An Efficient Formal Synthesis of (−)-Balanol by Using Ruthenium-Catalyzed Asymmetric Hydrogenation

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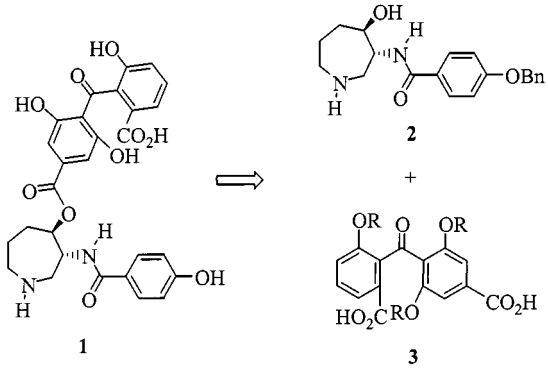
An efficient formal synthesis of (–)-balanol is reported. The ten-step sequence leading to a key precursor **4** features a highly stereoselective synthesis of the functionalized hexahydroazepine core through dynamic kinetic resolution of a racemic α-amido β-keto ester using a ruthenium(II)-catalyzed hydrogenation reaction.

Introduction

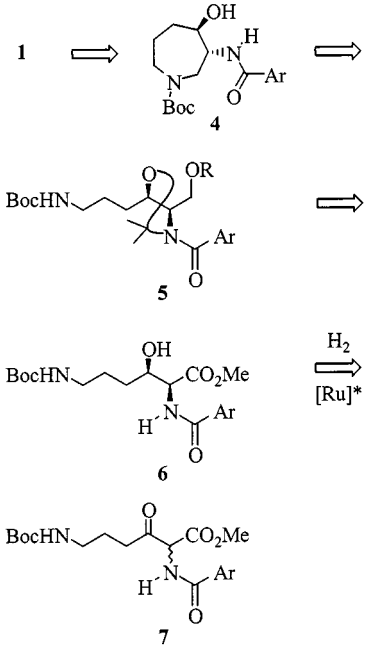
Balanol (**1**), a metabolite produced by the fungus *Verticillium balanoides*, was isolated and characterized in 1993 by Kulanthaivel et al.[1] It has been found to show remarkable inhibitory properties towards protein kinase C (PKC),[2] a family of phospholipid-dependent serine/threonine protein kinases that play an important role in cell growth, signal transduction and differentiation. Since the activated PKC enzyme has been implicated in a number of human diseases, such as cancer, cardiovascular disorders, HIV infection or central nervous system dysfunction, inhibitors of PKC may be useful therapeutic agents.[3] Hence, the synthesis of balanol and its analogs has been the subject of numerous studies. Several approaches to the chiral hexahydroazepine unit have recently been reported[4] and total syntheses of balanol have been achieved by six groups.[5] Most of these syntheses involve coupling of the chiral hexahydroazepine-containing fragment **2** with the benzophenone moiety **3** (Scheme 1).



Scheme 1

In connection with our efforts to develop practical and enantioselective methods for the synthesis of biologically active natural products, we were interested in an approach to (−)-balanol using the ruthenium-mediated dynamic kinetic resolution[6] for the construction of the two contiguous stereogenic centers.

We chose as a target the properly functionalized hexahydroazepine ring **4**, which is a highly elaborated intermediate in the total synthesis of balanol (Scheme 2).[7] The seven-membered ring could be obtained by cyclization of compound **5** while the key step of our approach involves ruthenium-mediated hydrogenation of racemic α-amido β-keto ester **7**, which would lead preferentially to compound *syn*-**6** with high diastereo- and enantioselectivities through dynamic kinetic resolution.



