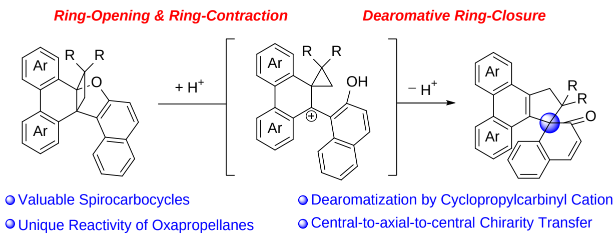
Synthesis of Polycyclic Spirocarbocycles via Acid-Promoted Ring-Contraction/Dearomative Ring-Closure Cascade of Oxapropellanes

Naoki Ogawa, Yousuke Yamaoka, Hiroshi Takikawa, and Kiyosei Takasu*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501 (Japan)

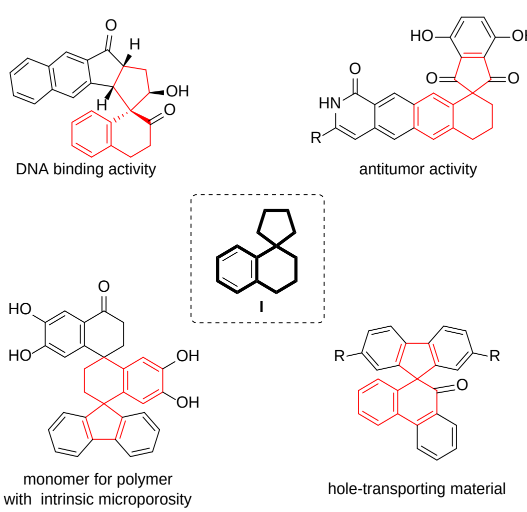
Supporting Information Placeholder



ABSTRACT: We report herein the development of an acid-promoted rearrangement of oxa[4.3.2]propellanes to afford polyaromatic-fused spiro[4.5]carbocycles. DFT calculations suggest that the reaction pathway involves generation of a cyclobutyl cation, ring-contraction to the cyclopropylcarbinyl cation, and dearomative ring closure by an internal 2-naphthol moiety. The resulting spirocarbocycles are synthetically valuable, as they could be transformed into two different polycyclic aromatic hydrocarbons via skeletal rearrangement. Syntheses of optically pure spirocarbocycles via a central-to-axial-to-central chirality transfer are also described.

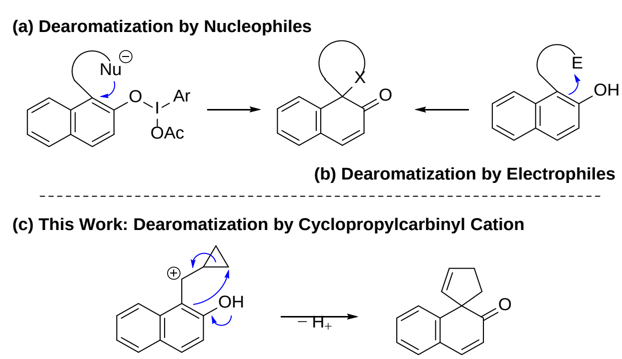
Among the many attractive spirocarbocycles, the benzospiro[4.5]decane skeleton (**I**) attracts considerable attention in a wide variety of research areas. A number of compounds possessing this skeleton in combination with polycyclic ring systems appear as biologically active compounds[1] and synthetic dyes[2] (Figure 1). They are also important as organic functional materials such as light-emitting diodes,[3] hole-transporting materials for solar cells,[4] and functional polymers.[5]

Figure 1. Representative Examples of Polycyclic Spirocarbocycles Possessing Benzospiro[4.5]decane Skeleton (I)



The advantages of this class of compounds, especially in materials science, is their rigid and stable and three-dimensional structures derived from the spirocyclic rings that enable the engineering of solid-state structures and properties.[6] In addition, their fused π-conjugation system is important for the luminescence and semiconducting properties of organic functional materials. Thus, developing new methods to prepare polycyclic spirocycles with benzospiro[4.5]decane skeletons is an important research objective in synthetic organic chemistry.

