Sequential [3 + 2] and [4 + 2] Cycloadditions for Stereoselective Synthesis of a Novel Polyheterocyclic Scaffold

Qing Lu,[†,‡] Xin, Huang,[†] Gonghua Song,[‡] Chung-Ming Sun,[§] Jerry P. Jasinski,[‖] Amanda C. Keeley,[‖] and Wei Zhang*,[†]

[†]Department of Chemistry, University of Massachusetts Boston, 100 Morrissey Boulevard, Boston, Massachusetts 02125, United States

[‡]Shanghai Key Laboratory of Chemical Biology, Institute of Pesticides and Pharmaceuticals, East China University of Science and Technology, Shanghai 200237, P. R. China

[§]Department of Applied Chemistry, National Chiao Tung University, Hsinchu 300-10, Taiwan (ROC)

[‖]Department of Chemistry, Keene State College, 220 Main Street, Keene, New Hampshire 03435, United States

S *Supporting Information*
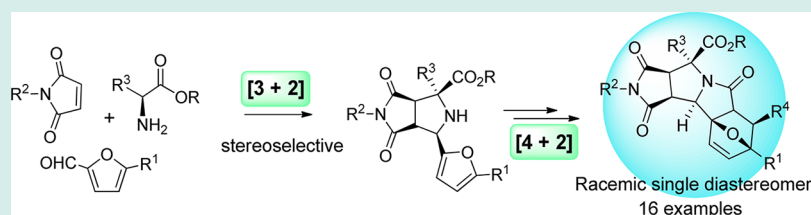
ABSTRACT: A strategy of combining [3 + 2] cycloaddition and intramolecular Diels−Alder reaction is developed for the synthesis of a novel polycyclic scaffold with skeletal and substitutional diversities. Intermediates generated from stereoselective [3 + 2] cycloaddition of azomethine ylides and maleimides were derivatized for intramolecular Diels−Alder reaction of furan to form highly condensed heterocyclic products as racemic single diastereomers.

KEYWORDS: sequential cycloadditions, stereoselective annulation, [3 + 2] cycloaddition, intramolecular Diels−Alder reaction, polyheterocyclic scaffold

