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COMPLEX STEREOCHEMICAL COURSE OF THE MITSUNOBU " INVERSION " OF ALLYLIC ALCOHOLS

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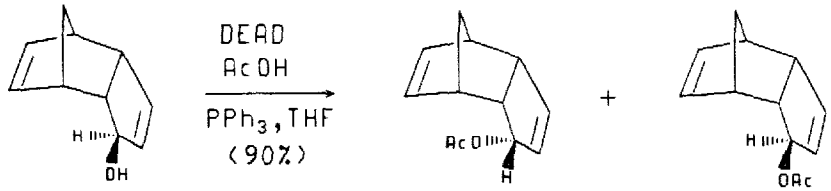
Summary: *The Mitsunobu esterification reaction of dicyclopentadienols yields mixtures of inversion and retention products. Deuterium labeling demonstrates variable levels of allylic rearrangement.*

The Mitsunobu esterification procedure has recently become a very important and useful tool in organic synthesis [1]. Its stereochemical outcome is almost invariably a clean inversion at the hydroxyl-bearing carbon [2]. In connection with an ongoing synthetic program, allylic acetate **2** (see Eq.1) was required. The precursor of choice was **1**, easily obtained by SeO_2 oxidation of endo-dicyclopentadiene [3]. When submitted to a standard Mitsunobu protocol (*AcOH, DEAD, PPh_3*, THF,rt) however, **1** surprisingly produced a 70:30 mixture of two allylic acetates, with the major product, **3**, resulting from retention of configuration. When the reaction was run at -40°C TLC indicated complete acetate formation [4], suggesting that it is not the inversion process that is particularly hindered; rather, the competing retention pathway is also an extremely facile one. At -40°C the ratio of retention (3) vs. inversion (2) was 61:39. (Eq.1)

(1)



1 **2** **3**

Examples of "abnormal" Mitsunobu reactions can occasionally be found in the literature. A stable, hindered alkoxyphosphonium intermediate that yields a retention product when heated with sodium benzoate has been described [5], while the esterification of cholesterol derivatives can proceed with rearrangements [6]. Mitsunobu reactions on dehydropyranosides, while normally proceeding with clean inversion at the carbinol center [7], in specific cases where the SN2 pathway is hindered by eclipsing substituents can give rise to allylic rearrangement [8]. On the

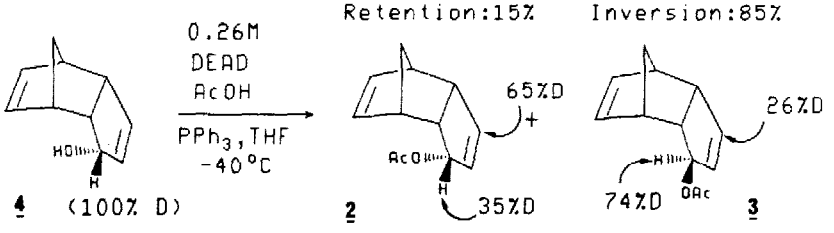
other hand, in allylic alcohols where no bias exists against the normal SN2 process,clean regiospecific inversion is invariably observed [7a,9,10a] or implied [10].

Further experiments were carried out in order to shed some light on the origin of the anomalous result described above. Oxidation of **1** (PCC,CH_2Cl_2,85%) followed by lithium aluminum deuteride (LAD) reduction produced **4** (>99% deuterated at the α carbon) in 57% yield [11,12].

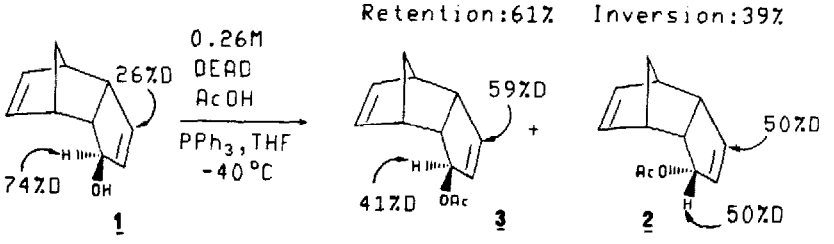
Mitsunobu reaction on **4** [4] produced, surprisingly, also a mixture of epimers, even though the inversion product predominated (Eq.2). The inseparable acetates were hydrolyzed (K_2CO_3,MeOH-water,72 h,rt) to yield the easily separable epimers **1**-D and **4**-D in 95% yield. Label distribution was calculated by careful ^{1}H-NMR integration on each individual epimer [13].

Scrambling of the label occurred in both products: the retention product was deuterated preferentially at the olefinic carbon, while the inversion product had the label still mainly at the carbinol center. Thus, even in a case where the SN2 reaction appears sterically favored (the convex face of the molecule is clearly more accessible), the retention process is still observable. Repetition of the reaction in Eq.1 on labeled **1** also revealed a complex regiochemical outcome: the inversion process was not an SN2 process, since complete deuterium scrambling was observed. The retention process was here also the result of predominant attack at the allylic carbon. Use of benzoic acid as the nucleophile (Eq.4) gave similar results : **4** produced 10% of a retention product (D labeling was preferentially at the olefinic carbon) and 90% of the inverted benzoate, with partial label scrambling. The effect of concentration was also briefly examined.

