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SYNTHETIC STUDIES TOWARDS FORSKOLIN

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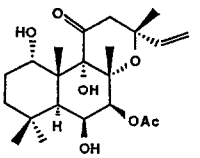
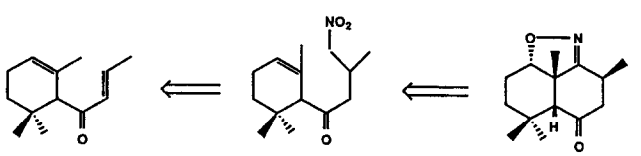
A model tricyclic system incorporating the complete array of oxygenated functions of the AB portion of forskolin has been synthetized. The highly substituted decalin unit of the natural target has been in turn assembled in a convenient way utilizing an intramolecular nitrile oxide cycloaddition reaction as key step.

The combination of biological activity and structural novelty[1] of the diterpene forskolin 1, featuring an uncommon arrangememnt of oxygenated functions, has commanded considerable synthetic interest.[2] This activity has recently culminated in the completion of the first total synthesis at the hands of Ziegler et al.,[3,4] followed shortly after by other two successful approaches.[5,6]



1

As a continuation of our efforts in this area[2d] we detail in this paper an efficient synthesis of a highly functionalized decalin system corresponding to the AB subunit of 1 and its transformation into a model tricyclic ring system possessing seven of the eight stereocenters of the natural product with the correct stereochemistry. The synthetic approach to assemble the decalin unit relies on a pivotal intramolecular nitrile oxide cycloaddition (INOC), a reaction continuously growing in both popularity and practicability in natural product synthesis. The key elements of our strategy are outlined in the following Scheme:



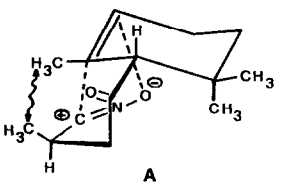
2 3 4

It is seen that a strategically functionalized AB ring such as **4** in which the isoxazoline ring could serve as a latent ß-hydroxyketone could be derived through the INOC cycloaddition of the nitrile oxide generated from the primary nitroderivative **3** which in turn could arise from **2**.

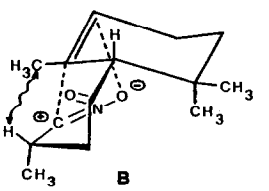
A considerable simplification of the problem is thereby achieved since **3** would be produced easily from the abundantly available α-damascone **2** by tetramethylguanidine-catalyzed[7] Michael addition of nitromethane in a multi-grams scale.

The nitro-derivative **3** possesses a very favourable array of substituents (i.e.: the four methyl groups as in the natural product) and suitably positioned functional groups (both partners for the cycloaddition step, the primary nitro group and a trisubstituted double bond, besides a carbonyl group).

With **3** in the hands, an INOC reaction was now induced with p-chlorophenylisocyanate[8] as the dehydrating agent producing the cycloadduct **4** as single isomer. The stereochemical outcome of the INOC reaction in which the nitro group derived nitrile oxide would add to the face of the olefin that bears the nitrobutyl chain, allowed to establish the stereochemistry of C-1 and C-10 relative to C-5. The stereochemistry assigned to the C-8 methyl group is based on the analysis of the two possible transition states A and B, the latter being sterically less congested than the former minimizing methyl-methyl interactions.



A



B

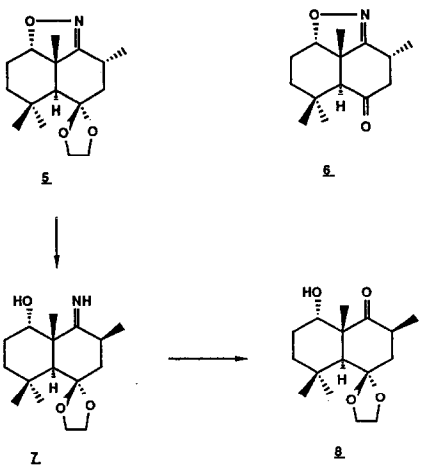
The expected but undesired cis-ring junction did not constitue a problem in view of the presence of the propitiously positioned carbonyl group, which could serve not only to effect the required cis ⟶ trans ring epimerization but also to allow the introduction of other functionalities.

However attempts to perform epimerization under basic conditions were unsuccessful and led us to a serendipitous discovery of a novel ring opening of the heterocyclic ring.[9]

This operation could be easily achieved by treatment of **4** which ethylene glycol in the presence of p-toluenesulfonic acid proceeding concomitantly with the acetalization to furnish a 3:1 mixture of the ketal **5** and the trans-fused ketone **6**, easily separated by flash-chromatography. Removal of the acetal from **5** by usual aqueous acid treatment led quantitatively to the parent ketone **6**, epimer of **4**.

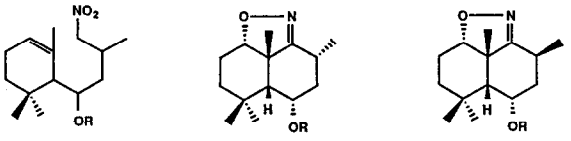
Unmasking of the heterocyclic nucleus of **5** by known hydrogenolytic methods preserving the protective group led interestingly to the formation of the ß-hydroxy-imine **7**, the proposed intermediate in the isoxazoline ⟶ ß-hydroxy ketone

interconversion, isolated for the first time concomitantly by Curran.[10]



Transformation of 7 into the ß-hydroxy ketone 8 was achieved by stirring for 12h in methylene chloride in the presence of wet silica gel.

While we were pleased both to discover the unusual behaviour of the isoxazoline ring toward the basic reagent[9] or to isolate the ß-hydroxy imine intermediate in the reduction step, this was not necessarily a good omen for our purposes, particularly considering the rather low yield of the initial cycloaddition step. Since the sp^2-hybridized carbon atom linking the nitrobutyl chain to the cyclohexene moiety in 3 was suspected to be responsible of the unsatisfactory outcome of the cycloaddition step limiting the conformational flexibility, the possibility that its removal might improve the efficiency of the INOC reaction was examined. Despite the deceptively straighforward reduction with sodium borohydride was completely unsuccessful, reaction of 3 with aluminum hydride afforded in high yield 9 which was then converted by treatment with acetic anhydride in pyridine into the corresponding acetyl derivative 10.



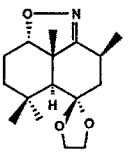
9 R = H
10 R = Ac

11 R = Ac
13 R = H

12 R = Ac
14 R = H

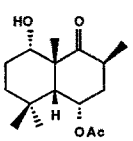
To our delight submitting 10 to the above described conditions for generating nitrile oxide a clean INOC reaction took place affording an 85% yield of a 3:1 mixture of the oily isoxazoline 11 and the crystalline 12, easily separated by silica gel column chromatography. In order to establish the stereochemical assignments made for these compounds, a sequence of chemical transformations was carried out. Refluxing 11 with aqueous methanolic potassium carbonate solution produ-

ced quantitatively the corresponding hydroxy-derivative **13**, which on Moffatt oxidation led to the formation of 1:1 mixture of epimeric ketones **4** and **6**. Treatment of the crude mixture of ketones with ethylene glycol in the presence of p-toluenesulfonic acid in benzene with azeotropic removal of water furnished the ketal **5** in 28% overall yield from **10**. When the same sequence was applied to the minor isomer **12**, the isomeric ketal **15** could be similarly obtained.



15

Even more interestingly, the Δ^2-isoxazoline ring of both **11** and **12** was smoothly cleaved by hydrogenolysis/hydrolysis with hydrogen gas and Ni-Raney in acetic acid:methanol:water system to produce the same ß-hydroxy ketone **16**, through epimerization at the carbon α to the carbonyl group of **17**, which has been sometimes isolated in sufficient quantity to afford separation by careful chromatography.



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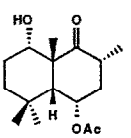

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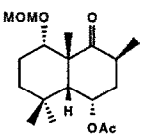


18

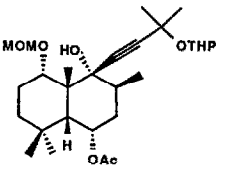
This finding allowed to avoid separation of the isomeric cycloadducts **11** and **12**, the mixture of which can be conveniently taken directly to **16** by standard reductive cleavage.

After protection of the hydroxyl function as the methoxymethyl ether (MOM) **18** by reaction with methylal in chloroform in the presence of P_2O_5[11] the stage was set for the introduction of a suitable carbon chain progenitor of the C-ring of the natural compound.

