Tetrahedron 66 (2010) 6569–6584

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# The first catalytic asymmetric total synthesis of *ent*-hyperforin

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ARTICLE INFO

*Article history:*
Received 6 March 2010
Received in revised form 15 May 2010
Accepted 21 May 2010
Available online 31 May 2010

This paper is dedicated to Professor Steven V. Ley on the occasion of his receipt of the 2009 Tetrahedron Prize

ABSTRACT

The first catalytic asymmetric total synthesis of *ent*-hyperforin was described here in detail. Keys to the success were a catalytic asymmetric Diels–Alder reaction, a stereoselective Clasien rearrangement, an intramolecular aldol cyclization, and a vinylogous Pummerer rearrangement. Along with the successful synthetic route, several attempted approaches toward the construction of bicyclo[3.3.1] core and the C2 oxidation were discussed.



## 1. Introduction

Polycyclic polyprenylated acylphloroglucinols (PPAPs) are naturally occurring products with a densely substituted bicyclo[3.3.1] nonanone core (Fig. 1).[1] Recent extensive studies revealed that some PPAPs exhibit interesting biological activities: garsubellin A (**2**) shows potent choline acetyltransferase inductive activity (154% at 10 μM compared to negative control)[2] and clusianone (**3**) shows *anti*-HIV activity.[3] Hyperforin (**1**), isolated from St. John's wort (*Hypericum perforatum*) in 1971,[4a] is representative of the PPAP family. Because of its inhibitory effects on the uptake of serotonin and other neurotransmitters, hyperforin is thought to be responsible for the antidepressant activity of St. John's wort.[5] Hyperforin also exhibits other noteworthy effects, such as its *anti*-malarial activity,[6] human histone deacetylase inhibitory activity,[7] and the induction of CYP3A4,[8] which suppresses the effectiveness of several drugs.

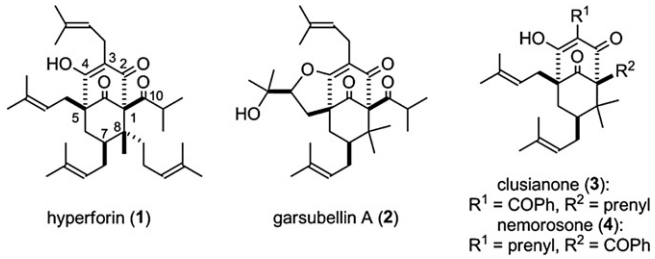


**Figure 1.** Representative PPAPs.

In addition to their unique biological activities, the complex structure of PPAPs makes them attractive synthetic targets.[9] After extensive synthetic studies of PPAPs, total syntheses of garsubellin A (**2**),[10] clusianone (**3**),[11] and nemorosone (**4**)[11d,f] were reported by several groups. Although biomimetic approaches using acylphloroglucinols as a reactant led to rapid construction of the key bicyclo [3.3.1]nonanone core and concise racemic total synthesis,[9e,11b,e] there is only one example of asymmetric synthesis using a late stage kinetic resolution with a stoichiometric amount of chiral lithium amide.[11c] Thus, the catalytic asymmetric synthesis of PPAPs remains a challenge. All of the synthesized PPAPs have a C8 *gem*-dimethyl substituent, and the necessity of stereoselective installation of additional C8 quaternary center in hyperforin would make its synthesis more difficult. Recently, our group accomplished the first catalytic asymmetric total synthesis of *ent*-hyperforin using a powerful catalytic asymmetric Diels–Alder reaction.[12] Here, we report the details of our synthesis of *ent*-hyperforin.

## 2. Results and discussion

Our group previously succeeded in the total synthesis of garsubellin A using the Claisen rearrangement–ring closing metathesis (RCM) sequence to construct the key bicyclo[3.3.1] core.[10a] Based on this result, our initial synthetic plan for hyperforin was as follows (Scheme 1). Based on the garsubellin A synthesis, allylic oxidation and C3-prenyl group installation by Stille coupling to bicyclo compound **5** would lead to hyperforin. The bicyclo[3.3.1] core of **5** could be constructed through a sequence of Claisen rearrangement of **7** and RCM of **6**. The Claisen rearrangement precursor **7** would be obtained from **8**, a product of a catalytic asymmetric Diels–Alder reaction previously developed in our group,[13] through alkylation and aldol

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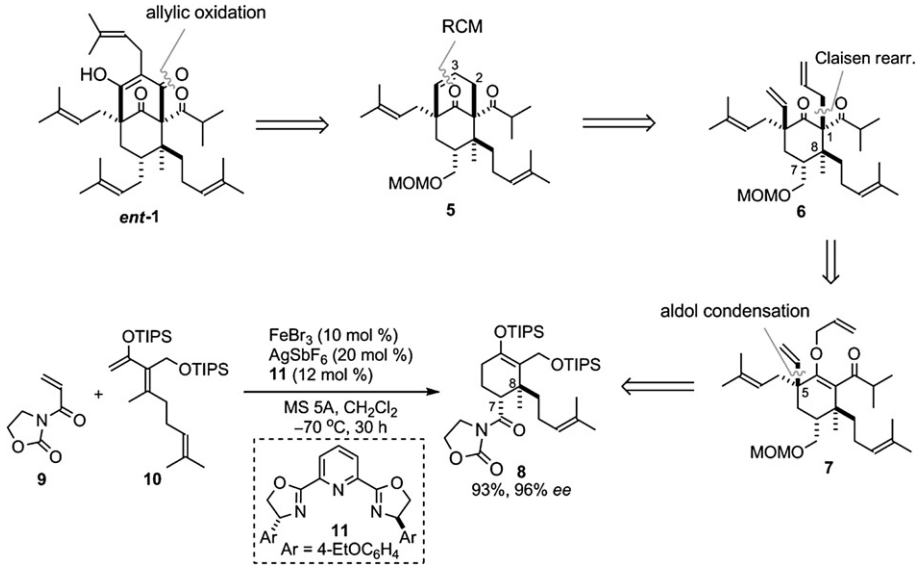
doi:10.1016/j.tet.2010.05.086

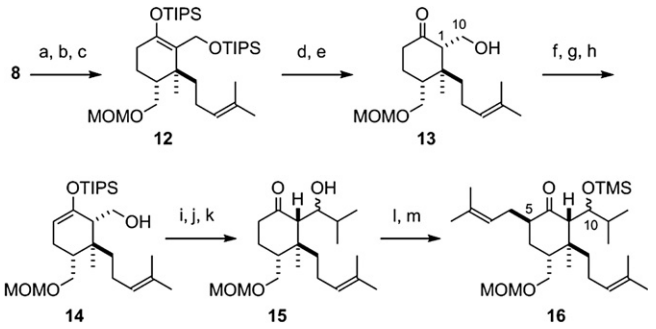



**Scheme 1.** Retrosynthetic analysis.

condensation at C5 followed by dehydration. The Diels–Alder reaction between **9** and **10** was promoted by a cationic iron–pybox (**11**) complex, and afforded the product **8** in 93% yield and 96% ee with complete *exo* selectivity (dr >33:1). The product has C7–C8 contiguous tertiary and quaternary stereocenters, which are required for hyperforin, and because this reaction can be routinely conducted in up to 20-g scale, it is a good starting point for the total synthesis of complex molecules. To establish a reliable synthetic route toward hyperforin, a significant amount of Diels–Alder product **8** was required. Hence, we utilized chiral pybox **11** derived from inexpensive (*R*)-4-hydroxyphenylglycine for the catalytic asymmetric Diels–Alder reaction, which resulted in the synthesis of *ent*-hyperforin (*ent*-**1**).

### 2.1. Claisen rearrangement–ring closing metathesis approach

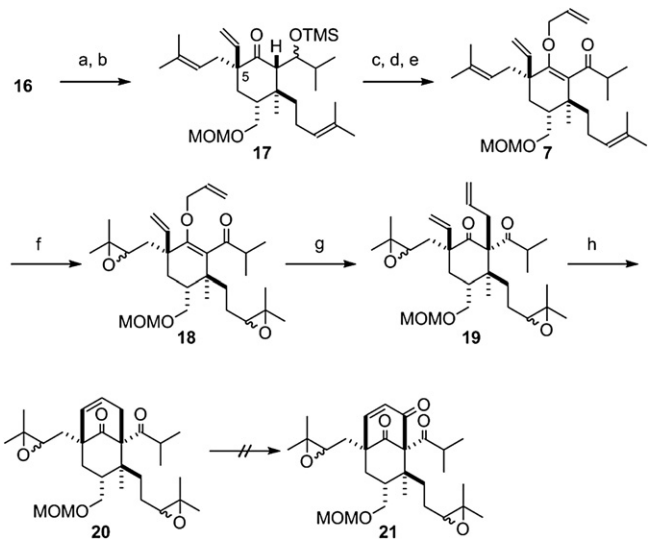
We first converted the Diels–Alder adduct **8** to MOM ether **12** in three steps: addition of thiolate, reduction, and protection, with high efficiency (Scheme 2). Because the C10 hydroxy group was readily eliminated to give the corresponding enone under various reaction conditions, cleavage of the two TIPS groups was conducted by a two-step sequence, which afforded primary alcohol **13**. Although the hydrolysis of enol TIPS ether gave a 1:1 diastereomixture at C1 and the following conversions were described from one isomer, the other isomer was also applicable for the total synthesis with comparable efficiency. Direct oxidation of **13** and subsequent addition of an isopropyl group to C10 were difficult due to the instability of the intermediate aldehyde derived from **13**. Hence, **15** was synthesized via **14**, which was produced from **13** by temporary protection of the primary alcohol with a TMS group, protection of the ketone as an enol silyl ether, and selective cleavage of the TMS ether. After oxidation of **14** with TPAP[14] followed by introduction of the isopropyl group under Barbier conditions (dr=5:1), hydrolysis of the silyl enol ether afforded ketone **15**. Multiple steps were required for the apparently simple conversion from **13** to **15**, but the overall yield was reasonable (58% over six steps). After protection of the C10 hydroxy group of **15** with a TMS group, prenylation of the kinetically produced lithium enolate proceeded exclusively from the axial β face at C5 to give **16**. The two diastereomers derived from the C10 stereocenter exhibited distinctly different reactivity in this step. One isomer showed excellent reactivity, but the other isomer decomposed a little under the same conditions. Therefore, the ratio of the product diastereomers was enriched to 9:1.




**Scheme 2.** Conversion of catalytic asymmetric Diels–Alder product. Reagents and conditions: (a) EtSLi, THF, 96%. (b) LAH, THF, 99%. (c) MOMCl, TBAI, *i*-$Pr_2NEt$, $CH_2Cl_2$, 94%. (d) TBAF, AcOH, THF. (e) HF·Py, pyridine, THF, 91% (two steps; dr=1:1). (f) TMSCl, $NEt_3$, $CH_2Cl_2$. (g) TIPSOTf, *i*-$Pr_2NEt$, $CH_2Cl_2$. (h) $K_2CO_3$, MeOH. (i) TPAP (10 mol %), NMO, MS 4 Å, $CH_3CN/CH_2Cl_2$. (j) 2-bromopropane, Li, THF (dr=5:1). (k) TBAF, AcOH, THF, 58% (six steps). (l) TMSCl, imidazole, DMF, 94%. (m) LDA, HMPA, prenyl bromide, THF, 89%.

The C5 quaternary center was constructed efficiently and stereoselectively by aldol condensation with acetaldehyde from the axial side, and the resulting hydroxy group was eliminated under Martin sulfurane conditions to give **17** (Scheme 3). Subsequent cleavage of the TMS ether, oxidation of the secondary alcohol with Dess–Martin reagent,[15] and O-allylation produced **7**. The stage was set for the key Claisen rearrangement, but heating **7** in toluene to 180 °C in a sealed tube equipment gave only a complex mixture. Similar results were obtained in the garsubellin A synthesis due to an unprotected C5 prenyl group. Although Mukaiyama hydration[16] to protect the prenyl groups gave a complicated reaction mixture, treatment with *m*-CPBA afforded selective epoxidation. The obtained diepoxide **18** was a complex diastereomeric mixture, but the subsequent Claisen rearrangement of **18**, which proceeded in moderate yield, and the critical RCM using a Hoveyda–Grubbs second generation catalyst[17] successfully produced the bicyclo [3.3.1] core. The structure was confirmed after converting the epoxides to prenyl groups ($VCl_3(THF)_3$, Zn, $CH_2Cl_2$).[18] Although the construction of bicyclo[3.3.1] core was achieved via the Claisen rearrangement–RCM sequence, the planned allylic oxidation at C2 was very difficult due to the presence of epoxides. The well-

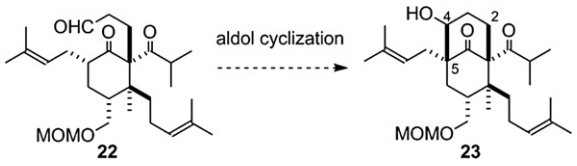
established $SeO_2$-mediated allylic oxidation and Barton's conditions,[19] which was successfully applied in the total synthesis of garsubellin A, resulted in decomposition. After the extensive investigation, we were forced to change our strategy.




**Scheme 3.** Claisen rearrangement–RCM approach toward bicyclic core. Reagents and conditions: (a) LDA, TMEDA, acetaldehyde, THF, >99%. (b) Martin sulfurane, toluene/$CH_2Cl_2$. (c) HF·Py, pyridine, THF, 73% (two steps). (d) DMP, $CH_2Cl_2$, 90%. (e) KHMDS, HMPA, allyl iodide, THF, 89%. (f) *m*-CPBA, $CH_2Cl_2$, 74%. (g) toluene, 180 °C, 46%. (h) Hoveyda–Grubbs second cat., toluene, 74%.

### 2.2. Claisen rearrangement–intramolecular aldol cyclization approach

Considering the problems of the RCM approach, we next chose an intramolecular aldol cyclization to construct the bicyclo[3.3.1] core (Scheme 4). The intramolecular aldol reaction has two main benefits. First, protection of the prenyl groups is not required, so the complex diastereomixture derived from the diepoxide can be avoided. Second, the obtained product has a C4 oxygen function, that is, useful for further oxidation at C2.




**Scheme 4.** Aldol cyclization approach.

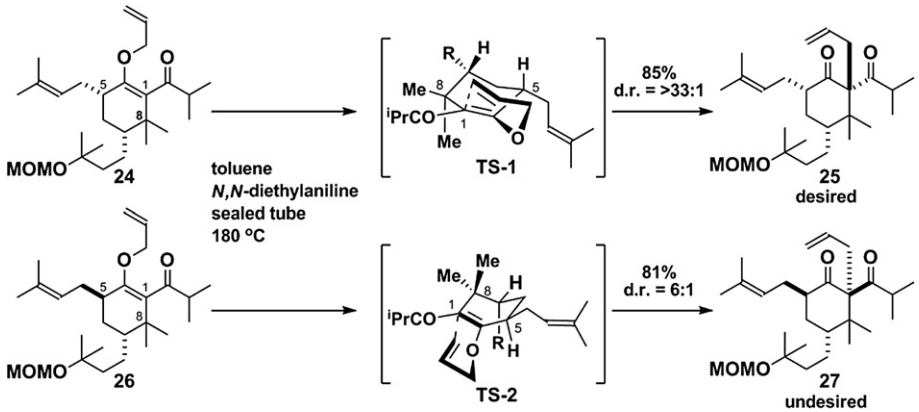
In this intramolecular aldol cyclization approach, we first focused on stereoselective construction of the C1 quaternary carbon center. Based on the successful production of the bicyclo[3.3.1] core discussed above, Claisen rearrangement is a reliable method for constructing this quaternary center. In addition, our model study clearly showed the importance of C5 stereochemistry to control the diastereoselectivity of the Claisen rearrangement (Scheme 5); the C5 prenyl group was a main factor in determining the conformation during the transition state and the rearrangement proceeded from the indicated face, avoiding steric repulsion between the pseudo axial methyl group at C8 and the allyl group.[20]

Therefore, the actual substrate, β-prenyl **16**, was converted to α-prenyl **28** before Claisen rearrangement through a deprotonation/kinetic protonation sequence (Scheme 6). Cleavage of the TMS ether, Dess–Martin oxidation, and O-allylation produced **29**, the precursor of the Claisen rearrangement. Consistent with the model study, thermal Claisen rearrangement of **29** proceeded selectively (dr=12:1) from the β face. In this reaction, it was necessary to add *N*,*N*-diethylaniline to remove the trace amount of acid that caused irreproducible results. At this point, three contiguous stereocenters, including two adjacent quaternary centers, were constructed with high selectivity. The key bicyclic intermediate **31** was synthesized uneventfully from **30** through selective hydroboration at the terminal double bond using disiamylborane [$(Sia)_2BH$], Dess–Martin oxidation, intramolecular aldol cyclization of resulting aldehyde **22**, and oxidation.

