hydroxy ketone 15[12] formed from each epoxide by desilylation was esterified to (*S*)-*O*-acetylmandelic acid[13] to form esters (16) which were analyzed by ^{1}H NMR spectroscopy.[6,14] As indicated in Scheme III, the diastereomeric excesses of 16 derived from each epoxide sample agree with those of the epoxides. In addition, *the major diastereomer of 16 is the same for each experiment.* Therefore, selectivity for epoxidation of the *same* face of the enolate ligand occurred, regardless of the absolute configuration of the silicon atom and irrespective of the existence of chirality on the silicon center. We conclude that the diastereofacial selectivity for the epoxidation of an alkoxysilyl enol ether by MCPBA is affected by a chiral alkoxy group and not by a chiral silicon center.

We considered our choice of the MCPBA epoxidation of silyl enol ethers to be the reaction least likely to exhibit stereoselectivity due to a stereogenic silicon center, because it would involve little, if any, sterically demanding coordination of the reagent to the alkoxysilyl group prior to the addition step. The results described above support this suspicion, but offer the prospect that a chiral alkoxy ligand on the silicon center will by itself offer some degree of a stereodirecting effect. It would be premature to discount the value of a stereogenic silicon center as a stereodirecting element for addition reactions of silyl enol ethers. We are currently investigating the stereochemistry of metal-mediated reactions of chiral alkoxysilyl enol ethers with the idea that metal complexation to the alkoxy ligand may draw the silicon closer to the enol ligand so that the silicon center may exert a significant steric effect upon the approach of reagents to the enol ether.

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Supplementary Material Available: Complete NMR data for compounds 4–14 and 16, IR data for compounds 4–9 (7 pages). Ordering information is given on any current masthead page.

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Avermectin Chemistry. 2. A Secure and Flawless Strategy for the Final Synthetic Stages[1,2]

Summary: A cycle of transformations on avermectin B_{1a} shows that problems of conjugation/deconjugation/epimerization during the final stages of synthesis of these systems may be obviated by having an exocyclic methylene at C4. Thus, the labile, biologically important C2 center in such precursors is not affected by oxidations, lactonizations, or rearrangements. Indeed, this location represents a safe place to "park" the Δ^3 bond while gross transformations of the avermectin skeleton are carried out.

Sir: Our recent studies have demonstrated that the final step(s) for a synthetic route to the avermectins (e.g., 1) need to be undertaken with extreme caution.[3] Thus, strategies which employ synthons for the "southern half", such as the "correct" (Δ^3) species I[4,5] or the conjugated (Δ^2) counterpart II[6] are potentially problematic. First, Ia goes readily to II, and deconjugation of II leads not to I, as originally had been claimed,[7a] but to the 2-epi isomer III, exclusively[3,7b] or predominantly,[8] depending on the conditions used (Scheme I). Second, we have observed[9] that oxidation of homoallylic alcohols, such as Ib, leads to substantial amounts of allylic cleavage to give enones, such as IV. *The fact that the C2 stereocenter and the Δ^3 double bond are both crucially important for biological activity[10a] demands a strategy that guarantees, simultaneously, the integrities of both structural entities.* The synthon V should fulfill these requirements, and in this manuscript, we disclose some pertinent results.

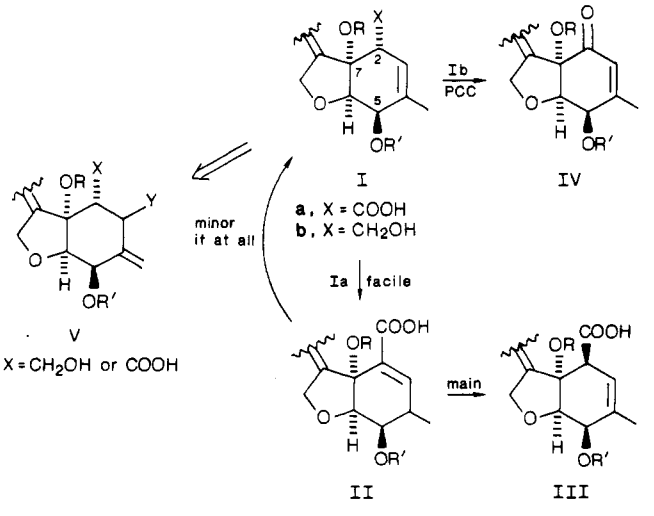
For V, there are two crucial requirements that need to be established: (i) Can macrolactonization be carried out with the exocyclic double bond in place? There is a threat of β-elimination of HY from V (X = "COOH"), which would give a highly conjugated system. (ii) Can the exo → endo rearrangement be carried out *on the macrolactone* without the problematic epimerization/conjugation, of which we had warned?[3]

