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Total synthesis of methyl L-daunosaminide hydrochloride via chiral 1,3-oxazine

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ABSTRACT

Total synthesis of methyl L-daunosaminide hydrochloride was achieved from readily available L-tyrosine. Key steps in this strategy were palladium(0) catalyzed stereoselective intramolecular oxazine formation and catalytic hydrogenation of oxazine intermediate. This paper reported ^{1}H and ^{13}C NMR data of α- and β-anomer of methyl L-daunosaminide hydrochloride.

1. Introduction

3-Amino-2,3,6-trideoxysugars were found in nature as structural constituent of glycosidic and oligosaccharide antibiotics.[1] L-Daunosamine **1** (3-amino-2,3,6-trideoxy-L-*lyxo*-hexose) is a glycosidic component of a number of important anthracycline antibiotics, such as daunomycin **3**[2] and adriamycin **4**,[3] which exhibit impressive activity against a broad range of experimental and human tumor types (Fig. 1).[2,4]

Various synthetic methods of 3-amino-2,3,6-trideoxyhexoses from both sugar and nonsugar starting materials have been documented due to their synthetic interest of controlling the chirality in the absence of neighboring groups at C-2, which affect the stereochemistry at the anomeric position.[5] In recent representative publications, Liu et al. demonstrated a highly efficient synthesis of L-*epi*-daunosamine glycosides via $BF_3{\cdot}OEt_2$ promoted tandem hydroamination and glycosylation on a protected scaffold.[5a] Friestad et al. reported the sequence of asymmetric dihydroxylation and a regio-reversed Wacker oxidation via the application of silicon-tethered vinyl addition under tin-free thiyl radical conditions complete a synthesis of L-daunosamine derivatives.[5b] Also, Lowary et al. described total synthesis of 2,3,6-trideoxy-3-aminohexo pyranoses via photochemically induced acyl nitrene aziridination reaction followed by regioselective hydrogenolytic cleavage of the aziridine as key steps.[5e]

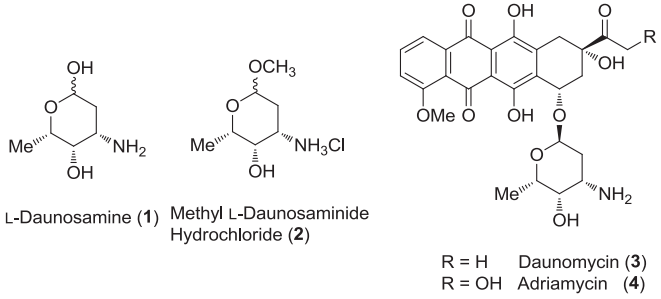

Fig. 1. Structure of L-daunosamine (**1**), methyl L-daunosaminide hydrochloride (**2**), and anthracycline antibiotics.

2. Results and discussion

As part of an ongoing research program aimed at developing asymmetric total syntheses of biologically active compounds,[6] we recently described a facile strategy for the preparation of DAB-1 and D-fagomine via palladium(0) catalyzed stereoselective

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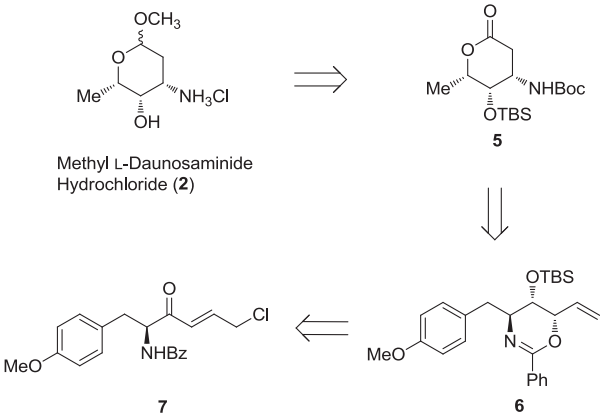
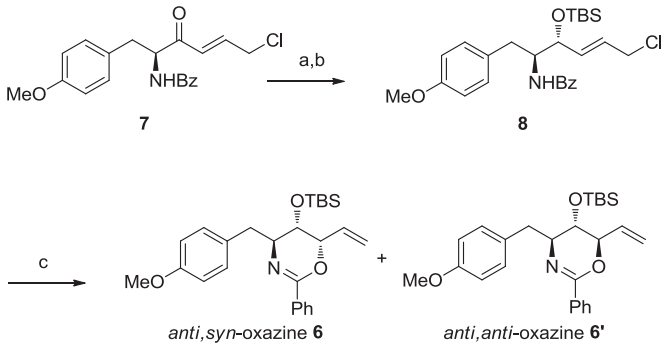
intramolecular oxazine formation and catalytic hydrogenation.[6d] As continuation of our previous works, we herein describe an asymmetric total synthesis of methyl L-daunosaminide hydrochloride **2**, the daunosamine derivative, which results in report of NMR spectroscopic data of its α- and β-anomer, starting from commercially available L-tyrosine via palladium(0) catalyzed stereoselective intramolecular oxazine formation followed by catalytic hydrogenation of oxazine intermediate as key steps.

Retrosynthetically, we envisioned that methyl L-daunosaminide hydrochloride **2** (Scheme 1) could be generated from lactone **5** through reduction and deprotection. Lactone **5** would come from *anti*,*syn*-oxazine **6** through a process involving ozonolysis, subsequent tributyltin hydride-mediated reduction, ruthenium catalyzed oxidation, and catalytic hydrogenation of oxazine intermediate with concomitant lactonization. In turn, the *anti*,*syn*-oxazine **6** could be prepared by the diastereoselective reduction of amino ketone **7** followed by intramolecular cyclization. The amino ketone **7** could be easily achieved from commercially available L-tyrosine according to the known procedure.[7]



Scheme 1. Retrosynthetic analysis.

