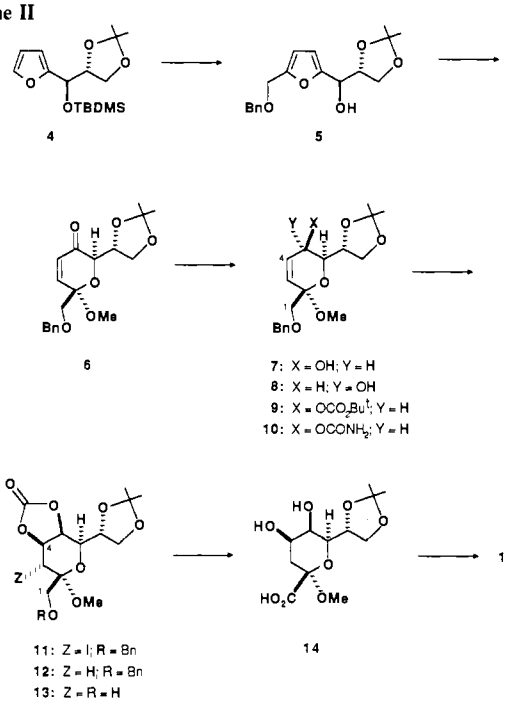
Scheme II



glyceraldehyde. Further applications of this fundamental synthetic strategy to the asymmetric synthesis of other important oxygenated natural products constitute the subject of current investigations, the results of which will be revealed in due course.

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Supplementary Material Available: Spectral details (^1H and ^{13}C NMR and specific rotations) for compounds **6**, **12**, **14**, and **1** (1 page). Ordering information is given on any current masthead page.

A Model for the Coenzyme B_{12} Dependent Glutamate–Methylaspartate Carbon Skeleton Rearrangement

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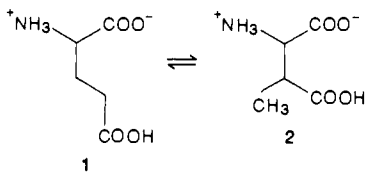
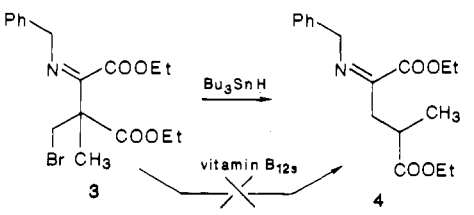
The carbon skeleton rearrangement in which L-glutamic acid (**1**) is transformed to L-*threo*-β-methylaspartic acid (**2**)[1] is the first step in the use of L-glutamate as a source of energy by the anaerobe *Clostridium tetanomorphum*.[2] This unusual rearrangement is especially intriguing in the context of the cognate coenzyme B_{12} dependent, enzyme-catalyzed, carbon skeleton rearrangements of methylmalonyl-CoA to succinyl-CoA[3] and methylitaconic acid to α-methyleneglutaric acid.[4] The migrating group in the latter transformations is unsaturated, and the rearrangements may be formulated in terms of cyclopropyloxy or cyclopropylcarbinyl intermediates, possibly involving free radicals or carbanions. In the glutamate to methylaspartate rearrangement (**1** ⇌ **2**) the migrating group is the glycyl fragment.[5] Since the migrating carbon is saturated, the rearrangement cannot occur by way of a cyclopropylcarbinyl intermediate. Nor can a direct radical rearrangement be involved without breach of precedent—no such free radical migrations of saturated carbon are known.



In earlier model studies, we succeeded in attaching methylaspartic acid and its diethyl ester to the cobalt atom of vitamin B_{12},[6a] but our efforts to effect rearrangement, under both thermal and photochemical conditions, failed to yield glutamate. Only unrearranged methylaspartate and methyleneaspartate were found among the amino acid and amino ester products.[6,7]

In considering other possible pathways for the rearrangement of **1** ⇌ **2**, one might hypothesize that the enzyme employs a Schiff base intermediate and, by prototopic rearrangement of the imine double bond, converts the migrating center from a saturated to an unsaturated carbon.[6b,8] We recently discovered a model Schiff base rearrangement in which the bromomethylmethylaspartate benzyl Schiff base **3** yielded the glutamate Schiff base **4** upon treatment with tri-*n*-butyltin hydride.[6b] However, model bromide



3 did not react with vitamin B_{12s};[6b] starting bromide was recovered unchanged. This was surprising, since vitamin B_{12s} is a potent nucleophile. The bromine atom in **3** is in a neopentyl environment, but a neopentyl center did not cause a problem in earlier models based on the methylmalonyl-CoA to succinyl-CoA rearrangement. Since the reactive center at nitrogen would be better stabilized in the transition state for migration when carrying a phenyl rather

