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

AUTHOR(S):
Ogawa, Naoki; Yamaoka, Yousuke; Takikawa, Hiroshi; Takasu, Kiyosei

CITATION:

ISSUE DATE:
2019-09

URL:
http://hdl.handle.net/2433/244810

RIGHT:
This document is the Accepted Manuscript version of a Published Work that appeared in final form in 'Organic letters', copyright © American Chemical Society after peer review and technical editing by the publisher. To access the final edited and published work see https://doi.org/10.1021/acs.orglett.9b02835. The full-text file will be made open to the public on 9 September 2020 in accordance with publisher’s ‘Terms and Conditions for Self-Archiving’. This is not the published version. Please cite only the published version.
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 compounds¹ and synthetic dyes² (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 spirocyles 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

(a) Dearomatization by Nucleophiles

(b) Dearomatization by Electrophiles

(c) This Work: Dearomatization by Cyclopropylcarbinyl Cation
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). 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 enables the spirocyclization of \( \beta \)-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). 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). We also reported the synthesis of oxapropellanes via a KHMDS-promoted domino [2+2] cycloaddition-SNAr reaction of readily available biaryl compounds (Scheme 2b). Based on these findings, we envisioned that oxapropellane 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 \( \beta \)-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](image)

**Table 1. Optimization of Reaction Conditions**

<table>
<thead>
<tr>
<th>entry</th>
<th>acid</th>
<th>temp. (°C)</th>
<th>time (h)</th>
<th>4a % yield</th>
<th>5a % yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TfOH</td>
<td>rt</td>
<td>2.0</td>
<td>75</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>TfOH</td>
<td>50</td>
<td>0.33</td>
<td>38</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>TfOH</td>
<td>−20</td>
<td>0.33</td>
<td>83</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>MsOH</td>
<td>rt</td>
<td>3.0</td>
<td>0</td>
<td>trace</td>
</tr>
<tr>
<td>5</td>
<td>BF₃OEt₂</td>
<td>rt</td>
<td>2.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>B(C₆F₅)₃</td>
<td>rt</td>
<td>5.5</td>
<td>31</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>Ph₃C·BF₄⁻</td>
<td>80</td>
<td>15</td>
<td>trace</td>
<td>19</td>
</tr>
</tbody>
</table>

*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 Ph₃CH as an internal standard. TfOH = trifluoromethanesulfonic acid; MsOH = methanesulfonic acid; DCE = 1,2-dichloroethane.*
yield. The geminal dimethyl group on the oxapropellane moiety is consistent with reported regioselectivity. Compound 4a was formed by nucleophilic attack (Figure 2). Compound 4d was also obtained in 31% isolated yield in this case, oxacycle 5e was not essential; compounds 5a and desired compound 4a were obtained in high yields. An electron donating group on the naphthol moiety instead of the carbon atom. The selectivity of products shifted 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 BF₃-OEt₂, B(C₆F₅)₃, and Ph₃C⁺BF₄− 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 (Ar₂) 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 (Ar₃) 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 moiety was not essential; compounds 4f–h lacking the gem-dimethyl group on the cyclopentane ring moiety could 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.

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

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

**Table 2. Scope of the Reaction**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>Oxapropellanes 1 (0.10–0.20 mmol)</td>
<td>79%</td>
</tr>
<tr>
<td>4b</td>
<td>Oxapropellanes 1 (0.10–0.20 mmol)</td>
<td>88%</td>
</tr>
<tr>
<td>4c</td>
<td>Oxapropellanes 1 (0.10–0.20 mmol)</td>
<td>78%</td>
</tr>
<tr>
<td>4d</td>
<td>Oxapropellanes 1 (0.10–0.20 mmol)</td>
<td>92%</td>
</tr>
<tr>
<td>4e</td>
<td>Oxapropellanes 1 (0.10–0.20 mmol)</td>
<td>62%</td>
</tr>
<tr>
<td>4f</td>
<td>Oxapropellanes 1 (0.10–0.20 mmol)</td>
<td>87%</td>
</tr>
<tr>
<td>4g</td>
<td>Oxapropellanes 1 (0.10–0.20 mmol)</td>
<td>74%</td>
</tr>
<tr>
<td>4h</td>
<td>Oxapropellanes 1 (0.10–0.20 mmol)</td>
<td>79%</td>
</tr>
<tr>
<td>4i</td>
<td>Oxapropellanes 1 (0.10–0.20 mmol)</td>
<td>84%</td>
</tr>
<tr>
<td>4j</td>
<td>Oxapropellanes 1 (0.10–0.20 mmol)</td>
<td>79%</td>
</tr>
</tbody>
</table>

*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. *Reaction was carried out for 80 min. *Reaction was carried out at room temperature for 10 min.
DFT calculations were conducted to evaluate the working mechanistic hypothesis proposed in Scheme 2c (Figure 3). The calculations suggested that in the presence of a Brønsted acid, oxapropellane 1 undergoes rapid ring-opening (ΔG° = 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 adjacent cyclopropane ring. The rate-determining step of the reaction is the key deaminative spirocyclization, whose activation free energy barrier was calculated to be 20.7 kcal/mol. The competitive nucleophilic at- clization, whose activation free energy barrier 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 316,17 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).

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 hexafluoropropanol (HFIP) facilitated elimination of the OH group followed by bond-selective migration of the adjacent Csp3–Csp2 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 Csp3–Csp2 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/deaminative 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, ¹H and ¹³C NMR spectra (PDF)
Crystalllographic data for compound (+)-1a (CIF)
Crystalllographic data for compound 4a (CIF)
Crystalllographic data for compound (+)-4a (CIF)
Crystalllographic data for compound (+)-4f (CIF)
Crystalllographic data for compound 5a (CIF)
Crystalllographic data for compound 6 (CIF)
Crystalllographic 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: 0000-0003-6411-8823
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 (JP19am010192j0003), and the Sasakawa Scientific Research Grant from The Japan Science Society. N.O. appreciates JSPS for a research fellowship for young scientists (JP19j14061).

REFERENCES