Synthesis of (−)-Steganone

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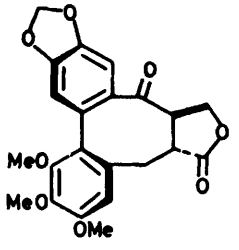
A novel, highly efficient route to the key steganone intermediate 2,3,4-trimethoxy-6,7-methylenedioxy-9-(pyrrolidin-1-yl)phenanthrene (8) is described. Resolution of the derived 5,6,7,8-tetrahydro-1,2,3-trimethoxy-10,11-methylenedioxy-8-oxodibenzo[*a*,*c*]cyclo-octene-6-carboxylic acid and further elaboration of the relevant enantiomer (11) leads to the first synthesis of enantiomerically pure (−)-steganone (1).

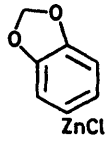
SINCE the first syntheses in the dibenzocyclo-octene lignan field carried out in Cambridge [1] and in Rochester [2] there has been considerable activity [3-6] in this area prompted by the pharmacological properties of members of this group of natural products. In particular the antileukaemic activity reported for steganacin has focussed special attention on the establishment of efficient synthetic routes to its immediate precursor and co-constituent steganone (1).†



(1)

Our original synthesis of these lignans employed as the key intermediate the substituted 9-(pyrrolidin-1-yl)phenanthrene (8). This was obtained by a photocyclisation which afforded a good yield only in small-scale preparations. To obviate this drawback the following high-yielding route was devised which could be scaled up without difficulty.

Treatment of 1-bromo-3,4-methylenedioxybenzene with n-butyl-lithium and subsequent reaction with zinc chloride gave the methylenedioxyphenylzinc chloride (2). Coupling of (2) with *N*-cyclohexyl-2-iodo-3,4,5-trimethoxybenzylideneamine [3] (3) in the presence of a nickel(0) catalyst [8] gave, after hydrolytic work-up, a high yield of the biphenyl aldehyde (4). Other recent modifications of the Ullmann reaction [3,5] gave much less satisfactory results. It has been suggested that nickel(0)-mediated couplings are ineffective when two *ortho*-substituents flank the reactive carbon sites.[3] We attribute the success of the above procedure to the chelating ability of the imine group of (3), which may stabilise the transient arylnickel intermediate.[9] Thus, although *N*-cyclohexyl-2-bromo-3,4,5-trimethoxybenzylideneamine underwent nickel(0)-catalysed coupling with (2) in moderate yield, there was no reaction with methyl 2-bromo-3,4,5-trimethoxybenzoate. A similar intramolecular ligand effect has been observed in the ambient temperature Ullmann reaction.[3]



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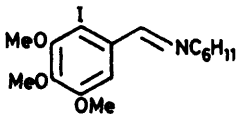

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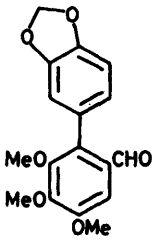

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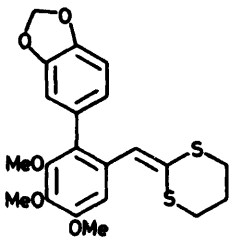

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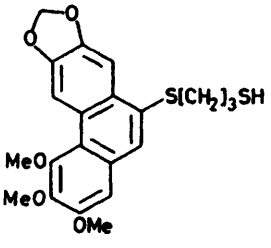

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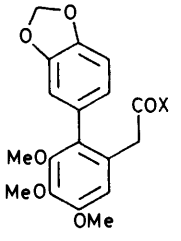
By reaction of the aldehyde (4) with lithio-2-trimethylsilyl-1,3-dithian [10] the keten dithioacetal (5) was produced. The normal acid-catalysed methanolysis [10] of (5) resulted in ready intramolecular electrophilic attack to yield the phenanthrene thioether (6). This complication could be avoided by carrying out the methanolysis in the presence of mercury(II) chloride, whereby the desired biphenyl ester (7; X = OMe) was obtained in high yield. Heating this ester with neat

† The absolute configuration of the *Steganotaenia* lignans has recently been shown [5,6] to be as delineated in (1), *i.e.* opposite to that originally proposed.[7]

pyrrolidine transformed it into the corresponding acylpyrrolidine (7; X = NC_4H_8) which underwent smooth cyclisation with phosphoryl chloride to give the required phenanthrene (8).

