Rearrangement Approaches to Cyclic Skeletons. XII. Acid-Catalyzed Isomerization of Bicyclo[3.2.1]oct-6-en-2-ones into Bicyclo[3.2.1]oct-3-en-2-ones without Racemization[1)]

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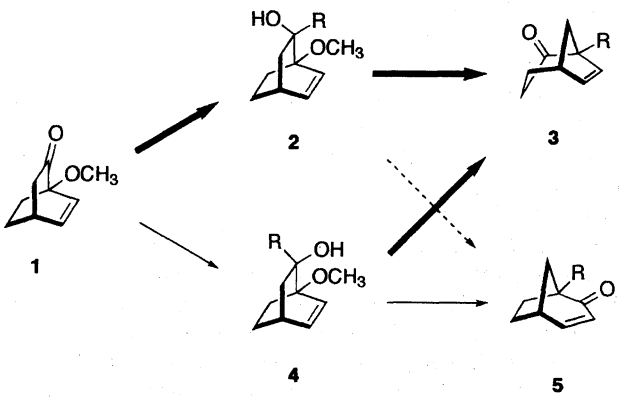
The treatment of a bicyclo[3.2.1]oct-6-en-2-one (**3**) with Amberlyst® (H-15) in boiling benzene gave a mixture of bicyclo[3.2.1]oct-3-en-2-one (**5**) and bicyclo[2.2.2]oct-5-en-2-one (**6**). The ratio of **5** to **6** was influenced by the substituent at the C-1 position of the ketone **3**. Chiral ketones **3** were transformed into the chiral α,β-unsaturated ketones **5** without racemization.

Recently, we improved a synthetic method for bicyclo-[3.2.1]oct-6-en-2-ones (**3**) starting from 1-methoxybicyclo-[2.2.2]oct-5-en-2-ones (**1**) through a pinacol-type rearrangement of the alcohols (**2** and **4**), as summarized in Scheme 1.[2)] Pioneers in this field had observed a concurrent conversion of ketones **3** into a mixture of the isomeric ketones (**5** and **6**), as shown in Scheme 2, under their reaction conditions to prepare **3** from **2** and **4**.[3)]Scheme 2 suggests that the optically active β,γ-unsaturated ketone (**3**) affords the optically active α,β-unsaturated ketone (**5**). It was pointed out, however, that the racemization of **3** might be possible, as shown in Scheme 3.[3)]

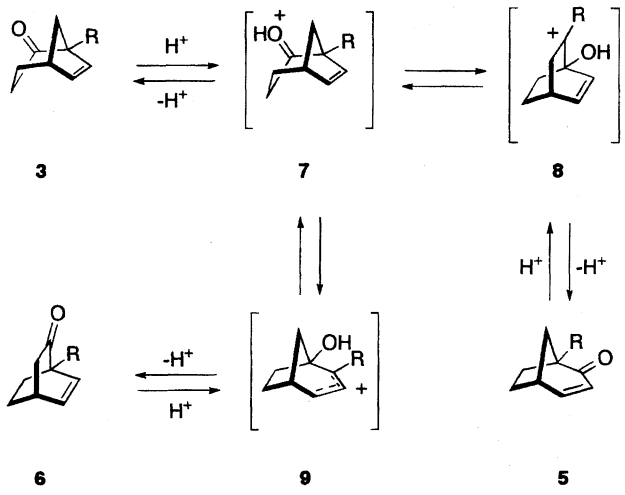
Very recently, a method for preparing chiral ketones **1** has been developed.[1)] We had already reported a synthetic route to **6** starting from the ketones **1** by a so-called bridgehead-substitution methodology.[4)] Thus, the remaining subject was a practical synthesis of the α,β-unsaturated ketones **5**. Furthermore, the enantiospecific transformation of **3** into **5** with inversion is of interest.[5)] The present paper describes substituent effects to the rearrangement of **3** to **5** and a stereochemical aspect of the reaction.



