Petroleum Research Fund, administered by the American Chemical Society, and by the Kirkpatrick and Kesler Funds for Coe College for summer fellowships to P.P.W., H.G., and K.H.H. Mass spectra were obtained at The University of Iowa High Resolution Mass Spectrometry Facility and NMR spectra at The University of Iowa High Field NMR Facility.

Supplementary Material Available: ^1H and ^{13}C NMR spectra for the diisopropylaniline mixtures isolated from reactions described in entries 2, 4, 6, 8, 10, 12, and 14–16 of Table I (18 pages). Ordering information is given on any current masthead page.

Optically Active Building Blocks from the SPAC Reaction: A Completely Asymmetric Synthesis of (4*S*-*cis*)-5-(Cyclohexylmethyl)-4-hydroxy-2-pyrrolidinone, a Statine Analogue

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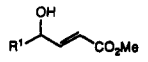
Factors that govern chemical and optical yields of methyl γ-hydroxy-α,β-unsaturated esters 1 formed in reactions of optically active sulfinylacetates 2 with aldehydes (the "SPAC" reaction) are defined. Racemic samples of these chirons (1) can be resolved via acylations mediated by crude preparations of the lipase *Pseudomonas* K-10 in organic solvents. Combinations of asymmetric SPAC reactions with these biocatalytic resolutions provide routes to highly optically active esters 1 in good yields. This methodology is applied in a completely asymmetric synthesis of (4*S*-*cis*)-5-(cyclohexylmethyl)-4-hydroxy-2-pyrrolidinone (15), a cyclic derivative of (3*S*,4*S*)-4-amino-5-cyclohexyl-3-hydroxypentanoic acid (ACHPA).

γ-Hydroxy-α,β-unsaturated esters 1 are versatile synthons.[2-9] The hydroxyl group of these compounds can be transformed into a leaving group and displaced with inversion of configuration via S_N2 processes, or with net retention via transient formation of π-allyl complexes.[10,11] Anti S_N2' displacement of the leaving group from such substrates is also well documented and provides access to α-substituted-β,γ-unsaturated esters.[12,13] Furthermore, the chiral hydroxymethine fragment can exert a powerful stereodirecting influence and this has been used in conjugate additions and similar reactions to produce β-functionalized derivatives.[14-22]



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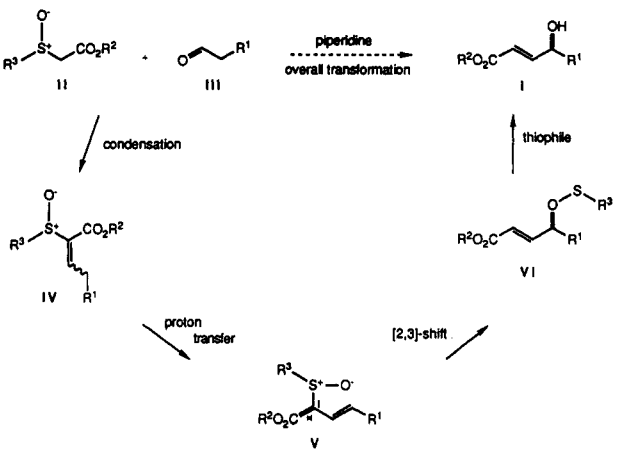
Scheme I. SPAC Reaction. Intermediate V Preferentially Adopts the Conformation Shown Due to 1,3-Allylic Strain



In view of this potential it is unfortunate that substances 1 in a high state of enantiomeric purity have been relatively inaccessible. Optically active samples are not, for instance, easily obtained via Sharpless' kinetic resolution/epoxidation[23] due to the deactivating influence of the ester substituent. The most practical approach to these chirons has been to react optically active α-hydroxy aldehyde

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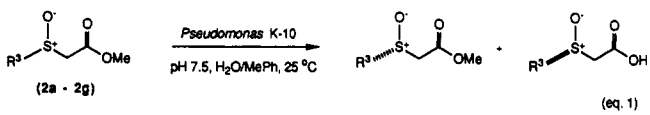
derivatives with stabilized Wittig reagents or phosphonate anions, but this does not address the problem of *forming* hydroxymethine centers with defined absolute stereochemistry. Consequently, applications of γ-hydroxy-α,β-unsaturated esters 1 in *asymmetric* synthesis have been limited.

Recently we developed an extremely convenient procedure for kinetic resolutions of methyl sulfinylacetates **2a–g**, which uses a crude preparation of the cheap, readily available, lipase *Pseudomonas* K-10 (eq 1).[24] Subsequently, we became interested in reactions of methyl sulfinylacetates with aldehydes to give γ-hydroxy-α,β-unsaturated compounds 1 in a single operation. Such transformations are experimentally simple but involve several mechanistic steps (Scheme I);[25-29] here they are referred to as SPAC (Sulfoxide Piperidine And Carbonyl) reactions for convenience. Previous literature indicated that monochiral sulfinylacetates can give SPAC reaction products I in around 60% ee,[30-32] so we set about enhancing induction in this process to develop methodology of practical value in asymmetric synthesis. This paper describes how SPAC reactions of simple aldehydes may be used to produce starting materials for nonracemic preparations and presents an illustrative synthesis of a statine analogue.



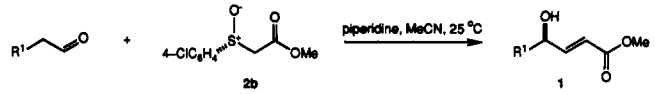
R^3 = 4-$NO_2C_6H_4$, 4-ClC_6H_4, Ph, 4-$MeOC_6H_4$, 2-Nap, n-Bu, and Cy.

Results and Discussion

When this research was initiated, it was unclear how steric and electronic properties of the sulfoxide substituent R^3 influence chemical and optical yields obtained in SPAC reactions; the appropriate experiments had not been performed, persumably due to practical problems associated with preparing a suitable range of monochiral sulfinylacetates. However, the resolution depicted in eq 1 provided a selection of reagents for this study. Results presented previously[24] indicate that aliphatic sulfoxides give low induction relative to those with an aromatic substituent and, amongst the latter, electron-deficient aromatic substituents are best.

It is necessary to pinpoint the origin of asymmetric induction in SPAC reactions with optically active sulfoxides to explain these observations.[24] Previous studies have shown intermediates IV can be observed via NMR but the allylic sulfoxides V cannot,[30,33] presumably because the [2,3]-sigmatropic shift restores conjugation of the ester with the alkene moiety (Scheme I). Attack of the thiophile on

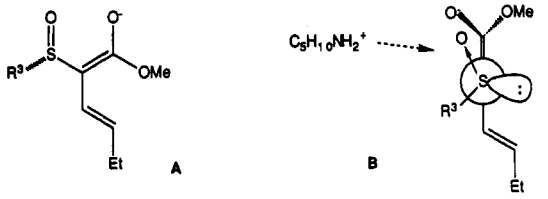
Table I. Effect of Aldehyde Structure on Chemical and Optical Yields in the SPAC Reaction



entry	R^1	reactn time (h)	1 no.	1 yield (%)[a]	1 ee (%)[b]
1	Me	19	**1a**	71	64
2	Et	23	**1b**	86	60
3	*n*-Pr	3	**1c**	65	75
4	*i*-$PrCH_2$	24	**1d**	54	74
5	$CyCH_2$	13	**1e**	83	60
6	$Me_2ThexSiO(CH_2)_2$	24	**1f**	75	68
7	*i*-Pr	21	**1g**	94	50
8	Ph	24	**1h**	16	~0

[a] Isolated after flash chromatography. [b] Determined via ^1H NMR/chiral shift reagent studies.

intermediate VI may be faster than the retro-[2,3] shift thus enforcing kinetic control. Extensive studies on Evans–Mislow rearrangements[34-36] of chiral allylic sulfoxides show that the sulfoxide chirality does not affect the stereochemical outcome because the sulfoxide rearranges on the face of the double bond which corresponds to minimum 1,3-allylic strain in the transition state (Scheme I).[37,38] Consequently, *configurations of alcohols formed in SPAC reactions are determined by the transient asymmetric center C[1] of intermediate V and asymmetry at the sulfoxide is significant in the preceding proton transfer step and thereafter it is unimportant.* This crucial proton transfer probably involves conjugate deprotonation by piperidine and α-protonation by piperidinium ions. We speculate that face selectivity in protonation of the intermediate enolate A occurs via the reactive conformation B as shown.



