Synthetic studies on clerodane diterpenoids. The total synthesis of (±)-2-oxo-5α,8α-13,14,15,16-tetranorclerod-3-en-12-oic acid

Hsing-Jang Liu, Kak-Shan Shia, Yongxin Han, Daqing Sun, and Yu Wang

Abstract: A general synthetic approach to diterpenoids of the *cis*-clerodane family has been developed, leading to the first total synthesis, in racemic form, of 2-oxo-5α,8α-13,14,15,16-tetranorclerod-3-en-12-oic acid (**2**). The key operation involved is the face-selective Diels–Alder reaction of dienone ester **10** with *trans*-piperylene, giving rise to adduct **11** containing the decalin nucleus and correct stereogenic centers common to many *cis*-clerodane diterpenoids.

Key words: *cis*-clerodanes, general synthetic approach, total synthesis, face-selective Diels–Alder reaction.

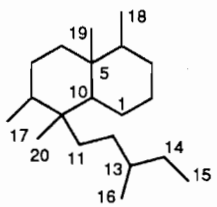
Résumé : On a développé une méthode générale de synthèse des diterpénoïdes de la famille du *cis*-clérodane qui a conduit à la première synthèse totale de l'acide 2-oxo-5α,8α-13,14,15,16-tétranorclérod-3-én-12-oïque (**2**) sous forme racémique. L'opération clé implique une réaction de Diels–Alder face spécifique de la diénone-ester **10** avec le *trans*-pipérylène qui conduit à l'adduit **11** contenant le noyau décaline et les centres stéréogéniques corrects pour plusieurs diterpénoïdes du *cis*-clérodane.

Mots clés : *cis*-clérodanes, méthode générale de synthèse totale, réaction de Diels–Alder face sélective.

[Traduit par la rédaction]

Introduction

Diterpenoids possessing the clerodane (**1**) carbon skeleton are widely distributed in nature and constitute one of the largest and, yet, still rapidly growing family of secondary metabolites. To date, more than 800 compounds have been isolated and structurally characterized from various natural sources, about one quarter in the last four years (1). Clerodanes are best



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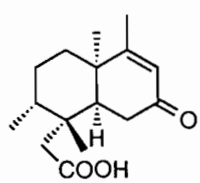
known for their antifeedant properties. Of the relatively few tested for biological activity, many were also found to possess interesting medicinal properties and are potentially useful as antiviral, antitumor, antifungal, antibiotic, anti-peptic ulcer, and psychotropic agents (1, 2). The structural complexity and biological activity associated with this class of natural products have attracted extensive effort towards their total syntheses. More than 15 successful syntheses have been reported for the sub-series of *trans*-clerodanes (Fig. 1) (3). Relatively few syntheses, however, are known for the *cis* sub-series of compounds (Fig. 1) (4). In virtually all of the reported syntheses, a linear approach to the specific target molecule is involved. Since naturally occurring clerodanes are vast in number and their structural differences are mainly due to stereochemistry, oxidation level, and oxygen contents of various centers, it is highly desirable to develop a general nonlinear synthetic approach, whereby a large number of target molecules can be synthesized by a common strategy with minor adjustments. We wish to demonstrate herein such an approach highlighted by the first total synthesis, in racemic form, of the title carboxylic acid **2**, which was recently isolated from *vellozia bicolor* L.B. Smith by Garcez and co-workers (5).



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Results and discussion

In recent years, an extensive study of the Diels–Alder chemistry of 4,4-dimethyl-2-cyclohexenones and several closely related cross-conjugated cyclic unsaturated β-dicarbonyl compounds has been carried out in our laboratories (6–12). On the basis of these studies, a general synthetic scheme

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This paper is dedicated to Professor William A. Ayer on the occasion of his 65th birthday.

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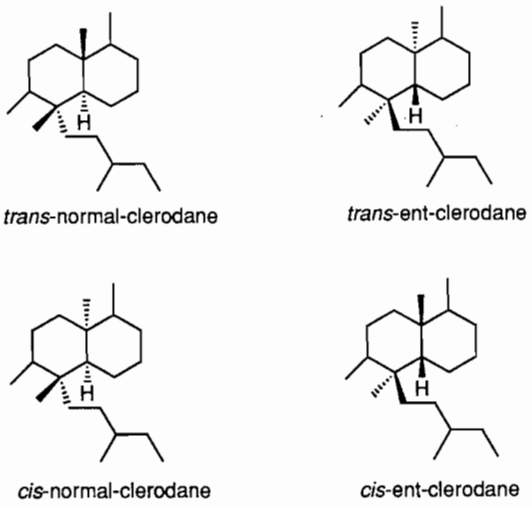
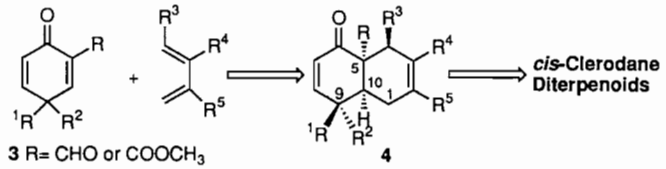
Fig. 1. Major structural types of clerodane diterpenoids.



Scheme 1.

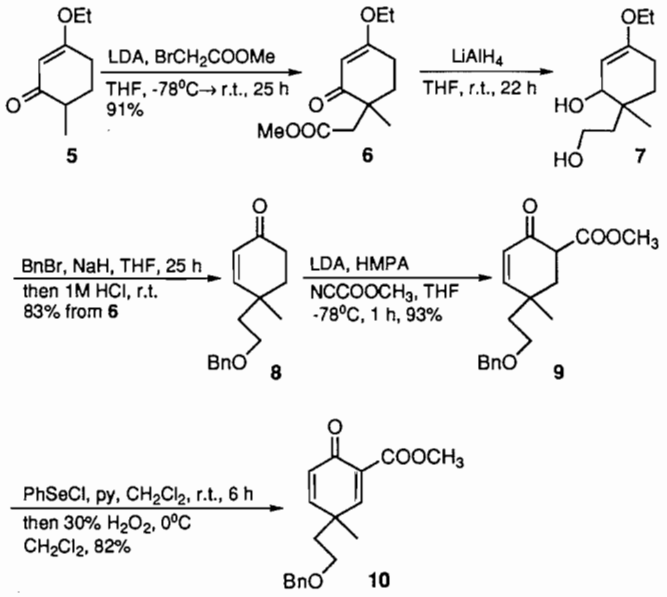


(Scheme 1) that would facilitate the rapid assembly of a variety of *cis*-clerodane diterpenes, especially the highly oxygenated ones, via a general intermediate **4** has been conceived. By this Diels–Alder approach, the relative stereochemistry of the three contiguous chiral centers C_5, C_9, and C_{10} (clerodane numbering) of **4** is expected to be arranged in the same manner as those of the natural *cis*-clerodanes based mainly on the following steric consideration. It is highly conceivable that, if R^2 is bulkier than R^1, addition of the diene to dienophile **3** will occur preferentially from the sterically less hindered R^1 face. This approach has now been experimentally realized, culminating in the total synthesis of 2-oxo-5α,8α-13,14,15,16-tetranorclerod-3-en-12-oic acid (**2**) in racemic form and the formation of several advanced intermediates potentially useful for the preparation of a variety of *cis*-clerodanes.

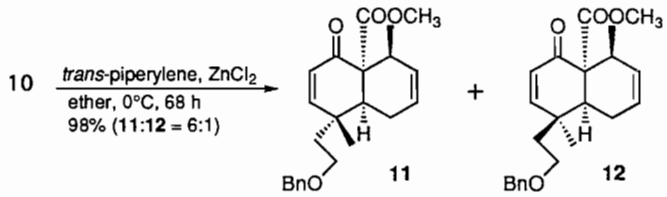
During the preliminary investigation, several dienophiles of formula **3** have been synthesized and explored. The outcome revealed that Diels–Alder adducts obtained with an angular aldehyde moiety α to the ketone carbonyl were not stable enough for further elaboration. A more practical dienophile **10**, a dienone with an α-ester group, was finally adopted.

Compound **10** was readily prepared from 3-ethoxy-6-methyl-2-cyclohexenone (**5**) (13) according to the synthetic sequence shown in Scheme 2. Stork–Danheiser alkylation (14) of **5** with methyl bromoacetate gave enone ester **6** in 91% yield. This compound was reduced with lithium aluminum hydride to give a mixture of two diastereomeric diols **7** in nearly equal amounts. Without further purification, the mixture of the unstable diols **7** was immediately subjected to selective benzylation with a slight excess of sodium hydride and benzyl bromide. Treatment of the crude product with dilute hydrochloric acid afforded enone **8** in 83% yield from **6**. Later,

Scheme 2.



Scheme 3.



it was found that, even if benzylation occurred at both hydroxyls when excess benzyl bromide and base were applied, the *bis*-benzylated product could also be easily converted into **8** under the same hydrolysis conditions. Enone **8** was subjected to carbomethoxylation using lithium diisopropylamide and methyl cyanoformate (15) to give keto ester **9** as a mixture of three isomers (a pair of epimers and an enol ester) in a ratio of 2:1.4:1 as indicated by the ^{1}H nmr spectrum. Keto ester **9** was then treated with phenylselenenyl chloride in the presence of pyridine (16). Oxidative elimination of the resulting selenide with hydrogen peroxide gave the required dienone ester **10** in 82% yield.

