JOC*Note*

Synthesis of β-Amino-α-hydroxy Esters and β-Amino-α-azido Ester by Sharpless Asymmetric Aminohydroxylation, Byproducts Analysis

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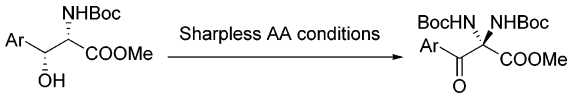

Synthesis of enantiomerically pure β-amino-α-hydroxy esters (**1**, **2**) and β-amino-α-azido ester (**3**) using Sharpless AA as a key step is described. A hitherto unreported side reaction, the oxidation of the β-hydroxy-α-amino ester (**5**) into the α,α-di-*tert*-butyloxycarbamoyl-β-ketoester (**8**) under AA conditions, is documented.

The Sharpless asymmetric aminohydroxylation (AA) provides an efficient one-step preparation of enantiomerically pure β-amino alcohols from alkenes using catalytic amounts of osmium, chiral ligands, and a nitrogen source such as sulfonamides,[1a,2] amides,[3] carbamates,[4] and aminoheterocycles.[5] There has been rapid improvement in both the scope and selectivity since Sharpless's initial reports.[6−9]

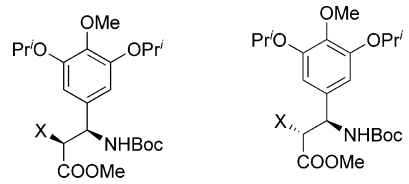

FIGURE 1.

In connection with our ongoing project aiming at the design and synthesis of compounds active against vancomycin-resistant enteroccoci (VRE),[10] an efficient synthesis of suitably protected, enantiomerically pure β-amino-α-hydroxy esters (**1**, **2**) and β-amino-α-azido ester (**3**, Figure 1) was required. For this purpose, the Sharpless AA, which could install the vicinal amino alcohol function of **1** in a single step with requisite relative and absolute stereochemistry, seems to be ideal. We report herein our studies on the Sharpless AA of cinnamates **4** that lead to efficient syntheses of compounds **1** to **3**. The isolation of hitherto unreported byproducts that are responsible for the decreased yields of AA products in certain circumstances will also be documented.

Initial experiments for the Sharpless AA of cinnamate **4** were carried out using *tert*-butyloxy carbamate as a nitrogen source and the $(DHQD)_2PHAL$[11] as a ligand (Scheme 1). In addition to AA products **1** and **5**, careful analysis of the reaction mixture led to the identification of aldehyde (**6**), acid (**7**), and α,α-di-*tert*-butyloxycarbamoyl-β-ketone ester (**8**). It was noticed that the relative ratio of these compounds was time-dependent. Prolonged reaction time led to a decrease of the yield of both amino alcohols **1** and **5**, with the concurrent increase of the amount of side products **6**−**8**. Under optimized conditions (*n*-PrOH/H_2O = 1/1, 10 °C, vigorous stirring, 1 h), the desired amino alcohol **1** was isolated in 70% yield together with its regioisomer **5** (11%), aldehyde **6** (7%), acid **7** (2%), and α,α-di-*tert*-butyloxycarbamoyl-β-ketone ester **8** (4%).

While aldehydes have occasionally been isolated in cinnamate aminohydroxylations,[12,13] the formation of compound **8** has never been reported under the Sharpless AA conditions. To elucidate the origin of byproduct **8**,

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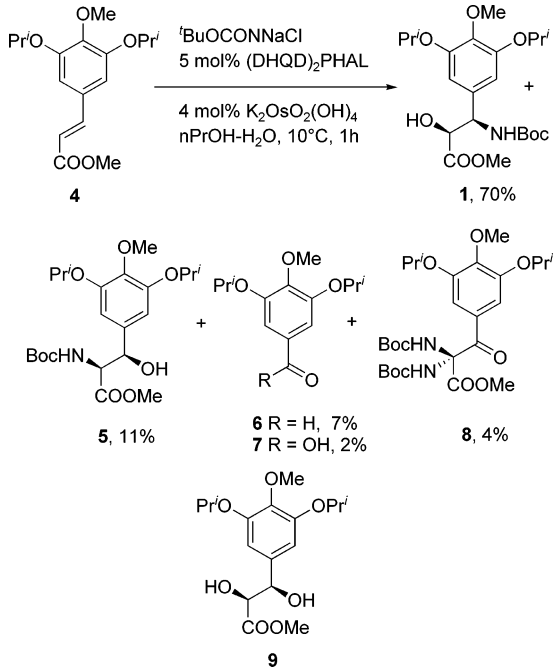
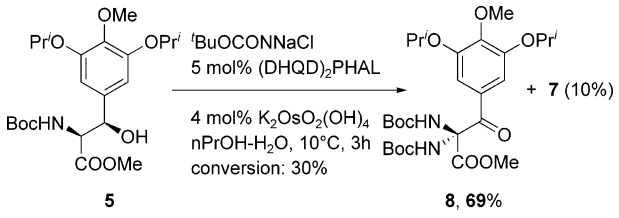
SCHEME 1



