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Efficient synthesis of (−)- and (+)-tricyclic compounds with enone functionalities in rings A and C. A novel class of orally active anti-inflammatory and cancer chemopreventive agents

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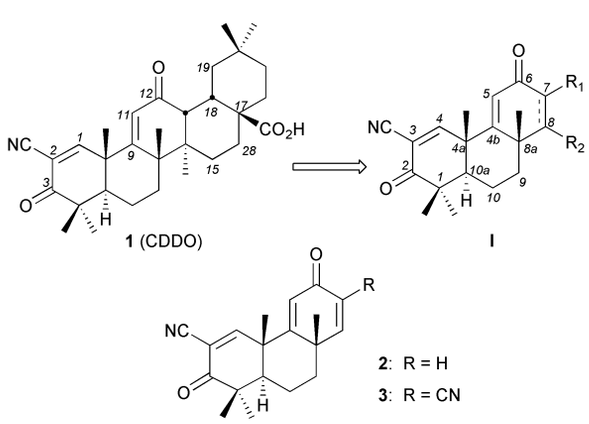
Novel tricyclic compounds with enone functionalities in rings A and C [tricyclic-bis-enone (TBE) compounds] were designed on the basis of the structure of a synthetic triterpenoid, 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO) (**1**), which is a promising drug candidate for prevention and/or treatment of cancer and inflammatory diseases whose pathogenesis may involve excessive production of nitric oxide (NO) and/or prostaglandins. A series of TBE compounds in racemic form shows high inhibitory activity against production of NO induced by interferon-γ (IFN-γ) in mouse macrophages. One of these compounds, (±)-(4aβ,8aβ,10aα)-1,2,4a,6,8a,9,10,10a-octahydro-1,1,4a,8a-tetramethyl-2,6-dioxophenanthrene-3,7-dicarbonitrile ((±)-**3**), is orally active at 15 mg kg^{-1} (single administration) in a preliminary *in vivo* study using mouse peritoneal inflammation induced by thioglycollate and IFN-γ. Therefore, we desired to synthesize optically active TBE compounds for a comparison of the biological potency of both enantiomers. We now describe the synthesis of both enantiomers of (4aβ,8aβ,10aα)-1,2,4a,6,8a,9,10,10a-octahydro-1,1,4a,8a-tetramethyl-2,6-dioxophenanthrene-3-carbonitrile (**2**) and **3** from commercially available simple compounds. Interestingly, (+)-**3** having the same configuration as the CDDO antipode shows about 10 times higher inhibitory activity than (−)-**3** on NO production in mouse macrophages. In contrast, (−)-**3** inhibits proliferation of MCF-7 breast cancer cells, whereas (+)-**3** does not.

Introduction

The concept that inflammation and carcinogenesis are related phenomena has been the subject of many studies that have attempted to link these two processes in a mechanistic fashion.[1,2] The enzymes that mediate the constitutive synthesis of nitric oxide (NO) and prostaglandins from arginine and arachidonate, respectively, have relatively little significance for either inflammation or carcinogenesis. In contrast, inducible nitric oxide synthase (iNOS) and inducible cyclooxygenase (COX-2) both have critical roles in the response of tissues to injury or infectious agents. These inducible enzymes are essential components of the inflammatory response, the ultimate repair of injury, and carcinogenesis.[3–5] Although physiological activity of iNOS and COX-2 may provide a definite benefit to the organism, aberrant or excessive expression of either iNOS or COX-2 has been implicated in the pathogenesis of many disease processes, particularly in Alzheimer's disease, Parkinson's disease, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, and carcinogenesis.[6–10]

Considerable effort has been devoted to developing new compounds that are direct inhibitors of the enzymatic activity of either iNOS or COX-2. An alternative approach is to find new agents that can prevent expression of the respective genes coding for these enzymes. Glucocorticoids and TGF-β are such molecules; they both suppress transcription or translation of iNOS and COX-2 genes.[11,12] A rationale thus exists to develop more selective agents for suppression of genes that might be overexpressed during the inflammatory or carcinogenic process. We have attempted to apply this strategy for the development and evaluation of novel tricyclic compounds which we designed for the reasons described below.

In a series of previous papers,[13–17] we have reported that a synthetic triterpenoid, 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO) (**1**) is a promising drug candidate for prevention and/or treatment of cancer and inflammatory diseases. During the development of CDDO, we found the very important structure–activity relationships that a 2-cyano-1-en-3-one in ring A and a 9(11)-en-12-one in ring C are essential for the extremely high potency of CDDO. Therefore, we reasoned that the entire oleanane skeleton might not be necessary for potency. Consequently, we have designed tricyclic compounds having the general formula **I** [tricyclic-bis-enone (TBE) compounds, *e.g.*, compounds **2** and **3**], which have the same A, B, and C rings as CDDO. A literature survey revealed that these TBE compounds are unknown.



Our rationale for pursuing the synthesis of these TBE compounds is as follows. Because they could be synthesized from commercially available small molecules, TBE compounds with various functionalities at different positions can be obtained. Such "diversity-oriented synthesis" could lead to new potential

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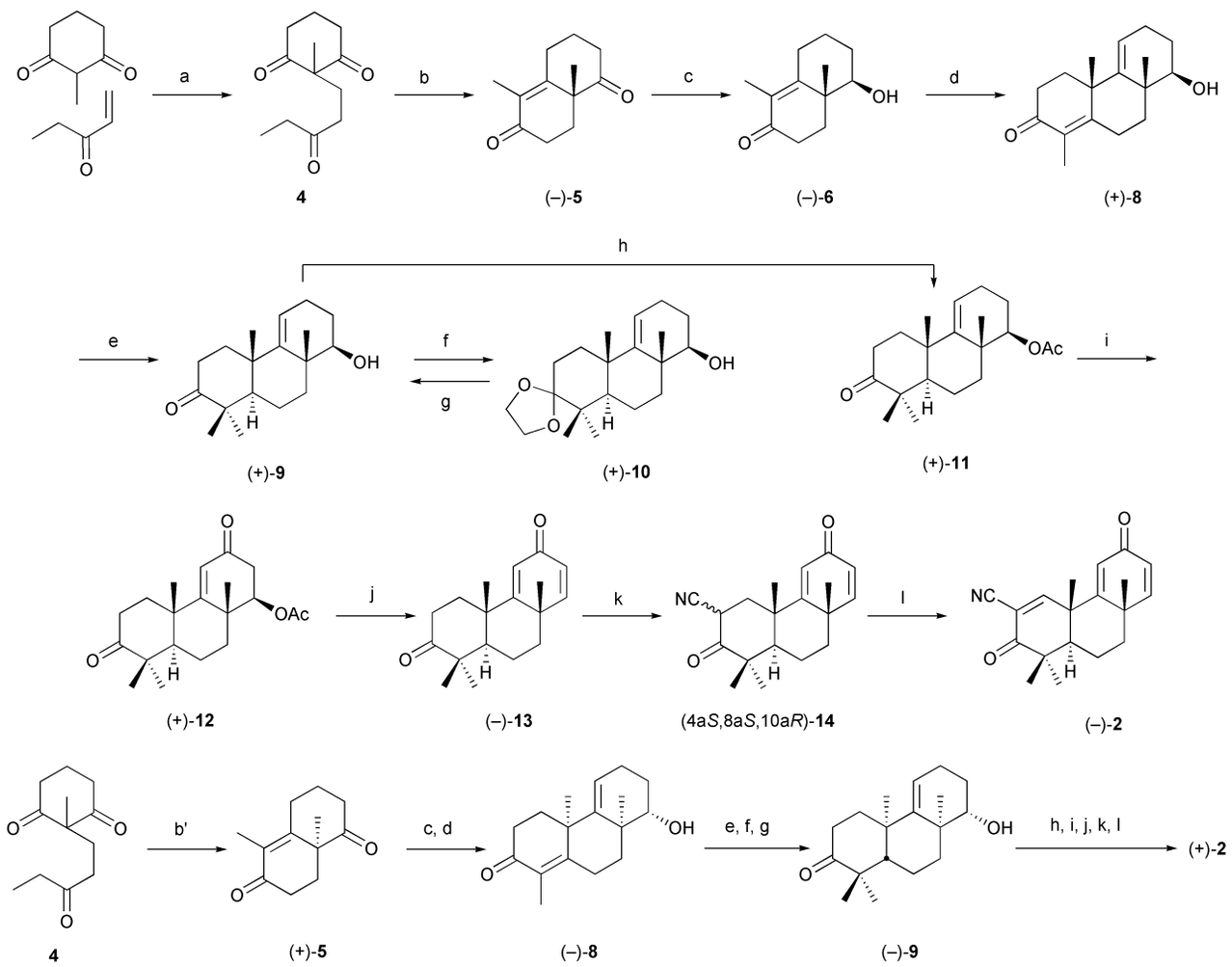


