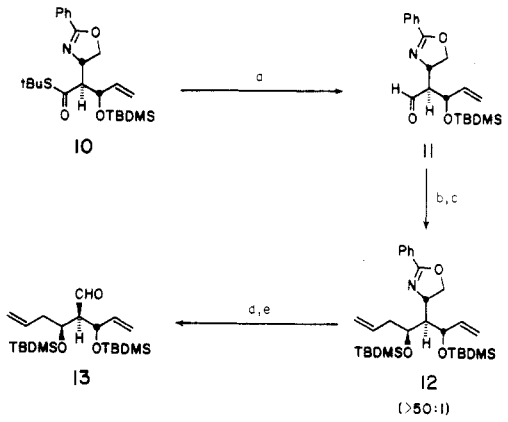
Scheme III[a]



[a] (a) Dibal, PhMe, −78 °C; (b) $Zn(allyl)_2$, THF, 0 °C; (c) TBDMSOTf, Et_3N, CH_2Cl_2, 0 °C; (d) Dibal, PhMe, 0 °C; (e) $NaIO_4$, EtOH, H_2O.

on an intervening chelate. The oxazoline is unmasked through reductive cleavage to a benzylamino alcohol[12] which is subsequently oxidized to aldehyde **13** through exposure to $NaIO_4$. Compound **13**, isolated as a single isomer in greater than 50% overall yield from **7**, may serve as a convenient precursor to subunits bearing side-chain carboxyl (amphotericin B, streptovaricin A) and hydroxy methylene groups (tylosin).

In summary, we have shown that β-amino thiol ester **7** may engage in highly stereoselective aldol condensations to afford adducts that are useful intermediates for branched-chain polyol fragments (e.g., **2**). The latent symmetry of **7** and its readily accessible enantiomer[13] confers considerable stereochemical latitude to this approach. Further application of this strategy to the synthesis of amphotericin B will be reported in due course.

Acknowledgment is made to the National Institutes of Health (AI 188889) for their generous support of this research.

Registry No. **4**, 1487-49-6; **6** (isomer 1), 103959-37-1; **6** (isomer 2), 103959-38-2; **6** (isomer 3), 103959-39-3; **6** (isomer 4), 103959-40-6; **7**, 102614-13-1; **9** (R = t-$BuMe_2SiOCH_2CH_2$), 103959-51-9; **9** (R = Ph), 103959-52-0; **9** (R = 3,4,5-$(MeO)_3C_6H_2$), 103959-53-1; **9** (R = p-$O_2NC_6H_4$), 103959-54-2; **9a** (R = C_2H_5), 103959-41-7; **9a** (R = t-$BuMe_2SiOCH_2CH_2$), 103959-42-8; **9a** (R = Ph), 103959-43-9; **9a** (R = 3,4,5-$(MeO)_3C_6H_2$), 103959-44-0; **9a** (R = p-$O_2NC_6H_4$), 103959-45-1; **9a** (R = CH_2=CH), 103959-46-2; **9a** (R = PhSCH=CH), 103959-47-3; **9a** (R = Me_3SiCH=CH), 103959-48-4; **11**, 103980-76-3; **12**, 103959-49-5; **13**, 103959-50-8; t-$BuMe_2SiOCH_2CH_2CHO$, 89922-82-7; CH_2=CHCHO, 107-02-8; PhSCH=CHCHO, 78998-83-1; Me_3SiCH=CHCHO, 58107-34-9; PhCHO, 100-52-7; C_2H_5CHO, 123-38-6; 3,4,5-$(MeO)_3C_6H_2CHO$, 86-81-7; p-$O_2NC_6H_4CHO$, 555-16-8; $Zn(allyl)_2$, 1802-55-7.

Supplementary Material Available: Physical and spectral data on the compounds in Table I and Scheme III (3 pages). Ordering information is given on any current masthead page.

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(13) The enantiomer of **7** is prepared from readily available D-aspartic acid.

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Phase-Managed Organic Synthesis. A New Synthesis of Mixed Formic Anhydrides

Summary: Two new mixed formic anhydrides, cinnamic formic anhydride and formic 4-methoxybenzoic anhydride, can be prepared in high yield (~80%) from equimolar mixtures of sodium formate and the appropriate acid chloride with a solid-phase copolymer of pyridine 1-oxide as catalyst, and they exhibit excellent selectivity as formylating agents of alcohols and amines.

