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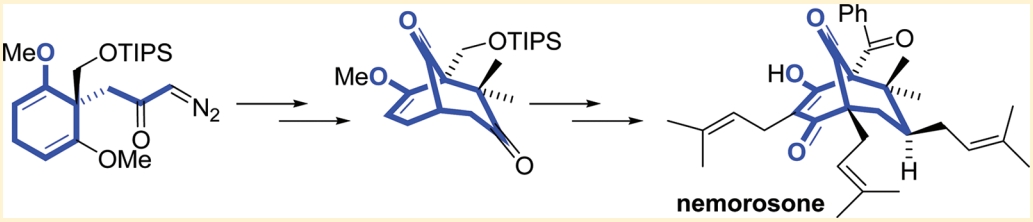
Stereoselective Total Synthesis of Nemorosone

Masahiro Uwamori, Aya Saito, and Masahisa Nakada*

Department of Chemistry and Biochemistry, Faculty of Science and Engineering, Waseda University, 3-4-1 Ohkubo, Shinjuku-ku, Tokyo 169-8555, Japan

Supporting Information



ABSTRACT: The highly stereoselective total synthesis of nemorosone via a new approach to the bicyclo[3.3.1]nonane-2,4,9-trione core which features intramolecular cyclopropanation of an α-diazo ketone, stereoselective alkylation at the C8 position, and regioselective ring-opening of cyclopropane is described. The total synthesis of nemorosone includes chemo- and stereoselective hydrogenation directed by the internal alkene.

INTRODUCTION

Polycyclic polyprenylated acylphloroglucinols (PPAPs) feature complex and diverse structures, including a highly oxygenated and densely substituted bicyclo[3.3.1]nonane-2,4,9-trione or bicyclo[3.2.1]octane-2,4,8-trione core complete with prenyl or geranyl side chains, among others (Figure 1).[1] The family of PPAPs consists of more than 110 members, and their number continues to increase. Interestingly, PPAPs having closely related structures show different and wide-ranging biological activities. For example, nemorosone exhibits anti-HIV and antitumor activities,[2] hyperforin shows antidepressant and antitumor activities,[3] and garsubellin A has anti-Alzheimer activity,[4] while the differences in their structures lie only in the substituents.

Consequently, development of a synthetic approach to the bicyclo[3.3.1]nonane-2,4,9-trione core would contribute to structure−activity relationship studies of PPAPs, with the potential of finding new artificial compounds that show significant biological activity. The intriguing structures and biological activities of PPAPs described above have made them attractive synthetic targets, and many synthetic studies,[5] as well as total syntheses,[6] have been reported thus far. Regarding nemorosone, two total syntheses were reported.[6c,e] However, most of these syntheses have been accomplished via cyclohexenone derivatives as the synthetic intermediates. We herein report the total synthesis of nemorosone via a new approach to the bicyclo[3.3.1]nonane-2,4,9-trione core, which can be applied to the synthesis of other PPAPs.

RESULTS AND DISCUSSION

Nemorosone and some PPAPs share the bicyclo[3.3.1]nonane-2,4,9-trione core, which incorporates stereogenic centers as well as oxygen functionalities at the same positions. Considering these structural features and the hidden symmetry in the structure, we started to develop an approach to the synthetic intermediate **4** that is common for PPAPs (Scheme 1).[7]

Our approach features intramolecular cyclopropanation (IMCP) of **1** (step I),[8] subsequent stereoselective alkylations of **2** (step II), and regioselective ring-opening of the cyclopropane ring in **3** (step III). As step I is the desymmetrization step, it would be made sufficiently enantioselective through the use of a chiral catalyst. Step II would enable the introduction of two different substituents at the C8 position to generate an all-carbon quaternary stereogenic center because the alkylation proceeds from the less hindered convex side. Hence, this approach allows for the stereoselective total synthesis of hyperforin. Step III regioselectively affords **4** because the electron-donating methoxy group on the cyclopropane and the electron-withdrawing ketone cooperatively enhance the ring-opening reaction.

Scheme 2 shows the retrosynthetic analysis of nemorosone to **4**. The C1 benzoyl and C2 hydroxyl groups of nemorosone were planned to be added at the last stage because the C1 benzoyl group basically suffers from nucleophilic addition and the C2 enol hydroxyl is reactive. Hence, the set precursor, **5**, could be obtained by the introduction of prenyl groups at the C3 and C5 positions of **6**. Alternatively, conversion of all the allyl groups at the C3, C5, and C7 positions to prenyl groups via cross-metathesis would also be possible if the introduction of prenyl groups proves difficult.[5c,6c,d,9] Compound **6** was thought to be obtained by allylic oxidation at the C4 position of **7**, which could be derived from **4** via the stereoselective construction of the C7 stereogenic center.

Scheme 3 shows the preparation of α-diazo-β-ketone **1** from 2,6-dimethoxybenzoic acid methyl ester **8**. Compound **8** was

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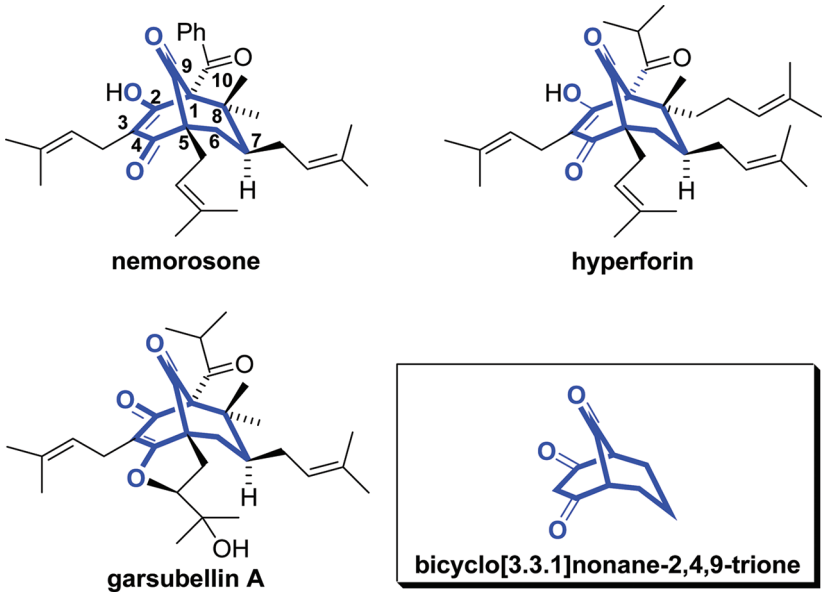
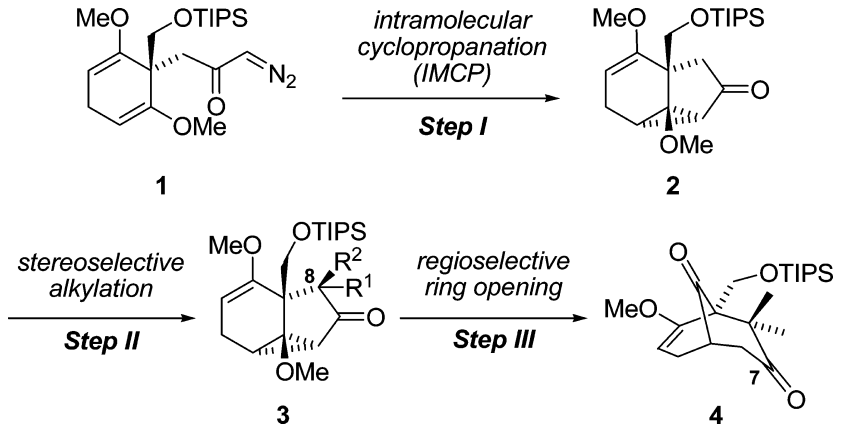
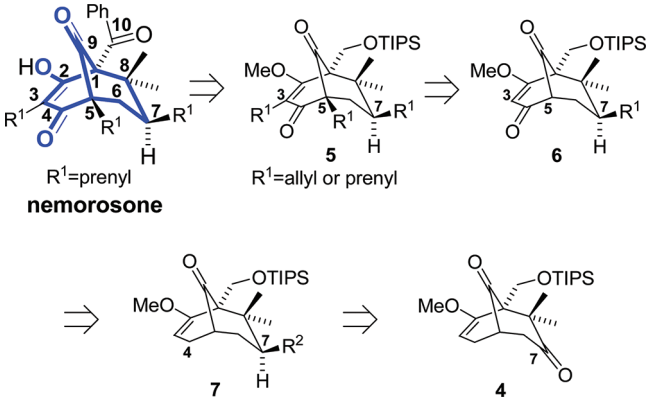


Figure 1. Structures of nemorosone, hyperforin, garsubellin A, and bicyclo[3.3.1]nonane-2,4,9-trione.

