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Regioselective Domino Metathesis of Unsymmetrical 7-Oxanorbornenes with Electron-Rich Vinyl Acetate toward Biologically Active Glutamate Analogues

Masato Oikawa,*[a,b] Minoru Ikoma,[b] Makoto Sasaki,[b] Martin B. Gill,[c] Geoffrey T. Swanson,[c] Keiko Shimamoto,[d] and Ryuichi Sakai[e]

Dedicated to Emeritus Professor H. Shirahama

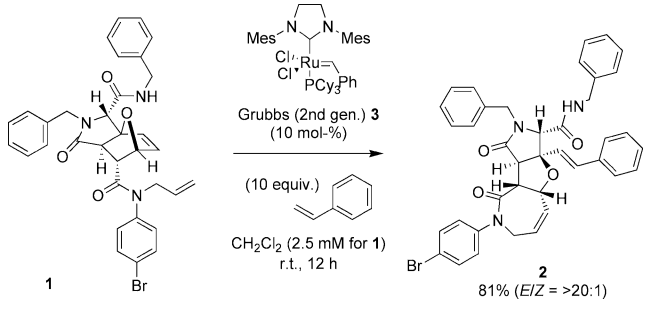
Keywords: Domino reactions / Regioselectivity / Carbenes / Combinatorial chemistry / Glutamate analogues / Metathesis

In this article a regioselective domino metathesis reaction of unsymmetrical 7-oxanorbornenes, readily available by a tandem Ugi/Diels–Alder reaction as a key step, promoted by the Hoveyda–Grubbs second-generation catalyst in the presence of electron-rich vinyl acetate as a cross metathesis (CM) substrate is reported. The mechanism for the unusually high regioselectivity observed in the CM reaction was investigated, and a reaction course where a Fischer-type carbene ["Ru"=CH(OAc)] generates a steric interaction is proposed. The metathesis products were further converted to four artificial glutamate analogues whose structures were inspired by naturally derived excitatory glutamate analogues, dysiherbaine and neodysiherbaine. Interestingly, one of the synthetic analogues (**28a**) induced a cataleptic state in mice. Further electrophysiological studies suggest that **28a** might inhibit excitatory synaptic transmission by a yet unknown indirect pathway.

Introduction

Olefin metathesis plays a crucial role in modern synthetic organic chemistry.[1] In a rough classification, three types of reactions have been known for olefin metathesis: cross metathesis (CM), ring-closing metathesis (RCM), and ring-opening metathesis (ROM). A combination of these metathesis reactions (domino reaction) is frequently used as a key reaction in multi-step syntheses of, for example, biologically active compounds. We have been studying domino metathesis reaction of 7-oxanorbornenes, because these compounds are readily converted into structurally complex heterocycles that are interesting in terms of molecular diversity.[2,3]

We recently reported that domino metathesis of 7-oxanorbornene **1** was cleanly converted to heterotricycle **2** in good yield (81%) with high regioselectivity (Scheme 1).[2] This observation is of particular interest, because metathesis of unsymmetrical norbornenes is, in general, poorly regioselective, as was reported by several groups.[4,5] However, Rainier recently demonstrated a highly regioselective domino metathesis reaction of norbornenes bearing a *p*-tolylsulfinyl (Ts) group as a substituent,[6–8] suggesting that a long-range electronic effect of a remote substituent can contribute to regiochemical control in metathesis reactions of norbornenes. In light of the regioselective metathesis reaction step, we envisaged that functionalized glutamate analogues could be prepared efficiently in a diversity-oriented manner.



Scheme 1. Our previous demonstration for regioselective domino metathesis of 7-oxanorbornene.[2]

[a] Graduate School of Nanobioscience, Yokohama City University,
Seto 22-2, Kanazawa-ku, Yokohama 236-0027, Japan
Fax: +81-45-787-2403
E-mail: moikawa@yokohama-cu.ac.jp
[b] Graduate School of Life Sciences, Tohoku University,
Aoba-ku, Sendai 981-8555, Japan
[c] Department of Molecular Pharmacology and Biological Chemistry, Northwestern University Feinberg School of Medicine,
303 E. Chicago Ave., Chicago, IL 60611, USA
[d] Suntory Institute for Bioorganic Research,
Mishima-gun, Osaka 618-8503, Japan
[e] Graduate School of Fisheries Sciences, Hokkaido University,
Minato-cho, Hakodate 041-8611, Japan

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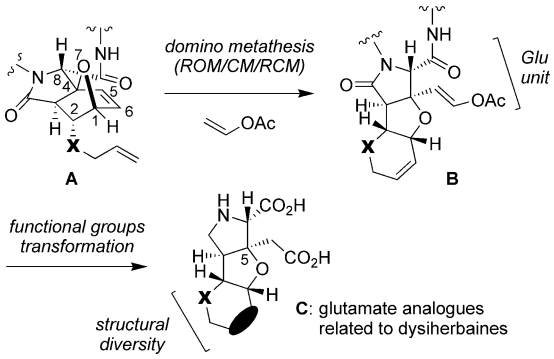
As shown in Scheme 2, regioselective domino metathesis of suitably functionalized 7-oxanorbornene **A** would provide heterotricycle **B**. After functional group transformations, several glutamate analogues **C** would be furnished with some structural diversity at the lowest third ring. Because the structure of **C** shares some structural units similar to marine sponge-derived excitatory amino acids dysiherbaine[9] and neodysiherbaine A,[10] it was anticipated to exhibit unique neuronal activities.



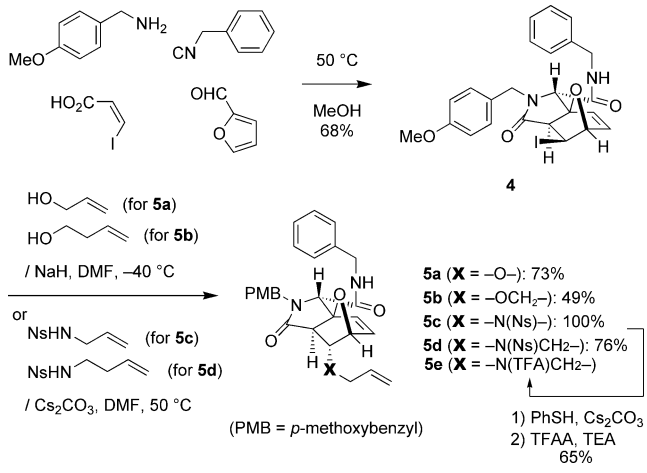
Scheme 2. Our strategy for the synthesis of artificial glutamate analogues by a key domino metathesis reaction in the presence of vinyl acetate.

In this paper, we report a full account[11,12] of the synthesis of biologically interesting glutamate analogues employing regioselective domino metathesis of unsymmetrical 7-oxanorbornenes as a key reaction. Because this regioselectivity is essential for efficient formation of glutamate-like functionality at earlier steps, we assessed for the origin of the selectivity. Evidence obtained in the present work supported that the mechanism that involves a directing effect by the amide carbonyl group is not applicable in this particular reaction, but that the Fischer carbene pathway is likely. Our recent progress in the biological evaluation for compound **28a** is also reported.

Results

Preparation of 7-Oxanorbornenes as Metathesis Substrates

7-Oxanorbornenes **5a**–**5e** with five heteroalkenyl groups were prepared in 2–3 steps as shown in Scheme 3. The molecular framework was readily constructed in a single tandem Ugi/Diels–Alder reaction[13] between 4-methoxybenzylamine (PMB-NH_2), benzyl isocyanide (Bn-NC), (*Z*)-3-iodoacrylic acid,[3] and 2-furfural. The reaction proceeded smoothly in MeOH at 50 °C for 4.5 h to give **4** in 68% yield as a sole product. The structure was determined from ^{1}H NMR spectra by analogy with those of closely related compounds reported earlier by us[14] and others.[13,15] It should be noted here that the use of sterically demanding iodine-substituted acrylate in the Diels–Alder reaction had not been reported before our demonstration in 2008,[3] and it also worked well in the present tandem reaction.



Scheme 3. Tandem Ugi/Diels–Alder reaction followed by introduction of heteroalkenyl groups to synthesize 7-oxanorbornenes as metathesis substrates.

Introduction of heteroalkenyl groups was next explored. After several experiments, it was found that, for alkenyloxy groups, the use of sodium alkoxide in DMF at –40 °C was effective, giving rise to **5a** and **5b** in 73 and 49% yields, respectively. On the other hand, *N*-Ns-*N*-alkenylamino groups (Ns = 2-nitrobenzenesulfinyl)[16] were introduced in combination with Cs_2CO_3 at elevated temperature (50 °C) to provide **5c** and **5d** in 100 and 76% yields, respectively. It should be noted that these reactions proceed via a sequence of elimination of hydrogen iodide followed by 1,4-conjugate addition, as we have mentioned recently,[3] and in all cases, the reactions were highly stereoselective.

Protecting group manipulation was further carried out on *N*-butenylamino product **5d** to see the effect of the groups on the metathesis reactions. Thus, the *N*-Ns group was removed by PhSH and Cs_2CO_3[16] followed by acylation with trifluoroacetic anhydride (TFAA) to give TFA amide **5e** in 65% yield.

Other 7-oxanorbornenes **6** and **7** (Figure 1) were also prepared according to our previous publication,[3] and used for control experiments in the metathesis study.

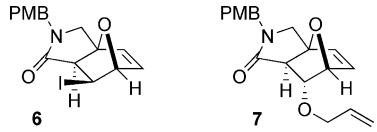


Figure 1. Two 7-oxanorbornenes without amide side chains, used for control metathesis experiments.

Domino Metathesis of 7-Oxanorbornenes

In the metathesis study of norbornenes, Rainier et al.[7] used Grubbs' second-generation catalyst **3**.[17] They reported that the catalyst was added twice to the mixture dur-

ing the reaction to complete the transformation, presumably due to the catalyst's instability. Indeed, we also encountered problem of incomplete reaction with Grubbs' second-generation catalyst **3** in these studies. Therefore, the Hoveyda–Grubbs second-generation catalyst **8**[18] (0.5–10 mol-%) was used in the present study, because the catalyst cycle is known to be initiated rapidly and to be stable. All reactions were carried out with 5 equiv. of vinyl acetate in benzene at room temp. The structures of the products were determined by ^{1}H NMR, including COSY spectra.

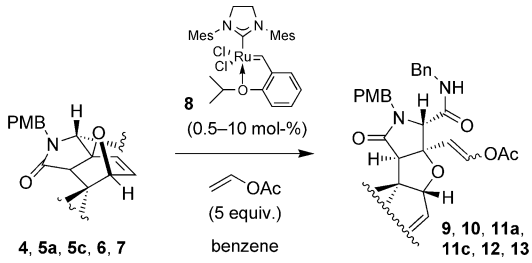
At first, 7-oxanorbornene **4** was subjected to the reaction (Table 1, run 1). The reaction was found to be highly regioselective to give heterobicycle **9** in 87% yield (*E*/*Z* = 13:1). Interestingly, with 7-oxanorbornene **6**, which lacks the *N*-Bn-amide side chain, the reaction was slow (24 h) with low yield and regioselectivity to give **10** as a mixture of all four possible isomers (31%, Table 1, run 2).

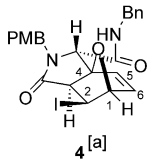
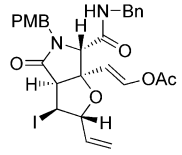
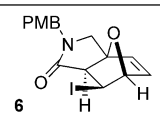
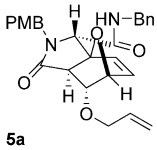
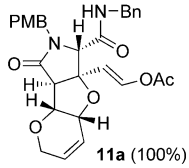
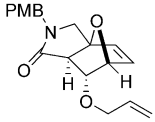
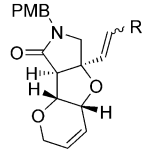
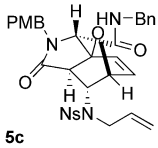
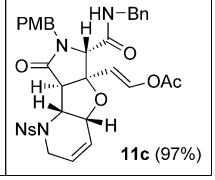
The reaction of 7-oxanorbornene **5a** bearing an allyloxy group was next examined, and found to provide heterotricycle **11a** rapidly at room temp. after 4 h in 100% yield (Table 1, run 3). The vinylic acetate moiety was also completely controlled to be in the *trans* configuration, as judged from the ^{1}H NMR spectrum [^3J(H,H) = 12.0 Hz]. In contrast, we have recently reported that 7-oxanorbornene **7**, without the *N*-Bn-amide side chain, was converted to heterotricycles **12** and **13** in 88% (*E*/*Z* = 5:4) and 10% yields, respectively (Table 1, run 4).[3] The ratio of the yields (88%:10%) provides information on the regioselectivity of the first ROM reaction, since it is generally accepted that no CM reaction takes place between monosubstituted olefins and vinyl acetate, and we also observed no reaction between vinyl acetate and triene intermediates **11b′**, **11d′**, and **11e′** (vide infra, Table 2). It is therefore conclusive that the first ROM reaction would be less regioselective for the simple 7-oxanorbornene **7** than **5a**.

N-Allyl-*N*-Ns-amine **5c** also reacted as smoothly as **5a** in the metathesis sequence to give heterotricycle **11c** in an excellent yield (97%, run 5). The geometry for the vinylic acetate moiety was again controlled exclusively to be *trans*, as in run 3.

Table 2 summarizes the results for domino metathesis reactions of 7-oxanorbornenes **5b**, **5d**, and **5e**, bearing butenyl groups, to form seven-membered heterocycles. It was soon realized that in all cases, the metathesis sequence stopped before RCM took place. We therefore quenched the reaction and the crude material was again subjected to the metathesis reaction for ring closure just with the metathesis catalyst **8**. For example, when 7-oxanorbornene **5b** was treated with vinyl acetate in the presence of metathesis catalyst **8** at 69 °C, triene **11b′** was cleanly obtained in 84% yield after 46 h (run 1). It should be noted that the reaction was completed cleanly even at room temp. The structure was unambiguously clarified by spectroscopic analysis, including ^{1}H and ^{13}C NMR, and the vinylic acetate moiety was found to be completely controlled to be the *trans* isomer. Triene **11b′** was then subjected to the second metathesis reaction with the metathesis catalyst **8** at 69 °C to promote the ring closure, giving rise to heterotricycle **11b** in 84% yield (2 steps) after 21 h. Since it was found that even crude triene could be used for the second metathesis, the intermediate trienes were conveniently used without purification for the ring closure in runs 2 and 3. Thus, heterotricycles **11d** and **11e** were readily obtained in 90 and 85% yields, respectively, without isolation of the intermediary trienes **11d′** and **11e′**. These results also indicated that an *N*-Ns-amine requires higher temperature (80 °C) for cyclization as compared to a TFA amide (69 °C), while the yields are nearly comparable.[19]

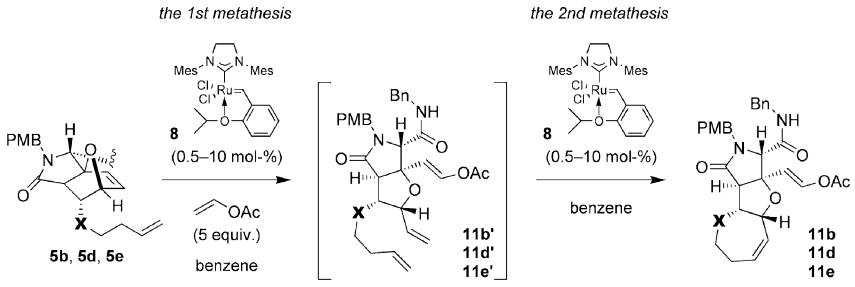
Table 1. Results for the domino metathesis reaction of 7-oxanorbornenes **4**, **5a**, **5c**, **6**, and **7**.

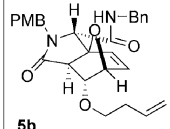
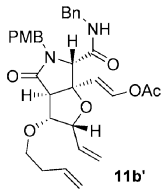
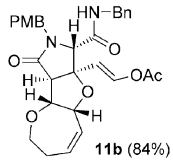
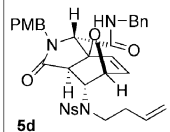
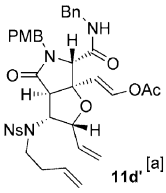
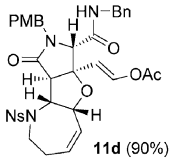
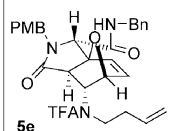
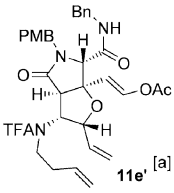
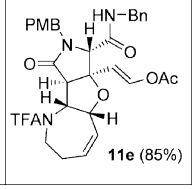


Run	Domino metathesis substrate	Reaction conditions	Product [% yield]
1	 **4**[a]	r.t., 14 h	 **9** (87%, *E*/*Z* = 13:1)
2	 **6**	r.t., 24 h	**10** (4 products)[a] (31%, 30:28:6:1)
3	 **5a**	r.t., 4 h	 **11a** (100%)
4	 **7**	r.t., 8.5 h	 [3] **12** (R = OAc; 88%, 5:4) **13** (R = H; 10%)
5	 **5c**	r.t., 11 h	 **11c** (97%)

[a] Diastereomeric ratio for **10** was determined by LC-MS analysis.

Table 2. Results for the domino metathesis reaction of 7-oxanorbornenes **5b**, **5d**, and **5e**.

