Lipase-Catalyzed Asymmetric Synthesis of Desprenyl-carquinostatin A and Descycloavandulyl-lavanduquinocin

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An asymmetric synthesis of the core carbazole structure, 6-desprenyl-carquinostatin 3 and 6-descycloavandulyl-lavanduquinocin 3, toward a total synthesis of carquinostatin A (1) and lavanduquinocin (2), has been established. Lipase QLM (Meito) catalyzed enantioselective acetylation of the racemic alcohol 6 gave the (−)-acetate 7 and the (+)-alcohol 6 with high enantioselectivity. The absolute stereochemistry of the (−)- and (+)-alcohol 6 have been determined to be *R*- and *S*-configurations, respectively, by the advanced Mosher method. In the same manner, the (−)-acetate 13 and the (+)-alcohol 12 have been obtained from the racemic alcohol 12. The (*R*)-(−)-acetate 13, derived from the (*R*)-(−)-acetate 7, was the same as the (−)-acetate 13, which has been determined to be (*R*)-configuration. Oxidation of the (*R*)-(−)-acetate 13 followed by hydrolysis afforded (*R*)-(−)-6-desprenyl-carquinostatin [and (*R*)-(−)-6-descycloavandulyl-lavanduquinocin] 3. In addition, oxidation of the (*S*)-(+)-alcohol 12 provided (*S*)-(+)-3, which is the enantiomer of 6-desprenyl-carquinostatin A (*R*)-(−)-3.

Key words lipase QLM; enantioselective acetylation; advanced Mosher method; desprenyl carquinostatin A; descycloavandulyl lavanduquinocin

The carbazole-3,4-quinone alkaloids, carquinostatin A (**1**)[1] and lavanduquinocin (**2**)[2] were isolated from *Streptomyces exfoliates* 2419-SVT2 and *Streptomyces viridochromogenes* by Seto and co-workers in 1993 and 1995, respectively. The structures of the two alkaloids were elucidated to be the same carbazole-3,4-quinone moiety by NMR spectral analyses and other spectroscopic experiments. The absolute stereochemistry of the C-11 position of the two alkaloids was the same *R*-configuration. Carquinostatin A (**1**) and lavanduquinocin (**2**) were also shown to be a potent neuronal cell protecting substance which exhibits a free radical scavenging activity. Total syntheses of these alkaloids have recently been developed by the Knölker group.[3—8] The transition metal-mediated and -catalyzed methodologies for the construction of the carbazole framework have been efficiently employed.

Throughout the course of this study, we have been interested in the synthetic development of biologically active condensed-heteroaromatic compounds, including natural products, by the thermal electrocyclic reactions of either conjugated hexatriene[9—17] or monoazahexatriene[18] systems incorporating one double bond from an aromatic or heteroaromatic portion. We recently reported the synthesis of the highly substituted carbazole alkaloids, carazostatin[9] and carbazoquinocins,[9,10] by the construction of the appropriate carbazole framework based on the allene-mediated electrocyclic reaction of the 6π-electron system involving the indole 2,3-bond. In the present paper, we describe the asymmetric synthesis of 6-desprenyl-carquinostatin A (6-descycloavandulyl-lavanduquinocin) **3**, which is a common carbazole framework of both alkaloids, based on a lipase-catalyzed esterification using a racemic alcohol **6** for the determination of the absolute stereochemistry of **3**. We chose the 3-ethoxy-2-methyl-1-(trifluoromethylsulfonyloxy)carbazole (**4**),[9,10] as a starting material, which was prepared in a six-step sequence from 3-iodoindole-2-carbaldehyde by the application of our methodology, as shown in the retrosynthetic Chart 1.

The required 1-allylcarbazole **5** was prepared from the triflate **4** and allyboronic acid pinacol ester in the presence of $PdCl_2$(dppf) in dimethylformamide (DMF) by the Suzuki–Miyaura reaction.[19,20] Subsequent the Wacker reaction[21] of **5** in the presense of palladium chloride(II) and copper chloride under an oxygen atmosphere gave the acetonylcarbazole **8**