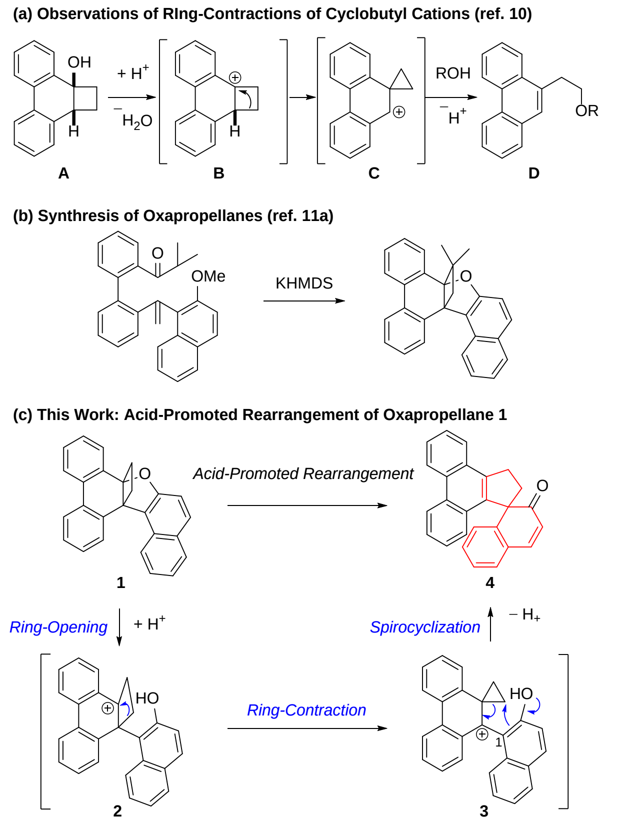
One rational approach to synthesizing this skeleton is the dearomative spirocyclization of naphthol compounds (Scheme



Scheme 1. Two Modes of the Dearomative Spirocyclization of Naphthols and the Strategy of This Work

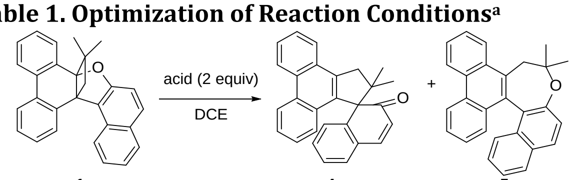
1). It is well known that heterocyclic spiro-compounds can be synthesized by intramolecular nucleophilic attack from an internal heteroatom to a naphthol moiety in the presence of a hypervalent iodine reagent (Scheme 1a).[7] However, utilization of this dearomatization strategy to give a carbocyclic spiro system like the benzospiro[4.5]decane skeleton is relatively limited. It has been shown that the elegant use of transition metal catalysts[8] enables the spirocyclization of β-naphthols to produce the benzospiro[4.5]decane skeleton. These methods utilized organometallic species as the electrophile and a naphthol ring as the nucleophile (Scheme 1b).[9] Herein, we wish to report a new strategy for the construction of the benzospiro[4.5]decane skeleton where naphthol ring is dearomatized by cyclopropylcarbinyl cation (Scheme 1c).

We previously reported that a cyclobutyl cation (**B**) generated from the corresponding cyclobutanol (**A**) underwent a ring-contraction rearrangement to form a cyclopropane intermediate (**C**), which reacted with external nucleophiles such as solvents and counteranions to form functionalized phenanthrenes (**D**) (Scheme 2a).[10] We also reported the synthesis of oxapropellanes **1** via a KHMDS-promoted domino [2+2] cycloaddition–S_NAr reaction of readily available biaryl compounds (Scheme 2b).[11] Based on these findings, we envisioned that oxapropellane **1** would be a viable precursor for the construction of a benzospiro[4.5]decane skeleton via dearomative spirocyclization (Scheme 2c): compound **1** would undergo C–O bond cleavage upon an acid treatment to form cyclobutyl cation **2** possessing a β-naphthol moiety, which would transform into cyclopropylcarbinyl cation **3** as a metastable intermediate by a ring-contraction rearrangement. If the cyclopropane ring of **3** reacts with the C1 carbon of the internal naphthol moiety, the desired benzo-fused