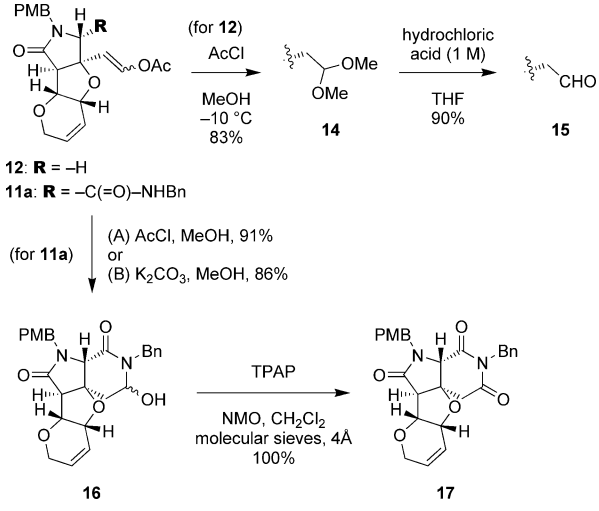


Run	Domino metathesis substrate	Reaction conditions for the 1st metathesis	Product by the 1st metathesis	Reaction conditions for the 2nd metathesis	Product [% yield] by the 2nd metathesis
1	 **5b**	69 °C, 46 h	 **11b'**	69 °C, 21 h	 **11b** (84%)
2	 **5d**	69 °C, 25 h	 **11d'** [a]	80 °C, 10 h	 **11d** (90%)
3	 **5e**	69 °C, 19 h	 **11e'** [a]	69 °C, 11 h	 **11e** (85%)

[a] Intermediates **11d′** and **11e′** were not isolated, but used directly for the second metathesis.

Synthesis of Artificial Glutamate Analogues

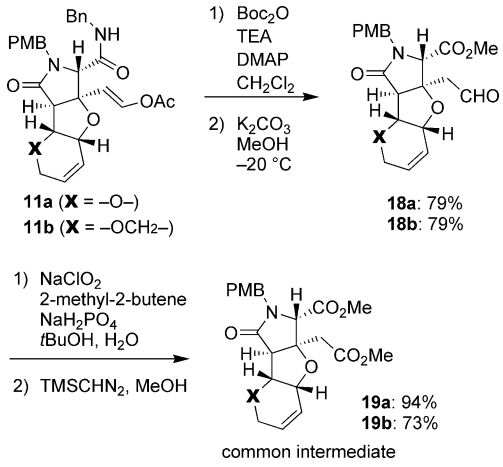
With metathesis products **11a** and **11b** in hand, we next explored a method that converted them into artificial glutamate analogues. Initially, transformation of the vinylic acetate moiety to a methyl ester was attempted, because we previously found that vinylic acetate **12** reacts readily with methanolic HCl at –10 °C to give methyl acetal **14** in 83% yield. The methyl acetal was subsequently hydrolyzed by hydrochloric acid (1 M) to provide aldehyde **15** in 90% yield (Scheme 4).[3] However, with the metathesis product **11a**, neither the acidic methanolysis nor alkaline hydrolysis furnished the desired aldehyde. Instead, hemiaminal **16** was provided in 91 and 86% yields, respectively. Although oxidation of **16** was found to give imide **17** in 100% yield, the route seemed to be inconvenient in terms of overall yield.



Scheme 4. Failed attempt to construct the glutamate structural unit from **11a**.

Therefore, we decided to modify the upper *N*-Bn-amide of the metathesis products **11a** and **11b** to transform them into artificial glutamate analogues. Synthesis of common intermediates **19a** and **19b** are summarized in Scheme 5. First, **11a** and **11b** were treated with Boc_2O, DMAP, and triethylamine (TEA) to form *N*-Boc-imides, which, in turn, were subjected to methanolysis at –20 °C (K_2CO_3, MeOH) carefully, to provide **18a** and **18b** in 79% yield for both compounds. After oxidation ($NaClO_2$, 2-methyl-2-butene, NaH_2PO_4),[20] the resulting carboxylic acids were esterified

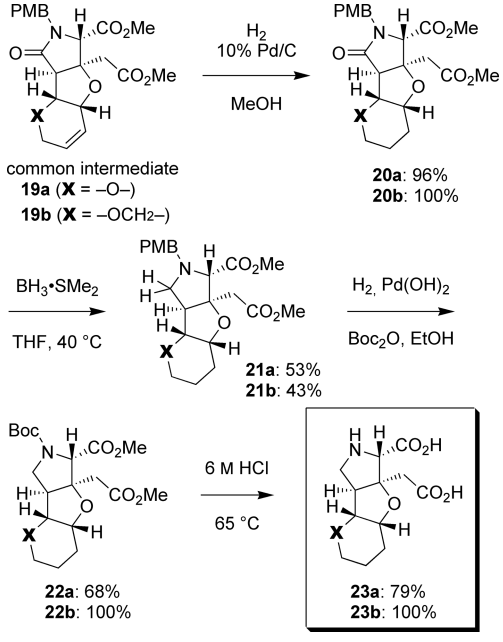
with TMS-CHN_2 to give diesters **19a** and **19b** in 94 and 73% yields, respectively.



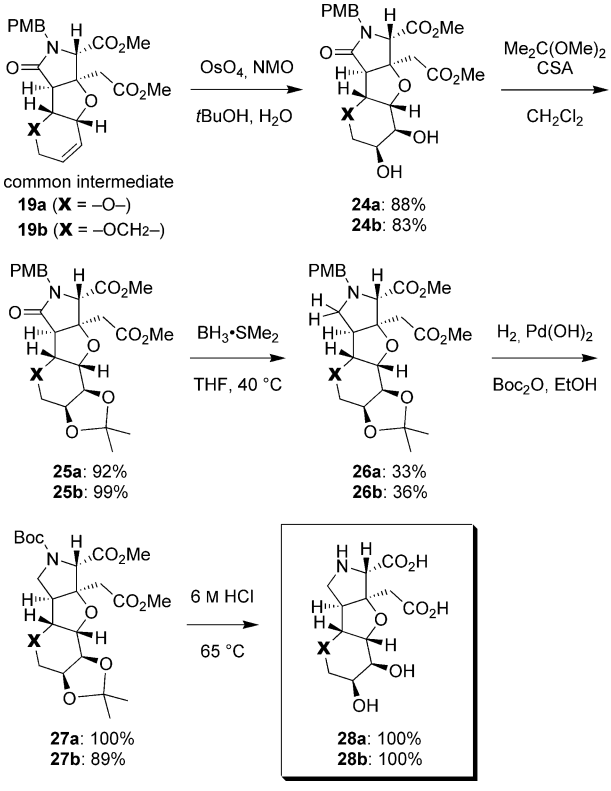
Scheme 5. Synthesis of common intermediates **19a** and **19b**.

From the common intermediates **19a** and **19b**, two artificial glutamate analogues **23a** and **23b**, wherein the olefinic double bonds are hydrogenated, were synthesized as shown in Scheme 6. The hydrogenation was performed by using 10% Pd/C as a catalyst under hydrogen atmosphere, giving rise to **20a** and **20b** in 96 and 100% yields, respectively. Selective reduction of the pyrrolidone was next attempted. It was first found that a two-step transformation via a thioamide (Lawesson's reagent,[21] toluene, 80 °C; $NaBH_4$, $NiCl_2{\cdot}6H_2O$, THF, MeOH) successfully gave **21a** from **20a** in 50% overall yield. However, this transformation was poorly reproducible and often accompanied by undesired side reactions, such as the decomposition of acid-sensitive groups such as the acetonide groups in **25a** and **25b** (vide infra). Fortunately, $BH_3{\cdot}SMe_2$[22] was found to promote the selective reduction at 40 °C to give pyrrolidines **21a** and **21b** in moderate yields (53 and 43%) with satisfactory reproducibility. From **21a** and **21b**, glutamate analogues **23a** and **23b** were synthesized by stepwise protective group manipulations, including conversion of the PMB groups to Boc groups under hydrogenolytic conditions (68 and 100%), and acidic hydrolysis for global deprotection (79 and 100%).

Dihydroxylated glutamate analogues **28a** and **28b** were also synthesized from the common intermediates **19a** and **19b** as shown in Scheme 7. These intermediates were stereoselectively dihydroxylated under standard conditions (OsO_4, NMO, *t*BuOH, H_2O) to give diols **24a** and **24b** in excellent yields (88 and 83%) with complete stereoselectivity. The diols were subsequently protected as acetonides (2,2-dimethoxypropane, CSA, CH_2Cl_2). The structures were confirmed by NOESY analysis as shown in Figure 2, which showed that dihydroxylation had taken place from the convex faces of the molecules. Application of the same sequence of reactions as those for the transformation of **20a**(**20b**) into **23a**(**23b**), to acetonides **25a** and **25b** successfully furnished dihydroxylated glutamate analogues **28a** and **28b** in 62 and 36% yields, respectively, for 3 steps each.



Scheme 6. Synthesis of two glutamate analogues, **23a** and **23b**, with saturated ether rings.



Scheme 7. Synthesis of two glutamate analogues, **28a** and **28b**, with dihydroxylated ether rings.

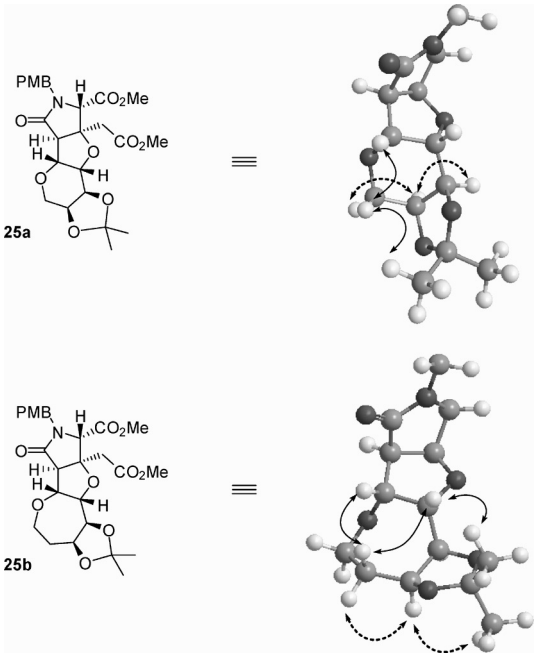


Figure 2. Key NOEs for stereochemical confirmation of compounds **25a** and **25b**. Plain and dashed arrows indicate NOEs observed at the β-side and the α-side of the molecules, respectively. PMB and two methyl esters are omitted for clarity.

Evaluation of Biological Activities

The biological activities of the artificial glutamate analogues **23a**, **23b**, **28a**, and **28b**, synthesized in the present study, were evaluated in vivo using a mouse behavioral assay, and in vitro by radioligand binding assays and by electrophysiological analyses.

Biological evaluation of four artificial glutamate analogues was first performed in mice behavioral assays,[23] because ligands for glutamate receptors (GluR) generally induce dose-dependent behavioral toxicity.[24] An intracranial injection of each compound (0.02 mg/mouse) induced a variety of behavioral changes that could be categorized into hyper- and hypoactive groups. The hyperactive group displayed stereotyped behavior such as scratching or hypersensitivity, while the hypoactive animals were in depression (loss of mobility) and some rigidity in the limbs was observed. Although the relationship between structure and activity type was not definitive, the saturated pyran **23a** was weakly hyperactive, while dihydroxylated pyran **28a** induced hypoactivity. Oxepanes **23b** and **28b** induced hyperactivity and caused a loss of balance, sudden running and jumping. It is noteworthy that in all cases, the mice recovered fully and were apparently normal by several hours after treatment. These in vivo activities, especially depression caused by **28a**, are unique and are not observed with parental dysiherbaines, which are potent convulsants.

The glutamate analogues **23a**, **23b**, **28a**, and **28b** were further characterized in radioligand binding assays using rat synaptic membranes.[24] It was found out, however, that none of these compounds replaced the radioactive ligands for (*S*)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid (AMPA), kainate (KA), or *N*-methyl-D-aspartate (NMDA) receptors, subtypes of ionotropic GluRs, even at 1×10^{-5} M.

The biological activity of the dihydroxylated pyran analogue **28a** was next evaluated by current- and voltage-clamp electrophysiological analyses from cultured hippocampal neurons. Consistent with the hypoactivity observed in behavioral experiments, **28a** markedly reduced excitatory neurotransmission in these highly active neuronal cultures. Voltage-clamp recordings of spontaneous bursts of excitatory synaptic currents revealed that the mean charge transfer mediated by activation of pharmacologically isolated AMPA/kainate-type ionotropic glutamate receptors declined by $43.5 \pm 10.5\%$ ($n = 3$, $p < 0.05$ in a Student's paired *t*-test) in the presence of **28a** (20×10^{-6} M). Similarly, spontaneous action potential firing was reduced by $39.2 \pm 11.6\%$ ($n = 3$, $p < 0.05$ in a Student's paired *t*-test) in highly active neurons. These data demonstrate that **28a** reduces neuronal excitability in the CNS, presumably through an indirect action on glutamatergic neurotransmission, which likely accounts for the depressive neuroactivity in the mouse bioassay. The precise mechanism(s) of action of **28a** and other analogues are the subject of active investigation.

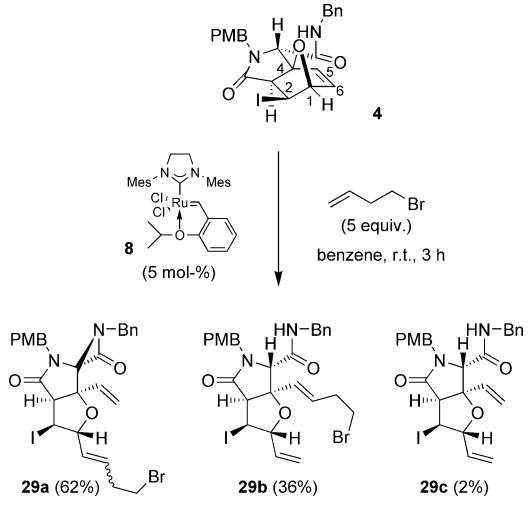
Discussion

Mechanism for the Regioselective Domino Metathesis

In this paper, we report the domino metathesis of unsymmetrical 7-oxanorbornenes with electron-rich vinyl acetate as a CM substrate. Although electron-rich olefins are generally a poor substrate for CM reactions, the domino metathesis reaction of 7-oxanorbornenes proceeded smoothly by virtue of the structural strain of the skeleton. It is also noteworthy that the regioselectivity was highly controlled, affording glutamic acid analogs (Tables 1 and 2). In the present study, we used the Hoveyda–Grubbs second-generation catalyst **8**,[18,25] which is also of significance, since most of the previous metathesis reactions with electron-rich olefins were studied with Grubbs' second-generation catalyst.[6,7,26,27]

For these regioselective metathesis reactions, either or both of two mechanisms could be operative. The first mechanism is an association mechanism, and the second one is a Fischer-type carbene mechanism. In the association mechanism, the reaction is guided by the interaction of the ruthenium metal center and an electron-donating group such as hydroxy or carbonyl groups involved in the metathesis substrate. Well-known examples are Cossy's synthetic study on amphidinol 3,[28] and Fürstner's macrocycle synthesis.[29] In connection with these studies, we initially thought that the association mechanism was primarily operative also in our case,[11] since the *N*-benzylamide carbonyl group was conveniently located at a position spatially close to the 7-oxanorbornene olefin in cases where the reactions were regioselective (Table 1 and Table 2). We thus tested the former mechanism by an experiment shown in Scheme 8. If the association mechanism were operable here,

the regioselectivity would rely on the type of catalyst-substrate interaction but not type of the olefin added. When 7-oxanorbornene **3** was treated with but-3-enyl bromide (5 equiv.) in the presence of metathesis catalyst **8** (5 mol-%), however, three products **29a**–**29c** were found to be generated (Scheme 8). The reaction proceeded quite smoothly and was completed in 3 h. This result was in clear contrast to the regioselective reaction with vinyl acetate (Table 1, run 1). It is generally accepted that domino metathesis of norbornenes starts with a ring-opening reaction with the metathesis catalyst (ROM),[5,30,31] by which regioselectivity is determined. If the reaction shares common or even similar intermediates at the earlier stage, then the comparable regioselectivity is expected. In our case, shown in Table 1 (run 1) and Scheme 8, however, the regioselectivity outcomes are far different, and we hence concluded that, 1) these two reactions do not share a common mechanism, but proceed via different mechanisms; and 2) the association mechanism is not primarily operative in these metathesis reactions.



Scheme 8. A control domino metathesis reaction of **4** in the presence of but-3-enyl bromide as a CM substrate.

