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Remote Stereoinductive Intramolecular Nitrile Oxide Cycloaddition: Asymmetric Total Synthesis and Structure Revision of (−)-11β-Hydroxycurvularin

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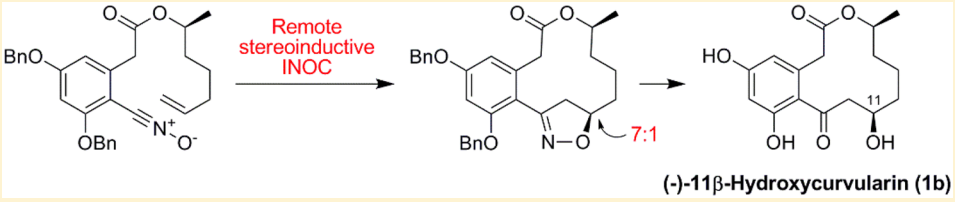
Supporting Information



ABSTRACT: The first total synthesis and structure revision of (−)-11β-hydroxycurvularin (**1b**), a macrolide possessing a β-hydroxyketone moiety, were accomplished. The β-hydroxyketone moiety in this natural product was introduced by cleavage of the N−O bond in an isoxazoline ring that was formed diastereoselectively in a 1,5-remote stereocontrolled fashion by employing intramolecular nitrile oxide cycloaddition.

Curvularins (**1**−**3**) are fungal polyketides that have the 3,5-dihydroxyphenylacetic acid macrolactone skeleton (Figure 1).[1] These macrolides (**1**−**3**) have attracted considerable

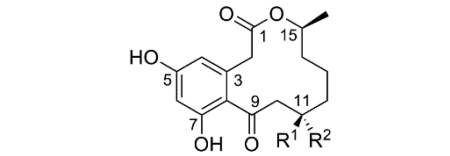


Figure 1. Structure of curvularins.

interest in the fields of biology and agriculture due to their diverse biological activity spectrum, including anti-inflammatory,[2] antitumor,[1d,3] spindle-poisoning,[1f] and sporulation-suppressing activity.[1g] Several groups have accomplished the total synthesis of (−)-curvularin (**3**)[4−7] and 11-methoxycurvularins (**2a**,**b**),[8] but no synthesis of the 11-hydroxycurvularins (**1a**,**b**) has yet been reported. The assigned stereochemistry at the C-11 position of **1a**,**b** was based on their ^{1}H NMR spectral data coupled with molecular mechanics calculations.[1c] The structures of the 11-methoxycurvularines (**2a**,**b**) were initially determined by comparison of the spectral data with those of **1a**,**b**[1e] but were revised later following the total synthesis of the natural products.[8] In the synthetic approaches to curvularins to date, macrocyclic intermediates were produced in moderate to low yields by all of the approaches used (intramolecular Friedel−Crafts acylation,[4,8] intramolecular esterification,[5] and aryne acyl-alkylation[6]) except for ring-closing metathesis.[7]

Intramolecular nitrile oxide cycloaddition (INOC) has been utilized in several macrocyclic natural product syntheses. An acrylate group has been used as a cyclization partner for the nitrile oxide moiety in INOC-based syntheses,[9−11] but aside from a maytansinoid approach,[12] no reports have yet appeared in which a terminal alkene not conjugated with a carbonyl group was used to construct a macrocycle via INOC in a natural product synthesis. The INOC strategy with an unconjugated terminal alkene has been utilized to synthesize only macrocyclic unnatural compounds.[13] We previously observed that conformational preferences in INOC play an important role in the course of macrocyclization during the synthesis of (+)-brefeldin A.[10] To demonstrate its utility in stereoselective macrocyclization in natural product synthesis, we set out to examine the feasibility of using INOC to construct a macrocycle from a substrate with an unconjugated terminal alkene moiety, and to check the stereooutcome of the reaction in a newly generated stereogenic center. We envisaged