Scheme 1 *Reagents and conditions*: (a) Et_3N, THF, reflux, 3 h, 81%; (b) (*R*)-(+)-phenylalanine, d-CSA, DMF, rt, 4 days, then 60–70 °C, 1 day, 80%; (b′) (*S*)-(−)-phenylalanine, d-CSA, DMF, rt, 4 days, then 60–70 °C, 1 day, 78%; (c) $NaBH_4$, EtOH, 0 °C, 30 min, 99%; (d) ethyl vinyl ketone, Na, MeOH, rt, 6.5 h, then reflux, 12 h, 51%; (e) Li, liquid NH_3, THF, −33 °C, 1 h, then CH_3I, −33 °C, 2 h; (f) ethylene glycol, PPTS, PhH, reflux, 4 h, 16% for 2 steps; (g) PPTS, aqueous acetone, reflux, 5 h, 95%; (h) Ac_2O, pyridine, rt, overnight, quant.; (i) CrO_3, *t*-BuOOH, CH_2Cl_2, rt, 3 h, 72%; (j) DBU, CH_2Cl_2, rt, 6.5 h, 95%; (k) LDA, THF, −78 °C, 20 min, then *p*-TsCN, THF, −78 °C, 5 min, 93%; (l) DDQ, PhH, reflux, 15 min, 73%.

anti-inflammatory and cancer chemopreventive drugs that have high oral potency and high water solubility for ease of administration and formulation, high biological selectivity for removal of possible side effects, and would be inexpensive for large scale synthesis.

In a preliminary communication,[18] we reported that these TBE compounds in racemic form show high inhibitory activity (IC_{50} = 1–10 nM level) against production of NO induced by interferon-γ (IFN-γ) in mouse macrophages. Moreover, (±)-**3** approaches the potency of CDDO in the above *in vitro* assay, and is orally active at 15 mg kg^{-1} (single administration) in a preliminary *in vivo* study using mouse peritoneal inflammation induced by thioglycollate and IFN-γ.

It is often the case that one enantiomer of a drug has greater potency and/or less toxicity than its antipode.[19] Therefore, the syntheses of optically active TBE compounds for a comparison of the biological potency of both enantiomers are very important. We have successfully synthesized both enantiomers of **2** and **3** in relatively few steps from commercially available compounds. In addition, we have found the unexpected racemization of the optically active intermediate **6** under Robinson annulation conditions during our synthesis of optically active **2**. The optically active TBE compounds **2** and **3** show unpredicted and interesting biological results.

We herein describe the full account of our synthetic work with these TBE compounds, including a possible racemization mechanism, and a brief description of the interesting biological results.

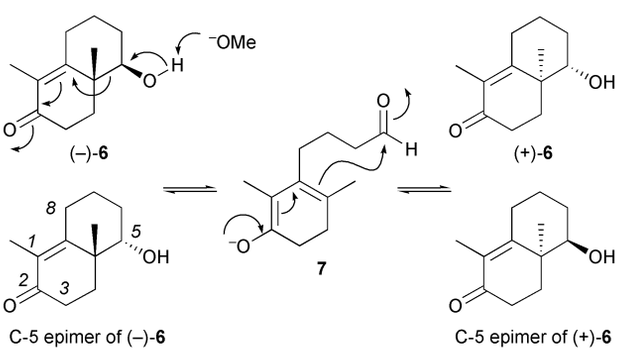
Results and discussion

We have synthesized both (−)-**2**, with the same configuration as CDDO, and its antipode (+)-**2** from the known bicyclic enones (−)-**5** and (+)-**5**,[20,21] respectively, according to the synthetic route shown in Scheme 1.

Optically active (−)-**5** was synthesized in 64% yield *via* achiral **4**[22] from ethyl vinyl ketone and 2-methyl-1,3-cyclohexanedione using (*R*)-(+)-phenylalanine.[20] Selective reduction[23] of (−)-**5** with sodium borohydride gave (−)-**6** ($[\alpha]_D^{26}$ −170 (*c* 1.2, $CHCl_3$), lit.,[23] $[\alpha]_D^{25}$ −164.6 (*c* 2.16, $CHCl_3$)) in 93% yield. The enantiomeric excess (ee) of (−)-**6** was determined to be 96% by ^1H and ^{19}F NMR of the (−)-*R*-α-methoxy-α-(trifluoromethyl)phenylacetyl ester ((−)-*R*-MTPA ester)[24,25] derived from (−)-**6**.

Although racemic **8** is a known compound,[26] (+)- and (−)-**8** have not been reported. Robinson annulation of (−)-**6** with ethyl vinyl ketone in the presence of sodium methoxide at reflux (the same method[26] as for racemic **8**) gave (+)-**8** (51% yield, 76% based on consumed **6**) and recovered starting material **6** (33% yield). Surprisingly, the optical rotation of the recovered **6** was nearly zero ($[\alpha]_D^{28}$ +2.4 (*c* 8.6, $CHCl_3$)). Although the product **8** is dextrorotatory ($[\alpha]_D^{27}$ +50 (*c* 2.0, $CHCl_3$)), chiral HPLC analysis indicated an ee of only 56%. This drastic decrease of the optical purities of **6** and **8** clearly shows that (−)-**6** is racemized under Robinson annulation conditions. We believe the reasons why (+)-**8** still retains the optical activity although (−)-**6** is completely racemized are as follows: (1) at the early

stage of this reaction, a considerable amount of (+)-**8** would be produced from (−)-**6**. (2) Once (+)-**8** is produced, it is not racemized under the reaction conditions. (3) Although (−)-**8** is produced from (+)-**6** and accumulated due to the racemization of (−)-**6**, (+)-**8** still retains optical activity owing to the initial considerable production of (+)-**8**. In addition to the decrease of optical purity of (+)-**8**, we found formation of a small amount (<5% yield) of the C-8 epimer of **8**[27] in a mixture of by-products by ^{1}H NMR. Although we could not detect the C-5 epimer of **6**, the epimer of **8** is clearly thought to be produced from the epimer of **6**. We speculate that racemization and C-5 epimerization of (−)-**6** occur *via* an interesting base–catalysed reverse vinylogous aldol reaction shown in Scheme 2. Because enolate **7** is achiral, racemization is inevitable. Since a hydroxyl group at C-5 of **6** is equatorial, it is reasonable that **6** is predominantly produced from **7** under such thermodynamic Robinson annulation conditions. We attempted to protect the hydroxyl group of (−)-**6** with various protective groups to prevent the racemization. However, benzylation conditions readily converted (−)-**6** into the racemic benzyl ether of **6**, whereas acetyl, pivaloyl, and *tert*-butyldimethylsilyl groups were readily cleaved under the Robinson annulation conditions. Therefore, we had no choice but to use (+)-**8** having a low ee for the next step.



Scheme 2 A mechanism for the racemization and C-5 epimerization of (−)-**6**.

Reductive methylation of (+)-**8** without a proton donor (the same known method[28] as for racemic **9**), followed by chromatography, gave crude (+)-**9** in 43% yield. Recrystallization of crude (+)-**9** from acetone afforded chemically pure crystals of nearly racemic **9** ($[a]_D^{24}$ −4.1 (*c* 0.32, $CHCl_3$), mass recovery rate, 25%). The residue ($[a]_D^{24}$ +38 (*c* 0.45, $CHCl_3$)) recovered from the mother liquor included enantio–enriched (+)-**9** and some impurities. Fortunately, chemically and optically pure (+)-**9** was obtained by ketalization of the residue, subsequent purification by column chromatography and recrystallization, followed by deketalization. This ketalization was accomplished with ethylene glycol in the presence of catalytic pyridinium *p*-toluenesulfonate (PPTS) in benzene at reflux.[29] Several iterative cycles of column chromatography and recrystallization gave pure (+)-**10** ($[a]_D^{27}$ +22 (*c* 0.26, $CHCl_3$)) in 16% yield from (+)-**8**. The ketal of (+)-**10** was removed with catalytic PPTS in aqueous acetone at reflux[29] to give (+)-**9** in 95% yield. The ee of (+)-**9** ($[a]_D^{27}$ +47 (*c* 0.38, $CHCl_3$)) was determined to be 90% by ^{1}H and ^{19}F NMR of the (−)-*R*-MTPA ester derived from (+)-**9**.[30]

