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Synthesis and absolute configuration of (1*S*,8*S*)-*as*-hydrindacene-1,8-diol as determined by the circular dichroism exciton chirality method

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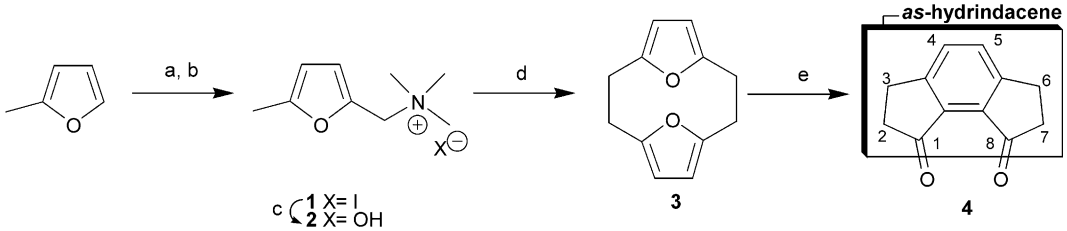
Abstract—2,3,6,7-Tetrahydro-*as*-indacene-1,8-dione **4** was prepared in 4 steps starting from 2-methyl-furan by modification of a literature procedure. Appliance of Noyori's asymmetric transfer hydrogenation, resulted in (1*S*,8*S*)-1,2,3,6,7,8-hexahydro-*as*-indacene-1,8-diol **5** in high yield (81%) and excellent enantioselectivity (>99% ee) or (8*S*)-8-hydroxy-3,6,7,8-tetrahydro-2*H*-*as*-indacen-1-one **6** in moderate yield (58%) and equally high enantioselectivity (98.5% ee), depending on the conditions. The asymmetric reduction was expected to yield the (*S*)-alcohols using the (*S*,*S*)-Ts-DPEN ligand, which was confirmed by the appliance of the exciton chirality method on the corresponding bis(*p*-dimethylamino)benzoate **7**.

The use of enantiomerically pure indane derivatives as chiral auxiliary or ligand has been extensively described in literature,[1] whereas reports of chiral ligands based on 1,2,3,6,7,8-hexahydro-*as*-indacene (Scheme 1, frame) are scarse.[2] Nevertheless, rigid 1,8-disubstituted *as*-hydrindacenes can become the cornerstone of an interesting new ligand architecture. In order to investigate the applicability of such structures in asymmetric synthesis, we needed to have facile access to *as*-hydrindacene-1,8-dione **4**[3] in multigram quantities. The intermediate [2.2](2.5)furanophane **3** was readily obtained using a procedure described for the synthesis of the structurally analogous [2.2]paracyclophane.[4] (Scheme 1).

Starting from the methylated Mannich adduct **1**, which was obtained on a 500 g scale in two easy steps from commercial 2-methyl-furan,[5] anion exchange using Ag_2O resulted in the intermediate ammonium hydroxide **2**. Subsequently, without isolation, **2** was dimerized to the furanocyclophane **3** on a 70 g scale while removing water in a Dean–Stark apparatus in the presence of a polymerization inhibitor. Further transformation of



Scheme 1. Reagents, conditions and yields: (a) $HNMe_2$·HCl, 37% H_2CO, 35 °C, 1.5 h then reflux 2 h, 85%; (b) MeI, EtOH, 0 °C, 97%; (c) Ag_2O, H_2O, rt, 2 h; (d) phenothiazine, toluene, Dean–Stark, reflux, 7 h, 71%; (e) (i) *m*-CPBA, CH_2Cl_2, −30 °C, 1.5 h then $Na_2S_2O_3$ (aq) and rt for 5 h; (ii) Na_2CO_3, MeOH, rt, 1.5 h, 88%.

