Tetrahedron: *Asymmetry* 19 (2008) 1407–1410

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Synthesis and characteristic stereostructure of a biphenanthryl ether

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ARTICLE INFO

Article history:
Received 4 April 2008
Accepted 1 May 2008

This paper is dedicated to the late Professor Kiyoshi Tanaka, who passed away December 8, 2004

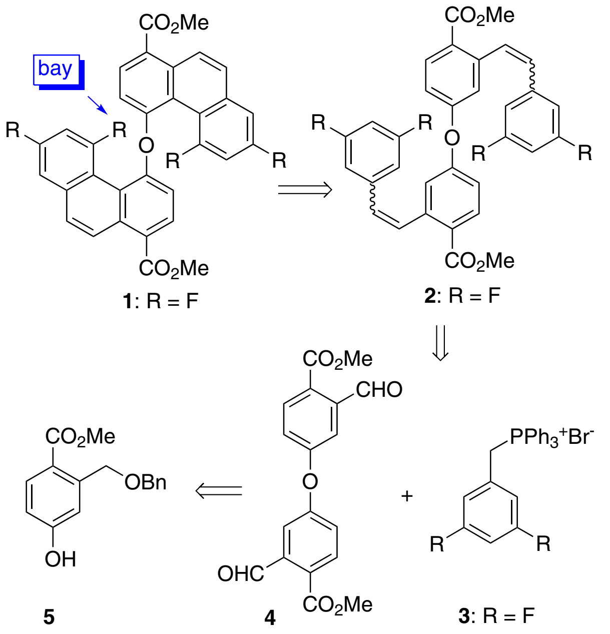
ABSTRACT

A biphenanthryl ether with substituents in the bay regions was efficiently synthesized for the first time. The unique stereostructure of **1** was clarified. Its twisted conformation and optical behavior as well as its characteristic supramolecular helical structure, which is constructed through a C–H···F hydrogen bonding network in the solid state, are discussed.

1. Introduction

Axially chiral compounds are promising resources for asymmetric synthesis and chiral recognition studies in host–guest chemistry. Among such compounds, chiral biaryls such as BINAP and BINOL are recognized as exceptionally powerful chiral inducers.[1] For these atropisomeric compounds, the chirality is generated by preventing bond rotation around the sp^2 carbon–sp^2 carbon single bond, which connects both naphthyl rings. On the other hand, biaryl compounds, which have two aromatic rings connected via a heteroatom, have not been well documented as axially chiral compounds. However, Fuji[2] and Clayden[3] have recently reported chiral binaphthyl and biphenyl ethers, respectively, in which an oxygen atom is present within the aryl rings. The restricted rotation of the sp^3 oxygen–sp^2 carbon single bond induces axial chirality in both these molecules.

During the course of our continuing studies on axially chiral molecules,[4] we have focused on using biaryl ether-type atropisomers to develop novel axially chiral compounds. For example, we have designed biphenanthryl ether **1**, a unique axially chiral molecule, by considering the π-face of the phenanthrene ring, which may construct a wide and relatively rigid chiral environment (Scheme 1). Moreover, we envisioned that the substituents (R) in the bay regions of both phenanthrene rings of **1** may enhance the rotational barrier around the C–O single bond. Among these derivatives,[5] **1** containing fluorine atoms gave crystals suitable for X-ray analysis. The analysis clearly demonstrates the unique chiral stereostructure, which includes both axial and helical chiralities. Herein, we report the synthesis and characteristic stereostructure of novel biphenanthryl ethers, which are promising candidates for unique axially chiral molecules.



Scheme 1. Retrosynthetic analysis of biphenanthryl ether **1**.