Dienone ester **10** proved to be an excellent dienophile. Under zinc chloride catalysis, it underwent cycloaddition with *trans*-piperylene to furnish adducts **11** (from the sterically less hindered methyl face) and **12** in 84% and 14% yield, respectively (Scheme 3). Slightly inferior results (95% yield; **11**:**12** = 5.3:1) were obtained when ferric chloride was used as a catalyst (CH_2Cl_2, −55°C, 21 h). The Diels–Alder adducts were readily separated by flash chromatography, and their regiochemistries were deduced by the following evidences. For the less polar major isomer **11**, the splitting pattern (ddd, J = 10, 7, 2 Hz) of the ring junction C_6 proton at δ 2.75 in the ^{1}H nmr spectrum clearly demonstrated that it was an *ortho* adduct. In a similar fashion, the minor isomer **12** showed a doublet of doublet of doublets (J = 10, 7, 2 Hz) for the C_6 proton at δ 2.68 suggesting that it was also an *ortho*-addition product. To determine the relative stereochemistry of each, extensive NOE

Fig. 2. NOE effects for **11**.

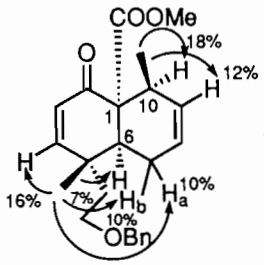
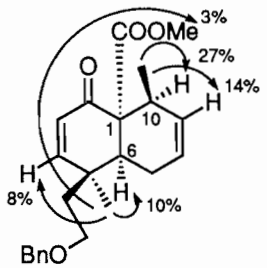


Fig. 3. NOE effects for **12**.

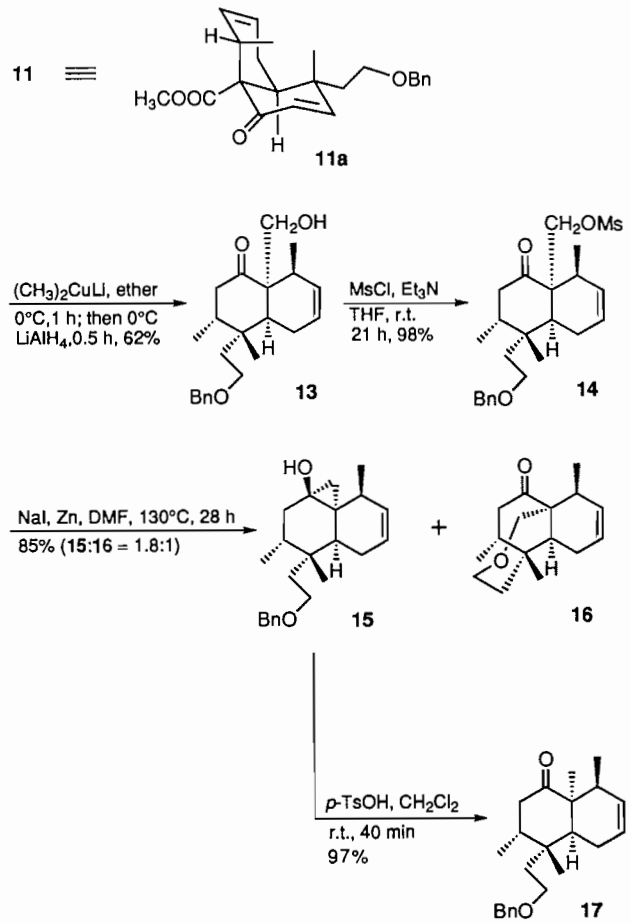


experiments were carried out for both compounds. For the major isomer, irradiation of the C_5 methyl at δ 1.10 resulted in enhancements for H_4 (16%), H_6 (6.9%), H_{7a} (10.2%), and H_{7b} (10.2%) (Fig. 2). On the other hand, irradiation of the C_5 methyl (δ 1.15) of the minor isomer gave enhancements for the methoxy methyl (2.8%), the C_4 vinylic proton (8.4%), and the C_6 proton (10%) (Fig. 3). No enhancements were observed for H_{7a} and H_{7b}. Therefore, structures **11** and **12** were assigned to the major and minor products, respectively.

Although, at this stage, the relative stereochemistry at each C_{10} position of **11** and **12** could not be confirmed based on the NOE studies, the configuration of this center in each case was tentatively assigned based on the previously observed preferential *endo*-to-ketone addition of *trans*-piperylene to several dienophiles resembling compound **10** (6). These structural assignments were later substantiated by the X-ray crystallographic analysis of a more advanced intermediate **16** (*vide* infra).

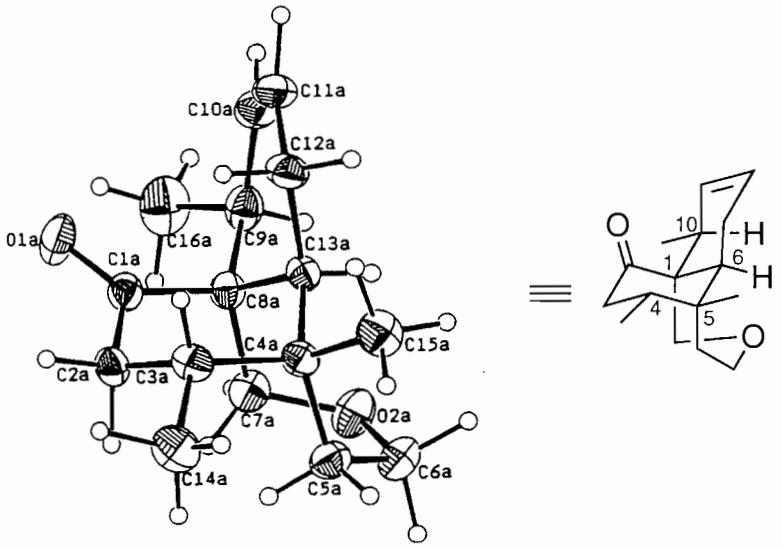
Adduct **11** possesses four contiguous stereogenic centers incorporated simultaneously in a correct sense for many naturally occurring *cis*-clerodanes. The remaining crucial stereogenic center was introduced via a conjugate addition process (Scheme 4). Treatment of adduct **11** with lithium dimethylcuprate followed by reduction of the resulting enolate with lithium aluminum hydride afforded keto alcohol **13** in 62% yield by a single operation. In this transformation, the enolate resulting from the conjugate addition served as an effective protecting group for the more reactive ketone carbonyl; thereby the desired reduction of the less reactive ester carbonyl could be achieved without further elaboration. Compound **13** was formed as the only stereoisomer, presumably via preferential axial addition of the cuprate to the sterically less hindered side of the conformer **11a**. To remove its hydroxy group, keto alcohol **13** was converted to the corresponding mesylate in quantitative yield using methanesulfonyl chloride and triethylamine. Reduction of mesylate **14** with sodium iodide and zinc dust (17) in DMF at 130°C gave rise to a 55% yield of cyclopropanol **15** and a 30% yield of the crystalline tricyclic ketone **16**, mp 74.5–76.0°C. The former product was likely formed via the addition of the intermediate carbanion resulting from the reductive removal of the methanesulfonyloxy group to the ketone carbonyl, and the latter via the displacement of the mesylate with the benzyl ether followed by debenzylation. Ketone **16** was subjected to X-ray crystallographic analysis. The crystal structure of **16** as shown in Fig. 4 made unambiguous the assignment of the five contiguous stereogenic centers along C_1, C_4, C_5, C_6, and C_{10} present in **16** and its precursors. Cyclopropanol **15** was found to be a suitable intermediate for the formation of the desired ketone **17** (Scheme 4). Upon exposure to a catalytic amount of *p*-toluenesulfonic acid in methylene chloride, it underwent rapid ring cleavage to give ketone **17** in 97% yield.

Scheme 4.

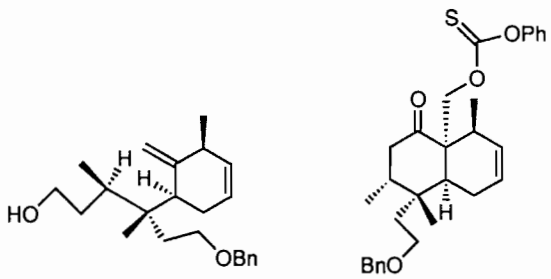


Several other methods were explored in attempts to produce the desired ketone **17** more efficiently. These efforts, however, were not fruitful. Reduction of mesylate **14** with an excess of lithium triethylborohydride in tetrahydrofuran gave rise to alcohol **18** as a result of the reduction of the ketone carbonyl followed by a Grob fragmentation and further reduction of the ensuing aldehyde. In another approach, keto alcohol **13** was transformed to thiocarbonate **19** in 72% yield by treatment with phenyl chlorothionoformate and pyridine in dichloromethane at room temperature. Unfortunately, other functionalities present in **19** were shown to be incompatible with

Fig. 4. The three-dimensional X-ray crystallographical strucutre of **16**.

