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Synthesis of 13β-Analogs of Azadiradione.

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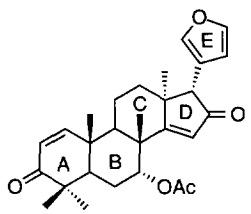
Abstract: The synthesis of keto ester **15** related to the limonoid antifeedant azadiradione has been achieved in nine steps starting from hydroxy ester **1**. The key steps involve a Nazarov cyclization **6**→**10** and a stereoselective epoxy ketone rearrangement to enone **13** →**15**.

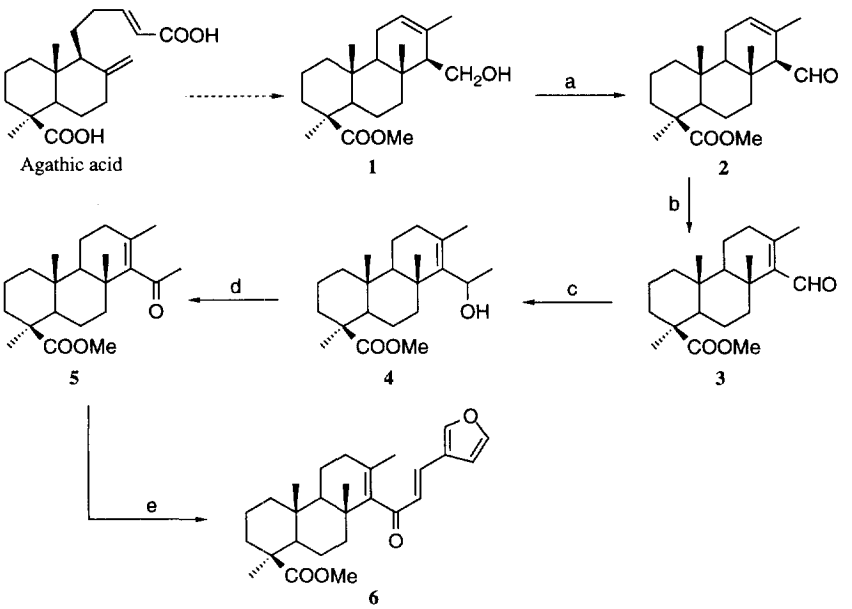
In recent years the Nazarov reaction has been recognised as a powerful and versatile method for the preparation of natural products containing a cyclopentenone unit in their structure[1]. In previous studies we have investigated application of the Nazarov reaction to the synthesis of model insect antifeedants and have devised a high-yielding route to the CDE fragment of azadiradione[2]. This provided compounds useful for structure-activity relationship studies.



Azadiradione

In the present work we prepared several compounds which contain some of the key features of the natural product azadiradione. The approach used for their construction is based upon the described strategy developed for the synthesis of the azadiradione CDE fragment.

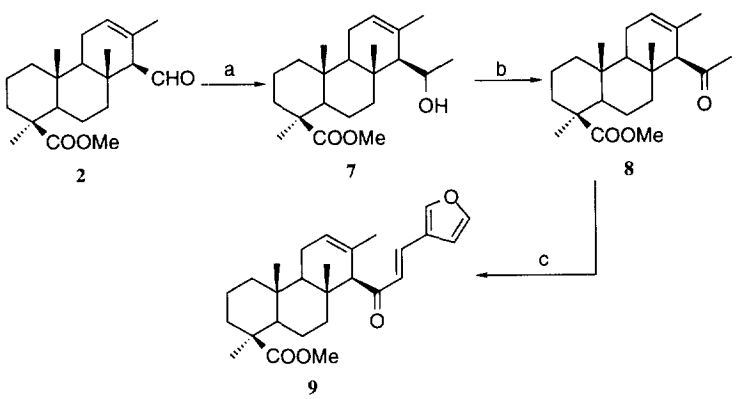
The tricyclic hydroxy ester **1**, readily available from agathic acid[3], was selected as starting material. The homoallylic alcohol was oxidized quantitatively by the Swern procedure to the aldehyde **2**. Subsequent isomerization of **2** was carried out with pTsOH in toluene under reflux to afford the conjugated aldehyde **3** in 74 % yield. Treatment of the oxoester **3** with MeLi in ether at -10 °C furnished the desired hydroxy ester **4** exclusively. Although there are two carbonyl group in **3**, the reaction is chemoselective due to steric hindrance of the carbonylic ester group and the higher electrophilic character of the aldehyde.



a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; b) pTsOH, benzene, 80 °C; c) MeLi, ether, -10 °C; d) Dess-Martin reagent, CH_2Cl_2; e) 3-Furaldehyde, NaOH, EtOH.

Further oxidation of the allylic alcohol **4** to the ketone **5** was accomplished either with manganese dioxide (41%), Jones (68 %) or Dess-Martin reagent[4] (95 %). The divinyl keto ester **6** was obtained in 80 % yield by simple aldolic condensation of the methyl ketone **5** with 3-furaldehyde in methanol, using sodium hydroxide as a basic agent[5].

