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BIOLOGICALLY ACTIVE QUASSINOIDS : SYNTHETIC METHODOLOGY FOR THE CONVERSION OF CHAPARRIN INTO GLAUCARUBOLONE ESTERS AND QUASSINOID ANALOGS[1]

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Abstract - *Biologically inactive but easily available chaparrin 2a has been converted into potent antileukemic C-15 esters of glaucarubolone 2b and quassinoid analogs in which the C-15 ester side chain has been replaced by an alkyl or alkenyl group. The synthetic methodology developed has been applied to the preparation of C-15 ester derivatives 15, 16, 17 and quassinoid analogs 12, 13 and 14.*

The quassinoids[2,3] are a group of degraded triterpenes and constitute the bitter principles isolated exclusively from the plants of the Simaroubaceae family. Interest in the quassinoids has accelerated rapidly with the finding by the National Cancer Institute, U.S.A., in 1975 that some of them possess strong antileukemic activity in the murine lymphocytic leukemia P-388 test system. Bruceantin 1 isolated from *Brucea antidyssenterica*[4] was selected for clinical trials in the U.S.A. Since then the quassinoids have been shown to exhibit a wide spectrum of useful biological activities such as anti-malarial, antiviral, amoebicidal, insecticidal, anti-feedent[5] and leishmanicidal properties.[6] Quassinoids have also attracted much attention as synthetic target molecules and numerous synthetic approaches have been developed[5] which include the total synthesis of the parent compound quassin[7] and also that of castelanolide.[8]

Structural requirements for the antineoplastic activity exhibited by numerous quassinoids are well established.[9] An A-ring enone function, a C-6 or C-15 ester function and an oxymethylene bridge between C-8 and C-11 or C-13 are essential structural features for optimal antineoplastic activity. Chaparrin 2a[10] which can be obtained in relatively large amounts from the Mexican Castela species lacks these structural features and does not possess antineoplastic activity.

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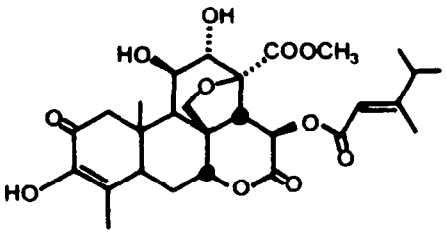

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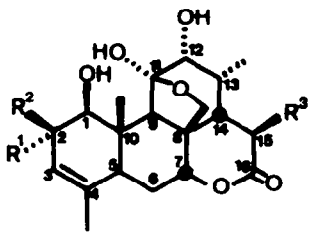
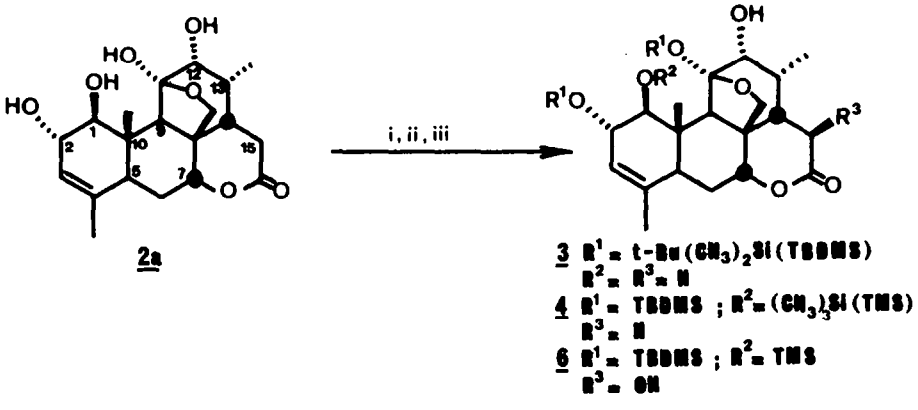


2a R^1 = OH ; R^2 = R^3 = H
2b R^1, R^2 = O ; R^3 = OH
2c R^1, R^2 = O ; R^3 = H

As part of our continuing study of quassinoids, we present herein a detailed account of the development of synthetic methodology for the conversion of chaparrin into the biologically active C-15 esters of glaucarubolone 2b, and chaparrinone 2c analogs in which the C-15 substituent is an alkyl or alkenyl group. In view of the potent antileukemic activity of bruceantin 1 and the promising activity of the synthetic quassinoid analog, 15β-heptylchaparrinone 13 we have also prepared a glaucarubolone C-15 ester 17 in which the ester side-chain is the same as that of bruceantin 1 and also the corresponding alkenyl analog 14. A preliminary account of a part of this study has already been published.[11]

Treatment of crude chaparrin 2a with excess t-butyldimethylsilyl chloride (TBDMSiCl/DMF/imidazole, 48 hrs)[12] at room temperature resulted in the formation of the disilyl derivative 3 in which the allylic hydroxyl group at C-2 and the C-11 hemiketal function were protected. Though this silylation procedure worked very well yielding 80% of 3 on a small scale, larger scale experiments gave unexpectedly low and variable yields of the disilyl ether 3 (40-45%). Moreover, with larger amounts of chaparrin the reaction was sluggish and required long reaction times. When the silylation step was carried out under essentially neutral conditions using the t-butyldimethylsilyl enol ether of 2,4-pentane-dione[13] as the silyl transfer reagent and a trace of p-toluenesulphonic acid, 3 was obtained in ~90% isolated yields.



