Ginkgolides and Glycine Receptors: A Structure–Activity Relationship Study

Stanislav Jaracz,[a] Koji Nakanishi,*[a] Anders A. Jensen,[b] and Kristian Strømgaard*[b]

Abstract: Ginkgolides from the *Ginkgo biloba* tree are diterpenes with a cage structure consisting of six five-membered rings and a unique *t*Bu group. They exert a variety of biological properties. In addition to being antagonists of the platelet activating factor receptor (PAFR), it has recently been shown that native ginkgolides are potent and selective antagonists of the inhibitory glycine receptor. Forty new ginkgolide derivatives have been prepared in good to high yields on milligram scales and investigated for their antagonistic properties at homomeric α1 glycine receptors, thus providing the first structure–activity relationship study of ginkgolides at glycine receptors. A high-throughput screening assay showed that native ginkgolide C was the most potent ligand, and that manipulation of any of the hydroxyl groups led to loss of activity at α1 glycine receptors.

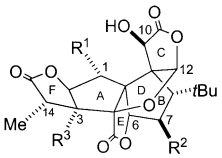
Keywords: inhibitors · medicinal chemistry · natural products · rearrangement · terpenoids

Introduction

The *Ginkgo biloba* tree is among the oldest living plants and is thus referred to as a "living fossil". It is admired for its unique beauty, especially its leaves, which have been exemplified by a poem by Johann Wolfgang von Goethe from 1815.[1] The *Ginkgo* tree has a long history of use in traditional Chinese medicine, but it was not until the 1960s that a standardized extract of *G. biloba* leaves, EGb 761, was introduced into the European markets.[2] Today the *G. biloba* extract is one of the most popular botanical medicines worldwide.

Numerous beneficial effects of EGb 761 have been postulated including improving peripheral vascular function, inhibition of thrombosis and embolism, neuroprotection in Alzheimer's disease and cognitive disorders, anti-inflammatory and antiproliferative activities, as well as antioxidant activities.[3] EGb 761 is a complex mixture of compounds, the main ingredients being flavonoids and terpene trilactones (ginkgolides and bilobalide) that comprise 24 and 6%, respectively, of the total extract.[4,5] It has been proposed that the flavonoids act as antioxidants, while the terpene trilactones are involved in anti-inflammation and prevention of blood clotting associated with the antagonistic activity at the platelet-activating factor (PAF) receptor.[6] However, the neuroprotective effects of EGb 761 have so far not been associated with specific components of the extract.[7,8]

The terpene trilactones, ginkgolides (Figure 1) and bilobalide, are unique components of EGb 761, the structures of which were elucidated in 1967.[9–15] The ginkgolides are diterpene trilactones with a cage-like skeleton consisting of six five-membered rings, that is, a spiro[4.4]nonane carbocyclic ring, three lactones, and a tetrahydrofuran moiety. Terpene trilactones from *G. biloba* are also among the very few natural products containing a *t*Bu group.



	R^1	R^2	R^3
Ginkgolide A (GA **1**)	H	H	OH
Ginkgolide B (GB, **2**)	OH	H	OH
Ginkgolide C (GC,**3**)	OH	OH	OH
Ginkgolide J (GJ, **4**)	H	OH	OH
Ginkgolide M (GM, **5**)	OH	OH	H

Figure 1. Ginkgolides A, B, C, J, and M.

In contrast to many studies on the neuroprotective effects of EGb 761, the ginkgolides have not been extensively studied, partly due to limited availability of pure ginkgolides. The discovery in 1985 that ginkgolide B (GB, **2**) was a potent antagonist of the PAF receptor (PAFR)[16,17] led to extensive structure–activity relationship (SAR) studies on this receptor.[18–28] However, the significance of these effects in relation to the neuroprotective effects of EGb 761 is not clear yet.[29]

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The first indication of a direct interaction of ginkgolides with important targets in the brain was discovered when ginkgolides were shown to be potent and highly selective antagonists of the inhibitory glycine receptor (GlyR).[30–32] The GlyR is a ligand-gated ion channel found primarily in the spinal cord and brain stem but also in higher brain regions such as the hippocampus and developing cortex, which consists of α1–α4 and β subunits.[33] Only a few ligands for GlyRs have been available, the classical example being the convulsant strychnine, a competitive antagonist. However, since the neuropharmacology and functional importance of GlyRs in higher brain regions is not well characterized,[34] new potent and selective ligands are needed for further investigations of the GlyR.

The aim of this study was to prepare various ether-, ester- and carbamoyl-derivatives of ginkgolide C by selective derivatization of the hydroxyl groups. In the following we describe the synthesis of forty derivatives of ginkgolide C. The ginkgolide derivatives thus prepared were then evaluated for their antagonistic activity of the GlyR by means of a fluorescence-based high-throughput screening assay.

Results and Discussion

In the present study ginkgolide C (GC, **3**) was chosen as the starting material because it carries the most hydroxyl groups of the ginkgolides, thus providing possibilities for more diverse library. Secondly, GC (**3**), together with GB (**2**), is the most potent GlyR antagonist amongst the native ginkgolides.[31] Inspection of the structure reveals three secondary and one tertiary hydroxyl groups, which exhibit different reactivities and can therefore be functionalized selectively. In general, 10-OH is the most reactive for alkylation and esterification.[35] However, acid-catalyzed esterification,[36] reaction of GC (**3**) with alkyl and aryl sulfonyl halides in the presence of pyridine[37,38] as well as silylation[39] takes place at 7-OH; a selective silylation at 1-OH in the presence of imidazole has also been described.[40]

The use of solid-phase synthesis (SPS) for the preparation of ginkgolide derivatives appeared to be particularly attractive, as the presence of multiple hydroxyl groups provides several options for connecting points. Hence various strategies were investigated, including silicon,[41,42] sulfonyl,[43] Wang,[44,45] and Rink amide[46] linkers. Interestingly, none of the solid-phase methods studied was superior to the traditional solution-phase chemistry. The initial problem associated with solid-phase synthesis was the difficulty of attaching ginkgolide C to the solid-phase due to a steric hindrance and small reactivity of the ginkgolide hydroxyl groups. After overcoming this obstacle with silyl linkers, bulkiness of the silyl linker hampered further derivatization in some cases whereas smaller linkers suffered from instability as evidenced by leaching. Selectivity of reactions on the solid-phase was also significantly decreased; the products cleaved from the resin were obtained in low yields with low purity. The most promising approach appeared to be the attachment of GC (**3**) via a 10-benzyloxy group to Wang resin; in this case the final cleavage from the support took place several atoms away from the ginkgolide itself (Figure 2). Although many hydroxyl group esterifications were performed on this system, it was concluded that reactivity and selectivity were both lower as compared with the same reactions in solution-phase; namely, the cleaved products were mixtures of the starting materials, desired products and over-esterified products. Hence, the solid-phase approach was abandoned and preparation of a ginkgolide library was performed via a similar approach but in solution.

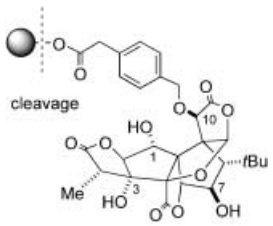
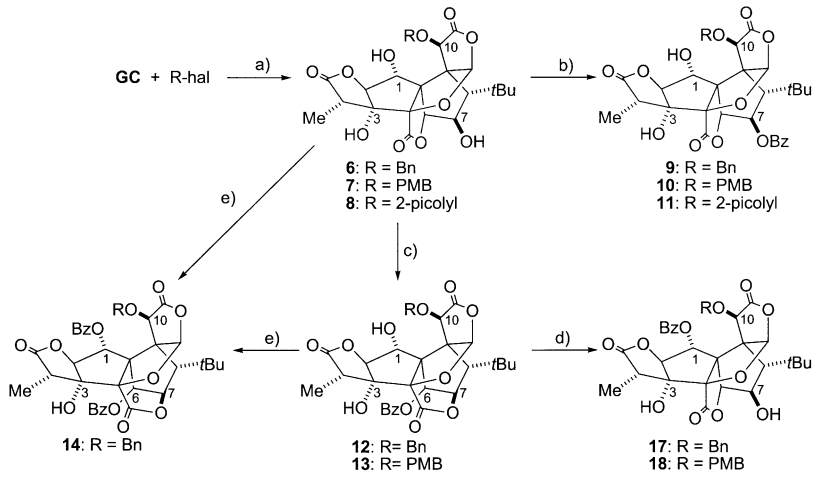


Figure 2. Ginkgolide C attached to Wang resin via 10-benzyloxy group.

In the first step, GC (**3**) was selectively alkylated at 10-OH with various benzyl-derived halides under mild reaction conditions to form **6**, **7**, and **8** in 94–97% yield (Scheme 1).[23,38] Hydrogen bonding between 1-OH and 10-OH as described by Corey[35] is responsible for enhanced reactivity of these hydroxyl groups. Thus, reaction with alkyl bromides in DMF with K_2CO_3 as a base yields mixture of 10-O and 1-O monoalkylates, generally within less than 2 h. Further alkylation does not occur even after several days of stirring. The 10-OH/1-OH selectivity seems to be influenced by the size of the incoming alkyl group. While benzyl-derived halides provide GC benzyl ethers in the ratio of 10:1 to 15:1, methyl iodide yields methyl ethers under identical conditions with only 1.7:1 selectivity.[39] Furthermore, mixtures of the monoalkyl ethers could not be separated by silica gel chromatography; attempts to separate them by recrystallization also failed.

In the next step, position 7 was derivatized by esterification in the presence of pyridine. Thus, a series of GC-7-benzoates **9**, **10** and **11** were prepared in 79–92% yield (Scheme 1). However, the use of Hünig's base (iPr$_2$EtN) instead of pyridine led to translactonization of ring E and formation of esters **12** and **13** at position 6. This remarkable difference in the reaction pattern is due to the higher basicity of Hünig's base. The translactonized anion intermediate is then stabilized by hydrogen bonding with 3-OH as reported previously (Figure 3).[36] Thus, iso-GC-6-benzoates **12** and **13** were synthesized in 75–77% yield. Iso-GC-1,6-bisbenzoate **14** was also prepared from **6** in 64% yield by increasing the amount of benzoylation reagent and prolonging the reaction time. Interestingly, the same reaction conditions applied to **13** provided only trace amounts of the corresponding iso-GC-1,6-bisbenzoate. Acetylation of **6** and **7** with acetic anhydride and Hünig's base led to bisacetates **15** and **16**, respectively, in about 80% yield (Scheme 2).

Very few reports are available on the selective derivatization of the 1-OH in GC. Although a selective silylation of 1-OH has been carried out by Weinges[40] the mechanism and



Scheme 1. Synthesis of ginkgolide C benzoates. a) K_2CO_3, DMF; b) BzCl (3 equiv), pyridine, CH_2Cl_2; c) Bz_2O (3 equiv), iPr_2EtN, CH_2Cl_2; d) iPr_2EtN, DMF, 100 °C; e) Bz_2O (6 equiv), iPr_2EtN, CH_2Cl_2; PMB = *p*-methoxybenzyl.

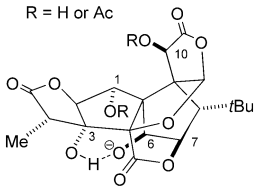
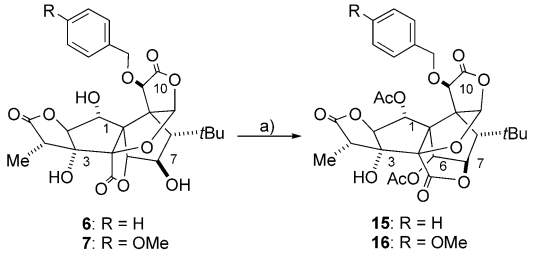


Figure 3. Stabilization of 6-O anion in translactonized GC as generated by iPr_2EtN.



Scheme 2. Synthesis of 10-alkoxy-iso-GC-1,6-bisacetates. a) Ac_2O (10 equiv), iPr_2EtN, CH_2Cl_2.

scope of this reaction are not clear. We found that selective derivatization of 1-OH can be achieved by acyl migration from 6-O (iso-GC derivatives) via a six-membered cycle intermediate (Scheme 3). Thus heating of iso-GC-6-benzoates **12** and **13** at 100 °C in DMF in the presence of a tertiary amine provided GC-1-benzoates **17** and **18**, respectively, in 78–80 % yield (Scheme 1). The driving force for this rearrangement is the lower thermodynamic stability of iso-GC skeleton than the original GC. Namely, the six-membered lactone ring E in iso-GC adopts a boat conformation. In addition, the bulky *t*Bu group in iso-GC suffers from diaxial steric interaction with 6-H. The tertiary 3-OH remained untouched as attempts to derivatization under more drastic esterification conditions led to elimination products.

All of the above reactions required protection of 10-OH. In order to evaluate the effect of 10-OH substitution for GlyR inhibition, deprotection was necessary. This was readily accomplished by oxidative removal of the *p*-methoxybenzyl (PMB) group in derivatives **10, 13**, and **18**. The reaction was facilitated by treatment with cerium(IV) ammonium nitrate to obtain **19**, **20**, and **21** in 68–81 % yield (Figure 4). However, the milder oxidation reagent dichlorodicyano quinone (DDQ) failed.

