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IMDAF/Aromatization Path of Halogenated Furylacrylamides and Furylpropiolamides to Dihydroisoquinolin-1(2*H*)-ones

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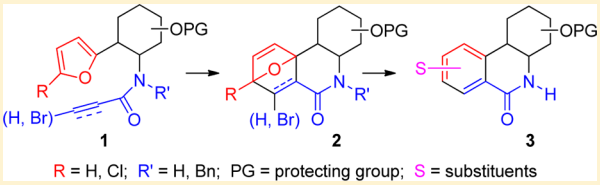
Supporting Information

ABSTRACT: Intramolecular Diels–Alder cycloadditions of chlorofuryl- (R = Cl) secondary (R′ = H) acrylamides and propiolamides of type **1** followed by (optional modification and) base-induced aromatization of the resulting chlorinated oxanorborn(adi)enes **2** afford *N*-free-dihydroisoquinolin-1(2*H*)-ones **3** with different aromatic substitution patterns.



INTRODUCTION

Isoquinolin-1(2*H*)-ones are important heterocyclic motifs in medicinal chemistry. Actually, isoquinolin-1(2*H*)-one derivatives have been identified as ligands for a variety of receptors and as agents for the treatment of a number of pathologies.[1,2] Our work in isoquinolinones originated from our interest in pancratistatin (**4**, Figure 1),[3,4] one of the most significant

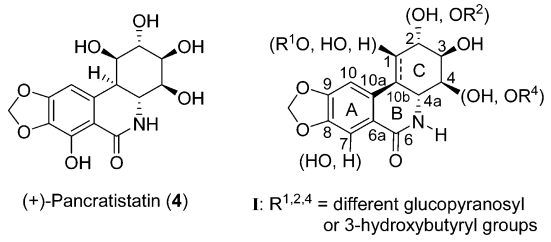


Figure 1. Structure and numbering of the isocarbostyril constituents of the Amaryllidaceae plant family: pancratistatin (**4**) and general structure (**I**).[7]

antitumoral constituents of Amaryllidaceae. This group of natural products, of which general structure **I** (Figure 1) features a dihydroisoquinolin-1(2*H*)-one substructure (rings A and B), are in fact commonly referred to as the "isocarbostyrils",[5,6] thus highlighting their A-B isoquinolinone part over the fused aminocyclohexitol subunit (ring C).[7]

To date, a number of analogues of pancratistatin with changes in the aminocyclitol portion have been synthesized and tested against human tumoral cell lines.[8] Except for some changes at position 1,[9] any other structural variation resulted in diminished activity. This suggests that the pharmacophore essentially requires every element the natural product has in ring C and makes the dihydroisoquinolinone fragment a relevant target for pharmacological tuning and for the eventual preparation of biological probes. This, in turn, calls for synthetic procedures able to supply differently substituted dihydroisoquinolin-1(2*H*)-ones.[10]

For that purpose, we identified compounds of type **1** (see Abstract graphic) as attractive precursors. In particular, halogenated furylamides **1** (R = X) in which a *secondary* (R′ = H) *α,β*-unsaturated amide is *N*-attached to a cyclohexitol ring next to a 2-furyl substituent halogenated at position 5, could in principle be transformed into dihydroisoquinolin-1(2*H*)-ones **3** in just two steps. A first intramolecular Diels–Alder cycloaddition of **1** (between their furan rings and the *N*-tethered unsaturated chains) would give bridgehead-halogenated oxanorbornene or oxanorbornadiene intermediates **2**. Subsequent opening/aromatization of **2** would then render the desired dihydroisoquinolin-1(2*H*)-ones **3**. We chose to use a halogen substituent next to the oxygen atom of the furan ring of **1** for two reasons: first, because of its known effect in facilitating IMDAF (intramolecular Diels–Alder furan) cycloadditions,[11] and second, to enable the aromatization process of **2** through elimination of the halide ion concomitant with the base-induced opening of its oxabicyclic ring system. In the event, and despite the lack of previous examples for the **1** → **2** → **3** pathway and of the reported failure of secondary amides of type **1** (R = R′ = H) to undergo cycloaddition,[12] we recently proved the viability of both steps starting with a chlorinated furylacrylamide of type **1** (R = Cl). Specifically, we performed the IMDAF cycloaddition of **1a** to **2a** (Scheme 2, **1a** → **2a** under conditions **A**) and the opening/aromatization of **2b** to **3b** (Scheme 3), which were both implemented into a new synthetic scheme to obtain racemic 7,9-dideoxy pancratistatin analogues from furfural.[13]

Herein, we describe further work on the furylamide → oxanorborn(adi)ene → dihydroisoquinolin-1(2*H*)-one pathway. In particular, we report on the stereochemical outcome of the IMDAF cycloaddition of acrylamides, the possibility of using propiolamides instead, and the feasibility to obtain different substitution patterns for the final dihydroisoquinolin-1(2*H*)-ones **3**. We also discuss the halogen effect in the cycloaddition of both acrylamides and propiolamides, as well as some attempts we

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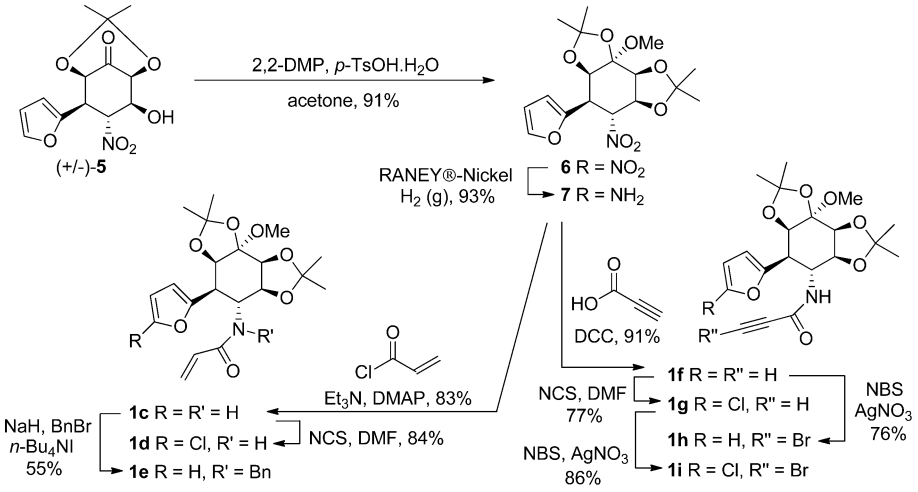
Scheme 1. Preparation of Acrylamides 1c−e and Propiolamides 1f−i from Known Nitrocyclitol (±)-5



made to improve the efficiency of the IMDAF reaction with some chlorinated acrylamides of type **1**.

