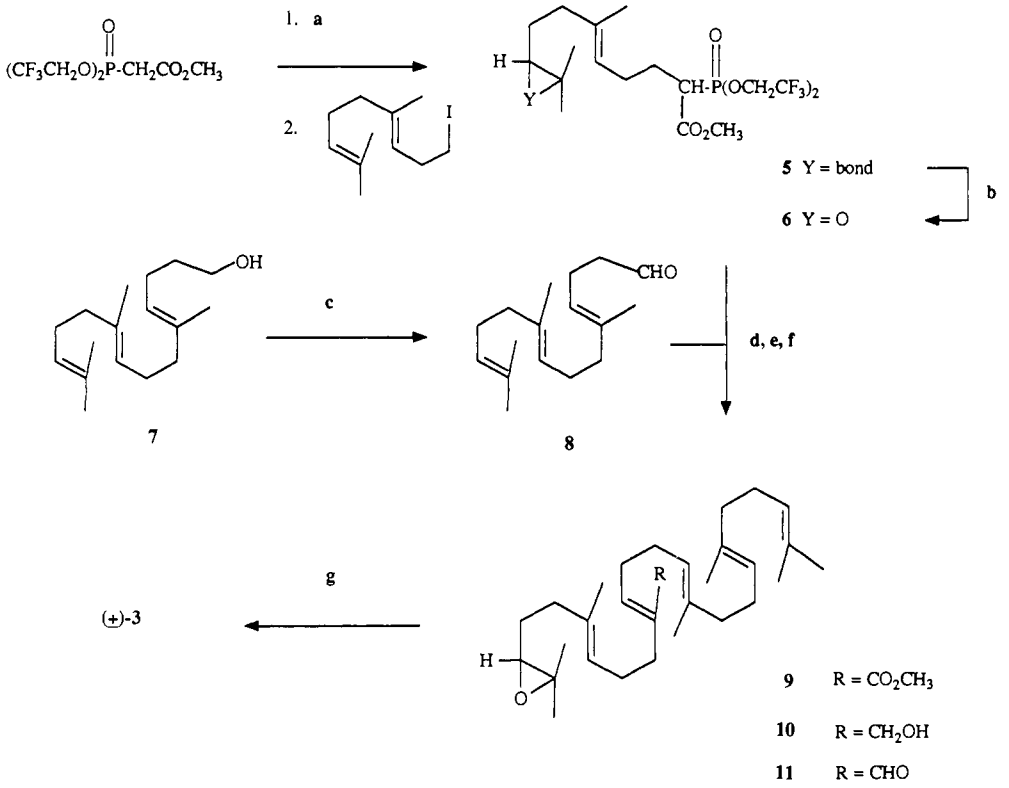
Scheme I[a]



[a] (a) 1.1 equiv of KH, 1 equiv of 18-crown-6, 10% HMPA–THF, −40 °C, 1 h. (b) 1. 1.2 equiv of NBS, 30% aqueous THF, 0 °C, 1 h; 2. K_2CO_3, CF_3CH_2OH (74% yield). (c) 6 equiv of CrO_3, 12 equiv of C_5H_5N, CH_2Cl_2, 0 °C, 6 h (93%). (d) 1.1 equiv of $KN(TMS)_2$, 5 equiv of 18-crown-6, THF, −50 °C, 1.5 h (58% *Z*-isomer). (e) 1 equiv of AlH_3, THF, −78 °C, 6 h (68%). (f) 1.5 equiv of pyridinium dichromate, DMF, −15 °C, 2 h, (89%). (g) 1.5 equiv of $Ph_3P{=}CH_2$, 10% HMPA–THF, −15 °C, 30 min (90%).

