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Intramolecular 1,3-Dipolar Cycloaddition-Mediated Stereoselective Synthesis of Disubstituted Cyclopentane: A Simple Model for the Cyclopentane Ring System of Polycyclic Oroidine Alkaloids

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Abstract: We present a diastereoselective synthesis of disubstituted cyclopentane **8** having a nitrogen-containing quaternary carbon center, which is found in axinellamine A (**5**) and related compounds. During this work, we found that the 1,3-dipolar cycloaddition product **24** immediately underwent intramolecular redox reaction at the newly formed morpholin-2-one moiety, thus affording disubstituted cyclopentane containing a tertiary amine (**9**) stereoselectively in good yield. The amine **9** was successfully converted into guanidine **31**, which corresponds to **8**, through iminium cation–enamine isomerization.

Keywords: axinellamine · cycloaddition · guanidine · oroidine · redox chemistry

Introduction

Alkaloids of the oroidine class are natural products isolated from marine sponges, mainly from *Agelasidae*, *Axinellidae*, *Dyctionellidae*, and *Hymeniacidonidae*.[1] This alkaloid family is structurally diverse as a consequence of metabolic transformations of oroidin (**1**), which contains pyrrole and imidazole groups; thus, the alkaloids are usually classified according to the number of oroidine-related fragments.[1a] Agelastatins **2** and **3**, and (+)-dibromophakellin (**4**) are typical monomeric oroidine alkaloids, while axinellamine A (**5**), massadine (**6**), and palau′amine (**7**) are classified as dimeric congeners.[2,3] Since these alkaloids contain a characteristic complex polycyclic ring system with contiguous asymmetric stereocenters (Figure 1), they have attracted the attention of synthetic chemists, and various synthetic approaches have been reported.[4,5]

In our work on this class of alkaloids,[4i,j] we became interested in the dimeric compounds **5**–**7**. These alkaloids commonly possess a synthetically challenging fully substituted pentacyclic ring with a spiro-fused system.[6] As the entry point for our synthetic studies of these alkaloids, we chose the disubstituted cyclopentane **8**, which contains two contiguous stereogenic centers corresponding to C11 and C16 of the alkaloids, as a simple model for the pentacyclic ring system. Herein, we describe the development of a diastereoselective synthesis of the disubstituted cyclopentane skeleton of **8**, which incorporates the nitrogen-containing quater-

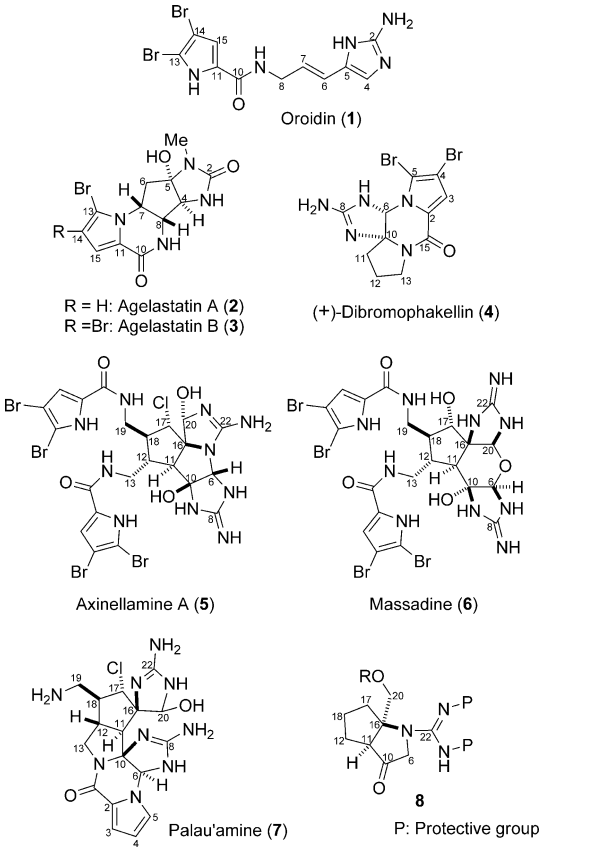

Figure 1. Structures of oroidin (**1**) and representative monomeric and dimeric analogs.

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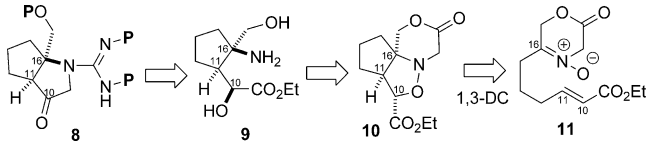
nary carbon centers of dimeric oroidin alkaloids, especially those related to axinellamine A (**5**). The key reaction proved to be an intramolecular 1,3-dipolar cycloaddition (1,3-DC), followed immediately by intramolecular redox transformation of the generated morpholin-2-one moiety of the product.

Our synthetic plan for disubstituted cyclopentane **8** is depicted in Scheme 1. In this synthesis, we planned to construct the quaternary carbon center at C16 by intramolecular 1,3-DC of **11**, which contains a cyclic nitrone and unsaturated ester.[7] During the reaction, the stereochemistry at C11 was expected to be controlled. Reduction and degradation of the N–O bond and morpholin-2-one moiety in **10** were expected to produce **8** via **9**.

