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TETRAHEDRON: *ASYMMETRY*

A new synthetic route to (3*R*,4*S*)-3-hydroxy-4-phenylazetidin-2-one as a taxol side chain precursor

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Abstract

A new synthetic route to (3*R*,4*S*)-3-hydroxy-4-phenylazetidin-2-one, an important precursor for the paclitaxel side chain, has been developed using intramolecular cyclization of *N*-(*p*-methoxyphenyl) (2*S*,3*R*)-2-acetoxy-3-bromo-3-phenylpropionamide which can be easily obtained by catalytic asymmetric dihydroxylation of *N*-(*p*-methoxyphenyl)-*trans*-cinnamide, followed by bromoacetylation.

1. Introduction

Paclitaxel (taxol, **1**), isolated from the bark of the Pacific Yew (*Taxus brevifolia*), is currently regarded as one of the most promising new drugs in cancer chemotheraphy and has recently been approved for treatment of metastatic ovarian and breast cancer.[1] Other researchers have revealed its effects against non-small cell lung cancer, head and neck cancer, glioblastoma and oesophageal cancer. In spite of attracting worldwide attention as a most promising anticancer chemotherapeutic drug, very low isolation yields (40–165 mg/kg of bark) of **1** from the stem bark of the yew tree leads to a supply problem. Fortunately, it has been found that 10-deacetyl baccatin-III **2**, possessing a very closely related structure to that of paclitaxel, can be readily extracted from the leaves of the European Yew (*Taxus baccata*) in high yield (ca. 1 g/kg of fresh leaves). It is important to recognize that the leaves are quickly regenerated and hence, through prudent harvesting, a large amount of 10-deacetyl baccatin-III **2** can be supplied continuously without threatening the survival of the yew species. From this renewable material, paclitaxel **1** could be obtained by partial synthesis, and the problem of supply could be solved. It should also be noted that 10-deacetyl baccatin-III is at least 1000 times less active than paclitaxel and only paclitaxel with C-13 side chain having (2*R*,3*S*)-configuration, *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine **3**, is active, which clearly

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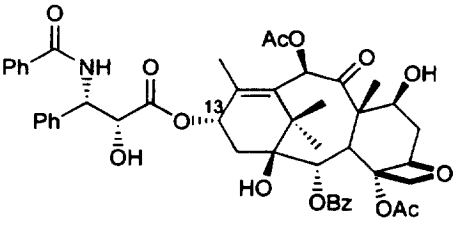
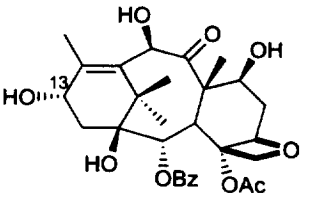
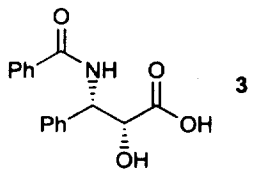
demonstrates the importance of this C-13 side chain for anticancer activity. Therefore, the development of short and practical synthetic routes to the enantiomerically pure phenylisoserine **3**, which are adaptable for industrial scale production, has become very important. Thus, much effort has been made in the preparation of enantiomerically enriched phenylisoserine derivatives — semi-synthesis drawing from the chiral pool,[2] enzymatic and/or microbial processes,[3] diastereoselective reactions with a covalently-bound chiral auxiliary or with chiral substrates,[4] asymmetric catalysis,[5] and chemical resolution of racemic acids.[6]



Paclitaxel (1, Taxol)



10-Deacetyl baccatin-III (2)



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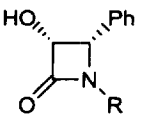
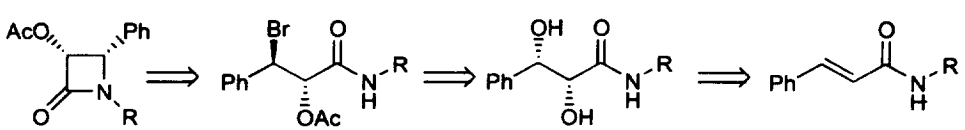