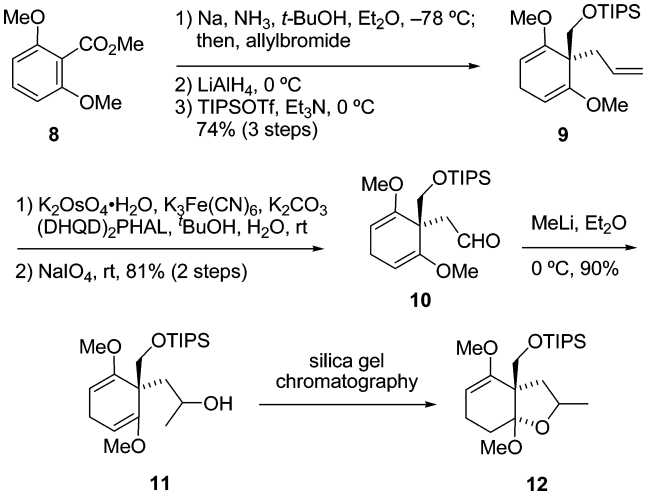
Scheme 1. New Approach to 4 via Cyclopropane 2



Scheme 2. Retrosynthetic Analysis of Nemorosone to 4



Scheme 3. Attempted Preparation of 13



subjected to Birch reduction, followed by a one-pot reaction with allylbromide, reduction of the methyl ester with lithium aluminum hydride, and protection of the primary hydroxyl group as a TIPS ether to afford **9**. Selective dihydroxylation of **9** and the following 1,2-diol cleavage afforded aldehyde **10**,[10] which was subjected to the reaction with a methyllithium to afford **11**. Since compound **11** was acid-sensitive, **12** was formed from **11** when it was subjected to the purification by silica gel chromatography.

Hence, we explored the one-pot procedure for converting **10** to methyl ketone **13** and found that **10** was converted to **13** by

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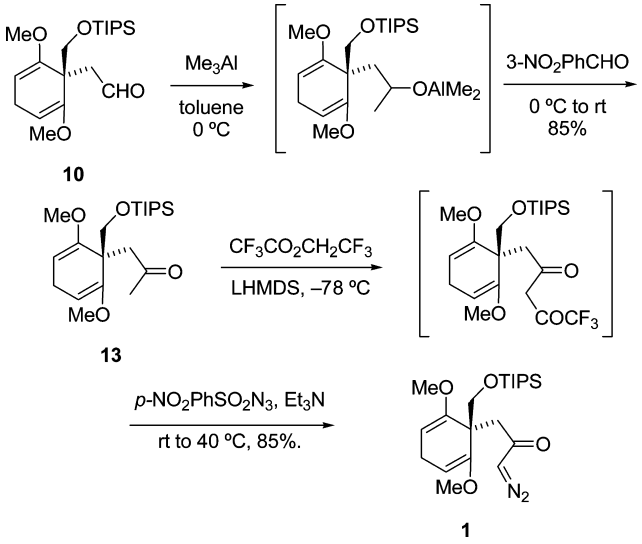
the one-pot methylation[11]−Oppenauer oxidation[12] protocol developed in this study (Scheme 4). That is, the reaction of **10**

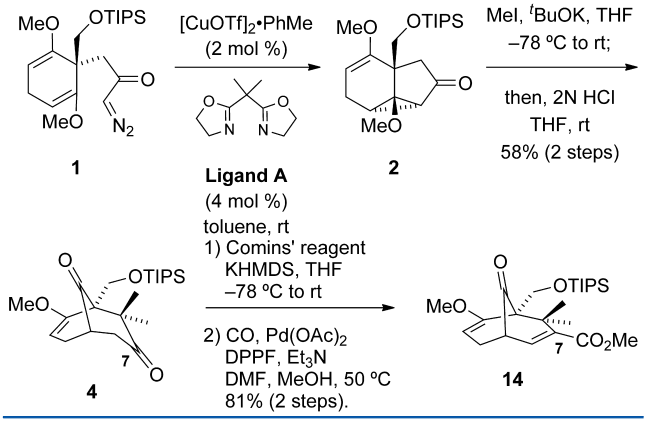
Scheme 4. Preparation of 1 via Two One-Pot Procedures



with trimethylaluminum afforded the alkoxide, which was subsequently treated with 3-nitrobenzaldehyde in a one-pot manner to afford **13** in 85% yield. Methyl ketone **13** was successfully converted to **1** according to Danheiser's protocol.[13] Initially, we isolated the trifluoroacetyled methyl ketone, which was prepared from **13**, and used it for the next diazotransfer reaction to prepare **1**, but soon found that the two reactions were able to carry out in a one-pot manner with high yield.

IMCP of **1** was carried out under conditions optimized by us (Scheme 5).[7,8] Since the IMCP of **1** with a chiral ligand was

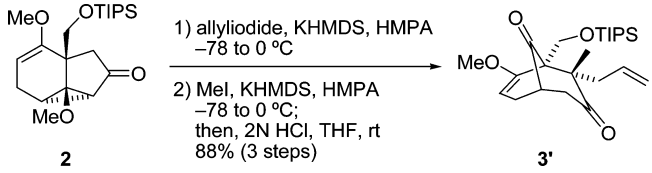
Scheme 5. Preparation of 14 via IMCP of 1



planned to be examined separately, IMCP of **1** was carried out with achiral **ligand A** to afford **2**. Since compound **2** is acid-sensitive, crude **2** was subjected to a reaction with excess methyl iodide and potassium *tert*-butoxide to afford a dimethylated compound, which was then treated with acid. The ring-opening reaction of cyclopropane proceeded regioselectively to afford diketone **4** as the single isomer (58%, three steps). Conversion of **4** to the corresponding enol triflate and subsequent palladium-mediated carbonylation afforded **14**.

We also found that the sequential allylation and methylation of **2** proceeded at the less-hindered convex face and subsequent treatment with acid afforded **3′** as the single product with excellent overall yield, which is a potential intermediate for the total synthesis of hyperforin (Scheme 6).

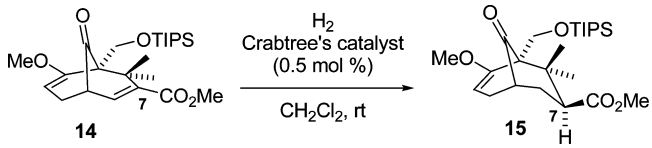
Scheme 6. Highly Stereoselective Preparation of 3′ from 2



To generate the C7 stereogenic center, chemo- and stereoselective reduction of the C6−C7 alkene in **14** was examined. Compound **14** has a methoxy group on the electron-rich C2−C3 alkene and an ester group on the electron-deficient C6−C7 alkene. Hence, the C6−C7 alkene of **14** was expected to be selectively reduced under suitable conditions. However, the reduction of **14** with common reagents that have been used for the reduction of α,β-unsaturated esters did not proceed, most probably owing to steric hindrance.

Fortunately, we found that hydrogenation of **14** with Crabtree's catalyst (0.5 mol %)[14] proceeded smoothly at room temperature to afford **15** as the single isomer (Scheme 7).

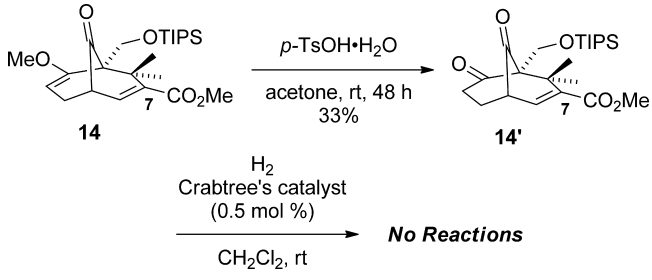
Scheme 7. Highly Stereoselective Hydrogenation of 14 To Afford 15



Interestingly, extensive ^{1}H NMR studies suggested that **15** has the desired C7 configuration. More usually, hydrogenation of the alkene in a bridge-ring system such as **14** selectively proceeds at the less hindered convex face. However, the structure of **15** indicated that hydrogenation of **14** exclusively occurred at the more hindered concave face. Therefore, we speculated that hydrogenation of **14** was directed by the C2−C3 alkene.

To confirm the directing effect of the C2−C3 alkene, hydrogenation of **14′**, which was prepared by acidic hydrolysis of **14**, was examined (Scheme 8). As the result, no reactions

Scheme 8. Preparation and Attempted Hydrogenation of 14′



occurred under the same conditions in Scheme 7, suggesting the directing effect by the C2−C3 alkene. To the best of our knowledge, stereoselective hydrogenation directed by the internal alkene has not been reported in the literature thus far.

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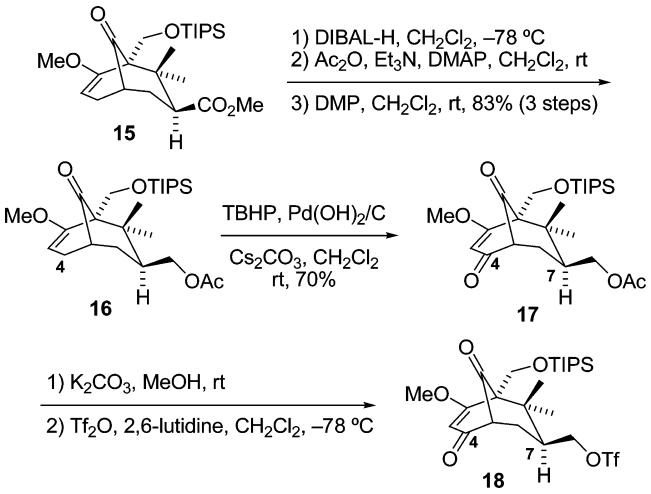
Reduction of **15** with DIBAL-H, subsequent selective acetylation of the primary hydroxyl group, and oxidation of the secondary hydroxyl group afforded **16** (Scheme 9). Allylic

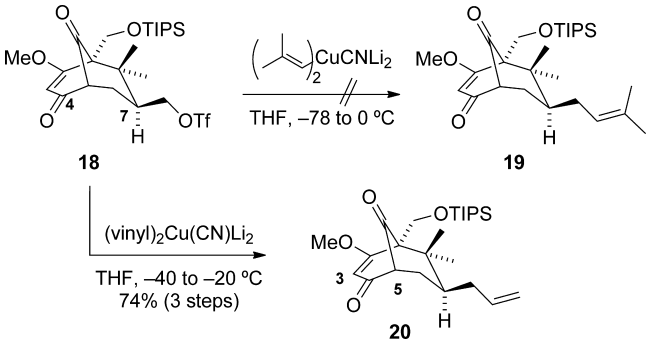
Scheme 9. Preparation of Triflate 18



oxidation at the C4 position of **16** successfully afforded **17**.[5t,15] The acetate of **17** was removed, and the resultant alcohol was converted to triflate **18** so as to introduce a prenyl group at the C7 position via a coupling reaction.