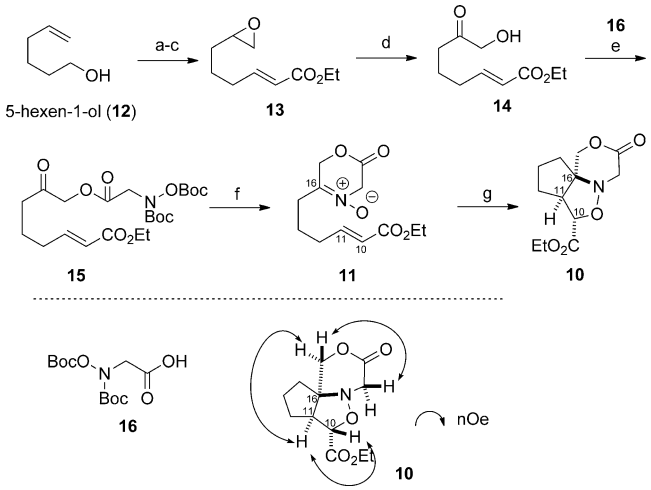


Scheme 1. Retrosynthetic analysis of disubstituted cyclopentane **8**.

Results and Discussion

Construction of the cyclopentane ring system **10** containing consecutive stereogenic centers at C11 and C16 by means of intramolecular 1,3-DC reaction is illustrated in Scheme 2.

Swern oxidation of the primary alcohol in 5-hexen-1-ol (**12**) followed by Horner–Emmons reaction of the resulting aldehyde generated the *E*-unsaturated ester, whose terminal olefin was selectively oxidized with *m*-CPBA (*m*-chloroperbenzoic acid) to give epoxide **13** in 92% yield (3 steps). The epoxide **13** was then treated with DMSO in the presence of a catalytic amount of TfOH (trifluoromethanesulfonic acid) at 100°C, and α-hydroxyketone **14** was obtained in 71% yield via the secondary carbocation, which was preferentially generated by TfOH.[8] The hydroxy group in **14** was acylated with *N*,*O*-bisBoc-*N*-hydroxyglycine (**16**) in the presence of EDCI (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide) to give **15**, which was treated with TFA to give nitrone **11** by deprotection of the two Boc groups followed by intramolecular cyclization of the resulting hydroxylamine with ketone. The intramolecular 1,3-DC of **11** proceeded at 40°C in toluene to give isoxazolidine **10** as a single diastereomer in 33% yield from **14** (3 steps). The stereochemistries in **10** were confirmed by means of nuclear Overhauser effect (nOe) NMR studies, which showed that the desired stereochemistries at C11 and C16 had been obtained.[9] In this 1,3-DC reaction, two transition states, that is, the pseudo-boat form (**11**-A) and the pseudo-chair form (**11**-B), can be considered (Figure 2). Since the chair-form transition state is more favorable, intramolecular 1,3-DC reaction proceeded exclusively from the transition state **11**-B, thereby affording the desired isomer **10**.



Scheme 2. Synthesis of isoxazolidine **10**. Reagents and conditions: a) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, 2 h, then Et_3N, 5 min, −78°C; b) triethylphosphonoacetate, NaH, THF, 0°C, 1 h; c) *m*-CPBA, CH_2Cl_2, rt, 6 h, 92% (3 steps); d) trifluoromethanesulfonic acid, molecular sieve 4 Å powder, DMSO, 100°C, 5.5 h, 71%; e) *N*,*O*-bisBoc-*N*-hydroxyglycine (**16**), EDCI, DMAP, CH_2Cl_2, 0°C, 0.5 h; f) TFA, CH_2Cl_2, rt, 6 h; g) toluene, $MgSO_4$, K_2CO_3, 40°C, 11 h, 33% (3 steps).

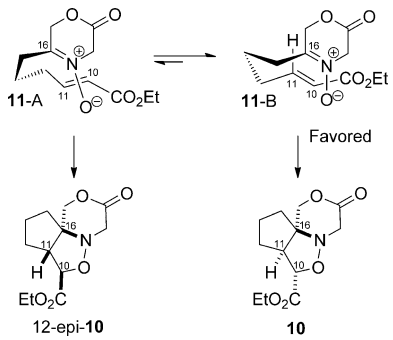
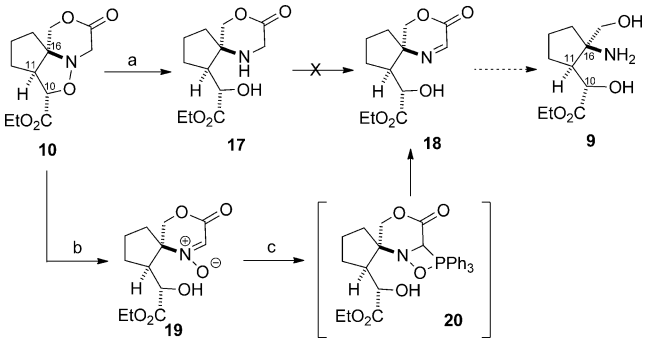


Figure 2. Transition state of the intramolecular 1,3-dipolar cycloaddition (1,3-DC) of **11**.