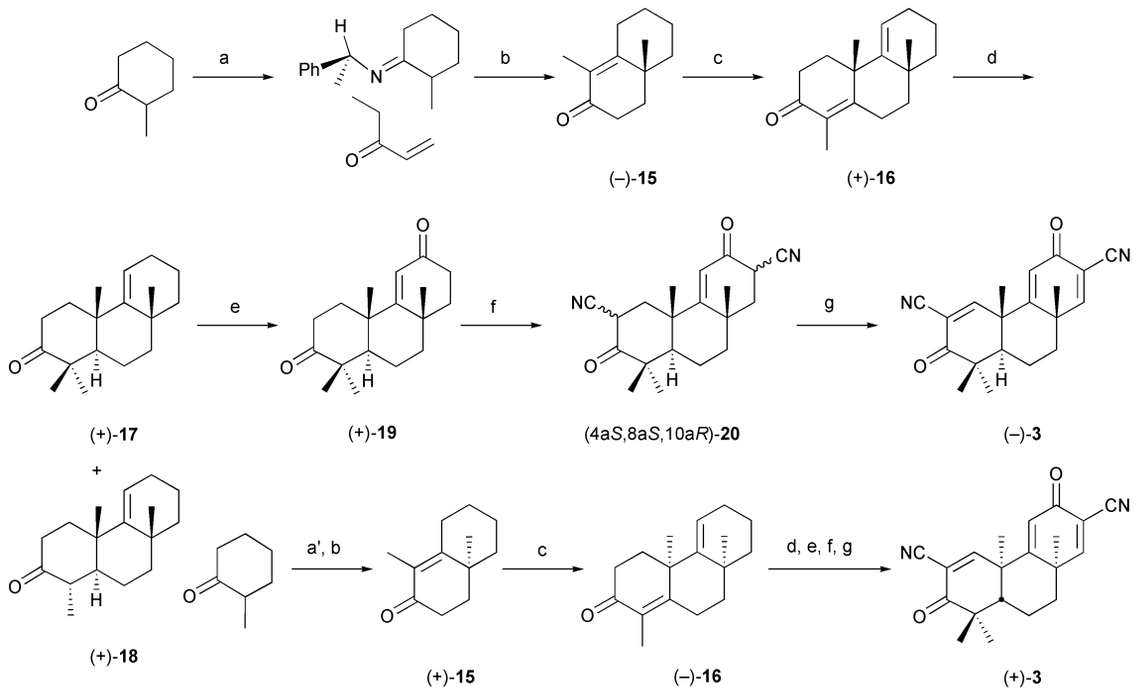
Acetylation of (+)-**9** with Ac_2O in pyridine gave (+)-**11** in quantitative yield. A chromium-mediated allylic oxidation of (+)-**11** with 70% *tert*-butyl hydroperoxide gave (+)-**12** in 72% (79% based on consumed (+)-**11**) yield.[31] Deacetoxylation of (+)-**12** with DBU in CH_2Cl_2 gave (−)-**13** in 95% yield.[32] Cyanation of the enolate of (−)-**13**, generated using LDA in THF, with *p*-toluenesulfonyl cyanide (*p*-TsCN) gave (4a*S*,8a*S*,10a*R*)-**14** as an isomeric mixture in 93% yield.[33] Oxidation of (4a*S*,8a*S*,10a*R*)-**14** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave (−)-**2**[34] ($[a]_D^{27}$ −115 (*c* 0.28, $CHCl_3$)) in 73% yield. Similarly, (+)-**2**[34] ($[a]_D^{26}$ +115 (*c* 0.31, $CHCl_3$)) was synthesized from (+)-**5**, which was obtained from **4** using (*S*)-(−)-phenylalanine, by the same sequence.

We have efficiently synthesized (−)-**3** with the same configuration as CDDO, and its antipode (+)-**3** in seven steps *via* bicyclic enones (−)-**15** and (+)-**15**,[35] respectively, from 2-methylcyclohexanone (Scheme 3). Noteworthy in this synthesis are the reductive methylation step using one equivalent of water to give compound **17** from **16**, and the double cyanation step using *p*-TsCN for the simultaneous introduction of two nitrile groups at C-3 and C-7 of **19** to afford dinitrile **20**. Optically active (−)-**15** was asymmetrically synthesized from a chiral imine, obtained from 2-methylcyclohexanone and (*S*)-(−)-α-methylbenzylamine, and ethyl vinyl ketone by a known method.[35] Tricyclic compound (+)-**16** was synthesized in 54% (71% based on consumed starting material) yield from (−)-**15** by a known method that was used for racemic **16**.[36]

The simple tricyclic compound **17** (both optically active and racemic) is an unknown compound. However, because this compound is potentially a very useful and important intermediate for the synthesis of various projected TBE compounds, we needed to synthesize **17** from **16** by reductive methylation. The standard reductive methylation procedure on α,β-unsaturated ketones usually involves (1) the generation of a specific lithium enolate by reduction of the corresponding α,β-unsaturated ketone with lithium in liquid ammonia with or without a proton donor, and (2) reaction of this enolate with excess methyl iodide either in liquid ammonia or some other solvent system at several temperatures from −78 °C to rt.[37] Following this general procedure, we attempted several conditions for the reductive methylation of racemic **16**. Finally, we found that the reductive methylation of **16** using 4.5 equivalents of lithium and one equivalent of water and quenching the excess lithium with isoprene, followed by the addition of methyl iodide at 0 °C gives the desired compound **17** and the known reduced compound **18**[38] in 63% and 13% yields, respectively. Interestingly, the reductive methylation of **16** without a proton donor or with proton donors other than water does not give **17**. For example, an attempt with 3.3 equivalents of lithium in liquid ammonia containing no proton donor did not give **17** but only **18** in 44% yield. Another attempt with 4.3 equivalents of lithium containing *tert*-butanol as a proton donor gave only **18** in moderate yield. Optically active (+)-**17** was also synthesized in a similar yield from (+)-**16** by this method.

A chromium-mediated allylic oxidation of (+)-**17** with 70% *tert*-butyl hydroperoxide gave (+)-**19** ($[a]_D^{27}$ +85 (*c* 0.50, $CHCl_3$)) in 67% yield. The ee of (+)-**19** was determined to be 90% by chiral HPLC analysis. Double cyanation of the bis-enolate of (+)-**19** with *p*-TsCN in THF successfully gave dinitrile (4a*S*,8a*R*,10a*R*)-**20** as an isomeric mixture. Finally, (−)-**3**[34] ($[a]_D^{26}$ −91 (*c* 0.52, $CHCl_3$)) was prepared in 68% yield (from (+)-**19**) by DDQ oxidation of (4a*S*,8a*R*,10a*R*)-**20**. Similarly, (+)-**3**[34] ($[a]_D^{26}$ +88 (*c* 0.55, $CHCl_3$)) was synthesized in five steps from (+)-**15**, which was prepared by the Robinson annulation of ethyl vinyl ketone with the chiral imine obtained from 2-methylcyclohexanone and (*R*)-(+)-α-methylbenzylamine by the same sequence. This successful synthesis of (−)-**3** and (+)-**3** suggests that we can synthesize various other TBE compounds efficiently and inexpensively.

We briefly report some interesting biological results of these optically active TBE compounds, **2** and **3**.[39] Unexpectedly, both (−)-**2** and (+)-**2** show almost the same inhibitory activity (IC_{50} = 60 nM) against production of NO induced by IFN-γ in mouse macrophages,[18] and also in several cancer cell lines.[40] It is remarkable that (+)-**3** (IC_{50} = 3.6 nM) having the same configuration as the CDDO antipode shows about 10 times higher inhibitory activity than (−)-**3** (IC_{50} = 42.5 nM) having the same configuration as CDDO on NO production in mouse macrophages. However, (−)-**3** inhibits proliferation of MCF-7 breast cancer cells in a dose-dependent manner, over a range of



Scheme 3 *Reagents and conditions*: (a) (*S*)-(−)-α-methylbenzylamine, toluene, reflux, 24 h; (a′) (*R*)-(+)-α-methylbenzylamine, toluene, reflux, 24 h; (b) 10% aqueous AcOH, MeOH, rt, 2 h; KOH, MeOH, reflux, 1 h, 50% for 2 steps; (c) NaH, DMSO, THF, reflux, 4.5 h, then 1-chloro-3-pentanone, −20 °C, 1.5 h; aqueous KOH, MeOH, reflux, 7.5 h, 54%; (d) Li (4.5 eq.), H_2O (1 eq.), liquid NH_3, THF, −33 °C, 1 h, then isoprene, −78 °C, then CH_3I, THF, 0 °C, 1 h, 56% for (+)-**17**; (e) CrO_3, *t*-BuOOH, CH_2Cl_2, rt, 1 h, 67%; (f) LDA (2.8 eq.), THF, −78 °C, 20 min, then *p*-TsCN (4 eq.), THF, −78 °C, 30 min; (g) DDQ, PhH, reflux, 15 min, 68% for 2 steps.

10–1000 nM, whereas (+)-**3** does not. These results were also unanticipated because we imagined that the potency of (−)-**3** would be equivalent to that of (+)-**3** in various assays based on the biological results of (−)-**2** and (+)-**2**.

These results clearly demonstrate that we have separated the biological properties of racemic **3** by the synthesis of its enantiomers, and, also, suggest that TBE compounds may be new anti-inflammatory and cancer chemopreventive drugs with increased selectivity.

Further syntheses and biological evaluation (*in vitro* and *in vivo*) of new TBE compounds, including optically active and/or water-soluble derivatives, are in progress.

