ORGANIC
LETTERS

2012
Vol. 14, No. 12
3166–3169

Synthesis of Chiral Helical 1,3-Oxazines[§]

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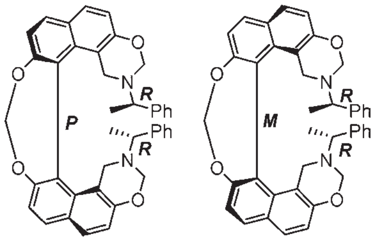
Received May 8, 2012

ABSTRACT



A series of novel 1,3-oxazines were prepared to construct a helical framework. The 1,3-oxazine attached to the phenanthrene unit showed a small bite angle θ (~12°), while the units attached to [4]helicene showed a larger θ (~35°) and exhibited helical isomers at ambient conditions. The diastereomers of the third type of helicene-like bis-oxazine attached to binaphthyl were easily separable and showed good thermal stability. All four diastereomers of bis-helicene were synthesized, and their absolute configuration was established.

A search for new chiral molecules with different shape, size, and functional group is an extremely crucial aspect of modern organic chemistry. This is particularly vital in the fields of molecular recognition, supramolecular and medicinal chemistry, asymmetric synthesis and enantioselective catalysis, material chemistry, etc. Among this class of compounds, helically chiral molecules find a unique place because of their special chiroptical properties. Since the pioneering work on helicene by Newman in 1956,[1] the area has presented a number of other helical molecules with a wide range of applications.[2−5]

Primarily the helically shaped molecules are of two types: carbohelicenes and helicenes with heteroatoms or heterohelicenes.[6,7] The heterohelicenes possessing a 1,3-oxazine unit in the framework are not reported in the

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[§] Dedicated to Professor B.V. Kamath on his 62nd birthday.

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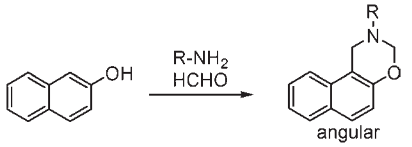
10.1021/ol301267r

literature, except for one system,[7d] although this heterocyclic moiety is present in a few biologically active molecules.[8] In this paper, we present the synthesis, characterization, and determination of absolute configuration of three types of novel helical 1,3-oxazines.

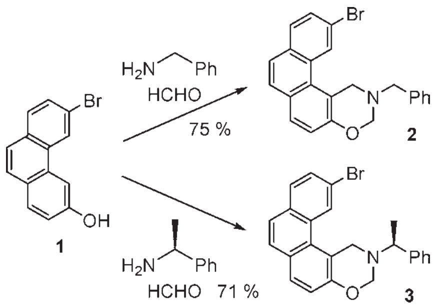
The synthetic strategy is based on a well-known conversion of 2-naphthol to angularly fused 1,3-oxazine when treated with a primary amine and excess of formaldehyde by an aromatic Mannich reaction (Scheme 1).[9]

Scheme 1. General Synthesis of 1,3-Oxazines from 2-Naphthol



The design of helically shaped 1,3-oxazine is based on the construction of the heterocyclic ring on the *ortho* fused aromatic ring system. Initially, phenanthrene was chosen for this purpose, and the oxazine of type A was synthesized from its hydroxyl derivative **1** (Scheme 2). Two derivatives **2** and **3** were sythesized from benzyl amine and (*S*)-α-methylbenzyl amine, respectively. The molecules prepared were fully characterized by usual spectral and analytical techniques.

Scheme 2. Synthesis of Oxazine of Type A



The presence of bromine helped its crystal quality, and single crystal analysis indicated a small bite angle θ (~12°) between the planes of the two terminal rings of the phenanthrene system in **2** (Figure 1). However, chiral-phase HPLC analysis showed only one peak confirming the absence of isomers in solution at ambient conditions.

The helical molecules with substantial bite angle show special chiroptical properties and high optical rotation. For practical applications, the helical shape also needs to be stable and free from conformational isomerization. In an effort to prepare a more rigid helical shape, the second set is designed with [4]helicene as the aromatic system. Two derivatives of type B were synthesized from hydroxy-[4]helicene **4** under similar reaction conditions (Scheme 3).