Scheme 2. Ar = *p*-(benzyloxy)benzene

Results and Discussion

The synthesis of the desired α-amido β-keto ester **7** began with the commercially available Boc-4-aminobutanoic acid

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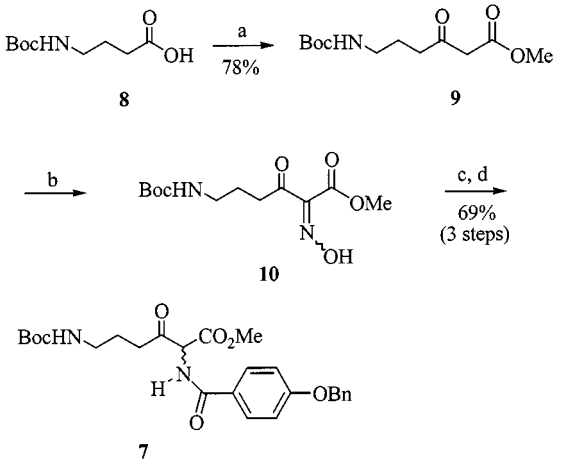
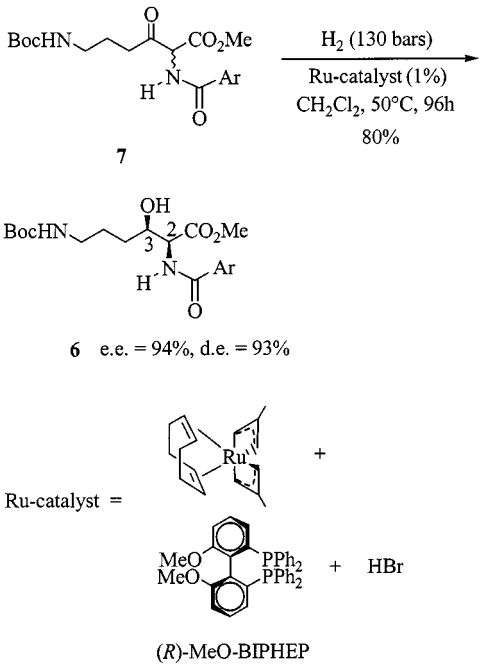
8, which was converted into the β-keto ester **9** using Masamune's procedure (Scheme 3).[8] The addition of carbonyl diimidazole to **8** followed by treatment with the magnesium salt of monomethyl malonic acid gave the requisite β-keto ester **9** in 78% yield. Reaction of **9** with sodium nitrite in a mixture of acetic acid and water afforded the oxime **10**. Hydrogenation with Pd/C in the presence of a stoichiometric amount of *p*-toluenesulfonic acid yielded the corresponding α-ammonium salt, which was subsequently converted into the desired α-amido β-keto ester **7** by treatment with triethylamine and *p*-(benzyloxy)benzoyl chloride (69% yield from **9**).



Scheme 3. (a) Im_2CO, THF, 25 °C, 6 h; $Mg^{2+}(^-OOCCH_2CO_2Me)_2$, THF, 25 °C, 18 h; (b) $NaNO_2$, $AcOH/H_2O$, 0 °C, 1 h; (c) H_2, Pd/C, PTSA (1 equiv.), MeOH, 25 °C, 18 h; (d) Et_3N, *p*-(benzyloxy)-benzoyl chloride, CH_2Cl_2, 0 to 25 °C, 1 h

It has been established in previous work that dynamic kinetic resolution of α-amido β-keto esters using ruthenium-catalyzed hydrogenation allowed the efficient preparation of *syn* β-hydroxy α-amino acids.[6,9] Preliminary studies of dynamic kinetic resolution using a ruthenium catalyst on methyl 2-acetamido 6-phthalimido-3-oxohexanoate have shown that complete conversion and high diastereo- and enantioselectivities could be obtained when the reaction was carried out at 50 °C in dichloromethane, under a high pressure of hydrogen (130 bars) and upon using MeO-BIPHEP as a ligand.[10] Thus, using our simple in situ preparation[11] of chiral Ru^{II}-catalysts under the above reaction conditions, the α-amido β-keto ester **7** was converted into a single stereoisomer **6** among four possible isomers with high diastereo- and enantioselectivities (*de* = 93%, *ee* = 94%, Scheme 4). The diastereo- and enantiomeric purities of **6** were determined by HPLC analysis of the (*R*)-MTPA esters.[12]