INTRODUCTION

Formation of multiple rings via sequential cycloaddition or cyclization reactions is powerful for the construction of diverse and complex discovery library scaffolds.[1,2] However, stereochemistry is a major challenge in the designing of such reaction sequences. If the first ring is generated in a nonstereoselective fashion, then only the right stereoisomer will undergo the next ring formation reaction. Taking the advantage of one-pot and stereoselective [3 + 2] cycloaddition reaction of aminoesters **1**, aldehydes **2**, and activated alkenes **3** to form the fused-proline derivatives **4**,[3] we have recently reported the synthesis of diverse heterocyclic compound libraries **5−7** through N-acylation of **4** and sequential cyclizations (Scheme 1).[4] Introduced in this paper is a new application of [3 + 2] adducts **4** for the synthesis of a new polycyclic scaffold **9**. We envisioned that introduction a dienenophile to **4** could generate intermediate **8** which has the right stereochemistry for intramolecular Diels−Alder reaction of furan to form compounds **9**.[5,6] The fragments of this novel skeleton are related to many pyrrolidine-fused biologically active compounds and natural products,[7] such as tricyclic thrombin inhibitor,[8] 1-epiaustraline,[9] and cantharidin.[10] Compound **9** is an attractive scaffold for the synthesis of a discovery library.
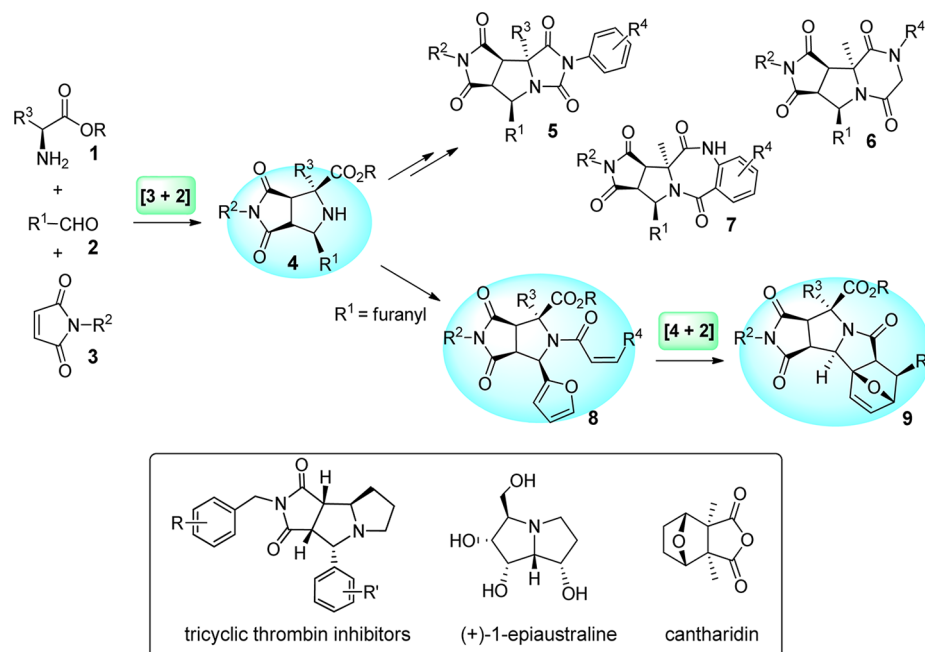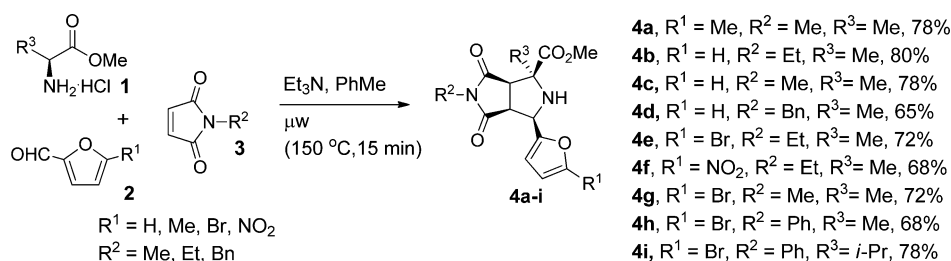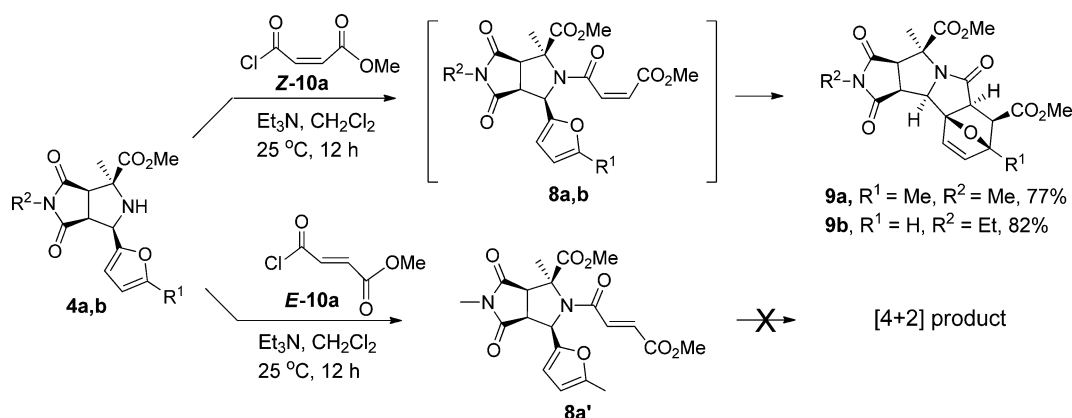
RESULTS AND DISCUSSION

The [3 + 2] cycloaddditions were conducted as a one-pot reaction of L-alanine or L-valine methyl esters **1**, 2-furanylaldehydes **2**, and maleimides **3** following previously reported procedures.[3] An equimolar mixture of these three components with Et₃N was heated under microwaves at 150 °C for 15 min to give compounds **4a−h** in 65−80% yields (Scheme 2). This is a highly stereoselective reaction, which gave cycloaddition products **4** as racemic single diastereomers. The chiral center from L-alanine and L-valine methyl esters is lost after reacted with the aldehyde to form imines and then azomethine ylides for [3 + 2] cycloaddtion.

