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Enantioselective synthesis of oseltamivir phosphate

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ABSTRACT

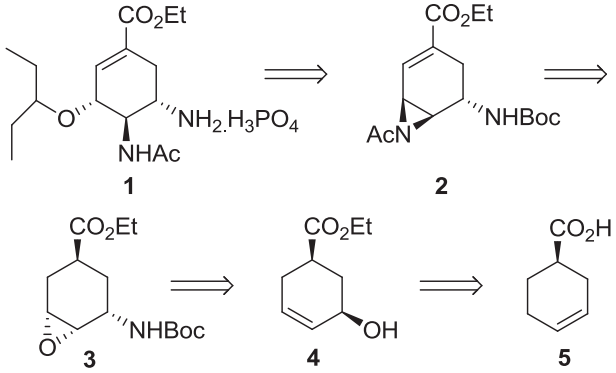
The key steps in the enantioselective synthesis of Tamiflu include an asymmetric Diels–Alder reaction, Mitsunobu inversion using Fukuyama modified Weinreb reagent, carbamate directed epoxidation. Epoxide opening with trimethylsilyl azide furnished a 3:1 mixture of regioisomers that converged to afford the same aziridine. Attempted preparation of the unsaturated ester regioselectively using 2-iodoxybenzoic acid (IBX) following Nicolaou's protocol failed. The unsaturated ester was prepared by phenylselenylation followed by selenoxide elimination.

1. Introduction

Oseltamivir phosphate (Tamiflu) **1**, is an approved orally effective neuraminidase inhibitor used for the treatment of human influenza[1] and H5N1 avian flu.[2] Numerous people have fallen victim to human influenza and H5N1 avian flu and it still continues to be a threat. A ready stock of Tamiflu is desirable to protect people from a future outbreak. Currently, Tamiflu is manufactured from (−)-shikimic acid or (−)-quinic acid,[3] however the limited availability of the chiral raw materials is a major drawback. This has propelled synthetic chemists worldwide to design alternate routes from non-natural readily available chemicals. Many interesting and ingenious laboratory scale syntheses,[3a,b,d,4] of which at least some can be adapted to commercial scale, have been reported. Herein we report an enantioselective synthesis of Tamiflu taking advantage of the Diels–Alder reaction.

2. Results and discussion

The retrosynthetic analysis is depicted in Scheme 1. The installation of the alkoxy group was envisaged by opening of the aziridine **2** towards the end of the synthesis. The aziridine **2** was envisioned to be obtained via regioselective opening of the epoxide **3**. The epoxide was traced down to allylic alcohol **4**, which is readily obtained from cyclohexene-3-carboxylic acid **5**.



Scheme 1. Retrosynthetic analysis of oseltamivir phospahate 1.

The synthesis began with (*R*)-cyclohexene carboxylic acid **5** (>99% ee) obtained readily in large scale by an asymmetric Diels–Alder reaction following a reported procedure.[5] Iodolactonization of **5** and dehydroiodination of **6** following Trost's protocol[6] yielded unsaturated lactone **7**, Scheme 2. Base catalyzed opening of **7** with ethanol furnished allylic alcohol **4**. The amino group at C5 (Tamiflu numbering) was introduced using the Fukuyama[7] modification of the Weinreb reagent[8] to furnish sulfonamide **8**.[9] Deprotection of the *p*-nosyl group under mild conditions using 2-thio ethanol[10] yielded allylic carbamate **9**. Stereoselective epoxidation directed by the carbamate moiety[11] furnished compound **3** as the sole product, Scheme 2.

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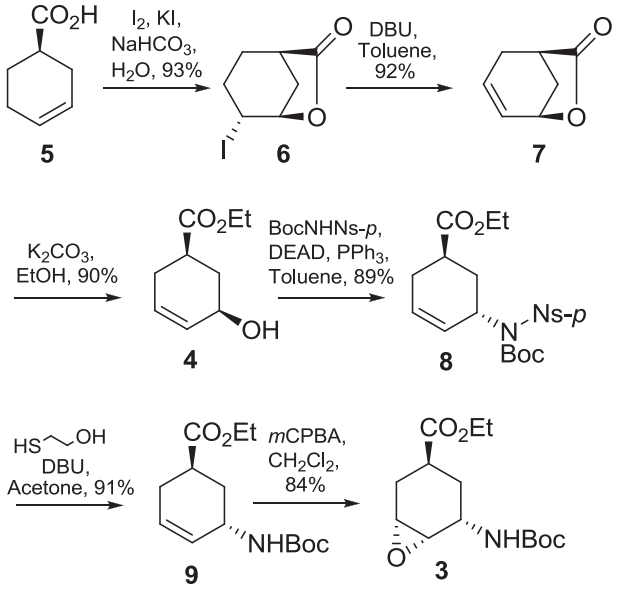
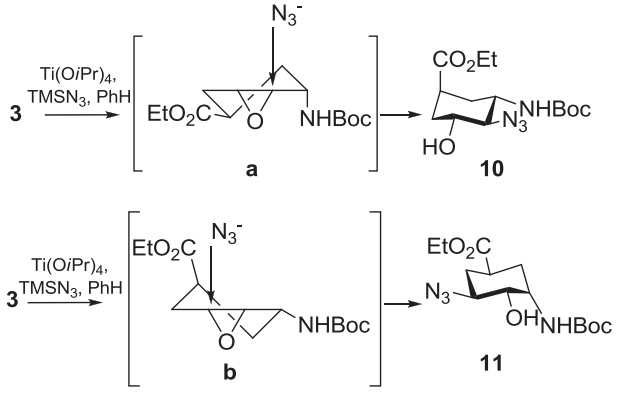


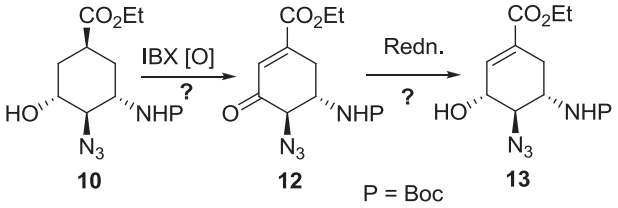
Scheme 2. Stereoselective preparation of epoxy carbamate **3**.

A regioselective opening of the epoxide at C3 was expected to furnish azido alcohol **10** via conformer '**a**'. The carboethoxy group was expected to preferentially occupy the equatorial position as in conformer '**a**' rather than the axial position as in '**b**' and selectively yield compound **10**. Treatment of **3** with ammonium azide in aq methanol[12] yielded a 2:1 mixture of azido alcohols **10** and **11**, respectively. Since epoxide opening was attempted at 60 °C, it is probable that compound **3** exists as conformer '**b**' too and thus leads to the formation of **11**. Exploring other reagents it was eventually found that with trimethylsilyl azide in the presence of Ti(O^iPr)$_4$,[13] the epoxide could be opened at 5 °C to rt. However, the ratio of **10** to **11** was only slightly better (3:1) under these conditions, Scheme 3.[14]



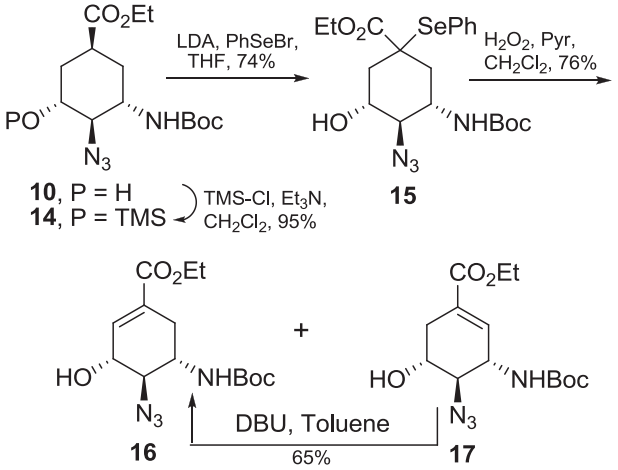
Scheme 3. Regioselective opening of epoxide **3**.