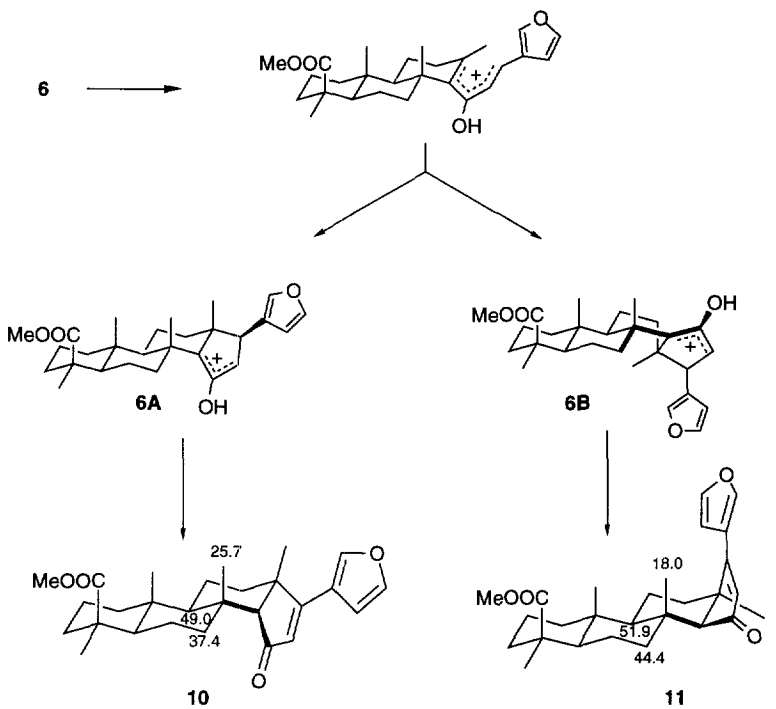
The same sequence was applied to the aldehyde **2**, which afforded the allyl vinyl ketoester **9** in 78 % overall yield passing through hydroxy ester **7** and keto ester **8**.



a) MeLi, -10 °C; b) Jones, acetone, 0 °C; c) 3-Furaldehyde, NaOH, EtOH.

Cationic electrocyclization of divinyl ketone **6** was performed with a 1:1 mixture of formic and phosphoric acids to afford after 7 hours at 75 °C a mixture of the two keto esters **10** and **11** in the ratio 6:4

respectively, with a 59 % yield. Under the same treatment the allyl vinyl ketone **9** requires 26 hours for completion to give the same keto ester mixture **10** and **11** with a lower yield (21%). When the acids used were acetic and sulphuric 2:1 in toluene, the reaction yield was 79 % and a keto ester ratio of 3:1 respectively, was obtained. The factors controlling the sense of torquoselection in the Nazarov cyclization are primarily steric in origin. Interestingly, the major product **10** arises from the intermediate **6A** with a 1,3 diaxial nonbonded interaction between methyl groups, while the opposite intermediate **6B** passes through a ring C boat conformation.

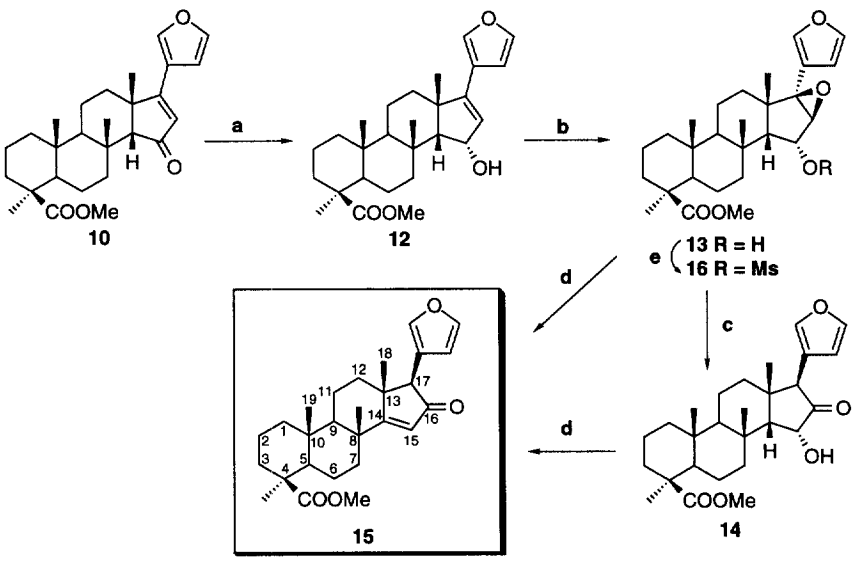


The respective structures of **10** and **11** were assigned on a basis of spectroscopic evidence. The H-C correlations and diamagnetic shielding effect of the enone system permitted us to assign the signal at 0.84 ppm in the ^{1}H NMR to the methyl group bonded to the C-8 carbon and the corresponding signal at 18.0 ppm in ^{13}C NMR to the minor Nazarov reaction product **11**. The respective signals in the major keto ester **10** appear at 1.19 ppm and 25.7 ppm. The most significant differences between keto esters **10** and **11** are observed in the ^{13}C NMR displacements. While in the major ketone **10** the signals assigned to carbons C-7 and C-9 shielded by D ring[6] appear at 37.4 ppm and 49.0 ppm, in the minor ketone **11** they appear at lower field, 44.4 ppm and 51.9 ppm, respectively.