Acid chloride **Z-10a** derived from maleic anhydride was used for N-acylation of **4a** and **4b**. One-pot acylation and sequential intramolecular [4 + 2] cycloaddition reactions were performed at room temperature to afford **9a** and **9b** in 77% and 82% isolated yields, respectively (Scheme 3). The dienophile in **8a,b** was so reactive that it does not require Lewis acid or heating to promote the cycloaddition reaction. This one-pot synthesis produced polyheterocyclic compounds **9** containing eight

Scheme 1. [3 + 2] Adducts 4 for the Synthesis of Diverse Heterocyclic Scaffolds 5−7 and 9

tricyclic thrombin inhibitors   (+)-1-epiaustraline   cantharidin

Scheme 2. Formation of 4 by Stereoselective [3 + 2] Cycloaddition

R^1 = H, Me, Br, NO_2
R^2 = Me, Et, Bn

4a, R^1 = Me, R^2 = Me, R^3= Me, 78%
4b, R^1 = H, R^2 = Et, R^3= Me, 80%
4c, R^1 = H, R^2 = Me, R^3= Me, 78%
4d, R^1 = H, R^2 = Bn, R^3= Me, 65%
4e, R^1 = Br, R^2 = Et, R^3= Me, 72%
4f, R^1 = NO_2, R^2 = Et, R^3= Me, 68%
4g, R^1 = Br, R^2 = Me, R^3= Me, 72%
4h, R^1 = Br, R^2 = Ph, R^3= Me, 68%
4i, R^1 = Br, R^2 = Ph, R^3= i-Pr, 78%

Scheme 3. N-Acylation and [4 + 2] Cycloaddition of 4a,b

9a, R^1 = Me, R^2 = Me, 77%
9b, R^1 = H, R^2 = Et, 82%

[4+2] product

stereogenic centers as racemic single diastereomers. For the comparison of [4 + 2] cycloadditions with Z- and E-dienophiles, acid chloride E-**10a** was used for the preparation of **8a′**. No intramolecular [4 + 2] cycloaddition product was observed from the reaction of **8a′** even under heating and using Lewis acid catalysts such as $AlCl_3$ and $Yb(OTf)_3$. Significant reactivity difference between **8a,b**, and **8a′** could be explained by the steric hindrance difference from the cis- and trans-dienophiles. We also attempted N-acylation of [3 + 2] cycloadddition product **4i** (R^3 = i-Pr), but failed to get

expected product under the same condition described in Scheme 3.

Compound **8c** bearing acryloyl dienophile was prepared through N-acylation of **4c** with acryloyl chloride **10b**. The intramolecular [4 + 2] cycloaddition reaction of **8c** with a less reactive dienophile needs to be prompted with Lewis acid (Table 1). The reaction was explored in different solvents including toluene, DMF, and water. The reaction mixture was heated under microwave between 120 and 150 °C. It was found that the reaction at 120 °C for 10 min in water using $Yb(OTf)_3$

Table 1. Optimization of [4 + 2] Cycloaddition of 8c
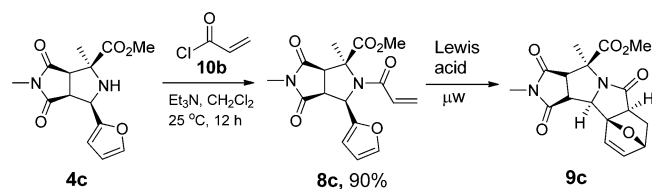
entry	solvent	time (min)	temp (°C)	Lewis acid[a]	9c (%)[b]
1	PhMe	30	150		10
2	PhMe	30	150	AlCl$_3$	30
3	PhMe	30	150	ZnCl$_2$	25
4	DMF	30	150		15
5	DMF	30	150	AlCl$_3$	35
6	DMF	30	150	ZnCl$_2$	26
7	H$_2$O	30	120		70
8	H$_2$O	30	150		78
9	H$_2$O	10	120	Yb(OTf)$_3$	94

