Table II. S_N Reactions of Methanesulfenyl Adducts of 2-Methylpropene

	reactants[a]			products		
						
X	(%)	(%)	Nuc	(%)	(%)	yield, %
Cl	10a (4)	10b (96)[b]	Me_3N[c]	6a (85)	6b (15)	90
Cl	10a (4)	10b (96)	$AgBF_4$; Me_3N[d]	6a (78)	6b (22)	34
SMe_2^+	8c (64)	8d (36)[b]	Me_3N	6a (82)	6b (18)	60[e]
Cl	10a (4)	10b (96)	Me_2NH[c]	11a (81)	11b (19)	88
Cl	10a (4)	10b (96)	$AgBF_4$; Me_2NH[d]	11a (80)	11b (20)	37
SMe_2^+	8c (64)	8d (36)	Me_2NH	11a (81)	11b (19)	80[f]
Cl	10a (4)	10b (96)	H_2O[g]	12a (3)	12b (97)	>90
SMe_2^+	8c (64)	8d (36)	H_2O[g]		12b (100)	>90

[a] 25 °C in $MeNO_2$. [b] Equilibrium composition. [c] Four days at room temperature. [d] $AgBF_4$ was added to chloride in $MeNO_2$ at 0 °C; the nucleophile was added to the supernatant at 25 °C. [e] Competitive demethylation gave Me_4N^+ (37%). [f] Demethylation gave Me_3NH^+ (14%). [g] With or without $NaHCO_3$, or K_2CO_3, or with $MeNO_2$ as cosolvent.

displacements, considerable fragmentation to Me_3NH^+ and Me_4N^+ may be expected—but none was found.

The overall results strongly suggest that, in solution, the sulfonium adducts **8** dissociate *reversibly* to episulfonium ions (eq 7), which accounts for the observed rearrangements, sulfide exchange, and the displacement reactions.[16] This being so, episulfonium ions generated by authenticated routes should react with external nucleophiles to give product mixtures similar to those obtained in the present experiments. Accordingly, methanesulfenyl chloride adducts of 2-methylpropene, **10a** and **10b**, were prepared and converted to the corresponding azasulfenyl adducts **6** by way of episulfonium ions.[17] As can be seen from Table II, the same adducts in essentially the same distribution were obtained from both the chlorides **10** and the sulfonium salts **8** despite the disparity in the initial composition of regioisomers, whether or not silver fluoroborate was employed to preform the episulfonium ions. The same result was obtained with other nucleophiles (Me_2NH and H_2O).

Although the reality of episulfonium ions has been questioned under some reaction conditions,[15b] we conclude that, in the reactions described herein, episulfonium ions are formed rapidly and reversibly from sulfenyl adducts of the type RS–C–C–X, where X = Cl and SR_2^+. We further suggest that the synthetically useful sulfenylation reactions of alkenes described by Trost and Shibata[12] proceed by a similar route—that is, by the initial rapid addition of **1** to the alkene followed by a slower nucleophilic displacement by way of episulfonium ions.

Acknowledgment. We gratefully acknowledge support of this work by Grant No. GM27319 awarded by the Institute for General Medical Sciences, DHEW.

