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

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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.

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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-carboxamidine⁸ 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 to benzylurea with benzylamine and Na₂CO₃ 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 CH₂Cl₂, EtOAc, etc.



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.



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 Na₂CO₃ to give benzylurea **5** in good yield. The urea was dehydrated with Ph₃P and CBr₄ 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.



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.



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 levoglucosenone²⁵ in our tetrodotoxin synthesis^{10b,26} (Scheme **4**). Stereo- and regioselective dihydroxylation of **13** with OsO₄(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 Na₂CO₃ in DMF under reflux conditions. Hydrogenation of terminal olefin of **16** in the presence of a benzyl group was achieved with PtO₂ 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.



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 ¹H-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.



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 ¹H-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.



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 Section³²

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 Na₂CO₃ (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 NH₄Cl solution. The mixture was extracted with Et₂O, and the combined extract was washed with brine, dried over anhydrous Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel 200 g, Et₂O/hexane = 1:1) to give benzylurea 5 (4.47 g, 74%) as a solid. Mp. 65-67 °C. IR (KBr) v_{max} 3348, 2970, 2918, 1637, 1561, 1455, 1375, 1265 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 1.35 (3H, s, CH₃), 1.57 (3H, br s, CH₃), 1.58-1.66 (2H, m, CH₂), 1.66 (3H, d, *J* = 1.0 Hz, CH₃), 1.88-1.98 (2H, m, CH₂), 4.31 (2H, d, *J* = 5.5 Hz, Ph-CH₂), 4.77 (1H, br s, NH), 5.02-5.08 (1H, m, Me₂C=CH-), 5.10 (1H, d, *J* = 10.0 Hz, -CH=CH₄H_B), 5.11 (1H, d, *J* = 17.0 Hz, -CH=CH₄H_B), 5.22 (1H, br s, NH), 5.91 (1H, dd, *J* = 17.0, 10.0 Hz, -CH=CH₂), 7.19-7.33 (5H, m, aromatic). ¹³C NMR (75 MHz, CDCl₃) 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 C₁₈H₂₆N₂O₁: 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), Ph₃P (399 g, 1.52 mmol) and Et₃N (0.21mL, 1.51 mmol) were dissolved in dry CH₂Cl₂ (5.0 mL) and the solution was cooled to 0 °C. To this solution was added dry CH₂Cl₂ (0.5 mL) solution of CBr₄ (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) v_{max} 2969, 2926, 2857, 2125 (N=C=N), 1454, 923 cm⁻¹. ¹H NMR (270 MHz, CDCl₃) δ 1.20 (3H, s, CH₃), 1.42 (2H, m, CH₂), 1.57 (3H, s, CH₃), 1.66 (3H, s, CH₃), 1.88-1.99 (2H, m, CH₂), 4.35 (2H, s, NCH₂Ph), 4.98-5.08 (1H, m, Me₂C=CH-), 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, -CH=CH₂), 7.18-7.33 (5H, m, aromatic). ¹³C NMR (67.9 MHz, CDCl₃) 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 C₁₈H₂₄N₂ (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 CH₂Cl₂ (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 CH₂Cl₂. The resulting solution was washed with water (×2), sat. NH₄Cl solution (×3) and brine (×3), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by preparative TLC (silica gel, CH₂Cl₂/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), Ph₃P (12.5 g, 47,8 mmol) and Et₃N (6.7 mL, 47.8 mmol) were dissolved in dry CH₂Cl₂ (130 mL), and the solution was cooled to 0 °C. To this solution was added dry CH₂Cl₂ (7 mL) solution of CBr₄ (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 = $1:1 \rightarrow 1:2$) 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 (x2). The combined organic layer was washed with water, sat. NH4Cl solution and brine (×3), dried over anhydrous Na2SO4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel 400 g, $CH_2Cl_2/acetone =$ 2:1 \rightarrow CH₂Cl₂/acetone /MeOH = 8:1:1) to give 7 (7.33 g, 75% in 2 steps) as a syrup. IR (KBr) v_{max} 3251, 3188, 3065, 2974, 1618 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 1.22 (3H, s, CH₃), 1.44-1.70 (4H, m, CH₂ × 2), 1.49 (3H, br s, CH_3), 1.65 (3H, br s, CH_3), 4.67-4.81 (4H, br, Ph- $CH_2 \times 2$), 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_AH_B), 5.77 (1H, dd, J = 18.0, 11.0 Hz, CH=CH_AH_B), 6.51 (1H, br s, NH), 7.29-7.39 (10H, m, aromatic). ¹³C NMR (75 MHz, CDCl₃) § 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 C₂₅H₃₄N₃ (M+H) 376.2753. Found: 376.2764.

