Study on the Synthesis of Brassinolide and Related Compounds. Part 15.† Formal Synthesis of Brassinolide *via* Stereoselective Sulphenate–Sulphoxide Transformation

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A formal synthesis of the natural growth-promoting steroid brassinolide is described, which involves construction of (22*R*,23*E*)-24-methyl-5β-cholest-23-ene-3α,6α,22-triol by methylation of (24*R*)- and (24*S*)-(22*E*)-24-phenylsulphinyl-5β-cholest-22-ene-3α,6α-diol followed by 1,3-sulphoxide–hydroxy transposition.

Brassinolide **1** and related compounds are plant-growth-promoting steroids. Owing to their novel structural features and their remarkable physiological activity, much effort has been expanded on the development of methods for their syntheses.[1]

Recently, we reported a novel method for the construction of the side-chain of brassinolide,[2] utilizing the β-alkylative 1,3-carbonyl transposition,[3] *i.e.* **2** ⟶ **4**. Stereoselective reduction of compound **4** with diisobutylaluminium hydride (DIBAL)[4] gave the (22*R*,23*E*)-24-methyl compound **5** which is the key intermediate for the construction of the side-chain of brassinolide (Scheme 1).

We now report another novel, efficient method for the construction of the side-chain of this compound by 1,3-sulphoxide–hydroxy transposition,[5] *i.e.* **11** ⟶ **5** and **12** ⟶ **5**. This transposition could be achieved from the sulphenate ester of the alcohols (*R*,*Z*)-**9** and (*S*,*Z*)-**10** which underwent [2,3]-sigmatropic rearrangement to give the sulphoxide (24*R*,*E*)-**11** and (24*S*,*E*)-**12** followed by methylation to give (22*R*,23*E*)-24-methyl compound **5**.

Compounds **9** and **10** were readily prepared either by stereoselective alkylation of C-20 carbaldehyde **6**[1f] with but-1-ynyl-3-methylstannane[6] or with 1,1-dibromo-3-methylbut-1-ene[7] followed by catalytic hydrogenation of the resulting compounds **7** and **8** (Scheme 1).

Treatment of (22*R*,*Z*)-**9** in tetrahydrofuran (THF) containing Et_3N with benzenesulphenyl chloride at −78 °C underwent [2,3]-sigmatropic rearrangement to afford the (24*R*,22*E*)-24-sulphoxide **11**, which was treated with lithium diisopropylamide (LDA) and iodomethane at −78 °C to give, *via* rearrangement, the sulphenate ester of alcohol **5** *via* the transition state **A**, and then cleavage at room temperature with trimethyl phosphite to give a mixture of (22*R*)-**5**[2] (47%) and (22*S*)-**5′** (6%) in the ratio 8.4:1 in 53% overall yield. Thus, conversion of *Z*-enol (22*R*)-**9** into *E*-enol (22*R*)-**5** was readily accomplished, although the yield of this reaction has not been optimized. The structure assignment of product **5′** was made based on that of its isomer **5**. Since the 22-(*p*-nitrobenzoyl) derivative of **5′** exhibited a positive Cotton effect at 262 nm (Δε 12.36), the configuration at C-22 could be assigned as being *S*.[8]

Similarly, when this reaction sequence was carried out on the (22*S*,*Z*)-enol **10**, a mixture of enols **5** and **5′** was also readily obtained in the ratio 6:1 in 56% overall yield.

Since either enol **9** or **10** gave the same compound **5** in this 1,3-sulphoxide–hydroxy transposition process, this same reaction sequence was carried out on a mixture of substrates **9** and **10**‡ to yield a mixture of enols **5** and **5′** in the ratio ~7:1 in 46% overall yield. The present method for the preparation of enol (22*R*)-**5** is both highly stereoselective and highly efficient.

