Dihydroxylation of 2-Vinylaziridine: Efficient Synthesis of D-*ribo*-Phytosphingosine

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Experimental Details

General ; All reactions were carried out under an atmosphere of nitrogen in oven-dried glasswares with magnetic stirring. Air sensitive reagents and solutions were transferred via syringe and were introduced to the apparatus through rubber septa. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm E. Merck pre-coated silica gel plates (60 F254). Visualization was accomplished with either UV light, or by immersion in solutions of ninhydrin, *p*-anisaldehyde, or phosphomolybdic acid (PMA) followed by heating on a hot plate for about 10 sec. Purification of reaction products was carried out by flash chromatography using Kieselgel 60 Art 9385 (230-400 mesh). ^{1}H-NMR and ^{13}C-NMR spectra were obtained using a Varian Gemini-300 (300 MHz for ^{1}H, and 75 MHz for ^{13}C), or a Varian Inova-500 (500 MHz for ^{1}H, and 125 MHz for ^{13}C) spectrometer. Chemical shifts are reported relative to chloroform (δ = 7.26) for ^{1}H NMR and chloroform (δ = 77.2) for ^{13}C NMR. Data are reported as (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.) Coupling constants are given in Hz. Ambiguous assignments were resolved on the basis of standard one dimensional proton decoupling experiments. Optical rotations were obtained using a Rudolph Autopol III digital polarimeter and optical rotation data was reported as follows: $[\alpha]^{25}_D$ (concentration c = g/100 mL, solvent). Elemental analyses were performed by the Organic Chemistry Research Center at Sogang University using a Carlo Erba EA 1180 elemental analyzer. High resolution mass spectra were recorded on a 4.7 Tesla IonSpec ESI-FTMS or a Micromass LCT ESI-TOF mass spectrometer. Chiral aziridines are available form Aldrich. All commercially available compounds were used as received unless stated otherwise.

(*R*)-2-{[(*Z*)-Hexadec-1-enyl]-1-[(*R*)-1-phenylethyl]}aziridine (2a). To a solution of pentadecyl triphenyl phosphonium bromide (758 mg, 1.37 mmol) in THF (0.3 M) was added 1.48 mL of 1.0 M solution of LiHMDS at -78 ^{o}C. After 10 min at -78 ^{o}C, 200 mg of aziridine-2(*S*)-carboxaldehyde was added at -78 ^{o}C. The resulting mixture was stirred for 2 h at rt and then quenched with sat. aqueous NH_4Cl. The mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under *vacuo*. Purification by column chromatography provided 392 mg of the product in 93% yield. $[\alpha]^{24}_D$ +87.0 (c=1.0, C_5H_5N); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.36-7.19 (m, 5H), 5.44 (dt, J = 11.1, 7.5 Hz, 1H), 5.04 (dd, J = 10.8, 9.0 Hz, 1H), 2.52 (q, J = 6.6 Hz, 1H), 2.08 (m, 1H), 1.90 (d, J = 2.7 Hz, 1H), 1.83 (m, 1H), 1.65 (d, J = 6.3 Hz, 1H), 1.44 (d, J = 6.6 Hz, 3H), 1.3-1.1 (m, 24H), 0.88 ppm (t, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 144.6, 132.8, 129.9, 128.4, 127.1, 126.9, 70.4, 64.9, 37.3, 35.2, 32.0, 29.9, 29.8, 29.7, 29.6, 29.5, 29.4, 29.4, 27.8, 23.3, 22.8, 14.2 ppm; HRMS: m/z calcd for $C_{26}H_{44}N$ $[M+H]^+$ 370.3474, found 370.3476.

(*R*)-2-{[(*E*)-Hexadec-1-enyl]-1-[(*R*)-1-phenylethyl]}aziridine (2b). $[\alpha]^{24}_D$ +44.6 (c=0.35, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.37-7.22 (m, 5H), 5.56 (dt, J = 15.3 , 6.9 Hz, 1H), 5.19 (dd, J = 15.6, 7.2 Hz, 1H), 2.52 (q, J = 6.4 Hz, 1H), 1.89 (d, J=3.6 Hz, 1H), 1.84(m, 1H), 1.58 (d, J=6.3 Hz, 1H), 1.43 (d, J = 6.6 Hz, 3H), 1.3-1.1 (m, 22H), 0.88 ppm (t, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 144.9,

133.4, 129.5, 128.3, 126.9, 126.8, 69.9, 40.3, 35.4, 32.5, 32.1, 29.9, 29.8, 29.7,29.5, 29.3, 29.2, 23.5, 22.9, 14.3 ppm; HRMS: m/z calcd for $C_{26}H_{43}N$ $[M+Na]^+$ 392.3296, found 392.3297.

