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A Practical and Azide-Free Synthetic Approach to Oseltamivir from Diethyl D-Tartrate

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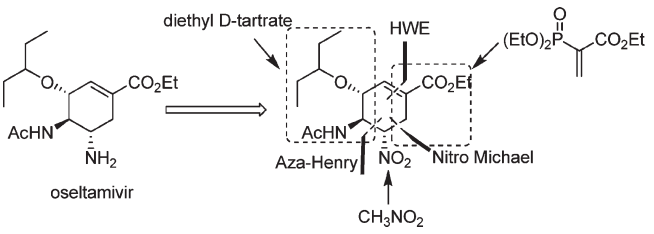

A short and practical synthesis of oseltamivir was accomplished in 11 steps from inexpensive and abundant diethyl D-tartrate starting material. This azide-free route featured an asymmetric aza-Henry reaction and a domino nitro-Michael/Horner−Wadsworth−Emmons (HWE) reaction as the key steps to construct the relevant cyclohexene ring of the product, which provided an economical and practical alternative for the synthesis of oseltamivir.

The recent spread of human influenza[1] and H5N1 avian flu[2] has caused serious concern over the worldwide epidemic. Although vaccination is the favorite approach to prevent influenza,[3] small molecular antiviral agents represent another potential strategy for the effective flu prevention and therapy.

The active site of influenza virus neuraminidase (NA) is highly conserved for all influenza virus A and B strains, which makes it an important anti-influenza drug target.[4] Up to now, many promising NA inhibitors with remarkable selectivity and activity have been designed and synthesized; two of them have reached the market in 1999, namely, zanamivir (Relenza)[5] and oseltamivir phosphate (Tamiflu).[6] It should be noted that oseltamivir phosphate is the most widely used antiviral drug for the treatment and prevention of influenza. The threat of avian and other seasonal influenzas has inevitably increased the worldwide demand for stocks of this drug, which also puts pressure on the relevant pharmaceutical companies and chemical producers.

The current manufacturing process for oseltamivir starts from (−)-shikimic acid or (−)-quinic acid, but the limited availability of the chiral raw materials is a major drawback. Moreover, the process also suffers from the use of potentially hazardous azide intermediates, long reaction procedures, and tedious separation and purification.[7]

Hence diverse synthetic approaches toward this important synthetic target have been developed, and very insightful reviews of their relative merits have also been published.[8] For example, Shibasaki and co-workers have developed four different approaches based on asymmetric ring opening of *meso*-aziridines or Diels−Alder reaction.[9] Corey et al. employed asymmetric Diels−Alder reaction as the initial step to synthesize oseltamivir phosphate in high yield.[10] More recently, Hayashi's group published an operationally simple and high-yielding (57%) approach to oseltamivir, which required nine reaction steps including three "one-pot" operations, and only one intermediate needed to be purified by column chromatography.[11]

As for the routes from natural chiral sources other than shikimic acid, Yao and co-workers reported the synthesis of a functionalized cyclohexene skeleton of oseltamivir via a ring-closing metathesis protocol starting from inexpensive L-serine.[12] Fang et al. explored a novel approach to oseltamivir using D-xylose as the chiral precursor.[13] Mandai's group published two synthetic routes, starting from readily available and inexpensive D-mannitol and L-methionine derivatives, respectively.[14] Recently Chen et al. also developed an efficient formal synthesis of oseltamivir phosphate with inexpensive D-ribose starting material.[15] However,

