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Selective Ring Expansion Alkylation of Formyl[2.2.1]bicyclic Carbinols with C-Nucleophiles: A Unique Route to Cyclopentane Derivatives

Te-Fang Yang,* Chih-Hao Tseng, Kuan-I Wu, and Chung-Nien Chang

Department of Applied Chemistry, Chaoyang University of Technology, Wufong, 413, Taichung, Taiwan, ROC

tfyang@cyut.edu.tw

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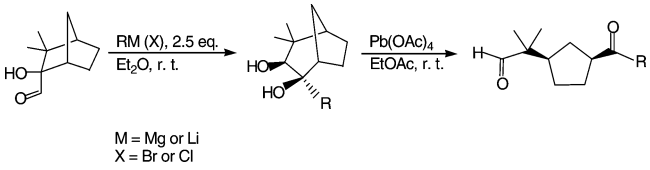


Reactions of camphor-, and camphene-derived formyl [2.2.1]-bicyclic carbinols with Grignard and organolithium reagents afford the corresponding regio- and stereospecific alkyl/aryl [3.2.1]bicyclic diols. Some of these bicyclic diols have been treated with lead tetraacetate to provide new chiral cyclopentane derivatives. A plausible mechanism of the ring expansion-alkylation reaction is proposed.

Bridged bicyclic alcohols are prone to rearrangement to form various bicyclic ketones under appropriate conditions. Especially, owing to its potential application to the synthesis of natural products or derivatives, the ring expansion of [2.2.1]-bicyclocarbinols has drawn much attention from organic chemists.[1] For example, the ring expansion of *endo*-norbornanol **1** (Figure 1) had been reported by Paquette, et al.[2] in 1992. They concluded that the bridge-head carbon atom of **1** migrated exclusively in the presence of toluenesulfonic acid. Furthermore, Paquette, Houk, and co-workers[3] found that *exo*-norbornanol **2** and its heterosubstituted derivatives could undergo an anionic oxy-Cope rearrangement to provide corresponding bicyclo[6.2.1]-undecenone analogues when the reactants were individually treated with potassium hexamethyldisilazide at low temperatures. The specialty of this reaction is that one of the sp^3-hybridized bridgehead carbon atoms became an sp^2-hybridized one upon the rearrangement. In addition, reaction of borneol **3** with iodine

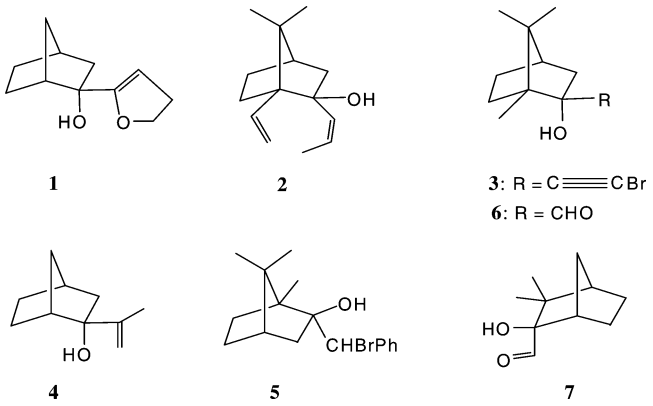
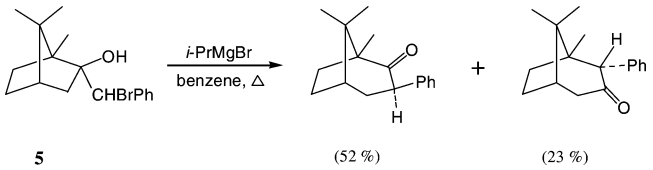


FIGURE 1. Some bridged bicyclic alcohols that undergo various ring-expansion reactions.