RESULTS AND DISCUSSION

Preparation of Acrylamides and Propiolamides of Type 1. All amides of type **1** used in this study were synthesized from furylcyclohexylamine (±)-**7**, itself prepared from the known protected nitrocyclitol (±)-**5**[14] in two steps, which consisted of a change of the protection pattern, by reaction with 2,2-dimethoxypropane and *p*-TsOH in acetone to afford **6**, followed by reduction with Raney nickel to **7** (Scheme 1). Treatment of **7** with acryloyl chloride in the presence of Et_3N and DMAP gave acrylamide **1c**, which was transformed into its furyl-chlorinated and *N*-benzylated analogues, **1d** and **1e**, using NCS in DMF, or NaH, benzyl bromide, and *n*-Bu_4NI in THF, respectively. DCC-promoted coupling of **7** with propiolic acid afforded propiolamide **1f**, which could be selectively monohalogenated, either in its furan ring (with NCS in DMF to give **1g**) or at the terminal position of the triple bond (with NBS and $AgNO_3$ to give **1h**), as well as sequentially dihalogenated ((i) NCS, DMF; (ii) NBS, $AgNO_3$, acetone) to render **1i**.

IMDAF of Acrylamides. Regarding the IMDAF cycloaddition of acrylamides, we first compared the behavior of acrylamide **1c** with its halogenated analogue **1d**. In the event, their heating in toluene in a closed tube for 2−3 days (at 120 °C external bath temperature and in the presence of $NaHCO_3$ for **1d**) afforded in every case the corresponding cycloadduct, **2c** and **2d**, respectively (Scheme 2). However, the process was far more efficient for the chlorinated acrylamide **1d** (84%) in comparison with its nonhalogenated analogue **1c** (22%), thus confirming the beneficial effect of halogen substitution for IMDAF reactions, in line with the observations of Padwa and Houk.[11]

As it happened for **2a**,[13] cycloadducts **2c** and **2d** were also obtained as single stereoisomers. The relative configuration of the three new stereocenters formed during the IMDAF step was determined on the basis of their ^1H NMR data, which followed similar trends for the three compounds. In particular, the coupling constants for protons H_{6a}, H_{7endo}, H_{7exo}, and H_8 in **2c** did not resemble those usually shown by *endo* oxabicycles of type **II** but followed the pattern typically observed for *exo* cycloadducts of type **III** (bottom of Scheme 2),[12b] in which H_{6a} is nearly coplanar with H_{7endo} and the carbonyl group is oriented away from the oxabicyclic $C_9{=}C_{10}$ double bond. In this respect, the signals for H_{7endo} (a dd at 1.64 ppm and coupling constants of 11.8 and 8.5 Hz with H_{7exo} and H_{6a}, respectively) and for H_{7exo} (a ddd at 2.56 ppm and coupling constants of 11.8, 4.7, and 3.3 Hz with H_{7endo}, H_8, and H_{6a}, respectively) were most diagnostic. Besides, the existence of reciprocal NOE effects between H_{6a} and H_{4a} clearly showed that both protons were oriented toward the same face in the final cycloadducts, thus establishing their formation through an *anti* transition state (TS1), in which the furan oxygen atom would be pointing toward the face of the cyclohexitol ring opposite to that one where H_{4a} is located.[15,16]

After evaluating the halogen effect in the IMDAF reaction of acrylamides and establishing the stereochemical outcome of the process, we next explored the possibility of forming isoquinolinones of type **3** having aromatic substitution different from that already obtained by conversion of **2b** into **3b** (Scheme 3), i.e., a phenolic hydroxyl group located *meta* with respect to the amide carbonyl. We did so by examining one of the options that the functionalization of the $C_9{=}C_{10}$ double bond in intermediates **2** offers to achieve that goal. In particular, we set out to study the formation of a dioxygenated isoquinolinone (present for example in the form of a methylenedioxy group between positions C8 and C9 in natural isocarbostyrils), starting from oxanorbornene **2d**. Oxidation of **2d** with *m*-CPBA in dichloroethane at 50 °C gave epoxide **8** isolated as a single stereoisomer, which would result from the attachment of the oxygen atom to the less hindered face of the C=C double bond in **2d**.[17] Treatment of **8** with *t*-BuOK in DMSO afforded, through opening of the ether bridge and elimination of the chlorine atom at the bridgehead position, followed by C_{10}-O bond cleaving and tautomerization processes, the corresponding (deprotonated) catechol, which was not isolated as such but as its derivative **3d** by heating with dibromomethane.

IMDAF of Propiolamides. Once the possibility of arriving at isoquinolinones dioxygenated at their aromatic ring by modification of intermediates **2** prior to their opening/aromatization was illustrated with the conversion of **2d** into **3d**, we looked at the potential use of propiolamides instead of acrylamides. Attempted cycloaddition of propiolamide **1g** (Scheme 1), which is chlorinated in its furan ring, gave only unreacted starting material or decomposition. Incorporation of an additional halogen atom, now at the terminal position of the triple bond, as in **1i**, allowed the IMDAF to take place to give the dihalogenated oxanorbornadiene **2i**, which was isolated in 37% yield (Scheme 4). In fact, the presence of a single halogen substituent at the alkyne end of the furylpropiolamide, as in **1h**,

