Natural Product Chemistry. Part 181.[1] Investigations on the Synthesis of Dihydropyrano- and Dihydrofurano-coumarins by Application of Catalytic Enantioselective *cis*-Dihydroxylation[2]

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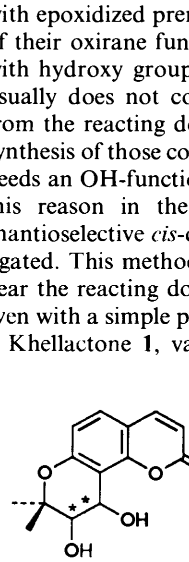
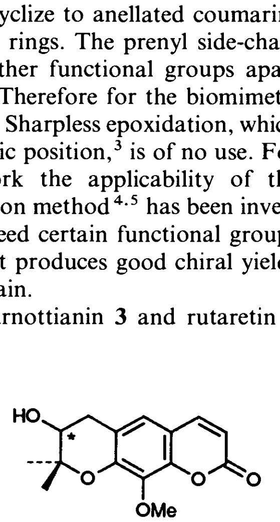
As part of a study on the applicability of catalytic enantioselective *cis*-dihydroxylation for the synthesis of dihydropyrano- and dihydrofurano-anellated coumarins new routes to (−)-*cis*-khellactone **1b**, (−)-*trans*-khellactone **1c** and rutaretin **4** have been developed.

During the biosynthesis of anellated coumarins, intermediates with epoxidized prenyl side-chains are formed. By the opening of their oxirane functions they cyclize to anellated coumarins with hydroxy groups in the new rings. The prenyl side-chain usually does not contain any other functional groups apart from the reacting double bond. Therefore for the biomimetic synthesis of those compounds the Sharpless epoxidation, which needs an OH-function in an allylic position,[3] is of no use. For this reason in the present work the applicability of the enantioselective *cis*-dihydroxylation method[4,5] has been investigated. This method does not need certain functional groups near the reacting double bond. It produces good chiral yields even with a simple prenyl side-chain.

Khellactone **1**, vaginidiol **2**, arnottianin **3** and rutaretin **4**



1a; (+)-*cis*(1*R*, 2*R*)
b; (−)-*cis*(1*S*, 2*S*)
c; (−)-*trans*(1*S*, 2*R*)



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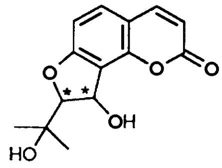
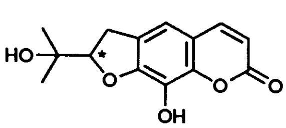


2a; (+)-*cis*(1*R*, 2*S*)
b; (−)-*cis*(1*S*, 2*R*)
c; 1,2-*trans*



4a; (−)-2*S*
b; (+)-2*R*

have been chosen as targets of synthesis because they represent coumarins with common hydroxylated dihydropyrano- and dihydrofurano-anellated ring systems, respectively.

Esterification of those molecules leads to a wide range of other natural coumarins. For example, the vasodilatory compounds of *Ammi visnaga*, samidine, dihydrosamidine and visnadine, can be derived from (+)-*cis*-khellactone **1a**.[6] For our studies we have chosen rare or non-natural enantiomers of compounds **1–4**, which possibly would show different biological activities than their better known enantiomers.

Results and Discussion

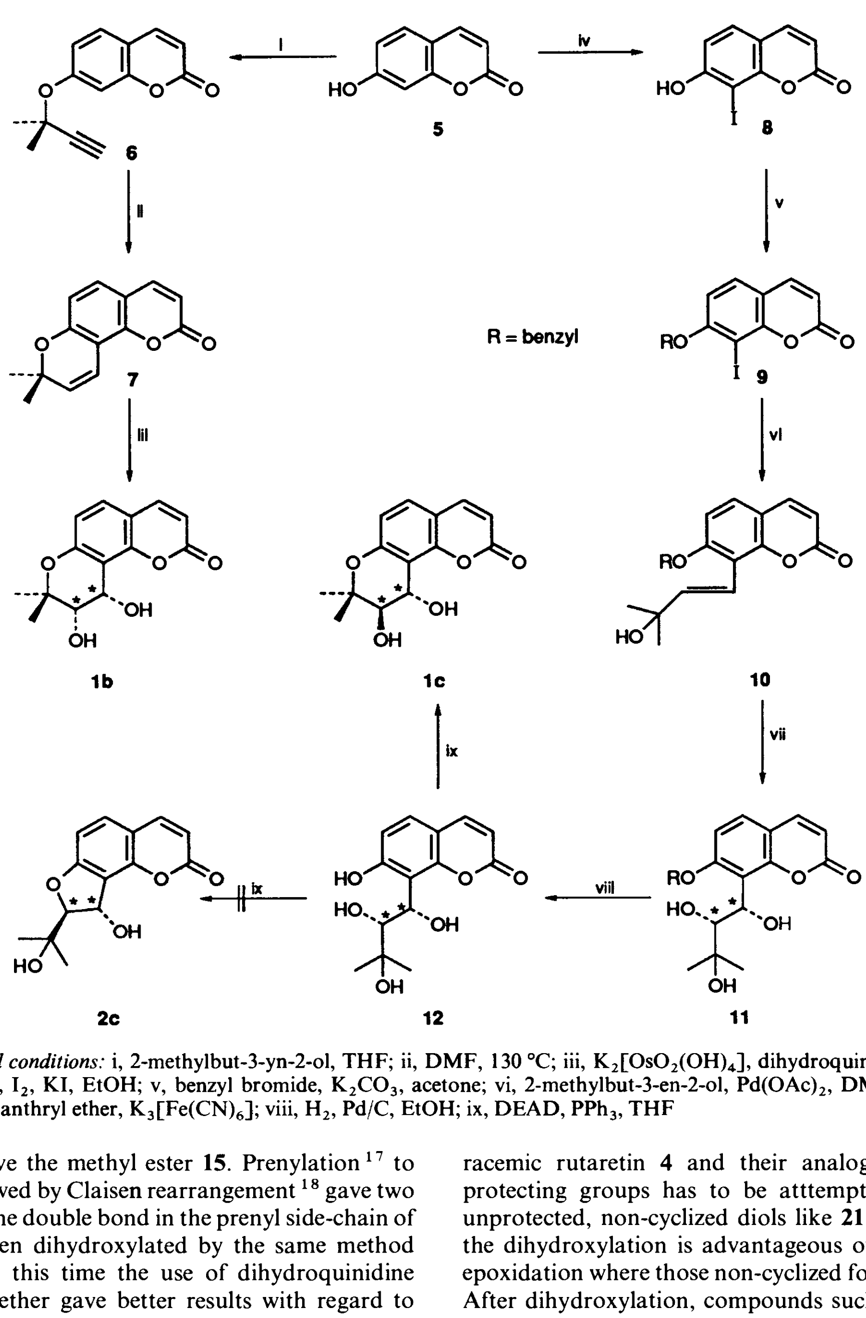
In 1992 (−)-*cis*-khellactone **1b** was isolated from *Peucedanum japonicum* Thunb. by Duh *et al.*[7] Its (+)-enantiomer **1a** had been found in *Sesili gummiferum* Pall. in 1971.[8] Our synthesis of (−)-*cis*-khellactone **1b** started from umbelliferone **5** (Scheme 1). The phenolic group of substrate **5** was alkynylated with 2-methylbut-3-yn-2-ol using Mitsunobu etherification.[9] By cyclization of the resulting ether **6** in dimethylformamide (DMF) the khellactone precursor, seseline **7**, was obtained. This compound was easily hydroxylated by enantioselective *cis*-dihydroxylation[4] to give (−)-*cis*-khellactone **1b** with an enantiomeric excess (e.e.) of 86%. Polarimetric analyses showed that in this case the use of dihydroquinidine 9-*O*-(4′-methyl-2′-quinolyl) ether as the chiral base gave better enantioselective results than did the use of dihydroquinidine 9-*O*-(9′-phenanthryl) ether.