(1) Schmidt, A. C. *Drugs* **2004**, *64*, 2031.
(2) Moscona, A. *N. Engl. J. Med.* **2005**, *353*, 1363.
(3) Centers for Disease Control and Prevention. *Prevention and control of influenza*. MMWR Morbid Mortal Wkly. Rep. **2000**, *49* (RR-3), 1.
(4) (a) Lew, W.; Chen, X.; Kim, C. U. *Curr. Med. Chem.* **2000**, *7*, 663. (b) Russell, R. J.; Haire, L. F.; Stevens, D. J.; Collins, P. J.; Lin, Y. P.; Blackburn, G. M.; Hay, A. J.; Gamblin, S. J.; Skehel, J. J. *Nature* **2006**, *443*, 45.
(5) Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H.; Zhang, L.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Laver, G.; Stevens, R. C. *J. Am. Chem. Soc.* **1997**, *119*, 681.
(6) von Itzstein, M.; Wu, W.-Y.; Kok, G. B.; Pegg, M. S.; Dyason, J. C.; Jin, B.; Phan, T. V.; Smythe, M. L.; White, H. F.; Oliver, S. W.; Colman, P. M.; Varghese, J. N.; Ryan, D. M.; Woods, J. M.; Bethell, R. C.; Hotham, V. J.; Cameron, J. M.; Penn, C. R. *Nature* **1993**, *363*, 418.
(7) Farina, V.; Brown, J. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 7330.
(8) (a) Magano, J. *Chem. Rev.* **2009**, *109*, 4398. (b) Shibasaki, M.; Kanai, M. *Eur. J. Org. Chem.* **2008**, 1839 and references therein.
(9) (a) Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312. (b) Mita, T.; Fukuda, N.; Roca, F. X.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 259. (c) Yamatsugu, K.; Kamijo, S.; Suto, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2007**, *48*, 1403. (d) Yamatsugu, K.; Yin, L.; Kamijo, S.; Kimura, Y.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1070.
(10) Yeung, Y. Y.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 6310.
(11) Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 1304.
(12) Cong, X.; Yao, Z.-J. *J. Org. Chem.* **2006**, *71*, 5365.
(13) Shie, J.-J.; Fang, J.-M.; Wang, S.-Y.; Tsai, K.-C.; Cheng, Y.-S. E.; Yang, A.-S.; Hsiao, S.-C.; Su, C.-Y.; Wong, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 11892.
(14) (a) Mandai, T.; Oshitari, T. *Synlett* **2009**, 783. (b) Oshitari, T.; Mandai, T. *Synlett*. **2009**, 787.
(15) Osato, H.; Jones, I. L.; Chen, A.; Chai, C. L. L. *Org. Lett.* **2010**, *12*, 60.

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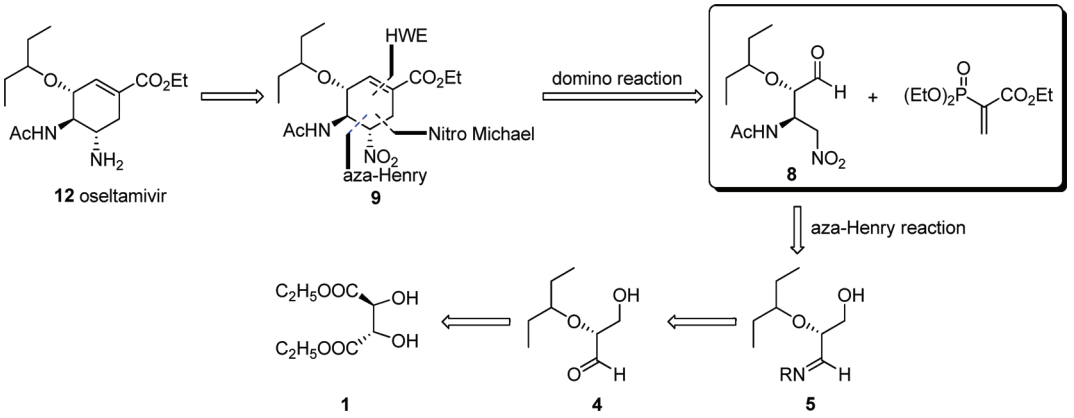
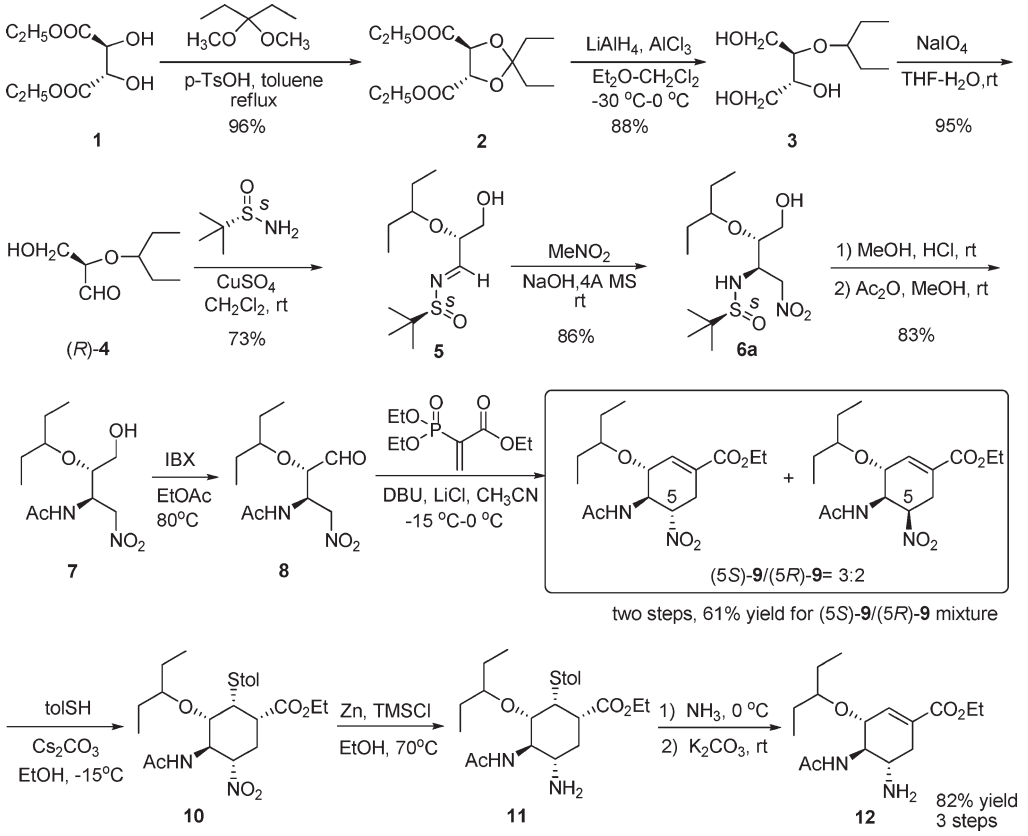
SCHEME 1. Retrosynthetic Analysis of Oseltamivir