Experimental

General

Melting points were determined on a Laboratory Devices Mel Temp capillary melting point apparatus and are uncorrected. Optical rotations were measured with a Jasco DIP-370 digital polarimeter. UV and IR spectra were recorded on a Hewlett-Packard 8451A Diode Array UV spectrophotometer and Perkin-Elmer 600 series FTIR spectrometer, respectively. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian XL-300 Fourier transform spectrometer. The chemical shifts are reported in δ (ppm) using the δ 7.27 signal of $CHCl_3$ (^{1}H NMR) and the δ 77.23 signal of $CDCl_3$ (^{13}C NMR) as internal standards. Low-resolution mass spectra and high-resolution MS data were obtained on a Micromass 70-VSE. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA, USA. TLC and preparative TLC were performed with Merck precoated TLC plates silica gel 60 F_{254}. Flash column chromatography was done with Select Scientific silica gel (230–400 mesh). Anhydrous CH_2Cl_2 and anhydrous THF were distilled from calcium hydride and sodium benzophenone ketyl–sodium metal under a nitrogen atmosphere, respectively. All experiments were performed under a nitrogen atmosphere. The standard work up method was as follows: an organic extract was washed with saturated aqueous $NaHCO_3$ solution (three times) and then saturated aqueous NaCl solution (three times), dried over anhydrous $MgSO_4$, and filtered. The solvent was removed *in vacuo* from the filtrate.

(+)-(4a*S*,8*R*,8a*R*)-(4aβ,8β,8aβ)-4,4a,6,7,8,8a,9,10-Octahydro-8-hydroxy-1,4a,8a-trimethylphenanthren-2(3*H*)-one (+)-8[26]. Sodium (410 mg, 18 mmol) was dissolved in anhydrous MeOH (15.4 mL) at 0 °C. To the solution was added a solution of (−)-(4a*R*,5*R*)-(4aα,5α)-4,4a,5,6,7,8-hexahydro-5-hydroxy-1,4a-dimethylnaphthalen-2(3*H*)-one ((−)-**6**)[23] (3.56 g, 18 mmol, $[\alpha]_D^{26}$ −170 (*c* 1.2, $CHCl_3$)) in anhydrous MeOH (12 mL) dropwise over 5 min, followed by a solution of ethyl vinyl ketone (2.85 g, 34 mmol) in anhydrous MeOH (3.6 mL) over 10 min. The solution was stirred at rt for 6.5 h and then 12 h at reflux. The solvent was removed *in vacuo* and the residue was dissolved in Et_2O (100 mL) and water (100 mL). The organic layer was washed with water (3 × 20 mL) and brine (15 mL), dried over $MgSO_4$. Removal of the solvent *in vacuo* gave 5.5 g of a crude oil. It was purified by flash column chromatography [hexanes : EtOAc, (1 : 1)] to give recovered (−)-**6** (1.16 g, 33%, $[\alpha]_D^{28}$ +2.4 (*c* 8.6, $CHCl_3$)) and (+)-**8** (2.44 g, 51%, 76% based on consumed (−)-**6**) as a clear, pale yellow oil that crystallized upon standing at −78 °C: mp 107–110 °C; $[\alpha]_D^{27}$ +50 (*c* 2.0, $CHCl_3$) (Found: C, 78.52; H, 9.50. $C_{17}H_{24}O_2$ requires C, 78.42; H, 9.29%); λ_{max}(EtOH)/nm 252 (log ε 3.76); ν_{max}(KBr)/cm^{-1} 3509, 2949, 1662, 1653; δ_H(300 MHz, $CDCl_3$) 5.50 (1H, t, *J* = 3.8 Hz, 5-H), 3.47 (1H, m, 8α-H), 2.67–2.41 (5H, m), 2.26–2.20 (2H, m), 2.10–1.95 (4H, m), 1.78 (3H, d, *J* = 0.7 Hz, 1-Me), 1.51 (1H, dd, *J* = 4.0, 12.1 Hz, 3-H), 1.42 (3H, s, Me), 1.27 (3H, s, Me); δ_C(75 MHz, $CDCl_3$) 198.7, 163.3, 148.3, 128.3, 120.2, 76.1, 41.4, 39.1, 35.1, 34.5, 34.1, 28.1, 26.1, 24.8, 24.6, 20.6, 11.4; *m*/*z* (EI) 260 (M^+, 84%), 245 (66), 242 (34), 227 (100), 216 (26), 201 (81), 159 (44); HRMS (EI): calc. for $C_{17}H_{24}O_2$ (M^+) 260.1776, found 260.1786. Chiral HPLC analysis: Both peaks of (−)-**8** and (+)-**8** were observed at 21 (area%, 22) and 26 min (area%, 78), respectively. [column, CHIRALPAK®AD™ (250 × 4.6 mm); mobile phase, hexanes : *i*-PrOH (95 : 5); flow rate, 1 mL min^{-1}; wavelength for the detection, 254 nm].

(−)-(4a*R*,8*S*,8a*S*)-(4aα,8α,8aα)-4,4a,6,7,8,8a,9,10-Octahydro-8-hydroxy-1,4a,8a-trimethylphenanthren-2(3*H*)-one (−)-8. The same procedure as for (+)-**8** gave (−)-**8** from (+)-(4a*S*,5*S*)-(4aβ,5β)-4,4a,5,6,7,8-hexahydro-5-hydroxy-1,4a-dimethylnaphthalen-2(3*H*)-one ((+)-**6**)[20,21,23] ($[a]_D^{26}$ +175 (*c* 0.77, $CHCl_3$)) as a crystalline solid: mp 95–100 °C; $[a]_D^{26}$ −48 (*c* 0.59, $CHCl_3$); HRMS (EI): calc. for $C_{17}H_{24}O_2$ (M^+) 260.1776, found 260.1784. The UV, IR, ^{1}H NMR, ^{13}C NMR, and MS were identical to those of (+)-**8**.

(+)-(4′a*S*,8′*R*,8′a*R*,10′a*R*)-(4′aβ,8′β,8′aβ,10′aα)-3′,4′,4′a,6′,7′,8′,8′a,9′,10′,10′a-Decahydro-8′-hydroxy-1′,1′,4′a,8′a-tetramethylspiro[1,3-dioxolane-2,2′(1′*H*)-phenanthrene] (+)-10. To liquid ammonia (*ca*. 160 mL) was added Li (712 mg, 103 mmol) at −78 °C. The solution was stirred at −78 °C for 20 min. A solution of (+)-**8** (ee, 56%) (7.37 g, 28.3 mmol) in THF (65 mL) was then added and the solution was stirred at −33 °C (bp of ammonia; temperature stabilized by a CCl_4 bath) for 1 h. The solution was cooled to −78 °C and iodomethane (14.6 mL, 235 mmol) was injected. For another 2 h the solution was stirred at −33 °C. After removal of ammonia, the resultant mixture was neutralized with 5% aqueous HCl solution (50 mL) and diluted with CH_2Cl_2 (200 mL) and water (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were worked up by the standard method to give 7.0 g of crude material. This solid was purified by flash column chromatography [hexanes : EtOAc (2 : 1)] to give crude (+)-**9** (3.4 g, 43%) as a colorless solid. This material was recrystallized from acetone to give four crops of crystals totalling 845 mg of nearly racemic crystals ($[a]_D^{24}$ −4.1 (*c* 0.32, $CHCl_3$)) and 2.45 g of enantiomerically enriched residue ($[a]_D^{24}$ +38 (*c* 0.45, $CHCl_3$)), including some impurities, recovered from the mother liquor.

To a solution of the material including enantio-enriched (+)-**9** and some impurities (2.45 g) in benzene (46 mL) was added PPTS (237 mg, 0.93 mmol) and ethylene glycol (9.5 mL). The mixture was stirred vigorously at reflux for 4 h with water removal by a Dean Stark trap filled with 4 Å molecular sieves. The benzene layer separated from the ethylene glycol layer, which was diluted with water (50 mL) and extracted with EtOAc (3 × 30 mL). The combined EtOAc and benzene layers were worked up by the standard method to give a solid (2.81 g). It was purified by flash column chromatography [hexanes : EtOAc (2.5 : 1)] followed by recrystallization from a mixture of hexanes and EtOAc with four additional iterative cycles on impure fractions and mother liquor residues to give (+)-**10** (1.43 g, 16% from (+)-**8**) as a colorless crystalline solid: mp 174–175 °C; $[a]_D^{27}$ +22 (*c* 0.26, $CHCl_3$) (Found: C, 75.02; H, 10.07. $C_{20}H_{32}O_3$ requires C, 74.96; H, 10.06%); ν_{max}(KBr)/cm^{-1} 3464, 2974, 2934, 2871; δ_H(300 MHz, $CDCl_3$) 5.31 (1H, t, *J* = 3.8 Hz, 5-H), 4.01–3.87 (4H, m, −OC*H*$_2$C*H*$_2$O–), 3.41 (1H, dd, *J* = 5.5, 10.6 Hz, 8α-H), 2.18–2.10 (2H, m), 1.96 (1H, dt, *J* = 3.2, 12.6 Hz), 1.91–1.84 (1H, m), 1.70–1.55 (7H, m), 1.31–1.20 (3H, m), 1.16, 1.13, 0.98, 0.86 (3H each, s, Me); δ_C(75 MHz, $CDCl_3$) 152.5, 116.4, 113.3, 78.9, 65.1, 65.0, 51.5, 42.6, 39.5, 39.4, 39.2, 36.1, 27.4, 26.3, 25.0, 23.8, 23.1, 20.6, 20.1, 18.5; *m*/*z* (EI) 320 (M^+, 3%), 100 (7), 99 (100), 86 (4), 55 (5); HRMS (EI): calc. for $C_{20}H_{32}O_3$ (M^+) 320.2351, found 320.2350.