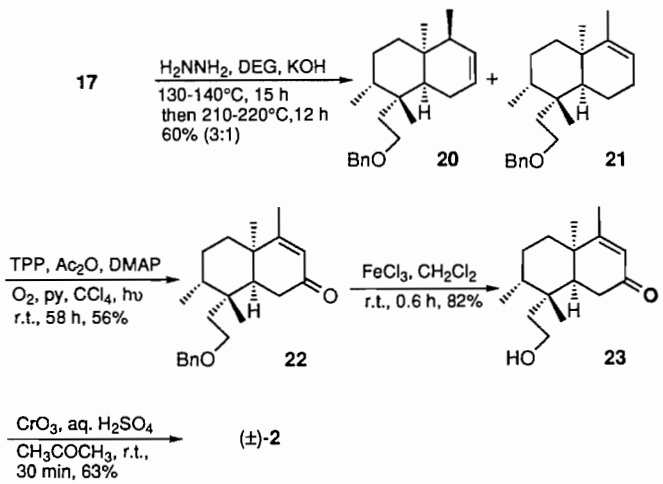


the reaction conditions required to remove the thiocarbonate moiety using tri-*n*-butyltin hydride.



Ketone **17** can, in principle, serve as a key intermediate for two groups of *cis*-clerodane diterpenes, one with an oxygen atom at C_6 (clerodane numbering), such as solidagolactones II–VIII (18–21), 6β-acetoxy-2-oxokolavenool (22), etc., and the other without an oxygen atom at C_6, such as solidagoic acid A (23, 24), tinotufolin B (25), 2-oxo-5α,8α-13,14,15,16-tetranorclerod-3-en-12-oic acid (**2**), etc. The total synthesis of **2** has been accomplished as follows (Scheme 5). The ketone carbonyl of **17** was removed by a Wolff–Kishner reduction using hydrazine, and potassium hydroxide in diethylene glycol at ~210°C. Two isomeric products **20** and **21** were formed in 3:1 ratio (^{1}H nmr analysis) and in a total yield of 60%. Subsequent irradiation (tungsten lamps) of this inseparable mixture in carbon tetrachloride in the presence of oxygen, 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine, acetic anhydride, pyridine, and 4-dimethylaminopyridine (26) gave rise to enone **22** (56% yield based on **20**) along with an unidentified product. The regioselectivity observed for the photooxygenation reaction was somewhat unusual. Instead of forming an enone system with a less substituted double bond following the "normal" regiochemical course of photooxygenation, the double bond moved towards the carbon center possessing a greater number of substituents. The unusual regiochemistry in the present case was nevertheless quite predictable based on the studies on several structurally closely related compounds in this series (27–29). However, exactly what controls the regiochemistry is

Scheme 5.



not fully understood. Enone **22** was subjected to treatment with ferric chloride (30) to effect the removal of the benzyl protecting group. Finally, alcohol **23** thus obtained in 82% yield was oxidized using Jones reagent (31) to afford the target clerodenoic acid **2** (63% yield) in racemic form, m.p. 226–227°C (236°C for the optically active natural **2** (5)). The spectral data (^{1}H nmr, ^{13}C nmr, and mass) of the synthetic material are in good agreement with those reported for the natural product.

Conclusion

The foregoing describes a simple nonlinear, general synthetic approach to diterpenoids of the clerodane family. Several advanced synthetic molecules, e.g., **13**, **17**, and **23**, are potentially useful for the preparation of a variety of naturally occurring compounds. Furthermore, by careful selection of the starting diene involved in the early Diels–Alder cycloaddition, oxygen functionalities can, in principle, also be directly incorporated to C_1, C_2, C_3, and C_{18}. Thus, by a small adjustment, the

demonstrated scheme should also facilitate the synthesis of those clerodanes oxygenated at one or more of these positions. The validity of this synthetic approach is illustrated with the total synthesis of (±)-2-oxo-5α,8α-13,14,15,16-tetranorclerod-3-en-12-oic acid (**2**).

Experimental

General

Melting points were recorded on a Kofler hot stage apparatus and are not corrected. Combustion elemental analyses were performed by the microanalytical laboratory of this department. Fourier transform infrared spectra (ir) were recorded on a Nicolet 7199 or Nicolet MX-1 FTIR spectrophotometer. Proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on a Bruker WH-80, Bruker WH-200, Bruker WH-300, Bruker WH-400, or Bruker AM-400 spectrometer using deuteriochloroform ($CDCl_3$) as solvent unless otherwise stated. Tetramethylsilane (TMS) was used as an internal reference. Coupling constants are reported to ±0.5 Hz. Chemical shift measurements are reported in ppm downfield from TMS in delta (δ) units. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Carbon-13 nuclear magnetic resonance (^{13}C nmr) spectra were recorded on a Varian Unity-500 (125 MHz) spectrometer or a Bruker WH-300 (75 MHz) NMR spectrometer, and were obtained as solutions in deuteriochloroform as the internal standard setting the central peak at 77.00 ppm. Carbon-13 multiplicities were derived from Carr–Purcell–Meiboom–Gill spin echo *J*-modulated experiments (APT or Attached Proton Test) (32, 33). Methyl and methine groups are shown as signals possessing an antiphase (a) with respect to the deuteriochloroform signal, whereas methylene groups, quaternary carbons, and carbonyl groups appear in phase (p) with it. Nuclear Overhauser enhancement (nOe) experiments were determined in the difference mode in which a control (undecoupled) spectrum was computer subtracted from the irradiated spectrum after Fourier transformation. Positive enhancements are defined as signals possessing an antiphase with respect to the irradiated signal. Samples for nOe measurements were deoxygenated with argon for 10 min prior to use. High-resolution electron impact mass spectra (hrms) were recorded using an A.E.I. model MS-50 mass spectrometer. Chemical ionization mass spectra (cims) were recorded on an A.E.I. model MS-12 mass spectrometer, using ammonia as the reagent gas. Spectral data are reported as *m/z* values.

All reactions were carried out under slight positive pressure of argon. Bulb-to-bulb distillation was performed using a Kugelrohr distillation apparatus. Flash chromatography developed by Still et al. (34) was used routinely for purification and separation of product mixtures, using silica gel (Merck) of 230–400 mesh. All solvents for chromatography were distilled prior to use. Concentrations of solvent systems used in column chromatography are given by volume, e.g., 20% ethyl acetate in petroleum ether means 20 parts of ethyl acetate by volume to 80 parts of petroleum ether by volume. Analytical thin-layer chromatography (tlc) was carried out on aluminum sheets precoated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck, Darmstadt). Ultraviolet-active materials were detected by visualization under a uv lamp (254 or 350 nm). For tlc, the visualization of the chromatograms was completed by dipping in an ethanol solution of vanillin (5%, w/v) and sulfuric acid (5%, v/v), followed by careful charring on a hot plate. Alternatively, an aqueous solution of phosphomolybdic acid (3%, w/v) containing ceric sulfate (0.5%,w/v) and sulfuric acid (3%, v/v) was used as the dipping solution, followed by charring on a hot plate.

Materials

Unless otherwise stated, all materials used are commercially available. All compounds made are racemic. Solvents used were distilled under an argon atmosphere from appropriate drying agents. Tetrahydrofuran (THF), diethyl ether, toluene, and 1,2-dimethoxyethane (DME) were dried with sodium and benzophenone. Acetone was predried with potassium carbonate, and then distilled from potassium permanganate. Diisopropylamine was obtained by distillation from sodium hydroxide or potassium hydroxide. Pyridine, benzene, dichloromethane, carbon tetrachloride, and triethylamine (TEA) were distilled from calcium hydride. Reactions requiring anhydrous conditions were performed in oven- or flame-dried glassware that was assembled and allowed to cool while being purged with argon. Argon was passed through a column of 4 Å molecular sieves and self-indicating silica gel.

