



アセチル化及び加水分解における選択性と立体遮蔽との関係(大学学部生の有機化学実験)

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Relationship between Selectivity and Steric Hindrance in Acetylation and/or Hydrolysis (An Undergraduate Organic Chemistry Experiment)

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アセチル化及び加水分解における選択性と立体的遮蔽との関係 (大学学部生の有機化学実験)

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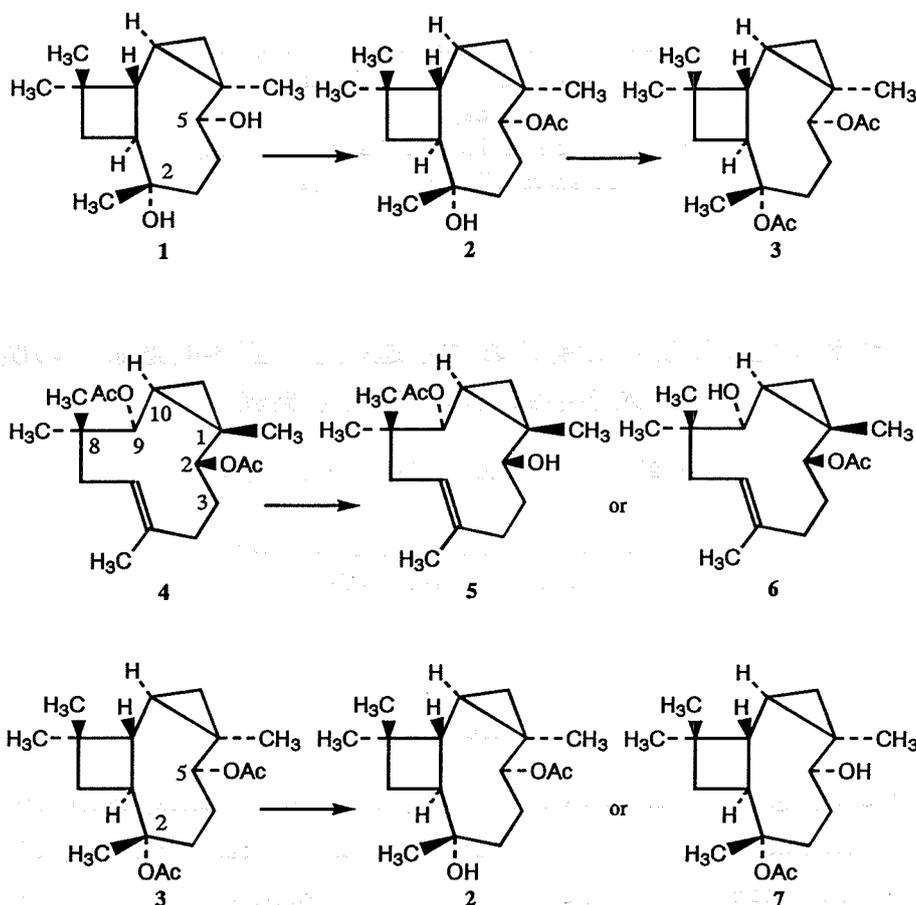
Abstract

Secondary hydroxyl group (5 position) was selectively converted to acetoxy group (monoacetate **2**) with acetic anhydride in pyridine in acetylation of two hydroxyl groups (secondary and tertiary) of tricyclocaryophyllanediol (**1**), since steric hindrance and shielding of secondary hydroxyl group were smaller than those of the tertiary hydroxyl group. The experiment in hydrolysis of acetoxy group was carried out using two model compounds: diacetate (**3**) of **1** (secondary and tertiary acetoxy group) and bicyclohumulenediol diacetate (**4**, two different secondary acetoxy groups). In the case of **4**, selective hydrolysis of acetoxy group at 2 position was conducted with sodium bicarbonate in aqueous methanol because of the low degree of steric hindrance and shielding at 2 position. On the bases of the above results in acetylation and hydrolysis, the product expected by student in the hydrolysis of **3** was **7**, but the actual product was **2**. The experiments allowed the student to discuss a relationship between steric hindrance and selectivity in acetylation and hydrolysis, to reach stereo acceleration in hydrolysis of **3** and to study fundamental procedures of organic experiments and analytical methods (IR and NMR).

