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Chiral building blocks from *R*-(–)-carvone: *N*-bromosuccinimide-mediated addition–sceletal rearrangement of (–)-*cis*-carveol

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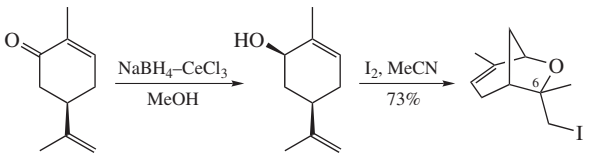
Synthetically valuable bicyclic blocks 5, 7 and 9 were prepared by the oxidative cleavage of the double bond of 4 with the $RuCl_3$–$NaIO_4$ system and O_3.

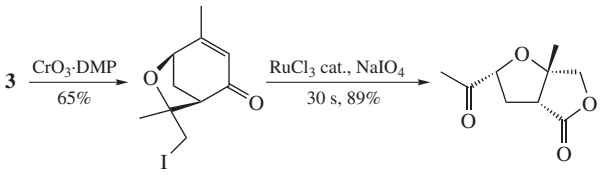
Over the last few years, available and inexpensive *R*-(–)-carvone **1** has been intensively used as a chiral starting material in the total synthesis of complex structures.[1] At the same time, (–)-carveol **2** has been less widely used in the total synthesis.[2] To transform (–)-carveol into new synthetically useful functionalized chiral blocks, we have planned to obtain and study the reactions of intramolecular (–)-carveol haloetherification products. According to published data, (–)-*cis*-carveol is produced by the reduction of (–)-carvone with $LiAlH_4$ in diethyl ether[3] or Red-Al[4] in THF at –78 °C and Luche reagent ($NaBH_4$–$CeCl_3$) in MeOH.[5–7] The latter procedure, which afforded **2** in 90% yield, is more convenient and practical. Oxacyclization reactions promoted by electrophilic agents are possible due to the favourable spatial orientation of the hydroxyl and isopropenyl groups in (–)-*cis*-carveol. For example, a quick synthesis of (+)-pinol from **2** by the oxymercuration–demercuration is known,[3] and the intramolecular bromoetherification of mentadienol by treatment with NBS was also described. At first, we tested I_2 as an electrophilic agent for the cyclization of **2**. The reaction of **2** with I_2 in MeCN was explored to initiate the intramolecular formation of the ether, resulting, as expected, in bicyclic iodine derivative **3** (Scheme 1). Compound **3** was considered as a more convenient partially protected synthetic equivalent of **2** for the following differentiation of functional groups to oxidative cleavage of a double bond because **3** can be smoothly fragmented into **2** by treating with Zn in EtOH.[8]



1 **2** **3**

Scheme 1

The (*S*)-configuration of the C^6 chiral centre in **3** was assigned by a set of chemical transformations illustrated in Scheme 2 to give **5**† from **3** *via* oxidation with CrO_3·DMP[9] and subsequent RuO_4 cleavage (Katsuki–Sharpless reaction).[10] Note that cyclohexenone **4** is synthetically attractive as self-protected and stable 4-oxo derivative of (–)-*cis*-carveol. Then, the reaction of the ozonolytic cleavage of a double bond in **4** was studied. The ozonolysis was carried out in a solution of MeOH at –78 °C, the residue was purified using column chromatography on SiO_2 after a standard work-up procedure. It was revealed that ketoaldehyde **6** initially observed (using TLC) transforms into enol **7**.



4 **5**

Scheme 2

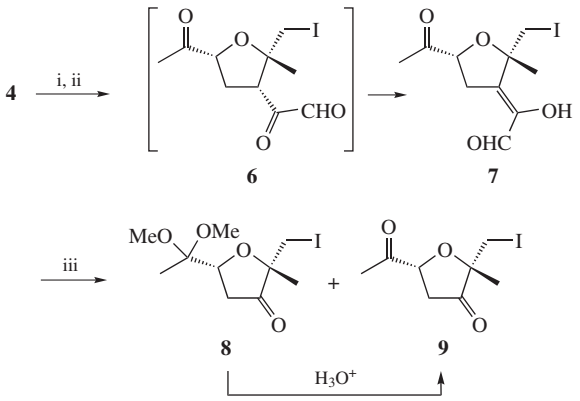
According to the spectral data, enol **7** is an isomeric pure compound, but the configuration of its double bond is not specified. The structure of a more preferable and less hindered *E*-isomer is shown below. During the ozonolysis of **4** (MeOH, –78 °C), enol **7** did not react with ozone. By this reason, the ozonolysis of **7** was carried out in a solution of MeOH at –40 °C. As a result, a mixture of furanones **8** and **9** was produced in a ratio of 1:1 (^{1}H NMR). The mixture was placed in an acidic water medium to transform into compound **9** (Scheme 3).†

