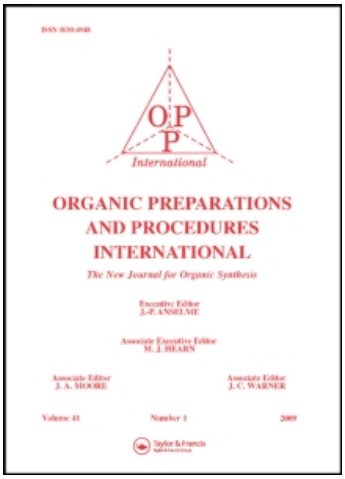

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AN EFFICIENT SYNTHESIS OF TRICYCLIC COMPOUNDS, (±)-(4aβ,8aβ,10aα)-1,2,3,4,4a,6,7,8,8a,9,10,10a-DODECAHYDRO-1,1,4a-TRIMETHYL-2-OXOPHENANTHRENE-8a-CARBOXYLIC ACID, ITS METHYL ESTER, AND (±)-(4aβ,8aβ,10aα)-3,4,4a,6,7,8,8a,9,10,10a-DECAHYDRO-8a-HYDROXYMETHYL-1,1,4a-TRIMETHYLPHENANTHREN-2(1*H*)-ONE

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AN EFFICIENT SYNTHESIS OF TRICYCLIC COMPOUNDS, (±)-(4aβ,8aβ,10aα)-1,2,3,4,4a,6,7,8,8a,9,10,10a-DODECAHYDRO-1,1,4a-TRIMETHYL-2-OXOPHENANTHRENE-8a-CARBOXYLIC ACID, ITS METHYL ESTER, AND (±)-(4aβ,8aβ,10aα)-3,4,4a,6,7,8,8a,9,10,10a-DECAHYDRO-8a-HYDROXYMETHYL-1,1,4a-TRIMETHYLPHENANTHREN-2(1*H*)-ONE

Submitted by (09/09/05)

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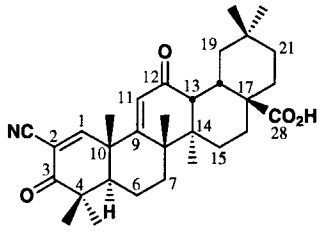
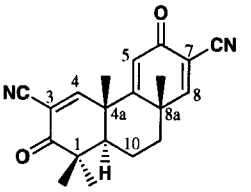
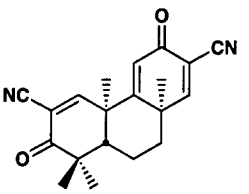
Our ongoing efforts for the improvement of anti-inflammatory and anti-proliferative activity of oleanolic acid analogues led us to discover 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO, **1**) and related compounds.[1]



1 CDDO



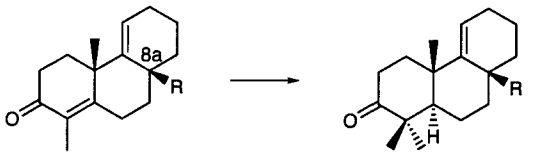
(–)-2



(+)-2

In connection with these investigations, we have found that tricyclic compounds with similar enone functionalities in rings A and C are also a novel class of highly active inhibitors of nitric oxide (NO) production in mouse macrophages.[2] In particular, *bis*-cyano enone (±)-**2** is orally active in a preliminary in vivo inflammation model.[2] In addition, we have found that (+)-**2** having the opposite configuration to that of CDDO shows 10 times higher inhibitory activity than (–)-**2** on NO production in mouse macrophages.[3]

These results encouraged us to design and synthesize analogues of **2**. Thus, we focused our attention on the modifications of the C-8a position, because some biologically active natural products have functionalities at the same position (*e. g.*, anti-tumor quassinoids[4]). For our projected synthesis of C-8a functionalized TBE compounds, the simple tricycles **3**-**5** are potentially very desirable intermediates.



6: R = CO_2H
7: R = CO_2Me
8: R = CH_2OH

3: R = CO_2H
4: R = CO_2Me
5: R = CH_2OH

We envisioned preparing **3**-**5** from the known acid **6**[5,6] by standard reductive methylation.[7] However, attempts to reductively methylate acid **6** with 5-7 equivalents of lithium in liquid ammonia containing no proton donor, followed by esterification with diazomethane gave **4** in 30% yield (average of 7 experiments, the yield fluctuates) along with many by-products. These by-products caused serious difficulty for the purification of **4**. An attempt with one equivalent of *tert*-butanol gave similar results as without a proton donor. Attempts to reductively methylate methyl ester **7**,[6] which is prepared from **6** with diazomethane, using 10 equivalents of lithium in liquid ammonia containing no proton donor gave the desired compounds **3**-**5** in low yield along with several by-products including enones **6** and **8**.

