

Recyclization reactions of 8,10-dibromocamphor with Grignard and organolithium compounds

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Grignard reagents and organolithium compounds react with 8,10-dibromocamphor to afford substituted 1-methyl-2-methylenebicyclo[3.2.0]heptanes. Recyclization proceeds via intramolecular enolate alkylation and Grob fragmentation of the reaction intermediates. All compounds have been characterized by ^1H , ^{13}C and ^{19}F NMR spectroscopy and their chemical composition proved by HRMS analyses. The relative spatial arrangement of substituents in the molecule of (1-methyl-2-methylenebicyclo[3.2.0]heptan-6-yl)diphenylmethanol was studied by NOESY experiments.

Introduction

Camphor is known as the naturally available starting material in a number of syntheses of more complex compounds from the middle of the XIX century. Nowadays many syntheses of steroids [1-3], terpenoids [4-12], vitamins [13-15] and other natural products [16-19] that involve camphor or its derivatives are described in the literature.

Camphor derived chiral auxiliaries can be prepared in both enantiomeric forms since the camphor itself is commercially available as R-(+) and S-(-) enantiomers [20-25].

The variety of unusual and even unique reactions of camphor combined with its natural occurrence explains the interest in further chemical modifications of this terpenoid ketone.

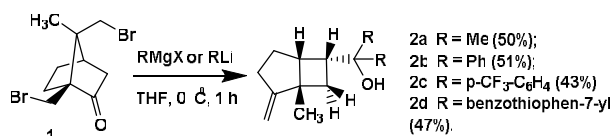
Even nowadays, comparing to other relatively simple natural molecules, the chemistry of camphor has many uncharted domains.

Electrophilic bromination is the very important approach in the preparation of bromo-functionalized terpenoid derivatives, which are common as intermediates in organic synthesis because of the ease of further modifications via nucleophilic substitutions or various skeletal rearrangements and cyclizations [26–30].

Herein we would like to present our investigation for the recyclization reactions of easily available 8,10-dibromocamphor [31] with Grignard and organolithium compounds.

Results and discussion

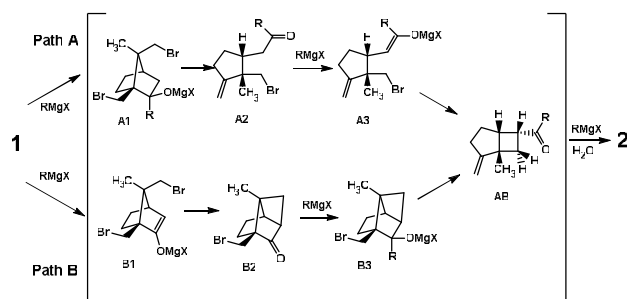
Compounds **2(a-d)** were obtained by recyclization of 8,10-dibromocamphor (**1**) with excess of Grignard or organolithium compounds (**Scheme 1**).



Scheme 1. Recyclization of 8,10-dibromocamphor.

The structure of bicyclo[3.2.0]heptane skeleton for compound **2b** was determined by 2D-NMR spectroscopy (H-H COSY, HMQC, HMBC, NOESY).

The first step of the reaction could be either nucleophilic addition to the carbonyl group of **1** (pathway A, **Scheme 2**) or alpha-deprotonation with the formation of enolate anion (pathway B, **Scheme 2**).

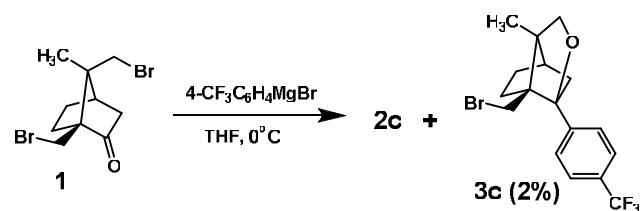


Scheme 2. Plausible pathways of 8,10-dibromocamphor recyclization.

Following *Path A* the alcoholate anion (**A1**) could undergo Grob fragmentation forming olefin (**A2**). This intermediate

hypothetically under strong basic conditions could form enolate (**A3**) and give bicyclo[3.2.0]heptane intermediate (**AB**) which adds the excess of metalloorganic reagent forming products **2**. On the *Path B* enolate anion (**B1**) could form tricyclic ketone (**B2**) as a product of intramolecular alkylation. Excess of the metalloorganic reagent could cause the formation of the same intermediate **AB** via alcoholate **B3**. Finally, ketone intermediate **AB** reacts with the excess of metalloorganic reagent forming compound **2**.

