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Grignard reagent-promoted selective ring expansion and alkylation of formyl borneol and isoborneol: a new route to highly substituted cyclopentanes

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Abstract—Formyl borneol, a [2.2.1]-bicyclic carbinol, reacts with various Grignard reagents to produce corresponding alkyl [3.2.1]-bicyclic diols, which can be converted to new highly substituted cyclopentanes, and further to 3-acyl-bornylenes. These ring expansion–alkylation reactions are highly selective. Reaction of formyl isoborneol with methyl magnesium bromide gave ring expansion-only and alkylation-only products.

Ring expansion of bridged bicyclic alcohols has drawn much attention from organic chemists in the last decade due to their potential application to the synthesis of natural products. For example, reaction of 2-bromo-ethynyl-2-norbornanol (compound **1**, Fig. 1) with iodine in the presence of Koser's reagent[1] gave a bicyclo-[3.2.1]octanone analogue.[2] In 1992, Paquette et al.[3] had efficiently carried out the ring expansion of norbornanol **2**. It was noted that the bridge-head carbon atom migrated exclusively during the reaction, which was catalyzed with toluenesulfonic acid. Recently, Ruggles and Maleczka,[4] have found that chlorinative ring expansion of [2.2.2]-bicyclic carbinols (e.g., compound **3**) could be induced by a bleach-acetic acid system, which possibly helped construct a concerted mechanism for the reaction. Furthermore, Paquette, Houk and coworkers[5] have also discovered that *exo*-norbornanols such as compound **4** undergo an anionic oxy-Cope rearrangement to form bicyclo[6.2.1] undecenones in the presence of potassium hexamethyldisilazane. On the other hand, Creary et al.[6] have reported that the ring expansion of bicyclic α-hydroxy ketones could occur in the presence of sodium methoxide. It is also known that the rearrangement of cyclic α-ketol[7] could be catalyzed by HCl or $NiCl_2$. The remarkable works mentioned above and the interesting results of our study on the reactions of hydroxymethyl borneol[8] prompted us to investigate the reactions of formyl borneol and its stereoisomer with Grignard reagents. We here report

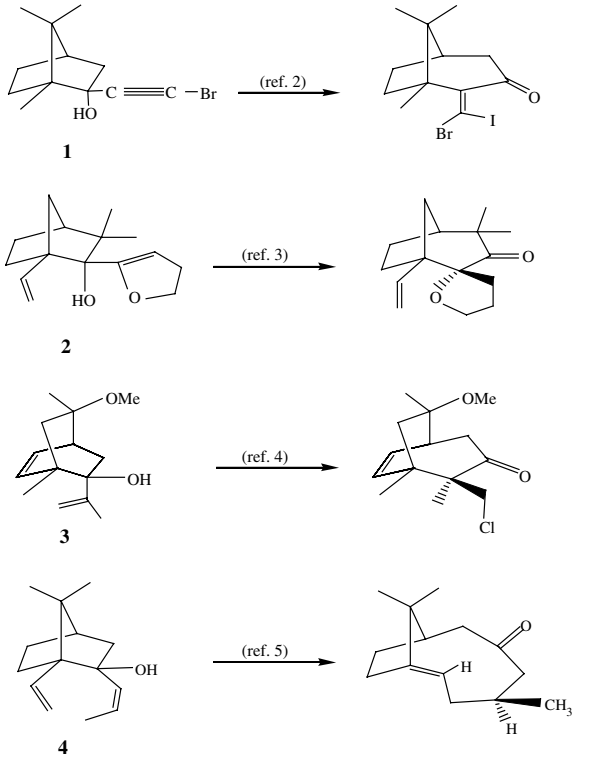

Figure 1. Selected bicyclic carbinols that undergo various ring expansion reactions.

Keywords: Ring expansion; Borneols; Grignard reagents.
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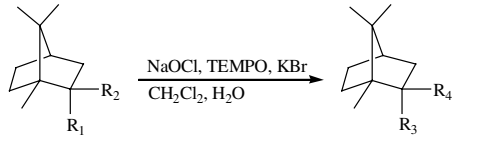


5: R_1 = OH, R_2 = CH_2OH
6: R_2 = OH, R_1 = CH_2OH

7 (99 %): R_3 = OH, R_4 = CHO
8 (98 %): R_3 = CHO, R_4 = OH

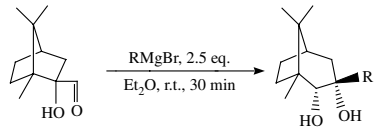
Scheme 1.

successful ring expansion–alkylation of the title compounds as well as the uses of the products obtained from the reaction.

As shown in Scheme 1, oxidation of **5** and **6**[8] with NaOCl in the presence of TEMPO[9] and potassium bromide produced good yields of carbinols **7** and **8**, respectively. Originally, formyl bicyclic carbinol **7** was treated with 1 equiv of methyl magnesium bromide at 0 °C with the expectation that it would yield diol **9** (Fig. 2). Surprisingly, however, a modest yield (45%) of diol **10** was obtained from the reaction, while diol **9** was not detected. In order to further investigate the reaction, we utilized two and half equivalents of MeMgBr, and the reaction was individually carried out in diethyl ether at various temperatures. As shown in Figure 2, this reaction yields diol **10** exclusively, and proceeds most efficiently at room temperature in 30 min. Further work has shown that these conditions to be generally applicable towards Grignard reagents containing various alkyl groups.

