Tetrahedron 65 (2009) 9854–9861

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Regio- and stereoselective rearrangements of formyl [2.2.1]bicyclic carbinols in methanol

Te-Fang Yang [a,*], Chih-Hao Tseng [b], Chien-Hung Shen [b], Li-Hsun Chen [b], Li-Ta Kao [b]

[a] Department of Applied Chemistry, National Chi Nan University, Puli, 545 Nantou, Taiwan, ROC
[b] Department of Applied Chemistry, Chaoyang University of Technology, Wufong, 413 Taichung, Taiwan, ROC

ARTICLE INFO

Article history:
Received 13 June 2009
Received in revised form
12 September 2009
Accepted 15 September 2009
Available online 22 September 2009

Keywords:
Ring expansion
Selective rearrangement
Bicyclic hydroxy ketones
Bicyclic dimer

ABSTRACT

Individual treatments of camphor- and camphene-derived formyl [2.2.1]bicyclic carbinols with blank methanol, methanol containing acidic acid, and methanol containing sodium methoxide provided corresponding [3.2.1]bicyclic hydroxy ketones. Rearrangement of each bicyclic carbinol was found to be regio- and stereoselective under neutral and acidic conditions. Mechanisms of these rearrangements were discussed.

1. Introduction

It is well known that keto rearrangement of α-hydroxy ketones occurs facilely under acidic or basic condition.[1,2] Especially, the ring expansion of norcamphor-derived [2.2.1]bicyclic hydroxy ketone in methoxide has been studied in detail by Creary and co-workers.[3] Similarly, the structures of α-hydroxy aldehydes also rearrange to ketols in the presence of appropriate reagents. For example, treatment of α-hydroxy-*p*-anisyl-phenylacetaldehyde (**1**, Fig. 1) with potassium hydroxide in aqueous methanol resulted in the 1,2-shift of non-substituted phenyl group, such that 4-methoxybenzoin was furnished.[4]

On the other hand, rearrangement of cyclic hydroxy aldehyde **2** occurred in the presence of boron trifluoride etherate[5] or catalytic amount of TsOH.[6] Obviously, during this ring expansion, the bonding between the quaternary carbon atom and the one bearing hydroxyl and formyl groups was cleaved. Furthermore, Benjamin et al.[7] had applied the ring expansion reaction to the conversion of a gibberellin aldehyde (**3**) into a 20-norkaurenoid lactone. Presumably, the tertiary carbon atom, instead of the quaternary one, shifted in the course of rearrangement of **3** and a chair-like transition state was formed.[7]

To the best of our knowledge, ring expansion of bicyclic hydroxy aldehyde has not yet been thoroughly investigated although Paquette et al.[8] had reported the first example (**4** and **5**, Fig. 1) of rearrangement of aldols that possess strained [2.2.2]bicyclic structure.[9] In addition, recently, it was observed in our lab that formyl borneol (**6**, Fig. 2) underwent ring expansion–alkylation in the presence of Grignard reagent, whereas formyl isoborneol (**7**) predominantly underwent keto rearrangement under the same conditions (Scheme 1).[10] It was speculated that the Grignard reagent primarily functioned as a base for the reaction of **7**. In order to further understand the characters of bicyclic hydroxy aldehyde system, we have systematically investigated the transmutations of formyl [2.2.1]bicyclic carbinols **6**–**8** (Fig. 2) in methanol under non-catalytic, acidic, and basic conditions, separately.

For the readily availability, carbinols **6**–**8** were prepared using the procedures previously reported by our group.[10] It was, then, found that these formyl [2.2.1]bicyclic alcohols (**6**–**8**) underwent selective rearrangements upon the individual treatments with blank methanol, methanol containing acetic acid, and methanol containing sodium methoxide, providing the corresponding [3.2.1]bicyclic α-hydroxy ketones or dimer.

2. Results and discussion

The results of rearrangement of camphor-derived carbinol **6** are shown in Table 1. Actually, *exo*-formyl [2.2.1]bicyclic alcohol **6** could undergo ring expansion and exclusively give [3.2.1]bicyclic

* Corresponding author. Tel.: +886 49 2910960; fax: +886 49 2917956.
E-mail address: tfyang@ncnu.edu.tw (T.-F. Yang).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.09.057

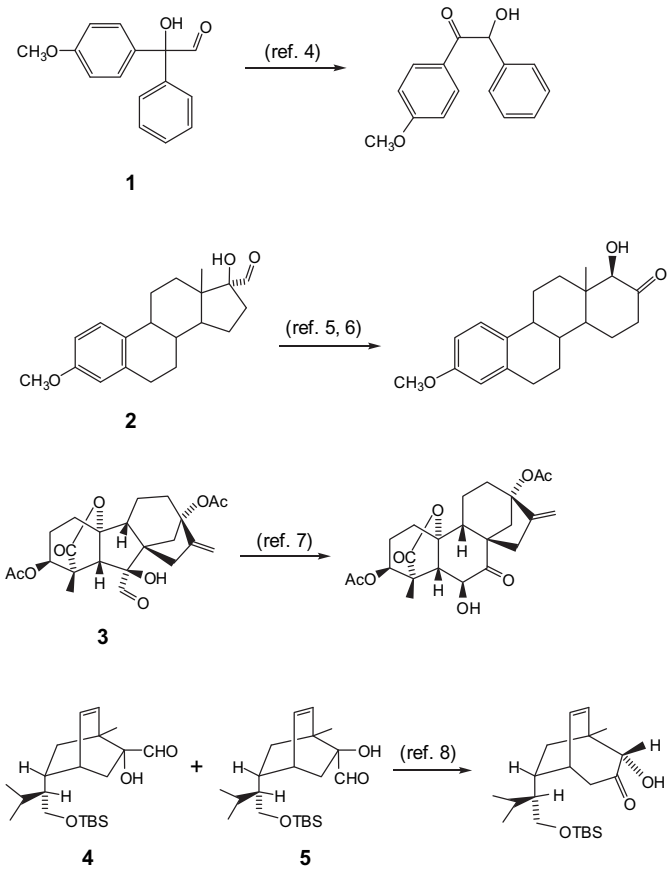


Figure 1. Rearrangements of some α-hydroxy aldehydes.