However, coupling reaction of **18** with the organocopper reagent derived from 2-methyl-1-propenyllithium did not take place (Scheme 10). To our delight, the coupling reaction of **18**

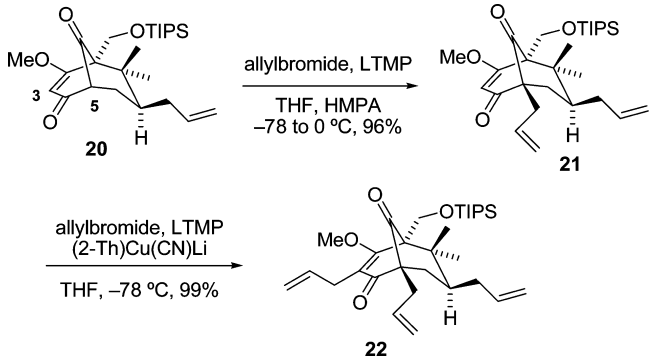
Scheme 10. Coupling Reactions of 18 with Cuprates



with divinyl cuprate smoothly afforded **20** without involving 1,4-addition in the enone system. Thereafter, the allyl group at the C7 position was planned to be converted to a prenyl group by cross-metathesis at a later stage of the synthesis.

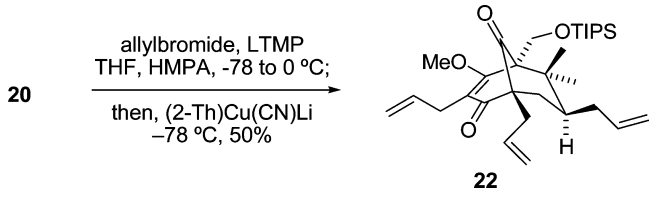
Since the cross-metathesis had to be carried out at the later stage, allylations at the C5 and C3 positions were carried out because all of the allyl groups at the C3, C5, and C7 positions were expected to be simultaneously converted to prenyl groups via the cross-metathesis. Allylation at the C5 position of **20** using LDA resulted in reduction of the C9 ketone, but use of LTMP solved this problem, successfully affording the C5-allylated product (Scheme 11).[5o,p,6e,16] Subsequent allylation at the C3 position did not take place under the same conditions as those used for the C5 allyation. However, as has been reported, use of thienylcuprate as the additive provided **22** in good yield.[5p,6c,17]

Scheme 11. Introduction of Allyl Groups at C5 and C3 Positions



Alternatively, although the overall yield was reduced, one-pot allylation at the C5 and C3 positions was found to be possible (Scheme 12). Thus, reaction of **20** with excess LTMP, followed

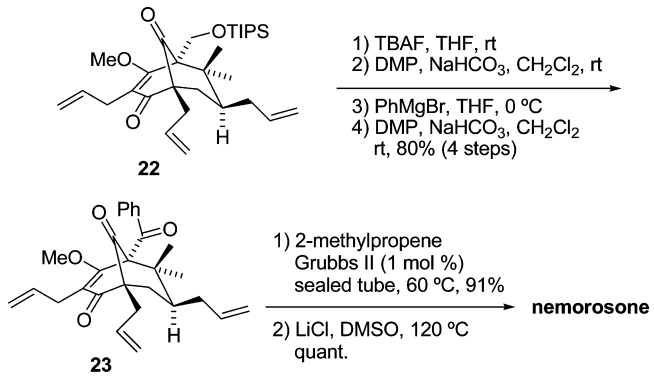
Scheme 12. One-Pot Introduction of Allyl Groups at C5 and C3 Positions



by the reaction with allylbromide, and subsequent addition of thienylcuprate afforded **22** in 50% yield.

Removal of the TIPS group of **22**, Dess–Martin oxidation, reaction with phenylmagnesium bromide, and further Dess–Martin oxidation afforded **23** (Scheme 13). The intermediate

Scheme 13. Total Synthesis of Nemorosone



aldehyde was suspected to be not so reactive because it was a sterically hindered neopentyl type aldehyde having a successive quaternary carbon center, but the addition of a phenylmagnesium bromide to the aldehyde selectively took place with high yield. The high yield could be attributed to the C2–C3 alkene and C9 ketone that would inductively activate the aldehyde. In addition, oxygen atoms of the C2 methoxy group and C9 ketone could act as directing groups that accelerate the addition of a phenylmagnesium bromide. The three allyl groups of **23** were cleanly converted to prenyl groups by cross-metathesis with Grubbs II catalyst and 2-methylpropene at

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60 °C in a sealed tube. Finally, the methyl group on the C2 hydroxyl group was successfully removed under Krapcho conditions.[5p,6d,e] The final product proved to be identical to nemorosone in all respects (^{1}H and ^{13}C NMR, IR, and HRMS),[2] confirming the total synthesis of nemorosone.

In summary, we have established a new synthetic route to the bicyclo[3.3.1]nonane-2,4,9-trione core of PPAPs via the intramolecular cyclopropanation (IMCP) (step I), subsequent stereoselective alkylations (step II), and regioselective ring-opening of cyclopropane (step III). The IMCP (step I) can be made enantioselective through the use of a chiral catalyst, and stereoselective alkylations (step II) enable the construction of the C8 all-carbon quaternary stereogenic center for the total synthesis of hyperforin. The total synthesis of nemorosone features the successful application of this new approach developed by us, wherein chemo- and stereoselective hydrogenation, which is directed by the internal alkene, precedes palladium-mediated allylic oxidation at the C4 position, one-pot allylations at the C5 and C3 positions, and global cross-metathesis with Grubbs II catalyst and 2-methyl-1-propene. Further synthetic studies of PPAPs on the basis of this research are underway and will be reported in due course.

EXPERIMENTAL SECTION

General Methods. ^{1}H and ^{13}C NMR spectra were recorded on 400 or 500 MHz spectrometers. ^{1}H and ^{13}C chemical shifts are reported in ppm downfield from tetramethylsilane (TMS, δ scale) with the solvent resonances as internal standards. The following abbreviations are used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; band, several overlapping signals; brs, broad; Cq, quaternary carbon; CH, methine carbon; CH_2, methylene carbon; CH_3, methyl carbon. IR spectra were recorded on a FT/IR spectrometer. To confirm the ^{1}H and ^{13}C NMR peak assignments (Supporting Information) and carbon multiplicities, ^{1}H NMR, BCM, DEPT, COSY, HMQC, HMBC, and NOESY methods were used. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm silica gel plates using UV light as visualizing agent and phosphomolybdic acid and heat as developing agents. Silica gel (60, particle size 0.040−0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on self-made 0.3 mm silica gel plates. THF and Et_2O were distilled from sodium/benzophenone ketyl. Toluene was distilled from sodium. MeOH was distilled with a small amount of magnesium and I_2. Benzene and MeCN were distilled from CaH_2, and all commercially available reagents were used without further purification. Optical rotations were measured on a polarimeterat a wavelength of 589 nm. High resolution mass spectra (HRMS) were obtained by either an electronspray ionization (ESI) recorded in a TOF mass spectrometer (Time-of-Flight mass spectrometer) or a fast atom bombardment (FAB) recorded in a DFMS (double-focusing mass spectrometer), and theoretical monoisotopic molecular masses were typically ≤5 ppm. Melting point was uncorrected. TLC R_f's of purified compounds are included.

*[(1-Allyl-2,6-dimethoxycyclohexa-2,5-dienyl)methoxy]-triisopropylsilane (**9**).* To a stirred solution of methyl 2,6-dimethoxybenzoate (33.6 g, 171 mmol) in Et_2O (114 mL) was added *t*-BuOH (18.0 mL, 189 mmol, 1.1 equiv) at room temperature, and then the mixture was cooled to −78 °C. To the mixture was added liquid NH_3 (230 mL), which was introduced via a dry ice condenser, and with stirring, sodium (9.46 g, 411 mmol, 2.4 equiv) was added in portions. After 30 min, allyl bromide (46.0 mL, 531 mmol, 3.1 equiv) was added dropwise. When the reaction was completed, NH_3 was allowed to evaporate overnight, and Et_2O (150 mL) and H_2O (150 mL) were added to the reaction mixture. The aqueous layer was extracted with Et_2O (100 mL × 2). The combined organic layer was washed with brine (350 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude ester **8a** (ca. 40.8 g) was used for the next step without further purification.

To a stirred suspension of $LiAlH_4$ (8.74 g, 187 mmol, 1.1 equiv) in Et_2O was added a solution of **8a** (ca. 40.8 g) in Et_2O (93 mL) at 0 °C. After the reaction was completed, to the mixture was added saturated aqueous Na_2SO_4 (20 mL), and the reaction mixture was stirred for 1 h. Then the mixture was filtered through a plug of Celite, and the filtrate was concentrated under reduced pressure. The crude alcohol **8b** (ca. 37.0 g) was used for the next step without further purification.