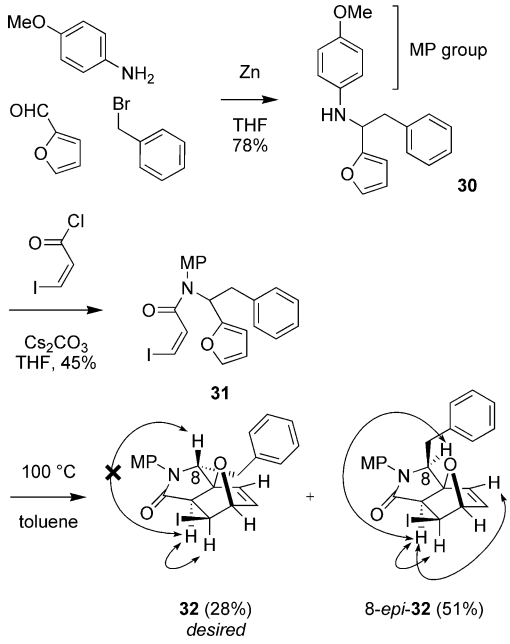
We next turned our attention to the Fischer-type carbene mechanism. Fischer-type carbenes are complexes containing an electron-donating group on the carbene carbon. They are thermodynamically stable and hence poorly reactive.[32,33] They are also generated when ROMP (ring-opening metathesis polymerization) reactions are terminated by electron-rich olefins such as ethyl vinyl ether.[34] In contrast to these common examples, remarkable catalytic activities of Fischer-type carbenes have often been reported. For example, Grubbs et al. reported that some Fischer-type carbenes initiate ROMP of strained cyclic olefins and RCM of diethyl diallylmalonate.[26] Fischer-type carbenes can be involved also in enyne ring-closing metathesis (RCM)[35] and intermolecular reaction (CM).[36] Ozawa et al. reported that Fischer-type selenocarbene complexes smoothly reacts with norbornene at room temp. to provide monomeric ring-opening cross metathesis (ROCM) products without formation of ROMP products.[37] More recently, highly regioselective ROCM reactions of unsymmetrical norbornenes with electron-rich olefins were successfully performed by Rainier et al.[6,7] Because precatalyst formation was reported to be essential for those reactions, it is plausible that a Fischer-type carbene mechanism was operative in their reactions.

We therefore attempted to detect a Fischer-type carbene complex by ^{1}H NMR spectroscopy. It has been reported that some Fischer-type carbene complexes are readily generated upon simply mixing in appropriate solvents. For example, Grubbs et al. reported that they detected the Fischer-type carbene that formed from $(PPh_3)_2(TFA)_2Ru$=CH–CH=CPh_2 and vinyl acetate before it rapidly decomposed.[32] Similarly, in the present study; when metathesis catalyst **8** and vinyl acetate (10 equiv.) were mixed at room temp. in C_6D_6, the carbene proton of **8** at 16.7 ppm disappeared in 1 min, and a new peak assignable to the Fischer carbene complex ["Ru"=CH(OAc)] was observed instead at 11.9 ppm, which was also observed in the Grubbs study.[32] The Fischer-type carbene complex was not stable, and decomposed after 12 h as judged from ^{1}H NMR spectra.

Since the Fischer-type carbene formation was much faster than the domino metathesis shown in Tables 1 and 2, we now believe a Fischer-type carbene was present during propagation phase.

The domino metathesis reaction of a 7-oxanorbornene substrate bearing a Bn group substituent instead of *N*-Bn-amide side chain at the C8-position was examined next to study whether association is involved in the domino metathesis reaction promoted by the Fischer-type carbene catalyst ["Ru"=CH(OAc)]. The substrate **32** was synthesized in 3 steps as shown in Scheme 9. A three-component coupling reaction between benzyl bromide, 2-furfural, and 4-methoxyaniline in the presence of zinc dust in THF, gave amine **30** in 78% yield.[38] Acylation with (*Z*)-3-iodoacryl chloride[3] in the presence of Cs_2CO_3 provided **31** (45%), which was further heated (100 °C) to promote an intramolecular Diels–Alder reaction to furnish **32** in 28% yield, accompanied by isomeric 8-*epi*-**32** in 51% yield. The structures were determined by NOESY analysis as indicated.

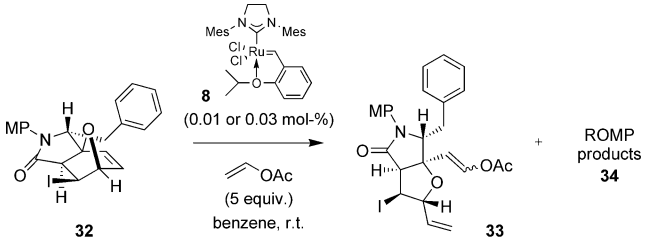
Results for the metathesis reaction of **32** in the presence of vinyl acetate are shown in Table 3. Under the same conditions as for **4**–**7** (see Tables 1 and 2), the reaction proceeded quite smoothly in 3 h to give heterobicycles (*E*)-**33** and (*Z*)-**33** in 26 and 33% isolated yields, respectively (run 1). NMR analyses (^{1}H NMR and COSY) indicated that the regioselectivity was identical with that for reactions of **4** and **5** (see Tables 1 and 2). Neither regioisomer corresponding to **29a** nor divinyl product corresponding to **29c** was detected. Instead, ROMP product **34** was found to be generated. Although **34** was obtained as a complex mixture, dimer **35** (Figure 3) was successfully isolated and characterized as, 1) a mixture of two olefin geometrical isomers, and 2) monoacetates that were introduced regioselectively. We then carried out the reaction under diluted conditions (3.8 mM, run 2). As expected, formation of the undesired ROMP product **34** was completely suppressed in run 2, and heterobicycle **33** was formed in 60% yield (*E*/*Z* = 50:50), accompanied by unreacted 7-oxanobornene **32** (28% yield). The high level of regioselectivity observed in the reaction



Scheme 9. Preparation of 7-oxanorbornene **32** for control experiments. Arrows on **32** and 8-*epi*-**32** indicate key NOEs for stereochemical assignments.

with the substrate lacking the *N*-Bn-amide side chain could be provided by steric interaction between 7-oxanorbornene **32** and the Fischer-type carbene catalyst ["Ru"=CH(OAc)]. The incomplete reaction in run 2 is probably due to decomposition of the metathesis catalyst **8** or the Fischer-type carbene, as observed in our NMR study (vide supra).

Table 3. Domino metathesis of 7-oxanorbornene **32** bearing a Bn substituent instead of an *N*-Bn-amide side chain at C8.



Run	Conditions (concentration for **32** and time)	**33** (%)	ROMP products **34** (%)[c]	Recovered **32** (%)
1	0.041 M, 3 h[a]	59% (*E*/*Z* = 44:56)	38%	0%
2	0.0038 M, 5 h[b]	60% (*E*/*Z* = 50:50)	0%	28%

[a] 0.01 equiv. of metathesis catalyst **8** was used. [b] 0.03 equiv. of metathesis catalyst **8** was used. [c] We assumed that the average MW was 559.4 (same as **33**).

Taken together, the above experimental results support that, 1) the mechanism based on Fischer-type carbene ["Ru"=CH(OAc)] is probably operative in our regioselective domino metathesis of 7-oxanorbornenes (designated as "**A**" in Scheme 2), and 2) the [2+2] cycloaddition may be controlled by some steric interactions between bulky substituents in the catalyst and substrate, but not by association between 7-oxanorbornene substrates and the active carbene species.[39,40]

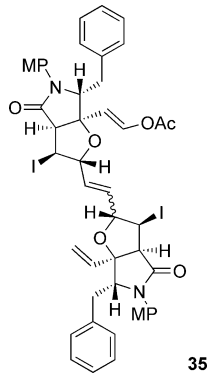


Figure 3. A dimer, **35**, isolated as one of the ROMP products in the domino metathesis of **32** (Table 3, run 1).

Novelty in Biological Properties of Artificial Glutamate Analogues

Starting from the domino metathesis products **11a** and **11b**, we successfully synthesized four artificial glutamate analogues in 8 steps (for **23a** and **23b**) and in 9 steps (for **28a** and **28b**) via advanced intermediates **19a** and **19b**. Total yields were 10.1% (for **23a**), 6.9% (for **23b**), 18.5% (for **28a**), and 4.7% (for **28b**). The key reaction is the chemoselective reduction of pyrrolidines by $BH_3{\cdot}SMe_2$ into pyrrolidones. Although the reaction proceeded only in moderate yields (40–62%), it was satisfactorily reproducible for all compounds.

Biological evaluation of the artificial glutamate analogues, **23a**, **23b**, **28a**, and **28b**, by intracranial injection in mice revealed that the dihydroxylated pyran **28a** was hypoactive, whereas other three analogues were hyperactive. The structures for the four analogues were inspired by dysiherbaine[9] and neodysiherbaine A,[10] which are naturally derived, excitatory amino acids, and the antagonist analogue MSVIII-19[41] (Figure 4). The discovery of hypoactive **28a** is particularly noteworthy, since dysiherbaines are lethally convulsant.

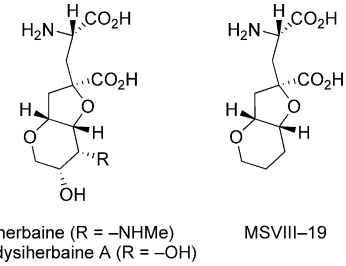


Figure 4. Dysiherbaine congeners[9,10] and the antagonistic analogue MSVIII-19.[41]

Although the electrophysiological assays suggested that **28a** inhibited the primary mediators of excitatory neurotransmitter currents, AMPA receptors, our radioligand

binding assays did not find evidence for direct binding of **28a** to any subtype of ionotropic glutamate receptor (AMPA, kainate or NMDA receptors). Therefore, it is possible that **28a** reduces spontaneous glutamatergic synaptic currents and action potential initiation through actions on other receptors or channels that dampen neuronal excitability. Alternatively, **28a** might bind to AMPA receptors with a very weak affinity that went undetected in the binding assays. Interestingly, our research group previously found that one of the dysiherbaine analogues MSVIII-19 (Figure 4) caused mice to fall into a coma-like sleep upon intracranial injection; physiological studies have indicated that it binds to GluR5 kainate receptors and acts as a functional antagonist.[41,42] It also reduced currents mediated by recombinant AMPA receptors (GluR1, 2 or 4) and excitatory postsynaptic currents (EPSCs) in mouse brain slices.[41,42] Generally, small molecules that modulate the synaptic function of ionotropic GluRs are of significant biomedical interest, because glutamatergic neurotransmission is essential for both basic operation of the CNS as well as higher brain functions such as memory formation, learning, or neuropathology of brain and nociception.[43] Starting from **28a**, further structural refinement and biological evaluation will be necessary to determine the precise mode of biological action of these novel glutamate analogues.

Conclusions

In summary, this paper describes our demonstration of regioselective domino metathesis of unsymmetrical 7-oxanorbornenes in the presence of electron-rich vinyl acetate as a CM substrate. In this study, it was concluded that the reaction was driven by a Fischer-type carbene ["Ru"= CH(OAc)], and the regioselectivity was controlled by steric interactions, but not by association. The metathesis products were further transformed into four biologically active, artificial glutamate analogues, one of which (compound **28a**) exhibited a novel hypoactivity on mice. It is thus proposed that natural-product-inspired diversity-oriented synthesis is a useful approach to develop novel biologically active compounds that modulate synaptic transmission through diverse mechanisms.

Unfortunately, the synthetic pathway shown in Schemes 6 and 7 was not applied to a synthesis of glutamate analogues from metathesis products **11c**, **11d**, and **11e**, which contain a nitrogen functionality at the lowest third ring. These reactions were inefficient in terms of synthetic steps and yields. The diminished reactivities, probably due to a presence of an *N*-protecting group which might sterically shield the heterotricycle skeleton, was also an obstacle. Instead, we have recently developed an improved synthetic pathway to twelve glutamate analogues including piperidine and azepane rings as the lowest third ring.[11] Efforts are in progress in our laboratories to develop artificial glutamate analogues with improved biological functions. Our highly regiocontrolled domino metathesis reaction will play a key role in the further studies.

Experimental Section

7-Oxanorbornene 4 (Tandem Ugi/Diels–Alder Reaction): To a stirred solution of furfural (0.500 mL, 5.31 mmol) in methanol (25 mL) at room temp. were added 4-methoxybenzylamine (0.459 mL, 3.54 mmol), (*Z*)-iodoacrylic acid (750 mg, 3.54 mmol), and benzyl isocyanide (0.647 mL, 5.31 mmol). After stirring at 50 °C for 4.5 h, the mixture was concentrated under reduced pressure and the residue was diluted with chloroform (200 mL). The solution was washed with saturated aqueous $NaHCO_3$ (100 mL), saturated aqueous NH_4Cl (100 mL), and brine (100 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20 g, hexane/EtOAc = 6:4) to give 7-oxanorbornene **4** (1.29 g, 68%) as a white solid. IR (film): $\tilde{\nu}$ = 2921, 1684, 1512, 1384, 1247, 1029, 701 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.30 (m, 3 H), 7.22 (d, J = 7.0 Hz, 2 H), 7.09 (d, J = 8.0 Hz, 2 H), 6.81 (d, J = 8.0 Hz, 2 H), 6.35 (d, J = 6.0 Hz, 1 H), 5.96 (br. s, 1 H), 5.25 (d, J = 1.5 Hz, 1 H), 5.04 (d, J = 15.5 Hz, 1 H), 5.96 (br. s, 1 H), 5.25 (d, J = 1.5 Hz, 1 H), 5.04 (d, J = 15.5 Hz, 1 H), 4.45 (dd, J = 14.5, 5.5 Hz, 1 H), 4.36 (dd, J = 14.5, 5.5 Hz, 1 H), 3.94 (s, 1 H), 3.89 (d, J = 15.5 Hz, 1 H), 3.86 (d, J = 15.5 Hz, 1 H), 3.76 (s, 3 H), 2.62 (d, J = 7.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.9, 166.8, 159.3, 137.3, 135.2, 135.0, 129.4, 128.9, 128.0, 128.0, 126.8, 114.3, 92.0, 88.8, 61.6, 55.3, 49.2, 45.4, 43.9, 18.2 ppm. HRMS (ESI, positive): calcd. for $C_{24}H_{24}IN_2O_4$ $[M + H]^+$ 531.0775; found 531.0782.

7-Oxanorbornene Allyl Ether 5a: To a stirred solution of allyl alcohol (7.80 mL, 11.3 mmol) in DMF (22 mL) at room temp. was added NaH (60% in mineral oil, 452 mg, 11.3 mmol). After 30 min, a solution of iodide **4** (1.011 g, 1.89 mmol) in DMF (44 mL) was added via a cannula, and the mixture was stirred at –40 °C for 1.5 h. The mixture was poured into saturated aqueous NH_4Cl (100 mL) and extracted with EtOAc (100 mL). The extract was washed with water (3 × 30 mL) and brine (50 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20 g, hexane/EtOAc = 7:3) to give allyl ether **5a** (633 mg, 73%) as a yellow solid. IR (film): $\tilde{\nu}$ = 3298, 2921, 1669, 1513, 1247, 1055, 701 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.28 (m, 3 H), 7.18 (d, J = 6.5 Hz, 2 H), 7.06 (d, J = 8.5 Hz, 2 H), 6.39 (s, 2 H), 6.03 (br. t, J = 5.0 Hz, 1 H), 5.87 (m, 1 H), 5.30 (dd, J = 17.5, 1.5 Hz, 1 H), 5.19 (d, J = 10.0 Hz, 1 H), 4.98 (d, J = 4.0 Hz, 1 H), 4.80 (d, J = 15.0 Hz, 1 H), 4.40 (dd, J = 14.8, 6.0 Hz, 1 H), 4.33 (s, 1 H), 4.32 (dd, J = 14.8, 6.0 Hz, 1 H), 4.10 (dd, J = 12.8, 5.0 Hz, 1 H), 4.03 (d, J = 14.5 Hz, 1 H), 4.02 (dd, J = 12.8, 5.0 Hz, 1 H), 3.97 (s, 1 H), 3.75 (s, 3 H), 2.45 (d, J = 2.0 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.4, 166.8, 159.1, 137.5, 134.6, 133.7, 133.5, 129.3, 128.7, 127.8, 127.7, 126.9, 117.6, 91.7, 79.4, 78.5, 71.3, 63.4, 55.1, 54.3, 45.3, 43.7 ppm. HRMS (ESI, positive): calcd. for $C_{27}H_{29}N_2O_5$ $[M + H]^+$ 461.2074; found 461.2071.

7-Oxanorbornene Butenyl Ether 5b: With the same procedure as for the synthesis of **5a**, **5b** (407 mg, 49%) was obtained as a yellow solid starting from **4** (900 mg, 1.75 mmol), NaH (430 mg, 10.4 mmol), and 3-buten-1-ol (903 mL, 10.41 mmol). IR (film): $\tilde{\nu}$ = 3074, 2912, 1667, 1513, 1247, 1031, 820, 713 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.27 (m, 3 H), 7.18 (d, J = 10.0 Hz, 2 H), 7.06 (d, J = 9.0 Hz, 2 H), 6.78 (d, J = 9.0 Hz, 2 H), 6.37 (dd, J = 8.5, 6.5 Hz, 2 H), 6.11 (br. t, J = 5.5 Hz, 1 H), 5.74 (m, 1 H), 5.05 (dd, J = 17.0, 2.0 Hz, 1 H), 5.00 (d, J = 10.5 Hz, 1 H), 4.96 (dd, J = 4.5, 1.5 Hz, 1 H), 4.80 (d, J = 15.0 Hz, 1 H), 4.39 (dd, J = 14.1, 6.0 Hz, 1 H), 4.33 (dd, J = 14.1, 6.0 Hz, 1 H), 4.27 (dd, J = 4.5, 2.0 Hz, 1 H), 4.02 (d, J = 15.0 Hz, 1 H), 3.97 (s, 1 H), 3.74

(s, 3 H), 3.60–3.53 (m, 2 H), 2.42 (d, J = 2.0 Hz, 1 H), 2.29 (dd, J = 7.0, 6.8 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.5, 166.8, 159.2, 137.5 (×2), 134.6, 133.5, 129.4, 128.7, 127.9, 127.8, 127.0, 116.6, 114.1, 91.7, 79.5, 79.0, 69.9, 63.5, 55.2, 54.2, 45.4, 43.7, 33.9 ppm. HRMS (ESI, positive): calcd. for $C_{28}H_{31}N_2O_5$ [M + H]$^+$ 475.2223; found 475.2215.

