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Diastereoselective Synthesis of All Stereoisomers of β-Methoxytyrosine, a Component of Papuamides

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β-Methoxytyrosine (β-OMeTyr) is a stereoundefined component of papuamides A and B, novel cyclodepsipeptides, with anti-HIV and cytotoxic activities. For structural determination and total synthesis of papuamides, all stereoisomers of β-OMeTyr were stereoselectively prepared from (*S*)- and (*R*)-serine, respectively.

Introduction

Papuamides A (**1**) and B (**2**),[1] novel cyclodepsipeptides, were isolated from the marine sponge genus *Theonella*, collected in Papua New Guinea by Boyd et al. Papuamides are known to strongly inhibit the infection of human T-lymphoblastanoid cells by HIV-1_{RF} and also exhibit potent cytotoxicity against a number of human cancer cell lines. These cycloheptadepsipeptides have a unique structure containing dihydroxytrimethyldecadienoic acid (Dhtda) and unusual amino acid residues such as (3*S*,4*R*)-3,4-dimethylglutamine (3,4-DiMeGln), (2*R*,3*R*)-3-hydroxyleucine (3-OHLeu), and β-methoxytyrosine (β-OMeTyr). The stereochemistry of papuamides remains to be determined because of the uncertainty regarding the stereochemistry in the β-OMeTyr and Dhtda parts. Interestingly, two unusual amino acids, β-OMeTyr and 3,4-DiMeGln, are also known as common components of the cyclodepsipeptide callipeltin A,[2] which shows anti-HIV and antifungal activities. The unique structures as well as interesting biological activities of these compounds led us and others[3] to investigate their synthesis. We have already reported a highly stereoselective synthesis of 3,4-DiMeGln[4] and 3-OHLeu.[5] To accomplish the total synthesis as well as structural determination of papuamides, we needed all four stereoisomers of β-OMeTyr in large quantities. Incidentally, there have been no reports to date on the synthesis of β-OMeTyr, although a number of stereoselective methods for accessing β-hydroxy amino acids exist.[6] Herein, we report a facile method for synthesis of all four stereoisomers of β-OMeTyr (**4**) from the Garner aldehyde[7] easily prepared from (*S*)- and (*R*)-serine.

Results and Discussion

We investigated a stereoselective addition to (*S*)-Garner aldehyde **5** derived from (*S*)-serine with 4-benzyloxyphenylmetal reagents **6** as a nucleophile in the presence of additives (Table 1). In general, medium stereoselections have been observed in the addition of a number of nucleophilic reagents[8,9] to the Garner aldehyde except for acetylenic compounds,[9] 2-trimethylsilylthiazole,[10] and fluorine-containing vinylhalides[11] as nucleophiles. As anticipated, in the case of the Grignard reagent and a mixed magnesium−lithium ate complex reagent[12] derived from benzyloxyphenyl bromide, low stereoselectivity was observed (runs 1 and 3). The corresponding zinc reagent in the presence of $AlCl_3$ was ineffective (run 2).[11] Treatment of aldehyde **5** with 2 equiv of 4-benzyloxyphenyllithium at −78 °C, however, preferentially produced anti adduct (2*S*,3*R*)-**7a** in a ratio of 4:1 (run 4).[13] Addition of Et_2AlCl (1 equiv) in this reaction disap-

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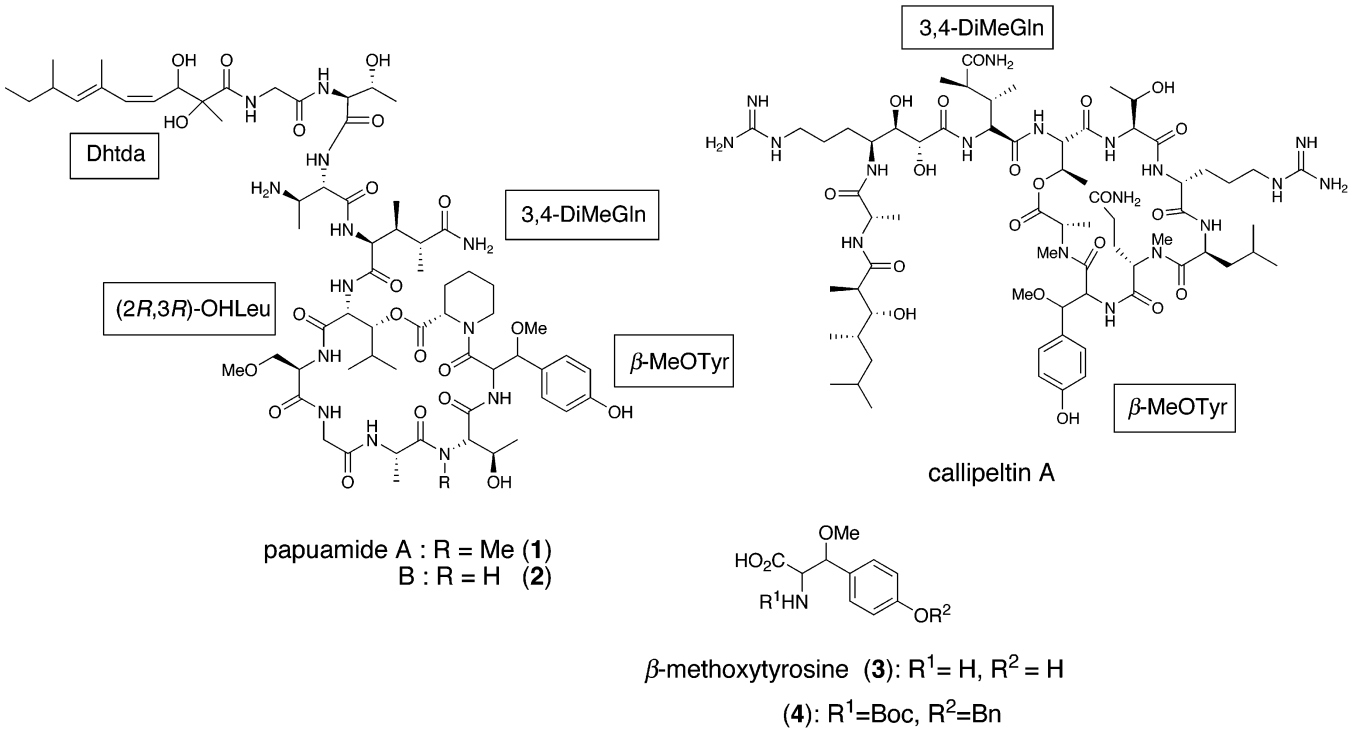