4a: R = H
4b: R = C(O)Ph

Greene et al.[7a,b] first reported a partial synthesis of paclitaxel, which involves the coupling of (2*R*,3*S*)-*N*-benzoyl-*O*-(1-ethoxyethyl)-3-phenylisoserine with suitably protected baccatin-III in the presence of an excess of DCC and DMAP in toluene at 75°C to give the corresponding ester. Unfortunately, under the above mentioned reaction conditions, the 2′-stereogenic center was easily epimerized. In order to prevent the epimerization at 2′-carbon, other coupling procedures have been developed.[8] Among these, especially, in the patent literature, Holton[8a,b] reported a new efficient coupling method using suitably protected optically active β-lactam **4b** as a side chain precursor, which allows no epimerization. Therefore, the development of enantioselective synthetic routes, adaptable for industrial scale production, to (3*R*,4*S*)-3-hydroxy-4-phenylazetidin-2-one **4a**, a key intermediate for **4b**, may be very important. The typical procedures for obtaining enantiomerically pure β-lactam **4a** involve 2,2-cycloaddition of an extremely moisture sensitive chiral ester enolate and *N*-trimethylsilyl benzaldimine.[8c–f] However, due to the sensitive reaction conditions and expensive chiral auxiliaries, these cycloaddition approaches are not practical for commercial production of **4a**. Now we have developed a new and more practical approach to the synthesis of optically active β-lactam **4a** using the intramolecular cyclization of β-bromocarboxamides which could be prepared starting from *trans*-cinnamide derivatives via catalytic asymmetric dihydroxylation (AD), followed by bromoacetylation (Scheme 1). The results are described in this paper.



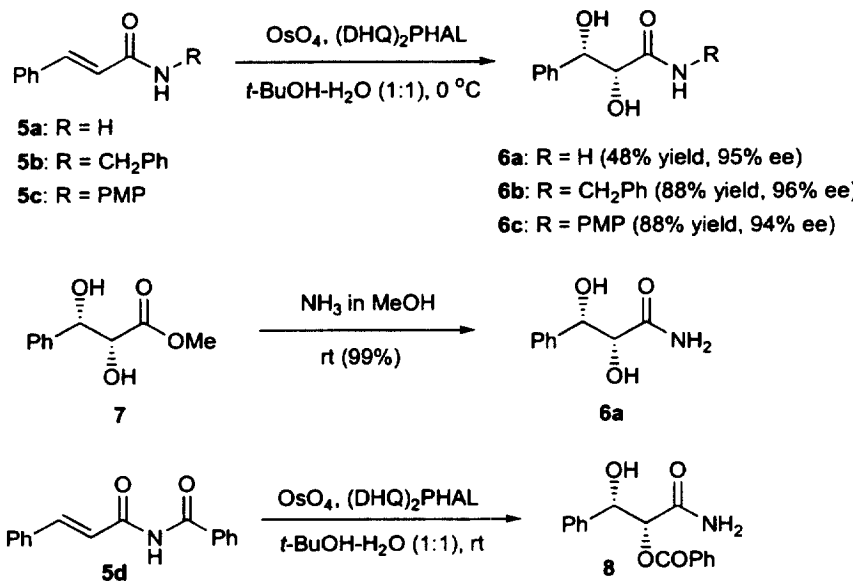
Scheme 1.

2. Results and discussion

Our synthetic approach to (3*R*,4*S*)-3-hydroxy-4-phenylazetidin-2-one **4a** outlined in Scheme 1 begins with readily available *trans*-cinnamide derivatives.

2.1. *AD reactions of* trans-*cinnamide derivatives* 5a–d

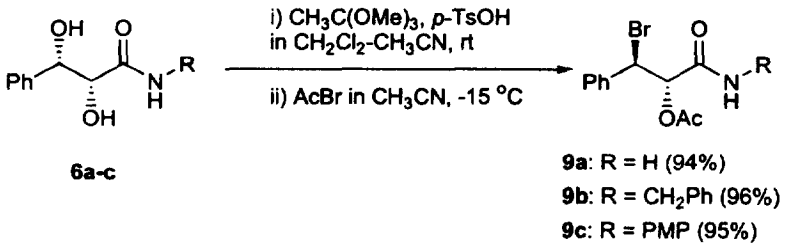
Firstly, *trans*-cinnamide derivatives **5a–d** were subjected to the $K_3Fe(CN)_6$-based catalytic AD process[9] using hydroquinine 1,4-phthalazinediyl diether ($(DHQ)_2PHAL$) as a chiral ligand. The diol-amides **6b,c** were obtained in high chemical yields and high ee's. In HPLC analyses (Chiralcel-AD, *i*-PrOH:hexane=1:9), the ee's of **6b,c** were shown to be 96% and 94%, respectively. However, the AD of the unsubstituted cinnamide **5a** afforded **6a** in only 48% yield. The diolamide **6a** could be obtained more efficiently by the reaction of enantiomerically enriched diol ester **7** with ammonia in ethanol at room temperature (>99% yield). Interestingly, the AD reaction of amide **5d** did not give the desired diol product, instead only **8** could be isolated. The formation of **8** from **5d** implies that under the dihydroxylation conditions of amide **5d**, the intramolecular benzoyl migration had arisen from amide nitrogen to oxygen at the 2-position of the initially formed diol or its osmate ester (Scheme 2).