It remained to introduce the double bond and the aziridine ring in **10** to secure compound **2**. Toward this goal, the regioselective introduction of the double bond was envisaged using IBX oxidation of **10**, following Nicolaou's protocol,[15] to obtain **12** followed by a stereoselective reduction to **13**, Scheme 4. The expectation was not reduced to practice. Attempted direct oxidation of alcohol **10** with an excess of IBX or attempted dehydrogenation of the intermediate ketone with IBX led to a complex mixture of products even in the presence of 4-methoxypyridine *N*-oxide.[16]



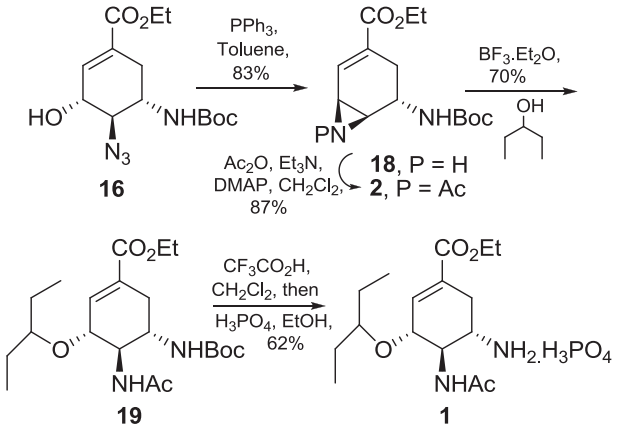
Scheme 4. Attempted preparation of unsaturated ketone **12**.

The double bond was introduced by selenoxide elimination. Protection of **10** as its trimethylsilyl ether **14** followed by treatment with excess of LDA and quenching with PhSeBr[17] yielded selenide **15**,[18] which suffered elimination on treatment with hydrogen peroxide in the presence of pyridine[17] to afford unsaturated esters **16** and **17** in a 1:1.5 ratio, respectively.[19,20] The unsaturated esters could be separated with difficulty and therefore the mixture was isomerized with DBU in toluene to furnish **16** in 65% yield, Scheme 5.[21]



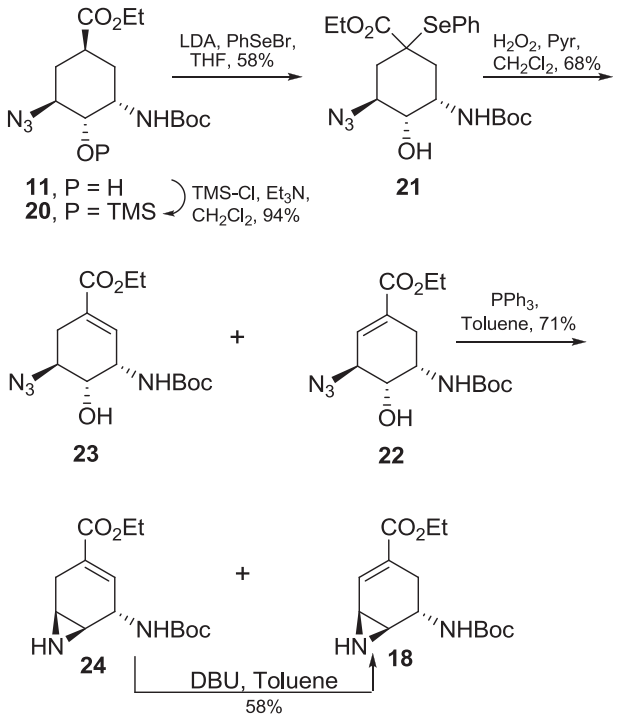
Scheme 5. Preparation of unsaturated ester **16**.

The azido alcohol **16** was readily converted to aziridine **18** by treatment with triphenylphosphine in toluene.[22] Acetylation furnished aziridine **2**, a known intermediate, which was converted to Tamiflu following reported conditions, Scheme 6.



Scheme 6. Stereoselective synthesis of tamiflu.

The regioisomeric azido alcohol **11** was transformed separately into aziridine **18** as depicted in Scheme 7. Protection of the hydroxy group as its silyl ether **20** followed by selenylation[23] and thermal elimination afforded a mixture of esters **22** and **23** in a 1:3 ratio, respectively, that proved difficult to separate. The mixture was subjected to treatment with triphenylphosphine to furnish aziridines **18** and **24** that could be readily separated. The latter was isomerized to **18** using DBU in toluene.[24]



Scheme 7. Stereoselective preparation of aziridine **18**.

3. Conclusion

In conclusion, we have achieved a new stereoselective synthesis of Tamiflu from cyclohexene carboxylic acid. The regioisomeric azido alcohols **10** and **11** converged to yield the same aziridine **18**. Attempts to introduce a double bond regioselectively using IBX as an oxidant following Nicolaou's protocol afforded a mixture of products. The regioisomeric unsaturated esters could be prepared by selenenylation followed by elimination of selenoxide to afford isomeric esters that were isomerized to the desired product. The overall yield was 4.31%.

4. Experimental

4.1. General remarks

All air or moisture sensitive reactions were carried out under nitrogen atmosphere. Solvents were distilled over Na/benzophenone ketyl for THF, over P_2O_5 followed by CaH_2 for DCM, and over P_2O_5 for toluene. Commercially available reagents were used without purification thin layer chromatography was performed on precoated silica gel plates. Column chromatography was carried out using silica gel (60–120 mesh). NMR spectra were recorded on a 200, 300 or 400 MHz spectrometer. ^{1}H and ^{13}C NMR samples were internally referenced to TMS (0.00 ppm). Melting points are uncorrected.

