Tetrahedron Vol. 42, No. 12, pp. 3323 to 3332, 1986
Printed in Great Britain

0040–4020/86 $3.00 + .00
Pergamon Journals Ltd.

SYNTHETIC STUDIES TOWARD TAXANES. A SULFUR BASED APPROACH TO THE BENZILIC ACID REARRANGEMENT†

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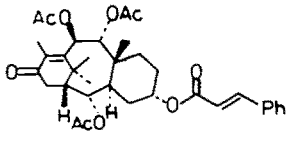
(*Received in UK* 19 *December* 1985)

Abstract - Based upon the notion of a three carbon intercalation as a synthetic approach to taxanes, a trans-perhydroindanone was required. In order to ensure the stereochemistry of the perhydroindanone, an approach based upon the stereocontrolled synthesis of a decalin followed by a ring contraction was adopted. In the course of this phase, a C-acylation based upon the use of copper enolates was employed. A ring-contraction sequence was developed initiated by a regioselective sulfenylation of a ketone. Acetoxylation of the resultant β-ketosulfide generated a monoprotected 1,2-diketone. Base treatment created a ring contracted α-hydroxycarboxylic acid which was cleaved directly to the nor-ketone. In this way, a suitable intermediate for elaboration into the taxanes was synthesized.

The taxanes, represented by taxinine 1[1] and taxol 2[2], comprise an interesting challenge because of the desire to understand the structural basis for the biological activity of this family of compounds and the unusual nature



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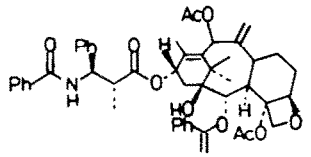

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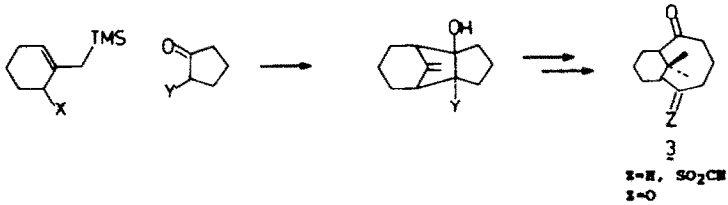
of the carbon skeleton[3]. In approaching the AB rings of this family, we developed a strategy based upon a three carbon intercalation as shown in eq. 1.[4]



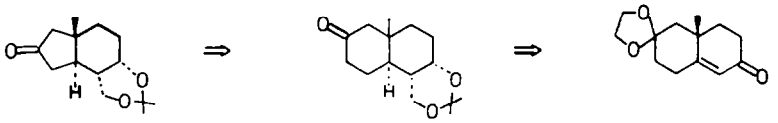
3
Z=H, SO_2CH_3
Z=O

(1)

In developing a synthesis of the taxanes along such lines, we require a perhydroindanone such as 4. Taking advantage of the ability to easily generate a trans-fused decalin, ring contraction from a precursor such as 5 would provide a ready entry to the requisite perhydroindanone. Dissolving metal reduction of the known octalone 6 should establish the proper ring fusion stereochemistry[5]

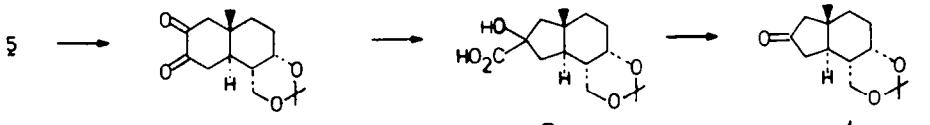
† Dedicated to Professor Ralph A. Raphael, on the occasion of his sixtyfifth birthday.

and provide a template to develop the correct stereochemistry of the substituents.



4 5 6

In pursuing such an approach, we considered employment of a benzilic acid type of rearrangement[6] for the ring contraction as outlined in eq. 2, since the



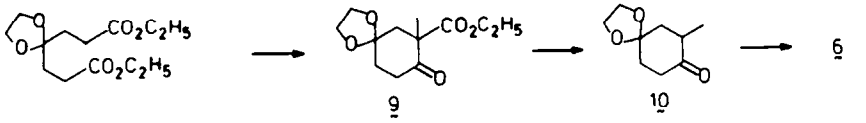
(2)

7 8 4

outlined in eq. 2, since the initial product of this rearrangement, an α-hydroxycarboxylic acid, can be readily degraded to a ketone[7]. In this paper, to report a synthesis of the perhydroindanone 4 employing a new approach for ring contraction via a sulfur based benzilic acid type of rearrangement.

