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Stereocontrolled syntheses of α-*C*-mannosyltryptophan and its analogues

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The total synthesis of α-*C*-mannosyltryptophan (C-Man-Trp), a naturally occurring *C*-glycosylamino acid, was achieved from a commercially available α-methyl-D-mannoside in 10 steps including the following key steps: the *C*-glycosidation of a mannose derivative with a stannylacetylene, Castro indole synthesis, and $Sc(ClO_4)_3$-promoted coupling with L-serine-derived aziridine carboxylate. The glucose- and galactose-analogues of C-Man-Trp were also synthesized in a similar manner. Conformational analyses of the synthesized *C*-glycosyltryptophan and its synthetic intermediate are briefly discussed.

Introduction

The carbohydrate moieties of glycoproteins and glycolipids are of great interest due to their numerous significant biological functions, including their involvement in cell–cell interactions, the immune response, the stabilization of proteins, local conformational changes of the protein backbone *etc.*[1] Most carbohydrate moieties are linked to asparagine through *N*-glycosidic bonds, or to serine/threonine through *O*-glycosidic bonds. There are a few other types of glycosides linked to tyrosine and cysteine on the protein surface.[2] However, until 1994, no *C*-glycosidic linkage between amino acids and carbohydrates had been identified among the proteins, whereas many synthetic *C*-glycosylamino acids have been reported as stable mimics of *N*- and *O*-glycosylamino acids; such synthetic compounds have been employed as probes for analyzing the biological functions of the corresponding naturally occurring sugar chains.[3] In 1994, Hofsteenge and co-workers discovered that tryptophan-7 of Ribonuclease 2 (RNase 2) from human urine was modified by a hexopyranose.[4] Surprisingly, extensive NMR analysis of the hexapeptide containing the modified tryptophan obtained from enzyme digestion of the RNase 2 revealed that mannose was connected to the 2-position (carbon atom) of the indole with an α-configuration, as shown in Fig. 1.[5] *C*-Mannosyltryptophan (C-Man-Trp, **1**) is the first example of a molecule with a *C*-glycosidic linkage between amino acid and carbohydrate found in proteins. Interestingly, the mannose moiety of C-Man-Trp was reported not to adopt the typical $^4C_1$ conformation, but instead adopted multiple conformations, including the unusual $^1C_4$ conformation and a twist-boat conformation, presumably due to the severe steric hindrance of the tryptophan at the anomeric position in the α-configuration, as well as due to the lack of anomeric effect.

This novel post- or co-translational modification is catalyzed by a microsome-associated enzyme, "*C*-mannosyltransferase", which has not been purified to date.[6] However, the enzyme activity has been detected in cell culture from many organisms such as mammals, nematodes, birds, amphibians, fish, but not in *Escherichia coli*, insects, or yeast.[7] This enzyme was found to recognize an amino acid sequence, Trp-x-x-Trp, to glycosylate the first Trp of this motif.[8] Such previous studies have indicated that C-Man-Trp is more common than expected,

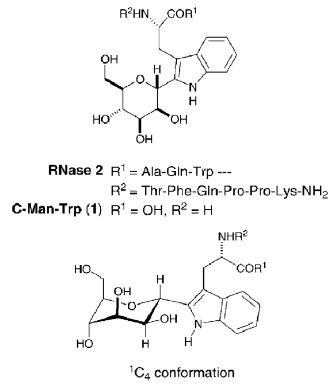

Fig. 1 Structure of α-*C*-mannosyltryptophan.

since the recognition sequence is contained in the TSR module and the WS motif (Trp-Ser-x-Trp-Ser) of many proteins such as extracellular matrix proteins, complement system proteins and cytokine receptors.[9] In fact, the C-Man-Trp residue has also been found in a variety of biologically important proteins such as interleukin 12β,[10] four terminal components of the human complement system,[11] properdine,[12] human platelet thrombospondin-1,[13] and the erythropoietin receptor.[14] On the other hand, C-Man-Trp (**1**) has been isolated as a monomer from human urine[15] and marine organisms.[16] However, despite these extensive studies, the biological function of this novel sugar residue has not yet been clarified, although some possibilities have been discussed in the literature.[9,17,18] In order to elucidate the biological function(s) of this residue, C-Man-Trp and its related compounds are indispensable; however, a sufficient amount of these compounds is not yet available from natural sources. In this context, we recently successfully carried out the total synthesis of C-Man-Trp (**1**)[19] in order to supply the materials necessary for biochemical research in this area of study, and two other syntheses of C-Man-Trp based on different synthetic strategies were also reported by Ito and Manabe[20] and Fujise and co-workers[21] prior to our synthesis. We describe herein the full details of our investigation of the synthesis of C-Man-Trp (**1**), as well as its α-glucose and α-galactose analogues.[22]

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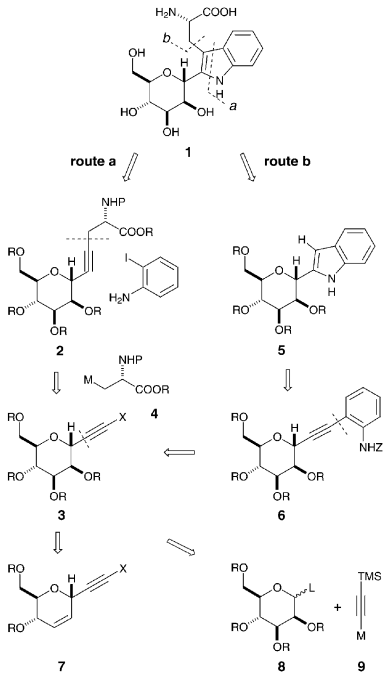
Results and discussion

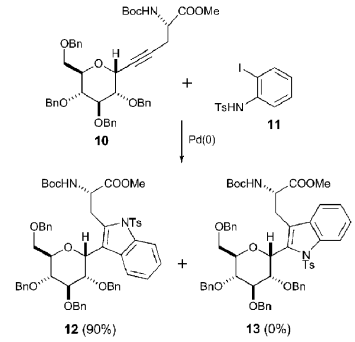
Synthetic plan

We considered two retrosynthetic plans for C-Man-Trp (**1**) and its analogues, as shown in Scheme 1. One approach (**route a**) is based on palladium-catalyzed heteroannulation developed by Larock[23] for the synthesis of an indole nucleus from *C*-glycosylpropargylglycine **2** and an *o*-iodoaniline derivative. Disconnection at the propargylic position of **2** led us to find α-sugar acetylene **3** and L-serine derivative **4**. This type of coupling with a palladium catalyst has been reported by Knochel and Jackson.[24] Another approach (**route b**) would be to synthesize the tryptophan moiety from *C*-glycosylindole **5**, *via* the corresponding dehydrotryptophan. The *C*-glycosylindole **5** would be synthesized by the Castro method from *o*-ethynylaniline **6**,[25] which could be obtained by Sonogashira coupling of the sugar acetylene **3** and the *o*-iodoaniline derivative. Both of these approaches would ultimately rely on the stereoselective synthesis of the α-sugar acetylene **3**. The stereocontrolled synthesis of such sugar acetylenes and their synthetic applications have been extensively developed in our laboratory,[26] where unsaturated sugar acetylene **7**[27] is prepared by *C*-glycosidation of tri-*O*-acetyl-D-glucal. We would therefore synthesize *C*-ethynylmannose **3** from dihydroxylation of **7** or by direct *C*-glycosidation of mannose derivative **8**. Vasella and co-workers have also extensively developed an alternate route for the synthesis of sugar acetylenes and their wide application,[28] which includes the stereocontrolled synthesis of **3** and its glucose analogue from the corresponding 1,6-anhydropyranose derivatives.[29] The above synthetic plan would be applicable for the synthesis of various analogues of C-Man-Trp (**1**) in the sugar moiety.

In our initial efforts to synthesize the glucose analogue of C-Man-Trp according to **route a**, the heteroannulation of α-*C*-glucosylpropargylglycine derivative **10** and *N*-toluenesulfonyl-2-iodoaniline (**11**) under Larock's conditions[23] gave not the desired product **13**, but instead the undesired regioisomer **12**, *iso*-tryptophan, as a single product (eqn. (1)).[30] To the best of our knowledge, this is the first example of complete reverse regioselectivity in a case of the Larock indole synthesis. Therefore we focused our attention on the second approach (**route b**) starting from α-sugar acetylene **7**.



Scheme 1 Synthetic plan of α-*C*-glycosyltryptophan exemplified by C-Man-Trp (**1**).



(1)

Synthesis of α-*C*-ethynylhexopyranoside through *C*-glycosidation

According to the synthetic plan as shown in Scheme 1, we attempted the dihydroxylation of cyclic olefin of the known compound **14a**[27] with OsO_4 and NMO (eqn. (2)). However, the desired product **15a** was obtained in a poor yield, probably because of the competitive oxidation of the acetylenic moiety. The same reaction of a phenyl-substituted acetylene such as **14b** prepared from **14a**[31] also gave a poor yield of the corresponding product **15b**. These fruitless results led us to develop a new method of carrying out the direct synthesis of α-ethynylmannose **3**[32] from the mannose derivative **8** with a silyl or stannylacetylene.For the *C*-glycosidation of D-mannose, 1,6-di-*O*-acetyl-

(2)

2,3,4-tri-*O*-benzyl-α-D-mannopyranose (**16**) was chosen as the glycosyl donor, due to its stability and availability (eqn. (3)). Thus, **16** was easily prepared from a commercially available methyl-α-D-mannopyranoside in 2 steps involving benzylation (NaH, BnBr in DMF) followed by acetolysis (conc. H_2SO_4 in Ac_2O).[33] Using substrate **16**, we examined the reaction conditions (Lewis acids and solvents) for *C*-glycosidation with bis(trimethylsilyl)acetylene, according to conditions previously developed in our laboratory.[26] In the case of mannose, we expected that steric hindrance of β-benzyloxy group at the 2-position and stereoelectronic effect would facilitate highly α-selective C–C bond forming reactions *via* the axial attack of silylacetylene at an oxonium ion. However, despite our extensive efforts,[34] we were unable to find any conditions that would give the desired product; even reaction with the relatively reactive 1-phenyl-2-(trimethylsilyl)acetylene gave only a 20% yield of the corresponding product. Thus, we next attempted the *C*-glycosidation with the much more reactive tri-*n*-butylstannyl(trimethylsilyl)acetylene (**20**). Further extensive examinations led us to conclude that the only combination to give the desired α-*C*-ethynylmannose **21** as a single product in high yield was the stannylacetylene **20** and TMSOTf in CH_2Cl_2 (entry 1 in Table 1). Interestingly, the acetyl group of the 6-hydroxyl group of **16** exerted an influence on the yield of the *C*-glycosidation; thus, *C*-glycosidation of the corresponding benzyl ether **17** under the same conditions afforded product **22** in a lower yield (entry 2). These results imply that the acetoxy group at the 6-position accommodates the reactivity of the anomeric center, presumably by an arming/disarming effect.[35] These successful results encouraged us to apply these conditions to synthesize the corresponding glucose and galactose analogues.[36] In the case of the *C*-glycosidation of glucose and galactose derivatives, the 1-acetoxy-2,3,4,6-tetra-*O*-benzyl derivatives **18** and **19** were found to be better substrates than the corresponding 1,6-diacetoxy derivatives with regard to the yields and reproducibility. The substrates **18** and **19** were easily prepared from the methyl-α-D-glucopyranoside and

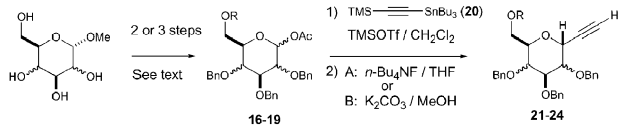
Table 1 *C*-Glycosidation of 1-acetylhexopyranosides (**16**–**19**) with stannylacetylene **20**

Entry	Substrate: Pyranose	R	α/β		Conditions for step 2	Product	Yield over 2 steps (%)
1	Mannose	Ac	1 : 0	**16**	A	**21**	83
2	Mannose	Bn	1 : 3	**17**	B	**22**	48
3	Glucose	Bn	0 : 1	**18**	B	**23**	71
4	Galactose	Bn	0 : 1	**19**	A	**24**	54

Table 2 Palladium-catalyzed coupling between α-ethylpyranose (**21**–**24**) and *N*-tosyl-2-iodoaniline (**11**)

Entry	Substrate	Sugar	R	Conditions	Temp./°C	Products: Ethynylaniline	Yield (%)	Indole	Yield (%)
1	**21**	Mannose	Ac	A	*rt*	**25**	96	**29**	0
2	**22**	Mannose	Bn	A	*rt*	**26**	57	**30**	0
3	**22**	Mannose	Bn	B	60	**26**	75	**30**	0
4	**23**	Glucose	Bn	A	60	**27**	0	**31**	44
5	**23**	Glucose	Bn	B	60	**27**	88	**31**	0
6	**24**	Galactose	Bn	A	60	**28**	0	**32**	46
7	**24**	Galactose	Bn	B	60	**28**	86	**32**	0

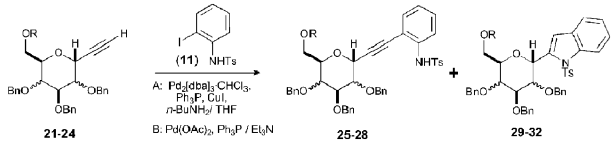
methyl-α-D-galactopyranoside, respectively, in a conventional manner involving benzylation of hydroxyl groups, acid hydrolysis of the methylglycoside, and acetylation of the hemiacetal. Although the stereoselectivity of the *C*-glycosidation turned out to be independent of the anomeric configuration of the acetate, we employed the β-acetates **18** and **19**, which were stereoselectively prepared by the acetylation of the corresponding hemiacetal with acetic anhydride and Et_3N in CH_2Cl_2.[37] The *C*-glycosidation of the substrates **18** and **19** with stannylacetylene **20** under the optimized conditions gave **23** and **24**, respectively, in good yields and with very high α-stereoselectivity (entries 3 and 4).[38,39] Desilylation of the silylacetylenes was carried out with *n*-Bu_4NF (TBAF) in THF (condition A) or potassium carbonate in methanol (condition B).



(3)

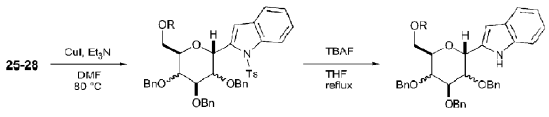
Synthesis of α-glycosylindole

With the α-*C*-ethynylhexoses in hand, we next focused on the construction of an indole nucleus from the terminal acetylenes according to our synthetic plan. α-Ethynyl-D-mannose **21** and **22** were coupled with *N*-tosyl-2-iodoaniline (**11**) under Sonogashira's conditions (condition A; in the presence of CuI and a palladium catalyst)[40] at room temperature to give mannosylethynylaniline **25** and **26** in 96 and 57% yields, respectively (Table 2, entries 1 and 2).[41] The yield of the coupling reaction between **22** and **11** was improved by an alternative copper-free condition (condition B) that consisted of a catalytic amount of $Pd(OAc)_2$ and Ph_3P in triethylamine as a solvent[42] (entry 3). In sharp contrast, the Sonogashira coupling of the glucose and galactose analogues **23** and **24** with **11** did not proceed at room temperature. When the reaction temperature was elevated to 60 °C, the coupling with concomitant indole cyclization took place to give indole **31** and **32** in 44 and 46% yields, respectively (entries 4 and 6). The copper-free condition (condition B) was found to be effective for the coupling reaction of **23** and **24**, which proceeded at 60 °C to give good yields of the products **27** and **28** without giving indoles **31** and **32** (entries 5 and 7).



(4)

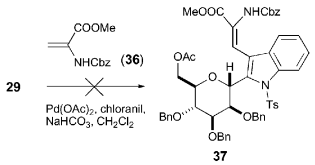
The resulting *o*-ethynylanilides **25**–**28** were then heated at 80 °C with CuI and triethylamine in DMF to give mannosylindole **29** and **30**, glucosylindole **31**, and galactosylindole **32** in good to high yields (Table 3). The tosyl protective group of the glycosylindole **29**–**32** was removed with TBAF in refluxing THF[43] to afford **33**–**36** in high yields. Thus, the efficient and highly stereocontrolled syntheses of α-*C*-glycosylindoles has been established.



(5)

Synthesis of the tryptophan moiety *via* dehydrotryptophan

We initially attempted the direct synthesis of a dehydromannosyltryptophan such as **37** from mannosylindole **29** and *N*-Cbz-dehydroalanine methyl ester **36** under Yokoyama and Murakami's conditions (eqn. (6));[44] however, no coupling products were detected, probably due to the steric hindrance around the 3-position of the indole.