*4.1.1. (R)-Cyclohex-3-enecarboxylic acid [**5**].* Under nitrogen, acryloyl chloride (1.52 mL, 18.75 mmol) was added over 30 min period to a stirred cold (−24 °C) solution of (*S*)-(+)-pantolactone (1.95 g, 15 mmol) and triethylamine (4.15 mL, 30 mmol) in anhydrous dichloromethane (150 mL). After stirring at −24 °C for 6 h dicloromethane (100 mL) was added and the organic layer was successively washed with 1 N HCl, saturated $NaHCO_3$ solution, water, brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude compound that was purified by column chromatography (eluent 8% EtOAc/hexane) to afford the acrylate ester (2.4 g, 87%) as a colorless liquid. R_f (10% EtOAc/hexane) 0.3; δ_H (300 MHz, $CDCl_3$) 6.51 (dd, J=17.4, 1.3 Hz, 1H), 6.20 (dd, J=17.4, 10.4 Hz, 1H), 5.96 (dd, J=10.4, 1.3 Hz, 1H), 5.40 (s, 1H), 4.03 (s, 2H), 1.21 (s, 3H), 1.11 (s, 3H). To a cold (−20 °C) solution of an excess of butadiene (3.54 mL) in a mixture of dichloromethane and hexane (7:1, 10 mL) was added a solution of the acrylate (1.84 g, 10 mmol) in a mixture of dichloromethane and hexane (7:1, 10 mL). A solution of $TiCl_4$ (1 mL, 1 M/petroleum ether) was added to the above mixture and stirred for 48 h at −20 °C. The reaction was quenched by addition of finely pulverized $Na_2CO_3 \cdot 10H_2O$ (1.2 g). The temperature was allowed to rise to rt when solid pellets formed. Filtration followed by evaporation of the filtrate afforded the crude compound that was purified by column chromatography (eluent 10% EtOAc/hexane) to afford the Diels–Alder adduct (1.71 g, 72%) as a solid. Mp 37–38 °C; R_f (20% EtOAc/hexane) 0.3; $[\alpha]_D^{25}$ +38 (*c* 1, $CHCl_3$); ν_{max} (KBr) 2966, 2927, 1791, 1745, 1152, 1096 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.74–5.59 (m, 2H), 5.32 (s, 1H), 3.99 (s, 2H), 2.77–2.64 (m, 1H), 2.35–2.25 (m, 2H), 2.17–2.00 (m, 3H), 1.84–1.66 (m, 1H), 1.18 (s, 3H), 1.08 (s, 3H); δ_C (75 MHz, $CDCl_3$) 173.6, 171.8, 126.2, 124.1, 75.3, 74.0, 39.5, 38.2, 26.8, 24.1, 23.4, 22.0, 19.1; *m*/*z* (MS-ESI) 239 $[M+H]^+$. A mixture of the Diels–Alder adduct (1.71 g, 7.2 mmol) and LiOH.H_2O (0.81 g, 21.7 mmol) in THF/water (5:4 38 mL) was vigorously stirred at rt for 26 h. THF was removed in vacuo, the aq solution acidified to pH 2 and extracted with *n*-pentane/DCM (98:2). After drying the organic layer over Na_2SO_4, the solvent was evaporated under reduced pressure. The residue was purified through column chromatography (eluent 15% EtOAc/hexane) to afford the acid **5** (0.86 g, 94%) as a viscous liquid. R_f (15% EtOAc/hexane) 0.3; $[\alpha]_D^{25}$ +93.7 (*c* 1, MeOH); (Reported $[\alpha]_D^{22}$ +95 (*c* 7, MeOH)); ν_{max} (KBr) 2968, 2932, 1720, 1624, 1224, 802 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.80–5.60 (m, 2H), 2.67–2.51 (m, 1H), 2.37–2.22 (m, 2H), 2.21–1.97 (m, 3H), 1.80–1.61 (m, 1H); δ_C NMR (75 MHz, $CDCl_3$): δ 182.5, 126.6, 124.9, 39.1, 27.1, 24.7, 24.2; *m*/*z* (MS-ESI) 149 $[M+Na]^+$.

*4.1.2. (1R,4R,5R)-4-Iodo-6-oxa-bicyclo[3.2.1]octane-7-one [**6**].* The acid **5** (0.86 g, 6.8 mmol) was added to a solution of $NaHCO_3$ (1.7 g, 20.4 mmol) in water (18 mL) and the mixture stirred until it became homogenous. The flask was then protected from light and the mixture was treated in one portion with a solution of a mixture of KI (6.7 g, 40.8 mmol) and iodine (1.81 g, 7.14 mmol) in water (18 mL). The reaction mixture was stirred at rt for 20 h and then extracted with $CHCl_3$ thrice. The combined organic extracts were washed successively with 10% aq $Na_2S_2O_3$, 10% aq $NaHCO_3$, water, and then dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude compound that was purified by column chromatography (eluent 10% EtOAc/hexane) to afford the iodolactone **6** (1.6 g, 93%) as a yellow solid. Mp 135–136 °C; $[\alpha]_D^{25}$ +37.2 (*c* 1, $CHCl_3$); (Reported $[\alpha]_D^{24}$ +37.6 (*c* 2.03, $CHCl_3$));[6] ν_{max} (KBr) 2961, 2926, 1773, 1262, 1105, 1078, 802 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.77 (t, J=5.4 Hz, 1H), 4.48 (t, J=4.3 Hz, 1H), 2.76 (d, J=12.3 Hz, 1H), 2.66–2.57 (m, 1H), 2.51–2.29 (m, 2H), 2.09 (dd, J=16.6, 4.3 Hz, 1H), 1.95–1.74 (m, 2H); δ_C (75 MHz, $CDCl_3$) 177.4, 79.8, 38.3, 34.2, 29.4, 23.8, 22.8; *m*/*z* (MS-ESI) 275 $[M+Na]^+$.

*4.1.3. (1R,5R)-6-Oxabicyclo[3.2.1]oct-3-en-7-one [**7**].* The above iodolactone **6** (1.6 g, 6.32 mmol) was dissolved in dry toluene (19 mL) containing freshly distilled 1,8-diazabicyclo[5.4.0]undec-7-ene

(DBU) (1.44 g, 9.48 mmol) and the reaction mixture was heated at reflux for 6 h, cooled, filtered, and filtrate was concentrated under reduced pressure. The residue was purified through column chromatography (eluent 10% EtOAc/hexane) to afford the unsaturated lactone **7** (0.72 g, 92%) as a pale yellow liquid. R_f (15% EtOAc/hexane) 0.3; $[\alpha]_D^{25}$ +178.7 (*c* 1, $CHCl_3$); (Reported $[\alpha]_D^{23}$ +179.2 (*c* 9.76, $CHCl_3$));[6] ν_{max} (KBr) 2964, 2932, 1776, 1612, 1105, 802 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.28–6.17 (m, 1H), 5.88–5.78 (m, 1H), 4.73 (t, *J*=5.4 Hz, 1H), 2.92–2.83 (m, 1H), 2.53–2.41 (m, 3H), 2.07 (d, *J*=11.1 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 179.3, 130.2, 129.2, 73.2, 37.9, 34.3, 29.0; *m*/*z* (MS-ESI) 147 $[M+Na]^+$.

*4.1.4. (1R,5R)-Ethyl-5-hydroxycyclohex-3-enecarboxylate [**4**].* To a stirred solution of the unsaturated lactone **7** (0.72 g, 5.81 mmol) in ethanol (12 mL) was added K_2CO_3 (160 mg, 1.16 mmol) at rt and the mixture stirred at the same temperature for 5 h. The reaction mixture was filtered through a Celite pad. Removal of ethanol under reduced pressure afforded the crude product that was purified by column chromatography (eluent 20% EtOAc/hexane) to afford the allylic alcohol **4** (0.89 g, 90%) as a yellow liquid. R_f (22% EtOAc/hexane) 0.3; $[\alpha]_D^{25}$ +37 (*c* 1, $CHCl_3$); ν_{max} (KBr) 3422, 2923, 2852, 1728, 1303, 1246, 1179, 1028 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.73–5.60 (m, 2H), 4.21–4.12 (m, 1H), 4.07 (q, *J*=7.5 Hz, 2H), 2.66–2.52 (m, 1H), 2.24–2.10 (m, 3H), 1.74–1.58 (m, 1H), 1.21 (t, *J*=7.5 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 174.9, 130.9, 126.2, 65.9, 60.4, 38.0, 34.0, 27.2, 13.8; *m*/*z* (MS-ESI) 193 $[M+Na]^+$; HRMS(ESI) calcd for $C_9H_{14}O_3Na$ $[M+Na]^+$ 193.0847, found 193.0840.