The assigned structures agree with the chemical behaviour; thus 13β isomer **10** is reduced to hydroxy ester **12** with a mixture of sodium borohydride/cerium trichloride in methanol at room temperature in thirty minutes, while the 13α isomer **11** is not reduced even at reflux temperature. It is clear from molecular models that the carbonyl group in C-14 in the 13β isomer **10** shows no steric hindrance from the β face while in the

11 isomer it exhibits severe impediments from both faces.

Transformation of the keto ester **10** into the analog of the azadiradione **15** was carried out in several different ways. The first approach consisted of a four step sequence: reduction with sodium borohydride afforded chemo- and stereoselectively the hydroxy ester **12** in 85 % yield. Subsequent treatment of **12** with m-chloroperoxybenzoic acid in CH_2Cl_2 at -40 °C gave only the epoxide **13** in 93 % yield. After reaction of **13** with a catalytic amount of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at -30 °C the hydroxy keto ester **14** was obtained exclusively in 70 % yield. The last step to the 13β-azadiradione analog **15** was attempted with thionyl chloride and phosphoryl chloride in pyridine without success. Fortunately, treatment of **14** with pTsOH in toluene afforded the keto ester **15** in 70 % yield.



a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH; b) mCPBA, CH_2Cl_2, -40 °C; c) $BF_3{\cdot}Et_2O$, CH_2Cl_2, -30 °C; d) pTsOH, Toluene, reflux; e) MsCl, Pyridine, 5 °C.

As an alternative to the above sequence the order of events was changed. Starting from the epoxy alcohol **13** the first dehydration step was attempted by mesylation and subsequent elimination, using DBU in toluene at reflux. However, after treatment of the mesylate **16** with DBU, the starting material was recovered. When the mesylate **16** was treated with pTsOH in toluene at reflux the desired analog **15** was obtained in 72 % overall yield from **13**.

After this experiment we attempted to transform the epoxy alcohol grouping in the cyclopentenone system in a single step. This could be viable if the protic acid pTsOH which promotes the dehydration of the hydroxy ketone promotes also the rearrangement of the epoxide to the ketone. As expected, treatment of **13** with pTsOH in toluene at reflux afforded only the keto ester **15** in 76 % yield.

The epoxide rearrangement of **13** to give either **14** or **15** is absolutely stereoselective[7]. The relative orientation of furan with respect to the C-13 methyl group was assigned on the basis of H-C correlations

(Table II) and the diamagnetic shielding effect caused in the methyl group by the furan which has been observed in related compounds[8].

The synthetic approach to 13β limonoid analogs described here is short and stereocontrolled. Its brevity stems from the effective cyclization and rearrangements methods. Further more, a new procedure for the formation of the required cyclopentenone portion has been established.

Table I ^{13}C NMR Chemical Shifts for **10-15**.

	10		**11**		**12**		**13**		**14**		**15**	
	C	H	C	H	C	H	C	H	C	H	C	H
1	39.3		39.7		40.2		39.2		39.8		39.8	
2	19.4		18.8		19.4		19.1		19.3		19.0	
3	37.8		37.9		38.1		38.1		38.9		37.9	
4	43.7		43.7		43.8		43.8		44.1		43.8	
5	56.7		57.3		57.3		57.2		57.6		56.7	
6	18.6		19.7		17.3		19.3		19.6		19.6	
7	37.4		44.4		40.9		40.4		40.4		40.1	
8	39.4		38.9		36.7		35.8		37.0		40.2	
9	49.0		51.9		53.8		53.5		51.5		57.8	
10	38.4		38.5		37.7		37.6		38.3		38.6	
11	18.8		17.7		19.1		17.3		18.4		17.8	
12	33.4		30.3		40.3		35.7		38.0		41.0	
13	47.4		45.7		47.5		42.5		39.2		48.1	
14	68.6	1.90	69.7	1.80	72.0		61.3		57.2		194.6	
15	209.0		209.9		76.7	4.80	72.7	4.20	74.9	4.29	122.4	5.81
16	128.3	6.09	127.5	6.17	126.5	5.65	65.0	3.55	218.5		206.8	
17	172.9		173.5		147.0		67.7		62.1	3.13	60.0	3.40
18	28.7	1.40	27.7	1.36	25.7	1.34	24.5	1.25	25.5	0.97	25.6	0.98
19	13.0	0.64	12.8	0.72	14.1	0.69	13.9	0.65	13.9	0.69	14.1	0.75
C-α	143.5	7.76	143.6	7.78	142.5	7.41	142.5	7.42	142.9	7.36	142.7	7.38
C-α'	142.1	7.44	142.9	7.46	139.0	7.36	141.3	7.35	141.1	7.28	141.4	7.40
C-β	119.5		119.7		120.3		119.1		120.3		118.8	
C-β'	109.9	6.55	110.0	6.58	110.2	6.40	110.6	6.36	111.2	6.20	111.3	6.19
CH_3-(C-8)	25.7	1.19	18.0	0.84	24.9	1.20	21.5	1.12	24.8	1.18	21.4	1.24
CH_3-(C-4)	28.5	1.11	28.6	1.17	28.6	1.19	28.6	1.17	28.7	1.17	28.6	1.19
CO-(C-4)	178.0		178.0		177.9		177.9		177.8		177.6	
CH_3-(-OMe)	51.1	3.59	51.2	3.62	51.1	3.65	51.1	3.63	51.0	3.64	51.2	3.65

