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TETRAHEDRON: *ASYMMETRY*

Application of asymmetric aminohydroxylation to heteroaromatic acrylates

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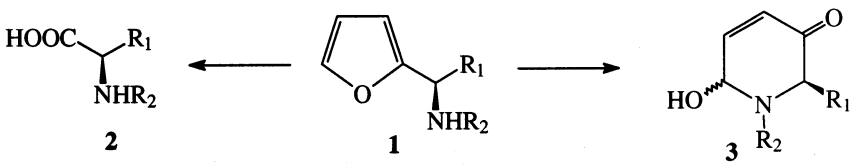
Abstract

Furyl and thienyl acrylates could be aminohydroxylated with high selectivity, but pyrrolyl acrylates resist aminohydroxylation under the present reaction conditions. The corresponding aminohydroxylation products, the 3-amino-2-hydroxy-3-(2-furyl)propionate derivative and the 3-amino-2-hydroxy-3-(2-thienyl)propionate derivative, could be easily converted to the β-hydroxy-α-amino acids. The dihydropyridone obtained from the 3-amino-2-hydroxy-3-(2-furyl)propionate derivative is a chiral building block for synthesis of polyhydroxy indolizidine alkaloids. © 2000 Published by Elsevier Science Ltd.

1. Introduction

Optically active α-furfuryl amine derivatives can be applied directly to the synthesis of natural and unnatural α-amino acids by oxidation of a furan ring to a carboxyl group (**1**→**2**) by ozonolysis[1] or oxidation with $RuCl_3/NaIO_4$[2] (Scheme 1). The most important application of these compounds is that they can be converted into the dihydropyridone derivatives (**1**→**3**) via the aza-Achmatowicz reaction[3] or Lefebvre oxidation[4] (Scheme 1). Therefore, α-furfuryl amine



Scheme 1.

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derivatives **1** are useful chiral building blocks for the synthesis of a great number of nitrogen containing natural products.[5]

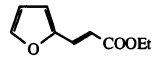
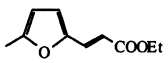
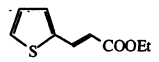
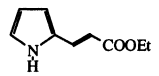
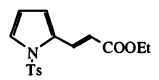
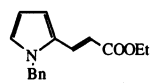
In our laboratory, we have developed some new methods for preparing chiral α-furfuryl amine derivatives, such as the kinetic resolution of racemic α-furfuryl amine derivatives,[6] diastereoselective addition of organometallic reagents to the imines[7] and reduction of azidoalcohol[8c] and their applications to the asymmetric synthesis of natural and unnatural amino acids,[9] piperidine alkaloids,[10] polyhydroxy indolizidine alkaloids[11] and 1-deoxyazasugars.[8] The Sharpless asymmetric aminohydroxylation (AA) of alkenes[12] has proved to be one of the most reliable methods for the asymmetric functionalization of alkenes, which allows the simultaneous introduction of a protected amino and a hydroxyl group onto an alkene. First, we employed α-furyl ethylene derivatives as substrates using chloramine-T or the sodium salt of *N*-chloroethylcarbamate as nitrogen sources, but only moderate regio- and stereoselectivity were achieved.[13] At about the same time, O'Doherty et al.[14] also applied this reaction to the same substrate but using the sodium salt of *N*-chlorobenzylcarbamate as the nitrogen source and got similar results. Herein we report our further application of this reaction to the furyl acrylates as well as the thienyl and pyrrolyl acrylates using *N*-bromoacetamide or sodium salt of *N*-chlorobenzylcarbamate as the nitrogen source, respectively.

