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Regioselective Domino Metathesis of 7-Oxanorbornenes and Its Application to the Synthesis of Biologically Active Glutamate Analogues

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Abstract

A highly regioselective domino metathesis reaction of 7-oxanorbornene was developed that employed an intramolecular association of an amide carbonyl group to a ruthenium metal centre. By using this reaction, twelve glutamate analogues inspired by dysiherbaine were efficiently synthesized over 12–14 steps; one of the analogues exhibited bioactivity consistent with central nervous system depression.

Keywords

Nitrogen heterocycles; Oxygen heterocycles; Combinatorial chemistry; Domino reactions; Metathesis; Regioselectivity

Introduction

The olefin metathesis reaction plays an important role in modern synthetic organic chemistry. [1] Although it has been shown to be useful for the synthesis of complex molecules, including biologically active natural products, the chemo- or regioselectivities are not always controlled well. For example, a series of domino ring-opening metathesis (ROM)/cross-metathesis (CM) reactions of unsymmetrical norbornene derivatives has been shown to be poorly regioselective. [2] However, these studies suggested that a long-range electronic effect of a remote substituent might be useful for controlling the regioselectivity; indeed, Rainier et al. found that a *p*-tolylsulfonyl group is efficient for realization of the regioselective domino ROM/CM sequence when it is introduced into a norbornene skeleton as a substituent. [3] We found independently that compound **1** was transformed into a seven-membered ring by ring-closing metathesis (RCM) in a good yield, whereas **2** was shown to be a mismatched substrate (Figure 1). [4] Although the details of the mechanism remain unclear, we speculated that the *upper* exocyclic

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Supporting Information (see footnote on the first page of this article): Full experimental details, spectroscopic data and calculation data.

amide carbonyl group (arrow) defined the regiochemistry by interacting with the ruthenium (Ru) metal centre[5] and led to kinetically controlled regioselective formation of the intermediary metallacyclobutane in the Chauvin mechanism.[6] In the present study, we investigated domino metathesis of various 7-oxanorbornenes to examine the origin of the regioselectivity we observed previously. We eventually found that the substrates with an *upper* exocyclic amide carbonyl group generally provided products with a high level of regioselectivity, whereas this was not the case for substrates without the carbonyl associating group. Regio- and chemoselectivity in the olefin metathesis directed by an internal functionality has been proposed by Cossy (CM),[7a] Fürstner (RCM),[5] Grubbs (CM)[7b] and Tayler (CM),[7c] but ours is the one to address the associating effect on the ROM reaction. [8] In addition, the present study demonstrates the utility of the reactions by preparing novel bioactive glutamate analogues (Scheme 1, compound **C**). Twelve novel and structurally diverse analogues of the marine toxin dysiherbaine[9] and its synthetic analogue MSVIII-19, which exhibited antagonist actions on ionotropic glutamate receptors (iGluRs)[10] (Figure 2), were conveniently prepared from oxanorbornene **A** by way of metathesis product **B** (Scheme 1). Interestingly, one of these unique cyclic analogues of glutamate exhibited marked central depressant activity in vivo and in vitro assays, suggesting that its molecular mechanism of action is fundamentally distinct from that of the parent dysiherbaine molecule.

Results and Discussion

The highly functionalized 7-oxanorbornene skeleton **3** was first constructed selectively in 68 % yield by tandem Ugi/Diels–Alder reactions by using furfural and (*Z*)-3-iodoacrylic acid for the aldehyde and carboxylic acid components, respectively (Scheme 2).[4c,12] Sterically demanding iodine-substituted acrylate was used in the intramolecular Diels–Alder reaction in a series of our study[4c] and also worked well in the present tandem reaction. Subsequently, four olefin groups were introduced into **3** by replacement of the iodo group. In order to introduce alkenyloxy groups, sodium hydride was used at $-40\text{ }^{\circ}\text{C}$ to give **4a** and **4b** with yields of 73 and 49 %, respectively. As an alternative approach, Cs_2CO_3 was used at $50\text{ }^{\circ}\text{C}$ for the preparation of 2-nitrobenzenesulfonamides (Ns-amides) **4c** (100 %) and **4d** (76 %). Ns-amide **4d** was further converted into trifluoroacetamide (TFA-amide) **4e** in two steps (65 % yield), thereby enabling us to examine the effects of these protecting groups on the metathesis reaction. Compounds **5** and **6**,[4c] which do not bear the *N*-benzyl (Bn) amide group, were also used for comparison.[11]

The metathesis reaction of 7-oxanorbornenes **3–6** with vinyl acetate in benzene was next examined by using Hoveyda–Grubbs second-generation catalyst **7**,[13a] as other catalysts, such as the Grubbs second-generation catalyst,[13b] did not sustain the catalytic activity long enough for the domino reaction of 7-oxanorbornenes.[4a] As shown in Table 1 (run 1), iodide **3** was treated at room temperature to generate **8** in 87 % yield with exclusive regio- (>99 %) and good stereoselectivities (*E/Z* = 13:1). The structure of **8** was unambiguously determined as the desired diastereomer by analysis of the ^1H – ^1H connectivities in the NMR spectra. The formation of **8** indicates that the intermediary Ru carbene was generated regioselectively at the C5 position despite severe steric repulsion with the fused pyrrolidone ring. Interestingly, in the absence of an *N*-benzylaminocarbonyl side chain, the same reaction with **5** generated a mixture of four products (**10**, 30:28:6:1) in only 31 % combined yield (Table 1, run 2). The metathesis reaction of **4a** proceeded well at room temperature up to 4 h to generate heterotricycle **9a** in quantitative yield (Table 1, run 3). In contrast, the reaction of **6** occurred slowly over 8.5 h and was not highly selective, yielding two products, **11** and **12**, by a less-regioselective ROM reaction (Table 1, run 4). Arjona et al.[14a] and Tadano et al.[14b] also observed this low selectivity in a closely related domino metathesis reaction. Thus, a directing effect of the amide carbonyl group (indicated by the arrow on **3**) should reasonably account for these selectivities. Interestingly, only a very small amount of the *cis* isomer was detected at the acetoxyalkenyl

moiety in the presence of the exocyclic carbonyl group. The CM reaction is now speculated to be kinetically controlled, and the selectivity in runs 1 and 3 indicates that the formation of a *trans*-metallacyclobutane intermediate is favoured, because of the steric bulkiness of the upper exocyclic amide group, whereas this is not the case for runs 2 and 4, where the sterically demanding group is absent. This is also supported by semiempirical molecular orbital calculations (PM3) for a model compound (see Supporting Information). The same result was also obtained with Ns-amide **4c**, which selectively produced **9c** in 97 % yield (Table 1, run 6).