Synthesis of Starting Material

For the synthesis of octalone 6, we chose to start from the ethylene ketal of diethyl 4-oxopimelate[8] as outlined in eq. 3 because of the ease of operating



(3)

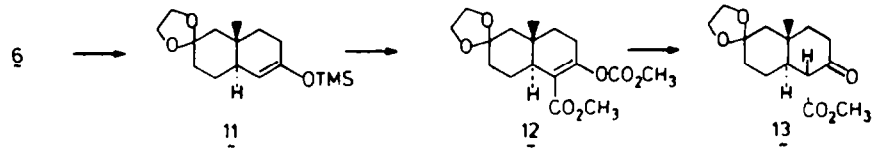
9 10

on large scale. Dieckmann cyclization with sodium ethoxide in benzene generates the sodium salt of the cyclized β-ketoester which is directly methylated to give 9 in 90% yield after distillation. Aqueous potassium hydroxide effects ester hydrolysis and decarboxylation to give the cyclohexanone 10 in 70% distilled yield. Robinson annulation of cyclohexanone 10 with methylvinyl ketone is best performed in ether with ethanolic potassium hydroxide[9] to give 45% yield of crystalline 6.

Elaboration of Ring A

Dissolving metal reduction followed by capture of the resultant enolate wth trimethylsilyl chloride sets the ring juncture stereochemistry and the regioselectivity for further alkylation or acylation as in eq. 4. The enol silyl ether, obtained in 85% yield, exhibits a single set of 14 signals in its ^{13}C spectrum with the angular methyl group appearing at δ15.2 indicative of the trans ring fusion.

Attempts to introduce a hydroxymethyl group from the kinetic enolate related

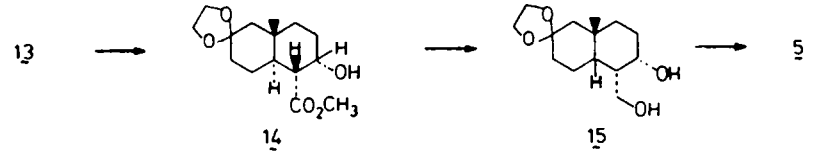


(4)

11 12 13

to 11 by condensation with formaldehyde[10] or alkylation with benzylchloromethyl ether[11] proved unsatisfactory. Carbomethoxylation is successful if the copper enolate is quenched with excess methyl chlorocarbonate to give the O,C-diacylated product 12[12]. The homogeneity of the compound is established by its combustion analysis, crystallinity, and its ^{13}C nmr spectrum which again shows a signal for the angular methyl group at δ15.7. Methanolic sodium methoxide removes the O-acyl group to give crystalline β-ketoester 13. The 13.2 Hz coupling between the protons on C(4) and C(5) confirms their diaxial nature, and thereby establishes the ester group as equatorial. Its stereochemistry is presumably thermodynamically controlled.

Because of the ease of enolization of the β-ketoester, reduction to the diol is best accomplished as a two-step operation. Reduction with L-selectride[13] leads to a single β-hydroxy ester according to ^{13}C nmr analysis of the crude

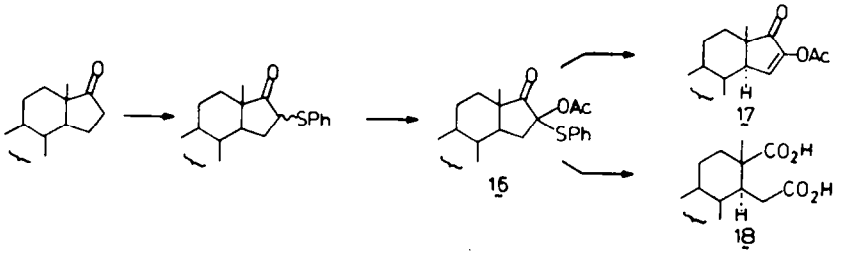


(5)

product 14 which shows only the requisite 15 signals. The δ16.0 absorption for the angular methyl group confirms the trans ring fusion. The axial stereochemistry is assigned on the basis of the coupling between the protons on C(3) and C(4) being only 2.6 Hz. Ester reduction with LAH and readjustment of the blocking groups as in eq. 5 proceeds uneventfully to give 5.