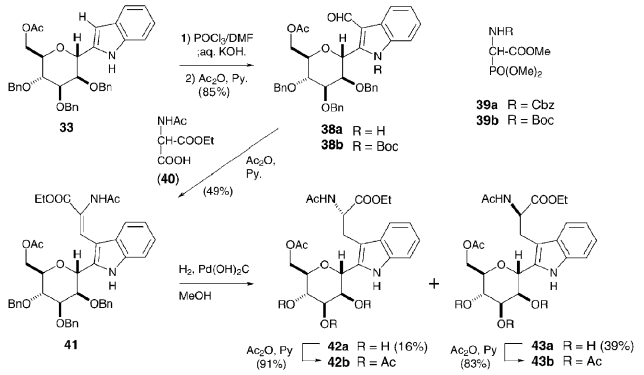
(6)

We therefore synthesized a dehydrotryptophan in stepwise fashion using an aldehyde **38** (Scheme 2). Vilsmeier formylation of **33** and subsequent acetylation of the resulting free hydroxyl group at the 6-position gave **38a**[45] in a good overall yield. However, the transformation of the aldehyde **38a** into the dehydrotryptophan proved to be problematic. For example, the coupling of *N*-Boc protected aldehyde **38b** with conventional Horner–Emmons reagents such as **39a** and **39b**[46] was sluggish, and gave poor yields of the corresponding dehydrotryptophans, even when a large excess of the reagent was used. Fortunately, we found that the aldehyde **38a**, when treated with

Table 3 Synthesis of glycosylindole

	Substrate			Synthesis of indole		Deprotection of Ts group	
Entry		Sugar	R	Products	Yield (%)	Products	Yield (%)
1	**25**	Mannose	Ac	**29**	88	**33**	90
2	**26**	Mannose	Bn	**30**	85	**34**	93
3	**27**	Glucose	Bn	**31**	89	**35**	98
4	**28**	Galactose	Bn	**32**	92	**36**	90

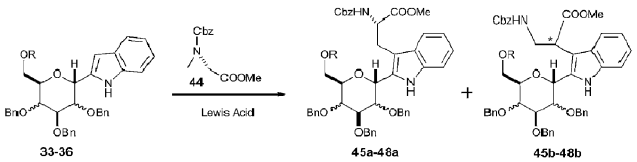
N-acetamide malonate monomethyl ester (**40**) in acetic anhydride and pyridine[47] afforded dehydrotryptophan **41** in 49% yield, with 39% recovered **38a**. The product **41** was hydrogenated with palladium on charcoal to give a mixture (1 : 2 – 2 : 3) of the diastereoisomer of amino acid **42a** and **43a**. The structures, with the exception of the absolute configuration of the amino acid moiety, were confirmed by the NMR spectra of the corresponding acetates**42b** and **43b**. The later experiments revealed that the minor product **42a** had the natural L-absolute configuration of the tryptophan moiety, as shown in Scheme 2; a fully protected C-Man-Trp methyl ester **45a** with a definite L-configuration (*vide infra*) was transformed into **42a** in three steps, including transesterification with KCN in EtOH, deprotection of the benzyl groups, and acetylation. The ^{1}H NMR spectra of the product were identical to those of the minor product **42b** obtained from **41** in Scheme 2. Thus, we synthesized the C-Man-Trp derivatives **42a** and **42b** with the natural configuration; however, it should be noted that the synthetic route contains several drawbacks such as the multi-step sequence required for the introduction of the amino acid functionality, the difficult separation of the mixture of diastereoisomers, and the remaining task of deprotection of the acetamide group.



Scheme 2 Synthesis of C-Man-Trp derivatives *via* dehydrotryptophan.

Synthesis of the tryptophan moiety *via* direct coupling between an indole and a chiral aziridine derivative

Rather than pursue the above inefficient route, we focused our attention on an alternative route that gives a configurationally definite amino acid residue. The Lewis acid-promoted coupling between tryptophan and aziridine carboxylate developed by Kozikowski (with $Zn(OTf)_2$)[48] and later by Bennani (with $Sc(OTf)_3$)[49] appeared to be a candidate. However, the reaction of mannosylindole **33** with L-serine-derived aziridine carboxylate **44**[50] in the presence of $Zn(OTf)_2$ did not give any coupling product, whereas the aziridine **44** decomposed under these conditions (Table 4, entry 1). When $Sc(OTf)_3$, reported as a superior Lewis acid, was employed, the coupling proceeded at 0 °C, but it gave a *ca.* 3 : 1 mixture of the regioisomers **45a** and **45b**, which were difficult to separate on a preparative scale (entry 2). Concurrent with these experiments, we examined a model reaction of 2-methylindole and aziridine **44** in the presence of $Sc(OTf)_3$; however, a mixture of the corresponding regioisomers was obtained. These unfavorable results led us to re-examine the reaction conditions using 2-methylindole as a test substrate. Extensive experimentation fortunately led us to find that $Sc(ClO_4)_3$[51] effected highly regioselective coupling between 2-methylindole and the aziridine **44** to afford the desired regioisomer (*i.e.*, the 2-methyltryptophan derivative). [52] Fortunately, the optimized condition could then be applied to the reaction of mannosylindole **33** and aziridine **44** to give the exclusive formation of the desired regioisomer **45a** in good yield (entry 3). Surprisingly, the coupling of a similar substrate **34**, which bears a benzyl ether on the 6-OH, with **44** gave a very low yield of the desired product **46a**[53] (entry 4). This low yield may be attributed to the steric hindrance of the benzyl ether of **34** and the instability of the product **46** under the acidic conditions. The same coupling of glucose and galactose analogues **35** and **36** gave the desired products **47** and **48**, respectively, in moderate yields (entries 5 and 6). In these cases, 5 Å molecular sieves were added to the reaction mixture in order to suppress the decomposition of the products, which would otherwise have caused low yields. [54]



(7)

Deprotection of esters and benzyl groups

The methyl ester and the acetate of **45a** were hydrolyzed with aqueous lithium hydroxide in 2-propanol to give a 71% yield of

Table 4 Lewis acid-promoted coupling of glycosylindole (**33**–**36**) and aziridine (**44**)

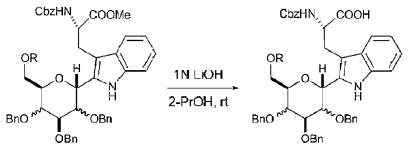
	Substrate						Product		
Entry	Sugar		R	Lewis acid	Solvent	Temp./°C		**a**/**b**[a]	Yield (%)
1	Mannose	**33**	Ac	$Zn(OTf)_2$	$CHCl_3$	80	**45**	—	0
2	Mannose	**33**	Ac	$Sc(OTf)_3$	CH_2Cl_2	0	**45**	3 : 1[b]	47
3	Mannose	**33**	Ac	$Sc(ClO_4)_3$	CH_2Cl_2	0	**45**	1 : 0	83
4	Mannose	**34**	Bn	$Sc(ClO_4)_3$	CH_2Cl_2[c]	0	**46**	1 : 0	5
5	Glucose	**35**	Bn	$Sc(ClO_4)_3$	CH_2Cl_2[c]	0	**47**	1 : 0	41
6	Galactose	**36**	Bn	$Sc(ClO_4)_3$	CH_2Cl_2[c]	0	**48**	1 : 0	43

[a] The ratio was determined by ^{1}H NMR spectra. [b] The by-product **45b** was isolated as a single diastereomer; the configuration of the newly asymmetric center (* in eqn. (7)) was not determined. [c] 5 Å MS were added.

Table 5 Deprotection of esters

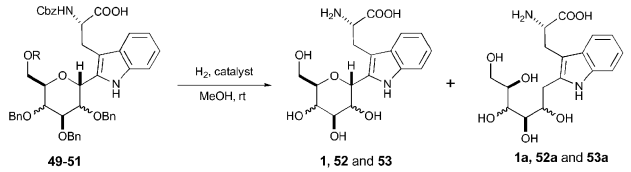
Entry	Substrate			Deprotection of esters		
		Sugar	R	Products	R	Yield (%)
1	**45a**	Mannose	Ac	**49**	H	70
2	**47a**	Glucose	Bn	**50**	Bn	86
3	**48a**	Galactose	Bn	**51**	Bn	85

49 (entry 1 in Table 5). The deprotection of **46** was not carried out because of the scarcity of the material. The methyl esters of **47a** and **48a** were removed under the same conditions to afford **50** and **51** in good yields.



45a-48a 49-51 (8)

On the other hand, hydrogenolytic deprotection of the benzyl groups was found to be problematic, because of the competitive side reaction of the cleavage of the pyranose ring (eqn. (8) and Table 6). In the case of the mannose derivative **49**, debenzylation was best carried out with Pearlman catalyst (20% $Pd(OH)_2$ on charcoal) in the presence of concentrated HCl for 3 hours to give C-Man-Trp (**1**) in good yield (entry 1). The same reaction in the absence of acid proceeded very slowly, whereas the prolonged reaction time decreased the yield of **1** because of the formation of the by-product **1a**. The ^1H and ^{13}C NMR spectra of the synthetic C-Man-Trp (**1**) were in good agreement with those of the natural product, which was isolated from human urine.[15a] However, when the conditions were applied to the galactose substrate **51**, a mixture of C-Gal-Trp (**52**) and the by-product **52a** was obtained in a ratio of approximately 2 : 1 (entry 2). After some experimentation, we found that 5% Pd–C in the presence of 1 N HCl was a good condition for the debenzylation of **51**, giving C-Gal-Trp (**52**) in good yield without **52a** (entry 3). When the glucose derivative **50** was treated under the conditions optimized for the galactose derivative **51**, a significant amount of the by-product **53a** was produced (entry 4). In this case, we fortunately found that 5% Pd–C in the absence of the acid was the condition required to afford C-Glu-Trp (**53**)[55] without giving **53a** (entry 5).



49-51 1, 52 and 53 1a, 52a and 53a (9)

Table 6 Deprotection of benzyl groups

Entry	Substrate			Conditions			Product	
		Sugar	R	Catalyst	Acid	Time/h	Yield (%)	Ratio[a]
1	**49**	Mannose	H	$Pd(OH)_2/C$	12 N HCl	3	71	**1**/**1a** (1 : 0)
2	**51**	Galactose	Bn	$Pd(OH)_2/C$	12 N HCl	3	83	**52**/**52a** (2 : 1)
3	**51**	Galactose	Bn	5% Pd/C	1 N HCl	25	70	**52**/**52a** (1 : 0)
4	**50**	Glucose	Bn	5% Pd/C	1 N HCl	17	70	**53**/**53a** (2 : 1)
5	**50**	Glucose	Bn	5% Pd/C	none	35	73	**53**/**53a** (1 : 0)

[a] The ratios were determined by ^1H NMR spectra.

Conformational analysis of C-Man-Trp and its synthetic intermediates

Hofsteenge and co-workers reported that C-Man-Trp in the peptide fragment of RNase2 protein exists as a multiple conformer, including an unusual $^1C_4$ conformation.[4,5] During our synthetic studies described above, we noticed that the coupling constant between H-1 and H-2 (J_{H1-H2}) of the hexopyranose ring depended on the substituent at the C-1 position. These observations prompted us to analyze the conformation of the α-*C*-glycosyl compounds synthesized in this study. The vicinal coupling constants of the pyranose ring are the most informative parameters for the analysis of conformation.[56] Table 7 shows the coupling constants of the synthetic *C*-glycosyltryptophan (C-Man-Trp, C-Glu-Trp and C-Gal-Trp) and its synthetic intermediates, along with typical data for the corresponding α-*O*-glycoside.[56]

α-Mannose acetylenes **21** and **22** adopt the typical $^4C_1$ conformation, judging from the vicinal coupling constants of the pyranose rings; a small coupling constant (2.5 Hz) between H-1 and H-2, and large coupling constants (9–10 Hz) between H-3 and H-4, and between H-4 and H-5, are observed. Since ethynylaniline-substituted mannoses **25** and **26** exhibit nearly the same coupling constants as those of **21** and **22**, these sugar acetylenes adopt the $^4C_1$ conformation. On the other hand, the larger coupling constants (J_{H1-H2} = 5–6 Hz) of *N*-tosylindole-substituted mannoses **29** and **30** clearly indicate a conformation that differs from $^4C_1$. Since the $^1C_4$ conformer exhibits a larger coupling constant between H-1 and H-2 (*vide infra*), these compounds are likely to exist as an equilibrium between $^4C_1$ and $^1C_4$ conformers, although the other coupling constants (J_{H3-H4} and J_{H4-H5}) are not yet available. When the Ts group of **29** and **30** was deprotected, the conformation of the resulting mannosylindoles **33** and **34** returned to a nearly $^4C_1$ conformation, judging from the coupling constants. In sharp contrast, 3-formylindole-substituted mannose **38a** clearly adopts the $^1C_4$ conformation,[57] judging from the large coupling constant (9.5 Hz) between H-1 and H-2, and the small coupling constant (1.5 Hz) between H-4 and H-5. Fully protected C-Man-Trp **45a** and **46a** also adopt a conformation close to $^1C_4$. However, C-Man-Trp (**1**) and C-Man-Trp in the peptide exhibit slightly smaller coupling constants for J_{H1-H2}, and larger coupling constants for J_{H4-H5}, than those of **45a** and **46a**. Consideration of these vicinal couplings together with the contradictory NOESY correlation (Fig. 2) led us to conclude that C-Man-Trp (**1**) and C-Man-Trp in the peptide largely adopt the $^1C_4$ conformation, but there exists a slight equilibrium between the $^1C_4$ and the $^4C_1$ conformations.

In the glucose series, most of the synthetic intermediates (**23**, **27**, **31**, and **35**) adopt a typical $^4C_1$ conformation, as based on the three large coupling constants observed (J_{H2-H3}, J_{H3-H4} and J_{H4-H5}). Unfortunately, the conformation of the fully protected C-Glu-Trp **47a** could not be analyzed due to the heavily overlapping ^1H NMR signals. The conformation of C-Glu-Trp (**53**) is a slightly distorted form of $^4C_1$, judging from the observation of smaller coupling constants (J_{H2-H3}, J_{H3-H4} and J_{H4-H5}) than those observed in typical $^4C_1$ conformers such as **23** and **27**.[58]

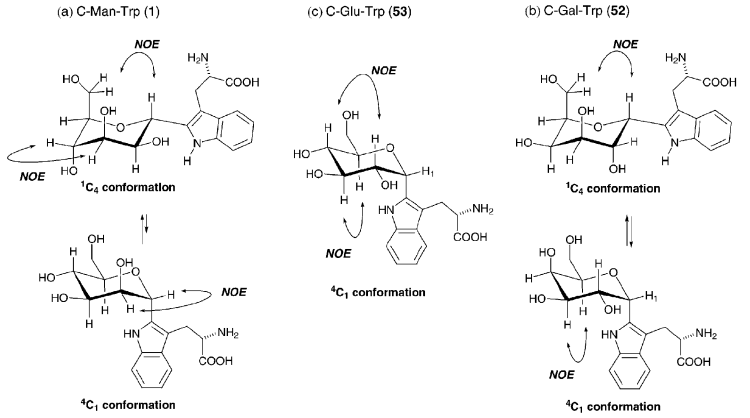


Fig. 2 Conformation of α-*C*-glycosyltryptophan and the observed NOESY correlations.

In the galactose series, galactosyl acetylene **24**, ethynylaniline-substituted galactose **28**, and indolylgalactose **36** adopt the $^4C_1$ conformation, as determined from the large coupling constants (9–10 Hz) between H-2 and H-3. On the other hand, conformational analyses of *N*-Ts-indolylmannose **32**, the fully protected C-Gal-Trp **48a**, and C-Gal-Trp (**52**) proved to be difficult because no characteristic coupling constants were observed. However, the contradictory NOESY correlations observed in **52** (Fig. 2) suggested that **52** exists as an equilibrium mixture between the $^4C_1$ and $^1C_4$ conformers.

These analyses suggested that the inversion ($^4C_1$ to $^1C_4$) of α-*C*-mannose and α-*C*-galactose is induced by some degree of steric hindrance due to a substituent such as an *N*-Ts protected indole and the presence of a tryptophan derivative at the anomeric position. These inverted $^1C_4$ conformations may be stabilized by one equatorial hydroxyl group at the C-2 or the C-4 position, respectively. In the case of α-*C*-glucose, the four equatorial substituents may stabilized the $^4C_1$ conformation, even when a bulky substituent such as an *N*-Ts-protected indole or a tryptophan derivative occupies the C-1 position.

Conclusion

The syntheses of C-Man-Trp (**1**) and its glucose and galactose analogues have been achieved in a highly stereoselective manner. The present studies revealed that the protective group at the 6-hydroxyl group of mannose derivatives significantly affected the reactivity of several reactions, including *C*-glycosidation with the the stannylacetylene and the $Sc(ClO_4)_3$-promoted coupling of the glycosylindole and aziridine. The yields of the palladium-catalyzed coupling of the sugar acetylene with an *o*-iodoaniline derivative and the $Sc(ClO_4)_3$-promoted coupling depended on the type of the carbohydrate.

