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Expedient Synthesis of *syn*-β-Hydroxy-α-amino acid derivatives: Phenylalanine, Tyrosine, Histidine and Tryptophan

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Abstract

An expedient synthesis of enantiomerically pure *threo*-β-hydroxy-α-amino acid derivatives of phenylalanine, tyrosine, histidine and tryptophan is described. The NBS-mediated radical bromination of the *N*,*N*-di-*tert*-butoxycarbonyl protected α-amino acids and subsequent treatment with silver nitrate in acetone provided the *trans*-oxazolidinones predominantly. The cesium carbonate catalyzed hydrolysis then generated the β-hydroxy amino acid derivatives in excellent overall yield from the amino acids themselves.

β-Hydroxy-α-amino acids are an interesting class of molecules due to their presence in numerous biologically active natural products. For example, β-hydroxytyrosine and β-hydroxyphenylalanine residues are found in clinically active glycopeptide antibiotics, such as vancomycin,[1] bouvardin,[2] orienticnic,[3] phomopsins,[4] ristocetin,[5] actaplanin,[5] and teicoplanin.[5] β-Hydroxyhistidine has also been found in bleomycin,[6] tallysomycin,[7] exochelins MN,[8a] and PF244.[8b] These highly functionalized amino acids are also useful building blocks for the synthesis of β-lactams,[9] β-fluoro-α-amino acids,[10] and sugars.[11]

Over the years several strategies have been developed for the asymmetric syntheses of β-hydroxy-α-amino acids including asymmetric aldol reaction[12] utilizing chiral oxazolidinones;[13] alkylation of chiral enolates from oxazolidinones,[14] oxazolidines,[15] bis-lactim ethers,[16] oxazolines[17] and imidazolidinones;[18] cycloaddition of chiral azomethine ylids;[19] enzymatic transformations;[20] stereoselective hydrolysis of aziridine carboxylate esters;[21] Sharpless asymmetric dihydroxylations;[22] asymmetric aminohydroxylations;[23] asymmetric epoxidations;[24] sulfonamide mediated asymmetric Strecker reaction;[25] imino [1,2]-Wittig rearrangement of hydroximates[26] and numerous others.[25] Most of these protocols involve multiple steps and the use of chiral auxiliaries or chiral catalysts, and often proceed with less than perfect stereocontrol.

In 1990, Easton and coworkers reported a method for diastereoselective conversion of amino acids to their β-hydroxy derivatives by direct side chain bromination of the amino acid derivatives with NBS, followed by treatment with silver nitrate in aqueous acetone.[27] For example, phenylalanine gave 1:1 mixture of the diastereomeric bromides and subsequently a 5:1 mixture of the *syn* and *anti* β-hydroxyphenylalanine derivatives. This side chain bromination requires an *N*-substituent such as phthaloyl or trifluoromethanesulfonyl, to deactivate the α-position towards hydrogen atom abstraction.[28] The phthaloyl group also participates in the hydrolysis step and is thereby responsible for the observed stereodifferentiation. The main limitation of the method is the use of the phthalimido and trifluoromethanesulfonamide protecting groups with their less than ideal hydrolysis conditions.

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In spite of this, the methodology has been applied in the synthesis of vancomycin,[22b] chloramphenicol,[29] cyclomarin C,[30] and residues of callipeltin A.[31] We report here on the use of *N*,*N*-di-*tert*-butoxycarbonyl protected amino acids in Easton's protocol and on the advantages that this affords.

The methyl ester of phenylalanine (**1**) was converted to the di-*N*-*tert*-butoxycarbonyl derivative **2**[32] by treatment with DMAP and $(Boc)_2O$.[33] The NBS-mediated bromination in CCl_4[34] then afforded the bromides (**3**) in a 1:1 mixture, which was treated with silver nitrate in acetone to afford the *trans* and *cis* oxazolidinones **4** and **5**, respectively, in 6:1 ratio and 70% yield. The oxazolidinones were completely separable by flash column chromatography and when individually subjected to hydrolysis with catalytic Cs_2CO_3 in methanol,[26] the *threo* (2*S*,3*R*) and *erythro* (2*S*,3*S*) β-hydroxy phenylalanines **6** and **8** were obtained in 80% and 79% yields, respectively, as single diastereomers (Scheme 1). When the hydrolysis reaction of **4** was performed in MeOH-D_4, no deuterium substitution at the α-centre was observed in the product **7**, indicating this step to be racemization free.