Double ring expansion of (8) with dimethyl but-2-ynedioate gave the dibenzocyclo-octene (9), which was transformed into the ester (10) by acidic hydrolysis. Catalytic hydrogenation over Raney nickel followed by basic hydrolysis gave the racemic oxo-acid (11). Resolution of (11) was carried out by conversion into the amides derived from (−)-(*S*)-2-amino-3-phenylpropan-1-ol,[11] and the resulting diastereoisomers were readily separated by preparative t.l.c. Low-temperature acidic hydrolysis of each then gave the (+)-oxo-acid (11) (absolute configuration as shown) and the corresponding (−)-oxo-acid. The low hydrolysis temperature prevented thermal isomerisation, and none of the atropisomeric biphenyls were detected in the resolved acids. The enantiomeric purity of the two acids was checked in the following manner. After conversion into their methyl esters with diazomethane, n.m.r. examination of each ester in the presence of the chiral lanthanoid shift reagent [12] $Eu(hfbc)_3$ showed no trace of its respective enantiomer; under the same conditions the enantiomeric singlets were cleanly resolved in the racemate ($\Delta\Delta\delta$ = 0.10 p.p.m.).

Base-catalysed condensation of the (+)-oxo-acid (11) with formaldehyde followed by Jones oxidation produced (+)-isosteganone (12), which was rearranged thermally to the atropisomeric (−)-steganone (1), identical with the naturally occurring ketone. This sixteen-step synthesis of (−)-steganone from 3,4,5-trimethoxybenzyl alcohol has been achieved in an overall yield of 10.3%. The specific rotation of our synthetic ketone (1) agreed closely with that recorded for the natural product.[7] The reported rotation of the ketone recently elaborated from a chiral lactone of known absolute configuration [5] shows the material obtained in this latter way to have been enantiomerically impure (*ca.* 70% enantiomeric excess).



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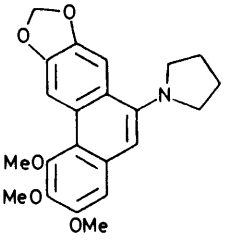

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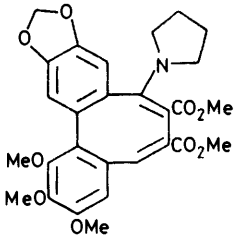

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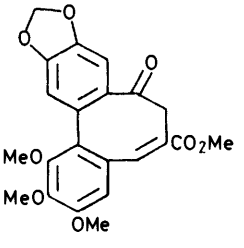

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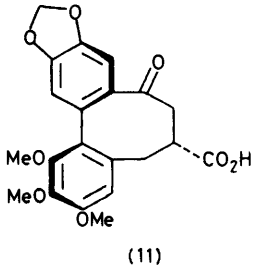

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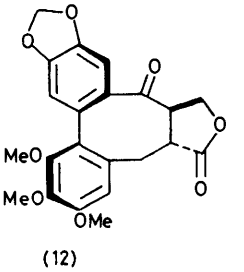

(12)

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage or a Buchi 510 apparatus. Spectrometric measurements were obtained on the following instruments: i.r., Perkin–Elmer 257 (solvent $CHCl_3$); i.v., Pye Unicam SP 8100 (solvent EtOH); ^1H n.m.r., Varian CFT20, HA 100 D or EM 390 (solvent $CDCl_3$; $SiMe_4$ internal standard); mass spectrometry MS30 or MS902. Thin layer chromatography (t.l.c.) was carried out on Merck silica 60 F_{254} and preparative t.l.c. was performed on Merck PF_{254} silica plates (1 mm thick). Extracts were dried with $MgSO_4$.

N-*Cyclohexyl*-2-*iodo*-3,4,5-*trimethoxybenzylideneamine* (3).—Iodine (58 g) in dichloromethane (1.5 l) was added over 3 h to a stirred solution of 3,4,5-trimethoxybenzyl alcohol (39.6 g) and silver trifluoroacetate (44.2 g) in dichloromethane (150 ml). The mixture was stirred for an additional 1 h, then filtered, and the precipitated salts were washed with dichloromethane. The filtrate was washed with aqueous sodium thiosulphate, water, and saturated aqueous sodium hydrogen carbonate, dried, and evaporated to give an oil that slowly crystallised (64.6 g, 98%). This product was sufficiently pure for the next step. A sample of the iodo-alcohol crystallised from light petroleum–ethyl acetate in needles, m.p. 57—58 °C (lit.,[3] 56.5—57.5 °C).

Freshly prepared pyridinium dichromate [13] was added to a solution of the iodo-alcohol (64 g) in dry dichloromethane (500 ml) and the mixture stirred vigorously under nitrogen at room temperature for 12 h. Addition of ether (1 l), filtration through silica gel, and evaporation gave the iodo-aldehyde (59.3 g, 93%) as a crystalline solid which was used directly for the next stage; a sample crystallised from aqueous methanol in needles, m.p. 66—67 °C (lit.,[3] 66—66.5 °C).