(*R*)-2-{[(*Z*)-Hex-1-enyl]-1-[(*R*)-1-phenylethyl]}aziridine (2c). $[\alpha]^{24}_D$ -124.2 (c=2.0, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.36-7.18 (m, 5H), 5.44 (dt, J = 10.2, 5.4 Hz, 1H), 5.04 (dd, J = 10.5, 8.7 Hz, 1H), 2.52 (q, J = 6.6 Hz, 1H), 2.08 (m, 1H), 1.87 (m, 3H), 1.65 (d, J = 6.6 Hz, 1H), 1.44 (d, J = 6.6 Hz, 3H), 1.25-1.1 (m, 6H), 0.82 ppm (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 144.6, 133.3, 129.2, 128.3, 126.8, 126.6, 70.1, 36.0, 36.0, 31.4, 29.2, 27.5, 23.2, 22.6, 14.1 ppm; HRMS: m/z calcd for $C_{17}H_{25}N$ $[M+Na]^+$ 266.1887, found 266.1887.

(*R*)-1-{(*R*)-1-phenylethyl)-2-[*(Z)*-styryl]}aziridine (2d). $[\alpha]^{24}_D$ +116.7 (c=0.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.40-7.15 (m, 7H), 6.99-6.96(m, 3H), 6.46 (d, J=11.7 Hz 1H), 5.36(dd, J=11.4, 8.7 Hz 1H), 2.54 (q, J=6.5 Hz 1H), 2.31(m, 1H), 1.98(d, J=3.3 Hz, 1H), 1.72(d, J=3.3Hz, 1H), 1.45(d, J=6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 144.8, 136.9, 132.1,131.3, 128.7, 128.5, 128.2, 127.1, 126.8, 126.8, 70.2, 37.1, 36.6, 23.6 ppm; HRMS: m/z calcd for $C_{18}H_{19}N$ $[M+Na]^+$ 272.1417, found 272.1419.

(*R*)-1-{(*R*)-1-phenylethyl)-2-[*(E)*-styryl]}aziridine (2e). $[\alpha]^{24}_D$ -251.1 (c=1.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.38-7.12 (m, 10H), 6.47(d, 15.9 Hz, 1H), 5.96(dd, J=15.9, 7.2 Hz, 1H), 2.56 (q, J=6.5 Hz, 1H), 2.04 (dd, J=6.9, 3.3 Hz, 1H), 2.00 (t, J=3.3Hz, 1H), 1.68(d, J= 6.1Hz, 1H) 1.44(d, J=6.3Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 144.4, 136.9, 131.1, 129.6, 128.5, 128.3, 127.2, 126.8, 126.5, 126.0, 69.8, 40.3, 36.0, 23.3 ppm; HRMS: m/z calcd for $C_{18}H_{19}N$ $[M+Na]^+$ 272.1417, found 272.1418.

(*R*)-1-{(*R*)-1-phenylethyl)-2-[*(Z)*-3-phenylprop-1-enyl]}aziridine (2f). $[\alpha]^{24}_D$ +58.7 (c=0.8, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.40-7.23 (m, 5H), 7.20-7.10 (m, 3H), 6.93-6.90(m, 2H), 5.59(dt, J=10.8, 7.6 Hz, 1H), 5.18 (dd, J=9, 7.5 Hz, 1H), 3.24(m, 2H), 2.56 (q, J=6.5Hz, 1H), 2.21 (m, 1H), 1.97 (d, J=3.3Hz, 1H), 1.72(d, J=6.6 Hz, 1H), 1.46(d, J=6.6Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 144.6, 140.4, 131.0, 130.3, 128.4, 128.4, 128.4, 127.0, 126.7, 125.9,70.2, 36.0, 35.9, 33.8, 23.3 ppm; HRMS: m/z calcd for $C_{19}H_{21}N$ $[M+Na]^+$ 286.1574, found 286.1576.

