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Design and Synthesis of Optically Pure Dibenzo-*difuso*-azacentrotriquinacene-based *Pseudo*-C_2-Symmetric Cyclic Hydroxamic Acid

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Cyclic hydroxamic acids are found in various natural products and bioactive compounds, which exhibit various bioactivities, such as HDAC inhibition and MMP inhibition. Furthermore, they have relatively high metal binding ability, therefore they can form various metal-complexes. Herein, we report design, synthesis and optical resolution of dibenzo-*difuso*-azacentrotriquinacene-based chiral cyclic hydroxamic acid (CHA). CHA was synthesized from dibenzosuberenone over 16 steps in 11% overall yield, including triflation of enol followed by reduction of triflates using Pd catalyst and oxidation of amide with MoO_5·2DMF as key steps. The optical resolution was achieved by recrystallization, and the structure and absolute configuration were determined by X-ray crystal analysis.

Keywords: Cyclic hydroxamic acid | *Difuso*-centrotriquinacene | Pseudo C_2 symmetry

Hydroxamic acid was first synthesized by H. Lossen in 1869, from diethyl oxalate and hydroxylamine.[1] It is known that it is a family of weak organic acids and has good metal-binding ability. The ability to chelate metal ions, such as Fe^{3+} and Zn^{2+}, has been widely explored in biology and medicine.[2,3] Among them, the cyclic hydroxamic acids are also found in natural products and bioactive compounds, such as HDAC inhibitors and MMP inhibitors[4] (Figure 1). Furthermore, the hydroxamic acids are also used in synthetic organic chemistry as chiral ligands. Since Sharpless et al. reported vanadium-catalyzed asymmetric epoxidation of allylic alcohols with hydroxamate as a chiral ligand in 1977,[5] various hydroxamate ligands were developed and applied to asymmetric reactions.[6]

Recently, Nolan et al. reported the synthesis and X-ray crystal structure analysis of metal complexes having cyclic hydroxamic acid as a ligand.[7] Consequently, this report implies that cyclic hydroxamic acid could form a stable metal complex with various metal ions in bidentate chelation manner. However, little has been reported on the application of cyclic hydroxamic acids to asymmetric reaction as chiral ligands. Therefore, we planned to synthesize a novel pseudo C_2 symmetric chiral cyclic hydroxamic acid as a ligand. It is generally considered that durability and C_2 symmetry will be required as features of chiral ligands for application to asymmetric reactions. The use of ligand having a rigid core is one of the methods to create a stronger and more stable asymmetric environment. We focused on the centrotriquinacenes as a rigid structure. Since the first synthesis of triquinacene was reported by Woodward *et al* in 1964,[8] many structural features and synthetic studies of centrotriquinacenes have been reported[9] because they are attractive as a stable hydrocarbon framework. We thought that the centrotriquinacene could be used as a novel rigid core in chiral ligand.

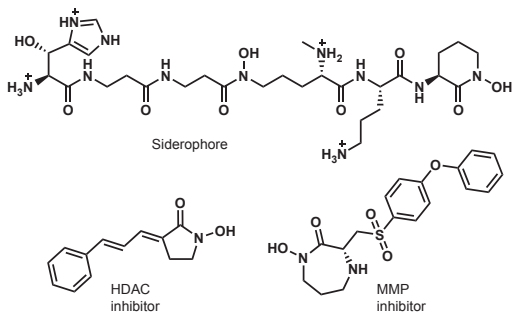
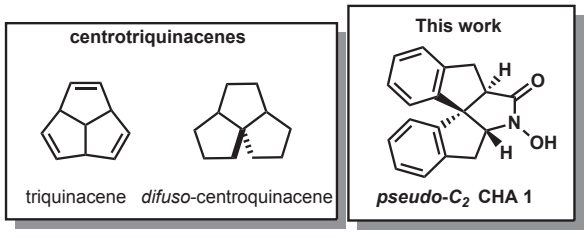


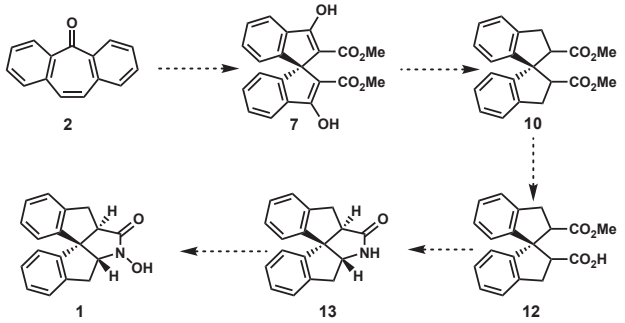
Figure 1. Cyclic hydroxamic acids as bioactive compounds.

