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

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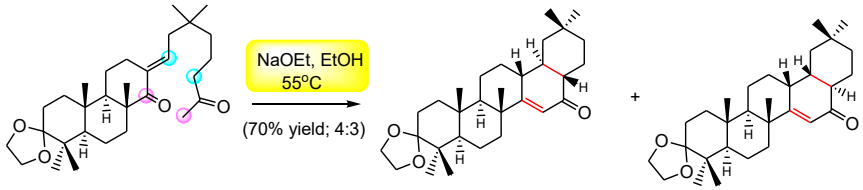


Received:
Accepted:
Published online:
DOI:

Abstract Chiral tricyclic terpene (-)-**6**, possessing a 6,6,6-membered framework and a 3,3-dimethyl-7-oxooctylidenyl side chain, underwent a double ring-closing reaction to give chiral pentacyclic terpenes (-)-**10** and (+)-**11** in a ratio of 4:3, involving an intramolecular Michael addition followed by aldol condensation reaction under basic conditions. Three new stereogenic centers were introduced in the initial Michael annulation reaction. Stereoselective installation of an ethoxycarbonyl group at C17 of (-)-**10** and (+)-**11** separately gave respective (+)-**5** and (-)-**4**, providing highly functionalized pentacyclic terpenoids with seven stereogenic centers. The structures and stereochemistry of (-)-**6** and (+)-**11** were established by single-crystal X-ray analyses, while that of (-)-**10** was through the x-ray analysis of (+)-**5**. 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 reaction.

Introduction

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 has been 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] antiobesity,[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, anti-tumor-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 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 may be used in the study of hypertension and vascular spasm.[10,16] 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 a retrosynthetic analysis (Figure 2). Keto-enone (-)-**6** could be made 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 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 Michael-aldol ring closing reactions of cyclohexyl keto-enester[18] and enol silyl ether of cyclohexanone tethered with 2-alkenyl esters[19] have been reported under Lewis-acid conditions to construct 4,5,6-tricyclic system and tricycle[4.2.1.0^{3,8}]nonanes, respectively. Tadano et al.[20] reported a four-step sequence of reactions to prepare 5,6,6-tricyclic system from a keto-enester tetrahydrofuran through a Michael addition-reduction-oxidation-aldol process. And, Mischne described a two-step annulation procedure of α,β-enedionyl alkanone under basic conditions to give a 6,6-bicyclic ring system.[21] The reported systems involved ene esters or 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 6,6,6-tricyclic skeleton has not been reported previously.

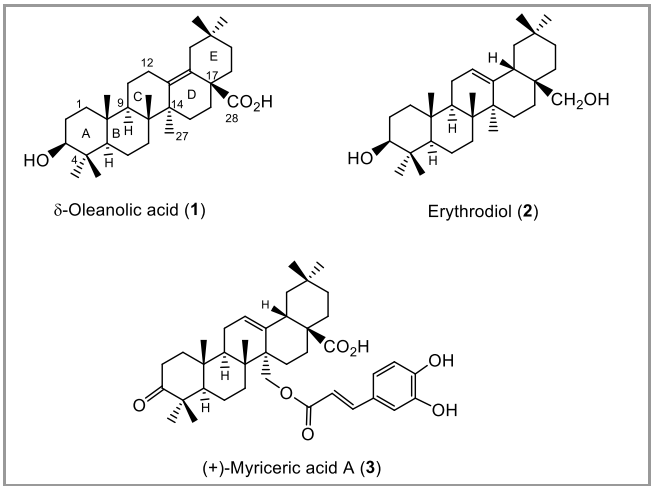


Figure 1 Representative bioactive pentacyclic triterpenoids.