Keywords: Chiral ligands; As-hydrindacene-1,8-diol; Circular dichroism; Exciton chirality method.
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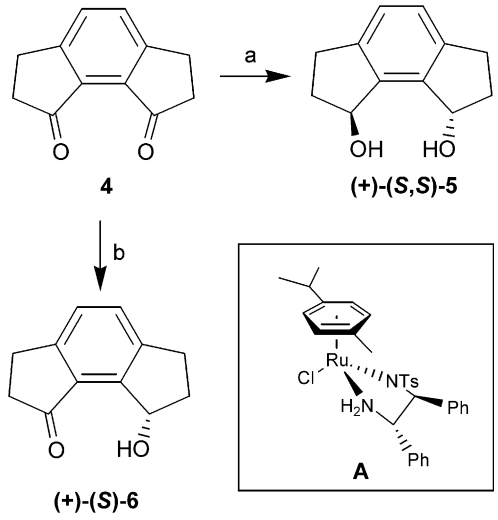
furanocyclophane **3** was accomplished by oxidizing a furan moiety employing *m*-CPBA, after which an in situ Diels–Alder reaction and dehydration with Na_2CO_3 in MeOH resulted in the desired 2,3,6,7-tetrahydro-*as*-indacene-1,8-dione **4**.[6] On a 20 g scale this proved to be a more practical approach than the photooxidation as reported in the original procedure.[3]

In order to obtain the C_2-symmetrical diol **5**, we submitted diketone **4** to Noyori's asymmetric transfer hydrogenation conditions,[7] applying an in situ prepared catalyst (**A**) derived from commercial (1*S*,2*S*)-(+)-*N*-*p*-tosyl-1,2-diphenylethylenediamine and $[RuCl_2(\eta^6\text{-cymene})]_2$ in a 5:2 formic acid–triethylamine mixture. This resulted in mono-hydrogenated keto-alcohol (+)-**6** or bis-hydrogenated diol (+)-**5**, depending on reaction time, temperature and catalyst loading (Scheme 2).

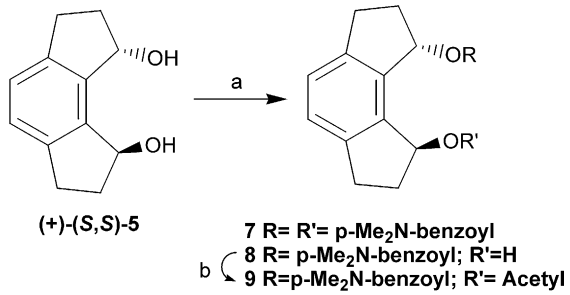
In this way, using 3% in situ generated catalyst **A**, diol (+)-**5** was obtained in high yield (81%) and excellent enantioselectivity (>99% ee) after 4 days at room temperature. In contrast, using only 1% of catalyst, mono-hydrogenated keto-alcohol (+)-**6** could be isolated in 58% yield and 98.5% ee after 54 h at room temperature. Repeating the latter reaction at 60 °C resulted in a dramatic increase of the reaction rate, allowing isolation of (+)-**6** in similar yield and enantiomeric excess after only 3 h. Finally, reduction at 60 °C for 24 h with 3% catalyst gave (+)-**5** in 73% yield and >99% ee.[8,9]

The absolute configuration obtained in the asymmetric reduction was predicted to be *S*, by analogy with the reduction of indanone to (*S*)-indanol using the same catalyst and given the fact that the enantiofacial differentiation occurs via a π–CH interaction of a metal saturated species and the aromatic ketone.[10]



Scheme 2. Reagents, conditions and yields: in situ preparation of catalyst **A**: $[RuCl_2(\eta^6\text{-cymene})]_2$, (*S*,*S*)-Ts-DPEN, NEt_3, (0.5:1.05:2), DMF, 80 °C, 1 h; (a) $HCOOH/NEt_3$ (molar ratio 5:2) and DMF (1:2), 3 mol% **A**, 96 h, rt, 81% (>99% ee) or 24 h, 60 °C, 73% (>99% ee); (b) $HCOOH/NEt_3$ (molar ratio 5:2) and DMF (1:2), 1 mol% **A**, 54 h, rt, 58% (~98.5% ee) or 3 h, 60 °C, 58% (~98.5% ee).