Abstract in Japanese:

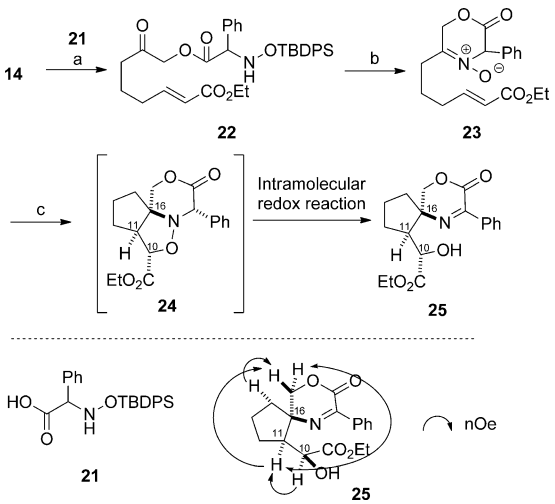
Palau'amine, massadine, axinellamine に代表される oroidine 2 量体型ピロールーイミダゾール系アルカロイド類は、含窒素四級炭素を含む特徴的な多置換シクロペンタン骨格を共通に有している。本研究では、当該骨格の構築法の確立を目的とし、そのモデル化合物として、含窒素四級炭素を含む二置換シクロペンタン化合物 **9** の合成について検討した。ニトロンと不飽和エステルを同一分子内に持つ **23** に対して分子内 1,3-双極子付加環化反応を行ったところ、反応は立体選択的に進行し含窒素四級炭素を含む二連続不斉点を一挙に構築しながら **25** を得ることができた。尚この際、イソキサゾリジン **24** からのレドックス反応が同時に進行することも見いだした。得られた **25** から種々の変換を行い、axinellamine 型の二環性骨格 **31** の合成に成功した。

With the isoxazolidine **10** in hand, reduction of the N–O bond (**10** to **17**) and removal of the morpholin-2-one moiety (**17** to **9**) via **18** were examined (Scheme 3). First, hydrogenolysis of **10** in the presence of a catalytic amount of Pd/C or $Pd(OH)_2$ in ethanol was examined for reduction of the N–O bond in **10**. However, the reaction did not proceed under these conditions, and only the starting compound **10** was recovered quantitatively. Addition of aqueous HCl was effective in the presence of $Pd(OH)_2$, and amine **17** was obtained in 89% yield. However, the following oxidation of the morpholin-2-one moiety to obtain imine **18** was problematic. We tried various oxidants, but the desired imine **18** was not formed, and only oxidation of the hydroxy group proceeded. Thus, we explored an alternative approach for conversion of **10** into **9**. When *m*-CPBA oxidation was applied to isoxazolidine **10**, nitrone **19** was obtained in 55% yield.[10] This was reduced with triphenylphosphine to give imine **18** in 66% yield.[11] Although imine **18**, a precursor for aminediol **9**, was obtained from **10**, the oxidation–reduction process was tedious. We envisaged that a more efficient conversion of **10** might be achieved by installing a phenyl group at the α-position of the morpholin-2-one moiety, since the resulting benzylic position would be labile to reduction, and aminediol **9** might be generated under simple reductive conditions from the 1,3-DC adduct.

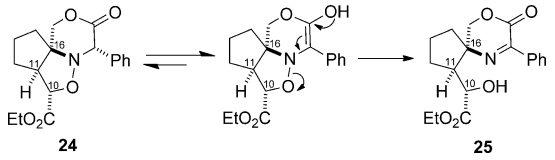


Scheme 3. Synthesis of imine **18** from isoxazolidine **10**. Reagents and conditions: a) $Pd(OH)_2$, H_2, HCl aq./EtOH, rt, 2 h, 89%; b) *m*-CPBA, CH_2Cl_2, rt, 1.5 h, 55%; c) PPh_3, toluene, 100 °C, 17 h, 66%.

Thus, the ester **22** was synthesized by esterification of alcohol **14** with phenylglycine derivative (±)-**21**[12] in the presence of EDCI (Scheme 4). The ester **22**, which was very labile under basic conditions, was converted into nitrone **23** by deprotection of the TBDPS group with TFA, with simultaneous dehydrative cyclization of the resulting hydroxylamine and ketone. The nitrone **23** was then subjected to 1,3-DC reaction by heating at 50 °C in dichloroethane. To our surprise, imine **25** was obtained stereoselectively in a single step from **23** in 74% yield (2 steps from **22**).[13] This result can be explained in terms of an intramolecular redox reaction; thus, enol formation of isoxazolidine **24** and subsequent N–O bond cleavage with recovery of the keto-form generated imine **25** (Scheme 5).



Scheme 4. Synthesis of imine **25**. Reagents and conditions: a) **21**, EDCI, DMAP, CH_2Cl_2, 0 °C, 1.5 h, 32%; b) TFA, CH_2Cl_2, rt, 1 h; c) 1,2-dichloroethane, rt to 50 °C, 1.5 h, 74% (2 steps).