Three factors indicate that conformation B should be the most reactive conformation. Firstly, interaction of the (nonbonding) orbital containing a sulfur lone pair with the π-orbital of the enolate (HOMO) destabilizes the latter, making it is energetically more compatible with unfilled orbitals on the protonating entity (LUMO); this produces net stabilization of incipient bond formation. Secondly, the sulfoxide substituent R^3 rests in the outside position, thus avoiding approach of the electrophile (which probably occurs at an acute angle with respect to the enolate π-system).[39] Finally, the sulfoxide oxygen is suitably disposed for transient hydrogen bonding with the proton to be delivered. If this model is correct, the observations presented earlier[24] are explicable. Electron-withdrawing substituents in the position labeled R^3 give maximum induction in the SPAC process because it is unfavorable for good σ-acceptor groups to adopt the position anti to the

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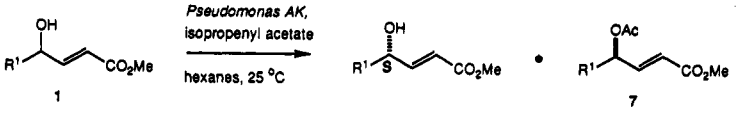
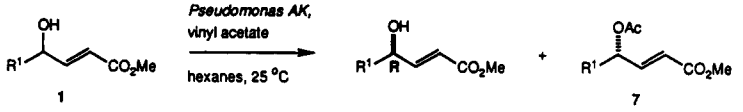
Table II. Biocatalytic Resolutions of "Straight Chain" γ-Hydroxy-α,β-unsaturated Methyl Esters



			unreacted alcohols		product acetates		
entry (compd)	R^1	time[a] (h)	ee (%)[b] (config)	yield (%)[c]	ee (%)[b] (config)	yield (%)[c]	E
1 (**1a**)	Me	49	>95 (*S*)	37[d]	91 (*R*)	39[d]	>30
2 (**1b**)	Et	116	>95 (*S*)	44	>95 (*R*)	45	>150
3 (**1c**)	*n*-Pr	400	>95 (*S*)	42	74 (*R*)	54	>20

[a] All the reactions were performed on a 1–2 mmol scale using equal masses of substrates and enzyme preparation, 0.2 M in heptane presaturated with pH 7.5 phosphate buffer, at 25 °C. [b] Enantiomeric excesses were determined by ^{1}H NMR using (Eu(hfc)$_3$. [c] Isolated yields after flash chromatography. [d] Some material was lost in the isolation procedure because this compound is slightly volatile.

Table III. Biocatalytic Resolutions of "Branched Chain" γ-Hydroxy-α,β-unsaturated Esters



			unreacted alcohols		product acetates		
entry (compd)	R^1	time[a] (days)	ee (%) (config)	yield (%)	ee (%) (config)	yield (%)	E
1 (**1g**)	*i*-Pr	6	14 (*R*)	46	19 (*S*)	43	1.6
2 (**1d**)	*i*-PrCH$_2$	7	37 (*R*)	40	28 (*S*)	55	2.5
3 (**1e**)	CyCH$_2$	6.5	54 (*R*)	51	77 (*S*)	36	13
4 (**1f**)	Si'O(CH$_2$)$_2$[b]	7	72 (*R*)	57	>95 (*S*)	35	>150

[a] All the reactions were performed on a 1–2 mmol scale using 5 mass equiv of enzyme and 10 molar equiv of vinyl acetate relative to substrate; 0.005 M in heptane presaturated with pH 7.5 phosphate buffer, at 25 °C. See Table II for information on determination of ee and yields. [b] Si' = Me$_2$ThexSi.

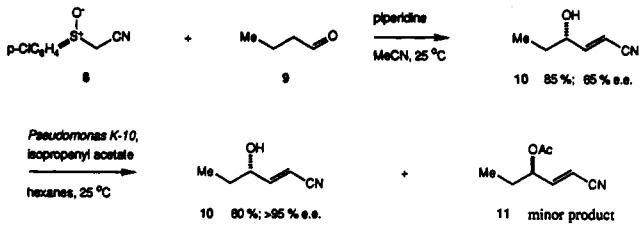
approaching electrophile (due to the electronic factors outlined in above).

In practice the (4-chlorophenyl)sulfinyl ester **2b** (R^3 = 4-ClC_6H_4) is favored over the others (i.e., **2a** and **2c–f**) even though the nitro compound **2a** (R^3 = 4-$NO_2C_6H_4$) gives slightly better induction (72 versus 79% ee). This is because 4-chlorothiophenol is cheaper than the corresponding nitro compound and commercial samples of the latter material are relatively impure.

Table I summarizes eight experiments in which (*R*)-methyl [(4-chlorophenyl)sulfinyl]acetate (**2b**) was reacted with a range of aldehydes to probe the effect of structural changes of this component on chemical and optical yields in the SPAC reaction. Good chemical yields were obtained in all cases except for the reaction of phenylacetaldehyde (entry 8) for which self-condensation of the aldehyde is a major competing factor. Phenylacetaldehyde is also unusual insofar as the product is virtually racemic. We speculate that transformation of intermediate IV to V in the SPAC reaction of this substrate (Scheme I, R^1 = Ph, R^2 = Me, R^3 = 4-ClC_6H_4) is reversible because conjugation of the phenyl group in allylic sulfoxide V stabilizes this intermediate. Consequently, the configuration at C^1 may be epimerized prior to the rearrangement, hence lack of stereoselectivity here reflects thermodynamic, rather than kinetic, control. All other aldehydes studied gave products with enantiomeric excesses in the ranges 50–75%. Consequently, good chemical yields and moderate optical yields can be obtained provided the aldehyde component is not particularly vulnerable to self-condensation.

It is also possible to obtain SPAC reaction products of high optical purity via kinetic resolutions of racemic materials. Tables II and III depict results obtained when SPAC reaction products were acylated in hexane[40–47] by

Scheme II. Enantiomeric Enrichment of a SPAC Product via Enzymatic Acylation



using an enol acetate[48–50] in the presence of the crude lipase preparation *Pseudomonas* K-10 (Amano). Table II indicates that *R* enantiomers of substrates 1 with straight-chain alkyl substituents are acylated in preference to their optical antipodes, and good enantiodiscrimination can be obtained (as indicated by the high *E* values).[51] However, Table III shows that substrates with branched-chain substituents behave differently, *the enantioselectivity is opposite so that S enantiomers are acylated in preference.* Entries 1 and 2 (Table III) describe resolutions for which the enantioselectivity is low, reflecting a transition between

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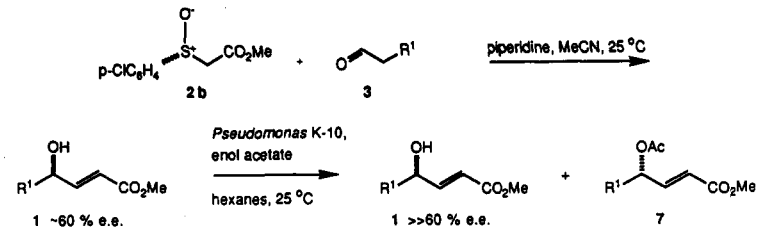
Table IV. Asymmetric Enrichment Sequences Employing [(4-Chlorophenyl)sulfinyl]acetate (2b)



		SPAC reaction		lipase resolution			
entry (compd)	R^1	yield (1)[a] (%)	ee (%)[b]	yield (1)[a] (%)	ee (%)[b]	time (days)	overall yield (%)
1 (1e)	$CyCH_2$	83	60	90	78	6	75
2 (1e)	$CyCH_2$	83	60	62	86	8	51
3 (1f)	$Si'O(CH_2)_2$[c]	75	63	86	92	6	65

[a] Isolated yields after flash chromatography. [b] Enantiomeric excesses were determined by ^1H NMR using $Eu(hfc)_3$. [c] Si' = $Me_2ThexSi$.

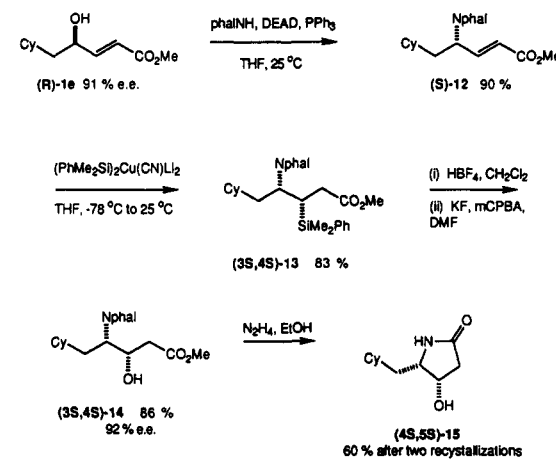
these extremes; enantioselection seems to increase as the substituent becomes more hydrophobic (entries 3 and 4).[52]

Rearrangements of optically active sulfinylacetates (depicted in Table I) give good chemical yields but with optical yields below the level that is generally of practical value. Conversely, the processes shown in Table II give products that are nearly optically pure; however, as with all kinetic resolutions of non-interconverting racemic mixtures, they are intrinsically wasteful unless both starting material and acylated product are required. Separately, asymmetric SPAC reactions and lipase-mediated resolutions of the products are of limited value, but in combination they constitute a powerful tool for non-racemic synthesis; SPAC reactions used in sequence with biocatalytic resolutions can give nearly enantiomeric pure products in high chemical yield (Scheme II). For instance, asymmetric SPAC reaction using the monochiral sulfinylnitrile 8 can be used to produce the α,β-unsaturated nitrile 10 in good yield and moderate enantiomeric excess. This sample is then exposed to *Pseudomonas* K-10/isopropenyl acetate, which removes all the detectable (^1H NMR/chiral shift) minor enantiomer (*R*) as the corresponding acetate 11. The maximum theoretical yield in this step is 82.5%, but only 60% was isolated due to problems associated with manipulating these volatile materials. Nevertheless, this "asymmetric enrichment"[53,54] procedure gives almost optically pure material in good chemical yield.

