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Revisit to Meinwald Rearrangement of Electron-Deficient Systems[1]

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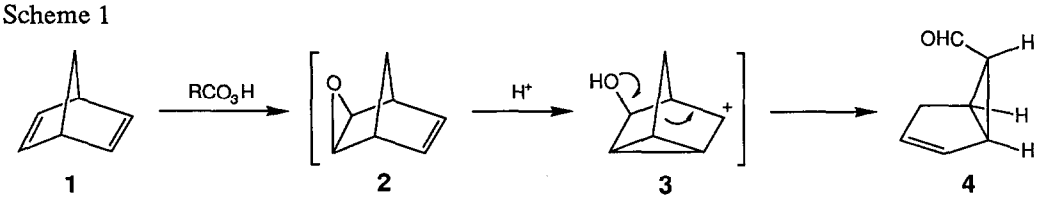
Abstract; *The monoester **6**, generated in situ by the enzymatic hydrolysis of the symmetric diester **5a** with pig liver esterase, undergoes extremely facile Meinwald-type rearrangement to afford the bicyclo[3.1.0]hex-2-ene derivative **8a** in quantitative yield.*

The conversion of norbornadiene **1** into bicyclo[3.1.0]hex-2-ene-*endo*-carbaldehyde **4** by peracid oxidation was reported by Meinwald in 1963[2]. The mechanism of this reaction is considered to involve the initial formation of the *exo*-monoepoxide **2** followed by the acid catalyzed rearrangement[3], and the latter process is called as Meinwald rearrangement (Scheme 1). In the synthetic point of view, this process, coupled with the high reactivity of the strained bicyclo[3.1.0]hexane ring system, has successfully been applied to the prostaglandin synthesis by Upjohn group[4].

Scheme 1



1 **2** **3** **4**

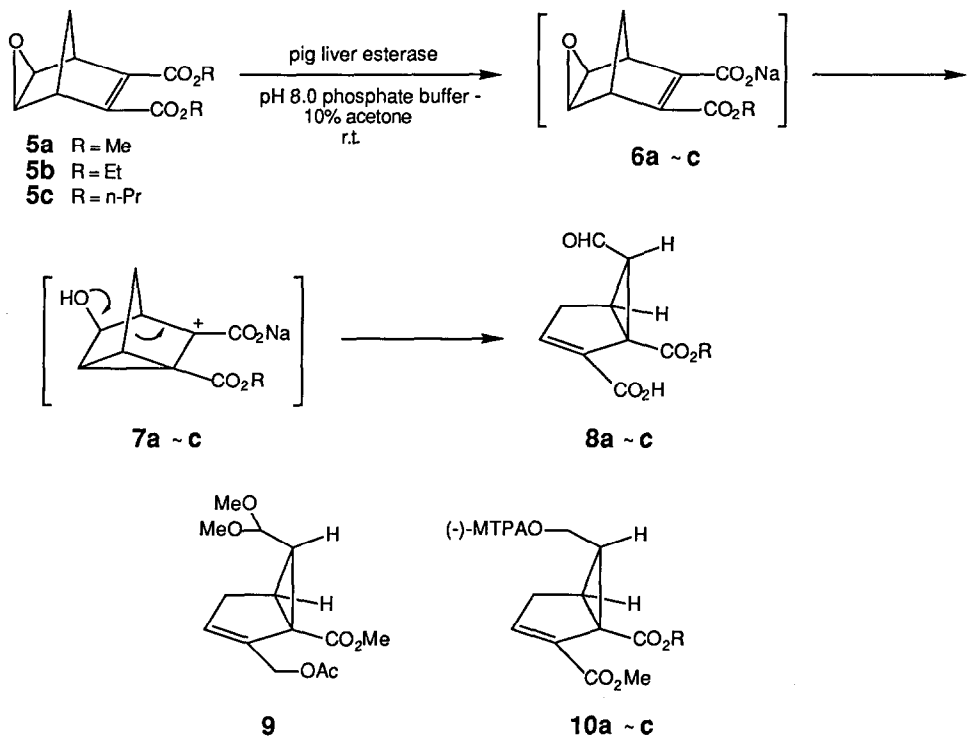
Contrary to the reactive and unstable monoepoxide **2**, the monoepoxides **5a~c** of the electron-defficient systems are found quite stable, and the difference can be reasonably explained by considering the stability of cationic intermediate of the rearrangement. Although Prinzbach observed the rearrangement of the monoepoxide **5a** (R=Me) by treatment with acid or heat, the yields of the rearranged product seemed to be not remarkable synthetically[5]. In this paper, we wish to report our own findings about the extremely facile Meinwald rearrangement of the electron defficient system which affords an interesting synthon **8a** in quantitative yield.