(−)-(4′a*R*,8′*S*,8′a*S*,10′a*S*)-(4′aα,8′α,8′aα,10′aβ)-3′,4′,4′a,6′,7′,8′,8′a,9′,10′,10′a-Decahydro-8′-hydroxy-1′,1′,4′a,8′a-tetramethylspiro[1,3-dioxolane-2,2′(1′*H*)-phenanthrene] (−)-10. Crude (−)-**9** was prepared by the same procedure as for crude (+)-**9**. It was recrystallized from a mixture of hexanes and ethyl acetate to give nearly racemic crystals ($[a]_D^{26}$ −3.2 (*c* 0.25, $CHCl_3$)) and enantiomerically enriched residue ($[a]_D^{28}$ −39 (*c* 0.52, $CHCl_3$)), including some impurities, recovered from the mother liquor. (−)-**10** was obtained from the material including enantio-enriched (−)-**9** and some impurities by the same method as for (+)-**10** as a colorless crystalline solid: mp 153–155 °C; $[a]_D^{26}$ −25 (*c* 0.30, $CHCl_3$); HRMS (EI): calc. for $C_{20}H_{32}O_3$ (M^+) 320.2351, found 320.2349. The IR, ^{1}H NMR, ^{13}C NMR, and MS were identical to those of (+)-**10**.

(+)-(4a*S*,8*R*,8a*R*,10a*R*)-(4aβ,8β,8aβ,10aα)-3,4,4a,6,7,8,8a,9,10,10a-Decahydro-8-hydroxy-1,1,4a,8a-tetramethylphenanthren-2(1*H*)-one (+)-9. A solution of (+)-**10** (605 mg, 1.89 mmol) and PPTS (199 mg, 0.79 mmol) in acetone (18 mL) and water (2 mL) was stirred at reflux for 5 h. After removal of acetone, the resultant mixture was diluted with a mixture of Et_2O and CH_2Cl_2 (2 : 1) (50 mL) and worked up by the standard method to give (+)-**9** (498 mg, 95%) as a colorless crystalline solid which was used without further purification: mp 134–136 °C; $[a]_D^{27}$ +47 (*c* 0.38, $CHCl_3$) (Found: C, 78.05; H, 10.39. $C_{18}H_{28}O_2$ requires C, 78.21; H, 10.21%); ν_{max}(KBr)/cm^{-1} 3348, 2973, 2937, 2867, 1706; δ_H(300 MHz, $CDCl_3$) 5.36 (1H, t, *J* = 3.7 Hz, 5-H), 3.43 (1H, dd, *J* = 5.0, 11.1 Hz, 8α-H), 2.71 (1H, ddd, *J* = 6.7, 12.6, 15.9 Hz, 3-H), 2.42 (1H, ddd, *J* = 3.2, 6.0, 15.7 Hz, 3-H), 2.25–2.15 (2H, m), 2.08 (1H, ddd, *J* = 3.3, 6.8, 13.2 Hz), 2.04 (1H, dt, *J* = 3.5, 13.0 Hz), 1.81–1.67 (5H, m), 1.60 (1H, ddd, *J* = 3.4, 6.3, 13.8 Hz), 1.37 (1H, dd, *J* = 2.4, 12.2 Hz), 1.29 (3H, s, Me), 1.23 (1H, dd, *J* = 3.9, 13.2 Hz), 1.18, 1.091, 1.086 (3H each, s, Me); δ_C(75 MHz, $CDCl_3$) 217.3, 151.5, 117.8, 78.7, 53.9, 48.0, 39.5, 39.1, 38.9, 38.2, 35.0, 26.3, 25.9, 25.0, 23.4, 21.9, 20.6, 19.6; *m*/*z* (EI) 276 (M^+, 16%), 261 (26), 258 (98), 232 (100), 217 (72), 203 (35), 189 (30), 175 (49), 147 (53), 119 (58) 106 (67); HRMS (EI): calc. for $C_{18}H_{28}O_2$ (M^+) 276.2089, found 276.2091. The IR, ^{1}H NMR, ^{13}C NMR, and MS were identical to those of the known compound (±)-**9**.[28]

(−)-(4a*R*,8*S*,8a*S*,10a*S*)-(4aα,8α,8aα,10aβ)-3,4,4a,6,7,8,8a,9,10,10a-Decahydro-8-hydroxy-1,1,4a,8a-tetramethylphenanthren-2(1*H*)-one (−)-9. The same procedure as for (+)-**9** gave (−)-**9** as a crystalline solid: mp 126–126.5 °C; $[a]_D^{26}$ −55 (*c* 0.38, $CHCl_3$); HRMS (EI): calc. for $C_{18}H_{28}O_2$ (M^+) 276.2089, found 276.2089. The IR, ^{1}H NMR, ^{13}C NMR, and MS were identical to those of (±)-**9** and (+)-**9**.

(+)-(4a*S*,8*R*,8a*R*,10a*R*)-(4aβ,8β,8aβ,10aα)-8-Acetoxy-3,4,4a,6,7,8,8a,9,10,10a-decahydro-1,1,4a,8a-tetramethylphenanthren-2(1*H*)-one (+)-11. A solution of (+)-**9** (199 mg, 0.72 mmol) and acetic anhydride (1 mL) in pyridine (2 mL) was stirred at rt overnight. The reaction mixture was cooled with an ice bath and MeOH (3.5 mL) was added slowly. The solution was concentrated *in vacuo* to give (+)-**11** (230 mg, quant.) as an amorphous solid which was used without further purification: $[a]_D^{27}$ +24 (*c* 0.32, $CHCl_3$) (Found: C, 74.42; H, 9.40. $C_{20}H_{30}O_3\cdot$ 1/4H_2O requires C, 74.38; H, 9.52%); ν_{max}(KBr)/cm^{-1} 2970, 2950, 2935, 2867, 2839, 1723, 1702; δ_H(300 MHz, $CDCl_3$) 5.38 (1H, t, *J* = 3.8 Hz, 5-H), 4.69 (1H, dd, *J* = 5.3, 11.1 Hz, 8α-H), 2.68 (1H, ddd, *J* = 6.7, 12.4, 15.9 Hz, 3-H), 2.42 (1H, ddd, *J* = 3.2, 6.2, 15.9 Hz, 3-H), 2.34–2.04 (3H, m), 2.06 (3H, s, COMe), 1.84–1.63 (5H, m), 1.58–1.50 (1H, m), 1.38 (1H, dd, *J* = 2.4, 12.0 Hz), 1.28 (3H, d, *J* = 0.7 Hz, Me), 1.27–1.15 (1H, m), 1.25 (3H, s, Me), 1.07 (6H, s, 2 × Me); δ_C(75 MHz, $CDCl_3$) 217.0, 171.0, 151.0, 118.0, 80.4, 53.6, 47.8, 39.0, 38.44, 38.41, 38.1, 34.8, 25.9, 24.6, 23.34, 23.28, 21.9, 21.8, 21.5, 19.3; *m*/*z* (EI) 317 ($[M - H]^+$, 9%), 258 (67), 257 (33), 125 (41), 106 (100); HRMS (EI): calc. for $C_{20}H_{29}O_3$ ($[M - H]^+$) 317.2117, found 317.2116.

(−)-(4a*R*,8*S*,8a*S*,10a*S*)-(4aα,8α,8aα,10aβ)-8-Acetoxy-3,4,4a,6,7,8,8a,9,10,10a-decahydro-1,1,4a,8a-tetramethylphenanthren-2(1*H*)-one (−)-11. The same procedure as for (+)-**11** gave (−)-**11** as a colorless crystalline solid: mp 153–153.5 °C; $[a]_D^{26}$ −42 (*c* 0.54, $CHCl_3$). The IR, ^{1}H NMR, ^{13}C NMR, and MS were identical to those of (+)-**11**.