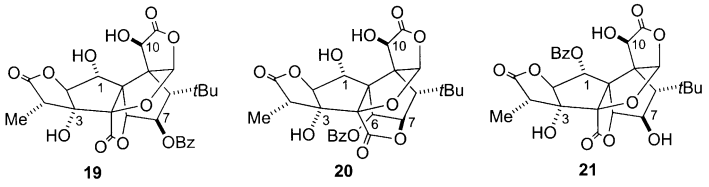
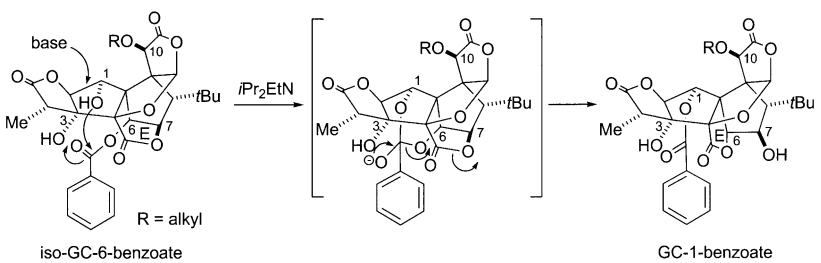
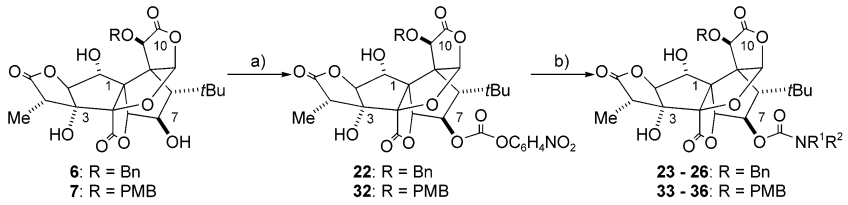


Figure 4. Benzoates of ginkgolide C.

Introduction of carbamate moieties into the various hydroxyl groups of ginkgolides was investigated next. Carbamates are versatile sources of additional interactions such as hydrogen bonding, hydrophobic interaction and steric repulsion. This could yield important information for SAR studies. Carbamates at 7-O were efficiently prepared from 10-benzyloxy-GC (**6**) in two steps (Scheme 4). Reaction with *p*-nitrophenylchloroformate and pyridine in CH_2Cl_2 gave **22** in 61 % yield. Active carbonate **22** was further reacted with various aliphatic amines in THF to yield carbamates **23–26** in 81–92 % yield (Table 1). Again, a remarkable difference was observed when Hünig's base was used instead of pyridine



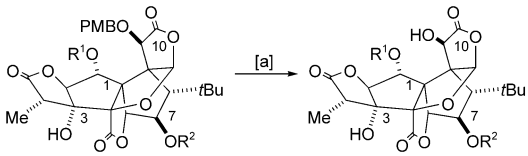
Scheme 3. Suggested mechanism of acyl migration from 6-O to 1-O with consequent translactonization of ring E.



Scheme 4. Synthesis of 7-O carbamates from 10-alkoxy-GC. a) $ClCOOC_6H_4NO_2$, pyridine, CH_2Cl_2; b) NHR^1R^2, THF; PMB = *p*-methoxybenzyl.

(Scheme 5). It is plausible that a highly reactive iso-GC 6-(*p*-nitrophenyl)carbonate is formed first, which reacts further with 1-OH as in the case of the migration of benzoate in **17**. The product of this reaction, however, is cyclic carbonate **27** with a carbonyl bridging 1-O and 6-O (Scheme 5). This active carbonate was unstable and hydrolyzed easily even on silica gel to form **6**. Treatment of **27** with various aliphatic amines in THF provided facile opening of the carbonate cycle to form carbamates at 1-O with consequent translactonization of ring E into the native form, **28–31**. All three reactions were finally performed in one pot to obtain the desired 1-O derivatives in 50–78% overall yield from **6** after a single column chromatography (Table 1). Even bulky amines such as *tert*-butyl amine reacted to completion in both cases forming **24** and **29**, ginkgolides with two *t*Bu groups. The corresponding sets of carbamates **33–36** (7-O) (Scheme 4) and **38–41** (1-O) (Scheme 5) were also prepared from **7**. Removal of the PMB group from **33–36** and **38–41** afforded the non-aromatic ginkgolide carbamates **42–49** (Table 2) in 60–86% yield.

Table 2. Chemical yields and biological activities of 7-O and 1-O carbamates of ginkgolide C.

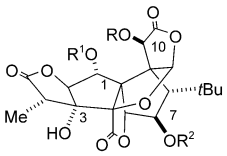


Compound	R^1	R^2	Yield [%]	Inhibition[b] [%]
42	H	CONHMe	69	NI
43	H	CONH*t*Bu	80	NI
44	H	$CONC_4H_8O$	60	44
45	H	$CONC_5H_{10}$	64	34
46	CONHMe	H	86	76
47	CONH*t*Bu	H	84	71
48	$CONC_4H_8O$	H	80	NI
49	$CONC_5H_{10}$	H	79	33

[a] $(NH_4)_2Ce(NO_3)_6$, MeCN/H_2O/$CHCl_3$. [b] Inhibition of 100 μM glycine-induced response by 100 μM of test compound; %-inhibition was calculated as: $(Response_{glycine} - Response_{test\ cmpd+glycine})/Response_{glycine}$. Values are means of three independent experiments performed in duplicate. NI = no inhibition, i.e., inhibition below 20%. PMB = *p*-methoxybenzyl.

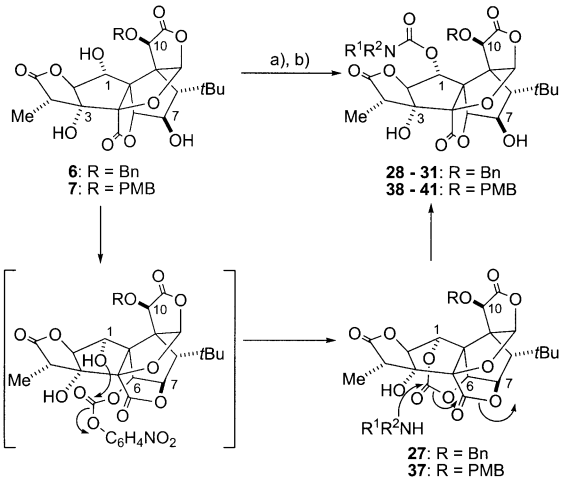
Biological activity: The ginkgolide derivatives were investigated in their abilities to antagonize glycine-induced responses from homomeric α1 GlyRs. In brief, homomeric α1 GlyR was stably expressed in HEK293 cells and a fluorescence-based membrane-potential kit was used to detect receptor activity.[47] The decrease in glycine response was measured by pre-incubation of the test compound prior to addition of 100 μM glycine. GC (**3**) was used as the reference compound. At a concentration of 10 μM GC (**3**) the response induced by glycine was inhibited by 97%. Due to the relatively low potency of all derivatives, they were investigated at concentrations of 100 μM for determination of the % inhibition (Tables 1–4). However, the fact that the parent compound GC (**3**) was found to be more potent than its derivatives showed the significant role played by the hydroxyl groups in GlyR interaction. Thus, in the discussion below it should be noted that the relative differences be-

Table 1. Chemical yields and biological activities of C-7 and C-1 carbamates of 10-alkoxy-GC.



Compound	R	R^1	R^2	Yield [%]	Inhibition[a] [%]
23	Bn	H	CONHMe	88[b]	NI
24	Bn	H	CONH*t*Bu	88[b]	29
25	Bn	H	$CONC_4H_8O$	92[b]	NI
26	Bn	H	$CONC_5H_{10}$	81[b]	NI
28	Bn	CONHMe	H	64[c]	NI
29	Bn	CONH*t*Bu	H	59[c]	42
30	Bn	$CONC_4H_8O$	H	78[c]	NI
31	Bn	$CONC_5H_{10}$	H	50[c]	31
33	PMB	H	CONHMe	74[d]	NI
34	PMB	H	CONH*t*Bu	77[d]	39
35	PMB	H	$CONC_4H_8O$	90[d]	NI
36	PMB	H	$CONC_5H_{10}$	86[d]	29
38	PMB	CONHMe	H	67[e]	NI
39	PMB	CONH*t*Bu	H	60[e]	33
40	PMB	$CONC_4H_8O$	H	75[e]	NI
41	PMB	$CONC_5H_{10}$	H	53[e]	NI

[a] Inhibition of 100 μM glycine-induced response by 100 μM of test compound; % inhibition was calculated as: $(Response_{glycine} - Response_{test\ cmpd+glycine})/Response_{glycine}$. Values are means of three independent experiments performed in duplicate. [b] From **22**. [c] From **6**. [d] From **32**. [e] From **7**. NI = no inhibition, i.e., inhibition below 20%. PMB = *p*-methoxybenzyl.



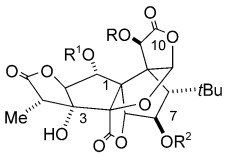
Scheme 5. Synthesis of 1-O carbamates from 10-alkoxy-GC; suggested mechanism. a) $ClCOOC_6H_4NO_2$, *i*$PrEt_2N$, CH_2Cl_2; b) NHR^1R^2, CH_2Cl_2/THF; PMB = *p*-methoxybenzyl.

tween these derivatives are only minor since all compounds are only weak antagonists of the GlyR.

Ginkgolide derivatives with carbamates in position 1 or 7, and a benzyl or PMB group in the 10-position were either inactive or only moderately active at the concentrations tested (Table 1). Interestingly, all derivatives with moderate activity contained a *t*Bu carbamate, and the presence of this group, rather than the position seems to be of importance for biological activity in this set of derivatives. For the corresponding carbamates without the benzyl or PMB group it appears that both the position and the nature of the substituent are of importance (Table 2): Compounds **46** and **47** show approximately 70% inhibition of the glycine responses, whereas other derivatives are either inactive or only moderately active. It is interesting to compare the activities of **46** with those of **28** and **38**, the only difference being the benzyl or PMB substitution at 10-OH. This indicates that 10-OH substitution is detrimental for activity towards GlyRs. Moreover, the activities of **46** and **47** compared with those of **42** and **43** show that substitution at 1-OH is preferred over 7-OH, while comparison with **48** and **49** indicates that there may be a limitation to the size of the substituent that is tolerated.

The benzylated or benzoylated derivatives of ginkgolide C showed a certain degree of variation in activities (Table 3). The most potent derivatives were those with only one benzyl substituent at 10-OH, such as compounds **6**, **7** and **8**. Particularly compound **8** with a 2-picolyl substituent exhibited 75% inhibition. Addition of benzoyl groups does not improve activity, while the presence of only one benzoyl group, such as **19** and **21** leads to a complete loss in activity. Finally, a range of iso-ginkgolide derivatives was investigated, with some showing reasonable potencies (Table 4). Particularly compound **12**, with a 90% inhibition in glycine responses is the most potent of the 40 derivatives. On the other hand, it is still considerably less potent than GC (**3**), a 30 μM concentration of **12** giving only a 39% inhibition.

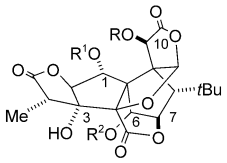
Table 3. Biological activities of ginkgolide C derivatives.



Compound	R	R^1	R^2	Inhibition[a] [%]
6	Bn	H	H	59
9	Bn	H	Bz	45
17	Bn	Bz	H	60
7	PMB	H	H	52
8	2-picolyl	H	H	75
10	PMB	H	Bz	35
18	PMB	Bz	H	NI
11	2-picolyl	H	Bz	51
19	H	H	Bz	NI
21	H	Bz	H	NI

[a] Inhibition of 100 μM glycine-induced response by 100 μM of test compound; % inhibition was calculated as: $(Response_{glycine} - Response_{test\ cmpd+glycine})/Response_{glycine}$. Values are means of three independent experiments performed in duplicate. NI = no inhibition, i.e., inhibition below 20%. PMB = *p*-methoxybenzyl.

Table 4. Biological activities of iso-ginkgolide C derivatives.



compound	R	R^1	R^2	Inhibition[a] [%]
12	Bn	H	Bz	90
15	Bn	Ac	Ac	21
16	PMB	Ac	Ac	36
14	Bn	Bz	Bz	42
13	PMB	H	Bz	49
20	H	H	Bz	63

[a] Inhibition of 100 μM glycine-induced response by 100 μM of test compound; %-inhibition was calculated as: $(Response_{glycine} - Response_{test\ cmpd+glycine})/Response_{glycine}$. Values are means of three independent experiments performed in duplicate.

Conclusion

We have shown that ginkgolide C in solution can be selectively transformed into various derivatives via rearrangement and migration. Particularly, a selective method for substitution at 1-OH has been found. Since hydroxyl groups that are unchanged in the product, for example, 3-OH and 7-OH, participate during the reaction process, their protection would presumably hamper the entire reaction. The role of 7-OH in the substitution of 1-OH described here is crucial. We have also investigated a solid-phase approach for preparation of a ginkgolide library. Ginkgolide C was successfully attached to solid-phase but the derivatization reactions on the resin were much less efficient as compared to solution-phase reactions. Particularly, selectivity was greatly diminished.

The synthesized ginkgolide derivatives were investigated as GlyR antagonists using a high-throughput screening

assay. In general, the ginkgolide derivatives prepared were less potent than the parent compound (**3**), and in many cases the derivatives were totally devoid of activity. These results indicate that substitutions of the hydroxyl groups in ginkgolides are not beneficial for antagonistic activity at GlyR, and clearly other means of improving the activity of the parent compounds will be required. In addition, these results show that the structure–activity relationships differ significantly from those observed with PAFR, as best exemplified by the iso-ginkgolide derivatives. When tested against PAFR, iso-GC acetates were devoid of activity;[36] however, in the present studies, although much less potent than the parent compound (**3**), the iso-ginkgolide derivative **12** was the most potent of the compounds tested.

Previous studies have indicated that ginkgolides might antagonize GlyRs by binding to an intra-ion channel site,[31] thus acting as a plug in the ion channel of the GlyR. Moreover, it has been suggested that the conformation of the ginkgolide is very important for antagonistic activity.[32] This study suggests that the hydroxyl groups are critical for the GlyR inhibition.