It was anticipated that the cis-ring junction would ensure that the concave nature of the molecule provides a high degree of stereocontrol in the creation of the quaternary center at the C-9 carbonyl of **18** with the correct stereochemistry.

Initial attempts to perform the addition of metallated vinyl compounds to **18** were unsuccessful owing to the steric hindrance of the adjacent methyl groups, while the relatively small carbanionic specie such as the acetylide ion derived from the tetrahydropyranyl ether of 2-methyl-3-butyn-2-ol in the presence of BuLi in THF at -78°C reacted cleanly to give rise to the adduct **19** in good yield.

The protection of the tertiary hydroxyl group was then accomplished under relatively mild conditions by treatment with methylal in chloroform in the presence of P_2O_5, producing the 1,3-dioxane derivative **20a** involving a comcomitant protective ether group exchange.



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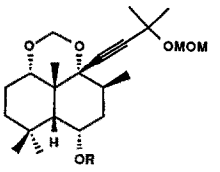
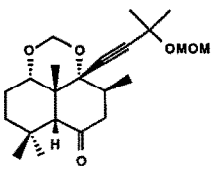


20a R = Ac
20b R = H

The stage was now set to adjust the ring junction stereochemistry. The acetyl group of 20a was removed by refluxing with methanolic sodium hydroxide to yield the secondary alcohol 20b, which was oxidized to the corresponding ketone 21 by action of PCC buffered with sodium acetate in methylene chloride. Epimerization to the required trans-ring junction easily occurred by treatment of 21 with sodium methoxide in refluxing methanol to produce the trans-ketone 22 quantitatively.



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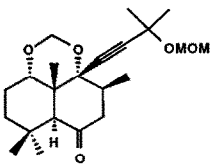

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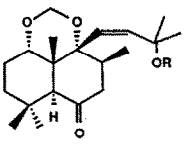


23

At this junction, a search for conditions necessary to reduce the triple bond of 22 led us to the fortuitous discovery that Lindlar's catalyst was incapable of promoting hydrogenation to the corresponding olefin 23, which could be obtained under 30 p.s.i. of hydrogen in the presence of W-2 Raney-nickel, as well as at hydrogen pressure up to approximately 750 p.s.i. in the presence of a variety of catalysts (e.g., Pd/C; PtO_2). The assigned stereochemistry has been confirmed by X-ray analysis (Fig.1).

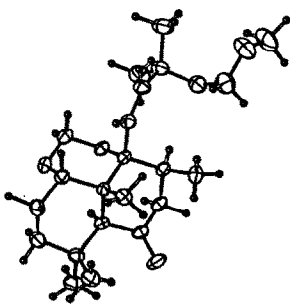
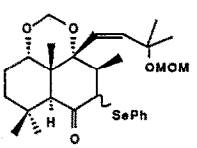


Fig. 1 - An ORTEP[12] view of 23 with thermal ellipsoids at the 40% probability level

Therefore we decided to investigate the feasibility of the construction of the pyranic ring starting from 23, in which the double bond would serve later as handle for further elaboration.

Thus we began the necessary manipulations for the introduction of the lacking oxygenated functions in the decalin system firstly transforming 23 into the corre-

sponding α,ß-unsaturated ketone 25a. This task could be readily effected through selenenylation[13] of the enolate of 23, generated by treatment with LDA in THF at -78°C, by action of phenylselenyl bromide prepared in situ from diphenyldiselenide and bromine, followed by oxidation of the intermediate 24 occurring with concomitant selenoxide elimination under mild conditions.



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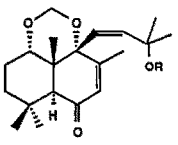
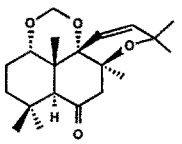


25a R = MOM
25b R = H



26

Several comments concerning the unreactivity of the double bond in the chain at C-9 are appropriate. Apart from the unusual reluctancy to undergo complete saturation even under forcing conditions, where hydrogenolysis of methoxymethyl ether moiety was the only detectable side reaction, the selenenylation step could be performed without any evidence of complications resulting from the reaction of the double bond with excess of phenylselenyl bromide. Moreover the oxidative selenoxide elimination could be selectively accomplished by ozonization. At this point, with 25a in hands, we examined the feasibility of the selective removal of methoxymethyl (MOM) group: in the event, an intramolecular Michael addition could be exploited as a way to obtain the pyranic ring. Rather surprisingly brief treatment of 25a with 70% perchloric acid in THF, furnished directly the tricyclic derivative 26; possessing the wrong stereochemistry at the newly formed ring junction as demonstrated by X-ray analysis. (Fig.2)

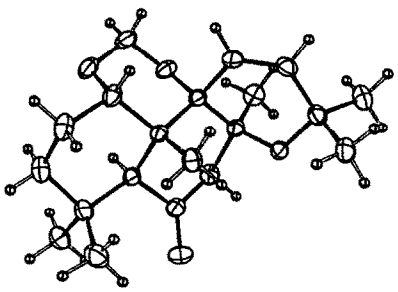


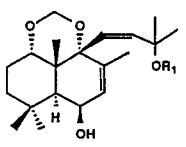
Fig. 2 - An ORTEP[12] view of 26 with thermal ellipsoids at the 40% probability level.

In order to obtain the pyranic ring closure with the correct stereochemistry we studied the elaboration of the vicinal triol array at C-6, C-7 and C-8.
To this end the enone 25a was reduced with DIBAH in toluene at -78°C to give the allylic alcohol 27, deriving from the attack of the reducing agent from the less encumbered face, which on Sharpless epoxidation[14] afforded a 3:1 mixture of the ß-epoxide 28a and the enone 25a easily separated by flash-chromatography. The stereochemical outcome of the reduction as well as the side reaction occurring during the epoxidation parallel the results obtained by Ziegler[2c] on structurally related compounds.

We reasoned that the epoxide moiety should undergo nucleophilic opening under basic conditions suitable to generate the alkoxide of the tertiary alcohol of the appended chain. Thus removal of the methoxymethyl (MOM) group by brief treatment with 70% perchloric acid in THF delivered the alcohol **28b**, which on treatment with sodium hydride led unexpectedly to the formation of **26**.

It seemed likely that **26** presumably arose from **25b** through intramolecular Michael addition in an analogous way as above mentioned.

To confirm this hypothesis we transformed **28a** into the corresponding acetyl derivative **28c** by standard method in order to preclude the formation of an α,ß-unsaturated ketone. Removal of MOM protective group of **28c** by acid treatment gave the alcohol **28d**, which was recovered unchanged after treatment with excess of sodium hydride.



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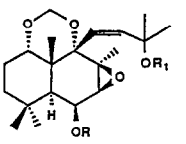
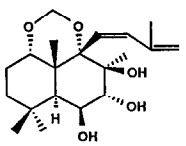
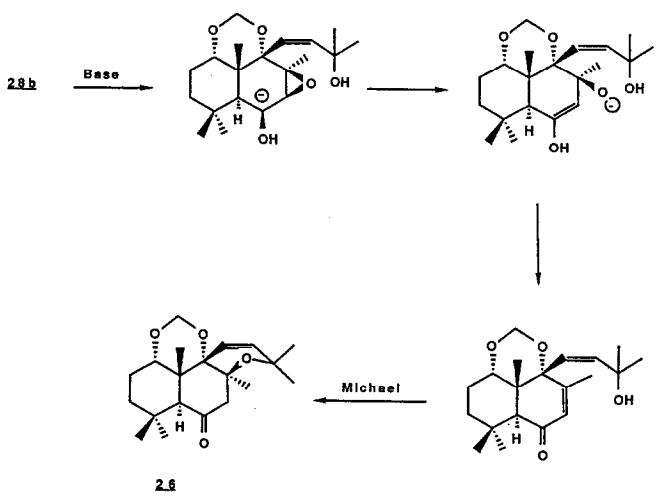


28a R_1 = MOM R = H
28b R_1 = R = H
28c R_1 = OMOM R = Ac
28d R_1 = H R = Ac



29

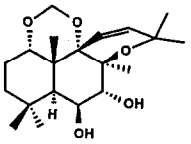
On the basis of these results we proposed a mechanism to rationalize the formation of **26** from **28b**.



26

To complete the scenario we studied also the acid-catalyzed opening of the epoxide moiety of **28a**. Its treatment with 20% sulfuric acid led to the formation of the diene **29**, which could be transformed to **30** by mercuric acetate-induced cyclization with subsequent reduction of the intermediate mercurial derivative with sodium

borohydride in the presence of sodium hydroxide.