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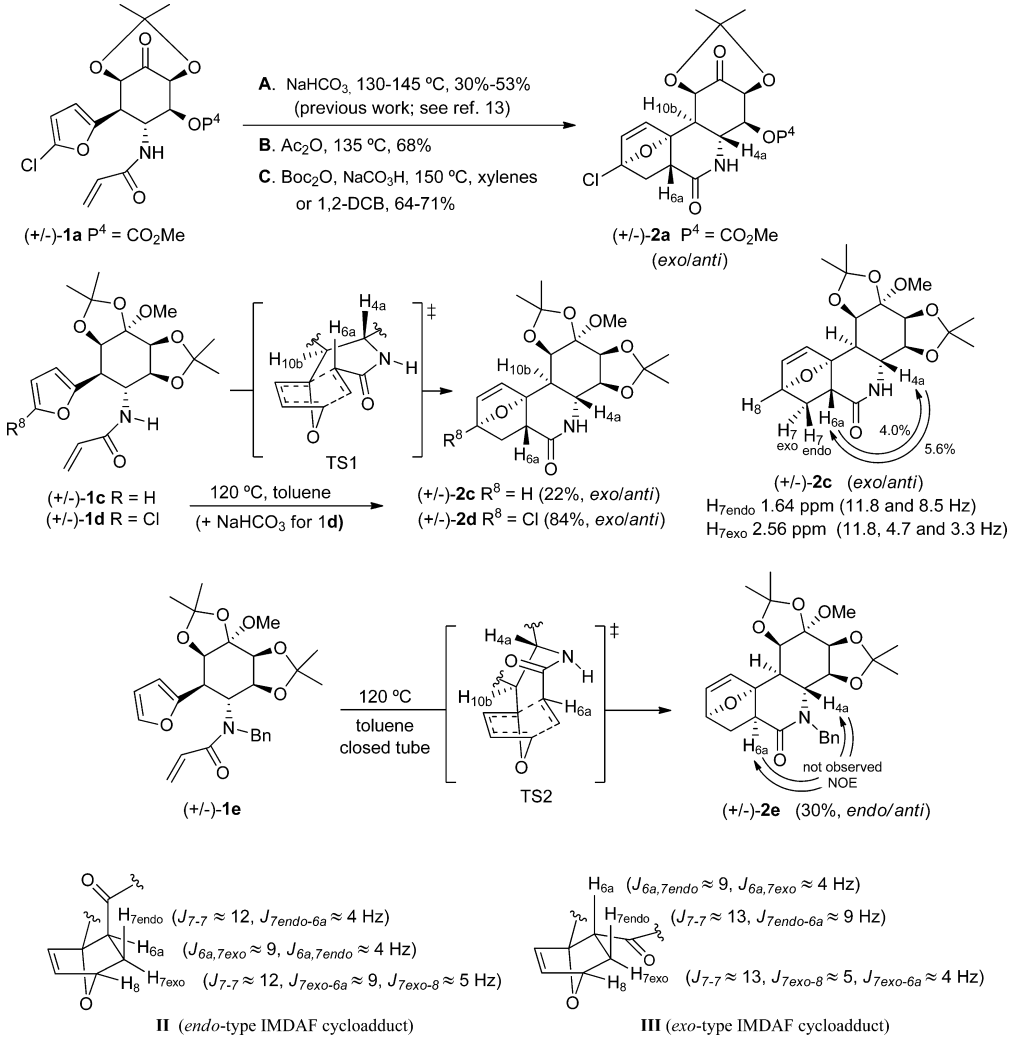
Scheme 2. (Above) IMDAF Cycloadditions of Furylacrylamides of Type 1; (Below) Coupling Pattern Typically Observed for *endo* (II) and *exo* (III) IMDAF Cycloadducts of Furylacrylamides (see ref 12b)



was enough to allow the cycloaddition to take place, albeit the corresponding oxanorbornadiene **2h** was isolated in a lower 30% yield as compared with the dihalogenated case. Taken together, these results thus appear to suggest that, when C≡C triple bonds are used as dienophiles in IMDAF reactions, a halogen atom at their terminal sp carbon could have a bigger beneficial effect on the cycloaddition than when located at its diene cycloaddition partner, the furan ring.

As compared to their oxanorbornene analogues, dihalogenated oxanorbornadienes such as **2i** offer new avenues for transformation. For example, substitution of the vinylic halogen at C7 can take place through addition/elimination, as demonstrated for **2i**, which on treatment with NaMeO in MeOH at 0 °C gave the dimethylketal **9**. Access to additional aromatic substitution patterns from oxanorbornadienes of type **2** is also possible when transformed into dihydroisoquinolinones **3**; in fact, **2i**, under the same conditions used to transform it into **9**, but now at rt, evolved to the 8-hydroxy-7-methoxy substituted analogue **3i** (which also incorporated an extra methoxy group at position C_{10b} at the aromatization step).

IMDAF of Tertiary Acrylamides. To improve the efficiency of the furylacrylamide cycloadditions, in particular those of **1a** and **1c**, which had taken place with yields of 30−53% and 22%, respectively (Scheme 2), we decided to evaluate the cycloaddition of tertiary acrylamide analogues, either generated by *in situ* acylation, as we tried with **1a**, or prepared and isolated before the IMDAF cycloaddition, as for the *N*-benzylated analogue of **1c**, the acrylamide **1e** (Scheme 2).

In the event, cycloaddition of **1e** gave the corresponding *N*-benzyl oxanorbornene **2e** with a yield (30%) only slightly better than for the conversion of the *N*-unprotected analogue **1c** into **2c** (22%, Scheme 2). The introduction of the benzyl substituent at the nitrogen atom fundamentally affected the stereochemical course of the cycloaddition; for secondary acrylamide **1c** it had taken place through an *exo*/*anti* pathway to **2c**, whereas now, for the tertiary amide **1e**, it proceeded through an *endo*/*anti* path to **2e**.[18]

The use of an acylating agent during the IMDAF cycloaddition of **1a**, either as a solvent (Ac_2O, closed reaction tube, external bath $T \approx 135$ °C, 6 h, Scheme 2, conditions **B**) or as a reagent [Boc_2O, 250−500 mol %, 4 h, in this case at higher temperatures (xylenes or 1,2-dichlorobenzene, closed reaction tube, external bath $T \approx 150$ °C) and in the presence of $NaHCO_3$ (120 mol %), Scheme 2, conditions **C**], resulted in the formation of cycloadduct **2a** with significantly improved yields in both cases [68% when performed in Ac_2O at the 20 mg scale, and 64−71% when with Boc_2O at a higher scale (300−480 mg)], a result

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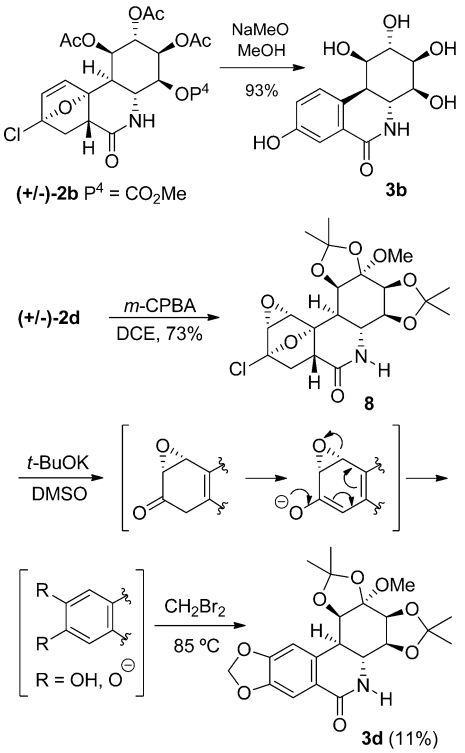
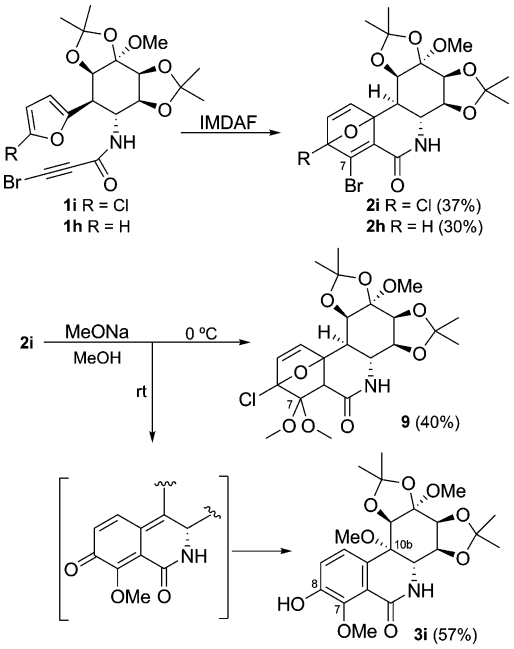
Scheme 3. Opening/Aromatization (2b → 3b)[13] and Epoxidation/Opening/Aromatization (2d → 3d) of Oxanorbornenes of Type 2 on Their Way to Dihydroisoquinolinones 3