Experimental Section

Materials and methods: All reactions were performed under argon at ambient temperature in dry solvents and yields refer to isolated products, unless otherwise stated. Ginkgolide C (**3**) originated from early structural studies,[9–13] and was recrystallized from ethanol/water and dried in desiccator. All other reagents were purchased and used as received. Polystyrene resin, Wang resin and bromopolystyrene resin were obtained from Advanced ChemTech, DES resin and sulfonyl chloride resin were obtained from Aldrich, Tentagel resin was purchased from Rapp-Polymere GmbH, Tübingen (Germany). Reactions were monitored by analytical TLC with silica gel 60 F_{254} and spots were visualized by heating and UV light (254 nm). Flash chromatography was performed using silica gel (230–400 mesh).

^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker (300, 400 or 500 MHz) spectrometers. The chemical shifts are expressed in ppm (δ) downfield from tetramethylsilane (in $CDCl_3$) or calibrated according to residual solvent peak as an internal standard (MeOD, δ 3.30). Assignment of peaks was achieved using 2D methods (COSY), by comparison with published data where available and comparison with ^{1}H NMR spectra of parent ginkgolides. In certain cases, HSQC was used instead of ^{13}C NMR. High-resolution mass spectra (HRMS) were measured on JEOL JMS-HX110/100A HF mass spectrometer under FAB conditions with NBA as the matrix. In general, all ginkgolide derivatives decomposed above 250 °C.

10-Benzyloxy-GC (6): Synthesis and analytical data as previously described.[38]

10-(4-Methoxy-benzyloxy)-GC (7): Powdered K_2CO_3 (315 mg, 2.28 mmol, 5 equiv) and 4-methoxybenzyl chloride (620 μL, 4.56 mmol, 10 equiv) were added to a solution of GC (**3**) (201 mg, 0.456 mmol) in DMF (2.28 mL). The mixture was stirred at 60 °C for 3 h and then stirred at room temperature for 5 h. The solution was concentrated under reduced pressure, an aq. phosphate buffer (pH 2–3, 10 mL) was added and the resulting solution was extracted with EtOAc (3×) and dried with $MgSO_4$. The crude product was purified by flash chromatography (40–100 % EtOAc/hexanes) to obtain **7** as a white powder (240 mg, 94 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.27 (m, 2 H_{AR}), 6.99–6.89 (m, 2 H_{AR}), 5.98 (s, 1 H, 12-H), 5.41 (d, J = 9.2 Hz, 1 H, benzylic), 5.12 (d, J = 4.4 Hz, 1 H, 6-H), 4.92 (s, 1 H, 10-H), 4.57 (d, J = 9.2 Hz, 1 H, benzylic), 4.52 (d, J = 7.9 Hz, 1 H, 2-H), 4.21 (dd, J = 3.4, 7.9 Hz, 1 H, 1-H), 4.13 (m, 1 H, 7-H), 3.83 (s, 3 H, OMe), 3.05 (q, J = 7.1 Hz, 1 H, 14-H), 2.88 (d, J = 3.4 Hz, 1 H, 1-OH), 2.75 (s, 1 H, 3-OH), 2.12 (d, J = 11.5 Hz, 1 H, 7-OH), 1.69 (d, J = 12.4 Hz, 1 H, 8-H), 1.30 (d, J = 7.0 Hz, 3 H, 16-CH_3), 1.23 (s, 9 H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.83, 171.03, 170.90, 160.56, 130.65, 126.36, 114.73, 110.13, 98.49, 90.70, 83.47, 79.33, 75.59, 75.31, 73.79, 67.08, 64.03, 55.31, 50.38, 41.65, 32.19, 29.08, 7.23; HRMS (FAB): *m/z*: calcd for $C_{28}H_{32}O_{12}$: 560.1894; found: 560.1866 $[M]^+$.

10-(2-Pyridinyl-methoxy)-GC (8): A mixture of 2-picolylchloride hydrochloride (401.4 mg, 2.45 mmol, 6 equiv) and EtOAc was washed with sat. aq. $NaHCO_3$ (2×), brine. The organic phase was subsequently dried with $MgSO_4$. After filtration and removal of EtOAc, free 2-picolyl chloride was added to a solution of GC (**3**) (179.6 mg, 0.408 mmol, 1 equiv) in DMF (2.04 mL) and powdered K_2CO_3 (338 mg, 2.45 mmol, 6 equiv) was added. The mixture was briefly heated to about 60 °C and then stirred at room temperature for 15 h. The solution was concentrated under reduced pressure, an aq. phosphate buffer (pH 2–3, 10 mL) was added and resulting solution was extracted with EtOAc (3×) and dried with $MgSO_4$. The crude product was purified by flash chromatography (50–100 % EtOAc/hexanes) to obtain **8** as a white powder (211.2 mg, 97 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54 (d, J = 4.9 Hz, 1 H_{AR}), 8.20 (d, J = 4.1 Hz, 1 H, 1-OH), 7.79–7.71 (m, 1 H_{AR}), 7.35–7.28 (m, 1 H_{AR}), 7.19–7.11 (m, 1 H_{AR}), 6.00 (s, 1 H, 12-H), 5.67 (d, J = 13.0 Hz, 1 H, benzylic), 5.43 (d, J = 4.3 Hz, 1 H, 6-H), 4.96 (s, 1 H, 10-H), 4.82 (d, J = 13.0 Hz, 1 H, benzylic), 4.66 (d, J = 7.6 Hz, 1 H, 2-H), 4.47–4.38 (m, 1 H, 1-H), 4.27–4.17 (m, 1 H, 7-H), 3.10 (s, 1 H, 3-OH), 3.08 (q, J = 7.0 Hz, 1 H, 14-H), 2.32 (d, J = 11.3 Hz, 1 H, 7-OH), 1.73 (d, J = 12.4 Hz, 1 H, 8-H), 1.30 (d, J = 7.0 Hz, 3 H, 16-CH_3), 1.18 (s, 9 H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.79, 171.45, 170.96, 154.52, 148.74, 137.41, 123.29, 120.37, 109.99, 98.74, 92.61, 83.06, 80.14, 75.36, 74.89, 73.81, 70.67, 67.62, 64.70, 50.55, 41.74, 32.27, 29.12, 7.33; HRMS (FAB): *m/z*: calcd for $C_{26}H_{30}O_{11}N$: 532.1819; found: 532.1844 $[M+H]^+$.

10-Benzyloxy-GC-7-benzoate (9): Benzoyl chloride (25 μL, 0.216 mmol, 5 equiv) was added to a solution of **6** (22.9 mg, 0.043 mmol) in CH_2Cl_2 (0.9 mL) and pyridine (0.15 mL, 1.85 mmol, 43 equiv). The mixture was stirred for 7 h and then quenched with aq. HCl (1 mL, 1 M), extracted with EtOAc (3×) and dried with $MgSO_4$. The crude product was purified by flash chromatography (30–50 % EtOAc/hexanes) to obtain **9** as a white powder (21.6 mg, 79 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12–8.05 (m, 2 H_{AR}), 7.68–7.58 (m, 1 H_{AR}), 7.53–7.40 (m, 7 H_{AR}), 6.08 (s, 1 H, 12-H), 5.50 (dd, J = 12.9, 4.3 Hz, 1 H, 7-H), 5.48 (d, J = 9.4 Hz, 1 H, benzylic), 5.41 (d, J = 4.3 Hz, 1 H, 6-H), 5.02 (s, 1 H, 10-H), 4.76 (d, J = 9.4 Hz, 1 H, benzylic), 4.51 (d, J = 7.9 Hz, 1 H, 2-H), 4.26 (dd, J = 7.9, 3.2 Hz, 1 H, 1-H), 3.07 (q, J = 7.0 Hz, 1 H, 14-H), 2.86 (d, J = 3.2 Hz, 1 H, 1-OH), 2.9–2.7 (br s, 1 H, 3-OH), 2.25 (d, J = 12.9 Hz, 1 H, 8-H), 1.31 (d, J = 7.0 Hz, 3 H, 16-CH_3), 1.20 (s, 9 H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.13, 170.97, 170.50, 164.84, 134.12, 133.95, 130.06, 129.85, 129.57, 128.80, 128.74, 128.60, 109.86, 98.34, 90.53, 83.41, 76.88, 75.39, 74.15, 74.01, 73.93, 67.83, 64.03, 48.60, 41.57, 32.13, 29.36, 7.26; HRMS (FAB): *m/z*: calcd for $C_{34}H_{35}O_{12}$: 635.2129; found: 635.2156 $[M+H]^+$.

10-(4-Methoxy-benzyloxy)-GC-7-benzoate (10): The compound was synthesized from **7** according to the procedure for **9**. Product was obtained as a white solid (92 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13–8.03 (m, 2 H_{AR}), 7.69–7.58 (m, 1 H_{AR}), 7.54–7.44 (m, 2 H_{AR}), 7.44–7.34 (m, 2 H_{AR}), 7.03–6.94 (m, 2 H_{AR}), 6.07 (s, 1 H, 12-H), 5.48 (dd, J = 12.8, 4.3 Hz, 1 H, 7-H), 5.40 (d, J = 9.3 Hz, 1 H, benzylic), 5.40 (d, J = 4.3 Hz, 1 H, 6-H), 4.99 (s, 1 H, 10-H), 4.70 (d, J = 9.3 Hz, 1 H, benzylic), 4.50 (d, J = 7.9 Hz, 1 H, 2-H), 4.25 (dd, J = 7.9, 3.4 Hz, 1 H, 1-H), 3.84 (s, 3 H, OMe), 3.06 (q, J = 7.0 Hz, 1 H, 14-H), 2.92 (d, J = 3.4 Hz, 1 H, 1-OH), 2.90 (s, 1 H, 3-OH), 2.24 (d, J = 12.8 Hz, 1 H, 8-H), 1.31 (d, J = 7.0 Hz, 3 H, 16-CH_3), 1.20 (s, 9 H, *t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.28, 171.00, 170.65, 164.84, 160.61, 133.94, 130.57, 130.05, 128.73, 128.59, 126.18, 114.82, 109.87, 98.31, 90.54, 83.41, 76.84, 75.05, 73.97, 73.94, 73.70, 67.81, 64.01, 55.33, 48.57, 41.61, 32.10, 29.34, 7.28; HRMS (FAB): *m/z*: calcd for $C_{35}H_{36}O_{13}$: 664.2156; found: 664.2129 $[M]^+$.

10-(2-Pyridinyl-methoxy)-GC-7-benzoate (11): The compound was synthesized from **8** according to the procedure for **9**. Product was obtained as a white solid (85 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.58 (d, J = 5.0 Hz, 1 H, 6-py), 8.42 (br s, 1 H, 1-OH), 8.08–8.00 (m, 2 H_{AR}), 7.79–7.71 (m, 1 H, 4-py), 7.65–7.56 (m, 1 H_{AR}), 7.51–7.42 (m, 2 H_{AR}), 7.35–7.28 (m, 1 H, 5-py), 7.15 (d, J = 7.9 Hz, 1 H, 3-py), 6.08 (s, 1 H, 12-H), 5.75 (d, J = 4.4 Hz, 1 H, 6-H), 5.68 (d, J = 13.1 Hz, 1 H, benzylic), 5.48 (dd, J = 12.8, 4.4 Hz, 1 H, 7-H), 5.03 (s, 1 H, 10-H), 4.89 (d, J = 13.1 Hz, 1 H, benzylic), 4.64 (d, J = 7.5 Hz, 1 H, 2-H), 4.48 (br d, J = 7.5 Hz, 1 H, 1-H), 3.09 (q, J =

7.0 Hz, 1H, 14-H), 2.88 (br s, 1H, 3-OH), 2.28 (d, J=12.8 Hz, 1H, 8-H), 1.31 (d, J=7.0 Hz, 3H, 16-CH_3), 1.18 (s, 9H, tBu); ^{13}C NMR (100 MHz, $CDCl_3$): δ=175.63, 171.53, 170.71, 164.87, 154.47, 148.85, 137.37, 133.78, 130.00, 128.84, 128.67, 123.28, 120.22, 109.94, 98.68, 92.62, 83.04, 77.53, 74.93, 74.35, 73.84, 70.65, 68.43, 64.61, 48.89, 41.76, 32.24, 29.39, 7.34; HRMS (FAB): m/z: calcd for $C_{33}H_{34}O_{12}N$: 636.2081; found: 636.2058 $[M+H]^+$.

10-Benzyloxy-isoGC-6-benzoate (12): Benzoic anhydride (23 mg, 0.102 mmol, 3 equiv) was added to a solution of **6** (18.0 mg, 0.034 mmol) in CH_2Cl_2 (0.87 mL) and iPr$_2$EtN (0.145 mL, 0.829 mmol, 24 equiv). The mixture was stirred for 11 h and then quenched with phosphate buffer (pH ~2–3, 1 mL) washed with brine. The organic phase was subsequently dried with $MgSO_4$. The crude product was purified by flash chromatography (30–50% EtOAc/hexanes) to obtain **12** as a white powder (16.6 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.15–8.09 (m, 2H$_{AR}$), 7.66–7.56 (m, 1H$_{AR}$), 7.52–7.38 (m, 7H$_{AR}$), 5.75 (s, 1H, 12-H), 5.48 (d, J=9.5 Hz, 1H, benzylic), 5.44 (d, J=4.0 Hz, 1H, 6-H), 5.17 (s, 1H, 10-H), 5.06 (d, J=3.9 Hz, 1H, 7-H), 4.91 (d, J=7.7 Hz, 1H, 2-H), 4.83 (d, J=9.5 Hz, 1H, benzylic), 4.28 (dd, J=7.6, 2.3 Hz, 1H, 1-H), 3.83 (s, 1H, 3-OH), 3.22 (q, J=7.1 Hz, 1H, 14-H), 3.22 (d, J=2.4 Hz, 1H, 1-OH), 2.30 (s, 1H, 8-H), 1.35 (d, J=7.1 Hz, 3H, 16-CH_3), 1.25 (s, 9H, tBu); ^{13}C NMR (100 MHz, $CDCl_3$): δ=176.38, 170.70, 166.56, 165.09, 134.18, 133.65, 130.19, 129.90, 129.46, 129.23, 128.80, 127.82, 110.02, 95.53, 91.96, 84.07, 78.81, 75.21, 74.29, 73.11, 69.90, 67.73, 62.86, 61.78, 41.47, 33.74, 29.71, 6.99; HRMS (FAB): m/z: calcd for $C_{34}H_{35}O_{12}$: 635.2129; found: 635.2097 $[M+H]^+$.

