JOC The Journal of Organic Chemistry

Article

Formal Total Synthesis of Atropurpuran

Takahiro Suzuki, Takeshi Koyama, Kenta Nakanishi, Susumu Kobayashi, and Keiji Tanino

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.0c01462 • Publication Date (Web): 16 Jul 2020

Formal Total Synthesis of Atropurpuran

Takahiro Suzuki,*,† Takeshi Koyama,‡ Kenta Nakanishi,‡ Susumu Kobayashi,§ Keiji Tanino*,†

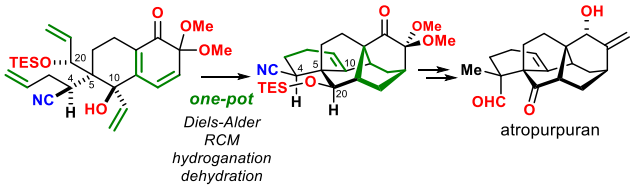
†Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo, 060-0810, Hokkaido, Japan

‡Graduate School of Chemical Sciences and Engineering, Hokkaido University, Sapporo, 060-0810, Hokkaido, Japan

§Faculty of Pharmaceutical Sciences, Tokyo University of Science, 2641 Yamazaki, Noda, Chiba 278-8510, Japan

E-mail: takahiro-suzuki@sci.hokudai.ac.jp (T. Suzuki); ktanino@sci.hokudai.ac.jp (K. Tanino)

ABSTRACT: Atropurpuran, isolated from the roots of *Aconitum hemsleyanum*, is a non-alkaloidal diterpene which possesses a unique pentacyclic skeleton that contains an unprecedented tetracyclo[5.3.3.$0^{4,9}$.$0^{4,12}$]tridecane unit. We report herein the formal total synthesis of atropurpuran. The key features of our synthetic route are a high diastereoselective construction of the tri- and tetrasubstituted carbons (i.e., C4, C5, C10, C20) through an Yb-catalyzed Mukaiyama aldol reaction in an aqueous medium and a one-pot operation including an intramolecular Diels-Alder reaction/ring-closing metathesis to construct the unique pentacyclic skeleton of atropurpuran.



INTRODUCTION

The *Aconitum* and *Delphinium* plants, which have been used as poisons and herbal medicines since ancient times, are known as a rich source of C18, C19, and C20 diterpene alkaloids.[1] These alkaloids have been well studied in terms of their chemical syntheses and medicinal chemistry due to their range of biological activities. However, the study of non-alkaloidal diterpenes from the genera *Aconitum*[2] and *Delphinium* has rarely been reported. The isolation of atisenol[3] (**1**) from A. *heterophylllum* was first reported in 1982, and recently, after a lapse of many years, three diterpenes, namely campylopin[4] (**2**), Guan Fu diterpenoid A[5] (**3**), and atropurpuran[6] (**4**) were isolated (Figure 1). This led to debate regarding the biogenesis of diterpene alkaloids, i.e., whether these diterpenes are biosynthetic intermediates or degradation products of the corresponding diterpene alkaloids.[7] Notably, atropurpuran possesses a novel pentacyclic skeleton, which is only present in three diterpene alkaloids, namely arcutines[8] (**5a–5c**), isolated from A. *arcuatum* Maxim. The biosyntheses of **4** and **5a–5c** has been proposed to include a 1,2-shift of the C10–C20 bond of the hetidane skeleton to form the C5–C20 bond; recently, a bioinspired Wargner-Meerwein approach from hetidine to arcutine was achieved by Li et al.[9] The resulting unprecedented pentacyclic carbon skeleton of **4** and **5a–5c** has also attracted significant attention from synthetic chemists due to its unique chemical structure. More specifically, the B–E rings constitute the tetracyclo[5.3.3.$0^{4,9}$.$0^{4,12}$]tridecane skeleton, which includes two bicyclo[2.2.2]octane units. This highly symmetrical (C_{2v}) skeleton, the hydrocarbon (**6**) of which was named "dibarrelane" by our group, had previously only been found in nature prior to our reported synthesis.[10] Moreover, we proposed that **6** is an important component of a novel class of saturated cage-like hydrocarbons.[11] Thus, we embarked on the synthetic study of atropurpuran, focusing particularly on the construction of the dibarrelane skeleton, and we revealed that an intramolecular Diels-Alder (IMDA) reaction strategy using masked o-benzoquinones (MOBs) is particularly effective in the construction of this skeleton. Following our synthetic study, many synthetic studies[12] and two total syntheses of **4** were reported. It should be noted that both total syntheses, i.e., by Qin's group[13] and Xu's group,[14] adopted the intramolecular Diels-Alder reaction strategy. Very recently three total syntheses of arcutines have also been achieved.[9,15,16] Thus, we herein report the total synthesis of **4** via a single-step construction of the pentacyclic skeleton using the IMDA reaction of MOBs and a subsequent one-pot operation.

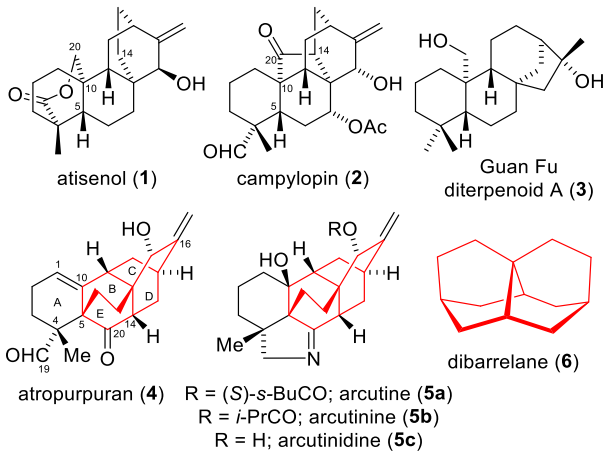
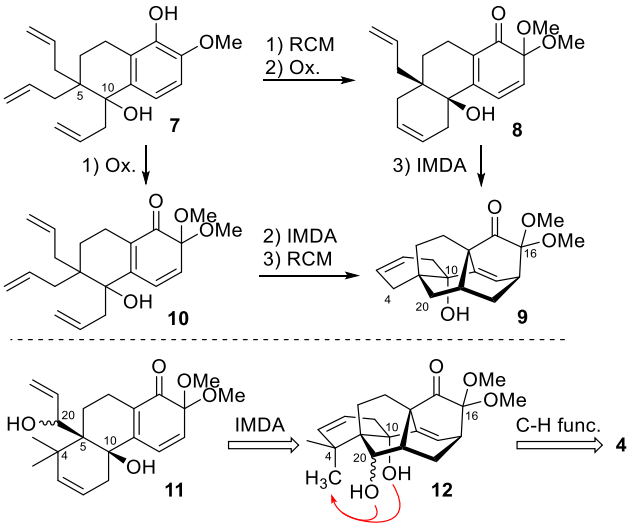


Figure 1. Atropurpuran and its related compounds (**1**-**6**)

RESULTS AND DISCUSSION

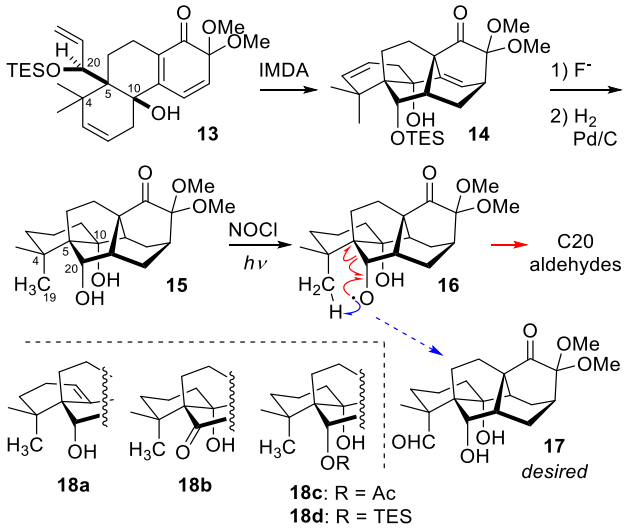
In our previous study,[10] the construction of atropurpuran skeleton **9** from phenol **7** was demonstrated using two strategies based on the IMDA reaction of MOBs (Scheme 1). One was the IMDA reaction of tricyclic MOB **8**, prepared by the ring-closing metathesis (RCM) and an oxidative dearomatization of phenol **7**. The other was the IMDA reaction of triallylated MOB **10** with a successive RCM. Applying the former method to the total synthesis of **4**, functional groups are required at the C4 and C20 positions. Thus, tricyclic MOB **11**, which possesses dimethyl groups at the C4 carbon in addition to a C20-secondary alcohol, is a potent IMDA precursor generating pentacyclic compound **12**. Then, a remote C-H functionalization directed by the hydroxyl groups at C10 and/or C20 alcohols the *exo*-methylenation at the C16 position converts pentacyclic compound **12** to atropurpouran.

Scheme 1. Previous Strategies toward the Atropurpuran skeleton



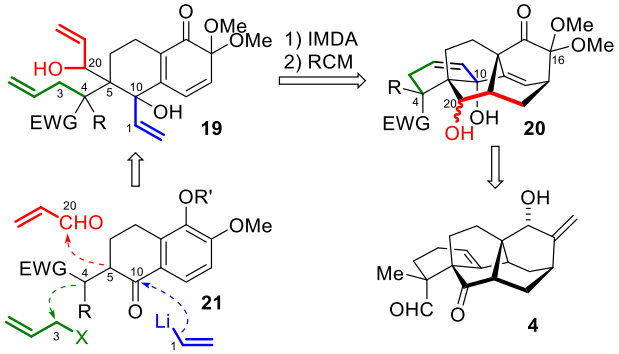
Scheme 2 illustrates our initial attempts based on the IMDA/C-H functionalization strategy. The tricyclic MOB **13** (see the Supporting Information) was successfully converted using the IMDA reaction to afford pentacyclic **14**. Removal of the TES group and hydrogenation provided diol **15** as a precursor for the C-H functionalization. The X-ray crystallographic analysis of diol **15** (see the Supporting Information) indicated that both hydroxyl groups are located within 3Å from the C19-carbon atom, enough to participate in the remote functionalization. However, all attempts using typical C-H functionalizations[17] (e.g. the Barton nitrite ester reaction, I_2/$Pb(OAc)_4$, I_2/PIDA, *etc.*) using diol **15** failed. Notably, the Barton nitrile ester reaction produced only undesired C20 aldehydes as analyzable by-products, which probably derived from an oxy-radical via a competitive C5–C20 bond cleavage. The Barton reaction using the alcohols **18a**-**18d** also resulted in the bond cleavage at C5–C20 and C5–C10 to form the more stable tertiary C5 radicals than the C19 primary radical. Transition metal-catalyzed C-H functionalizations[18] of diol **15** did not result in any reaction or failed to install the requisite directing groups. Therefore, the investigation of the IMDA/C-H functionalization strategy was pretermitted.

Scheme 2. Initial Attempts to a remote C-H Functionalization Strategy



The sequential IMDA/RCM strategy (Scheme 3) was considered next. MOB **19**, which possesses adjacent C4 and C5 quaternary carbons in addition to C20-secondary and C10-tertiary alcohols, is a potent precursor for the IMDA/RCM reaction. The key reaction should provide the pentacyclic compound **20** in a highly regio- and diastereoselective manner. Furthermore, MOB **19** could be prepared via three C-C bond-forming reactions from tetralone **21**, i.e., an aldol reaction (C5–C20), the addition of a vinyllithium reagent (C1–C10), and alkylation of the carbanion (C3–C4). These reactions, however, are particularly challenging in terms of controlling the diastereoselectivities and overcoming increasing steric repulsions. Considering its reactivity and steric advantage, the cyano group was selected as an electron withdrawing group (EWG) at the C4 position.