On the other hand, pseudo C_2 symmetrical chiral ligands also have been reported as efficient chiral sources.[10] For example, Moberg et al. reported synthesis of pseudo C_2 symmetric N,P-ligand. They were applied to palladium catalyzed allylic alkylation as a chiral ligand, and good yields and high enantioselectivities were reported.[10a] Although reports of pseudo C_2 symmetric ligands are rare, it has been shown in the literature that the pseudo C_2 symmetric ligands are also efficient ligand. Therefore, within development of novel pseudo C_2 symmetric ligands remains room for research, and synthesis of novel pseudo C_2 symmetric molecules is important. We designed a novel dibenzo-*difuso*-azacentrotoriquinacene-based cyclic hydroxamic acid. Herein, we report the establishment of a synthetic route and optical resolution of *pseudo*-C_2 CHA **1** (Scheme 1).

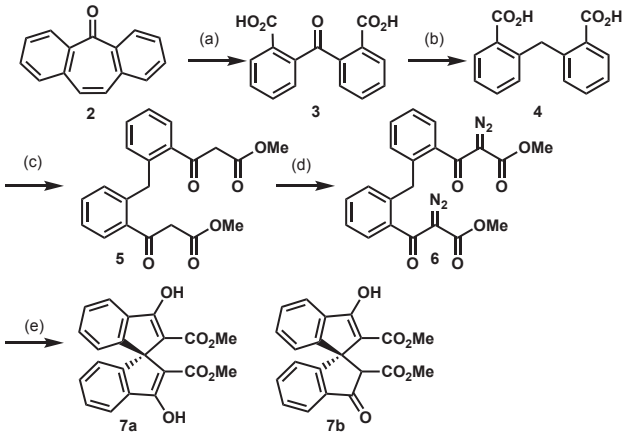
Our synthetic strategy toward cyclic hydroxamic acid is shown in Scheme 2. According to Hashimoto's report,[11] 3,3′-dioxo-1,1′-spirobiindane-2,2′-dicarboxylic acid dimethyl ester **7** would be prepared from dibenzosuberenone **2** in 6 steps. The hydroxyl function of **7** could be removed via reduction to afford diester **10**. A half-ester **12** could be obtained from diester **10** via hydrolysis, condensation of dicarboxylic acid into cyclic acid anhydride, and ring-opening reaction with NaOMe. By exposing the carboxylic acid **12** to Curtius rearrangement conditions, it would be converted to isocyanate, followed by hydrolysis and intramolecular cyclization to give an azacentrotriquinacene **13**. Finally, oxidation of **13** could afford CHA **1**.



Scheme 1. Purpose of this study.



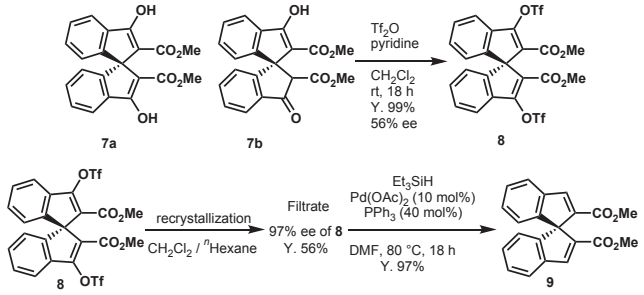
Scheme 2. Synthetic strategy of CHA **1**.



Scheme 3. (a) $KMnO_4$ Na_2CO_3/acetone, H_2O, rt, 24 h. (b) Zn, $CuSO_4$ $5H_2O$/28% NH_3 aq., H_2O, 110 °C, 36 h. (c) i) $SOCl_2$, DMF/toluene, reflux, 16 h, ii) MeOAc, ^{n}BuLi, ^{i}Pr_2NH/THF, −78 °C to 0 °C, 1 h. (d) MsN_3 Et_3N/CH_3CN, rt, 1 h. (e) Rh_2[*S*-PTTL]$_4$ 2EtOAc/toluene, 0 °C, 1 h.

We initially prepared keto-dicarboxylic acid **3** from commercially available dibenzosuberenone via oxidation with $KMnO_4$ (99% yield). Compound **3** was exposed to activated zinc powder (13.0 equiv) in the presence of a catalytic amount of $CuSO_4 \cdot 5H_2O$ in 28%-NH_3 aq. and H_2O at 110 °C for 36 h to afford dicarboxylic acid **4** in good yield. Treatment of **4** with thionyl chloride (10.0 equiv.) in the presence of a catalytic amount of DMF in toluene at reflux for 18 h afforded the corresponding acid chloride, which was then reacted with methyl acetate and LDA in THF to furnish β-keto ester **5** in 85% yield (keto vs enol = 2:1, determined by ^{1}H NMR). The treatment of β-keto ester **5** with MsN_3 in CH_3CN at room temperature for 1 h gave diazo **6** in 96% yield. The intramolecular benzylic C-H insertion of carbenoid derived from diazo **6** in the presence of a catalytic amount of Rh_2[*S*-PTTL]$_4$ in toluene gave the 1,1′-spirobiindane dimethyl ester **7** in 92% yield. It was obtained as an equilibrium mixture of bisenol form **7a** and keto-enol form **7b**, the ratio was 1:3.6 determined by ^{1}H NMR (Scheme 3).