The above studies also enabled us to supply a variety of C-Man-Trp-related compounds for biochemical research. In fact, we prepared some derivatives from the synthetic C-Man-Trp, and employed these materials for a lectin assay and in a search for C-Man-Trp binding proteins. These studies revealed that C-Man-Trp could not be recognized by conventional mannose lectins such as Con A (Concanavarin A) and MBL (Mannose-Binding Lectin), and we also found several C-Man-Trp binding proteins in mouse serum.[59]

Table 7 Vicinal coupling constants of the pyranose moiety of the synthetic *C*-glycosides and their conformations

C-Glycosides	J_{H1-H2}	J_{H2-H3}	J_{H3-H4}	J_{H4-H5}	Favoured conformation
α-*O*-Man[56]	1.8	3.8	10.0	9.8	$^4C_1$
Man-acetylene **21**	2.5	2.5	9.0	9.0	$^4C_1$
Man-acetylene **22**	2.5	2.5	10.0	*n.d.*	$^4C_1$
Man-ethynylaniline **25**	2.5	2.5	*n.d.*	*n.d.*	$^4C_1$
Man-ethynylaniline **26**	2.5	2.5	9.0	9.0	$^4C_1$
Man-(*N*-Ts)indole **29**	5.0	2.5	*n.d.*	*n.d.*	$^4C_1 \rightleftharpoons {}^1C_4$
Man-(*N*-Ts)indole **30**	6.0	2.5	*n.d.*	*n.d.*	$^4C_1 \rightleftharpoons {}^1C_4$
Man-indole **33**	3.0	3.0	*n.d.*	8.0	$^4C_1$
Man-indole **34**	2.5	2.5	8.5	8.5	$^4C_1$
Man-formylindole **38a**	9.5	2.5	4.0	1.5	$^1C_4$
Man-Trp (protected form) **45a**	9.0	*n.d.*	3.5	1.0	$^1C_4$
Man-Trp (protected form) **46a**	9.0	*n.d.*	*n.d.*	*n.d.*	$^1C_4$
α-*C*-Man-Trp (**1**)	8.0	3.0	5.0	3.0	$^1C_4$
α-*C*-Man-Trp (**1**) (in RNase2)[4]	7.8	3.2	5.5	3.8	$^1C_4$
α-*O*-Glu[56]	3.6	9.5	9.5	9.5	$^4C_1$
Glu-acetylene **23**	6.0	9.5	9.5	9.5	$^4C_1$
Glu-ethynylaniline **27**	6.0	10.0	10.0	10.0	$^4C_1$
Glu-(*N*-Ts)indole **31**	6.0	8.0	8.0	10.0	$^4C_1$
Glu-indole **35**	6.0	10.0	8.0	10.0	$^4C_1$
Glu-Trp (protected form) **47a**	*n.d.*	*n.d.*	*n.d.*	*n.d.*	n.d.
α-*C*-Glu-Trp (**53**)	5.5	8.5	8.5	8.5	$^4C_1$
α-*O*-Gal[56]	3.8	10.0	3.8	1.0	$^4C_1$
Gal-acetylene **24**	6.0	9.0	3.0	1.0	$^4C_1$
Gal-ethynylaniline **28**	6.0	10.0	3.0	3.0	$^4C_1$
Gal-(*N*-Ts)indole **32**	2.5	5.0	3.0	6.0	n.d.
Gal-indole **36**	5.0	9.0	3.0	3.0	$^4C_1$
Gal-Trp (protected form) **48a**	3.5	6.5	3.0	4.5	n.d.
α-*C*-Gal-Trp (**52**)	4.5	7.5	3.5	3.5	$^4C_1 \rightleftharpoons {}^1C_4$

Peptide sequencing by the Edman degradation method and mass spectrometry approaches such as MS/MS have been employed for the identification of C-Man-Trp from proteins;[60] however, because of the identical molecular weight of these analogues, such analytical methods have not yet enabled differentiation between types of sugar (mannose, glucose, or galactose) nor determination of the configuration of the anomeric (α, β) positions. At present, NMR analysis is the only means of determining the chemical structures of carbohydrates including their stereochemistries. However, in general, the amount of sample required for NMR measurement is difficult to obtain from natural proteins. We anticipate that peptide sequencing utilizing the synthetic analogues of C-Man-Trp as authentic samples will render it possible to conduct trace analysis in order to discriminate between these analogues of identical molecular weight. To this end, syntheses of the β-analogues of C-Man-Trp are currently ongoing in our laboratories.

Experimental

General

Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Infrared spectra (IR) were recorded on a JASCO FT/IR-8300 spectrophotometer and are reported in wavenumbers (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Bruker AMX-600 (600 MHz), Bruker ARX-400 (400 MHz), Bruker AVANCE-400 (400 MHz) and Varian Gemini-2000 (300 MHz) spectrometers. Data are reported as follows; chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, br = broadened, m = multiplet), coupling constant and assignment. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Bruker AMX-600 (150 MHz), Bruker ARX-400 (100 MHz), Bruker AVANCE-400 (100 MHz) and Varian Gemini-2000 (75 MHz) spectrometers. High resolution mass spectra (HRMS) were recorded on a JEOL JMS-700 spectrometer and reported in *m/z*. Elemental analyses were performed by the Analytical Laboratory at the Graduate School of Bioagricultural Sciences, Nagoya University. Reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel coated glass plate 60 F254 (Merck, η 1.05715). Cica-reagent silica gel 60 (particle size 0.063–0.2 mm ASTM) was used for open-column chromatography. Preparative thin-layer chromatographic separations were carried out on 0.5 mm silica gel plates 60 F254 (Merck, η 1.05774). Unless otherwise noted, non-aqueous reactions were carried out in oven-dried (120 °C) or flame-dried glassware under nitrogen atmosphere. Dry THF was distilled from potassium metal with benzophenone. Dry CH_2Cl_2 was distilled from CaH_2 under nitrogen atmosphere. Et_3N, *n*-$BuNH_2$ and pyridine were dried over anhydrous KOH. $Sc(ClO_4)_3$ was prepared according to the literature.[49,50] All other commercially available reagents were used as received.

Synthesis of α-*C*-ethynylhexose through *C*-Glycosidation in Table 1

(6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-mannopyranosyl)ethyne (21) (entry 1). (1) Diacetate **16** (3.00 g, 5.62 mmol) was dissolved in dry CH_2Cl_2 (60 ml) and cooled to 0 °C. To this solution were added tributylstannyl(trimethylsilyl)ethyne **20** (3.50 ml, 8.99 mmol) and TMSOTf (2.00 ml, 10.1 mmol) successively. After stirring at rt for 15 h, the reaction was quenched with sat. $NaHCO_3$ solution and sat. Rochelle salt solution, and then extracted with CH_2Cl_2 (×3). The combined organic layer was washed with water (×2) and brine (×1), dried over anhydrous Na_2SO_4, and concentrated. (2) The residue was dissolved in THF (80 ml) and H_2O (8 ml), and then *n*-Bu_4NF (1 M in THF, 11 ml, 11.0 mmol) was added. After stirring at rt for 90 min, sat. NH_4Cl solution was added, and the resulting mixture was extracted with Et_2O (×3). The combined organic layer was washed with H_2O (×2) and brine (×2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in CH_3CN (*ca.* 100 ml), the solution was washed with hexane (100 ml × 5) to remove the tin residue,[61] and concentrated. The residue was purified by silica gel column chromatography (Et_2O–hexane = 1 : 3) to give α-ethynylmannose **21** (2.32 g, 83% in 2 steps) as an oil: $[\alpha]_D^{27}$ +192 (*c* 0.86, $CHCl_3$); IR (KBr) ν_{max} 3276, 3031, 2872, 2112, 1740, 1454, 1237 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.07 (3H, s, OAc), 2.54 (1H, d, J = 2.5 Hz, C≡C*H*), 3.84 (1H, t, J = 2.5 Hz, H-2), 3.90 (1H, t, J = 9 Hz, H-4), 3.99 (1H, ddd, J = 9, 4.5, 2.5 Hz, H-5), 4.07 (1H, dd, J = 9, 3 Hz, H-3), 4.32 (1H, dd, J = 12, 4.5 Hz, H-6), 4.38 (1H, dd, J = 12, 2.5 Hz, H-6), 4.59 (1H, d, J = 11 Hz, CH_AH$_B$Ph), 4.62 (2H, br s, CH_2Ph), 4.66 (1H, d, J = 12 Hz, CH_CH$_D$Ph), 4.74 (1H, d, J = 12 Hz, CH$_C$$H_D$Ph), 4.80 (1H, t, J = 2.5 Hz, H-1), 4.94 (1H, d, J = 11 Hz, CH$_A$$H_B$Ph), 7.27–7.41 (15H, m, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 63.5, 66.0, 71.9, 72.1, 73.0, 74.4, 75.3, 76.1, 77.7, 78.3, 80.1, 127.8, 128.2, 128.4, 137.8, 138.1, 170.9; MS (FAB) *m/z* 501 (M + H); Anal. Calcd. for $C_{38}H_{32}O_6$: C, 74.38; H, 6.44. Found: C, 74.38; H, 6.49.

(2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl)ethyne (22). (1) To an ice-cold solution of **17** (1.00 g, 1.72 mmol) and stannylacetylene **20** (1.10 ml, 2.81 mmol) in dry CH_2Cl_2 (30 ml) was added TMSOTf (0.70 ml, 3.37 mmol). After stirring at 0 °C for 2 h, the mixture was quenched with sat. $NaHCO_3$ solution and sat. Rochelle salt solution, and extracted with CH_2Cl_2 (×3). The combined organic layer was washed with H_2O (×2) and brine (×1), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. (2) The residue was dissolved in THF (20 ml) and H_2O (2 ml). To this solution was added *n*-Bu_4NF (1 M in THF, 3.7 ml, 3.7 mmol). After stirring at rt for 1 h, sat. NH_4Cl solution was added. The resulting mixture was extracted with ether (×3). The combined organic layer was washed with water (×2) and brine (×2), dried over anhydrous Na_2SO_4, and concentrated. The residue was dissolved in CH_3CN (*ca.* 30 ml), and the solution was washed with hexane (×4) and evaporated. The residue was purified by column chromatography (Et_2O–hexane = 1 : 3 → 1 : 2) to give **22** (450 mg, 48% in 2 steps) as an oil: $[\alpha]_D^{30}$ +22.7 (*c* 1.05, $CHCl_3$), lit.[30] $[\alpha]_D$ +23.5 (*c* 0.9, $CHCl_3$); IR (KBr) ν_{max} 3279, 3029, 2869, 2111, 1604, 1496, 1454, 1365, 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.50 (1H, d, J = 2.5 Hz, C≡C*H*), 3.72 (1H, dd, J = 11, 1.5 Hz, H-6), 3.79 (1H, dd, J = 11, 4.5 Hz, H-6), 3.83 (1H, t, J = 2.5 Hz, H-2), 3.94–4.01 (2H, m, H-4, H-5), 4.03 (1H, dd, J = 10, 2.5 Hz, H-3), 4.52 (1H, d, J = 10.5 Hz, CH_AH$_B$Ph), 4.54 (1H, d, J = 12 Hz, CH_CH$_D$Ph), 4.58 (1H, d, J = 11.5 Hz, CH_EH$_F$Ph), 4.61 (1H, d, J = 11.5 Hz, CH$_E$$H_F$Ph), 4.65 (1H, d, J = 12 Hz, CH$_C$$H_D$Ph), 4.66 (1H, d, J = 12.5 Hz, CH_GH$_H$Ph), 4.74 (1H, d, J = 12.5 Hz, CH$_G$$H_H$Ph), 4.82 (1H, t, J = 2.5 Hz, H-1), 4.88 (1H, d, J = 10.5 Hz, CH$_A$$H_B$Ph) 7.13–7.40 (20H, m, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.9, 69.1, 71.8, 72.0, 73.3, 74.7, 74.7, 75.2, 76.1, 77.4, 78.5, 80.1, 127.4, 127.6, 127.6, 127.7, 127.8, 128.0, 128.2, 128.2, 128.3, 128.3, 137.8, 138.2, 138.2, 138.3; HRMS (FAB) for $C_{36}H_{37}O_5$ (M + H) calcd. 549.2641, found 549.2576; Anal. Calcd. for $C_{36}H_{36}O_5$: C, 78.81; H, 6.61. Found: C, 78.68; H, 6.89.

(2,3,4,5-Tetra-*O*-benzyl-α-D-glucopyranosyl)ethyne (23). (1) Glucosylacetate **18** (1.07 g, 1.89 mmol) was azeotropically dried from toluene and dissolved in dry CH_2Cl_2 (20 ml) and tributylstannyl(trimethylsilyl)ethyne **20** (1.27 ml, 3.21 mmol) was added. To this solution cooled to 4 °C was added TMSOTf (0.38 ml, 1.89 mmol). After stirring at 4 °C for 3 h, additional TMSOTf (0.38 ml, 1.89 mmol) and the stannylacetylene **20** (0.22 ml, 0.57 mmol) were added. The reaction mixture was stirred at 4 °C for additional 15 h. The reaction was quenched with sat. $NaHCO_3$ solution, and the mixture was extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with H_2O (×2) and brine (×2), dried over Na_2SO_4, and concentrated.

(2) The residue was purified by column chromatography (silica gel 150 g, Et_2O–hexane = 1 : 10 → 1 : 3) to afford the crude product (0.98 g) containing a small amount of stannane. The crude product was dissolved in MeOH (19.6 ml) and treated with K_2CO_3 (0.98 g) at rt for 1 h. The reaction was quenched with saturated NH_4Cl solution, and extracted with AcOEt (×3). The combined organic extracts were washed with H_2O (×2) and brine (×2), dried over anhydrous Na_2SO_4, and concentrated. To remove stannous residue, the residue was dissolved in CH_3CN and the solution was washed with hexane (×3) and evaporated. The residue was purified by silica gel (40 g) column chromatography (Et_2O–hexane = 1 : 3 → 1 : 2) to afford ethynylglucose **23** (0.71 g, 71% in 2 steps) as a colorless oil: $[\alpha]_D^{22}$ +41.0 (*c* 0.800, $CHCl_3$), lit.[62] $[\alpha]_D$ +46.7 (*c* 1.7, $CHCl_3$); IR (KBr) ν_{max} 3285, 3031, 2869, 2113, 1455, 1090 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.59 (1H, d, *J* = 2.5 Hz, C≡C*H*), 3.62 (1H, t, *J* = 9.5 Hz, H-4), 3.64 (1H, dd, *J* = 9.5, 6 Hz, H-2), 3.65 (1H, dd, *J* = 11, 2 Hz, H-6), 3.74 (1H, dd, *J* = 11, 3.5 Hz, H-6), 3.96 (1H, t, *J* = 9.5 Hz, H-3), 3.95–4.01 (1H, m, H-5), 4.47 (1H, d, *J* = 12 Hz, C$H_A$$H_B$Ph), 4.47 (1H, d, *J* = 11 Hz, C$H_C$$H_D$Ph), 4.60 (1H, d, *J* = 12 Hz, CH$_A$$H_B$Ph), 4.69 (1H, d, *J* = 12 Hz, C$H_E$$H_F$Ph), 4.73 (1H, dd, *J* = 6, 2.5 Hz, H-1), 4.75 (1H, d, *J* = 12 Hz, CH$_E$$H_F$Ph), 4.83 (1H, d, *J* = 11 Hz, C$H_G$$H_H$Ph), 4.83 (1H, d, *J* = 11 Hz, CH$_C$$H_D$Ph), 4.99 (1H, d, *J* = 11 Hz, CH$_G$$H_H$Ph), 7.10–7.40 (20H, m, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.6, 68.4, 73.1, 73.5, 73.6, 75.2, 75.7, 77.3, 77.6, 78.5, 78.7, 83.1, 127.7, 127.8, 127.8, 128.0, 128.1, 128.4, 128.6, 137.9, 138.2, 138.8; MS (FAB) *m*/*z* 549 (M + H); Anal. Calcd. for $C_{36}H_{36}O_5$: C, 78.81; H, 6.61. Found: C, 78.80; H, 6.60.

