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A One-Pot Intramolecular Tandem Michael–Aldol Annulation Reaction for the Synthesis of Chiral Pentacyclic Terpenes

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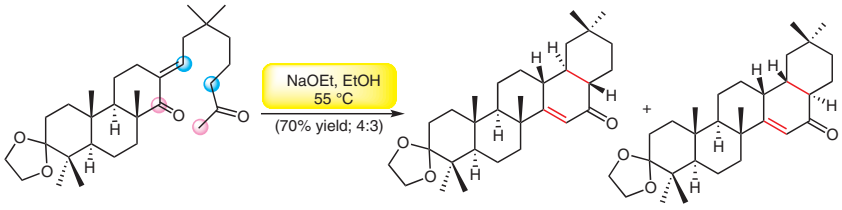

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Abstract A chiral tricyclic terpene possessing a 6,6,6-tricyclic framework and a 3,3-dimethyl-7-oxooctylidenyl side chain undergoes a double ring-closing reaction to give two chiral pentacyclic terpenes in a ratio of 4:3 via an intramolecular Michael addition followed by aldol condensation under basic conditions. Three new stereogenic centers are introduced in the initial Michael annulation reaction. Stereoselective installation of an ethoxycarbonyl group at C17 of the two pentacyclic terpenes separately gives the corresponding highly functionalized pentacyclic terpenoids with seven stereogenic centers. The structures and stereochemistry of key intermediates and products are established through X-ray crystallographic analysis. A mechanism is proposed for explaining the stereochemistry in the Michael annulation reaction.

Key words 1,4-addition, chiral synthesis, double ring-closing, pentacyclic triterpenes, tandem Michael–aldol annulation

Pentacyclic triterpenes are widely found in more than 90% of *Diospyros* (Syn: Persimmon, ebony) plants.[1,2] They are biosynthesized through the cyclization of squalene and usually contain over seven asymmetric centers. The genus *Diospyros* consists of tropical trees and shrubs and is known for its medicinal usage.[1–3] Many important biological activities are associated with oleanane-type pentacyclic triterpenes such as anticancer,[4] anti-inflammatory,[5] antimicrobial,[1,6] anti-obesity,[7] kinase inhibition,[8] vasodilation,[9–11] and anti-HIV activities.[12] Figure 1 shows three representative bioactive pentacyclic triterpenes of the oleanane type. δ-Oleanolic acid (**1**), isolated from the leaves of loquat, possesses anti-inflammatory, antitumor-promoting,[13] and cholesterol ester transfer protein inhibitory[14] effects. Erythrodiol (**2**), an olive oil constituent, was found to enhance cholesterol efflux via an increase of the ATP-binding cassette transporter A1 (ABCA1) protein level in human macrophages.[15] Myriceric acid A (**3**), isolated from twigs of *Myrica cerifera*, is a potent endothelin receptor antagonist, which can be used in the study of hypertension and vascular spasm.[10,16]

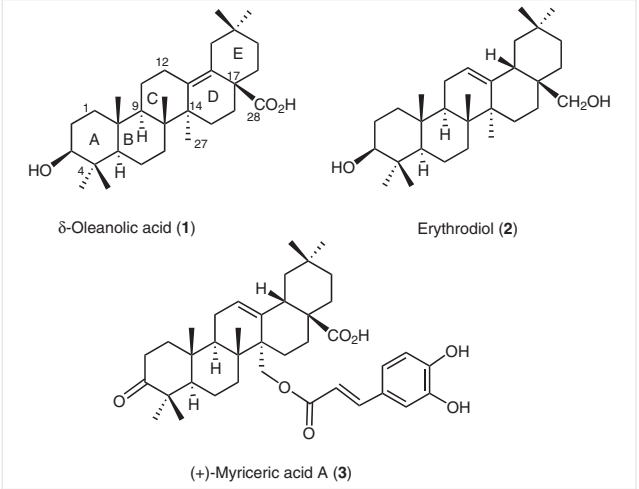

Figure 1 Representative bioactive pentacyclic triterpenoids

In the pursuit of asymmetric synthesis of bioactive pentacyclic triterpenes, two isomeric pentacyclic enone molecules, (–)-**4** and (+)-**5**, were anticipated to be assembled in a one-pot double intramolecular tandem Michael–aldol condensation reaction from tricyclic keto-enone (–)-**6**, as illustrated in the retrosynthetic analysis shown in Scheme 1. Keto-enone (–)-**6** could be prepared from a Mukaiyama aldol condensation of a reported tricyclic ketone (–)-**7** (>98% ee)[17] and 7-oxooctanal **8**. Pentacyclic terpenes (–)-**4** and (+)-**5** possess seven asymmetric centers and all the asymmetric centers of (–)-**4** are identical to those of oleanane triterpenes. These two molecules may serve as chemical probes for mechanistic studies of oleanane bioactivities due to their differences at C17 and C18. Previously, tandem

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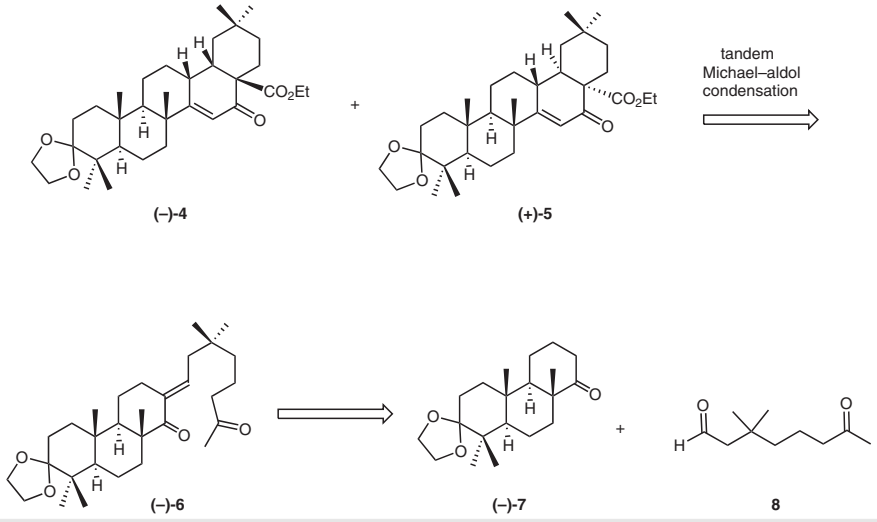
Michael–aldol ring-closing reactions of a cyclohexyl keto-enester[18] and enol silyl ethers of cyclohexanone tethered with 2-alkenyl esters[19] have been reported under Lewis acid conditions to construct 4,5,6-tricyclic systems and tricyclo[4.2.1.0^{3,8}]nonanes, respectively. Tadano et al.[20] reported a four-step sequence of reactions to prepare a 5,6,6-tricyclic system from a keto-enester tetrahydrofuran through a Michael addition–reduction–oxidation–aldol process. In addition, Mischne described a two-step annulation procedure of an α,β-enedionyl alkanone under basic conditions to give a 6,6-bicyclic ring system.[21] The reported systems involved ene esters or an enedione as the synthetic intermediates. A one-pot tandem Michael–aldol double annulation reaction of an exocyclic enone system, such as (–)-**6**, for the regioselective construction of a 6,6,6-tricyclic skeleton has not been reported previously.

