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A Scalable Synthesis of (*R*)-3,5-Dihydro-4*H*-dinaphth[2,1-*c*:1′2′-*e*]azepine

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Abstract:

Environmentally benign scalable procedures are developed to supply enantiomerically pure (*R*)-3,5-dihydro-4*H*-dinaphth[2,1-*c*:1′2′-*e*]azepine 1 as its hydrogen oxalate salt in a five-step overall yield of 41%, which consist of the following: (1) bis *O*-triflation of (*R*)-1,1′-bi-2-naphthol 8 [$(CF_3SO_2)_2O$, pyridine, PhMe; quantitative yield]; (2) Kumada's cross-coupling [MeMgI, $NiCl_2$(dppp), *tert*-BuOMe; 96% yield]; (3) radical bromination [*N*-bromosuccinimide, 2,2′-azobisisobutyronitrile, cyclohexane; 54% yield]; (4) cyclization [allylamine, Et_3N, THF, 86%]; (5) *N*-deallylation [1,3-dimethylbarbituric acid, $Pd(OAc)_2$, Ph_3P, PhMe] followed by crystalline salt formation with oxalic acid (overall 92% yield).

Introduction

C_2-Symmetric chiral 3,5-dihydro-4*H*-dinaphth[2,1-*c*:1′2′-*e*]azepine **1** was exploited in designing chiral quaternary ammonium salts as asymmetric phase-transfer catalysts in our laboratory,[1] which culminated in the development of the versatile unique catalysts of a rigid *N*-spiro structure **2** (Figure 1).[2] Besides serving chiral recognition in our phase-transfer catalysis (PTC) endeavor,[3] the conformational rigidity of dihydroazepine **1** around its C_2-symmetric axis has been used to advantage in devising chiral auxiliaries for asymmetric synthesis, which include (1) Hawkins' asymmetric ammonia synthon **1** for the stereoselective carbon−nitrogen bond formation in a Michael addition sense;[4] (2) Cram's chiral controllers **3** and **4** in the asymmetric addition of organolithium reagents to aldehydes;[5] (3) Rosini and Salvadori's chiral ligand **3** for stoichiometric OsO_4-mediated enantioselective dihydroxylation of olefins;[6] (4) Mazaleyrat's chiral acyl anion equivalent **5** for the stereoselective addition to aldehydes;[7] (5) Aggarwal and Wang's imminium salt **6** for the asymmetric catalysis of epoxidation of unfunctionalized alkenes using Oxon as a co-oxidant;[8] and (6) Rychnovsky's chiral nitroxyl catalyst **7** for the enantioselective oxidation of secondary alcohols using NaOCl as a co-oxidant.[9]

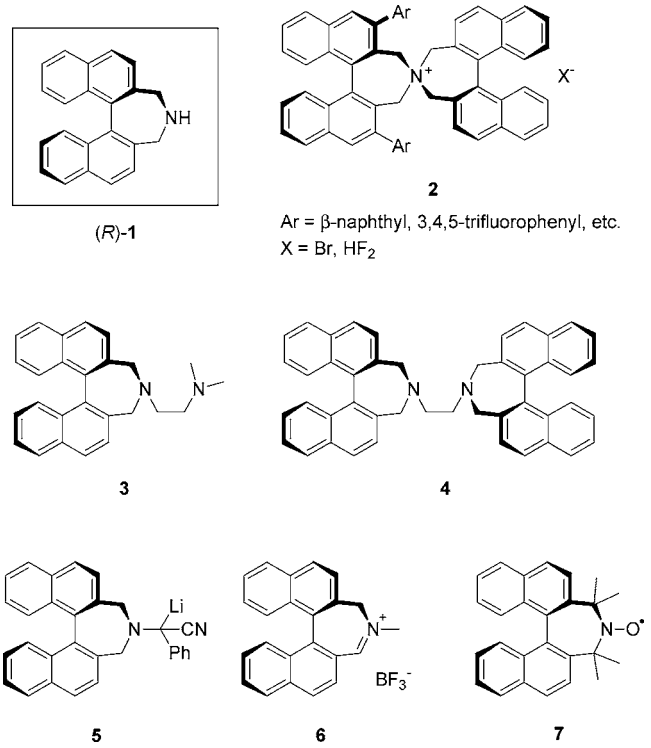

Figure 1. **Structure of (*R*)-3,5-dihydro-4*H*-dinaphth-[2,1-*c*:1′2′-*e*]azepine 1 and asymmetric controllers featuring it.**