The chelation-controlled hydride reduction of **7** using lithium tri-*tert*-butoxyaluminum hydride yielded *anti*-amino alcohol with excellent stereoselectivity (*anti*/*syn*>10:1 by ^{1}H NMR spectroscopy).[6] The secondary alcohol was then protected with the silyl ether with *tert*-butyldimethylsilyl chloride (TBSCl) and imidazole in *N*,*N*-dimethylformamide (DMF) to afford the cyclization precursor **8** in 92% yield. Under the conditions of $Pd(PPh_3)_4$, NaH, and *n*-Bu_4NI in THF at 0 °C, stereoselective intramolecular cyclization of the allyl chloride **8** afforded *anti*,*syn*-oxazine **6** and *anti*,*anti*-oxazine **6′** as a 10:1 mixture (^{1}H NMR spectroscopy) in 72% yield (Scheme 2).[8]



Scheme 2. Reagents and conditions: (a) $LiAlH(O^tBu)_3$, −78 °C, 85%; (b) TBSCl, imidazole, DMF, rt, 92%; (c) $Pd(PPh_3)_4$, NaH, *n*-Bu_4NI, THF, 0 °C, 72%.

The stereochemistry of the oxazine obtained above was elucidated by ^{1}H NMR spectroscopy. The relative configuration of each diastereomer of the oxazine products, obtained after the silica gel column separation, was determined by a comparison of their coupling constants and a measurement of NOE effect. The large coupling constant of $J_{4,5}$=6.0 Hz as in *anti*,*syn*-oxazine **6**, was caused by the pseudo-diaxial relationship between the two adjacent protons in six-membered ring. The small coupling constants of $J_{5,6}$=3.5 Hz as in *anti*,*syn*-oxazine **6**, are typically because of the pseudo-axial-equatorial relationship between the two adjacent protons in six-membered ring. NOE enhancement for compound **6** is shown below: there is 8.82% NOE between H^5 and H^6, 0.29% between H^5 and H^4, but no NOE effective between H^4 and H^6 (Fig. 2).

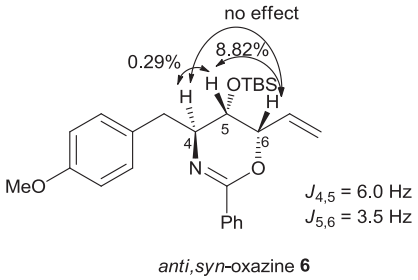
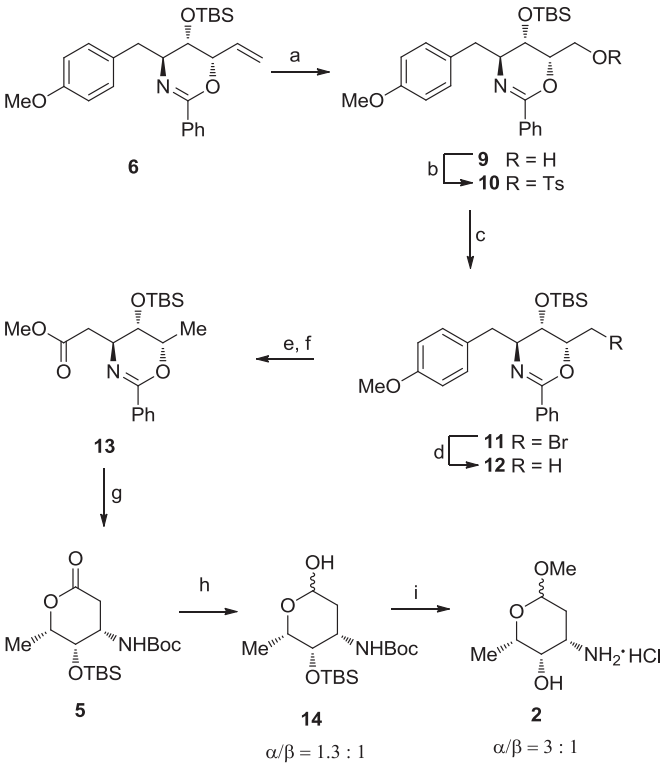


Fig. 2. Coupling constants and NOE spectroscopic data of **6**.

Also, *anti*,*syn*-oxazine **6** has almost similar ^{1}H NMR patterns to previously reported benzyl oxazine compounds.[6e] Protons of the terminal olefin and H^5 have peaks at 6.0 and 3.73 ppm, respectively. In addition, the coupling constant of the newly generated chiral center (H^5–H^6) of compound **6** has the similar value 3.5 Hz, compared to all *anti*,*syn*-oxazines previously reported and the stereochemistry was finally confirmed by its conversion into methyl L-daunosaminide hydrochloride **2**.

Total synthesis of methyl L-daunosaminide hydrochloride **2** is described in Scheme 3. The terminal olefin in compound **6** was converted to the alcohol **9** by ozonolysis followed by reduction with $NaBH_4$. Primary alcohol **9** was treated with tosyl chloride in the presence of Et_3N and DMAP in dichloromethane to afford the tosylate **10** in good yield. Then, tosylate **10** was treated with lithium bromide in *N*,*N*-dimethylformamide (DMF) to afford bromide **11**. Bromide **11** was subjected to a radical reduction [tributyltin hydride (Bu_3SnH), catalytic 2,2′-azobis(isobutyronitrile) (AIBN)] to afford **12** in 75% yield.[9] Oxidation of *p*-methoxyphenyl group of **12** with $RuCl_3$ (0.1 equiv) and $NaIO_4$ (17 equiv) in $CCl_4/CH_3CN/H_2O$ (2:2:3)[10] gave the sequence of catalytic hydrogenation[6b,c] and in situ lactonization.[11] Subsequent reduction of the lactone **5** using DIBAL-H gave the protected lactol **14** as an 1.3:1 mixture of anomers in 93%. The assignment of relative stereochemistry for protected lactol **14** was made on the basis of the ^{1}H NMR spectra (Fig. 3). The two small coupling constants (equatorial–equatorial interaction and equatorial–axial interaction) of **14a** between protons H-1 (δ 5.34, dd) and H-3 of 2.5 Hz, and between H-1 and H-2 of 2.5 Hz exhibited by α-anomeric proton are consistent with an axial disposition of the hydroxyl group. A large coupling constant (axial–axial interaction) between protons H-1 (δ 4.79, ddd) and H-3 of 9.5 Hz, confirmed that this was the β-anomer, **14b**. The coupling pattern of anomeric hydrogen of protected lactol **14** shows good agreements with the coupling pattern of anomeric hydrogen of *N*-benzoyl L-daunosamine reported by Grasselli et al.[12]