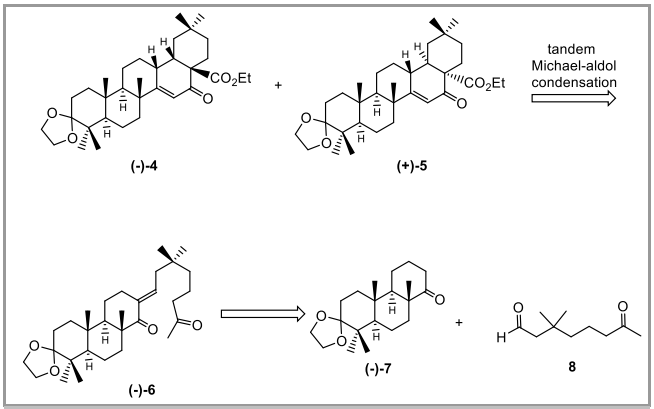
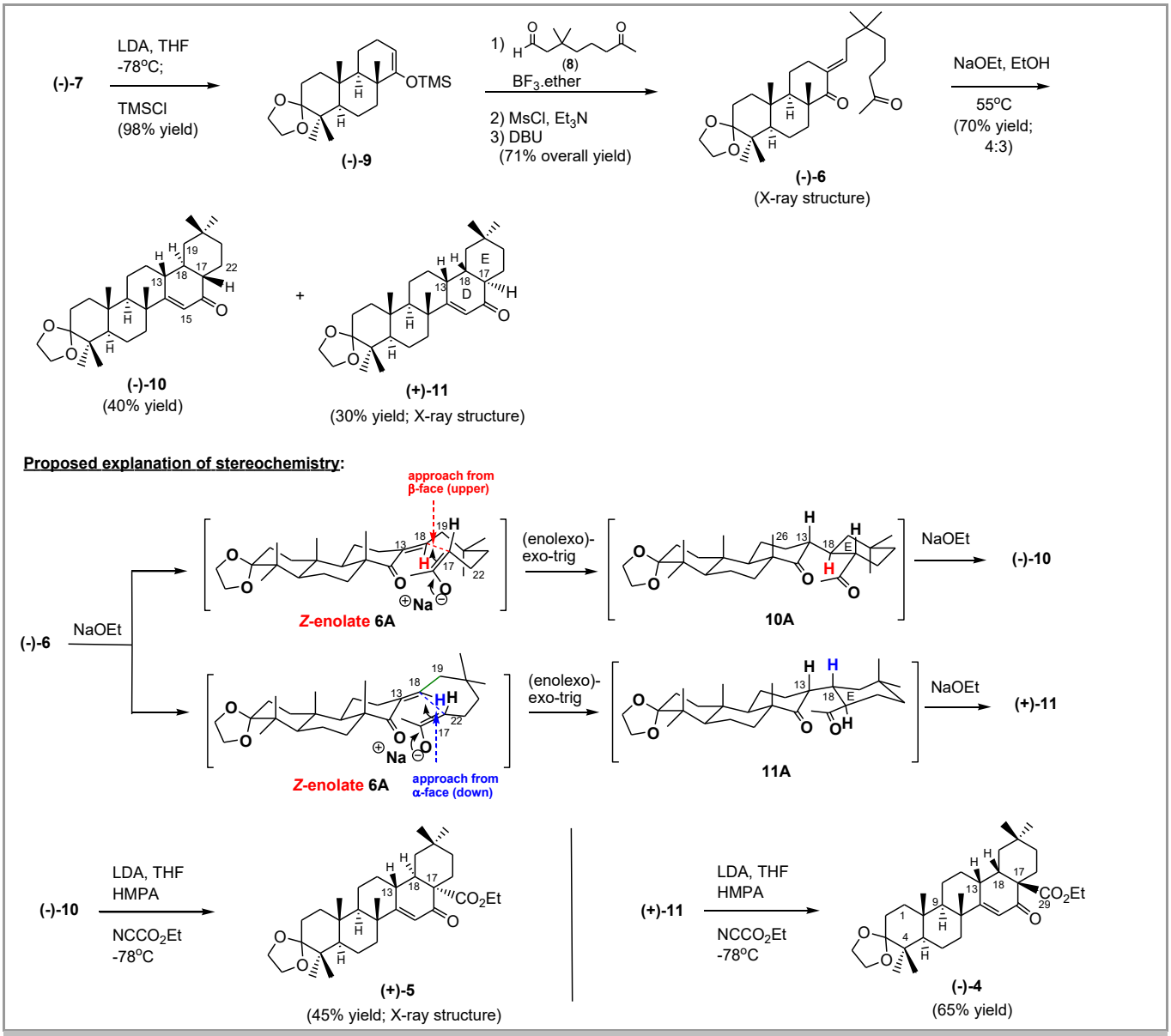


Figure 2 Retrosynthesis of pentacyclic terpenoids *via* a double-intramolecular tandem Michael-aldol annulation reaction.