30

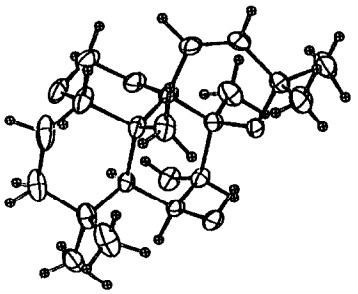
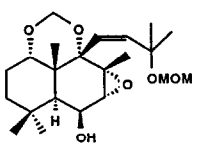


Fig. 3 - An ORTEP[12] view of 30 with thermal ellipsoids at the 40% probability level.

The tricyclic compound 30 has the wrong stereochemistry not only at the pyranic ring junction but also at C-7, as confirmed by X-ray analysis (Fig.3). These finding suggested to address our efforts towards the preparation of the α-epoxide 31 from 27, a task readily accomplished by treatment with m-chloroperbenzoic acid. While the exposure of 31 to the usual acid conditions gave the undesired tryciclic compound 30, as anticipated, the opening of the epoxide moiety by treatment with potassium hydroxide in ethylene glycol proceeded satisfactorily to produce the triol 32, which was promptly cyclized to the model compound 33 contamined by small quantities of the dehydration product 34 by usual acid treatment.



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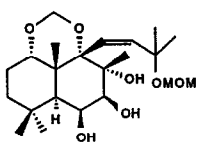

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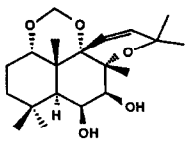
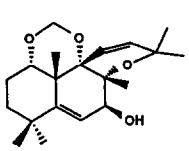


33

In order to investigate the functionalization of the double bond of 33, we proceeded to protect the cis-vicinal diol moiety as the acetonide 35 by treatment with 2,2-dimethoxypropane in the presence of pyridinium p-toluenesulfonate.

Performing the required functionalization of the double bond of 35, should be a trivial task but its unreactivity towards oxidation and electrophilic attack precluded the practical realization of such a tactic.

This unavoidable but not entirely unexpected inertness of the olefin moiety precluded the efficacious utilization of this plan towards forskolin although it can be adapted to the design of structural analogues forcing us to modify the strategy for the construction of the pyranic ring of the natural target. These investigations are in advanced course in our laboratories and will be reported in details in due time.



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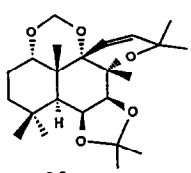

35

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 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. Flash-chromatography was carried out with Merck silica gel (230-400 mesh).

Materials: The tetrahydropyranyl ether of 2-methyl-3-butyn-2-ol has been prepared in this way: To a cooled (-20°C) solution of 2-methyl-3-butyn-2-ol (3 g, 37.51 mmol) in 30 ml of CH_2Cl_2 were added 4.9 ml of dihydropyran (53.57 mmol) and few crystals of p-toluensulphonic acid. The resulting mixture, stirred for 1 h, was washed with saturated solution of $NaHCO_3$ and dried. After elimination of the solvent at reduced pressure, the residue was purified by distillation at 30 mmHg (b.p; 72°C) to give 3-methyl-3-tetrahydropyranyloxy-butyne (5.8 g, 96%).
^{1}H NMR ($CDCl_3$): δ 1.5 (s, 3H), 1.52 (s, 3H), 2.41 (s, 1H), 3.5 (m, 1H), 3.9 (m, 1H), 5.07 (m, 1H).

3-Methyl-4-nitro-1-(2,6,6-trimethyl-2-cyclohexene-1-yl)1-butanone 3

A mixture of nitromethane (50 ml), α-damascone (10 g, 50.8 mmol), tetramethylguanidine (0.5 ml) was stirred at room temperature for 2 h. The progress of the reaction was followed by TLC (eluent: ether-light petroleum 1:4). The reaction mixture was washed with dilute hydrochloric acid and extracted with ether. The organic extract was dried, the solvent removed at reduced pressure and the residue distilled at 0.1 mmHg to give 3 (11.86 g, 90%) b.p. 95-97°C (Found: C, 66.22; H, 9.23; N, 5.69. $C_{14}H_{23}NO_3$ requires C, 66.37; H, 9.15; N, 5.53): IR (neat): 1710, 1550 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.9 (s, 3H), 0.92 (s, 3H), 1.07 (d, 3H, J=6Hz), 1.6 (m, 3H), 4.25-4.5 (m, 2H), 5.56 (m, 1H).

(3α,5aβ,8aβ,8bβ)-(±)-3,4,5a,6,7,8,8a,8b-Octahydro-3,6,6,8b-tetramethyl-5H-naphth[1,8-cd] isoxazol--5-one 4

A solution of 3-chlorophenyl isocyanate (4 g, 26 mmol) in 40 ml of benzene was added slowly (48 h) to a boiling solution of 3 (2.53 g, 10 mmol) in 20 ml of benzene containing several drops of triethylamine. To the cooled reaction mixture aqueous ammonia (20 ml) was added and the stirring continued for an additional 30 min. The precipitated 3-chlorophenyl-urea was removed by filtration and the filtrate concentrated in vacuo. The residue was purified by flash-chromatography (eluent: ether-light petroleum 1:1) to afford (0.47 g, 20%) of 4 as a solid m.p. 95-97°C (Found: C, 71.29; H, 9.13; N, 6.11. $C_{14}H_{21}NO_2$ requires C, 71.45; H, 9.00; N, 5.95): IR ($CHCl_3$): 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.93 (s, 3H), 1.00 (s, 3H); 1.18 (s, 3H), 1.37 (d, 3H, J=6Hz), 4.27 (dd, 1H, J=8Hz, J=7.5Hz).

(3'α,5'aα,8'aβ,8'bβ)-(±)-3',4',5'a,6',7',8',8'a,8'b-Octahydro-3',6',6',8'b-tetramethyl-spiro[1,3--dioxolane-2,5'-[5H]-naphth[1,8-cd]-isoxazole 5

A solution of 4 (0.5 g, 2.1 mmol), 0.4 ml of ethylene glycol and 60 mg of p-toluensulphonic acid in 20 ml of benzene was refluxed for 24 h under coninuous removal of water with a Dean-Stark apparatus. The reaction mixture was washed with saturated sodium bicarbonate solution and the separed organic layer was dried and the solvent removed at reduced pressure. The residue was purified by flash-chromatography (eluent: ether-light petroleum 2:1) to give 5 (0.33 g, 55%) m.p. 73-74°C and 0.1 g of 6 m.p. 117-119°C.
(Found: C, 68.86; H, 8.91; N, 5.09. $C_{16}H_{25}NO_3$ requires C, 68.78; H, 9.02; N, 5.01): ^{1}H NMR ($CDCl_3$): δ 0.99 (s, 3H), 1.15 (s, 3H), 1.25 (d, 3H, J=6Hz), 1.37 (s, 3H), 2.77 (m, 1H), 3.92-4.00 (m, 4H), 4.12 (dd, 1H, J=8Hz, J=9Hz).

(3α,5aα,8aβ,8bβ)-(±)-3,4,5a,6,7,8,8a,8b-Octahydro-3,6,6,8b-tetramethyl-5H-naphth[1,8-cd] isoxazol--5-one 6

A mixture of 5 (0.24 g, 0.86 mmol) in THF (15 ml) was treated with 20% sulphuric acid (4 ml) at room temperature for 4 h. After elimination of the solvent at reduced pressure the residue was extracted with $CHCl_3$. The dried organic extracts were concentrated in vacuo and the residue was crystallized from pentane to give 0.19 g of 6 (95%) m.p. 117-119°C.
(Found: C, 71.19; H, 9.15; N, 6.14. $C_{14}H_{21}NO_2$ requires C, 71.45; H, 9.00; N, 5.95): IR (nujol): 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.87 (s, 3H), 1.12 (s, 3H), 1.25 (s, 3H), 1.40 (d, 3H, J=7Hz), 2.2 (s, 1H), 4.22 (dd, 1H, J=8Hz, J=9Hz.

(3'α 4'aß,5'α 8'aα)-(±)-Octahydro-4'imino-3',4'a,8',8'-tetramethyl-spiro [1,3-dioxolane-2,1'(2'H)--naphthalen]-5'-ol 7

A solution of **5** (3.46 g, 12.4 mmol) in methanol (45 ml) containing acetic acid (6 ml) and water (3 ml) was hydrogenated in the presence of W2 Raney Nickel for 24 h at room temperature and atmospheric pressure of hydrogen. After filtration of the catalyst through Celite, the solvent was eliminated in vacuo, the residue was extracted with $CHCl_3$ and washed with saturated aqueous sodium bicarbonate. The dried organic phase was concentrated at reduced pressure to give **7** as a solid (3.14 g, 90%) m.p. 99-100°C.