Finally, removal of the Boc and TBS groups under acidic condition (6 N HCl, MeOH, rt) afforded methyl L-daunosaminide hydrochloride **2** as a 3:1 mixture of anomers. The assignment of relative



Scheme 3. Reagents and conditions: (a) O_3, MeOH, −78 °C then $NaBH_4$, 0 °C, 86%; (b) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 89%; (c) LiBr, DMF, 60 °C, 84%; (d) Bu_3SnH, AIBN, toluene, 100 °C, 75%; (e) $NaIO_4$, $RuCl_3$, $CCl_4/CH_3CN/H_2O$=2:2:3, rt; (f) CH_2N_2, EtOH, rt, 76%, for two steps; (g) $Pd(OH)_2$, H_2, Boc_2O, hexane/MeOH=2:3, rt, 68%; (h) DIBAL-H, THF, −78 °C, 93%; (i) 6 N HCl, MeOH, rt, 76%.

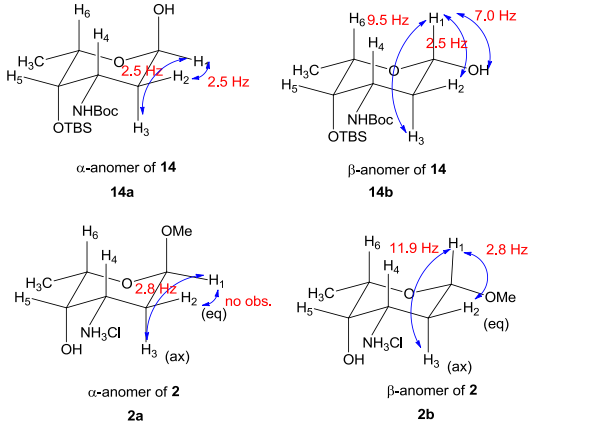


Fig. 3. Stereochemical identification of protected lactol **14** and methyl L-daunosaminide hydrochloride **2**.

stereochemistry for **2** was made on the basis of the ^1H NMR spectra. The mixed NMR spectrum of **2** shows two isomeric signals. One of them shows a good agreement with the chemical shift and coupling pattern of α-anomer reported by Davies et al.[5k] The small coupling constants of **2a** between protons H-1 (δ 4.85, d) and H-3 of 2.8 Hz exhibited by proton H-1 in the α-anomer are consistent with an axial disposition of the hydroxyl group. The assignment of the minor isomer described unknown by Sibi et al.[5l] was made on the basis of the ^1H NMR spectrum, indicating that this is the β-anomer. A large coupling constant between protons H-1 (δ 4.51, d) and H-3 of 11.9 Hz and a small coupling constant between protons H-1 and H-2 of 2.8 Hz, exhibited that H-1 is an axial disposition indicating β-anomer, **2b**. The optical rotation **2**, $[\alpha]_D^{25}$ −142 (*c* 0.9, MeOH), compared to the reported value, $[\alpha]_D^{25}$ −140 (*c* 1.0, MeOH),[5l] confirmed the absolute configuration of **2**. The net result was synthesis from a linear sequence of 11 steps from the amino ketone **7** in 9.9% overall yield for methyl L-daunosaminide hydrochloride **2**.

3. Conclusions

We have demonstrated the total synthesis of methyl L-daunosaminide hydrochloride **2** starting from readily available L-tyrosine via palladium-catalyzed stereoselective intramolecular oxazine formation followed by catalytic hydrogenation of oxazine intermediate. Also, we have reported structural identification of its α- and β-anomer by NMR spectroscopic data, clearly. The coupling pattern of the anomeric hydrogen in the ^1H NMR spectra of methyl L-daunosaminide hydrochloride enabled determination of the anomeric configuration. Further extension of this work to the syntheses of structurally related natural products are in progress.

4. Experimental

4.1. General information

Optical rotations were measured with a polarimeter in the solvent specified. ^1H and ^{13}C NMR spectroscopic data were recorded with FT-NMR 125, 175, 500 or 700 MHz. Chemical shift values are reported in parts per million relative to TMS or $CDCl_3$, as the internal standard, and coupling constants are reported in Hertz. IR spectra were measured with a FT-IR spectrometer. Mass spectroscopic data were obtained with Jeol JMS 700 high resolution mass spectrometer of magnetic sector—electric sector double focusing analyzer. Flash chromatography was executed using mixtures of ethyl acetate and hexane as the eluents. Unless otherwise noted, all nonaqueous reactions were carried out under an argon atmosphere with commercial grade reagents and solvents. Tetrahydrofuran (THF) was distilled from sodium and benzophenone (indicator). Methylene chloride (CH_2Cl_2) was distilled from calcium hydride.