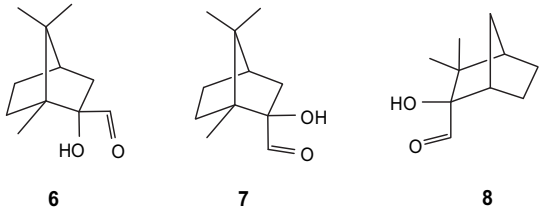
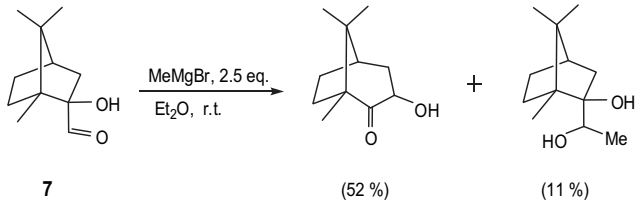


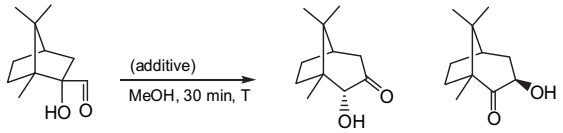
Figure 2. Formyl [2.2.1]bicyclic carbinols that undergo isomerizations in MeOH.



Scheme 1. Reaction of formyl isoborneol (**7**) in the presence of Grignard reagent.

hydroxyl ketone **9** in blank methanol at various temperatures (entries 1–3) without any catalyst. Furthermore, the rearrangement of **6** at room temperature and 0 °C could proceed more smoothly in the presence of acetic acid (entries 5 and 6) than in the blank solvent (entries 2 and 3). However, the yield of **9** could not be significantly improved by increasing the temperature to reflux (entry 4). On the other hand, upon the addition of catalytic amount of sodium methoxide (entries 7–9) to the solvent, compound **9** was also the only isomer furnished. Surprisingly, however, treatment of **6** with excess amount of base (entries 10–12) caused dramatic change in the behavior of rearrangement. Although **9** was also

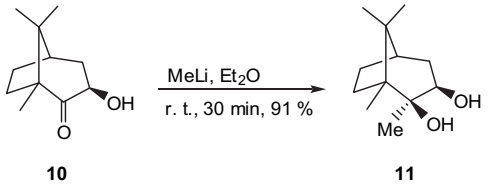
Table 1
Results of rearrangement of **6**



Entry	Additive (equiv)	*T*	Product/(ratio)	Yield (%)
1	(None)[a]	Reflux	**9**	90
2	(None)[a]	rt	**9**	64
3	(None)[a]	0 °C	**9**	64
4	AcOH (3.0)	Reflux	**9**	88
5	AcOH (3.0)	rt	**9**	87
6	AcOH (3.0)	0 °C	**9**	80
7	MeONa (0.2)	Reflux	**9**	92
8	MeONa (0.2)	rt	**9**	63
9	MeONa (0.2)	0 °C	**9**	53
10	MeONa (3.0)	Reflux	**9**:**10**/1:4[b]	80[c]
11	MeONa (3.0)	rt	**9**:**10**/3:1[b]	62[c]
12	MeONa (3.0)	0 °C	**9**	49

[a] In blank methanol.
[b] Ratio was determined in terms of ^{1}H NMR spectrum of the mixture of the two products.
[c] Total yield of the two products.

exclusively afforded at 0 °C (entry 12), the yield of it was relatively low. Furthermore, it is noticeable that the formation of **10** in methanol was helped by excess amount of sodium methoxide at high temperatures (entries 10 and 11). Since the single crystal of **10** could not be obtained, this compound was converted to diol **11** (Scheme 2). The absolute structures of **9** and **11** were then individually determined with X-ray diffraction.[11] Thus, the orientation of hydroxyl groups on **9** and **10** was both confirmed.



Scheme 2. Methylation of bicyclic hydroxyl ketone **10**.

A plausible overall mechanism for the rearrangement of carbinol **6** is illustrated in Figure 3. In order to demonstrate how hydroxy ketone **9** was exclusively produced in blank methanol, the structure of **6** is partially numbered as shown in Figure 3(A). Presumably, the carbonyl group on **6** was further polarized by methanol, which is a strong polar protic solvent. Thus, the oxygen atom of the carbonyl group is further partially negative, and the carbon atom (C3) further partially positive, such that C1 or C4 was induced to attack C3. Upon the molecular model study on the course of rearrangement of **6**, we deduced that it was significantly favorable for C1–C2 bond to break, and then for C1 to attack C3 from the *re*-face (route a), resulting in the formation of **9** (a $_2C^6$ conformation), in which the hydroxyl group on C3 is equatorial. Alternatively, if the formation of **10** (a $_3C^6$ conformation) occurred, then C2–C4 would have to break. Thus, C1–C2 bond would rotate ~180° such that C3 swung down and C2 relatively flopped up, then C4 could attack C3 (route b). Accordingly, it is speculated that the process for the formation of **10** was kinetically less favorable comparing with that for the formation of **9**. The outcome of the rearrangement of **6** in methanol containing acetic acid and sodium methoxide as shown in Figure 3(B) and (C), respectively, might be also explained in terms of the kinetics theory mentioned above.