*4.1.5. (1R,5S)-Ethyl-5-(N-(tert-butoxycarbonyl)-4-nitrophenylsulfonamido)cyclohex-3-enecarboxylate [**8**].* A mixture of allylic alcohol **4** (0.89 g, 5.23 mmol), triphenylphosphine (1.37 g, 5.23 mmol), BocNHNS-*p* (1.54 g, 5.23 mmol) was dissolved in toluene (26 mL). The solution was cooled at −20 °C, diethyl azodicarboxylate (0.89 mL, 5.23 mmol) was added dropwise over 10 min and stirred further at the same temperature for 6 h. Removal of toluene under reduced pressure afforded a residue that was purified by column chromatography (eluent 15% EtOAc/hexane) to afford sulfonamide **8** (2.11 g, 89%) as a pale yellow solid. Mp 113–114 °C; R_f (20% EtOAc/hexane) 0.3; $[\alpha]_D^{25}$ −39 (*c* 1, $CHCl_3$); ν_{max} (KBr) 2980, 2924, 1729, 1532, 1356, 1149, 741 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.35 (d, *J*=8.8 Hz, 2H), 8.10 (d, *J*=8.8 Hz, 2H), 5.81–5.71 (m, 1H), 5.54–5.43 (m, 1H), 5.25–5.12 (m, 1H), 4.30–4.08 (m, 2H), 2.99–2.90 (m, 1H), 2.51–2.22 (m, 4H), 1.37 (s, 9H), 1.31 (t, *J*=6.9 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 174.0, 150.0, 149.9, 145.9, 128.9, 127.1, 127.0, 123.8, 84.9, 60.6, 53.4, 37.5, 29.4, 27.6, 25.3, 13.9; *m*/*z* (MS-ESI) 477 $[M+Na]^+$; HRMS(ESI) calcd for $C_{20}H_{26}O_8N_2NaS$ $[M+Na]^+$ 477.1321, found 477.1307.

*4.1.6. (1R,5S)-Ethyl-5-(tert-butoxycarbonylamino)cyclohex-3-enecarboxylate [**9**].* To a stirred solution of sulfonamide **8** (2.11 g, 4.65 mmol) in acetone (14 mL) was added DBU (1.4 mL, 9.3 mmol) followed by 2-mercapto ethanol (0.64 mL, 9.3 mmol). The reaction mixture was stirred for 3 h at rt. Acetone was distilled off under reduced pressure, the resulting residue was purified by column chromatograohy (eluent 12% EtOAc/hexane) to afford the carbamate **9** (1.13 g, 91%) as a white solid. Mp 77–78 °C; R_f (18% EtOAc/hexane) 0.3; $[\alpha]_D^{25}$ −101.5 (*c* 1, $CHCl_3$); ν_{max} (KBr) 3365, 2974, 2927, 1714, 1518, 1247, 1169, 1055, 1027 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.63 (d, *J*=9.8 Hz, 1H), 5.46 (dd, *J*=9.8, 4.1 Hz, 1H), 4.93 (d, *J*=5.8 Hz, 1H), 4.08–3.97 (m, 1H), 3.92 (q, *J*=7.2 Hz, 2H), 2.50–2.29 (m, 1H), 2.15–1.76 (m, 3H), 1.58 (td, *J*=13.0, 4.9 Hz, 1H), 1.22 (s, 9H), 1.03 (t, *J*=7.2 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 174.6, 154.5, 128.4, 126.1, 78.5, 59.9, 43.6, 34.8, 31.4, 27.9, 26.9, 13.9; *m*/*z* (MS-ESI) 292 $[M+Na]^+$; HRMS(ESI) calcd for $C_{14}H_{23}NO_4Na$ $[M+Na]^+$ 292.1533, found 292.1524.

*4.1.7. (1R,3S,5S,6S)-Ethyl-5-(tert-butoxycarbonylamino)-7-oxabicyclo[4.1.0]heptane-3-carboxylate [**3**].* To a solution of carbamate **9** (1.13 g, 4.23 mmol) in CH_2Cl_2 (21 mL), *m*CPBA (0.81 g, 4.65 mmol) was added at 0 °C. After stirring for 6 h, CH_2Cl_2 (10 mL) was added and the organic layer washed successively with aq saturated $NaHCO_3$ solution, water, brine, dried over Na_2SO_4, and filtered. Concentration under reduced pressure, afforded the crude product that was purified through column chromatography (eluent 15% EtOAc/hexane) to afford the epoxy ester **3** (1.01 g, 84%) as a white solid. Mp 101–102 °C; R_f (20% EtOAc/hexane) 0.3; $[\alpha]_D^{25}$ −43.5 (*c* 1, $CHCl_3$); ν_{max} (KBr) 3365, 2978, 2931, 1714, 1507, 1367, 1244, 1171, 1051 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.03 (d, *J*=8.1 Hz, 1H), 4.21–4.12 (m, 1H), 4.08 (q, *J*=7.2 Hz, 2H), 3.36–3.29 (m, 1H), 3.24 (t, *J*=3.7 Hz, 1H), 2.57–2.43 (m, 1H), 2.17 (dd, *J*=15.2, 4.5 Hz, 1H), 2.01–1.87 (m, 1H), 1.77–1.53 (m, 2H), 1.39 (s, 9H), 1.20 (t, *J*=7.2 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 174.5, 155.0, 79.4, 60.6, 53.9, 53.1, 43.7, 33.7, 30.3, 28.3, 26.3, 14.1; *m*/*z* (MS-ESI) 308 $[M+Na]^+$; HRMS(ESI) calcd for $C_{14}H_{23}NO_5Na$ $[M+Na]^+$ 308.1471, found 308.1473.

*4.1.8. (1S,3S,4R,5R)-Ethyl-4-azido-3-(tert-butoxycarbonylamino)-5-hydroxycyclohexanecarboxylate [**10**] and (1S,3S,4S,5S)-ethyl-3-azido-5-(tert-butoxycarbonylamino)-4-hydroxycyclohexanecarboxylate [**11**].* To a stirred solution of epoxy ester **3** (584 mg, 1.78 mmol) in anhydrous benzene (10 mL) cooled at 5 °C was added $TMSN_3$ (0.81 mL, 6.15 mmol), followed by $Ti(O^iPr)_4$ (0.73 mL, 2.46 mmol). The reaction mixture was stirred for 2 h gradually allowing the temperature to rise to rt. The reaction mixture was diluted with diethyl ether (10 mL) followed by addition of 5% H_2SO_4 (5 mL). The reaction mixture was stirred vigorously for 1 h. The layers were separated and the aq layer extracted with diethyl ether twice. The combined organic layers were washed successively with aq saturated $NaHCO_3$, water, brine, dried over Na_2SO_4, filtered, and concentrated to furnish the crude product. The crude product was purified by column chromatography (eluent 20% EtOAc/hexane) to afford the regioisomeric azido alcohols **10** and **11** in a 3:1 ratio, respectively, in 86% yield.

Compound **10**. White solid; mp 126–127 °C; R_f (30% EtOAc/hexane) 0.3; $[\alpha]_D^{25}$ −37 (*c* 1, $CHCl_3$); ν_{max} (KBr) 3352, 2981, 2107, 1723, 1689, 1531, 1203, 1171, 1019 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.39–5.19 (m, 1H), 4.11 (q, *J*=7.2 Hz, 2H), 3.84–3.59 (m, 2H), 3.44–3.25 (m, 1H), 2.85–2.75 (m, 1H), 2.32–2.07 (m, 2H), 1.81–1.57 (m, 2H), 1.42 (s, 9H), 1.23 (t, *J*=7.2 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 174.1, 155.1, 79.8, 69.0, 68.1, 60.9, 49.6, 35.7, 32.5, 31.2, 28.3, 14.1; *m*/*z* (MS-ESI) 351 $[M+Na]^+$; HRMS(ESI) calcd for $C_{14}H_{24}N_4O_5Na$ $[M+Na]^+$ 351.1635, found 351.1644.