After much experimentation, it was found that the addition of one equivalent of water dramatically improves this reductive methylation reaction. Thus, the reductive methylation of **7** using 7.2 equivalents of lithium and *one equivalent of water* followed by quenching the excess

lithium with isoprene, and then methyl iodide at –78°C cleanly produced **3-5** in 38%, 15%, and 36% yields (total 89%), respectively. The yields are reproducible and **3-5** were prepared several times by this procedure. These compounds can be easily separated by extracting the acid with aqueous base, followed by column chromatography (see Experimental Section). In addition, they were easily converted to a single compound. For example, oxidation (*e. g.*, Jones reagent and RuO_2-$NaIO_4$ etc.) of alcohol **5** gave acid **3**, and both acid **3** and methyl ester **4** were converted to alcohol **5** in three steps (ketalization, reduction with $LiAlH_4$, and deketalization). Acid **3** may be an important intermediate for the synthesis of abietane and totarane diterpenoids.

EXPERIMENTAL SECTION

Melting points were determined on a capillary melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 300 MHz or 75 MHz, respectively. Elemental analyses were performed by Atlantic Microlab, Inc, Norcross, GA. THF was purified by a solvent purification system. All other solvents (analytical grade) and reagents were used as received.

(±)-(4aβ,8aβ,10aα)-1,2,3,4,4a,6,7,8,8a,9,10,10a-Dodecahydro-1,1,4a-trimethyl-2-oxophenanthrene-8a-carboxylic acid (3), its Methyl Ester (4), and (±)-(4aβ,8aβ,10aα)-3,4,4a,6,7,8,8a,9,10,10a-Decahydro-8a-hydroxymethyl-1,1,4a-trimethylphenanthren-2(1*H*)-one (5).- To liquid ammonia (100 mL) was added lithium (600 mg, 86 mmol, 7.2 eq, sliced ribbon). The solution was stirred at –78°C for 15 min. Compound **7**[6] (3.5 g, 12 mmol) and water (218 mg, 12 mmol, 1 eq) in THF (47 mL) were added dropwise and the mixture was stirred under reflux at –33°C (bp of ammonia) (with the aid of a CCl_4 bath) for 1 h. The mixture was cooled to –78°C and isoprene (approx. 1.25 mL) was injected until the blue color disappeared turning the solution cloudy white. To this mixture were successively added THF (17.5 mL) and iodomethane (17.5 mL) dropwise. The reaction mixture was stirred under reflux at –33°C for 1 h. After removal of the ammonia with the aid of a nitrogen stream, 10% aqueous HCl (2 x 60 mL, 2 x 30 mL) was added to the mixture to acidify. The acidic mixture was extracted with CH_2Cl_2 (4 x 50 mL). The combined organic extracts were washed with brine (2 x 25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 3.8 g of crude product. A solution of the material in ethyl acetate (100 mL) was extracted with 5% aqueous NaOH solution (2 x 25 mL) and water (1 x 25 mL). The aqueous basic extract was acidified with 10% aqueous HCl to give a cloudy suspension. The acidic aqueous mixture was extracted with ethyl acetate (3 x 25 mL). The extract was washed with water (3 x 25 mL), brine (1 x 25 mL), dried over $MgSO_4$, and filtered. The filtrate was evaporated *in vacuo* to give acid **3** as an amorphous solid (1.33 g, 38%). The organic layer including neutral compounds was washed with saturated aqueous ammonium chloride (2 x 25 mL) and brine (2 x 25 mL), dried over $MgSO_4$, and filtered. The filtrate was evaporated *in vacuo* to give a residual oil (2.33 g) that was purified by flash column chromatography [hexanes:EtOAc 3:1, followed by 2:1] to give methyl ester **4** (547 mg, 15%) and alcohol **5** (1.21 g, 36%) as crystalline solids.

Acid **3**: IR (KBr): 3200, 2943, 1691, 1457 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.72 (1 H, dd, J = 3.1, 4.6 Hz), 2.73 (1 H, ddd, J = 6.3, 13.6, 15.8 Hz), 2.58 (1 H, dt, J = 3.2, 13.4 Hz), 2.41 (1 H, ddd, J = 3.0, 5.2, 15.8 Hz), 2.20-1.20 (13 H m)[8] 1.16, 1.06, 1.04 (3 H each, s). ^{13}C NMR ($CDCl_3$): δ 217.0, 183.3, 144.5, 122.4, 54.5, 48.0, 45.5, 40.2, 38.34, 38.27, 36.8, 35.0, 25.8, 25.5, 22.2, 21.04, 21.03, 18.0. EIMS (70 eV) *m/z*: 290 [M^+] (20), 245 (26), 91 (100). HREIMS: Calcd for $C_{18}H_{26}O_3$ 290.1882. Found: 290.1880.

