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Efficient synthesis of enantiomerically pure *trans*-2,5-bis(arylethynyl)pyrrolidines. A new entry into C_2-symmetric chiral secondary amines

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Abstract

A new class of C_2-symmetric pyrrolidine derivatives bearing arylethynyl groups at the 2,5-positions has been synthesized in enantiomerically pure form from 1,7-octadiyne-3,6-diol in five steps. Some notable features of the synthesis are: (i) the formation of a separable diastereomeric mixture of pyrrolidine carbamates using a newly prepared chiral chloroformate; and (ii) the development of a new method for the deprotection of the carbamate via a novel SmI_2-promoted electron transfer process.

1. Introduction

The development of asymmetric synthesis is one of the major expanding fields in organic chemistry. A number of chiral auxiliaries have so far been devised for this purpose. Among them, 2,5-disubstituted pyrrolidines bearing a C_2 axis of symmetry constitute an important class[1,2] since Whitesell and Felman first reported *trans*-2,5-dimethylpyrrolidine as a useful chiral auxiliary for the enantioselective alkylation of enamines derived from it.[3] However, there are no examples where the side chains at the 2,5-positions on the pyrrolidine rings are composed of *sp* carbons. With the expectation that the introduction of an arylethynyl group as a side chain would effectively extend the original chirality on the pyrrolidine ring to remote positions without affording serious steric hindrance around the pyrrolidine nitrogen, we have synthesized *trans*-(2*R*,5*R*)-bis(arylethynyl)pyrrolidines **1a** and **1b** in enantiomerically pure forms.

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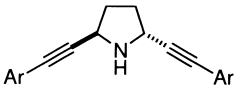
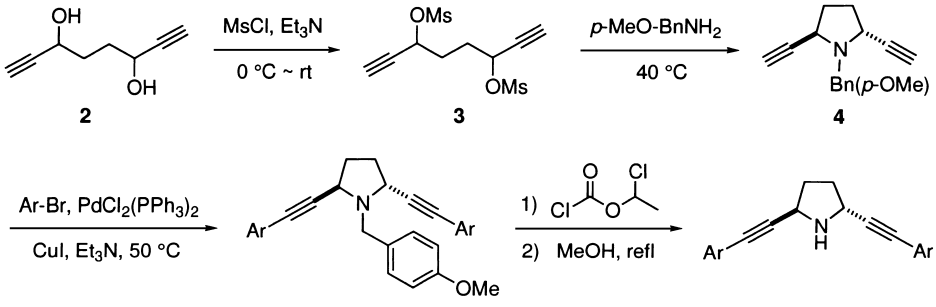


1a : Ar = 2-naphthyl
1b : Ar = 4-biphenylyl

2. Results and discussion

The synthetic route is shown in Scheme 1. A diastereomeric mixture of 1,7-octadiyne-3,6-diol **2** was prepared from succinaldehyde and monolithium acetylide according to the literature.[4] These isomeric diols could not be separated by column chromatography. Fortunately, however, the *dl*-rich (*dl*:*meso*=9:1) diol **2** was conveniently obtained by filtration because the *meso*-diol selectively solidified out from the oily mixture upon being allowed to stand at room temperature. Mesylation of the *dl*-rich diol **2** proceeded smoothly under the standard conditions to give the desired dimesylate **3** in 82% yield. Cyclization of **3** with an excess of 4-methoxybenzylamine was initially performed in CH_2Cl_2 at 0°C and then at 40°C to afford a diastereomeric mixture of *N*-protected 2,5-diethynylpyrrolidines **4** in high yields. At this stage, the *N*-protected *trans*-2,5-diethynylpyrrolidine *dl*-**4** was completely separated from the corresponding *cis*-isomer by column chromatography on silica gel to give the pure *trans*-isomer in 77% isolated yield. Introduction of an aryl group to the terminal acetylenic moiety on the pyrrolidine ring of *dl*-**4** was performed by Sonogashira's protocol[5] using aryl bromide in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ and CuI (10 mol%) in triethylamine. The 2-naphthyl derivative *dl*-**5a** and the 4-biphenylyl derivative *dl*-**5b** were obtained in 91 and 71% yields, respectively. For the debenzylation of *dl*-**5a** and *dl*-**5b**, Olofson's protocol[6] was successfully applied: the *N*-acylation with α-chloroethyl chloroformate was followed by the methanolysis of the resulting carbamates. The acetylenic moieties were intact under these conditions and the desired *trans* 2,5-bis(arylethynyl)pyrrolidines were obtained in high yields (*dl*-**1a**, 81%; *dl*-**1b**, 96%).