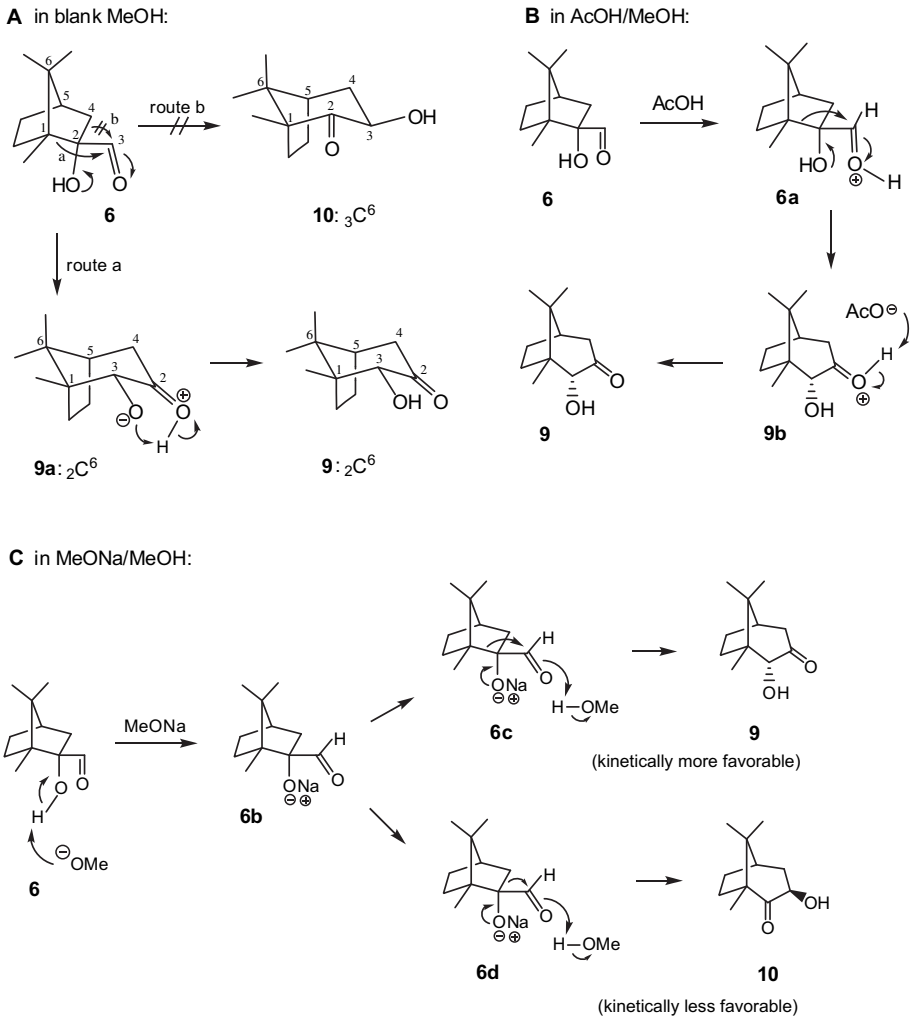
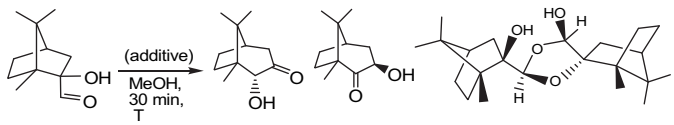


Figure 3. Plausible mechanisms for the rearrangement of compound **6** in (A) blank methanol, (B) methanol containing AcOH, and (C) methanol containing MeONa.

On the other hand, as shown in Table 2, rearrangement of camphor-derived *endo*-formyl [2.2.1]bicyclic carbinol **7** in blank methanol did not afford hydroxyl ketone **9**. Instead, **10** was provided as the only product in near quantitative yield at high temperature (entry 1). However, **7** could not rearrange at all at low temperatures (entries 2 and 3). Thus, it is realized that acetic acid helped the formation of **10** at room temperature (entry 5) and 0 °C (entry 6). As expected, the rearrangement of **7** at high temperature under the acidic condition gave **10** in good yield (entry 4). On the other hand, **10** was furnished as the only product in relatively low yields (entries 7–9) when **7** was mixed with catalytic amount (0.2 equiv) of sodium methoxide. Nevertheless, **9** was provided as the minor product in the presence of excess amount of NaOMe at reflux (entry 10). Furthermore, surprisingly, treatment of **7** with excess amount of sodium methoxide (3 equiv) at low temperatures (entries 11 and 12) stereoselectively afforded dimer **12**, whose absolute structure was confirmed with X-ray crystallography (Fig. 4).[11]

A plausible overall mechanism for the rearrangement of carbinol **7** is illustrated in Figure 5. In order to demonstrate how hydroxy ketone **10** was exclusively produced in blank methanol, the structure of **7** is partially numbered as shown in Figure 5(A). Presumably, the carbonyl group on **7** was further polarized by methanol, which is a strong polar protic solvent. Thus, the oxygen atom of the carbonyl group is further partially negative, and the carbon atom (C3) further partially positive, such that C1 or C4 was induced to attack C3.

Table 2
Results of isomerization of **7**



Entry	Additive (equiv)	*T*	Product/ (ratio)	Yield (%)
1	(None)[a]	Reflux	**10**	99
2	(None)[a]	rt	(n.r.)[b]	—
3	(None)[a]	0 °C	(n.r.)[b]	—
4	AcOH (3.0)	Reflux	**10**	86
5	AcOH (3.0)	rt	**10**	83
6	AcOH (3.0)	0 °C	**10**	78
7	MeONa (0.2)	Reflux	**10**	75
8	MeONa (0.2)	rt	**10**	42
9	MeONa (0.2)	0 °C	**10**	26
10	MeONa (3.0)	Reflux	**9**:**10**/1:5.5[c]	73[d]
11	MeONa (3.0)	rt	**12**	52
12	MeONa (3.0)	0 °C	**12**	41

[a] In blank methanol.
[b] No reaction.
[c] Ratio was determined in terms of ^{1}H NMR spectrum of the mixture of the two products.
[d] Total yield of the two products.

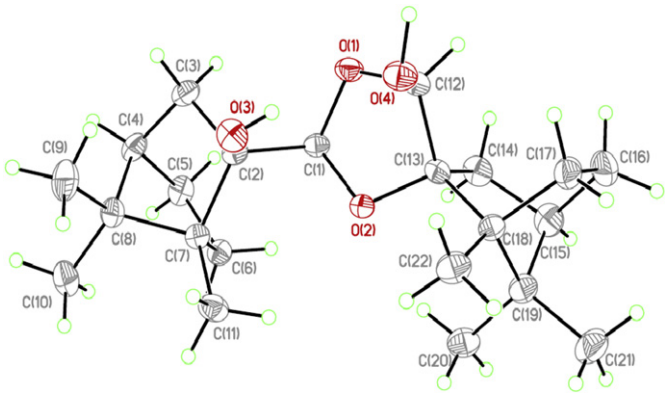


Figure 4. ORTEP drawing of dimer **12**.

The results of rearrangement of camphene-derived formyl [2.2.1]bicyclic carbinol **8** in methanol are listed in Table 3. Similar to the situation occurred to carbinol **6**, carbinol **8** underwent ring expansion and exclusively gave a single isomer of [3.2.1]bicyclic hydroxyl ketone (**13**) in blank methanol at reflux (entry 1), room temperature (entry 2), and 0 °C (entry 3). Although the rearrangement of **8** could be also carried out smoothly under acidic condition at various temperatures (entries 4–6), the yields of **13** were not better than the situation observed in the blank solvent. Thus, in order to obtain **13**, it was not necessary to add acetic acid to the methanol. On the other hand, the formation of **14** could be catalyzed by sodium methoxide (entries 7–9), which shows stronger catalytical ability at higher temperature, similar to the phenomenon observed in the case of carbinol **6**. Surprisingly, treatment of **8** with excess amount (3 equiv) of the base at reflux gave a mixture of isomers **13** and **14**, in favor of the latter (entry 10).