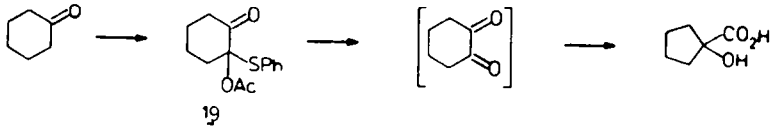
Modified Benzilic Acid Rearrangement. Synthesis of a Perhydroindanone

To effect a benzilic acid rearrangement, we require access to a diketone or its equivalent. We have previously shown that sulfenylation[14] followed by acetoxylation[15] of carbonyl compounds (eq. 6) proceeds readily. Conversion of



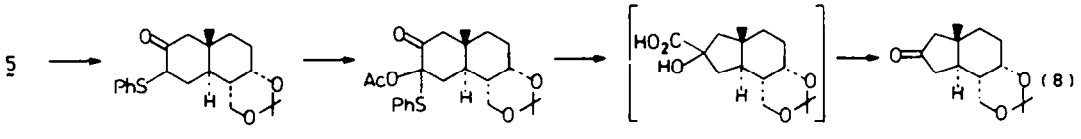
(6)

the α-acetoxysulfide 16 to its sulfoxide and thermolysis provides the specifically enolized 1,2-diketone derivative 17. Alternatively, treatment of 16 with basic hydrogen peroxide effects cleavage to the diacid 18, a reaction that is typical of an α-diketone which may be unmasked under the basic reaction conditions. Such a reaction suggests that an α-acetoxysulfide such as 19 may suffer direct benzilic acid rearrangement through in situ generation of an α-diketone as in eq. 7.



(7)

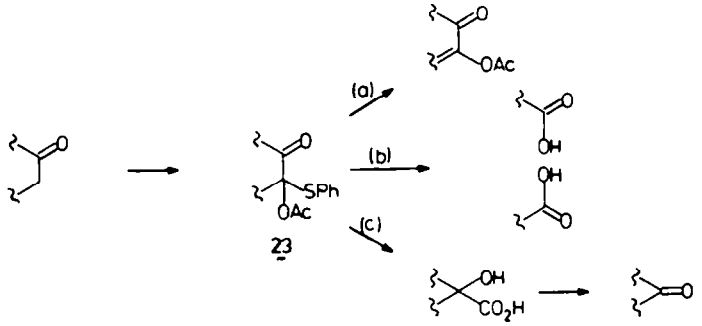
In the case of decalone 5, the trans ring juncture should direct enolization to C(7)[16]. Sulfenylation produces the β-ketosulfide 20 predominantly as one stereoisomer and, presumably, as only one regioisomer in 75% yield. Acetoxylation produces 21 in 90% yield as a 2:1 diastereomeric mixture. Aqueous potassium hydroxide in refluxing THF effects hydrolysis and in situ rearrangement to give the α-hydroxycarboxylic acid 22. Subjection of the crude 22 directly to lead tetraacetate in acetic acid provides 4 as a crystalline solid, mp 78-80°. The nmr data demonstrates the integrity of the trans ring junction. The bridgehead hydrogen appears at 2.74 as a ddd, J=13.6, 12.1, and 7.7 Hz. The two large couplings correspond to two trans diaxial-like protons β to the bridgehead proton. In addition, the ^{13}C shift for the angular methyl group appears at δ16.9. Such a value is consistent only with a trans ring fusion.



(8)

Discussion

The importance of β-ketosulfides in synthesis has grown dramatically in recent years[17]. The impetus for finding new applications of these versatile intermediates stems from the discovery of their ease of generation by the direct sulfenylation of carbonyl compounds. The development of the very easy α-acetoxylation, presumably via a Pummerer-type of process, makes these intermediates the equivalent of 1,2-diketones but with better control. For



(9)

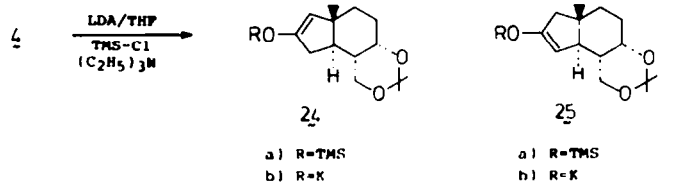
example, 1,2-diketones frequently exist as their mono-enolized tautomers. The sulfoxide pyrolysis permits conversion of acetoxysulfide 23 to a specifically enolized tautomer regardless of which is thermodynamically preferred (eq. 9a). Basic hydrogen peroxide effects vicinal cleavage of 23 to a dicarboxylic acid (eq. 9b). As a result of the present study, simple base treatment of 23 provides direct benzilic acid rearrangement (eq. 9c). The ease of oxidative cleavage of the α-hydroxyacid to a ketone makes this ring contraction sequence particularly useful.