We decided to test these questions by retrograde and synthetic transformations on avermectin B_1 (**1a**).

The primary alcohol **1b** is known to be the product of selenium dioxide oxidation of **1a**[10] (Scheme II). After some differential protection to give **1c**, the lactone was reduced and the resulting diol was adjusted to give the free allylic alcohol **2**. For endo → exo double bond rearrangement, the chemistry of Nicolaou[11] was utilized to obtain the primary selenide **3**, and Clive's selenoxide rearrangement[12] then gave 4a as a single isomer. Notably, both processes (i.e., **2** → **3** → **4a**) can be carried out in "one pot" in over 90% overall yield.

After appropriate functional group adjustments, the primary alcohol **4b** was oxidized, and the resulting hydroxy

Scheme I



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(2) Presented, in part, at the International UNESCO Workshop on Natural Products of Potential Medical Value, Tel Aviv, Israel, Dec 15–17, 1986, and at the 4th International Conference on the Chemistry of Biologically Active Natural Products, Budapest, Hungary, Aug 10–14, 1987.

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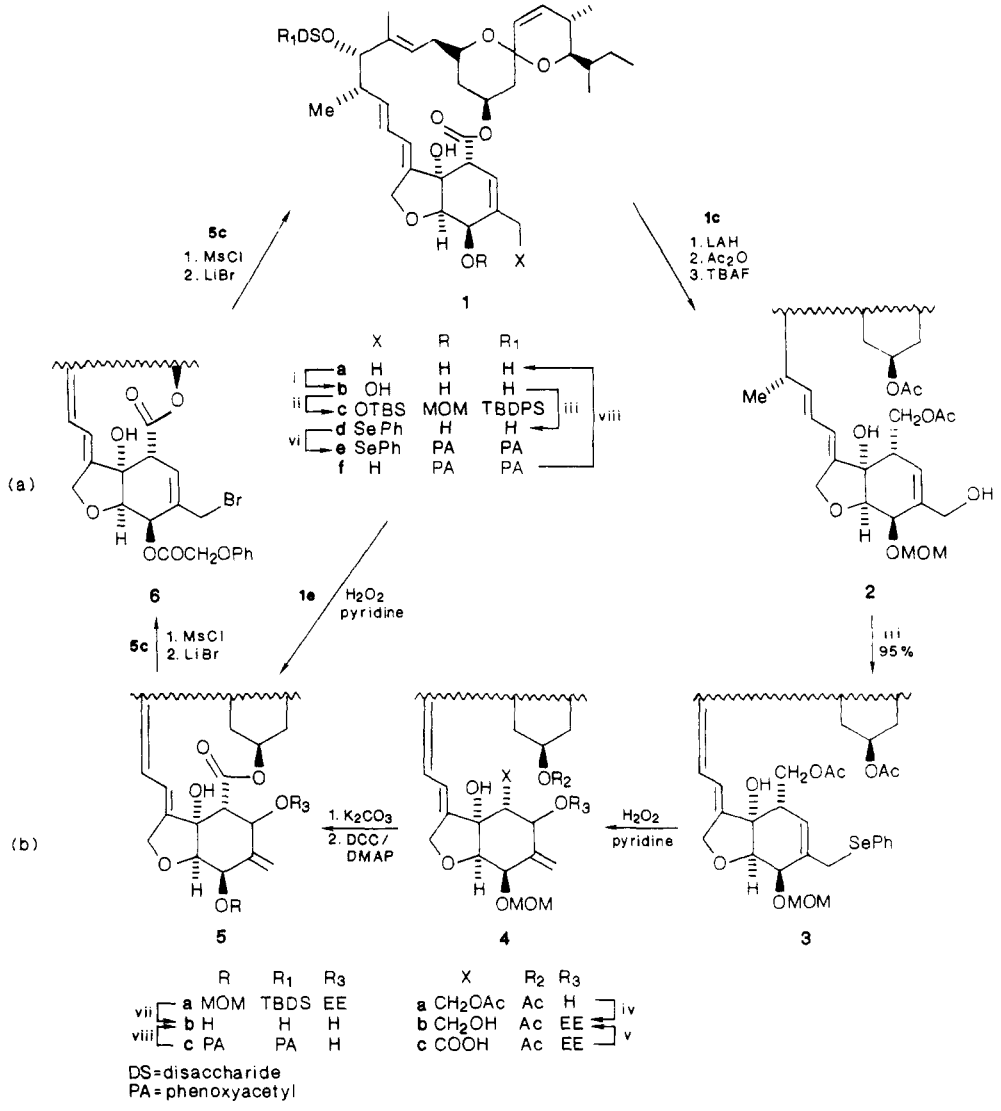
Scheme II[a]