6-(Carbomethoxymethyl)-3-ethoxy-6-methyl-2-cyclohexenone (6)

To a solution of diisopropylamine (8.3 mL, 59 mmol) in THF (17 mL) at 0°C under an argon atmosphere, was added *n*-BuLi (34 mL, 1.6 M in hexane) slowly. The mixture was stirred at 0°C for 15 min and then cooled down to −78°C. A solution of 3-ethoxy-6-methyl-2-cyclohexenone (**5**) (7.65 g, 49 mmol) in THF (20 mL) was added dropwise over a period of 15 min. The resulting mixture was stirred at −78°C for 1 h, and methyl bromoacetate (9.6 mL, 98 mmol) was added in one portion. The mixture was allowed to warm up slowly to room temperature and stirred overnight. Saturated ammonium chloride was added and the mixture was extracted with ether (3 × 40 mL). The extracts were combined, washed with water, brine, and dried over magnesium sulfate. Filtration and concentration followed by bulb-to-bulb distillation at 128–130°C/0.7 Torr (1 Torr = 133.3 Pa) gave rise to the alkylation product **6** (10.2 g, 91% yield) as a light yellow oil: ir (CH_2Cl_2 cast): 1737 (C=O, ester) and 1654 (C=O, enone) cm^{-1}; ^{1}H nmr (200 MHz) δ: 5.29 (d, *J* = 1 Hz, 1 H, -C=C**H**-C=O), 3.91 (q, *J* = 7 Hz, 1 H, CH_3C**H**HO-), 3.90 (q, *J* = 7 Hz, 1 H, CH_3CH**H**O-), 3.62 (s, 3 H, -COOC**H**$_3$), 2.79 (d, *J* = 15.5 Hz, 1 H, -C**H**HCOOCH$_3$), 2.35 (d, *J* = 15.5 Hz, 1 H, -CH**H**COOCH$_3$), 2.60–2.19 (m, 3 H), 1.81–1.67 (m, 1 H), 1.35 (t, *J* = 7 Hz, 3 H, C**H**$_3$CH$_2$O-), and 1.16 (s, 3 H, -C**H**$_3$); ^{13}C nmr (75 MHz) δ: 200.18 (p), 174.54 (p), 171.64 (p), 101.31 (a), 63.87 (p), 50.84 (a), 42.33 (p), 41.76 (p), 31.56 (p), 26.08 (p), 22.33 (a), and 13.98 (a); hrms M$^+$: 226.1200 (calcd. for $C_{12}H_{18}O_4$: 226.1205). Anal. calcd. for $C_{12}H_{18}O_4$: C 63.70, H 8.02; found: C 63.70, H 8.39.

4-(2-Benzyloxyethyl)-4-methyl-2-cyclohexenone (8)

To a suspension of lithium aluminium hydride (0.81 g, 21.3 mmol) in THF (20 mL) at 0°C under an argon atmosphere, was added dropwise a solution of enone ester **6** (2.1 g, 9.3 mmol) in THF (20 mL). The resulting mixture was stirred at 0°C for 1 h and then at room temperature for 21 h. To the mixture cooled to 0°C and diluted with ether (30 mL), were added alternately

portions of water (0.12 mL) and 3 N NaOH (0.12 mL) over a period of 1 h. The resulting grey suspension was stirred for another hour and filtered. The residue was washed thoroughly with ether. The filtrate was concentrated to give the crude product (1.9 g), which, without purification, was dissolved in THF (18 mL) and added to a suspension of sodium hydride (0.48 g, 11.4 mmol) in THF (20 mL) at 0°C under argon. The mixture was stirred for 1 h (0°C→room temperature), and then benzyl bromide (3.25 g, 19 mmol) was introduced at 0°C. After stirring at room temperature for 25 h, the solution was acidified to pH = 1-1.5 with 1 N HCl, and the resulting solution stirred for 2 h. After the hydrolysis was complete, the mixture was extracted with ether (3 × 40 mL). The extracts were combined and washed with saturated sodium bicarbonate, water, and brine. After being dried over magnesium sulfate, the solution was filtered and concentrated to give the crude product. Flash chromatography using ethyl acetate and hexane (20:80) gave compound **8** (1.88 g, 83% yield from **6**) as a light yellow oil. Alternatively, it could be distilled at 175°C/1 torr to give the product as a colorless oil: ir ($CHCl_3$ cast): 1680 (C═O, enone), 738 and 698 (C-H bending, aromatic) cm^{-1}; ^1H nmr (300 MHz) δ: 7.32 (m, 5 H, aromatic **H**), 6.75 (d, J = 10 Hz, 1 H, -C**H**═CH-C═O), 5.86 (d, J = 10 Hz, 1 H, -CH═C**H**-C═O), 4.49 (s, 2 H, -OC**H**$_2$Ph), 3.51–3.64 (m, 2 H, -C**H**$_2$OBn), 2.47 (m, 2 H), 2.02 (ddd, J = 15, 7, 7 Hz , 1 H, -C**H**HC═O), 1.73–1.90 (complex, 3 H), and 1.18 (s, 3 H, -C**H**$_3$); ^{13}C nmr (75 MHz) δ: 199.27 (p), 158.75 (a), 138.11 (p), 128.31 (a, 2 × aromatic **C**), 127.54 (a), 127.49 (a, 2 × aromatic **C**), 127.12 (a), 73.04 (p), 66.59 (p), 40.20 (p), 34.92 (p), 34.05 (p, 2 × -**C**H$_2$-), and 25.19 (a); hrms M^+: 244.1459 (calcd. for $C_{16}H_{20}O_2$: 244.1463). Anal. calcd. for $C_{16}H_{20}O_2$: C 78.65, H 8.25; found: C 78.93, H 8.52.

4-(2-Benzyloxyethyl)-6-carbomethoxy-4-methyl-2-cyclohexenone (9)

To a suspension of sodium hydride (60% dispersion in mineral oil, 4.21 g, 105 mmol) in THF (20 mL) under an argon atmosphere, was added dimethyl carbonate (17 mL, 180 mmol). The mixture was brought to boiling, and then a solution of enone **8** (11.3 g, 46 mmol) in THF (20 mL) was added dropwise over a period of 30 min. The resulting mixture was heated under reflux for 24 h and then cooled to 0°C. Ice-cold 1 N HCl (35 mL) was added cautiously to the mixture, and the resulting solution extracted with ether (3 × 50 mL). The extracts were combined and washed with water and brine. After being dried over magnesium sulfate, the solution was filtered and concentrated to give the crude product. Flash chromatography using ethyl acetate and hexane (10:90) gave keto ester **9** (7.56 g, 54% yield) as a yellowish oil: ir ($CHCl_3$ cast): 1744 (C═O, ester), 1681 (C═O, enone), 1626 and 1592 (C═C, enol ester), 738 and 698 (C-H bending, aromatic) cm^{-1}; ^1H nmr (300 MHz), three isomers in a ratio of 2:1.4:1; isomer 1: δ: 7.32 (m, 5 H, aromatic **H**), 6.81 (dd, J = 10, 2 Hz, 1 H, -C**H**═CHCO), 5.90 (d, J = 10 Hz, 1 H, -CH═C**H**CO), 4.48 (s, 2 H, -OC**H**$_2$Ph), 3.78 (s, 3 H, -COOC**H**$_3$), 3.50–3.65 (m, 2 H, -C**H**$_2$OBn), 1.64–2.50 (m), and 1.21 (s, 3 H, -C**H**$_3$); isomer 2: δ: 6.72 (dd, J = 10, 1.5 Hz, 1 H, -C**H**═CHCO), 5.92 (d, J = 10 Hz, 1 H, -CH═C**H**CO), 4.49 (s, 2 H, -OC**H**$_2$Ph), 3.74 (s, 3 H, -COOC**H**$_3$), and 1.18 (s, 3 H, -C**H**$_3$); isomer 3: δ: 11.87 (s, 1 H, -C═C-O**H**), 6.11 (d, J = 10 Hz, 1 H, -C**H**═CHCO), 5.88 (d, J = 10 Hz, 1 H, -CH═C**H**CO), 4.47 (s, 2 H, -OC**H**$_2$Ph), 3.73 (s, 3 H, -COOC**H**$_3$), and 1.07 (s, 3 H, -C**H**$_3$); hrms M^+: 302.1515 (calcd. for $C_{18}H_{22}O_4$: 302.1518). Anal. calcd. for $C_{18}H_{22}O_4$: C 71.49, H 7.34; found: C 71.41, H 7.39.

Alternatively, the above carbomethoxylation could be achieved by the following method in higher yield. *n*-Butyllithium (6.06 mL, 2.5 M in hexane) was added to a stirred solution of anhydrous diisopropylamine (2.25 mL, 15.9 mmol) in THF (20 mL) at 0°C under an atmosphere of argon. After 30 min, the temperature was lowered to −78°C, a solution of enone **8** (1.85 g, 7.58 mmol) in THF (10 mL) was added dropwise to the mixture over a period of 15 min, and stirring continued at 0°C for 1 h. The temperature was lowered again to −78°C, and then HMPA (1.45 mL, 8.34 mmol) was added, followed by the addition of methyl cyanoformate (0.91 mL, 11.4 mmol) in one portion. After stirring for 1 h at −78°C, the mixture was warmed up to room temperature and quenched with cold water (10 mL). The product was extracted into ether (3 × 20 mL), dried ($MgSO_4$), filtered, concentrated, and chromatographed on silica gel (10% ethyl acetate in hexane) to afford compound **9** (2.1 g, 93% yield) as a yellowish oil.

