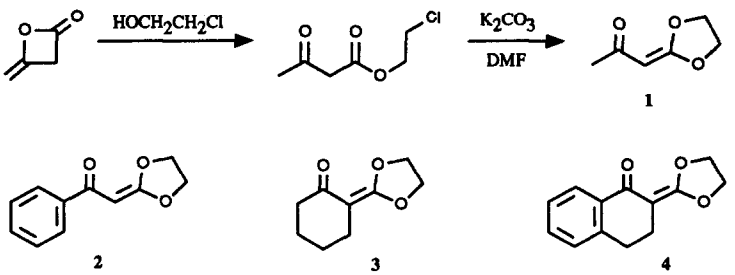


Figure 1

Studies on Achiral Acylketene Acetals.

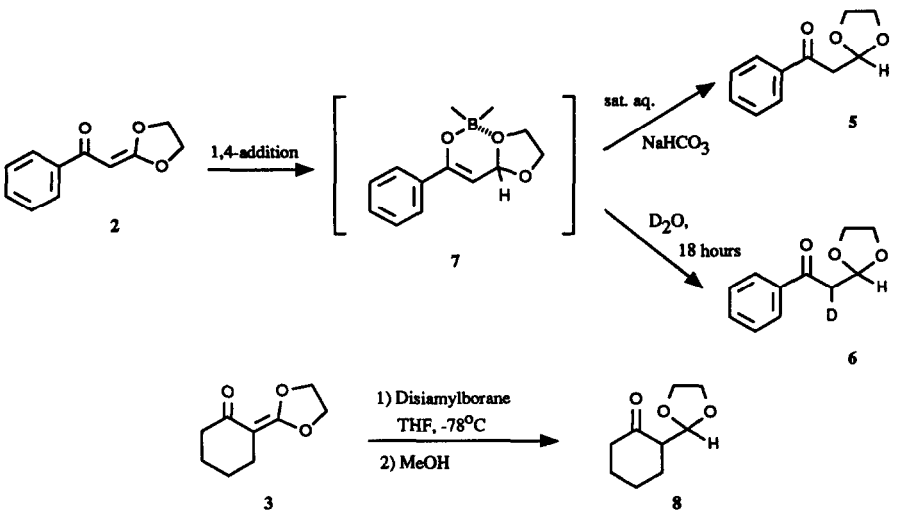
The investigation began with the synthesis of simple achiral substrate by following the method of Broadhurst.[10] This methodology relies on intramolecular *O*-alkylation of a 3-oxo-(2-haloethyl)ester enolate generated *in situ* with excess K_2CO_3 in DMF. The subsequent ring closure followed in a 5-(*Enolexo*)-*Exo*-*Tet*[18] manner. The resulting acylketene acetals were isolated in good to excellent yields by simple filtration of the reaction solution and solvent removal. In addition to repeating the Broadhurst synthesis of **1**, we also prepared **2**, **3** and **4** from acetophenone, cyclohexanone and α-tetralone, respectively, via β-keto methylester formation (NaH, $(CH_3O)_2C{=}O$) and titanate transesterification[19] (β-chloroethanol, $Ti(O\text{-}i\text{-}Pr)_4$) prior to cyclization.



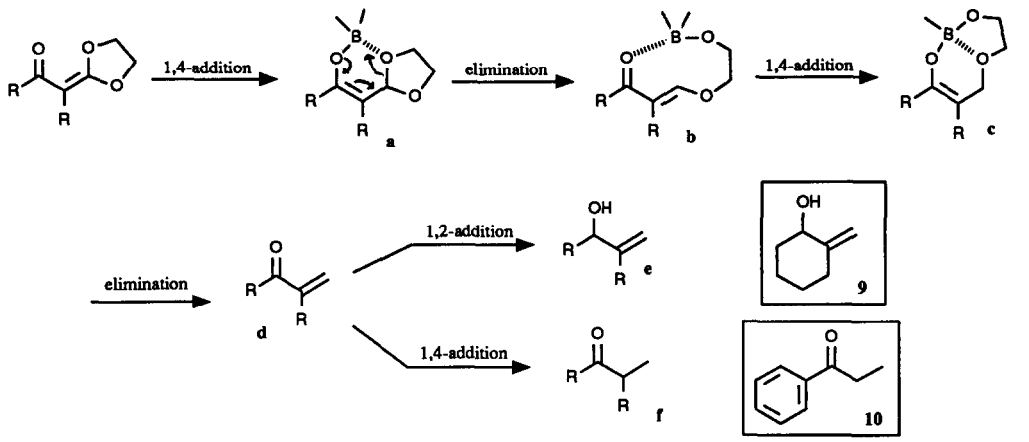
Hydride reduction of the carbonyl moiety of an acylketene acetal would produce an α-unsubstituted-β-hydroxy acid upon ketal removal. Such compounds have proven difficult to prepare by conventional aldol procedures.[20] Treatment of both **1** and **3** with $LiAlH_4$ at -78°C resulted in a multitude of products. Reduction of **2** with H_3B:THF complex at -78°C for 30 minutes in THF, followed by mild protic workup, yielded the β-keto acetal **5** in 70% isolated yield. Similar results were obtained with thexylborane, disiamylborane and catecholborane. Use of a D_2O workup resulted in a single deuterium atom introduced in the α-position, providing **6**, thereby suggesting the intermediacy of boron enolate **7**.[21-23]

Nonaromatic acylketene acetal **3** also served as a substrate for this conjugate hydroboration reaction. Reaction of **3** with disiamyl borane at -78°C in THF for 10 minutes, followed by MeOH quench, provided **8** in 50% isolated unoptimized yield.

When higher temperature and/or more equivalents of the borane reagent were employed, the yield of β-keto acetal **8** diminished and ring-opened products, such as **9**, were isolated in substantial yields. Aberrant product **10** was isolated from the borane reductions of **2** under similar conditions. These unexpected reaction products may be accounted for by the further reduction of the substrate via electron donation induced cleavage.[24]

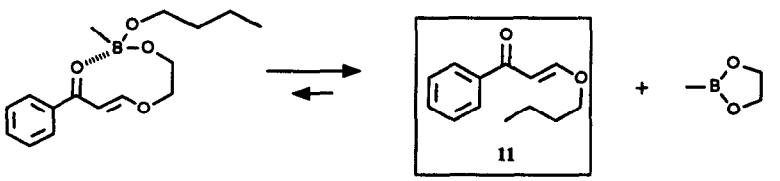


It is reasonable to assume that an unshared electron pair from an acetal oxygen could coordinate with the vacant boron *p*-orbital as in boron enolate **a**. This liaison would facilitate β-elimination to produce **b**. Conjugate hydride addition would generate another chelated boron enolate **c**. A second β-elimination would occur to form enone **d**. Enone **d** could undergo either 1,2-reduction to allyl alcohol **e** (synonymous with **9**) or 1,4-reduction to ketone **f** (synonymous with **10**).



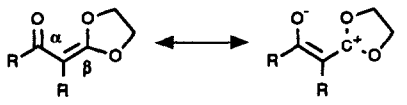
Additionally, irregular product **11** was isolated in 24% yield from a reaction of **2** that employed an old bottle of BH_3:THF (titer down from 1.0 *M* to 0.73 *M*).[25] Borane reductively cleaves THF and slowly forms tri-*n*-butyl borate at, or below, room temperature.[26] The presence of product **11** suggests that, during the addition-elimination sequence above, an equilibrium exists in which borate is able to exchange the butoxide ligand for the bidentate glycol moiety of the substrate.[27]

The overall conjugate hydroboration-reduction of enones is uncommon but has been observed in several other conjugated systems.[23b,28] One would also expect the enone system of an acylketene acetal to be electronically activated through positive charge stabilization from the acetal oxygens as shown in the resonance structure below. Indeed, the ^{13}C NMR resonances of these enone systems indicate the β-position to be very electropositive (Table 1).[29] Additionally, the enforced *cisoid* geometry of acylketene acetal **3** is



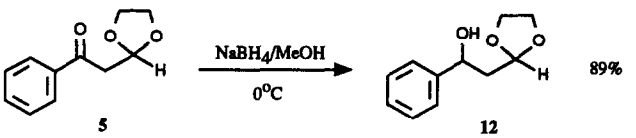
ideal for precomplexation of the borane reagent. This facilitates the formation of a six-center transition state for hydride transfer.[30] The IR spectrum of **2** suggests that it also assumes a *cisoid* geometry, since the enone's C=C stretching absorption near 1570 cm^{-1} is as intense as the C=O stretch at 1659 cm^{-1}.[31]

Table 1

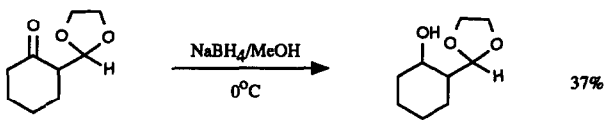


	^{13}C NMR (δ)		
	carbonyl carbon	α	β
1	195.0	79.8	168.0
2	197.8	87.1	165.3
3	188.2	74.8	170.0
4	185.7	86.2	165.8

Melillo, *et al.*, reduced the boron enolate of a vinylogous urethane with $NaCNBH_3$ in acetic acid.[23b] Attempted reduction of the boron enolate derived from **3** to the corresponding β-hydroxy acetal in a similar manner was unsuccessful. However, reduction of β-keto acetals **5** and **8** to the corresponding β-hydroxy acetals **12** and **13**, respectively, with $NaBH_4$ in methanol at 0°C was successful. Product **13** was present as an approximately 1 to 1 mixture of *syn* to *anti* isomers as evidenced by ^1H NMR integration of the acetal proton.