With insoluble silver salts such as silver carbonate or silver oxide, only the *erythro* bromide reacted to give the *trans*-oxazolidinone (**4**) in 48% yield. The *threo* isomer remained unreacted and was isolated in 45% yield (Scheme 2). When the bromides (**3**) were treated with silver trifluoromethanesulfonate, the oxazolidinones **9** and **10** were formed in a 10:1 ratio in favor of the *trans* isomer, with complete cleavage of the *N*-*tert*-butoxycarbonyl group (Scheme 2).[31] The drastic conditions[35] required for the hydrolysis of **9** and **10** prompted their conversion to **4** and **5** with $(Boc)_2O$ and DMAP.[36] The high selectivity in the conversion of **3** to **9** and **10** is offset by the lower yield and, all things considered, caused us to favor silver nitrate conditions.

The NBS-mediated bromination of **12** yielded the diastereomeric bromides (**13**) as a 1:1 mixture, which was immediately treated with silver nitrate in acetone to afford the *trans* and *cis* oxazolidinones **14** and **15** in 65% yield and 15:1 ratio. Inspection of the ^1H NMR spectrum of the diastereomeric bromides revealed that the *trans* oxazolidinone (**14**) formation was initiated even before the addition of the silver salt. The *trans* isomer was hydrolyzed uneventfully to β-hydroxytyrosine derivative **16** using cesium carbonate in methanol in 77% yield (Scheme 3).

The radical bromination of **18**[37] provided the *threo* bromide **19** and the *trans* oxazolidinone **20**. This mixture was subsequently treated with silver nitrate in acetone to afford the *trans* oxazolidinones **20** and **21** which differ by the presence of a *tert*-butoxycarbonyl group, in 62% yield. Attempted hydrolysis of **20** or **21** under a wide variety of conditions produced the dehydrohistidine derivative **22**. We reasoned that the free imidazole nitrogen is responsible for the elimination reaction, and that an imidazole protecting group, stable under mild basic conditions, would solve the problem. Accordingly, **21** was reacted with trityl chloride and triethylamine in dichloromethane and, after the removal of the excess trityl chloride, the reaction mixture was treated with catalytic cesium carbonate (20 mol%) in methanol leading directly to the formation of the desired (2*S*,3*S*) β-hydroxyhistidine derivative **23** in 74% yield (Scheme 4).

Interestingly, the NBS-mediated radical bromination of **25**[32] directly formed the *trans* oxazolidinone **26** in 72% yield. The cesium carbonate catalyzed hydrolysis was straightforward and produced the desired product (**27**) in 84% yield (Scheme 5).

In conclusion we have demonstrated an improved synthetic route for enantiomerically pure *threo*-β-hydroxy-α-amino acids from the amino acids themselves. As the aryl substituents became progressively more electron donating in nature from phenylalanine to tryptophan, the conversion of the intermediate bromides to the oxazolidinones became easier and was associated with increased stereoselectivity in this step.

Experimental Section

1. General procedure for the synthesis of oxazolidinones.[27]

A mixture of amino acid derivatives and NBS (1 equiv.) in CCl_4 (0.05 M) was heated at reflux for 45 mins.[38] under nitrogen, whilst being irradiated with a 250 W Kr lamp. The mixture was then cooled to room temperature, filtered and concentrated. To a solution of the concentrate in acetone (0.05 M), silver nitrate (1.5 equiv.) was added. The reaction mixture was stirred at room temperature in dark for 2 h. Then the reaction mixture was filtered through a celite pad and the filtrate was concentrated. The concentrate was diluted with ethyl acetate and washed with saturated NH_4Cl solution, water and brine. The organic layer was dried and concentrated. Chromatographic purification afforded the oxazolidinones.

2. General procedure for the hydrolysis of oxazolidinones.[26]

A solution of the oxazolidinone in methanol was treated with Cs_2CO_3 (20 mol%) and stirred at room temperature for 2.5 h. Then the reaction mixture was concentrated and the concentrate was diluted with ethyl acetate and washed with saturated NH_4Cl solution, water and brine. The organic layer was dried and concentrated. Chromatographic purification afforded the β-hydroxy-α-amino acid derivatives.