To a stirred solution of **8b** (ca. 37.0 g) in CH_2Cl_2 (180 mL) were added Et_3N (62.7 mL, 450 mmol, 2.6 equiv) and TIPSOTf (53.2 mL, 198 mmol, 1.2 equiv) successively at 0 °C. After the reaction was completed, saturated aqueous $NaHCO_3$ solution (180 mL) was added to the reaction mixture, and the aqueous layer was extracted with CH_2Cl_2 (150 mL × 2). The combined organic layer was washed with brine (400 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 50/1) to afford **9** (49.6 g, 79%) as an oil: R_f = 0.85 (hexane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68−5.50 (1H, m), 4.95−4.87 (2H, m), 4.79 (2H, t, J = 4.0 Hz), 3.73 (2H, s), 3.49 (6H, s), 2.78−2.71 (2H, m), 2.20 (2H, d, J = 7.0 Hz), 1.00 (21H, brs); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9 (Cq), 135.0 (CH), 115.6 (CH_2), 93.8 (CH), 65.1 (CH_2), 54.1 (CH_3), 50.2 (Cq), 34.7 (CH_2), 24.1 (CH_2), 17.9 (CH_3), 12.0 (CH); IR (neat) ν_{max} 2942, 2865, 1698, 1464, 1225, 1208, 1137 cm^{-1}; HRMS (FAB-DFMS) $[M + H]^+$ calcd for $C_{21}H_{39}O_3Si$ 367.2668, found 367.2682.

*2-[2,6-Dimethoxy-1-((triisopropylsilyloxy)methyl)cyclohexa-2,5-dienyl]acetaldehyde (**10**).* To a stirred solution of $K_2OsO_4{\cdot}2H_2O$ (118 mg, 0.320 mmol, 0.3 mol %) in H_2O (305 mL) were added $(DHQD)_2PHAL$ (623 mg, 0.800 mmol, 0.75 mol %), K_2CO_3 (44.2 g, 319.7 mmol, 3.0 equiv), and $K_3Fe(CN)_6$ (105 g, 320 mmol, 3.0 equiv) successively at room temperature. Then, to the reaction mixture was added a solution of **9** (39.1 g, 106.6 mmol) in *t*-BuOH (305 mL) at room temperature. After the reaction was completed, saturated aqueous Na_2SO_3 solution (200 mL) was added to the reaction mixture, and the aqueous layer was extracted with Et_2O (300 mL × 3). The combined organic layer was washed with brine (500 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude diol **9a** (ca. 44.9 g) was used for the next step without further purification.

To a stirred solution of **9a** (ca. 44.9 g) in MeOH (373 mL) was added a solution of $NaIO_4$ (26.3 g, 123.2 mmol) in H_2O (373 mL) at 0 °C, and the reaction mixture was warmed to room temperature. After the reaction was completed, water (746 mL) was added to the reaction mixture, and the aqueous layer was extracted with Et_2O (500 mL × 3). The combined organic layer was washed with brine (700 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford **10** (31.9 g, 81%) as a white powder: R_f = 0.35 (hexane/ethyl acetate = 10/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.58 (1H, t, J = 3.0 Hz), 4.85 (2H, t, J = 4.0 Hz), 3.77 (2H, s), 3.50 (6H, s), 2.85−2.75 (2H, m), 2.44 (2H, d, J = 3.0 Hz), 0.99 (21H, brs); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.0 (Cq), 152.0 (Cq), 94.3 (CH), 64.5 (CH_2), 54.3 (CH_3), 47.3 (Cq), 43.9 (CH_2), 24.0 (CH_2), 17.7 (CH_3), 12.0 (CH); IR (neat) ν_{max} 2941, 2865, 1720, 1695, 1205, 1125, 1065 cm^{-1}; HRMS (FAB-DFMS) $[M + H]^+$ calcd for $C_{20}H_{37}O_4Si$ 369.2461, found 369.2449; mp 58−59 °C.

*1-[2,6-Dimethoxy-1-((triisopropylsilyloxy)methyl)cyclohexa-2,5-dienyl]propan-2-one (**13**).* To a stirred solution of **10** (33.5 g, 90.8 mmol) in toluene was added a solution of Me_3Al in toluene (50 mL, 100 mmol, 1.1 equiv) at 0 °C, and the reaction mixture was stirred at 0 °C for 4 h. To the reaction mixture was added 3-nitrobenzaldehyde (62.1 g, 272 mmol, 3.0 equiv) at 0 °C, and the resulting mixture was warmed to room temperature. After the reaction was completed, CH_2Cl_2 (200 mL) and saturated aqueous Rochelle salt solution (200 mL) were added to the reaction mixture, and the resultant mixture was stirred for 1 h. Then the mixture was filtered through a plug of Celite, and the aqueous layer was extracted with CH_2Cl_2 (200 mL × 2). The combined organic layer was washed with saturated aqueous $NaHCO_3$

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(400 mL) and then washed with brine (500 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford **13** (29.6 g, 85%) as an oil: R_f = 0.50 (hexane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.80 (2H, t, J = 4.0 Hz), 3.70 (2H, s), 3.50 (6H, s), 2.77 (2H, brs), 2.56 (2H, s), 2.00 (3H, s), 0.99 (21H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.6 (Cq), 152.3 (Cq), 94.0 (CH), 65.3 (CH_2), 54.1 (CH_3), 48.4 (Cq), 44.7 (CH_2), 30.9 (CH_3), 24.0 (CH_2), 17.7 (CH_3), 11.9 (CH); IR (neat) ν_{max} 2941, 2865, 1710, 1698, 1663, 1464, 1385, 1352, 1225, 1211, 1077 cm^{-1}; HRMS (FAB-DFMS) $[M + H]^+$ calcd for $C_{21}H_{39}O_4Si$ 383.2618, found 383.2625.

*1,3-Dimethoxy-2-[(triisopropylsilyloxy)methyl]-2-(3-diazo-2-oxopropyl)-1,3-cyclohexadiene (**1**).* To a stirred solution of LHMDS in THF (72.3 mL, 76.6 mmol, 1.1 equiv) was added a solution of **13** (27.7 g, 72.3 mmol) in THF (145 mL) at −78 °C, and the reaction mixture was stirred for 30 min at the same temperature. Then, to the reaction mixture was added 2,2,2-trifluoroethyl trifluoroacetate (10.7 mL, 79.6 mmol, 1.1 equiv) in one portion at −78 °C, and then was added water (3.9 mL, 217 mmol, 3.0 equiv) at 0 °C. The resulting mixture was warmed up to room temperature and stirring was continued for additional 1 h. To the reaction mixture was added Et_3N (101 mL, 723 mmol, 10 equiv) and p-$NO_2PhSO_2N_3$ (49.5 g, 217 mmol, 3.0 equiv), and the mixture was warmed up to 40 °C. After the reaction was completed, the reaction mixture was diluted with Et_2O (400 mL × 1), and washed with 10% NaOH aqueous solution (100 mL × 3). The organic layer was washed with brine (500 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2) to afford **1** (24.7 g, 84%) as a yellow powder: R_f = 0.30 (hexane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.21 (1H, brs), 4.83 (2H, t, J = 4.0 Hz), 3.70 (2H, brs), 3.53 (6H, s), 2.78 (2H, t, J = 4.0 Hz), 2.50 (2H, brs), 0.96 (21H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.0 (Cq), 151.9 (Cq), 94.5 (CH), 65.3 (CH_2), 54.5 (Cq), 54.2 (CH_3), 48.8 (Cq), 42.0 (CH_2), 24.0 (CH_2), 17.7 (CH_3), 11.9 (CH); IR (neat) ν_{max} 2942, 2865, 2098, 1698, 1643, 1464, 1386, 1355, 1206, 1133 cm^{-1}; HRMS (FAB-DFMS) $[M + H]^+$ calculated for $C_{21}H_{37}O_4N_2Si$ 409.2523, found 409.2522; mp 60−61 °C.

(1R,5S*)-1-[(Triisopropylsilyloxy)methyl]-8,8-dimethyl-2-methoxybicyclo[3.3.1]non-2-ene-7,9-dione (**4**).* To a stirred solution of $[CuOTf]_2$·PhMe (161 mg, 0.311 mmol, 2 mol %) in toluene (6.2 mL) was added a solution of **ligand A**[18] (112 mg, 0.623 mmol, 4 mol %) in toluene (6.2 mL) at room temperature, and the reaction mixture was stirred at the same temperature for 30 min. Then, to the reaction mixture was added a solution of **1** (6.35 g, 15.6 mmol) in toluene (31.1 mL) at room temperature. After the reaction was completed, saturated aqueous $NaHCO_3$ solution (50 mL) was added to the reaction mixture, and the aqueous layer was extracted with Et_2O (100 mL × 3). The combined organic layer was washed with brine (400 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude cyclopropane **2** (ca. 6.52 g) was unstable under acidic conditions. Therefore, it was used for the next step without further purification.

To a stirred solution of crude **2** (ca. 6.52 g) in THF (71.5 mL) and HMPA (14.3 mL) was added *t*-BuOK (5.78 g, 51.5 mmol, 3.3 equiv) at 0 °C. After 30 min, to the reaction mixture was added MeI (6.41 mL, 17.2 mmol, 6.6 equiv) at 0 °C. After the reaction was completed, saturated aqueous $NaHCO_3$ solution (50 mL) was added to the reaction mixture, and the aqueous layer was extracted with EtOAc (100 mL × 3). The combined organic layer was washed with brine (300 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude dimethyl cyclopropane **2a** (ca. 11.3 g) was unstable under acidic conditions. Therefore, it was used for the next step without further purification.

