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Synthesis of 2-acetoxy[5]helicene by sequential double aromatic oxy-Cope rearrangement

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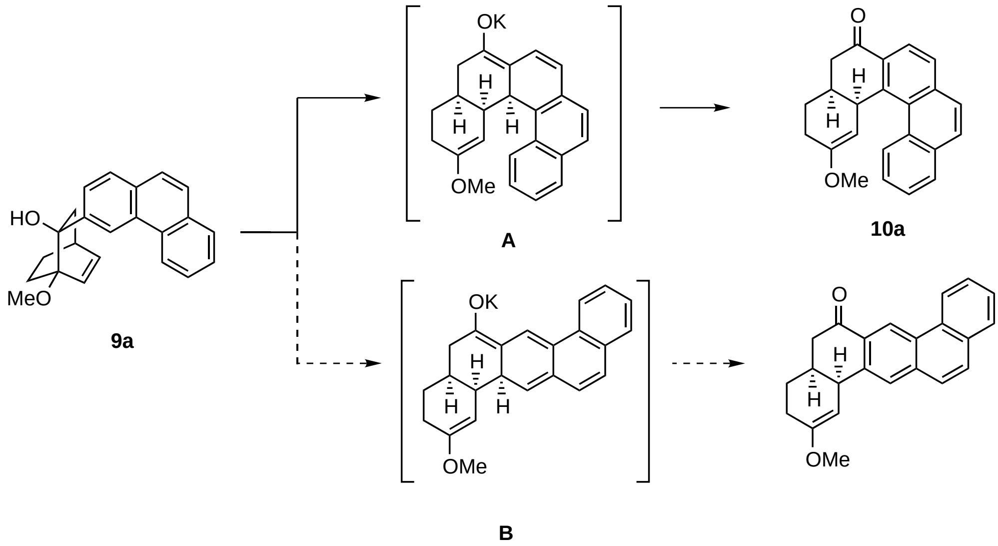
Abstract—Synthesis of 2-acetoxy[5]helicene has been achieved by sequential double aromatic oxy-Cope rearrangement strategy. Combination of 1-methoxybicyclo[2.2.2]oct-5-en-2-one and *p*-bromophenylmagnesium bromide gave 3-bromophenanthrene through several steps including an aromatic oxy-Cope rearrangement as a key step. The second oxy-Cope rearrangement and the following transformation gave 2-acetoxy[5]helicene by similar procedure. © 2002 Elsevier Science Ltd. All rights reserved.

Helicenes are known as helical compounds consisting of *ortho*-fused aromatic rings, which are considered as potentially useful[4] for asymmetric molecular recognition,[1] and as asymmetric catalyst[2] and liquid crystal molecule.[3] In addition, there has been lately a growing interest in their optical properties, caused by unique twisted nonplanar π-electron systems. The most practical and widely used route to the synthesis of these compounds is the photocyclization of stilbenes.[5] These reactions, however, are usually carried out in diluted conditions, which impeded production in large quantity. Although several non-photochemical approaches have been investigated, for example, Diels–Alder reaction of *p*-benzoquinone,[6] intramolecular McMurry reaction, intramolecular Friedel–Crafts reaction,[7] and so on, general and efficient approaches are still scarce.



Scheme 1. Aromatic oxy-Cope rearrangement of bicyclo[2.2.2]octene derivative **9a**.

Keywords: aromatization; bridged bicyclic compound; aromatic oxy-Cope rearrangement; helicenes.

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We have previously reported a novel oxy-Cope rearrangement of benzene derivatives, the so-called aromatic oxy-Cope rearrangement.[8] In the course of this research, we wondered if the oxy-Cope products could be transformed into fused aromatic compounds resulting in the formation of a variety of substituted phenanthrene derivatives. The introduction of the formed phenanthrene derivative into bicyclo[2.2.2]octene systems would be possible for the construction of further condensed aromatic compounds by the second oxy-Cope rearrangement. In the aromatic oxy-Cope rearrangement, like in other aromatic sigmatropic rearrangements, the disadvantages caused by dearomatization have long been pointed out. Probably the reaction will proceed via the preferable intermediate **A**, because the unfavorable intermediate **B** will lose larger dearomatization energy than **A** as shown in Scheme 1. Thus, the reaction will give **10a** exclusively.

In this paper, we describe the synthesis of 2-acetoxy[5]helicenes via an intermediate **10a**–**b** by novel sequential double oxy-Cope rearrangement.