Table II $^{1}H/^{13}C$ long range correlations.

10		**11**		**15**	
H	C	H	C	H	C
CH_3 (C-4)	3, 4, 5, -CO_2Me (C-4)	CH_3 (C-4)	3, 4, 5, -CO_2Me (C-4)	CH_3 (C-4)	3, 4, 5, -CO_2Me (C-4)
CH_3 (C-8)	7, 8, 9, 14	CH_3 (C-8)	7, 8, 9, 14	CH_3 (C-4)	8, 9, 14
C-14	8, 9, 13, 15, 18, CH_3 (C-8)	C-14	7, 9, 15, 18, CH_3 (C-8)	C-17	12, 13, 16, C-α, C-β, C-β', 18
C-18	12, 13, 14, 17	C-18	12, 13, 14, 17	C-18	12, 13, 14, 17
C-19	1, 5, 9, 10	C-19	1, 5, 9, 10	C-19	1, 5, 9, 10

Experimental

General Methods. Commercial reagents were used as received. Dichloromethane, dimethylsulfoxide, pyridine and triethylamine were distilled under nitrogen over calcium hydride. Benzene, ether, and toluene were distilled from sodium. Acetone, ethanol, hexane and methanol were distilled before use. Melting points were determined on a hot-stage apparatus and are not corrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 200 and 50 MHz respectively. IR spectra were obtained as thin films. All reactions were carried out under an atmosphere of nitrogen in glassware dried overnight and cooled under nitrogen. Reactions were monitored by TLC. Flash column chromatographies were carried out using silica gel 60 (0.040-0.063 mm Merck). Organic extracts were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure with the aid of a rotary evaporator.

Methyl ent-15-oxo-isocopal-12-en-19-oate 2.- A solution of dimethyl sulfoxide (0.35 mL, 4.94 mmol) in CH_2Cl_2 (1.3 mL) was added dropwise to a stirred solution of oxalyl chloride (0.21 mL, 2.47 mmol) in CH_2Cl_2 (8.1 mL) under N_2 at -60 °C. After 5 min, a solution of the alcohol **1** (750 mg, 2.24 mmol) in CH_2Cl_2-DMSO (3:1, 3.2 mL) was added dropwise. The reaction mixture was stirred for a further 20 min, triethylamine (1.6 mL, 11.7 mmol) was added at -60 °C, and stirring was continued for a further 10 min. Then, it was allowed to warm to room temperature and water was added. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined extracts were washed with water, dried and filtered. The solvent was removed to afford the aldehyde **2** as a crystalline product (7.42, 100 %): mp. 120-121 °C; IR 2980, 1700 cm^{-1}; ^{1}H NMR δ: 0.74 (s, 3H), 1.06 (s, 3H), 1.17 (s, 3H), 1.61 (s, 3H), 3.63 (s, 3H), 5.64 (m, 1H), 9.68 (d, 1H, J = 5 Hz) ppm; Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.95; H, 9.62.

Methyl ent-15-oxo-isocopal-13-en-19-oate 3.- To a solution of aldehyde **2** (720 mg, 2.17 mmol) in dry benzene (2.5 mL), pTsOH (37 mg, 0.22 mmol) was added and the mixture was heated at reflux temperature for 2 h. Then, saturated aqueous $NaHCO_3$ was added. The organic phase was separated and the aqueous phase was extracted with ether. Extracts were washed with brine and dried. Distillation at reduced presure afforded a crude which was chromatographed using hexane-ether (6:4) to give the aldehyde **3** (533 mg, 74%) as a solid compound: mp. 97-98 °C; IR: 2980, 1720, 1640 cm^{-1}; ^{1}H NMR δ: 0.67 (s, 3H), 1.14 (s, 3H), 1.17 (s, 3H), 2.00 (s, 3H), 3.62 (s, 3H), 10.02 (s, 1H) ppm; MS m/z (relative intensity) 332 (58, M^+), 317 (24), 303 (48), 257 (20), 223 (34), 181 (22), 149 (34), 135 (40), 121 (100), 109 (59), 93 (56), 81 (70), 67 (58); Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.99; H, 9.78.