Methyl (4*S*,5*R*)-3-*N*-*tert*-butoxycarbonyl-5-phenyl-1,3-oxazolidin-2-oxo-4-carboxylate (4) and Methyl (4*S*,5*S*)-3-*N*-*tert*-butoxycarbonyl-5-phenyl-1,3-oxazolidin-2-oxo-4-carboxylate (5).[26, 14b]

Following the general procedure 1 and eluting with 16–18% ethyl acetate in hexane **4** and **5** were obtained in 6: 1 ratio and 70% yield. **4**: $[\alpha]^{22}_D$ +28.3 (*c* 1.6); ^{1}H NMR (500 MHz) δ: 7.43-7.36 (m, 5H), 5.38-5.37 (d, *J* = 4.0 Hz, 1H), 4.63-4.62 (d, *J* = 4.5 Hz, 1H), 3.88 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (125 MHz) δ: 169.0, 150.7, 148.4, 137.1, 129.5, 129.2, 125.0, 84.9, 75.9, 63.7, 53.3, 27.8. **5**: $[\alpha]^{24}_D$ +45.2 (*c* 1.2); ^{1}H NMR (400 MHz) δ:7.36-7.28 (m, 5H), 5.72-5.70 (d, *J* = 9.2 Hz, 1H), 4.97-4.94 (d, *J* = 8.4 Hz, 1H), 3.23 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (100 MHz) δ: 167.3, 151.1, 148.5, 132.7, 129.5, 128.5, 126.1, 84.8, 75.5, 62.3, 52.2, 27.8.

N-*tert*-Butoxycarbonyl-(2*S*,3*R*)-β-hydroxy-L-phenylalanine methyl ester (6).[26]

Following the general procedure 2, and eluting with 20% ethyl acetate in hexane, **6** was obtained in 80% yield. $[\alpha]^{22}_D$ −14.8 (*c* 1.3); ^{1}H NMR (400 MHz) δ: 7.35-7.23 (m, 5H), 5.41-5.39 (d, *J* = 8.4 Hz, 1H), 5.20 (s, 1H), 4.52-4.50 (d, *J* = 7.6 Hz, 1H), 3.73 (s, 3H), 3.16 (bs, 1H), 1.31 (s, 9H); ^{13}C NMR (100 MHz) δ: 171.5, 155.7, 139.9, 128.3, 128.0, 126.0, 80.0, 73.8, 59.5, 52.6, 28.2.

Methyl (4*S*,5*R*)-3-*N*-*tert*-butoxycarbonyl-5-(4-*tert*-butoxycarbonyloxyphenyl)-1,3-oxazolidin-2-oxo-4-carboxylate (14) and Methyl (4*S*,5*S*)-3-*N*-*tert*-butoxycarbonyl-5-(4-*tert*-butoxycarbonyloxyphenyl)-1,3-oxazolidin-2-oxo-4-carboxylate (15)

Following the general procedure 1 and eluting with 16–18% ethyl acetate in hexane **14** and **15** were obtained in 15: 1 ratio and 65% yield. **14**: $[\alpha]^{22}_D$ +31.2 (*c* 0.7); ^{1}H NMR (400 MHz) δ:7.40-7.38 (d, *J* = 8.4 Hz, 2H), 7.25-7.23 (d, *J* = 8.8 Hz, 2H), 5.38-5.37 (d, *J* = 4.8 Hz, 1H), 4.61-4.60 (d, *J* = 4.8 Hz, 1H), 3.87 (s, 3H), 1.55 (s, 9H), 1.48 (s, 9H); ^{13}C NMR (100 MHz) δ:168.9, 151.7, 151.6, 150.6, 148.3, 134.6, 126.2, 122.2, 85.0, 84.1, 75.3, 63.7, 53.3, 27.8, 27.7; ESI-HRMS Calcd for $C_{21}H_{27}NO_9$ $[M + Na]^+$: 460.1583. Found 460.1568. **15**: $[\alpha]^{22}_D$ +33.8 (*c* 1.2); ^{1}H NMR (400 MHz) δ:7.32-7.30 (d, *J* = 9.2 Hz, 2H), 7.20-7.18 (d, *J* = 8.0 Hz, 2H), 5.72-5.70 (d, *J* = 8.8 Hz, 1H), 4.95-4.93 (d, *J* = 9.6 Hz, 1H), 3.26 (s, 3H), 1.54 (s, 9H), 1.49 (s, 9H); ^{13}C NMR (100 MHz) δ:167.2, 151.8, 150.9, 148.5, 130.0, 127.3, 121.5, 84.9, 83.9,

74.9, 62.2, 52.4, 27.7, 27.5; ESI-HRMS Calcd for $C_{21}H_{27}NO_9$ [M + Na]$^+$: 460.1583. Found 460.1581.

