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3,4-BISMETHYLENECYCLOPENTANONE ETHYLENE KETAL: A USEFUL DIENE FOR [6.5] RING SYSTEMS: APPLICATION TO A FORMAL SYNTHESIS OF GIBBERELLIC ACID

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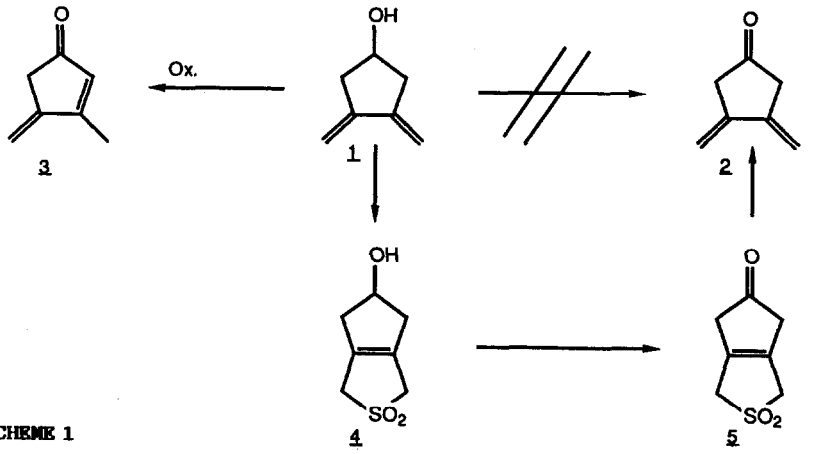
Abstract: A convenient preparation of 3,4-bismethylenecyclopentanone ethylene ketal, a new valuable diene for Diels-Alder reaction, designed to produce functionalized [6.5] ring systems, is described. A formal synthesis of gibberellic acd GA_3 using as starting materials two cycloadducts derived from the title compound demonstrates the value and the applicability of this methodology for the construction of functionalized hydrindane systems.

The widespread occurrence of [6.5] ring systems in natural products represents a continuous stimulus for the development of a significant number of methodologies for the construction of functionalized derivatives as a necessary prelude to any synthetic venture in the field.[1,2]

In considering a Diels-Alder approach to [6.5] ring systems the vast majority of methods focus on reacting substituted 1,4-butadienes with 2-cyclopenten-1--ones as dienophiles.[3] The alternative strategy, i.e. functionalized bismethylene cyclopentanes as dienic components with suitable dienophiles has received comparatively less attention, the main reasons for its underutilization being the unavailability of practical methods for the preparation of such functionalized dienes.[4]

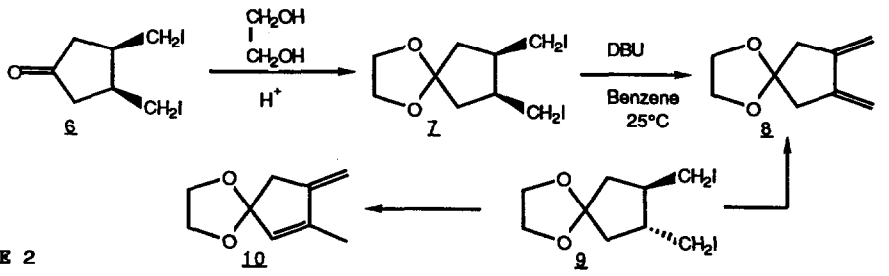
Dowd[5] had, in fact, reported the preparation of the very unstable 3,4-bis--methylenecyclopentanol **1**, generating the diene moiety by Cope method from the corresponding bis-amine oxide (170°C, 0.001 mm). Attempts to perform the oxidation to the corresponding ketone **2** led to the isolation of the rearranged ketone **2**. However **2** could be obtained by trapping **1** with sulfur dioxide and performing the oxidation on the derived adduct **4** to produce **5** which was eventually pyrolyzed at 430°C (0.001 mm) to yield 3,4-bismethylenecyclopentanone **2**. (Scheme 1)