Sir: During a continuing investigation of the application of multiple-phase techniques to organic synthesis, we discovered that a solid-phase copolymer of 4-vinylpyridine 1-oxide[1] (P4-VP-NO) is a particularly effective catalyst for the formation of mixed formic anhydrides, eq 1. This

$$\mathrm{RCOCl + HCOO^-Na^+ \xrightarrow[CH_3CH,\ rt]{P4\text{-}VP\text{-}NO} RCOOCOH + NaCl} \quad (1)$$

1: R = PhCH=CH
2: R = 4-MeOPh

method utilizes mixtures equimolar in acid chloride and sodium formate to obtain high isolated yields (~80%) of the corresponding stable mixed anhydride. Anhydrous acetonitrile proved to be a suitable solvent. Catalysis of the reaction is believed to involve acylation of P4-VP-NO to form the 1-acyloxy derivative **3**, which then acylates formate ion to give the mixed formic anhydride as shown in Scheme I.[2-5] Some results obtained with this new synthetic method are summarized in Table I. It is especially noteworthy that the stable mixed formic anhydrides obtained in this manner are excellent formylating agents, Table II.

Formylation of nucleophiles is an important synthetic procedure accomplished by a wide variety of methods. An effective approach available for relatively unreactive substrates (e.g., alcohols, phenols) uses acetic formic anhydride generated in situ from formic acid–acetic anhydride mixtures with catalysis by tertiary amines.[6-8] Formic anhydride itself is highly unstable and may be studied only at temperatures below −40 °C.[9] It decomposes to formic acid and carbon monoxide, eq 2. Several mixed formic anhydrides are known which vary widely in stability.[10-12]

$$\mathrm{RCOOCOH \rightarrow RCOOH + CO} \quad (2)$$

R = H, alkenyl, alkoxy, alkyl, aryl

(1) The solid-phase copolymer of 4-vinylpyridine 1-oxide used as a catalyst in this study, P4-VP-NO, was prepared by oxidizing Reillex 425, available from Reilly Tar & Chemical Corporation, Indianapolis, with 30% hydrogen peroxide in glacial acetic acid (Ochiai, E. *Aromatic Amine Oxides*; Elsevier Publishing Company: Amsterdam, 1974; p 24).
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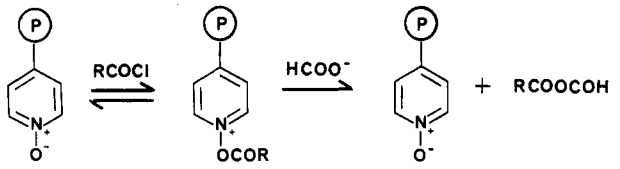
Scheme I



3

Table I. Synthesis of Mixed Formic Anhydrides[a]

reactants RCOCl	anhydrides[b] total yield (%)	mole ratio RCOO-COH	mole ratio RCOO-COR	lit. ref mixed anhydrides
	Catalysis by P4-VP-NO[c]			
R = Me	7.2	0.00	1.00	15
Me_3C	47.9	0.83	0.17	12
Ph	60.4	0.85	0.15	19, 20
4-MeOPh	88.9	0.97	0.03	this work
PhCH=CH	88.7	0.94	0.06	this work
PhCH=CH[d]	54.9	0.87	0.13	
PhCH=CH[e]	71.6	0.96	0.04	
	Catalysis by P4-VP[c]			
PhCH=CH	67.5	0.80	0.20	
PhCH=CH[d]	56.3	0.92	0.08	
	No Catalyst			
PhCH=CH[e]	44.1	1.00	0.00	

[a] Reaction mixtures contained 5 mmol of acid chloride, 1.0 equiv of dried and powdered sodium formate, 0.20 g of P4-VP-NO or P4-VP (Reillex 425), and 20 mL of anhydrous acetonitrile, and they were stirred vigorously with Teflon-coated stir bars for 1.5 h at room temperature unless otherwise noted. Products were isolated after filtering reaction mixtures, diluting (2.5×) filtrates with dichloromethane, washing with 5% aqueous sodium bicarbonate, drying over anhydrous magnesium sulfate, and rotary evaporation. [b] Identity of known products was established by comparison of IR and ^1H NMR spectral data with published values. New anhydrides gave mass spectra with appropriate molecular ions (ref 17 and 18). Composition of product mixtures was estimated by integration of ^1H NMR spectra of isolated materials. [c] Reference 1. [d] Reaction mixture contained 5 mmol of acid chloride, 1.1 equiv of formic acid, 1.5 equiv of P4-VP-NO or P4-VP, and 20 mL of dichloromethane and it was stirred for 1 h at 0 °C. The product mixture obtained with P4-VP-NO catalysis included 12.4% unreacted cinnamoyl chloride; with P4-VP catalysis the reaction was complete. [e] The reactions were run at 0 °C for 60 min. The product mixture of the uncatalyzed reaction contained 52.1% unreacted cinnamoyl chloride and 1.9% cinnamic acid. The product mixture with catalysis by P4-VP-NO contained 20.7% cinnamoyl chloride and 4.7% cinnamic acid.

