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GUAIANOLIDES. 2. TOTAL SYNTHESIS OF (±)-COMPRESSANOLIDE AND (±)-ESTAFIATIN

A.A. Devreese, M. Demuynck, P.J. De Clercq[1] and M. Vandewalle*

State University of Ghent, Department of Organic Chemistry,
Laboratory for Organic Chemistry,
Krijgslaan, 281 (S.4), B-9000 GENT (Belgium)

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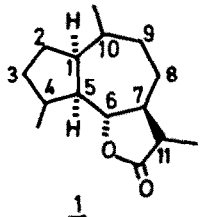
Summary - (±)-Compressanolide was obtained from the perhydroazulenic lactone 6 via a 5-step sequence. Lactone 8 could be used as an intermediate for the synthesis of (±)-estafiatin via epimerization of the dehydrated ketones 23 and 24 to cis-fused 25. These constitute the first total syntheses in this area.

The guaianolides, which constitute one of the gest families within the sesquiterpene lacto-[2], have notoriously lacked an approach by to- synthesis, in contrast with the related udoguaianolides[3]. In the preceding paper we e described a general and efficient entry of orrectly functionalized guaiane-skeleton h provision of the adequate relative stereo- mistry, as schematized by 1. Central in our nning was the reductive opening of epoxides which led, after ozonolysis of the side-chain double bond and oxidation, to the corresponding lactones 6-9.

The correct stereochemistry at all ring fusions (cf. 1) is present in lactones 6 and 7, while it can be obtained from 8 provided that an epimerization at C-1 can be performed. The functionalities present at C-4 and at C-10 should allow for further transformation to natural products. This will be exemplified by the conversion of 6 into (±)-compressanolide (10)[4], and of 8 into (±)-estafiatin (11)[5].



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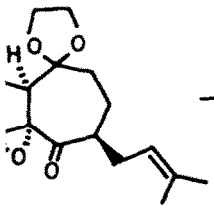
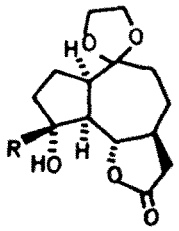
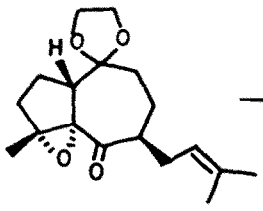


R = Me
R = H



6 R = Me
7 R = H



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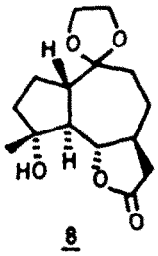

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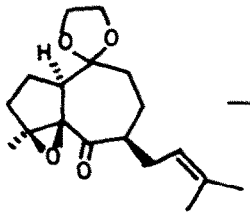

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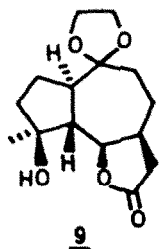
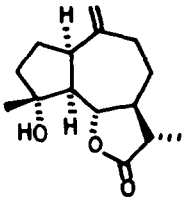


9

The synthesis of compressanolide, on which we reported previously, constitutes the first total synthesis of a naturally occurring guaianolide in racemic form[6]. Estafiatin, which has been obtained previously by means of partial synthesis[7], is also obtained for the first time by total synthesis[8]. The third key-lactone 9, to which we have access to, however, does not possess the correct stereochemistry pattern (cf. 1) for general guaianolide synthesis.



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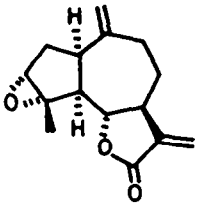

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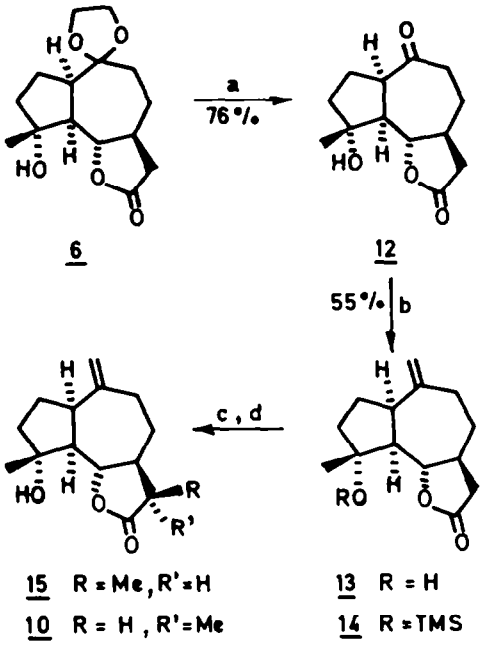


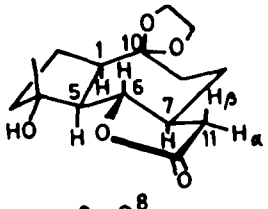
a, CH_3COCH_3, H_2SO_4; b, $CH_2{=}P\phi_3$, THF; c, TMSCl, Et_3N, DMAP, CH_2Cl_2; d, LDA, THF, -78°C; MeI, HMPT.