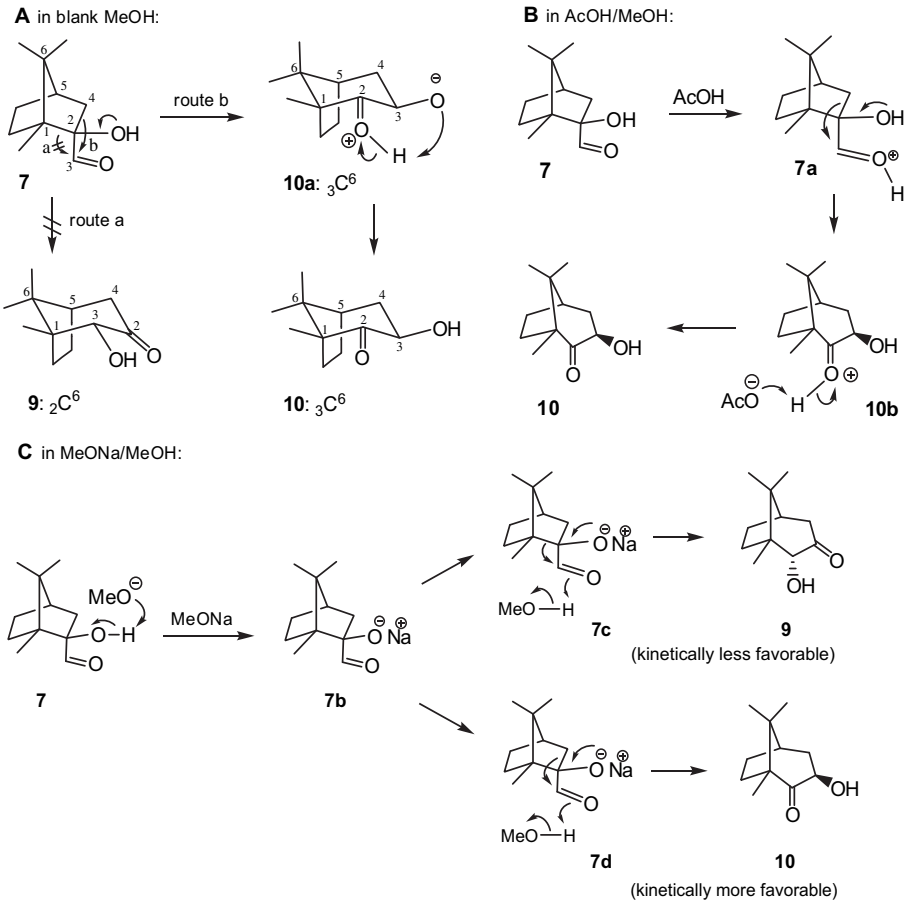
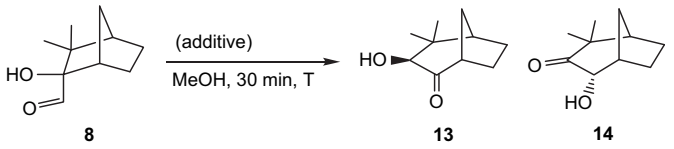


Figure 5. Plausible mechanisms for the rearrangement of compound **7** in (A) blank methanol, (B) methanol containing AcOH, and (C) methanol containing MeONa.

On contrary to the case of **6**, our molecular model study on that of **7** revealed that it was relatively favorable for C2–C4 bond to break and then for C4 to attack C3 from *re*-face (route b), resulting in the formation of **10** (a $_3C^6$ conformation), in which the hydroxyl group on C3 is equatorial, too. Alternatively, if the formation of **9** (a $_2C^6$ conformation) occurred, then C1–C2 would have to break. Consequently, C2–C4 bond had to rotate ~180° such that C3 swung up and C2 relatively flopped down, then, C1 could attack C3 (route a). Thus, it was concluded that the process for the formation of **9** was kinetically less favorable than that for the formation of **10**. On the other hand, the outcome of the rearrangement of **7** in methanol containing acetic acid and sodium methoxide as shown in Figure 5(B) and (C), respectively, might be also explained in terms of the same reason as depicted above.

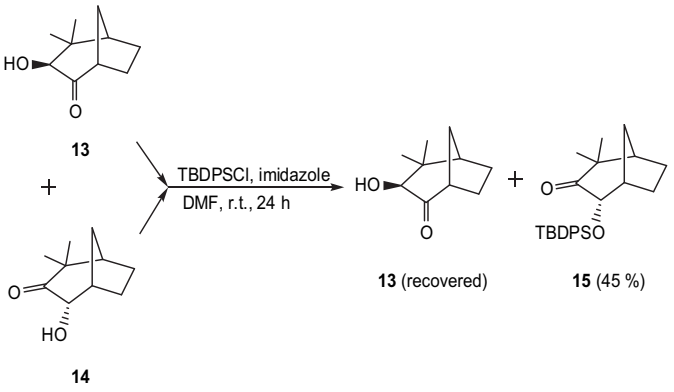
However, the ratio of **14** decreased when the experiment was carried out at room temperature and 0 °C (entries 11 and 12). Since isomers **13** and **14** were not separable with silica gel column chromatography, the mixture was further treated with *tert*-butyl diphenylsilyl chloride (TBDPSCl, Scheme 3) in the presence of imidazole. It was found that the hydroxyl group on **14** could be protected by TBDPSCl and **15** was obtained, whereas that on **13** was not altered. Presumably, the hydroxyl group on **13** is sterically hindered, such that it was not accessible to the bulky protecting group. Consequently, bicyclic ketone **15** was isolated, then, *tert*-butyl diphenylsilyl group removed with tetrabutyl ammonium fluoride to afford **14** in 56% yield (Scheme 4). In order to determine the configurations of new chiral centers, bearing hydroxyl groups on bicyclic hydroxyl ketones **13** and **14**, the two new compounds were