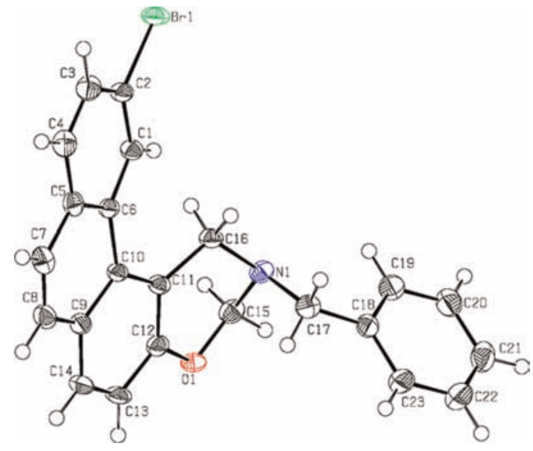
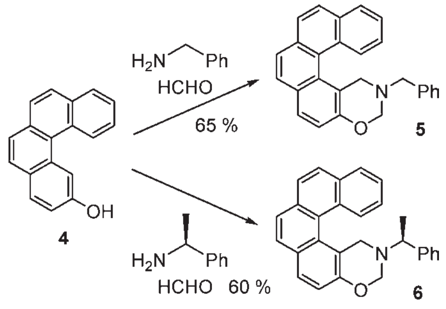


Figure 1. ORTEP diagram of compound **2** (type A).

Scheme 3. Synthesis of Oxazine of Type B



The ^{1}H NMR analysis of **5** showed two sets of *dd* for the protons of the oxazine ring against the two *s* for compound **2**. Further confirmation of the helical shape was obtained from the single-crystal analysis of **5** (Figure 2), where a considerable bite angle θ (~35°) was observed between the two terminal rings of the helicene system.

The third type of helical oxazine was planned where two oxazine rings are attached to the central helical unit. Accordingly, type C is synthesized from the 7,7′-dihydroxy-2,2′-binaphthol **7**[10] via atropisomeric intermediates **8a** and **8b** (Scheme 4). The intermediates were at first purified from the reaction mixture, and subsequently, one of them (**8a**) was isolated by recrystallization. The separated pure diastereomer **8a** was then transformed to the methylene-bridged compound **9a** by reaction with diiodomethane and Cs_2CO_3.[7c]

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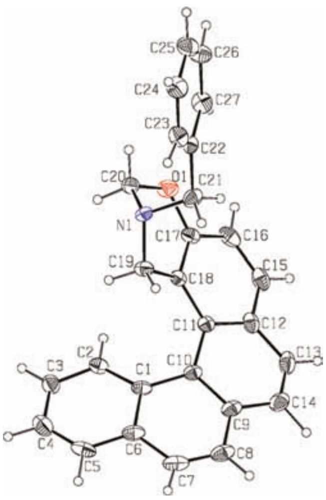
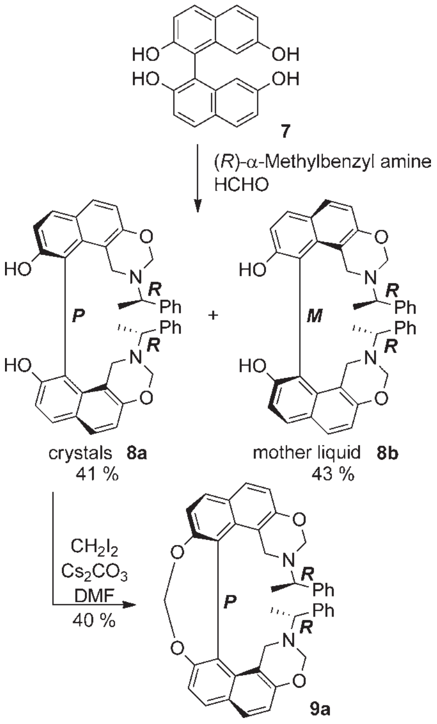


Figure 2. ORTEP diagram of compound **5** (type B).

Scheme 4. Synthesis of Helical Bis-oxazines of Type C



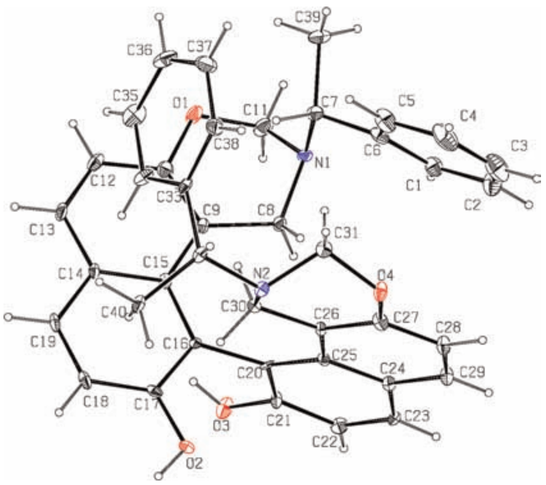


Figure 3. ORTEP diagram of compound **8a**, clearly establishing the (*P*) configuration (or *S*) at the chiral axis.