*4.1.1. N-((2S,3R,E)-3-((tert-Butyldimethylsilyl)oxy)-6-chloro-1-(4-methoxyphenyl)hex-4-en-2-yl)benzamide (**8**).* $LiAlH(O^tBu)_3$ (1.0 M solution in THF, 0.91 mL, 0.91 mmol) was added to a solution of **7** (216 mg, 0.60 mmol) in EtOH (6 mL) at −78 °C. After the reaction mixture was stirred at the same temperature for 3 h, aqueous citric acid (10%, 1 mL) was added. The resulting mixture was warmed to rt and extracted with EtOAc (30 mL×2). The organic layers were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude product. The crude material was purified by chromatography on a silica gel column (hexanes/EtOAc, 3:1) to give the *anti*-amino alcohol (185 mg, 85%, *anti/syn*>10:1 by ^1H NMR spectroscopy) as a white solid; mp 150–152 °C; $[\alpha]_D^{25}$ −38.41 (*c* 0.4, $CHCl_3$); R_f=0.25 (hexanes/EtOAc, 2:1); IR (neat) ν_{max}=3358, 2944, 2832, 1453, 1033, 636 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.84 (dd, *J*=9.0, 14.5 Hz, 1H), 2.94 (dd, *J*=5.0, 14.0 Hz, 1H), 3.77 (s, 3H), 3.97 (br s, 1H), 4.05–4.07 (m, 2H), 4.38–4.44 (m, 2H), 5.88 (dd, *J*=5.5, 15.5 Hz, 1H), 5.98 (dtd, *J*=1.0, 7.0, 15.0 Hz, 1H), 6.22 (d, *J*=7.5 Hz, 1H), 6.83–6.85 (m, 2H), 7.14–7.15 (m, 2H), 7.35–7.38 (m, 2H), 7.45–7.49 (m, 1H), 7.58–7.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.1, 44.4, 55.5, 56.8, 73.8, 114.4, 127.2, 128.8, 128.9, 129.5, 130.3, 132.0, 133.4, 134.2, 158.7, 169.0; HRMS (FAB^+) calcd for $C_{20}H_{22}ClNO_3$ $[M+H]^+$ 360.1366, found 360.1370.

TBSCl (160 mg, 1.06 mmol) and imidazole (72 mg, 1.06 mmol) were added to a stirred solution of the alcohol (319 mg, 0.89 mmol) in anhydrous DMF (3 mL) at rt under argon. The reaction mixture was stirred at rt for 12 h, then quenched with H_2O (10 mL), and extracted with EtOAc (50×2 mL). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo.

The residue was purified by silica gel column chromatography (hexanes/EtOAc, 10:1) to give **8** (387 mg, 92%) as a white solid; mp 108–110 °C; $[\alpha]_D^{25}$ −21.64 (*c* 2.5, $CHCl_3$); R_f=0.76 (hexanes/EtOAc, 2:1); IR (neat) ν_{max}=3332, 2948, 2832, 1637, 1513, 1451, 1249, 1033, 837, 778, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.04 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 2.84 (dd, *J*=9.0, 14.5 Hz, 1H), 2.94 (dd, *J*=5.5, 14.5 Hz, 1H), 3.75 (s, 3H), 4.05 (d, *J*=6.0 Hz, 2H), 4.38 (dddd, *J*=3.5, 5.0, 9.0, 9.0 Hz, 1H), 4.50 (dd, *J*=4.0, 4.0 Hz, 1H), 5.87 (dd, *J*=5.0, 15.5 Hz, 1H), 5.92 (td, *J*=6.0, 16.0 Hz, 1H), 6.04 (d, *J*=8.5 Hz, 1H), 6.80–6.82 (m, 2H), 7.13–7.14 (m, 2H), 7.36–7.46 (m, 3H), 7.58–7.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.8, −4.0, 18.4, 26.1, 34.0, 44.6, 55.5, 55.5, 73.4, 114.2, 126.9, 128.0, 128.8, 130.2, 130.3, 131.6, 134.8, 134.8, 158.4, 167.2; HRMS (FAB$^+$) calcd for $C_{26}H_{36}ClNO_3Si$ $[M+H]^+$ 474.2231, found 474.2227.

*4.1.2. (4S,5S,6S)-5-((tert-Butyldimethylsilyl)oxy)-4-(4-methoxybenzyl)-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine (**6**).* NaH (55% in mineral oil, 37 mg, 1.56 mmol) and *n*-Bu_4NI (288 mg, 0.78 mmol) were added to a stirred solution of allyl chloride **8** (370 mg, 0.78 mmol) in anhydrous THF (3.9 mL) at 0 °C. After stirred for 5 min, $Pd(PPh_3)_4$ (90 mg, 0.078 mmol) was added to the mixture and stirring was allowed to continue for 12 h at the same temperature. The reaction mixture was filtered through a pad of silica and then evaporated under reduced pressure to give the crude product. Purification of this material by silica gel chromatography (hexanes/EtOAc, 30:1) gave **6** (246 mg, 72%) as a colorless oil; $[\alpha]_D^{25}$ −62.82 (*c* 0.5, $CHCl_3$); R_f=0.77 (hexanes/EtOAc, 3:1); IR (neat) ν_{max}=3382, 2948, 2833, 1661, 1452, 1115, 1032, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.87 (s, 9H), 2.78 (dd, *J*=7.5, 13.5 Hz, 1H), 2.84 (dd, *J*=6.3, 14.0 Hz, 1H), 3.54 (ddd, *J*=6.0, 6.0, 7.5 Hz, 1H), 3.73 (dd, *J*=3.5, 5.5 Hz, 1H), 3.77 (s, 3H), 4.69 (ddd, *J*=1.5, 3.5, 5.0 Hz, 1H), 5.26 (td, *J*=1.5, 12.0 Hz, 1H), 5.30 (td, *J*=1.5, 17.5 Hz, 1H), 5.99 (ddd, *J*=5.0, 10.5, 15.5 Hz, 1H), 6.84–6.85 (m, 2H), 7.22–7.23 (m, 2H), 7.33–7.41 (m, 3H), 7.95–7.96 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.5, −4.1, 18.2, 26.0, 39.9, 55.5, 59.5, 68.3, 75.6, 114.0, 117.7, 127.6, 128.2, 130.6, 130.9, 131.3, 133.5, 133.8, 152.9, 158.4; HRMS (FAB$^+$) calcd for $C_{26}H_{35}NO_3Si$ $[M+H]^+$ 438.2464, found 438.2462.