Subject to steric requirements of the acylating agents and the hydroxyl groups, it is sometimes possible to acylate one of the hydroxyl groups of a di-alcohol selectively. Selective deacylation of diesters is also sometimes possible, and depends on the steric factor.¹⁾ It is important that students in the undergraduate organic chemistry laboratory understand the above selectivity owing to steric

factor. We describe here a simple model experiment related to selective acetylation of diol and selective hydrolysis of diacetate. The experiment allows the students to understand a relationship between steric hindrance and selectivity, and to discover stereo acceleration.

Tricyclocaryophyllanediol (**1**) and bicyclohumulenediol diacetate (**4**) as a model compound in the experiment are previously prepared from humulene²⁾ by known methods.^{3,4)} These structures and



Scheme 1.

relative configurations are shown in the formulas (Scheme 1). The solid wedges indicate the bond that extends forward from the plane of the page, and the dotted lines represent the bond that projects to the rear of the plane. The acetylation of secondary (position 5) and tertiary (position 2) hydroxyl groups in the diol **1** is carried out with Ac_2O in pyridine at room temperature. Because steric hindrance at position 5 is generally smaller than that at position 2, it is easy to expect the monoacetate product (**2**). In order to answer the question of the possibility of acetylation at position 2, the acetylation of **2** with Ac_2O in triethylamine is tested immediately in the presence of 4-dimethylaminopyridine.⁵⁾ On the other hand, the above diacetate **3** and **4** are used in the experiment of selective hydrolysis with NaHCO_3 in aqueous acetone.

Before the experiment of hydrolysis, the expected product (selectivity) from considering steric factor can be asked of the student.

In the compound **4** with two secondary acetoxy groups (position 2 and 9), it must be considered that

steric hindrance around these is effected by shielding both neighboring sides. Because position 2 is interposed between tertiary (position 1) and quaternary (position 3) carbon, and position 9 is inserted between secondary (position 8) and quaternary (position 10) carbon, it is appeared that the position 2 is more masked by the two neighboring sides and is protected against hydrolysis. The obtained compound from 4 is only 5.

The hydrolyzed product from the diacetate 3 is most easily anticipated as molecule 7 by the student on the grounds of the result obtained in the acetylation of 1, but the resulting compound is actually 2 not 7. This result contrary to their prediction causes them to discuss the degree of steric hindrance and shielding at the two reactive sites (position 2 and 5), and to reach the conclusion that stereo acceleration accelerates the rate of hydrolysis of the tertiary acetoxy group (position 2) for release of steric compression and repulsion.⁶⁾

The progress of the reaction, purity after recrystallization and eluting situation of silica gel column chromatography are monitored by thin layer chromatography (TLC) on silica gel. Selectivity of the reactions and structure of the products are revealed by ¹H-NMR spectroscopic analysis, which is an important technique in the undergraduate organic laboratory. Comparison of ¹H-NMR spectrum of compound 1, 2 and 3 shows that the acetylation of hydroxyl group on C-5 of 1 causes to lower a peak (3.17 ppm) of the proton on C-5 to 4.47 ppm and adds a new singlet peak (2.01 ppm) for the methyl proton of acetoxy group, and that more acetylation of the hydroxyl group on C-2 of 2 increases a singlet peak