N-tert-Butoxycarbonyl-*O-tert*-butoxycarbonyl-(2*S*,3*R*)-β-hydroxy-L-tyrosine methyl ester (16)

Following the general procedure 2, and eluting with 26% ethyl acetate in hexane, **16** was obtained in 77% yield. [α]$^{22}_D$ -10.5 (*c* 1.0); ^{1}H NMR (400 MHz) δ: 7.37-7.35 (d, *J* = 8.0 Hz, 2H), 7.14-7.12 (d, *J* = 7.6 Hz, 2H), 5.34-5.32 (d, *J* = 8.8 Hz, 1H), 5.18 (s, 1H), 4.49-4.47 (d, *J* = 8.4 Hz, 1H), 3.73 (s, 3H), 1.53 (s, 9H), 1.32 (s, 9H); ^{13}C NMR (100 MHz) δ:171.3, 155.7, 151.8, 150.6, 137.4, 127.1, 121.1, 83.6, 80.2, 73.3, 59.4, 52.6, 28.2, 27.7; ESI-HRMS Calcd for $C_{20}H_{29}NO_8$ [M + Na]$^+$: 434.1791. Found 434.1772.

Methyl (4*S*,5*S*)-3-*N-tert*-butoxycarbonyl-5-{4-*N*-(*tert*-butoxycarbonyl)imidazolyl}-1,3-oxazolidin-2-oxo-4-carboxylate (20) and Methyl (4*S*,5*S*)-3-*N-tert*-butoxycarbonyl-5-imidazolyl-1,3-oxazolidin-2-oxo-4-carboxylate (21)

Following the general procedure 1 and eluting with 26–80% ethyl acetate in hexane **20** and **21** were obtained in 1.5: 1 ratio and 62% yield. **20**: [α]$^{22}_D$ +97.7 (*c* 0.4); ^{1}H NMR (500 MHz) δ: 8.09 (s, 1H), 7.47 (s, 1H), 5.35-5.34 (d, *J* = 4.0 Hz, 1H), 5.01-5.00 (d, *J* = 4.0 Hz, 1H), 3.84 (s, 3H), 1.61 (s, 9H), 1.48 (s, 9H); ^{13}C NMR (125 MHz) δ: 169.0, 150.6, 148.4, 146.4, 138.7, 138.0, 116.0, 86.7, 84.7, 71.1, 60.9, 53.2, 27.83, 27.81; ESI-HRMS Calcd for $C_{18}H_{25}N_3O_8$ [M + Na]$^+$: 434.1539. Found 434.1523. **21**: [α]$^{22}_D$ +76.5 (*c* 0.7); ^{1}H NMR (500 MHz) δ: 11.39 (bs, 1H), 7.69 (s, 1H), 7.18 (s, 1H), 5.41-5.40 (d, *J* = 4.5 Hz, 1H), 5.14-5.13 (d, *J* = 4.0 Hz, 1H), 3.81 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (125 MHz) δ: 169.3, 151.8, 148.5, 136.8, 135.8, 116.1, 85.0, 71.9, 61.3, 53.2, 27.8; ESI-HRMS Calcd for $C_{13}H_{17}N_3O_6$ [M + Na]$^+$: 334.1015. Found 334.1027.

