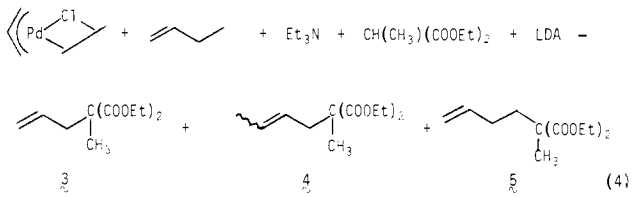
$CH(CH_3)(COOEt)_2$ and LDA at −60 °C) at −60 °C, followed by warming to and stirring at 25 °C for several days, resulted in the production of **3** in 262% yield by GC (196% isolated by preparative layer chromatography).[17] Repetition of this experiment led to GC yields of **3** ranging from 220 to 291%.

This reaction was not limited to propene. Carrying out the above experiment with π-allylpalladium chloride and excess 1-butene produced butenyl products **4** and **5**[18] (0.6:1) in overall 125% yield, as well as **3** (50%) from direct alkylation of the starting allyl complex (eq 4). Attack at the less substituted



(4)

position of butene predominated, as is usual for π-allylpalladium complexes. Pent-1-ene and hex-1-ene reacted similarly, giving mixtures of olefin isomers, although the reaction was slower and less efficient than with propene. Surprisingly, cyclopentene, cyclohexene, and allylbenzene failed to produce allylic alkylation products under these reaction conditions.

π-Allylpalladium chloride or $PdCl_2(CH_3CN)_2$ were the best sources of palladium for the above reactions. Use of $Pd(CH_3CN)_4(BF_4)_2$[19] or (π-allyl)$Pd(BF_4)$[20] produced only small amounts of allylic alkylation product. Since these reactions always produced a great deal of metallic palladium, and since it was difficult to devise a mechanism involving homogeneous complexes as catalysts, the possibility of heterogeneous catalysis was probed. The reaction described in eq 3 was rerun. After 6 h at 25 °C, the mixture, which contained large amounts of suspended metallic palladium, was centrifuged, and half of the clear supernatant was transferred to a degassed vessel, while the remainder of the liquid phase was left in contact with the palladium precipitate. Analysis of both fractions showed 94% **1**, 7% **2** and 21% **3**. After an additional 2 days at 25 °C, the transferred fraction remained clear (no Pd(0) precipitate) and contained 96% **1**, 8% **2** and 18% **3**, while the solution left in contact with the palladium precipitate analyzed for 98% **1**, 5% **2** and 98% **3**. That is, the homogeneous fraction produced no additional allylic alkylation product (**3**) after separation from metallic palladium, while the same solution left in contact with the precipitate produced an additional 80% **3**. This result is also reproducible and clearly implicates heterogeneous catalysis. Other heterogeneous Pd catalysts were checked for activity in this system, but they were all considerably less active. Thus 10% Pd on carbon, 5% Pd on silica gel, and 10% $PdCl_2$ on silica gel all catalyzed the reaction of propene with diethyl methylmalonate in the presence of triethylamine, but only ~20–25% yields of allylic alkylation product **3** (based on palladium) were obtained. Even smaller amounts (10–15%) of vinyl alkylation product **1** were obtained. Similarly, "Rieke Palladium"[21] was prepared by the reduction of $PdCl_2$ with potassium in the presence of 2 and 4 equiv of triethylamine. These complexes also produced **3** in only low yield. Finally, the homogeneous Pd(0) complex, bis(dibenzilideneacetato)-palladium,[22] gave only ~20% allylic alkylation. Thus the heterogeneous Pd generated by the reaction of $PdCl_2$ or π-allylpalladium chloride with stabilized carbanions and propene is a more efficient catalyst than the other types examined.

Although the mechanism of this catalytic allylic alkylation of olefins is not yet clear, the process is related to the palladium catalyzed amination of allyl alcohols and esters,[23] and alkylation of allyl ethers and esters by stabilized carbanions[2-15,23,24] or enamines,[25] all of which are thought to proceed via π-allylpalladium complex intermediates produced by Pd insertion into the allylic carbon–heteroatom bond. The reaction reported in this communication must involve insertion of palladium into an allylic C–H bond to produce a π-allylpalladium hydride, which reacts further to form the observed products. This process is similar to that observed with $(CH_3CH{=}CH_2)NiPF_3$, which is in equilibrium with (π-allyl)$Ni(H)PF_3$ at low temperatures.[26] Studies are in progress to elucidate the mechanism and to extend the lifetime and increase the rate of this allylic alkylation of olefins.