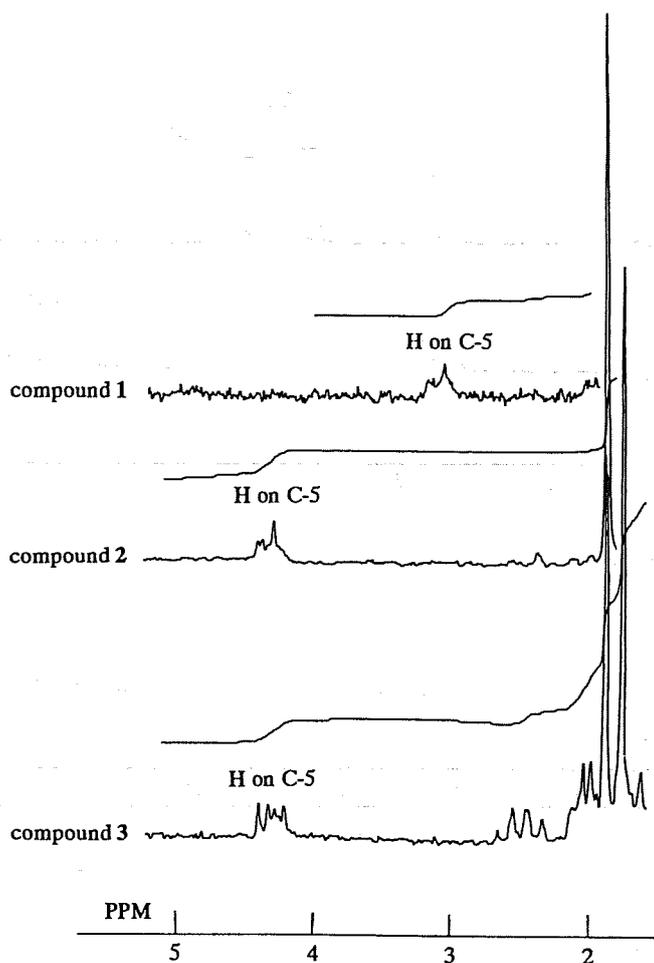


Figure 1. NMR spectra (90-MHz, CDCl_3) of compound 1, 2 and 3 in the range of about 2 to 5 ppm.

(1.89 ppm) due to methyl proton of acetoxy group (Figure 1). Compare 5 with 4 which shows a doublet at 4.41 ppm for the proton on C-2, a doublet of doublet at 3.98 ppm for the proton on C-9, and each singlet at 1.88 and 1.90 ppm for methyl proton of acetoxy group, a large transfer of peak of the proton on C-2 to up-field (2.76 ppm) and decrease of a singlet for the methyl proton of acetoxy group in ^1H -NMR of 5 suggest selective hydrolysis at position 2 (Figure 2). Table 1 summarizes R_f values from TLC analysis, melting points and the yields of products.

