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Synthesis and domino metathesis of functionalized 7-oxanorbornene analogs toward cis-fused heterocycles

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Abstract

Here, we report our strategy to synthesize structurally diverse cis-fused heterocycles via 7-oxanorbornene analogs. By the intramolecular Diels–Alder reaction of 3-iodoacrylamide, followed by the domino metathesis reaction, the cis-fused heterobicyclic skeleton was efficiently constructed in 5–8 steps.

Keywords: Cis-fused heterocycle; Diels–Alder reaction; Domino metathesis; 7-Oxanorbornene

1. Introduction

Polyethers, which are primarily isolated from marine resources, are a class of natural products exhibiting interesting biological activities such as fish poisoning.[1] Many synthetic studies have been actively conducted to confirm their proposed complex structure as well as to clarify the precise biological function at a molecular level.[2] Although cyclic ethers are generally fused into each other in trans-relationships in these polyether-class natural products, cis-fused cyclic ethers are observed in dysiherbaines (5/6-ring system),[3,4] herbicidin (5/6-ring system),[5] and maitotoxin (C56–C75 moiety, 6/6-ring system).[6] A cis-fused 5/7-bicyclic system has also been used as a key intermediate in tetrahydrofuran natural products.[7] With regard to synthetic strategies, those for trans-fused cyclic ethers are generally applicable to cis-fused ones, namely, 5- or 6-*exo-tet* cyclization of epoxy alcohol,[4,8] intramolecular 1,4-conjugate addition of hydroxy group to α,β-unsaturated carbonyl compounds,[9] intramolecular nucleophilic etherication of iodo- or sulfonyloxy alcohol,[10] pinacol-type ring closure,[11] ring-closing metathesis,[12] ring-expansion reaction of bromoepoxide,[13] and RuO_4-mediated oxidative cyclization.[14]

We have been interested in cis-fused bicyclic skeletons as a platform for diversity-oriented synthesis (DOS)[15] to form a diverse collection of small molecules used for research in the field of chemical biology. Therefore, we have started a program directed toward a short-step and efficient synthesis of cis-fused heterocycles that include not only ethers but also amine functionalities. Here, we report our primary results obtained by a series of studies.[16]

2. Results and discussion

Our strategy to carry out DOS on the 7-oxanorbornene skeleton **A** to yield the heterocycle **C** is represented in Scheme 1. The norbornene **A** would be synthesized by the *exo*-selective Diels–Alder reaction of a furan derivative and a dienophile. We have anticipated that the introduction of the stereochemically well-defined leaving group **X** into **A** would ultimately lead the skeleton to the cis-fused heterobicycle **C**.

It was planned that alkenyl groups were next added to the norbornene **A** to yield the stereochemistry-inverted diene **B**. The alkenyl groups are important for achieving functional and skeletal diversities in the final product **C**. S_N2-type stereochemical inversion would enable this transformation. The key domino reaction (**B** → **C**) involves the so-called 'ring-rearrangement metathesis'[17] and attachment of the exocyclic alkenyl

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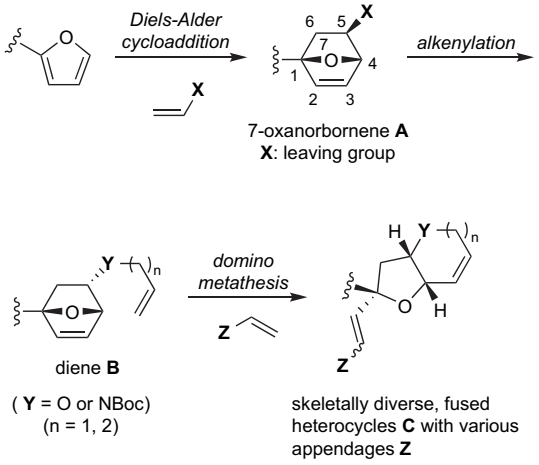
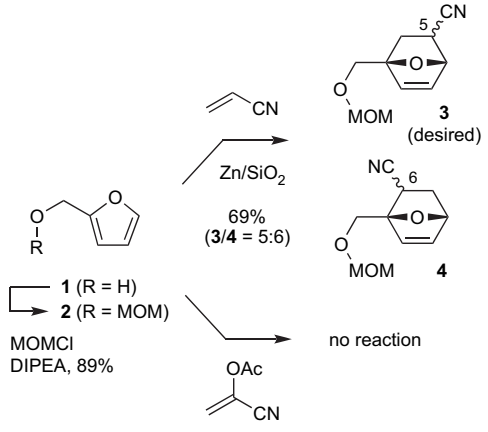
substituent **Z** so that variations are realized in the skeleton and appendage.



Scheme 1. Our strategy to synthesize cis-fused, various heterocycles.

In 2000, Arjona et al. have reported a closely related transformation of 7-oxanorbornene analogs into bicyclic ethers.[18] Since they used 7-oxanorbornene-5-ol as the starting material, their method is limited to bicyclic ethers, and they have, in fact, demonstrated the synthesis of only the 5/6-bicyclic ether system. In our study, however, we carry out the synthesis of functionally and skeletally diverse heterocycles with various appendages, hence, it is advantageous when the generated compounds are used for biological evaluation.

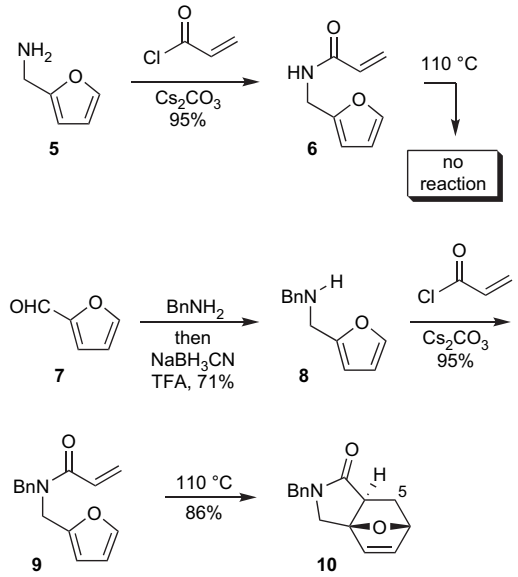
The synthesis of 5-substituted-7-oxanorbornene was first attempted by using the intermolecular Diels–Alder reaction, as shown in Scheme 2. Furfuryl alcohol (**1**) was protected as MOM ether (MOMCl, DIPEA, DMAP) to give **2**[19] in 89% yield. For the next Diels–Alder reaction of furan, acidic conditions are generally avoided because furan often suffers decomposition.[20] Our preliminary study using furfuryl acetate as a model compound, however, showed that thermal conditions using acrylonitrile as a solvent were not satisfactory in terms of the yield (31%) below its boiling point (77 °C). Therefore, mildly acidic conditions were explored, and it was found that



Scheme 2. An intermolecular Diels–Alder approach to 7-oxanorbornenes.

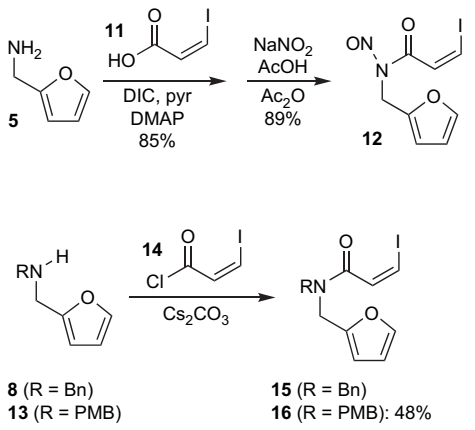
$ZnCl_2/SiO_2$ (48% yield)[21] produced better results than ZnI_2 (13% yield)[22] or the uncatalyzed thermal process (data not shown). Thus, the furan **2** was treated with acrylonitrile with the aid of $ZnCl_2/SiO_2$ to give regioisomers **3** and **4** in 69% combined yield with a selectivity of 5:6, as determined by ^1H NMR analysis (Scheme 2). Because each regioisomer was obtained as a mixture of stereomeric isomers, the intermolecular Diels–Alder reaction generated four products with poor selectivity. In addition, neither the $ZnCl_2/SiO_2$-promoted nor the thermal Diels–Alder reaction proceeded between **2** and 1-cyanovinyl acetate,[23] indicating that the intermolecular Diels–Alder process is not efficient in the construction of the 7-oxanorbornene framework **A** in Scheme 1. Hence, we studied an approach by the intramolecular Diels–Alder reaction to construct the desired 7-oxanorbornene with high regio- and stereoselectivities.