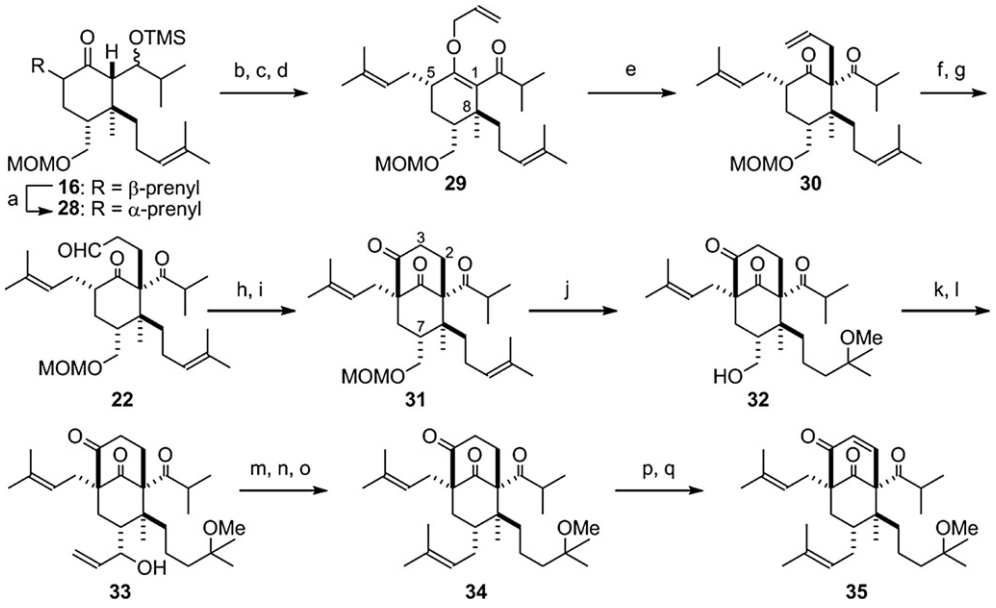
From **31**, the remaining tasks were to: (1) convert the C7 MOM ether moiety into a prenyl group, (2) oxidize C2, and (3) install a prenyl group at C3. Of these tasks, conversion of the C7 MOM ether to a prenyl group was conducted first. Cleavage of the MOM ether under acidic conditions proceeded with concomitant protection of the homoprenyl group at C8 to give **32**. This unplanned selective protection was desirable because the reactive homoprenyl group caused an undesired RCM rather than cross-metathesis at a later stage. Swern oxidation of **32** followed by the addition of a vinyl Grignard reagent afforded allylic alcohol **33** as a single isomer, which was deoxygenated through acetylation and a palladium-catalyzed allylic reduction.[11e,21] The subsequent cross-metathesis with isobutene using the Hoveyda–Grubbs second generation catalyst produced a third prenyl group at C7.[17,22] Then, **34** was oxidized to enone **35** under the conventional palladium-mediated conditions.[23]

### 2.3. Intermolecular approach toward C2 oxidation

The oxidation of C2 was studied next, but this task proved to be very difficult. As a first attempt, selective epoxidation of the electron-deficient olefin was examined using model substrate **36**



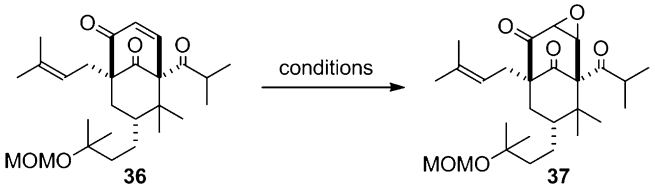

**Scheme 5.** Selectivity of Claisen rearrangement.




**Scheme 6.** Construction of the bicyclic core. Reagents and conditions: (a) LDA, THF; $NH_4Cl$ aq, 88% (dr >33:1). (b) HF·Py, pyridine, THF. (c) DMP, $CH_2Cl_2$, 96% (two steps). (d) NaHMDS, allyl bromide, HMPA, THF, >99%. (e) toluene, *N*,*N*-diethylaniline, 170 °C, >99% (dr=12:1). (f) $(Sia)_2BH$, THF; $H_2O_2$ aq, NaOH aq, EtOH, 81%. (g) DMP, $CH_2Cl_2$, 91%. (h) NaOEt, EtOH. (i) DMP, $CH_2Cl_2$, 86% (two steps). (j) (+)-CSA, MeOH, 66% (three cycles). (k) $(COCl)_2$, DMSO, $CH_2Cl_2$; $NEt_3$, 95%. (l) vinylmagnesium bromide, THF, 92% (dr >33:1). (m) $Ac_2O$, DMAP, *i*-$Pr_2NEt$, $CH_2Cl_2$, 98%. (n) $Pd(PPh_3)_4$ (20 mol %), $HCO_2NH_4$, toluene, 95%. (o) Hoveyda–Grubbs second cat. (15 mol %), 2-methyl-2-butene, $CH_2Cl_2$, >99%. (p) TMSCl, $NEt_3$, DMAP, $CH_2Cl_2$, 84%. (q) $Pd(OAc)_2$, DMSO, $O_2$, >99%.

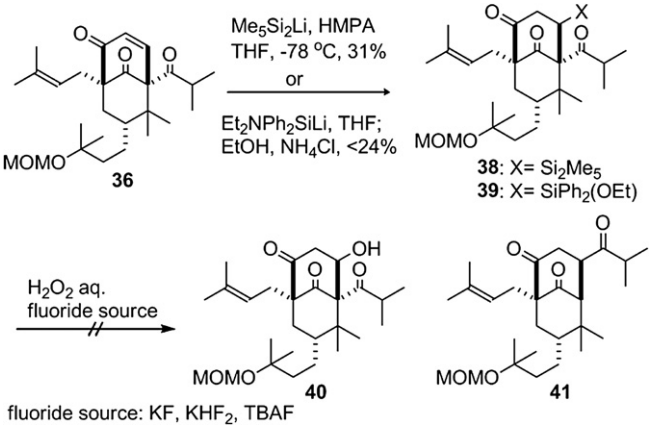
(Table 1). Conventional conditions, such as using a base and $H_2O_2$ in the presence or absence of a phase transfer catalyst, resulted in decomposition of the substrate. The failure would be attributed to the instability of the substrate or the product under rather basic conditions. In addition, catalytic epoxidation using La-BINOL–triphenylarsine oxide complex,[24] which proceeds under milder conditions than conventional methods and sometimes shows special reactivity toward unreactive substrates, did not work, possibly due to the highly congested nature of the C2-position, which is next to the quaternary carbon center.

**Table 1**
Epoxidation of enone




| Entry | Conditions | Results |
|---|---|---|
| 1 | LiOH aq, $H_2O_2$ aq, $CH_3CN$ | decomp. |
| 2 | NaOH aq, $H_2O_2$ aq, $CH_3CN$ | decomp. |
| 3 | TBAF, $H_2O_2$ aq, DMSO | decomp. |
| 4 | NaOH aq, $H_2O_2$ aq, TBAB, toluene | decomp. |
| 5 | TBHP, Triton B, toluene | decomp. |
| 6 | (*S*)-BINOL, $Ph_3As{=}O$, $La(OiPr)_3$ TBHP, MS4 Å, THF | NR |

In the second attempt, we used conjugate addition of a silyl group followed by Tamao–Fleming oxidation (Scheme 7).[25] It is well known that a silyl group can be used as a masked hydroxy functionality, and it usually attacks electrophiles in a 1,4-addition manner. The reaction might not be very sensitive to steric factors due to the high nucleophilicity of a silyl anion and a large atomic radius of a silicon atom. It was also applicable in our case; two types of silyl groups were introduced to afford β-silyl ketones **38** and **39**. Although the yields were far from satisfactory, it is noteworthy that a proper nucleophile could be introduced at the highly congested C2-position. With the desired β-silyl ketones in hand, Tamao–Fleming oxidation was examined using $H_2O_2$ as an oxidant with some fluoride sources or bases. These conditions gave complex mixtures, however, and the only detectable side product was **41**; the silyl group, activated by fluoride, was removed from the substrate before oxidation, and the resulting anion attacked the neighboring isopropyl ketone. More reactive oxidants were not a good choice because of the prenyl group.



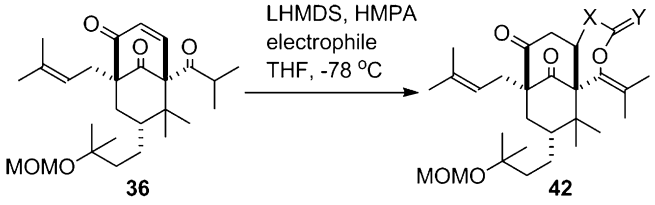

**Scheme 7.** Tamao–Fleming oxidation approach.

## 2.4. Intramolecular approach toward C2 oxidation

As mentioned above, one of the reasons for the failure in C2 oxidation may have been the highly congested nature of this position. To overcome this issue, we planned to use the C1 isopropyl ketone as a nucleophile anchor; selective formation of an isopropyl ketone enolate, trapping it with carbon dioxide, with the resulting

nucleophilic oxygen attacking the enone. Based on this idea, not only carbon dioxide but also isocyanates and carbon disulfide were examined with LHMDS as a base to generate the enolate (Table 2). Only carbon disulfide gave the desired product in high yield, and the other reagents did not react at all. The conversion of sulfur to oxygen was examined next. We investigated the radical approach, Pummerer rearrangement, and addition elimination approaches, but none of them were successful. Though further conversion was not accomplished, this result showed clear potential for the intramolecular approach using isopropyl ketone as the anchor.

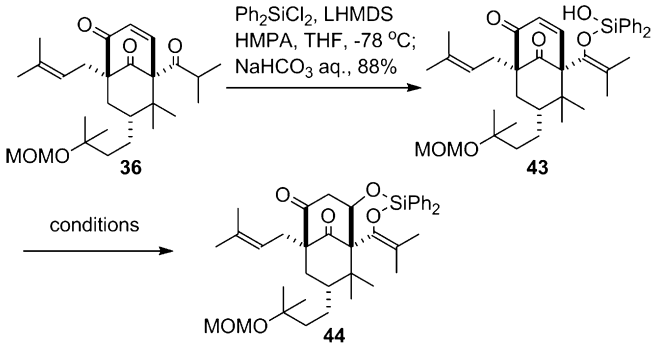
**Table 2**
Intramolecular approach




| Entry | Electrophile | Yield |
|---|---|---|
| 1 | $CO_2$ | NR |
| 2 | EtNCO | NR |
| 3 | PhNCO | NR |
| 4 | $CS_2$ | 91% |

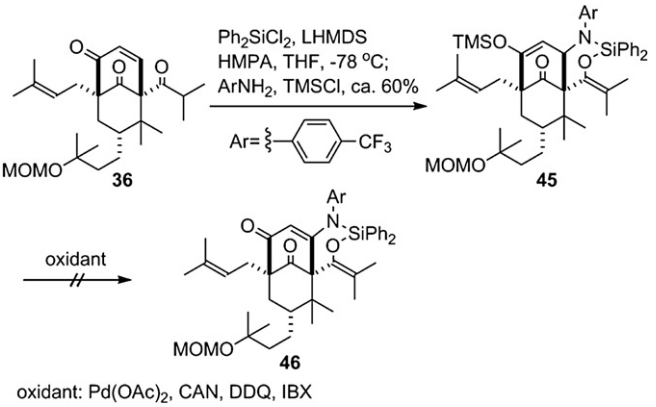
Silyl dichloride was the next candidate tether; after trapping the enolate, addition of another nucleophile, such as water or amine, would displace the remaining chloride and consequently add to the enone intramolecularly. The use of water as a nucleophile gave silanol **43** in good yield, and it was relatively stable. To induce the oxy-Michael reaction, several amine bases, strong bases, and a Pd catalyst were tested, but **43** did not have sufficient reactivity to produce **44**, and the harsh conditions resulted in cleavage of the silyl group (Table 3).

**Table 3**
Intramolecular addition of silanol




| Entry | Conditions | Results |
|---|---|---|
| 1 | DBU (20 mol %), THF, rt | **36** |
| 2 | *i*-$Pr_2NEt$ (20 mol %), THF, 50 °C | NR |
| 3 | *i*-$Pr_2NH$ (20 mol %), THF, 50 °C | NR |
| 4 | KHMDS (20 mol %), THF, −10 °C | **36** |
| 5 | $(CH_3CN)_2PdCl_2$ (50 mol %), $CH_2Cl_2$, rt. | decomp. |

The addition of nitrogen instead of oxygen is an alternative pathway because of its higher nucleophilicity. If nitrogen is incorporated at C2, conversion to oxygen would be possible via enamine or imine formation followed by hydrolysis. As expected, the addition of amines produced the desired 1,4-addition products, but the Si–N bond was too labile for further transformation in the case of allyl amine and aniline as nucleophiles (retro-Mannich reaction occurred). Electron deficient *p*-trifluoromethylaniline, however, showed different behavior (Scheme 8). Compound **36** was treated with LHMDS in the presence of diphenyldichlorosilane, and after formation of enol silyl ether, *p*-trifluoromethylaniline and TMSCl were added. Due to its rather low nucleophilicity, 1,4-addition did not proceed in the absence of TMSCl, but the stability of the product was moderate and tolerated under several reaction conditions. In this case, however, the electron deficient nature of *p*-trifluoromethylaniline prevented oxidation to the imine, and attempts toward enamine formation failed under various conditions.

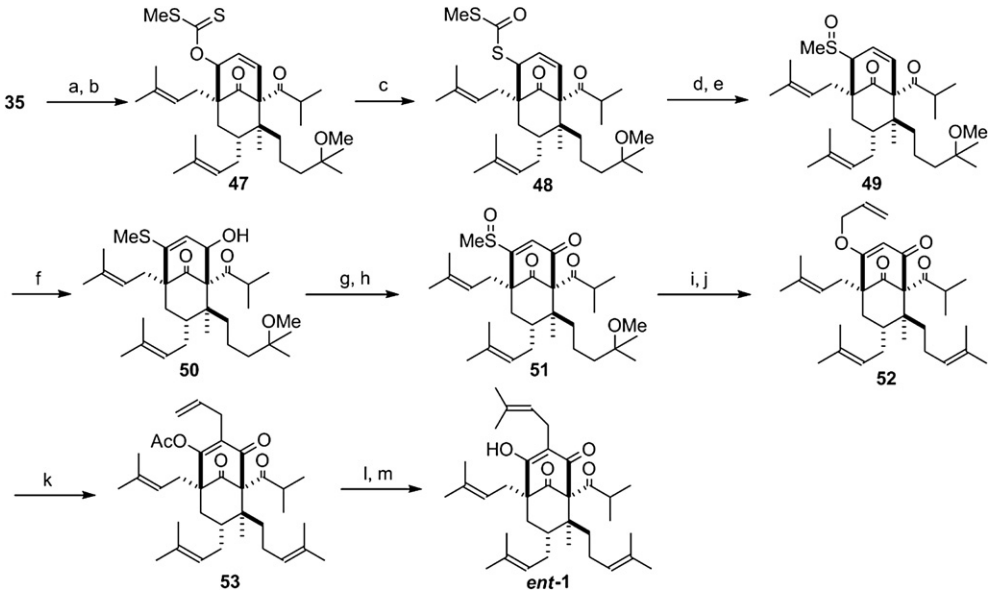



**Scheme 8.** Intramolecular addition of silyl aniline.

## 2.5. Successful oxidation of C2 by vinylogous Pummerer rearrangement and completion of the total synthesis

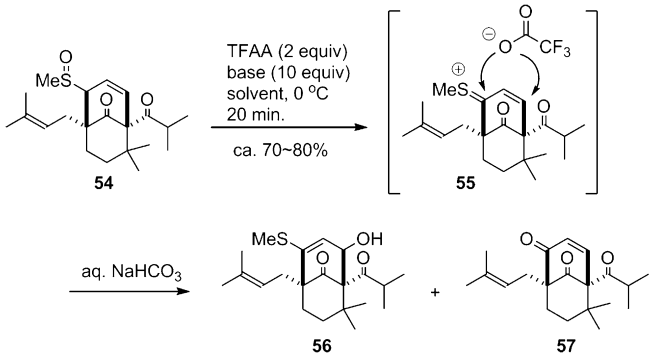
Finally, we planned to incorporate a sulfur atom at the C2-position and hoped that subsequent Pummerer rearrangement would give the desired oxygen function. Because intermolecular addition of thiols to the C2-position did not proceed at all, we chose a [3,3]-sigmatropic rearrangement of xanthate **47**, which was efficiently produced from enone **35** (Scheme 9). Thermal rearrangement of **47** proceeded cleanly, but the expected functionalization at C2 did not occur. Instead, dithioate **48** was obtained by a [1,3] rearrangement.[26] This result would be due to the rather rigid skeleton of **47**, therefore unable to form a proper conformation required for the expected [3,3]-sigmatropic rearrangement. This finding, however, led us to attempt a vinylogous Pummerer rearrangement for the oxidation of C2.[27] The intermediate thionium cation would be highly electrophilic, making it possible to introduce an oxygen functionality at the C2-position.

Based on this hypothesis, we studied the critical vinylogous Pummerer rearrangement intensively using sulfoxide **54** as a model substrate (Table 4). Treatment of **54** with trifluoroacetic anhydride in the presence of $NEt_3$ resulted in the vinylogous Pummerer rearrangement and normal Pummerer rearrangement proceeding at comparable rates, thereby affording, after hydrolysis, a 1:1.1 mixture of the desired allylic alcohol **56** and enone **57** (entry 1). Encouraged by this result, we then optimized the reaction conditions. The regioselectivity was greatly influenced by the base used. Among the bases examined, pyridine preferentially afforded **56** in moderate selectivity (entry 2; **56**/**57**=3:1). The selectivity was improved by increasing the steric bulkiness of the pyridine-derived bases. 2,6-Di-*tert*-butylpyridine was finally found to be the optimum base, giving **56** as the major product with a selectivity of 8.3:1 (entry 4).