Acknowledgment. This investigation was supported by Grant No. R01 CA 18680 awarded by the National Cancer Institute, Department of Health, Education, and Welfare.

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(17) The isolated material was identical in all respects with that prepared by the reaction of allyl bromide with $LiC(CH_3)(COOEt)_2$.
(18) The isolated material was identical in all respects with material prepared by reaction of crotyl bromide and 3-chloro-1-butene, respectively, with $LiC(CH_3)(COOEt)_2$.
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Bis Heteroannulation. 1. Model Studies in the Synthesis of Highly Oxygenated Sesquiterpenes

Sir:

The uncovering of significant biological activity in certain highly oxygenated members of the sesquiterpene class has been greeted with an enormous outpouring of effort directed toward either the partial, or total, synthesis of representative compounds.[1] We, too, have recently been attracted to this area, but, while the structural diversity of these materials is renowned (cf. Chart I), we have chosen in our own efforts to focus on a number of subtle features which are apparently held in common. Namely, (1) they either contain a furan ring *or* a functionality *in principle* derivable from a furan ring; (2) the more biologically active compounds usually contain an oxygen functionality adjacent to the furan or lactone ring juncture;[2] and (3) most of the stereochemically interesting features are contained about the periphery of a single ring. These points,

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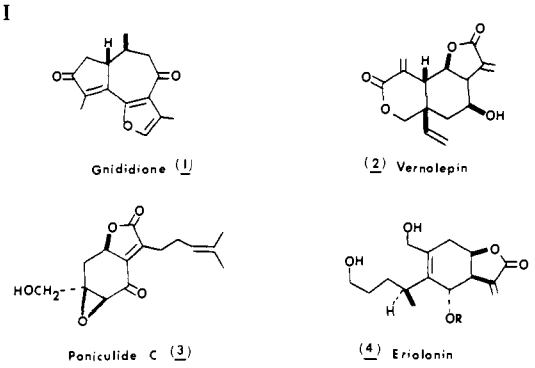
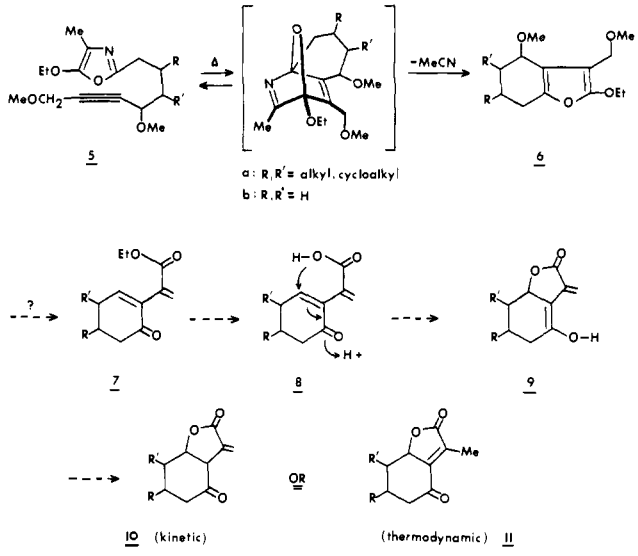
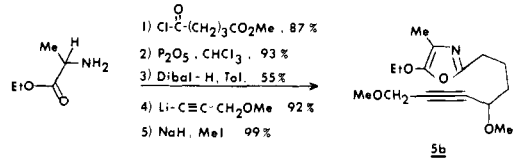
Chart I



Scheme I



Scheme II



we feel, should be amenable to exploitation and it is with this goal in mind that we have been experimenting with a concept which we loosely define as "bis heteroannulation" (Scheme I).