4-(2-Benzyloxyethyl)-2-carbomethoxy-4-methyl-2,5-cyclohexadienone (10)

Pyridine (0.51 mL, 5.9 mmol) was added slowly to a solution of phenylselenenyl chloride (1.10 g, 5.7 mmol) in dichloromethane (25 mL) at 0°C. After 20 min, keto ester **9** (1.4 g, 4.6 mmol) in dichloromethane (10 mL) was added. The mixture was stirred at 0°C for 1 h and then at room temperature for 6 h. The organic layer was separated, washed with 10% HCl (2 × 10 mL), and cooled again to 0°C. A solution of 30% H_2O_2 was added successively (0.2 mL every 5 min) until the white precipitate was formed. After an additional 20 min, H_2O (5 mL) was added. The organic layer was separated, and the aqueous solution extracted with dichloromethane (2 × 20 mL). The combined extracts were washed with water, saturated aqueous sodium bicarbonate, and brine. After being dried over $MgSO_4$, the solution was filtered and concentrated. The residue was subjected to flash chromatography using ethyl acetate and hexane (30:70) as the eluant to give dienone ester **10** (1.14 g, 82% yield) as a light yellow oil: ir (CH_2Cl_2 cast): 1741 (C═O, ester), 1664 (C═O, enone), 739 and 699 (C-H bending, aromatic) cm^{-1}; ^1H nmr (300 MHz) δ: 7.59 (d, J = 3 Hz, 1 H, -C**H**═C-COOCH$_3$), 7.21–7.36 (m, 5 H, aromatic **H**), 6.78 (dd, J = 10, 3 Hz, 1 H, -C**H**═CHC═O), 6.29 (d, J = 10 Hz, 1 H, -CH═C**H**C═O), 4.35 (s, 2 H, -OC**H**$_2$Ph), 3.80 (s, 3 H, -COOC**H**$_3$), 3.26–3.41 (m, 2 H, -C**H**$_2$OBn), 1.97–2.13 (m, 2 H, -C**H**$_2$CH$_2$OBn), and 1.32 (s, 3 H, -C**H**$_3$); ^{13}C nmr (75 MHz) δ: 181.59 (p), 165.03 (p), 160.88 (a), 153.52 (a), 137.77 (p), 130.53 (p), 129.19 (a), 128.34 (a, 2 × aromatic **C**), 127.62 (a, 2 × aromatic **C**), 73.15 (p), 66.66 (p), 52.18 (a), 41.05 (p), 40.54 (p), and 25.98 (a); hrms M^+: 300.1353 (calcd. for $C_{18}H_{20}O_4$: 300.1361). Anal. calcd. for $C_{18}H_{20}O_4$: C 71.98, H 6.71; found: C 71.81, H 6.76.

(1*R**,5*R**,6*S**,10*S**)-5-(2-Benzyloxyethyl)-1-carbomethoxy-5,10-dimethylbicyclo[4.4.0]deca-3,8-dien-2-one (11) and (1*R**,5*S**,6*S**,10*S**)-5-(2-benzyloxyethyl)-1-carbomethoxy-5,10-dimethylbicyclo[4.4.0]deca-3,8-dien-2-one (12)

$ZnCl_2$ (1.0 g, 7.5 mmol) in a three-neck round bottom flask was fused under argon and then cooled to room temperature.

Dry ether (25 mL) was added and the $ZnCl_2$ was crushed to small pieces using a spatula. The mixture was stirred for 15 min until a fine suspension was formed. It was then cooled to 0°C and a solution of dienone ester **10** (0.75 g, 2.5 mmol) in ether (20 mL) was added dropwise. After the addition, the cloudy suspension turned clear, presumably due to the complexation of the dienophile and $ZnCl_2$. *trans*-Piperylene (3.75 mL, 7.52 mmol) was added and the resulting mixture was stirred under argon at 0°C for 68 h. The solution was quenched by addition of water and made basic with saturated aqueous sodium bicarbonate. The aqueous solution was extracted with ether (2 × 15 mL) and the combined extracts were washed with water, saturated sodium bicarbonate, and brine. Drying ($MgSO_4$), filtration, concentration, and flash chromatography using ethyl acetate and petroleum ether (5:95) gave adduct **11** (0.77 g, 84% yield) as a colorless oil: ir ($CHCl_3$ cast): 1725 (C=O, ester), 1690 (C=O, enone), 734 and 699 (C-H bending, aromatic) cm^{-1}; ^1H nmr (300 MHz) δ: 7.32 (m, 5 H, aromatic **H**), 6.29 (dd, *J* = 10, 2 Hz, 1 H, -C**H**=CHC=O), 5.92 (d, *J* = 10 Hz, 1 H, -CH=C**H**C=O), 5.57 (ddd, *J* = 10, 4, 2 Hz, 1 H, C-9 **H**), 5.50 (ddd, *J* = 10, 7, 3 Hz, 1 H, C-8 **H**), 4.52 (d, *J* = 14 Hz, 1 H, -OC**H**HPh), 4.48 (d, *J* = 14 Hz, 1 H, -OCH**H**Ph), 3.69 (s, 3 H, -COOC**H**$_3$), 3.58–3.66 (m, 2 H, -C**H**$_2$OBn), 2.83 (m, 1 H, C-10 **H**), 2.75 (ddd, *J* = 10, 7, 2 Hz, 1 H, C-6 **H**), 2.16 (dm, *J* = 18 Hz, 1 H, C-7 **H**$_a$), 1.95 (dm, *J* = 18 Hz, 1 H, C-7 **H**$_b$), 1.78 (dd, *J* = 14, 7 Hz, 1 H, -C**H**HCH$_2$OBn), 1.72 (dd, *J* = 14, 7 Hz, 1 H, -CH**H**CH$_2$OBn), 1.22 (d, *J* = 7 Hz, 3 H, C-10 C**H**$_3$), and 1.10 (s, 3 H, C-5 C**H**$_3$); ^{13}C nmr (75 MHz) δ: 196.33 (p), 174.54 (p), 152.27 (a), 138.37 (p), 130.62 (a), 128.42 (a, 2 × aromatic **C**), 127.57 (a, 2 × aromatic **C**), 127.32 (a), 123.36 (a), 73.12 (p), 66.64 (p), 59.29 (p), 52.37 (a), 43.07 (a), 39.61 (p), 39.10 (p), 37.66 (a), 26.62 (p), 24.22 (a), and 16.87 (a); hrms M^+: 368.1980 (calcd. for $C_{23}H_{28}O_4$: 368.1987). Anal. calcd. for $C_{23}H_{28}O_4$: C 74.97, H 7.66; found: C 75.03, H 7.81.

Further elution gave adduct **12** (0.13 g, 14% yield) as a colorless oil: ir ($CHCl_3$ cast): 1726 (C=O, ester), 1689 (C=O, enone), 735 and 699 (C-H bending, aromatic) cm^{-1}; ^1H nmr (300 MHz) δ: 7.33 (m, 5 H, aromatic **H**), 6.29 (dd, *J* = 10, 2 Hz, 1 H, -C**H**=CHC=O), 5.85 (d, *J* = 10 Hz, 1 H, -CH=C**H**C=O), 5.56 (ddd, *J* = 10, 4, 2 Hz, 1 H, C-9 **H**), 5.47 (ddd, *J* = 10, 7, 3 Hz, 1 H, C-8 **H**), 4.51 (d, *J* = 14 Hz, 1 H, -OC**H**HPh), 4.49 (d, *J* = 14 Hz, 1 H, -OCH**H**Ph), 3.71 (s, 3 H, -COOC**H**$_3$), 3.54–3.66 (m, 2 H, -C**H**$_2$OBn), 2.75 (m, 1 H, C-10 **H**), 2.68 (ddd, *J* = 10, 7, 2 Hz, 1 H, C-6 **H**), 2.30 (dddd, *J* = 19, 7, 4, 3 Hz, 1 H, C-7 **H**$_a$), 2.02 (dm, *J* = 19 Hz, 1 H, C-7 **H**$_b$), 1.93 (ddd, *J* = 14, 8, 6 Hz, 1 H, -C**H**HCH$_2$OBn), 1.64 (ddd, *J* = 14, 8, 6 Hz, 1 H, -CH**H**CH$_2$OBn), 1.26 (d, *J* = 7 Hz, 3 H, C-10 C**H**$_3$), and 1.15 (s, 3 H, C-5 C**H**$_3$); ^{13}C nmr (75 MHz) δ: 196.23 (p), 174.65 (p), 152.03 (a), 138.16 (p), 130.55 (a), 128.46 (a, 2 × aromatic **C**), 127.71 (a), 127.58 (a, 2 × aromatic **C**), 127.04 (a), 123.37 (a), 73.26 (p), 65.67 (p), 59.22 (p), 52.20 (a), 46.27 (a), 39.81 (p), 38.75 (a), 38.69 (p), 27.04 (p), 24.78 (a), and 16.69 (a); hrms M^+: 368.1984 (calcd. for $C_{23}H_{28}O_4$: 368.1987).