Scheme 2. Previous Work and Current Strategy toward Polycyclic Spirocarbocycles

Table 1. Optimization of Reaction Conditions[a]



1a 4a 5a

entry	acid	temp. (°C)	time (h)	**4a** % yield	**5a** % yield
1	TfOH	rt	2.0	75	22
2	TfOH	50	0.33	38	46
3	TfOH	−20	0.33	83	7
4	MsOH	rt	3.0	0	trace
5	BF_3OEt_2	rt	2.0	0	0
6	$B(C_6F_5)_3$	rt	5.5	31	15
7	$Ph_3C^+BF_4^-$	80	15	trace	19

[a]Reactions were performed with **1a** (0.050 mmol) and acid (2.0 equiv) in DCE (1.0 mL). Yields were determined by ^{1}H NMR of the crude reaction mixtures using Ph_3CH as an internal standard. TfOH = trifluoromethanesulfonic acid; MsOH = methanesulfonic acid; DCE = 1,2-dichloroethane.

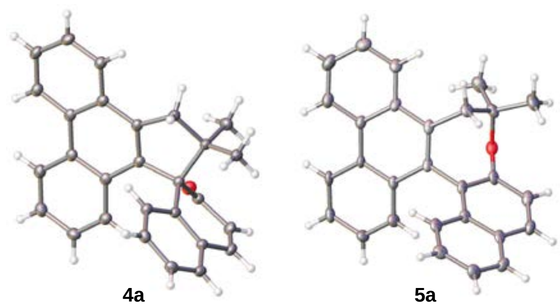


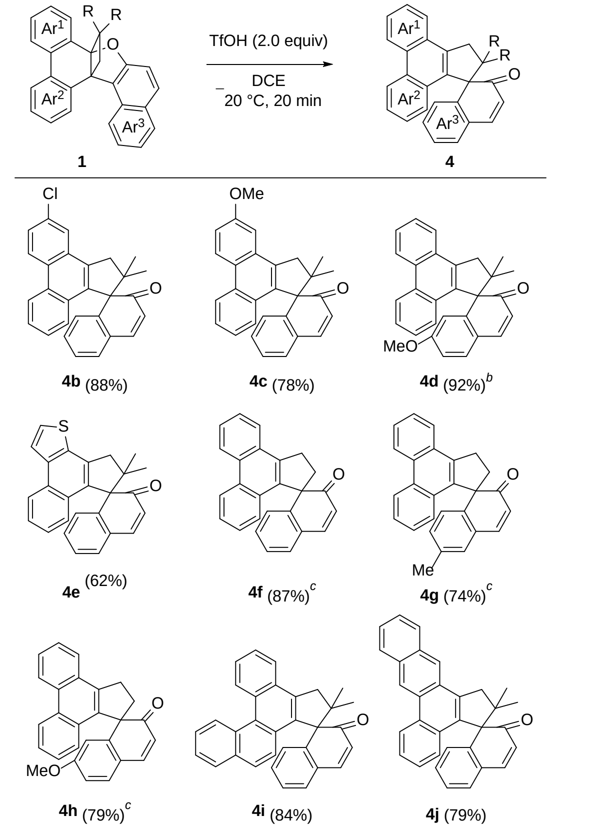
Figure 2. Crystal Structures of Compounds 4a and 5a. Thermal ellipsoids are shown at 50% probability.

spiro[4.5]decane **4** will be produced. It is well known that Friedel–Crafts (type) alkylations of alkyl cations with aromatics usually suffer from undesired hydride or alkyl group migrations due to the instability of the carbocations, leading to undesired products, mixtures of isomers, or both.[12] We envisaged that the utilization of cyclopropylcarbinyl cation intermediate **3** would overcome these side reactions thanks to the stabilization of the carbocation by the cyclopropane ring,[13] while having sufficient reactivity toward the naphthol ring owing to its high ring strain.