The sulfinylnitrile reagent 8 employed in Scheme II was prepared via an Andersen resolution but sulfinylacetate **2b** is accessible via the much less arduous *Pseudomonas* K-10 mediated hydrolysis (vide supra). Consequently, SPAC sequences that involve the latter reagent in conjunction with a biocatalytic resolution illustrate the versatility of lipases in organic synthesis: *Pseudomonas K-10 catalyses the aqueous hydrolysis used to resolve sulfinyl acetate **2b** and enantioselective acylations of the SPAC reaction products in hexane.* Results presented in Table IV underline this point.

Finally, compound 15 was synthesized to illustrate how SPAC methodology can be used in organic synthesis (Scheme III). A SPAC reaction of the resolved [((*R*)-4-chlorophenyl)sulfinyl]acetate (**2b**) gave product **1e** (R^1 = $CyCH_2$; Cy = cyclohexyl) in 60% ee with the *R* enantiomer in excess; the optical purity of this material was then enriched by using biocatalytic acylation with *Pseudomonas* K-10 (cf. Table IV). Mitsunobu displacement[55] of the

Scheme III. Asymmetric Synthesis of Statine Analogue 15



hydroxyl group with phthalimide established γ-nitrogen functionality with inversion of configuration to give the protected allylamine derivative (*S*)-**12** without formation of detectable amounts (^1H NMR) of S_N2' displacement products. Addition of the silylcuprate[56-58] "$(PhMe_2Si)_2Cu(CN)Li_2$"[59] to this α,β-unsaturated ester (**12**) gives predominantly syn addition as proven by analysis of the final product **15** (vide infra). When this cuprate addition is performed at 0 °C, a significant amount of the anti product is formed (syn:anti = 3:1 by HPLC), but at −78 °C the syn:anti ratio is at least 24:1.

We propose the reactive conformation shown below to account for syn addition of the silylcuprate reagent to α,β-unsaturated ester **12**. This model satisfies four important criteria: (i) secondary orbital interactions mix the σ^* orbital of the best σ-acceptor substituent on the chiral center (the phthalimido group) with the π^* of the alkene producing a low energy LUMO which is more compatible with the HOMO (occupied orbital of the nucleophile); (ii) steric repulsion between the (relatively large) phthalimido group and the approaching nucleophile is minimized; (iii) steric repulsion between the methylenecyclohexyl substituent and a nucleophile (the cuprate) approaching at an obtuse angle is relieved; and (iv) 1,3-allylic strain between the alkene hydrogen nearest the ester and the $CyCH_2$ substituent is attenuated because these groups are

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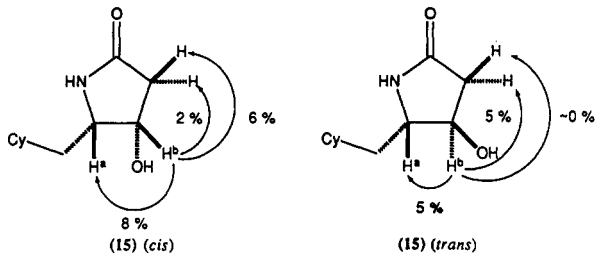
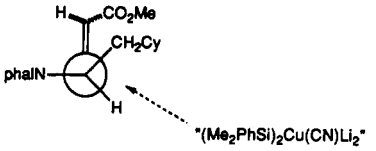


Figure 1. Difference NOE experiments for lactam 15 and its trans isomer (irradiation at H^b in both cases).

not eclipsed. Additions of alkylcuprates to similar substrates can be either syn or anti selective.[14,15,18] Those that are syn selective involve cuprates of large alkyl groups or cuprates whose reactivity is adjusted by Lewis acidic additives; we propose that d-π^* back-bonding from the metal is not critical in determining diastereofacial selectivity in these examples. Conversely, frontier orbitals involved in alkene to copper π-complexation[60-62] may control the anti selective processes. Parenthetically we note that additions to Z-γ-substituted-α,β-unsaturated esters are governed predominantly by steric factors because minimization of 1,3-allylic strain[38] becomes the overriding concern.



Conversion of the silyl functionality of compound 13 into a hydroxyl group might have been problematic; all conditions for such transformations involve developing negative charge on the silicon atom which, in this particular substrate, could lead to antiperiplanar elimination of the phthalimido group. In the event this proved not to be an obstacle. Transformation of silane 13 into alcohol 14 was effected smoothly by using conditions developed by Tamao and co-workers.[63] Finally, liberation of the amino group via treatment with hydrazine also brought about ring closure to give the product 15 in good yield.

Lactam 15 has been synthesized previously but comparison of physical data for our sample with that in the literature[64] is inconclusive due to the peculiar physical properties of this product, i.e., crystals of the racemic form are less soluble than those of enantiomerically pure material but have higher melting points.[65] Recrystallization of optically active product therefore can cause a decrease in specific rotation and an increase in melting range. Indeed the physical data for samples obtained via the route described above did not quite match that published even though the NMR data are identical and combustion analyses gave accurate results. Consequently, difference NOE studies of lactam 15 were undertaken in an attempt to confirm the relative stereochemistry. An 8% enhancement between the hydroxymethine proton and the other methine proton was observed, greater than any other enhancement between the hydroxymethine proton and the methylene protons in the lactam ring (Figure 1). En-

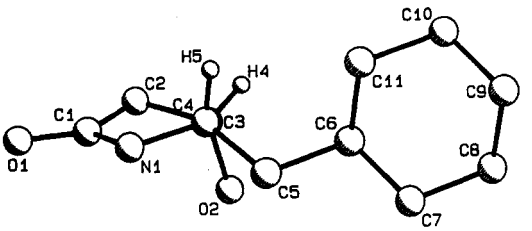


Figure 2. Abbreviated PLUTO digram of (4S-*cis*)-5-(cyclohexylmethyl)-4-hydroxy-2-pyrrolidone (15).

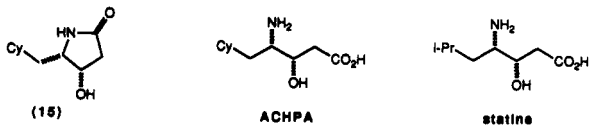
Table V. Selected Bond Parameters for Lactam 15

	Distances (Å)		
C1–C2	1.505 (8)	C2–C3	1.505 (8)
C3–C4	1.534 (8)	N1–C4	1.455 (7)
N1–C1	1.330 (7)	C1–O1	1.240 (7)
C4–C5	1.520 (8)	C5–C6	1.511 (8)
	Angles (deg)		
C1–C2–C3	103.8 (6)	C2–C3–C4	102.6 (5)
C3–C4–N1	100.9 (5)	C4–N1–C1	113.5 (5)
N1–C1–O1	125.8 (6)	C2–C1–O1	126.6 (7)
N1–C4–C5	113.4 (5)	C3–C4–C5	116.3 (5)
C4–C3–O2	111.9 (5)	C2–C3–O2	113.0 (5)
H5–C4–C3	108.70	H4–C3–C4	109.60

couraged, but not convinced, by these results we repeated the cuprate addition at room temperature, separated diastereomers via preparative HPLC, and obtained a small amount of a compound tentatively characterized (^{1}H NMR data only) as the anti analogue of silane 13. This was carried through the synthesis to give the trans isomer of lactam 15, which was also analyzed via NMR double irradiation techniques. The NOE enhancements between the methine protons of this compound were, as expected, less than that for the cis isomer 15; however, they were not substantially smaller (Figure 1).

Finally, lactam 15 was analyzed by single-crystal X-ray diffraction, which confirmed cis stereochemistry of this product, and, by inference, addition of the silylcuprate reagent to substrate 12 gave the syn silane 13. Figure 2 contains an abbreviated PLUTO diagram of lactam 15 and Table V gives important bond parameters for these materials. The dihedral angle between the methine protons of this material in the solid state is 35°.

Lactam 15 can be ring opened[64] to 4-amino-5-cyclohexyl-3-hydroxypentanoic acid (ACHPA), an analogue of statine. Peptidomimetics containing statine can be potent inhibitors of protease enzymes[66] and sequences containing ACHPA can have even more potent activities.[67] Most syntheses of statine and related compounds[64,67,68] begin with naturally occurring amino acid derivatives.[69] The synthesis presented in Scheme III, however, is completely asymmetric; it illustrates how statine surrogates can be prepared from achiral materials, an approach that may be valuable for syntheses of analogues that cannot be prepared from amino acids or other readily available chirons.



