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印楝素类柠檬苦素化合物 ABD 核心骨架的快速合成

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摘要 为实现印楝素类柠檬苦素及其类似物的快速合成, 报道了从香芹酮出发, 高立体选择性地合成印楝素 ABD 三环母核结构的方法. 合成路线的亮点是通过分子内的乙腈氧化物-烯烃环加成反应, 以很好的立体选择性实现反式十氢萘环体系的快速构建. 接下来通过 Sonogashira 偶联、异噁唑啉开环、甲磺酰化及分子内的 S_N2 取代等一系列简单高效的反应, 实现了印楝素三环骨架的规模合成, 总路线共 13 步, 总收率 6.1%. 该中间体可以作为合成印楝素及其类似物的高官能团化左翼片段, 与目前方法相比, 此方法操作简便, 易于实现, 为实现该类天然产物的合成奠定了基础.

关键词 印楝素; 柠檬苦素; 反式十氢萘环; 分子内乙腈氧化物-烯烃环加成(INOC)反应; 异噁唑啉

A Feasible Route to Access the ABD Skeleton in Azadirachtin-Type Limonoids

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Abstract In an effort to rapidly construct the azadirachtin-type limonoids and analogues, a highly diastereoselective synthesis of the ABD tricyclic core in azadirachtin-type limonoids from (−)-carvone has been developed. The synthetic avenue features an intramolecular nitrile oxide-alkene cycloaddition (INOC) reaction to assemble the *trans*-decalin system in highly stereoselective manner. By further utilizing an efficient sequence of Sonogashira coupling, isoxazoline reduction, stereocontrolled dihydroxylation, mesylation and intramolecular S_N2 substitution, a scalable stereoselective synthesis of the tricyclic core skeleton of azadirachtin in 13 linear steps was achieved with 6.1% total yield. This intermediate can serve as a highly functionalized left-wing fragment for the synthesis of azadirachtin and its analogues. Compared with existing methods, the methods reported herein are simple, reliable, easy to implement, and significantly advances research on the synthesis of the azadirachtin-type limonoids.

Keywords azadirachtin; limonoids; *trans*-decalin; intramolecular nitrile oxide-alkene cycloaddition (INOC) reaction; isoxazoline

1 Introduction

The limonoids isolated from the *Meliaceae* plants possess antifeedant, insecticidal, insect growth disrupting, fungicidal, bactericidal and other activities.[1] Among these limonoids, azadirachtin (azadirachtin A)[2] is known as one of the most potent and environmentally-friendly anti-insect compounds. Currently, structure-activity relationship (SAR) studies of azadirachtin are limited to derivatization or degradation of the natural product.[3] To this end, a de novo synthesis of azadirachtin and its analogues would greatly improve the scope of future SAR studies.[4]

Azadirachtin represents a formidable synthetic challenge and has attracted significant attention from the synthetic community. The strategic disconnection of the C(8)—C(14) bond proved key in the retrosynthesis, effectively dividing the molecule into two fragments to be unified at a late stage. The left-wing fragment features a densely functionalized *trans*-decalin core, and several methods have been developed for its construction (Scheme 1). For example, in the "relay total synthesis" by Ley,[5] synthesis of left

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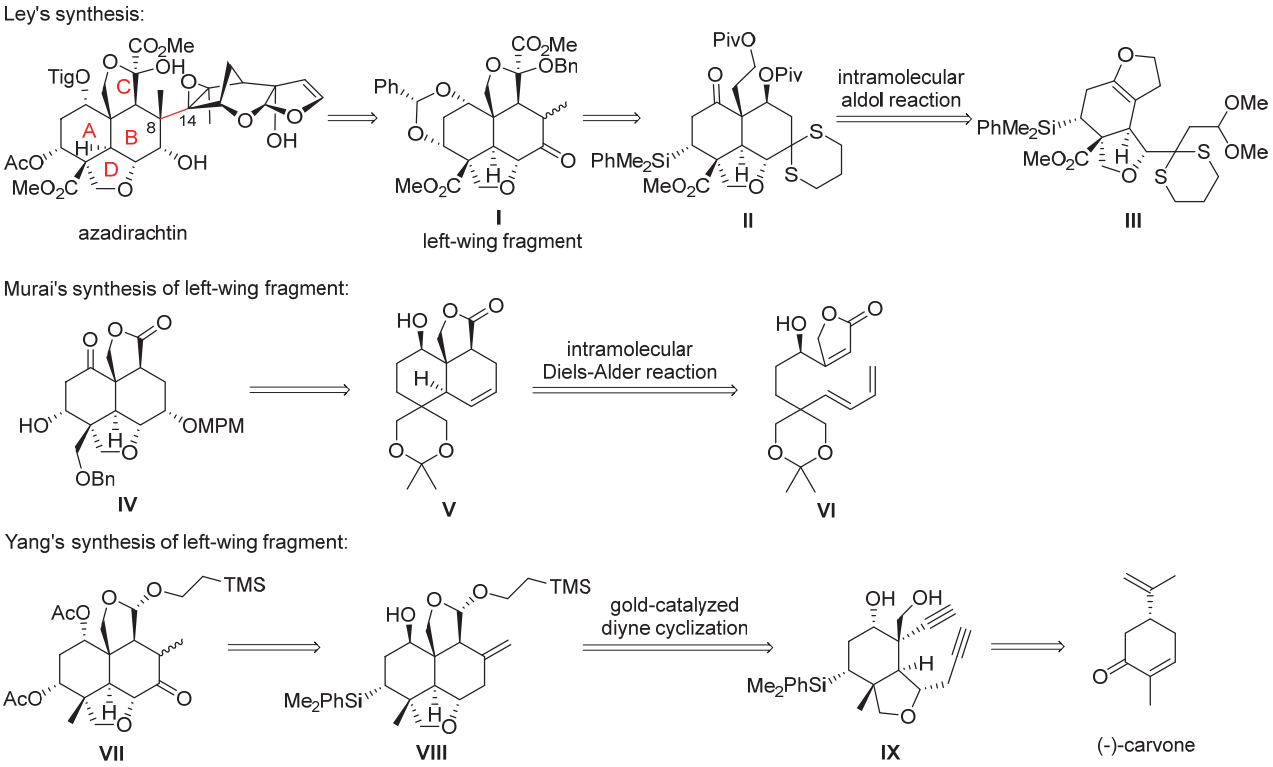
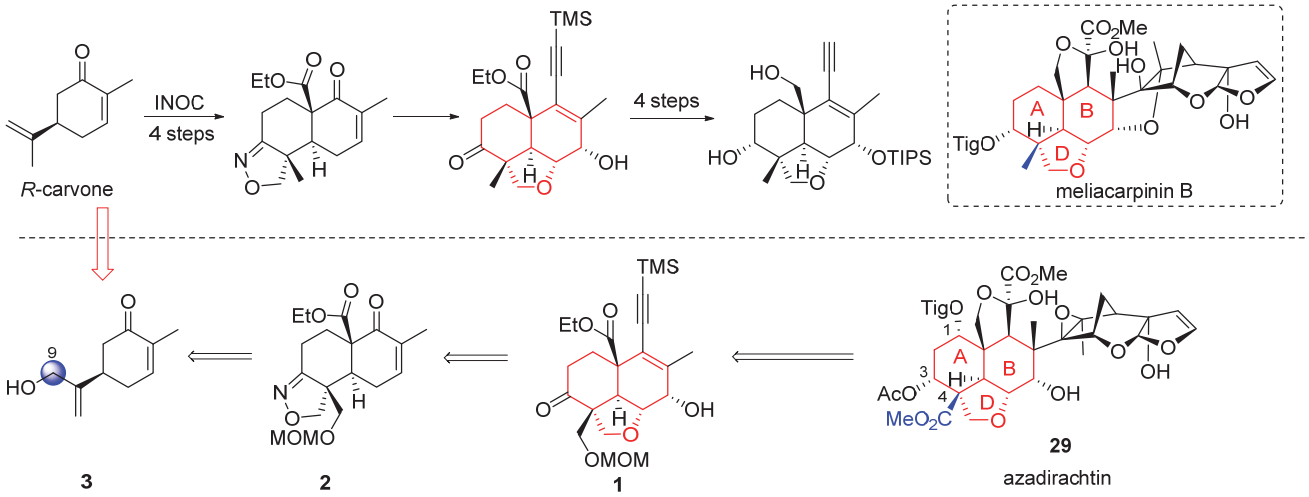


Scheme 1 Selected syntheses of left-wing fragment of azadirachtin

fragment **I** features an intramolecular aldol reaction that constructs the densely functionalized *trans*-decalin core.[6] Alternatively, in the synthetic studies of Murai, an intramolecular Diels-Alder reaction was used [7] to furnish the *trans*-decalin unit with good diastereoselectivity, after which a sequence of functional group manipulations forged the ABCD core structure of azadirachtin. Besides these, the Yang group[8] developed a novel gold-catalyzed diyne cyclization reaction to install the *trans*-decalin framework, providing a concise sequence to the tetracyclic core structure of azadirachtin-type limonoids. Although extensive work has been published,[9] a rapid, scalable, and enantioselective route for the preparation of densely functionalized left fragment has yet to be obtained.