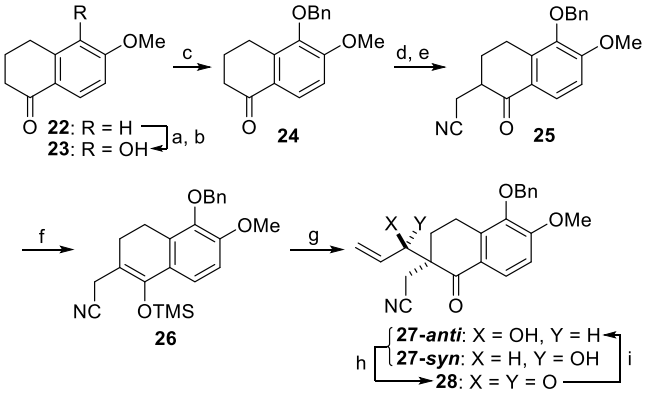
Scheme 3. IMDA/RCM Strategy toward Atropurpuran



Preparation of the MOB began with bromination of the commercial 6-methoxy-1-tetralone[19] (**22**) and subsequent Hartwig hydroxylation to give phenol **23**, the synthesis of which previously required six steps from *ortho*-eugenol as reported in our previous study (Scheme 4). Following the Bn protection of phenol **23** and a Mannich reaction of the

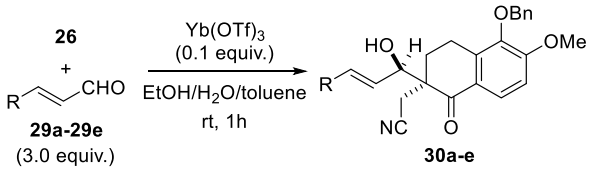
resulting tetralone **24**, treatment of the resulting mixture of β-aminoketone and enone with MeI/KCN afforded nitrile **25**.[20] After thorough investigation into the aldol reaction between nitrile **25** and acrolein,[21] we found that a lanthanoid-catalyzed Mukaiyama aldol reaction carried out in aqueous media originally reported by Kobayashi[22] was optimal. According to Baran's procedure in the total synthesis of taxol,[23] the treatment of enol silyl ether **26** with 10 equivalents of acrolein and $Yb(OTf)_3$ as a catalyst in toluene/EtOH/H_2O for 3 days provided aldol adducts **27-*anti*** and **27-*syn***, although no selectivity was observed (**27-*anti*:27-*syn*** = 1:1.3). Due to the substantial amount of impurities derived from acrolein, the purification of aldol products **27-*anti*** and **27-*syn*** was not possible. Thus, Jones oxidation of the mixture was carried out to obtain diketone **28** in 72% yield from **25**, and Luche reduction of diketone **28** afforded **27-*anti*** in 57% isolated yield as the major product (**27-*anti*:27-*syn*** = 5.7:1). Due to not only the unsatisfactory diastereoselectivities[24] in the aldol reaction and the Luche reduction, in addition to a discontinuation of sales of acrolein as a reagent, we investigated the Mukaiyama aldol reaction using other *α,β*-unsaturated aldehydes that could be easily transformed to **27-*anti*** via an olefin metathesis reaction (Table 1). The Mukaiyama aldol reaction using crotonaldehyde **29a** under the same conditions essentially reached completion within 1 h to give **30a** in an improved yield and diastereoselectivity (entry 1, 76% yield, dr = 9.9:1). The Mukaiyama aldol reaction was then repeated using bulkier aldehydes **29b–29e** (entries 2–5); however, relatively poor yields and/or selectivities were obtained. Indeed, we were unable to provide a clear explanation for the high diastereoselectivity of **30a**. However, the fact that prolongation of the reaction time resulted in a decrease in the diastereoselectivity suggested an unfavored *retro*-aldol/aldol process during the Mukaiyama aldol reaction. Notably, this result could enable an enantioselective total synthesis of **4** via a catalytic asymmetric Mukaiyama aldol reaction. (see the Supporting Information)

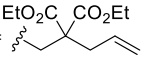
Scheme 4. Synthesis of Aldol 27-*anti*[a]



[a] Reagents and conditions: a) 47% HBr aq, 30% H_2O_2 aq., H_2O/AcOH, 54%; b) $Pd_2(dba)_3$, *t*-BuXPhos, 6M KOH aq., 1,4-dioxane, 80 °C, 61%; c) BnBr, K_2CO_3, DMF, 97%; d) HCHO aq., Me_2NH_2Cl, Ac_2O, 95 °C; e) MeI, DMF, then KCN, NH_4Cl, H_2O, 95 °C, 88% (2 steps); f) TMSOTf, Et_3N, CH_2Cl_2, 0 °C; g) acrolein, $Yb(OTf)_3$, toluene/EtOH/H_2O; h) CrO_3, acetone, 0 °C, 72% (3 steps); i) $NaBH_4$, $CeCl_3$•$7H_2O$, MeOH/CH_2Cl_2, −78 °C, 57% for **27-*anti***, 10% for **27-*syn***.

Table 1. Mukaiyama Aldol Reaction with *β*-Substituted *α,β*-Unsaturated Aldehydes

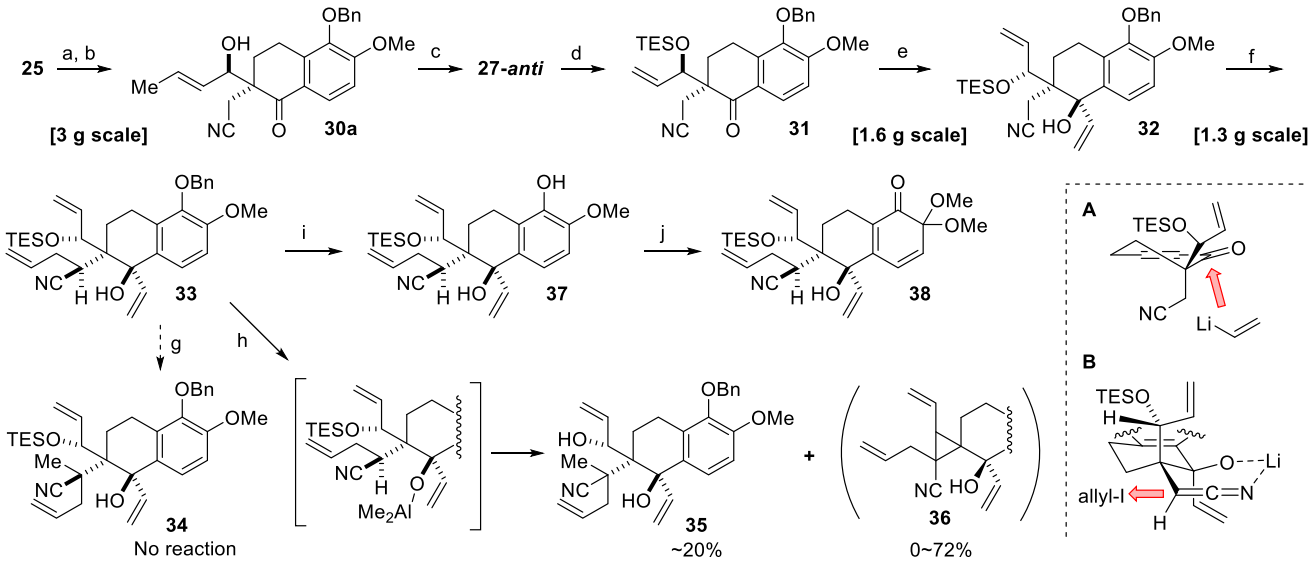


entry	aldehydes	yield of **30**[a] (%)	dr (*anti*:*syn*)
1	**29a** (R = Me)	76	9.9:1
2	**29b** (R = Ph)	76	3.0:1
3	**29c** (R = TMS)	57	3.1:1
4	**29d** (R = )	60[b]	7.9:1
5	**29e** (R =)	70[b]	5.1:1

[a] Two-step yields from ketone **25**, [b] NMR yield.

The alternative transformation from **25** to **27-*anti*** on gram-scale was subsequently achieved via a Mukaiyama aldol reaction and cross metathesis under an ethylene atmosphere in 72% yield (3 steps) and with a high diastereoselectivity (Scheme 5). Following the TES protection of **27-*anti***, an addition reaction of vinyl lithium to ketone **31** provided *tert*-alcohol **32** in 63% yield as a single diastereomer via conformer **A**. The deprotonation of **32** with $LiNEt_2$ in THF at −78 °C and allylation of the resulting α-cyanocarbanion afforded **33** in 90% yield and with a high diastereoselectivity, which could be accounted for by the chelation control effect via intermediate **B**.[25] Notably, the allylation using a diastereomer of **32** (20-*epi*-**32**, prepared from **27-syn**) under the same conditions afforded a diastereomeric mixture (see the Supporting Information). Iterative alkylation using **33** with iodomethane to construct the quaternary carbon center at the C4 position would then be expected to provide the desired product with the same stereochemistry of atropurpuran. Although the methylation of **33** under the same conditions as the allylation process gave no reaction, when $AlMe_3$ was employed to mask the hydroxy group, **33** underwent alkylation and desilylation to afford diol **35** in a low yield (~20%), along with a certain amount of cyclopropane **36** (0~72%). Due to the low yield and poor reproducibility, methylation at the C4 position was postponed to the later stages of the synthetic protocol. Removal of benzyl group of **33** with LDBB and oxidative dearomatization of the resulting phenol **37** with $PhI(OAc)_2$ gave MOB **38**.

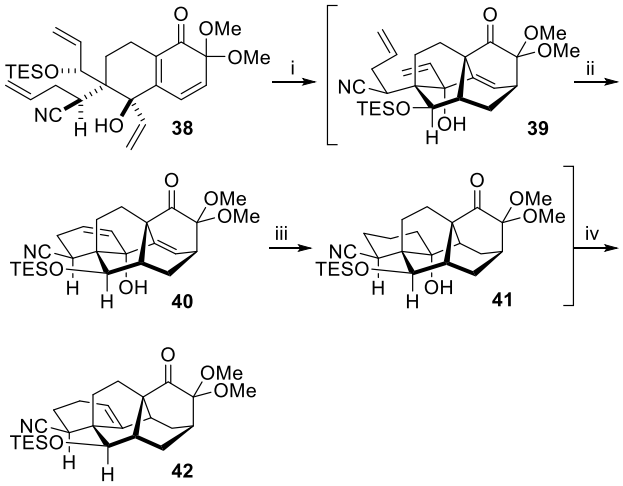
Scheme 5. Preparation of MOB 38[a]



[a] Reagents and conditions: a) TMSOTf, Et_3N, CH_2Cl_2, 0 °C; b) **29a**, $Yb(OTf)_3$, toluene/EtOH/H_2O, 0 °C; c) Hoveyda-Grubbs 2nd generation catalyst, ethylene (balloon), toluene, 72%, dr = 10/1 (3 steps); d) TESCl, imidazole, DMAP, CH_2Cl_2/DMF, 0 °C to rt, 97%; e) vinyl-Li, THF, −78 °C, 63%, 13% of recovered **31**; f) $LiNEt_2$, allyl iodide, THF, −78 °C, 90%; g) $LiNEt_2$, HMPA, MeI, THF, -78 °C; h) Me_3Al, THF, 0 °C; then $LiNEt_2$, HMPA, MeI, THF, -78 to 0 °C; i) LDBB, *t*-BuOH, THF, −78 °C, 81%; j) $PhI(OAc)_2$, $NaHCO_3$, CH_2Cl_2/MeOH, 0 °C, 96%. TES = triethylsilyl, DMAP = 4-dimethylaminopyridine, LDBB = lithium di-tert-butylbiphenyl.

With MOB **38** in hand, we moved on to investigate construction of the atropurpuran skeleton (Scheme 6). Heating at 180 °C in *tert*-butylbenzene, MOB **38** underwent a regioselective IMDA reaction to give tetracyclic compound **39** as the sole product. Since this thermal Diels-Alder reaction required no reagents, and the following two steps are both catalytic reactions, we attempted to conduct the following steps as a one-pot process. Thus, the Hoveyda-Grubbs 2nd generation catalyst was added to the reaction mixture at 50 °C to construct the A-ring of atropurpuran. Following completion of the RCM reaction, $Pd(OH)_2/C$ was added to the mixture containing **40**, and the atmosphere was replaced with hydrogen gas. Purification of the resulting mixture provided pentacyclic compound **41** in 62% yield from MOB **38**. X-ray crystallographic structural analysis of compound **41** (see the Supporting Information) confirmed that all stereocenters were successfully generated in the previous steps of our synthesis. The subsequent reaction, namely elimination of the *tert*-alcohol with $SOCl_2$ and pyridine, could be also included in this one-pot reaction, and as a result MOB **38** underwent a one-pot IMDA/RCM/hydrogenation/elimination operation to yield the atropurpuran skeleton **42** in 56% yield (average, 87% yield). It is noted that this one-pot transformation reformed all five C-C double bonds of **38** to three 6-membered rings, with the construction of three C-C bonds and four stereocenters.

Scheme 6. One-pot Construction of Pentacyclic Skeleton 42[a]

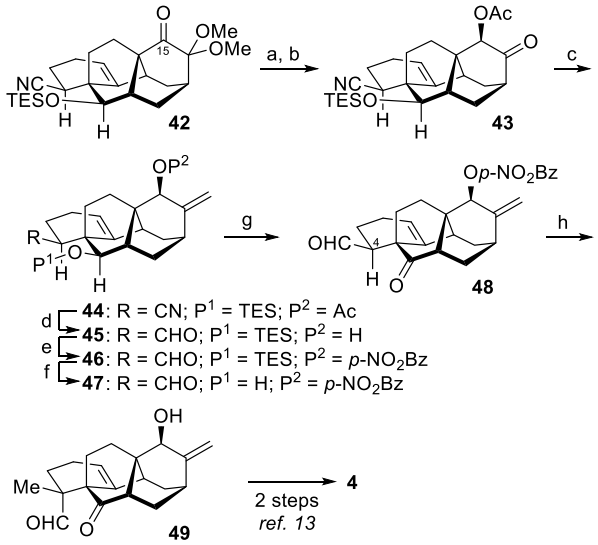


[a] Reagents and conditions: i. *t*-BuPh, 180 °C, 1 h; ii. Hoveyda-Grubbs 2nd generation catalyst, 50 °C, 2 h; iii. H_2, $Pd(OH)_2/C$, THF, 2 h; iv, $SOCl_2$, pyridine, 5.5 h, 56%.