SCHEME 2. Synthesis of Oseltamivir from Diethyl D-Tartrate



there were always some drawbacks associated with these methods, such as expensive starting materials, long synthetic routes, hazardous azide intermediates, and relatively low yields. Herein we report the development of a new azide-free 11-step synthesis of oseltamivir starting from inexpensive and abundant diethyl D-tartrate.

Our retrosynthetic analysis is shown in Scheme 1. Nitro compound **9** was considered as the key precursor, which could be assembled by a domino nitro Michael/Horner–Wadsworth–Emmons (HWE) reaction[11,16] from nitroalkane **8**. Compound **8** could be obtained from asymmetric aza-Henry reaction of *N*-protected imine **5**. The corresponding aldehyde **4** could be prepared in three steps from commercially available diethyl D-tartrate, in which the 3-pentyl group with requisite stereochemistry could be conveniently introduced.

On the basis of the above analysis, we started the synthetic route from chiral diethyl D-tartrate **1** (Scheme 2). First, treatment of **1** with 3,3-dimethoxypentane afforded the corresponding ketal **2** nearly quantitatively. Upon treatment with $LiAlH_4$ and $AlCl_3$, both the ester and the ketal functionalities of **2** were reduced smoothly to afford triol **3** in 88% yield. In this way the 3-pentyl group with requisite stereochemistry was introduced conveniently. Then triol **3** was treated with $NaIO_4$, and the vicinal diol group was oxidized to give crude 2-*O*-pentyl D-glyceraldehyde **4** in

(16) Kraus, G. A.; Goronga, T. *Synthesis* **2007**, 1765.

95% yield. It is worth noting that aldehyde **4** was unstable and should be used for the next reaction without delay. In addition, the aforementioned three steps have already been carried out in >25-g scale without the need of column chromatographic purification.