In connection with our enzymatic approach to biologically significant compounds[1], we became interested in the enzymatic hydrolysis of the symmetric diester **5a** with pig liver esterase to obtain the corresponding chiral monoester. Thus, dimethyl ester **5a** was treated with pig liver esterase[6] in 0.05M pH 8.0 phosphate buffer containing 10% acetone at 30°C for 5 hr. Usual work-up afforded the monoester as an almost quantitative yield. However, the product was not the expected monoester. The ^{1}H-NMR spectrum showed the presence of a formyl group (δ 9.36) and an olefinic proton (δ 6.8) which is characteristic to the β proton of the α,β-unsaturated carbonyl derivative. Based on ^{1}H- and ^{13}C-NMR spectra, the product was assigned as 6-formyl-2-methoxycarbonyl-bicyclo[3.1.0]hex-2-ene-1-carboxylic acid **8a**[7]. The enoic moiety was presumed to be α,β-unsaturated carboxylic acid rather than the isomeric unsaturated ester. The assignment of the regiochemistry was supported as follows; **8a** was treated with p-TsOH in methanol at 0°C to convert the aldehyde into the dimethyl acetal, and then the carboxyl group was selectively reduced and transformed to the acetoxymethyl derivative **9**

[(1) $ClCO_2Et$, Et_3N / THF, 0°C; (2) $NaBH_4$ / THF-H_2O, 0°C; (3) Ac_2O, Py / CH_2Cl_2, r.t.]. In ^1H-NMR spectrum, the olefinic proton appeared at δ 5.6 in accordance with the structure **9**.

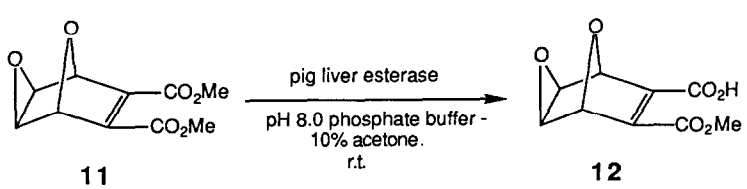
The enantiomeric excess of **8a** was determined to be 48% e.e. by ^{19}F-NMR spectra after converting to the (-)-MTPA ester derivative **10a** [(1) CH_2N_2 / Et_2O, (2) $NaBH_4$ / THF, (3) (-)-MTPACl, pyridine / CCl_4]. The assignment of the absolute configuration of **8** was tentatively made based on the analogy of the enzymatic hydrolysis of the several related bicyclic diesters developed during the synthesis of nucleoside derivatives[8].

Scheme 2



This extremely facile rearrangement was very surprising, because we have already examined the enzymatic hydrolysis of the oxa-analogue **11** which was successfully applied to the synthesis of nucleoside antibiotic cordycepin[8b]. In this case, the monoacid **12** (80~85% e.e.) was isolated in quantitative yield, and no rearrangement took place in pH 8.0 phosphate buffer (Scheme 3).