7-Oxanorbornene *N*-Allyl-*N*-Ns-Amide 5c: To a stirred solution of iodide **4** (201.1 mg, 0.38 mmol) in DMF (5.0 mL) at room temp. were added *N*-allyl-2-nitrobenzenesulfonamide (138 mg, 0.57 mmol) and Cs_2CO_3 (1.14 mmol). After stirring at 50 °C for 10 h, the mixture was cooled to room temp., poured into saturated aqueous NH_4Cl (20 mL), and extracted with EtOAc (50 mL). The extract was washed with water (3 × 10 mL) and brine (30 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (4 g, hexane/EtOAc = 5:5) to give Ns-amide **5c** (244.5 mg, 100%) as a yellow solid. IR (film): $\tilde{\nu}$ = 3087, 2933, 1695, 1541, 1513, 1359, 1247, 1173, 1031, 737, 589 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.15 (dd, J = 7.3, 2.0 Hz, 1 H), 7.76–7.70 (m, 2 H), 7.64 (dd, J = 7.3, 2.0 Hz, 1 H), 7.35–7.29 (m, 3 H), 7.19 (d, J = 7.0 Hz, 1 H), 7.03 (d, J = 9.0 Hz, 2 H), 6.79 (d, J = 9.0 Hz, 2 H), 6.50 (dd, J = 6.0, 1.5 Hz, 1 H), 6.35 (d, J = 6.0 Hz, 1 H), 5.98 (br. t, J = 5.5 Hz, 1 H), 5.68 (m, 1 H), 5.18 (d, J = 11.5 Hz, 1 H), 5.16 (s, 1 H), 5.07 (d, J = 11.5 Hz, 1 H), 4.83 (d, J = 15.0 Hz, 1 H), 4.46 (t, J = 3.5 Hz, 1 H), 4.43 (dd, J = 15.0, 6.5 Hz, 1 H), 4.31 (dd, J = 15.0, 6.5 Hz, 1 H), 3.94 (d, J = 15.0 Hz, 1 H), 3.92 (s, 1 H), 3.88 (br. s, 2 H), 3.75 (s, 3 H), 2.93 (d, J = 3.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.7, 166.7, 159.3, 138.5, 137.2, 135.7, 134.0, 133.9, 133.5, 132.1, 132.0, 130.8, 129.5, 128.9, 128.0, 127.8, 126.6, 124.3, 117.9, 114.2, 91.2, 81.9, 62.9, 59.8, 55.2, 50.4, 49.8, 45.4, 43.8 ppm. HRMS (ESI, positive): calcd. for $C_{33}H_{33}N_4O_8$ [M + H]$^+$ 645.2014; found 645.2018.

7-Oxanorbornene *N*-Butenyl-*N*-Ns-Amide 5d: With the same procedure as for the synthesis of **5c**, **5d** (1.04 g, 85%) was obtained as a yellow solid starting from **4** (1.00 g, 1.87 mmol), Cs_2CO_3 (1.22 g, 3.74 mmol), and *N*-(3-*b*utenyl) 2-nitrobenzenesulfonamide (719 mg, 2.81 mmol). IR (film): $\tilde{\nu}$ = 3088, 2933, 1695, 1542, 1512, 1355, 1246, 1173, 1032, 681, 589 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.17 (d, J = 8.0 Hz, 1 H), 7.77–7.65 (m, 3 H), 7.36–7.30 (m, 3 H), 7.21 (d, J = 7.0 Hz, 2 H), 7.03 (d, J = 8.5 Hz, 2 H), 6.79 (d, J = 8.5 Hz, 2 H), 6.47 (d, J = 6.0 Hz, 1 H), 6.37 (d, J = 6.0 Hz, 1 H), 6.03 (br. s, 1 H), 5.61 (m, 1 H), 5.21 (d, J = 4.0 Hz, 1 H), 5.01 (d, J = 5.5 Hz, 1 H), 4.99 (s, 1 H), 4.86 (d, J = 15.0 Hz, 1 H), 4.43 (dd, J = 14.5, 5.5 Hz, 1 H), 4.36 (dd, J = 14.5, 5.5 Hz, 1 H), 3.95 (d, J = 15.0 Hz, 1 H), 3.93 (s, 1 H), 3.75 (s, 3 H), 3.21 (m, 2 H), 2.81 (d, J = 4.0 Hz, 1 H), 2.43 (m, 1 H), 2.08 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.7, 166.8, 159.4, 137.0, 136.0, 133.9, 133.8, 133.6, 132.2, 132.1, 130.3, 129.6, 129.0 (×2), 128.1, 127.9, 126.5, 124.4, 121.2, 117.7, 114.3, 91.1, 82.2, 62.9, 60.0, 55.3, 50.9, 47.4, 45.5, 44.0, 33.9 ppm. HRMS (ESI, positive): calcd. for $C_{34}H_{35}N_4O_8S$ [M + H]$^+$ 659.2170; found 659.2179.

TFA Amide 5e: To a stirred solution of **5d** (1.00 g, 1.50 mmol) in acetonitrile (20 mL) at 0 °C were added thiophenol (0.308 mL, 3.00 mmol) and Cs_2CO_3 (733 mg, 2.3 mmol). After stirring at room temp. for 2.5 h, the mixture was then poured into saturated aqueous $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The combined extracts were dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20 g, methanol/chloroform = 1:9) to give the free amine (628 mg, 88%) as a pale yellow oil, which was used in the next reaction without characterization. To a stirred solution of the resulting amine (426.8 mg, 0.099 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added TEA (0.138 mL, 0.992 mmol) and TFAA (0.138 mL, 0.992 mmol). After stirring at room temp. for 30 min, the mixture was then poured into saturated aqueous $NaHCO_3$ (50 mL) and extracted with EtOAc (2 × 100 mL). The combined extracts were washed with brine (30 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (8 g, hexane/EtOAc = 3:1) to give TFA amide **5e** (379.6 mg, 74%) as a pale yellow oil. IR (film): $\tilde{\nu}$ = 2934, 1697, 1540, 1513, 1417, 1246, 1204, 1146, 700 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.29 (m, 3 H), 7.20 (d, J = 7.5 Hz, 2 H), 7.05 (d, J = 8.5 Hz, 2 H), 6.79 (d, J = 8.5 Hz, 2 H), 6.34 (d, J = 5.5 Hz, 1 H), 6.21 (d, J = 6.0 Hz, 1 H), 6.11 (br. t, J = 5.0 Hz, 1 H), 5.68 (m, 1 H), 5.68 (s, 1 H), 5.16 (d, J = 17.0 Hz, 1 H), 5.08 (d, J = 10.5 Hz, 1 H), 4.88 (d, J = 14.5 Hz, 1 H), 4.43–4.34 (m, 3 H), 3.97 (d, J = 17.0 Hz, 1 H), 3.95 (s, 1 H), 3.74 (s, 3 H), 3.60 (m, 1 H), 3.15 (m, 1 H), 2.88 (d, J = 3.5 Hz, 1 H), 2.65 (m, 1 H), 2.35 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.4, 166.9, 159.3, 157.7, 137.1, 135.3, 134.2, 132.8, 129.5, 128.8, 128.0, 127.8, 126.6, 118.3, 117.3, 114.2, 90.8, 80.7, 62.6, 58.9, 55.2, 51.7, 46.7, 45.4, 43.8, 32.6 ppm. HRMS (ESI, positive): calcd. for $C_{30}H_{31}N_3O_5$ [M + H]$^+$ 570.2210; found 570.2198.

Heterobicycle 9: To a stirred solution of **4** (200 mg, 0.38 mmol) in benzene (5.0 mL) at room temp. were added vinyl acetate (0.173 mL, 1.87 mmol) and catalyst **8** (2.3 mg, 0.0038 mmol) under argon atmosphere. After 14 h, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (4 g, hexane/EtOAc = 7:3) to give heterobicycle **9** (205.7 mg, 87%, *E*/*Z* = 13:1) as a colorless oil. IR (film): $\tilde{\nu}$ = 3042, 1759, 1683, 1557, 1540, 1513, 1212, 1028, 699 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 (d, J = 12.0 Hz, 1 H), 7.33–7.28 (m, 3 H), 7.20 (d, J = 7.5 Hz, 2 H), 7.02 (d, J = 8.5 Hz, 2 H), 6.78 (d, J = 8.5 Hz, 2 H), 5.78–5.71 (m, 2 H), 5.43 (d, J = 12.0 Hz, 1 H), 5.42 (d, J = 14.5 Hz, 1 H), 5.36 (d, J = 10.0 Hz, 1 H), 5.05 (d, J = 14.5 Hz, 1 H), 4.41 (dd, J = 10.5, 7.0 Hz, 1 H), 4.34 (dd, J = 14.8, 6.0 Hz, 1 H), 4.29 (dd, J = 10.1, 7.0 Hz, 1 H), 3.92 (dd, J = 10.1, 7.0 Hz, 1 H), 3.78 (d, J = 14.5 Hz, 1 H), 3.76 (s, 3 H), 3.52 (s, 1 H), 3.09 (d, J = 7.0 Hz, 1 H), 2.10 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.8, 167.5, 167.3, 159.2, 139.3, 137.3, 133.0, 129.7, 128.7, 128.0, 127.7, 127.0, 121.1, 114.1, 112.6, 87.2, 84.7, 69.9, 55.2, 53.6, 45.3, 43.7, 20.6, 20.0 ppm. HRMS (ESI, positive): calcd. for $C_{28}H_{30}N_2O_6I$ [M + H]$^+$ 617.1143; found 617.1151.

Heterobicycle 10: To a stirred solution of 7-oxanorbornene **6** (50.0 mg, 0.122 mmol) in benzene (3.0 mL) at room temp. were added vinyl acetate (0.0567 mL, 0.611 mmol) and catalyst **8** (3.80 mg, 0.00611 mmol) under argon atmosphere. After stirring for 24 h, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (4 g, hexane/EtOAc = 7:3) to give heterobicycle **10** (18.5 mg, 31%) as a brown oil. The oil was an inseparable mixture of four diastereomers as judged from LC-MS and ^{1}H NMR spectra. HRMS (ESI, positive, for the major isomer): calcd. for $C_{20}H_{23}INO_5$ [M + H]$^+$ 484.0621; found 484.0620.

Heterotricycle 11a: To a stirred solution of **5a** (310 mg, 0.64 mmol) in benzene (5.0 mL) at room temp. were added vinyl acetate (0.312 mL, 3.37 mmol) and catalyst **8** (2.1 mg, 0.0032 mmol) under argon atmosphere. After 4 h, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (4 g, hexane/EtOAc = 6:4) to give heterotricycle **11a** (345.9 mg, 100%) as a brown liquid. IR (film): $\tilde{\nu}$ = 2835, 1758, 1682, 1541, 1513, 1455, 1246, 1219, 1090, 1031, 700 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34 (d, J = 12.0 Hz, 1 H), 7.33–7.27 (m,

3 H), 7.21 (d, J = 6.5 Hz, 2 H), 7.00 (d, J = 8.5 Hz, 2 H), 6.79 (d, J = 8.5 Hz, 2 H), 6.04 (dd, J = 10.0, 3.5 Hz, 1 H), 5.94 (d, J = 10.0, 2.5 Hz, 1 H), 5.78 (br. t, J = 5.5 Hz, 1 H), 5.41 (d, J = 12.0 Hz, 1 H), 5.03 (d, J = 14.5 Hz, 1 H), 4.43 (dd, J = 14.5, 6.0 Hz, 1 H), 4.38 (d, J = 3.5 Hz, 1 H), 4.34 (dd, J = 14.5, 6.0 Hz, 1 H), 4.10 (dd, J = 17.0, 3.5 Hz, 1 H), 4.10 (br. s, 1 H), 3.98 (d, J = 17.0 Hz, 1 H), 3.76 (s, 3 H), 3.71 (d, J = 14.5 Hz, 1 H), 3.66 (s, 1 H), 3.33 (s, 1 H), 2.05 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.6, 167.9 (×2), 159.5, 139.2, 137.6, 131.4, 130.0, 129.9, 129.0, 128.3, 128.0, 127.4, 122.0, 114.5, 113.2, 85.6, 78.5, 74.0, 71.6, 64.2, 59.0, 55.5, 45.4, 44.1, 21.0 ppm. HRMS (ESI, positive): calcd. for $C_{29}H_{31}N_2O_7$ $[M + H]^+$ 519.2126; found 519.2119.

Heterotricycle 11b: To a stirred solution of **5b** (298.1 mg, 0.63 mmol) in benzene (7.0 mL) at 69 °C were added vinyl acetate (0.291 mL, 3.15 mmol) and catalyst **8** (3.9 mg, 0.0063 mmol) under argon atmosphere. After 46 h, the mixture was concentrated under reduced pressure. The Ru catalyst was removed by passing through a short pad of silica gel (6 g, hexane/EtOAc = 4:6). The filtrate was concentrated under reduced pressure to give a residue which was mainly composed of triene ROM/CM product **11b′** (84% yield on isolation, E/Z = >20:1). The resulting residue was, without purification, dissolved in benzene (7.0 mL). To the stirred mixture at 69 °C was added catalyst **8** (3.9 mg, 0.0063 mmol). After 21 h, the mixture was cooled to room temp. and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (6 g, hexane/EtOAc = 6:4) to give heterotricycle **11b** (281.9 mg, 84%, E/Z > 20:1) as a brown liquid. IR (film): $\tilde{\nu}$ = 2932, 1757, 1674, 1513, 1455, 1246, 1217, 1111, 1031, 699 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 (d, J = 12.0 Hz, 1 H), 7.32–7.26 (m, 3 H), 7.16 (d, J = 7.0 Hz, 1 H), 7.00 (d, J = 8.5 Hz, 2 H), 6.79 (d, J = 8.5 Hz, 2 H), 5.79 (m, 1 H), 5.74 (br. s, 1 H), 5.60 (dd, J = 11.8, 4.0 Hz, 1 H), 5.40 (d, J = 12.0 Hz, 1 H), 5.01 (d, J = 14.5 Hz, 1 H), 4.48–4.45 (m, 2 H), 4.42 (dd, J = 14.5, 6.0 Hz, 1 H), 4.34 (dd, J = 14.5, 6.0 Hz, 1 H), 3.94 (m, 1 H), 3.76 (s, 3 H), 3.72 (d, J = 14.5 Hz, 1 H), 3.65 (d, J = 1.5 Hz, 1 H), 3.57 (m, 1 H), 3.30 (s, 1 H), 2.34–2.28 (m, 2 H), 2.06 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.8, 167.6 (×2) 159.1, 138.8, 137.4, 129.8, 129.5, 128.5, 127.8, 127.5, 127.1, 125.7, 114.0, 112.3, 83.9, 83.0, 82.5, 71.0, 69.0, 59.9, 55.1, 44.9, 43.6, 30.6, 20.6 ppm. HRMS (ESI, positive): calcd. for $C_{30}H_{33}N_2O_7$ $[M + H]^+$ 533.2282; found 533.2281.

Data for Intermediate Triene 11b′: IR (film): $\tilde{\nu}$ = 2931, 1758, 1675, 1551, 1513, 1453, 1370, 1247, 1216, 1108, 1035, 930, 700, 649, 596 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40 (d, J = 12.0 Hz, 1 H), 7.32–7.26 (m, 3 H), 7.21–7.20 (m, 2 H), 7.00 (d, J = 8.5 Hz, 2 H), 6.78 (d, J = 8.5 Hz, 2 H), 5.94 (m, 1 H), 5.85 (br. s, 1 H), 5.72 (m, 1 H), 5.41 (d, J = 12.0 Hz, 1 H), 5.26 (d, J = 17.0 Hz, 1 H), 5.23 (d, J = 10.0 Hz, 1 H), 5.02–4.94 (m, 3 H), 4.43 (dd, J = 14.5, 6.0 Hz, 1 H), 4.31 (dd, J = 14.5, 6.0 Hz, 1 H), 4.28 (dd, J = 8.0, 3.5 Hz, 1 H), 4.21 (d, J = 3.5 Hz, 1 H), 3.75 (s, 3 H), 3.71 (d, J = 15.0 Hz, 1 H), 3.69 (s, 1 H), 3.54–3.43 (m, 1 H), 2.24 (m, 2 H), 2.08 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.9, 167.7, 167.6, 159.3, 138.7, 137.3, 135.0, 133.1, 129.7, 128.7, 128.0, 127.8, 127.1, 119.2, 116.4, 114.2, 112.7, 85.2, 84.8, 83.6, 71.5, 69.2, 57.3, 55.3, 45.1, 43.8, 34.0, 20.7 ppm. HRMS (ESI, positive): calcd. for $C_{32}H_{37}N_2O_7$ $[M + H]^+$ 561.2595; found 561.2600.