With 2-*O*-pentyl glyceraldehyde **4** in hand, the asymmetric aza-Henry reaction of imine with nitromethane was studied. At first, we chose *N*-Boc-protected α-amido sulfone (*R*)-**5b** as a precursor to generate the imine substrate in situ, hoping the large steric hindrance of *N*-Boc group could have a strong stereocontrol on the reaction. Under optimized conditions, the asymmetric aza-Henry reaction proceeded smoothly to afford **6b** in 78% yield and 5:1 diastereoselectivity.[17] To further improve the diastereoselectivity, we turned our attention to the enantiopure sulfoxide *N*-protecting auxiliary, which could be incorporated into a wide range of imines and afford high levels of stereocontrol for a variety of reactions.[18] Using $CuSO_4$ as a Lewis acid catalyst and water scavenger, sulfinyl aldimine **5** was prepared in high yield from the condensation of 2-*O*-pentyl glyceraldehyde **4** and (*S*)-(−)-*tert*-butylsulfinamide. For the asymmetric aza-Henry reaction of the aldimine,[19] in the presence of NaOH (5 equiv) and powdered 4 Å molecular sieves, a 10:1 dr mixture of nitroamines **6a/6b** was obtained in 86% yield after 24 h at rt. The diastereoisomers were separated by column chromatography, and the major isomer has the same absolute and relative configuration at the two stereogenic centers as in oseltamivir. Removal of the *tert*-butylsulfinamide protecting group and acetylation of the resulting amine with Ac_2O led to the formation of acetamide **7**.

The subsequent transformation was the construction of the cyclohexenecarboxylate skeleton. Compound **7** was oxidized to the corresponding aldehyde **8** by IBX (3 equiv.) in EtOAc under refluxing conditions. This transformation proceeded very smoothly, and no epimerization product was observed. Then aldehyde **8** was subjected to a domino reaction by first treating it with vinylphosphonate via a Michael reaction, followed by an intramolecular HWE reaction[11] with in situ generated phosphonate to provide **9** in 61% yield and 3:2 diastereoselectivity. The major diastereomer (5*S*)-**9** had the desired configuration and could be separated by column chromatography and converted to oseltamivir directly, by reduction with Zn/AcOH, in 71% yield.

To further improve the overall yield of oseltamivir, we also adopted Hayashi's strategy[11] to convert the undesired (5*R*)-isomer to (5*S*)-isomer. Treating (5*S*)-**9**/(5*R*)-**9** mixture with *p*-toluenethiol and Cs_2CO_3 afforded the Michael product **10** in excellent yield as the (5*S*)-isomer exclusively. Then nitro compound **10** was reacted with zinc under acidic conditions to provide amine **11**. Subsequently ammonia gas was bubbled into the reaction mixture to form a Zn(II)-NH_3 complex, and the addition of K_2CO_3 promoted the elimination of *p*-toluenethiol to give oseltamivir **12**. Compound **12** was purified by acid/base extraction and was obtained in 82% overall yield from **9** through the last three steps. The properties of (−)-oseltamivir thus obtained were identical to those reported in the literature.[9a,11] (^{1}H and ^{13}C NMR spectra, IR spectrum, R_f value, and optical rotation).

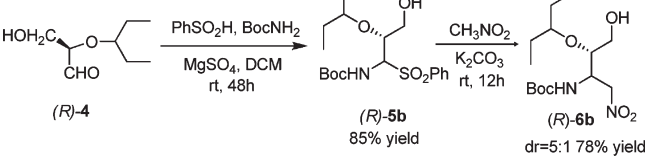
In summary, a short and practical synthesis of oseltamivir has been accomplished from diethyl D-tartrate, which involved an asymmetric aza-Henry reaction and a domino nitro Michael/HWE reaction as the key steps to construct the relevant cyclohexene ring. The advantages of this route include the following: (1) all reagents are inexpensive, (2) the starting material diethyl D-tartrate is abundant and readily available, (3) mild reaction conditions and azide-free synthetic procedure decrease the operational hazard, and (4) no heavy metals are used. This new approach requires 11 steps with 21% overall yield, potentially providing an economical and practical alternative for the efficient synthesis of oseltamivir.[20]