5 12

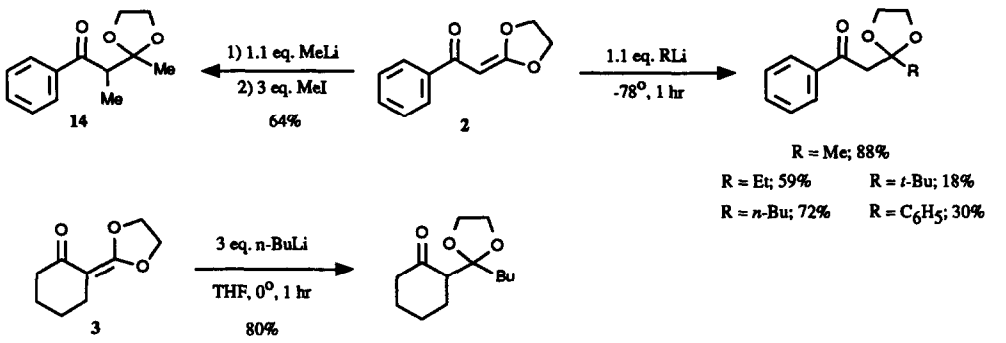


8 13

Following these initial studies of hydroboration, the use of organometallic reagents was investigated. The addition of either methyl-, ethyl- or *n*-butyllithium to **2** in THF at -78°C for 1 hour followed by mild acid workup gave very good yields of conjugate addition products, with no evidence of 1,2-addition occurring. In these unoptimized preliminary reactions, *t*-butyllithium gave only an 18% yield of 1,4-addition product. Slightly better results were obtained with phenyllithium, which provided a 30% yield of 1,4-addition product. Hydrolyzed starting material (resulting from the workup) was the only other isolated compound.

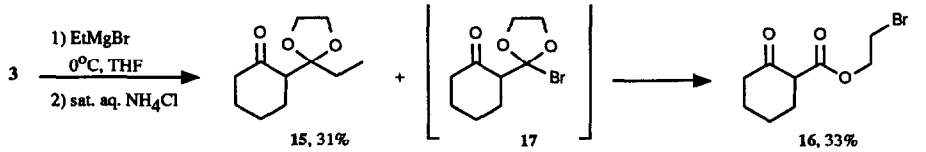
Compound **3** also served as a substrate for these transformations, although reaction conditions played a more critical role. Only at higher temperatures and with an excess of alkyllithium reagent did this compound give a satisfactory yield of 1,4-addition product with *n*-BuLi. Experiments conducted at lower temperatures indicated competition of the 1,2-addition pathway. This difference in reactivity *vis á vis* **2** could be due to the acidic α′-hydrogens present and/or to the extended π-system of **3** versus **2**.[32]

The intermediacy of a lithium enolate in the above reactions was demonstrated by alkylation at the α-position with methyl iodide. Addition of excess methyl iodide after the initial reaction of **2** with



methyllithium in THF at -78°C, followed by warming to room temperature, afforded **14** in 64% unoptimized yield. Also, the product from proton quench of the enolate was isolated in 16% yield, indicating that the intermediate enolate is somewhat unreactive. Indeed, attempts to react acylketene acetal/methyl lithium reaction mixtures with the less electrophilic allyl bromide were unsuccessful. This lack of reactivity may be a manifestation of the acylketene acetal functioning as a bidentate ligand for the metal ion.

The addition of Grignard reagents were also studied. Compound **3** reacted with EtMgBr at 0°C in THF to provide **15** in 31% isolated yield. Also isolated from this reaction was β-bromo ethyl ester **16** in 33% yield. One explanation for this unexpected product would involve the conjugate addition of Br^- to produce unstable bromoacetal **17**, which subsequently decomposes to provide **16**.[33] In Et_2O solvent production of **16** was suppressed but 1,2-addition of Et^- became problematic. The reaction of **3** with EtMgI and EtMgCl, under a wide variety of reaction conditions, gave mixtures of 1,2- and 1,4-addition products (in approximately equal molar ratios) with no evidence of conjugate halide addition. Compound **3** did not react with higher order cuprates,[34] $Et_3ZnMgBr$[35] and Et_2Zn.[36] This lack of reactivity may be the result of conformational and/or electronic factors. Yamamoto *et al.*[37] and Oppolzer *et al.*[38] have suggested that *cisoid* conformers react more poorly than *transoid* conformers with certain organocuprates. These conclusions are supported by the theoretical calculations of Morokuma and coworkers, which have shown the importance of enone conformation as it relates to regioselective additions of organocopper reagents.[39] Alternatively, or in addition, to this conformational question is the role of the β-oxygen substituents. Alexakis *et al.*[40] and Nakamura *et al.*[41] have demonstrated that no reaction will occur between an organocuprate and the mono-enol ether of a 1,3-cyclohexanedione. Nonspecific coupling occurred only with the addition of a Lewis acid to produce mixtures of 1,2- and 1,4-adducts. Likewise, Boring and Sindelar noted problems with the addition of organocuprates to pyranones.[29b]

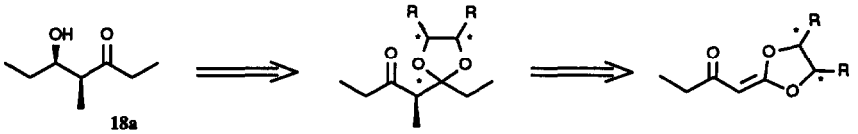


Studies on Enantiomerically Pure Acylketene Acetals

The synthesis and reactivity of enantiomerically pure acylketene acetals were explored next. As a test case, the synthesis of the rice and maize weevil aggregation pheromone "sitophilure" ((4*S*, 5*R*)-5-hydroxy-4-methyl-3-heptanone, **18a**[42]) was pursued. Several synthetic routes have been developed toward this agriculturally important molecule,[43] and analytical data exists on all four stereoisomers,[43a] allowing for the ready determination of the sense of induced chirality.

The strategy, shown in retrosynthetic form below, was to add ethyllithium to a homochiral acylketene acetal and quench the resulting enolate diastereofacially with methyl iodide. The resulting β-keto acetal,

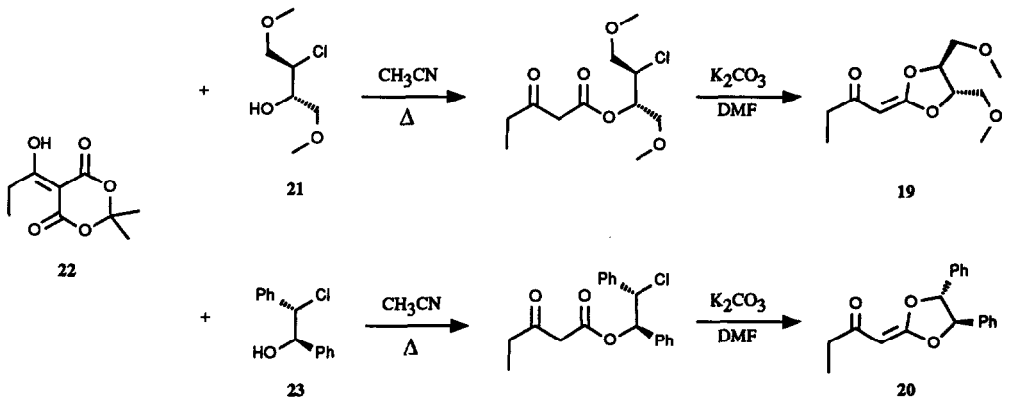
having the correct methyl stereochemistry, would be reduced stereoselectively to β-hydroxy acetal. Removal of the acetal auxiliary would give sitophilure.



18a

Two homochiral acylketene acetals, **19** and **20**, were initially chosen for these experiments. The auxiliary substituents of **19**, methoxy methyl groups, could be capable of providing additional metal chelation for the initial enolate quench reaction and for the subsequent reduction of the carbonyl functionality. Matsumoto and coworkers[44] successfully used a homochiral acetal with methoxy methyl auxiliaries for the stereoselective reduction of a β-keto acetal. Compound **20**, with phenyl substituents, could exert control through electronic and/or steric effects.