Seven-membered heterocycles were generated in runs 5, 7, and 8 (Table 1), suggesting that the course of the metathesis (ROM/CM) reactions had occurred, although the reactions were slow and did not reach completion even after heating at 69 °C. In fact, the intermediary ROM/CM bicyclic product with a 5/5 ring system was isolated as the sole product by the first metathesis reaction of **4b** (Table 1, run 5; see the Supporting Information), suggesting again that the directing effect of the *upper* exocyclic amide carbonyl group occurred in the ROM. In these runs, desired seven-membered heterocycles **9b**, **9d** and **9e** were eventually obtained cleanly after a second metathesis reaction, which was performed on the purified bicyclic product in the absence of vinyl acetate (see the Supporting Information). These observations indicated that this metathesis sequence takes place in the order of regioselective ROM, CM and RCM.[15] Nitrogen protecting groups were found to have no significant effect on these metathesis reactions (Table 1, run 7 vs. run 8).

Our experiment thus demonstrated that a neighbouring amide carbonyl group can direct regiochemistry in the ROM reaction of norbornenes (Scheme 3, **D**→**E**→**F**).[2b,2c,3a,16] This is a unique example of a directing effect of the carbonyl group in olefin metathesis, because stable chelation of the oxygen atom usually causes a drastic loss of reactivity in the metal centre.[5,7] It is likely, however, that the sterically hindered *cis*-fused pyrrolidone ring system hampers the formation of a “too stable” chelate with the amide oxygen atom when metallacyclobutane **E** is formed, allowing the successive CM and RCM reactions to proceed smoothly, leading to tricycles **9a–e** by way of triene **G**. Some of the intermediates were optimized at PM3 to rationalize the reaction course (see the Supporting Information). It should also be noted here that although we currently believe that the associating mechanism shown in Figure 1 and Scheme 3 is the most plausible from a series of our studies,[4] a Fischer carbene mechanism[17] cannot be completely ruled out with the present data. In the latter case, steric interaction of the large ruthenium Fischer carbene complex would determine the regioselectivity. A more detailed discussion will be described in a full account of this work.

The metathesis products were further converted into glutamate analogues by functional group transformation reactions as follows. For seven-membered nitrogen heterocycles, TFA-protected **9e** was employed, because of the low reactivity of **9d** that was often encountered in the subsequent series of syntheses. First, the exocyclic Bn amide was treated with Boc₂O, followed by careful methanolysis of the generated Boc imide and the acetyl (Ac) group at –20 °C to give a moderate yield of the ester aldehyde (**13a–c**, **13e**; Scheme 4). The aldehyde functionality was further transformed into a methyl ester in two steps, and the *p*-methoxybenzyl (PMB) group was removed by ceric ammonium nitrate (CAN) at –10 °C to obtain **14a–c** and **14e**. For the deoxygenation of the pyrrolidone carbonyl group, several methods were attempted, including reduction with borane or silyl hydride. We eventually found that the reduction of the imidate with NaBH₃CN, derived from **14a–c** and **14e** by using the Meerwein reagent,[18] was the most efficient in our case, giving the desired pyrrolidine in good yields (59–85 %). The amine functionality was temporarily protected with a Boc group to yield **15a–c** and **15e**. At this stage, the Ns group in **15c** was replaced with a Boc group for the simultaneous generation of the active functional groups later. Finally, **15a**, **15b**, **15e** and **15f** were transformed into dihydroxylated glutamate analogues by a sequence of diastereoselective dihydroxylation from the convex β-face by OsO₄, followed by acidic hydrolysis to give **16–19** in fairly good yields.

Total yields were 9.5–16.0 % over 13–15 steps starting from (*Z*)-3-iodoacrylic acid. We also achieved the synthesis of another eight analogues, which exhibit structural diversity in the lowest third ring as shown in Scheme 5.

In our preliminary biological evaluations, both in vivo and in vitro, these artificial glutamate analogues were found to have bioactivities that contrasted those elicited by the parent dysiherbaine or neodysiherbaine A,[19] which are potent convulsants. Namely, intracranial injection of compound **16** in mice induced profound hypoactivity (20 µg/mouse, *n* = 3) consistent with a cataleptic state.[20] This hypoactivity likely arose from attenuation of central excitatory neurotransmission, because **16** also markedly reduced both action potential firing frequency and spontaneous excitatory synaptic currents in current- and voltage-clamp electrophysiological analyses from cultured hippocampal neurons. Interestingly, however, **16** did not displace radioactive ligands for NMDA, kainate or AMPA receptors (constituent members of the iGluR superfamily) from rat brain synaptic membranes in radioligand binding assays, suggesting that the immobilization of the mice and marked attenuation of neuronal excitability might not arise from direct inhibition of iGluRs. Additional studies to define the mechanism of action of this compound are ongoing.

Conclusions

In conclusion, we developed a highly regioselective domino metathesis (ROM/CM/RCM) reaction of 7-oxanorbornenes. The selectivity was proposed to be controlled by association of a neighbouring amide carbonyl group to the ruthenium metal centre. A nearly common sequence consisting of 12–14 steps of reactions yielded *cis*-fused heterocycles with a high level of efficiency (14.0–23.5 % total yields from **3**). By using this pathway, we achieved the synthesis of 12 unique glutamate analogues with structural resemblance to dysiherbaines. Preliminary biological evaluation revealed unexpected neuronal inhibition and cataleptic mouse behavioural activity by **16**. Thus, our present work demonstrates that synthetic strategies toward skeletally and functionally diverse glutamate analogues may generate bioactive compounds that modulate synaptic transmission through distinct mechanisms. It should be noted that small molecules that modulate the synaptic function of iGluRs are of significant biomedical interest, as glutamatergic neurotransmission is essential for higher brain functions such as memory formation, learning or neuropathology of brain and nociception.[21] Further biological evaluation and structure refinement may lead to the identification of both the pharmacophore and the molecular target(s) of these novel glutamate analogues. Our regioselective domino metathesis approach will also play a key role in further studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

