Synthesis of 1,8-di(1-adamantyl)naphthalenes as single enantiomers stable at ambient temperatures†

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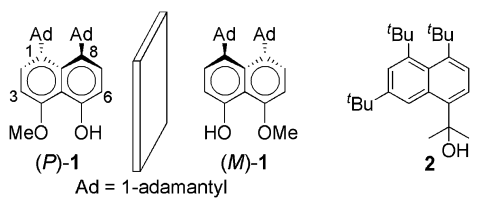
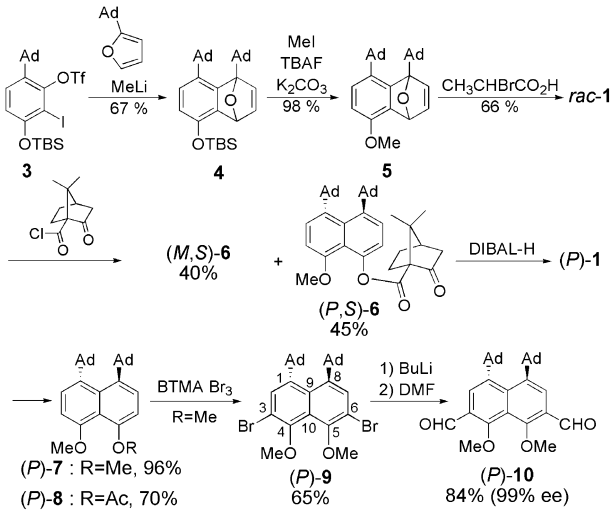
Received 4th August 2010, Accepted 27th October 2010
DOI: 10.1039/c0cc03025b

Single enantiomers of 1,8-di(1-adamantyl)naphthalenes were synthesized by the [4 + 2]cycloaddition reaction of 6-adamantylbenzyne and 2-adamantylfuran. The enantiomers were resolved by conversion into diastereomeric ketopinic acid esters. The absolute configuration was determined by X-ray analysis. Kinetic studies by CD revealed an enantiomerization barrier of 29 kcal mol^{-1} for 1,8-(1-adamantyl)naphthalenes.

The construction of distorted aromatic nuclei has been a challenge in chemistry.[1] A notable feature of such aromatics is their chirality, which imparts a three-dimensional structure to planar aromatic rings and produces closely related isomeric compounds. Helicenes are aromatic compounds having such distorted chiral structures because of steric repulsions between the terminal substituents, and an optically active [6]helicene was reported in the 1950s,[2] which is stable to heat. As the number of benzene rings decreases, its thermal stability decreases, and [5]helicene, [4]helicene and [3]helicene racemize at room temperature. Introduction of appropriate alkyl substituents retards isomerization, and substituted helicenes such as 10-methyldibenzo[*c*,*g*]phenanthrene,[3] 1,12-dimethylbenzo[*c*]-phenanthrene,[4] and 4-(*tert*-butyl)-5-methylphenanthrene[3,5] were isolated as single enantiomers. However, no naphthalenes, [2]helicene, that are stable at ambient temperature as single enantiomers have been reported yet.[6] Among 1,8-disubstituted naphthalenes[7,8] possessing chiral distorted structures, the 1,8-di(*tert*-butyl)naphthalene derivative[9] **2** was reported to racemize at room temperature with an enantiomerization energy of 22.5 kcal mol^{-1}. In this paper, we describe the synthesis and resolution of 1,8-di(1-adamantyl)naphthalene **1**,[10] which is stable at ambient temperatures as a single enantiomer.





Scheme 1

The chiral naphthalene skeleton was constructed by an improved benzyne method (Scheme 1).[9] The Diels–Alder adduct **4** was obtained by the reaction of 6-adamantylbenzyne[11] generated from *o*-iodophenyl trifluoromethanesulfonate **3** with 10 eq. of 2-(1-adamantyl)furan. The major product **4** having 1,8-di(1-adamantyl) groups was obtained in 67% yield, and the 1,5-di(1-adamantyl) isomer in 12% yield. Then, **4** was converted to the methyl ether **5**, and acid-mediated ring opening using 2-bromopropionic acid produced the racemic naphthalene *rac*-**1** in 66% yield. The effect of acid was crucial, and strong acids such as aqueous HCl and TFA produced no **1**. Then, *rac*-**1** was converted to an isomeric mixture of the (1*S*)-ketopinic esters (*P*,*S*)-**6** and (*M*,*S*)-**6**; the former was isolated by recrystallization from dichloromethane in 45% yield (>99% de). The other diastereomer (*M*,*S*)-**6** was obtained by recrystallization of the residue from dichloromethane/hexane in 40% yield (>99% de). The stereochemistry of (*P*,*S*)-**6** was determined by X-ray analysis.[13] Interestingly, (*P*,*S*)-**6** and (*M*,*S*)-**6** were conformationally stable at room temperature for one month, and heating (*P*,*S*)-**6** at 80 °C for 6 h in toluene (0.025 M) resulted only in a weak epimerization (95% de).