*4.1.2.1. ((4S,5S,6S)-5-((tert-Butyldimethylsilyl)oxy)-4-(4-methoxybenzyl)-2-phenyl-5,6-dihydro-4H-1,3-oxazin-6-yl)methanol (**9**).* A solution of the oxazine **6** (515 mg, 1.18 mmol) in anhydrous MeOH (10 mL) was cooled to −78 °C. O_3 was passed through the solution until the starting material had been consumed (TLC analysis). The resulting blue solution was purged with oxygen for 10 min, and then $NaBH_4$ (53 mg, 1.41 mmol) was added. After stirring the mixture at rt for 30 min, saturated aqueous NH_4Cl was added. The reaction mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexanes/EtOAc, 4:1) to afford alcohol **9** (450 mg, 86%) as a colorless oil; $[\alpha]_D^{25}$ −45.36 (*c* 0.7, $CHCl_3$); R_f=0.33 (hexanes/EtOAc, 4:1); IR (neat) ν_{max}=3381, 2947, 2833, 1662, 1452, 1115, 1032, 659 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.08 (s, 3H), −0.06 (s, 3H), 0.82 (s, 9H), 2.12 (br s, 1H), 2.59 (dd, *J*=8.5, 14.0 Hz, 1H), 3.02 (dd, *J*=6.5, 14.0 Hz, 1H), 3.67 (ddd, *J*=3.0, 6.5, 8.5 Hz, 1H), 3.80 (s, 3H), 3.85 (m, 2H), 3.93–3.97 (m, 1H), 4.30 (ddd, *J*=3.0, 4.0, 7.0 Hz, 1H), 6.86–6.88 (m, 2H), 7.18–7.20 (m, 2H), 7.36–7.44 (m, 3H), 7.94–7.96 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.6, 18.1, 25.9, 40.9, 55.5, 60.7, 63.1, 65.9, 74.5, 114.2, 127.5, 128.3, 130.7, 133.9, 153.8, 158.6; HRMS (FAB$^+$) calcd for $C_{25}H_{35}NO_4Si$ $[M+H]^+$ 442.2414, found 442.2416.

*4.1.2.2. ((4S,5S,6S)-5-((tert-Butyldimethylsilyl)oxy)-4-(4-methoxybenzyl)-2-phenyl-5,6-dihydro-4H-1,3-oxazin-6-yl)methyl 4-methylbenzenesulfonate (**10**).* TsCl (97 mg, 0.51 mmol), Et_3N (0.11 mL 0.85 mmol), and DMAP (5 mg, 0.043 mmol) were added to a solution of alcohol **9** (188 mg, 0.43 mmol) in anhydrous CH_2Cl_2 (4 mL) at rt under argon. The reaction mixture was stirred at rt for 6 h. The reaction was quenched with saturated aqueous NH_4Cl solution (2 mL), and the resulting mixture was extracted with CH_2Cl_2 (15×2 mL). The organic layer was washed with brine, dried over $MgSO_4$, and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography (hexanes/EtOAc, 10:1) to afford **10** (226 mg, 89%) as a white solid; mp 115–117 °C; $[\alpha]_D^{25}$ −21.84 (*c* 1.3, $CHCl_3$); R_f=0.35 (hexanes/EtOAc, 6:1); IR (neat) ν_{max}=3381, 2947, 2833, 1662, 1452, 1115, 1032, 678 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.12 (s, 3H), −0.10 (s, 3H), 0.77 (s, 9H), 2.41 (s, 3H), 2.56 (dd, *J*=8.5, 14.0 Hz, 1H), 2.96 (dd, *J*=6.0, 14.0 Hz, 1H), 3.58 (ddd, *J*=3.5, 6.0, 8.0 Hz, 1H), 3.79 (dd, *J*=3.0, 3.0 Hz, 1H), 3.81 (s, 3H), 4.21 (dd, *J*=7.5, 10.5 Hz, 1H), 4.25 (dd, *J*=4.5, 11.0 Hz, 1H), 4.43 (ddd, *J*=2.5, 4.0, 7.0 Hz, 1H), 6.86–6.88 (m, 2H), 7.15–7.17 (m, 2H), 7.29–7.36 (m, 4H), 7.41–7.44 (m, 1H), 7.79–7.84 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.7, −4.5, 18.1, 21.9, 25.8, 40.7, 55.5, 60.3, 64.9, 69.1, 72.0, 114.2, 127.6, 128.2, 130.1, 130.3, 130.7, 130.7, 132.9, 133.4, 145.2, 153.0, 158.6; HRMS (FAB$^+$) calcd for $C_{32}H_{41}NO_6SSi$ $[M+H]^+$ 596.2502, found 596.2500.

*4.1.3. (4S,5S,6R)-6-(Bromomethyl)-5-((tert-butyldimethylsilyl)oxy)-4-(4-methoxybenzyl)-2-phenyl-5,6-dihydro-4H-1,3-oxazine (**11**).* LiBr (37 mg, 0.42 mmol) was added to a stirred solution of **10** (125 mg, 0.21 mmol) in anhydrous DMF (2 mL) at rt under argon. The reaction mixture was refluxed for 12 h and then quenched with H_2O (2 mL). The aqueous layer was extracted with EtOAc (10×2 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/EtOAc, 20:1) to afford **11** (75 mg, 84%) as a white solid; mp 208–210 °C; $[\alpha]_D^{25}$ −32.36 (*c* 2.5, $CHCl_3$); R_f=0.5 (hexanes/EtOAc, 10:1); IR (neat) ν_{max}=3384, 2949, 2836, 1651, 1452, 1115, 1023, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.12 (s, 3H), −0.07 (s, 3H), 0.81 (s, 9H), 2.52 (dd, *J*=9.0, 14.0 Hz, 1H), 3.11 (dd, *J*=5.0, 13.5 Hz, 1H), 3.55 (dd, *J*=7.0, 10.0 Hz, 1H), 3.58 (dd, *J*=7.0, 10.0 Hz, 1H), 3.71 (ddd, *J*=2.5, 5.5, 9.0 Hz, 1H), 3.80 (s, 3H), 3.98 (dd, *J*=2.0, 2.5 Hz, 1H), 4.33 (dt, *J*=2.0, 6.5 Hz, 1H), 6.87–6.89 (m, 2H), 7.18–7.20 (m, 2H), 7.36–7.45 (m, 3H), 7.94–7.96 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.6, −4.5, 18.1, 25.9, 30.1, 41.0, 55.5, 61.2, 64.6, 73.9, 114.3, 127.6, 128.3, 130.3, 130.7, 130.7, 133.6, 153.8, 158.6; HRMS (FAB$^+$) calcd for $C_{25}H_{34}BrNO_3Si$ $[M+H]^+$ 506.1553, found 506.1567.