We first investigated the reaction of oxa[4.3.2]propellane **1a** by treatment with various acids (Table 1). The treatment of compound **1a** with TfOH at room temperature afforded the desired spirocarbocycle **4a** in 75% yield, albeit the undesired oxacycle **5a** was also formed in 22% yield (entry 1). The structures of these two compounds were unambiguously determined by X-ray crystallographic studies (Figure 2). Compound **4a** was formed by nucleophilic attack from the C1 carbon of the naphthol ring to the cyclopropane ring at the more substituted carbon atom, which is in accordance with reported regioselectivity.[14] Compound **5a** apparently formed via nucleophilic attack to the cyclopropane ring of intermediate **3** from the oxygen atom of the naphthol moiety instead of the carbon atom. The selectivity of products sifted toward oxacycle **5a** at a higher reaction temperature (entry 2). On the other hand, lowering the reaction temperature to −20 °C effectively improved the selectivity to give the desired compound **4a** in 83% yield (entry 3). MsOH, a weaker Brønsted acid, did not promote the spirocyclization of compound **1a**, and desired compound **4a** was not detected (entry 4). Lewis acids such as $BF_3{\bullet}OEt_2$, $B(C_6F_5)_3$, and $Ph_3C^+BF_4^-$ were not effective (entries 5–7).

With optimized reaction conditions in hand, the scope of the reaction was examined with attention to the reactivity dependence upon the substituent(s) and aromatic ring systems (Table 2). Both electron donating and withdrawing groups on the benzene ring (Ar^1) of substrates **1** were well tolerated, and the desired spirocycles **4b** and **4c** were obtained in high yields. An electron donating group on the naphthalene ring (Ar^3) was also tolerated, and compound **4d** was obtained in 92% yield. Incorporating a heteroaromatic ring system resulted in compound **4e** in 62% yield. In this case, oxacycle **5e** was also obtained in 31% isolated yield. The geminal dimethyl group on the oxapropellane was not essential; compounds **4f–h** lacking the *gem*-dimethyl group on the cyclopentane ring moiety could

Table 2. Scope of the Reaction[a]



[a]Reaction conditions; oxapropellanes **1** (0.10–0.20 mmol) and TfOH (2.0 equiv) in DCE (0.05 M) at −20 °C for 20 min. Isolated yields are given. [b]Reaction was carried out for 80 min. [c]Reaction was carried out at room temperature for 10 min.

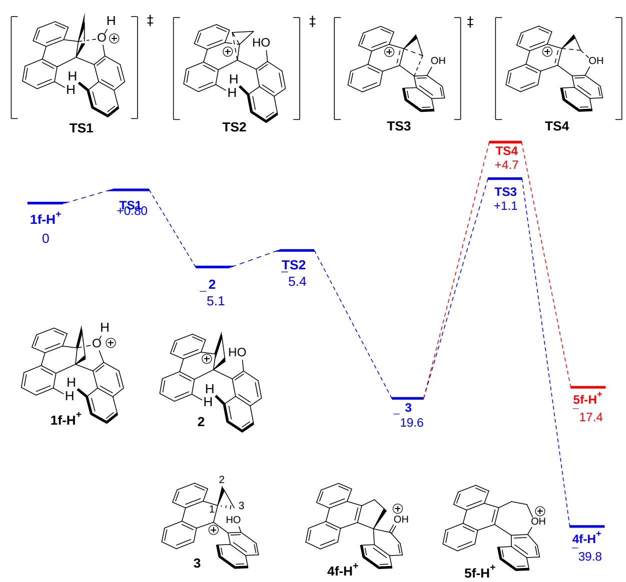
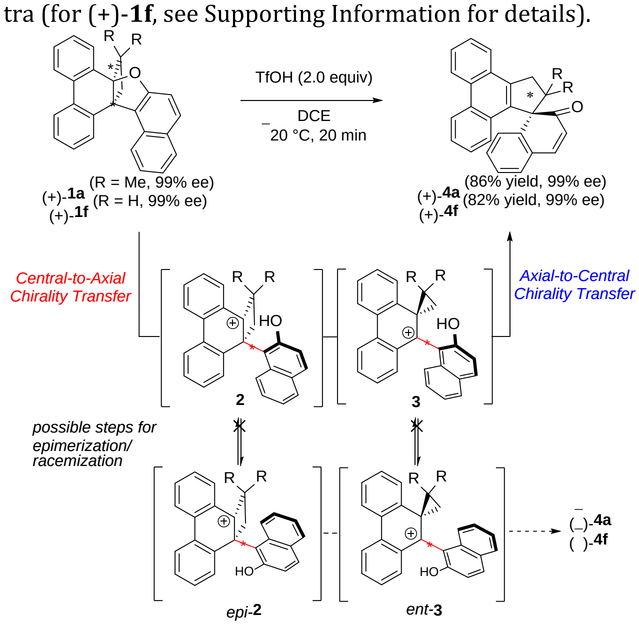