2a

i, ii, iii

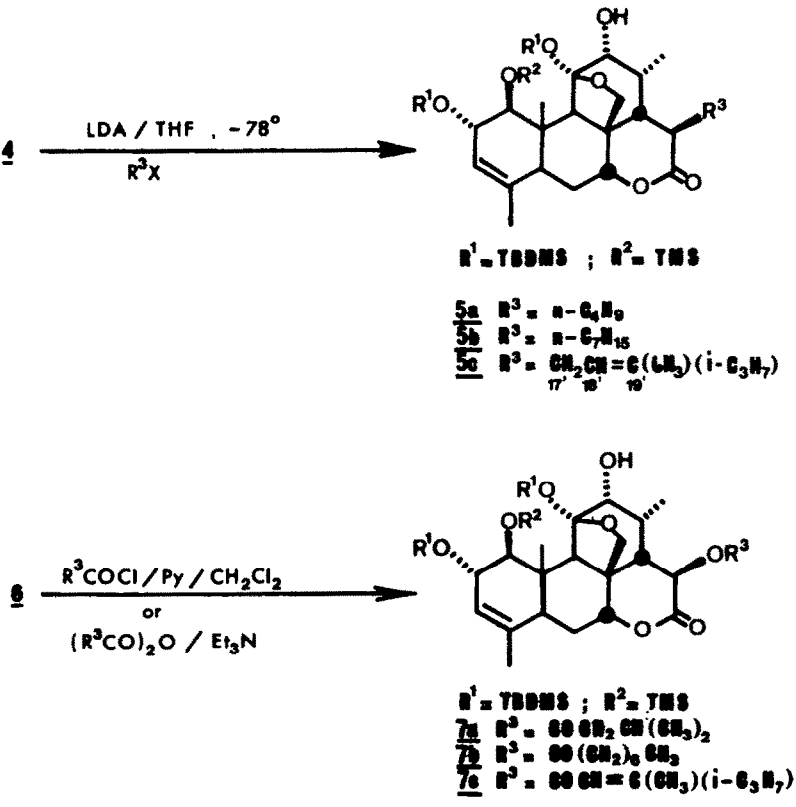
3 R^1 = t-Bu$(CH_3)_2$Si (TBDMS)
R^2 = R^3 = H
4 R^1 = TBDMS ; R^2 = $(CH_3)_3$Si (TMS)
R^3 = H
6 R^1 = TBDMS ; R^2 = TMS
R^3 = OH

i = TBDMSiCl / DMF / Imidazole (40-45%) or TBDMS-enol ether of 2,4-pentanedione / DMF (85-88%)
ii = TMSTf / Pyridine / $CHCl_3$ (95-98%)
iii = LDA / THF, -78°C MoOPH and temperature raised to -44°C (40-45%) or KHMDS / THF, -78°C, Ph-SO_2-N(O)=CH-Ph (66-70%)

Yields (in brackets) refer to pure isolated compounds

Initially we tried to utilize 3 as the starting material for the preparation of the 15β-hydroxy and 15β-alkyl derivatives without prior protection of the C-1 hydroxyl group, relying instead on steric hindrance by the b-butyldimethylsilyl groups to prevent its unwanted participation in subsequent steps. Although 3 underwent smooth deprotonation with excess lithium diisopropyl amide and subsequent alkylation with methyl iodide at -78°C to afford stereospecifically the corresponding 15β-methyl lactone, its derived lithium enolate was unreactive towards the molybdenum peroxide reagent MoO_5-pyridine-HMPA (MoOPH)[14] at -78°C and afforded complex product mixtures at higher temperatures. In addition, attempted alkylation of the lithium enolate of 3 with poorer electrophiles such as butyl or heptyl iodide at 0°C gave many products.

Reasoning that base induced intramolecular silyl group migration might be responsible for the complexity of these product mixtures we sought to protect the hydroxyl function at C-1. This could be achieved in quantitative yields using trimethylsilyl triflate (TMS-triflate/pyridine-$CHCl_3$)[15] and the resultant trisilyl derivative 4 could be used without further purification. Direct oxidation of the lithium enolate of the trisilyl lactone 4 to form the 15β-hydroxy derivative 6 was the next step in our planned synthetic methodology. Thus, 4 was treated sequentially at -78°C with excess lithium diisopropyl amide and MoOPH and subsequently the temperature was raised to -44°C. NMR spectra of crude reaction products revealed a two component mixture consisting of 6 and 4 in ratios as high as 4:1. Careful chromatographic separation gave the 15-hydroxyl trisilyl lactone 6 in 40-45% yields. The yield of 6 could not be increased by varying the reaction conditions (temperature, concentration of reagents etc.) or by reversing the order of addition of the reagents. In an effort to improve the efficiency of this transformation we investigated the use of the recently developed 2-sulfonyloxaziridine reagents of Davis.[16] Treatment of the potassium enolate of 4 (prepared by exposure of 4 to potassium hexamethyldisilazide (KHMDS)[17]) with 2-phenylsulfonyl-3-phenyloxaziridine ($C_6H_5SO_2$-N⟨O⟩CH-C_6H_5) at -78°C resulted in the formation of 6 in ~70% isolated yields.



In the NMR spectrum of 6 (see experimental) the C-15 proton appears as a doublet at δ 4.55 (J=12 Hz) which is consistent with the desired β configuration of the newly introduced hydroxyl group at C-15. This stereochemical result is in accord with the expectation, based on molecular models, that the α-face of the enolate derived from 4 should be inaccessible to incoming electrophiles. Alternatively, treatment of the lithium enolate of 4 in the presence of HMPA as a cosolvent with alkyl halides yielded the 15β-alkyl derivatives; 5a, 5b and 5c, in excellent yields.

The hydroxy lactone 6 furnished the corresponding C-15 ester derivatives upon treatment with the appropriate acyl halide in a 1:1 mixture of pyridine-dichloromethane. The trisilyl C-15 esters 7a-7b were obtained as crystalline solids after chromatographic purification.

The C-15 hydroxyl group of the potent antileukemic quassinoid bruceantin 1 is esterified with E-3,4-dimethylpent-2-enoic acid and we sought to prepare the corresponding glaucarubolone ester utilizing the hydroxy lactone 6. E-3,4-dimethylpent-2-enoic acid was obtained upon hydrolysis of the corresponding ethyl ester which in turn was obtained as a 9:1 mixture of E:Z isomers by the Horner-Emmons reaction of 3-methyl-2-butanone with sodio triethyl phosphonoacetate. The E-isomer was separated by column chromatography over silica gel using benzene as the eluent. The corresponding acyl halide could not be obtained in a pure state by various methods due to its instability. Attempted esterification of 6 with slightly impure acyl halide resulted in complex product mixtures containing polar materials presumably formed by partial desilylation of 6. However, the esterification of 6 could be achieved cleanly and in high yields *via* the corresponding anhydride (formed *in situ* using chlorosulphonyl isocyanate as the dehydrating agent) in the presence of triethylamine[18] to give the ester 7c as a crystalline solid in 90% yield after chromatography.