Experimental Section

(2*R*,3*R*)-3-(Pentan-3-yloxy)butane-1,2,4-triol (3). Aluminum chloride (28.9 g, 218 mmol) in 70 mL of dry diethyl ether was added in a dropwise manner to a suspension of lithium aluminum hydride (8.3 g, 218 mmol) in diethyl ether (80 mL) at −30 °C. The mixture was stirred for 30 min, and 70 mL dry dichloromethane was added rapidly. Then the reaction mixture was warmed to 0 °C, and into it a solution of diethyl (4*S*,5*S*)-2,2-diethyl-1,3-dioxolane-4,5-dicarboxylate **2** (32.4 g, 118 mmol) in dry dichloromethane (70 mL) was added in a dropwise manner. After stirring at room temperature for 1 h and refluxing for 2 h, the mixture was cooled to −25 °C, and into it were added cautiously deionized water (7 mL) and 23 mL of aqueous potassium hydroxide solution (15.8 g, 280 mmol). Subsequently the cooling bath was removed, and the mixture was stirred at room temperature until the gray color completely disappeared. (Efficient stirring was always required to ensure good yield.) The suspension was filtered through a sintered-glass funnel containing a 2-cm pad of Celite, and the inorganic precipitate was extracted with 500 mL of dichloromethane in a Soxhlet apparatus for 3 days. The combined extract and filtrate were evaporated under reduced pressure. After drying over phosphorus pentoxide (P_2O_5) in an evacuated desiccator, 20.3 g (88% yield) of colorless oil **3** was obtained and used directly in the next step. An analytical sample of **3** was prepared by chromatography on silica gel (1:1 hexane/ EtOAc). $[\alpha]^{20}_D = +20.1$ (*c* 0.525, $CHCl_3$). IR (neat): 3383, 2965, 2936, 2879, 2361, 1649, 1462, 1385, 1047, 965, 872, 675 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.68−3.83 (m, 4H), 3.51 (m, 1H), 3.33 (m, 1H), 3.02 (m, 2H), 2.61 (m, 1H), 1.94 (s, 1H), 1.53 (m, 4H), 0.90 (t, J = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 81.5, 77.4, 77.3, 77.1, 76.8, 71.7, 63.3, 60.8, 26.2, 25.8, 9.6, 9.4. HRMS (ESI): m/z [M − H]$^-$ calculated for $[C_9H_{19}O_4]^-$ 191.1283, found 191.1293.

***N*-((*S*,*S*$_S$)-3-Hydroxy-2-(pentan-3-yloxy)propylidene)-2-methylpropane-2-sulfinamide (5).** Anhydrous $CuSO_4$ (26.7 g, 169 mmol)

(17) Attempted aza-Henry reaction using *N*-Boc-protected α-amido sulfone (*R*)-**5b** as precursor to generate imine substrate in situ:



(18) Reviews: (a) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869. (b) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984.

(19) Garcia Ruano, J. L.; Topp, M.; Lopez-Cantarero, J.; Aleman, J.; Remuinan, M. J.; Cid, M. B. *Org. Lett.* **2005**, *7*, 4407.

(20) After the acceptance of this paper, a sugar-based synthesis of Tamiflu was reported. Ma, J.; Zhao, Y.; Ng, S.; Zhang, J.; Zeng, J.; Than, A.; Chen, P.; Liu, X.-W. *Chem.−Eur. J.* **2010**, *16*, 4533.

and (*S*)-(−)-*tert*-butanesulfinamide (73.2 mmol, 8.8 g) were added to a solution of aldehyde **4** (9.0 g, 56.3 mmol) in CH_2Cl_2 (150 mL) sequently. After stirring at room temperature for 3 days, the reaction mixture was filtered through a pad of Celite, and the residue was washed with CH_2Cl_2 (120 mL). The combined filtrate was concentrated in vacuo and purified by flash column chromatography (SiO_2, 25% EtOAc in hexane as eluent) to give compound **5** (10.8 g, 73%) as a yellow oil. $[\alpha]^{20}_D = +175$ (*c* 0.79, $CHCl_3$). IR (neat): 3433, 2964, 2934, 2877, 1625, 1461, 1365, 1088, 926, 585 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.05 (d, J = 4.0 Hz, 1H), 4.29−4.32 (m, 1H), 3.76−3.79 (m, 1H), 3.36 (m, 1H), 1.53−1.59 (m, 4H), 1.20 (s, 9H), 0.92 (t, J = 7.2 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.2, 82.0, 79.4, 56.9, 26.4, 25.4, 22.4, 9.7, 9.2. HRMS (ESI): m/z $[M - H]^-$ calculated for $[C_{12}H_{24}NO_3S]^-$ 262.1477, found 262.1474.

