

Stereoselective Reduction of Methyl Vinyl Ketone Dimer

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The stereoselectivity of the reaction between methyl vinyl ketone dimer, which contains two possible sites of chelation, and zinc borohydride or diisobutylaluminum hydride has been studied in order to illuminate the factors involved in the high levels of asymmetric induction obtained in the bicyclic system. The conditions for the formation of the exo-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane are DIBAH reduction of MVK dimer in ether at reflux followed by acidic cyclization, and for the endo isomer are $Zn(BH_4)_2$ reduction with $ZnCl_2$ at 0 °C.

Introduction

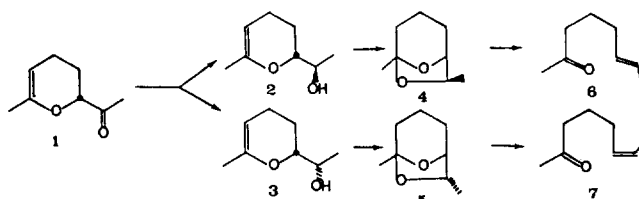
In view of the increasing number of biologically active natural products containing bicyclic ketals¹ and their derivatives,² much attention has recently been focused on efficient approaches toward these systems. In particular, the 6,8-dioxabicyclo[3.2.1]octane series have been an interesting synthetic challenge within the past decade.³ The pioneering work in this field has been established by Mundy and co-workers.⁴ They also showed the stereoselectivity from the exo bicyclic ketal (4) to the trans- δ , ϵ -unsaturated ketone (6) and from the endo bicyclic ketal (5) to the cis- δ , ϵ -unsaturated ketone (7) by the fragmentation reaction (Scheme 1).⁵ However, there are not much reports on the stereoselective synthesis of the exo and endo bicyclic ketals, which are not easily separated from each other.

The stereoselectivity of the reaction between methyl vinyl ketone dimer (1), which contains two possible sites of chelation, and zinc borohydride and diisobutylaluminum hydride has been studied in order to illuminate the factors involved in the high levels of asymmetric induction obtained in the bicyclic system.

We now report a very simple one-flask synthesis, which results in quantitative yield of 60% de mixture richer in the exo isomer (4). A mixture richer in the endo isomer (5) (>60% de) can be obtained by a modification of the procedure.

Results and Discussion

Methyl vinyl ketone (MVK) dimer (1) is prepared by Diels-Alder reaction of methyl vinyl ketone in autoclave at 170 °C for 3 hrs.⁶ This dimeric ketone is then reduced to give the corresponding secondary carbinol shown in Scheme 1. At this point, a mixture of threo- and erythro-alcohols, which can be cyclized to a mixture of exo and endo ketals by the reaction with *p*-toluenesulfonic acid,⁶ has been produced. The exo ketal (4) should be derived from the threo-alcohol (2) and the endo ketal (5) from the erythro-alcohol (3). These can be conformed by the molecular model study. Therefore, the key point in the synthesis of exo and endo ketals is the selective reduction of the ketone (1) to the threo-alcohol (2) or to the erythro-alcohol (3). The exo-endo stereochemistry of the C-7 methyl group is determined by the sodium borohydride reduction of the precursor methyl ketone.⁷ In all of



Scheme 1.

Mundy's experiences using general methodology for this stereoselective synthesis, they have been hindered by the inability to provide a clean preference for one of the isomers.⁸ They seem to find a general alcohol isomer ratio of about 60:40, which is expressed later by a 60:40 ratio of exo and endo ketals, respectively. Exo and endo ketals are easily identified by the chemical shift of the proton NMR spectroscopy. The chemical shift of endo-methyl at C-7 appears at more downfield than that of exo-methyl.⁵ We found that the exo ketal (4) comes out earlier than the endo isomer (5) in the gas chromatography using SE-30 column and so the product mixture were easily analyzed as shown in Table 1.