Registry No. 1 BF_4^-, 5797-67-7; 4, 33696-21-8; **6a** BF_4^-, 81206-91-9; **6b** BF_4^-, 81206-93-1; **6c** BF_4^-, 81206-95-3; **6d** BF_4^-, 81206-97-5; **8a** BF_4^-, 81206-99-7; **8b** BF_4^-, 81207-00-3; **8c** BF_4^-, 81207-02-5; **8d** BF_4^-, 81207-04-7; **9** (n = 3) BF_4^-, 81207-06-9; **9** (n = 4) BF_4^-, 81207-07-0; **10a**, 19826-04-1; **10b**, 13012-55-0; **11a**, 81207-08-1; **11b**, 81207-09-2; **12a**, 27874-69-7; **12b**, 33657-46-4; *trans*-(2-methylthiocyclohex-1-yl)-trimethylammonium BF_4^-, 81207-11-6; *trans*-2-methylthio-1-dimethylaminocyclohexane, 81207-12-7; *trans*-(3-methylthiotetrahydropyran-2-yl)trimethylammonium BF_4^-, 81207-14-9; *trans*-3-methylthio-2-dimethylaminotetrahydropyran, 81207-15-0; 1,3,3-trimethyl-1,4-dithiepanium BF_4^-, 81207-17-2; 1,2,2-trimethyl-1,4-dithiepanium BF_4^-, 81207-19-4; 1,3,3-trimethyl-1,4-dithiocanium BF_4^-, 81207-21-8; 1,2,2-trimethyl-1,4-dithiocanium BF_4^-, 81219-00-3; *trans*-1,2,3-trimethyl-1,4-dithiepanium BF_4^-, 81207-23-0; *cis*-1,2,3-trimethyl-1,4-dithiepanium BF_4^-, 81207-25-2; *trans*-1,2,3-trimethyl-1,4-dithiocanium BF_4^-, 81207-27-4; *cis*-1,2,3-trimethyl-1,4-dithiocanium BF_4^-, 81207-29-6; (2,2-dimethyl-2-(3-methylthiopropyl)ethyl)trimethylammonium BF_4^-, 81207-31-0; (1,1-dimethyl-2-(3-methylthiopropyl)ethyl)trimethylammonium BF_4^-, 81207-33-2; (2,2-dimethyl-2-(4-methylthiobutyl)ethyl)trimethylammonium BF_4^-, 81207-35-4; (1,1-dimethyl-2-(4-methylthiobutyl)-ethyl)trimethylammonium BF_4^-, 81207-37-6; (*R*,R**)-(1,2-dimethyl-2-(3-methylthiopropyl)ethyl)trimethylammonium BF_4^-, 81207-39-8; (*R*,S**)-(1,2-dimethyl-2-(3-methylthiopropyl)ethyl)trimethylammonium BF_4^-, 81207-41-2; (*R*,R**)-(1,2-dimethyl-2-(4-methylthiobutyl)ethyl)-trimethylammonium BF_4^-, 81207-43-4; (*R*,S**)-(1,2-dimethyl-2-(4-methylthiobutyl)ethyl)trimethylammonium BF_4^-, 81207-45-6; cyclopentene, 142-29-0; 3,4-dihydro-2*H*-pyran, 110-87-2; *cis*-2-butene, 590-18-1; *trans*-2-butene, 624-64-6; 2-methylpropene, 115-11-7.

(16) It is worth noting that the sulfonium salt produced by methylation of 1,4-dithiane is stable to NMe_3—reflecting difficulty in forming an episulfonium ion by internal displacement.

(17) (a) Mueller, W. H.; Butler, P. E. *J. Am. Chem. Soc.* **1968**, *90*, 2075. (b) Lucchini, V.; Modena, G.; Zaupa, T.; Capozzi, G. *J. Org. Chem.* **1982**, *47*, 590.

A New β-Lactam Synthesis

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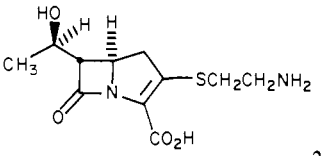
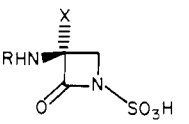
Interest in natural and semisynthetic β-lactam structures has recently surged with the discovery of thienamycin (**1**), an unusually



1



2, X = OCH_3
R = γ-D-glutamyl-D-alanyl

potent carbapenem antibiotic,[1] and the monobactams (e.g., sulfazecin (**2**), a family of monocyclic 2-azetidinone-*N*-sulfonic acids found in bacteria.[2,3] These substances possess reactive β-lactam linkages and exhibit promising antibiotic activity against both Gram-positive and Gram-negative organisms.[3,4] In this communication we disclose the oxidative cyclization of β,γ-unsaturated amidosulfamoyl esters and related structures to N-sulfonylated halo β-lactams which can be dehalogenated to afford structural

(1) For leading references, see: Salzmann, T. N.; Ratcliffe, R. N.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161.

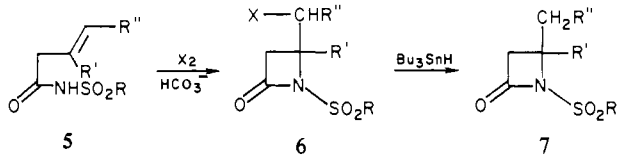
(2) Imada, A.; Kitano, K.; Kintaka, K.; Muroi, M.; Asai, M. *Nature (London)* **1981**, *289*, 590.