In its most general sense this concept is based on an intramolecular variant of the well-known reaction of oxazoles with acetylenic dienophiles,[3] and the term bis heteroannulation is meant to imply that two ring structures are being formed as part of a simultaneous reaction sequence; one of these rings will be represented by a substituted furan nucleus (hence the prefix "hetero"), while the other will be carbocyclic in nature and could, in theory, be of any size. Of particular interest was the possibility that compounds of type **6** might well be induced to undergo a solvolytic ring opening leading directly to methylene ester **7**, and ultimately this latter material could serve as a versatile precursor to compounds of either the methylene lactone or butenolide class. We have now tested this hypothesis on the model compound **5b** and present our initial results below.

The requisite acetylenic oxazole **5b** was prepared in a straightforward fashion as diagrammed in Scheme II,[4] and we now can report that reproducible yields of 80–90% in the conversion of **5b** to **6b** (cf. Scheme I) are also attainable if suitable precautions are taken. Thus, for example, 1.10 g (3.91 mmol) of oxazole **5b** was dissolved in 65 mL of freshly distilled ethylbenzene (Na) containing 78 mg of hydroquinone. The system was protected from light and stirred at gentle reflux with exclusion of moisture for a period of ~72 h,[5] during which time TLC analysis showed a gradual disappearance of **5b** (R_f 0.50) concomitant with the formation of ethoxyfuran **6b** (R_f 0.75, silica gel, 20% Et_2O/CH_2Cl_2). Upon completion the reaction was concentrated and chromatographed to give 0.89 g (94%) of pale yellow **6b** (0.76 g, 80%, colorless oil after distillation at 78 °C (0.05 mm); NMR ($CDCl_3$) δ 1.34 (3 H, t, J = 7 Hz), 1.7–2.7 (6 H, m), 3.28 (3 H, s), 3.42 (3 H, s), 4.18 (2 H, q, J = 7 Hz), 4.20 (1 H, m), 4.24 (2 H, d, J = 4 Hz)).

In addition, we were gratified to find that **6b** was in fact ideally suited for its eventual conversion to the methylene ester **7b**. Thus, the desired transformation could be cleanly accomplished under mild acid catalysis[6] (85–90% yield, 1 N H_2SO_4, 15 min at room temperature. colorless oil, bp 58 °C (0.05 mm); NMR ($CDCl_3$) δ 1.25 (3 H, t, J = 7 Hz), 2.04 (2 H, m), 2.46 (4 H, m), 4.18 (2 H, q, J = 7 Hz), 5.63 (1 H, d, J = 1.8 Hz), 6.16 (1 H, d, J = 1.8 Hz), 6.88 (1 H, t, J = 4 Hz)), and furthermore, we have observed that, *under more vigorous conditions, ethoxy furan* **6b** *could be transformed directly to methylbutenolide* **11b** (60–65% yield, 1 N H_2SO_4, 30–36-h reflux, colorless oil, bp 100 °C (0.5 mm)), slowly solidifying under vacuum to a crystalline solid (mp 55–58 °C; NMR ($CDCl_3$) δ 1.53–2.85 (6 H, br m), 2.04 (3 H, d, J = 2 Hz, collapsing to a singlet upon irradiation at 4.98), 4.98 (1 H, m, collapsing to a triplet, J = 2.5 Hz, upon irradiation at 2.04 Hz)). Also, butenolide **11b** was available in still higher yield from the methylene ester **7b** (90%, 1 N H_2SO_4, 16-h reflux; ~75% overall from ethoxyfuran **6b**), and, finally, we have demonstrated that each of these transformations proceeds through the intermediacy of the methylene acid **8b**[7] (itself available in excellent yield by alkaline hydrolysis of **7b**).

In closing, it is worth noting that **11b** contains many of the structural features of paniculide C (**3**), and we feel confident that intermediates of type **7** will provide access to a variety of related functionalities as well. These latter possibilities are currently under active investigation.

Acknowledgment. Financial support of this work by the National Institutes of Health (Grant No. CA 20483), the National Science Foundation (Grant No. 78-00633), and the Research Corporation is gratefully acknowledged.

Supplementary Material Available: Table of physical and chemical properties of new compounds (1 page). Ordering information is given on any current masthead page.