Compound **11**. White solid; mp 125–126 °C; R_f (30% EtOAc/hexane) 0.4; $[\alpha]_D^{25}$ −44 (*c* 1, $CHCl_3$); ν_{max} (KBr) 3352, 2981, 2107, 1725, 1683, 1206, 1171, 1019 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.14–4.90 (m, 1H), 4.11 (q, *J*=7.2 Hz, 2H), 4.05–3.95 (m, 1H), 3.93–3.75 (m, 1H), 3.64–3.49 (m, 1H), 2.68–2.50 (m, 1H), 2.25–2.06 (m, 2H), 1.77–1.52 (m, 2H), 1.43 (s, 9H), 1.25 (t, *J*=7.2 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 174.1, 157.2, 80.7, 73.5, 69.4, 61.2, 50.6, 36.6, 31.5, 30.9, 28.7, 14.4.

*4.1.9. (1S,3S,4R,5R)-Ethyl-4-azido-3-(tert-butoxycarbonylamino)-5-(trimethylsilyloxy)cyclohexanecarboxylate [**14**].* To a solution of azido alcohol **10** (432 mg, 1.32 mmol) in CH_2Cl_2 (6.6 mL) Et_3N (0.36 mL, 2.65 mmol) followed by TMS–Cl (0.17 mL, 1.32 mmol) were added at 0 °C. After 30 min the reaction mixture was diluted with CH_2Cl_2 (5 mL), washed with with water, brine, and dried over Na_2SO_4. Filtration and concentration furnished the crude product that was purified by column chromatography (eluent 10% EtOAc/hexane) to afford the silyl ether **14** (500 mg, 95%) as a white solid. Mp 117–118 °C; R_f (10% EtOAc/hexane) 0.3; $[\alpha]_D^{25}$ −50 (*c* 1, $CHCl_3$); ν_{max} (KBr) 3361, 2968, 2104, 1723, 1523, 1253, 1172, 844 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.32–5.08 (m, 1H), 4.14 (q, *J*=6.9 Hz, 2H), 3.90–3.77 (m, 1H), 3.73–3.55 (m, 1H), 3.38–3.27 (m, 1H), 2.83–2.70 (m, 1H), 2.22–2.01 (m, 2H), 1.78–1.57 (m, 2H), 1.44 (s,

9H), 1.25 (t, J=6.9 Hz, 3H), 0.16 (s, 9H); δ_C (75 MHz, $CDCl_3$) 174.1, 154.9, 79.5, 70.3, 66.6, 60.8, 48.8, 35.0, 32.8, 30.7, 28.3, 14.2, −0.2; m/z (MS-ESI) 423 $[M+Na]^+$; HRMS(ESI) calcd for $C_{17}H_{32}N_4O_5NaSi$ $[M+Na]^+$ 423.2033, found 423.2039.

*4.1.10. (1S,3S,4S,5S)-Ethyl-3-azido-5-(tert-butoxycarbonylamino)-4-(trimethylsilyloxy)cyclohexanecarboxylate [**20**].* The silyl ether **20** was prepared following the procedure detailed above for the preparation of **14**. The crude product was purified through column chromatography (eluent 8% EtOAc/hexane) to afford the compound **20** (166 mg, 94%) as a white solid. Mp 116–117 °C; R_f (8% EtOAc/hexane) 0.3; $[\alpha]_D^{25}$ −58 (c 1, $CHCl_3$); ν_{max} (KBr) 3361, 2968, 2104, 1723, 1523, 1253, 1172, 844 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.59 (d, J=4.7 Hz, 1H), 4.13 (q, J=7.2 Hz, 2H), 3.90–3.82 (m, 1H), 3.60 (dd, J=8.7, 4.3 Hz, 1H), 3.42 (td, J=10.7, 4.3 Hz, 1H), 2.62–2.49 (m, 1H), 2.36–2.23 (m, 1H), 2.19–2.06 (m, 1H), 1.70–1.50 (m, 2H), 1.46 (s, 9H), 1.27 (t, J=7.2 Hz, 3H), 0.18 (s, 9H); δ_C (75 MHz, $CDCl_3$) 173.8, 155.9, 79.6, 73.9, 61.4, 60.7, 50.8, 36.0, 31.4, 30.4, 28.3, 14.1, −0.1.

*4.1.11. (3S,4R,5R)-Ethyl-4-azido-3-(tert-butoxycarbonylamino)-5-hydroxy-1-(phenylselanyl)cyclohexanecarboxylate [**15**].* To a solution of diisopropylamine (0.43 mL, 3.13 mmol) in THF (7.5 mL) was added n-BuLi (1.25 mL, 2.5 M/hexanes) at 0 °C under nitrogen. The reaction mixture was stirred at same temperature for 15 min, then cooled to −78 °C. A solution of silyl ether **14** (500 mg, 1.25 mmol) in THF (2 mL) was added dropwise and the reaction mixture stirred for 45 min at the same temperature. To a solution of diphenyl diselenide (0.49 g, 1.56 mmol) in THF (3 mL) in another round bottomed flask was added bromine (0.08 mL, 1.56 mmol) while vigorously stirring at rt. After 10 min the resultant phenyl selenyl bromide was transferred via canula to the enolate solution at −78 °C. Immediately decolourisation was observed. After stirring for 30 min at −78 °C the reaction mixture was poured into an aq solution of 1 N HCl (50 mL) and 50% ether:pentane mixture(50 mL). This was stirred for 30 min. The layers were separated and the aq layer extracted with ether, the combined organic extracts were successively washed with water, aq saturated $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated to furnish the crude product. The crude product was purified by column chromatography (eluent 15% EtOAc/hexane) to afford the selenyl compound **15** (448 mg, 74%) as a gummy liquid. R_f (22% EtOAc/hexane) 0.3; $[\alpha]_D^{25}$ −48 (c 1, $CHCl_3$); ν_{max} (KBr) 3366, 2975, 2930, 2104, 1697, 1521, 1259, 1171, 1021, 744 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.55 (d, J=6.9 Hz, 2H), 7.42 (t, J=6.9 Hz, 1H), 7.32 (t, J=6.9 Hz, 2H), 4.62 (d, J=7.9 Hz, 1H), 4.17–4.03 (m, 2H), 3.41–3.13 (m, 3H), 2.61–2.48 (m, 2H), 1.95–1.78 (m, 1H), 1.78–1.61 (m, 1H), 1.44 (s, 9H), 1.20 (t, J=7.2 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 171.1, 154.9, 137.9, 129.7, 128.9, 125.8, 80.0, 70.1, 69.9, 61.5, 51.0, 45.1, 40.8, 39.6, 28.2, 13.8; m/z (MS-ESI) 507 $[M+Na]^+$; HRMS(ESI) calcd for $C_{20}H_{28}N_4O_5NaSe$ $[M+Na]^+$ 507.1114, found 507.1122.

*4.1.12. (3S,4S,5S)-Ethyl-3-azido-5-(tert-butoxycarbonylamino)-4-hydroxy-1-(phenylselanyl)cyclohexanecarboxylate [**21**].* The compound **21** was prepared from **20** following the procedure detailed above for the preparation of **15**. The crude product was purified by column chromatography (eluent 15% EtOAc/hexane) to afford the compound **21** (116 mg, 58%) as a gummy liquid. R_f (18% EtOAc/hexane) 0.3; $[\alpha]_D^{25}$ −39 (c 1, $CHCl_3$); ν_{max} (KBr) 3366, 2975, 2930, 2104, 1697, 1521, 1259, 1171, 1021, 744 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.48 (d, J=6.8 Hz, 2H), 7.35 (t, J=6.8 Hz, 1H), 7.25 (t, J=6.9 Hz, 2H), 5.21–5.12 (m, 1H), 4.13–3.90 (m, 3H), 3.52 (dd, J=9.8, 4.5 Hz, 1H), 3.44–3.28 (m, 1H), 2.60–2.42 (m, 2H), 1.94–1.83 (m, 1H), 1.69–1.53 (m, 1H), 1.36 (s, 9H), 1.20 (t, J=7.5 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 171.4, 151.5, 137.9, 129.4, 129.1, 124.7, 80.4, 74.9, 62.7, 59.5, 50.3, 47.6, 40.0, 38.9, 28.0, 13.9.