(Found: C, 68.23; H, 9.59; N, 4.89. $C_{16}H_{27}NO_3$ requires C, 68.29; H, 9.67; N, 4.98): IR (nujol): 3300, 1630 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.92 (s,3H), 1.00 (d, 3H, J=6Hz), 1.12 (s, 3H), 1.63 (s, 3H), 2.77 (m,1H), 3.00 (dd, 1H, J=5Hz, J=11Hz), 3.70-4.02 (m, 4H), 6.27 (m, 2H).

(3'α,4'aß,5'α,8'aα)-(±)-Octahydro-5'-hydroxy-3',4'a,8',8'-tetramethyl-spiro [1,3-dioxolane-2,1'-(4'H)-naphthalen]-4'-one 8

A solution of **7** (3.14 g, 11.16 mmol) in CH_2Cl_2 (30 ml) was stirred in the presence of wet silica gel (8 g) at 60°C for 12 h. After filtration and evaporation of the solvent at reduced pressure, **8** was obtained quatitatively as a crystalline compound m.p. 103-104°C (pentane). (Found: C, 67.92; H, 9.41. $C_{16}H_{26}O_4$ requires C, 68.05; H, 9.28): IR (nujol): 3500, 1690 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.92 (s, 3H), 1.02 (d, 3H, J=6Hz), 1.12 (s, 3H), 1.62 (s, 3H), 2.9 (m, 1H), 3.55 (m, 1H), 3.70-4.07 (m, 4H).

2,6,6-Trimethyl-α-(2-methyl-3-nitropropyl)-2-cyclohexene-1-methanol 9

To a well stirred ice-cooled suspension of $LiAlH_4$ (0.51 g, 13.44 mmol) in dry ether (20 ml) $AlCl_3$ (0.6 g, 4.5 mmol) was added and the mixture left at the same temperature for 5 min. After further 10 min. at room temperature, the mixture was cooled at 0°C and a solution of **3** (3.03 g, 11.97 mmol) in dry ether (20 ml) was added dropwise. Stirring was continued for 15 min at 0°C and a further 30 min at room temperature, the excess of reducing agent was decomposed by careful addition of water and the ethereal solution was acidified with hydrochloric acid. The organic phase was separated and dried, and the solvent was removed in vacuo. The nitroalcohol **9** (3 g, 98.3%) was obtained as an oil.

(Found: C, 65.70; H, 9.76; N, 5.39. $C_{14}H_{25}NO_3$ requires C, 65.85; H, 9.87; N, 5.49): IR (neat): 3500, 1555 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.87 (s, 3H), 0.98 (s, 3H), 1.1 (m, 3H), 1.77 (m,3H), 3.65-4.055 (m,1H), 4.15-4.65 (m, 2H), 5.7 (m, 1H).

2,6,6-Trimethyl-α-(2-methyl-3-nitropropyl)-2-cyclohexene-1-methanol acetate 10

An ice-cooled solution of **9** (1.7 g, 6.66 mmol) in pyridine (5 ml) was treated with Ac_2O (2 ml, 21.2 mmol). After 6 h at room temperature the mixture was poured into water, acidified with hydrochloric acid and extracted with ether. The extracts were washed with brine and 5% $NaHCO_3$ solution, dried and concentrated to leave quantitatively **10** as an oil.

(Found: C, 64.75; H, 9.42; N, 4.79. $C_{16}H_{27}NO_4$ requires C, 64.62; H, 9.15; N, 4.71): IR (neat) 1740, 1555 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.85 (s, 3H), 0.97 (s, 3H), 1.05 (d, 3H, J=6Hz), 1.75 (m, 3H), 2.00 (s, 3H), 4.15-4.50 (m, 2H), 5.15 (m, 1H), 5.4 (m, 1H).

(3α,5α,5aß,8aß,8bß-(±) 11 and (3ß,5α,5aß,8aß,8bß)-(±)-4,5,5a,6,7,8,8a,8b-Octahydro-3,6,6,8b--tetramethyl-3H-naphth[1,8-cd]isoxazol-5-ol acetate 12

A solution of 3-chlorophenyl isocyanate (4 g, 26 mmol) in benzene (40 ml) was added slowly (48 h) to a boiling solution of **10** (3 g, 10.1 mmol) in benzene (20 ml) containing several drops of triethylamine. To the cooled reaction mixture aqueous ammonia (20 ml) was added and the mixture stirred for an aditional 30 min. The precipitated 3-chlorophenylurea was removed by filtration and the filtrate concentrated in vacuo. The residue was purified by flash-chromatography (eluent: ether--light petroleum 1:1) to afford a 90% yield a 3:1 mixture of **11**, oil with the following analytical and spectral data: (Found: C, 69.02; H, 8.81; N, 5.34. $C_{16}H_{25}NO_3$ requires C, 68.78; H, 9.02; N, 5.01): IR (neat): 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (s, 3H), 1.10 (s, 3H), 1.27 (d, 3H, J=6Hz), 1.32 (s, 3H), 2.05 (s, 3H), 4.17 (dd, 1H, J=7Hz, J=8Hz), 5.41 (m, 1H) and **12**, m.p. 106-107°C with the following analytical and spectral data: (Found: C, 68.81; H, 8.89; N, 4.97. $C_{16}H_{25}NO_3$ requires C, 68.78; H, 9.02; N, 5.01): IR (nujol): 1740 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.95 (s, 3H), 1.06 (s, 3H), 1.32 (d, 3H, J=6Hz), 1.37 (s, 3H), 2.00 (s, 3H), 4.37 (dd, 1H, J=7Hz, J=9Hz), 5.27 (m, 1H).

(3α,5α,5aß,8aß,8bß)-(±)-4,5,5a,6,7,8,8a,8b-Octahydro-3,6,6,8b-tetramethyl-3H-naphtho[1,8-cd]isoxazol-5-ol 13

A solution of **11** (2.18 g, 7.8 mmol) in 3:1 aqueous methanol (20 ml) containing potassium carbonate (2.6 g, 18 mmol) was refluxed for 4 h. Removal of the methanol in vacuo, extraction of the residue with $CHCl_3$ and usual work-up afforded quantitatively the alcohol **13** as an oil. (Found: C, 70.72; H, 10.08; N, 5.98. $C_{14}H_{23}NO_2$ requires C, 70.85; H, 9.77; N, 5.90): IR (neat): 3300 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.05 (s, 6H), 1.20 (d, 3H, J=6Hz), 1.32 (s, 3H), 3.97-4.52 (m, 2H).

(3'α,5'aα,8'aβ,8'bβ)-(±)-3',4',5'a, 6',7',8',8'a,8'b-Octahydro-3',6',6',8'b-tetramethyl-spiro[1,3-dioxolane-2,5'-(5H)-naphtho[1,8-cd]isoxazole] 15

A mixture of **13** (1.85 g, 7.8 mmol), dicyclohexylcarbodiimide (DCC) (4.41 g, 21 mmol), trifluoroacetic acid (0.625 ml, 8 mmol), pyridine (1.17 ml), dry DMSO (12.86 ml, 181 mmol) and dry benzene (28 ml) was stirred for 5 h at room temperature. After addition of ether (30 ml), oxalic acid (1.8 g) in methanol (4 ml) was added carefully. The mixture was stirred for 30 min, filtered and the filtrate was repeatedly washed with brine, dried and the solvent evaporated in vacuo to afford a residue which was purified by flash-chromatography (eluent: ether-light petroleum 2:1) giving a mixture of **4** and **6** (1.4 g, 78%).

The two epimeric ketones were ketalized as above described for **4** affording the same ketal **5** in 60% yield.

(2β,4α,4aβ,8α,8aβ)-(±)-Octahydro-4-acetyloxy-8-hydroxy-2,5,5,8a-tetramethyl-(2H)-naphthalen-1-one 16

A solution of **11** (6.92 g, 24.8 mmol) in methanol (90 ml) containing acetic acid (12 ml) and water (6 ml) was hydrogenated in the presence of Raney nickel W-2 for 24 h at room temperature and atmospheric pressure. After filtration of the catalyst through Celite, the solvent was removed in vacuo, the residue was extracted with $CHCl_3$ and washed with saturated aqueous $NaHCO_3$. The dried organic phase was concentrated at reduced pressure to give **16** as a solid (5.93 g, 85%) m.p. 139-140°C (pentane). The same product was obtained when the epimeric **12** was hydrogenolyzed. (Found: C, 68.01; H, 9.19. $C_{16}H_{26}O_4$ requires C, 68.05; H, 9.28): IR (nujol): 3500, 1745, 1700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.00 (s, 3H), 1.10 (d, 3H, J=6Hz), 1.17 (s, 3H), 1.42 (s, 3H), 2.17 (s, 3H), 3.57 (t, 1H, J=3Hz), 3.62 (s, 1H), 5.37 (m, 1H). Evaporation of the mother's liquors of crystallization followed by flash-chromatography of the residue (eluent: ether-light petroleum 1:1) gave a little amount of **17** m.p. 35°C. ^1H NMR ($CDCl_3$): 0.96 (s, 3H), 1.03 (d, 3H, J=6Hz), 1.08 (s, 3H), 1.60 (s, 3H), 2.06 (s, 3H), 2.8 (m, 1H), 3.15 (dd, 1H, J=4Hz, J=8Hz), 3.50 (s, 1H), 5.85 (m, 1H).