N-tert-Butoxycarbonyl-4-*N*^{im}-triphenylmethyl-(2*S*,3*S*)-β-hydroxy-L-hystidine methyl ester (23)

A solution of **21** (0.19 g, 0.61 mmol) and trityl chloride (0.35 g, 1.22 mmol) in CH_2Cl_2 (3 mL) was treated with Et_3N (170μL, 1.22 mmol) and stirred at room temperature for 1.5h. Then the reaction mixture was concentrated and the excess trityl chloride was removed by filtering through short silica gel column. The filtrate was concentrated and further dissolved in methanol. The methanolic solution was treated with cesium carbonate (0.4 g, 0.12 mmol) at room temperature for 2 h. Then the reaction mixture was concentrated and the concentrate was diluted with ethyl acetate and washed with saturated NH_4Cl solution, water and brine. The organic layer was dried and concentrated. The chromatographic purification using 55% ethyl acetate in hexane afforded **23** (0.24 g, 74%). [α]$^{22}_D$ -14.5 (*c* 1.0); ^{1}H NMR (400 MHz) δ:7.36 (s, 1H), 7.34-7.29 (m, 9H), 7.12-7.09 (m, 6H), 6.79 (s, 1H), 5.71-5.69 (d, *J* = 8.4 Hz, 1H), 5.13 (s, 1H), 4.59-4.57 (d, *J* = 9.2 Hz, 1H), 4.33 (bs, 1H), 3.69 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (100 MHz) δ:171.5, 155.7, 142.2, 140.2, 138.5, 129.8, 128.1, 128.09, 118.2, 79.6, 75.5, 68.7, 58.2, 52.4, 28.3; ESI-HRMS Calcd for $C_{31}H_{33}N_3O_5$ [M + Na]$^+$: 550.2318. Found 550.2315.

Methyl (4*S*,5*S*)-3-*N-tert*-butoxycarbonyl-5-{*N*-(*tert*-butoxycarbonyl)indolyl}-1,3-oxazolidin-2-oxo-4-carboxylate (26)

Following the general procedure 1 and eluting with 14% ethyl acetate in hexane **26** in 72% yield. [α]$^{22}_D$ +24.9 (*c* 2.3); ^{1}H NMR (500 MHz) δ:8.21-8.19 (d, *J* = 8.0 Hz, 1H), 7.68 (s, 1H), 7.59-7.58 (d, *J* = 8.0 Hz, 1H), 7.41-7.38 (t, *J* = 8.0 Hz, 1H), 7.32-7.26 (t, *J* = 8.0 Hz, 1H), 5.67-5.66 (d, *J* = 3.5 Hz, 1H), 4.84-4.83 (d, *J* = 3.5 Hz, 1H), 3.92 (s, 3H), 1.67 (s, 9H), 1.50 (s, 9H); ^{13}C NMR (125 MHz) δ:169.0, 150.7, 149.2, 148.5, 136.1, 126.6, 125.4, 123.7, 123.4, 118.8, 116.5, 115.8, 84.9, 84.7, 71.6, 61.8, 53.4, 28.1, 27.8; ESI-HRMS Calcd for $C_{23}H_{28}N_2O_8$ [M + Na]$^+$: 483.1743. Found 483.1725.

N-*tert*-Butoxycarbonyl-*N*^{in}-*tert*-butoxycarbonyl-(2*S*,3*S*)-β-hydroxy-L-tryptophan methyl ester (27)