FIGURE 1. Papuamides (A and B) and callipeltin A.

TABLE 1[a]

run	M	additive	temp (°C)	anti:syn **7a**:**7b**	yields[b] (%)
1	MgBr		−78	1:1	50
2[c]	ZnBr	$AlCl_3$ (0.3 equiv)	50		d
3[e]	$Mg^+Bu_2Li^-$		−78	2:1	67
4	Li		−70	4:1	50
5	Li	Et_2AlCl (1.0 equiv)	−78	3:2	28
6	Li	LiBr (2.5 equiv)	−78	3:1	71

[a] All reactions were carried out using a mixture of Garner aldehyde (1 equiv) and aryl metal **6** (2 equiv) in THF under an argon atmosphere. [b] Combined yield of anti and syn. [c] Zinc reagent **6** (1.2 equiv) was used. [d] No reaction. [e] Mixed magnesium−lithium reagent **6** (1.3 equiv) was used.

pointingly decreased the stereoselectivity and chemical yield (run 5). On the other hand, when 2.5 equiv of LiBr was added, the chemical yield was improved in similar selectivity (run 6). This condition was reliable and gave reproducible results on a multigram scale. Fortunately, after one recrystallization of this adduct from ether−petroleum ether, pure (2*S*,3*R*)-**7a** (mp 124 °C, $[\alpha]^{29}_D$ −20.0 (*c* 0.58, $CHCl_3$)) was obtained in 42% yield. The relative stereochemistry of (2*S*,3*R*)-**7a** was confirmed by the observation of a typical proton coupling constant at C-4 of dioxolane **8** (Scheme 1).

Separation of the syn adduct **7b** from a mixture of adducts **7a** and **7b**, however, failed on column chromatography and crystallization. In addition, no reversal of stereoselection in the addition of 4-benzyloxyphenylmetals to aldehyde **5** was observed under any conditions. Therefore, we turned our attention to the stereoselective reduction of ketone **9** prepared from oxidation of adducts **7a** and **7b**. A mixture of adducts **7a** and **7b** was treated with Dess−Martin periodinane (DMP) in dichloromethane at room temperature for 15 h to give ketone **9** in quantitative yield. The stereoselective reduction of ketone **9** with K-Selectride sluggishly proceeded to give (2*S*,3*S*)-**7b** in a ratio of 97:3 in 98% yield (Scheme 2).[14] However, **7b** thus obtained was found to be partially racemized (85% ee) by HPLC analysis. The unexpected racemization seemed to be derived from the DMP oxidation. To overcome the undesired racemization, we attempted use of Parikh−Doering method[15] (85% ee) and potassium permanganate oxidation[10] (74% ee), but the results were comparable to the DMP oxidation. Finally, we examined the racemization during the K-Selectride reduction. The optically pure **9**[16] was carefully treated with K-Selectride at −78 °C for 72 h. HPLC analysis of (2*S*,3*S*)-**7b** thus obtained showed it to be of 76% ee and clearly disclosed the extensive racemization during the reduction. As a result, the oxidation of **7a** and **7b** was found to proceed with no or little racemization. To our knowledge, there is no precedent for such K-Selectride-mediated racemization of chiral ketones. Fortunately, this scalemic compound (2*S*,3*S*)-**7b** (>94% de) was also purified with one recrystallization to give pure (2*S*,3*S*)-**7b**.

The adduct was converted to the corresponding β-OMeTyr as follows (Scheme 3). Methylation of (2*S*,3*R*)-**7a** with iodomethane−sodium hydride in THF afforded methyl ether **10** in 97% as a colorless oil. The selective removal of acetonide was accomplished by treatment of *p*-TsOH in methanol at room temperature for 4 h to afford amino alcohol **11**. The final conversion to carboxylic acid by oxidation in a single step (Jones oxidation, PDC/DMF, $RuCl_3$−$NaIO_4$, platinum-mediated oxygenation)