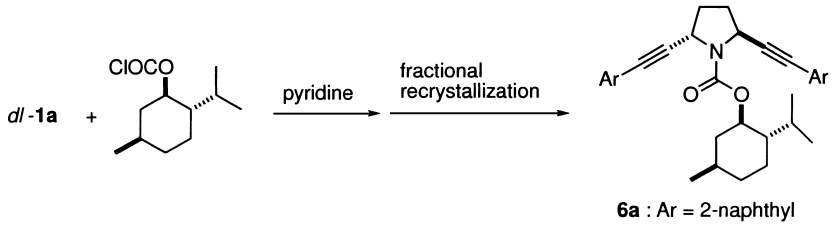


dl-**5a** : Ar = 2-naphthyl
dl-**5b** : Ar = 4-biphenylyl

dl -**1a** : Ar = 2-naphthyl
dl -**1b** : Ar = 4-biphenylyl

Scheme 1.

Since many attempts to resolve *dl*-**1a** using conventional chiral non-racemic acids ended in failure, *dl*-**1a** was converted to a diastereomeric mixture of the carbamates with (1*R*,2*S*,5*R*)-menthyl chloroformate (Scheme 2). Fractional recrystallization of the mixture using a hexane/ether/CH_2Cl_2 solvent system afforded one diastereomer **6a**, the absolute configuration of which was determined by X-ray crystallographic analysis to have the (2*S*,5*S*) configuration with respect to the pyrrolidine ring. The ORTEP drawing of **6a** is shown in Fig. 1.



Scheme 2.

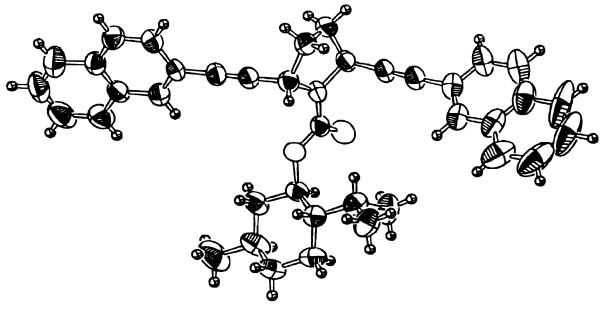
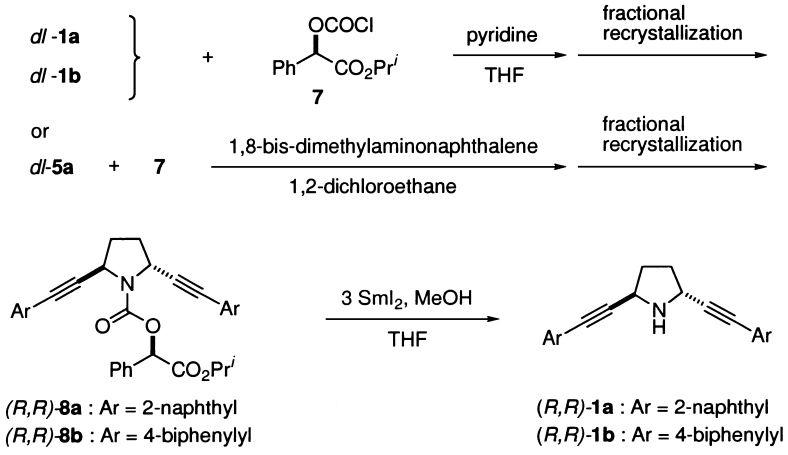


Figure 1. The ORTEP drawing of the compound **6a**

With enantiomerically pure carbamate **6a** in hand, we next tried to remove the *N*-carbomenthoxy group. Unfortunately, however, all efforts to cleave the *N*-acyl bond using literature protocols were unsuccessful mainly because of the nucleophile-susceptible propargylic amine structure of **6a**.[7] In order to circumvent this problem, we developed a different type of chiral chloroformate **7**, the α-oxy ester structure of which was expected to become, in the later stage, a good trigger for the cleavage of the *N*-acyl bond of the corresponding carbamate (e.g. **8**).