(2β,4α,4aβ,8α,8aβ)-(±)-Octahydro-4-(acetyloxy)-8-(methoxymethyloxy-2,5,5,8a-tetramethyl-(2H)-naphthalen-1-one 18

To a magnetically stirred ice-cooled suspension of P_2O_5 (50 g) in dry $CHCl_3$ (100 ml), methylal (100 ml) and **16** (5 g, 17.7 mmol) were added. After completion of the reaction (checked by T.L.C.) about 2 h, the mixture was poured into an ice-cooled sodium carbonate solution. The remaining oil in the reaction flask was washed out with sodium carbonate solution and the combined mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried and evaporated. The residue was purified by flash-chromatography (eluent: ether-light petroleum 1:1) to afford **18** (4.1 g, 71%) m.p. 72-73°C. (Found: C, 66.08; H, 9.43. $C_{18}H_{30}O_5$ requires C, 66.23; H, 9.26): IR (nujol): 1740, 1700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.97 (s, 3H), 1.02 (d, 3H, J=6Hz), 1.15 (s, 3H), 1.38 (s, 3H), 2.1 (s, 3H), 3.25 (s,3H), 3.5 (m, 1H), 4.47 (AB system, 2H, J=6Hz), 5.1 (m, 1H).

(1α,2β,4α,4aβ,8α,8aβ)-(±)-Decahydro-4-(acetyloxy)-8-(methoxymethyloxy)-2,5,5,8a-tetramethyl-1-[3-(tetrahydro-2H-pyran-2-yl)oxy -3-methyl-1-butynyl]-1-naphthalenol 19

A cold (-78°C) magnetically stirred solution of 3-methyl-3-tetrahydropyranyloxy-butyne (2.32 g, 13.8 mmol) in 40 ml of dry THF was blanketed with argon and treated with n-butyl-lithium (8.6 ml of 1.6 M in hexane; 14 mmol). After 30 min the reaction mixture was allowed to warm at 0°C and was stirred at this temperature for 30 min. To the solution further cooled at -78°C **18** (1.5 g, 4.6 mmol) was added and stirring continued for 6 h. Following careful addition of NH_4Cl solution, the product was extracted with ether (x3), and the combined extracts were dried and evaporated. The residue was purified by flash-chromatography (eluent: ether-light petroleum 1:1) to give 2.17 g (96%) of **19** as a solid m.p. 85-86 (pentane). (Found: C, 67.89; H, 9.32. $C_{28}H_{46}O_7$ requires C, 67.98; H, 9.37): IR (nujol): 3550, 1750 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.9 (s, 3H), 1.0 (d, 3H, J=7Hz), 1.12 (s, 3H), 1.37 (s, 3H), 1.5 (s, 3H), 1.52 (s, 3H), 2.02 (s, 3H), 2.72 (m, 1H), 3.3 (m, 1H), 3.37 (s, 3H), 3.55 (m, 1H), 3.67 (m, 1H), 3.87 (m, 1H), 4.6 (AB system, 2H, J=6Hz), 4.9 (m, 2H).

(3aβ,4β,6α,6aβ,9aβ,9bβ)-(±)-Decahydro-4,7,7,9b-tetramethyl-3a-[3-(methoxymethyloxy)-3-methyl-1-butynyl]-naphtho[1,8-de]-1,3-dioxin-6-ol acetate 20a

To a stirred ice-cooled suspension of P_2O_5 (9 g) in dry $CHCl_3$ (20 ml), methylal (18 ml) and **19** (1.59 g, 3.22 mmol) were added. After completion of the reaction (checked by T.L.C., about 4 h at room temperature), the mixture was poured into an ice-cooled sodium carbonate solution. The remaining oil in the reaction flask was washed out with Na_2CO_3 solution and the combined mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried and evaporated. The residue was purified by flash-chromatography (eluent: ether-light petroleum 1:1) to afford **20a** (1.26 g, 92.7%) as an oil. (Found: C, 67.93; H, 9.31. $C_{24}H_{38}O_6$ requires C, 68.22; H, 9.07): IR (film): 1750 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.92 (s, 3H), 1.15 (s, 3H), 1.14 (d, 3H, J=7Hz), 1.36 (s, 3H), 1.52 (s, 6H), 2.02 (s, 3H), 2.22 (m, 1H), 3.33 (s, 3H), 3.47 (m, 1H), 4.85 (s, 2H), 4.95 (m, 1H), 4.95 (AB system, 2H, J=5Hz).

(3aß,4ß,6α,6aß,9aß,9bß)-(±)-Decahydro-4,7,7,9b-tetramethyl-3a-[3-(methoxymethyloxy)-3-methyl-1-butynyl]-naphtho[1,8-de]-1,3-dioxin-6-ol 20b

A solution of **20a** (2.0 g, 4.74 mmol) in methanol (30 ml), water (4 ml) containing sodium hydroxide (0.8 g, 20 mmol) was refluxed for 6 h. Most of the solvent was removed in vacuo, than the mixture was extracted with $CHCl_3$. The dried organic extracts were evaporated at reduced pressure to give **20b** as an oil in quantitative yield. (Found: C, 69.22; H, 9.38. $C_{22}H_{36}O_5$ requires C, 69.44; H, 9.54): IR (film): 3550 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.13 (s, 6H), 1.18 (d, 3H, J=7Hz), 1.35 (s, 6H), 3.36 (s, 3H), 3.53 (m, 1H), 4.02 (m, 1H), 4.85 (s, 2H), 5.07 (AB system, 2H, J=6Hz).

(3aß,4ß,6aß,9aß,9bß)-(±)-3a,4,6a,7,8,9,9a,9b-Octahydro-4,7,7,9b-tetramethyl-3a-[3-(methoxymethyloxy)-3-methyl-1-butynyl]-5H-naphtho[1,8-de]-1,3-dioxin-6-one 21

To a stirred suspension of pyridinium chlorochromate (PCC) (1.28 g, 5.9 mmol), sodium acetate (0.1 g, and four pellets of molecular sieves 4A in dry CH_2Cl_2 (10 ml), a solution of **20b** (0.5 g, 1.31 mmol) in CH_2Cl_2 (4 ml) was added. The mixture, stirred at room temperature for 4 h, was diluted with ether (40 ml) and the solid residue was washed (x3) with ether. The ethereal extracts was filtered through fluorisil, dried and evaporated at reduced pressure to give **21** in quantitative yield as an oil. (Found: C, 69.93; H, 8.87. $C_{22}H_{34}O_5$ requires C, 69.81; H, 9.05): IR (film): 1725 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.07 (s, 3H), 1.15 (s, 3H), 1.42 (s, 3H), 1.46 (d, 3H, J=7Hz), 1.52 (s, 6H), 2.33 (s, 1H), 3.35 (s, 3H), 3.42 (m, 1H), 4.85 (s, 2H), 4.9 (AB system, 2H, J=6Hz).

(3aß,4ß,6aα,9aß,9bß)-(±)-3a,4,6a,7,8,9,9a,9b-Octahydro-4,7,7,9b-tetramethyl-3a-[3-(methoxymethyloxy)-3-methyl-1-butynyl]-5H-naphtho[1,8-de]-1,3-dioxin-6-one 22

A solution of **21** (1.1 g, 2.65 mmol) in methanol (20 ml) containing 0.4 g of sodium was refluxed for 6 h. The solvent was removed in vacuo and the residue was extracted with ether, washed with water and dried. After evaporation of the solvent, the residue was purified by flash-chromatography (eluent: ether-light petroleum 1:2) to give **22** in quantitative yield as an oil. (Found: C, 69.69; H, 9.17. $C_{22}H_{34}O_5$ requires C, 69.81; H, 9.05): IR (film): 1715 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.01 (s, 3H), 1.1 (s, 3H), 1.2 (d, 3H, J=7Hz), 1.23 (s, 3H), 3.36 (s, 3H), 3.37 (s, 1H), 3.7 (m, 1H), 4.86 (s, 2H), 5.2 (AB system, 2H, J=6Hz).