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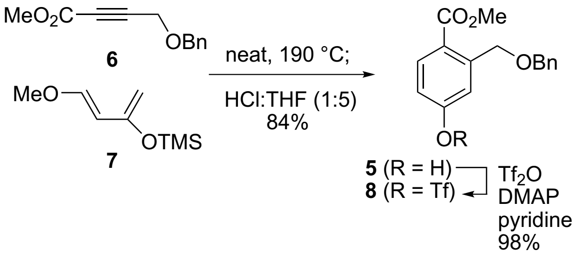
doi:10.1016/j.tetasy.2008.05.001

2. Results and discussion

Scheme 1 illustrates the heart of our synthetic plan. Because direct coupling of phenanthrol derivatives is difficult, the phenanthrene skeleton is constructed after preparing the bis-phenol ether. Moreover, because a photocyclization reaction[6] is a suitable method for preparing the phenanthrene ring, stilbene derivative **2** is an ideal intermediate. The double bond of stilbene **2** could be constructed by a Wittig reaction of **3** and **4**. The advantage of this method is that it easily provides diverse derivatives due to the ready availability of substituted benzyl halides, precursors of phosphonium salt **3**. Because the biphenyl ether **4** can be constructed according to Buchwald's protocol,[7] 3,4-disubstituted phenol **5** is a suitable starting material.

Disubstituted phenol **5** was prepared using an intermolecular Diels–Alder reaction (Scheme 2). Upon treatment of alkyne **6** and Danishefsky's diene **7**, the cycloadditon reaction proceeded smoothly in a regioselective manner. After an acidic work-up provided 3,4-disubstituted phenol **5** in good yield, the other coupling partner triflate **8** was prepared by treatment of **5** with trifluoromethanesulfonic anhydride in pyridine.



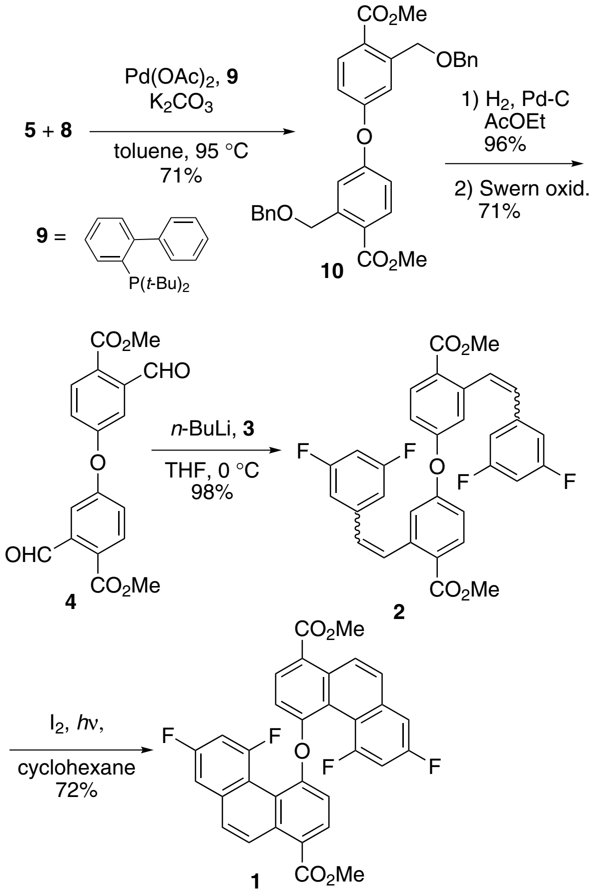
Scheme 2. Preparation of 2-substituted phenol **5** and triflate **8**.

The coupling reaction of phenol **5** and aryl triflate **8** was accomplished by Buchwald's protocol.[7] Upon treatment of **5** and **8** in the presence of a combination of $Pd(OAc)_2$ and ligand **9** catalyst with K_2CO_3 in toluene, the coupling reaction proceeded smoothly to provide desired symmetrical biphenyl ether **10** in 71% yield (Scheme 3).

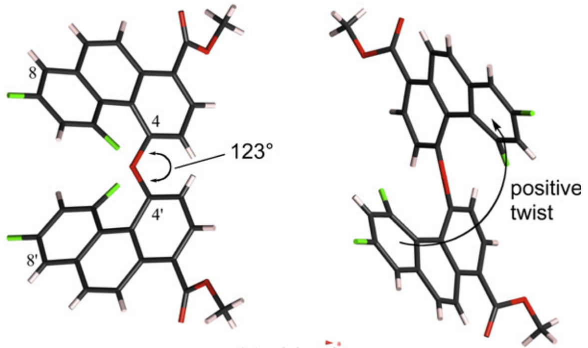
After removing the Bn ether of **10** under hydrogenolysis conditions, Swern oxidation of the corresponding diol gave aldehyde **4** in good yield. A benzyl-type ylide was generated by treatment with *n*-BuLi and phosphonium salt **3**, and subsequent subjection to aldehyde **4**. The Wittig reaction proceeded smoothly to provide stilbene derivative **2** as an *E*/*Z* mixture. The phenanthrene skeleton was efficiently constructed by photoirradiation of **2** in the presence of I_2, and a double cyclization–aromatization reaction proceeded smoothly to give desired biphenanthryl ether **1**.[8] To our surprise, the crystals of **1** exhibited an optically active form and a detailed analysis is discussed in the following paragraph.

