Pergamon

Tetrahedron 55 (1999) 4325–4340

TETRAHEDRON

New Synthetic Route of Guanidine from Trichloroacetamide for Tetrodotoxin and Its Related Compounds.

Toshio Nishikawa, Norio Ohyabu, Noboru Yamamoto, and Minoru Isobe*

Laboratory of Organic Chemistry, School of Bioagricultural Sciences,
Nagoya University, Chikusa, Nagoya, 464-8601, Japan

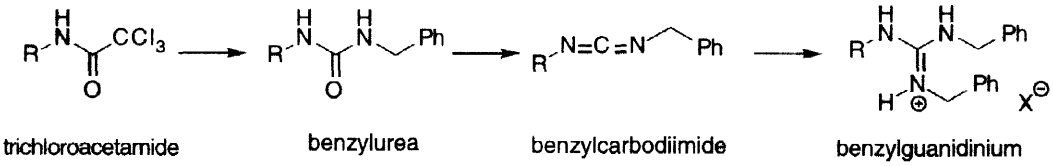
Received 26 November 1998; accepted 10 February 1999

Abstract: Trichloroacetamide was transformed into dibenzylguanidinium salt in three steps. Attempted debenzylation was very difficult in the guanidinium form even under high pressure hydrogen and high temperature conditions. On the other hand, the benzyl groups on acetylated guanidine were easily deprotected by hydrogenolysis under 1 atm of hydrogen. These methods were applied to the syntheses of tetrodotoxin-related compounds. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: guanidine; protecting group; hydrogenolysis; toxins

Introduction

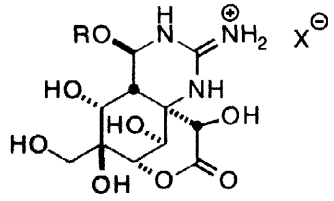
Guanidine groups have been found in many important natural products and are known to play significant roles in their biological activities.[1] Accordingly, many methods for synthesizing guanidine group have been reported.[2] The widely used methods for introduction of such functionality include the reaction of amine with electrophilic reagents such as cyanamide,[3] carbodiimide,[4] thiourea,[5] isothiourea,[6] aminoiminomethansulfonic acid,[7] and pyrazole-1-carboxamidine[8] derivatives.[9] In our synthetic studies on tetrodotoxin (**1**),[10] a well-known toxic principle of puffer fish poisoning,[11,12,13] we needed a new synthetic route of guanidine from trichloroacetamide because deprotection of the trichloroacetamide group in our intermediate was difficult due to the presence of a variety of functional groups.[14] To overcome this problem, we subsequently developed a synthesis of dibenzylguanidinium compound from trichloroacetamide that did not proceed through unprotected amine, as shown in **Scheme 1**.[15] The trichloroacetamide was easily prepared by the so-called Overman rearrangement of allylic alcohol,[16] and the amide was transformed to benzylurea with benzylamine and Na_2CO_3 as base.[17] The urea was dehydrated to benzylcarbodiimide, which was converted into dibenzylguanidinium salt by addition of benzylamine.[4] The another advantage of this method is that it maintains the solubility of the dibenzylguanidinium compounds toward organic solvents, such as CH_2Cl_2, EtOAc, etc.



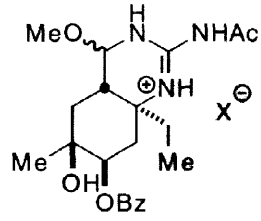
Scheme 1

Herein we describe (i) the details of our benzylguanidine synthesis from trichloroacetamide, (ii) the deprotection procedures of these benzyl groups on guanidine, and (iii) the synthesis of cyclic guanidine-containing compounds related to tetrodotoxin, such as compound **3**, based on our guanidine synthesis.

PII: S0040-4020(99)00140-4



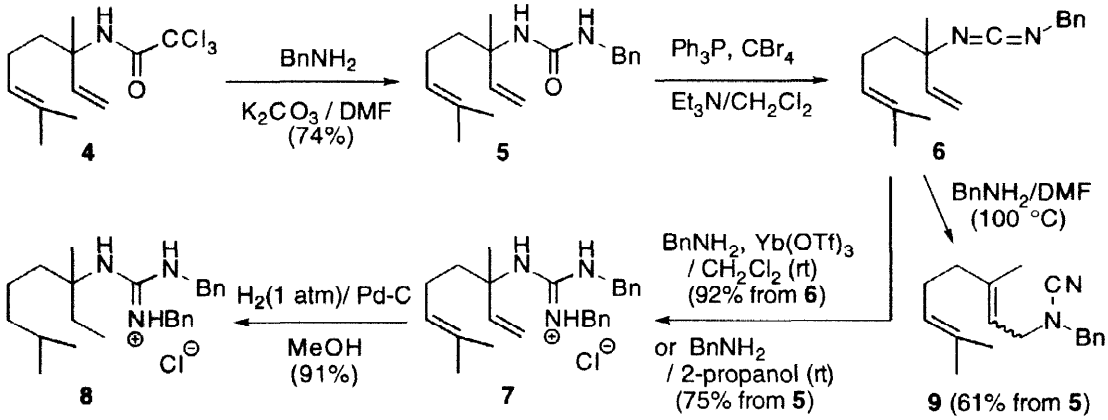
tetrodotoxin (lactone form) **1** R = H
methoxy tetrodotoxin **2** R = Me



3

Synthesis of dibenzylguanidine from trichloroacetamide

In order to determine the conditions for the debenzylation of guanidine, we chose dibenzylguanidine hydrochloride **8** as a simple model substrate whose synthesis is exemplified by our guanidine synthesis from 3,7-dimethyl-3-trichloroacetamido-1,6-octadiene (**4**),[18] as shown in **Scheme 2**. The trichloroacetamide **4**, was heated with benzylamine in the presence of Na_2CO_3 to give benzylurea **5** in good yield. The urea was dehydrated with Ph_3P and CBr_4 to afford carbodiimide **6**. In our previous report,[15] the carbodiimide reacted with benzylamine in the presence of $Yb(OTf)_3$ at ambient temperature to give dibenzylguanidine hydrochloride **7**. Under high temperature (100 °C), [3,3] sigmatropic rearrangement of the allylic carbodiimide hydrochloride **6** took place even in the presence of benzylamine to give a cyanamide **9** as a major product.[19] We found that the addition reaction using 2-propanol as solvent without catalyst also gave dibenzylguanidine hydrochloride **7** in good overall yield, but not **9**. Two olefins in **7** were hydrogenated with 20% Pd-C in MeOH to afford **8** prior to the examination of hydrogenolytic conditions. Under such hydrogenation conditions, no benzyl groups were affected at all.

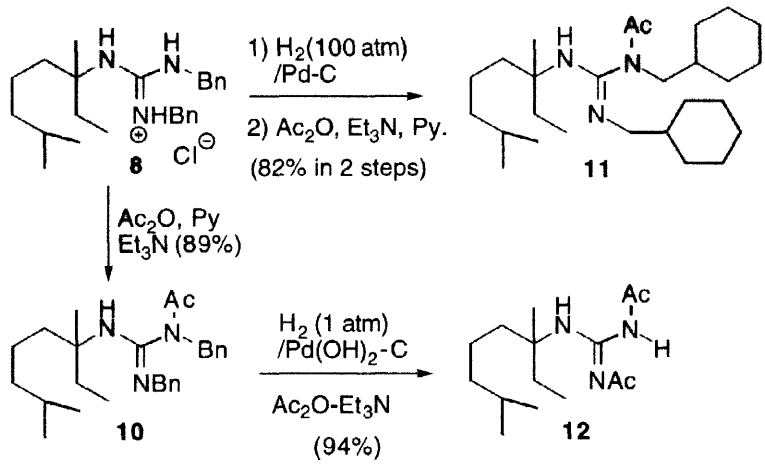


Scheme 2

Debenzylation of dibenzylguanidine

We have examined conditions for hydrogenolysis toward the dibenzylguanidine hydrochloride **8** according to the deprotection methods of benzylamines reported in the literature.[20,21] In this examination, the crude mixture was acetylated with acetic anhydride, pyridine and triethylamine for easy analysis of the products. Hydrogenolysis conditions, including use of Pearlman's catalyst ($Pd(OH)_2$-C), presence of acid, catalytic hydrogen transfer using formic acid as a hydrogen source,[22] etc., did not affect any benzyl groups of **8**. Forcing conditions under high pressure (100 atm) of hydrogen and high temperature (150 °C) did not

deprotect benzyl groups of **8**, but hydrogenation of the benzyl groups took place to afford a dicyclohexylmethyl guanidine derivative **11** after acetylation, as shown in **Scheme 3**.