(+)-Vaginidiol **2a** was found in *Selinum vaginatum* for the first time in 1971.[10] The chosen synthetic pathway to its non-natural enantiomers should lead only to the *trans*-dihydroxylated coumarin **2c** and not to its *cis*-isomer **2b**. This was due to the mechanism of the Heck reaction used, leading to a *trans*-substituted double bond in the side-chain of compound **10**. The subsequent *cis*-dihydroxylation of this double bond always forms a *threo*-diol **11** so that after ring closure the substituents of the new furanoid ring should be *trans* to one other.

To synthesize compound **2c**, umbelliferone **5** was iodinated[11] to give compound **8** and the phenolic group was protected by benzylation[12] in the first two steps. Subsequently the resulting iodide **9** was alkenylated by a phase-transfer-catalysed variation of the Heck reaction[13] to give product **10**, which was hydroxylated using the same method as for the synthesis of (−)-*cis*-khellactone **1b**. However, this time the yield was very low and it seems possible that the resulting triol **11** is able to inactivate the osmium catalyst by forming stable osmate esters and thereby to slow down the reaction. (Since compound **10** is an allylic alcohol, Sharpless epoxidation would probably give better results in this case.) Cleavage of the protecting group was easily achieved by hydrogenolysis, leading to tetraol **12**, which was cyclized under Mitsunobu conditions using triphenylphosphine and diethyl azodicarboxylate (DEAD).[9] Although both the pyrano, **1c**, and the furano derivative **2c** had been expected, only khellactone **1c** could be isolated from the reaction mixture. It seems that, under Mitsunobu etherification conditions, the formation of the six-membered ring is preferred. Optical-rotation measurements showed that (−)-*trans*-khellactone **1c** had been formed in 46% e.e.

(−)-Rutaretin **4a** was isolated from *Ruta graveolens* in 1967.[14] In glucosidated form it is one of the main components of this plant.[15] To synthesize its (+)-enantiomer **4b** a synthetic pathway had to be developed, that at the same time should lead to arnottianin **3**, a dihydropyranocoumarin. The results are shown in Scheme 2.

The synthesis started with daphnetine **13**, which reacted with dichlorodiphenylmethane to protect its phenolic OH groups.[16] The lactone ring of the resulting diphenyl ketal **14** was opened



Scheme 1 *Reagents and conditions:* i, 2-methylbut-3-yn-2-ol, THF; ii, DMF, 130 °C; iii, $K_2[OsO_2(OH)_4]$, dihydroquinidine 4-methyl-2-quinolyl ether, K_3 $[Fe(CN)_6]$; iv, I_2, KI, EtOH; v, benzyl bromide, K_2CO_3, acetone; vi, 2-methylbut-3-en-2-ol, $Pd(OAc)_2$, DMF; vii, $K_2[OsO_2(OH)_4]$, dihydroquinidine 9-phenanthryl ether, $K_3[Fe(CN)_6]$; viii, H_2, Pd/C, EtOH; ix, DEAD, PPh_3, THF

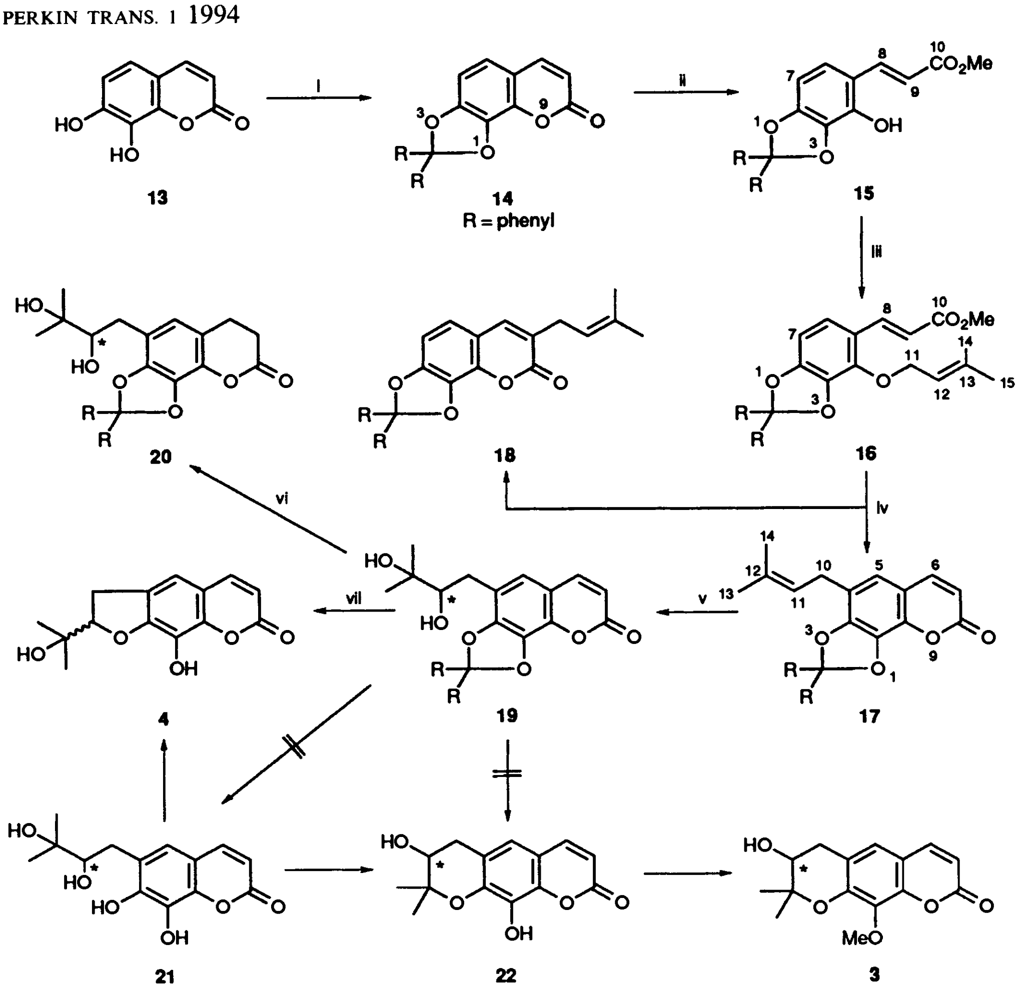
by methanolate to give the methyl ester **15**. Prenylation[17] to give the ether **16** followed by Claisen rearrangement[18] gave two products **17** and **18**. The double bond in the prenyl side-chain of compound **17** was then dihydroxylated by the same method described before, but this time the use of dihydroquinidine 9-*O*-(9′-phenanthryl) ether gave better results with regard to enantioselectivity. In the next step deprotection of the diol **19** should give the catechol **21** that should be cyclizable to give rutaretin **4** as well as demethylarnottianin **22**. However, hydrogenolysis led only to the reduced α-chromene system **20**. Therefore another method had to be applied to remove the diphenyl ketal group. The use of boron trichloride[19] to cleave the ether gave a good yield of rutaretin **4** at a temperature of −77 °C but not the expected catechol **21**, and owing to the Lewis-acid catalysis of the boron ion only the racemic form of compound **4** was obtained. The six-membered-ring form of demethylarnottianin **22** could not be isolated.