and Koser's reagent[4] did afford 2-[(*Z*)-bromoiodomethylidene]-bicyclo-[3.2.1]octan-3-one and its regioisomer.[5] Several years ago, another example of halogen-containing ring expansion of [2.2.1]bicyclocarbinol framework was presented by Ruggles and Maleczka.[6] They successfully carried out the ring expansion of isopropenyl[2.2.1]bicyclocarbinol **4** in 6 h at 0 °C, utilizing a bleach−acetic acid system as the promoter.[6] Recently, a catalytic rearrangement of cyclic α-ketol has been investigated by Brunner et al.[7a,b] On the other hand, ring expansion reactions of α-hydroxy ketones with sodium methoxide and that of aminomethyl bicyclio[2.2.1]heptan-2-ol with sodium nitrite under acidic condition also take place.[7c−e] In 1974, Sisti and Rusch[8] had reported that [2.2.1]bicyclic carbinol **5** (Figure 1), derived from camphor, underwent ring expansion in the presence of one equivalent of *i*-propyl magnesium bromide to afford [3.2.1]bicyclooctanones (Scheme 1).

SCHEME 1



All the reactions mentioned above and, as we reported very recently,[9] the reaction of formyl isoborneol with MeMgBr primarily gave ring-expanded bridged bicyclic ketones. However, the reaction of formyl borneol (**6**) with either 1 or 2.5

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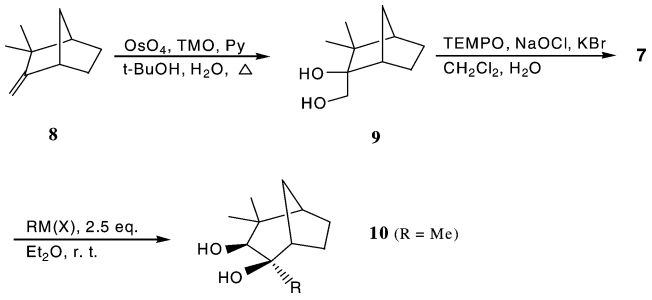
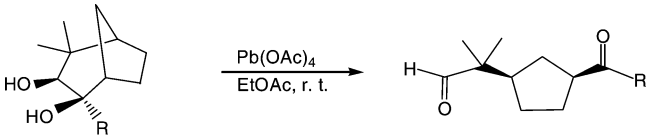
SCHEME 2



SCHEME 3



10: R = Me
14: R = Et
16: R = Allyl
17: R = *n*-Bu
21: R = Ph

24 (94 %): R = Me
25 (90 %): R = Et
26 (80 %): R = Allyl
27 (81 %): R = *n*-Bu
28 (89 %): R = Ph

equiv of various Grignard reagents provided alkyl[3.2.1]bicyclic diols instead of ketones.[9] It should be emphasized that **5** underwent ring expansion only,[8] whereas **6** did consecutively undergo a ring expansion-alkylation reaction when both of them were individually treated with 1 equiv of the same reagent. These interesting results impelled us to further study the reactions of other formyl[2.2.1]bicyclic carbinol analogues with some C-nucleophiles. We herein report the individual ring expansion alkylation of camphor- and camphene-based formyl[2.2.1]bicyclic carbinols (**6** and **7**) with Grignard reagents (RMgX) and alkyl/aryl lithium compounds (RLi), which were both adopted as the C-nucleophile donors for the reaction.

In order to obtain carbinol **7** (Scheme 2), (+)-camphene (**8**), which is commercially available, was adopted as the starting material. Treatment of **8** with *N*,*N*-dimethyl-methanamine oxide[10] in the presence of a catalytic amount of OsO_4 (Scheme 2) provided diol **9** (91% yield, 98% de). It is noteworthy that Uchida, et al. had reported the preparation of the enantiomer of **9**,[11] which could be obtained in slight or low yields (2−39%) from the electrochemical oxidation reaction of camphene in acetic acid followed by the treatment with aqueous sodium bicarbonate. In addition, treatment of camphene with $KMnO_4$ in aqueous acetone[11c] also gave the enantiomer of **9** in low (∼12%) yield. In our lab, then, the primary hydroxyl group in **9** was further oxidized with NaOCl and TEMPO in the presence of KBr to afford formyl carbinol **7** in good (90%) yield.