The ring expansion–alkylation reaction of formyl borneol (**7**) was carried out first, and the results are summarized in Table 1. Various commercial available Grignard reagents were employed for the reaction, which turned out to be highly regio- and stereoselective. The absolute molecular structure of each product was determined in terms of X-ray diffraction. In each case, among all possible regio- and stereoisomers of the [3.2.1]bicyclo product, the isomer containing two vicinal *endo*-hydroxyl groups and possessing the new alkyl group attached to the ring carbon atom, which is the farthest one to the bridge head carbon is the only product observed. A possible mechanism of the ring expansion–alkylation reaction is illustrated in Figure 3. It is deduced that the bridgehead carbon atom exclusively migrated right after the first molecule of Grignard reagent chelated[10] to the hydroxyl and formyl groups, as shown in **7a**. The alkyl group of the second molecule of Grignard reagent, then, attacked the new formed carbonyl group in **7b** from the *re*-face and diastereomer **10** or **11** was exclusively produced. Thus, the phenomenon that migration of bridgehead atom occurred contrasts with the phenomenon observed on the acid-catalyzed fenchone analog[3] ring expansion, in which the ring-carbon bearing dimethyl groups dominantly migrated. Since the oxygen atom of the carbonyl group on **7b** is chelated with 2 equiv of magnesium halide, as shown in Figure 3, the reactivity of **7b** is higher than that of **7**, on which the carbonyl group is chelated with 1 equiv of magnesium halide.

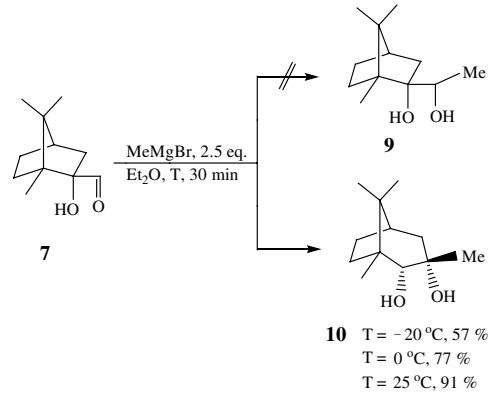
Table 1. The ring expansion–alkylation results



7 **10** or **11**

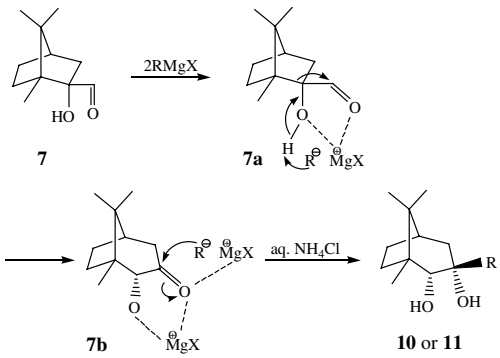
Entry	Grignard reagent[a]	Product[b]		Yield (%)[c]
1	MeMgBr	R: CH_3	**10**	91
2	EtMgBr	R: CH_2CH_3	**11a**	72
3	$CH_2CHMgBr$	R: $CH{=}CH_2$	**11b**	70
4	$CH_3CCMgBr$	R: $C{\equiv}CCH_3$	**11c**	71
5	PhMgBr	R:	**11d**	67
6	BnMgBr	R:	**11e**	49
7	CyclopentylMgBr	R:	**11f**	18
8	CH_2CHCH_2MgCl	R: $CH_2CH{=}CH_2$	**11g**	76
9	*i*-Pr-MgCl	R:	**11h**	64
10	*n*-BuMgCl	R: $(CH_2)_3CH_3$	**11i**	63

[a] All the reagents were purchased from commercial suppliers, and used without further purification.
[b] The configuration of each new chiral centre was determined with X-ray diffraction.
[c] Yields of isolated products.



7 **9** **10** T = −20 °C, 57 %
T = 0 °C, 77 %
T = 25 °C, 91 %

Figure 2. Effect of temperature on ring expansion–methylation yield.