Multiple fused six-membered ring systems are often synthesized by intramolecular Diels–Alder reactions[22] and cation-π cyclizations,[23] whilst a successful tandem intramolecular Michael–aldol double annulation reaction under weakly basic conditions may afford an alternative pathway for the construction of pentacyclic triterpenes possessing various functional groups, substituents, and stereogenic centers. Accordingly, we investigated the synthesis of pentacyclic terpenes starting from a previously reported optically pure tricyclic ketone (–)-**7** (>98% ee).[17] We adapted Mukaiyama's aldol addition reaction[24] of enol silyl ether (–)-**9** and aldehyde **8** for the synthesis of intermediate (–)-**6**. Enol silyl ether (–)-**9** was readily synthesized in 98% yield from the treatment of ketone (–)-**7** with 1.2 equivalents of lithium diisopropylamide (LDA) in THF at –78 °C followed by trimethylsilyl chloride (TMSCl) (Scheme 2). The exocyclic enone (–)-**6** was obtained in 71% overall yield by a sequence of reactions: (i) coupling of (–)-**9** and **8** in the presence of 2.5 equivalents of $BF_3{\cdot}Et_2O$ in dichloromethane at –78 °C, (ii) mesylation of the resulting β-hydroxy ketone with methanesulfonyl chloride (MsCl) and triethylamine in diethyl ether, and (iii) β-elimination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in a mixture of dichloromethane and toluene. Only one stereoisomer at the alkene function, i.e., with *E*-stereochemistry, was isolated, and no *Z*-isomer was detected. The alkene stereochemistry of (–)-**6** was confirmed by a single-crystal X-ray analysis (Figure 2; CCDC 1922116).[25] The one-pot tandem Michael–aldol condensation reaction of (–)-**6** was affected by treatment with 2 equivalents of sodium ethoxide in ethanol at 55 °C to give a mixture of (–)-**10** and (+)-**11** in a ratio of 4:3. They were separated by silica gel column chromatography and the structure of (+)-**11** was established from a single-crystal X-ray analysis (Figure 3; CCDC 1922117),[25] revealing the stereochemistry of the newly generated stereogenic centers at C13, 17, and 18. The stereochemistry at C13 and C18 of (–)-**10** was determined from the single-crystal X-ray structure of (+)-**5** (*vide infra*), while the stereochemistry at C17 was based on the following assumptions (Scheme 2). It is likely that *Z*-enolate **6A** forms predominantly from the deprotonation of (–)-**6** with sodium ethoxide in ethanol or the *Z*-enolate **6A** undergoes a Michael addition reaction faster than the corresponding *E*-enolate (Scheme 2). The sodium ion of the enolate is solvated by ethanol and a loose or acyclic transition state for the formation of the enolate ion results, leading to a greater ratio of *Z*/*E* enolates.[26] The *E*-enolate has a greater repulsion derived from the *cis*-stereochemistry of the C15 (methyl) and C22 alkyl substituent than that of the *Z*-enolate (due to solvation of the sodium ion). *Z*-Enolate **6A** approaches the enone moiety from the β-face (or upper face) with the C17–C22 and C18–C19 bonds in gauche orientation, providing a stable chair



Scheme 1 Retrosynthesis of pentacyclic terpenoids via a double intramolecular tandem Michael–aldol annulation reaction

conformation of the E ring in the transition state. The resulting C13,14-enolate undergoes protonation from the β-face (upper face), since a more stable *anti*-C18,C26 stereochemistry (**10A**) is formed. On the other hand, protonation at the α-face (or down face) of the C13,14-enolate would provide a less stable stereoisomer, deriving from a 1,3-diaxial interaction between the C26 methyl and C18-cyclohexyl ring. Similarly, *Z*-enolate **6A** can approach the enone moiety from the α-face (or down face) with the C17–C22 and C18–C19 bonds in gauche orientation, providing a chair conformation of the E ring, which subsequently undergoes protonation from the β-face to give **11A**. The approach from the α-face is slightly less favorable since the concave face of the tricyclic structure is more crowded than the convex face. The plausible mechanism explains the *trans*-stereochemistry at C17 and C18 and the ratio of 4:3 of (–)-**10** and (+)-**11**.

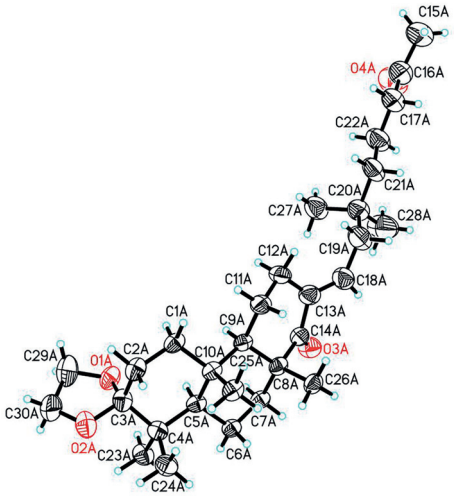


Figure 2 ORTEP drawing of the single-crystal X-ray analysis of compound (–)-**6**; CCDC 1922116. Selected bond lengths (Å) and angles (°): C5–C10 1.554(5), C8–C9 1.574(5), C9–C10 1.561(5), C8–C14 1.530(6), C14–O3 1.216(5), C13–C14 1.503(6), C13–C18 1.343(7), C16–O4 1.230(10); C2–C3–C4 112.8(3), C3–C4–C5 107.9(3), C1–C10–C5 108.3(3), C8–C9–C10 115.5(3), C7–C8–C14 109.0(3), C13–C14–O3 121.2(4), C14–C13–C18 117.6(5), C17–C16–O4 122.4(6)

The installation of an ester moiety at C17 was accomplished by the treatment of (–)-**10** and (+)-**11** separately with LDA in THF at –78 °C, followed by the addition of ethyl cyanoformate to give a 45% yield of (+)-**5** and 65% yield of (–)-**4**, respectively (Scheme 2). The structure of (+)-**5** was firmly determined from a single-crystal X-ray analysis (Figure 4; CCDC 1922118).[25] It appears that the cyanoformate reacted with the enolate of (–)-**10** from the α-face, the same face as that of the C18-hydrogen, resulting in less repulsion from the ethyl ester group with C18-H than the C19 alkyl. This produced the *syn*-stereochemistry of C17-CO_2Et and