The preliminary study for the intramolecular Diels–Alder reaction is shown in Scheme 3. Initially, we found that the acrylamide **6**, prepared by the N-acylation of furfurylamine (**5**) with acryl chloride in the presence of Cs_2CO_3, does not undergo the desired reaction in refluxing toluene. To drive the reaction, we subjected *N*,*N*-dialkyl acrylamide[24] to the Diels–Alder reaction. The substrate **9** was synthesized by the reductive alkylation of $BnNH_2$ with furfural (**7**) (azeotropic removal of water; $NaBH_4CN$, TFA), followed by N-acylation in 67% overall yield. We observed that upon heating, **9** was smoothly converted into 7-oxanorbornene **10** in good yield (86%) as the sole product. Encouraged by the formation of **10**, we then attempted to introduce a leaving group at the C5 position.



Scheme 3. An intramolecular Diels–Alder approach to 7-oxanorbornenes.

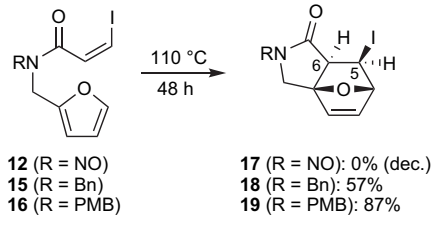
For synthetic efficiency of the common intermediate **A** in Scheme 1, we introduced the leaving group before the intramolecular Diels–Alder reaction. We first synthesized three *cis*-3-iodoacrylamides **12**, **15**, and **16** to explore the Diels–Alder reaction (Scheme 4). The *N*-nitrosoamide **12** was synthesized by the reaction of $NaNO_2$ and Ac_2O in AcOH with the intermediary acrylamide, prepared from *cis*-3-iodoacrylic acid (**11**)[25]



Scheme 4. Preparation of *cis*-3-iodoacrylamides.

and furfurylamine (**5**) (DIC, pyridine, DMAP) in 76% overall yield. On the other hand, the *N*-Bn and *N*-PMB acrylamides **15** and **16** were synthesized by the acylation of the secondary amines **8** and **13**, respectively, which were prepared by the reductive alkylation of $BnNH_2$ or $PMB-NH_2$ with furfural (**7**) by the procedure shown in Scheme 3.

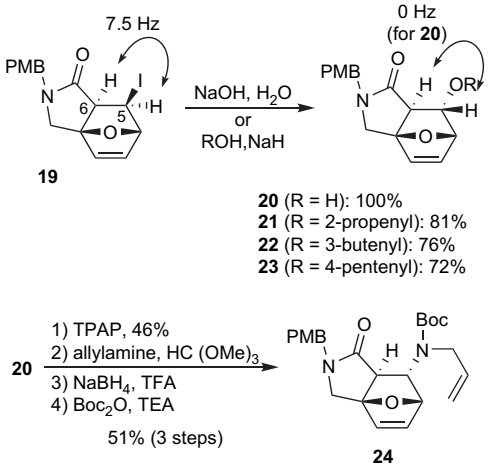
The intramolecular Diels–Alder reaction of the *cis*-3-iodoacrylamides **12**, **15**, and **16** was examined by refluxing in toluene for 48 h (Scheme 5). It was found that the desired 7-oxanorbornene **17** was not obtained from the *N*-nitrosoamide **12**, since the nitroso group decomposed during heating to 110 °C. In contrast, the amides with benzyl-type groups **15** and **16** smoothly reacted at 110 °C to give **18** and **19** in 57% (2 steps from **8**) and 87% yields, respectively. In both cases, the stereoselectivity was completely controlled, giving rise to the *exo*-adducts **18** and **19** as the sole products. The structures were confirmed by ^{1}H NMR and MS analyses; more importantly, the $^3J_{H5,H6}$ values were 8.1 and 7.5 Hz for **18** and **19**, respectively. This is the first example of the Diels–Alder reaction of a sterically demanding, *cis*-3-iodoacrylic acid derivative.[26]



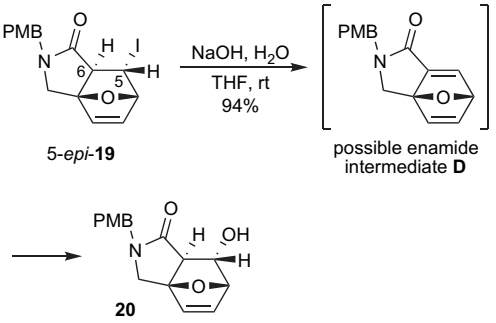
Scheme 5. Intramolecular Diels–Alder reaction of *cis*-3-iodoacrylamides.

After obtaining **18** and **19** with a leaving group at the C5 position, we examined the introduction of alkenyl groups. Since we encountered problems while removing the Bn protecting group on the pyrrolidone ring (for example, treatment of **18** with LDBB caused decomposition), further studies were carried out with the PMB-protected 7-oxanorbornene **19**. The removal of the PMB group was found to be selectively effected in moderate yield (>70%) by a two-step process including CAN treatment followed by exposure to K_2CO_3 in MeOH.[27]

Initially, we found that NaOH in wet THF quantitatively converted the iodide **19** into the alcohol **20** at rt (Scheme 6). ^{1}H NMR analysis indicated that the stereochemistry at C5 inverted during the reaction (see $^3J_{H5,H6}$ values drawn on **19** and **20**). Since the stereochemical result does not exclude other possible mechanisms, e.g., the elimination at the C5–C6 bond followed by the 1,4-conjugate addition of a hydroxide anion to the generated C5–C6 double bond, there is no definite mechanism for the displacement of the iodo group with the hydroxy group. Certainly, it was found that C5-*epi*-**19**, prepared from the (*E*)-acrylamide isomer of **16**, smoothly converted into the same *endo*-alcohol **20** under the same hydrolysis conditions (Scheme 7). A similar example has been also reported by Helmchen,[28] and we are now working on a more detailed mechanistic study for this displacement reaction.



Scheme 6. Introduction of alkenyl groups to 7-oxanorbornenes.



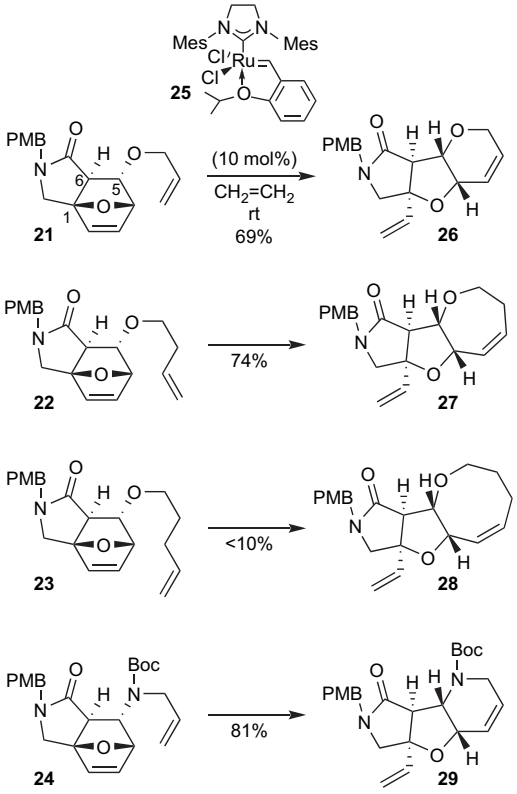
Scheme 7. Retention of stereochemistry in hydrolysis of C5-epimer of **19**.