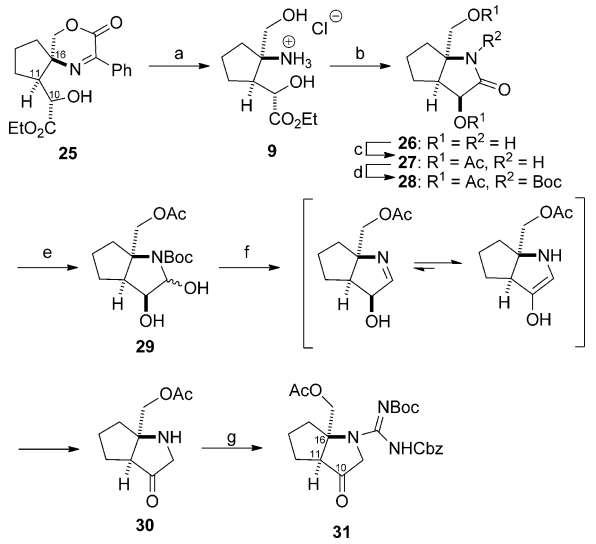
Scheme 5. Proposed mechanism for the formation of imine **25** from isoxazolidine **24**.

The cyclic imine **25** was further converted into bicyclic ketone with guanidine **31** (Scheme 5). The cyclic imine **25** was hydrolyzed under acidic conditions with HCl to give amine-diol **9** as a hydrochloric acid salt. Treatment of the salt **9** with triethylamine in methanol concurrently generated lactam **26**, whose two hydroxy groups were acetylated with acetic anhydride to give diacetate **27** in 82% yield from **25** (3 steps). After protection of the amino group with Boc (95% yield), the resulting lactam **28** was reduced to aminal **29** with lithium borohydride in 71% yield. In this reaction, the acetyl group on the secondary alcohol was deprotected simultaneously. Subsequently, the Boc group was deprotected with TFA in dichloromethane to give ketone **30** through an iminium cation–enamine isomerization.[14] Finally, guanylation was carried out with pseudothiourea **32**[15] in the presence of silver (I) triflate and triethylamine, and guanidine **31** was obtained in 43% yield (2 steps). Compound **31** has a disubstituted cyclopentane skeleton with a nitrogen-containing quaternary carbon center and can be regarded as a simple model of the pentacyclic core structure of dimeric oroidin alkaloids, especially those related to axinellamine A (**5**).

Scheme 6

Conclusions

We achieved a diastereoselective synthesis of guanidine **31** with a disubstituted pentacyclic ring system. The contiguous



Scheme 6. Synthesis of guanidine **31**. Reagents and conditions: a) HCl, MeOH, 50 °C, 7 h; b) Et_3N, MeOH, rt., 5 h; c) Ac_2O, pyridine, rt, 5 h, 82 % (3 steps); d) Boc_2O, DMAP, Et_3N, rt, 1 h, 95 %; (e) $LiBH_4$, THF, rt, 1 h, 71 %; f) TFA, CH_2Cl_2, rt, 3 h; g) *N*-Boc-*N'*-Cbz-isothiopseudourea (**32**), AgOTf, Et_3N, DMF, rt, 1 h, 43 % (2 steps).

stereogenic centers at C11 and C16 involving a nitrogen-containing quaternary carbon center in **31** were selectively constructed by intramolecular 1,3-DC reaction with cyclic nitrone **11** or **23**. In the case of 1,3-DC reaction with **23**, intramolecular redox reaction proceeded immediately following the 1,3-DC reaction, effectively affording cyclic imine **25** in a single step in good yield. Further elaboration of **25** led to the guanidine **31**, which we regard as a simple model of the pentacyclic ring system of dimeric oroidin alkaloids, especially those related to axinellamine A (**5**).

Experimental Section

General

Flash chromatography was performed on Silica gel 60 (spherical, particle size 40–100 μm; Kanto), Chromatorex NH (particle size 75–150 μm; Fuji Silysia), or Florisil (particle size 75–150 μm; Wako). ^1H and ^{13}C NMR spectra were recorded on JEOL JNM-AL 300, JNM-ECX 400, and JNM-ECA 500 spectrometers. The spectra are referenced internally according to residual solvent signals of $CDCl_3$ (^1H NMR; $\delta = 7.26$ ppm, ^{13}C NMR; $\delta = 77.0$ ppm). Data for ^1H NMR were recorded as follows: chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; br, broad) integration, and coupling constant (Hz). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). Mass spectra were recorded on a JEOL JMS-T100 LC spectrometer in the ESI-MS mode using methanol as a solvent.