Despite such wide applicability, neither our synthetic approaches to a single enantiomer of **1**[1,10] nor those reported hitherto from other laboratories[4a,c,5,6] seemed amenable to scale-up as each of them suffered from practical drawbacks

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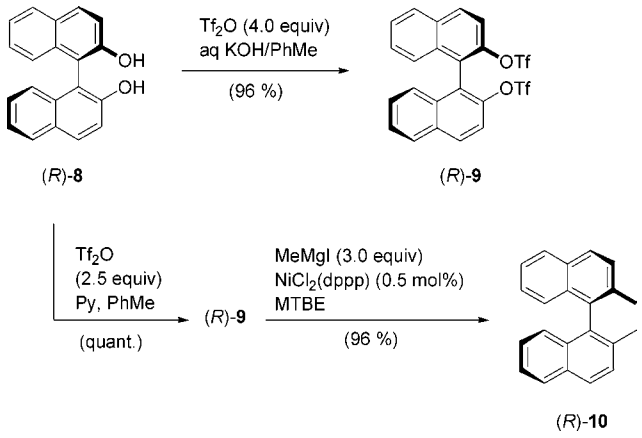
Scheme 1. **Bis *O*-triflation and Ni(0)-catalyzed cross-coupling**



of its own. For instance, with regard to our five-step synthesis of (*S*)-**1** [(1) bis *O*-triflation of (*S*)-1,1′-bi-2-naphthol;[1,10] (2) Kumada's Ni(0)-catalyzed cross-coupling with MeMgI;[1,10] (3) radical bromination;[1,10] (4) double alkylation on allylamine;[1,10] (5) Pd(0)-catalyzed *N*-deallylation[10]], the following issues should be addressed for the synthesis to become scalable: (1) purification by column chromatography after every reaction; (2) application of cryogenic conditions (*O*-triflation at −78 °C); (3) use of CH_2Cl_2 [*O*-triflation and Pd(0)-catalyzed *N*-deallylation]; (4) use of highly flammable Et_2O [Kumada's Ni(0)-catalyzed cross-coupling], and (5) difficulty in isolating (*S*)-**1** as free-flowing, easy-to-handle crystals. Thus, to resolve all those scale-up problems and to supply our own PTC program with both enantiomers of **1** in quantity, we chose to adapt the synthetic route mentioned above for practical processes and succeeded eventually with incremental modifications as discussed in detail below.

Results and Discussion

Both enantiomers of 1,1′-bi-2-naphthol **8** are commercially available;[11] therefore, we chose (*R*)-**8** (99.8% ee) as the starting point of our synthetic maneuvers and converted it into (*R*)-dihydroazepine **1** to illustrate the best practices of our investigation.

Bis *O*-Triflation. When (*R*)-**8** was treated with trifluoromethanesulfonic anhydride (Tf_2O) in the presence of Et_3N in CH_2Cl_2 at −78 °C, bis *O*-triflation proceeded uneventfully.[1] However, the reaction would remain less practical and difficult to scale-up unless use of a halogenated solvent (CH_2Cl_2) or cryogenic conditions (−78 °C) could be eliminated.

Hence, to run the bis *O*-triflation at higher temperatures under environmentally benign conditions,[12] a milder acid scavenger than Et_3N should be employed in combination with a widely accepted hydrocarbon solvent (Scheme 1): when a PhMe solution of (*R*)-**8** was treated with Tf_2O (2.5 equiv) in the presence of pyridine (4.0 equiv) at 0 °C and the resulting mixture was stirred at room temperature, the bis *O*-triflation went to completion in 3 h with little coloration to afford (*R*)-bis *O*-triflate **9** quantitatively, which was pure enough to be used in the next step without further purification.

Table 1. **Cross-coupling of (*R*)-9 with methyl Grignard reagent by the catalysis of $NiCl_2$(dppp)[a]**

solvent {[(*R*)-**9**] (M)}	MeMgX (equiv)	temp (°C)	reaction time (h)	ee (%) of (*R*)-**10**[b]	yield (%)
Et_2O {0.28}	X = I (5.0)	35	13	99.3	93.5
THF {0.16}	X = Cl (5.0)	40	4	88.4	82.0
MTBE {0.25}	X = I (3.0)	55	0.5	99.6	96.1

[a] $NiCl_2$(dppp), 0.5 mol %. [b] Determined by chiral HPLC: Chiralpak OD (Daicel; 4.6 mmϕ × 250 mm), 25 °C; *n*-hexane/*i*-PrOH (99.8:0.2), 0.5 mL/min; UV at 240 nm; t_R 9.5 min for (*S*)-**10**, 12.3 min for (*R*)-**10**.