(3) Sykes, R. B.; Cimarusti, C. M.; Bonner, D. P.; Bush, K.; Floyd, D. M.; Georgopapadakou, N. H.; Koster, W. H.; Liu, W. C.; Parker, W. L.; Principe, P. A.; Rathnum, M. L.; Slusarchyk, W. A.; Trejo, W. H.; Wells, J. S. *Nature (London)* **1981**, *291* 489.

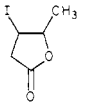
(4) Abraham, E. P. *Sci. Am.* **1981**, *244*, 76.

0002-7863/82/1504-3233$01.25/0

Table I



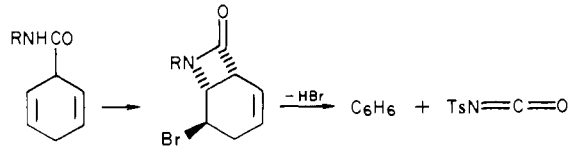
5 6 7

substrate	product[15] yield[a,b]	reduced β-lactam[15] yield[a,b]
5a R = *p*-$CH_3C_6H_4$ R′ = R″ = H	6a, X = Br (67%,[c] 43%)	7a (92%)
5a	6a, X = I (83%)	7a (97%)
5b R = OCH_3 R′ = R″ = H	6b, X = Br (12%)	
5b	6b, X = I (12%)	
5c R = OEt R′ = R″ = H	6c, X = I (77%)	7c (50%)[d]
5d R = OCH_2CCl_3 R′ = R″ = H	6d, X = Br (40%)	
5d	6d, X = I (95%)	7d, R = OCH_2CHCl_2 (100%)
5e R = OCH_2CCl_3 R′ = CH_3; R″ = H	6e, X = I (95%)	7e, OCH_2CHCl_2 (99%)
5f R = OCH_2CCl_3 R′ = H; R″ = CH_3	 10 (90%)	

[a] Reported yields are for recrystallized or flash-chromatographed products. Satisfactory NMR, IR, and mass spectral data were obtained for all new compounds. [b] Satisfactory combustion analyses were obtained for all stable products. [c] Crude yield of virtually pure product. [d] Estimated yield only, for this extremely unstable product.

analogues of the monobactams.

While enoic acids under the well-known halolactonization reaction,[5] olefinic amides, apparently without exception,[6-9] also form lactones and not lactams when oxidatively cyclized with Br_2 or I_2. To test whether lowering the pK_a of the carboxamide group might favor nucleophilic attack by nitrogen, we prepared *N*-tosyl amide **3** by condensing 1,4-dihydrobenzoyl chloride with *p*-



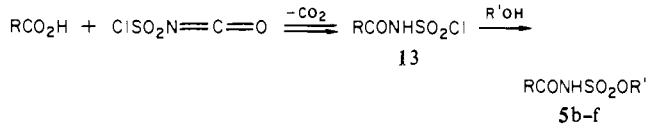
3 4

3, R = *p*-$CH_3C_6H_4SO_2$

$CH_3C_6H_4SO_2NH_2$ (NaH, THF, 67%, mp 141–145 °C). Bromination of **3** in aqueous $NaHCO_3$ produced bicyclic *N*-tosyl-bromo β-lactam **4** in 60% yield.[9,10] The azetidinone structure of **4** was easily distinguished from an isomeric pyrrolidone or a four- or five-membered imino ether by its IR spectrum, which closely resembled those of *N*-chlorosulfonyl β-lactams.[11] Like its corresponding bromo β-lactone,[12] **4** underwent a smooth, base-induced elimination of HBr and TsNCO (IR characterization) to form benzene in quantitative yield (DBU, $CHCl_3$, 0 °C).

A variety of N-sulfonylated β,γ-unsaturated amides was prepared (see Table I), which established the scope and generality of this new ring-forming process for a number of monocyclic β-lactams.[13,14]

Halogenation of acyl sulfamates **5b–f** furnished *N*-sulfonate ester analogues of the monobactams not otherwise accessible by alcoholysis of 2 + 2 olefin–chlorosulfonyl isocyanate (CSI) adducts.[16] Ester **5c** was best prepared by reaction of lithio methyl sulfamate ($LiNHSO_2OCH_3$, 2 equiv, THF) with 3-butenoyl chloride. Alcoholysis of *N*-chlorosulfonyl amides **13** also afforded an expedient route to **5c** and **5d**; however, considerable olefin isomerization occurred in the reaction of enoic acids with CSI leading to **13**.