With the enantiomerically enriched (*ee* = 94%) compound **6** in hand, we were able to complete our synthetic approach to the hexahydroazepine ring **4** (Scheme 5). α-Amido β-hydroxy ester **6** was first protected as the corresponding oxazolidine **11** using 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid. Reduction of **11**

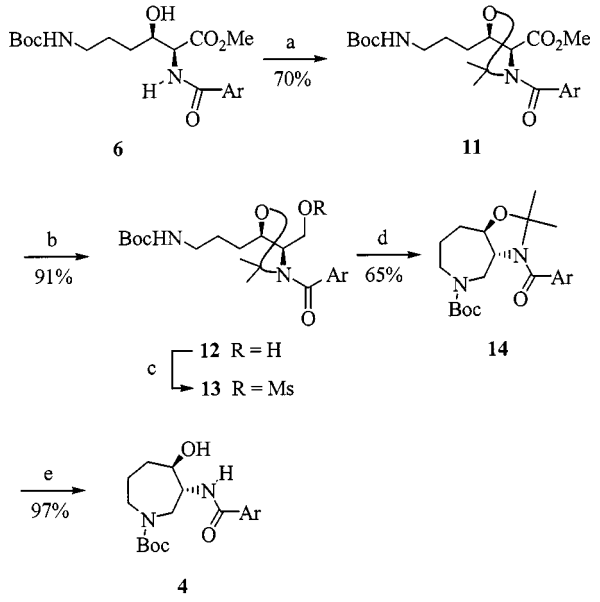


Scheme 4

to the primary alcohol **12** using calcium borohydride proceeded in good yield. In order to obtain the hexahydroazepine core, **12** was first converted into the corresponding mesylate derivative **13**, which was subsequently treated with potassium *tert*-butoxide at room temperature[5d] to furnish **14** in 65% overall yield. Finally, removal of the acetonide protecting group with *p*-toluenesulfonic acid furnished the desired chiral azepine alcohol **4**, whose spectral data were found to be in agreement with reported literature data.[5g] The enantiomeric purity and absolute configuration of (3*R*,4*R*)-**4** were determined by comparison with the literature value of the optical rotation: $[\alpha]_D^{25} = -2.3$ (*c* = 1.30, MeOH), ref.[7] $[\alpha]_D^{24} = -2.9$ (*c* = 1.30, MeOH). The coupling of the chiral hexahydroazepine **4** with the benzophenone fragment has been accomplished several times using the Mukaiyama procedure.[5]

Conclusion

In summary, a formal synthesis of a (−)-balanol precursor starting from commercially available Boc-4-aminobutanoic acid was carried out in ten steps and 17.3% overall yield. The ruthenium-mediated dynamic kinetic resolution of racemic α-amido β-keto ester **7** allowed the highly stereocontrolled construction of both stereogenic centers of the seven-membered hexahydroazepine ring in one single step. Our approach to the hexahydroazepine moiety appears to be one of the shortest and compares favorably with other reported syntheses. This methodology should provide a convenient entry to a number of structurally diverse compounds for biological evaluations as potential PKC inhibitors.



Scheme 5. (a) 2,2-dimethoxypropane, CH_2Cl_2, PTSA, 25 °C, 15 h; (b) $Ca(BH_4)_2$, EtOH/THF, −20 to 25 °C, 1 h; (c) MsCl, Et_3N, CH_2Cl_2, 0 °C, 20 min; (d) *t*BuOK, THF, 25 °C, 2 h 50 min; (e) PTSA, MeOH, 25 °C, 2 h

Experimental Section

General: All solvents were dried and distilled prior to use. All reactions were carried out under argon. − ^1H and ^{13}C NMR spectra were recorded with a Bruker AC 200 or 400 spectrometer. − IR spectra: Perkin−Elmer 983G spectrophotometer. − Mass spectra: Hewlett−Packard 5989A (70 eV) mass spectrometer. − Column chromatography: Merck silica gel (0.040−0.063 mesh). TLC analysis: Merck Art 5554 DC Alufolien Kieselgel 60 PF_{254}. Polarimeter: Perkin−Elmer 241. − Amines and CH_2Cl_2 were dried and distilled from CaH_2. THF and diethyl ether were dried and distilled from sodium-benzophenone. Yields were calculated on the basis of isolated products.