2. Results and discussion

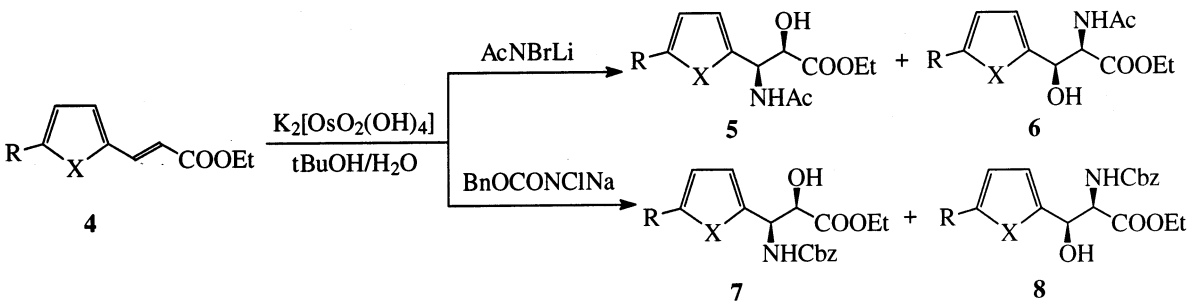
The acrylates **4a**–**4f** were readily synthesized by Wittig reactions from the corresponding aldehydes and ethyl phosphoraylidene acetate. We first carried out the aminohydroxylation of **4a**–**4f** using $(DHQ)_2PHAL$ as the chiral ligand, and the lithium salt of *N*-bromoacetamide as the nitrogen source.[15] The aminohydroxylation of **4a** proceeded sluggishly at 0°C in low yields, but proceeded smoothly in 54% yield in 70% conversion at 25°C with moderate regioselectivity but low enantioselectivity (entry 1, Table 1). However, when increasing the electron density in the furan moiety by the donor methyl substituent (entry 2, Table 1), the AA reaction occurred smoothly at 0°C, but the regioselectivity and enantioselectivity were very low. In contrast to the furyl acrylates (entries 1 and 2, Table 1), the thienyl acrylate **4c** proved to be an excellent substrate for the AA both in terms of reactivity and selectivity (entry 3, Table 1). A single recrystallization of the product **5c** was enough to remove the minor regioisomer. The pyrrolyl acryates **4c**–**4e** proved to be problematic substrates (entries 4–6, Table 1). No AA reactions occurred even on raising the reaction temperature and changing the nitrogen protecting groups.

Owing to the failure to obtain the desired AA product of the furyl acrylate using *N*-bromoacetamide as the nitrogen source, we turned our attention to another nitrogen source, the sodium salt of *N*-chlorobenzylcarbamate[16] (Scheme 2, Table 2). The furyl acrylate **4a** could be aminohydroxylated both with high regioselectivity and high enantioselectivity (entry 1, Table 2). Moreover, the regioisomer could be separated by flash chromatography. Unlike a recent report,[17] we obtained the AA products of 3-[2-(5-methylfuryl)] acrylate **4b** with excellent regioselectivity and enantioselectivity in 68% yield (entry 2, Table 2). The thienyl acrylate was also aminohydroxylated smoothly with high regioselectivity and enantioselectivity in the case of the sodium salt of *N*-chlorobenzylcarbamate (entry 3, Table 2). The pyrrolyl acrylates were not good substrates using the sodium salt of *N*-chlorobenzylcarbamate as the nitrogen source (entry 4–6, Table 2). When *t*-butyl methyl ether was added in the reaction mixture to increase the solubility of substrates, the dihydroxylated product was mainly obtained instead of the AA product for **4e**[16a] in 55% yield.

Table 1
AA reactions using AcNLiBr as the nitrogen source

entry	substrate	reaction temp.	5:6[a]	yield	%ee of 5[b]
1		25°C	7:1	54%[c]	30%
2		0°C	1:1.5	52%	10%
3		0°C	>14:1	81%	87%
4		25°C	–	0	–
5		25°C	–	0	–
6		25°C	–	0	–

[a] Ratio of **5** to **6** regioisomers determined by ^{1}H NMR. [b] Determined by HPLC analysis on Chiralpak AS column with n-hexane-iPrOH as the eluent. [c] Yield based on 70% conversion.

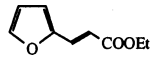
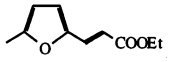
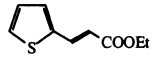
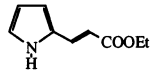
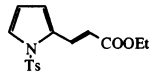
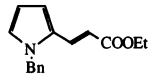


Scheme 2.