(*R*)-1-{(*R*)-1-phenylethyl)-2-[*(E)*-3-phenylprop-1-enyl]}aziridine (2g). $[\alpha]^{24}_D$ +21.7 (c=0.3, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.38-7.11 (m, 10H), 5.72(dt, J=15.3, 7.4 Hz, 1H), 5.29(dd, J=15.3, 7.2 Hz, 1H), 3.31(d, J=6.6Hz, 2H), 2.54(q, J=6.6 Hz, 1H), 1.91(6.6 Hz, 1H), 1.87(d, J=3.3Hz, 1H), 1.61(d, J=6.3 Hz, 1H), 1.43(d, J=6.6Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 144.7, 140.4, 131.4, 131.2, 128.6, 128.4, 128.3, 126.8, 126.7, 126.1, 69.8, 39.9, 38.7, 35.4, 23.3 ppm; HRMS: m/z calcd for $C_{19}H_{21}N$ $[M+Na]^+$ 286.1574, found 286.1576.

(*R,Z*)-1-benzyl-2-(hexadec-1-enyl)aziridine (2h). $[\alpha]^{24}_D$ +35.3 (c=0.3, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.38-7.28 (m, 5H), 5.58 (dt, J= 10.8, 7.5 Hz, 1H), 5.1 (dd, J= 10.5, 9.3 Hz, 1H), 3.56(d, J=1.8 Hz, 2H), 2.25 (m, 1H), 2.20(q, J= 3.9Hz, 2H), 1.1.853.3Hz, 1H), 1.70(d, J=6.3hz, 1H), 1.40-1.25 (m, 24H), 0.93 (t, J=6.5Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 139.1, 133.1, 129.3, 128.3, 127.8, 126.9, 64.6, 36.8, 35.5, 32.0, 29.7, 29.6, 29.5, 29.3, 29.2, 27.7, 22.7, 14.1 ppm; HRMS: m/z calcd for $C_{25}H_{41}N$ $[M+Na]^+$ 378.3139, found 378.3140.

(1*S*,2*R*)-1-{[(*R*)-1-Phenylethyl]aziridine-2-yl)}hexadecane-1,2-diol (3Aa). To a solution of 50 mg of the substrate (**2a**) and NMO (3.0 equiv.) in Acetone/H_2O (9:1) (0.1 M) pre-cooled to 0 ºC was added a solution of 40 µL of OsO_4 (5 wt % in H_2O). The solution was stirred until the reaction was completed (TLC analysis, ca. 4 h) at 0 ºC. The reaction was quenched by aqueous sodium sulfite solution, extracted with CH_2Cl_2, dried over Na_2SO_4 and purified by column chromatography to give 46.0 mg of *ribo* **3a** and 3.0 mg of *threo* **3b** in 83% and 5% yield, respectively. $[\alpha]^{25}_D$ +14.0 (c=1.0, C_5H_5N); ^{1}H

NMR (300 MHz, $CDCl_3$) δ = 7.35-7.25 (m, 5H), 3.52-3.43 (m, 2H), 2.59 (q, J = 6.6 Hz, 1H), 2.03 (d, J = 3.3 Hz, 1H), 1.70-1.66 (m, 1H), 1.49 (d, J = 6.6 Hz, 1H), 1.42 (d, J = 6.6 Hz, 3H), 1.35-1.10 (m, 26H), 0.88 ppm (t, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 144.1, 128.5, 127.3, 126.6, 73.3, 71.5, 69.5, 38.3, 31.9, 31.6, 30.3, 29.6, 29.3, 25.8, 22.9, 22.6, 14.1 ppm; HRMS: m/z calcd for $C_{26}H_{46}NO_2$ $[M+H]^+$ 404.3529, found 404.3522.