10-(4-Methoxy-benzyloxy)-isoGC-6-benzoate (13): The compound was synthesized from **7** according to the procedure for **12**. Product was obtained as a white solid (75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.15–8.08 (m, 2H$_{AR}$), 7.62–7.55 (m, 1H$_{AR}$), 7.48–7.39 (m, 2H$_{AR}$), 7.38–7.30 (m, 2H$_{AR}$), 6.96–6.88 (m, 2H$_{AR}$), 5.74 (s, 1H, 12-H), 5.42 (d, J=4.0 Hz, 1H, 6-H), 5.40 (d, J=9.4 Hz, 1H, benzylic), 5.16 (s, 1H, 10-H), 5.06 (d, J=4.0 Hz, 1H, 7-H), 4.91 (d, J=7.7 Hz, 1H, 2-H), 4.76 (d, J=9.4 Hz, 1H, benzylic), 4.27 (dd, J=7.7, 2.6 Hz, 1H, 1-H), 3.84 (s, 1H, 3-OH), 3.79 (s, 3H, OMe), 3.30 (d, J=2.7 Hz, 1H, 1-OH), 3.22 (q, J=7.1 Hz, 1H, 14-H), 2.30 (s, 1H, 8-H), 1.35 (d, J=7.1 Hz, 3H, 16-CH_3), 1.25 (s, 9H, tBu); ^{13}C NMR (75 MHz, $CDCl_3$): δ=176.40, 170.84, 166.61, 165.11, 160.71, 134.17, 130.98, 130.23, 128.80, 127.88, 125.78, 114.76, 110.06, 95.51, 91.98, 84.11, 78.86, 74.94, 73.86, 73.12, 69.96, 67.76, 62.91, 61.79, 55.31, 41.49, 33.76, 29.39, 6.99; HRMS (FAB): m/z: calcd for $C_{35}H_{36}O_{13}$: 664.2156; found: 664.2165 $[M]^+$.

10-Benzyloxy-isoGC-1,6-bisbenzoate (14): Benzoic anhydride (19.9 mg, 0.090 mmol, 6 equiv) was added to a solution of **6** (9.3 mg, 0.015 mmol) in CH_2Cl_2 (0.38 mL) and iPr$_2$EtN (63 μL, 0.36 mmol, 24 equiv). The mixture was stirred for 20 h and then quenched with aq. HCl (1 mL, 1 M), washed with brine. The organic phase was subsequently dried with $MgSO_4$. The crude product was purified by flash chromatography (30–50% EtOAc/1% AcOH/hexanes) to obtain **14** as a white powder (7.1 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.25–8.18 (m, 2H$_{AR}$), 7.66–7.58 (m, 3H$_{AR}$), 7.52–7.37 (m, 3H$_{AR}$), 7.21–7.13 (m, 2H$_{AR}$), 7.11–7.03 (m, 2H$_{AR}$), 7.02–6.95 (m, 3H$_{AR}$), 6.02 (d, J=5.1 Hz, 1H, 1-H), 5.79 (d, J=4.0 Hz, 1H, 6-H), 5.69 (s, 1H, 12-H), 5.03 (d, J=4.0 Hz, 1H, 7-H), 5.01 (s, 1H, 10-H), 4.88 (d, J=5.1 Hz, 1H, 2-H), 4.86 (s, 2H, benzylic), 3.66 (s, 1H, 3-OH), 3.41 (q, J=7.3 Hz, 1H, 14-H), 2.25 (s, 1H, 8-H), 1.39 (d, J=7.3 Hz, 3H, 16-CH_3), 1.08 (s, 9H, tBu); ^{13}C NMR (75 MHz, $CDCl_3$): δ=175.91, 170.05, 166.74, 165.61, 163.78, 134.37, 133.92, 133.08, 130.21, 129.58, 129.22, 128.98, 128.91, 128.62, 128.29, 128.25, 127.96, 109.00, 96.69, 92.51, 84.72, 79.05, 74.05, 73.78, 72.94, 71.02, 67.11, 64.01, 61.61, 41.42, 33.73, 29.21, 8.60; HRMS (FAB): m/z: calcd for $C_{41}H_{39}O_{13}$: 739.2391; found: 739.2381 $[M+H]^+$.

10-Benzyloxy-isoGC-1,6-bisacetate (15): Acetic anhydride (15 μL, 0.16 mmol, 10 equiv) was added to a solution of **6** (8.5 mg, 0.016 mmol) in CH_2Cl_2 (0.15 mL) and iPr$_2$EtN (28 μL, 0.16 mmol, 10 equiv). Mixture was stirred for 12 h and then quenched with aq. HCl (1 mL, 1 M), extracted with EtOAc (3×). The organic phase was subsequently dried with $MgSO_4$. The crude product was purified by flash chromatography (40–50% EtOAc/hexanes) to obtain **15** as a white powder (8.0 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.43–7.38 (m, 5H$_{AR}$), 5.66 (d, J=3.7 Hz, 1H, 1-H), 5.63 (s, 1H, 12-H), 5.51 (d, J=4.1 Hz, 1H, 6-H), 5.30 (d, J=10.6 Hz, 1H, benzylic), 5.01 (s, 1H, 10-H), 4.83 (d, J=4.1 Hz, 1H, 7-H), 4.72 (d, J=10.6 Hz, 1H, benzylic), 4.48 (d, J=3.7 Hz, 1H, 2-H), 3.31 (q, J=7.5 Hz, 1H, 14-H), 3.30 (s, 1H, 3-OH), 2.20 (s, 1H, 8-H), 2.12 (s, 3H, Ac), 1.31 (d, J=7.5 Hz, 3H, 16-CH_3), 1.30 (s, 3H, Ac), 1.19 (s, 9H, tBu); ^{13}C NMR (75 MHz, $CDCl_3$): δ=175.87, 170.07, 168.74, 167.87, 166.51, 135.22, 128.93, 128.76 (2 C), 108.60, 97.31, 92.04, 84.47, 78.99, 74.98, 74.25, 73.29, 70.13, 67.20, 63.67, 61.55, 41.21, 33.63, 29.26, 20.59, 19.52, 9.56; HRMS (FAB): m/z: calcd for $C_{31}H_{35}O_{13}$: 615.2078; found: 615.2083 $[M+H]^+$.

10-(4-Methoxy-benzyloxy)-isoGC-1,6-bisacetate (16): The compound was synthesized from **7** according to the procedure for **15**. Product was obtained as a white solid (79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.31–7.24 (m, 2H$_{AR}$), 6.93–6.86 (m, 2H$_{AR}$), 5.64 (d, J=3.8 Hz, 1H, 1-H), 5.63 (s, 1H, 12-H), 5.45 (d, J=4.1 Hz, 1H, 6-H), 5.18 (d, J=10.4 Hz, 1H, benzylic), 5.00 (s, 1H, 10-H), 4.82 (d, J=4.1 Hz, 1H, 7-H), 4.69 (d, J=10.4 Hz, 1H, benzylic), 4.50 (d, J=3.8 Hz, 1H, 2-H), 3.81 (s, 3H, OMe), 3.34 (s, 1H, 3-OH), 3.30 (q, J=7.5 Hz, 1H, 14-H), 2.20 (s, 1H, 8-H), 2.12 (s, 3H, Ac), 1.39 (s, 3H, Ac), 1.30 (d, J=7.5 Hz, 3H, 16-CH_3), 1.17 (s, 9H, tBu); ^{13}C NMR (100 MHz, $CDCl_3$): δ=175.34, 169.65, 168.21, 167.33, 165.97, 159.46, 130.36, 126.79, 113.65, 108.29, 96.83, 91.75, 84.15, 78.70, 74.18, 73.84, 72.62, 69.90, 66.87, 63.41, 61.28, 55.17, 41.08, 33.52, 29.27, 20.53, 19.62, 9.40; HSQC correlation spectra measured; HRMS (FAB): m/z: calcd for $C_{32}H_{36}O_{14}$: 644.2105; found: 644.2082 $[M]^+$.

10-Benzyloxy-GC-1-benzoate (17): iPr$_2$EtN (50 μL, 0.29 mmol, 12 equiv) was added to a solution of **12** (15.6 mg, 0.025 mmol) in DMF (0.40 mL) and mixture was stirred for 3 h at 100 °C. Solvent was removed under reduced pressure, a residue was treated with phosphate buffer (pH 2–3, 1 mL), then extracted with EtOAc (3×) and combined organic layers were dried with $MgSO_4$. The crude product was purified by flash chromatography (30–50% EtOAc/hexanes) to obtain **17** as a white solid (12.2 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.64–7.59 (m, 2H$_{AR}$), 7.51–7.45 (m, 1H$_{AR}$), 7.31–7.25 (m, 2H$_{AR}$), 6.98–6.91 (m, 2H$_{AR}$), 6.88–6.83 (m, 3H$_{AR}$), 6.03 (s, 1H, 12-H), 5.89 (d, J=6.1 Hz, 1H, 1-H), 5.46 (d, J=4.4 Hz, 1H, 6-H), 5.17 (d, J=11.0 Hz, 1H, benzylic), 4.85 (s, 1H, 10-H), 4.70 (d, J=6.1 Hz, 1H, 2-H), 4.56 (d, J=10.9 Hz, 1H, benzylic), 4.42–4.33 (m, 1H, 7-H), 3.28 (q, J=7.2 Hz, 1H, 14-H), 3.4–2.9 (br s, 1H, 3-OH), 2.65–2.3 (br s, 1H, 7-OH), 1.76 (d, J=12.3 Hz, 1H, 8-H), 1.33 (d, J=7.2 Hz, 3H, 16-CH_3), 1.15 (s, 9H, tBu); ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.91, 170.70, 170.25, 163.47, 134.66, 133.23, 129.56, 128.70, 128.34, 128.24, 128.11, 128.02, 109.34, 99.62, 92.14, 84.27, 80.32, 75.64, 75.25, 74.30, 73.55, 66.47, 65.09, 50.57, 41.20, 32.34, 29.13, 7.94; HRMS (FAB): m/z: calcd for $C_{34}H_{35}O_{12}$: 635.2129; found: 635.2148 $[M+H]^+$.

10-(4-Methoxy-benzyloxy)-GC-1-benzoate (18): The compound was synthesized from **13** according to the procedure for **17**. Product was obtained as a white solid (80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.64–7.58 (m, 2H$_{AR}$), 7.52–7.45 (m, 1H$_{AR}$), 7.32–7.25 (m, 2H$_{AR}$), 6.91–6.85 (m, 2H$_{AR}$), 6.39–6.33 (m, 2H$_{AR}$), 6.02 (s, 1H, 12-H), 5.84 (d, J=6.2 Hz, 1H, 1-H), 5.44 (d, J=4.4 Hz, 1H, 6-H), 5.10 (d, J=10.5 Hz, 1H, benzylic), 4.83 (s, 1H, 10-H), 4.68 (d, J=6.2 Hz, 1H, 2-H), 4.47 (d, J=10.5 Hz, 1H, benzylic), 4.42–4.33 (m, 1H, 7-H), 3.60 (s, 3H, OMe), 3.28 (q, J=7.1 Hz, 1H, 14-H), 3.09 (s, 1H, 3-OH), 2.37 (d, J=12.0 Hz, 1H, 7-OH), 1.74 (d, J=12.3 Hz, 1H, 8-H), 1.33 (d, J=7.1 Hz, 3H, 16-CH_3), 1.18 (s, 9H, tBu); ^{13}C NMR (125 MHz, $CDCl_3$): δ=174.72, 170.67, 170.31, 163.43, 159.24, 133.01, 129.88, 129.57, 128.71, 128.18, 126.84, 113.44, 109.33, 99.43, 92.11, 84.25, 80.32, 75.62, 74.99, 74.24, 73.31, 66.39, 65.09, 54.81, 50.65, 41.17, 32.34, 29.17, 7.85; HRMS (FAB): m/z: calcd for $C_{35}H_{36}O_{13}$: 664.2156; found: 664.2170 $[M]^+$.

GC-7-Benzoate (19): An aq. solution of $(NH_4)_2Ce(NO_3)_6$ (14.7 μL, 24 μmol, 2 equiv, 1.63 M) was added to a solution of **10** (8.0 mg, 12.0 μmol) in acetonitrile (150 μL) and $CHCl_3$ (49 μL). The mixture was stirred for 14 h, volatiles were removed under reduced pressure and residue was purified by flash chromatography (30–100% EtOAc/1% AcOH/hexanes) to obtain **19** as a white powder (4.4 mg, 68%). ^{1}H NMR (400 MHz, CD_3OD): δ=8.11–8.05 (m, 2H$_{AR}$), 7.70–7.62 (m, 1H$_{AR}$), 7.57–7.49 (m, 2H$_{AR}$), 6.20 (s, 1H, 12-H), 5.54–5.46 (m, 2H, 6-H and 7-H), 5.19 (s, 1H, 10-H), 4.57 (d, J=7.6 Hz, 1H, 2-H), 4.22 (d, J=7.6 Hz, 1H, 1-H), 3.02 (q, J=7.1 Hz, 1H, 14-H), 2.29–2.22 (m, 1H, 8-H), 1.23 (d, J=7.1 Hz, 3H, 16-CH_3), 1.18 (s, 9H, tBu); HSQC correlation spectra measured; HRMS (FAB): m/z: calcd for $C_{27}H_{28}O_{12}Na$: 567.1478; found: 567.1472 $[M+Na]^+$.

