



Synthesis of oxa[9]helicene derivatives by cyclodehydration of 1,1'-bibenzo[*c*]phenanthrene-2,2'-diol using phosphorus pentoxide

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ABSTRACT

A new one-step cyclization reaction has been established for the synthesis of oxa[9]helicene derivatives, containing eight ortho-condensed benzene rings and one furan ring. 1,1'-Bibenzo[*c*]phenanthrene-2,2'-diols (HEBPOLs) afforded the corresponding oxa[9]helicenes by refluxing with phosphorous pentoxide (P_2O_5) in *o*-dichlorobenzene. Enantiomerically pure oxa[9]helicenes were also synthesized with retention of the configuration and enantiopurity (>98% ee) from the corresponding enantiomerically pure HEBPOLs.

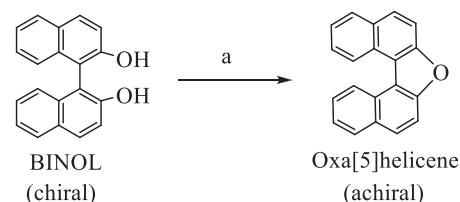
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Introduction

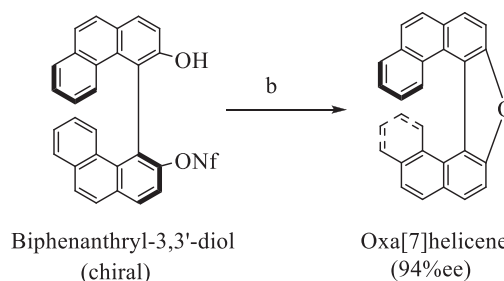
Helicenes are polycyclic aromatic compounds composed of angularly annulated benzene rings, which contain inherent torsional strain because of their helical structure. In the past decade, many helicenes [1] and related molecules, such as aza-[2] and thia-helicenes [3], have been developed because of their extraordinary and unique property, i.e., helical chirality in combination with unique π -electron systems, which makes them highly attractive for application in various fields of science. However, less attention has been paid to oxa[*n*]helicenes, which are oxygen-containing heterocyclic derivatives [4]. In recent decades, there have been many reports on synthetic methods for oxa[*n*]helicene derivatives, and many organic chemists have been interested in the syntheses and applications of these compounds. For example, a series of oxahelicene-like molecules were synthesized by cobalt (I)-mediated [2 + 2 + 2] cycloisomerization of branched oxygen-containing aromatic alkynes, similar to the previously reported carbohelicene derivatives [5].

The cyclodehydration of poly-condensed 2,2'-bisphenol derivatives is considered one of the most potent and attractive methods for the syntheses of oxahelicene derivatives with helical condensed structures. Although several oxahelicene derivatives have been synthesized by this method [6], there has been no reported example of obtaining optically active oxahelicene derivatives with helical chirality from axially chiral bisphenol derivatives. Indeed, BINOLs have axial chirality, but the corresponding oxa[5]helicene

A: Zhang's work



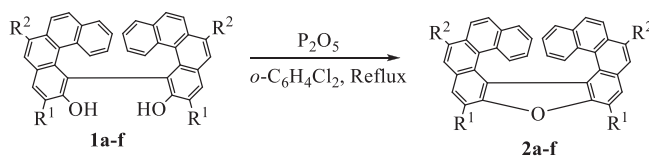
B: Nozaki's work



Scheme 1. Reported example of synthesis of oxahelicene derivative by furan ring formation. (a) HY-zeolite, *o*-dichlorobenzene; (b) $Pd_2(dba)_3 \cdot CHCl_3$, diphenyl phosphine, K_3PO_4 , 100 °C, 123 h.