A solution of the iodo-aldehyde (59 g) and cyclohexylamine (18.2 g) in dry toluene (250 ml) was heated under nitrogen in a Dean–Stark apparatus for 4 h. Removal of solvent under reduced pressure gave the iodo-imine (3), which crystallised from light petroleum as prisms (67 g, 91%), m.p. 71—72 °C (lit.,[3] 72—73 °C) (Found: C, 47.6; H, 5.55; N, 3.5%; M^+, 403. Calc. for $C_{16}H_{22}INO_3$: C, 47.65; H, 5.5; N, 3.45%; *M*, 403).

4,5,6-*Trimethoxy*-3′,4′-*methylenedioxybiphenyl*-2-*carbaldehyde* (4).—A solution of n-butyl-lithium (63 ml; 1.6M in hexane) was added dropwise to a stirred solution of 3,4-methylenedioxyphenyl bromide [14] (19.2 g) in dry tetrahydrofuran (180 ml) at −78 °C under nitrogen. After 20 min, anhydrous zinc chloride (13.1 g) in dry tetrahydrofuran (100 ml) was added; the mixture was then allowed to warm to room temperature and stirring continued for 1 h. In a separate flask, di-isobutylaluminium hydride (3.2 ml; 1.5M in toluene) was added dropwise to a stirred solution of nickel(II) acetylacetonate (620 mg) and triphenylphosphine (2.5 g) in dry tetrahydrofuran (200 ml) under nitrogen. After 20 min, the iodo-imine (3) (32.2 g) in dry tetrahydrofuran (100 ml) was added in one portion. The mixture was then cooled to −20 °C and the above 3,4-methylenedioxyphenylzinc chloride solution was added *via* a stainless steel cannula. After 4 h the mixture was allowed to warm to room temperature, water (10 ml) was added, and the solvent was removed under reduced pressure. The syrupy residue was dissolved in dichloromethane (300 ml) and heated under reflux with hydrochloric acid (2M; 300 ml) for 1.5 h. The organic layer was separated and the aqueous layer extracted with dichloromethane. The combined organic extracts were washed with water and brine, dried, and evaporated. Crystallisation of the residue from methanol–water (9 : 1) gave the *biphenyl aldehyde* (4) (20.6 g, 82%) as rhombs, m.p. 89—90 °C (Found: C, 64.8; H, 5.35%; M^+, 316.0950. $C_{17}H_{16}O_6$ requires C, 64.55; H, 5.1%; M, 316.0947); $\nu_{max.}$ 1 675, 1 580, 1 480, 1 460, 1 330, and 1 140 cm^{-1}; $\lambda_{max.}$ 322infl (log ε 3.73), 285 (4.14), 247infl (4.19), and 227 nm (4.42); τ 0.35 (1 H, s, CHO), 2.68 (1 H, s, H-3), 3.15 (1 H, d, J 7 Hz, H-5′), 3.19 (1 H, br, s, H-2′), 3.24 (1 H, d br, s, J 7 Hz, H-6′), 4.01 (2 H, s, OCH_2O), and 6.02, 6.07, and 6.37 (9 H, 3s, 3 × OCH_3); *m/z* 316 (100%, M^+), 271 (8), 243 (18), and 215 (10).

Attempted coupling using the Ziegler procedure [3] failed to produce the biphenyl aldehyde (4). A mixed Ullmann coupling between 2-bromo-3,4,5-trimethoxybenzaldehyde and 3,4-methylenedioxyphenyl iodide using Brown's procedure [5] gave a multi-component mixture from which (4) could be isolated in 32% yield.

