Two Isolable Conformers of Dihydropentahelicenediol Derivatives: Stereochemical Property and Its Utility for Asymmetric Reactions

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Conformation of dihydropentahelicenediol **2** and the related compounds was studied. Two isolable conformers, i.e. the diequatorial and the diaxial forms, interconvert only at elevated temperatures, where the equilibrium ratio depends on bulkiness of the substituents attached to the hydroxy groups. The palladium-catalyzed asymmetric allylic substitution was used to test the potential utility of phosphine derivatives, **6eq** and **6ax**, as chiral ligands.

During the synthetic studies on some natural products (Figure 1),[1] we became interested in the phenanthrenediol motif embedded as a partial structure in these molecules. Among two conformers associated with the rotation around the biaryl axis, the diequatorial conformer is stabilized in aprotic solvents by the hydrogen bonding between two hydroxy groups, while the diaxial counterpart is preferred in protic solvents due to the steric repulsion of the solvated hydroxy groups.[2] Although this conformational issue most likely has biological relevance, these natural products are undergoing fairly rapid conformational change.

We reasoned that, if these conformers could be separated, they might be useful for biological studies, and also find use in selective organic synthesis. In this relation, we reported the synthesis of enantiopure *trans*-diol **2** via the SmI_2-mediated pinacol cyclization of (*R*)-2,2′-binaphthyldicarbaldehyde (**1**).[1a] Although the kinetic product was only composed of the diequatorial form **2eq**, we became interested in obtaining its diaxial counterpart **2ax**, differing from **2eq** in the helicity and the relative orientation of two hydroxy groups. We expected that these conformers would be isolable and handled as separated entities, because of the pentahelicene-like structure. In this communication, we wish to describe the study along these lines.

Simple heating of **2eq** in toluene (reflux, 1 h) led to a conformer equilibration, giving the diaxial conformer **2ax**, albeit in a very minor amount (3% assessed by ^{1}H NMR). This was proven to be the equilibrium ratio (**2eq**/**2ax** = 97/3), because

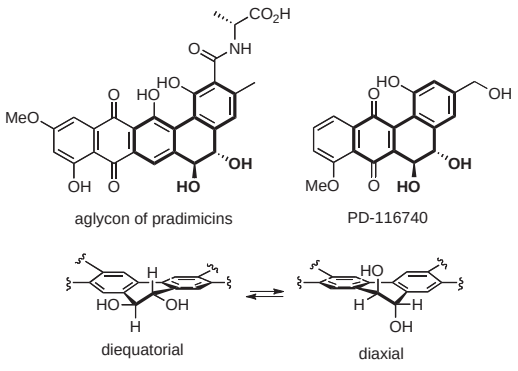
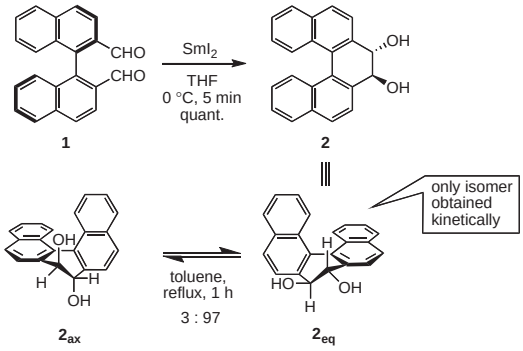


Figure 1.



Scheme 1. Preparation and conformational behavior of pentahelicene derivative **2**.

the same ratio was reached by heating of **2ax** for 1.5 h or **2eq** for 8 h in toluene (reflux), respectively.[3] This great preference of the diequatorial conformer **2eq** could be ascribed to the intramolecular hydrogen bonding between two hydroxy groups.

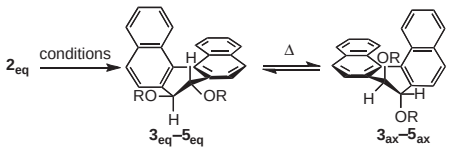
A notable point is that *these conformers were easily separable by silica-gel column chromatography* [R_f values on TLC (silica gel 60, hexane/EtOAc = 1/1): **2eq** = 0.28, **2ax** = 0.20], *and remained stable at room temperature*. The barrier for the conformational change was assessed by studying the time course of the isomerization from **2ax** (thermodynamically unfavorable conformer) into **2eq** by HPLC to show that $\Delta G^{\ddagger}_{\mathbf{2ax}\rightarrow\mathbf{2eq}}$ in toluene at 25 °C is 28 kcal/mol,[4] high enough to allow the handling as *a stable conformer* at ambient temperature.