As mentioned above, the reactions of camphor-based formyl-[2.2.1]bicyclic carbinol (**6**) with various Grignard reagents have been previously described.[9] Now, the new finding is that

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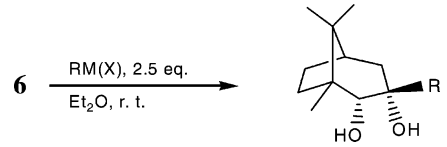
TABLE 1. Ring Expansion−Alkylation Results of Carbinol 6



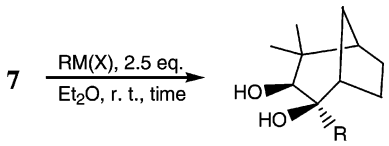
entry	RM(X)[a]	time (min)	product[c]	yield (%)[e]
1	MeMgBr[b]	30	**11** (R = Me)[d]	91
2	MeLi	30	**11** (R = Me)[d]	90
3	PhMgBr[b]	30	**12** (R = Ph)	67
4	PhLi	30	**12** (R = Ph)	65
5	*n*-BuMgCl[b]	30	**13** (R = *n*-Bu)[d]	63
6	*n*-BuLi	30	**13** (R = *n*-Bu)[d]	77

[a] All the reagents were purchased from commercial suppliers and used without further purification. [b] Data have been shown in ref 9. [c] >99% de. [d] The configuration of each new chiral center was determined with X-ray diffraction. [e] Yields of isolated products.

carbinol **6** also reacted with lithium reagents and gave the same products as those provided by the reactions with corresponding Grignard reagents (Table 1). Thus, individual reactions of **6** with both types of C-nucleophile donors showed the same chemoselectivity and regio- and stereochemical (>99% de) behaviors. Although the reaction time of some experiments (entries 5 and 6) has been prolonged for 60 min, the yield of each product was not improved. In addition, it showed that the nucleophilicities of methyl and phenyl lithium compounds (entries 2 and 4) were close to those of corresponding Grignard reagents (entries 1 and 3). The mechanism of reaction of **6** with Grignard reagents has been previously illustrated.[9] Thus, it is expected that the mechanism of the reaction of **6** with alkyl/aryl lithium compounds is similar to that of the reaction of **6** with Grignard reagents.

As shown in Table 2, the reactions of formyl carbinol **7** with various Grignard and organolithium reagents were carried out individually under conditions similar to those adopted for the reaction of **6**. In each case, among all possible regio- and stereoisomers of the [3.2.1]bicyclic diol structure, the isomer containing two vicinal *exo*-hydroxyl groups and possessing the new alkyl group attached to the ring carbon, which is the closest one to the bridgehead carbon, is the only product isolated and determined (>99% de). In order to search for a shorter reaction time for **7**, some experiments have been carried out in 15 min. After the time period for the reactions with MeMgBr and EtMgBr was prolonged from 15 to 30 min, the yields of **10** and **14** (entries 1, 2, 4, and 5) were not obviously improved. However, the yields of products **15**, **21**, and **22** were significantly improved after the reaction time was increased (entries 6, 7, 14, 15, 17, and 18). Although the reactions with allylMgCl, *n*-BuMgCl, vinylMgBr, and $CH_3CCMgBr$ (entries, 8, 9, 11, and 12) were individually carried out in 15 and 30 min, the yields of the corresponding products given in both time periods were almost the same. Interestingly, the reaction with phenyl ethynyl magnesium bromide (entry 13) also afforded the expected product in good yield. However, cyclopentyl magnesium bromide (entry 19) was not a good C-nucleophile donor for the reaction. This phenomenon is probably due to the steric effect caused by the nonplanar cyclopentyl moiety.[9] Some lithium reagents (entries 3 and 10) showed almost the same reactivity as their corresponding Grignard reagents did. Nevertheless, phenyl lithium (entry 16) was more reactive than phenyl magnesium bromide (entry 15).