The experimental results show that enantioselective *cis*-dihydroxylation is a promising method for the synthesis of hydroxylated dihydropyrano- and dihydrofurano-anellated systems with chiral centres. Diols can be obtained in good yields and with a certain enantioselectivity, as measured optical rotations show. In the case of vaginidiol **2** and other dihydrofuranocoumarins another cyclization method must be applied to form the five-membered ring. It must guarantee an inversion during the nucleophilic attack of the carbon atom to prevent racemization. To synthesize arnottianin **3** or non-racemic rutaretin **4** and their analogues the use of other protecting groups has to be atttempted which will lead to unprotected, non-cyclized diols like **21** during cleavage. Here the dihydroxylation is advantageous over an enantioselective epoxidation where those non-cyclized forms would be unstable. After dihydroxylation, compounds such as **12** or **21** can then be transformed into either the six- or the five-membered ring systems, depending on the cyclization method used (the Mitsunobu reaction seems to prefer the dihydropyran system).

Experimental

UV (in MeOH) and IR (in KBr) spectra were recorded on a Shimadzu UV-160A and a Shimadzu IR-470 spectrophotometer respectively. The EI and HR mass spectra were recorded on Varian MAT-44S (70 eV) and Finnigan MAT-312 spectrometers. The ^1H and ^{13}C NMR spectra were run on a Varian Gemini-200 spectrometer operating at 200 and 50 MHz, respectively, with spectra referenced to tetramethylsilane signals. The chemical shifts are in ppm (δ) and coupling constants (*J*) are in Hz. $[\alpha]_D$ Values, measured at 25 °C, are given in 10^{-1} deg cm^2 g^{-1}, concentrations of the solutions used for optical measurements in mg cm^{-3}. The purity of compounds was checked on silica gel GF_{254}-coated plates. Light petroleum refers to the fraction boiling in the range 66–70 °C.

Synthesis of Seseline **7**.—To a solution of umbelliferone **5**



Scheme 2 *Reagents and conditions:* i, dichlorodiphenylmethane, 160 °C; ii, NaOMe, MeOH, reflux; iii, 1-bromo-3-methylbut-2-ene K_2CO_3, acetone; iv, *N,N*-diethylaniline, 180 °C; v, $K_2[OsO_2(OH)_4]$, dihydroquinidine 9-phenanthryl ether, $K_3[Fe(CN)_6]$; vi, H_2, Pd/C, EtOH; vii, BCl_3, CH_2Cl_2, −76 °C

(648 mg, 4 mmol), triphenylphosphine (1.57 g, 6 mmol) and DEAD (1.06 g, 6 mmol) in dried tetrahydrofuran (THF) (50 cm^3) was added 2-methylbut-3-yn-2-ol (504 mg, 6 mmol) and the mixture was stirred at room temperature under nitrogen for 10 h. The solvent was evaporated off and the residue was heated to 130 °C in DMF (50 cm^3) under nitrogen for 5 h. Subsequent purification by column chromatography on silica gel with chloroform as eluent yielded seseline **7** (349 mg, 38%), m.p. 117.5 °C (lit.,[20] 119–120 °C) (Found: C, 73.8; H, 5.2. $C_{14}H_{12}O_3$ requires C, 73.68; H, 5.26%); ν_{max}/cm^{-1} 1721 (C=O), 1627 (C=C, α,β-unsaturated ketone), 1595 (arom. C=C), 1457 and 1380 (C–H), 1259 (C–O) 833 (2 vic. arom. H); λ_{max}/nm 329.2, 292.4 and 216.8; $\delta_H(CDCl_3)$ 1.48 (6 H, s, 11- and 12-H_3), 5.73 (1 H, d, $J_{2,1}$ 10.2, 2-H), 6.23 (1 H, d, $J_{8,7}$ 9.5, 8-H), 6.72 (1 H, d, $J_{5,6}$ 8.5, 5-H), 6.88 (1 H, d, $J_{1,2}$ 10.2, 1-H), 7.21 (1 H, d, $J_{6,5}$ 8.5, 6-H) and 7.60 (1 H, d, $J_{7,8}$ 9.5, 7-H); $\delta_C(CDCl_3)$ 28.18 (C-11, -12), 75.26 (C-3), 109.35 (C-6a), 112.66 (C-5), 113.57 (C-10b), 113.80 (C-8), 115.05 (C-2), 127.82 (C-1), 130.80 (C-6), 143.94 (C-7), 150.18 (C-10a), 156.38 (C-4a) and 161.03 (C-9); *m/z* 228 (24%, M^+), 213 (100, $M^+ - CH_3$), 185 (14, 213 − CO), 157 (9, 185 − CO), 128 (26), 86 (16) and 51 (20).