SCHEME 1

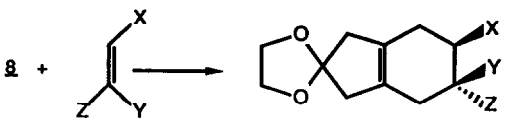
An alternative which is simple and, above all, more amenable to adaptation by nonspecialized laboratories presented itself.[6] In embarking in our studies we were strongly influenced by the ready availability[7] of cis-3,4-diiodomethyl cyclopentanone 6, which could be envisioned as convenient starting material. It was found that 6, after conversion to the corresponding ethylene ketal 7 by conventional procedure, could be readily converted to the new diene 8 simply by treatment with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in benzene solution at room temperature. The corresponding reaction performed on the known trans-isomer 9 led to formation of 1:1 mixture of 8 and the rearranged diene 10.

The latter became the sole reaction product performing the dehydrohalogenation of 9 at 0°C both in DMSO or benzene solution. However 9 could be easily taken to 8 by operating in toluene at 0°C. This behaviour may be accounted for on the different stereochemistry of the substrates which may cause competition between E_1 and E_2 elimination processes. (Scheme 2)



SCHEME 2

With compound 8 available in copious quantities, we soon found that we had at our disposal a versatile and valuable diene for Diels-Alder reaction, designed to produce functionalized [6.5] ring systems. (Scheme 3)



11a X = Z = H ; Y = CO_2Me
b X = H ; Y = CO_2Me ; Z = Me
c X = Z = CO_2Me ; Y = H
d X = Y = H ; Z = COMe
e XY = -CO-O-CO- ; Z = H
f X = OAc ; Y = H ; Z = CO_2Me
g X = H ; Y = CO_2Me ; Z = OAc

SCHEME 3

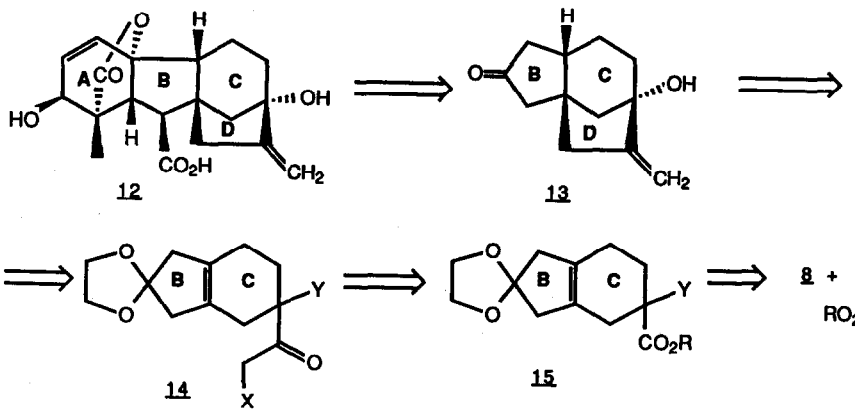
In this paper we describe the cycloaddition reactions of 8 with a variety of dienophiles and its application to a formal synthesis of gibberellic acid GA_3. In order to establish the general viability of the Diels-Alder reaction of 8, we investigated its cycloaddition with several common dienophiles. We found that the best conditions necessary for cycloaddition consisted in refluxing the crude benzene or toluene solution of the volatile diene 8, resulting from the dehydrohalogenation of 7 and 9 respectively, in approximately 1:2 ratio diene:dienophile until complete disappearance of the diene. It proved reasonably reactive giving rise to fair to good yields of cycloadducts (see experimental) with no serious attempts at optimization.

The symmetrical nature of 8 did not pose the problem of controlling the regiospecificity, a benefit which may well compensate the lack of stereochemistry at the ring junction of the derived products.

To further illustrate the synthetic value of the new functionalized diene 8, we envisioned the possibility of using some of the derived cycloadducts in the construction of the tricyclic framework 13, a key intermediate along the route to gibberellic acid GA_3 12.[8,9,10] In the event, a formal synthesis of this popular target would be realized. The synthesis of 13 had posed an exciting problem as a consequence of the unexpectedly high degree of steric strain associated with the cis BC ring fusion and the unusual bicyclo [3.2.1] octane CD ring system incorporating the bridgehead-hydroxy and methylene functions. The successful approaches to this significant tricyclic intermediate have involved strategically the construction of the D ring into a preformed BC nucleus,

featuring elegant solutions to control the stereochemistry at the BC ring juncture and to manipulate the substitution pattern.