This sequence compares quite favorably to traditional ring contraction procedures to convert a cyclic ketone to its next smaller cycloalkanone. For example, the diazoketone ring contraction[18] requires at least two steps to form the α-diazoketone from a ketone and the ring contraction produces the simple carboxylic acid[19]. At least two[20] and as many as five[21] additional steps must be employed to complete the sequence.

The carboxylation of 11 is also noteworthy[22]. C-Acylation must precede O-acylation since the product of O-acylation is presumably inert to further reaction. The successful formation of 12 suggests that the copper or mixed copper-lithium enolate inhibits O-acylation or promotes C-acylation. Insufficient data exist to provide more insight into this observation, but it may prove to be more generally useful. The trapping of the enolates derived from conjugate addition of organocuprates to enones has previously been effectively acylated at carbon[12]. Presumably the same intermediates are involved in both cases. This approach offers an alternative to the use of less available carbomethoxylating agents[23].

While a one step conversion of the β-ketoester to the diol could be envisioned, the requirement for diastereoselective reduction to the axial alcohol and the need to avoid problems of enolization of the β-ketoester led us to use L-selectride. Its success precluded our examination of other reducing agents.

The availability of the requisite perhydroindanone 4 in only ten steps from the known octalone 6 led us to preliminarily explore its enolization in conjunction with its elaboration to the taxanes. Kinetic enolate generation



produces a 2:1 mixture of 24 and 25. Nmr analysis of the vinyl protons (24, δ4.80; 25, δ4.68) established the regiochemistry. The tendency of 3,3-disubstituted cyclopentanones to enolize preferentially toward the sterically more encumbered methylene group even under conditions of kinetic enolate generation has previously been noted[24]. Sulfenylation under reversible enolate generation conditions proceeds virtually quantitatively to a mixture of β-ketosulfides in which one diastereomer of 24 greatly dominates (>80% of mixture). The stereochemistry presumably reflects thermodynamics and is

tentatively assigned as beta on the known thermodynamic preference of similar substitution in trans-perhydroindanones to prefer the beta orientation. The startling high regioselectivity may reflect an even higher thermodynamic bias of this ketone to enolize towards the more hindered methylene group compared to the kinetic ratio. However, a kinetic argument in which the enolate 24b is more reactive than the alternative enolate 25b cannot be ruled out. Under such circumstances, the 1,3-interactions that can be considered to slow down reactions of 25b must be traded off against the neopentyl nature of 24b. Furthermore, the use of phenylthiobenzenesulfinate as the sulfenylating agent could be argued to trap the enolates faster than their equlibration should occur. Regardless of the source of the effect, the selective enolization of 4 provides the opportunity for its further elaboration towards the taxanes.

EXPERIMENTAL

Elemental analyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, MI or Galbraith Lab Inc. Knoxville, TN. Melting points were measured on a Thomas Hoover apparatus and are uncorrected. Boiling points are uncorrected. Infrared spectra were recorded on a Beckmann Acculab 7. All ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ solution. ^{1}H NMR spectra were determined on a JEOLCO MH-100 (100 MHz) instrument or a Bruker WH-270 (270 MHz) instrument. ^{1}H chemical shifts are reported in ppm (Me_4Si at 0 ppm). ^{13}C spectra were measured on a JEOLCO FX 200 (50.10 MHz) or a Varian XL100 (25.2 MHz) instrument. ^{13}C chemical shifts are given in ppm ($CDCl_3$ at 77 ppm). Mass spectra were obtained on an AEI-902 instrument at an ionizing current of 98 mA and an ionizing voltage of 70 eV. Data are reported as m/e (%).

6-Ethylenedioxy-4a-methyl-2-trimethylsilyloxy-3,4,4a,5,6,7,8,8a-octahydronaphthalene (11)

At -78°C, 1.50 g (0.22 mol) of lithium wire, cut in small pieces, were added to 1 L of ammonia freshly distilled over sodium. After 30 min at -78°C; a mixture of 13.3 g (60 mmol) of enone 6, 5.0 mL (52.6 mmol) of t-butanol and 75 mL of THF was added dropwise over 30 min at -78°C. After the addition was complete, stirring was continued for 10 min, followed by addition of isoprene until the blue color disappeared. The white, cloudy mixture with the oily lithium enolate on the bottom was then freed from the ammonia by warming in a water bath and blowing nitrogen gas over the contents in the flask. Most of the THF was then removed by using aspirator vacuum and the residue was dried completely with an oil pump (1.0 mm Hg) for 1 h.