**Scheme 9.** Completion of the total synthesis. Reagents and conditions: (a) $NaBH_4$, MeOH, 95% (dr >33:1). (b) $CS_2$, NaH, THF; MeI, >99%. (c) toluene, 150 °C. (d) EtSLi, THF; MeI, $NEt_3$, 98% (two steps). (e) $NaBO_3 \cdot 4H_2O$, AcOH (dr=1.3:1), 95%. (f) TFAA, 2,6-di-*tert*-butylpyridine, $CH_2Cl_2$, −40 °C; $H_2O$, 65% (dr >33:1). (g) $H_2O_2$, HFIP, 87% (dr=9:1). (h) DMP, $CH_2Cl_2$, 86%. (i) Amberlyst 15DRY, toluene, 55%. (j) LiH, allyl alcohol, 67%. (k) $Pd_2dba_3 \cdot CHCl_3$ (10 mol %), (*S*)-tol-BINAP (20 mol %), THF; $Ac_2O$, pyridine, 50%. (l) Hoveyda–Grubbs second cat. (15 mol %), 2-methyl-2-butene, $CH_2Cl_2$, 34%. (m) $K_2CO_3$, MeOH, 94%.

**Table 4**
Selectivity of the vinylogous Pummerer rearrangement




| Entry | Solvent | Base | 56:57[a] |
|---|---|---|---|
| 1 | Toluene | $Et_3N$ | 1:1.1 |
| 2[b] | Toluene | Pyridine | 3.0:1 |
| 3 | $CH_2Cl_2$ | 2,6-Lutidine | 3.6:1 |
| 4[c] | $CH_2Cl_2$ | 2,6-Di-*tert*-butylpyridine | 8.3:1 |

[a] Determined by $^1H$ NMR spectroscopy.
[b] 5 equiv of TFAA were used.
[c] 3 equiv of TFAA were used.

Having optimized the vinylogous Pummerer rearrangement with model substrate **54**, we applied the conditions to the actual substrate **49**, which was synthesized from **48** through thiolysis followed by S-methylation and S-oxidation[28] (Scheme 9). As expected, the vinylogous Pummerer rearrangement of **49** proceeded preferentially (4:1) to the normal Pummerer rearrangement under the optimized conditions, thereby providing the desired allylic alcohol **50** in 65% yield. The final task was to install the prenyl group at C3. S-Oxidation using $H_2O_2$ in hexafluoroisopropanol[29] followed by Dess–Martin oxidation of the allylic alcohol afforded sulfoxide **51**. After deprotection of the homoprenyl group through elimination of the methoxy group by treatment with an acidic resin, an addition/elimination sequence using allyl alcohol afforded allyl ether **52**. The catalyzed intramolecular allyl transfer presumably proceeded via a π-allyl–palladium intermediate, and enol acetate **53** was obtained in 50% yield after O-acetylation in a one pot reaction. It is noteworthy that thermal, microwave-assisted, and Lewis acid-mediated Claisen rearrangement of **52** only produced a trace amount of the product (giving either complex mixtures or no product). Finally, cross-metathesis to introduce the prenyl group at C3, and methanolysis of the acetate under basic conditions completed the total synthesis of *ent*-hyperforin (*ent*-**1**). $^1H$, $^{13}C$ NMR, and IR spectroscopic data as well as mass spectrometric data were all identical with the reported values. The optical rotation of synthesized *ent*-**1** was opposite to that of the natural isomer ($[\alpha]_D^{23}$ −36.8 (*c* 0.38, EtOH); lit. +41)[4] (Fig. 2).

## 3. Conclusion

In conclusion, we achieved the first catalytic asymmetric total synthesis of *ent*-hyperforin. The key reactions were: (1) an iron-catalyzed asymmetric Diels–Alder reaction to produce contiguous C7 and C8 stereocenters; (2) a stereoselective Claisen rearrangement to produce the bridgehead quaternary carbon atom at C1; (3) an intramolecular aldol reaction to produce the highly substituted bicyclic core; and (4) a vinylogous Pummerer rearrangement to install the oxygen functionality at the C2-position. These basic methods are applicable to the asymmetric synthesis of other PPAPs and analogues of hyperforin. Further improvements in the efficiency of the reactions, however, may be necessary for such applications. Studies are ongoing and will be reported in due course.

## 4. Experimental

### 4.1. General

Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a JEOL JNM-LA500 or ECX500 spectrometer, operating at 500 MHz for $^1H$ NMR and 125.65 MHz for $^{13}C$ NMR. Chemical shifts were reported in parts per million on the $\delta$ scale relative to residual $CHCl_3$ ($\delta$=7.26 for $^1H$ NMR and $\delta$=77.0 for $^{13}C$ NMR) as an internal

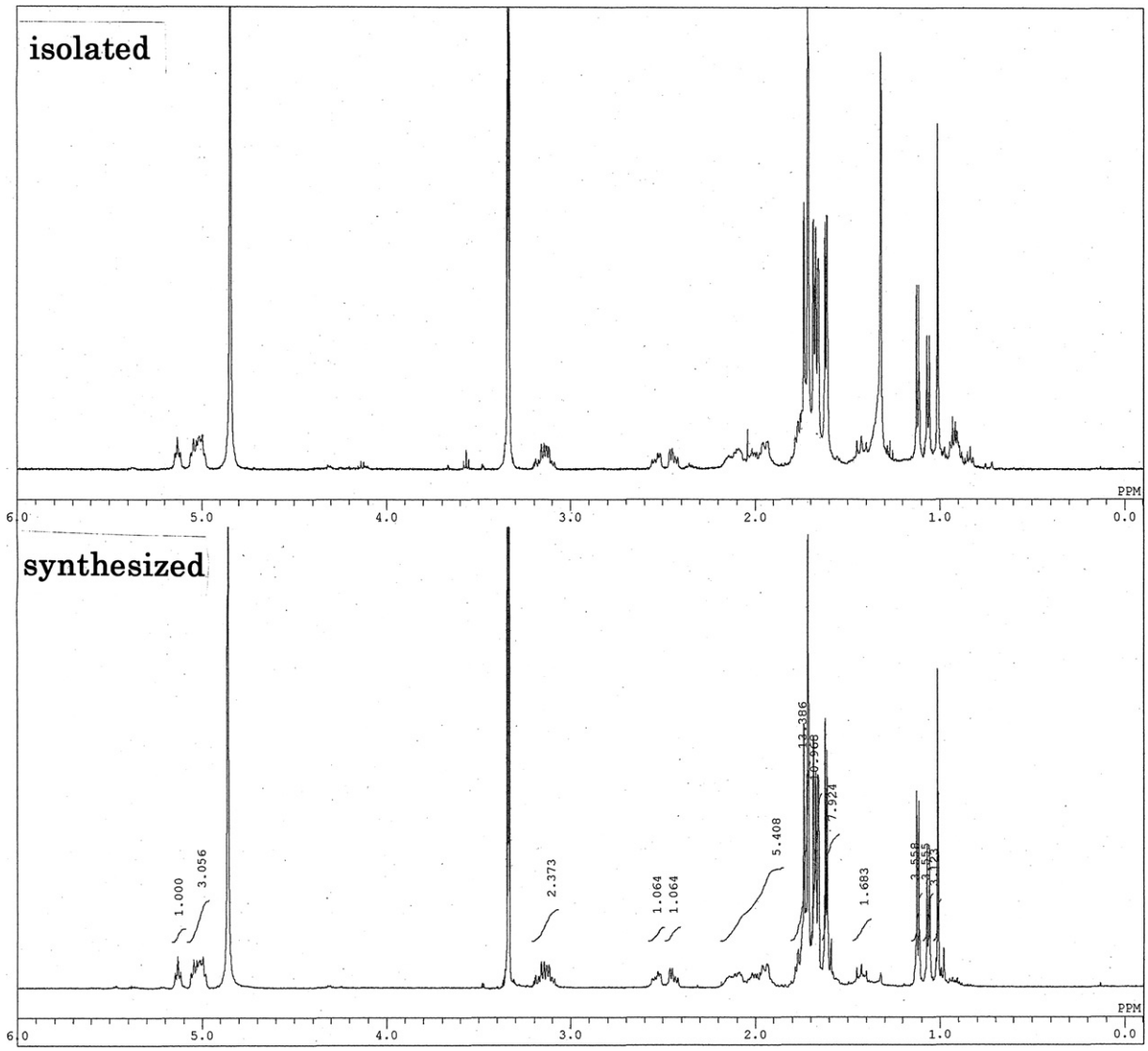



**Figure 2.** $^1$H NMR of hyperforin.

reference. Optical rotations were measured on a JASCO P-1010 polarimeter. ESI mass spectra were measured on Waters-ZQ4000 or JEOL The AccuTOF JMS-T100LC. EI mass spectra were measured on a JEOL JMS-BU20 GCmate. Column chromatography was performed with silica gel Merck 60 (230–400 mesh ASTM) or silica gel 60 N (KANTO CHEMICAL, spherical, neutral, 40–100 μm). Reactions were carried out in dry solvents under an argon atmosphere, unless otherwise stated. Dry tetrahydrofuran (THF) was purchased from Kanto Chemical. Co., Inc., or freshly distilled from $Ph_2CO$–Na. Other reagents were used as received from commercial sources, unless otherwise stated. Carbon numbering was shown in Figure 3.

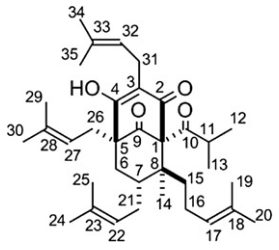
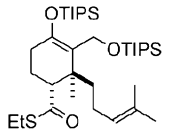


**Figure 3.** Numbering of hyperforin.

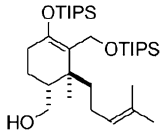
*4.1.1. (7R,8S)-S-Ethyl 8-methyl-8-(4-methylpent-3-enyl)-9-(triisopropylsilyloxy)-1-((triisopropylsilyloxy)methyl)cyclohex-1-enecarbothioate.*




To a solution of EtSH (2.1 ml, 28.5 mmol) in THF (81 ml) was added *n*-BuLi (11.9 ml, 19.0 mmol; 1.59 M in *n*-hexane) at 0 °C. After being stirred at the same temperature for 50 min, the resulting mixture was transferred to a solution of **8** (6.18 g, 9.51 mmol) in THF (63 ml) at 0 °C. The reaction was stirred at the same temperature for 30 min, and then quenched with saturated $NH_4Cl$ aq. The organic layer was separated and the aqueous layer was further extracted twice with diethyl ether. The combined organic layer was washed with water and brine, dried over $Na_2SO_4$, and concentrated to give a yellow oil. The residue was purified by column chromatography ($SiO_2$; EtOAc/hexane=1/50) to give thiol ester (5.68 g, 9.10 mmol, 96% yield) as a colorless oil. $^1$H NMR ($C_6D_6$) $\delta$: 5.34 (t, $J$=6.4 Hz, C17–1H), 5.09 (d, $J$=11.3 Hz, C10–1H), 4.42 (d, $J$=11.3 Hz,

C10–1H), 2.87 (dd, *J*=2.5, 11.3 Hz, C7–1H), 2.65–2.75 (m, SC*H*$_2$CH$_3$–2H), 2.46–2.54 (m, C5–1H), 1.87–2.19 (m, C5–1H, C6–2H, C15–1H, 16–2H), 1.75–1.80 (m, C15–1H), 1.69 (s, C20–3H), 1.68 (s, C19–3H), 1.63 (s, C14–3H), 1.14–1.17 (m, OTIPS–21H), 1.06–1.09 (m, OTIPS–21H), 1.05 (t, *J*=7.4 Hz, SCH$_2$C*H*$_3$–3H); $^{13}$C NMR (C$_6$D$_6$) *δ*: 198.7, 145.8, 129.5, 124.2, 118.5, 58.1, 54.1, 39.8, 37.2, 28.7, 24.6, 23.8, 22.8, 22.2, 21.1, 17.2, 17.1, 13.8, 12.6, 11.3; IR (neat, cm$^{-1}$): *ν* 1694; MS (EI) *m*/*z* 624 (M$^+$); HRMS (EI) calcd for C$_{35}$H$_{68}$O$_3$SSi$_2$ (M$^+$): 624.4428, Found: 624.4421; [*α*]$_D^{25}$ −24.2 (*c* 1.30, CH$_2$Cl$_2$) (87% ee).

*4.1.2. ((7R,8S)-8-Methyl-8-(4-methylpent-3-enyl)-9-(triisopropylsilyloxy)-1-((triisopropylsilyloxy)methyl)cyclohex-1-enyl)methanol.*




A solution of thiol ester (5.68 g, 9.10 mmol) in THF (18 ml) was added to a suspension of LAH (1.73 g, 45.5 mmol) in THF (35 ml) at 0 °C. The reaction was stirred at the same temperature for 45 min, and quenched by the successive addition of water (1.7 ml), 15% NaOH aq (1.7 ml), and water (5.1 ml). The resulting mixture was vigorously stirred for 30 min at room temperature. The white suspension was filtered through a pad of Celite, washed with CH$_2$Cl$_2$, and concentrated to give a pale yellow oil. The residue was purified by column chromatography (SiO$_2$; EtOAc/hexane=1/15 to 1/10) to give alcohol (5.23 g, 9.22 mmol, 100% yield) as a white solid. $^1$H NMR (C$_6$D$_6$) *δ*: 5.29 (t, *J*=6.1 Hz, C17–1H), 5.10 (d, *J*=11.2 Hz, C10–1H), 4.42 (d, *J*=11.2 Hz, C10–1H), 3.68 (dd, *J*=3.4, 10.1 Hz, C21–1H), 3.21 (dd, *J*=9.2, 10.1 Hz, C21–1H), 2.02–2.15 (m, C5–1H, C7–1H, C16–2H), 1.87–2.00 (m, C5–1H, 6–1H), 1.60–1.79 (m, C6–1H, 15–2H), 1.69 (s, C20–3H), 1.63 (s, C19–3H), 1.29 (s, C14–3H), 1.17–1.20 (m, OTIPS–21H), 1.07–1.11 (m, OTIPS–21H); $^{13}$C NMR (C$_6$D$_6$) *δ*: 146.9, 129.4, 119.0, 61.7, 58.3, 40.9, 38.4, 36.7, 29.1, 24.7, 22.6, 22.6, 20.2, 17.4, 17.2, 16.6, 12.8, 11.4; IR (neat, cm$^{-1}$): *ν* 3307, 1647; MS (EI) *m*/*z* 566 (M$^+$); HRMS (EI) calcd for C$_{33}$H$_{66}$O$_3$Si$_2$ (M$^+$): 566.4550, Found: 566.4549; [*α*]$_D^{25}$ −25.7 (*c* 0.86, CH$_2$Cl$_2$) (87% ee).

*4.1.3. Triisopropyl((7R,8S)-7-((methoxymethoxy)methyl)-8-methyl-8-(4-methylpent-3-enyl)-1-((triisopropylsilyloxy)methyl)cyclohex-9-enyloxy)silane (**12**).* To a solution of alcohol (5.23 g, 9.2 mmol) in CH$_2$Cl$_2$ (100 ml) were added *i*-Pr$_2$EtN (4.88 ml, 28 mmol) and MOMCl (2.13 ml, 28 mmol) at 0 °C. The resulting mixture was gradually warmed to room temperature, and stirred for 15.5 h. The reaction was quenched with water, and the organic layer was separated. The aqueous layer was further extracted twice with diethyl ether. The combined organic layer was washed with water and brine, dried over Na$_2$SO$_4$, and concentrated to give a yellow oil. The residue was purified by column chromatography (SiO$_2$; EtOAc/hexane=1/30) to give **12** (5.29 g, 8.66 mmol, 94% yield) as a colorless oil. $^1$H NMR (C$_6$D$_6$) *δ*: 5.31 (t, *J*=7.0 Hz, C17–1H), 5.11 (d, *J*=11.0 Hz, C10–1H), 4.54 (d, *J*=6.4 Hz, OC*H*$_2$OCH$_3$–1H), 4.51 (d, *J*=6.4 Hz, OC*H*$_2$OCH$_3$–1H), 4.44 (d, *J*=11.0 Hz, C10–1H), 3.75 (dd, *J*=3.4, 9.2 Hz, C21–1H), 3.31 (dd, *J*=9.2, 9.2 Hz, C21–1H), 3.21 (s, OCH$_2$OC*H*$_3$–3H), 2.18–2.26 (m, C5–1H), 2.06–2.18 (m, C5–1H, C6–1H, C16–2H), 1.87–2.03 (m, C6–1H, C7–1H, C15–1H), 1.77–1.84 (m, C15–1H), 1.68 (s, C20–3H), 1.63 (s, C19–3H), 1.30 (s, C14–3H), 1.18–1.20 (m, OTIPS–21H), 1.07–1.11 (m, OTIPS–21H); $^{13}$C NMR (C$_6$D$_6$) *δ*:146.8, 129.4, 124.6, 119.1, 95.8, 67.5, 58.4, 38.7, 38.5, 36.6, 29.2, 24.7, 22.7, 22.6, 20.9, 17.4, 17.2, 16.6, 12.8, 11.4; IR (neat, cm$^{-1}$): *ν* 1646; MS (EI) *m*/*z* 610 (M$^+$); HRMS (EI) calcd for C$_{35}$H$_{70}$O$_4$Si$_2$ (M$^+$): 610.4813, Found: 610.4808; [*α*]$_D^{23}$ −25.1 (*c* 0.87, CH$_2$Cl$_2$) (87% ee).

*4.1.4. (7R,8S)-1-(Hydroxymethyl)-7-((methoxymethoxy)methyl)-8-methyl-8-(4-methylpent-3-enyl)cyclohexanone (**13**).* To a solution of **12** (3.34 g, 5.47 mmol) and acetic acid (3.3 ml, 54.7 mmol) in THF (60 ml) was added TBAF (27 ml, 27 mmol; 1 M in THF) at 0 °C. The resulting mixture was stirred at room temperature for 50 h. The reaction was quenched with water, and the organic layer was separated. The aqueous layer was further extracted twice with EtOAc. The combined organic layer was washed with water and brine, dried over Na$_2$SO$_4$, and concentrated to give a yellow oil, which was passed through a short column chromatography (SiO$_2$; EtOAc/hexane=1/1). The products were used in the next step without further purification.