(3aß(Z),4ß,6aα ,9aß,9bß)-(±)-3a,4,6a,7,8,9,9a,9b-Octahydro-4,7,7,9b-tetramethyl-3a-[3-(methoxymethyloxy)-3-methyl-1-butenyl]-5H-naphtho[1,8-de]-1,3-dioxin-6-one 23

A solution of **22** (1.4 g, 3.82 mmol) in methanol (50 ml) was hydrogenated in the presence of Raney nickel W-2 in the Parr apparatus at room temperature and under 30 p.s.i. of hydrogen for 4 h. After filtration of the catalyst through Celite, the solvent was removed at reduced pressure and the residue was purified by flash-chromatography (eluent: ether-light petroleum 1:1) to give **23** as a solid (1.3 g, 94%) m.p. 77-78°C (pentane). (Found: C, 69.40; H, 9.58. $C_{22}H_{36}O_5$ requires C, 69.44; H, 9.54): IR (nujol): 1710 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.0 (s, 3H), 1.01 (d, 3H, J=7Hz), 1.02 (s, 3H), 1.26 (s, 3H), 1.4 (s, 6H), 3.0 (m, 2H), 3.31 (s, 3H), 3.52 (s, 1H), 3.57 (m, 1H), 4.61 (s, 2H), 5.0 (AB system, 2H, J=6Hz), 5.6 (AB system, 2H, J=14Hz).

(3aß(Z),4ß,6aα ,9aß,9bß)-(±)-3a,4,6a,7,8,9,9a,9b-Octahydro-5-phenylselenenyl-4,7,7,9b-tetramethyl-3a-[3-(methoxymethyloxy)-3-methyl-1-butenyl]-5H-naphtho[1,8-de]-1,3-dioxin-6-one 24

To a solution of lithium diisopropylamide, prepared from diisopropylamine (0.92 ml, 6.51 mmol) and 1.6 M butyllithium in hexane (4 ml, 6.38 mmol) under nitrogen at -78°C, a solution of **23** (1 g, 2.63 mmol) in THF (3 ml) was added dropwise. After enolate formation was complete (15 min), a solution of phenylselenyl bromide, prepared from diphenyl diselenide (1 g, 11.3 mmol) and bromine (0.16 ml, 11 mmol), in 4 ml of THF was added dropwise at -78°C. After 10 min the reaction was quenched by addition of water and extracted with ether (3x15 ml). The extract was dried and the solvent was stripped to yield **24** as an oil. This material was used in the next step without any additional purification. A sample of **24** was purified by flash-chromatography (eluent: ether-light petroleum 1:1) to give an oil with the following spectroscopic data. ^1H NMR ($CDCl_3$): δ 1.03 (s, 3H), 1.1 (s, 3H), 1.25 (d, 3H, J=5Hz), 1.48 (s, 6H), 3.43 (s, 3H), 3.6 (m, 1H), 3.66 (s, 1H), 4.66 (d, 1H, J=4Hz), 4.8 (s, 2H), 5.13 (AB system, 2H, J=14Hz), 7.2-7.73 (m, 5H).

(3aß(Z),6aα,9aß,9bß)-(±)-6a,7,8,9,9a,9b-hexahydro-4,7,7,9b-tetramethyl-3a-[3-(methoxymethyloxy)-3-methyl-1-butenyl]-3aH-naphtho[1,8-de]-1,3-dioxin-6-one 25a

To a 100 ml 3-necked round bottom flask fitted with a stopper, a gas dispersion tube and a drying tube was added 50 ml of CH_2Cl_2 and the crude phenylselenenylketone **24**. The reaction was cooled to -78°C and O_3 was bubbled through the solution until turned blue. The mixture was purged with nitrogen (to remove the excess of O_3) until colorless and 1 ml of diisopropylamine was added. The contents of the flask were poured directly into 50 ml of refluxing CCl_4 containing 1 ml of diisopropylamine. After 10 min at reflux the reaction was cooled and washed with water, dried and the solvent was removed. The residue was purified by flash-chromatography (eluent: ether-light petroleum 1:2) to give **25a** (0.8 g, 81%) as a solid m.p. 74-75°C. (Found: C, 69.94; H, 8.88. $C_{22}H_{34}O_5$ requires C, 69.81; H, 9.05): IR (nujol): 1675 (broad) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.08 (s, 3H), 1.17 (s, 3H), 1.25 (s, 3H), 1.33 (s, 3H), 1.38 (s, 3H), 1.9 (d, 3H, J=1.5Hz), 3.28 (s, 3H), 3.36 (s,

1H), 3.62 (m, 1H), 4.6 (s, 2H), 5.2 (AB system, 2H, J=7Hz), 5.53 (AB system, 2H, J=4Hz), 5.72 (d, 1H, J=1.5Hz).

(7aß,10aα,10bß,12a)-(±)-7a,9,10,10a,10b,11,12,12a-Octahydro-2,2,10,10,10b,12a-hexamethyl-2H,6H-1--benzopyrano[4a,5,6-de][1,3,2]-benzodioxin-11-one 26

A solution of 25a (0.45 g, 1.19 mmol) in THF (40 ml) containing perchloric acid 70% (1 ml) was stirred at room temperature for 15 min. The mixture was poured in saturated solution of $NaHCO_3$ and extracted with ether. The dried ethereal extracts were evaporated in vacuo and the residue was purified by flash-chromatography (eluent: ether-light petroleum 1:2) to give 26 (0.28 g, 70%) as a solid m.p. 119-120°C (methanol). (Found: C, 71.65; H, 9.31. $C_{20}H_{30}O_4$ requires C, 71.82; H, 9.04): IR (nujol): 1730 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.05 (s, 3H), 1.07 (s, 3H), 1.22 (s, 3H), 1.3 (s, 3H), 1.33 (s, 6H), 2.52 (AB system, 2H, J=14Hz), 3.46 (s, 1H), 3.62 (m, 1H), 5.2 (AB system, 2H, J=7Hz), 6.07 (AB system, 2H, J=11Hz).

(3aß(Z),6ß,6a ,9aß)-(±)-3a,6,6a,7,8,9,9a,9b-Octahydro-4,7,7,9b-tetramethyl-3a- 3-(methoxymethyl-oxy)-3-methyl-1-butenyl -naphtho 1,8-de -1,3-dioxin-6-ol 27

A cold (-78°C) solution of the enone 25a (1 g, 2.64 mmol) in dry toluene (7 ml) was treated with diisobutylaluminium hydride (9.1 ml of 1.2 M in toluene) and magnetically stirred at -78°C for 30 min. The reaction mixture was allowed to warm at 0°C, washed with saturated ammonium chloride solution, dried and concentrated. The residue was purified by flash-chromatography (eluent: ether-light petroleum 1:1) to give 27 (0.72 g, 72%) as an oil. (Found: C, 69.75; H, 9.47. $C_{22}H_{36}O_5$ requires C, 69.84; H, 9.54): IR (film): 3555 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.12 (s, 3H), 1.33 (s, 3H), 1.36 (s, 3H), 1.38 (s, 6H), 1.77 (d, 3H, J=1Hz), 2.2 (m, 1H), 3.35 (s, 3H), 3.42 (m, 1H), 4.42 (m, 1H), 4.67 (AB system, 2H, J=3Hz), 5.05 (AB system, 2H, J=7Hz), 5.45 (AB system, 2H, J=6Hz), 5.7 (m, 1H).

(3aß(Z),4 ,5 ,6ß,6a ,9aß,9bß)-(±)-4,5-Epoxydecahydro-4,7,7,9b-tetramethyl-3a- 3-(methoxymethyl-oxy)-3-methyl-1-butenyl -naphtho 1,8-de -1,3-dioxin-6-ol 28a

To amixture of 27 (2 g, 5.26 mmol), $VO(acac)_2$ (50 mg) in 5 ml of anhydrous benzene, stirred and heated at the reflux, was added dropwise tert-butylhydroperoxide (4.4 ml 3M in toluene). After 30 min the cooled mixture was washed with a saturated solution of Na_2SO_3 and extracted with ether. After drying and solvent removal the crude residue was purified by flash-chromatography (eluent: ether-light petroleum 1:1) to give 28a (1.2 g, 58%) m.p. 91-93°C and the above reported enone 25a (0.45 g, 22.6%). (Found: C, 66.68; H, 9.09. $C_{22}H_{36}O_6$ requires C, 66.64; H, 9.15): IR (nujol): 3500 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.12 (s, 3H), 1.27 (s, 3H), 1.37 (s, 6H), 1.45 (s, 6H), 2.0 (d, 1H, J=4Hz), 3.36 (s, 3H).