*4.1.13. (3S,4R,5S)-Ethyl-4-azido-5-(tert-butoxycarbonylamino)-3-hydroxycyclohex-1-enecarboxylate [**16**] and (3S,4R,5R)-ethyl-4-azido-3-(tert-butoxycarbonylamino)-5-hydroxycyclohex-1-enecarboxylate [**17**].* To a stirred solution of compound **15** (300 mg, 0.62 mmol) in CH_2Cl_2 (3 mL) was added pyridine (0.13 mL, 1.48 mmol), followed by 30% H_2O_2 (0.21 g, 1.8 mmol) at rt. After 30 min the reaction mixture was diluted with CH_2Cl_2 (6 mL) washed with aq 10% Na_2CO_3 solution, water, 10% HCl solution, brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure to furnish the crude product, that was purified by column chromatography (eluent 20% EtOAc/hexane) to afford an inseparable mixture of unsaturated esters **16** and **17** in a 2:3 ratio, respectively (152 mg, 76%). R_f (23% EtOAc/hexane) 0.3; δ_H (300 MHz, $CDCl_3$) 6.78–6.72 (m, 1H), 6.69–6.61 (m, 1H), 4.99 (d, J=7.9 Hz, 1H), 4.65–4.27 (m, 2H), 4.19 (q, J=7.2 Hz, 3H), 3.90–3.70 (m, 2H), 3.59–3.46 (m, 2H), 2.93–2.75 (m, 2H), 2.42–2.24 (m, 2H), 1.47 (s, 18H), 1.28 (t, J=7.2 Hz, 6H).

*4.1.14. (3S,4R,5S)-Ethyl-4-azido-5-(tert-butoxycarbonylamino)-3-hydroxycyclohex-1-enecarboxylate [**16**].* To a solution of the mixture of unsaturated esters **16** and **17** (152 mg, 0.47 mmol) in toluene (3.1 mL) was added DBU (20 μL, 0.09 mmol) at rt. After 24 h of stirring at rt, toluene was removed under reduced pressure and the residue was purified by column chromatography (eluent 20% EtOAc/hexane) to afford the unsaturated ester **16** (97 mg, 65%) as a white solid. Mp 133–134 °C; 10% of aromatized compound was observed; R_f (23% EtOAc/hexane) 0.3; $[\alpha]_D^{25}$ −59 (c 1, $CHCl_3$); ν_{max} (KBr) 3361, 2929, 2856, 2106, 1697, 1529, 1368, 1254, 1165, 703 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.77–6.65 (m, 1H), 4.95–4.81 (m, 1H), 4.33–4.25 (m, 1H), 4.19 (q, J=7.2 Hz, 2H), 3.78–3.64 (m, 1H), 3.51 (dd, J=10.5, 7.9 Hz, 1H), 2.82 (dd, J=18.1, 5.2 Hz, 1H), 2.41–2.25 (m, 1H), 1.46 (s, 9H), 1.30 (t, J=7.2 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 165.8, 155.4, 138.1, 129.1, 80.2, 70.8, 67.3, 61.2, 49.2, 30.9, 28.3, 14.1; m/z (MS-ESI) 349 $[M+Na]^+$; HRMS(ESI) calcd for $C_{14}H_{22}N_4O_5Na$ $[M+Na]^+$ 349.1483, found 349.1487.

*4.1.15. (3S,4S,5S)-Ethyl-3-azido-5-(tert-butoxycarbonylamino)-4-hydroxycyclohex-1-enecarboxylate [**22**] and (3S,4S,5S)-ethyl-5-azido-3-(tert-butoxycarbonylamino)-4-hydroxycyclohex-1-enecarboxylate [**23**].* The compound **22** and **23** were prepared from **21** following the procedure detailed above for the preparation of **16** and **17**. The crude product was purified by column chromatography (eluent 18% EtOAc/hexane) to afford an inseparable mixture of unsaturated esters **22** and **23** in a 1:3 ratio, respectively (52 mg, 68%). R_f (21% EtOAc/hexane) 0.3; δ_H (300 MHz, $CDCl_3$) 6.77–6.68 (m, 1H), 6.66–6.59 (m, 1H), 5.02–4.88 (m, 2H), 4.33–4.16 (m, 4H), 4.12–4.00 (m, 2H), 3.99–3.86 (m, 2H), 3.63–3.45 (m, 2H), 2.85–2.63 (m, 1H), 2.60–2.40 (m, 1H), 2.39–2.18 (m, 1H), 2.10–1.92 (m, 1H), 1.46 (s, 18H), 1.31 (t, J=7.2 Hz, 6H).

*4.1.16. (1S,5S,6R)-Ethyl-5-(tert-butoxycarbonylamino)-7-azabicyclo[4.1.0]hept-2-ene-3-carboxylate [**18**].* To a solution of azido alcohol **16** (97 mg, 0.3 mmol) in toluene (3 mL) was added triphenylphosphine (79 mg, 0.3 mmol) at rt and the reaction mixture was refluxed for 3 h. After removal of the solvent under reduced pressure, ether (5 mL) was added, and the mixture cooled to 0 °C. The precipitated triphenylphosphine oxide was removed by decantation and the filtrate evaporated. This procedure was repeated twice to remove any traces of triphenylphosphine oxide. The residue obtained after removal of ether was purified by column chromatography (eluent 40% EtOAc/hexane) to afford aziridine **18** (70 mg, 83%) as a gummy liquid. R_f (50% EtOAc/hexane) 0.3; $[\alpha]_D^{25}$ −44.9 (c 1, $CHCl_3$); ν_{max} (KBr) 3259, 2977, 2929, 1706, 1437, 1176, 1119, 722 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.25–7.13 (m, 1H), 4.52–4.32 (m, 2H), 4.17 (q, J=6.8 Hz, 2H), 2.89–2.70 (m, 1H), 2.68–2.47 (m, 2H), 2.44–2.24 (m, 1H), 1.42 (s, 9H), 1.28 (t, J=6.8 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 166.6, 155.0, 137.6, 132.9, 79.4, 60.5, 42.7, 36.8, 28.2, 26.3, 25.4, 14.0; m/z (MS-ESI)

305 $[M+Na]^+$; HRMS(ESI) calcd for $C_{14}H_{22}N_2O_4Na$ $[M+Na]^+$ 305.1604, found 305.1610.

*4.1.17. (1S,5S,6S)-Ethyl-5-(tert-butoxycarbonylamino)-7-azabicyclo [4.1.0]hept-3-ene-3-carboxylate [**24**].* The inseparable mixture of azido alcohols **22** and **23** upon treatment with triphenylphosphine as detailed above for the preparation of **18** yielded a separable mixture of compounds **18** and **24**. The crude product was purified by column chromatography (eluent 40% EtOAc/hexane) to afford initially compound **18** and then compound **24** (23 mg, 71%) isolated yield as a gummy liquid. R_f (60% EtOAc/hexane) 0.3; $[\alpha]_D^{25}$ −38 (*c* 1, $CHCl_3$); ν_{max} (KBr) 3259, 2977, 2929, 1706, 1437, 1176, 1119, 722 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.74–6.64 (m, 1H), 4.70–4.59 (m, 1H), 4.56–4.47 (m, 1H), 4.16 (q, *J*=6.8 Hz, 2H), 2.91–2.79 (m, 1H), 2.54–2.33 (m, 3H), 1.45 (s, 9H), 1.28 (t, *J*=6.8 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 166.6, 155.1, 139.2, 132.8, 79.9, 60.7, 45.4, 37.2, 28.3, 24.1, 22.6, 14.1.