In the meantime, *O*-triflation under biphasic aqueous conditions [30% (w/v) aqueous K_3PO_4/PhMe] was also explored,[13] and in contrast to Frantz's report, 15% aqueous KOH solution turned out to be the optimum base for the bis *O*-triflation in question. Indeed, (*R*)-bis *O*-triflate **9** was obtained in 96% yield under such Schotten−Baumann conditions; however, it took as long as 48 h and required as much as 4 equiv of Tf_2O for the bis *O*-triflation to be driven to completion. Hence, as far as bis *O*-triflation of 1,1′-bi-2-naphthol **8** was concerned, the biphasic conditions [15% (w/v) aqueous KOH solution/PhMe] should be less amenable to scale-up than the homogeneous conditions (pyridine/PhMe) identified in our laboratory.

Cross-Coupling with MeMgI. Since its advent in the 1980s,[14] Kumada's cross-coupling of Grignard reagents with aryl halides or triflates by the catalysis of Ni(0)-phosphine complexes has found wide application in synthetic organic chemistry, as demonstrated in part by our successful assemblage of **2**.[1] However, use of highly flammable Et_2O detracted from its practical value in terms of safety, and to the best of our knowledge, Kumada's cross-coupling has not been effected with either enantiomer of **9** in a solvent other than Et_2O so far.[15]

Thus, ethereal solvents in common industrial use and much safer than Et_2O were explored to run the cross-coupling reaction of MeMgI with (*R*)-bis *O*-triflate **9** in a scalable manner (Table 1). When a THF solution of (*R*)-**9** was treated with MeMgCl (5.0 equiv; 3.0 M solution in THF, available from Aldrich) at 40 °C, the cross-coupling by the catalysis of $NiCl_2$(dppp) (0.5 mol %) appeared to proceed uneventfully to give (*R*)-**10** in 82% yield. Actually, however, it suffered partial racemization with a decrease in the enantiomeric purity of (*R*)-**10** to 88.4% ee as indicated by chiral HPLC analysis (Chiralpak OD).

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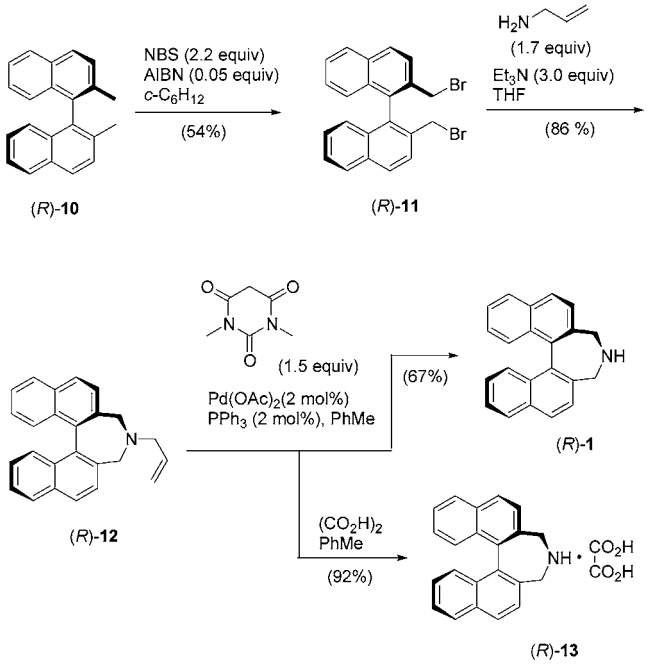
Scheme 2. **Bromination and dihydroazepine ring closure**



Considering that the cross-coupling in Et_2O could be effected at 35 °C (boiling point of Et_2O) without affecting the enantiomeric purity of (*R*)-**10**,[1,10a] we believed such loss of stereochemical integrity should be restored if THF could be replaced with an acyclic ethereal solvent of structural resemblance to Et_2O. In fact, (*R*)-**9** did undergo cross-coupling with MeMgI (3.0 equiv) in the presence of $NiCl_2$-(dppp) (0.5 mol %) in *tert*-butyl methyl ether (MTBE) at 55 °C (boiling point of MTBE) without detectable racemization, and (*R*)-**10** of 99.6% ee was obtained in 96.1% yield after filtration through a short pad of silica gel; (*R*)-**10** thus obtained was pure enough to be employed in the next step (Scheme 1).