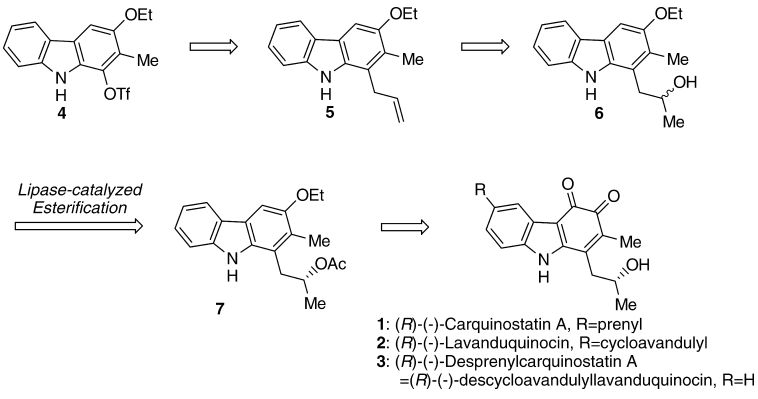

Chart 1

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followed by reduction of **8** with $NaBH_4$ provided the racemic alcohol **6** (Chart 2). Next, we investigated the enzymatic resolution of **6** with lipase PS (Amano) or lipase QLM (Meito). The results of the kinetic resolution by transesterification are shown in Table 1. Of the lipases, lipase QLM showed high enantioselectivities for this substrate. The influence of a solvent in the enantioselectivity was also examined, and diisopropyl ether (*i*-Pr_2O) gave the best result. Enantiomeric excess of the (−)-acetate **7** and the (+)-alcohol **6** were measured by HPLC on a CHIRALPAC AD column.

The absolute configuration of these compounds **6** was examined by the advanced Mosher method[22,23] using 2-methoxy-2-(1-naphthyl)propionic acid (MαNP acid). The (−)-acetate **7** was hydrolyzed with aqueous 1 M K_2CO_3/MeOH to give the (−)-alcohol **6**. Both alcohols ((−)-**6** and (+)-**6**) were treated with (*R*)- and (*S*)-MαNP acid in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 to produce the four MαNP esters (**9a**, **b** and **10a**, **b**). The absolute stereochemistry can be elucidated by the difference of calculated chemical shift on their NMR spectra. In the MαNP ester **9a**, **b** ((−)-**6**+MαNP acid), the 10-H resonated at upper field in the (*R*)-ester **9a** than in the (*S*)-ester **9b** ($\Delta\delta$, −0.32 ppm and −0.04 ppm. $\Delta\delta=\delta_R-\delta_S$). Moreover, 12-H appeared upfield for the (*S*)-ester **9b** than for the (*R*)-ester **9a** ($\Delta\delta$, +0.13 ppm). The other MαNP ester **10a**, **b** ((+)-**6**+MαNP acid) was completely a result of the contrariety of ester **9a**, **b**. Based on the analyses of their NMR spectra, the absolute stereochemistry of (+)- and (−)-alcohol **6** were determined to be *S*- and *R*-configurations, respectively (Chart 3).

Cleavage of the ethyl ether of **8** with boron tribromide (BBr_3) afforded the 3-hydroxycarbazole **11**, which was reduced with $NaBH_4$ to provide the racemic alcohol **12**. Subsequent lipase-catalyzed enantioselective esterification of **12** with lipase QLM and vinyl acetate in *i*-Pr_2O gave the (−)-acetate **13** (98% ee) and (+)-alcohol **12** (97% ee) (Chart 4). The spectral data and the retention time by HPLC of (−)-acetate **13** were identical with those of the (*R*)-(−)-acetate **13** prepared by treatment of (*R*)-(−)-**7** with BBr_3 in all respects. Consequently, the absolute stereochemistry of (−)-**13** and (+)-**12** was determined to be *R*- and *S*-configuration, respec-

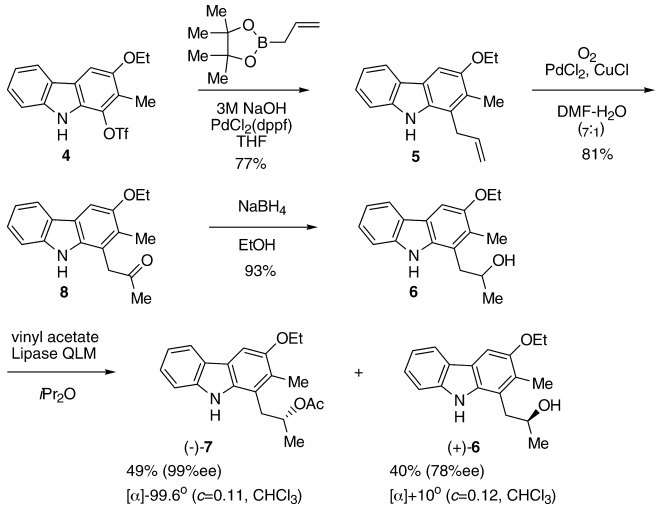

Chart 2

Table 1. Kinetic Resolution of (±)-**6** by Lipase-Catalyzed Acetylation

Run	Lipase	Solvent	Time (h)	Acetate **7** %	(% ee)	Alcohol **6** %	(% ee)
1	Lipase PS	CH_2Cl_2	24	—	—	98	—
2	Lipase PS	THF	24	—	—	96	—
3	Lipase PS	*t*-BuOMe	48	19	(98)	75	(8)
4	Lipase PS	Et_2O	48	12	(10)	71	(9)
5	Lipase PS	CH_3CN	48	6	(13)	56	—
6	Lipase PS	*i*-Pr_2O	48	4	(97)	90	—
7	Lipase QLM	*t*-BuOMe	24	40	(99)	54	(70)
8	Lipase QLM	*i*-Pr_2O	24	49	(99)	40	(78)

The enantiomeric excess (%ee) was determined by HPLC on CHIRALPAC AD.