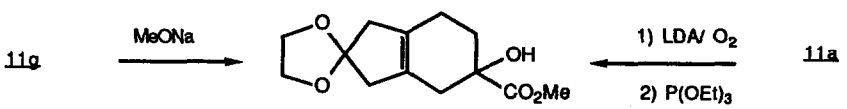
Two cycloadducts derived from 8, namely 11a and 11g, appeared to be convenient starting materials for an approach to 13 through adaptation of Mander's original idea[11] of an intramolecular cyclization onto the double bond at the ring junction of a substituted hydrindene derivative 14, in turn calling for a bicyclic ester 15 with the requisite functions suitably introduced in the opening cycloaddition between 8 and a simple dienophile. The synthetic design is retrosynthetically summarized in the following Scheme (Scheme 4).



SCHEME 4

The cycloadduct 11g, originating by cycloaddition of 8 and 2-propenoic-2--acetyloxy acid methyl ester, seemed particularly suitable for our purposes, incorporating the important bridghead-hydroxy function together with a useful ester function as a precursor for the construction of the necessary carbon chain for assembling the D ring.

Thus 11g was easily transformed into the corresponding hydroxy ester 16 by treatment with sodium methoxide. It is interesting to note that 16 could also be readily obtained by α -oxygenation of the enolate derived from the cycloadduct 11a followed by decomposition of the intermediate hydroperoxide by action of triethyl phosphite[12] (Scheme 5).

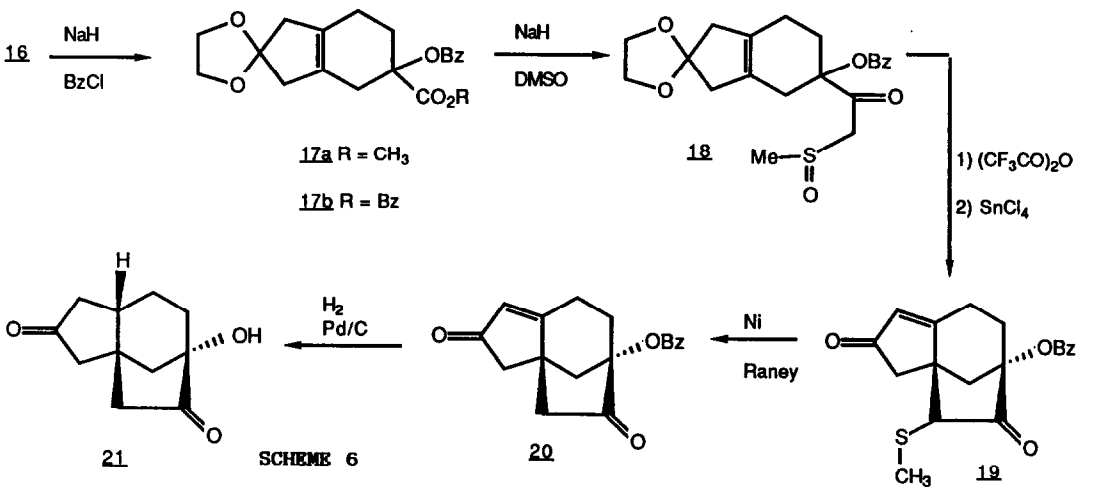


SCHEME 5

The hydroxy group in 16 was subsequently protected as the benzyl ether 17a by treatment with sodium hydride and benzyl bromide. The by-product 17b formed concomitantly by trans-esterification could be easily separated by chromatography and recycled by conventional procedures. Conversion of 17a to corresponding ß-ketosulfoxide 18 was achieved in the presence of dimsyl anion generated in situ by DMSO and sodium hydride. The Pummerer rearrangement promoted by exposure of 18 to trifluoroacetic anhydride following the method developed by Mander [13] during his extensive work in this area, and the subsequent treatment with stannic chloride produced the tricyclic compound 19, with concomitant removal of ketal protecting group.

The formation of 19 as sole product, as anticipated by previous experiences made by Mander [13] on different substrates is noteworthy.