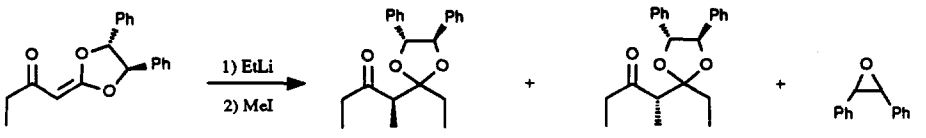
The homochiral halohydrin required for the auxiliary of substrate **19**, (2*S*,3*R*)-1,4-dimethoxy-3-chloro-2-butanol (**21**), was derived from natural (*R*,*R*)-tartaric acid.[45] Reacting alcohol **21** with Meldrum's acid adduct **22**[46] affords the corresponding ester in 82% isolated yield. Cyclization of this ester with K_2CO_3 in DMF proceeded smoothly to acylketene acetal **19** in 97% isolated yield. In like manner, **22** reacted with enantiomerically pure β-chloro alcohol **23**[45] to give β-keto ester product in 98% isolated yield. Cyclization to acylketene acetal **20** with K_2CO_3 in DMF occurred in 95% isolated yield.



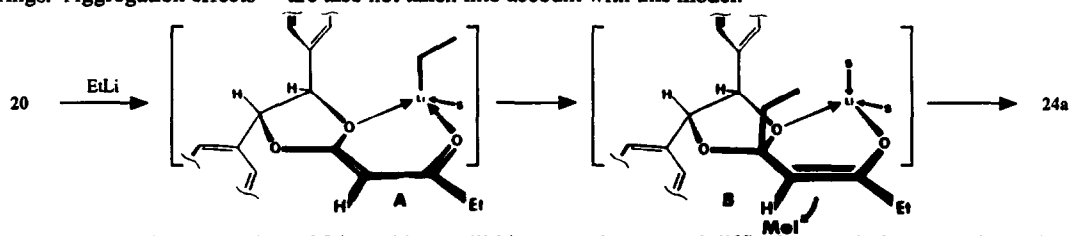
Our attempts to effect conjugate addition of EtLi[47] to substrate **19**, with a subsequent MeI quench, were unsuccessful. Complex mixtures of desired material together with both 1,2-carbonyl addition product and α′-alkylated adduct were routinely produced. The best isolated yield of conjugate addition product was 24% with the diastereomers isolated by HPLC in a ratio of 3 to 1. Reactions with higher order cuprates[34] were also unsuccessful. The use of EtMgCl resulted in 1,2-carbonyl addition in good yield.

The addition of ethyllithium to **20** at 0°C in THF, followed by MeI quench, gave the diastereomers **24a** and **24b** in 42% combined, isolated yield. Neither GC nor HPLC analysis were able to differentiate between **24a** and **24b**, but ^{1}H NMR at 300 MHz indicated the ratio of **24a** to **24b** to be in excess of 10 to 1, respectively. Also, variable but substantial yields of stilbene oxide and unmethylated material were consistently isolated from this reaction. It was discovered that when more than one equivalent of ethyllithium was employed, the yield of **24** would significantly diminish and the amount of stilbene oxide would increase. This may have been the result of acetal fragmentation within the lithium enolate, as previously described for the boron enolates formed from achiral acylketene acetals.

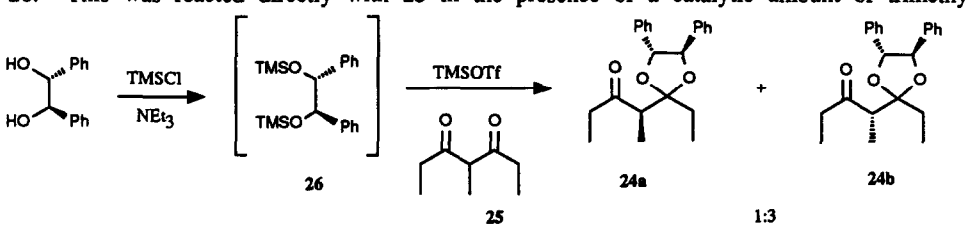
The substantial diastereoselectivity of this reaction can be explained by strict chelation control. Precomplexation[48a,b] of **20** with EtLi affords **A**, in which the EtLi σ-bond is aligned parallel to the π-system



for effective transfer of Et⁻. In accord with the work of Meyers,[49] the subsequent suprafacial [1,5] sigmatropic rearrangement would produce a chelated enolate, shown in **B**. On the assumption that the same lone pair of electrons from the acetal moiety continues to chelate the lithium ion, the β-position's ethyl group effectively shields the *pro-R* face of the α-position during enolate quench with MeI. This latter step can be viewed, in a formal sense, as a 1,2-chiral induction process because the β-position is chiral by virtue of one acetal oxygen's chelation to lithium. However, this rational does not explain why **A**, in which there is a 1,3-interaction between the closest phenyl ring and the ethyl group, is formed in preference to the configuration where the ethyl group is on the opposite face of the molecule and farther away from the phenyl rings. Aggregation effects[48c] are also not taken into account with this model.

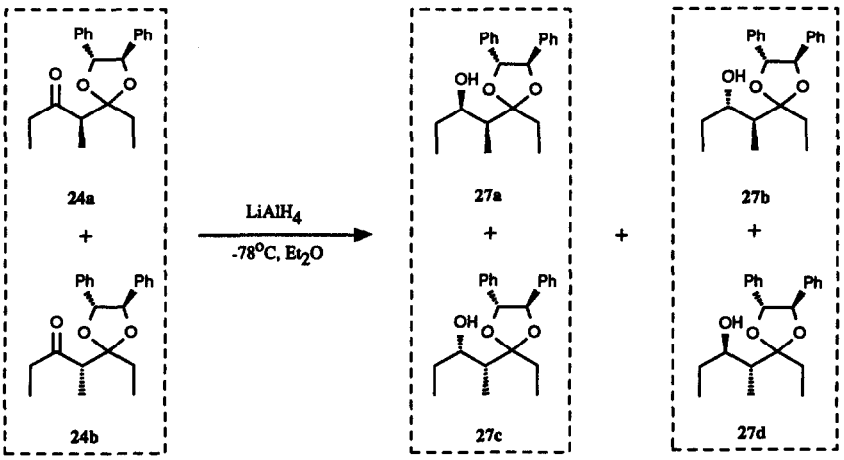


Large scale preparation of **24** by this ethyllithium reaction proved difficult to optimize. An alternative approach to **24** was developed which took advantage of the diastereoselective ketalization of 4-methyl-3,5-heptane-dione **25** with homochiral diols. Mixed Claisen condensation between 3-pentanone and ethyl propionate provided **25** in 50% distilled yield. Following the procedures of Noyori and coworkers,[50] (*R,R*)-hydrobenzoin[51] was reacted with trimethylsilyl chloride and triethylamine in THF to form bis-TMS ether **26**. This was reacted directly with **25** in the presence of a catalytic amount of trimethylsilyl



trifluoromethanesulfonate (TMSOTf) to form **24a** and **24b** in 66% isolated yield. The ratio of **24a** to **24b** by this route was 1 to 3. Note that this procedure provided **24b** in excess whereas the acylketene acetal sequence gave **24a** as the predominant diastereomer. Although enzymes are known to differentiate enantiotopic groups in meso compounds, there are relatively few synthetic examples of this type of desymmetrization process.[52]

The $LiAlH_4$ reduction of a >10 to 1 mixture **24a** to **24b** (from the acylketene acetal route) provided a mixture of four diastereomeric alcohols **27** in 88% yield. Of the four alcohols, two (**27a** and **27b**) were in large excess over the others and had to have come from **24a**. HPLC separated the four diastereomeric alcohols into two pairs; **27a/27c** and **27b/27d**, with no further separation possible.[53] These assignments were further corroborated by the reductions of mixtures of **24a** and **24b** (1 to 3, respectively) obtained from the mono-ketalization route. The resultant diastereomeric mixtures of **27** were enriched in **27c** and **27d**.



We were able to study the reduction of **24a** and **24b** with a number of different agents. The results indicate that reduction preferentially occurs to give *anti* alcohols **27b** and **27d** (Table 2). While disappointing for the synthesis of sitophilure (**27a** is required), *anti* β-hydroxy carbonyl compounds, which derive from **27b** and **27d** by ketal removal (see below), are difficult to prepare by conventional aldol methods. Reductions of **24** with $NaBH_4$/MeOH are particularly stereoselective.