To a solution of the residue and pyridine (5 ml) in THF (80 ml) was added HF–Py (10 ml) slowly at 0 °C. The mixture was stirred at room temperature for 22 h. The reaction was poured into ice cooled 25% NH$_3$ aq slowly to be neutralized. The organic layer was separated and the aqueous layer was further extracted twice with EtOAc. The combined organic layer was washed with water and brine, dried over Na$_2$SO$_4$, and concentrated to give a yellow oil. The residue was purified by column chromatography (SiO$_2$; EtOAc/hexane=1/3) to give **13**-*α* (*α*-hydroxymethyl: 742 mg, 2.49 mmol, 46% yield) and **13**-β (β-hydroxymethyl: 729 mg, 2.45 mmol, 45%) as a colorless oil.

*4.1.4.1. (1S)-α-Hydroxymethyl (**13**-α).* $^1$H NMR (CDCl$_3$) *δ*: 5.01 (t, *J*=7.3 Hz, C17–1H), 4.56 (d, *J*=6.6 Hz, OC*H*$_2$OCH$_3$–1H), 4.54 (d, *J*=6.6 Hz, OC*H*$_2$OCH$_3$–1H), 3.89 (dd, *J*=9.2, 11.6 Hz, C10–1H), 3.63 (dd, *J*=3.7, 9.4 Hz, C21–1H), 3.52 (dd, *J*=3.2, 11.6 Hz, C10–1H), 3.29 (s, OCH$_2$OC*H*$_3$–3H), 3.20 (dd, *J*=8.6, 9.4 Hz, C21–1H), 2.62 (dd, *J*=3.2, 9.2 Hz, C1–1H), 2.27–2.39 (m, C5–2H), 2.13–2.25 (m, C6–1H, C7–1H), 2.04–2.12 (m, C16–1H), 1.89–1.97 (m, C16–1H), 1.57–1.63 (m, C6–1H, C20–3H), 1.56 (s, C19–3H), 1.40 (ddd, *J*=4.9, 12.6, 15.3 Hz, C15–1H), 1.27 (ddd, *J*=4.9, 12.9, 15.3 Hz, C15–1H), 0.63 (s, C14–3H); $^{13}$C NMR (CDCl$_3$) *δ*: 214.0, 130.9, 122.3, 95.5, 66.4, 56.7, 56.5, 54.1, 41.4, 40.3, 40.1, 35.5, 25.3, 24.6, 20.1, 17.4, 16.5; IR (neat, cm$^{-1}$): *ν* 3487, 1707; MS (EI) *m*/*z* 298 (M$^+$); HRMS (EI) calcd for C$_{17}$H$_{30}$O$_4$ (M$^+$): 298.2144, Found: 298.2141; [*α*]$_D^{23}$ 14.9 (*c* 1.53, CHCl$_3$) (96% ee).

*4.1.4.2. (1R)-β-Hydroxymethyl (**13**-β).* $^1$H NMR (CDCl$_3$) *δ*: 4.99 (t, *J*=7.0 Hz, C17–1H), 4.66 (d, *J*=6.5 Hz, OC*H*$_2$OCH$_3$–1H), 4.63 (d, *J*=6.5 Hz, OC*H*$_2$OCH$_3$–1H), 4.02 (dd, *J*=9.8, 11.0 Hz, C10–1H), 3.70–3.80 (m, C21–2H), 3.57 (dd, *J*=2.8, 11.0 Hz, C10–1H), 3.37 (s, OCH$_2$OC*H*$_3$–3H), 2.58 (dd, *J*=2.8, 9.8 Hz, C1–1H), 2.40–2.51 (m, C5–1H), 2.33–2.40 (m, C5–1H), 1.94–2.10 (m, C6–2H, C7–1H), 1.76–1.92 (m, C16–2H), 1.64 (s, C20–3H), 1.55 (s, C19–3H), 1.29 (ddd, *J*=5.2, 12.5, 13.8 Hz, C15–1H), 1.15 (ddd, *J*=4.6, 12.5, 12.5 Hz, 15–1H), 1.09 (s, C14–3H); $^{13}$C NMR (CDCl$_3$) *δ*:213.3, 130.6, 122.6, 95.5, 65.9, 58.9, 57.3, 54.2, 40.6, 38.5, 36.4, 35.6, 24.5, 23.0, 21.2, 20.3, 16.4; IR (neat, cm$^{-1}$): *ν* 3446, 1704; MS (EI) *m*/*z* 298 (M$^+$); HRMS (EI) calcd for C$_{17}$H$_{30}$O$_4$ (M$^+$): 298.2144, Found: 298.2144; [*α*]$_D^{23}$ 21.8 (*c* 2.02, CHCl$_3$) (96% ee).

*4.1.5. (1S,7R,8S)-1-(1-Hydroxy-2-methylpropyl)-7-((methoxymethoxy)methyl)-8-methyl-8-(4-methylpent-3-enyl)cyclohexanone (**15**).* To a solution of **13**-*α* (10.4 g, 34.9 mmol) in CH$_2$Cl$_2$ (230 ml) were added NEt$_3$ (14.7 ml, 105 mmol) and TMSCl (8.9 ml, 69.8 mmol) at 0 °C. The mixture was stirred at the same temperature for 30 min. The reaction was quenched with NEt$_3$ (15 ml) and water (60 ml). The organic layer was separated and the aqueous layer was further extracted with diethyl ether. The combined organic layer was washed with water and brine, dried over Na$_2$SO$_4$,

and concentrated to give a pale yellow oil. The obtained TMS ether was used in next step without purification.

To a solution of the residue in $CH_2Cl_2$ (230 ml) were added *i*-$Pr_2NEt$ (21.2 ml, 122 mmol) and TIPSOTf (23.5 ml, 87.3 mmol) at −78 °C over 10 min. The mixture was stirred for 15 min at the same temperature, and additionally for 12 h at 0 °C. The reaction was quenched with $NEt_3$ (20 ml) and water (60 ml), and the organic layer was separated. The aqueous layer was further extracted with diethyl ether. The combined organic layer was washed with water and brine, dried over $Na_2SO_4$, and concentrated to give pale a yellow oil. The obtained TIPS enol ether was used in next step without purification.

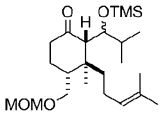
To a solution of the residue in MeOH (350 ml) was added $K_2CO_3$ (2.41 g, 17.4 mmol) at 0 °C, and the mixture was stirred for 1 h at the same temperature. Additional $K_2CO_3$ (2.41 g, 17.4 mmol) was added, and the mixture was stirred for 5.3 h. The reaction was quenched with saturated $NH_4Cl$ aq, and the organic layer was separated. The aqueous layer was extracted twice with diethyl ether. The combined organic layer was washed with water and brine, dried over $Na_2SO_4$, and concentrated to give **14** as a yellow oil. The obtained alcohol **14** was used in next step without further purification.

To a solution of **14** and MS 4 Å (19.4 g) in $CH_2Cl_2$ (210 ml) and $CH_3CN$ (22 ml) were added NMO (12.3 g, 105 ml) and TPAP (1.23 g, 3.29 mmol) at 0 °C. The mixture was stirred for 1 h at the same temperature and additionally for 1.5 h at room temperature. The mixture was filtered through a short pad silica gel, which was washed with $CH_2Cl_2$. The collected organic layer was concentrated to give a pale yellow oil. The obtained aldehyde was used in next step without further purification.

To a solution of the residue in THF (230 ml) were added 2-bromopropane (9.9 ml, 105 mmol) and Li wire (1.2 g, 175 mmol) at 0 °C, and the mixture was stirred vigorously at the same temperature. After 2.5 h, additional 2-bromopropane (1.8 ml, 19.1 mmol) and Li wire (720 mg, 104 mmol) were added. After being stirred for 3 h, Li wire (225 mg, 32.4 mmol) was added again, and the mixture was stirred for 30 min. The reaction was quenched with MeOH (30 ml), stirred for 30 min at 0 °C. After addition of saturated $NH_4Cl$ aq, the organic layer was separated, washed with water and brine. The aqueous layer was extracted twice with diethyl ether. The combined organic layer was washed with water and brine, dried over $Na_2SO_4$, and concentrated to give a pale yellow oil (a 1:5 diastereomixture derived from C-10). The obtained alcohol was used in next step without further purification.

To a solution of the residue in THF (350 ml) were added AcOH (20.0 ml, 349 mmol) and TBAF (175 ml, 175 mmol; 1.0 M in THF) at 0 °C over 30 min. The mixture was stirred for 12.5 h at the same temperature. The reaction was quenched with water at 0 °C. After removal of organic solvent by evaporation, the aqueous layer was extracted three times with diethyl ether. The combined organic layer was washed with saturated $NaHCO_3$ aq, dried over $Na_2SO_4$, and concentrated to give a pale yellow oil. The residue was purified by column chromatography ($SiO_2$; EtOAc/hexane=1/10 to 1/4) to give **15** (6.94 g, 20.4 mmol; 58% yield for six steps, a 1:5 diastereomixture derived from C-10) as a pale yellow oil.

*4.1.6. (1S,7R,8S)-7-((Methoxymethoxy)methyl)-8-methyl-1-(2-methyl-1-(trimethylsilyloxy)propyl)-8-(4-methylpent-3-enyl) cyclohexanone.*




To a solution of **15** (6.86 g, 20.2 mmol) in DMF (168 ml) were added imidazole (6.88 g, 101 mmol) and TMSCl (7.75 ml, 60.6 mmol) at 0 °C. The mixture was stirred at the same temperature for 2 h, and quenched with water. The organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layer was washed twice with water and brine, dried over $Na_2SO_4$, and concentrated to give a yellow oil. The residue was purified by column chromatography ($SiO_2$; EtOAc/hexane=1/9) to give TMS ether (7.85 g, 19.0 mmol, 94% yield, a 1:5 diastereomixture derived from C−10) as a pale yellow oil.

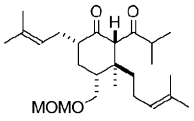
*4.1.7. (1S,5R,7R,8S)-7-((Methoxymethoxy)methyl)-8-methyl-1-(2-methyl-1-(trimethylsilyloxy)propyl)-5-(3-methylbut-2-enyl)-8-(4-methylpent-3-enyl)cyclohexanone (**16**).* To a solution of *N,N*-diisopropylamine (659 μl, 4.70 mmol) in THF (18 ml) was added *n*-BuLi (2.7 ml, 4.28 mmol; 1.5 M in *n*-hexane) at 0 °C. The mixture was stirred for 30 min at the same temperature. This LDA solution was added to a solution of TMS ether (353 mg, 855 μmol) in THF (21 ml) at −78 °C. After being stirred at 0 °C for 40 min, HMPA (2.23 ml, 12.8 mmol) and prenyl bromide (988 μl, 8.55 mmol) were added at −78 °C and the mixture was stirred at 0 °C for 25 min. The reaction was quenched with pH 6.9 buffer and stirred for 20 min at 0 °C and additionally for 20 min at room temperature. The organic layer was separated, and the aqueous layer was further extracted with diethyl ether twice. The combined organic layer was washed with water and brine, dried over $Na_2SO_4$, and concentrated to give a yellow oil. The residue was purified by column chromatography ($SiO_2$; EtOAc/hexane=1/100 to 1/40 to 1/30) to give **16** (365 mg, 759 μmol; 89% yield, a 9:1 diastereomixture derived from C−10) as a pale yellow oil.

*Major isomer.* $^1H$ NMR ($CDCl_3$) $\delta$: 5.05–5.10 (m, C27−1H), 4.96–5.01 (m, C17−1H), 4.62 (d, $J$=6.7 Hz, $OCH_2OCH_3$−1H), 4.60 (d, $J$=6.7 Hz, $OCH_2OCH_3$−1H), 4.21 (dd, $J$=2.9, 8.0 Hz, C10−1H), 3.71 (dd, $J$=3.5, 9.2 Hz, C21−1H), 3.36 (s, $OCH_2OCH_3$−3H), 3.27 (dd, $J$=9.2, 9.2 Hz, C21−1H), 2.80 (d, $J$=8.0 Hz, C1−1H), 2.35–2.44 (m, C5−1H, C11−1H), 2.15–2.24 (m, C6−1H, C7−1H), 2.04–2.10 (m, C26−2H), 1.95–2.00 (m, C16−2H), 1.77–1.86 (m, C6−1H), 1.69 (s, C30−3H), 1.66 (s, C20−3H), 1.64 (s, C29−3H), 1.62 (s, C19−3H), 1.39–1.49 (m, C15−1H), 1.23–1.35 (m, C15−1H), 0.93 (d, $J$=6.9 Hz, C12−3H), 0.86 (s, C14−3H), 0.79(d, $J$=6.9 Hz, C13−3H), 0.15 (s, OTMS−9H); $^{13}C$ NMR ($CDCl_3$) $\delta$: 216.5, 133.6, 131.2, 124.3, 120.9, 96.6, 75.7, 68.0, 55.2, 54.8, 49.9, 45.1, 38.4, 38.1, 33.8, 31.5, 29.8, 25.7, 25.7, 22.3, 20.9, 18.6, 18.0, 17.7, 16.4, 1.3; IR (neat, $cm^{-1}$): $\nu$ 1703; MS (ESI) $m/z$ 503 $(M+Na)^+$; HRMS (ESI) calcd for $C_{28}H_{52}O_4Si$ $(M+Na)^+$: 503.3533, Found: 503.3530; $[\alpha]_D^{26}$ −70.2($c$ 1.07, $CHCl_3$) (80% ee).

*4.1.8. (1S,5S,7R,8S)-7-Methoxymethoxymethyl-8-methyl-5-(3-methyl-but-2-enyl)-8-(4-methyl-pent-3-enyl)-1-(2-methyl-1-trimethylsilanyloxy-propyl)-cyclohexanone (**28**).* To a solution of *N,N*-diisopropylamine (2.2 ml, 15.5 mmol) in THF (62.9 ml) was added *n*-BuLi (9.4 ml, 14.9 mmol; 1.59 M in *n*-hexane) at 0 °C. The mixture was stirred for 35 min at the same temperature. The mixture was cooled to −78 °C, and then **16** (1.49 g, 3.10 mmol) in THF (20 ml) was added over 15 min. The mixture was stirred for 80 min at 0 °C. The reaction was quenched with saturated $NH_4Cl$ aq and the organic layer was separated. The aqueous layer was further extracted twice with EtOAc. The combined organic layer was washed with water and brine, dried over $Na_2SO_4$, and concentrated to give a pale yellow oil. The residue was purified by column chromatography ($SiO_2$; EtOAc/hexane=1/25) to give **28** (1.31 g, 2.72 mmol; 88% yield, a 9:1 diastereomixture) as a pale yellow oil. *Major isomer.* $^1H$ NMR ($CDCl_3$) $\delta$: 5.04–5.08 (m, C17−1H, C27−1H), 4.61 (d, $J$=6.4 Hz, $OCH_2OCH_3$−1H), 4.59 (d, $J$=6.4 Hz, $OCH_2OCH_3$−1H), 4.39 (dd, $J$=3.7, 8.0 Hz, C10−1H), 3.72 (dd, $J$=3.1, 9.5 Hz, C21−1H), 3.35 (s, $OCH_2OCH_3$−3H), 3.17 (dd, $J$=9.2, 9.5 Hz, C21−1H), 2.69 (d, $J$=8.0 Hz, C1−1H), 2.30–2.38 (m, C5−1H, C11−1H), 2.16–2.30 (m, C7−1H, C26−2H), 2.02–2.14 (m, C16−2H), 1.93 (ddd, $J$=7.4, 7.4, 14.7 Hz, C6−1H), 1.69 (s, C30−3H), 1.66 (s, C20−3H), 1.63 (s, C29−3H), 1.59

(s, C19–3H), 1.46–1.54 (m, C6–1H), 1.19–1.28 (m, C15–2H), 0.92 (d, *J*=7.0 Hz, C12–3H), 0.78(d, *J*=7.0 Hz, C13–3H), 0.74 (s, C14–3H), 0.14 (s, OTMS–9H); $^{13}$C NMR ($CDCl_3$) $\delta$: 214.3, 132.7, 131.0, 124.4, 122.0, 96.7, 75.3, 68.0, 57.0, 55.2, 51.6, 46.2, 42.5, 36.5, 34.9, 34.4, 27.7, 25.8, 25.7, 22.3, 20.0, 18.1, 17.8, 17.7, 17.4, 1.1; IR (neat, $cm^{-1}$): $\nu$ 1709; MS (ESI) *m*/*z* 503 $(M+Na)^+$; HRMS (ESI) calcd for $C_{28}H_{52}O_4Si$ $(M+Na)^+$: 503.3533, Found: 503.3535; $[\alpha]_D^{25}$ −45.8(*c* 1.24, $CHCl_3$) (80% ee).

*4.1.9. (1S,5S,7R,8S)-1-Isobutyryl-7-((methoxymethoxy)methyl)-8-methyl-5-(3-methylbut-2-enyl)-8-(4-methylpent-3-enyl) cyclohexanone.*



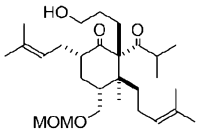

To a solution of **28** (5.64 g, 11.7 mmol) in THF (117 ml) was added pyridine (11.7 ml, 145 mmol) and HF–Py (23.4 ml) at 0 °C. The mixture was stirred at the same temperature for 1.5 h, and then poured into ice cooled 25% $NH_3$ aq to be neutralized. The organic phase was separated and the aqueous phase was further extracted twice with EtOAc. The combined organic layer was washed twice with saturated $NaHCO_3$ and brine, dried over $Na_2SO_4$, and concentrated to give a pale yellow oil, which was used in next step without further purification.