To a stirred solution of **2a** (ca. 11.3 g) in THF (23.0 mL) was added 2 N HCl (4.6 mL) at 0 °C. After the reaction was completed, saturated aqueous $NaHCO_3$ solution (100 mL) was added to the reaction mixture, and the aqueous layer was extracted with Et_2O (100 mL × 3). The combined organic layer was washed with brine (200 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by recrystallization (hexane) to afford **4** (4.52 g, 58% (three steps)) as a white powder: R_f = 0.60 (hexane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.74 (1H, dd, J = 5.5, 1.5 Hz), 4.25 (1H, d, J = 8.5 Hz), 3.95 (1H, d, J = 8.5 Hz), 3.46 (3H, s), 3.02 (1H, dd, J = 16.5, 7.5 Hz), 2.94−2.85 (1H, brs), 2.56 (1H, ddd, J = 16.5, 5.5, 2.0 Hz), 2.42 (1H, d, J = 16.5 Hz), 2.27 (1H, ddd, J = 16.5, 5.5, 1.5 Hz), 1.17 (3H, s), 1.10−1.01 (21H, brs), 0.99 (3H s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.5 (Cq), 207.3 (Cq), 154.6 (Cq), 93.4 (CH), 60.9 (Cq), 57.5 (CH_2), 54.5 (CH_3), 53.7 (Cq), 45.1 (CH_2), 44.7 (CH), 30.7 (CH_2), 23.4 (CH_3), 19.4 (CH_3), 17.9 (CH_3), 12.0 (CH); IR (neat) ν_{max} 2956, 2940, 2864, 1729, 1708, 1656, 1458, 1241, 1217, 1105, 1089, 1063 cm^{-1}; HRMS (FAB-DFMS) $[M + H]^+$ calcd for $C_{22}H_{39}O_4Si$ 395.2618, found 395.2632; mp 106−107 °C.

(1R,5S*,8S*)-1-[(Triisopropylsilyloxy)methyl]-8-allyl-8-methyl-2-methoxybicyclo[3.3.1]non-2-ene-7,9-dione (**3′**).* To a stirred solution of **2** (ca. 1.46 g), which was prepared from **1** (1.40 g, 3.43 mmol), in THF (16.0 mL) and HMPA (14.0 mL) was added KHMDS in toluene (23.0 mL, 11.5 mmol, 3.0 equiv) at −78 °C. After 30 min, to the reaction mixture was added allyl iodide (2.10 mL, 23.0 mmol, 6.0 equiv) at −78 °C. The resultant solution was warmed to 0 °C. After the reaction was completed, saturated aqueous $NaHCO_3$ solution (50 mL) was added to the reaction mixture, and the aqueous layer was extracted with Et_2O (50 mL × 3). The combined organic layer was washed with brine (200 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude allylated cyclopropane **2b** (ca. 3.57 g) was unstable under acidic conditions. Therefore, it was used for the next step without further purification.

To a stirred solution of **2b** (ca. 3.57 g) in THF (35.3 mL) and HMPA (7.1 mL) was added KHMDS in toluene (67.8 mL, 33.9 mmol, 4.0 equiv) at −78 °C. After 30 min, to the reaction mixture was added methyl iodide (4.22 mL, 67.8 mmol, 8.0 equiv) at −78 °C. After the reaction was completed, saturated aqueous $NaHCO_3$ solution (100 mL) was added to the reaction mixture, and the aqueous layer was extracted with Et_2O (100 mL × 3). The combined organic layer was washed with brine (400 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude cyclopropane **2c** (ca. 3.21 g) was unstable under acidic conditions. Therefore, it was used for the next step without further purification.

To a stirred solution of **2c** (ca. 3.21 g) in THF (36.9 mL) was added 2 N HCl (7.4 mL) at 0 °C. After the reaction was completed, saturated aqueous $NaHCO_3$ solution (100 mL) was added to the reaction mixture, and the aqueous layer was extracted with Et_2O (200 mL × 3). The combined organic layer was washed with brine (300 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford **3′** (1.26 g, 88% (three steps)) as a white powder: R_f = 0.50 (hexane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92−5.81 (1H, m), 5.05−4.95 (2H, m), 4.76 (1H, dd, J = 5.5, 2.0 Hz), 4.20 (1H, d, J = 8.5 Hz), 4.08 (1H, d, J = 8.5 Hz), 3.48 (3H, s), 3.01 (1H, dd, J = 15.5, 6.5 Hz), 2.89 (1H, t, J = 6.5 Hz), 2.83 (1H, dd, J = 14.5, 4.5 Hz), 2.60 (1H, ddd, J = 16.5, 6.5, 2.0 Hz), 2.37 (1H, dd, J = 15.5, 1.0 Hz), 2.29 (1H, ddd, J = 16.5, 5.5, 1.0 Hz), 2.12 (1H, dd. J = 14.5, 9.5 Hz), 1.11−0.98 (21H, brs), 0.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.0 (Cq), 206.8 (Cq), 154.3 (Cq), 136.1 (CH), 117.3 (CH_2), 93.8 (CH), 61.9 (Cq), 57.6 (CH_2), 55.6 (CH_3), 54.5 (Cq), 45.1 (CH), 44.9 (CH_2), 37.4 (CH_2), 30.5 (CH_2), 19.7 (CH_3), 17.9 (CH_3), 12.0 (CH); IR (neat) ν_{max} 2941, 2865, 1715, 1659, 1463, 1426, 1238, 1164, 1129, 1109, 1011 cm^{-1}; HRMS (FAB-DFMS) $[M + H]^+$ calcd for $C_{24}H_{41}O_4Si$ 421.2774, found 421.2788; mp 59−60 °C.

(1R,5S*)-1-[(Triisopropylsilyloxy)methyl]-8,8-dimethyl-2-methoxy-9-oxobicyclo[3.3.1]nona-2,6-diene-7-carboxylic Acid Methyl Ester (**14**).* To a stirred solution of **4** (6.40 g, 16.2 mmol) and Comins' reagent (2-[*N*,*N*-bis(trifluoromethanesulfonyl)amino]-5-chloropyridine)[19] (7.00 g, 17.8 mmol, 1.1 equiv) in THF (66.5 mL) was added KHMDS in toluene (35.6 mL, 17.8 mmol, 1.1 equiv) dropwise at −78 °C. The resultant solution was warmed to room temperature. After the reaction was completed, saturated aqueous $NaHCO_3$ solution (100 mL) was added to the reaction mixture, and the aqueous layer was extracted with Et_2O (200 mL × 3). The combined

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organic layer was washed with 10% NaOH (300 mL) and brine (300 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 15/1) to afford **4a** (7.33 g, 86%) as a white powder: R_f = 0.70 (hexane/ethyl acetate = 5/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.67 (1H, d, J = 5.5 Hz), 4.81 (1H, dd, J = 5.5, 2.0 Hz), 4.27 (1H, d, J = 8.5 Hz), 3.92 (1H, d, J = 8.5 Hz), 3.52 (3H, s), 3.07−2.98 (1H, m), 2.57 (1H, ddd, J = 16.5, 5.5, 2.0 Hz), 2.35 (1H, ddd, J = 16.5, 5.5, 1.5 Hz), 1.23 (3H, s), 1.07−1.00 (21H, brs), 0.95 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.4 (Cq), 155.2 (Cq), 154.3 (Cq), 118.3 (Cq), 116.9 (CH), 93.7 (CH), 61.1 (Cq), 57.9 (CH_2), 54.4 (CH_3), 47.1 (Cq), 43.8 (CH), 28.4 (CH_2), 22.4 (CH_3), 21.7 (CH_3), 17.9 (CH_3), 12.1 (CH); IR (neat) ν_{max} 2943, 2866, 1741, 1659, 1465, 1417, 1246, 1209, 1140, 1004, 983 cm^{-1}; HRMS (FAB-DFMS) $[M + H]^+$ calcd for $C_{23}H_{38}F_3O_6SSi$ 527.2110, found 527.2117; mp 46−47 °C.

A solution of **4a** (5.79 g, 11.0 mmol), Et_3N (4.60 mL, 33.0 mmol, 3.0 equiv), $Pd(OAc)_2$ (113.6 mg, 0.506 mmol, 0.046 equiv), and dppf (560 mg, 1.01 mmol, 0.092 equiv) in MeOH/DMF (1/1, 110 mL) was stirred under an atmosphere of CO at 50 °C. After the reaction was completed, saturated aqueous NH_4Cl solution (100 mL) was added to the reaction mixture, and the aqueous layer was extracted with Et_2O (200 mL × 2). The combined organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 15/1) to afford **14** (4.50 g, 94%) as a white powder: R_f = 0.45 (hexane/ethyl acetate = 10/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.59 (1H, d, J = 5.0 Hz), 4.76 (1H, dd, J = 5.5, 2.0 Hz), 4.31 (1H, d, J = 8.5 Hz), 3.97 (1H, d, J = 8.5 Hz), 3.70 (3H, s), 3.48 (3H, s), 2.97 (1H, dt, J = 5.0, 2.0 Hz), 2.55 (1H, ddd, J = 16.5, 5.0, 2.0 Hz), 2.34 (1H, ddd, J = 16.5, 5.5, 2.0 Hz), 1.32 (3H, s), 1.10 (3H, s), 1.08−1.00 (21H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.1 (Cq), 167.1 (Cq), 155.1 (Cq), 140.0 (Cq), 137.9 (CH), 93.4 (Cq), 62.4 (Cq), 58.1 (CH_2), 54.4 (CH_3), 51.5 (CH_3), 47.7 (Cq), 46.0 (CH), 28.3 (CH_2), 23.5 (CH_3), 22.7 (CH_3), 17.9 (CH_3), 12.1 (CH); IR (neat) ν_{max} 2943, 2865, 1737, 1720, 1656, 1463, 1330, 1245, 1230, 1155, 1127, 1106, 1045 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{24}H_{40}NaO_5Si$ 459.2543, found 459.2535; mp 111−113 °C.