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Conclusions

Biocatalytic resolutions of sulfinylacetates are a convenient route to reagents for asymmetric SPAC reactions. Using methyl[(4-chlorophenyl)sulfinyl]acetate (**2b**), these SPAC processes consistently give good chemical yields and moderate optical yields of γ-hydroxy-α,β-unsaturated esters **1**, irrespective of the aldehyde structure (provided the latter is not particularly prone to self-condensation). Racemic γ-hydroxy-α,β-unsaturated compounds **1** can be resolved via biocatalytic resolutions in organic solvents, a resolution mediated by the same lipase (*Pseudomonas* K-10) used for resolution of the sulfinylacetate reagents. Used in tandem, asymmetric SPAC reactions and biocatalytic resolutions of SPAC reaction provide useful syntheses of optically pure allylic alcohols **1**, which may be used as chirons in organic synthesis.

Experimental Section

General Procedures. Melting points were uncorrected. HPLC was performed with a UV–vis detector. High-field NMR spectra were recorded on an IBM 300-MHz or 250-MHz Bruker instrument using $CDCl_3$ solvent. In cases where abbreviated DEPT sequence experiments were carried out during ^{13}C NMR experiments, the carbon multiplicities are listed as (C) quaternary, (CH_2) methylene, and (CH/CH_3) methine/methyl. The purity of all products was assessed as >95% via ^1H and ^{13}C NMR analyses. Unless otherwise indicated, the optical purities were measured via ^1H NMR analyses of samples with added (+)-Eu(hfc)$_3$. Thin-layer chromatography was performed on silica gel 60 F_{254} plates from Whatman. Flash chromatography was performed on SP silica gel 60 (230–400-mesh ASTM).

Tetrahydrofuran (THF) was distilled immediately before use from sodium benzophenone ketyl. Dichloromethane was freshly distilled from CaH_2 before use. Acetonitrile was distilled from P_2O_5 before use.

Procedure A: Methyl γ-Hydroxy-α,β-unsaturated Esters 1. A 1.0 M solution of the aldehyde (5.0 equiv) in acetonitrile was added over ~1 h to a stirred solution of piperidine (5.0 equiv) and a 0.5 M solution of the methyl sulfinylacetate (1.0 equiv) in acetonitrile under N_2. The resulting light brown solution was stirred at 25 °C for the time specified. Removal of the volatiles in vacuo gave the crude product, which was purified by flash chromatography.

(*E*)-Methyl 4-Hydroxyhept-2-enoate[32,33,70] (1c, R¹ = *n*-Pr) from Sulfinylacetates 2a–g.[24] Procedure A was used, and the product was isolated via flash chromatography (20% ethyl acetate in hexane) as an oil: R_f 0.3 (20% ethyl acetate in hexane); ^1H NMR δ 6.95 (dd, J = 15.6 and 4.88 Hz, 1 H), 6.03 (dd, J = 15.6 and 1.52 Hz, 1 H), 4.32 (m, 1 H), 3.74 (s, 3 H), 0.84–1.64 (m, 8 H); IR (neat) 3450 (br st), 1725 (st), 1670 (md) cm^{-1}.

Reactions of Methyl [((*R*)-4-Chlorophenyl)sulfinyl]acetate (2b) with Aldehydes (Table I). Procedure A was used. The following products were isolated via flash chromatography, eluting with ethyl acetate–hexane mixtures of the appropriate composition (10–30% EtOAc). **(*E*)-Methyl 4-hydroxypent-2-enoate[25,71–73] (1a, R¹ = Me):** an oil, R_f 0.3 (20% ethyl acetate in hexane); ^1H NMR δ 6.96 (dd, J = 15.7 and 4.63 Hz, 1 H), 6.02 (dd, J = 15.7 and 1.56 Hz, 1 H), 4.49 (m, 1 H), 3.74 (s, 3 H), 1.69 (br s, 1 H), 1.32 (d, J = 9.63 Hz, 3 H). **(*E*)-Methyl 4-hydroxyhex-2-enoate[10,21,27,28,33,74] (1b, R¹ = Et):** an oil, R_f 0.3 (20% ethyl acetate in hexane); ^1H NMR δ 6.94 (dd, J = 15.6 and 4.96 Hz, 1 H), 6.04 (dd, J = 15.6 and 1.53 Hz, 1 H), 4.25 (m, 1 H), 3.74 (s, 3 H), 1.71 (br s, 1 H), 1.61 (m, 2 H), 0.96 (t, J = 7.43 Hz, 3 H); IR (neat) 3450 (br md), 1725 (st), 1670 (md) cm^{-1}. **(*E*)-Methyl 4-hydroxy-6-methylhept-2-enoate (1d, R¹ = *i*-PrCH$_2$):** an oil, R_f 0.3 (20% ethyl acetate in hexane); ^1H NMR δ 6.95 (dd, J = 15.6 and 5.02 Hz, 1 H), 6.04 (dd, J = 15.6 and 1.45 Hz, 1 H), 4.37 (m, 1 H), 3.74 (s, 3 H), 0.93 (d, J = 6.60 Hz, 6 H), 0.84–1.81 (m, 4 H); ^{13}C NMR δ 167.2 (C), 151.3 (CH/CH_3), 119.3 (CH/CH_3), 69.2 (CH/CH_3), 51.7 (CH/CH_3), 45.6 (CH_2), 24.5 (CH/CH_3), 23.1 (CH/CH_3), 22.1 (CH/CH_3); IR (neat) 3450 (br md), 1725 (st), 1670 (md) cm^{-1}; MS (EI, 70 eV) m/e (rel intensity) 172 (1, M$^+$), 149 (100); HRMS calcd for $C_9H_{16}O_3$ 172.10993, found 172.11009. **(*E*)-Methyl 5-cyclohexyl-4-hydroxypent-2-enoate (1e, R¹ = CyCH$_2$):** colorless crystals, mp 54–56 °C, R_f 0.4 (20% ethyl acetate in hexane); ^1H NMR δ 6.94 (dd, J = 15.6 and 4.89 Hz, 1 H), 6.03 (dd, J = 15.6 and 1.51 Hz, 1 H), 4.40 (m, 1 H), 3.73 (s, 3 H), 0.86–1.79 (m, 14 H); ^{13}C NMR δ 167.1 (C), 151.1 (CH/CH_3), 119.5 (CH/CH_3), 68.9 (CH/CH_3), 51.7 (CH/CH_3), 44.5 (CH_2), 33.9 (CH_2), 32.9 (CH_2), 26.5 (CH_2), C 26.3 (CH_2), 26.2 (CH_2); IR ($CHBr_3$) 3450 (br md), 1720 (st), 1670 (md) cm^{-1}; MS (EI, 70 eV) m/e (rel intensity) 212 (0.5, M$^+$), 183 (29), 88 (100); HRMS calcd for $C_{12}H_{20}O_3$ 212.14123, found 212.14101. **Methyl-6-(dimethylthexylsiloxy)-4-hydroxyhex-2-enoate (1f, R¹ = Me$_2$(CHMe$_2$CMe$_2$)SiO(CH$_2$)$_2$):** an oil, R_f 0.4 (20% ethyl acetate in hexane); ^1H NMR δ 6.94 (dd, J = 15.6 and 4.04 Hz, 1 H), 6.13 (dd, J = 15.6 and 1.61 Hz, 1 H), 4.55 (m, 1 H), 3.84 (m, 2 H), 3.73 (s, 3 H), 1.56–1.86 (m, 3 H), 0.87 (d, J = 6.83 Hz, 6 H), 0.84 (s, 6 H), 0.82 (m, 1 H), 0.11 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR δ 167.2 (C), 150.3 (CH/CH_3), 119.7 (CH/CH_3), 70.9 (CH/CH_3), 61.7 (CH_2), 51.6 (CH/CH_3), 37.3 (CH_2), 34.1 (CH/CH_3), 20.2 (CH/CH_3), 18.5 (CH/CH_3), -3.6 (CH/CH_3); IR (neat) 3500 (br st), 1730 (st), 1665 (md) cm^{-1}; MS (EI, 30 eV) m/e (rel intensity) 271 (1), 182 (28), 105 (100); HRMS calcd for $C_{15}H_{30}O_4Si$ 302.191317, found 302.19106. **(*E*)-Methyl 4-hydroxy-5-methylhex-2-enoate[75] (1g, R¹ = *i*-Pr):** an oil, R_f 0.3 (20% ethyl acetate in hexane); ^1H NMR δ 6.96 (dd, J = 15.6 and 5.01 Hz, 1 H), 6.05 (dd, J = 15.6 and 1.42 Hz, 1 H), 4.10 (m, 1 H), 3.74 (s, 3 H), 0.86–1.86 (m, 8 H); ^{13}C NMR δ 166.9 (C), 149.7 (CH/CH_3), 120.0 (CH/CH_3), 75.2 (CH/CH_3), 51.2 (CH/CH_3), 33.3 (CH/CH_3), 17.9 (CH/CH_3), 17.3 (CH/CH_3); IR (neat) 3470 (br md), 1725 (st), 1665 (md) cm^{-1}. **(*E*)-Methyl 4-hydroxy-4-phenylbut-2-enoate (1h, R¹ = Ph):** an oil, R_f 0.3 (20% ethyl acetate in hexane); ^1H NMR δ 7.29 (m, 5 H), 7.05 (dd, J = 15.6 and 4.80 Hz, 1 H), 6.18 (dd, J = 15.6 and 1.72 Hz, 1 H), 5.37 (m, 1 H), 3.73 (s, 3 H), 2.10 (br s, 1 H); IR (neat) 3450 (br md), 1725 (st), 1675 (md), 1600 (wk), 1520 (md), 1500 (md) cm^{-1}.