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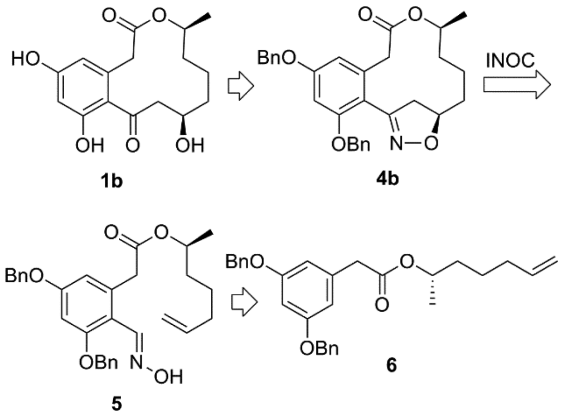
that (−)-11β-hydroxycurvularin (**1b**) would be an ideal macrocyclic natural product for this investigation because the structural simplicity of **1b** could clarify the effect of the C-15 position stereochemistry on the newly generated C-11 stereogenic center via INOC. Described herein is a concise asymmetric total synthesis of (−)-11-β-hydroxycurvularin (**1b**) that features a macrocycle construction based on a novel remote stereoinductive INOC.

Our retrosynthetic analysis for **1b** called for macrolactone **4b** as a key intermediate. We envisioned that the construction of macrolactone **4b** from acyclic precursor **5** by INOC would be regio- and stereoselective due to conformational bias. DFT (density functional theory) calculations were carried out to evaluate all feasible conformers of macrolactones **4a**−**d** (Table S2 in the Supporting Information). Macrolactone **4b** was found to be the most stable and to have the lowest barrier for the INOC reaction in CH_2Cl_2, as described later. These DFT calculation results suggested that the hydroxyl group in (−)-11-β-hydroxycurvularin (**1b**) could be introduced in a 1,5-remote stereocontrolled manner. Oxime **5** could be easily produced from ester **6** via formylation and subsequent oxime formation (Scheme 1).

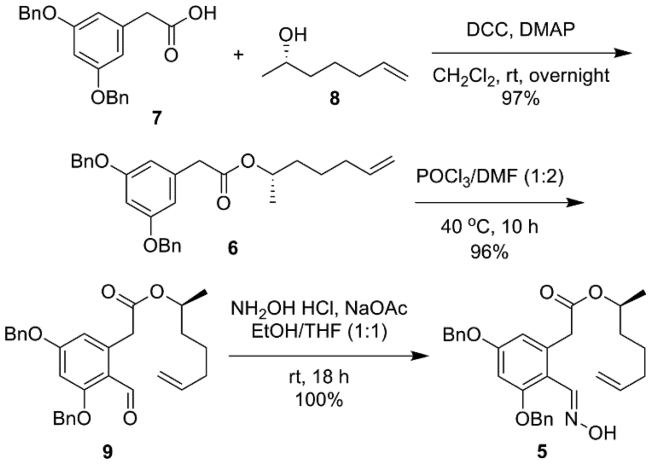
Scheme 1. Retrosynthetic Plan for (−)-11β-Hydroxycurvularin (1b)



The requisite INOC substrate **5** was prepared from the commercially available phenylacetic acid **7** by a straightforward manner as depicted in Scheme 2. Esterification of **7** with the known alcohol **8**[14] produced ester **6**, which was formylated to aldehyde **9** via Vilsmeier−Haack reaction in an overall 93% yield.[15] Aldehyde **9** was converted to oxime **5** (E/Z, >99:1) in quantitative yield.

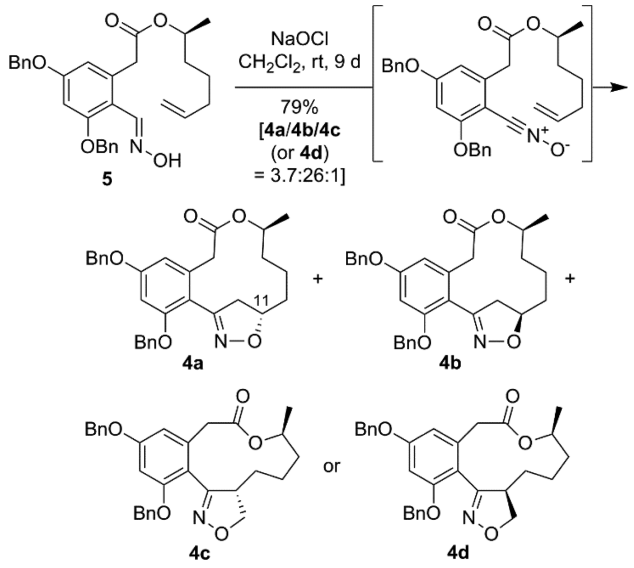
With this INOC substrate **5** in hand, we attempted to construct a macrocycle. The INOC reaction of oxime **5** was challenging because it possesses two orientations and two facial directions of approach of the olefin to the nitrile oxide moiety that is generated during the reaction. Moreover, we previously observed during the course of the synthesis of (+)-brefeldin A that the intermolecular nitrile oxide cycloaddition proceeded preferentially with an acrylate group in the presence of a terminal alkene not conjugated with a carbonyl group,[10b] The result implies that an unconjugated terminal alkene is less reactive than an acrylate group in nitrile oxide cycloaddition. A precedent also showed that a 12-membered macrocycle was constructed in low yield by INOC.[13e] Although we were concerned about the regio- and stereoselectivity of addition and the reactivity of the terminal alkene, we nonetheless attempted