*4.1.4. (4S,5S,6S)-5-((tert-Butyldimethylsilyl)oxy)-4-(4-methoxybenzyl)-6-methyl-2-phenyl-5,6-dihydro-4H-1,3-oxazine (**12**).* A stirred solution of bromide **11** (69 mg, 0.14 mmol), *n*-Bu_3SnH (76 μL, 0.27 mmol), and AIBN (2 mg, 0.014 mmol) in toluene (1 mL) was heated to 100 °C. After 12 h, the reaction mixture was cooled to rt and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/EtOAc, 20:1) to afford **12** (44 mg, 75%) as a colorless oil; $[\alpha]_D^{25}$ −52.13 (*c* 1.2, $CHCl_3$); R_f=0.20 (hexanes/EtOAc, 20:1); IR (neat) ν_{max}=3382, 2947, 2833, 1662, 1452, 1115, 1032, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.05 (s, 3H), −0.04 (s, 3H), 0.86 (s, 9H), 1.33 (d, *J*=6.5 Hz, 3H), 2.68–2.73 (m, 1H), 2.91–2.95 (m, 1H), 3.63–3.66 (m, 2H), 3.80 (s, 3H), 4.33 (dq, *J*=3.0, 6.5 Hz, 1H), 6.86–6.88 (m, 2H), 7.21–7.23 (m, 2H), 7.34–7.42 (m, 3H), 7.93–7.94 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.5, −4.4, 16.2, 18.2, 26.0, 40.7, 55.5, 60.0, 67.8, 70.7, 114.0, 127.5, 128.1, 130.4, 130.8, 131.2, 134.3, 154.0, 158.4; HRMS (FAB$^+$) calcd for $C_{25}H_{35}NO_3Si$ $[M+H]^+$ 426.2464, found 426.2462.

*4.1.5. Methyl 2-((4S,5S,6S)-5-((tert-butyldimethylsilyl)oxy)-6-methyl-2-phenyl-5,6-dihydro-4H-1,3-oxazin-4-yl)acetate (**13**).* $NaIO_4$ (743 mg, 3.47 mmol) and $RuCl_3$ (4 mg, 0.020 mmol) were added to a cooled (0 °C) solution of compound **12** (87 mg,

0.20 mmol) in a mixed solvent system ($CCl_4/CH_3CN/H_2O$=1:1:1.5, 3.5 mL) The reaction mixture was stirred for 6 h at rt, quenched with brine (2 mL), and filtered through a Celite pad. The filtrate was concentrated in vacuo to give the crude carboxylic acid, which was used without purification in the next reaction. To an ethereal solution of CH_2N_2 was added dropwise a stirred solution of the above crude product in Et_2O (2 mL) until the reaction mixture turned yellow. The mixture was stirred for 2 h at rt. Evaporation of solvents yielded crude compound. The residue was purified by flash column chromatography (hexanes/EtOAc, 10:1) to provide **13** (59 mg, 76%) as a colorless oil; $[\alpha]_D^{25}$ −44.51 (*c* 0.7, $CHCl_3$); R_f=0.42 (hexanes/EtOAc, 6:1); IR (neat) ν_{max}=3382, 2947, 2883, 1663, 1452, 1115, 1032, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.12 (s, 3H), 0.90 (s, 9H), 1.36 (d, *J*=6.5 Hz, 3H), 2.55 (dd, *J*=7.5, 15.0 Hz, 1H), 2.62 (dd, *J*=6.5, 15.0 Hz, 1H), 3.74 (s, 3H), 3.80 (dd, *J*=3.5, 6.0 Hz, 1H), 3.92 (ddd, *J*=6.5, 6.5, 6.5 Hz, 1H), 4.35 (dq, *J*=4.0, 6.5 Hz, 1H), 7.32–7.41 (m, 3H), 7.89–7.91 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.5, −4.3, 15.5, 18.2, 25.9, 39.6, 51.9, 54.3, 68.3, 71.5, 127.6, 128.1, 130.6, 133.8, 154.2, 172.3; HRMS (FAB^+) calcd for $C_{20}H_{31}NO_4Si$ $[M+H]^+$ 378.2101, found 378.2099.

*4.1.6. tert-Butyl (2S,3S,4S)-3-(tert-butyldimethylsilyloxy)-2-methyl-6-oxotetrahydro-2H-pyran-4-ylcarbamate (**5**).* A stirred solution of compound **13** (80 mg, 0.21 mmol) in a 3:2 mixture of hexane and MeOH (5 mL) was stirred at rt for 12 h under an atmosphere of hydrogen in the presence of a catalytic quantity of 20% palladium hydroxide on charcoal (37 mg, 0.053 mmol) and $(Boc)_2O$ (234 mg, 1.06 mmol). The catalyst was then removed by filtration through Celite, and the solvents were evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (hexanes/EtOAc, 2:1) to afford a lactone **5** (52 mg, 68%) as a white solid; mp 107–109 °C; $[\alpha]_D^{25}$ −10.91 (*c* 1.5, $CHCl_3$); R_f=0.33 (hexanes/EtOAc, 2:1); IR (neat) ν_{max}=3358, 2947, 2832, 1663, 1453, 1033, 658 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.12 (s, 3H), 0.93 (s, 9H), 1.35 (d, *J*=6.5 Hz, 3H), 1.45 (s, 9H), 2.49 (dd, *J*=12.0, 17.5 Hz, 1H), 2.71 (dd, *J*=6.5, 17.5 Hz, 1H), 3.99 (s, 1H), 4.01–4.07 (m, 1H), 4.42 (q, *J*=6.5 Hz, 1H), 4.47 (d, *J*=7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.1, −3.9, 18.1, 18.5, 26.1, 28.6, 31.4, 49.1, 69.2, 80.6, 169.2; HRMS (FAB^+) calcd for $C_{17}H_{34}NO_5Si$ $[M+H]^+$ 360.2206, found 360.2204.