Scheme 4. IMDAF/Aromatization Path of Halogenated Furylpropiolamides 1 to Dihydroisoquinolinones 3



probably related to diene activation through temporary amide-acylation.

CONCLUSIONS

In summary, the IMDAF reaction of *N*-unprotected acrylamides of type **1** to secondary *δ*-lactams **2** takes place through an *exo*/*anti* TS and benefits from halogenation at the furyl ring and when performed in the presence of Boc_2O. Protection at the nitrogen in the form of a benzyl group mainly affected the stereochemical course of the reaction favoring the *endo*/*anti* pathway. The halogen atom at the furan ring of **1**, besides facilitating the IMDAF step to **2**, made possible the subsequent opening and aromatization of the oxabicyclic system by simple treatment with base. The two-step synthetic process (**1** → **2** → **3**) is able to afford different substitution patterns in the final *N*-free dihydroisoquinolin-1(2*H*)-ones **3**. Propiolamides of type **1** halogenated at the terminal position of the C≡C triple bond also undergo the IMDAF/aromatization procedure through the corresponding oxanorbornadienes and offer new avenues to obtain additional substitution patterns in the final products.

EXPERIMENTAL SECTION[19]

Nitrodiketal (±)-6. 2,2-Dimethoxypropane (6.2 mL, 50.46 mmol) and *p*-TsOH·H_2O (128 mg, 0.67 mmol) were added to a solution of **5**[14] (1 g, 3.36 mmol) in acetone (2 mL) under argon. After the mixture had been stirred for 14 h at rt, Et_3N was added, and the volatiles were removed (rotary evaporator). Chromatography (7% EtOAc/hexane) gave **6** as an oil (1.13 g, 91%): R_f (10% EtOAc/hexane) = 0.34; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 7.32 (t, *J* = 1.3 Hz, 1H), 6.32−6.29 (m, 2H), 5.12 (dd, *J* = 12.5, 7.6 Hz, 1H), 4.85 (dd, *J* = 7.6, 7.6 Hz, 1H), 4.46 (d, *J* = 2.9 Hz, 1H), 4.42 (d, *J* = 7.6 Hz, 1H), 3.57 (dd, *J* = 12.5, 2.9 Hz, 1H), 3.46 (s, 3H), 1.58 (s, 3H), 1.56 (s, 3H), 1.50 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 148.1, 142.6, 111.9, 111.7, 110.8, 108.9, 103.9, 86.0, 82.3, 78.2, 77.4, 51.2, 39.8, 27.1, 26.5, 26.0, 25.8; HRMS [CI-MS, $(M + H)^+$] *m*/*z* calcd for $C_{17}H_{24}NO_8$ 370.1502, found 370.1505.

Amine (±)-7. A suspension of **6** (3.21 g, 8.68 mmol) and Raney nickel (∼8 mL) in MeOH (40 mL) was stirred at rt under a H_2 atmosphere. After completion of the reduction (as monitored by TLC), the catalyst was filtered off and washed with MeOH (100 mL) and EtOAc (100 mL). The combined washings and the filtrate were combined and evaporated in vacuo to afford amine **7** as an oil (2.93 g, 93%): R_f (80% EtOAc/hexane) = 0.34; ^{1}H NMR ($CDCl_3$, 250 MHz) *δ* 7.40−7.36 (m, 1H), 6.36 (dd, *J* = 2.9, 1.9 Hz, 1H), 6.30 (d, *J* = 2.9 Hz, 1H), 4.35 (d, *J* = 2.8 Hz, 1H), 4.27 (d, *J* = 7.6 Hz, 1H), 4.12 (dd, *J* = 7.6, 7.6 Hz, 1H), 3.51 (dd, *J* = 11.9, 7.6 Hz, 1H), 3.45 (s, 3H), 2.84 (dd, *J* = 11.9, 2.8 Hz, 1H), 1.55 (s, 3H), 1.54 (s, 3H), 1.49 (s, 3H), 1.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) *δ* 151.9, 141.6, 111.0, 110.4, 110.1, 108.2, 104.4, 83.3, 81.7, 78.2, 50.6, 49.8, 42.6, 26.9, 26.4, 26.1, 25.4; LRMS (CI-MS) *m*/*z* (%) 324.2 (6), 340.2 [$(M + H)^+$, 57]; HRMS [CI, $(M + H)^+$] *m*/*z* calcd for $C_{17}H_{26}NO_6$ 340.1760, found 340.1764.

Acrylamide (±)-1c. Acryloyl chloride (145 *μ*L, 1.78 mmol), Et_3N (248 *μ*L, 1.78 mmol), and DMAP (40 mg, 0.32 mmol) were added to a solution of **7** (550 mg, 1.62 mmol) in dry CH_2Cl_2 (8 mL) under argon. After stirring for 20 min, 2,6-di-*tert*-butyl-4-methylphenol (143 mg, 0.65 mmol) was added to the mixture, and the volatiles were removed in vacuo. Chromatography (30% EtOAc/hexane) afforded **1c** as an oil (527 mg, 83%): R_f (70% EtOAc/hexane) = 0.68; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 7.31−7.26 (m, 1H), 6.31−6.22 (m, 2H), 6.09 (dd, *J* = 17.0, 1.3 Hz, 1H), 5.88 (dd, *J* = 17.0, 10.3 Hz, 1H), 5.72 (br s, 1H), 5.52 (dd, *J* = 10.3, 1.3 Hz, 1H), 4.67 (dd, *J* = 7.5, 7.5 Hz, 1H), 4.41 (d, *J* = 2.8 Hz, 1H), 4.37−4.27 (m, 2H), 3.58 (dd, *J* = 12.4, 2.8 Hz, 1H), 3.45 (s, 3H), 1.58 (s, 3H), 1.56 (s, 3H), 1.49 (s, 3H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 166.0, 151.6, 141.7, 130.9, 126.6, 111.4, 110.6, 110.6, 108.8, 104.3, 83.5, 78.6, 78.1, 51.1, 50.5, 39.7, 27.2, 26.6, 26.3, 26.0; LRMS (CI-MS) *m*/*z* (%) 336.2 (6), 394.2 [$(M + H)^+$, 12]; HRMS [CI-MS, $(M + H)^+$] *m*/*z* calcd for $C_{20}H_{28}NO_7$ 394.1866, found 394.1869.