The inclination of α-ketoaldehyde **6** for the enolization is not quite clear. The possible reasons are steric hindrance and electrostatic repulsion of all-*cis* oxo functions and CH_2I substituent in compound **6**. In this case, enolization in α-ketoaldehyde fragment decreases somewhat the strain in the highly strained substituted

† *(2R,3aR,6aS)-2-Acetyl-6a-methyltetrahydrofuro[3,4-b]furan-4(2H)-one* **5**: white crystalline solid, yield 89%, mp 98–99 °C; $[\alpha]_D^{20}$ +11.8 (*c* 0.63, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.44 (s, 3H), 2.16 (s, 3H), 2.47–2.52 (m, 1H), 2.63–2.70 (m, 1H), 2.89–2.92 (m, 1H), 4.19 (d, 1H, *J* 9 Hz), 4.44–4.48 (m, 1H), 4.54 (d, 1H, *J* 9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.2, 25.5, 31.6, 49.2, 75.3, 83.1, 87.9, 177.5, 208.1. IR (KBr, ν/cm^{-1}): 1759, 1720. MS (APCI), *m/z* (%): 185 $[M + H]^+$ (100), 202 (93.5), 217 (58.1). Found (%): C, 58.54; H, 6.59. Calc. for $C_9H_{12}O_4$ (%): C, 58.70; H, 6.52.

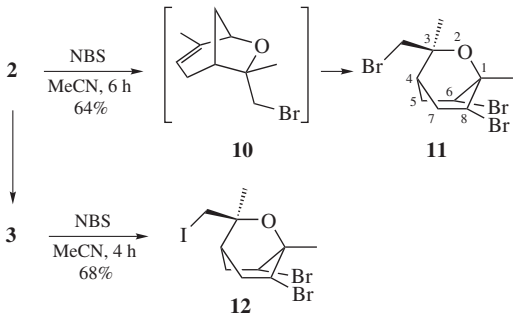
(2S,5R)-5-Acetyl-2-iodomethyl-2-methyldihydrofuran-3-one **9**: yellow oil, yield 61%; $[\alpha]_D^{20}$ +105.5 (*c* 2.35, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.39 (s, 3H), 2.45 (s, 3H), 2.72–2.75 (m, 2H), 3.26 (d, 1H, *J* 9 Hz), 3.35 (d, 1H, *J* 9 Hz), 4.60–4.65 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 9.35, 20.86, 26.47, 37.49, 77.65, 82.39, 208.60. IR (KBr, ν/cm^{-1}): 1761, 1716. Found (%): C, 33.85; H, 4.01; I, 44.61. Calc. for $C_8H_{11}IO_3$ (%): C, 34.06; H, 3.93; I, 44.99.

(3S,6S,7R)-6,7-Dibromo-3-bromomethyl-1,3-dimethyl-2-oxabicyclo[2.2.2]-octane **11**: white crystalline solid, yield 64%, mp 86–87 °C; $[\alpha]_D^{20}$ –26.1 (*c* 5.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.39 (s, 3H), 1.51 (s, 3H), 2.16 (m, 1H), 2.29–2.32 (m, 2H), 2.81–2.90 (m, 2H), 3.22 (d, 1H, *J* 10.5 Hz), 3.34 (d, 1H, *J* 10.5 Hz), 4.13–4.24 (m, 2H). ^{13}C NMR (75 MHz, [$^2H_6$]acetone) δ: 25.3, 26.1, 34.8, 37.4, 38.0, 40.5, 48.6, 48.8, 76.4, 78.3. IR (KBr, ν/cm^{-1}): 1458, 1449, 1379, 1088. Found (%): C, 30.91; H, 3.77; Br, 61.01. Calc. for $C_{10}H_{15}Br_3O$ (%): C, 30.69; H, 3.84; Br, 61.38.



Scheme 3 *Reagents and conditions*: i, O_3, MeOH, –78 °C, Me_2S; ii, SiO_2, EtOAc; iii, O_3, MeOH, –40 °C, Me_2S, 2 N HCl.