2-(4,5,6-*Trimethoxy*-3′,4′-*methylenedioxybiphenyl*-2-*ylmethylene*)-1,3-*dithian* (5).—To a stirred solution of 2-trimethylsilyl-1,3-dithian [10] (12.2 g) in dry tetrahydrofuran (200 ml) at −20 °C under nitrogen was added dropwise n-butyl-lithium (42 ml; 1.6M in hexane). After 3 h the biphenyl aldehyde (4) (20 g) in dry tetrahydrofuran (100 ml) was added slowly and the solution allowed to warm to room temperature. After 21 h water (20 ml) was added; the layers were separated and the aqueous layer was extracted with ether. The combined organic layers were washed with aqueous 10% potassium hydroxide, water, and brine, dried, and evaporated to give the *dithian* (5) (25.4 g, 92%), crystallising from methanol in prisms, m.p. 100—101 °C (Found: C, 60.5; H, 5.35%; M^+, 418.0905. $C_{21}H_{22}S_2O_5$ requires C, 60.25; H, 5.3%; M, 418.0909); $\nu_{max.}$ 1 595, 1 485, 1 330, 1 130, and 1 045 cm^{-1}; $\lambda_{max.}$ 310 (log ε 4.35), 294 (4.36), 263 (4.25), and 209infl nm (4.5); τ 2.93 (1 H, s, H-3′), 3.11—3.25 (3 H, m, H-2′, -5′ and -6′), 3.50 (1 H, s, ArCH=), 4.00 (2 H, s, OCH_2O), 6.06 (6 H, s, 2 × OCH_3), 6.38 (3 H, s, OCH_3), 7.07 (4 H, ' t ', J 6 Hz, 2 × SCH_2), and 7.78 (2 H, m, CCH_2C); *m/z* 418 (100%, M^+), 403 (15), 387 (10), 299 (20), 202 (10), and 119 (45).

Attempted Methanolysis of the Dithian (5).—A solution of the dithian (5) (420 mg) and toluene-*p*-sulphonic acid (40 mg) in methanol (20 ml) was heated under reflux for 2 h under nitrogen.[10] Removal of solvent left a glass which crystallised from light petroleum–ethyl acetate to give 2,3,4-*trimethoxy*-6,7-*methylenedioxy*-9-*phenanthryl* 3-*mercaptopropyl sulphide* (6) as needles, m.p. 151—152.5 °C (Found: C, 60.1; H, 5.2%; M^+, 418.0912. $C_{21}H_{22}S_2O_5$ requires C, 60.25; H, 5.3%; M, 418.0909); $\nu_{max.}$ 1 605, 1 465, 1 240, 1 150, 1 105, and 1 040 cm^{-1}; $\lambda_{max.}$ 365 (log ε 3.23), 348 (3.21), 316 (3.8), 289 (4.29), and 262 nm (4.61); τ 0.88 (1 H, s, H-5), 2.05, 2.30, and 3.01 (3 H, 3s, 3 × ArH), 3.90 (2 H, s, OCH_2O), 5.98 (6 H, s, 2 × OCH_3), 6.00 (3 H, s, OCH_3), 6.93 (2 H, t, J 7 Hz, $ArSCH_2$), 7.31 (2 H, ' q ', J 7 Hz, CH_2SH), 8.05 (2 H, ' q ', J 7 Hz, $C-CH_2-C$), and 8.65 (1 H, t, J 7 Hz, SH); *m/z* 418 (35%; M^+), 384 (15), 344 (15), 161 (50), and 110 (100).

Methyl 2-(3,4-*Methylenedioxyphenyl*)-3,4,5-*trimethoxyphenylacetate* (7; X = OMe).—A solution of mercury(II) chloride (28.5 g) in warm hydrochloric acid (0.3M; 60 ml) was added to a stirred solution of the dithian (5) (20.9 g) in hot methanol (600 ml). The resulting milky mixture was heated under reflux for 10 min, then cooled and diluted with ether (200 ml). After filtration through Florisil the solution was neutralised with sodium hydrogen carbonate and concentrated under reduced pressure. The residue was extracted with ether and the extracts were washed with aqueous sodium hydrogen carbonate and brine, dried, and evaporated to give the *ester* (14.8 g, 82%) as a crystalline mass sufficiently pure for use in the next step. A sample crystallised from light petroleum–ethyl acetate in prisms, m.p. 87—88 °C (Found: C, 63.4; H, 5.5%; M^+, 360.1205. $C_{19}H_{20}O_7$ requires C, 63.35; H, 5.6%; M, 360.1209); $\nu_{max.}$ 1 730, 1 600, 1 485, 1 325, 1 130, and 1 040 cm^{-1}; $\lambda_{max.}$ 286 (log ε 4.03) and 242infl nm (4.14); τ 3.18 (1 H, d, J 7 Hz, H-5′), 3.33 (1 H, br, s, H-2′), 3.38 (1 H, d, br, s, J 7 Hz, H-6′), 3.39 (1 H, s, H-6), 4.06 (2 H, s, OCH_2O), 6.14, 6.15, 6.40, and 6.42 (12 H, 4s, 4 × OCH_3), and 6.61 (2 H, s, $ArCH_2$); *m/z* 360 (100%; M^+), 301 (5), 286 (8), 285 (15), 271 (20), and 270 (15).