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Table 1Screening and synthesis of oxa[9]helicenes (**2**) through dehydration of HEBPOLs (**1**).

| Entry ^a | Substrate | Solvent | Reagents ^b | Product/%Yield ^c |
|--------------------|---|---|--|-----------------------------|
| 1 | 1a (R ¹ , R ² = H) | CHCl ₃ | <i>p</i> TSA | 2a /0 |
| 2 | 1a (R ¹ , R ² = H) | CHCl ₃ | TfOH | 2a /0 |
| 3 | 1a (R ¹ , R ² = H) | toluene | <i>p</i> TSA | 2a /0 |
| 4 | 1a (R ¹ , R ² = H) | toluene | TfOH | 2a /trace |
| 5 | 1a (R ¹ , R ² = H) | toluene | P ₂ O ₅ | 2a /trace |
| 6 | 1a (R ¹ , R ² = H) | <i>o</i> -xylene | <i>p</i> TSA | 2a /0 |
| 7 | 1a (R ¹ , R ² = H) | <i>o</i> -xylene | TfOH | 2a /22 |
| 8 | 1a (R ¹ , R ² = H) | <i>o</i> -xylene | P ₂ O ₅ | 2a /38 |
| 9 | 1a (R ¹ , R ² = H) | <i>o</i> -C ₆ H ₄ Cl ₂ | <i>p</i> TSA | 2a /12 |
| 10 | 1a (R ¹ , R ² = H) | <i>o</i> -C ₆ H ₄ Cl ₂ | TfOH | 2a /53 |
| 11 | 1a (R ¹ , R ² = H) | <i>o</i> -C ₆ H ₄ Cl ₂ | PPA ^d | 2a /8 |
| 12 | 1a (R ¹ , R ² = H) | <i>o</i> -C ₆ H ₄ Cl ₂ | P ₂ O ₅ ^b | 2b /trace |
| 13 | 1a (R ¹ , R ² = H) | <i>o</i> -C ₆ H ₄ Cl ₂ | P ₂ O ₅ | 2a /84 |
| 14 | 1b (R ¹ = Me, R ² = H) | <i>o</i> -C ₆ H ₄ Cl ₂ | P ₂ O ₅ | 2b /72 |
| 15 | 1c (R ¹ = Et, R ² = H) | <i>o</i> -C ₆ H ₄ Cl ₂ | P ₂ O ₅ | 2c /69 |
| 16 | 1d (R ¹ = ^{<i>i</i>} Bu, R ² = H) | <i>o</i> -C ₆ H ₄ Cl ₂ | P ₂ O ₅ | 2d /67 |
| 17 | 1e (R ¹ = H, R ² = Br) | <i>o</i> -C ₆ H ₄ Cl ₂ | P ₂ O ₅ | 2e /76 |
| 18 | 1f (R ¹ = H, R ² = Ph) | <i>o</i> -C ₆ H ₄ Cl ₂ | P ₂ O ₅ | 2f /74 |

^a All the reactions were conducted at reflux conditions for 12–24 h.^b All the reagents were used in 4 equivalents. In entry 12, 1 equivalent of P₂O₅ was used. ^c Isolated yield. ^d PPA: polyphosphoric acid (containing ca. 15% of water).

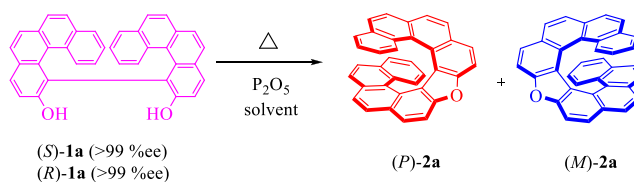
derivatives do not have sufficient stability to retain their helical chirality [4c,6a] (Scheme 1, A). In addition, these reactions require relatively high temperatures, such as those achieved from refluxing in *o*-dichlorobenzene. Therefore, when this method is adopted for the synthesis of higher-order oxa[*n*]helicene derivatives with more stable helical [7] chirality, determining whether the helical chirality could be maintained under these reaction conditions is an important issue.