The completion of the synthesis of the putative natural sterols was accomplished as follows: **4** was converted to the 3β-acetate and then treated with 1.2 equiv of *m*-CPBA in CH_2Cl_2 at 23 °C to afford the 24,25-epoxide (93%). Oxidative cleavage of the C-14 vinyl appendage and sequential deoxygenation of the 24,25-oxido group was performed in one-pot by ozonolysis of the 24,25-epoxy 3β-acetate in 1:4 CH_2Cl_2–methanol[19] at −78 °C and treatment of the crude ozonolysis mixture with an excess of Zn/AcOH/NaI[20] (−78 °C for 1 h then 40 °C for 6 h) to produce 30-oxolanosteryl acetate. Cleavage of the 3β-acetoxy group by K_2CO_3/MeOH gave 30-oxolanosterol, (−)-**2**, $[\alpha]_D^{23} = -322°$, in 43% overall yield from the lanostatriene (−)-**4**. Lastly, reduction of (−)-**2** with $NaBH_4$ in methanol at 0 °C gave (+)-30-hydroxylanosterol **1** (98%) $[\alpha]_D^{23} = +57°$. Support for the identity of the synthetic sterols (+)-**1** and (−)-**2** was obtained by hydrogenating (1 atm H_2, PtO_2, 23 °C) each sterol to afford the corresponding 24,25-dihydrosterols whose melting points, IR, NMR, mass spectroscopic, and optical rotation data were in agreement with those previously reported.[3a,21]

The synthesis described herein illustrates a new approach to the asymmetric preparation of C-30 functionalized lanosterols where the key transformation invokes oxidosqualene cyclase in bakers' yeast for the construction of the steroid nucleus from a completely acyclic progenitor. However, an attempt to apply this enzymic cyclization method to an isomeric substrate possessing a vinyl appendage at C-15 in the squalene backbone was not successful. This latter result supports our recent hypothesis that structural features perturbing the β-face region, but not the α-face, of the substrate's chair–boat–chair conformation interfere with the enzyme's normal cyclizing operation.[14]

Acknowledgment. We gratefully acknowledge the American Heart Association and the American Cancer Society for their generous support of this work.

(19) Velluz, L.; Muller, G.; Mathieu, J.; Poittevin, A. *Tetrahedron* **1960**, *9*, 145–148.
(20) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112–127.
(21) (a) Gibbons, G. F.; Mitropoulos, K. A.; Pullinger, C. R. *Biochem. Biophys. Res. Commun.* **1976**, *69*, 781–789. (b) Tabicik, C.; Aliau, S.; Serrou, B.; Crastes de Paulet, A. *Ibid.* **1981**, *101*, 1087–1095. (c) Shafiee, A.; Trzaskos, J. M.; Paik, Y. K.; Gaylor, J. L. *J. Lipid Res.* **1986**, *27*, 1–10. (d) Parish, E. J.; Schreopfer, G. J., Jr. *Ibid.* **1981**, *22*, 859–868.

The Furan Approach to Higher Monosaccharides. A Concise Total Synthesis of (+)-KDO

Stephen F. Martin* and Paul W. Zinke[1]

Department of Chemistry, The University of Texas Austin, Texas 78712

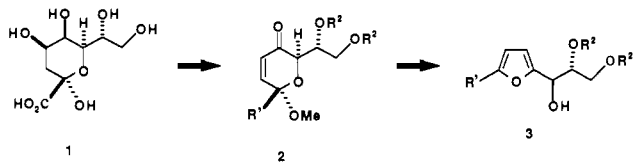
Received November 4, 1988

The higher monosaccharide 3-deoxy-D-*manno*-2-octulosonic acid, (+)-KDO (**1**), is the essential ketosidic component that links the carbohydrate and lipid subunits of lipopolysaccharides (LPS) of Gram negative bacteria;[2] incorporation of KDO appears to be vital for the growth and proliferation of these bacteria. Significant interest in the design and synthesis of KDO analogues as potential antibiotics[3] has been aroused consequent to recent discoveries that derivatives of 2-deoxy-KDO are effective inhibitors of LPS biosynthesis.[4] Although several syntheses of KDO and its analogues have been reported,[5] with one exception,[5c] carbohydrate precursors

(1) Recipient of a National Research Service Award from the National Institutes of Health.
(2) Unger, F. M. In *Adv. Carbohydr. Chem. Biochem.* **1981**, *38*, 323.
(3) (a) Sharon, N. *Complex Carbohydrates; Their Chemistry, Biosynthesis and Functions*; Addison-Wesley: Reading, MA, 1975. (b) Higgins, C. *Nature* **1987**, *327*, 655.
(4) (a) Hammond, S. M.; Claesson, A.; Jansson, A. M.; Larsson, L.-G.; Pring, B. G.; Town, C. M.; Ekstrom, B. *Nature* **1987**, *327*, 730. (b) Crich, D.; Ritchie, T. J. *J. Chem. Soc., Chem. Commun.* **1988**, 985. (c) Schmid, W.; Christian, R.; Zbiral, E. *Tetrahedron Lett.* **1988**, *29*, 3643.