We then proceeded to the final stage of the formal total synthesis of **4** (Scheme 7). Initially, the keto acetal moiety at the C15 and C16 positions of **42** was converted to allyl acetate **44** over 3 steps. Reduction of C15 ketone with $NaBH_4$ proceeded from the α-face to give an alcohol with the undesired stereochemistry (α:β = 8.5:1). One-pot acetal hydrolysis[26]/acetylation and a subsequent Wittig *exo*-

methylenation of ketone **43** provided acetate **44**. DIBAL reduction of the nitrile group of **44** also took place upon removal of the acetyl group, and so alcohol **45** was protected with the *p*-NO_2Bz group[27] to afford aldehyde **46**. Removal of the TES group and subsequent Dess-Martin oxidation afforded keto aldehyde **48** in 57% yield (2 steps). According to Qin's synthesis,[13] α-methylation of the aldehyde was achieved by treating **48** with *t*-BuOK and iodomethane in *t*-BuOH, and a sequential acidic saponification gave 15-*epi*-atropurpuran **49**. We found that using *t*-BuOH/CH_2Cl_2 (2:1) as a solvent at 0 °C slightly increased the yield and diastereoselectivity of **49** (54%, dr = 8:1). All spectral data of **49** were identical to those reported for Qin's intermediate.

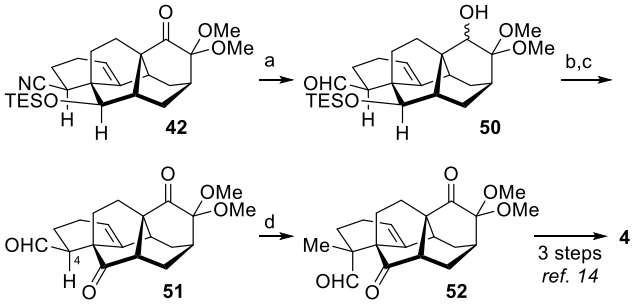
Scheme 7. Formal Total Synthesis of Atropurpuran via Qin's intermediate[a]



[a] Reagents and conditions: a) $NaBH_4$, MeOH, −78 to −45 °C, dr = 8.5:1; b) $LiBF_4$, wet MeCN; then Ac_2O, pyridine, DMAP, 0 °C, 62% (2 steps); c) Ph_3PCH_3Br, *t*-BuOK, THF, 0 °C to rt, 66%; d) DIBAL, CH_2Cl_2, −78 °C to rt, 79%; e) *p*-NO_2BzCl, pyridine, DMAP, CH_2Cl_2, 0 °C, 86%; f) HF• pyridine, THF, 0 °C to rt, 78%; g) Dess-Martin periodinane, H_2O, CH_2Cl_2, 0 °C to rt, 73%; h) *t*-BuOK, MeI, *t*-BuOH/CH_2Cl_2, 0 °C; then 1M HCl, 54% (dr = 8:1). DIBAL = diisobutylaluminum hydride.

During the development of our synthetic route, Xu and colleagues reported the total synthesis of **4**[14] via an IMDA reaction using MOB prepared from 1-tetralone. They revealed that intermediate **52** is a desirable precursor for **4** using a 3-step transformation. We therefore focused on the transformation of **42** to **52** (Scheme 8). Thus, the DIBAL reduction of nitrile and ketone moieties of **42** gave aldehyde **50** in 97% yield. Removal of the TES group and subsequent Dess-Martin oxidation of the resulting diol afforded ketoaldehyde **51**. All spectral data of **51** were found to be identical to those of Xu's intermediate, originally reported as 4-*epi*-**51**.[28] X-ray crystallographic analysis of our synthetic **51** (see the Supporting Information) confirmed the stereochemistry of C4 to be *β*-CHO. According to Xu's report, ketoaldehyde **51** was treated with MeI and *t*-BuOK in *t*-BuOH to give Xu's intermediate **52** and 4-*epi*-**52** (33 and 12%, respectively), along with recovered **51** and 4-*epi*-**51** (28 %). The aforementioned conditions for the methylation of **48** (in *t*-BuOH/CH_2Cl_2 at 0 °C) gave the desired **52** (39%, 43% based on recovered **51** and 4-*epi*-**51**) and 4-*epi*-**52** (10%).

Scheme 8. Formal Total Synthesis of Atropurpuran via Xu's intermediate[a]



[a] Reagents and conditions: a) DIBAL, CH_2Cl_2, −78 °C to rt, 97%; b) HF•pyridine, THF, 0 °C to rt, 94%; c) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 50%; d) *t*-BuOK, MeI, *t*-BuOH/CH_2Cl_2, 0 °C, 39%.

In conclusion, we achieved the formal total synthesis of atropurpuran based on an IMDA reaction (overall 0.36% yield, 21-step longest linear sequence from commercial tetralone **22**). This synthetic route features the successive construction of the C4, C5, C10, and C20 stereocenters of Diels-Alder precursor **27** in a highly diastereoselective manner, based on the use of an Yb-catalyzed Mukaiyama aldol reaction (C5 and C20), the addition of vinyllithium (C10), and allylation of the α-cyanocarbanion (C4). In addition, it features a one-pot transformation from **38** to **42**, which provided a simple solution to construction of the atropurpuran skeleton. Moreover, the Mukaiyama aldol reaction using crotonaldehyde not only avoided the use of acrolein, but also paved the way for the enantioselective total synthesis of atropurpuran, of which studies are currently underway in our group.

EXPERIMENTAL SECTION

General Information and Reagents. Infrared spectra were recorded on a JASCO FT-IR 4100 spectrometer with an ATR unit. Absorbance frequencies are recorded in reciprocal centimeters (cm^{-1}). High-resolution mass spectra (HRMS) were obtained from a Thermo Scientific Exactive for electrospray ionization (ESI). HRMS data are reported as m/e (relative intensity), with accurate mass reported for the molecular ion $[M+Na]^+$, $[M+H]^+$. ^1H and ^{13}C NMR spectra were recorded on a JEOL ECA-500 spectrometer operating at either 500 MHz (^1H NMR) or 125 MHz (^{13}C NMR) in $CDCl_3$ as a solvent. Chemical shifts for NMR were reported in ppm relative to the chemical sift of the residual solvent (^1H NMR, 7.26 ppm for $CDCl_3$, ^{13}C NMR, 77.0 ppm for $CDCl_3$. Multiplicities are indicated as; br (broad), s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Coupling constants (*J*) are reported in Hertz (Hz). All reactions sensitive to oxygen or moisture were performed under an atmosphere of dry argon in flame-dried glassware. Reaction mixtures at elevated temperatures were heated in an oil bath unless otherwise noted. Et_3N, 2,6-lutidine, *i*-Pr_2NEt, and pyridine were distilled from CaH_2 and stored over KOH. Dry THF, CH_2Cl_2, DMF, EtOH, and toluene was purchased from KANTO Chemical Industries Ltd. in anhydrous Grade. Chemical

reagents were commercial grades and were used without any purification unless otherwise noted. The aldehydes ((*E*)-3-(trimethylsilyl)propenal[29] (**29c**), (2*E*)-4-(2-propen-1-yloxy)-2-butenal[30] (**29d**), diethyl 2-allyl-2-[(2*E*)-4-oxobut-2-enyl]malonate[31] (**29e**)) were prepared by the known procedures individually. Flash chromatography was performed with Silica Gel 60N (spherical, neutral), purchased from KANTO Chemical Industries Ltd, unless otherwise noted. Analytical thin layer chromatography (TLC) was performed using commercial silica gel plates (E. Merck, Silica Gel 60 F_{254}).

*5-Benzyloxy-6-methoxy-1-tetralone **24***. To a suspension of 6-methoxytetralone **22** (50.0 g, 284 mmol) in AcOH (50 mL) and H_2O (150 mL) was added 47% HBr aqueous solution (36 mL, 312 mmol) and the mixture was stirred vigorously at room temperature. To the mixture was added 30% H_2O_2 aqueous solution (57 mL, 568 mmol) dropwise using a dropping funnel over 1 h, and the reaction was stirred for overnight. After completion of the reaction, the mixture was poured into an ice-water (800 mL) and the resulting precipitation was filtered, rinsed with water, and dried in vacuo. The crude product (including 2,5-dibromo-6-methoxytetralone) was recrystallized from *i*-PrOH/H_2O to afford 5-bromo-6-methoxy-1-tetralone (38.8 g, 54%) as a white solid. The spectral data were identical to those reported.[20] To a solution of 5-bromo-6-methoxy-1-tetralone (26.0 g, 102 mmol) in 1,4-dioxane (260 mL) were added 6M KOH aqueous solution (78 mL, 510 mmol), $Pd_2(dba)_3$•$CHCl_3$ (528 mg, 0.510 mmol), and tBuXPhos (434 mg, 1.02 mmol) at room temperature. The mixture was stirred at 80 °C for 14 h. After completion of the reaction, the mixture was acidified with 1M HCl aqueous solution. After removal of 1,4-dioxane by rotary evaporator, the mixture was extracted with CH_2Cl_2 by three times. The combined organic layers were dried with $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane: EtOAc = 10:1 to 2:1) to afford **23** (11.9 g, 61%) as an off-white solid. To a solution of **23** (9.01 g, 46.9 mmol) in DMF (47 ml) were added K_2CO_3 (12.9 g, 93.3 mmol, 2.0 eq.), and BnBr (8.40 ml, 70.6 mmol, 1.5 eq.), and the mixture was stirred for 3 h at room temperature. The reaction mixture was quenched with a saturated NH_4Cl aqueous solution and extracted with ether. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 4/1) to afford **24** (12.9 g, 97%) as a yellow solid. The spectral data of **23** and **24** were identical to those reported in our previous study.[10]

*Ketonitrile **25***. To a solution of $HNMe_2$•HCl (1.53 g, 18.7 mmol, 1.58 eq.) in HCHO aq. (1.41 mL, 19.0 mmol, 1.6 eq.) was added Ac_2O (17 mL) at room temperature. After stirring for 1 h, **24** (3.35 g, 11.9 mmol) was added into the reaction mixture in one portion. The mixture was heated to 95 °C and stirred for 30 min. After cooling to room temperature, the mixture was basified with 2 M NaOH aqueous solution. The resulting mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. To the crude mixture (including β-aminoketone and enone) were added DMF (17 mL) and MeI (2.22 mL, 35.7 mmol, 3.0 eq.) at room temperature, the mixture was stirred for 17 h. After removal of remained MeI under reduced pressure, H_2O (8.5 mL), NH_4Cl (0.763 g, 14.3 mmol, 1.2 eq.), and KCN (1.16 g, 17.9 mmol, 1.5 eq.) were added to the mixture. After stirring for 1 h at 95 °C, additional KCN (1.16 g, 17.9 mmol, 1.5 eq.) was added and the mixture was stirred for 1 h. After cooling to room temperature, the reaction mixture was diluted with H_2O, extracted with EtOAc and the organic layer dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (*n*-hexane: EtOAc = 3:1) to afford **25** (3.37 g 88% yield) as a yellow solid. Mp: 102-103 °C (recrystallized from EtOAc/*n*-hexane); R_f 0.26 (*n*-hexane: EtOAc = 2:1 v/v); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 7.86 (1H, d, *J* = 8.6 Hz), 7.41-7.36 (5H, m), 6.93 (1H, d, *J* = 8.6 Hz), 5.03 (1H, d, *J* = 11.5 Hz), 5.00 (1H, d, *J* = 11.5 Hz), 3.97 (3H, s), 3.19 (1H, dt, *J* = 17.2, 2.9 Hz), 3.00 (1H, dd, *J* = 17.2, 4.6 Hz), 2.73-2.70 (1H, m), 2.64-2.53 (2H, m), 2.38 (1H, ddd, *J* = 13.2, 7.5, 4.6 Hz), 1.82 (1H, ddd, *J* = 26.1, 13.2, 4.0 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ: 194.6, 157.0, 143.7, 138.1, 137.0, 128.25, 128.19, 128.0, 125.1, 124.7, 118.5, 110.3, 74.3, 55.7, 43.5, 27.9, 22.9, 18.1; IR (ATR) ν_{max} 2945, 2885, 1669, 1588, 1277, 1073, 995, 751, 698 cm^{-1}; HRMS (m/z): calcd. for $C_{20}H_{19}O_3NNa^+$ $[M+Na]^+$, 344.1257; found, 344.1258.