Synthesis of 3-bromophenanthrene **7** was achieved as illustrated in Scheme 2. The reaction of bicyclo[2.2.2]ketone **1**[9] with *p*-bromophenylmagnesium bromide gave (1*R**,2*S**,4*S**)-alcohol **2** in 43% yield as a major product. An oxy-Cope reaction was carried out using 3 equiv. of KH in the presence of 1 equiv. of 18-crown-6 in THF at 0°C. Tricyclic condensed oxy-Cope product **3** was obtained in 89% yield. Hydrolysis of **3** with aqueous $(COOH)_2$ in THF yielded diketone **4**, which was then reduced to **5** by $NaBH_4$ in EtOH. Dehydration with *p*-TsOH in boiling xylene gave a mixture of regioisomers **6**. Further treatment of **6** with DDQ in boiling xylene gave 3-bromophenanthrene **7** in 30% yield from **3**. The obtained **7** led to Grignard reagent by magnesium for the continuing transformations illustrated in Scheme 3.

According to an analogous procedure, 3-(phenanthrenyl)bicyclo[2.2.2]octanol **9a** was obtained using 3-phenanthrylmagnesium bromide **8a**. Aromatic oxy-Cope rearrangement reaction of **9a** with 3 equiv. of KH and 1 equiv. of 18-crown-6 in THF at 0°C afforded fused-ring compound **10a** in 49% yield. Reduction of the carbonyl group by $NaBH_4$ gave **11a**. After dehydration and hydrolysis of the alcohol **11a**, ketone **12a** was given. After the enolacetylation and aromatization, racemic 2-acetoxy[5]helicene **14a**[10] was obtained in 34% yield from compound **10a**. Similarly, 2-acetoxy-11,14-dimethyl[5]helicene **14b** could be obtained from **1** using 5,8-dimethyl-3-phenanthrylmagnesium bromide **8b**.

The optimized helical structure (MOPAC97-AM1) of **14a** is shown in Fig. 1. The predicted distance between H_1 and H_{14} is 2.598 Å. The significant NOE (2.0%) between H_1 and H_{14} observed by NOESY1D experiment greatly supports this structure.

In summary, we have demonstrated a novel synthesis of 2-acetoxy[5]helicene by oxy-Cope rearrangement strategy. Applications of this strategy to the synthesis of other helical systems are under investigation.

Acknowledgements

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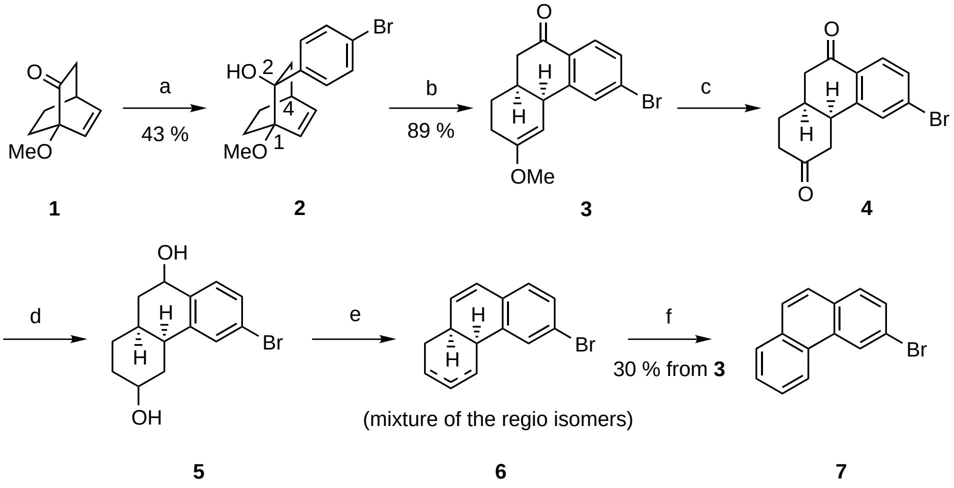
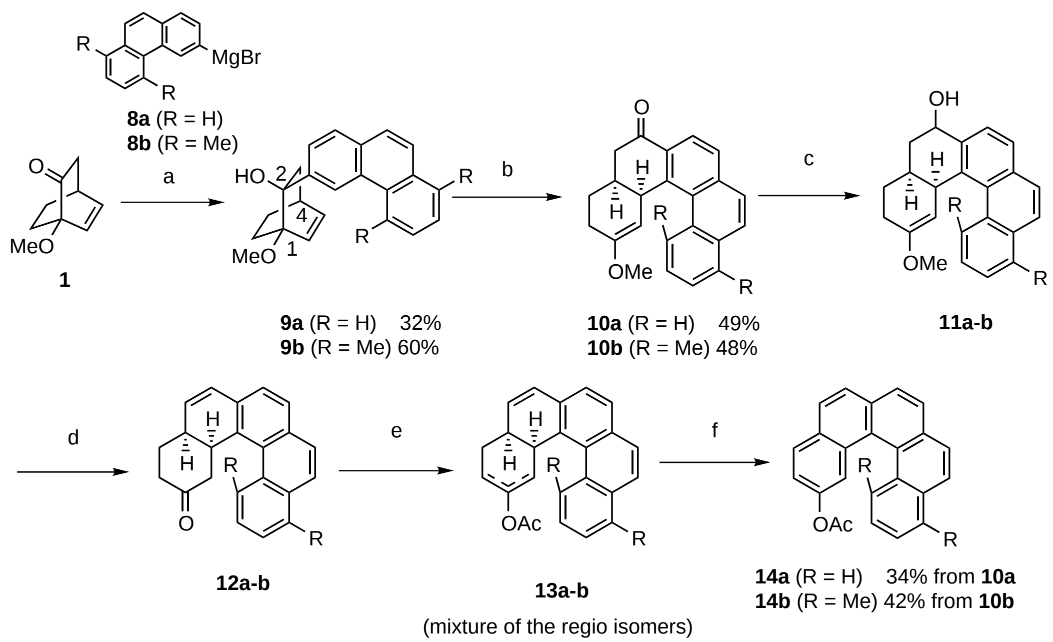