Synthesis

Epoxide 13: To a solution of DMSO (9.1 mL, 127.4 mmol) in CH_2Cl_2 (200 mL) was added $(COCl)_2$ (4.3 mL, 51.0 mmol) at −78 °C under N_2 atmosphere. After stirring for 15 min, 5-hexen-1-ol (**12**) (3.0 mL, 25.5 mmol) was added to the above solution, and the mixture was stirred for 2 h at −78 °C. Then Et_3N (35.3 mL, 254.8 mmol) was added to the mixture. After stirring for 5 min, the reaction was quenched with H_2O and warmed to room temperature. The mixture was extracted twice with CH_2Cl_2, and the combined organic layer was dried over $MgSO_4$, filtered, and concentrated to give crude aldehyde. To a solution of NaH (60 %, 2.55 g, 63.7 mmol) in THF (240 mL) was added triethylphosphonoacetate (10.2 mL, 51.0 mmol) at 0 °C under N_2 atmosphere. After stirring for 5 min, crude aldehyde (25.5 mmol) in THF (15 mL) was added to the above solution and the mixture was stirred for 1 h at 0 °C. The reaction was quenched with aqueous sat. NH_4Cl and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated to give crude ester. To a solution of ether (4.24 g, 25.2 mmol) in CH_2Cl_2 (200 mL) was added *m*-CPBA (11.4 g, 51.0 mmol) at 0 °C under N_2 atmosphere. After stirring for 6 h at room temperature, the reaction was quenched with aqueous 10 % $Na_2S_2O_3$ and sat. $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 8:1) to give epoxide **13** (4.31 g, 23.4 mmol, 92 %). Spectral data for ester **13**: ^1H NMR (400 MHz, $CDCl_3$) $\delta = 6.93$ (dt, $J = 6.9$, 15.6 Hz, 1H), 5.84–5.80 (m, 1H), 4.17 (q, $J = 6.9$ Hz, 2H) 2.92–2.88 (m, 1H), 2.74 (t, $J = 4.6$ Hz, 1H), 2.46 (q, $J = 2.8$ Hz, 1H), 2.26 (dq, $J = 1.4$, 7.3 Hz, 2H), 1.72–1.46 (m, 4H), 1.27 ppm (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 166.6$, 148.3, 121.8, 60.2, 51.9, 46.9, 31.8, 31.7, 24.4, 14.2 ppm; HRMS (ESI, $M + Na^+$) calcd for $C_{10}H_{16}NaO_3$ 207.0997, found 207.1005.

α-Hydroxyketone 14: To a solution of epoxide **13** (4.31 g, 23.4 mmol) and molecular sieve 4 Å powder (4.68 g) in DMSO (50 mL) was added TfOH (410 μL, 4.68 mmol) at room temperature under N_2 atmosphere. After stirring for 5.5 h at 100 °C, the reaction was quenched with aqueous sat. $NaHCO_3$ and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 4:1) to give α-hydroxyketone **14** (3.30 g, 16.5 mmol, 71 %). Spectral data for α-hydroxyl ketone **14**: ^1H NMR (400 MHz, $CDCl_3$) $\delta = 6.85$ (dt, $J = 6.9$, 15.1 Hz, 1H), 5.80–5.76 (m, 1H), 4.18 (d, $J = 2.8$ Hz, 1H), 4.13 (q, $J = 7.8$ Hz, 2H), 3.16 (br, 1H), 2.40 (t, $J = 7.3$ Hz, 2H), 2.19 (q, $J = 7.3$ Hz, 2H), 1.77 (quint, $J = 7.3$ Hz, 2H), 1.23 ppm (t, $J = 7.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 209.0$, 166.3, 147.3, 122.2, 68.0, 60.2, 37.2, 31.1, 21.6, 14.1 ppm; HRMS (ESI, $M + Na^+$) calcd for $C_{10}H_{16}NaO_4$ 223.0946, found 223.0986.

Carboxylic acid 16: To a solution of *N,O*-bis(*tert*-butoxycarbonyl)hydroxylamine[16] (9.0 g, 38.61 mmol) in DMF (77 mL) was added NaH (60 %, 1.55 g, 38.61 mmol), benzyl 2-bromoacetate (7.3 mL, 46.33 mmol), and tetrabutylammonium iodide (713 mg, 1.93 mmol) at 0 °C under N_2 atmosphere. After stirring for 5 h at room temperature, the reaction was quenched with aqueous sat. NH_4Cl and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give crude benzyl ester (12.1 g). To a solution of benzyl ester (408 mg, 1.07 mmol) in MeOH (17 mL) was added 10 % Pd/C (40.8 mg), and the reaction mixture was stirred at room temperature under an atmosphere of hydrogen gas (balloon). After 2 h, ethyl acetate was added to the reaction mixture. Subsequently, the mixture was filtered through a pad of Celite and eluted with ethyl acetate. The filtrates were concentrated in vacuo, and the residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1) to give carboxylix acid **16** (307 mg, 1.06 mmol, 98 %). Spectral data for carboxylic acid **16**: ^1H NMR (300 MHz, $CDCl_3$) $\delta = 4.36$ (s, 2H), 1.53 (s, 9H), 1.49 ppm (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 172.1$, 154.6, 152.4, 85.7, 83.9, 52.0, 27.9, 27.6 ppm; HRMS (ESI, $M + Na^+$) calcd for $C_{12}H_{21}NNaO_7$ 314.1216, found 314.1204.

Isoxazolidine 10: To a solution of α-hydroxyketone **14** (458 mg, 2.29 mmol) in CH_2Cl_2 (20 mL) was added EDCI·HCl (1.07 g, 6.87 mmol), carboxylic acid **16** (2.00 g, 6.87 mmol), and DMAP (84 mg, 0.69 mmol) at 0 °C under N_2 atmosphere. After stirring for 30 min, the reaction was quenched with phosphate buffer (pH 7.0) and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo at below 25 °C to give ester **15** (650 mg). To a solution of crude ester **15** (608 mg) in CH_2Cl_2 (20 mL) was added $MgSO_4$ (2.0 g) and TFA (4 mL) at 0 °C under N_2 atmosphere. After stirring for 6 h at room temperature, the reaction was diluted with CH_2Cl_2, filtered, and concentrated