And, also, we modified the procedure a little bit easier by using aqueous 10% HCl solution for the work-up of the reduction product instead of one more reaction for cyclization of the alcohol to ketal by using *p*-toluenesulfonic acid in reflux.⁶ As shown in Table 1, we used zinc borohydride or diisobutylaluminum hydride as a nucleophile for the reduction with or without zinc chloride as a Lewis acid. We used methylene chloride, tetrahydrofuran or ether as a solvent and the reaction proceeded at various temperatures. In most cases, the reduction and the cyclization yielded quantitatively to the corresponding product.

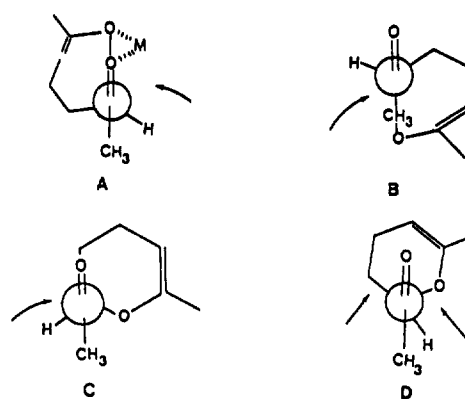
The exo ketal (4) is preferred from the $Zn(BH_4)_2$ reduction with or without $ZnCl_2$ at -78 °C (entries 5, 9, 12, 15, 18, 21) and the solvent effect does not show at this temperature. But the same reaction at 0 °C, the endo ketal (5) is preferred and getting increased in methylene chloride or ether as a solvent with a Lewis acid (entries 7, 20). We used $ZnCl_2$, $BF_3(Et_2O)$, TMSOTf, $AlCl_3$ and $TiCl_3$ as a Lewis acid and found that only $ZnCl_2$ does not give any by-products. When we tried this reduction with diisobutylaluminum hydride, the reaction was quite different depending on solvent systems. At -78 °C, the reaction in tetrahydrofuran without $ZnCl_2$ (entry 31) or the reaction in ether with $ZnCl_2$ (entry 44) gives the 83:17 mixture richer in the exo isomer (4). But the same result is

Table 1. Stereoselectivity of Reduction and Cyclization of Methyl Vinyl Ketone Dimer