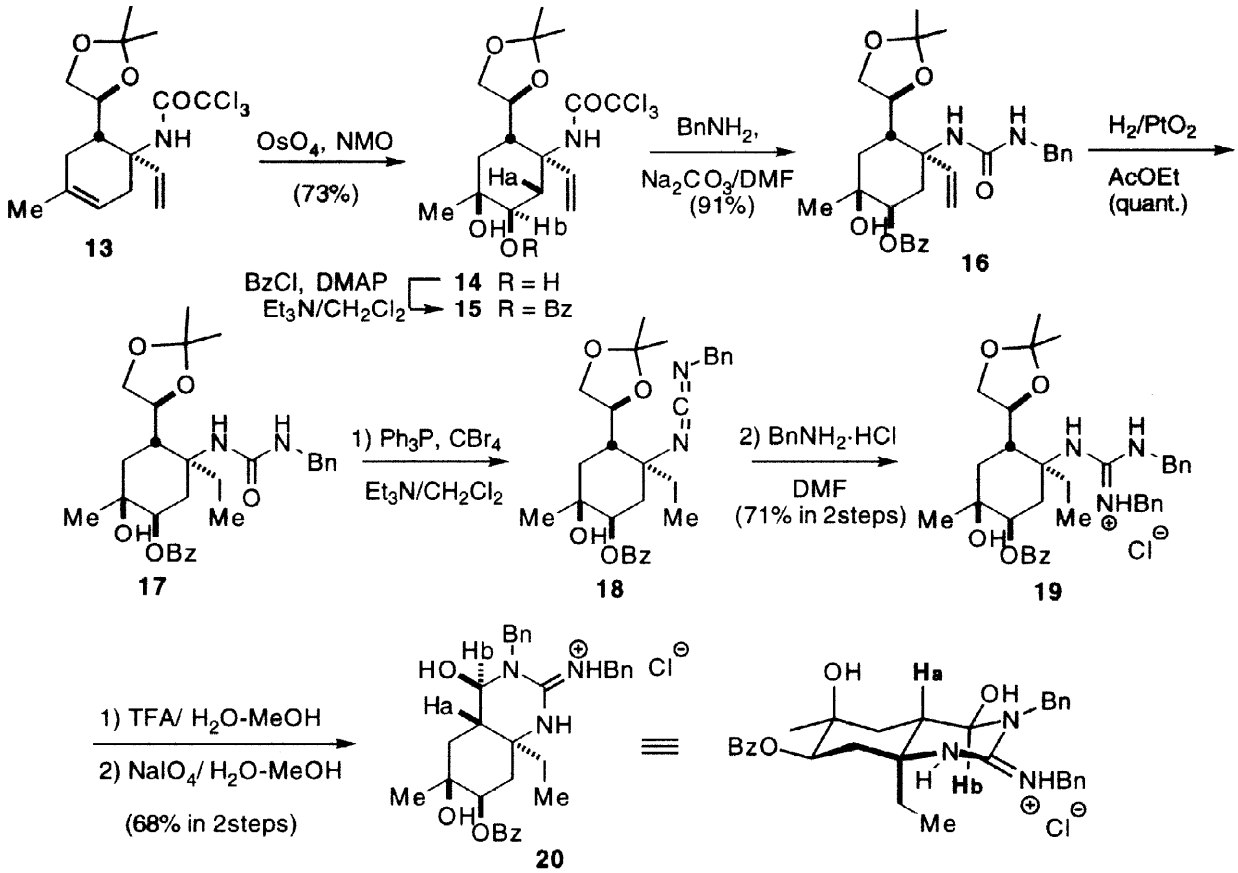
Scheme 3

In contrast to the dibenzylguanidinium salt **8**, we found that benzyl groups on the acetylated guanidine **10** were easily removed with concomitant acetylation under hydrogenolysis conditions that included use of Et_3N and acetic anhydride as solvents to afford diacetylguanidine **12** in high yield. The above results indicated that benzyl groups on acetylated guanidine were more labile than those of free guanidine (guanidinium salt) toward the hydrogenolysis conditions, although the reason for this increased lability remains uncertain. Since an acetyl group was used as a protective group of guanidine in the total synthesis of racemic tetrodotoxin,[12,23] this debenzylation should be an important procedure in our tetrodotoxin synthesis.[24]

Synthesis of cyclic guanidines related to tetrodotoxin

The success of the above debenzylation method prompted us to the synthesis of cyclic guanidinium compound **3** as a model study for the total synthesis of tetrodotoxin. The synthesis commenced with a key intermediate **13**, which was prepared from levoglucosenone[25] in our tetrodotoxin synthesis[10b,26] (**Scheme 4**). Stereo- and regioselective dihydroxylation of **13** with OsO_4(cat.) and NMO gave the diol **14**,[27] which was protected as a benzoate **15**. Stereochemistry of the newly generated asymmetric center was established from the coupling constant (J = 12 Hz) observed between Ha and Hb in **15**. The trichloroacetamide of **15** was transformed into the urea **16** with benzylamine and Na_2CO_3 in DMF under reflux conditions. Hydrogenation of terminal olefin of **16** in the presence of a benzyl group was achieved with PtO_2 catalyst to give **17** in quantitative yield. Dehydration of **17** by the above-mentioned conditions gave a thermally stable carbodiimide **18** due to the lack of allylic moiety. In this specific case, we found that benzylamine hydrochloride could be added to the carbodiimide **18** in DMF at 100 °C to easily give a dibenzylguanidine hydrochloride **19** in good yield.[28] Acetonide of **19** was hydrolyzed and the resulting diol was cleaved with sodium periodate to afford cyclic guanidinium hydrochloride **20**. The configuration of the aminal moiety was determined from the large coupling constant (J = 9.5 Hz) between Ha and Hb, which was the same as that (J = 9.5 Hz)[11,29] for tetrodotoxin (**1**). However, we could not deprotect the benzyl groups of **20**,

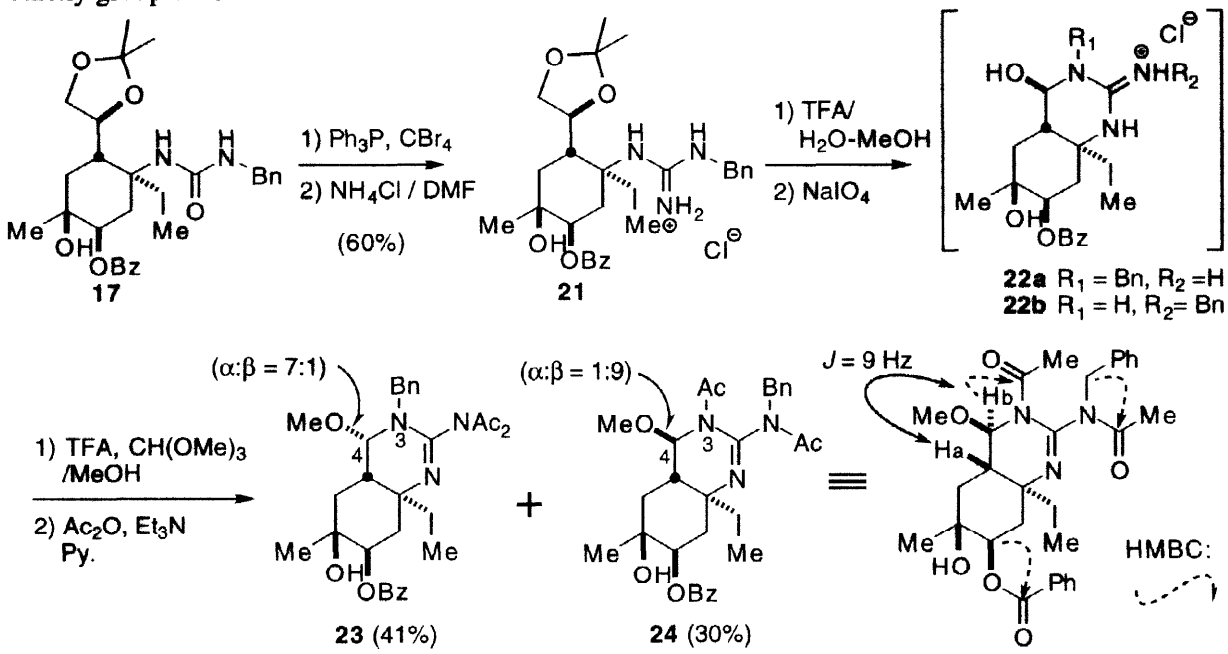
because the attempted acetylation of **20** failed. This guanidinium compound **20** was soluble in CH_2Cl_2, $CHCl_3$ and EtOAc.



Scheme 4

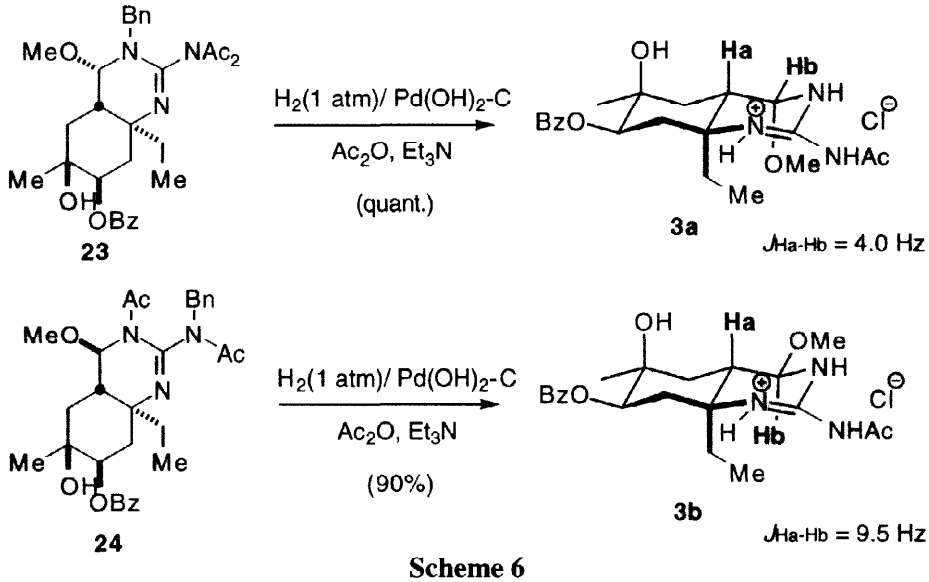
Next, we planned to synthesize a monobenzylguanidinium compound **21** instead of the dibenzyl compound **19**, with the expectation that a cyclic guanidinium **22** obtainable from **21** might be acetylated (**Scheme 5**). Ammonium chloride was found to react with the carbodiimide **18** in DMF at 100 °C to give our desired monobenzylguanidine hydrochloride **21** in 60% yield from **17**. Hydrolysis of the acetonide and subsequent oxidative cleavage of the corresponding diol gave a mixture of cyclic guanidine hydrochlorides **22a** and **22b**. The hydroxy group of the aminal position was changed to a methoxy group during stirring in MeOH with TFA and trimethyl orthoformate. The guanidine moiety was acetylated to afford a mixture of acetyl guanidine **23** and **24** in 41% and 30% yields, respectively. Acetylation of **22** without changing the hydroxy group to a methoxy group gave a dehydro product.[30] The structure of the product **24** was established from the following NMR experiments. The stereochemistry of the methoxy group in **24** was determined to be equatorial from a coupling constant (J = 9 Hz). Location of the acetyl groups was confirmed by HMBC spectrum. On the other hand, the ^{1}H-NMR spectrum of another product **23** was too broad to confirm its structure at this stage, although the structure of **23** could be deduced from the corresponding debenzylation product **3a** (*vide infra*). Interestingly, methoxy group of the product **23** having a benzyl group at the N-3 position (tetrodotoxin numbering) was situated at the C-4 position in axial orientation, while methoxy group of the product **24** having an acetyl group at the N-3 position was situated

in equatorial orientation.[31] This was due to the steric interactions between substituents on N-3 and the methoxy group on C-4.



Scheme 5

Finally, we achieved the debenzylation of these two compounds **23** and **24** under the conditions established above to give the acetyl guanidine hydrochlorides **3a** and **3b** in high yields, respectively (**Scheme 6**). Analyses of ^{1}H-NMR of the final products revealed the configuration of methoxy groups shown in **Scheme 6**. The product **3a** exhibited a smaller coupling constant (J = 4.0 Hz) between Ha and Hb, indicating that the methoxy group occupied an axial position. This coupling constant is comparable to the value (4.9 Hz) of naturally occurring 11-deoxy-4-*epi*-tetrodotoxin.[29] The compound **3b** showed the coupling constant in 9.5 Hz and thus took a configuration similar to that of tetrodotoxin.