Anal. Calcd for $C_{18}H_{26}O_3$•1/4 H_2O: C, 73.31; H, 9.06. Found: C, 73.52; H, 8.92

Methyl ester **4**: mp 90-92°C. IR (KBr): 2941, 2858, 1716, 1445 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.68 (1 H, dd, J = 3.5, 4.6 Hz), 3.70 (3 H, s), 2.73 (1 H, ddd, J = 6.4, 13.6, 16.0 Hz), 2.60 (1 H, dt, J = 3.3, 13.3 Hz), 2.41 (1 H, ddd, J = 3.0, 5.2, 16.0 Hz), 2.30-1.06 (12 H, m),[8] 1.06 (6 H, s), 1.03 (3 H, s). ^{13}C NMR ($CDCl_3$): δ 216.7, 177.4, 145.1, 121.8, 54.6, 51.9, 47.9, 45.6, 40.1, 38.6, 38.3, 36.8, 35.0, 25.8, 25.6, 22.1, 21.0, 20.0, 18.2. EIMS (70 eV) *m/z*: 304 [M^+] (31), 245 (100), 159 (33). HREIMS: Calcd for $C_{19}H_{28}O_3$ 304.2038. Found: 304.2039.

Anal. Calcd for $C_{19}H_{28}O_3$•1/5 H_2O: C, 74.09; H, 9.29. Found: C, 73.99: H, 9.22

Alcohol **5**: mp 109-110°C. IR (KBr): 3454, 2931, 2859, 1645, 1448 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.67 (1 H, t, J = 3.8 Hz), 3.68 (2 H, s), 2.68 (1 H, ddd, J = 6.6, 12.5, 15.7 Hz), 2.43 (1 H, ddd, J = 3.3, 5.9, 15.7 Hz), 2.20-1.00 (14 H, m)[8], 1.20 (3 H, d, J = 0.6 Hz), 1.08 (3 H, s), 1.06 (3 H, s). ^{13}C NMR ($CDCl_3$): δ 217.0, 148.0, 123.0, 67.0, 54.1, 47.9, 39.7, 39.0, 38.0, 37.1, 36.7, 34.9, 26.1, 26.0, 22.6, 21.8, 19.7, 18.1. EIMS (70 eV) *m/z*: 276 [M^+] (6.1), 245 (100), 227 (10), 203 (6.1). HREIMS: Calcd for $C_{18}H_{28}O_2$ 276.2089. Found: 276.2082.

Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 77.92; H, 10.12

Acknowledgment.- We thank Dr. Steven Mullen (University of Illinois) for the mass spectra. This investigation was supported by funds from NIH Grant 5R03-CA105294.

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8. Overlapped signals which cannot be assigned.

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A SYNTHESIS OF SELECTED *o,o'*-DISUBSTITUTED DIARYLACETIC ESTERS AND DIARYLMETHANES

Submitted by: (7/26/05) Richard A. Bunce* and James E. Schammerhorn†

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A recent project required access to 2-(2-nitrobenzyl)benzoic acid (**4a**) for a cyclization study to prepare 5,11-dihydro-6*H*-dibenz[*b.e*]azepin-6-one.[1] This compound has been previously synthesized by nitration of 2-benzylbenzoic acid,[2] but it was not purified from the accompanying C-4 nitration product. We, therefore, sought a method to prepare the C-2 nitrated compound in pure form. Our synthetic plan involved (1) nucleophilic aromatic substitution of the 2-[2-(methoxycarbonyl)phenyl]acetate anion (**2a**) to 2-fluoro-1-nitrobenzene, (2) basic hydrolysis of the two esters, and (3) selective decarboxylation of the doubly benzylic acid group.[3] Previous work in this laboratory[4] and by others[5] has shown that stabilized anions can be added to 2- and 4-halo-1-nitrobenzenes by nucleophilic aromatic substitution but, to date, additions of methyl phenylacetate derivatives bearing anion-stabilizing electron withdrawing groups at C-2 of the aromatic ring have not been described. We report here our results on the application of this strategy to the synthesis of several *o,o'*-disubstituted diarylacetic esters and diarylmethanes.