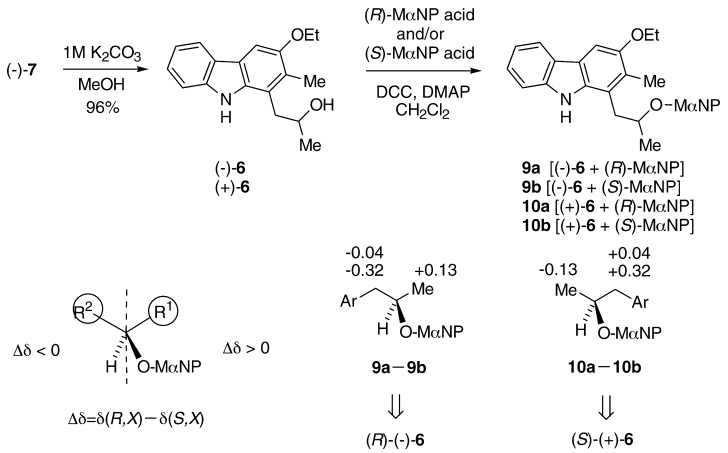

Chart 3

tively. Finally, oxidative treatment of the (−)-acetate **13** with benzeneseleninic anhydride[10] [$(PhSeO)_2O$] gave the carbazole-3,4-quinone (*R*)-(−)-**14**, which was hydrolyzed with aqueous 1 M K_2CO_3/MeOH to yield the desprenyl-carquinostatin A (descycloavandulyl-lavanduquinocin) (*R*)-(−)-**3**. In the same way, treatment of the (*S*)-(+)-alcohol **12** with $(PhSeO)_2O$ also gave its enantiomer (*S*)-(+)-**3** (Chart 5).

In conclusion, a synthesis of the functionalized core carbazole, (*R*)-(−)-6-desprenyl-carquinostatin A [(*R*)-(−)-6-descycloavandulyl-lavanduquinocin] **3** together with its enantiomer (*S*)-(+)-**3**, have been completed by the lipase-catalyzed enantioselective esterification, followed by the determination of the absolute stereochemistry based on the advanced Mosher method, by using the key compound, 3-ethoxy-2-methyl-1-(trifluoromethylsulfonyloxy)carbazole (**4**). In addition, it has been demonstrated that a new synthetic route toward a total synthesis of carquinostatin A (**1**) and lavanduquinocin (**2**) has been provided.

Experimental

All melting points were measured on a Yanagimoto micro-melting point apparatus MP-500D and were uncorrected. IR spectra were recorded on a Shimadzu FT-IR-8500 spectrophotometer using attenuated total reflection (ATR) method. ^{1}H- and ^{13}C-NMR spectra were taken with a JEOL AL-300 instrument using tetramethylsilane as an internal standard. Mass spectra (MS) were determined by a Shimadzu QP5050 and/or Shimadzu 9020DF spectrometers. All air sensitive reactions were run under an argon atmosphere. Solvents were distilled by normal methods (THF was dried over sodium benzophenone ketyl, CH_2Cl_2 was dried over P_2O_5, DMF was dried over CaH_2). Silica gel $60PF_{254}$ (60—100 mesh, Merck Art 7744) was used for column chromatography.