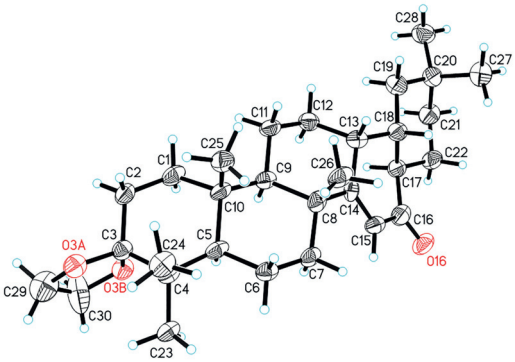


Figure 3 ORTEP drawing of the single-crystal X-ray analysis of compound (+)-**11**; CCDC 1922117. Selected bond lengths (Å) and angles (°): C5–C10 1.548(11), C8–C9 1.574(11), C9–C10 1.553(11), C8–C14 1.513(11), C13–C14 1.494(11), C14–C15 1.543(11), C15–C16 1.448(12), C16–O16 1.238(10); C2–C3–C4 112.7(7), C3–C4–C5 108.9(6), C1–C10–C5 106.0(6), C8–C9–C10 115.4(6), C7–C8–C14 112.7(7), C13–C14–C15 119.2(8), C14–C15–C16 124.7(8), C15–C16–O16 120.7(8)

C18-H. Based on this observation, it is assumed that the reaction of the enolate ion of (+)-**11** and ethyl cyanoformate gave *syn*-product (–)-**4**, in which the electrophile approaches from the less hindered β-face of the enolate ion.

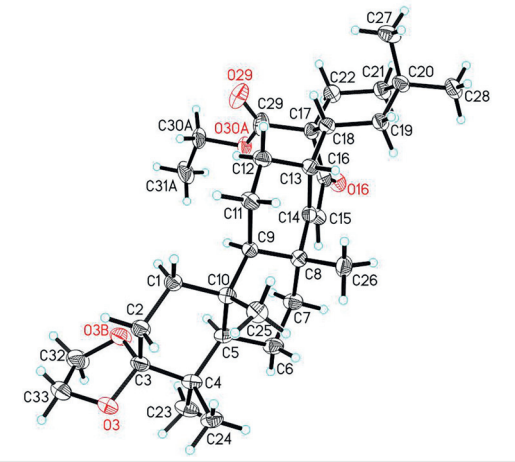


Figure 4 ORTEP drawing of the single-crystal X-ray analysis of compound (+)-**5**; CCDC 1922118. Selected bond lengths (Å) and angles (°): C5–C10 1.562(2), C8–C9 1.564(2), C9–C10 1.560(2), C8–C14 1.528(2), C14–C15 1.340(2), C15–C16 1.462(3), C16–C17 1.534(2), C17–C29 1.521(3); C2–C3–C4 112.34(15), C3–C4–C5 106.80(13), C7–C8–C14 110.99(14), C13–C14–C15 121.70(16), C15–C16–O16 121.59(16), C15–C16–C17 116.24(14), C22–C17–C29 105.39(15), C16–C17–C29 109.66(15)

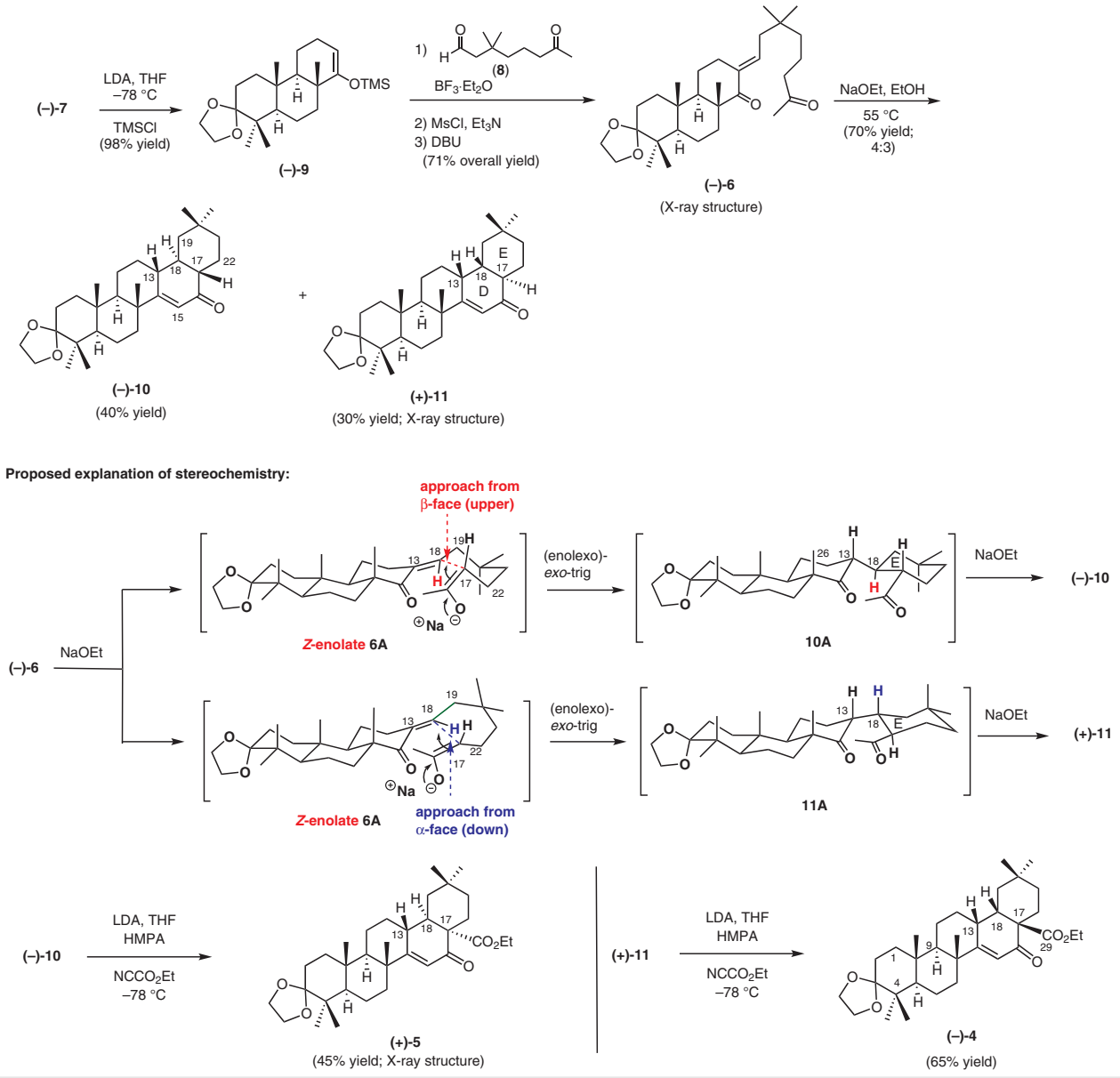
The synthesis of 7-oxooctanal **8** was accomplished by a key 1,4-addition reaction of the cuprate reagent derived from 5-bromo-4,4,-dimethylpentene (**13**) with methyl vinyl ketone. Bromide **13** was generated from 2,2-dimethyl-4-pentenal (**12**), the preparation of which was readily achieved via a reported Claisen rearrangement procedure[27]