The CD exciton chirality method is very powerful for the determination of the absolute stereochemistry of chiral organic compounds.[11] In order to confirm the absolute stereochemistry of diol (+)-**5**, bis(*p*-Me_2N)-benzoate **7** and its *O*-acetyl-mono(*p*-Me_2N)benzoate **9** (Scheme 3) were synthesized. Both **7** (ε = 55,700) and **9** (ε = 28,200) exhibit strong π–π^*-absorption at λ_{max} = 311 nm (Fig. 1). In contrast to the case of UV-spectra, a striking dif-



Scheme 3. Reagents, conditions and yields: (a) *p*-Me_2N-benzoylchloride, THF, DMAP, 60 °C, 24 h; 57% of **7** and 38% of **8**; (b) Ac_2O, DMAP, pyridine, rt, 1 h; 72%.

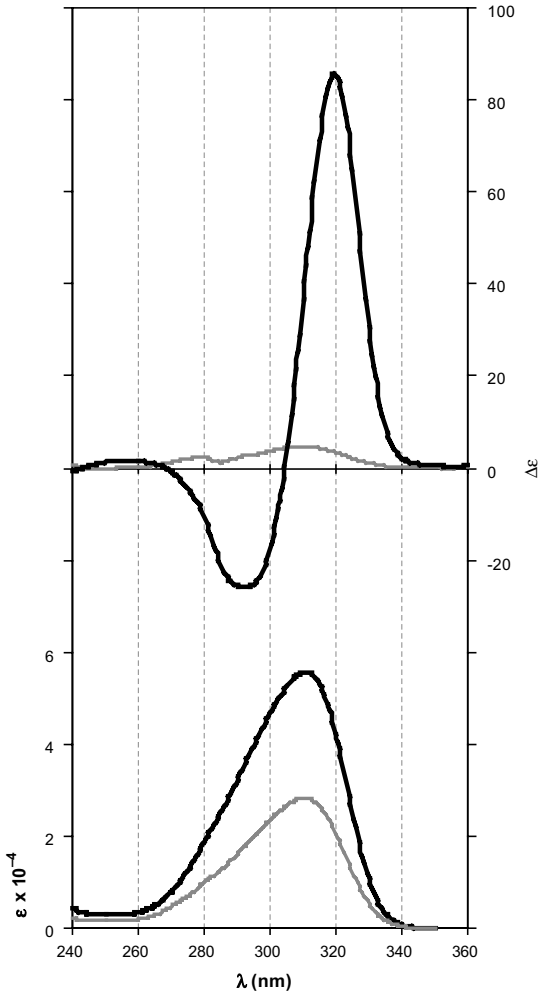


Figure 1. UV (bottom) and CD (top) spectra of bis(*p*-Me_2N-benzoate) **7** (bold black line) and *p*-Me_2N-benzoyl-acetyl derivative **9** (thin gray line) in CH_3CN.

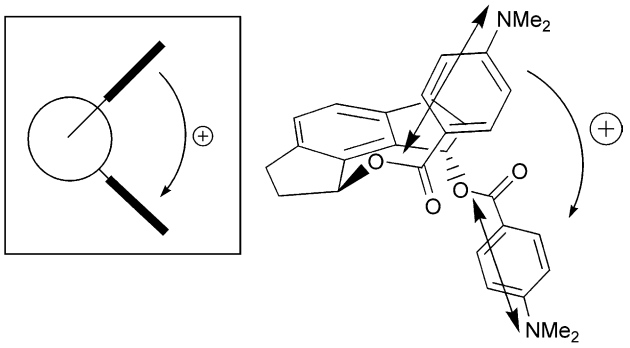


Figure 2. The positive chirality constituted by the two benzoate moieties, resulting in a positive first and a negative second Cotton effect.