This aminohydroxylation of the furyl acrylate for the preparation of α-furfuryl amine derivatives probably has advantage over our previous methods. Since the AA product bears the hydroxyl group, which is vicinal to the amino group, it is a useful building block for preparation of β-hydroxy-α-aminoacids and dihydropyridone **12**. The latter possesses an α-hydroxy carboxylate in the C_2-position of the pyridone ring, so it is particularly favorable for the synthesis of polyhydroxy indolizidine alkaloids such as castanospermine **13**.

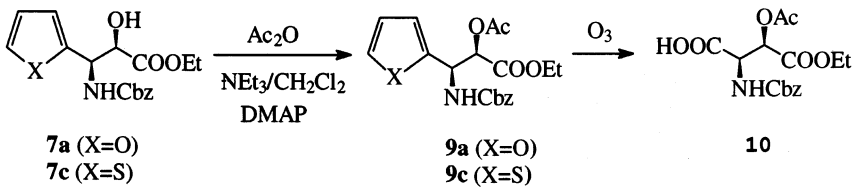
After the hydroxyl group was protected with acetic anhydride, 3-(benzyloxycarbonylamino)-2-hydroxy-3-(2-furyl)propionate **7a** and 3-(benzyloxycarbonylamino)-2-hydroxy-3-(2-thienyl) propionate **7c**, were subjected to ozonolysis at 0°C using CH_2Cl_2/MeOH (10:1) as a solvent to lead to the β-hydroxy-α-aminoacid derivative **10** in 63 and 66% yields, respectively (Scheme 3).

Table 2
AA reactions using BnOCONNaCl as the nitrogen source

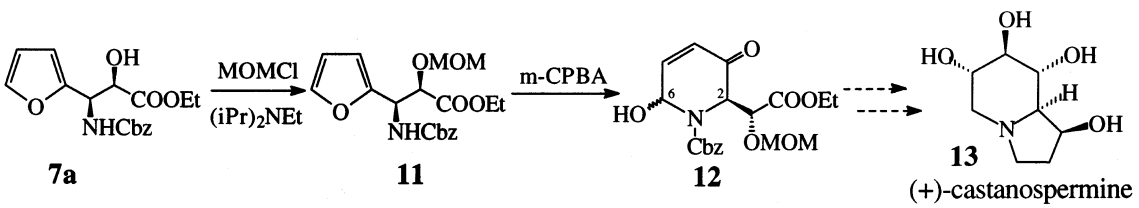
entry	substrate	7:8[a]	yield	%ee of 7[b]
1		7:1	62%[c]	87%
2		>20:1	68%[d]	99%
3		>20:1	71%	99%
4		–	0	–
5		–	0	–
6		–	0	–

[a] Ratio of **7** to **8** regioisomers determined by ^{1}H NMR. [b] Determined by HPLC analysis on Chiralpak AS column with n-hexane-iPrOH as the eluent. [c] Yield based on 59% conversion. [d] Yield based on 78% conversion

The synthesis towards the polyhydroxy indolizidine alkaloids starting from **7a** was demonstrated (Scheme 4). After the hydroxyl group was protected by MOMCl, **11** was treated with *m*-CPBA[8c] to afford the desired dihydropyridone **12**, which is a preferable intermediate of polyhydroxy indolizidine alkaloids such as castanospermine **13**, which possess potent bioactivity as inhibitors of glucosidase and glycoprotein processing[18] and also exhibit interesting anticancer, antiviral and immunoregulatory activities.[19] We are currently advancing this intermediate towards the synthesis of these alkaloids.



Scheme 3.



Scheme 4.

In conclusion, the furyl and thienyl acrylates could be aminohydroxylated with high selectivity, but the pyrrolyl acrylates resist AA in the present reaction conditions. The 3-amino-2-hydroxy-3-(2-furyl)propionate derivative **7a** and 3-amino-2-hydroxy-3-(2-thienyl)propionate derivative **7c** could be easily converted to β-hydroxy-α-aminoacid. Dihydropyridone **12** obtained from 3-amino-2-hydroxy-3-(2-furyl)propionate derivative **7a** is an excellent building block for the synthesis of polyhydroxy indolizidine alkaloids, such as castanospermine **13** which is our ultimate goal.