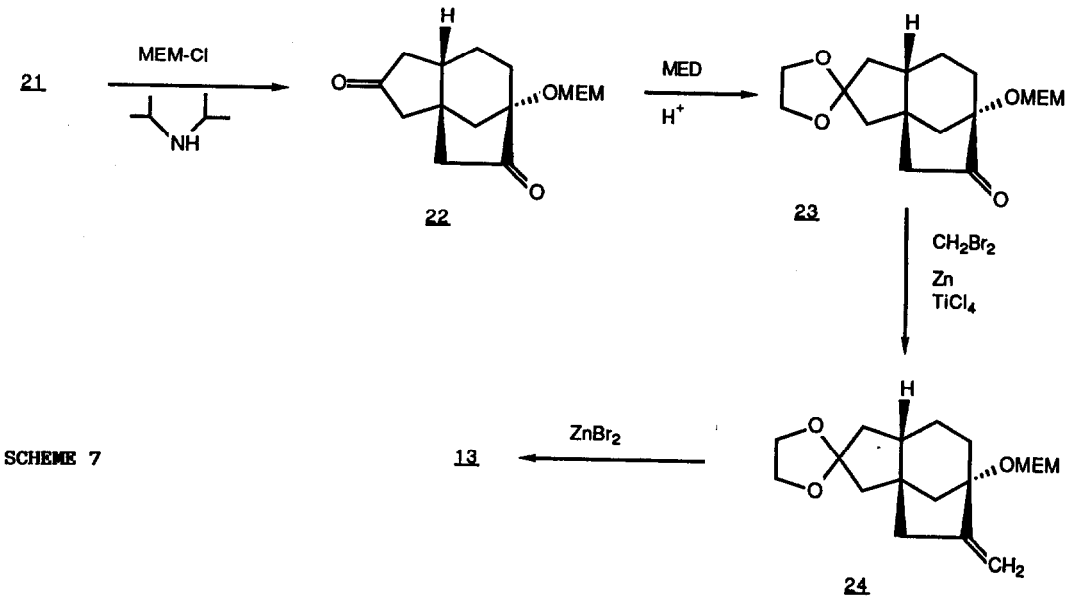
Desulfurization of 19 by heating in boiling ethanol in the presence of previously deactivated Nickel Raney proceeded uneventfully to yield 20, which underwent stereoselective palladium catalyzed hydrogenation to produce 21. The α-benzyloxy group serves as a critical function in establishing the stereochemical course of the hydrogenation which takes place faster than hydrogenolytic removal of the protective group. (Scheme 6)



SCHEME 6

Protection of the hydroxy group of the tricyclic ketone 21 using excess methoxyethoxymethyl (MEM) chloride and diisopropylethylamine in methylene chloride furnished 22. Its chemoselective ketalization by ketal exchange technique

afforded **23** which was submitted to the action of the complex derived from methylene bromide, zinc and titanium tetrachloride[14] to produce the known[9] **24**, which was eventually transformed to the key tricyclic compound **13**, the structure of which was unambiguosly assigned by Stork ten years ago.[8] (Scheme 7)



SCHEME 7

Since **23** has been already taken[9] to gibberellic acid GA_3 this approach constitues a new formal synthesis of this important target.

In summary it is seen that diene **8** reacts with a broad range of dienophiles to provide entries to a variety of [6.5] ring systems, making this sequence of particular use for the synthesis of natural compounds as illustrated in the case of **13**.

Experimental

Melting points and boiling points are uncorrected. Reaction courses and product mixtures were routinely monitored by thin-layer chromatography (TLC) on silica gel precoated F_{254} Merck plates. Infrared (IR) spectra were measured on a Perkin Elmer 297 spectrometer. Nuclear magnetic resonance (^{1}H NMR) spectra were obtained with a Brucker AC 200 spectrometer for solution in $CDCl_3$ and peak positions are given in parts per million downfield from tetramethylsilane as an internal standard. All drying operations were carried out with anhydrous magnesium sulphate. Light petroleum refers to the fractions boiling range 40-60°C and ether to diethyl ether.

cis-7,8-Diiodomethyl-1,4-dioxaspiro[4,4]nonane 7.