Scheme 2.

2.2. *Bromoacetylation of diolamides* 6a–c

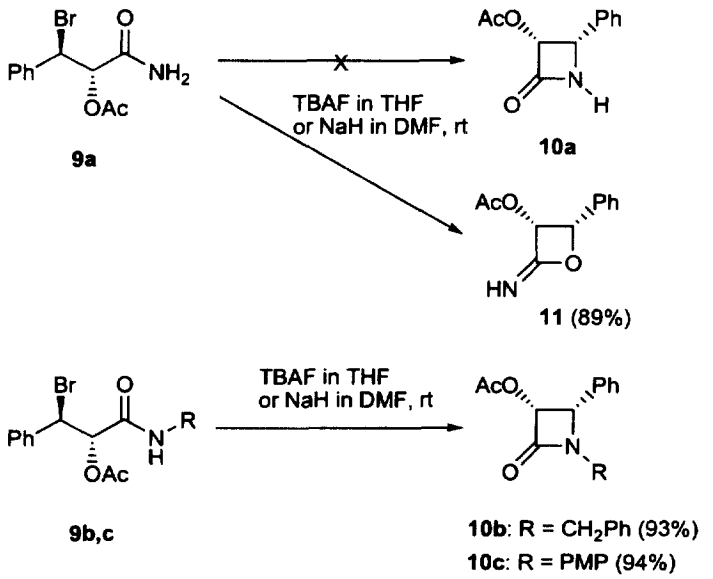
As the second step, the diol amides **6a–c** were efficiently converted to the acetoxy bromo amides **9a–c** by reaction with trimethyl orthoacetate in the presence of catalytic amounts of *p*-TsOH at room temperature (1 h), followed by treatment with acetyl bromide at −15°C (3 h) (Scheme 3).[10] The products can be easily purified by simple recrystallization from Et_2O or benzene/hexane.



Scheme 3.

2.3. *Intramolecular cyclization of β-bromocarboxamides 9a–c*

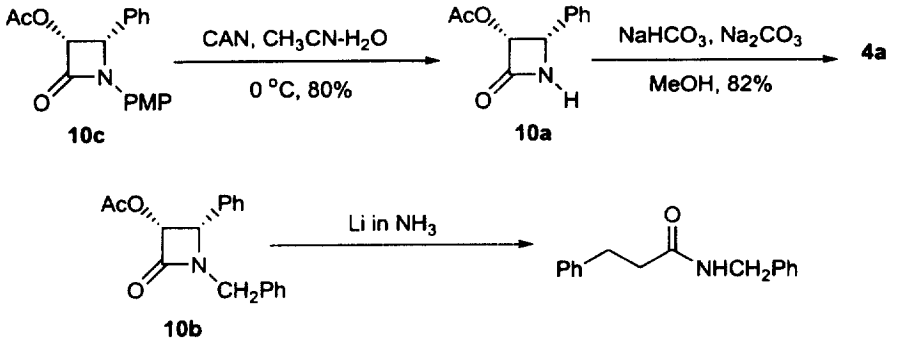
The treatment of the 2-acetoxy-3-bromocarboxamides **9b,c** with tetrabutylammonium fluoride (TBAF) in THF at room temperature gave the desired azetidinone **10b,c** almost quantitatively.[11] However, the same reaction with **9a** did not afford the desired azetidinone **10a**, instead only iminoxetane **11** was obtained (Scheme 4). The structure of **11** was assigned on the basis of the spectroscopic data. The IR spectrum showed an intensive absorption at 1715 cm^{-1}, attributed to the exocyclic imino function (O–C=NH). In the case of **10b,c**, the IR spectra showed an intensive absorption in the 1750–1760 cm^{-1} region, attributed to the exocyclic carbonyl function (O=C–N). Furthermore, the mass spectrum of **11** revealed, besides the molecular ion peak (*m/z* 205), a characteristic fragment pattern of **11**, i.e. the ketene imine (AcOCH=C=NH; *m/z* 99) and benzaldehyde (*m/z* 106) which can only be obtained from the oxetane structure of **11** via retrocycloaddition along one of the two main axes of the ring.