0002-7863/89/1511-2311$01.50/0

Scheme I



have been the principal starting materials. It therefore occurred to us that there existed ample opportunity for the development of a general strategy which would be readily applicable to the asymmetric synthesis of KDO as well as other biologically important higher monosaccharides. The key feature of our approach involves the oxidative conversion of suitably functionalized furfuryl carbinols as **3** into dihydropyranones **2** (Scheme I).[6] As we have previously demonstrated, the dihydropyranone ring thus derived provides an excellent template for the efficient and highly stereoselective introduction of a variety of new functional groups and substituents. The reduction of this strategy to practice by application to the facile total synthesis of (+)-KDO (**1**) constitutes the subject of the present report.

Preparation of the optically pure furfuryl carbinol **5** commenced with the highly stereoselective addition of 2-furyllithium to isopropylidene-D-glyceraldehyde[7] [$ZnBr_2$ (1.0 equiv), THF, 0 °C, 12 h][8] followed by trapping the intermediate alkoxide in situ with *tert*-butyldimethylsilyl chloride (1 equiv) to give **4** in 53% overall yield;[9] only traces of the epimeric, protected alcohol could be detected[10] (Scheme II). Metalation of the furan ring of **4** [*t*-BuLi (1 equiv), THF, −78 °C → 0 °C, 4 h] and sequential addition of benzyl chloromethyl ether (0 °C → 25 °C, 12 h) and (n-Bu)$_4$NF (25 °C, 12 h) then furnished **5** in 92% yield.[11] At this juncture, it was necessary to employ tactics for the oxidative processing of the furan ring that would not simultaneously effect removal of the acid labile acetonide protecting group. Imposition of this restriction eliminated from possible contention the use of more traditional procedures involving Br_2/MeOH.[12] Thus, treatment of **5** with *t*-BuOOH, in the presence of VO(acac)$_2$ (CH_2Cl_2, 25 °C, 6 h),[13] and subsequent O-methylation (Ag_2O, excess MeI, 25 °C, 24 h) of the resulting lactols (α/β = 4.5:1) delivered a readily separable mixture (4.5:1) of methyl glycoside **6** together with its β-anomer in 75% combined overall yield from **5**.

The next stage of the synthetic plan required stereoselective reduction of the carbonyl function of **6** to provide the axial allylic alcohol **7** and subsequent introduction of the hydroxyl group at C(4) by some process involving an electrophile-induced cyclization[14] of a suitable derivative of **7**. Although hydride reduction of **6** with either $NaBH_4$ or DIBAL-H furnished the equatorial allylic alcohol **8** as the major product (e.g., **7**:**8** = 1:2–3), use of K-Selectride (THF, −78 °C, 30 min) afforded the desired allylic alcohol **7** as the major product (**7**:**8** = 9.8:1; 97% combined yield).[15] The tactic that was initially envisioned for the stereoselective installation of the hydroxyl function at C(4) involved the iodine-induced cyclization of the carbonate[16] **9** to afford the iodocarbonate **11**. Although **9** was easily prepared from **7** (n-BuLi, Et_2O; BOC-ON; 99% yield), numerous attempts to induce its cyclization to **11** employing a variety of electrophilic species returned only starting material. Presumably this failure can be attributed to the unfavorable steric interactions experienced by the C(1) methylene and the incoming oxygen nucleophile in the six-membered boat transition state required for cyclization. We therefore turned our attention to the cyclization of the related carbamate **10**, which was prepared from **7** ($Cl_3CCONCO$,[17] CH_2Cl_2; K_2CO_3, MeOH, H_2O; 95%), since precedent existed for the preparation of cyclic carbonates from axially oriented carbamates.[18] However, the cyclization of **10** [I(Collidine)$_2ClO_4$ (3 equiv), MeCN, 72 h; H_2O, 12 h] proved to be extraordinarily sluggish. Despite extensive experimentation, it has not been possible to define satisfactory conditions to effect complete conversion of **10** to the iodocarbonate **11**, and **11** was isolated in only 31% yield (91% based upon recovered starting material). Since preliminary efforts to achieve the simultaneous and efficient removal of the iodide function from C(3) and the protecting group from the C(1) hydroxyl were unavailing, we examined stepwise alternatives. An efficient protocol commenced with the radical removal[19] of iodide [HSn(n-Bu)$_3$, AIBN, $PhCH_3$, reflux, 3 h] to give **12**,[20] followed by hydrogenolysis of the *O*-benzyl group [H_2 (60 psi), Raney Ni, EtOH, 25 °C, 48 h] to furnish the primary alcohol **13** in 78% overall yield from **11**.