A mixture of **6** (6.6 g, 18 mmol), 2-methyl-2-ethyl-1,3-dioxolane (MED) (30 ml), ethylene glycol (0.6 ml) and p-toluenesulfonic acid (0.24 g) was stirred at room temperature for 4h. Triethylamine was added, followed by benzene (30 ml) and water (12 ml). The organic layer was separated, dried and concentrated to give quantitatively **7** contaminated by small amount of MED but suitable for further transformation in the next step. A sample was purified by flash-chromatography on silica gel (eluent: ether-light petroleum 1:1): ^{1}H NMR ($CDCl_3$): δ 1.5-2.4 (m,6H), 3.02-3.52 (m,4H), 3.9 (s,4H). Calc. for $C_9H_{14}O_2I_2$: C, 26.47; H, 3.43. Found: C, 26.59; H, 3.32%.

7,8-Bismethylen-1,4-dioxaspiro[4,4]nonane 8

An ice-cooled solution of **7** (13.2 g, 32.3 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (19.3 ml) in benzene (66 ml) was stirred at room temperature for 3h. The crude mixture was filtered through Celite, washed with water, dried and used without further purification in the next step. A sample purified by distillation showed the following spectroscopic data: IR (neat): 3080, 1620 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.7 (m,4H), 3.9 (s,4H), 4.9 (m,2H), 5.3 (m,2H). Calc. for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.93; H, 8.01%.

7-Methyl-8-methylene-1,4-dioxaspiro[4.4]non-6-ene 10

An ice-cooled solution of **9** (6.6 g, 16.1 mmol) and DBU (9.6 ml) in benzene (70 ml) was stirred at 70°C for 1h. The mixture was filtered through Celite, washed with water and dried. After removal of the solvent at reduced pressure, the residue was distilled at 30 mm Hg (b.p. 61°C) to give **10** (2.18 g, 90%) as an oil: IR (neat): 1645 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.2 (s,3H), 3.0 (s,2H), 3.99 (m,4H), 5.25 (m,1H), 5.42 (m,1H), 6.15 (s,1H). Calc. for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 71.04; H, 8.04%.

The same result was obtained when reaction was performed at 0°C in DMSO) as a solvent.

Diels-Alder reaction of 8: general procedure

To the crude benzene solution of diene **8** derived from **7** (6.6 g, 16.1 mmol) the dienophile (32 mmol) was added and the mixture refluxed for the required time. The cooled reaction mixture was washed with water and dried. After elimination of the solvent at reduced pressure the cycloadducts were purified by flash-chromatography on silica gel (eluent: ether-n-hexane 1:1). The dienophile, reaction time, yield, IR, ^{1}H NMR are given below.

Hexahydro-spiro(1,3-dioxolane-2,2'-[2H]-inden)-5'-carboxylic acid methyl ester 11a

Methyl acrylate; 23h; 88%; oil: IR (neat): 1730 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.9-2.55 (m, 11H), 3.7 (s,3H), 3.9 (s,4H). Calc. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.47; H, 7.55%.

Hexahydro-5'-methyl-spiro(1,3-dioxolane-2,2'-[2H]-inden)-5'-carboxylic acid methyl ester 11b

Methyl methacrylate; 48h, 33%; oil: IR (neat): 1730 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.17 (s,3H), 1.57-2.2 (m,6H), 2.5 (m,4H), 3.66 (s,3H), 3.9 (s,4H). Calc. for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.57; H, 7.89%.

(5'α,6'β)-Hexahydro-spiro(1,3-dioxolane-2,2'-[2H]-inden)-5',6'-dicarboxylic acid diethyl ester 11c

Diethyl fumarate; 12h; 60%; m.p. 74°C (light petroleum); IR (nujol): 1740 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.2 (t,6H,J=7Hz), 1.75-2.4 (m,4H), 2.5 (m,4H), 2.25-3.1 (m,2H), 3.9 (s,4H), 4.25 (q,4H,J=7 Hz). Calc. for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Found: C, 60.72; H, 6.71%.