Hydroxy-directed epoxidation of enol **5** with *m*-chloroperoxybenzoic acid (MCPBA) afforded epoxide **13**[2] in 93% yield. Completion of the side-chain synthesis by reduction of the oxirane **13** with $LiBH_4$–$Ti(OPr^i)_4$[9] with inversion at C-24 showed 7:1 regioselectivity for formation of the vicinal glycol, protected as its acetonide **14**, in 84% yield.

The overall yield from C-20 carbaldehyde **6** to the acetonide **14** in six steps was 33%. This is one of the best methods to date for the construction of the side-chain of brassinolide. Compound **14** could be readily converted into brassinolide **1** by a known procedure.[1f]

Experimental

The silica gel used for flash chromatography was silica gel H (10–40 μ) (Qingdao Chemical Plant, China). Iodine vapour and vanillin were used for colour development. M.p.s were determined on a Buchi 535 instrument and are uncorrected. Optical rotations were measured on an Autopol III polarimeter. IR spectra were recorded for KBr disks on a Zeiss-75 model spectrometer. ^1H NMR spectra were recorded on Varian XL-200 (200 MHz), EM 360L (60 MHz) and JEOL SX-90 (90 MHz) spectrometers with $SiMe_4$ as internal standard. *J*-Values are given in Hz. Mass spectra were run on JMS-01 and MAT-711 spectrometers. CD measurements were made on a JASCO 500-C instrument. HPLC was performed on a Waters HPLC 246z instrument on μ-Bondapak CN 3.9–150 mm, 20000 psi column. Elemental analyses were performed by the Analytical Department of this Institute. Light petroleum refers to the fraction boiling in the range 60–90 °C.

(22R)-5β-*Cholest*-23-*yne*-3α,6α,22-*triol* **7** *and* (22S)-5β-*Cholest*-23-*yne*-3α,6α,22-*triol* **8**.— *Method A*. To a stirred solution of 1,1-dibromo-3-methylbut-1-ene (1.6 cm^3) in dry THF (500 cm^3) at −78 °C was added 1.5 mol dm^{-3} BuLi in diethyl ether (10 cm^3) under N_2 and the mixture was stirred for 1 h, then was warmed to room temperature for *ca.* 1 h, then was recooled to −78 °C and a solution of aldehyde **6** (R = Ac) (500 mg) in dry THF (10 cm^3) was added. The reaction mixture

