Pergamon

Tetrahedron 57 (2001) 8959–8964

TETRAHEDRON

Acceleration of hetero-Michael reaction by symmetrical pentacyclic guanidines

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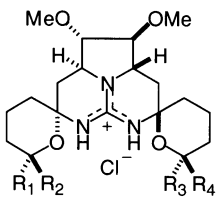
Received 19 July 2001; accepted 7 September 2001

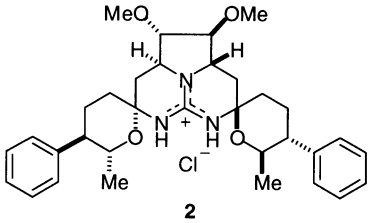
Abstract—Symmetrical pentacyclic guanidines **1a–c** and **2** which contain the core skeleton of 13,14,15-isocrmbescidine 800, have been synthesized. In the presence of catalytic amounts of these guanidines **1**, the reaction rate of the conjugate addition of pyrrolidine (**9**) to γ-crotonolactone (**10**) could be enhanced depending upon the size of the cavities and substituents on tetrahydropyran rings of **1** and **2**.

1. Introduction

The guanidine group present in the side chain of arginine is ubiquitous in an enzyme that binds anionic substrates and also contributes to the stabilization of protein's three-dimensional structures by forming salt with carboxylate function.[1] In nature a variety of guanidine-containing natural products have been isolated which have attracted much attention because of their interesting activities, mostly arising from the two peculiar parallel interactions including hydrogen bonding of the guanidinium ion with phosphate-containing biomolecules.[2] Due to the strong ability of guanidine to set a pair of zwitter ionic hydrogen bonds with anionic compounds and to stabilize their anionic transition state, the guanidine-contained molecules suggest to us their use as a new reaction vessel. In addition, the partial protonation from guanidine-containing molecules (hosts) through the substrate molecules (guests) can be expected to influence the guests reactivities by changing the electronic properties.[3] As a consequence, several synthetic applications have appeared using not only guanidines but also amidines as a catalyst. For example, Strecker reaction,[4a,b] acylataion,[4c] silylation,[4d] Wittig and Horner–Emmons reactions,[4e] Diels–Alder reaction,[4f] Henry reaction,[4g] epoxidation,[4h] and Michael reaction.[4i–l] Inspired by these recent advances in guanidine and amidine-mediated reactions, we decided to investigate the possibilities of developing the cyclic compounds an non-metal containing organic chiral catalyst, which are not considered to have much unfavorable environment effect.

We planned to synthesize four new symmetric pentacyclic guanidines **1a–c** and **2** for the achievement of new chiral catalysts on the basis of our recent studies[5] concerning the synthesis of ptilomycalin A[6] and its analogs.[7] The sustituents on the tetrahydropyran rings of guanidine **1** and **2** can be expected to control the conformation of the core structure around the guanidine moiety through their favorable equatorial position and provide us with a variety cavity of sizes around the guanidine.





2

1a R_1=Me, R_2 =H, R_3=H, R_4 =Me
1b R_1=H, R_2 =Me, R_3=Me, R_4 =H
1c R_1=Me, R_2 =H, R_3=Me, R_4 =H

2. Results and discussion

Following the procedure in our previous paper,[5] we synthesized a family of new symmetrical pentacyclic guanidine analogs **1a–c** and **2**, which can be seen in the core structure of 13,14,15-isocrambescidine 800 (Scheme 1). The 1,3-dipolar cycloaddition reaction of the optically active nitrone **3**,[8] obtained from L-(+)-tartaric acid, and olefin **4**[9] in toluene at 110°C, stereoselectively gave isoxazolidine **6** in 50–70% yield. The isoxazolidine **7** was treated with *m*-CPBA to regenerate the nitrone regioselectively,[10] which was subjected to the second 1,3-dipolar cycloaddition reaction with an olefin **4**[9] to provide isoxazoline **7** in 40–60% yield. After hydrogenation of **7** with Pd–C, the pyrrolidine **8** was subjected to bis *N*-Boc thiourea with $HgCl_2$[11]

Keywords: pentacyclic guanidine; organic chiral catalysts; 1,3-dipolar cycloaddition reaction; hetero-Michael reaction.