*Diketone **28***. To a solution of **25** (10.834 g, 33.7 mmol) in CH_2Cl_2 (55 mL) were added Et_3N (19.7 mL, 142 mmol, 4.2 eq.) and TMSOTf (12.8 mL, 70.8 mmol, 2.1 eq.) at 0 °C. After stirring for 2 h at 0 °C, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with hexane. The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford silyl enol ether **26** including di-TMS compound. To the crude mixture were added toluene (52.7 mL), acrolein (22.4 mL, 337 mmol, 10 eq.) and $Yb(OTf)_3$ (2.09 g, 3.37 mmol, 0.1 eq.) in EtOH/H_2O (131 mL/13.1 mL) at room temperature. After stirring for 3 days, the mixture was diluted with H_2O, concentrated under reduced pressure to remove EtOH and acrolein, and extracted with ether. The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture of **27-*anti*** and **27-*syn*** including impurity derived from acrolein was used for the next step without further purification. To a solution of the crude mixture of **27-*anti*** and **27-*syn*** in acetone (300 mL) was added Jones reagent (excess) at 0 °C until the color of mixture turned to red. After stirring 30 min, the reaction mixture was quenched with *i*-PrOH, filtered over Celite, extracted with ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (*n*-hexane: EtOAc = 3:1), additionally purified by silica gel column chromatography (toluene: EtOAc = 9:1) to afford diketone **28** (9.179 g, 72% yield) as colorless oil. R_f 0.48 (*n*-hexane: EtOAc = 1:1 v/v); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 7.92 (1H, d, *J* = 8.6 Hz), 7.39-7.33 (5H, m), 6.97 (1H, d, *J* = 8.6 Hz), 6.51-6.39 (2H, m), 5.70 (1H, dd, *J* = 9.7, 2.3 Hz), 5.03 (1H, d, *J* = 11.5 Hz), 4.99 (1H, d, *J* = 11.5 Hz), 3.98 (3H, s), 2.92-2.77 (4H, m), 2.59 (1H, ddd, *J* = 13.8, 5.2, 5.2 Hz), 2.17-2.12 (1H, ddd, *J* = 14.9, 9.8, 5.2 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ: 193.7, 192.9, 157.5, 143.4, 137.4, 136.7, 131.3, 130.1, 128.11, 128.09, 127.9, 125.4, 124.5, 116.4, 110.6, 74.0, 58.8, 55.6, 29.2, 21.8, 19.5; IR (ATR) ν_{max} 2941, 2248, 1697, 1667, 1586, 1281, 1216, 1074, 912, 821, 733, 700 cm^{-1}; HRMS (m/z): calcd. for $C_{23}H_{21}O_4NNa^+$ $[M+Na]^+$, 398.1363; found, 398.1372.

*Aldol **27-anti** and **27-syn***. To a solution of **28** (0.7639 g, 2.03 mmol) and $CeCl_3$•$7H_2O$ (1.13 g, 3.05 mmol, 1.5 eq.) in MeOH (10.1 mL) and THF (10.1 mL) was added $NaBH_4$ (19.2 mg, 0.508 mmol, 0.25 eq.) at –78 °C, and the reaction mixture was stirred for 30 min at the same temperature. Another $NaBH_4$ (20.0 mg, 0.529 mmol, 0.25 eq.) was added to the mixture and the mixture was stirred for 60 min. Again, another $NaBH_4$ (20.0 mg, 0.529 mmol, 0.25 eq.) was added to the mixture and the mixture was stirred for 90 min. The reaction mixture was quenched with acetone and saturated NH_4Cl aqueous solution,

and MeOH was removed by rotary evaporator. The residue was diluted with H_2O, extracted with ether. The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (*n*-hexane: EtOAc = 3:1), to afford **27-*anti*** (437 mg, 57% yield) as colorless oil and **27-*syn*** (76.6 mg, 10% yield) as colorless oil.

27-*anti*: R_f 0.44 (*n*-hexane: EtOAc = 1:1 v/v); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 7.89 (1H, d, *J* = 8.6 Hz), 7.37-7.35 (5H, m), 6.97 (1H, d, *J* = 9.2 Hz), 5.88 (1H, ddd, *J* = 16.6, 10.3, 6.3 Hz), 5.40 (1H, d, *J* = 16.6 Hz), 5.37 (1H, d, *J* = 10.3 Hz), 5.07 (1H, d, *J* = 10.9 Hz), 5.01 (1H, d, *J* = 11.5 Hz), 4.41 (1H, d, *J* = 6.3 Hz), 3.99 (3H, s), 2.89 (1H, d, *J* = 17.2 Hz), 2.85-2.70 (2H, m), 2.60 (1H, s), 2.54 (1H, d, *J* = 17.2 Hz), 2.22-2.18 (1H, m), 2.07-2.02 (1H, m); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ: 197.5, 157.4, 143.5, 137.5, 137.0, 134.1, 128.5, 128.4, 128.3, 126.0, 124.3, 119.1, 118.0, 110.8, 74.4, 73.3, 55.9, 49.6, 28.6, 19.2, 19.1; IR (ATR) ν_{max} 3466, 2940, 2251, 1673, 1588, 1490, 1455, 1442, 1281, 1216, 1074, 999, 821, 750, 700 cm^{-1}; HRMS (m/z): calcd. for $C_{23}H_{23}O_4NNa^+$ $[M+Na]^+$, 400.1519; found, 400.1520.

27-*syn*: R_f 0.39 (*n*-hexane: EtOAc = 1:1 v/v); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 7.84 (1H, d, *J* = 8.6 Hz), 7.38-7.36 (5H, m), 6.95 (1H, d, *J* = 8.6 Hz), 5.76 (1H, ddd, *J* = 17.2, 10.9, 6.9 Hz), 5.29 (1H, d, *J* = 17.2 Hz), 5.26 (1H, d, *J* = 10.9 Hz), 5.05 (1H, d, *J* = 10.9 Hz), 5.18 (1H, d, *J* = 11.5 Hz), 4.23 (1H, t, *J* = 6.9 Hz), 3.98 (3H, s), 2.94 (1H, dt, *J* = 18.3, 7.5 Hz), 2.81 (1H, d, *J* = 7.5 Hz), 2.80 (1H, d, *J* = 16.6 Hz), 2.70 (1H, ddd, *J* = 17.0, 8.0, 5.2 Hz), 2.59 (1H, d, *J* = 16.6 Hz), 2.25 (1H, ddd, *J* = 13.2, 8.0, 5.2 Hz), 2.06-2.01 (1H, m); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ: 196.9, 157.2, 143.4, 137.5, 136.8, 135.0, 128.2, 128.1, 128.0, 125.3, 124.8, 117.9, 117.6, 110.5, 74.1, 72.3, 55.7, 50.2, 27.7, 19.6, 19.2; IR (ATR) ν_{max} 2944, 2360, 1671, 1588, 1489, 1281, 1075, 909, 728 cm^{-1}; HRMS (m/z): calcd. for $C_{23}H_{23}O_4NNa^+$ $[M+Na]^+$, 400.1519; found, 400.1522.

General procedure for Table 1. The same procedure for enol etherification of **25** (64.2 mg, 0.20 mmol) provided a mixture of **26** and di-TMS compound. To a solution of the mixture in toluene (0.32 mL), were added $Yb(OTf)_3$ (12.4 mg, 0.020 mmol, 0.1 eq.) in EtOH/H_2O (0.8 mL/0.08 mL) at room temperature. After stirring for 2 h, 1H-NMR confirmed that the mixture of **26** and di-TMS compound was converged on **26**. Then, the corresponding aldehyde **29a**-**29e** (3.0 eq.) was added to the reaction mixture. After stirring for 1 h at room temperature, the mixture was diluted with H_2O, extracted with ether. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to afford a diastereomeric mixture of aldol **30b**-**30e**. The analytic sample of **30a** and its diastereomer **30a-syn** was obtained by a silica gel column chromatography (*n*-hexane: EtOAc = 5:1).

30a: R_f 0.26 (*n*-hexane: EtOAc = 3:2 v/v); ^{1}HNMR ($CDCl_3$, 500 MHz) δ: 7.89 (1H, d, *J* = 8.6 Hz), 7.38-7.36 (5H, m), 6.96 (1H, d, *J* = 8.6 Hz), 5.80 (1H, dq, *J* = 14.9, 6.9 Hz), 5.52 (1H, dd, *J* = 16.0, 6.9 Hz), 5.07 (1H, d, *J* = 10.9 Hz), 5.00 (1H, d, *J* = 10.9 Hz), 4.33 (1H, dd, *J* = 7.5 Hz), 3.98 (3H, s), 2.89 (1H, d, *J* = 17.2 Hz), 2.84-2.70 (2H, m), 2.55 (1H, d, *J* = 17.2 Hz), 2.50 (1H, d, *J* = 2.3 Hz), 2.19-2.15 (1H, m), 2.05-2.00 (1H, m), 1.75 (3H, d, *J* = 6.3 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ: 197.9, 157.5, 143.6, 137.7, 137.1, 131.3, 128.6, 128.5, 128.3, 127.0, 126.0, 124.4, 118.1, 110.8, 74.5, 73.5, 55.9, 49.7, 29.1, 19.3, 19.1, 17.9; IR (ATR) ν_{max} 3475, 2940, 1676, 1589, 1490, 1455, 1283, 1075, 970 cm-1; HRMS (m/z): calcd. for $C_{24}H_{25}O_4NNa^+$ $[M+Na]^+$, 414.1676; found, 414.1676.

30a-syn: R_f 0.33 (n-hexane:EtOAc = 2:1 v/v); ^{1}HNMR ($CDCl_3$, 500 MHz) δ: 8.37 (1H, d, *J* = 8.6 Hz), 7.38-7.36 (5H, m), 6.95 (1H, d, *J* = 8.6 Hz), 5.70 (1H, dq, *J* = 14.9, 6.3 Hz), 5.40 (1H, dd, *J* = 15.5, 7.5 Hz), 5.04 (1H, d, *J* = 10.9 Hz), 5.02 (1H, d, *J* = 10.9 Hz), 4.18 (1H, dd, *J* = 7.4, 7.4 Hz), 3.98 (3H, s), 2.96 (1H, dt, *J* = 18.3, 5.8 Hz), 2.79 (2H, m), 2.66 (1H, dq, *J* = 9.4, 8.6, 5.2 Hz), 2.41 (1H, d, *J* = 16.6 Hz), 2.01 (1H, m), 2.00 (1H, m), 1.68 (3H, d, *J* = 6.3 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ: 198.1, 157.6, 143.7, 137.9, 137.1, 131.0, 128.6, 128.5, 128.3, 128.2, 125.6, 125.0, 117.3, 110.7, 74.8, 74.5, 56.0, 49.7, 28.0, 20.3, 19.5, 17.8; IR (ATR) ν_{max} 3475, 2979, 2946, 2360, 1672, 1589, 1490, 1455, 1283, 1216, 1075, 1008, 968, 919, 824, 752, 700 cm^{-1}; HRMS (m/z): calcd. for $C_{24}H_{25}O_4NNa^+$ $[M+Na]^+$, 414.1676; found, 414.1673.

*Alternative route to **27-anti** via **30a***. To a solution of **25** (3.03 g, 9.34 mmol) in CH_2Cl_2 (18.9 mL) were added Et_3N (5.18 mL, 37.4 mmol, 4.0 eq.) and TMSOTf (3.38 mL, 18.7 mmol, 2.0 eq.) at 0 °C. After stirring for 2 h at 0 °C, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with hexane. The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. To crude mixture of **26** and di-TMS compound were added toluene (15.1 mL), $Yb(OTf)_3$ (0.58 g, 0.93 mmol, 0.1 eq.) in EtOH/H_2O (37.4 mL/3.74 mL) at room temperature. After stirring for 2 h, 1H-NMR confirmed that the mixture of **26** and di-TMS compound was converged on **26**. Crotonaldehyde **29a** (2.31 mL, 28.0 mmol, 3.0 eq.) was added to the reaction mixture at 0 °C. After stirring for 4 h at 0 °C, another $Yb(OTf)_3$ (0.58 g, 0.93 mmol, 0.1 eq.) was added. After stirring for 5 h at 0 °C, another $Yb(OTf)_3$ (0.58 g, 0.93 mmol, 0.1 eq.) was added. After stirring for 12 h at 0 °C, the mixture was diluted with H_2O, concentrated under reduced pressure to remove EtOH, extracted with ether. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude **30a** was used for the next step without further purification. To a solution of crude **30a** in toluene (93 mL) was added Hoveyda-Grubbs 2nd generation catalyst (293 mg, 0.467 mmol, 0.1 eq.) under an argon atmosphere. The argon gas was purged with ethylene gas, and the mixture was stirred under an ethylene atmosphere. After stirring for 1.5 h, the ethylene was purged with argon and the crude mixture was directly purified by silica gel column chromatography (*n*-hexane: EtOAc = 1:0 to 3:1) to afford **27-*anti*** (2.55 g, 72% yield (3 steps from **25**)).