Scheme 2. Preparation of an Intramolecular Nitrile Oxide Cycloaddition Substrate



INOC of oxime **5** under conventional conditions. Initially, amines were used to accelerate nitrile oxide formation, and isoxazolines **4a**,**b** were obtained as mixtures with unidentified byproducts. To our delight, oxime **5** underwent smooth INOC in the absence of amines to produce a bridged isomer **4b** as the major component along with its diastereomer **4a** and a trace amount of one of the fused isomers **4c**,**d** in good yield and with good regio- and diastereoselectivity [79%, **4a**/**4b**/**4c** (or **4d**) = 3.7:26:1, Scheme 3].[16] At this stage, the stereochemistry of **4a**,**b**

Scheme 3. Intramolecular Nitrile Oxide Cycloaddition



was tentatively determined by the analysis of the NOESY spectra and on the basis of the DFT calculation results. To the best of our knowledge, this constitutes the first example of the remote stereoinductive construction of a macrocycle employing INOC in a natural product synthesis where both remote stereoinduction and macrocycle formation were achieved at the same time. In a number of natural product syntheses, the conformational preferences of macrocycles have been used for the stereoinduction of pre-existing macrocycles,[17] and stereoinductive macrocyclization strategies have also been utilized with acyclic precursors bearing a stereogenic center(s) close to the ring formation sites.[18] However, remote stereoinductive

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macrocyclization has rarely been attempted in natural product synthesis.[19] Remote stereoinduction has been achieved mostly in acyclic systems and proceeds either without cyclization[20] or with cyclization to provide 5- and 6-membered rings.[21]

To understand the conformational effects on INOC reactions, we carried out DFT calculations for the four feasible macrolactones **4a**–**d** in which -OMe groups replace the -OBn groups (Figure S1). Because there are many possible conformations to form a macrocyclic ring via INOC, the most stable conformers of **4a**–**d** were first searched, and the corresponding transition state structures were investigated. All DFT calculations were carried out at the B3LYP/6-311++G(d,p)//B3LYP/6-31+G(d) level of theory using the conductor-like polarizable continuum model (CPCM)[22] for solvation free energies in CH_2Cl_2 implemented in the Gaussian 03 program[23] (computational details in the Supporting Information). Systematic searching over all conformational space yielded six, six, eight, and five local minima for **4a**–**d**, respectively. The optimized structures are shown in Figure S2, and their torsion angles and relative thermodynamic properties in CH_2Cl_2 at 25 °C are listed in Table 1 and Table S2.

Table 1. Calculated Thermodynamic Properties of 4a–d in CH_2Cl_2 at 25 °C[a]

conformer[b]	ΔE_e[c]	ΔH[c]	ΔG[c]	P[d]	$\Delta G^{\ddagger}$[e]
4b-1	0.00	0.00	0.00	50.4	29.62
4b-2	0.88	0.70	0.26	32.7	
4b-3	0.69	0.72	0.79	13.2	
4a-1	3.77	3.65	3.26	0.2	31.06
4c-1	4.85	5.17	4.87	0.0	31.93
4d-1	5.16	5.39	5.41	0.0	34.34

[a]Calculated at the B3LYP/6-311++G(d,p)//B3LYP/6-31+G(d) level of theory with solvation free energies at the CPCM B3LYP/6-31+G(d) level of theory. [b]Other local minima are listed in Tables S1 and S2. [c]ΔE_e, ΔH, and ΔG are relative electronic energies, relative enthalpies, and relative Gibbs free energies in kcal mol^{-1}, respectively. [d]Populations (%) were calculated using ΔG values at 25 °C. [e]The barriers (kcal mol^{-1}) for INOC reactions relative to the Gibbs free energy of the reactant of **4d**-1.