(3aß(Z),4 ,5 ,6ß,6a ,9aß,9bß)-(±)-4,5-Epoxydecahydro-4,7,7,9b-tetramethyl-3a- 3-hydroxy-3-methyl--1-butenyl -naphtho 1,8-de -1,3-dioxin-6-ol 28b

A mixture of 27 (1.5 g, 3.79 mmol) in 100 ml of THF was treated with perchloric acid 70% (3 ml) at room temperature for 30 min. The solution was neutralized with saturated solution of $NaHCO_3$ and extracted with ether. After drying and solvent removal the solid residue was crystallized from ether-light petroleum (1:1) to afford 28b (1 g, 75%) as a solid m.p. 182-184°C. (Found: C, 68.12; H, 9.07. $C_{20}H_{32}O_5$ requires C, 68.15; H, 9.15): IR (nujol): 3450 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.15 (s, 3H), 1.3 (s, 3H), 1.37 (s, 9H), 1.42 (s, 3H), 1.57 (d, 1H, J=5Hz, exchanged on D_2O addition), 3.42 (s, 1H, J=6Hz), 3.45 (m, 1H), 4.6 (m, 1H), 4.87 (s, 1H, exchanged on D_2O addition), 5.12 (AB system, 2H, J=6Hz), 5.62 (AB system, 2H, J=15Hz).

Treatment of 28b (0.5 g, 1.42 mmol) in DMF (5 ml) with four equivalents of NaH at 60°C for 6 h followed by usual work-up of the reaction mixture afforded 26 (0.35 g, 74%).

(3aß(Z),4 ,5 ,6ß,6a ,9aß,9bß)-(±)-4,5-Epoxydecahydro-4,7,7,9b-tetramethyl-3a 3-(methoxymethyloxy)--3-methyl-1-butenyl -naphtho 1,8-de -1,3-dioxin-6-ol acetate 28c

An ice-cooled solution of 28a (0.34 g, 0.86 mmol) in pyridine (2 ml) was treated with Ac_2O (0.5 ml). After 12 h at room temperature the mixture was diluted with ether, washed with water and saturated sodium bicarbonate solution. The dried extracts were concentrated in vacuo and the residue was purified by flash-chromatography (eleunt: ether:light petroleum 1:1) to afford 28c (0.26 g, 69% as an oil. (Found: C, 65.57; H, 8.91. $C_{24}H_{38}O_7$ requires C, 65.73; H, 8.73): IR (film): 1735 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.0 (s, 3H), 1.1 (s, 3H), 1.2 (s, 3H), 1.25 (s, 3H), 1.37 (s, 6H), 2.02 (s, 3H), 2.2 (d, 1H, J=2.5Hz), 3.27 (m, 1H), 3.32 (s, 3H), 3.37 (d, 1H, J=6Hz), 4.7 (s, 2H), 4.97 (AB system, 2H, J=6Hz), 5.25 (m, 1H), 5.47 (AB system, 2H, J=15Hz).

(3aß(Z),4α,5α,6ß,6aα, 9aß,9bß)-(±)-4,5-Epoxydecahydro-4,7,7,9b-tetramethyl-3a-[3-hydroxy-3-methyl--1-butenyl]-naphtho 1,8-de -1,3-dioxin-6-ol acetate 28d

A solution of **28c** (0.26 g, 0.59 mmol) in THF (10 ml) containing perchloric acid 70% (0.15 ml) was stirred at room temperature for 30 min. The mixture was poured into saturated solution of sodium bicarbonate and extracted with ether. The dried ethereal extracts were evaporated at reduced pressure and the residue was purified by flash-chromatography (eluent: ether-light petroleum 1:1) to give **28d** (0.16 g, 69%) as colorless crystals m.p. 144°C. (Found: C, 66.99; H, 8.65. $C_{22}H_{34}O_6$ requires C, 66.98; H, 8.69): IR (nujol): 3450, 1740 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.1 (s, 3H), 1.17 (s, 3H), 1.35 (s, 3H), 1.38 (s, 6H), 2.1 (s, 3H), 2.17 (d, 1H, J=5Hz), 3.45 (d, 1H, J=6Hz), 3.5 (m, 1H), 4.83 (s, 1H, exchanged on D_2O addition), 5.1 (AB system, 2H, J=6Hz), 5.5 (m, 1H), 5.62 (AB system, 2H, J=15Hz).

(3aß(Z),4ß,5α,6ß,6aα,9aß,9bß)-(±)-Decahydro-4,7,7-9b-tetramethyl-3a-[3-methyl-1-butadienyl]-naphtho[1,8-de]-1,3-dioxin-4,5,6-triol 29

A solution of **28a** (0.4 g, 1 mmol) in THF (6 ml) containing a diluted solution of sulphuric acid 20% (0.8 ml) was stirred for 2 days at room temperature. The solvent was removed at reduced pressure and the residue was extracted with $CHCl_3$. The dried organic extracts were evaporated in vacuo and the residue was purified by flash-chromatography (eluent: ether-light petroleum 1:1) to afford **29** (0.2 g, 56%) as colorless crystals m.p. 160-161°C. (Found: C, 68.09; H, 9.02. $C_{20}H_{32}O_5$ requires C, 68.15; H, 9.15): IR (nujol): 3400 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.12 (s, 3H), 1.36 (s, 3H), 1.45 (s, 3H), 1.52 (s, 3H), 1.77 (s, 1H, exchanged on D_2O addition), 1.9 (s, 3H), 2.52 (d, 1H, J=2Hz), 3.15 (d, 1H, J=7Hz, exchanged on D_2O addition), 3.4 (m, 1H), 3.6 (m, 1H), 4.25 (s, 1H, exchanged on D_2O addition), 4.47 (m, 1H), 4.97 (AB system, 2H, J=6Hz), 5.0 (m, 1H), 5.92 (AB system, 2H, J=14Hz).

(7aß,10aα,10bß,11ß,12α,12aα)-(±)-7a,9,10,10a,10b,11,12,12a-Octahydro-2,2,10,10,10b,12a-hexamethyl--2H,8H-1-benzopyrano[4a,5,6-de][1,3,2]-benzodioxin-11,12-diol 30

In a flask, fitted with a magnetic stirrer, was placed 0.3g (0.94 mmol) of mercuric acetate. To this were added 5 ml of water (in which the salt dissolves) and then a solution of the triol **29** (0.32 g, 0.9 mmol) in THF (5 ml). A finely divided yellow precipitate appeared and its disappearance can be correlated to the extent of reaction. The clear and colorless solution was stirred for 15 min at room temperature to complete the oxymercuration stage. Then 5 ml of 3 M sodium hydroxide were added, followed by 5 ml of a solution 0.5 M of sodium borohydride in 3 M sodium hydroxide. After 10 min sodium chloride was added to saturate the water layer and the mixture was extracted with ether. The dried ethereal extracts were evaporated and the residue was purified by flash-chromatography (eluent: ether-light petroleum 2:1) to afford **30** (0.2 g, 62.5%) as a solid m.p. 110°C (pentane). (Found: C, 68.11; H, 9.18. $C_{20}H_{32}O_5$ requires C, 68.15; H, 9.15); IR (nujol): 3400 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.1 (s, 3H), 1.3 (s, 3H), 1.35 (s, 3H), 1.36 (s, 3H), 1.42 (s, 3H), 1.45 (s, 3H), 2.3 (d, 1H, J=2Hz), 2.75 (d, 1H, J=10Hz, exchanged on D_2O addition), 3.25 (d, 1H, J=9Hz, exchanged on D_2O addition), 3.4 (m, 1H), 3.6 (dd, 1H, J=10Hz, J=4Hz), 4.3 (dd, 1H, J=9Hz, J=2Hz), 5.7 (AB system, 2H, J=7Hz), 6.02 (AB system, 2H, J=11Hz).