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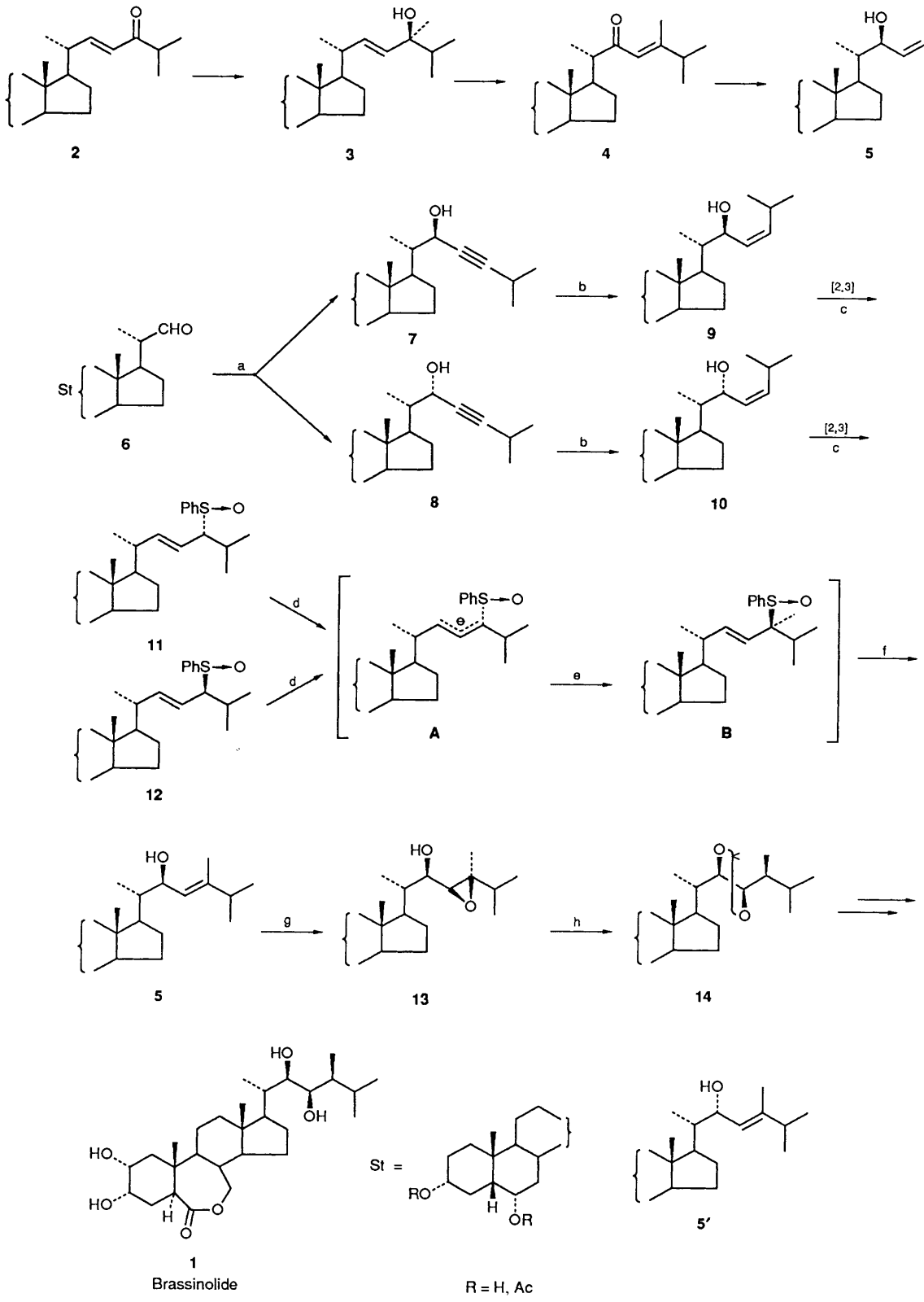
‡ The mixture of enols **9** and **10** was prepared by catalytic hydrogenation of the mixture of compounds **7** and **8** obtained from the reaction of the C-20 carbaldehyde **6** with 1,1-dibromo-3-methylbut-1-ene.[7] The overall yield of this two-step reaction is up to 90%. The advantages of using the *Z*-isomers **9** and **10** over the corresponding *E*-isomers were the high yield of the catalytic hydrogenation and the ease of manipulation.



Scheme 1 *Reagents:* a, $TiCl_4$, $Bu_3SnC{\equiv}CPr^i$ or BuLi, $Pr^iCH{=}CBr_2$; b, H_2, $Pd/BaSO_4$; c, PhSCl, Et_3N, THF; d, LDA, THF; e, MeI; f, $P(OMe)_3$, MeOH; g, MCPBA, CH_2Cl_2; h, (i) $Ti(OPr^i)_4$, $LiBH_4$, C_6H_6–THF; then (ii) $(MeO)_2CMe_2$, PTSA

was stirred at this temperature for 2 h and then quenched with saturated aq. NH_4Cl. After extraction with CH_2Cl_2, the combined extracts were washed with brine and then dried over Na_2SO_4. After removal of the solvent under reduced pressure, the oily residue was dissolved in 2% KOH–MeOH and the mixture was stirred at room temperature overnight. Work-up as usual gave a crude product, which was chromatographed on silica gel [light petroleum–acetone (4:1) as eluent] to give compound **7** (272 mg, 57%), m.p. 159–160 °C; $[\alpha]_D$ 18.6° (*c* 1.05, $CHCl_3$) {lit.,[7] m.p. 159–160 °C; $[\alpha]_D$ 19.03° (*c* 0.89)} and compound **8** (138 mg, 29%), m.p. 153–155 °C; $[\alpha]_D$ 13.8° (*c* 0.83, $CHCl_3$) {lit.,[7] m.p. 154 °C; $[\alpha]_D$ 12.8° (*c* 0.59,