To a solution of crude mixture in $CH_2Cl_2$ (117 ml) was added Dess–Martin periodinane (9.93 g, 23.4 mmol) at 0 °C and stirred at the same temperature. After being stirred for 35 min, Dess–Martin periodinane (993 mg, 2.34 mmol) was added again and stirred for 15 min. The reaction was quenched with $Na_2S_2O_3$ aq and the organic layer was separated. The aqueous phase was further extracted twice with diethyl ether. The combined organic layer was washed twice with saturated $NaHCO_3$ aq and brine, dried over $Na_2SO_4$, and concentrated to give a pale yellow oil. The residue was purified by column chromatography ($SiO_2$; EtOAc/hexane=1/15) to give diketone (4.58 g, 113 mmol; 96% yield for two steps) as a pale yellow oil. $^1$H NMR ($CDCl_3$); $\delta$: 5.06–5.12 (m, C27–1H), 4.95–5.01 (m, C17–1H), 4.63 (d, *J*=6.4 Hz, $OCH_2OCH_3$–1H), 4.61 (d, *J*=6.4 Hz, $OCH_2OCH_3$–1H), 3.87 (s, C1–1H), 3.69 (dd, *J*=3.4, 9.5 Hz, 21–1H), 3.36 (s, $OCH_2OCH_3$–3H), 3.24 (dd, *J*=9.5, 9.5, C21–1H), 2.35–2.51 (m, C5–1H, C11–1H, C26–2H), 2.09–2.20 (m, C6–1H, C7–1H), 1.97 (ddd, *J*=8.0, 8.0, 15.6 Hz, C16–1H), 1.75–1.84 (m, C16–1H), 1.68 (s, C30–3H), 1.66 (s, C20–3H), 1.60 (s, C29–3H), 1.58 (s, C19–3H), 1.49–1.57 (m, C6–1H), 1.30–1.48 (m, C15–2H), 1.07 (d, *J*=6.7 Hz, C12–3H), 1.03 (d, *J*=6.7 Hz, C13–3H), 1.02 (s, C14–3H); $^{13}$C NMR ($CDCl_3$) $\delta$: 210.6, 209.5, 133.3, 131.9, 123.4, 121.3, 96.7, 67.4, 66.5, 55.2, 50.8, 44.6, 42.7, 41.9, 36.8, 33.1, 27.5, 25.8, 25.6, 21.9, 18.5, 18.0, 17.8, 17.6; IR (neat, $cm^{-1}$): $\nu$ 1724, 1703; MS (ESI) *m*/*z* 429 $(M+Na)^+$; HRMS (ESI) calcd for $C_{25}H_{42}O_4$ $(M+Na)^+$: 429.2981, Found: 429.2971; $[\alpha]_D^{25}$ −59.6 (*c* 1.20, $CHCl_3$) (80% ee).

*4.1.10. 1-((5S,7R,8S)-2-(Allyloxy)-7-((methoxymethoxy)methyl)-8-methyl-5-(3-methylbut-2-enyl)-8-(4-methylpent-3-enyl)cyclohex-1-enyl)-11-methylpropan-10-one (**29**).* To a solution of diketone (3.72 g, 9.15 mmol) were added HMPA (19.1 ml, 110 mmol) and NaHMDS (45.8 mml, 45.8 mmol; 1.0 M in THF) at 0 °C. The mixture was stirred for 35 min at the same temperature, and then allyl bromide (15.7 ml, 183 mmol) was added slowly. The mixture was stirred for 10 min and additionally for 50 min at room temperature. The reaction was quenched with pH 6.9 buffer and stirred vigorously for 1 h. The organic layer was separated and the aqueous layer was further extracted twice with diethyl ether. The combined organic layer was washed twice with water and brine, dried over $Na_2SO_4$, and concentrated to give a yellow oil. The residue was purified by column chromatography (neutral silica gel EtOAc/hexane=1/30) to give **29** (4.10 g, 9.18 mmol; 100% yield) as a pale yellow oil. $^1$H NMR ($CDCl_3$) $\delta$: 5.85 (tdd, *J*=5.8, 10.3, 17.2 Hz, $OCH_2CHCH_2$–1H), 5.20 (d, *J*=17.2 Hz, $OCH_2CHCH_2$–1H), 5.09–5.31 (m, $OCH_2CHCH_2$–1H, C27–1H), 5.03–5.09 (m, C17–1H), 4.60 (d, *J*=6.9 Hz, $OCH_2OCH_3$–1H), 4.59 (d, *J*=6.9 Hz, $OCH_2OCH_3$–1H), 4.19 (dd, *J*=5.8, 12.6 Hz, $OCH_2CHCH_2$–1H), 3.97 (dd, *J*=5.8, 12.6 Hz, $OCH_2CHCH_2$–1H), 3.63 (dd, *J*=2.9, 9.2 Hz, C21–1H), 3.33 (s, $OCH_2OCH_3$–3H), 3.17 (dd, *J*=9.2, 9.8 Hz, C21–1H), 2.75 (sep, *J*=6.9 Hz, C11–1H), 2.39–2.47(m, C1–1H), 2.27–2.34 (m, C7–1H), 1.92–2.05 (m, C6–1H, C16–1H, C26–2H4H), 1.76–1.84 (m, C16–1H), 1.68 (s, C30–3H), 1.63 (s, C20–3H), 1.59 (s, C29–3H), 1.58 (s, C19–3H), 1.23–1.44 (m, C6–1H, C15–2H), 1.09 (d, *J*=6.9 Hz, C12–3H), 1.03 (d, *J*=6.9 Hz, C13–3H), 0.94 (s, C14–3H); $^{13}$C NMR ($CDCl_3$) $\delta$: 212.5, 157.2, 133.8, 133.1, 133.0, 130.9, 124.7, 121.5, 117.2, 96.6, 71.8, 68.0, 55.1, 42.5, 39.6, 38.6, 37.7, 35.9, 30.2, 28.1, 25.8, 25.6, 23.4, 23.0, 18.8, 18.7, 17.9, 17.5; IR (neat, $cm^{-1}$): $\nu$ 1687; MS (ESI) *m*/*z* 469 $(M+Na)^+$; HRMS (ESI) calcd for $C_{28}H_{46}O_4$ $(M+Na)^+$: 469.3294, Found: 469.3283; $[\alpha]_D^{31}$ −9.3 (*c* 1.01, $CHCl_3$) (80% ee).

*4.1.11. (1S,5S,7R,8S)-1-Allyl-1-isobutyryl-7-((methoxymethoxy) methyl)-8-methyl-5-(3-methylbut-2-enyl)-8-(4-methylpent-3-enyl) cyclohexanone (**30**).* A solution of **29** (135 mg, 302 μmol) and *N*,*N*-diethylanilline (5.4 μl, 30.2 μmol) in toluene (600 μl) in sealed tube was heated at 170 °C for 7 h. The mixture was cooled to room temperature and diluted with diethyl ether. The mixture was washed with 1 M HCl aq, saturated $NaHCO_3$ aq and brine, dried over $Na_2SO_4$, and concentrated to give a yellow oil. The residue was purified by column chromatography ($SiO_2$; EtOAc/hexane=140 to 30) to give **30** (137 mg, 307 μmol, 100% yield; dr=12:1) as a colorless oil. $^1$H NMR ($CDCl_3$) $\delta$: 5.13–5.25 (m, C3–1H), 5.07–5.13 (m, C27–1H), 5.00–5.05 (m, C17–1H), 4.89–4.98 (m, C4–2H), 4.66 (d, *J*=6.7 Hz, $OCH_2OCH_3$–1H), 4.63 (d, *J*=6.7 Hz, $OCH_2OCH_3$–1H), 3.72 (dd, *J*=2.8, 9.2 Hz, C21–1H), 3.38 (s, $OCH_2OCH_3$–3H), 3.29–3.32 (m, C2–1H, C21–1H), 2.99 (sep, *J*=6.5 Hz, C11–1H), 2.33–2.50 (m, C2–1H, C5–1H, C6–1H, C7–1H, C26–1H), 1.92–2.13 (m, C16–2H, C26–1H), 1.68 (s, C30–3H), 1.66 (s, C20–3H), 1.61 (s, C29–3H), 1.59 (s, C19–3H), 1.25–1.44 (m, C6–1H, C15–2H), 1.18 (d, *J*=6.5 Hz, C12–3H), 1.08 (d, *J*=6.5 Hz, C13–3H), 0.92 (s, C14–3H); $^{13}$C NMR ($CDCl_3$) $\delta$: 216.7, 211.7, 133.9, 133.6, 132.1, 124.5, 122.0, 117.8, 97.1, 75.9, 69.4, 55.7, 48.1, 45.0, 41.4, 40.7, 36.7, 36.3, 32.4, 28.0, 26.2, 26.0, 24.3, 21.9, 20.8, 19.9, 18.1, 18.0; IR (neat, $cm^{-1}$): $\nu$ 1709, 1690; MS (ESI) *m*/*z* 469 $(M+Na)^+$; HRMS (ESI) calcd for $C_{28}H_{46}O_4$ $(M+Na)^+$: 469.3294, Found: 469.3286; $[\alpha]_D^{27}$ +8.59 (*c* 1.31, $CHCl_3$) (80% ee).

*4.1.12. (1S,5S,7R,8S)-1-(3-Hydroxypropyl)-1-isobutyryl-7-((methoxymethoxy)methyl)-8-methyl-5-(3-methylbut-2-enyl)-8-(4-methylpent-3-enyl)cyclohexanone.*




To a solution of $BH_3$·THF (5.4 ml, 5.91 mmol; 1.09 M in THF) was added 2-methyl-2-butene (1.3 ml, 11.8 mmol) at 0 °C, and the resulting mixture was stirred for 2 h to generate disiamylborane. Freshly prepared disiamylborane was added to a solution of **30** (881 mg, 1.97 mmol) in THF (20 ml) at 0 °C. The mixture was stirred for 40 min at the same temperature. The reaction was quenched with EtOH (6.4 ml), then 3 M NaOH aq (3.2 ml) and 30% $H_2O_2$ aq (3.2 ml) were added carefully to the mixture. After being stirred vigorously for 1 h at room temperature, the mixture was diluted with EtOAc and brine. The organic layer was separated and the aqueous layer was further extracted twice with EtOAc. The combined organic layer was washed with $Na_2S_2O_3$ aq, water and brine, dried over $Na_2SO_4$, and concentrated to give a pale yellow oil. The

residue was purified by column chromatography ($SiO_2$; EtOAc/hexane=1/3) to give alcohol (743 mg, 1.60 mmol, 81% yield) as a colorless oil. $^1$H NMR ($CDCl_3$) $\delta$: 5.08–5.12 (m, C27–1H), 4.99–5.02 (m, C17–1H), 4.62 (d, $J$=6.9 Hz, OC$H_2$OCH$_3$–1H), 4.59 (d, $J$=6.9 Hz, OC$H_2$OCH$_3$–1H), 3.69 (dd, $J$=3.5, 9.2 Hz, C21–1H), 3.53–3.57 (m, C4–1H), 3.22–3.51 (m, C4–1H), 3.35 (s, OCH$_2$OC$H_3$–3H), 3.30 (dd, $J$=9.2, 9.2 Hz, C21–1H), 2.98 (sep, $J$=6.3 Hz, C11–1H), 2.40–2.49 (m, C2–1H, C5–1H, C7–1H, C26–1H), 2.30–2.35 (m, C6–1H), 1.82–2.11 (m, O$H$–1H, C2–1H, C16–2H, C26–1H), 1.68 (s, C30–3H), 1.65 (s, C20–3H), 1.60 (s, C29–3H), 1.59 (s, C19–3H), 1.31–1.45 (m, C6–1H, C15–2H), 1.18 (d, $J$=6.3 Hz, C12–3H), 1.05 (d, $J$=6.3 Hz, C13–3H), 0.90–1.03 (m, C3–2H), 0.91 (s, C14–3H); $^{13}$C NMR ($CDCl_3$) $\delta$: 217.0, 212.3, 133.4, 131.2, 124.2, 121.5, 96.7, 75.5, 69.1, 62.6, 55.3, 47.0, 44.8, 41.2, 40.6, 35.7, 32.0, 28.5, 27.8, 27.5, 25.8, 25.6, 24.1, 21.7, 20.3, 19.5, 17.8, 17.6; IR (neat, cm$^{-1}$): $\nu$ 3436, 1705, 1688; MS (ESI) $m/z$ 487 (M+Na)$^+$; HRMS (ESI) calcd for $C_{28}H_{48}O_5$ (M+Na)$^+$: 487.3399, Found: 487.3392; $[\alpha]_D^{27}$ −12.9 ($c$ 1.16, $CHCl_3$) (80% ee).

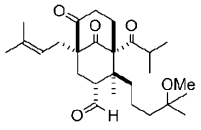
*4.1.13. 3-((1S,5S,7R,8S)-1-Isobutyryl-7-((methoxymethoxy)methyl)-8-methyl-5-(3-methylbut-2-enyl)-8-(4-methylpent-3-enyl)-9-oxocyclohexyl)propanal (**22**).* To a solution of alcohol (247 mg, 532 μmol) in $CH_2Cl_2$ (5.3 ml) was added Dess–Martin periodinane (338 mg, 798 μmol) at 0 °C. The mixture was stirred at the same temperature for 10 min, and additionally for 2 h at room temperature. The reaction was quenched with $Na_2S_2O_3$ aq and the organic layer was separated. The aqueous layer was further extracted twice with diethyl ether. The combined organic layer was washed twice with saturated $NaHCO_3$ aq and brine, dried over $Na_2SO_4$, and concentrated to give a pale yellow oil. The residue was purified by column chromatography (neutral silica gel EtOAc/hexane=1/10) to give **22** (223 mg, 482 μmol, 91% yield) as a colorless oil. $^1$H NMR ($CDCl_3$) $\delta$: 9.65 (s, C4–1H), 5.08–5.11 (m, C27–1H), 4.99–5.03 (m, C17–1H), 4.65 (d, $J$=6.9 Hz, OC$H_2$OCH$_3$–1H), 4.62 (d, $J$=6.9 Hz, OC$H_2$OCH$_3$–1H), 3.72 (dd, $J$=3.5, 9.3 Hz, C21–1H), 3.37 (s, OCH$_2$OC$H_3$–3H), 3.34 (dd, $J$=9.2, 9.3 Hz, C21–1H), 2.91 (sep, $J$=6.3 Hz, C11–1H), 2.64–2.72 (m, C5–1H), 2.41–2.50 (m, C7–1H, C26–1H), 2.29–2.41 (m, C2–1H, C6–1H), 1.91–2.14 (m, C3–2H, C16–2H, C26–1H), 1.73–1.82 (m, C2–1H), 1.69 (s, C30–3H), 1.66 (s, C20–3H), 1.60 (s, C19–3H, C29–3H), 1.43 (dd, $J$=12.6, 25.2 Hz, C6–1H), 1.32–1.37 (m, C15–2H), 1.22 (d, $J$=6.3 Hz, C12–3H), 1.07 (d, $J$=6.3 Hz, C13–3H), 0.96 (s, C14–3H); $^{13}$C NMR ($CDCl_3$) $\delta$: 216.5, 212.5, 200.6, 133.6, 131.7, 124.0, 121.3, 96.7, 75.2, 68.9, 55.3, 47.0, 44.6, 41.1, 40.5, 40.0, 35.6, 31.5, 27.8, 25.8, 25.6, 24.1, 23.3, 21.7, 20.3, 19.6, 17.8, 17.6; IR (neat, cm$^{-1}$): $\nu$ 1725, 1706, 1689; MS (ESI) $m/z$ 485 (M+Na)$^+$; HRMS (ESI) calcd for $C_{28}H_{46}O_5$ (M+Na)$^+$: 485.3243, Found: 485.3234; $[\alpha]_D^{25}$ −13.9 ($c$ 1.01, $CHCl_3$) (80% ee).

*4.1.14. (1S,5S,7R,8S)-1-Isobutyryl-7-((methoxymethoxy)methyl)-8-methyl-5-(3-methylbut-2-enyl)-8-(4-methylpent-3-enyl)bicyclo[3.3.1]nonane-4,9-dione (**31**).* To a solution of **22** (2.62 g, 5.66 mmol) in EtOH (57 ml) was added NaOEt (193 mg, 2.83 mmol) at 0 °C. The mixture was stirred for 10 min at the same temperature and additionally for 130 min at room temperature. The reaction was quenched with $NH_4Cl$ aq, and the organic solvent was removed by evaporation. The aqueous layer was extracted three times with EtOAc. The combined organic layer was washed with water and brine to give secondary alcohol **23** as a yellow oil, which was used in next step without further purification.