(Scheme 3). Hence, condensation of allyl alcohol and isobutyraldehyde in the presence of 1% of *p*-toluenesulfonic acid (TsOH) in mesitylene at 220 °C gave a 90% yield of aldehyde **12**. This aldehyde was reduced with sodium borohydride in methanol at 25 °C followed by bromination with triphenylphosphine and bromine in DMF to furnish a 59% overall yield of bromide **13**.[28] For the 1,4-addition reaction, attempted generation of the required organometallic reagent from bromide **13** with *t*-BuLi, *n*-BuLi, or magnesium turnings under various reaction conditions failed.[28] The required Grignard reagent, 2,2-dimethyl-4-pentenylmagnesium bromide, was eventually prepared from **13** by using activated magnesium metal. The activated magnesium was prepared by following a reported method,[29] involving treatment of magnesium turnings with a catalytic amount of anthracene and 1,2-dibromoethane (2.5 mol% each) in THF. Treatment of this Grignard reagent with cuprous iodide–dimethyl sulfide complex in a mixture of dimethyl sulfide and diethyl ether at –20 °C followed by methyl vinyl ketone afforded a 57% yield of alkenone **14**. The conversion of **14** into 7-oxooctanal **8** (56% yield) was performed by oxidative cleavage of the alkene function of **14** with a catalytic amount of osmium tetroxide and sodium periodate in a mixture of 1,4-dioxane and water.

Table 1 Formulas, Crystal Data, Methods of Collection and Methods of Structure Solution and Refinement of the X-ray Structures of (–)-**6**, (+)-**11**, and (+)-**5**

Molecule	(–)-**6**	(+)-**11**	(+)-**5**
Formula	$C_{30}H_{48}O_4$	$C_{30}H_{46}O_3$	$C_{33}H_{50}O_5$
Fw	472.68	454.67	526.73
T (K)	200(2)	120(2)	120(2)
λ (Å)	1.54178	0.71073	0.71073
Crystal system	monoclinic	monoclinic	monoclinic
Space group	*C*2 (No. 14)	$P2_1$ (No. 4)	$P2_1$ (No. 4)
a (Å)	39.1723(14)	6.1638(15)	6.9861(6)
b (Å)	6.1227(2)	25.051(6)	18.3571(16)
c (Å)	35.5409(13)	16.398(4)	11.4738(10)
α (deg)	90	90	90
β (°)	105.5786(14)	100.462(14)	100.925(4)
γ (°)	90	90	90
V (Å^3)	8211.0(5)	2489.9(11)	1444.8(2)
Z	12 (molecules)	4 (molecules)	2 (molecules)
Diffractometer	Bruker Platinum 135; Cu rotating anode/optical mirrors	Bruker APEX II; Mo sealed tube/monochromator	Bruker APEX II; Mo sealed tube/monochromator
d_{calcd} (mg/m^3)	1.147	1.213	1.211
absorption coefficient (mm^{-1})	0.576	0.076	0.079
F(000)	3120	1000	576
2θ range (°)	2.34–68.48	1.50–30.14	2.12–30.99
reflections collected	30565	22870	12501
independent reflections/R_{int}	10714/0.049	12174/0.104	4320/0.021
% completeness /θ (°)	99.2/66.00	99.8/25.24	98.1/25.00
absorption correction	multi-scan	multi-scan	multi-scan
max, min transmission	1.000, 0.711	1.000, 0.607	1.000, 0.983
least squares refinement method	full matrix on F^2	full matrix on F^2	full matrix on F^2
data/restraints/parameters	10714/47/925	12174/1/608	4320/1/361
GOF (on F^2)	1.085	1.012	1.025
data observed ($I > 2\sigma$)	1628	5174	3975
R_1(obsd); wR_2(all)[a]	0.077; 0.245	0.094; 0.241	0.039; 0.105
max/min residual electron density (e$^-$/Å^3)	0.50/–0.41	0.39/–0.38	0.27/–0.17

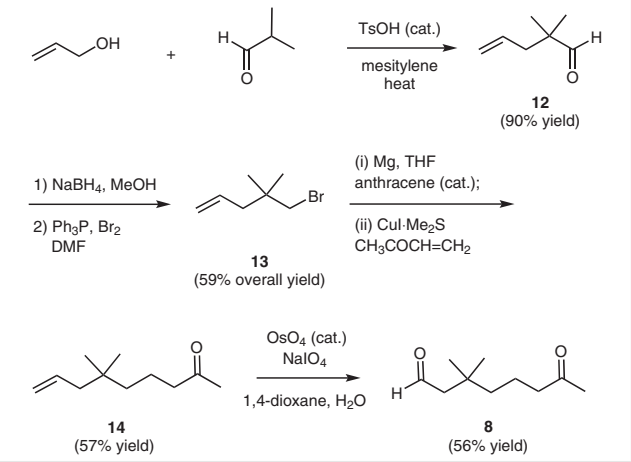
[a] $R_1 = \Sigma ||F_0| - |F_c|| / \Sigma |F_0|$; $wR_2 = \{\Sigma[w(F_0^2 - F_c^2)^2] / \Sigma[w(F_0^2)^2]\}^{1/2}$



Scheme 2 Synthesis of pentacyclic terpenes (–)-**4** and (+)-**5**

The single-crystal X-ray structural analyses were carried out on molecules (–)-**6**, (+)-**11**, and (+)-**5**, and their formulas, crystal data, methods of collection, and methods of structure solution and refinement are listed in Table 1.[25] The X-ray structures have been deposited at The Cambridge Crystallographic Data Centre and details of the data collection and structural solutions and refinement are described in the Supporting Information. Selected bond lengths and angles are summarized in Figures 2–4. The single-crystal X-ray analyses confirm the structural assignments of the three molecules.