Results and Discussion

Multiple fused six-membered ring systems often synthesized by intramolecular Diels-Alder reactions[22] and cation-π cyclizations,[23] 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 a 98% yield from the treatment of ketone (-)-**7** with 1.2 equiv. of lithium diisopropylamide (LDA) in THF at -78 °C followed by trimethylsilyl chloride (TMSCl) (Scheme 1). *Exo*-cyclic enone (-)-**6** was made in 71% overall yield by a sequence of reactions: (i) coupling of (-)-**9** and **8** in the presence of 2.5 equiv. of BF_3•ethereal in dichloromethane at -78 °C; (ii) mesylation of the resulting β-hydroxyl 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., *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 3; CCDC 1922116). The one-pot tandem Michael-aldol condensation reaction of (-)-**6** was affected by the treatment with 2 equiv. 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 4; CCDC 1922117), revealing the stereochemistry of newly generated stereogenic centers at C13, 17, and 18. The stereochemistry at C13 and 18 of (-)-**10** were found from the single-crystal X-ray structure of (+)-**5** (*vide infra*) while the stereochemistry at C17 was based on the following assumptions (Scheme 1). 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 Michael addition reaction faster than the corresponding *E*-enolate (Scheme 1). The sodium ion of the enolate solvates by ethanol and a loose or acyclic transition state for the formation of enolate ion results, leading to a greater ratio of *Z*/*E* enolates.[25] The *E*-enolate has a greater repulsion derived from the *cis*-stereochemistry of C15 (methyl) and C22 alkyl substituent than that of *Z*-enolate (due to solvation of the sodium ion). *Z*-Enolate **6A** approaches the enone moiety from the β-face (or upper face) with C17-22 and C18-19 bonds at gauche orientation, providing a stable chair 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 C26 methyl and C18-cyclohexyl ring. Similarly, *Z*-enolate **6A** can approach the enone moiety from the α-face (or down face) with C17-22 and C18-19 bonds at gauche orientation, providing a chair conformation of the E-ring, which subsequently undergoes protonation from 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 a ratio of 4:3 of (-)-**10** and (+)-**11**.

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 ethyl cyanoformate to give a 45% yield of (+)-**5** and 65% yield of (-)-**3**, respectively. The structure of (+)-**5** was firmly determined from a single-crystal X-ray analysis (Figure 5; CCDC 1922118). It appears that cyanoformate reacted with the enolate of (-)-**10** from the α-face, same face as that of C18-hydrogn, resulting in a lesser repulsion from the ethyl ester group with C18-H than C19 alkyl. This produced the *syn*-stereochemistry of C17-CO_2Et and C18-H. Based on this observation, it is assumed that the reaction of 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.



Scheme 1 Synthesis of pentacyclic terpenes (-)-**4** and (+)-**5**.