Among this group of potential formylating agents, only acetic formic anhydride has been used extensively.[13-15] However, Zwikker and co-workers[12] found formic trimethylacetic anhydride to be a more selective N-formylating agent. The three α-methyl groups reduced the reactivity of the trimethylacetyl carbonyl substantially.

We like others have found mixed formic anhydrides to be prone to disproportionation and/or decomposition in the presence of carboxylic acids, salts, and the tertiary amines commonly used as transacylation catalysts.[6] Therefore, we were pleasantly surprised to find that the polymeric pyridine 1-oxide, P4-VP-NO, catalyzes formation of some mixed formic anhydrides from sodium formate and an acid chloride at rates much faster than subsequent disproportionation and other degradative pathways. The reaction is also sensitive to reactant/catalyst ratio. Product yields optimized at a reactant to catalyst molar ratio of 10, presumably a consequence of maximizing anhydride formation vs. disproportionation/decomposition. Product formation is accelerated approximately twofold by 0.10 equiv of P4-VP-NO at 0 °C, Table I. The related 4-vinylpyridine polymer (P4-VP) was not an effective catalyst. In its presence, the rate of mixed anhydride formation remained at the level of the uncatalyzed reaction, Table I. Pyridine 1-oxide itself catalyzes the reaction but the mixed formic anhydride so produced is quite unstable in the presence of trace amounts of *N*-oxide.

Attempts to convert mixtures of formic acid and acid chlorides to mixed formic anhydrides in the presence of either P4-VP-NO or P4-VP were only moderately successful.[16] Catalysis by P4-VP-NO and P4-VP at 0 °C for 1 h gave cinnamic formic anhydride in 48% and 52% yield, respectively, Table I.

Two of the newly synthesized anhydrides, cinnamic formic anhydride,[17] **1**, and formic 4-methoxybenzoic anhydride,[18] **2**, are thermally stable solids. Treatment of alcohols and amines with **1** and **2** leads exclusively to the formylated product in essentially quantitative yield in reactions with primary and secondary amines. Product yields are also high with the less nucleophilic alcohols.

Table II. Representative Formylation Experiments[a]

RCOOCOH, R = nucleophile	base/catalyst	reactn time (min)	formamide/formate ester[b] yield (%)	lit. ref
PhCH=CH $PhNH_2$		60	96.0	22, 23
$PhCH_2NHMe$		30	98.8	26
$H_2NCH(CH_2Ph)$-COOMe·HCl	aq K_2CO_3[c]	30	96.3	24
4-MeOPh $PhCH_2NH_2$		30	96.7	22, 25
$PhCH_2NHMe$		30	99.7	26
$PhNH_2$		60	99.0	22, 23
PhNHMe		60	91.2	22, 25
$H_2NCH(CH_2Ph)$-COOMe·HCl	aq K_2CO_3[c]	30	96.5	24
$PhCH_2OH$		120	87.5	22, 25
	$NaHCO_3$[d]	120	78.0	
cyclohexanol		180	80.7	6b, 22
	2,6-lutidine[e]	180	80.7	
1-methylcyclohexanol		240	81.8[f]	this work
	2,6-lutidine[e]	900	78.7[f]	

[a] Reactions were carried out at room temperature with well-stirred mixtures of 5 mmol of mixed formic anhydride and 1.0 equiv of nucleophile in 10 mL of dichloromethane unless otherwise noted. [b] The yields are based on isolated products which had melting points and/or IR and NMR spectra identical with those reported in the literature. [c] A solution of 1.0 equiv of potassium carbonate in 10 mL of water and vigorous stirring was used in reactions with amine hydrochloride. [d] Powdered sodium bicarbonate (1.0 equiv) was used as base/catalyst with anhydrous acetonitrile as solvent in this reaction. [e] The base/catalyst in this reaction was 0.01 equiv of 2,6-lutidine. [f] bp 40 °C/1.5 torr; IR (neat) ν_{CO} 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.13 (s, 1 H (COH)), 1.3–2.4 (m, 13 H ($C_6H_{10}Me$)); MS, m/z 142 (M), 96 (base).