3. Experimental

3.1. General

Melting points were determined with a Büchi 535 melting point apparatus and were uncorrected. Reactions were monitored by using thin layer chromatography (TLC). The silica gel used in flash chromatography was silica gel H (10–40 μm) which was produced by Qingdao Chemical Plant, China. IR spectra were measured on a Schimadzu IR 400 spectrometer. ^{1}H NMR spectra were recorded on a Bruker AM-300 (300 MHz) with $CDCl_3$ as solvent and values were reported in ppm using TMS or residual $CHCl_3$ as internal standard. MS spectra were conducted on a Finnigan 4021 GC–MS instrument and JMS-01U spectrometer. The optical rotations, were measured at 20°C on a Perkin–Elmer 241 MC automatic polarimeter in a 1 dm cell and recorded in units of 10^{-1} deg cm^2 g^{-1}. Element analysis was performed by the analytical department of this institute.

3.2. General procedure for the N-bromoacetamide-based AA

All *N*-bromoacetamide-based AA reactions (entries 1–6 in Table 1) were performed as described here for **5c** (entry 3, Table 1).

3.2.1. Synthesis of *5c*

In 3 ml of an aqueous solution of $LiOH{\cdot}H_2O$ (42.8 mg, 1.02 mmol), $K_2[OsO_2(OH)_4]$ (14.7 mg, 0.04 mmol, 4 mol%) was dissolved with stirring. After addition of *t*-BuOH (6 mL), $(DHQ)_2PHAL$ (39 mg, 0.05 mmol, 5 mol%) was added and the mixture was stirred for 10 min to give a clear solution. Water (6 mL) was added subsequently, and the mixture was immersed in an ice bath to 0°C. After addition of **4c** (182 mg, 1 mmol), *N*-bromoacetamide (151.8 mg, 1.1 mmol) was added in one portion (which resulted in an immediate color change to green) and the mixture was vigorously stirred at the same temperature. The reaction was monitored by TLC. After 12 h the reaction mixture was treated with Na_2SO_3 (0.5 g). After stirring at room temperature for 30 min, ethyl acetate (10 mL) was added. The organic layer was separated, and the water layer was extracted with ethyl acetate (3×10 mL). The combined organic extracts were washed with brine (5 mL), and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate 1:1) and recrystallized from petroleum ether:ethyl acetate to give 208 mg (81% yield, 87% ee) of **5c**. $[\alpha]_D^{20} = +43$ ($c = 1$, EtOH); m.p. 112–114°C; ^{1}H NMR δ: 1.32 (t, 3H, $J = 7.00$ Hz, Et), 1.99 (s, 3H, Ac), 4.30 (q, 2H, $J = 7.10$ Hz, Et), 4.54 (m, 1H, NH), 5.84 (d, 1H, $J = 9.26$ Hz), 6.20 (d, 1H, $J = 9.04$ Hz), 6.98 (m, 1H), 7.11 (m, 1H), 7.24 (m, 1H); IR: 3326,

3207, 1718 cm^{-1}; MS m/z: 258 (M^++1), 239 (M^+–H_2O), 199 (M^+–NHAc), 154; anal. calcd for $C_{11}H_{15}NO_4S$: C, 51.35; H, 5.88; N, 5.44. Found: C, 51.28; H, 5.84; N, 5.35.