(2,3,4,5-Tetra-*O*-benzyl-α-D-galactopyranosyl)ethyne (24). (1) A two-necked round-bottomed flask was charged with galactosylacetate **19** (565 mg, 0.971 mmol) azeotropically dried from toluene and connected to a vacuum/argon line. The flask was evacuated and then filled with argon. This evacuation/filling cycle was repeated three times. The reagent was dissolved in dry CH_2Cl_2 (17 ml) and tributylstannyl(trimethylsilyl)ethyne **20** (0.76 ml, 1.94 mmol) was added. To this solution cooled to 5 °C was added TMSOTf (0.19 ml, 0.971 mmol). After stirring at 5 °C for 3 h 55 min, additional TMSOTf (0.19 ml, 0.971 mmol) was added. The reaction mixture was stirred at 5 °C for additional 12 h 35 min. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with AcOEt (×3). The combined organic extracts were washed with H_2O (×2) and brine (×2), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by silica gel (60 g) column chromatography (AcOEt–hexane = 1 : 7) to afford the product (753 mg) containing a small amount of stannane. (2) The product (753 mg) was dissolved in THF–H_2O (21.5 : 1.1 ml) and *n*-Bu_4NF (1.21 ml, 1.21 mmol, 1 M in THF) was added. After stirring at rt for 1 h 35 min, *n*-Bu_4NF (1.21 ml, 1.21 mmol, 1 M in THF) was added. The reaction mixture was stirred at room temperature for additional 45 min. The reaction was quenched with NH_4Cl solution and extracted with AcOEt (×3). The combined organic extracts were washed with H_2O (×2) and brine (×2), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by silica gel (35 g) column chromatography (AcOEt–hexane = 1 : 7) to afford α-1-ethynylgalactose **24** (289 mg, 54% in 2 steps): $[\alpha]_D^{25}$ +38 (*c* 0.49, $CHCl_3$), lit.[36] $[\alpha]_D$ +31.1 (*c* 1.7, $CHCl_3$); IR (KBr) ν_{max} 3287, 3031, 2112, 2871, 1455, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.52 (1H, d, *J* = 2.5 Hz, C≡C*H*), 3.50 (1H, dd, *J* = 9, 7 Hz, H-6), 3.54 (1H, dd, *J* = 9, 6 Hz, H-6), 3.88 (1H, dd, *J* = 10, 3 Hz, H-3), 3.97 (1H, dd, *J* = 3, 1 Hz, H-4), 4.09 (1H, dd, *J* = 9, 6 Hz, H-2), 4.12 (1H, br td, *J* = 6.5, 1 Hz, H-5), 4.39 (1H, d, *J* = 12 Hz, C$H_A$$H_B$Ph), 4.48 (1H, d, *J* = 12 Hz, CH$_A$$H_B$Ph), 4.56 (1H, d, *J* = 11.5 Hz, C$H_C$$H_D$Ph), 4.71 (1H, d, *J* = 12 Hz, C$H_E$$H_F$Ph), 4.74 (1H, d, *J* = 12 Hz, C$H_G$$H_H$Ph), 4.79 (1H, d, *J* = 12 Hz, CH$_G$$H_H$Ph), 4.79 (1H, dd, *J* = 6, 2.5 Hz, H-1), 4.85 (1H, d, *J* = 12 Hz, CH$_E$$H_F$Ph), 4.93 (1H, d, *J* = 11.5 Hz, CH$_C$$H_D$Ph), 7.20–7.42 (20H, m, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$) δ 67.2, 68.6, 72.6, 73.1, 73.2, 73.4, 74.7, 74.8, 75.1, 76.3, 78.9, 80.1, 127.5, 127.6, 127.6, 127.8, 128.0, 128.3, 128.3, 128.4, 137.9, 138.2, 138.6, 138.7; MS (FAB) *m*/*z* 549 (M + H); Anal. Calcd. for $C_{36}H_{36}O_5$: C, 78.81; H, 6.61. Found: C, 78.79; H, 6.47.

Palladium catalyzed coupling between sugar acetylene and *N*-tosyl-2-iodoaniline

Synthesis of 1-(6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-mannopyranosyl)-2-*o*-(*p*-toluenesulfoamidyl)phenylethyne (25) under condition A in Table 2 (entry 1). α-Ethynylmannose **21** (620 mg, 1.24 mmol), $Pd_2[dba]_3{\cdot}CHCl_3$ (31 mg, 0.031 mmol), Ph_3P (31 mg, 0.12 mmol), CuI (23 mg, 0.12 mmol) and *N*-tosyl-2-iodoaniline **11** (892 mg, 2.40 mmol) were placed in a two-necked flask. The flask was filled with argon and then dry THF (20 ml) and *n*-$BuNH_2$ (0.60 ml, 6.2 mmol) were added successively. After stirring at rt for 3 h under argon, the reaction was quenched with sat. NH_4Cl solution and then extracted with EtOAc (×3). The combined organic layer was washed with sat. NH_4Cl solution (×2), H_2O (×2) and brine (×2), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (ether–hexane = 1 : 1) to give **25** (883 mg, 96%): $[\alpha]_D^{24}$ +40 (*c* 0.97, $CHCl_3$); IR (KBr) ν_{max} 2870, 2218, 1740, 1239, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.10 (3H, s, OAc), 2.28 (3H, s, CH_3 of Ts), 3.87 (1H, t, *J* = 2.5 Hz, H-2), 3.89–4.02 (3H, m, H-3, 4, 5), 4.35 (1H, dd, *J* = 12, 5 Hz, H-6), 4.41 (1H, dd, *J* = 12, 2 Hz, H-6), 4.61 (1H, d, *J* = 10.5 Hz, C$H_A$$H_B$Ph), 4.66 (2H, s, C$H_2$Ph), 4.73 (1H, d, *J* = 12.5 Hz, C$H_C$$H_D$Ph), 4.79 (1H, d, *J* = 12.5 Hz, CH$_C$$H_D$Ph), 4.96 (1H, d, *J* = 10.5 Hz, CH$_A$$H_B$Ph), 4.99 (1H, d, *J* = 2.5 Hz, H-1), 7.00 (1H, td, *J* = 7.5, 1 Hz, aromatic), 7.00 (1H, br s, N*H*), 7.09 (2H, d, *J* = 8 Hz, aromatic), 7.15 (1H, dd, *J* = 7.5, 1.5 Hz, aromatic), 7.23–7.44 (16H, m, aromatic), 7.57 (1H, dd, *J* = 8.5, 1 Hz, aromatic), 7.63 (2H, d, *J* = 8, Hz, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 21.5, 63.5, 66.6, 72.1, 72.2, 73.4, 74.4, 75.5, 76.1, 80.0, 84.0, 90.5, 112.5, 119.6, 124.2, 127.2, 127.8, 127.9, 128.3, 128.5, 128.5, 128.5, 130.0, 130.3, 132.6, 135.9, 137.7, 137.9, 137.9, 144.1, 171.0; MS (FAB) *m*/*z* 746 (M + H); Anal. Calcd. for $C_{44}H_{43}NO_8S$: C, 70.85; H, 5.81, N, 1.88. Found: C, 70.86; H, 5.92; N, 1.77.

Synthesis of 1-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-2-*o*-(*p*-toluenesulfoamidyl)phenylethyne (26) under condition B in Table 2 (entry 3). A two-necked round-bottomed flask was charged with α-ethynylmannose 21 (151 mg, 0.276 mmol), *N*-tosyl-2-iodoaniline 11 (205 mg, 0.551 mmol) and PPh_3 (7.2 mg, 0.027 mmol), and connected to a vacuum/argon line. The flask was evacuated and then filled with argon. This evacuation/filling cycle was repeated three times. Et_3N (4.5 ml, distilled from CaH_2) was added and the solution was heated to 60 °C with stirring. After these reagents were completely dissolved, $Pd(OAc)_2$ (3.1 mg, 0.014 mmol) was added and the mixture was stirred at 60 °C for 2 h 20 min. The mixture was cooled to rt, quenched with saturated NH_4Cl solution, and extracted with AcOEt (×3). The combined organic extracts were washed with saturated NH_4Cl solution (×2), H_2O (×2) and brine (×2), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by silica gel (18 g) column chromatography (CH_2Cl_2 → AcOEt–hexane = 1 : 4) to afford mannosyl-α-1-ethynylaniline 26 (165 mg, 75%): $[\alpha]_D^{30}$ +46.6 (*c* 1.00, $CHCl_3$); IR (KBr) ν_{max} 3260, 3063, 3031, 2869, 2216, 1953, 1812 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.25 (3H, s, CH_3 of Ts), 3.76 (1H, dd, *J* = 10.5, 2 Hz, H-6), 3.81 (1H, dd, *J* = 10.5, 5 Hz, H-6), 3.86 (1H, t, *J* = 2.5 Hz, H-2), 3.88–3.90 (1H, m, H-5), 3.97 (1H, dd, *J* = 9, 3 Hz, H-3), 4.03 (1H, t, *J* = 9 Hz, H-4), 4.55 (1H, d, *J* = 10.5 Hz, C$H_A$$H_B$Ph), 4.57 (1H, d, *J* = 12 Hz, C$H_C$$H_D$Ph), 4.64 (1H, d, *J* = 12 Hz, C$H_E$$H_F$Ph), 4.67 (1H, d, *J* = 12 Hz, CH$_E$$H_F$Ph), 4.68 (1H, d, *J* = 12 Hz, CH$_C$$H_D$Ph) 4.73 (1H, d, *J* = 12.5 Hz, C$H_G$$H_H$Ph), 4.79 (1H, d, *J* = 12.5 Hz, CH$_G$$H_H$Ph), 4.90 (1H,

d, J = 10.5 Hz, CH_AH_BPh), 5.00 (1H, d, J = 2 Hz, H-1), 6.98 (1H, td, J = 7.5, 1 Hz, aromatic), 7.03 (1H, s, N*H*), 7.06 (2H, d, J = 8 Hz, Ts), 7.13–7.44 (22H, m, aromatic), 7.57 (1H, d, J = 8 Hz, aromatic), 7.62 (2H, d, J = 8 Hz, Ts); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 66.6, 69.1, 72.0, 72.2, 73.5, 74.7, 75.2,75.3, 76.2, 80.1, 83.7, 90.4, 112.7, 119.5, 124.2, 127.2, 127.5, 127.7, 127.8, 127.9, 128.2, 128.3, 128.4, 128.5, 129.6, 130.2, 130.4, 132.6, 134.9, 135.9, 137.8, 138.1, 138.1, 138.3, 144.0; Anal. Calcd. for $C_{49}H_{47}NO_7S$: C, 74.12; H, 5.97, N, 1.76. Found: C, 74.12; H, 6.04; N, 1.59.

1-(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)-2-*o*-(*p*-toluenesulfoamidyl)phenylethyne (27). Following the procedure of the entry 3, **27** (854 mg, 88%) was obtained as a yellow oil from α-1-ethynylglucose **23** (672 mg, 1.23 mmol) after silica gel (100 g) column chromatography (Et_2O–hexane = 1 : 3): $[\alpha]_D^{29}$ +52.5 (c 0.83, $CHCl_3$); IR (KBr) ν_{max} 3261, 3032, 2870, 2226, 1492, 1454, 1345, 1161, 1090 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (3H, s, C*H*$_3$ of Ts), 3.66 (1H, t, J = 10 Hz, H-4), 3.67 (1H, dd, J = 10.5, 2 Hz, H-6), 3.75 (1H, dd, J = 10.5, 3.5 Hz, H-6), 3.76 (1H, dd, J = 10, 6 Hz, H-2), 3.90 (1H, br d, J = 10 Hz, H-5), 3.98 (1H, t, J = 10 Hz, H-3), 4.49 (1H, d, J = 12.5 Hz, CH_AH_BPh), 4.50 (1H, d, J = 11 Hz, CH_CH_DPh), 4.61 (1H, d, J = 12.5 Hz, CH_AH_BPh), 4.80 (1H, d, J = 13 Hz, CH_EH_FPh), 4.85 (1H, d, J = 11 Hz, CH_CH_DPh), 4.86 (1H, d, J = 6 Hz, H-1), 4.90 (1H, d, J = 11 Hz, CH_GH_HPh), 5.01 (1H, d, J = 13 Hz, CH_EH_FPh), 5.12 (1H, d, J = 11 Hz, CH_GH_HPh), 6.96 (1H, t, J = 8 Hz, aromatic), 7.08 (2H, d, J = 8 Hz, Ts), 7.12–7.16 (2H, m, aromatic), 7.22–7.44 (22H, m, aromatic), 7.59 (1H, d, J = 8 Hz, aromatic), 7.70 (2H, d, J = 8 Hz, Ts), 7.88 (1H, s, N*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 67.6, 68.4, 73.5, 73.5, 74.0, 75.2, 75.8, 77.2, 78.3, 83.7, 84.3, 91.9, 111.7, 117.6, 123.4, 127.3, 127.7, 127.8, 128.1, 128.1, 128.4, 128.4, 128.6, 129.7, 130.0, 131.5, 136.4, 137.8, 137.9, 138.1, 138.7, 139.0, 143.9; HR-MS (FAB) for $C_{49}H_{48}NO_7S$ (M + H) calcd. 794.3152, found 794.3178.

1-(2,3,4,6-Tera-*O*-benzyl-α-D-galactopyranosyl)-2-*o*-(*p*-toluenesulfoamidyl)phenylethyne (28). Following the procedure of entry 3, **28** (909 mg, 86%) was obtained as a yellow oil from α-1-ethynylgalactose **24** (732 mg, 1.34 mmol) after silica gel (100 g) column chromatography (Et_2O–hexane = 1 : 3 → 1 : 1): $[\alpha]_D^{25}$ +157 (c 1.05, $CHCl_3$); IR (KBr) ν_{max} 3262, 3031, 2872, 2227, 1492, 1455, 1344, 1161, 1092 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (3H, s, C*H*$_3$ of Ts), 3.51 (1H, dd, J = 10, 7 Hz, H-6), 3.56 (1H, dd, J = 10, 6 Hz, H-6), 3.92 (1H, dd, J = 10, 3 Hz, H-3), 3.99 (1H, br d, J = 3 Hz, H-4), 4.05 (1H, br t, J = 6.5 Hz, H-5), 4.20 (1H, dd, J = 10, 6 Hz, H-2), 4.40 (1H, d, J = 12 Hz, CH_AH_BPh), 4.49 (1H, d, J = 12 Hz, CH_AH_BPh), 4.58 (1H, d, J = 11.5 Hz, CH_CH_DPh), 4.83 (1H, d, J = 11.5 Hz, CH_EH_FPh), 4.84 (1H, d, J = 13 Hz, CH_GH_HPh), 4.94 (1H, d, J = 6 Hz, H-1), 4.95 (1H, d, J = 12 Hz, CH_CH_DPh), 4.96 (1H, d, J = 11.5 Hz, CH_EH_FPh), 5.06 (1H, d, J = 13 Hz, CH_GH_HPh), 6.96 (1H, t, J = 7.5 Hz, aromatic), 7.09 (2H, d, J = 8.5 Hz, Ts), 7.21–7.38 (20H, m, aromatic), 7.40–7.46 (3H, m, aromatic), 7.57 (1H, d, J = 8 Hz, aromatic), 7.67 (2H, d, J = 8.5 Hz, Ts), 7.88 (1H, s, N*H*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 68.2, 68.7, 73.0, 73.2, 73.5, 73.8, 74.5, 74.9, 74.9, 80.8, 83.1, 92.4, 112.0, 117.7, 123.4, 127.3, 127.6, 127.7, 127.8, 127.9, 128.0, 128.3, 128.3, 128.3, 128.4, 128.5, 129.6, 129.9, 131.6, 136.4, 137.9, 138.4, 138.5, 138.7, 139.1, 143.9; Anal. Calcd. for $C_{49}H_{47}NO_7S$: C, 74.12; H, 5.97, N, 1.76. Found: C, 74.11; H, 5.77; N, 1.72.

2-(6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-mannopyranosyl)-1-(*p*-toluenesulfonyl)indole (29). To a solution of ethynylaniline **25** (3.71 g, 4.99 mmol) in Et_3N (60 ml) and DMF (30 ml) was added CuI (187 mg, 0.98 mmol). After stirring at 80 °C for 30 min, water was added. The mixture was extracted with AcOEt (×3). The combined organic layer was washed with aqueous NH_4Cl solution (×2), water (×2) and brine (×2), and concentrated. The residue was purified by silica gel column chromatography (ether–hexane = 1 : 2) to give **29** (3.28 g, 88%): $[\alpha]_D^{27}$ +82.2 (c 1.15, $CHCl_3$). IR (KBr) ν_{max} 1736, 1455, 1369, 1175, 1090 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (3H, s, OAc), 2.28 (3H, s, C*H*$_3$ of Ts), 3.83–3.97 (4H, m, H-3, 4, 5, 6), 4.28 (1H, dd, J = 5, 2.5 Hz, H-2), 4.40 (1H, dd, J = 12, 6 Hz, H-6), 4.56 (1H, d, J = 11.5 Hz, CH_AH_BPh), 4.60 (1H, d, J = 12 Hz, CH_CH_DPh), 4.61 (1H, d, J = 12 Hz, CH_EH_FPh), 4.67 (2H, d, J = 12 Hz, CH_CH_DPh and CH_EH_FPh), 4.72 (1H, d, J = 11.5 Hz, CH_AH_BPh), 5.98 (1H, d, J = 5 Hz, H-1), 6.37 (1H, s, indole), 7.06 (2H, d, J = 8.5 Hz, aromatic), 7.20 (1H, t, J = 7.5 Hz, indole), 7.25–7.36 (17H, m, aromatic), 7.67 (2H, d, J = 8.5 Hz, aromatic), 8.13 (1H, d, J = 8.5 Hz, indole); MS (FAB) m/z 746 (M + H); Anal. Calcd. for $C_{44}H_{43}NO_8S$: C, 70.85; H, 5.81, N, 1.88. Found: C, 70.84; H, 5.78; N, 1.78.

2-(2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl)-1-(*p*-toluenesulfonyl)indole (30). Following the procedure for **29**, **30** (135 mg, 85%) was obtained from ethynylaniline **26** (159 mg, 0.20 mmol) after silica gel (7 g) column chromatography (AcOEt–hexane = 1 : 4): $[\alpha]_D^{29}$ +69.9 (c 0.80, $CHCl_3$); IR (KBr) ν_{max} 3295, 3031, 2869, 1496, 1455, 1097 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22 (3H, s, C*H*$_3$ of Ts), 3.57 (1H, d, J = 10, 3 Hz, H-6), 3.86–3.91 (2H, m, H-3, 5), 3.94–4.02 (2H, m, H-4, 6), 4.28 (1H, dd, J = 6, 2.5 Hz, H-2), 4.54 (2H, s, C*H*$_2$Ph), 4.55–4.69 (6H, m, C*H*$_2$Ph ×3), 6.01 (1H, d, J = 6 Hz, H-1), 6.46 (1H, s, indole), 6.98 (2H, d, J = 8 Hz, Ts), 7.16–7.36 (23H, m, aromatic), 7.69 (2H, d, J = 8 Hz, Ts), 8.11 (1H, d, J = 8 Hz, aromatic);^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 68.1, 69.1, 71.6, 72.4, 73.3, 74.9, 75.4, 76.0, 76.4, 92.3, 112.1, 115.5, 121.0, 122.4, 123.7, 124.8, 126.8, 126.9, 127.4, 127.7, 127.8, 127.9, 128.0, 128.2, 128.4, 129.0, 129.4, 129.5, 129.6 137.5, 138.2, 138.4, 138.7, 139.1, 144.2, 144.4; HR-MS (FAB) for $C_{49}H_{48}NO_7S$ (M + H) calcd. 794.3152, found 794.3168.