(1R,5S*)-1-[(Triisopropylsilyloxy)methyl]-8,8-dimethyl-2,9-dioxobicyclo[3.3.1]non-6-ene-7-carboxylic Acid Methyl Ester (**14′**).* A solution of **14** (11.0 mg, 0.0252 mmol) in acetone/H_2O (40/1, 1.0 mL) was added *p*-toluene sulfonic acid monohydrate (9.6 mg, 0.0504 mmol, 2.0 equiv) at room temperature. The reaction mixture was stirred at room temperature for 48 h before being quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with Et_2O (10 mL × 3). The combined organic layer was washed with brine (20 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford **14′** (3.5 mg, 33%) as an oil: R_f = 0.45 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (1H, d, J = 7.0 Hz), 4.25 (1H, d, J = 10.5 Hz), 4.11 (1H, d, J = 10.5 Hz), 3.73 (3H, s), 3.26 (1H, dd, J = 10.5, 4.5 Hz), 2.62−2.41 (2H, m), 2.10−1.98 (1H, m), 1.97−1.85 (1H, m), 1.25 (3H, s), 1.18 (3H, s), 1.06−1.02 (21H, brs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.9 (Cq), 206.0 (Cq), 166.0 (Cq), 140.8 (Cq), 136.4 (CH), 75.3 (Cq), 59.1 (CH_2), 51.8 (CH_3), 48.0 (Cq), 46.5 (CH), 36.7 (CH_2), 24.1 (CH_2), 22.0 (CH_3), 21.5 (CH_3), 17.9 (CH_3), 11.9 (CH); IR (neat) ν_{max} 2943, 2867, 1743, 1721, 1705, 1462, 1435, 1316, 1239, 1113, 1039 cm^{-1}; HRMS (FAB-DFMS) $[M + H]^+$ calcd for $C_{23}H_{39}O_5Si$ 423.2567, found 423.2576.

(1R,5S*,7S*)-7-Acetoxymethyl-1-[(triisopropylsilyloxy)methyl]-8,8-dimethyl-2-methoxybicyclo[3.3.1]non-2-en-9-one (**16**).* To a stirred solution of **14** (1.00 g, 2.29 mmol) in CH_2Cl_2 (11.4 mL) was added Crabtree's catalyst (9.2 mg, 11.5 μmol, 0.5 mol %) at room temperature under an atmosphere of Ar, and the reaction mixture was stirred under an atmosphere of H_2 at room temperature. After the reaction was completed, saturated aqueous NH_4Cl solution (30 mL) was added to the reaction mixture, and the aqueous layer was extracted with CH_2Cl_2 (50 mL × 2). The combined organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude ester **15** (ca. 1.03 g) was used for the next step without further purification.

To a stirred solution of crude **15** (ca. 1.03 g) in CH_2Cl_2 (11.7 mL) was added a solution of DIBAL-H in toluene (7.40 mL, 1.01 M, 7.47 mmol, 3.3 equiv) at −78 °C. After the reaction was completed, saturated aqueous Rochelle salt (50 mL) was added to the reaction mixture, and the resultant mixture was stirred for 1 h. Then the mixture was filtered through a plug of Celite, and the aqueous layer was extracted with EtOAc (100 mL × 3). The combined organic layer was washed with brine (200 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude diol **15a** (ca. 997.5 mg) was used for the next step without further purification.

To a stirred solution of **15a** (ca. 997.5 mg) in CH_2Cl_2 (24.2 mL) were added Et_3N (1.01 mL, 7.25 mmol, 3.2 equiv), DMAP (29.5 mg, 0.242 mmol, 0.11 equiv), and Ac_2O (0.25 mL, 2.66 mmol, 1.2 equiv) successively at room temperature. After the reaction was completed, saturated aqueous $NaHCO_3$ solution (20 mL) was added to the reaction mixture, and the aqueous layer was extracted with Et_2O (40 mL × 3). The combined organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude acetate **15b** (ca. 1.08 g) was used for the next step without further purification.

To a stirred solution of **15b** (ca. 1.08 g) in CH_2Cl_2 (23.8 mL) were added Dess−Martin periodinane (3.04 g, 7.13 mmol, 3.1 equiv) and $NaHCO_3$ (2.00 g, 27.8 mmol, 12 equiv) at room temperature. After the reaction was completed, Et_2O (50 mL) and a mixture of saturated aqueous $NaHCO_3$ solution (60 mL) and saturated aqueous $Na_2S_2O_3$ solution (60 mL) were added to the reaction mixture. The aqueous layer was extracted with Et_2O (50 mL × 2). The combined organic layer was washed with brine (20 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford **16** (832 mg, 80% (4 steps)) as a white powder: R_f = 0.25 (hexane/ethyl acetate=10/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.03−4.95 (1H, m), 4.22 (1H, d, J = 8.0 Hz), 4.18 (1H, dd, J = 11.0, 4.0 Hz), 4.00 (1H, d, J = 8.0 Hz), 3.74 (1H, dd, J = 11.0, 8.5 Hz), 3.50 (3H, s), 2.67−2.53 (2H, m), 2.43−2.33 (1H, m), 2.24 (1H, dd, J = 15.5, 4.5 Hz), 2.04 (3H, s), 1.93 (1H, ddd, J = 13.5, 4.5, 2.0 Hz), 1.79−1.68 (1H, m), 1.08 (3H, s), 1.06−1.00 (21H, m), 0.68 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.5 (Cq), 171.1 (Cq), 153.1 (Cq), 97.4 (CH), 65.8 (CH_2), 62.9 (Cq), 58.0 (CH_2), 54.3 (CH_3), 44.2 (CH), 43.7 (Cq), 40.6 (CH), 36.8 (CH_2), 29.9 (CH_2), 24.3 (CH_3), 21.0 (CH_3), 17.9 (CH_3), 17.8 (CH_3), 12.1 (CH); IR (neat) ν_{max} 2942, 2864, 1743, 1726, 1663, 1464, 1365, 1236, 1211, 1102, 1033 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{25}H_{44}NaO_5Si$ 475.2856, found 475.2838; mp 93−94 °C.

(1R,5R*,7S*)-7-Acetoxymethyl-1-[(triisopropylsilyloxy)methyl]-8,8-dimethyl-2-methoxybicyclo[3.3.1]non-2-ene-4,9-dione (**17**).* To a stirred solution **16** (17.3 mg, 0.0382 mmol) in CH_2Cl_2 (0.55 mL) was added $Pd(OH)_2/C$ (2.0 mg, 3.77 μmol, 0.099 equiv), Cs_2CO_3 (62.2 mg, 0.191 mmol, 5.0 equiv), and TBHP in decane (34.8 μL, 0.191 mmol, 5.0 equiv) successively at room temperature. After the reaction was completed, the reaction mixture was filtered through a plug of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 3/2) to afford **17** (12.4 mg, 70%) as a white powder: R_f = 0.45 (hexane/ethyl acetate = 1/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (1H, s, H-3), 4.35 (1H, d, J = 8.5 Hz), 4.16 (1H, dd, J = 11.0, 3.5 Hz), 4.05 (1H, d, J = 8.5 Hz), 3.77 (3H, s), 3.71 (1H, dd, J = 11.0, 9.0 Hz), 3.25 (1H, dd, J = 5.0, 2.5 Hz), 2.21 (1H, ddd, J = 13.5, 5.0, 2.5 Hz), 2.13−2.03 (1H, m), 1.98 (3H, s), 1.76 (1H, dt, J = 13.5, 5.0 Hz), 1.09 (3H, s), 1.07−0.92 (21H, m), 0.74 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.4 (Cq), 194.5 (Cq), 176.9 (Cq), 170.8 (Cq), 108.0 (CH), 65.5 (Cq), 64.4 (CH_2), 60.5 (CH), 57.5 (CH_2), 56.4 (CH_3), 42.8 (Cq), 40.2 (CH), 32.5 (CH_2), 24.3 (CH_3), 20.8 (CH_3), 17.8 (CH_3), 17.1 (CH_3), 11.9 (CH); IR (neat) ν_{max} 2942, 2865, 1737, 1658, 1592, 1463, 1379, 1367, 1343, 1237, 1218, 1202, 1108 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{25}H_{42}NaO_6Si$ 489.2648, found 489.2637; mp 130−131 °C.

(1R,5R*,7S*)-7-Allyl-1-[(triisopropylsilyloxy)methyl]-8,8-dimethyl-2-methoxybicyclo[3.3.1]non-2-ene-4,9-dione (**20**).* To a solution of

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17 (514.6 mg, 1.10 mmol) in MeOH (22.0 mL) was added K_2CO_3 (304.6 mg, 2.20 mmol, 2.0 equiv) at room temperature. After the reaction was completed, the reaction mixture was concentrated under reduced pressure. The residue was diluted with Et_2O (30 mL) and H_2O (30 mL). The aqueous layer was extracted with Et_2O (50 mL × 2). The combined organic layer was washed with brine (100 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude alcohol **17a** (ca. 535.1 mg) was used for the next step without further purification.