Scheme 4.

The intramolecular cyclization of the β-halocarboxamides in the presence of base can involve nucleophilic substitution of halide by either the *N* or the *O* atom, which generally depends on the base and the solvent. Generally, *N*-substitution predominates with strong bases in polar solvents, whereas with weak bases in non polar solvents the products of *O*-substitution are normally observed.[12] Thus, to find appropriate reaction conditions favoring the formation of the wanted β-lactam **10a** from **9a**, the reactions were carried out with strong bases in polar solvents (NaH in THF, NaH in DMF, NaH in DMSO, KH in DMF, *n*-BuLi in THF etc.). However, all reactions examined by us so far gave only iminooxetane **11**.

As a final step, the oxidative cleavage of the N-PMP group of **10c** using ceric ammonium nitrate (CAN) in aqueous CH_3CN at 0°C gave (3*R*,4*S*)-3-acetoxy-4-phenylazetidin-2-one **10a** in 80% yield. Hydrolysis of **10a** afforded the desired azetidinone **4a** in 82%. However, the reductive debenzylation of **10b** was not successful in various conditions. The reaction of **10b** in dissolving metals (Li/NH_3) cleaved the N–C^4 bond to give *N*-benzyl-3-phenylpropionamide (Scheme 5). It is well known that the reductive N–C^4 bond cleavage in 4-arylazetidin-2-one proceeds exclusively in a palladium catalyzed hydrogenolysis and thus the benzyl–nitrogen bond remains intact.[13]



Scheme 5.

In conclusion, optically active β-lactam **4a** was successfully prepared by intramolecular cyclization of (2*S*,3*R*)-*N*-(*p*-methoxyphenyl)-2-acetoxy-3-bromo-3-phenylpropionamide **9c** which could be easily obtained starting from *N*-(*p*-methoxyphenyl)-*trans*-cinnamide **5c** via catalytic asymmetric dihydroxylation and bromoacetylation (5 steps, 51% overall yield). The present method provides a practical access to enantiopure 4-hydroxyazetidinone **4a**. Furthermore, all reactions proceed under mild reaction conditions and all intermediates can be easily purified by simple recrystallization, which makes scale-up feasible.

3. Experimental section

3.1. General

Chromatographic purification of products was carried out by flash chromatography using Merck silica gel 60 (230–400 mesh). Thin layer chromatography was carried out on Merck silica gel 60F plates. Melting points were measured with a Thomas Hoover capillary melting point apparatus and were uncorrected. Optical rotation was measured on a AUTOPOL III polarimeter (Rudolph Research). ^1H NMR (300 MHz) and ^{13}C NMR (75.0 Hz) spectra were recorded on a Varian Gemini 300 spectrometer using TMS as an internal standard. IR spectra were recorded on a MIDAC 101025 FT-IR spectrometer and main absorption frequencies were given in cm^{-1}. Elemental analyses were performed at the Advanced Analytical Research Center in KIST using a Perkin–Elmer 240 C elemental analyzer.

3.2. (2R,3S)-2,3-Dihydroxy-3-phenylpropionamide (6a)

Method 1: (2*R*,3*S*)-Methyl-2,3-dihydroxy-3-phenylpropionate (**7**) (2.0 g, 10.2 mmol, $[\alpha]_D$=+10.1 (*c* 1.02, $CHCl_3$), 94% ee) in MeOH was stirred at room temperature by passing NH_3 gas through the mixture until the reaction was completed. The solvent was evaporated, and the residue was simply purified by stirring in CH_2Cl_2 to give **6a** as a white solid (1.85 g, 99%, $[\alpha]_D$=+71.4 (*c* 1.02, H_2O)).