*3.2.2. Synthesis of **5a***

The preparation of **5a** was carried out according to general procedure by using 0.166 g of **4a** (1 mmol). The reaction mixture was stirred at 25°C for 20 h. The crude product was purified by column chromatography (petroleum ether:ethyl acetate 1:1) to give the starting material **4a** (0.050 g, 70% conversion) and an oil **5a** (0.091 g, 54% yield). ^{1}H NMR δ: 1.32 (t, 3H, J=7.00 Hz, Et), 2.01 (s, 3H, Ac), 4.27 (q, 2H, J=7.00 Hz, Et), 4.59 (d, 1H, J=1.14 Hz, NH), 5.64 (dd, 1H, J=1.92, 9.26 Hz), 6.25 (d, 1H, J=9.25 Hz), 6.30 (m, 1H), 6.34 (m, 1H), 7.38 (d, 1H, J=1.10 Hz); IR: 3326, 3210, 1743, 1718 cm^{-1}; MS m/z: 242 (M^++1), 224 (M^++1-H_2O), 183 (M^+–NHAc), 138; anal. calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27; N, 5.81. Found: C, 54.31; H, 6.56; N, 5.42.

*3.2.3. Synthesis of the mixture of **5b** and **6b***

The preparation of the mixture of **5b** and **6b** was carried out according to general procedure by using 0.180 g of **4b** (1 mmol). The reaction mixture was stirred at 0°C for 12 h. The crude product was purified by column chromatography (petroleum ether:ethyl acetate 2:3) to give a white solid, a mixture of **5b** and **6b** (ratio 1:1.5) (0.132 g, 52% yield). ^{1}H NMR for **5b**: δ: 1.30 (t, 3H, J=7.00 Hz, Et), 2.00 (s, 3H, Ac), 2.27 (s, 3H, Me), 4.27 (q, 2H, J=7.00 Hz, Et), 4.56 (br s, 1H, NH), 5.57 (m, 1H), 5.90 (m, 1H), 6.17 (m, 1H), 6.30 (d, 1H, J=8.30 Hz); ^{1}H NMR for **6b**: δ: 1.30 (t, 3H, J=7.00 Hz, Et), 2.04 (s, 3H, Ac), 2.27 (s, 3H, Me), 4.27 (q, 2H, J=7.00 Hz, Et), 4.97 (dd, 1H, J=3.53, 8.55 Hz), 5.13 (br s, 1H, NH), 5.90 (m, 1H), 6.17 (m, 2H); IR: 3356, 3219, 1741cm^{-1}; MS m/z: 256 (M^++1), 238 (M^++1-H_2O), 197 (M^+–NHAc), 152, 111; anal. calcd for $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.18; H, 6.78; N, 5.37.

3.3. General procedure for the benzyl carbamate-based AA

All benzyl carbamate-based AA reactions (entries 1–6 in Table 2) were performed as described here for **7a** (entry 1, Table 2).

*3.3.1. Synthesis of **7a***

A 50 mL round-bottom flask was charged with benzyl carbamate (0.182 g, 1.20 mmol) and *t*-BuOH (4 mL). To this stirred solution were added a freshly prepared aqueous solution of NaOH (0.046 g, 1.15 mmol in 7.5 mL water) and *tert*-butyl hypochlorite (0.125 g, 1.15 mmol). After 10 min, a solution of $(DHQ)_2PHAL$ (40 mg, 0.05 mmol, 5 mol%) in *t*-BuOH (3.5 mL) was added. Ethyl furylacrylate **4a** (0.166 g, 1 mmol, dissolved in 5 mL of *t*-BuOH) was then added, followed by addition of $K_2OsO_2(OH)_4$ (15 mg, 0.08 mmol, 4 mol%). The mixture was stirred at 25°C for 3.5 h, and a saturated aqueous sodium sulfite solution (10 mL) was added to quench the reaction. The two phases were separated, and the aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organic phase was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under the reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate 8:1–3:1) to afford the starting material **4a** (0.068 g, 59% conversion), the desired product **7a** (0.122 g, 62% yield, 87% ee) as an oil and the regioisomer **8a** (0.016 g, 8% yield) as an oil. For **7a**: $[\alpha]_D^{20}$=+23.3 (c=0.9, EtOH); ^{1}H NMR δ: 1.26 (t, 3H, J=7.03 Hz, Et), 4.26 (q, 2H, J=7.02 Hz, Et), 4.59 (d, 1H, J=1.75 Hz,