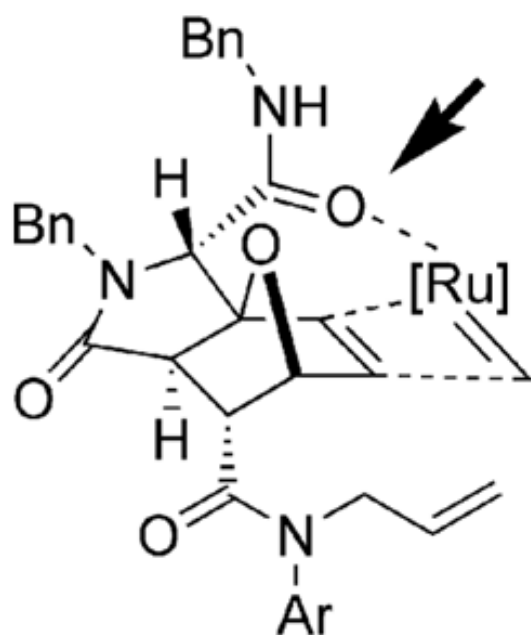
Acknowledgments

This research was financially supported by the Ministry of Education, Culture, Sports, Science and Technology, Japan (Priority Area 16073202). A research fellowship to M.I. from the Japan Society for the Promotion of Science (JSPS) is gratefully acknowledged. We thank one of the reviewers for valuable comments for the possible involvement of a Fischer carbene mechanism in these studies.

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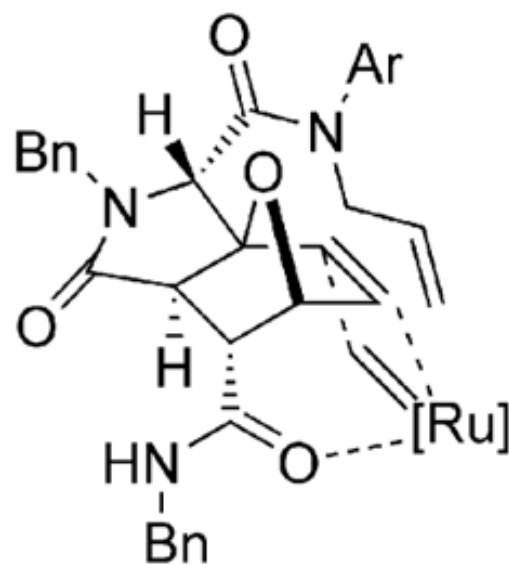
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**1**

excellent substrate
for ROM/CM/RCM
(81–82% yield)

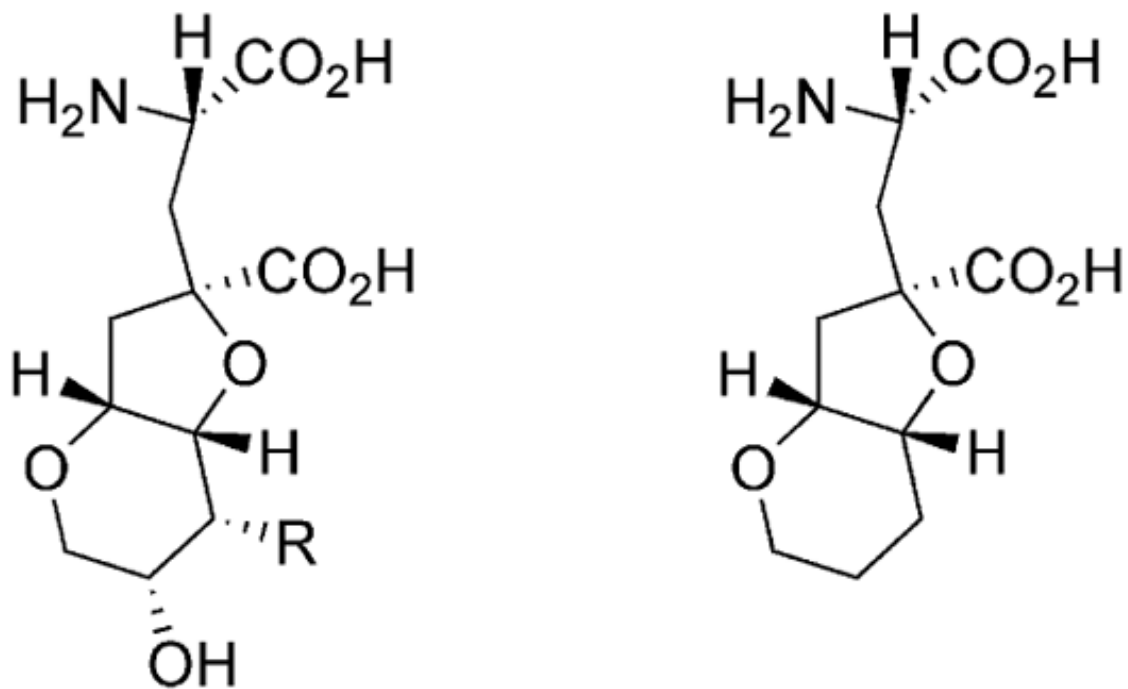
matched

**2**

poor substrate
for ROM/CM/RCM
(30–65% yield)

mismatched

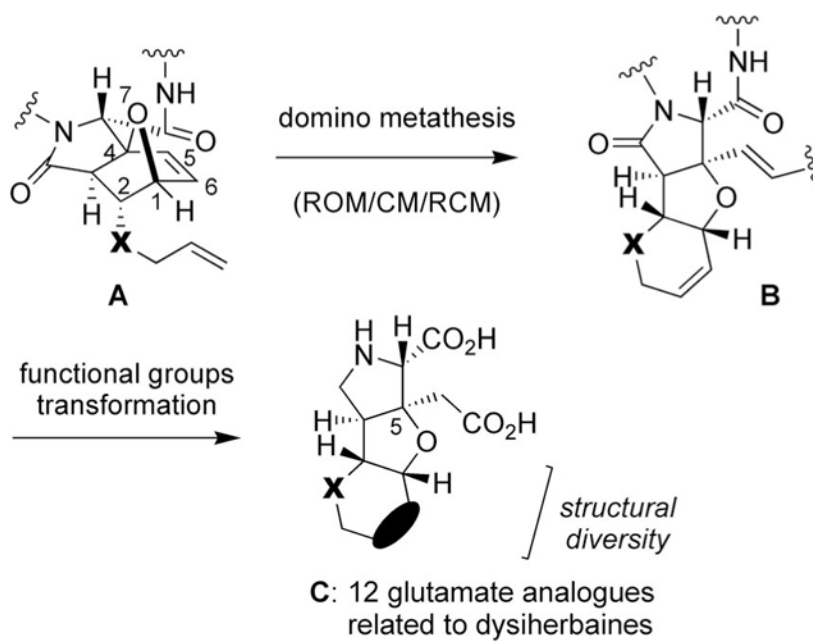
Figure 1.
Our previous observation suggested a directing effect of the exocyclic carbonyl group.[4]
Pointing arrow indicates the proposed coordinating site to the Ru metal centre in the matched case.