The white residue was then dissolved in 240 mL of dry THF followed by the addition of 45 mL of triethylamine. After chilling the mixture to about -50°C, 39 mL (0.31 mol) of freshly distilled (from tributylamine) chlorotrimethylsilane was added over 1 min. The resultant mixture was stirred overnight at rt, then cold hexane and cold saturated sodium bicarbonate in water were added. The aqueous layer was separated and extracted again with hexane. The combined hexane solutions were washed with saturated sodium bicarbonate solution in water and dried (K_2CO_3). The hexane was removed under vacuum and the residue distilled under vacuum to afford 15.2 g (51 mmol, 85%) of a colorless liquid (bp 100-115°C, 0.05 mm Hg). IR (liq. film): 1660 cm^{-1}. NMR (100 MHz, $CDCl_3$) δ4.39 1H bs, 3.71, 4H, m; 1.0-2.0, 11H, m; 0.77, 3H, s, 0.10, s, 9H ^{13}C NMR (50 MHz): δ149.5, 109.4, 107.2, 64.3, 63.2, 47.2, 42.7, 38.1, 35.9, 33.1, 27.1, 25.7, 15.2, 0.2 ppm.

(1-Carbomethoxy-6-ethylenedioxy-4a-methyl-3,4,4a,5,6,7,8,8a-octahydro-2-naphthalenyl)methyl carbonate (12)

To a solution of 15.0 g (50.6 mmol) of TMS enol ether 11 in 400 mL of anhydrous ether was added dropwise over 30 min at 0°C and with mechanical stirring 82 mL of 1.25 N methyllithium in ether (102.5 mmol). The resultant clear solution was stirred at rt for 90 min. Then, 9.6 g (50.4 mmol) of dry copper(I) iodide was added and stirring was continued for 30 min. The mixture turned bright yellow. It was then cooled to 0°C followed by addition of 15 mL (18.3 g, 194 mmol) of methyl chloroformate over 30 sec. The mixture was stirred overnight at rt. The colorless solution was decanted from the grey precipitate. Ether was added to the residue in the flask and this mixture was filtered with suction. The solid was washed with ether and the filtrate was combined with the ether solution, obtained from decantation. The resultant solution was washed with 1% sodium bisulfate solution in water (200 mL) and brine (200 mL) and then dried ($MgSO_4$). The ether was removed under vacuum and the residue (oily solid) was recrystallized from a mixture of benzene and hexane to afford 8.72 g (25.6 mmol, 51%) of crystals. Another recrystallization yielded analytically pure material; mp 106-108° (closed tube). IR (KBr pellet): 1755, 1720, 1665 cm^{-1}. ^{1}H NMR (270 MHz): δ3.8-4.1 (m, 4H), 3.84 (s, 3H), 3.74 (s, 3H), 2.55 (m, 1H), 2.34 (dm, J=11 Hz, 1H), 2.17 (dm, J=20 Hz, 1H), 1.88 (dm, J=11 Hz, 1H), 1.4-1.75 (m, 7H), 1.11 (s, 3H). ^{13}C NMR (25 MHz): 166.4 (s), 153.2 (s), 149.9 (s), 122.1 (s), 108.6 (s), 64.5 (t), 63.4 (t), 55.1 (q), 51.4 (q), 47.1 (t), 43.3 (d), 36.7 (s), 35.6 (t), 33.5 (t), 24.4 (t), 21.7 (t), 15.7 (q). Anal. Calcd for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11; MW, 340.1515. Found: C, 60.09; H, 7.17; MW, 340.1523.

1-Carbomethoxy-6-ethylenedioxy-4a-methyl-octahydro-2(1H)-naphthalenone (13)

Enol carbonate 12 (8.72 g, 25.6 mmol) was stirred at rt for 2 h with 150 mL of methanol and 18 mL of a 1.47 N (26.5 mmol) solution of sodium methoxide in methanol. Most of the methanol was then removed under vacuum. To the residue