Unfortunately, all our attempts to examine the possible intermediate compounds and preferable path of these transformations failed due to high reactivity of all intermediates under the reaction conditions. The reaction of 8,10-dibromocamphor with one or two equivalents of Grignard reagent results the mixture of starting material and corresponding final compound **2**. The only minor product that we could identify was the tricyclic compound **3c** (**Scheme 3**). It could be formed as a product of intramolecular alkylation in **A1**.



Scheme 3. Formation of **3c**

Following the both possible pathways A and B one could suggest the epimerization of intermediate **AB** under strong basic conditions.

The relative spatial arrangement of the substituents in the molecule **2b** was studied by NOESY experiments and reveals the *cis*-configuration of cyclopentane ring and diaryl carbinol substituent at the cyclobutane ring (**Figure 1**).

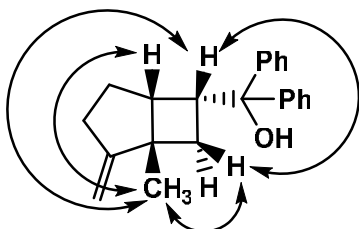


Figure 1. NOESY correlations for **2c**.

Experimental part

Solvents were purified according to the standard procedures. ^1H , ^{13}C , ^{19}F and two-dimensional (Noesy, Cosy, HSQC) NMR spectra were recorded on Mercury 400 Varian (400.4 MHz) and Bruker 170 Avance 500 spectrometer (499.9 MHz). Chemical shifts are reported in ppm downfield from TMS as the internal standard. HRMS were recorded on Infinity 1260 UHPLC system coupled to an 6224 Accurate Mass TOF LC/MS system (Agilent Technologies, Singapore). The synthesis of **1** was performed using a previously described procedure [31].

2-(1-methyl-2-methylenebicyclo[3.2.0]heptan-6-yl)propan-2-ol 2a: 8,10-Dibromocamphor (0.50 g, 0.0016 mol) was dissolved in tetrahydrofuran (20 mL) in a three-necked flask under argon. After cooling to 0 °C, Grignard reagent - MeMgCl (3

M in tetrahydrofuran) (3 ml, 0.009 mol) was added dropwise. The reaction mixture was stirred at room temperature overnight. After cooling to 0 °C the solution was quenched with water (50 ml) and stirred during 1 h. The reaction mixture was diluted dichloromethane (60 ml) and water (20 ml). The organic layer was separated, washed with brine (2*30 ml) and dried over Na_2SO_4 . The solvents were evaporated under the reduced pressure to give a crude product as yellow oil. The title compound was purified by flash chromatography (6:1 hexanes/ethyl acetate) as white crystals.

2-(1-methyl-2-methylenebicyclo[3.2.0]heptan-6-yl)propan-2-ol (2a). Yield 125 mg, 50 %. Mp 45–47 °C. ^1H NMR (400 MHz, CDCl_3 , δ): 4.71 (s, 1H), 4.59 (s, 1H), 2.81–2.72 (m, 1H), 2.44–2.37 (m, 2H), 2.32–2.22 (m, 2H), 1.99–1.93 (m, 1H), 1.77–1.71 (m, 1H), 1.68–1.58 (m, 1H), 1.23 (s, 3H), 1.22 (s, 3H), 1.07 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3 , δ): 161.1, 101.1, 71.9, 46.7, 42.8, 40.7, 34.8, 33.6, 29.1, 26.9, 25.7, 22.1. HRMS calcd for $\text{C}_{12}\text{H}_{20}\text{O}$: 180.1514; found: 180.1515.