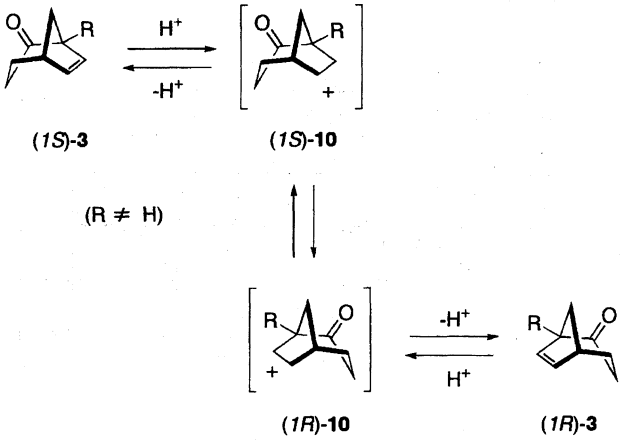
Scheme 1. Preparation of **3** from **1** (R^1 = CH_3 or H) through pinacol-type rearrangement.

Results and Discussion

In order to establish a practical route for **5** from **1**, we first



Scheme 2. Acid-catalyzed isomerization processes of **3**.



Scheme 3. The postulated racemization process of **3**.

Table 1. Acid-Catalyzed Isomerizations of (±)-Bicyclo[3.2.1]oct-6-en-2-ones[a)]

Ketones **3**	R	Reaction time	Consumption[b)]	Products (composition)[b)]				Yield[c)]
		h	%					%
3a	Ph	1	> 99.5	**5a**	(91)	**6a**	(9)	88
3b	Vinyl	1	> 99	**5b**	(91)	**6b**	(9)[d)]	68
3c	Bu	2.5	> 99	**5c**	(62)	**6c**	(38)	82

a) A reaction was carried out in a 0.2 M benzene solution with Amberlyst® (0.68 g per millimolar amount of **3**) at 80 °C (bath temperature). b) Determined by VPC. c) A total yield of the products purified by column chromatography. d) The NMR spectrum indicated the presence of some unidentified products.

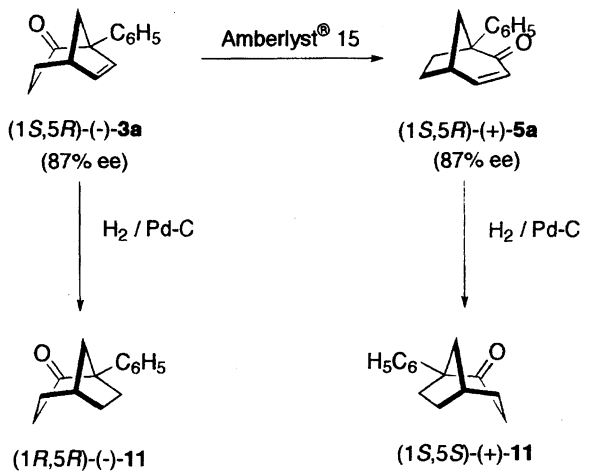
tried the isomerization of racemic ketones **3** to **5** shown in Scheme 2. Because of the slow equilibrium accompanying unidentified products,[3)] we sought reaction conditions for the rapid disappearance of **3**. After several attempts, we noticed the utility of the cation-exchange resin Amberlyst® (H-15). The results are listed in Table 1.

When the substituent at the bridgehead was a cation-stabilizing group, the β,γ-unsaturated ketone (**3**) was rapidly consumed. The desired **5** and the isomer **6** were obtained in a ratio of 10 to 1. In the case of **3b**, however, **5b** was accompanied by not only **6b**, but also unidentified products. A reaction of the bridgehead butyl ketone (**3c**) gave **5c** as the major product, while the selectivity was low.

In order to understand the stereochemical aspect of the isomerization, the β,γ-unsaturated ketone (1*S*,5*R*)-(−)-**3a** (87% ee) was prepared from a bridgehead-methoxy ketone (1*S*,5*R*)-**1a** (87% ee)[1)] by a sequential treatment with PhMgBr and with *p*-toluenesulfonic acid (TsOH) in boiling benzene. The treatment of the ketone (1*S*,5*R*)-(−)-**3a** with the cation-exchange resin under the same conditions listed in Table 1 gave the α,β-unsaturated ketone (+)-**5a** (87% ee). A catalytic hydrogenation of (1*S*,5*R*)-(−)-**3a** using Pd–C gave (1*R*, 5*R*)-(−)-**11**. A similar treatment of (+)-**5a** gave (+)-**11**. This outcome indicates that the absolute configuration of the α,β-unsaturated ketone (+)-**5a** is 1*S*,5*R*, and that the racemization of **3** shown in Scheme 4 should be a very slow process, if it competes with isomerization into **5** and **6**.