The compound (*P*,*S*)-**6** was reduced by DIBAL-H at room temperature to produce optically pure naphthol (*P*)-**1** (>99% ee) in 99% yield. Similarly to (*P*,*S*)-**6**, (*P*)-**1** was conformationally stable at room temperature, and minimal racemization (93% ee) occurred after heating at 80 °C for 6 h in toluene (0.025 M). The naphthol (*P*)-**1** could be methylated and acetylated at room temperature without racemization. The dimethoxynaphthalene (*P*)-**7** was 3,6-dibrominated using benzyltrimethylammonium tribromide (BTMA Br_3)[12] and formylated to give (*P*)-**10** (99% ee), again without racemization.

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† Electronic supplementary information (ESI) available: Experimental details for the synthesis of compounds, CD and UV-vis spectra, the determination of rate constant *k*, and crystallographic data of (*P*,*S*)-**6** and (*P*)-**9**. CCDC 777112 and 777113. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc03025b

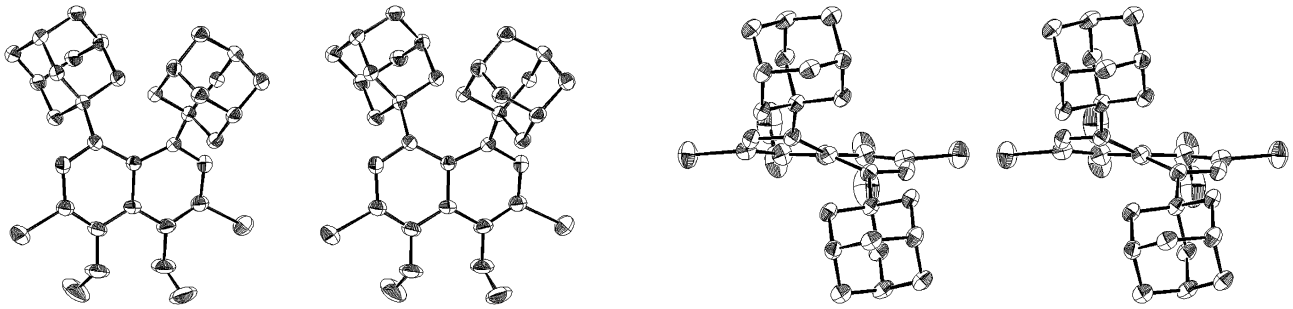


Fig. 1 Stereoscopic ORTEPS of two views of the X-ray structure of (*P*)-**9**.

The structure of the dibromonaphthalene (*P*)-**9** was confirmed by X-ray analysis (Fig. 1).[13] The adamantyl carbons C11 and C21 were displaced above and below the naphthalene mean plane by 0.34 Å for C1 and C8, and by 1.358 Å for C11 and C21, which resulted in the right-handed helical structure of the naphthalene system. Also noted was very high pyramidalization values[14] of −20.6 deg and +20.6 deg for C1 and C8, respectively, which generated the (*R*) central chirality both at C1 and C8. This is a novel distorted naphthalene ring system, which does not racemize at ambient temperatures. (*P*,*S*)-**6**, (*P*)-**9**, and 1,3,6,8-tetra(*tert*-butyl)naphthalene[8,9] possessed similar naphthalene structures. The results indicated that the torsion energies of these distorted naphthalenes were similar, and that the conformational stability of 1,8-di-(1-adamantyl)naphthalenes arose from the higher energy in the transition state. The CD spectra of the chiral naphthalenes (*P*,*S*)-**6**, (*P*)-**7**, and (*P*)-**9** were similar, whereas those of (*P*)-**10** showed a 40 nm bathochromic shift (Fig. 2).