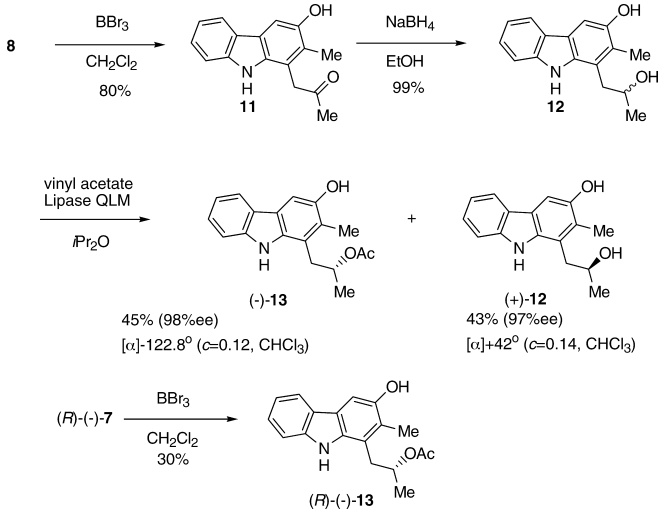

Chart 4

1-Allyl-3-ethoxy-2-methylcarbazole (5) 2-Allyl-4,4,5,5-tetramethyl-1,3,2-dioxaboralane (187 μl, 0.99 mmol) was added to a mixture of the triflate **4** (246 mg, 0.66 mmol), 3 M NaOH (0.64 ml, 1.98 mmol) and $PdCl_2$(dppf) (49 mg, 0.06 mmol) in THF (10 ml) under Ar atmosphere. The stirred mixture was heated at 85 °C for 2 h. After being cooled to r.t., the mixture was quenched with water, and was then extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc–hexane (3 : 97, v/v) as an eluent to give the allylcarbazole **5** (134 mg, 77%): mp 83—85 °C (from hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.50 (3H, t, J=6.9 Hz), 2.36 (3H, s), 3.69 (2H, dt, J=1.8, 1.8, 5.4 Hz), 4.14 (2H, q, J=6.9 Hz), 5.05 (1H, dq, J=1.8, 1.8, 17.2 Hz), 5.09 (1H, dq, J=1.8, 1.8, 10.2 Hz), 6.03 (1H, ddd, J=5.4, 10.2, 17.2 Hz), 7.18 (1H, dt, J=1.1, 8.1 Hz), 7.34 (1H, dt, J=1.1, 8.1 Hz), 7.41 (1H, d, J=8.1 Hz), 7.42 (1H, s), 7.84 (1H, br s), 7.98 (1H, d, J=8.1 Hz). MS m/z: 265 (M^+). HR-MS m/z: 265.1471 (Calcd for $C_{18}H_{19}NO$: 265.1467).

1-Acetonyl-3-ethoxy-2-methylcarbazole (8) A mixture of $PdCl_2$ (17 mg, 0.094 mmol) and CuCl (93 mg, 0.94 mmol) in DMF–H_2O (7 : 1, 4 ml) was stirred at r.t. for 30 min under an O_2 atmosphere. A solution of allylcarbazole **5** (249 mg, 0.94 mmol) in DMF–H_2O (7 : 1, 6 ml) was added to a reaction mixture at the same temperature, and was then stirred at the same temperature for 4 h under an O_2 atmosphere. The reactant was quenched with 10% HCl, and was then extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc–hexane (3 : 7, v/v) as an eluent to give the acetonylcarbazole **8** (215 mg, 81%): mp 169—170 °C (from pet. Et_2O). IR (ATR) ν: 1708 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.51 (3H, t, J=7.0 Hz), 2.17 (3H, s), 2.48 (3H, s), 4.01 (2H, s), 4.16 (2H, q, J=7.0 Hz), 7.18 (1H, t, J=6.9 Hz), 7.37 (1H, t, J=6.9 Hz), 7.45 (1H, d, J=6.9 Hz), 7.46 (1H, s), 7.97 (1H, d, J=6.9 Hz), 8.34 (1H, br s). MS m/z: 281 (M^+). HR-MS m/z: 281.1425 (Calcd for $C_{18}H_{19}NO_2$: 281.1416).

3-Ethoxy-1-(2-hydroxypropyl)-2-methylcarbazole (6) $NaBH_4$ (64 mg, 1.70 mmol) was added to a solution of acetonylcarbazole **8** (400 mg, 1.42 mmol) in EtOH (50 ml) under ice-cooled water, and was then stirred at the same temperature for 1 h. The reaction mixture was quenched with water, and was then extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc–hexane (3 : 7, v/v) as an eluent to give the alcohol **6** (375 mg, 93%): mp 141—142 °C (from Et_2O–pet. Et_2O); IR (ATR) ν: 3374 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, d, J=6.2 Hz), 1.50 (3H, t, J=6.9 Hz), 2.36 (3H, s), 3.03 (1H, dd, J=8.1, 14.3 Hz), 3.15 (1H, dd, J=3.3, 14.3 Hz), 4.15 (2H, q, J=6.9 Hz), 4.20—4.25 (1H, m), 7.15 (1H, dt, J=1.1, 8.1 Hz), 7.35 (1H, dt, J=1.1, 8.1 Hz), 7.42 (1H, d, J=8.0 Hz), 7.43 (1H, s), 7.97 (1H, d, J=8.0 Hz), 8.42 (1H, br s). MS m/z: 283 (M^+). HR-MS m/z: 283.1579 (Calcd for $C_{18}H_{21}NO_2$: 283.1572).

(−)-1-(2-Acetoxypropyl)-3-ethoxy-2-methylcarbazole (−)-(7) and (+)-3-Ethoxy-1-(2-hydroxypropyl)-2-methylcarbazole (+)-(6) iPr$_2$O (10 ml), vinyl acetate (98 μl, 1.06 mmol), and the alcohol **6** (30 mg, 0.11 mmol) were added to the lipase QLM (60 mg). The mixture was stirred at 32 °C for 24 h. The reaction mixture was filtered and the volatiles were removed under reduced pressure to give the products. The crude product was purified by preparative TLC using EtOAc–hexane (3 : 7, v/v) as an eluent to give the acetate (−)-**7** (17 mg, 49%) and an alcohol (+)-**6** (12 mg, 40%).