The introduction of alkenyl groups into **19** was first attempted by the O-alkylation of the alcohol **20** with various alkenyl bromides such as 2-propenyl bromide (allyl bromide), 3-butenyl bromide, and 4-pentenyl bromide using NaH or KHMDS as a base. While the 2-propenyl ether **21** was obtained in 68% yield, other alkenyl ethers (**22**, **23**) were not available by this procedure (data not shown). Therefore, we attempted the procedure by the displacement of the iodide **19** with various

alkoxy groups (Scheme 6). Here, sodium alkoxide was first generated by the treatment of 2-propen-1-ol (allyl alcohol), 3-buten-1-ol, and 4-penten-1-ol with NaH in DMF, and it was then reacted with the iodide **19** at −10 °C to give three ethers **21**–**23** in acceptable yields (72–81%).

For the synthesis of the protected amine **24**, a rather tedious long-step transformation was performed on the alcohol **20**. This transformation involved oxidation (TPAP, NMO),[29] reductive alkylation by 2-propenylamine ($HC(OMe)_3$, $NaBH_4$, TFA), and Boc protection (Boc_2O, TEA), and provided the Boc-protected secondary amine **24** in 23% overall yield.[30]

At this stage, it is possible to carry out the 'ring rearrangement' of the 7-oxanorbornene skeleton, leading to the heterotricycles by the domino metathesis reaction including ring-opening metathesis (ROM) and ring-closing metathesis (RCM). According to reports,[31] only a limited number of studies by us[32] and others[33] can be found on the domino metathesis reaction of 1,5,6-trisubstituted norbornenes. Here, 10 mol % of the second-generation Hoveyda–Grubbs catalyst **25**[34] was used for the reaction because the second-generation Grubbs catalyst[35] was found to be incapable of sustaining the activity throughout the reaction (Scheme 8). Ethylene gas was also added to the mixture to effectively drive the reaction. All reactions were carried out in CH_2Cl_2 at rt, and by this procedure, the 2-propenyl ether **21** was readily converted into the heterotricycle **26** in 69% yield after 1 h. A seven-membered ether **27** was also smoothly obtained from the butenyl ether **22** in 74% yield after 3 h. The formation of an eight-membered ether was, however, sluggish and traces (<10%) of **28** were detected only by LC–MS analysis. The major product was a dimer apparently formed by ROM



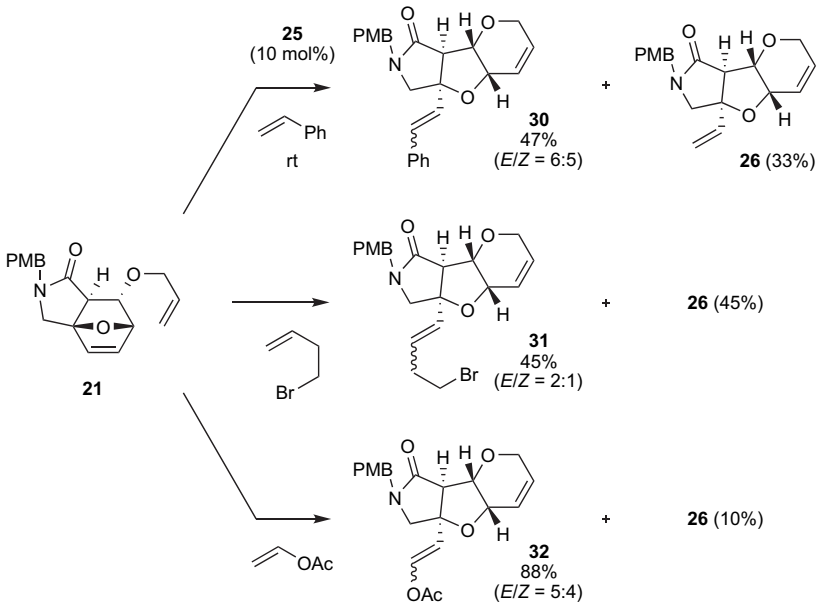
Scheme 8. ROM/RCM of 7-oxanorbornenes.

followed by intermolecular cross metathesis (CM) dimerization.[18,36] The low yield in the formation of the cis-fused eight-membered ring by the RCM has been stated by Grubbs et al.[37] and Furstner and Langemann.[38] The last example of this ROM/RCM process is the reaction of the Boc-protected allylic amine **24**, which reacted instantly within 1 h to give the protected six-membered amine **29** in good yield (81%). All products were characterized on the basis of NMR and LC–MS analyses. Although some improvements are still needed, especially for the synthesis of the eight-membered cyclic ether **28**, we have been able to synthesize three skeletally and functionally distinct heterotricycles in only 5 steps for **26** and **27** and 8 steps for **29** starting from furfural (**7**). This synthetic efficiency is apparently due to the intramolecular Diels–Alder reaction of *cis*-3-iodoacrylamide (Scheme 5) and displacement of the iodo group with alkenyl functionalities (Scheme 6), developed in the present study.

We then attempted the introduction of various appendages in the skeleton by the CM reaction. The elusion of the undesirable CM pathway with ethylene[39] must be considered in this type of domino metathesis of norbornenes.

Reaction conditions identical to those in Scheme 8 were employed, however, a CM reactant was added instead of ethylene gas. Three reactions with different CM reactants were examined as shown in Scheme 9. In all reactions, the products were unambiguously determined on the basis of ^1H NMR, ^{13}C NMR, and LC–MS analyses. Initially, styrene was used as the CM reactant to give the heterotricycle **30** in 47% yield as a diastereomeric mixture at the styryl moiety (*E*/*Z*=6:5). The undesired heterotricycle **26** was also obtained in this reaction in 33% yield. It is generally accepted that ROM occurs first in the domino metathesis of strained norbornenes.[40] Our results indicate that the first ROM reaction is poorly regioselective.

Interestingly, because of the possible involvement of some thermodynamic equilibration and ruthenium alkylidene (e.g., [Ru]=CHPh) species in the reaction, the ratio of the desired product **30** to the undesired product **26** was not consistent with that in the other reactions as follows. The use of 3-butenyl bromide as the CM reactant produced the desired compound **31** and the undesired compound **26** in equal yields (45%). The results obtained with vinyl acetate were interesting and encouraging. Although a small amount (10% yield) of **26** was still generated, the desired heterotricycle **32** was provided by the domino metathesis in fairly good yield (88%). Cross metathesis with such an electron-rich olefin is generally delayed or ceases. To the best of our knowledge, there are only three other examples including our paper.[41,42] Although the reason is not quite clear at present, we suspect that the use of this type of electron-rich olefin may be beneficial to the high regioselectivity in some specific cases. Recently, we have discovered neighboring amide carbonyl groups as the regioselectivity-controlling factor in the domino metathesis of 7-oxanorbornenes.[41] The use of this effect in combination with electron-rich CM reactants such as vinyl acetate is expected to be a general method for highly selective CM reactions.

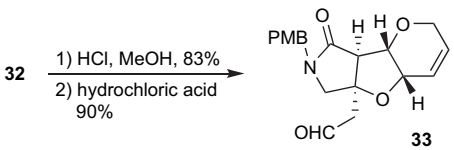


Scheme 9. ROM/RCM/CM of 7-oxanorbornenes.

The heterotricycle **32** was found to further undergo selective functional group transformations (Scheme 10). The vinyl acetate moiety was selectively reacted with HCl in MeOH generated in situ from AcCl and MeOH to give dimethyl acetal, which was subsequently hydrolyzed by hydrochloric acid to provide the aldehyde **33** in 75% overall yield. We have also found that the nitrogen functional group can be introduced into the α-position of the aldehyde in **33** by using an organocatalytic reaction (data not shown).[43] The synthesis of the artificial glutamate analogs by using these transformations is underway, and the results will be reported in the future.