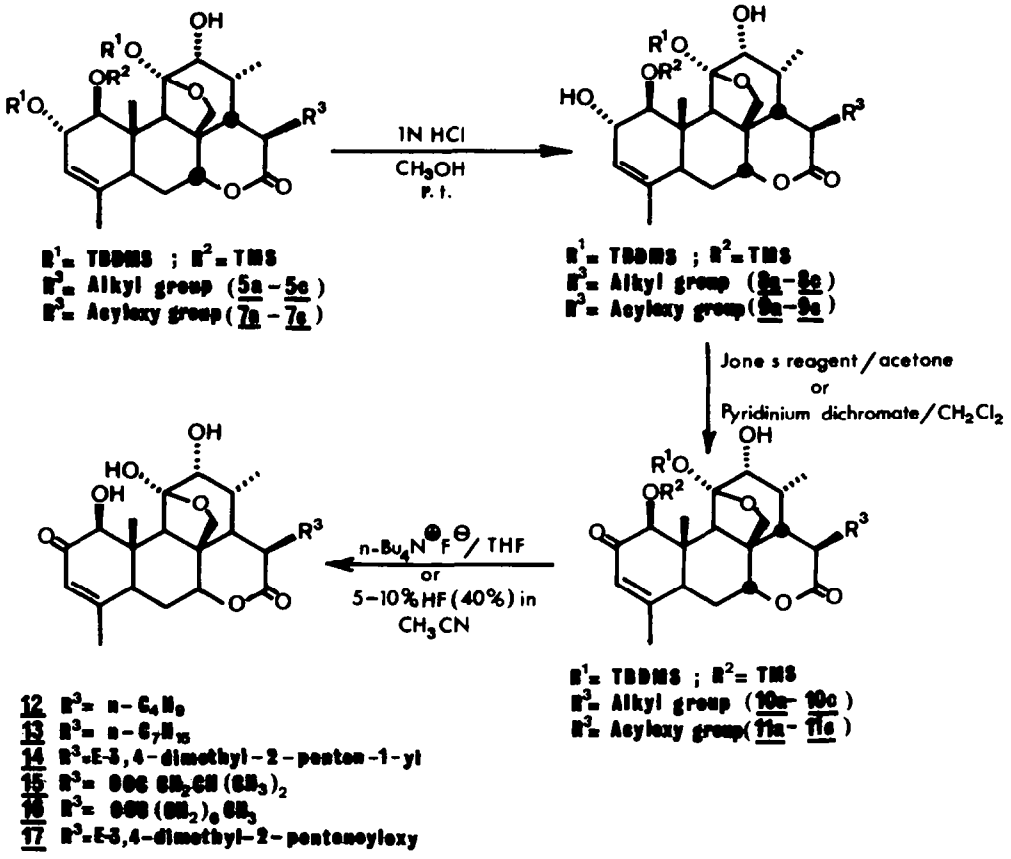
For the preparation of the alkenyl analog 5c the lithium enolate of 4 was treated with pure E-3,4-dimethyl-2-penten-1-yl bromide. Reduction of ethyl E-3,4-dimethyl-2-pentenoate ($LiAlH_4/Et_2O$) afforded the corresponding allylic alcohol which was converted to the required allylic bromide using Corey's procedure (Me_2S; N-bromosuccinimide; dichloromethane; 0°C).[19] The allylic bromide was purified by distillation under reduced pressure just prior to its use.

With the D-ring functionalization completed, there remained introduction of the enone function in the A-ring. The C-2 allylic hydroxyl could be deprotected selectivly in both the C-15 ester and alkyl series upon treatment with 1N methanolic HCl.[11] This reaction was complete within 15 minutes at ambient temperature. Jones oxidation of the allylic hydroxyl group, under carefully controlled conditions, generated the desired A-ring enone moiety. Pyridinium dichromate[20] proved to be a more suitable (no products due to overoxidation) oxidizing agent especially in the case of the C-15 alkenyl analog 8c.

The remaining silyl protecting groups at C-1 and C-11 could be removed by treatment of a 0.3 M solution of the disilyl ether in THF with tetra-n-butylammonium fluoride but the isolated yields of the deprotected materials were disappointingly low (30-45%). Yields could be increased to ~60% by using a more dilute solution (0.06 M) of the disilyl ether, however purification of the fully deprotected products obtained was frequently difficult and required repeated chromatographic separations. These problems were overcome when it was found that high yields (80-90%) of the desilylated products could be obtained in a straightforward manner upon exposure of the disilyl ethers to acetonitrile containing 5-10% by volume of a 40% aqueous HF solution.[21]

The synthetic methodology presented here has been utilized for the preparation of the C-15 glaucarubolone ester derivatives 15, 16, 17 and the quassinoid analogs 12, 13 and 14. Preliminary biological screening of 12, 13, and 16 showed that all of them cause significant inhibition of cell transformation induced by Rous sarcoma virus[22] at the 1μg/ml dose level. 15-βheptylchaparrinone 13 showed interesting antileukemic activity in the murine lymphocytic leukemia *in vivo* PS-388 test system (T/C of 135 at a 20 mg/kg dose level). It was chosen as

a tumor panel compound by the National Cancer Institute, U.S.A., for intensive testing in various systems. Compound 17, prepared in analogy with bruceantin 1, showed significant antileukemic activity in the PS-388 in vivo test system (T/C of 138 at 1 mg/kg dose level). Compoudn 14, the alkyl analog of 14, showed good activity in the PS-388 in vitro test system (ED_{50} 0.24μg/ml) but was inactive at the dose levels tested in the corresponding in vivo system (T/C of 100 at a 1 mg/kg dose level). Compounds 13 and 17 are presently listed as "deferred" by the NCI.[23]



12 R^3= n-C_4H_9
13 R^3= n-C_7H_{15}
14 R^3=E-3,4-dimethyl-2-penten-1-yl
15 R^3= $CH_2CH(CH_3)_2$
16 R^3= $(CH_2)_6CH_3$
17 R^3=E-3,4-dimethyl-2-pentenoyloxy

EXPERIMENTAL

The infra-red spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer in chloroform solutions or as nujol mulls. ^{1}H-NMR spectra were recorded on a Varian T-60 (60 MHz) or Brucker WM-400 spectrometer. Coupling constants are reported in Hz. The ultra-violet spectra were measured in EtOH on a Duospec 203 (Jobin-Yvon) spectrophotometer. EI mass spectra were recorded on an AEI MS-50 mass spectrometer and the High-resolution mass spectra on Kratos MS-80 mass spectrometer. Melting points were determined on a Kofler melting point apparatus and are uncorrected. Optical rotations were determined at room temperature on a Roussel-Jouan Quick polarimeter.