Scheme 3

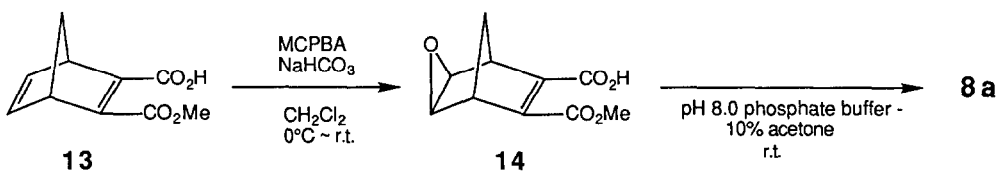


We have also examined the diethyl and di-n-propyl esters, **5b** and **5c**, respectively. In the case of **5b**, the rearranged product **8b** was obtained quantitatively, and the enantiomeric excess was determined to be 65% e.e. in a similar manner. However, the n-propyl ester **5c** was not a good substrate for the enzyme, and after 6hr of incubation, the monoacid **8c** (28% e.e.) was isolated in 37% yield along with the recovery of the diester **5c** in 48% yield.

In these reactions, the formation of the rearranged diester could not be observed, and when dimethyl ester **5a** was stirred for 5 hr in the same buffer solution without pig liver esterase, the starting diester was recovered quantitaively. These results clearly show that the rearranged product **8** is formed through the intermediary monocarboxylate **6** rather than the alternative sequence involving the initial rearrangement of the diester, followed by the enzymatic hydrolysis of the ester group attached to the olefinic carbon.

In separate experiments, the epoxy monoester **14** (racemic) was prepared from the monoester **13** [1.2 eq. MCPBA, 3.0 eq. $NaHCO_3$, / CH_2Cl_2, 0°C~r.t.]. During the oxidation, the resulting monoepoxide underwent rearrangement to some extent, probably because of the presence of sodium bicarbonate. However, the isolated epoxy acid **14** was found to be stable in neutral or slightly acidic media at room temperature, and the rearrangement proceeded in refluxing ethyl acetate. On the other hand, when **14** was allowed to stand in pH 8.0 phosphate buffer-10% acetone, the rearrangement took place smoothly at room temperature to afford **8a** in quantitative yield (Scheme 4).

Scheme 4



From these observations, we can conclude that the reactivity towards the rearrangement increases in the order of the diester **5**, monoacid **14**, and the carboxylate **6**, and depends upon the facility of the localization of π-electron of the carbon-carbon double bond in such electron defficient systems. In other words, the presumed carbocation generated from the carboxylate **6a** might be most stable among the three carbocations including those from the carboxylic acid **14** or the methyl ester **5a**[9]. The regiochemical course of this rearrangement can also be explained by the above discussion. Furthermore, the stability of the monoacid **12** toward rearrangement might be due to the inductive effect of the oxygen in the allylic position to the double bond which destabilizes the cationic intermediate, the oxa-analogue of **7a**[10].

The present results have shown that the Meinwald-type rearrangement does occur smoothly even in the electron defficient system if the substituents are properly chosen. It should be pointed out that the formation of **8a** was most easily accomplished in a basic media contrary to usual acid-caltalyzed rearrangement.

We are currently carrying out the rearrangement of other electron defficient systems, and the results will appear in due course.

Acknowledgment:

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References and Notes:

1. Construction of Novel Chiral Synthons with Enzymes and Application to Natural Product Synthesis, Part 24. See for Part 23; M. Nakada, S. Kobayashi, S. Iwasaki, S. Okuda, and M. Ohno, *Tetrahedron Lett.*, **29**, 3951 (1988).
2. J. Meinwald, S. S. Labana, and M. S. Chadha, *J. Am. Chem. Soc.*, **85**, 582 (1963).
3. J. Meinwald, S. S. Labana, L. L. Labana, and G. H. Wahl, Jr., *Tetrahedron Lett.*, **1965**, 1789.
4. U. Axen, F. H. Lincoln, and J. L. Thompson, *J. Chem. Soc., Chem. Commun.*, **1969**, 303; R. C. Kelly, V. VanRheenen, I. Schletter, and M. D. Pillai, *J. Am. Chem. Soc.*, **95**, 2746 (1973); D. R. White, *Tetrahedron Lett.*, **1976**, 1753 and references cited herein.
5. H. Prinzbach and M. Klaus, *Angew. Chem., Int. Ed. Engl.*, **8**, 276 (1969): In our hands, treatment of **5a** with catalytic $BF_3{\cdot}OEt_2$ in CH_2Cl_2 (5 min, room temperature) or catalytic AcOH (26 hr, reflux) afforded the rearranged product **15a** in 23% and 31% yields, respectively. The structure **15a** was confirmed to be identical with the methyl ester of **8a** obtained from the treatment of **8a** with CH_2N_2 in all respects (^{1}H-NMR, tlc).
6. Purchased from Sigma Co. (E 3128).
7. **8a:** $[\alpha]_D^{20}$ +72.3° (*c* 0.96, MeOH); ^{1}H-NMR (100MHz, $CDCl_3$), δ 2.4~3.1 (4H, m), 3.76 (3H, s), 6.8 (1H, m), 8.7 (1H, br), 9.36 (1H, d, *J*=4.0Hz); ^{13}C-NMR (25MHz, $CDCl_3$), δ 34.1 (t), 35.5 x2(d x2), 45.1 (s), 53.3 (q), 132.5 (s), 147.8 (d), 168.9 (s), 170.4 (s), 198.2 (d).
8b: $[\alpha]_D^{20}$ +70.5° (*c* 2.0, MeOH); ^{1}H-NMR (100MHz, $CDCl_3$), δ 1.20 (3H, q, *J*=7.2Hz), 2.5~3.1 (4H, m), 4.16 (1H, dq, *J*=10.8, 7.2Hz), 4.30 (1H, dq, *J*=10.8, 7.2Hz), 6.8 (1H, m), 8.9 (1H, br), 9.28 (1H, d, *J*=4.0Hz); ^{13}C-NMR (25MHz, $CDCl_3$), δ 13.4 (q), 33.1 (t), 34.4 x2 (d x2), 44.3 (s), 61.4 (t), 132.1 (s), 146.7 (d), 168.0 (s), 168.9 (s), 197.6 (d).
8c: $[\alpha]_D^{20}$ +49.8° (*c* 1.14, MeOH); ^{1}H-NMR (100MHz, $CDCl_3$), δ 0.85 (3H, q, *J*=7.8Hz), 1.5 (2H, sextet, *J*=7.8Hz), 2.3~3.0 (4H, m), 3.99 (1H, dt, *J*=10.5, 7.8Hz), 4.15 (1H, dt, *J*=10.5, 7.8Hz), 6.8 (1H, m), 9.3 (1H, br), 9.30 (1H, d, *J*=4.0Hz); ^{13}C-NMR (25MHz, $CDCl_3$), δ 9.9 (q), 21.4 (t), 33.0 (t), 34.4 x2 (d x2), 44.4 (s), 66.9 (t), 131.7 (s), 146.2 (d), 167.6 (s), 168.8 (s), 197.0 (d).
10a: MS *m/e* 442 (M^+); Rf 0.29 (Hex:AcOEt=3:1).
10b: MS *m/e* 456 (M^+); Rf 0.36 (Hex:AcOEt=3:1).
10c: MS *m/e* 470 (M^+); Rf 0.43 (Hex:AcOEt=3:1).
14: ^{13}C-NMR (25MHz, $CDCl_3$), δ 54.3 (q), 54.7 (d), 54.9 (d), 78.9 (d), 80.3 (d), 145.9 (s), 160.3 (s), 164.6 (s), 166.1 (s).
8. (a) Y. Ito, T. Shibata, M. Arita, H. Sawai, and M. Ohno, *J. Am. Chem. Soc.*, **103**, 6739 (1981); (b) M. Ohno, Y. Ito, M. Arita, T. Shibata, K. Adachi, and H. Sawai, *Tetrahedron, Symposia in Print*, **40**, 145 (1984); (c) M. Arita, K. Adachi, Y. Ito, H. Sawai, and M. Ohno, *J. Am. Chem. Soc.*, **105**, 4049 (1983).
9. Synchronized rearrangement and participation of the carboxylate ion through α-lactone are also considered to be attractive, but the detailed study on the mechanism needs further investigation.
10. The similar electronic effect of the allylic oxygen on the destabilization of the carbocation has been discussed in the excellent review about Woodward's synthesis of prostaglandins; I. Ernst, *Angew. Chem. Int. Ed. Engl.*, **15**, 207 (1976).

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