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First determination of the absolute stereochemistry of a naturally occurring 1,1′-biphenanthrene, (−)-blestriarene C, and its unexpected photoracemization†

Tetsutaro Hattori,* Yuhi Shimazumi, Osamu Yamabe, Eiji Koshiishi and Sotaro Miyano*
Department of Biomolecular Engineering, Graduate School of Engineering, Tohoku University, Aramaki-Aoba 07, Aoba-ku, Sendai 980-8579, Japan. E-mail: hattori@orgsynth.che.tohoku.ac.jp; Fax: +81-22-217-7293; Tel: +81-22-217-7263

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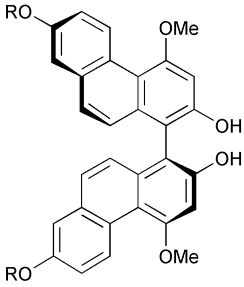
A naturally occurring 1,1′-biphenanthrene, blestriarene C, was prepared and its absolute stereochemistry was determined to be S_a-(−) by an empirical method, during which the compound was found to undergo rapid photoracemization even under ambient light exposure.

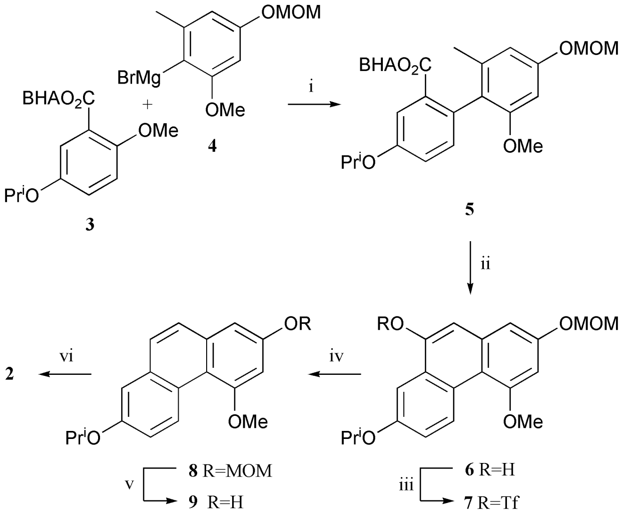
There are a certain number of 1,1′-biphenanthrene compounds, *e.g.* (−)-blestriarene C (cirrhopetalanthrin, **1**), isolated from orchids along with analogues having 9,10-dihydro- and 9,9′,10,10′-tetrahydro-1,1′-biphenanthrene frameworks.[1,2] These compounds generally possess at least three hydroxy and/or methoxy groups in total on each phenanthrene half, two being at the 2,2′-positions. Therefore, they may exist as nonracemic atropisomeric substances, as is the case for some of the isolated ones.[1a,d,2g] However, no studies have ever tried to determine their absolute stereochemistries, not to mention their single-enantiomer preparations. In this connection, we have recently reported that the CD exciton chirality method is not suitable for determining the axial chirality of 1,1′-biphenanthrenes,[3] although it is a well-known nonempirical method often applied to biaryl compounds.[4] We have set out to prepare such a biphenanthrene, (−)-blestriarene C (**1**),[1,5] which is reported to be active against gram-positive bacteria,[1a] and to determine its absolute stereochemistry by *the axial chirality recognition method* developed in this laboratory (*vide infra*).[6] During this study, we have found that blestriarene C undergoes rapid photoracemization even under ambient light exposure and thus the compound isolated from nature cannot be optically pure.



