Chirality

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Planar-Chiral [7]Orthocyclophanes**

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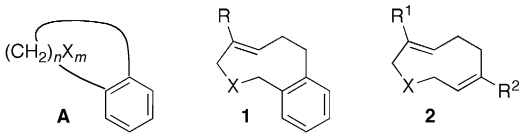
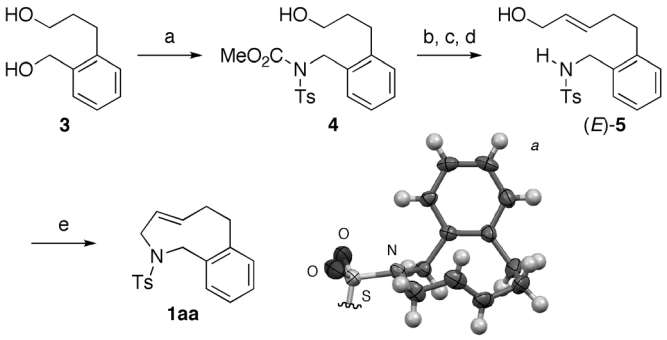
Medium-sized bridged cyclophanes have attracted considerable interest because of their unusual conformational, chemical, and spectroscopic properties caused by deformation and strain in the aromatic ring and in the bridging ansa chain.[1] Among cyclophanes, meta- or paracyclophanes having dynamic planar chirality have generated much theoretical and synthetic interest as unique chiral molecules. In contrast, their regioisomer, that is, orthocyclophane (**A**) does not



attract much attention owing to its less interesting topology and lack of planar chirality.[2] However, the introduction of a properly designed ansa chain, which can be on the outside of the plane of the benzene ring and decrease the flexibility of the molecule, may create stable planar chirality, even in simple orthocyclophanes. Herein we report the design and synthesis of the planar-chiral [7]orthocyclophanes **1** having an *E* alkene in the ansa chain, as well as a detailed stereochemical analysis and a demonstration of their utility in synthesis.

Recently, we discovered a novel class of planar-chiral heterocycles (**2**) which consist of a bis(allylic) skeleton and the heteroatom X (X = O, NTs, SO_n; Ts = 4-toluenesulfonyl).[3] The chirality of these compounds originates from the presence of suitably located *E* and *Z* alkenes in the nine-membered ring.[4] On the basis of this stereochemical phenomenon, we anticipated that the orthocyclophane **1**, in which the *Z* alkene of **2** is replaced by a benzene ring, may display planar chirality. It is also expected that **1** can achieve thermal stability, which **2** does not exhibit (see below). The details of the study are provided below.

At the outset, we examined the synthesis of the nitrogen-containing orthocyclophane **1aa** (X = NTs, R = H) from the known diol **3** (Scheme 1). The Mitsunobu reaction of **3** and $TsNHCO_2Me$ proceeded with high group selectivity and



Scheme 1. Synthesis and X-ray analysis of **1aa**: a) $TsNHCO_2Me$, PPh_3, DEAD, THF, −78→0 °C, 78%; b) DMP, CH_2Cl_2, 0 °C→RT, 84%; c) $(EtO)_2POCH_2CO_2Et$, NaH, THF, −78→0 °C, 90% [>98% (*E*)]; d) DIBAL, CH_2Cl_2, −78 °C, quant. [94% (*E*): The *Z* isomer was separated by silica gel choromatography]; e) PPh_3, DEAD, THF, −78→0 °C, 90%. DEAD = diethyl azodicarboxylate, DIBAL = diisobutylaluminium hydride, DMP = Dess–Martin periodinane, THF = tetrahydrofuran, Ts = 4-toluenesulfonyl. For the ORTEP drawing of **1aa** the thermal ellipsoids are shown at 50% probability and the tolyl group has been omitted for clarity.

provided the amide alcohol **4** as the only product in 78% yield.[5] The Dess–Martin oxidation of the alcohol moiety of **4** followed by the Horner–Wadsworth–Emmons reaction and treatment with DIBAL provided the key intermediate (*E*)-**5** in 71% yield (three steps). The intramolecular Mitsunobu reaction of (*E*)-**5** under a high dilution conditions (ca. 0.01 M) provided the desired cyclic amide **1aa** in excellent yield (90%). It should be noted that only a negligible amount of dimerized product (< 1%) was formed in this reaction. The orthocyclophane **1aa** afforded a crystal suitable for X-ray analysis. The analysis reveals that the ansa chain is located on the outside of the plane of the benzene ring and both the benzene ring and alkene moieties of the ansa chain form chiral planes in the solid state (Scheme 1).[6]