Benzyl 3,7,7-trimethylocta-2,6-dienylcyanamide (9). To an ice-cold solution of CBr₄ (294 mg, 0.89 mmol) in dry CH₂Cl₂ (2.5 mL) was added Ph₃P (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 Et₃N (0.25 mL, 1.78 mmol) in CH₂Cl₂ (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 Na₂CO₃ (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 NH₄Cl solution and brine, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (silica gel 5 g, ether/hexane = $1:10 \rightarrow 1:5$) to give cyanamide 9 (29 mg, 61% in 2 steps) as an oil. IR (KBr) v_{max} 2923, 2210 (N-C=N), 1668, 1455, 1376 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 1.55 (3H × 1/3, s, CH₃), 1.57 (3H × 2/3, s, CH₃), 1.61 (3H × 2/3, s, CH₃), 1.65 (3H × 1/3, s, CH₃), 1.69 (3H × 1/3, s, CH₃), 1.78 (3H × 1/3, s, CH₃), 1.95-2.17 (4H, m, CH₂CH₂), 3.52 (1H × 1/3, br d, J = 7 Hz, C=CH-CH₂-N), $3.54 (1H \times 2/3, d, J = 7 Hz, C=CH-CH_2-N), 4.15 (2H, s, Ph-CH_2), 4.98-5.04 (1H, m. olefinic), 5.05-5.11 (1H)$ × 2/3, m, olefinic), 5.24-5.34 (1H, m, olefinic), 7.31-7.40 (5H, m, aromatic). 13 C NMR (75 MHz, CDCl₃) 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 C₁₈H₂₄N₂ (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 H₂ gas. After stirring at rt for 2 days under H₂ 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 \rightarrow 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) v_{max} 3255, 3091, 3064, 2952, 1617 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 0.55 (3H, t, *J* = 7.0 Hz, CH₂-CH₃), 0.76 (6H, d, *J* = 6.5 Hz, CH-CH₃ x2), 0.77-0.89 (2H, m), 0.97 (2H, q, *J* = 7.0 Hz, CH₃-CH₂), 1.21 (3H, s, CH₃), 1.24-1.70 (5H, m), 4.76 (4H, br s, Ph-CH₂ × 2), 5.03 (1H, br s, NH), 7.22-7.33 (6H, m, aromatic), 7.37-7.46 (4H, m, aromatic), 8.07 (2H, br s, NH × 2). ¹³C NMR (75 MHz, CDCl₃) 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 C₂₅H₃₈N₃Cl: 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), Ac₂O (20 mL) and Et₃N (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 \rightarrow 1:2) to give acetyl guanidine **10** (1.11 g, 89%) as an oil. IR (KBr) v_{max} 3349, 2955, 2869, 1675, 1645, 1523, 1495, 1455, 1384, 1350, 1251, 1227 cm^{-1.} ¹H NMR (300 MHz, CDCl₃) \otimes 0.68 (3H × 1/2, t, *J* = 7.5 Hz, CH₂-CH₃), 0.72 (3H × 1/2, t, *J* = 7.5 Hz, CH₂-CH₃), 0.84 (3H × 1/2, d, *J* = 6.5 Hz, CH-CH₃), 0.84 (3H × 1/2, d, *J* = 6.5 Hz, CH-CH₃), 0.84 (3H × 1/2, d, *J* = 6.5 Hz, CH-CH₃), 0.85 (3H × 1/2, s, C-CH₃), 1.15 (3H × 1/2, s, C-CH₃), 1.40-1.72 (5H, m), 2.08 (3H, s, CO-CH₃), 3.38 (1H, br s, NH), 3.96 (1H × 1/2, d, *J* = 14.0 Hz, Ph-CH_AH_B), 3.97 (1H × 1/2, d, *J* = 14.0 Hz, Ph-CH_AH_B), 4.24 (1H, d, *J* = 15.5 Hz, Ph-CH_AH_B), 4.30 (1H, d, *J* = 15.5 Hz, Ph-CH_AH_B), 5.22 (1H × 1/2, d, *J* = 14.0 Hz, Ph-CH_AH_B), 5.23 (1H × 1/2, d, *J* = 14.0 Hz, Ph-CH_AH_B), 7.17-7.34 (10H, m, aromatic). ¹³C NMR (75 MHz, CDCl₃) \otimes 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 C₂₇H₃₉N₃O₁: 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 H₂ 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 Ac₂O (0.5 mL), pyridine (1.0 mL) and Et₃N (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, CDCl₃) δ 0.83 (3H, t, *J* = 7.5 Hz, CH₂-CH₃), 0.87 (6H, d, *J* = 6.5 Hz, CH-CH₃ × 2), 0.89-1.89 (31H, m), 1.21 (3H ×1/2, s, CH₃), 1.24 (3H ×1/2, s, CH₃), 2.05 (3H, s, CO-CH₃), 2.75-2.84 (1H, overlapped, NH-CH_AH_B), 2.78 (1H, dd, *J* = 13.5, 7.0 Hz, NH-CH_AH_B), 2.87 (1H, dd, *J* = 12.5, 6.5 Hz, NH-CH_AH_B), 3.54 (1H, br s, NH), 3.63 (1H, dd, *J* = 13.5, 7.0 Hz, NH-CH_AH_B). ¹³C NMR (75 MHz, CDCl₃) 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 Ac₂O (9.0 mL) and Et₃N (0.45 mL) was degassed and filled with H₂ gas. The mixture was stirred for 2.7 days with vigorous stirring under H₂ 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) v_{max} 3282, 3249, 3117, 2958, 1699, 1618, 1459, 1377, 1330, 1209 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 0.84 (3H, t, *J* = 7.5 Hz, CH₂-CH₃), 0.87 (6H, d, *J* = 6.5 Hz, (CH₃)₂-CH), 1.11-1.32 (4H, m), 1.35 (3H, s, CH₃), 1.48-1.96 (5H, m), 2.10 (3H, s, CO-CH₃), 2.15 (3H, s, CO-CH₃), 9.95 (1H, br s, NH), 13.16 (1H, br s, NH). ¹³C NMR (75 MHz, CDCl₃) 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 C₁₅H₂₉N₃O₂ : 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 OsO4 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 H₂O (5 mL). After stirring at rt for 4 h, aqueous NaHSO₃ solution was added. The resulting mixture was acidified with 1N HCl and extracted with AcOEt (x3). Combined organic layer was dried over anhydrous Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel 40 g, ether/hexane = $10:1 \rightarrow$ ether only) to give diol 14 (895 mg, 73%) as a solid. Mp. 61-63 °C. $[\alpha]_D^{26}$ +22.0 (c 1.15, CHCl₃). IR (KBr) v_{max} 3448, 3321, 2986, 2935, 1724, 1526, 1381, 1373, 1261, 1216, 1160, 1057 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 1.22 (1 H, dd, J = 14.0, 12.5 Hz, CH₃-C-CH_{ax}H_{eq}) 1.28 (3 H, s, CH₃), 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-CH), 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- $CH_{A}H_{B}$), 3.67 (1 H, dd, J = 12.0, 5.0 Hz, HO-CH), 3.96 (1 H, ddd, J = 9.5, 9.0, 5.5 Hz, -O-CH), 4.09 (1 H, dd, J = 8.0, 5.5 Hz, -O-CH_AH_B), 5.41 (1H, d, J = 16.5 Hz, $-CH=CH_AH_B$, 5.42 (1H, d, J = 11.0 Hz, $-CH=CH_AH_B$), 5.89 (1H, dd, J = 16.5, 11.0 Hz, $CH_2=CH$), 8.95 (1H, br s, NH). ¹³C NMR (75 MHz, CDCl₃) 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 C₁₆H₂₄N₁O₅Cl₃: 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), Et₃N (0.63 mL, 4.52 mmol) and DMAP (15 mg, 0.12 mmol) in CH₂Cl₂ (17 mL) was added BzCl (0.17 mL, 1.51 mmol). After stirring at rt for 2 h, the mixture was quenched with sat. NH₄Cl solution and then extracted with CH₂Cl₂ (×3). The combined organic layer was dried over anhydrous Na₂SO₄, evaporated under reduced pressure. The residue was purified by column chromatography (silica gel 30 g, ether/hexane = 1:1 \rightarrow 3:1) to give benzoate 15 (610 mg, 91%) as crystals. Mp. 196-197 °C (from ether-hexane). [α]_D²⁷ +12.4 (*c* 1.31, CHCl₃). IR (KBr) v_{max} 3504, 3315, 2987, 2938, 1719, 1522, 1273, 1159, 1109, 1069, 1028 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 1.25 (3H, s, CH₃), 1.35-1.46 (2H, overlapped, CH₃-C-CH₂), 1.38 (3H, s, CH₃), 1.45 (3H, s, CH₃), 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-CH), 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-CH), 4.13 (1H, dd, *J* = 7.5, 5.5 Hz, -O-CH_AH_B), 5.20 (1H, dd, *J* = 12.0, 4.5 Hz, BzO-CH), 5.53 (1H,