(−)-**7**: The optical purity was 99% ee by HPLC (CHIRALPAC AD; 10% iPrOH–hexane). $[\alpha]_D^{23}$ −99.6° (c=0.11, $CHCl_3$). IR (ATR) ν: 1716 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, d, J=6.2 Hz), 1.51 (3H, t, J= 6.9 Hz), 2.17

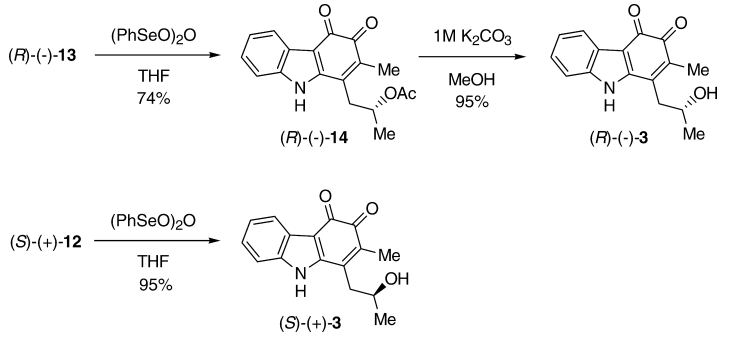

Chart 5

(3H, s), 2.38 (3H, s), 3.11 (1H, dd, J=9.9, 13.2 Hz), 3.32 (1H, dd, J=2.9, 13.2 Hz), 4.14 (2H, q, J=6.9 Hz), 5.05—5.13 (1H, m), 7.16 (1H, dt, J=1.1, 8.0 Hz), 7.36 (1H, dt, J=1.1, 8.0 Hz), 7.42 (1H, s), 7.50 (1H, d, J=8.1 Hz), 7.97 (1H, d, J=8.1 Hz), 8.42 (1H, br s). MS m/z: 325 (M^+). HR-MS m/z: 325.1691 (Calcd for $C_{20}H_{23}NO_3$: 325.1678).

(+)-**6**: The optical purity was 78% ee by HPLC (CHIRALPAC AD; 10% *i*PrOH–hexane). $[\alpha]_D^{23}$ +10.0° (c=0.12, $CHCl_3$). mp 146—147 °C ($CHCl_3$–hexane). IR (ATR) ν: 3370 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, d, J=6.2 Hz), 1.50 (3H, t, J=6.9 Hz), 2.36 (3H, s), 3.03 (1H, dd, J=8.1, 14.3 Hz), 3.14 (1H, dd, J=3.3, 14.3 Hz), 4.15 (2H, q, J=6.9 Hz), 4.20—4.25 (1H, m), 7.15 (1H, dt, J=1.1, 8.1 Hz), 7.35 (1H, dt, J=1.1, 8.1 Hz), 7.42 (1H, d, J=8.0 Hz), 7.43 (1H, s), 7.97 (1H, d, J=8.0 Hz), 8.42 (1H, br s). MS m/z: 283 (M^+). HR-MS m/z: 283.1580 (Calcd for $C_{18}H_{21}NO_2$: 283.1572).

(−)-3-Ethoxy-1-(2-hydroxypropyl)-2-methylcarbazole (−)-(6) An acetate (−)-**7** (30 mg, 0.092 mmol) was hydrolyzed with aqueous 1 M K_2CO_3 (1 ml) and MeOH (3 ml) at r.t. for 1.5 h to give an (−)-alcohol. The reaction mixture was quenched with water, and was then extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc–hexane (3 : 7, v/v) as an eluent to give the alcohol (−)-**6** (25 mg, 96%): mp 143—144 °C (from $CHCl_3$–hexane). $[\alpha]_D^{23}$ −22.9° (c=0.120, $CHCl_3$). IR (ATR) ν: 3370 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, d, J=6.2 Hz), 1.50 (3H, t, J=6.9 Hz), 2.36 (3H, s), 3.03 (1H, dd, J=8.1, 14.3 Hz), 3.14 (1H, dd, J=3.3, 14.3 Hz), 4.15 (2H, q, J=6.9 Hz), 4.20—4.25 (1H, m), 7.15 (1H, dt, J=1.1, 8.1 Hz), 7.35 (1H, dt, J=1.1, 8.1 Hz), 7.42 (1H, d, J=8.0 Hz), 7.43 (1H, s), 7.97 (1H, d, J=8.0 Hz), 8.42 (1H, br s). MS m/z: 283 (M^+). HR-MS m/z: 283.1576 (Calcd for $C_{18}H_{21}NO_2$: 283.1572).