SCHEME 2



pure amino alcohols **1**, **5**, and diol **9** (Scheme 1) were resubmitted to the Sharpless AA conditions (3 h). It was found that **1**, **5**, and **9** decomposed under these conditions, yielding different product mixtures. Besides a transesterification product (methyl ester to propyl ester), 4-methoxy-3,5-diisopropyloxy benzoic acid (**7**) was produced from all these reactions, while 4-methoxy-3,5-diisopropyloxy benzaldehyde was isolated only from the diol (**9**) and, more importantly, the ketone ester **8** was generated only from the β-hydroxy-α-amino ester **5** (Scheme 2). From this observation, the following mechanistic hypothesis was proposed to account for the formation of ketone ester **8** from **5** (Scheme 3). Oxidation of benzylic alcohol followed by N-chlorination gave intermediate **11**, which upon deprotonation and elimination of chloride should provide imine **12**. Nucleophilic addition of *tert*-butyl carbamidate anion onto the resulting imine would provide the observed compound **8**. In this transformation, the *N*-chloro-*N*-sodiocarbamate acted as a chloronium ion donor, as a base, and then as a nucleophile. Alternatively,[14] enolization of β-keto ester (**10**) followed by second aminohydroxylation on the resulting enolate (**13**) would lead to the intermediate **14**, which upon hydrolysis would afford the observed compound **8**.[15] Since amino alcohols **1** and **5** did not follow the same reaction paths under the identical conditions, we suspected that the overall process might be triggered by the oxidation of benzylic alcohol. Control experiments have shown that the same transformation did not proceed in the absence of osmium tetraoxide or *N*-chloro-*N*-sodio *tert*-butyl carbamate. It is thus possible that oxidation of the benzylic alcohol to ketone may be promoted by the complex formed between these two species in analogy with the chemistry of chloroamine-T.[16] Reaction of phenoxyacetamidopenicillanate with ethyl *N*-chloro-*N*-sodiocarbamate to provide 6,6-diacylaminopenicillinate has previously been reported by Campbell and co-workers. [17]

The conversion of β-hydroxy-α-amino ester to the corresponding β,β-di-*tert*-butyloxycarbamoyl ketoester under Sharpless AA conditions is not restricted to compound **5** with an electron-rich aromatic ring. Thus, the *N*-Boc DL-threophenylserine (**15**) was partially transformed into the same type of compound under identical conditions (Scheme 4). Although more detailed studies are required, these results indicated a generality of this undesired reaction that may reduce the efficiency of the AA process.

With the efficient one-step preparation of amino alcohol **1** in hand, compounds **2** and **3** were readily synthesized, as is shown in Scheme 5. Mesylation of the secondary alcohol (MsCl, pyridine) gave the corresponding mesylate **17** in 98% yield.[18] Reaction of **17** with cesium acetate in benzene in the presence of 18-crown-6 followed by selective hydrolysis of acetate provided the (2*R*,3*R*)-**2** in 54% overall yield. On the other hand, nucleophilic displacement of mesylate by azide (NaN_3, DMSO, 50 °C) afforded the azido derivative (2*R*,3*R*)-**3** in 91% yield.[19]

In summary, we have developed efficient syntheses of enantiomerically pure β-amino-α-hydroxy esters (**1**, **2**) and β-amino-α-azido ester (**3**) using Sharpless AA as a key step. Oxidation of one of the AA products, the β-hydroxy-α-amino ester, into the α,α-di-*tert*-butyloxycarbamoyl-β-ketoester under AA conditions was reported for the first time and might decrease the yield of AA or give an incorrect estimation of the real regioisomeric ratio. This will be particularly true if β-hydroxy-α-amino acid was the desired regioisomer. Indeed, analysis of literature data indicated that the Sharpless AA of cinnamate using anthraquinone ligands [$(DHQD)_2AQN$ or $(DHQ)_2AQN$] leading to β-hydroxy-α-amino ester as a major regioisomer usually proceeded with lower chemical yield.[20] The partial decomposition of this regioisomer following the pathway shown in Scheme 3 may partially account for the reduced yield. We suspect that any effort

(14) This mechanism has been proposed by one of the referees; we are grateful for this suggestion. However, at the present time, we do not have any experimental evidence to differentiate these two alternatives.