Procedure B: Biocatalytic Resolutions (Table II). Isopropenyl acetate (10.0 equiv) was added to a suspension of the crude lipase preparation *Pseudomonas* K-10 (~0.5 mass equiv) in a 1.0 M solution of the methyl γ-hydroxy-α,β-unsaturated ester (1.00 equiv) in 90–110 °C petroleum ether (saturated with water) and stirred for the time specified. The reaction was stopped by filtering through Celite and volatiles were then removed in vacuo to give the crude mixture of the product and the unreacted starting material. These were separated by flash chromatography (ethyl acetate/hexane eluant, 20–30% EtOAc).

Biocatalytic Resolutions of 1a–c. Procedure B was applied under the conditions indicated in Table II. **Methyl 4-Acetoxypent-2-enoate[79–81] (7, R¹ = Me).** Recovered starting material **1a** (R¹ = Me) was isolated as an oil: $[\alpha]^{25}_D$ +20° (*c* 2.4, $CHCl_3$). The product **7** (R¹ = Me) was also obtained as an oil: R_f 0.7 (20% ethyl acetate in hexane); $[\alpha]^{25}_D$ +30° (*c* 2.3, $CHCl_3$); ^1H NMR δ 6.87 (dd, J = 15.7 and 5.00 Hz, 1 H), 5.95 (dd, J = 15.7 and 1.62 Hz, 1 H), 5.48 (m, 1 H), 3.74 (s, 3 H), 2.08 (s, 3 H), 1.35 (d, J = 6.66 Hz, 3 H); IR (neat) 1730 (st), 1710 (st), 1660 (md) cm^{-1}. **Methyl 4-Acetoxyhex-2-enoate[78,79] (7, R¹ = Et).** Resolved starting material **1b** (R¹ = Et) was obtained as an oil: $[\alpha]^{25}_D$ +24° (*c* 3.1, $CHCl_3$). The product **7** (R¹ = Et) was also obtained as an oil: R_f 0.7 (20% ethyl acetate in hexane); $[\alpha]^{25}_D$ +28° (*c* 3.8, $CHCl_3$); ^1H NMR δ 6.84 (dd, J = 15.8 and 5.37 Hz, 1 H), 5.94 (dd, J = 15.8 and 1.35 Hz, 1 H), 5.34 (m, 1 H), 3.74 (s, 3 H), 2.09 (s,

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3 H), 1.70 (m, 2 H), 0.92 (t, J = 7.44 Hz, 3 H); IR (neat) 1730 (st), 1710 (st), 1660 (md) cm^{-1}. **Methyl 4-Acetoxyhept-2-enoate**[70,76,77] **(7, R^1 = *n*-Pr).** Unreacted starting material (1c) was isolated as an oil: $[\alpha]^{25}_D$ +21° (c 1.6, $CHCl_3$). The product 7 (R^1 = *n*-Pr) was also obtained as an oil: R_f 0.7 (20% ethyl acetate in hexane); $[\alpha]^{25}_D$ +18° (c 4.5, $CHCl_3$); ^{1}H NMR δ 6.84 (dd, J = 15.7 and 5.36 Hz, 1 H), 5.93 (dd, J = 15.7 and 1.37 Hz, 1 H), 5.39 (m, 1 H), 3.73 (s, 3 H), 2.08 (s, 3 H), 1.24–1.68 (m, 4 H), 0.91 (t, J = 7.31 Hz, 3 H); IR (neat) 1740 (st), 1730 (st), 1665 (md) cm^{-1}.

Procedure C: Biocatalytic Resolutions (Table III). A crude lipase preparation of *Pseudomonas* K-10 (5 mass equiv) was added to a solution of vinyl acetate (10.0 equiv) and the methyl γ-hydroxy-α,β-unsaturated ester (1.00 equiv, 0.005 M) in 35–60 °C petroleum ether and stirred for the time specified. The reaction was stopped by filtering through Celite and volatiles were then removed in vacuo to give the crude mixture of the product and unreacted starting material. These were separated by flash chromatography (ethyl acetate/hexane eluant, 20–30% EtOAc).

Biocatalytic Resolutions of 1d–f. Procedure C was applied under the conditions indicated in Table III. **Methyl 4-Acetoxy-5-cyclohexylpent-2-enoate (7, R^1 = CyCH$_2$).** Recovered starting material 1e was isolated as yellow crystals: $[\alpha]^{25}_D$ – 5.5° (c 1.7, $CHCl_3$). The product 7 (R^1 = $CyCH_2$) was obtained as an oil: R_f 0.6 (20% ethyl acetate in hexane); ^{1}H NMR δ 6.84 (dd, J = 15.6 and 5.31 Hz, 1 H), 5.92 (dd, J = 15.6 and 1.26 Hz, 1 H), 5.47 (m, 1 H), 3.73 (s, 3 H), 2.08 (s, 3 H), 0.85–1.75 (m, 13 H); ^{13}C NMR δ 170.1 (C), 166.6 (C), 146.3 (CH/CH_3), 120.8 (CH/CH_3), 70.5 (CH/CH_3), 51.7 (CH/CH_3), 41.4 (CH_2), 33.8 (CH/CH_3), 33.5 (CH_2), 32.9 (CH_2), 26.4 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 21.1 (CH/CH_3); IR ($CHBr_3$) 1740 (st), 1730 (st), 1665 (md) cm^{-1}; MS (EI, 30 eV) m/e (rel intensity) 228 (28), 226 (62), 212 (80), 211 (53), 113 (100); HRMS calcd for $C_{14}H_{22}O_4$ 254.15179, found 254.15152. **Methyl 4-Acetoxy-6-methylhept-2-enoate (7, R^1 = *i*-PrCH$_2$).** Resolved starting material 1d was isolated as an oil: $[\alpha]^{25}_D$ –9.6° (c 0.50, $CHCl_3$). The product 7 (R^1 = *i*-$PrCH_2$) was also obtained as an oil: R_f 0.5 (20% ethyl acetate in hexane); $[\alpha]^{25}_D$ –6.0° (c 1.7, $CHCl_3$); ^{1}H NMR δ 6.84 (dd, J = 15.7 and 5.46 Hz, 1 H), 5.93 (dd, J = 15.7 and 1.43 Hz, 1 H), 5.45 (m, 1 H), 3.73 (s, 3 H), 2.08 (s, 3 H), 1.38–1.70 (m, 3 H), 0.92 (m, 6 H); ^{13}C NMR δ 170.2 (C), 166.6 (C), 146.1 (CH/CH_3), 120.9 (CH/CH_3), 71.1 (CH/CH_3), 51.8 (CH/CH_3), 42.8 (CH_2), 24.6 (CH/CH_3), 22.9 (CH/CH_3), 22.2 (CH/CH_3), 21.1 (CH/CH_3); IR (neat) 1745 (st), 1735 (st), 1665 (md) cm^{-1}; MS (EI, 70 eV) m/e (rel intensity) 182 (2), 83 (100); HRMS calcd for $[M - CH_3OH]^+$ $C_{10}H_{14}O_3$ 182.09428, found 182.09428. **Methyl 4-Acetoxy-6-(dimethylthexylsiloxy)hex-2-enoate (7, R^1 = Me$_2$(CHMe$_2$CMe$_2$)SiO(CH$_2$)$_2$).** Recovered starting material 1f was obtained as an oil. The product 7 (R^1 = $Me_2(Me_2CHCMe_2)SiO(CH_2)_2$) was also obtained as an oil; R_f 0.6 (20% ethyl acetate in hexane); $[\alpha]^{25}_D$ –17° (c 0.90, $CHCl_3$); ^{1}H NMR δ 6.88 (dd, J = 15.8 and 5.42 Hz, 1 H), 5.92 (dd, J = 15.8 and 1.42 Hz, 1 H), 5.54 (m, 1 H), 3.73 (s, 3 H), 3.63 (m, 2 H), 2.08 (s, 3 H), 1.84 (m, 2 H), 0.89 (m, 1 H), 0.86 (d, J = 6.86 Hz, 6 H), 0.82 (s, 6 H), 0.06 (s, 6 H); ^{13}C NMR δ 170.0 (C), 166.5 (C), 146.0 (CH/CH_3), 120.9 (CH/CH_3), 70.0 (CH/CH_3), 58.3 (CH_2), 51.8 (CH/CH_3), 38.8 (CH_2), 34.2 (CH/CH_3), 25.1 (C), 21.0 (CH/CH_3), 20.3 (CH/CH_3), 18.5 (CH/CH_3), –3.4 (CH/CH_3), –3.5 (CH/CH_3); IR (neat) 1745 (st), 1735 (st), 1665 (md) cm^{-1}; MS (EI, 30 eV) m/e (rel intensity) 309 (1), 307 (1), 271 (2), 117 (100); HRMS matched for $[M - SiMe_3]^+$ calcd for $C_{14}H_{23}O_5$ 271.15453, found 271.15492. **Methyl 4-Acetoxy-5-methylhex-2-enoate (7, R^1 = *i*-Pr).** Recovered starting material 1g was isolated as an oil: $[\alpha]^{25}_D$ –3.6° (c 2.6, $CHCl_3$). The product 7 (R^1 = iPr) was also obtained as an oil: R_f 0.7 (20% ethyl acetate in hexane); $[\alpha]^{25}_D$ –0.67° (c 2.7, $CHCl_3$); ^{1}H NMR δ 6.84 (dd, J = 15.7 and 5.50 Hz, 1 H), 5.92 (dd, J = 15.7 and 1.21 Hz, 1 H), 5.23 (m, 1 H), 3.73 (s, 3 H), 2.08 (s, 3 H), 1.95 (m, 1 H), 0.91–0.94 (m, 6 H); ^{13}C NMR δ 170.2 (C), 166.5 (C), 144.5 (CH/CH_3), 122.0 (CH/CH_3), 76.9 (CH/CH_3), 51.8 (CH/CH_3), 31.9 (CH/CH_3), 21.0 (CH/CH_3), 18.1 (CH/CH_3), 17.8 (CH/CH_3); IR (neat) 1740 (st), 1730 (st), 1665 (md) cm^{-1}; MS (EI, 30 eV) m/e (rel intensity) 159 (37), 157 (25), 43 (100); HRMS calcd for $[M - CH_3CO]^+$ $C_8H_{13}O_3$ 157.086455, found 157.08641.