(+)-(4a*S*,8*R*,8a*R*,10a*R*)-(4aβ,8β,8aβ,10aα)-8-Acetoxy-4,4a,7,8,8a,9,10,10a-octahydro-1,1,4a,8a-tetramethylphenanthrene-2,6(1*H*,3*H*)-dione (+)-12. By a modification of the procedure of Muzart,[31] to a solution of (+)-**11** (230 mg, 0.72 mmol) in

CH_2Cl_2 (3.1 mL) was added *tert*-butyl hydroperoxide (70% in water, 1.2 mL, 8.1 mmol) followed by CrO_3 (87 mg, 0.87 mmol). Upon addition of CrO_3 an initial, rapid gas evolution occurred. The solution was stirred at rt for 3 h. The reaction mixture was then diluted with a mixture of Et_2O and CH_2Cl_2 (2 : 1) (15 mL) and washed with 5% aqueous NaOH solution (3 × 2 mL) and 5% aqueous HCl solution (2 × 2 mL). The resultant solution was worked up by the standard method to give 225 mg of crude material. It was purified by flash column chromatography [hexanes : EtOAc (1.5 : 1) followed by hexanes : EtOAc (1 : 1)] to give (+)-**11** (20 mg) and (+)-**12** (172 mg, 72%, 79% based on consumed (+)-**11**) as a crystalline solid: mp 192–193 °C; $[\alpha]_D^{27}$ +44 (*c* 0.23, $CHCl_3$) (Found: C, 72.09; H, 8.50. $C_{20}H_{28}O_4$ requires C, 72.26; H, 8.49%); λ_{max}(EtOH)/nm 240 (log ε 4.20); ν_{max}(KBr)/cm^{-1} 3001, 2972, 2954, 2869, 1745, 1728, 1701, 1666, 1588; δ_H(300 MHz, $CDCl_3$) 5.96 (1H, s, 5-H), 5.06 (1H, dd, *J* = 5.5, 12.6 Hz, 8α-H), 2.75–2.47 (4H, m), 2.19 (1H, ddd, *J* = 3.7, 7.1, 13.1 Hz), 2.10, (3H, s, COMe), 1.98–1.64 (5H, m), 1.59 (1H, dd, *J* = 2.4, 12.0 Hz), 1.40, 1.35 (3H each, s, Me), 1.11 (6H, s, 2 × Me); δ_C(75 MHz, $CDCl_3$) 215.4, 197.3, 176.7, 170.3, 124.2, 76.2, 52.0, 47.8, 40.4, 40.0, 39.3, 37.2, 37.1, 34.2, 26.3, 23.3, 21.8, 21.2, 20.8, 18.8; *m*/*z* (EI) 332 (M^+, 16%), 272, (14), 247 (20), 246 (100), 190 (22), 122 (63); HRMS (EI): calc. for $C_{20}H_{28}O_4$ (M^+) 332.1988, found 332.1989.

(−)-(4a*R*,8*S*,8a*S*,10a*S*)-(4aα,8α,8aα,10aβ)-8-Acetoxy-4,4a,7,8,8a,9,10,10a-octahydro-1,1,4a,8a-tetramethylphenanthrene-2,6(1*H*,3*H*)-dione (−)-12. The same procedure as for (+)-**12** gave (−)-**12** as an amorphous solid: $[\alpha]_D^{26}$ −40 (*c* 0.53, $CHCl_3$). The UV, IR, ^{1}H NMR, ^{13}C NMR, and MS were identical to those of (+)-**12**.

(−)-(4a*S*,8a*S*,10a*R*)-(4aβ,8aβ,10aα)-4,4a,8a,9,10,10a-Hexahydro-1,1,4a,8a-tetramethylphenanthrene-2,6(1*H*,3*H*)-dione (−)-13. To a solution of (+)-**12** (150 mg, 0.45 mmol) in CH_2Cl_2 (2.5 mL) was added DBU (60 mg, 0.39 mmol). After 1.5 h of stirring at rt, more DBU (20 mg) was added. After an additional 2 h, more DBU (20 mg) was added. After a further 1 h, more DBU (20 mg) was added. After a final 3 h, the reaction mixture was diluted with EtOAc (15 mL) and washed with 5% aqueous HCl solution (3 × 3 mL). The acidic washings were back extracted with EtOAc (6 mL). The combined organic layers were worked up by the standard method to give (−)-**13** (117 mg, 95%) as a crystalline solid and was used without further purification: mp 110–111 °C; $[\alpha]_D^{22}$ −72 (*c* 0.46, $CHCl_3$) (Found: C, 78.50; H, 8.93. $C_{18}H_{24}O_2 \cdot 1/5H_2O$ requires C, 78.34; H, 8.91%); λ_{max}(EtOH)/nm 242 (log ε 4.27); ν_{max}(KBr)/cm^{-1} 3013, 2942, 2851, 1704, 1665, 1621, 1593, 1453; δ_H(300 MHz, $CDCl_3$) 6.69 (1H, d, *J* = 9.8 Hz, 8-H), 6.16–6.13 (2H, m, 5-H and 7-H), 2.77 (1H, ddd, *J* = 6.7, 12.8, 16.3 Hz, 3-H), 2.49 (1H, ddd, *J* = 2.9, 5.9, 16.3 Hz, 3-H), 2.15 (1H, ddd, *J* = 2.9, 6.7, 13.1 Hz), 1.96–1.68 (4H, m), 1.54–1.42 (2H, m), 1.42, 1.40, 1.13, 1.10 (3H each, s, Me); δ_C(75 MHz, $CDCl_3$) 215.1, 187.9, 172.9, 159.0, 125.2, 123.4, 53.7, 48.2, 41.1, 40.6, 37.6, 37.1, 34.4, 27.3, 25.9, 21.9, 20.6, 19.2; *m*/*z* (EI) 272 (M^+, 100%), 229 (47), 215 (23), 187 (28), 173 (29), 148 (53), 135 (36), 122 (87), 107 (41), 91 (45); HRMS (EI): calc. for $C_{18}H_{24}O_2$ (M^+) 272.1776, found 272.1778.

(+)-(4a*R*,8a*R*,10a*S*)-(4aα,8aα,10aβ)-4,4a,8a,9,10,10a-Hexahydro-1,1,4a,8a-tetramethylphenanthrene-2,6(1*H*,3*H*)-dione (+)-13. The same procedure as for (−)-**13** gave (+)-**13** as an amorphous solid: $[\alpha]_D^{26}$ +68 (*c* 0.36, $CHCl_3$);. The UV, IR, ^{1}H NMR, ^{13}C NMR, and MS were identical to those of (−)-**13**.

(−)-(4a*S*,8a*S*,10a*R*)-(4aβ,8aβ,10aα)-1,2,4a,6,8a,9,10,10a-Octahydro-1,1,4a,8a-tetramethyl-2,6-dioxophenanthrene-3-carbonitrile (−)-2 [34]. To a solution of LDA [170 μL (0.34 mmol) of 2.0 M solution in heptane–THF–ethylbenzene] in anhydrous THF (0.125 mL) was added a solution of (−)-**13** (66 mg, 0.24 mmol) in anhydrous THF (0.5 mL) in a dry ice–*i*-PrOH bath at −78 °C. The reaction mixture was allowed to warm to rt over the course of 20 min. The mixture was then transferred with the aid of THF (3 × 0.2 mL) by a gas tight syringe to a stirred suspension of *p*-TsCN (93 mg, 0.51 mmol) in anhydrous THF (0.25 mL) at −78 °C. The reaction mixture was stirred for 5 min at −78 °C and then saturated aqueous NH_4OH solution (0.15 mL) was added. The reaction mixture was acidified with 5% aqueous HCl solution (2 mL) and extracted with EtOAc (3 × 6 mL). The combined organic extracts were worked up by the standard method to give (4a*S*,8a*S*,10a*R*)-**14** (66 mg, 93%, an isomeric mixture) as a crystalline solid. Major tautomer of (4a*S*,8a*S*,10a*R*)-**14**: δ_H(300 MHz, $CDCl_3$) 6.71 (1H, d, *J* = 9.9 Hz, 8-H), 6.18 (1H, d, *J* = 9.6 Hz, 7-H), 6.11 (1H, d, *J* = 1.8 Hz, 5-H), 2.46 (1H, d, *J* = 15.0 Hz, 4-H), 2.35 (1H, d, *J* = 15.0 Hz, 4-H), 1.39, 1.27, 1.25, 1.20 (3H each, s, Me). A mixture of (4a*S*,8a*S*,10a*R*)-**14** and DDQ (52 mg, 0.23 mmol) in anhydrous benzene (6.5 mL) was heated under reflux for 15 min. After removal of insoluble matter, the filtrate was evaporated *in vacuo* to give a residue (97 mg). The residue was purified by flash column chromatography [hexanes–EtOAc (1 : 1.5)] to give (−)-**2** (48 mg, 73%) as an amorphous solid: $[\alpha]_D^{27}$ −115 (*c* 0.28, $CHCl_3$) (Found: C, 76.06; H, 7.43, N 4.50. $C_{19}H_{21}NO_2 \cdot 1/4\ H_2O$ requires C, 76.10; H, 7.23; N, 4.67%); λ_{max}(EtOH)/nm 240 (log ε 4.33); ν_{max}(KBr)/cm^{-1} 2977, 2950, 2874, 2234, 1688, 1681, 1624; δ_H(300 MHz, $CDCl_3$) 8.04 (1H, s, 4-H), 6.72 (1H, d, *J* = 9.8 Hz, 8-H), 6.20 (1H, dd, *J* = 1.5, 9.7 Hz, 7-H), 6.17 (1H, d, *J* = 1.5 Hz, 5-H), 2.05–1.85 (5H, m), 1.61, 1.45, 1.25, 1.17 (each 3H, s, Me); δ_C(75 MHz, $CDCl_3$) 196.3, 186.6, 165.2, 164.6, 158.6, 125.2, 123.4, 114.5, 114.1, 51.3, 45.3, 44.3, 41.3, 38.2, 26.7, 26.0, 22.8, 21.7, 18.3; *m*/*z* (EI) 295 (M^+, 32%), 280 (34), 267 (18), 252 (100), 226 (50), 201 (70), 121 (73); HRMS (EI): calc. for $C_{19}H_{21}NO_2$ (M^+) 295.1572, found: 295.1576.