Scheme 6

In summary, we have developed a new guanidine synthesis from trichloroacetamide that includes a deprotection procedure. During this study, we found that the benzyl group on guanidinium salt was inert to hydrogenolysis, but the benzyl group on acetylated guanidine was readily removed under the same conditions. Based on these results, we synthesized tetrodotoxin-related compounds containing cyclic guanidine. In previous structural studies of tetrodotoxin, it was reported that methoxy-tetrodotoxin (**2**) could be transformed into tetrodotoxin (**1**) under aq. HCl.[11b] Consequently, these studies should provide an important synthetic route for critical cyclic guanidine in our tetrodotoxin synthesis. Further investigations toward the total synthesis of tetrodotoxin and its analogs are currently underway in our laboratory.

Experimental Section[32]

3-(*N''*-Benzylureido)-3,7-dimethylocta-1,6-diene (5). To a solution of the trichloroacetamide **4** (6.36 g, 21.3 mmol) dissolved in DMF (100 mL) were added Na_2CO_3 (11.28 g, 106 mmol) and benzylamine (2.79 mL, 25.6 mmol). The solution was heated at 100 °C for 17 h with vigorous stirring. After cooling to rt, the mixture was diluted with ether, and the resulting solution was poured into ice-cold aqueous NH_4Cl solution. The mixture was extracted with Et_2O, and the combined extract was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel 200 g, Et_2O/hexane = 1:1) to give benzylurea **5** (4.47 g, 74%) as a solid. Mp. 65-67 °C. IR (KBr) ν_{max} 3348, 2970, 2918, 1637, 1561, 1455, 1375, 1265 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (3H, s, CH_3), 1.57 (3H, br s, CH_3), 1.58-1.66 (2H, m, CH_2), 1.66 (3H, d, J = 1.0 Hz, CH_3), 1.88-1.98 (2H, m, CH_2), 4.31 (2H, d, J = 5.5 Hz, Ph-CH_2), 4.77 (1H, br s, N*H*), 5.02-5.08 (1H, m, Me_2C=C*H*-), 5.10 (1H, d, J = 10.0 Hz, -CH=CH_AH_B), 5.11 (1H, d, J = 17.0 Hz, -CH=CH_AH_B), 5.22 (1H, br s, N*H*), 5.91 (1H, dd, J = 17.0, 10.0 Hz, -C*H*=CH_2), 7.19-7.33 (5H, m, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 22.3, 24.6, 25.5, 40.4, 44.1, 56.1, 113.3, 123.8, 127.1, 127.3, 128.5, 131.9, 139.5, 144.4, 157.7. Anal. Calcd for $C_{18}H_{26}N_2O_1$: C, 75.48; H, 9.15; N, 9.78. Found: C, 75.49; H, 9.24; N, 9.75.

1-Vinyl-1,5-dimethyl-5-hexenylbenzylcarbodiimide (6). The benzylurea **5** (218 mg, 0.761 mmol), Ph_3P (399 g, 1.52 mmol) and Et_3N (0.21mL, 1.51 mmol) were dissolved in dry CH_2Cl_2 (5.0 mL) and the solution was cooled to 0 °C. To this solution was added dry CH_2Cl_2 (0.5 mL) solution of CBr_4 (505 mg, 1.52 mmol), and the mixture was allowed to warm to rt. After stirring at rt for 1 h, the mixture was concentrated. The residue (43.8 g) was purified by column chromatography (silica gel 35 g, hexane → ether/hexane = 1:20) to give carbodiimide **6** (63 mg, 31%) as an oil. IR (KBr) ν_{max} 2969, 2926, 2857, 2125 (N=C=N), 1454, 923 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.20 (3H, s, CH_3), 1.42 (2H, m, CH_2), 1.57 (3H, s, CH_3), 1.66 (3H, s, CH_3), 1.88-1.99 (2H, m, CH_2), 4.35 (2H, s, NCH_2Ph), 4.98-5.08 (1H, m, Me_2C=C*H*-), 4.99 (1H, dd, J = 10, 1 Hz, -CH=CH_AH_B), 5.10 (1H, dd, J = 17, 1 Hz, -CH=CH_AH_B), 5.69 (1H, dd, J = 17, 10 Hz, -C*H*=CH_2), 7.18-7.33 (5H, m, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 17.6, 23.0, 25.6, 27.3, 42.5, 50.6, 61.5, 112.6, 123.9, 127.5, 127.8, 128.5, 131.6, 138.6, 140.0, 143.0. HRMS (EI) Calcd for $C_{18}H_{24}N_2$ (M^+) 268.1939. Found 268.1930.

3-(*N'*, *N''*-Dibenzylguanidino)-3,7-dimethyl-octa-1,6-diene hydrochloride (7).

by using Yb(OTf)$_3$: To a solution of the carbodiimide **6** (27 mg, 0.10 mmol) and benzylamine (22 μL, 0.20 mmol) in dry CH_2Cl_2 (1.0 mL) was added $Yb(OTf)_3$ (63 mg, 0.10 mmol). After stirring at rt for 42 h, the

mixture was diluted with CH_2Cl_2. The resulting solution was washed with water (×2), sat. NH_4Cl solution (×3) and brine (×3), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by preparative TLC (silica gel, CH_2Cl_2/acetone/MeOH = 8:1:1) to give **7** (38 mg, 92%) as a syrup.

by using 2-propanol: The benzylurea **5** (6.85 g, 23.9 mmol), Ph_3P (12.5 g, 47,8 mmol) and Et_3N (6.7 mL, 47.8 mmol) were dissolved in dry CH_2Cl_2 (130 mL), and the solution was cooled to 0 °C. To this solution was added dry CH_2Cl_2 (7 mL) solution of CBr_4 (15.9 g, 47.8 mmol), and the mixture was allowed to warm to rt. After stirring at rt for 1.5 h, the mixture was concentrated. Triphenylphosphine oxide in the residue (43.8 g) was removed by column chromatography (silica gel 200 g, ether/hexane = 1:1 → 1:2) to give carbodiimide **6** (12.8 g). The carbodiimide **6** (12.8 g) was dissolved in 2-propanol (200 mL), and benzylamine (13.1 mL, 120 mmol) was added . After stirring at rt for 3.7 days, the mixture was diluted with water, and partitioned. The aqueous layer was extracted with CH_2Cl_2 (×2). The combined organic layer was washed with water, sat. NH_4Cl solution and brine (×3), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel 400 g, CH_2Cl_2/acetone = 2:1 → CH_2Cl_2 /acetone /MeOH = 8:1:1) to give **7** (7.33 g, 75% in 2 steps) as a syrup. IR (KBr) ν_{max} 3251, 3188, 3065, 2974, 1618 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (3H, s, CH_3), 1.44-1.70 (4H, m, CH_2 × 2), 1.49 (3H, br s, CH_3), 1.65 (3H, br s, CH_3), 4.67-4.81 (4H, br, Ph-CH_2 × 2), 4.88-4.96 (1H, m, olefinic proton), 5.09 (1H, d, J = 18.0 Hz, -CH=CH_AH$_B$), 5.20 (1H, d, J = 11.0 Hz, CH=CH$_A$$H_B$), 5.77 (1H, dd, J = 18.0, 11.0 Hz, CH=CH$_A$H$_B$), 6.51 (1H, br s, NH), 7.29-7.39 (10H, m, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 21.4, 23.4, 25.4, 39.6, 45.0, 58.2, 116.5, 122.7, 127.9, 128.0, 128.7, 132.2, 136.0, 142.4, 154.1. HR-MS (FAB) Calcd for $C_{25}H_{34}N_3$ (M+H) 376.2753. Found: 376.2764.

Benzyl 3,7,7-trimethylocta-2,6-dienylcyanamide (9). To an ice-cold solution of CBr_4 (294 mg, 0.89 mmol) in dry CH_2Cl_2 (2.5 mL) was added Ph_3P (233 mg, 0.89 mmol), and the mixture was allowed to warm to rt. To this mixture was added a solution of the benzylurea **5** (51 mg, 0.178 mmol) and Et_3N (0.25 mL, 1.78 mmol) in CH_2Cl_2 (0.5 mL) through a cannula. After stirring at rt for 30 min, the mixture was concentrated to a small volume, which was subjected to a short silica gel column chromatography to give partially purified carbodiimide (100 mg). A mixture of the carbodiimide, benzylamine (29 mL, 0.27 mmol) and Na_2CO_3 (37 mg) in DMF (3 mL) was heated at 100 °C for 20 h with vigorous stirring. After cooling to rt, the mixture was diluted with AcOEt. The resulting solution was washed with water, aqueous NH_4Cl solution and brine, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (silica gel 5 g, ether/hexane = 1:10 → 1:5) to give cyanamide **9** (29 mg, 61% in 2 steps) as an oil. IR (KBr) ν_{max} 2923, 2210 (N–C≡N), 1668, 1455, 1376 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.55 (3H × 1/3, s, CH_3), 1.57 (3H × 2/3, s, CH_3), 1.61 (3H × 2/3, s, CH_3), 1.65 (3H × 1/3, s, CH_3), 1.69 (3H × 1/3, s, CH_3), 1.78 (3H × 1/3, s, CH_3), 1.95-2.17 (4H, m, CH_2CH_2), 3.52 (1H ×1/3, br d, J = 7 Hz, C=CH-CH_2-N), 3.54 (1H × 2/3, d, J = 7 Hz, C=CH-CH_2-N), 4.15 (2H, s, Ph-CH_2), 4.98-5.04 (1H, m. olefinic), 5.05-5.11 (1H × 2/3, m, olefinic), 5.24-5.34 (1H, m, olefinic), 7.31-7.40 (5H, m, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 17.5, 17.6, 23.3, 25.5, 25.6, 26.1, 26.3, 32.0, 39.5, 47.5, 47.7, 54.4, 54.7, 116.9, 117.7, 123.4, 123.6, 128.5, 128.8, 132.0, 132.3, 134.9, 143.4, 143.5. EIMS *m/z* 268 (M^+). HR-MS (EI) for $C_{18}H_{24}N_2$ (M^+), calcd 268.1939, found 268.1939.