(15) Osminium tetroxide-catalyzed aminohydroxylation of silyl enol ethers has been reported; see: Phukan, P.; Sudalai, A. *Tetrahedron: Asymmetry* **1998**, *9*, 1001−1005.

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(19) Enantiomeric excess (ee) of these compounds was found to be higher than 95% by analyzing their tripeptide derivatives. A copy of a ^{1}HNMR spectrum of one of these derivatives can be found in Supporting Information.

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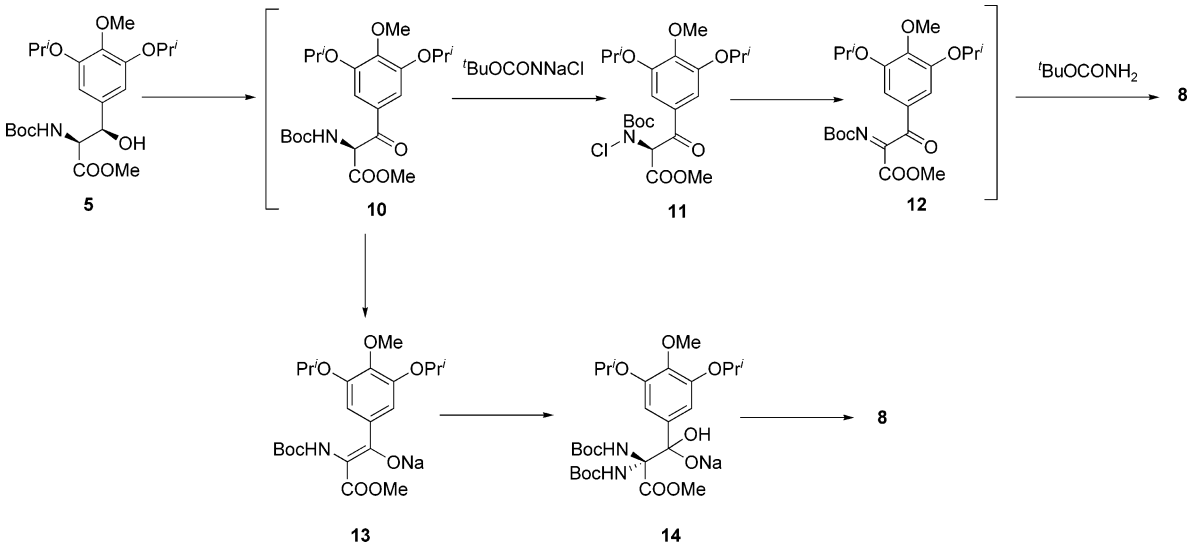
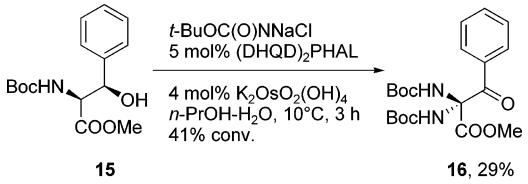
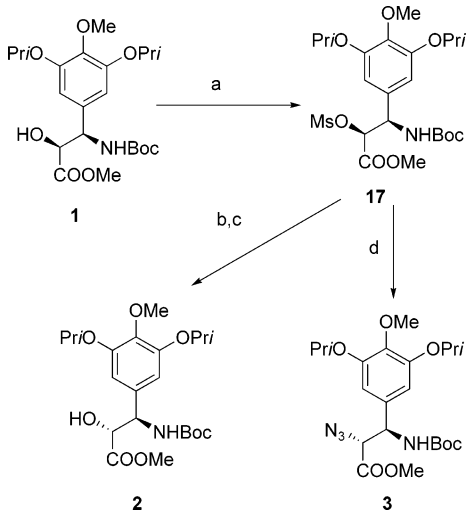
SCHEME 3



SCHEME 4



SCHEME 5[a]



[a] Reagents and conditions: (a) MsCl, Py, 0 °C, 98%; (b) CsOAc, PhH, 18-C-6, reflux; (c) K_2CO_3, MeOH−H_2O, rt, 15 min, 54%; (d) NaN_3, DMSO, 50 °C, 91%.

aiming at avoiding this side reaction will increase the chemical efficiency of the Sharpless AA process.