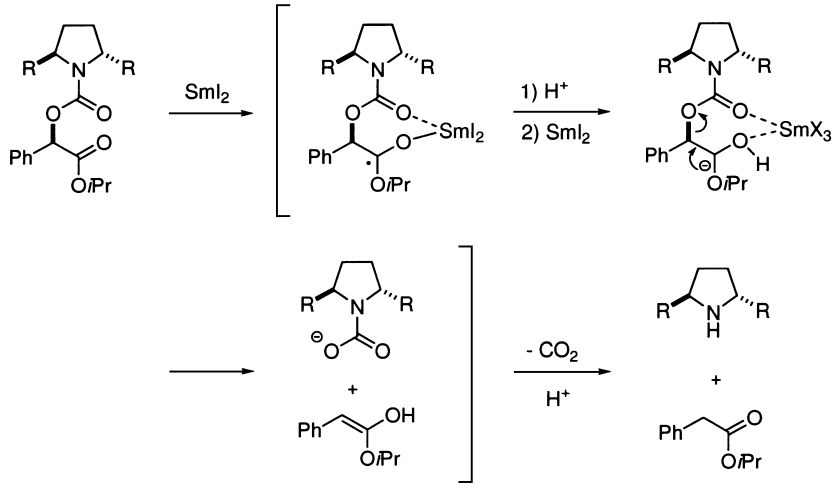
The requisite chloroformate, isopropyl (*R*)-(chloroformyloxy)phenylacetate **7**, was prepared from (*R*)-mandelic acid in two steps: (1) esterification under acidic conditions; and (2) chloroformylation[8] of the resulting (*R*)-isopropyl mandelate[9] with triphosgene. The reaction of the racemic pyrrolidine *dl*-**1a** with the chiral chloroformate **7** afforded the corresponding carbamates (*R,R*)-**8a** and (*S,S*)-**8a** in 97% yield as a 1:1 diastereomeric mixture (Scheme 3). Alternatively, they could directly be prepared from the *N*-protected amine *dl*-**5a** in 74% yield (91% based on the recovered starting material) by treating it with excess chloroformate **7** in the presence of a catalytic amount of 1,8-bis(dimethylamino)naphthalene in refluxing 1,2-dichloroethane. Fractional recrystallization of the diastereomeric mixture from hexane/ether/CH_2Cl_2 gave one diastereomer as transparent crystals in 30% yield (maximum 50% in theory). This crystal was, however, found not to be suitable for X-ray structural analysis. Therefore, removal of the *N*-protective group of the crystalline carbamate **8a** was investigated. As we had already found that α-oxy esters were successfully deoxygenated by the use of SmI_2 under mild conditions,[10] we applied this protocol to the above deprotection step. As expected, the SmI_2-promoted electron transfer reaction proceeded very smoothly at room temperature to give the desired free amine (*R,R*)-**1a** in high yield (92%). The enantiomeric excess of this compound was determined to be >99% by HPLC using Chiralpak AD eluted with a hexane–*i*-PrOH mixture, and the (*R,R*) configuration was confirmed, after converting the amine to the corresponding menthyl carbamate with (1*R*,2*S*,5*R*)-menthyl chloroformate, by the comparison of its rotation and ^{1}H NMR spectrum with those of the authentic one whose absolute configuration had been determined by X-ray crystallographic analysis.

As shown in Scheme 4, the deprotection reaction seems to involve the successive two-electron transfer process: (1) one electron reduction of the ester carbonyl; and (2) second electron transfer



Scheme 3.

to give the β-oxycarbanion species from which β-elimination of the *N*-carboxylate anion would take place. The resulting carbamic acid carboxylate would then release carbon dioxide to give the free amine. As the present electron transfer-based deprotection method using SmI_2 is so mild and unique, the mandelyloxycarbonyl (Moc) group may be registered as a useful chiral *N*-protective group. Other carbamates having a similar α-oxy ester structure should also be effective as *N*-protective groups.



Scheme 4.

In a similar manner, the biphenylyl derivatives, (*R*,*R*)-**8b** and (*R*,*R*)-**1b**, were prepared from *dl*-**1b** in good yields, although their absolute configurations were tentatively assigned based on the spectroscopic (^{1}H NMR) and optical (CD) similarities to the corresponding 2-naphthyl derivatives (*R*,*R*)-**8a** and (*R*,*R*)-**1a**, respectively. The strategy presented here possesses considerable flexibility for the introduction of a variety of substituents at the terminal positions of the acetylenic moieties. The potential of the chiral pyrrolidines **1a** and **1b** as well as their derivatives as a chiral controller in asymmetric synthesis is currently underway in our laboratory.