In summary, a facile synthesis of chiral pentacyclic terpenes, possessing seven asymmetric centers and four functional groups, from a chiral tricyclic terpene has been accomplished in six steps and involving a tandem intramolecular Michael–aldol condensation reaction. Two stereoisomers at carbons 17 and 18 are produced in the initial Michael addition reaction, likely due to the addition of *Z*-enolate **6A** onto the enone moiety from both the β- and α-faces. Subsequent protonation of the resulting cyclic enolate ion from the β-face is stereoselective. The C3-cyclic acetonide protecting group can be removed to prepare ketone or alcohol derivatives, and stereoselective introduction of a



Scheme 3 Synthesis of 3,3-dimethyl-7-oxooctanal (**8**)

substituent, such as a cyano group, onto C14 (from the α-face) of (–)-**4** and (+)-**5** is possible.[17] Hence, the synthesized chiral pentacyclic terpenes may be converted into various bioactive natural products.

Chemicals were purchased from Fisher Scientific, VWR international LLC, and Chem-Impex International, Inc. All solvents were dried over appropriate drying agents, for example, CaH_2 (for DMF, dichloromethane, and acetonitrile) and Na/benzophenone (for THF and diethyl ether), followed by distillation. Column chromatography was carried out on silica gel (200–400 mesh; from Natland International Co., Research Triangle Park, NC). Melting points were determined using a Thomas Hoover Uni-melt apparatus. Specific rotations were recorded using a Perkin-Elmer model 241 polarimeter. ^{1}H NMR (400 MHz) and ^{13}C NMR spectra (100 MHz) were recorded on a Varian Unity plus 400-MHz spectrometer or a Bruker Avance Neo 400-MHz NMR spectrometer, and measured from a solution in $CDCl_3$ unless otherwise mentioned. The chemical shift data for each signal are given in units of δ relative to TMS (δ = 0) or $CHCl_3$ (δ = 7.26) for ^{1}H NMR spectra and relative to $CDCl_3$ (δ = 77.0) for ^{13}C NMR spectra. Mass spectra were obtained using an API 2000-triple quadrupole ESI-MS/MS mass spectrometer (Applied Biosystems). High-resolution mass spectra were obtained using an LCT Premier (Waters Corp., Milford MA) time-of-flight mass spectrometer. The instrument was operated at 10,000 resolution (W mode) with dynamic range enhancement that attenuates large intensity signals. Mass correction for exact mass determinations was made automatically with the lock mass feature in the MassLynx data system. A reference compound in an auxiliary sprayer is sampled every third cycle by toggling a 'shutter' between the analysis and reference needles. The reference mass is used for a linear mass correction of the analytical cycles. Single-crystal X-ray structures were obtained using a Siemens SMART 1000 low-temperature (LT-2A) single-crystal X-ray diffractometer and a Bruker MicroStar microfocus rotating anode operating at 45 kV and 60 mA, and equipped with Helios high-brilliance multilayer X-ray optics.

(–)-Trimethyl{(4a′*R*,8a′*R*)-1′,1′,4a′,8a′-tetramethyl-3′,4′,4a′,4b′,5′,6′,8a′,9′,10′,10a′-decahydro-1′*H*-spiro[[1,3]-dioxolane-2,2′-phenanthrene]-8′-yloxy}silane [(–)-9]

Trimethylsilyl chloride (TMSCl) was distilled over CaH_2 and then mixed with distilled Et_3N (in a ratio of 7:1 for TMSCl and Et_3N). The resulting suspension was centrifuged for 10 min and the clear supernatant was used for the silylation reaction. To a cold (–78 °C) solution of diisopropylamine (50 μL, 0.35 mmol) in dry THF (1.5 mL) under argon was added *n*-BuLi (0.21 mL, 1.6 M in hexane, 0.33 mmol) and the solution was stirred for 30 min. To a cold (–78 °C) solution of (–)-**7** (0.10 g, 0.33 mmol, >98% ee)[17] in THF (2 mL) under argon was added the above LDA solution via cannula. The solution was stirred at 25 °C for 2 h, cooled to –78 °C. TMSCl (0.14 mL, 1 mmol) was added and the mixture was stirred at –78 °C for 30 min. The reaction solution was diluted with 5% aqueous NH_4OH solution (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layer was washed with water and brine, dried (anhydrous Na_2SO_4), concentrated, and column chromatographed on silica gel using a mixture of hexane, dichloromethane and diethyl ether (5:3:1) as eluent to give pure (–)-**9**.

Yield: 0.11 g (98%); viscous oil; $[\alpha]_D^{25}$ = –32 (*c* 0.55, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.52–4.50 (m, 1 H, =CH), 3.98–3.87 (m, 4 H, 2 CH_2O), 2.06–1.78 (m, 4 H), 1.67–1.11 (m, 10 H), 1.05 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3), 0.88 (s, 3 H, CH_3), 0.83 (s, 3 H, CH_3), 0.15 (s, 9 H, $SiMe_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 113.6, 100.0, 65.1 (2 C), 55.9, 53.8, 42.5, 39.6, 37.1 (2 C), 36.9, 27.1, 24.9, 23.1, 20.9, 20.0, 18.5, 17.9, 16.7, 0.6 (3 C).

MS (EI): *m*/*z* (%) = 415.1 (100) $[M + Na]^+$.

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{40}NaO_3Si$: 415.2639; found: 415.2643.

2,2-Dimethylpent-4-enal (12)[27]

To a round-bottom flask equipped with a Vigreux column (30 cm length), a Dean–Stark apparatus, and a reflux condenser, were added allyl alcohol (21.7 g, 0.375 mol), isobutyraldehyde (40.5 g, 0.56 mol), *p*-toluenesulfonic acid (0.125 g, 6.5 mmol) and mesitylene (70 mL). The solution was stirred and heated at 220 °C for 48 h, and during this time water was collected in the Dean–Stark apparatus. The solution was cooled to 25 °C and distilled under normal pressure to give aldehyde **12**.

Yield: 40 g (90%); colorless liquid; bp 124–125 °C/760 mm (Lit.[27] 124–126 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.50 (s, 1 H, CHO), 5.77–5.67 (m, 1 H, =CH), 5.11–5.06 (m, 2 H, $=CH_2$), 2.23 (d, *J* = 7.6 Hz, 2 H, CH_2), 1.07 (s, 6 H, 2 CH_3).