Previously, we disclosed a route to synthesize the ABD ring system of meliacarpinin B,[10] a meliacarpin-type limonoid. The route features an intramolecular nitrile oxide-alkene cycloaddition (INOC) reaction that constructs the *trans*-decalin unit from commercially available (−)-carvone. Herein, we report our application of this method in the synthesis of the ABD core in azadirachtin using C(9)-hydroxy (−)-carvone **3** (Scheme 2).[11] We envision that tricycle **1** could be used as a functionalized left-wing fragment of azadirachtin and other azadirachtin-type limonoids.



Scheme 2 Retrosynthtic analysis of azadirachtin

2 Results and discussion

Our synthesis commenced with the preparation of *trans*-decalin unit **2** (Scheme 3). Starting from (−)-carvone, a modified two-step sequence involving chlorination and hydrolysis afforded compound **3**[11] with an improved yield of 64% (over 2 steps) compared to previously reported procedures. Large-scale (>200 g) synthesis could also be carried out with this simplified procedure, and no significant drop of yield was observed. After this, the primary alcohol was protected with a methyloxymethyl (MOM) group to afford **5** in 95% yield. Enone **5** was then subjected to LiHMDS and the resulting enolate was quenched with Mander's reagent to provide *β*-keto-esters **6** as a mixture of diastereoisomers with 6.5∶1 *dr*. Subsequent Michael addition to acrolein provided aldehyde **7**, which then underwent condensation with hydroxyl amine hydrochloride to give the INOC precursor **8**. The INOC reaction went smoothly by using the conventional aq. NaClO-dichloromethane (DCM) condition, providing the *trans*-decalin **2** in 50% yield with excellent diastereoselectivity.

Next, we aimed to construct the tetrahydrofuran D ring (Scheme 4). Compound **2** was first deprotonated with NaHMDS and the resulting enolate was quenched with *N*-phenylbis(trifluoromethanesulfonimide) ($PhNTf_2$) to afford enol triflate **9** in 71% yield. Subsequent reductive cleavage of the isooxazoline ring of compound **9** using our previously developed condition (Fe/AcOH, 60 ℃)[10] gave 64% of the desired *β*-hydroxy ketone **10** along with 27% of *retro*-aldol product **11** (single isomer, absolute stereochemistry of C(4) was not determined). Further screening showed that weaker acid NH_4Cl[12] led to exclusive *retro*-aldol product **11** in 84% yield, whereas stronger acid conc. HCl afforded 93% yield of desired product **10** without any *retro*-aldol reaction. Notably, the MOM protecting group remained despite the strongly acidic conditions.

Having optimized our isoxazoline ring opening condition, the crude *β*-hydroxy ketone **10** was mesylated, and the less substituted olefin was selectively dihydroxylated to give diol **13** in 70% yield over 3 steps. Subsequent ring closure went smoothly to afford tricyclic compound **14** in 75% yield. Unfortunately, Sonogashira coupling of triflate **14** failed to give the desired product **1** in the next step. In probing the reactivity of triflate **14**, it was discovered that Pd-catalyzed reductive detriflation could be performed smoothly with $Pd(OAc)_2$/dppf, generating compound **15** in 87% yield. Using PPh_3 instead of dppf as ligand resulted in comparable yield, although longer reaction times were required.

Gratifyingly, Sonogashira coupling reaction could be achieved using enol triflate **9**, affording desired coupling product **16** in 77% yield (Scheme 5). However, subsequent isoxazoline ring opening again proved troublesome, with significant *retro*-aldol reaction observed and incomplete conversion. After extensively screening conditions, it was found that 15 equiv. of Fe and AcOH (10 equiv. in previous example[10]) as well as elevated reaction temperature (70 ℃ vs 60 ℃) are necessary to give complete conversion of the starting material. Further optimization by increasing the amount of AcOH to 20 equiv. gave cleaner result with exclusive formation of the desired *β*-hydroxy ketone **17** in 76% yield. Other conditions such as Raney-Ni/H_2,[13] $TiCl_3$[14] or $Mo(CO)_6$[15] all failed to give the desired product. After that, mesylation and dihydroxylation of **17** went smoothly to give the diol **20** in 70% yield over 2 steps. Finally, ring closure via an intramolecular displacement of the mesylate forged the tetrahydrofuran ring, which delivered the desired tricyclic core **1** in 71% yield.

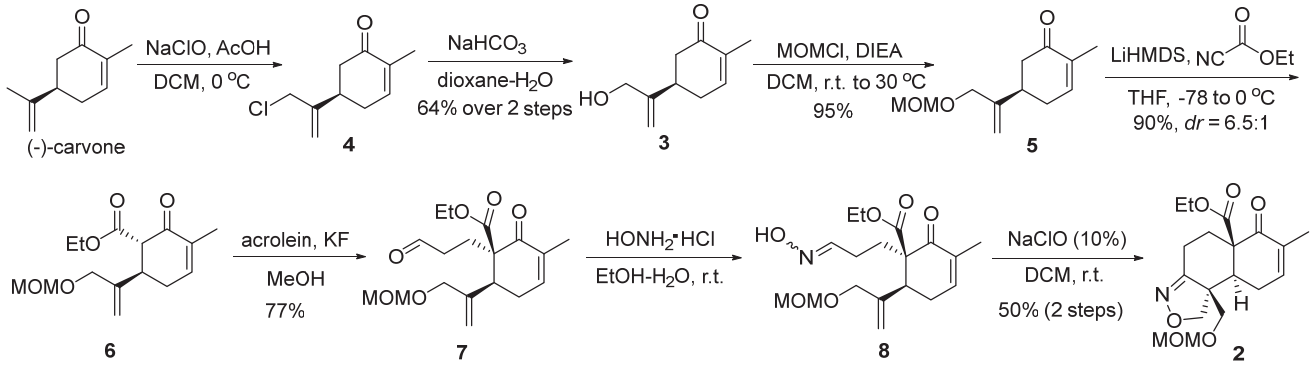
3 Conclusions

In summary, we utilized a stereoselective INOC reaction to assemble the *trans*-decalin system, and a fully functionalized left-wing fragment **1** of azadirachtin-type limonoids was prepared in 13 linear steps from (−)-carvone. Further studies towards the synthesis of azadirachtin-type limonoids are in progress in our laboratory.