Synthesis of the Ester 9a from (−)-6 and (*R*)-MαNP Acid A mixture of the alcohol (−)-**6** (5 mg, 17.6 μmol), (*R*)-MαNP acid (4.9 mg, 21.2 μmol), DCC (6.2 mg, 29.9 μmol), and DMAP (1.1 mg, 8.8 μmol) in CH_2Cl_2 (1 ml) was stirred at r.t. for 24 h under a N_2 atmosphere. The reaction mixture was quenched with water, and was then extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 5 g) using EtOAc–hexane (1 : 9, v/v) as an eluent to give the ester **9a** (7.5 mg, 86%). ^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, d, J=6.2 Hz), 1.46 (3H, t, J=7.0 Hz), 1.91 (3H, s), 2.22 (3H, s), 2.72 (1H, dd, J=8.8, 14.0 Hz), 3.06 (3H, s), 3.13 (1H, dd, J=4.8, 14.0 Hz), 4.10 (2H, q, J=7.0 Hz), 5.11—5.17 (1H, m), 7.17 (1H, t, J=7.0 Hz), 7.34—7.65 (7H, m), 7.85—7.90 (2H, m), 7.96 (1H, d, J=7.7 Hz), 8.44—8.47 (1H, m), 9.28 (1H, br s). MS m/z: 495 (M^+).

Synthesis of the Ester 9b from (−)-6 and (*S*)-MαNP Acid The same procedure as above was carried out using the alcohol (−)-**6** (5 mg, 17.6 μmol), (*S*)-MαNP acid to give the ester **9b** (8 mg, 91%). ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, d, J=6.2 Hz), 1.48 (3H, t, J=7.0 Hz), 1.78 (3H, s), 2.31 (3H, s), 3.00—3.09 (1H, m), 3.04 (3H, s), 3.18 (1H, dd, J=5.8, 14.0 Hz), 4.12 (2H, q, J=7.0 Hz), 5.07—5.15 (1H, m), 7.18 (1H, t, 7.0 Hz), 7.32—7.54 (7H, m), 7.81—7.89 (2H, m), 7.97 (1H, d, J=8.0 Hz), 8.26 (1H, d, J=7.5 Hz), 8.88 (1H, br s). MS m/z: 495 (M^+).

Synthesis of the Ester 10a from (+)-6 and (*R*)-MαNP Acid The same procedure as above was carried out using the alcohol (+)-**6** (5 mg, 17.6 μmol), (*R*)-MαNP acid to give the ester **10a** (8 mg, 91%). ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, d, J=6.2 Hz), 1.48 (3H, t, J=7.0 Hz), 1.79 (3H, s), 2.32 (3H, s), 3.00—3.09 (1H, m), 3.04 (3H, s), 3.18 (1H, dd, J=5.8, 14.0 Hz), 4.13 (2H, q, J=7.0 Hz), 5.07—5.16 (1H, m), 7.18 (1H, t, J=7.0 Hz), 7.32—7.54 (7H, m), 7.81—7.89 (2H, m), 7.98 (1H, d, J=8.0 Hz), 8.26 (1H, d, J=7.5 Hz), 8.88 (1H, br s). MS m/z: 495 (M^+).

Synthesis of the Ester 10b from (+)-6 and (*S*)-MαNP Acid The same procedure as above was carried out using the alcohol (+)-**6** (5 mg, 17.6 μmol), (*S*)-MαNP acid to give the ester **10b** (8.5 mg, 97%). ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, d, J=6.2 Hz), 1.46 (3H, t, J=7.0 Hz), 1.93 (3H, s), 2.22 (3H, s), 2.73 (1H, dd, J=8.8, 14.0 Hz), 3.06 (3H, s), 3.13 (1H, dd, J=4.8, 14.0 Hz), 4.10 (2H, q, J=7.0 Hz), 5.11—5.18 (1H, m), 7.17 (1H, t, J=7.0 Hz), 7.34—7.65 (7H, m), 7.85—7.90 (2H, m), 7.96 (1H, d, J=7.7 Hz), 8.44—8.47 (1H, m), 9.28 (1H, br s). MS m/z: 495 (M^+).

1-Acetonyl-3-hydroxy-2-methylcarbazole (11) A solution of BBr_3 (60 μl, 0.63 mmol) in CH_2Cl_2 (2 ml) was added to a stirred solution of 3-ethoxycarbazole **8** (89 mg, 0.32 mmol) in CH_2Cl_2 (4 ml) at −78 °C under a N_2 atmosphere. After being gradually warmed to r.t., the mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc–hexane (3 : 17, v/v) as an eluent to give the 3-hydroxycarbazole **11** (64 mg, 80%): mp 169—170 °C (from EtOAc–hexane). IR (ATR) ν: 3397, 1697 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.17 (3H, s), 2.49 (3H, s), 4.00 (2H, s), 4.66 (1H, br s), 7.15 (1H, dt, J=2.0, 6.9 Hz), 7.36 (1H, dt, J=2.0, 6.9 Hz), 7.41 (1H, s), 7.43 (1H, dd, J=2.0, 6.9 Hz), 7.93 (1H, d, J=6.9 Hz), 8.29 (1H, br s). MS m/z: 253 (M^+). HR-MS m/z: 253.1097 (Calcd for $C_{16}H_{15}NO_2$: 253.1103).