Conformer **4b**-1 was found to be most preferred with a population of 50.4% followed by conformer **4b**-2 with a relative Gibbs free energy of ΔG = 0.26 kcal mol^{-1} (32.7%) in CH_2Cl_2. The third most preferred conformer was **4b**-3 with ΔG = 0.79 kcal mol^{-1} (13.2%). The values of ΔG were calculated to be 3.26, 4.87, and 5.41 kcal mol^{-1} for the most preferred conformers **4a**-1, **4c**-1, and **4d**-1 of the other isomers, respectively. From the calculations, the total populations in descending order were **4b** (99.5%) ≫ **4a** (0.5%) > **4c** (0.0%) or **4d** (0.0%) in CH_2Cl_2, which are consistent with the results obtained from experiments (Scheme 3). In particular, a comparative analysis of the thermodynamic properties indicated that electronic contributions play a role in determining the ΔG values in CH_2Cl_2. The barriers for transition state ($\Delta G^{\ddagger}$) of the INOC reactions that yield the four isomers **4b**-1, **4a**-1, **4c**-1, and **4d**-1 were calculated to be 29.62, 31.06, 31.93, and 34.34 kcal mol^{-1} in CH_2Cl_2, respectively (Figures S3 and S4). The lowest barrier of the transition state for the formation of **4b**-1 (**4b**-1-TS) was ascribed to the lowest electronic energy at the B3LYP/6-311++G(d,p) level of theory. The conformational relationship between the C-16 methyl group and C-13 methylene group may play an important role in stabilizing **4b**-1-TS, where the staggered conformation is "anti" whereas it is "gauche" in the transition state for the formation of **4a**-1 (**4a**-1-TS). Thus, the higher population of **4b** conformers and the lowest barrier for transition state are consistent with the view that the formation of **4b** via the INOC reaction is both *thermodynamically* and *kinetically* favored in CH_2Cl_2.

The optimized structure of the transition state for **4b**-1 is shown in Figure 2. The slow formation of **4b** via the INOC reaction is also consistent with its high reaction barrier of ∼30 kcal mol^{-1}.

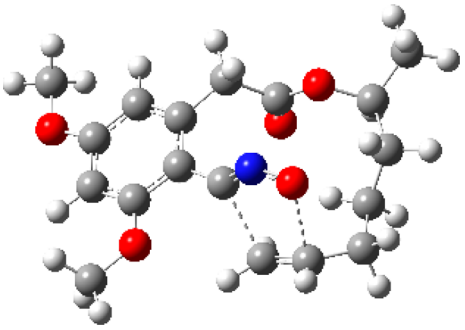
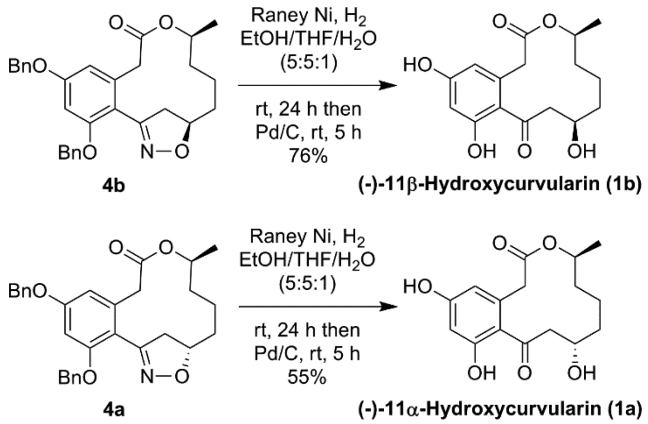


Figure 2. Optimized structure of the transition state for **4b**-1 by DFT methods.

