Practical synthesis of chiral 9,9′-spirobixanthene-1,1′-diol

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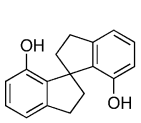
A concise four-step synthesis of 9,9′-spirobixanthene-1,1′-diol is reported, featuring a practical preparation at large scale without the use of column chromatography purification. Co-crystallization with *N*-benzylcinchonidinium chloride and *N*-benzylquininium chloride rendered the optically pure product in both enantiomers.

Introduction

Connected with quaternary carbon, spiro aromatic compounds are of more conformational rigidity than atropisomeric biaryl analogues, constituting a desirable element in the design of chiral ligands for transition metal catalyzed asymmetric reactions. Although first synthesized in the 1930s,[1] the significance of spirans in asymmetric catalysis has not been well recognized until recently.[2] Soon after Chan's work on spirophosphinite,[2a] Birman designed and synthesized a new C_2-symmetric 1,1′-spirobiindane-7,7′-diol **1**.[2b] Improved resolution of **1** *via* co-crystallization[3] enabled Zhou *et al.* to prepare a series of spiro ligands for asymmetric catalysis.[2d,e,i] Following a strategy similar to the synthesis of **1**, Zhou *et al.* also prepared 9,9′-spirobifluorene-1,1′-diol **2**.[4] Meanwhile, we have developed 9,9′-spirobixanthene-1,1′-diol **3** and its phosphoramidite derivatives for highly enantioselective hydrogenation and conjugate addition reactions.[2f,g] Although the two step synthesis of **3** is highly convergent without the extra protection and deprotection steps that are required for the preparation of **1** and **2**, the Lewis-acid mediated simultaneous cyclization and demethylation involve harsh work up with hydrochloric acid and column chromatography separation. In searching for a practical synthesis of 9,9′-spirobixanthene-1,1′-diol, **3**, on a large scale, we report herein a convenient four step procedure without the use of column chromatography purification.



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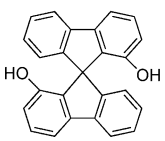

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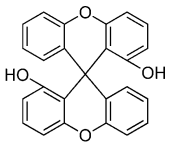

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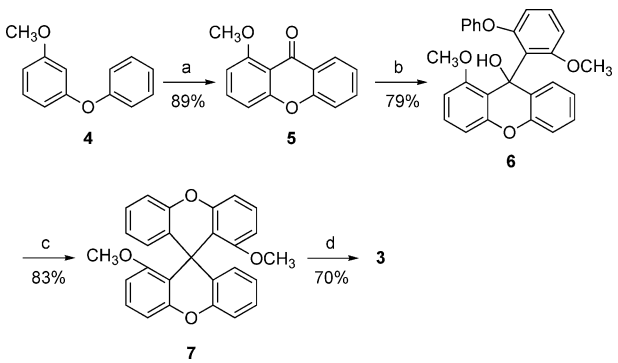
Results and discussion

Acid-mediated cyclization of tertiary alcohols is a classic method for the synthesis of spirans.[1] Compared with double cyclization of ketones, it remains rarely explored so far for the preparation of spiro diols such as **1**, **2**, and **3**. An attempt to prepare **2** *via* an alcohol intermediate was unsuccessful due to an uncontrollable side reaction under bromination conditions.[4] For our target molecule **3**, we envisaged that a straightforward route can be accessed through the key intermediate **6**, which will be subject to cyclization and then demethylation to give the desired product (Scheme 1). A prerequisite for this approach is that the precursor 1-methoxyxanthone **5** shall be assembled in an efficient way. Inspired by recent advances in synthetic chemistry utilizing directed metalation strategy,[5] we found that **5** can be prepared directly from 3-phenoxyanisole **4** *via* tandem directed *ortho* metalation (D*o*M) and directed remote metalation (DreM).[6] Thus 2-methoxy-*N*,*N*-dimethyl-6-phenoxybenzamide was first generated *via* D*o*M by selective deprotonation of **4** with *n*-BuLi at −78 °C and then treatment with equivalent amount of dimethylcarbamyl chloride. Without being isolated, this intermediate was *in situ* converted to **5** in the presence of LDA *via* DreM. Addition of another lithiated **4** to **5** produced the tertiary alcohol **6** as expected, which further underwent ring closure in refluxing HCl and HOAc to form the spirocyclic backbone. In the final step, BBr_3 was initially tested as demethylation reagent. To our surprise, side reaction occurred without the formation of **3**. After screening several available reagents, we found that refluxing **7** in melt pyridine·HCl for less than 30 minutes gave the desired product **3** in satisfactory yield.