d, J = 10.5 Hz, -CH=CH_AH_B), 5.62 (1H, d, J = 16.5 Hz, -CH=CH_AH_B), 6.01 (1H, dd, J = 16.5, 10.5 Hz, CH₂=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). ¹³C NMR (75 MHz, CDCl₃) 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 C₂₃H₂₈N₁O₆Cl₃: 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), Na₂CO₃ (750 mg, 7.08 mmol), BnNH₂ (0.23 mL, 2.10 mmol) and DMF (25 mL) was heated under reflux with vigorous stirring. After 35 min., BnNH₂ (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 NH₄Cl. The mixture was extracted with AcOEt (x3). The combined organic layer was washed with sat. NH₄Cl solution (×3), brine (x1), dried over anhydrous Na₂SO₄ 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, CHCl₃). IR (KBr) v_{max} 3381, 2984, 2936, 1717, 1654, 1542, 1453, 1372, 1316, 1274, 1115, 1070, 1027 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 1.20-1.42 (2H, overlapped, CH₃-C-CH₂), 1.21 (3H, s, CH₃), 1.31 $(3H, s, CH_3), 1.35 (3H, s, CH_3), 2.27 (1H, br t, J = 12.5 Hz, BzO-CH-CH_{ax}H_{cq}), 2.32-2.42 (1H, m, NH-C-$ 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_AH_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 = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, J = 12.0, 4.5 Hz, BzO-CH), 5.46 (1H, dd, Hz) 10.5, 1.0 Hz, $-CH=CH_AH_B$), 5.56 (1H, dd, J = 16.5, 1.0 Hz, $-CH=CH_AH_B$), 6.03 (1H, dd, J = 16.5, 10.5 Hz, CH₂=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). ¹³C NMR (75 MHz, CDCl₃) & 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 C₂₉H₃₆N₂O₆: 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 PtO₂ (11 mg, 0.048 mmol). The suspension was degassed and filled with H₂ 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, CHCl₃). IR (KBr) v_{max} 3390, 2982, 2935, 1717, 1654, 1551, 1453, 1372, 1316, 1273, 1116, 1056, 1027 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 1.09 (3H, t, *J* = 7.0 Hz, CH₂-CH₃), 1.22 (3H, s, CH₃), 1.33 (6H, s, CH₃x2), 1.30-1.37 (1H, overlapped, CH₃-C-CHaxHeq), 1.44 (1H, dd, *J* = 14.0, 4.5 Hz, CH₃-C-CH_{ax}H_{eq}), 1.57 (1H, dq, *J* = 14.0, 7.0 Hz, CH₃-CH_AH_B), 1.93 (1H, dq, *J* = 14.0, 7.0 Hz, CH₃-CH_AH_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_AH_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_AH_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). ¹³C NMR (75 MHz, CDCl₃) 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 C₂₉H₃₈N₂O₆: 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 CBr₄ (399 mg, 1.02 mmol) in dry CH₂Cl₂ (3.0 mL) was added Ph₃P (268 mg, 1.02 mmol). After dissolving the Ph₃P, 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 CH₂Cl₂ (3.0 mL) and Et₃N (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 = $1:2 \rightarrow 3:1$) to give carbodiimide 18 (96 mg) as an oil. IR (KBr) v_{max} 3503, 2980, 2938, 2124 (N=C=N), 1717, 1456, 1273, 1114, 1056 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 0.96 (3H, t, J = 7.0 Hz, CH₂-CH₃), 1.15 (1H, dq, J = 14.0, 7.0 Hz, CH₃-CH_AH_B), 1.25 (3H, s, CH_3), 1.34 (3H, s, CH_3), 1.35 (1H, dd, J = 14.0, 13.0 Hz, CH_3 -C- $CH_{ax}H_{eq}$), 1.43 (3H, s, CH_3), 1.58 (1H, dq, dq, dq), 1.58 (1H, dq), 1. J = 14.0, 7.0 Hz, CH₃-CH_AH_B), 1.81 (1H, dd, J = 14.0, 4.0 Hz, CH₃-C-CH_{ax}H_{eq}), 1.84 (1H, br t, J = 12.0Hz, BzO-CH-CH_{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-CH), 3.58 (1H, t, J = 8.0 Hz, -O-CH_AH_B), 3.86 (1H, dd, J = 8.0, 6.0 Hz, -O-CH_AH_B), 4.30-4.41 (1H, m, -O-CH, 4.35 (2H, s, Ph-CH₂), 4.70 (1H, dd, J = 11.5, 4.0 Hz, BzO-CH), 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). ¹³C NMR (75 MHz, CDCl₃) & 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 BnNH₂·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 Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel 5 g, AcOEt/MeOH = 9:1 \rightarrow 7:3) to give 19 (197 mg, 71% in 2 steps) as a syrup. $[\alpha]_D^{26}$ -8.1 (c 0.44, CHCl₃). 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, CDCl₃) δ 0.78 (3H, t, J = 7.0 Hz, CH₂-CH₃), 0.87 (3H, s, CH₃), 1.09 (3H, s, CH₃), 1.19 (1H, br t, J = 13.0 Hz, CH₃-C-CH_{ax}H_{ea}), 1.27 (3H, s, CH₃), 1.51-1.61 (2H, m, CH₃-C-CH_{ax}H_{eq} & CH₃-CH_AH_B), 1.74-1.89 (2H, m, BzO-CH-CH_{ax}H_{eq} & CH₃-CH_AH_B), 2.42 (1H, br t, J = 12.0 Hz, BzO-CH-CH_{ax}H_{eq}), 2.65-2.76 (1H, m, NH-C-CH), 3.57 (1H, br t, J = 8.0 Hz, -O-CH_AH_B), 3.76-3.86 (1H, m, -O-CH), 3.97 (1H, dd, J = 7.5, 5.5 Hz, -O-CH_AH_B), 4.60-4.84 (4H, br, Ph-CH₂ × 2), 4.65 (1H, dd, J = 11.0, 4.5 Hz, BzO-CH), 5.18 (1H, br s, NH), 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, NH). ¹³C NMR (75 MHz, CDCl₃) & 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 C₃₆H₄₆O₃N₅ (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 NaIO₄ (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. NH₄Cl solution (×2) and brine (×2), dried over anhydrous Na₂SO₄, 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, CHCl₃). IR (KBr) v_{max} 3384, 3245, 3065, 3034, 2973, 2942, 1717, 1612, 1584, 1455, 1316, 1273, 1179, 1111, 1073, 1027 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 0.49 (3H, br t, J = 7.5 Hz, CH₂-CH₃), 0.89-1.13 (1H, m, CH₃-CH_AH_B), 1.29 (3H, s, C-CH₃), 1.34 (1H, br t, J = 13.5 Hz, CH₃-C-CH_{ax}H_{eq}), 1.39-1.52 (1H, m, CH₃-CH_AH_B), 2.19-2.37 (3H, overlapped, CH₃-C-CHaxHeq, & BzO-CH-CH₂), 2.68-2.80 (1H, m, NH-C-CH), 4.38 (1H, d, J = 9.5 Hz, HO-CH-N), 4.48 (1H, br d, J = 15.0 Hz, Ph-CH_AH_B), 4.74 (1H, d, J = 15.0 Hz, Ph-CH_AH_B), 4.74-4.83 (1H, overlapped, BzO-CH), 4.99 (1H, br d, J = 15.0 Hz, Ph-CH_AH_B), 5.14 (1H, d, J = 15.0 Hz, Ph-CH_AH_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 D₂O), 8.06-8.12 (2H, m, aromatic). ¹³C NMR (75 MHz, CDCl₃) 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 C₃₂H₃₈N₃O₄ (M+H) 528.2862. Found: 528.2864.