was added 150 mL of methylene chloride and 150 mL of an aqueous saturated solution of ammonium chloride. The organic layer was separated and the aqueous layer extracted with methylene chloride. The combined organic layers were washed with water and dried ($MgSO_4$). Evaporation of the solvent left a white solid which was recrystallized from a mixture of benzene and hexane to afford 5.59 g (19.8 mmol, 75%) of needles. Another recrystallization produced analytically pure material, mp 106-108°C. IR (KBr): 1735, 1715 cm^{-1}. ^1H NMR (270 MHz): δ3.85-4.05 (m, 4H), 3.76 (s, 3H), 3.22 (d, 13.2 Hz, 1H), 2.53 (ddd, J=16, 13, 7, 1H), 2.41 (ddd, J=16, 5, 2, 1H) 1.95 (m, 1H), 1.4-1.85 (m, 8H), 1.21 (s, 3H). ^{13}C NMR (50 MHz): δ205.0 (s), 170.0 (s), 108.2 (s), 64.4 (t), 63.4 (t), 59.4 (d), 51.7 (q), 47.8 (t), 45.8 (d), 39.9 (t), 36.8 (t), 34.6 (t), 33.7 (s), 24.6 (t), 16.2 (q). Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.84; MW 282.1461. Found: C, 63.69; H, 7.87; MW, 282.1420.

1-Carbomethoxy-decahydro-6-ethylenedioxy-4a-methyl-2-naphthalenol (14)

To a solution of 1.50 g (5.31 mmol) of β-ketoester 13 in 25 mL of THF was added over 5 min at -78°C 5.6 mL of a 1N (5.6 mmol) solution of L-selectride in THF. The mixture was stirred for 2 h between -78° and -60°C, warmed up to rt in 2 h and then stirred at rt for 1 h. Excess hydride was destroyed by slowly adding 3.3 mL of ethanol followed by 0.9 mL of water. Subsequently, a mixture of 2.2 mL of a 10% aqueous solution of potassium hydroxide and 3.3 mL of 30% aqueous hydrogen peroxide was added very slowly with cooling in ice. After completion of addition of the peroxide mixture and stirring for another 15 min at rt, solid potassium carbonate was added to saturate the aqueous layer. After separation of the organic layer, the aqueous layer was extracted with ether. The combined organic layers were washed with a little brine, dried (K_2CO_3) and freed from volatiles under vacuum to afford a colorless solid (1.14 g, 4.01 mmol, 76%). Recrystallization from hexane yielded crystals, mp 102-104°C. ^1H NMR (270 MHz): δ4.11 (broad s, 1H), δ3.8-4.0 (m, 4H), 3.72 (s, 3H), 3.50 (broad s, 1H), 2.44 (dd, 12.9, 2.6 Hz, 1H), 1.95 (td, J=12, 3.5, 1H), 1.35-1.90 (m, 8H), 1.10-1.26 (m, 2H), 1.00 (s, 3H). ^{13}C NMR (50 (MHz): δ176.4, 108.6, 66.5, 64.3, 63.2, 51.3, 48.7, 47.6, 39.2, 35.6, 34.7, 34.5, 26.9, 23.5, 16.0 ppm. Calcd. for $C_{15}H_{24}O_5$: 284.1617. Found: 284.1623.

Decahydro-6-ethylenedioxy-1-hydroxymethyl-4a-methyl-2-naphthalenol (15)

The crude hydroxy ester 14 (1.14 g, 4.01 mmol) was dissolved in 25 mL of ether and this solution added slowly to a suspension of 260 mg (6.8 mmol) of lithium aluminum hydride in 15 mL of ether. The mixture was then refluxed for 2 h. After cooling a mixture of 1.4 mL of methanol and 8 mL of ether was added slowly, followed by a saturated solution of ammonium chloride in water until the salts precipitated. The ether solution was decanted and the residue washed twice with 20 mL of ether. The combined organic solutions were dried (K_2CO_3) and the solvents were then removed under vacuum to leave a white solid (940 mg, 3.67 mmol, 91%). One recrystallization from toluene afforded analytically pure material, 129-130°C. IR (KBr): 3380 cm^{-1}. ^1H NMR (270 MHz): δ4.18 (br s, 1H), 3.85-4.0 (m, 6H), 2.80 (br s, 1H), 2.56 (br s, 1H), 1.1-1.95 (m, 12H), 0.98 (s, 3H). ^{13}C NMR (50 MHz): δ109.0 (s), 71.4 (d), 64.4 (t), 64.0 (t), 63.2 (t), 48.9 (t), 40.9 (d), 37.6 (d), 35.8 (t), 35.4 (t), 34.7 (s), 28.8 (t), 21.9 (t), 16.2 (q). Anal. Calcd. for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44; MW, 256.1668. Found: C, 65.61; H, 9.40; MW, 256.1673.