Figure 3. Computed Energy Profile for the Rearrangements of Oxapropellane 1f. Free Energies (kcal/mol) Calculated at mPW1PW91/6-311+G(2d,p)-CPCM(DCE)//B3LYP/6-31G(d,p)-CPCM(DCE) are Displayed.

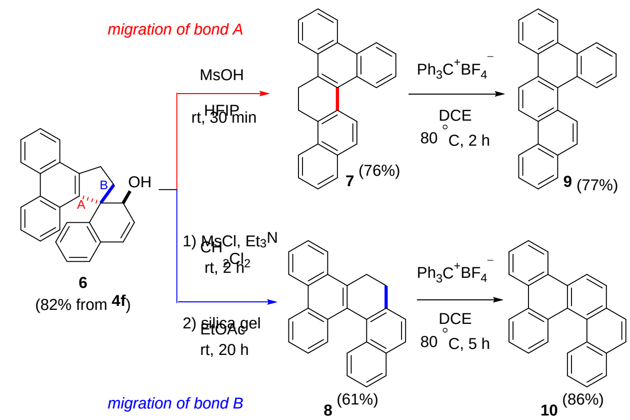
also be obtained in good to excellent yields by using a slightly higher reaction temperature. To our delight, reaction with a further extended π-system was also successful, affording compounds **4i** and **4j** in 84% and 79% yields, respectively.

DFT calculations were conducted to evaluate the working mechanistic hypothesis proposed in Scheme 2c (Figure 3). The calculationsuggested that in the presence of a Brønsted acid, oxapropellane **1** undergoes rapid ring-opening ($\Delta G^{\ddagger}$ = 0.80 kcal/mol) followed by essentially barrierless ring-contraction to form cyclopropylcarbinyl cation **3**. The single bonds of the cyclopropane ring adjacent to the carbocation, C1−C2 and C1−C3, are significantly longer (1.60 and 1.61 Å, respectively) than that of unsubstituted cyclopropane (1.51 Å),[15] which confirms that stabilization of the carbocation by the cyclopropane ring is effective in this case. The driving force of the rapid ring-opening/ring-contraction sequence is the release of the high ring strain of the propellane structure and the formation of a carbocation stabilized by the adjunct cyclopropane ring. The rate-determining step of the reaction is the key dearomative spirocyclization, whose activation free energy barrier was calculated to be 20.7 kcal/mol. The competitive nucleophilic attack from the oxygen atom to the cyclopropane ring of **3**, which affords oxacycle **5f**, was calculated to be disadvantageous by 3.6 kcal/mol.

We recognized that these rearrangements of oxapropellanes have great potential for the synthesis of optically active spirocycles via chirality transfer from starting materials **1** (Scheme 3) To examine this hypothesis, optically active (+)-**1a** (99% ee) was prepared by preparative chiral HPLC and subjected to the optimized reaction conditions. We were pleased to find that (+)-**4a** was obtained without any loss of optical purity. The chirality transfer from oxapropellane (+)-**1f** (99% ee) to compound (+)-**4f** was also successful. These results indicated that the epimerization/racemization by bond rotation along the chiral axis in intermediates **2** and **3**[16, 17] did not occur during the entire reaction cascade, realizing the sequential central-to-axial-to-central chirality transfer.[18–20] The absolute configurations of these compounds, shown in Scheme 3, were determined by X-ray crystallography (for (+)-**1a**, (+)-**4a** and (+)-**4f**) or CD spectra (for (+)-**1f**, see Supporting Information for details).