A solution to this problem has been reported by Nozaki et al. [7] One hydroxy group was nonafluorobutansulfonated and then O-arylated by using a palladium catalyst to obtain an oxa[7]helicene derivative. This reaction successfully suppressed racemization by proceeding at 100 °C, but it took a longer reaction time of 123 h (Scheme 1, B). In our previous studies, we achieved the synthesis of oxa[9]helicenes by the reaction of benzofused-2,2'-diphenylquinone derivatives using Lawesson's reagent [8], phosphorus pentasulfide [8], alcohols [9], thiols [10], and some halogenating

reagents [11]. As an extension of these studies, we have explored the reactivity of helical 1,1'-bibenzo[*c*]phenanthrene-2,2'-diols (HEBPOLs) **1a-f** in racemic as well as in enantiomerically pure forms. The starting HEBPOLs **1a-f** were synthesized by oxidative coupling of 2-hydroxybenzo[*c*]phenanthrenes using CuCl(OH)-TMEDA, followed by reduction [12]. The enantiomerically pure (>99% ee) HEBPOLs **1a-f** were obtained via diastereomeric separation using HPLC, with subsequent hydrolysis of the diastereomers [13]. Herein we present a new one-step approach to the preparation of oxa[9]helicenes **2a-f** by furan ring formation via dehydrocyclization of racemic and enantiomerically pure **1a-f**.

Results and discussion

First, we investigated the dehydrocyclization of non-substituted HEBPOL **1a** with Brønsted acids, such as *p*-toluene sulfonic acid (*p*TSA) and trifluoromethane sulfonic acid (TfOH). The former is

Table 2Syntheses of optically active oxa[9]helicene derivatives (*P*)- and (*M*)-**2a**.

| Entry ^a | Substrate | Solvent | Temp | % Yield ^b / %ee of 2a ^c (Config.) |
|--------------------|-------------------------|---|--------|--|
| 1 | (<i>S</i>)- 1a | <i>o</i> -C ₆ H ₄ Cl ₂ | Reflux | 85/22 (<i>P</i>) |
| 2 | (<i>S</i>)- 1a | <i>o</i> -C ₆ H ₄ Cl ₂ | 160 °C | 63/74 (<i>P</i>) |
| 3 | (<i>S</i>)- 1a | C ₆ H ₅ Cl | Reflux | 22/>98 (<i>P</i>) |
| 4 | (<i>R</i>)- 1a | <i>o</i> -C ₆ H ₄ Cl ₂ | Reflux | 87/23 (<i>M</i>) |
| 5 | (<i>R</i>)- 1a | <i>o</i> -C ₆ H ₄ Cl ₂ | 160 °C | 62/73 (<i>M</i>) |
| 6 | (<i>R</i>)- 1a | C ₆ H ₅ Cl | Reflux | 20/>98 (<i>M</i>) |

^a The reactions of entries 1 and 4 were conducted for 12 h, entries 2 and 5 for 72 h, and entries 3 and 6 for 96 h.^b Isolated yield.^c %ee was determined by analytical HPLC (column: Chiralpak IB®, mobile phase: TBME, flow rate: 0.8 ml/min, 310 nm).