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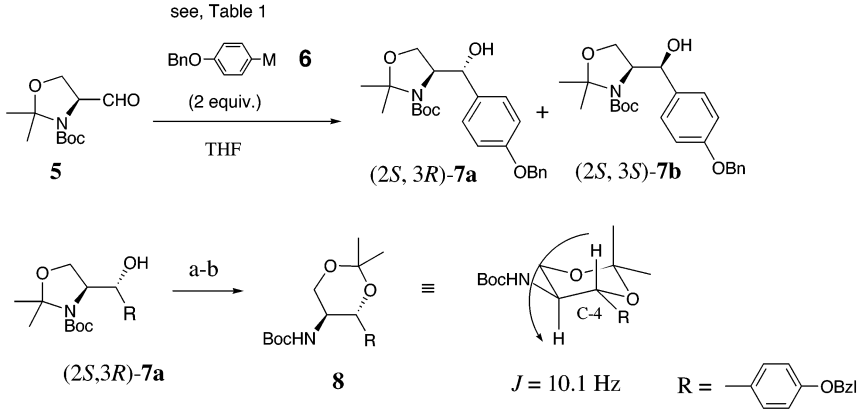
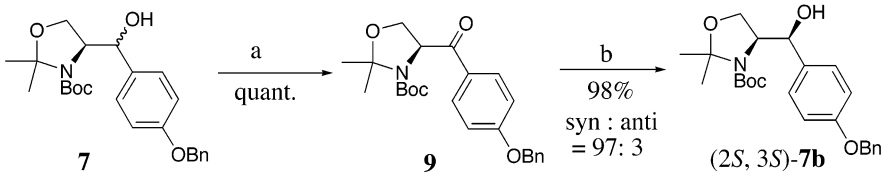
(16) The enantiomeric purity of **9** was measured by HPLC analysis using a chiral column (Daicel Chiralcel OJ, 25 cm; 10% *i*-PrOH in *n*-hexane; flow rate = 0.5 mL/min; (*S*)-**9**, 41.8 min; (*R*)-**9**, 35.7 min) and found to be *S* (>99% ee).

SCHEME 1[a]



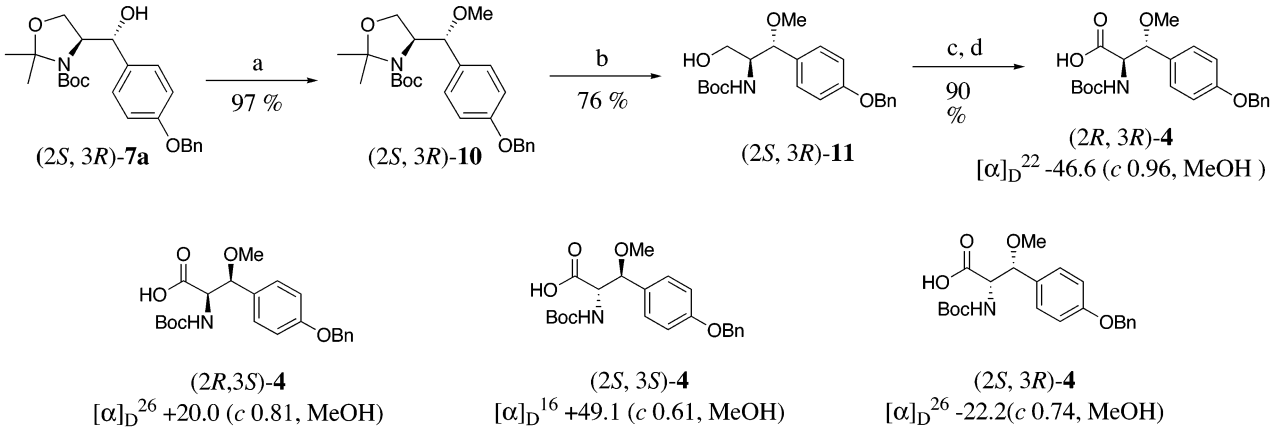
[a] Reaction conditions: (a) *p*-TsOH/MeOH; (b) PPTS, 2,2-dimethoxypropane, CH_2Cl_2.

SCHEME 2[a]



[a] Reaction conditions: (a) Dess−Martin periodinane (1.5 equiv), CH_2Cl_2, rt, 15 h; (b) K-Selectride (4 equiv), THF, −78 °C, 38 h.

SCHEME 3[a]



[a] Reaction conditions: (a) MeI (1.5 equiv), NaH (1.1 equiv), THF, rt, 15 h; (b) *p*-TsOH·H_2O (0.2 equiv), MeOH, rt, 4 h; (c) SO_3·Py, DMSO, Et_3N, CH_2Cl_2, −15 °C, 10 min; (d) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, *t*-BuOH−H_2O, rt, 1 h.

disappointingly gave decomposed products. Fortunately, oxidation of **11** by use of a sequential procedure ((1) SO_3·Py, DMSO, −15 °C, 10 min; (2) $NaClO_2$, KH_2PO_4, *t*-BuOH−H_2O, room temperature, 1 h), however, gave the desired carboxylic acid (2*R*,3*R*)-**4** (mp 106−109 °C, $[\alpha]^{22}_D$ −46.6 (*c* 0.96, MeOH))[15,17] in 90% yield without epimerization. According to this procedure, (2*S*,3*S*)-**7b** was also converted to (2*R*,3*S*)-**4** (mp 96−98 °C, $[\alpha]^{26}_D$ +20.0 (*c* 0.81, MeOH)) in 75% yield in four steps. These protected *β*-OMeTyrs agree with the (*R*)-amino acid series. For the preparation of the (*S*)-amino acid series, application of this synthetic route to the (*R*)-Garner aldehyde afforded the desired (2*S*,3*S*)-**4** (mp 97−99 °C, $[\alpha]^{16}_D$ +49.1 (*c* 0.61, MeOH)) and (2*S*,3*R*)-**4** (mp 109−111°C, $[\alpha]^{26}_D$ −22.2 (*c* 0.74, MeOH)) with similar stereoselection and chemical yields. Now, we have all four stereoisomers of the protected *β*-OMeTyr for determination of the stereochemistry of *β*-OMeTyr in papuamides.