Enantioselective Synthesis of (−)-cis-*Khellactone* **1b**.—To a suspension of dihydroquinidine 9-*O*-(4′-methyl-2′-quinolyl) ether (117 mg, 0.25 mmol), $K_3[Fe(CN)_6]$ (990 mg, 3 mmol) and sodium carbonate (415 mg, 3 mmol) in water–*tert*-butyl alcohol (1:1; 15 cm^3) was added $K_2[OsO_2(OH)_4]$ (6.78 mg, 18 μmol). The reaction mixture was stirred at room temperature for 10 min, followed by addition of seseline **7** (228 mg, 1 mmol). After stirring of the mixture for 48 h, aq. $Na_2SO_3{\cdot}7H_2O$ (770 mg, 3 mmol in 10 cm^3) was added and the mixture was extracted successively with dichloromethane and ethyl acetate. The dried organic layers were evaporated and a residue (230 mg) was obtained. Purification by column chromatography gave (−)-*cis*-khellactone **1b** (162 mg, 62%), m.p. 165.0 °C [lit.,[8] 174.5–175 °C (pure enantiomer)] (Found: C, 64.0; H, 5.1. $C_{14}H_{14}O_5$ requires C, 64.12; H, 5.34%); $[\alpha]_D$ −70.6 (*c* 0.98, $CHCl_3$); ν_{max}/cm^{-1} 3425 (O–H), 1715 (C=O), 1602 and 1561 (arom. C=C), 1403 (O–H), 1365 (C–H), 1114 (C–OH) and 841 (2 vic. arom. H); λ_{max}/nm 325.8, 257.2 and 205.2; $\delta_H(CDCl_3)$, 1.41 (3 H, s, 11-H), 1.46 (3 H, s, 12-H_3), 3.31 (1 H, d, $J_{2\text{-OH},2}$ 5.9, 2-OH), 3.87 (1 H, dd, $J_{2,2\text{-OH}}$ 6.0, $J_{2,1}$ 5.9, 2-H), 4.30 (1 H, d, $J_{1\text{-OH},1}$ 4.3, 1-OH), 5.22 (1 H, dd, $J_{1,2}$ 5.4, $J_{1,1\text{-OH}}$ 4.3, 1-H), 6.26 (1 H, d, $J_{8,7}$ 9.5, 8-H), 6.80 (1 H, d, $J_{5,6}$ 8.7, 5-H), 7.33 (1 H, d, $J_{6,5}$ 8.7, 6-H) and 7.67 (1 H, d, $J_{7,8}$ 9.5, 7-H); $\delta_C(CDCl_3)$ 21.80 (C-11), 24.96 (C-12), 61.35 (C-2), 70.98 (C-1), 79.02 (C-3), 110.70 (C-6a), 112.20 (C-5), 112.36 (C-10b), 114.90 (C-8), 128.65 (C-6), 144.25 (C-7), 154.68 (C-10a), 156.48 (C-4a) and 160.81 (C-9); *m/z* 262 (12%, M^+), 213 (7), 191 (100), 162 (17), 134 (17), 91 (16), 72 (38) and 57 (69).

Synthesis of 8-*Iodoumbelliferone* **8**.—8-Iodoumbelliferone **8** was prepared as described in ref. 11.

Benzylation of 8-*Iodoumbelliferone* **8**.—To a solution of compound **8** (2.10 g, 7.5 mmol) in acetone (100 cm^3) were added sodium carbonate (9.66 g, 75.0 mmol) and benzyl bromide (12.83 g, 75.0 mmol). After 8 h under reflux the reaction mixture was filtered, the solvent was evaporated off, and the residue was crystallized from toluene–light petroleum to give *compound* **9** (2.65 g, 93.5%), m.p. 169.0–169.5 °C (Found: C, 50.9; H, 3.0; I, 33.2. $C_{16}H_{11}IO_3$ requires C, 50.81; H, 2.91; I, 33.58%); ν_{max}/cm^{-1} 1715 (C=O), 1599 and 1543 (arom. C=C), 1238 (C–OC), 1058 (arom. C–I) and 822 (2 vic. arom. H); λ_{max}/nm 316.8, 263.6 and 207.2; $\delta_H(CDCl_3)$ 5.26 (2 H, s, PhCH_2), 6.24 (1 H, d, $J_{3,4}$ 9.5, 3-H), 6.82 (1 H, d, $J_{6,5}$ 8.6, 6-H), 7.38 (1 H, d, $J_{5,6}$ 8.6, 5-H), 7.39 (5 H, m, Ph) and 7.55 (1 H, d, $J_{4,3}$ 9.5, 4-H); $\delta_C(CDCl_3)$ 71.42 (PhCH$_2$), 76.80 (C-8), 108.99 (C-6), 113.85 (C-4a), 113.99 (C-3), 126.87 (Ph C-*m*), 128.21 (Ph C-*o*), 128.65 (Ph C-*p*), 128.98 (C-5), 134.09 (Ph-C-*i*) 143.02 (C-4), 155.08 (C-8a), 160.41 (C-2) and 160.71 (C-7); *m/z* 378 (6%, M$^+$), 251 (4, M$^+$ – I), 91 (100), 76 (4), 65 (8) and 57 (5).

Vinylation of 7-Benzyloxy-8-iodocoumarin **9**.—Compound **9** (1.51 g, 4 mmol), 2-methylbut-3-en-2-ol (2.58 g, 30 mmol), tetrabutylammonium bromide (4.36 g, 13.50 mmol), sodium carbonate (1.13 g, 13.50 mmol) and Pd(OAc)$_2$ (89.8 mg, 0.40 mmol) were added to DMF (20 cm^3). The reaction mixture was heated to 90 °C under nitrogen for 48 h. After filtration, and evaporation of the solvent, the residue was purified by column chromatography with toluene–ethyl acetate (1:1). *Compound* **10** was obtained (786 mg, 58.5%), m.p. 157.5–158.5 °C (Found: C, 74.7; H, 5.7. $C_{21}H_{20}O_4$ requires C, 75.00; H, 5.95%); ν_{max}/cm^{-1} 3445 (O–H), 1690 (C=O), 1600, 1555 and 1513 (arom. C=C), 1450 and 1360 (C–H), 1297 (O–H), 1128 (C–OH), 827 (2 vic. arom. H) and 750 and 715 (5 vic. arom. H); λ_{max}/nm 385.4, 320.4, 282.0, 253.4 and 211.8; $\delta_H(CDCl_3)$ 1.41 (6 H, s, 12- and 13-H$_3$), 1.88 (1 H, s, 11-OH), 5.21 (2 H, s, PhCH_2), 6.26 (1 H, d, $J_{3,4}$ 9.5, 3-H), 6.76 (1 H, d, $J_{10,9}$ 16.97, 10-H), 6.87 (1 H, d, $J_{9,10}$ 16.97, 9-H), 6.93 (1 H, d, $J_{6,5}$ 8.7, 6-H), 7.27 (1 H, d, $J_{5,6}$ 8.7, 5-H), 7.40 (5 H, m, Ph) and 7.61 (1 H, d, $J_{4,3}$ 9.5, 4-H); $\delta_C(CDCl_3)$ 29.84 (C-12, -13), 71.09 (PhCH$_2$), 71.57 (C-8), 109.19 (C-6), 113.18 (C-4a), 113.30 (C-3), 114.28 (C-10), 114.37 (C-11), 126.89 (Ph C-*m*), 127.23 (C-5), 128.25 (Ph C-*o*), 129.03 (Ph C-*p*), 136.10 (Ph C-*i*), 143.77 (C-9), 144.92 (C-4), 152.71 (C-8a), 159.28 (C-7) and 160.86 (C-2); *m/z* 336 (3%, M$^+$), 278 (2, M$^+$ – Me$_2$CO), 228 (6, M$^+$ – C$_6$H$_5$CH$_2$OH), 213 (64), 187 (23), 131 (12), 91 (100) and 65 (52).