Scheme 1 Reagents and conditions: (a) (i) *n*-BuLi (1.2 equiv.), THF, −78 °C, (ii) Me_2NCOCl (1 equiv.), THF, −78 °C, (iii) LDA (2.4 equiv.), THF, 0 °C; (b) lithiated **4** (1 equiv.), THF, −78 °C; (c) HCl, HOAc, reflux; (d) pyridine·HCl, reflux.

Our recent studies[2f] showed that *rac*-**3** can be resolved efficiently *via* co-crystallization with some alkaloid-derived quaternary

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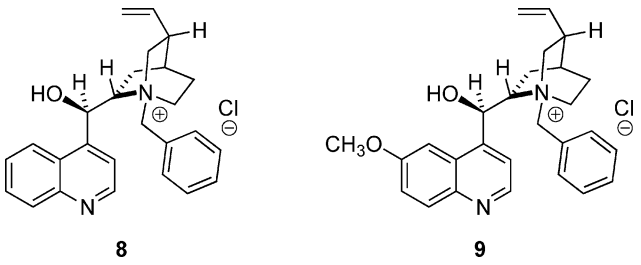
ammonium salts, *i.e.*, *N*-benzylcinchoninium chloride **8** and *N*-benzylquininium chloride **9**. Differing only in a methoxy group, **8** preferentially forms co-crystals with (*R*)-**3** whereas **9** with (*S*)-**3**. X-ray diffraction experiments further confirmed the absolute configuration of the resolved enantiomers, revealing distinct molecular packing modes of the co-crystals of (*R*)-**3**:**8** and (*S*)-**3**:**9** developed from acetonitrile (Fig. 1 and 2).



8 **9**

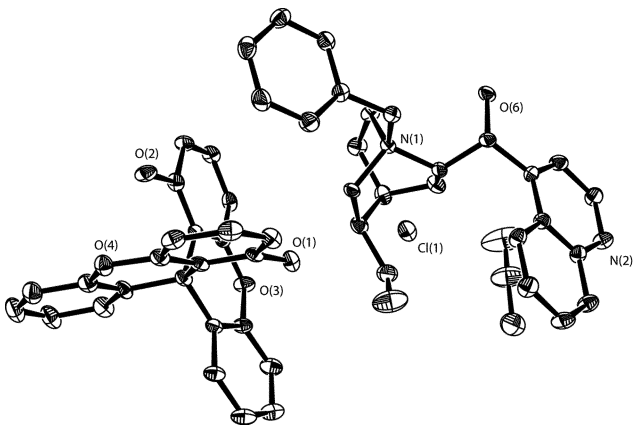


Fig. 1 ORTEP representation of co-crystal of (*R*)-**3** and *N*-benzylcinchoninium chloride **8** (1 : 1) at 50% probability for the drawing of thermal ellipsoids (hydrogen atoms and solvent molecules are omitted for clarity).