The existence of isolable enantiomers of **1aa** in solution was revealed by HPLC analysis using a chiral stationary column equipped with a CD spectropolarimeter. As shown in Figure 1, both enantiomers of **1aa** were successfully separated on an analytical as well as a semi-preparative scale.[7] The

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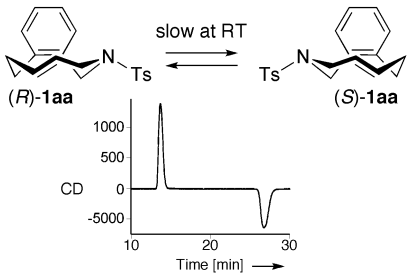


Figure 1. HPLC analysis of **1aa** using a chiral stationary column.[7]

absolute stereochemistry of **1aa** was determined to be *R* for the (−)-isomer, based on the stereochemistry of its [2,3]-Wittig rearrangement product (see below). The half-lives of the optical activity ($t_{1/2}$) for **1aa** in *n*-hexane at 40, 50, and 60 °C are 6.88, 1.87, and 0.553 hours, respectively. The activation parameters for the racemization of **1aa** are calculated from an Eyring plot by the analysis of the rate constants of racemization as $\Delta H^{\neq} = 25.5$ kcal mol^{-1} and $\Delta S^{\neq} = 0.546$ cal mol^{-1} K^{-1}. This result clearly demonstrates that **1aa** has stable chirality at ambient temperature.[8] In addition, it was found that the stereochemical stability of this class of orthocyclophanes is considerably increased by the introduction of a substituent on the ansa chain.[9] For example, the half-lives of the optical activity of the methyl-substituted derivative **1ab** (X = NTs, R = Me) in *n*-heptane at 60, 70, 80, and 90 °C are 453, 125, 34.0, and 11.9 hours, respectively, and the activation parameters for the racemization are $\Delta H^{\neq} =$ 28.7 kcal mol^{-1} and $\Delta S^{\neq} = -3.13$ cal mol^{-1} K^{-1}. The absolute stereochemistry of the enantiomers of **1aa** and **1ab** were determined by transformation to a known compound and X-ray analysis (Figure 2), respectively.[6]

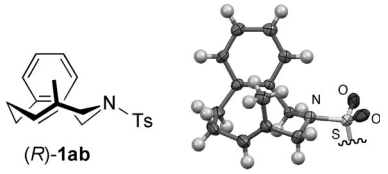


Figure 2. ORTEP drawing of (*R*)-**1ab**. Thermal ellipsoids are shown at 50% probability and the tolyl group has been omitted for clarity.

It is noteworthy that the orthocyclophane **1a** (X = NTs, R = H, Me) differs from the bis(allylic) cycle **2** in terms of thermal stability. For example, **2a** (X = NTs, R^1 and R^2 = H) easily converts into the transannular Cope rearrangement product **6** when heated at 110 °C for 1 hour. In sharp contrast, **1aa** and **1ab** were not changed even when heated at 110 °C for 7.5 hours, and were quantitatively recovered.[10] These results show that **1a** is a manageable chiral molecule having stable planar chirality and sufficient thermal stability for standard handling.

The enantioenriched form of the orthocyclophane can be obtained not only by HPLC separation but also by our recently developed asymmetric cyclization method.[11] For example, the cyclization of the achiral precursor **7** with the D-glucose-derived alkoxide **8** at −10 °C in CH_2Cl_2 provided (*R*)-**1ab** with 63% *ee*.[12] The enantiomerically pure form of (*R*)-**1ab** can be obtained from the fractional crystallization of this enantio-enriched product.

At this stage, the basic and important question arises as to the type of influence the atom X has on the stereochemical behavior of orthocyclophane **1**. In particular, we were interested in the carbon congener **1b** (X = CH_2), which was synthesized by Cope and Fordice in 1967.[13] They carried out a subtle stereochemical study of **1b**, including the preparation of a platinum complex, recrystallization, and liberation of the platinum moiety. However, an optically active form of **1b** could not be isolated and, hence, they concluded that **1b** might not have significant planar chirality at ambient temperature.[14] To revisit Cope's historic orthocyclophane **1b** and to gain an insight into the influence of X on stereochemical behavior, we synthesized **1b** and the oxygen congener **1c** (X = O).[15] A stereochemical analysis of these in a manner similar to that of **1a** showed that both **1b** and **1c** have isolable enantiomers in solution at ambient temperature (Figure 3).