3. Experimental

Melting points were measured with a Yanagimoto MP-S3 micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Jeol SP170011-0055 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were measured using a Jeol JNM-EX 400. Chemical shifts are given by δ relative to that of internal Me_4Si (TMS). Mass spectra were obtained using a Shimadzu GCMS QP-5000. Fast atom bombardment mass spectra (FABMS) were obtained with a Jeol JMS-HX110A. Rotations were measured using a Horiba SEPA-300. Circular dichroism (CD) spectra were recorded on a Jeol J-720W instrument. Enantiomeric excesses were determined by chiral HPLC using Chiralpak AD. Elemental analyses were performed on a Yanagimoto MT3 CHN instrument or were accomplished at the service center for the elementary analysis of organic compounds, Kyushu University. Analytical thin layer chromatography (TLC) was performed on a silica gel plate (Merck, Kieselgel 60 F254, 20×20 cm, 0.25 mm). All solvents were purified before use; ether and tetrahydrofuran (THF) were dried over sodium benzophenone ketyl radical while dichloromethane (CH_2Cl_2) and 1,2-dichloroethane ($ClCH_2CH_2Cl$) were distilled from calcium hydride (CaH_2). All reactions were carried out under an atmosphere of argon or nitrogen. Commercially available compounds were purchased and used without further purification.

3.1. (R*,R*)-3,6-Bis(methanesulfonyloxy)-1,7-octadiyne *3*

To a solution of 1,7-octadiyne-3,6-diol[4] (**2**, *dl*:*meso*=9:1, 1.1 g, 8.0 mmol) in CH_2Cl_2 (20 mL) at 0°C was slowly added methanesulfonyl chloride (1.36 mL, 17.6 mmol). Triethylamine (2.68 mL, 19.2 mmol) was added dropwise with vigorous stirring while the temperature was maintained at 0°C. After the addition was complete, the mixture was allowed to warm to room temperature and then quenched with 1N HCl. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated $(NH_4)_2SO_4$, saturated NaCl, dried over $MgSO_4$, filtered, and concentrated. The crude oil was separated by column chromatography (silica gel, hexane:EtOAc=1:1) to give the corresponding bis(methanesulfonate) (**3**, *dl*:*meso*=ca. 9:1, 1.93 g, 82%) as a pale yellow solid. Mp 96.2–110.6°C; IR (KBr) 3276, 3033, 2942, 2123, 1357, 1328, 1170, 944, 858, 688, 518 cm^{-1}; ^{1}H NMR (*dl*-**3**, 400 MHz, $CDCl_3$) δ 2.13–2.19 (m, 4H), 2.76 (s, 2H), 3.14 (s, 6H), 5.27 (t, 2H). Anal. calcd for $C_{10}H_{14}O_6S_2$: C, 40.81; H, 4.79%. Found: C, 40.64; H, 4.78%.

3.2. (2R*,5R*)-N-4′-Methoxybenzyl-2,5-diethynylpyrrolidine dl-*4*

To a solution of (*R**,*R**)-3,6-bis(methanesulfonyloxy)-1,7-octadiyne (2.04 g, 6.93 mmol) in CH_2Cl_2 (14 mL) at 0°C was added 4-methoxybenzylamine (3.17 mL, 24.3 mmol). The mixture was stirred at room temperature for 3 h, then heated at 40°C for 12 h with stirring. After cooling, the reaction mixture was treated with 1N NaOH, then extracted with hexane:ether=1:1. The combined organic layer was washed with saturated NaCl, and dried over $MgSO_4$. After removal of the solvent, the remaining oil was separated by column chromatography (silica gel, hexane:EtOAc=20:1) to give the corresponding (2*R**,5*R**)-*N*-4′-methoxybenzyl-2,5-diethynylpyrrolidine (1.29 g, 5.39 mmol, 77%) as a colorless oil. IR (neat) 3290, 2954, 2832, 1612, 1513, 1247, 1172, 1035, 646 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89–2.04 (m, 2H), 2.15–2.29 (m, 2H), 2.35 (s, 1H), 2.36 (s, 1H), 3.18 (s, 3H), 3.49 (d, 1H, *J*=12.4 Hz), 3.54 (s, 2H), 4.14 (d, 1H, *J*=12.4 Hz), 6.84 (d, 2H, *J*=8.8 Hz), 7.33 (d, 2H, *J*=8.8 Hz); MS (FAB) *m/z* (rel. intensity) 240 (M^++1; 29), 239 (18), 238 (26), 121 (100). HRMS (FAB) calcd for $C_{16}H_{18}NO$: 240.1388. Found: 240.1389 (M^++1). Anal. calcd for $C_{16}H_{17}NO$: C, 80.29; H, 7.16; N, 5,86%. Found: C, 80.13; H, 7.17; N, 5.81%.