3-Hydroxy-1-(2-hydroxypropyl)-2-methylcarbazole (12) $NaBH_4$ (16 mg, 0.43 mmol) was added to a solution of acetonylcarbazole **11** (54 mg, 0.21 mmol) in EtOH (10 ml) under ice-cooled water, and was then stirred at the same temperature for 1 h. The reaction mixture was quenched with water, and was then extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc–hexane (1 : 1, v/v) as an eluent to give the alcohol **12** (54 mg, 99%): mp 133—135 °C (from EtOAc–hexane). IR (ATR) ν: 3384 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, d, J=6.4 Hz), 2.37 (3H, s), 3.04 (1H, dd, J=8.0, 14.3 Hz), 3.15 (1H, dd, J=3.6, 14.3 Hz), 4.18—4.26 (1H, m), 4.62 (1H, br s), 7.16 (1H, dt, J=1.1, 8.1 Hz), 7.35 (1H, dt, J=1.1, 8.1 Hz), 7.37 (1H, s), 7.43 (1H, d, J=8.1 Hz), 7.93 (1H, d, J=8.1 Hz), 8.41 (1H, br s). MS m/z: 255 (M^+). HR-MS m/z: 255.1263 (Calcd for $C_{16}H_{17}NO_2$: 255.1259).

1-(2-Acetoxypropyl)-3-hydroxy-2-methylcarbazole (−)-(13) and 3-Hydroxy-1-(2-hydroxypropyl)-2-methylcarbazole (+)-(12) *i*-Pr_2O (10 ml), vinyl acetate (198 μl, mmol), and the alcohol **12** (23 mg, 0.09 mmol) were added to the lipase QLM (60 mg). The mixture was stirred at 32 °C for 48 h. The reaction mixture was filtered and the volatiles were removed under reduced pressure to give the products. The crude product was purified by preparative TLC using EtOAc–hexane (3 : 7, v/v) as an eluent to give the acetate (−)-**13** (12 mg, 45%) and the alcohol (+)-**12** (10 mg, 43%).

(−)-**13**: The optical purity was 98% ee by HPLC (CHIRALCEL OD; 15% *i*PrOH–hexane). $[\alpha]_D^{23}$ −122.8° (c=0.12, MeOH). mp 152—154 °C (from EtOAc–hexane). IR (ATR) ν: 3351, 1708 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, d, J=6.3 Hz), 2.17 (3H, s), 2.40 (3H, s), 3.10 (1H, dd, J=10.0, 13.2 Hz), 3.33 (1H, dd, J=3.3, 13.2 Hz), 5.02—5.12 (1H, m), 7.15 (1H, t, J=7.7 Hz), 7.37 (1H, s), 7.37 (1H, t, J=7.7 Hz), 7.50 (1H, d, J=7.7 Hz), 7.93 (1H, d, J=7.7 Hz), 9.49 (1H, s). MS m/z: 297 (M^+). HR-MS m/z: 297.1368 (Calcd for $C_{18}H_{19}NO_3$: 297.1365).

(+)-**12**: The optical purity was 97% ee by HPLC (CHIRALCEL OJ; 15% *i*PrOH–hexane). $[\alpha]_D^{23}$ +42.0° (c=0.14, $CHCl_3$). mp 134—136 °C (EtOAc–hexane). IR (ATR) ν: 3390 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, d, J=6.2 Hz), 2.37 (3H, s), 3.04 (1H, dd, J=8.0, 14.3 Hz), 3.15 (1H, dd, J=3.7, 14.3 Hz), 4.17—4.28 (1H, m), 4.73 (1H, br s), 7.16 (1H, t, J=7.0 Hz), 7.36 (1H, t, J=7.0 Hz), 7.38 (1H, s), 7.39 (1H, d, J=7.0 Hz), 7.93 (1H, d, J=7.0 Hz), 8.44 (1H, s). MS m/z: 255 (M^+). HR-MS m/z: 255.1250 (Calcd for $C_{16}H_{17}NO_2$: 255.1259).