(1-methyl-2-methylenebicyclo[3.2.0]heptan-6-yl)diphenylmethanol 2b: 8,10-Dibromocamphor (0.50 g, 0.0016 mol) was dissolved in tetrahydrofuran (20 mL) in a three-necked flask under argon. After cooling to 0 °C, Grignard reagent - PhMgCl (2 M in tetrahydrofuran) (4 ml, 0.008 mol) was added dropwise. The reaction mixture was stirred at room temperature overnight. After cooling to 0 °C the

solution was quenched with water (50 ml) and stirred for 1 h. The reaction mixture was diluted with dichloromethane (60 ml) and water (20 ml). The organic layer was separated, washed with brine (2*30 ml) and dried over Na₂SO₄. The solvents were evaporated under the reduced pressure to give a crude product as yellow oil. The title compound was purified by flash chromatography (6:1 hexanes/ethyl acetate) as white crystals.

(1-methyl-2-methylenebicyclo[3.2.0]heptan-6-yl)diphenylmethanol (2b). Yield 0.25 g, 51 %. Mp 73–75°C. ¹H NMR (400 MHz, CDCl₃, δ): 7.49 (d, *J* = 8.3 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.30-7.25 (m, 5H), 7.20-7.18 (m, 1H), 4.77 (s, 1H), 4.66 (s, 1H), 3.50 (q, *J* = 9.5 Hz, 1H), 2.97-2.91 (m, 1H), 2.57 (t, *J* = 9 Hz, 1H), 2.36 (t, *J* = 11 Hz, 1H), 2.38-2.29 (m, 1H), 2.23 (br. s, 1H), 2.02-1.98 (m, 1H), 1.79-1.75 (m, 1H), 1.48 (quint, *J* = 10.6 Hz, 1H), 1.36 (s, 3H). ¹³C NMR (100 MHz, CDCl₃, δ): 161.2, 147.8, 146.1, 128.3, 128.1, 126.8, 126.7, 126.5, 125.8, 101.5, 79.4, 48.3, 43.3, 39.9, 34.7, 34.2, 26.0, 22.4. HRMS calcd for C₂₂H₂₄O: 304.1827; found: 304.1929.

1-methyl-2-methylenebicyclo[3.2.0]heptan-6-yl)bis(4-(trifluoromethyl)phenyl)methanol 2c: 8,10-Dibromocamphor (0.50 g, 0.0016 mol) was dissolved in tetrahydrofuran (20 mL) in a three-necked flask under argon. After cooling to 0°C, Grignard reagent - (4-

trifluoromethylphenyl)magnesium bromide (1 M in tetrahydrofuran) (8 ml, 0.008 mol) was added dropwise. The reaction mixture was stirred at room temperature overnight. After cooling to 0 °C the solution was quenched with water (50 ml) and stirred during 1 h. The reaction mixture was diluted dichloromethane (60 ml) and water (20 ml). The organic layer was separated, washed with brine (2*30 ml) and dried over Na₂SO₄. The solvents were evaporated under the reduced pressure to give a crude product as yellow oil. Crude product was purified by flash chromatography (6:1 hexanes/ethyl acetate) to give compounds **2c** and **3c** in the form of white crystals.

1-methyl-2-methylenebicyclo[3.2.0]heptan-6-yl)bis(4-(trifluoromethyl)phenyl)methanol (2c). Yield 0.30 g, 43 %. ¹H NMR (400 MHz, CDCl₃, δ): 7.65-7.55 (m, 4H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 4.78 (s, 1H), 4.66 (s, 1H), 3.51 (q, *J* = 9.4 Hz, 1H), 2.87 (q, *J* = 11 Hz, 1H), 2.59 (t, *J* = 9 Hz, 1H), 2.40 (br. s, 1H), 2.36-2.24 (m, 2H), 1.87 (t, *J* = 10.9 Hz, 1H), 1.75 (t, *J* = 11 Hz, 1H), 1.50 (quint, *J* = 10.5 Hz, 1H), 1.35 (s, 3H). ¹³C NMR (100 MHz, CDCl₃, δ): 160.3, 150.5, 149.2, 129.43 (q, ²*J*_{CCF} = 32 Hz), 129.24 (q, ²*J*_{CCF} = 32 Hz), 126.7, 126.1, 125.4, 125.2, 124.06 (q, ¹*J*_{CF} = 270 Hz), 124.04 (q, ¹*J*_{CF} = 273 Hz), 102.2, 79.1, 47.9, 43.4, 39.5, 34.5, 33.7, 25.8, 22.4. ¹⁹F NMR (376 MHz, CDCl₃, δ): -62.42, -62.47.