N-[2-(3,4-*Methylenedioxyphenyl*)-3,4,5-*trimethoxyphenylacetyl*]*pyrrolidine* (7; X = NC_4H_8).—A solution of the ester (7; X = OMe) (13 g) in dry pyrrolidine (100 ml) was heated under reflux under nitrogen for 10 h and the solvent then removed under reduced pressure. The residue was dissolved in ethyl acetate, and rapidly washed with dilute hydrochloric acid, dilute aqueous sodium hydroxide, and water. Drying and evaporation gave the *acylpyrrolidine* (13.8 g, 96%) as a substantially pure glass. A sample was purified by preparative t.l.c. (ethyl acetate) (R_F 0.27) (Found: C, 66.0; H, 6.6; N, 3.55%; M^+, 399.1698. $C_{22}H_{25}NO_6$ requires C, 66.15; H, 6.3; N, 3.5%; M, 399.1682); $\nu_{max.}$ 1 630, 1 480, 1 430, 1 115, 1 110, and 1 020 cm^{-1}; $\lambda_{max.}$ 285 (log ε 4.04) and 241infl nm (4.19); τ 3.16 (1 H, d, J 7 Hz, H-5′), 3.28 (1 H, s, H-6), 3.31 (1 H, br, s, H-2′), 3.37 (1 H, dd, J 1 and 7 Hz, H-6′), 4.04 (2 H, s, OCH_2O), 6.11 (6 H, s, 2 × OCH_3), 6.38 (3 H, s, OCH_3), 6.56 (4 H, m, 2 × CH_2N), 6.61 (2 H, s, $ArCH_2$), and 8.40 (4 H, m, CCH_2CH_2C); *m/z* 399 (100%; M^+), 271 (40), 241 (8), 185 (10), and 151 (18).

2,3,4-*Trimethoxy*-6,7-*methylenedioxy*-9-(*pyrrolidin*-1-*yl*)-*phenanthrene* (8).—A solution of the amide (7; X = NC_4H_8) (13.8 g) and phosphoryl chloride (7 ml) in dry chloroform (140 ml) was heated under reflux under nitrogen for 5 h. The mixture was poured into aqueous ammonia (10%; 200 ml) and stirred vigorously for 30 min. The layers were separated and the aqueous layer was extracted with

dichloromethane. The combined organic layers were washed with water and brine, dried (K_2CO_3), and evaporated to give the phenanthrene (8) (12.3 g, 94%), crystallising from 95% ethanol as pale yellow rhombs, m.p. 133—135 °C (lit.,[1] 133—135 °C) (Found: M^+, 381.1578. Calc. for $C_{22}H_{23}NO_5$ M, 381.1576).

Dimethyl 1,2,3-*Trimethoxy*-10,11-*methylenedioxy*-8-(*pyrrolidin*-1-*yl*)*dibenzo*[a,c]*cyclo*-*octene*-6,7-*dicarboxylate* (9).—A solution of the phenanthrene (8) (11 g) and dimethyl but-2-ynedioate (8.7 g) in dry 1,4-dioxan (100 ml) was heated under reflux under nitrogen for 24 h. More acetylenic diester (4.3 g) was added and the heating continued for a further 20 h. Evaporation under reduced pressure and crystallisation of the residue from ethanol gave the enamine diester (9) (13.4 g, 89%) as pale yellow needles, m.p. 226—228 °C (lit.,[1] 226—228 °C) (Found: M^+, 523.1856. Calc. for $C_{28}H_{29}NO_9$: M, 523.1843).

Methyl 7,8-*Dihydro*-1,2,3-*trimethoxy*-10,11-*methylenedioxy*-8-*oxodibenzo*[a,c]*cyclo*-*octene*-6-*carboxylate* (10).—A solution of the enamine diester (9) (10.5 g) in methanol (250 ml) was heated under reflux under nitrogen with hydrochloric acid (5%; 250 ml) for 3 h. Removal of methanol under reduced pressure, extraction with dichloromethane, washing with water and brine, drying, and evaporation gave a mixture of the desired oxo-ester and the corresponding acid. This mixture was dissolved in methanol (500 ml), concentrated sulphuric acid (3 ml) was added, and the solution was heated under reflux for 4 h. Concentration under reduced pressure, dilution with ethyl acetate, washing with water, saturated aqueous sodium hydrogen carbonate and brine, drying, and evaporation gave the oxo-ester (10) (7.6 g, 93%), which crystallised from methanol in plates, m.p. 144—145 °C (lit.,[1] 144—145 °C) (Found: M^+, 412.1156. Calc. for $C_{22}H_{20}O_8$: M, 412.1158).