In summary, we have succeeded in stereoselective synthesis of all four stereoisomers of the protected *β*-OMeTyr from (*S*)- and (*R*)-serine for the first time. Further investigation directed toward structural determination of papuamides and their total synthesis is under way in this laboratory.

Experimental Section

Melting points were uncorrected. IR spectra were recorded on a FT/IR spectrometer. NMR spectra were recorded at 400 or 500 MHz for proton and at 100 or 125 MHz for carbon

(17) The optical purity of (2*R*,3*R*)-**4** was confirmed by HPLC analysis of the corresponding methyl ester using a chiral column (Daicel Chiralcel OD-H.; 10% *i*-PrOH in *n*-hexane; flow rate = 0.5 mL/min; (2*R*,3*R*)-**4**, 10.4 min; (2*S*,3*S*)-**4**, 12.4 min).

nuclei. FAB mass spectra were obtained by using an *m*-nitrobenzyl alcohol matrix. Optical rotations were measured at the sodium D line. Column chromatography was carried out on silica gel 230−400 mesh.

(4*S*)-4-[(1*R*)-1-(4-Benzyloxyphenyl)hydroxymethyl]-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidine [(2*S*,3*R*)-7a]. To a solution of *O*-benzyl *p*-bromophenol (13.8 g, 52.34 mmol) and LiBr (11.4 g, 130.8 mmol) in THF (235 mL) was added dropwise *n*BuLi (38.9 mL, 57.57 mmol) at −78 °C. The mixture was stirred at −78 °C for 45 min. A solution of (*S*)-Garner aldehyde (5.68 g, 24.77 mmol) in THF (26.4 mL) was added. After the mixture was stirred at −78 °C for 4 h, the reaction was quenched by addition of saturated aqueous ammonium chloride (63.0 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (250 g, 3:1 *n*-hexane/ethyl acetate) to give **7** (7.29 g, 71%). Pure (2*S*,3*R*)-**7a** (4.3 g, 42%) was obtained by recrystallization from ether−petroleum ether: mp 124 °C; $[\alpha]^{29}_D$ −20.0 (*c* 0.58, $CHCl_3$); IR (KBr) 3568, 2981, 1699, 1512, 1387, 1177 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 328K) δ 1.17−1.58 (15H, m), 3.78−4.00 (2H, m), 4.27 (1H, m), 5.00 (1H, m), 5.06 (2H, s), 6.95 (2H, d, J = 8.5 Hz), 7.28−7.43 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$, 328 K) δ 28.5, 70.2, 94.7, 114.5, 114.9, 115.1, 127.1, 127.4, 127.9, 128.5, 133.7, 137.3, 158.4. Anal. Calcd for $C_{24}H_{31}NO_5$: C, 69.71; H, 7.56; N, 3.39. Found: C, 69.80; H, 7.62; N, 3.35.

(4*R*)-4-[(1*S*)-1-(4-Benzyloxyphenyl)-hydroxymethyl]-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidine [*ent*-7a, (2*R*,3*S*)-7a]. Prepared as described for (2*S*,3*R*)-**7a** with (*R*)-Garner aldehyde: mp 126−128 °C (petroleum ether); $[\alpha]^{29}_D$ +18.7 (*c* 0.62, $CHCl_3$); IR (KBr) 3566, 2981, 1698, 1610, 1383, 1084, 854 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.45−1.53 (15H, m), 3.85 (1H, brs), 4.02 (1H, d, J = 9.1 Hz), 4.17 (1H, brs), 5.00 (1H, s), 5.06 (2H, s), 6.95 (2H, d, J = 6.6 Hz), 7.27−7.42 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4, 70.0, 114.3, 114.6, 114.8, 127.0, 127.4, 127.9, 128.5, 137.0, 158.1. Anal. Calcd for $C_{24}H_{31}NO_5$: C, 69.71; H, 7.56; N, 3.39. Found: C, 69.84; H, 7.62; N, 3.34.

(4*R*,5*S*)-4-(4-Benzyloxyphenyl)-5-*tert*-butoxycarbonyl-amino-1,3-dioxane (8). A mixture of (2*S*,3*R*)-**7a** (30 mg, 0.073 mmol) and *p*-TsOH·H_2O (2.8 mg, 0.015 mmol) in methanol (1.6 mL) was stirred at room temperature for 5 h. The reaction mixture was concentrated in vacuo. Ethyl acetate was added to the residue, and the insoluble material was removed by filtration. The filtrate was concentrated in vacuo to give diol (19 mg, 70%). The diol (19 mg, 0.051 mmol) was dissolved in dichloromethane (1.0 mL), and pyridinium *p*-toluenesulfonate (13 mg, 0.051 mmol) and 2,2-dimethoxypropane (0.16 mL, 1.322 mmol) were added to the solution. The mixture was stirred at room temperature for 19 h. The reaction mixture was concentrated in vacuo. The residue was purified by chromatography on silica gel (10 g,2:1 *n*-hexane/ethyl acetate) to give **8** (14 mg, 67%): ^1H NMR (400 MHz, d_6-DMSO) δ 1.08−1.57 (15H, m), 3.39−3.46 (1H, m), 3.63−3.74 (2H, m), 4.64 (1H, d, J = 10.1 Hz), 5.08 (2H, s), 6.76 (1H, m), 6.95 (2H, d, J = 8.6 Hz), 7.20−7.44 (7H, m).