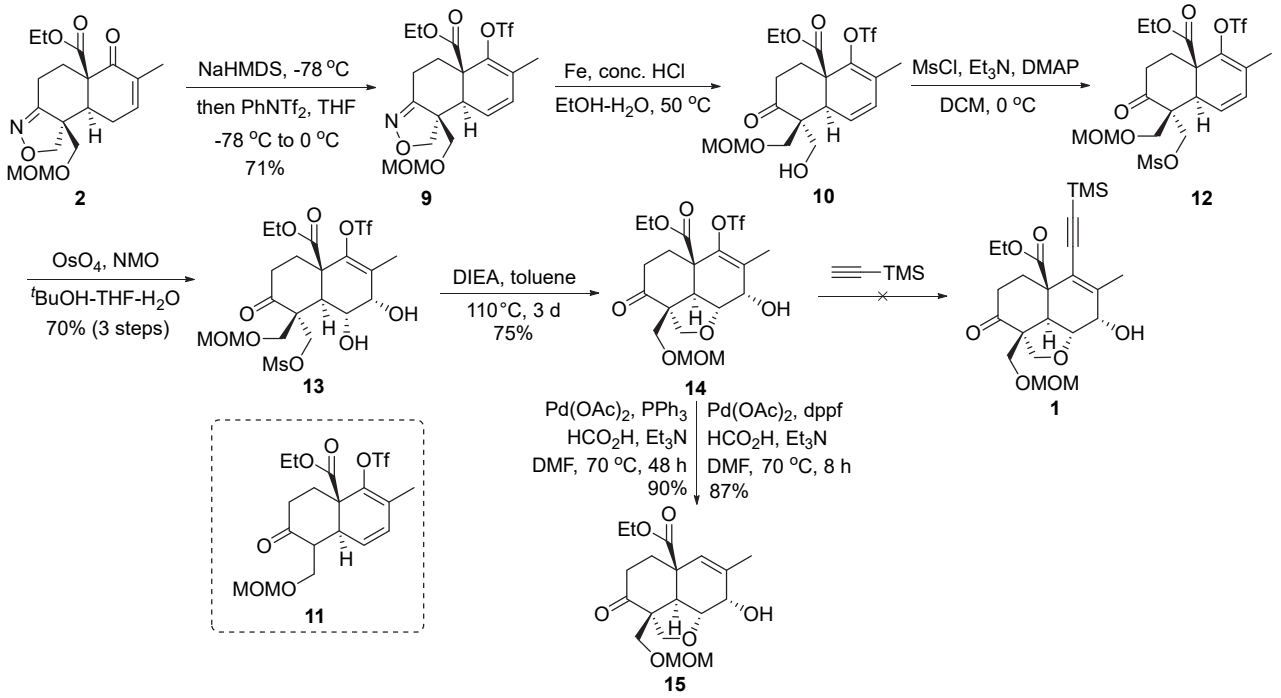
4 Experimental section

4.1 Reagents and instruments

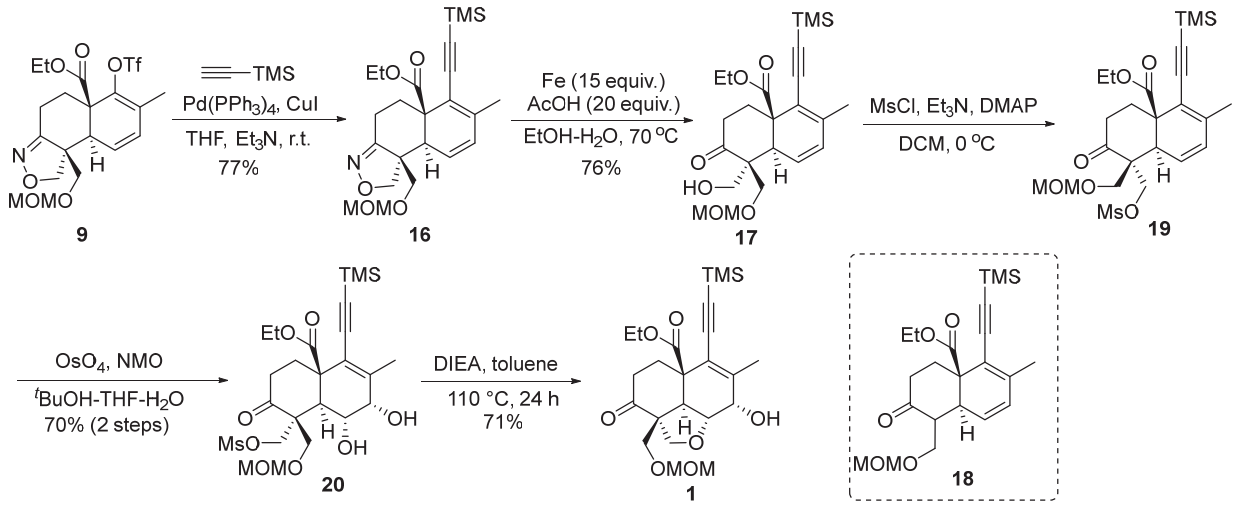
All reactions involving air- and moisture-sensitive reagents were carried out under argon atmosphere using standard syringe-septum cap techniques. Unless otherwise noted, reagents were purchased from commercial suppliers and used without further purification. Tetrahydrofuran (THF), diethyl ether (Et_2O), toluene were distilled from sodium/benzophenone ketyl before use. DCM and tri-



Scheme 3 Construction of *trans*-decalin **2**



Scheme 4 Construction of enol triflate tricyclic core



Scheme 5 Construction of alkyne tricyclic core

ethylamine (Et_3N) were distilled from calcium hydride before use. Reactions were monitored by thin layer chromatography (TLC) carried out on silica gel GF254 plates using UV light or basic aqueous potassium permanganate as visualizing agent. Column chromatography was performed on silica gel (200～300 mesh). ^1H NMR and ^{13}C NMR spectra were recorded on Bruker AMX-400 spectrometers (at 400 MHz and 101 MHz, respectively) and calibrated by using residual undeuterated chloroform (δ_H 7.26) and $CDCl_3$ (δ_C 77.16) as internal references. IR spectra were recorded on a Bruker 550 spectrometer. Melting points (m.p.) were recorded on a RY-1A apparatus. High-resolution mass spectra (HRMS) were acquired using Varian 7.0T FTMS or Agilent 6520 Q-TOF LC/MS with electrospray ionization (ESI) source.

4.2 Chemical synthesis procedures

4.2.1 Synthesis of (*R*)-5-(3-chloroprop-1-en-2-yl)-2-methylcyclohex-2-enone (**4**)

To a stirred solution of (−)-carvone (40.0 g, 266 mmol, 1.0 equiv.) and AcOH (25 mL, 426 mmol, 1.6 equiv.) in DCM (400 mL) was added aq. NaClO (10%, 600 mL, 806 mmol, 3.0 equiv.) over a period of 2 h at 0 ℃, and the mixture was stirred for a further 0.5 h (another 80 mL, 0.4 equiv. aq. NaClO was added if TLC indicated the existence of starting material). The layer was separated and aqueous layer was extracted with DCM (200 mL×2). The combined organic layer was washed with brine (200 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by column chromatography [SiO_2,

V(petroleum ether)∶*V*(EtOAc)=10∶1] to afford **4** (43.6 g, 236 mmol) as a light yellow oil with 89% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.78～6.70 (m, 1H), 5.24 (brs, 1H), 5.04 (brs, 1H), 4.07 (brs, 2H), 3.01～2.89 (m, 1H), 2.69～2.49 (m, 2H), 2.42～2.24 (m, 2H), 1.85～1.70 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 199.1, 146.6, 144.3, 135.6, 115.2, 47.0, 43.1, 37.9, 31.4, 15.7. The NMR data is in accordance with literature.[11b] Also the crude product can be used for next step directly without diminish the yield.

4.2.2 Synthesis of (*R*)-5-(3-hydroxyprop-1-en-2-yl)-2-methylcyclohex-2-enone (**3**)

The synthesis procedure was conducted by following the literature procedure.[11b] To a stirred solution of **4** (43.6 g, 236 mmol, 1.0 equiv.) in dioxane/H_2O (*V*∶*V*=1∶3, 800 mL) was added $NaHCO_3$ (49.6 g, 591 mmol, 2.5 equiv.). The reaction mixture was stirred at reflux for 24 h before being cooled to room temperature. The mixture was diluted with H_2O (400 mL) and then extracted with DCM (300 mL×3). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by column chromatography [SiO_2, *V*(petroleum ether)∶*V*(EtOAc)=1∶1] to afford **3** (28.3 g, 170 mmol) as a light yellow oil with 72% yield. The NMR data is in accordance with literatue.[11b]

4.2.3 Synthesis of (*R*)-5-(3-(methoxymethoxy)prop-1-en-2-yl)-2-methylcyclohex-2-enone (**5**)

To a stirred solution of **3** (10.0 g, 60.2 mmol, 1.0 equiv.) and *N*,*N*-diisopropylethylamine (DIEA) (15.5 g, 120.4 mmol, 2.0 equiv.) in DCM (120 mL) was added MOMCl (7.22 g, 90.3 mmol, 1.5 equiv.) dropwise at 0 ℃, and the mixture was stirred overnight at 30 ℃. The reaction was quenched with saturated aq. $NaHCO_3$ solution (60 mL) and extracted with DCM (50 mL×2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by column chromatography [SiO_2, *V*(petroleum ether)∶*V*(EtOAc)=10∶1] to afford **5** (12.0 g, 57.2 mmol) as a colorless oil with 89% yield. $[\alpha]_D^{15}$ −63.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.77～6.71 (m, 1H), 5.16 (s, 1H), 4.99 (s, 1H), 4.62 (s, 2H), 4.05 (s, 2H), 3.37 (s, 3H), 2.88～2.78 (m, 1H), 2.69～2.57 (m, 1H), 2.57～2.45 (m, 1H), 2.45～2.25 (m, 2H), 1.80～1.76 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 199.5, 147.1, 144.5, 135.6, 112.6, 95.7, 77.4, 69.1, 55.5, 43.2, 38.5, 31.5, 15.7; IR (KBr) *v*: 2926, 2888, 1672, 1442, 1368, 1260, 1213, 1149, 1103, 1048, 911, 765 cm^{-1}; HRMS calcd for $C_{12}H_{18}NaO_3$ $(M+Na)^+$ 233.1148, found 233.1142.

4.2.4 Synthesis of (1*S*,6*R*)-ethyl 6-(3-(methoxymethoxy)prop-1-en-2-yl)-3-methyl-2-oxocyclohex-3-enecarboxylate (**6**)

To a stirred solution of **5** (12.0 g, 57.2 mmol, 1.0 equiv.) in THF (120 mL) was added LiHMDS (1.0 mol/L in THF, 75 mL, 74.6 mmol, 1.3 equiv.) dropwise at −78 ℃. The mixture was stirred for 20 min at −78 ℃ before ethyl cyanoformate (7.36 g, 74.6 mmol, 1.3 equiv.) was added. The resulting mixture was warmed up to 0 ℃ and stirred for 0.5 h before quenched with saturated aq. $NaHCO_3$ (60 mL) solution. The mixture was diluted with H_2O (60 mL) and extracted with EtOAc (60 mL×3). The combined organic layer was washed with brine (40 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by column chromatography [SiO_2, *V*(petroleum ether)∶*V*(EtOAc)=8∶1] to afford **6** (14.5 g, 51.5 mmol, *dr* 6.5∶1) as a light yellow oil with 90% yield. $[\alpha]_D^{15}$ −72.2 (*c* 2.0, $CHCl_3$). Data for the major isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.75～6.71 (m, 1H), 5.19 (s, 1H), 5.07 (s, 1H), 4.61 (s, 2H), 4.24～4.15 (m, 2H), 4.06 (s, 2H), 3.59 (d, *J*=12.9 Hz, 1H), 3.37 (s, 3H), 3.24～3.12 (m, 1H), 2.64～2.54 (m, 1H), 2.45～2.31 (m, 1H), 1.80 (s, 3H), 1.26 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 194.8, 169.7, 145.7, 144.4, 134.8, 113.9, 95.5, 69.0, 60.9, 58.7, 55.4, 41.6, 31.9, 15.7, 14.2; IR (KBr) *v*: 2982, 2929, 2894, 1738, 1673, 1447, 1370, 1258, 1151, 1110, 1046, 917, 760 cm^{-1}; HRMS calcd for $C_{15}H_{22}NaO_5$ $(M+Na)^+$ 305.1359, found 305.1350.