3-(*N'*, *N''*-Dibenzylguanidino)-3,7-dimethyloctane hydrochloride (8). A solution of **7** (4.38 g, 10.67 mmol) and 20% Pd-C (4.38 g) dissolved in MeOH (80 mL) was degassed and filled with H_2 gas. After stirring at rt for 2 days under H_2 atmosphere, the mixture was filtered through the pad of Super-Cel, the pad was washed with MeOH. The combined filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 100 g, AcOEt/MeOH = 9:1 → 8:2) to give **8** (4.02 g, 91%) as crystals. Analytical sample was prepared by crystallization from AcOEt. Mp. 147-148 °C. IR (KBr) ν_{max} 3255, 3091, 3064, 2952, 1617 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.55 (3H, t, *J* = 7.0 Hz, CH_2-C*H*$_3$), 0.76 (6H, d, *J* = 6.5 Hz, CH-C*H*$_3$ x2), 0.77-0.89 (2H, m), 0.97 (2H, q, *J* = 7.0 Hz, CH_3-C*H*$_2$), 1.21 (3H, s, C*H*$_3$), 1.24-1.70 (5H, m), 4.76 (4H, br s, Ph-C*H*$_2$ × 2), 5.03 (1H, br s, N*H*), 7.22-7.33 (6H, m, aromatic), 7.37-7.46 (4H, m, aromatic), 8.07 (2H, br s, N*H* × 2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.4, 20.7, 22.3, 22.4, 24.8, 27.6, 31.7, 38.6, 38.8, 45.4, 58.3, 127.9, 128.0, 128.7, 136.5, 153.4. Anal. Calcd for $C_{25}H_{38}N_3Cl$: C, 72.17; H, 9.21; N, 10.10. Found: C, 72.17; H, 9.40; N, 10.21.

3-(*N'*, *N''*-Dibenzyl-N'-acetylguanidino)-3.7-dimethyloctane (10). A mixture of **8** (1.24 g, 2.98 mmol) in pyridine (40 mL), Ac_2O (20 mL) and Et_3N (4.0 mL) was stirred at rt for 4 h. The mixture was diluted with toluene and evaporated in vacuo. The residue was purified by column chromatography (silica gel 100 g, ether/hexane = 1:3 → 1:2) to give acetyl guanidinc **10** (1.11 g, 89%) as an oil. IR (KBr) ν_{max} 3349, 2955, 2869, 1675, 1645, 1523, 1495, 1455, 1384, 1350, 1251, 1227 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.68 (3H × 1/2, t, *J* = 7.5 Hz, CH_2-C*H*$_3$), 0.72 (3H × 1/2, t, *J* = 7.5 Hz, CH_2-C*H*$_3$), 0.84 (3H × 1/2, d, *J* = 6.5 Hz, CH-C*H*$_3$), 0.84 (3H × 1/2, d, *J* = 6.5 Hz, CH-C*H*$_3$), 0.85 (3H × 1/2, d, *J* = 6.5 Hz, CH-C*H*$_3$), 0.85 (3H × 1/2, d, *J* = 6.5 Hz, CH-C*H*$_3$), 0.98-1.15 (4H, m), 1.13 (3H × 1/2, s, C-C*H*$_3$), 1.15 (3H × 1/2, s, C-C*H*$_3$), 1.40-1.72 (5H, m), 2.08 (3H, s, CO-C*H*$_3$), 3.38 (1H, br s, N*H*), 3.96 (1H × 1/2, d, *J* = 14.0 Hz, Ph-C*H*$_A$H$_B$), 3.97 (1H × 1/2, d, *J* = 14.0 Hz, Ph-C*H*$_A$H$_B$), 4.24 (1H, d, *J* = 15.5 Hz, Ph-C*H*$_A$H$_B$), 4.30 (1H, d, *J* = 15.5 Hz, Ph-CH$_A$*H*$_B$), 5.22 (1H × 1/2, d, *J* = 14.0 Hz, Ph-CH$_A$*H*$_B$), 5.23 (1H × 1/2, d, *J* = 14.0 Hz, Ph-CH$_A$*H*$_B$), 7.17-7.34 (10H, m, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.8, 7.9, 21.1, 21.2, 21.3, 22.4, 22.5, 22.6, 23.0, 27.8, 30.1, 37.3, 39.3, 48.8, 52.1, 56.1, 126.2, 126.9, 127.9, 128.1, 128.7, 128.9, 137.3, 141.4, 145.0, 169.4. Anal. Calcd for $C_{27}H_{39}N_3O_1$: C, 76.92; H, 9.32; N, 9.97. Found: C, 77.01; H, 9.36; N, 10.02.

3-(*N'*, *N''*-Dicyclohexylmethyl-N'-acetylguanidino)-3.7-dimethyloctane (11). To a solution of **8** (20 mg, 0.048 mmol) dissolved in MeOH (3.0 mL) was added 25% Pd-C (21 mg). The reaction vessel was placed in stainless steel autoclave. The mixture was stirred at 150 °C for 16 h under ca. 100 atm of H_2 gas. After cooling to rt, the mixture was filtered. The filtrate was evaporated under reduced pressure to give crude product (17 mg). The residue was dissolved in Ac_2O (0.5 mL), pyridine (1.0 mL) and Et_3N (0.1 mL), and the solution was stirred at rt for 5 h. The mixture was diluted with toluene, and evaporated in vacuo. The residue was purified by preparative TLC (silica gel, ether/hexane = 2:1) to give acetylguanidine **11** (12 mg, 82% in 2 steps) as an oil. ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (3H, t, *J* = 7.5 Hz, CH_2-C*H*$_3$), 0.87 (6H, d, *J* = 6.5 Hz, CH-C*H*$_3$ × 2), 0.89-1.89 (31H, m), 1.21 (3H ×1/2, s, C*H*$_3$), 1.24 (3H ×1/2, s, C*H*$_3$), 2.05 (3H, s, CO-C*H*$_3$), 2.75-2.84 (1H, overlapped, NH-C*H*$_A$H$_B$), 2.78 (1H, dd, *J* = 12.5, 6.5 Hz, NH-C*H*$_A$H$_B$), 2.87 (1H, dd, *J* = 12.5, 6.5 Hz, NH-CH$_A$*H*$_B$), 3.54 (1H, br s, N*H*), 3.63 (1H, dd, *J* = 13.5, 7.0 Hz, NH-CH$_A$*H*$_B$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.9, 21.4, 22.5, 22.6, 23.3, 23.5, 25.8, 26.2, 26.6, 28.0, 30.6, 31.2, 31.4, 31.5, 31.6, 36.9, 37.1, 37.5, 39.4, 39.9, 52.2, 55.3, 55.9, 144.4, 170.0. FAB-MS *m/z* 434 (M+H).

3-(*N'*, *N''*-Diacetylguanidino)-3,7-dimethyloctane (12). A suspension of the acetylguanidine **10** (165 mg, 0.418 mmol) and $Pd(OH)_2$-C (Pearlman's catalyst, 170 mg) in Ac_2O (9.0 mL) and Et_3N (0.45 mL) was degassed and filled with H_2 gas. The mixture was stirred for 2.7 days with vigorous stirring under H_2 atmosphere. The mixture was filtered through the pad of Super-Cel, the pad was washed with AcOEt. The combined filtrate was evaporated with toluene in vacuo. The residue was purified by column chromatography (silica gel 10 g, ether/hexane = 1:3) to give diacetylguanidine **12** (109 mg, 94%) as an oil. IR (KBr) ν_{max} 3282, 3249, 3117, 2958, 1699, 1618, 1459, 1377, 1330, 1209 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (3H, t, J = 7.5 Hz, CH_2-CH_3), 0.87 (6H, d, J = 6.5 Hz, (CH_3)$_2$-CH), 1.11-1.32 (4H, m), 1.35 (3H, s, CH_3), 1.48-1.96 (5H, m), 2.10 (3H, s, CO-CH_3), 2.15 (3H, s, CO-CH_3), 9.95 (1H, br s, N*H*), 13.16 (1H, br s, N*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.8, 21.1, 22.4, 22.5, 23.7, 25.0, 27.6, 28.6, 30.9, 38.1, 39.2, 58.0, 153.8, 172.7, 185.3. Anal. Calcd for $C_{15}H_{29}N_3O_2$: C, 63.57; H, 10,31; N, 14.83. Found: C, 63.57; H, 10.61; N, 14.70.

Synthesis of diol 14. The trichloroacetamide **13** (1.13 g, 2.96 mmol) was dissolved in acetone (20 mL) and water (5 mL). To this solution were added aqueous OsO_4 solution (0.15 M, 1.5 mL, 0.23 mmol) and a solution of NMO (485 mg, 4.14 mmol) in acetone (20 mL) and H_2O (5 mL). After stirring at rt for 4 h, aqueous $NaHSO_3$ solution was added. The resulting mixture was acidified with 1N HCl and extracted with AcOEt (x3). Combined organic layer was dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel 40 g, ether/hexane = 10:1 → ether only) to give diol **14** (895 mg, 73%) as a solid. Mp. 61-63 °C. $[\alpha]_D^{26}$ +22.0 (*c* 1.15, $CHCl_3$). IR (KBr) ν_{max} 3448, 3321, 2986, 2935, 1724, 1526, 1381, 1373, 1261, 1216, 1160, 1057 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (1 H, dd, J = 14.0, 12.5 Hz, CH_3-C-CH_{ax}H$_{eq}$) 1.28 (3 H, s, CH_3), 1.35 (1 H, dd, J = 14.0, 3.5 Hz, CH_3-C-CH$_{ax}$*H$_{eq}$*), 1.37 (3 H, s, CH_3), 1.42 (3H, s, CH_3), 1.85 (1H, dd, J = 12.5, 12.0 Hz, CH(OH)-CH_{ax}H$_{eq}$), 2.27 (1 H, ddd, J = 12.5, 9.5, 3.5 Hz, NH-C-C*H*), 3.23 (1 H, dd, J = 12.5, 5.0 Hz, CH(OH)-CH$_{ax}$*H$_{eq}$*), 3.64 (1 H, dd, J = 9.0, 8.0 Hz, -O-CH_AH$_B$), 3.67 (1 H, dd, J = 12.0, 5.0 Hz, HO-C*H*), 3.96 (1 H, ddd, J = 9.5, 9.0, 5.5 Hz, -O-C*H*), 4.09 (1 H, dd, J = 8.0, 5.5 Hz, -O-CH$_A$*H$_B$*), 5.41 (1H, d, J = 16.5 Hz, -CH=CH_AH$_B$), 5.42 (1H, d, J = 11.0 Hz, -CH=CH$_A$*H$_B$*), 5.89 (1H, dd, J = 16.5, 11.0 Hz, CH_2=C*H*), 8.95 (1H, br s, N*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.1, 26.6, 26.8, 35.4, 37.3, 43.0, 61.7, 69.3, 69.8, 70.8, 76.3, 93.7, 110.0, 117.8, 132.1, 160.3. Anal. Calcd for $C_{16}H_{24}N_1O_5Cl_3$: C, 46.12; H, 5.80; N, 3.36. Found: C, 46.13; H, 5.71; N, 3.15.