Simultaneous N–O bond cleavage and debenzylation of isoxazoline **4b** with fresh Raney-Ni and Pd/C under a hydrogen atmosphere gave (−)-11β-hydroxycurvularin (**1b**) in 76% yield: $[\alpha]^{20}_D$ −35.0 (*c* 1.00, EtOH) as shown in Scheme 4.[24]

Scheme 4. Completion of the Synthesis of (−)-11β-Hydroxycurvularin (1b)



However, we found that the spectral data for synthetic **1b** were not identical with the reported data from the natural product assigned previously as (−)-11β-hydroxycurvularin but rather were in agreement with those for (−)-11α-hydroxycurvularin: [natural: $[\alpha]^{26}_D$ −29.4 (*c* 0.33, EtOH)].[1c,d] For the results to be confirmed further, isoxazoline **4a** was converted to (−)-11α-hydroxycurvularin (**1a**) under conditions similar to those used for **4b** in 55% yield: $[\alpha]^{20}_D$ −13.0 (*c* 1.00, EtOH). The spectral data of synthetic **1a** were in good agreement with the reported spectral data of the natural product previously assigned as (−)-11β-hydroxycurvularin: [natural: $[\alpha]^{24}_D$ −10.9 (*c* 0.19, EtOH)].

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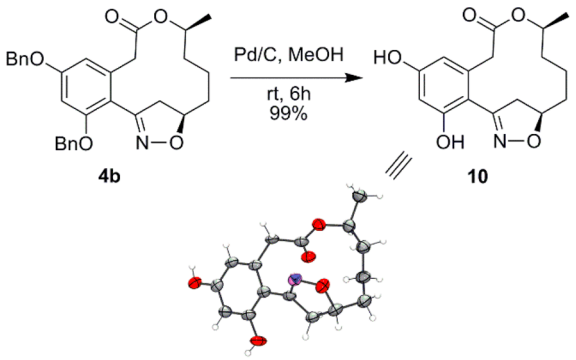
Thus, we decided to determine unambiguously the configuration of stereocenter C-11 newly generated from INOC through X-ray crystallography. Dibenzylether **4b** was deprotected to isoxazoline **10**, which was crystallized (Scheme 5). The results of an X-ray crystallographic study revealed that

Scheme 5. Synthesis and X-ray Crystal Structure of Isoxazoline 10



the configuration of C-11 position in **10** is (*R*) in accordance with the analysis of NOESY spectra of **4b**. In particular, the X-ray structure for isoxazoline **10** is quite similar to the structure of **4b**-1 optimized by DFT methods (Figure S2).

In summary, we have achieved the first total synthesis of (−)-11*β*-hydroxycurvularin (**1b**) from the commercially available phenylacetic acid **7** and the readily available alcohol **8** in 5 steps and in 47% overall yield. During the course of this study, the spectral data of 11-hydroxycurvularines (**1a,b**) were revised. The synthesis is highly practical and can provide gram quantities of **1b** for animal studies as well as demonstrating the versatility of INOC in macrocyclic natural product synthesis. Our remote stereoinductive INOC strategy is unique in that the remote stereoinduction and macrocycle formation occur simultaneously.

EXPERIMENTAL SECTION

(*S*)-Hept-6-en-2-yl 2-(3,5-bis(benzyloxy)phenyl)acetate (6). A mixture of carboxylic acid **7** (2.00 g, 5.7 mmol), alcohol **8** (0.79 g, 6.9 mmol), DCC (1.78 g, 8.6 mmol), and DMAP (0.07 g, 0.6 mmol) in CH_2Cl_2 (19 mL) was stirred overnight at room temperature under a nitrogen atmosphere. The mixture was diluted with hexanes (60 mL) and filtered through a plug of cotton. The filtrate was concentrated, and the resulting residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 3:1) to give ester **6** (2.47 g, colorless oil) in 97% yield: $[\alpha]^{20}_D$ +6.30 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.45−7.34 (m, 10H), 6.59 (s, 1H), 6.58 (s, 1H), 6.57−6.56 (m, 1H), 5.80−5.75 (m, 1H), 5.04(s, 4H), 5.01 (dd, *J* = 17.1, 1.5 Hz, 1H), 4.96−4.92 (m, 2H), 3.55 (s, 2H), 2.05 (q, *J* = 6.9 Hz, 2H), 1.62−1.60 (m, 1H), 1.54−1.49 (m, 1H), 1.43−1.36 (m, 2H), 1.23 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.2, 160.2, 138.6, 137.1, 136.6, 128.8, 128.2, 127.7, 114.9, 108.6, 101.0, 71.6, 70.2, 42.2, 35.5, 33.6, 24.8, 20.1; IR (neat) 3030, 2928, 1724, 1591, 1450, 1147; HRMS (EI, magnetic sector) *m*/*z* calcd for $C_{29}H_{32}O_4$ (M^+) 444.2301, found 444.2307.