Syntheses of benzyl carbodiimide 18 and monobenzylguanidine hydrochloride 21. CBr4 (900 mg, 2.71 mmol) was dissolved in dry CH2Cl2 (8.0 mL) and cooled to 0 °C. To this solution was added Ph3P (712 mg, 2.71 mmol). The resulting solution was added to a solution of the urea 17 (308 mg, 0.603 mmol) and Et₃N (0.84 mL, 6.0 mmol) in dry CH₂Cl₂ (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 \rightarrow 3:1) to give carbodimide 18 (249 mg) as an oil. This product was enough pure for the next reaction. A suspension of the carbodiimide 18 (249 mg) and NH₄Cl (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 (x3). The combined organic layer was washed with sat. NH₄Cl solution (×3) and brine (×2) dried over anhydrous Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel 16 g, AcOEt \rightarrow AcOEt/MeOH = 9:1) to give **21** (197 mg, 60% in 2 steps) as a syrup. $[\alpha]_D^{27}$ -21.3 (c 1.65, CHCl₃). IR (KBr) v_{max} 3310, 3188, 2982, 2936, 1717, 1654, 1629, 1453, 1373, 1316, 1274, 1217, 1159, 1115, 1070 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) & 0.91 (3H, br t, J = 7.0 Hz, CH₂-CH₃), 1.20-1.30 (1H, overlapped, CCH₃-C-CH_{ax}H_{eq}), 1.27 (3H, s, CH_3), 1.29 (3H, s, CH_3), 1.30 (3H, s, CH_3), 1.56 (1H, dd, J = 14.0, 4.5 Hz, CH_3 -C- $CH_{ax}H_{eq}$), 1.64-1.74 (1H, 1H, 1H), 1.64-1.74 (1H), 1.6 m, CH₃-CH_AH_B), 1.83 (1H, dq, J = 14.0, 7.0 Hz, CH₃-CH_AH_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- $CH_{ax}H_{eq}$), 2.59-2.70 (1H, m, NH-C-CH), 3.66 (1H, br t, J = 12.5 Hz, BzO-CH- $CH_{ax}H_{eq}$), 2.59-2.70 (1H, m, NH-C-CH), 3.66 (1H, br t, J = 12.5 Hz, BzO-CH- $CH_{ax}H_{eq}$), 2.59-2.70 (1H, m, NH-C-CH), 3.66 (1H, br t, J = 12.5 Hz, BzO-CH- $CH_{ax}H_{eq}$), 2.59-2.70 (1H, m, NH-C-CH), 3.66 (1H, br t, J = 12.5 Hz, BzO-CH- $CH_{ax}H_{eq}$), 2.59-2.70 (1H, m, NH-C-CH), 3.66 (1H, br t, J = 12.5 Hz, BzO-CH- $CH_{ax}H_{eq}$), 2.59-2.70 (1H, m, NH-C-CH), 3.66 (1H, br t, J = 12.5 Hz, BzO-CH- $CH_{ax}H_{eq}$), 2.59-2.70 (1H, m, NH-C-CH), 3.66 (1H, br t, J = 12.5 Hz, BzO-CH- $CH_{ax}H_{eq}$), 2.59-2.70 (1H, m, NH-C-CH), 3.66 (1H, br t, J = 12.5 Hz, BzO-CH- $CH_{ax}H_{eq}$), 2.59-2.70 (1H, m, NH-C-CH), 3.66 (1H, br t, J = 12.5 Hz, BzO-CH- $CH_{ax}H_{eq}$), 2.59-2.70 (1H, m, NH-C-CH), 3.66 (1H, br t, J = 12.5 Hz, BzO-CH- $CH_{ax}H_{eq}$), 2.59-2.70 (1H, m, NH-C-CH), 3.66 (1H, br t, J = 12.5 Hz, BzO-CH- $CH_{ax}H_{eq}$), 2.59-2.70 (1H, m, NH-C-CH), 3.66 (1H, br t, J = 12.5 Hz, BzO-CH- $CH_{ax}H_{eq}$), 2.59-2.70 (1H, m, NH-C-CH), 3.66 (1H, br t, J = 12.5 Hz, BzO-CH- $CH_{ax}H_{eq}$), 2.59-2.70 (1H, m, NH-C-CH), 3.66 (1H, br t, J = 12.5 Hz, BzO-CH- $CH_{ax}H_{eq}$), 2.59-2.70 (1H, m, NH-C-CH), 3.66 (1H, br t, J = 12.5 Hz, BzO-CH- $CH_{ax}H_{eq}$), 2.59-2.70 (1H, m, NH-C-CH), 3.66 (1H, br t, J = 12.5 Hz, BzO-CH- $CH_{ax}H_{eq}$), 2.59-2.70 (1H, m, NH-C-CH), 3.66 (1H, br t, J = 12.5 Hz, BzO-CH- $CH_{ax}H_{eq}$), 2.59-2.70 (1H, m, NH-C-CH), 3.66 (1H, br t, J = 12.5 Hz, BzO-CH- $CH_{ax}H_{eq}$), 2.59-2.70 (1H, m, NH-C-CH), 3.66 (1H, br t, J = 12.5 Hz, BzO-CH- $CH_{ax}H_{eq}$), 2.59-2.70 (1H, m, NH-C-CH), 3.66 (1H, br t, J = 12.5 Hz, BzO-CH- $CH_{ax}H_{eq}$), 2.59-2.70 (1H, m, NH-C-CH), 3.66 (1H, br t, J = 12.5 Hz, BzO-CH- $CH_{ax}H_{eq}$), 3.66 (1H, br t, J = 12.5 Hz, BzO-CH- $CH_{ax}H_{eq}$), 3.66 (1H, br t, J = 12.5 Hz, BzO-CH- $CH_{ax}H_{eq}$), 3.66 (1H, br t, J = 12.5 Hz, BzO-CH- $CH_{ax}H_{eq}$) 7.5 Hz, -O-CH_AH_B), 3.93-4.03 (1H, m, -O-CH), 4.06 (1H, dd, J = 7.5, 5.5 Hz, -O-CH_AH_B), 4.36 (1H, br dd, J = 15.0, 5.5 Hz, Ph-CH_AH_B), 4.44 (1H, br dd, J = 15.0, 5.5 Hz, Ph-CH_AH_B), 4.73 (1H, dd, J = 11.5, 4.5 Hz, BzO-CH), 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, NH). ¹³C NMR (75 MHz, CDCl₃) & 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 C₂₉H₄₀O₃N₅ (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 H₂0 (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 H₂O (8.0 mL). To the mixture was added NaIO₄ (116 mg, 0.542 mmol). After stirring at rt for 3 h, the mixture was quenched with H₂O and extracted with AcOEt (\times 3). The combined organic layer was washed with sat.