Synthesis of benzoate 15. To a solution of the diol **14** (521 mg, 1.25 mmol), Et_3N (0.63 mL, 4.52 mmol) and DMAP (15 mg, 0.12 mmol) in CH_2Cl_2 (17 mL) was added BzCl (0.17 mL, 1.51 mmol). After stirring at rt for 2 h, the mixture was quenched with sat. NH_4Cl solution and then extracted with CH_2Cl_2 (×3). The combined organic layer was dried over anhydrous Na_2SO_4, evaporated under reduced pressure. The residue was purified by column chromatography (silica gel 30 g, ether/hexane = 1:1 → 3:1) to give benzoate **15** (610 mg, 91%) as crystals. Mp. 196-197 °C (from ether-hexane). $[\alpha]_D^{27}$ +12.4 (*c* 1.31, $CHCl_3$). IR (KBr) ν_{max} 3504, 3315, 2987, 2938, 1719, 1522, 1273, 1159, 1109, 1069, 1028 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (3H, s, CH_3), 1.35-1.46 (2H, overlapped, CH_3-C-CH_2), 1.38 (3H, s, CH_3), 1.45 (3H, s, CH_3), 2.14 (1H, dd, J = 12.5, 12.0 Hz, BzO-CH-CH_{ax}H$_{eq}$), 2.39 (1H, br td, J = 10.5, 5.5 Hz, NH-C-C*H*), 3.38 (1H, dd, J = 12.5, 4.5 Hz, BzO-CH-CH$_{ax}$*H$_{eq}$*), 3.67 (1H, dd, J = 8.5, 7.5 Hz, -O-CH_AH$_B$), 4.05 (1H, ddd, J = 9.5, 8.5, 5.5 Hz, -O-C*H*), 4.13 (1H, dd, J = 7.5, 5.5 Hz, -O-CH$_A$*H$_B$*), 5.20 (1H, dd, J = 12.0, 4.5 Hz, BzO-C*H*), 5.53 (1H,

d, J = 10.5 Hz, -CH=CH_AH$_B$), 5.62 (1H, d, J = 16.5 Hz, -CH=CH$_A$$H_B$), 6.01 (1H, dd, J = 16.5, 10.5 Hz, CH$_2$=CH), 7.43-7.50 (2H, m, aromatic), 7.56-7.63 (1H, m, aromatic), 8.00-8.05 (2H, m, aromatic), 8.91 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.1, 26.6, 26.9, 33.6, 35.7, 43.1, 61.4, 69.4, 69.7, 73.8, 76.1, 93.7, 110.2, 118.8, 128.5, 129.7, 131.4, 133.4, 160.1, 165.5. Anal. Calcd for $C_{23}H_{28}N_1O_6Cl_3$: C, 53.04; H, 5.42; N, 2.69. Found: C, 52.98; H, 5.43; N, 2.69.

Synthesis of benzylurea 16. A mixture of the trichloroacetamide **15** (734 mg, 1.41 mmol), Na_2CO_3 (750 mg, 7.08 mmol), $BnNH_2$ (0.23 mL, 2.10 mmol) and DMF (25 mL) was heated under reflux with vigorous stirring. After 35 min., $BnNH_2$ (0.045 mL, 0.41 mmol) was added and the mixture was stirred for additional 20 min. The mixture was cooled to rt and diluted with aqueous NH_4Cl. The mixture was extracted with AcOEt (x3). The combined organic layer was washed with sat. NH_4Cl solution (×3), brine (×1), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel 30 g, ether) to give benzylurea **16** (651 mg, 91%) as an oil. $[\alpha]_D^{27}$ +5.28 (*c* 1.29, $CHCl_3$). IR (KBr) ν_{max} 3381, 2984, 2936, 1717, 1654, 1542, 1453, 1372, 1316, 1274, 1115, 1070, 1027 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20-1.42 (2H, overlapped, CH_3-C-CH_2), 1.21 (3H, s, CH_3), 1.31 (3H, s, CH_3), 1.35 (3H, s, CH_3), 2.27 (1H, br t, J = 12.5 Hz, BzO-CH-CH_{ax}H$_{eq}$), 2.32-2.42 (1H, m, NH-C-CH), 3.25 (1H, dd, J = 12.5, 4.0 Hz, BzO-CH-CH$_{ax}$$H_{eq}$), 3.56-3.66 (1H, m, -O-CH_AH$_B$), 3.97-4.07 (2H, overlapped, -O-CH, -O-CH$_A$$H_B$), 4.28 (1H, dd, J = 14.5, 5.5 Hz, Ph-CH_AH$_B$), 4.34 (1H, dd, J = 14.5, 5.5 Hz, Ph-CH$_A$$H_B$), 4.52 (1H, br t, J = 5.5 Hz, Bn-NH), 5.17 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 10.5, 1.0 Hz, -CH=CH_AH$_B$), 5.56 (1H, dd, J = 16.5, 1.0 Hz, -CH=CH$_A$$H_B$), 6.03 (1H, dd, J = 16.5, 10.5 Hz, CH$_2$=CH), 6.40 (1H, br s, C-NH), 7.20-7.35 (5H, m, aromatic), 7.40-7.47 (2H, m, aromatic), 7.53-7.60 (1H, m, aromatic), 8.00-8.05 (2H, m, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8, 26.5, 26.9, 35.4, 36.0, 42.9, 44.5, 59.8, 69.2, 69.8, 74.4, 76.4, 109.5, 117.6, 127.2, 127.3, 128.4, 128.5, 128.6, 129.7, 129.9, 133.1, 134.9, 139.2, 157.1, 165.6. Anal. Calcd for $C_{29}H_{36}N_2O_6$: C, 68.48; H, 7.14; N, 5.51. Found: C, 68.50; H, 7.00; N, 5.31.

Synthesis of benzylurea 17. To a solution of the benzylurea **16** (504 mg, 0.991 mmol) in AcOEt (15 mL) was added PtO_2 (11 mg, 0.048 mmol). The suspension was degassed and filled with H_2 gas. After vigorous stirring at rt for 3 h, the mixture was filtered through the pad of Super-Cel. The filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel 10 g, ether → ether/EtOAc = 1:1) to give **17** (504 mg, quant.) as crystals. Mp. 109-110 °C (from ether-hexane). $[\alpha]_D^{26}$ -8.76 (*c* 1.12, $CHCl_3$). IR (KBr) ν_{max} 3390, 2982, 2935, 1717, 1654, 1551, 1453, 1372, 1316, 1273, 1116, 1056, 1027 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (3H, t, J = 7.0 Hz, CH$_2$-CH_3), 1.22 (3H, s, CH_3), 1.33 (6H, s, CH_3x2), 1.30-1.37 (1H, overlapped, CH$_3$-C-CH_{ax}Heq), 1.44 (1H, dd, J = 14.0, 4.5 Hz, CH$_3$-C-CH$_{ax}$$H_{eq}$), 1.57 (1H, dq, J = 14.0, 7.0 Hz, CH$_3$-CH_AH$_B$), 1.93 (1H, dq, J = 14.0, 7.0 Hz, CH$_3$-CH$_A$$H_B$), 2.62 (1H, dd, J = 12.5, 4.0 Hz, BzO-CH-CH$_{ax}$$H_{eq}$), 2.60-2.69 (1H, m, NH-C-CH), 2.77 (1H, br t, J = 12.5 Hz, BzO-CH-CH_{ax}H$_{eq}$), 3.59 (1H, br t, J = 8.0 Hz, -O-CH_AH$_B$), 4.01 (1H, ddd, J = 9.5, 8.5, 5.5 Hz, -O-CH), 4.09 (1H, dd, J = 7.5, 5.5 Hz, -O-CH$_A$$H_B$), 4.27 (1H, dd, J = 14.5, 5.5 Hz, Ph-CH_AH$_B$), 4.34 (1H, dd, J = 14.5, 5.5 Hz, Ph-CH$_A$$H_B$), 4.43 (1H, br t, J = 5.5 Hz, Bn-NH), 4.91 (1H, dd, J = 12.0, 4.0 Hz, BzO-CH), 5.31 (1H, br s, -C-NH), 7.21-7.35 (5H, m, aromatic), 7.40-7.48 (2H, m, aromatic), 7.53-7.60 (1H, m, aromatic), 8.01-8.06 (2H, m, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.1, 25.0, 25.9, 26.4, 26.7, 32.9, 37.0,

42.1, 44.4, 58.7, 69.7, 69.8, 74.6, 76.6, 109.2, 127.2, 127.4, 128.4, 128.6, 129.7, 130.0, 133.1, 139.3, 158.0, 165.9. Anal. Calcd for $C_{29}H_{38}N_2O_6$: C, 68.21; H,7.50; N, 5.49. Found: C, 68.22; H, 7.63; N, 5.48.