1,3-Dioxo-dodecahydro-2,2,8a-trimethyl-7(8H)-phenanthrenone (5)

The crude diol 15 (1.11 g, 4.33 mmol) was stirred with 25 mL of THF and 10 mL of 5% aqueous hydrochloric acid for 3 h at rt. Most of the THF was then evaporated under vacuum. The residue was neutralized with a solution of potassium carbonate in water and then saturated with sodium chloride. This aqueous mixture was then extracted three times with ether. The combined extracts were dried (K_2CO_3) and the solvent evaporated. The residue was boiled in 25 mL of acetone in the presence of a few crystals of p-toluenesulfonic acid monohydrate for 2 h. After cooling, solid potassium carbonate was added and the solvent removed under vacuum. To the residue were added water and CH_2Cl_2. The residue was taken up in water and methylene chloride and the aqueous layer further extracted with methylene chloride. Usual extraction afforded a methylene chloride solution. After drying the organic layer (K_2CO_3), the solution was evaporated under vacuum to afford a yellow oil which was purified by using flash chromatography (4 cm diameter column, length 15 cm, eluent ethyl acetate/hexane 1:3) furnishing 777 mg of a white solid (3.08 mmol, 71%). Two recrystallizations from hexane yielded analytically pure material, mp 92-94°C. IR (KBr): 1715 cm^{-1}. ^1H NMR (270 MHz): δ4.15 (q, J=2 Hz, 1H), 3.98 (dd, 12.5, 2.9 Hz, 1H), 3.90 (dd, 12.1, 1.5 Hz, 1H), 2.06-2.46 (m, 4H), 2.30 (d, J=15 Hz, 1H), 2.12 (d, J=15 Hz, 1H), 1.58-1.85 (m, 3H), 1.47 (s, 3H), 1.44 (s, 3H), 1.11-1.45 (m, 3H) 0.81 (s, 3H). ^{13}C NMR (50.10 MHz): δ210.6 (s), 98.0 (s),

66.7 (d), 60.7 (t), 56.1 (t), 40.8 (t), 37.2 (s), 36.4 (d), 35.8 (d), 34.7 (t), 29.3 (q), 26.6 (t), 24.9 (t), 18.7 (q), 16.4 (q). Anal. Calc'd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.47; H, 9.36.

1,3-Dioxo-dodecahydro-6-phenylthio-2,2,8a-trimethyl-7(8H)-phenanthrenone (20)

Over 15 min, a solution of 631 mg (2.5 mmol) of ketone 5 in 6.25 mL of THF was added to a -78° solution of LDA generated from 0.425 mL (3.03 mmol) of diisopropylamine and 1.88 mL (1.5 N, 2.82 mmol) of n-butyllithium in 12.5 mL of THF. The mixture was stirred at -78°C for 30 min and at rt for 60 min. After adding 12.5 mL of HMPA, 550 mg (2.52 mmol) of diphenyldisulfide was added to the orange solution. The mixture turned yellow and was stirred overnight at rt. Then water and a 1:1 mixture of ether and pentane were added. The organic layer was separated and the aqueous layer extracted again with the same solvent mixture. The combined organic layers were washed with water and brine and dried (K_2CO_3). The solvent was removed under vacuum to leave a yellow oil, which was flash chromatographed (hexane/ethyl acetate 3:1; R_f of 22 on TLC (ether): 0.65) to yield 680 mg of colorless oil (1.89 mmol, 75%). IR (liq film): 1705, 1380 cm^{-1}. ^1H NMR (100 MHz): δ7.1-7.6 (m, 5H), 3.64-4.20 (m, 4H), 1.0-3.2 (m, 10H), 1.48, 1.45, 1.42 and 1.40 (4 singlets, 6H), 0.81 and 0.76 (2 singlets, 3H). ^{13}C NMR (270 MHz): predominant isomer: δ204.9 (s), 133.6 (s), 132.1 (d), 128.5 (d), 126.9 (d), 98.1 (s), 66.5 (d), 60.6 (t), 57.2 (d), 56.0 (t), 38.1 (s), 37.2 (d), 35.5 (d), 34.2 (t), 33.5 (t), 29.5 (q), 26.6 (t), 18.7 (q), 16.4 (q).