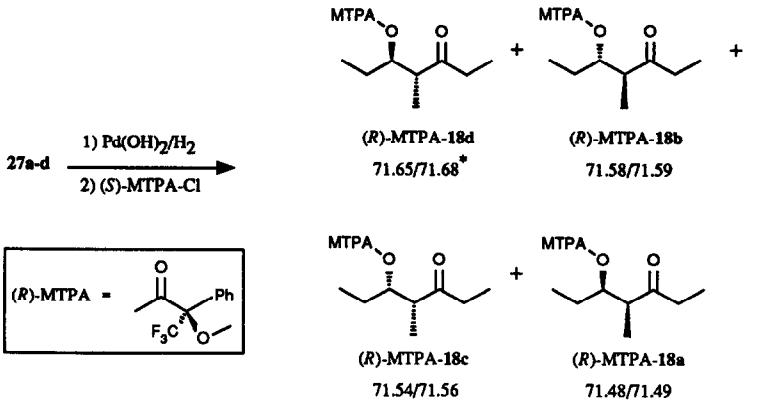
Table 2

Conditions	24a [H]→ 27a	+ 27b	24b [H]→ 27c	+ 27d
$LiAlH_4/Et_2O$/-78°C	1	4.3	1	9
DIBAl-H/Et_2O/-78°C	1	1.6	1	1.7
$NaBH_4$/MeOH/0°C*	1	28	1	37
(*t*-BuO)$_2$AlHLi/0°C	NR		NR	
H_3B:THF/THF/0°C	1	2	1	2
9-BBN/THF/23°C	NR		NR	
Et_3BHLi/THF/-78°C	1	9	1	4.5
(*i*-Bu)$_2$Al(*n*-Bu)HLi/THF/-78°C	1	6.3	1	5.3
$LiAlH_4/MgBr_2/Et_2O$/-100°C	1	10	1	10
$Zn(BH_4)_2/Et_2O$/23°C	1	7	1	4

*Results are from the enantiomers of 24a and 24b

To understand our reduction results, we undertook a preliminary computer-assisted molecular model investigation of **24a** and **24b**.[54] Both space-filling models and computational studies indicate a very hindered system as a result of the phenyl groups. Therefore, metal complexation with an acetal oxygen for controlled hydride transfer does not appear to be in operation. The minimized structures of **24a** and **24b** indicate that the methyl group seems to have little steric effect on hindering either face of the carbonyl. By comparison, the effect imparted by the ethyl group attached to the central carbon of the acetal moiety is substantial. A hydride moiety on its trajectory toward the carbonyl carbon[55] would experience significant hindrance to approach to the *pro-R* face caused by the ethyl group. This effect is small on the *pro-S* face.

The next steps in the synthesis of sitophilure involved the deprotection of **27** to **18**, followed by derivatization to the (*R*)-α-methoxy-α-trifluoromethylphenylacetates (MTPA esters)[56] for comparison to literature ^{19}F NMR values.[43a] A 12: 4: 1.4: 1 mixture of **27d**: **27b**: **27c**: **27a** was hydrogenated with $Pd(OH)_2$ catalyst[43d] in Et_2O to yield solid 1,2-diphenyl ethane and **18**. This crude mixture was reacted directly with (*S*)-MTPA-Cl and gave an inseparable mixture of (*R*)-MTPA-**18a-d** in 31% isolated yield. The ^{19}F NMR spectrum of these diastereomers showed a 19: 4.2: 1.6: 1 mixture of (*R*)-MTPA-**18d**: (*R*)-MTPA-**18b**: (*R*)-MTPA-**18c**: (*R*)-MTPA-**18a**. The reaction was repeated on a 4 to 1 mixture of **27d** to **27b**. The crude reaction mixture obtained from hydrogenation of these diastereomers was reacted with (*S*)-MTPA-Cl and gave a 4 to 1 mixture of (*R*)-MTPA-**18d** to (*R*)-MTPA-**18b**, allowing the correlation of absolute stereochemistry for all compounds prepared in this synthetic study.



* literature[43a] ^{19}F NMR resonance/experimental resonance

Conclusion.[57]

Several methods for the synthesis of achiral and enantiomerically pure acylketene acetals from simple starting material have been developed. These reactions give high yields, and the products are stable if kept below 0°C away from moisture.

In accord with the outline in Figure 1, the oxidation state of the β-carbon of acylketene acetals can be manipulated in a predictable manner. The β-keto acetals and ketals derived from acylketene acetals with borane reducing agents and organolithium reagents, respectively, are useful intermediates in organic synthesis,[58] and this protocol adds to the growing list of approaches to the monoacetals of β-dicarbonyl compounds.[59] In addition, one of us (J.P.K.) has recently reported[60] the conjugate addition of ethoxide ion to acylketene acetals, resulting in the formation of β-keto mixed orthoesters. This transformation has the effect of masking the β-carbon in the acid oxidation state. Thus, the transformations necessary to produce the triad of β-hydroxy carbonyl compounds depicted in Figure 1 from the point of view of the β-carbon are in place.

Stereochemical induction in the alkyllithium/MeI treatment of homochiral acylketene acetals appears to be quite high. However, the yield is modest at best, and more work is needed before this protocol is synthetically viable. The alternative asymmetric synthesis of **24** *via* the differentiation of a meso dione allows for the facile synthesis of β-keto ketals. Finally, the stereoselectivity in the reduction of α-substituted-β-keto ketals is very high and consistently affords *anti* product, which is difficult to obtain by the conventional aldol reaction.

Work is continuing on many aspects of acylketene acetal chemistry and will be reported in due course.

Experimental.

General Procedures. Nuclear Magnetic Resonance (NMR) spectra were obtained at 300 MHz for protons (^{1}H NMR) and 75 MHz for carbons (^{13}C NMR) on a General Electric GN-300. Signal assignments are reported in δ, parts per million (ppm), from tetramethylsilane in the following format: chemical shift (multiplicity, coupling constants, integration, nuclei assignments). Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Proton chemical shifts were referenced in $CDCl_3$ to the residual $CHCl_3$ signal (7.26 ppm). Carbon chemical shifts were referenced to the solvent in a similar manner: $CDCl_3$ (77.09 ppm). Multiplicities of ^{13}C NMR peaks were determined from APT or DEPT data. Low resolution mass spectra (MS) were obtained on a Finnigan 4000 Mass Spectrometer. Sample ionization was initiated by either electron bombardment (EI) or chemical ionization (CI). High resolution mass spectra (HRMS) were obtained at the UC Riverside Analytical Chemistry Instrumentation Facility. Mass spectral data are reported in the following format: MS or HRMS (ionization type), *m/z* = mass of fragment (mass of parent ion ± assignment of the fragment cleaved or added, % intensity of that spectral line with respect to the base peak). A Nicolet Analytical Instruments 5MX Fourier Transform spectrophotometer was utilized to obtain infrared spectra (IR). Characteristic infrared absorptions are reported in cm^{-1} as well as the solvent used in the solution cell. Melting points were obtained on a Thomas-Hoover instrument and are reported uncorrected. Optical rotations were recorded from a Perkin-Elmer 141 Polarimeter at the sodium D line. Rotations are reported in the following format: $[a]^{25}_D$ rotation (concentration in g/100 mL, solvent). Combustion analyses were obtained at Atlantic Microlab, Inc. of Atlanta, Georgia.

All reactions were carried out with oven- or flame-dried glassware under a positive nitrogen atmosphere. Reactions were monitored by thin layer chromatography (TLC) on Kieselgel silica 60 F-254 plates or by gas-liquid chromatography (GC) on a Hewlett Packard 5890 gas chromatograph equipped with a flame ionizing detector. Flash chromatography was carried out using Merck grade 60, 230-400 mesh silica gel. A Waters Associates Model 6000A high pressure liquid chromatography (HPLC) pump equipped with a Regis "semi-prep" 10 μm, 60Å silica gel, 25 cm x 10 mm i.d. column and a difference refractive index detector were employed for the separation of diastereomers.

Hexanes, ethyl acetate, acetonitrile and CH_2Cl_2 were distilled from CaH_2 when anhydrous conditions were required. $CHCl_3$ was purified by washing with water then dried and distilled from P_2O_5. All anhydrous ethers were distilled from sodium benzophenone ketyl immediately before use in a reaction.

The following procedure is representative for the preparation of acylketene acetals **2**, **3**, and **4**.

2-(3-Oxo-3-phenylpropylidene)-1,3-dioxolane (2). A flask containing THF (60 mL) and hexane-washed NaH (3.08 g, 0.128 mol) was treated dropwise with a solution of acetophenone (7.48 mL, 64.2 mmol) in THF (10 mL). The resulting mixture reacted for 30 minutes at room temperature before a dropwise addition of dimethylcarbonate (29.6 mL, 0.351 mol) was begun. The ensuing exothermic reaction refluxed without additional heat for 20 minutes, after which reflux was continued 4 hours with the aid of an external heat source. The semi-solid mixture was cooled to room temperature, 3*M* acetic acid added to acidify the solution to pH 4, and Et_2O (40 mL) added. After separation of the organic phase, the aqueous layer was further extracted with Et_2O (2 X 40 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (1 X 40 mL), brine (1 X 40 mL) and dried over anhydrous $MgSO_4$. Filtration of the drying agent and removal of solvent under vacuum afforded 10.86 g (95%) of β-keto methylester suitable for further reactions without purification. ^{1}H NMR ($CDCl_3$): δ 3.75 (s, 3 H), 3.80 (s, from enol), 4.01 (s, 2 H), 5.68 (s, from enol), 7.41-7.94 (m, 5 H), 12.38 (s, from enol). ^{13}C NMR ($CDCl_3$): δ 45.77 (t), 52.55 (q), 126.16 (d), 128.59 (d), 128.80 (d), 133.86 (s), 168.02 (s), 192.41 (s). IR (neat) (cm^{-1}): 3048, 1746, 1670. EIMS (20 eV) *m/z* (relative intensity): 178 (M^+, 22), 146 (12), 105 (100).