3. Conclusion

In conclusion, we have successfully carried out the short-step synthesis (5–8 steps) of cis-fused heterobicycles fused with a pyrrolidone ring. The synthesis features novel uses of *cis*- (or even *trans*-, which led to 5-*epi*-**19**) 3-iodoacrylamide for the intramolecular Diels–Alder reaction with furan. The displacement of the iodo group with various alkenyl groups, followed by domino metathesis, leads to the skeletally and functionally distinct heterotricycles with various appendages. Since cis-fused bicyclic ethers or their related structures are often found in natural products, this approach would be useful for synthesizing them and their analogs.[44] Future studies will be focused on such synthesis.



Scheme 10. Further chemoselective transformation on the cis-fused heterotricycle **32**.

4. Experimental

4.1. General

The experimental techniques and the characterizing apparatuses used are summarized in our previous paper.[45] The Hoveyda–Grubbs catalyst **25** (second generation, [301224-40-8])[34] was purchased from Aldrich Co.

4.2. Synthetic study toward cis-fused heterocycles

4.2.1. 2-((Methoxymethoxy)methyl)furan (2)[19]

To a stirred solution of furfuryl alcohol (**1**, 2.0 mL, 23 mmol) in CH_2Cl_2 (50 mL) at 0 °C were added MOMCl (5.8 mL, 28 mmol) and DIPEA (6.0 mL, 35 mmol). The mixture was stirred at rt for 10 h, and then washed with water (50 mL), saturated aqueous NH_4Cl (50 mL), and brine (50 mL). The organic layer was dried over 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 the MOM ether **2** (2.91 g, 89%) as a colorless oil: IR (film) 1081, 1020, 882, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (m, 1H), 6.33 (br s, 2H), 4.66 (s, 2H), 4.52 (s, 2H), 3.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.8, 142.4, 109.9, 108.3, 97.8, 52.6; HRMS (EI, positive) calcd for $C_7H_{10}O_3$ (M^+) 142.0630, found 142.0632.

4.2.2. 5-Cyano-1-((methoxymethoxy)methyl)-7-oxanorbornene (3) and 5-cyano-1-((methoxymethoxy)-methyl)-7-oxanorbornene (4)

To a stirred solution of the furan **2** (100 mg, 0.70 mmol) in acrylonitrile (7.0 mL) at rt was added $ZnCl_2/SiO_2$ (2.00 g, 1.40 mmol).[21] After 2 days, insoluble materials were removed by filtration and the filtrate was concentrated under reduced

pressure. The residue was purified by column chromatography on silica gel (5 g, hexane/EtOAc=7:3) to give the 7-oxanorbornenes **3** and **4** (1:1, 283.6 mg, 69%) as an inseparable mixture (colorless oil): IR (film) 2363, 2239, 1153, 1114, 1043, 926, 710 cm^{-1}; ^1H NMR (for **3**, 300 MHz, $CDCl_3$) δ 6.61 (dd, J=5.9 Hz, 1.5 Hz, 1H), 6.39 (d, J=6.0 Hz, 1H), 5.12 (dd, J=4.7, 1.8 Hz, 1H), 4.73 (s, 2H), 4.14 (s, 2H), 3.41 (s, 3H), 3.03 (dd, J=9.3, 6.0 Hz, 1H), 2.43 (dd, J=9.3, 4.5 Hz, 1H), 1.66 (dd, J=6.0, 4.5 Hz, 1H); ^1H NMR (for **4**, 300 MHz, $CDCl_3$) δ 6.38 (d, J=6.0 Hz, 1H), 6.35 (dd, J=6.0, 1.5 Hz, 1H), 5.21 (d, J=1.5 Hz, 1H), 4.70 (s, 2H), 4.02 (d, J=3.3 Hz, 2H), 3.38 (s, 3H), 2.50 (dd, J=8.7, 3.6 Hz, 1H), 2.02 (dd, J=11.6, 3.9 Hz, 1H), 1.80 (dd, J=11.6, 8.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 137.8, 137.8, 137.7, 134.6, 134.5, 133.9, 133.2, 120.3, 120.0, 96.9, 96.6, 96.6, 96.6, 89.9, 88.8, 81.6, 79.2, 79.2, 78.4, 66.0, 65.8, 65.4, 64.5, 55.6, 55.4, 55.4, 55.4, 33.6, 33.2, 30.2, 29.7, 28.1, 27.3; HRMS (EI, positive) calcd for $C_{10}H_{13}NO_3$ (M^+) 195.0895, found 195.0846.

*4.2.3. N-Furfurylacrylamide (**6**)*

To a stirred solution of furfurylamine (**5**, 0.0213 mL, 0.23 mmol) in THF (2.0 mL) at 0 °C were added acryl chloride (0.0206 mL, 0.25 mmol) and Cs_2CO_3 (112 mg, 0.34 mmol). After stirring at rt for 30 min, saturated aqueous NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (20 mL). The extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1 g, hexane/EtOAc=85:15) to give the acrylamide **6** (35.4 mg, 95%) as a colorless oil: IR (film) 3276, 3068, 1658, 961, 806, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (t, J=1.2 Hz, 1H), 6.32 (dd, J=3.9, 1.2 Hz, 1H), 6.27 (dd, J=9.9, 2.1 Hz, 1H), 6.23 (d, J=3.9 Hz, 1H), 6.08 (dd, J=17.1, 9.9 Hz, 1H), 5.90 (br s, 1H), 5.65 (dd, J=17.1, 2.1 Hz, 1H), 4.50 (d, J=5.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 151.0, 142.3, 130.4, 127.0, 110.4, 107.7, 36.5; HRMS (ESI, positive) calcd for $C_8H_{10}NO_2$ [$(M+H)^+$] 152.0712, found 152.0707.

*4.2.4. N-Benzylfurfurylamine (**8**)*

A solution of furfural (**7**, 5.0 mL, 0.051 mol) and benzylamine (6.0 mL, 0.055 mol) in benzene (100 mL) was heated to reflux and water generated was removed azeotropically. After 4 h, the mixture was concentrated under reduced pressure and dissolved in MeOH (50 mL). To the stirred solution at 0 °C were successively added $NaBH_3CN$ (3.0 g, 0.079 mol) and TFA (4.1 mL, 0.055 mol). After 30 min, the mixture was allowed to warm to rt and stirring was continued for 1 h. The mixture was then concentrated under reduced pressure, diluted with EtOAc (50 mL), and washed with aqueous NaOH (1 M, 30 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (160 g, hexane/EtOAc=8:2) to give the amine **8** (8.84 g, 96%) as a yellow oil: IR (film) 1506, 1456, 1146, 1009, 807, 736, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.32 (m, 3H), 7.25–7.24 (m, 2H), 6.31 (dd, J=3.0, 1.5 Hz, 1H), 6.16 (d, J=3.0 Hz, 1H), 3.77 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5, 141.6, 139.5, 128.2, 128.1, 126.9, 110.0, 107.0, 52.5, 45.0; HRMS (ESI, positive) calcd for $C_{12}H_{14}NO$ [$(M+H)^+$] 188.1070, found 188.1071.

*4.2.5. N-Benzyl-N-furfurylacrylamide (**9**)*

By the same procedure for the synthesis of **6**, the acrylamide **9** (a mixture of two rotamers in a ratio of 3:2) was synthesized from **8** in 97% yield as a yellow oil: IR (film) 1652, 1436, 1206, 978, 735, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.27 (m, 5H), 7.20 (br d, 1H), 6.76 (m, 0.4H), 6.54 (m, 0.6H), 6.48 (d, J=2.4 Hz, 0.6H), 6.40 (d, J=2.1 Hz, 0.4H), 6.30 (br s, 0.6H), 6.24 (br s, 0.4H), 6.16 (br s, 0.4H), 5.72 (m, 1H), 4.65 (br s, 1H), 4.61 (br s, 2H), 4.38 (br s, 0.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 166.6, 150.6, 150.0, 142.6, 142.2, 136.9, 136.4, 129.0, 128.8, 128.7, 128.5, 128.2, 127.7, 127.5, 127.4, 127.3, 126.3, 110.3, 108.9, 108.1, 50.3, 48.3, 43.4, 41.5; HRMS (ESI, positive) calcd for $C_{15}H_{16}NO_2$ [$(M+H)^+$] 242.1181, found 242.1170.