The spectral data are in agreement with those reported.[27]

2,2-Dimethylpent-4-en-1-ol

To a solution of aldehyde **12** (40.0 g, 0.35 mol) in MeOH (400 mL) was added a solution of sodium borohydride (4.8 g, 0.13 mol) in 0.2 M aqueous NaOH (60 mL) slowly over 30 min. The resulting solution was stirred at 25 °C for 10 h, concentrated on a rotary evaporator, diluted with aqueous 10% NH_4Cl solution (50 mL), and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a mixture of hexane and diethyl ether (1:1) as eluent to give 2,2-dimethylpent-4-en-1-ol

Yield: 38 g (90%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.94–5.82 (m, 1 H, =CH), 5.07–5.04 (m, 2 H, $=CH_2$), 3.34 (s, 2 H, CH_2O), 2.03 (d, *J* = 8.0 Hz, 2 H, CH_2), 0.89 (s, 6 H, 2 CH_3).

The spectral data are in agreement with those reported.[24]

5-Bromo-4,4-dimethylpentene (13)[28]

To a solution of triphenylphosphine (12.0 g, 45.9 mmol) in DMF (30 mL) under argon was added bromine (7.7 g, 48.8 mmol) and the resulting mixture was stirred for 30 min. A solution of 2,2-dimethyl-4-penten-1-ol (5.0 g, 43.8 mmol) in DMF (30 mL) was added slowly and the resulting black solution was heated at 130 °C for 2 h, cooled to 25 °C, and diluted with water (70 mL). The mixture was extracted with pentane (3 × 100 mL), and the combined organic layer was washed with water and brine, and dried ($MgSO_4$). The pentane solvent was distilled off under normal pressure and the residue was distilled at 180 °C to give bromide **13** with a pleasant odor.

Yield: 4.5 g (65%); colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.83–5.72 (m, 1 H, =CH), 5.12–5.07 (m, 2 H, $=CH_2$), 3.28 (s, 2 H, CH_2Br), 2.11 (d, *J* = 7.4 Hz, 2 H, CH_2), 1.02 (s, 6 H, 2 CH_3).

The spectral data are in agreement with those reported.[28]

6,6-Dimethyl-8-nonen-2-one (14)

Activation of magnesium: magnesium turnings were washed with 1 N HCl solution several times until a shiny surface appeared, and then washed with (i) distilled water several times to remove HCl, (ii) methanol, and (iii) diethyl ether. The resulting magnesium was dried under vacuum for 1 h at 50 °C to give activated magnesium. To a mixture of activated magnesium (7.0 g, 0.23 mol) and anthracene (1.0 g, 5.6 mmol) in dry THF (100 mL) under argon was added 1,2-dibromoethane (0.5 mL, 5.7 mmol), and the mixture was stirred under reflux for 5 min. After cooling to 25 °C, the mixture was stirred for 14 h to give a green-orange colored mixture (a green color appeared after stirring for 1 h). To this solution was added 5-bromo-4,4-dimethylpentene (**13**) (1.0 g, 5.7 mmol) and the mixture was heated under reflux with a heat gun. Subsequently, additional bromide **13** (7.0 g, 39.8 mmol) was added slowly via a syringe to maintain a gentle reflux of the THF. After completion of the addition of **13**, the mixture was stirred at 25 °C for 30 min, heated at reflux for 2 h, and then cooled to 25 °C to give a black-colored Grignard reagent. To a three-neck flask equipped with a thermometer were added cuprous iodide–dimethyl sulfide complex (CuI·Me_2S), (5.75 g, 27.8 mmol), dimethyl sulfide (15 mL) and dry diethyl ether (20 mL) under argon. The mixture was cooled to –40 °C and the aforementioned Grignard reagent was added via a cannula slowly to maintain the temperature below –30 °C. The mixture was stirred for 40 min at –20 °C, cooled to –40 °C and treated with a solution of methyl vinyl ketone (1.4 g, 26.1 mmol) in diethyl ether (3 mL). The mixture was stirred for 2 h at 10 °C, diluted with a mixture of aqueous NH_4Cl and NH_4OH (200 mL, 4:1) and stirred for 10 min. The resulting blue solution was extracted with diethyl ether (4 × 50 mL) and the combined organic layers were washed twice with 10% aqueous NH_4OH, water, and brine, dried ($MgSO_4$), and distilled under normal pressure to remove diethyl ether and THF. The residue was column chromatographed on silica gel using a mixture of hexane and diethyl ether (15:1) as eluent to give ketone **14**.

Yield: 1.6 g (57%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.84–5.73 (m, 1 H, =CH), 5.01–4.94 (m, 2 H, $=CH_2$), 2.38 (t, *J* = 7.6 Hz, 2 H, $COCH_2$), 2.12 (s, 3 H, $COCH_3$), 1.94 (d, *J* = 7.6 Hz, 2 H, CH_2C=), 1.58–1.49 (m, 2 H), 1.16–1.12 (m, 2 H), 0.85 (s, 6 H, 2 CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.4, 135.8, 116.9, 46.5, 44.7, 41.5, 33.3, 30.1, 27.1 (2 C, *gem*-dimethyl), 18.7.

MS (EI): *m*/*z* (%) = 191.2 (80) $[M + Na]^+$.

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{20}NaO$: 191.1406; found: 191.1410.

3,3-Dimethyl-7-oxooctanal (8)

To a solution of ketone **14** (1.0 g, 6.0 mmol) in 1,4-dioxane (30 mL) and H_2O (6 mL) at 25 °C was added OsO_4 (12 mg, 0.06 mmol). The solution was stirred for 40 min to give a dark brown mixture. Sodium periodate (2.5 g, 12 mmol) was added in portions over 20 min, and the resulting solution was stirred at 25 °C for 4 h, diluted with water (50 mL), and extracted with diethyl ether (4 × 40 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$), and distilled under normal pressure to remove diethyl ether and most of the 1,4-dioxane. The crude product was purified by silica gel column chromatography using a mixture of hexane and diethyl ether (1:1) as eluent to give aldehyde **8**.

Yield: 0.52 g (56%); light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.83 (t, *J* = 3.2 Hz, 1 H, CHO), 2.42 (t, *J* = 6.8 Hz, 2 H, $COCH_2$), 2.27 (d, *J* = 3.2 Hz, 2 H, CH_2CHO), 2.13 (s, 3 H, $COCH_3$), 1.61–1.53 (m, 2 H), 1.32–1.27 (m, 2 H), 1.05 (s, 6 H, 2 CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.9, 203.8, 54.8, 44.2, 42.2, 33.7, 30.0, 27.6 (2 C, *gem*-dimethyl), 18.5.

MS (EI): *m*/*z* (%) = 193.2 (40) $[M + Na]^+$.

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_{18}NaO_2$: 193.1204; found: 193.1211.