6-Acetoxy-1,3-dioxo-dodecahydro-6-phenylthio-2,2,8a-trimethyl-7(8H)-phenanthrenone (21)

A mixture of 680 mg (1.89 mmol) of β-ketosulfide 20 (purified by flash chromatography), 3.0 g (6.8 mmol) of lead tetraacetate and 25 mL of benzene was refluxed for 1 h. Soon a white precipitate arose. After cooling to about 50°C, 7 mL of ethyleneglycol was added and the mixture stirred for 10 min at about 40-50°C. The mixture was then cooled to rt and diluted with benzene. The glycol layer was separated and extracted once again with benzene. The combined benzene solutions were washed twice with brine and dried (K_2CO_3). The benzene was evaporated under vacuum to afford an almost colorless powder (714 mg, 1.71 mmol, 91%), mp 135-155°C, pure according to TLC (R_f; SiO_2, ether, 0.50). IR (KBr): 1745, 1720, 1380 cm^{-1}. ^1H NMR (270 MHz): two isomers in ratio of about 2:1; δ7.3-7.6 (m, 5H), 4.14 (br s, minor) and 4.08 (br s, major) (total 1H), 3.94 (dd, J=11.5, 1.5, minor), and 3.82 (dd, J=12, 2.5, major) (total 1H), 3.75 (br d, J=11.5, minor) and 3.49 (br d, J=12, major) (total 1H), 2.92 (br d, J=15 Hz, 1H), 2.40-2.60 (m, 2H), 2.06-2.32 (m, 2H), 2.17 (s) and 2.10 (s) (total 3H), 1.06-1.86 (m), 1.51 (s, minor), 1.48 (s, minor), 1.40 (s, minor), 1.36 (s, minor) (total 6H), 1.22 (d, J=9) and 1.11 (d, J=11, minor) (total 1H), 1.04 (s, minor), 0.83 (s, major) (total 3H). MS: 418 (0.3), 403 (0.4), 360 (0.3), 309 (1.8), 300 (1.4), 251 (5.2), 191 (10.9), 152 (5.6), 110 (15.3), 78 (23.4), 43 (100).

6,8-Dioxo-dodecahydro-3a,7,7-trimethyl-1H-benz(e)inden-2-one (4)

A mixture of the crude ketone 21 (418 mg, 1.0 mmol), 12 mL of THF, 12 mL of water and 700 mg (12.5 mmol) of potassium hydroxide was degassed and then refluxed under a nitrogen atmosphere for 14 h. Subsequently most of the THF was removed under vacuum, and the residue (yellow mixture) diluted with water, and extracted twice with ether. To the aqueous solution was then added the same volume of ether and the mixture cooled to lower than 5°C. At a temperature between 0 and 5°C and with vigorous stirring, a dilute aqueous sodium bisulfate solution was added slowly until the mixture was acidic. The organic layer was separated and the aqueous layer extracted with ether. The combined ether solutions were washed with brine and dried ($MgSO_4$). The solvent was then removed under vacuum to leave a yellow oil (smell of benzenethiol). This oil was dissolved in 12 mL of acetic acid and stirred with 1.0 g (2.26 mmol) of lead tetraacetate and 800 mg (9.75 mmol) of sodium acetate for 2 h. The acetic acid was then mostly removed under vacuum. The residue was stirred with 10 mL of ethylene glycol and 50 mL of benzene for 15 min. The benzene layer was separated and the glycol layer extracted with benzene. The combined benzene solutions were washed with brine (twice), dried (K_2CO_3) and evaporated. The residue was purified with flash chromatography (eluent hexane/EtOAc 2:1) to give 120 mg (0.50 mmol, 50%) of a slowly solidifying slightly yellow oil, which was pure according to ^{13}C NMR. Recrystallization from hexane afforded crystals, mp 78-80°C. Sublimation (bath temp. 80-85°C, 0.5 mm Hg) furnished analytically pure material.
IR (KBr): 1730, 1380 cm^{-1}. ^1H NMR (270 MHz): δ4.20 (q, J=2 Hz, 1H), 4.08 (dd, 12.1, 2.9 Hz, 1H), 3.59 (dd, 12.1, 1.1 Hz, 1H), 2.74 (ddd, 7.7, 12.1, 13.6 Hz, 1H), 2.37 (dd, 7.4, 18.0 Hz, 1H), 2.15, d, J=17.1 Hz, 1H; 2.10, d, J=17.1 Hz, 1H, 1.50-1.95 (m, 6H), 1.47 (s, 3H), 1.41 (s, 3H), 0.90 (s, 3H). ^{13}C NMR (50.10

MHz): δ216.7, 98.1, 66.4, 62.2, 55.5, 38.9, 38.7, 38.2, 35.1, 29.7, 27.5, 18.6, 16.9 ppm. Anal. Calc'd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30, Found: C, 70.70; H, 9.19.

ACKNOWLEDGMENT

We thank the National Institutes of Health for their generous support of our programs.

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