3.3. (2R*,5R*)-N-4′′-Methoxybenzyl-2,5-bis(2′-naphthylethynyl)pyrrolidine dl-**5a**

To a mixture of 2-bromonaphthalene (3.9 g, 18.9 mmol), CuI (164 mg, 0.86 mmol), and $PdCl_2(PPh_3)_2$ (603 mg, 0.86 mmol) in triethylamine (20 mL) was added a solution of (2*R**,5*R**)-*N*-4′-methoxybenzyl-2,5-diethynylpyrrolidine (2.05 g, 8.57 mmol) in triethylamine (23 mL). The mixture was heated to 50°C and stirred for 12 h. After removal of the excess of triethylamine by distillation, the residue was diluted with ether. The mixture was passed through a short Celite column, and the eluate was concentrated. The remaining residue was separated by column chromatography (silica gel, hexane:EtOAc=15:1 then 10:1) to give the corresponding (2*R**,5*R**)-*N*-4′′-methoxybenzyl-2,5-bis(2′-naphthylethynyl)pyrrolidine (3.82 g, 91%) as a colorless solid. Mp 139.5–140.5°C (colorless needles after recrystallization from hexane/EtOAc); IR (KBr) 3052, 2987, 2952, 2915, 2827, 2790, 1610, 1511, 1351, 1301, 1247, 1174, 1039, 862, 819 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.12–2.16 (m, 2H), 2.36–2.41 (m, 2H), 3.76 (d, 1H, *J*=12.5 Hz), 3.77 (s, 3H), 3.95 (s, 2H), 4.34 (d, 1H, *J*=12.5 Hz), 6.88 (d, 2H, *J*=8.8 Hz), 7.46 (d, 2H, *J*=5.3 Hz), 7.47 (dd, 2H, *J*=3.9, 5.3 Hz), 7.50 (d, 2H, *J*=4.3 Hz), 7.51 (dd, 2H, *J*=3.9, 5.4 Hz), 7.77 (d, 2H, *J*=8.8 Hz), 7.78 (d, 2H, *J*=5.3 Hz), 7.79 (d, 2H, *J*=4.3 Hz), 7.98 (s, 2H); MS (FAB) *m/z* (rel. intensity) 493 (M^++1; 20), 492 (54), 491 (27), 490 (27), 340 (13), 154 (15), 121 (100). HRMS (FAB) calcd for $C_{36}H_{30}NO$: 492.2328. Found: 492.2327 (M^++1). Anal. calcd for $C_{36}H_{29}NO$: C, 87.95; H, 5.95; N, 2.85%. Found: C, 87.82; H, 5.96; N, 2.96%.

3.4. (2R*,5R*)-N-4′′-Methoxybenzyl-2,5-bis(4′-biphenylylethynyl)pyrrolidine dl-**5b**

Yield: 71%. Mp 141.0–142.0°C (colorless needles after recrystallization from hexane/EtOAc); IR (KBr) 3448, 2782, 1612, 1511, 1484, 1349 1317, 1299, 1243, 1170, 1108, 1031, 840, 817, 765, 725, 698; ^1H NMR (400 MHz, $CDCl_3$) δ 2.08–2.12 (m, 2H), 2.32–2.38 (m, 2H), 3.69 (d, 1H, *J*=12.7 Hz), 3.80 (s, 3H), 3.84–3.89 (m, 2H), 4.28 (d, 1H, *J*=12.7 Hz), 6.88 (d, 2H, *J*=8.8 Hz), 7.34–7.61 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 30.32, 52.78, 53.45, 55.34, 85.49, 89.28, 113.71, 122.25, 126.79, 128.95, 130.63, 131.16, 132.24, 140.49, 140.91, 158.79; MS (FAB) *m/z* (rel. intensity) 544 (M^++1; 16), 154 (100), 121 (22), 108 (9). HRMS (FAB) calcd for $C_{40}H_{34}NO$: 544.2640. Found: 544.2645 (M^++1). Anal. calcd for $C_{40}H_{33}NO$: C, 88.36; H, 6.12; N, 2.58%. Found: C, 88.52; H, 6.13; N, 2.62%.