Hexahydro-5'-acetyl-spiro(1,3-dioxolane-2,2'-[2H]-inden) 11d

Methyl vinyl ketone; 30h; 93%; oil: IR (neat): 1710 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.8-2.3 (m,6H), 2.2

(s,3H), 2.4-2.7 (m,5H), 3.9 (s,4H). Calc. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.16; H, 8.09%.

(5'α,6'α)-Hexahydro-spiro(1,3-dioxolane-2,2'-[2H]-inden)5',6'-dicarboxylic anhydride 11e

Maleic anhydride; 18h; 90%; m.p. 144-145°C (ether): IR (nujol): 1850, 1780 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.3-3.0 (m,4H), 3.2-3.5 (m,2H), 3.9 (s,4H). Calc. for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.27; H, 5.59%.

(5'α,6'β)-Hexahydro-6'-acetyloxy-spiro(1,3-dioxolane-2,2'-[2H]-inden)-5'-carboxylic acid methyl ester 11f

Methyl ß-acetoxyacrylate; 114h; 15%; oil: IR (neat): 1740, 1720 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.0 (s,3H), 2.12 (s,3H), 1.8-3.17 (m,9H), 3.9 (s,4H), 4.3 (m,1H). Calc. for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Found: C, 60.72; H, 6.82%.

Hexahydro-5'-acetyloxy-spiro(1,3-dioxolane-2,2'-[2H]-inden)-5'-carboxylic acid methyl ester 11g

2-Propenoic acid-2-acetyloxy methyl ester; 48h; 45%; oil: IR (neat): 1740 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.0-2.7 (m,4H), 2.8 (m,4H), 3.0-3.4 (m,2H), 3.7 (s,6H), 3.9 (s,4H). Calc. for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Found: C, 60.73; H, 6.70%.

Hexahydro-5'-hydroxy-spiro(1,3-dioxolane-2,2'-[2H]-inden)-5'-carboxylic acid methyl ester 16

A solution of diisopropylamine (0.65 g, 6.35 mmol) in tetrahydrofuran (10 ml) was cooled to 0°C under argon. Over a period of 10 min a 1.6 M n-butyllithium solution in hexane (4 ml, 6.4 mmol) was added through a syringe. The mixture was stirred at 0°C for 20 min, then cooled to -78°C. A solution of the ester **11a** (1 g, 4.2 mmol) in THF (40 ml) was added and the mixture was stirred for 1h before the introduction of a stream of anhydrous oxygen. After 4h the stream of oxygen was removed and triethyl phosphite (1.56 ml) was added. The solution was stirred for 20 min, then poured into a mixture of saturated NH_4Cl (20 ml) and $CHCl_3$ (50 ml). The separated organic phase was dried and evaporated at reduced pressure to give a residue which was purified by flash-chromatography on silica gel (eluent: ether) to give **16** (0.83 g, 77%) as a colorless solid m.p. 81-82°C. IR (nujol): 3240, 1730 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.7-2.2 (m, 6H), 2.5 (m,7H), 3.7 (s,3H), 3.9 (s,4H). Calc. for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.33; H, 7.07%. The same product was obtained in quantitative yield by refluxing for 6h a mixture of **11g** (2.96 g, 10 mmol) in methanol (50 ml) containing sodium methoxide (0.5 g).

Hexahydro-5'-benzyloxy-spiro(1,3-dioxolane-2,2'-[2H]-inden)-5'-carboxylic acid methyl ester 17a

To a stirred suspension of sodium hydride (1.8 g, 50% dispersion in mineral oil, 37.5 mmol) washed with pentane (2x10 ml) in dry THF (10 ml) a solution of the hydroxy ester **16** (3.05 g, 12 mmol) in THF (10 ml) was added dropwise. Stirring was continued at room temperature for 15 min., then benzyl bromide (5.13 g, 30 mmol) was added and the reaction mixture refluxed for 12h. The solvent was evaporated at reduced pressure after treatment of the cooled mixture with water. The residue was extracted with ether, dried and the solvent was removed at reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: ether - light petroleum 1:1) to afford **17a** (2.7 g, 66.8%): IR (neat): 1730 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.1 (m,4H), 2.5 (m,6H), 3.7 (s,3H), 3.9 (s,4H), 5.0 (m,2H), 7.4 (s,5H). Calc. for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.73; H, 6.94% and **17b** (1.4 g, 28.2%) m.p. 60-61°C: IR (nujol): 1720 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.1 (m, 4H), 2.5 (m,6H), 3.9 (S, 4H, 4.6 (m,2H), 5.1 (s,2H), 7.35 (s,5H), 7.4 (s,5H). Calc. for $C_{26}H_{28}O_5$: C, 74.26; H, 6.71. Found: C, 74.30; H, 6.67%. The latter was transformed into **17a** by saponification and subsequent esterification with diazomethane.