Chlorofurylacrylamide (±)-1d. *N*-chlorosuccinimide (476 mg, 3.57 mmol) was added to a solution of **1c** (1.17 g, 2.97 mmol) in dry DMF (16 mL) under argon. After stirring for 12 h at rt, the reaction mixture was neutralized with Et_3N, treated with 2,6-di-*tert*-butyl-4-methylphenol (131 mg, 0.60 mmol), and the volatiles were removed in vacuo. Chromatography (25% EtOAc/hexane) afforded **1d** as an oil (1.07 g, 84%): R_f (40% EtOAc/hexane) = 0.43; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 6.29 (d, *J* = 3.3 Hz, 1H), 6.17−6.06 (m, 2H), 6.02 (d, *J* = 3.3 Hz,

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1H), 5.95 (dd, J = 17.0, 10.3 Hz, 1H), 5.56 (dd, J = 10.3, 1.3 Hz, 1H), 4.60 (dd, J = 7.6, 7.6 Hz, 1H), 4.45−4.34 (m, 2H), 4.32 (d, J = 7.6 Hz, 1H), 3.49−3.40 (m, 4H), 1.60 (s, 3H), 1.56 (s, 3H), 1.51 (s, 3H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.8, 151.1, 134.6, 130.6, 126.6, 111.3, 111.1, 110.5, 107.0, 104.1, 82.9, 78.3, 78.0, 50.9, 49.6, 39.9, 27.0, 26.4, 26.2, 25.8; LRMS (CI-MS) m/z (%) 428.1 [$(M + H)^+$, 100]; HRMS [CI-MS, $(M + H)^+$] m/z calcd for $C_{20}H_{27}ClNO_7$ 428.1476, found 428.1474.

***N*-Benzylacrylamide (±)-1e.** NaH (14 mg, 0.35 mmol), benzyl bromide (46 μL, 0.39 mmol), and n-Bu_4NI (10 mg, 0.028 mmol) were successively added to solution of **1c** (55 mg, 0.14 mmol) in dry THF under argon. The mixture was stirred for 2 h at 40 °C, diluted with H_2O (1 mL), and extracted with EtOAc (3 × 1 mL). Chromatography (15% EtOAc/hexane) afforded **1e** as a ∼1:1 mixture of amide rotamers (oil, 37 mg, 55%,): R_f (25% EtOAc/hexane) = 0.48; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36−7.21 (m, 10H), 7.22−7.09 (m, 4H), 6.77 (dd, J = 17.1, 10.8 Hz, 1H), 6.38−6.25 (m, 4H), 6.25−6.17 (m, 2H), 6.06 (dd, J = 16.6, 10.3 Hz, 1H), 5.89 (dd, J = 12.5, 8.1 Hz, 1H), 5.66 (dd, J = 10.8, 1.7 Hz, 1H), 5.55 (dd, J = 8.7, 3.7 Hz, 1H), 5.45 (dd, J = 10.4, 1.9 Hz, 1H), 5.13 (t, J = 6.8 Hz, 1H), 5.06 (d, J = 16.5 Hz, 1H), 4.87 (dd, J = 11.9, 7.9 Hz, 1H), 4.46 (dd, J = 8.3, 2.6 Hz, 2H), 4.44−4.38 (m, 3H), 4.37 (d, J = 2.0 Hz, 1H), 4.35−4.28 (m, 2H), 4.26 (s, 1H), 4.16 (dd, J = 7.4, 7.4 Hz, 1H), 4.10 (d, J = 7.8 Hz, 1H), 3.85 (d, J = 16.5 Hz, 1H), 3.78 (dd, J = 12.0, 6.4 Hz, 1H), 3.44 (s, 3H), 3.42 (s, 3H), 3.27 (dd, J = 11.9, 2.3 Hz, 1H), 3.13 (dd, J = 12.5, 2.5 Hz, 1H), 1.60 (s, 3H), 1.58 (s, 3H), 1.54 (s, 3H), 1.52 (s, 3H), 1.46 (s, 3H), 1.44 (s, 3H), 1.09 (s, 3H), 1.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.3, 168.1, 141.8, 141.5, 140.9, 138.8, 138.4, 137.1, 128.3, 128.2, 127.4, 127.2, 127.0, 126.58, 126.4, 111.2, 110.9, 110.5, 110.5, 110.0, 109.8, 109.1, 108.6, 108.5, 104.1, 83.9, 83.8, 78.7, 78.4, 78.3, 76.0, 75.6, 61.8, 56.4, 55.6, 51.7, 50.8, 50.8, 45.8, 39.9, 39.4, 37.8, 27.1, 26.8, 26.1, 26.0, 25.9, 25.7, 25.2, 24.9; LRMS (CI-MS) m/z (%) 484.3 [$(M + H)^+$, 6]; HRMS [CI-MS, $(M + H)^+$] m/z calcd for $C_{27}H_{34}NO_7$ 484.2335, found 484.2332.

Propiolamide (±)-1f. Propiolic acid (131 μL, 2.12 mmol) was added to a solution of DCC (511 mg, 2.47 mmol) in dry CH_2Cl_2 (12 mL) at 0 °C under argon. After stirring for 10 min, a solution of amine **7** (600 mg, 1.77 mmol) in dry CH_2Cl_2 (5.6 mL) was added. The suspension was stirred for 20 min at 0 °C and filtered, and the solvent was evaporated. Chromatography (25% EtOAc/hexane) gave **1f** as an oil (633 mg, 91%): R_f (40% EtOAc/hexane) = 0.48; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (s, 1H), 6.36−6.28 (m, 2H), 6.21 (d, J = 5.3 Hz, 1H), 4.63 (dd, J = 7.6, 7.6 Hz, 1H), 4.41 (d, J = 2.7 Hz, 1H), 4.37−4.29 (m, 1H), 4.29−4.18 (m, 1H), 3.56 (dd, J = 12.4, 2.7 Hz, 1H), 3.45 (s, 3H), 2.69 (s, 1H), 1.58 (s, 3H), 1.57 (s, 3H), 1.52 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.3, 151.1, 142.0, 111.4, 110.7, 110.7, 109.0, 104.2, 83.2, 78.5, 77.7, 73.1, 51.1, 51.0, 39.5, 27.2, 26.6, 26.2, 26.0; LRMS (CI-MS) m/z (%) 334.2 (33), 392.2 [$(M + H)^+$, 17]; HRMS [CI-MS, $(M + H)^+$] m/z calcd for $C_{20}H_{26}NO_7$ 392.1709, found 392.1709.