Following the general procedure 2, and eluting with 22% ethyl acetate in hexane, **27** was obtained in 84% yield. $[\alpha]^{22}_{D}$ −12.5 (*c* 1.0); ^{1}H NMR (400 MHz) δ:8.13-8.12 (d, *J* = 6.4 Hz, 1H), 7.62-7.59 (d, *J* = 12.0 Hz, 1H), 7.33-7.29 (t, *J* = 8.0 Hz, 1H), 7.25-7.21 (t, *J* = 7.6 Hz, 1H), 5.50-5.49 (d, *J* = 3.6 Hz, 1H), 5.46 (s, 1H), 4.68-4.66 (d, *J* = 8.0 Hz, 1H), 3.77 (s, 3H), 2.98 (bs, 1H), 1.65 (s, 9H), 1.34 (s, 9H); ^{13}C NMR (125 MHz) δ:171.5, 155.8, 149.5, 135.6, 128.3, 124.7, 123.4, 122.8, 119.8, 119.3, 115.4, 83.9, 80.1, 68.4, 58.1, 52.7, 28.2; ESI-HRMS Calcd for $C_{22}H_{30}N_2O_7$ $[M + Na]^+$: 457.1951. Found 457.1933.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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34. A reviewer has indicated that this type of amino acid side chain bromination with NBS also proceeds well in α,α,α-trifluorotoluene.
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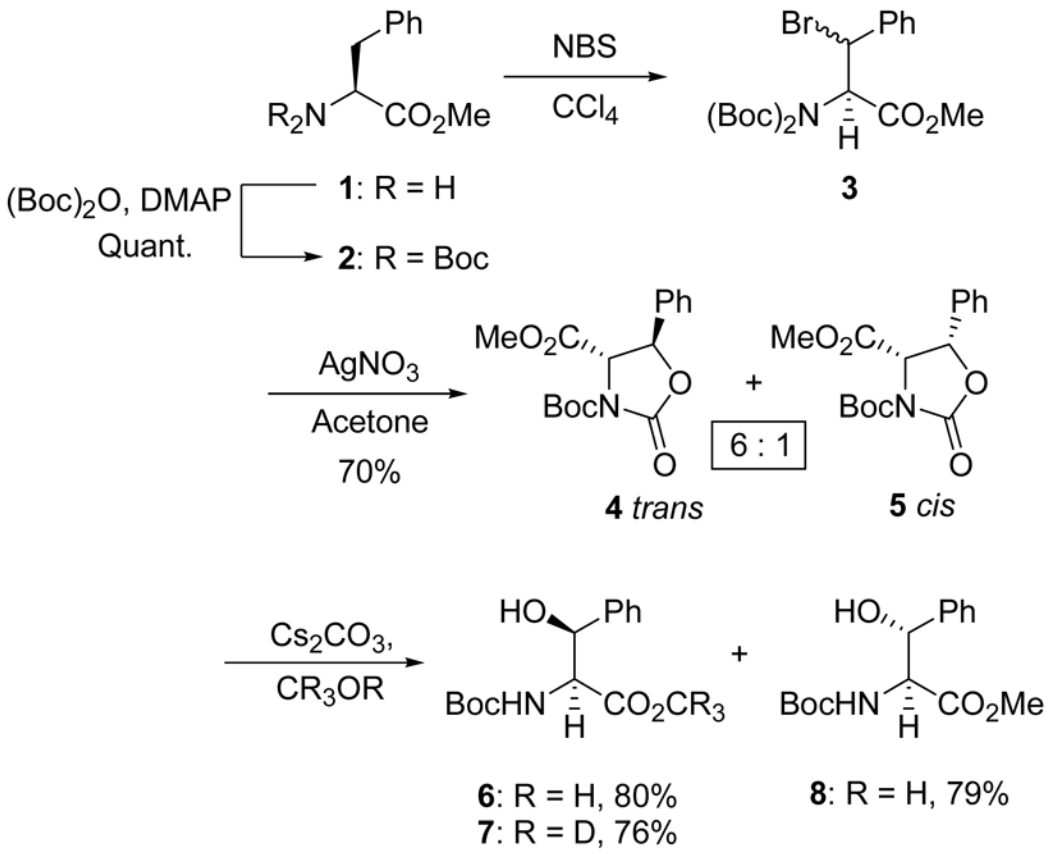
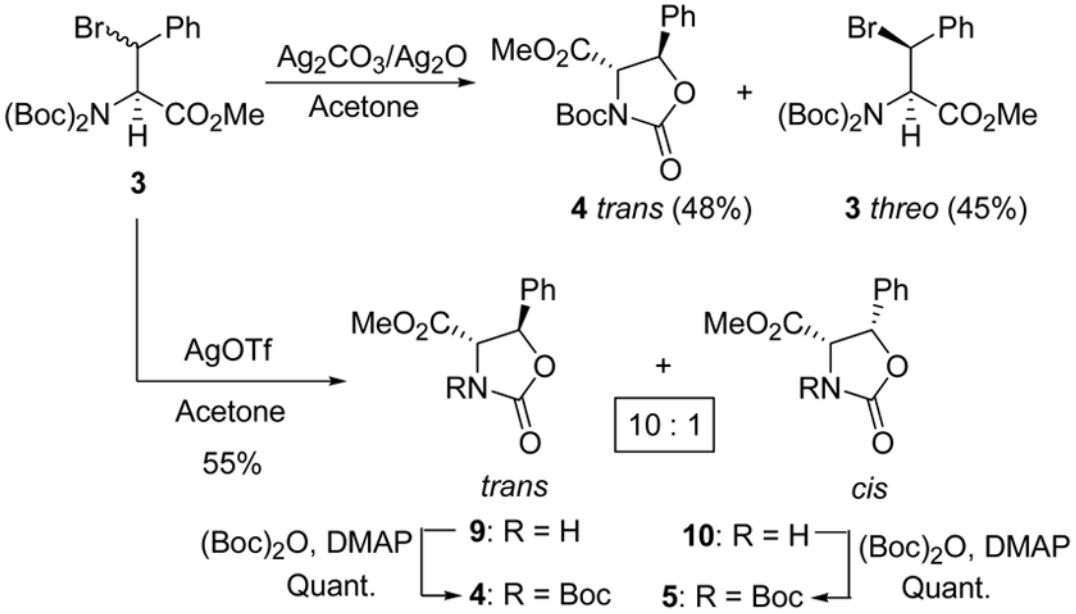
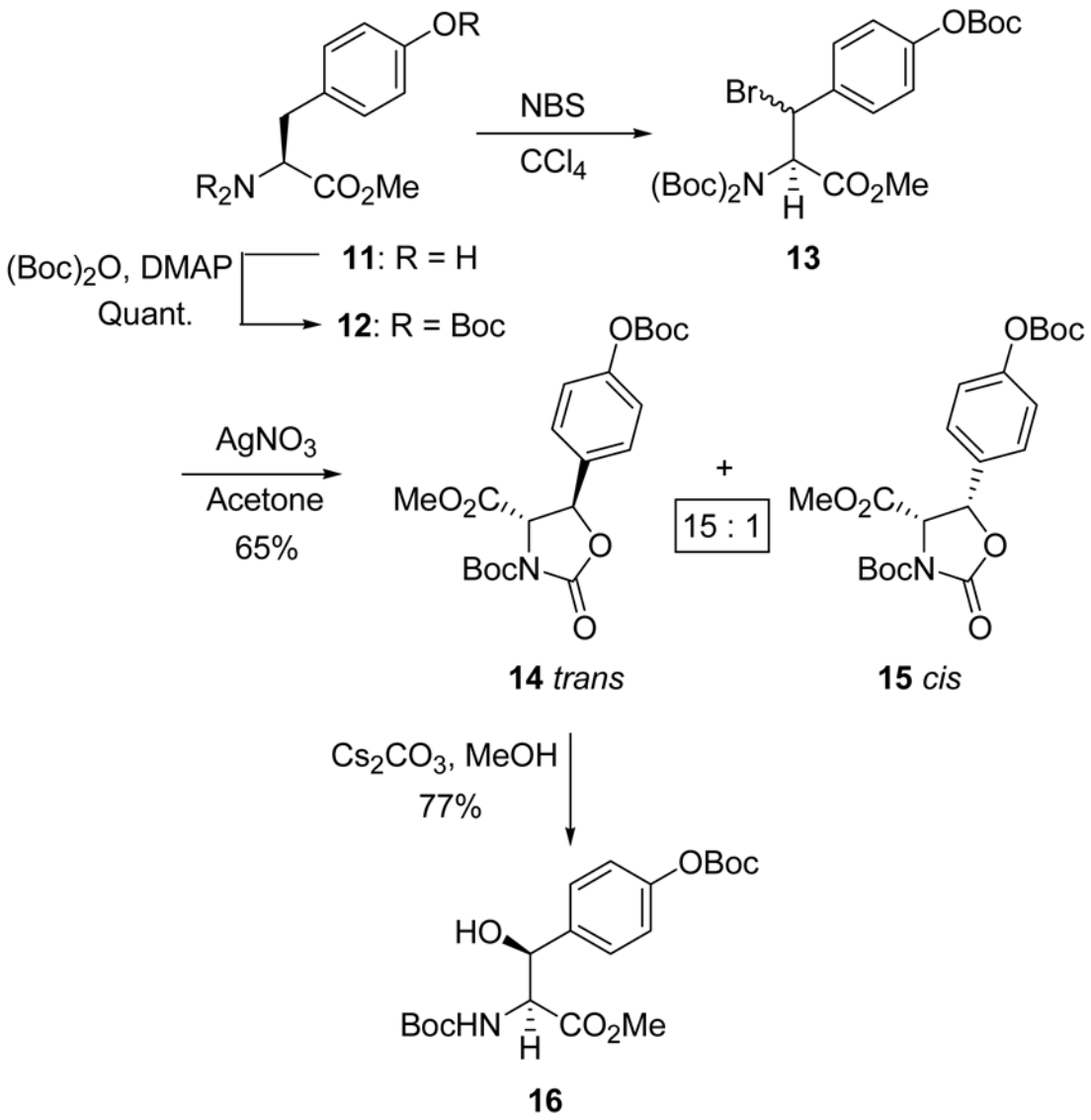
38. For 18 and 25, the bromination reactions were continued for 2h and 3h, respectively.