To a solution of the crude mixture in $CH_2Cl_2$ (57 ml) was added Dess–Martin periodinane (3.60 g, 8.49 mmol) at 0 °C. After being stirred at the same temperature for 1 h, Dess–Martin periodinane (600 mg, 1.30 mmol) was added again. The reaction was stirred for 40 min, quenched with $Na_2S_2O_3$ aq, and the organic layer was separated. The aqueous layer was further extracted with diethyl ether. The combined organic layer was washed twice with $NaHCO_3$ aq and brine, dried over $Na_2SO_4$, and concentrated to give a yellow oil. The residue was purified by column chromatography ($SiO_2$; EtOAc/hexane=1/15 to 1/10) to give **31** (2.38 g, 5.17 mmol; 91% yield for two steps) as a pale yellow oil. $^1$H NMR ($CDCl_3$) $\delta$: 5.01–5.10 (m, C17–1H, C27–1H), 4.57 (d, $J$=6.7 Hz, OC$H_2$OCH$_3$–1H), 4.55 (d, $J$=6.7 Hz, OC$H_2$OCH$_3$–1H), 3.60 (dd, $J$=3.4, 9.5 Hz, C21–1H), 3.33 (s, OCH$_2$OC$H_3$–3H), 3.25 (dd, $J$=9.5, 9.5 Hz, C21–1H), 2.68–2.73 (m, C3–1H), 2.56 (sep, $J$=6.4 Hz, C11–1H), 2.33–2.45 (m, C3–1H, C6–1H, C26–1H), 2.20–2.31 (m, C2–1H, C7–1H, C16–1H, C26–1H), 1.84–1.93 (m, C2–1H, C16–1H), 1.50–1.70 (m, C19–3H, C20–3H, C29–3H, C30–3H, C6–1H, C15–1H), 1.39–1.46 (m, C15–1H), 1.26 (d, $J$=6.4 Hz, C12–3H), 1.18 (d, $J$=6.4 Hz, C13–3H), 0.98 (s, C14–3H); $^{13}$C NMR ($CDCl_3$) $\delta$: 212.8, 211.0, 210.9, 135.7, 132.3, 124.4, 118.4, 97.0, 70.9, 68.3, 66.1, 55.7, 48.1, 43.5, 42.0, 41.4, 39.9, 38.0, 31.6, 26.3, 26.0, 25.9, 23.4, 20.9, 20.8, 18.2, 18.0, 14.3; IR (neat, cm$^{-1}$): $\nu$ 1718, 1703; MS (ESI) $m/z$ 483 (M+Na)$^+$; HRMS (ESI) calcd for $C_{28}H_{44}O_5$ (M+Na)$^+$: 483.3086, Found: 483.3080; $[\alpha]_D^{22}$ −23.8 ($c$ 1.27, $CHCl_3$) (80% ee).

*4.1.15. (1S,5S,7R,8S)-7-(Hydroxymethyl)-1-isobutyryl-8-(4-methoxy-4-methylpentyl)-8-methyl-5-(3-methylbut-2-enyl)bicyclo[3.3.1]nonane-4,9-dione (**32**).* To a solution of **31** (2.38 g, 5.17 mmol) in MeOH (52 ml) was added (+)-CSA (3.60 g, 15.5 mmol) at room temperature. The mixture was heated to 50 °C and stirred for 5 h at the same temperature. The reaction was quenched with $NaHCO_3$ aq and the organic layer was separated. The aqueous layer was further extracted twice with EtOAc. The combined organic layer was washed with water and brine, dried over $Na_2SO_4$, and concentrated to give a yellow oil. The residue was purified by column chromatography ($SiO_2$, EtOAc/hexane=1/3 to 1/1) to give **32** and only MOM cleaved product. MOM cleaved product could be converted to **32** under the same condition. After two cycles of this reaction, **32** (1.53 g, 3.41 mmol, 66% yield) was obtained as a colorless oil. $^1$H NMR ($CDCl_3$) $\delta$: 5.05–5.08 (m, C27–1H), 3.77 (dd, $J$=2.9, 10.9 Hz, C21–1H), 3.34 (dd, $J$=9.2, 9.7 Hz, C21–1H), 3.15 (s, OC$H_3$–3H), 2.70 (d, $J$=11.5 Hz, C3–1H), 2.56 (sep, $J$=6.9 Hz, C11–1H), 2.33–2.44 (m, C3–1H, C6–1H, C26–1H), 2.21–2.31 (m, C2–1H, C7–1H, C26–1H), 1.74–1.80 (m, C2–1H), 1.65 (s, C30–3H), 1.57 (s, C29–3H), 1.53–1.60 (m, C6–1H, C15–1H), 1.42–1.48 (m, C15–1H), 1.35 (dd, $J$=7.4, 8.6 Hz, C17–2H), 1.26 (d, $J$=6.9 Hz, C13–3H), 1.18–1.23 (m, C16–1H), 1.18 (d, $J$=6.9 Hz, C12–3H), 1.13 (s, C19–3H), 1.12 (s, C20–3H), 1.10–1.15 (m, C16–1H), 0.96 (s, C14–3H); $^{13}$C NMR ($CDCl_3$) $\delta$: 212.6, 210.7, 210.6, 135.3, 118.0, 74.5, 70.4, 65.7, 62.7, 49.1, 47.9, 45.4, 41.6, 40.6, 40.5, 39.6, 38.2, 31.2, 25.9, 25.1, 24.9, 23.0, 21.0, 20.5, 20.4, 17.8, 14.2; IR (neat, cm$^{-1}$): $\nu$ 3425, 1717, 1701; MS (ESI) $m/z$ 471 (M+Na)$^+$; HRMS (ESI) calcd for $C_{27}H_{44}O_5$ (M+Na)$^+$: 471.3086, Found: 471.3075; $[\alpha]_D^{28}$ −13.6 ($c$ 1.25, $CHCl_3$) (80% ee).

*4.1.16. (1S,5S,7R,8S)-1-Isobutyryl-8-(4-methoxy-4-methylpentyl)-8-methyl-5-(3-methylbut-2-enyl)-4,9-dioxobicyclo[3.3.1]nonane-7-carbaldehyde.*

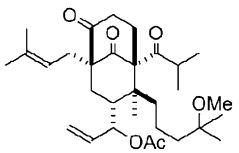



To a solution of oxalyl chloride (49.9 μl, 590 μmol) in $CH_2Cl_2$ was added a solution of DMSO (83.8 μl, 1.18 mmol) at −78 °C. The reaction was stirred for 5 min. Then, a solution of **32** (52.8 mg, 118 μmol) in $CH_2Cl_2$ (590 μl) was added to the mixture at −78 °C. After 35 min, $NEt_3$ (495 μl, 3.54 mmol) was added at −78 °C, then warmed to room temperature and stirred for 45 min. The reaction was quenched with water, and the organic layer was separated. The aqueous layer was further extracted twice with EtOAc. The combined organic layer was washed with water and brine, dried over

$Na_2SO_4$, and concentrated to give a yellow oil. The residue was purified by column chromatography ($SiO_2$, EtOAc/hexane=1/4) to give aldehyde (49.8 mg, 112 μmol, 95% yield) as a yellow oil. $^1H$ NMR ($CDCl_3$) $\delta$: 9.70 (d, $J$=2.3 Hz, C21−1H), 5.01−5.05 (m, C27−1H), 3.11 (s, OC$H_3$−3H), 2.68−2.71 (m, C3−1H), 2.51−2.56 (m, C7−1H, C11−1H), 2.19−2.37 (m, C2−2H, C3−1H, C26−2H), 2.09 (dd, $J$=4.0, 13.7 Hz, C6−1H), 1.92 (dd, $J$=13.2, 13.7 Hz, C6−1H), 1.67−1.79 (m, C15−1H, C16−1H), 1.62 (s, C30−3H), 1.57 (s, C29−3H), 1.47−1.54 (m, C15−1H), 1.34 (dd, $J$=7.5, 8.0 Hz, C17−2H), 1.23 (d, $J$=6.3 Hz, C12−3H), 1.16 (d, $J$=6.9 Hz, C12−3H), 1.10 (s, C19−3H), 1.09 (s, C20−3H), 1.08 (s, C14−3H), 1.06−1.10 (m, C16−1H); $^{13}C$ NMR ($CDCl_3$) $\delta$: 211.8, 209.6, 209.3, 201.5, 135.8, 117.5, 74.2, 69.4, 64.6, 54.5, 49.0, 48.9, 41.4, 40.5, 39.5, 37.7, 36.1, 30.9, 25.9, 25.0, 24.9, 22.8, 20.5, 20.5, 20.3, 17.8, 15.8; IR (neat, $cm^{-1}$): $\nu$ 1718, 1704; MS (ESI) $m/z$ 469 $(M+Na)^+$; HRMS (ESI) calcd for $C_{27}H_{42}O_5$ $(M+Na)^+$: 469.2930, Found: 469.2917; $[\alpha]_D^{26}$ −32.9 ($c$ 1.24, $CHCl_3$) (80% ee).

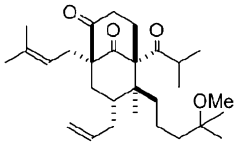
*4.1.17. (1S,5S,7R,8S)-7-(1-Hydroxyallyl)-1-isobutyryl-8-(4-methoxy-4-methylpentyl)-8-methyl-5-(3-methylbut-2-enyl)bicyclo[3.3.1]nonane-4,9-dione (**33**).* To a solution of aldehyde (167 mg, 374 μmol) in THF (3.7 ml) was added vinylmagnesium bromide (598 μl, 598 μmol; 1.0 M in THF) at −78 °C. After being stirred for 40 min at the same temperature, the reaction was quenched with saturated $NH_4Cl$ aq, and the organic layer was separated. The aqueous layer was further extracted twice with EtOAc. The combined organic layer was washed with water and brine, dried over $Na_2SO_4$, and concentrated to give a yellow oil. The residue was purified by column chromatography ($SiO_2$; EtOAc/hexane=1/5 to 1/4) to give **33** (163 mg, 343 μmol, 92% yield) as a white solid. $^1H$ NMR ($CDCl_3$) $\delta$: 5.82 (ddd, $J$=5.2, 10.4, 17.1 Hz, C22−1H), 5.18 (d, $J$=17.1 Hz, C23−1H), 5.14 (d, $J$=10.4 Hz, C23−1H), 5.02−5.06 (m, C27−1H), 4.35 (br s, C21−1H), 3.13 (s, OC$H_3$−3H), 2.64 (dd, $J$=4.9, 13.5 Hz, C3−1H), 2.56 (sep, $J$=6.4 Hz, C11−1H), 2.35 (d, $J$=7.3 Hz, C26−2H), 2.17−2.24 (m, C3−1H, C7−1H), 2.12 (dd, $J$=5.5, 16.5 Hz, C6−1H), 2.03 (dd, $J$=4.0, 13.4 Hz, C2−1H), 1.86 (dd, $J$=13.4, 13.5 Hz, C2−1H), 1.62 (s, C30−3H), 1.58 (s, C29−3H), 1.52−1.62 (m, C6−1H, C15−1H), 1.34−1.44 (m, C15−1H, C16−1H, C17−2H), 1.23 (d, $J$=6.4 Hz, C12−3H), 1.16 (d, $J$=6.4 Hz, C13−3H), 1.17 (s, C19−3H), 1.12 (s, C20−3H), 1.11 (s, C14−3H), 1.07−1.12 (m, C16−1H); $^{13}C$ NMR ($CDCl_3$) $\delta$: 212.5, 211.0, 210.2, 141.0, 135.1, 118.1, 114.5, 74.5, 70.6, 70.0, 65.6, 49.1, 46.2, 41.7, 40.7, 39.7, 38.3, 35.5, 31.4, 25.9, 25.1, 24.9, 23.0, 21.0, 20.8, 20.4, 17.8, 15.5; IR (neat, $cm^{-1}$): $\nu$ 3421, 1717, 1701; MS (ESI) $m/z$ 497 $(M+Na)^+$; HRMS (ESI) calcd for $C_{29}H_{46}O_5$ $(M+Na)^+$: 497.3243, Found: 497.3238; $[\alpha]_D^{26}$ +10.4 ($c$ 1.60, $CHCl_3$) (80% ee).

*4.1.18. 21-((1S,5S,7R,8S)-1-Isobutyryl-8-(4-methoxy-4-methylpentyl)-8-methyl-5-(3-methylbut-2-enyl)-4,9-dioxobicyclo[3.3.1]nonan-7-yl)allyl acetate.*




To a solution of **33** (163 mg, 343 μmol) in $CH_2Cl_2$ (3.4 ml) were added $i$-$Pr_2NEt$ (300 μl, 1.72 mmol), DMAP (21.0 mg, 172 μmol), and acetic anhydride (163 μl, 1.72 mmol) at 0 °C. The mixture was stirred at the same temperature for 30 min, and quenched with water. The organic layer was separated and the aqueous layer was further extracted twice with EtOAc. The combined organic layer was washed with water and brine, dried over $Na_2SO_4$, and concentrated to give a yellow oil. The residue was purified by column chromatography ($SiO_2$; EtOAc/hexane=1/5) to give allyl acetate (174 mg, 337 μmol, 98% yield) as a pale yellow oil. $^1H$ NMR ($CDCl_3$) $\delta$: 5.66 (ddd, $J$=5.2, 10.7, 17.1 Hz, C22−1H), 5.45 (d, $J$=5.2 Hz, C21−1H), 5.15 (d, $J$=10.7 Hz, C23−1H), 5.07 (d, $J$=17.1 Hz, C23−1H), 5.02−5.05 (m, C27−1H), 3.14 (s, OC$H_3$−3H), 2.66 (dd, $J$=4.0, 12.2 Hz, C3−1H), 2.53 (sep, $J$=6.4 Hz, C11−1H), 2.37 (d, $J$=7.6 Hz, C26−2H), 2.07−2.26 (m, C2−1H, C3−1H, C6−1H, C7−1H), 2.01(s, OCOC$H_3$−3H), 1.86 (dd, $J$=13.4, 13.5 Hz, C2−1H), 1.68 (dd, $J$=4.0, 13.4 Hz, C6−1H), 1.63 (s, C30−3H), 1.58 (s, C29−3H), 1.44−1.55 (m, C15−2H), 1.30−1.40 (m, C16−1H, C17−2H), 1.23 (d, $J$=6.4 Hz, C12−3H), 1.16(d, $J$=6.4 Hz, C13−3H), 1.12 (s, C19−3H), 1.11 (s, C20−3H), 1.06−1.12 (m, C16−1H), 0.94 (s, C14−3H); $^{13}C$ NMR ($CDCl_3$) $\delta$: 212.0, 210.6, 209.9, 169.5, 136.0, 135.4, 117.9, 116.1, 74.4, 71.2, 70.3, 65.5, 49.0, 48.8, 45.1, 41.7, 40.4, 39.7, 38.4, 36.2, 31.4, 25.9, 25.1, 24.9, 23.0, 21.1, 20.9, 20.8, 20.4, 17.8, 14.8; IR (neat, $cm^{-1}$): $\nu$ 1741, 1718, 1703; MS (ESI) $m/z$ 539 $(M+Na)^+$; HRMS (ESI) calcd for $C_{31}H_{48}O_6$ $(M+Na)^+$: 539.3349, Found: 539.3352; $[\alpha]_D^{25}$ +18.8 ($c$ 0.61, $CHCl_3$) (80% ee).

*4.1.19. (1S,5S,7R,8S)-7-Allyl-1-isobutyryl-8-(4-methoxy-4-methylpentyl)-8-methyl-5-(3-methylbut-2-enyl)bicyclo[3.3.1]nonane-4,9-dione.*

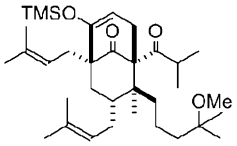



The reaction solvent toluene was degassed before the reaction. $Pd(PPh_3)_4$ (77.9 mg, 67.4 μmol) and ammonium formate (85.1 mg, 1.35 mmol) were dissolved in toluene (4.8 ml) at room temperature. After being stirred for 10 min, a solution of the allyl acetate (174 mg, 337 μmol) in toluene (2.4 ml) was added. The resulting mixture was stirred at 100 °C for 2.5 h. The reaction was diluted with water and extracted three times with EtOAc. The combined organic layer was washed with water and brine, dried over $Na_2SO_4$, and concentrated to give a yellow oil. The residue was purified by column chromatography ($SiO_2$; EtOAc/hexane=1/8) to give C7-allyl product (146 mg, 318 μmol, 95% yield) as a pale yellow oil. $^1H$ NMR ($CDCl_3$) $\delta$: 5.59−5.69 (m, C22−1H), 4.96−5.05 (m, C23−2H, C27−1H), 3.13 (s, OC$H_3$−3H), 2.64−2.69 (m, C3−1H), 2.56 (sep, $J$=6.9 Hz, C11−1H), 2.29−2.33 (m, C26−2H), 2.16−2.24 (m, C3−1H, C6−1H, C7−1H, C21−2H), 1.62 (s, C30−3H), 1.57 (s, C29−3H), 1.46−1.66 (m, C2−2H, C6−1H, C15−1H), 1.23 (d, $J$=6.9 Hz, C12−3H), 1.22−1.43 (m, C15−1H, C16−2H, C17−2H), 1.16 (d, $J$=6.9 Hz, C12−3H), 1.11 (s, C19−3H), 1.11 (s, C20−3H), 0.94 (s, C14−3H); $^{13}C$ NMR ($CDCl_3$) $\delta$: 212.6, 210.7, 210.7, 136.7, 135.2, 118.1, 116.7, 74.4, 70.6, 66.0, 49.0, 48.7, 42.0, 41.9, 40.6, 39.6, 38.3, 33.6, 31.2, 25.9, 25.1, 25.0, 23.0, 21.0, 20.6, 20.5, 17.8, 13.7; IR (neat, $cm^{-1}$): $\nu$ 1737, 1718, 1702; MS (ESI) $m/z$ 481 $(M+Na)^+$; HRMS (ESI) calcd for $C_{29}H_{46}O_4$ $(M+Na)^+$: 481.3294, Found: 481.3284; $[\alpha]_D^{25}$ +2.5 ($c$ 0.68, $CHCl_3$) (80% ee).