IsoGC-6-benzoate (20): An aq. solution of $(NH_4)_2Ce(NO_3)_6$ (6.2 μL, 10 μmol, 2 equiv, 1.63 M) was added to a solution of **13** (3.3 mg, 5.0 μmol)

in acetonitrile (63 μL) and $CHCl_3$ (20 μL). The mixture was stirred for 3 h, volatiles were removed under reduced pressure and residue was purified by flash chromatography (30–70% EtOAc/1% AcOH/hexanes) to obtain **20** as a white powder (2.2 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18–8.11 (m, 2H_{AR}), 7.63–7.55 (m, 1H_{AR}), 7.48–7.40 (m, 2H_{AR}), 5.75 (s, 1H, 12-H), 5.64 (d, J = 3.9 Hz, 1H, 6-H), 5.30 (s, 1H, 10-H), 5.06 (d, J = 3.9 Hz, 1H, 7-H), 5.00 (d, J = 7.7 Hz, 1H, 2-H), 4.26 (d, J = 7.7 Hz, 1H, 1-H), 3.78 (s, 1H, 3-OH), 3.40 (q, J = 7.1 Hz, 1H, 14-H), 2.29 (s, 1H, 8-H), 1.37 (d, J = 7.1 Hz, 3H, 16-CH_3), 1.26 (s, 9H, tBu); HSQC correlation spectra measured; HRMS (FAB): m/z: calcd for $C_{27}H_{29}O_{12}$: 545.1659; found: 545.1666 $[M+H]^+$.

GC-1-Benzoate (21): An aq. solution of $(NH_4)_2Ce(NO_3)_6$ (9.8 μL, 16 μmol, 2 equiv, 1.63 M) was added to a solution of **18** (5.3 mg, 8.0 μmol) in acetonitrile (100 μL) and $CHCl_3$ (32 μL). The mixture was stirred for 1.5 h, aq. solution of $(NH_4)_2Ce(NO_3)_6$ (4.9 μL, 8 μmol, 1 equiv, 1.63 M) was added and mixture was further stirred for 12 h. Volatiles were removed under reduced pressure and residue was purified by flash chromatography (40–70% EtOAc/hexanes) to obtain **21** as a white powder (2.6 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98–7.90 (m, 2H_{AR}), 7.67–7.58 (m, 1H_{AR}), 7.51–7.41 (m, 2H_{AR}), 6.05 (s, 1H, 12-H), 5.77 (d, J = 6.8 Hz, 1H, 1-H), 5.47 (d, J = 4.3 Hz, 1H, 6-H), 5.09 (d, J = 1.9 Hz, 1H, 10-H), 4.77 (d, J = 6.8 Hz, 1H, 2-H), 4.40–4.28 (m, 1H, 7-H), 3.56 (d, J = 1.9 Hz, 1H, 10-OH), 3.22 (q, J = 7.1 Hz, 1H, 14-H), 2.86 (s, 1H, 3-OH), 2.25 (d, J = 11.7 Hz, 1H, 7-OH), 1.75 (d, J = 12.3 Hz, 1H, 8-H), 1.33 (d, J = 7.1 Hz, 3H, 16-CH_3), 1.19 (s, 9H, tBu); HSQC correlation spectra measured; HRMS (FAB): m/z: calcd for $C_{27}H_{29}O_{12}$: 545.1659; found: 545.1641 $[M+H]^+$.

7-(4-Nitro-phenoxycarbonyloxy)-10-Benzyloxy-GC (22): A solution of p-nitrophenyl chloroformate (39.6 mg, 0.195 mmol, 3 equiv) in CH_2Cl_2 (0.3 mL) was added to a solution of **6** (34.7 mg, 0.065 mmol) in CH_2Cl_2 (0.82 mL) and pyridine (187 μL, 2.31 mmol, 35 equiv). The mixture was stirred for 50 min and then quenched with aq. HCl (2 mL, 1 M), extracted with EtOAc (3×). The combined organic layers were subsequently dried with $MgSO_4$. The crude product was recrystallized from $CHCl_3$ to obtain **22** as a white crystals (27.8 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.36–8.27 (m, 2H_{AR}), 7.50–7.32 (m, 7H_{AR}), 6.07 (s, 1H, 12-H), 5.47 (d, J = 9.4 Hz, 1H, benzylic), 5.47 (d, J = 4.3 Hz, 1H, 6-H), 5.08 (dd, J = 12.8, 4.3 Hz, 1H, 7-H), 4.99 (s, 1H, 10-H), 4.72 (d, J = 9.4 Hz, 1H, benzylic), 4.51 (d, J = 7.8 Hz, 1H, 2-H), 4.25 (dd, J = 7.8, 3.5 Hz, 1H, 1-H), 3.05 (q, J = 7.0 Hz, 1H, 14-H), 2.88 (br s, 1H, 3-OH), 2.79 (d, J = 3.5 Hz, 1H, 1-OH), 2.18 (d, J = 12.8 Hz, 1H, 8-H), 1.32 (d, J = 7.0 Hz, 3H, 16-CH_3), 1.23 (s, 9H, tBu).

7-Methylcarbamoyloxy-10-benzyloxy-GC (23): $MeNH_2$ in THF (14 μL, 28 μmol, 3 equiv, 2 M) was added to a solution of **22** (6.4 mg, 9.3 μmol) in THF (0.17 mL). The mixture was stirred for 25 min and then quenched with sat. aq. NH_4Cl, extracted with EtOAc (3×) and dried with $MgSO_4$. The crude product was purified by flash chromatography (40–50% EtOAc/hexanes) to obtain **23** as a white solid (4.8 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.37 (m, 5H_{AR}), 6.02 (s, 1H, 12-H), 5.44 (d, J = 9.4 Hz, 1H, benzylic), 5.28 (d, J = 4.4 Hz, 1H, 6-H), 5.21 (dd, J = 12.8, 4.4 Hz, 1H, 7-H), 4.96 (s, 1H, 10-H), 4.84 (br q, J ~4.8 Hz, 1H, -NH-), 4.73 (d, J = 9.4 Hz, 1H, benzylic), 4.49 (d, J = 7.8 Hz, 1H, 2-H), 4.21 (dd, J = 7.8, 3.4 Hz, 1H, 1-H), 3.03 (q, J = 7.0 Hz, 1H, 14-H), 2.92 (s, 1H, 3-OH), 2.86 (d, J = 4.9 Hz, 3H, CH_3), 2.80 (d, J = 3.4 Hz, 1H, 1-OH), 2.00 (d, J = 12.8 Hz, 1H, 8-H), 1.30 (d, J = 7.0 Hz, 3H, 16-CH_3), 1.16 (s, 9H, tBu); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.17, 171.04, 170.59, 154.68, 134.15, 129.78, 129.53, 128.82, 109.92, 98.37, 90.61, 83.41, 77.30, 75.36, 74.20, 74.10, 74.02, 67.65, 63.90, 48.50, 41.58, 32.12, 29.31, 27.72, 7.25; HRMS (FAB): m/z: calcd for $C_{29}H_{34}O_{12}N$: 588.2081; found: 588.2069 $[M+H]^+$.

7-*tert*-Butylcarbamoyloxy-10-benzyloxy-GC (24): tBuNH_2 (3.4 μL, 32 μmol, 4 equiv) was added to a solution of **22** (5.5 mg, 7.9 μmol) in THF (0.16 mL). The mixture was stirred for 40 min and then quenched with aq. HCl (1 mL, 1 M), extracted with EtOAc (3×) and dried with $MgSO_4$. The crude product was purified by flash chromatography (30–50% EtOAc/hexanes) to obtain **24** as a white solid (4.4 mg, 88%). The product was further purified by reverse-phase HPLC. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48–7.38 (m, 5H_{AR}), 6.02 (s, 1H, 12-H), 5.43 (d, J = 9.5 Hz, 1H, benzylic), 5.28 (d, J = 4.2 Hz, 1H, 6-H), 5.18 (dd, J = 12.5, 4.2 Hz, 1H, 7-H), 4.96 (s, 1H, 10-H), 4.79 (s, 1H, -NH-), 4.75 (d, J = 9.5 Hz, 1H, benzylic), 4.50 (d, J = 7.8 Hz, 1H, 2-H), 4.21 (dd, J = 7.9, 3.4 Hz, 1H, 1-H), 3.04 (q, J = 7.0 Hz, 1H, 14-H), 2.81 (d, J = 3.4 Hz, 1H, 1-OH), 2.69 (s, 1H, 3-OH), 1.98 (d, J = 12.8 Hz, 1H, 8-H), 1.35 (s, 9H, tBu), 1.30 (d, J = 7.0 Hz, 3H, 16-CH_3), 1.15 (s, 9H, tBu); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.08, 171.09, 170.62, 152.11, 134.16, 129.73, 129.50, 128.85, 109.97, 98.34, 90.56, 83.43, 77.56, 75.39, 74.10, 74.07, 73.38, 67.65, 63.95, 50.93, 48.65, 41.53, 32.10, 29.33, 28.82, 7.21; HSQC correlation spectra measured; HRMS (FAB): m/z: calcd for $C_{32}H_{39}O_{12}NNa$: 652.2370; found: 652.2368 $[M+Na]^+$.

7-(Morpholine-4-carbonyloxy)-10-benzyloxy-GC (25): Morpholine (2 μL, 23 μmol, 3 equiv) was added to a solution of **22** (5.2 mg, 7.5 μmol) in THF (0.15 mL). The mixture was stirred for 25 min and then quenched with aq. HCl (1 mL, 1 M), extracted with EtOAc (3×) and dried with $MgSO_4$. The crude product was purified by flash chromatography (40–50% EtOAc/hexanes) to obtain **25** as a white solid (6.0 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.38 (m, 5H_{AR}), 6.03 (s, 1H, 12-H), 5.44 (d, J = 9.4 Hz, 1H, benzylic), 5.32–5.23 (m, 2H, 6-H and 7-H), 4.97 (s, 1H, 10-H), 4.74 (d, J = 9.4 Hz, 1H, benzylic), 4.48 (d, J = 7.8 Hz, 1H, 2-H), 4.22 (dd, J = 7.8, 3.5 Hz, 1H, 1-H), 3.77–3.33 (m, 8H, morph.), 3.04 (q, J = 7.0 Hz, 1H, 14-H), 2.93 (s, 1H, 3-OH), 2.80 (d, J = 3.5 Hz, 1H, 1-OH), 2.09–2.00 (m, 1H, 8-H), 1.30 (d, J = 7.0 Hz, 3H, 16-CH_3), 1.17 (s, 9H, tBu); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.16, 171.02, 170.53, 152.99,134.10, 129.78, 129.51, 128.80, 109.88, 98.39, 90.58, 83.40, 77.14, 75.30, 74.68, 74.06, 73.97, 67.56, 66.59 (morph.), 66.48 (morph.), 63.94, 48.62, 44.48 (morph.), 44.21 (morph.), 41.57, 32.13, 29.31, 7.27; HRMS (FAB): m/z: calcd for $C_{32}H_{38}O_{13}N$: 644.2343; found: 644.2333 $[M+H]^+$.

7-(Piperidine-carbonyloxy)-10-benzyloxy-GC (26): Piperidine (2.1 μL, 22 μmol, 3 equiv) was added to a solution of **22** (5.0 mg, 7.2 μmol) in THF (0.15 mL). The mixture was stirred for 30 min and then quenched with aq. HCl (1 mL, 1 M), extracted with EtOAc (3×) and dried with $MgSO_4$. The crude product was purified by flash chromatography (30–40% EtOAc/hexanes) to obtain **26** as a white solid (3.8 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.37 (m, 5H_{AR}), 6.03 (s, 1H, 12-H), 5.43 (d, J = 9.4 Hz, 1H, benzylic), 5.32–5.23 (m, 2H, 6-H and 7-H), 4.97 (s, 1H, 10-H), 4.74 (d, J = 9.4 Hz, 1H, benzylic), 4.48 (d, J = 7.8 Hz, 1H, 2-H), 4.21 (dd, J = 7.8, 3.4 Hz, 1H, 1-H), 3.57–3.33 (m, 4H, piper.), 3.04 (q, J = 7.0 Hz, 1H, 14-H), 2.79 (d, J = 3.4 Hz, 1H, 1-OH), 2.78 (s, 1H, 3-OH), 2.10–1.99 (m, 1H, 8-H), 1.71–1.40 (m, 6H, piper.), 1.30 (d, J = 7.0 Hz, 3H, 16-CH_3), 1.17 (s, 9H, tBu); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.14, 171.12, 170.63, 152.94, 134.13, 129.73, 129.50, 128.80, 109.93, 98.37, 90.58, 83.39, 77.23, 75.33, 74.37, 74.04, 74.01, 67.57, 63.97, 48.66, 45.20 (piper.), 41.56, 32.12, 29.31, 25.89 (piper.), 25.55 (piper.), 24.22 (piper.), 7.25; HRMS (FAB): m/z: calcd for $C_{33}H_{40}O_{12}N$: 642.2551; found: 642.2579 $[M+H]^+$.

10-Benzyloxy-isoGC-1,6-carbonate (27): A solution of p-nitrophenyl chloroformate (11.0 mg, 54.6 μmol, 3 equiv) in CH_2Cl_2 (50 μL) was added to a solution of **6** (9.6 mg, 18.2 μmol) in CH_2Cl_2 (113 μL) and iPr$_2$EtN (19.1 μL, 0.109 mmol, 6 equiv). The mixture was stirred for 15 min and then quenched with aq. HCl (1 mL, 1 M), extracted with EtOAc (3×) and dried with $MgSO_4$. The crude product was purified by flash chromatography (30–50% EtOAc/hexanes) to obtain **27** as a white solid (9.3 mg, 92%, 82% purity). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.28 (m, 5H_{AR}), 5.82 (s, 1H), 5.63 (s, 1H), 5.49 (d, J = 10.6 Hz, 1H), 5.05 (s, 1H), 4.88 (d, J = 4.0 Hz, 1H), 4.79 (d, J = 10.6 Hz, 1H), 4.76 (d, J = 4.0 Hz, 1H), 4.73 (s, 1H), 3.26 (q, J = 7.8 Hz, 1H), 2.96 (s, 1H), 2.28 (s, 1H), 1.35 (d, J = 7.8 Hz, 3H), 1.11 (s, 9H, tBu); MS (FAB): m/z: calcd for $C_{28}H_{29}O_{12}$: 557.17; found: 557.56 $[M+H]^+$.