[a]1 equiv. [b]Detected by LC-MS.

as a Lewis acid gave 94% LC yield of **9c** (entire **9**). It is worthy to mention that even without Lewis acid, the reaction in water at 150 °C for 30 min was able to afford 78% LC yield of **9c** (entry 8), which is better than the reactions in toluene or DMF even with a Lewis acid.
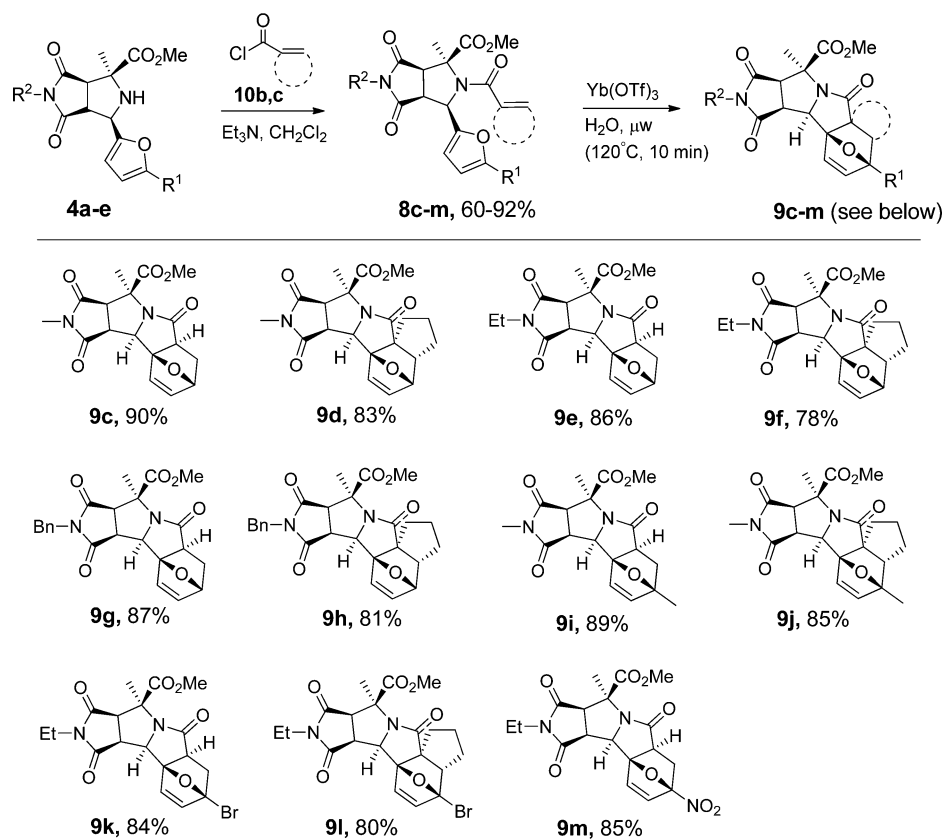
Intramolecular [4 + 2] cycloaddition of compounds **8** with acryloyl dienophiles generated from **10b** and **10c** were performed under the optimized reaction condition (Table 2). Products **9c–m** were synthesized in 78–90% isolated yields. The stereochemical structure of **9c** was confirmed by single crystal X-ray structure analysis (Figure 1).[11] The intramolecular
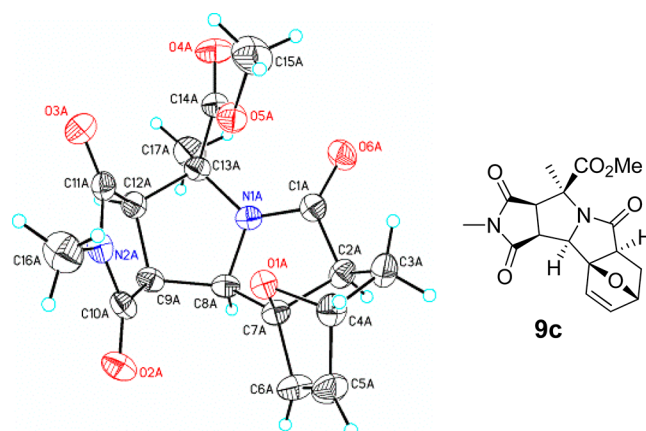
**Figure 1.** X-ray structure of **9c**.