NH), 5.11 (br s, 2H, CH_2Ph), 5.37 (d, 1H, $J=9.06$ Hz), 5.51 (m, 1H), 6.30 (d, 1H, $J=3.02$ Hz), 6.33 (m, 1H), 7.35 (m, 5H, Ph), 7.38 (d, 1H, $J=1.07$ Hz); IR: 3369, 1731 cm^{-1}; MS m/z: 334 (M^++1), 316 (M^++1-H_2O), 183 (M^+–NHCbz), 230; anal. calcd for $C_{17}H_{19}NO_6$: C, 61.25; H, 5.75; N, 4.20. Found: C, 61.20; H, 5.56; N, 4.19. For **8a**: $[\alpha]_D^{20}=+2.5$ ($c=0.8$, EtOH); ^1H NMR δ: 1.27 (t, 3H, $J=7.13$ Hz, Et), 4.24 (q, 2H, $J=7.03$ Hz, Et), 4.75 (d, 1H, $J=6.25$ Hz), 5.10 (br s, 2H, CH_2Ph), 5.21 (d, 1H, $J=2.95$ Hz, NH), 5.61 (d, 1H, $J=8.40$ Hz), 6.32 (m, 2H), 7.27–7.34 (m, 6H); IR: 3412, 1728 cm^{-1}; MS m/z: 334 (M^++1), 316 (M^++1-H_2O), 288, (M^+–EtO), 97; anal. calcd for $C_{17}H_{19}NO_6$: C, 61.25; H, 5.75; N, 4.20. Found: C, 61.21; H, 5.81; N, 4.17.

3.3.2. Synthesis of **7b**

The preparation of **7b** was carried out according to general procedure by using 0.180 g of **4b** (1 mmol). The reaction mixture was stirred at 25°C for 3 h. The crude product was purified by column chromatography (petroleum ether:ethyl acetate:dichloromethane 5:5:1) to give the starting material **4b** (0.040 g, 78% conversion) and an oil **7b** (0.184 g, 68% yield, 99% ee). $[\alpha]_D^{20}=+18.8$ ($c=0.9$, EtOH); ^1H NMR δ: 1.27 (t, 3H, $J=7.03$ Hz, Et), 2.26 (s, 3H, Me), 4.25 (q, 2H, $J=7.00$ Hz, Et), 4.56 (br s, 1H, NH), 5.10 (br s, 2H, CH_2Ph), 5.29 (d, 1H, $J=9.00$ Hz), 5.50 (d, 1H, $J=9.72$ Hz), 5.90 (m, 1H), 6.16 (d, 1H, $J=2.93$ Hz), 7.36 (m, 5H, Ph); IR: 3377, 1732 cm^{-1}; MS m/z: 348 (M^++1), 330 (M^++1-H_2O), 244; anal. calcd for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.09; N, 4.03. Found: C, 61.93; H, 6.16; N, 3.96.

3.3.3. Synthesis of **7c**

The preparation of **7c** was carried out according to general procedure by using 0.182 g of **4c** (1 mmol). The reaction mixture was stirred at 25°C for 3 h. The crude product was purified by column chromatography (petroleum ether:ethyl acetate 5:1) and recrystallized from petroleum ether:ethyl acetate to give a colorless solid **7c** (0.246 g, 71% yield, 99% ee). $[\alpha]_D^{20}=+32$ ($c=0.75$, EtOH); m.p. 89–90°C; ^1H NMR δ: 1.27 (t, 3H, $J=7.04$ Hz, Et), 4.25 (q, 2H, $J=7.00$ Hz, Et), 4.51 (br s, 1H, NH), 5.10 (m, 2H, CH_2Ph), 5.57 (m, 2H), 6.97 (dd, 1H, $J=3.70$, 5.00 Hz), 7.09 (d, 1H, $J=2.88$ Hz), 7.24 (m, 1H), 7.33 (m, 5H, Ph); IR: 3356, 3318, 1741, 1676 cm^{-1}; MS m/z: 350 (M^++1), 332 (M^++1-H_2O), 246, 199 (M^+–NHCbz); anal. calcd for $C_{17}H_{19}NO_5S$: C, 58.44; H, 5.48; N, 4.01. Found: C, 58.32; H, 5.31; N, 3.93.