Methyl 4-Acetoxy-5-cyclohexylpent-2-enoate (7, R^1 = CyCH$_2$), "Enantiomeric Enrichment Procedure". General procedure C was used with 0.212 (1.00 mmol, 1.00 equiv) of 1e (60% ee—*R* enantiomer in excess). The reaction was stirred at 25 °C for 6 days. Flash chromatography (10–20% ethyl acetate in hexane) provided recovered starting material 1e (0.191 g, 90%) as colorless crystals (78% ee); 0.033 g (13%) of the product 7 (R^1 = $CyCH_2$) was also obtained as an oil: $[\alpha]^{25}_D$ –7.0° (c 1.2, $CHCl_3$); 45% ee. When this reaction was repeated but using an 8-day reactiontime, recovered starting material 1e (0.131 g, 62%) was isolated as colorless crystals in 86% ee; 0.071 g (28%) of the product 7 (R^1 = $CyCH_2$) was also obtained as an oil: 39% ee.

Methyl 4-Acetoxy-6-(dimethylthexylsiloxy)hex-2-enoate (7, R^1 = Me$_2$(CHMe$_2$CMe$_2$)SiO(CH$_2$)$_2$), "Enantiomeric Enrichment Procedure". General procedure C was used with 0.302 g (1.00 mmol, 1.00 equiv) of 1f (63% ee—*R* enantiomer in excess). The reaction was stirred at 25 °C for 6 days. Flash chromatography (10–20% ethyl acetate in hexane) provided recovered starting material 1f (0.260 g, 86%) as an oil: $[\alpha]^{25}_D$ +5.19° (c 13.1, $CHCl_3$); 92% ee (from ^{1}H NMR using chiral Eu(III)—*R* enantiomer in excess); 0.022 g (7%) of the product 7 was also obtained as an oil.

[(*S*)-4-Chlorophenyl)sulfinyl]acetonitrile[31] **(8).** To a stirred solution of 25.0 mmol (2.50 equiv) of lithium diisopropylamide in 33.0 mL of THF and 13.2 mL of hexane at –78 °C was added 1.03 g (25.0 mmol, 2.50 equiv) of acetonitrile. The resulting white suspension was stirred at –78 °C for 30 min. A solution of 3.15 g (10.0 mmol, 1.00 equiv) of (1*S*,2*R*,5*S*)-menthyl (*R*)-(+)-4-chlorobenzenesulfinate was then added over 10 min and the resulting deep red solution was stirred at –78 °C for 45 min and then at –23 °C for 75 min. The reaction was carefully quenched by the addition of 50 mL of saturated NH_4Cl. The organic layer was collected and the aqueous layer extracted with 3 × 100 mL of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$). Removal of the volatiles in vacuo followed by flash chromatography (20–100% ethyl acetate in hexane) provided the product (1.48 g, 74%) as brown crystals: R_f 0.1 (20% ethyl acetate in hexane); ^{1}H NMR δ 7.61 (m, 4 H), 3.86 (d, J = 15.9 Hz, 1 H), 3.66 (d, J = 15.9 Hz, 1 H); ^{13}C NMR δ 139.6 (C), 139.1 (C), 130.0 (CH/CH_3), 125.6 (CH/CH_3), 111.0 (C), 44.6 (CH_2); IR ($CHBr_3$) 2250 (wk) cm^{-1}.

(*E*)-4-Hydroxyhex-2-enenitrile (10). General procedure A was used with 1.40 g (7.00 mmol, 1.00 equiv) of (*S*)-4-chlorophenyl)acetonitrile (8) (0.25 M in acetonitrile) and a solution of 1.01 g (14.0 mmol, 2.00 equiv) of butyraldehyde (0.7 M) in acetonitrile. The reaction was stirred at 25 °C for 1 h; 50 mL of a 0.10 M solution of tartaric acid was then added and the mixture extracted with 3 × 200 mL of ether. The combined organic layers were dried ($MgSO_4$). Removal of the volatiles in vacuo followed by flash chromatography (20% ethyl acetate in hexane) provided the product (0.660 g, 85%) as an oil: R_f 0.3 (20% ethyl acetate in hexane); 65% ee (from ^{1}H NMR of MTPA [1-methoxy-1-(trifluoromethyl)phenylacetic acid] ester—*S* enantiomer in excess); ^{1}H NMR δ 6.74 (dd, J = 16.2 and 3.90 Hz, 1 H), 5.67 (dd, J = 16.2 and 1.89 Hz, 1 H), 4.26 (m, 1 H), 1.82 (br s, 1 H), 1.61 (m, 2 H), 0.97 (t, J = 7.42 Hz, 3 H); ^{13}C NMR δ 157.0 (CH/CH_3), 117.5 (C), 98.6, (CH/CH_3) 71.9 (CH/CH_3), 29.2 (CH_2), 9.3 (CH/CH_3); IR (neat) 3420 (br st), 2230 (st), 1635 (md), 1600 (wk), 1520 (md), 1500 (md) cm^{-1}; MS (EI, 70 eV) m/e (rel intensity) 111 (5, M$^+$), 54 (100); HRMS calcd for C_6H_9NO 111.068405, found 111.06839.

4-Acetoxyhex-2-enenitrile (11), "Enantiomeric Enrichment Procedure". Equal masses [i.e., 1 "mass equivalent"] (0.555 g) of a crude lipase preparation of *Pseudomonas* K-10 and substrate (nitrile 10, 5.00 mmol, 1.00 equiv) [65% ee—*S* enantiomer in excess] were dissolved in 4.55 g (45.5 mmol, 9.10 equiv) of isopropenyl acetate and stirred at 25 °C for 38 h. The reaction was stopped by filtering through Celite; volatiles were then removed in vacuo to give the crude mixture of the product and unreacted starting material. Flash chromatography (10–20% ethyl acetate in hexane) provided recovered starting material 10 (0.330 g, 60%) as an oil: $[\alpha]^{25}_D$ +47° (c 1.5, $CHCl_3$), i.e., *S* configuration;[31] >95% ee (from ^{1}H NMR of MTPA ester). The product 11, 0.180 g (24%), was also obtained as an oil: R_f 0.7 (20% ethyl acetate in hexane); $[\alpha]^{25}_D$ +7.2° (c 1.7, $CHCl_3$); 24% ee; ^{1}H NMR δ 6.62 (dd, J = 16.1 and 5.52 Hz, 1 H), 5.51 (dd, J = 16.1 and 1.39 Hz, 1 H), 5.30 (m, 1 H), 2.10 (s, 3 H), 1.69 (m, 2 H), 0.92 (t, J = 7.40 Hz, 3 H); ^{13}C NMR δ 169.8 (C), 151.7 (CH/CH_3), 116.6 (C), 100.6 (CH/CH_3), 73.2 (CH/CH_3), 26.5 (CH_2), 20.8 (CH/CH_3), 9.0 (CH/CH_3); IR (neat) 2225 (md), 1745 (st), 1640 (md) cm^{-1}; MS (EI, 70 eV) m/e (rel intensity) 153 (4, M$^+$), 43 (100); HRMS calcd

for $C_8H_{11}O_2$ 153.078965, found 153.07870.