Methyl ent-15-hydroxy-15-methyl-isocopal-13-en-19-oate 4.- To a stirred solution of aldehyde **3** (500 mg, 1.51 mmol) in ether (7.8 mL) at -10 °C under N_2, a solution of methyl lithium (1.5 M in ether, 1.1 mL, 1.66 mmol) was gradually added. The mixture was stirred at -10 °C for 30 min. Then, saturated aqueous NH_4Cl was added, the organic phase was separated, and the aqueous phase was extracted with ether. Extracts were washed with brine and dried. Distillation at reduced pressure afforded an amorphous solid identified as **4** (514 mg, 98 %): IR 3400, 2980, 1720 cm^{-1}; ^1H NMR δ 0.71 (s, 3H), 0.94 (s, 3H), 1.18 (s, 3H), 1.40 (d, 3H, J = 8 Hz), 1.88 (s, 3H), 3.63 (s, 3H), 4.58 (q, 1H, J = 8 Hz) ppm; MS m/z (relative intensity) 348 (8, M^+), 304 (64), 289 (26), 236 (45), 177 (38), 149 (40), 121 (100), 107 (72), 81 (70), 69 (64); Anal. Calcd. for $C_{22}H_{36}O_3$: C, 75.82; H, 10.41. Found: C, 75.75; H, 10.49.

Methyl ent-15-oxo-15-methyl-isocopal-13-en-19-oate 5.- To a solution of alcohol **4** (400 mg, 1.15 mmol) in dry CH_2Cl_2 (17 mL), Dess-Martin periodinane (534 g, 1.26 mmol) in dry CH_2Cl_2 (2.1 mL) was added while stirring at room temperature under argon. When alcohol **4** had been completely consumed (15 min), the reaction mixture was poured into a solution of $NaHCO_3$ (10 mL, 1M) and $Na_2S_2O_3$ (67 mL, 0.125M) and stirred for 15 min. The organic layer was washed with H_2O and dried. The combined solvent portions were concentrated in vacuo to afford a crystalline product identified as the ketone **5** (380 mg, 95 %): mp 149 °C; $[\alpha]_D$=-33.96 (c=0.63, $CHCl_3$); IR: 2980, 1720, 1690 cm^{-1}; ^1H NMR δ 0.63 (s, 3H), 1.12 (s, 3H), 1.14 (s, 3H), 1.49 (s, 3H), 2.21 (s, 3H), 3.58 (s, 3H) ppm; MS m/z (relative intensity): 346 (10, M^+), 318 (34), 235 (38), 175 (28), 161 (22), 149 (34), 135 (44), 121 (86), 93 (66), 81 (90), 67 (70), 55 (100); Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 75.37; H, 9.97.

Condensation of methyl ent-15-oxo-15-methyl-isocopal-13-en-19-oate 5 with 3-furaldehyde.- To a solution of the ketone **5** (415 mg, 1.22 mmol) in ethanol (1.5 mL), 3-furaldehyde (119 mg, 1.22 mmol) and NaOH (97 mg, 2.44 mmol) were gradually added. The reaction was stirred vigorously for 2 h at room temperature. The mixture was concentrated in vacuo to afford a residue which was dissolved with water and extracted with ether. The organic layers were washed with brine, dried and filtered. The solvent was evaporated and the residue was purified by flash chromatography using hexane-ether (8:2) as the eluting solvent, to give an amorphous solid identified as **6** (407 mg, 80% yield): $[\alpha]_D$=-22.3 (c=0.96, $CHCl_3$); IR 2980, 1720, 1690, 1600 cm^{-1}; ^1H NMR δ 0.69 (s, 3H), 1.13 (s, 3H), 1.23 (s, 3H), 1.51 (s, 3H), 3.62 (s, 3H), 6.44 (d, $1H_a$, J = 16 Hz), 6.62 (m, 1H-β'), 7.26 (d, $1H_b$, J = 16 Hz), 7.45 (m, 1H-α), 7.70 (m, 1H-α') ppm; ^{13}C NMR δ 13.7, 17.8, 19.0, 19.9, 20.7, 21.5, 28.4, 32.4, 37.8, 38.1, 38.9, 39.9, 43.7 (2), 51.0, 54.7, 57.1, 107.5, 123.0, 129.5 (2), 134.8, 143.5, 144.4, 144.8, 177.6, 200.0 ppm; MS m/z (relative intensity) 424 (40, M^+), 343 (20), 303 (10), 243 (11), 202 (30), 121 (100), 84 (72).