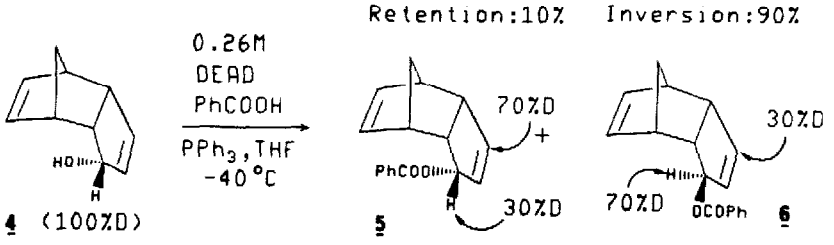
(2)



(3)



(4)

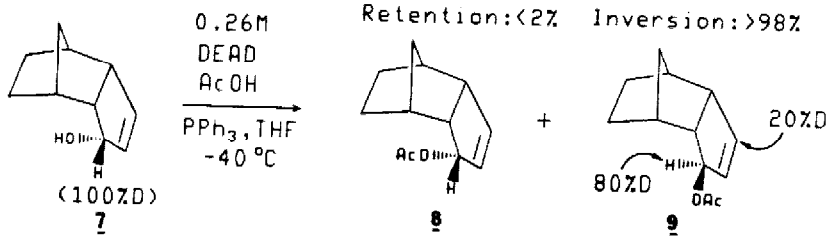


Use of **4** as substrate (0.026 M, AcOH as nucleophile, ten-fold dilution vs.above experiments) gave 92% inversion (83% α-D vs. 17% γ-D) and only 8% retention (label distribution not determined). The inversion products in Eq.2-4 could arise by competition between SN2 (the normal mode) and SN2' [14,15] processes. On the other hand, retention must arise through an SNI pathway to an extent of no less of 35%, and possibly as high as 100% (Eq.2). If retention is mainly the result of a unimolecular process and inversion the result of a bimolecular one, ten-fold dilution of the reactants should drastically alter product distribution in favor of retention (Eq.2). The fact that a small effect in the opposite sense was observed strongly suggests that SN2/SN2' pathways play a minor role here, and the mechanism involves solvolysis of the intermediate alkoxyphosphonium ion [2] to an allyl cation that is not entirely free.

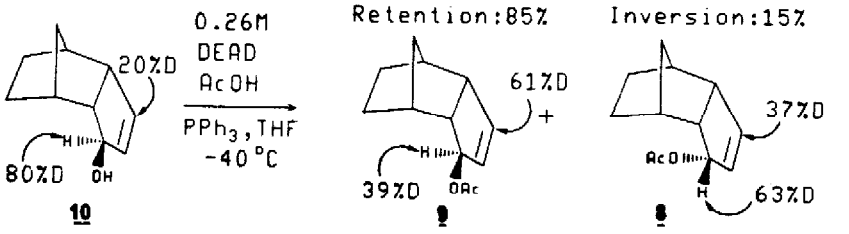
In order to examine the effect of the isolated double bond on the chemistry discussed above, alcohols **7**-D and **10**-D were prepared [16]. Mitsunobu reaction under typical conditions[4] indicated that saturation of the remote double bond increases the steric hindrance for attack of acetate from the concave face, completely eliminating the retention process for **7** and resulting in almost exclusive retention for **10** [16] (85% vs. 15% inversion). (Eq.5,6)

These results show that the Mitsunobu esterification reaction of allylic alcohols, in contrast to previous assumptions [10], can occur with modes other than simple SN2 displacement, even when the retention pathway is sterically disfavored. Since there is no apparent uniqueness to the dicyclopentadienyl system in this respect, it is suggested that care should be exercised in making assumptions on the stereochemical course of the Mitsunobu reaction of allylic alcohols.

(5)



(6)



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4) The following procedure is representative: The alcohol was dissolved in dry THF to the specified concentration,PPh_3 (1.5 eq.) was added,followed by AcOH (1.5 eq.) and,after cooling to -40°C,by DEAD (1.5 eq.).After 1.5h the temperature reached -10°C. Quenching ($MeOH/H_2O$, then ethyl acetate) was followed by extraction and careful flash chromatography, yielding the mixture of acetates in yields ranging from 88% to 97% in all cases described.

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11) The literature procedure was used: Woodward,R.B.;Katz,T.J. Tetrahedron **1959**,5,70. An overreduction product was invariably also obtained. Purification was achieved,with some difficulty,by flash chromatography (10% ethyl acetate in hexane).

12) All new products were characterized by ^{1}H-NMR and elemental analysis. Incorporation of deuterium was verified by high-resolution mass spectrometry.

13) Separation by flash chromatography (10% to 30% ethyl acetate gradient in hexane) proceeded without difficulty. Ratios (± 2%) were assigned by ^{1}H-NMR using the following signals:
For **1** : H_α 4.04(m) H_β 5.57(m) H_γ 5.74(m).
For **4** : H_α 4.65(t) H_β 5.57(s) H_γ 5.57(s).

14) Review: Magid,R.M. Tetrahedron **1980**,36,1901.

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16) Compound **7** is described in : Fiaud,J.C.;Legros,J.Y. J.Org.Chem. **1987**,52,1907. Deuteration was carried out with LAD in ether (50% yld. after careful flash chromatography). **10** was obtained from **9** (K_2CO_3,MeOH-water,72h at rt,97% yld.). Relevant NMR data are: For **7** : H_α 4.84(m) H_β 5.70(m) H_γ 5.77(m).
For **10** : H_α 4.64(br.s) H_β 5.77(m) H_γ 5.89(m).

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