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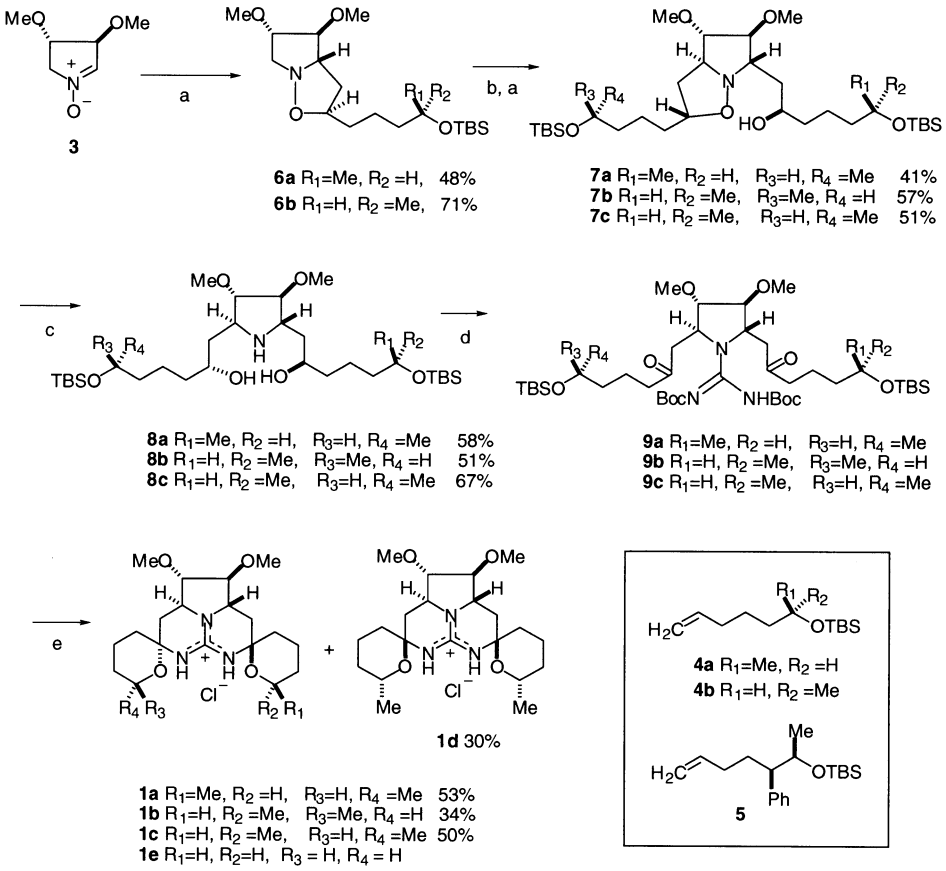
PII: S0040-4020(01)00907-3



Scheme 1. (a) **4**, Toluene, reflux, 24 h; (b) mCPBA, 0°C, CH_2Cl_2, 10 min; (c) Pd/C, H_2, EtOH, rt, 24 h; (d) (i) bis-*N*-Boc thiourea, $HgCl_2$, DMF, rt, 1 h, (ii) TPAP, NMO, rt, 1 h, (e) HCl/MeOH, rt, 24 h.

and subsequent treatment under TPAP-NMO conditions[12] to oxidize the diol that gave the guanylated diketone **9**. Deprotection of Boc and TBS groups took place by treatment with methanolic hydrogen chloride, and double N, O-acetalization simultaneously occurred to give the symmetric pentacyclic guandiene **1** in 30–50% yield. During the synthesis of **1b**, it was accompanied by **1d** (30%; structure was confirmed with the X-ray crystallography) at the final N, O-acetalization step. With following the same reaction sequences described above, pentacylic guanidine **2** was synthesized with nitron **3** and olefin **5**.[9]

The X-ray crystallographic analyses of **1a–c** and **2** were performed in order to establish the cavity sizes around the guanidines (Fig. 1). It was realized that **1a** has a closed-type cavity similar to **1e**.[5,13] In contrast, **1b** has an open-type cavity and **1c** has almost a half-size cavity between those **1a** and **1b** (half open-type cavity). At the final N,O-acetalization step under acidic conditions during the synthesis of **1**, the chair conformation of the forming spiro tetrahydropyran rings are fixed in a way to avoid 1,3-diaxial repulsion between the methyl group and guanidine-containing ring, thus in a case of **1a**, two tetrahydropyran rings are situated closer to each other that form a small cavity (close-type). In turn, the two rings in **1b** are situated away from each other which makes a large cavity (open-type). On the other hand, pentacyclic guanidine **2**, which has the phenyl substituent on tetrahydropyran ring at C3′ position of **1a**, has the similar close-type cavity but deeper than that of **1a** and **1e** from the X-ray crystallographic analysis. These observations show that the stereochemistries and positions of the substituents on tetrahydropyran ring can control the cavity size of petacyclic guanidine of **1** and **2**.

With these pentacyclic guanidines **1** and **2** which have the variety cavity size around the guanidine function in hand, we investigated their application as catalysts in the hetero-Michael reaction of pyrrolidine (**9**) with an unsaturated lactone **10**. This reaction is already considerably attractive as a catalytic reaction model for cyclic guanidines.[4i,j] The reaction was carried out under conditions identical to Mendoza's procedures[4i,j] (ratio of **9**, **10** and catalyst **1** or **2** is 1:1:0.1, concentration of the substrates **9** and **10** is controlled at 0.3 M in $CDCl_3$). With the guanidine **1a**, **1b** and **1c** as a catalyst, 2.3, 8.3 and 3.4-fold increase in the reaction rate were observed, respectively, over the uncatalyzed reaction conditions. In the case of **1e**, almost the same reaction acceleration effect as **1a** was found. Interestingly, the reaction was accelerated as the similar level of **1b** when the phenyl and methyl substituted pentacyclic guanidine on its tetrahydropyran rings **2** was used as the catalyst even it has the close-type cavity. The phenyl group of guanidine **2** probably assisted to take the lactone **10** into its guanidine core site through the π–π interactions between the phenyl group of **2** and **10**, and the reaction was accelerated. These results show that the lactone **10** recognized the cavity of **1**