13 5b-f

Sensitive amidosulfamoyl esters were optimally prepared by heating the requisite carboxylic acid with β,β,β-trichloroethoxysulfonyl isocyanate (TSI)[17] (C_6H_6, reflux), which afforded **5d–f** in excellent yield. The diminished rate of TSI cycloaddition to olefins, especially in benzene, resulted in a generally useful preparation of functionalized carboxamides for this work.

Dehalogenation of **6** was best achieved by using Bu_3SnH (5 equiv, THF, room temperature) and provided access to **7a,c–e** (see Table), which are new representatives of the monobactams. The additional cleavage of just one chlorine from the trichloroethoxy substituent in **7d** and **7e** was a noteworthy side reaction.

This methodology leads most efficiently to four-membered lactams,[18] which are probably formed under kinetic control.[19] In support of this idea, PhSeCl-induced cyclization of **5f** at −78 °C gave a butyrolactam that could be trapped by selenoxide elimination in the cold. Otherwise, warming to room temperature furnished exclusively the five-membered imino ether.

Acknowledgment. We thank the National Science Foundation and National Institutes of Health for partial support of this research. In particular, a predoctoral traineeship to R.D.W. on NIH

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(6) Corey, E. J.; Fleet, W. J.; Kato, M. *Tetrahedron Lett.* **1973**, 3963.
(7) Clive, D. L. J.; Wong, C. K.; Kiel, W. A.; Menchen, S. M. *J. Chem. Soc., Chem. Commun.* **1978**, 379.
(8) A Russian group [Rengevitch, E. N.; Staninets, V. L.; Shilov, E. A. *Proc. Acad. Sci. USSR* **1962**, *146*, 787] claimed that allylacetamide formed a γ-lactam by iodine-induced cyclization. Only IR data were presented. We have repeated this experiment under the standard, two-phase reaction conditions and can report that 5-(iodomethyl)butyrolactone is the exclusive product. It appears likely that earlier workers observed the intermediate imino ether.
(9) **4**: mp 146–147.5 °C; CIMS (methane) 356 (92%), 358 (100%) isotopic M^+; EIMS 198 (base, $TsNH{=}C{=}O^+$); IR λ_{max} ($CHCl_3$) 5.58 μm; no imine absorption.
(10) Satisfactory spectral data and elemental combustion analysis were obtained for this and all other new substances.
(11) Clauss, K. *Tetrahedron Lett.* **1974**, 1271.
(12) Holbert, G. W.; Weiss, L. B.; Ganem, B. *Tetrahedron Lett.* **1976**, 4435.
(13) The cyclization of *N*-tosylbutenoic acid amide **5a** (mp 93.5–94.5 °C) represents a typical procedure. A solution of Br_2 (1.03 equiv, 0.5 M in CH_2Cl_2) was aded dropwise at room temperature to **5a** (0.83 g, 3.5 mmol) in aqueous $NaHCO_3$ (5 mL). When the red color had completely discharged (several minutes), the layers were separated. The aqueous layer was extracted three times with CH_2Cl_2, and the combined organic layers were washed once with $Na_2S_2O_3$, dried ($MgSO_4$), and concentrated in vacuo to afford 0.74 g (67%) of virtually pure **6a** (43% after recrystallization).
(14) It is also possible to construct 3,4-disubstituted β-lactams in a single operation by successive alkylation–cyclization of α,β-unsaturated amides. Thus *N*-tosyl crotonamide dianion reacted with acetaldehyde and then Br_2 to furnish *N*-tosyl-3-(hydroxyethyl)-4-(bromomethyl)azetidinone in moderate yield.
(15) Representative spectral data: **6a** (X = Br) mp 114–115 °C; IR 5.58 μm; NMR ($CDCl_3$, 300 MHz) δ 4.26 (m, 1 H, CHN), 3.85, 3.59 (ABX, 2 H, CH_2Br, J = 10.8, 7.9, 3.1 Hz), 3.11, 2.93 (ABX, 2 H, CH_2CO, J = 18, 5.8, 3.1 Hz), 2.44 (s, 3 H, $ArCH_3$). **6a**: (X = I) mp 132.5–133 °C. **6d**: (X = Br) mp 141.5–142.5 °C; **6d**: (X = I, mp 152.5–153 °C; NMR 4.84 (s, 2 H, OCH_2), 4.30 (m, 1 H, CHN), 3.74, 3.43 (ABX, 2 H, CH_2I, J = 10, 8, 3 Hz), 3.33, 3.00 (ABX, 2 H, CH_2CO, J = 16.8, 6.4, 3.2 Hz. **6e**: (X = I), mp 61.5–63.5 °sC; NMR 4.85 (s, 2 H, OCH_2), 3.68 (s, 2 H, CH_2I), 3.31, 2.88 (AB, 2 H, CH_2CO, J = 18 Hz. **7a**: mp 94.5–95.5 °C; NMR 4.16 (m, 1 H, CHN), 3.13, 2.60 (ABX, 2 H, CH_2CO, J = 16, 6, 3 Hz), 1.52 (d, 3 H, CH_3, J = 5.9 Hz). **7d**: mp 58.5–59 °C; NMR 5.87 (t, 1 H, $CHCl_2$, J = 5.8 Hz), 4.58 (d, 2 H, OCH_2, J = 5.8 Hz), 4.33 (m, 1 H, CHN), 3.32, 2.78 (ABX, 2 H, CH_2CO, J = 16.4, 6.3, 3.3 Hz), 1.59 (d, 3 H, CH_3, J = 6.3 Hz).
(16) Graf, R. *Justus Liebigs Ann. Chem.* **1963**, *661*, 111. Graf, R. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 172.
(17) Lohaus, G. *Chem. Ber.* **1972**, *105*, 2791.
(18) Both *N*-tosyl- and *N*-(*tert*-butyldimethylsilyl)-4-pentenamide derivatives produced mostly five-membered lactones via imino ethers.
(19) Many of the halo β-lactams here reported were relatively unstable; **6d**, which could be recrystallized from CH_3OH, decomposed rapidly upon dissolution in Me_2SO.