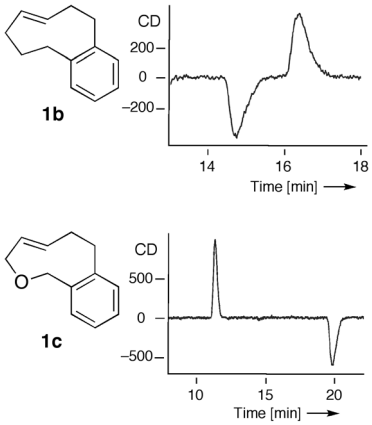
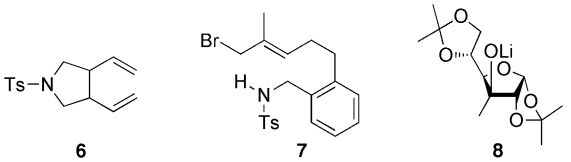


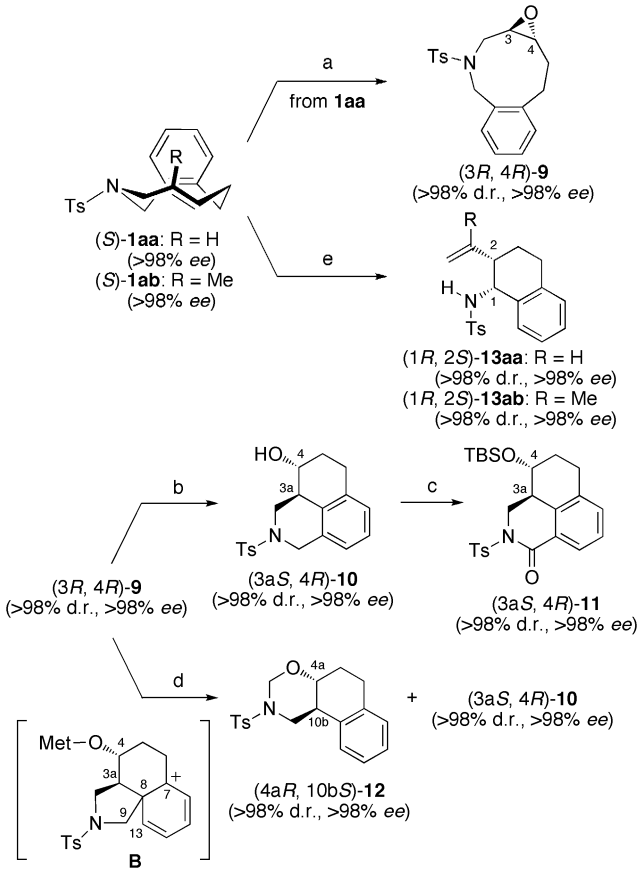
Figure 3. HPLC analyses of **1b** and **1c** using a chiral stationary column.[7]

The activation parameters for the racemization of **1b** and **1c** are calculated from an Eyring plot by the analysis of the rate constants of racemization as $\Delta H^{\neq} = 22.8$ kcal mol^{-1} and $\Delta S^{\neq} = -3.31$ cal mol^{-1} K^{-1}, and $\Delta H^{\neq} = 25.1$ kcal mol^{-1} and $\Delta S^{\neq} = -4.62$ cal mol^{-1} K^{-1}, respectively. From these data, along with the data for **1aa** described above, the half-lives of the optical activity ($t_{1/2}$) of **1aa**, **1b**, and **1c** at 25 °C were calculated. The resulting order of $t_{1/2}$ is **1c** (380 h) > **1aa** (56.7 h) > **1b** (4.35 h). This trend is consistent with the reverse bond length order of C-X (C-O < C-N < C-C).[16] These results show that the stereochemical stability of **1** is highly dependent upon the embedded atom X in the ansa chain.