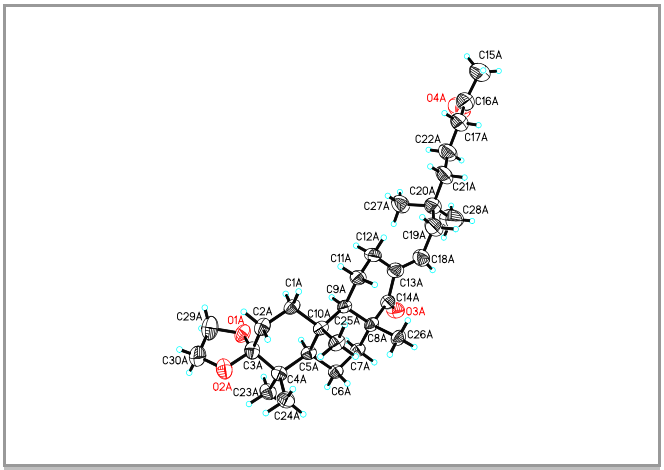


Figure 3 ORTEP drawing of the single-crystal X-ray analysis of compound (-)-**6**; CCDC 1922116. Selected bond lengths (Å) and angles (°): C5-C10 1.554(5), C8-C9 1.574(5), C9-C10 1.561(5), C8-C14 1.530(6), C14-O3 1.216(5), C13-C14 1.503(6), C13-C18 1.343(7), C16-O4 1.230(10); C2-C3-C4 112.8(3), C3-C4-C5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

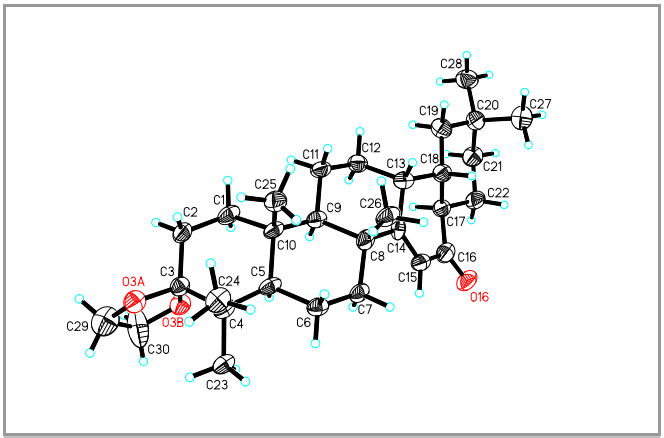


Figure 4 ORTEP drawing of the single-crystal X-ray analysis of compound (+)-**11**; CCDC 1922117. Selected bond lengths (Å) and angles (°): C5-C10 1.548(11), C8-C9 1.574(11), C9-C10 1.553(11), C8-C14 1.513(11), C13-C14 1.494(11), C14-C15 1.543(11), C15-C16 1.448(12), C16-O16

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).

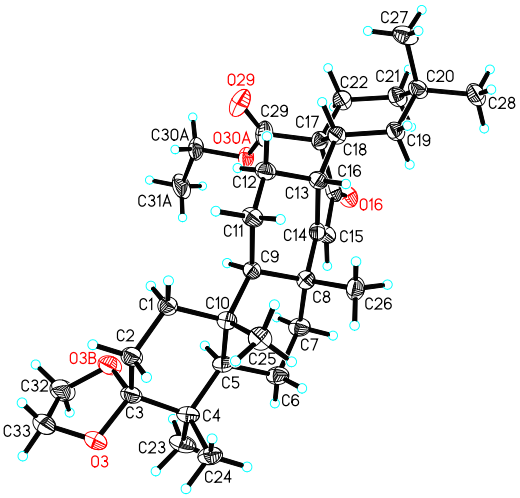
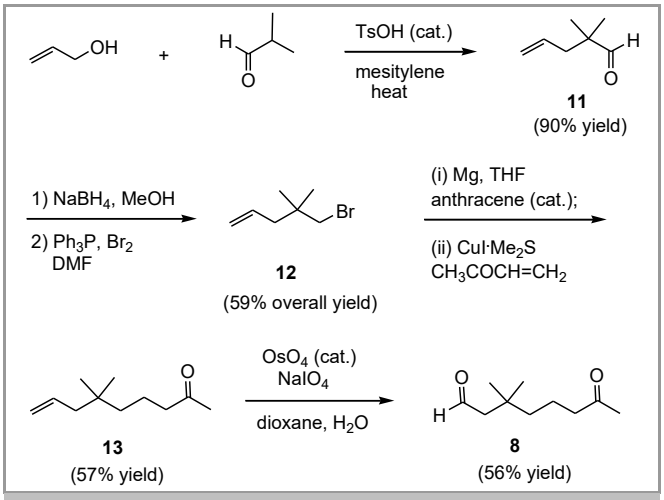