All solvents and reagents were purified and dried by standard procedures. Analytical TLC was carried out on Merck Kieselgel 60, F_{254} plastic plates (Art. N° 5735) and for column chromatography Merck silica gel (Art. N° 7736 and 7734) were employed. H_2SO_4 spray or I_2 vapour were used for visualization.

Preparation of 2,11-di-t-butyldimethylsilyl chaparrin 3

Method A. - To a suspension of chaparrin 2a (2.0 g, 5.26 mmol) in 10 ml of dry DMF was added 5.01 g (73.7 mmol) of dried imidazole under argon atmosphere and magnetic stirring. To the well stirred suspension was added t-butyldimethylsilyl chloride (10.504 g, 69.69 mmol).

The reaction mixture was stirred at room temperature. The initial suspension slowly clears but the reaction mixture again becomes heterogeneous (~24 hrs). After 55 hrs the reaction appears to be complete (TLC). The reaction mixture was filtered to remove undissolved solids. The solid was washed with ethyl acetate and the filtrate partitioned between ethyl acetate and water. The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure to yield a colourless viscous oil (4.4 g). Silica gel column chromatography yielded pure 3, 1.33 g (41.5%). An analytical sample was prepared by crystallization from dichloromethane, m.p. 208-210°C, $M^{+\cdot}$ 608. Its ^{1}H-NMR spectrum[11] was in full agreement with the proposed structure. Anal. Calcd. for $C_{32}H_{56}O_7Si_2$: C, 63.11; H, 9.27. Found: C, 62.86; H, 9.26.

Method B. - The silyl transfer reagent 2,4-pentanedione-t-butyldimethylsilyl enol ether was prepared according to the literature method.[13] To a stirred suspension of chaparrin 2a (3.30 g, 8.68 mmol) in 18 ml dry DMF (~0.5 M) under argon atmosphere was added the silyl transfer reagent (8.4 g, 39.18 mmol) followed by ~20 mg of p-toluenesulfonic acid. The reaction mixture was stirred at 40°C for 84 hrs when TLC examination showed no further reaction. The reaction mixture was cooled to room temperature and partitioned between ethyl acetate (300 ml) and water (100 ml). Usual work-up gave a yellowish viscous liquid (7.4 g) which on chromatography yielded 4.8 g of pure 3 (91%).

Preparation of 2,11-di-t-butyldimethylsilyl-1-trimethylsilyl chaparrin 4

To a stirred solution of 3 (1.29 g, 2.12 mmol) in dry $CHCl_3$ (21 ml) at room temperature and under argon atmosphere was added dry pyridine (532 µl, 6.58 mmol) followed by neat trimethylsilyl triflate (1.168 ml, 6.04 mmol). The reaction was monitored by TLC. After 1 hr 45 minutes the reaction was quenched by careful addition of 6 ml of saturated $NaHCO_3$ solution. Chloroform was removed under reduced pressure and the residue was diluted with ethyl acetate and water. Work-up of the organic phase gave a colourless viscous oil which became a white foam when placed under high vacuum, yield = 1.43 g (99%). $M^{+\cdot}$ 680. IR($CHCl_3$) 3425, 2950, 2850, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 5.29 (br s, H-3), 4.71 (br s, OH), 4.29 (br t, J=3, H-7), 4.01, 3.54 (2d, J=9, $-CH_2O-$), 3.99 (m, H-2), 3.61 (d, J=4.6, H-12), 3.31 (d, J=8.0, H-1), 2.75 (s, H-9), 2.72 (d,d; J=14, 19; H-15α), 2.52 (d,d; J=5, 19; H-15β), 2.29 (br d, J=13, H-5), 2.17 (m, H-13), 2.02 (d,t; J=3, 15; H-6α), 1.79 (m, H-14), 1.70 (br t, J~15, H-6β), 1.63 (s, Me-4), 1.14 (s, Me-10), 0.96 and 0.88 (s, Me_3CSi), 0.91 (d, J=7, Me-13), 0.25, 0.22, 0.17 and 0.09 (s, MeSi).

Preparation of 2,11-di-t-butyldimethylsilyl-1-trimethylsilyl glaucarubol 6

The title compound was prepared by the oxidation of the metal enolate derived from 4 using MoOPH or $C_6H_5SO_2N$(O)CHPh as the oxidizing agents.

MoOPH oxidation

The reagent, MoOPH, was prepared by the published procedure[14] and dried under high vacuum for 3 days at room temperature over P_2O_5 with protection from light.

A solution of 4 (680 mg, 1 mmol) in dry THF (5 ml) was slowly added to a stirred solution of LDA (0.92 M, 3.26 ml, 3 eq.) cooled to -78°C under an argon atmosphere. The reaction mixture was stirred at -78°C for 1 hr and then added in a dropwise manner to a well stirred suspension of MoOPH (2.02 g, 4.65 mmol) in dry THF (5 ml) at -44°C. The reaction was monitored by TLC (hexane-EtOAc 1:1). When no further reaction was evident (~6 hrs) the reaction mixture was quenched by addition of 2 ml of saturated NH_4Cl followed by 10 ml of saturated Na_2SO_3 solution. This heteregenous mixture was allowed to attain room temperature and stirred for 3 hrs and then transferred to a separatory funnel with the aid of EtOAc. The organic phase was washed successively with saturated NH_4Cl (2 x 20 ml), brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product (840 mg) on chromatographic purification gave pure 6 (292.5 mg, 42%). In addition, 205 mg (~30%) of the starting lactone 4 was recovered.