TABLE 2. Ring Expansion−Alkylation Results of Carbinol 7



entry	RM(X) (C-Nu donor)	time (min)	product[a]	yield (%)[b]
1	MeMgBr	15	**10** (R = Me)	92
2	MeMgBr	30	**10** (R = Me)	94
3	MeLi	30	**10** (R = Me)	91
4	EtMgBr	15	**14** (R = Et)	82
5	EtMgBr	30	**14** (R = Et)	85
6	*i*-PrMgCl	15	**15** (R = *i*-Pr)	45
7	*i*-PrMgCl	30	**15** (R = *i*-Pr)	70
8	allylMgCl	15	**16** (R = Allyl)	77
9	*n*-BuMgCl	15	**17** (R = *n*-Bu)	79
10	*n*-BuLi	30	**17** (R = *n*-Bu)	80
11	vinylMgBr	15	**18** (R = $CHCH_2$)	76
12	$CH_3CCMgBr$	15	**19** (R = $CHCH_3$)	78
13	PhCCMgBr	30	**20** (R = CCPh)	83
14	PhMgBr	15	**21** (R = Ph)	52
15	PhMgBr	30	**21** (R = Ph)	70
16	PhLi	30	**21** (R = Ph)	82
17	BnMgCl	15	**22** (R = Bn)	63
18	BnMgCl	30	**22** (R = Bn)	79
19	cyclopentylMgBr	30	**23** (R = cyclopentyl)	23

[a] >99% de given by each experiment. [b] Yields of isolated products.

A plausible mechanism of the ring expansion-alkylation reaction of **7** is illustrated in Figure 2. Presumably, as described in the reaction of **6**[9], the alkyl/aryl moiety of the first molecule of organometallic reagent functioned as a base instead of a nucleophile and attacked the proton of hydroxyl group on **7** at the beginning of reaction. It is deduced that the ring-carbon atom which possesses two methyl groups was forced to migrate and attack the formyl moiety from the *si*-face right after the first molecule of the organometallic reagent chelated[12] to the hydroxyl and formyl groups as shown in structure **7a**. This phenomenon is a sharp contrast to that observed in the reaction of **6** but consistent with that shown by the ring expansion of the dihydrofuranyl carbinol-bearing fenchone skeleton under acidic conditions, which forced the bridgehead carbon atom to migrate exclusively.[2a] The migration of the ring-carbon atom in **7a** resulted in formation of the new carbonyl group shown in structure **7b**. The alkyl/aryl moiety of second molecule of organometallic reagent, then, functioned as a nucleophile and attacked the newly formed carbonyl group in **7b** from the *si*-face, too. Finally, the [3.2.1]bicyclic *syn*-diols (Scheme 2) were exclusively obtained after workup.

In order to search for the application of the title reaction, diol **11** has been previously converted to new, highly substituted chiral cyclopentanes,[9,13] which could be potential valuable synthons for the preparation of α-campholanic acid and

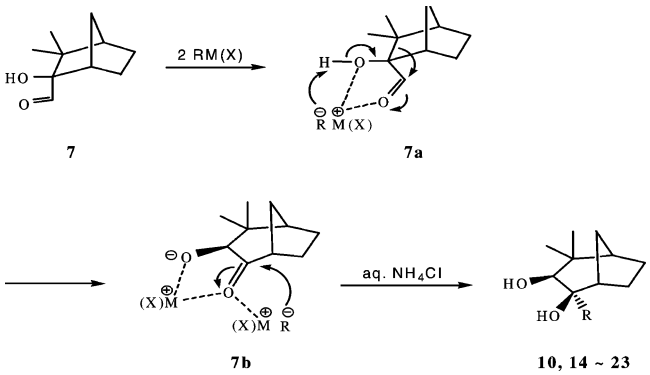


FIGURE 2. Plausible mechanism for the ring expansion-alkylation reaction of 7.

Polysantol.[14] Thus, the C−C bonds between vicinyl hydroxyl groups on diols **10**, **14**, **16**, **17**, and **21** (Seheme 3) were also oxidatively cleaved with $Pb(OAc)_4$ at room temperature to provide fencholic acid derivatives **24**[15]−**28**, respectively. The application of these disubstituted cyclopentanes (**24**[15]−**28**) to the synthesis of some natural product analogues is under investigation.