(+)-(4a*R*,8a*R*,10a*S*)-(4aα,8aα,10aβ)-1,2,4a,6,8a,9,10,10a-Octahydro-1,1,4a,8a-tetramethyl-2,6-dioxophenanthrene-3-carbonitrile (+)-2 [34]. (+)-**2** was obtained *via* (+)-**14** from (+)-**13** by the same method as for (−)-**2** as an amorphous solid: $[\alpha]_D^{26}$ +115 (*c* 0.31, $CHCl_3$) (Found: C, 76.13; H, 7.33, N 4.48. $C_{19}H_{21}NO_2 \cdot 1/4\ H_2O$ requires C, 76.10; H, 7.23; N, 4.67%). The UV, IR, ^{1}H NMR, ^{13}C NMR, and MS were identical to those of (−)-**2**.

(+)-(4a*S*,8a*R*)-(4aβ,8aβ)-4,4a,6,7,8,8a,9,10-Octahydro-1,4a,8a-trimethylphenanthren-2(3*H*)-one (+)-16. To a suspension of prewashed (with hexanes) NaH (1.32 g of 60% oil dispersion, 33 mmol) in anhydrous THF (90 mL) and anhydrous DMSO (10 mL) containing MeOH (0.07 mL) was added (−)-(4a*S*)-4,4a,5,6,7,8-hexahydro-1,4a-dimethylnaphthalen-2(3*H*)-one ((−)-**15**) (6.0 g, 34 mmol, $[\alpha]_D^{27}$ −152 (*c* 3.0, EtOH)) with the aid of anhydrous THF (10 mL). The solution was heated under reflux for 4.5 h and was then cooled to −20 °C. A solution of 1-chloro-3-pentanone (4.66 g, 38 mmol) in anhydrous THF (14 mL) was added with vigorous stirring over a 30 min period. The reaction mixture was stirred at −20 °C for 1 h and allowed to warm to rt over a 4 h period. After removal of the solvent *in vacuo*, MeOH (43 mL) and 20% aqueous KOH solution (43 mL) were added. The mixture was heated under reflux for 7.5 h. After removal of the solvent *in vacuo*, the resultant residue was taken up in water (300 mL) and the aqueous mixture was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic extracts were washed with brine (60 mL) and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave an oil. The oil was purified by Kugelrohr distillation, affording recovered starting material (−)-**15** (1.47 g, 25%) and (+)-**16** (4.40 g, 54%, 71% based on consumed starting material) as an oil (bp 129–135 °C (0.1–0.03 Torr)). The oil was purified by flash column chromatography [hexanes : EtOAc (7 : 1)] to give (+)-**16** (3.59 g) as a semisolid: $[\alpha]_D^{24}$ +110 (*c* 2.5, $CHCl_3$). The IR, ^{1}H NMR, ^{13}C

NMR, and MS were identical to those of the known compound (±)-**16**.[36]

(−)-(4a*R*,8a*S*)-(4aα,8aα)-4,4a,6,7,8,8a,9,10-Octahydro-1,4a,8a-trimethylphenanthren-2(3*H*)-one (−)-16. The same method as for (+)-**16** gave (−)-**16** from (+)-(4a*R*)-4,4a,5,6,7,8-hexahydro-1,4a-dimethylnaphthalen-2(3*H*)-one ((+)-**15**, $[\alpha]_D^{27}$ +153 (*c* 3.3, EtOH), lit.,[35] $[\alpha]_D^{20}$ +199 (*c* 3, EtOH)) as a semisolid: $[\alpha]_D^{26}$ −137 (*c* 2.6, $CHCl_3$). The IR, ^{1}H NMR, ^{13}C NMR, and MS were identical to those of (±)-**16** and (+)-**16**.

(±)-(4aβ,8aβ,10aα)-3,4,4a,6,7,8,8a,9,10,10a-Decahydro-1,1,4a,8a-tetramethylphenanthren-2(1*H*)-one (±)-17 and (±)-(1α,4aβ,8aβ,10aα)-3,4,4a,6,7,8,8a,9,10,10a-decahydro-1,4a,8a-trimethylphenanthren-2(1*H*)-one (±)-18. To liquid ammonia (*ca*. 50 mL) was added Li (255 mg, 37 mmol, 4.5 eq.) at −78 °C. The solution was stirred at −78 °C for 20 min. A solution of (±)-**16** (2.0 g, 8.2 mmol) and water (147 mg, 8.2 mmol, 1 eq.) in freshly distilled THF (27 mL) was added dropwise and the solution was stirred at −33 °C (bp of ammonia; temperature stabilized by a CCl_4 bath) for 1 h. The solution was cooled to −78 °C and isoprene (*ca*. 0.5 mL) was injected until the blue color disappeared, followed by additional THF (10 mL). After removal of ammonia with the aid of a N_2 stream at rt, to the remaining mixture were added successively iodomethane (10 mL, 160 mmol) and THF (10 mL) in an ice bath. The mixture was stirred in the ice bath for 1 h. The mixture was neutralized with 10% aqueous HCl solution (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic extracts were worked up by the standard method to give 2.16 g of crude material. This solid was purified by flash column chromatography [hexanes : EtOAc (7 : 1)] to give (±)-**17** (1.34 g, 63%) as a colorless oil that became a semisolid upon standing and (±)-**18** (270 mg, 13%) as an oil. (±)-**17**: mp 34.5–35.5 °C (Found: C, 82.89; H, 11.05. $C_{18}H_{28}O$ requires C, 83.02; H, 10.84%); ν_{max}(KBr)/cm^{-1} 3049, 2929, 2864, 1707; δ_H(300 MHz, $CDCl_3$) 5.37 (1H, t, *J* = 3.8 Hz, 5-H), 2.71 (1H, ddd, *J* = 6.7, 12.6, 15.9 Hz, 3-H), 2.41 (1H, ddd, *J* = 3.1, 6.0, 15.8 Hz, 3-H), 2.09–2.03 (3H, m), 1.82–1.28 (10H, m), 1.25, 1.22 (3H each, s, Me), 1.08 (6H, s, 2 × Me); δ_C(75 MHz, $CDCl_3$) 217.4, 152.0, 118.1, 54.4, 48.0, 43.0, 42.9, 39.2, 37.9, 35.0, 34.5, 28.6, 26.4, 25.9, 22.8, 21.8, 19.8, 18.3; *m*/*z* (EI) 260 (M^+, 48%), 245 (70), 203 (36), 175 (42), 147 (52), 125 (100), 109 (83); HRMS (EI): calc. for $C_{18}H_{28}O$ (M^+) 260.2140, found 260.2134. (±)-**18**: ν_{max}(neat)/cm^{-1} 2981, 2869, 1711, 1456; δ_H(300 MHz, $CDCl_3$) 5.41 (1H, t, *J* = 3.8 Hz, 5-H), 2.56–2.47 (1H, m), 2.39 (1H, ddd, *J* = 2.2, 5.1, 15.0 Hz, 3-H), 2.31 (1H, d, *J* = 6.3 Hz), 2.09–2.05 (3H, m), 1.73–1.49 (8H, m), 1.46–1.42 (1H, m), 1.30 (1H, dd, *J* = 3.0, 13.3 Hz), 1.27, 1.22 (3H each, s, Me), 1.00 (3H, d, *J* = 6.6 Hz, CHC*H*$_3$); δ_C(75 MHz, $CDCl_3$) 213.7, 150.4, 119.3, 52.7, 45.2, 43.3, 42.3, 38.9, 38.8, 38.2, 34.2, 28.9, 26.6, 22.7, 20.6, 18.4, 11.9; *m*/*z* (EI) 245 (M^+, 57%), 231 (100), 138 (75), 108 (94), 93 (90); HRMS (FAB): calc. for $C_{17}H_{27}O$ ([M + H]$^+$) 247.2062, found: 247.2063.