Experimental Section

Sharpless AA of Cinnamate 4. To a solution of *tert*-butyl carbamate (741.0 mg, 6.2 mmol) in *n*-PrOH (8.0 mL) was sequentially added a solution of NaOH (249.0 mg, 6.1 mmol in 15.0 mL water) and *t*-BuOCl (freshly prepared, 0.7 mL, 6.1 mmol). After the reaction mixture was stirred at room temperature for 3 min, a solution of $(DHQD)_2PHAL$ (82 mg, 0.1 mmol) in *n*-PrOH (7.0 mL) was added, and the solution was stirred at room temperature for 5 min, the reaction flask was cooled in a cold-water bath. To the reaction mixture was added ester **1** (616 mg, 2 mmol) in *n*-PrOH and H_2O (1:1, 10.0 mL) and $K_2OsO_2(OH)_4$ (29.4 mg, 0.08 mmol). After the mixture was stirred for 1 h at 10 °C (the color of solution turned from green to green-yellow), Na_2SO_3 (1.0 g) was added to the reaction mixture and the mixture was stirred for 10 min. The reaction mixture was extracted with EtOAc. The organic phase was washed with 5% K_2CO_3, saturated $NaHCO_3$, H_2O, and brine and dried over anhydrous Na_2SO_4. The volatile was removed under reduced pressure, and the residue was purified by flash chromatography (Hept/AcOEt = 8:1 to 2:1) to afford compound **1** (620.0 mg, 70%), the regioisomer **5** (96.0 mg, 11%), the aldehyde **6** (37.0 mg, 7.3%), and keto ester **8** (40.0 mg, 3.6%). The aqueous phase was acidified with aqueous HCl (5%) and extracted with EtOAc; the organic phase was washed with H_2O and brine and dried over anhydrous Na_2SO_4. After evaporation of solvent, the residue was purified by flash chromatography (Hept/AcOEt = 4:1) to afford acid **7** (11.0 mg, 2.1%). **Compound 1:** $[\alpha]^{23}_D$ −9 (*c* 0.6, $CHCl_3$); IR ($CHCl_3$) ν 3525, 3035, 2981, 2936, 2831, 1750, 1710, 1590, 1493, 1368, 1320, 1273, 1165, 1116 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.57 (s, 2H), 5.33 (d, 1H, J = 9.4 Hz), 5.07 (m, 1H), 4.50 (hept, 2H, J = 6.1 Hz), 4.43 (m, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.16 (d, 1H, J = 3.8 Hz), 1.41 (s, 9H), 1.33 (d, 12H, J = 6.1 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.2, 155.2, 151.7 (2C), 140.5, 134.4, 108.1 (2C), 79.8, 73.6, 71.6 (2C), 60.3, 54.8, 52.7, 28.2 (3C), 22.1 (4C); MS (ESI) *m/z* 464 (M + Na); HRMS (ESI) *m/z* calcd for $C_{22}H_{35}NO_8Na$ (M + Na) 464.2260, found 464.2252. **Compound 5:** $[\alpha]^{23}_D$ −2 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) ν 3446, 3007, 2980, 2936, 2831, 1753, 1714, 1590, 1493, 1439, 1368, 1320, 1273 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.53 (s, 2H), 5.34 (d, 1H, J = 9.4 Hz), 5.07 (brs, 1H), 4.52−4.42 (m, 3H), 3.73 (s, 3H), 3.70 (s, 3H), 3.28 (brs, 1H), 1.31 (s, 9H), 1.30 (d, 12H, J = 6.1 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 171.4, 155.6, 151.4 (2C), 140.3, 135.2, 107.2 (2C), 79.8, 73.3, 71.4 (2C), 60.3, 59.4, 52.4, 28.1 (3C), 22.1 (4C); MS (ESI) *m/z* 464 (M + Na); HRMS (ESI) *m/z* calcd for $C_{22}H_{35}NO_8Na$ (M + Na) 464.2260, found 464.2252. **Compound 8:** IR ($CHCl_3$) ν 3418, 2982, 2937, 2854, 1754, 1717, 1709, 1481, 1468, 1369, 1252, 1168, 1114, 1078, 1023, 1001, 863 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (s, 2H), 7.01 (s, 2H), 4.53 (hept, 2H, J = 6.0 Hz), 3.86 (s, 3H), 3.73 (s, 3H), 1.35 (d, 12H, J = 6.0 Hz), 1.34 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.3, 168.1, 154.2 (2C), 151.5 (2C), 146.2, 127.5, 110.8 (2C), 80.1(2C), 73.9, 72.0 (2C), 60.9, 54.5, 28.4 (6C), 22.4 (4C); MS (ESI) *m/z* 577 (M + Na), 593 (M + K); HRMS (ESI) *m/z* calcd for $C_{27}H_{42}N_2O_{10}Na$ (M + Na) 577.2737, found 577.2751.