Heterotricycle 11c: Using the same procedure as for the synthesis of **11a**, **11c** (1.07 g, 97%) was obtained as a brown solid starting from **5c** (1.00 g, 1.42 mmol), catalyst **8** (19.6 mg, 0.032 mmol), and vinyl acetate (0.727 mL, 7.85 mmol). IR (film): $\tilde{\nu}$ = 2940, 1758, 1696, 1542, 1513, 1370, 1245, 1172, 1031, 682, 583 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.42 (d, J = 8.0 Hz, 1 H), 7.81–7.68 (m, 3 H), 7.34–7.30 (m, 3 H), 7.20 (d, J = 7.5 Hz, 2 H), 7.05 (d, J = 8.5 Hz, 2 H), 6.83 (d, J = 8.5 Hz, 2 H), 5.91 (dd, J = 10.5, 5.0 Hz, 1 H), 5.80–5.77 (m, 2 H), 5.46 (d, J = 12.5 Hz, 1 H), 5.04 (d, J = 14.5 Hz, 1 H), 4.95 (t, J = 6.5 Hz, 1 H), 4.75 (d, J = 6.5 Hz, 1 H), 4.38 (dd, J = 14.5, 5.5 Hz, 1 H), 4.32 (dd, J = 14.5, 5.5 Hz, 1 H), 4.19 (dd, J = 18.5, 5.0 Hz, 1 H), 3.81 (s, 3 H), 3.77 (d, J = 14.5 Hz, 1 H), 3.16 (d, J = 4.0 Hz, 1 H), 2.11 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2, 167.6, 166.9, 159.3, 128.0, 138.1, 137.4, 133.9, 132.3, 132.1, 129.7, 128.6 (×2), 128.2, 128.0, 127.6, 127.4, 126.8, 126.1, 124.2, 114.2, 112.6, 84.5, 72.8, 70.6, 57.9, 55.2, 54.6, 45.0, 43.6, 40.3, 20.6 ppm. HRMS (ESI, positive): calcd. for $C_{35}H_{35}N_4O_{10}S$ $[M + H]^+$ 703.2068; found 703.2076.

Heterotricycle 11d: Using the same procedure as for the synthesis of **11b**, **11d** (220.1 mg, 90%) was obtained as a brown solid starting from **5d** (225.9 mg, 0.343 mmol), catalyst **8** (21.5 mg, 0.034 mmol), and vinyl acetate (0.159 mL, 1.720 mmol). IR (film): $\tilde{\nu}$ = 3033, 2975, 1757, 1697, 1542, 1246, 1165, 681 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.43 (d, J = 8.0 Hz, 1 H), 7.81 (t, J = 7.5 Hz, 1 H), 7.72 (t, J = 7.5 Hz, 2 H), 7.60 (d, J = 8.0 Hz, 1 H), 7.31 (d, J = 13.0 Hz, 1 H), 7.31–7.27 (m, 3 H), 7.18 (d, J = 5.5 Hz, 2 H), 6.97 (d, J = 8.5 Hz, 2 H), 6.78 (d, J = 8.5 Hz, 2 H), 5.96 (dt, J = 11.5, 3.5 Hz, 1 H), 5.69 (br. t, J = 5.5 Hz, 1 H), 5.60 (m, 1 H), 5.51 (d, J = 13.0 Hz, 1 H), 5.09 (d, J = 14.5 Hz, 1 H), 4.81 (d, J = 5.5 Hz, 1 H), 4.35 (d, J = 5.5 Hz, 2 H), 3.83 (s, 3 H), 3.77 (d, J = 9.5 Hz, 1 H), 3.77 (s, 3 H), 3.59 (d, J = 15.0 Hz, 1 H), 3.54 (s, 1 H), 3.45 (m, 1 H), 2.69 (s, 1 H), 2.67 (m, 1 H), 2.37 (d, J = 17.5 Hz, 1 H), 2.10 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.8, 167.6, 166.8, 159.4, 147.6, 138.0, 137.1, 133.8, 132.9, 132.7, 132.1, 129.9, 128.7, 128.2, 128.0, 127.8, 126.7, 123.7, 120.6, 114.3, 112.1, 84.2, 82.4, 70.8, 65.6, 59.8, 55.2, 45.0, 43.7, 42.8, 33.3, 20.6 ppm. HRMS (ESI, positive): calcd. for $C_{36}H_{37}N_4O_{10}S$ $[M + H]^+$ 717.2225; found 714.2218.

Heterotricycle 11e: Using the same procedure as for the synthesis of **11b**, **11e** (363.0 mg, 94%) was obtained starting from **5e** (354.0 mg, 0.620 mmol), catalyst **8** (38.8 mg, 0.062 mmol), and vinyl acetate (0.288 mL, 3.11 mmol). IR (film): $\tilde{\nu}$ = 2934, 1760, 1696, 1514, 1210, 1035, 700 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, ca 7:3 mixture of rotamers): δ = 7.41 (d, J = 12.5 Hz, 0.3 H), 7.35 (d, J = 12.5 Hz, 0.7 H), 7.31–7.18 (m, 5 H), 7.02 (d, J = 8.0 Hz, 0.6 H), 7.00 (d, J = 8.0 Hz, 1.4 H), 6.80 (d, J = 12.5 Hz, 0.7 H), 6.78 (d, J = 8.0 Hz, 0.6 H), 6.11 (br. s, 1 H), 5.94 (dt, J = 11.5, 4.0 Hz, 0.7 H), 5.88 (dt, J = 11.5, 4.0 Hz, 0.3 H), 5.65 (d, J = 12.5 Hz, 0.7 H), 5.64 (d, J = 12.5 Hz, 0.3 H), 5.57 (m, 1 H), 5.19–5.02 (m, 2 H), 4.76 (d, J = 5.0 Hz, 1.4 H), 4.46 (dd, J = 14.5, 6.0 Hz, 1 H), 4.39–4.35 (m, 2 H), 4.15 (t, J = 6.5 Hz, 0.7 H), 4.04–3.85 (m, 3.3 H), 3.85–3.77 (m, 6 H), 3.74–3.65 (m, 3 H), 3.55 (m, 1 H), 3.23 (d, J = 11.5 Hz, 1.4 H), 2.72 (m, 0.3 H), 2.50–2.22 (m, 1.7 H), 2.10 (s, 0.9 H), 2.08 (s, 2.1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.2, 170.8, 167.7, 167.6, 166.9, 166.8, 166.5, 166.3, 159.4, 159.3, 138.3, 137.9, 137.8, 137.7, 137.5, 137.3, 130.0 (×2), 128.5, 128.4, 128.2, 128.1, 127.5, 127.2, 126.9, 126.7, 121.2, 120.4, 114.2 (×2), 113.0, 112.6 ppm. HRMS (ESI, positive): calcd. for $C_{36}H_{37}N_4O_{10}S$ $[M + H]^+$ 717.2225; found 717.2217.

Aminal 16: To a stirred solution of vinylic acetate **11a** (1.3 mg, 0.0025 mmol) in MeOH (0.5 mL) and CH_2Cl_2 (0.5 mL) at –10 °C was added AcCl (0.38 mL, 0.0051 mmol). After 12 h, the mixture was quenched with TEA (0.5 mL) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (0.1 g, hexane/EtOAc = 5:5) to give aminal **16** (1.1 mg, 91%) as a colorless solid. IR (film): $\tilde{\nu}$ = 2917, 2247, 1658, 1513, 1453, 1247, 1091, 911, 730, 697 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.19 (m, 7 H), 6.85 (d, J = 8.5 Hz, 2 H), 6.04 (dd, J =

9.8, 3.0 Hz, 1 H), 5.88 (ddd, *J* = 9.8, 4.5, 4.5 Hz, 1 H), 5.14 (d, *J* = 14.0 Hz, 1 H), 5.05 (d, *J* = 2.5 Hz, 1 H), 4.67 (d, *J* = 14.5 Hz, 1 H), 4.62 (d, *J* = 14.5 Hz, 1 H), 4.38 (d, *J* = 14.0 Hz, 1 H), 4.29 (d, *J* = 2.5 Hz, 1 H), 4.17 (dd, *J* = 16.8, 4.5 Hz, 1 H), 4.07 (d, *J* = 16.8 Hz, 1 H), 3.91 (s, 1 H), 3.78 (s, 3 H), 3.71 (dd, *J* = 2.5, 2.5 Hz, 1 H), 2.46 (dd, *J* = 14.3, 2.5 Hz, 1 H), 2.34 (d, *J* = 2.5 Hz, 1 H), 2.05 (dd, *J* = 14.3, 2.5 Hz, 1 H) ppm. HRMS (ESI, positive): calcd. for $C_{27}H_{29}N_2O_6$ $[M + H]^+$ 477.2026; found 477.2029.

Imide 17: To a stirred solution of aminal **16** (1.0 mg, 0.0021 mmol) and molecular sieves (4 Å, 1.0 mg) in CH_2Cl_2 (0.5 mL) at 0 °C were added NMO (0.74 mg, 0.0063 mmol) and TPAP (0.15 mg, 0.0004 mmol). After 30 min, the mixture was filtered, and the fitrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (0.2 g, hexane/EtOAc = 7:3) to give imide **17** (1.0 mg, 100%) as a colorless solid. IR (film): $\tilde{\nu}$ = 2918, 1680, 1514, 1384, 1248, 1059, 850, 698 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.27–7.24 (m, 5 H), 7.21 (d, *J* = 9.0 Hz, 1 H), 6.85 (d, *J* = 9.0 Hz, 1 H), 6.06 (dd, *J* = 10.5, 4.0 Hz, 1 H), 5.89 (ddd, *J* = 10.5, 2.0, 2.0 Hz, 1 H), 5.15 (d, *J* = 14.5 Hz, 1 H), 4.24 (d, *J* = 14.5 Hz, 1 H), 4.18 (dd, *J* = 16.5, 2.0 Hz, 1 H), 4.04 (d, *J* = 16.5 Hz, 1 H), 3.69–3.95 (m, 2 H), 3.79 (s, 3 H), 3.34 (d, *J* = 16.5 Hz, 1 H), 3.08 (s, 1 H), 2.80 (d, *J* = 16.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 169.6, 169.3, 168.5, 159.4, 131.4, 130.2, 128.6, 128.5, 127.9, 126.9, 126.0, 121.7, 114.2, 80.4, 78.3, 73.6, 64.2, 63.0, 56.7, 55.3, 45.0, 43.8, 41.1 ppm. HRMS (FAB, positive): calcd. for $C_{27}H_{27}N_6O_2$ $[M + H]^+$ 475.1869; found 475.1875.

Ester Aldehyde 18a: To a stirred solution of *N*-Bn-amide **11a** (290.0 mg, 0.56 mmol) in CH_2Cl_2 (5.0 mL) at 0 °C were added Boc_2O (0.396 mL, 1.69 mmol), TEA (0.310 mL, 2.24 mmol) and DMAP (34 mg, 0.28 mmol). After 2.5 h, the mixture was diluted with EtOAc (20 mL), washed with saturated aqueous NH_4Cl (20 mL) and brine (20 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (6 g, hexane/EtOAc = 7:3) to give the intermediate *N*-Boc-imide (329 mg, 95%) as a white solid. IR (film): $\tilde{\nu}$ = 2892, 2836, 1697, 1513, 1250, 1147, 1032, 848, 700 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 12.0 Hz, 1 H), 7.29–7.21 (m, 5 H), 6.96 (d, *J* = 8.0 Hz, 2 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 6.02–5.96 (m, 2 H), 5.41 (s, 1 H), 5.22 (d, *J* = 12.0 Hz, 2 H), 4.84 (d, *J* = 15.0 Hz, 1 H), 4.80 (d, *J* = 14.5 Hz, 1 H), 4.70 (d, *J* = 15.0 Hz, 1 H), 4.39 (d, *J* = 2.5 Hz, 1 H), 4.15 (d, *J* = 2.0 Hz, 1 H), 4.08 (dd, *J* = 13.5, 3.0 Hz, 1 H), 3.97 (d, *J* = 13.5 Hz, 1 H), 3.75 (s, 3 H), 3.74 (d, *J* = 14.5 Hz, 1 H), 3.29 (s, 1 H), 2.02 (s, 3 H), 1.30 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.1, 171.6, 167.3, 159.2, 151.9, 139.1, 137.2, 130.8, 130.0, 128.3, 127.4, 127.1, 122.1, 114.1, 112.5, 85.9, 84.8, 78.1, 73.9, 69.7, 63.9, 58.7, 55.2, 47.8, 45.3, 27.6, 20.6 ppm. HRMS (ESI, positive): calcd. for $C_{34}H_{39}N_2O_9$ $[M + H]^+$ 619.2650; found 619.2660.

To a stirred solution of intermediate *N*-Boc-imide (290.0 mg, 0.56 mmol) in methanol (15 mL) at –20 °C was added K_2CO_3 (36.6 mg, 0.27 mmol). After 5 h, the mixture was poured into saturated aqueous NH_4Cl (30 mL), and the mixture was extracted with EtOAc (50 mL). The extract was washed with brine (50 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (6 g, hexane/EtOAc = 7:3) to give ester aldehyde **18a** (178 mg, 84%) as a white solid. IR (film): $\tilde{\nu}$ = 2954, 1745, 1696, 1513, 1441, 1248, 1030, 684 cm^{-1}. ^1H NMR (500 MHz, C_6D_6): δ = 9.67 (s, 1 H), 703 (d, *J* = 8.5 Hz, 2 H), 6.67 (d, *J* = 8.5 Hz, 2 H), 5.53 (dd, *J* = 5.5, 2.0 Hz, 1 H), 5.32 (dd, *J* = 10.0, 3.5 Hz, 1 H), 4.97 (d, *J* = 14.5 Hz, 1 H), 4.39 (d, *J* = 2.0 Hz, 1 H), 4.34 (s, 1 H), 3.94 (s, 1 H), 3.92 (d, *J* = 14.5 Hz, 1 H), 3.60 (dd, *J* = 17.0, 4.0 Hz, 1 H), 3.42 (d, *J* = 17.0 Hz, 1 H), 3.30 (s, 1 H), 3.22 (s, 3 H), 3.09 (s, 3 H), 2.87 (d, *J* = 16.5 Hz, 1 H), 2.45 (d, *J* = 16.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, C_6D_6): δ = 198.4, 170.5, 169.8, 159.8, 130.9, 130.1, 128.3, 122.0, 114.4, 85.1, 78.8, 74.1, 69.4, 63.9, 58.2, 54.7, 51.8, 49.1, 45.5 ppm. HRMS (ESI, positive): calcd. for $C_{21}H_{23}NO_7Na$ $[M + Na]^+$ 424.1367; found 424.1366.

Ester Aldehyde 18b: Using the same procedure as for the synthesis of **18a**, intermediate *N*-Boc-imide for **18b** (311.7 mg, 95%) was obtained as a white solid starting from **11b** (275.0 g, 0.52 mmol), Boc_2O (0.364 mL, 1.55 mmol), DMAP (19.1 mg, 0.15 mmol), and TEA (0.215 mL, 1.55 mmol). IR (film): $\tilde{\nu}$ = 2834, 1692, 1513, 1249, 1147, 847, 630 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 12.5 Hz, 1 H), 7.28–7.21 (m, 5 H), 6.96 (d, *J* = 8.5 Hz, 2 H), 6.78 (d, *J* = 8.5 Hz, 2 H), 5.75 (dt, *J* = 12.0, 5.5 Hz, 1 H), 5.66 (dd, *J* = 12.0, 4.0 Hz, 1 H), 5.37 (s, 1 H), 5.22 (d, *J* = 12.5 Hz, 1 H), 4.83 (d, *J* = 12.5 Hz, 1 H), 4.77 (d, *J* = 14.5 Hz, 1 H), 4.69 (d, *J* = 15.0 Hz, 1 H), 4.58 (br. s, 1 H), 4.47 (d, *J* = 3.0 Hz, 1 H), 3.91 (m, 1 H), 3.77–3.74 (m, 4 H), 3.58 (m, 1 H), 3.27 (s, 1 H), 2.30 (m, 2 H), 2.04 (s, 3 H), 1.30 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2, 172.0, 167.3, 159.2, 151.8, 139.2, 137.1, 130.0, 129.1, 128.2, 128.1, 127.4, 127.0, 126.4, 114.1, 111.9, 84.7, 84.5, 83.4, 82.3, 69.5, 69.0, 60.1, 55.2, 47.8, 45.3, 30.4, 27.6, 20.6 ppm. HRMS (ESI, positive): calcd. for $C_{35}H_{41}N_2O_9$ $[M + H]^+$ 633.2807; found 633.2803.

Using the same procedure as for the synthesis of **18a**, **18b** (147.1 mg, 83%) was obtained as a white solid starting from intermediate *N*-Boc-imide for **18b** (270.0 mg, 0.43 mmol) and K_2CO_3 (29.5 mg, 0.21 mmol). IR (film): $\tilde{\nu}$ = 2953, 1743, 1698, 1514, 1436, 1249, 1177, 1027, 683 cm^{-1}. ^1H NMR (500 MHz, C_6D_6): δ = 9.86 (s, 1 H), 7.16 (d, *J* = 8.5 Hz, 2 H), 6.80 (d, *J* = 8.5 Hz, 2 H), 5.60 (dd, *J* = 11.8, 3.5 Hz, 1 H), 5.45 (m, 1 H), 5.06 (d, *J* = 15.0 Hz, 1 H), 4.67 (s, 1 H), 4.66 (d, *J* = 14.5 Hz, 1 H), 4.48 (s, 1 H), 4.11 (d, *J* = 14.5 Hz, 1 H), 3.65 (m, 1 H), 3.44 (s, 1 H), 3.36 (s, 3 H), 3.22 (s, 3 H), 3.21 (m, 1 H), 3.08 (d, *J* = 17.3 Hz, 1 H), 2.62 (d, *J* = 17.3 Hz, 1 H), 1.85 (m, 2 H) ppm. ^{13}C NMR (125 MHz, C_6D_6): δ = 198.6, 171.0, 169.8, 159.8, 130.1, 128.9, 128.5, 126.7, 114.4, 83.8, 83.7, 82.5, 69.2, 68.8, 59.5, 54.7, 51.8, 48.7, 45.6, 30.0 ppm. HRMS (ESI, positive): calcd. for $C_{22}H_{25}NO_7Na$ $[M + H]^+$ 438.1523; found 438.1518.