Bromination and Dihydroazepine Ring Closure. With two one-carbon appendages installed in place, (*R*)-**10** was subjected to radical bromination,[1] where simple workup procedures were explored which would allow (*R*)-**11** to be isolated in a substantially pure state (Scheme 2): A 14% (w/v) solution of (*R*)-**10** in cyclohexane was heated with *N*-bromosuccinimide (NBS, 2.2 equiv) in the presence of 2,2′-azobisisobutyronitrile (AIBN, 0.05 equiv) at reflux for 2 h. On complete consumption of (*R*)-**10** as monitored by TLC [AcOEt/*n*-hexane (1:10)], AcOEt (one-third the volume of the cyclohexane employed) was added to dissolve byproduct(s) in it. The mixture was then poured into water (two times the volume of the cyclohexane employed) to precipitate (*R*)-**11** as crystals in 54% yield immediately while succinimide remained dissolved in the aqueous phase.

To close a dihydroazepine ring, allyamine was used as an ammonia surrogate according to Hawkins' protocol.[4c] When Et_3N (3.0 equiv) was used as an acid scavenger, double displacement on (*R*)-**11** with allylamine (1.7 equiv) proceeded smoothly in THF at 55 °C and went to completion in 3 h. (*R*)-*N*-Allydihydroazepine **12** of substantial purity was eventually obtained in 85% yield after reslurrying its crude crystals in acetone (1:1 v/w).

Nitrogen Deprotection and Isolation of the Final Products. Having served *N*,*N*-bisalkylation in closing the dihydroazepine ring, the extra *N*-ally group was supposed to be removed (Scheme 2). Such cleavage could be effected either by solvolysis of the enamine arising from olefin isomerization caused by Wilkinson's catalyst [$Rh(PPh_3)_3$-Cl][1,4c] or by displacement on the π-allyl palladium complex with 1,3-dimethylbarbituric acid (NDMBA),[10,16] and the latter protocol should be more cost effective in view of Pd being less expensive than Rh.

The Pd(0)-catalyzed *N*-deallylation of (*R*)-**12** could be carried out successfully in our laboratory by the combined use of $Pd(OAc)_2$ and Ph_3P in CH_2Cl_2 in place of light-sensitive $(Ph_3P)_4Pd$.[10] Despite such improvement in the catalyst handling, however, use of CH_2Cl_2 as a reaction medium still detracted from the practical advantages of this process. Thus, the *N*-deallylation in question was attempted in a nonhalogenated solvent in common use in industry: A PhMe solution of (*R*)-**12** was treated with NDMBA (1.5 equiv) in the presence of $Pd(OAc)_2$ and Ph_3P (each 2 mol %) at 35 °C for 3 h. On completion of the reaction, the PhMe solution was washed with 1 M aqueous NaOH solution to remove NDMBA-derived acidic materials. It was then extracted with an aqueous solution of a mineral acid, such as HCl and H_2SO_4, to separate basic (*R*)-**1** from the neutral metal complex, but precipitation of tarry materials hampered the extraction. However, when 50% aqueous AcOH solution was used in the extraction, such annoying events could be avoided. Hence, (*R*)-**1** was extracted conveniently into 50% aqueous AcOH, which, on basification with 48% aqueous NaOH solution, was extracted with PhMe to recover crude (*R*)-**1** as crystalline solids. Recrystallization from MeOH (2 v/w) finally provided purified (*R*)-**1** as discrete, free-flowing solids in 66.8% yield, the enantiomeric purity of which was determined to be 99.8% ee by chiral HPLC (Chiralpak AD-H).

While (*R*)-dihydroazepine **1** of high purity could be obtained, product isolation by partition was demanding, and what was worse, the isolation yield was far from satisfactory. Therefore, isolation of (*R*)-**1** as a crystalline salt was explored: On completion of the Pd(0)-catalyzed *N*-deallylation, the reaction mixture was washed with 1 M aqueous NaOH solution. Oxalic acid (1.5 equiv) was then added to form the hydrogen oxalate salt of (*R*)-**1**, which precipitated instantaneously from the PhMe solution with little, if any, loss of material as easy-to-handle crystalline solids. Eventually, enantiomerically pure (*R*)-**1**·$(CO_2H)_2$, (*R*)-**13**, was obtained in 92% yield, with its off-enantiomer being undetected by chiral HPLC (Chiralpak AD-H).