1-Methylcarbamoyloxy-10-benzyloxy-GC (28): A solution of p-nitrophenyl chloroformate (10.6 mg, 52.6 μmol, 3 equiv) in CH_2Cl_2 (50 μL) was added to a solution of **6** (9.3 mg, 17.6 μmol) in CH_2Cl_2 (110 μL) and iPr$_2$EtN (18.4 μL, 0.105 mmol, 6 equiv). The mixture was stirred for 15 min and $MeNH_2$ (2 M in THF, 26 μL, 52.6 μmol, 3 equiv) and THF (80 μL) were added. The mixture was then stirred for additional 25 min and then quenched with aq. HCl (1 mL, 1 M), extracted with EtOAc (3×) and dried with $MgSO_4$. The crude product was purified by flash chromatography (50–100% EtOAc/hexanes) to obtain **28** as a white solid (6.6 mg, 64%). ^{1}H NMR (300 MHz, 320 K, $CDCl_3$): δ = 7.42–7.2 (m, 5H_{AR}), 5.96 (s, 1H, 12-H), 5.55 (d, J = 6.0 Hz, 1H, 1-H), 5.39 (d, J = 11.5 Hz, 1H, benzylic), 5.19 (d, J = 4.3 Hz, 1H, 6-H), 4.82 (s, 1H, 10-H), 4.64 (br d, J = 11.5 Hz, 1H, benzylic), 4.62 (d, J = 6.0 Hz, 1H, 2-H), 4.38–4.25 (m, 1H, 7-H), 4.26 (m, 1H, -NH-), 3.20 (q, J = 7.2 Hz, 1H, 14-H), 2.92 (s, 1H, 3-OH), 2.29 (br d, J ~4.1 Hz, 3H, CH_3), 2.16 (d, J = 11.5 Hz,

1H, 7-OH), 1.69 (d, J=12.3 Hz, 1H, 8-H), 1.31 (d, J=7.2 Hz, 3H, 16-CH_3), 1.15 (s, 9H, *t*Bu); HSQC correlation spectra was measured; HRMS (FAB): *m/z*: calcd for $C_{29}H_{34}O_{12}N$: 588.2081; found: 588.2103 $[M+H]^+$.

1-*tert*-Butylcarbamoyloxy-10-benzyloxy-GC (29): A solution of *p*-nitrophenyl chloroformate (4.2 mg, 21 μmol, 3 equiv) in CH_2Cl_2 (20 μL) was added to a solution of **6** (3.7 mg, 7.0 μmol) in CH_2Cl_2 (50 μL) and *i*Pr_2EtN (7.3 μL, 42 μmol, 6 equiv). The mixture was stirred for 15 min and *t*BuNH_2 (7.4 μL, 70 μmol, 10 equiv) and THF (40 μL) were added. The mixture was then stirred for additional 12 h and then quenched with aq. HCl (1 mL, 1 M), extracted with EtOAc (3×) and dried with $MgSO_4$. The crude product was purified by flash chromatography (40–50% EtOAc/hexanes) to obtain **29** as a white solid (2.6 mg, 59%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.40–7.22 (m, 5H_{AR}), 5.93 (s, 1H, 12-H), 5.55 (d, J=5.1 Hz, 1H, 1-H), 5.32 (d, J=12.3 Hz, 1H, benzylic), 5.22 (d, J=4.3 Hz, 1H, 6-H), 4.81 (br d, J=11.5 Hz, 1H, benzylic), 4.79 (s, 1H, 10-H), 4.67 (d, J=5.1 Hz, 1H, 2-H), 4.53 (br s, 1H, -NH-), 4.36–4.24 (m, 1H, 7-H), 3.21 (q, J=7.3 Hz, 1H, 14-H), 3.17 (br s, 1H, 3-OH), 2.13 (br d, J=12.0 Hz, 1H, 7-OH), 1.65 (d, J=12.3 Hz, 1H, 8-H), 1.32 (d, J=7.3 Hz, 3H, 16-CH_3), 1.12 (s, 9H, *t*Bu), 1.03 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.20, 170.34, 169.47, 151.09, 135.55, 128.12 (2), 127.85, 108.52, 99.96, 91.90, 84.08, 80.10, 75.19, 74.94, 74.61, 66.53, 65.05, 50.75, 50.43, 40.94, 32.16, 28.97, 28.49, 8.57; HRMS (FAB): *m/z*: calcd for $C_{32}H_{40}O_{12}N$: 630.2551; found: 630.2554 $[M+H]^+$.

1-(Morpholine-4-carbonyloxy)-10-benzyloxy-GC (30): A solution of *p*-nitrophenyl chloroformate (7.2 mg, 36 μmol, 3 equiv) in CH_2Cl_2 (50 μL) was added to a solution of **6** (6.3 mg, 12.0 μmol) in CH_2Cl_2 (60 μL) and *i*Pr_2EtN (12.5 μL, 72 μmol, 6 equiv). The mixture was stirred for 15 min and morpholine (6.3 μL, 72 μmol, 6 equiv) was added. The mixture was then stirred for additional 1 h and then quenched with aq. HCl (1 mL, 1 M), extracted with EtOAc (3×) and dried with $MgSO_4$. The crude product was purified by flash chromatography (50–100% EtOAc/hexanes) to obtain **30** as a white solid (6.0 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.41–7.31 (m, 3H_{AR}), 7.29–7.21 (m, 2H_{AR}), 5.99 (s, 1H, 12-H), 5.60 (d, J=5.6 Hz, 1H, 1-H), 5.40 (d, J=11.5 Hz, 1H, benzylic), 5.15 (d, J=4.4 Hz, 1H, 6-H), 4.85 (s, 1H, 10-H), 4.71 (d, J=5.6 Hz, 1H, 2-H), 4.62 (d, J=11.5 Hz, 1H, benzylic), 4.38–4.28 (m, 1H, 7-H), 3.60 (s, 1H, 3-OH), 3.5–3.2 (m, 6H, morph.), 3.21 (q, J=7.2 Hz, 1H, 14-H), 2.78–2.67 (m, 1H, morph.), 2.50 (d, J=11.7 Hz, 1H, 7-OH), 2.49–2.38 (m, 1H, morph.), 1.72 (d, J=12.3 Hz, 1H, 8-H), 1.32 (d, J=7.2 Hz, 3H, 16-CH_3), 1.18 (s, 9H, *t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$): δ=175.04, 170.60, 169.99, 152.15, 136.20, 128.65, 128.42, 127.44, 109.11, 99.90, 92.16, 84.12, 80.21, 75.85, 75.65, 73.24, 66.51, 66.15, 65.87, 65.07, 50.40, 43.73, 43.48, 41.19, 32.40, 29.16, 8.30; HRMS (FAB): *m/z*: calcd for $C_{32}H_{38}O_{13}N$: 644.2343; found: 644.2355 $[M+H]^+$.

1-(Piperidine-carbonyloxy)-10-benzyloxy-GC (31): A solution of *p*-nitrophenyl chloroformate (13 mg, 64 μmol, 3 equiv) in CH_2Cl_2 (80 μL) was added to a solution of **6** (11.3 mg, 21.3 μmol) in CH_2Cl_2 (112 μL) and *i*Pr_2EtN (22.4 μL, 128 μmol, 6 equiv). The mixture was stirred for 15 min and piperidine (12.6 μL, 128 μmol, 6 equiv) and THF (80 μL) were added. The mixture was then stirred for additional 40 min and then quenched with aq. HCl (1 mL, 1 M), extracted with EtOAc (3×) and dried with $MgSO_4$. The crude product was purified by flash chromatography (35–70% EtOAc/hexanes) to obtain **31** as a white solid (6.8 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.39–7.28 (m, 3H_{AR}), 7.28–7.21 (m, 2H_{AR}), 5.97 (s, 1H, 12-H), 5.57 (d, J=5.3 Hz, 1H, 1-H), 5.38 (d, J=11.5 Hz, 1H, benzylic), 5.14 (d, J=4.4 Hz, 1H, 6-H), 4.84 (s, 1H, 10-H), 4.72 (d, J=5.3 Hz, 1H, 2-H), 4.65 (d, J=11.5 Hz, 1H, benzylic), 4.37–4.28 (m, 1H, 7-H), 3.57 (s, 1H, 3-OH), 3.50–3.38 (m, 1H, piper.), 3.35–3.23 (m, 1H, piper.), 3.22 (q, J=7.3 Hz, 1H, 14-H), 2.60–2.49 (m, 1H, piper.), 2.47–2.37 (m, 1H, piper.), 2.36 (d, J=12.0 Hz, 1H, 7-OH), 1.70 (d, J=12.3 Hz, 1H, 8-H), 1.61–1.50 (m, 1H, piper.), 1.45–1.25 (m, 5H, piper.), 1.32 (d, J=7.3 Hz, 3H, 16-CH_3), 1.16 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ=175.00, 170.80, 170.02, 152.22, 136.16, 128.54, 128.17, 127.75, 108.98, 100.23, 92.23, 84.26, 80.39, 76.07, 75.64, 75.44, 73.12, 66.80, 65.17, 50.47, 44.64, 44.49, 41.15, 32.38, 29.17, 25.52, 24.96, 23.89, 8.53; HRMS (FAB): *m/z*: calcd for $C_{33}H_{40}O_{12}N$: 642.2551; found: 642.2521 $[M+H]^+$.

7-(4-Nitro-phenoxycarbonyloxy)-10-(4-methoxy-benzyloxy)-GC (32): A solution of *p*-nitrophenyl chloroformate (34.2 mg, 0.170 mmol, 2 equiv) in CH_2Cl_2 (0.2 mL) was added to a solution of **7** (47.6 mg, 0.085 mmol) in CH_2Cl_2 (0.53 mL) and pyridine (121 μL, 1.50 mmol, 18 equiv) at 0 °C. The mixture was allowed to warm up slowly to room temperature while stirring. After 2.5 h the reaction was quenched with aq. HCl (2 mL, 1 M), extracted with EtOAc (3×) and dried with $MgSO_4$. The crude product was purified by flash chromatography (30–50% EtOAc/hexanes) to obtain **32** as a white powder (42.6 mg, 69%) and unreacted starting material **7** (9.5 mg, 20%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.35–8.27 (m, 2H_{AR}), 7.46–7.38 (m, 2H_{AR}), 7.35–7.28 (m, 2H_{AR}), 6.95–6.88 (m, 2H_{AR}), 6.06 (s, 1H, 12-H), 5.45 (d, J=4.3 Hz, 1H, 6-H), 5.38 (d, J=9.3 Hz, 1H, benzylic), 5.05 (dd, J=12.8, 4.3 Hz, 1H, 7-H), 4.98 (s, 1H, 10-H), 4.66 (d, J=9.3 Hz, 1H, benzylic), 4.51 (d, J=7.8 Hz, 1H, 2-H), 4.25 (dd, J=7.8, 3.5 Hz, 1H, 1-H), 3.80 (s, 3H, OMe), 3.06 (q, J=7.0 Hz, 1H, 14-H), 3.04 (s, 1H, 3-OH), 2.87 (d, J=3.5 Hz, 1H, 1-OH), 2.17 (d, J=12.8 Hz, 1H, 8-H), 1.30 (d, J=7.0 Hz, 3H, 16-CH_3), 1.22 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.90, 170.11, 170.07, 160.41, 154.72, 150.82, 145.52, 130.36, 125.94, 125.28, 121.48, 114.71, 109.65, 98.23, 90.48, 83.43, 78.17, 75.69, 74.93, 73.90, 73.72, 67.77, 63.85, 55.38, 48.48, 41.70, 32.24, 29.42, 7.46.

7-Methylcarbamoyloxy-10-(4-methoxy-benzyloxy)-GC (33): The compound was synthesized from **32** according to the procedure for **23**. Product was obtained as a white solid (74%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.36 (d, J=8.5 Hz, 2H_{AR}), 6.95 (d, J=8.5 Hz, 2H_{AR}), 6.01 (s, 1H, 12-H), 5.35 (d, J=9.3 Hz, 1H, benzylic), 5.26 (d, J=4.3 Hz, 1H, 6-H), 5.19 (dd, J=12.8, 4.4 Hz, 1H, 7-H), 4.94 (s, 1H, 10-H), 4.83 (br q, J ~4.8 Hz, 1H, -NH-), 4.67 (d, J=9.3 Hz, 1H, benzylic), 4.49 (d, J=7.8 Hz, 1H, 2-H), 4.20 (dd, J=7.8, 3.3 Hz, 1H, 1-H), 3.82 (s, 3H, OMe), 3.03 (q, J=7.0 Hz, 1H, 14-H), 2.90 (s, 1H, 3-OH), 2.89–2.80 (m, 4H, CH_3 and 1-OH), 1.99 (d, J=12.8 Hz, 1H, 8-H), 1.29 (d, J=7.0 Hz, 3H, 16-CH_3), 1.15 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.69, 170.52, 170.15, 160.10, 154.19, 130.13, 125.81, 114.45, 109.55, 98.01, 90.31, 83.15, 74.78, 73.96, 73.77, 73.40, 67.43, 63.70, 55.14, 48.35, 41.47, 32.01, 29.21, 27.61, 7.24; HRMS (FAB): *m/z*: calcd for $C_{30}H_{34}O_{13}N$: 616.2030; found: 616.2056 $[M-H]^+$.