The crystal structure clearly shows the positively twisted conformation of **1**[9] where the dihedral angle of both phenanthrene rings (C4,C8–C4′,C8′) is 64° (Fig. 1a and b). This observation indicates that the biphenanthryl ether can be an atropisomer if the C–O bond possesses a substantial rotational barrier. The bond angle of C4–O–C4′ in the biaryl ether moiety is 123° (Fig. 1a). Moreover, the phenanthrene rings themselves have helical chiralities due to the repulsion between the oxygen atom of the ether linkage and the substituent (F atom) in the bay positions (the torsion angle of C4′,C4a′–C4b′,C5′: 25°) (Fig. 1c). Therefore, each molecule has three chiral twists. These structural features might be promising for further applications of **1** as a chiral source for chiral recognition as well as in asymmetric synthesis.

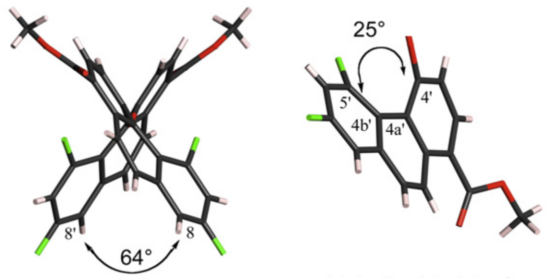
The space group (*C*2) indicates that the crystals are themselves chiral. Indeed, crystal packing clearly shows that the homo-chiral



Scheme 3. Preparation of biphenanthryl ether **1**.



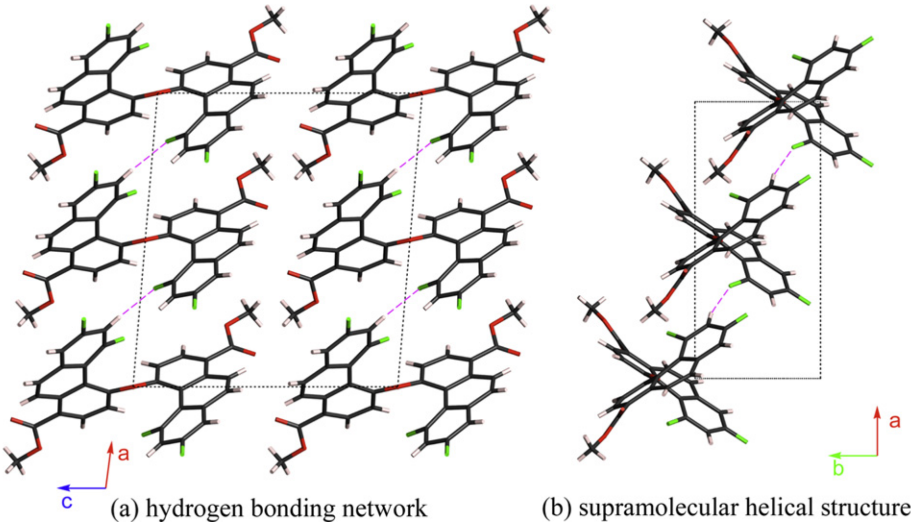
(a) side views



(b) top view

(c) helical twist of phenanthrene ring

Figure 1. Stereostructure of (*P*)-**1**.



(a) hydrogen bonding network

(b) supramolecular helical structure

Figure 2. Packing diagram of (*P*)-**1**.

molecules are self-assembled into optically active crystals (Fig. 2a). The hydrogen bonding network (red dotted line) between the acidic C–H by virtue of the neighboring F functional groups and the F atom in the bay region might play an important role in homo-chiral crystallization (Fig. 2a). Interestingly, the molecules, which are connected by C–H···F hydrogen bonding (H···F: 2.526 Å), form the supramolecular helical structure as shown in Figure 2b.