Figure 5 ORTEP drawing of the single-crystal X-ray analysis of compound (+)-**5**; CCDC 1922118. Selected bond lengths (Å) and angles (°): C5-C10 1.562(2), C8-C9 1.564(2), C9-C10 1.560(2), C8-C14 1.528(2), C14-C15 1.340(2), C15-C16 1.462(3), C16-C17 1.534(2), C17-C29 1.521(3); C2-C3-C4 112.34(15), C3-C4-C5 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** generated from 2,2-dimethyl-4-pentenal (**12**), whose preparation was readily available *via* a reported Claisen rearrangement procedure[26] (Scheme 2). 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**. It was reduced with sodium borohydride in methanol at 25 °C followed by bromination with triphenylphosphine and bromine in DMF furnished a 59% overall yield of bromide **13**.[27] For the 1,4-addition reaction, attempted generation of the required organometallic reagent from bromide **13** with *t*-BuLi, *n*-BuLi, or magnesium turning under various reaction conditions failed.[27] The needed Grignard reagent, 2,2-dimethyl-4-pentenylmagnesium bromide, was eventually made successfully from **13** by using an activated magnesium metal. The activated magnesium was prepared by following a reported method[28] through the treatment of magnesium turning with catalytic amounts 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** to 7-oxooctanal **8** (56% yield) was performed by an 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.



Scheme 2 Synthesis of 3,3-dimethyl-7-oxooctanal (**8**).

The single-crystal X-ray structural analyses were carried out on molecules (-)-**6**, (+)-**11**, and (+)-**5**, and their formulas, crystal data, method of collection, and methods of structure solution and refinement are depicted in Table 1. The X-ray structures have been deposited to the Cambridge Crystallographic Data Centre and details for data collection and structural solution and refinement were described in the Supporting Information. Selective bond lengths and angles are summarized in Figures 3 – 5. The single-crystal X-ray analyses confirm the structural assignments of the three molecules.

Table 1 Formulas, crystal data, method of collection, and methods of structure solution and refinement of x-ray structures of (-)-**6**, (+)-**11**, and (+)-**5**.

Molecules	(-)-**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 syst	Monoclinic	Monoclinic	Monoclinic
space group	C2 (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 (deg)	105.5786(14)	100.462(14)	100.925(4)
γ (deg)	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
abs coeff (mm^{-1})	0.576	0.076	0.079
F(000)	3120	1000	576
2θ range (deg)	2.34-68.48	1.50-30.14	2.12-30.99
reflns collected	30565	22870	12501
independent reflections/R_{int}	10714/0.049	12174/0.104	4320/0.021
% completeness /theta(deg)	99.2/66.00	99.8/25.24	98.1/25.00
abs corr	Multi-scan	Multi-scan	Multi-scan

max, min transm	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/ params	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] $R_1 = \Sigma \| |F_0| - |F_d| \| / \Sigma |F_0|$; $wR_2 = \{ \Sigma [w(F_0^2 - F_c^2)^2] / \Sigma [w(F_0^2)^2] \}^{1/2}$