4.2.5 Synthesis of (1*R*,6*S*)-ethyl 6-(3-(methoxymethoxy)prop-1-en-2-yl)-3-methyl-2-*oxo*-1-(3-*oxo*-propyl)-cyclohex-3-enecarboxylate (**7**)

To a stirred solution of **6** (5.0 g, 17.7 mmol, 1.0 equiv.) in MeOH (30 mL) were added KF (2.05 g, 35.4 mmol, 2.0 equiv.) and acrolein (2.3 mL, 35.4 mmol, 2.0 equiv.) at room temperature. Additional acrolein (0.35 mL, 5.3 mmol, 0.3 equiv.) was added every 8～10 h until TLC indicated the consumption of starting material. The reaction was quenched with saturated aq. NH_4Cl solution (20 mL) and H_2O (40 mL), and the mixture was extracted with EtOAc (30 mL×3). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by column chromatography [SiO_2, *V*(petroleum ether)∶*V*(EtOAc)=8∶1 to 4∶1] to afford **7** (4.61 g, 13.6 mmol) as a colorless oil with 77% yield. $[\alpha]_D^{15}$ +32.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.72 (s, 1H), 6.77 (s, 1H), 5.29 (s, 1H), 5.05 (s, 1H), 4.59 (s, 2H), 4.20～4.05 (m, 2H), 4.03～3.93 (m, 2H), 3.35 (s, 3H), 2.95 (dd, *J*=10.1, 4.7 Hz, 1H), 2.84～2.73 (m, 2H), 2.58～2.28 (m, 3H), 2.11～2.02 (m, 1H), 1.81 (s, 3H), 1.22 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 201.5, 196.0, 170.4, 145.0, 144.4, 135.0, 116.8, 95.8, 70.1, 61.4, 59.9, 55.6, 44.4, 39.4, 30.1, 24.7, 16.5, 14.1; IR (KBr) *v*: 2929, 2830, 1727, 1663, 1444, 1366, 1207, 1152, 1048, 919 cm^{-1}; HRMS calcd for $C_{18}H_{27}O_6$ $(M+H)^+$ 339.1802, found 339.1796.

4.2.6 Synthesis of (1*R*,6*S*)-ethyl 1-(3-(hydroxyimino)-propyl)-6-(3-(methoxymethoxy)prop-1-en-2-yl)-3-methyl-2-oxocyclohex-3-enecarboxylate (**8**)

To a stirred solution of **7** (4.61 g, 13.6 mmol, 1.0 equiv.) in EtOH (30 mL) were added H_2O (15 mL), hydroxylamine hydrochloride (1.42 g, 20.4 mmol, 1.5 equiv.) and NaOAc (1.67 g, 20.4 mmol, 1.5 equiv.) at room temperature, and the mixture was stirred for 0.5 h. The reaction

was diluted with H_2O (40 mL) and extracted with DCM (20 mL×3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was used for next step without purification. A small sample was purified by column chromatography [SiO_2, *V*(petroleum ether)∶*V*(EtOAc)=3∶1] to afford **8** as a colorless oil. $[\alpha]_D^{15}$ +30.1 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 7.38 (t, *J*=5.8 Hz, 0.6H), 6.80 (s, 1H), 6.73 (s, 0.4H), 5.30 (s, 1H), 5.06 (d, *J*=3.0 Hz, 1H), 4.62 (s, 2H), 4.18～4.07 (m, 2H), 4.05～3.96 (m, 2H), 3.36 (s, 3H), 3.05 (td, *J*=11.3, 4.7 Hz, 1H), 2.90～2.75 (m, 1H), 2.60～2.20 (m, 4H), 2.10～1.86 (m, 3H), 1.82 (s, 3H), 1.26～1.18 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 195.91, 195.89, 170.59, 170.49, 151.44, 151.38, 145.5, 145.2, 144.42, 144.37, 135.0, 116.5, 116.3, 95.78, 95.74, 77.5, 77.2, 76.8, 70.2, 70.0, 61.38, 61.36, 60.5, 60.3, 55.54, 55.51, 43.2, 42.6, 30.0, 29.9, 28.8, 28.2, 24.8, 20.3, 16.5, 14.0; IR (KBr) *ν*: 3362, 3095, 2929, 1733, 1662, 1445, 1366, 1257, 1211, 1152, 1102, 1047, 920, 766 cm^{-1}; HRMS calcd for $C_{18}H_{28}NO_6$ $(M+H)^+$ 354.1911, found 354.1910.

4.2.7 Synthesis of (5a*R*,9a*S*,9b*S*)-ethyl 9b-((methoxymethoxy)methyl)-7-methyl-6-*oxo*-1,4,5,5a,6,9,9a,9b-octahydronaphtho[2,1-*c*]isoxazole-5a-carboxylate (**2**)

To a stirred solution of crude **8** in DCM (136 mL) was added dropwise an aq. NaClO solution (10%, 20 mL, 27.2 mmol, 2.0 equiv.) within 15 min. The resulting mixture was stirred at room temperature for 10 h before it was diluted with brine (20 mL). The organic phase was dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by column chromatography [SiO_2, *V*(petroleum ether)∶*V*(EtOAc)=6∶1 to 3∶1] to afford **2** (2.39 g, 6.8 mmol) as a light yellow oil with 50% (2 steps) yield. $[\alpha]_D^{15}$ −24.9 (*c* 2.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 6.82 (d, *J*=5.4 Hz, 1H), 4.58～4.50 (m, 3H), 4.19～4.07 (m, 2H), 3.90 (d, *J*=8.1 Hz, 1H), 3.63～3.55 (m, 2H), 3.30 (s, 3H), 3.19～3.07 (m, 1H), 3.01～2.93 (m, 1H), 2.79～2.72 (m, 1H), 2.58 (td, *J*=14.2, 4.8 Hz, 1H), 2.34 (dd, *J*=12.0, 4.4 Hz, 1H), 2.12～2.02 (m, 1H), 1.75 (s, 3H), 1.44 (td, *J*=13.9, 4.7 Hz, 1H), 1.22 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 194.8, 169.5, 159.5, 145.8, 133.3, 96.7, 77.5, 66.3, 61.9, 59.1, 56.6, 55.7, 50.7, 31.2, 26.9, 20.8, 16.6, 13.9; IR (KBr) *ν*: 2933, 2892, 1723, 1669, 1445, 1363, 1262, 1204, 1162, 1105, 1041, 861, 759 cm^{-1}; HRMS calcd for $C_{18}H_{26}NO_6$ $(M+H)^+$ 352.1755, found 352.1754.

4.2.8 Synthesis of (5a*R*,9a*S*,9b*S*)-ethyl 9b-((methoxymethoxy)methyl)-7-methyl-6-(((trifluoromethyl)sulfonyl)oxy)-1,4,5,5a,9a,9b-hexahydronaphtho[2,1-*c*]isoxazole-5a-carboxylate (**9**)

To a stirred solution of **2** (5.85 g, 16.6 mol, 1.0 equiv.) in THF (100 mL) was added NaHMDS (2.0 mol/L in THF, 11 mL, 21.6 mmol, 1.3 equiv.) dropwise at −78 ℃. The mixture was stirred for 3 min at −78 ℃ before $PhNTf_2$ (8.30 g, 23.2 mmol, 1.4 equiv.) was added. The resulting mixture was warmed up to 0 ℃ and stirred for 0.5 h before it was quenched with saturated aq. NH_4Cl (40 mL) solution. The mixture was diluted with H_2O (40 mL) and extracted with EtOAc (40 mL×3). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by column chromatography [SiO_2, *V*(petroleum ether)∶*V*(EtOAc)=8∶1 to 3∶1] to afford **9** (5.7 g, 11.8 mmol) as a colorless oil with 71% yield. $[\alpha]_D^{15}$ +152.8 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 5.91 (brs, 2H), 4.69 (d, *J*=8.0 Hz, 1H), 4.60～4.54 (m, 2H), 4.25～4.05 (m, 2H), 3.91 (d, *J*=7.9 Hz, 1H), 3.64～3.57 (m, 2H), 3.33 (s, 3H), 3.23 (s, 1H), 2.87～2.72 (m, 2H), 2.68～2.57 (m, 1H), 1.89 (s, 3H), 1.71～1.61 (m, 1H), 1.25 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 170.2, 159.0, 143.8, 128.4, 128.2, 127.7, 118.66 (q, *J*=320.3 Hz), 96.7, 77.6, 66.5, 62.0, 58.7, 55.7, 53.9, 49.3, 31.5, 20.7, 16.3, 13.8; ^{19}F NMR ($CDCl_3$, 376 MHz) *δ*: −72.77; IR (KBr) *ν*: 2939, 2889, 1727, 1446, 1215, 1139, 1106, 1043, 951, 848, 757, 663, 593 cm^{-1}; HRMS calcd for $C_{19}H_{25}F_3NO_8S$ $(M+H)^+$ 484.1239, found 484.1247.