Entry	1 $\xrightarrow[\text{H}^+]{\text{reagent(s)}}$ 4 (exo) + 5 (endo)		Temp.	Exo:Endo
	Reagent (s)	Solvent		
1	LiAlH ₄	THF	rt	62:38
2	BaBH ₄	2-Propanol	rt	56:44
3	Zn(BH ₄) ₂	CH ₂ Cl ₂	rt	45:55
4	Zn(BH ₄) ₂	CH ₂ Cl ₂	0 °C	40:60
5	Zn(BH ₄) ₂	CH ₂ Cl ₂	-78 °C	82:18
6	Zn(BH ₄) ₂ + ZnCl ₂	CH ₂ Cl ₂	rt	32:68
7	Zn(BH ₄) ₂ + ZnCl ₂	CH ₂ Cl ₂	0 °C	19:81
8	Zn(BH ₄) ₂ + ZnCl ₂	CH ₂ Cl ₂	-20 °C	34:66
9	Zn(BH ₄) ₂ + ZnCl ₂	CH ₂ Cl ₂	-78 °C	86:14
10	Zn(BH ₄) ₂	THF	rt	48:52
11	Zn(BH ₄) ₂	THF	0 °C	36:64
12	Zn(BH ₄) ₂	THF	-78 °C	76:24
13	Zn(BH ₄) ₂ + ZnCl ₂	THF	rt	39:61
14	Zn(BH ₄) ₂ + ZnCl ₂	THF	0 °C	35:65
15	Zn(BH ₄) ₂ + ZnCl ₂	THF	-78 °C	81:19
16	Zn(BH ₄) ₂	E.E	rt	45:55
17	Zn(BH ₄) ₂	E.E	0 °C	39:61
18	Zn(BH ₄) ₂	E.E	-78 °C	82:18
19	Zn(BH ₄) ₂ + ZnCl ₂	E.E	rt	40:60
20	Zn(BH ₄) ₂ + ZnCl ₂	E.E	0 °C	20:80
21	Zn(BH ₄) ₂ + ZnCl ₂	E.E	-78 °C	80:20
22	DIBAH	CH ₂ Cl ₂	rt	78:22
23	DBAH	CH ₂ Cl ₂	-20 °C	65:35
24	DIBAH	CH ₂ Cl ₂	-78 °C	69:31
25	ZnCl ₂ + DIBAH	CH ₂ Cl ₂	rt	51:49
26	ZnCl ₂ + DIBAH	CH ₂ Cl ₂	-20 °C	49:51
27	ZnCl ₂ + DIBAH	CH ₂ Cl ₂	-78 °C	54:46
28	DIBAH	THF	rt	70:30
29	DIBAH	THF	0 °C	65:35
30	DIBAH	THF	-10 °C	70:30
31	DIBAH	THF	-78 °C	83:17
32	ZnCl ₂ + DIBAH	THF	rt	45:55
33	ZnCl ₂ + DIBAH	THF	0 °C	48:52
34	ZnCl ₂ + DIBAH	THF	-78 °C	49:51
35	DIBAH	E.E	reflux	84:16
36	DIABH	E.E	rt	82:18
37	DIBAH	E.E	0 °C	75:25
38	DIABH	E.E	-20 °C	68:32
39	DIBAH	E.E	-78 °C	68:32
40	ZnCl ₂ + DIBAH	E.E	reflux	57:43
41	ZnCl ₂ + DIBAH	E.E	rt	37:63
42	ZnCl ₂ + DIBAH	E.E	0 °C	42:58
43	ZnCl ₂ + DIBAH	E.E	-20 °C	49:51
44	ZnCl ₂ + DIBAH	E.E	-78 °C	83:17

appeared in the reaction in ether without ZnCl₂ at reflux (entry 35). However, methylene chloride does not seem to be a good solvent in diisobutylaluminum hydride reduction in this system (entries 22–27).

The results presented in Table 1 can be rationalized by reference to Figure 1 wherein we assume that hydride attack

**Figure 1.** Models for hydride addition to methyl vinyl ketone dimer.

on ketones always occurs from the less encumbered side of the ring methylene or the ring oxygen. Models A, B and C (Figure 1) are proposed to rationalize the experimental results. A is the Cram chelate rule model,⁹ while B and C correspond to the Cornforth dipolar model¹⁰ or the Felkin model.¹¹ The bridged structure A is expected to control the stereoselectivity when the reagent is capable of chelation with the ring oxygen and the carbonyl oxygen. The endo ketal (5) could be derived from this chelating structure. Structures B and C are assumed to be important in the absence of chelation to the ring oxygen. This nonchelating structures B and C should favor the exo ketal (4) which is achieved as a major isomer at -78 °C even when chelating reagents such as zinc chloride and zinc borohydride are used.¹² We might assume the chelating ability depressed at this lower temperature. However, the best condition for chelation is achieved at 0 °C yielding the endo ketal (5) as a major product. The reduction with sodium borohydride or lithium aluminum hydride does not show any stereoselectivity and gives the 60:40 mixture of exo and endo ketals respectively (entries 1, 2). This result can be explained by the Bartlett model D which shows the comparable bulkiness between the ring oxygen and the ring methylene towards the hydride attack.¹³

In conclusion, the condition for the reduction of MVK dimer (1) to exo ketal (4) are entry 35 which is the DIBAH reduction in ether at reflux and entries 5, 9, 12, 15, 18, 21, 31 and 44 which are the Zn(BH₄)₂ reduction at -78 °C. And the conditions for the reduction of MVK dimer (1) to endo ketal (5) are entries 7 and 20 which are the Zn(BH₄)₂ reduction with ZnCl₂ at 0 °C.