With spirobiindane dimethyl ester **7** in hand, we examined reduction of **7** (Scheme 4). The reduction of **7** was then examined via derivatization of enol into trifluoromethanesulfonate followed by silane reduction using Pd catalyst. Reaction conditions for the synthesis of triflate were examined in the



Scheme 4. Reduction of **7**.

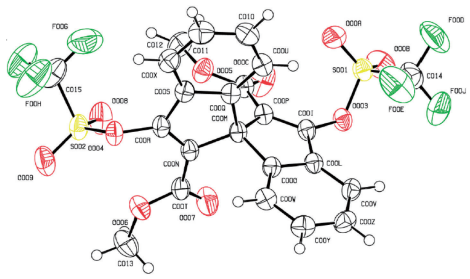
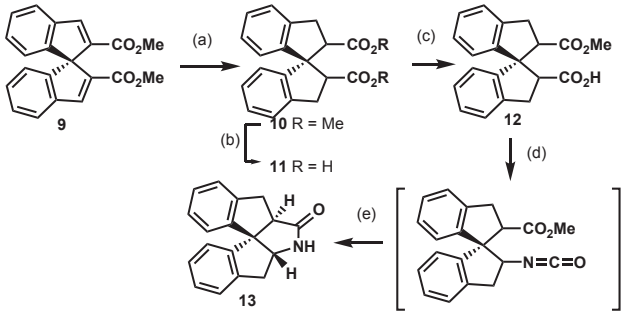


Figure 2. ORTEP diagram of **8**. X-ray crystal data for **8**: space groupe *P*-1; $a = 9.968$ (2) Å, $b = 11.092$ (2) Å, $c = 12.423$ (2) Å; $\beta = 75.14°$; $V = 1259.08$ (5) Å^3; $Z = 2$; Cu Kα radiation (−50 °C); $R = 0.0041$, $R_w = 0.116$.

presence of Tf_2O and various bases in CH_2Cl_2 (See ESI). After some trials, we obtained optimized conditions: Tf_2O (5.0 equiv.), pyridine (10.0 equiv.), and DMAP (10 mol %) in CH_2Cl_2 at ambient temperature for 18 h, giving the triflate **8** in 99% yield. The optical purity was found by chiral HPLC to be 56% ee, which was slightly lower than Hashimoto's reported value (68% ee, after decarboxylation of **7**).[11] Triflate **8** could be recrystallized in CH_2Cl_2/hexane to afford colorless crystal. The optical purity of the crystal **8** was checked by chiral HPLC analysis to be racemic. On the other hand, the optical purity of the filtrate of **8** was 97% ee. These results suggested that the crystal of triflate **8** formed a racemic compound. Indeed, it could be determined by X-ray crystal analysis (Figure 2). The reduction of enantiomerically enriched triflate **8** with triethylsilane in the presence of a catalytic amount of $Pd(OAc)_2$ in DMF afforded the spirobiindene **9** in 97% yield.

Next, we examined selective 1,4-reduction of α,β-unsaturated ester of spirobiindene **9** (Scheme 5). Various conditions were tried, e.g. H_2/Pd-C, $Pd(OH)_2$, and $NaBH_4$ etc, but the reactions were not completed (See ESI) to give a mixture of starting material, mono reductant and spirobiindane **10**. Then, we examined one-electron reduction by Mg/MeOH. It occurred smoothly to give spirobiindane **10** in 99% yield. A hydrolysis of diester of **10** was performed in the presence of KOH in MeOH, THF and H_2O under reflux conditions for 1 h to give dicarboxylic acid **11** in 99% yield. The dicarboxylic acid **11** was condensed in Ac_2O at 100 °C for 18 h to give cyclic carboxylic acid anhydride. Without further purification, it was immediately subjected to ring opening reaction with NaOMe in MeOH to afford half-ester **12** in 99% yield. To obtain azacentrotriquinacene **13**, we examined Curtius rearrangement using DPPA, subsequently hydrolysis/intramolecular cyclization. Half-ester **12** was ex-



Scheme 5. (a) Mg/MeOH, rt, 1 h. (b) KOH/MeOH, THF, H_2O, reflux, 1 h. (c) i) Ac_2O reflux, 18 h, ii) NaOMe/MeOH, rt, 1 h. (d) DPPA, Et_3N/toluene, reflux, 18 h. (e) Et_3N, KOH/1,4-dioxane, H_2O, 130 °C, 72 h.