Table 3
Results of rearrangement of **8**

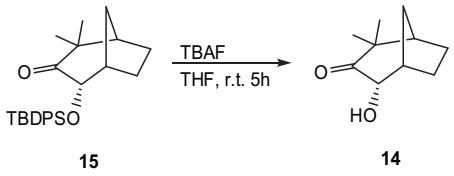


Entry	Additive (equiv)	*T*	Product(s)/(ratio)[b]	Yield (%)
1	(None)[a]	Reflux	**13**	96
2	(None)[a]	rt	**13**	86
3	(None)[a]	0 °C	**13**	86
4	AcOH (3.0)	Reflux	**13**	92
5	AcOH (3.0)	rt	**13**	85
6	AcOH (3.0)	0 °C	**13**	80
7	MeONa (0.2)	Reflux	**13**:**14**/4:1	90[c]
8	MeONa (0.2)	rt	**13**	85
9	MeONa (0.2)	0 °C	**13**	60
10	MeONa (3.0)	Reflux	**13**:**14**/1:3	87[c]
11	MeONa (3.0)	rt	**13**:**14**/6:1	79[c]
12	MeONa (3.0)	0 °C	**13**:**14**/25:1	79[c]

[a] In blank methanol.
[b] Ratio was determined in terms of ^{1}H NMR spectrum of the mixture of the two products.
[c] Total yield of the two products.



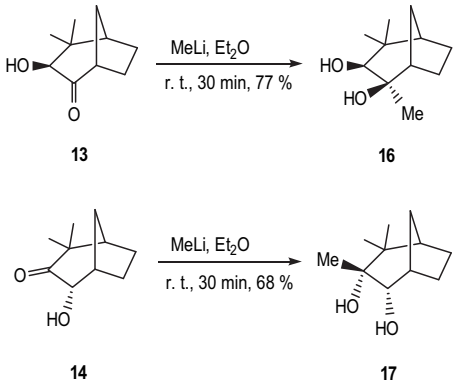
Scheme 3. Kinetic resolution of bicyclic hydroxyl ketones **13** and **14**.



Scheme 4. Removal of the protecting group on bicyclic keto silyl ether **15**.

to individually react with methyl lithium to provide [3.2.1]bicyclic diols **16** and **17**, respectively (Scheme 5). Finally, the absolute stereo structures of **16** and **17** were determined in terms of X-ray crystallography.[11] It is noteworthy that the characterization data of diol **16** had been previously reported.[10a] Thus, the orientations of hydroxyl groups on **13** and **14** were confirmed with those of corresponding hydroxyl groups on **16** and **17**, respectively.

A plausible overall mechanism for the rearrangement of carbinol **8** is illustrated in Figure 6. In order to demonstrate how hydroxy ketone **13** was exclusively produced in blank methanol, the structure of **8** is partially numbered as shown in Figure 6(A). Presumably, the carbonyl group on **8** was further polarized by methanol, which is a strong polar protic solvent. Thus, the oxygen atom of the carbonyl group is further partially negative, and the carbon atom (C3) further partially positive, such that C1 or C4 was induced to attack C3. Based



Scheme 5. Methylation of bicyclic hydroxyl ketones **13** and **14**.

on the molecular model study, it is deduced that C2–C4 bond had broken at the beginning of rearrangement. Then, C4 attacked C3 smoothly from the *si*-face (route a), resulting in the formation of **13** (a $_3C^6$ conformation), in which the hydroxyl group on C3 is equatorial. Alternatively, if the formation of **14** (a $_2C^6$ conformation) occurred, then C1–C2 would have to break. Thus, C2–C4 bond would rotate somewhat such that C3 swung up and C2 flopped down, then, C1 could attack C3 (route b). Accordingly, comparing with the process for the formation of **13**, it is concluded that the process for the formation of **14** was kinetically less favorable, due to higher energy barrier. The outcome of the rearrangement of **8** in methanol containing acetic acid and sodium methoxide as shown in Figure 6(B) and (C), respectively, might be also explained in terms of the same reason as depicted above. On the other hand, it is noted although both **7** and **8** are bicyclic carbinols bearing an *endo*-formyl group, the former is less reactive than the latter at low temperatures (see entries 2 and 3 in Table 2). Presumably, since the secondary ring-carbon (C-4 as shown in Fig. 5) on **7** possesses less electron density than does the corresponding quaternary ring-carbon (C-4 as shown in Fig. 6) on **8**, such that the former attacks the *endo*-formyl group much less easily than does the latter.[12]

3. Conclusion

In conclusion, camphor- and camphene-derived formyl [2.2.1]bicyclic carbinols could rearrange smoothly in blank methanol at reflux[13] to provide the corresponding regio- and stereospecific [3.2.1]bicyclic α-hydroxyl ketones.[14] For each individual bicyclic carbinol, the rearrangement that occurred in the presence of excess amount of acetic acid and the rearrangement that occurred in the presence of catalytic amount (0.2 equiv) of sodium methoxide gave the same product as the rearrangement that occurred in blank methanol did. However, the addition of excess amount of sodium methoxide (3.0 equiv) to each bicyclic carbinol in methanol may result in the formation of the other isomer of the product or the formation of a dimer of the reactant (Table 2). The application of this reaction to the synthesis of some useful compounds or natural product analogs is under investigation.[14]

4. Experimental

4.1. General information

All reactions were carried out in round bottom flasks. When necessary, moisture-sensitive solvents were dried with standard methods and transferred via a syringe. Crude product solutions were dried on Na_2SO_4 and concentrated with a rotary evaporator