(±)-5,6,7,8-*Tetrahydro*-1,2,3-*trimethoxy*-10,11-*methylenedioxy*-8-*oxodibenzo*[a,c]*cyclo*-*octene*-6-*carboxylic Acid* (±)-(11).—A solution of the unsaturated oxo-ester (10) (3.1 g) in methyl acetate (120 ml) was reduced with hydrogen at 1 atm in the presence of pre-reduced Raney nickel (9 g; grade W-4). After 2.5 h filtration and evaporation gave the saturated oxo-ester (2.9 g, 94%), which crystallised from propan-2-ol in prisms, m.p. 128—129 °C (lit.,[1] 127—129 °C) (Found: M^+, 414.1312. Calc. for $C_{22}H_{22}O_8$: M, 414.1315). To a suspension of this oxo-ester (2.1 g) in methanol (40 ml) was added a solution of lithium hydroxide (1.2 g) in water (30 ml), and the mixture was stirred at room temperature for 12 h. The resulting homogeneous solution was diluted with aqueous potassium hydroxide (5%; 20 ml) and extracted with dichloromethane. The aqueous solution was acidified with concentrated hydrochloric acid and extracted with ethyl acetate. The extracts were washed with water and brine, dried, and evaporated to give the (±)-oxo-acid (11) (1.9 g, 95%), which crystallised from benzene–light petroleum in needles, m.p. 145—147 °C (lit.,[1] 144—146 °C) (Found: M^+, 400.1164. Calc. for $C_{21}H_{20}O_8$: M, 400.1158).

Resolution of the Racemic Oxo-acid (11).—Freshly distilled thionyl chloride (1 ml) was added to the (±)-oxo-acid (11) (1 g) at 0 °C under nitrogen. The resulting solution was warmed to room temperature and stirred for 2 h. The excess of thionyl chloride was removed under reduced pressure and the resulting acid chloride kept *in vacuo* (0.5 mmHg) for 4 h. It was then dissolved in dry tetrahydrofuran (15 ml) and added to a stirred solution of (−)-(*S*-2-amino-3-phenylpropan-1-ol (570 mg) and triethylamine (1 ml) at 0 °C under nitrogen.[11] After 30 min stirring at 0 °C the solvent was removed under reduced pressure, the residue dissolved in methanol (50 ml), and sulphuric acid (3M; 12 ml) added. The mixture was stirred at room temperature for 4 h to hydrolyse a small amount of oxazoline by-product. It was then neutralised with sodium hydrogen carbonate, diluted with water (50 ml), and extracted with ethyl acetate. The extracts were washed with hydrochloric acid (5%), saturated aqueous sodium hydrogen carbonate, and brine, dried, and evaporated to give a mixture of non-crystalline diastereoisomeric hydroxyamides (1.23 g; 93%). Preparative t.l.c. (ethyl acetate; double elution) readily separated them (R_F 0.41, 0.53) into a less polar diastereoisomer (525 mg, 76%) and a more polar diastereoisomer (500 mg, 73%). The less polar isomer showed $[\alpha]_D^{20}$ −11.0° (*c* 1.50 in $CHCl_3$) (Found: M^+, 533.2039. $C_{30}H_{31}NO_8$ requires M, 533.2050); $\nu_{max.}$ 3 620, 3 600—3 200, 3 440, 1 655, 1 620, 1 480, 1 405, 1 240, 1 120, and 1 040 cm^{-1}; τ 2.40 (1 H, s, H-9), 2.81 (5 H, br, s, C_6H_5), 3.37 and 3.46 (2 H, 2s, H-4 and H-12), 3.62—3.81 (1 H, br, s, CONH), 3.94 and 3.97 (2 H, 2d, *J* 1 Hz, OCH_2O), 5.76—6.03 (1 H, m, CHN), 6.10 and 6.13 (6 H, 2s, 2 × OCH_3), 6.12—6.63 (2 H, m, CH_2OH), and 7.07—7.41 (7 H, m, aliphatic); *m/z* 533 (11%, M^+), 515 (15), 383 (35), 328 (100), and 314 (15). The more polar isomer exhibited $[\alpha]_D^{20}$ −66.8° (*c* 1.50 in $CHCl_3$) (Found: M^+, 533.2063); $\nu_{max.}$ identical with above isomer; τ 2.38, 2.76, 3.36, 3.48, 3.95, 3.97, 5.60—6.05, 6.10, 6.13, 6.18—6.57, 6.42, and 7.06—7.59; *m/z* 533 (45%, M^+), 444 (12), 383 (50), 328 (100), and 314 (30).