$CHCl_3$)}. The spectroscopic data were identical with those previously reported.[7]

Method B. To a stirred solution of compound **6** (200 mg) in dry THF (20 cm^3) at −78 °C was added tributyl-(3-methylbut-1-ynyl)stannane (1 cm^3) under N_2. After the reaction mixture had been stirred at −78 °C for 10 min, $TiCl_4$ (1 cm^3) was added and the reaction mixture was stirred at −78 °C for 1 h. The reaction mixture was then allowed to warm to −20 °C, and was then worked up as usual. The oily residue was dissolved in stirred 5% KOH–MeOH at room temperature overnight. After removal of the solvent under reduced pressure the residue was extracted with CH_2Cl_2. The extract was worked up as usual to give a mixture of compounds **7** and **8** in the ratio 9:1 (HPLC). Flash chromatography on silica gel [light petroleum–acetone (3:1) as eluent] gave compound **7** (128 mg, 71.1%), m.p. 157–159 °C. The m.p. of this compound was not depressed on admixture with the compound obtained in the above experiment, and spectroscopic data were also identical with those obtained in the above experiment.

(22R,23Z)-5β-*Cholest*-23-*ene*-3α,6α,22-*triol* **9** *and* (22S,23Z)-5β-*Cholest*-23-*ene*-3α,6α,22-*triol* **10**.—To a suspension of Lindlar catalyst (50 mg) in ethanol (10 cm^3) was added compound **7** (100 mg). The mixture was hydrogenated for 6 h, the catalyst was filtered off, and the solvent was removed under reduced pressure to give *compound* **9** (96 mg, 95%), m.p. 162–164 °C; $[\alpha]_D$ 11.30° (*c* 0.3, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3300 (OH) and 1680 (C=C); δ_H(60 MHz; CCl_4) 0.63 (3 H, s, 18-H_3), 0.80 (3 H, s, 19-H_3), 0.91 (9 H, s, 21-, 26- and 27-H_3), 3.60 (1 H, m, 3-H), 4.00 (1 H, m, 6-H), 4.10 (1 H, m, 22-H) and 5.20 (2 H, m, 23- and 24-H); *m/z* 418 (M^+), 400 ($M^+ - H_2O$) and 382 ($M^+ - 2H_2O$) (Found: C, 74.3; H, 10.8. $C_{27}H_{46}O_3 \cdot H_2O$ requires C, 74.31; H, 11.01%).

Catalytic hydrogenation of compound **8** (100 mg) was performed with Lindlar catalyst (50 mg). After work-up as described for compound **7**, the enol **10** was obtained (95 mg, 94%), m.p. 126–127 °C; $[\alpha]_D$ 21.8° (*c* 0.196, $CHCl_3$) {lit.,[7] m.p. 125–127 °C: $[\alpha]_D$ −21.14° (MeOH)}. The spectroscopic data were identical with those previously reported.[7]

Catalytic hydrogenation of a mixture of ynols **7** and **8** (200 mg) obtained from method A was performed as described above to give a mixture (181 mg) of enols **9** and **10** in the ratio 2:1, which was used for the following experiment, part C.

(22R,23E)-24-*Methyl*-5β-*cholest*-23-*ene*-3α,6α,22-*triol* **5** *and* (22S,23E)-24-*Methyl*-5β-*cholest*-23-*ene*-3α,6α,22-*triol* **5′**.—*A.* To a stirred solution of compound **9** (200 mg, 0.48 mmol) in dry THF (10 cm^3) at −78 °C were added Et_3N (1 cm^3) and benzenesulphenyl chloride (0.5 cm^3, 4.32 mmol) under N_2. The reaction mixture was kept at −78 °C for 2 h and was then quenched with saturated aq. NH_4Cl and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4. and concentrated under reduced pressure to give compound **11** as an oily residue, which was triturated with light petroleum to afford a solid (205 mg), which was used directly in the next step.