Scheme 2. Synthesis of 3-bromophenanthrene **7**. *Reagents and conditions*: (a) *p*-bromobenzylmagnesium bromide, THF, 0°C–rt; (b) KH, 18-crown-6, THF, 0°C; (c) $(COOH)_2$ aq., THF, rt; (d) $NaBH_4$, EtOH, rt; (e) *p*-TsOH, xylene, reflux; (f) DDQ, xylene, reflux.



Scheme 3. Synthesis of 2-acetoxy[5]helicenes **14a**–**b**. *Reagents and conditions*: (a) **8a**–**b**, THF, 0°C–reflux; (b) KH, 18-crown-6, THF, 0°C; (c) $NaBH_4$, EtOH, rt; (d) *p*-TsOH, benzene, reflux; (e) LHMDS, Ac_2O, THF, −78°C to rt; (f) DDQ, benzene, reflux.

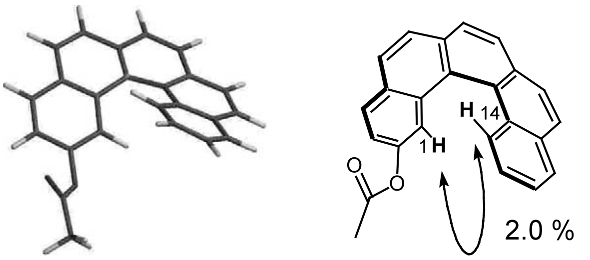


Figure 1. The most stable structure of **14a** calculated by MOPAC 97-AM1 and NOE observed between 1-H and 14-H of **14a**.

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10. 2-Acetoxy[5]helicene (**14a**): mp 172–173°C; IR (KBr) 1757, 1603, 1516, 1205 and 847 cm^{-1}; UV–vis (CH_3OH) $\lambda_{max(nm)}$ (log ε) 333 (4.22), 313 (4.49), 305 (4.51), 270 (4.58); ^1H NMR (300 MHz, $CDCl_3$) $\delta = 8.56$ (1H, d, $J = 8.4$ Hz), 8.19 (1H, d, $J = 2.4$ Hz), 7.84–7.97 (8H, m), 7.51 (1H, ddd, $J = 0.9$, 6.9 and 7.2 Hz), 7.32 (1H, ddd, $J = 1.5$, 7.2 and 8.7 Hz), 7.25 (1H, dd, $J = 2.4$ and 8.4 Hz), 2.20 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 169.71$, 147.46, 132.66, 132.57, 132.26, 131.59, 130.64, 130.29, 129.18, 128.84, 127.79, 127.66, 127.61, 127.14, 127.01, 127.00, 126.64, 126.40, 126.33, 126.25, 124.83, 121.12, 120.63, 21.02; EI-MS (70 eV) *m*/*z* (%) 336 (M^+, 50), 293 ($[M-C_2H_3O]^+$, 47), 276 ($[M-C_2H_3O_2]^+$, 100).