(S_a)-(−)-**1** R = H
(S_a)-(−)-**2** R = Pr^i

Racemic diisopropyl ether (**2**) of tetraol **1** was readily prepared as shown in Scheme 1. In previous papers,[7] we reported that ester function substantially activates an *ortho*-alkoxy group for nucleophilic aromatic substitution (S_NAr) reaction by various nucleophiles, which provides a convenient substitute for the oxazoline-mediated *ortho*-alkoxy displacement from aryloxazolines (the Meyers reaction).[8] The ester-mediated S_NAr protocol was applied to the reaction of 2,6-di-*tert*-butyl-4-methoxyphenyl (BHA) ester of 5-isopropyl-2-methoxybenzoic acid,[9] ester **3**, with a Grignard reagent **4** to give biphenyl **5** in excellent yield. It was reported that *N,N*-diethyl-2′-methylbiphenyl-2-carboxamide on treatment with LDA in THF gave the benzyl anion, which attacked intramolecularly to the carbonyl carbon to afford phenanthren-9-ol after spontaneous enolization of the resulting ketone.[10] The method was extended to the cyclization of ester **5**, by conducting in THF using 4.0 equiv. of LDA at room temperature according to the reported procedure to give phenanthrol **6** only in 12% yield. It was found, however, that utilization of HMPA as a cosolvent, in combination with lithium diethylamide as a base, significantly increased the product yield (88%) even at lower temperature. Reductive removal of the 9-hydroxy group of phenanthrol **6**, followed by deprotection of the 2-hydroxy moiety of the resulting phenanthrene **8**, gave phenanthrol **9**, which was oxidatively coupled in the presence of a copper(II) complex to give biphenanthrol **2**.[11]

The axial chirality recognition method predicts that two biaryl-*o,o*′-diyl units should have the same axial twist to form a 12-membered cyclic diester, *e.g.* compound **10**, because of the steric requirements imposed by the bulky and rigid components.[6] This provides a convenient method for recognizing axial chirality of a biaryl half of unknown stereochemistry by forming a cyclic diester with the other biaryl half of known axial chirality. This method was applied to determine the absolute stereochemistry of (−)-blestriarene C (Scheme 2). Thus, treatment of racemic biphenanthrol **2** with 1.0 equiv. of (R_a)-1,1′-binaphtharene-2,2′-dicarbonyl chloride in refluxing benzene–triethylamine in the presence of DMAP picked up only one enantiomer (R_a)-**2** among the racemate to allow cyclization



Scheme 1 *Reagents and conditions*: i, benzene, reflux, 24 h, 91%; ii, LiNEt$_2$, THF–HMPA (3:2), 0 °C, 2 h, 88%; iii, Tf$_2$O, NEt$_3$, CH$_2$Cl$_2$, −78 °C, 1.5 h, 96%; iv, HCO$_2$H, NEt$_3$, Pd(OAc)$_2$, PPh$_3$, DMF, 65 °C, 16.5 h, 96%; v, 1.5 mol dm^{-3} HCl, MeOH, 60 °C, 7 h, 93%; vi, 1-phenylethylamine, Cu(NO$_3$)$_2$·3H$_2$O, MeOH, rt, 4 h, 92%.

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† Electronic supplementary information (ESI) available: Spectral and physical data of compounds **2** and **5**–**10**. See http://www.rsc.org/suppdata/cc/b2/b207517b/

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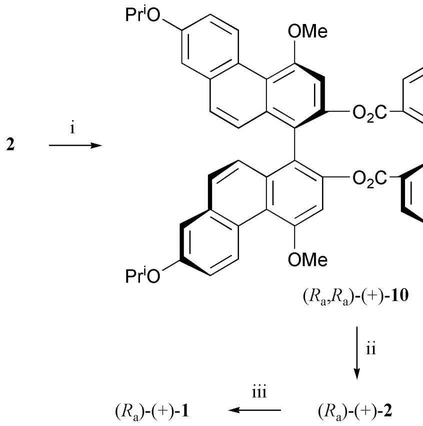

Scheme 2 *Reagents and conditions*: i, (R_a)-1,1′-binaphthalene-2,2′-dicarbonyl chloride, DMAP, NEt_3, benzene, reflux, 6 h, 10%; ii, $LiAlH_4$, THF, 0 °C, 15 min then rt, 3 h, 94%, 95% ee; iii, BCl_3, CH_2Cl_2, 0 °C, 2 h, 97%, 14% ee.

to give diastereomerically pure cyclic diester **10**, which should be R_a,R_a configuration. Reductive cleavage of diester **10** with $LiAlH_4$ gave dextrorotatory biphenanthrol **2** of 95% ee, which was then treated with BCl_3 to give tetraol **1** of the same sign. Thus, the absolute stereochemistry of tetraol **1**, as well as biphenanthrol **2**, was assigned to be R_a-(+). Therefore, naturally occurring (−)-blestriarene C should have S_a configuration.