(–)-(4a′*S*,8a′*R*,*E*)-7′-(3,3-Dimethyl-7-oxooctylidene)-1′,1′,4a′,8a′-tetramethyldecahydro-1′*H*-spiro[[1,3]dioxolane-2,2′-phenanthren]-8′(3′*H*)-one [(–)-6]

To a solution of compound (–)-**9** (0.50 g, 1.1 mmol) and aldehyde **8** (0.23 g, 1.3 mmol) in dichloromethane (25 mL) under argon at –78 °C was added BF_3·Et_2O (0.34 mL, 2.7 mmol). The solution was stirred at –78 °C for 5 h, diluted with saturated aqueous $NaHCO_3$ (5 mL) and water (20 mL), warmed to 25 °C, and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as eluent to give tricyclic ketone (–)-**7** (30 mg, 9% recovery) and a mixture of aldol products (0.43 g) (stereoisomers at C13 and C18), which was used in the subsequent dehydration reaction directly. To a cold (0 °C) solution of the aforementioned aldol products (0.43 g, 0.91 mmol) and Et_3N (1.3 mL, 8.1 mmol) in dried diethyl ether (30 mL) under argon was added methanesulfonyl chloride (0.34 g, 3 mmol). The solution was stirred at 25 °C for 14 h, diluted with 5% aqueous NH_4Cl solution (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with 10% aqueous $NaHCO_3$, water and brine, dried (anhydrous Na_2SO_4), and concentrated to dryness under vacuum. The residue was dissolved in a mixture of dichloromethane and toluene (20 mL, 1:1) under argon and treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.28 g, 1.82 mmol) at 25 °C. The resulting solution was stirred for 15 h, diluted with aqueous NH_4Cl, and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a mixture of hexane, dichloromethane and ether (5:3:1) as eluent to give tricycle (–)-**6**.

Yield: 0.35 g (83% overall); white solid; mp 81.5–83.0 °C; $[\alpha]_D^{25}$ = –32.5 (*c* 0.385, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.39 (t, *J* = 5.6 Hz, 1 H, =CH), 3.99–3.85 (m, 4 H, 2 OCH_2), 2.77 (dd, *J* = 15.6, 5.6 Hz, 1 H), 2.39 (t, *J* = 7.6 Hz, 2 H), 2.13 (s, 3 H, $COCH_3$), 2.12–1.62 (m, 9 H), 1.58–1.16 (m, 10 H), 1.05 (s, 3 H, CH_3), 0.95 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3), 0.89 (s, 6 H, 2 CH_3), 0.85 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.4, 208.0, 137.1, 135.2, 113.2, 65.12, 65.11, 54.2, 53.1, 47.8, 44.6, 42.4, 41.7, 39.9, 38.0, 36.9, 35.9, 34.4, 30.2, 27.23, 27.19, 27.0, 26.8, 23.1, 20.1 (2 C), 19.1, 18.7, 18.3, 16.7.

MS (EI): *m*/*z* (%) = 495.3 (70) $[M + Na]^+$.

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{30}H_{48}NaO_4$: 495.3450; found: 495.3481.

The product was crystallized from diethyl ether to give single crystals and the structure was verified by X-ray analysis.

(–)-(6a′*R*,8a′*S*,12a′*R*,12b′*R*,14b′*R*)-4′,4′,6a′,11′,11′,14b′-Hexamethyl-4′,4a′,5′,6′,6a′,8a′,9′,10′,11′,12′,12a′,12b′,13′,14′,14a′,14b′-hexadecahydro-1′*H*-spiro[[1,3]dioxolane-2,3′-picen]-8′(2′*H*)-one [(–)-10] and (+)-(6a′*R*,8a′*R*,12a′*S*,12b′*R*,14b′*R*)-4′,4′,6a′,11′,11′,14b′-Hexamethyl-4′,4a′,5′,6′,6a′,8a′,9′,10′,11′,12′,12a′,12b′,13′,14′,14a′,14b′-hexadecahydro-1′*H*-spiro[[1,3]dioxolane-2,3′-picen]-8′(2′*H*)-one [(+)-11]

To a solution of distilled ethanol (5 mL) under argon at 25 °C was added sodium (11 mg, 0.46 mmol) and the resulting solution was stirred for 10 min until all the sodium metal had dissolved. To a solution of (–)-**6** (0.11 g, 0.23 mmol) in distilled ethanol (40 mL) under argon was added the above sodium ethoxide solution via cannula. The resulting yellow solution was stirred at 55 °C for 14 h, cooled to 25 °C, neutralized with acetic acid, and concentrated under vacuum to remove ethanol and water. The residue was diluted with water and extracted with ethyl acetate (3 × 30 mL). The combined organic layer washed with water and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a mixture of hexane, dichloromethane and diethyl ether (7.5:3:1) as eluent to give products (–)-**10** and (+)-**11**.

Compound (–)-10 (Less Polar Product)

Yield: 45 mg (40%); white solid; mp 203.0–205.0 °C; $[\alpha]_D^{25}$ = –34.0 (*c* 0.15, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.81 (d, *J* = 2.0 Hz, 1 H, =CH), 3.98–3.87 (m, 4 H, 2 OCH_2), 2.33–2.25 (m, 1 H), 2.17–2.09 (m 1 H), 2.02 (ddd, *J* = 15.6, 8.4, 4.4 Hz, 1 H), 1.87–1.57 (m, 5 H), 1.52–1.29 (m, 9 H), 1.26–1.09 (m, 6 H), 1.09 (s, 3 H, CH_3), 0.94 (s, 3 H, CH_3), 0.93 (s, 6 H, 2 CH_3), 0.86 (s, 6 H, 2 CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.9, 174.7, 119.5, 113.2, 65.1 (2 C), 56.7, 53.3, 48.5, 44.4, 42.3, 41.2, 41.1, 40.5, 38.8, 38.1, 37.9, 37.0, 33.4, 32.8, 30.6, 27.1, 24.8, 23.1, 23.0, 21.5, 20.4, 20.1, 18.7, 16.6.

MS (EI): *m*/*z* (%) = 477.3 $[M + Na]^+$.

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{30}H_{46}NaO_3$: 477.3345; found: 477.3360.

Compound (+)-11 (More Polar Product)

Yield: 35 mg (30%); white solid; mp 201.0–203.5 °C; $[\alpha]_D^{25}$ = +222.5 (*c* 0.19, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.75 (s, 1 H, =CH), 4.02–3.84 (m, 4 H, 2 OCH_2), 2.37 (dt, *J* = 13.2, 4.4 Hz, 1 H), 2.09–1.61 (m, 6 H), 1.58–1.17 (m, 12 H), 1.14–0.98 (m, 4 H), 1.13 (s, 3 H, CH_3), 0.94 (s, 9 H, 3 CH_3), 0.87 (s, 3 H, CH_3), 0.84 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.7, 176.6, 118.1, 113.1, 65.08, 65.02, 59.7, 53.7, 44.0, 43.2, 42.3, 41.9, 39.3, 38.38, 38.35, 37.9, 37.1, 36.7, 33.5, 30.6, 28.0, 27.0, 24.2, 23.1, 22.0, 21.5, 20.7, 20.1, 18.6, 16.2.