[4 + 2] cycloaddition is sensitive to the steric hindrance of the dienophile. It was found that compounds **8n–p** failed to afford desired [4 + 2] cycloaddition products even under increased reaction temperature and time (Scheme 4). The thiophene analog **8q** was also failed for the cycloaddition reaction.

To further diversify the functional group on product ring skeleton and explore the scope of intramolecular [4 + 2] cycloaddition reactions, an allyl group was introduced to [3 + 2] cycloaddition products **4** through N-allylation with **11**. The allylation and cycloaddition reactions were performed in one-pot to give products **9n–p** in 75–80% yields (Scheme 5). Because of the electron-donating effect, the bromo on the furan facilitate the cycloaddition. If the Br is substituted with Me or
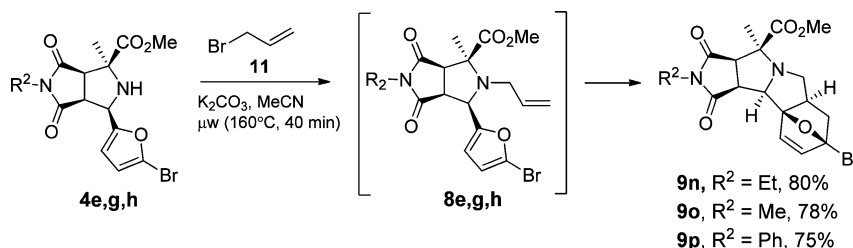
Table 2. N-Acylation and [4 + 2] Cycloaddition

Scheme 4. Substrates Failed for Intramolecular [4 + 2] Cycloadditions
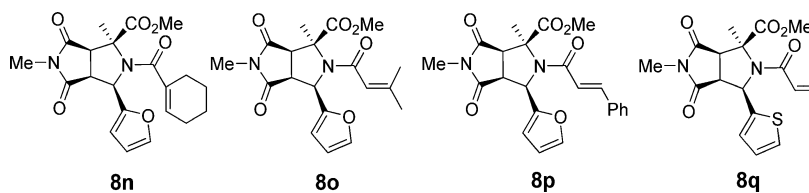
Scheme 5. One-Pot N-Allylation and [4 + 2] Cycloaddition

NO$_2$, the cycloaddition could not happen even under heating and using a Lewis acid a catalyst.

CONCLUSION

We have developed a straightforward and efficient method for the synthesis of a novel hetereocyclic scaffold through the combination of [3 + 2] and [4 + 2] cycloaddition reactions. The dieonophiles were readily introduced to the stereoselective [3 + 2] adducts through N-acylation or N-allylation reactions. The intramolecular [4 + 2] cycloaddition precursors have the right stereochemistry to give polyhetereocyclic compounds as racemic single diastereomers. Since the product scaffold has skeletal and substitution diversities, this synthetic method can be readily extended for the synthesis of compound libraries. In addition, the scaffold of the final product could be further diversified by opening of the oxo-bridge.[12]

EXPERIMENTAL PRODUCTION

General Experimental Details. All chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian NMR spectrometer. LC-MS were performed on an Agilent 2100 system. A C$_{18}$ column (5.0 μm, 6.0 × 50 mm) was used for analysis. The mobile phase solvents were MeOH and water both containing 0.05% trifluoro acetic acid. A linear gradient was started from 75:25 MeOH/H$_2$O to 100% MeOH in 5.0 min at a flow rate of 0.7 mL/min. The chromatograms were recorded at UV 210, 254, and 365 nm. Low resolution mass spectra were recorded in APCI (atmospheric pressure chemical ionization). High resolution mass (HRMS) spectra were obtained on a Finnigan/MAT 95XL-T spectrometer. Flash chromatography separations were performed on YAMAZEN AI-580 system with Agela silica gel (12 or 20 g, 230−400 μm mesh) cartridges. The microwave reactions were performed on a Biotage Initiator 8 system.