With the chiral orthocyclophanes in hand, we turned our attention to transforming their planar chirality into central

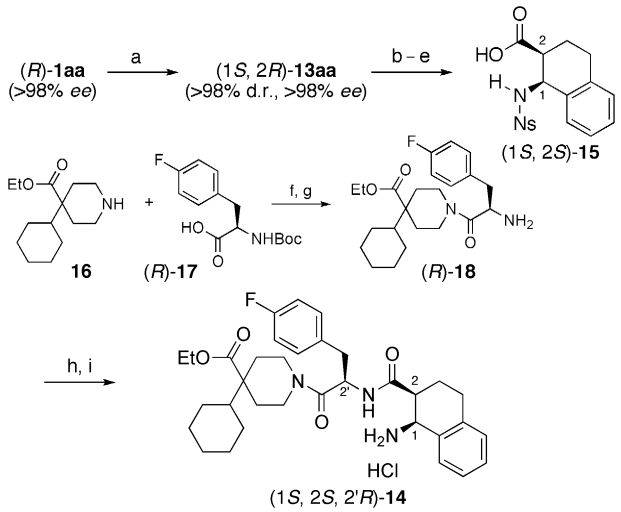


chirality using either inter- or intramolecular reactions.[17] First, the epoxidation reaction of (*S*)-**1aa** (>98% *ee*) was performed using *m*CPBA and quantitatively provided the epoxide (3*R*, 4*R*)-**9** (Scheme 2).[6,12] This result attests to the fact that the epoxidation reaction only occurs from the outer peripheral face. The epoxide (3*R*, 4*R*)-**9** would be a suitable substrate for further transannular reactions. Indeed, a $TiCl_4$-promoted reaction of (3*R*, 4*R*)-**9** provided the unique tricyclic compound (3a*S*, 4*R*)-**10** in excellent yield (96%), in a stereospecific manner.[6,12] The resulting (3a*S*, 4*R*)-**10** can be transformed into (3a*S*, 4*R*)-**11**, which contains the core structure of palonosetron, by RuO_2-catalyzed oxidation.[18] Interestingly enough, a similar transannular reaction of (3*R*, 4*R*)-**9** with $BF_3{\cdot}OEt_2$ afforded a different tricyclic compound, (4a*R*, 10b*S*)-**12**, as the major product (84%),[6,12] along with a small amount of (3a*S*, 4*R*)-**10** (6%). These Lewis acid promoted reactions should involve the same cationic intermediate **B**, which is formed by the epoxide cleavage and subsequent intramolecular Friedel–Crafts reaction. Then, 1,2-migration of C9 from the C8 position to the C13 position provides (3a*S*, 4*R*)-**10**. In contrast, an O–C9 bond formation in **B** will provide (4a*R*, 10b*S*)-**12**.[19] In another reaction, the base treatment of (*S*)-**1aa** and (*S*)-**1ab** with *n*BuLi in THF at −78→−20°C provides the transannular aza-[2,3]-Wittig rearrangement products (1*R*, 2*S*)-**13aa** and (1*R*, 2*S*)-**13ab**, respectively, in excellent yields (**13aa**: quant., **13ab**: 87%) with high stereoselectivity.[12] These transformations of planar chirality clearly show that the enantioenriched orthocyclophane **1** could serve as a versatile synthetic precursor for a variety of chiral nitrogen-containing compounds with central chirality.



Scheme 2. Transformations of (*S*)-**1aa** and (*S*)-**1ab**: a) *m*CPBA, CH_2Cl_2, 0°C→RT, quant.; b) $TiCl_4$, CH_2Cl_2, 0°C, 96%; c) 1. TBSOTf, 2,6-lutidine, DMF, RT, 65%; 2) RuO_2 (cat.), $NaIO_4$ aq., EtOAc, RT, 92%; d) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0°C, (4a*R*, 10b*S*)-**12** (84%) and (3a*S*, 4*R*)-**10** (6%); e) *n*BuLi, THF, −78→−20°C, (1*R*, 2*S*)-**13aa** from (*S*)-**1aa** (quant.), (1*R*, 2*S*)-**13ab** from (*S*)-**1ab** (87%). DMF = *N*,*N*′-dimethylformamide, *m*CPBA = *meta*-chloroperbenzoic acid, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