The stability of single enantiomers of naphthalenes was estimated quantitatively. Time courses of the CD intensity at 330 nm (370 nm for (*P*)-**10**) were recorded for (*P*,*S*)-**6**, (*P*)-**7**, (*P*)-**8**, (*P*)-**9**, and (*P*)-**10** in the temperature range of 90–110 °C in *o*-dichlorobenzene. From the rate constant k (s^{-1}), the enantiomerization barrier $\Delta G^{\ddagger}$ (kcal mol^{-1}), activation energy E_a (kcal mol^{-1}), activation enthalpy $\Delta H^{\ddagger}$ (kcal mol^{-1}), and activation entropy $\Delta S^{\ddagger}$ (cal mol^{-1} K^{-1}) were obtained (Table 1).[15] (*P*,*S*)-**6**, (*P*)-**7**, and (*P*)-**8** possessed a considerably larger activation barrier, $\Delta G^{\ddagger}$ = 29 kcal mol^{-1}, than 1,8-di(*tert*-butyl)naphthalene derivative **2**, $\Delta G^{\ddagger}$ = 22.5 kcal mol^{-1}, which was considered to indicate the high stability of 1-adamantyl derivatives to racemization. The larger $\Delta H^{\ddagger}$ of *ca.* 28 kcal mol^{-1} of (*P*,*S*)-**6**, (*P*)-**7**, and (*P*)-**8** than that of

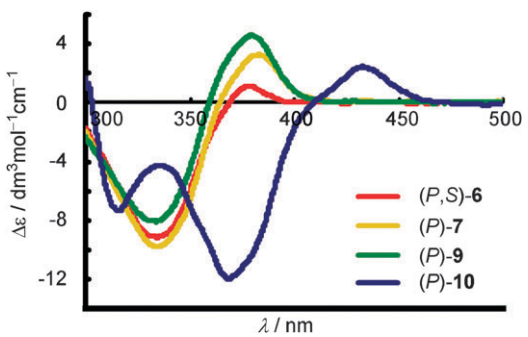


Fig. 2 CD spectra of chiral naphthalenes (*o*-dichlorobenzene, 0.1 mM, 25 °C).

Table 1 Enantiomerization barrier[a]

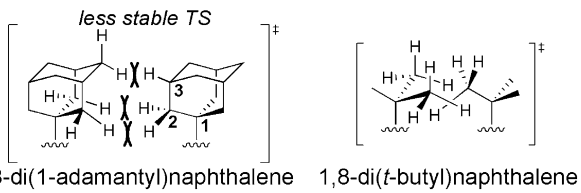
	k 10^{-5} s^{-1}	$\Delta G^{\ddagger}$/ kcal mol^{-1}	$\Delta H^{\ddagger}$/ kcal mol^{-1}	$\Delta S^{\ddagger}$/ cal mol^{-1} K^{-1}
(*P*,*S*)-**6**	4.6	29.3	27.0	−6.0
(*P*)-**7**	7.0	29.0	28.0	−2.4
(*P*)-**8**	5.5	29.1	27.3	−4.8
(*P*)-**9**	2.0	29.9	37.1	19.0
(*P*)-**10**	2.3	29.8	35.4	14.9
2[b]		22.5 (22)	(18.5)	(−8.4)

[a] Values at 105 °C. [b] Activation parameter at 144 °C. Calculated values for 1,8-di(*tert*-butyl)naphthalene are shown in parentheses, ref. 9.

1,8-di(*tert*-butyl)naphthalene, 18.5 kcal mol^{-1}, may be ascribed to the steric repulsion in the former in the transition state. Such a marked difference between the adamantyl and *tert*-butyl groups has not been reported yet.[16] The difference was attributed to the difficulty in the cogwheel rotation of 1-adamantyl substituents in the transition state (Scheme 2). *tert*-Butyl groups can be placed in the naphthalene plane without inducing a strong steric repulsion. In contrast, the repulsive proximity of 2-methylene and 3-methine hydrogen atoms was substantial for the 1-adamantyl derivatives in the planar transition state.

As indicated by the results for (*P*)-**9** and (*P*)-**10**, substitutions at the 3- and 6-positions of the naphthalene ring caused *ca.* 1 kcal mol^{-1} increase in $\Delta G^{\ddagger}$ (Table 1). The different $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values of these derivatives from those of (*P*)-**7** and (*P*)-**8** were noted. The larger $\Delta H^{\ddagger}$ values of (*P*)-**9** and (*P*)-**10** may be considered to be associated with the buttressing effect, and the increase in $\Delta S^{\ddagger}$ suggests a different mechanism of the racemization, for example, the elongation of a C–C bond in the transition state.

In summary, we synthesized stable single enantiomers of 1,8-di(1-adamantyl)naphthalenes with distorted helical structure. Our method provides a series of chiral naphthalenes in gram quantities, whose applications are now under investigation in our laboratory.



Scheme 2 A plausible transition state for enantiomerization

This work was financially supported by JSPS (No. 22790003), GCOE program, and TU-ERYS.

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