Representative Procedure for [3 + 2] Cycloadditions. A solution of L-alanine methyl ester (HCl salt) **1** (0.25 g, 2 mmol), furfural **2** (0.19 g, 2 mmol), N-methylmaleimide **3** (0.25 g, 2 mmol), and Et$_3$N (860 μL) in 1 mL of toluene was heated under microwave at 150 °C for 15 min. After aqueous work up, the concentrated crude product was purified by flash chromatography (1:1 hexanes/EtOAc) to give product **4c** (0.45

g, 78% yield): yellow solid; mp 162−164 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.37 (s, 1H), 6.36 (d, J = 1.3 Hz, 2H), 4.76 (d, J = 8.9 Hz, 1H), 3.88 (s, 3H), 3.52 (dd, J = 8.7, 7.8 Hz, 1H), 3.32 (d, J = 7.6 Hz, 1H), 2.90 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 175.4, 174.7, 172.1, 149.1, 142.6, 110.4, 108.3, 67.7, 57.4, 56.7, 52.7, 49.9, 25.0, 23.7; MS (APCI) m/z 293.1 (M$^+$ + 1).

Representative Procedures for the Synthesis of 9a and 9b by Intramolecular Diels−Alder Reaction. A solution of maleic anhydride (0.019 g, 0.2 mmol) in 1.0 mL of MeOH was irradiated under microwave at 120 °C for 10 min. The solvent was removed in vacuo to give crude monomethyl maleate (0.023 g, 92% yield). To a solution of crude monomethyl maleate in 5 mL of CH$_2$Cl$_2$ was added oxalyl chloride (30 μL, 0.35 mmol) and 1 drop of DMF at room temperature. After 2 h, the reaction mixture was concentrated in vacuo to give acid chloride (0.024 g, 90% yield). To a stirred solution of [3 + 2] cycloaddition **4a** (0.031 g, 0.1 mmol) and Et$_3$N (43 μL, 0.3 mmol) in 5 mL of CH$_2$Cl$_2$ was added the acid chloride at room temperature and stirred for 12 h. After aqueous work up, the concentrated crude product was purified chromatography (1:2 hexanes/EtOAc) to give product **9a** as a single diastereomeric product (0.032 g, 77% yield): yellow solid; mp 192−195 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.54 (d, J = 5.8 Hz, 1H), 6.08 (d, J = 5.7 Hz, 1H), 4.89 (d, J = 10.4 Hz, 1H), 3.62 (d, J = 11.1 Hz, 1H), 3.56 (d, J = 2.7 Hz, 6H), 3.30 (d, J = 9.2 Hz, 1H), 3.10 (d, J = 3.3 Hz, 1H), 2.93 (d, J = 3.3 Hz, 1H), 2.81 (s, 3H), 1.60 (d, J = 2.4 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 174.4, 173.3, 170.9, 170.9, 168.2, 137.8, 133.3, 107.1, 91.8, 89.5, 65.1, 62.8, 59.5, 59.3, 52.5, 52.4, 43.1, 25.3, 25.2, 18.6; MS (APCI) m/z 419.1 (M$^+$ + 1).

Representative Procedure for the Synthesis of 9c−m by Intramolecular Diels−Alder Reaction. To a solution of [3 + 2] cycloaddition **4c** (0.029 g, 0.1 mmol) and Et$_3$N (43 μL, 0.3 mmol) in 5 mL of CH$_2$Cl$_2$ was added acryloyl chloride (0.013 g, 0.16 mmol) at room temperature. After 12 h, water was added to the reaction mixture and the mixture was extracted with EtOAc. Concentration of the combined organic layer gave crude compound **8c** (0.030 g, 90% yield). A solution of **8c** (0.030 g, 0.08 mmol) and Yb(OTf)$_3$ (0.053 g, 0.08 mmol) in 0.5 mL of water was irradiated under microwave at 120 °C for 10 min. After aqueous work up and concentration,