ference is observed between CD spectra of monobenzoate **9** and di-benzoate **7**. Monobenzoate **9** shows a weak positive Cotton effect ($\Delta\varepsilon = 4.7$) in the region of the absorption maximum $\lambda_{max} = 311$ nm. In contrast, the CD spectrum of **7** shows a strong exciton split CD Cotton effect centred at 305 nm: a positive first extremum at 320 nm ($\Delta\varepsilon = 86$) and a negative second extremum at 292 nm ($\Delta\varepsilon = -26$). The large difference between the circular dichroism of **7** and **9** can therefore only be attributed to the chiral exciton coupling of the two identical *p*-Me_2N-benzoate chromophores.[11] The positive amplitude ($A = 112$) indicates a clockwise screw sense between the two benzoate moieties (Fig. 2).[12] The absolute configuration is therefore assigned as (1*S*,8*S*)-**5** and (8*S*)-**6**. Transformation of (+)-**5** and (+)-**6** into chiral N- and P-ligands, and their application in asymmetric catalysis is under current investigation and will be published in due course. As enantiomeric (1*R*,2*R*)-(−)-*N*-*p*-tosyl-1,2-diphenylethylenediamine is commercially available as well, our approach also constitutes a synthesis of (−)-**5** and (−)-**6**, and hence will allow access to both enantiomeric series of all derived N- and P-ligands.