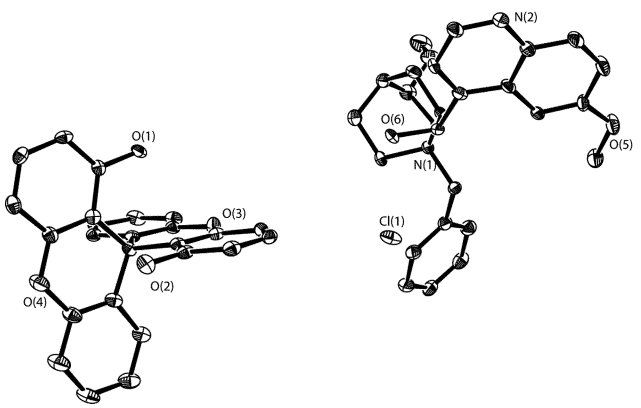


Fig. 2 ORTEP representation of co-crystal of (*S*)-**3** and *N*-benzylquininium chloride **9** (1 : 1) at 50% probability for the drawing of thermal ellipsoids (hydrogen atoms and solvent molecules are omitted for clarity).

Conclusions

In summary, we have established a concise synthesis of 9,9′-spirobixanthene-1,1′-diol **3** in four steps. Because no column chromatography is applied throughout the whole procedure, the title compound can be prepared and resolved conveniently at large scale. Application of chiral **3** and its derivatives for asymmetric catalysis will be reported in due course.

Experimental

General

All reactions were carried out using standard Schlenk techniques unless specified otherwise. The degassed dry solvents are used throughout each experiment. 3-Phenoxyanisole was prepared according to literature. The other chemicals used in this work were purchased from either Aldrich or Acros Inc. ^{1}H NMR and ^{13}C NMR data were recorded on Bruker DPX-300, CDPX-300, and AMX-360 spectrometers. MS data were recorded on KRATOS mass spectrometer for LR-APCI and HR-APCI. Chiral HPLC anaylsis was carried out on a Waters 600 chromatography equipped with an UV detector (254 nm) and a Chiralcel OD-H column. X-ray single crystal diffraction intensity data were measured on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a MoKα fine-focus sealed tube ($\lambda = 0.71073$ Å) operated at 1600 watts power (50 kV, 32 mA).

Synthetic details

1-Methoxyxanthone (5). To the solution of **4** (24.6 g, 0.123 mol) in THF (100 mL) was added *n*-BuLi (2.5 M, 50.7 mL, 0.142 mol) at −78 °C in 1.5 h. After being stirred at this temperature for 1 h, it was allowed to warm slowly to room temperature over 1 h. Then it was cooled to −78 °C and added into the solution of dimethylcarbamic chloride (11.3 mL, 0.123 mol) in THF (50 mL) at −78 °C in 30 min. After stirring at this temperature for 1 h, the cooling bath was removed and it was warmed to room temperature over 4 h. Then it was added dropwise into freshly prepared LDA solution (0.3 mol in 370 mL dry THF) at 0 °C, which was stirred overnight. Aqueous HCl (3 N, 100 mL) was introduced carefully to quench the reaction mixture at 0 °C. The organic phase was separated and washed with saturated $NaHCO_3$ solution and brine. The water layer was extracted with EtOAc, washed with saturated $NaHCO_3$ solution, and brine. The combined organic solution was dried with anhydrous Na_2SO_4 and concentrated. The crude product was triturated with EtOAc/hexane (1 : 9) to afford **5** as light yellow powder (24.8 g, 89%). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 3.98 (s, 3H, ArO–CH_3), 6.83 (d, 1H, $J = 8.3$ Hz, Ar–*H*), 7.06 (dd, 1H, $J_1 = 8.5$ Hz, $J_2 = 0.9$ Hz, Ar–*H*), 7.34 (td, 1H, $J_1 = 7.9$ Hz, $J_2 = 1.0$ Hz, Ar–*H*), 7.41–7.44 (m, 1H, Ar–*H*), 7.59–7.68 (m, 2H, Ar–*H*), 8.22 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 1.7$ Hz, Ar–*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.7, 105.6, 110.3, 112.8, 117.5, 123.3, 124.0, 127.1, 134.4, 135.0, 155.3, 158.4, 161.0, 176.8. HRMS *m*/*z* found: 226.0636, calculated: 226.0630.