*Triethylsilyl ether **31***. To a solution of **27-*anti*** (2.55 g, 6.75 mmol), imidazole (1.10 g, 16.2 mmol, 2.4 eq.) and DMAP (0.105 g, 0.675 mmol, 0.1 eq.) in CH_2Cl_2 (61 mL) and DMF (6.1 mL) was added TESCl (1.36 mL, 8.10 mmol, 1.2eq.) at 0 °C. After stirring 1 h at room temperature, the reaction mixture was quenched with MeOH (7.6 mL) and saturated NH_4Cl solution, extracted with *n*-hexane. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (*n*-hexane: EtOAc = 8:1), to afford **31** (3.22 g, 97% yield) as colorless oil. R_f 0.54 (*n*-hexane: EtOAc = 2:1 v/v); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 7.83 (1H, d, *J* = 8.6 Hz), 7.40-7.34 (5H, m), 6.95 (1H, d, *J* = 8.6 Hz), 5.81-5.74 (1H, m), 5.24 (2H, m), 5.12 (1H, d, *J* = 10.9 Hz), 4.98 (1H, d, *J* = 10.9 Hz), 4.37 (1H, d, *J* = 6.9 Hz), 3.97 (3H, s), 3.05 (1H, d, *J* = 16.6 Hz), 2.86 (1H, ddd, *J* = 9.2, 5.8, 3.5 Hz), 2.63 (1H, ddd, *J* = 17.8, 11.5, 5.7 Hz), 2.41 (1H, d, *J* = 17.2 Hz), 2.14 (1H, ddd, *J* = 14.3, 12.0, 5.7 Hz), 2.06 (1H, ddd, *J* = 14.3, 5.2, 3.5 Hz), 0.79 (9H, t, *J* = 8.0 Hz), 0.37 (6H, dq, *J* = 7.5, 2.3 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ: 195.4, 156.8, 143.4,

137.2, 136.9, 135.7, 128.7, 128.4, 128.3, 125.6, 125.1, 118.7, 118.4, 110.6, 74.3, 73.9, 55.9, 51.2, 28.4, 19.7, 19.6, 6.6, 4.6; IR (ATR) ν_{max} 2952, 2911, 2875, 1681, 1590, 1489, 1281, 1076 cm^{-1}; HRMS (m/z): calcd. for $C_{29}H_{37}O_4NNaSi^+$ $[M+Na]^+$, 514.2380 found, 514.2384.

Tert-alcohol ***32***. To a solution of *n*-BuLi in hexane (3.0 mL, 8.2 mmol, 2.5 eq.) was added tetravinyltin (595 µL, 3.28 mmol, 1.0 eq.) at room temperature. A white solid precipitated immediately. The suspension was stirred for 30 min at room temperature. After cooling to −78 °C, a solution of ketone **31** (1.62 g, 3.28 mmol) in THF (36 mL) was added to the reaction mixture. The reaction mixture was stirred for 25 min at the same temperature. The reaction mixture was quenched with AcOH in THF, neutralized with saturated $NaHCO_3$ solution, and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (*n*-hexane: EtOAc = 1:0 to 8:1), to afford **32** (1.08 g, 63% yield) as colorless oil and recovered **31** (0.213 g, 13%). R_f 0.23 (*n*-hexane: EtOAc = 4:1 v/v); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 7.45-7.30 (6H, m), 6.86 (1H, d, *J* = 8.6 Hz), 6.02 (1H, ddd, *J* = 16.9, 9.8, 9.8 Hz), 5.86 (1H, dd, *J* = 16.6, 10.3 Hz), 5.30-5.24 (3H, m), 5.15 (1H, dd, *J* = 10.3, 1.7 Hz), 5.12-5.07 (2H, m), 4.98 (1H, d, *J* = 11.5 Hz), 4.31 (1H, d, *J* = 9.2 Hz), 3.90 (3H, s), 2.86 (1H, d, *J* = 17.8 Hz), 2.75-2.61 (3H, m), 1.97-1.83 (2H, m), 0.79 (9H, t, *J* = 8.0 Hz), 0.52-0.38 (6H, m); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ: 151.2, 144.2, 141.1, 137.7, 136.0, 134.2, 128.6, 128.4, 128.3, 128.0, 121.6, 119.6, 119.3, 115.4, 110.7, 79.2, 79.0, 73.9, 55.7, 43.3, 26.2, 19.3, 17.7, 6.4, 4.9; IR (ATR) ν_{max} 3434, 2956, 2912, 2876, 1487, 1455, 1415, 1278, 1083, 1003 cm^{-1}; HRMS (m/z): calcd. for $C_{31}H_{41}O_4NNaSi^+$ $[M+Na]^+$, 542.2697; found, 542.2694.

Triene ***33***. To a solution of **32** (1.307 g, 2.52 mmol) in THF (63 mL) was added freshly prepared $LiNEt_2$ (12.6 mmol, 5.0 eq.) in THF (2.5 mL) at −78 °C. After stirring 1 h at the same temperature, allyl iodide (1.61 mL, 17.6 mmol, 7.0 eq.) was added to the mixture. The reaction mixture was stirred for additional 1 h at the same temperature and quenched with a solution of AcOH in THF. Saturated $NaHCO_3$ solution was added to the mixture and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (*n*-hexane: EtOAc = 8:1), to afford **33** (1.26 g, 90% yield) as colorless oil. R_f 0.23 (*n*-hexane: EtOAc = 4:1 v/v); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 7.45-7.33 (6H, m), 6.89 (1H, d, *J* = 8.6 Hz), 6.10 (1H, dd, *J* = 17.8, 11.5 Hz), 5.96-5.82 (2H, m), 5.54 (1H, s), 5.29-5.20 (2H, m), 5.16-5.06 (4H, m), 5.00 (1H, d, *J* = 11.5 Hz), 4.43 (1H, d, *J* = 8.6 Hz), 3.89 (3H, s), 2.93 (1H, dd, *J* = 10.9, 4.6 Hz), 2.87-2.80 (2H, m), 2.72-2.67 (2H, m), 2.09 (1H, ddd, *J* = 14.3, 9.8, 9.8 Hz), 1.63-1.57 (1H, m), 0.76 (9H, t, *J* = 8.0 Hz), 0.44-0.34 (6H, m); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ: 151.1, 144.1, 141.6, 137.8, 136.4, 135.3, 135.1, 128.44, 128.36, 128.07, 128.06, 121.7, 121.4, 119.4, 117.8, 115.3, 111.1, 80.1, 79.0, 74.1, 55.8, 45.3, 35.9, 33.8, 26.5, 20.1, 6.4, 4.7; IR (ATR) ν_{max} 3422, 2955, 2917, 2876, 1732, 1488, 1280, 1084, 1042, 1000, 929, 808, 743, 699 cm^{-1}; HRMS (m/z): calcd. for $C_{34}H_{45}O_4NNaSi^+$ $[M+Na]^+$, 582.3010; found, 582.3015.

Phenol ***37***. To a solution of **33** (1.81 g, 3.24 mmol) in THF (32 mL) and *t*-BuOH (0.92 mL, 9.71 mmol, 3.0 eq.) was added freshly prepared 1M LDBB (excess) in THF at −78 °C until the color of the reaction mixture turned dark blue. After stirring 15 min at the same temperature, the reaction mixture was quenched with AcOH in THF. Saturated $NaHCO_3$ solution was added to the mixture and extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (*n*-hexane: EtOAc = 6:1), to afford **37** (1.23 g, 81% yield) as colorless oil. R_f 0.45 (*n*-hexane: EtOAc = 2:1 v/v); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 7.18 (1H, d, *J* = 8.6 Hz), 6.80 (1H, d, *J* = 8.6 Hz), 6.12 (1H, dd, *J* = 16.6, 10.3 Hz), 5.99 (1H, ddd, *J* = 17.8, 8.6, 8.6 Hz), 5.93-5.85 (1H, m), 5.71 (1H, s), 5.53 (1H, s), 5.34-5.14 (6H, m), 4.55 (1H, d, *J* = 8.6 Hz), 3.87 (3H, s), 2.97 (1H, dd, *J* = 10.3, 5.7 Hz), 2.89-2.70 (4H, m), 2.20 (1H, ddd, *J* = 14.4, 9.7, 9.2 Hz), 1.73 (1H, dd, *J* = 14.4, 8.1 Hz), 0.76 (9H, t, *J* = 8.0 Hz), 0.45-0.36 (6H, m); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ: 144.6, 141.8, 141.5, 136.5, 135.5, 135.0, 121.4, 119.9, 119.2, 117.7, 116.8, 114.9, 109.1, 80.0, 78.9, 56.0, 45.5, 35.7, 33.7, 26.3, 19.2, 6.2, 4.6; IR (ATR) ν_{max} 3427, 2954, 2911, 2877, 2235, 1490, 1460, 1441, 1414, 1335, 1280, 1239, 1173, 1083, 1048, 1001, 927, 857, 806, 729 cm^{-1}; HRMS (m/z): calcd. for $C_{27}H_{39}O_4NNaSi^+$ $[M+Na]^+$, 492.2541; found, 492.2544.

MOB ***38***. To a solution of **37** (0.648 g, 1.38 mmol) and $NaHCO_3$ (0.353 g, 4.20 mmol, 3.0 eq.) in CH_2Cl_2 (7.0 mL) and MeOH (7.0 mL) was added $PhI(OAc)_2$ (0.496 g, 1.54 mmol, 1.1 eq.) at 0 °C. After stirring 15 min at room temperature, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane: EtOAc = 1:0 to 6:1) to afford **38** (0.660 g, 96% yield) as yellow oil. R_f 0.45 (*n*-hexane: EtOAc = 2:1 v/v); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 6.61 (1H, d, *J* = 10.3 Hz), 6.26 (1H, d, *J* = 10.3 Hz), 5.95-5.75 (4H, m), 5.63 (1H, d, *J* = 16.0 Hz), 5.38-5.33 (2H, m), 5.28 (1H, d, *J* = 17.2 Hz), 5.16-5.10 (2H, m), 4.56 (1H, d, *J* = 8.6 Hz), 3.34 (3H, s), 3.33 (3H, s), 2.82-2.72 (3H, m), 2.45 (1H, dd, *J* = 20.1, 7.5 Hz), 2.33-2.25 (1H, m), 2.06 (1H, ddd, *J* = 14.4, 10.3, 4.1 Hz), 1.61 (1H, dd, *J* = 12.6, 4.6 Hz), 0.88 (9H, t, *J* = 8.0 Hz), 0.56 (6H, q, *J* = 8.0 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ: 195.0, 149.3, 137.2, 135.5, 134.6, 132.3, 126.5, 124.9, 120.6, 120.3, 118.7, 118.0, 90.4, 78.9, 78.8, 50.0, 49.9, 44.7, 36.6, 33.4, 25.9, 18.6, 6.4, 4.8; IR (ATR) ν_{max} 3383, 2840, 2877, 2235, 1675, 1457, 1415, 1186, 1143, 1038, 1003, 951, 931, 832, 801, 746 cm^{-1}; HRMS (m/z): calcd. for $C_{28}H_{41}O_5NNaSi^+$ $[M+Na]^+$, 522.2646; found, 522.2650.

Pentacyclic ***42***. A solution of **38** (0.443 g, 0.888 mmol) in *t*-BuPh (88.8 mL) in a sealed tube was heated in an aluminium heating block to 180 °C for 1 h. After the reaction mixture was cooled to room temperature, Hoveyda-Grubbs 2nd generation catalyst (56 mg, 0.0888 mmol, 0.1 eq.) was added. After stirring for 2 h at 50 °C, the reaction mixture was cooled to room temperature. To the reaction mixture, THF (18 mL) and 10% $Pd(OH)_2/C$ (0.44 g, 100 wt%) were added under an argon atmosphere and the argon was purged with H_2 gas. After stirring under H_2 atmosphere for 2 h, H_2 gas was purged with argon gas; and then pyridine (18 mL) and $SOCl_2$ (0.64 mL, 8.88 mmol, 10 eq.) were added to the reaction mixture at 0 °C. After stirring for 5.5 h at room temperature, the reaction mixture was quenched with *i*-PrOH and directly purified by silica gel column chromatography (*n*-hexane: EtOAc = 1:0 to 4:1) to afford **42** (0.227 g, 56% yield) as white solid. To determine the structure of the intermediates **40** and **41**, the reactions were individually terminated by silica gel column chromatography. The overall yield from **38** (0.198 g, 0.396 mmol) to **40** (0.108 g) was 68%, that from **38** (0.523 g, 1.05 mmol) to **41** (0.314 g) was 63%, respectively.