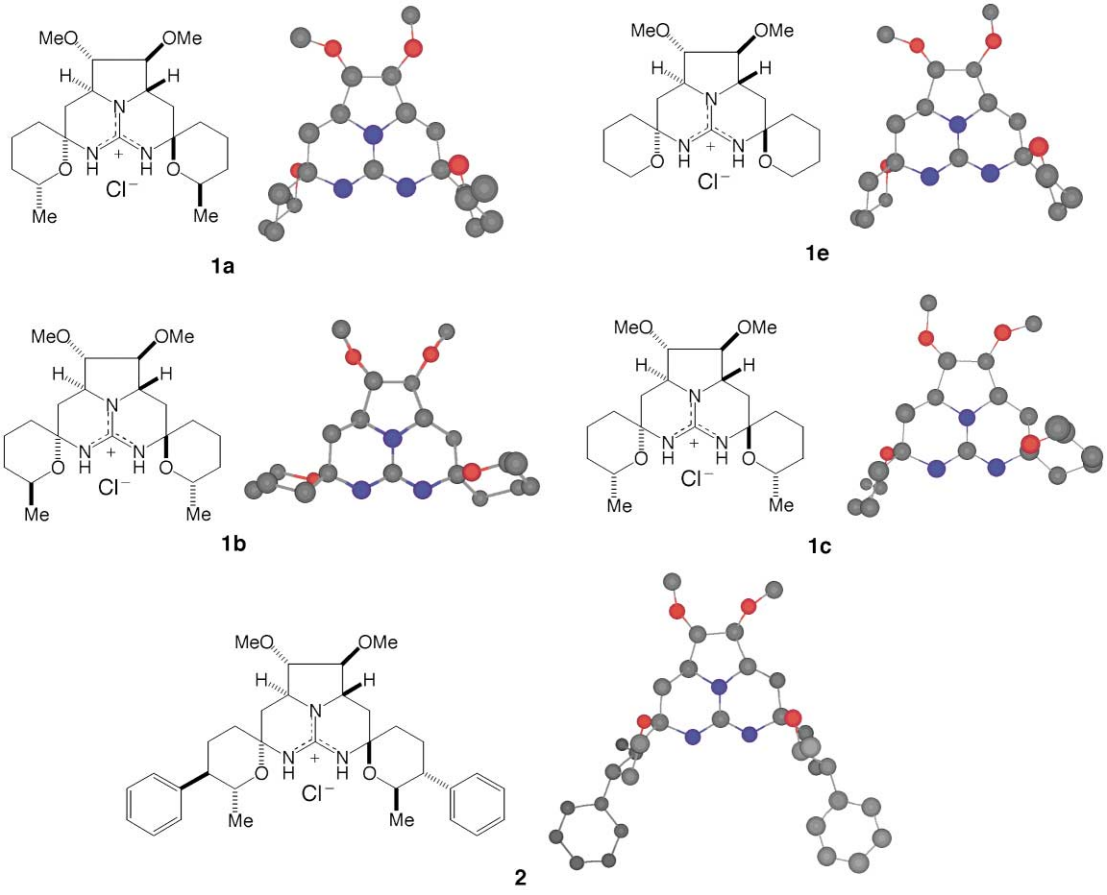
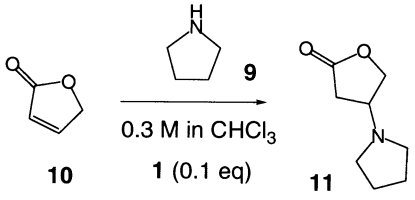


Figure 1. X-Ray structures of **1a–c**, **1e** and **2**.

and **2**, and the reactivity of **10** was activated simultaneously through a two-point hydrogen bonding interaction with the guanidinium moiety of **1** and **2**,[4i] thus the reaction rate can be controlled in proportion to the cavity size and sustituents on tetrahydropyran rings of the guanidine **1** and **2**.[14]



base	$t_{1/2}$ min	rel. rate increase
none	190	----
1a	82	2.3
1e	78	2.4
1b	23	8.3
1c	57	3.4
2	30	6.3

3. Conclusion

In summary, we have designed and synthesized the symmetrical pentacyclic guanidine **1** and **2** having various cavity sizes as a catalyst for the hetero-Michael reaction, and its reaction rate could be controlled depending upon the cavity size and substituents of **1** and **2**. Our efforts toward the applications for variety types of reactions with guanidines **1** and **2** as a catalyst are under investigated.