β-Keto methylester (1.66 g, 9.3 mmol), 2-chloroethanol (50 mL) and titanium tetra-*iso*-propoxide (2.1 mL, 9.3 mmol) were heated to reflux overnight. After cooling to room temperature, the mixture was treated

with 5% hydrochloric acid (5 ml), followed by addition of water and Et_2O (50 mL each). The organic layer was separated and the aqueous layer was further extracted with Et_2O (3 X 20 mL). The organic layers were combined, washed with saturated aqueous $NaHCO_3$ (20 mL), brine (20 mL), and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded 2.0 g of crude oil, after which chromatography (1 to 1 hexane to Et_2O) afforded 2-chloroethyl benzoylacetate (1.6 g, 5.9 mmol, 63%). ^1H NMR ($CDCl_3$): δ 3.68 (t, 2 H, J = 5.5 Hz), 4.06 (s, 2 H), 4.42 (t, 2 H, J = 5.5 Hz), 5.75 (s, from enol), 7.43-7.95 (m, 5 H), 12.36 (s, from enol). ^{13}C NMR ($CDCl_3$): δ 41.26 (t), 45.74 (t), 64.86 (t), 126.23 (d), 128.57 (d), 128.90 (d), 133.97 (s), 167.25 (s), 192.14 (s). IR (neat) (cm^{-1}): 1748, 1687. EIMS (20 eV) *m/z* (relative intensity): 228 (M^+, 1), 226 (M^+, 3), 178 (5), 105 ($PhCO^+$, 100).

To a DMF solution (15 mL) of β-chloroethyl ester (1.84 g, 6.7 mmol) was added powdered, oven-dried K_2CO_3 (3.73 g, 26.9 mmol). The mixture was stirred for 16 hours at room temperature, at which time the solvent was removed under high vacuum. The resulting solid was chromatographed on oven dried silica gel (THF) to afford 1.22 g (96%) of desired acylketene acetal **2** as an orange solid. mp: 98-99°C. ^1H NMR ($CDCl_3$): δ 4.50 (t, 2 H, J = 7.8 Hz), 4.69 (t, 2 H, J = 7.8 Hz), 5.74 (s, 1 H), 7.38-7.50 (m, 3 H), 7.87-7.90 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 65.6 (t), 68.5 (t), 74.8 (d), 127.5 (d), 128.3 (d), 131.5 (d), 140.0 (s), 170.0 (s), 188.1 (s). IR ($CDCl_3$) (cm^{-1}): 2921, 1659, 1583, 1562. EIMS (20 eV) *m/z* (relative intensity): 191 (M^++1, 5), 190 (M^+, 21), 113 (100). Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.47; H, 5.30. Found: C, 69.47; H, 5.34.

2-(Ketene ethylene acetal)-cyclohexanone (3). Isolated in 38% yield from cyclohexanone, following the procedure for **2**, as a white solid. mp. 49.0-49.5°C. ^1H NMR ($CDCl_3$): δ 1.63-1.78 (m, 4 H), 2.83-2.44 (m, 4 H), 4.35-4.41 (m, 2 H), 4.56-4.62 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 23.3 (t), 24.6 (t), 30.4 (t), 30.9 (t), 65.7 (t), 68.4 (t), 87.1 (s), 165.3 (s), 197.8 (s). EIMS (20 eV) *m/z* (relative intensity): 169 (M^++1, 16), 168 (M^+, 76), 112 (100).

2-(Ketene ethylene acetal)-1-tetralone (4). Isolated in 15% yield from **9**, following the procedure for **2**, as a white solid. mp: 107-108°C. ^1H NMR ($CDCl_3$): δ 2.70-2.75 (m, 2 H), 2.84-2.89 (m, 2 H), 4.23 (t, 2 H, J = 7.5 Hz), 4.65 (t, 2 H, J = 7.5 Hz), 7.16-7.39 (m, 3 H), 8.04-8.07 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ 23.62 (t), 29.99 (t), 65.66 (t), 68.42 (t), 86.23 (s), 126.62 (d), 127.23 (d), 127.70 (d), 131.67 (s), 142.36 (s), 165.78 (s), 165.65 (s). IR ($CDCl_3$) (cm^{-1}): 2955, 1661, 1602, 1579, 1555. EIMS (20 eV) *m/z* (relative intensity): 216 (M^+, 100).

2-(2-Oxo-2-phenyl-ethyl)-1,3-dioxolane (5). To a THF solution (5 mL) of **2** (0.1416 g, 0.595 mmol) at -78°C was added H_3B:THF (0.654 mmol., 1.1 eq.). After 1 hour, saturated aqueous $NaHCO_3$ (1 mL) was added and the solution stirred to room temperature. The reaction solution was extracted with Et_2O (3 X 3 mL) and the combined extracts dried with anhydrous $MgSO_4$. Removal of the Et_2O under high vacuum provided clean **5** as an oil that slowly crystallized (90.0 mg, 0.42 mmol., 70%). mp: 57.5-58.0°C. ^1H NMR ($CDCl_3$): δ 3.34 (d, 2 H, J = 4.8 Hz), 3.87-4.02 (m, 4 H), 5.44 (t, 1 H, J = 4.8 Hz), 7.43-7.59 (m, 3 H), 7.94-8.10 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 43.5 (t), 65.1 (t), 101.5 (d), 128.4 (d), 128.7 (d), 133.4 (s), 137.0 (d), 196.6 (s). IR (neat) (cm^{-1}): 2892, 1685. EIMS (20 eV) *m/z* (relative intensity): 120 ($PhCOCH_2^-$, 42), 105 ($PhCO^+$, 99), 73 (ethylene acetal cation, 100).

2-(2-(1,3-Dioxolane)) cyclohexanone (8). To a THF solution (2 mL) at 0°C was added H_3B:THF (1.86 mmol). To this solution was added 2-methyl-2-butane (4.48 mmol, 0.475 mL) and the solution stirred 2 hours. The solution was cooled to -78°C and **3** (0.142 g, 0.844 mmol) in THF (2 mL) was added. After 30 minutes, MeOH (1 mL) was added and the solution warmed to room temperature. The reaction solution was extracted with Et_2O (3 X 30 mL) and the combined extracts dried with anhydrous $MgSO_4$. The solvent was removed under high vacuum and the resulting oil chromatographed (EtOAc) to provide **8** (71.7 mg, 0.42 mmol, 50%). ^1H NMR ($CDCl_3$): δ 1.20-1.93 (m, 6 H), 2.20-2.51 (m, 3 H), 3.91 (s, 4 H), 5.21 (d, 1 H, J = 4.2 Hz). IR (neat) (cm^{-1}): 2950, 1714. CIMS (*iso*-butane) *m/z* (relative intensity): 170 (M^+, 100).

2-Methylene cyclohexanol (9). To a THF solution (4 mL) containing **3** (112.5 mg, 0.6696 mmol) at 0°C was added H_3B:THF (0.7366 mmol, 1.1 eq.). After 1 hour the solution was quenched with saturated aqueous $NaHCO_3$ (1 mL) and extracted with Et_2O (3 x 3 mL). The combined extracts were dried with anhydrous $MgSO_4$ and concentrated under vacuum to an oil. This oil was chromatographed (1 to 1 hexane to

EtOAc) and gave **9** (42.0 mg, .20 mmol, 30%) as an oil. ^{1}H NMR ($CDCl_3$): δ 1.34-1.50 (m, 2 H), 1.60-1.66 (m, 2 H), 1.79-1.84 (m, 1 H), 1.93-2.06 (m, 2 H), 2.37-2.44 (m, 1 H), 4.08-4.14 (m, 1 H), 4.75 (s, 1 H), 4.88 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 23.9 (t), 27.8 (t), 33.6 (t), 36.7 (t), 72.7 (d), 105.1 (t), 151.7 (s).

***trans*-3-Butoxy-1-phenyl-pentenone (11).** To a THF solution (5 mL) containing **2** (109.8 mg, 0.463 mmol) at 0°C was added H_3B:THF (0.73 *M*, 0.47 mmol, 1.1 eq.). After 1 hour, the solution was quenched with saturated aqueous $NaHCO_3$ (1 mL) and extracted with Et_2O (3 x 5 mL). The combined extracts were dried with anhydrous $MgSO_4$ and concentrated to an oil. This oil was chromatographed (1 to 1 hexane to Et_2O) and gave **11** (23.0 mg, 0.111 mmol, 24%) as an oil. ^{1}H NMR ($CDCl_3$): δ .961 (t, 3 H, *J* = 7.2 Hz), 1.36-1.51 (m, 2 H), 1.68-1.77 (m, 2 H), 3.99 (t, 2 H, *J* = 6.6 Hz), 6.35 (d, 1 H, *J* = 12.3 Hz), 7.41-7.55 (m, 2 H), 7.76 (d, 1 H, *J* = 12.3 Hz), 7.89 (dd, 3 H, *J* = 7.8, 9.0 Hz). ^{13}C NMR ($CDCl_3$): δ 13.7 (q), 19.0 (t), 31.2 (t), 72.1 (t), 102.1 (d), 128.0 (d), 128.5 (d), 132.6 (d), 138.9 (s), 164.5 (d), 190.7 (s). IR (neat) (cm^{-1}): 2953, 1665. EIMS (20 eV) *m/z* (relative intensity): 205 (M^++1, 4), 204 (M^+, 5), 161 (34), 147 (100).