(*S*)-Hept-6-en-2-yl 2-(3,5-bis(benzyloxy)-2-formylphenyl)-acetate (9). To a solution of ester **6** (2.54 g, 5.7 mmol) in DMF (10 mL) was added $POCl_3$ (5.0 mL) dropwise. The mixture was stirred for 10 h at 40 °C under a nitrogen atmosphere and slowly poured into chilled saturated aqueous NaOAc solution. The mixture was vigorously stirred for 2 h and filtered. The filter cake was dissolved in ether, and insoluble materials were filtered off. The filtrate was concentrated, and the resulting crude product was recrystallized from a mixture of EtOAc and hexanes (1:5) to give aldehyde **9** (2.59 g, white solid) in 96% yield: $[\alpha]^{20}_D$ −6.10 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.54 (s, 1H), 7.43−7.35 (m, 10H), 6.60 (d, *J* = 1.9 Hz, 1H), 6.67 (d, *J* = 1.7 Hz, 1H), 5.86−5.77 (m, 1H), 5.13 (s, 2H), 5.11 (s, 2H), 5.05−5.01 (m, 1H), 4.97−4.94 (m, 2H), 3.95 (s, 2H), 2.08 (q, *J* = 6.8 Hz, 2H), 1.68−1.63 (m, 1H), 1.57−1.40 (m, 3H), 1.27 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.1, 170.9, 164.5, 163.8, 139.7, 138.8, 136.0, 135.9, 128.9, 128.8, 128.5, 128.4, 127.7, 127.4, 117.7, 114.7, 111.1, 99.2, 71.4, 70.8, 70.4, 41.1, 35.4, 33.6, 24.7, 20.1; IR (neat) 3030, 2929, 1717, 1674, 1595, 1150; HRMS (EI, magnetic sector) *m*/*z* calcd for $C_{30}H_{32}O_5$ (M^+) 472.2250, found 472.2253.

(*S,E*)-Hept-6-en-2-yl 2-(3,5-bis(benzyloxy)-2-((hydroxy-imino)methyl)phenyl)acetate (5). A mixture of aldehyde **9** (50.0 mg, 0.11 mmol), NH_2OH·HCl (8.0 mg, 0.12 mmol), and NaOAc (9.0 mg, 0.11 mmol) in EtOH/THF (1:1) was stirred overnight at room temperature. The mixture was concentrated at reduced pressure, and the residue was dissolved in EtOAc. The solution was washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated at reduced pressure to give oxime **5** (52.1 mg, white solid) in 100% yield. The product was pure enough to collect spectral data and was carried on to the next step without further purification. Data for **5**: $[\alpha]^{20}_D$ +5.10 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.59 (s, 1H), 7.43−7.35 (m, 10H), 6.57 (s, 1H), 6.52 (s, 1H), 5.87−5.78 (m, 1H), 5.07(s, 4H), 5.02−4.93 (m, 3H), 3.93 (d, *J* = 16.7 Hz, 1H), 3.87 (d, *J* = 16.7 Hz, 1H), 2.09−2.03 (m, 2H), 1.65−1.58 (m, 1H), 1.54−1.35 (m, 3H), 1.23 (d, *J* = 5.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.3, 160.2, 159.1, 147.3, 138.8, 136.6, 136.5, 136.2, 128.8, 128.7, 128.3, 128.1, 127.7, 127.4, 114.8, 113.6, 110.3, 99.4, 71.1, 70.7, 70.2, 42.0, 35.4, 33.5, 24.7, 20.1; IR (neat) 3359, 2926, 1714, 1600, 1580, 1151; HRMS (EI, magnetic sector) *m*/*z* calcd for $C_{30}H_{33}NO_5$ (M^+) 487.2359, found 487.2355.