All that remained to complete the synthesis of (+)-KDO was the oxidation of the C(1) primary alcohol to a carboxyl group and deprotection of the various hydroxyl functions. Attempts to effect the direct oxidation of the C(1) hydroxyl to a carboxyl group failed, but a convenient stepwise procedure was devised that entailed Swern oxidation of **13** followed by oxidation of the intermediate aldehyde under conditions that proceeded with concomitant hydrolysis of the carbonate moiety (Ag_2O, 1 N NaOH, 25 °C, 12 h) to furnish **14** in 77% overall yield. Simultaneous hydrolysis of methyl glycoside and the acetonide protecting group was accomplished by treatment of **13** with DOWEX 50W(H^+) (H_2O, 80 °C, 1.5 h). The crude product mixture was then exposed to 5% NH_4OH (0 °C, 24 h), and, after lyophilization and purification by sequential chromatography (MeOH/$CHCl_3$/H_2O, 10:10:1) on cellulose and Sephadex G-10, (+)-KDO (**1**) was isolated as its ammonium salt in 44% yield. The ammonium salt of the synthetic (+)-KDO thus obtained was identical (mp, mixed mp, ^1H and ^{13}C NMR, $[\alpha]_D$ and TLC) with an authentic sample of **1**.[21]

Thus, a concise and efficient total synthesis of (+)-KDO has been completed in 11 steps from furan and isopropylidene-D-

(5) (a) Collins, P. M.; Overend, W. G.; Shing, T. *J. Chem. Soc., Chem. Commun.* **1981**, 1139. (b) Schmidt, R. R.; Betz, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 430. (c) Danishefsky, S. J.; Pearson, W. H.; Segmuller, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 1280. Danishefsky, S. J.; DeNinno, M. P.; Chen, S. *J. Am. Chem. Soc.* **1988**, *110*, 3929. (d) Imoto, M.; Kusumoto, S.; Shiba, T. *Tetrahedron Lett.* **1987**, *28*, 6235. (e) Bednarski, M. D.; Crans, D. C.; DiCosimo, R.; Simon, E. S.; Stein, P. D.; Whitesides, G. M. *Tetrahedron Lett.* **1988**, *29*, 427. (f) Branchaud, B. P.; Meier, M. S. *Tetrahedron Lett.* **1988**, *29*, 3191. (g) Itoh, H.; Kaneko, T.; Tanami, K.; Yoda, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3356. (g) See also in ref 2.

(6) (a) Martin, S. F.; Guinn, D. E. *J. Org. Chem.* **1987**, *52*, 5588. (b) Martin, S. F.; Campbell, C. L.; Gluchowski, C.; Chapman, R. C. *Tetrahedron* **1988**, *44*, 3171 and references cited therein.

(7) Jackson, D. Y. *Synth. Commun.* **1988**, *18*, 337.

(8) Suzuki, K.; Yuki, Y.; Mukaiyama, T. *Chem. Lett.* **1981**, 1529. These workers obtained a 19:1 ratio of the unprotected anti and syn adducts upon reaction of 2-furfuryllithium and isopropylidene-D-glyceraldehyde under similar conditions.

(9) The structure assigned to each compound was in full accord with its spectral (^1H and ^{13}C NMR, IR and mass) characteristics. Analytical samples of all new compounds were obtained by distillation, recrystallization, preparative HPLC, or flash chromatography and gave satisfactory combustion analysis (C, H) and/or identification by high resolution mass spectrometry.