Preparation of 6 using 2-(phenylsulfonyl)-3-phenyloxaziridine reagent

The reagent, 2-phenylsulfonyl-3-phenyloxaziridine[16] was prepared according to the published procedure. It was purified by repeated crystallization from EtOAc/n-pentane m.p. 97°C (dec.).

To a cooled (-78°C) solution of potassium hexamethyldisilazide (KHMDS) in THF (0.75 M, 2 ml), freshly titrated against (+)-10-camphorsulphonic acid in 50% aqueous EtOH with phenolphtalein as indicator, was slowly added a solution of 4 (680 mg, 1 mmol) in 2 ml of dry THF under an argon atmosphere and efficient magnetic stirring. The mixture was stirred for 1 hr followed by addition of a solution of the reagent in 5 ml dry THF (0.39 g, 1.5 mmol). After 2 hrs, when no further reaction was evident (TLC check) the reaction was quenched by adding 3 ml of saturated NH_4Cl and allowed to attain room temperature. A standard aqueous work-up gave a colourless residue which on chromatography (3:1 hexane-EtOAc) gave pure 6 (508 mg, 73%) as a white foam, $M^{+\cdot}$ 696. IR($CHCl_3$) 3410, 2920, 2850, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 5.28 (br s, H-3), 4.70 (s, OH), 4.55 (d, J=12, H-15), 4.35 (br t, J=3, H-7), 3.95 and 3.56 (2d, J=9,

-CH_2O-), 3.93 (m, H-2), 3.67 (d, J=5, H-12), 3.27 (d, J=8, H-1), 2.82 (s, H-9), 2.35 (br d, J=13, H-5), 2.25 (m, H-13), 2.02 (d, t; J=2.5, 15; H-6α), 1.81 (m, H-14), 1.76 (br t, J=15, H-6β), 1.62 (s, Me-4), 1.19 (d, J=7, Me-13), 1.15 (s, Me-10), 0.99, 0.90 (s, Me_3CSi), 0.25, 0.23, 0.12, 0.09 (s, Me-Si).

Preparation of 15β-alkyl derivatives of 4

General procedure. - To a stirred solution of LDA (3 eq., freshly titrated) at -78°C under an argon atmosphere, was slowly added a solution of 4 in dry THF (1 eq., 0.1 M). The reaction mixture was stirred for 2 hrs and then neat alkyl halide (~5 eq.) was added followed by dry hexamethylphosphoric triamide (HMPA) (3 eq.). The reaction temperature was raised to between -20°C and 0°C and stirring was continued for the appropriate time (TLC check) until no change in product composition was evident. The reaction mixture was quenched with saturated NH_4Cl solution (1-5 ml) and slowly brought to room temperature. Dilution with EtOAc and washing of the organic phase with saturated NH_4Cl (x 2), brine, drying over Na_2SO_4 and concentration under reduced pressure afforded the crude products which were purified by column chromatography.

15β-n-butyl-2,11,di-t-butyldimethylsilyl-1-trimethylsilyl chaparrin 5a. - Treatment of 4 (73.4 mg, 0.108 mmol) with LDA (3 eq.) followed by n-BuI (5 eq.) and HMPA (3 eq.) gave 5a, 71 mg (89%) as a white foam. $M^{+\cdot}$ 736. ^{1}H-NMR ($CDCl_3$) δ 5.29 (br s, H-3), 4.61 (s, OH), 4.36 (br t, J=2.5, H-7), 4.01 and 3.53 (2d, J=9, -CH_2O-), 3.99 (m, H-2), 3.61 (d, J=5, H-12), 3.33 (d, J=8, H-1), 2.95 (m, H-15), 2.65 (s, H-9), 2.52 (br d, J=14, H-5), 1.64 (s, Me-4), 1.25 (m, $(CH_2)_3$), 1.14 (s, Me-10), 1.08 (d, J=7, Me-13), 1.0 and 0.9 (s, Me_3CSi), 0.88 (t, J=7, butyl methyl), 0.24, 0.21, 0.19, 0.09 and 0.08 (s, Me-Si).

15β-n-heptyl-2,11-di-t-butyldimethylsilyl-1-trimethylsilyl chaparrin 5b. - Treatment of 4 with LDA (3 eq.), n-heptyl iodide (5 eq.) and HMPA (3 eq.) as above gave 5b, yield 90%. It was crystallized from EtOH m.p. 127-128°C. $M^{+\cdot}$ 778. ^{1}H-NMR ($CDCl_3$) δ 5.28 (br s, H-3), 4.58 (s, OH), 4.34 (br t, J=3, H-7), 3.99 and 3.52 (2d, J=9, -CH_2O-), 3.98 (m, H-2), 3.61 (d, J=5, H-12), 3.32 (d, J=8, H-1), 2.95 (m, H-15), 2.65 (s, H-9), 2.52 (br d, J=13.5, H-5), 2.27 (m, H-13), 1.99 (d,t; J=2.5, 14.5; H-6α), 1.85 (br t, J=14.5, H-6β), 1.62 (s, Me-4), 1.22 (m, heptyl-CH_2-), 1.12 (s, Me-10), 1.11 (t, J=7, Me(heptyl)), 0.98 and 0.89 (s, MeCSi), 0.25, 0.21, 0.18, 0.09 (s, Me-Si). Calcd for $C_{42}H_{78}O_7Si_3$: C, 64.73, H, 10.08. Found: C, 64.57, H, 10.02%.