Method 2: To a well-stirred mixture of $(DHQ)_2PHAL$ (0.264 g, 0.34 mmol), $K_3Fe(CN)_6$ (6.71 g, 20.4 mmol), K_2CO_3 (2.82 g, 20.4 mmol) and $CH_3SO_2NH_2$ (0.65 g, 6.8 mmol) in *t*-BuOH and H_2O (1/1, v/v, 30 mL) was added 1% aqueous solution of OsO_4 (0.0346 g, 0.136 mmol, 3.46 mL) at 0°C. After stirring for 1 h, the amide **5a** (1.0 g, 6.8 mmol) was added and stirring was continued at 0°C. When the reaction was complete (ca. 4 days), sodium metabisulfite (1.94 g, 10.2 mmol) was added and stirred for 2 h. The reaction mixture was extracted with EtOAc and the aqueous layer was reextracted with *n*-BuOH. The combined organic extracts were concentrated in vacuo. The residue was purified by stirring with EtOAc to give **6a** as a white solid (0.59 g, 48%, 95% ee). The % ee was determined by comparison of the $[\alpha]_D$ value with the same compound prepared by method 1: mp 157°C; $[\alpha]_D$=+72.2 (*c* 1.04, H_2O); ^1H NMR (300 MHz, DMSO-d_6) δ 7.51–7.32 (m, 7H), 5.43 (d, *J*=6.9 Hz, 1H), 5.25 (d, *J*=6.9 Hz, 1H), 5.01 (dd, *J*=6.9, 2.4 Hz, 1H), 4.00 (dd, *J*=6.9, 2.4 Hz, 1H); ^{13}C NMR (75.0 MHz, DMSO-d_6) δ 178.7, 147.2, 131.6, 130.6, 79.6, 77.2; IR (KBr) 3445, 3375, 3306, 1694, 1660, 1611, 1133, 1053, 734, 709 cm^{-1}; anal. calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.7; H, 6.07; N, 7.59.

3.3. N-*Benzyl (2R,3S)-2,3-dihydroxy-3-phenylpropionamide (**6b**)*

To a well-stirred mixture of $(DHQ)_2PHAL$ (0.039 g, 0.050 mmol), $K_3Fe(CN)_6$ (1.95 g, 5.91 mmol), K_2CO_3 (0.82 g, 5.91 mmol) and $CH_3SO_2NH_2$ (0.19 g, 1.97 mmol) in *t*-BuOH and H_2O (1/1, v/v, 15 mL) was added 1% aqueous solution of OsO_4 (0.005 g, 0.020 mmol, 0.5 mL) at 0°C. After stirring for 1 h, the amide **5b** (0.467 g, 1.97 mmol) was added and stirring was continued at 0°C. When the reaction was complete (18 h), sodium metabisulfite (0.56 g, 2.95 mmol) was added and stirred for 2 h. The reaction mixture was extracted with EtOAc. After evaporation, the residue was purified by chromatography on silica gel (EtOAc:hexane=1:1) to give **6b** as a white solid (0.47 g, 88%, 96% ee): mp 106–107°C; $[\alpha]_D$=+78.0 (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, DMSO-d_6) δ 8.20 (t, *J*=6.1 Hz, 1H), 7.40–7.20 (m, 10H), 5.35 (d, *J*=6.90 Hz, 1H), 5.33 (d, *J*=6.90 Hz, 1H), 4.93 (dd, *J*=6.90, 3.0 Hz, 1H), 4.31 (d, *J*=6.1 Hz, 2H), 4.02 (dd, *J*=6.90, 3.0 Hz, 1H); ^{13}C NMR (75.0 MHz, DMSO-d_6) δ 176.2, 147.0, 143.4, 132.1, 131.6, 131.1, 130.6, 79.8, 77.4, 45.8; IR (KBr) 3394, 3110, 1650, 1544, 1122, 1050, 742, 708 cm^{-1}; anal. calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.7; H, 6.33; N, 5.28; determination of enantiomeric excess: Chiralcel AD, *i*-PrOH:hexane=1:9, flow rate 1.0 mL/min, 254 nm, 23.3 min (2*S*,3*R*), 25.3 min (2*R*,3*S*).