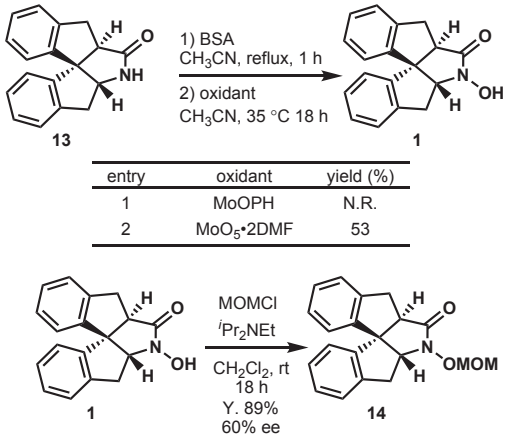
posed to Curtius rearrangement conditions (DPPA, Et_3N in toluene at reflux for 18 h) to give isocyanate, which was then hydrolyzed by alkaline solution and followed by intramolecular cyclization with Et_3N in 2M-KOH and 1,4-dioxane at 130 °C for 72 h to give the azacentrotriquinacene **13** in 54% yield.

Finally, we examined oxidation of amide **13** to CHA **1**. Typically, oxidation of amide to hydroxamate was performed by silylation with *N*,*O*-bis(trimethylsilyl)acetoamide (BSA) followed by oxidation with Vedjes reagent (MoOPH).[12] We attempted the oxidation of azacentrotriquinacene **13** under these conditions, but it did not proceed. We thought that MoOPH was decomposed by heating. Therefore, we chose $MoO_5 \cdot 2DMF$, which is reported as a stable oxidant of amide to hydroxamic acid.[13] The oxidation was performed by silylation with BSA in CH_3CN for 1 hour at 80 °C followed by treatment with $MoO_5 \cdot 2DMF$ in CH_3CN for 18 h at 35 °C to give CHA **1** in 53% yield. With CHA **1** in hand, the optical purity was measured by chiral HPLC after the hydroxy group of hydroxamic acid **1** was protected with MOMCl in 89% yield. The optical purity was 60% ee, and it suggested that some steps would induce racemization (Scheme 6).

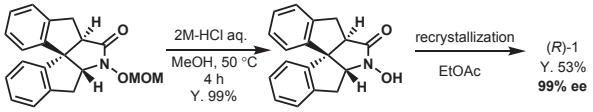
It was thought that the racemization would occur when hydrolysis of diester **9** and/or preparation steps of azacentrotriquinacene **13**. To obtain the optically pure **1**, we examined optical resolution of **1**. At this stage, various optical resolution agents were also tested; however, optically pure **1** was not obtained.

Then, we tried recrystallization of CHA **1**, but crystals did not appear. It was thought that the obstruction of crystallization might be metal impurities within hydroxamic acid **1**. To remove the impurities from **1**, first, CHA **1** was converted to *O*-MOM product **14**, which was purified by silica-gel column chromatography. Next, the *O*-MOM hydroxamic acid **14** was removed under acidic conditions at 50 °C to give the SpiroCHA **1** in excellent yield (Scheme 7). The hydroxamic acid was recrystallized from EtOAc. Fortunately, single crystals of **1** grew from EtOAc solution at ambient temperature. The structure of **1** could be determined by X-ray crystallographical analysis, and we succeeded in obtaining optically pure (*R*)-CHA **1** in 53% yield (Figure 3).

In conclusion, we have designed and synthesized a novel dibenzo-*difoso*-azacentrotriquinacene-based chiral cyclic hydroxamic acid. Synthesis of the cyclic hydroxamic acid from



Scheme 6. The oxidation of azacentrotriquinacene **13** and MOM protection.



Scheme 7. Optical resolution of **1**.

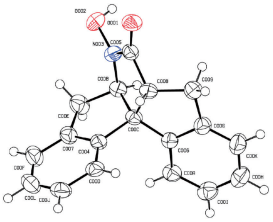


Figure 3. ORTEP diagram of (*R*)-**1**. X-ray crystal date for (*R*)-**1**: space group $P3_2$; $a = 10.443$ (10) Å, $b = 10.443$ (10) Å, $c = 11.111$ (10) Å; $\beta = 90.00°$; $V = 1049.34$ (2) Å^3; $Z = 3$; Cu Kα radiation (−50 °C); $R = 0.0030$, $R_w = 0.076$.

dibenzosuberenone was achieved in 11% overall yield in 16 steps. Although racemization occurred slightly in some steps, the optical resolution of **1** was sufficient for recrystallization after removing impurities to give the optically pure (*R*)-1 in 53% yield. The structure of **1** was successfully verified by X-ray crystal analysis. Further studies are in progress to apply the cyclic hydroxamic acid **1** to asymmetric oxidation as a chiral ligand.

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