(+)-(4a*S*,8a*R*,10a*R*)-(4aβ,8aβ,10aα)-3,4,4a,6,7,8,8a,9,10,10a-Decahydro-1,1,4a,8a-tetramethylphenanthren-2(1*H*)-one (+)-17. The same method as for (±)-**17** gave (+)-**17** (yield, 56%) and (+)-**18** (yield, 18%) from (+)-**16** as a semisolid and an oil, respectively. (+)-**17**: $[\alpha]_D^{27}$ +38 (*c* 0.75, $CHCl_3$) (Found: C, 82.81; H, 11.09. $C_{18}H_{28}O$ requires C, 83.02; H, 10.84%). (+)-**18**: $[\alpha]_D^{27}$ +52 (*c* 2.0, $CHCl_3$). The IR, ^{1}H NMR, ^{13}C NMR, and MS of both compounds were identical to those of (±)-**17** and (±)-**18**, respectively.

(−)-(4a*R*,8a*S*,10a*S*)-(4aα,8aα,10aβ)-3,4,4a,6,7,8,8a,9,10,10a-Decahydro-1,1,4a,8a-tetramethylphenanthren-2(1*H*)-one (−)-17. The same method as for (±)-**17** gave (−)-**17** from (−)-**16** as a semisolid: $[\alpha]_D^{27}$ −47 (*c* 0.50, $CHCl_3$). The IR, ^{1}H NMR, ^{13}C NMR, and MS were identical to those of (±)-**17**.

(+)-(4a*S*,8a*S*,10a*R*)-(4aβ,8aβ,10aα)-4,4a,7,8,8a,9,10,10a-Octahydro-1,1,4a,8a-tetramethylphenanthrene-2,6(1*H*,3*H*)-dione (+)-19. To a stirred solution of (+)-**17** (140 mg, 0.54 mmol) in CH_2Cl_2 (2.3 mL) was added *tert*-butyl hydroperoxide (70%, 0.9 mL) followed by CrO_3 (66 mg, 0.66 mmol) in an ice bath. Then, the mixture was stirred at rt for 1 h. The reaction mixture was diluted with a mixture of Et_2O and CH_2Cl_2 (2:1) (20 mL). The organic layer was washed with 5% aqueous NaOH solution (3 × 4 mL) and 5% aqueous HCl solution (2 × 3 mL), and then worked up by the standard method to give a residue (158 mg). It was purified by flash column chromatography [hexanes : EtOAc (2 : 1)] to give (+)-**19** (99 mg, 67%) as an amorphous solid: $[\alpha]_D^{27}$ +85 (*c* 0.50, $CHCl_3$) (Found: C, 78.53; H, 9.57. $C_{18}H_{26}O_2$ requires C, 78.79; H, 9.55%); λ_{max}(EtOH)/nm 242 (log ε 4.14); ν_{max}(KBr)/cm^{-1} 2975, 2945, 2870, 1698, 1665, 1592, 1462; δ_H(300 MHz, $CDCl_3$) 5.84 (1H, s, 5-H), 2.70 (1H, ddd, *J* = 7.1, 11.5, 16.1 Hz, 3-H), 2.64–2.45 (2H, m), 2.38 (1H, ddd, *J* = 2.2, 4.5, 18.1 Hz), 2.15 (1H, ddd, *J* = 3.7, 7.1, 13.2 Hz), 1.93–1.78 (4H, m), 1.73 (1H, ddd, *J* = 2.4, 5.2, 13.1 Hz), 1.68–1.56 (2H, m), 1.48–1.42 (1H, m), 1.39, 1.32, 1.13, 1.12 (3H each, s, Me); δ_C(75 MHz, $CDCl_3$) 215.9, 201.0, 178.2, 123.0, 52.9, 48.1, 41.8, 41.5, 40.3, 36.9, 36.0, 34.4, 34.0, 26.4, 26.3, 22.7, 21.9, 19.5; *m*/*z* (EI) 274 (M^+, 23%), 259 (16), 246 (8), 177 (22), 152 (36), 124 (100); HRMS (EI): calc. for $C_{18}H_{26}O_2$ (M^+) 274.1933, found 274.1935. Chiral HPLC analysis: Both peaks of (−)-**19** and (+)-**19** were observed at 19 (area%, 5) and 21 min (area%, 95), respectively. [column, CHIRALPAK®AD™ (250 × 4.6 mm); mobile phase, hexanes : *i*-PrOH (95 : 5); flow rate, 1 mL min^{-1}; wavelength for the detection, 254 nm].

(−)-(4a*R*,8a*R*,10a*S*)-(4aα,8aα,10aβ)-4,4a,7,8,8a,9,10,10a-Octahydro-1,1,4a,8a-tetramethylphenanthrene-2,6(1*H*,3*H*)-dione (−)-19. The same method as for (+)-**19** gave (−)-**19** from (−)-**17** as a colorless crystalline solid: mp 109–111 °C; $[\alpha]_D^{27}$ −97 (*c* 0.50, $CHCl_3$). The UV, IR, ^{1}H NMR, ^{13}C NMR, and MS were identical to those of (+)-**19**. Chiral HPLC analysis was performed under the same conditions as for (+)-**19**. Both peaks of (−)-**19** and (+)-**19** were observed at 19 (area%, 95) and 21 min (area%, 5), respectively.

(−)-(4a*S*,8a*S*,10a*R*)-(4aβ,8aβ,10aα)-1,2,4a,6,8a,9,10,10a-Octahydro-1,1,4a,8a-tetramethyl-2,6-dioxophenanthrene-3,7-dicarbonitrile (−)-3[34]. To a solution of LDA [350 μL (0.70 mmol, 2.8 eq.) of 2.0 M solution in heptane–THF–ethylbenzene] in anhydrous THF (1 mL) was added a solution of (+)-**19** (69 mg, 0.25 mmol) in anhydrous THF (1.7 mL) in a dry ice–*i*-PrOH bath at −78 °C. The reaction mixture was stirred at −78 °C for 20 min. To the mixture, which was cooled at −78 °C, was added by a gas tight syringe a suspension of *p*-TsCN (181 mg, 1.0 mmol, 4 eq.) in anhydrous THF (0.7 mL with the aid of additional THF, 2 × 0.7 mL). The reaction mixture was stirred for 30 min at −78 °C and then saturated aqueous NH_4OH solution (1.5 mL) was added. The reaction mixture was allowed to warm to rt. It was acidified with 10% aqueous HCl solution (6 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were worked up by the standard method to give (4a*S*,8a*S*,10a*R*)-**20** (90 mg, an isomeric mixture). A mixture of (4a*S*,8a*S*,10a*R*)-**20** and DDQ (107 mg, 0.47 mmol) in anhydrous benzene (8 mL) was heated under reflux for 15 min. After removal of insoluble matter, the filtrate was evaporated *in vacuo* to give a residue (133 mg). The residue was purified by preparative TLC [hexanes : EtOAc (1 : 2)] to give (−)-**3** (55 mg, 68%) as a crystalline solid: mp >210 °C (dec.); $[\alpha]_D^{26}$ −91 (*c* 0.52, $CHCl_3$) (Found: C, 75.00; H, 6.27, N 8.64. $C_{20}H_{20}N_2O_2$ requires C, 74.98; H, 6.29; N, 8.74%); λ_{max}(EtOH)/nm 238 (log ε 4.29); ν_{max}(KBr)/cm^{-1} 2980, 2944, 2873, 2236, 1672, 1460; δ_H(300 MHz, $CDCl_3$) 7.99 (1H, s), 7.39 (1H, s), 6.28 (1H, s, 5-H), 2.13–2.07 (1H, m), 2.02–1.91 (2H, m), 1.85 (1H, dd, *J* = 2.7, 12.0 Hz), 1.67–1.59 (1H, m), 1.63, 1.55, 1.27, 1.18 (3H each, s, Me); δ_C(75 MHz, $CDCl_3$) 195.8, 179.6, 167.3, 165.9, 163.1, 122.3,

114.6, 114.3, 114.2, 113.5, 51.0, 45.4, 44.4, 42.4, 37.5, 26.2, 25.9, 22.8, 21.7, 18.1; *m/z* (EI) 320 (M^+, 28%), 305 (40), 277 (48), 226 (100), 174 (46), 160 (40); HRMS (EI): calc. for $C_{20}H_{20}N_2O_2$ (M^+) 320.1525, found, 320.1522.

(+)-(4a*R*,8a*R*,10a*S*)-(4aα,8aα,10aβ)-1,2,4a,6,8a,9,10,10a-Octahydro-1,1,4a,8a-tetramethyl-2,6-dioxophenanthrene-3,7-dicarbonitrile (+)-3[34]**.** The same method as for (−)-**3** gave (+)-**3** from (−)-**19** as a colorless crystalline solid: mp >210 °C (dec.); $[\alpha]_D^{26}$ +88 (*c* 0.55, $CHCl_3$) (Found: C, 74.83; H, 6.25, N 8.65. $C_{20}H_{20}N_2O_2$ requires C, 74.98; H, 6.29; N, 8.74%). The UV, IR, ^{1}H NMR, ^{13}C NMR, and MS were identical to those of (−)-**3**.

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