4. Experimental

4.1. General

Optical rotations were recorded with a JASCO DIP-370 polarimeter. IR spectra were measured with a JASCO VALOR-III FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on JNM-EX-300 and DELTA-NMR-ECP500 instruments. Mass spectra were recorded on JEOL JMA-HX110 spectrometers. Flash chromatography was performed on silica gel 60 (230–400 mesh; E-Merck Darmstadt, Germany).

4.1.1. (2*R*,3a*S*,4*S*,4′*R*,5*S*)-2-[4′-(*tert*-Butyldimethylsilyloxy)pentyl]-4,5-dimethoxyhexahydropyrrolo[1,2-*b*]isoxazole (6a). A mixture of crude nitrone **3** (2.40 g, 16.6 mmol) and **4a** (33.1 mmol) in toluene (280 mL) was stirred at 95°C for 24 h. After cooling the reaction mixture to room temperature, the solvent was evaporated in vacuo, and the residue was purified with silica gel chromatography (hexanes/ether, 1:1) to give **6a** (2.96 g, 48%) as a clear

brown oil. $[\alpha]_D^{25}=-1.5$ (*c* 3.0, $CHCl_3$). IR (neat) 3350, 2915, 1720, 1470, 1380, 1280, 1120 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.10 (m, 1H), 3.75 (m, 2H), 3.55 (m, 3H), 3.37 (m, 3H), 3.36 (s, 3H),3.03 (s, 1H),2.17 (m, 1H), 2.02 (m, 1H), 1.40 (m, 6H), 1.09 (d, *J*=6.0 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 3H), −0.02 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 88.45, 82.31, 69.78, 69.24, 68.59, 66.90, 57.49, 56.56, 50.89, 39.75, 37.71, 25.88, 23.69, 21.75, 18.17, −4.43, −4.81. HRMS (FAB, M+H) calcd for $C_{19}H_{40}NO_4Si$ 374.2727, found 374.2724.

4.1.2. (2*R*,2″*R*,3a*S*,4*S*,4′*R*,5*S*,6*S*,6″*R*)-2-[4′-(*tert*-Butyldimethylsilyloxy)pentyl]-6-[6″-(*tert*-butyldimethylsilyloxy-2″-hydroxyheptyl)-4,5-dimethoxyhexahydropyrrolo-[1,2-*b*]isoxazole (7a). To a solution of **6a** (1.93 g, 5.20 mmol) in dichloromethane was added *m*-CPBA (1.0 g, 5.9 mmol) at 0°C and the resulting mixture was stirred for 20 min. $Ca(OH)_2$ was added to the reaction mixture and stirred for another 10 min at room temperature. The mixture was filtered through a pad of Celite and the filtrates were concentrated in vacuo to give nitrone as a clear brown oil. A mixture of the generated nitrone and **4a** (3.55 g, 15.6 mmol) in toluene (130 mL) was heated at 100°C for 24 h. After removal of the solvent under reduced pressure, the residue was purified with silica gel chromatography (hexanes/ether 7:3) to give **7a** (1.30 g, 41%) as a clear light brown oil. $[\alpha]_D^{25}=-19.0$ (*c* 1.2, $CHCl_3$). IR (neat) 3425, 2925, 1720, 1460, 1380, 1260, 1105 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.06 (m, 1H), 3.88 (m, 1H), 3.75 (m, 2H), 3.50 (m, 3H), 3.44(s, 3H), 3.36 (s, 3H), 3.16 (m, 1H), 2.09 (m, 2H), 1.75 (t, *J*=5.4 Hz, 2H), 1.40 (m, 12H), 1.08 (d, *J*=6.0 Hz, 6H), 0.86 (s, 9H), 0.85 (s, 9H), 0.06 (s, 6H), 0.01 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 89.51, 85.82, 75.65, 68.87, 68.58, 68.29, 66.57, 65.72, 58.64, 57.62, 40.91, 39.72, 39.52, 38.51, 37.45, 32.72, 25.90, 25.89, 23.74, 23.69, 22.50, 21.87, 18.14, 18.11, −4.39, −4.44, −4.70, −4.72. HRMS (FAB, M+H) calcd for $C_{32}H_{68}NO_6Si_2$ 618.4585, found 618.4586.

4.1.3. (2*S*,2′*R*,3*S*,4*S*,5*S*,6′*R*)-2,5-[6′-(*tert*-Butyldimethylsilyloxy)-2′hydroxyheptyl]-3,4-dimethoxypyrrolidine (8a). A mixture of isoxazolidine **7a** (1.5 g, 2.43 mmol) and 10% Pd–C (370 mg) in ethanol (15 mL) was stirred at room temperature for 1 day under hydrogen. Reaction mixture was filtered thorough a pad of Celite and the filtrates were concentrated in vacuo. The residue was purified with silica gel chromatography (hexanes/ethyl acetate, 1:1, 0:1) to give **8a** (870 mg, 58%). $[\alpha]_D^{25}=-45.1$ (*c* 0.7, $CHCI_3$). IR (neat) 3370, 2930, 1480, 1260, 1110 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.75 (brs, 1H), 3.91 (m, 2H), 3.76 (m, 4H), 3.60 (m, 2H), 3.39 (s, 6H), 2.01 (m, 2H), 1.74 (m, 2H), 1.42 (m, 12H), 1.26 (m, 2H), 1.08 (d, *J*=7 Hz, 6H), 0.85 (s, 18H), 0.01 (s, 12H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 87.62, 68.49, 67.93, 39.56, 36.81, 39.69, 36.67, 37.04, 25.90, 23.67, 21.76, 18.12, −4.34, −4.66. HRMS (FAB, M+H) calcd for $C_{32}H_{70}NO_6Si_2$ 620.4742, found 620.4752.