(4*S*)-4-(4-Benzyloxybenzoyl)-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidine (9). To a stirred solution of (2*S*,3*R*)-**7a** (1.5 g, 3.63 mmol) in dichloromethane (12.1 mL) at 0 °C was added Dess−Martin periodinane (2.0 g, 4.72 mmol). After the mixture was stirred at room temperature for 19 h, the reaction was quenched by addition of 2 N NaOH (30 mL) and then the mixture diluted with dichloromethane (30 mL). The aqueous layer was separated and extracted with dichloromethane (3 × 30 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (40 g, 5:1 *n*-hexane/ethyl acetate) to give **9** (1.48 g, >99%) as colorless solids: mp 180−3 °C (ethyl acetate); $[\alpha]^{26}_D$ −32.3 (*c* 0.52, $CHCl_3$); IR (KBr) 2980, 1700, 1598, 1392, 1248, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 and 1.50 (9H, s), 1.61 and 1.73 and 1.76 (6H, m), 3.93 (1H, m), 4.29 (1H, m), 5.12 and 5.14 (2H, s), 5.37 (1H, m), 6.99−7.05 (2H, m), 7.34−7.44 (5H, m), 7.90 (2H, d, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7 and 24.7 (rotamers), 25.4 and 25.8 (rotamers), 28.3 and 28.4 (rotamers), 61.3 and 61.5 (rotamers), 65.9 and 66.3 (rotamers), 70.1 and 70.2 (rotamers), 80.2 and 80.7 (rotamers), 94.5 and 95.2 (rotamers), 114.8 and 114.9 (rotamers), 127.5, 128.1, 128.3, 128.7, 130.4 and 130.7 (rotamers), 136.0 and 136.1 (rotamers), 151.3 and 152.1 (rotamers), 162.9 and 162.9 (rotamers), 193.6 and 194.3 (rotamers). Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N, 3.40. Found: C, 70.01; H, 7.04; N, 3.37.

(4*R*)-4-(4-Benzyloxybenzoyl)-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidine (*ent*-9). Prepared as described for (2*S*,3*R*)-**7a** with *ent*-**7a**: mp 179−83 °C (ethyl acetate); $[\alpha]^{26}_D$ +31.4 (*c* 0.63, $CHCl_3$); IR (KBr) 2966, 1698, 1598, 1392, 1248, 1176, 1091 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 and 1.50 (9H, s), 1.57 (3H, s)1.75 (3H, s), 3.93 (1H, m), 4.29 (1H, m), 5.12 and 5.14 (2H, s), 5.38 (1H, m), 6.99−7.05 (2H, m), 7.33−7.45 (5H, m), 7.90 (2H, d, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7 and 24.8 (rotamers), 25.4 and 25.8 (rotamers), 28.2 and 28.4 (rotamers), 61.3 and 61.5 (rotamers), 65.9 and 66.3 (rotamers), 70.1 and 70.2 (rotamers), 80.2 and 80.7 (rotamers), 94.5 and 95.2 (rotamers), 114.8 and 114.9 (rotamers), 127.5, 128.1, 128.3, 128.7, 130.4 and 130.7 (rotamers), 136.0, 151.3 and 152.1 (rotamers), 162.9, 193.4. Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N, 3.40. Found: C, 70.06; H, 7.14; N, 3.41.

(4*S*)-4-[(1*S*)-1-(4-Benzyloxyphenyl)hydroxymethyl]-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidine [(2*S*,3*S*)-7b]. To a stirred solution of **9** (4.8 g, 11.7 mmol) in THF (166 mL) was added K-Selectride in THF (46.7 mL, 46.7 mmol) at −78 °C. After the mixture was stirred at −70 °C for 36 h, the reaction was quenched by addition of 2 N NaOH (50 mL) at −70 °C followed by 30% H_2O_2 (25.1 mL) at −15 °C. The mixture was stirred at the same temperature for 3 h. The insoluble material was removed by filtration through a pad of Celite. The aqueous phase of the filtrate was separated and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (150 g, 3:1 *n*-hexane:ethyl acetate) to give (2*S*,3*S*)-**7b** (4.80 g, 98%) as colorless solids. Pure (2*S*,3*S*)-**7b** was obtained by recrystallization from ether−petroleum ether: mp 103−108 °C; $[\alpha]^{25}_D$ +9.75 (*c* 0.5, $CHCl_3$); IR (KBr) 3432, 2972, 1672, 1511, 1406, 1244, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.5 Hz), 1.18 (3H, d, J = 6.2 Hz), 1.49 (9H, s), 3.62−3.76 (3H, m), 4.14−4.17 (1H, m), 4.70 (1H, d, J = 8.5 Hz), 5.06 (2H, s), 6.94 (2H, d, J = 8.7 Hz), 7.28 (2H, d, J = 8.6 Hz), 7.30−7.42 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 65.0, 70.2, 94.7, 115.1, 127.4, 127.9, 128.5, 128.6, 137.2, 158.8. Anal. Calcd for $C_{24}H_{31}NO_5$: C, 69.71; H, 7.56; N, 3.39. Found: C, 69.51; H, 7.53; N, 3.35.

(4*R*)-4-[(1*R*)-1-(4-Benzyloxyphenyl)hydroxymethyl]-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidine [*ent*-7b, (2*R*,3*R*)-7b]. Prepared as described for (2*S*,3*S*)-**7b** with *ent*-**9**: mp 100−103 °C; $[\alpha]^{26}_D$ −9.05 (*c* 0.49, $CHCl_3$); IR (KBr) 3432, 2970, 1672, 1510, 1406, 1245, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 328 K) δ 1.49−1.53 (15H, m), 3.64−3.73 (2H, m), 4.14−4.18 (1H, m), 4.69 (1H, d, J = 8.8 Hz), 5.06 (2H, s), 6.94 (2H, d, J = 8.5 Hz), 7.25−7.42 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2 and 28.4 (rotamers), 63.8 and 64.9 (rotamers), 70.0, 94.6, 114.6 and 114.9 (rotamers), 127.5, 128.0, 128.5 and 128.6 (rotamers), 134.5, 137.0, 155.6 and 158.6 (rotamers). Anal. Calcd for $C_{24}H_{31}NO_5$: C, 69.71; H, 7.56; N, 3.39. Found: C, 69.39; H, 7.55; N, 3.53.