2,2-Bis-*tert*-butoxycarbonylamino-3-oxo-3-phenyl-proionic Acid Methyl Ester (16). IR ($CHCl_3$) ν 3418, 3032, 3011, 2983, 2933, 1755, 1714, 1599, 1481, 1471, 1448, 1394, 1369, 1277,

1256, 1156, 1051, 1017, 876 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, 2H, J = 7.0 Hz), 7.54 (t, 1H, J = 7.0 Hz), 7.40 (t, 2H, J = 7.7 Hz), 7.02 (brs, 2H), 3.74 (s, 3H), 1.33 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.3, 167.4, 153.9 (2C), 133.6, 132.8, 129.3 (2C), 128.4 (2C), 80.8 (2C), 73.6, 54.1, 28.0 (6C); MS (ESI) *m/z* 431.0 (M + Na), 447.0 (M + K); HRMS (ESI) *m/z* calcd for $C_{20}H_{28}N_2O_7Na$ (M + Na) 431.1794, found 431.1784.

3-*tert*-(2*S*,3*R*)Butoxycarbonylamino-3-(3,5-diisopropoxy-4-methoxy-phenyl)-2-methanesulfonyloxy-propionic Acid Methyl Ester (17). To a solution of alcohol **1** (1.0 g, 2.28 mmol) in anhydrous pyridine (freshly distilled over CaH_2, 11.0 mL) was added dropwise MsCl (0.21 mL, 2.73 mmol) at 0 °C. After being stirred at 0 °C for 2 h and at room temperature for 2 h, the reaction mixture was quenched by addition of MeOH (2 mL) and extracted with EtOAc. The organic phase was washed with 5% HCl, saturated $NaHCO_3$, H_2O, and brine and dried over anhydrous Na_2SO_4. The solvent was evaporated, and the residue was purified by flash chromatography (Hept/AcOEt = 3:1) to afford compound **15** (1.16 g, 98%): mp 66−69 °C; $[\alpha]^{23}_D$ −1. (*c* 0.2, $CHCl_3$); IR ($CHCl_3$) ν 3662, 3549, 3433, 3021, 2983, 2936, 2673, 2578, 1760, 1719, 1583, 1454, 1438, 1393, 1369, 1218, 1175, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.53 (s, 2H), 5.30 (m, 2H), 5.17 (brs, 1H), 4.52 (hept, 2H, J = 5.9 Hz), 3.82 (s, 3H), 3.78 (s, 3H), 2.86 (s, 3H), 1.41 (s, 9H), 1.32 (d, 12H, J = 5.9 Hz); ^{13}C NMR (62.5 MHz, CD_3OD) δ 169.4, 159.8, 153.3, 142.0, 134.6, 109.6, 82.1, 80.1, 73.0, 61.3, 57.2, 53.6, 38.9, 29.0, 22.8; MS (ESI) *m/z* 542 (M + Na); HRMS (ESI) *m/z* calcd for $C_{23}H_{37}NO_{10}NaS$ (M + Na) 542.2036, found 542.2034.

3-*tert*-(2*R*,3*R*)Butoxycarbonylamino-3-(3,5-diisopropoxy-4-methoxy-phenyl)-2-azido-propionic Acid Methyl Ester (3). To a solution of compound **17** (1.17 g, 2.25 mmol) in anhydrous DMSO (7.4 mL) was added NaN_3 (293.0 mg, 4.5 mmol). After being stirred at 50 °C for 24 h under Ar, the reaction mixture was cooled to room temperature, diluted with H_2O, and extracted with EtOAc; the organic phase was washed with H_2O and brine and dried over anhydrous Na_2SO_4. The solvent was evapotated, and the residue was purified by flash chromatography (Hept/AcOEt = 4:1) to afford azide **3** (954.0 mg, 91%): $[\alpha]^{23}_D$ −3 (*c* 0.5, MeOH); IR ($CHCl_3$) ν 3441, 2982, 2937, 2832, 2117, 1720, 1711, 1589, 1492, 1438, 1368, 1317, 1247, 1160, 1110, 1082, 1005 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.49 (s, 2H), 5.31 (d, 1H, J = 8.1 Hz), 5.08 (m, 1H), 4.49 (hept, 2H, J = 5.9 Hz), 4.42 (d, 1H, J = 3.7 Hz), 3.78 (s, 3H), 3.69 (s, 3H), 1.43 (s, 9H), 1.32 (d, 12 H, J = 5.9 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 171.8, 159.2, 152.0, 148.4, 135.6, 109.0, 80.5, 71.9, 66.9, 65.3, 60.6, 55.7, 52.8, 28.4, 22.3; MS (ESI) *m/z* 489 (M + Na); HRMS (ESI) *m/z* calcd for $C_{22}H_{34}N_4O_7Na$ (M + Na) 489.2325, found 489.2329.