4.2.9 Synthesis of (1*R*,4a*R*,8a*S*)-ethyl 1-(hydroxymethyl)-1-((methoxymethoxy)methyl)-6-methyl-2-*oxo*-5-(((trifluoromethyl)sulfonyl)oxy)-1,2,3,4,4a,8a-hexahydronaphthalene-4a-carboxylate (**10**)

To a stirred solution of **9** (1.65 g, 3.90 mmol, 1.0 equiv.) in EtOH (20 mL) were added H_2O (20 mL) and Fe powder (2.18 g, 39.0 mmol, 10.0 equiv.) at room temperature, and the mixture was warmed up to 50 ℃. Conc. HCl (3.2 mL, 39.0 mmol, 10 equiv.) was added dropwise and stirred for 3 h at the same temperature. The reaction was cooled to room temperature and quenched with saturated aq. $NaHCO_3$ (30 mL), the resulting mixture was passed through a pad of celite and the filtercake was washed with EtOAc. The filtrate was concentrated to remove most of EtOH and EtOAc, the residue was diluted with H_2O (30 mL) and extracted with EtOAc (10 mL×3). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was used for next step without purification. A small sample was purified by column chromatography [SiO_2, *V*(petroleum ether)∶*V*(EtOAc)=6∶1] to afford **10** as a colorless oil. $[\alpha]_D^{15}$ +135.7 (*c* 2.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 6.17 (dd, *J*=9.6, 2.6 Hz, 1H), 5.91 (dd, *J*=9.6, 3.3 Hz, 1H), 4.54～4.48 (m, 2H), 4.25～4.07 (m, 3H), 3.91 (d, *J*=10.4 Hz, 1H), 3.69～3.63 (m, 2H), 3.58 (d, *J*=11.8 Hz, 1H), 3.29 (s, 3H), 2.83～2.72 (m, 1H), 2.69～2.61 (m, 1H), 2.55～2.47 (m, 1H), 1.97 (td, *J*=13.3, 5.6 Hz, 1H), 1.90 (s, 3H), 1.25 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 210.8, 170.8, 143.7, 128.2, 127.9, 127.5, 118.5 (q, *J*=320.1 Hz), 96.7, 68.1, 63.2, 61.8, 56.5, 55.6, 48.6, 47.2, 36.2, 29.5, 15.9, 13.8; ^{19}F NMR ($CDCl_3$, 376 MHz) *δ*: −73.18; IR (KBr) *ν*: 3475, 2942, 2891, 1720, 1408, 1215, 1141, 1106, 1043, 887, 817, 759, 666, 593 cm^{-1}; HRMS calcd for $C_{19}H_{26}F_3O_9S$ $(M+H)^+$ 487.1244, found 487.1236.

4.2.10 Synthesis of (4a*R*,8a*S*)-ethyl 1-((methoxymethoxy)methyl)-6-methyl-2-*oxo*-5-(((trifluoromethyl)sulfonyl)oxy)-1,2,3,4,4a,8a-hexahydronaphthalene-4a-carboxylate (**11**)

To a stirred solution of **9** (50 mg, 0.10 mmol, 1.0 equiv.) in EtOH (1 mL) were added H_2O (1 mL), NH_4Cl (53 mg, 1.0 mmol, 10.0 equiv.) and Fe powder (56 mg, 1.0 mmol, 10.0 equiv.) at room temperature, the mixture was warmed up to 60 ℃ and stirred for 6 h. The reaction was cooled down to room temperature and passed through a pad of celite, the filtercake was washed with EtOAc and the filtrate was concentrated to remove most of EtOH and EtOAc, the residue was diluted with H_2O (3 mL) and extracted with EtOAc (1 mL×3). The combined organic layer was washed with brine (3 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography [SiO_2, *V*(petroleum ether)∶*V*(EtOAc)=6∶1] to afford **11** (39 mg, 0.086 mmol) as a colorless oil with 84% yield. $[\alpha]_D^{15}$ +63.8 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) *δ*: 6.03 (d, *J*=9.4 Hz, 1H), 5.89 (d, *J*=9.4 Hz, 1H), 4.61 (d, *J*=6.4 Hz, 1H), 4.54 (d, *J*=6.4 Hz, 1H), 4.23～4.08 (m, 3H), 3.72 (d, *J*=10.0 Hz, 1H), 3.33～3.23 (m, 5H), 2.59～2.32 (m, 3H), 2.14～2.03 (m, 1H), 1.91 (s, 3H), 1.24 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 207.6, 170.7, 143.7, 130.9, 127.5, 127.2, 118.8 (q, *J*=320.3 Hz), 96.9, 62.9, 61.8, 55.5, 49.7, 49.0, 44.2, 37.0, 28.8, 15.8, 14.0; ^{19}F NMR ($CDCl_3$, 376 MHz) *δ*: −73.43; IR (KBr) *v*: 2961, 2924, 2362, 2334, 1721, 1407, 1260, 1214, 1095, 1021, 801 cm^{-1}; HRMS calcd for $C_{18}H_{23}F_3NaO_8S$ $(M+Na)^+$ 479.0958, found 479.0952.

4.2.11 Synthesis of (1*S*,4a*R*,8a*S*)-ethyl 1-((methoxymethoxy)methyl)-6-methyl-1-(((methylsulfonyl)oxy)methyl)-2-*oxo*-5-(((trifluoromethyl)sulfonyl)oxy)-1,2,3,4,4a,8a-hexahydronaphthalene-4a-carboxylate (**12**)

To a stirred solution of crude **10**, Et_3N (1.2 mL, 0.80 mmol, 2.0 equiv.) and 4-dimethylaminopyridine (DMAP) (50 mg, 0.39 mmol, 0.1 equiv.) in DCM (20 mL) was added MsCl (670 mg, 5.85 mmol, 1.5 equiv.) at 0 ℃, and the mixture was stirred for 30 min at the same temperature. The reaction was quenched with saturated aq. $NaHCO_3$ solution (10 mL) and extracted with DCM (10 mL×2). The combined organic layer was washed with 1 mol/L HCl (10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was used for next step without purification. A small sample was purified by column chromatography [SiO_2, *V*(petroleum ether)∶*V*(EtOAc)=6∶1] to afford **12** as a colorless oil. $[\alpha]_D^{15}$ +126.6 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 6.14 (dd, *J*=9.7, 2.3 Hz, 1H), 5.96 (dd, *J*=9.7, 3.1 Hz, 1H), 4.79 (d, *J*=10.1 Hz, 1H), 4.70～4.53 (m, 2H), 4.28 (d, *J*=10.1 Hz, 1H), 4.24～4.09 (m, 2H), 3.84 (d, *J*=10.6 Hz, 1H), 3.73 (d, *J*=10.7 Hz, 1H), 3.62～3.59 (m, 1H), 3.29 (s, 3H), 3.07 (s, 3H), 2.87～2.76 (m, 1H), 2.71～2.62 (m, 1H), 2.59～2.51 (m, 1H), 1.99 (td, *J*=13.4, 5.4 Hz, 1H), 1.92 (s, 3H), 1.27 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 206.5, 170.6, 143.4, 128.4, 128.2 126.6, 118.7 (q, *J*=320.4 Hz), 96.7, 69.4, 67.8, 62.2, 55.8, 54.7, 48.6, 46.7, 37.0, 35.9, 31.7, 29.3, 16.0, 13.8; ^{19}F NMR ($CDCl_3$, 376 MHz) *δ*: −73.05; IR (KBr) *v*: 2955, 1723, 1457, 1408, 1359, 1216, 1175, 1139, 1106, 1042, 955, 850, 815, 756 cm^{-1}; HRMS calcd for $C_{20}H_{28}F_3O_{11}S_2$ $(M+H)^+$ 565.1020, found 565.1018.

4.2.12 Synthesis of (1*S*,4a*R*,7*S*,8*R*,8a*S*)-ethyl 7,8-dihydroxy-1-((methoxymethoxy)methyl)-6-methyl-1-(((methylsulfonyl)oxy)methyl)-2-*oxo*-5-(((trifluoromethyl)sulfonyl)oxy)-1,2,3,4,4a,7,8,8a-octahydronaphthalene-4a-carboxylate (**13**)

To a stirred solution of crude **12** in THF (12 mL), ^{t}BuOH (12 mL) and H_2O (3 mL) were added NMO (673 mg, 5.85 mmol, 1.5 equiv.) and OsO_4 (0.16 mol/L in THF, 1.2 mL, 0.19 mmol, 0.05 equiv.) at 0 ℃, and the mixture was stirred overnight at room temperature. The reaction was quenched with saturated aq. $Na_2S_2O_3$ solution (10 mL) and the stirring was continued for 30 min. The mixture was diluted with H_2O (20 mL) and extracted with EtOAc (10 mL×3). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by column chromatography [SiO_2, *V*(petroleum ether)∶*V*(EtOAc)=3∶1 to 1∶1] to afford **13** (1.64 g, 2.74 mmol) as a white solid with 70% (3 steps) yield. m.p. 138～140 ℃; $[\alpha]_D^{15}$ +51.3 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 4.77 (d, *J*=9.6 Hz, 1H), 4.67～4.62 (m, 2H), 4.56～4.49 (m, 2H), 4.38 (d, *J*=9.6 Hz, 1H), 4.33 (d, *J*=3.3 Hz, 1H), 4.23～4.07 (m, 2H), 4.01 (d, *J*=10.9 Hz, 1H), 3.68 (d, *J*=10.9 Hz, 1H), 3.38 (s, 3H), 3.10 (d, *J*=11.4 Hz, 1H), 3.01 (s, 3H), 2.97 (brs, 1H), 2.86 (ddd, *J*=17.1, 10.1, 5.1 Hz, 1H), 2.69～2.52 (m, 2H), 2.08～2.02 (m, 1H), 2.01 (s, 3H), 1.28 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 207.4, 171.4, 144.9, 129.6, 118.49 (q, *J*=319.6 Hz), 97.4, 73.4, 70.5, 67.2, 66.9, 63.1, 56.3, 53.7, 50.2, 41.9, 37.4, 35.7, 28.3, 15.5, 13.6; ^{19}F NMR ($CDCl_3$, 376 MHz) *δ*: −74.00; IR (KBr) *v*: 2955, 1723, 1457, 1408, 1359, 1216, 1175, 1139, 1106, 1042, 955, 850, 815, 756 cm^{-1}; HRMS cacld for $C_{20}H_{33}F_3NO_{13}S_2$ $(M+NH_4)^+$ 616.1340, found 616.1332.