1-Methoxy-9-(2-methoxy-6-phenoxyphenyl)xanthen-9-ol (6). Lithiation of **4** (20.6 g, 0.103 mol) was achieved as described in the previous step (43.3 mL 2.5 M *n*-BuLi and 100 mL THF were

used), and the solution was added into the solution of **5** (23.3 g, 0.103 mol) in THF (400 mL) at −78 °C within 1 h, then stirred overnight. The reaction mixture was quenched with saturated NH_4Cl solution at 0 °C, and then extracted with CH_2Cl_2. The organic phase was washed with brine, dried with anhydrous Na_2SO_4, and concentrated. The crude product was triturated with acetone to afford **6** as white powder (34.7 g, 79%). ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.73 (s, 3H, ArO–CH_3), 3.83 (s, 3H, ArO–CH_3), 6.38 (d, 1H, $J = 8.2$ Hz, Ar–*H*), 6.49–6.56 (m, 3H, Ar–*H*), 6.66–6.71 (m, 2H, Ar–*H*), 6.87 (d, 1H, $J = 7.9$ Hz, Ar–*H*), 6.94–7.00 (m, 3H, Ar–*H*), 7.07–7.16 (m, 5H, Ar–*H*), 7.48 (d, 1H, $J = 7.9$ Hz, Ar–*H*); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 56.1, 57.3, 70.8, 105.7, 108.8, 109.3, 114.1, 115.4, 116.8, 118.1, 122.6, 123.0, 128.1, 128.2, 128.3, 128.6, 129.1, 129.5, 149.8, 150.6, 154.6, 157.4, 158.4, 158.5. HRMS *m*/*z* found: 426.1473, calculated: 426.1467.

1,1′-Dimethoxy-9,9′-spirobixanthene (7). The tertiary alcohol **6** (34.7 g, 0.081 mol), acetic acid (300 mL), and concentrated HCl (200 mL) were refluxed for 6 h. After acetic acid was removed under reduced pressure, the residue was dissolved in CH_2Cl_2, washed with saturated $NaHCO_3$ solution, brine, and dried with anhydrous Na_2SO_4, and then concentrated. The crude product was triturated with acetone to afford **7** as white powder (27.5 g, 83%). ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.25 (s, 6H, ArO–CH_3), 6.39 (dd, 2H, $J_1 = 8.2$ Hz, $J_2 = 1.0$ Hz, Ar–*H*), 6.77–6.84 (m, 6H, Ar–*H*), 7.04–7.16 (m, 6H, Ar–*H*); ^{13}C NMR (90 MHz, $CDCl_3$) δ 42.1, 55.8, 100.6, 111.6, 116.5, 122.6, 124.1, 128.2, 130.4, 131.9, 132.6, 149.6, 150.5, 159.6. HRMS *m*/*z* found: 408.1347, calculated: 408.1362.

9,9′-Spirobixanthene-1,1′-diol (3). The mixture of **7** (4.9 g, 0.013 mol) and pyridine·HCl (30.4 g, 0.263 mol) were melted with a heating mantle and reflux for 25 minutes. After cooled to room temperature, the reaction mixture was diluted with HCl solution (4 N, 90 mL) and extracted with EtOAc (100 mL). The organic phase was washed with HCl (4 N, 10 mL) twice, water, saturated $NaHCO_3$ solution, brine, and dried with anhydrous Na_2SO_4, and then concentrated. The crude product was triturated with acetone to afford **3** as white powder (3.2 g, 70%). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 6.30 (dd, 2H, $J_1 = 8.0$ Hz, $J_2 = 1.2$ Hz, Ar–*H*), 6.60 (dd, 2H, $J_1 = 8.2$ Hz, $J_2 = 1.2$ Hz, Ar–*H*), 6.78–6.80 (m, 4H, Ar–*H*), 6.96–7.10 (m, 6H, Ar–*H*), 8.15 (s, 2H, Ar–O*H*); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 38.3, 107.3, 110.8, 115.5, 116.4, 123.1, 127.6, 128.7, 131.5, 131.9, 150. 0, 151.7, 156.5. HRMS *m*/*z* found: 380.1036, calculated: 380.1049.