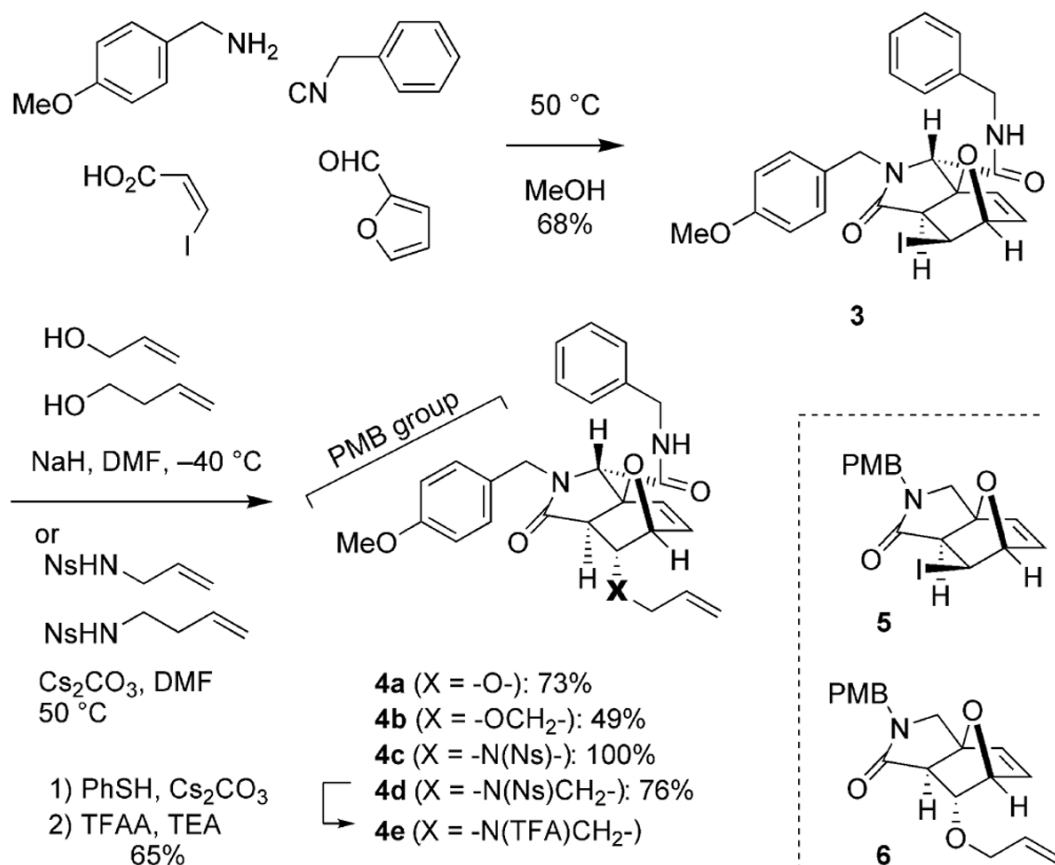
dysiherbaine ($\text{R} = -\text{NHMe}$)
neodysiherbaine A ($\text{R} = -\text{OH}$)

MSVIII-19

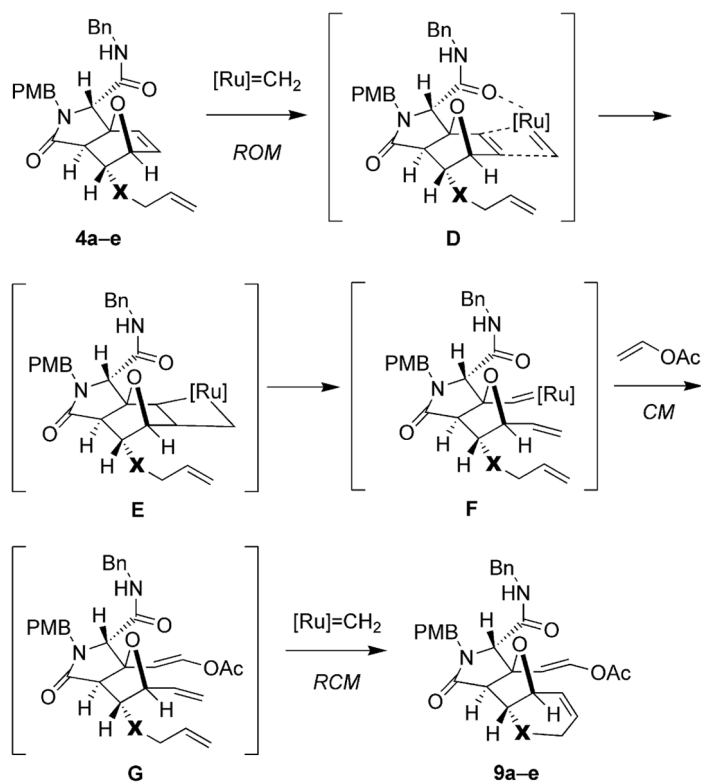
Figure 2.
Dysiherbaine congeners[9] and its antagonistic analogue MSVIII-19.[10]