(4*S*)-4-[(1*R*)-1-(4-Benzyloxyphenyl)methoxymethyl]-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidine [(2*S*,3*R*)-10]. To a stirred solution of (2*S*,3*R*)-**7a** (500 mg, 1.21 mmol) in THF (25.2 mL) was added NaH (53 mg, 1.33 mmol, 60% oil

dispersion) at 0 °C, and the mixture was stirred at room temperature for 10 min. The reaction mixture was cooled to 0 °C, and iodomethane (0.12 mL, 1.81 mmol) was added to the mixture. The mixture was stirred for 10 h with gradual warming to room temperature. The reaction mixture was diluted with ether (30 mL) and saturated aqueous sodium bicarbonate (15 mL). The aqueous layer was separated and extracted with ether (3 × 30 mL). The combined organic extracts were washed with brine (50 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (30 g, 7:1 *n*-hexane/ethyl acetate) to give (2*S*,3*R*)-**10** (500 mg, 97%) as a colorless oil: $[\alpha]^{27}_D$ −10.7 (*c* 0.31, $CHCl_3$); IR (KBr) 2931, 1695, 1611, 1510, 1385, 1245, 1172, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26−1.71 (15H, m), 3.30 (3H, m), 3.72−3.80 (1H, m), 3.90−4.14 (2H, m), 4.11−4.59 (1H, m), 5.03 (2H, m), 6.96 (2H, m), 7.21−7.42 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 25.9, 28.4, 63.5, 64.4, 70.0, 74.6, 94.6, 114.6 and 114.9 (rotamers), 127.1, 127.4, 127.9, 128.6, 133.4, 137.0, 158.2; HRFABMS (NBA) calcd for $C_{25}H_{34}NO_5$ (M + H) 428.2437, found 428.2420.

(4*S*)-4-[(1*S*)-1-(4-Benzyloxyphenyl)methoxymethyl]-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidine [(2*S*,3*S*)-10]. Prepared as described for (2*S*,3*R*)-**10** with (2*S*,3*S*)-**7b**: $[\alpha]^{29}_D$ −41.7 (*c* 0.59, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.78−1.52 (15H, m), 3.27 (3H, s), 3.89−4.74 (4H, m), 5.07 (2H, s), 6.95 (2H, d, *J* = 8.4 Hz), 7.21 (2H, d, *J* = 8.2 Hz), 7.26−7.43 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 25.5, 28.5, 57.2, 60.5, 69.9, 114.4, 127.4, 127.9, 128.5, 128.9, 130.3, 137.0, 158.6; HRFABMS (NBA) calcd for $C_{25}H_{34}NO_5$ (M + H) 428.2437, found 428.2420.

(4*R*)-4-[(1*S*)-1-(4-Benzyloxyphenyl)methoxymethyl]-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidine [(2*R*,3*S*)-10]. Prepared as described for (2*S*,3*R*)-**10** with *ent*-**7a**: $[\alpha]^{27}_D$ +9.68 (*c* 0.37, $CHCl_3$); IR (neat) 2979, 1699, 1509, 1365, 1233 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 and 1.34 (rotamer, 9H, s), 1.52−1.78 (6H, m), 3.31 (3H, s), 3.73−3.82 (1H, m), 3.91−4.05 (1H, m), 4.10−4.15 (1H, m), 4.36−4.59 (1H, m), 5.05 (2H, s), 6.97−6.98 (2H, m), 7.22−7.45 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3 and 24.9 (rotamers), 26.6 and 26.8 (rotamers), 28.2 and 28.3 (rotamers), 62.3 and 62.5 (rotamers), 63.6 and 64.4 (rotamers), 70.0, 94.1 and 94.7 (rotamers), 114.6 and 114.8 (rotamers), 127.4, 128.0 and 128.1 (rotamers), 128.6, 131.3, 137.0, 158.4; HRFABMS (NBA) calcd for $C_{25}H_{34}NO_5$ (M + H) 428.2437, found 428.2408.

(4*R*)-4-[(1*R*)-1-(4-Benzyloxyphenyl)methoxymethyl]-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidine [(2*R*,3*R*)-10]. Prepared as described for (2*S*,3*R*)-**10** with *ent*-**7b**: $[\alpha]^{29}_D$ +40.7 (*c* 0.61, $CHCl_3$); IR (neat) 2931, 1737, 1698, 1509, 1365, 1230 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.77−1.71 (15H, m), 3.27 (3H, s), 3.88−4.74 (4H, m), 5.06 (2H, s), 6,95 (2H, d, *J* = 8.5 Hz), 7.20 (2H, d, *J* = 8.5 Hz), 7.30−7.43 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 25.5, 28.5, 57.3, 60.4, 70.0, 80.3, 114.4, 127.5, 127.9, 128.6, 128.9, 130.3, 137.0, 158.6; HRFABMS (NBA) calcd for $C_{25}H_{34}NO_5$ (M + H) 428.2437, found 428.2420.