3.4. N-(p-*Methoxyphenyl) (2R,3S)-2,3-dihydroxy-3-phenylpropionamide (**6c**)*

To a well-stirred mixture of $(DHQ)_2PHAL$ (0.039 g, 0.05 mmol), $K_3Fe(CN)_6$ (1.95 g, 5.91 mmol), K_2CO_3 (0.82 g, 5.91 mmol) and $CH_3SO_2NH_2$ (0.19 g, 1.97 mmol) in *t*-BuOH and H_2O (1/1, v/v, 15 mL) was added 1% aqueous solution of OsO_4 (0.005 g, 0.020 mmol, 0.5 mL) at 0°C. After stirring for 1 h, the amide **5c** (0.50 g, 1.97 mmol) was added and stirring was continued at 0°C. When the reaction was complete (24 h), sodium metabisulfite (0.56 g, 2.95 mmol) was added and stirred for 2 h. The reaction mixture was extracted with EtOAc. After evaporation, the residue was purified by recrystallization from *i*-PrOH to give **6c** as a white solid (0.50 g, 88%, 94% ee): mp 199–201°C; $[\alpha]_D$=+113.3 (*c* 0.13, MeOH); ^1H NMR (300 MHz, DMSO-d_6) δ 9.44 (s, 1H), 7.58 (d, *J*=9.0 Hz, 2H), 7.43–7.19 (m, 5H), 6.87 (d, *J*=9.0 Hz, 2H), 5.52 (d, *J*=6.5 Hz, 1H), 5.39 (d, *J*=6.5 Hz, 1H), 4.97 (dd, *J*=6.5, 2.8 Hz, 1H), 4.07 (dd, *J*=6.5, 2.8 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (75.0 MHz, DMSO-d_6) δ 74.6, 159.3, 147.0, 135.7, 131.6, 130.7, 130.6, 125.0, 117.7, 80.3, 77.4, 59.1; IR (KBr) 3354, 3316, 1644, 1548, 1512, 1250, 1108, 1034, 824, 706 cm^{-1}; anal. calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.6; H, 6.00; N, 4.95;

determination of enantiomeric excess: Chiralcel AD, *i*-PrOH:hexane=1:9, flow rate 1.0 mL/min, 254 nm, 56.6 min (2*S*,3*R*), 35.6 min (2*R*,3*S*).

3.5. (2R,3S)-2-Benzoyloxy-3-hydroxy-3-phenylpropionamide (8)

To a well-stirred mixture of $(DHQ)_2PHAL$ (0.039 g, 0.05 mmol), $K_3Fe(CN)_6$ (1.97 g, 5.97 mmol), K_2CO_3 (0.83 g, 5.97 mmol) and $CH_3SO_2NH_2$ (0.19 g, 1.99 mmol) in *t*-BuOH and H_2O (1/1, v/v, 15 mL) was added 1% aqueous solution of OsO_4 (0.005 g, 0.020 mmol, 0.5 mL) at rt. After stirring for 1 h, **5d** (0.5 g, 1.99 mmol) was added and stirring was continued at 0°C. When the reaction was complete (72 h), sodium metabisulfite (0.57 g, 2.98 mmol) was added and stirred for 2 h. The reaction mixture was extracted with EtOAc. After evaporation, the residue was purified by column chromatography (EtOAc:hexane=1:1) to give **8** as a white solid (0.24 g, 42%): mp 152–153°C; $[\alpha]_D=-31.1$ (*c* 0.10, MeOH); ^1H NMR (300 MHz, DMSO-d_6) δ 8.05 (d, *J*=7.6 Hz, 2H), 7.70–7.20 (m, 8H), 6.22 (d, *J*=2.2 Hz, 1H), 5.84 (d, *J*=7.1 Hz, 1H), 4.20 (dd, *J*=7.1, 2.2 Hz, 1H); ^{13}C NMR (75.0 MHz, DMSO-d_6) δ 173.2, 165.0, 138.3, 133.6, 129.7, 129.5, 128.8, 128.6, 128.2, 127.9, 127.7, 126.7, 126.5, 76.7, 74.1; IR (KBr) 3422, 3196, 1704, 1666, 1280, 1112, 714 cm^{-1}; anal. calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 66.9; H, 5.34; N, 4.88.

3.6. (2S,3R)-2-Acetoxy-3-bromo-3-phenylpropionamide (9a)

A solution of the diol amide **6a** (0.9 g, 4.97 mmol), *p*-TsOH (0.013 g, 0.075 mmol) and trimethyl orthoacetate (1.51 g, 12.57 mmol, 1.61 mL) in CH_2Cl_2/CH_3CN (v/v=1/1, 20 mL) was stirred at room temperature for 1 h. The volatiles were removed under reduced pressure, and the residue was taken up in CH_3CN (20 mL). After cooling the solution to −15°C, CH_3COBr (1.16 g, 9.44 mmol, 0.76 mL) was added dropwise, and stirring was continued for 3 h at −15°C. The reaction mixture was poured into water and extracted with EtOAc. The organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc:hexane=2:1) to give **9a** as a white solid (1.34 g, 94%): mp 106–107°C; $[\alpha]_D=-100.0$ (*c* 1.10, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.46–7.25 (m, 5H), 5.90 (br s, 2H), 5.74 (d, *J*=6.4 Hz, 1H), 5.45 (d, *J*=6.4 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 170.1, 170.0, 137.1, 129.6, 129.3, 129.1, 76.4, 50.6, 21.2; IR (KBr) 3455, 3306, 3176, 1766, 1666, 1217, 1107, 1083, 799, 709, 619, 529 cm^{-1}; anal. calcd for $C_{11}H_{12}BrNO_3$: C, 46.18; H, 4.23; N, 4.90. Found: C, 46.2; H, 4.18; N, 4.79.