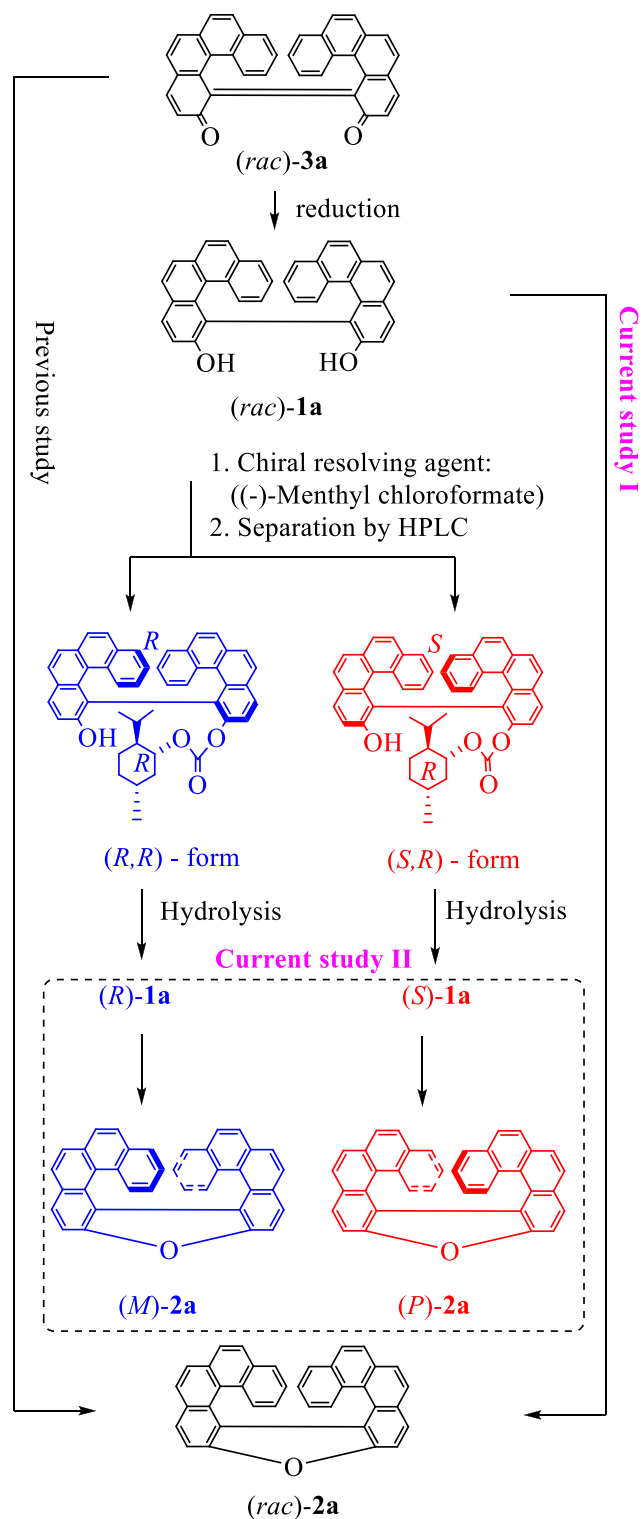
the most commonly used catalyst in the cyclodehydration reaction of BINOL derivatives. The use of relatively low-boiling solvents, such as CHCl_3 and toluene, did not give the desired product **2a** in a usable yield. (Table 1, entries 1–4). Despite conducting the reaction with *p*TSA in *o*-xylene, **2a** was not also obtained (Table 1, entry 6), while with TfOH, **2a** was obtained in 22% yield (Table 1, entry 7). When phosphorus pentoxide (P_2O_5) was used, **2a** was produced in a slightly higher yield of 38% (Table 1, entry 8). When toluene and *o*-xylenes were used as solvent, use of P_2O_5 gave higher yields of **2a** than the use of *p*TSA and TfOH (entries 4–8). This tendency became more remarkable when the reaction was conducted in *o*-dichlorobenzene, where **2a** was obtained in the maximum yield of 84% (Table 1, entry 13). On the other hand, when polyphosphoric acid (PPA) was used in place of P_2O_5 for comparison, **2a** was obtained in 8% yield. (entry 11). In addition, with 1 equivalent of P_2O_5 only a trace amount of **2a** was obtained (entry 12). Therefore, considering all the screenings, it was found that it is necessary to use an excess amount of P_2O_5 . Under these optimized reaction conditions, other substituted HEBPOLS **1b–f** also reacted successfully to give **2b–f** respectively, in fairly good yields (Table 1, entries 14–18) [14].