 NH_4Cl solution (x2), 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), Ac₂O (2.5 mL) and Et₃N (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 (x2), dried over anhydrous Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel 10g, ether/hexane = $3:1 \rightarrow 5:1 \rightarrow$ 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) v_{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, CDCl₃) & 1.02 (3H, br s, CH₃), 1.28 (3H, s, CH_3), 2.25 (6H, s, $CO-CH_3 \times 2$), 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). ¹³C NMR (75 MHz, CDCl₃) & 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 C₃₀H₃₈N₃O₆ (M+H) 536.2760. Found: 536.2764. 24: IR (KBr) v_{max} 3436, 3066, 3033, 2965, 2928, 2855, 1718, 1682, 1637, 1603, 1577, 1453, 1374, 1316, 1273, 1215, 1109 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 1.04 (3H, t, J = 7.0 Hz, CH₂-CH₃), 1.30 (3H, s, C-CH₃), 1.22-1.33 (1H, overlapped, CH₃-CH_AH_B)1.55 (1H, br t, J = 13.0 Hz, CH₃-C-CH_{ax}H_{eq}), 1.71 (1H, dq, J = 14.0, 7.0 Hz, CH₃-CH₄H_B), 1.89 (1H, br t, J = 12.0 Hz, BzO-CH-CH_{ax}H_{ea}), 2.06 (1H, dd, J = 13.5, 3.5Hz, CH₃-C-CH_{ax}H_{eq}), 2.10 (3H, s, -CO-CH₃), 2.14-2.24 (1H, m, NH-C-CH), 2.32 (3H, s, -CO-CH₃), 2.47 $(1H, dd, J = 12.5, 4.5 Hz, BzO-CH-CH_{ax}H_{eq}), 3.52 (3H, s, -O-CH_3), 4.65 (1H, br d, J = 14.0 Hz, Ph CH_AH_B$), 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 = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, J = 12.0, 4.5 Hz, BzO-CH), 5.09 (1H, d, = 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). ¹³C NMR (75 MHz, CDCl₃) 8 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 C₃₀H₃₈N₃O₆ (M+H) 536.2760. Found: 536.2758.