*4.2.6. Bn-protected 7-oxanorbornene **10***

A solution of the acrylamide **9** (1.00 g, 4.2 mmol) in toluene (40 mL) was heated to reflux for 24 h. The mixture was then concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (20 g, hexane/EtOAc=1:1) to give the 7-oxanorbornene **10** (858 mg, 86%) as a colorless oil: IR (film) 1683, 1424, 1360, 1087, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.16 (m, 5H), 6.32–6.27 (m, 2H), 5.00 (d, J=4.8 Hz, 1H), 4.52 (d, J=15.0 Hz, 1H), 4.38 (d, J=15.0 Hz, 1H), 3.76 (d, J=11.4 Hz, 1H), 3.49 (d, J=11.4 Hz, 1H), 2.41 (dd, J=8.9, 3.3 Hz, 1H), 2.17 (dt, J=11.7, 3.9 Hz, 1H), 1.53 (dd, J=11.7, 5.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 137.0, 133.1, 128.7, 128.3, 127.8, 127.5, 88.9, 79.0, 48.8, 47.5, 46.5, 28.0; HRMS (ESI, positive) calcd for $C_{15}H_{16}NO_2$ [$(M+H)^+$] 242.1181, found 242.1169.

*4.2.7. (Z)-N-Furfuryl-3-iodo-N-nitrosoacrylamide (**12**)*

To a stirred solution of the furfurylamine (**5**, 21.3 mg, 0.23 mmol) in CH_2Cl_2 (2.0 mL) at rt were added (*Z*)-3-iodoacrylic acid (**11**, 50.0 mg, 0.23 mmol), pyridine (0.0283 mL, 0.35 mmol), DMAP (2.8 mg, 0.02 mmol), and DIC (0.043 mL, 0.28 mmol). After 3 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (0.5 g, hexane/EtOAc=1:1) to give (*Z*)-*N*-furfuryl-3-iodoacrylamide (54.2 mg, 85%) as a yellow oil.

To a stirred solution of (*Z*)-*N*-furfuryl-3-iodoacrylamide (25.6 mg, 0.092 mmol) obtained above in AcOH (1.0 mL) and Ac_2O (0.2 mL) at −10 °C was added $NaNO_2$ (330 mg, 4.8 mmol). After 1 h, iced water (20 mL) was added and the mixture was extracted with Et_2O (20 mL). The extract was washed with aqueous $NaHCO_3$ (5%, 5×20 mL) and brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1 g, hexane/EtOAc=1:1) to give the *N*-nitrosoamide **12** (25.8 mg, 89%) as a yellow oil: IR (film) 1717, 1507, 1311, 1010, 996, 788, 748 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$) δ 8.14 (d, J=9.0 Hz, 1H), 7.79 (d, J=9.0 Hz, 1H), 7.26 (dd, J=2.1, 1.5 Hz, 1H), 6.25 (s, 2H), 4.98 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 147.3, 142.4, 128.2, 110.4, 109.7, 97.8, 34.6; HRMS (EI, positive) calcd for $C_8H_7IN_2O_3$ (M^+) 305.9501, found 305.9505.

*4.2.8. N-(4-Methoxybenzyl)furfurylamine (**13**)*

By the same procedure for the synthesis of **8**, the 4-methoxybenzylamine **13** was synthesized from furfural (**7**) in 97% yield as a colorless oil: IR (film) 3324, 1512, 1456, 1247, 1174, 1035, 919, 813, 737 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (dd, J=1.8, 0.9 Hz, 2H), 7.22 (d, J=8.7 Hz, 2H), 6.84 (d, J=8.7 Hz, 2H), 6.30 (dd, J=3.0, 1.8 Hz, 1H), 6.16 (d, J=2.4 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 2H), 3.70 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 153.7, 141.6, 131.8, 129.3, 113.6, 109.9, 106.8, 55.0, 52.0, 45.1; HRMS (ESI, positive) calcd for $C_{13}H_{16}NO_2$ [$(M+H)^+$] 218.1176, found 218.1182.

*4.2.9. (Z)-N-Furfuryl-N-benzyl-3-iodoacrylamide (**15**)*

To a stirred solution of the benzylamine **8** (219 mg, 1.2 mmol) in THF (7.0 mL) at rt were added (*Z*)-3-iodoacryl chloride (**14**, 167 mg, 0.79 mmol) and Cs_2CO_3 (772 mg, 2.4 mmol). After 12 h, saturated aqueous NH_4Cl (50 mL) was added and the mixture was extracted with EtOAc (30 mL). The extract was dried over Na_2SO_4 and concentrated under reduced pressure to give the crude **15**, which was used for the next reaction without purification.

*4.2.10. (Z)-N-Furfuryl-N-(4-methoxybenzyl)-3-iodoacrylamide (**16**)*

By the same procedure for the synthesis of **15**, the 3-iodoacrylamide **16** was synthesized from **13** in 48% yield as a pale yellow oil, which was immediately used for the next reaction without characterization. An (*E*)-acrylamide isomer was also obtained in 26% yield.

*4.2.11. Bn-protected 5-iodo-7-oxanorbornene **18***

By the same procedure for the synthesis of **10**, the 7-oxanorbornene **18** was synthesized from **15** in 57% yield (2 steps from **8**) as a colorless solid: IR (film) 3028, 1688, 1424, 1356, 1154, 733, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.17 (m, 5H), 6.50 (d, J=5.7 Hz, 1H), 6.36 (dd, J=5.7, 1.8 Hz, 1H), 5.28 (d, J=1.8 Hz, 1H), 4.59 (d, J=14.4 Hz, 1H), 4.51 (d, J=14.4 Hz, 1H), 3.87 (d, J=8.1 Hz, 1H), 3.73 (d, J=12.3 Hz, 1H), 3.51 (d, J=12.3 Hz, 1H), 2.45 (d, J=8.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 136.1, 135.7, 135.4, 128.8, 128.0, 127.7, 90.4, 88.8, 50.0, 47.4, 46.8, 18.3; HRMS (ESI, positive) calcd for $C_{15}H_{15}INO_2$ [$(M+H)^+$] 368.0142, found 368.0155.

*4.2.12. PMB-protected 5-iodo-7-oxanorbornene **19***

By the same procedure for the synthesis of **10**, the 7-oxanorbornene **19** was synthesized from **16** in 87% yield as a colorless solid: IR (film) 2932, 1684, 1512, 1246, 1175, 1032, 707 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, J=8.7 Hz, 2H), 6.86 (d, J=8.7 Hz, 2H), 6.50 (d, J=5.7 Hz, 1H), 6.34 (dd, J=5.7, 2.1 Hz, 1H), 5.27 (d, J=2.1 Hz, 1H), 4.54 (d, J=14.4 Hz, 1H), 4.42 (d, J=14.4 Hz, 1H), 3.86 (d, J=8.1 Hz, 1H), 3.78 (s, 3H), 3.70 (d, J=12.0 Hz, 1H), 3.49 (d, J=12.0 Hz, 1H), 2.43 (d, J=7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 159.0, 136.1, 135.3, 129.3, 127.7, 114.1, 90.3, 88.7, 55.2, 50.1, 47.2, 46.2, 18.4; HRMS (ESI, positive) calcd for $C_{16}H_{17}INO_3$ [$(M+H)^+$] 398.0248, found 398.0252.