Diester 19a: To a stirred solution of aldehyde **18a** (222.7 mg, 0.55 mmol) in *t*BuOH (15.0 mL) and water (5.0 mL) at room temp. were added 2-methyl-2-butene (0.291 mL, 2.75 mmol), $NaH_2PO_4 \cdot 2H_2O$ (94.2 mg, 0.60 mmol), and $NaClO_2$ (148.3 mg, 1.65 mmol). After 5 h, the mixture was diluted with CH_2Cl_2 (50 mL), and the mixture was washed with hydrochloric acid (1 M, 20 mL) and brine (20 mL). The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in methanol (15.0 mL) and cooled to 0 °C. TMS-CHN_2 (2 M in Et_2O, 0.84 mL, 1.68 mmol) was added, and the mixture was allowed to warm to room temp. After stirring for 30 min, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (6 g, hexane/EtOAc = 4:6) to give diester **19a** (235.4 mg, 94%) as a white solid. IR (film): $\tilde{\nu}$ = 2953, 1744, 1698, 1513, 1437, 1248, 1178, 1049, 822, 684 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.10 (d, *J* = 8.5 Hz, 2 H), 6.82 (d, *J* = 8.5 Hz, 2 H), 6.02 (dd, *J* = 10.5, 3.5 Hz, 1 H), 5.93 (m, 1 H), 4.81 (d, *J* = 14.5 Hz, 1 H), 4.39 (d, *J* = 3.0 Hz, 1 H), 4.34 (s, 1 H), 4.15 (dd, *J* = 17.3, 3.5 Hz, 1 H), 4.03 (d, *J* = 17.3 Hz, 1 H), 4.01 (s, 1 H), 4.00 (d, *J* = 14.5 Hz, 1 H), 3.77 (s, 3 H), 3.61 (s, 3 H), 3.58 (s, 3 H), 3.37 (s, 1 H), 3.11 (d, *J* = 16.5 Hz, 1 H), 2.75 (d, *J* = 16.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ =

170.8, 170.3, 170.1, 159.2, 130.6, 129.7, 127.1, 122.5, 114.1, 85.1, 78.3, 73.6, 68.2, 64.1, 57.7, 55.2, 52.4, 51.7, 45.4, 40.1 ppm. HRMS (ESI, positive): calcd. for $C_{22}H_{25}NO_8Na$ [M + Na]$^+$ 454.1472; found 454.1477.

Diester 19b: Using the same procedure as for the synthesis of **19a**, **19b** (139.3 mg, 73%) was obtained as a colorless oil starting from **18b** (147.1 mg, 0.35 mmol), 2-methyl-2-butene (0.226 mL, 2.14 mmol), $NaH_2PO_4{\cdot}2H_2O$ (73.3 mg, 0.47 mmol), $NaClO_2$ (115.3 mg, 1.28 mmol), and TMS-CHN_2 (2 M in Et_2O, 0.35 mL, 0.70 mmol). IR (film): $\tilde{\nu}$ = 2953, 1744, 1698, 1513, 1437, 1248, 1047, 820 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.08 (d, J = 8.5 Hz, 2 H), 6.81 (d, J = 8.5 Hz, 2 H), 5.73 (dt, J = 11.5, 5.5 Hz, 1 H), 5.58 (dd, J = 11.5, 3.5 Hz, 1 H), 4.77 (d, J = 14.5 Hz, 1 H), 4.49–4.47 (m, 2 H), 4.30 (s, 1 H), 4.02 (d, J = 14.5 Hz, 1 H), 3.93 (m, 1 H), 3.77 (s, 3 H), 3.66 (m, 1 H), 3.62 (s, 3 H), 3.56 (s, 3 H), 3.34 (s, 1 H), 3.11 (d, J = 17.0 Hz, 1 H), 2.72 (d, J = 17.0 Hz, 1 H), 2.38–2.26 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.4, 170.3, 170.0, 159.2, 129.7, 128.3, 127.2, 127.1, 114.1, 83.7, 83.3, 81.8, 68.7, 68.0, 58.9, 55.2, 52.3, 51.6, 45.3, 39.4, 29.9 ppm. HRMS (ESI, positive): calcd. for $C_{23}H_{27}NO_8Na$ [M + Na]$^+$ 468.1629; found 468.1634.

Tetrahydropyran 20a: To a stirred solution of **19a** (12.2 mg, 0.028 mmol) in MeOH (0.5 mL) at room temp. was added Pd/C (10 wt.-%, 0.6 mg). The mixture was stirred vigorously under hydrogen atmosphere for 1 h. The catalyst was then removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1 g, hexane/EtOAc = 2:8) to give **20a** (11.8 mg, 96%) as a colorless oil. IR (film): $\tilde{\nu}$ = 2849, 1746, 1695, 1513, 1433, 1250, 1166, 1105, 1030, 821, 658 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.09 (d, J = 8.5 Hz, 2 H), 6.81 (d, J = 8.5 Hz, 2 H), 4.78 (d, J = 15.0 Hz, 1 H), 4.31 (s, 1 H), 4.24 (br. s, 1 H), 3.96 (d, J = 15.0 Hz, 1 H), 3.86 (dd, J = 9.5, 2.0 Hz, 1 H), 3.77 (m, 4 H), 3.63 (s, 3 H), 3.58 (s, 3 H), 3.34 (dd, J = 9.5, 9.5 Hz, 1 H), 3.21 (br. s, 1 H), 3.18 (d, J = 17.0 Hz, 1 H), 2.77 (d, J = 17.0 Hz, 1 H), 2.00 (br. d, J = 14.5 Hz, 1 H), 1.75 (m, 1 H), 1.62 (m, 1 H), 1.31 (ddd, J = 14.5, 3.0, 3.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.1, 170.3, 170.2, 159.2, 129.9, 127.2, 114.1, 84.4, 78.6, 76.6, 69.0, 66.4, 58.0, 55.2, 52.4, 51.7, 45.3, 39.9, 24.8, 19.8 ppm. HRMS (FAB, positive): calcd. for $C_{22}H_{28}NO_8$ [M + H]$^+$ 434.1815; found 434.1817.

Oxepane 20b: Using the same procedure as for the synthesis of **20a**, **20b** (30.0 mg, 100%) was obtained as a white solid starting from **19b** (30.0 mg, 0.067 mmol) and Pd/C (10 wt.-%, 3 mg). IR (film): $\tilde{\nu}$ = 2949, 1746, 1698, 1514, 1437, 1249, 1176, 1078, 1051, 823, 737 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.07 (d, J = 9.0 Hz, 2 H), 6.80 (d, J = 9.0 Hz, 2 H), 4.72 (d, J = 14.5 Hz, 1 H), 4.35 (d, J = 4.5 Hz, 1 H), 4.25 (s, 1 H), 4.14 (dd, J = 12.3, 4.5 Hz, 1 H), 4.05 (m, 1 H), 4.03 (d, J = 14.5 Hz, 1 H), 3.75 (s, 1 H), 3.06 (d, J = 16.0 Hz, 1 H), 2.73 (d, J = 16.0 Hz, 1 H), 2.07 (m, 1 H), 1.77–1.56 (m, 2 H), 1.22 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.6, 170.3, 170.2, 159.2, 129.6, 127.1, 114.1, 87.0, 84.9, 84.7, 74.4, 67.8, 59.1, 55.2, 52.3, 51.7, 45.4, 39.5, 32.2 (×2), 21.4 ppm. HRMS (FAB, positive): calcd. for $C_{23}H_{30}NO_8$ [M + H]$^+$ 448.1971; found 448.1965.

Pyrrolidine 21a: To a stirred solution of pyrrolidone **20a** (9.2 mg, 0.021 mmol) in THF (0.5 mL) at 0 °C was added $BH_3{\cdot}SMe_2$ (1.0 M solution in THF, 0.11 mL, 0.110 mmol). The mixture was stirred vigorously under Ar atmosphere at 40 °C for 48 h. The mixture was then quenched by the addition of MeOH (1 mL) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1 g, hexane/EtOAc = 85:15) to give pyrrolidine **21a** (4.7 mg, 53%) as a colorless oil. IR (film): $\tilde{\nu}$ = 2847, 1746, 1612, 1513, 1438, 1253, 1171, 1038, 647, 732 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.15 (d, J = 9.0 Hz, 2 H), 6.81 (d, J = 9.0 Hz, 2 H), 4.13 (br. s, 1 H), 3.89 (s, 1 H), 3.81 (br. d, J = 11.0 Hz, 1 H), 3.78 (s, 3 H), 3.71 (s, 3 H), 3.64 (s, 3 H), 3.63 (d, J = 13.0 Hz, 1 H), 3.60 (br. s, 1 H), 3.43 (d, J = 13.0 Hz, 1 H), 3.24 (dd, J = 11.5, 11.5 Hz, 1 H), 3.07 (dd, J = 9.5, 9.5 Hz, 1 H), 3.02 (d, J = 15.0 Hz, 1 H), 2.76 (d, J = 15.0 Hz, 1 H), 2.70 (dd, J = 15.0, 4.5 Hz, 1 H), 2.32 (dd, J = 15.0, 4.5 Hz, 1 H), 2.14 (br. d, J = 15.0 Hz, 1 H), 1.86 (m, 1 H), 1.62 (m, 1 H), 1.27 (br. d, J = 15.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.3, 171.0, 158.7, 130.1, 129.7, 113.6, 91.4, 81.5, 76.6, 74.2, 66.6, 55.2, 55.1, 53.6, 53.0, 51.5, 51.2, 40.9, 25.0, 20.0 ppm. HRMS (FAB, positive): calcd. for $C_{22}H_{30}NO_7$ [M + H]$^+$ 420.2022; found 420.2027.

Pyrrolidine 21b: Using the same procedure as for the synthesis of **21a**, **21b** (11.3 mg, 43%) was obtained as a colorless oil starting from **20b** (27.4 mg, 0.061 mmol). IR (film): $\tilde{\nu}$ = 2934, 1746, 1697, 1612, 1513, 1439, 1250, 1176, 1110, 822, 736 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.16 (d, J = 9.0 Hz, 2 H), 6.82 (d, J = 9.0 Hz, 2 H), 4.26 (m, 1 H), 4.04 (dd, J = 12.3, 5.0 Hz, 1 H), 3.80 (s, 1 H), 3.77 (s, 3 H), 3.69 (s, 3 H), 3.64–3.60 (m, 5 H), 3.48 (d, J = 13.5 Hz, 1 H), 3.19 (m, 1 H), 3.16 (dd, J = 9.5, 9.5 Hz, 1 H), 2.89 (d, J = 15.5 Hz, 1 H), 2.78 (d, J = 15.5 Hz, 1 H), 2.76 (dd, J = 9.5, 4.5 Hz, 1 H), 2.38 (dd, J = 9.5, 4.5 Hz, 1 H), 2.03 (m, 1 H), 1.85–1.66 (m, 3 H), 1.66 (m, 1 H), 1.26 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.4, 171.0, 158.7, 130.1, 129.7, 113.6, 91.5, 91.0, 84.1, 74.1, 72.7, 55.2, 54.8, 54.6, 51.5, 51.3, 41.0, 31.9, 30.6, 20.7 ppm. HRMS (FAB, positive): calcd. for $C_{23}H_{32}NO_7$ [M + H]$^+$ 434.2179; found 434.2170.

***N*-Boc-Pyrrolidine 22a:** To a stirred solution of PMB amine **21a** (18.0 mg, 0.043 mmol) in EtOH (0.5 mL) at room temp. were added palladium hydroxide (10 wt.-% on carbon, 2.0 mg) and Boc_2O (0.0500 mL, 0.215 mmol). The mixture was stirred vigorously under hydrogen atmosphere for 24 h. The catalyst was then removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1 g, hexane/EtOAc = 15:85) to give **22a** (12.0 mg, 68%) as a white solid. IR (film): $\tilde{\nu}$ = 1742, 1701, 1391, 1250, 1169, 1105, 1041, 897 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers): δ = 4.72 (br. s, 1 H), 4.05 (br. s, 1 H), 3.84 (m, 2 H), 3.78 (br. s, 1 H), 3.67 (m, 6 H), 3.34–3.14 (m, 3 H), 2.92–2.82 (m, 1 H), 2.76–2.66 (m, 1 H), 2.10 (m, 1 H), 1.80 (m, 1 H), 1.64 (m, 1 H), 1.42–1.38 (m, 9 H), 1.32 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, selected): δ = 171.1, 170.5, 154.1, 91.7, 81.8, 80.5, 75.8, 69.5, 66.4, 52.0, 51.6, 48.6, 40.3, 28.3, 28.2, 24.9, 19.8 ppm. HRMS (ESI, positive): calcd. for $C_{19}H_{29}NO_8Na$ [M + Na]$^+$ 422.1785; found 422.1791.

***N*-Boc-Pyrrolidine 22b:** Using the same procedure as for the synthesis of **22a**, **22b** (11.3 mg, 92%) was obtained as a white solid starting from **21b** (11.3 mg, 0.026 mmol). IR (film): $\tilde{\nu}$ = 1701, 1384, 1070 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers): δ = 4.67 (br. s, 1 H), 3.30 (m, 1 H), 4.10 (m, 1 H), 3.91–3.86 (m, 2 H), 3.67 (m, 6 H), 3.31–3.19 (m, 2 H), 3.14–3.04 (m, 1 H), 2.99–2.89 (m, 1 H), 2.61–2.53 (m, 1 H), 2.09 (m, 1 H), 1.77–1.65 (m, 4 H), 1.42–1.37 (m, 9 H), 1.27–1.20 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, selected): δ = 171.3, 170.3, 154.0, 91.2, 90.0, 83.9, 80.4, 74.0, 68.7, 52.9, 52.0, 51.6, 49.4, 39.6, 32.1, 31.8, 28.2, 21.4 ppm. HRMS (ESI, positive): calcd. for $C_{20}H_{31}NO_8Na$ [M + Na]$^+$ 436.1941; found 436.1946.

Glutamate Analogue 23a: A suspension of fully protected glutamate analogue **22a** (5.4 mg, 0.014 mmol) in hydrochloric acid (6 M, 0.5 mL) was heated at 65 °C for 10 h. The reaction mixture was then cooled to room temp. and concentrated under reduced pressure. The residue was purified by column chromatography on re-

versed-phase silica gel (500 mg, water). The active fractions were lyophilized to afford glutamate analogue **23a** (2.6 mg, 63%) as a white solid. IR (film): $\tilde{\nu}$ = 1717, 1704, 1419, 1199, 1104, 1050 cm^{-1}. ^1H NMR (500 MHz, D_2O): δ = 4.22 (s, 1 H), 4.18 (s, 1 H), 3.90 (s, 1 H), 3.83 (dd, J = 12.8, 10.0 Hz, 1 H), 3.78 (d, J = 13.5 Hz, 1 H), 3.32 (t, J = 12.0 Hz, 1 H), 3.17 (d, J = 16.5 Hz, 1 H), 3.06 (dd, J = 12.8, 9.0 Hz, 1 H), 2.95 (t, J = 9.0 Hz, 1 H), 2.92 (d, J = 16.5 Hz, 1 H), 1.97 (br. d, J = 14.0 Hz, 1 H), 1.81–1.65 (m, 2 H), 1.34 (d, J = 16.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, D_2O/CD_3OD = 15:1): δ = 174.2, 168.7, 89.9, 78.9, 75.4, 67.5, 66.5, 52.7, 45.2, 40.4, 23.5, 19.2 ppm. HRMS (ESI, positive): calcd. for $C_{12}H_{18}NO_6$ $[M + H]^+$ 272.1129; found 272.1133.

Glutamate Analogue 23b: Using the same deprotection procedure as for the synthesis of **23a**, **22b** (2.4 mg, 0.014 mmol) was deprotected to give glutamate analogue **23b** (1.4 mg, 77%) as a white solid. IR (film): $\tilde{\nu}$ = 1716, 1635, 1397, 1085, 1062, 979 cm^{-1}. ^1H NMR (500 MHz, D_2O): δ = 4.39 (ddd, J = 7.0, 6.0, 3.5 Hz, 1 H), 4.22 (s, 1 H), 4.10 (d, J = 3.5 Hz, 1 H), 4.03 (d, J = 12.0 Hz, 1 H), 3.91 (t, J = 11.0 Hz, 1 H), 3.29 (m, 1 H), 3.11 (d, J = 16.5 Hz, 1 H), 3.09 (d, J = 7.5 Hz, 1 H), 2.93 (dd, J = 11.0, 7.5 Hz, 1 H), 2.82 (d, J = 16.5 Hz, 1 H), 2.06 (m, 1 H), 1.71 (m, 1 H), 1.64–1.60 (m, 3 H), 1.25 (m, 1 H) ppm. ^{13}C NMR (125 MHz, D_2O/CD_3OD = 15:1): δ = 174.6, 170.2, 90.2, 88.9, 83.6, 74.2, 68.2, 53.4, 46.9, 41.0, 31.5, 31.0, 20.9 ppm. HRMS (ESI, positive): calcd. for $C_{13}H_{19}NO_6$ $[M + H]^+$ 286.1293; found 286.1285.