To a solution of the less polar isomer (425 mg) in 1,2-dimethoxyethane (10 ml) was added sulphuric acid (6M; 10 ml), and the mixture was stirred under nitrogen at 35 °C for 28 h. The solution was poured into water and extracted repeatedly with dichloromethane. The combined extracts were washed with water, then extracted with aqueous potassium hydroxide (5%). The basic extract was washed with dichloromethane then acidified to pH 3 with concentrated hydrochloric acid. Extraction with dichloromethane, washing with water and brine, drying, and evaporation gave the (+)-*oxo-acid* (11) (265 mg, 82%), which crystallised from light petroleum–ethyl acetate in needles, m.p. 130—132°; $[\alpha]_D^{20}$ +36.6° (*c* 1.53 in $CHCl_3$) (Found: M^+, 400.1165. $C_{21}H_{20}O_8$ requires M, 400.1158); spectroscopic data as for racemate; c.d. λ 186, Δε −18.6; 221, −29.1; 243, +29.1; 275, −0.42; 297, +6.64; 339, +1.32, 349, +1.35.

Similarly obtained from the more polar amide was the (−)-*oxo-acid* [enantiomer of (11)], $[\alpha]_D^{20}$ −36.4° (*c* 1.50 in $CHCl_3$); c.d. λ 185, Δε +16.1; 221, +25.6; 243, −25.6; 275, +0.44; 298, −6.0; 339, −1.09; 348, −1.09.

The purity of the two enantiomers was confirmed by treating them independently with diazomethane. Both esters showed a methyl singlet at τ 6.43 but in the presence of tris-[3-(heptafluorobutanoyl)-(+)-camphorato]-europium[12] (molar ratio 0.091 : 1) this signal shifted to τ 5.65 for the (+)-oxo-acid ester and to τ 5.55 for the (−)-oxo-acid ester, each enantiomer showing no trace of the other. The clear-cut ΔΔδ value of 0.10 p.p.m. enabled an enantiomer purity of at least 95% to be assigned to the (+)- and the (−)-oxo-acids.

(+)-*Isosteganone* (12).—To a solution of the (+)-oxo-acid (11) (175 mg) in aqueous potassium hydroxide (5%; 15 ml) was added aqueous formaldehyde (37%; 3 ml) and the mixture was stirred under nitrogen for 1 h. The solution

was acidified with concentrated hydrochloric acid and extracted with chloroform. The extracts were well washed with water and brine, dried, and evaporated. The residue was dissolved in acetone (10 ml) and treated dropwise with Jones reagent at 0 °C until the orange colour persisted. The excess of oxidant was destroyed with propan-2-ol, the solution was filtered through Celite, and the precipitated salts were washed with acetone. The combined filtrate and washings were evaporated and the residue was dissolved in ethyl acetate and rapidly washed with aqueous potassium hydroxide. The basic washings were acidified with hydrochloric acid and extracted with dichloromethane to give unchanged (+)-oxo-acid (100 mg). The ethyl acetate extract was washed with water and brine, dried, and evaporated to give a glass. Preparative t.l.c. (light petroleum–ethyl acetate, 1 : 1) gave (+)-isosteganone (12) (R_F 0.60) (64 mg, 83% based on consumed oxo-acid), $[\alpha]_D^{20}$ +150° (*c* 1.50 in $CHCl_3$), (Found: M^+, 412.1164. Calc. for $C_{22}H_{20}O_8$: *M*, 412.1158); spectroscopic data as for racemate.[1]

In some preparations of isosteganone a by-product was obtained which proved to be *isosteganyl formate*. The racemate crystallised from light petroleum–chloroform, m.p. 265—268 °C (decomp.) (Found: M^+, 442.1245. $C_{23}H_{22}O_9$ requires *M*, 442.1263); $\nu_{max.}$ 1 775 and 1 730 cm^{-1}. This material was readily converted into isosteganone by hydrolysis with aqueous methanolic sodium hydroxide and Jones oxidation. The formate presumably arose from oxidation of an intermediate hydroxymethylisosteganol; decomposition of this hemiacetal by careful water washing of the crude hydroxymethylation product before oxidation prevented the production of the formate.

(−)-*Steganone* (1).—A solution of (+)-isosteganone (12) (41.2 mg) in dry xylene (2 ml) was heated under reflux under nitrogen for 1 h. Removal of solvent under reduced pressure gave (−)-steganone (1) (38 mg, 92%), crystallising from 95% ethanol in needles, m.p. 155.5—157 °C (lit.,[5,7] 155—156 °C); $[\alpha]_D^{20}$ −197° (*c* 0.77, in $CHCl_3$) (lit.,[5] $[\alpha]_D^{20}$ −140°; lit.,[7] $[\alpha]_D^{20}$ −202°) (Found: M^+, 412.1157. Calc. for $C_{22}H_{20}O_8$: *M*, 412.1158); spectroscopic data as for racemate,[1] c.d. λ 201 nm, Δε −31.0; 218, +396; 244, −41.0; 276, +5.29; 304, −6.85; 338, −1.01. The c.d. data correlate well in the 220 and 240 nm region with those reported [15] for the gomisin group of dibenzocyclo-octene lignans; thus (−)-steganone and its congeners possess the same biphenyl chirality as this group.