4.2.13 Synthesis of (2a*R*,2a^1*S*,5a*R*,8*S*,8a*R*)-ethyl 8-hydroxy-2a-((methoxymethoxy)methyl)-7-methyl-3-*oxo*-6-(((trifluoromethyl)sulfonyl)oxy)-2a,2a1,3,4,5,5a,8,8a-octahydro-2*H*-naphtho[1,8-*bc*]furan-5a-carboxylate (**14**)

To a stirred solution of **13** (660 mg, 1.10 mmol, 1.0 equiv.) in toluene (11 mL) was added DIEA (712 mg, 5.52 mmol, 5.0 equiv.) at room temperature, the mixture was warmed up to 100 ℃ and stirred for 3 d. After cooled to room temperature, the mixture was directly concentrated in vacuo. The resulting residue was purified by column chromatography [SiO_2, *V*(petroleum ether)∶*V*(EtOAc)=3∶1] to afford **14** (415 mg, 0.83 mmol) as a yellow solid with 75% yield. m.p. 66～68 ℃; $[\alpha]_D^{15}$ +81.5 (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 4.59～4.51 (m,

3H), 4.45 (d, J=4.6 Hz, 1H), 4.32～4.20 (m, 3H), 4.05 (d, J=8.8 Hz, 1H), 3.79 (d, J=9.7 Hz, 1H), 3.64 (d, J=9.7 Hz, 1H), 3.29 (s, 3H), 3.16～3.03 (m, 1H), 2.89 (dd, J=13.0, 6.4 Hz, 1H), 2.53～2.44 (m, 2H), 2.02 (s, 3H), 1.83 (td, J=13.2, 5.0 Hz, 1H), 1.34 (t, J=7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 206.2, 170.0, 146.5, 133.2, 118.54 (q, J=319.9 Hz) 96.6, 73.2, 72.5, 68.9, 64.9, 63.0, 56.9, 55.7, 51.3, 48.8, 37.3, 33.9, 16.7, 13.8; ^{19}F NMR ($CDCl_3$, 400 MHz) δ: −78.43; IR (KBr) ν: 2944, 2894, 1726, 1408, 1215, 1140, 1100, 1039, 950, 877, 757 cm^{-1}; HRMS calcd for $C_{19}H_{29}F_3NO_{10}S$ $(M+NH_4)^+$ 520.1459, found 520.1455.

4.2.14 Synthesis of (2a*R*,2a^1*S*,5a*S*,8*S*,8a*R*)-ethyl 8-hydroxy-2a-((methoxymethoxy)methyl)-7-methyl-3-*oxo*-2a,2a1,3,4,5,5a,8,8a-octahydro-2*H*-naphtho[1,8-*bc*]furan-5a-carboxylate (**15**)

To a stirred solution of **14** (80 mg, 0.16 mmol, 1.0 equiv.) in DMF (1 mL) were added $Pd(OAc)_2$ (7 mg, 0.032 mmol, 0.2 equiv.), dppf (22 mg, 0.04 mmol, 0.25 equiv.), Et_3N (138 mg, 0.96 mmol, 6.0 equiv.) and HCO_2H (37 mg, 0.80 mmol, 5.0 equiv.) sequentially at room temperature, the mixture was warmed up to 70 ℃ and stirred overnight. After cooled to room temperature, the mixture was diluted with H_2O (6 mL) and extracted with EtOAc (2 mL×3). The combined organic layer was washed with brine (2 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by column chromatography [SiO_2, *V*(petroleum ether)∶*V*(EtOAc)=6∶1 to 3∶1] to afford **15** (49 mg, 0.14 mmol) as a colorless oil with 87% yield. $[\alpha]_D^{15}$ +98.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.51 (s, 1H), 4.61～4.48 (m, 3H), 4.27～4.13 (m, 4H), 4.01 (d, J=8.8 Hz, 1H), 3.76～3.64 (m, 2H), 3.27 (s, 3H), 2.93～2.71 (m, 2H), 2.65 (brs, 1H), 2.37 (dd, J=14.7, 4.0 Hz, 1H), 2.23 (d, J=12.3 Hz, 1H), 1.89 (s, 3H), 1.59 (td, J=13.1, 4.8 Hz, 1H), 1.30 (t, J=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 207.5, 172.8, 139.4, 127.1, 96.6, 74.1, 72.6, 68.3, 66.3, 61.8, 57.4, 55.6, 49.9, 46.2, 37.6, 36.4, 22.1, 14.1; IR (KBr) ν: 2959, 1719, 1450, 1389, 1266, 1207, 1153, 1103, 1035, 801, 755 cm^{-1}; HRMS cacld for $C_{18}H_{27}O_7$ $(M+H)^+$ 355.1750, found 355.1751.

4.2.15 Synthesis of (5a*R*,9a*S*,9b*S*)-ethyl 9b-((methoxymethoxy)methyl)-7-methyl-6-((trimethylsilyl)-ethynyl)1,4,5,5a,9a,9b-hexahydronaphtho[2,1-*c*]isoxazole-5a-carboxylate (**16**)

To a stirred solution of **9** (1.0 g, 2.07 mmol, 1.0 equiv.) in THF (10 mL) and Et_3N (2 mL) were added trimethylsilylacetylene (0.6 mL, 4.13 mmol, 2.0 equiv.), CuI (59 mg, 0.31 mmol, 0.15 equiv.) and $Pd(PPh_3)_4$ (167 mg, 0.14 mmol, 0.07 equiv.) sequentially at room temperature, and the mixture was stirred for 5 h at same temperature. The reaction was quenched with H_2O (20 mL), and the mixture was extracted with EtOAc (8 mL×3). The combined organic layer was washed with brine (8 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by column chromatography [SiO_2, *V*(petroleum ether)∶*V*(EtOAc)=8∶1] to afford **16** (694 mg, 1.60 mmol) as a light brown oil with 77% yield. $[\alpha]_D^{18}$ +65.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.95 (dd, J=9.6, 3.1 Hz, 1H), 5.89 (dd, J=9.6, 2.5 Hz, 1H), 4.68 (d, J=7.9 Hz, 1H), 4.61～4.53 (m, 2H), 4.13～4.06 (m, 2H), 3.90 (d, J=7.9 Hz, 1H), 3.63～3.54 (m, 2H), 3.31 (s, 3H), 3.03～2.93 (m, 2H), 2.82～2.75 (m, 1H), 2.40 (td, J=14.2, 4.7 Hz, 1H), 1.96 (s, 3H), 1.56 (td, J=13.8, 4.4 Hz, 1H), 1.23 (t, J=7.1 Hz, 3H), 0.20 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 171.6, 160.0, 141.9, 128.9, 128.4, 118.7, 104.3, 101.2, 96.6, 77.4, 67.0, 61.0, 59.1, 55.6, 51.6, 46.8, 34.9, 21.2, 20.8, 14.0, 0.1; IR (KBr) ν: 2963, 2902, 2132, 1722, 1445, 1264, 1210, 1102, 1039, 849, 801, 757 cm^{-1}; HRMS cacld for $C_{23}H_{34}NO_5Si$ $(M+H)^+$ 432.2201, found 432.2204.