3.7. N-Benzyl (2S,3R)-2-acetoxy-3-bromo-3-phenylpropionamide (9b)

Compound **9b** was prepared from **6b** as for **9a**: **6b** (0.80 g, 2.95 mmol), *p*-TsOH (0.038 g, 0.22 mmol), trimethyl orthoacetate (0.90 g, 7.46 mmol, 0.96 mL) and CH_3COBr (0.69 g, 1.90 mmol, 0.45 mL). The crude product was purified by silica gel column chromatography (EtOAc:hexane=1:1) to give **9b** as a white solid (1.07 g, 96%): mp 96–97°C; $[\alpha]_D=-62.7$ (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.48–6.92 (m, 10H), 6.33 (br s, 1H), 5.82 (d, *J*=5.7 Hz, 1H), 5.54 (d, *J*=5.7 Hz, 1H), 4.34 (d of ABq, *J*=15.0, 6.9 Hz, 1H and 15.0, 4.8 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 170.0, 166.9, 137.7, 137.3, 129.6, 129.5, 129.3, 129.2, 128.2, 128.1, 77.0, 51.2, 43.9, 21.3; IR (KBr) 3286, 1751, 1671, 1566, 1247, 709 cm^{-1}; anal. calcd for $C_{18}H_{18}BrNO_3$: C, 57.46; H, 4.82; N, 3.72. Found: C, 57.1; H, 4.94; N, 3.70.

3.8. N-(p-*Methoxyphenyl*) (2S,3R)-2-acetoxy-3-bromo-3-phenylpropionamide (**9c**)

Compound **9c** was prepared from **6c** as for **9a**: **6c** (5.0 g, 17.4 mmol), *p*-TsOH (0.045 g, 0.26 mmol), trimethyl orthoacetate (5.29 g, 44.0 mmol, 5.62 mL) and CH_3COBr (4.07 g, 33.1 mmol, 2.68 mL). The crude product was purified by recrystallization from benzene:hexane (2:1) to give **9c** as a white solid (6.47 g, 95%): mp 148°C; $[\alpha]_D=-18.3$ (*c* 1.13, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.26 (m, 5H), 7.16 (d, *J*=8.7 Hz, 2H), 6.75 (d, *J*=8.7 Hz, 2H), 5.73 (d, *J*=6.6 Hz, 1H), 5.45 (d, *J*=6.6 Hz, 1H), 3.71 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 170.1, 165.1, 158.0, 137.3, 129.7, 129.3, 129.2, 123.2, 114.9, 77.3, 56.1, 51.1, 21.3; IR (KBr) 3306, 1755, 1601, 1551, 1521, 1237 cm^{-1}; anal. calcd for $C_{18}H_{18}BrNO_4$: C, 55.12; H, 4.63; N, 3.57. Found: C, 54.8; H, 4.73; N, 3.44.

3.9. (3R,4S)-N-*Benzyl*-3-acetoxy-4-phenylazetidin-2-one (**10b**)

To the solution of **9b** (0.70 g, 1.86 mmol) in THF (15 mL), tetrabutylammonium fluoride (1.0 M solution in THF, 7.44 mL) was added at room temperature. After stirring for 3 h, the reaction mixture was poured into water and extracted with EtOAc. The organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (EtOAc:hexane=1:1) to give **10b** as a white solid (0.51 g, 93%): mp 74–75°C; $[\alpha]_D=+3.2$ (*c* 1.2, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.15 (m, 10H), 5.79 (d, *J*=4.4 Hz, 1H), 4.77 (d, *J*=4.4 Hz, 1H), 4.42 (ABq, *J*=14.6 Hz, 2H), 1.68 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 170.0, 162.0, 157.3, 133.0, 131.0, 129.5, 129.2, 128.6, 119.5, 115.1, 77.1, 62.1, 56.1, 20.5; IR (KBr) 3276, 1756, 1661, 1237, 1083, 734, 709 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{15}NO_2$ (M–CH_3CO): 253.1103. Found: 253.1116.