in vacuo at below 25 °C. The residue was dissolved in toluene (10 mL), and K_2CO_3 (354 mg) and $MgSO_4$ (2.0 g) were added at room temperature under N_2 atmosphere. After stirring for 11 h at 40 °C, the reaction was quenched with aqueous sat. $NaHCO_3$ and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo at below 25 °C. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 3:1) to give isoxazolidine **10** (179 mg, 0.70 mmol, 2 steps 33 %). Spectral data for isoxazolidine **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.34 (d, J = 12.4 Hz, 1H), 4.23 (q, J = 7.3 Hz, 2H), 4.13 (d, J = 12.4 Hz, 1H), 4.06 (d, J = 8.7 Hz, 1H), 4.05 (d, J = 16.5 Hz, 1H), 3.81 (d, J = 16.5 Hz, 1H), 2.99 (t, J = 7.3 Hz, 1H), 1.96–1.76 (m, 6H), 1.30 ppm (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.7, 168.3, 80.0, 73.4, 70.5, 61.7, 56.9, 52.8, 35.0, 30.1, 23.2, 14.1 ppm; HRMS (ESI, $M+Na^+$) calcd for $C_{12}H_{17}NNaO_5$ 278.1004, found 278.1010.

Nitrone 19: To a solution of isoxazolidine **10** (21 mg, 0.083 mmol) in CH_2Cl_2 (1 mL) was added *m*-CPBA (28 mg, 0.124 mmol) at 0 °C under N_2 atmosphere. After stirring for 1.5 h at room temperature, the reaction was quenched with aqueous 10 % $Na_2S_2O_3$ and sat. $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 1:1) to give nitrone **19** (12.4 mg, 0.046 mmol, 55 %). Spectral data for nitrone **19**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.16 (s, 1H), 4.79 (d, J = 12.6 Hz, 1H), 4.47 (d, J = 9.2 Hz, 1H), 4.22 (q, J = 7.5 Hz, 2H), 4.19 (d, J = 12.0, 1H), 3.18 (br, 1H), 2.41–2.35 (m, 1H), 2.16–2.10 (m, 2H), 2.06–1.94 (m, 2H), 1.92–1.86(m, 1H), 1.65–1.57 (m, 1H), 1.29 ppm (t, 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.7, 159.1, 126.1, 77.7, 71.6, 71.2, 62.0, 50.8, 36.3, 30.3, 24.0, 14.1 ppm; HRMS (ESI, $M+Na^+$) calcd for $C_{12}H_{17}NNaO_6$ 294.0954, found 294.0953.

Imine 18: To a solution of nitrone **19** (96 mg, 0.35 mmol) in toluene (4 mL) was added PPh_3 (372 mg, 1.42 mmol) at room temperature under N_2 atmosphere. After stirring for 17 h at 100 °C, the reaction was concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 3:1) to give imine **18** (60.3 mg, 0.235 mmol, 66 %). Spectral data for imine **18**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71 (s, 1H), 4.55 (d, J = 11.5 Hz, 1H), 4.31 (dd, J = 5.5, 7.3 Hz, 1H), 4.22 (q, J = 7.3 Hz, 2H), 4.15 (d, J = 11.5 Hz, 1H), 3.50 (d, J = 8.7 Hz, 1H), 2.15–1.54 (m, 6H) 1.29 ppm (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.1, 154.8, 150.6, 72.5, 71.7, 66.8, 61.5, 48.3, 36.9, 28.7, 23.6, 14.2 ppm; HRMS (ESI, $M+Na^+$) calcd for $C_{12}H_{17}NNaO_5$ 278.1004, found 278.0969.

Carboxylic acid 21: To a solution of (±)-mandelic acid (1.00 g, 6.57 mmol) and K_2CO_3 (2.72 g, 19.7 mmol) in DMF (40 mL) was added allyl bromide (556 μL, 6.57 mmol) at room temperature under N_2 atmosphere. After stirring for 5 h, the reaction was quenched with aqueous sat. NH_4Cl and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 10:1 to 5:1) to give the allyl ester (1.15 g, 5.98 mmol, 91 %). Spectral data for the allyl ester: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45–7.31 (m, 5H), 5.88–5.78 (m, 1H), 5.21–5.12 (m, 3H), 4.71–4.61 (m, 2H), 3.46 ppm (d, J = 5.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.3, 138.1, 131.0, 128.5, 128.4, 126.5, 118.7, 72.8, 66.4 ppm; HRMS (ESI, $M+Na^+$) calcd for $C_{11}H_{12}NaO_3$ 215.0684, found 215.0699.

To a solution of allyl ester (28 mg, 0.143 mmol) and DIEA (98.5 μL, 0.572 mmol) in CH_2Cl_2 (1 mL) was added Tf_2O (27 μL, 0.157 mmol) at −78 °C under N_2 atmosphere. After stirring for 15 min, $NH_2OTBDPS$ (42 mg, 0.286 mmol) in CH_2Cl_2 (1 mL) was added to the above solution, and the mixture was stirred at room temperature. After stirring for 2 h, the reaction was quenched with aqueous sat. $NaHCO_3$ at 0 °C. The mixture was extracted with twice with CH_2Cl_2, and the combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 100:1 to 50:1) to give hydroxylamine (30.7 mg, 0.069 mmol, 48 %). Spectral data for hydroxylamine: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77–7.01 (m, 15H), 5.97–5.87 (m, 1H), 5.34–5.21 (m, 2H), 4.81–4.65 (m, 2H), 4.47 (s, 1H), 1.09 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.2, 136.0, 135.9, 135.8, 135.7, 133.5, 133.4, 133.2, 131.8, 129.7, 129.6, 128.5, 128.0, 127.5, 118.4, 69.3, 65.6, 27.2, 19.1 ppm; HRMS (ESI, $M+Na^+$) calcd for $C_{27}H_{31}NNaO_3Si$ 468.1971, found 468.1961.