*4.1.20. (1S,5S,7R,8S)-5-Isobutyryl-8-(4-methoxy-4-methylpentyl)-8-methyl-5,7-bis(3-methylbut-2-enyl)bicyclo[3.3.1]nonane-4,9-dione (**34**).* To a solution of C7-allyl compound (146 mg, 318 μmol) in $CH_2Cl_2$ (8 ml) and 2-methyl-2-butene (8 ml) was added Hoveyda−Grubbs second catalyst at room temperature. The resulting mixture was stirred at 40 °C for 1 h. DMSO (1.1 ml) was added to the reaction mixture and it was stirred for 7 h at the same temperature. The mixture was directly evaporated and purified by column chromatography ($SiO_2$; EtOAc/hexane=1/15 to 1/10) to give **34** (162 mg, 332 μmol, 100% yield) as a white solid. $^1H$ NMR ($CDCl_3$) $\delta$: 5.02−5.05 (m, C27−1H), 4.96−4.99 (m, C22−1H), 3.13 (s, OC$H_3$−3H), 2.65−2.68 (m, C3−1H), 2.56 (sep, $J$=6.4 Hz, C11−1H), 2.31−2.33 (m, C26−2H), 2.18−2.22 (m, C3−1H, C21−2H), 2.15 (dd, $J$=4.0, 13.5 Hz, C6−1H), 2.00−2.04 (m, C7−1H), 1.68 (s, C30−3H), 1.63 (s, C24−3H), 1.58 (s, C29−3H), 1.54 (s, C25−3H), 1.46−1.70 (m, C2−2H, C6−1H, C15−1H), 1.24−1.42 (m, C15−1H, C16−2H, C17−2H), 1.24 (d, $J$=6.4 Hz, C12−3H), 1.16 (d, $J$=6.4 Hz, C13−3H),

1.11 (s, C19–3H), 1.11 (s, C20–3H), 0.96 (s, C14–3H); $^{13}$C NMR ($CDCl_3$) $\delta$: 212.7, 210.9, 210.8, 135.1, 133.1, 122.5, 118.2, 74.4, 70.7, 66.1, 49.0, 48.8, 43.1, 42.3, 41.7, 40.5, 39.6, 38.4, 31.3, 27.6, 25.9, 25.8, 25.1, 25.0, 23.0, 21.2, 20.5, 20.4, 17.9, 17.8, 13.7; IR (neat, $cm^{-1}$): $\nu$ 1718, 1702; MS (ESI) $m/z$ 509 $(M+Na)^+$; HRMS (ESI) calcd for $C_{31}H_{50}O_4$ $(M+Na)^+$: 509.3607, Found: 509.3604; $[\alpha]_D^{25}$ −2.6 ($c$ 1.06, $CHCl_3$) (80% ee).

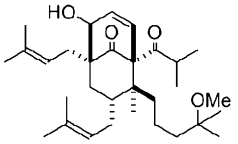
*4.1.21. (1S,5S,7R,8S)-1-Isobutyryl-8-(4-methoxy-4-methylpentyl)-8-methyl-5,7-bis(3-methylbut-2-enyl)-4-(trimethylsilyloxy)bicyclo[3.3.1]non-3-en-9-one.*




To a solution of **34** (1.33 g, 2.73 mmol) in $CH_2Cl_2$ (27 ml) were added $NEt_3$ (7.63 ml, 54.6 mmol), DMAP (667 mg, 5.46 mmol), and TMSCl (3.49 ml, 27.3 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 40 h. The reaction was quenched with saturated $NH_4Cl$ aq at −78 °C. The organic layer was separated, and the aqueous layer was further extracted twice with EtOAc. The combined organic layer was washed with water and brine, dried over $Na_2SO_4$, and concentrated to give a brown oil. The residue was purified by column chromatography (neutral silica gel; EtOAc/hexane=1/15 to 1/10 to 1/6) to give TMS enol ether (1.28 g, 2.29 mmol, 84% yield) as a pale yellow oil. $^1$H NMR ($CDCl_3$) $\delta$: 5.04–5.12 (m, C22–1H, C27–1H), 4.99 (dd, $J$=3.5, 4.0 Hz, C3–1H), 3.16 (s, OC$H_3$–3H), 2.58–2.66 (m, C11–1H, C26–2H), 2.26 (dd, $J$=6.9, 14.9 Hz, C21–1H), 2.20 (dd, $J$=6.9, 14.9 Hz, C21–1H), 2.04–2.08 (m, C6–1H), 1.84–1.90 (m, C7–1H), 1.71–1.78 (m, C2–2H), 1.68 (s, C30–3H), 1.67 (s, C24–3H), 1.60 (s, C29–3H), 1.57 (s, C25–3H), 1.54–1.68 (m, C6–1H, C15–1H), 1.25–1.40 (m, C15–1H, C16–1H, C17–1H), 1.18 (d, $J$=6.3 Hz, C12–3H), 1.13 (s, C19–3H), 1.13 (s, C20–3H), 1.06 (d, $J$=6.3 Hz, C13–3H), 0.88 (s, C14–3H), 0.20 (s, O*TMS*–9H); $^{13}$C NMR ($CDCl_3$) $\delta$: 215.0, 211.4, 150.2, 132.5, 123.6, 121.1, 102.4, 74.5, 70.6, 54.8, 49.1, 47.3, 43.5, 40.5, 39.6, 39.6, 38.7, 29.8, 27.1, 26.4, 25.9, 25.8, 25.2, 25.1, 22.1, 21.5, 20.0, 18.0, 17.8, 13.6, 0.21; IR (neat, $cm^{-1}$): $\nu$ 1710, 1671; MS (ESI) $m/z$ 581 $(M+Na)^+$; HRMS (ESI) calcd for $C_{34}H_{58}O_4Si$ $(M+Na)^+$: 581.4002, Found: 581.4005; $[\alpha]_D^{28}$ −32.5 ($c$ 0.96, $CHCl_3$) (80% ee).

*4.1.22. (1S,5S,7R,8S)-1-Isobutyryl-8-(4-methoxy-4-methylpentyl)-8-methyl-5,7-bis(3-methylbut-2-enyl)bicyclo[3.3.1]non-2-ene-4,9-dione (**35**).* To a solution of TMS enol ether (166 mg, 297 μmol) in DMSO (3.0 ml) was added $Pd(OAc)_2$ (133 mg, 594 μmol) at room temperature. The atmosphere in the flask was replaced with $O_2$, and the mixture was stirred at room temperature for 10.5 h. The reaction mixture was directly purified by column chromatography ($SiO_2$; EtOAc/hexane=1/10 to 1/6) to give **35** (145 mg, 299 μmol, 100% yield) as a pale yellow oil. $^1$H NMR ($CDCl_3$) $\delta$: 7.28 (d, $J$=10.4 Hz, C2–1H), 6.55 (d, $J$=10.4 Hz, C3–1H), 5.01–5.03 (m, C27–1H), 4.91–4.95 (m, C22–1H), 3.13 (s, OC$H_3$–3H), 2.68 (sep, $J$=6.9 Hz, C11–1H), 2.44 (d, $J$=6.9 Hz, C26–2H), 1.99 (dd, $J$=5.2, 13.2 Hz, C6–1H), 1.77–1.81 (m, C22–2H), 1.62–1.69 (m, C24–3H, C25–3H, C29–3H, C30–3H), 1.17–1.44 (m, C6–1H, C7–1H, C15–2H, C16–2H, C17–2H), 1.13 (d, $J$=6.9 Hz, C12–3H), 1.11 (s, C19–3H), 1.11 (s, C14–3H, C20–3H), 1.08 (d, $J$=6.9 Hz, C13–3H); $^{13}$C NMR ($CDCl_3$) $\delta$: 211.1, 206.4, 199.1, 146.1, 134.5, 133.5, 132.8, 122.0, 119.3, 74.2, 73.4, 67.0, 67.0, 49.1, 47.7, 40.7, 40.7, 39.2, 38.0, 28.8, 27.8, 25.9, 25.8, 25.0, 21.0, 20.1, 19.9, 18.0, 17.9, 16.2; IR (neat, $cm^{-1}$): $\nu$ 1719, 1681; MS (ESI) $m/z$ 507 $(M+Na)^+$; HRMS (ESI) calcd for $C_{31}H_{48}O_4$ $(M+Na)^+$: 507.3450, Found: 507.3449; $[\alpha]_D^{29}$ −14.1 ($c$ 1.36, $CHCl_3$) (80% ee).

*4.1.23. (1S,5S,7R,8S)-4-Hydroxy-1-isobutyryl-8-(4-methoxy-4-methylpentyl)-8-methyl-5,7-bis(3-methylbut-2-enyl)bicyclo[3.3.1]non-2-en-9-one.*



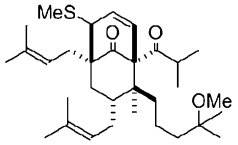

To a solution of **35** (144 mg, 297 μmol) in MeOH (3 ml) was added $NaBH_4$ (56.4 mg, 1.49 mmol) at −20 °C. The reaction mixture was stirred at the same temperature for 10 min, and quenched with water and diluted with EtOAc. The organic layer was separated, and the aqueous layer was further extracted twice with EtOAc. The combined organic layer was washed with water and brine, dried over $Na_2SO_4$, and concentrated to give a pale yellow oil. The residue was purified by column chromatography ($SiO_2$; EtOAc/hexane=1/4) to give alcohol (148 mg, 304 μmol, 100% yield) as a colorless oil. $^1$H NMR ($CDCl_3$) $\delta$: 6.10 (dd, $J$=2.3, 10.3 Hz, C3–1H), 5.95 (dd, $J$=1.8, 10.3 Hz, C2–1H), 5.26–5.30 (m, C27–1H), 5.09–5.13 (m, C22–1H), 4.37 (br s, C4–1H), 3.12 (s, OC$H_3$–3H), 2.62 (sep, $J$=6.3 Hz, C11–1H), 2.41 (dd, $J$=9.2, 14.3 Hz, C26–1H), 2.29 (dd, $J$=4.6, 14.3 Hz, C26–1H), 1.98–2.14 (m, C6–1H, C7–1H, C21–2H), 1.73 (s, C30–3H), 1.70 (s, C24–3H), 1.66 (s, C29–3H), 1.58 (s, C25–3H), 1.55–1.66 (m, C6–1H), 1.20–1.40 (m, C15–2H, C16–2H, C17–2H), 1.09–1.10 (m, C12–3H, C19–3H, C20–3H), 1.04 (s, C14–3H), 1.00 (d, $J$=6.3 Hz, C13–3H); $^{13}$C NMR ($CDCl_3$) $\delta$: 213.2, 210.8, 135.3, 133.8, 132.6, 127.2, 123.1, 120.1, 75.8, 74.4, 72.0, 56.4, 49.0, 47.9, 40.7, 40.1, 39.9, 37.9, 34.4, 33.4, 28.3, 26.1, 25.9, 25.1, 25.1, 20.9, 20.3, 19.8, 18.0, 17.9, 15.9; IR (neat, $cm^{-1}$): $\nu$ 1720, 1705; MS (ESI) $m/z$ 509 $(M+Na)^+$; HRMS (ESI) calcd for $C_{31}H_{50}O_4$ $(M+Na)^+$: 509.3607, Found: 509.3604; $[\alpha]_D^{28}$ −9.3 ($c$ 0.99, $CHCl_3$) (80% ee).

*4.1.24. O-(1S,5S,7R,8S)-1-Isobutyryl-8-(4-methoxy-4-methylpentyl)-8-methyl-5,7-bis(3-methylbut-2-enyl)-9-oxobicyclo[3.3.1]non-2-en-4-yl S-methyl carbonodithioate (**47**).* To a solution of alcohol (1.02 g, 2.10 mmol) and $CS_2$ (761 μl, 12.6 mmol) was added NaH (504 mg; 50–72% in oil) at 0 °C. The reaction mixture was stirred at the same temperature. After being stirred for 30 min, MeI (784 μl, 12.6 mmol) was added at 0 °C, and the mixture was stirred for 30 min. The reaction mixture was quenched with saturated $NH_4Cl$ aq. The organic layer was separated, and the aqueous layer was further extracted twice with EtOAc. The combined organic layer was washed with water and brine, dried over $Na_2SO_4$, and concentrated to give a yellow oil. The residue was purified by column chromatography ($SiO_2$; EtOAc/hexane=1/20) to give **47** (1.24 g, 2.15 mmol, 100% yield) as a yellow oil. $^1$H NMR ($CDCl_3$) $\delta$: 6.31 (dd, $J$=2.9, 10.3 Hz, C3–1H), 6.22 (br s, C4–1H), 6.07 (dd, $J$=1.8, 10.3 Hz, C2–1H), 5.09–5.15 (m, C22–1H, C27–1H), 3.12 (s, OC$H_3$–3H), 2.61 (sep, $J$=6.9 Hz, C11–1H), 2.58 (s, SC$H_3$–3H), 2.29–2.37 (m, C26–2H), 2.08–2.13 (m, C21–2H), 1.98–2.05 (m, C6–1H), 1.72 (s, C30–3H), 1.65 (s, C24–3H), 1.59 (s, C29–3H), 1.56–1.68 (m, C7–1H), 1.52 (s, C25–3H), 1.17–1.43(m, C6–1H, C15–2H, C16–2H, C17–2H), 1.09–1.11 (m, C12–3H, C19–3H, C20–3H), 1.07 (s, C14–3H), 1.01 (d, $J$=6.9 Hz, C13–3H); $^{13}$C NMR ($CDCl_3$) $\delta$: 214.7, 212.4, 208.6, 135.0, 132.8, 129.4, 129.3, 123.2, 119.0, 83.9, 74.3, 72.1, 55.1, 49.0, 48.4, 40.7, 40.4, 40.0, 38.0, 36.6, 33.2, 27.9, 26.0, 25.9, 25.1, 21.0, 20.3, 19.9, 18.7, 18.0, 17.7, 15.5; IR (neat, $cm^{-1}$): $\nu$ 1723, 1712; MS (ESI) $m/z$ 599 $(M+Na)^+$; HRMS (ESI) calcd for $C_{33}H_{52}O_4S_2$ $(M+Na)^+$: 599.3205, Found: 599.3214; $[\alpha]_D^{32}$ +31.5 ($c$ 1.30, $CHCl_3$) (80% ee).

*4.1.25. S-(1S,5R,7R,8S)-1-Isobutyryl-8-(4-methoxy-4-methylpentyl)-8-methyl-5,7-bis(3-methylbut-2-enyl)-9-oxobicyclo[3.3.1]non-2-en-*

*4-yl S-methyl carbonodithioate (**48**).* The solution of **47** (31.6 mg, 54.8 μmol) in toluene (570 μl) was stirred at 150 °C (sealed tube) for 11 h. The reaction was cooled to room temperature and concentrated to give **48** as a yellow oil, which was used for next reaction without purification.

*4.1.26. (1S,5R,7R,8S)-1-Isobutyryl-8-(4-methoxy-4-methylpentyl)-8-methyl-5,7-bis(3-methylbut-2-enyl)-4-(methylthio)bicyclo[3.3.1]non-2-en-9-one.*

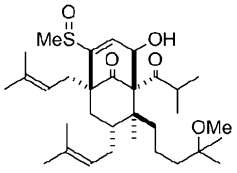



To a solution of **48** in THF (570 μl) was added EtSLi (860 μl, 172 μmol; 0.2 M in THF) at 0 °C and stirred. After being stirred at the same temperature for 25 min, MeI (53.5 μl, 859 μmol) and $NEt_3$ (120 μl, 859 μmol) were added to the mixture. The resulting mixture was stirred at room temperature for 105 min. The reaction was quenched with saturated $NH_4Cl$ aq. The organic layer was separated, and the aqueous layer was further extracted twice with EtOAc. The combined organic layer was washed with water and brine, dried over $Na_2SO_4$, and concentrated to give a yellow oil. The residue was purified by column chromatography ($SiO_2$; EtOAc/hexane=1/30 to 1/20 to 1/10) to give sulfide (27.7 mg, 53.6 μmol; 98% yield for two steps) as a yellow oil. $^1H$ NMR ($CDCl_3$) $\delta$: 6.21 (dd, *J*=2.9, 10.3 Hz, C3−1H), 5.84 (dd, *J*=2.3, 10.3 Hz, C2−1H), 5.21−5.25 (m, C27−1H), 5.11−5.15 (m, C22−1H), 3.51 (br s, C4−1H), 3.13 (s, OC*H*$_3$−3H), 2.65 (sep, *J*=6.3 Hz, C11−1H), 2.27 (d, *J*=7.5 Hz, C26−2H), 2.18 (s, SC*H*$_3$−3H), 1.98−2.12 (m, C6−1H, C21−2H), 1.72 (s, C30−3H), 1.70 (s, C24−3H), 1.65 (s, C29−3H), 1.58 (s, C25−3H), 1.55−1.62 (m, C7−1H), 1.17−1.43(m, C6−1H, C15−2H, C16−2H, C17−2H), 1.10−1.11 (m, C12−3H, C19−3H, C20−3H), 0.99−1.02 (m, C14−3H, C13−3H); $^{13}C$ NMR ($CDCl_3$) $\delta$: 213.1, 211.3, 134.3, 132.8, 132.5, 125.4, 123.0, 120.7, 74.3, 72.2, 55.2, 54.5, 49.0, 48.8, 40.8, 40.7, 39.9, 38.3, 38.0, 32.9, 28.0, 26.0, 25.7, 25.1, 25.1, 20.9, 20.4, 19.8, 17.9, 17.7, 15.6, 15.5; IR (neat, $cm^{-1}$): $\nu$ 1721, 1706; MS (ESI) *m*/*z* 539 $(M+Na)^+$; HRMS (ESI) calcd for $C_{32}H_{52}O_3S$ $(M+Na)^+$: 539.3535, Found: 539.3539; $[\alpha]_D^{26}$ +5.3 (*c* 0.80, $CHCl_3$) (80% ee).