(*R*)-1-(2-Acetoxypropyl)-3-hydroxy-2-methylcarbazole (*R*)-(−)-(13) A solution of BBr_3 (21 μl, 0.22 mmol) in CH_2Cl_2 (2 ml) was added to a stirred solution of carbazole (*R*)-(−)-**7** (36 mg, 0.11 mmol) in CH_2Cl_2 (2 ml) at −78 °C under a N_2 atmosphere. After being gradually warmed to r.t., the mixture was stirred at r.t. for 3 h and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc–hexane (3 : 17, v/v) as an eluent to give the acetate (*R*)-(−)-**13** (10 mg, 30%). The absolute stereochemistry of the acetate (−)-**13**, derived from the alcohol **12** as described above procedure, was determined to be *R*-configuration by HPLC (CHIRALCEL OD; 15% *i*PrOH–hexane), because the retention time of the acetate (−)-**13** has shown the same retention time in the comparison with the acetate (*R*)-(−)-acetate **13**. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, d, J=6.3 Hz), 2.17 (3H, s), 2.40 (3H, s), 3.10 (1H, dd, J=10.0, 13.2 Hz), 3.33 (1H, dd, J=3.3, 13.2 Hz), 5.03—5.13 (1H, m), 7.15 (1H, t, J=7.7 Hz), 7.37 (1H, s), 7.37 (1H, t, J=7.7 Hz), 7.50 (1H, d, J=7.7 Hz), 7.94 (1H, d, J=7.7 Hz), 9.50 (1H, s). MS m/z: 297 (M^+).

(*R*)-1-(2-Acetoxypropyl)-2-methylcarbazole-3,4-dione (*R*)-(−)-(14) A solution of 3-hydroxycarbazole (−)-**13** (22 mg, 0.074 mmol) in THF (2 ml) was added to a stirred suspension of 70% $(PhSeO)_2O$ (76 mg, 0.15 mmol) in THF (2 ml). The mixture was stirred at 50 °C for 30 min. After being cooled to r.t., the reaction mixture was diluted with EtOAc. The mixture was washed with aqueous 10% Na_2CO_3 solution, water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc–hexane (1 : 1, v/v) as an eluent to give the carbazole-3,4-quinone (*R*)-(−)-**14** (17 mg, 74%). mp 221—223 °C (from EtOAc–hexane). IR (ATR) ν: 1735, 1662 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, d, J=6.2 Hz), 2.06 (3H, s), 2.25 (3H, s), 2.88—3.02 (2H, m), 4.86—4.95 (1H, m), 7.25—7.31 (2H, m), 7.46—7.49 (1H, m), 8.10—8.13 (1H, m), 11.10 (1H, s). MS m/z: 311 (M^+). HR-MS m/z: 311.1175 (Calcd for $C_{18}H_{17}NO_4$: 311.1158).

(*R*)-1-(2-Hydroxypropyl)-2-methylcarbazole-3,4-dione (*R*)-(−)-(3) A carbazole-3,4-quinone (−)-**14** (17 mg, 0.055 mmol) was hydrolyzed with

aqueous 1 M K_2CO_3 (2 ml) and MeOH (3 ml) at r.t. for 3 h to give an (−)-alcohol. The reaction mixture was quenched with water, and was then extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc–hexane (7 : 3, v/v) as an eluent to give the alcohol (*R*)-(−)-**3** (14 mg, 95%): mp 201—203 °C (EtOAc). IR (ATR) *ν*: 3208, 1716, 1619 cm^{-1}. ^{1}H-NMR ($CDCl_3$) *δ*: 1.25 (3H, d, *J*=6.3 Hz), 1.94 (3H, s), 2.77—2.79 (2H, m), 3.93—4.00 (1H, m), 4.90 (1H, br s), 7.22—7.25 (2H, m), 7.51—7.53 (1H, m), 7.84—7.87 (1H, m), 11.10 (1H, s). MS *m*/*z*: 269 (M^+). HR-MS *m*/*z*: 269.1059 (Calcd for $C_{16}H_{15}NO_3$: 269.1052).

(*S*)-1-(2-Hydroxypropyl)-2-methylcarbazole-3,4-dione (*S*)-(+)-(3) A solution of alcohol (+)-**12** (9 mg, 0.035 mmol) in THF (1 ml) was added to a stirred suspension of 70% $(PhSeO)_2O$ (36 mg, 0.071 mmol) in THF (1 ml). The mixture was stirred at 50 °C for 30 min. After being cooled to r.t., the reaction mixture was diluted with EtOAc. The mixture was washed with aqueous 10% Na_2CO_3 solution, water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc–hexane (7 : 3, v/v) as an eluent to give the carbazole-3,4-quinone (*S*)-(+)-**3** (9 mg, 95%) mp 198—201 °C (from EtOAc). IR (ATR) *ν*: 3208, 1716, 1619 cm^{-1}. ^{1}H-NMR ($CDCl_3$) *δ*: 1.25 (3H, d, *J*=6.3 Hz), 1.93 (3H, s), 2.76—2.78 (2H, m), 3.95—3.97 (1H, m), 4.89 (1H, br s), 7.21—7.25 (2H, m), 7.51—7.54 (1H, m), 7.84—7.87 (1H, m), 12.25 (1H, br s). MS *m*/*z*: 269 (M^+). HR-MS *m*/*z*: 269.1066 (Calcd for $C_{16}H_{15}NO_3$: 269.1052).

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