To a solution of compound **11** (190 mg, 0.37 mmol) in dry THF (12 cm^3) at −78 °C was added LDA (1.5 cm^3, 1.0 mol dm^{-3} in THF) under N_2. The reaction mixture was kept at −78 °C for 2 h, and then MeI (54 mg, 0.37 mmol) was added. The reaction mixture was stirred at −78 °C for 2 h and was then warmed to room temperature. A solution of $(MeO)_3P$ (1.2 cm^3) in MeOH (5 cm^3) was added and the mixture was stirred at room temperature overnight before being quenched with saturated aq. NH_4Cl and extracted with CH_2Cl_2. The extracts were washed with brine and then dried over Na_2SO_4. The solvent was removed under reduced pressure to give a mixture of enols **5** and **5′** as a solid in the ratio 8.4:1 (HPLC).

This mixture was separated by flash chromatography on silica gel [acetone–light petroleum (1:4) as eluent] to give compound **5** (76 mg, 47%), m.p. 173–174 °C; $[\alpha]_D$ −14.6° (*c* 1.1, $CHCl_3$) {lit.,[2b] m.p. 173–174 °C; $[\alpha]_D$ −14.59° (*c* 1.1, $CHCl_3$)}; ν_{max}(KBr)/cm^{-1} 3300 (OH) and 1630 (C=C); δ_H(60 MHz; $CDCl_3$) 0.64 (3 H, s, 18-H_3), 0.97 (3 H, s, 19-H_3), 0.90 (6 H, d, *J* 4, 26- and 27-H_3), 1.04 (3 H, s, 21-H_3), 1.60 (3 H, s, 24-Me), 3.60 (1 H, m, 6-H), 4.01 (1 H, m, 3-H), 4.46 (1 H, dd, *J* 7.2, 1.4, 22-H) and 5.36 (1 H, d, *J* 7.2, 23-H); *m/z* 433 ($M^+ + 1$), 414 ($M^+ - H_2O$) and 396 ($M^+ - 2H_2O$) (Found: C, 77.4; H, 11.4. Calc. for $C_{28}H_{48}O_3$: C, 77.70; H, 11.11%).

B. The procedure as described for compound **9** was carried out in this case using compound **10** (120 mg, 0.287 mmol) in THF (5 cm^3), triethylamine (1 cm^3) and benzenesulphenyl chloride (0.5 cm^3, 4.32 mmol). After work-up as described for compound **9**, the sulphoxide **12** was obtained (128 mg, 86%). This product was used directly for the next step. The procedure as described for compound **11** was performed with the isomer **12** (120 mg, 0.23 mmol) in THF (10 cm^3), LDA (1 cm^3; 1.0 mol dm^{-3} in THF), MeI (33 mg, 0.238 mmol) and a solution of $(MeO)_3P$ (1 cm^3) in MeOH (1 cm^3). After work-up as described for compound **11**, enols **5** (72 mg, 61.8%) and **5′** (10 mg, 8.6%) were obtained. The overall yield was 70.4%.

Compound **5** had m.p. 173–174 °C, $[\alpha]_D$ −15.5° (*c* 0.37, $CHCl_3$). The product showed no depression of m.p. when admixed with the product obtained from reaction A. The spectroscopic data were also identical with those of the product from reaction A. Compound **5′** had m.p. 104–107 °C, $[\alpha]_D$ −12.71° (*c* 0.60, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3350 (OH) and 1640 (C=C); δ_H(60 MHz; $CDCl_3$) 0.65 (3 H, s, 18-H_3), 0.90 (6 H, s, 19- and 21-H_3), 3.4–3.9 (2 H, m, 3- and 6-H), 4.10 (1 H, d, *J* 7, 22-H) and 5.30 (1 H, d, *J* 7, 23-H); *m/z* 414 ($M^+ - H^2O$) and 396 ($M+ - 2H_2O$).