Conclusions

Practical processes to access (*R*)-dihydroazepine **1** were established with elaborate modifications to methods that had been devised to assemble chiral *N*-spiro quaternary ammonium salt **2** in our laboratory.[1,10] The critical issues addressed from a practical viewpoint are as follows: (1)

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replacement of environmentally unacceptable CH_2Cl_2 with PhMe in both bis *O*-triflation [(*R*)-**8** → (*R*)-**9**] and *N*-deallylation [(*R*)-**12** → (*R*)-**1**]; (2) replacement of easy-to-ignite Et_2O with safer *tert*-BuOMe in Kumada's cross-coupling [(*R*)-**9** → (*R*)-**10**] without affecting the stereochemical integrity of (*R*)-**10**; (3) no application of cryogenic conditions to the bis *O*-triflation [(*R*)-**8** → (*R*)-**9**]; (4) no resort to column chromatography throughout the overall processes; (5) simple isolation of the final product, (*R*)-**1**, as its hydrogen oxalate salt, (*R*)-**13**. With all these improvements in combination, enantiomerically pure (*R*)-**13** was now obtained in 41% overall yield from (*R*)-1,1′-bi-2-naphthol **8** in five steps.

Experimental Section

Melting points were measured on an Electrothermal 1A8104 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 400 MHz on a Varian UNITY-400 spectrometer with tetramethylsilane as an internal standard. FT-IR spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. Mass spectra were recorded on a Hitachi M-8000 mass spectrometer (ESI). Elemental analyses were performed on an Elementar vario EL analyzer. Optical rotations were measured on a Horiba SEPA-200 polarimeter. Thin-layer chromatography (TLC) was performed on Merck Kieselgel 60 plates (0.25 mm thick, art 1.057 14).

(*R*)-1,1′-Bi-2-naphthol Bis(trifluoromethanesulfonate) 9. Under an atmosphere of nitrogen, trifluoromethanesulfonic anhydride (49.3 g, 174 mmol) was added dropwise to a stirred and ice-cooled solution of (*R*)-1,1′-bi-2-naphthol **8** (Kankyo Kagaku Center Co., Ltd.; 99.8% ee; 20.0 g, 69 mmol) and pyridine (22.1 g, 279 mmol) in PhMe (140 mL) over 40 min at 2−9 °C (internal temperature). After addition was complete, the cooling bath was removed and the mixture was stirred at room temperature (20−25 °C) for 3 h. Consumption of (*R*)-**8** was confirmed by TLC [AcOEt/*n*-hexane (1:4); R_f 0.16 for (*R*)-**8**, 0.46 for (*R*)-**9**]. PhMe (100 mL), H_2O (100 mL), and 35% aqueous HCl (30 mL) were added in sequence at room temperature (20−25 °C). The layers were separated, and the PhMe layer was washed with H_2O (100 mL × 2) and saturated aqueous NaCl solution (100 mL × 1). The PhMe solution was dried ($MgSO_4$) and concentrated in vacuo [40−50 °C (bath temperature), 50−60 mmHg] to give crude (*R*)-**9** (36.4 g, quantitative) as an off-white solid: mp 64−74 °C (lit.:[17] mp 82−85 °C); $[\alpha]^{20}_D$ −151° (*c* 0.29, $CHCl_3$) {lit.:[17] $[\alpha]^{23}_D$ −146.0° (*c* 1, $CHCl_3$)}; IR ν_{max} (KBr) 1507, 1421, 1215, 1136, 961, 938, 830 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 8.14 (2H, d, J = 8.8 Hz), 8.01 (2H, d, J = 8.0 Hz), 7.62 (2H, d, J = 8.0 Hz), 7.59 (2H, ddd, J = 1.2 Hz, 6.8 Hz, 8.4 Hz), 7.41 (2H, ddd, J = 1.2 Hz, 6.8 Hz, 8.4 Hz), 7.27−7.24 (2H, m). This was employed in the next step without further purification.