Methyl ent-15-hydroxy-15-methyl-isocopal-12-en-19-oate 7.- To a stirred solution of aldehyde **2** (100 mg, 0.30 mmol) in ether (1.5 mL) at -10 °C under N_2, a solution of methyl lithium (1.5 M in ether, 0.22 mL, 0.33 mmol) was gradually added. The mixture was stirred at -10 °C for 30 min. Then, saturated aqueous NH_4Cl was added, the organic phase was separated, and the aqueous phase was extracted with ether. Extracts were washed with brine and dried. Distillation under reduced pressure afforded an amorphous solid identified as **7** (93 mg, 89 %): mp 118-119 °C; IR 3400, 2980, 1720 cm^{-1}; ^1H NMR δ 0.71 (s, 3H), 0.95 (s, 3H), 1.15 (s, 3H), 1.35 (d, 3H, J = 8 Hz), 1.86 (s, 3H), 3.62 (s, 3H), 4.12 (q, 1H, J = 8 Hz), 5.55 (br s, 1H) ppm; MS m/z (relative intensity) 348 (2, M^+), 304 (50), 236 (40), 177 (45), 161 (30), 135 (38), 121 (100), 107 (72), 91 (65), 79 (45), 67 (45), 55 (60); Anal. Calcd. for $C_{22}H_{36}O_3$: C, 75.82; H, 10.41. Found: C,

75.99; H, 10.37.

Methyl ent-15-oxo-15-methyl-isocopal-12-en-19-oate 8.- To a stirred and ice-cooled solution of **7** (80 mg,0.23 mmol) in acetone (6 mL) Jones reagent was added dropwise until the red color in solution became permanent after 5 min. Then, isopropilic alcohol was added. The solvent was evaporated under reduced presure to affrod a residue which was dissolved in water and extracted with ether. The extracts were washed with brine, dried and evaporated to afford a solid product identified as keto ester **8** (76 mg,96 %): mp 96-97 °C; $[\alpha]_D$=+4.12 (c=1.48, $CHCl_3$); IR 2980, 1720 cm^{-1}; ^1H RMN δ 0.74 (s, 3H), 0.92 (s, 3H), 1.20 (s, 3H), 1.54 (s, 3H), 2.18 (s, 3H), 3.63 (s, 3H), 5.60 (m, 1H) ppm; MS m/z (relative intensity) 346 (46, M^+), 303 (45), 243 (35), 177 (25), 161 (28), 135 (58), 121 (100), 109 (90), 91 (60), 79 (52), 55 (54); Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 75.15; H, 9.92.

Condensation of methyl ent-15-oxo-15-methyl-isocopal-12-en-19-oate 8 with 3-furaldehyde.- To a solution of the ketone **8** (60 mg, 0.17 mmol) in ethanol (0.3 mL), 3-furaldehyde (17 mg, 0.17 mmol) and NaOH (13.6 mg, 0.34 mmol) were gradually added. The reaction was stirred vigorously for 2 h at room temperature. The mixture was concentrated in vacuo to afford a residue which was dissolved with water and extracted with ether. The organic layers were washed with brine, dried and filtered. The solvent was evaporated and the residue was purified by flash chromatography using hexane-ether (8:2) as the eluting solvent, to give a product identified as **9** (65 mg, 88 %): $[\alpha]_D$=-2.01 (c=1.44, $CHCl_3$); IR 2980, 1720, 1685 cm^{-1}; ^1H NMR δ 0.74 (s, 3H), 0.94 (s, 3H), 1.16 (s, 3H), 1.50 (s, 3H), 3.62 (s, 3H), 5.57 (m, 1H), 6.47 (d, $1H_a$, J = 16 Hz), 6.60 (m, 1H-β'), 7.41 (d, $1H_b$, J = 16 Hz), 7.43 (m, 1H-α), 7.69 (m, 1H-α') ppm; MS m/z (relative intensity) 424 (10, M^+), 346 (19), 303 (21), 275 (23), 173 (37), 121 (100), 84 (72).

Cyclization of divinyl ketone 6.- A) Divinyl ketone **6** (190 mg, 0.45 mmol) was dissolved in 85 % phosphoric acid (0.5 mL) and 90 % formic acid (0.5 mL) and the mixture was heated at 75 °C for 7 h under a nitrogen atmosphere. After cooling, the reaction was treated with water and extracted with ether. The organic layer was washed with NaOH (2 %) and brine, dried and evaporated. The residue was chromatographed using hexane-ether (7:3) as eluent.

The first fraction (67 mg, 35 %), which was a crystalline product, was identified as 4α,8β-dimethyl-17-(3'-furyl)-4β-methoxycarbonyl-14β-androst-16-en-15-one **10**: mp 202-203 °C; $[\alpha]_D$=+69.31 (c=0.44, $CHCl_3$); IR 2980, 1720, 1690, 1600 cm^{-1}; ^1H NMR δ 0.64 (s, 3H), 1.11 (s, 3H), 1.19 (s, 3H), 1.40 (s, 1H), 1.90 (s, 1H), 3.59 (s, 3H), 6.09 (s, 1H), 6.55 (m, 1H-β'), 7.44 (m, 1H-α), 7.76 (m, 1H-α') ppm; MS m/z (relative intensity) 424 (20, M^+), 364 (4), 279 (16), 235 (5), 149 (55), 137 (14), 112 (15), 95 (24), 81 (48), 69 (95), 55 (100); Anal. Calcd. for $C_{27}H_{36}O_4$: C, 76.38; H, 8.55. Found: C, 76.31; H, 8.64.