To our surprise, the optical purity of tetraol **1** thus obtained was found to be only 14% ee as judged by a chiral HPLC analysis, which was ascribed to photoracemization (*vide infra*). Optical resolution of racemic tetraol **1** could be achieved by HPLC on a preparative scale using a cellulose-derived chiral column (Daicel Chiralpak AD, 250 mm × 20 mm i.d.) with hexane–ethanol (1:1) as the eluent, which gave several ten milligram yields of both of the enantiomers in up to 95% ee.

Fig. 1 shows a decrease in the optical purity of tetraol **1** under fluorescent lamp illumination.‡ The reaction followed first-order kinetics, the apparent rate constant k_{rac} under the conditions being 1.90×10^{-4} s^{-1}. No side products were detected by HPLC and the racemization was completely suppressed under dark. Diisopropyl ether **2** also had a tendency toward the racemization ($k_{rac} = 1.07 \times 10^{-6}$ s^{-1}) (Fig. 1), while 1,1′-biphenanthrene-2,2′-diol did not. Biaryl compounds have been reported to racemize under strong UV irradiation by several reaction mechanisms. For example, 1,1′-binaphthalene reportedly racemizes through its triplet excited state where the rotation barrier of the biaryl axis is diminished compared to that in its ground state,[12] 5*H*-dibenzo[*b*,*d*]pyrans through biaryl quinone methides,[13] 1,1′-binaphthalene-2,2′-diol through an intermediate formed by intramolecular addition of 2′-hydroxy group to the C_2–C_3 bond,[14] and so on. However, these mechanisms seem not to explain the marked tendency of the present compounds toward racemization. The importance of the presence of a 7-hydroxy or alkoxy substituent may suggest that the reaction proceeds *via* quinone-like intermediates.

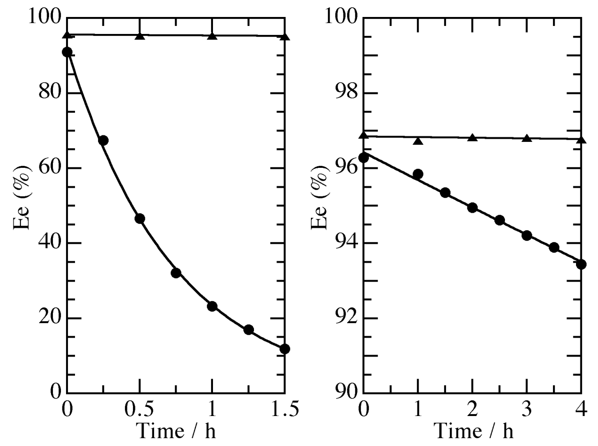

Fig. 1 Racemization of (−)-blestriarene C (left) and its diether (−)-**2** (right) under fluorescent lamp illumination (●) or dark (▲).

It should be noted that a sample of tetraol (−)-**1** showed an $[\alpha]_D^{28}$ value of −101.6 in methanol (*c* 0.525), while its optical purity was estimated to be 95–92% ee by HPLC analyses conducted before and after the rotation measurement. Therefore, naturally occurring (−)-blestriarene C, the specific rotation of which was reported to be −16.7,[1a] seems to have partially racemized during isolation from the plant. Further studies on the photoracemization mechanism are in progress.

Notes and references

‡ A solution of a nonracemic biphenanthrene (120 μmol dm^{-3} in ethanol) in a quartz cuvette (10 × 10 mm) was placed 15 cm behind a 18 W fluorescent lamp (Hitachi, FL20SS N/18-B) at 22 °C under air and a decrease in the enantiomeric purity of the sample was monitored by HPLC.

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