Enantioselective cis-*Dihydroxylation of Compound* **10**.—Compound **10** (336 mg, 1 mmol) was treated exactly as described for the synthesis of (–)-*cis*-khellactone **1b** except that dihydroquinidine 9-*O*-(9′-phenanthryl) ether was used as the chiral base. Work-up of the reaction mixture gave compound **11** (107.4 mg, 29.2%), m.p. 145.0–146.0 °C; $[\alpha]_D$ –22.1 (*c* 0.95, CHCl$_3$); ν_{max}/cm^{-1} 3445 (O–H), 1767 (s, C=O), 1455 and 1381 (C–H), 1327 (O–H), 1117 (C–OH), 849 (2 vic. arom. H) and 777 and 710 (5 vic. arom. H); λ_{max}/nm 321.2, 257.6 and 207.0; $\delta_H(CDCl_3)$ 1.19 (3 H, s, 12-H$_3$), 1.36 (3 H, s, 13-H$_3$), 3.23 (1 H, s, 10-OH), 3.54 (1 H, d, $J_{10,9}$ 2.4, 10-H), 4.64 (1 H, s, 9-OH), 5.19 (2 H, s, PhCH_2), 5.69 (1 H, d, $J_{9,10}$ 2.43, 9-H), 6.25 (1 H, d, $J_{3,4}$ 9.5, 3-H), 6.94 (1 H, d, $J_{6,5}$ 8.7, 6-H), 7.37 (1 H, d, $J_{5,6}$ 8.7, 5-H), 7.41 (5 H, m, Ph) and 7.63 (1 H, d, $J_{4,3}$ 9.5, 4-H); $\delta_C(CDCl_3)$ 26.28 (C-12), 26.47 (C-13), 68.84 (C-10), 71.72 (PhCH$_2$), 73.46 (C-11), 78.37 (C-9), 109.46 (C-6), 113.48 (C-3), 113.55 (C-4a), 117.36 (C-8), 127.67 (Ph C-*m*), 128.20 (Ph C-*o*), 128.76 (Ph C-*p*), 128.97 (C-5), 135.34 (Ph C-*i*), 143.79 (C-4), 152.88 (C-8a), 159.54 (C-7) and 160.06 (C-2); *m/z* 370 (4%, M$^+$), 312 (7, M$^+$ –Me$_2$CO), 279 (46, M$^+$ – C$_6$H$_5$CH$_2$), 234 (12), 189 (23), 153 (23), 91 (100), 77 (57) and 55 (34).

Cleavage of the Protecting Benzyl Group by Hydrogenolysis.—Compound **11** (100 mg, 0.27 mmol) was dissolved in ethanol (5 cm^3), the solution was acidified by 4 drops of glacial acid, and catalyst (10% Pd on activated charcoal) (20 mg) was added. Hydrogenolysis was carried out at room temperature until hydrogen (6 cm^3, ~0.27 mmol) had been used. The catalyst was removed by filtration over silica gel and the reaction product was purified by TLC to give *compound* **12** (70.1 mg, 92.7%), m.p. 184.5–185.0 °C (Found: C, 60.4; H, 6.0;. $C_{14}H_{16}O_6$ requires C, 60.00; H, 5.71%); $[\alpha]_D$ –36.7 (*c* 0.97, CHCl$_3$); ν_{max}/cm^{-1} 3425 (O–H), 1699 (C=O), 1598, 1573 and 1541 (arom. C=C), 1447 (C–H), 1390 (O–H) and 835 (2 vic. arom. H); λ_{max}/nm 331.8, 273.8 and 205.6; δ_H([^{2}H$_6$]acetone) 1.35 (3 H, s, 12-H$_3$), 1.49 (3 H, s, 13-H$_3$), 3.60 (1 H, s, 10-H), 6.13 (1 H, d, $J_{3,4}$ 9.5, 3-H), 6.61 (1 H, d, $J_{6,5}$ 8.5, 6-H), 7.40 (1 H, d, $J_{5,6}$ 8.5, 5-H) and 7.84 (1 H, d, $J_{4,3}$ 9.5, 4-H); δ_C([^{2}H$_6$]acetone) 27.14 (C-12), 27.40 (C-13), 70.85 (C-10), 75.14 (C-11), 78.34 (C-9), 111.73 (C-6), 111.93 (C-3), 116.98 (C-4a), 117.75 (C-8), 128.95 (C-5), 145.34 (C-4), 153.04 (C-8a), 160.83 (C-7) and 163.34 (C-2); *m/z* 280 (7%, M$^+$), 263 (9, M$^+$ – OH), 205 (34, 263 – Me$_2$CO), 191 [100, M$^+$ – Me$_2$C(OH)CH(OH)], 176 (70, 205 – COH), 147 (20, 176 – COH), 134 (14), 107 (24), 91 (33) 72 (54) and 59 (77).

Cyclization of Tetraol **12**: *Synthesis of* (–)-trans-*Khellactone* **1c**.—Compound **12** (60 mg, 0.2 mmol) was treated as described under synthesis of seseline **7** except that a triple amount of solvent was used to prevent intermolecular etherification. No heating in DMF was carried out. After evaporation of the solvent the residue was purified by column chromatography to give (–)-trans-*khellactone* **1c** instead of *trans*-vaginidiol **2c** (8.3 mg, 15%), m.p. 158.5–161.0 °C (Found: C, 64.2; H, 5.45. $C_{14}H_{14}O_5$ requires C, 64.12; H, 5.34%); $[\alpha]_D$ –8.3 (*c* 0.67, CHCl$_3$).