Synthesis of cyclic guanidine hydrochloride 3a. To a solution of 23 (60 mg, 0.11 mmol) in Ac₂O (3.0 mL) and Et₃N (0.1 mL) was added Pd(OH)₂-C (Pearlman's catalyst, 60 mg). The reaction vessel was degassed and filled with H₂ gas. After being stirred at rt for 4 days under H₂ 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 Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel 6g, AcOEt \rightarrow AcOEt/MeOH = 20:1 \rightarrow 9:1) to give 3a (50 mg, quant.) as a syrup. [α]_D²⁷ -97 (*c* 0.24, CH₃OH). 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, CDCl₃) δ 1.05 (3H, t, *J* = 7.0 Hz, CH₂-CH₃), 1.32 (3H, s, C-CH₃), 1.71 (1H, dq, *J* = 14.0, 7.0 Hz, CH₃-CH_AH_B), 1.78-1.93 (3H, overlapped, BzO-CH-CH_{ax}H_{eq} & CH₃-C-CH_{ax}H_{eq}), 2.02 (1H, dq, *J* = 14.0, 7.0 Hz, CH₃-CH_AH_B), 2.08 (3H, s, CO-CH₃), 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-CH₃), 4.44 (1H, d, *J* = 4.0 Hz, MeO-CH-N), 4.91 (1H, dd, *J* = 11.5, 4.0 Hz, BZO-CH-(2H, m, aromatic)). ¹³C NMR (75