***N*-((2*R*,3*S*,S_S)-4-Hydroxy-1-nitro-3-(pentan-3-yloxy)-butan-2-yl)-2-methylpropane-2-sulfinamide (6a).** Powdered NaOH (5 g, 124 mmol) was added to a slurry of *N*-sulfinylimine **5** (6.5 g, 24.7 mmol) and 4 Å MS in $MeNO_2$ (150 mL) at room temperature. After stirring for 24 h, the mixture was filtered through a short pad of silica gel and concentrated in vacuo. The crude product was purified by flash column chromatography (SiO_2, 40% EtOAc in hexane as eluent) to give compound **6a** (6.6 g, 86% yield, dr = 10:1, determined by ^1H NMR) as a yellow oil. $[\alpha]^{20}_D = +32.8$ (*c* 0.25, $CHCl_3$). IR (neat): 3934, 2854, 2557, 1492, 1442, 1173 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.71−4.81 (m, 2H), 4.27−4.33 (m, 1H), 4.10 (d, J = 9.6 Hz, 1H), 3.58−3.74 (m, 3H), 3.34 (q, J = 6.0 Hz, 1H), 2.89 (s, 1H), 1.49 (m, 1H), 1.23 (s, 9H), 0.89 (t, J = 7.2 Hz, 3H), 0.88 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.2, 82.0, 79.4, 63.7, 57.0, 26.4, 25.4, 9.7, 8.2. HRMS (ESI): m/z $[M - H]^-$ calculated for $[C_{13}H_{27}N_2O_5S]^-$ 323.1641, found 323.1639.

***N*-((2*R*,3*S*)-4-Hydroxy-1-nitro-3-(pentan-3-yloxy)butan-2-yl)-acetamide (7).** Compound **6a** (986 mg, 3 mmol) was added to a saturated HCl solution in methanol (30 mL) and stirred at room temperature for 2 h. Then the reaction mixture was carefully poured into a saturated $NaHCO_3$ solution (20 mL), and the mixture was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic extracts were washed with saturated brine (40 mL) and dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, the resulting amine was dissolved in 15 mL methanol and into it was added acetic anhydride (0.42 mL, 4.5 mmol). The mixture was stirred for 30 min at room temperature and was concentrated and purified by flash column chromatography (SiO_2, 1:1 hexane/EtOAc as eluent) to afford **7** (652 mg, 83% yield) as a white wax. $[\alpha]^{20}_D = +13.4$ (*c* 1.0, $CHCl_3$). IR (KBr, film): 2343, 2047, 1520, 1312, 1139, 1122, 1067, 951, 863, 575 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.02 (d, J = 7.8 Hz, 1H), 4.98 (dd, J = 7.2, 15.2 Hz, 2H), 4.60 (m, 1H), 3.81 (dd, J = 8.8, 11.6 Hz, 1H), 3.60−3.71 (m, 2H), 3.26 (q, J = 6.0 Hz, 1H), 2.01 (s, 3H), 1.47 (m, 4H), 0.87 (t, J = 7.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.7, 81.3, 76.2, 75.8, 60.3, 48.8, 26.1, 25.7, 22.9, 9.5, 9.3. HRMS (ESI): m/z $[M - H]^-$ calculated for $[C_{11}H_{21}N_2O_5]^-$ 261.1450, found 261.1445.