Experimental

NMR spectra were recorded on a Varian EM-360L using TMS as an internal standard. IR spectra were taken on a Shimadzu IR-435 spectrometer. GLC analysis were performed using a Shimadzu GC-7A gas chromatography equipped with 7' × 1/8", 10% SE-30 column.

General procedure for exo-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane (4). A solution of 0.2 g (1.4 mmole) methyl vinyl ketone dimer (1) dissolved in THF (2 ml) was stirred under nitrogen at -78 °C and 2 eq. of DIBAH (1M solution in THF) was added dropwise. The reaction mixture were stirred for 2 hrs at -78 °C and then quenched with 10 ml of 15%

aqueous HCl solution. The reaction product was extracted three times with ether (20 ml \times 3) and the organics were separated and dried over anhydrous magnesium sulfate. The ether was removed by rotatory evaporator. The GLC analysis indicated an exo/endo ratio of 83:17 (quantitative yield).

General procedure for endo-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane (5). To a dried ZnCl_2 (2 eq.) was added dropwise 0.2 g (1.4 mmol) of methyl vinyl keton dimer (1) in 2 ml of CH_2Cl_2 and 3 eq. of $\text{Zn}(\text{BH}_4)_2$ (0.8M solution in THF) respectively at 0°C. After 2 hrs stirring at 0°C, 10 ml of 15% aqueous HCl solution was added to this reaction mixture and worked-up as above. The GLC analysis indicated an exo/endo ratio of 19:81 (quantitative yield).

$^1\text{H-NMR}$ (CDCl_3) of (4): δ (ppm) 4.20 (1H, m), 3.99 (1H, br s), 1.70 (6H, br s), 1.42 (3H, s), 1.19 (3H, d, $J=10$ Hz).

$^1\text{H-NMR}$ (CDCl_3) of (5): δ (ppm) 4.18 (2H, m), 1.70 (6H, br s), 1.42 (3H, s), 1.31 (3H, partially buried doublet).

IR (neat) of (4): 2935, 1460, 1443, 1380, 1237, 1185, 1099, 1011, 976, 839 cm^{-1} .

IR (neat) of (5): 2934, 1464, 1442, 1379, 1259, 1190, 1097, 1020, 837 cm^{-1} .

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Initial State and Transition State Solvation for the Solvolysis of $\text{trans}[\text{Co}(\text{N-eten})_2\text{Cl}_2]^+$ in Binary Aqueous Mixtures: Excess Free Energy, Free Energy Cycle and Reaction Mechanism

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The rates of solvolysis of $\text{trans}[\text{Co}(\text{N-eten})_2\text{Cl}_2]^+$ (N-eten; N-ethylethylenediamine) have been investigated using spectrophotometric method in binary aqueous mixtures containing methyl alcohol, isopropyl alcohol, *t*-butyl alcohol, ethylene glycol and glycerol. The values of ΔH^\ddagger and ΔS^\ddagger obtained from temperature effect on the rate constants were 80~84 kJmol^{-1} and -28~-45 $\text{JK}^{-1}\text{mol}^{-1}$. Extrema found in the variation of the enthalpy and entropy of activation with solvent composition correlated very well with extrema in the variation of the physical properties of mixture which relate to sharp change in the solvent structure. The reaction mechanism was discussed in terms of correlation diagrams involving the excess molar Gibbs function of mixing for the binary mixtures. The behavior of this cobalt(III) complex was compared with that of *t*-butyl chloride. The application of free energy cycle to the process initial state to transition state in water and in the mixture showed that the solvation of transition state had dominant effect on the rates in the mixtures. It was found that S_{N1} character was increased with increasing the content of co-solvent in the mixture.

Introduction

There have been numerous studies of solvolysis of cobalt

(III)-ammine complexes in mixed solvents.¹⁻¹⁰ The solvent effects on initial state and transition state in organic and inorganic reactions were published and reviewed.¹¹⁻¹⁶ It has