Similarly, an isomerization reaction of (1*S*,5*R*)-(−)-**3c** (98% ee)[6)] gave (1*S*,5*R*)-**5c** (98% ee). The reaction profile is listed in Fig. 1.

Thus, from **3**, the enantiospecific synthesis of **5** with inversion has been accomplished.



Scheme 4. Stereochemical correlation between **3** and **5**.

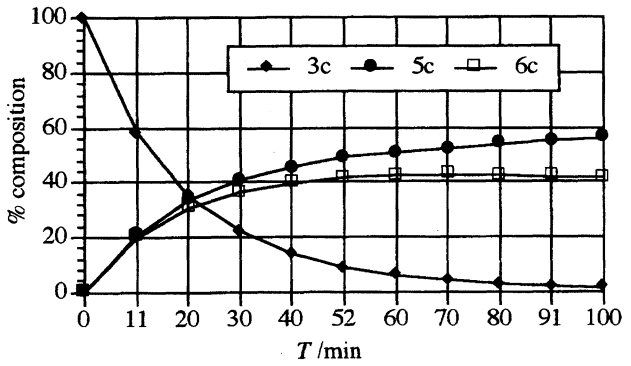


Fig. 1. Conversion of (1*S*,5*R*)-(−)-**3c** under the conditions listed in the Experimental section.

Experimental

General. The ^{1}H NMR spectra were measured at 300 and 600 MHz in $CDCl_3$ using TMS [$(CH_3)_4Si$] as an internal standard. COSY and NOESY experiments were frequently employed for assigning the stereostructures. HRMS were determined with a JEOL JMS-HX110 mass spectrometer. The ORD spectra were measured with a JASCO model ORD/UV-5 optical rotatory dispersion recorder. Amberlyst® (H-15, ion-exchange capacity 4.4 mequiv g^{-1}) was purchased from Organo Co., Ltd. THF was distilled from sodium diphenylketyl under argon immediately prior to use. Benzene was distilled from P_2O_5. All of the preparative reactions were monitored by analytical TLC using Merck pre-coated silica-gel $60F_{254}$ plates. VPC was carried out on a fused silica capillary column (Shimadzu CPBl-M-25-025). Column chromatography was performed by using Merck silica-gel 60 (70—230 mesh ASTM). Flash chromatography was carried out on Cica–Merck silica-gel 60 (230—400 mesh ASTM). The optical purities were determined on HPLC equipped with a chiral column (250×4.6 mm, Daicel CHIRALCEL OJ® or CHIRALCEL OC®). Semi-preparative HPLC was performed by using a Merck Hiber prepacked column RT (250×10 mm).

Preparation of 1-Phenylbicyclo[3.2.1]oct-3-en-2-one ((±)-5a) as a General Procedure for Amberlyst® Catalyzed Isomerization. 1-Phenylbicyclo[3.2.1]oct-6-en-2-one ((±)-**3a**)[2)] (196 mg, 1.00 mmol), Amberlyst® (681 mg), and dry benzene (5 cm^3) were placed in a flask equipped with a serum cap and a reflux condenser connected to a $CaCl_2$ tube. The resulting mixture was heated under reflux in a preheated oil bath at 80 °C. The reaction was monitored by VPC. After refluxing for 1 h, this mixture was allowed to cool to

room temperature. The resin was filtered and washed with CH_2Cl_2. The organic solutions were combined and concentrated to give a solid. Chromatography of the solid on silica gel (5 : 1 hexane–ethyl acetate) gave (±)-**5a**[2] (156 mg, 0.0796 mmol, 80%) and (±)-**6a**[4] (15.0 mg, 0.0765 mmol, 8%).