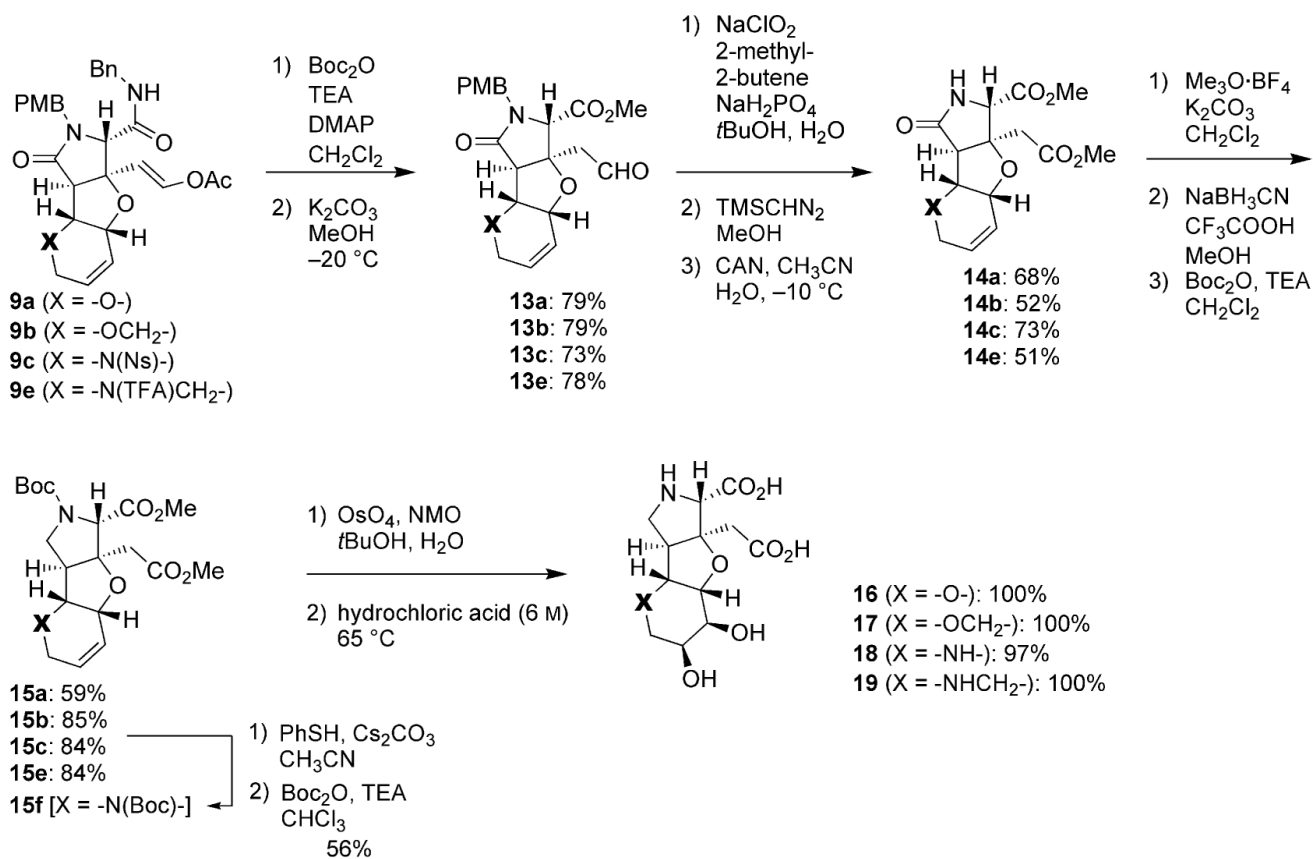
Scheme 1.
Our strategy for the synthesis of the glutamate analogues.

**Scheme 2.**

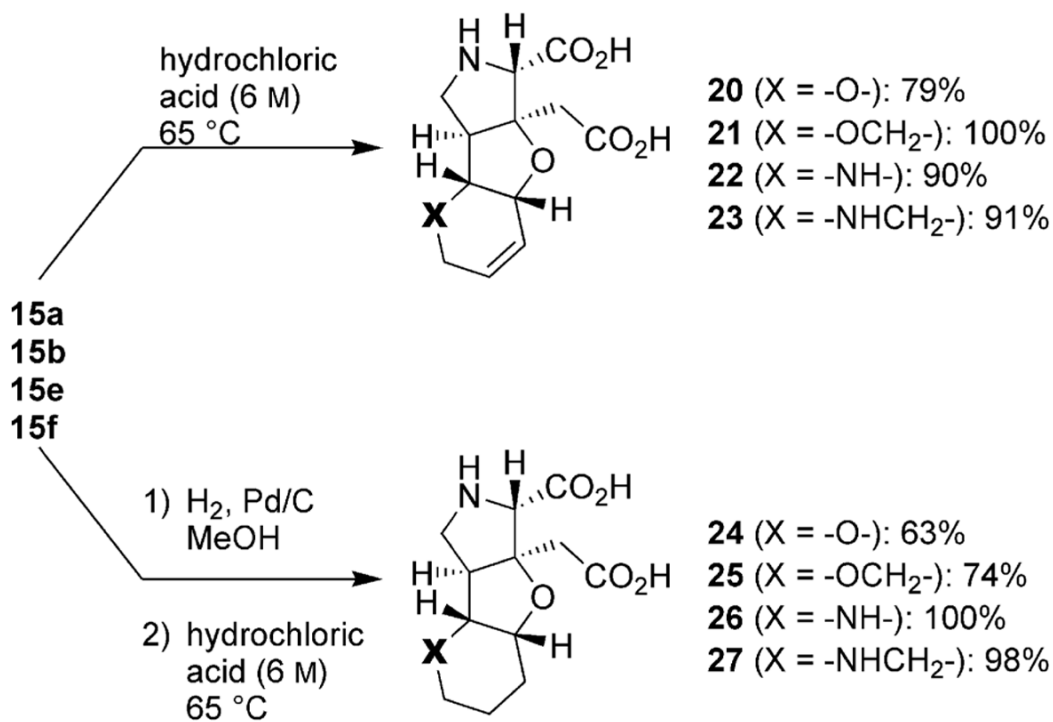
Replacement of the iodide with four heteroalkenyl groups leading to **4a–e**, and the structure of simple 7-oxanorboronenes **5** and **6** used for control experiments.



Scheme 3.
Proposed reaction pathway for domino metathesis of dienes **4a-e**.

**Scheme 4.**

Functional groups transformation to set the glutamate moiety.