15β-(E-3,4-dimethyl-2-penten-1-yl)-2,11-di-t-butyldimethylsilyl-1-trimethylsilyl chaparrin 5c

Preparation of E-3,4-dimethyl-2-penten-1-yl bromide. - To a stirred suspension of NaH (4.8 g, 0.2 mol) in 80 ml dry diglyme under argon atmosphere and at 0°C was added triethyl phosphonoacetate (44.8 g, 0.2 mol) in a dropwise manner. The mixture was stirred at 0°C till evolution of hydrogen ceased (~90 minutes). To the clear solution was added freshly distilled methyl isopropylketone (17.2 g, 0.2 mol). The reaction mixture was stirred for 3 hrs at 0°C and subsequently for 2 hrs at room temperature. It was again cooled to 0°C and diluted with 450 ml of water and transferred to a separatory funnel and extracted with ether. The ether extracts were washed with water, brine, dried over $MgSO_4$ and concentrated under reduced pressure to give ethyl 3,4-dimethyl-2-pentenoate as a faintly yellow clear liquid. Yield 31 g (99%). ^{1}H-NMR indicated a 9:1 mixture of E/Z isomers. Column chromatography over silica gel using benzene as the eluent afforded the pure E-isomer (the Z isomer elutes faster). ^{1}H-NMR ($CDCl_3$) δ 5.45 \$br s, =CH), 4.0 (q, J=7, CH_2CH_3), 2.28 (sept, J=7, Me_2CH-), 2.06 (s, =CMe), 1.23 (t, J=7, CH_2CH_3), 1.04 (d, J=7, Me_2CH). $LiAlH_4$ reduction of the ester (22.29 g, 0.143 mol; $LiAlH_4$, 15.2 g, 0.399 mol; dry ether 400 ml) gave E-3,4-dimethyl-2-penten-1-ol. It was purified by distillation under reduced pressure (b.p. 82°C, 20 mm) yield: 14.2 g (87%). ^{1}H-NMR ($CDCl_3$) δ 5.25 (br, t, J=7, =CH), 4.04 (d, J=7, =$CHCH_2$OH), 2.15 (sept, J=7, Me_2CH-), 1.93 (s, OH), 1.62 (br s, =CMe), 0.99 (d, J=7, Me_2CH).

The E-3,4-dimethyl-2-penten-1-ol was converted into the corresponding allylic bromide, E-3,4-dimethyl-2-penten-1-yl bromide, using Corey's procedure.[19] To a solution of N-bromosuccinimide (5.4 g, 30 mmol) in dry CH_2Cl_2 (100 ml) was added at 0°C neat Me_2S (2.23 g, 36 mmol). The resultant yellow slurry was stirred for 1 hr at 0°C, cooled to -20°C and a solution of E-3,4-dimethyl-2-penten-1-ol (2.28 g, 20 mmol) in 10 ml dry CH_2Cl_2 was added dropwise. The yellow colour slowly disappeared at which point the temperature was raised to 0°C and the reaction mixture was diluted with 150 ml of n-pentane and poured into ice-cold water (100 ml) contained in a separatory funnel. The organic phase was worked up in a standard fashion to give E-3,4-dimethyl-2-penten-1-yl bromide which was purified by distillation under reduced pressure b.p. 52°C (~20 mm). ^{1}H-NMR ($CDCl_3$) δ 5.38 (br t, J=7.5, =CH), 3.90 (d, J=7.5, CH_2Br), 2.18 (sept, J=7, Me_2CH), 1.65 (br s, =CMe), 0.97 (d, J=7, Me_2CH).

Preparation of 15β-(E-3,4-dimethyl-2-penten-1-yl)-2,11-di-t-butyldimethylsilyl-1-trimethylsilyl chaparrin 5c

To a solution of LDA (0.7 M) in THF (6.85 ml, 4.8 mmol) at -78°C under an argon atmosphere was slowly added a 0.2 M solution of 4 (1.2 g, 1.76 mmol) in dry THF. The mixture

was stirred for 2 hrs at -78°C then freshly distilled E-3,4-dimethyl-2-penten-1-yl bromide (1.06 g, 6.0 mmol) was added. The reaction mixture was stirred at -78°C for 1 hr and then at -20°C for 3 hrs. The mixture was quenched with saturated NH_4Cl solution (5 ml) and slowly brought to room temperature. It was worked up in a standard fashion to afford a yellow oil (1.86 g) which was passed down a short column of silica gel (28 g) (15:1 hexane-EtOAc) to yield 5c as white foam (1.1 g, 80%) which crystallized from methanol m.p. 116-117°C. $M^{+\cdot}$ 776 ($C_{42}H_{76}O_7Si_3$). IR ($CHCl_3$) 3450, 2935, 2855, 1740 cm^{-1}. NMR ($CDCl_3$) δ 5.30 (br s, H-3), 5.09 (t, J=7, CH_2-CH=), 4.62 (s, OH), 4.35 (br t, J=3, H-7), 4.01 and 3.53 (2d, J=9, $-CH_2O-$), 3.99 (m, H-2), 3.64 (d, J=5, H-12), 3.35 (d, J=8, H-1), 3.08 (m, H-15), 2.67 (s, H-9), 2.63 (m, CH-C=), 2.45 (m, CH-C=), 2.54 (br d, J=14, H-5), 2.32 - 2.18 (m, H-13 + $CHMe_2$), 1.98 (dt, J=3, 14.8, H-6α), 1.73 (m, H-14), 1.70 (br t, J=15, H-6β), 1.64 (br s, Me-4), 1.57 (br s, Me-19'), 1.15 (s, Me-10), 1.12 (d, J=7, Me-13), 0/99 (m, Me_3C-Si + $CHMe_2$), 0.92 (Me_3C-Si), 0.24, 0.21, 0.19, 0.10 and 0.08 (s, Me-Si).

Preparation of 15β-ester derivatives of 6

To a solution (0.06 M) of 6 in pyridine-CH_2Cl_2 (1:1) was added neat acid halide (10 eq.) with efficient stirring. The mixture was stirred at room temperature and the reaction monitored by TLC. The esterification was usually complete in ~5 hrs. The reaction mixture was quenched with saturated $NaHCO_3$ and stirred for an additional 1 hr. It was then diluted with EtOAc and the organic phase was washed with saturated $NaHCO_3$ (x 2), brine, dried over Na_2SO_4 and concentrated under reduced pressure to give the crude 15β ester which was purified by chromatography over silica gel (3:1 hexane-EtOAc).