THF system, and it is a driving force of the transformation **6** → **7**. An unexpected result was obtained during the study of the reaction of **2** with NBS. The experiment showed that this reaction led smoothly to an individual compound, the spectral characteristics of which corresponded to the structure of bicyclic tribromide **11**.† Similarly, **3** was transformed into trihalo derivative **12** similar to **11** by treating with NBS in MeCN (Scheme 4).



Scheme 4

Finally, the structure of **11** was confirmed by the X-ray data (Figure 1).‡ This work presents a new skeleton rearrangement of *cis*-carveol, which accompanied the bromination of the latter by NBS. Wolinsky *et al.*[11] described the Favorsky type rearrangement and Grob type fragmentation of carvone tribromides. The synthesis of dibromide similar to **11** *via* bromine-assisted epoxide ring expansion of (+)-*cis*-limenone oxide was also described by Davies *et al.*[12] The mechanism of the rearrangement **2** → **11** can be gleaned from the smooth formation of iodo ether **3** in the reaction of **2** with I_2. It looks as if the reaction of **2** with NBS also started by the generation of analogous bromo ether **10**,[13]

‡ *Crystallographic data for* **11**. Crystals of **11**, $C_{10}H_{15}Br_3O$, M = 390.95, are rhombic, space group $P2_12_12_1$, at 100 K: a = 8.905(2), b = 11.483(2) and c = 12.345(3) Å, V = 1262.5(4) Å^3, Z = 4, d_{calc} = 2.057 g cm^{-3}, crystal size 0.55×0.25×0.15 mm. Intensities of 6489 reflections were measured with a Bruker APEX2 CCD diffractometer [λ(MoKα) = 0.71073 Å, ω-scans, $2\theta_{max}$ = 56°] and 3010 independent reflections (R_{int} = 0.0570) were used in a further refinement. Reflection intensities were integrated using the SAINT software and the SADABS semi-empirical method. The structure was solved by a direct method and refined by the full-matrix least-squares against F^2_{hkl} in an anisotropic (for non-hydrogen atoms) approximation. For **11** the refinement converged to wR_2 = 0.0875 and GOF = 0.998 for all independent reflections [R_1 = 0.0439 was calculated against F_{hkl} for 2292 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using the SHELXTL software.

CCDC 707529 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2010.

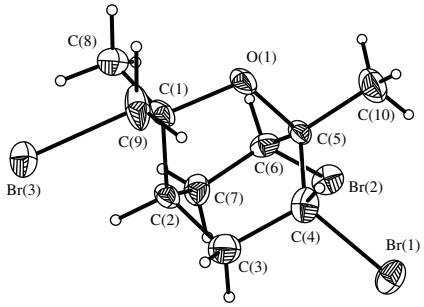
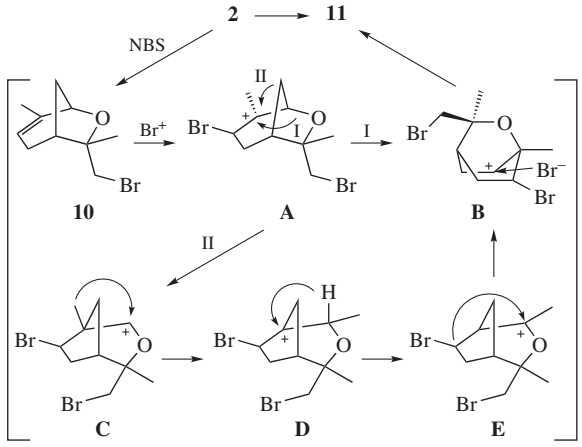


Figure 1 Molecular structure of **11**.

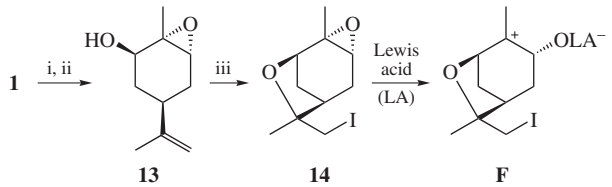


Scheme 5

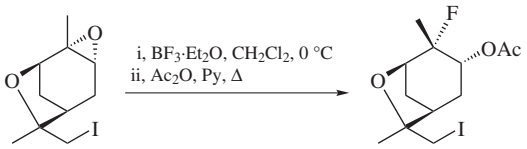
which further coordinates Br^+ to give bromonium cation **A**, undergoing further transformation as detailed in Scheme 5.