MHz, CD₃OD) 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 C₂₁H₃₀N₃O₅ (M+H) 404.2185. Found: 404.2184.

Synthesis of cyclic guanidine hydrochloride 3b. To a solution of 24 (73 mg, 0.14 mmol) in Ac₂O (3.0 mL) and Et₃N (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 Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel 5g, AcOEt \rightarrow AcOEt/MeOH = 20:1 \rightarrow 9:1) to give **3b** (54 mg, 90%) as a syrup. [α]_D²⁶-8.3 (*c* 0.29, CH₃OH). 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, CDCl₃) δ 1.05 (3H, t, J = 7.0 Hz, CH_2 - CH_3 , 1.31 (3H, s, C- CH_3), 1.43 (1H, br t, J = 13.5 Hz, CH_2 - $C-CH_{ax}H_{eq}$), 1.49 (1H, dq, J = 14.0, 7.0Hz, CH_3 - CH_AH_B), 1.73 (1H, dq, J = 14.0, 7.0 Hz, CH_3 - CH_AH_B), 1.95 (1H, br t, J = 12.0 Hz, BzO-CH- $CH_{ax}H_{eg}$, 2.07 (3H, s, CO-CH₃), 2.09 (1H, dd, J = 13.5, 3.5 Hz, CH₃-C-CH_{ax} H_{eg}), 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-CH), 3.42 (3H, s, -O-CH₃), 4.47 (1H, d, J = 9.5 Hz, MeO-CH-N), 4.92 (1H, dd, J = 11.5, 4.0 Hz, BzO-CH), 7.43-7.51 (2H, m, aromatic), 7.57-7.64 (1H, m, aromatic), 8.02-8.08 (2H, m, aromatic). ¹³C NMR (75 MHz, CD₃OD) & 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 C₂₁H₃₀N₃O₅ (M+H) 404.2185. Found: 404.2178.

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- 28. Other conditions (in 2-propanol or Yb(OTf)₃ in CH₂Cl₂) also yielded the product, but the reactions were very slow.
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- 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.