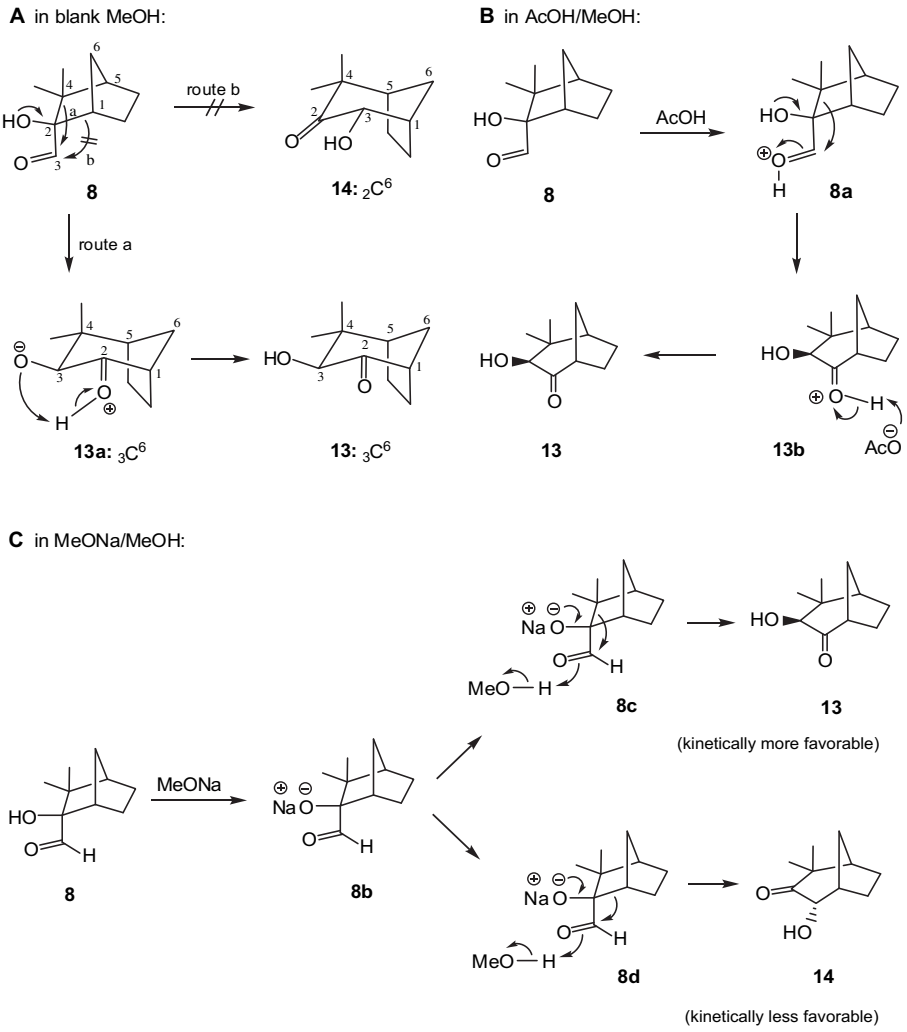


Figure 6. Plausible mechanisms for the rearrangement of compound **8** in (A) blank methanol, (B) methanol containing AcOH, and (C) methanol containing MeONa.

below 40 °C at ~30 Torr. Silica gel column chromatography was performed employing 230–400 mesh silica gel. TLC was performed on silica gel sheets with organic binder and detected by 0.5% phosphor-molybdic acid solution in 95% ethanol. Melting points were measured on a Fargo MP-1D apparatus and were uncorrected. An FT/IR spectrophotometer (Perkin–Elmer-paragon 500) was used for obtaining the infrared spectra. Data were expressed as wave number of absorption (cm^{-1}). ^1H NMR and ^{13}C NMR spectra were obtained using a 200 MHz (Varian) spectrometer. Chemical shifts (δ scale) were expressed in parts per million downfield from tetramethylsilane (δ=0.00). ^1H NMR data were presented as follows: chemical shift, multiplicity (s=singlet, br s=broad singlet, d=doublet, dd=doublet of doublet, t=triplet, m=multiplet and/or multiple resonances), coupling constant in Hz (hertz), integration. Optical rotation was recorded on JASCO (P-1010), digital polarimeter at room temperature.

4.2. General procedure for the rearrangements of bicyclic carbinols 6, 7, and 8 in blank methanol

Formyl [2.2.1]bicyclic carbinol **6**, **7** (0.20 g, 1.10 mmol), or **8** (0.20 g, 1.19 mmol) was dissolved in methanol (10 ml). After being stirred at various temperatures (0 °C, room temperature or reflux) for 30 min, the solution was concentrated under reduced pressure. The residue was then purified with flash column chromatography (6:1, *n*-hexane/EtOAc) to give the corresponding [2.2.1]bicyclic hydroxyl ketone.

4.3. General procedure for the rearrangements of bicyclic carbinols 6, 7, and 8 in methanol containing acetic acid

Formyl [2.2.1]bicyclic carbinol **6**, **7** (0.20 g, 1.10 mmol), or **8** (0.20 g, 1.19 mmol) was dissolved in methanol (10 ml). To the solution was then added acetic acid (0.20 g, 3.30 mmol). After being stirred at various temperatures (0 °C, room temperature or reflux) for 30 min, the reaction mixture was rapidly concentrated under reduced pressure. To the residue was, then, immediately added dichloromethane (20 ml). The organic layer was collected and washed with water (3×10 ml), dried (Na_2SO_4), filtered, and the filtrate was rapidly concentrated under reduced pressure. The residue was then purified with flash column chromatography (6:1, *n*-hexane/EtOAc) to give the corresponding [2.2.1]bicyclic hydroxyl ketone.

4.4. General procedure for the rearrangements of bicyclic carbinols 6, 7, and 8 in methanol containing sodium methoxide

Formyl [2.2.1]bicyclic carbinol **6**, **7** (0.20 g, 1.10 mmol), or **8** (0.20 g, 1.19 mmol) was dissolved in methanol (10 ml). To the

solution was then added sodium methoxide (0.012 g, 0.22 mmol or 0.18 g, 3.30 mmol). After being stirred at various temperatures (0 °C, room temperature or reflux) for 30 min, the reaction mixture was rapidly concentrated under reduced pressure. To the residue was, then, immediately added dichloromethane (20 ml). The organic layer was collected and washed with water (3×10 ml), dried (Na_2SO_4), filtered, and the filtrate was rapidly concentrated under reduced pressure. The residue was then purified with flash column chromatography (6:1, *n*-hexane/EtOAc) to give the corresponding [2.2.1]bicyclic hydroxyl ketone or dimer.

4.5. Data of [3.2.1]bicyclic hydroxyl ketones

4.5.1. Compound ***9***. White solid: R_f=0.48 (1:6, hexane/EtOAc); mp 194–203 °C; $[\alpha]_D^{23}$ +21.0 (0.1, EtOH); IR (KBr): 3479 (br), 2957, 2929, 2881, 1711, 1451, 1370 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.05 (d, *J*=2.2 Hz, 1H), 3.62 (d, *J*=2.2 Hz, 1H), 2.79 (m, 1H), 2.33 (dd, *J*=15.4, 3.0 Hz, 1H), 2.06–1.62 (m, 3H), 1.42–1.24 (m, 2H), 1.21 (s, 3H), 1.04 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 211.9, 78.9, 51.5, 46.3, 44.6, 44.3, 28.6, 26.8, 24.1, 18.4, 16.4. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.55; H, 9.55.