7-*tert*-Butylcarbamoyloxy-10-(4-methoxy-benzyloxy)-GC (34): The compound was synthesized from **32** according to the procedure for **24**. Product was obtained as a white solid (77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.41–7.35 (m, 2H_{AR}), 6.99–6.91 (m, 2H_{AR}), 6.01 (s, 1H, 12-H), 5.34 (d, J=9.3 Hz, 1H, benzylic), 5.26 (d, J=4.3 Hz, 1H, 6-H), 5.15 (dd, J=12.8, 4.2 Hz, 1H, 7-H), 4.94 (s, 1H, 10-H), 4.81 (s, 1H, -NH-), 4.69 (d, J=9.3 Hz, 1H, benzylic), 4.50 (d, J=7.9 Hz, 1H, 2-H), 4.20 (dd, J=7.9, 3.4 Hz, 1H, 1-H), 3.82 (s, 3H, OMe), 3.03 (q, J=7.0 Hz, 1H, 14-H), 2.94 (s, 1H, 3-OH), 2.88 (d, J=3.4 Hz, 1H, 1-OH), 1.97 (d, J=12.8 Hz, 1H, 8-H), 1.35 (s, 9H, *t*Bu), 1.29 (d, J=7.0 Hz, 3H, 16-CH_3), 1.15 (s, 9H, *t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$): δ=175.29, 171.18, 170.78, 160.56, 152.11, 130.63, 126.24, 114.76, 109.96, 98.34, 90.58, 83.42, 77.55, 75.02, 74.01, 73.62, 73.35, 67.61, 63.90, 55.30, 50.89, 48.60, 41.60, 32.08, 29.31, 28.79, 7.27; HRMS (FAB): *m/z*: calcd for $C_{33}H_{41}O_{13}N$: 659.2578; found: 659.2582 $[M]^+$.

7-(Morpholine-4-carbonyloxy)-10-(4-methoxy-benzyloxy)-GC (35): The compound was synthesized from **32** according to the procedure for **25**. Product was obtained as a white solid (90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.36 (d, J=8.6 Hz, 2H_{AR}), 6.95 (d, J=8.6 Hz, 2H_{AR}), 6.02 (s, 1H, 12-H), 5.36 (d, J=9.3 Hz, 1H, benzylic), 5.30–5.19 (m, 2H, 6-H and 7-H), 4.95 (s, 1H, 10-H), 4.68 (d, J=9.3 Hz, 1H, benzylic), 4.48 (d, J=7.8 Hz, 1H, 2-H), 4.21 (d, J=7.8 Hz, 1H, 1-H), 3.82 (s, 3H, OMe), 3.78–3.33 (m, 8H, morph.), 3.04 (q, J=7.0 Hz, 1H, 14-H), 2.85 (br s, 2H, 3-OH and 1-OH), 2.09–1.99 (m, 1H, 8-H), 1.30 (d, J=7.0 Hz, 3H, 16-CH_3), 1.16 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.59, 170.48, 170.08, 160.11, 152.52, 130.13, 125.79, 114.45, 109.53, 98.04, 90.29, 83.15, 76.92, 74.76, 74.47, 73.76, 73.40, 67.38, 66.36 (morph.), 66.29 (morph.), 63.78, 55.14, 48.54, 44.35 (morph.), 44.08 (morph.), 41.45, 32.04, 29.23, 7.24; HRMS (FAB): *m/z*: calcd for $C_{33}H_{39}O_{14}N$: 673.2371; found: 673.2402 $[M]^+$.

7-(Piperidine-carbonyloxy)-10-(4-methoxy-benzyloxy)-GC (36): The compound was synthesized from **32** according to the procedure for **26**. Product was obtained as a white solid (86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.36 (d, J=8.7 Hz, 2H_{AR}), 6.94 (d, J=8.7 Hz, 2H_{AR}), 6.01 (s, 1H, 12-H), 5.35 (d, J=9.3 Hz, 1H, benzylic), 5.29–5.20 (m, 2H, 6-H and 7-H), 4.95 (s, 1H, 10-H), 4.68 (d, J=9.3 Hz, 1H, benzylic), 4.48 (d, J=7.9 Hz, 1H, 2-H), 4.20 (dd, J=7.9, 3.4 Hz, 1H, 1-H), 3.81 (s, 3H, OMe), 3.53–3.37 (m, 4H, piper.), 3.04 (q, J=7.0 Hz, 1H, 14-H), 2.95 (s, 1H, 3-OH),

2.86 (d, $J=3.4$ Hz, 1H, 1-OH), 2.03 (d, $J=12.2$ Hz, 1H, 8-H), 1.68–1.42 (m, 6H, piper.), 1.30 (d, $J=7.0$ Hz, 3H, 16-CH_3), 1.16 (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=174.96$, 170.85, 170.47, 160.31, 152.74, 130.39, 126.09, 114.68, 109.85, 98.32, 90.59, 83.39, 77.41, 75.01, 74.44, 74.04, 73.60, 67.62, 64.03, 55.38, 48.80, 45.25 (piper.), 41.74, 32.27, 29.47, 26.07 (piper.), 25.71 (piper.), 24.39 (piper.), 7.51; HRMS (FAB): *m/z*: calcd for $C_{34}H_{40}O_{13}N$: 670.2500; found: 670.2526 $[M-H]^+$.

1-Methylcarbamoyloxy-10-(4-methoxy-benzyloxy)-GC (38): The compound was synthesized from **7** according to the procedure for **28**. Product was obtained as a white solid (67%). ^{1}H NMR (400 MHz, $CDCl_3$, 330 K): $\delta=7.25$–7.15 (m, 2H_{AR}), 6.90–6.80 (m, 2H_{AR}), 5.94 (s, 1H, 12-H), 5.53 (d, $J=5.7$ Hz, 1H, 1-H), 5.24 (d, $J=11.1$ Hz, 1H, benzylic), 5.18 (d, $J=4.3$ Hz, 1H, 6-H), 4.79 (s, 1H, 10-H), 4.69–4.54 (m, 2H, 2-H and benzylic), 4.39 (brs, 1H, -NH-), 4.32–4.21 (m, 1H, 7-H), 3.80 (s, 3H, OMe), 3.19 (q, $J=7.2$ Hz, 1H, 14-H), 3.01 (s, 1H, 3-OH), 2.42 (brs, 3H, Me), 2.19 (d, $J=10.8$ Hz, 1H, 7-OH), 1.68 (d, $J=12.3$ Hz, 1H, 8-H), 1.30 (d, $J=7.2$ Hz, 3H, 16-CH_3), 1.13 (s, 9H, *t*Bu); ^{13}C NMR (75 MHz, CD_3OD, 320 K): $\delta=177.90$, 172.80, 172.52, 161.06, 156.56, 130.42, 114.94, 114.84, 110.68, 102.23, 94.34, 85.44, 81.36, 77.21, 77.03, 76.12, 73.68, 68.12, 66.20, 55.86, 51.35, 42.59, 33.17, 29.63, 27.31, 9.42; HRMS (FAB): *m/z*: calcd for $C_{30}H_{34}O_{13}N$: 616.2030; found: 616.2028 $[M-H]^+$.

1-*tert*-Butylcarbamoyloxy-10-(4-methoxy-benzyloxy)-GC (39): The compound was synthesized from **7** according to the procedure for **29**. Product was obtained as a white solid (60%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 7.23 (d, $J=8.6$ Hz, 2H_{AR}), 6.86 (d, $J=8.6$ Hz, 2H_{AR}), 5.91 (s, 1H, 12-H), 5.55 (d, $J=4.6$ Hz, 1H, 1-H), 5.21 (d, $J=4.3$ Hz, 1H, 6-H), 5.15 (d, $J=11.8$ Hz, 1H, benzylic), 4.82 (brd, $J=11.8$ Hz, 1H, benzylic), 4.75 (s, 1H, 10-H), 4.67 (d, $J=5.0$ Hz, 1H, 2-H), 4.62 (brs, 1H, -NH-), 4.30–4.19 (m, 1H, 7-H), 3.80 (s, 3H, OMe), 3.23 (brs, 1H, 3-OH), 3.20 (q, $J=7.3$ Hz, 1H, 14-H), 2.17 (d, $J=11.8$ Hz, 1H, 7-OH), 1.63 (d, $J=12.3$ Hz, 1H, 8-H), 1.32 (d, $J=7.3$ Hz, 3H, 16-CH_3), 1.19 (s, 9H, *t*Bu), 1.01 (s, 9H, *t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=174.94$, 171.01, 170.25, 159.72, 151.70, 130.14, 127.77, 113.88, 108.79, 100.34, 92.26, 84.41, 80.41, 75.27, 73.96, 72.16, 66.83, 65.29, 55.31, 50.92, 50.51, 41.06, 32.20, 29.02, 28.72, 8.68; HRMS (FAB): *m/z*: calcd for $C_{33}H_{40}O_{13}N$: 658.2500; found: 658.2516 $[M-H]^+$.

1-(Morpholine-4-carbonyloxy)-10-(4-methoxy-benzyloxy)-GC (40): The compound was synthesized from **7** according to the procedure for **30**. Product was obtained as a white solid (75%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.20$ (d, $J=8.5$ Hz, 2H_{AR}), 6.88 (d, $J=8.5$ Hz, 2H_{AR}), 5.97 (s, 1H, 12-H), 5.57 (d, $J=5.3$ Hz, 1H, 1-H), 5.23 (d, $J=11.0$ Hz, 1H, benzylic), 5.11 (d, $J=4.3$ Hz, 1H, 6-H), 4.82 (s, 1H, 10-H), 4.71 (d, $J=5.3$ Hz, 1H, 2-H), 4.62 (d, $J=11.0$ Hz, 1H, benzylic), 4.32–4.21 (m, 1H, 7-H), 3.82 (s, 3H, OMe), 3.57 (s, 1H, 3-OH), 3.54–3.33 (m, 5H, morph.), 3.31–3.18 (m, 1H, morph.), 3.21 (q, $J=7.2$ Hz, 1H, 14-H), 2.89–2.66 (m, 2H, morph.), 2.39 (d, $J=11.7$ Hz, 1H, 7-OH), 1.69 (d, $J=12.3$ Hz, 1H, 8-H), 1.32 (d, $J=7.2$ Hz, 3H, 16-CH_3), 1.15 (s, 9H, *t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=175.06$, 170.66, 170.21, 159.75, 152.38, 129.64, 128.01, 113.97, 108.99, 100.08, 92.15, 84.25, 80.20, 76.28, 75.54, 74.97, 72.83, 66.68, 66.21 (morph.), 65.94 (morph.), 65.12, 55.41, 50.41, 43.84 (morph.), 41.16, 32.33, 29.14, 8.49; HRMS (FAB): *m/z*: calcd for $C_{33}H_{38}O_{14}N$: 672.2292; found: 672.2307 $[M-H]^+$.

1-(Piperidine-carbonyloxy)-10-(4-methoxy-benzyloxy)-GC (41): The compound was synthesized from **7** according to the procedure for **31**. Product was obtained as a white solid (53%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 7.20 (d, $J=8.6$ Hz, 2H_{AR}), 6.87 (d, $J=8.6$ Hz, 2H_{AR}), 5.95 (s, 1H, 12-H), 5.54 (d, $J=5.0$ Hz, 1H, 1-H), 5.22 (d, $J=11.0$ Hz, 1H, benzylic), 5.10 (d, $J=4.4$ Hz, 1H, 6-H), 4.80 (s, 1H, 10-H), 4.72 (d, $J=5.0$ Hz, 1H, 2-H), 4.64 (d, $J=11.0$ Hz, 1H, benzylic), 4.32–4.22 (m, 1H, 7-H), 3.81 (s, 3H, OMe), 3.55 (s, 1H, 3-OH), 3.52–3.40 (m, 1H, piper.), 3.32–3.19 (m, 1H, piper.), 3.22 (q, $J=7.3$ Hz, 1H, 14-H), 2.77–2.56 (m, 2H, piper.), 2.25 (d, $J=12.0$ Hz, 1H, 7-OH), 1.68 (d, $J=12.3$ Hz, 1H, 8-H), 1.63–1.50 (m, 1H, piper.), 1.49–1.29 (m, 5H, piper.), 1.32 (d, $J=7.3$ Hz, 3H, 16-CH_3), 1.14 (s, 9H, *t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=174.88$, 170.81, 170.20, 159.63, 152.37, 129.89, 128.07, 113.88, 108.86, 100.36, 92.18, 84.36, 80.38, 76.45, 75.56, 74.77, 72.68, 66.95, 65.25, 55.36, 50.53, 44.84 (piper.), 44.62 (piper.), 41.11, 32.31, 29.15, 25.56 (piper.), 25.09 (piper.), 23.98 (piper.), 8.68; HRMS (FAB): *m/z*: calcd for $C_{34}H_{40}O_{13}N$: 670.2500; found: 670.2510 $[M-H]^+$.

7-Methylcarbamoyloxy-GC (42): An aq. solution of $(NH_4)_2Ce(NO_3)_6$ (10.6 μL, 17.3 μmol, 2 equiv, 1.63 M) was added to a solution of **33** (5.3 mg, 8.7 μmol) in acetonitrile (108 μL) and $CHCl_3$ (35 μL). The mixture was stirred for 1.5 h, aq. solution of $(NH_4)_2Ce(NO_3)_6$ (5.3 μL, 8.7 μmol, 1 equiv, 1.63 M) was added and mixture was further stirred for 12 h. Volatiles were removed under reduced pressure and residue was purified by flash chromatography (40–99% EtOAc/1% AcOH/hexanes) to obtain **42** as a white powder (3.0 mg, 69%). ^{1}H NMR (300 MHz, 315 K, CD_3OD): $\delta=6.11$ (s, 1H, 12-H), 5.32 (d, $J=4.3$ Hz, 1H, 6-H), 5.18 (dd, $J=12.8$, 4.3 Hz, 1H, 7-H), 5.13 (s, 1H, 10-H), 4.54 (d, $J=7.6$ Hz, 1H, 2-H), 4.18 (d, $J=7.6$ Hz, 1H, 1-H), 3.00 (q, $J=7.0$ Hz, 1H, 14-H), 2.74 (s, 3H, CH_3), 2.00 (d, $J=12.9$ Hz, 1H, 8-H), 1.22 (d, $J=7.0$ Hz, 3H, 16-CH_3), 1.14 (s, 9H, *t*Bu); HSQC correlation spectra measured; HRMS (FAB): *m/z*: calcd for $C_{22}H_{28}O_{12}N$: 498.1612; found: 498.1633 $[M+H]^+$.