*4.1.7. tert-Butyl ((2S,3S,4S)-3-(tert-butyldimethylsilyloxy)-6-hydroxy-2-methyltetrahydro-2H-pyran-4-yl)carbamate (**14**).* DIBAL-H (1.0 M, 0.22 mL) was added to a stirred solution of **5** (66 mg, 0.18 mmol) in anhydrous THF (2 mL) at −78 °C. The reaction mixture was stirred for 2 h at −78 °C and then was quenched by the addition of saturated sodium potassium tartrate at −78 °C. The resulting mixture was extracted with EtOAc (10×2 mL). The organic layer was washed with brine, dried over $MgSO_4$, and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography (hexanes/EtOAc, 2:1) to afford protected lactol **14** (62 mg, 93%) as a white solid; mp 106–108 °C; $[\alpha]_D^{25}$ −5.0 (*c* 1.0, $CHCl_3$); R_f=0.27 (hexanes/EtOAc, 2:1); IR (neat) ν_{max}=3358, 2945, 2832, 1667, 1452, 1115, 1033, 658 cm^{-1}; HRMS (FAB^+) calcd for $C_{17}H_{35}NO_5Si$ $[M+H]^+$ 362.2363, found 362.2361.

α-Anomer: ^1H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.95 (s, 9H), 1.13 (d, *J*=6.5 Hz, 3H), 1.44 (s, 9H), 1.62–1.66 (m, 1H), 1.81–1.89 (m, 1H), 2.38 (br, 1H), 4.10 (m, 2H), 4.49 (d, *J*=9.0 Hz, 1H), 5.34 (dd, *J*=2.5, 2.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −3.6, −3.5, 18.1, 18.2, 28.6, 28.6, 30.5, 46.7, 67.0, 71.3, 92.0, 155.1.

β-Anomer: ^1H NMR (500 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.96 (s, 9H), 1.21 (d, *J*=6.5 Hz, 3H), 1.44 (s, 9H), 1.60–1.66 (m, 1H), 1.81–1.89 (m, 1H), 2.90 (d, *J*=7.0 Hz, 1H), 3.54 (q, *J*=6.5 Hz, 1H), 3.60 (d, *J*=2.0 Hz, 1H), 3.71–3.76 (m, 2H), 4.59 (d, *J*=9.0 Hz, 1H), 4.79 (ddd, *J*=2.5, 7.0, 9.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.1, 18.7, 18.7, 26.3, 26.4, 34.1, 50.6, 70.1, 72.3, 94.9, 155.1.

*4.1.8. (2S,3S,4S)-4-Amino-6-methoxy-2-methyltetrahydro-2H-pyran-3-ol hydrochloride (**2**).* HCl (6 N solution, 0.2 mL) was added to a solution of above lactol (21 mg, 0.058 mmol) in MeOH (1 mL), and the reaction mixture was stirred at rt for 10 h. The solvent was then removed in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH, 5:1) to give **2** (9 mg, 76%) as a white solid; $[\alpha]_D^{25}$ −142 (*c* 0.9, MeOH); mp 185–188 °C; R_f=0.2 ($CHCl_3$/MeOH, 5:1); IR (neat) ν_{max}=3455–3279, 3062–2770 cm^{-1}; HRMS (FAB^+) calcd for $C_7H_{16}ClNO_3$ $[M-Cl]^+$ 162.1130, found 162.1127.

α-Anomer: ^1H NMR (700 MHz, pyridine-d_5) δ 1.39 (d, *J*=6.3 Hz, 3H), 2.42 (dd, *J*=4.2, 12.6 Hz, 1H), 2.49 (ddd, *J*=2.8, 12.6, 12.6 Hz, 1H), 3.27 (s, 3H), 3.93 (q, *J*=6.3 Hz, 1H), 4.23 (d, *J*=11.9 Hz, 1H), 4.48–4.50 (br s, 1H), 4.81 (d, *J*=2.1 Hz, 1H); ^{13}C NMR (175 MHz, pyridine-d_5) δ 17.1, 29.4, 47.8, 54.2, 66.4, 67.2, 97.7.

β-Anomer: ^1H NMR (700 MHz, pyridine-d_5) δ 1.43 (d, *J*=6.3 Hz, 3H), 2.37 (ddd, *J*=11.9, 11.9, 11.9 Hz, 1H), 2.62 (dd, *J*=2.8, 12.6 Hz, 1H), 3.47 (s, 3H), 3.68–3.71 (q, *J*=5.6 Hz, 1H), 4.07 (d, *J*=12.6 Hz, 1H), 4.40 (br s, 1H), 4.51–4.53 (dd, *J*=1.4, 9.8 Hz, 1H); ^{13}C NMR (175 MHz, pyridine-d_5) δ 17.1, 31.4, 50.8, 55.8, 66.8, 71.9, 101.1.