MS (EI): *m*/*z* (%) = 477.4 (60) $[M + Na]^+$.

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{30}H_{46}NaO_3$: 477.3345; found: 477.3359.

Compound (+)-**11** was crystallized from a mixture of diethyl ether and hexane (1:1) to give single crystals and the structure was solved by X-ray analysis.

(+)-(6a′*R*,8a′*S*,12a′*R*,12b′*R*,14b′*R*)-Ethyl 4′,4′,6a′,11′,11′,14b′-Hexamethyl-8′-oxo-2′,4′,4a′,5′,6′,6a′,8′,8a′,9′,10′,11′,12′,12a′,12b′,13′,14′,14a′,14b′-octadecahydro-1′*H*-spiro[[1,3]dioxolane-2,3′-picene]-8a′-carboxylate [(+)-5]

[LDA was prepared by following the procedure described in the synthesis (–)-**9** and was titrated prior to use]. To a cold (–78 °C) solution of (–)-**10** (0.173 g, 0.38 mmol) in THF (2 mL) under argon was added a solution of LDA (0.57 mmol) in THF (1 mL) by syringe. The resulting solution was stirred at –78 °C for 1 h, HMPA (0.102 g, 0.57 mmol) was added and the mixture was stirred for 15 min. Next, ethyl cyanoformate (75 mg, 0.76 mmol) was added and the mixture was stirred for 30 min. The reaction mixture was diluted with aqueous NH_4Cl solution and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a mixture of hexane, dichloromethane and diethyl ether (8:3:1) as eluent to give pure (+)-**5**.

Yield: 90 mg (45%); white solid; mp 153–155 °C; $[\alpha]_D^{25}$ = 91.3 (*c* 0.425, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.79 (s, 1 H, =CH), 4.16–4.06 (m, 2 H, CO_2CH_2), 3.95–3.84 (m, 4 H, 2 OCH_2), 2.54 (dd, *J* = 12.8, 4.4 Hz, 1 H), 2.34 (ddd, *J* = 13.6, 7.2, 3.2 Hz, 1 H), 2.15 (dd, *J* = 13.6, 3.6 Hz, 1 H), 1.92 (d, *J* = 12.0 Hz, 1 H), 1.80 (td, *J* = 13.6, 3.2 Hz, 2 H), 1.71–1.57 (m, 5 H), 1.51–1.28 (m, 6 H), 1.24 (t, *J* = 7.6 Hz, 3 H, $CH_3CH_2O_2C$), 1.18–1.10 (m, 5 H), 1.08 (s, 3 H, CH_3), 0.98 (s, 3 H, CH_3), 0.94 (s, 3 H, CH_3), 0.92 (s, 3 H, CH_3), 0.85 (s, 3 H, CH_3), 0.83 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.2, 174.6, 172.3, 117.8, 113.2, 65.2 (2 C), 61.4, 58.6, 55.6, 53.6, 43.6, 42.9, 42.4, 41.4, 39.5, 38.3, 38.1, 37.1, 34.96, 34.95, 32.9, 30.6, 27.5, 27.1, 24.6, 23.2, 22.0, 21.3, 20.2, 18.7, 16.4, 14.3.

MS (EI): *m*/*z* (%) = 549.4 (100) $[M + Na]^+$.

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{50}NaO_5$: 549.3556; found: 549.3559.

The product was crystallized from a mixture of diethyl ether and hexane (1:1) to give single crystals and the structure was solved by X-ray analysis.

(–)-(6a′*R*,8a′*R*,12a′*S*,12b′*R*,14b′*R*)-Ethyl 4′,4′,6a′,11′,11′,14b′-Hexamethyl-8′-oxo-2′,4′,4a′,5′,6′,6a′,8′,8a′,9′,10′,11′,12′,12a′,12b′,13′,14′,14a′,14b′-octadecahydro-1′*H*-spiro[[1,3]dioxolane-2,3′-picene]-8a′-carboxylate [(–)-4]

To a cold (–78 °C) solution of (+)-**11** (40 mg, 0.088 mmol) in dried diethyl ether (1 mL) under argon was added freshly prepared LDA (0.12 mmol) in diethyl ether (1 mL), and the solution was stirred at –78 °C for 1 h. HMPA (24 mg, 0.12 mmol) was added and the mixture was stirred at –78 °C for 15 min. Next, ethyl cyanoformate (18 mg, 0.17 mmol) added and the mixture was for 30 min. The reaction mixture was diluted with aqueous NH_4Cl solution and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with

water and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a mixture of hexane, dichloromethane and diethyl ether (6:3:1) as eluent to give pure (–)-**4**.

Yield: 30 mg (65%); white solid; mp 205–207 °C; $[\alpha]_D^{25}$ = –62.8 (*c* 0.20, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.88 (d, *J* = 2.4 Hz, 1 H, =CH), 4.16–4.05 (m, 2 H, CO_2CH_2), 3.96–3.86 (m, 4 H, 2 OCH_2), 2.89–2.82 (m, 1 H), 2.59 (dt, *J* = 14.0, 4.4 Hz, 1 H), 2.35 (dt, *J* = 13.2, 2.8 Hz, 1 H), 1.90–1.78 (m, 2 H), 1.74–1.60 (m, 4 H), 1.50–1.40 (m, 5 H), 1.33–1.23 (m, 8 H), 1.19 (t, *J* = 7.6 Hz, 3 H, $CH_3CH_2O_2C$), 1.05 (s, 3 H, CH_3), 0.93 (s, 6 H, 2 CH_3), 0.91 (s, 3 H, CH_3), 0.85 (s, 6 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.1, 173.3, 172.4, 120.4, 113.4, 65.2 (2 C), 61.4, 58.3, 57.0, 53.2, 42.4, 42.3, 38.7, 38.2, 37.9, 37.1, 36.1, 35.6, 34.7, 33.4, 31.0, 30.4, 27.13, 27.05, 24.8, 23.8, 23.0, 20.5, 20.0, 18.6, 16.8, 14.4.

MS (EI): *m*/*z* (%) = 549.4 (80) $[M + Na]^+$.

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{50}NaO_5$: 549.3556; found: 549.3552.

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Supporting Information

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