4.1.4. (1*S*,2*S*,2a*S*,4*R*,6′*R*,7*R*,8a*S*)-1,2-Dimethoxy-4,7-(6′-methyl-2′-tetrahydropyranyl)-2,2a,3,4,5,7,8,8a-octahydro-1*H*-5,6,8b-triazaacenaphthylene hydrochloride (1a). To a mixture of pyrrolidine **8a** (900 mg, 1.45 mmol), bis-Boc-thiourea (440 mg, 1.60 mmol) and triethylamine (0.71 mL, 5.10 mmol) in DMF (4 mL) was added $HgCl_2$(433 mg, 1.60 mmol) at 0°C and the resulting mixture was stirred for 30 min. The reaction mixture was diluted with ethyl acetate and filtered through a pad of Celite. The filtrates were washed with brine and the organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified with silica gel chromatography (hexanes/ethyl acetate, 6:1, 2:1) to give the corresponding bis-Boc protected guanidine (1.04 g, 83%). To the guanidine (1.04 g, 1.20 mmol) in dichloromethane (30 mL) was added 4-methylmorpholine *N*-oxide (80 mg, 4.8 mmol) and a catalytic amount of tetrapropylammonium perruthenate, and the mixture was stirred at room temperature for 30 min. The reaction mixture was loaded on a short silica gel column directly (hexanes/ethyl acetate, 1:1) to give diketone **9a** (1.0 g). The diketone **9a** (1.0 g, 1.2 mmol) was dissolved in hydrogen chloride solution in methanol (80 mL) and the mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated in vacuo, and the residue was purified with silica gel chromatography (chloroform/methanol, 100:1) to give **1a** (320 mg, 53%) as a white crystal. Mp 245–246°C (decomposition). $[\alpha]_D^{24}=+148.7$ (*c* 1.2, $CHCl_3$). IR (neat) 3100, 2950, 1600, 1620, 1450, 1340, 1200, 1120, 1020 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 10.03, (s, 2H), 3.93 (m, 2H), 3.74 (s, 2H), 3.63 (m, 2H), 3.54 (s, 6H), 2.29 (m, 4H), 1.82 (d, *J*=13 Hz, 2H), 1.76 (m, 5H), 1.63 (m, 2H), 1.19 (m, 2H), 1.09 (d, *J*=6.0 Hz, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.8, 86.34, 80.92, 67.11, 59.41, 52.23, 38.73, 34.48, 32.30, 21.82, 18.59. HRMS (FAB, M+H) calcd for $C_{21}H_{36}N_3O_4$ 394.2706, found 394.2706.

4.1.5. (2*R*,3a*S*,4*S*,4′*S*,5*S*)-2-[4′-(*tert*-Butyldimethylsilyloxy)pentyl]-4,5-dimethoxyhexahydropyrrolo[1,2-*b*]-isoxazole (6b). From nitrone **3** (1.12 g, 7.60 mmol) and **4b** (2 equiv., 15.2 mmol) was obtained **6b** (2.0 g, 71%) as a clear brown oil after purification with silica gel chromatography (hexanes/ether, 1:1). $[\alpha]_D^{25}=-15.7$ (*c* 2.1, $CHCI_3$). IR (neat) 2950, 1470, 1380, 1475, 1260, 1120, 1110 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.07 (m, 1H), 3.73 (m, 2H), 3.54 (m, 3H), 3.35 (s, 3H) 3.34 (s, 3H), 3.03 (m, 1H), 2.16 (m, 1H), 2.03 (m, 1H), 1.59 (m, 1H), 1.43 (m, 4H), 1.36 (m, 2H), 1.07 (d, *J*=6 Hz, 3H), 0.84 (s, 9H), 0.01 (6H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 90.18, 83.95, 75.71, 68.96, 68.26, 58.29, 57.45, 57.40, 40.49, 39.49, 33.39, 25.74, 23.59, 22.48, 17.95, −4.55, −4.87. HRMS (FAB, M+H) calcd for $C_{19}H_{40}NO_4Si$ 374.2727, found 374.2725.