*4.1.18. Compound **18** from **24**.* To a solution of the aziridine **24** (23 mg, 0.08 mmol) in toluene (1 mL) was added DBU (5 μL, 0.02 mmol) at rt. After 24 h of stirring at rt, toluene was removed under reduced pressure and the residue was purified by column chromatography (eluent 40% EtOAc/hexane) to afford aziridine **18** (13 mg, 58%) as a gummy liquid. 15% of aromatized compound observed; R_f (50% EtOAc/hexane) 0.3; $[\alpha]_D^{25}$ −44.9 (*c* 1, $CHCl_3$); ν_{max} (KBr) 3259, 2977, 2929, 1706, 1437, 1176, 1119, 722 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.25–7.13 (m, 1H), 4.52–4.32 (m, 2H), 4.17 (q, *J*=6.8 Hz, 2H), 2.89–2.70 (m, 1H), 2.68–2.47 (m, 2H), 2.44–2.24 (m, 1H), 1.42 (s, 9H), 1.28 (t, *J*=6.8 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 166.6, 155.0, 137.6, 132.9, 79.4, 60.5, 42.7, 36.8, 28.2, 26.3, 25.4, 14.0.

*4.1.19. (1S,5S,6R)-Ethyl-7-acetyl-5-(tert-butoxycarbonylamino)-7-azabicyclo[4.1.0]hept-2-ene-3-carboxylate [**2**].* To a solution of the aziridine **18** (70 mg, 0.25 mmol) in anhydrous CH_2Cl_2 (1.25 mL) cooled at 0 °C were added Et_3N (67 μL, 0.5 mmol), DMAP (1 mg), and acetic anhydride (28 μL, 0.28 mmol) successively and the mixture was stirred for 30 min at ambient temperature. The reaction mixture was diluted with CH_2Cl_2 (3 mL) and washed with 10% aq citric acid solution, water, brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the crude product, which was purified by column chromatography (eluent 1% Et_3N, 19% EtOAc, 80% hexane) to afford **2** (71 mg, 87%) as a pale yellow liquid. R_f (30% EtOAc/hexane) 0.3; $[\alpha]_D^{25}$ −101.2 (*c* 1, $CHCl_3$); (Reported $[\alpha]_D^{29}$ −102.4 (*c* 0.92, $CHCl_3$));[4q] ν_{max} (KBr) 3346, 2977, 2927, 1708, 1524, 1367, 1253, 1169 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.23–7.14 (m, 1H), 4.58–4.47 (m, 1H), 4.41 (d, *J*=8.3 Hz, 1H), 4.20 (q, *J*=7.5 Hz, 2H), 3.15–3.03 (m, 2H), 2.79–2.67 (m, 1H), 2.42–2.28 (m, 1H), 2.14 (s, 3H), 1.43 (s, 9H), 1.31 (t, *J*=7.5 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 181.2, 165.7, 154.9, 133.6, 130.2, 79.9, 60.9, 41.9, 40.9, 31.8, 28.2, 26.6, 23.0, 14.1; *m*/*z* (MS-ESI) 325 $[M+H]^+$; HRMS(ESI) calcd for $C_{16}H_{25}N_2O_5$ $[M+H]^+$ 325.1772, found 325.1763.

*4.1.20. (3R,4R,5S)-Ethyl-4-acetamido-5-(tert-butoxycarbonylamino)-3-(pentan-3-yloxy)cyclohex-1-enecarboxylate [**19**].* To a stirred solution of **2** (71 mg, 0.22 mmol) in 3-pentanol (4.2 mL), a solution of $BF_3 \cdot Et_2O$ in 3-pentanol (1 M, 0.32 mL, 0.32 mmol) was added at −20 °C. After 30 min, the reaction was diluted with EtOAc and quenched with saturated $NaHCO_3$ solution. The aq layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. After removal of the solvent under reduced pressure the crude product was purified through column chromatography (eluent 40% EtOAc/hexane) to afford **19** (62 mg, 70%) as a colorless solid. Mp 139–140 °C; R_f (50% EtOAc/hexane) 0.3; $[\alpha]_D^{25}$ −95.8 (*c* 1, $CHCl_3$); (Reported $[\alpha]_D^{29}$ −97.1 (*c* 0.92, $CHCl_3$));[4q] ν_{max} (KBr) 3422, 2925, 1715, 1688, 1658, 1248 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.74 (m, 1H), 6.17 (d, *J*=8.1 Hz, 1H), 5.30 (d, *J*=9.5 Hz, 1H), 4.19 (q, *J*=7.3 Hz, 2H), 4.07–3.94 (m, 2H), 3.80–3.68 (m, 1H), 3.40–3.31 (m, 1H), 2.72 (dd, *J*=17.6, 5.1 Hz, 1H), 2.35–2.23 (m, 1H), 1.96 (s, 3H), 1.55–1.45 (m, 4H), 1.41 (s, 9H), 1.29 (t, *J*=7.3 Hz, 3H), 0.92–0.84 (m, 6H); δ_C (75 MHz, $CDCl_3$): δ 170.7, 165.7, 156.3, 137.6, 129.3, 82.1, 79.4, 75.7, 60.8, 54.4, 49.2, 30.9, 28.4, 26.2, 25.8, 23.3, 14.3, 9.6, 9.3; *m*/*z* (MS-ESI) 413 $[M+H]^+$; HRMS(ESI) calcd for $C_{16}H_{25}N_2O_5$ $[M+H]^+$ 413.2666, found 413.2651.

*4.1.21. Ethyl-(3R,4R,5S)-4-acetamide-5-amino-3-(1-ethylpropoxy) cyclohexene-1-carboxylate phosphate [**1**].* To a stirred solution of **19** (62 mg, 0.15 mmol) in CH_2Cl_2 (1 mL), TFA (0.22 mL) was added at rt. The resulting solution was stirred for 1 h at the same temperature. After removing solvent under reduced pressure, the residue was dissolved in CH_2Cl_2 (3 mL), and saturated $NaHCO_3$ aq solution was added at 4 °C. The aq layer was extracted with CH_2Cl_2 (10 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. To a stirred solution of crude product in EtOH (2.4 mL), a solution of H_3PO_4 in EtOH (1 M, 0.3 mL, 0.3 mmol) was added at room temperature. After the resulting solution was warmed to 50 °C, crystallization commenced. The mixture was slowly cooled down to 4 °C. The crystals were collected and washed with acetone and hexane to afford **1** (32 mg, 71% yield) as white crystals. Mp 205–206 °C; $[\alpha]_D^{25}$ −26.4 (*c* 1, H_2O); (Reported $[\alpha]_D^{29}$ −27.1 (*c* 0.97, H_2O));[4q] ν_{max} (KBr) 3422, 2362, 2342, 1715, 1658, 1248 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.81 (m, 1H), 4.33–4.26 (m, 1H), 4.26–4.17 (m, 1H), 4.06–3.98 (m, 1H), 3.60–3.47 (m, 2H), 2.97–2.88 (m, 1H), 2.54–2.42 (m, 1H), 2.04 (s, 3H), 1.58–1.46 (m, 3H), 1.45–1.36 (m, 1H), 1.24 (t, *J*=7.3 Hz, 3H), 0.84 (t, *J*=7.7 Hz, 3H), 0.80 (t, *J*=7.7 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 175.9, 168.0, 138.5, 128.2, 84.9, 75.7, 63.0, 53.2, 49.7, 28.8, 26.1, 25.6, 23.0, 13.9, 9.1, 9.0; *m*/*z* (MS-ESI) 313 $[M+H]^+$; HRMS(ESI) calcd for $C_{16}H_{29}N_2O_4$ $[M+H]^+$ 313.2132, found 325.2127.