3-*tert*-(2*R*,3*R*)Butoxycarbonylamino-3-(3,5-diisopropoxy-4-methoxy-phenyl)-2-hydroxy-propionic Acid Methyl Ester (2). To a solution of compound **17** (230 mg, 0.44 mmol) in anhydrous benzene (10 mL) was added CsOAc (340.0 mg, 1.77 mmol) and 18-crown-6 (118.0 mg, 0.44 mmol). After being refluxed for 24 h under Ar, the reaction mixture was cooled to room temperature and then filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (Hept/AcOEt = 4:1) to afford the desired ester (145.0 mg, 80%); starting material (35.0 mg) was also recovered: $[\alpha]^{23}_D$ −18 (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) 3448, 3020, 2981, 2937, 1751, 1712, 1589, 1493, 1438, 1370, 1317, 1230, 1224, 1211, 1159, 1116, 1006 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.51 (s, 2H), 5.36 (d, 1H, J = 4.7 Hz), 5.30−5.10 (m, 2H), 4.49 (hept, 2H, J = 6.1 Hz), 3.80 (s, 3H), 3.64 (s, 3H), 2.15 (s, 3H), 1.44 (s, 9H), 1.33 (d, 12H, J = 6.1 Hz); ^{13}C NMR (62.5 MHz, CD_3OD) δ 169.9, 168.1, 154.8, 151.7, 141.2, 132.0, 109.0, 80.1, 74.8, 74.2, 71.7, 60.4, 54.7, 52.3, 28.3, 22.2, 20.6; MS (ESI) *m/z* 506 (M + Na); HRMS (ESI) *m/z* calcd for $C_{24}H_{37}NO_9Na$ (M + Na) 506.2366, found 506.2360. To a solution of the acetate (220.0 mg, 0.46 mmol) in MeOH (30.0 mL) and H_2O (3.0 mL) was added K_2CO_3 (188.0 mg, 1.37 mmol). After the mixture was stirred at room temperature for 20 min, it was then acidified with citric acid to pH = 2−3 and concentrated under reduced pressure. The residue was diluted with H_2O and extracted with EtOAc. The combined organic phase was washed with H_2O and brine and dried over Na_2SO_4. The solvent was evaporated, and the residue was purified by flash chromatography (Hept/AcOEt = 2:1) to afford compound **2** (134.0 mg, 67%): $[\alpha]^{23}_D$ −14 (*c* 2, $CHCl_3$); IR ($CHCl_3$) 3529, 3444, 3020, 3013, 2981, 2935, 2832, 1740, 1710, 1589, 1493, 1440, 1368, 1317, 1275, 1232, 1162, 1117, 1080, 1052, 1006 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.46 (s, 2H), 5.47 (d, 1H, J = 8.2 Hz), 4.97 (m, 1H), 4.57 (m, 1H), 4.48 (m, 2H), 3.79 (s, 3H), 3.72 (s, 3H), 1.64 (brs, 1H), 1.44 (s, 9H), 1.33 (d, 6H, J = 6.0 Hz), 1.31 (d, 6H, J = 6.0 Hz); ^{13}C NMR (62.5 MHz, CD_3OD) δ 172.3, 155.1, 151.8, 141.3, 131.9, 109.2, 108.4, 80.0, 73.7, 73.4, 71.8, 60.5, 56.7, 52.6, 28.4, 22.3; MS (ESI) *m/z* 464 (M + Na); HRMS (ESI) *m/z* calcd for $C_{22}H_{35}NO_8Na$ (M + Na) 464.2260, found 464.2252.

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Supporting Information Available: Copies of ^1H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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