INOC Products 4a,b. To a solution of oxime **5** (1.88 g, 3.86 mmol) in CH_2Cl_2 (1.9 L) was added aqueous NaOCl solution (10−15% aqueous solution, 30 mL). The mixture was stirred for 9 d at room temperature and washed with brine. The aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 5:1) to give isoxazoline **4b** (1.25 g, white solid) in 67% yield and **4a** with one of the fused isomers **4c,d** [0.23 g, white solid, **4a**/**4c** (or **4d**), 3.7:1 by the analysis of ^{1}H 500 MHz NMR) as a mixture in 12% yield. Isoxazoline **4a** was carried on to the next step without further purification. Data for **4b**: $[\alpha]^{20}_D$ −2.60 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42−7.32 (m, 10H), 6.57 (s, 1H), 6.56 (s, 1H), 5.19−5.16 (m, 1H), 5.06 (d, *J* = 4.0 Hz, 2H), 5.03 (d, *J* = 6.8 Hz, 2H), 4.83−4.79 (m, 1H), 4.30 (d, *J* = 16.1 Hz, 1H), 3.52 (dd, *J* = 16.6, 10.6 Hz, 1H), 3.36 (d, *J* = 16.6 Hz, 1H), 2.76 (dd, *J* = 16.6, 4.1 Hz, 1H), 1.91−1.80 (m, 2H), 1.75−1.60 (m, 3H), 1.39−1.35 (m, 1H), 1.26 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.4, 160.4, 158.5, 155.3, 136.6, 128.8, 128.7, 128.3, 128.1, 127.7, 127.4, 110.3, 99.8, 80.1, 72.7, 70.6, 70.3, 41.6, 40.8, 35.5, 31.5, 20.7, 18.8; IR (neat) 3028, 2927, 1719, 1578, 1150, 1070; HRMS (EI, magnetic sector) *m*/*z* calcd for $C_{30}H_{31}NO_5$ (M^+) 485.2202, found 485.2198. Data for **4a** with **4c** (or **4d**): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.45−7.35 (m, 10H), 6.60 (d, *J* = 2.0 Hz, 1H), 6.52 (d, *J* = 2.0 Hz, 1H), 5.07 (s, 2H), 5.05 (s, 2H), 5.00−4.96 (m, 1H), 4.88−4.84 (m, 1H), 4.71 (d, *J* = 16,8 Hz, 1H), 3.77 (dd, *J* = 17,3, 12.0 Hz, 1H), 3.43 (d, *J* = 16.8 Hz, 1H), 3.01 (dd, *J* = 17.3, 4.4 Hz, 1H), 1.94−1.86 (m, 2H), 1.60−1.39 (m, 4H), 1.13 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.3, 160.0, 158.9, 155.7, 136.4, 136.3, 128.9, 128.8, 128.8, 128.3, 127.7, 113.1, 110.1, 99.7, 79.5, 72.1, 71.0, 70.3, 41.9, 41.7, 35.8, 31.4, 19.8, 17.1; IR (neat) 3028, 2930, 1715, 1599, 1160, 1069; HRMS (EI, magnetic sector) *m*/*z* calcd for $C_{30}H_{31}NO_5$ (M^+) 485.2202, found 485.2200.

(−)-11*β*-Hydroxycurvularin (1b).[1c,d] To a solution of isoxazoline **4b** (255 mg, 0.525 mmol) in a mixture of EtOH, THF, and H_2O (EtOH/THF/H_2O, 5:5:1, 5.3 mL) was added freshly activated Raney Ni (2 spatula scoops). The mixture was stirred for 24 h at room temperature under a hydrogen atmosphere. To the mixture was added a catalytic amount of Pd/C (5% on activated carbon, 10 mg). The

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mixture was stirred for 5 h at room temperature under a hydrogen atmosphere and then filtered through a pad of Celite. The filtrate was concentrated, and the resulting residue was purified by flash column chromatography on silica gel to give (−)-11β-hydroxycurvularin (**1b**) (123 mg, white solid) in 76% yield: $[\alpha]^{20}_{D}$ −35.0 (*c* 1.00, EtOH), −22.3 (*c* 1.00, acetone); ^{1}H NMR (acetone-d_6, 500 MHz) δ 6.43(s, 1H), 6.36 (s, 1H), 4.98−4.95 (m, 1H), 4.03−3.99 (m, 1H), 3.84 (d, *J* = 15.3 Hz, 1H), 3.71 (d, *J* = 15.3 Hz, 1H), 3.32 (dd, *J* = 13.6, 2.5 Hz, 1H), 3.10 (dd, *J* = 13.3, 10.2 Hz, 1H), 1.75−1.68 (m, 2H), 1.56−1.41 (m, 4H), 1.14 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 204.4, 170.7, 160.7, 159.3, 137.6, 120.6, 112.5, 102.8, 71.5, 67.8, 53.9, 40.0, 35.1, 32.0, 19.4, 19.3; IR (neat) 3336, 2940, 1689, 1610, 1585, 1257, 1156; HRMS (EI, magnetic sector) *m*/*z* calcd for $C_{16}H_{20}O_6$ (M^+) 308.1260, found 308.1261.