As an example, the asymmetric synthesis of the peptide (1*S*, 2*S*, 2′*R*)-**14**, a potent compound for selective agonists of the melanocortin-4 receptor (MC4R) developed by Bakshi and colleagues, was carried out (Scheme 3).[20] The peptide(1*S*, 2*S*, 2′*R*)-**14** has a bicyclic *cis*-β-amino acid moiety, which can be made from the aza-[2,3]-Wittig rearrangement product (1*S*, 2*R*)-**13aa**. Our synthesis started from the aza-[2,3]-Wittig rearrangement of enantiopure (*R*)-**1aa** under the above-mentioned reaction conditions, which provided (1*S*, 2*R*)-**13aa** as a single stereoisomer. The change of the protective group on the nitrogen atom from the Ts to Ns group and subsequent oxidation of the vinyl group afforded the desired *cis*-β-amino acid derivative (1*S*, 2*S*)-**15** in excellent yield.[6,12,21,22] Finally, EDC-promoted condensation of (1*S*, 2*S*)-**15** and the amine (*R*)-**18**, derived from **16** and (*R*)-**17**, and subsequent removal of the Ns group provided (1*S*, 2*S*, 2′*R*)-**14** as a single stereoisomer. Thus, the asymmetric synthesis of (1*S*, 2*S*, 2′*R*)-**14** was achieved from the planar-chiral orthocyclophane (*R*)-**1aa** in seven steps with an overall yield of 26%.



Scheme 3. Asymmetric synthesis of the peptide (1*S*, 2*S*, 2′*R*)-**14**: a) *n*BuLi, THF, −78→−20°C, quant.; b) LiNaph, THF, −78°C, 98%; c) NsCl, Et_3N, DMAP, CH_2Cl_2, 0°C→RT, 95%; d) O_3, MeOH-CH_2Cl_2, −78°C then PPh_3, −78→0°C, 92%; e) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl-2-butene, *t*BuOH-H_2O, RT, quant.; f) DCC, DMAP, CH_2Cl_2, 0°C, 73%; g) TFA, CH_2Cl_2-H_2O, 0°C→RT, quant.; h) EDC·HCl, DMAP, CH_2Cl_2, 0°C, 41%; i) PhSH, K_2CO_3, DMF, RT, 74%. Boc = *tert*-butoxycarbonyl, DCC = *N*,*N*′-dicyclohexylcarbodiimide, DMAP = 4-(dimethylamino)pyridine, EDC = *N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide, LiNaph = lithium naphthalenide, Ns = 2-nitrobenzenesulfonyl, TFA = trifluoroacetic acid.

In summary, the synthesis, stereochemical analysis, and transformation of the newly designed [7]orthocyclophanes **1** have been described. Incorporation of an *E*-olefinic ansa chain into the orthocyclophane contributes to the conformational rigidity relevant to planar chirality and also provides unique reactivity and synthetic utility. More detailed studies on the relationship between the structure and the stereochemical stability of orthocyclophanes and their synthetic applications are in progress.

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[5] The exact origin of the group selectivity is not clear at present. Further studies to clarify the generality and mechanism of the group selective Mitsunobu reaction are now underway.

[6] The structures of **1aa**, **1ab**, **9**, **10**, **12**, and **15** were determined by X-ray crystallography. See the Supporting Information for details.

[7] HPLC analyses of **1aa**, **1ab**, **1b**, and **1c** were performed with CHIRALCEL OD-H (4.6 mm × 250 mm) at room temperature. See the Supporting Information for details.

[8] The observed stereochemical stability of **1aa** is lower than that of **2a** (X = NTs, R^1, R^2 = H) ($\Delta H^{\ddagger}$ = 26.3 kcal mol^{-1}); see Ref. [3c]. This difference is reasonably explained by an increase in the flexibility of the ring due to the introduction of a benzene ring, which has a longer bond length than that of the *Z* alkene.

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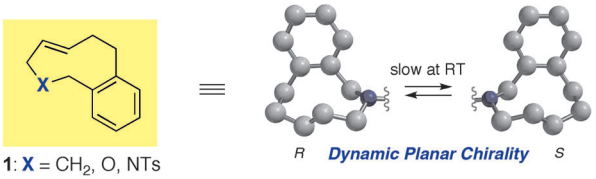
[22] Based on the absolute stereochemistry of **15** and the steric course of the [2,3]-Wittig rearrangement, the absolute stereochemistry of **1aa** was determined as *R* for the (−)-isomer.

Communications

Chirality

K. Tomooka,* C. Iso, K. Uehara,
M. Suzuki, R. Nishikawa-Shimono,
K. Igawa _____ ■■■■–■■■■

Planar-Chiral [7]Orthocyclophanes



Just plain chiral: The [7]orthocyclophanes **1**, having an *E*-olefinic ansa chain, exhibit planar chirality at ambient temperature and their stereochemical stabilities are highly dependent upon the embedded X group in the ansa chain. Inter- and intramolecular transformations of **1** (where X = NTs) provide a variety of nitrogen-containing chiral molecules in a stereospecific manner. Ts = 4-toluenesulfonyl.