Here two alternative transformation ways are possible. The simplest way is concerted bromonium ion opening and migration of the antiperiplanar CO bond in **A** to form carbocation **B** attacked stereoselectively with Br^- (path I). In this case, the direction of Br^- attack is characterized by the fact that a carbonium centre in **A** is stabilized by a neighbouring O atom and in its three-centred oxonium fragment an antiperiplanar Br^- approach is advantageous. The following mechanism (path II) is a classic migration of C–C and C–H bonds. In cation **A** the migration of the bridge bond leads to oxonium cation **C**, which transforms into **D** by 1,2-migration of the methyl group. The 1,2-migration of hydride in the latter leads to more stable oxonium cation **E**, which finally collapses to the symmetric structure of **11** *via* the migration of a Br-containing carbon atom and the addition of Br^- to **B**. Then, to estimate the migration properties of the bonds in variants I and II, model epoxide **14** was synthesized (Scheme 6).

However, the use of Et_3SiOTf in CH_2Cl_2 at –78 °C to initiate the decomposition of **14** led to a mixture of products. On the contrary, using $BF_3{\cdot}Et_2O$ resulted in a single product, which was isolated and characterized as acetate **15** (Scheme 7). The observed NOE between Me (δ 1.36 ppm) and H (δ 5.10 ppm), CH_2I and H (δ 5.10 ppm) confirms their *cis* orientation.



Scheme 6 *Reagents and conditions*: i, 30% H_2O_2, MeOH, 0.3 N K_2CO_3; ii, $NaBH_4$–$CeCl_3$, MeOH, 5–10 °C; iii, I_2, $NaHCO_3$, MeCN.



14 **15**

Scheme 7

To obtain a deeper insight into the chemical nature of cation **A**, we performed *ab initio* MO calculations of the structural and electronic properties of key intermediates, including **A**, products of its unimolecular transformation **B** and **C**, transition states of both pathways, TS_{AB} and TS_{AC} as well as stationary points of the further isomerization of **C**, **D** and TS_{CD}. All computations were performed on the RI-MP2/L1 level of theory using the Priroda software package.[14] The structures were fully optimized, and the RI-MP2/L2 refinement of total energy was used along with RI-MP2/L1 harmonic frequency calculations to obtain the standard enthalpy H^0_{298} and free energy G^0_{298} of the states of interest. The geometry of the equilibrium structure of intermediate **A** is shown in Figure 2. The definitive features of its structure was found to be the almost formed C(2)–O bond (1.583 Å, bond order of 0.70) as well as the substantially weakened C(1)–O bond (1.532 Å, bond order of 0.73); *i.e.*, intermediate **A** represents the oxirane-type structure. The driving force of the formation of an oxirane ring is, obviously, the prominent affinity of the oxygen lone pairs to the cationic centre of the intermediate. Thus, the structure of **A** by itself presupposes the isomerisation pathway *via* further weakening of the C(1)–O bond, which finally leads to intermediate **B**. Another possibility is a classical transformation of **A** *via* the shift of C(7) atom to the cationic C(2) atom and charge migration to the C(1) atom, resulting in intermediate **C**. The activation barrier for the **A** → **B** isomerization (22.7 kcal mol^{-1}) is comparable to that of the **A** → **C** reaction, being only 2.6 kcal mol^{-1} higher.

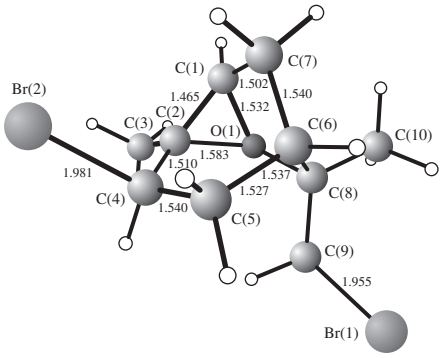


Figure 2 Equilibrium structure of intermediate **A**.

The former reaction is endothermic by 14.3 kcal mol^{-1}, whereas the latter one is 4.9 kcal mol^{-1} exothermic. These results indicate the preferable formation of classic cation **C** rather than **B**. However, the further transformation of **C** (**C** → **D**) requires an activation energy of 43.6 kcal mol^{-1}, whereas approaching of the counterion Br^- to **B** and their barrierless annihilation lead to the stable molecular product of the reaction. Thus, our theoretical results ultimately predict that the overall expenditure of energy prohibits the classical way of the cation transformation, and the novel alkoxy migration mechanism is the most likely isomerization reaction for intermediate **A**.

Online Supplementary Materials

Analytical and spectral data for compounds **2–4**, **7**, **12–15** can be found in the online version at doi:10.1016/j.mencom.2010.03.004.

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