Experimental Section

Procedure for Dihydroxylation of 8. To a mixture of **8** (2.0 g, 14.7 mmol), *N*,*N*-dimethylmethanamine oxide (2.48 g, 22.3 mmol) in *t*-BuOH (30 mL), water (5 mL), and pyridine (2.0 mL) was added dropwise osmium tetroxide (2.5% in *t*-BuOH, 1.48 mL, 0.114 mmol). The reaction mixture was heated at reflux for 5 h, then cooled to room temperature and quenched with sodium bicarbonate (20%, 10 mL). The mixture was extracted with petroleum ether, washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified with flash column chromatography (1:1 hexane/EtOAc) to give **9** (2.2 g, 90% yield, 90% de) as a white solid: mp 194−196 °C; $[\alpha]_D^{27} = +12.1$ (0.01, CH_2Cl_2); IR (KBr) 3369 (br), 2963, 2881, 1464 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.71 (dd, J = 6.0 Hz, 11.2 Hz, 1H), 3.58 (dd, J = 4.4 Hz, 11.2 Hz, 1H), 2.81(dd, J = 4.4 Hz, 6.0 Hz, OH), 2.48 (s, OH), 2.13−1.11 (m, 8H), 1.02 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 81.9, 63.9, 49.7, 47.2, 43.4, 34.5, 25.3, 23.7, 22.7, 21.6. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.88; H, 10.36.

Procedure for Preparation of 7. To a mixture of **9** (1.0 g, 5.87 mmol), TEMPO (0.03 g, 0.19 mmol), KBr (0.13 g, 1.10 mmol), $NaHCO_3$ (0.13 g, 1.55 mmol) in CH_2Cl_2 (40 mL) and H_2O (5 mL) at 0 °C was added dropwise NaOCl (5.2 mL, 10.76 mmol). After the reaction mixture was stirred at 0 °C for 1 h, $NaHSO_3$ (5%, 10 mL) was added. Then, the mixture was extracted with CH_2Cl_2, washed with H_2O, dried (Na_2SO_4), and filtered. The filtrate was concentrated under reduced pressure to give **7** as a white solid: mp 98−100 °C; $[\alpha]_D^{27} = +9.4$ (0.01, CH_2Cl_2); IR (KBr) 3483 (br), 2957, 2880, 1709, 1461, 1338 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 10.07 (s, 1H), 3.56 (br s, 1H), 2.23−1.17 (m, 2H), 1.92−1.30 (m, 6H), 1.10 (s, 3H),

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0.99 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 207.4, 84.0, 49.9, 48.9, 48.6, 37.3, 25.6, 24.0, 22.4, 21.5. HRMS calcd for $C_{10}H_{16}O_2$: 168.1150; found: 168.1155.

General Procedure for the Reaction of Carbinol 6 or 7 with the Grignard and Organolithium Reagents. To a solution of carbinol **6** (0.45 g, 2.47 mmol) or **7** (0.50 g, 2.98 mmol) in diethyl ether (10 mL) was added dropwise a Grignard or lithium reagent (2.5 equiv). The reaction mixture was stirred at room temperature for 30 min and then quenched with aqueous NH_4Cl and extracted with ethyl acetate (3 × 10 mL). The organic layers were combined and washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified with flash column chromatography (6:1 hexane/EtOAc) to give the corresponding [3.2.1]bicyclic diol.

General Procedure for the Ring-Cleavage of Bicyclic Diols 10, 14 ,16, 17, and 21. A solution of [3.2.1]bicyclic diol (0.43 mmol) in ethyl acetate (5 mL) was treated with lead tetraacetate (0.56 mmol). The reaction mixture was stirred at room temperature for 5 min and then quenched with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The organic layers were combined and washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified with flash column chromatography (3:1 hexane/EtOAc) to give the corresponding cyclopentane derivative.

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Supporting Information Available: Procedure for preparation of camphene-based formyl[2.2.1]bicyclic carbinol, experimental details for the ring expansion-alkylation reaction and the preparation of cyclopentane derivatives **24**−**28**, ^{1}H and ^{13}C NMR spectra and characterization data of the products (**7**, **9**−**28**). This material is available free of charge via the Internet at http://pubs.acs.org.

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