(−)-11α-Hydroxycurvularin (1a).[1c,d] To a solution of isoxazoline **4a** contaminated with **4c** or **4d** [**4a**/**4c**(or **4d**), 3.7:1, 56.0 mg, 0.12 mmol] in EtOH/THF/H_2O (5:5:1, 1.2 mL) was added freshly activated Raney Ni (1 spatula scoop). The mixture was stirred for 24 h at room temperature under a hydrogen atmosphere. To the mixture was added a catalytic amount of Pd/C (5% on activated carbon, 5 mg). The mixture was stirred for 5 h at room temperature under a hydrogen atmosphere and then filtered through a pad of Celite. The filtrate was concentrated, and the resulting residue was purified by flash column chromatography on silica gel to give (−)-11α-hydroxycurvularin (**1a**) (15.4 mg, white solid) in 55% yield: $[\alpha]^{20}_{D}$ −13.0 (*c* 1.00, EtOH); ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.95 (brs, 2H), 6.42 (d, *J* = 2.0 Hz, 1H), 6.36 (d, *J* = 2.0 Hz, 1H), 4.87−4.82 (m, 1H), 4.14−4.11 (m, 1H), 3.83 (d, *J* = 15.1 Hz, 1H), 3.71 (d, *J* = 15.1 Hz, 1H), 3.55 (d, *J* = 13.1 Hz, 1H), 2.90 (dd, *J* = 12.8, 10.5 Hz, 1H), 1.75−1.68 (m, 1H), 1.63−1.56 (m, 1H), 1.53−1.29 (m, 3H), 1.22−1.19 (m, 1H), 1.12 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 204.9, 170.9, 160.4, 158.5, 137.0, 121.2, 112.1, 102.7, 73.5, 67.1, 54.5, 39.5, 35.6, 32.5, 22.7, 21.5; IR (neat) 3245, 2970, 2930, 1694, 1586, 1260, 1154, 1040; HRMS (EI, magnetic sector) *m*/*z* calcd for $C_{16}H_{20}O_6$ (M^+) 308.1260, found 308.1258.

Isoxazoline 10. A mixture of dibenzyl ether **4b** (158 mg, 0.33 mmol) and Pd/C (5% on activated carbon, 10 mg) in MeOH was stirred for 6 h at room temperature under a hydrogen atmosphere. The mixture was filtered through a pad of Celite. The filtrate was concentrated at reduced pressure, and the resulting residue was purified by column chromatography to afford isoxazoline **10** (98 mg, white solid) in 99% yield: $[\alpha]^{20}_{D}$ (*c* 1.00, EtOH); ^{1}H NMR (CD_3OD, 600 MHz) δ 6.28 (d, *J* = 4.1 Hz, 2H), 5.11−5.08 (m, 1H), 4.84−4.80 (m, 1H), 4.05 (d, *J* = 16.0 Hz, 1H), 3.65 (dd, *J* = 17.7, 11.1 Hz, 1H), 3.35 (s, 1H), 2.72 (dd, *J* = 17.7, 4.4 Hz, 1H), 1.86−1.79 (m, 2H), 1.74−1.57 (m, 3H), 1.40−1.32 (m, 1H), 1.23 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 173.3, 159.3, 157.9, 156.8, 136.3, 110.9, 108.6, 101.6, 80.3, 73.0, 41.5, 40.2, 35.7, 31.4, 19.8, 18.7; IR (neat) 3295, 2933, 1698, 1609, 1469, 1169; HRMS: (EI, magnetic sector) *m*/*z* calcd for $C_{16}H_{19}NO_5$ (M^+) 305.1263, found 305.1263.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02760.

Details for DFT calculations, characterization data for β-hydroxyketone **11**, copies of the ^{1}H and ^{13}C NMR spectra for all new compounds and **1a**,**b**, and copies of the NOESY and HMBC spectra of **4b** (PDF)

X-ray crystallographic data for isoxazoline **10** (ZIP)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to Prof. Deukjoon Kim on the occasion of his 68th birthday.

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