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(8) There are significant reservations, discussed in ref 6b, regarding the use of a Schiff base model for this rearrangement.
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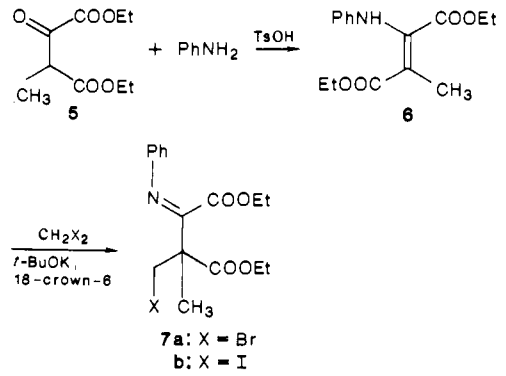
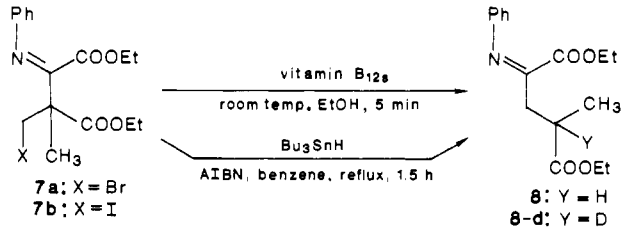
Scheme I



than a benzyl group,[10] we developed a synthesis of the phenyl substituted Schiff base.

Treatment of oxalylpropionate **5** with aniline in refluxing benzene for 48 h in the presence of *p*-toluenesulfonic acid yielded enamine **6**[11,12] (87%) (Scheme I). When **6** was treated with dibromomethane (or diiodomethane) in the presence of potassium *tert*-butoxide and 18-crown-6 in benzene at room temperature for 24 h, Schiff base **7a** (or **7b**) was produced (77% yield).[12] The imine double bond in **3** and in **7a** and **7b** was established to have the *Z* configuration by nuclear Overhauser experiments.

Methylaspartate Schiff base derivatives **7a** and **7b** rearrange to glutamate Schiff base **8** upon treatment with vitamin B_{12s} in ethanol at room temperature in the dark for 5 min (56% yield)[12] or upon refluxing for 90 min in benzene with tri-*n*-butyltin hydride in the presence of AIBN. The position of the methyl group in



rearrangement product **8** was established by direct comparison with an authentic sample of diethyl 4-methyl-2-ketoglutarate following hydrolysis of product **8**. The location of the methyl shows that the glycyl Schiff base fragment is the migrating group.[13] When the vitamin B_{12s} rearrangement is conducted in EtOD, deuterium is incorporated at the position adjacent to the methyl group in product **8-d**.[12] Although this indicates that the reaction is terminated as a carbanion, it is quite possible that the rearrangement occurs by way of a radical intermediate and that is followed by electron transfer from coenzyme B_{12} and then by protonation. The same product (**8-d**) is obtained when iodide **7b** is treated with tri-*n*-butyltin deuteride.

The rearrangement of **7a** and **7b** to **8** under the influence of vitamin B_{12s} constitutes a new model for the glutamate–methylaspartate rearrangement.

Diphenylamine and hydroquinone were not effective inhibitors of the reactions of **7** with either vitamin B_{12s} or tri-*n*-butyltin hydride. *m*-Dinitrobenzene, on the other hand, inhibited the tri-*n*-butyltin hydride rearrangement but had no effect on the vitamin B_{12s} promoted rearrangement. This finding suggests that the mechanisms of the rearrangements carried out under the two sets of conditions may be different. Caution is required in reaching such a conclusion because one is not certain which step of the chain is intercepted by *m*-dinitrobenzene.[14]

In a comparison between the vitamin B_{12s} dependent and the tri-*n*-butyltin hydride[9k] promoted methylmalonate rearrangement models, there is no contest; the B_{12} model is more efficient (by an order of magnitude) in yielding rearrangement product, and the conditions for the B_{12} reaction are far more suitable for a biological model reaction.[9g-j] In the present experiments the choice between the two sets of reaction conditions is more difficult, since both are quite efficient in terms of yield. Even so, the vitamin B_{12} reaction may again be more biorelevant in terms of rate, mildness of reaction conditions, and compatibility of the hydroxylic medium.

Acknowledgment. This research was generously supported by the Institute for General Medical Sciences of the National Institutes of Health under grant GM 19906. We thank Professor Richard L. Schowen for his helpful comments.

(10) This line of argument would not be appropriate for a radical process since the corresponding carbonyl compound rearranges readily.[6b] See also: Dowd, P.; Choi, S.-C. *J. Am. Chem. Soc.* **1987**, *109*, 3493.

(11) The configuration about the double bond of **6** has been established to be *Z* by NOE experiments.

(12) All yields cited are those of isolated, pure products. All new substances showed satisfactory spectral data.

(13) See ref 9g regarding a similar experiment and conclusion.

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Electron-Transfer Photofragmentation Reactions: Analogies and Divergences of the Reactivity of Ditertiary Amines As Compared with Aminoalcohols

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The electron-transfer quenching of excited acceptors by amines and subsequent chemical reactions have been topics of extensive study.[1-10] Among the various reactions of the photogenerated radical ion pairs, fragmentation via C–C bond cleavage has been shown to be prominent and often a chemically clean path for aminoalcohols, aminoketones, and other systems;[11-15] recent experiments have shown that the dehydrofragmentation of aminoalcohols is strongly acceptor-dependent and consistent with a mechanism in which the acceptor anion radical acts as a base to promote cleavage of the donor cation radical in a reaction closely analogous to the two-electron "Grob" fragmentation.[16,17] We

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