The obtained compounds **2a–f** were characterized by ^1H NMR and ^{13}C NMR spectroscopic studies. The structure of oxa[9]helicene **2a** was confirmed by X-ray diffraction analysis, as reported in our previous manuscript [8]. Based on the above results, we planned to synthesize enantiomerically pure oxa[9]helicene (*P*)- and (*M*)-**2a** by dehydrocyclization of enantiomerically pure 1,1'-bibenzo[*c*]phenanthrene-2,2'-diols (HEBPOLs) (*S*)- and (*R*)-**1a**, which were obtained by diastereomeric separation of HEBPOLS, followed by hydrolysis, according to our previously reported methods [13]. After obtaining both enantiomerically pure HEBPOL derivatives, viz. (*S*)- and (*R*)-**1a**, we conducted dehydrocyclization using (*S*)-**1a** as the starting substrate under the same reaction conditions and obtained the expected oxa[9]helicene (*P*)-**2a** in excellent yield (85%). Unfortunately, the resulting oxa[9]helicene **2a** was not enantiomerically pure and showed only 22% enantiomeric excess (ee). This was demonstrated by stereochemical studies using a chiral-phase column (Chiralpak IB[®]; mobile phase: TBME = 100%) (Table 2, entry 1) [15].

The reaction was then performed at a slightly lower temperature of 160 °C, without changing any other conditions, to suppress the racemization of (*S*)-**2a**. The reaction remained incomplete even after 72 h, and gave an isolated yield of 63%. Interestingly, an increase in the enantiomeric excess (74% ee) of (*P*)-**2a** was observed (Table 2, entry 2). This indicated that if the reaction can be carried out at lower temperatures, the desired compounds could be synthesized in enantiomerically pure forms. To confirm this hypothesis, the same reaction was conducted in refluxed chlorobenzene ($\text{C}_6\text{H}_5\text{Cl}$) under the same reaction conditions. Fortunately, the enantiopurity of the resulting product (*P*)-**2a** was approximately equal (>98% ee) to that of the starting substrate (>99% ee). However, the isolated yield was very low (22%), and most of the starting substrate (*S*)-**1a** remained unreacted even after 96 h (Table 2, entry 3).

Similar trends in isolated yield and enantiopurity were observed in the formation of (*M*)-**2a** from (*R*)-**1a** (Table 2, entries 4–6). Both the enantiomerically pure (*S*)-**1a** and (*P*)-**2a** were refluxed in *o*-dichlorobenzene for 12 h to investigate the cause of the decrease in the enantiomeric excess. In the case of (*P*)-**2a**, no decrease in the enantiomeric excess was observed, whereas, in the case of (*S*)-**1a**, it decreased to 20%ee. Therefore, it is clear that loss in the enantiomeric excess of the formed (*P*)-/(*M*)-**2a** was due to the low thermal stability of (*S*)-/(*R*)-**1a**.

In a previous paper, we have already reported the syntheses of oxa[9]helicene derivatives by deoxygenative cyclization reaction of benzofused-2,2'-diphenylquinones **3a** in racemic form [8]



Scheme 2. Syntheses of enantiomerically pure and racemic oxa[9]helicene derivatives 2.

(Scheme 2). On the other hand, enantiomerically pure HEBPOLS ((*S*)- and (*R*)-**1a**) used in this study were also obtained as synthetic intermediates in the previously reported procedure for obtaining enantiomerically pure quinones **3a** (oxidized forms of (*R*)- and (*S*)-**1a**). [12a] Therefore, the synthesis protocol described herein successfully provided both (*P*)- and (*M*)-**2a** in enantiomerically pure forms (Scheme 2). The absolute configurations of (*S*)- or (*R*)-

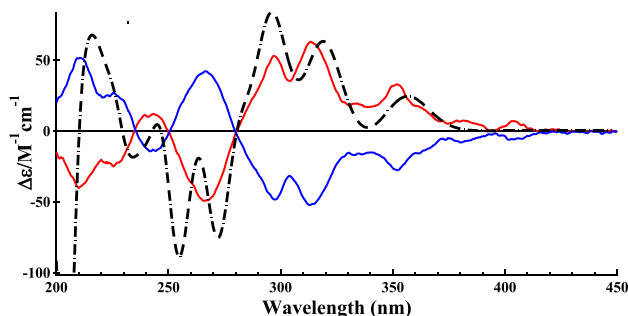


Fig. 1. Experimental and calculated ECD of **2a** in MeCN. ((*P*)-**2a** (7.75×10^{-6} M, red line), (*M*)-**2a** (7.64×10^{-6} M, blue line)). The spectra calculated by TD-DFT calculations (CAM-B3LYP/6-311G(2d,2p) for (*P*)-**2a** (dotted line) has been multiplied a scale factor of 0.29.