4.5.2. Compound ***10***. White solid: R_f=0.32 (1:6, hexane/EtOAc); mp 170–180 °C; $[\alpha]_D^{23}$ −28.8 (0.1, EtOH); IR (KBr): 3471 (br), 2958, 2874, 1707, 1457, 1390 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.22 (m, 1H), 3.54, (d, *J*=2.2 Hz, 1H), 2.36–2.14 (m, 2H), 1.93 (m, 1H), 1.80–1.60 (m, 4H), 1.00 (s, 3H), 0.93 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 215.7, 70.1, 56.8, 47.9, 44.3, 37.9, 34.0, 27.3, 23.3, 19.8, 13.4. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.16; H, 9.56.

4.5.3. Compound ***12***. White solid: R_f=0.65 (3:1, hexane/EtOAc); mp 182–184 °C; $[\alpha]_D^{25}$ −82.9 (0.2, CH_2Cl_2); IR (KBr): 3346 (br), 2938, 2872, 1446, 1361 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.09 (s, 1H), 4.97 (s, 1H), 2.66 (br, 2H), 2.02–1.26 (m, 14H), 1.09 (s, 3H), 1.04 (s, 3H), 1.02 (s, 3H), 0.96 (s, 3H), 0.85 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 105.8, 99.4, 92.9, 78.9, 51.8, 50.4, 49.8, 49.6, 44.8, 44.7, 42.6, 41.1, 30.0, 29.9, 27.1, 27.0, 21.0, 20.4, 19.9, 19.6, 11.3, 10.6. HRMS calcd for $C_{22}H_{36}O_4$: 364.2614; found: 364.2610.

4.5.4. Compound ***13***. Syrup: R_f=0.72 (1:3, hexane/EtOAc); $[\alpha]_D^{25}$ +1.7 (0.1, EtOH); IR (KBr): 3469 (br), 2950, 2891, 1707, 1536, 1460 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.94 (d, *J*=4.1 Hz, 1H), 3.22 (d, *J*=4.1 Hz, 1H), 2.86 (m, 1H), 2.11–1.54 (m, 7H), 1.19 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 214.0, 77.9, 48.5, 46.4, 44.9, 35.4, 27.0, 25.2, 24.7, 20.4. HRMS calcd for $C_{10}H_{16}O_2$: 168.1150; found: 168.1152.

4.6. Preparation of 11

To a solution of **10** (0.55 g, 6.04 mmol) in diethyl ether (10 ml) was added methyl lithium (1.6 M in ether, 0.15 g, 6.96 mmol). The reaction mixture was stirred at room temperature for 30 min, then quenched with aqueous ammonium chloride, and extracted with ethyl acetate (3×20 ml). The organic layers were combined, washed with water, dried (Na_2SO_4), filtered, and the filtrate was concentrated under reduced pressure. The residue was purified with flash column chromatography (3:1, *n*-hexane/EtOAc) to give **11** (0.55 g, 91%) as a solid: R_f=0.43 (3:1, hexane/EtOAc); mp 189–194 °C; $[\alpha]_D^{25}$ −21.3 (0.1, EtOH); IR (KBr): 3412 (br), 2941, 2870, 1448, 1373 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.52 (m, 1H), 2.06 (d, *J*=8.2 Hz, 1H), 1.83–1.62 (m, 5H), 1.50 (m, 2H), 1.32 (m, 1H), 1.22 (s, 3H), 1.16 (s, 3H), 0.96 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 78.0, 70.7, 48.9, 44.7, 44.2, 35.1, 33.0, 27.1, 26.0, 23.1, 21.7, 13.9. Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.86; H, 11.02.

4.7. Preparation of 15

To a solution of a mixture of **13** and **14** (1:3, 1.30 g, 7.74 mmol) in DMF (30 ml) was added imidazole (1.58 g, 23.21 mmol). After the new mixture was stirred for 30 min, *tert*-butyl diphenylsilyl chloride (2.30 g, 12.18 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 24 h, then quenched with water (20 ml), and extracted with ethyl acetate (3×20 ml). The organic layers were combined, washed with water, dried (Na_2SO_4), filtered, and the filtrate was concentrated under reduced pressure. The residue was purified with flash column chromatography (30:1, *n*-hexane/EtOAc) to give **15** (1.40 g, 45%) as a syrup: R_f=0.47 (10:1, hexane/EtOAc); $[\alpha]_D^{25}$ +1.6 (0.1, EtOAc); IR (neat): 3070, 2964, 2857, 1961, 1891, 1821, 1723, 1589, 1471, 1426 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.71–7.30 (m, 10H), 4.32 (d, *J*=2.6 Hz, 1H), 2.36 (m, 1H), 2.02–1.26 (m, 7H), 1.11 (s, 9H), 1.00 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 212.6, 136.0, 135.8, 129.5, 127.4, 78.0, 49.2, 48.1, 44.6, 32.9, 26.9, 26.0, 25.4, 22.7, 22.5, 19.5. Anal. Calcd for $C_{26}H_{34}SiO_2$: C, 76.80; H, 8.43. Found: C, 76.51; H, 8.66.

4.8. Preparation of 14 from 15

Compound **15** (1.00 g, 2.46 mmol) was dissolved with THF (25 ml) in a round bottom flask. To the solution was added tetrabutyl ammonium fluoride (1.28 g, 4.90 mmol). After the reaction mixture was stirred at room temperature for 5 h, water (20 ml) was added. The mixture was then extracted with ethyl acetate (3×20 ml). The organic layers were combined, washed with water, dried (Na_2SO_4), and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified with flash column chromatography (10:1, *n*-hexane/EtOAc) to give **14** (0.23 g, 56%) as a syrup: R_f=0.72 (1:3, hexane/EtOAc); $[\alpha]_D^{25}$ +10.86 (0.1, EtOAc); IR (neat): 3490 (br), 2958, 2880, 1706, 1460, 1384, 1071, 1021 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.37 (dd, *J*=3.8, 3.0 Hz, 1H), 3.72 (d, *J*=3.2 Hz, 1H), 2.60 (m, 1H), 2.31 (d, *J*=12.6 Hz, 1H), 2.04 (m, 1H), 1.68–1.42 (m, 5H), 1.24 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 215.9, 76.0, 49.0, 48.6, 43.5, 32.5, 26.2, 25.2, 22.3, 21.8. HRMS calcd for $C_{10}H_{16}O_2$: 168.1150; found: 168.1148.