Scheme 3. Chirality Transfer in the Rearrangement of Oxapropellanes 1a and 1f



Scheme 4. Synthetic Transformations of Spirocarbocycle 4

Finally, the synthetic application of the spirocarbocycles prepared by this method was investigated. It was found that spirocarbocycles are attractive as synthetic intermediates for two different types of polycyclic aromatic hydrocarbons (PAHs) via bond-selective skeletal rearrangements (Scheme 4). 1,2-Reduction of the enone moiety of **4f** by Luche's method proceeded smoothly to give alcohol **6** in good yield. After screening several reaction conditions for the skeletal rearrangement of alcohol **6**, it was found that treatment with MsOH in hexafluoroisopropanol (HFIP) facilitated elimination of the OH group followed by bond-selective migration of the adjacent C_{sp3}−C_{sp2} bond (bond A) and rearomatization of the naphthalene ring to give compound **7** in 76% isolated yield along with 16% of minor product **8**. Oxidation of compound **7** gave benzo-fused picene **9**, which would be attractive as an organic field-effect transistor.[21] Alternatively, mesylation of alcohol **6** followed by treatment with silica gel in EtOAc resulted in the elimination of the OMs group and migration of the C_{sp3}−C_{sp3} bond (bond B) to afford compound **8** in 61% yield over two steps along with 9% of compound **7**. Oxidation of compound **8** afforded a helical PAH, benzo-fused [5]helicene **10**, whose unique structure and properties have attracted considerable attention in a variety of research areas.[22,23] These results highlight the synthetic utility of spirocycles **4** obtained by this method. Although the origin of the bond selectivity during the skeletal rearrangement is not yet fully clear, the elimination of the leaving group and migration of the C−C bond seemed to proceed in a stepwise rather than concerted manner under both reaction conditions, as the relative configuration of the OH group did not significantly affect the bond selectivity.[24]

In summary, an acid-promoted cascade ring-contraction/dearomative ring-closure reaction was developed to synthesize polycyclic spirocarbocycles. A variety of substituted and π-extended targets were obtained in high yields. Optically active spirocycles were also successfully synthesized via sequential central-to-axial-to-central chirality transfer. Bond-selective rearrangement of the reaction products highlighted the synthetic utility of the spirocycles obtained by this method.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publication website.

Supplementary figures, experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra (PDF)
Crystallographic data for compound (+)-**1a** (CIF)
Crystallographic data for compound **4a** (CIF)
Crystallographic data for compound (+)-**4a** (CIF)
Crystallographic data for compound (+)-**4f** (CIF)
Crystallographic data for compound **5a** (CIF)
Crystallographic data for compound **6** (CIF)
Crystallographic data for compound **7** (CIF)

AUTHOR INFORMATION

Corresponding Author

*kay-t@pharm.kyoto-u.ac.jp.

ORCID

Naoki Ogawa: 0000-0002-1120-7647
Yousuke Yamaoka: 0000-0003-3641-8823
Hiroshi Takikawa: 0000-0002-4414-2129
Kiyosei Takasu: 0000-0002-1798-7919

Notes

The authors declare no competing financial interest(s).

ACKNOWLEDGMENT

We thank JSPS KAKENHI Grant Number JP19H03350, JP19K22185, MEXT KAKENHI Grant Number JP18H04406 in Middle Molecular Strategy, and AMED Platform for Supporting Drug Discovery and Life Science Research (JP19am0101092j0003), and the Sasakawa Scientific Research Grant from The Japan Science Society. N.O. appreciates JSPS for a research fellowship for young scientists (JP19J14061).

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