*4.1.27. (1S,5R,7R,8S)-1-Isobutyryl-8-(4-methoxy-4-methylpentyl)-8-methyl-5,7-bis(3-methylbut-2-enyl)-4-(methylsulfinyl)bicyclo[3.3.1]non-2-en-9-one (**49**).* To a solution of sulfide (926 mg, 1.79 mmol) in AcOH (17.9 ml) was added $NaBO_3 \cdot 4H_2O$ (826 mg, 5.37 mmol) at room temperature. The resulting mixture was stirred at the same temperature for 45 min. The reaction was diluted with water. The aqueous layer was extracted twice with EtOAc. The combined organic layer was washed twice with saturated $NaHCO_3$ aq and with brine, dried over $Na_2SO_4$, and concentrated to give a yellow oil. The residue was purified by column chromatography ($SiO_2$; EtOAc/hexane=1/2 to 3/2) to give **49** (910 mg, 1.71 mmol, 95% yield, a 1.3:1 diastereomixture derived from S) as a yellow oil.

*4.1.28. (1R,5R,7R,8S)-2-Hydroxy-1-isobutyryl-8-(4-methoxy-4-methylpentyl)-8-methyl-5,7-bis(3-methylbut-2-enyl)-4-(methylthio)bicyclo[3.3.1]non-3-en-9-one (**50**).* To a solution of **49** (910 mg, 1.71 mmol) and 2,6-di-*tert*-butylpyridine (1.73 ml, 7.79 mmol) in $CH_2Cl_2$ (17 ml) was added TFAA (712 μl, 5.13 mmol) at −40 °C. The resulting mixture was stirred at the same temperature for 2 h. The reaction was quenched with saturated $NaHCO_3$ aq. The organic layer was separated, and the aqueous layer was further extracted twice with EtOAc. The combined organic layer was washed with water and brine, dried over $Na_2SO_4$, and concentrated to give a yellow oil. The residue was purified by column chromatography ($SiO_2$; EtOAc/hexane=1/6 to 1/3) to give **50** (590 mg, 1.11 mmol, 65% yield) as a yellow oil. $^1H$ NMR ($CDCl_3$) $\delta$: 5.66 (d, *J*=5.7 Hz, C3−1H), 5.13 (dd, *J*=5.2, 5.7 Hz, C2−1H), 4.95−5.02 (m, C22−1H, C27−1H), 3.43 (sep, *J*=6.9 Hz, C11−1H), 3.15 (s, OC*H*$_3$−3H), 2.50 (dd, *J*=5.7, 15.5 Hz, C26−1H), 2.26 (s, SC*H*$_3$−3H), 2.26−2.30 (m, C26−1H), 1.90−2.05 (m, O*H*−1H, C6−1H, C21−2H), 1.68 (s, C30−3H), 1.66 (s, C24−3H), 1.63 (s, C29−3H), 1.63−1.75 (m, C7−1H), 1.56 (s, C25−3H), 1.23−1.49 (m, C6−1H, C15−2H, C16−2H, C17−2H), 1.13 (s, C19−3H), 1.12 (s, C20−3H), 1.11 (d, *J*=6.9 Hz, C12−3H), 1.09 (d, *J*=6.9 Hz, C13−3H), 0.81 (s, C14−3H); $^{13}C$ NMR ($CDCl_3$) $\delta$: 218.7, 208.5, 146.3, 133.1, 133.0, 122.5, 120.0, 118.9, 74.7, 74.2, 71.2, 57.2, 49.1, 47.8, 41.9, 40.0, 38.9, 38.6, 35.5, 31.5, 27.5, 25.8, 25.8, 25.3, 25.2, 21.0, 19.8, 19.5, 18.4, 18.1, 18.0, 15.2; IR (neat, $cm^{-1}$): $\nu$ 1720, 1685; MS (ESI) *m*/*z* 555 $(M+Na)^+$; HRMS (ESI) calcd for $C_{32}H_{52}O_4S$ $(M+Na)^+$: 555.3484, Found: 555.3490; $[\alpha]_D^{28}$ +24.8 (*c* 1.37, $CHCl_3$) (80% ee).

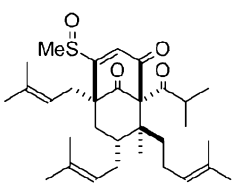
*4.1.29. (1R,5R,7R,8S)-2-Hydroxy-1-isobutyryl-8-(4-methoxy-4-methylpentyl)-8-methyl-5,7-bis(3-methylbut-2-enyl)-4-(methylsulfinyl)bicyclo[3.3.1]non-3-en-9-one.*




To a solution of **50** (15.9 mg, 29.8 μmol) in HFIP (300 μl) was added 30% $H_2O_2$ aq (15 μl) at room temperature. The resulting mixture was stirred at the same temperature for 15 min. The reaction was quenched with saturated $Na_2S_2O_3$ aq. The organic layer was separated, and the aqueous layer was further extracted twice with EtOAc. The combined organic layer was washed with water and brine, dried over $Na_2SO_4$, and concentrated to give a yellow oil. The residue was purified by column chromatography ($SiO_2$; EtOAc/hexane=1/1 to 2/1) to give sulfoxide (14.2 mg, 25.9 μmol, 87% yield, a 9:1 diastereomixture derived from S) as a pale yellow oil.

*4.1.30. (1S,5R,7R,8S)-1-Isobutyryl-8-(4-methoxy-4-methylpentyl)-8-methyl-5,7-bis(3-methylbut-2-enyl)-4-(methylsulfinyl)bicyclo[3.3.1]non-3-ene-2,9-dione (**51**).* To a solution of sulfoxide (504 mg, 918 μmol) in $CH_2Cl_2$ (9.2 ml) was added Dess−Maritn periodinane (780 mg, 1.84 mmol) at room temperature. After being stirred at the same temperature for 40 min, the reaction was quenched with $Na_2S_2O_3$ aq. The organic layer was separated and the aqueous layer was further extracted twice with ether. The combined organic layer was washed twice with $NaHCO_3$ aq and brine, dried over $Na_2SO_4$, and concentrated to give a yellow oil. The residue was purified by column chromatography ($SiO_2$; EtOAc/hexane=1/4) to give **51** (433 mg, 791 μmol, 86% yield, a 9:1 diastereomixture) as a pale yellow oil.

*4.1.31. (1S,5R,7R,8S)-1-Isobutyryl-8-methyl-5,7-bis(3-methylbut-2-enyl)-8-(4-methylpent-3-enyl)-4-(methylsulfinyl)bicyclo[3.3.1]non-3-ene-2,9-dione.*



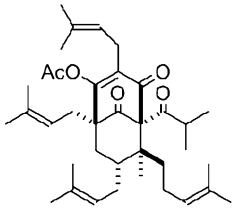

To a solution of **51** (11.1 mg, 20.3 μmol) in toluene (200 μl) was added Amberlyst 15DRY (11.1 mg). The resulting mixture was stirred at 80 °C for 1.5 h. After cooling to room temperature, Amberlyst 15DRY was filtrated and the filtrate was concentrated to give a yellow oil. The residue was purified by column chromatography

($SiO_2$; EtOAc/hexane=1/5) to give C8-homoprenyl product (7.2 mg, 14 μmol, 69% yield, a 9:1 diastereomixture) as a pale yellow oil.

*4.1.32. (1S,5S,7R,8S)-4-(Allyloxy)-1-isobutyryl-8-methyl-5,7-bis(3-methylbut-2-enyl)-8-(4-methylpent-3-enyl)bicyclo[3.3.1]non-3-ene-2,9-dione (**52**).* To a solution of C8-homoprenyl compound (120 mg, 233 μmol) in allyl alcohol (2.3 ml) was added LiH (9.3 mg, 1.2 μmol) at −40 °C. The resulting mixture was stirred at the same temperature for 39.5 h. The reaction was quenched with saturated $NH_4Cl$ aq. The organic layer was separated, and the aqueous layer was further extracted twice with EtOAc. The combined organic layer was washed with water and brine, dried over $Na_2SO_4$, and concentrated to give a yellow oil. The residue was partially purified by column chromatography ($SiO_2$; Hexane/toluene=2/3 to toluene only) to give **52** as a colorless oil, which was used for next step without further purification.

*4.1.33. (1S,5S,7R,8S)-3-Allyl-5-isobutyryl-6-methyl-1,7-bis(3-methylbut-2-enyl)-6-(4-methylpent-3-enyl)-4,9-dioxobicyclo[3.3.1]non-2-en-2-yl acetate (**53**).* The reaction solvent THF was degassed before the reaction. $Pd_2dba_3\cdot CHCl_3$ (7.6 mg, 7.3 μmol) and (*S*)-tol-BINAP (10.0 mg, 14.7 μmol) were dissolved into THF (490 μl). After being stirred at room temperature for 30 min, a solution of **52** (37.3 mg, 73.3 μmol) in THF (1.5 ml) was added to the mixture. The resulting mixture was stirred for 2.5 h at room temperature, then $Ac_2O$ (13.9 μl, 147 μmol) and pyridine (11.9 μl, 147 μmol) were added. After 1 h, additional $Ac_2O$ (27.8 μl, 294 μmol) and pyridine (23.8 μl, 294 μmol) were added, and the mixture was stirred for 1.5 h. The reaction was quenched with water. The organic layer was separated, and the aqueous layer was further extracted twice with EtOAc. The combined organic layer was washed with water and brine, dried over $Na_2SO_4$, and concentrated to give an orange oil. The residue was purified by column chromatography ($SiO_2$; EtOAc/hexane=1/30) to give an inseparable mixture of **53** and unknown byproduct (20.4 mg; 4:1 mixture) as a colorless oil. This mixture was further purified by HPLC. HPLC purification was performed on JASCO HPLC systems containing of following: pump, PU-980; detector, UV-970, measured at 210 nm; column, Shiseido HPLC PACKED COLUMN, SG 80 A; mobile phase, dichloromethane/hexane=1/1; flow rate, 5.0 mL/min. $^1$H NMR ($CDCl_3$) $\delta$: 5.66–5.75 (m, C32–1H), 4.99–5.06 (m, C17–1H, C22–1H, C27–1H, C33–2H), 3.13 (dd, *J*=6.3, 15.5 Hz, C31–1H), 2.92 (dd, *J*=6.3, 15.5 Hz, C31–1H), 2.50 (dd, *J*=6.9, 15.5 Hz, C26–1H), 2.32 (dd, *J*=6.9, 15.5 Hz, C26–1H), 2.24 (s, OCOC*H*$_3$–3H), 2.07–2.14 (m, C6–1H, C21–1H), 2.02 (dd, *J*=4.6, 14.3 Hz, C21–1H), 1.97 (sep, *J*=6.9 Hz, C11–1H), 1.71–1.91 (m, C6–1H, C7–1H, C16–2H), 1.69 (s, C20–3H, C30–3H), 1.67 (s, C29–3H), 1.64 (s, C19–3H), 1.59 (s, C24–3H), 1.55 (s, C25–3H), 1.36–1.42 (m, C5–2H), 1.10 (d, *J*=6.9 Hz, C12–3H), 1.01 (s, C14–3H), 0.99 (d, *J*=6.9 Hz, C13–3H); $^{13}$C NMR ($CDCl_3$) $\delta$: 208.4, 206.0, 193.3, 166.6, 164.1, 134.2, 133.5, 132.9, 132.5, 131.2, 124.6, 122.4, 118.9, 116.4, 84.4, 57.3, 49.9, 42.9, 42.3, 38.1, 36.4, 30.0, 28.7, 27.1, 25.9, 25.7, 25.7, 25.0, 21.2, 20.6, 20.4, 18.1, 17.9, 17.7; IR (neat, $cm^{-1}$): $\nu$ 1777, 1732, 1656, 1638; MS (ESI) *m*/*z* 573 $(M+Na)^+$; HRMS (ESI) calcd for $C_{35}H_{50}O_5$ $(M+Na)^+$: 573.3556, Found: 573.3562; $[\alpha]_D^{23}$ −78.8 (*c* 0.82, $CHCl_3$) (80% ee).

*4.1.34. (1S,5S,7R,8S)-5-Isobutyryl-6-methyl-1,3,7-tris(3-methylbut-2-enyl)-6-(4-methylpent-3-enyl)-4,9-dioxobicyclo[3.3.1]non-2-en-2-yl acetate.*




To a solution of **53** (14.4 mg, 26 μmol) in $CH_2Cl_2$ (650 μl) and 2-methyl-2-butene (650 μl) was added Hoveyda–Grubbs second catalyst (2.4 mg, 3.9 μmol). The resulting mixture was stirred at 40 °C for 30 min, and after cooling to room temperature the solvent was removed by evaporator. The residue was purified by column chromatography ($SiO_2$; EtOAc/hexane=1/30) to give *O*-acetyl-*ent*-hyperforin (5.2 mg, 9.0 μmol, 34% yield) as a colorless oil. $^1$H NMR ($CDCl_3$) $\delta$: 4.98–5.06 (m, C17–1H, C22–1H, C27–1H, C32–1H), 3.03 (dd, *J*=7.0, 15.0 Hz, C31–1H), 2.84 (dd, *J*=7.1, 15.0 Hz, C31–1H), 2.48 (dd, *J*=6.7, 15.3 Hz, C26–1H), 2.33 (dd, *J*=7.0, 15.3 Hz, C26–1H), 2.23 (s, OC*H*$_3$–3H), 2.06–2.13 (m, C6–1H, C21–1H), 1.93–2.01 (m, C11–1H, C21–1H), 1.72–1.89 (m, C6–1H, C7–1H, C16–2H), 1.69 (s, C20–3H, C30–3H), 1.67 (s, C29–3H), 1.65 (s, C19–3H), 1.64 (s, C24–3H), 1.59 (s, C34–3H), 1.55 (s, C25–3H, C35–3H), 1.35–1.43 (m, C15–2H), 1.10 (d, *J*=6.7 Hz, C12–3H), 1.00 (s, C4–3H), 0.98 (d, *J*=6.7 Hz, C13–3H); $^{13}$C NMR ($CDCl_3$) $\delta$: 208.5, 206.2, 193.4, 166.5, 162.7, 134.0, 132.9, 131.1, 124.7, 122.5, 119.8, 119.1, 84.4, 57.0, 49.8, 42.8, 42.2, 38.1, 36.4, 30.0, 27.1, 25.9, 25.7, 25.6, 25.0, 23.9, 21.1, 20.5, 20.3, 18.1, 17.9, 17.7, 17.6, 13.5; IR (neat, $cm^{-1}$): $\nu$ 1777, 1732, 1657, 1634; MS (ESI) *m*/*z* 601 $(M+Na)^+$; HRMS (ESI) calcd for $C_{37}H_{54}O_5$ $(M+Na)^+$: 601.3869, Found: 601.3868; $[\alpha]_D^{23}$ −71.8 (*c* 0.44, $CHCl_3$) (80% ee).

*4.1.35. ent-Hyperforin (ent-**1**).* To a solution of *O*-acetyl-*ent*-hyperforin (1.7 mg, 2.9 μmol) in methanol (100 μl) was added $K_2CO_3$ (0.9 mg, 6.5 μmol) at 0 °C. The resulting mixture was stirred at the same temperature for 35 min. The reaction was quenched with $NH_4Cl$ aq. The organic layer was separated and the aqueous layer was further extracted twice with EtOAc. The combined organic layer was washed with water and brine, dried over $Na_2SO_4$, and concentrated to give a pale yellow oil. The residue was purified by column chromatography ($SiO_2$; EtOAc/hexane=1/5) to give *ent*-**1** (1.5 mg, 2.8 μmol, 94% yield) as a colorless oil. $^1$H NMR ($CD_3OD$) $\delta$: 5.11–5.15 (m, C32–1H), 4.97–5.07 (m, C17–1H, C22–1H, C27–1H), 3.17 (dd, *J*=7.0, 14.7 Hz, C31–1H), 3.11 (dd, *J*=6.7, 14.7 Hz, C31–1H), 2.54 (dd, *J*=6.7, 14.1 Hz, C26–1H), 2.44 (dd, *J*=7.0, 14.1 Hz, C26–1H), 1.90–2.19 (m, C6–1H, C11–1H, C16–2H, C21–1H), 1.74 (s, C30–3H), 1.72 (s, C20–3H, C29–3H), 1.69 (s, C19–3H), 1.68 (s, C24–3H), 1.66–1.79 (m, C7–1H, C15–2H, C21–1H), 1.66 (s, C34–3H), 1.62 (s, C25–3H), 1.61 (s, C35–3H), 1.38–1.47 (m, C6–1H), 1.12 (d, *J*=6.4 Hz, C12–3H), 1.06 (d, *J*=6.4 Hz, C13–3H), 1.01 (s, C14–3H); $^{13}$C NMR ($CDCl_3$) $\delta$: 135.44, 135.04, 132.63, 126.98, 124.73, 123.66, 122.82, 121.90, 43.94, 41.68, 38.81, 31.59, 29.52, 27.02, 26.90, 26.83, 26.74, 26.33, 23.43, 22.86, 22.01, 19.10, 19.01, 18.94, 18.70, 16.13; IR (neat, $cm^{-1}$): $\nu$ 3336, 1724, 1601; MS (ESI) *m*/*z* 559 $(M+Na)^+$; HRMS (ESI) calcd for $C_{35}H_{52}O_4$ $(M+Na)^+$: 559.3763, Found: 559.3763; $[\alpha]_D^{23}$ −36.8 (*c* 0.38, EtOH) (80% ee).

## Acknowledgements

Financial support was provided by a Grant-in-Aid for Young Scientists (S) and Scientific Research (S) from JSPS. Y.S. and H.U. thank JSPS for research fellowships.

## Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.05.086.

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