(4*S*)-(*E*)-Methyl 5-Cyclohexyl-4-phthalimidopent-2-enoate ((*S*)-12). Diethyl azodicarboxylate (2.78 g, 16.0 mmol, 1.05 equiv) was added to a solution of 3.22 g (15.2 mmol, 1.00 equiv) of (*R*)-1e (R^1 = $CyCH_2$) (91% ee), 3.98 (15.2 mmol, 1.00 equiv) of triphenylphosphine, and 2.23 g (15.2 mmol, 1.00 equiv) of phthalimide in 75 mL of THF at 0 °C under N_2. The reaction was allowed to warm to 25 °C and stirred for 21 h. Volatiles were removed in vacuo and the orange residue obtained was dissolved in the minimum amount of ether. On cooling triphenylphosphine oxide crystallized out and this was filtered off, washing with ether. Volatiles were removed in vacuo from the filtrate and purification by flash chromatography (10–20% ethyl acetate in hexane) gave the product (4.67 g, 90%) as an oil: R_f 0.4 (20% ethyl acetate in hexane); $[\alpha]^{25}_D$ −1.39° (*c* 11.3, $CHCl_3$); ^1H NMR δ 7.78 (m, 4 H), 7.15 (dd, *J* = 15.8 and 6.68 Hz, 1 H), 5.90 (dd, *J* = 15.8 and 1.16 Hz, 1 H), 5.02 (m, 1 H), 3.71 (s, 3 H), 0.87–2.19 (m, 13 H); ^{13}C NMR δ 167.4 (C), 165.9 (C), 145.0 (CH/CH_3), 133.9 (CH/CH_3), 131.4 (C), 123.0 (CH/CH_3), 121.9 (CH/CH_3), 51.3 (CH/CH_3), 48.9 (CH/CH_3), 38.5 (CH_2), 33.9 (CH/CH_3), 32.9 (CH_2), 32.2 (CH_2), 26.1 (CH_2), 25.7 (CH_2), 25.6 (CH_2); IR (neat) 1780 (st), 1725 (st), 1670 (md) cm^{-1}; MS (EI, 70 eV) *m/e* (rel intensity) 341 (4, M^+), 184 (100); HRMS calcd for $C_{20}H_{23}NO_4$ 341.16269, found 341.16272.

(3*S*,4*S*)-Methyl 5-Cyclohexyl-3-(dimethylphenylsilyl)-4-phthalimidopentanoate ((3*S*,4*S*)-13). A 0.8 M solution of (dimethylphenylsilyl)lithium (25.0 mL, 20.0 mmol, 2.00 equiv) of was added to a suspension of 0.896 g (10.0 mmol, 1.00 equiv of CuCN in 30 mL of THF at 0 °C under N_2. The reaction was stirred at 0 °C for 30 min. The dark red solution was then cooled to −78 °C and a solution of 3.41 g (10.0 mmol, 1.00 equiv) of (*S*)-12 in 12 mL of THF was added dropwise. The dark red solution was stirred at −78 °C for 30 min and then left at −23 °C overnight, followed by 2 h at 0 °C. Methanol (15 mL) was added to quench the reaction. Ether (200 mL) and 100 mL of a 10:1 saturated NH_4Cl/1 M NaOH solution were added. The organic layer was collected and the aqueous layer extracted with 2 × 150 mL of ether. After drying ($MgSO_4$) the combined organic layers and removal of the volatiles in vacuo, purification by flash chromatography (5–10% ethyl acetate in hexane) gave the product (3.96 g, 83%) as an oil: R_f 0.7 (20% ethyl acetate in hexane); $[\alpha]^{25}_D$ −14.7° (*c* 13.1, $CHCl_3$); 93% de (from HPLC using silica column) ^1H NMR δ 6.99–7.61 (m, 9 H), 4.51 (m, 1 H), 3.58 (s, 3 H), 2.59 (m, 2 H), 0.65–2.42 (m, 14 H), 0.35 (s, 3 H), 0.27 (s, 3 H); ^{13}C NMR δ 173.9 (C), 168.7 (C), 139.3 (C), 137.0 (C), 133.8 (CH/CH_3), 133.6 (CH/CH_3), 133.4 (CH/CH_3), 133.0 (CH/CH_3), 131.7 (C), 129.5 (CH/CH_3), 128.6 (CH/CH_3), 127.8 (CH/CH_3), 127.5 (CH/CH_3), 122.9 (CH/CH_3), 51.6 (CH/CH_3), 49.6 (CH/CH_3), 36.9 (CH_2), 34.4 (CH/CH_3), 34.2 (CH_2), 32.2 (CH_2), 31.8 (CH_2), 26.4 (CH_2), 26.1 (CH_2), 25.8 (CH_2), 0.0 (CH/CH_3), −2.8 (CH/CH_3), −5.0 (CH CH_3); IR (neat) 1765 (md), 1745 (st), 1710 (st) cm^{-1}; MS (EI, 70 eV) *m/e* (rel intensity) 477 (0.8, M^+), 55 (100); HRMS calcd for $C_{28}H_{35}NO_4Si$ 477.233512, found 477.23242.

(3*S*,4*S*)-Methyl 5-Cyclohexyl-3-hydroxy-4-phthalimidopentanoate ((3*S*,4*S*)-14). A portion of 1.33 g (7.00 mmol, 2.00 equiv) of HBF_4·OEt_2 (85%) was added to a solution of 1.67 g (3.50 mmol, 1.00 equiv) of (3*S*,4*S*)-13 in 14 mL of CH_2Cl_2 under N_2. The reaction was stirred at 25 °C for 12 h. The volume of the resulting orange solution was made up to 130 mL with CH_2Cl_2 and then washed with 60 mL of water followed by 2 × 60 mL of saturated NaCl solution. After drying ($MgSO_4$), the volatiles were removed in vacuo to give the fluorosilyl intermediate as a yellow oil, which was used without characterization at this stage. *m*-Chloroperbenzoic acid (MCPBA, 2.13 g, 10.5 mmol, 3.00 equiv of 85%) was added to a solution of the above intermediate and 0.407 g (7.00 mmol, 2.00 equiv) of anhydrous KF in 15 mL of dimethylformamide (DMF) at 10 °C. The reaction was stirred at 25 °C for 12 h and then poured into 250 mL of water and extracted with 5 × 75 mL of ether. The combined ether layers were washed with 250 mL of saturated $NaHSO_3$ solution, 3 × 80 mL of saturated $NaHCO_3$ solution, and 80 mL of water. After drying ($MgSO_4$) and removal of the volatiles in vacuo, purification by flash chromatography (20–30% ethyl acetate in hexane) gave the product (1.08 g, 86%) as colorless crystals (recrystallized from ethyl acetate/hexane): mp 93–97 °C; R_f 0.1 (20% ethyl acetate in hexane); $[\alpha]^{25}_D$ −21° (*c* 1.7, $CHCl_3$); 92% ee from ^1H NMR using chiral Eu(III); ^1H NMR δ 7.78 (m, 4 H), 4.42 (m, 2 H), 3.76 (br s, 1 H), 3.67 (s, 3 H), 2.48 (m, 2 H), 0.82–2.08 (m, 13 H); ^{13}C NMR δ 171.7 (C), 169.1 (C), 134.2 (CH/CH_3), 131.5 (C), 123.4 (CH/CH_3), 68.9 (CH/CH_3), 53.0 (CH/CH_3), 51.8 (CH/CH_3), 39.5 (CH_2), 36.1 (CH_2), 34.2 (CH/CH_3), 33.6 (CH_2), 32.3 (CH_2), 26.3 (CH_2), 26.0 (CH_2), 25.8 (CH_2); IR ($CHBr_3$) 3440 (st), 1775 (md), 1740 (st), 1710 (st) cm^{-1}; MS (EI, 70 eV) *m/e* (rel intensity) 359 (0.3, M^+), 174 (100); HRMS calcd for $C_{20}H_{25}NO_5$ 359.1732, found 359.1731.

(4*S*-*cis*)-5-(Cyclohexylmethyl)-4-hydroxy-2-pyrrolidinone ((4*S*-*cis*)-15). Anhydrous hydrazine (0.962 g, 30.0 mmol, 30.0 equiv) was added to a solution of 0.359 g (1.00 mmol, 1.00 equiv) of (3*S*,4*S*)-14 in 3.0 mL of absolute ethanol. The resulting yellow solution was refluxed for 3 h. The reaction was allowed to cool and the colorless crystals that formed were filtered off, washing with ethanol. Volatiles were removed in vacuo from the filtrate and ethyl acetate then added to the remaining yellow solid. After warming, the resultant hot solution containing some undissolved material was filtered again, washing with ethyl acetate. Removal of the volatiles in vacuo from the filtrate and two recrystallizations from ethyl acetate gave the product (4*S*-*cis*)-15 (0.118 g, 60%) as colorless crystals: mp 165–166 °C; R_f 0.2 (ethyl acetate); $[\alpha]^{25}_D$ −30° (*c* 0.070, $CHCl_3$) [lit.[64] $[\alpha]^{25}_D$ = −25.6° (*c* 0.99, $CHCl_3$)]; ^1H NMR δ 5.79 (br s, 1 H), 4.39 (m, 1 H), 3.73 (m, 1 H), 2.62 (dd, J = 17.2 and 5.81 (Hz, 1 H), 2.32 (dd, J = 17.2 and 1.9 Hz, 1 H), 0.82–1.73 (m, 14 H); ^{13}C NMR δ 176.0 (C), 69.5 (CH/CH_3), 57.0 (CH/CH_3), 41.1 (CH_2), 36.3 (CH_2), 34.9 (CH/CH_3), 33.9 (CH_2), 33.1 (CH_2), 26.4 (CH_2), 26.23 (CH_2), 26.17 (CH_2); IR ($CHBr_3$) 3440 (st), 3270 (st), 1725 (st), 1665 (md), 1455 (st) cm^{-1}; MS (EI, 70 eV) *m/e* (rel intensity) 197 (39, M^+), 39 (100); HRMS calcd for $C_{11}H_{19}NO_2$ 197.1416, found 197.1412. Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.87; H, 9.74; N, 7.15.