*4.2.13. Alcohol **20***

To a stirred solution of the iodide **19** (18.0 mg, 0.44 mmol) in THF (45 mL) at 0 °C was added aqueous NaOH (2 M, 9 mL). After 5 h, hydrochloric acid (2 M, 3 mL) was added and the mixture was extracted with EtOAc (10 mL). The extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (0.1 g, hexane/EtOAc=1:4) to give the alcohol **20** (12.8 mg, 100%) as a colorless solid: IR (film) 3392, 2933, 1684, 1669, 1512, 1362, 1247, 1036, 838, 720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, J=8.0 Hz, 2H), 6.84 (d, J=8.0 Hz, 2H), 6.56 (d, J=3.3 Hz, 1H), 6.48 (dd, J=3.3, 2.7 Hz, 1H), 4.97 (d, J=2.7 Hz, 1H), 4.73 (br s, 1H), 4.49 (d, J=9.0 Hz, 1H), 4.36 (d, J=9.0 Hz, 1H), 3.77 (s, 3H), 3.75 (d, J=7.2 Hz, 1H), 3.42 (d, J=7.2 Hz, 1H), 2.31 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 158.8, 135.1, 134.9, 129.3, 114.2, 90.3, 80.5, 71.2, 58.1, 55.3, 49.2, 46.0; HRMS (ESI, positive) calcd for $C_{16}H_{17}NO_4$ [$(M+H)^+$] 288.1230, found 288.1229.

*4.2.14. 2-Propenyl ether **21***

A suspension of 2-propen-1-ol (0.0206 mL, 0.30 mmol) and NaH (60% in mineral oil, 12 mg, 0.3 mmol) in DMF (1.0 mL) was stirred at rt for 30 min. This suspension was then cooled to −10 °C and added to a stirred solution of the iodide **19** (19.9 mg, 0.05 mmol) in DMF (1.0 mL) at −10 °C. After 30 min, saturated aqueous NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (20 mL). The extract was washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (0.5 g, hexane/EtOAc=1:1) to give the 2-propenyl ether **21** (11.7 mg, 81%) as a colorless solid: IR (film) 2910, 1686, 1513, 1470, 1247, 1112, 1032, 839, 720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, J=8.5 Hz, 1H), 6.84 (d, J=8.5 Hz, 1H), 6.51 (d, J=6.0 Hz, 1H), 6.42 (dd, J=6.0, 2.0 Hz, 1H), 5.89 (ddt, J=17.0, 10.5, 5.5 Hz, 1H), 5.31 (dd, J=17.0, 1.5 Hz, 1H), 5.19 (dd, J=10.5, 1.5 Hz, 1H), 4.99 (dd, J=5.0, 2.0 Hz, 1H), 4.50 (d, J=14.5 Hz, 1H), 4.35 (d, J=14.5 Hz, 1H), 4.35 (d, J=5.0, 2.0 Hz, 1H), 4.13 (dd, J=12.5, 5.5 Hz, 1H), 4.05 (dd, J=12.5, 5.5 Hz, 1H), 3.77 (s, 3H), 3.75 (d, J=11.5 Hz, 1H), 3.42 (d, J=11.5 Hz, 1H), 2.23 (d, J=2.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 159.1, 134.8, 133.9, 129.3, 128.0, 117.7, 114.1, 90.1, 79.6, 78.3, 71.6, 55.3, 55.2, 49.2, 46.0; HRMS (ESI, positive) calcd for $C_{19}H_{22}NO_4$ [$(M+H)^+$] 328.1549, found 328.1542.

*4.2.15. 3-Butenyl ether **22***

By the same procedure for the synthesis of **21**, the 3-butenyl ether **22** was synthesized from **19** in 76% yield as a colorless

solid: IR (film) 3075, 1688, 1513, 1362, 1248, 1126, 840, 717 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, J=9.0 Hz, 1H), 6.84 (d, J=9.0 Hz, 1H), 6.50 (d, J=5.5 Hz, 1H), 6.40 (dd, J=5.5, 1.0 Hz, 1H), 5.76 (ddt, J=17.0, 10.0, 7.0 Hz, 1H), 5.06 (dd, J=17.0, 1.5 Hz, 1H), 5.00 (dd, J=10.0, 1.5 Hz, 1H), 4.99 (dd, J=4.3, 1.0 Hz, 1H), 4.51 (d, J=14.5 Hz, 1H), 4.35 (d, J=14.5 Hz, 1H), 4.29 (dd, J=4.3, 1.5 Hz, 1H), 3.77 (s, 1H), 3.75 (d, J=11.5 Hz, 1H), 3.65–3.56 (m, 2H), 3.42 (d, J=11.5 Hz, 1H), 2.31 (q, J=7.0 Hz, 1H), 2.27 (d, J=1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 159.1, 134.9, 134.7, 129.3, 128.3, 128.0, 116.6, 114.1, 90.1, 79.6, 78.8, 70.1, 55.4, 55.3, 49.2, 46.0, 33.9; HRMS (ESI, positive) calcd for $C_{20}H_{24}NO_4$ [(M+H)$^+$] 342.1705, found 342.1713.

4.2.16. 4-Pentenyl ether **23**

By the same procedure for the synthesis of **21**, the 4-pentenyl ether **23** was synthesized from **19** in 72% yield as a colorless solid: IR (film) 3075, 1688, 1513, 1419, 1361, 1247, 1127, 840, 718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, J=8.7 Hz, 2H), 6.84 (d, J=8.7 Hz, 2H), 6.49 (dd, J=5.7 Hz, 1H), 6.40 (dd, J=5.7, 1.5 Hz, 1H), 5.78 (ddt, J=15.9, 12.5, 6.9 Hz, 1H), 5.00 (dd, J=12.5, 1.2 Hz, 1H), 4.96 (dd, J=4.5, 1.5 Hz, 1H), 4.95 (dd, J=15.9, 1.2 Hz, 1H), 4.50 (d, J=14.7 Hz, 1H), 4.35 (d, J=14.7 Hz, 1H), 4.27 (dd, J=4.5, 2.1 Hz, 1H), 3.77 (s, 1H), 3.75 (d, J=12.9 Hz, 1H), 3.56 (m, 2H), 3.41 (d, J=12.9 Hz, 1H), 2.25 (d, J=2.1 Hz, 1H), 2.06 (q, J=6.9 Hz, 2H), 1.68–1.59 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 159.4, 138.4, 135.2, 134.9, 129.6, 128.3, 115.1, 114.1, 90.4, 79.9, 79.1, 70.3, 55.7, 55.5, 49.4, 46.3, 30.4, 28.1; HRMS (ESI, positive) calcd for $C_{21}H_{26}NO_4$ [(M+H)$^+$] 356.1856, found 356.1870.

4.2.17. Boc-protected 2-propenylamine **24**

To a stirred solution of the alcohol **20** (65.1 mg, 0.23 mmol) in CH_2Cl_2 (2.5 mL) at rt were added MS4A (65 mg), NMO (54.0 mg, 0.46 mmol), and TPAP (8.1 mg, 0.023 mmol). After 1 h, insoluble materials were removed by filtration through a pad of Celite® and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (2 g, hexane/EtOAc=1:1) to give the intermediary ketone (30.0 mg, 46%) as a colorless oil: IR (film) 2937, 1773, 1684, 1513, 1419, 1353, 1177, 1031, 834, 732, 579 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, J=8.5 Hz, 2H), 6.85 (d, J=8.5 Hz, 2H), 6.64 (d, J=6.0 Hz, 1H), 6.59 (dd, J=6.0, 1.5 Hz, 1H), 4.65 (d, J=1.5 Hz, 1H), 4.50 (d, J=14.5 Hz, 1H), 4.44 (d, J=14.5 Hz, 1H), 3.79 (d, J=12.5 Hz, 1H), 3.78 (s, 3H), 3.56 (d, J=12.5 Hz, 1H), 2.79 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 158.8, 135.1, 134.9, 129.3, 127.8, 114.2, 90.3, 80.5, 71.2, 58.1, 55.3, 49.2, 46.0; HRMS (ESI, positive) calcd for $C_{16}H_{16}NO_4$ [(M+H)$^+$] 286.1079, found 286.1071.