Protection of the Phenolic Groups in Daphnetine **13**.—A mixture of compound **13** (5.34 g, 30 mmol) and dichlorodiphenylmethane (7.11 g, 30 mmol) was heated to 160 °C for 10 min. After cooling of the mixture to 80 °C, toluene (150 cm^3) was added, the suspension was filtered, and the residue was washed thoroughly with warm toluene. While the residue was kept the combined organic layers were evaporated to a volume of 100 cm^3 and the product **14** was precipitated by addition of light petroleum. After filtration the combined residues were crystallized from toluene–light petroleum to give ketal **14** (9.05 g, 88.2%), m.p. 199.5–200.0 °C (Found: C, 76.9; H, 4.2. $C_{22}H_{14}O_4$ requires C, 77.19; H, 4.09%); ν_{max}/cm^{-1} 1724 (C=O), 1631 (C=C, α,β-unsaturated ketone), 1601, 1565 and 1514 (arom. C=C), 1268 and 1045 (C–OC), 845 (2 vic. arom. H) and 768 and 693 (5 vic. arom. H); λ_{max}/nm 317.4, 264.0 and 206.4; $\delta_H(CDCl_3)$ 6.23 (1 H, d, $J_{7,6}$ 9.6, 7-H), 6.86 (1 H, d, $J_{4,5}$ 8.2, 4-H), 6.99 (1 H, d, $J_{5,4}$ 8.2, 5-H), 7.39 (6 H, m, Ph), 7.59 (1 H, d, $J_{6,7}$ 9.6, 6-H) and 7.61 (4 H, m, Ph); $\delta_C(CDCl_3)$ 105.71 (C-4), 113.50 (C-7), 115.12 (C-5a), 119.66 (C-2), 121.83 (C-5), 126.18 (Ph C-*m*), 128.69 (Ph C-*o*), 129.45 (Ph C-*p*), 133.48 (C-9b), 139.36 (Ph C-*i*), 143.67 (C-9a), 143.87 (C-6), 150.87 (C-3a) and 159.79 (C-8); *m/z* 342 (26%, M$^+$), 265 (68, M$^+$ – C$_6$H$_5$), 237 (12, 265 – CO), 181 (4), 165 (48), 105 (100), 77 (52) and 51 (23).

Synthesis of the Methyl Ester **15**.—Sodium (4.6 g, 200 mmol) was dissolved in dried methanol (150 cm^3), the solution was filtered, and lactone **14** (6.84 g, 20 mmol) was added. The solution was heated under reflux and the formation of the methyl ester **15** was measured by TLC. When the reaction was complete the solution was evaporated to half of its volume, ice (400 cm^3) was added and the mixture was acidified to pH 4 with dil. hydrochloric acid. The precipitated product was filtered immediately to give clean *ester* **15** (6.90 g, 92.2%), m.p. 179.5–180.0 °C (Found: C, 74.0; H, 5.0. $C_{23}H_{18}O_5$ requires C, 73.80; H, 4.81%); ν_{max}/cm^{-1} 3340 (O–H), 1676 (C=O), 1614 (arom. C=C), 1446 and 1370 (C–H), 1266 (C–OC), 798 (2 vic. arom. H) and 760 and 698 (5 vic. arom. H); λ_{max}/nm 313.8, 250.4 and

204.8; δ_H($CDCl_3$) 3.77 (3 H, s, CO_2Me), 3.89 (1 H, s, 4-OH), 6.51 (1 H, d, $J_{2,3}$ 16.1, 2-H), 6.50 (1 H, d, $J_{7,6}$ 8.3, 7-H), 7.02 (1 H, d, $J_{6,7}$ 8.3, 6-H), 7.38 (6 H, m, Ph), 7.58 (4 H, m, Ph) and 7.88 (1 H, d, $J_{3,2}$ 16.1, 3-H); δ_C($CDCl_3$) 51.67 (OMe), 101.67 (C-7), 115.81 (C-9), 118.66 (C-5), 123.86 (C-6), 126.42 (C-2), 126.60 (Ph C-*m*), 128.49 (Ph C-*o*), 129.49 (Ph C-*p*), 135.72 (C-3a), 140.16 (C-4), 140.83 (Ph C-*i*), 141.58 (C-8), 150.00 (C-7a) and 169.38 (C-10); *m*/*z* 374 (15%, M^+), 343 (6, $M^+ - OCH_3$), 315 (6, 343 − CO), 265 (39, 343 − C_6H_6), 237 (10, 265 − CO), 165 (43), 105 (100), 77 (47) and 51 (17).

Prenylation of the Methyl Ester **15**.—A mixture of the phenol **15** (5.61 g, 15 mmol), sodium carbonate (8.40 g, 60 mmol) and 1-bromo-3-methylbut-2-ene (2.98 g, 20 mmol) in dried acetone (250 cm^3) was refluxed under TLC control. When the reaction was complete the mixture was filtered, the solvent was evaporated off, and the residue was dissolved in ethyl acetate. The solution was washed successively with brine, saturated aq. sodium hydrogen carbonate, and brine, and then was evaporated to dryness. Purification of the residue by column chromatography with toluene yielded *compound* **16** (5.22 g, 78.7%), m.p. 71.0–72.0 °C (Found: C, 76.3; H, 5.9. $C_{28}H_{26}O_5$ requires C, 76.02; H, 5.88%); ν_{max}/cm^{-1} 1709 (C=O), 1613 and 1585 (arom. C=C), 1471 (C–H), 1264 and 1045 (C–OC), 799 (2 vic. arom. H), 779 (R_2C=CHR) and 699 (5 vic. arom. H); λ_{max}/nm 312.6, 251.0, 215.7 and 204.0; δ_H($CDCl_3$) 1.66 (3 H, s, 15-H_3), 1.74 (3 H, s, 14-H_3), 3.77 (3 H, s, OMe), 4.84 (2 H, d, $J_{11,12}$ 7.0, 11-H_2), 5.51 (1 H, t, $J_{12,11}$ 7.0, 12-H), 6.40 (1 H, d, $J_{9,8}$ 16.1, 9-H), 6.61 (1 H, d, $J_{7,6}$ 8.3, 7-H), 7.06 (1 H, d, $J_{6,7}$ 8.3, 6-H), 7.38 (6 H, m, Ph), 7.57 (4 H, m, Ph) and 7.88 (1 H, d, $J_{8,9}$ 16.1, 8-H); δ_C($CDCl_3$) 18.10 (C-15), 25.72 (C-14), 51.43 (OMe), 68.94 (C-11), 103.43 (C-7), 116.44 (C-9), 117.78 (C-5), 119.96 (C-12), 121.79 (C-2), 122.76 (C-6), 126.32 (Ph C-*m*), 128.31 (Ph C-*o*), 129.29 (Ph C-*p*), 137.10 (C-3a), 139.11 (C-13), 139.84 (C-4), 140.54 (C-8), 141.74 (Ph C-*i*), 150.47 (C-7a) and 168.09 (C-10); *m*/*z* 442 (1%, M^+), 374 (18, $M^+ - C_5H_8$), 343 (4, 374 − OCH_3), 315 (7, 343 − CO), 265 (36, 343 − C_6H_6), 237 (13, 265 − CO), 165 (41), 131 (7), 105 (100), 77 (36), 69 (47) and 55 (19).