7-*tert*-Butylcarbamoyloxy-GC (43): An aq. solution of $(NH_4)_2Ce(NO_3)_6$ (10.6 μL, 17.3 μmol, 2 equiv, 1.63 M) was added to a solution of **34** (5.7 mg, 8.6 μmol) in acetonitrile (108 μL) and $CHCl_3$ (35 μL). The mixture was stirred for 1.5 h, aq. solution of $(NH_4)_2Ce(NO_3)_6$ (5.3 μL, 8.7 μmol, 1 equiv, 1.63 M) was added and mixture was further stirred for 12 h. Volatiles were removed under reduced pressure and residue was purified by flash chromatography (40–70% EtOAc/1% AcOH/hexanes) to obtain **43** as a white powder (3.7 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.01$ (brs, 1H, OH), 5.98 (s, 1H, 12-H), 5.42 (brs, 1H, 6-H), 5.16 (dd, $J=12.8$, 4.1 Hz, 1H, 7-H), 5.14 (s, 1H, 10-H), 4.96 (s, 1H, -NH-), 4.69 (d, $J=7.9$ Hz, 1H, 2-H), 4.32 (brd, $J=7.9$ Hz, 1H, 1-H), 4.23 (brs, 2H, OH), 3.14 (brq, $J=7.1$ Hz, 1H, 14-H), 1.98 (d, $J=12.8$ Hz, 1H, 8-H), 1.31 (s, 9H, *t*Bu), 1.27 (d, $J=7.1$ Hz, 3H, 16-CH_3), 1.10 (s, 9H, *t*Bu); HSQC correlation spectra measured; HRMS (FAB): *m/z*: calcd for $C_{25}H_{34}O_{12}N$: 540.2081; found: 540.2098 $[M+H]^+$.

7-(Morpholine-4-carbonyloxy)-GC (44): An aq. solution of $(NH_4)_2Ce(NO_3)_6$ (10.6 μL, 17.3 μmol, 2 equiv, 1.63 M) was added to a solution of **35** (5.8 mg, 8.7 μmol) in acetonitrile (108 μL) and $CHCl_3$ (35 μL). The mixture was stirred for 1.5 h, aq. solution of $(NH_4)_2Ce(NO_3)_6$ (5.3 μL, 8.7 μmol, 1 equiv, 1.63 M) was added and mixture was further stirred for 12 h. Volatiles were removed under reduced pressure and residue was purified by flash chromatography (50–99% EtOAc/1% AcOH/hexanes) to obtain **44** as a white powder (2.9 mg, 60%). ^{1}H NMR (400 MHz, CD_3OD): $\delta=6.14$ (s, 1H, 12-H), 5.34 (d, $J=4.4$ Hz, 1H, 6-H), 5.24 (dd, $J=12.8$, 4.4 Hz, 1H, 7-H), 5.15 (s, 1H, 10-H), 4.54 (d, $J=7.6$ Hz, 1H, 2-H), 4.18 (d, $J=7.6$ Hz, 1H, 1-H), 3.73–3.37 (m, 8H, morph.), 3.00 (q, $J=7.1$ Hz, 1H, 14-H), 2.06 (d, $J=12.8$ Hz, 1H, 8-H), 1.22 (d, $J=7.1$ Hz, 3H, 16-CH_3), 1.15 (s, 9H, *t*Bu); HSQC correlation spectra measured; HRMS (FAB): *m/z*: calcd for $C_{25}H_{32}O_{13}N$: 554.1874; found: 554.1874 $[M+H]^+$.

7-(Piperidine-carbonyloxy)-GC (45): An aq. solution of $(NH_4)_2Ce(NO_3)_6$ (10.6 μL, 17.3 μmol, 2 equiv, 1.63 M) was added to a solution of **36** (5.8 mg, 8.6 μmol) in acetonitrile (108 μL) and $CHCl_3$ (35 μL). The mixture was stirred for 1.5 h, aq. solution of $(NH_4)_2Ce(NO_3)_6$ (5.3 μL, 8.7 μmol, 1 equiv, 1.63 M) was added and mixture was further stirred for 12 h. Volatiles were removed under reduced pressure and residue was purified by flash chromatography (40–70% EtOAc/1% AcOH/hexanes) to obtain **45** as a white powder (3.0 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.21$ (brs, 1H, OH), 5.98 (s, 1H, 12-H), 5.41 (brs, 1H, 6-H), 5.25 (dd, $J=12.8$, 4.3 Hz, 1H, 7-H), 5.14 (s, 1H, 10-H), 4.68 (d, $J=7.9$ Hz, 1H, 2-H), 4.36 (brs, 1H, OH), 4.32 (brd, $J=7.9$ Hz, 1H, 1-H), 3.55–3.26 (m, 4H, piper.), 3.15 (m, 1H, 14-H), 2.04 (d, $J=12.8$ Hz, 1H, 8-H), 1.75–1.40 (m, 6H, piper.), 1.26 (d, $J=7.0$ Hz, 3H, 16-CH_3), 1.11 (s, 9H, *t*Bu); HSQC correlation spectra measured; HRMS (FAB): *m/z*: calcd for $C_{26}H_{34}O_{12}N$: 552.2081; found: 552.2067 $[M+H]^+$.

1-Methylcarbamoyloxy-GC (46): An aq. solution of $(NH_4)_2Ce(NO_3)_6$ (6.9 μL, 11.2 μmol, 2 equiv, 1.63 M) was added to a solution of **38** (3.5 mg, 5.6 μmol) in acetonitrile (70 μL) and $CHCl_3$ (23 μL). The mixture was stirred for 6.5 h, aq. solution of $(NH_4)_2Ce(NO_3)_6$ (6.9 μL, 11.2 μmol, 2 equiv, 1.63 M) was added and mixture was further stirred for 12 h. Volatiles were removed under reduced pressure and residue was purified by flash chromatography (70–99% EtOAc/1% AcOH/hexanes) to obtain **46** as a white powder (2.4 mg, 86%). ^{1}H NMR (400 MHz, CD_3OD): $\delta=6.06$ (s, 1H, 12-H), 5.46 (d, $J=5.3$ Hz, 1H, 1-H), 5.22 (d, $J=4.1$ Hz, 1H, 6-H), 5.07 (s, 1H, 10-H), 4.66 (d, $J=5.5$ Hz, 1H, 2-H), 4.31 (dd, $J=12.6$, 4.1 Hz, 1H, 7-H), 3.10 (q, $J=7.2$ Hz, 1H, 14-H), 2.83–2.68 (m, 3H, Me), 1.78 (d, $J=12.5$ Hz, 1H, 8-H), 1.27 (d, $J=7.2$ Hz, 3H, 16-CH_3), 1.22 (s,

9H, *t*Bu); HSQC correlation spectra measured; HRMS (FAB): *m/z*: calcd for $C_{22}H_{28}O_{12}N$: 498.1612; found: 498.1618 $[M+H]^+$.

1-*tert*-Butylcarbamoyloxy-GC (47): An aq. solution of $(NH_4)_2Ce(NO_3)_6$ (6.9 μL, 11.2 μmol, 2 equiv, 1.63 M) was added to a solution of **39** (3.7 mg, 5.6 μmol) in acetonitrile (70 μL) and $CHCl_3$ (23 μL). The mixture was stirred for 6 h, aq. solution of $(NH_4)_2Ce(NO_3)_6$ (6.9 μL, 11.2 μmol, 2 equiv, 1.63 M) was added and mixture was further stirred for 12 h. Volatiles were removed under reduced pressure and residue was purified by flash chromatography (40–70% EtOAc/hexanes) to obtain **47** as a white powder (2.5 mg, 84%). ^{1}H NMR (400 MHz, CD_3OD): $\delta = 6.05$ (s, 1H, 12-H), 5.45 (d, $J = 5.1$ Hz, 1H, 1-H), 5.28 (d, $J = 4.2$ Hz, 1H, 6-H), 5.06 (s, 1H, 10-H), 4.64 (d, $J = 5.1$ Hz, 1H, 2-H), 4.33 (dd, $J = 12.4$, 4.2 Hz, 1H, 7-H), 3.10 (q, $J = 7.3$ Hz, 1H, 14-H), 1.77 (d, $J = 12.4$ Hz, 1H, 8-H), 1.34 (s, 9H, *t*Bu), 1.27 (d, $J = 7.3$ Hz, 3H, 16-CH_3), 1.22 (s, 9H, *t*Bu); HSQC correlation spectra measured; HRMS (FAB): *m/z*: calcd for $C_{25}H_{34}O_{12}N$: 540.2081; found: 540.2075 $[M+H]^+$.

1-(Morpholine-4-carbonyloxy)-GC (48): An aq. solution of $(NH_4)_2Ce(NO_3)_6$ (11.8 μL, 19.2 μmol, 2 equiv, 1.63 M) was added to a solution of **40** (6.5 mg, 9.6 μmol) in acetonitrile (120 μL) and $CHCl_3$ (39 μL). The mixture was stirred for 6.5 h, aq. solution of $(NH_4)_2Ce(NO_3)_6$ (11.8 μL, 19.2 μmol, 2 equiv, 1.63 M) was added and mixture was further stirred for 12 h. Volatiles were removed under reduced pressure and residue was purified by flash chromatography (70–99% EtOAc/1% AcOH/hexanes) to obtain **48** as a white powder (4.3 mg, 80%). ^{1}H NMR (400 MHz, CD_3OD): $\delta = 6.10$ (s, 1H, 12-H), 5.39 (d, $J = 6.6$ Hz, 1H, 1-H), 5.22 (d, $J = 4.2$ Hz, 1H, 6-H), 5.09 (s, 1H, 10-H), 4.74 (d, $J = 6.6$ Hz, 1H, 2-H), 4.28 (dd, $J = 12.4$, 4.2 Hz, 1H, 7-H), 3.76–3.62 (m, 4H, morph.), 3.58–3.38 (m, 4H, morph.), 3.12 (q, $J = 7.1$ Hz, 1H, 14-H), 1.79 (d, $J = 12.4$ Hz, 1H, 8-H), 1.28 (d, $J = 7.1$ Hz, 3H, 16-CH_3), 1.22 (s, 9H, *t*Bu); HSQC correlation spectra measured; HRMS (FAB): *m/z*: calcd for $C_{25}H_{32}O_{13}N$: 554.1874; found: 554.1874 $[M+H]^+$.

1-(Piperidine-carbonyloxy)-GC (49): An aq. solution of $(NH_4)_2Ce(NO_3)_6$ (6.9 μL, 11.2 μmol, 2 equiv, 1.63 M) was added to a solution of **41** (3.8 mg, 5.6 μmol) in acetonitrile (70 μL) and $CHCl_3$ (23 μL). The mixture was stirred for 6.5 h, aq. solution of $(NH_4)_2Ce(NO_3)_6$ (6.9 μL, 11.2 μmol, 2 equiv, 1.63 M) was added and mixture was further stirred for 12 h. Volatiles were removed under reduced pressure and residue was purified by flash chromatography (50–100% EtOAc/hexanes) to obtain **49** as a white powder (2.5 mg, 79%). ^{1}H NMR (400 MHz, CD_3OD): $\delta = 6.09$ (s, 1H, 12-H), 5.40 (d, $J = 6.4$ Hz, 1H, 1-H), 5.22 (d, $J = 4.2$ Hz, 1H, 6-H), 5.08 (s, 1H, 10-H), 4.71 (d, $J = 6.4$ Hz, 1H, 2-H), 4.32 (dd, $J = 12.4$, 4.2 Hz, 1H, 7-H), 3.68–3.50 (m, 2H, piper.), 3.46–3.20 (m, 2H, piper.), 3.12 (q, $J = 7.2$ Hz, 1H, 14-H), 1.79 (d, $J = 12.4$ Hz, 1H, 8-H), 1.75–1.52 (m, 6H, piper.), 1.28 (d, $J = 7.2$ Hz, 3H, 16-CH_3), 1.22 (s, 9H, *t*Bu); HSQC correlation spectra measured; HRMS (FAB): *m/z*: calcd for $C_{26}H_{34}O_{12}N$: 552.2081; found: 552.2061 $[M+H]^+$.

Functional glycine receptor assay: Pharmacological activities of the compounds were evaluated in a FLIPR Membrane Potential Assay (Molecular Devices, Crawley, UK) using a HEK293 cell line stably expressing the human homomeric α1 GlyR.[47] Briefly, α1 GlyR-HEK293 cells were split into poly-D-lysine-coated 96-well black Opti-plates (Packard). 16–24 h later, the medium was aspirated, and 100 μL KREBS Buffer [140 mM NaCl/4.7 mM KCl/2.5 mM $CaCl_2$/1.2 mM $MgCl_2$/10 mM HEPES/11 mM D-glucose, pH 7.4] supplemented with FLIPR Membrane Potential Assay loading dye and various concentrations of the test compounds was added to the wells. The plate was incubated at 37 °C in a humidified 5% CO_2 incubator for 30 min and assayed in a NOVOstar (BMG Labtechnologies, Offenburg, Germany) measuring emission at 560 nm caused by excitation at 530 nm. Fluorescence measurements were performed immediately before and up to 1 min after addition of glycine (final concentration 100 μM) to the wells. The experiments were performed in duplicate at least three times for each compound. Percentage inhibition was calculated as: $(Response_{glycine} - Response_{test\ cmpd+glycine})/Response_{glycine}$. Inhibition below 20% was characterized as no inhibition (NI).

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