(3aß(Z),4ß,5ß,6ß,6aα ,9aß,9bß)-(±)-4,5-Epoxydecahydro-4,7,7,9b-tetramethyl-3a-[3-(methoxymethyl-oxy)-3-methyl-1-butenyl]-naphtho[1,8-de]-1,3-dioxin-6-ol 31

To an ice-cooled stirred mixture of **27** (0.25 g, 0.66 mmol) in dichloromethane (4 ml) containing sodium bicarbonate (0.1 g), was added a solution of m-chloroperbenzoic acid (0.3 g) in dichloromethane (2 ml). The reaction mixture was stirred at room temperature for 6 h, then was filtered, washed with saturated solution of Na_2SO_3 and dried. Solvent evaporation gave a residue which was purified by crystallization affording **31** in quantitative yield as colorless solid m.p. 125-126°C (pentane). (Found: C, 66.69; H, 9.04. $C_{22}H_{36}O_6$ requires C, 66.64; H, 9.15): IR (nujol): 3470 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.9 (s, 3H), 1.16 (s, 3H), 1.35 (s, 3H), 1.44 (s, 3H), 1.47 (s, 6H), 1.71 (s, 1H), exchanged on D_2O addition), 2.14 (d, 1H, J=3.5Hz), 2.97 (s, 1H), 3.38 (s, 3H), 3.55 (m, 1H), 4.66 (m, 1H), 4.77 (AB system, 2H, J=7.4Hz), 5.1 (AB system, 2H, J=5.5Hz), 5.58 (AB system, 2H, J=16Hz).

The epoxide **31** submitted to the acid treatment as above afforded **30** in 80% yield.

(3aß(Z),4α ,5ß,6ß,6aα ,9aß,9bß)-(±)-Decahydro-4,7,7,9b-tetramethyl-3a-[3-(methoxymethyloxy)-3--methyl-1-butenyl]-naphtho[1,8-de]-1,3-dioxin-4,5,6-triol 32

A solution of **31** (0.35 g, 0.88 mmol) in ethylene glycol (7 ml) containing sodium hydroxide (0.7 g) was heated at 100°C for 24 h. The solvent was removed at reduced pressure (0.01 mmHg), the residue was treated with water and extracted with ether. The dried ethereal extracts were evaporated and the residue was purified by flash chromatography (eluent: ether-light petroleum 2:1) to give **32** (0.3 g, 82%) as colorless crystals m.p. 85-86°C (pentane). (Found: C, 63.91; H, 9.16. $C_{22}H_{38}O_7$ requires C, 63.74; H, 9.24): IR (nujol): 3400 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.15 (s, 3H), 1.16 (s, 3H), 1.17 (s, 3H), 1.42 (s, 3H), 1.44 (s, 6H), 1.69 (s? 1H, exchanged on D_2O addition), 3.03 (m, 2H), 3.38 (s, 3H), 3.55 (m, 2H), 4.8 (AB system, 2H, J=6Hz), 5.1 (AB system, 2H, J=5Hz), 5.42 (AB system, 2H, J=15Hz), 5.72 (s, 1H, exchanged on D_2O addition).

(7aß,10aα ,10bß,11ß,12ß,12aß)-(±)-7a,9,10,10a,10B,11,12,12a-Octahydro-2,2,10,10,1010b,12a-hexamethyl-2H,8H-1-benzopyrano[4a,5,6-de][1,3,2]-benzodioxin-11,12-diol 33

Submitting 32 to the acid treatment, above described for the preparation of 30 at 50°C for 4 h, gave a 3:1 mixture of the tricyclic alcohol 33 and the alkene 34 in 80% yield. Flash-chromatography (eluent:ether:light petroleum 3:1) allowed easy separation of 30 as a solid m.p. 145-146°C (pentane) having the following analytical and spectral data: (Found: C, 67.98; H, 9.30. $C_{20}H_{32}O_5$ requires C, 68.15; H, 9.15): IR (nujol): 3400 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.92 (s, 3H), 1.03 (s, 3H), 1.22 (s, 3H), 1.27 (s, 6H), 1.28 (s, 3H), 1.68 (s, 1H, exchanged on D_2O addition), 2.45 (dd, 1H, J=2.5Hz, J=25Hz, exchanged on D_2O addition), 2.67 (d, 1H, J=10Hz), 3.7-4.1 (m, 3H), 4.75 (AB system, 2H, J=6Hz), 6.1 (AB system, 2H, J=10Hz); and 34 m.p. 134-135°C (pentane) having the following analytical and spectral data: (Found: C, 71.81; H, 8.99. $C_{20}H_{30}O_4$ requires C, 71.85; H, 8.98): IR (nujol): 3500 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.12 (s, 3H), 1.14 (s, 3H), 1.19 (s, 3H), 1.21 (s, 3H), 1.28 (s, 3H), 1.30 (s, 3H), 1.70 (s, 1H, exchanged on D_2O addition), 3.72 (m, 1H), 4.65 (d, 1H, J=2Hz), 4.80 (AB system, 2H, J=6Hz), 5.57 (d, 1H, J=2Hz), 6.05 (AB system, 2H, J=10Hz).

(7aß-10aα ,10bß,11ß,12ß,12aß)-(±)-7a,9,10,10a,10b,11,12,12a-Octahydro-2,2,10,1010b,12a-hexamethyl--2H,8H-1-benzopyrano[4a,5,6-de][1,3,2]-benzodioxin-11,12-diol acetonide 35

Reaction of 33 (0.5 g, 1.42 mmol) with 2,2-dimethoxypropane (5 ml) and few crystals of pyridinium p-toluensulphonate at room temperature for 24 h afforded 35 in quantitative yield, after the usual work-up, as colorless needles m.p. 135-136°C (pentane). (Found: C, 70.35; H, 9.21. $C_{23}H_{36}O_5$ requires C, 70.41; H, 9.18): ^1H NMR ($CDCl_3$): δ 0.94 (s, 3H), 1.03 (s, 3H), 1.28 (s,3H), 1.30 (s, 3H), 1.33 (s, 3H), 1.37 (s, 3H), 1.40 (s, 1H), 1.46 (s, 1H), 2.75 (d, 1H, J=6Hz), 3.6-4.0 (m, 3H), 5.0 (AB system, 2H, J=5Hz), 6.12 (AB system, 2H, J=10Hz).

Crystallography

Intensity data were collected on an Enraf-Nonius CAD4 diffractometer with monochromated Mok_α radiation and $\omega/2\theta$ scan technique. Cell parameters were obtained from least-squares refinement of the setting angles of 25 centered reflections in the range $10<\theta<15°$. Intensities were corrected from Lorentz and polarization. Scattering factors were taken from International Tables for X-ray Cristallography.[15]

The structures were solved by direct methods (MULTAN82)[16] and difference Fourier syntheses. Weights for the last refinement cycles were applied according to the scheme $\omega=4F_o^2/\left[\sigma^2(F_o^2)+(p\,F_o^2)\right]$ and the discrepancy factors used, were: $R=\Sigma|\Delta F_o|/\Sigma|F_o|$ and $R_w=(\Sigma w|\Delta F_o|^2/\Sigma w|F_o|^2)^{1/2}$.

All calculations were done using the SDP system of programs.[17]

The final electron density maps showed no significant residual electron density.

Crystal Data

Compound 23

$C_{22}H_{34}O_5$, M=378.5, monoclinic, space group $P2_1/n$, a=6.330(1), b=14.576(2), c=22.837(2)Å, ß=93.04(1)°, V=2104.2 $Å^3$, D_c=1.19g cm^{-3}, Z=4; Number of independent reflections =3689, number with $I>3\sigma(I)$ used in the refinement =1971. Structure refined by full-matrix least-squares methods using anisotropic temperature factors for all non-H atoms; all H-atoms found in the difference map but not refined; discrepancy factors R=0.054, R_w=0.070 (p=0.04) and S=2.15.

Compound 26

$C_{20}H_{30}O_4$, M=334.5, triclinic, space group $P\bar{1}$, a=10.595(2), b=12.152(1), c=8.073(1) Å, =106.53(1), ß=105.65(1), γ=66.29(1)°, V=897.9 $Å^3$, D_c=1.24g cm^{-3}, Z=2. Number of independent reflections =3906, number with $I>3\sigma(I)$ used in the refinement =2868. Structure refined by full-matrix least square methods using anisotropic temperature factors for all non-H atoms; calculated Hydrogens; discrepancy factors R=0.046, R_w=0.069 (p=0.05) and S=2.01.

Compound 30

$C_{20}H_{32}O_5$, M=352.5, triclinic, space group, $P\bar{1}$, a=12.948(3), b=13.615(3), c=12.197(4)A, α =101.16(2), ß=111.88(2), γ=69.48(2)°, V=1863.7$Å^3$, D_c=1.26g cm^{-3}, Z=4-Number of independent reflections =8121, number with $I>3\sigma(I)$ used in the refinement =4570. Structure refined by blocked-matrix least squares methods (2 blocks) using anisotropic temperature factors for all non-H atoms, isotropic for O-H hydrogen atoms, calculated C-H hydrogens; discrepancy factors R=0.060, R_w=0.080 (p=0.05), S=2.12.

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