In summary, a facile synthesis of chiral pentacyclic terpenes possessing seven asymmetric centers and four functional groups from a chiral tricyclic terpene was accomplished in six steps involving a tandem intramolecular Michael-aldol condensation reaction. Two stereoisomers at carbons 17 and 18 produced in the initial Michael addition reaction, likely due to the addition of *Z*-enolate **6A** onto the enone moiety from both β- and α-faces. The 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 the ketone or alcohol derivatives, and stereoselective introduction of a substituent, such as a cyano group, onto C14 (from α-face) of (-)-**4** and (+)-**5** are 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 appropriated drying agent such as CaH_2 (for DMF, dichloromethane, and acetonitrile), or Na/benzophenone (for THF and diethyl ether) followed by distillation. Column chromatography was carried out on silica gel (200 - 400 mesh). ^{1}H NMR spectra (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 on ^{1}H NMR are given in units of δ relative to TMS (δ = 0 ppm) or $CHCl_3$ (δ = 7.26 ppm) and on ^{13}C NMR are given in units of δ relative to $CDCl_3$ (δ = 77.0 ppm). Mass spectra were obtained from an API 2000-triple quadrupole ESI-MS/MS mass spectrometer (Applied Biosystems). High-resolution mass spectra were obtained from a 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 from a Siemens SMART 1000 low-temperature (LT-2A) single-crystal X-ray diffractometer and a Bruker MicroStar microfocus rotating anode operating at 45kV 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 the distilled TMSCl was then mixed with distilled Et_3N (in a ratio of 7:1 for TMSCl and Et_3N). The resulting suspension was centrifuged for 10 minutes, and the clear supernatant was used for the silylation reaction. To a cold (-78 °C) solution of 50 μL (0.35 mmol) of diisopropylamine in 1.5 mL dry THF under argon, was added 0.21 mL (0.33 mmol) of *n*-BuLi (1.6 M in hexane) and the solution was stirred for 30 minutes. To a cold (-78 °C) solution of 0.10 g (0.33 mmol) of (-)-**7** (>98% ee)[17] in 2 mL THF under argon was added the above LDA solution via cannula. The solution was stirred at 25 °C for 2 hours and cooled to -78 °C. To it, was added TMSCl (0.14 mL, 1 mmol), and the mixture stirred at -78 °C for 30 minutes. The reaction solution was diluted with 20 mL of 5% aqueous NH_4OH solution and extracted three times with diethyl ether (20 mL each). 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 an eluent to give 0.11 g of pure (-)-**9** (98 % yield).

$[\alpha]_D^{25}$ = -32 (0.55, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.50 – 4.87 (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 (2C), 55.9, 53.8, 42.5, 39.6, 37.1 (2C), 36.9, 27.1, 24.9, 23.1, 20.9, 20.0, 18.5, 17.9, 16.7, 0.6 (3C).

MS (electrospray ionization): 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).[26] To a round-bottom flask equipped with a Vigreux column (30 cm length), a Dean-Stark apparatus, and a reflux condenser, were added 21.7 g (0.375 mol) of allyl alcohol, 40.5 g (0.56 mol) of isobutyraldehyde, 0.125 g (6.5 mmol) of *p*-toluenesulfonic acid, and 70 mL of mesitylene. The solution stirred and heat at 220 °C for 48 h, and during this time water collected on the Dean-Stark apparatus. The solution was cooled to 25 °C and distilled under normal pressure to give 40 g (90 % yield) of **12** as a colorless liquid.

Bp 124 – 125 °C/760 mm (lit.[26] 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 is in agreement with that reported.[26]

2,2-Dimethylpent-4-en-1-ol. To a solution of 40.0 g (0.35 mol) of aldehyde **12** in 400 mL of MeOH, was added a solution of sodium borohydride (4.8 g, 0.13 mol) in 60 mL of 0.2 M aqueous

NaOH solution slowly over 30 minutes. The resulting solution was stirred at 25 °C for 10 h, concentrated on a rotary evaporator, diluted with 50 mL of aqueous 10% NH_4Cl solution, and extracted three times with diethyl ether (100 mL each). The combined organic layers 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 an eluent to give 2,2-dimethylpent-4-en-1-ol as a colorless oil (38 g, 90% yield).

^{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 is in agreement with that reported.[24]

5-Bromo-4,4-dimethylpentene (13).[27] To a solution of 12.0 g (45.9 mmol) of triphenylphosphine in 30 mL of DMF under argon, was added 7.7 g (48.8 mmol) of bromine, and the mixture was stirred for 30 min. To it, a solution of 5.0 g (43.8 mmol) of 2,2-dimethyl-4-pentenol in 30 mL DMF was added slowly. The resulting black solution was heated at 130 °C for 2 h, cooled to 25 °C, and diluted with 70 mL of water. The mixture was extracted three times with pentane (100 mL each), 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 4.5 g (65 % yield) of **13** as a colorless liquid with pleasant odor.