Claisen Rearrangement of Compound **16**.—Compound **16** (4.42 g, 10 mmol) was dissolved in *N*,*N*-diethylaniline (50 cm^3) and the solution was heated to 180 °C for 5 h. Subsequently the cooled solution was diluted with ethyl acetate (250 cm^3) and washed successively with 1 mol dm^{-3} hydrochloric acid and brine. After evaporation of the organic solvent, raw product (3.91 g) was obtained. This was purified by column chromatography with toluene to give lactone **17** (2.96 g, 72.1%), m.p. 122.5–123.0 °C (Found: C, 79.2; H, 5.4. $C_{27}H_{22}O_4$ requires C, 79.02; H, 5.37%); ν_{max}/cm^{-1} 1727 (C=O), 1641 (C=C, α,β-unsaturated ketone), 1608 and 1585 (arom. C=C), 1449 (C–H), 1271 and 1087 (C–OC), 819 (2 vic. arom. H) and 758 and 721 (5 vic. arom. H); λ_{max}/nm 323.8, 263.4 and 207.8; δ_H($CDCl_3$) 1.77 (3 H, s, 14-H_3), 1.78 (3 H, d, $J_{13,11}$ 1.1, 13-H_3), 3.38 (1 H, d, $J_{10,11}$ 7.4, 10-H), 5.31 (1 H, tq, $J_{11,10}$ 7.4, $J_{11,13}$ 1.1, 11-H), 6.19 (1 H, d, $J_{7,6}$ 9.5, 7-H), 6.79 (1 H, s, 5-H), 7.39 (6 H, m, Ph) and 7.60 (5 H, m, Ph, 6-H); δ_C($CDCl_3$) 17.92 (C-14), 25.77 (C-13), 27.81 (C-10), 113.25 (C-7), 114.84 (C-5a), 119.32 (C-4), 120.76 (C-11), 121.46 (C-5), 126.18 (Ph C-*m*), 126.42 (C-2), 128.24 (Ph C-*o*), 129.04 (Ph C-*p*), 132.82 (C-9b), 133.97 (Ph C-*i*), 136.83 (C-12), 139.63 (C-9a), 144.04 (C-6), 149.02 (C-3a) and 160.13 (C-8); *m*/*z* 410 (21%, M^+), 355 (11, M^+ − CH=CMe_2), 333 (13, $M^+ - C_6H_5$), 228 (13, 333 − C_6H_5CO), 213 (10), 167 (73), 128 (15), 105 (100), 91 (12), 77 (61) and 51 (31).

Compound **18**, a regioisomer of compound **17**, was also obtained (393.6 mg, 9.6%), m.p. 135.0–135.5 °C (Found: C, 79.3; H, 5.5%); ν_{max}/cm^{-1} 1725 (C=O), 1636 (C=C), 1598 and 1574 (arom. C=C), 1448, 1385 (C–H), 1275 (C–OC), 809 (2 vic. arom. H) and 752 and 699 (5 vic. arom. H); λ_{max}/nm 318.6, 264.2 and 207.2; δ_H($CDCl_3$) 1.67 (3 H, s, 14-H_3), 1.79 (3 H, d, $J_{13,11}$ 0.9, 13-H_3), 3.21 (1 H, d, $J_{10,11}$ 7.2, 10-H), 5.28 (1 H, m, 11-H), 6.83 (1 H, d, $J_{4,5}$ 8.2, 4-H), 6.93 (1 H, d, $J_{5,4}$ 8.2, 5-H), 7.38 (7 H, m, Ph, 6-H) and 7.58 (4 H, m, Ph); δ_C($CDCl_3$) 17.81 (C-14), 25.77 (C-13), 29.88 (C-10), 105.53 (C-4), 115.90 (C-5a), 119.25 (C-7), 119.37 (C-11), 120.83 (C-5), 125.75 (C-2), 126.12 (Ph C-*m*), 128.27 (Ph C-*o*), 129.36 (Ph C-*p*), 132.38 (C-9b), 135.51 (Ph C-*i*), 137.27 (C-12), 138.56 (C-6), 139.52 (C-9a), 149.76 (C-3a) and 160.98 (C-8); *m*/*z* 410 (9%, M^+), 395 (1, $M^+ - CH_3$), 355 (9), 333 (14, $M^+ - C_6H_5$), 165 (44), 149 (10), 105 (100), 77 (33) and 55 (12).

Enantioselective cis-*Dihydroxylation of Compound* **17**.—According to the synthesis of (−)-*cis*-khellactone **1b** the reaction was carried out with the chiral base dihydroquinidine 9-*O*-(9′-phenanthryl) ether. Work-up of the reaction mixture gave diol **19** (1.22 g, 55.0%), m.p. 185.0–186.0 °C; $[\alpha]_D$ +45.8 (*c* 1.08, $CHCl_3$); ν_{max}/cm^{-1} 3435 (O–H), 1724 (C=O), 1611 and 1586 (arom. C=C), 1448 and 1381 (C–H), 1314 (O–H), 1144 (C–OH) and 778 and 699 (5 vic. arom. H); λ_{max}/nm 324.0, 263.4 and 209.0; δ_H($CDCl_3$) 1.29 (3 H, s, 14-H_3), 1.34 (3 H, s, 13-H_3), 2.41 (1 H, s, 12-OH), 2.64 (1 H, dd, $J_{11,10A}$ 14.1, $J_{11,10B}$ 10.5, 11-H), 2.71 (1 H, s, 11-OH), 2.97 (1 H, dd, $J_{10A,11}$ 14.1, $J_{10A,10B}$ 2.0, 10-H^A), 3.72 (1 H, dd, $J_{10B,11}$ 10.5, $J_{10B,10A}$ 2.0, 10-H^B), 5.93 (1 H, d, $J_{7,6}$ 9.6, 7-H), 6.90 (1 H, s, 5-H), 7.35 (7 H, m, Ph, 6-H) and 7.61 (4 H, m, Ph); δ_C($CDCl_3$) 23.73 (C-14), 26.47 (C-13), 31.92 (C-10), 72.79 (C-12), 77.70 (C-11), 113.28 (C-7), 114.88 (C-5a), 118.15 (C-4), 123.03 (C-5), 126.14 (Ph C-*m*), 126.22 (C-2), 128.44 (Ph C-*o*), 129.53 (Ph C-*p*), 132.88 (C-9b), 133.98 (Ph C-*i*), 139.45 (C-9a), 149.35 (C-3a) and 160.03 (C-8); *m*/*z* 444 (10%, M^+), 385 (15, $M^+ - Me_2COH$), 355 (7, 385 −CHOH), 279 (4, $M^+ - Ph_2C$ + H), 251 (2, 279 − CO), 167 (100), 105 (84), 77 (51) and 59 (84).