In order to enhance the availability of **2ax**, we sought to *break the hydrogen bonding*, which was achieved by masking two hydroxy groups in **2**. For example, acetylation of **2eq** (Ac_2O, pyridine, 25 °C, 1 h) smoothly gave the corresponding bis-acetate **3eq** as its diequatorial form unchanged. However, heating in toluene (reflux, 20 h) gave a mixture (**3eq**/**3ax** = 45/55). Installation of silyl groups made the equilibrium more favorable of the diaxial conformers. Although treatment of **2eq** with *t*-BuMe_2SiCl [imidazole, DMF, 25 °C, 12 h] gave only the mono-silyl ether as its diequatorial form in 88% yield, a longer reaction at higher temperature (100 °C, 20 h) led to a clean formation of bis-silyl ether **4** in 98% yield. At this stage, the conformer ratio (**4eq**/**4ax**) was 32/68, suggesting that the gauche repulsion of two vicinal substituents, destabilized the diequatorial conformer.[5]

Double installation of more bulky silyl group (TBDPS) was also achieved at high temperature (100 °C, 20 h) to give 93% yield of bis-silyl ether **5**, which, delightedly, was only composed of the diaxial form **5ax**. Even after heating of **5ax** in toluene for 8 h, no trace of the diequatorial isomer **5eq** was observed.

The conformer **5ax** could be deprotected to give the free diaxial conformer **2ax** (eq 1); treatment of **5ax** with *n*-Bu_4NF

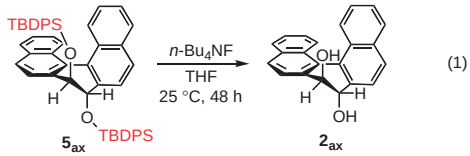
Table 1.



Conditions	R	Yield/%	eq/ax[c]
Ac_2O, pyridine[a]	Ac (**3**)	97	45/55
TBDMSCl,[d] imidazole[b]	TBDMS (**4**)	98	32/68
TBDPSCl,[d] imidazole[b]	TBDPS (**5**)	93	<1/>99

[a]At 25 °C, 1 h. [b]In DMF at 100 °C, 20 h. [c]Equilibrium ratio in toluene at 100 °C. [d]TBDMS = *t*-butyldimethylsilyl, TBDPS = *t*-butyldiphenylsilyl.

in THF (25 °C, 48 h) gave **2ax** in 85% yield with a trace amount (<3%) of diequatorial conformer **2eq**. After column chromatography (silica gel, hexane/EtOAc = 1/1), pure diaxial conformer **2ax** was obtained as a white powder (mp 125–128 °C).[6]



(1)

With two stable and separable conformers, **2eq** and **2ax**, in hand, we focused our attention to test their potentials as scaffolds in organic synthesis. As a preliminary example, we prepared the phosphine derivatives **6eq** and **6ax** to assess their enantio-controlling potentials. Condensation of diol **2eq** with two moles of 2-diphenylphosphinobenzoic acid was effected with water-soluble carbodiimide (EDCI), giving diester **6eq** in 80% yield. In a similar manner, diester **6ax** was obtained from **2ax** in 88% yield. Compounds **6eq** and **6ax** were also conformationally stable at ambient temperature (Figure 2).[7]

As a test reaction to use these phosphine derivatives **6eq** and **6ax**, the palladium-catalyzed asymmetric allylic substitution was examined (Table 2).[8] The reaction of **7** with dimethyl malonate in the presence of ligand **6ax**, [Pd(η^3-allyl)Cl]$_2$, *N*,*O*-(bistrimethylsilyl)acetamide (BSA), and KOAc at 40 °C cleanly gave the corresponding product **8** [Nu = CH(CO$_2$Me)$_2$] in 93% yield with 82% ee (Run 1).[9,10]

By contrast, the enantio-selectivity was significantly lower with the diequatorial counterpart **6eq** (Run 2). These results clearly showed that two conformers provided different chiral environments. Interestingly, when benzylamine was the nucleophile, **6eq** gave a better enantioselectivity (Run 4) in comparison with the case of **6ax** (Run 3).

Further work is now in progress in our laboratories.

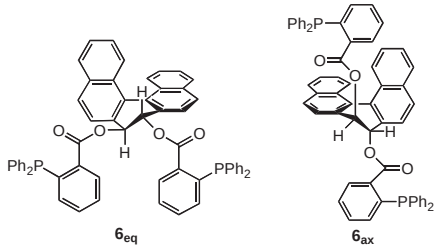
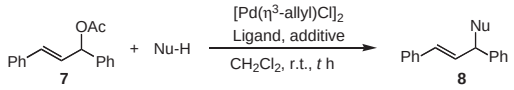


Figure 2.