6a-(bromomethyl)-3a-methyl-1-(4-(trifluoromethyl)phenyl)hexahydro-1H-1,4-methanocyclopenta[c]furan (3c). Yield 12 mg, 2 %. Mp 113–115°C. ¹H NMR (400 MHz, CDCl₃, δ): 7.63–7.58 (m, 4H), 3.89 (d, *J* = 8.2 Hz, 1H), 3.70 (d, *J* = 8.3 Hz, 1H), 3.39 (d, *J* = 10.7 Hz, 1H), 3.28 (d, *J* = 10.6 Hz, 1H), 2.12–2.09 (m, 1H), 2.04–1.92 (m, 2H), 1.91–1.76 (m, 3H), 1.54–1.48 (m, 1H), 1.07 (s, 3H). ¹³C NMR (100 MHz, CDCl₃, δ): 142.0, 129.58 (q, ²*J*_{CCF} = 32 Hz), 126.1, 124.92, 124.23 (q, ¹*J*_{CF} = 270 Hz), 90.4, 70.6, 58.2, 57.7, 44.8, 41.9, 32.4, 29.7, 23.8, 13.1. ¹⁹F NMR (376 MHz, CDCl₃, δ): -62.83. HRMS calcd for C₁₇H₁₈BrF₃O: 374.0493; found: 374.0491.

bis(benzo[b]thiophen-7-yl)(1-methyl-2-methylenebicyclo[3.2.0]heptan-6-yl)methanol 2d: 7-Bromobenzothiophene (1.70 g, 0.008 mol) was dissolved in THF (20 ml) in a three-necked flask under argon. The solution was cooled to -60°C and *n*-Buli (2.5 M solution, 0.008 mol, 3.2 ml) was added dropwise. The reaction mixture was stirred at -60°C for 20 minutes and the solution of 8,10-dibromocamphor (0.5 g, 0.0016 mol) in THF (10 ml) was added dropwise. The solution was stirred at room temperature overnight. After cooling to 0°C the solution was quenched with water (20 ml) and stirred for 1 h. The reaction mixture was diluted with dichloromethane (60 ml) and water (20 ml). The organic layer was separated, washed with brine (2*30 ml) and dried over Na₂SO₄. The solvents were

evaporated under the reduced pressure to give a crude product. The title compound was purified by flash chromatography (6:1 hexanes/ethyl acetate) as colorless oil.

bis(benzo[b]thiophen-7-yl)(1-methyl-2-methylenebicyclo[3.2.0]heptan-6-yl)methanol (2d). Yield 0.31 g, 47 %. ¹H NMR (400 MHz, CDCl₃, δ): 7.84–7.82 (m, 1H), 7.79–7.74 (m, 2H), 7.68–7.65 (m, 1H), 7.40–7.26 (m, 5H), 7.14 (s, 1H), 4.80 (s, 1H), 4.68 (s, 1H), 3.56 (dd, *J* = 9.4, 9.6 Hz, 1H), 3.02–2.92 (m, 1H), 2.84 (br. s, 1H), 2.70–2.64 (m, 1H), 2.46–2.32 (m, 2H), 2.22–2.15 (m, 1H), 2.03–1.97 (m, 1H), 1.60–1.49 (m, 1H), 1.39 (s, 3H). ¹³C NMR (100 MHz, CDCl₃, δ): 160.7, 152.0, 150.4, 139.8, 139.63, 139.61, 139.4, 124.5 (2C), 124.44, 124.39, 123.8 (2C), 122.5, 122.4, 120.6, 120.3, 101.9, 77.8, 48.1, 43.3, 41.7, 34.7, 34.3, 26.0, 22.3.

Conclusions

Recyclization reactions of 8,10-dibromocamphor with Grignard and organolithium compounds afford the substituted 1-methyl-2-methylenebicyclo[3.2.0]heptanes.

Recyclization proceeds via intramolecular enolate alkylation and Grob fragmentation of the reaction intermediates. All compounds have been characterized by ¹H, ¹³C and ¹⁹F NMR spectroscopy and their chemical composition proved by HRMS analyses.

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