Preparation of 2,11-di-t-butyldimethylsilyl-1-trimethylsilyl-15β-O-isovaleryl glaucarubol 7a

To a solution of 6 (348 mg, 0.5 mmol) in mixture of pyridine-CH_2Cl_2 (1:1, 8 ml) was added neat isovaleryl chloride (600 mg, 0.61 ml, 5 mmol, 10 eq.). The reaction mixture was stirred at room temperature. After 5 hrs no further reaction was evident (TLC check). Usual work-up gave a yellowish oil strongly smelling of pyridine which was chromatographed over silica gel (3:1 hexane-EtOAc) to give pure 7a, 222 mg (57%). Crystallization from a mixture of EtOH-MeOH (1:1) provided an analytical sample[11] m.p. 182-183°C, $M^{+\cdot}$ 780.

Preparation of 2,11-di-t-butyldimethylsilyl-1-trimethylsilyl-15β-O-octanoyl glaucarubol 7b

To a stirred solution of 6 (119.7 mg, 0.172 mmol) in a mixture of pyridine-CH_2Cl (1:1) (3 ml) was added neat octanoyl-chloride (280 mg, 1.72 mmol, 10 eq.). The mixture was stirred at room temperature and monitored by TLC. Usual work-up yielded a brownish liquid which on chromatography gave pure 7b as a white foam, yield 102 mg (72%) $M^{+\cdot}$ 822.

Preparation of 2,11-di-t-butyldimethylsilyl-1-trimethylsilyl-15β-O-(E-3,4-dimehtyl-2-pentenoyl) glaucarubol 7c

To a stirred solution of E-3,4-dimethyl-2-pentenoic acid (512 mg, 4 mmol) in dry CH_2Cl_2 (2 ml) under an argon atmosphere was added triethylamine (425 mg, 4.2 mmol). The solution was cooled to 0°C and neat chlorosulfonylisocyanate (219 mg, 2 mmol) was added. The reaction mixture was stirred for 4 hrs at room temperature and then a solution of 6 (120 mg, 0.172 mmol) in dry CH_2Cl_2 (1 ml) was added followed by 4-dimethylaminopyridine (122 mg, 1 mmol). The reaction mixture was stirred at room temperature until all of the starting material 6 had been consumed (8 hrs, TLC check). Water (5 ml) was added and the solution was extracted with EtOAc. Work-up gave a yellowish viscous oil (219 mg) which on chromatography gave pure 7c (125 mg, 90%) which was crystallized from methanol m.p. 128-129°C. IR ($CHCl_3$) 3645, 3418, 1735, 1500 cm^{-1}. MS (EI): $M^{+\cdot}$ 806. ^{1}H-NMR ($CDCl_3$) δ 5.75 (s, O_2CCH=), 5.45 (br d, J=11, H-15), 5.28 (br s, H-3), 4.39 (br t, J=2.5, H-7), 3.99 and 3.54 (2d, J=9, $-CH_2O-$), 3.97 (m, H-2), 3.66 (br s, H-12), 3.31 (d, J=7, H-1), 2.79 (s, H-9), 2.45 (br d, J=13, H-5), 2.25 (m, H-14), 2.12 (m, H-13), 2.02 (d, t; J=3, 14; H-6α), 1.71 (br t, J=14, H-6β), 1.63 (s, Me-4), 1.15 (s, Me-10), 1.09 (d, J=7, $CHMe_2$), 1.00 (d, J=7, Me-13), 0.97 and 0.88 (s, Me_3CSi), 0.25, 0.22, 0.11 and 0.08 (Me-Si).

Selective deprotection at C-2: General method for the preparation of compounds 8a - 8c and 9a - 9c

To a solution of the trisilyl ether dissolved in methanol (0.02 M) was added an amount of 1N HCl corresponding to 1 molar equivalent of HCl. The reaction mixture was stirred for exactly 15 minutes at room temperature and, thereafter, neutralized by dropwise addition of saturated $NaHCO_3$ solution. Most of the methanol was removed under reduced pressure and the residue was diluted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated to give the corrresponding C-1, C-11-disilyl ether in generally quantitative yield.

8a: 98.5%, $M^{+\cdot}$ 622. 8b: 99%, $M^{+\cdot}$ 664. 8c: 97%, $M^{+\cdot}$ 662. 9a:[11] 96%, $M^{+\cdot}$ 666. 9b: 95%, $M^{+\cdot}$ 708. 9c: 98%, $M^{+\cdot}$ 692.

Generation of A-ring enone function: Preparation of disilyl enones 10a - 10c, 11a and 11b

Jones oxidation procedure : General method. - To a stirred solution of the 2-hydroxy derivative (8a -9b) in acetone (0.015 M solution) was added at room temperature Jones reagent (1 eq., 0.0023 mmol/µl). The reaction mixture at once became green and was stirred for exactly 3 minutes. The reaction mixture was quenched with 10% aqueous Na_2SO_3 and saturated $NaHCO_3$. A standard aqueous work-up and filtration down a short column of silica gel yielded the enones 10a - 10c, 11a and 11b.

Oxidation of 9c -> 11c using pyridinium dichromate

To a solution of 9c (134 mg, 0.2 mmol) in dry CH_2Cl_2 (2.5 ml) was added pyridinium dichromate (114.2 mg, 0.4 mmol) under an argon atmosphere. The heterogeneous mixture was stirred at room temperature and monitored by TLC. After 10 hrs the reaction was complete. The mixture was diluted with hexane-CH_2Cl_2 (2:1, 5 ml) and filtered over a small bed of silica gel (~2 g). The silica gel bed was washed two times with 10 ml portions of hexane-CH_2Cl_2 (2:1). The combined filtrates were evaporated to dryness to yield crude 11c which was purified by chromatography. 10a: 94%, $M^{+\cdot}$ 662 m.p. 220-221°C (EtOAc). λ_{EtOH} 242 nm (ε 15840). $[\alpha]_D$ +2.86° (c=0.7, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 5.97 (br s, H-3), 4.85 (s, OH), 4.45 (br s, H-7), 4.01 and 3.58 (2d, J=9, $-CH_2O-$), 3.96 (s, H-1), 3.66 (d, J=4, H-12), 3.02 (m, H-15), 2.90 (br d, J=13, H-5), 2.87 (s, H-9), 2.16 (d t, J=2.5, 14; H-6α), 1.91 (s, Me-4), 1.85 (br t, J=14, H-6β), 1.25 (m, $-(CH_2)_n-$), 1.17 (s, Me-10), 1.10 (d, J=7, Me-13), 0.96 (s, Me_3CSi), 0.87 (t, J=7 Hz, Me-$(CH_2)_n$), 0.26, 0.21 and 0.20 (Me-Si). 10c= 95%, $M^{+\cdot}$ 660. 11a: 94%, $M^{+\cdot}$ 664. 11b: 95%, $M^{+\cdot}$ 706. 11c: 95%, $M^{+\cdot}$ 690.