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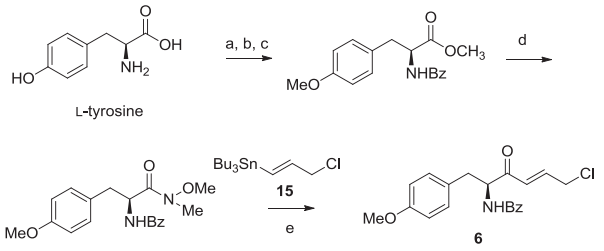
Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.02.033. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. Hauser, F. M.; Ellenberger, S. R. *Chem. Rev.* **1986**, *86*, 35–67.
2. (a) Arcamone, F.; Franceschi, G.; Orezzi, P.; Cassinelli, G.; Barbieri, W.; Mondelli, R. *J. Am. Chem. Soc.* **1964**, *86*, 5334–5335; (b) Arcamone, F.; Cassinelli, G.; Orezzi, P.; Franceschi, G.; Mondelli, R. *J. Am. Chem. Soc.* **1964**, *86*, 5335–5336.
3. Arcamone, F.; Franceschi, G.; Penco, S.; Selva, A. *Tetrahedron Lett.* **1969**, *10*, 1007–1010.
4. (a) Horton, D.; Weckerle, W. *Carbohydr. Res.* **1975**, *44*, 227–240; (b) Grethe, G.; Mitt, T.; Williams, T. H.; Uskokovic, M. R. *J. Org. Chem.* **1983**, *48*, 5309–5315; (c) Nagumo, S.; Umezawa, I.; Akiyama, J.; Akita, H. *Chem. Pharm. Bull.* **1995**, 171–173.
5. For selected recent syntheses of 3-amino-2,3,6-trideoxyhexoses, see: (a) Ding, F.; William, R.; Wang, F.; Ma, J.; Ji, L.; Liu, X. *Org. Lett.* **2011**, *13*, 652–655; (b) Friestad, G. K.; Jiang, T.; Mathies, A. K. *Org. Lett.* **2007**, *9*, 777–780; (c) Fan, E.; Shi, W.; Lowary, T. L. *J. Org. Chem.* **2007**, *72*, 2917–2928; (d) Doi, T.; Shibata, K.; Kinbara, A.; Takahashi, T. *Chem. Lett.* **2007**, *36*, 1372–1373; (e) Mendlik, M. T.; Tao, P.; Hadad, C. M.; Coleman, R. S.; Lowary, T. L. *J. Org. Chem.* **2006**, *71*, 8059–8070; (f) Matsushima, Y.; Kino, J. *Tetrahedron Lett.* **2006**, *47*, 8777–8780; (g) Hayman, C. M.; Larsen, D. S.; Simpson, J.; Bailey, K. B.; Gill, G. S. *Org. Biomol. Chem.* **2006**, *4*, 2794–2800; (h) Parker, K. A.; Chang, W. *Org. Lett.* **2005**, *7*, 1785–1788; (i) Effenberger, F.; Roos, J. *Tetrahedron: Asymmetry* **2000**, *21*, 1085–1095; (j) Szechner, B.; Achmatowicz, O.; Badowaska-Roslonek, K. *Pol. J. Chem.* **1999**, *73*, 1133–1141; (k) Davies, S. G.; Smyth, G. D.; Chippindate, A. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3089–3104; (l) Sibi, M. P.; Lu, J.; Edwards, J. *J. Org. Chem.* **1997**, *62*, 5864–5872; (m) Daley, L.; Roger, P.; Monneret, C. *J. Carbohydr. Chem.* **1997**, *16*, 25–48.
6. (a) Jin, T.; Mu, Y.; Kim, G. W.; Kim, S. S.; Kim, J. S.; Huh, S. I.; Lee, K. Y.; Joo, J. E.; Ham, W. H. *Asian J. Org. Chem.* **2012**, *1*, 232–237; (b) Mu, Y.; Kim, J. Y.; Jin, X.; Park, S. H.; Joo, J. E.; Ham, W. H. *Synthesis* **2012**, *44*, 2340–2346; (c) Mu, Y.; Jin, T.; Kim, G. W.; Kim, J. S.; Kim, S. S.; Tian, Y. S.; Oh, C. Y.; Ham, W. H. *Eur. J. Org. Chem.* **2012**, 2614–2620; (d) Kim, J. Y.; Mu, Y.; Jin, X.; Park, S. H.; Pham, V. T.; Song, D. K.; Lee, K. Y.; Ham, W. H. *Tetrahedron* **2011**, *67*, 9426–9432; (e) Pham, V. T.; Joo, J. E.; Lee, K. Y.; Kim, T. W.; Mu, Y.; Ham, W. H. *Tetrahedron* **2010**, *66*, 2123–2131.
7. The requisite α,β-unsaturated ketone **6** was prepared in high yield from the commercially available L-tyrosine by the five steps sequence shown in following scheme.



Reagents and conditions: (a) $SOCl_2$, MeOH, reflux, (b) BzCl, Et_3N, MeOH, 0 °C, (c) K_2CO_3, MeI, DMF, 93% three steps; (d) MeNHOMe·HCl, $AlMe_3$, CH_2Cl_2, 90%; (e) **15**, MeLi·LiBr, −78 °C, 79%.

8. (a) Joo, J. E.; Pham, V. T.; Tian, Y. S.; Chung, Y. S.; Oh, C. Y.; Lee, K. Y.; Ham, W. H. *Org. Biomol. Chem.* **2008**, *6*, 1498–1501; (b) Joo, J. E.; Lee, K. Y.; Pham, V. T.; Tian, Y. S.; Ham, W. H. *Org. Lett.* **2007**, *9*, 3627–3630; (c) Joo, J. E.; Lee, K. Y.; Pham, V. T.; Ham, W. H. *Eur. J. Org. Chem.* **2007**, 1586–1593.
9. (a) Oh, H.; Kang, H. *Tetrahedron* **2010**, *66*, 4307–4317; (b) Fortner, K. C.; Kato, D.; Tanaka, Y.; Shair, M. D. *J. Am. Chem. Soc.* **2010**, *132*, 275–280; (c) Monrad, R. N.; Pipper, C. B.; Madsen, R. *Eur. J. Org. Chem.* **2009**, 3387–3395.
10. (a) Kim, I. S.; Ryu, C. B.; Li, Q. R.; Zee, O. P.; Jung, Y. H. *Tetrahedron Lett.* **2007**, 6258–6261; (b) Nunez, M. T.; Martin, V. S. *J. Org. Chem.* **1990**, *55*, 1928–1932; (c) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.
11. Bernadat, G.; George, N.; Couturier, C.; Masson, G.; Schlama, T.; Zhu, J. *Synlett* **2011**, 576–578.
12. Fronza, G.; Fuganti, C.; Grasselli, P. *J. Chem. Soc., Perkin Trans. 1* **1982**, 885–891.