Chlorofurylpropiolamide (±)-1g. *N*-Chlorosuccinimide (380 mg, 2.85 mmol) was added to a solution of **1f** (930 mg, 2.38 mmol) in dry DMF (12 mL) under argon. After stirring for 7.5 h at rt, the reaction mixture was neutralized with Et_3N and treated with 2,6-di-*tert*-butyl-4-methylphenol (105 mg, 0.48 mmol), and the solvent was removed in vacuo. Chromatography (25% EtOAc/hexane) afforded **1g** as an oil (780 mg, 77%): R_f (35% EtOAc/hexane) = 0.34; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.31 (s, 1H), 6.19 (d, J = 8.4 Hz, 1H), 6.08 (s,1H), 4.54 (dd, J = 7.5, 7.5 Hz, 1H), 4.41−4.37 (m, 1H), 4.37−4.21 (m, 2H), 3.52−3.38 (m, 4H), 2.74 (s, 1H), 1.58 (s, 3H), 1.56 (s, 3H), 1.50 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.3, 150.7, 135.2, 111.6, 111.5, 110.9, 107.3, 104.2, 82.9, 78.4, 77.8, 73.5, 51.1, 50.5, 39.8, 27.2, 26.6, 26.3, 26.0; LRMS (CI-MS) m/z (%) 426.0 [$(M + H)^+$, 77]; HRMS [CI-MS, $(M + H)^+$] m/z calcd for $C_{20}H_{25}ClNO_7$ 426.1320, found 426.1325.

Bromopropiolamide (±)-1h. $AgNO_3$ (73 mg, 0.43 mmol) was added to a solution of **1f** (260 mg, 0.66 mmol) in dry acetone (5.2 mL) at 0 °C. After stirring for 5 min, NBS (130 mg, 0.73 mmol) was added to the mixture. After 25 more min at 0 °C, the mixture was filtered, and the filtrate was evaporated in vacuo. Chromatography (20% EtOAc/hexane) afforded **1h** as an oil (237 mg, 76%): R_f (30% EtOAc/hexane) = 0. 43; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (dd, J = 1.7, 0.8 Hz, 1H), 6.35−6.23 (m, 2H), 6.13 (d, J = 8.1 Hz, 1H), 4.56 (dd, J = 7.6, 7.6 Hz, 1H), 4.36 (d, J = 2.8 Hz, 1H), 4.31−4.15 (m, 2H), 3.49 (dd, J = 12.4, 2.8 Hz, 1H), 3.41 (s, 3H), 1.54 (s, 3H), 1.53 (s, 3H), 1.46 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.0, 151.1, 141.9, 111.4, 110.7, 109.6, 108.9, 104.2, 83.2, 78.5, 77.6, 75.2, 51.1, 51.0, 39. 5, 27.2, 26.6, 26.2, 26.0; HRMS [ESI-TOF, $(M + H)^+$] m/z calcd for $C_{20}H_{25}BrNO_7$ 470.0814, found 470.0817.

Chlorofurylbromopropiolamide (±)-1i. $AgNO_3$ (134 mg, 0.79 mmol) was added to a solution of **1g** (440 mg, 1.03 mmol) in dry acetone (9 mL) at 0 °C. After stirring for 5 min, NBS (220 mg, 1.24 mmol) was added to the mixture. After an additional 1 h at 0 °C, the suspension was filtered, and the filtrate was evaporated in vacuo. Chromatography (15% EtOAc/hexane) afforded **1i** as an oil (450 mg, 86%): R_f (30% EtOAc/hexane) = 0.67; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.29 (d, J = 3.0 Hz, 1H), 6.16−6.02 (m, 2H), 4.51 (dd, J = 7.6, 7.6 Hz, 1H), 4.38 (d, J = 2.3 Hz, 1H), 4.35−4.19 (m, 2H), 3.44 (s, 3H), 3.40 (br d, J = 12.4 Hz, 1H), 1.57 (s, 3H), 1.56 (s, 3H), 1.50 (s, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.9, 150.6, 135.1, 111.4, 111.3, 110.7, 107.2, 104.0, 82.7, 78.3, 77.6, 74.9, 50.9, 50.3, 39.7, 27.0, 26.4, 26.2, 25.8; LRMS (CI-MS) m/z (%) 473.9 (10), 506.0 [$(M + H)^+$, 41]; HRMS [CI-MS, $(M + H)^+$] m/z calcd for $C_{20}H_{24}ClBrNO_7$ 504.0425, found 504.0401.

Oxanorborn(adi)enes (±)-2c-e,h,i. Compounds **2c,d,e,h,i** were prepared by heating (external bath $T \approx 120$ °C) the corresponding furylamide precursors **1c,d,e,h,i** (in the presence of 120 mol % of $NaHCO_3$ for cases **1d,h,i**) in toluene (∼0.1 M) in a closed reaction tube for 24 h (3 days for **1c,e**), followed by solvent evaporation and final silica gel column chromatography of the residue so obtained (under the elution conditions specified).

2c [from **1c** (30 mg), column eluent 50% EtOAc/hexane, 6.5 mg, 22%, oil, R_f (50% EtOAc/hexane) = 0.24 (unreacted **1c** was partially recovered, 12 mg, 40%)]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.66 (d, J = 5.8 Hz, 1H), 6.46 (dd, J = 5.8, 1.6 Hz, 1H), 5.97 (s, 1H), 4.89 (dd, J = 4.7, 1.6 Hz, 1H), 4.55 (d, J = 2.4 Hz, 1H), 4.25 (d, J = 7.7 Hz, 1H), 4.17 (dd, J = 7.7, 7.7 Hz, 1H), 3.91 (dd, J = 12.1, 7.7 Hz, 1H), 3.43 (s, 3H), 2.56 (ddd, J = 11.8, 4.7, 3.3 Hz, 1H), 2.26 (dd, J = 8.5, 3.3 Hz, 1H), 2.18 (dd, J = 12.1, 2.4 Hz, 1H), 1.64 (dd, J = 11.8, 8.5 Hz, 1H), 1.65 (s, 3H) 1.55 (s, 3H), 1.54 (s, 3H), 1.52 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.5, 138.7, 135.9, 111.2, 104.8, 89.1, 81.7, 79.8, 78.3, 78.0, 51.0, 49. 6, 43.4, 39.6, 31.1, 27.0, 26.8, 26.1, 25.7; LRMS (CI-MS) m/z (%) 394.1 [$(M + H)^+$, 90]; HRMS [CI-MS, $(M + H)^+$] m/z calcd for $C_{20}H_{28}NO_7$ 394.1866, found 394.1856.