Preparation of (1*S*,5*R*)-(−)-1-Phenylbicyclo[3.2.1]oct-6-en-2-one ((1*S*,5*R*)-(−)-3a). To a solution of a chiral ketone ((1*S*)-(+)-**1a**) (87% ee, 130 mg, 0.856 mmol) in THF (4.3 cm^3) was added dropwise a solution of PhMgBr (2.00 M solution in benzene–ether, 0.64 cm^3, 1 M = 1 mol dm^{-3}) at 0 °C under argon. The mixture was stirred for 3 h at 0 °C, treated with saturated aqueous NH_4Cl, and extracted with three portions of ether. The combined extracts were washed with saturated brine, dried over $MgSO_4$, and concentrated to give a mixture of the tertiary alcohols and others (241 mg). A solution of this mixture and TsOH (11.4 mg, 0.0600 mmol) in benzene (15 cm^3) was heated under reflux for 30 min. The reaction mixture was diluted with ether, washed with saturated aqueous $NaHCO_3$, and with saturated brine, and dried over $MgSO_4$. Evaporation of the solvents gave an oil (257 mg). Flash chromatography of the oil (5 : 1 hexane–ethyl acetate) gave **3a** (90 mg; mp 84.0—84.8 °C; (c 4.09×10^{-3}, isooctane, 13.5 °C) $[\phi]_{589}$ −904°, $[\phi]_{325}$ −31800°, $[\phi]_{318}$ −23300°, $[\phi]_{314}$ −24100°, and $[\phi]_{304}$ 0°) and a mixture of **3a** and **5a**. The enantiomeric excess of **3a** was 87%; HPLC using Chiral OJ (50 : 1 hexane–2-propanol, flow rate 1.0 cm^3 min^{-1}) showed a large peak due to (1*S*,5*R*)-(−)-**3a** at 44.0 min and a small peak due to (1*R*,5*S*)-(+)-**3a** at 50.0 min. The IR and ^{1}H NMR spectra of (−)-**3a** were identical with those of (±)-**3a**.

Isomerization to (1*S*,5*R*)-(−)-1-Phenylbicyclo[3.2.1]oct-3-en-2-one ((1*S*,5*R*)-5a). The β,γ-unsaturated ketone (−)-**3a** (68.3 mg, 0.345 mmol) was treated with Amberlyst® H-15 (229 mg) similarly to that described previously. An aqueous work-up of the reaction mixture gave a mixture of **5a** and **6a** (62.5 mg). The enantiomeric excess of the ketone **5a** was 87%; HPLC using Chiral OJ (15 : 1 hexane–ethanol, flow rate 1.0 cm^3 min^{-1}) showed a large peak due to (+)-**5a** at 38.4 min and a small peak due to (−)-**5a** at 43.8 min. Flash chromatography of the mixture (63.0 mg) gave the α,β-unsaturated ketone **5a** (17.4 mg; mp 64.3—65.5 °C;(c 1.87×10^{-2}, isooctane, 16 °C) $[\phi]_{589}$ +576°, $[\phi]_{380}$ +5800°, $[\phi]_{371}$ +4290°, $[\phi]_{362}$ +6590°, $[\phi]_{353}$ +1860°, $[\phi]_{347}$ +3340°, $[\phi]_{342}$ 0°, $[\phi]_{338}$ −1320°, $[\phi]_{332}$ −582°, $[\phi]_{324}$ −2940°, $[\phi]_{317}$ −2280°, and $[\phi]_{331}$ −2850°) and a mixture of **5a** and **6a** (43.2 mg). IR and ^{1}H NMR spectra of (+)-**5a** were identical with those of (±)-**5a**.