2-(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)-1-(*p*-toluenesulfonyl)indole (31). Following the procedure for **29**, **31** (301 mg, 89%) was obtained as a yellow oil from ethynylaniline **27** (338 mg, 0.427 mmol) after silica gel (16 g) column chromatography (AcOEt–hexane = 1 : 5 → 1 : 4): $[\alpha]_D^{27}$ +157 (c 1.05, $CHCl_3$); IR (KBr) ν_{max} 3029, 2866, 1454, 1367, 1175, 1092 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (3H, s, C*H*$_3$ of Ts), 2.94 (1H, dd, J = 11, 2 Hz, H-6′), 3.43 (1H, br d, J = 10 Hz, H-5), 3.50 (1H, dd, J = 11, 3.5 Hz, H-6), 3.74 (1H, dd, J = 10, 8 Hz, H-4), 4.14 (1H, t, J = 8 Hz, H-3), 4.23 (1H, dd, J = 8, 6 Hz, H-2), 4.39 (1H, d, J = 12.5 Hz, CH_AH_BPh), 4.47 (1H, d, J = 11 Hz, CH_CH_DPh), 4.48–4.58 (3H, m, CH_2Ph & CH_AH_BPh), 4.75 (1H, d, J = 11 Hz, CH_CH_DPh), 4.77 (1H, d, J = 11.5 Hz, CH_GH_HPh), 4.98 (1H, d, J = 11.5 Hz, CH_GH_HPh), 6.11 (1H, d, J = 6 Hz, H-1), 7.03 (2H, d, J = 8 Hz, Ts), 7.04 (1H, s, indole), 7.10–7.35 (22H, m, aromatic), 7.49 (1H, d, J = 8 Hz, indole), 7.68 (2H, d, J = 8 Hz, Ts), 8.19 (1H, d, J = 8 Hz, indole); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 68.3, 68.8, 72.3, 72.7, 73.3, 74.3, 74.5, 77.4, 78.5, 81.5, 114.7, 115.2, 121.2, 123.7, 125.0, 126.6, 127.6, 127.7, 127.8, 127.9, 127.9, 128.1, 128.3, 128.4, 128.9, 129.6, 135.6, 136.5, 137.6, 137.8, 138.2, 138.3, 138.5, 144.5; Anal. Calcd. for $C_{49}H_{47}NO_7S$: C, 74.12; H, 5.97, N, 1.76. Found: C, 74.14; H, 6.08; N, 1.75.

2-(2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl)-1-(*p*-toluenesulfonyl)indole (32). Following the procedure for **29**, **32** (879 mg, 92%) was obtained as a yellow oil from ethynylaniline **28** (951 mg, 1.20 mmol) after silica gel (45 g) column chromatography (AcOEt–hexane = 1 : 5): $[\alpha]_D^{27}$ +126 (c 0.525, $CHCl_3$); IR (KBr) ν_{max} 3031, 2872, 1453, 1369, 1174, 1088 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (3H, s, C*H*$_3$ of Ts), 3.84 (1H, dd, J = 12, 3 Hz, H-6), 3.85 (1H, dd, J = 5, 3 Hz, H-3), 4.04 (1H, dd, J = 12, 8 Hz, H-6), 4.12 (1H, dd, J = 6, 3 Hz, H-4), 4.16 (1H, d, J = 12 Hz, CH_AH_BPh), 4.21 (1H, d, J = 12 Hz, CH_AH_BPh), 4.26 (1H, dd, J = 5, 2.5 Hz, H-2), 4.33 (1H, d, J = 12 Hz, CH_CH_DPh), 4.35–4.38 (1H, m, H-5), 4.48 (1H, d,

J = 12 Hz, CH_CH_DPh), 4.52 (1H, d, J = 12 Hz, CH_EH_FPh), 4.56 (1H, d, J = 12 Hz, CH_GH_HPh), 4.57 (1H, d, J = 12 Hz, CH_EH_FPh), 4.76 (1H, d, J = 12 Hz, CH_GH_HPh), 5.83 (1H, d, J = 2.5 Hz, H-1), 6.92–6.99 (5H, m, aromatic), 7.11–7.39 (20H, m, aromatic), 7.44 (1H, d, J = 8 Hz, indole), 7.52 (2H, d, J = 8 Hz, Ts), 8.18 (1H, d, J = 8 Hz, indole); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 65.6, 66.5, 71.8, 72.2, 72.9, 73.1, 73.4, 74.7, 75.1, 75.9, 113.3, 115.3, 120.9, 123.9, 124.5, 126.3, 127.4, 127.5, 127.7, 127.8, 128.1, 128.3, 128.3, 128.4, 129.7, 130.1, 135.5, 137.5, 137.6, 137.8, 138.4, 138.5, 138.6, 144.7; Anal. Calcd. for $C_{49}H_{47}NO_7S$: C, 74.12; H, 5.97; N, 1.76. Found: C, 74.12; H, 6.03; N, 1.68.

Typical experimental procedure for deprotection of Ts group in Table 3

2-(6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-mannopyranosyl)-1-indole (33). To a solution of tosyindole **29** (205 mg, 0.276 mmol) in THF (6 ml) was added *n*-Bu_4NF (1M, 1.4 ml, 1.4 mmol). After stirring at rt for 50 min, the reaction mixture was quenched with sat. NH_4Cl solution. The resulting mixture was extracted with Et_2O (×2). The combined organic layer was washed with water (×2), sat. NH_4Cl solution (×1) and brine (×1), dried over anhydrous Na_2SO_4, and concentrated. The residue was dissolved in pyridine (1 ml) and Ac_2O (1 ml). The solution was stirred at rt for 30 min, and then diluted with toluene. The mixture was evaporated *in vacuo* and subjected to silica gel column chromatography (ether–hexane = 1 : 1) to give **33** (147 mg, 90% in 2 steps) as a colorless oil: $[\alpha]_D^{27}$ +68 (*c* 0.82, $CHCl_3$). IR (KBr) ν_{max} 3030, 2874, 1734, 1456, 1364, 1239, 1096, 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09 (3H, s, OAc), 3.59 (1H, dt, J = 8, 4 Hz, H-5), 3.89–3.94 (2H, m, H-3, 4), 4.17 (1H, br t, J = 3 Hz, H-2), 4.34 (2H, d, J = 4 Hz, H-6), 4.58 (1H, d, J = 11 Hz, CH_AH_BPh), 4.65 (1H, d, J = 12 Hz, CH_CH_DPh), 4.71 (2H, br s, CH_2Ph), 4.72 (1H, d, J = 12 Hz, CH_CH_DPh), 4.84 (1H, d, J = 11 Hz, CH_AH_BPh), 5.24 (1H, d, J = 3 Hz, H-1), 5.86 (1H, s, indole), 7.07 (1H, t, J = 7.5 Hz, aromatic), 7.16 (1H, t, J = 7.5 Hz, aromatic), 7.22–7.40 (16H, m, aromatic), 7.46 (1H, d, J = 7.5 Hz, aromatic), 8.35 (1H, br s, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 63.6, 70.9, 72.3, 72.8, 73.5, 74.5, 74.9, 75.1, 78.7, 100.8, 110.8, 120.0, 120.4, 122.3, 127.8, 127.8, 128.0, 128.0, 128.1 128.3, 128.4, 128.6, 134.3, 135.8, 138.0, 138.0, 138.1, 170.9; MS (FAB) *m/z* 592 (M + H); Anal. Calcd. for $C_{37}H_{37}NO_6S$: C, 75.11; H, 6.30, N, 2.37. Found: C, 75.13; H, 6.35; N, 2.29.

2-(2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl)-1*H*-indole (34). Following the procedure for **33**, **34** (101 mg, 93%) was obtained from **30** (135 mg, 0.170 mmol) after silica gel (6 g) column chromatography (AcOEt:hexane = 1 : 4): $[\alpha]_D^{30}$ +53.0 (*c* 0.99, $CHCl_3$); IR (KBr) ν_{max} 3311, 3087, 3062, 3030, 2867, 2630, 1953, 1881, 1811 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54–3.62 (1H, m, H-5), 3.69–3.78 (2H, m, H-6 × 2), 3.88 (1H, dd, J = 8.5, 2.5 Hz, H-3), 3.92 (1H, t, J = 8.5 Hz, H-4), 4.16 (1H, t, J = 2.5 Hz, H-2), 4.50 (1H, d, J = 11 Hz, CH_AH_BPh), 4.55 (1H, d, J = 12 Hz, CH_CH_DPh), 4.60 (1H, d, J = 12 Hz, CH_CH_DPh), 4.62 (1H, d, J = 12 Hz, CH_EH_FPh), 4.71 (1H, d, J = 12 Hz, CH_EH_FPh), 4.72 (1H, d, J = 12.5 Hz, CH_GH_HPh), 4.78 (1H, d, J = 12.5 Hz, CH_GH_HPh), 4.83 (1H, d, J = 11 Hz, CH_AH_BPh), 5.24 (1H, m, H-1), 5.80 (1H, br s, indole), 7.00–7.55 (24H, m, aromatic), 8.46 (1H, br s, N*H*);^{13}C NMR (75 MHz, $CDCl_3$) δ 69.6, 71.2, 72.2, 72.7, 73.3, 74.5, 74.8, 75.1, 75.2, 79.0, 100.2, 110.9, 119.7, 120.2, 122.1, 127.5, 127.6, 127.7, 127.9, 128.1, 128.3, 128.4, 128.5, 134.6, 135.8, 137.9, 138.2, 138.2; MS (FAB) *m/z* 640 (M + H); HR-MS (FAB) for $C_{42}H_{41}NO_5$ (M + H), calcd. 640.3063, found 640.2963; Anal. Calcd. for $C_{42}H_{41}NO_5$: C, 78.85; H, 6.46, N, 2.19. Found: C, 78.86; H, 6.42; N, 2.13.

2-(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)-1*H*-indole (35). Following the procedure for **33**, **35** (353 mg, 98%) was obtained as an orange oil from **31** (446 mg, 0.563 mmol) after silica gel (11 g) column chromatography (AcOEt–hexane = 1 : 5): $[\alpha]_D^{23}$ +122 (*c* 0.449, $CHCl_3$); IR (KBr) ν_{max} 3427, 3032, 2870, 1455, 1072 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (1H, dd, J = 10, 8 Hz, H-4), 3.65 (1H, dd, J = 11, 4 Hz, H-6), 3.69 (1H, dd, J = 11, 2 Hz, H-6), 3.72 (1H, ddd, J = 10, 4, 2 Hz, H-5), 3.96 (1H, dd, J = 10, 8 Hz, H-3), 4.02 (1H, dd, J = 10, 6 Hz, H-2), 4.47 (1H, d, J = 11 Hz, CH_AH_BPh), 4.51 (1H, d, J = 12 Hz, CH_CH_DPh), 4.61 (1H, d, J = 12 Hz, CH_CH_DPh), 4.78 (1H, d, J = 11 Hz, CH_EH_FPh), 4.79 (1H, d, J = 11 Hz, CH_AH_BPh), 4.81 (1H, d, J = 10.5 Hz, CH_GH_HPh), 4.84 (1H, d, J = 11 Hz, CH_EH_FPh), 4.97 (1H, d, J = 10.5 Hz, CH_GH_HPh), 5.39 (1H, d, J = 6 Hz, H-1), 6.71 (1H, s, indole), 7.06–7.10 (2H, m, aromatic), 7.14 (1H, t, J = 8 Hz, indole), 7.20–7.39 (20H, m, aromatic), 7.57 (1H, d, J = 8 Hz, indole), 8.82 (1H, s, N*H* of indole); ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.1, 70.4, 73.2, 73.5, 73.8, 74.8, 75.6, 78.2, 80.7, 82.6, 102.7, 110.9, 119.8, 120.5, 121.9, 127.6, 127.6, 127.7, 127.7, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.6, 134.5, 135.7, 137.8, 138.0, 138.2, 138.6; Anal. Calcd. for $C_{42}H_{41}NO_5$: C, 78.85; H, 6.46; N, 2.19. Found: C, 78.86; H, 6.52; N, 2.27.

2-(2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl)-1*H*-indole (36). Following the procedure for **33**, **36** (641 mg, 90%) was obtained as a yellow oil from **32** (879 mg, 1.11 mmol) after silica gel (22 g) column chromatography (AcOEt–hexane = 1 : 5): $[\alpha]_D^{23}$ +80.9 (*c* 1.13, $CHCl_3$); IR (KBr) ν_{max} 3425, 3031, 2869, 1455, 1090 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.52 (1H, dd, J = 10, 5 Hz, H-6), 3.77 (1H, dd, J = 10, 7 Hz, H-6), 3.84 (1H, dd, J = 9, 3 Hz, H-3), 3.90 (1H, t, J = 3 Hz, H-4), 3.96 (1H, m, H-5), 4.34 (1H, br dd, J = 9, 5 Hz, H-2), 4.45 (1H, d, J = 12 Hz, CH_AH_BPh), 4.53 (1H, d, J = 12 Hz, CH_AH_BPh), 4.59 (1H, d, J = 11.5 Hz, CH_CH_DPh), 4.68 (1H, br d, J = 11 Hz, CH_EH_FPh), 4.72 (2H, s, CH_2Ph), 4.78 (1H, br d, J = 11 Hz, CH_EH_FPh), 4.88 (1H, d, J = 11.5 Hz, CH_CH_DPh), 5.39 (1H, d, J = 5 Hz, H-1), 6.60 (1H, s, indole), 7.08 (1H, td, J = 7, 1 Hz, indole), 7.14 (1H, td, J = 7, 1 Hz, indole), 7.21–7.38 (21H, m, aromatic), 7.56 (1H, d, J = 8 Hz, indole), 8.87 (1H, s, N*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 68.7, 69.8, 73.0, 73.3, 74.0, 74.1, 74.6, 77.7, 78.6, 101.8, 110.9, 119.6, 120.4, 121.6, 127.6, 127.7, 128.0, 128.2, 128.4, 128.4, 128.5, 135.2, 135.7, 138.1, 138.2, 138.5; Anal. Calcd. for $C_{42}H_{41}NO_5$: C, 78.85; H, 6.46; N, 2.19. Found: C, 78.84; H, 6.50; N, 2.26.

2-(6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-mannopyranosyl)-1*H*-3-formylindole (38a). To ice-cold dry DMF (5 ml) was added $POCl_3$ (59 µl, 0.63 mmol). To this solution was added indole **33** (146 mg, 0.25 mmol). After stirring for 15 min, the mixture was diluted with an ice-cold aqueous solution of KOH (3.52 g in 20 ml water) and stirred at 90 °C for 30 min. The mixture was allowed to stand overnight at rt, and then extracted with EtOAc (×3). The combined organic extracts were washed with H_2O (×2) and sat. NH_4Cl solution (×2) and brine (×2), dried over anhydrous Na_2SO_4, and concentrated. The residue was dissolved in pyridine (2 ml) and Ac_2O (2 ml). After the solution was stirred at rt for 20 min, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography (Et_2O–hexane = 2 : 1) to give aldehyde **38a** (131 mg, 85% in 2 steps): $[\alpha]_D^{27}$ −6.82 (*c* 1.02, $CHCl_3$); IR (KBr) ν_{max} 2927, 1740, 1651, 1455, 1368, 1233, 1103, 1039 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (3H, s, O*Ac*), 3.61 (1H, dd, J = 4, 1.5 Hz, H-4), 3.82 (1H, dd, J = 9.5, 2.5 Hz, H-2), 3.89 (1H, dd, J = 4, 2.5 Hz, H-3), 4.10 (1H, d, J = 12 Hz, CH_AH_BPh), 4.14 (1H, dd, J = 12.5, 4 Hz, H-6), 4.20 (1H, d, J = 12 Hz, CH_AH_BPh), 4.27 (1H, ddd, J = 9, 4, 1.5 Hz, H-5), 4.40 (1H, d, J = 12 Hz, CH_CH_DPh), 4.49 (1H, d, J = 12 Hz, CH_CH_DPh), 4.60 (1H, d, J = 12 Hz, CH_EH_FPh), 4.77 (1H, d, J = 12Hz, CH_EH_FPh), 4.77 (1H, dd, J = 12.5, 9 Hz, H-6), 5.60 (1H, d, J = 9.5 Hz, H-1), 7.00 (2 H, m, aromatic), 7.08–7.40 (16H, m, aromatic), 8.37 (1H, m, aromatic), 9.08 (1H, br s, N*H*), 10.26 (1H, s, C*H*O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 61.5, 65.0, 72.1, 72.3, 73.1, 73.7, 75.1, 75.3, 75.7, 111.1, 116.0, 122.2, 122.7, 123.8, 125.9, 127.9, 127.9,

128.0, 128.1, 128.2, 128.3, 128.3, 128.6, 128.7, 135.0, 137.1, 137.3, 137.8, 146.4, 170.9, 186.0; MS (FAB) *m/z* 620 (M + H); Anal. Calcd. for $C_{44}H_{43}NO_8S$: C, 73.65; H, 6.02, N, 2.26. Found: C, 73.67; H, 6.06; N, 2.17.