Table 2.[a]



Run	Nu-H[b]	Ligand[c]	Additive	*t*	Yield/%[e]	*R*/*S*[f]
1	$CH_2(CO_2Me)_2$	**6ax**	BSA, KOAc[d]	3	93	9/91
2	$CH_2(CO_2Me)_2$	**6eq**	BSA, KOAc[d]	3	95	32/68
3	$BnNH_2$	**6ax**	—	2	91	85/15
4	$BnNH_2$	**6eq**	—	5	91	95/5

[a]5 mol % of Pd-catalyst was employed. [b]2 mol equiv. [c]10 mol %. [d]2 mol equiv. of BSA and 5 mol % of KOAc were employed. [e]Isolated yield. [f]The ratio was determined by HPLC (see, refs 9, 10).

This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday.

References and Notes

1 a) K. Ohmori, M. Kitamura, K. Suzuki, *Angew. Chem., Int. Ed.* **1999**, *38*, 1226. b) M. Kitamura, K. Ohmori, T. Kawase, K. Suzuki, *Angew. Chem., Int. Ed.* **1999**, *38*, 1229. c) K. Ohmori, M. Tamiya, M. Kitamura, H. Kato, M. Oorui, K. Suzuki, *Angew. Chem., Int. Ed.* **2005**, *44*, 3871. d) K. Ohmori, K. Mori, Y. Ishikawa, H. Tsuruta, *Angew. Chem., Int. Ed.* **2004**, *43*, 3167.

2 a) R. N. Armstrong, D. A. Lewis, H. L. Ammon, S. M. Presad, *J. Am. Chem. Soc.* **1985**, *107*, 1057. b) T. Eguchi, K. Kondo, K. Kakinuma, H. Uekusa, Y. Ohashi, K. Mizoue, Y.-F. Qiao, *J. Org. Chem.* **1999**, *64*, 5371. c) H. Kato, K. Ohmori, K. Suzuki, *Chirality* **2000**, *12*, 548.

3 $\Delta G^{383}_{2eq-2ax} = 2.2$ kcal/mol.

4 The first rate constants *k* for isomerization were estimated from a plot of ln[**2ax**] as a function of *t*. The Eyring activation parameters were obtained for the calculation of the kinetic parameters for isomerization from **2ax** to **2eq**. The ratios of **2ax**/**2eq** were determined by HPLC analysis [Mightysil 60 column, 0.46 × 25 cm, *i*-PrOH/hexane (1/9), 1.0 mL/min flow rate, monitored CD absorption at 254 nm]. The retention times were 8.2 min for **2eq** and 3.9 min for **2ax**. The CD coefficient ($\Delta\varepsilon_{2eq}/\Delta\varepsilon_{2ax}$) at 254 nm was 1.1.

5 a) M. A. Tius, J. Busch-Petersen, *Tetrahedron Lett.* **1994**, *35*, 5181. b) T. Hosoya, Y. Ohashi, T. Matsumoto, K. Suzuki, *Tetrahedron Lett.* **1996**, *37*, 663.

6 **2ax**: IR (KBr) $\nu = 3322$, 1594, 1506, 1390 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.75 (d, 2H, $J = 7.6$ Hz), 4.93 (d, 2H, $J = 7.6$ Hz), 7.28 (ddd, 2H, $J = 8.1$, 6.8, 1.3 Hz), 7.50 (ddd, 2H, $J = 8.1$, 6.8, 1.1 Hz), 7.59 (brd, 2H, $J = 8.1$ Hz), 7.70 (d, 2H, $J = 8.1$ Hz), 7.93 (brd, 2H, $J = 8.1$ Hz), 7.96 (d, 2H, $J = 8.1$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 73.0, 125.2, 126.0, 127.1, 128.1, 128.4, 129.1, 130.1, 130.4, 134.4, 134.8.

7 Conformational flipping was only observed at elevated temperature (toluene, reflux, 20 h), giving a 66/34 mixture of **6eq** and **6ax**. R_f values (silica gel, hexane/EtOAc = 4/1) for **6eq** and **6ax** were 0.7 and 0.5, respectively.

8 Reviews, see: a) B. M. Trost, *Chem. Rev.* **1996**, *96*, 395. b) B. M. Trost, M. R. Machacek, A. Aponick, *Acc. Chem. Res.* **2006**, *39*, 747.

9 A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, A. Tijani, *J. Am. Chem. Soc.* **1994**, *116*, 4062.

10 T. Hayashi, A. Yamamoto, Y. Ito, E. Yoshioka, H. Miura, K. Yanagi, *J. Am. Chem. Soc.* **1989**, *111*, 6301.

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