(*R*)-2,2′-Dimethyl-1,1′-binaphthyl 10. Under an atmosphere of nitrogen, a solution of MeI (3.90 g, 27.5 mmol) in *tert*-butyl methyl ether (MTBE, 4.0 mL) was added dropwise to a stirred suspension of Mg turnings (660 mg, 27.1 mmol) in MTBE (7.0 mL) such that gentle reflux was maintained throughout the addition. The mixture was allowed to cool to 30 °C where MTBE (5.0 mL) and $NiCl_2$(dppp) (250 mg, 0.46 mmol) were added in sequence. A solution of crude (*R*)-**9** (5.00 g, 9.08 mmol) in MTBE (20 mL) was added dropwise, and the mixture was stirred and heated under reflux (at 55 °C) for 30 min. Consumption of (*R*)-**9** was confirmed by TLC [AcOEt/*n*-hexane (1:4); R_f 0.46 for (*R*)-**9**, 0.79 for (*R*)-**10**]. The mixture was allowed to cool to room temperature (20−25 °C). PhMe (30 mL) was added, and the mixture was poured into ice-chilled water (50 mL). To the mixture was added 35% aqueous HCl (5.0 mL). The layers were separated, and the organic layer was washed with H_2O (30 mL × 2) and saturated aqueous NaCl solution (30 mL × 1). The organic solution was dried ($MgSO_4$) and concentrated in vacuo [40−50 °C (bath temperature), 50−60 mmHg]. The solid residue (2.60 g) was mounted on a short pad of silica gel (Merck Kieselgel 60, 7.8 g). Elution with AcOEt/*n*-hexane (1:4; 200 mL) gave (*R*)-**10** (2.46 g, 96.1%) as white crystals: 99.6% ee [HPLC: column, Chiralpak OD (Daicel; 4.6 mmϕ × 250 mm), 25 °C; eluent, *n*-hexane/*i*-PrOH (99.8:0.2), 0.5 mL/min; detection, UV at 240 nm; injected was 1 μL of a solution of the crystals (1.0 mg) in MTBE (1.0 mL); t_R 9.5 min for (*S*)-**10** (0.2%), 12.3 min for (*R*)-**10** (99.8%)]. Mp 77−79 °C; $[\alpha]^{20}_D$ −42.6° (*c* 0.20, $CHCl_3$) {lit.:[15b] $[\alpha]^{20}_D$ −35.6° (*c* 1.0, $CHCl_3$) for (*R*)-**10** of 94% ee}; IR ν_{max}(KBr) 3045, 2910, 1503, 1421, 1219, 815, 744 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 7.89 (2H, d, J = 8.4 Hz), 7.87 (2H, d, J = 8.4 Hz), 7.50 (2H, d, J = 8.4 Hz), 7.39 (2H, ddd, J = 1.2 Hz, 6.8 Hz, 8.4 Hz), 7.20 (2H, ddd, J = 1.2 Hz, 6.8 Hz, 8.4 Hz), 7.04 (2H, dd, J = 1.2 Hz, 8.4 Hz), 2.03 (6H, s).

(*R*)-2,2′-Bis(bromomethyl)-1,1′-binaphthyl 11. To a suspension of (*R*)-**10** (24.4 g, 86.4 mmol) in cyclohexane (170 mL) was added *N*-bromosuccinimide (NBS, 33.8 g, 190 mmol) followed by 2,2′-azobisisobutyronitrile (AIBN, 0.70 g, 4.26 mmol) at room temperature (20−25 °C). The mixture was stirred and heated at reflux for 2 h, during which the progress of the reaction was monitored by TLC [AcOEt/*n*-hexane (1:10); R_f 0.60 for (*R*)-**10**, 0.49 for (*R*)-**11**]. On consumption of (*R*)-**10**, the mixture was allowed to cool to room temperature (20−25 °C), and AcOEt (56 mL) was added with stirring. The mixture was poured into H_2O (350 mL). The biphasic mixture was stirred for not longer than an hour by which solids had ceased to precipitate. Crystalline solids were collected by filtration and air-dried overnight (8−12 h) to give (*R*)-**11** (20.6 g, 54.3%): mp 178−181 °C (lit.:[18] 171−174 °C); $[\alpha]^{20}_D$ +160.5° (*c* 0.11, benzene) [lit.:[18] $[\alpha]^{20}_D$ +148° (*c* 1.7 benzene)]; IR ν_{max} (KBr) 3045, 1507, 1432, 1211, 826, 759 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 8.02 (2H, d, J = 8.8 Hz), 7.93 (2H, d, J = 8.0 Hz), 7.75 (2H, d, J = 8.4 Hz), 7.49 (2H, ddd, J = 1.2 Hz, 6.8 Hz, 8.0 Hz), 7.27 (2H, ddd, J = 1.2 Hz, 6.8 Hz, 8.0 Hz), 7.07 (2H, dd, J = 0.8 Hz, 8.8 Hz), 4.26 (4H, s).