2-(6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-mannopyranosyl)-1*H*-3-(ethyl-2-acetoamido-1-propenoyl)-1*H*-indole (41). Aldehyde **38a** (66 mg, 0.11 mmol) and *N*-acetamide malonate monomethyl ester (**40**) (24 mg, 0.17 mmol) were dissolved in pyridine (3 ml) and Ac_2O (1 ml). After stirring at rt for 3 h, **40** (10 mg, 0.072 mmol) was added and stirring was continued for 3 h. Silica gel (2 g) was added and the mixture was heated at 60 °C for 14 h and then filtered through a pad of Super Cel. The filtrate was concentrated and the residue was dissolved in H_2O and extracted with EtOAc (×3). The combined extracts were washed with sat. NH_4Cl solution, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography (Et_2O–hexane = 3 : 1) to give **41** (40 mg, 49%) and the recovered aldehyde **38a** (26 mg, 39%): $[\alpha]_D^{26}$ +1.53 (*c* 0.60, $CHCl_3$); IR (KBr) ν_{max} 1740, 1721, 1678, 1496, 1455, 1372, 1240, 1104, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (3H, t, $J = 7$ Hz, OCH_2CH_3), 2.02 (3H, s, Ac), 2.33 (3H, s, Ac), 3.67 (1H, dd, $J = 4.5$, 3 Hz, H-4), 3.89 (1H, dd, $J = 4.5$, 2.5 Hz, H-3), 4.03 (1H, m, H-2), 4.14 (1H, m, H-5), 4.19 (1H, dd, $J =$ 12, 3.5 Hz, H-6), 4.27 (2H, m, OCH_2CH_3), 4.51 (2H, s, CH_2Ph), 4.58 (1H, d, $J = 12$ Hz, CH_AH_BPh), 4.62–4.70 (3H, m, H-6 and CH_2Ph), 4.73 (1H, d, $J = 12$ Hz, CH_AH_BPh), 5.33 (1H, br d, $J = 7.5$ Hz, H-1), 6.93 (1H, br s, NHAc), 7.04 (1H, d, $J =$ 7.5 Hz, aromatic), 7.09–7.36 (16H, m, aromatic), 7.44 (1H, d, $J = 8$ Hz, aromatic), 7.49 (1H, s, CH=CCOOEt), 8.85 (1H, br s, NH of indole); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 20.8, 23.0, 53.4, 61.3, 62.0, 66.5, 72.0, 72.5, 73.2, 74.4, 75.0, 75.7, 108.7, 111.4, 120.6, 122.7, 123.1, 125.4, 126.0, 127.8, 127.9, 128.1, 128.4, 128.5, 128.6, 135.5, 136.2, 137.5, 137.6, 137.9, 165.1, 168.8, 171.0; MS (FAB) *m/z* 747 (M + H); HR-MS (FAB) for $C_{44}H_{47}N_2O_9$ (M + H) calcd. 747.3282, found 747.3199.

Reduction of dehydrotryptophan 41. Dehydrotryptophan **41** (22 mg, 0.029 mmol) was dissolved in MeOH (0.8 ml) and $Pd(OH)_2/C$ (22 mg) was added. The reaction vessel was filled with hydrogen gas. After stirring vigorously at rt for 32 h, the mixture was filtered through a pad of Super Cel, and the filtrate concentrated. The residue was purified by preparative TLC (10% MeOH–CH_2Cl_2) to give **42a** (2.2 mg, 16%, polar) and **43a** (5.5 mg, 39%, less polar).

3-[Ethyl-2(*S*)-acetamidopropanoyl]-2-α-D-mannosyl-1*H*-indole (42a). ^1H NMR (400 MHz, $CDCl_3$) δ 1.11 (3H, t, $J = 7.5$ Hz, OCH_2CH_3), 1.76 (3H, s, Ac), 1.92 (3H, s, Ac), 3.16 (1H, dd, $J = 14.5$, 10 Hz, $CH_AH_BCHCOOEt$), 3.32 (1H, dd, $J = 14.5$, 6 Hz, $CH_AH_BCHCOOEt$), 3.80–4.15 (6H, m, H-3, 4, 5, 6, OCH_2CH_3), 4.26 (1H, br d, $J = 8.5$ Hz, H-2), 4.48 (3H, br s, OH x3), 4.67 (1H, m, CHCOOEt), 4.93 (1H, dd, $J = 12.5$, 9 Hz, H-6), 5.10 (1H, d, $J = 8.5$ Hz, H-1), 7.03 (1H, t, $J = 7.5$ Hz, aromatic), 7.09 (1H, t, $J = 7.5$ Hz, aromatic), 7.21 (1H, d, $J =$ 8 Hz, aromatic), 7.35 (1H, br d, $J = 6$ Hz, NHAc), 7.49 (1H, d, $J = 8$ Hz, aromatic), 9.34 (1H, br s, NH of indole); MS (FAB) *m/z* 479 (M + H).

3-[Ethyl-2(*R*)-acetamidopropanoyl]-2-α-D-mannosyl-1*H*-indole (43a). ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (3H, t, $J = 7$ Hz, OCH_2CH_3), 1.58 (3H, s, Ac), 1.98 (3H, s, Ac), 3.14 (1H, dd, $J = 14.5$, 9.5 Hz, $CH_AH_BCHCOOEt$), 3.34 (1H, dd, $J = 14.5$, 5.5 Hz, $CH_AH_BCHCOOEt$), 3.85–4.21 (8H, m, H-3, 4, 5, 6, OCH_2CH_3, OH × 2), 4.28 (1H, dd, $J = 8.5$, 2 Hz, H-2), 4.81 (1H, td, $J = 9.5$, 5 Hz, CHCOOEt), 4.96 (1H, dd, $J = 13$, 9.5 Hz, H-6), 5.13 (1H, d, $J = 8.5$ Hz, H-1), 5.22 (1H, br s, OH), 6.63 (1H, br s, NHAc), 7.03 (1H, t, $J = 7$ Hz, aromatic), 7.08 (1H, t, $J = 7$ Hz, aromatic), 7.20 (1H, d, $J = 7.5$ Hz, aromatic), 7.43 (1H, d, $J = 7.5$ Hz, aromatic), 9.39 (1H, br s, NH of indole); MS (FAB) *m/z* 479 (M + H).

3-[Ethyl-2(*S*)-acetamidopropanoyl]-2-(2,3,4,6-tetra-*O*-acetyl-α-D-mannosyl)-1*H*-indole (42b). A solution of **42a** (2.0 mg, 0.0036 mmol) in Ac_2O (0.2 ml) and pyridine (0.2 ml) was stirred at rt for 24 h. The mixture was evaporated *in vacuo* and purified by preparative TLC (AcOEt) to give tetraacetate **42b** (2.0 mg, 91%): $[\alpha]_D^{25}$ +42.6 (*c* 0.28, $CHCl_3$); IR (KBr) ν_{max} 2927, 1749, 1372, 1225, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (3H, t, $J = 7$ Hz, $COOCH_2CH_3$), 1.89 (3H, s, Ac), 2.01 (3H, s, Ac), 2.08 (3H, s, Ac), 2.14 (3H, s, Ac), 2.19 (3H, s, Ac), 3.28 (1H, dd, $J = 14.5$, 6.5 Hz, $CH_AH_BCHCOOEt$), 3.37 (1H, dd, $J = 14.5$, 7.5 Hz, $CH_AH_BCHCOOEt$), 3.93–4.01 (1H, m, $OCH_AH_BCH_3$), 4.04–4.11 (2H, m, H-5, $OCH_AH_BCH_3$), 4.20 (1H, dd, $J = 12$, 3.5 Hz, H-6), 4.72 (1H, dd, $J = 12$, 8 Hz, H-6), 4.78 (1H, q, $J = 7$ Hz, CHCOOEt), 5.19 (1H, dd, $J = 6.5$, 5 Hz, H-4), 5.34 (1H, d, $J = 7$ Hz, H-1), 5.36 (1H, dd, $J = 6.5$, 3 Hz, H-3), 5.71 (1H, dd, $J = 7$, 3 Hz, H-2), 6.32 (1H, br d, $J = 7.5$ Hz, NHAc), 7.12 (1H, td, $J = 7.5$, 1 Hz, indole), 7.21 (1H, td, $J = 7.5$, 1 Hz, indole), 7.36 (1H, d, $J = 8$ Hz, indole), 7.53 (1H, d, $J = 7.5$ Hz, indole), 8.46 (1H, br s, NH of indole); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 20.7, 20.8, 20.8, 23.0, 27.1, 29.7, 53.1, 61.2, 61.5, 67.4, 67.7, 68.0, 69.0, 73.8, 110.5, 111.4, 118.8, 120.1, 123.0, 128.5, 129.7, 135.5, 169.6, 169.7, 170.3, 172.5; MS (FAB) *m/z* 605 (M + H); HRMS (FAB+) for $C_{19}H_{37}O_{12}N_2$ (M + H), 605.2347, found 605.2325.

3-[Ethyl-2(*R*)-acetamidopropanoyl]-2-(2,3,4,6-tetra-*O*-acetyl-α-D-mannosyl)-1*H*-indole (43b). Following the procedure for **42b**, tetraacetate **43b** (6.0 mg, 34%) was obtained from **43a** (5.5 mg, 0.012 mmol) after preparative TLC (AcOEt): $[\alpha]_D^{27}$ +33.2 (*c* 0.53, $CHCl_3$); IR (KBr) ν_{max} 2936, 1743, 1668, 1372, 1227, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (3H, t, $J = 7$ Hz, $COOCH_2CH_3$), 1.88 (3H, s, Ac), 2.02 (3H, s, Ac), 2.10 (3H, s, Ac), 2.12 (3H, s, Ac), 2.19 (3H, s, Ac), 3.21 (1H, dd, $J = 15$, 8.5 Hz, $CH_AH_BCHCOOEt$), 3.35 (1H, dd, $J = 15$, 6 Hz, $CH_AH_BCHCOOEt$), 4.01–4.17 (3H, m, H-5, $COOCH_2CH_3$), 4.22 (1H, dd, $J = 12$, 3.5 Hz, H-6), 4.71 (1H, dd, $J = 12$, 7.5 Hz, H-6), 4.85 (1H, td, $J = 8$, 6 Hz, CHCOOEt), 5.20 (1H, dd, $J =$ 6.5, 5 Hz, H-4), 5.33 (1H, dd, $J = 6.5$, 3 Hz, H-3), 5.43 (1H, d, $J = 6.5$ Hz, H-1), 5.72 (1H, dd, $J = 6.5$, 3 Hz, H-2), 6.31 (1H, br d, $J = 7.5$ Hz, NHAc), 7.13 (1H, td, $J = 7.5$, 1 Hz, indole), 7.21 (1H, td, $J = 7.5$, 1 Hz, indole), 7.36 (1H, d, $J = 8$ Hz, indole), 7.58 (1H, d, $J = 8$ Hz, indole), 8.50 (1H, br s, indole NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 20.7, 20.7, 20.8, 22.9, 27.0, 53.0, 61.4, 67.5, 68.0, 69.0, 73.9, 110.5, 111.4, 118.8, 120.1, 123.1, 128.1, 129.5, 135.6, 169.5, 169.8, 170.0, 170.2, 170.7, 172.4; MS (FAB) *m/z* 605 (M + H); HRMS (FAB) for $C_{19}H_{37}O_{12}N_2$ (M + H), 605.2347, found 605.2346.

$Sc(OTf)_3$-promoted coupling between mannosylindole 33 and aziridine 44 (entry 2 in Table 4)

Mannosylindole **33** (50 mg, 0.085 mmol) and aziridine **44** (40 mg, 0.17 mmol) were dissolved in dry CH_2Cl_2 (2.0 ml). To this solution cooled to 0 °C was added $Sc(OTf)_3$ (83 mg, 0.17 mmol). After stirring at the same temperature for 3 h, sat. $NaHCO_3$ solution was added. The resulting mixture was extracted with EtOAc (×3). The combined organic layer was washed with H_2O (×2) and brine (×2), dried over anhydrous Na_2SO_4, passed through a column packed with Na_2CO_3, and evaporated. The residue was purified by column chromatography (silica gel 30 g, ether–hexane = 1 : 1 to 3 : 1) to give **45** (33 mg, 47%, **45a** : **45b** = *ca.* 3 : 1 from ^1H NMR) as an oil. A portion of this oil was separated by preparative TLC (ether–hexane = 1 : 1; CH_2Cl_2 ×3) to give pure **45a** and **45b**.

2-(6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-mannopyranosyl)-L-(*N*-carbobenzyloxyl)tryptophan methyl ester (45a). $[\alpha]_D^{23}$ +14.5 (c 0.35, $CHCl_3$); IR (KBr) ν_{max} 3328, 3031, 2449, 1724, 1518, 1454, 1221, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.89 (3H, s, OAc), 3.15 (1H, dd, $J = 14.5$, 10.5 Hz, $CH_AH_BCHCOOCH_3$), 3.37 (1H, dd $J = 14.5$, 4.5 Hz, $CH_AH_BCHCOOCH_3$), 3.55 (1H,

dd, $J = 3.5$, 1 Hz, H-4), 3.75 (3H, s, COOCH_3), 3.83–3.88 (2H, m, H-2, H-3), 4.04 (1H, d, $J = 13$ Hz, CH_AH$_B$Ph), 4.06 (1H, dd, $J = 12$, 4 Hz, H-6), 4.12 (1H, d, $J = 13$ Hz, CH$_A$$H_B$Ph), 4.17 (1H, br dd, $J = 9$, 4 Hz, H-5), 4.34 (1H, d, $J = 12$ Hz, CH_CH$_D$Ph), 4.46 (1H, d, $J = 12$ Hz, CH$_C$$H_D$Ph), 4.56 (1H, d, $J = 12$ Hz, CH_EH$_F$Ph), 4.64 (1H, br dt, $J = 10.5$, 4.5 Hz, CHCOOCH$_3$), 4.73 (1H, d, $J = 12$ Hz, CH$_E$$H_F$Ph), 4.78 (1H, dd, $J = 12$, 9 Hz, H-6), 4.87 (1H, d, $J = 12$ Hz, CH_GH$_H$Ph), 4.99 (1H, d, $J = 12$ Hz, CH$_G$$H_H$Ph), 5.20 (1H, d, $J = 9$ Hz, H-1), 6.37 (1H, d, $J = 5$ Hz, NH-Cbz), 6.70 (1H, d, $J = 7.5$ Hz, indole), 7.01 (1H, t, $J = 7.5$ Hz, indole), 7.09–7.39 (21H, m, aromatic), 7.64 (1H, d, $J = 7.5$ Hz, indole), 8.18 (1H, s, NH of indole); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 26.7, 52.3, 54.6, 61.3, 64.3, 66.7, 70.8, 71.7, 72.5, 73.5, 74.7, 75.0, 109.1, 111.2, 118.8, 119.7, 122.5, 127.7, 127.8, 128.1, 128.2, 128.3, 128.5, 133.3, 135.7, 136.3, 137.1, 137.3, 137.8, 156.2, 170.8, 173.2; MS (FAB) m/z 827 (M + H); HR-MS (FAB) for $C_{49}H_{51}O_{10}N_2$ (M + H), 827.3544, found 827.3536.