2-(2′-Hydroxy-2′-phenyl)ethyl-1,3-dioxolane (12). To a MeOH solution (4 mL) of **5** (54.7 mg, 0.228 mmol) at 0°C was added a MeOH solution (2 mL) containing $NaBH_4$ (14.0 mg, 0.365 mmol, 1.6 eq.). After 20 minutes, H_2O (5 mL) was added and the solution was stirred at room temperature for 18 hours. Solid NaCl (1 g) was added and the solution extracted with Et_2O (4 X 5 mL). The extracts were combined and dried with anhydrous $MgSO_4$. The solvent was removed under high vacuum to provide clean **12** (49.2 mg, 0.203 mmol, 89%). ^{1}H NMR ($CDCl_3$): δ 2.11-2.15 (m, 2 H), 3.32 (bs, 1 H), 3.89-3.92 (m, 2 H), 4.02-4.10 (m, 2 H), 5.00-5.07 (m, 2 H), 7.25-7.40 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ 42.5 (t), 64.9 (t), 65.1 (t), 70.4 (d), 103.26 (d), 125.8 (d), 127.5 (d), 128.5 (d), 143.9 (s). IR (neat) (cm^{-1}): 3460, 2885. CIMS (*iso*-Bu) *m/z* (relative intensity): 193 (M^+-1, 2), 177 (M^++1-H_2O, 2), 151 (4), 116 (5), 73 (100).

2-(Carboxaldehyde ethylene acetal)-cyclohexanol (13). To a MeOH solution (3 mL) containing **8** (140.7 mg, 0.828 mmol) at 0°C was added $NaBH_4$ (50.0 mg, 1.32 mmol, 1.6 eq.). After stirring 2 hours, H_2O (2 mL) was added and the solution stirred at room temperature for 18 hours. Solid NaCl (1 g) was added and the solution extracted with Et_2O (3 X 5 mL). The extracts were combined and dried with anhydrous $MgSO_4$. Removal of the solvent under vacuum provided an oil which was chromatographed (EtOAc) affording **13** as a 1:1 mixture of *erythro*/*threo* isomers (52.5 mg, 0.31 mmol, 37%). ^{1}H NMR ($CDCl_3$): δ 1.15-1.85 (m, 10 H), 2.82 (bs, 1 H), 3.80-4.04 (m, 4 H), 4.76 (d, .5 H, *J* = 5.7 Hz), 4.84 (d, .5 H, *J* = 3.0 Hz). IR (neat) (cm^{-1}): 3472, 2931. EIMS (20 eV) *m/z* (relative intensity): 173 (M^+-1, 1), 155 (M^+-H_2O, 6), 91 (37), 73 (100).

The following procedure is representative for additions of organolithium reagents to **2** and **3**.

3-(Oxo-ethylene acetal)-1-oxo-1-phenyl butane. To a THF solution (5 mL) containing MeLi (0.796 mmol, 1.1 eq.) at -78°C was added **2** (0.138 g, 0.724 mmol) dissolved in THF (4 mL) over 5 minutes. The solution stirred 1 hour and was quenched with saturated aqueous $NaHCO_3$ (2 mL). After slowly warming to room temperature (3 hours), the solution was extracted with Et_2O (3 X 5 mL). The extracts were combined and dried with anhydrous $MgSO_4$. Concentration of the extract under vacuum provided 0.154 g of clear oil, which was chromatographed (1 to 2 Hexane to Et_2O) to provide β-keto ketal product (0.123 g, 0.601 mmol, 83%). ^{1}H NMR ($CDCl_3$): δ 1.51 (s, 3 H), 3.33 (s, 2 H), 3.88-3.99 (m, 4 H), 7.42-7.55 (m, 3 H), 7.96-7.99 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 25.01 (q), 47.52 (t), 64.80 (t), 108.48 (s), 127.06 (d), 128.53 (d), 128.72 (d), 133.09 (s), 197.10 (s). IR (neat) (cm^{-1}): 2989, 1678. EIMS (20 eV) *m/z* (relative intensity): 207 (M^++1, 1), 191 (M^+-CH_3^-, 27), 105 ($PhCO^+$, 79), 87 (M^+-$PhCOCH_2^-$, 100).

3-(Oxo-ethylene acetal)-1-oxo-1-phenyl pentane. This was isolated in 59% yield from **2**, following the procedure above, as an oil. ^{1}H NMR ($CDCl_3$): δ .96 (t, 3 H, *J* = 7.2 Hz), 1.85 (q, 2 H, *J* = 7.2 Hz), 3.30 (s, 2 H), 3.90-3.94 (m, 4 H), 7.42-7.57 (m, 3 H), 7.96-7.99 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 8.07 (q), 31.39 (t), 45.94 (t), 65.25 (t), 110.71 (s), 128.50 (d), 128.74 (d), 133.04 (d), 137.90 (s), 197.52 (s). IR (neat) (cm^{-1}): 2968, 1673. CIMS (*iso*-Bu) *m/z* (relative intensity): 221 (M^++1, 3), 209 (47), 191 (100).

3-(Oxo-ethylene acetal)-1-oxo-1-phenyl heptane. This was isolated in 72% yield from **2**, following the procedure above, as an oil. ^{1}H NMR ($CDCl_3$): δ .89 (t, 3 H, *J* = 7.2 Hz), 1.29-1.40 (m, 4 H), 1.82 (t, 2 H, *J* = 7.2 Hz), 3.30 (s, 2 H), 3.86-3.93 (m, 4 H), 7.41-7.57 (m, 3 H), 7.97 (bd, 2 H, *J* = 7.2 Hz). ^{13}C NMR

($CDCl_3$): δ 14.16 (q), 22.90 (t), 25.93 (t), 38.28 (t), 45.84 (t), 65.16 (t), 110.47 (s), 128.72 (d), 133.03 (d), 137.89 (s), 197.46 (s). IR (neat) (cm^{-1}): 2960, 1667. EIMS (20 eV) *m/z* (relative intensity): 249 (M^++1, .5), 205 (2), 191 (M^+-*n*-Bu$^-$, 82), 129 (M^+-$PhCOCH_2^-$, 100).

3-(Oxo-ethylene acetal)-4,4-dimethyl-1-oxo-1-phenyl pentane. This was isolated in 18% yield from **2**, following the procedure above, as an oil. ^1H ($CDCl_3$): δ 1.04 (s, 9 H), 3.34 (s, 2 H), 3.64-3.82 (m, 4 H), 7.41-7.56 (m, 3 H), 7.99-8.02 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 25.36 (q), 41.45 (s), 43.01 (t), 66.43 (t), 115.46 (s), 128.42 (d), 129.06 (d), 132.89 (d), 138.21 (s), 199.63 (s). IR (neat) (cm^{-1}): 2955, 1678. CIMS (*iso*-Bu) *m/z* (relative intensity): 247 (M^+-1, 4), 191 (M^+-*t*-Bu$^-$, 49), 129 (M^+-$PhCOCH_2^-$, 100).

1-(Oxo-ethylene acetal)-3-oxo-1,3-diphenyl-propane. This was isolated in 30% yield from **3**, following the procedure above, as an oil. ^1H NMR ($CDCl_3$): δ 3.59 (s, 2 H), 3.74-3.79 (m, 2 H), 3.93-3.98 (m, 2 H), 7.29-7.45 (m, 5 H), 7.51-7.57 (m, 3 H), 7.94-7.97 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 48.81 (t), 64.78 (t), 108.61 (s), 125.68 (d), 128.35 (d), 128.98 (d), 132.96 (d), 137.80 (s), 142.10 (s), 196.26 (s). IR (neat) (cm^{-1}): 2896, 1678. CIMS (*iso*-Bu) *m/z* (relative intensity): 269 (M^++1, 2), 225 (57), 149 (M^+-$PhCOCH_2^-$, 100).

2-(1-(Oxo-ethylene acetal)pentyl) cyclohexanone. This was isolated in 80% yield from **3**, following the procedure above, when 3 eq. of *n*-BuLi were employed at 0°C. ^1H NMR ($CDCl_3$): δ .89 (t, 3 H, J = 7.2 Hz), 1.26-1.29 (m, 4 H), 1.46-1.77 (m, 4 H), 1.87-1.93 (m, 2 H), 2.28-2.50 (m, 2 H), 2.69-2.72 (m, 1 H), 3.90-3.96 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ 14.21 (q), 23.02 (t), 24.63 (t), 25.67 (t), 28.08 (t), 28.85 (t), 35.74 (t), 43.22 (t), 56.89 (d), 65.39 (t), 65.47 (t), 111.22 (s), 204.31 (s). IR (neat) (cm^{-1}): 2966, 1715. EIMS (20 eV) *m/z* (relative intensity): 227 (M^++1, 4), 169 (M^+-*n*-Bu$^-$, 66), 129 (100).