(2*S*,3*S*,4*R*)-2-[(*R*)-1-Phenylethylamino]octadecane-1,3,4-triol (4). To a round bottom flask was charged with 120 mg of the substrate (**3a**) in CH_2Cl_2 (0.3 M). AcOH (5 equiv. of the substrate) was added at rt and the mixture was stirred for 8 h. The reaction was quenched with aqueous $NaHCO_3$, extracted with CH_2Cl_2 and concentrated in *vacuo*. The crude product was dissolved in EtOH (0.3 M) and KOH (3 equiv.) was added. After stirring 3 h at RT, the reaction mixture was quenched with water. The mixture was extracted with CH_2Cl_2, dried over Na_2SO_4 and purified by column chromatography to give 116 mg of the product (**4**) in 93% yield; $[\alpha]^{25}_D$ +29.2 (c=1.0, C_5H_5N); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.34-7.24 (m, 5H), 3.94 (q, J = 6.6 Hz, 1H), 3.79 (d, J = 5.7 Hz , 2H), 3.52-3.48 (m, 1H), 3.32 (t, J = 6.9 Hz, 1H), 2.58-2.57 (m, 1H), 1.39 (d, J = 6.6 Hz, 3H), 1.30-1.24 (m, 26H), 0.88 ppm (t, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 144.4, 128.9, 127.7, 127.2, 74.1, 73.9, 58.9, 55.7, 33.3, 32.2, 29.9, 29.6, 25.6, 24.9, 22.9, 14.3 ppm; HRMS: m/z calcd for $C_{26}H_{48}NO_3$ $[M+H]^+$ 422.3634, found 422.3639.

(2*S*,3*S*,4*R*)-2-Aminooctadecane-1,3,4-triol (1, D-*ribo*-phytosphingosine). To a solution of the substrate (**4**) (100 mg, 0.24 mmol) in EtOH (0.3 M) was added $Pd(OH)_2$ (20 wt %) at rt under H_2(g) 100 psi. The reaction mixture was filtered and the filtrate was concentrated in *vacuo*. Purification by column chromatography provided 70 mg of the product (**1**) in 92% yield. $[\alpha]^{24}_D$ +10.1 (c=1.0, C_5H_5N) [lit.[1] $[\alpha]^{20}_D$ +9.5 (c=1.0, C_5H_5N); lit.[2] $[\alpha]^{23}_D$ +7.6 (c=1.0, C_5H_5N)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.75 (dd, J = 10.8, 4.2 Hz, 1H), 3.56 (dd, J = 10.8, 6.6 Hz, 1H), 3.5-3.4 (m, 1H), 3.36-3.24 (m, 2H), 2.99-2.90 (m, 1H), 1.80-1.70 (m, 1H), 1.60-1.50 (m, 3H), 1.40-1.20 (m, 24H), 0.88 (t, J = 6.3 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 77.4, 75.4, 65.1, 56.8, 35.6, 33.9, 31.8, 31.6, 31.3, 27.4, 24.6, 15.3 ppm; HRMS: m/z calcd for $C_{18}H_{40}NO_3$ $[M+H]^+$ 318.3008, found 318.3006.

***N*-Boc-(2S,3S,4R)-2-Aminooctadecane-1,3,4-triol (5).** To a solution of the substrate (**4**) (50 mg, 0.12 mmol) in EtOH (0.2 M) was added $Pd(OH)_2$ (20 wt%) and $(Boc)_2O$ (52 mg, 0.24 mmol) at rt under 100 psi of H_2(g). When the reaction was completed, it was filtered and the filtrate was concentrated in *vacuo*. Purification by column chromatography provided 47 mg of the product (**5**) in 95% yield. $[\alpha]^{25}_D$ +7.7 (c=1.0, $CHCl_3$), +7.9 (c=0.7, $CHCl_3$) [lit.[1] $[\alpha]^{26}_D$ +7.7 (c=1.0, $CHCl_3$); lit.[3] $[\alpha]^{22}_D$ +7.9 (c=1.0, CHCl3)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.36 (d, J = 7.5 Hz, 1H), 3.85-3.90 (m, 2H), 3.76 (m, 1H), 3.63-3.69 (br, m, 2H), 3.44 (br, d, J = 6.5 Hz, 2H), 2.91 (br, 1H), 1.67-1.72 (m, 2H), 1.45 (s, 9H), 1.26-1.31 (m, 24H), 0.88 (t, J = 7Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ =156.7, 80.3, 76.4, 73.1, 62.1, 53.2, 33.3, 32.1, 29.89, 29.87, 29.85, 29.83, 29.6, 28.5, 26.1, 22.9, 14.3 ppm; HRMS: m/z calcd for $C_{23}H_{47}NNaO_5$ $[M+Na]^+$ 440.3352, found 440.3359.