1-[Hexahydro-5'-benzyloxy-spiro(1,3-dioxolane-2,2'-[2H]-inden-5'-yl)]-2-(methylsulfinyl)-ethanone 18

Dry DMSO (4.3 ml) was added under nitrogen to sodium hydride (0.28 g, 50% dispersion in mineral oil, 5.8 mmol) washed with pentane (2x5 ml) and the mixture stirred for 45 min at 70°C. A solution of **17a** (1 g, 2.9 mmol) in dry THF (5 ml) was then added and the resulting solution stirred for 30 min at room temperature, poured in water, acidified with H_3PO_4 and extracted with $CHCl_3$. The combined extracts were washed with brine, dried and concentrated in vacuo. The residue was purified by flash-chromatography on silica gel (eluent: ethyl acetate -

methanol 9:1) to give **18** (1.05 g, 93%): IR (neat): 1710 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.1-3.0 (m,10H), 2.7 (s,3H), 3.7 (s,4H), 4.0-4.2 (m,2H,J=2Hz), 4.4 (m,2H), 7.4 (s,5H). Calc. for $C_{21}H_{26}O_5S$: C, 64.60; H, 6.71. Found: C, 64.62; H, 6.80%.

(6β,8aα)-Tetrahydro-6-benzyloxy-8-thiomethyl-6,8a-methanoazulen-(1H,6H)-2,7-dione 19

Trifluoroacetic anhydride (0.2 ml) was added under nitrogen to a cooled (5°C) solution of **18** (0.5 g, 1.28 mmol) in CH_2Cl_2 (6 ml). After being stirred for 4h, the mixture was neutralized with a solution of saturated sodium bicarbonate and extracted with ether. The combined organic layers were dried and the solvent removed at reduced pressure. The solution of the crude trifluoroacetyl derivative in CH_2Cl_2 (4 ml) was treated with $SnCl_4$ (0.18 ml) and stirred at 0°C for 20 min. The mixture was then poured into saturated aqueous sodium bicarbonate solution, extracted with CH_2Cl_2 and the extracts dried. After removal of the solvent in vacuo, the crude residue was flash-chromatographed on silica gel (eluent: ether) to give **19** (0.25 g, 50%) as white crystals: m.p. 148-150°C (ether - petroleum light); IR (nujol): 1750, 1710, 1620 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.41 (s, 3H), 3.27 (s, 1H), 4.6 (m,2H), 6.0 (m,1H), 7.25 (m,5H). Calc. for $C_{13}H_{20}O_3S$: C, 60.92; H, 7.87. Found: C, 60.81; H, 8.09%.

(6β,8aα)-Tetrahydro-6-benzyloxy-6,8a-methanoazulen-(1H,6H)-2,7-dione 20

A solution of **19** (1.2 g, 4.8 mmol) in ethanol (40 ml) was refluxed for 3h in the presence of Ni Raney W2 previously deactivated by refluxing for 2h in acetone. The cooled mixture was filtered through a pad of Celite and the solvent removed at reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: ether) to afford **20** (0.74 g, 73%) as a white crystals: m.p. 95-97°C (ether - pentane 1:2); IR (nujol): 1750, 1710, 1630 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.1-3.1 (m,8H), 5.1 (m,2H), 5.7 (m,1H), 7.4 (s,5H). Calc. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.49; H, 6.39%.