β-Keto Ester 9: To a solution of Boc-4-aminobutanoic acid (20.0 g, 93.8 mmol) in THF (50 mL) was added carbonyl diimidazole (18.3 g, 113 mmol) at 25 °C. After stirring at room temperature for 6 h, the magnesium salt of methyl malonic acid (19.4 g, 75 mmol) was added. The reaction mixture was stirred for 18 h at 25 °C and the solvent was removed. The residue was partitioned between Et_2O and aqueous 1 M HCl and the layers were separated. The aqueous phase was extracted with ether and the combined organic layers were washed with saturated aqueous $NaHCO_3$, dried with $MgSO_4$, filtered, and concentrated. Purification of the residue by flash chromatography (silica gel, 50% EtOAc in cyclohexane) afforded **9** (19.5 g, 78%) as a pale yellow oil. − IR (film): $\tilde{\nu}$ = 3400 (broad, NH), 1745 (C=O), 1710 (C=O) cm^{-1}. − ^1H NMR (200 MHz, $CDCl_3$): δ = 3.71 (s, 3 H), 3.44 (s, 2 H), 3.10 (q, 2 H, *J* = 6.5 Hz), 2.57 (t, 2 H, *J* = 7.0 Hz), 1.76 (quint, 2 H, *J* = 7.0 Hz), 1.41 (s, 9 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 202.1, 167.5, 155.9, 78.9, 52.1, 48.8, 39.8, 28.2, 23.7. − MS (CI, NH_3); *m*/*z* (%): 260 [M^+ + 1] (31). − $C_{12}H_{21}NO_5$ (259.3): calcd. C 55.58, H 8.16, N 5.40; found C 55.42, H 8.33, N 5.29.

Oxime 10: To a solution of β-keto ester **9** (259 mg, 1.0 mmol) in acetic acid (1.2 mL) was added, at 0 °C, a solution of sodium nitrite (183 mg, 2.6 mmol) in water. The reaction mixture was stirred for 1 h at 0 °C, diluted with Et_2O and treated with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with Et_2O and the combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated to give **10** as a pale yellow solid. The crude product was used in the next reaction without further purification. An analytical sample of **10** was prepared by recrystallization from cyclohexane/EtOAc (m.p. 84 °C). − IR (thin film): $\tilde{\nu}$ = 3300 (broad, NH and OH), 1750 (C=O), 1690 (C=O), 1520 (C=N) cm^{-1}. − ^1H NMR (200 MHz, $CDCl_3$): δ = 3.87 (s, 3 H), 3.15 (q, 2 H, *J* = 6.8 Hz), 2.81 (t, 2 H, *J* = 7.2 Hz), 1.84 (m, 2 H), 1.42 (br s, 9 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 195.0, 162.2, 156.8, 150.2, 80.3, 52.5, 39.9, 34.6, 28.2, 23.6. − MS (CI, NH_3); *m*/*z* (%): 306 [M^+ + 18] (20).