(4*S*-*trans*)-5-(Cyclohexylmethyl)-4-hydroxy-2-pyrrolidinone ((4*S*-*trans*)-15). The silylcuprate addition to (*S*)-12 was carried out as described above but at 0 °C. The de was 51% (cf. 93% de at −78 °C) in favor of (3*S*,4*S*)-13. The minor diasteromer (3*R*,4*S*)-13 was separated by HPLC. The diasteromer (4*S*-*trans*)-15 was then synthesized in the same way as (4*S*-*cis*)-15: ^1H NMR δ 5.91 (br s, 1 H), 4.39 (m, 1 H), 3.73 (m, 1 H), 2.62 (dd, *J* = 17.1 and 5.79 Hz, 1 H), 2.32 (dd, *J* = 17.1 and 1.87 Hz, 1 H), 0.82–1.73 (m, 14 H); ^{13}C NMR ^{13}C NMR δ 176.0 (C), 69.5 (CH/CH_3), 57.0 (CH/CH_3), 41.1 (CH_2), 36.3 (CH_2), 34.9 (CH/CH_3), 34.0 (CH_2), 33.1 (CH_2), 26.4 (CH_2), 26.23 (CH_2), 26.17 (CH_2); IR ($CHBr_3$) 3440 (st), 3270 (st), 1725 (st), 1665 (md), 1455 (st) cm^{-1}.

X-ray Diffraction Analysis. A clear, colorless crystal of 15 was mounted on a glass fiber with epoxy cement. Data were collected on a Rigaku AFC5S four-circle automated diffractometer using Mo Kα radiation. Primitive cell parameters, determined from 19 random reflections, indicated a monoclinic cell, which was confirmed by the Laue symmetry check. The space group $P2_1/n$ (#14) was determined from intensity statistics and systematic absences. The structure was solved with SHELXS86 followed by full-matrix least-squares difference refinements using TEXSAN (v. 2.0) and converged with R = 0.067 and R_w = 0.074. Nitrogen and oxygen were refined with anisotropic thermal parameters; all other non-hydrogen atoms were refined isotropically. Hydrogen atoms were included in calculated positions and were not refined. The equivalent reflections were averaged, and the data were corrected for LP effects and anomalous dispersion, but not for absorption or decay.

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Registry No. (*S*)-1a, 116560-93-1; (*S*)-1b, 130323-18-1; (*S*)-1c, 106426-92-0; (*R*)-1d, 130323-22-7; (*R*)-1e, 130323-23-8; (*R*)-1f, 130323-24-9; (*R*)-1g, 130323-21-6; (±)-1h, 131934-05-9; (*R*)-2a,

125761-96-8; (*R*)-**2b**, 102340-69-2; (*R*)-**2c**, 98639-89-5; (*R*)-**2d**, 102340-68-1; (*R*)-**2e**, 131933-99-8; (*S*)-**2f**, 125761-98-0; (*R*)-**2g**, 125761-99-1; (*R*)-**7a**, 130255-31-1; (*R*)-**7b**, 130323-19-2; (*R*)-**7c**, 130323-20-5; (*S*)-**7d**, 130255-33-3; (*S*)-**7e**, 130255-34-4; (*S*)-**7f**, 130255-35-5; (*S*)-**7g**, 130255-32-2; **8**, 109574-74-5; **9**, 123-72-8; **10**, 130323-25-0; **11**, 131934-00-4; (*S*)-**12**, 131934-01-5; (3*S*,4*S*)-**13**, 131973-33-6; (3*R*,4*S*)-**13**, 131934-04-8; (3*S*,4*S*)-**14**, 131934-02-6; (4*S*,5*S*)-**15**, 126910-76-7; (4*S*-*trans*)-**15**, 131934-03-7; ACHPA, 105192-90-3; CH_3CH_2CHO, 123-38-6; $CH_3(CH_2)_3CHO$, 110-62-3; $Me_2CHCH_2CH_2CHO$, 1119-16-0; $CyCH_2CH_2CHO$, 4361-28-8; $Me_2ThexSiO(CH_2)_3CHO$, 125382-48-1; Me_2CHCH_2CHO, 590-86-3; $PhCH_2CHO$, 122-78-1; CH_3CN, 75-05-8; $Me_2PhSiLi$, 3839-31-4; (1*S*,2*R*,5*S*)-menthyl (*R*)-(+)-4-chlorobenzenesulfinate, 109667-51-8; lipase, 9001-62-1.

Supplementary Material Available: ORTEP diagram and tables of crystallographic data collection, atomic coordinates, and anisotropic thermal parameters and ^1H and ^{13}C NMR spectra for each new compound described (32 pages). Ordering information is given on any current masthead page.

Tandem Reactions in 4-Siloxy-1-benzopyrylium Salts: Introduction of Substituents and Cyclohexene and Cyclopentane Annulation in Chromones

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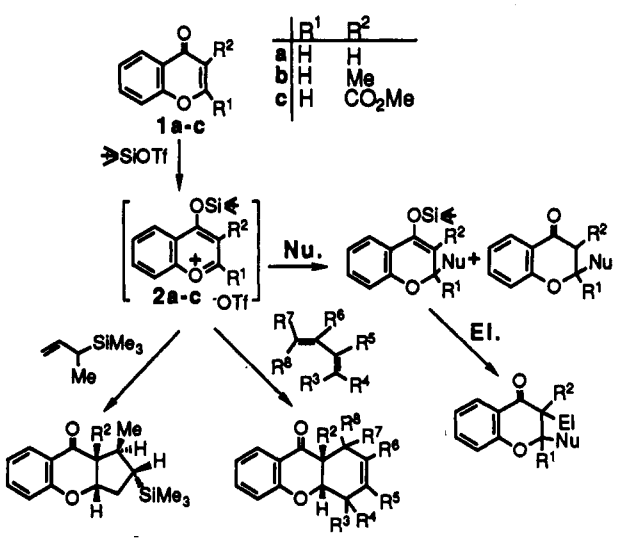
Reactions of 4-[(*tert*-butyldimethylsilyl)oxy]-1-benzopyrylium triflates (**2a–c**) with silyl enol ethers (**3a–d**) or allyl organometallic reagents (**5a–c**) afforded the corresponding 2-substituted 4-siloxy-2*H*-1-benzopyrans (**4a–d** and **6a–d**) along with 2,3-dihydrobenzopyrone derivatives (**7a–c**). An unexpected cyclopentane annulation to give **8a,b** was observed in the reaction of **2a,b** with 3-(trimethylsilyl)-1-butene (**5d**). Treatment of the products (**4a** and **6a**) with electrophiles (iminium salt, NBS, and NCS) converted them into the corresponding 2,3-disubstituted 2,3-dihydrobenzopyrone derivatives (**9a–c**). Reaction of benzopyrylium salts (**2a,b**) with α,β-unsaturated ketones (**10a–g**) in the presence of *tert*-butyldimethylsilyl triflate and 2,6-lutidine gave cyclohexene annulation products (xanthone derivatives, **11a–j**) in moderate to high yield. The reaction mechanisms are explained in terms of stereoelectronic and 1,3-allylic strain effects together with steric hindrance during the reaction.

Various natural products containing the chromone or xanthone skeletons have been isolated.[1] Introduction of substituents into chromone (4*H*-1-benzopyran-4-one) ring has been studied from the standpoint of the development of synthetic methodology and the mechanistic interest in the reactions of these heterocycles.[2] Although chromones can be regarded as α,β-unsaturated ketones, there are few synthetic methods for introduction of carbon nucleophiles at the C_2 position of the heterocyclic ring without ring opening or ring transformation of the heterocycle.[2a,e,f] In this connection, Wallace and his co-workers found that alkylcopper boron trifluoride complexes are effective in the introduction of an alkyl group into the C_2 position of chromone derivatives.[2g,i] Furthermore, they showed that cycloaddition of an activated chromone bearing an electron-withdrawing group at C_3 with butadienes gives xanthone derivatives by using a catalytic amount of titanium(IV) chloride.[3] However, this ring closure at the α,β-unsaturated ketone moiety of the chromone did not proceed without an activating group at C_3.

Scheme I



We have developed a facile and useful method for regioselective introduction of carbon nucleophiles into α-pyrones via pyrylium cations by means of *tert*-butyldimethylsilyl triflate.[4] During the course of this study, it

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