4.1.6. (2*R*,2″*R*,3a*S*,4*S*,4′*S*,5*S*,6*S*,6″*S*)-2-[4′-(*tert*-Butyldimethylsilyloxy)pentyl]-6-[6″-(*tert*-butyldimethylsilyloxy-2″-hydroxyheptyl)]-4,5-dimethoxyhexahydropyrrolo[1,2-*b*]isoxazole (7b). From **6b** (2.0 g, 5.4 mmol) in 2 steps was obtained **7b** (1.9 g, 57%) as a clear light brown oil after purification with silica gel chromatography (hexanes/ether, 4:1). $[\alpha]_D^{25}=-27.4$ (*c* 1.3, $CHCl_3$). IR (neat) 3470, 2940, 1460, 1380, 1250, 1120 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.05 (m, 1H) 3.87 (m, 1H), 3.74 (m, 2H), 4.65 (m, 3H) 3.44 (s, 3H), 3.35 (s, 3H), 3.17 (m, 1H), 2.16 (m, 1H), 2.03 (m, 1H) 1.75 (t, *J*=5.4 Hz, 2H), 1.65 (m, 1H), 1.38 (m, 11H), 1.08 (d, *J*=6.0 Hz, 3H), 0.85 (s, 9H), 0.84 (s, 9H), 0.04 (s, 6H), 0.01 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 89.41, 85.79, 75.57, 68.87, 68.51, 68.20, 66.50, 65.67, 58.44, 57.45, 40.81, 39.75, 39.41, 38.46, 32.68, 25.80, 25.77, 23.64, 21.93, 17.98, −4.51,

−4.55, −4.80, −4.83. HRMS (FAB, M+H) calcd for $C_{32}H_{68}NO_6Si_2$ 618.4585, found 618.4581.

4.1.7. (2*S*,2′*R*,3*S*,4*S*,5*S*,6′*S*)-2,5-[6′-(*tert*-Butyldimethylsilyloxy)-2′-hydroxyheptyl]-3-4-dimethoxypyrrolidine (8b). From **7b** (1.89 g, 3.05 mmol) was obtained **8b** (967 mg, 51%) as clear light brown oil after purification with silica gel chromatography (hexanes/ethyl acetate, 1:1, 0:1). $[\alpha]_D^{25}$=−46.4 (*c* 0.9, $CHCl_3$). IR (neat) 3375, 2950, 1470, 1260, 1110 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.27 (brs, 1H), 3.86 (m. 2H), 3.75 (m, 2H), 3.62 (m, 2H), 3.54 (m, 2H), 3.69 (s, 6H), 1.88 (m, 4H), 1.66 (m, 2H), 1.53 (m, 2H), 1.39 (m, 10H), 1.09 (d, *J*=7 Hz, 6H), 0.86 (s, 18H), 0.02 (s, 12H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 88.97, 68.70, 68.55, 58.94, 57.72, 39.69, 37.30, 37.04, 25.90, 23.73, 22.03, 18.12, −4.36, −4.66. HRMS (FAB, M+H) calcd for $C_{32}H_{70}NO_6Si_2$ 620.4742, found 620.4747.

4.1.8. (1*S*,2*S*,2a*S*,4*R*,6′*S*,7*R*,8a*S*)-1,2-Dimethoxy-4,7-(6′-methyl-2′-tetrahydropyranyl)-2,2a,3,4,5,7,8,8a-octahydro-1*H*-5,6,8b-triazaacenaphthylene hydrochloride (1b) and (1*S*,2*S*,2a*S*,4*R*,6′*S*,7*S*,8a*S*)-1,2-dimethoxy-4,7-(6′-methyl-2′-tetrahydropyranyl)-2,2a,3,4,5,7,8,8a-octahydro-1*H*-5,6,8b-triazaacenaphthylene hydrochloride (1d). From **8b** (414 mg, 0.67 mmol) in 3 steps after separation and purification with silica gel chromatography ($CHCl_3$/CH_3OH, 100:0.5, 100:1) were obtained **1b** (98 mg, 34%) and **1d** (90 mg, 30%) as white crystals. Data for **1b**: mp 189–190°C (decomposition). $[\alpha]_D^{24}$=+92.5 (*c* 0.6 $CHCl_3$). IR (neat) 3180, 2960, 1650, 1620, 1450, 1180, 1120, 1030 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 9.54 (s, 2H) 3.56 (m, 4H), 3.51 (s, 6H), 2.80 (d, *J*=12.5 Hz, 2H), 1.82 (m, 6H), 1.12 (d, *J*=6.0 Hz, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.7, 86.05, 81.79, 68.55, 59.30, 52.00, 34.77, 31.46, 30.73, 22.07, 20.02. HRMS (FAB, M+H) calcd for $C_{21}H_{36}N_3O_4$ 394.2706, found 394.2714. Data for **1d**: mp 161–162°C. $[\alpha]_D^{24}$=+59.2 (*c* 0.6, $CHCl_3$). IR (neat) 3180, 2920, 1660, 1630, 1440, 1110 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 10.11 (s, 1H), 9.54 (s, 1H), 4.19 (m, 1H), 3.68 (m, 1H), 3.60 (m, 3H), 3.54 (s, 3H), 3.53 (s, 3H), 3.39 (m, 1H), 2.87 (d, *J*=13 Hz, 1H), 2.44 (d, *J*=13 Hz, 1H), 2.17 (m, 2H), 2.09 (m, 2H), 1.92 (m, 4H), 1.71 (m, 2H), 1.57 (m, 1H), 1.49 (m, 1H), 1.24 (m, 1H), 1.18 (d, *J*=6.0 Hz, 3H), 1.12 (d, *J*=6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.9, 86.93, 86.71, 83.31, 81.76, 68.76, 68.52, 59.53, 59.25, 53.88, 51.96, 42.14, 37.77, 34.62, 32.23, 31.61, 31.24, 22.12, 22.05, 20.06, 18.09. HRMS (FAB, M+H) calcd for $C_{21}H_{36}N_3O_4$ 394.2706, found 394.2712.