(*R*)-3,5-Dihydro-4-(2-propenyl)dinaphth[2,1-*c*:1′2′-*e*]-azepine 12. Under an atmosphere of nitrogen, allylamine (2.20 g, 38.5 mmol) was added to a stirred solution of (*R*)-

(17) The mp and $[\alpha]_D$ values of (*R*)-**9** recorded in the Aldrich catalog are cited as authentic ones.

(18) Harris, J. M.; McDonald, R.; Vederas, J. C. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2669−2674.

11 (10.0 g, 22.7 mmol) and Et_3N (6.90 g, 68.2 mmol) in THF (70.0 mL) at room temperature (20−25 °C). The mixture was stirred and heated at 55 °C for 3 h. The completion of the reaction was confirmed by TLC [AcOEt/*n*-hexane (1:4); R_f 0.56 for (*R*)-**11**, 0.11 for (*R*)-**12**]. To the mixture was added PhMe (70 mL) followed by 1 M aqueous NaOH solution (70 mL). The layers were separated, and the organic layer was washed with H_2O (70 mL × 2) and saturated aqueous NaCl solution (70 mL × 1). The organic solution was dried ($MgSO_4$) and concentrated in vacuo [40−50 °C (bath temperature), 50−60 mmHg] to give a solid residue (7.40 g), which was suspended in acetone (7.40 mL) and rinsed with stirring. The precipitated crystals were collected by filtration and air-dried overnight (8−12 h) to give (*R*)-**12** (6.50 g, 84.7%): mp 177−178 °C; $[\alpha]^{20}_D$ −396.3° (*c* 0.24, $CHCl_3$); IR ν_{max}(KBr) 3037, 2940, 2791, 1641, 1589, 1510, 1447, 1338, 1237, 1118, 998, 920, 826, 755, 542 cm^{-1}; ^1H NMR δ ($CDCl_3$) 7.95 (4H, d, J = 8.4 Hz), 7.55 (2H, d, J = 8.4 Hz), 7.48−7.44 (4H, m), 7.29−7.24 (2H, m), 6.06−5.96 (1H, m), 5.31−5.21 (2H, m), 3.74 (2H, d, J = 12.6 Hz), 3.16 (2H, d, J = 12.6 Hz), 3.14−3.10 (2H, m).

(*R*)-3,5-Dihydro-4*H*-dinaphth[2,1-*c*:1′2′-*e*]azepine 1. Under an atmosphere of nitrogen, 1,3-dimethylbarbituric acid (NDMBA, 1.90 g, 11.9 mmol), $Pd(OAc)_2$ (300 mg, 0.15 mmol), and Ph_3P (160 mg, 0.60 mmol) were added in sequence to a solution of (*R*)-**12** (2.50 g, 7.45 mmol) in PhMe (25.0 mL) at room temperature (20−25 °C). The mixture was stirred and heated at 35 °C for 3 h. Consumption of (*R*)-**12** was confirmed by TLC [AcOEt/MeOH (1:1); R_f 0.83 for (*R*)-**12**, 0.19 for (*R*)-**1**]. To the stirred mixture was added 1 M aqueous NaOH solution (25 mL). The layers were separated, and the PhMe layer was washed with H_2O (25 mL × 3) and saturated aqueous NaCl solution (25 mL × 1). The PhMe solution was extracted with 50% (w/w) aqueous AcOH solution (20 mL × 3), wherein the absence of (*R*)-**1** in the PhMe layer was confirmed by TLC conducted under the same conditions as specified above. To the combined 50% (w/w) aqueous AcOH extracts was added 48% aqueous NaOH solution (32.5 mL) with ice cooling to make the mixture litmus alkali. The mixture was extracted with PhMe (20 mL). The PhMe extract was washed with H_2O (30 mL × 2) and saturated aqueous NaCl solution (30 mL × 1), dried ($MgSO_4$), and concentrated in vacuo to give a crystalline solid (2.33 g). This was recrystallized from MeOH (4.5 mL) to give (*R*)-**1** (1.47 g, 66.8%): 99.8% ee [HPLC: column, Chiralpak AD-H (Daicel; 4.6 mmϕ × 250 mm), 25 °C; eluent, *n*-hexane/EtOH (9:1) + 0.1% (v/v) Et_2-NH, 0.5 mL/min; detection, UV at 254 nm; injected was 1 μL of a solution of (*R*)-**1** (1.0 mg) in EtOH (0.5 mL); t_R 14.2 min for (*R*)-**1** (99.9%), 17.0 min for (*S*)-**1** (0.1%)]. Mp 73−84 °C [lit.:[4a] 73−84 °C for (*S*)-**1**]; $[\alpha]^{20}_D$ −585.5° (*c* 0.23, $CHCl_3$) {lit.:[4a] $[\alpha]^{20}_D$ +620° (*c* 0.7, $CHCl_3$) for (*S*)-**1**}; IR ν_{max}(KBr) 3045, 2940, 2866, 1507, 1465, 1447, 1365, 1350, 1088, 1028, 819, 755 cm^{-1}; ^1H NMR δ ($CDCl_3$) 7.97 (2H, d, J = 8.4 Hz), 7.95 (2H, d, J = 8.4 Hz), 7.57 (2H, d, J = 8.4 Hz), 7.48−7.43 (4H, m), 7.28−7.24 (2H, m), 3.83 (2H, d, J = 12.4 Hz), 3.51 (2H, d, J = 12.4 Hz); MS *m*/*z* 296 [$(M + H)^+$].