α-Amido β-Keto Ester 7: To a solution of oxime **10** (288 mg, 1.0 mmol) in MeOH (30 mL) were added *p*-toluenesulfonic acid (190 mg, 1.1 mmol) and 10% Pd/C (35 mg, 0.03 mmol). The suspension was placed under a hydrogen atmosphere (1 bar), stirred overnight, filtered through Celite and concentrated to give the ammonium salt as a yellow powder. The crude product was dissolved in CH_2Cl_2 (2.4 mL) and treated with *p*-(benzyloxy)benzoyl chloride (345 mg, 1.4 mmol) and triethylamine (357 μL, 2.5 mmol). After being stirred at 0 °C for 15 min and a further 1 h at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated. Purification of the residue by flash chromatography (silica gel, 60% EtOAc in cyclohexane) afforded **7** (336 mg, 69% from **10**) as a white powder (m.p. 92 °C). − IR (thin film): $\tilde{\nu}$ = 3450 (NH), 1720 (C=O), 1690 (C=O), 1620 (C=C) cm^{-1}. − ^1H NMR (250 MHz, $CDCl_3$): δ = 7.73 (d, 2 H, *J* = 8.8 Hz), 7.34−7.18 (m, 5 H), 6.93 (d, 2 H, *J* = 8.8 Hz), 5.33 (d, 1 H, *J* = 6.2 Hz), 5.04 (s, 2 H), 3.76 (s, 3 H), 3.06 (m, 2 H), 2.75 (t, 2 H, *J* = 7.0 Hz), 1.79−1.72 (m, 2 H), 1.35 (s, 9 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 201.0, 166.8, 166.2, 161.7, 156.0, 136.1, 129.1, 128.6, 128.1, 127.3, 125.2, 114.6, 79.1, 70.0, 62.6, 53.3, 39.4, 37.9, 28.3, 23.7. − MS (CI, NH_3); *m*/*z* (%): 485 [M^+ + 1] (35). − $C_{26}H_{32}N_2O_7$ (484.5): calcd. C 64.45, H 6.66, N 5.78; found C 64.43, H 6.79, N 5.62.

α-Amido β-Hydroxy Ester 6: (*R*)-MeO-BIPHEP (7.0 mg, 0.012 mmol) and $CODRu(2\text{-methylallyl})_2$ (3.2 mg, 0.01 mmol, commercially available from Acros) were placed in a Schlenk tube and dissolved in 1 mL of acetone (degassed by 3 cycles of vacuum/argon at room temperature). To this suspension was added a 0.15 N methanolic HBr solution (147 μL, 0.022 mmol) and the mixture was stirred at 25 °C for 30 min. After evaporation of the solvent under vacuum, a solution of **7** (484 mg, 1.0 mmol) in CH_2Cl_2 (1 mL) was added to the ruthenium catalyst. The resulting mixture was placed under 130 bars of hydrogen at 50 °C for 96 h and the solvent was removed. Purification of the residue by flash chromatography (silica gel, 50% EtOAc in cyclohexane) afforded **6** (389 mg, 80%) as a white powder (m.p. 51 °C). − $[\alpha]_D^{25}$ = +12 (*c* = 1.0, $CHCl_3$). − IR (thin film): $\tilde{\nu}$ = 3400 (broad, OH and NH), 1750 (C=O), 1700 (C=O), 1650 (C=O), 1600 (C=C) cm^{-1}. − ^1H NMR (200 MHz, $CDCl_3$): δ = 7.83 (d, 2 H, *J* = 8.8 Hz), 7.44−7.35 (m, 5 H), 7.02 (d, 2 H, *J* = 8.8 Hz), 5.13 (s, 2 H), 4.89 (dd, 1 H, *J* = 8.8 and 2.0 Hz), 4.79 (m, 1 H), 4.27 (m, 2 H), 3.79 (s, 3 H), 3.16 (m, 2 H), 1.63 (m, 2 H), 1.41 (s, 9 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.7, 167.3, 161.5, 156.4, 136.2, 129.1, 128.6, 128.1, 127.3, 126.0, 114.5, 79.2, 72.0, 70.0, 56.6, 52.5, 39.9, 30.6, 28.2, 26.4. − MS (CI, NH_3); *m*/*z* (%): 487 [M^+ + 1] (21). − $C_{26}H_{34}N_2O_7$ (486.6): calcd. C 64.18, H 7.04, N 5.76; found C 64.06, H 7.04, N 5.65.