Table 3

Optical Rotation (OR) values of (*P*)- and (*M*)-**2a**.

| Entry | Compound | Con. / (M) ^a | Specific OR [α] _D ²⁵ | Molar OR [Φ] ^b |
|-------|-------------------------|-------------------------|---|----------------------------------|
| 1 | (<i>P</i>)- 2a | 1.13×10^{-2} | +2087 ^a | +9778 |
| 2 | (<i>M</i>)- 2a | 1.12×10^{-2} | −1907 ^a | −8935 |

^a Solution prepared in MeCN for [α]_D²⁵ measurement ($\lambda = 589$ nm).

^b Molar Optical Rotation, [Φ] = $10^{-2} \times [\alpha]_D \times M_w$

1a (HEBPOLs) were unequivocally assigned by analysis of an X-ray structure of the related diastereomer containing the (−)-menthyl moiety as the internal standard [13].

Therefore, the configurations of the produced **2a** were assigned as (*P*)-**2a** and (*M*)-**2a**, respectively, based on the retention of the configuration of **1a**. Furthermore, the observed pattern of the ECD spectrum of (*P*)-**2a** is similar to the calculated one of (*P*)-**2a**; thus, we conclude that (*S*)- and (*R*)-**1a** were converted to (*P*)- and (*M*)-**2a** respectively. The ECD spectra of (*P*)-/(*M*)-**2a** are shown in Figure 1. The optimization by B3LYP/6-31G(d) and the following TDDFT calculations were performed with Gaussian 16 [16] at the CAM-B3LYP/6-311G(2d,2p) level with the IEFPCM solvent model for acetonitrile. The optical rotation value of (*M*)-**2a** ($[\alpha]_D^{25} = -1907$) was almost identical to the reported one ($[\alpha]_D^{19} = -2647.2$) [4a] (Table 3). These values are smaller than that of all-benzenoid[9]helicene ($[\alpha]_D^{25} = 8100$) [17].

Conclusion

In summary, a new and simple one-step process has been developed to synthesize oxo[9]helicene derivatives **2a-f** by cyclodehydration of 1,1'-bibenzo[*c*]phenanthrene-2,2'-diols (HEBPOLs) using P₂O₅ as a dehydrating agent in refluxing *o*-dichlorobenzene. Enantiomerically pure (*P*)- and (*M*)-**2a** were also synthesized from substrates (*S*)- and (*R*)-**1a**, respectively, with retention of configuration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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- [14] General preparation method for 11-oxa[9]helicenes (**2a-f**): A Starting 1,1'-bibenzo[*c*]phenanthrene-2,2'-diol (HEBPOLs) **1** (0.05 mmol) were transferred in a round bottom flask with dehydrating agent (P₂O₅) in *o*-dichlorobenzene. The reaction mixture was then refluxed for 12–24 hours. After completion of the reaction, the solvent was evaporated, and the crude mixture was passed through a normal phase column chromatography, where chloroform (CHCl₃) was used as eluting solvent to obtain pure 11-oxa[9]helicenes (**2a-f**).
- [15] Enantiomeric excess (ee) of (*P*)- and (*M*)-**2a**: Determined by analytical HPLC (Chiralpak IB[®], tert-Butyl methyl ether 100%; flow rate 0.8 ml/min; 25 °C; 310

- nm) first peak: $t_{R1} = 5.88$ min for (M)-2a; second peak: $t_{R2} = 12.90$ min for (P)-2a.
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