(2*S*,3*R*)-3-(4-Benzyloxyphenyl)-2-*tert*-butoxycarbonylamino-3-methoxy-1-propanol [(2*S*,3*R*)-11]. To a stirred solution of (2*S*,3*R*)-**10** (1.9 g, 4.44 mmol) in methanol (44.6 mL) was added *p*-TsOH·H_2O (169 mg, 0.9 mmol). After stirring at room temperature for 4 h, the reaction mixture was concentrated in vacuo. The residue was redissolved in ethyl acetate (30 mL). The solution was washed with saturated aqueous sodium bicarbonate (15 mL) and brine (15 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (30 g, 1:1 *n*-hexane/ethyl acetate) to give (2*S*,3*R*)-**11** (1.36 g, 79%) as colorless solids: mp 76−77 °C; $[\alpha]^{26}_D$ −19.7 (*c* 0.53, $CHCl_3$); IR (KBr) 3360, 2982, 1685, 1532, 1244, 1173, 1064 cm^{-1}; H NMR (400 MHz, $CDCl_3$) δ 1.44 (9H, s), 2.73 (1H, brs), 3.31 (3H, m), 3.48−3.54 (1H, m), 3.66 (1H, brs), 3.84 (1H, d, *J* = 11.5 Hz), 4.52 (1H, brs), 6.99 (2H, d, *J* = 8.8 Hz), 7.21−7.45 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 56.2, 57.9, 61.5, 70.0, 79.5, 85.7, 114.9, 127.5, 127.8, 128.0, 128.6, 130.3, 136.9, 155.8, 158.5. Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.20; H, 7.54; N, 3.61. Found: C, 68.22; H, 7.65; N, 3.38.

(2*S*,3*S*)-3-(4-Benzyloxyphenyl)-2-*tert*-butoxycarbonylamino-3-methoxy-1-propanol [(2*S*,3*S*)-11]. Prepared as described for (2*S*,3*R*)-**11** with (2*S*,3*S*)-**10**: mp 62−65 °C; $[\alpha]^{28}_D$ +43.2 (*c* 0.72, $CHCl_3$); IR (KBr) 3498, 3326, 2932, 1670, 1510, 1176 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (9H, s), 3.23 (3H, s), 3.66−3.76 (3H, m), 4.36 (1H, d, *J* = 4.3 Hz), 5.06 (2H, s), 6.97 (2H, d, *J* = 8.5 Hz), 7.22 (2H, d, *J* = 8.6 Hz), 7.33−7.44 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 56.9, 57.2, 63.8, 70.0, 79.6, 82.8, 114.8, 127.4, 128.0, 128.2, 128.6, 130.5, 136.9, 158.7. Anal. Calcd for $C_{22}H_{29}NO_5 \cdot 1/3H_2O$: C, 67.15; H, 7.60; N, 3.56. Found: C, 67.05; H, 7.61 N, 3.47.

(2*R*,3*S*)-3-(4-Benzyloxyphenyl)-2-*tert*-butoxycarbonylamino-3-methoxy-1-propanol [(2*R*,3*S*)-11]. Prepared as described for (2*S*,3*R*)-**11** with (2*R*,3*S*)-**10**: mp 70−72 °C; $[\alpha]^{29}_D$ +19.7 (*c* 0.5, $CHCl_3$); IR (KBr) 3360, 2821, 1688, 1611, 1536, 1243, 1064 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (9H, m), 2.81 (1H, d, *J* = 7.4 Hz), 3.30 (3H, s), 3.48−3.54 (1H, m), 3.66 (1H, brs), 3.84 (1H, dt, *J* = 2.9, 11.5 Hz), 4.52 (1H, s), 5.06 (2H, s), 5.38 (1H, d, *J* = 7.5 Hz), 6.99 (2H, d, *J* = 8.8 Hz), 7.25 (2H, d, *J* = 8.4 Hz), 7.31−7.45 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 56.2, 57.9, 60.3, 61.5, 70.0, 79.5, 85.7, 114.9, 127.4, 127.8, 128.0, 128.6, 130.3, 136.9, 158.5; Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.20; H, 7.54; N, 3.61. Found: C, 68.33; H, 7.62; N, 3.64.

(2*R*,3*R*)-3-(4-Benzyloxyphenyl)-2-*tert*-butoxycarbonylamino-3-methoxy-1-propanol [(2*R*,3*R*)-11]. Prepared as described for (2*S*,3*R*)-**11** with (2*R*,3*R*)-**10**: mp 60−63 °C; $[\alpha]^{28}_D$ −40.9 (*c* 0.72, $CHCl_3$); IR (KBr) 3490, 3324, 2932, 1691, 1510, 1176 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (9H, s), 3.24 (3H, s), 3.65−3.76 (3H, m), 4.36 (1H, d, *J* = 4.2 Hz), 5.06 (2H, s), 6.97 (2H, d, *J* = 8.6 Hz), 7.21 (2H, d, *J* = 8.6 Hz), 7.31−7.45 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 56.9, 60.4, 63.9, 70.0, 79.6, 82.9, 114.8, 127.5, 128.0, 128.2, 128.6, 130.4, 136.9, 158.7. Anal. Calcd for $C_{22}H_{29}NO_5 \cdot 1/3H_2O$: C, 67.15; H, 7.60; N, 3.56. Found: C, 67.45; H, 7.44; N, 3.64.

(2*R*,3*R*)-3-(4-Benzyloxyphenyl)-2-*tert*-butoxycarbonylamino-3-methoxypropionic Acid [(2*R*,3*R*)-4]. To a stirred solution of (2*S*,3*R*)-**11** (1.00 g, 2.58 mmol) in dichloromethane (7.7 mL) was added triethylamine (1.80 mL, 12.9 mmol) at −15 °C. A solution of pyridine−sulfur trioxide complex (2.04 g, 12.9 mmol) in DMSO (7.7 mL) was added to the above solution in one portion. The mixture was stirred at the same temperature for 10 min. The mixture was poured into ice-saturated sodium chloride (225 mL) and extracted with cold ether (3 × 100 mL). The combined organic extracts were washed with 10% citric acid (50 mL) and brine (50 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to give an aldehyde, which was used in the following reaction without further purification.