3.5. (2R*,5R*)-2,5-Bis(2′-naphthylethynyl)pyrrolidine dl-**1a**

To a solution of (2*R**,5*R**)-*N*-4′′-methoxybenzyl-2,5-bis(2′-naphthylethynyl)pyrrolidine (*dl*-**5a**, 1.5 g, 3.05 mmol) and a catalytic amount of 1,8-bis(dimethylamino)naphthalene in 1,2-dichloroethane (15 mL) at 0°C was added α-chloroethyl chloroformate (1.7 mL, 15.25 mmol). The mixture was allowed to warm to room temperature, then refluxed for 18 h. After removal of the solvent, the residue was separated by column chromatography (silica gel, hexane:EtOAc=15:1) to give the corresponding carbamate as a mixture of two diastereomers (1.35 g, 2.81 mmol, 92%) as a white solid. This compound was used directly without further separation. The carbamate (923 mg, 1.93 mmol) was dissolved in MeOH (38 mL), then refluxed for 1.5 h. After removal of the solvent, the residue was separated by column chromatography (silica gel, hexane:EtOAc:triethylamine=700:100:0.5) to give the corresponding (2*R**,5*R**)-2,5-bis(2′-naphthylethynyl)pyrrolidine (*dl*-**1a**, 700 mg, 1.87 mmol, 97%) as a pale yellow solid, recrystallization of which from hexane/AcOEt afforded a colorless solid. Mp 131.5–132.0°C; IR (KBr) 3284, 3052, 2962, 1592, 1498, 1346, 1272, 1220, 1078, 962, 948, 900, 867, 819, 740, 478, 468 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.6 (br s, 1H), 2.04–2.12 (m, 2H), 2.39–2.46 (m, 2H), 4.45 (t, 2H, *J*=5.4 Hz), 7.46–7.94 (m, 14H); CIMS (2-methylpropane) *m/z* (rel. intensity) 372 (M^++1; 100), 370 (13),

344 (12), 343 (35), 220 (40), 219 (12). Anal. calcd for $C_{28}H_{21}N$: C, 90.57; H, 5.76; N, 3.72%. Found: C, 90.53; H, 5.70; N, 3.77%.

3.6. (2R*,5R*)-2,5-Bis(4′-biphenylylethynyl)pyrrolidine dl-**1b**

Yield 96%. Mp 175.2–176.4°C (a pale yellow solid after recrystallization from hexane/EtOAc); IR (KBr) 3353, 3050, 3033, 2987, 2946, 1594, 1484, 1448, 1403, 1330, 1153, 1004, 840, 763, 719, 690, 559; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (br s, 1H), 2.01–2.07 (m, 2H), 2.17–2.42 (m, 2H), 4.39–4.41 (m, 2H), 7.33–7.56 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 32.42, 48.58, 82.79, 91.79, 122.09, 127.01, 127.08, 127.67, 128.91, 132.13, 140.43, 140.87; MS (FAB) *m/z* (rel. intensity) 424 (M^++1; 52), 154 (100). Anal. calcd for $C_{32}H_{25}N$: C, 90.74; H, 5.95; N, 3.31%. Found: C, 90.52; H, 5.93; N, 3.37%.

3.7. (1R,2S,5R)-Menthyl [(2′R,5′′R)-2′,5′-bis(2′′-naphthylethynyl)pyrrolidinyl]carbamate **6a**

To a solution of (2*R**,5*R**)-*N*-4′′-methoxybenzyl-2,5-bis(2′-naphthylethynyl)pyrrolidine (*dl*-**1a**, 260.1 mg, 0.70 mmol) and (1*R*,2*S*,5*R*)-menthyl chloroformate (180 μL, 0.84 mmol) in THF (7 mL) at 0°C was slowly added pyridine (125 mL, 1.54 mmol). The mixture was stirred at room temperature for 30 min. The addition of ether to the mixture produced a precipitate. The entire mixture was passed through a short silica gel column. The eluate was concentrated and the residue was separated by column chromatography (silica gel, hexane:EtOAc=40:1) to give the corresponding (1*R*,2*S*,5*R*)-menthyl [(2′*R**,5′*R**)-2′,5′-bis(2′′-naphthylethynyl)pyrrolidinylcarbamate (382.1 mg, 99%). Recrystallization of the above carbamate from hexane/ether/CH_2Cl_2 afforded one diastereomer **6a**, which was later found to have the (2′*R*,5′*R*) configuration, as a white solid. Mp 171.0–172.5°C; $[\alpha]_D^{18.0}$=−256 (*c* 1.0, $CHCl_3$); IR (KBr) 3446, 2923, 1691, 1596, 1396, 1326, 1265, 1176, 1112, 892, 860, 819, 769, 754, 476 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84–2.60 (m, 22H), 4.75 (dt, 1H, *J*=4.4, 10.7 Hz), 4.89–4.99 (m, 2H), 7.46–7.93 (m, 14H). Anal. calcd for $C_{39}H_{39}NO_2$: C, 84.58; H, 7.10; N, 2.53%. Found: C, 84.34; H, 7.10; N, 2.50%. X-Ray crystallographic analysis. $C_{39}H_{39}NO_2$, *M*=553.74, monoclinic, space group $P2_1$, *a*=13.269(1), *b*=14.403(1), *c*=17.846(1) Å, β=108.826(5)°, *V*=3228.2(4) Å^3, *Z*=4, D_{calc}=1.139 g cm^{-3}, graphite monochromated radiation λ(CuKα)=1.54178 Å, μ=5.35 cm^{-1}, *T*=23.0°C. Data collected on a Rigaku AFC7R diffractometer. The structure was solved by direct methods. Final agreement statistics are: *R*=0.044, *Rw*=0.039. The authors have deposited the atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