[a] (i) SeO_2/tBuOOH;[10a] (ii) $Me_2C(OMe)_2$; *t*-$BuPh_2SiCl$; CSA; *t*-$BuMe_2SiCl$; $MeOCH_2Cl$; (iii) *N*-(phenylseleno)phthalimide/Bu_3P/CH_2Cl_2;[11] (iv) CH_2=CHOEt/PPTs; K_2CO_3; *t*-$BuMe_2SiCl$; Ac_2O; *n*-Bu_4NF; (v) PDC/DMF; (vi) $PhOCH_2COCl$; (vii) CSA/MeOH; HF/pyridine; (viii) MeOH/NH_3.

acid **4c** was lactonized to obtain **5a**, thereby satisfying requirement i.

Requirement ii was then evaluated. Controlled reaction of tetrol **1b** with the Nicolaou reagent[11] led to the primary selenide **1d** with complete chemoselectivity, and after protection, *specifically as the phenoxyacetate*[13] **1e**, the Clive rearrangement[12] was effected to afford **5c**. *That the material thus prepared had the same skeleton as the substance obtained from* ***4*** *was established by converting both* ***5a*** *and* ***5c*** *into the same triol,* ***5b***.

Sulfonation of **5c**, followed by brominolysis, led to **6** smoothly, but debromination of the latter was problematic. Thus, treatment with either tri-*n*-butyltin hydride or zinc in ethanol led to an approximate 1:1 mixture of products of S_N2 and S_N2' reduction. However, with sodium borohydride in dimethylformamide,[15] there were no complications, and the product **1f** was then converted into **1a** by treatment with methanolic ammonia.[13]

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(13) The choice of protecting groups at O5 and O4″ for the final stages is crucial. For example, (i) CH_3CO cannot be removed cleanly by bases, such as NaOMe or NH_4OH; however, $PhOCH_2CO$ can. (ii) Removal of silyl groups with *n*-Bu_4NF is messy, but HF/pyridine is satisfactory.[14] (iii) CH_3OCH_2 can be removed from O5 easily with camphorsulfonic acid/methanol, but removal from O4′ is more difficult and is accompanied by partial cleavage of the disaccharide moiety.
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In summary, V emerges as an excellent synthon for the southern half of the avermectin, since the key transformations involving oxidation at C1, macrolactonization, and S_N2' rearrangement can be carried out confidently at the final stages without affecting the key C2 center. *In addition, the ability to move the biologically critical* Δ^3 *double bond of 1 into a safe exocyclic "holding position" presents novel opportunities for semisynthetic studies in the avermectins.*

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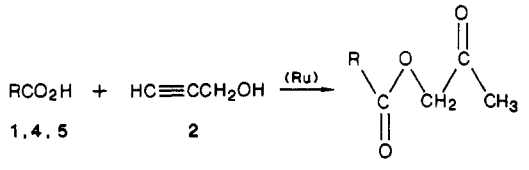
Synthesis of β-Oxopropyl Esters by Catalytic Addition of Carboxylic Acids and N-Protected Amino Acids to Propargyl Alcohol

Summary: The synthesis of β-oxopropyl esters results from the addition of saturated and unsaturated carboxylic acids or N-protected amino acids to propargyl alcohol in the presence of (arene)(phosphine)ruthenium(II) catalysts.