(10) Although the anti isomer is generally the major product, the stereochemistry of nucleophilic additions of organometallic reagents to 2,3-isopropylidene glyceraldehyde is known to vary significantly (anti/syn = 9:91 to >95:<5) depending upon the reaction conditions, nucleophile, metal counterion, and solvent. For some leading references see: (a) Pikul, S.; Jurczak, J. *Tetrahedron Lett.* **1985**, *26*, 4145. (b) Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447.

(11) Although it was also possible to prepare corresponding 5-carbomethoxy-2-furfuryl carbinols, all attempts to effect their oxidative processing to the corresponding dihydropyranones without concomitant hydrolysis of the acetonide protecting group failed.

(12) Several alternate procedures including Br_2, Py, MeCN/H_2O; $^1O_2$, CH_2Cl_2; and *m*-CPBA, CH_2Cl_2 were also found to effect the requisite oxidation without adversely affecting the acid-sensitive acetonide; however, in each case the yield was unsatisfactory.

(13) Ho, T.-L.; Sapp, S. G. *Synth. Commun.* **1983**, *13*, 207.

(14) For related examples, see: Bartlett, P. A. *Asymmetric Synthesis, Vol 3, Stereodifferentiating Addition Rections Part B*; Morrison, J. D., Ed.; Academic Press, Inc.: Orlando, FL, 1984; pp 411–454.

(15) Nakata, T.; Takao, S.; Fukui, M.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 3873.

(16) Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.; Jernstedt, K. K. *J. Org. Chem.* **1982**, *47*, 4013.

(17) Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109.

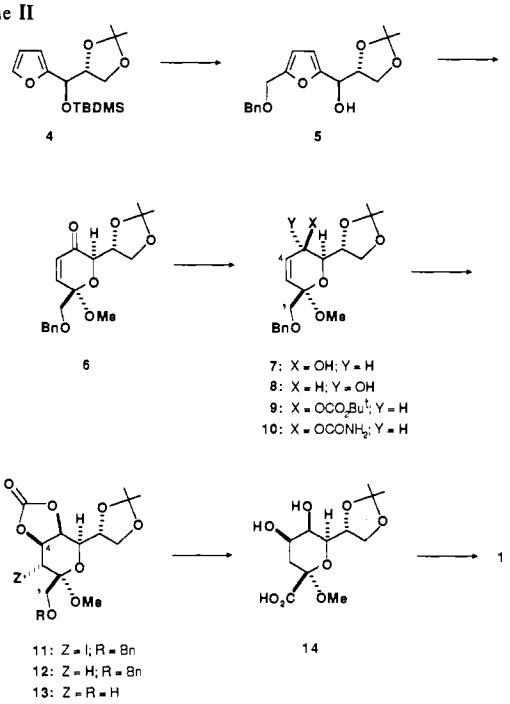
(18) Pauls, H. W.; Fraser-Reid, B. *J. Carbohydr. Chem.* **1985**, *4*, 1.

(19) Kuivila, H. G. *Synthesis* **1970**, 499.

(20) The stereochemistry of **12** was established by single-crystal X-ray analysis, and these results will be reported independently. We thank Dr. Vincent Lynch for this determination.

(21) Purchased from Sigma Chemical Company.

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.

Acknowledgment. We thank the National Institutes of Health (GM 31077) for their generous support of this research and the National Science Foundation and the National Institutes of Health for providing funds for NMR and mass spectral facilities. Finally, we are indebted to Dr. Franz Scheidl of Hoffmann-LaRoche for performing the combustion analyses.

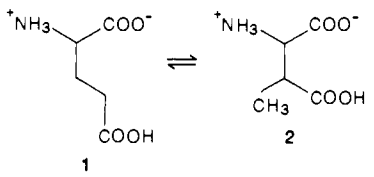
Supplementary Material Available: Spectral details (^1H and ^{13}C NMR and specific rotations) for compounds **6**, **12**, **14**, and **1** (1 page). Ordering information is given on any current masthead page.