(1*S**,4*R**,5*R**,6*S**,10*S**)-5-(2-Benzyloxyethyl)-1-(1-hydroxymethyl)-4,5,10-trimethylbicyclo[4.4.0]dec-8-en-2-one (13)

A suspension of CuI (1.4 g, 7.3 mmol) in ether (20 mL) in a flame-dried round bottom flask was cooled to 0°C under argon. Methyllithium (10.5 mL, 1.4 M in ether) was added dropwise over a period of 5 min, and the resulting solution was stirred at 0°C for 1 h. Enone ester **11** (900 mg, 2.44 mmol) in ether (5 mL) was then introduced slowly over a period of 25 min. After the resulting yellow mixture was stirred for 1 h, lithium aluminium hydride (0.28 g, 7.3 mmol) was added. The reaction mixture turned into a dark suspension immediately after the addition of lithium aluminium hydride. This dark suspension was stirred for 30 min. Saturated aqueous ammonium chloride (10 mL) was added carefully until gas evolution ceased, followed by the addition of 3 N HCl (18 mL). The mixture was extracted with ether (4 × 20 mL). The combined extracts were washed with water (2 × 10 mL), saturated aqueous sodium bicarbonate, and brine. Drying (magnesium sulfate), filtration, and concentration gave the crude product, which was subjected to chromatography. Elution with ethyl acetate and hexane (20:80) gave alcohol **13** (501 mg, 61% yield) as a colorless oil: ir (CH_2Cl_2 cast): 3448 (br, OH), 1692 (C=O, ketone), 736 and 698 (C-H bending, aromatic) cm^{-1}; ^1H nmr (500 MHz) δ: 7.31 (m, 5 H, aromatic **H**), 5.85 (dt, *J* = 10, 4.5 Hz, 1 H, C-8 **H**), 5.75 (dd, *J* = 10, 5 Hz, 1 H, C-9 **H**), 4.49 (s, 2 H, -OC**H**$_2$Ph), 3.58 (d, *J* = 11 Hz, 1 H, -C**H**HOH), 3.55 (t, *J* = 7 Hz, 2 H, -C**H**$_2$OBn), 3.45 (d, *J* = 11 Hz, 1 H, -CH**H**OH), 3.26 (br s, 1 H, -O**H**), 2.50 (m, 1 H, C-10 **H**), 2.36 (dd, *J* = 10.5, 10.5 Hz, 1 H, C-3 **H**), 2.00–2.19 (complex, 5 H), 1.60 (m, 2 H), 1.10 (d, *J* = 7 Hz, 3 H, C-10 C**H**$_3$), 0.97 (s, 3 H, C-5 C**H**$_3$), and 0.89 (d, *J* = 6.5 Hz, 3 H, C-4 C**H**$_3$); ^{13}C nmr (125 MHz) δ: 219.94 (p), 138.30 (p), 132.36 (a), 132.20 (a), 128.21 (a, 2 × aromatic **C**), 127.65 (a, 2 × aromatic **C**), 126.60 (a), 73.25 (p), 69.36 (p), 67.01 (p), 55.24 (p), 45.95 (p), 41.63 (a), 37.32 (p), 35.07 (a), 34.84 (p), 33.03 (a), 22.67 (p), 22.53 (a), 17.31 (a), and 15.53 (a); cims $[M+NH_4]^+$: 374. Anal. calcd. for $C_{23}H_{32}O_3$: C 77.49, H 9.05; found: C 77.29, H 9.26.

(1*S**,4*R**,5*R**,6*S**,10*S**)-5-(2-Benzyloxyethyl)-1-(1-mesyloxymethyl)-4,5,10-trimethylbicyclo[4.4.0]dec-8-en-2-one (14)

To a solution of alcohol **13** (110 mg, 0.31 mmol) and triethylamine (0.22 mL, 1.5 mmol) in THF (8 mL) at 0°C under an argon atmosphere, mesyl chloride (0.12 mL, 1.5 mmol) was added slowly. The reaction mixture was stirred at room temperature for 21 h, at which time 1 N HCl (3 mL) was added. The mixture was extracted with ether (3 × 15 mL), and the extracts were combined and washed with saturated aqueous sodium bicarbonate, water, and brine. The solution was dried over magnesium sulfate, filtered, and concentrated to afford the crude product, which was purified by flash chromatography on silica gel. Elution with ethyl acetate and hexane (5:95) gave mesylate **14** (131 mg, 98% yield) as a colorless oil: ir (CH_2Cl_2 cast): 1701 (C=O, ketone), 1357 and 1176 (S=O), 737 and 699 (C-H bending, aromatic) cm^{-1}; ^1H nmr (300 MHz) δ: 7.35 (m, 5 H, aromatic **H**), 5.91 (m, 1 H, -C**H**=CH-), 5.67 (m, 1 H, -CH=C**H**-), 4.54 (d, *J* = 12 Hz, 1 H, -OC**H**HPh), 4.51 (d, *J* = 9.5 Hz, 1 H, -C**H**HOMs), 4.44 (d, *J* = 12 Hz, 1 H, -OCH**H**Ph), 4.04 (d, *J* = 9.5 Hz, 1 H, -CH**H**OMs), 3.57 (m, 2 H, -C**H**$_2$OBn), 2.96 (s, 3 H, -OSO$_2$C**H**$_3$), 2.43 (dd, *J* = 7.5, 4.5 Hz, 1 H), 2.31 (dd, *J* = 16, 6 Hz, 1 H), 1.96–2.03 (complex, 5 H), 1.50–1.72 (complex, 2 H), 1.03 (d, *J* = 7 Hz, 3 H, C-10 C**H**$_3$), 1.00 (s, 3 H, C-5 C**H**$_3$), and 0.91 (d, *J* = 6.5 Hz, 3 H, C-4 C**H**$_3$); ^{13}C nmr (75 MHz) δ: 213.39 (p), 138.45 (p), 130.93 (a), 128.43 (a, 2 × aromatic **C**), 127.80 (a, 2 × aromatic

C), 127.61 (a), 127.40 (a), 74.05 (p), 73.25 (p), 67.04 (p), 54.20 (p), 45.24, (p), 39.60 (a), 37.28 (p), 37.09 (a), 35.60 (a), 35.23 (p), 34.36 (a), 22.88 (p), 22.76 (a), 17.13 (a), and 15.70 (a); hrms M^+: 434.2127 (calcd. for $C_{24}H_{34}O_5S$: 434.2127).

(1*S,3*S**,5*R**,6*R**,7*S**,11*S**)-6-(2-Benzyloxyethyl)-5,6,11-trimethyltricyclo[5.4.0.0^{1,3}]undec-9-en-3-ol (15) and (1*S**,2*S**,6*S**,7*R**,14*R**)-2,7,14-trimethyl-10-oxatricyclo[5.4.3.0^{1,6}]tetradec-3-en-12-one (16)**

To a stirred solution of mesylate **14** (0.11 g, 0.25 mmol) in DMF (10 mL with 0.15% H_2O), were added sodium iodide (0.36 g, 2.5 mmol) and zinc powder (0.33 g, 5.0 mmol). The reaction mixture was immersed in a preheated oil bath at 130°C and maintained at that temperature for 28 h. The mixture was then filtered to remove excess sodium iodide and zinc powder. The filtrate was poured into water (6 mL) and extracted with 15% ethyl acetate in hexane (3 × 15 mL). The combined organic layers were then washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residual oil was purified by flash chromatography using ethyl acetate and hexane (6:94) to give tricyclic ketone **16** (19 mg, 30% yield) as a white solid, which was recrystallized from ethyl acetate and *n*-hexane to form a crystalline compound: mp 74.5–76.0°C; ir ($CHCl_3$ cast): 1704 (C=O, ketone) cm^{-1}; ^1H nmr (300 MHz) δ: 5.53 (m, 2 H, -C**H**=C**H**-), 4.21 (d, *J* = 13.5 Hz, 1 H, -C**H**HO-), 4.00 (m, 2 H, -CH_2C$\mathbf{H}_2$O-), 3.61 (d, *J* = 13.5 Hz, 1 H, -CH**H**O-), 2.63 (dd, *J* = 16.5, 8.5 Hz, 1 H, -C**H**HC=O), 2.10–2.36 (complex, 5 H), 1.92 (m, 1 H), 1.57 (dd, *J* = 5.5, 4.5 Hz, 1 H), 1.51 (dd, *J* = 5.5, 4.5 Hz, 1 H), 1.26 (d, *J* = 7.5 Hz, 3 H, C-2 C$\mathbf{H}_3$), 1.05 (s, 3 H, C-7 C$\mathbf{H}_3$), and 0.98 (d, *J* = 6.5 Hz, 3 H, C-14 C$\mathbf{H}_3$); ^{13}C nmr (APT) δ: 211.87 (p), 131.85 (a), 123.00 (a), 69.54 (p), 65.68 (p), 58.11 (p), 49.81 (a), 46.78 (p), 38.79 (p), 38.75 (a), 36.59 (a), 35.52 (p), 27.23 (a), 25.22 (p), 16.72 (a), and 15.92 (a); hrms M^+: 248.1788 (calcd. for $C_{16}H_{24}O_2$: 248.1778). Anal. calcd. for $C_{16}H_{24}O_2$: C 77.38, H 9.74; found: C 77.34, H 9.63.