3.4. Synthesis of **9a**

To a solution of compound **7a** (0.105 g, 0.315 mmol) in CH_2Cl_2 (3 ml) were added triethylamine (0.088 ml, 0.63 mmol) and DMAP (77 mg, 0.63 mmol) at 0°C. After being stirred for 0.5 h, acetic anhydride (0.06 mL, 0.63 mmol) was added at the same temperature. The mixture was then stirred at 0°C for an additional 2 h. Water (5 ml) was added and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, evaporated under reduced pressure to afford a crude oil which was purified by flash column chromatography on silica gel (petroleum ether:ethyl acetate 6:1) to afford an oil **9a** (0.101 g, 85% yield). $[\alpha]_D^{20}=+8.7$ ($c=0.4$, EtOH); ^1H NMR δ: 1.26 (t, 3H, $J=7.14$ Hz, Et), 2.10 (s, 3H, Ac), 4.20 (q, 2H, $J=7.18$ Hz, Et), 5.12 (br s, 2H, CH_2Ph), 5.46 (d, 1H, $J=2.28$ Hz), 5.54 (m, 2H), 6.23 (d, 1H, $J=3.23$ Hz), 6.32 (dd, 1H, $J=1.86$, 3.28 Hz) 7.35 (m, 6H); IR: 3345, 1741, 1726 cm^{-1}; MS m/z: 376 (M^++1), 316 (M^+–OAc), 269 (M^++1-OBn), 230, 225 (M^+–NHCbz); anal. calcd for $C_{19}H_{21}NO_7$: C, 60.79; H, 5.64; N, 3.73. Found: C, 60.79; H, 5.87; N, 3.89.

3.5. Synthesis of **9c**

To a solution of compound **7c** (0.141g, 0.404 mmol) in CH_2Cl_2 (3 ml) were added triethylamine (0.118 mL, 0.85 mmol) and DMAP (0.103 g, 0.85 mmol) at 0°C. After being stirred for 0.5 h, acetic anhydride (0.08 mL, 0.85 mmol) was added at the same temperature. The mixture was then stirred at 0°C for an additional 2 h. Water (5 ml) was added and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, evaporated under reduced pressure to afford a crude oil, which was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate 5:1) to afford an oil **9c** (0.154 g, 97% yield). $[\alpha]_D^{20}=+10.7$, ($c=1.5$, EtOH); ^{1}H NMR δ: 1.26 (t, 3H, $J=7.02$ Hz, Et), 2.17 (s, 3H, Ac), 4.20 (q, 2H, $J=7.00$ Hz, Et), 5.10 (m, 2H, CH_2Ph), 5.36 (d, 1H, $J=1.77$ Hz, NH), 5.60 (d, 1H, $J=9.42$ Hz), 5.74 (d, 1H, $J=9.96$ Hz), 6.96 (m, 1H), 7.03 (m, 1H) 7.25 (m, 1H), 7.35 (m, 5H, Ph); IR: 3346, 1747, 1720 cm^{-1}; MS m/z: 392 (M^++1), 332 (M^+–OAc), 285 (M^++1-OBn), 246; anal. calcd for $C_{19}H_{21}NO_6S$: C, 58.30; H, 5.41; N, 3.58. Found: C, 58.17; H, 5.42; N, 3.28.