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6. Experimental procedure for the synthesis of **4**: Furanocyclophane **3** (20.0 g; 0.106 mol) was dissolved in 500 mL $CHCl_3$ and cooled to −30 °C. *m*-CPBA (20.1 g; 0.116 mol; ~90% purity) was added, followed by two more portions (2 × 0.6 g; 2 × 3.48 mmol), respectively, after 30 and 60 min. The mixture was stirred for 30 min more at −30 °C and then quenched with 0.1 M aqueous $Na_2S_2O_3$. After warming to room temperature, stirring was continued for 5 h. The white heterogenous mixture was poured into 250 mL aqueous $NaHCO_3$ (satd) and extracted with $CHCl_3$ (2 × 250 mL). The combined organic fractions were washed with 150 mL $NaHCO_3$ and the volatiles were removed in vacuo, resulting in 21.1 g crude mixture. The white solid was dissolved in 800 mL MeOH and 200 mL aqueous Na_2CO_3 (satd) was added. After 1.5 h the reaction mixture was poured into H_2O (1 L) and extracted with $CHCl_3$ (3 × 1 L) After drying over anhydrous $MgSO_4$, filtration and removal of the solvent in vacuo, the solid residue was redissolved and filtered over 100 mL silicagel using $CHCl_3$/EtOAc 6:4 as eluent. Evaporation of the volatiles in vacuo resulted in 18.2 g crude mixture. Recrystallization from MeOH gave 17.4 g (0.0934 mol; 88%) **4** as a pale yellow solid. Selected data for **4**: mp 211–212 °C (lit. 208–209);[3] δ_H (500 MHz; $CDCl_3$): 2.70–2.75 (4H, m,), 3.15–3.20 (4H, m), 7.65 (2H, s); δ_C (125 MHz; $CDCl_3$): 26.2 (CH_2), 36.8 (CH_2), 132.3 (CH), 134.6 (C), 156.3 (C), 203.5 (C) ppm.
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8. Selected data for (+)-**5**: mp 155.5–156.5 °C; $[\alpha]_D^{20}$ +70.5 (*c* 1.09, $CHCl_3$); δ_H (500 MHz, $CDCl_3$): 1.91 (2H, dddd [app. dq], $J = 8.4, 9.3, 9.3, 12.5$ Hz), 2.56 (2H, dddd, $J = 2.0, 7.1, 7.5, 12.5$ Hz), 2.77 (2H, ddd, $J = 7.5, 9.3, 15.0$ Hz), 2.94 (2H, ddd, $J = 2.0, 9.3, 15.0$ Hz), 5.47 (2H, dd [app. t], $J = 7.1, 8.4$ Hz), 7.10 (2H, s); δ_C (125 MHz; $CDCl_3$): 29.7 (CH_2), 35.9 (CH_2), 75.6 (CH), 124.5 (CH), 140.7 (C), 141.1 (C) ppm; HPLC: Chiralcel OD-H column, solvent: *n*-hexane/EtOH (97:3), flow rate = 1 mL/min, T = 35 °C, retention times: (1*S*,8*S*)-**5** = 14.2 min, (1*R*,8*R*)-**5** = 16.1 min.
Selected data for (+)-**6**: mp 108–110 °C; $[\alpha]_D^{20}$ +94.4 (*c* 1.01, $CHCl_3$); δ_H (500 MHz; $CDCl_3$): 2.03 (1H, dddd [app. dq], $J = 8.2, 9.5, 9.5, 13.0$ Hz), 2.61 (dddd, 1H, $J = 1.8, 7.8, 8.0, 13.0$ Hz), 2.69–2.80 (2H, m), 2.87 (1H, ddd, $J = 8.0, 9.5, 15.9$ Hz), 3.04 (1H, ddd, $J = 1.8, 9.5, 15.9$ Hz), 3.14–3.23 (2H, m), 5.58 (1H, dd, $J = 7.8, 8.2$ Hz), 7.34 (1H, d, $J = 7.8$ Hz), 7.44 (1H, d, $J = 7.8$ Hz); δ_C (125 MHz; $CDCl_3$): 26.6 (CH_2), 30.3 (CH_2), 33.9 (CH_2), 36.5 (CH_2), 75.3 (CH), 126.0 (CH), 131.7 (CH), 133.5 (C), 142.2 (C), 144.8 (C), 154.9 (C), 210.3 (C) ppm; HPLC: Chiralcel OD-H column, solvent: *n*-hexane/EtOH (98:2), flow rate=1 mL/min, T = 35 °C, retention times = (8*S*)-**6** = 11.5 min, (8*R*)-**6** = 12.8 min.
9. Together with (+)-**5**, ~5% (+)-**6** and ~2% *meso*-diol were isolated applying 3% catalyst at rt; using 1% catalyst at rt or 60 °C, 25–30% of a mixture of diols was isolated together with (+)-**6**. With 3% catalyst at 60 °C for 24 h, 18% (+)-**6** and 6% *meso*-diol were obtained as byproducts. Selected data for *meso*-diol: mp 109 °C (lit. 111.0–111.8 °C)[3]; δ_H (500 MHz; $CDCl_3$): 2.01 (2H, dddd, $J = 4.9, 6.5, 9.0, 13.6$ Hz), 2.50 (2H, dddd, $J = 4.7, 7.3, 8.8, 13.6$ Hz), 2.83 (2H, ddd, $J = 6.5, 8.8, 15.6$ Hz), 3.08 (2H, ddd, $J = 4.7, 9.0, 15.6$ Hz), 5.46 (2H, dd, $J = 4.9, 7.3$ Hz), 7.14 (2H, s); δ_C (125 MHz; $CDCl_3$): 30.3 (CH_2),

34.7 (CH_2), 75.7 (CH), 124.9 (CH), 141.3 (C), 142.0 (C) ppm.
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12. Due to the irreversible nature of the transfer hydrogenation in a 5:2 $HCOOH/NEt_3$ mixture, the absolute configuration of (8*S*)-**6** can be related to (1*S*,8*S*)-**5**. This was confirmed by the reduction of (8*S*)-**6** into a mixture of *meso*- and (1*S*,8*S*)-**5** (3:1) with $NaBH_4$ in MeOH.