Acetonide 11: To a solution of **6** (330 mg, 0.7 mmol) in acetone (1 mL) were added 2,2-dimethoxypropane (1 mL, 7 mmol) and *p*-

toluenesulfonic acid (1 mg, $7\cdot10^{-3}$ mmol). The reaction mixture was stirred overnight at 25 °C, concentrated and washed with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated. Purification of the residue by flash chromatography (silica gel, 70% EtOAc in cyclohexane) afforded **11** (258 mg, 70%) as a white powder (m.p. 50 °C). − $[\alpha]_D^{25} = -46$ (c = 1.0, $CHCl_3$). − IR (thin film): $\tilde{\nu}$ = 3380 (broad, NH), 1750 (C=O), 1700 (C=O), 1640 (C=O), 1600 (C=C) cm^{-1}. − ^1H NMR (400 MHz, $CDCl_3$): δ = 7.20 (m, 9 H), 5.08 (s, 2 H), 4.65 (br s, 1 H), 4.25 (br s, 1 H), 4.10 (m, 1 H), 3.38 (m, 3 H), 3.17 (m, 2 H), 1.72 (s, 3 H), 1.68 (m, 4 H), 1.65 (s, 3 H), 1.44 (s, 9 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.2, 168.3, 159.8, 156.0, 136.3, 129.5, 128.6, 128.5, 128.0, 127.3, 114.4, 96.6, 79.0, 69.8, 66.6, 52.3, 40.0, 30.5, 28.3, 25.9. − MS (CI, NH_3); *m/z* (%): 527 [M^+ + 1] (20). − $C_{29}H_{38}N_2O_7$ (526.6): calcd. C 66.14, H 7.27, N 5.32; found C 66.20, H 7.38, N 5.14.

Alcohol 12: To a suspension of anhydrous calcium chloride (350 mg, 3.1 mmol) in THF (1.8 mL) was added a solution of **11** (235 mg, 0.45 mmol) in EtOH (3 mL) at 25 °C. The mixture was cooled to −20 °C and sodium borohydride (204 mg, 5.4 mmol) was added. After being stirred for 15 min at −20 °C and a further 45 min at room temperature, the reaction mixture was diluted with Et_2O and hydrolyzed with saturated aqueous Na_2SO_4 until a white suspension was formed. The mixture was filtered through Celite and concentrated. Purification of the residue by flash chromatography (silica gel, 60% EtOAc in cyclohexane) afforded **12** (200 mg, 89%) as a white solid. − $[\alpha]_D^{25} = -15$ (c = 1.0, $CHCl_3$). − IR (thin film): $\tilde{\nu}$ = 3400 (broad, NH and OH), 1690 (C=O), 1610 (C=O), 1600 (C=C) cm^{-1}. − ^1H NMR (200 MHz, $CDCl_3$): δ = 7.80 (d, 2 H, J = 8.8 Hz), 7.45−7.39 (m, 5 H), 7.04 (d, 2 H, J = 8.8 Hz), 5.15 (s, 2 H), 4.18 (d, 1 H, J = 11.2 Hz), 4.15−4.08 (m, 2 H), 3.83 (d, 1 H, J = 11.2 Hz), 3.11 (m, 2 H), 1.82−1.40 (m, 4 H), 1.53 (s, 3 H), 1.47 (s, 3 H), 1.44 (s, 9 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 169.2, 160.0, 156.3, 136.3, 130.0, 128.5, 128.3, 128.0, 127.4, 114.6, 95.3, 79.2, 75.7, 70.0, 65.0, 61.9, 39.6, 30.6, 28.3, 26.3. − MS (CI, NH_3); *m/z* (%): 499 [M^+ + 1] (100). − $C_{28}H_{38}N_2O_6$ (498.6): calcd. C 67.45, H 7.68, N 5.62; found C 67.81, H 7.69, N 5.01.