the crude product were purified on flash chromatography (1:2 hexanes:EtOAc) to give **9c** (0.027 g, 90% yield): white solid, mp 188−191 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.27 (s, 1H), 6.50 (d, J = 5.8 Hz, 1H), 6.41 (dd, J = 5.9, 1.6 Hz, 1H), 5.08 (dd, J = 4.7, 1.6 Hz, 1H), 5.02 (d, J = 10.2 Hz, 1H), 3.67 (s, 3H), 3.63 (d, J = 9.9 Hz, 1H), 3.41 (d, J = 9.2 Hz, 1H), 2.94 (s, 3H), 2.62 (dd, J = 8.7, 3.3 Hz, 1H), 2.18−2.07 (m, 1H), 1.70 (s, 3H), 1.48 (dd, J = 11.8, 8.8 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 174.6, 173.4, 171.5, 168.4, 137.3, 131.2, 91.0, 79.7, 64.5, 62.6, 59.8, 52.8, 52.7, 43.2, 28.6, 25.5, 25.0; MS (APCI) m/z 347.1 (M$^+$ + 1); HRMS (ESI-TOF) calcd for C$_{17}$H$_{19}$N$_2$O$_6$ 347.1243 ([M + 1]$^+$), found 347.1237 ([M + 1]$^+$).

Representative Procedure for the Synthesis of 9n−p by Intramolecular Diels−Alder Reaction. A solution of [3 + 2] cycloaddition **4e** (0.029 g, 0.1 mmol), K$_2$CO$_3$ (0.021 g 0.15 mmol), and allyl bromide (0.018 g, 0.15 mmol) in 0.5 mL of MeCN was irradiated under microwave at 160 °C for 40 min. After aqueous workup, combined AcOEt extracts were concentrated, and the resulted crude product was purified on flash chromatography (1:2 hexanes/EtOAc) to give product **9n** (0.033 g, 80% yield): brown solid; mp 108−115 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.38 (d, J = 5.6 Hz, 1H), 6.27 (d, J = 5.6 Hz, 1H), 4.07 (dd, J = 17.9, 7.6 Hz, 1H), 3.74 (s, 3H), 3.34 (dt, J = 16.0, 7.6 Hz, 5H), 2.75 (dd, J = 9.3, 7.1 Hz, 1H), 2.33 − 2.21 (m, 1H), 1.97 (d, J = 5.0 Hz, 2H), 1.38 (s, 3H), 1.07 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 175.7, 174.6, 174.1, 140.3, 134.7, 91.5, 89.9, 66.4, 64.8, 58.4, 52.3, 50.6, 50.0, 43.3, 42.9, 34.6, 21.8, 12.7; MS (APCI) m/z 426.0 (M$^+$ + 1).

ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H, ^{13}C NMR, and MS spectrum for selected intermediates and final products, and X-ray structure for **9c**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*Tel: 617-287-6147. Fax: 9617-287-6030. E-mail: wei2.zhang@umb.edu.

Author Contributions

W.Z., G.S., and C.-M.S. conceived and designed the experiments, Q.L. and X.H. performed the experiments, J.P.J. and A.C.K conducted X-ray single crystal structure analysis, and W.Z. and Q.L. wrote the manuscript and Supporting Information.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

DEDICATION

This paper is dedicated to Professor Dennis P. Curran on the occasion of his 60th birthday.

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(11) Crystal data for **9c**, C$_{17}$H$_{18}$N$_2$O$_6$, M = 346.33, monoclinic, a = 19.6023(7) Å, b = 9.3326(3) Å, c = 20.4991(8) Å, β = 116.287(5)°, U = 3362.3(2) Å^3, T = 293(2) K, space group P 21/a, Z = 4, D_c = 1.368g/cm^3, Agilent Gemini EOS CCD diffractometer, μ(Cu Kα) = 0.883 mm^{-1}, 20981 independent reflections (6593 observed), 457 parameters, R_{int} = 0.0335, R = 0.0434, wR(F^2) = 0.1068, thermal ellipsoids probability level is 30%. CCDC 911595.

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