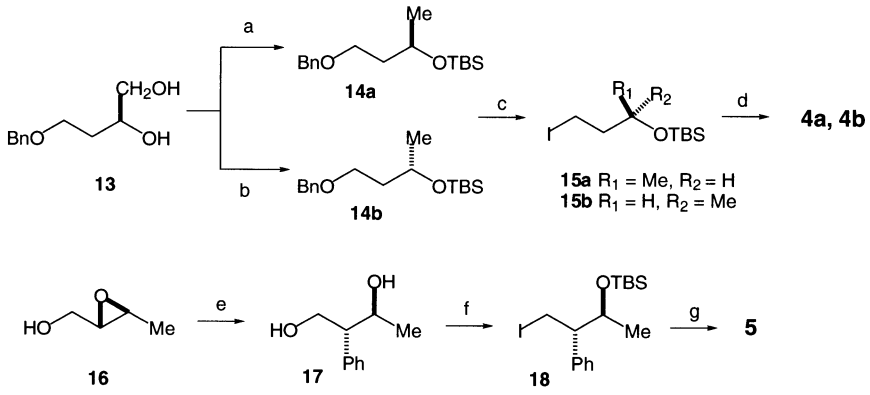
4.1.9. (2*R*,2″*R*,3a*S*,4*S*,4′*R*,5*S*,6*S*,6″*S*)-2-[4′-(*tert*-Butyldimethylsilyloxy)pentyl]-6-[6″-(*tert*-butyldimethylsilyloxy-2″-hydroxyheptyl)]-4,5-dimethoxyhexahydropyrrolo[1,2-*b*]isoxazole (7c). From **6a** (2.5 g, 6.7 mmol) and **4b** in 2 steps was obtained **7c** (5.1 g, 51%) as a clear light brown oil after purification with silica gel chromatography (hexanes/ether, 7:3). $[\alpha]_D^{25}$=−17.0 (*c* 2.0, $CHCl_3$). IR (neat) 3480, 2950, 1740, 1470, 1380, 1280, 1120 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.05 (m, 1H), 3.85 (m, 1H), 3.76 (m, 2H), 3.50 (m, 3H), 3.43 (s, 3H), 3.35 (s, 3H), 3.18 (m, 1H), 2.14 (m, 2H), 1.76 (t, *J*=5.4 Hz, 2H), 1.40 (m, 12H), 1.09 (d, *J*=6.0 Hz, 6H), 0.86 (s, 9H), 0.85 (s, 9H), 0.06 (s, 6H), 0.01 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 89.55, 85.84, 75.65, 68.86, 68.58, 68.35, 66.61, 65.74, 58.61, 57.60, 40.94, 39.75, 39.55, 38.49, 37.48, 32.82, 25.91, 25.88, 23.73, 23.69, 22.60, 21.86, 18.14, 18.12, −4.40, −4.44, −4.69, −4.72. HRMS (FAB, M+H) calcd for $C_{32}H_{68}NO_6Si_2$ 618.4585, found 618.4586.

4.1.10. (2*S*,2′*S*,3*R*,4*R*,5*S*,6′*R*/6′*S*)-2,5-[6′-(*tert*-Butyldimethylsilyloxy)-2′-hydroxyheptyl]-3,4-dimethoxypyrrolidine (8c). From **7c** (1.5 g, 2.4 mmol) was obtained **8c** (1.0 g, 67%) as a clear light brown oil after purification with silica gel chromatography (hexanes/ethyl acetate, 1:1, 0:1). $[\alpha]_D^{25}$=−11.2 (*c* 1.0, $CHCl_3$). IR (neat) 3420, 3375, 2850, 1590, 1630, 1465, 1390, 1260, 1220, 1110 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.69 (m, 2H), 3.73 (m, 4H), 3.57 (m, 2H), 3.39 (s, 6H), 1.98 (m, 2H), 1.71 (m, 2H), 1.41 (m, 12H), 1.08 (d, *J*=6 Hz, 6H), 0.86 (s, 18H), 0.02 (s, 12H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 88.47, 68.55, 68.49, 68.38, 58.89, 58.81, 57.80, 57.78, 39.66, 39.56, 39.56, 36.67, 37.10, 36.97, 25.89, 23.73, 23.66, 21.99, 21.78, 18.11, −4.44, −4.67. HRMS (FAB, M+H) calcd for $C_{32}H_{70}NO_6Si_2$ 620.4742, found 620.4733.