To a stirred solution of **17a** (ca. 535.1 mg) in CH_2Cl_2 (11 mL) was added 2,6−lutidine (0.38 mL, 3.30 mmol, 3.0 equiv) and Tf_2O (0.28 mL, 1.65 mmol, 1.5 equiv) successively at −78 °C. After the reaction was completed, saturated aqueous $NaHCO_3$ solution (60 mL) was added to the reaction mixture. The aqueous layer was extracted with Et_2O (50 mL × 2). The combined organic layer was washed with saturated aqueous $CuSO_4$ solution (100 mL), brine (20 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude triflate **18** (ca. 645.0 mg) was unstable. Therefore, it was used for the next step without further purification.

To a solution of **18** (ca. 645.0 mg) in THF (4.4 mL) was added $(vinyl)_2Cu(CN)Li_2$ (7.92 mL, 0.25M, 1.98 mmol, 2.0 equiv)[20] at −40 °C. After the reaction was completed, 30% aqueous NH_4OH solution (30 mL) was added to the reaction mixture. The aqueous layer was extracted with Et_2O (30 mL × 3). The combined organic layer was washed with brine (80 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford **20** (408.2 mg, 88% (three steps)) as a white powder: R_f = 0.25 (hexane/ethyl acetate = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87, 5.65−5.51 (1H, m), 4.97 (1H, s), 4.95 (1H, d, J = 4.5 Hz), 4.37 (1H, d, J = 8.5 Hz), 4.07 (1H, d, J = 8.5 Hz), 3.77 (3H, s), 3.22 (1H, brs), 2.28−2.22 (2H, m), 1.83−1.67 (1H, m), 1.65−1.51 (2H, m), 1.07−0.95 (21H, m), 1.04 (3H, s), 0.71 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.2 (Cq), 195.0 (Cq), 177.2 (Cq), 136.5 (CH), 116.8 (CH_2), 107.8 (CH), 65.8 (Cq), 61.1 (CH), 57.9 (CH_2), 56.3 (CH_3), 43.6 (Cq), 40.4 (CH), 34.1 (CH_2), 33.9 (CH_2), 24.2 (CH_3), 17.8 (CH_3), 16.4 (CH_3), 11.9 (CH); IR (neat) ν_{max} 2942, 2864, 1736, 1657, 1592, 1463, 1341, 1249, 1213, 1198, 1131, 1101 cm^{-1}; HRMS (FAB-DFMS) $[M + H]^+$ calcd for $C_{25}H_{43}O_4Si$ 435.2931, found 435.2910; mp 136−137 °C.

(1R,5R*,7S*)-5,7-Diallyl-1-[(triisopropylsilyloxy)methyl]-8,8-dimethyl-2-methoxybicyclo[3.3.1]non-2-ene-4,9-dione* ***(21)***. To a stirred solution of **20** (17 mg, 0.0391 mmol) in THF (1 mL) was added LTMP (0.78 mL, 0.5 M, 0.391 mmol, 10 equiv) at −78 °C, and stirring was continued for 1 h at the same temperature. Then, to the reaction mixture were added HMPA (0.25 mL) and allyl bromide (0.05 mL, 0.587 mmol, 15 equiv). After the reaction was completed, saturated aqueous NH_4Cl solution (10 mL) was added to the reaction mixture and the aqueous layer was extracted with Et_2O (10 mL × 3). The combined organic layer was washed with brine (20 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 5/1) to afford **21** (17.9 mg, 96%) as a white powder: R_f = 0.25 (hexane/ethyl acetate = 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (1H, s), 5.77−5.65 (1H, m), 5.64−5.53 (1H, m), 5.08−4.88 (4H, m), 4.43 (1H, d, J = 8.0 Hz), 4.10 (1H, d, J = 8.0 Hz), 3.77 (3H, s), 2.55 (1H, dd, J = 14.0, 7.0 Hz), 2.50 (1H, dd, J = 14.0, 7.0 Hz), 2.25−2.12 (1H, m), 1.95 (1H, dd, J = 13.0, 4.0 Hz), 1.82−1.70 (1H, m), 1.65−1.51 (1H, m), 1.25 (1H, t, J = 13.0 Hz), 1.09−0.97 (24H, m), 0.69 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.1 (Cq), 196.3 (Cq), 175.9 (Cq), 136.6 (CH), 134.1 (CH), 117.6 (CH_2), 116.8 (CH_2), 108.1 (CH), 65.8 (Cq), 63.2 (Cq), 58.3 (CH_2), 56.1 (CH_3), 43.6 (Cq), 41.8 (CH_2), 40.9 (CH), 34.9 (CH_2), 33.9 (CH_2), 24.3 (CH_3), 17.89 (CH_3), 17.88 (CH_3), 16.3 (CH_3), 12.0 (CH); IR (neat) ν_{max} 2941, 2865, 1731, 1655, 1600, 1463, 1376, 1342, 1240, 1214, 1105 cm^{-1}; HRMS (FAB-DFMS) $[M + H]^+$ calcd for $C_{28}H_{47}O_4Si$ 475.3244, found 475.3225; mp 58−59 °C.

(1R,5R*,7S*)-3,5,7-Triallyl-1-[(triisopropylsilyloxy)methyl]-8,8-dimethyl-2-methoxybicyclo[3.3.1]non-2-ene-4,9-dione* ***(22)***. To a stirred solution of **21** (24.9 mg, 0.0525 mmol) in THF (2 mL) was added LTMP (0.53 mL, 0.5 M, 0.263 mmol, 5.0 equiv) at −78 °C, and stirring was continued for 30 min at the same temperature. Then to the reaction mixture was added (2-Th)Cu(CN)Li[16] (2.9 mL, 0.1 M, 0.289 mmol, 5.5 equiv), and after the resulting mixture was stirred for 30 min at the same temperature, allyl bromide (22.8 μL, 0.263 mmol, 5.0 equiv) was added to the reaction mixture. After the reaction was completed, 30% aqueous NH_4OH solution (10 mL) was added to the reaction mixture, and the aqueous layer was extracted with Et_2O (10 mL × 3). The combined organic layer was washed with brine (20 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford **22** (26.6 mg, 99%) as a white powder: R_f = 0.20 (hexane/ethyl acetate = 15/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.97−5.82 (1H, m), 5.72−5.61 (1H, m), 5.61−5.50 (1H, m), 5.08−4.85 (6H, m), 4.43 (1H, d, J = 8.5 Hz), 4.10 (1H, d, J = 8.5 Hz), 4.02 (3H, s), 3.34 (1H, ddt, J = 16.0, 5.5, 2.0 Hz), 3.27 (1H, ddt, J = 16.0, 5.5, 2.0 Hz), 2.54 (1H, dd, J = 14.0, 7.0 Hz), 2.49 (1H, dd, J = 14.0, 7.0 Hz), 2.22−2.12 (1H, m), 1.93 (1H, dd, J = 13.0, 4.5 Hz), 1.75−1.63 (1H, m), 1.60−1.50 (1H, m), 1.24 (1H, t, J = 12.5 Hz), 1.17−0.98 (24H, m), 0.67 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.6 (Cq), 197.0 (Cq), 174.1 (Cq), 136.7 (CH), 136.2 (CH), 134.1 (CH), 124.7 (Cq), 117.6 (CH_2), 116.6 (CH_2), 115.3 (CH_2), 67.5 (Cq), 63.1 (Cq), 62.6 (CH_3), 59.4 (CH_2), 44.2 (Cq), 42.5 (CH_2), 40.6 (CH), 35.3 (CH_2), 33.8 (CH_2), 28.5 (CH_2), 24.4 (CH_3), 18.1 (CH_3), 18.0 (CH_3), 16.3 (CH_3), 12.3 (CH); IR (neat) ν_{max} 2944, 2867, 1731, 1655, 1640, 1601, 1464, 1376, 1239, 1100 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{31}H_{50}NaO_4Si$ 537.3376, found 537.3351.

(1R,5R*,7S*)-3,5,7-Triallyl-1-[(triisopropylsilyloxy)methyl]-8,8-dimethyl-2-methoxybicyclo[3.3.1]non-2-ene-4,9-dione* ***(22)*** *(One-Pot Procedure).* To a stirred solution of **21** (21.8 mg, 0.0502 mmol) in THF (1.5 mL) was added LTMP (0.50 mL, 0.5 M in THF, 0.25 mmol, 5.0 equiv) at −78 °C, and stirring was continued at the same temperature for 2 h. Then, to the reaction mixture were added HMPA (0.19 mL) and allyl bromide (21.7 μL, 0.251 mmol, 5.0 equiv). After 30 min, to the reaction mixture was added LTMP (0.50 mL, 0.5 M in THF, 0.25 mmol, 5.0 equiv) at −78 °C, and stirring was continued at the same temperature for 1 h. Then, to the reaction mixture was added (2-Th)Cu(CN)Li (2.5 mL, 0.1 M, 0.25 mmol, 5.0 equiv) at the same temperature, and after 30 min, allyl bromide (21.7 μL, 0.251 mmol, 5.0 equiv) was added. After the reaction was completed, 30% aqueous NH_4OH solution (10 mL) was added to the reaction mixture, and the aqueous layer was extracted with Et_2O (10 mL × 3). The combined organic layer was washed with brine (20 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford **22** (13.0 mg, 50%) as a white powder.