40: white solid; Mp. 189-191 °C (recrystallized from EtOAc/*n*-hexane); R_f 0.22 (*n*-hexane: EtOAc = 2:1 v/v); ^{1}H-NMR ($CDCl_3$,

500 MHz) δ: 6.50 (1H, d, *J* = 6.3 Hz), 6.14 (1H, dd, *J* = 9.2, 1.7 Hz), 5.88-5.84 (1H, m), 3.44-3.38 (2H, m), 3.34 (3H, s), 3.26 (3H, s), 3.29-3.24 (1H, m), 2.80-2.72 (1H, m), 2.54-2.48 (1H, m), 2.39 (1H, dd, *J* = 13.2, 6.9 Hz), 2.16 (1H, dd, *J* = 10.9, 10.3 Hz), 2.09-2.02 (2H, m), 1.81 (1H, d, *J* = 9.2 Hz), 1.67 (1H, ddd, *J* = 13.2, 10.3, 10.3 Hz), 1.57-1.48 (2H, m), 0.94 (9H, t, *J* = 8.0 Hz), 0.70-0.57 (6H, m); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ: 203.6, 144.4, 130.1, 129.1 (2C), 122.0, 94.8, 79.7, 73.5, 52.4, 52.2, 50.4, 49.3, 48.9, 42.2, 33.2, 29.5, 26.2, 17.6, 17.5, 6.9, 4.8; IR (ATR) ν_{max} 3478, 2953, 2910, 2874, 1733, 1139, 1109, 1090, 1058, 998, 849 cm^{-1}; HRMS (m/z): calcd. for $C_{26}H_{37}O_5NNaSi^+$ $[M+Na]^+$, 494.2333; found, 494.2331.

41: white solid; Mp. 209-211 °C (recrystallized from CH_2Cl_2/*n*-hexane); R_f 0.22 (*n*-hexane: EtOAc = 2:1 v/v); ^1H-NMR ($CDCl_3$, 500 MHz) δ: 3.91 (1H, s), 3.30 (3H, s), 3.29 (3H, s), 2.91 (1H, dd, *J* = 12.6, 4.0 Hz), 2.31-2.24 (2H, m), 2.17-2.11 (1H, m), 1.98 (1H, dd, *J* = 12.6, 3.6 Hz), 1.90 (1H, dd, *J* = 13.8, 4.0 Hz), 1.81-1.55 (11H, m), 1.43 (1H, d, *J* = 13.7 Hz), 1.10 (1H, s), 0.97 (9H, t, *J* = 8.0 Hz), 0.74-0.59 (6H, m); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ: 208.7, 122.4, 96.6, 78.6, 72.1, 50.2, 49.2, 44.9, 43.6, 43.1, 41.1, 36.9, 32.7, 32.6, 27.5, 27.2, 21.2, 19.9, 19.7, 15.9, 7.0, 4.8; IR (ATR) ν_{max} 3456, 2942, 2894, 2874, 1726, 1123, 1068, 1041, 1011, 836, 730 cm^{-1}; HRMS (m/z): calcd. for $C_{26}H_{41}O_5NNaSi^+$ $[M+Na]^+$, 498.2646; found, 498.2648.

42: Mp. 69-70 °C (recrystallized from CH_2Cl_2/*n*-hexane); R_f 0.53 (*n*-hexane: EtOAc = 2:1 v/v); ^1H-NMR ($CDCl_3$, 500 MHz) δ: 5.67-5.63 (1H, m), 3.48 (1H, s), 3.28 (3H, s), 3.28 (3H, s), 2.89 (1H, dd, *J* = 4.6, 4.0 Hz), 2.44 (1H, d, *J* = 9.2 Hz), 2.36-2.22 (4H, m), 2.10 (1H, d, *J* = 17.8 Hz), 2.04-1.99 (1H, m), 1.93-1.88 (1H, m), 1.86-1.75 (3H, m), 1.71-1.51 (3H, m), 1.28-1.22 (1H, m), 0.95 (9H, t, *J* = 8.0 Hz), 0.60 (6H, q, *J* = 8.0 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 208.0, 142.6, 121.9, 120.7, 97.1, 79.2, 50.2, 49.3, 45.7, 41.6, 41.8, 36.5, 32.9, 31.8, 30.6, 29.1, 23.0, 22.3, 22.1, 21.1, 6.8, 4.8; HRMS (m/z): calcd. for $C_{26}H_{39}O_4NNaSi^+$ $[M+Na]^+$, 480.2541; found, 480.2541.

*Acetate **43***. To a solution of **42** (0.144 g, 0.314 mmol) in MeOH (3.14 mL) was added $NaBH_4$ (36 mg, 0.943 mmol, 3.0 eq.) at –78 °C. The reaction mixture was stirred at –45 °C for 2 h. The reaction mixture was quenched with saturated NH_4Cl solution and MeOH was removed by rotary evaporator. The residue was diluted with H_2O, extracted with ether. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was used for the next step without further purification. To the crude mixture in MeCN (3.14 mL) and H_2O (63 μL) was added $LiBF_4$ (88 mg, 0.94 mmol 3.0 eq.) at room temperature. After stirring for 2 h (with monitoring the completion of hydrolysis by TLC), Ac_2O (0.31 mL), pyridine (0.63 mL) and DMAP (4.9 mg, 0.031 mmol, 0.1 eq.) was added at 0 °C. After stirring for 1 h at room temperature, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (*n*-hexane: EtOAc = 6:1), to afford **43** (89.3 mg, 62% yield, dr = 8.5:1) as a white solid. Mp. 152-154 °C (recrystallized from EtOAc/*n*-hexane); R_f 0.13 (*n*-hexane: EtOAc = 4:1 v/v); ^1H-NMR ($CDCl_3$, 500 MHz) δ: 5.73-5.73 (1H, m), 5.23 (1H, s), 3.45 (1H, s), 2.98 (1H, dd, *J* = 3.4, 1.7 Hz), 2.59-2.57 (1H, m), 2.40-2.37 (2H, m), 2.30-2.28 (1H, m), 2.19-2.13 (6H, m), 2.02 (1H, dd, *J* = 6.0, 6.0 Hz), 1.95-1.91 (1H, m), 1.88-1.71 (3H, m), 1.62-1.58 (7H, m), 1.45-1.41 (2H, m), 0.97 (9H, t, *J* = 8.0 Hz), 0.59 (6H, q, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 125MHz) δ 210.9, 170.2, 142.1, 122.8, 120.5, 77.9, 75.4, 41.7, 41.2, 39.5, 38.5, 35.9, 32.7, 31.4, 29.9, 24.2, 23.3, 21.9 (2C), 20.4, 6.8, 4.8; FT-IR (ATR) ν_{max} 2955, 2902, 2874, 2235, 1744, 1733, 1457, 1374, 1241, 1113, 1082, 1072, 1047, 1015, 1000, 834, 723 cm^{-1}; HRMS (m/z): calcd. for $C_{26}H_{37}O_4NNaSi^+$ $[M+Na]^+$, 478.2384; found, 478.2383.

*Allyl acetate **44***. To a solution of Ph_3PCH_3Br (60.6 mg, 0.170 mmol, 3.5 eq.) in THF (1 mL) was added *t*-BuOK (16.3 mg, 0.146 mmol, 3.0 eq.) at room temperature. After stirring for 30 min, a solution of **43** (22.2 mg, 0.0485 mmol) in THF (0.3 mL) was added at 0 °C. The reaction mixture was stirred for 9 h at room temperature. The reaction was quenched with saturated NH_4Cl solution and extracted with ether. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (CH_2Cl_2), to afford **44** (14.4 mg, 66% yield) as white solid. Mp. 103-104 °C (recrystallized from CH_2Cl_2/*n*-hexane); R_f 0.50 (*n*-hexane: EtOAc = 4:1 v/v); ^1H-NMR ($CDCl_3$, 500 MHz) δ: 5.61 (1H, br), 5.37 (1H, s), 4.94 (1H, s), 4.81 (1H, s), 3.40 (1H, s), 2.89 (1H, dd, *J* = 5.2, 3.4 Hz), 2.31-2.29 (3H, m), 2.14-1.98 (6H, m), 1.90-1.80 (3H, m), 1.69-1.67 (1H, m), 1.60-1.52 (2H, m), 1.33-1.21 (3H, m), 0.97 (9H, t, *J* = 8.0 Hz), 0.61 (5H, t, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 125MHz) δ 171.1, 150.4, 143.7, 121.6, 121.1, 108,8, 80.0, 74.0, 41.4, 38.3, 37.1, 36.2, 36.0, 35.4, 34.9, 32.0, 24.9, 23.5, 22.5, 22.3, 21.0, 6.8, 4.9; FT-IR (ATR) ν_{max} 2937, 2874, 1737, 1458, 1370, 1233, 1113, 1070, 1034, 1004, 974, 909, 835, 810, 742, 725 cm^{-1}; HRMS (m/z): calcd. for $C_{27}H_{39}O_3NNaSi^+$ $[M+Na]^+$, 476.2591; found, 476.2593.

*Alcohol **45***. To a solution of **44** (0.120 g, 0.265 mmol) in CH_2Cl_2 (0.53 mL) was added DIBAL in toluene (1.29 mL, 1.32 mmol, 5.0 eq.) at –78 °C. The reaction mixture was stirred for 1 h at room temperature, then EtOAc (2 mL) and 10% tartaric acid aq. (5 mL) was added to the mixture. The reaction mixture was stirred for additional 1 h at room temperature, extracted with ether. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (*n*-hexane: EtOAc = 9:1), to afford **45** (86.6 mg, 79% yield) as colorless oil. R_f 0.41 (*n*-hexane: EtOAc = 4:1 v/v) ; ^1H-NMR ($CDCl_3$, 500 MHz) δ: 9.81 (1H, d, *J* = 4.1 Hz), 5.52 (1H, s), 5.03 (1H, s), 4.97 (1H, s), 3.83 (1H, s), 3.49 (1H, s), 2.32-2.28 (2H, m), 2.17-1.95 (6H, m), 1.85 (1H, d, *J* = 10.3 Hz), 1.64 (2H, d, *J* = 5.7 Hz), 1.51-1.45 (2H, m), 1.39-1.33 (2H, m), 1.29-1.18 (1H, m), 0.95 (9H, t, *J* = 8.1 Hz), 0.61 (6H, q, *J* = 8.1 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ: 205.8, 155.6, 144.9, 121.7, 109.1, 84.6, 73.5, 53.5, 43.8, 37.3, 37.1, 36.8, 36.4, 36.1, 36.0, 26.3, 23.9, 21.4, 21.2, 6.9, 4.9; IR (ATR) ν_{max} 3501, 2931, 2872, 1714, 1457, 1415, 1238, 1068, 1003, 897, 817, 726 cm^{-1}; HRMS (m/z): calcd. for $C_{25}H_{38}O_3NaSi^+$ $[M+Na]^+$, 437.2485; found, 437.2482.

*Nitrobenzoate **46***. To a solution of **45** (31.9 mg, 77 μmol) in CH_2Cl_2 (0.77 mL) was added *p*-NO_2BzCl (71 mg, 0.38 mmol, 5.0 eq.), pyridine (0.38 mL) and DMAP (1.2 mg, 7.7 μmol, 0.1 eq.) at room temperature. After stirring for 3 h, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with ether. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (*n*-hexane: EtOAc = 20:1), to afford **46** (37.0 mg, 86% yield) as white solid. Mp. 116-117 °C (recrystallized from EtOAc/*n*-hexane); R_f 0.56 (*n*-hexane: EtOAc = 4:1 v/v); ^1H-NMR ($CDCl_3$, 500 MHz) δ: 9.78 (1H, d, *J* = 3.4 Hz), 8.28 (2H, d, *J* = 8.0 Hz), 8.19 (2H, d, *J* = 8.0 Hz), 5.57 (1H, s), 5.54 (1H, s), 5.08 (1H, s), 5.03 (1H, s), 3.56 (1H, s), 2.42 (1H, s), 2.32 (1H, dd, *J* = 7.5,

10.9 Hz), 2.24-2.00 (7H, m), 1.71-1.60 (4H, m), 1.52-1.43 (2H, m), 1.32 (1H, dt, *J* = 6.9, 11.5 Hz), 1.00 (9H, t, *J* = 8.0 Hz), 0.66 (6H, q, *J* = 7.8 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ: 205.3, 164.5, 150.6, 149.7, 143.9, 135.9, 130.7, 123.6, 122.3, 112.2, 84.1, 75.9, 53.4, 43.6, 38.5, 37.0, 36.6, 36.2, 36.0, 35.5, 26.5, 23.9, 21.1, 21.1, 7.0, 4.9; IR (ATR) ν_{max} 2934, 2874, 1713, 1608, 1530, 1460, 1334, 1267, 1101, 1073, 1011, 958, 918, 870, 839, 801, 716 cm^{-1}; HRMS (m/z): calcd. for $C_{32}H_{41}O_6NNaSi^+$ $[M+Na]^+$, 586.2595; found, 586.2607.