To a stirred solution of the ketone (11.0 mg, 0.039 mmol) thus obtained above in $HC(OMe)_3$ (0.5 mL) at rt was added 2-propenylamine (0.0116 mL, 0.154 mmol). After 14 h, the mixture was concentrated under reduced pressure, and the residue was dissolved in MeOH (0.5 mL) and cooled to 0 °C. To this solution were added $NaBH_4$ (1.8 mg, 0.047 mmol) and TFA (0.0032 mL, 0.043 mmol), and the mixture was stirred for 2 h. Saturated aqueous $NaHCO_3$ (5 mL) was then added and the mixture was extracted with EtOAc (2×5 mL). The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (0.5 mL), to which were then added TEA (0.011 mL, 0.15 mmol) and Boc_2O (0.018 mL, 0.085 mmol). After stirring at rt for 5 h, saturated aqueous NH_4Cl (1 mL) was added and the mixture was extracted with EtOAc (5 mL). The extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (0.5 g, hexane/EtOAc=7:3) to give the Boc amide **24** (8.5 mg, 51%) as a colorless solid: IR (film) 2932, 1690, 1513, 1247, 1034, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, J=8.5 Hz, 2H), 6.84 (d, J=8.5 Hz, 2H), 6.46 (d, J=5.0 Hz, 2H), 6.39 (dd, J=5.0, 1.0 Hz, 2H), 5.74 (ddt, J=17.0, 10.0, 4.7 Hz, 1H), 5.39 (br s, 1H), 5.13 (dd, J=17.0, 1.0 Hz, 1H), 5.09 (dd, J=10.0, 1.0 Hz, 1H), 4.49 (d, J=14.7 Hz, 1H), 4.42 (br s, 1H), 4.35 (d, J=14.7 Hz, 1H), 3.92 (dd, J=17.6, 4.8 Hz, 1H), 3.77 (s, 3H), 3.72 (dd, J=11.7, 4.7 Hz, 1H), 3.65 (dd, J=17.6, 4.8 Hz, 1H), 3.43 (dd, J=11.7, 4.7 Hz, 1H), 2.53 (d, J=3.6 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 159.5, 156.0, 136.0, 134.8, 134.0, 129.5, 128.0, 116.0, 114.2, 89.9, 89.1, 81.9, 80.6, 58.0, 55.3, 52.3, 48.9, 46.1, 28.3; HRMS (ESI, positive) calcd for $C_{24}H_{30}N_2NaO_5$ [(M+Na)$^+$] 449.2047, found 449.2055.

4.2.18. Heterotricycle **26**

To a stirred solution of the diene **21** (7.0 mg, 0.021 mmol) in CH_2Cl_2 (8.3 mL), saturated with ethylene gas by bubbling for 15 min, at rt was added second-generation Hoveyda–Grubbs catalyst **25** (0.13 mg, 0.21 μmol).[34] 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=6:4) to give the heterotricycle **26** (4.8 mg, 69%) as a colorless solid: IR (film) 2935, 1684, 1512, 1246, 1090, 1032, 764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, J=8.4 Hz, 2H), 6.82 (d, J=8.4 Hz, 2H), 6.05 (dd, J=10.1, 3.6 Hz, 1H), 5.98 (dd, J=10.1, 3.0 Hz, 1H), 5.96 (dd, J=16.7, 10.5 Hz, 1H), 5.29 (d, J=16.7 Hz, 1H), 5.11 (d, J=10.5 Hz, 1H), 4.49 (d, J=14.7 Hz, 1H), 4.34 (d, J=3.0 Hz, 1H), 4.33 (d, J=14.7 Hz, 1H), 4.15 (dd, J=16.4, 3.6 Hz, 1H), 4.08 (br s, 1H), 4.04 (d, J=16.4 Hz, 1H), 3.78 (s, 3H), 3.42 (d, J=11.1 Hz, 1H), 3.31 (d, J=11.1 Hz, 1H), 3.15 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 159.2, 138.6, 131.0, 129.4, 127.7, 122.1, 114.9, 84.9, 78.7, 73.3, 64.2, 59.8, 57.0, 55.3, 46.0; HRMS (ESI, positive) calcd for $C_{19}H_{22}NO_4$ [(M+Na)$^+$] 328.1543, found 328.1550.

4.2.19. Heterotricycle **27**

By the same procedure for the synthesis of **26**, the heterotricycle **27** was synthesized from **22** in 74% yield as a colorless solid: IR (film) 2933, 1684, 1512, 1247, 1031, 816, 763 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, J=8.4 Hz, 2H), 6.82 (d, J=8.4 Hz, 2H), 5.97 (dd, J=17.1, 10.8 Hz, 1H), 5.81 (ddd, J=11.6, 5.1, 5.1 Hz, 1H), 5.66 (dd, J=11.6, 4.5 Hz, 1H), 5.34 (dd, J=17.1, 0.9 Hz, 1H), 5.13 (dd, J=10.8,

0.9 Hz, 1H), 4.47 (dd, J=9.2, 4.5 Hz, 1H), 4.46 (d, J=14.7 Hz, 1H), 4.44 (br d, J=9.2 Hz, 1H), 4.34 (d, J=14.7 Hz, 1H), 3.97 (dt, J=12.0, 5.1 Hz, 3H), 3.78 (s, 3H), 3.63 (dt, J=12.0, 5.1 Hz, 1H), 3.40 (d, J=11.1 Hz, 2H), 3.29 (d, J=11.1 Hz, 2H), 3.14 (br s, 1H), 2.34 (dd, J=5.1, 5.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 159.2, 138.3, 129.8, 129.5, 127.7, 126.3, 115.0, 114.1, 83.4, 82.9, 82.6, 69.1, 61.2, 57.0, 55.3, 46.0, 30.6; HRMS (ESI, positive) calcd for $C_{20}H_{24}NO_4$ [$(M+H)^+$] 342.1705, found 342.1705.

*4.2.20. Heterotricycle **29***

By the same procedure for the synthesis of **26**, the heterotricycle **29** was synthesized from **24** in 81% yield as a colorless solid: IR (film) 2928, 1699, 1249, 1163, 839, 736, 701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (br s, 1H), 7.13 (br s, 2H), 6.82 (br s, 2H), 5.91 (dd, J=11.0, 17.0 Hz, 1H), 5.75 (br s, 2H), 5.14 (br d, J=17.0 Hz, 1H), 5.01 (br d, J=11.0 Hz, 1H), 4.58 (br d, J=5.0 Hz, 1H), 4.55–4.35 (m, 4H), 4.23 (br d, J=18.5 Hz, 1H), 3.77 (br s, 3H), 3.52 (br d, J=18.5 Hz, 1H), 3.33 (d, J=4.0 Hz, 1H), 3.30 (br s, 1H), 3.19 (d, J=4.0 Hz, 1H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 159.1, 154.2, 140.2, 129.6, 129.4, 128.0, 125.7, 114.1, 113.2, 84.8, 84.1, 80.7, 73.3, 58.0 (×2), 55.2 (×2), 45.7, 28.3; HRMS (ESI, positive) calcd for $C_{24}H_{31}N_2O_5$ [$(M+H)^+$] 427.2233, found 449.2228.

*4.2.21. Styryl heterotricycle **30***

To a stirred solution of the diene **21** (3.0 mg, 9.2 μmol) in CH_2Cl_2 (2.5 mL) at rt were added styrene (0.0053 mL, 0.046 mmol) and the second-generation Hoveyda–Grubbs catalyst **25** (0.3 mg, 0.46 μmol).[34] After 12 h, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (0.5 g, hexane/EtOAc=7:3) to give the styryl heterotricycles **30** (*E*/*Z*=6:5, 1.2 mg, 47%) and **26** (0.75 mg, 33%). The styryl heterotricycle **30** is a brown solid: IR (film) 2933, 1684, 1512, 1248, 1090, 753, 695 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.15 (m, 5H), 7.16 (d, J=9.0 Hz, 2H), 6.86 (d, J=9.0 Hz, 2H), 6.59 (d, J=16.0 Hz, 1H), 6.28 (d, J=16.0 Hz, 1H), 6.07 (dd, J=10.3, 3.5 Hz, 1H), 6.02 (dd, J=11.5, 1.5 Hz, 1H), 4.50 (d, J=14.5 Hz, 1H), 4.39 (d, J=14.5 Hz, 1H), 4.37 (s, 1H), 4.15 (dd, J=14.0, 3.0 Hz, 1H), 4.06 (t, J=15.0 Hz, 2H), 3.53 (d, J=11.5 Hz, 1H), 3.40 (d, J=11.5 Hz, 1H), 3.24 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 159.2, 136.4, 133.6, 131.2, 130.0, 129.8, 129.5, 128.4, 128.1, 127.7, 126.6, 122.0, 114.2, 85.0, 78.7, 73.3, 64.2, 60.2, 57.5, 55.3, 46.1; HRMS (ESI, positive) calcd for $C_{25}H_{26}NO_4$ [$(M+H)^+$] 404.1856, found 404.1868.