2-(6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-mannopyranosyl)-3-[methyl-(3-*N*-benzyloxycarboxylamido)-2-propionyl-1*H*-indole (45b). IR (KBr) ν_{max} 3356, 3032, 2925, 1729, 1455, 1243, 1075, 1028 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.96 (3H, s, O*Ac*), 3.55 (3H, s, COOCH_3), 3.62 (1H, br d, $J = 4$ Hz, H-4), 3.68 (1H, br dt, $J = 14$, 7 Hz, CH_AH$_B$NHCbz), 3.89–3.94 (2H, m, H-3 and CH$_A$$H_B$NHCbz), 3.95 (1H, br d, $J = 9$, 1.5 Hz, H-2), 4.14 (1H, d, $J = 12.5$ Hz, PhCH_AH$_B$O), 4.14–4.21 (2H, m, H-5 and H-6), 4.24 (1H, d, $J = 12.5$ Hz, PhCH$_A$$H_B$O), 4.38 (1H, t, $J = 7.5$ Hz, ArCHCOOMe), 4.42 (1H, d, $J = 12$ Hz, PhCH_CH$_D$O), 4.49 (1H, d, $J = 12$ Hz, Ph–CH$_C$$H_D$O), 4.62 (1H, d, $J = 12$ Hz, PhCH_EH$_F$O), 4.75 (1H, dd, $J = 12$, 8 Hz, H-6). 4.78 (1H, d, $J = 12$ Hz, PhCH$_E$$H_F$O), 4.98 (1H, d, $J = 12$ Hz, PhCH_GH$_H$O), 5.01 (1H, d, $J = 12$ Hz, PhCH$_G$$H_H$O), 5.38 (1H, d, $J = 9.5$ Hz, H-1), 5.40 (1H, t, $J = 6$ Hz, NHCbz), 6.97 (2H, br d, $J = 7$ Hz, aromatic), 7.09 (1H, t, $J = 7.5$ Hz, aromatic), 7.13 (2H, t, $J = 7.5$ Hz, aromatic), 7.16–7.38 (19H, m, aromatic), 7.61 (1H. br d, $J = 8$ Hz, aromatic), 8.31 (1H, br s, NH of indole); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.8, 42.1, 42.8, 51.8, 61.9, 64.8, 66.4, 71.6, 72.0, 73.5, 73.9, 75.0, 75.2, 75.7, 109.4, 111.1, 119.2, 119.9, 122.3, 127.3, 127.7, 127.8, 127.9, 128.0, 128.0, 128.3, 128.4, 128.5, 128.6, 133.5, 135.5, 136.8, 137.5, 137.6, 138.1, 156.3, 171.0, 173.6; HR-MS (FAB) for $C_{49}H_{51}O_{10}N_2$ (M + H), 827.3544, found 827.3453.

Sc(ClO$_4$)$_3$-promoted coupling between mannnosylindole 33 and aziridine 44 (entry 3 in Table 4). Caution! We have never encountered any problem with the explosion of Sc(ClO$_4$)$_3$; however, we suggest that Sc(ClO$_4$)$_3$ should be handled with special care, because metal perchlorates have potentially explosive properties. In particular, drying of the reagent with heating under vacuum should be conducted in a hood with a safety shield.

Sc(ClO$_4$)$_3$ (60 mg, 0.175 mmol) was placed in the reaction vessel and dried with a Kugelrohr distillation apparatus under reduced pressure (1.4 mmHg) at 150 °C for 14 h, and then cooled to 0 °C. In a separate flask, mannnosylindole **33** (52 mg, 0.087 mmol) and aziridine **44** (41 mg, 0.175 mmol) were dried azeotropically with benzene, and dissolved in CH_2Cl_2 (1.5 ml). This solution was added to the reaction vessel *via* cannula. The reaction mixture was stirred at the same temperature for 5 h and directly subjected to column chromatography (Et_2O–hexane = 1 : 2 → 1 : 1) to give **45a** (59 mg, 83%) as a colorless oil.

2-(2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl)-L-(*N*-carbobenzyloxy)tryptophan methyl ester (46a) (entry 4 in Table 4). Sc(ClO$_4$)$_3$ (54 mg, 0.156 mmol) placed in the reaction vessel was freeze-dried with benzene for 1 h, then cooled to 0 °C. To this flask were added 5 Å MS (75 mg) and the vessel was connected to a vacuum/argon line. The flask was evacuated and then filled with argon. This evacuation/filling cycle was repeated three times. In an separated flask, mannnosylindole **34** (50 mg, 0.078 mmol) and aziridine **44** (37 mg, 0.156 mmol) were dried azeotropically with benzene, and dissolved in dry CH_2Cl_2 (1.5 ml). The solution was added to the reaction vessel *via* cannula. The reaction mixture was stirred at the same temperature for 2 h and directly subjected to column chromatography (silica gel 10 g, AcOEt–hexane = 1 : 6 → 1 : 4) followed by repeated preparative TLC (AcOEt–hexane = 1 : 4; Et_2O–hexane = 1 : 2) to give **53** (3.3 mg, 4.9%) as a yellow oil: $[a]_D^{30}$ +14.5 (*c* 0.165, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.11 (1H, dd, $J = 14$, 10 Hz, CH_AH$_B$CHCOOCH$_3$), 3.37 (1H, dd, $J = 14$, 4.5 Hz, CH$_A$$H_B$CHCOOCH$_3$), 3.76–3.82 (3H, m, H-3, H-4, H-6), 3.77 (3H, s, COOCH_3), 3.85–3.91 (2H, m, H-2, H-6), 4.08 (1H, d, $J = 12.5$ Hz, CH_AH$_B$Ph), 4.17 (1H, d, $J = 12.5$ Hz, CH$_A$$H_B$Ph), 4.24 (1H, br t, $J = 7$ Hz, H-5), 4.39 (1H, d, $J = 12$ Hz, CH_CH$_D$Ph), 4.41 (1H, d, $J = 15$ Hz, CH_EH$_F$Ph), 4.46 (1H, d, $J = 15$ Hz, CH$_E$$H_F$Ph), 4.51 (1H, d, $J = 12$ Hz, CH$_C$$H_D$Ph), 4.55 (1H, d, $J = 12$ Hz, CH_GH$_H$Ph), 4.66 (1H, d, $J = 12$ Hz, CH$_G$$H_H$Ph), 4.66 (1H, ddd, $J = 10$, 5.5, 4.5 Hz, CHCOOCH$_3$), 4.90 (1H, d, $J = 12$ Hz, CH_IH$_J$Ph), 5.02 (1H, d, $J = 12$ Hz, CH$_I$$H_J$Ph), 5.11 (1H, d, $J = 9$ Hz, H-1), 6.43 (1H, d, $J = 5.5$ Hz, NHCbz), 6.74 (2H, dd, $J = 8$, 1 Hz, aromatic), 7.04 (1H, t, $J = 8$ Hz, aromatic), 7.11–7.41 (25H, m, aromatic), 7.66 (1H, d, $J = 8$ Hz, aromatic), 8.21 (1H, s, NH of indole); HR-MS (FAB) for $C_{54}H_{55}O_9N_2$ (M + H), 875.3908, found 875.3903.

2-(2,3,4,6-*O*-Tetrabenzyl-α-D-glucopyranosyl)-L-(*N*-carbobenzyloxy)tryptophan methyl ester (47a) (entry 5 in Table 4). Following the procedure for **46**, **47a** (30.2 mg, 41%) was obtained as a yellow oil from glucosylindole **35** (54 mg, 0.085 mmol) after column chromatography (silica gel 10 g, Et_2O–hexane = 1 : 3 → 1 : 2 → 1 : 1): $[a]_D^{22}$ +75.3 (*c* 1.00, $CHCl_3$); IR (KBr) ν_{max} 3407, 3032, 2869, 1719, 1454, 1071 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.23 (1H, dd, $J = 14.5$, 5 Hz, CH_AH$_B$CHCOOCH$_3$), 3.41 (1H, dd, $J = 14.5$, 8 Hz, CH$_A$$H_B$CHCOOCH$_3$), 3.61 (3H, s, COOC$H_3$), 3.56–3.72 (4H, m, H-4, H-5, H-6 and H-6), 3.91–3.99 (2H, m, H-2, H-3), 4.46 (1H, d, $J = 12$ Hz, CH_AH$_B$Ph), 4.50 (1H, d, $J = 11$ Hz, CH_CH$_D$Ph), 4.57 (1H, m, CHCOOCH$_3$), 4.58 (1H, d, $J = 12$ Hz, CH$_A$$H_B$Ph), 4.63 (1H, d, $J = 11$ Hz, CH_EH$_F$Ph), 4.71 (1H, d, $J = 11$ Hz, CH$_E$$H_F$Ph), 4.77 (1H, d, $J = 11$ Hz, CH$_C$$H_D$Ph), 4.80 (1H, d, $J = 11$ Hz, CH_GH$_H$Ph), 4.90 (1H, d, $J = 11$ Hz, CH$_G$$H_H$Ph), 5.03 (2H, s, C$H_2$Ph), 5.46–5.50 (2H, m, H-1, NHCbz), 7.06–7.37 (28H, m, aromatic), 7.53 (1H, d, $J = 8$ Hz, indole), 9.26 (1H, s, NH of indole); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.9, 52.1, 55.1, 66.8, 69.4, 69.6, 73.5, 73.6, 73.8, 74.6, 75.0, 78.2, 80.8, 81.8, 109.5, 111.2, 118.4, 119.8, 122.2, 127.6, 127.7, 127.8, 128.0, 128.2, 128.3, 128.3, 128.4, 128.4, 128.7, 128.9, 132.0, 135.4, 136.6, 137.3, 138.2, 138.3, 138.5, 155.8, 172.8; HR-MS (FAB) Calcd. for $C_{54}H_{54}N_2O_9$ (M + H): 875.3908. Found: 875.3833.

2-(2,3,4,6-*O*-Tetrabenzyl-α-D-galctopyranosyl)-L-*N*-(carbobenzyloxy)tryptophan methyl ester (48a). Following the procedure for **46**, **48a** (65 mg, 43%) was obtained as a yellow oil from galactosylindole **36** (111 mg, 0.174 mmol) after column chromatography (silica gel 15 g, AcOEt–hexane = 1 : 6 → 1 : 4): $[a]_D^{22}$ +23.2 (*c* 0.75 $CHCl_3$); IR (KBr) ν_{max} 3411, 3332, 3031, 2869, 1722, 1455, 1089 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 40 °C) δ 3.15 (1H, dd, $J = 14$, 6 Hz, CH_AH$_B$CHCOOCH$_3$), 3.21–3.30 (1H, m, CH$_A$$H_B$CHCOOCH$_3$), 3.52 (3H, s, COOC$H_3$), 3.74 (1H, dd, $J = 11$, 4 Hz, H-6), 3.86 (1H, dd, $J = 6.5$, 3 Hz, H-3), 3.96 (1H, dd, $J = 11$, 7 Hz, H-6), 4.00 (1H, dd, $J = 6.5$, 3.5 Hz, H-2), 4.04 (1H, dd, $J = 4.5$, 3 Hz, H-4), 4.11 (1H, br dt, $J = 7.5$, 4 Hz, H-5), 4.32 (1H, br d, $J = 11.5$ Hz, CH_AH$_B$Ph), 4.43 (1H, d, $J = 12$ Hz, CH_CH$_D$Ph), 4.45 (1H, br d, $J = 11.5$ Hz, CH$_A$$H_B$Ph), 4.49 (1H, d, $J = 12$ Hz, CH$_C$$H_D$Ph), 4.52–4.58 (1H, m, C$H$COOCH$_3$), 4.58 (1H, d, $J = 12$ Hz, CH_EH$_F$Ph), 4.62 (1H, d, $J = 12$ Hz, CH_GH$_H$Ph), 4.70 (1H, d, $J = 12$ Hz, CH$_E$$H_F$Ph), 4.73 (1H, d, $J = 12$ Hz, CH$_G$$H_F$Ph), 4.96–5.00 (2H, m, C$H_2$Ph), 5.36 (1H, d, $J = 3.5$ Hz, H-1), 5.34–5.44 (1H, br, NH–Cbz), 7.03–7.07 (2H, m, aromatic), 7.12 (1H, t,

J = 7.5 Hz, indole), 7.16–7.32 (25H, m, aromatic), 7.51 (1H, d, J = 8 Hz, indole), 8.84 (1H, br s, N*H* of indole); ^{13}C NMR (150 MHz, $CDCl_3$) δ 27.0, 52.2, 55.0, 66.6, 66.8, 67.2. 73.0, 73.2, 73.2, 73.7, 73.9, 74.2, 76.5, 78.3, 111.0, 118.5, 119.5, 122.1, 127.7, 127.8, 127.9, 128.1, 128.3, 128.4, 128.5, 128.5, 132.5, 135.3, 137.4, 138.3, 138.4, 155.9, 172.8; HRMS (FAB) Calcd. for $C_{54}H_{54}N_2O_9$ (M + H): 875.3908. Found: 875.3915.

Deprotection of ester and benzyl groups

2-α-D-Mannopyranosyl-L-tryptophan (1). (1) To a solution of **45** (21.8 mg, 0.0264 mmol) in 2-propanol (1.1 ml) was added 1 N LiOH solution (0.079 ml). After stirring at rt for 2 h, the mixture was quenched with sat. NH_4Cl solution. The mixture was acidified to pH 1 with 1 N HCl and then extracted with EtOAc (×2). The combined organic extracts were washed with water (×2) and brine (×2), dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by preparative TLC (10% MeOH–CH_2Cl_2 × 2) to give carboxylic acid **49** (14.1 mg, 70%) as a colorless oil. (2) $Pd(OH)_2$/C (19 mg) was placed in a reaction vessel, and a solution of **49** (19 mg, 0.025 mmol) in MeOH (1.0 ml) and a solution of conc. HCl (0.4 µl, 0.005 mmol) in MeOH (0.4 ml) were successively added *via* cannula. After the reaction vessel was filled with H_2, the mixture was vigorously stirred for 3 h at rt. The resulting mixture was filtered through a pad of Hyflo Super-Cel and the filtrate was concentrated under reduced pressure. The residue was purified by TLC ($CHCl_3$–MeOH–H_2O = 65 : 65 : 15) and lyophilized to give **1** (6.5 mg, 71%) as a white amorphous solid: $[\alpha]_D^{23}$ +29.6 (*c* 1.20, H_2O); ^{1}H NMR (600 MHz, D_2O) δ 3.36 (1H, dd, J = 15.5, 9 Hz, CH_AH$_B$CHCOOH), 3.56 (1H, dd, J = 15.5, 5 Hz, CH$_A$$H_B$CHCOOH), 3.74 (1H, dd, J = 12.5, 3 Hz, H-6), 3.90 (1H, dt, J = 9, 3 Hz, H-5), 3.96 (1H, dd, J = 5, 3 Hz, H-4), 4.03 (1H, dd, J = 9, 5 Hz, C*H*COOH), 4.13 (1H, dd, J = 5, 3 Hz, H-3), 4.26 (1H, dd, J = 12.5, 9 Hz, H-6), 4.44 (1H, dd, J = 8, 3 Hz, H-2), 5.18 (1H, d, J = 8 Hz, H-1), 7.22 (1H, t, J = 8 Hz, indole), 7.32 (1H, t, J = 8 Hz, indole), 7.54 (1H, d, J = 8 Hz, indole), 7.75 (1H, d, J = 8 Hz, indole); ^{13}C NMR (150 MHz, D_2O) δ 28.7, 58.0, 61.8, 68.9, 70.5, 71.7, 73.3, 81.8, 111.1, 114.7, 121.5, 122.7, 125.7, 129.9, 136.2, 138.8, 177.2; MS (FAB) *m*/*z* 367 (M + H); HRMS (FAB) for $C_{17}H_{23}O_7N_2$ (M + H), 367.1505, found 367.1506.

2-α-D-Galctopyranosyl-L-tryptophan (52) (entry 3 in Table 5; entry 3 in Table 6). (**1**) To a solution of **48a** (17.5 mg, 0.020 mmol) in 2-propanol (0.5 ml) was added 1 N LiOH solution (0.06 ml, 0.06 mmol). After stirring at rt for 25 h, sat. NH_4Cl solution was added. The mixture was adjusted to pH 2 with 1 N HCl and then extracted with EtOAc (×3). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by preparative TLC (10% MeOH–CH_2Cl_2) to give **51** (14.5 mg, 85%). (2) A two-necked flask was charged with Pd/C (9.4 mg) and connected to inlet adaptor. The flask was evacuated and then filled with nitrogen. A solution of **51** (9.4 mg, 0.011 mmol) in MeOH (0.28 ml) and 1 N HCl (2.0 µl) were added. The flask was then evacuated and then filled with hydrogen. After vigorous stirring for 25 h, the mixture was filtered through a pad of Hyflo Super-Cel, and the precipitate was washed with MeOH and H_2O. The combined filtrate was concentrated. The residue (5.1 mg) was purified by preparative TLC ($CHCl_3$–MeOH–H_2O = 65 : 65 : 15) to give **52**, which was further purified by reverse phase column chromatography (Cosmosil 75C_{18}, H_2O as eluant) to give **52** (2.8 mg, 70%): $[\alpha]_D^{30}$ +22.2 (*c* 0.185, H_2O); ^{1}H NMR (600 MHz, D_2O) δ 3.50 (1H, dd, J = 15, 5.5 Hz, CH_AH$_B$CHCOOH), 3.56 (1H, dd, J = 15, 8 Hz, CH$_A$$H_B$CHCOOH), 3.76 (1H, dd, J = 12, 3.5 Hz, H-6), 3.90 (1H, dt, J = 9, 3.5 Hz, H-5), 4.02 (1H, dd, J = 12, 9 Hz, H-6), 4.08 (1H, dd, J = 8, 5.5 Hz, C*H*COOH), 4.17 (1H, t, J = 3.5 Hz, H-4), 4.19 (1H, dd, J = 7.5, 3.5 Hz, H-3), 4.29 (1H, dd, J = 7.5, 4.5 Hz, H-2), 5.55 (1H, d, J = 4.5 Hz, H-1), 7.22 (1H, t, J = 8 Hz, indole), 7.31 (1H, t, J = 8 Hz, indole), 7.54 (1H, d, J = 8 Hz, indole), 7.74 (1H, d, J = 8 Hz, indole); ^{13}C NMR (150 MHz, D_2O) δ 28.5 (*C*H_2CHCOOH), 57.8 (*C*HCOOH), 62.4 (C-6), 70.1 (C-4), 70.4 (C-1), 72.5 (C-2), 73.4 (C-3), 78.2 (C-5), 111.1 (C-3 of indole), 114.7 (C-7 of indole), 121.4 (C-4 of indole), 122.6 (C-5 of indole), 125.5 (C-6 of indole), 130.0 (C-3a), 135.9 (C-2 of indole), 138.4 (C-7a), 177.4 (*C*OOH); HRMS (FAB) Calcd. for $C_{17}H_{22}N_2O_7$ (M + H): 367.1505, Found: 367.1500.