3-(Oxo-ethylene acetal)-2-methyl-1-oxo-1-phenyl butane (14). To a THF solution (5 mL) containing MeLi (0.80 mmol, 1.2 eq.) at -78°C was added **2** (0.126 g, 0.663 mmol) dissolved in THF (4 mL). After 1 hour, MeI (0.125 mL, 1.99 mmol., 3 eq.) was added. The solution warmed to room temperature overnight and was quenched with saturated aqueous $NaHCO_3$ (3 mL). The solution was extracted with Et_2O (4 X 5 mL) and the extracts were combined and dried with anhydrous $MgSO_4$. The solvent was removed under vacuum and provided 0.142 g of red oil. Chromatography of this oil (1 to 1 hexane to Et_2O) yielded **14** (92.7 mg, 0.424 mmol, 64%) and the corresponding unmethylated β-keto ketal (21.5 mg, 0.106 mmol, 16%). (**14**): ^1H NMR ($CDCl_3$): δ 1.28 (d, 3 H, J = 6.9 Hz), 1.41 (s, 3 H), 3.85-3.99 (m, 5 Hz), 7.42-7.57 (m, 3 H), 7.94-7.97 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 13.72 (q), 21.69 (q), 48.06 (d), 64.79 (t), 64.88 (t), 110.90 (s), 128.52 (d), 132.89 (d), 138.07 (s), 201.75 (s). IR (neat) (cm^{-1}): 2899, 1683. CIMS (*iso*-Bu) *m/z* (relative intensity): 221 (M^++1, 1), 177 (77), 149 (28), 105 (69), 87 (100).

2-(1-(Oxo-ethylene acetal)propyl) cyclohexanone (15) and **2-Carb-(2-bromoethoxy) cyclohexanone (16).** To a THF solution (5 mL) containing EtMgBr (1.32 mmol, 3 eq.) at 0°C was added **3** (74.0 mg, 0.441 mmol) dissolved in THF (1 mL). After 30 minutes, the solution was warmed to room temperature and saturated aqueous NH_4Cl (1 mL) added. The solution was extracted with Et_2O (3 X 5 mL) and the combined extracts dried with anhydrous $MgSO_4$. Solvent removal under vacuum supplied an oil which was chromatographed (1 to 1 hexane to Et_2O) and provided **15** (26.4 mg, 0.137 mmol, 31%) and **16** (36.1 mg, 0.146 mmol, 33%). (**15**): ^1H NMR ($CDCl_3$): δ .81 (t, 3 H, J = 7.2 Hz), 1.55-1.70 (m, 4 H), 1.84-1.89 (m, 3 H), 2.03-2.06 (m, 1 H), 2.20-2.49 (m, 2 H), 2.65-2.69 (m, 1 H), 3.89-3.93 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ 7.76, 24.54, 28.03, 28.62, 28.79, 43.13, 56.49, 65.45, 65.50, 111.40, 204.67. IR (neat) (cm^{-1}): 2932, 1708. EIMS (20 eV) *m/z* (relative intensity): 199 (M^++1, .1), 169 (M^+-Et$^-$, 69), 101 (M^+- cyclohexanone anion, 100). (**16**): ^1H NMR ($CDCl_3$): δ 1.60-1.70 (m, 4 H), 2.24-2.30 (m, 4 H), 3.55 (t, 2 H, J = 6.0 Hz), 4.45 (t, 2 H, J = 6.0 Hz), 12.00 (s, 1 H, from enol). ^{13}C NMR ($CDCl_3$): δ 21.91, 22.36, 23.41, 27.13, 28.81, 29.26, 30.01, 41.64, 57.16, 63.48, 64.30, 97.49, 172.03, 173.15. EIMS (20 eV) *m/z* (relative intensity): 250 (M^+, 25), 248 (M^+, 23), 124 (74), 68 (100).

(4*S*,5*S*)-4,5-Di(methoxymethyl)-2-(2′-oxo-butylidene)-1,3-dioxolane (19). A CH_3CN solution (25 mL) of Meldrum's acid adduct **22** (3.46 g, 17.3 mmol) and halohydrin **21** (2.428 g, 14.4 mmol) was refluxed 24 hours. The solvent was removed under vacuum and the resulting residue chromatographed (1 to 5 Et_2O to hexane) to afford the desired β-keto ester (3.125 g, 11.73 mmol, 82%) as an oil. $[\alpha]_D^{23}$ = 1.4 (c = 1.5, MeOH). ^1H NMR ($CDCl_3$): δ 1.07 (t, 3 H, J = 7.2 Hz), 2.56 (q, 2 H, J = 7.2 Hz), 3.35 (s, 3 H), 3.38 (s, 3 H),

3.49 (s, 3 H), 3.58-3.70 (m, 4 H), 4.26-4.29 (m, 1 H), 5.27-5.32 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ 7.58, 36.37, 48.98, 57.29, 59.21, 59.31, 70.77, 72.96, 166.27, 202.88. IR (neat) (cm^{-1}): 2937, 1749, 1716. EIMS (20 eV) *m/z* (relative intensity): 269 (M^++1, 1), 267 (M^++1, 3), 205 (21), 185 (42), 131 (76), 99 (100).

To a DMF solution (5 mL) containing the above ester (0.121 g, 0.453 mmol) was added oven-dried, powdered K_2CO_3 (0.252 g, 1.81 mmol, 4 eq.). The solution stirred at room temperature for 18 hours and was concentrated under high vacuum. Chromatography (THF) of the residue gave **19** (101.2 mg, 0.440 mmol, 97%) as an oil. $[\alpha]_D^{23}$ = .03 (c = 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.05 (t, 3 H, *J* = 7.2 Hz), 2.42 (q, 2 H, *J* = 7.2 Hz), 3.29 (s, 3 H), 3.89 (s, 3 H), 3.56-3.72 (m, 4 H), 4.56-4.62 (m, 1 H), 4.72-4.75 (m, 1 H), 4.87 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 9.10 (q), 35.71 (t), 59.71 (t), 71.18 (t), 71.33 (t), 77.93 (d), 78.17 (d), 80.63 (d), 168.29 (s), 198.94 (s). IR (neat) (cm^{-1}): 2936, 1677, 1626. Accurate mass calcd. for $C_{11}H_{18}O_5$ 230.2631, found 230.1154.

(4*R*,5*R*)-4,5-Diphenyl-2(2′-oxo-butylidene)-1,3-dioxolane (20). A CH_3CN solution (25 mL) of Meldrum's acid adduct **22** (2.619 g, 13.1 mmol) and halohydrin **23** (2.342 g, 10.1 mmol) was refluxed 24 hours. The solvent was removed under vacuum and the resulting residue chromatographed ($CHCl_3$) to afford the corresponding β-keto ester (3.245 g, 9.82 mmol, 98%) as an oil. ^1H NMR ($CDCl_3$): δ .95 (t, 3 H, *J* = 7.2 Hz), 2.18-2.37 (m, 2 H), 3.31 (s, 2 H), 5.14 (d, 1 H, *J* = 7.2 Hz), 6.20 (d, 1 H, *J* = 7.2 Hz), 7.28-7.34 (m, 10 H). ^{13}C NMR ($CDCl_3$): δ 7.54 (q), 35.94 (t), 49.00 (t), 63.89 (d), 79.02 (d), 127.88 (d), 128.33 (d), 128.47 (d), 128.91 (d), 129.03 (d), 136.03 (s), 137.11 (s), 165.69 (s), 202.39 (s). IR (neat) (cm^{-1}): 2979, 1748, 1716. Anal. Calcd: C, 68.98; H, 5.79. Found: C, 68.17; H, 5.73.

A DMF solution (20 mL) containing the above β-keto ester (3.218 9.74 mmol) and oven-dried, powdered K_2CO_3 (5.4 g, 39.0 mmol, 4 eq.) was stirred at room temperature for 18 hours. The solvent was removed under high vacuum and the resulting residue chromatographed (4 to 1 hexane to THF). This provided acylketene acetal **20** (2.701 g, 9.25 mmol, 95 %) as a white solid. m.p. 95.0-95.5°C. $[\alpha]_D^{20}$ = -0.1 (c = 1.4, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.11 (t, 3 H, *J* = 7.5 Hz), 2.57 (q, 2 H, *J* = 7.5 Hz), 5.09 (s, 1 H), 5.30 (d, 1 H, *J* = 7.8 Hz), 5.50 (d, 1 H, *J* = 7.8 Hz), 7.28-7.45 (m, 10 H). ^{13}C NMR ($CDCl_3$): δ 9.03 (q), 35.73 (t), 79.19 (d), 85.99 (d), 88.55 (d), 126.34 (d), 129.25 (d), 129.77 (d), 134.72 (s), 168.17 (s), 199.12 (s). IR ($CDCl_3$) (cm^{-1}): 1626, 1579. EIMS (20 eV) *m/z* (relative intensity): 294 (M^+, 3), 265 (78), 197 (100). Anal. Calcd: C, 77.53; H, 6.16. Found: C, 77.39; H, 6.18.