Diol 24a: To a stirred solution of olefin **19a** (39.1 mg, 0.091 mmol) in *t*BuOH (0.6 mL) at room temp. was added a solution of NMO (50% in water, 0.3 mL) and OsO4 (1% in *t*BuOH, 0.300 mL, 0.003 mmol). After 10 h, saturated aqueous $Na_2S_2O_4$ (5 mL) was added, and the mixture was extracted with EtOAc (3 × 5 mL). The combined extracts were washed with brine (2 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1 g, hexane/EtOAc = 3:7) to give diol **24a** (37.1 mg, 88%) as a colorless amorphous solid. IR (film): $\tilde{\nu}$ = 3389, 2917, 1745, 1680, 1513, 1439, 1250, 1177, 1082, 842, 742, 658 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.12 (d, J = 9.0 Hz, 2 H), 6.85 (d, J = 9.0 Hz, 2 H), 4.78 (d, J = 14.5 Hz, 1 H), 4.50 (br. s, 1 H), 4.33 (s, 1 H), 4.09 (br. s, 1 H), 3.99 (d, J = 14.5 Hz, 1 H), 3.90 (m, 1 H), 3.87 (dd, J = 2.5, 2.5 Hz, 1 H), 3.80 (s, 3 H), 3.67–3.65 (m, 4 H), 3.61 (s, 3 H), 3.54 (dd, J = 10.5, 10.5 Hz, 1 H), 3.28 (s, 1 H), 3.10 (d, J = 16.5 Hz, 1 H), 2.91 (br. s, 1 H), 2.77 (d, J = 16.5 Hz, 1 H), 2.54 (br. d, J = 7.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6, 170.1, 169.9, 159.3, 130.0, 126.8, 114.2, 84.6, 82.1, 76.4, 68.8, 66.5, 64.5, 64.1, 57.0, 55.3, 52.5, 51.8, 45.4, 39.9 ppm. HRMS (FAB, positive): calcd. for $C_{22}H_{28}NO_{10}$ $[M + H]^+$ 466.1713; found 466.1720.

Diol 24b: Using the same procedure as for the synthesis of **24a**, **24b** (89.6 mg, 83%) was obtained as a colorless oil starting from **19b** (80.4 mg, 0.172 mmol). IR (film): $\tilde{\nu}$ = 3401, 2918, 1744, 1691e, 1612, 1514, 1439, 1249, 1177, 1065, 919, 734, 642 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.07 (d, J = 9.0 Hz, 2 H), 6.82 (d, J = 9.0 Hz, 2 H), 4.66 (d, J = 15.5 Hz, 1 H), 4.59 (d, J = 4.5 Hz, 1 H), 4.22 (s, 1 H), 4.19 (br. s, 1 H), 4.13 (dd, J = 7.5, 4.5 Hz, 1 H), 4.11 (d, J = 15.5 Hz, 1 H), 3.94 (m, 1 H), 3.91 (br. d, J = 7.5 Hz, 1 H), 3.78–3.74 (m, 4 H), 3.64 (s, 3 H), 3.55 (s, 3 H), 3.55 (s, 3 H), 3.29 (s, 1 H), 3.02 (d, J = 16.0 Hz, 1 H), 2.75 (d, J = 16.0 Hz, 1 H), 2.56 (br. s, 1 H, OH), 2.32 (br. s, 1 H, OH), 1.91 (m, 1 H), 1.79 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.1, 170.1, 170.0, 159.2, 129.7, 127.0, 114.0, 87.2, 84.9, 84.2, 77.5, 71.8, 68.0, 67.4, 59.3, 55.2, 52.4, 51.9, 45.5, 39.3, 34.7 ppm. HRMS (FAB, positive): calcd. for $C_{23}H_{30}NO_{10}$ $[M + H]^+$ 480.1870; found 480.1872.

Acetonide 25a: To a stirred solution of diol **24a** (20.0 mg, 0.043 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C were added 2,2-dimethoxypropane (0.0158 mL, 0.129 mmol) and CSA (2.0 mg, 0.0086 mmol). The mixture was stirred vigorously at room temp. for 1 h. The reaction mixture was then quenched by the addition of triethylamine (1 mL) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1 g, hexane/EtOAc = 7:3) to give **25a** (20.0 mg, 92%) as a colorless oil. IR (film): $\tilde{\nu}$ = 2917, 1746, 1700, 1513, 1438, 1249, 1176, 1065, 854, 734 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.09 (d, J = 8.0 Hz, 2 H), 6.83 (d, J = 8.0 Hz, 2 H), 4.81 (d, J = 14.5 Hz, 1 H), 4.39 (br. d, J = 2.0 Hz, 1 H), 4.31 (br. d, J = 2.0 Hz, 1 H), 4.30 (s, 1 H), 4.16 (m, 1 H), 4.03 (br. s, 1 H), 3.93 (d, J = 14.5 Hz, 1 H), 3.78–3.76 (m, 4 H), 3.62 (s, 3 H), 3.60 (s, 3 H), 3.33 (s, 1 H), 3.10 (dd, J = 11.0 Hz, 1 H), 3.00 (d, J = 16.5 Hz, 1 H), 2.72 (d, J = 16.5 Hz, 1 H), 1.42 (s, 3 H), 1.31 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.3, 170.0 (×2), 159.3, 130.0, 126.9, 114.2, 108.9, 84.0, 77.9, 74.4, 72.3, 68.5, 68.3, 65.8, 57.3, 55.3, 52.5, 51.8, 45.4, 40.0, 28.1, 26.0 ppm. HRMS (FAB, positive): calcd. for $C_{25}H_{32}NO_{10}$ $[M + H]^+$ 506.2026; found 506.2032.

Acetonide 25b: Using the same procedure as for the synthesis of **25a**, **25b** (84.2 mg, 99%) was obtained as a colorless oil starting from **24b** (78.5 mg, 0.164 mmol). IR (film): $\tilde{\nu}$ = 2952, 1745, 1700, 1612, 1513, 1438, 1249, 1210, 1174, 1065, 843, 684 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.06 (d, J = 8.5 Hz, 2 H), 6.78 (d, J = 8.5 Hz, 2 H), 4.58 (d, J = 15.0 Hz, 1 H), 4.52 (d, J = 6.0 Hz, 1 H), 4.35 (dd, J = 7.5, 6.0 Hz, 1 H), 4.32 (m, 1 H), 4.28 (s, 1 H), 4.18 (d, J = 15.0 Hz, 1 H), 4.17 (dd, J = 7.5, 6.0 Hz, 1 H), 3.86 (dd, J = 11.5, 5.0 Hz, 1 H), 3.79 (dd, J = 11.5, 5.0 Hz, 1 H), 3.75 (s, 3 H), 3.64 (s, 3 H), 3.51 (s, 3 H), 3.35 (s, 1 H), 3.04 (d, J = 16.0 Hz, 1 H), 2.82 (d, J = 16.0 Hz, 1 H), 2.09–1.99 (m, 2 H), 1.45 (s, 3 H), 1.31 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.3, 170.0, 169.6, 159.2, 129.7, 126.9, 114.0, 108.2, 86.7, 85.2, 81.1, 78.9, 73.9, 67.3, 65.7, 58.3, 55.2, 52.4, 51.9, 45.7, 39.2, 29.9, 27.5, 24.4 ppm. HRMS (FAB, positive): calcd. for $C_{26}H_{34}NO_{10}$ $[M + H]^+$ 520.2183; found 520.2181.

Pyrrolidine 26a: Using the same procedure as for the synthesis of **21a**, **26a** (13.2 mg, 33%) was obtained as a colorless oil starting from pyrrolidone **25a** (40.0 mg, 0.079 mmol). IR (film): $\tilde{\nu}$ = 2951, 1743, 1613, 1512, 1436, 1248, 1150, 1063, 855, 735 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.15 (d, J = 8.5 Hz, 2 H), 6.82 (d, J = 8.5 Hz, 2 H), 4.43 (br. d, J = 4.5 Hz, 1 H), 4.36 (br. s, 1 H), 4.18 (m, 1 H), 3.92 (s, 1 H), 3.78–3.76 (m, 4 H), 3.73–3.70 (m, 4 H), 3.63–3.61 (m, 4 H), 3.43 (d, J = 13.5 Hz, 1 H), 3.14 (dd, J = 9.5, 9.5 Hz, 1 H), 3.03 (dd, J = 10.5, 10.5 Hz, 1 H), 2.87 (d, J = 15.0 Hz, 1 H), 2.80 (dd, J = 9.5, 4.0 Hz, 1 H), 2.75 (dd, J = 10.5, 10.5 Hz, 1 H), 2.44 (dd, J = 9.5, 4.0 Hz, 1 H), 1.43 (s, 3 H), 1.34 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.9, 170.7, 158.8, 129.8, 129.7, 113.7, 108.7, 90.9, 80.7, 78.6, 73.7, 72.0, 68.6, 65.7, 55.2, 54.9, 53.2, 53.0, 51.6, 51.2, 40.9, 28.1, 26.0 ppm. HRMS (FAB, positive): calcd. for $C_{25}H_{34}NO_9$ $[M + H]^+$ 492.2234; found 492.2229.

Pyrrolidine 26b: Using the same procedure as for the synthesis of **21a**, **26b** (15.3 mg, 36%) was obtained as a colorless oil starting from **25b** (43.4 mg, 0.084 mmol). IR (film): $\tilde{\nu}$ = 2916, 1743, 1613, 1512, 1436, 1248, 1168, 1039, 821, 683 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.16 (d, J = 8.5 Hz, 2 H), 6.82 (d, J = 8.5 Hz, 2 H), 4.39–4.30 (m, 3 H), 3.90 (dd, J = 5.0, 2.5 Hz, 1 H), 3.78 (s, 3 H), 3.78–3.73 (m, 2 H), 3.67 (s, 3 H), 3.64 (s, 3 H), 3.64–3.56 (m, 3 H), 3.25 (dd, J = 9.0, 9.0 Hz, 1 H), 2.95 (dd, J = 4.0, 2.5 Hz, 1 H), 2.88 (d, J = 15.0 Hz, 1 H), 2.84 (d, J = 15.0 Hz, 1 H), 2.52 (dd, J = 9.0, 3.5 Hz, 1 H), 2.02–1.90 (m, 2 H), 1.48 (s, 3 H), 1.32 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.1, 170.4, 158.5, 129.8, 129.5, 113.4, 107.3, 91.6, 85.5, 84.3, 79.2, 73.6, 73.5, 65.1, 55.2, 55.0, 54.8,

53.5, 51.3, 51.1, 39.8, 30.5, 27.1, 24.0 ppm. HRMS (FAB, positive): calcd. for $C_{26}H_{36}NO_9$ [M + H]$^+$ 506.2390; found 506.2387.

***N*-Boc-Pyrrolidine 27a:** Using the same procedure as for the synthesis of **22a**, **27a** (11.5 mg, 100%) was obtained as a white solid starting from **26a** (12.0 mg, 0.024 mmol). IR (film): $\tilde{\nu}$ = 2980, 1744, 1703, 1392, 1249, 1170, 1063, 858, 764 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.68 (br. s, 1 H), 4.40 (br. d, J = 4.5 Hz, 1 H), 4.28 (br. s, 1 H), 4.18 (m, 1 H), 3.91 (br. s, 1 H), 3.87 (d, J = 11.5 Hz, 1 H), 3.74 (dd, J = 11.3, 6.0 Hz, 1 H), 3.67–3.62 (m, 5 H), 3.40 (dd, J = 11.3, 3.5 Hz, 1 H), 3.07–2.94 (m, 3 H), 2.63 (d, J = 16.0 Hz, 1 H), 1.44–1.32 (m, 15 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.8, 170.2, 153.8, 108.9, 91.3, 81.0, 80.7, 77.8, 72.0, 69.2, 68.4, 65.7, 52.1, 51.7, 51.4, 48.7, 40.2, 28.3, 28.2, 26.0 ppm. HRMS (FAB, positive): calcd. for $C_{22}H_{34}NO_{10}Na$ [M + Na]$^+$ 472.2183; found 472.2180.

***N*-Boc-Pyrrolidine 27b:** Using the same procedure as for the synthesis of **22a**, **27b** (6.0 mg, 97%) was obtained as a white solid starting from **26b** (6.5 mg, 0.0129 mmol). IR (film): $\tilde{\nu}$ = 2979, 1747, 1702, 1395, 1247, 1212, 1169, 1065, 919, 732 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.74 (s, 1 H), 4.02 (br. s, 1 H), 3.83–3.64 (m, 10 H), 3.58 (dd, J = 11.5, 3.0 Hz, 1 H), 3.18 (m, 1 H), 2.84 (d, J = 16.5 Hz, 1 H), 2.79 (d, J = 16.5 Hz, 1 H), 2.03 (m, 1 H), 1.92 (m, 1 H), 1.48 (s, 3 H), 1.38 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.9, 169.8, 153.8, 108.1, 91.1, 84.6, 82.8, 80.7, 79.3, 73.6, 68.7, 65.5, 52.0, 51.8, 49.3, 38.4, 30.2, 28.3, 28.2, 27.3, 24.2 ppm. HRMS (FAB, positive): calcd. for $C_{23}H_{36}NO_{10}$ [M + H]$^+$ 486.2339; found 486.2340.

Glutamate Analogue 28a: Using the same deprotection procedure as for the synthesis of **23a**, **27a** (11.6 mg, 0.025 mmol) was deprotected to give glutamate analogue **28a** (7.2 mg, 100%) as a white solid. IR (film): $\tilde{\nu}$ = 3419, 1716, 1634, 1403, 1240, 1088 cm^{-1}. ^{1}H NMR (500 MHz, D_2O): δ = 4.39 (s, 1 H), 4.18 (s, 1 H), 4.07 (s, 2 H), 3.86–3.82 (m, 2 H), 3.55 (dd, J = 11.0, 5.0 Hz, 1 H), 3.42 (t, J = 11.0 Hz, 1 H), 3.13 (d, J = 17.0 Hz, 1 H), 3.09–3.00 (m, 2 H), 2.90 (d, J = 17.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, D_2O/CD_3OD = 15:1): δ = 175.7, 170.3, 92.0, 82.4, 78.6, 78.5, 67.3, 65.8, 65.3, 53.2, 46.9, 42.0 ppm. HRMS (ESI, positive): calcd. for $C_{12}H_{18}NO_8$ [M + H]$^+$ 304.1027; found 304.1032.

Glutamate Analogue 28b: Using the same deprotection procedure as for the synthesis of **23a**, **27b** (7.7 mg, 0.016 mmol) was deprotected to give glutamate analogue **28b** (5.0 mg, 100%) as a white solid. IR (film): $\tilde{\nu}$ = 3420, 1748, 1623, 1375, 1223, 1036 cm^{-1}. ^{1}H NMR (500 MHz, D_2O): δ = 4.34 (s, 1 H), 4.28 (dd, J = 7.5, 4.5 Hz, 1 H), 4.19 (d, J = 4.5 Hz, 1 H), 4.10 (d, J = 4.0 Hz, 1 H), 3.96–3.87 (m, 3 H), 3.55 (t, J = 13.0 Hz, 1 H), 3.12 (d, J = 16.5 Hz, 1 H), 3.11 (dd, J = 12.5, 7.0 Hz, 1 H), 2.96 (dd, J = 10.8, 7.0 Hz, 1 H), 2.86 (d, J = 16.5 Hz, 1 H), 1.89 (ddd, J = 18.8, 13.0, 4.5 Hz, 1 H), 1.69 (dd, J = 13.3, 4.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, D_2O/CD_3OD = 15:1): δ = 174.3, 170.2, 90.7, 86.7, 86.0, 77.0, 72.8, 68.4, 68.3, 53.2, 47.0, 40.4, 34.4 ppm. HRMS (ESI, positive): calcd. for $C_{13}H_{20}NO_8$ [M + H]$^+$ 318.1183; found 318.1193.

Heterobicycles 29a–29c: To a stirred solution of **4** (51.0 mg, 0.096 mmol) and 4-bromobutene (0.0485 mL, 0.478 mmol) in benzene (1.1 mL) at room temp. was added catalyst **8** (3.0 mg, 0.0048 mmol). After 1 h, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (0.5 g, hexane/EtOAc = 4:6) to give an inseparable mixture of heterobicycles **29a** (62%), **29b** (36%), and **29c** (2%) as colorless oils. Analytical samples were prepared by recycling gel-permeation liquid chromatography (GPC-LC) using $CHCl_3$ as an eluent.