Syntheses of benzylcarbodiimide 18 and dibenzylguanidine hydrochloride 19: To a ice-cold solution of CBr_4 (399 mg, 1.02 mmol) in dry CH_2Cl_2 (3.0 mL) was added Ph_3P (268 mg, 1.02 mmol). After dissolving the Ph_3P, the mixture was immediately added to a solution of the urea **17** (116 mg, 0.227 mmol, dried by azeotropic removal of water with benzene) in dry CH_2Cl_2 (3.0 mL) and Et_3N (0.32 mL, 2.3 mmol) via cannula tubing. The mixture was stirred at rt for 20 min and concentrated. The residue was purified by column chromatography (silica gel 8g, ether/hexane = 1:2 → 3:1) to give carbodiimide **18** (96 mg) as an oil. IR (KBr) ν_{max} 3503, 2980, 2938, 2124 (N=C=N), 1717, 1456, 1273, 1114, 1056 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (3H, t, *J* = 7.0 Hz, CH_2-C*H*$_3$), 1.15 (1H, dq, *J* = 14.0, 7.0 Hz, CH_3-C*H*$_A$H$_B$), 1.25 (3H, s, C*H*$_3$), 1.34 (3H, s, C*H*$_3$), 1.35 (1H, dd, *J* = 14.0, 13.0 Hz, CH_3-C-C*H*$_{ax}$H$_{eq}$), 1.43 (3H, s, C*H*$_3$), 1.58 (1H, dq, *J* = 14.0, 7.0 Hz, CH_3-CH$_A$*H*$_B$), 1.81 (1H, dd, *J* = 14.0, 4.0 Hz, CH_3-C-CH$_{ax}$*H*$_{eq}$), 1.84 (1H, br t, *J* = 12.0 Hz, BzO-CH-C*H*$_{ax}$H$_{eq}$), 1.97 (1H, dd, *J* = 12.0, 4.0 Hz, BzO-CH-CH$_{ax}$*H*$_{eq}$), 2.39 (1H, dt, *J* = 13.0, 4.0 Hz, N-C-C*H*), 3.58 (1H, t, *J* = 8.0 Hz, -O-C*H*$_A$H$_B$), 3.86 (1H, dd, *J* = 8.0, 6.0 Hz, -O-CH$_A$*H*$_B$), 4.30-4.41 (1H, m, -O-C*H*), 4.35 (2H, s, Ph-C*H*$_2$), 4.70 (1H, dd, *J* = 11.5, 4.0 Hz, BzO-C*H*), 7.15-7.21 (1H, m, aromatic), 7.24-7.33 (4H, m, aromatic), 7.46-7.53 (2H, m, aromatic), 7.59-7.65 (1H, m, aromatic), 8.03-8.07 (2H, m, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.3, 24.6, 24.8, 26.2, 26.8, 33.9, 35.2, 44.4, 50.3, 61.5, 65.6, 69.8, 74.1, 74.4, 107.3, 127.3, 127.5, 128.3, 128.4, 129.4, 129.6, 133.1, 138.4, 139.2, 165.5. To a solution of the carbodiimide **18** (96 mg) in DMF (5.0 mL) was added $BnNH_2$·HCl (163 mg, 1.13 mmol). The mixture was heated at 100 °C for 2 h with vigorous stirring. After cooling to rt, the mixture was quenched with water and the resulting solution was extracted with CH_2Cl_2 (×3). The combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel 5 g, AcOEt/MeOH = 9:1 → 7:3) to give **19** (197 mg, 71% in 2 steps) as a syrup. $[\alpha]_D^{26}$ -8.1 (*c* 0.44, $CHCl_3$). IR (KBr) ν_{max} 3313, 3258, 2981, 2935, 1717, 1621, 1454, 1381, 1373, 1352, 1316, 1274, 1215, 1179, 1159, 1115, 1070, 1027 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (3H, t, *J* = 7.0 Hz, CH_2-C*H*$_3$), 0.87 (3H, s, C*H*$_3$), 1.09 (3H, s, C*H*$_3$), 1.19 (1H, br t, *J* = 13.0 Hz, CH_3-C-C*H*$_{ax}$H$_{eq}$), 1.27 (3H, s, C*H*$_3$), 1.51-1.61 (2H, m, CH_3-C-CH$_{ax}$*H*$_{eq}$ & CH_3-C*H*$_A$H$_B$), 1.74-1.89 (2H, m, BzO-CH-CH$_{ax}$*H*$_{eq}$ & CH_3-CH$_A$*H*$_B$), 2.42 (1H, br t, *J* = 12.0 Hz, BzO-CH-C*H*$_{ax}$H$_{eq}$), 2.65-2.76 (1H, m, NH-C-C*H*), 3.57 (1H, br t, *J* = 8.0 Hz, -O-C*H*$_A$H$_B$), 3.76-3.86 (1H, m, -O-C*H*), 3.97 (1H, dd, *J* = 7.5, 5.5 Hz, -O-CH$_A$*H*$_B$), 4.60-4.84 (4H, br, Ph-C*H*$_2$ × 2), 4.65 (1H, dd, *J* = 11.0, 4.5 Hz, BzO-C*H*), 5.18 (1H, br s, N*H*), 7.13-7.24 (6H, m, aromatic), 7.43-7.53 (6H, m, aromatic), 7.57-7.64 (1H, m, aromatic, 8.15-8.20 (2H, m, aromatic), 8.47 (1H, br s, N*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.4, 25.6, 25.7, 25.8, 25.9, 31.7, 37.3, 41.7, 45.8, 60.0, 69.4, 69.6, 74.0, 76.0, 109.4, 128.1, 128.3, 128.5, 128.9, 129.8, 130.0, 133.3, 136.4, 153.6, 166.1. HRMS (FAB) Calcd for $C_{36}H_{46}O_3N_5$ (M+H) 600.3437. Found: 600.3432.

Synthesis of cyclic guanidine hydrochloride 20. To a solution of **19** (41 mg, 0.064 mmol) in MeOH (1.2 mL) and H_2O (0.4 mL) was added TFA (1.6 mL). After stirring at 60 °C for 1.5 h, the mixture was cooled to rt, diluted with benzene, and evaporated under reduced pressure. The residue (diol) was dissolved in MeOH (1.6 mL) and H_2O (1.6 mL), and $NaIO_4$ (20 mg, 0.094 mmol) was added. After stirring at rt for 3 h, the mixture was diluted with water. The resulting solution was extracted with AcOEt (×3). The combined organic layer was washed with sat. NH_4Cl solution (×2) and brine (×2), dried over anhydrous Na_2SO_4, and

evaporated under reduce pressure. The residue was purified by preparative TLC (silica gel, AcOEt/MeOH = 8:2) to give **20** (24 mg, 68% in 2 steps) as an oil. $[\alpha]_D^{26}$ -59 (*c* 0.16, $CHCl_3$). IR (KBr) ν_{max} 3384, 3245, 3065, 3034, 2973, 2942, 1717, 1612, 1584, 1455, 1316, 1273, 1179, 1111, 1073, 1027 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.49 (3H, br t, *J* = 7.5 Hz, CH_2-C*H*$_3$), 0.89-1.13 (1H, m, CH_3-C*H*$_A$H$_B$), 1.29 (3H, s, C-C*H*$_3$), 1.34 (1H, br t, *J* = 13.5 Hz, CH_3-C-C*H*$_{ax}$H$_{eq}$), 1.39-1.52 (1H, m, CH_3-CH$_A$*H*$_B$), 2.19-2.37 (3H, overlapped, CH_3-C-CHaxHeq, & BzO-CH-C*H*$_2$), 2.68-2.80 (1H, m, NH-C-C*H*), 4.38 (1H, d, *J* = 9.5 Hz, HO-C*H*-N), 4.48 (1H, br d, *J* = 15.0 Hz, Ph-C*H*$_A$H$_B$), 4.74 (1H, d, *J* = 15.0 Hz, Ph-C*H*$_A$H$_B$), 4.74-4.83 (1H, overlapped, BzO-C*H*), 4.99 (1H, br d, *J* = 15.0 Hz, Ph-CH$_A$*H*$_B$), 5.14 (1H, d, *J* = 15.0 Hz, Ph-CH$_A$*H*$_B$), 7.12-7.33 (10H, m, aromatic), 7.35-7.42 (2H, m, aromatic), 7.50-7.58 (1H, m, aromatic), 7.96-8.20 (1H, br, exchangeable with D_2O), 8.06-8.12 (2H, m, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$) δ 6.0, 21.7, 26.5, 31.6, 36.7, 44.0, 45.6, 48.7, 55.0, 70.5, 74.0, 80.6, 127.9, 128.4, 128.5, 128.7, 128.8, 128.9, 129.7, 129.9, 133.3, 134.9, 136.1, 152.3, 166.2. HRMS (FAB) Calcd for $C_{32}H_{38}N_3O_4$ (M+H) 528.2862. Found: 528.2864.

Syntheses of benzyl carbodiimide 18 and monobenzylguanidine hydrochloride 21. CBr_4 (900 mg, 2.71 mmol) was dissolved in dry CH_2Cl_2 (8.0 mL) and cooled to 0 °C. To this solution was added Ph_3P (712 mg, 2.71 mmol). The resulting solution was added to a solution of the urea **17** (308 mg, 0.603 mmol) and Et_3N (0.84 mL, 6.0 mmol) in dry CH_2Cl_2 (8.0 mL) via cannula tubing. After stirring at rt for 20 min, the mixture was concentrated. The residue was purified by column chromatography (silica gel 25 g, ether/hexane = 1:2 → 3:1) to give carbodiimide **18** (249 mg) as an oil. This product was enough pure for the next reaction. A suspension of the carbodiimide **18** (249 mg) and NH_4Cl (323 mg, 6.04 mmol) in DMF (12 mL) was heated at 100 °C for 18 h with vigorous stirring. After cooling to rt, the mixture was quenched with water, and the resulting solution was extracted with CH_2Cl_2 (×3). The combined organic layer was washed with sat. NH_4Cl solution (×3) and brine (×2) dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel 16 g, AcOEt → AcOEt/MeOH = 9:1) to give **21** (197 mg, 60% in 2 steps) as a syrup. $[\alpha]_D^{27}$ -21.3 (*c* 1.65, $CHCl_3$). IR (KBr) ν_{max} 3310, 3188, 2982, 2936, 1717, 1654, 1629, 1453, 1373, 1316, 1274, 1217, 1159, 1115, 1070 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (3H, br t, *J* = 7.0 Hz, CH_2-C*H*$_3$), 1.20-1.30 (1H, overlapped, CCH$_3$-C-C*H*$_{ax}$H$_{eq}$), 1.27 (3H, s, C*H*$_3$), 1.29 (3H, s, C*H*$_3$), 1.30 (3H, s, C*H*$_3$), 1.56 (1H, dd, *J* = 14.0, 4.5 Hz, CH_3-C-CH$_{ax}$*H*$_{eq}$), 1.64-1.74 (1H, m, CH_3-C*H*$_A$H$_B$), 1.83 (1H, dq, *J* = 14.0, 7.0 Hz, CH_3-CH$_A$*H*$_B$), 2.14 (1H, dd, *J* = 13.0, 4.5 Hz, BzO-CH-CH$_{ax}$*H*$_{eq}$), 2.37 (1H, br t, *J* = 12.5 Hz, BzO-CH-C*H*$_{ax}$H$_{eq}$), 2.59-2.70 (1H, m, NH-C-C*H*), 3.66 (1H, br t, *J* = 7.5 Hz, -O-C*H*$_A$H$_B$), 3.93-4.03 (1H, m, -O-C*H*), 4.06 (1H, dd, *J* = 7.5, 5.5 Hz, -O-CH$_A$*H*$_B$), 4.36 (1H, br dd, *J* = 15.0, 5.5 Hz, Ph-C*H*$_A$H$_B$), 4.44 (1H, br dd, *J* = 15.0, 5.5 Hz, Ph-CH$_A$*H*$_B$), 4.73 (1H, dd, *J* = 11.5, 4.5 Hz, BzO-C*H*), 7.27-7.39 (5H, m, aromatic), 7.41-7.48 (2H, m, aromatic), 7.54-7.61 (1H, m, aromatic), 8.07-8.12 (2H, m, aromatic), 8.72 (1H, br s, N*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.5, 25.5, 25.6, 25.7, 26.2, 31.7, 36.7, 41.1, 45.4, 59.9, 69.0, 69.6, 73.9, 75.5, 109.3, 127.2, 128.2, 128.3, 128.4, 129.1, 129.6, 129.9, 133.2, 135.6, 155.8, 166.1. HRMS (FAB) Calcd for $C_{29}H_{40}O_3N_5$ (M+H) 510.2968. Found: 510.2958.