C. The procedure as described for compound **9** was carried out with, in this case, a mixture of substrates **9** and **10** (~2:1) (74 mg, 0.173 mmol) in THF (10 cm^3), triethylamine (1 cm^3) and benzenesulphenyl chloride (0.3 cm^3, 0.52 mmol). The product obtained was used directly for the next step. The procedure as described for compound **11** was performed with LDA (1 cm^3; 1.0 mol dm^{-3} in THF), MeI (30 mg, 0.2 mmol) and a solution of $(MeO)_3P$ (1 cm^3) in MeOH (1 cm^3). After work-up as described for compound **11**, enols **5** (29 mg, 37.9%) and **5′** (4 mg, 5.2%) were obtained. Compound **5** had m.p. 170–173 °C, $[\alpha]_D$ −13.9° (*c* 0.6, $CHCl_3$). It showed no m.p. depression when admixed with the product obtained from reaction A. The spectroscopic data were also identical with those of the product obtained from reaction A.

(22R,23R,24S)-23,24-*Epoxy*-24-*methyl*-5β-*cholestane*-3α,6α,-22-*triol* **13**.—To a solution of enol **5** (50 mg) in dry CH_2Cl_2 (10 cm^3) was added MCPBA (45 mg) and the mixture was stirred at room temp. for 20 h before being washed successively with saturated aq. $NaHCO_3$, brine, and water and dried over Na_2SO_4. After removal of the solvent under reduced pressure the solid residue was recrystallized from CH_2Cl_2–light petroleum to give compound **13** (48 mg, 93%), m.p. 139–140 °C; $[\alpha]_D$ −9.2° (*c* 0.74, $CHCl_3$). The spectroscopic data were identical with those previously reported.[2]

(22R,23R,24S)-22,23-*Isopropylidenedioxy*-24-*methyl*-5β-*cholestane*-3α,6α,*diol* **14**.—To a solution of compound **13** (15 mg) in dry THF (0.5 cm^3) were added benzene (2 cm^3) and $Ti(OPr^i)_4$ (0.2 cm^3) under N_2 at room temp. After the reaction mixture had been stirred for 10 min $LiBH_4$ (10 mg) was added and the reaction mixture was stirred at room temperature for 10 h. After addition of diethyl ether (10 cm^3) and 5% H_2SO_4 (1 cm^3) the mixture was extracted with CH_2Cl_2. The extract was washed with water and dried over Na_2SO_4. The solvent was removed under reduced pressure. The oily residue was dissolved in

acetone (5 cm^3) and treated with toluene-*p*-sulphonic acid (PTSA) (3 mg) 2,2-dimethoxypropane (0.2 cm^3). The reaction mixture was then stirred at room temp. for 3 h. Work-up as usual gave compound **14** (15 mg, 84%), m.p. 167–168 °C: (lit.,[2] 166–167 °C); ν_{max}(KBr)/cm^{-1} 3450 (OH) and 1380 ($CHMe_2$); δ_H(200 MHz; $CDCl_3$) 0.65 (3 H, s, 18-H_3), 0.80 and 0.84 (6 H, 2 d, *J* 8, 26- and 27-H_3), 0.99 (3 H, s, 19-H_3), 1.34 (3 H, s, CMe), 1.36 (3 H, s, CMe), 3.68 (1 H, m, 6-H), 3.80 (1 H, m, 3-H), 3.82 (1 H, dd, *J* 9, 4, 23-H) and 3.98 (1 H, d, *J* 9, 22-H); *m*/*z* 490 (M^+) and 472 ($M^+ - H_2O$) (Found: C, 73.6; H, 10.9. Calc. for $C_{31}H_{54}O_4 \cdot H_2O$: C, 73.20; H, 11.00%).

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