Preparation of 1-Phenylbicyclo[3.2.1]octan-2-one ((±)-11). To a solution of (±)-**3a** (29.2 mg, 0.147 mmol) in ethyl acetate (2.0 cm^3) was added 5% Pd–C (10 mg). The mixture was stirred under hydrogen at room temperature for 3 h. The resulting mixture was filtered through a silica-gel column (230—400 mesh ASTM, height 5 cm). Evaporation of the solvent gave (±)-**11** (30.6 mg): Mp 75.0—75.8 °C; IR (KBr) 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 7.35—7.20 (3H, m), 2.68—2.26 (2H, m), 2.45—2.31 (2H, m), 2.27—2.19 (2H, m), 2.19—2.02 (2H, m), and 1.95—1.80 (3H, m); ^{13}C NMR ($CDCl_3$) δ = 212.3 (s), 142.4 (s), 127.8 (2C, d), 127.6 (2C, d), 126.4 (d), 61.9 (t), 42.5 (t), 35.5 (t), 35.4 (t), 34.6 (d), 32.7 (t), and 28.8 (t).

Hydrogenation of (1*S*,5*R*)-(−)-3a for Preparation of (1*R*,5*R*)-(−)-1-Phenylbicyclo[3.2.1]octan-2-one ((1*R*,5*R*)-(−)-11). Hydrogenation of the chiral β,γ-unsaturated ketone (1*S*,5*R*)-(−)-**3a** (7.3 mg) under similar conditions described above gave (−)-**11** (6.8 mg): Mp 72—72.8 °C; (c 3.65×10^{-2}, isooctane, 17 °C) $[\phi]_{589}$ −132°, $[\phi]_{319}$ −2830°, $[\phi]_{314}$ −2290°, and $[\phi]_{309}$ −2410°. The IR spectrum of (−)-**11** were identical with those of (±)-**11**.

Hydrogenation of (1*S*,5*R*)-(+)-5a. Hydrogenation of the chiral α,β-unsaturated ketone (1*S*,5*R*)-(+)-**5a** (15.6 mg) under similar conditions described above gave (1*S*,5*S*)-(+)-1-phenylbicyclo[3.2.1]octan-2-one ((+)-**11**, 15.7 mg): Mp 73.5—74.3 °C; (c 1.96×10^{-2}, isooctane, 18 °C) $[\phi]_{589}$ +153°, $[\phi]_{319}$ +2830°, $[\phi]_{313}$ +2260° $[\phi]_{309}$ +2430°. The IR and ^{1}H NMR spectra of (+)-**11** were identical with those of (±)-**11**.

Isomerization of (1*S*,5*R*)-(−)-1-Butylbicyclo[3.2.1]oct-6-en-2-one (1*S*,5*R*)-(−)-3c). A β,γ-unsaturated ketone (−)-**3c** (132 mg, 0.74 mmol, 98% ee) was treated with Amberlyst® H-15 (500 mg) for 100 min similarly to that described previously. The aqueous work-up gave a mixture of **5c** and **6c** (120 mg). The enantiomeric excess of the ketone **5c** was 98%; HPLC using CHIRALCEL OC® (200 : 1 hexane–2-propanol, flow rate 1.0 cm^3 min^{-1}) showed a large peak due to (1*S*,5*R*)-**5c** at 9.9 min and a small peak due to (1*R*,5*S*)-**5c** at 11.0 min.

References

1) Part XI of this series, see: T. Uyehara, M. Ishikawa, F. Iikura, N. Yoneta, M. Ueno, and T. Sato, *Bull. Chem. Soc. Jpn.*, **70**, (1997).

2) T. Uyehara, T. Inayama, T. Furuta, T. Kato, Y. Yamamoto, M. Ueno, and T. Sato, *Bull. Chem. Soc. Jpn.*, **69**, 1727 (1996).

3) I. Alfaro, W. Ashton, K. L. Rabone, and N. A. J. Rogers, *Tetrahedron*, **30**, 559 (1974).

4) T. Uyehara, K. Osanai, M. Sugimoto, I. Suzuki, and Y. Yamamoto, *J. Am. Chem. Soc.*, **111**, 5411 (1986).

5) For an example of the enantiospecific syntheses of the α,β-unsaturated ketones **5** from the β,γ-unsaturated ketones **3** with retention, see: T. Uyehara, T. Murayama, K. Sakai, M. Ueno, and T. Sato, *Tetrahedron Lett.*, **40**, 7295 (1996).

6) A chemoenzymatic method to prepare both enantiomers of the β,γ-unsaturated ketones **3** will be published soon.