*Aldehyde **47***. To a solution of **46** (37.0 mg, 66 μmol) in THF (0.66 mL) was added HF·Py (0.6 mL, 0.66 mmol, 10 eq.) at 0 °C. After stirring for 1 h at room temperature, the reaction mixture was quenched with TMSOMe (1 mL) and concentrated under reduced pressure, The resulting residue was purified by silica gel column chromatography (*n*-hexane: EtOAc = 6:1 to 3:1), to afford **47** (23.0 mg, 78% yield) as colorless oil. R_f 0.22 (*n*-hexane: EtOAc = 3:1 v/v); ^{1}HNMR ($CDCl_3$, 500 MHz) δ: 9.79 (1H, d, *J* = 4.6 Hz), 8.29 (2H, d, *J* = 8.6 Hz), 8.19 (2H, d, *J* = 8.6 Hz), 5.58 (1H, s), 5.52 (1H, s), 5.12 (1H, s), 5.04 (1H, s), 3.64 (1H, s), 2.43-2.38 (2H, m), 2.29-1.93 (8H, m), 1.72-1.67 (4H, m), 1.40 (1H, d, *J* = 12.6 Hz), 1.35-1.25 (2H, m); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ: 206.9, 164.7, 150.5, 149.6, 143.6, 135.8, 130.8, 123.6, 122.0, 112.9, 84.2, 75.8, 54.1, 43.8, 38.68, 38.67, 37.4, 36.8, 35.9, 34.7, 26.5, 24.0, 20.6, 20.5; IR (ATR) ν_{max} 3422, 2933, 2867, 1718, 1606, 1528, 1459, 1408, 1338, 1269, 1103, 1040, 719 cm^{-1}; HRMS (m/z): calcd. for $C_{26}H_{27}O_6NNa^+$ $[M+Na]^+$, 472.1734; found, 472.1731.

*Ketoaldehyde **48***. To a solution of **47** (23.0 mg, 51 μmol) in CH_2Cl_2 (0.51 mL) and H_2O (3 μL) was added Dess-Martin Periodinane (65 mg, 0.15 mmol, 3.0 eq.) at 0 °C. After stirring for 1 h at room temperature, the reaction mixture was quenched with saturated $NaHCO_3$ solution and saturated $Na_2S_2O_3$ solution, extracted with ether. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (*n*-hexane: EtOAc = 6:1) to give **48** (16.8 mg, 73% yield) as white solid. Mp. 205-207 °C (recrystallized from EtOAc/*n*-hexane); R_f 0.52 (*n*-hexane: EtOAc = 2:1 v/v); ^{1}HNMR ($CDCl_3$, 500 MHz) δ: 9.75 (1H, s), 8.30 (2H, d, *J* = 8.6 Hz), 8.18 (2H, d, *J* = 8.6 Hz), 5.67 (1H, s), 5.57 (1H, d, *J* = 4.6 Hz), 5.23 (1H, s), 5.12 (1H, s), 3.29 (1H, dd, *J* = 12.6, 2.3 Hz), 2.73 (1H, d, *J* = 11.5 Hz), 2.45 (1H, s), 2.41-2.39 (1H, m), 2.30 (1H. d, *J* = 13.2 Hz), 2.22-2.00 (4H, m), 1.83-1.73 (3H, m), 1.62-1.49 (2H, m), 1.25-1.21 (2H, m); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ: 216.4, 203.2, 164.5, 156.6, 148.1, 141.6, 135.5, 130.7, 123.7, 123.1, 114.6, 75.3, 51.3, 47.7, 42.7, 38.3, 38.0, 36.1, 35.7, 30.6, 25.6, 24.7, 23.8, 17.6; IR (ATR) ν_{max} 2923, 2851, 1713, 1605, 1527, 1459, 1339, 1267, 1116, 1104, 722 cm^{-1}; HRMS (m/z): calcd. for $C_{26}H_{25}O_6NNa^+$ $[M+Na]^+$, 470.1574; found, 470.1572.

*15-Epi-atropurpuran **49***. To a solution of **48** (62.8 mg, 0.140 mmol) in *t*-BuOH (3.1 mL) and CH_2Cl_2 (3.1 mL) was added *t*-BuOK (157 mg, 1.40 mmol, 10 eq.) in *t*-BuOH (3.1 mL) at 0 °C. After stirring for 10 min at 0 °C, MeI (0.44 mL, 7.02 mmol, 50 eq.) was added. After stirring for 24 h at 0 °C, the reaction mixture was quenched with 1M HCl aq., and stirred for 40 min at room temperature. Then, the mixture was neutralized with saturated $NaHCO_3$ solution, and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (*n*-hexane: EtOAc = 10:1) to afford **49** (23.7 mg, 54% yield, dr = 8:1) as white solid. R_f 0.16 (*n*-hexane: EtOAc = 2:1 v/v); ^{1}HNMR ($CDCl_3$, 500 MHz) δ: 9.65 (1H, s), 5.56 (1H, m), 5.08 (1H, s), 5.04 (1H, s), 4.02 (1H, s), 2.56 (1H, d, *J* = 10.9 Hz), 2.37 (1H, s), 2.24 (1H, dd, *J* = 9.8, 9.8 Hz), 2.15-1.80 (8H, m), 1.66-1.53 (4H, m), 1.19 (1H, ddd, *J* = 13.2, 6.9, 1.8 Hz), 1.03 (3H, s); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ: 217.4, 205.6, 154.0, 142.3, 121.9, 111.3, 73.1, 54.9, 45.2, 41.8, 39.1, 38.7, 35.7, 35.1, 31.1, 30.2, 26.2, 25.2, 21.9, 17.4; IR (ATR) ν_{max} 3411, 2937, 2866, 2729, 1710, 1668, 1461, 1059, 1017, 900 cm^{-1}; HRMS (m/z): calcd. for $C_{20}H_{25}O_3^+$ $[M+H]^+$, 313.1798; found, 313.1798.

*Ketoaldehyde **51***. To a solution of **42** (149.7 mg, 0.327 mmol) in CH_2Cl_2 (3.3 mL) was added 1.0 M solution of DIBAL in hexane (1.6 mL, 1.6 mmol, 5.0 eq.) at −78 °C. After stirring for 1.5 h at room temperature, the reaction mixture was cooled at 0 °C and quenched with EtOAc and 10% tartaric acid aqueous solution. After stirring for 1 h, the reaction mixture was extracted with ether. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (*n*-hexane: EtOAc = 5:1), to afford **50** (147.0 mg, 97%, dr = 3:2) as colorless oil. To a solution of **50** (128.1 mg, 0.277 mmol) in THF (1.4 mL) and pyridine (1.4 mL) was added HF·Py (0.4 mL, 2.8 mmol, 10 eq.) at 0 °C. After stirring for 5 h at room temperature, the reaction mixture was cooled at 0 °C and quenched with TMSOMe. After stirring for 1 h, the reaction mixture was concentrated under reduced pressure to remove MeOH and Py. The resulting residue was purified by silica gel column chromatography (*n*-hexane: EtOAc = 5:1 to 1:1), to afford a diastereomeric mixture of the resulting diol (90.9 mg, 94%, dr = 3:2) as colorless oil. To a solution of the mixture of diol (80.2 mg, 0.23 mmol) and $NaHCO_3$ (190 mg, 2.3 mmol, 10 eq.) in CH_2Cl_2 (2.3 mL) was added Dess-Martin Periodinane (290 mg, 0.69 mmol, 3.0 eq.) at 0 °C. After stirring for 2 h at room temperature, the reaction mixture was quenched with saturated $NaHCO_3$ solution and aqueous $Na_2S_2O_3$ solution. After stirring for 1 h, the reaction mixture was extracted with ether. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (*n*-hexane: EtOAc = 4:1), to afford **51** (39.5 mg, 50%) as a white solid. Mp. 131 °C (recrystallized from EtOAc/*n*-hexane); R_f 0.59 (*n*-hexane: EtOAc = 1:1 v/v); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 9.73 (1H, s), 5.59 (1H, d, *J* = 5.7 Hz), 3.33 (3H, s), 3.32 (3H, s), 3.28 (1H, dd, *J* = 2.9, 13.2 Hz), 2.70-2.66 (1H, m), 2.49 (1H, ddd, *J* = 2.9, 2.9, 10.9 Hz), 2.40-2.32 (2H, m), 2.20-2.09 (4H, m), 2.03-1.99 (2H, m), 1.81 (1H, d, *J* = 11.5 Hz), 1.75-1.65 (2H, m), 1.53-1.50 (1H, m), 1.22 (1H, ddd, *J* = 13.8, 6.3, 1.7 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ: 214.6, 205.6, 202.9, 141.4, 123.6, 97.2, 50.8, 50.2, 49.4, 47.5, 46.8, 45.3, 37.8, 33.6, 30.8, 25.6, 24.3, 23.8, 21.3, 17.6; IR (ATR) ν_{max} 2945, 2930, 2832, 1734, 1716, 1456, 1438, 1148, 1129, 1061, 913, 836 cm^{-1}; HRMS (m/z): calcd. for $C_{20}H_{24}O_5NNa^+$ $[M+Na]^+$, 367.1516; found, 367.1517.

*Xu's intermediate **52***. To a solution of **51** (28.0 mg, 0.0813 mmol) in *t*-BuOH (4 mL) and CH_2Cl_2 (2 mL) in a polypropylene test tube was added a 1.0 M solution of *t*-BuOK in THF (0.325 mL, 0.325 mmol, 4.0 eq.) and MeI (50 μL, 0.813 mmol, 10 eq.) at 0 °C. After stirring for 8 h at 0 °C, another *t*-BuOK solution (0.081 mL, 0.0813 mmol, 1.0 eq.) and MeI (13 μL, 0.203 mmol, 2.5 eq.) was added. After stirring for 3 h at 0 °C, again another *t*-BuOK solution (0.081 mL, 0.0813 mmol, 1.0 eq.) and MeI (13 μL, 0.203 mmol, 2.5 eq.) was added. After stirring for 1 h at 0 °C, the reaction mixture was quenched with saturated $NaHCO_3$ solution, extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by PTLC (*n*-hexane: EtOAc = 3:1×2), to afford *epi*-**52** (10 %, 2.9 mg) **51** (3%, 0.7 mg),

52 (11.3 mg, 39% (43% based on recovered **51** and *epi*-**51**)) as white solid, and *epi*-**51** (8%, 2.3 mg).

52: Mp. 167-168 ℃ (recrystallized from EtOAc/*n*-hexane); R_f 0.25 (*n*-hexane: EtOAc = 4:1 v/v ×2); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 9.68 (1H, s), 5.65 (1H, s), 3.34 (3H, s), 3.31 (3H, s), 2.80-2.73 (1H, m), 2.44-2.31 (3H, m), 2.20-1.92 (5H, m), 1.90-1.60 (5H, m), 1.30-1.23 (1H, m), 1.04 (3H, s); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ: 214.2, 205.6, 204.9, 141.0, 122.9, 97.3, 54.4, 50.3, 49.4, 46.9, 45.3, 45.2, 38.4, 33.5, 30.1, 29.8, 26.0, 25.8, 21.9, 21.3, 17.4; IR (ATR) ν_{max} 2937, 2824, 2727, 1729, 1708, 1457, 1149, 1057, 1045, 1028, 1004, 914, 839 cm^{-1}; HRMS (m/z): calcd. for $C_{21}H_{26}O_5Na^+$ [M+Na]$^+$, 381.1673; found, 381.1678.

Epi-**51**: R_f 0.21 (*n*-hexane: EtOAc = 4:1 v/v ×2); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 9.84 (1H, s), 5.74 (1H, m), 3.34 (3H, s), 3.31 (3H, s), 2.78-2.72 (1H, m), 2.49-2.38 (2H, m), 2.38 (2H, m), 2.28-2.20 (1H, m), 2.18-2.02 (4H, m), 2.00-1.92 (1H, m), 1.88-1.72 (3H, m), 1.71-1.62 (1H, m), 1.54 (1H, dt, *J* = 10.9, 6.9 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ: 213.3, 206.0, 202.6, 141.8, 124.9, 97.2, 53.6, 50.0, 49.8, 49.7, 47.2, 45.2, 37.4, 33.7, 31.9, 29.3, 25.9, 23.6, 21.8, 20.9; IR (ATR) ν_{max} 2943, 2827, 2837, 1717, 1458, 1148, 1052, 978, 837 cm^{-1}; HRMS (m/z): calcd. for $C_{20}H_{24}O_5NNa^+$ [M+Na]$^+$, 367.1516; found, 367.1521.