(3aα,6β,8aα)-Hexahydro-6-hydroxy-3a,6-methanoazulen-(3H,4H)-2,5-dione 21

A solution of **20** (0.5 g, 1.77 mmol) in methanol (30 ml) was hydrogenated at room temperature in the presence of 10% palladium on carbon under 1 atm of hydrogen gas. After 12h, the mixture was filtered through a pad of Celite and the solvent removed at reduced pressure. Flash chromatography of the residue on silica gel (eluent: ether) afforded **21** (0.3 g, 90%): m.p. 113-115°C (pentane); IR (nujol): 3450, 1745 cm^{-1}. Calc. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.07; H, 7.32%.

(3aα,6β,8aα)-Hexahydro-6-[(2-methoxyethoxy)methoxy]-3a,6-methanoazulen-(3H,4H)-2,5-dione 22

To a solution of **21** (0.5 g, 2.575 mmol) in CH_2Cl_2 (30 ml) were added diisopropylethylamine (1.3 ml, 7.7 mmol) and MEM-chloride (0.85 ml, 7.7 mmol). Water (30 ml) and the mixture stirred for 24h at room temperature was added, the organic phase separated, dried and concentrated at reduced pressure. The residue was flash chromatographes on silica gel (eluent: ethyl acetate) to afford **22** (0.55 g, 84%) as a white solid: m.p. 104-106°C; IR (nujol): 1745 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.6-2.6 (m,13H), 3.3 (s,3H), 3.4-3.8 (m,4H), 4.6-4.9 (AB system, 2H, J=8 Hz). Calc. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.88; H, 7.92%.

(3'aα,6'β,8'aα)-Tetrahydro-6'[(2-methoxyethoxy)methoxy]-spiro[1,3-dioxolane-2,2'(3'H)-[1H-3a,6-methanoazulen]-5'(4'H)-one 23

A mixture of **22** (0.6 g, 2.4 mmol), 2-methyl-2-ethyl-1,3-dioxolane (MED) (5 ml), ethylene glycol (0.12 ml) and few crystals of p-toluene sulfonic acid was stirred at room temperature for 1h. Triethylamine (0.3 ml) was added, followed by benzene (20 ml) and water (20 ml). The organic layer was separated, dried and concentrated in vacuo to give **23** in essentially quantitative yield : IR (neat): 1750 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.5-2.6 (m, 13H), 3.4 (s, 3H), 3.5-3.8 (m, 4H), 3.8-4.1 (m, 4H), 4.6-4.9 (AB system, 2H, J=8Hz). Calc. for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.49; H, 8.11%.

(3'aα,6'β,8'aα)-Hexahydro-6'-[(2-methoxyethoxy)methoxy]-5'methylene-spiro 1,3-dioxolane-2,2'-(3'H)-[1H,3a,6]-methanoazulene] 24

To a solution of **19** (0.29 g, 1 mmol) in dry CH_2Cl_2, the previously prepared Hoshima reagent (CH_2Br_2-Zn-$TiCl_4$ system) was added until the solution became dark brown. After being stirred at 25°C for 30 min, the mixture was diluted with ethr and the organic layer washed with saturated aqueous solution of sodium bicarbonate. The organic extract was dried and concentrated in vacuo. The residue was flash chromatographed on silica gel (eluent: ether) to

give 24 (0.26 g, 90%) as a colorless oil: ^{1}H NMR ($CDCl_3$): δ 1.5-2.6 (m, 13H), 3.4 (s,3H), 3.5-3.8 (m,4H), 3.8-4.1 (m,4H), 4.6-5.0 (m,4H). Calc. for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.53; H, 8.77%.

(3a ,6ß,8a)-Hexahydro-6-hydroxy-5-methylene-1H-3a,6-methanoazulen-2(3H)-one 13

To asolution of 24 (0.29 g, 1 mmol) in dry CH_2Cl_2 (10 ml), zinc bromide was added and the mixture stirred for 12h at room temperature. Water (5 ml) was added, the organic layer separated, washed with water (2x5 ml), dried and concentrated under reduced pressure; The residue was purified by flash crhomatography on silica gel (eluent: ether) to give 13 (0.15 g, 82%) as a white crystals: m.p. 114-116°C.[8,9,10] IR (nujol): 3450, 1745 cm^{-1}. ^{1}H NMR ($CDCl_3$):δ 1.5-2.6 (m, 14H), 4.9 (t,1H), 5.1 (t,1H). Calc. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.06; H, 8.42%.

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