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(17) **1**, white solid, 96.3 mol % by NMR, mp 36–38 °C; IR (neat) ν_{CO} 1775, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.23 (s, 1 H (COH)), 7.90 (d, 1 H, J = 16 Hz (=CHCO)), 6.40 (d, 1 H (CH=)), 7.48 (s, 5 H (Ph)); MS, m/z 176 (M), 131 (base).
(18) **2**, white solid, 97.0 mol % by NMR, mp 66.5–67.5 °C; IR (neat) ν_{CO} 1770, 1755, 1745, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.37 (s, 1 H (COH)), 8.13 (d, 2 H, J = 8 Hz (Ph-2,6)), 7.03 (d, 2 H (Ph-3.5)), 3.91 (s, 3 H (OCH_3)); MS, m/z 180 (M), 135 (base).

Significantly, the tertiary alcohol, 1-methylcyclohexanol, is readily formylated by these mixed formic anhydrides (Table II). These results are consistent with earlier experiments which indicate high selectivity of nucleophiles for the formyl carbonyl in mixed formic anhydrides, especially those with the second carbonyl deactivated via steric and/or electronic factors. Formate ester synthesis is extremely sensitive to the presence of acids and bases.[6,19] We find that formylation of both amines and alcohols occurs most cleanly in the absence of any catalyst (Table II).

A detailed investigation of the synthesis and synthetic applications of mixed formic anhydrides is underway in our laboratory. A full report of the work will be made available when it is completed.

Acknowledgment. We gratefully acknowledge financial support for this project from Reilly Tar & Chemical Corporation. We thank Robert Barbush, Merrill-Dow, for mass spectral analysis of new mixed anhydrides.

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Spiro Asymmetric Induction. Synthesis of Optically Pure α-Hydroxy Acid Derivatives by Alkylation of a Chiral Glycolate Enolate

Summary: The enolates of spiro-fused dioxolanones **4A** and **4B** serve as chiral glycolate enolate equivalents, providing either enantiomer of the α-substituted α-hydroxy esters **13** upon alkylation and hydrolysis.

Sir: Optically pure hydroxy acids are not only important biological substances but are valuable starting materials for the asymmetric synthesis of natural products.[2] In conjunction with another synthetic project, we required optically pure α-hydroxy acids of considerable complexity. In this paper, we report a route to such compounds based on the alkylation of chiral glycolate enolates.[3] Either

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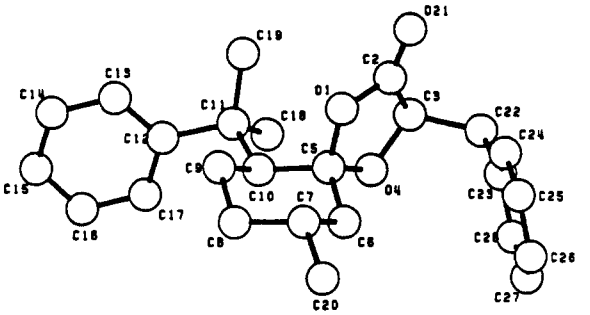
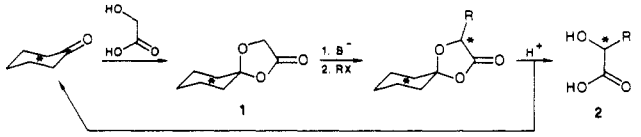


Figure 1. Structure and numbering scheme for 11C.

enantiomer of several α-hydroxy esters are produced in 100% optically pure form using a recyclable chiral auxilliary.

A survey of the literature revealed that chiral glycolic acid enolates are known[4,17] and rely on attachment of a chiral auxilliary to either the hydroxyl or carboxyl group, resulting in variable degrees of asymmetric induction. We reasoned that rigid attachment of the chiral auxilliary to both functional groups would result in a more defined steric environment. To this end, we have examined the enolate chemistry of 1,3-dioxolan-4-ones **1** derived from glycolic acid by spiro fusion to a chiral cyclohexanone. Alkylation followed by hydrolysis should afford hydroxy acid **2** accompanied by recovered chiral auxilliary (eq 1).



(1)

It should be noted that Seebach[5] and Frater[6] have reported the alkylation of chiral dioxolanones derived from α-branched optically active α-hydroxy acids and pivaldehyde, providing α,α-disubstituted α-hydroxy acid derivatives ("self-reproduction of chirality"). However, this method is conceptually different from that presented herein, since the chiral starting material is fully incorporated into the products.

The requisite dioxolanones were prepared from menthone[7] and 8-phenylmenthone[8] with trimethylsilyl ((tri-

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