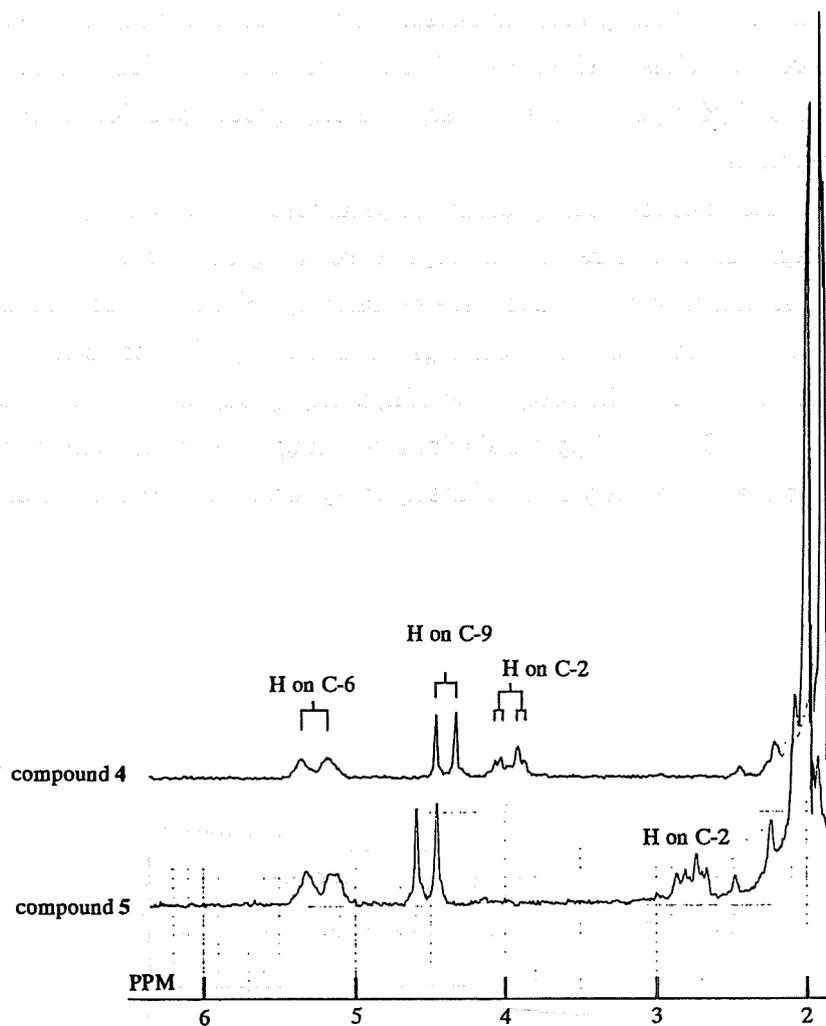


Figure 2. NMR spectra (60-MHz, CDCl_3) of compound 4 and 5 in the range of about 2 to 6 ppm.

Table 1. R_f values (Developing Solvent EtOAc: Benzene 1: 4), Melting Points and Yields

Compound No.	R_f	Melting Point	% Yield
1	0.06	205-206	-
2	0.29	-	55(Acetylation) 56(Hydrolysis)
3	0.86	-	90
4	0.76	140-142	-
5	0.25	126-127	80

Experimentation

Melting points are determined in open capillaries and are uncollected. $^1\text{H-NMR}$ spectra are measured at 60 MHz on a Hitachi R20B instrument and at 90 MHz on a Hitachi R-90H instrument. Chemical shifts are reported in δ units by using $(\text{H}_3\text{C})_4\text{Si}$ as the internal standard. Coupling constants (J value) appear in Hz units. Splitting patterns are designed as "s, d, dd, m and br"; these symbols indicate "singlet, doublet, doublet of doublet, multiplet and broad," respectively. IR adsorption spectra are recorded on a JASCO model IRA-1 spectrophotometer on NaCl cell.

Silica gel 60 (70-230 mesh ASTM, Cat.-No. 7734, MERCK Co., Ltd.) of 30 times' the weight of the crude product is used for chromatography. Silica gel TLC is carried out using TLC pre-coated plates (Silica gel 60 F254, MERCK Co., Ltd.) with appropriate solvent systems; EtOAc/Benzene (20/80, 10/90 and 2/98), and visualized by spraying color-producing reagent (5% $\text{Ce}(\text{SO}_4)_2$ in 1M- H_2SO_4 or 3.5% $\text{P}_2\text{O}_5 \cdot 24\text{MoO}_3 \cdot x\text{H}_2\text{O}$ in EtOH) and the heating on hot plate.

EtOAc and benzene for chromatography, TLC and extraction are prepared from first class reagents by distillation.