4.2.16 Synthesis of (1*R*,4a*R*,8a*S*)-ethyl 1-(hydroxymethyl)-1-((methoxymethoxy)methyl)-6-methyl-2-*oxo*-5-((trimethylsilyl)ethynyl)-1,2,3,4,4a,8a-hexahydronaphthalene-4a-carboxylate (**17**)

To a stirred solution of **16** (640 mg, 1.48 mmol, 1.0 equiv.) in EtOH (10 mL) were added H_2O (10 mL) and Fe powder (1.24 g, 22.2 mmol, 15 equiv.) at room temperature, and the mixture was warmed up to 70 ℃. AcOH (1.78 g, 29.6 mmol, 20 equiv.) was added dropwise and stirred for 6 h at same temperature. The reaction was cooled to room temperature and quenched with saturated aq. $NaHCO_3$ (10 mL), the resulting mixture was passed through a pad of celite and the filtercake was washed with EtOAc. The filtrate was concentrated to remove most of EtOH and EtOAc, the residue was diluted with H_2O (5 mL) and extracted with EtOAc (8 mL×3). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by column chromatography [SiO_2, *V*(petroleum ether)∶*V*(EtOAc)=6∶1] to afford **17** (490 mg, 1.13 mmol) as a colorless oil with 76% yield. $[\alpha]_D^{18}$ +8.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.15 (dd, J=9.7, 2.9 Hz, 1H), 5.97 (dd, J=9.8, 3.3 Hz, 1H), 4.53～4.48 (q, J=6.6 Hz, 2H), 4.31 (dd, J=12.0, 5.6 Hz, 1H), 4.17～4.09 (m, 2H), 3.90 (d, J=10.5 Hz, 1H), 3.66 (d, J=10.5 Hz, 1H), 3.60～3.50 (m, 1H), 3.38～3.36 (m, 1H), 3.27 (s, 3H), 2.94 (ddd, J=13.9, 5.4, 2.9 Hz, 1H), 2.67 (td, J=14.7, 5.6 Hz, 1H), 2.49～2.42 (m, 1H), 2.20～2.15 (m, 1H), 1.98 (s, 3H), 1.83 (td, J=14.1, 4.2 Hz, 1H), 1.23 (d, J=7.1 Hz, 3H), 0.21 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 212.6, 172.0, 142.2, 129.0, 128.4, 118.8, 103.6, 101.4, 96.6, 68.2, 62.2, 61.0, 57.0, 55.6, 46.4, 44.5, 37.5, 33.8, 20.6, 14.0, 0.2; IR (KBr) ν: 3483, 2960, 2897, 2132, 1718, 1450, 1257, 1211, 1104, 1040, 849, 757 cm^{-1}; HRMS cacld for $C_{23}H_{35}O_6Si$ $(M+H)^+$ 435.2197, found 435.2199.

4.2.17 Synthesis of (4a*R*,8a*S*)-ethyl 1-((methoxymethoxy)methyl)-6-methyl-2-*oxo*-5-((trimethylsilyl)ethynyl)-1,2,3,4,4a,8a-hexahydronaphthalene-4a-carboxylate (**18**)

To a stirred solution of **16** (50 mg, 0.12 mmol, 1.0

equiv.) in EtOH (1 mL) were added H_2O (1 mL) and Fe powder (97 mg, 1.73 mmol, 15 equiv.) at room temperature, and the mixture was warmed up to 70 ℃. AcOH (104 mg, 1.73 mmol, 15 equiv.) was added dropwise and stirred for 6 h at same temperature. The reaction was cooled to room temperature and quenched with saturated aq. $NaHCO_3$ (1 mL), the resulting mixture was passed through a pad of celite and the filtercake was washed with EtOAc. The filtrate was concentrated to remove most of EtOH and EtOAc, the residue was diluted with H_2O (3 mL) and extracted with EtOAc (1 mL×3). The combined organic layer was washed with brine (1 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by column chromatography [SiO_2, *V*(petroleum ether)∶*V*(EtOAc)=10∶1 to 4∶1] to afford **17** (33 mg, 0.076 mmol) and **18** (7 mg, 0.017 mmol) sequentially.

Compound **17**: Colorless oil, 65% yield.

Compound **18**: Colorless oil, 15% yield. $[\alpha]_D^{18}$ −99.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 6.06 (dd, *J*=9.6, 2.1 Hz, 1H), 5.93 (dd, *J*=9.6, 2.9 Hz, 1H), 4.60 (d, *J*=6.5 Hz, 1H), 4.52 (d, *J*=6.5 Hz, 1H), 4.15～4.06 (m, 3H), 3.74 (dd, *J*=10.1, 3.3 Hz, 1H), 3.29 (s, 3H), 3.23～3.17 (m, 1H), 3.00～2.93 (m, 1H), 2.75～2.65 (m, 1H), 2.55～2.46 (m, 1H), 2.33～2.18 (m, 1H), 1.99 (s, 3H), 2.03～1.91 (m, 1H), 1.21 (t, *J*=7.1 Hz, 3H), 0.20 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 208.7, 172.1, 141.6, 131.8, 128.1, 118.6, 103.0, 102.2, 96.8, 62.7, 60.9, 55.4, 49.7, 47.2, 41.8, 38.2, 32.6, 20.4, 14.2, 0.2; IR (KBr) *v*: 2962, 2136, 1719, 1453, 1264, 1101, 1038, 850, 802, 755 cm^{-1}; HRMS cacld for $C_{22}H_{32}NaO_5Si$ $(M+Na)^+$ 427.1911, found 427.1915.

4.2.18 Synthesis of (1*S*,4a*R*,8a*S*)-ethyl 1-((methoxymethoxy)methyl)-6-methyl-1-(((methylsulfonyl)oxy)methyl)-2-*oxo*-5-((trimethylsilyl)ethynyl)-1,2,3,4,4a,8a-hexahydronaphthalene-4a-carboxylate (**19**)

To a stirred solution of **17** (480 mg, 1.10 mmol, 1.0 equiv.), Et_3N (0.32 mL, 2.21 mmol, 2.0 equiv.) and DMAP (13 mg, 0.11 mmol, 0.1 equiv.) in DCM (10 mL) was added MsCl (189 mg, 1.66 mmol, 1.5 equiv.) at 0 ℃, and the mixture was stirred for 0.5 h at the same temperature. The reaction was quenched with saturated aq. $NaHCO_3$ solution (10 mL) and extracted with DCM (5 mL×2). The combined organic layer was washed with 1 mol/L HCl (5 mL) and brine (5 mL), dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was used for next step without purification. A small sample was purified by column chromatography [SiO_2, *V*(petroleum ether)∶*V*(EtOAc)=5∶1] to afford **19** as a colorless oil. $[\alpha]_D^{18}$ +18.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 6.10 (dd, *J*=9.7, 2.7 Hz, 1H), 5.99 (dd, *J*=9.7, 3.2 Hz, 1H), 4.88 (d, *J*=10.1 Hz, 1H), 4.51～4.44 (m, 2H), 4.24 (d, *J*=10.1 Hz, 1H), 4.16～4.09 (m, 2H), 3.81 (d, *J*=10.8 Hz, 1H), 3.72 (d, *J*=10.8 Hz, 1H), 3.34～3.31 (m, 1H), 3.25 (s, 3H), 3.06 (s, 3H), 2.96～2.89 (m, 1H), 2.70～2.59 (m, 1H), 2.53～2.46 (m, 1H), 1.98 (s, 3H), 1.84 (td, *J*=14.2, 4.2 Hz, 1H), 1.23 (t, *J*=7.1 Hz, 3H), 0.20 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 207.3, 171.8, 142.3, 129.1, 127.4, 118.7, 104.2, 101.1, 96.5, 68.6, 67.9, 61.2, 55.7, 55.2, 46.3, 44.1, 36.9, 36.8, 33.3, 31.7, 20.6, 14.0, 0.2; IR (KBr) *v*: 2960, 2901, 2133, 1720, 1457, 1358, 1174, 1104, 1040, 962, 849, 755 cm^{-1}; HRMS cacld for $C_{24}H_{36}NaO_8SSi$ $(M+Na)^+$ 535.1792, found 535.1796.

4.2.19 Synthesis of (1*S*,4a*R*,7*S*,8*R*,8aS)-ethyl 7,8-dihydroxy-1-((methoxymethoxy)methyl)-6-methyl-1-(((methylsulfonyl)oxy)methyl)-2-*oxo*-5-((trimethylsilyl)ethynyl)-1,2,3,4,4a,7,8,8a-octahydronaphthalene-4a-carboxylate (**20**)

To a stirred solution of crude **19** in THF (6 mL), ^{t}BuOH (6 mL) and H_2O (1.5 mL) were added NMO (167 g, 1.43 mmol, 1.3 equiv.) and OsO_4 (0.16 mol/L in THF, 0.34 mL, 0.055 mmol, 0.05 equiv.) at 0 ℃, and the mixture was stirred overnight at room temperature. The reaction was quenched with saturated aq. $Na_2S_2O_3$ solution (6 mL) and the stirring was continued for 0.5 h. The mixture was diluted with H_2O (6 mL) and extracted with EtOAc (6 mL×4). The combined organic layer was washed with brine (6 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by column chromatography [SiO_2, *V*(petroleum ether)∶*V*(EtOAc)=4∶1 to 1∶1] to afford **20** (422 mg, 0.77 mmol) as a light brown solid with 70% (2 steps) yield. m.p. 136～138 ℃; $[\alpha]_D^{18}$ +109.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 4.79 (d, *J*=9.4 Hz, 1H), 4.74～4.65 (m, 1H), 4.60～4.54 (m, 2H), 4.54 (d, *J*=9.5 Hz, 1H), 4.18～4.08 (m, 4H), 3.92 (d, *J*=10.5 Hz, 1H), 3.68 (d, *J*=10.5 Hz, 1H), 3.32 (s, 3H), 3.01 (s, 4H), 2.85～2.74 (m, 3H), 2.67～2.56 (m, 1H), 2.07 (s, 3H), 1.84～1.75 (m, 1H), 1.24 (t, *J*=7.1 Hz, 3H), 0.15 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 208.7, 173.1, 142.5, 122.4, 101.9, 100.4, 97.1, 73.0, 70.9, 67.3, 67.1, 61.8, 56.1, 54.3, 50.1, 41.1, 37.3, 36.9, 31.5, 20.6, 14.0, 0.0; IR (KBr) *v*: 3484, 2960, 2143, 1719, 1453, 1354, 1255, 1174, 1100, 1041, 967, 849, 756 cm^{-1}; HRMS calcd for $C_{24}H_{38}NaO_{10}SSi$ $(M+Na)^+$ 569.1847, found 569.1850.