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REFERENCES

[1] D. Becker, L. R. Hughes, and R. A. Raphael, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1674; *J. Chem. Soc., Chem. Commun.*, 1974, 430; L. R. Hughes and R. A. Raphael, *Tetrahedron Lett.*, 1976, 1543; E. R. Larson and R. A. Raphael, *ibid.*, 1979, 5041.

[2] A. S. Kende and L. S. Liebeskind, *J. Am. Chem. Soc.*, 1976, **98**, 267; A. S. Kende, L. S. Liebeskind, C. Kubiak, and R. Eisenberg, *ibid.*, p. 6389.

[3] F. E. Ziegler, I. Chliwner, K. W. Fowler, S. J. Kanfer, S. J. Kuo, and N. D. Sinha, *J. Am. Chem. Soc.*, 1980, **102**, 790; F. E. Ziegler and J. A. Schwartz, *J. Org. Chem.*, 1978, **43**, 985; F. E. Ziegler, K. W. Fowler, and N. D. Sinha, *Tetrahedron Lett.*, 1978, 2767.

[4] E. Ghera and Y. Ben-David, *J. Chem. Soc., Chem. Commun.*, 1978, 480; M. Mervič and E. Ghera, *J. Am. Chem. Soc.*, 1977, **99**, 7673; E. Ghera, Y. Gaoni, and S. Shoua, *ibid.*, 1976, **98**, 3627; E. Ghera, Y. Ben-David, and D. Becker, *Tetrahedron Lett.*, 1977, 463; R. E. Damon, R. H. Schlessinger, and J. F. Blount, *J. Org. Chem.*, 1976, **41**, 3772; G. R. Krow, K. M. Damordaran, E. Michener, R. Wolf, and J. Guare, *ibid.*, 1978, **43**, 3950; T. Biftu B. G. Hazra, and R. Stevenson, *J. Chem. Soc., Chem. Commun.*, 1978, 491.

[5] J. P. Robin, O. Gringore, and E. Brown, *Tetrahedron Lett.*, 1980, 2709; E. Brown, R. Dhal, and J. P. Robin, *ibid.*, 1979, 733; E. Brown and J. P. Robin, *ibid.*, 1978, 3613; 1977, 2015.

[6] K. Tomioka, T. Ishiguro, and K. Koga, *Tetrahedron Lett.*, 1980, 2973; K. Tomioka, H. Mizuguchi, and K. Koga, *ibid.*, 1979, 1409; K. Tomioka, T. Ishiguro, and K. Koga, *J. Chem, Soc., Chem. Commun.*, 1979, 652.

[7] S. M. Kupchan, R. W. Britton, M. F. Ziegler, C. J. Gilmore, R. J. Restivo, and R. F. Bryan, *J. Am. Chem. Soc.*, 1973, **95**, 1335.

[8] E. Negishi, A. O. King, and N. Okukado, *J. Org. Chem.*, 1977, **42**, 1821.

[9] M. Hidai, T. Kashiwagi, I. I. Keuchi, and Y. Ushida, *J. Organomet. Chem.*, 1971, **30**, 279.

[10] D. Seebach, M. Kolb, and B. T. Gröbel, *Chem. Ber.*, 1973, **106**, 2277; D. Seebach and M. Kolb, *Liebigs Ann. Chem.*, 1977, 811.

[11] H. Seki, K. Koga, H. Matsuo, S. Ohki, I. Matsuo, and S. Yamada, *Chem. Pharm. Bull.*, 1965, **13**, 995; G. Helmchen, G. Nill, D. Flockerzi, and M. Youssef, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 63.

[12] R. R. Fraser, M. A. Petit, and J. K. Saunders, *J. Chem. Soc., Chem. Commun.*, 1971, 1450; H. L. Goering, J. N. Eikenberry, and G. S. Koermer, *J. Am. Chem. Soc.*, 1971, **93**, 5913.

[13] E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, 1979, 399.

[14] W. J. Gensler and J. E. Stouffer, *J. Org. Chem.*, 1958, **23**, 908.

[15] Y. Iyeka, H. Taguchi, I. Yosioka, Y. Iitaka, and H. Kobayashi, *Chem. Pharm. Bull.*, 1979, **27**, 1383, 1395.