Acetylation of 1 and 2. A 50-ml round-bottomed flask is fitted with a calcium chloride tube. The diol **1** (200 mg), pyridine (6 ml) and Ac_2O (6 ml) are added to the flask, and the mixture is magnetically stirred at room temperature for 24 h. Aliquots of the mixture are removed with the capillary, spotted on silica gel TLC plates and developed in EtOAc/benzene (5:95) solvent. Detection is carried out with color-producing reagent. After this time, the mixture is diluted with water (30 ml) with stirring at room temperature, and is extracted three times with benzene. The combined extracts are washed with saturated solution of NaHCO_3 and water, and are dried with Na_2SO_4 . The solvent is removed by rotary evaporation and the residue (160 mg) dissolved in the minimum volume of benzene. This solution is poured into a silica gel column prepared using benzene and eluted with EtOAc/benzene (5:95-10:90). The colorless fractions are monitored with TLC (developing solvent EtOAc/benzene 2:98) and fractions containing the main product (approximate R_f 0.29) are collected. Solvent removal by rotary evaporation yields compound **2** (130 mg, 55% yield). Moreover, the remaining diol **1** is eluted with EtOAc/benzene (20:80) and recovered (40 mg, 20% yield). The spectrum of **2** shows peaks as follows: IR (Neat) 3200-3600 (hydroxyl group on C-2), 1730 (carbonyl group of acetate on C-5) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) δ 0.2-0.8 (3H, m, proton of cyclopropane ring), 1.02 (6H, s, geminate dimethyl proton on C-10), 1.10, 1.16 (each 3H, s, methyl proton on C-6 and -2), 2.00 (3H, s, methyl proton of acetoxy group on C-5), 4.45 (1H, m, proton on C-5) ppm.

Acetylation of **2** (100 mg) is achieved by the same manner as described above except that Ac_2O (1 ml), Et_3N (1.5 ml) and 4-dimethylaminopyridine (110 mg) are used. Chromatographic separation (eluting solvent EtOAc:benzene 2:98) of the crude product gives diacetate **3** (103 mg, 90% yield). The spectrum of **3** is described below: IR (Neat) 1725 (carbonyl group of acetate on C-2 and -5) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) δ 0.2-0.8 (3H, m, proton of cyclopropane ring), 1.02 (6H, s, geminate dimethyl proton on C-10), 1.10 (3H, s, methyl proton on C-6), 1.36 (3H, s, methyl proton on C-2), 1.89 (3H, s, methyl proton of acetoxy group on C-2), 2.01 (3H, s, methyl proton of acetoxy group on C-5), 4.40 (1H, dd, $J = 6, 11$ Hz, proton on C-5) ppm.

Hydrolysis of diacetate 3 and 4. To a 50 ml round-bottomed flask fitted with a reflux condenser are added 200 mg of diacetate 3, 2 ml of saturated NaHCO₃ solution, 7 ml of acetone and 5 ml of water. The mixture is magnetically stirred and refluxed gently in an oil bath for 24 h. The flask is removed from the oil bath and cooled for a time undisturbed. The mixture is diluted with 30 ml of water and extracted three times with benzene. The combined extracts are washed with water and are dried with Na₂SO₄. Removal of the solvent by rotary evaporation yields a crude oil, which is separated by chromatography on silica gel using 5:95 EtOAc:benzene as eluting solvent to yield 2 (97 mg, 56%).

Hydrolysis of 4 and extraction of the product are accomplished in the same way. The solvent is removed by rotary evaporation, and the residue is recrystallized from hexane to yield 5 (140 mg, 80%): melting point 126-127°C; IR (Nujol) 3450 (hydroxyl group on C-2) and 1710 (carbonyl group of acetate on C-9) cm⁻¹; ¹H-NMR (CDCl₃) δ 0.15 (1H, dd, J = 4, 6 Hz, proton of cyclopropane ring), 0.65 (1H, dd, J = 4, 9.5 Hz, proton of cyclopropane ring), 0.90, 1.04, 1.14 (each 3H, s, methyl proton on C-1 and -8), 1.67 (3H, br s, methyl proton on C-5), 2.00 (3H, s, methyl proton of acetoxy group on C-9), 2.76 (1H, dd, J = 3.5, 8.5 Hz, proton on C-2), 4.52 (1H, d, J = 8.5 Hz, proton on C-9), 5.22 (1H, br d, J = 10.5 Hz, olefinic proton on C-6) ppm.

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