*4.2.22. 4-Bromo-1-butenyl heterotricycle **31***

By the same procedure for the synthesis of **30**, the 4-bromo-1-butenyl heterotricycle **31** (*E*/*Z*=2:1) was synthesized from **21** in 45% yield accompanied by undesired **26** (45%) as brown solid: IR (film) 2934, 1683, 1513, 1248, 1213, 1085, 1020, 810 cm^{-1}; ^{1}H NMR (for the (*E*)-isomer, 300 MHz, $CDCl_3$) δ 7.13 (d, J=8.0 Hz, 2H), 6.85 (d, J=8.0 Hz, 2H), 6.05 (dd, J=7.0, 5.5 Hz, 1H), 5.98 (d, J=7.0 Hz, 1H), 5.69 (dt, J=17.0, 7.5 Hz, 1H), 5.29 (d, J=17.0 Hz, 1H), 4.49 (d, J=15.0 Hz, 1H), 4.34 (d, J=15.0 Hz, 1H), 4.15 (dd, J=17.0, 4.0 Hz, 1H), 4.07 (d, J=17.0 Hz, 2H), 4.06 (br s, 1H), 3.42 (d, J=11.0 Hz, 1H), 3.41 (m, 1H), 3.31 (d, J=11.0 Hz, 1H), 3.30 (m, 1H), 3.16 (s, 1H), 2.75 (m, 1H), 2.66 (m, 1H); ^{13}C NMR (for the (*E*)-isomer, 125 MHz, $CDCl_3$) δ 170.3, 159.1, 138.6, 131.0, 127.7, 114.9, 114.2, 84.8, 78.7, 73.2, 64.2, 59.8, 57.0, 55.2, 45.9, 35.3, 31.9; HRMS (ESI, positive) calcd for $C_{21}H_{25}NO_4$ [$(M+H)^+$] 434.0967, found 434.0970.

*4.2.23. 2-Acetoxyvinyl heterotricycle **32***

By the same procedure for the synthesis of **30**, the 2-acetoxyvinyl heterotricycle **32** (*E*/*Z*=5:4) was synthesized from **21** in 88% yield accompanied by undesired **26** (10%) as a brown solid: IR (film) 2935, 1757, 1684, 1513, 1247, 1213, 1088, 1035, 818, 763 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, J=12.2 Hz, 1.3H), 7.16 (d, J=9.0 Hz, 2H), 7.13 (d, J=9.0 Hz, 2H), 6.97 (d, J=7.0 Hz, 1H), 6.85 (d, J=9.0 Hz, 2.6H), 6.83 (d, J=9.0 Hz, 2H), 6.05 (dd, J=10.8, 3.0 Hz, 2.6H), 5.96 (m, 1H), 5.57 (d, J=12.3 Hz, 1.3H), 5.27 (d, J=7.0 Hz, 1H), 4.51–4.45 (m, 2.3H), 4.37–4.31 (m, 4.6H), 4.19–3.96 (m, 6.9H), 3.78 (s, 3.9H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 170.2, 167.7, 166.5, 159.2, 159.2, 137.4, 133.1, 131.4, 131.0, 129.6, 129.5, 127.9, 127.6, 122.0, 121.9, 116.5, 115.6, 114.2, 114.1, 85.4, 82.9, 82.5, 78.6, 76.6, 73.4, 72.6, 64.4, 64.1, 60.5, 59.9, 58.6, 57.2, 55.3, 46.1, 46.0, 20.6, 20.5; HRMS (ESI, positive) calcd for $C_{19}H_{22}NO_4$ [$(M+H)^+$] 386.1604, found 386.1602.

*4.2.24. Aldehyde **33***

To a stirred solution of the vinyl acetate **32** (78.4 mg, 0.20 mmol) in MeOH (2.0 mL) at −10 °C was added AcCl (0.0284 mL, 0.40 mmol). After 12 h, saturated aqueous $NaHCO_3$ (10 mL) was added and the mixture was extracted with EtOAc (20 mL). The extract was washed with brine (15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (2 g, hexane/EtOAc=6:4) to give the intermediary dimethyl acetal (65.1 mg, 83%) as a colorless solid: IR (film) 2925, 1684, 1516, 1247, 1034, 819, 742 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, J=8.7 Hz, 2H), 6.86 (d, J=8.7 Hz, 2H), 6.04 (dd, J=10.7, 4.2 Hz, 1H), 5.96 (dd, J=10.7, 3.5 Hz, 1H), 4.58 (q, J=3.0 Hz, 1H), 4.49 (d, J=14.4 Hz, 1H), 4.32 (br d, J=4.2 Hz, 1H), 4.29 (d, J=14.4 Hz, 1H), 4.32 (s, 1H), 4.29 (d, J=14.4 Hz, 1H), 4.18 (dd, J=17.4, 3.5 Hz, 1H), 4.06 (d, J=17.4 Hz, 1H), 3.99 (br s, 1H), 3.80 (s, 3H), 3.43 (d, J=11.4 Hz, 1H), 3.30 (d, J=11.4 Hz, 1H), 3.28 (s, 3H), 3.24 (s, 3H), 3.17 (s, 1H), 2.17 (dd, J=14.1, 3.0 Hz, 1H), 1.95 (dd, J=14.1, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 159.1, 131.0, 129.3, 128.0, 122.3, 114.1, 101.9, 83.3, 78.8, 72.8, 62.3, 58.8, 57.8, 55.3, 53.7, 52.3, 45.9, 41.4; HRMS (ESI, positive) calcd for $C_{21}H_{28}NO_6$ [$(M+H)^+$] 390.1917, found 390.1917.

To a stirred solution of the intermediary dimethyl acetal (65.1 mg, 0.17 mmol) thus obtained above in THF (5.0 mL) at rt was added hydrochloric acid (1 M, 5.0 mL). After 5 h, saturated aqueous $NaHCO_3$ (10 mL) was added and the mixture was extracted with EtOAc (20 mL). The extract was dried

over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (2 g, hexane/EtOAc=1:1) to give the aldehyde **33** (55.9 mg, 90%) as a colorless solid: IR (film) 2935, 2837, 1717, 1684, 1514, 1437, 1248, 1089, 1031, 818, 735, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.72 (d, J=1.5 Hz, 1H), 7.13 (d, J=8.5 Hz, 2H), 6.84 (d, J=8.5 Hz, 2H), 6.05 (dd, J=10.3, 3.5 Hz, 1H), 5.94 (dt, J=10.3, 2.0 Hz, 1H), 4.47 (d, J=14.5 Hz, 1H), 4.33 (d, J=14.5 Hz, 1H), 4.30 (br d, J= 2.0 Hz, 1H), 4.17 (dd, J=16.5, 3.5 Hz, 1H), 4.08 (d, J=16.5 Hz, 1H), 4.00 (br t, J=2.0 Hz, 1H), 3.79 (s, 3H), 3.44 (d, J=11.5 Hz, 1H), 3.33 (d, J=11.5 Hz, 1H), 3.15 (s, 1H), 3.02 (dd, J=17.0, 1.5 Hz, 1H), 2.78 (dd, J=17.0, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2, 170.0, 159.2, 131.3, 129.4, 127.6, 121.8, 114.2, 82.1, 78.4, 73.1, 64.4, 58.8, 57.5, 55.3, 51.7, 46.0; HRMS (ESI, positive) calcd for $C_{19}H_{22}NO_5$ [$(M+H)^+$] 344.1498, found 344.1492.

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