Azepane 14: A solution of alcohol **12** (200 mg, 0.4 mmol) in CH_2Cl_2 (2 mL) was cooled to 0 °C and treated with triethylamine (84 μL, 0.6 mmol) and methanesulfonyl chloride (38 μL, 0.48 mmol). After stirring at 0 °C for 20 min, the solution was quenched by the addition of water (2 mL) and extracted with EtOAc. The combined organic layers were washed with water and brine, dried with Na_2SO_4, filtered, and concentrated. The crude product was dissolved in THF (20 mL, 0.02 mmol) and a solution of potassium *tert*-butoxide (400 μL, 1.0 M in THF) was added dropwise over 50 min at room temperature. After being stirred for a further 2 h, the reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated. Purification of the residue by flash chromatography (silica gel, 40% EtOAc in cyclohexane) afforded **14** (115 mg, 65%) as a colorless oil. − $[\alpha]_D^{25} = -131$ (c = 1.0, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 1690 (C=O), 1620 (C=O), 1600 (C=C) cm^{-1}. − ^1H NMR (400 MHz, C_6D_6, 70 °C): δ = 7.37 (d, 2 H, J = 8.8 Hz), 7.23−7.09 (m, 5 H), 6.78 (d, 2 H, J = 8.8 Hz), 4.74 (s, 2 H), 3.96 (td, 1 H, J = 10.3 and 2.4 Hz), 3.85 (td, 1 H, J = 9.1 and 6.3 Hz), 3.53 (br s, 2 H), 3.18 (br dd, 1 H, J = 12.4 and 5.8 Hz), 2.39 (m, 1 H), 2.06 (m, 1 H), 1.72 (s, 3 H), 1.64 (s, 3 H), 1.73−1.58 (m, 1 H), 1.45−1.35 (m, 2 H), 1.38 (s, 9 H). − ^{13}C NMR (100 MHz, C_6D_6, 70 °C): δ = 168.2, 160.8, 154.9, 137.4, 131.9, 129.2, 128.7, 127.6, 115.3, 96.2, 79.4, 78.4, 70.6, 63.9, 48.9, 45.4, 31.7, 28.5, 27.0, 25.7. − MS (CI, NH_3); *m/z* (%): 481 [M^+ + 1] (100). − $C_{28}H_{36}N_2O_5$ (480.60): calcd. C 69.98, H 7.55, N 5.83; found C 69.17, H 7.39, N 5.37.

1,1-Dimethylethyl (3*R*)-*trans*-Hexahydro-4-hydroxy-3-{[4-(phenylmethoxy)benzoyl]amino}-1*H*-azepine-1-carboxylate (4): To a solution of **14** (115 mg, 0.24 mmol) in MeOH (1 mL) was added *p*-toluenesulfonic acid (4 mg, 2.4×10^{-2} mmol). After stirring at 25 °C for 2 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated. Purification of the residue by flash chromatography (silica gel, 60% EtOAc in cyclohexane) afforded **4** (104 mg, 98%) as a colorless oil. − $[\alpha]_D^{25} = -2.3$ (c = 1.30, MeOH), ref.[7] $[\alpha]_D^{24} = -2.9$ (c = 1.30, MeOH). − IR (film): $\tilde{\nu}$ = 3400 (broad, NH and OH), 1660 (broad, C=O), 1600 (C=C) cm^{-1}. − ^1H NMR (200 MHz, $CDCl_3$): δ = 8.97 (br d, 1 H, J = 5.4 Hz), 7.89 (d, 2 H, J = 8.8 Hz), 7.47−7.32 (m, 5 H), 7.04 (d, 2 H, J = 8.8 Hz), 5.14 (s, 2 H), 4.14−4.07 (m, 3 H), 3.80 (m, 1 H), 3.30 (dd, 1 H, J = 15.5 and 5.2 Hz), 2.75 (td, 1 H, J = 13.0 and 3.6 Hz), 1.95−1.62 (m, 4 H), 1.51 (s, 9 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 168.4, 161.6, 157.3, 135.4, 129.1, 128.6, 128.1, 127.5, 125.9, 114.6, 80.8, 79.8, 70.1, 60.7, 50.5, 49.9, 32.8, 28.4, 27.2. − MS (CI, NH_3); *m/z* (%): 441 [M^+ + 1] (100).

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[12] Column, Chiralcel OD-H; flow rate, 1.0 mL/min; eluent, 9:1 hexane/propan-2-ol; detection, 254 nm; t_R: 38.1 min, (*R*)-MTPA ester of *syn*-**6** (2*S*,3*R*) isomer; t_R: 21.9 min, (*R*)-MTPA ester of *syn*-**6** (2*R*,3*S*) isomer; t_R: 25.9 min and 30.4 min, (*R*)-MTPA esters of *anti*-**6** isomers.

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