(*R*)-3,5-Dihydro-4*H*-dinaphth[2,1-*c*:1′2′-*e*]azepine Hydrogen Oxalate 13. Under an atmosphere of nitrogen, NDMBA (1.20 g, 7.69 mmol), $Pd(OAc)_2$ (200 mg, 0.09 mmol), and Ph_3P (90.0 mg, 0.36 mmol) were added in sequence to a solution of (*R*)-**12** (1.50 g, 4.47 mmol) in PhMe (15.0 mL) at room temperature (20−25 °C). The mixture was stirred and heated at 35 °C for 5 h. Consumption of (*R*)-**12** was confirmed by TLC [AcOEt/MeOH (1:1); R_f 0.83 for (*R*)-**12**, 0.19 for (*R*)-**1**]. To the mixture was added 1 M aqueous NaOH solution (15 mL). The layers were separated, and the PhMe layer was washed with H_2O (20 mL × 3) and saturated NaCl aqueous solution (20 mL × 1). To the stirred PhMe solution was added oxalic acid (610 mg, 6.77 mmol) at room temperature (20−25 °C). The stirring was continued at room temperature until precipitation of crystalline solids ceased. The precipitated solids were collected by filtration, suspended in H_2O (12 mL), and rinsed with stirring. The solids were filtered off and dried in vacuo with heating at an oven temperature of 40 °C for 10 h to give (*R*)-**13** (1.58 g, 91.9%) as white powders: 100% ee [HPLC: column, Chiralpak AD-H (Daicel; 4.6 mmϕ × 250 mm), 25 °C; eluent, *n*-hexan/EtOH (9:1) + 0.1% (v/v) Et_2NH, 0.5 mL/min; detection, UV at 254 nm; injected was 1 μL of a solution of (*R*)-**13** (1.0 mg) in EtOH (0.5 mL); t_R 14.2 min for (*R*)-**1** (100%), 17.0 min for (*S*)-**1** (0%)]. Mp 72−76 °C; $[\alpha]^{20}_D$ −223.9° (*c* 0.24, MeOH); IR ν_{max}(KBr) 3433, 3045, 2955, 2746, 2605, 1735, 1634, 1596, 1211, 815, 748 cm^{-1}; ^1H NMR δ (CD_3OD) 8.21 (2H, d, J = 8.4 Hz), 8.11 (2H, d, J = 8.4 Hz), 7.79 (2H, d, J = 8.4 Hz), 7.62 (2H, ddd, J = 3.6 Hz, 4.4 Hz, 8.4 Hz), 7.40−7.38 (4H, m), 4.41 (2H, d, J = 13.6 Hz), 3.76 (2H, d, J = 13.2 Hz), 2.36 (0.54H, s; 0.18 mol of PhMe). Anal. Calcd for $C_{24}H_{19}NO_4$·0.18 C_7H_8 (PhMe)·0.35 H_2O: C, 74.30; H, 5.23; N, 3.43. Found: C, 74.1; H, 5.1; N 3.3. Karl Fisher analysis: 1.4% (w/w) H_2O (0.35 mol).

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