To a solution of hydroxylamine (251 mg, 0.564 mmol) and $[Pd(PPh_3)_4]$ (13 mg, 0.011 mmol) in THF (5 mL) was added morpholine (98 μL, 1.13 mmol) at 0 °C under N_2 atmosphere. After stirring for 30 min, the reaction was quenched with H_2O and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 15:1 to 2:1) to give carboxylic acid **21** (138 mg, 0.341 mmol, 60 %). Spectral data for carboxylic acid **21**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77–7.08 (m, 15H), 4.65 (s, 1H), 4.47 (s, 1H), 1.09 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.8, 136.0, 135.6, 133.2, 132.8, 129.8, 129.6, 128.7, 128.6, 128.0, 127.6, 69.2, 27.2, 19.1 ppm; HRMS (ESI, $M+Na^+$) calcd for $C_{24}H_{27}NNaO_3Si$ 428.1658, found 428.1647.

Ester 22: To a solution of α-hydroxyketone **14** (92 mg, 0.457 mmol), carboxylic acid **21** (371 mg, 0.915 mmol), and DMAP (11 mg, 0.091 mmol) in CH_2Cl_2 (4 mL) was added EDCI·HCl (377 mg, 1.371 mmol) at 0 °C under N_2 atmosphere. After stirring for 1.5 h, the reaction was quenched with H_2O and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 50:1 to 30:1) to give ester **22** (86 mg, 0.146 mmol, 32 %). Spectral data for ester **22**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.79–7.11 (m, 15H), 6.88 (dt, J = 6.4, 15.1 Hz, 1H), 6.02 (br, 1H), 5.81 (d, J = 15.6 Hz, 1H), 4.72 (d, J = 2.8 Hz, 2H), 4.60 (s, 1H), 4.20 (q, J = 6.9 Hz, 2H), 2.40 (dq, J = 3.7, 7.3 Hz, 2H), 2.14 (q, J = 6.9 Hz, 2H), 1.73 (quint, J = 7.3 Hz, 2H), 1.30 (t, J = 7.3 Hz, 3H), 1.12 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 203.3, 171.9, 166.4, 147.7, 135.9, 135.6, 133.3, 132.7, 129.8, 129.6, 128.7, 128.6, 128.0, 127.5, 122.0, 69.1, 68.4, 60.2, 37.6, 31.0, 27.2, 21.1, 19.1, 14.2 ppm; HRMS (ESI, $M+Na^+$) calcd for $C_{34}H_{41}NNaO_6Si$ 610.2601, found 610.2572.

Imine 25: To a solution of ester **22** (86 mg, 0.146 mmol) in CH_2Cl_2 (1 mL) was added TFA (0.5 mL) at room temperature under N_2 atmosphere. After stirring for 1 h, the reaction was concentrated in vacuo, and the residue was dissolved in 1,2-dichloroethane (1.5 mL). The mixture was then heated at 50 °C for 30 min, concentrated in vacuo, and the residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 50:1 to 30:1) to give imine **25** (35.8 mg, 0.106 mmol, 74 %). Spectral data for imine **25**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.94–7.91 (m, 2H), 7.52–7.40 (m, 3H), 4.52 (d, J = 11.4 Hz, 1H), 4.35 (q, J = 4.5 Hz, 1H), 4.23 (d, J = 11.4 Hz, 1H), 4.02 (q, J = 7.2 Hz, 2H), 2.36–2.29 (m, 1H), 2.26–2.17 (m, 2H), 2.05–1.93 (m, 2H), 1.75–1.60 (m, 2H), 1.05 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 174.0, 156.2, 155.3, 133.4, 131.2, 128.6, 128.2, 72.1, 66.8, 61.2, 47.6, 35.9, 28.6, 23.6, 13.7 ppm; HRMS (ESI, $M+Na^+$) calcd for $C_{18}H_{21}NNaO_5$ 354.1317, found 354.1330.

Lactam 27: To a solution of imine **25** (432 mg, 1.28 mmol) in methanol (5 mL) was added HCl (1 mL) at room temperature. After stirring for 7 h at 50 °C, the reaction was concentrated in vacuo to give crude amine **9**. To a solution of crude amine **9** in methanol (5 mL) was added Et_3N (1 mL) at room temperature. After stirring for 5 h at room temperature, the reaction was concentrated in vacuo to give lactam **26**. To a solution of crude lactam **26** in Ac_2O (7 mL) was added pyridine (7 mL) at room temperature. After stirring for 5 h, the reaction was concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 1:1 to 1:5) to give lactam **27** (267 mg, 1.05 mmol, 82 %, 3 steps). Spectral data for lactam **27**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.60–6.56 (br, 1H), 5.37 (d, J = 8.9 Hz, 1H), 4.26 (d, J = 11.4 Hz, 1H), 3.96 (d, J = 11.4 Hz, 1H), 2.93–2.86 (m, 1H), 2.17 (s, 3H), 2.09 (s, 3H), 1.80–1.63 ppm (br m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.8, 170.6, 170.2, 71.7, 68.4, 67.6, 45.4, 36.8, 25.9, 24.6, 20.8, 20.6 ppm; HRMS (ESI, $M+Na^+$) calcd for $C_{12}H_{17}NNaO_5$ 278.1004, found 278.1004.