Sir: β-Oxoalkyl esters have been shown to be useful intermediates for access to heterocyclic derivatives such as furanones or imidazoles,[1] due to their reactive oxoalkyl carbonyl group, and for peptide synthesis,[2] as activated esters toward amino groups.

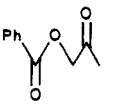
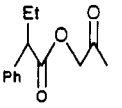
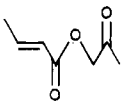
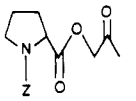
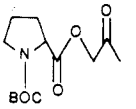
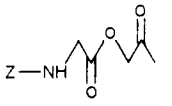
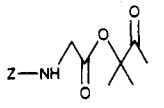
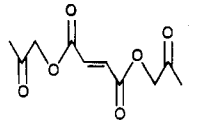
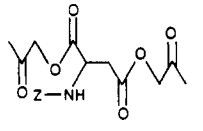
β-Oxopropyl esters are usually prepared by nucleophilic substitution of β-oxoalkyl halides by carboxylates in the presence of base[2,3] or by reaction of hydroxypropanone with acyl halides.[4] We report a new route to β-oxoalkyl esters by direct reaction of carboxylic acids with propargyl alcohols, thus avoiding the use of halide derivatives. This synthesis ensues from our studies on the addition of carboxylic acids to alkynes to afford enol esters.[5] We now show that the reaction of carboxylic acids with propargyl alcohol, catalyzed by $RuCl_2(PR_3)$(arene) complexes, proceeds differently: β-oxopropyl esters are formed in one step, under mild conditions (60 °C, 6 h), according to the following equation, and the reaction can be extended to diacids and N-protected amino acids. In a typical ex-



1, $PhCO_2H$ (a); Ph(Et)$CHCO_2H$ (b); $CH_3CH{=}CHCO_2H$ (c); Z-L-Pro (d); BOC-L-Pro (e); Z-L-Gly (f)
4, $HO_2CCH{=}CHCO_2H$
5, Z-L-Asp; Boc = $Me_3COC(O)$-; Z = $PhCH_2OC(O)$-

periment, Z-glycine (**1f**) (4.18 g, 20 mmol), $RuCl_2(PMe_3)$(*p*-cymene)[6] (0.072 g, 0.2 mmol), and propargyl alcohol (1.4 mL, 24 mmol) were dissolved under a nitrogen atmosphere in 10 mL of dry toluene. The reaction mixture was heated at 60 °C for 6 h. The ester **3f** which precipitated on partial evaporation of toluene was crystallized from a CH_2Cl_2/Et_2O (1/5) mixture to give pure product in 62% yield. Other esters **3**, **8**–**10** were obtained in a

Table I. Addition of Carboxylic Acids to Propargylic Alcohols with $RuCl_2(PMe_3)$(*p*-cymene)

acids	prepargylic alcohols[a]	esters (yield, %)[b]
1a	2[d]	 **3a** (92)
1b	2	 **3b** (30)
1c	2	 **3c** (85)
1d	2	 **3d** (74)
1e	2	 **3e** (41)
1f	2	 **3f** (62)
1f	6[c]	 **8** (45)
4	2	 **9** (30)
5	2	 **10** (40)

[a] General conditions: 60 °C; 6 h. [b] Isolated pure product. All compounds have been fully characterized spectrally (infrared, ^1H NMR) and by high resolution mass spectroscopy. Elemental composition has been established by combustion analysis for **3f** and **9**. [c] At 80 °C (6 h). [d] **2**, $HC{\equiv}CCH_2OH$; **6**, $HC{\equiv}CC(Me)_2OH$.

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