2d [from **1d** (680 mg), column eluent 30% EtOAc/hexane, 571 mg, 84%, oil, R_f (40% EtOAc/hexane) = 0.34]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.81 (d, J = 5.6 Hz, 1H), 6.44 (d, J = 5.6 Hz, 1H), 6.32 (s, 1H), 4.53 (d, J = 1.7 Hz, 1H), 4.30−4.10 (m, 2H), 3.87 (dd, J = 12.1, 7.3 Hz, 1H), 3.43 (s, 3H), 2.80 (dd, J = 11.9, 3.4 Hz, 1H), 2.45 (dd, J = 8.3, 3.4 Hz, 1H), 2.25 (dd, J = 11.9, 8.3 Hz, 1H), 2.19 (dd, J = 12.1, 2.0 Hz, 1H), 1.54 (s, 3H), 1.53 (s, 3H), 1.51 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.8, 140.7, 137.3, 111.4, 104.8, 98.3, 88.2, 81.3, 79.5, 78.2, 51.0, 49.4, 47.1, 40.2, 39.6, 27.0, 26.8, 26.1, 25.7; LRMS (CI-MS) m/z (%) 428.1 [$(M + H)^+$, 100]; HRMS [CI-MS, $(M + H)^+$] m/z calcd for $C_{20}H_{27}ClNO_7$ 428.1476, found 428.1472.

2e [from **1e** (37 mg), column eluent 30% EtOAc/hexane, 11 mg, 30%, oil, R_f (30% EtOAc/hexane) = 0.13 (unreacted **1e** was partially recovered, 8 mg, 22%)]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37−7.14 (m, 5H), 6.48 (d, J = 5.8 Hz, 1H), 5.72 (d, J = 5.8 Hz, 1H), 5.46 (d, J = 14.1 Hz, 1H), 5.04 (dd, J = 4.6, 1.8 Hz, 1H), 4.53−4.40 (m, 2H), 4.34−4.26 (m, 2H), 3.80 (dd, J = 11.6, 7.9 Hz, 1H), 3.40 (s, 3H), 2.55 (dd, J = 9.1, 4.6 Hz, 1H), 2.34 (dd, J = 11.6, 1.8 Hz, 1H), 2.26 (ddd, J = 11.6, 9.1, 4.6 Hz, 1H), 1.73 (dd, J = 11.6, 4.6 Hz, 1H), 1.61 (s, 3H), 1.39 (s, 3H), 1.36 (s, 3H), 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8, 138.3, 137.5, 131.4, 129.9 (2C), 128.2 (2C), 127.4, 112.2, 111.4, 104.8, 100.1, 83.9, 81.3, 80.7, 80.5, 80.1, 54.8, 51.3, 47.7, 46.2, 42.3, 29.7, 26.5, 26.2, 25.9; HRMS [CI-MS, $(M + H)^+$] m/z calcd for $C_{27}H_{34}NO_7$ 484.2335, found 484.2327.

2h [from **1h** (29 mg) in the presence of $NaHCO_3$ (6.2 mg), column eluent 40% EtOAc/hexane, 8.6 mg, 30%, oil, R_f (40% EtOAc/hexane) = 0.25]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (d, J = 5.2 Hz, 1H), 7.15 (d, J = 5.2 Hz, 1H), 6.07 (s, 1H), 5.24 (d, J = 1.6 Hz, 1H), 4.54 (s, 1H), 4.28 (d, J = 7.6 Hz, 1H), 4.21−4.04 (dd, J = 7.6, 7.6 Hz, 1H),

3.92 (dd, J = 12.2, 7.6 Hz, 1H), 3.43 (s, 3H), 2.42 (br d, J = 12.2 Hz, 1H), 1.60 (s, 3H), 1.55 (s, 6H), 1.52 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.8, 147.4, 144.5, 140.5, 139.8, 111.4, 110.8, 104.4, 92.6, 87.9, 80.9, 78.3, 77.9, 50.6, 36.8, 26.9, 26.8, 25.9, 25.6; HRMS [CI-MS, $(M + H)^+$] m/z calcd for $C_{20}H_{25}BrNO_7$ 470.0814, found 470.0818.

2i [from **1i** (635 mg) in the presence of $NaHCO_3$ (158 mg), column eluent 25% EtOAc/hexane, 235 mg, 37%, oil, R_f (40% EtOAc/hexane) = 0.27]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (d, J = 5.3 Hz, 1H), 6.94 (d, J = 5.3 Hz, 1H), 6.28 (s, 1H), 4.57 (d, J = 2.2 Hz, 1H), 4.27 (d, J = 7.4 Hz, 1H), 4.16 (dd, J = 7.4, 7.4 Hz, 1H), 3.91 (dd, J = 12.5, 7.4 Hz, 1H), 3.43 (s, 3H), 2.40 (br d, J = 12.5 Hz, 1H), 1.55 (s, 3H), 1.55 (s, 3H), 1.52 (s, 3H), 1.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.7, 147.8, 145.7, 142.9, 140.8, 111.6, 110.9, 104.5, 104.4, 90.7, 80.7, 77.9, 77.8, 50.7, 50.1, 36.3, 26.9, 26.8, 25.9, 25.6; LRMS (CI-MS) m/z (%) 506.0 [$(M + H)^+$, 100]; HRMS [CI-MS, $(M + H)^+$] m/z calcd for $C_{20}H_{24}ClBrNO_7$ 504.0425, found 504.0431.

Oxanorbornene (±)-2a. A stirred suspension of **1a** (300 mg, 0.73 mmol), $NaHCO_3$ (73 mg, 0.87 mmol), and Boc_2O (792 mg, 3.61 mmol) in 1,2-dichlorobenzene (7.2 mL) was heated in a closed tube for 5 h at 150 °C (external bath temp). Removal of the solvent in vacuo and column chromatography (silica gel, 40% EtOAc/hexane) afforded **2a** as an oil (220 mg, 73%).[20]

Epoxide 8. A solution of **2d** (500 mg, 1.17 mmol) in dry DCE (3 mL) was added to suspension of *m*-CPBA (864 mg, 3.51 mmol) in dry DCE (4.3 mL) under argon, and the mixture was stirred for 5 h at 50 °C. Solvent removal and chromatography (35% EtOAc/hexane) afforded **8** as an oil (375 mg, 73%): R_f (50% EtOAc/hexane) = 0.36; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.61 (s, 1H), 4.71 (d, J = 2.3 Hz, 1H), 4.10–4.31 (m, 2H), 4.00 (d, J = 3.2 Hz, 1H), 3.82 (dd, J = 12.2, 7.0 Hz, 1H), 3.56 (d, J = 3.2 Hz, 1H), 3.43 (s, 3H), 2.75 (dd, J = 12.7, 4.0 Hz, 1H), 2.56 (dd, J = 8.8, 4.0 Hz, 1H), 2.35 (dd, J = 12.7, 8.8 Hz, 1H), 2.18 (dd, J = 12.2, 2.3 Hz, 1H), 1.55 (s, 3H), 1.54 (s, 3H), 1.51 (s, 3H), 1.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 170.8, 111.5, 111.3, 104.7, 95.4, 84.3, 80.6, 79.3, 78.1, 54.1, 53.0, 51.0, 49.3, 46.9, 40.4, 38.0, 27.0, 26.7, 26.1, 25.7; HRMS [ESI-TOF, $(M + H)^+$] m/z calcd for $C_{20}H_{27}ClNO_8$ 444.1425, found 444.1425.