Further elution gave compound **15** (47 mg, 55% yield) as a colorless oil: ir (CH_2Cl_2 cast): 3436 (br, OH), 735 and 696 (C-H bending, aromatic) cm^{-1}; ^1H nmr (300 MHz) δ: 7.32 (m, 5 H, aromatic **H**), 6.22 (m, 1 H, -C**H**=CH-), 5.96 (m, 1 H, -CH=C**H**-), 4.50 (s, 2 H, -OC$\mathbf{H}_2$Ph), 3.49 (t, *J* = 8 Hz, 2 H, -C$\mathbf{H}_2$OBn), 1.92–2.23 (complex, 6 H), 1.56–1.72 (complex, 3 H), 1.46 (m, 1 H), 1.08 (s, 3 H, C-7 C$\mathbf{H}_3$), 1.06 (d, *J* = 7 Hz, 3 H, C-2 C$\mathbf{H}_3$), 0.83 (d, *J* = 7 Hz, 3 H, C-8 C$\mathbf{H}_3$), 0.58 (dd, *J* = 5, 1.5 Hz, 1 H, cyclopropyl **H**), 0.52 (d, *J* = 5 Hz, 1 H, cyclopropyl **H**); hrms M^+: 340.2393 (calcd. for $C_{23}H_{32}O_2$: 340.2402).

(1*S,4*R**,5*R**,6*S**,10*S**)-5-(2-Benzyloxyethyl)-1,4,5,10-tetramethylbicyclo[4.4.0]dec-8-en-2-one (17)**

To a solution of compound **15** (60 mg, 0.18 mmol) in dichloromethane (5 mL) at room temperature, was added a crystal of *p*-toluenesulfonic acid. After stirring for 40 min, the reaction mixture was diluted with dichloromethane (6 mL) and then washed with saturated aqueous sodium bicarbonate, water, and brine. The organic solution was dried over $MgSO_4$, filtered, and concentrated. Flash chromatography of the residue with 10% ethyl acetate in hexane gave **17** (58 mg, 97% yield) as a colorless oil: ir ($CHCl_3$ cast): 1695 (C=O, ketone), 735 and 698 (C-H bending, aromatic) cm^{-1}; ^1H nmr (300 MHz) δ: 7.31 (m, 5 H, aromatic **H**), 5.85 (m, 1 H, -C**H**=CH-), 5.72 (m, 1 H, -CH=C**H**-), 4.52 (d, *J* = 12 Hz, 1 H, -OC**H**HPh), 4.48 (d, *J* = 12 Hz, 1 H, -OCH**H**Ph), 3.57 (m, 2 H, -C$\mathbf{H}_2$OBn), 2.23 (dd, *J* = 13, 9 Hz, 1 H, -C**H**HC=O), 2.21 (dd, *J* = 8, 4 Hz, 1 H), 2.04–2.18 (complex, 3 H), 1.96 (t, *J* = 7 Hz, 1 H), 1.58–1.71 (complex, 3 H), 1.27 (s, 3 H, C-1 C$\mathbf{H}_3$), 1.00 (d, *J* = 7 Hz, 3 H, C-10 C$\mathbf{H}_3$), 0.98 (s, 3 H, C-5 C$\mathbf{H}_3$), and 0.91 (d, *J* = 6.5 Hz, 3 H, C-4 C$\mathbf{H}_3$); ^{13}C nmr (75 MHz) δ: 217.10 (p), 138.44 (p), 132.67 (a), 129.61 (a, 2 × aromatic **C**), 128.44 (a, 2 × aromatic **C**), 127.62 (a), 126.70 (a), 73.19 (p), 67.13 (p), 51.05 (p), 47.53 (a), 45.07 (p), 39.43 (a), 37.70 (p), 35.87 (a), 35.18 (p), 29.50 (a), 23.70 (p), 23.14 (a), 17.08 (a), and 16.05 (a); hrms M^+: 340.2395 (calcd. for $C_{23}H_{32}O_2$: 340.2402).

(3*R,4*R**)-6-Benzyloxy-3,4-dimethyl-4-((1*S**,5*S**)-5-methyl-6-methylene-3-cyclohexenyl)-1-hexanol (18)**

To a solution of compound **14** (0.15 g, 0.35 mmol) in dry THF (8 mL) at 0°C under an argon atmosphere, was added lithium triethylborohydride (1.38 mL, 1.0 M in THF). After the mixture was stirred at 0°C for 30 min and then at room temperature for 3 h, the reaction was quenched with water (3 mL), and the aqueous phase was extracted with ether (2 × 10 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give an oil, which was purified by flash chromatography using 10% ethyl acetate in hexane as eluant to yield **18** (0.1 g, 82% yield) as a colorless oil: ir (CH_2Cl_2 cast): 3342 (OH, broad) cm^{-1}; ^1H nmr (300 MHz) δ: 7.35 (m, 5 H, aromatic **H**), 5.62 (m, 1 H, -C**H**=CH-), 5.41 (m, 1 H, -CH=C**H**-), 4.97 (br s, 1 H, **H**HC=C), 4.88 (d, *J* = 1.5 Hz, 1 H, H**H**C=C), 4.42 (s, 2H, -OC$\mathbf{H}_2$Ph), 3.65 (m, 1H), 3.45–3.56 (complex, 3 H), 2.88 (m, 1 H), 2.45 (dd, *J* = 10, 5 Hz, 1H), 2.05–2.31 (complex, 2 H), 1.95 (m, 1 H), 1.85 (dd, *J* = 10, 7 Hz, 1 H), 1.62–1.75 (complex, 2 H), 1.35 (br s, 1 H, -O**H**), 1.18 (m, 1 H), 1.09 (d, J = 7 Hz, 3 H, -C$\mathbf{H}_3$), 1.0 (s, 3 H, -C$\mathbf{H}_3$), 0.89 (d, *J* = 7 Hz, 3 H, -C$\mathbf{H}_3$); hrms [M − C_5H_8]$^+$: 274.1934 (calcd. for $C_{18}H_{26}O_2$: 274.1933); cims $[M+H]^+$: 343, $[M+NH_4]^+$: 360.

(1*S,4*R**,5*R**,6*S**,10*S**)-5-(2-Benzyloxyethyl)-1-(1-phenoxythiocarbonyloxymethyl)-4,5,10-trimethylbicyclo[4.4.0]dec-8-en-2-one (19)**

Keto alcohol **13** (0.12 g, 0.34 mmol) was dissolved in dichloromethane (10 mL) and cooled to 0°C under an atmosphere of argon. 4-Dimethylaminopyridine (5 mg), pyridine (0.05 mL, 0.68 mmol), and phenyl chlorothionoformate (0.08 mL, 0.64 mmol) were introduced sequentially to the stirred solution. After stirring at room temperature for 20 h, the reaction mixture was poured into ice-cold 1 M hydrochloric acid and extracted with ether (3 × 10 mL). The extracts were washed with ice-cold 1 M hydrochloric acid, water, dried ($MgSO_4$), filtered, and concentrated. The residue was subjected to flash chromatography on silica gel, eluting with 10% ethyl acetate in hexane to give **19** (0.1 g, 70% yield) as a light yellow oil: ir (CH_2Cl_2 cast): 1703 (C=O, ketone), 1590 (C=C stretching, aromatic),1290 and 1200 (C=S) cm^{-1}; ^1H nmr (300 MHz) δ: 7.16–7.39 (complex, 8 H, aromatic **H**), 7.00 (m, 2 H, aromatic **H**), 5.82 (m, 1 H, -C**H**=CH-), 5.61 (m, 1 H, -CH=C**H**-), 4.67 (d, *J* = 10.5 Hz, 1 H, -C**H**HOCSOPh), 4.43 (s, 2 H, -OC$\mathbf{H}_2$Ph), 4.41 (d, *J* = 10.5 Hz, 1 H, -CH**H**OCSOPh), 3.53 (m, 2 H, -C$\mathbf{H}_2$OBn), 2.34 (dd, *J* = 8, 3.5 Hz, 1 H), 2.24 (dd, *J* = 17, 6 Hz, 1 H, -C**H**HCO-), 1.93–2.19 (complex, 6 H), 1.61 (ddd, *J* =

8, 8, 2 Hz, 1 H), 1.00 (d, J = 7 Hz, 3 H, C-10 CH_3), 0.98 (s, 3 H, C-5 CH_3), and 0.86 (d, J = 7 Hz, 3 H, C-4 CH_3); cims $[M+NH_4]^+$: 494.