Preparation of EtLi in benzene. To a pentane solution (40 mL) containing pentane washed granular Li^o (1.526 g, 0.22 mol) under argon was slowly added a pentane solution (10 mL) of EtBr (7.46 mL, 0.10 mol). After self-refluxing (~1 hour), the purple solution was heated to reflux an additional hour. The heat source was removed and the pentane evaporated with a stream of argon. Benzene (50 mL) was added to the purple solid and the suspension stirred for 15 minutes after which the solution was left to settle for 1 hour. The pale yellow supernatant was transferred *via* cannula through an inline celite filter into another vessel for use. Samples of this solution were titrated with 1.0 *M* *sec*-butyl alcohol in xylene containing 1,10-phenanthroline indicator[61] and indicated EtLi present at 0.75 *M*. (Total base concentration, determined by back-titration of a water quenched aliquot with 1.0 *M* HCl to the phenolphthalein end point, was 0.80 *M*.) An aliquot tested with acidified $AgNO_3$ was negative for LiBr. This solution will last 2 weeks at room temperature.

(1′*S*,4*R*,5*R*)-4,5-Diphenyl-2-ethyl-2-(1′-methyl-2′-oxo)butyl-1,3-dioxolane (24a) and (1′*R*,4*R*,5*R*)-4,5-Diphenyl-2-ethyl-2-(1′-methyl-2′-oxo)butyl-1,3-dioxolane (24b). To a THF solution (5 mL) containing acylketene acetal **20** (95.2 mg, 0.324 mmol) at 0°C was added EtLi (0.74 *M* in benzene, 0,356 mmol, 1.1 eq.). After 10 minutes, MeI (0.203 mL, 3.24 mmol, 10 eq.) was added. The solution slowly warmed to room temperature overnight. Saturated aqueous $NaHCO_3$ (3 mL) was added and the solution extracted with Et_2O (3 x 3 mL). The combined extracts were dried with anhydrous $MgSO_4$ and concentrated to an oil. This oil was chromatographed (5 to 1 hexane to Et_2O) to afford a >10 to 1 mixture of **24a** to **24b** (46.0 mg, 0.136 mmol, 42%) as an oil. ^1H NMR ($CDCl_3$): δ 1.03 (t, *J* = 7.2 Hz, from **24b**), 1.06 (t, 3 H, *J* = 7.2 Hz), 1.16 (t, 3 H, *J* = 7.2 Hz), 1.29 (d, 3 H, *J* = 7.2 Hz), 1.34 (d, *J* = 7.2 Hz, from **24b**), 1.90-2.04 (m, 2 H),

2.54-2.67 (m, 1 H), 2.72-2.87 (m, 1 H), 2.72-2.87 (m, 1 H), 3.32 (q, 1 H, J = 7.2 Hz), 4.67 (d, 1 H, J = 8.7 Hz), 4.73 (d, 1 H, J = 8.7 Hz), 4.85 (d, J = 9.0 Hz, from **24b**), 7.17-7.49 (m, 10 H). IR (neat) (cm^{-1}): 2998, 1708.

To a THF solution (18 mL) of (*R,R*)-hydrobenzoin (0.6556 g, 3.064 mmol) and triethylamine (0.896 mL, 6.43 mmol) at 0°C was added trimethylsilyl chloride (0.817 mL, 6.43 mmol). After 30 minutes, the reaction solution was warmed to room temperature and stirred for 24 hours. The solvent was removed under vacuum and hexane (20 mL) was added. The supernatant was transfered *via* cannula through an inline celite filter into another vessel. (This procedure was repeated three times.) The hexane was removed under vacuum and CH_2Cl_2 (10 mL) added, followed by dione **25** (0.435 g, 2.064 mmol). The solution was cooled to -78°C and TMSOTf (6 μL, 0.031 mmol, 0.01 eq.) added. The solution stirred for 5 hours and then warmed slowly to room temperature overnight. Saturated aqueous $NaHCO_3$ (10 mL) was added and the organic layer removed. The aqueous layer was further extracted with CH_2Cl_2 (2 x 15 mL) and the combined extracts dried with anhydrous $MgSO_4$. Removal of the solvent under vacuum and chromatography (3 to 1 hexane to EtOAc) of the residue afforded a 1 to 3 mixture of **24a** to **24b** (0.6841 g, 2.02 mmol, 66%).

4-Methyl-heptane-3,5-dione (25). To an Et_2O solution (100 mL) containing hexane washed NaH (4.4 g, 0.183 mol) at 0°C was added 3-pentanone (19.35 mL, 0.183 mol). After 10 minutes, ethyl propionate (21.0 mL, 0.183 mol) was added and the solution stirred at room temperature for 18 hours. The reaction solution was poured into 5% aqueous HCl (100 ml) at 0°C and the organic layer removed. The remaining aqueous solution was further extracted with Et_2O (2 x 30 mL) and the combined extracts dried with anhydrous $MgSO_4$. Removal of the solvent afforded an oil which was distilled to provide dione **25** (b.p. at ~190°C (12.95 g, 90.0 mmol, 50%). ^1H NMR ($CDCl_3$): δ 1.06 (t, 6 H, J = 7.2 Hz), 1.30 (d, 3 H, J = 7.2 Hz), 2.45 (q, 4 H, J = 7.2 Hz), 3.68 (q, 1 H, J = 7.2 Hz). IR (neat) (cm^{-1}): 1989, 1710.

(1′*S*,2′R,4*R*,5*R*)-4,5-Diphenyl-2-ethyl-2-(1′-methyl-2′-hydroxy)butyl-1,3-dioxolane (27a), (1′*S*,2′S,4*R*,5*R*)-4,5-Diphenyl-2-ethyl-2-(1′-methyl-2′-hydroxy)butyl-1,3-dioxolane (27b), (1′*R*,2′S,4*R*,5*R*)-4,5-Diphenyl-2-ethyl-2-(1′-methyl-2′-hydroxy)butyl-1,3-dioxolane (27c), and (1′*R*,2′R,4*R*,5*R*)-4,5-Diphenyl-2-ethyl-2-(1′-methyl-2′-hydroxy)butyl-1,3-dioxolane (27d). To a stirred suspension of $LiAlH_4$ (6 mg, 0.15 mmol) in Et_2O (2 mL) was added an Et_2O solution (0.5 mL) containing a 10 to 1 mixture of **24a** to **24b** (25.0 mg, 0.074 mmol). After 2 hours, the reaction was quenched with H_2O (1 mL) and extracted with Et_2O (2 x 5 mL). The combined extracts were dried with anhydrous $MgSO_4$ and concentrated to an oil. HPLC separation gave **27b/27d** (16.0 mg, 0.043 mmol, 59%) and **27a/27c** (6.0 mg, 0.022 mmol, 29%) as oils. **27b/27d**; Discernable signals in ^1H NMR ($CDCl_3$): (**27d**) δ 3.68 (br t, CHOH), 4.28 (s, OH). (**27b**) δ 3.88 (br t, CHOH), 4.30 (s, OH). IR (neat) (cm^{-1}): 3516, 2981. EIMS (20 eV) *m/z* (relative intensity): 341 (M^++1, faint), 311 (M^+-C_2H_5, 1). **27a/27c**; Discernable signals in ^1H NMR ($CDCl_3$): (**27c**) δ 3.01 (s, OH), 4.17 (br t, CHOH). (**27a**) δ 3.09 (s, OH), 4.07 (br t, CHOH).IR (neat) (cm^{-1}): 3516, 2980. Accurate mass calcd for $C_{22}H_{28}O_3$ 340.4667, found 341.2117.

(*R*)-MTPA-18a-d. To an Et_2O solution (5 mL) containing a 12: 4: 1.4: 1 mixture of **27d**: **27b**: **27c**: **27a** (0.2287 g, 0.6726 mmol) was added $Pd(OH)_2$ (~ 20 mg). An atmosphere of H_2 was maintained, with a rubber balloon, over the stirred solution for 18 hours. The solution was filtered and concentrated under vacuum to afford a clear oil, **1a-d**, and a white solid, 1,2-diphenylethane. This mixture was dissolved in CCl_4 (0.5 mL) and added to a CCl_4 solution (2 mL) containing pyridine (2 mL) and (*S*)-MTPA-Cl (0.179 mL, 0.942 mmol, 1.4 eq.) at room temperature in a small test tube. The reaction mixture was shaken and allowed to stand for 3 hours. Excess 3-dimethylamino-1-propylamine (0.170 mL) was added and the resulting solution diluted with Et_2O (3 mL). This solution was washed with cold 5% aqueous HCl (1 x 2 mL), cold saturated aqueous Na_2CO_3 (1 x 2 mL), brine (1 x 2 mL), and dried with anhydrous $MgSO_4$. The filtered Et_2O solution was concentrated to an oil and chromatographed (benzene) to afford a inseparable 19: 4.2: 1.6: 1 mixture of (*R*)-MTPA-**18d**: (*R*)-MTPA-**18b**: (*R*)-MTPA-**18c**: (*R*)-MTPA-**18a** (75.8 mg, 0.209 mmol, 31%) as an oil.

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