3.8. Isopropyl (R)-(chloroformyloxy)phenylacetate **7**

To a solution of isopropyl (*R*)-mandelate[8] (2.8 g, 14.4 mmol) in a mixed solvent of toluene (10 mL) and CH_2Cl_2 (5 mL) at 0°C was successively added triphosgene (2.14 g, 10.8 mmol) and quinoline (1.9 mL, 16 mmol). The mixture was stirred for 12 h at room temperature, cooled to 0°C, and quenched with 10% HCl. After the organic layer was separated, the aqueous layer was extracted with ether (twice). The combined organic layers were washed with saturated NaCl, dried over $MgSO_4$, and concentrated. The brown residue was separated by column chromatography (silica gel, hexane:EtOAc=50:1) to give the corresponding isopropyl (*R*)-(chloroformyloxy)phenylacetate (**7**, 2.96 g, 11.5 mmol, 80%) as a colorless oil. $[\alpha]_D^{19.7}$=−93.1 (*c* 1.73, $CHCl_3$); IR (neat) 1778, 1749, 1220, 1147, 1103, 821, 676 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, 3H, *J*=6.4 Hz), 1.28 (d, 3H, *J*=6.4 Hz), 5.09 (sep, 1H, *J*=6.4 Hz), 5.91 (s, 1H), 7.39–7.47 (m, 5H). Anal. calcd for $C_{12}H_{13}ClO_4$: C, 56.24; H, 5.12%. Found: C, 56.33; H, 5.17%.

3.9. Isopropyl (R)-[(2′R,5′R)-2′,5′-bis(2′′-naphthylethynyl)pyrrolidinylcarbonyloxy]phenylacetate **8a**

Preparation from *dl*-**1a**: To a solution of *dl*-**1a** (645 mg, 1.73 mmol) and **7** (535 mg, 2.08 mmol) in dry THF (17 mL) was added pyridine (308 mL, 3.8 μmol) at 0°C, and then the mixture was stirred for 5 h at room temperature. Ether (ca. 20 mL) was added and the entire mixture was passed through a short column of silica gel. After evaporation of the solvents, the crude product was subjected to column chromatography (SiO_2, hexane:EtOAc=12:1) to give isopropyl (*R*)-[(2′*R**,5′*R**)-2′,5′-bis(2′′-naphthylethynyl)pyrrolidinylcarbonyloxy]phenylacetate (994 mg, 97%) as a mixture of diastereomers.

Preparation from *dl*-**5a**: A mixture of *dl*-**5a** (533 mg, 1.08 mmol), **7** (1.39 g, 5.4 mmol), and a catalytic amount of 1,8-bis(dimethylamino)naphthalene was gently refluxed in 1,2-dichloroethane (5.4 mL) for 16 h. After removal of the solvent, the residue was separated by column chromatography to give the corresponding carbamate (476 mg, 74%) as a mixture of diastereomers along with the starting material (97.7 mg, 18%).

Fractional recrystallization of the above carbamate (476 mg) from hexane/ether/CH_2Cl_2 afforded one diastereomer (**8a**, 141 mg, 30%) as a white solid. Mp 172.9–173.3°C; $[\alpha]_D^{24.9}$=+207 (*c* 1.0, $CHCl_3$); IR (KBr) 2987, 1749, 1712, 1496, 1396, 1103, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (d, 3H, *J*=6.4 Hz), 1.20 (d, 3H, *J*=6.4 Hz), 2.27–2.35 (m, 2H), 2.64–2.69 (m, 2H), 4.99–5.05 (m, 3H), 5.89 (s, 1H), 7.31–7.34 (m, 3H), 7.43–7.49 (m, 5H), 7.59–7.65 (m, 3H), 7.72–7.82 (m, 6H), 7.93 (br s, 1H), 8.08 (br s, 1H); MS (FAB) *m/z* (rel. intensity) 592 (M^++1; 30), 591 (12), 590 (19), 550 (25), 440 (29), 415 (22), 414 (58), 398 (41), 396 (42), 370 (29), 354 (28), 264 (30), 220 (76), 218 (31), 178 (48), 165 (42), 155 (40), 154 (36), 152 (20), 136 (39), 135 (100), 107 (56), 91 (93), 79 (24). HRMS (FAB) calcd for $C_{40}H_{34}NO_4$: 592.2488. Found: 592.2484 (M^++1). Anal. calcd for $C_{40}H_{33}NO_4$: C, 81.20; H, 5.62; N, 2.37%. Found: C, 81.11; H, 5.63; N, 2.09%.