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References and notes

1. (a) Kim, C. U.; Lew, W.; Williams, M. A.; Wu, H.; Zhang, L.; Chen, X.; Escarpe, P. A.; Mendel, D. B.; Laver, W. G.; Stevens, R. C. *J. Med. Chem.* **1998**, *41*, 2451; (b) Schmidt, A. C. *Drugs* **2004**, *64*, 2031.
2. (a) Moscona, A. *N. Engl. J. Med.* **2005**, *353*, 1363; (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 (London)* **2006**, *443*, 45.
3. (a) Rohloff, J. C.; Kent, K. M.; Postich, M. J.; Becker, M. W.; Chapman, H. H.; Kelly, D. E.; Lew, W.; Louie, M. S.; McGee, L. R.; Prisbe, E. J.; Schultze, L. M.; Yu, R. H.; Zhang, L. *J. Org. Chem.* **1998**, *63*, 4545; (b) Federspiel, M.; Fischer, R.; Hennig, M.; Mair, H.-J.; Oberhauser, T.; Rimmler, G.; Albiez, T.; Bruhin, J.; Estermann, H.; Gandert, C.; Gockel, V.; Gotzo, S.; Hoffmann, U.; Huber, G.; Janatsch, G.; Lauper, S.; Rockel-Stabler, O.; Trussardi, R.; Zwahlen, A. G. *Org. Process Res. Dev.* **1999**, *3*, 266; (c) Karpf, M.; Trussardi, R. *J. Org. Chem.* **2001**, *66*, 2044 and references therein; (d) Harrington, P. J.; Brown, J. D.; Foderaro, T.; Hughes, R. C. *Org. Process Res. Dev.* **2004**, *8*, 86.
4. (a) 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, W. G.; Stevens, R. C. *J. Am. Chem. Soc.* **1997**, *119*, 681; (b) Karpf, M.; Trussardi, R. *J. Org. Chem.* **2001**, *66*, 2044; (c) Cong, X.; Yao, Z.-J. *J. Org. Chem.* **2006**, *71*, 5365; (d) Yeung, Y.-Y.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 6310; (e) Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312; (f) Shie, J.-J.; Fang, J.-M.; Wang, S.-Y.; Tasi, 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; (g) Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5734; (h) Yamatsugu, K.; Kamijo, S.; Suto, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2007**, *48*, 1403; (i) Bromfield, K. M.; Graden, H.; Hagberg, D. P.; Olsson, T.; Kann, N. *Chem. Commun.* **2007**, 3183; (j) Mita, T.; Fukuda, N.; Roca, F. X.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 259; (k) Kipassa, N. T.; Okamura, H.; Kina, K.; Hamada, T.; Iwagawa, T. *Org. Lett.* **2008**, *10*, 815; (l) Zutter, U.; Iding, H.; Spurr, P.; Wirz, B. *J. Org. Chem.* **2008**, *73*, 4895; (m) Matveenko, M.; Willis, A. C.; Banwell,

M. G. *Tetrahedron Lett.* **2008**, *49*, 7018; (n) Shie, J.-J.; Fang, J.-M.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 5788; (o) Trost, B. M.; Zhang, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 3759; (p) Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 1304; (q) Yamatsugu, K.; Yin, L.; Kamijo, S.; Kimura, Y.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1070; (r) Mandai, T.; Oshitari, T. *Synlett* **2009**, 783; (s) Oshitari, T.; Mandai, T. *Synlett* **2009**, 787; (t) Sullivan, B.; Carrera, I.; Drouin, M.; Hudlicky, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 4229; (u) Nie, L.-D.; Shi, X.-X. *Tetrahedron: Asymmetry* **2009**, *20*, 124; (v) Nie, L.-D.; Shi, X.-X.; Ho, K. H.; Lu, W.-D. *J. Org. Chem.* **2009**, *74*, 3970; (w) Karpf, M.; Trussardi, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 5760; (x) Weng, J.; Li, Y.-B.; Wang, R. —B.; Feng-Quan Li, F. —Q.; Liu, C.; Chan, A. S. C.; Lu, G. *J. Org. Chem.* **2010**, *75*, 3125; (y) Ishikawa, H.; Hayashi, Y. *Fain Kemikaru* **2010**, *39*, 5; (z) Ishikawa, H.; Hayashi, Y. *Kagaku to Seibutsu* **2010**, *48*, 156; (aa) Werner, L.; Machara, A.; Hudlicky, T. *Adv. Synth. Catal.* **2010**, *352*, 195; (ab) For a review see: Magano, J. *Chem. Rev.* **2009**, *109*, 4398.

5. (a) Poll, T.; Metter, J. O.; Helmchen, G. *Angew. Chem.* **1985**, *97*, 116; (b) Poll, T.; Sebezak, A.; Hartmann, H.; Helmchen, G. *Tetrahedron Lett.* **1985**, *26*, 3095; (c) Corey, E. J.; Huang, H.-C. *Tetrahedron Lett.* **1989**, *30*, 5235.
6. Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730.
7. Fukuyama, T.; Cheung, M.; Kan, T. *Synlett* **1999**, 1301.
8. Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D., Jr.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709.
9. The Mitsunobu reaction proceeds cleanly in a S_N2 fashion without epimerization as understood from the amide, prepared from the amine obtained by deprotection of **9** and (*S*)—methoxy mandelic acid.
10. Miller, S. C.; Scanlan, T. S. *J. Am. Chem. Soc.* **1997**, *119*, 2301.
11. (a) Kocovsky, P.; Stary, I. *J. Org. Chem.* **1990**, *55*, 3236; (b) Berkowitz, D. B.; Pedersen, M. L. *J. Org. Chem.* **1995**, *60*, 5368; (c) Jenmalm, A.; Berts, W.; Luthman, K.; Csoreg, I.; Hacksell, U. *J. Org. Chem.* **1995**, *60*, 1026; (d) Jenmalm, A.; Luthman, K. *Tetrahedron Lett.* **1998**, *39*, 3213.
12. Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560.
13. Sinou, D.; Emziane, M. *Tetrahedron Lett.* **1986**, *27*, 4423.
14. Epoxide opening in a related compound, possessing the bulky *tert*-butyldiphenylsiloxymethyl substituent (instead of the carboethoxy group in **3**) in which conformer '**a**' was expected to be predominant relative to '**b**', afforded a 7:3 ratio of azido alcohols. The structure was assigned to azido alcohols **10** and **11** by analysis of the ^{1}H NMR spectra of the corresponding acetates, the methine protons appeared δ 4.95 as a dt (J=3.8, 9.1 Hz) and at δ 4.7 as a dd (J=4.4, 10.3 Hz), respectively.
15. Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596.
16. Nicolaou, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 993.
17. Prepared in situ from PhSeSePh and Br_2, see: Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.
18. A single isomer was observed, however, its structure was not assigned.
19. The trimethylsilyl group suffered deprotection probably during workup.
20. The selenenylation proceeded in poor yield (30%) using substrate **11**.
21. After 36 h compounds **16** and **17** were isolated in a 3:1 ratio, respectively.
22. (a) Ittah, Y.; Sasson, Y.; Shahak, I.; Isaroom, S.; Blum, J. *J. Org. Chem.* **1978**, *43*, 4271; (b) Tanner, D.; Somfai, P. *Tetrahedron Lett.* **1987**, *28*, 1211.
23. Structure was not assigned to compound **23**.
24. After 36 h compounds **18** and **24** were isolated in a 3:2 ratio, respectively.