2-α-D-Glucopyranosyl-L-tryptophan (53) (entry 2 in Table 5; entry 5 in Table 6). (**1**) To a solution of **47a** (11.8 mg, 0.014 mmol) in 2-propanol (0.6 ml) was added 1 N LiOH solution (41 µl, 0.041 mmol). After stirring at rt for 1.5 h, sat. NH_4Cl solution was added. The pH of the mixture was adjusted to 2 with 1 N HCl and then extracted with EtOAc (×3). The combined organic layers were washed with water (×2) and brine (×2), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by preparative TLC (10% MeOH–CH_2Cl_2) to give **50** (10.0 mg, 86%). (2) A two-necked flask was charged with Pd/C (13 mg) and connected to inlet adaptor. The flask was evacuated and then filled with nitrogen. A solution of **50** (13 mg, 0.015 mmol) in MeOH (0.40 ml) was added. The flask was then evacuated and then filled with hydrogen. After vigorous stirring for 34.5 h, the mixture was filtered through a pad of Hyflo Super-Cel, and the precipitate was washed with MeOH and H_2O. The combined filtrate was concentrated. The residue (6.3 mg) was purified by preparative TLC ($CHCl_3$–MeOH–H_2O = 65 : 65 : 15) to give **53**, which was further purified by reverse phase column chromatography (Cosmosil 75C_{18}, H_2O as eluant) to give **53** (4.0 mg, 73%): $[\alpha]_D^{30}$ +19.5 (*c* 0.200, H_2O); ^{1}H NMR (600 MHz, D_2O) δ 3.47 (1H, dt, J = 8.5, 4 Hz, H-5), 3.51 (2H, br d, J = 7 Hz, CH_2CHCOOH), 3.56 (1H, t, J = 8.5 Hz, H-4), 3.79 (2H, br d, J = 4 Hz, H-6), 4.04 (1H, t, J = 8.5 Hz, H-3), 4.08–4.11 (1H, m, C*H*COOH), 4.10 (1H, dd, J = 8.5, 5.5 Hz, H-2), 5.58 (1H, d, J = 5.5 Hz, H-1), 7.22 (1H, t, J = 7.5 Hz, indole), 7.30 (1H, t, J = 7.5 Hz, indole), 7.55 (1H, d, J = 7.5 Hz, indole), 7.74 (1H, d, J = 7.5 Hz, indole); ^{13}C NMR (150 MHz, D_2O) δ 28.5 (*C*H_2CHCOOH), 58.1 (*C*HCOOH), 63.3 (C-6), 72.4 (C-4), 72.5 (C-1), 74.4 (C-2), 76.7 (C-3), 78.2 (C-5), 111.5 (C-3 of indole), 114.9 (C-7 of indole), 121.3 (C-4 of indole), 122.7 (C-5 of indole), 125.5 (C-6 of indole), 129.9 (C-3a), 135.6 (C-2 of indole), 138.5 (C-7a), 177.5 (*C*OOH); HR-MS (FAB) Calcd. for $C_{17}H_{22}N_2O_7$ (M + H): 367.1505. Found: 367.1507.

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References and notes

1 For reviews: (*a*) R. A. Dwek, *Chem. Rev.*, 1996, **96**, 683–720; (*b*) A. Varki, *Essentials of Glycobiology*: Cold Spring Harbor Laboratory Press, New York, 1999, pp. 1–15.
2 C. M. Taylor, *Tetrahedron*, 1988, **54**, 11317–11362.
3 For review of synthetic *C*-glycosyl amino acids, see: (*a*) A. Dondoni and A. Marra, *Chem. Rev.*, 2000, **100**, 4395–4422; (*b*) F. Schweizer, *Angew. Chem., Int. Ed.*, 2002, **41**, 230–253.
4 J. Hofsteenge, D. R. Müller, T. Beer, A. Löffler, W. J. Richter and J. Vliegenthart, *Biochemistry*, 1994, **33**, 13524–13530.
5 T. Beer, J. Vliegenthart, A. Löffler and J. Hofsteenge, *Biochemistry*, 1995, **34**, 11785–11789.

6 M.-A. Doucey, D. Hess, R. Cacan and J. Hofsteenge, *Mol. Biol. Cell*, 1998, **9**, 291–300.
7 J. Krieg, W. Glasner, A. Vicentini, M.-A. Doucy, A. Löffer, D. Hess and J. Hofsteenge, *J. Biol. Chem.*, 1997, **272**, 26687–26692.
8 J. Krieg, S. Hartmann, A. Vicentini, W. Gläsner, D. Hess and J. Hofsteenge, *Mol. Biol. Cell*, 1998, **9**, 301–309.
9 A. Furmanek and J. Hofsteenge, *Acta Biochem. Pol.*, 2000, **47**, 781–789.
10 M.-A. Doucey, D. Hess, M. J. J. Blommers and J. Hofsteenge, *Glycobiology*, 1999, **9**, 435–441.
11 J. Hofsteenge, M. Blommers, D. Hess, A. Furmanek and O. Miroshnichenko, *J. Biol. Chem.*, 1999, **274**, 32786–32794.
12 S. Hartmann and J. Hofsteenge, *J. Biol. Chem.*, 2000, **275**, 28569–28574.
13 J. Hofsteenge, K. G. Huwiler, B. Macek, D. Hess, J. Lawler, D. F. Mosher and J. Peter-Katalinic, *J. Biol. Chem.*, 2001, **276**, 6485–6498.
14 A. Furmanek, D. Hess, H. Rogniaux and J. Hofsteenge, *Biochemistry*, 2003, **42**, 8452–8458.
15 (*a*) K. Horiuchi, O. Yonekawa, K. Iwahara, T. Kanno, T. Kurihara and Y. Fujise, *J. Biochem.*, 1994, **115**, 362–366; (*b*) B. Gutsche, C. Grun, D. Scheutzow and M. Herderich, *Biochem. J.*, 1999, **343**, 11–19.
16 A. Garcia, L. A. Lenis, C. Jimenez, C. Debitus, E. Quinoa and R. Riguera, *Org. Lett.*, 2000, **2**, 2765–2767.
17 G. E. Richite, B. E. Moffat, R. B. Sim, P. Morgan, R. A. Dwek and P. M. Rudd, *Chem. Rev.*, 2002, **102**, 305–319.
18 C-Man-Trp found in urine and serum was reported to be a potential candidate as a marker molecule for renal function, see: R. Takahira, K. Yonemura, O. Yonekawa, K. Iwahara, T. Kanno, Y. Fujise and A. Hishida, *Am. J. Med.*, 2001, **110**, 192–197.
19 (*a*) T. Nishikawa, M. Ishikawa and M. Isobe, *Synlett*, 1999, 123–125; (*b*) T. Nishikawa, M. Ishikawa, K. Wada and Isobe, *Synlett*, 2001, 945–947.
20 (*a*) S. Manabe and Y. Ito, *J. Am. Chem. Soc.*, 1999, **121**, 9754–9755; (*b*) S. Manabe, Y. Marui and Y. Ito, *Chem. Eur. J.*, 2003, **9**, 1435–1447.
21 H. Fujise, H. Horiuchi, K. Adachi, H. Sano and K. Suzuki, *World Patent* WO99/0411; (*Chem. Abstr.*, 1999, 130).
22 Syntheses of C-Glu-Trp and C-Gal-Trp described in this paper were preliminarily presented at the annual meeting of the Japan Society for Bioscience, Biotechnology and Agrochemistry, Abstracts, p. 18, Kyoto, Japan, March 2001.
23 (*a*) R. C. Larock and E. K. Yum, *J. Am. Chem. Soc.*, 1991, **113**, 6689–6690; (*b*) R. C. Larock, E. K. Yum and M. D. Refvik, *J. Org. Chem.*, 1998, **63**, 7652–7662.
24 (*a*) M. C. Yeh and P. Knochel, *Tetrahedron Lett.*, 1989, **30**, 4799–4802; (*b*) N. J. Dunn, R. F. W. Jackson, J. Pietruszka and D. Turner, *J. Org. Chem.*, 1995, **60**, 2210–2215.
25 (*a*) C. E. Castro, E. J. Gaughan and D. C. Owsley, *J. Org. Chem.*, 1966, **31**, 4071–4078; (*b*) J. Fujiwara, Y. Fukutani, H. Sano, K. Maruoka and H. Yamamoto, *J. Am. Chem. Soc.*, 1983, **105**, 7177–7179.
26 (*a*) M. Isobe, R. Nishizawa, S. Hosokawa and T. Nishikawa, *Chem. Commun.*, 1998, 2665–2676; (*b*) M. Isobe and K. Kira, *J. Synth. Org. Chem.*, 2000, **58**, 23–30; (*c*) M. Isobe and K. Kira, *J. Synth. Org. Chem.*, 2000, **58**, 99–107.
27 Y. Ichikawa, M. Isobe, M. Konobe and T. Goto, *Carbohydr. Res.*, 1987, **171**, 193–199.
28 (*a*) A. Vasslla, *Pure Appl. Chem.*, 1998, **70**, 426–430; (*b*) J. Alzeer and A. Vasella, *Helv. Chim. Acta*, 1995, **78**, 242; (*c*) R. Bürli and A. Vasella, *Helv. Chim. Acta*, 1996, **79**, 1159–1168.
29 J. Stichler-Bonaparte and A. Vasellla, *Helv. Chim. Acta*, 2001, **84**, 2355–2367.
30 T. Nishikawa, K. Wada and M. Isobe, *Biosci., Biotechnol., Biochem.*, 2002, **66**, 2273–2278.
31 The phenylacetylene **14b** was synthesized from **14a** in 2 steps: desilylation of the TMS group with TBAF and then Sonogashira coupling with *N*-tosyl-2-idodoaniline.
32 Compound **3** (R = Bn, X = H, **22**) has been reported as a minor product in the synthesis of a β-ethylymannose derivative. See: T. Lowray, M. Meldal, A. Helmboldt, A. Vasella and K. Bock, *J. Org. Chem.*, 1998, **63**, 9657–9668.
33 (*a*) R. Shah, J. Baptista, G. R. Perdomo, J. P. Carver and J. J. Krepinsky, *J. Carbohydr. Chem.*, 1987, **6**, 645–660; (*b*) G. Zhang, Z. Guo and Y. Hui, *Synth. Commun.*, 1997, **27**, 1907–1917.
34 We tested various Lewis acids such as $BF_3{\cdot}OEt_2$, TMSOTf, $SnCl_4$ and $TiCl_4$ (in CH_2Cl_2 or CH_3CN).
35 For the arming/disarming effect, see: (*a*) D. R. Mootoo, P. Konradsson, U. Udodong and B. Fraser-Reid, *J. Am. Chem. Soc.*, 1988, **110**, 5583–5584; (*b*) C. S. Burgey, R. Vollerthum and B. Fraser-Reid, *J. Org. Chem.*, 1996, **61**, 1609–1618.
36 α-C-Glycosidations of 1-haloglucose derivatives with stannylacetylenes have been reported: (*a*) D. Zhai, W. Zhai and R. M. Williams, *J. Am. Chem. Soc.*, 1988, **110**, 2501–2505; (*b*) L. Jobron, C. Leteux, A. Veyrieres and J.-B. Beau, *J. Carbohydr. Chem.*, 1994, **13**, 507–512.
37 For an example of the synthesis of β-acetylglucoside and galactoside. See: M. Bols and H. C. Hansen, *Acta Chem. Scand.*, 1993, **47**, 818–822.
38 In the case of glucose and galactose, a trace amount of the corresponding β-anomer (>20 : 1) was detected in the ^{1}H NMR spectra.
39 Dondoni and co-workers have reported the synthesis of α-ethynylglucose **23** and α-ethynylgalactose **24** under the same conditions as we have developed for the synthesis of C-Man-Trp. See:(*a*) A. Dondoni, G. Mariotti and A. Marra, *Tetrahedron Lett.*, 2000, **41**, 3483–3486; (*b*) A. Dondoni, G. Moriotti and A. Marra, *J. Org. Chem.*, 2002, **67**, 4475–4486.
40 K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, 4467–4470.
41 The coupling of **21** with an unprotected *o*-iodoaniline as a coupling partner gave a good yield of the desired product; however, the resulting *o*-ethynylaniline did not undergo indole cyclization even under forcing conditions.
42 W. B. Austin, N. Bilow, W. J. Kelleghan and K. S. Lau, *J. Org. Chem.*, 1989, **54**, 52280–2286.
43 A. Yasuhara and T. Sakamoto, *Tetrahedron Lett.*, 1998, **39**, 595–596.
44 Y. Yokoyama, T. Matsumoto and Y. Murakami, *J. Org. Chem.*, 1995, **60**, 1486–1487.
45 The mannose moiety of **38a** has the unusual $^1C_4$ conformation, judging from coupling constant (9.5 Hz) between H-1 and H-2 in its ^{1}H NMR spectra.
46 (*a*) U. Schmidt, A. Lieberknecht and J. Wild, *Synthesis*, 1984, 53–60; (*b*) U. Schmidt, H. Griesser, V. Leitenberger, A. Liberknecht, R. Mangold, R. Meyer and B. Riedel, *Synthesis*, 1992, 487–490.
47 U. Hengartner, D. Valentine Jr., K. K. Johnson, M. M. Larscheid, F. Pigott, F. Scheidl, J. W. Scott, R. C. Sun, J. M. Townsend and T. H. Williams, *J. Org. Chem.*, 1979, **44**, 3741–3747.
48 K. Sato and A. P. Kozikowski, *Tetrahedron Lett.*, 1989, **30**, 4073–4076.
49 Y. L. Bennani, G.-D. Zhu and J. C. Freeman, *Synlett*, 1998, 754–756.
50 (*a*) K. Nakajima, F. Takai, T. Tanaka and K. Okawa, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 1577–1578; (*b*) S. Kato, H. Harada and T. Morie, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3219–3225.
51 I. Hachiya and S. Kobayashi, *Tetrahedron Lett.*, 1994, **35**, 3319–3321.
52 For the scope and limitation of the synthesis of tryptophan with $Sc(ClO_4)_3$ as a Lewis acid, see: T. Nishikawa, S. Kajii, K. Wada, M. Ishikawa and M. Isobe, *Synthesis*, 2002, 1658–1662.
53 The same coupling with other Lewis acid such as $BF_3{\cdot}OEt_2$ and $Sc(OTf)_3$ was reported by Ito and co-workers to give a miserable result, see ref. 20(b).
54 Addition of 3 Å MS instead of 5 Å MS retarded the reaction. For the effect of molecular sieves in reactions with lanthanide triflates, see:T. Tokiwano, K. Fujiwara and A. Murai, *Chem. Lett.*, 2000, 272–273, and references cited therein.
55 The same compound was synthesized by Manabe and Ito, based on a different synthetic strategy – see ref. 20.
56 V. S. Raghavendra Rao, P. K. Qasba, and P. V. Balaji, R. Chandrasekaran, *Conformation of Carbohydrates*, Harwood Academic Publishers, Amsterdam, Netherlands, 1998, pp. 49–90.
57 For examples of the $^1C_4$ conformation of *C*- and *O*-mannosides, see: (*a*) T. G. George, P. Szolcsanyi, S. G. Koenig, D. E. Paterson, Y. Isshiki and A. Vasella, *Helv. Chim. Acta*, 2004, **87**, 1287–1298; (*b*) T. Kumazawa, S. Sato, S. Matsuba and J. Onodera, *Carbohydr. Res.*, 2001, **332**, 103–108; (*c*) H. Yamada, M. Nakatani, T. Ikeda and Y. Marumoto, *Tetrahedron Lett.*, 1999, **40**, 5573.
58 For examples of the $^1C_4$ conformation of *C*- and *O*-glucosides, see: (*a*) H. Abe, M. Terauchi, A. Matsuda and S. Shuto, *J. Org. Chem.*, 2003, **68**, 7439–7447; (*b*) C. Rousseau and O. R. Martin, *Org. Lett.*, 2003, **5**, 3765–3766.
59 T. Nishikawa, S. Kajii, C. Sato, Z. Yasukawa, K. Kitajima and M. Isobe, *Bioorg. Med. Chem.*, 2004, **12**, 2343–2348.
60 For the Edmann degradation of C-Man-Trp, see: J. Hofsteenge, A. Löffler, D. R. Müller, W. J. Richter, T. de Beer and J. F. G. Vligenthart, in *Techniques in Protein Chemistry, VII*, ed. D. R. Marshak, Academic Press, New York, 1996, pp. 163–171.
61 J. M. Berge and S. M. Roberts, *Synthesis*, 1979, 471–472.
62 G. Goekjian, T.-C. Wu, H.-Y. Kang and Y. Kishi, *J. Org. Chem.*, 1991, **56**, 6422–6434.