ASSOCIATED CONTENT

Supporting Information.
This material is available free of charge via the Internet at http://pubs.acs.org.
Scheme for the preparation of tricyclic MOB **13**; details of the further transformation from **27-syn**, the catalytic asymmetric Mukaiyama aldol reaction, and the methylation of aldehyde **48**; compound characterization data; and ^{1}H and ^{13}C NMR spectral data for all new compounds (PDF)
FAIR Data is available as Supporting Information for Publication and includes the primary NMR FID files for all new compounds.
Crystallographic information for **15** (CIF)
Crystallographic information for **40** (CIF)
Crystallographic information for **47** (CIF)

AUTHOR INFORMATION

Corresponding Author

* Takahiro Suzuki
ORCID: 0000-0002-3842-1025
E-mail: takahiro-suzuki@sci.hokudai.ac.jp
* Keiji Tanino
ORCID: 0000-0002-0580-0125
E-mail: ktanino@sci.hokudai.ac.jp

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This research was supported in part by JSPS KAKENHI Grant Numbers JP15H05842 in Middle Molecular Strategy, JP18H01970 in Grant-in-Aid for Scientific Research(B), JP20K05485 in Grant-in-Aid for Scientific Research(C), and the Photo-excitonix Project in Hokkaido University. We thank Mr. Naoki Egashira (Taiho Pharma) and Dr Atsuhiro Takano (KOWA CO. Ltd.) for the preliminary investigation of the total synthesis. We also thank the Naito Foundation, the Uehara Memorial Foundation, the Astellas Foundation for Research on Metabolic Disorders, the Research Foundation for Pharmaceutical Sciences, and the Akiyama Life Science Foundation for financial support.

REFERENCES

[1] Reviews: (a) Wang, F.-P.; Chen, Q.-H.; Liu, X.-Y. Diterpenoid alkaloids. *Nat. Prod. Rep.* **2010**, *27*, 529–570. (b) Liang, X.; Gao, Y.; Luan, S. Two decades of advances in diterpenoid alkaloids with cytotoxicity activities. *RSC Adv.*, **2018**, *8*, 23937–23946. (c) Wada, K.; Yamashita, H. Cytotoxic Effects of Diterpenoid Alkaloids Against Human Cancer Cells. *Molecules* **2019**, *24*, 2317.

[2] Yin, T.; Zhou H.; Cai, L.; Ding, Z. Non-alkaloidal constituents from the genus Aconitum: a review. *RSC Adv*., **2019**, *9*, 10184–10194.

[3] Pelletier, S. W.; Ateya, A.-M. M.; Finer-Moore, J.; Mody, N. V.; Schramm, L. C. Atisenol, A New *ent*-atisene diterpenoid lactone from *Aconitum heterophyllum*. *J. Nat. Prod.* **1982**, *45*, 779–781.

[4] Wang, F.-P. ; Yan, L.-P. Campylopin from *Delphinium campylocentrum*, the first hetidane C20-diterpene, suggests a new alkaloid biogenetic pathway, *Tetrahedron* **2007**, *63*, 1417–1420.

[5] Yang, C.-H.; Wang, X.-C.; Tang, Q.-F.; Liu, W.-Y.; Liu, J.-H. A New Diterpenoid and a new diterpenoid alkaloid from *Aconitum coreanum*. *Helv. Chim. Acta.* **2008**, *91*, 759–765.

[6] Tang, P.; Chen, Q.-H.; Wang, F.-P. Atropurpuran, a novel diterpene with an unprecedented pentacyclic cage skeleton, from *Aconitum hemsleyanum* var. *atropurpureum*. *Tetrahedron Lett.* **2009**, *50*, 460–462.

[7] (a) Weber, M.; Owens, K. Sarpong, R. Atropurpuran—missing biosynthetic link leading to the hetidine and arcutine C_{20}-diterpenoid alkaloids or an oxidative degradation product? *Tetrahedron Lett*. **2015**, *56*, 3600–3603; (b) Kumar, V.; Malhortra, N.; Pal, T.; Chauhan, R. S. Molecular dissection of pathway components unravel atisine biosynthesis in a non-toxic Aconitum species, A. heterophyllum Wall. *3 Biotech*, **2016**, 6:106.

[8] (a) Tashkhodzhaev, B.; Saidkhodzhaeva, S. A.; Bessonova, I. A.; Antipin, M. Y. Arcutin-a new type of diterpene alkaloids. *Chem. Nat. Compd.* **2000**, *36*, 79–83; (b) Saidkhodzhaeva, S. A.; Bessonova, I. A.; Abdullaev, N.D. Arcutinine, a new alkaloid from *Aconitum arcuatum*. *Chem. Nat. Compd.* **2001**, *37*, 466–469.

[9] Zhou, S.; Xia, K.; Leng, X.; Li, A. Asymmetric total synthesis of arcutinidine, arcutinine, and arcutine. *J. Am. Chem. Soc.* **2019**, *141*, 13718–13723.

[10] Suzuki, T.; Sasaki, A.; Egashira, N.; Kobayashi, S. A synthetic study of atropurpuran: construction of a pentacyclic framework by an intramolecular reverse-electron-demand Diels–Alder reaction. *Angew. Chem. Int. Ed.* **2011**, *50*, 9177–9179.

[11] Suzuki, T., Okuyama, H.; Takano, S.; Suzuki, S., Shimizu, I.; Kobayashi, S. Synthesis of dibarrelane, a dibicyclo[2.2.2]octane hydrocarbon. *J. Org. Chem.* **2014**, *79*, 2803–2808.

[12] (a) Hayashi, R.; Ma, Z. X.; Hsung, R. P. A tandem 1,3-H-shift–6π-electrocyclization–cyclic 2-amido-diene intramolecular Diels–Alder cycloaddition approach to BCD-ring of atropurpuran. *Org. Lett.* **2012**, *14*, 252–255; (b) Chen, H.; Zhang, D.; Xue, F.; Qin, Y. Synthesis of the atropurpuran A-ring via an organocatalytic asymmetric intramolecular Michael addition. *Tetrahedron* **2013**, *69*, 3141–3148; (c) Chen, H.; Li, X.-H.; Gong, J.; Song, H.; Liu, X.-Y.; Qin, Y. Synthetic approach to the functionalized tricyclic core of atropurpuran. *Tetrahedron* **2016**, *72*, 347–353; (d) Jarhad, D. B.; Singh, V. π^4s + π^2s Cycloaddition of spiroepoxycyclohexa-2,4-dienone, radical cyclization, and oxidation–aldol–oxidation cascade: synthesis of BCDE ring of atropurpuran. *J. Org. Chem.,* **2016**, *81*, 4304–4309.

[13] Gong, J.; Chen, H.; Liu, X.-Y.; Wang, Z.-X.; Nie, W.; Qin, Y. Total synthesis of atropurpuran. *Nat. Commun.* **2016**, *7*:12183.

[14] Xie, S.; Chen, G.; Yan, H.; Hou, J.; He, Y.; Zhao, T.; Xu, J. 13-Step total synthesis of atropurpuran. *J. Am. Chem. Soc.* **2019**, *141*, 3435–3439.

[15] (a) Nie, W.; Gong, J.; Chen, Z.; Liu, J.; Tian, D.; Song, H.; Liu, X.-Y.; Qin, Y. Enantioselective total synthesis of (−)-arcutinine. *J. Am. Chem. Soc.* **2019**, *141*, 9712–9718; (b) Owen, K. R.; McCowen, S. V.; Blackford, K. A.; Ueno, S.; Hirooka, Y.; Weber, M.; Sarpong, R. Total synthesis of the diterpenoid alkaloid arcutinidine using a strategy inspired by chemical network analysis. *J. Am. Chem. Soc.* **2019**, *141*, 13713–13717.

[16] A recent review for the synthesis of aructane skeleton: McCowen, S. V.; Nicolle, A. D.; Sarpong, R. Retrosynthetic strategies and their impact on synthesis of arcutane natural products. *Chem. Sci.* **2020**, *accepted manuscript* (doi: 10.1039/D0SC01441A).

[17] Recent reviews: (a) Čeković, Ž. Reactions of d-carbon radicals generated by 1,5-hydrogen transfer to alkoxyl radicals. *Tetrahedron* **2003**, *59*, 8073–8090; (b) Gutekunst, W. R.; Baran, P. S. C–H functionalization logic in total synthesis. *Chem. Soc. Rev.* **2011**, *40*, 1976–1991; (c) Stateman, L. M.; Nakafuku, K. M.; Nagib, D. A. Remote C–H functionalization via selective hydrogen atom transfer. *Synthesis* **2018**, *50* 1569–1586.

[18] (a) Schönecker, B.; Zheldakova, T.; Liu, Y.; Kötteritzsch, M.; Günther, W.; Görls, H. Biomimetic hydroxylation of nonactivated CH_2 groups with copper complexes and molecular oxygen. *Angew. Chem., Int. Ed.* **2003**, *42*, 3240–3244; (b) Schönecker, B.; Zheldakova, T.; Lange, C.; Günther, W.; Görls, H.; Bohl, M. Intramolecular γ-hydroxylations of nonactivated C-H bonds with copper complexes and molecular oxygen. *Chem. - Eur. J.* **2004**, *10*, 6029–6042; (c) Lawrence, J. D.; Takahashi, M.; Bae, C.; Hartwig, J. F. Regiospecific functionalization of methyl C-H bonds of alkyl groups in reagents with heteroatom functionality. *J. Am. Chem. Soc.* **2004**, *126*, 15334–15335; (d) Simmons, E. M.; Hartwig, J. F. Catalytic functionalization of unactivated primary C–H bonds directed by an alcohol. *Nature* **2012**, *483*, 70–73; (e) Li, B.; Driess, M.; Hartwig, J. F. Iridium-catalyzed regioselective silylation of secondary alkyl C–H bonds for the synthesis of 1,3-diols. *J. Am. Chem. Soc.* **2014**, *136*, 6586–6589.

[19] Podgoršek, A.; Stavber, S.; Zupan, M.; Iskra, J. Environmentally benign electrophilic and radical bromination 'on water': H_2O_2–HBr system versus *N*-bromosuccinimide. *Tetrahedron* **2009**, *65*, 4429–4439.

[20] Bakewell, S. J.; Coates M. B., Corner, M. B.; Reeves, M. L.; Warrington, B. H. Inotropic, vasodilator and low K_m, cAMP-selective, cGMP-inhibited phosphodiesterase (PDE III) inhibitory activities of 4*a*-methyl-4,4*a*-dihydro-5*H*-indeno[l,2-*c*]pyridazin-3(2*H*)-ones and 4*a*-methyl-4,4*a*,5,6-tetrahydrobenzo[*h*]cinnolin-3(2*H*)-ones. *Eur. J. Med. Chem.* **1990**, *25*, 765–774.

[21] Aldol reaction in basic condition using **25** gave almost no reaction. Mukaiyama aldol reactions under normal conditions (using $TiCl_4$, $BF_3{\cdot}OEt_2$, etc. in aprotic solvents) gave complex mixture.

[22] Kobayashi, S.; Hachiya, I.; Yamanoi, Y. Repeated use of the catalyst in $Ln(OTf)_3$-catalyzed aldol and allylation reactions. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2342–2344.

[23] Ishihara, Y.; Mendoza, A.; Baran, P. S. Total synthesis of taxane terpenes: cyclase phase. *Tetrahedron* **2013**, *69*, 5685–5701.

[24] In principal, the further transformation using minor diastereomer **27-*syn*** is also possible. However, the low yield of addition of vinyllithium reagent and low selectivity of alkylation of α-cyanocarbanion are underlying problems. See the Supporting Information.

[25] (a) Alkylation of lithiated 4-alkoxynitrile, see: Yang, X.; Fleming, F. F. C- and N-Metalated nitriles: the relationship between structure and selectivity. *Acc. Chem. Res.* **2017**, *50*, 2556-2568; (b) Pitta, B. R.; Steward, O. W.; Fleming F. F. Electrophile-dependent alkylations of lithiated 4-alkoxyalk-4-enenitriles. *J. Org. Chem.* **2018**, *83*, 2753–2762.

[26] Sacher, J. R.; Weinreb, S. M. Construction of the azocane (azacyclooctane) moiety of the lycopodium alkaloid lycopladine H via an intramolecular hydroaminomethylation Strategy. *Org. Lett.*, **2012**, *14*, 2172–2175.

[27] Methylation using the acetate analog of **44** resulted in a low yield of **45** due to a concurrent saponification of acetate, which caused an etherification to give *O*-Me-**45**.

[28] The NMR spectra data of 4-*epi*-**47**, obtained by epimerization using *t*-BuOK, were not identical of those of **47**. See the Supporting Information.

[29] Jung, M. E.; Gaede, B. Synthesis and Diels-Alder reactions of E-1-trimethylsilylbuta-1,3-diene. *Tetrahedron* **1979**, *35*, 621–625.

[30] (a) García-Gómez, G.; Moretó, J. M. Intramolecular Ni-mediated cyclizations with α,ω–dienals. *Eur. J. Org. Chem.* **2001**, 1359-1369; b) Doyle, M. P.; Peterson, C. S.; Protopopova, M. N.; Marnett, A. B.; Parker, D. L.; Ene, D. G.; Lynch, V. Macrocycle formation by catalytic intramolecular cyclopropanation. A New general methodology for the synthesis of macrolides. *J. Am. Chem. Soc.* **1997**, *119*, 8826–8837.

[31] Hansen, E. C.; Lee D. Efficient and *Z*-selective cross-metathesis of conjugated enynes. *Org. Lett.* **2004**, *6*, 2035–2038.