(1*S,2*S**,6*R**,7*R**,8*R**)-7-(2-Benzyloxyethyl)-1,2,7.8-tetramethylbicyclo[4.4.0]dec-3-ene (20) and (1*R**,6*S**,7*R**,8*R**)-7-(2-Benzyloxyethyl)-1,2,7,8-tetramethylbicyclo[4.4.0]dec-2-ene (21)**

To a solution of ketone **17** (28 mg, 0.08 mmol) in diethylene glycol (7 mL) at room temperature, were added potassium hydroxide (32 mg, 0.56 mmol) and anhydrous hydrazine (0.2 mL, 4.0 mmol). The mixture was heated at 130–140°C for 12 h under argon. The temperature was then raised to 220°C to remove water and excess hydrazine using a Dean–Stark apparatus, and maintained at 210-220°C for 10 h. The reaction mixture was then cooled, diluted with water (6 mL), acidified with aqueous NH_4Cl, and extracted with ethyl acetate (3 × 10 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated to give a yellow oil, which was chromatographed using 5% ethyl acetate in hexane to furnish an inseparable 3:1 mixture of compounds **20** and **21** (16 mg, 60% yield) as a colorless oil: ir (CH_2Cl_2 cast): 736 and 697 (C-H bending, aromatic) cm^{-1}; ^1H nmr (300 MHz) δ: **20**: 5.57 (m, 1 H, -C**H**=CH-), 5.29 (m, 1 H, -CH=C**H**-), 4.57 (d, J = 12 Hz, 1 H, -OC**H**HPh), 4.50 (d, J = 12 Hz, 1 H, -OCH**H**Ph), 3.54 (m, 2 H, -CH_2OBn), 1.14 (s, 3 H, -CH_3), 0.93 (s, 3 H, -CH_3), 0.87 (d, J = 7 Hz, 3 H, -CH_3), and 0.85 (d, J = 7 Hz, 3 H, -CH_3); **21**: 5.32 (m, 1 H, -C=C**H**-), 4.52 (s, 2 H, -OCH_2Ph), 3.70 (m, 2 H, -CH_2OBn), 1.61 (s, 3 H, -CH=CCH_3), 1.17 (s, 3 H, -CH_3), 0.93 (d, J = 7 Hz, 3 H, C-8 CH_3), and 0.81 (s, 3 H, -CH_3); hrms $[M-C_5H_8]^+$: 258.1984 (calcd. for $C_{18}H_{26}O$: 258.1983); cims $[M + NH_4]^+$: 344.

(1*S,6*R**,9*R**,10*R**)-10-(2-Benzyloxyethyl)-5,6,9,10-tetramethylbicyclo[4.4.0]dec-4-en-3-one (22)**

A solution of the 3:1 mixture of **20** and **21** (25 mg, 0.07 mmol), acetic anhydride (0.06 mL, 0.5 mmol), pyridine (0.05 mL, 0.5 mmol), a catalytic amount of 4-dimethylaminopyridine, and 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (2 mg) in dry carbon tetrachloride (40 mL) was saturated with oxygen for 10 min and then irradiated with two 200 W tungsten lamps for 58 h. During this period a gentle stream of oxygen was bubbled through the reaction mixture. After 58 h, irradiation was stopped and oxygen was bubbled through the solution for another 10 h. The reaction mixture was washed sequentially with saturated aqueous sodium bicarbonate (2 × 5 mL), 1 M hydrochloric acid (2 × 5 mL), saturated aqueous copper sulfate (1 × 5 mL), and saturated aqueous sodium chloride. After being dried over $MgSO_4$, the organic solution was filtered and concentrated. The resulting residue was subjected to flash chromatography using 5–15% ethyl acetate in hexane as the eluant to give **22** (11 mg, 56% yield based on **20**) as a colorless oil as well as an unidentified uv-active product (6.2 mg). For compound **22**: ir (CH_2Cl_2 cast): 1661 (C=O, enone), 736 and 697 (C-H bending, aromatic) cm^{-1}; ^1H nmr (300 MHz) δ: 7.32 (m, 5 H, aromatic, **H**), 5.88 (br s, 1 H, -C=C**H**C=O), 4.48 (s, 2 H, -OCH_2Ph), 3.50 (m, 2 H, -CH_2OBn), 2.73 (dd, J = 18, 6 Hz, 1 H, -C**H**HC=O), 2.60 (dd, J = 18, 3 Hz, 1 H, -C**H**HC=O), 1.95 (d, J = 1.5 Hz, 3 H, C-5 CH_3), 1.91 (dd, J = 6, 3 Hz, 1 H, C-1 **H**), 1.78–1.86 (complex, 2 H), 1.40–1.65 (complex, 5 H), 1.25 (s, 3 H, C-6 CH_3), 0.97 (d, J = 7 Hz, 3 H, C-9 CH_3), and 0.86 (s, 3 H, C-10 CH_3); hrms M^+: 340.2400 (calcd. for $C_{23}H_{32}O_2$: 340.2402).

(1*S,6*R**,9*R**,10*R**)-10-(2-Hydroxyethyl)-5,6,9,10-tetramethylbicyclo[4.4.0]dec-4-en-3-one (23)**

To a solution of compound **22** (4.0 mg, 0.012 mmol) in dry dichloromethane (6 mL) under an atmosphere of argon, was added anhydrous $FeCl_3$ (7 mg, 0.04 mmol) in one portion. After stirring for 50 min at room temperature, the reaction was quenched by addition of water (1 mL). The aqueous solution was separated and extracted with dichloromethane (2 × 6 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give the crude product, which was purified by flash chromatography with ethyl acetate and hexane (50:50) to afford **23** (2.4 mg, 82% yield) as a colorless oil: ir (CH_2Cl_2 cast): 3439 (OH, broad) and 1651 (C=O, enone) cm^{-1}; ^1H nmr (300 MHz) δ: 5.89 (br s, 1 H, -C=C**H**C=O), 3.69 (t, J = 7.5 Hz, 2 H, -CH_2OH), 2.75 (dd, J = 18, 6 Hz, 1 H, -C**H**HC=O), 2.59 (dd, J = 18, 3 Hz, 1 H, -CH**H**C=O), 1.96 (br s, 3 H, C-5 CH_3), 1.92 (dd, J = 6, 3 Hz, 1 H, C-1 **H**), 1.79–1.88 (complex, 2 H), 1.40–1.68 (complex, 6 H), 1.27 (s, 3 H, C-6 CH_3), 1.11 (d, J = 7 Hz, 3 H, C-9 CH_3) and 0.89 (s, 3 H, C-10 CH_3); hrms M^+: 250.1931 (calcd. for $C_{16}H_{26}O_2$: 250.1932), $[M - H_2O]^+$: 232.1825 (calcd. for $C_{16}H_{24}O$ 232.1827).

(±)-2-Oxo-5α,8α-13,14,15,16-tetranorclerod-3-en-12-oic acid (2)

Enone **23** (1.6 mg, 0.006 mmol) was dissolved in acetone (4 mL, distilled over $KMnO_4$) and the solution was cooled to 10°C. Freshly prepared Jones reagent (0.02 mL) was added dropwise, and the resulting solution stirred for 30 min at room temperature. Water was added to dissolve all green precipitates and the aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give the crude product, which was subjected to flash chromatography using ethyl acetate and hexane (50:50) as the eluant to afford pure acid (1.1 mg, 63% yield) as a white powder: mp 226–227°C; ir (CH_2Cl_2 cast): 3300–2450 (OH, carboxylic acid), 1725 (C=O, carboxylic acid), and 1628 (C=O, enone) cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ: 8.7 (br s, 1 H, -COO**H**), 5.90 (br s, 1 H, -C=C**H**C=O), 2.79 (dd, J = 18, 6.5 Hz, 1 H, -C**H**HC=O), 2.56 (d, J = 15 Hz, 1 H, -C**H**HCOOH), 2.48 (dd, J = 18, 2.5 Hz, 1 H, -CH**H**C=O), 2.21 (d, J = 15 Hz, 1 H, -CH**H**COOH), 2.07 (dd, J = 6.5, 2.5 Hz, 1 H, C-10 **H**), 2.00 (m, 1 H), 1.97 (d, J = 1 Hz, 3 H, C-4 CH_3), 1.85 (dm, J = 14 Hz, 1 H), 1.45–1.70 (m, 2 H), 1.30–1.36 (m, 1 H), 1.28 (s, 3 H, C-5 CH_3), 1.06 (s, 3 H, C-9 CH_3), and 1.05 (d, J = 7.5 Hz, 3 H, C-8 CH_3); ^1H nmr (200 MHz, $CDCl_3$–C_5D_5N) δ: 5.90 (br s, 1 H,-C=C**H**C=O), 3.06 (br s, 1 H, -$COO^-C_5D_5N^+$H), 2.79 (dd, J = 18, 6.5 Hz, 1 H, -C**H**HC=O), 2.59 (d, J = 15 Hz, 1 H, -C**H**HCOOH), 2.54 (dd, J = 18, 2.5 Hz, 1 H, -CH**H**C=O), 2.24 (d, J = 15 Hz, 1 H, -CH**H**COOH), 2.13 (dd, J = 6.5, 2.5 Hz, 1 H, C-10 **H**), 2.11 (m, 1 H), 1.97 (d, J = 1 Hz, 3 H, C-4 CH_3), 1.85 (dm, J = 14 Hz, 1 H), 1.50–1.75 (m, 3 H), 1.29 (s, 3 H, C-5 CH_3), 1.13 (s, 3 H, C-9 CH_3), and 1.09 (d, J = 7.5 Hz, 3 H, C-8 CH_3); ^{13}C nmr (125 MHz, $CDCl_3$) δ: 198.5, 176.1, 168.6, 128.6, 45.9, 42.2, 39.8, 39.6, 35.7, 35.5, 31.0, 29.6, 26.6, 23.5, 20.9, and 15.0; hrms M^+: 264.1721 (calcd. for

$C_{16}H_{24}O_3$: 264.1725), $[M - CH_3]^+$: 249.1488 (calcd. for $C_{15}H_{21}O_3$: 249.1490), $[M - CH_3COOH]^+$: 204.1509 (calcd. for $C_{14}H_{20}O$: 204.1514).

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