Syntheses of acetylguanidine 23 and 24. To a solution of **21** (197 mg, 0.36 mmol) in MeOH (6.0 mL) and H_20 (2.0 mL) was added TFA (8.0 mL). After stirring at 60 °C for 2 h, the mixture was diluted with benzene, and evaporated under reduced pressure. The crude diol was dissolved in MeOH (8.0 mL) and H_2O (8.0 mL). To the mixture was added $NaIO_4$ (116 mg, 0.542 mmol). After stirring at rt for 3 h, the mixture was quenched with H_2O and extracted with AcOEt (×3). The combined organic layer was washed with sat.

NH_4Cl solution (×2), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue (cyclic guanidine) was dissolved in TFA (5.3 mL), MeOH (5.3 mL), and $CH(OMe)_3$ (5.3 mL). After stirring at rt for 3 days, the mixture was concentrated. A solution of the crude product in pyridine (5.0 mL), Ac_2O (2.5 mL) and Et_3N (0.1 mL) was stirred at rt for 3 days. The mixture was evaporated in vacuo. The residue was dissolved in AcOEt. The solution was washed with water (×2), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel 10g, ether/hexane = 3:1 → 5:1 → ether only) to give **23** (79 mg, 41 % as an oil in 4 steps) and **24** (58 mg, 30 % as an oil in 4 steps). **23**: IR (KBr) ν_{max} 3470, 3065, 3032, 2969, 2934, 2882, 2856, 1717, 1674, 1637, 1603, 1453, 1368, 1315, 1271, 1211, 1182, 1158, 1111 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (3H, br s, CH_3), 1.28 (3H, s, CH_3), 2.25 (6H, s, CO-CH_3 × 2), 2.41 (1H, dd, J = 12.0, 4.0 Hz), 3.46 (3H, s, -O-CH_3), 4.70-5.54 (3H, br), 7.20-7.34 (5H, br, aromatic), 7.43-7,51 (2H, m, aromatic), 7.57-7.63 (1H, m, aromatic), 8.00-8.05 (2H, m, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.7 (br), 15.1, 23.5 (br), 25.8, 27.2, 35.3, 40.2 (br), 48.9 (br), 58.6, 65.8, 69.4, 70.5 (br), 74.7 (br), 87.9 (br), 127.4, 127.9, 128.2, 128.5, 129.3, 129.5, 129.7, 129.9, 133.3, 165.7, 170.7, 172.3. HRMS (FAB) Calcd for $C_{30}H_{38}N_3O_6$ (M+H) 536.2760. Found: 536.2764. **24**: IR (KBr) ν_{max} 3436, 3066, 3033, 2965, 2928, 2855, 1718, 1682, 1637, 1603, 1577, 1453, 1374, 1316, 1273, 1215, 1109 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (3H, t, J = 7.0 Hz, CH_2-CH_3), 1.30 (3H, s, C-CH_3), 1.22-1.33 (1H, overlapped, CH_3-C$H_A$$H_B$)1.55 (1H, br t, J = 13.0 Hz, CH_3-C-C$H_{ax}$$H_{eq}$), 1.71 (1H, dq, J = 14.0, 7.0 Hz, CH_3-$CH_A$$H_B$), 1.89 (1H, br t, J = 12.0 Hz, BzO-CH-C$H_{ax}$$H_{eq}$), 2.06 (1H, dd, J = 13.5, 3.5 Hz, CH_3-C-$CH_{ax}$$H_{eq}$), 2.10 (3H, s, -CO-C$H_3$), 2.14-2.24 (1H, m, NH-C-CH), 2.32 (3H, s, -CO-CH_3), 2.47 (1H, dd, J = 12.5, 4.5 Hz, BzO-CH-$CH_{ax}$$H_{eq}$), 3.52 (3H, s, -O-C$H_3$), 4.65 (1H, br d, J = 14.0 Hz, Ph-C$H_A$$H_B$), 4.97 (1H, br d, J = 14.0 Hz, Ph-$CH_A$$H_B$), 4.92 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 9.0 Hz, MeO-CH-N), 7.20-7.33 (3H, m, aromatic), 7.40-7.50 (4H, m, aromatic), 7.56-7.63 (1H, m, aromatic), 8.02-8.08 (2H, m, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.4, 20.1, 23.9, 24.1, 27.0, 35.4, 37.3, 44.1, 49.5, 58.0, 58.8, 70.1, 74.8, 87.4, 127.5, 128.3, 128.5, 128.8, 129.6, 129.8, 133.3, 136.6, 146.1, 165.8, 170.5, 171.3. HRMS (FAB) Calcd for $C_{30}H_{38}N_3O_6$ (M+H) 536.2760. Found: 536.2758.

Synthesis of cyclic guanidine hydrochloride 3a. To a solution of **23** (60 mg, 0.11 mmol) in Ac_2O (3.0 mL) and Et_3N (0.1 mL) was added $Pd(OH)_2$-C (Pearlman's catalyst, 60 mg). The reaction vessel was degassed and filled with H_2 gas. After being stirred at rt for 4 days under H_2 atmosphere, the mixture was filtered through the pad of Super-Cel. The filtrate was diluted with toluene and concentrated under reduced pressure. The residue was re-dissolved in AcOEt. The solution was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel 6g, AcOEt → AcOEt/MeOH = 20:1 → 9:1) to give **3a** (50 mg, quant.) as a syrup. $[\alpha]_D^{27}$ -97 (*c* 0.24, CH_3OH). IR (KBr) ν_{max} 3369, 3249, 3067, 2972, 2932, 1718, 1668, 1603, 1453, 1375, 1318, 1273, 1187, 1112, 1093, 1074, 1062, 1026 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (3H, t, J = 7.0 Hz, CH_2-CH_3), 1.32 (3H, s, C-CH_3), 1.71 (1H, dq, J = 14.0, 7.0 Hz, CH_3-C$H_A$$H_B$), 1.78-1.93 (3H, overlapped, BzO-CH-C$H_{ax}$$H_{eq}$ & CH_3-C-C$H_{ax}$$H_{eq}$), 2.02 (1H, dq, J = 14.0, 7.0 Hz, CH_3-$CH_A$$H_B$), 2.08 (3H, s, CO-C$H_3$), 2.20 (1H, dd, J = 11.5, 4.0 Hz, BzO-CH-$CH_{ax}$$H_{eq}$), 2.49 (1H, br dt, J = 11.0, 4.0 Hz, NH-C-CH), 3.35 (3H, s, -O-CH_3), 4.44 (1H, d, J = 4.0 Hz, MeO-CH-N), 4.91 (1H, dd, J = 11.5, 4.0 Hz, BzO-CH), 7.44-7.51 (2H, m, aromatic), 7.57-7.64 (1H, m, aromatic), 8.01-8.07 (2H, m, aromatic). ^{13}C NMR (75

MHz, CD_3OD) δ 8.7, 25.4, 25.9, 27.3, 35.0, 37.2, 41.0, 57.3, 57.8, 71.9, 76.2, 85.0, 130.5, 131.7, 132.1, 135.4, 153.2, 168.4, 177.3. HR-MS (FAB) Calcd for $C_{21}H_{30}N_3O_5$ (M+H) 404.2185. Found: 404.2184.

Synthesis of cyclic guanidine hydrochloride 3b. To a solution of **24** (73 mg, 0.14 mmol) in Ac_2O (3.0 mL) and Et_3N (0.1 mL) was added $Pd(OH)_2$-C (Pearlman's catalyst, 75 mg). The reaction vessel was degassed and filled with H_2 gas. After stirring at rt for 2 weeks under 1 atm of H_2 atmosphere, the mixture was filtered through the pad of Super-Cel. The filtrate was diluted with toluene and concentrated under reduced pressure. The residue was re-dissolved in AcOEt. The solution was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel 5g, AcOEt → AcOEt/MeOH = 20:1 → 9:1) to give **3b** (54 mg, 90%) as a syrup. $[\alpha]_D^{26}$ -8.3 (*c* 0.29, CH_3OH). IR (KBr) ν_{max} 3352, 3220, 3069, 2972, 2940, 1717, 1664, 1600, 1452, 1375, 1317, 1273, 1180, 1112, 1089, 1055, 1026 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (3H, t, *J* = 7.0 Hz, CH_2-C*H*$_3$), 1.31 (3H, s, C-C*H*$_3$), 1.43 (1H, br t, *J* = 13.5 Hz, CH_3-C-C*H*$_{ax}$H$_{eq}$), 1.49 (1H, dq, *J* = 14.0, 7.0 Hz, CH_3-C*H*$_A$H$_B$), 1.73 (1H, dq, *J* = 14.0, 7.0 Hz, CH_3-CH$_A$*H*$_B$), 1.95 (1H, br t, *J* = 12.0 Hz, BzO-CH-C*H*$_{ax}$H$_{eq}$), 2.07 (3H, s, CO-C*H*$_3$), 2.09 (1H, dd, *J* = 13.5, 3.5 Hz, CH_3-C-CH$_{ax}$*H*$_{eq}$), 2.17 (1H, dd, *J* = 12.0, 4.0 Hz, BzO-CH-CH$_{ax}$*H*$_{eq}$), 2.41 (1H, ddd, *J* = 12.5, 9.5, 3.5 Hz, NH-C-C*H*), 3.42 (3H, s, -O-C*H*$_3$), 4.47 (1H, d, *J* = 9.5 Hz, MeO-C*H*-N), 4.92 (1H, dd, *J* = 11.5, 4.0 Hz, BzO-C*H*), 7.43-7.51 (2H, m, aromatic), 7.57-7.64 (1H, m, aromatic), 8.02-8.08 (2H, m, aromatic). ^{13}C NMR (75 MHz, CD_3OD) δ 8.1, 24.5, 25.5, 27.2, 33.7, 37.4, 42.0, 57.1, 57.7, 71.6, 76.3, 86.0, 130.5, 131.7, 132.0, 135.4, 153.7, 168.5, 177.6. HR-MS (FAB) Calcd for $C_{21}H_{30}N_3O_5$ (M+H) 404.2185. Found: 404.2178.