Resolution of *rac*-(3). The mixture of *rac*-**3** (3.14 g, 8.26 mmol) and *N*-benzylcinchonidinium chloride **8** (1.84 g, 4.37 mmol) was suspended in 30 mL of acetonitrile (CH_3CN) and refluxed for 6 h. After cooled naturally to room temperature, the white precipitate was collected by filtration, which was again suspended in 20 mL of CH_3CN and refluxed for another 6 h. When it was cooled to room temperature, the precipitate (1 : 1 complex of (*R*)-**3** and **8**) was collected from the mother solution by filtration and washed twice with small amount of CH_3CN. The solid was then stirred in EtOAc (30 mL) and diluted HCl (2 N, 20 mL) until the entire solid was dissolved. The organic phase was then separated and washed with 2 N HCl (20 mL) and brine, dried over Na_2SO_4. Evaporation of the solvent under reduced pressure produced enantiomerically pure (*R*)-**3** as a white powder (1.24 g, 79% yield, >99.9% ee). $[\alpha]_D^{20} = +40.2$ (*c* 1.0, $CHCl_3$). To obtain the other enantiomer of **3**, the mother solution was concentrated, and refluxed with *N*-benzylquininium chloride **9** (1.97 g, 4.37 mmol) in CH_3CN (30 mL) for 6 h. After being cooled to room temperature, the precipitate (1 : 1 complex of (*S*)-**3** and **9**) was collected by filtration, washed with small amount of CH_3CN. Treatment of the co-crystal with EtOAc (30 mL) and 2 N HCl (20 mL) resulted in two layers. The organic phase was separated, washed with 2 N HCl (20 mL) and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure produced enantiomerically pure (*S*)-**3** as white powder (1.22 g, 78% yield, 99.8% ee). The ee value of **3** was determined by HPLC at 25 °C using isopropanol/hexane (4 : 96) as eluent, 1 mL min^{-1}, $t_R = 31.6$ min, $t_S = 36.3$ min.

Crystal structure determination of (*R*)-3:8. A clear flat-needle shaped crystal of (*R*)-**3**:**8** grown from CH_3CN was selected with approximate dimensions 0.40 × 0.18 × 0.15 mm, and used for the X-ray crystallographic analysis. **Crystal data**. $C_{53}H_{48}ClN_3O_5$ (moiety formula $C_{26}H_{29}N_2O{\cdot}C_{25}H_{16}O_4{\cdot}C_2H_3N{\cdot}Cl$), $M = 842.39$, monoclinic, $a = 14.322(4)$ Å, $b = 8.975(2)$ Å, $c = 17.157(4)$ Å, $U = 2185.2(10)$ Å^3, $T = 95(2)$ K, space group $P2_1$, $Z = 2$, μ(Mo Kα) = 0.141 mm^{-1}, the *R* value for the refinement with 6628 observed data is 0.0571 and the wR_2 value for refinement of all 9403 data is 0.1637.†

Crystal structure determination of (*S*)-3:9. A clear brick shaped crystal of (*S*)-**3**:**9** grown from CH_3CN was selected with approximate dimensions 0.28 × 0.21 × 0.20 mm, and used for the X-ray crystallographic analysis. **Crystal data**. $C_{63.53}H_{64.29}Cl_1N_{7.76}O_6$ (moiety formula $C_{27}H_{31}N_2O_2{\cdot}C_{25}H_{16}O_4{\cdot}5.764(C_2H_3N){\cdot}Cl$), $M = 1068.00$, orthorhombic, $a = 9.2512(15)$ Å, $b = 19.807$ (3) Å, $c = 34.048(5)$ Å, $U = 6238.7(17)$ Å^3, $T = 98(2)$ K, space group $P2_12_12_1$, $Z = 4$, μ(Mo Kα) = 0.120 mm^{-1}, the *R* value for the refinement with 12467 observed data is 0.0670 and the wR_2 value for refinement of all 14773 data is 0.1690.†

Acknowledgements

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