Desilylation of disilylenones: Preparation of compounds 12 - 17

A. Desylilation with tetra-n-butylammonium fluoride. - To a stirred solution of the enone (0.3 m in dry THF) under argon atmosphere was added a solution of tetra-n-butylammoniumfluoride in THF (1 M solution, 2 eq.). The reaction mixture turned yellowish-brown. It was stirred at room temperature and the reaction monitored by TLC. The desilylation was usually complete in ~45 minutes. Neat glacial acetic acid (10 eq.) was added and stirring continued for additional 15 minutes. Most of the solvent was removed under reduced pressure and the residue was dissolved in EtOAc/MeOH (9:1) and passed over a short column of silica gel (0.07 g silica gel/mg of starting enone). The solvent was evaporated to dryness and the residue was purified by chromatography (yields 30-45%).

B. Desilylation with 5-10% aqueous HF (40% aqueous solution) in acetonitrile. - A solution of the disilylenone (~0.4 M) in a mixture consisting of 90-95% by volume acetonitrile and 5-10% by volume 40% aqueous HF was stirred at room temperature and monitored by TLC. Deprotection was usually complete in ~6 hrs. The reaction mixture was diluted with EtOAc and the organic phase was washed with water (x 2), brine and dried over Na_2SO_4. Evaporation of the solvent gave the fully deprotected product which was purified by chromatography (yields 88-92%).

12: $M^{+\cdot}$ 434. Spectral and physical data[11] in accordance with the assigned structure.

13: $M^{+\cdot}$ 476 (HRMS: found 476.2755; calculated for $C_{27}H_{40}O_7$, 476.2765) ^{1}H-NMR ($CDCl_3$) δ 6.15 (br s, H-3), 4.54 (br s, H-7), 4.06 (s, H-1), 3.96 and 3.66 (2d, J=9, $-CH_2O-$), 3.53 (d, J=4.5, H-12), 3.17 (m, H-15), 3.03 (br d, J=13.5, H-5), 2.59 (s, H-9), 2.40 (m, H-13), 2.25 (d,t; J=3, 15; H-6α), 2.02 (s, Me-4), 1.97 (br t, J=14, H-6β), 1.27 m, $(CH_2)_n$), 1.19 (s, Me-10), 1.17 (d, J=7, Me-13), 0.88 (t, J=7, heptyl methyl).

14: $M^{+\cdot}$ 474 (HRMS: found 474.2608; calculated for $C_{27}H_{38}O_7$, 474.2617) ^{1}H-NMR ($CDCl_3$): δ 6.15 (br s, H-3), 5.13 (t, J=7, $CH_2-CH=$), 4.47 (br s, H-7), 4.06 (s, H-1), 3.96 and 3.65 (2d, J=9, $-CH_2O-$), 3.54 (d, J=4, H-12), 3.20 (m, H-15), 3.06 (br d, J=14, H-5), 2.68 (m, CH_ACH=), 2.58 (s, H-9), 2.56 (m, $CHMe_2$), 2.39 (m, H-13), 2.19 (m, H-6α and CH_BCH=), 2.03 (s, Me-4), 1.98 (br t, J=14, H-6β), 1.84 (d,d; J=7, 11; H-14), 1.61 (s, $CH_2CH=CCH_3$), 1.22 (d, J=7, Me-13), 1.19 (s, Me-10), 0.99 (d, J=7, $CHMe_2$).

15: $M^{+\cdot}$ 478. Spectral and physical data[11] are in accordance with the assigned structure.

16: $M^{+\cdot}$ 520 (HRMS: found 520.2682; calculated for $C_{28}H_{40}O_9$, 520.2671). IR ($CHCl_3$) 3575, 3280, 2930, 1740, 1670 cm^{-1}. NMR ($CDCl_3$) δ 6.13 (br s, H-3), 5.59 (br d, J=11.5, H-15), 4.01 (s, H-1), 3.95 and 3.68 (2d, J=9, $-CH_2O-$), 3.56 (d, J=4, H-12), 2.97 (br d, J=13.5, H-5), 2.76 (s, H-9), 2.40-2.26 (m, 5H), 2.02 (s, Me-4), 1.66 (m, H-13), 1.28 (m, $(CH_2)_5$), 1.20 (s, Me-10), 1.11 (d, J=7, Me-13), 0.88 (t, J=7, octanoate methyl).

17: $M^{+\cdot}$ 504 (HRMS: found 504.2348; calculated for $C_{27}H_{36}O_9$, 504.2359). IR ($CHCl_3$) 3565, 3285, 2930, 1742, 1670, 1615, 810 cm^{-1}. NMR ($CDCl_3$) δ 7.85 (s, OH), 6.16 (br s, H-3), 5.73 (s, $O_2CCH=$), 5.54 (d, J= 12, H-15), 5.20 (br s, OH), 4.67 (br s, H-7), 4.07 (s, H-1), 3.97 and 3.70 (2d, J=9, $-CH_2O-$), 3.57 (d, J=4, H-12), 3.01 (br d, J=13.5, H-5), 2.76 (s, H-9), 2.40-2.22 (m, 5H), 2.17 (s, $O_2CCHCCH_3$), 2.02 (s, Me-4), 2.01 (br t, J=14, H-6β), 1.21 (s, Me-10), 1.12 (d, J=7, Me-13), 1.07 (d, J=7, $CHMe_2$).

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