Attempt to Cleave the Protecting Diphenyl Ketal Group by Hydrogenolysis.—Compound **19** (100 mg, 1.1 mmol) was treated according to the method of cleavage of the protecting benzyl group in compound **11**. The reaction was worked up when no more hydrogen was used. TLC of the residue gave compound **20** (82.5 mg, 82.1%), m.p. 180.0 °C; ν_{max}/cm^{-1} 3420 (O–H), 1701 (C=O), 1603 and 1559 (arom. C=C), 1453 and 1378 (C–H), 1248 (O–H), 1125 (C–OH) and 841 (single arom. H); λ_{max}/nm 207.6; δ_H($CDCl_3$) 1.26 (3 H, s, 13-H_3), 1.30 (3 H, s, 14-H_3), 2.44 (1 H, s, 12-OH), 2.56 (1 H, dd, $J_{11,10A}$ 14.0, $J_{11,10B}$ 10.4, 11-H), 2.76 (5 H, m, 10-H^A, 6- and 7-H_2), 3.68 (1 H, dd, $J_{10B,11}$ 10.4, $J_{10B,10A}$ 2.3, 10-H^B), 6.54 (1 H, s, 5-H), 7.33 (6 H, m, Ph) and 7.51 (4 H, m, Ph); δ_C($CDCl_3$) 23.73 (C-14), 26.47 (C-13), 29.59 (C-6), 32.07 (C-10), 76.47 (C-12), 77.11 (C-11), 78.00 (C-7), 116.34 (C-5a), 117.41 (C-4), 118.43 (C-2), 121.39 (C-5), 126.24 (Ph C-*m*), 128.36 (Ph C-*o*), 129.77 (Ph C-*p*), 133.80 (C-9b), 134.64 (Ph C-*i*), 139.90 (C-9a), 146.18 (C-3a) and 167.63 (C-8); *m*/*z* 446 (4%, M^+), 387 (6, $M^+ - Me_2COH$), 357 (6, 387 − CHOH), 193 (11), 167 (100), 105 (76), 91 (13), 77 (40) and 59 (52).

Cleavage of the Protecting Diphenyl Ketal Group by Boron Trichloride: Synthesis of (±)-*Rutaretin* **4**.—To a solution of compound **19** (500 mg, 1.13 mmol) in dichloromethane (20 cm^3) at a temperature of −77 °C was added boron trichloride (4.5 cm^3, 4.5 mmol; 1 mol dm^{-3} in dichloromethane). The solution was stirred for 20 min and warmed to room temperature over this period. After addition of 10% aq. KOH (7.7 cm^3, 13.5 mmol) and subsequent acidification with hydrochloric acid (10%) the mixture was diluted with water (20 cm^3) and the organic layer was separated. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate. The solvent was evaporated off and the residue was purified by column chromatography to give *compound* **4** (136.7 mg, 40.1%), m.p. 167.0–168.0 °C [lit.,[14] 192–193 °C (pure enantiomer)] (Found: C, 64.4; H, 5.4. $C_{14}H_{14}O_5$ requires C, 64.12; H, 5.34%); $[\alpha]_D$ 0.0 (*c* 0.95, $CHCl_3$); ν_{max}/cm^{-1} 3410 (O–H), 1699 (C=O), 1610 and 1584 (arom. C=C), 1449 and 1380 (C–H), 1419 (O–H) and 1080 (C–OH); λ_{max}/nm 333.6, 265.0 and 211.4; $\delta_H(CDCl_3)$ 1.27 (3 H, s, 11-H_3), 1.45 (3 H, s, 12-H_3), 3.25 (2 H, m, 3-H_2), 4.80 (1 H, dd, $J_{2,3A}$ 9.3, $J_{2,3B}$ 8.3, 2-H), 6.14 (1 H, d, $J_{6,5}$ 9.6, 6-H), 6.73 (1 H, s, 4-H), and 7.50 (1 H, d, $J_{5,6}$ 9.6, 5-H); $\delta_C(CDCl_3)$ 24.05 (C-11), 25.01 (C-12), 30.55 (C-3), 68.96 (C-10), 72.35 (C-2), 113.15 (C-6), 116.39 (C-4a), 118.46 (C-3a), 125.30 (C-4), 132.21 (C-9), 142.85 (C-8a), 144.48 (C-5), 150.53 (C-9a) and 161.38 (C-7); *m/z* 262 (27%, M^+), 229 (12), 204 (70, $M^+ - Me_2CO$), 203 (85, $M^+ - Me_2COH$), 191 (32), 176 (37, 204 − CO), 175 (14, 203 − CO), 147 (24, 176 − CO), 91 (37), 77 (26) and 59 (100).

References

1 Part 180, J. Reisch and K. Schiwek, *Liebigs Ann. Chem.*, 1994, 317.
2 A. A. W. Voerste, part of Ph. D. Thesis, University of Münster, 1994.
3 D. Schinzer, *Nachr. Chem., Tech. Lab.*, 1989, **37**, 1294.
4 S. G. Hentges and K. B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 4236.
5 W. A. Herrmann and S. J. Eder, *Chem. Ber.*, 1993, **126**, 31.
6 H. D. Schröder, W. Bencze, O. Halpern and H. Schmid, *Chem. Ber.*, 1959, **92**, 2338.
7 Ch.-Y. Duh, S.-K. Wang and Y.-Ch. Wu, *Phytochemistry*, 1992, **31**, 1829.
8 B. E. Nielsen, P. K. Larsen and J. Lemmich, *Acta Chem. Scand.*, 1971, **25**, 529.
9 O. Mitsunobu, *Synthesis*, 1981, 1.
10 T. R. Seshadri, M. S. Sood, K.-L. Handa and Vishwapaul, *Indian J. Chem.*, 1971, **9**, 418.
11 S. S. Lele, M. G. Patel and S. Sethna, *J. Indian Chem. Soc.*, 1966, **37**, 755.
12 Th. W. Greene and P. G. M. Wuts, in *Protective Groups in Organic Chemistry*, Wiley, New York, 1991, p. 143.
13 J. Reisch, H. M. T. B. Herath and N. S. Kumar, *Liebigs Ann. Chem.*, 1990, 931.
14 G. Schneider, H. Müller and P. Pfaender, *Arch. Pharm. (Weinheim, Ger.)*, 1967, **300**, 73.
15 G. Schneider and H. Müller, *Arch. Pharm. (Weinheim, Ger.)*, 1967, **300**, 913.
16 L. Jurd, *J. Am. Chem. Soc.*, 1959, **81**, 4606.
17 R. D. H. Murray and Z. D. Jorge, *Tetrahedron*, 1984, **40**, 3129, 5229.
18 R. D. H. Murray and L. T. Frobes, *Tetrahedron*, 1978, **34**, 1411.
19 D. H. R. Barton, L. Bould, J. Clive, P. D. Magnus and T. Hase, *J. Chem. Soc. C*, 1971, 2204.
20 F. M. Dean, *Prog. Chem. Org. Mat. Prod.*, 1952, **9**, 225.

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