3.10. (3R,4S)-N-(p-*Methoxyphenyl*)-3-acetoxy-4-phenylazetidin-2-one (**10c**)

Compound **10c** was prepared from **9c** as above for **10b**: **9c** (11.1 g, 28.3 mmol) and tetrabutylammonium fluoride (1.0 M solution in THF, 113.2 mL). The crude product was purified by recrystallization from methanol to give **10c** as a white solid (7.82 g, 94%): mp 144–145°C; $[\alpha]_D=+10.8$ (*c* 0.74, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.26 (m, 7H), 6.81 (d, *J*=9.0 Hz, 2H), 5.94 (d, *J*=4.9 Hz, 1H), 5.34 (d, *J*=4.9 Hz, 1H), 3.75 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 169.9, 162.0, 157.3, 133.0, 131.0, 129.5, 129.2, 128.6, 119.5, 115.1, 77.1, 62.1, 56.1, 20.5; IR (KBr) 1756, 1521, 1232, 1112 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{15}NO_3$ (M–CH_3CO): 269.1052. Found: 269.1054.

3.11. 2-*Imino*-(3S,4S)-3-acetoxy-4-phenyloxetane (**11**)

A solution of **9a** (0.5 g, 1.75 mmol) in THF (20 mL) was treated with tetrabutylammonium fluoride (1.0 M solution in THF, 7.0 mL) at room temperature for 3 h under a nitrogen atmosphere. The reaction mixture was poured into water and extracted with EtOAc. The organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc:hexane=2:1) to give **11** as a white solid (0.32 g, 89%): mp 86–87°C; $[\alpha]_D=-90.9$ (*c* 0.25, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.42 (br s, 1H), 7.40–7.27 (m, 5H), 4.00 (d, *J*=1.9 Hz, 1H), 3.61 (d, *J*=1.9 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 167.3, 136.7, 129.1, 128.63, 128.57, 75.2, 52.7, 49.1, 20.4; IR (KBr) 3345, 1740, 1715, 1511, 1207, 759, 704 cm^{-1}; MS (EI) *m/z* (relative abundance) 205 (1), 162 (2), 120 (31), 106 (39), 99 (100); anal. calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 63.2; H, 5.45; N, 6.59.

3.12. (3R,4S)-3-Acetoxy-4-phenylazetidin-2-one (10a)

To the solution of **10c** (2.1 g, 6.74 mmol) in CH_3CN (60 mL) was added slowly a solution of $(NH_4)_2Ce(NO_3)_6$ (11.08 g, 20.24 mmol) in water (90 mL) at 0°C. The mixture was stirred at 0°C for 1 h and diluted with water (150 mL). The mixture was then extracted with EtOAc. The organic extracts were neutralized with 5% sodium bicarbonate and the aqueous extracts were washed with EtOAc. The combined organic extracts were washed with 10% sodium sulfite, 5% sodium bicarbonate, and brine, successively. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc:hexane=2:1) to give **4c** as a white solid (1.10 g, 80%): mp 181°C; $[\alpha]_D=-15.7$ (*c* 1.04, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (br s, 1H), 7.40–7.20 (m, 5H), 5.84 (d, *J*=4.6 Hz, 1H), 4.99 (d, *J*=4.6 Hz, 1H), 1.66 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 169.6, 166.2, 135.5, 128.8, 128.0, 78.7, 58.1, 20.3; IR (KBr) 1760, 1730, 1237, 714 cm^{-1}; anal. calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.4; H, 5.41; N, 6.53.

3.13. (3R,4S)-3-Hydroxy-4-phenylazetidin-2-one (4a)

To the solution of **10a** (0.7 g, 3.41 mmol) in MeOH (5 mL), saturated $NaHCO_3$ (7.0 mL) and Na_2CO_3 (0.036 g, 0.34 mmol) were added at room temperature. After the disappearance of the starting material, the reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (EtOAc:hexane=2:1) to give **4a** as a white solid (0.46 g, 82%): mp 187°C; $[\alpha]_D=+182$ (*c* 1.04, MeOH); ^1H NMR (300 MHz, DMSO-d_6) δ 8.47 (bs, 1H), 7.35–7.20 (m, 5H), 5.82 (d, *J*=6.8 Hz, 1H), 4.95 (dd, *J*=6.8, 4.5 Hz, 1H), 4.70 (d, *J*=4.5 Hz, 1H).

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