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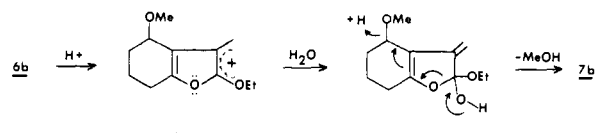
(4) Satisfactory elemental analyses and spectral data were obtained for all new compounds reported. All yields refer to isolated and purified materials.
(5) Although slow, we point out that this reaction is actually representative of a so-called "least favorable case". That is, the intramolecular nature of these reactions should be even more favored in multicyclic systems (cf. compound **5**, R, R' = cycloalkyl) since the reacting centers are held more rigidly in proximity to each other (fewer degrees of freedom).
(6) We believe that the mechanism of this reaction involves an initial formation of the highly stabilized carbonium ion i, followed by its trapping with water



to give ii and either a sequential or concerted ring opening concomitant with the loss of a second molecule of methanol. In contrast, simple alkoxyfurans are known to hydrolyze by a process involving 1,4 addition of water: J. E. Garst, *J. Org. Chem.*, **39**, 2920 (1974).

(7) Although the conversion of **8b** to **11b** appears in a formal sense to be in violation of "Baldwin's rules", it has recently been pointed out that these rules do not necessarily obtain with oxygen nucleophiles under acid catalysis: J. E. Baldwin, R. C. Thomas, L. I. Kruse, and L. Silberman, *J. Org. Chem.*, **42**, 3846 (1977).

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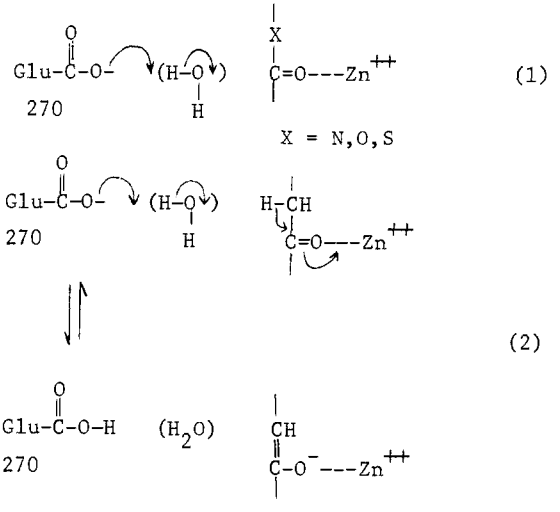
Carboxypeptidase A Catalyzed Enolization of a Ketonic Substrate. A New Stereochemical Probe for an Enzyme-Bound Nucleophile

Sir:

We report here our discovery that carboxypeptidase A (CPA) catalyzes stereospecifically the exchange of hydrogens present in an activated methylene group of a ketonic substrate with those of the aqueous solvent. Hydrolytic reactions at the active site of CPA have been postulated[1,2] to involve either nucleophilic attack by the γ-carboxylate group of Glu-270 or attack by water aided by this residue acting as a general base. The active site Zn(II) ion, which is essential to enzymic activity, is believed to assist the hydrolytic process by polarizing the substrate's carbonyl group. As illustrated, eq 1 and 2 in Scheme I, if a methylene analogue of a peptide or ester substrate were bound in the active site in a manner similar to that of the hydrolytically labile compound, then hydrogen abstraction from the methylene group of this ketone might be catalyzed by the aforementioned functional residues. According to this proposal, either the γ-carboxylate group of Glu-270 or a water molecule assisted by this residue might extract a proton from the methylene group of the ketonic substrate to produce an enolate anion which could be stabilized by the Zn(II) ion with its positive charge.

In order to test the hypothesis of Scheme I, we have examined the possibility that hydrogen-deuterium exchange at the methylene group of 3-*p*-methoxybenzoyl-2-benzylpropionic acid-3,3-d_2 (**1**-d_2) might be catalyzed by CPA_γ. This compound is an analogue of two categories of CPA substrates, *N*-acyl-L-phenylalanines or *O*-acyl-L-β-phenyllactates. Decarboxylation at 180 °C of the malonic acid derivative prepared by condensation of α-bromo-*p*-methoxyacetophenone