To clarify the optical behavior of **1**, CD was measured after dissolving the crystals in MeOH. However, the Cotton effect was not detected even at −100 °C.

On the other hand, obvious Cotton effects were observed in the solid state (Fig. 3).[10] The relationship between the sign of the Cotton effect and the stereostructure of **1**[9] affords a correlation of a negative Cotton effect (green color) and the positively twisted conformation of (*P*)-**1** as depicted in Figure 1.[11] Interestingly, both positive (blue color) and negative Cotton effects randomly appear with the crystals obtained from distinct trials of crystallization. This suggests that **1** asymmetrically crystallizes to give optically active crystals.[12]

Next, we investigated the activation energy of racemization of **1**. Due to the lack of apparent CD of **1** in solution, a dynamic NMR study of benzyl protected derivative **11**,[13] which was prepared by an ester exchange reaction of **1** with benzyl alcohol,

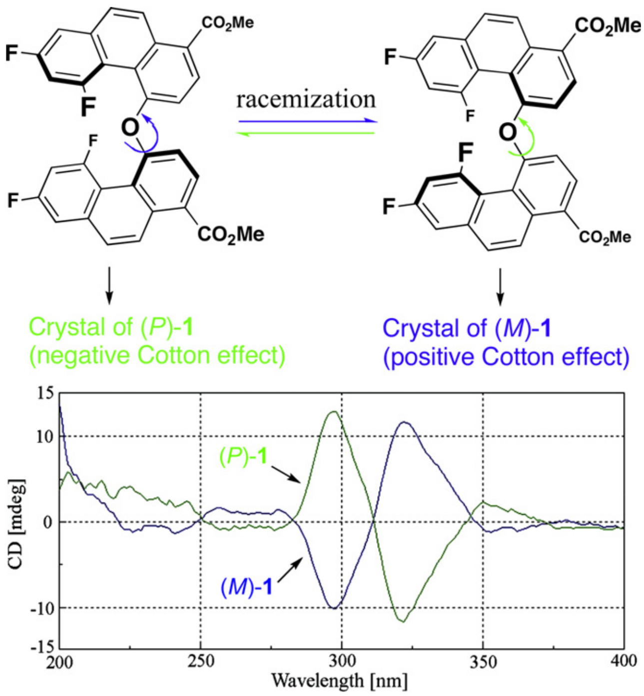


Figure 3. Solid-state CD spectra of the crystals of **1**.

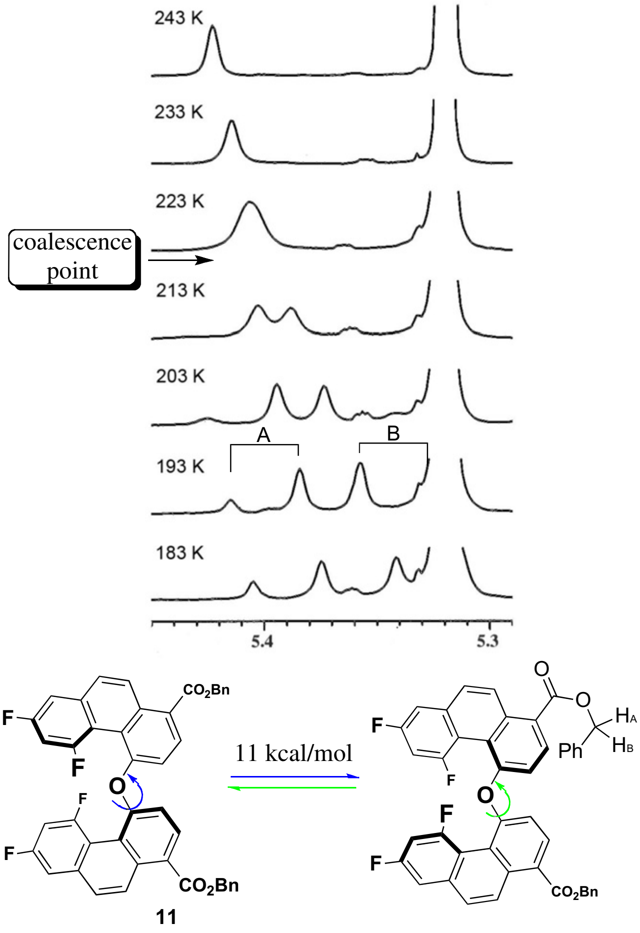


Figure 4. Dynamic NMR of **11**.

was carried out as shown in Figure 4. The calculated racemization barrier using a coalescence temperature of the prochiral benzyl protons (H_A and H_B) of −55 °C was 11 kcal/mol (Fig. 4).[14] This means that the C–O bond of **1** almost rotates freely, and the helical twist of the phenanthrene rings is rapidly inverting, which gives a smooth racemization in solution at ambient temperature. On the other hand, in solid state, the chirality is completely fixed to give optically active crystals.