Lactam 28: To a solution of lactam **27** (141 mg, 0.554 mmol), Et_3N (192 μL, 1.39 mmol), and DMAP (7 mg, 0.055 mmol) in CH_2Cl_2 (5 mL) was added Boc_2O (242 mg, 1.11 mmol) at room temperature under N_2 atmosphere. After stirring for 1 h, the reaction was quenched with aqueous sat. NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 10:1 to 2:1)

to give lactam **28** (187 mg, 0.526 mmol, 95%). Spectral data for lactam **28**: ^{1}H NMR (300 MHz, $CDCl_3$) δ=5.50 (d, J=9.3 Hz, 1H), 4.79 (d, J=11.4 Hz, 1H), 3.97 (d, J=11.4 Hz, 1H), 2.82–2.73 (m, 1H), 2.16 (s, 3H), 2.08 (s, 3H), 2.07–1.97 (brm, 2H), 1.85–1.58 (brm, 4H), 1.53 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=169.9, 169.7, 169.5, 148.8, 83.6, 71.2, 70.9, 66.5, 44.8, 37.0, 27.6, 26.6, 24.7, 20.4, 20.2 ppm; HRMS (ESI, $M+Na^+$) calcd for $C_{17}H_{25}NNaO_7$ 378.1529, found 378.1567.

Aminal 29: To a solution of lactam **28** (335 mg, 0.944 mmol) in THF (5 mL) was added $LiBH_4$ in THF (630 μL, 1.89 mmol) at 0°C under N_2 atmosphere. After stirring for 1 h at room temperature, the reaction was quenched with aqueous sat. NH_4Cl and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=3:1 to 2:1) to give aminal **29** (210.3 mg, 0.667 mmol, 71%). Spectral data for aminal **29**: ^{1}H NMR (300 MHz, $CDCl_3$) δ=5.41 (d, J=3.8 Hz, 1H), 5.03 (dd, J=4.1, 7.6 Hz, 1H), 4.73 (d, 11.4 Hz, 1H), 3.79 (d, J=11.0 Hz, 1H), 2.93 (q, J=7.6 Hz, 1H), 2.10 (s, 3H), 1.84–1.61 (m, 6H), 1.49 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=170.8, 154.7, 88.7, 81.3, 75.2, 73.3, 66.4, 49.4, 37.1, 28.4, 26.0, 25.4, 21.0 ppm; HRMS (ESI, $M+Na^+$) calcd for $C_{15}H_{25}NNaO_6$ 338.1580, found 338.1579.

Guanidine 31: To a solution of aminal **29** (11 mg, 0.035 mmol) in CH_2Cl_2 (5 mL) was added TFA (0.1 mL) at room temperature. After stirring for 3 h at room temperature, the reaction was concentrated in vacuo to give crude amine **30**. To a solution of crude amine **30** (0.035 mmol), Et_3N (9.7 μL, 0.071 mmol), and *N*-Boc-*N*′-Cbz-isothiopseudourea (**32**; 19 mg, 0.053 mmol) in DMF (0.3 mL) was added AgOTf (14 mg, 0.053 mmol) at room temperature under N_2 atmosphere. After stirring for 1 h, the reaction mixture was diluted with ethyl acetate and filtered through a pad of Celite. The filtrates were washed with H_2O and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by Florisil column chromatography (*n*-hexane/ethyl acetate=5:1 to 1:1) to give guanidine **31** (7.6 mg, 0.015 mmol, 43%). Spectral data for guanidine **31**: ^{1}H NMR (300 MHz, $CDCl_3$) δ=9.99 (br, 1H), 7.41–7.30 (m, 5H), 5.30 (d, J=11.4 Hz, 1H), 5.14 (s, 2H), 5.12 (d, J=9.6 Hz, 1H), 4.36 (d, J=19.3 Hz, 1H), 4.14 (d, J=18.2 Hz, 1H), 4.10 (d, J=11.3 Hz, 1H), 2.87–2.70 (m, 1H), 2.02 (s, 3H), 1.97–1.68 (brm, 6H), 1.47 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=210.3, 170.4, 162.2, 153.3, 150.3, 136.6, 128.6, 128.4, 128.1, 127.9, 127.9, 82.7, 67.4, 66.9, 57.0, 56.9, 35.2, 29.6, 28.2, 28.0, 25.8, 20.7 ppm; HRMS (ESI, $M+Na^+$) calcd for $C_{24}H_{31}N_3NaO_6$ 469.2060, found 469.2049.

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[13] Stereochemistries at C11 and C16 are controlled by the same transition state (see Scheme 2).

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