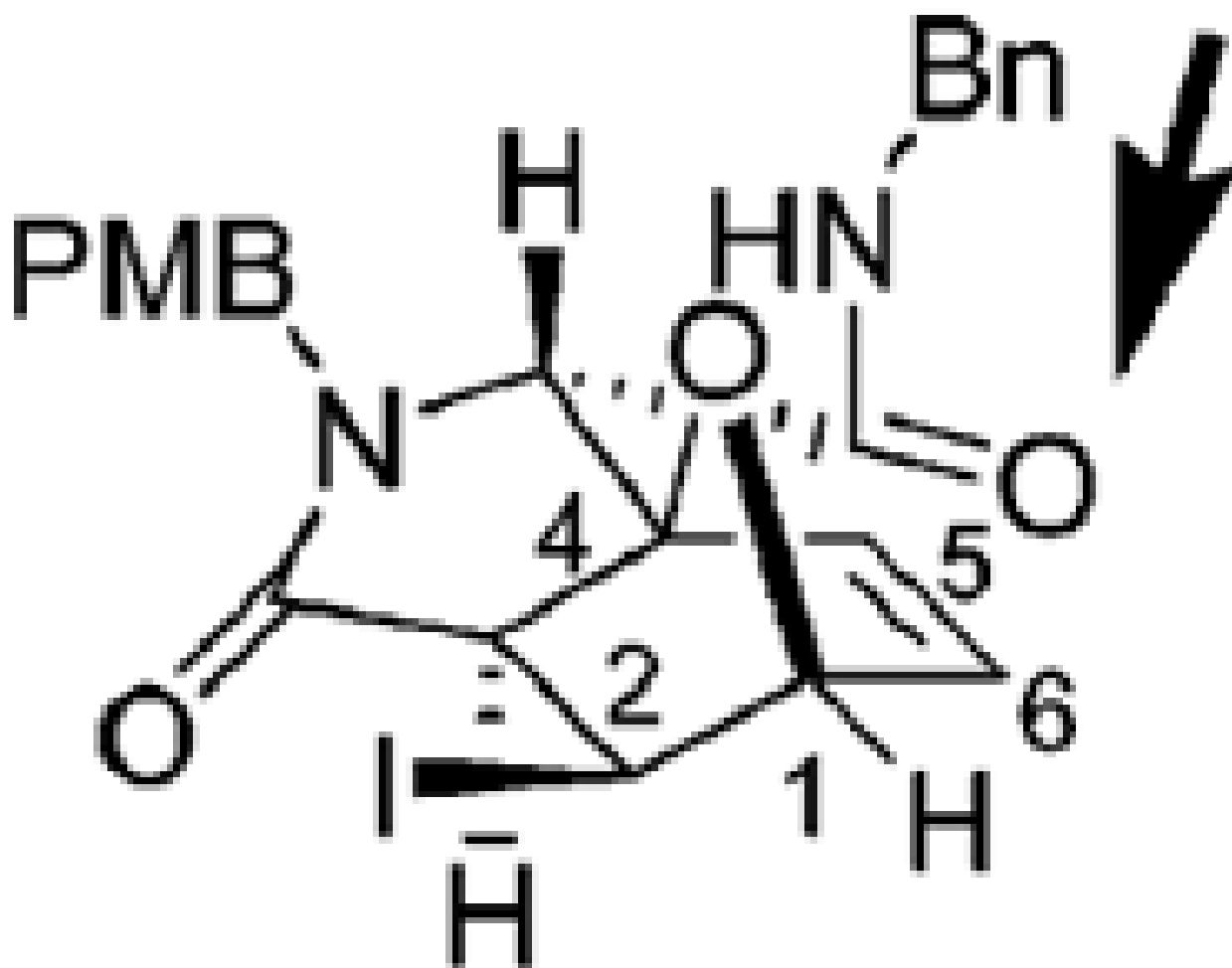


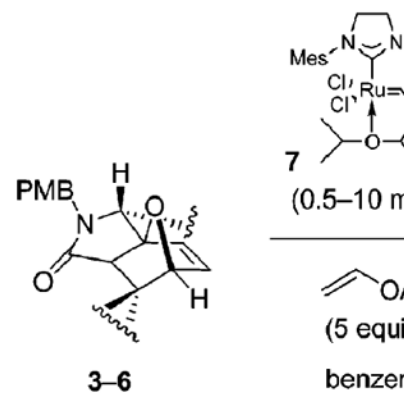
Scheme 5.
 Synthesis of eight glutamate analogues.

Table 1Results for the domino metathesis reaction of 7-oxanorbornenes **3–6**.^a

Run	Domino metathesis substrate
1	

1

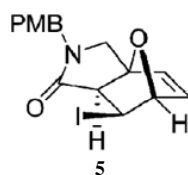
**3^b**

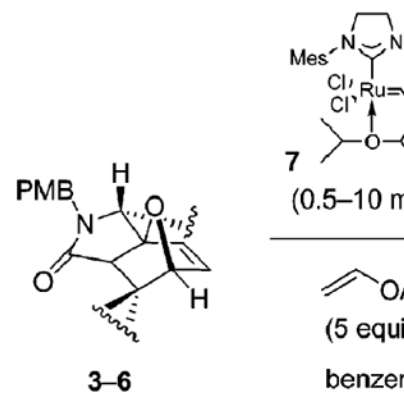


Run

Domino metathesis substrate

2

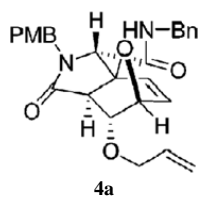


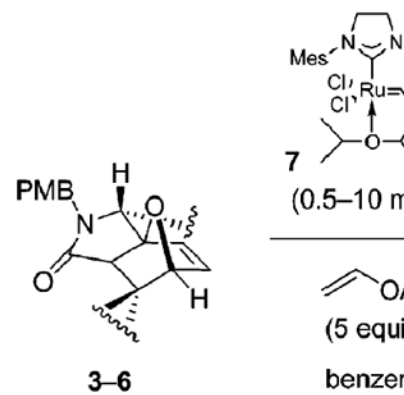


Run

Domino metathesis substrate

3

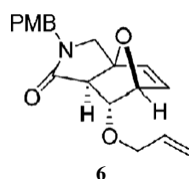


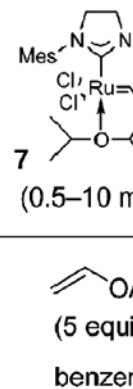
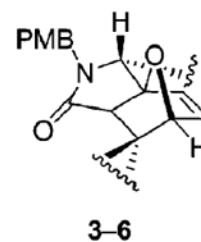