Grant GM-97273 is gratefully acknowledged.

Registry No. 3, 81255-64-3; **4**, 81255-65-4; **5a**, 81255-66-5; **5b**, 81255-67-6; **5c**, 81255-68-7; **5d**, 81255-69-8; **5e**, 81255-70-1; **5f**, 81255-71-2; **6a** (X = Br), 81255-72-3; **6a** (X = I), 81255-73-4; **6b** (X = Br), 81255-74-5; **6b** (X = I), 81255-75-6; **6c** (X = I), 81255-76-7; **6d** (X = Br), 81255-77-8; **6d** (X = I), 81278-79-7; **6e** (X = I), 81255-78-9; **7a**, 81255-79-0; **7c**, 81255-80-3; **7d**, 81255-81-4; **7e**, 81255-82-5; 1,4-dihydrobenzoyl chloride, 3217-88-7; p-$CH_3C_6H_4SO_2NH_2$, 70-55-3.

Utilization of Enolpyruvate by the Carboxybiotin Form of Transcarboxylase: Evidence for a Nonconcerted Mechanism

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Carboxyl transfers by biotin enzymes

$$\text{E-biotin-}CO_2^- + RH \rightleftharpoons \text{E-biotin-H} + RCO_2^-$$

share two features of possible mechanistic significance: proton replacement is always with retention of configuration, and proton activation as measured by isotope exchange between substrate and water does not occur unless the enzyme is in the carboxybiotin form and the reaction conditions are complete.[2] The generality of these properties has been taken as evidence for a coupling of proton abstraction with carboxyl transfer in a concerted electrophilic displacement mechanism.[2,3] Notwithstanding these generalizations and because the proton to be replaced is invariably neighboring to a potential electron-withdrawing center, usually a carbonyl or carboxyl group, a stepwise "carbanion" mechanism is a plausible alternative.[4] The carbanion, enol or aci acid, could then either form a tetrahedral adduct at the carboxy center of the carboxybiotin or directly attack bound CO_2 formed from the carboxybiotin.[5] Stubbe et al.[4] have provided the only evidence for a carbanion mechanism. Transcarboxylase (TC) and propionyl-CoA carboxylase were found to eliminate HF from β-fluoropropionyl CoA giving acrylyl-CoA and "CO_2" equally and at rates normal for the carboxylation of propionyl-CoA. A concerted mechanism should have resulted in (fluoromethyl)-malonyl-CoA which, though stable enough to have been detected was not observed.

Further support for the stepwise mechanism would be obtained if enzymes that carboxylate pyruvate were shown to convert enolpyruvate to pyruvate and oxalacetate. Enolpyruvate can be generated by action of a phosphatase on phosphoenolpyruvate (PEP).[6] The product of this reaction has sufficient stability ($t_{1/2} \simeq 5$ min at pD 6) to be studied as a substrate by both kinetic and stereochemical approaches as was done with pyruvate kinase.[6] Similar experiments are now reported with transcarboxylase.