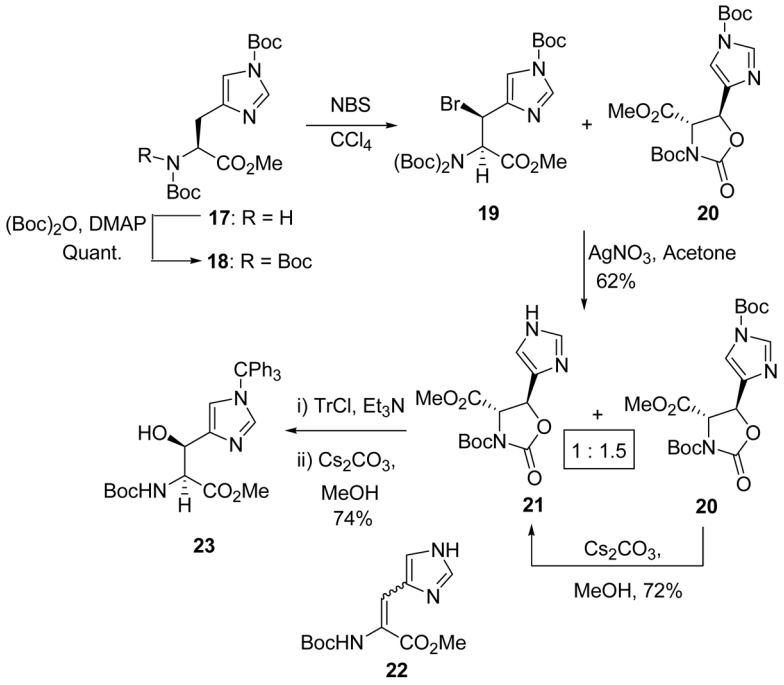
Scheme 1.
Synthesis of β-hydroxy phenylalanine.