^{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 is in agreement with that reported.[27]

6,6-Dimethyl-8-nonen-2-one (14). Activation of magnesium: magnesium turning was washed with 1*N* HCl solution several times until a shiny surface appeared, 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 7.0 g (0.23 mol) of activated magnesium and 1.0 g (5.6 mmol) of anthracene in 100 mL of dry THF under argon, was added 0.5 mL (5.7 mmol) of 1,2-dibromoethane, and the mixture was stirred under reflux for 5 min. After cooling to 25 °C, the mixture stirred for 14 h to give a green-orange color mixture (a green color showed up after stirring for 1 h). To it was added 1.0 g (5.7 mmol) of 5-bromo-4,4-dimethylpentene (**13**), and the mixture was heated under reflux with a heat gun. Subsequently, 7.0 g (39.8 mmol) of **13** were 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 cooled to 25 °C to give a black-colored Grignard reagent. To a three-neck flask equipped with a thermometer under argon, were added 5.75 g (27.8 mmol) of cuprous iodide-dimethyl sulfide complex (CuI•Me_2S), 15 mL of dimethyl sulfide, and 20 mL of dry diethyl ether. 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 minutes at -20 °C, cooled to -40 °C, and added a solution of 1.4 g (26.1 mmol) of methyl vinyl ketone in 3 mL of diethyl ether. The mixture stirred for 2 h at 10 °C, diluted with a mixture of 200 mL of aqueous NH_4Cl and NH_4OH (4:1), and stirred for 10 minutes. The resulting blue solution was extracted four times with diethyl ether (50 mL each), and the combined organic layers were washed with 10 % aqueous NH_4OH twice, water, and brine, dried ($MgSO_4$), and distilled to remove diethyl ether and THF under normal pressure. The residue was column chromatographed on silica gel using a mixture of hexane and diethyl ether (15:1) as an eluent to give 1.6 g (57% yield) ketone **14** as a 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 (2C, gem-dimethyl), 18.7.

MS (electrospray ionization): 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 1.0 g (6.0 mmol) of ketone **14** in 30 mL of dioxane and 6 mL of H_2O at 25 °C, was added 12 mg (0.06 mmol) of OsO_4. The solution was stirred for 40 min to give a dark brown solution. To it, 2.5 g (12 mmol) of sodium periodate was added in portions over 20 min, and the resulting solution was stirred at 25 °C for 4 h, diluted with 50 mL of water, and extracted with four times with diethyl ether (40 mL each). The combined organic layers were washed with water, and brine, dried ($MgSO_4$), and distilled to remove diethyl ether and most of dioxane under normal pressure. The crude product was purified by silica gel column chromatography using a mixture of hexane and diethyl ether (1:1) as an eluent to give 0.52 g (56% yield) aldehyde **8** as a 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 (2C, gem-dimethyl), 18.5.

MS (electrospray ionization): 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 0.50 g (1.1 mmol) of compound **(-)-9** and 0.23 g (1.3 mmol) of aldehyde **8** in 25 mL dichloromethane under argon at -78 °C, was added 0.34 mL (2.7 mmol) of BF_3•ethereal. The solution stirred at -78 °C for 5 h, diluted with 5 mL saturated aqueous $NaHCO_3$ and 20 mL of water, warmed to 25 °C, and extracted three times with ethyl acetate (30 mL each). 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 30 mg (9% recovery) of tricyclic ketone (-)-**7** and 0.43 g of a mixture of aldol products (stereoisomers at C13 and C18), which was used in the subsequent dehydration reaction

directly. To a cold (0 °C) solution of 0.43 g (0.91 mmol) of the aforementioned aldol products and 1.3 mL (8.1 mmol) of Et_3N in 30 mL dried diethyl ether under argon, was added 0.34 g (3 mmol) of methanesulfonyl chloride. The solution stirred at 25 °C for 14 h, diluted with 20 mL of 5% aqueous NH_4Cl solution, and extracted three times with ethyl acetate (30 mL each). 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 under argon was dissolved in 20 mL of a mixture of dichloromethane and toluene (1:1) and added 0.28 g (1.82 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 25 °C. The resulting solution stirred for 15 h, diluted with aqueous NH_4Cl, and extracted three times with ethyl acetate (30 mL each). 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 an eluent to give 0.35 g (83% overall yield) of (-)-**6** as a white solid.