Transcarboxylase [methylmalonyl-CoA:pyruvate carboxytransferase (EC 2.1.3.1)] has been extensively studied both structurally and mechanistically.[7] It is a multimeric structure in which three kinds of subunits integrate their separate functions: (1) activating the methylmalonyl-CoA for carboxylation of biotin and formation of propionyl-CoA, (2) carrying the carboxylated biotin, and (3) activating the pyruvate for carboxylation, giving the β-keto acid oxalacetate. The enzyme is able to carry out pyruvate–oxalacetate exchange in the absence of either of the CoA substrates.[8]

Table I. Ketonization of Enolpyruvate by Transcarboxylase

additions[a]	1	2	3	4
(S)-MMCoA	–	+	+	–
(S)-prop-CoA	–	–	–	+
avidin	–	–	+	–
τ, min	6	0.9	5	5.7
(enolpyruvate, $\mu M)_{ss}$	15	4	20	25

[a] Each incubation of 1 mL in >95% D_2O (pD 6.4, 21 °C) contained Na maleate (50 mM), acid phosphatase (4×10^{-3} units), transcarboxylase (0.23 units), NADH (0.25 mM), LDH (4 units), and 2 mM PEP added last. The noted additions were (S)-methylmalonyl-CoA (250 μM), (S)-propionyl-CoA (500 μM), and avidin (1.5 μM). The reaction was followed in a 2-mm path length cuvette. The lag time, τ, was determined by extending the recorded trace of the rate in the steady state to the time axis.[6b] The concentration of enolpyruvate was determined as pyruvate present in the acid-quenched reaction mixture.[6b]

As done earlier,[6b] ketonization of enolpyruvate was followed by monitoring the reduction of pyruvate with NADH and lactate dehydrogenase (LDH).

$$\text{PEP} \xrightarrow{\text{Pase}} \text{enolpyruvate} \rightarrow \text{pyruvate} \xrightarrow{\text{LDH}} \text{lactate}$$

In the reaction begun with Pase, enolpyruvate accumulates until its ketonization rate equals the rate of its formation, which is fixed by the Pase rate. Any catalysis of ketonization should shorten the lag time necessary to reach this steady state and lower the concentration of enolpyruvate present in the steady state. As seen in Table I transcarboxylase shortened the lag time, τ, but only when methylmalonyl-CoA was also present. The concentration of enolpyruvate was then greatly decreased. Enolpyruvate was determined with LDH as pyruvate that arose after acid quenching. The LDH present during the incubation kept the pyruvate present prior to quenching to an undetectable level.[6b] The requirement for methylmalonyl-CoA is consistent with observations made with several biotin enzymes that activation of the C–H bond of the substrate appears to require carboxylating conditions. Malic dehydrogenase (MDH), added with the methylmalonyl-CoA and LDH, did not accelerate the oxidation of NADH, indicating that oxalacetate was at best a minor product. This was confirmed by analysis of labeled products by ion-exchange chromatography. In the presence of excess LDH the malate formed was <10% of the lactate. Avidin, known to interact specifically with biotin, blocked the action of transcarboxylase in the ketonization of enolpyruvate.

If enolpyruvate is indeed an intermediate, the observation that the overall reaction proceeds with retention[9] requires that the additions of proton or CO_2 occur from the same face of the plane of that molecule. With specifically labeled PEP-3-T to generate the enolpyruvate in D_2O, the specific formation of chiral methyl pyruvate would establish the direction of approach of D^+ (Scheme I). The 2.1-fold intramolecular H/D isotope effect of transcarboxylase in forming oxalacetate from pyruvate[9] yields, after reduction, (S)-malate that will be ~2-fold greater in tritium content at one poisition of its methylene group. Only the *pro-R* hydrogen at C-3 of the malate is activated by fumarase. A similar procedure has been used earlier for this purpose.[6a,9] *Direct* carboxylation of (Z)- or (E)-enolpyruvate-3-T by transcarboxylase would produce oxalacetate which becomes (S)-malate-3-T, from which fumarase would exchange either all or none of the tritium depending on the direction of carboxylation. Scheme I illustrates the consequences of D^+ or CO_2 addition by transcarboxylase to the face of enolpyruvate that is designated that *si* face by reference to C-2.

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