4.9. General procedure for the preparation of bicyclic diols 16 and 17

To a solution of hydroxyl ketone **13** or **14** (0.20 g, 1.19 mmol) in diethyl ether (10 ml) was added methyl lithium (1.6 M in ether, 0.03 g, 1.40 mmol). The reaction mixture was stirred at room temperature for 30 min, then quenched with aqueous ammonium chloride, and extracted with ethyl acetate (3×10 ml). The organic layers were combined, washed with water, dried (Na_2SO_4), filtered, and the filtrate was concentrated under reduced pressure. The residue was purified with flash column chromatography (6:1, *n*-hexane/EtOAc) to give the bicyclic diol **16** or **17**. Data of **16** (0.09 g, 41%): a solid; mp 137–138 °C; $[\alpha]_D^{25}$ +23.5 (0.1, EtOAc); IR (KBr): 3364 (br), 2935, 2866, 1660, 1630, 1454, 1365 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.02 (d, *J*=8.7 Hz, 1H), 2.30 (d, *J*=12.0 Hz, 1H), 2.06 (m, 1H), 1.86 (d, *J*=8.7 Hz, 1H), 1.76–1.35 (m, 6H), 1.23 (s, 3H), 1.17 (m, 1H), 1.04 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 76.6, 75.6, 46.6, 46.5, 39.2, 29.4, 27.1, 26.1, 25.9, 24.3, 21.1. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.33; H, 11.19. Data of **17** (0.19 g, 86%): a solid: R_f=0.61 (1:3, hexane/EtOAc); mp 163–166 °C; $[\alpha]_D^{25}$ −1.8 (0.1, EtOAc); IR (KBr): 3406, 2980, 2924, 2876, 1460, 1364 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.54 (dd, *J*=7.2, 3.6 Hz, 1H), 2.78 (d, *J*=7.2 Hz, 1H), 2.16–1.74 (m, 5H), 1.60 (m, 1H), 1.50–1.20 (m, 3H), 1.08 (s, 3H), 0.97 (s, 3H), 0.89 (s, 3H); ^{13}C NMR

(50 MHz, $CDCl_3$): δ 76.4, 75.1, 47.7, 42.1, 40.2, 32.6, 27.6, 25.3, 23.5, 22.8, 22.1. HRMS calcd for $C_{11}H_{20}O_2$: 184.1463; found: 184.1454.

Acknowledgements

This work was supported by National Science Council of Taiwan, R.O.C. (Grant NSC 88- 2113-M-324-005), which is gratefully acknowledged. The authors thank the Instrumental Center at National Taiwan University for the elemental analyses and the Regional Instruments Center at National Chung-Hsing University for high resolution mass spectra.

References and notes

1. (a) Stavely, H. E. *J. Am. Chem. Soc.* **1941**, *63*, 3127–3131; (b) Curtin, D. Y.; Leskowitz, S. *J. Am. Chem. Soc.* **1951**, *73*, 2633–2636; (c) Turner, R. B. *J. Am. Chem. Soc.* **1953**, *75*, 3484–3488; (d) Brunner, H.; Kagan, H. B.; Kreutzer, G. *Tetrahedron: Asymmetry* **2001**, *12*, 497–499; (e) Brunner, H.; Kagan, H. B.; Kreutzer, G. *Tetrahedron: Asymmetry* **2003**, *14*, 2177–2187; (f) Sharp, D. B.; Miller, E. L. *J. Am. Chem. Soc.* **1952**, *74*, 5643–5646.
2. Paquette, L. A.; Hofferberth, J. E. *Org. React.* **2003**, *62*, 477–567.
3. (a) Creary, X.; Geiger, C. C. *J. Am. Chem. Soc.* **1982**, *104*, 4151–4162; (b) Creary, X.; Inocencio, P. A.; Underiner, T. L.; Kostromin, R. *J. Org. Chem.* **1985**, *50*, 1932–1938.
4. Ferstandig, L. L.; Butler, J. C.; Straus, A. E. *J. Am. Chem. Soc.* **1954**, *76*, 5777–5799.
5. Miller, T. C. *J. Org. Chem.* **1969**, *34*, 3829–3833.
6. Bull, J. R.; Steer, L. M. *Tetrahedron* **1990**, *46*, 5389–5400.
7. Benjamin, L. J.; Mander, L. N.; Willis, A. C. *Tetrahedron Lett.* **1996**, *37*, 8937–8940.
8. Paquette, L. O.; Guevel, R.; Sakamoto, S.; Kim, I. H.; Crawford, J. *J. Org. Chem.* **2003**, *68*, 6096–6107.
9. Similar to the situation observed for hydroxy aldehyde **2**, the quaternary carbon atoms on **4** and **5** shifted instead of the secondary ones.
10. (a) Yang, T.-F.; Tseng, C.-H. T.; Wu, K.-I.; Chang, C.-N. *J. Org. Chem.* **2007**, *72*, 7034–7037; (b) Yang, T.-F.; Zhang, Z.-N.; Tseng, C.-H.; Chen, L.-H. *Tetrahedron Lett.* **2005**, *46*, 1917–1920; (c) Yang, T.-F.; Chao, H.-H.; Lu, Y.-H.; Tsai, C.-J. *Tetrahedron* **2003**, *59*, 8827–8831.
11. Crystallographic data for structures **9**, **11**, **12**, **16**, and **17** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 734153, CCDC 734154, CCDC 734155, CCDC 734156, and CCDC 734157, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
12. (a) Paquette, L. A.; Andrews, J. F. P.; Vanucci, C.; Lawhorn, D. E.; Negri, J. T.; Rogers, R. D. *J. Org. Chem.* **1992**, *57*, 3956–3965; (b) McIntosh, J. M.; Cassidy, K. C. *Can. J. Chem.* **1991**, *69*, 1315–1319.
13. Carbinol **7** did not rearrange at room temperature and 0 °C in blank methanol.
14. It is noticeable that this is a very interesting and important information since each bicyclic α-hydroxyl ketone, produced in the blank methanol in situ, is expected to cool down to 0 °C. Then, to this cold solution will be directly added appropriate amount of $NaBH_4$, and the new stereospecific bicyclic diol be provided for further synthetic purposes.