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

Soo-Chang Choi and Paul Dowd*

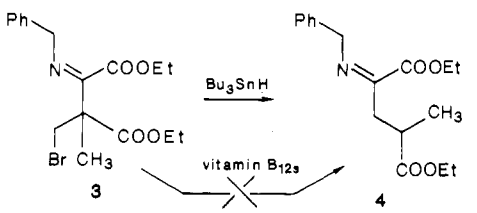
Department of Chemistry
University of Pittsburgh
Pittsburgh, Pennsylvania 15260
Received September 12, 1988

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

(1) Barker, H. A.; Weissbach, H.; Smyth, R. D. *Proc. Natl. Acad. Sci. U.S.A.* **1958**, *44*, 1093–1097.
(2) Barker, H. A.; Smyth, R. D.; Weissbach, H.; Munch-Petersen, A.; Toohey, J. I.; Ladd, J. N.; Volcani, B. E.; Wilson, R. M. *J. Biol. Chem.* **1967**, *235*, 181–190. Weissbach, H.; Toohey, J. I.; Barker, H. A. *Proc. Natl. Acad. Sci. U.S.A.* **1959**, *45*, 521–525.
(3) Stadtman, E. R.; Overath, P.; Eggerer, H.; Lynen, F. *Biochem. Biophys. Res. Commun.* **1960**, *1*, 2. Eggerer, H.; Overath, P.; Lynen, F.; Stadtman, E. R. *J. Am. Chem. Soc.* **1960**, *82*, 2643. Stjernholm, R.; Wood, H. G. *Proc. Natl. Acad. Sci. U.S.A.* **1961**, *47*, 303. Flavin, M.; Ochoa, S. *J. Biol. Chem.* **1957**, *229*, 965.
(4) Kung, H. F.; Cederbaum, S.; Tsai, L.; Stadtman, T. C. *Proc. Natl. Acad. Sci. U.S.A.* **1970**, *65*, 978. Tsai, L.; Pastan, I.; Stadtman, E. R. *J. Biol. Chem.* **1966**, *241*, 1807. Kung, H. F.; Stadtman, T. C. *J. Biol. Chem.* **1971**, *246*, 3378.
(5) Munch-Peterson, A.; Barker, H. A. *J. Biol. Chem.* **1958**, *230*, 649.
(6) (a) Dowd, P. In *Vitamin B_{12}, Proceedings of the Third European Symposium on Vitamin B_{12} and Intrinsic Factor*; Zagalak, B., Friedrich, W., Eds.; Walter de Gruyter: Berlin, 1979; pp 565–568. (b) Dowd, P.; Choi, S.-C.; Duah, F.; Kaufman, C. *Tetrahedron* **1988**, *44*, 2137.
(7) See, however: Murakami, Y.; Hisaeda, Y.; Ohno, T. *Chem. Lett.* **1987**, 1357. Murakami, Y.; Hisaeda, Y.; Ozaki, T.; Ohno, T.; Fan, S.-D.; Matsuda, Y. *Chem. Lett.* **1988**, 839–842. No indication is given here concerning the nature of the migrating group.
(8) There are significant reservations, discussed in ref 6b, regarding the use of a Schiff base model for this rearrangement.
(9) (a) Dowd, P.; Shapiro, M. *Tetrahedron* **1984**, *40*, 3063. (b) Dowd, P.; Shapiro, M. *J. Am. Chem. Soc.* **1976**, *98*, 3724. (c) Bidlingmaier, G.; Flohr, H.; Kempt, U. M.; Krebs, T.; Rētey, J. *Angew. Chem.* **1975**, *87*, 877. (d) Flohr, H.; Pannhorst, W.; Rētey, J. *Angew. Chem.* **1976**, *88*, 613. (e) Flohr, H.; Pannhorst, W.; Rētey, J. *Helv. Chim. Acta* **1978**, *61*, 1565. (f) Rētey, J. In *Vitamin B_{12}*; Zagalak, B., Friedrich, W., Eds.; Walter de Gruyter: Berlin, 1979; pp 439–460. (g) Scott, A. I.; Kang, K. *J. Am. Chem. Soc.* **1977**, *99*, 1997. (h) Scott, A. I.; Kang, J.; Dalton, D.; Chung, S. K. *J. Am. Chem. Soc.* **1978**, *100*, 3603. (i) Scott, A. I.; Kang, J.; Dowd, P., Trivedi, B. K. *Bioorganic Chem.* **1980**, *9*, 426. (j) Scott, A. I.; Hansen, J. B.; Chung, S. K. *J. Chem. Soc., Chem. Commun.* **1980**, 388. (k) Wollowitz, S.; Halpern, J. *J. Am. Chem. Soc.* **1984**, *106*, 8319.

0002-7863/89/1511-2313$01.50/0