The second fraction (55 mg, 24 %), which was a crystalline product, was identified as 4α,8β-dimethyl-17-(3'-furyl)-4β-methoxycarbonyl-13α-androst-16-en-15-one **11**: mp 164-165 °C; $[\alpha]_D$=+17.17 (c=0.53, $CHCl_3$); IR 2980, 1720, 1690, 1600 cm^{-1}; ^1H NMR δ: 0.72 (s, 3H), 0.84 (s, 3H), 1.17 (s, 3H), 1.36 (s, 1H), 1.80 (s, 1H), 3.62 (s, 3H), 6.17 (s, 1H), 6.58 (m, 1H-β'), 7.46 (m, 1H-α), 7.78 (m, 1H-α') ppm; MS m/z (relative intensity) 424 (75, M^+), 364 (12), 235 (18), 162 (100), 121 (12), 81 (18); Anal. Calcd. for $C_{27}H_{36}O_4$: C, 76.38; H, 8.55. Found: C, 76.44; H, 8.41.

B) Treatment of a solution of divinyl ketone **6** (190 mg, 0.45 mmol) with 0.1 ml of a mixture 2:1 of acetic acic and 98 % sulphuric acid afforded, after the same workup followed by chromatography, keto ester **10** (112

mg, 59 %) and keto ester **11** (38 mg, 20 %).

Cyclization of allyl vinyl ketone 9.- Allyl vinyl ketone **9** (50 mg, 0.12 mmol) was dissolved in 85 % phosphoric acid (0.5 mL) and 90 % formic acid (0.5 mL) and the mixture was heated at 75 °C for 26 h under a nitrogen atmosphere. After the same workup used for the cyclization of divinyl ketone **6**, the residue was chromatographed using hexane-ether (7:3) as eluent to obtain keto ester **10** (7.5 mg, 15 %) and keto ester **11** (3 mg, 6 %).

4α,8β-dimethyl-17-(3'-furyl)-15α-hydroxy-4β-methoxycarbonyl-14β-androst-16-ene 12.- To a mixture of keto ester **10** (240 mg, 0.57 mmol) and $CeCl_3 \cdot 7H_2O$ (212 mg, 0.57 mmol) in methanol (10 mL) $NaBH_4$ (433 mg, 11.4 mmol) was added in small amounts. The mixture was stirred for 30 min. Then, the solvent was distilled under reduced presure and the residue was treated with water and extracted with ether. The extracts were then washed with brine and dried. The solvent was evaporated under reduced presure to afford a solid identified as hydroxy ester **12** (206 mg, 85 %): $[\alpha]_D$=+42.69 (c=0.70, $CHCl_3$); mp 142-143 °C; IR: 3300, 2980, 1700 cm^{-1}; ^1H NMR δ: 0.69 (s, 3H), 1.19 (s, 3H), 1.20 (s, 3H), 1.34 (s, 3H), 3.65 (s, 3H), 4.80 (dd, 1H, J = 2 and J' = 8 Hz), 5.65 (d, 1H, J = 2 Hz), 6.40 (m, 1H-β'), 7.36 (m, 1H-α), 7.41 (m, 1H-α') ppm; MS m/z (relative intensity) 426 (22, M^+), 398 (8), 349 (9), 302 (75), 287 (42), 259 (25), 235 (18), 213 (12), 163 (60), 121 (45), 91 (52), 81 (68), 69 (100); Anal. Calcd. for $C_{27}H_{38}O_4$: C, 76.02; H, 8.98. Found: C, 76.17; H, 8.83.

4α,8β-Dimethyl-16,17β-epoxy-17α-(3'-furyl)-15α-hydroxy-4β-methoxycarbonyl-14β-androstane 13.- A solution of m-chloroperoxybenzoic acid (217 mg, 1.24 mmol) in dry CH_2Cl_2 (4 mL) was added dropwise at -40 °C to a solution of the allylic alcohol **12** (180 mg, 0.42 mmol) in dry CH_2Cl_2 (1mL) and the resulting mixture was stirred at this temperature for 15 min. A solution of $NaHSO_3$ (10 %) was added and the resulting heterogeneous mixture was stirred and gradually warmed to room temperature. The organic layer was separated, and the aqueous phase was extracted twice with ether. The combined extracts were washed with NaOH (0.5 N), water and brine and then dried and filtered. Evaporation of the solvent afforded a residue, which was flash chromatographed using hexane-ether (6:4) as the eluting solvent to give the epoxide alcohol **13** (173 mg, 93 %): mp 169 °C; $[\alpha]_D$=+32.4 (c=0.49, $CHCl_3$); IR 3400, 2980, 1720 cm^{-1}; ^1H NMR δ 0.65 (s, 3H), 1.12 (s, 3H), 1.17 (s, 3H), 1.25 (s, 3H), 3.55 (s, 1H), 3.63 (s, 3H), 4.20 (m, 1H), 6.36 (m, 1H-β'), 7.35 (m, 1H-α), 7.42 (m, 1H-α') ppm; Anal. Calcd. for $C_{27}H_{38}O_5$: C, 73.27; H, 8.65. Found: C, 73.20; H, 8.59.