3.10. Isopropyl (R)-[2′,5′-bis(4′′-biphenylylethynyl)pyrrolidinylcarbonyloxy]phenylacetate **8b**

The (2′*R*,5′*R*)-configuration is tentatively assigned. Mp 224.9–225.6°C (colorless needles); $[\alpha]_D^{23.7}$=+212 (*c* 0.341, CH_2Cl_2); IR (KBr) 3029, 2977, 2933, 2873, 1747, 1720, 1484, 1446, 1403, 1375, 1332, 1263, 1220, 1174, 1126, 1066, 844, 765, 732, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (d, 3H, *J*=6.34 Hz), 1.21 (d, 3H, *J*=5.86 Hz), 2.23–2.30 (m, 2H), 2.59–2.62 (m, 3H), 4.95–5.04 (m, 3H), 5.87 (s, 1H), 7.34–7.63 (m, 23H); ^{13}C NMR ($CDCl_3$) δ 21.49, 21.78, 32.17, 32.90, 49.34, 49.69, 69.05, 76.0, 82.40, 82.81, 89.15, 89.39, 121.80, 122.07, 126.88, 126.99, 127.08, 127.50, 127.65, 128.62, 128.91, 132.35, 140.43, 140.49, 140.94, 153.12, 168.69; MS (FAB) *m/z* (rel. intensity) 644 (M^++1; 19), 466 (16), 422 (8), 289 (17), 154 (100). HRMS (FAB) calcd for $C_{44}H_{38}NO_4$: 644.2800. Found: 644.2803 (M^++1). Anal. calcd for $C_{44}H_{37}NO_4$: C, 82.09; H, 5.79; N, 2.18%. Found: C, 81.83; H, 5.79; N, 2.20%.

3.11. (2R,5R)-2,5-Bis(2′-naphthylethynyl)pyrrolidine **1a**

To a solution of isopropyl (*R*)-[(2′*R*,5*R*)-2′,5′-bis(2′′-naphthylethynyl)pyrrolidinylcarbonyloxy]-phenylacetate (**8a**, 90 mg, 0.152 mmol) and MeOH (18 μL, 0.456 mmol) in THF (2.5 mL) was added an SmI_2–THF solution (0.1 mol dm^{-3}, 4.5 mL, 0.45 mmol). The mixture was stirred for 90 min at room temperature, then quenched with oxygen. The resulting yellow solution was added to diethylene glycol (43 μL, 0,76 mmol), and then filtered through a short silica gel column with THF as the eluent. The eluate was concentrated, and the residue was separated by column chromatography (silica gel, hexane:EtOAc:triethylamine=700:100:0.5) to give the corresponding (2*R*,5*R*)-2,5-bis(2′-naphthylethynyl)pyrrolidine [**1a**, 51.7 mg, 0.139 mmol, 92%, >99% ee (Chiralpak

AD, hexane:*i*-PrOH=9:1, retention time: 48.8 min, cf. 43.5 min for the opposite enantiomer)]. Mp 117.5–118.5°C; $[\alpha]_D^{24.0}$=+268 (*c* 1.0, $CHCl_3$). CD (CH_2Cl_2) λ_{ext} 252 nm (+). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.6 (br s, 1H), 2.04–2.12 (m, 2H), 2.39–2.46 (m, 2H), 4.45 (br t, 2H), 7.46–7.94 (m, 14H). HRMS (FAB) calcd for $C_{28}H_{22}N$: 372.1752. Found: 372.1703 (M^++1).

*3.12. 2,5-Bis(4′-biphenylylethynyl)pyrrolidine **1b***

The (2*R*,5*R*)-configuration is tentatively assigned. Yield: 80% [>99% ee (Chiralpak AD, hexane:*i*-PrOH=9:1, retention time: 35.7 min, cf. 18.7 min for the opposite enantiomer)]. Mp 184.7–186.0°C (a pale yellow solid); $[\alpha]_D^{26.8}$=+154 (*c* 0.075, $CHCl_3$). CD (CH_2Cl_2) λ_{ext} 238 nm (+). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (br s, 1H), 2.01–2.07 (m, 2H), 2.17–2.42 (m, 2H), 4.39–4.41 (m, 2H), 7.33–7.56 (m, 18H). HRMS (FAB) calcd for $C_{32}H_{26}N$: 424.2065. Found: 424.2018 (M^++1).

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