Dimethylketal 9. A solution of oxanorbornene **2i** (100 mg, 0.20 mmol) in MeOH (1.2 mL) was treated with NaMeO (5.4 M in MeOH, 293 μL) and stirred for 30 min at 0 °C. The pH was adjusted to 5 with 1 M aqueous HCl, and the methanol was evaporated in vacuo. Extraction (EtOAc, 3 × 1 mL) and chromatography (65% EtOAc/hexane) afforded **9** as an oil (38 mg, 40%): R_f (60% EtOAc/hexane) = 0.22; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.54 (d, J = 5.8 Hz, 1H), 6.48 (d, J = 5.8 Hz, 1H), 5.75 (s, 1H), 4.56 (d, J = 2.4 Hz, 1H), 4.30–4.16 (m, 2H), 3.80 (dd, J = 11.7, 7.1 Hz, 1H), 3.52 (s, 3H), 3.40 (s, 3H), 3.37 (s, 3H), 2.67 (s, 1H), 2.17 (dd, J = 11.7, 2.4 Hz, 1H), 1.52 (s, 9H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 172.7, 142.5, 140.8, 119.7, 111.8, 110.3, 108.1, 105.5, 81.0, 80.0, 79.1, 59.9, 50.9, 50.6, 50.0, 49.6, 39.9, 26.5, 26.3, 26.2, 25.9; HRMS [ESI-TOF, M^+] m/z calcd for $C_{22}H_{30}ClNO_9$ 487.1609, found 487.1599.

Opening/Aromatization (8 → 3d and 2i → 3i). 3d. A solution of **8** (130 mg, 0.29 mmol) in DMSO (1.4 mL) under argon at rt was treated first with *t*-BuOK (115 mg, 1.03 mmol) and, after 20 min, with CH_2Br_2 (82 μL, 1.17 mmol). The mixture was stirred for 7.5 h at 85 °C, diluted with H_2O (3 mL), and filtered off. The precipitate was purified by column chromatography (45% EtOAc/hexane) to give **3d** as an oil (37 mg, 11%): R_f (50% EtOAc/hexane) = 0.36; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55 (s, 1H), 6.83 (s, 1H), 6.08 (s, 1H), 6.01 (s, 2H), 4.84 (d, J = 1.8 Hz, 1H), 4.39–4.19 (m, 2H), 3.98 (dd, J = 13.5, 7.3 Hz, 1H), 3.48 (s, 3H), 3.01 (br d, J = 13.6 Hz, 1H), 1.53 (s, 3H), 1.42 (s, 3H), 1.38 (s, 3H), 1.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.4, 151.6, 147.2, 131.9, 122.9, 111.8, 111.3, 108.2, 105.7, 104.7, 101.9, 81.0, 79.8, 78.1, 51.2, 51.0, 37.7, 27.1, 26.8, 26.1, 25.7; HRMS [ESI-TOF, $(M + H)^+$] m/z calcd for $C_{21}H_{26}NO_8$ 420.1658, found 420.1656.

3i. A solution of **2i** (435 mg, 0.89 mmol) in MeOH (3 mL) was treated with NaMeO (5.4 M in MeOH, 825 μL) and stirred for 8 h at rt. The pH was adjusted to 5 with a 0.1 M aqueous solution of HCl, and the methanol was evaporated in vacuo. Extraction with EtOAc (3 × 2 mL) and chromatography (silica gel, 65% EtOAc/hexane) afforded **3i** as an oil (228 mg, 57%): R_f = 0.27 (60% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.24–7.13 (m, 2H), 6.32 (s, 1H), 5.97 (s, 1H), 4.75 (s, 1H), 4.58 (d, J = 7.5 Hz, 1H), 4.41 (dd, J = 7.5, 7.5 Hz, 1H), 4.10 (d, J = 7.5 Hz, 1H), 3.98 (s, 3H), 3.49 (s, 3H), 3.00 (s, 3H), 1.54 (s, 3H), 1.53 (s, 3H), 1.40 (s, 3H), 1.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.1, 150.6, 147.5, 126.7, 124.0, 121.9, 118.4, 111.3, 110.8, 105.5, 83.2, 78.5, 77.8, 75.2, 62.5, 55.0, 52.0, 51.1, 27.4, 26.4, 25.9, 25.5; LRMS (CI-MS) m/z (%) 452.1 [$(M + H)^+$, 92]; HRMS [CI-MS, $(M + H)^+$] m/z calcd for $C_{22}H_{30}NO_9$ 452.1921, found 452.1935.

■ ASSOCIATED CONTENT

Supporting Information

General procedures, selected NOE data for **3i**, selected NMR data (δ, J, and NOE) for IMDAF cycloadducts **2a,c-e**, structures for all possible diastereoisomers of the IMDAF process for acrylamides of type **1**, and copies of NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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(15) When describing the relative stereochemistry of compounds **2** in this article, the terms *anti* and *syn* refer to the orientation of the bridging oxygen atom of the oxabicycle relative to that of H_{4a}: if they are on the same side, the *syn* designation is used, and if they are on opposite sides, the *anti* designation applies.

(16) For a more detailed analysis showing the structures of all four possible diastereoisomers of the IMDAF process for acrylamides of type **1** as well as sketches of their corresponding TSs, see the Supporting Information.

(17) For a recent example of oxanorbornene epoxidation, see: Namboothiri, I. N. N.; Ganesh, M.; Mobin, S. M.; Cojocaru, M. *J. Org. Chem.* **2005**, *70*, 2235−2243.

(18) Some of the minor nonidentified compounds observed by TLC in the cycloaddition reaction of **1e** to **2e** could correspond to stereoisomers of the major cycloadduct **2e**.

(19) For general procedures, see the Supporting Information.

(20) For the preparation of compound **2a** under nonacylating conditions, as well as for its analytical and spectroscopic data, see ref 13, in which **2a** is numbered as **18a**.