The crude aldehyde, 2-methyl-2-butene (1.37 mL, 12.9 mmol), and potassium dihydrogenphosphate (351 mg, 2.58 mmol) was dissolved in ^{t}BuOH (74.5 mL)−water (19.9 mL). Sodium chlorite (875 mg, 7.74 mmol) was added portionwise at 0 °C. After stirring at room temperature for 1 h, the reaction mixture was cooled to 0 °C, acidified with 10% citric acid, and extracted with ethyl acetate (3 × 70 mL). The combined extracts were washed with brine (30 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (25 g, 1:4 *n*-hexane/ethyl acetate) to give (2*R*,3*R*)-**4** (978 mg, 90%) as colorless solids: mp 106−109 °C; $[\alpha]^{22}_D$ −46.6 (*c* 0.96, MeOH); IR (KBr) 3359, 2981, 1722, 1512, 1242 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (9H, s), 3.32 (3H, s), 4.36 (1H, m), 4.58 (1H, m), 5.06 (2H, s), 6.98 (2H, d, *J* = 7.6 Hz), 7.25 (2H, d, *J* = 7.6 Hz), 7.40−7.47 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 57.3, 58.2, 70.0, 80.3, 82.9, 114.8, 127.5, 128.0, 128.4, 128.6, 128.8, 136.8, 155.3, 159.0, 174.2. Anal. Calcd for $C_{22}H_{27}NO_6 \cdot 2/3H_2O$: C, 63.91; H, 6.91; N, 3.39. Found: C, 63.77; H, 6.82; N, 3.39.

(2*R*,3*S*)-3-(4-Benzyloxyphenyl)-2-*tert*-butoxycarbonylamino-3-methoxypropionic Acid [(2*R*,3*S*)-4]. Prepared as described for (2*R*,3*R*)-**4** with (2*S*,3*S*)-**11**: mp 96−98 °C; $[\alpha]^{26}_{D}$ +20.0 (*c* 0.81, MeOH); IR (KBr) 3437, 2931, 1732, 1682, 1505 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (9H, s), 3.28 (3H, s), 4.51 (1H, dd, J = 2.8, 9.3 Hz), 4.81 (1H, d, J = 2.6 Hz), 5.05 (2H, s), 5.34 (1H, d, J = 8.8 Hz), 6.97 (2H, d, J = 8.4 Hz), 7.25 (2H, d, J = 8.4 Hz), 7.30−7.44 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.9, 56.9, 57.3, 70.0, 80.0, 82.0, 114.8, 127.5, 128.0, 128.2, 128.6, 129.1, 136.9, 155.6, 158.8, 174.7. Anal. Calcd for $C_{22}H_{37}NO_6 \cdot H_2O$: C, 62.99; H, 6.97; N, 3.34. Found: C, 62.96; H, 6.59; N, 3.10.

(2*S*,3*S*)-3-(4-Benzyloxyphenyl)-2-*tert*-butoxycarbonylamino-3-methoxypropionic Acid [(2*S*,3*S*)-4]. Prepared as described for (2*R*,3*R*)-**4** with (2*R*,3*S*)-**11**: mp 107−110 °; $[\alpha]^{16}_{D}$ +49.1 (*c* 0.61, MeOH); IR (KBr) 3342, 2980, 1690, 1610, 1511, 1245, 1172 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 (9H, s), 3.31 (3H, s), 4.34−4.36 (1H, m), 4.53−4.63 (1H, m), 5.04 (2H, s), 6.98 (2H, d, J = 8.3 Hz), 7.25−7.43 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 57.3, 58.2, 60.4, 70.0, 80.2, 82.9, 114.8, 127.4, 128.0, 128.4, 128.7, 128.9, 136.8, 155.3, 158.9, 174.5; Anal. Calcd for $C_{22}H_{27}NO_6$: C, 65.82; H, 6.78; N, 3.49. Found: C, 66.19; H, 6.95; N, 3.43.

(2*S*,3*R*)-3-(4-Benzyloxyphenyl)-2-*tert*-butoxycarbonylamino-3-methoxypropionic Acid [(2*S*,3*R*)-4]. Prepared as described for (2*R*,3*R*)-**4** with (2*R*,3*R*)-**11**: mp 109−111 °C; $[\alpha]^{26}_{D}$ −22.2 (*c* 0.74, MeOH); IR (KBr) 3460, 2930, 1733, 1652, 1507, 1368, 1228 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (9H, s), 3.27 (3H, s), 4.35 (1H, dd, J = 2.6, 9.4 Hz), 4.82 (1H, d, J = 2.5 Hz), 5.04 (2H, s), 5.38 (1H, d, J = 9.5 Hz), 6.96 (2H, d, J = 8.6 Hz), 7.24 (2H, d, J = 8.6 Hz), 7.30−7.46(5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.1, 57.3, 59.0, 60.5, 70.0, 80.0, 82.1, 114.8, 127.4, 128.0, 128.1, 128.6, 129.2, 136.8, 155.6, 158.8, 174.8. Anal. Calcd for $C_{22}H_{27}NO_6 \cdot 1/3H_2O$: C, 64.85; H, 6.84; N, 3.44. Found: C, 64.57; H, 6.84; N, 3.44.

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