4α,8β-Dimethyl-17β-(3'-furyl)-15α-hydroxy-4β-methoxycarbonyl-14β-androstan-16-one 14.- A solution of the epoxide alcohol **13** (80 mg, 0.18 mmol) in CH_2Cl_2 (2.5 mL) was treated with boron trifluoride etherate (0.038 mL), left for 5 min at -30 °C, and then water (4 mL) was added. The organic layer was separated and the aqueous phase was extracted with ether. The combined extracts were washed with brine and then dried and filtered. Removal of the solvent afforded a residue identified as hydroxy-ketone ester **14** (56 mg, 70 %): mp=169 °C; $[\alpha]_D$=+49.35 (c=0.78, $CHCl_3$); IR 3400, 2980, 1720 cm^{-1}; ^1H NMR δ 0.69 (s, 3H), 0.97 (s, 3H), 1.17 (s, 3H), 1.18 (s, 3H), 3.13 (s, 1H), 3.64 (s, 3H), 4.29 (m, 1H), 6.20 (m, 1H-β'), 7.28 (m, 1H-α), 7.36 (m, 1H-α') ppm; Anal. Calcd. for $C_{27}H_{38}O_5$: C, 73.27; H, 8.65. Found: C, 73.34; H, 8.70.

4α,8β-Dimethyl-17β-(3'-furyl)-15α-hydroxy-4β-methoxycarbonyl-14β-androst-14-en-16-one 15.- To a solution of hydroxy keto ester **14** (30 mg, 0.06 mmol) in toluene (1 mL), a catalytic amount

of pTsOH was added and the mixture was heated at reflux for 30 min. Then, a saturated solution of $NaHCO_3$ was added and the mixture extracted with ether. The extracts were washed with H_2O and brine and dried. The solvent was evaporated under reduced pressure to afford a solid identified as keto ester **15** (20 mg, 70 %): mp 157 °C; $[\alpha]_D$=+24.10 (c=1.64, $CHCl_3$); IR 2928, 1723, 1694 cm^{-1}; ^1H NMR δ 0.75 (s, 3H), 0.98 (s, 3H), 1.19 (s, 3H), 1.24 (s, 3H), 3.40 (s, 1H), 3.65 (s, 3H), 5.81 (s, 1H), 6.19 (m, 1H-β'), 7.38 (m, 1H-α), 7.40 (m, 1H-α') ppm; MS m/z (relative intensity) 424 (41, M^+), 362 (40), 284 (43), 174 (78), 105 (41), 91 (61), 67 (71), 55 (100); Anal. Calcd. for $C_{27}H_{36}O_4$: C, 76.38; H, 8.55. Found: C, 76.43; H, 8.61

4α,8β-Dimethyl-16,17β-epoxy-17α-(3'-furyl)-15α-hydroxy-4β-methoxycarbonyl-14β-androstane 16.- To a stirred and ice-cooled solution of epoxide alcohol **13** (10 mg, 0.02 mmol) in pyridine (0.2 mL), a solution of MsCl (5 mg, 0.04 mmol) in CH_2Cl_2 (0.1 mL) was added. The mixture was stirred for 24 h at 5 °C. The mixture was then poured onto ice water and extracted several times with ether. The extracts were washed with 2N HCl aqueous solution, $NaHCO_3$ saturated aqueous solution and brine, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to afford the mesylate **16** (10 mg, 85 %). ^1H NMR δ 0.65 (s, 3H) 1.13 (s, 3H), 1.17 (s, 3H), 1.30 (s, 3H), 3.12 (s, 3H), 3.64 (s, 3H), 3.87 (m, 1H), 5.15 (m, 1H), 6.37 (m, 1H-β'), 7.38 (m, 1H-α), 7.44 (m, 1H-α') ppm.

4α,8β-Dimethyl-17β-(3'-furyl)-15α-hydroxy-4β-methoxycarbonyl-14β-androst-14-en-16-one 15 from 16.- Following the same procedure used with the hydroxy keto ester **14**, the treatment of mesylate **16** (10 mg, 0.02 mmol) with pTsOH afforded **15** (8 mg, 85 %).

4α,8β-Dimethyl-17β-(3'-furyl)-15α-hydroxy-4β-methoxycarbonyl-14β-androst-14-en-16-one 15 from 13.- Following again the same procedure used above, treatment of the epoxide alcohol **13** (55 mg, 0.12 mmol) with pTsOH afforded **15** (40 mg, 76 %).

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