The single-crystal X-ray analysis confirmed the absolute configuration of the chiral axis to be *P* for the crystallized isomer **8a** (Figure 3).[11] Since the methylene bridge formation will retain the stereochemistry of the axis of **8a**, the absolute configuration of the methylene-bridged compound **9a** was accepted to be *RPR*. Helical compound **9a** has a large specific optical rotation ($[\alpha]_D$ +884) and molecular OR ($[\Phi]_D$ +5487), while the open structure **8a** showed specific rotation of only +204. This enhancement of the degree of optical rotation when the atropisomeric open structure is converted to a rigid form by introducing the bridge is in accordance with recent observations.[7c] The cyclized form with the methylene bridge also provides stability to the helical shape, and a solution of **9a** was refluxed in toluene for over 12 h without any visible thermal isomerization.

A similar synthetic process followed for the preparation of all four diastereoisomers of the helically chiral bis-oxazines (Figure 4). Isomer **9b** was prepared from **8b**, while the other two isomers **11a** and **11b** were prepared from the corresponding two diastereomers of **10a** and **10b** obtained from **7** and (*S*)-α-methylbenzylamine.

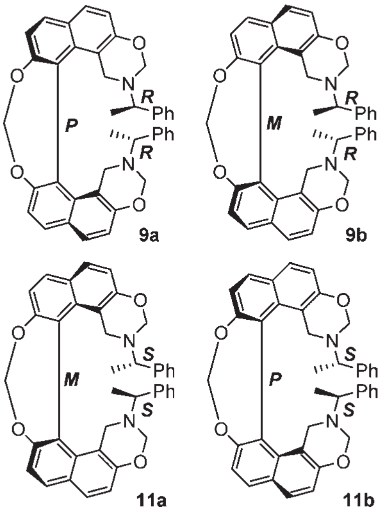


Figure 4. Four diastereoisomers of the bis-oxazines of type C.

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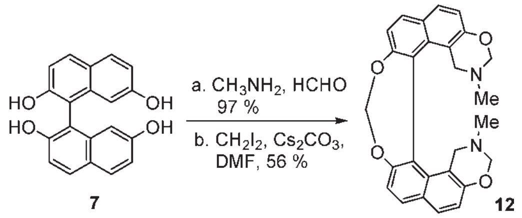
[11] The crystal of **9a** could not be satisfactorily solved by X-ray diffraction analysis.

Scheme 5. Synthesis of *N*-Me-bis-oxazine of Type C



The synthesis of the isomers of type C is quite straightforward and can be carried out on a multigram scale for further applications and study.

Another derivative of 1,3-oxazine of type C with a single helical chiral unit was synthesized by selecting methylamine in place of optically active amine (Scheme 5). The molecule **12** was isolated as a racemate of two helical enantiomers.

Chiral-phase HPLC analysis of the compound **5** and **12** was performed in order to establish the stability of isomers in solution at ambient conditions (Figure 5). The first molecule attached with four ortho fused aromatic rings **5** did show the presence of two helical isomers, but the separation was never up to the baseline, probably indicating their dynamic behavior. At the same time, the two helical isomers of **12** were clearly separated to the baseline indicating their stability.

Helical oxazines show typical UV and CD spectral features (Figure 6).[12] The presence of two opposite bisignate couplets, a positive one at around 270 nm and a negative at 292 nm, are attributed to the *P* configuration (**9a**). As expected, the two enantiomers of the pair **9a** and **11a** show identical but opposite CD curves.

In conclusion, a series of new helical oxazines were synthesized which showed high degree of optical rotation and particularly the bis-oxazines of type C had considerable thermal stability.

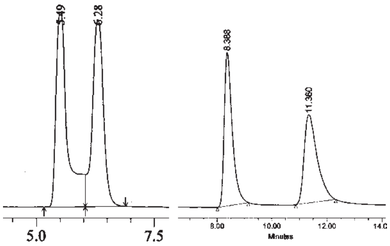


Figure 5. Chiral HPLC analysis of **5** (left) and **12** (right).

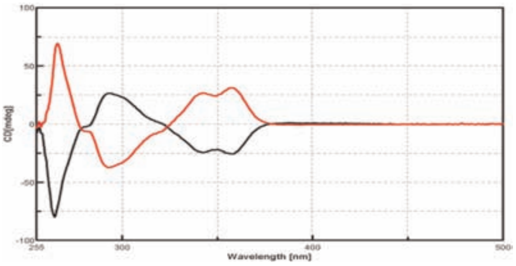


Figure 6. CD spectra of bis-oxazine enantiomer pair *RPR*-**9a** (red) and *SMS*-**11a** (black) (c 0.5 × 10^{-7} mol in acetonitrile).

Acknowledgment. This work was supported by a SERC project of Department of Science and Technology, New Delhi (SR/SI/OC-42/2006). We thank the DST and CSIR (SRF) for the fellowship to H.R.T. and Prof. B. V. Kamath, Head, Department of Chemistry, for the facilities and encouragement.

Supporting Information Available. Experimental procedures, spectroscopic data, CD spectra, and X-ray crystal data of the reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.