Phytosphingosine tetraacetate (6). To a solution of the substrate (**1**) (40 mg, 0.13 mmol) was added Pyridine (1.5 mL) and Acetic anhydride (1.5 mL) at rt under N_2 atmosphere. The reaction mixture was stirred overnight. To the reaction mixture was added aqueous $CuSO_4$ solution (4 mL) and neutralized with sat. aqueous $NaHCO_3$ (5 mL). The reaction mixture was extracted with EtOAc (3 mL X 5) and the organic layer was washed with aqueous $CuSO_4$ solution (3 mL x 3). The organic layer was concentrated in *vacuo* and purified by column chromatography to provide 60 mg of the product (**6**) in 98% yield. $[\alpha]^{23}_D$ +22.7 (c=1.0, $CHCl_3$) [lit.[1] $[\alpha]^{20}_D$ +21.9 (c=1.1, $CHCl_3$)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ =6.03 (d, J = 9 Hz, 1H), 5.08 (dd, J = 3 Hz, 8.4 Hz, 1H), 4.92 (dt, J = 3.3 Hz, 9.3 Hz, 1H), 4.45 (m, 1H), 4.27 (dd, J = 4.8 Hz, 11.7 Hz, 1H), 3.98 (dd, J = 3 Hz, 11.7 Hz, 1H), 2.06 (s, 3H), 2.03 (s, 6H), 2.00 (s, 3H), 1.23-1.30 (m, 26H), 0.86 (t, J = 6.3Hz, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.2, 170.9, 170.2, 169.8, 73.1, 72.2, 63.0, 47.7, 32.0, 29.76, 29.71, 29.67, 29.58, 29.44, 29.39, 28.3, 25.6,

23.3, 22.8, 21.1, 20.84, 20.81, 14.2 ppm; HRMS: m/z calcd for $C_{26}H_{47}NNaO_7$ $[M+Na]^+$ 508.3250, found 508.3256.