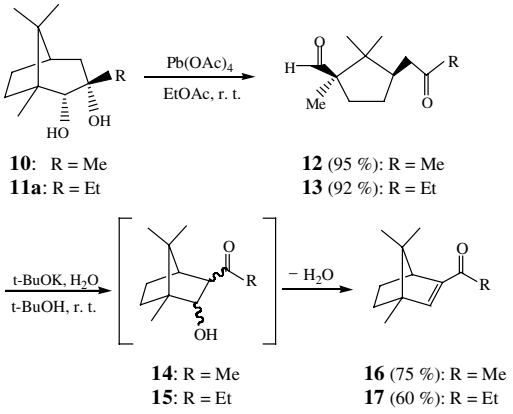
7 **7a** **7b** **10** or **11**

Figure 3. A possible mechanism of the ring expansion–alkylation reaction.

expansion–alkylation reaction. For alkyl magnesium bromides, the yield of alkylated diol is roughly inversely proportional to the bulkiness of the alkyl group on the Grignard reagent (entries 1–7); a similar situation was also observed in the reactions of alkyl magnesium chlorides (entries 8–10). It is noteworthy that the reagents bearing vinyl (entry 3) and propynyl (entry 4) groups perform almost as well as the one bearing ethyl moiety (entry 2) in the reaction. The reactions with both benzyl and cyclopentyl magnesium bromides (entries 6 and 7) gave the diol products (**11e** and **11f**) in relatively low yields (49% and 18%, respectively). Presumably, the nonplanar cyclopentyl group causes steric hinderance such that the alkyl anion cannot function as a good base at the beginning of the reaction, and is therefore not a good nucleophile for attacking the carbonyl group. On the other hand, the reaction with phenyl magnesium bromide (entry 5) gave the diol product (**11d**) in relatively satisfactory yield (67%). This phenomenon is reasonable, since a planar phenyl group exposes a flat,[11] less sterically demanding surface than do the nonplanar cyclopentyl and benzyl groups.

As part of a study of the applications of the title reaction, diols **10** and **11a** were individually treated with lead tetraacetate[12] (Scheme 2) to provide ethanones **12** and **13**, which are new highly substituted chiral cyclopentanes and could be valuable synthons for the preparation of α-campholanic acid[13] analogue. Intramolecular aldol condensation of **12** and **13** was then carried out in the presence of potassium *t*-butoxide to give acyl bornylenes **16** and **17**. Although acyl borneols **14** and **15** could not be isolated, accordingly, they were obtained as the aldol reaction products, which individually underwent dehydration in situ at this stage.

In the case of reaction of formyl isoborneol (**8**) with methyl magnesium bromide (Scheme 3), the same conditions as those used in that of **7** were adopted. However, the ring expansion–alkylation product was not observed. Instead, bicyclo[3.2.1]-hydroxyoctanone **18** (a ring expansion product) and bicyclo[2.2.1]-carbinol **19** (an alkylation product) were obtained. Presumably, the methylene group bearing C-3 on the ring exclusively migrated during the formation of **18**. This situation is similar to that observed in the fenchone[3] series (see above). In 1991, McIntosh[14] and Cassidy has reported a different method for the preparation of compound **18**, which could be oxidized by air at ambient temperature to form a homocamphoric anhydride after several days. Although the yield of carbinol **19** was very low (11%), it is a product given by an addition reaction, which we originally wanted to carry out by using **7** as the reactant.



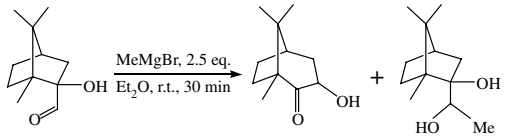
10: R = Me
11a: R = Et

12 (95 %): R = Me
13 (92 %): R = Et

14: R = Me
15: R = Et

16 (75 %): R = Me
17 (60 %): R = Et

Scheme 2.



8 **18** (52%) **19** (11%)

Scheme 3.

In conclusion, the reaction[15] of formyl borneol (**7**) with various Grignard reagents is highly chemo-, regio- and stereoselective. Products[16] given by the reaction could be converted to new highly substituted cyclopentane analogues. Conversion of some diols listed in Table 1 to chiral auxiliaries, which are expected to be useful in asymmetric borane reduction,[17] is under investigation.

Acknowledgements

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15. *General procedure*: To a solution of formyl borneol (**7**, 0.6 g, 3.30 mmol) in diethyl ether (20 mL) was added dropwise the Grignard reagent (3 M in Et_2O, 2.73 mL, 8.25 mmol). The reaction was stirred at room temperature for 30 min, then quenched with aqueous NH_4Cl and extracted with ethyl acetate (3×20 mL). The organic layers were combined and washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (6:1, *n*-hexane/EtOAc) to give the [3.2.1]-bicyclic diol.
16. *Compound* **10**: solid, $[\alpha]_D^{25} = +5.9$ (0.10, CH_2Cl_2); mp 87–88 °C; IR (KBr): 3361 (br), 2966, 1366, 1026 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 0.85 (s, 3H), 0.87 (s, 3H), 0.91 (s, 3H), 1.21 (s, 3H), 1.59–2.00 (m, 7H), 2.26 (s, OH), 2.38 (dd, OH, J = 3.6, 7.2 Hz), 3.36 (dd, 1H, J = 1.4, 7.2 Hz), ^{13}C NMR (50 MHz, $CDCl_3$): 16.9, 18.8, 24.6, 26.1, 27.8, 30.9, 41.5, 44.3, 44.5, 46.9, 70.6, 77.8. HRMS (FAB, MH^+) calcd for $C_{12}H_{22}O_2$: 198.1620; found: 198.1619.
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