Data for (*E*)-Isomer of 29a: IR (film): $\tilde{\nu}$ = 2918, 1693, 1660, 1513, 1416, 1246, 1031, 750, 632 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.19 (m, 5 H), 7.03 (d, J = 8.5 Hz, 2 H), 6.78 (d, J = 8.5 Hz, 2 H), 5.84 (ddd, J = 15.5, 6.5, 6.5 Hz, 1 H), 5.79 (dd, J = 16.8, 11.0 Hz, 1 H), 5.66 (br. s, 1 H), 5.47 (d, J = 16.8 Hz, 1 H), 5.44 (dd, J = 15.5, 10.5 Hz, 1 H), 5.20 (d, J = 11.0 Hz, 1 H), 5.06 (d, J = 14.5 Hz, 1 H), 4.39 (dd, J = 14.3, 5.5 Hz, 1 H), 4.31 (dd, J = 14.3, 5.5 Hz, 1 H), 4.29 (dd, J = 10.5, 8.0 Hz, 1 H), 3.85 (dd, J = 8.0, 7.5 Hz, 1 H), 3.78 (d, J = 14.5 Hz, 1 H), 3.76 (s, 3 H), 3.50 (s, 1 H), 3.40 (m, 2 H), 3.08 (d, J = 7.5 Hz, 1 H), 2.64 (dd, J = 14.0, 6.5 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.9, 167.2, 159.2, 137.2, 135.1, 134.1, 129.8, 128.8, 128.1 (×2), 128.0, 127.1, 117.8, 114.2, 86.7, 86.5, 69.8, 55.3, 53.1, 45.3, 43.8, 35.4, 31.4, 20.7 ppm. HRMS (FAB, positive): calcd. for $C_{28}H_{31}O_4N_2BrI$ [M + H]$^+$ 665.0512; found 665.0513.

Data for (*Z*)-Isomer of 29a: IR (film): $\tilde{\nu}$ = 2918, 1692, 1660, 1514, 1417, 1031, 732, 645 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.20 (m, 5 H), 7.04 (d, J = 8.5 Hz, 2 H), 6.80 (d, J = 8.5 Hz, 2 H), 6.02 (br. s, 1 H), 5.80–5.72 (m, 2 H), 5.45 (d, J = 16.5 Hz, 1 H), 5.35 (dd, J = 9.0, 9.0 Hz, 1 H), 5.18 (d, J = 10.5 Hz, 1 H), 5.10 (d, J = 10.8, 7.0 Hz, 1 H), 3.75 (s, 3 H), 3.68 (d, J = 14.5 Hz, 1 H), 3.56 (s, 1 H), 3.45–3.32 (m, 2 H), 3.07 (d, J = 7.0 Hz, 1 H), 2.71–2.66 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.9, 167.2, 159.3, 137.2, 135.0, 134.4, 129.6, 128.7, 128.0, 127.9, 127.4, 127.2, 117.9, 114.2, 86.5, 81.3, 69.8, 55.3, 53.0, 45.2, 43.8, 31.5, 31.4, 20.4 ppm. HRMS (FAB, positive): calcd. for $C_{28}H_{31}O_4N_2BrI$ [M + H]$^+$ 665.0512; found 665.0513.

Data for (*E*)-Isomer of 29b: IR (film): $\tilde{\nu}$ = 2920, 1693, 1660, 1555, 1513, 1417, 1247, 1030, 732, 699, 647 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.20 (m, 5 H), 7.03 (d, J = 9.0 Hz, 1 H), 6.78 (d, J = 9.0 Hz, 1 H), 5.86 (m, 1 H), 5.78 (m, 1 H), 5.48 (d, J = 17.0 Hz, 1 H), 5.43 (d, J = 17.0 Hz, 1 H), 5.19 (d, J = 11.0 Hz, 1 H), 5.06 (d, J = 14.5 Hz, 1 H), 4.39 (dd, J = 15.5, 6.0 Hz, 1 H), 4.34 (dd, J = 15.5, 6.0 Hz, 1 H), 4.30 (dd, J = 9.5, 9.5 Hz, 1 H), 3.85 (dd, J = 9.5, 7.0 Hz, 1 H), 3.78 (d, J = 14.5 Hz, 1 H), 3.77 (s, 3 H), 3.52 (s, 1 H), 3.25 (m, 2 H), 3.09 (d, J = 7.0 Hz, 1 H), 2.43 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.0, 167.2, 159.2, 137.2, 133.2, 130.8, 130.1, 129.8, 129.6, 127.9, 120.9, 117.8, 114.2, 87.2, 81.3, 69.8, 53.1, 45.3, 43.8 (×2), 34.8, 31.5, 20.2 ppm. HRMS (FAB, positive): calcd. for $C_{28}H_{31}O_4N_2BrI$ [M + H]$^+$ 665.0512; found 665.0520.

Data for 29c: IR (film): $\tilde{\nu}$ = 2917, 1692, 1660, 1514, 1416, 1246, 1030, 753, 700 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.20 (m, 5 H), 7.03 (d, J = 8.5 Hz, 2 H), 6.78 (d, J = 8.5 Hz, 2 H), 5.77 (m, 1 H), 5.72 (dd, J = 10.5, 7.0 Hz, 1 H), 5.95 (br. s, 1 H), 5.49 (dd, J = 16.8, 1.5 Hz, 1 H), 5.44 (d, J = 17.0 Hz, 1 H), 5.35 (d, J = 10.0 Hz, 1 H), 5.19 (d, J = 10.5, 1.5 Hz, 1 H), 5.08 (d, J = 15.0 Hz, 1 H), 4.40 (dd, J = 14.5, 6.0 Hz, 1 H), 4.37 (dd, J = 14.5, 6.0 Hz, 1 H), 4.31 (dd, J = 11.0, 7.0 Hz, 1 H), 3.86 (dd, J = 11.0, 7.5 Hz, 1 H), 3.78 (d, J = 15.0 Hz, 1 H), 3.76 (s, 3 H), 3.51 (s, 1 H), 3.09 (d, J = 7.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.9, 167.2, 159.2, 137.1, 135.1, 133.2, 129.8, 128.8, 128.1, 127.9, 127.1, 121.0, 117.9, 114.2, 87.2, 86.5, 69.8, 55.3, 53.2, 45.3, 43.9, 20.2 ppm. HRMS (FAB, positive): calcd. for $C_{26}H_{28}O_4N_2I$ [M + H]$^+$ 559.1094; found 559.1100.

Amine 30: A solution of 2-furfural (0.254 mL, 3.0 mmol) and 4-methoxyaniline (739 mg, 6.0 mmol) in THF (9.0 mL) was stirred at room temp. under Ar for 30 min, and then benzyl bromide (1.07 mL, 9.0 mmol) and Zn dust (589 mg, 9.0 mmol) were added. The resultant mixture was stirred for 24 h, quenched with 1% hydrochloric acid, and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried with Na_2SO_4 and concentrated under re-

duced pressure. The residue was purified by column chromatography on silica gel (20 g, hexane/EtOAc = 9:1) to give amine **30** (685.3 mg, 78%) as a yellow oil. IR (film): $\tilde{\nu}$ = 3389, 3027, 2931, 1603, 1511, 1239, 1037, 819, 736 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.35 (br. s, 1 H), 7.23–7.17 (m, 3 H), 7.03 (d, J = 7.0 Hz, 2 H), 6.71 (d, J = 8.5 Hz, 2 H), 6.23 (br. s, 1 H), 6.00 (br. s, 1 H), 4.64 (dd, J = 6.0, 6.0 Hz, 1 H), 3.70 (s, 3 H), 3.18 (dd, J = 12.5, 6.0 Hz, 1 H), 3.14 (dd, J = 12.5, 6.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.3, 152.4, 141.4, 140.9, 137.4, 129.2, 128.3, 126.6, 115.3, 114.7, 110.2, 106.7, 55.6, 54.1, 40.9 ppm. HRMS (FAB, positive): calcd. for $C_{19}H_{19}O_2N$ $[M + H]^+$ 293.1416; found 293.1421.

Amide 31: To a stirred solution of amine **30** (500.0 mg, 1.704 mmol) in THF (5.0 mL) at room temp. were added (*Z*)-3-iodoacryl chloride (737.9 mg, 3.408 mmol) and Cs_2CO_3 (1.100 g, 3.408 mmol). After 1 h, saturated aqueous NH_4Cl (50 mL) was added, and the mixture was extracted with EtOAc (50 mL). The extract was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20 g, hexane/EtOAc = 9:1) to give amide **31** (361.6 mg, 45%) as a yellow solid. IR (film): $\tilde{\nu}$ = 3372, 2917, 1650, 1509, 1385, 1250, 1025, 740 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.31 (br. s, 1 H), 7.25–7.16 (m, 4 H), 7.17 (m, 1 H), 6.86–6.69 (m, 5 H), 6.50 (d, J = 8.5 Hz, 1 H), 6.34 (dd, J = 8.0, 8.0 Hz, 1 H), 6.23 (dd, J = 3.0, 1.5 Hz, 1 H), 3.77 (s, 3 H), 3.19 (dd, J = 8.0, 4.5 Hz, 1 H), 3.15 (dd, J = 8.0, 4.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.3, 159.4, 152.3, 141.7, 137.2, 132.9, 130.5, 129.1, 128.4, 126.5, 114.1, 110.3, 109.8, 109.3, 88.8, 55.4, 53.1, 36.4 ppm. HRMS (FAB, positive): calcd. for $C_{22}H_{21}IO_3N$ $[M + H]^+$ 474.0566; found 474.0573.

7-Oxanorbornene 32: A solution of amide **31** (360.0 mg, 0.761 mmol) in toluene (30 mL) was heated to 100 °C for 24 h. The mixture was then concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (10 g, hexane/EtOAc = 7:3) to give 7-oxanenorbornene **32** (100.0 mg, 28%) and 7-*epi*-**32** (184.6 mg, 51%) as colorless oils.

Data for 32: IR (film): $\tilde{\nu}$ = 2916, 1697, 1512, 1248, 1034, 833, 680 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.49 (d, J = 9.0 Hz, 1 H), 7.28–7.15 (m, 5 H), 6.92 (d, J = 9.0 Hz, 1 H), 6.53 (d, J = 6.0 Hz, 1 H), 6.31 (dd, J = 6.0, 2.0 Hz, 1 H), 5.23 (d, J = 2.0 Hz, 1 H), 4.72 (dd, J = 8.3, 3.5 Hz, 1 H), 3.81 (d, J = 8.0 Hz, 1 H), 3.79 (s, 3 H), 3.17 (dd, J = 15.3, 3.5 Hz, 1 H), 3.07 (dd, J = 15.3, 8.3 Hz, 1 H), 2.26 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.1, 157.5, 153.6, 153.5, 134.5, 130.2, 128.9, 128.8, 128.3, 125.2, 114.4, 93.1, 88.3, 60.9, 55.4, 48.9, 35.5, 18.7 ppm. HRMS (FAB, positive): calcd. for $C_{22}H_{21}IO_3N$ $[M + H]^+$ 474.0566; found 474.0566.

Data for 7-*epi*-32: IR (film): $\tilde{\nu}$ = 2954, 1701, 1511, 1248, 1035, 842 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.16 (m, 7 H), 6.96 (d, J = 8.5 Hz, 2 H), 6.13 (dd, J = 5.5, 2.0 Hz, 1 H), 5.95 (d, J = 5.5 Hz, 1 H), 5.36 (d, J = 2.0 Hz, 1 H), 4.62 (dd, J = 11.0, 4.5 Hz, 1 H), 3.88 (d, J = 7.5 Hz, 1 H), 3.82 (s, 3 H), 2.98 (dd, J = 13.3, 11.0 Hz, 1 H), 2.92 (dd, J = 13.3, 4.5 Hz, 1 H), 2.45 (d, J = 7.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.9, 158.1, 136.8, 136.2, 133.0, 129.7, 128.2, 127.0, 126.5, 125.1, 114.3, 91.8, 88.3, 60.6, 55.4, 49.8, 33.5, 19.4 ppm. HRMS (FAB, positive): calcd. for $C_{22}H_{21}IO_3N$ $[M + H]^+$ 474.0566; found 474.0565.

Heterobicycle 33: To a stirred solution of 7-oxanorbornene **32** (36.4 mg, 0.077 mmol) and vinyl acetate (0.454 mL, 0.385 mmol) in benzene (20 mL) at room temp. was added catalyst **8** (1.5 mg, 0.0023 mmol). After 5 h, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (0.5 g, hexane/EtOAc = 8:2) to give vinylic acetate **33** (*E*/*Z* = 1:1, 25.8 mg, 60%) as a colorless oil, together with unreacted **32** (10.0 mg, 28%).

Data for (*E*)-Isomer of 33: IR (film): $\tilde{\nu}$ = 2916, 1762, 1699, 1512, 1395, 1249, 1205, 1035, 831, 751, 679 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.41 (d, J = 9.0 Hz, 2 H), 7.18–7.11 (m, 4 H), 7.01 (d, J = 6.5 Hz, 2 H), 6.83 (d, J = 9.0 Hz, 2 H), 5.73 (m, 1 H), 5.54 (d, J = 10.0 Hz, 1 H), 5.41 (d, J = 17.0 Hz, 1 H), 5.35 (d, J = 7.5 Hz, 1 H), 4.46–4.40 (m, 2 H), 4.00 (dd, J = 8.8, 8.5 Hz, 1 H), 3.77 (s, 3 H), 2.02–2.80 (m, 3 H), 2.12 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.8, 167.5, 157.5, 138.8, 136.1, 133.5, 130.0, 129.3, 128.4, 126.7, 125.0, 121.2, 114.3, 113.4, 87.3, 85.6, 69.2, 55.5, 53.3, 36.5, 20.6, 20.3 ppm. HRMS (FAB, positive): calcd. for $C_{26}H_{27}O_5NI$ $[M + H]^+$ 560.0934; found 560.0939.

Data for (*Z*)-Isomer of 33: IR (film): $\tilde{\nu}$ = 2916, 1762, 1699, 1512, 1395, 1249, 1205, 1035, 831, 751, 679 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.41 (d, J = 9.0 Hz, 2 H), 7.18–7.11 (m, 3 H), 7.13 (d, J = 7.5 Hz, 1 H), 7.00 (d, J = 6.5 Hz, 2 H), 6.89 (d, J = 9.0 Hz, 2 H), 5.71 (m, 1 H), 5.37 (d, J = 17.0 Hz, 1 H), 5.28 (d, J = 10.0 Hz, 1 H), 4.95 (d, J = 7.5 Hz, 1 H), 4.56 (dd, J = 6.8, 4.5 Hz, 1 H), 4.48 (dd, J = 8.5, 8.5 Hz, 1 H), 4.11 (dd, J = 8.8, 8.5 Hz, 1 H), 3.79 (s, 3 H), 3.27 (d, J = 8.0 Hz, 1 H), 2.86 (dd, J = 14.8, 6.8 Hz, 1 H), 2.80 (dd, J = 14.8, 4.5 Hz, 1 H), 2.16 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.0, 166.7, 157.7, 136.2, 134.4, 134.2, 129.9, 129.5, 128.3, 126.6, 125.4, 119.9, 114.4, 112.0, 87.2, 86.3, 68.4, 55.5, 54.0, 35.6, 22.5, 20.7 ppm. HRMS (FAB, positive): calcd. for $C_{26}H_{27}O_5NI$ $[M + H]^+$ 560.0934; found 560.0942.

Data for Dimer 35: IR (film): $\tilde{\nu}$ = 2917, 1762, 1700, 1511, 1386, 1248, 1034, 831, 681 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.45–6.80 (m, 19 H), 6.02 (d, J = 15.0 Hz, 1 H), 5.93 (dd, J = 15.3, 6.0 Hz, 2 H), 5.73 (dddd, J = 17.0, 17.0, 10.3, 7.5 Hz, 1 H), 5.52 (d, J = 12.0 Hz, 1 H), 5.41 (d, J = 17.0 Hz, 1 H), 5.35 (d, J = 10.0 Hz, 1 H), 4.50–4.38 (m, 4 H), 4.01–3.98 (m, 2 H), 3.77 (s, 3 H), 3.76 (s, 3 H), 3.00–2.78 (m, 6 H), 2.10 (s, 3 H) ppm. HRMS (FAB, positive): calcd. for $C_{48}H_{47}O_8N_2I_2$ $[M + H]^+$ 1033.1422; found 1033.1421.

Neuronal Culture and Electrophysiology: Rat hippocampal neurons were isolated from E18 embryos and cultured as described previously.[24] Electrophysiological recordings were performed at 17–28 d in vitro with a Multiclamp 700A amplifier and pClamp 10 software (MDS Analytical Technologies, Sunnyvale, CA). Spontaneous action potentials were recorded using the current-clamp configuration in HEPES-buffered saline external solution and K-methanesulfonate-based internal solution. Neurons examined in this study had spontaneous frequencies of action potential firing of >0.5 Hz. AMPA/kainate-mediated excitatory postsynaptic currents (EPSCs) were recorded in voltage-clamp in extracellular solution containing bicuculline methiodide and picrotoxin (10 μM and 50 μM, respectively) to block $GABA_A$ receptors and D-APV (50 μM) to inhibit NMDA receptors. CsF/CsCl-based internal solution was used for voltage-clamp recordings. All recordings were made at room temperature, and drugs were bath-applied. Analyses of EPSCs were carried out in Clampfit (MDS Analytical Technologies) and consisted of charge transfer analysis (current area) during 1–2 min recording segments in the absence and presence of **28a**. Action potential frequencies were analyzed using MiniAnal software (Synaptosoft, Decatur, GA). Statistical analysis was performed using GraphPad Prism 4 (La Jolla, CA).

Supporting Information (see also the footnote on the first page of this article): General experimental methods, LC-MS spectrum for **10**, and ^1H and ^{13}C NMR spectra for all compounds. NOESY spectra for **25a**, **25b**, **32**, and 8-*epi*-**32**. ^1H NMR spectra for monitoring Fischer-type carbene formation.

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