References

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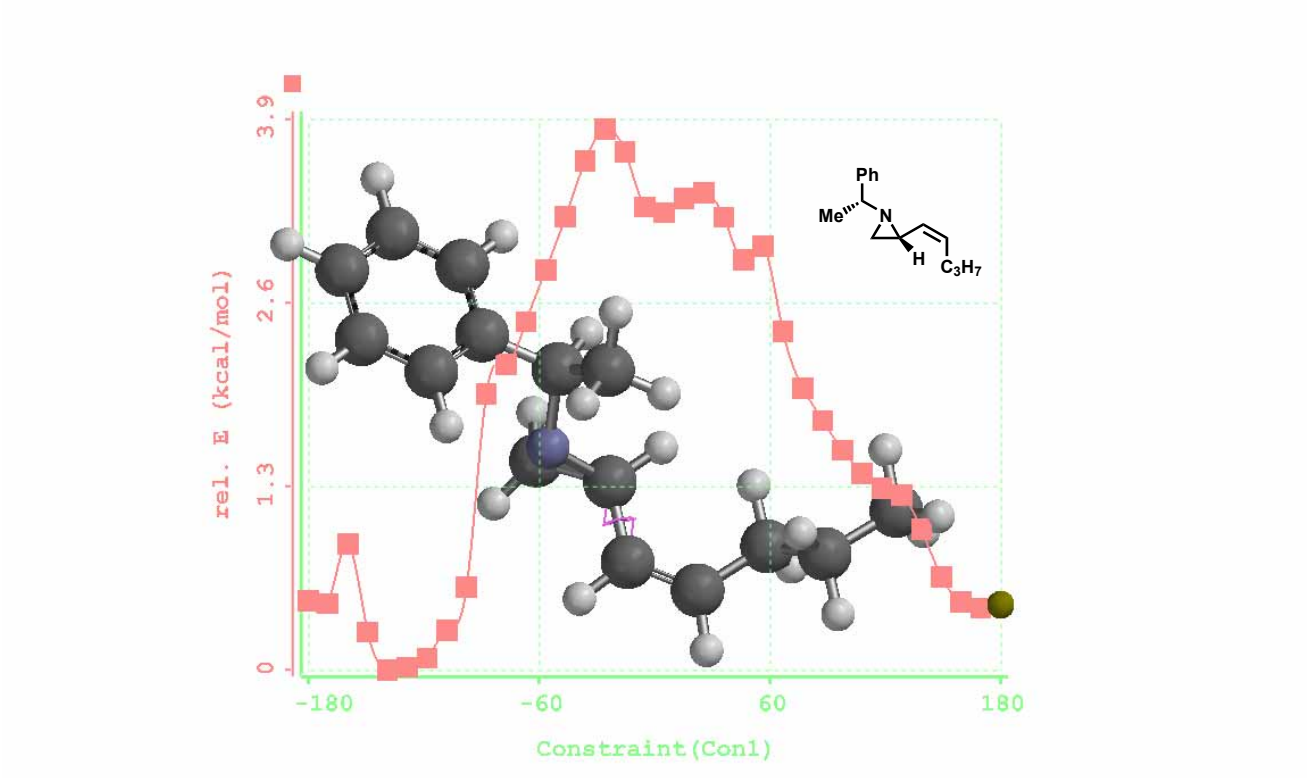
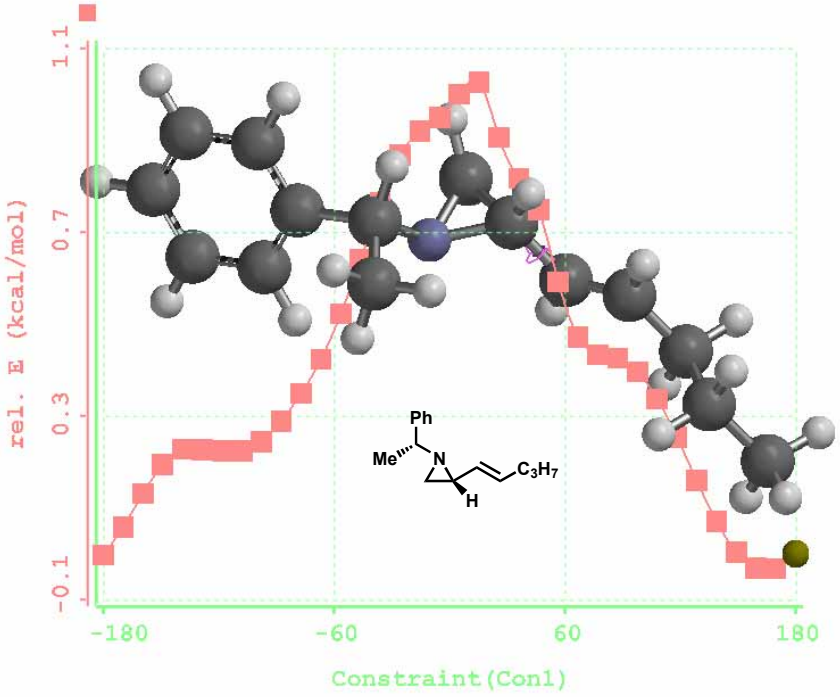
Calculation of the rotational energy barrier regarding to the Figure 2.

Rotational energy barriers along the bond between C2 of the aziridine and C1 of the vinyl group were calculated by the simplified compounds with shorter alkyl chain length as (*Z*)- and (*E*)-(*S*)-2-[pent-1-enyl]-1-[(*R*)-1-phenylethyl]}aziridine. These values would give insights into the rotations such as a, b and a', b' in Fig. 2 for the compounds (*Z*)-(**2a**) and (*E*)-(*R*)-2-[hexadec-1-enyl]-1-[(*R*)-1-phenylethyl]}aziridine (**2a**). At first minimum energy conformers for each of two compounds were calculated on the basis of PM3 method written in the commercial package program Spartam 04, whose structures were shown in the following figures. Then rotational energies along the C-C bond between C2 of the aziridine and C1 of the vinyl group were calculated by 10 degree in the same manner as a and b for (*Z*)-isomer and a' and b' for (*E*)-isomer in Fig. 2. The rotational energy barrier for (*Z*)-(*R*)-2-[pent-1-enyl]-1-[(*R*)-1-phenylethyl]}aziridine was 3.9 Kcal/mol while (*E*)-isomer has 1.1 Kcal/mol. The energy difference between the conformers **A** and **B** was about 3.2 Kcal/mol that was much larger than 0.9 Kcal/mol for the difference of **A**' and **B**'.




rel. E (kcal/mol)
1.1
0.7
0.3
-0.1
-180
-60
60
180
Constraint(Con1)
Ph
Me
N
H
C3H7