Mp 81.5 – 83.0 °C; $[\alpha]_D^{25}$ = -32.5, (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 (2C), 19.1, 18.7, 18.3, 16.7.

MS (electrospray ionization): 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 compound was crystallized from diethyl ether to give single crystals, whose 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 5 mL of distilled ethanol under argon at 25 °C was added 11 mg (0.46 mmol) of sodium, and the solution was stirred for ten minutes and all sodium metal dissolved. To a solution of 0.11 g (0.23 mmol) of (-)-**6** in 40 mL of distilled ethanol 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 diluted with water and extracted three times with ethyl acetate (30 mL each). 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 an eluent to give 45 mg (40% yield) of (-)-**10** and 35 mg (30% yield) of (+)-**11** as white solids. Compound (-)-**10** (less polar product):

Mp 203.0 – 205.0 °C; $[\alpha]_D^{25}$ = -34.0, (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 (2C), 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 (electrospray ionization): 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):

Mp 201.0 – 203.5 °C; $[\alpha]_D^{25}$ = + 222.5° (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, 3H, 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, 38.4, 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 (electrospray ionization): 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.

The compound was crystallized from a mixture of diethyl ether and hexane (1:1) to give single crystals, whose 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 titrated prior to usage]. To a cold (-78 °C) solution of 0.173 g (0.38 mmol) of (-)-**10** in 2 mL THF under argon, was added a solution of 0.57 mmol of LDA in 1 mL THF by syringe. The solution was stirred at -78 °C for 1 h, added 0.102 g (0.57 mmol) of HMPA, stirred for 15 min, added 75 mg (0.76 mmol) of ethyl cyanoformate, and stirred for 30 min. The solution diluted with aqueous NH_4Cl solution and extracted three times with ethyl acetate (20 mL each). 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 an eluent to give 90 mg (45% yield) of pure (+)-**5** as a white solid.

Mp 153 – 155°C; $[\alpha]^{D}_{25}$= +91.3 (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, C$\underline{H}_3$$CH_2O_2$C), 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 (2C), 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 (electrospray ionization): 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 compound was crystallized from a mixture of diethyl ether and hexane (1:1) to give single crystals, whose 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 40 mg (0.088 mmol) of (+)-**11** in 1 mL of dried diethyl ether under argon, was added freshly prepared LDA (0.12 mmol) in 1 mL of diethyl ether, and the solution was stirred at -78 °C for 1 h. To it, HMPA (24 mg, 0.12 mmol) was added, stirred at -78 °C for 15 min, added 18 mg (0.17 mmol) of ethyl cyanoformate, stirred for 30 minutes, diluted with aqueous NH_4Cl solution, and extracted three times with ethyl acetate (10 mL each). The combined organic layers 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 an eluent to give 30 mg (65 % yield) of pure (-)-**4** as a white solid.

Mp 205 – 207 °C; $[\alpha]_D^{25}$ = -62.8, (0.20, $CHCl_3$).

^1H 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, $C\underline{H}_3CH_2O_2C$), 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 (2C), 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 (electrospray ionization): 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.

Funding Information

Research reported in this publication was supported in part by the American Heart Association, Heartland Affiliate (0750115Z) and National Science Foundation (CHE-1662705). This material was based upon work in part supported by the National Science Foundation under 1826982 (to DHH) for the purchase of a NMR spectrometer and CHE-0923449 (to VWD) for the purchase of an x-ray diffractometer and software used in this study.

Acknowledgment

SK thanks the Council of Higher Education of Turkey for a research fellowship.

Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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