The stereostructure of **1** is quite informative for designing novel stable atropisomeric derivatives. Moreover, **1** has appropriate functional groups such as methyl ester moieties as well as fluorine atoms for further chemical modifications. From these aspects, **1** should be a potential scaffold for developing chiral biphenanthryl ether derivatives.

3. Conclusions

In conclusion, novel chiral biphenanthryl ether derivatives were developed, and their unique stereostructure was clarified. The stereostructure presented here may be a useful structural basis to further develop chiral inducers and/or ligands using biphenanthryl ether frameworks. Further chemical modifications of **1** toward stable atropisomers are currently underway.

Acknowledgments

This work was financially supported by the SUNBOR Foundation, the Uehara Memorial Foundation, the 21st Century COE Program, and a Grant-in-Aid for Scientific Research on Priority Areas 17025011 from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan.

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5. We synthesized several biphenanthryl ether derivatives where the methyl groups in the bay positions were substituted. Detailed synthetic procedures will be described in due course.
6. For a review see: Mallory, F. B.; Mallory, C. W. *Org. React.* **1984**, *30*, 1–39.
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8. The CO_2Me groups of cyclization precursor **2** are essential for regioselective cyclization.
9. Crystallographic data for **1**: $C_{32}H_{18}F_4O_5$, $M = 558.48$, monoclinic, space group $C2$, $T = 298$ K, $a = 14.425(2)$ Å, $b = 6.5297(12)$ Å, $c = 12.973(3)$ Å, $\alpha = 90°$, $\beta = 94.773(14)°$, $\gamma = 90°$, $V = 1217.7(4)$ Å^3, $Z = 2$, $D = 1.259$ g/cm^3, λ (Cu Kα) = 1.54178 Å, $R = 0.0434$, $wR_2[F^2] = 0.1204$ for 2195 unique reflections. The absolute structure of **1** was determined by the Flack parameter method.
10. The KBr tablet (13 μg of **1** per 40 mg of KBr) was prepared for solid-state CD measurement.
11. This suggests that the exciton chirality method cannot simply be applied to biphenanthryl ether derivatives. Further investigation of this optical behavior are currently under way.
12. For examples of asymmetric crystallization (chiral transformation), see the following references and references cited therein: (a) Matsuura, T.; Koshima, H. *J. Photochem. Photobiol. C: Photochem. Rev.* **2005**, *6*, 7–24; (b) Sakamoto, M. *J. Photochem. Photobiol. C: Photochem. Rev.* **2006**, *7*, 183–196; (c) Azumaya, I.; Uchida, D.; Kato, T.; Yokoyama, A.; Tanatani, A.; Takayanagi, H.; Yokozawa, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 1360–1363; (d) Kato, T.; Okamoto, I.; Tanatani, A.; Hatano, T.; Uchiyama, M.; Kagechika, H.; Masu, H.; Katagiri, K.; Tominaga, M.; Yamaguchi, K.; Azumaya, I. *Org. Lett.* **2006**, *8*, 5017–5020.
13. *Experimental procedure for* **11**: To a stirred solution of **1** (50 mg, 0.0895 mmol) in toluene (6 ml) were added $Ti(O^iPr)_4$ (79 mg, 0.269 mmol) and BnOH (120 mg, 1.07 mmol). The reaction mixture was refluxed for 3 h using a Dean–Stark trap. The reaction was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexanes/EtOAc = 9:1) to give **11** (29.2 mg, 46%) as a pale yellow oil.
14. Dynamic NMR of methyl-substituted derivatives have been measured. However, the complexity of the spectra due to the presence of two different conformers at low temperature makes the calculation of the racemization barrier difficult.