4.1.11. (1*S*,2*S*,2a*S*,4*R*,6′*R*/6′*S*,7*R*,8a*S*)-1,2-Dimethoxy-4,7-(6′-methyl-2′-tetrahydropyranyl)-2,2a,3,4,5,7,8,8a-octahydro-1*H*-5,6,8b-triaza-acenaphthylene hydrochloride (1c). From **8c** (1.0 g, 1.1 mmol) in 3 steps was obtained **1c** (250 mg, 50%) after purification with silica gel chromatography ($CHCl_3$/CH_3OH, 100:1) as a white crystal. Mp 193–194°C (decomposition). $[\alpha]_D^{24}$=−29.5 (*c* 0.5, $CHCl_3$). IR (neat) 3180, 2950, 1660, 1630, 1200, 1120, 1040 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 10.15 (s, 1H), 9.48 (s, 1H), 3.96 (m, 1H), 3.63 (s, 4H), 3.56 (s, 3H), 3.53 (s, 3H), 2.85 (d, *J*=12 Hz, 1H), 2.27 (s, 2H), 1.75 (m, 12H), 1.35 (m, 1H), 1.17 (d, *J*=6 Hz, 3H), 1.09 (d, *J*=6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.80, 86.77, 85.78, 81.81, 80.96, 68.64, 67.18, 59.40, 59.36, 52.24, 52.06, 38.88, 34.87, 34.51, 32.29, 31.60, 30.82, 22.18, 21.85, 20.09, 18.45. HRMS (FAB, M+H) calcd for $C_{21}H_{36}N_3O_4$ 394.2706, found 394.2710.

4.1.12. (1*S*,2*S*,2a*S*,4*R*,5′*R*,6′*R*,7*R*,8a*S*)-1,2-Dimethoxy-4,7-(6′-methyl-5′-phenyl-2′-tetrahydropyranyl)-2,2a,3,4,5,7,8,8a-octahydro-1*H*-5,6,8b-triazaacenaphthylene hydrochloride (2). Data for **2**: mp 256–259°C (decomposition). $[\alpha]_D^{25}$=+0.9 (*c* 0.3, $CHCl_3$). IR (neat) 2600, 1590, 1620, 1500, 1460, 1300, 1100, 940 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 10.62 (s, 2H), 7.51 (d, *J*=7 Hz, 4H), 7.32 (m, 2H), 7.20 (t, *J*=7.0 Hz, 4H), 4.10 (m, 2H), 3.81 (m, 2H), 3.69 (m, 2H), 3.58 (s, 6H), 2.76 (m, 2H), 2.37 (m, 4H), 2.05 (m, 2H), 1.89 (m, 2H), 1.75 (m, 2H), 1.26 (m, 2H), 0.90 (d, *J*=6.0 Hz, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.00, 142.18, 128.59, 128.42, 128.25, 126.65, 86.41, 80.75, 71.57, 59.47, 52.34, 50.03, 38.45, 35.16, 26.08, 19.75. HRMS (FAB, M+H) calcd for $C_{33}H_{44}N_3O_4$ 546.3332, found 546.3334.

Crystallographic data (excluding structure factors) for structures 1a–1c, 2 have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 170374–170377. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].



Scheme 2. (a) (i) *p*TsCl, Bu_2SnO, Et_3N, 85%, (ii) $LiAlH_4$, (iii) TBSCl, imidazole, 92% (2 steps); (b) (i) PivCl, Py, 99%, (ii) MsCl, Py, 92%, (iii) K_2CO_3, MeOH, (iv) $LiAlH_4$, 82% (2 steps), (v) TBSCl, imidazole, 89%; (c) (i) $Pd(OH)_2$, H_2, 93–99%, (ii) I_2, PPh_3, 75%, (d) CuCN, MeLi, Allyltributhyltin, 84%; (e) (i) PhLi, CuBr/Me_2S, 74%, (ii) $NaIO_4$, 50%; (f) (i) *p*TsCl, Bu_2SnO, Et_3N, 62%, (ii) TBSOTf, 2,6-lutidine, 92%, (iii) NaI, 79%; (g) CuCN, MeLi, Allyltributyltin, 94%.

Acknowledgements

We thank Dr Kimiko Kobayashi (RIKEN, X-ray analysis) and Ms Kumiko Harata (RIKEN, Mass spectral measurement). A. G. thanks JST (Japan Science and Technology Corporation) for the STA postdoctoral fellowship. Tore Co., Ltd. is greatly acknowledged for the financial support. This work was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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9. Olefins **4** and **5** were prepared as shown in Scheme 2.
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13. The configurational structure of compound **1e** published in our previous paper (Ref. 5) is incorrect. The absolute stereochemistry of this compound should be corrected as presented in this paper.
14. We expected some chirality induction of the hetero-Michael reaction with **1** or **2**, no induction, unfortunately, has yet to be observed with both catalysts under these conditions.[4j]