3.6. Synthesis of **10**

To a solution of **9a** (72 mg, 0.20 mmol) or **9c** (78 mg, 0.20 mmol) in CH_2Cl_2:MeOH (10:1) (11 mL) was passed ozone at 0°C for approximately 15 min until a light blue color appeared. The reaction mixture was bubbled with N_2 for 5 min at 0°C to remove the excess ozone, and then Me_2S was added (1 mL). After stirring at rt for 1 h, the reaction mixture was concentrated to give a crude oil, which was purified by flash chromatography on silica gel to afford **10** as an oil (50 mg, 74% for **9a**), (48 mg, 68% for **9c**); $[\alpha]_D^{20}=-10.8$ ($c=1.3$, EtOH); ^{1}H NMR δ: 1.26 (t, 3H, $J=7.20$ Hz, Et), 2.11 (s, 3H, Ac), 4.15 (q, 2H, $J=7.19$ Hz, Et), 5.12 (m, 3H), 5.61 (m, 2H), 7.33 (m, 5H, Ph); IR: 3367, 1752 cm^{-1}; MS m/z: 353 (M^+), 310 (M^+–Ac), 246 (M^+–OBn), 204 (M^++1-NHCbz); anal. calcd for $C_{16}H_{19}NO_8\cdot 3/4H_2O$: C, 52.43; H, 5.63; N, 3.82. Found: C, 52.43; H, 5.97; N 3.32.

3.7. Synthesis of **11**

To a solution of **7a** (0.200 g, 0.6 mmol) in CH_2Cl_2 (0.7 mL) was added DMAP (7 mg, 0.057 mmol), iPr$_2$NEt (0.63 mL, 3.6 mmol) and MOMCl (0.18 mL, 2.4 mmol) at rt. After stirring at rt for 10 h, 1 mL water was added and the mixture was stirred for 10 min. The reaction mixture was extracted with 50 mL ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, evaporated under reduced pressure to afford a crude oil, which was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate 6:1) to afford an oil **11** (0.187 g, 82.6% yield). $[\alpha]_D^{20}=+45.5$ ($c=0.85$, EtOH); ^{1}H NMR δ: 1.26 (t, 3H, $J=7.00$ Hz, Et), 3.10 (s, 3H, OMe), 4.21 (q, 2H, $J=7.00$ Hz, Et), 4.51 (d, 1H, $J=6.96$ Hz, OCH_aH_bO), 4.64 (d, 1H, $J=1.68$ Hz, NH), 4.69 (d, 1H, $J=6.81$ Hz, OCH_aH_bO), 5.11 (br s, 2H, CH_2Ph), 5.43 (d, 1H, $J=9.78$ Hz), 5.63 (d, 1H, $J=9.57$ Hz), 6.25 (d, 1H, $J=3.18$ Hz), 6.33 (dd, 1H, $J=1.64$, 3.16 Hz), 7.35 (m, 6H); IR: 3333, 1749, 1730 cm^{-1}; MS m/z: 378 (M^++1), 362 (M^+–CH_3), 316 (M^+–OCH_2OCH_3), 230; anal. calcd for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14; N, 3.71. Found: C, 60.61; H, 6.15; N, 3.67.

3.8. Synthesis of **12**

To a solution of **11** (0.120 g, 0.32 mmol) in 10 ml of dichloromethane was added *m*-CPBA (0.066 g, 0.38 mmol). After being stirred for 8 h at rt, the solvent was evaporated under reduced pressure to give the crude product which was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate 3:1) to afford an oil **12** (0.098 g, 78% yield). $[\alpha]_D^{20}=+70.3$ ($c=1.8$, EtOH); ^{1}H NMR δ: 1.28 (t, 3H, $J=7.14$ Hz, Et), 3.23 (s, 3H, OMe), 4.02–4.18 (m, 2H), 4.62 (m, 3H), 5.20 (m, 3H), 6.01 (d, 1H, $J=4.38$ Hz, 6′-H), 6.21 (d, 1H, $J=10.37$ Hz, 4′-H), 6.96 (dd, 1H, $J=4.84$, 10.27 Hz, 5′-H), 7.37 (m, 5H, Ph); IR: 3364, 1750, 1713, 1689 cm^{-1}; MS m/z: 376 (M^++1-H_2O), 332 (M^+–OCH_2OCH_3); anal. calcd for $C_{19}H_{23}NO_8$: C, 58.01; H, 5.89; N, 3.56. Found: C, 58.01; H, 5.98; N, 3.53.

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