Run

Domino metathesis substrate

4

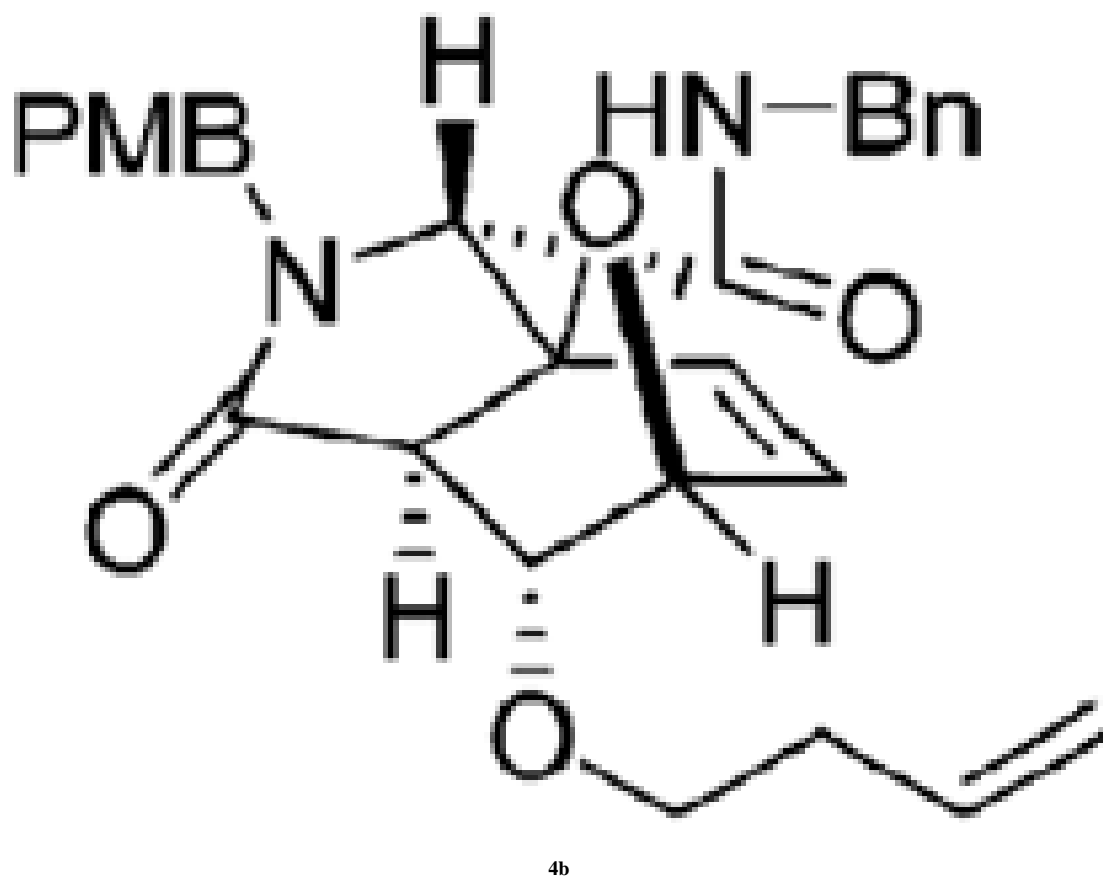


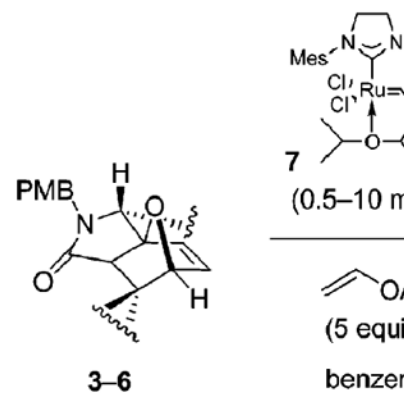


Run

Domino metathesis substrate

5

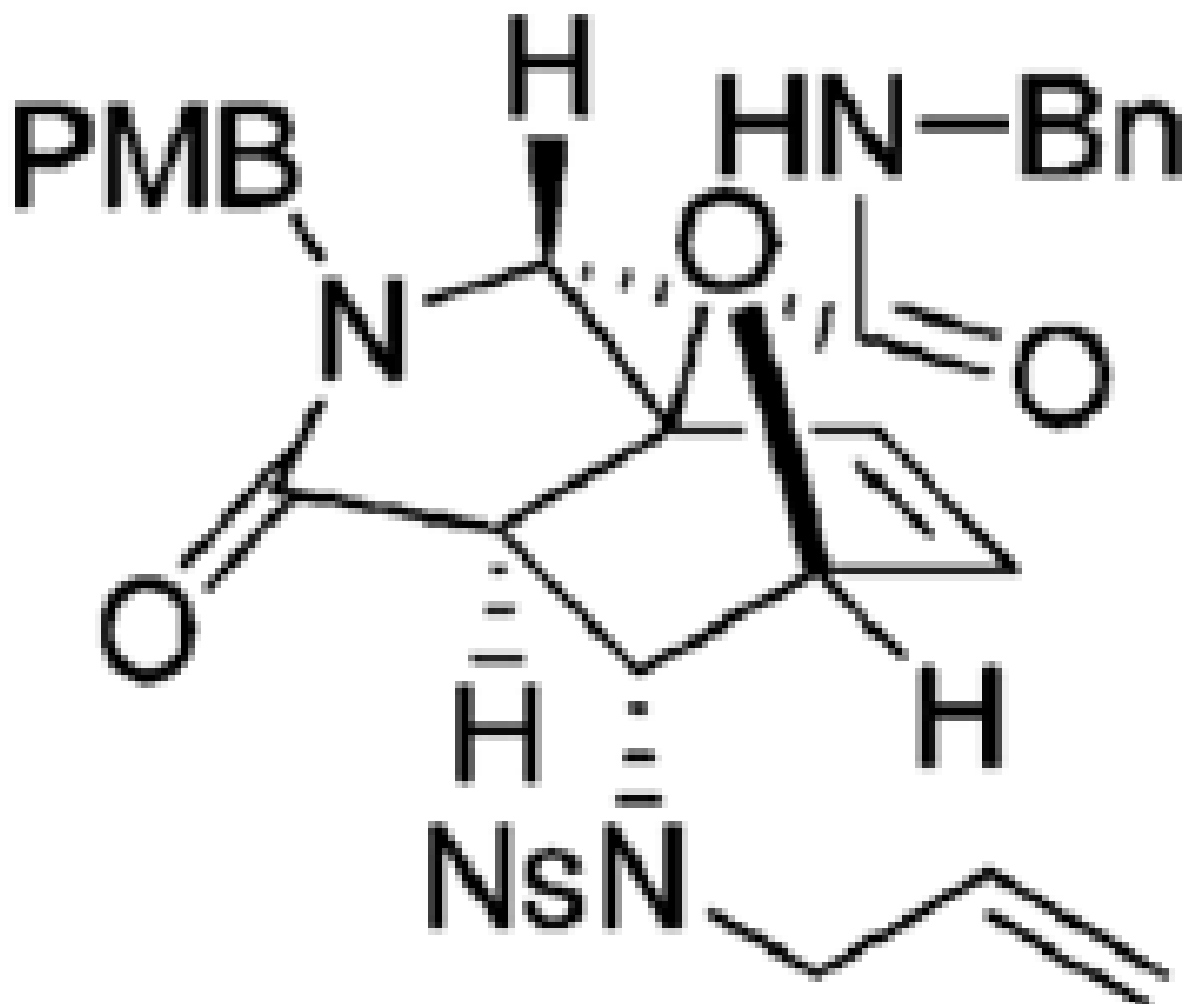


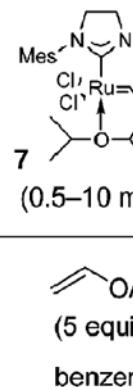
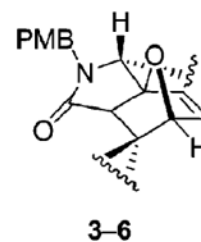


Run

Domino metathesis substrate

6

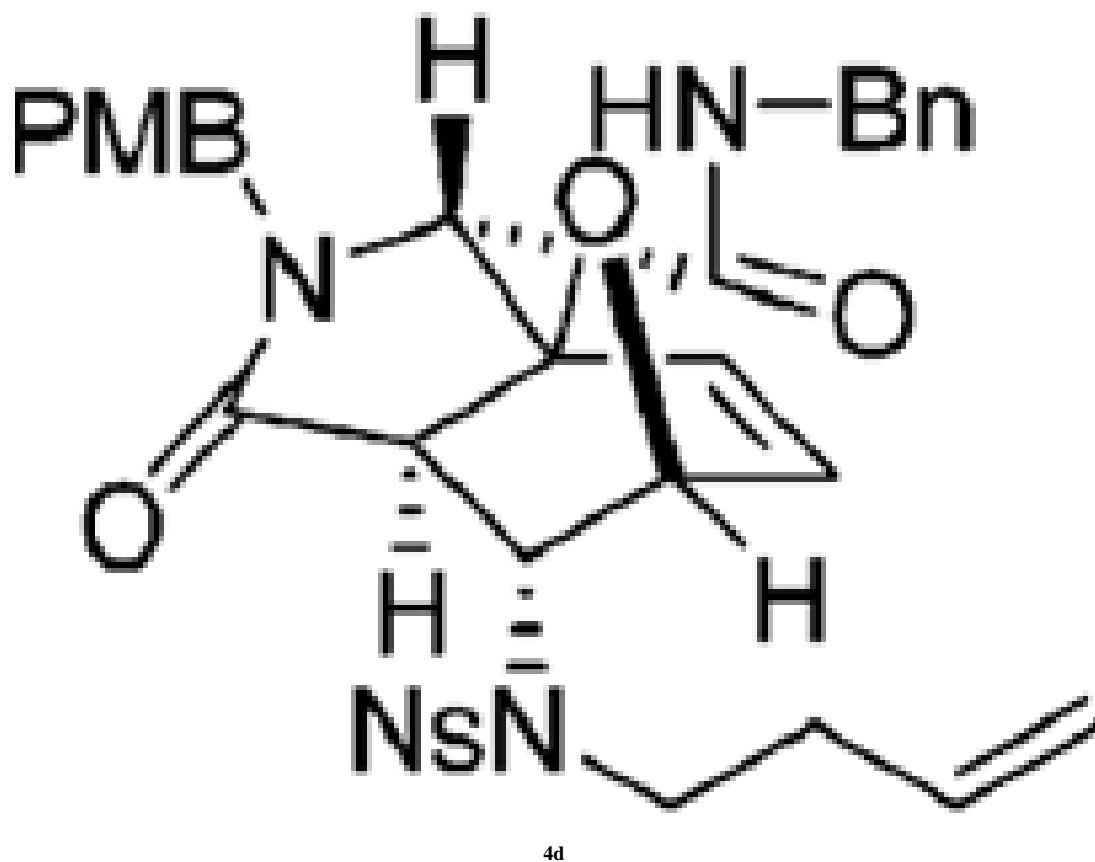


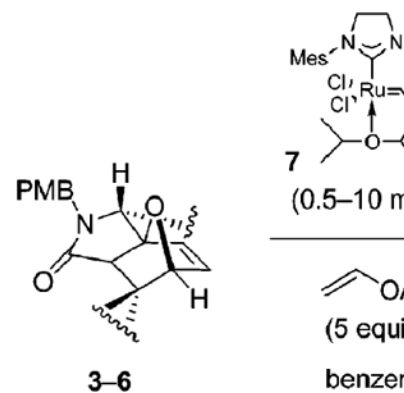


Run

Domino metathesis substrate

7

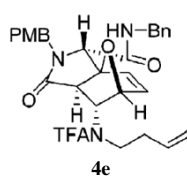




Run

Domino metathesis substrate

8



^aPMB = 4-methoxybenzyl.

^bAn arrow pointing to **3** indicates the proposed coordinating site to the Ru metal centre.

^cDiastereomeric ratio for **10** was determined by LC-MS analysis.