4.2.20 Synthesis of (5a*R*,9a*S*,9b*S*)-ethyl 9b-((methoxymethoxy)methyl)-7-methyl-6-((trimethylsilyl)ethynyl)-1,4,5,5a,9a,9b-hexahydronaphtho[2,1-*c*]isoxazole-5a-carboxylate (**1**)

To a stirred solution of **20** (400 mg, 0.73 mmol, 1.0 equiv.) in toluene (10 mL) was added DIEA (473 mg, 3.66 mmol, 5.0 equiv.) at room temperature, the mixture was warmed up to 110 ℃ and stirred for 24 h. After cooled to room temperature, the mixture was directly concentrated in vacuo. The resulting residue was purified by column chromatography [SiO_2, *V*(petroleum ether)∶*V*(EtOAc)=4∶1] to afford **1** (329 mg, 0.52 mmol) as a light yellow solid with 71% yield. m.p. 120～122 ℃; $[\alpha]_D^{19}$ +123.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 4.56～4.48 (m, 3H), 4.33 (d, *J*=4.5 Hz, 1H), 4.28～4.18 (m, 3H), 4.00 (d, *J*=8.0 Hz, 1H), 3.73 (d, *J*=9.9 Hz, 1H), 3.63 (d, *J*=9.9 Hz, 1H), 3.27 (s, 3H), 3.03～2.89 (m, 2H), 2.64 (s, 1H), 2.43 (dd, *J*=13.9, 4.8 Hz, 1H), 2.27 (d, *J*=12.4 Hz, 1H), 2.09 (s, 3H), 1.70～1.58 (m, 1H), 1.31 (t, *J*=7.1 Hz,

3H), 0.17 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 207.7, 172.0, 144.8, 122.1, 103.0, 99.7, 96.6, 73.3, 72.6, 68.7, 65.8, 62.0, 57. 2, 55.6, 49.7, 48.3, 37.8, 36.1, 21.5, 14.2, 0.02; IR (KBr) v: 3429, 2960, 2898, 2143, 1722, 1447, 1258, 1190, 1151, 1101, 1038, 850, 752 cm^{-1}; HRMS cacld for $C_{23}H_{34}NaO_7Si$ $(M+Na)^+$ 473.1966, found 473.1970.

Supporting Information ^{1}H NMR and ^{13}C NMR spectra of new compounds. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn/.

References

[1] Schmutterer, H. *The Neem Tree*, Wiley-VCH, Weinheim, **1995**.

[2] (a) Buterworth, J. H.; Morgan, E. D. *Chem. Commun.* **1968**, *35*, 23.
(b) Morgan, E. D. *Bioorg. Med. Chem.* **2009**, *17*, 4096.

[3] (a) Mordue (Luntz), A. J.; Simmonds, M. S. J.; Ley, S. V.; Blaney, W. M.; Mordue, W.; Nasiruddin, M.; Nisbet, A. J. *Pestic. Sci.* **1998**, *54*, 277.
(b) Ley, S. V.; Denholm, A. A.; Wood, A. *Nat. Prod. Rep.* **1993**, *10*, 109.

[4] Denholm, A. A.; Jennens, L.; Ley, S. V.; Wood, A. *Tetrahedron* **1995**, *51*, 6591.

[5] (a) Veitch, G. E.; Boyer, A.; Ley, S. V. *Angew. Chem., Int. Ed.* **2008**, *47*, 9402.
(b) Veitch, G. E.; Beckmann, E.; Burke, B. J.; Boyer, A.; Maslen, S. L.; Ley, S. V. *Angew. Chem., Int. Ed.* **2007**, *46*, 7629.
(c) Veitch, G. E.; Beckmann, E.; Burke, B. J.; Boyer, A.; Ayats, C.; Ley, S. V. *Angew. Chem., Int. Ed.* **2007**, *46*, 7633.
(d) Ley, S. V.; Abad-Somovilla, A.; Anderson, J. C.; Ayats, C.; Bänteli, R.; Beckmann, E.; Boyer, A.; Brasca, M. G.; Brice, A.; Broughton, H. B.; Burke, B. J.; Cleator, E.; Craig, D.; Denholm, A. A.; Denton, R. M.; Durand-Reville, T.; Gobbi, L. B.; Göbel, M.; Gray, B. L.; Grossmann, R. B.; Gutteridge, C. E.; Hahn, N.; Harding, S. L.; Jennens, D. C.; Jennens, L.; Lovell, P. J.; Lovell, H. J.; de la Puente, M. L.; Kolb, H. C.; Koot, W.-J.; Maslen, S. L.; McCusker, C. F.; Mattes, A.; Pape, A. R.; Pinto, A.; Santafianos, D.; Scott, J. S.; Smith, S. C.; Somers, A. Q.; Spilling, C. D.; Stelzer, F.; Toogood, P. L.; Turner, R. M.; Veitch, G. E.; Wood, A.; Zumbrunn, C. *Chem.-Eur. J.* **2008**, *14*, 10683.

[6] For studies towards the left-wing fragment by the Ley group, see: (a) Ley, S. V.; Lovell, P. J.; Slawin, A. M. Z.; Smith, S. C.; Williams, D. J.; Wood, A. *Tetrahedron* **1993**, *49*, 1675.
(b) Kolb, H. C.; Ley, S. V. *Tetrahedron Lett.* **1991**, *32*, 6187.
(c) Kolb, H. C.; Ley, S. V.; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2735.
(d) Koot, W.-J.; Ley, S. V. *Tetrahedron* **1995**, *51*, 2077.
(e) Ley, S. V.; Lovell, P. J.; Smith, S. C.; Wood, A. *Tetrahedron Lett.* **1991**, *32*, 6183.

[7] (a) Kanoh, N.; Ishihara, J.; Murai, A. *Synlett* **1995**, 895.
(b) Yamamoto, Y.; Ishihara, J.; Kanoh, N.; Murai, A. *Synthesis* **2000**, 1894.
(c) Yamamoto, Y.; Ishihara, J.; Kanoh, N.; Murai, A. *Synthesis* **2000**, 1894.

[8] (a) Shi, H.; Tan, C. H.; Zhang, W. B.; Zhang, Z. C.; Long, R.; Gong, J. X.; Luo, T. P.; Yang, Z. *J. Org. Chem.* **2016**, *81*, 751.
(b) Shi, H.; Tan, C. H.; Zhang, W. B.; Zhang, Z. C.; Long, R.; Luo, T. P.; Yang, Z. *Org. Lett.* **2015**, *17*, 2342.

[9] For other synthetic studies toward azadirachtin, see: Watanabe's work: (a) Mori, N.; Kitahara, T.; Mori, K.; Watanabe, H. *Angew. Chem., Int. Ed.* **2015**, *54*, 14920.
(b) Watanabe, H.; Watanabe, T.; Mori, K.; Kitahara, T. *Tetrahedron Lett.* **1997**, *38*, 4429.
Tanino's work: (c) Sakurai, K.; Tanino, K. *Tetrahedron Lett.* **2015**, *56*, 496.
Nicolaou's work: (d) Nicolaou, K. C.; Sasmal, P. K.; Koftis, T. V.; Converso, A.; Loizidou, E.; Kaiser, F.; Roecker, A. J.; Dellios, C. C.; Sun, X.-W.; Petrovic, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 3447.
(e) Nicolaou, K. C.; Sasmal, P. K.; Roecker, A. J.; Sun, X.-W.; Mandal, S.; Converso, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3443.
(f) Nicolaou, K. C.; Roecker, A. J.; Monenschein, H.; Guntupalli, P.; Follmann, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3637.
(g) Nicolaou, K. C.; Follmann, M.; Roecker, A. J.; Hunt, K. W. *Angew. Chem., Int. Ed.* **2002**, *41*, 2103.
(h) Nicolaou, K. C.; Roecker, A. J.; Follmann, M.; Baati, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2107.

[10] Dong, C. M.; Qiao, T. J.; Xie, Y.; Zhang, X.; Ao, J. L.; Liang, G. X. *Org. Chem. Front.* **2020**, *7*, 1890.

[11] (a) Kobayashi, K.; Kunimura, R.; Takagi, H.; Hirai, M.; Kogen, H.; Hirota, H.; Kuroda, C. *J. Org. Chem.* **2018**, *83*, 703.
(b) Xuan, M.; Paterson, I.; Dalby, S. M. *Org. Lett.* **2012**, *14*, 5492.

[12] Jiang, D. H.; Chen, Y. W. *J. Org. Chem.* **2008**, *73*, 9181.

[13] Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024.

[14] Stepanov, A. V.; Veselovsky, V. V. *Russ. Chem. Bull.* **2002**, *51*, 359.

[15] Baraldi, P. G.; Barco, A.; Benetti, S.; Manfredini, S.; Simoni, D. *Synthesis* **1987**, 276.

(Cheng, F.)