(1S,5R*,7S*)-3,5,7-Triallyl-1-benzoyl-8,8-dimethyl-2-methoxybicyclo[3.3.1]non-2-ene-4,9-dione* ***(23)***. To a stirred solution of **22** (50.8 mg, 0.0987 mmol) in THF (3 mL) was added TBAF (0.49 mL, 1.0 M in THF, 0.49 mmol, 5.0 equiv) at room temperature. After the reaction was completed, saturated aqueous NH_4Cl (3 mL) was added to the reaction mixture, and the aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layer was washed with brine (10 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude **22a** (ca. 55.9 mg) was used for the next step without further purification.

To a stirred solution of crude **22a** (ca. 55.9 mg) in CH_2Cl_2 (3.0 mL) were added Dess−Martin periodinane (62.4 mg, 0.148 mmol, 1.5 equiv) and $NaHCO_3$ (41.5 mg, 0.494 mmol, 5.0 equiv) at room temperature. After the reaction was completed, Et_2O (15 mL) and a mixture of saturated aqueous $NaHCO_3$ solution (10 mL) and saturated aqueous $Na_2S_2O_3$ solution (10 mL) were added to the reaction mixture. The aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layer was washed with brine (20 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude **22b** (ca. 53.5 mg) was used for the next step without further purification.

To a stirred solution of **22b** (ca. 53.5 mg) in THF (3 mL) was added a solution of PhMgBr in THF (0.22 mL, 0.50 M, 0.109 mmol, 1.1 equiv) at −78 °C. Stirring was continued at −78 °C for 30 min. After the reaction was completed, saturated aqueous NH_4Cl (10 mL)

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was added to the reaction mixture, and the aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layer was washed with brine (10 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude **22c** (ca. 63.5 mg) was used for the next step without further purification.

To a stirred solution of **22c** (ca. 63.5 mg) in CH_2Cl_2 (3.0 mL) were added Dess−Martin periodinane (103.9 mg, 0.247 mmol, 2.5 equiv) and $NaHCO_3$ (62.2 mg, 0.720 mmol, 7.5 equiv) at room temperature. After the reaction was completed, Et_2O (10 mL) and a mixture of saturated aqueous $NaHCO_3$ solution (10 mL) and saturated aqueous $Na_2S_2O_3$ solution (10 mL) were added to the reaction mixture. The aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layer was washed with brine (20 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 15/1) to afford **23** (34.1 mg, 80% (four steps)) as an oil: R_f = 0.40 (hexane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (2H, d, J = 7.5 Hz,), 7.44 (1H, d, J = 7.5 Hz), 7.31 (2H, d, J = 7.5 Hz), 5.92−5.81 (1H, m), 5.81−5.70 (1H, m), 5.65−5.51 (1H, m), 5.18−5.10 (1H, m), 5.09−5.03 (2H, m), 5.03−4.93 (3H, m), 3.45 (3H, s), 3.30 (2H d, J = 6.0, 1.8 Hz), 2.64 (1H, dd, J = 14.0, 7.5 Hz), 2.57 (1H, dd, J = 14.0, 7.5 Hz), 2.35−2.26 (1H, m), 1.98 (1H, dd, J = 13.0, 4.5 Hz), 1.84−1.72 (1H, m), 1.71−1.61 (1H, m), 1.47 (1H, t, J = 13.0 Hz), 1.34 (3H, s), 1.19 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.3 (Cq), 196.3 (Cq), 193.0 (Cq), 170.9 (Cq), 137.0 (Cq), 136.6 (CH), 135.7 (CH), 133.8 (CH), 132.2 (CH), 128.2 (CH), 128.1 (CH), 121.2 (Cq), 119.0 (CH_2), 116.8 (CH_2), 115.9 (CH_2), 74.2 (Cq), 64.8 (Cq), 61.8 (CH_3), 47.7 (Cq), 42.9 (CH_2), 41.4 (CH), 34.4 (CH_2), 33.6 (CH_2), 28.2 (CH_2), 24.4 (CH_3), 16.2 (CH_3); IR (neat) ν_{max} 3078, 2922, 2851, 1721, 1702, 1656, 1600, 1445, 1393, 1242, 1217 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{28}H_{32}NaO_4$ 455.2198, found 455.2180.

(1R,5R*,7S*)-1-Benzoyl-4-hydroxy-8,8-dimethyl-3,5,7-tris(3-methylbut-2-enyl)bicyclo[3.3.1]non-3-ene-2,9-dione (Nemorosone).* Compound **23** (19.4 mg, 0.0448 mmol) and Grubbs II catalyst (0.38 mg, 4.48 μmol, 1 mol %) were added to a sealed tube. Liquid isobutene (5 mL) was added via a dry ice condenser to the sealed tube cooled at −78 °C. The closed sealed tube was slowly warmed to 60 °C. After being stirred for 4 h, the sealed tube was cooled to −78 °C, opened, and warmed to room temperature to vent off the excess isobutene. The residue was purified by flash chromatography (hexane/ethyl acetate = 15/1) to afford **23a** (21.1 mg, 91%) as an oil: R_f = 0.40 (hexane/ethyl acetate = 10/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (2H, d, J = 7.5 Hz), 7.43 (1H, t, J = 7.5 Hz), 7.29 (2H, d, J = 7.5 Hz), 5.01 (2H, brs), 4.91 (1H, brs), 3.45 (3H, s), 3.34 (1H, dd, J = 16.0, 6.0 Hz), 3.22 (1H, dd, J = 16.0, 6.0 Hz), 2.56 (1H, dd, J = 14.5, 7.0 Hz), 2.47 (1H, dd, J = 14.5, 7.5 Hz), 2.09 (1H, brs), 1.94 (1H, dd, J = 13.5, 4.0 Hz), 1.66 (17H, brs), 1.55 (3H, s), 1.44 (1H, t, J = 13.5 Hz), 1.34 (3H, s), 1.18 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.9 (Cq), 197.1 (Cq), 193.1 (Cq), 169.9 (Cq), 137.0 (Cq), 134.4 (Cq), 133.2 (Cq), 133.0 (Cq), 132.1 (CH), 128.4 (CH), 127.9 (CH), 123.2 (Cq), 122.5 (CH), 121.5 (CH), 119.7 (CH), 73.9 (Cq), 65.1 (Cq), 61.5 (CH_3), 47.8 (Cq), 43.1 (CH_2), 42.5 (CH), 29.5 (CH_2), 27.7 (CH_2), 26.0 (CH_3), 25.8 (CH_3), 25.6 (CH_3), 24.4 (CH_3), 23.2 (CH_2), 18.1 (CH_3), 18.0 (CH_3), 17.8 (CH_3), 16.2 (CH_3); IR (neat) ν_{max} 2966, 2915, 2360, 2341, 1721, 1703, 1665, 1604, 1446, 1391, 1337, 1241, 1217 cm^{-1}; HRMS (FAB-DFMS) $[M]^+$ calcd for $C_{34}H_{44}O_4$ 516.3240, found 516.3254.

To a stirred solution of **23a** (25.8 mg, 0.0499 mmol) in DMSO (1 mL) was added LiCl (21.2 mg, 0.499 mmol, 10 equiv), and the mixture was heated at 120 °C for 1 h. The reaction mixture was then cooled to room temperature, diluted with water (2 mL) and extracted with Et_2O (10 mL × 2). The combined organic layer was washed with brine (10 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford **nemorosone** (quant) as an oil: R_f = 0.40 (h exane/ethyl acetate = 4/1); ^{1}H NMR (500 MHz, CD_3OD) δ 7.56 (2H, d, J = 7.5 Hz), 7.43 (1H, t, J = 7.5 Hz), 7.26 (2H, t, J = 7.5 Hz), 5.09 (1H, t, J = 7.5 Hz), 5.01 (2H, brs), 3.13 (1H, dd, J = 15.0, 7.5 Hz), 3.08 (1H, dd, J = 15.0, 7.5 Hz), 2.53 (1H, dd, J = 14.5, 6.5 Hz), 2.48 (1H, dd, J = 14.5, 6.5 Hz), 2.19−2.10 (1H, m), 2.02 (1H, dd, J = 13.0, 3.5 Hz), 1.79−1.71 (2H, m), 1.69 (3H, s), 1.66 (3H, s), 1.65 (9H, s), 1.59 (3H, s), 1.43 (1H, t, J = 13.0 Hz), 1.34 (3H, s), 1.11 (3H, s); ^{13}C NMR (125 MHz, CD_3OD) δ 209.7 (Cq), 195.2 (Cq), 138.4 (Cq), 135.2 (Cq), 134.3 (Cq), 133.5 (Cq), 133.2 (CH), 129.7 (CH), 128.9 (CH), 124.2 (CH), 122.5 (CH), 121.10 (Cq), 121.07 (CH), 78.3 (Cq), 62.1 (Cq), 49.1 (Cq), 44.7 (CH_2), 42.4 (CH), 30.6 (CH_2), 28.3 (CH_2), 26.4 (CH_3), 26.17 (CH_3), 26.15 (CH_3), 24.5 (CH_3), 23.9 (CH_2), 18.4 (CH_3), 18.3 (CH_3), 18.1 (CH_3), 16.4 (CH_3). Because of tautomerism C-2 and C-4 carbons could not be identified in the ^{13}C NMR spectrum.; IR (neat) ν_{max} 3297, 2964, 2923, 2855, 2359, 2342, 1723, 1699, 1581, 1446, 1372, 1220, 1186 cm^{-1}; HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{33}H_{42}NaO_4$ 525.2981, found 525.2991.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR assignments and spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Phone and Fax: +813-5286-3240. E-mail: mnakada@waseda.jp.

Notes

The authors declare no competing financial interest.

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