Scheme I



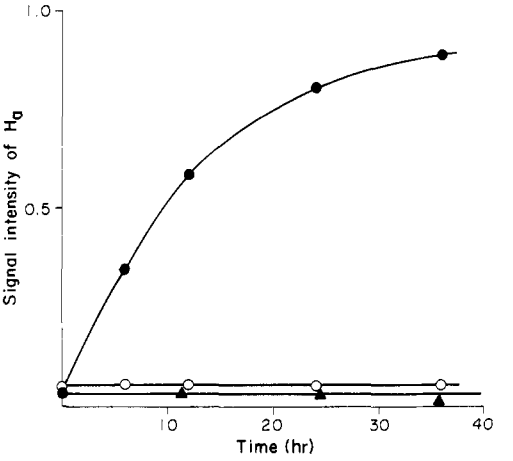


Figure 1. Time dependence of the signal intensity of the H_a proton: (●) (R)-(−)-**1**-d_2 (2.0×10^{-3} M), CPA_γ (9.5×10^{-5} M); (○) (*S*)-(+)-**1**-d_2 (2.0×10^{-3} M), CPA_γ (9.5×10^{-5} M); (▲) (*R*)-(−)-**1**-d_2 (2.0×10^{-3} M), CPA_γ (9.0×10^{-5} M), *dl*-benzylsuccinic acid (3.2×10^{-3} M).

(Aldrich) and diethyl benzylmalonate led to the synthesis of **1**. Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08. Found: C, 72.50; H, 6.30. Deuterium was introduced into the methylene group at the 3 position of **1** by hydrogen-deuterium exchange in alkaline deuterium oxide solution (0.5 M NaOD, 12 h, 23 °C).

Resolution of **1**-d_2 was accomplished by repeated recrystallization from ethyl ether of the salt formed with enantiomerically pure methylbenzylamine (Aldrich). The enantiomers, (+)-**1**-d_2, mp 91.0–92.5 °C, α^{23}_D 19.9° (*c* 11.35, ethyl acetate) and (−)-**1**-d_2, mp 90.5–91.5 °C, α^{23}_D −19.3° (*c* 10.0, ethyl acetate) were obtained using (+)- and (−)-methylbenzylamine, respectively.

Hydrogen-deuterium exchange was initiated by adding **1**-d_2 to CPA_γ solutions.[3] By observation of the signal intensity of the ^1H NMR spectrum, incorporation of protons into the methylene group could be followed. At 270 MHz, the diastereotopic protons on the methylene group of **1** appear separately at 2.98 ppm (H_a) and 3.33 ppm (H_b).[4] Under the neutral pH conditions usually optimal for the hydrolytic action of CPA_γ (0.05 M Tris-HCl, 0.5 M NaCl, pH 7.5),[5] exchange at the H_a position could readily be observed in the case of (−)-**1**.[6,7]

Figure 1 shows the time course of the increase of the H_a signal in (−)-**1** under the above-mentioned conditions. The introduction of hydrogen from the solvent follows apparent first-order kinetics. At a CPA_γ concentration of 9.5×10^{-5} M, the observed k_{obsd} was found to be 1.75×10^{-5} s^{-1}. In contrast, under these conditions (+)-**1** did not exhibit any appreciable exchange.[6] This difference is consistent with the hypothesis that the exchange reaction is catalyzed in the asymmetric environment of the active site. As a test of the nature of the exchange process, 3.2×10^{-3} M *dl*-benzylsuccinic acid was added and it was found that the exchange at the H_a position of (−)-**1** was greatly retarded (Figure 1). Since *dl*-benzylsuccinic acid is a potent competitive inhibitor of the hydrolytic action of CPA ($K_i = 1.1 \times 10^{-6}$ M),[8] the inhibition seen for the exchange reaction at the H_a position provides strong evidence that the latter process occurs at the active site.

Binding of both (+)-**1** and (−)-**1** at the active site was examined in a study of inhibitory effects of these compounds on the hydrolysis of *O*-(*trans*-*p*-chlorocinnamoyl)-L-β-phenyllactate. At pH 7.5 (0.05 M Tris-HCl, 0.5 M NaCl, 25 °C), the inhibition constants (K_i) estimated were 4.9×10^{-5} M and 1.1×10^{-4} M, respectively.

The difference between the two enantiomers of **1** in the rate

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