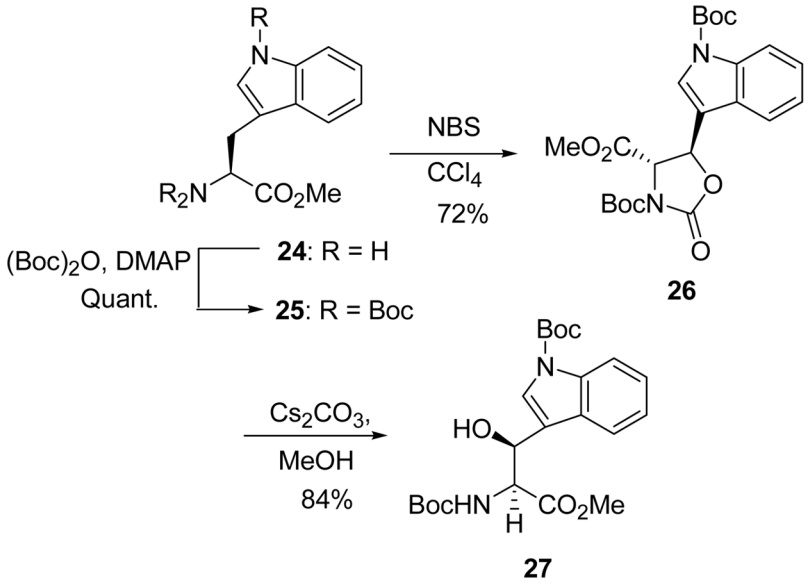
Scheme 2.
Effect of Other Silver Salts.



Scheme 3.
Synthesis of β-hydroxytyrosine.



Scheme 4.
Synthesis of β-hydroxyhistidine.



Scheme 5.
Synthesis of β-hydroxytryptophan.