(3*R*,4*R*,5*S*)-Ethyl-4-acetamido-5-nitro-3-(pentan-3-yloxy-)-cyclohex-1-enecarboxylate (9). Ethyl 2-(diethoxyphosphoryl)-acrylate (778 mg, 3.3 mmol) was added to a solution of aldehyde **8** (575 mg, 2.2 mmol) in CH_3CN (6 mL) at −15 °C. Then 1,8-diazabicyclo[5.4.0]undec-7-ene (670 mg, 4.4 mmol) and lithium chloride (185 mg, 4.4 mmol) were added. After stirring at −15 °C for 14 h, the resulting mixture was warmed to 0 °C and stirred for 2 h. The solution was diluted with MeOH (10 mL), followed by the addition of NH_4Cl (233 mg, 4.4 mmol). Then the mixture was diluted with CH_2Cl_2 (20 mL) and washed successively with 10 mL saturated solutions of NH_4Cl, $NaHCO_3$, and NaCl. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, 3:1 hexane/EtOAc as eluent) to afford compound **9** (459 mg, 1.34 mmol) as a white solid in 61% yield and 3:2 dr (determined by ^1H NMR). Characterization for major diastereoisomer (5*S*)-**9**: Mp 141.3−143.5 °C. $[\alpha]^{20}_D = -63.7$ (*c* 1.01, $CHCl_3$). IR (KBr, film): 2787, 2126, 1605, 1517, 1342, 1140, 1067, 951, 862 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.80 (t, J = 2.0 Hz, 1H), 5.81 (d, J = 8.4 Hz, 1H), 4.92 (ddd, J = 3.2, 6.8, 8.6 Hz, 1H), 4.72 (m, 1H), 4.18 (q, J = 7.2 Hz, 2H), 4.05 (m, 1H), 3.45 (q, J = 5.6 Hz, 1H), 2.97 (d, J = 7.2 Hz, 1H), 1.92 (s, 1H), 1.43−1.55 (m, 4H), 1.25 (t, J = 7.2 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H), 0.82 (t, J = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.3, 164.3, 134.3, 127.6, 81.7, 79.1, 71.3, 60.4, 49.1, 25.4, 25.3, 24.5, 22.2, 13.2, 8.3. HRMS (ESI): m/z $[M - H]^-$ calculated for $[C_{16}H_{25}N_2O_6]^-$ 341.1713, found 341.1717.

(1*S*,2*R*,3*S*,4*R*,5*S*)-Ethyl-4-acetamido-5-nitro-3-(pentan-3-yloxy)-2-(*p*-tolylthio)-cyclohexanecarboxylate (10). To a solution of nitro ester **9** (171 mg, 0.5 mmol) in EtOH (2 mL) were added *p*-toluenethiol (248 mg, 2 mmol) and Cs_2CO_3 (488 mg, 1.5 mmol) at −15 °C. Then the resulting mixture was stirred at −15 °C for 48 h before being quenched with cold 2 N HCl (5 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL) for three times. The combined organic layer was washed with saturated $NaHCO_3$ solution (12 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 3:1 hexane/EtOAc) to afford **10** (220 mg, 95% yield) as a white solid. Mp: 167.5−170.0 °C. $[\alpha]^{20}_D = -32.8$ (*c* 1.01, $CHCl_3$). IR (KBr, film): 2130, 1657, 1361, 1162, 1068, 951, 861, 546, 517 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.38 (m, 2H), 7.07 (m, 2H), 6.23 (d, J = 6.8 Hz, 1H), 5.44 (ddd, J = 12.4, 11.1, 4.9 Hz, 1H), 4.38 (dd, J = 10.4, 4.0 Hz, 1H), 4.16−4.00 (m, 2H), 3.91 (m, 2H), 3.21 (m, 1H), 2.91 (m, 1H), 2.52 (m, 1H), 2.40 (m, 1H), 2.31 (s, 3H), 1.95 (s, 3H), 1.49−1.39 (m, 2H), 1.26−1.22 (m, 4H), 0.82 (t, J = 6.4 Hz, 3H), 0.62 (t, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.6, 170.1, 137.4, 132.7, 131.5, 129.5, 83.1, 80.9, 73.7, 61.4, 55.4, 54.2, 42.9, 27.9, 25.2, 24.1, 23.7, 21.0, 13.9, 9.1, 8.7. HRMS (ESI): m/z $[M + H]^+$ calculated for $[C_{23}H_{35}N_2O_6S]^+$ 467.2213, found 467.2216.

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Supporting Information Available: Experimental procedures and characterization data for compounds **2**, **3**, **5**−**7**, **9**, **10**, and **12**, and copies of ^1H NMR and ^{13}C NMR spectra of these compounds. This material is available free of charge via the Internet at http://pubs.acs.org.