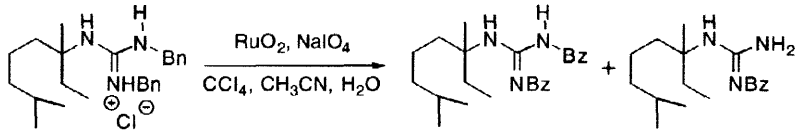
Acknowledgment. We are grateful to Mr. K. Koga for NMR measurements and to Mr. S. Kitamura (analytical laboratory in this school) for elemental analyses and measurements of HR-MS. Levoglucosenone used for the synthesis of the intermediate **13** was supplied from Japan Tobacco Inc. and Yuki Gousei Yakuhin Co. Ltd., whom we thank. This work was financially supported by Iyakushigen Kenkyushinkoukai (the Fujisawa Foundation), JSPS-RFTF and a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of Japan.

References and Notes

1. For recent reviews, see: Berlinck, R. G. S. *Prog. Chem. Org. Nat. Prod.* **1995**, *66*, 120-295. (b) Berlinck, R. G. S. *Nat. Prod. Rep.* **1996**, 377-409.
2. For a review: Yamamoto, Y.; Kojima, S. In *The Chemistry of Amidines and Imidates*; Patai. S.; Rappoport, Z., Eds.; John Wiley & Sons: New York, 1991; Vol. 2; Chapter 10, p 486-526.
3. For a review: Schow, S. In *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L.A. Ed. Wiley: Sussex UK, 1996, p 1408-1410.
4. Reviews on carbodiimide: (a) Williams, A.; Ibrahim, I. T. *Chem. Rev.* **1981**, *81*, 589-636. (b) Mikolajczyk, M.; Kielbasinski, O. *Tetrahedron* **1981**, *37*, 233-284.
5. Recent leading references: (a) Poss, M. A.; Iwanowicz, E.; Reid, J. A.; Lin, J.; Gu, Z. *Tetrahedron Lett.* **1992**, *33*, 5933-5936. (b) Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7677-7680. (c) Levallet, C.; Lerpiniere, J.; Ko, S. Y. *Tetrahedron* **1997**, *53*, 5291-5304. (d) Yong, Y. F.; Kowalski, J. A.; Lipton, M. A. *J. Org. Chem.* **1997**, *62*, 1540-1542.

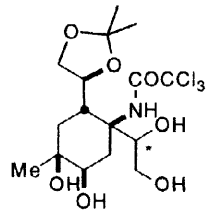
6. Recent leading references: (a) Bergeron, R. J.; McManis, J. S. *J. Org. Chem.* **1987**, *52*, 1700-1703. (b) Tian, Z.; Edwards, P.; Roeske, R. W. *Int. J. Peptide Protein Res.* **1992**, *40*, 119-126. (c) Chandrakumar, N. S. *Synth. Commun.* **1996**, *26*, 2613-2616. (d) Palmer, D. C. In *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L.A. Ed. Wiley: Sussex UK, 1996, p 3523-3525.
7. (a) Miller, A. In *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L.A. Ed. Wiley: Sussex UK, 1996, p 176-178. (b) Miller, A. E.; Bischoff, J. J. *Synthesis* **1986**, 777-779. (c) Kim, K.; Lin, Y.-T.; Mosher, H. S. *Tetrahedron Lett.* **1988**, *29*, 3183-3186.
8. (a) Bernatowicz, M. S. In *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L.A. Ed. Wiley: Sussex UK, 1996, p 4343-4344. (b) Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *Tetrahedron Lett.* **1993**, *34*, 3389-3392. (c) Drake, B.; Patek, M.; Leble, M. *Synthesis* **1994**, 579-582.
9. Quite recently, bisprotected guanidine triflate was reported as efficient guanidinylation reagent.: Feichtinger, K.; Zapf, C.; Sings, H. L.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 3804-3805.
10. (a) Isobe, M.; Fukuda, Y.; Nishikawa, T.; Chabert, P.; Kawai, T.; Goto, T. *Tetrahedron Lett.* **1990**, *31*, 3327-3330. (b) Yamamoto, N.; Nishikawa, T.; Isobe, M. *Synlett* **1995**, 505-506. (c) Bamba, M.; Nishikawa, T.; Isobe, M. *Tetrahedron* **1998**, *54*, 6639-6650.
11. For the structure: (a) Goto, T.; Kishi, Y.; Takahashi, S.; Hirata, Y. *Tetrahedron* **1965**, *21*, 2059-2088. (b) Tsuda, K.; Ikuma, S.; Kawamura, M.; Tachikawa, R.; Sakai, K.; Tamura, C.; Amakasu, O. *Chem. Pharm. Bull.* **1964**, *12*, 1357-1374. (c) Woodward, R. B. *Pure. Appl. Chem.* **1964**, *9*, 49-74.
12. For racemic total synthesis: (a) Kishi, Y.; Aratani, M.; Fukuyama, T.; Nakatsubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *J. Am. Chem. Soc.* **1972**, *94*, 9217-9219. (b) Kishi, Y.; Fukuyama, T.; Aratani, M.; Nakatsubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *J. Am. Chem. Soc.* **1972**, *94*, 9219-9221.
13. For recent reports on the synthetic efforts from other laboratories: (a) Burgey, C. S.; Vollerthun, R.; Fraser-Reid, B. *J. Org. Chem.* **1996**, *61*, 1609-1618. (b) Sato, K.; Kajihara, Y.; Nakamura, Y.; Yoshimura, J. *Chem. Lett.* **1991**, 1559-1562. (c) Keana, J. F. W.; Bland, J. S.; Boyle, P. J.; Erion, M.; Hartling, R.; Husman, J. R.; Roman, R. B. *J. Org. Chem.* **1983**, *48*, 3627-3631.
14. In our previous report[10a] on the synthesis of a simple model compound of tetrodotoxin, we used harsh conditions (6N NaOH/EtOH, 50 °C, 12 h) to deprotect the trichloroacetamide.
15. Yamamoto, N.; Isobe, M. *Chem. Lett.* **1994**, 2299-2302.
16. Review on the Overman rearrangement: (a) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218-224. (b) Ritter, K. In *Houben-Weyl. Stereoselective Synthesis.* E 21, Vol. 9; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; Thieme: Stuttgart, **1996**; p 5677-5699.
17. Petrov, J.; Atanassova, I.; Balabanova, A.; Mollov, N. *Izv. Khim.* **1990**, *23*, 53-57.
18. Clizbe, L. A.; Overman, L. E. *Org. Synth.* **1988**, *Coll. Vol. 6*, 507-511.
19. Treatment of **6** with benzylamine hydrochloride in DMF at 100 °C for 3.5 h gave a mixture of the dibenzylguanidinium chloride **7** (23% from **5**) and the urea **5**.
20. (a) Greene, T. W.; Wuts, P. G. *Protective Groups in Organic Synthesis*, 2nd ed., John Wiley & Sons, Inc. 1991, p 364-366. (b) Kocienski, P. J. *Protecting Groups*, Georg Thieme Verlag, 1994, p 220-227.

21. We have not examined Birch reduction conditions for debenzylation, because we considered that such conditions would not be compatible with a variety of functional groups of tetrodotoxin molecule.
22. Johnstone, R. A. W.; Wilby, A. H. *Chem. Rev.* **1985**, *85*, 129-170.
23. For other example: Hong, C. Y.; Kishi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 9693-9694.
24. Alternatively, the benzylguanidine hydrochloride **8** was oxidized with RuO_4[24a] to give a mixture of di-benzoylguanidine **i** and monobenzoylguanidine **ii**. Deprotection of one benzoyl group of **i** proceeded to give **ii**, while further debenzoylation of **ii** did not readily give the corresponding guanidinium compound under acidic or alkaline conditions. For the oxidation with RuO_4, see: (a) Carisen, P. H.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936-3938.



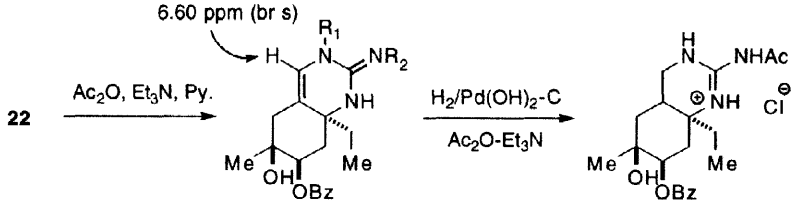
8 i (43%) ii (40%)

25. Isobe, M.; Yamamoto, N.; Nishikawa, T. In *Levoglucosenone and Levoglucosans, Chemistry and Applications.* Witczak, Z. J. Ed.; ATL PRESS, pp. 99-118, 1994.
26. Nishikawa, T.; Asai, M.; Ohyabu, N.; Isobe, M. *J. Org. Chem.* **1998**, *63*, 188-192.
27. The by-product was tetraol **iii** as a single stereoisomer (18%) whose stereochemistry (*) was not determined.



iii

28. Other conditions (in 2-propanol or $Yb(OTf)_3$ in CH_2Cl_2) also yielded the product, but the reactions were very slow.
29. Yasumoto, T.; Yotsu, M.; Murata, M.; Naoki, H. *J. Am. Chem. Soc.* **1988**, *110*, 2344-2345.
30. The structure was **iv**, which was hydrogenated to give guanidinium compound **v** having no aminal moiety found in tetrodotoxin.



iv R_1 = Bn, R_2 = Ac
R_1 = Ac, R_2 = Bn

v

31. The ratios of α to β methoxy-group configuration in **23** and **24** were determined by the integration values of the methoxy peaks (chemical shift of MeO in **23**: major 3.55 ppm, minor 3.46 ppm. chemical shift of MeO in **24**: major 3.67 ppm, minor 3.52 ppm) in the ^1H NMR spectrum. These ratios were comparable to those of the debenzylated products **3a** and **3b**.
32. General experimental details have been described: ref. 26.