Scheme 1

(±)-Compressanolide (10)

In view of its structural features (i.e., tertiary alcohol at C-4) and stereochemistry at C-1, C-4, C-5, C-6 and C-7, lactone 6 is an ideal intermediate for the synthesis of compressanolide (10). Deketalization to 12 (sulfuric acid, acetone; 76 % yield), followed by Wittig reaction with methylenetriphenylphosphorane in tetrahydrofuran gave the exocyclic olefin 13 in 55 % yield. After protection of the tertiary alcohol in 13 as trimethylsilylether (trimethylsilylchloride, triethylamine and 4-dimethylaminopyridine in methylene chloride; 80 %), the lactone 14 was deprotonated (lithium diisopropylamide in tetrahydrofuran) and methylated with methyl iodide in hexamethylphosphoramide. After acid work-up a mixture of diastereoisomers at C-11 was obtained, i.e., 15 and (±)-compressanolide 10 in 63 % and 16 % yield, respectively (after separation on silicagel). The inversion of configuration at C-11 in the undesired 15 was only partially achieved by treatment with lithium diisopropylamide, followed by quenching with ammonium chloride, leading to a 1:3 mixture of the desired (±)-compressanolide (10) and 15, respectively. The TLC behavior and spectral properties (^{1}H NMR 360 MHz, IR, MS) of synthetic 10 showed it to be identical with an authentic sample of compressanolide[9].

The ^{1}H NMR spectral parameters of the lactones within this series (i.e., 6, 12, 13, 15 and 10) show a marked constancy in the J patterns of H-1, H-5, H-6, H-7 and H-11, with average J values for H-1/H-5, H-5/H-6 and H-6/H-7 of 12-12.5 Hz, 11-11.3 Hz and 9.25-10 Hz, respectively. The down field shift of H-6 in ketal 6 (i.e., 4.52 ppm) compared to the other products of this series (i.e., 3.92-4.17 ppm) is in accord with the syn-diaxial position of the oxygen-atom at C-10 in a C^8 conformation, as found in the solid state[10].

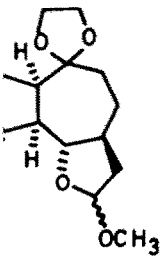


6, C^8

The availability of both isomers at C-11, i.e., 15 and 10, also allows for the unambiguous assignment of the geminal protons at C-11 in this series : the β-oriented hydrogen at C-11 resonates at high field (δ 2.2-2.3 ppm; $J(H_\beta\text{-}11/H\text{-}7)$=

5-12.5 Hz) compared to the α-oriented proton 2.6-2.7 ppm; $J(H_\alpha\text{-}11/H\text{-}7)$ = 7-8 Hz).

The dehydratation of the tertiary alcohol C-4 would have provided an entry to a num- of guaianolides. This transformation (e.g. 6) could, however, in our hands, not be re- zed in a synthetic useful way. For the pose of synthesizing guaianolides bearing unsaturation at C-4 we therefore turned attention first to the nor-derivative 7.



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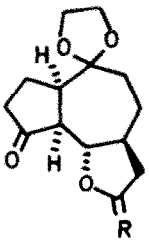


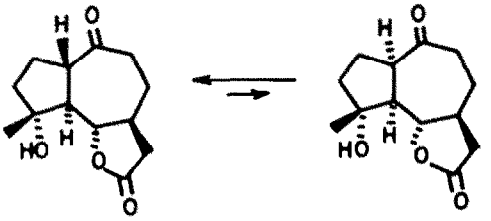
16 R = O
18 R = H,OCH3

one 16, expected upon oxidation of 7, uld in principle be a possible substrate this purpose. 16 was indeed obtained n oxidation with pyridinium dichromate methylene chloride. Subsequent Wittig fination with methylene triphenylphospho- e (n-BuLi/THF or sodium tert-amylate/to- ne modifications), however, proved fully uccessful. Equally frustrating were si- ar attempts on 18. The latter product obtained from 3 by successive treatments n lithium in liq. ammonia/NH_4Cl, ozone in ylene chloride/dimethylsulfide, and ace- isation with methanol/oxalic acid to 17 % overall yield from 3), followed by lins oxidation (quantitative).

-Estafiatin (11)

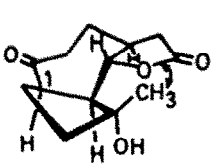
The successful use of key-lactone 8 for ıtual guaianolide synthesis critically de- ds on the outcome of two transformations : the possibility for epimerization at C-1 ome stage of the synthesis; (2) the suc- sful dehydratation, preferably to a $\Delta^{3,4}$ in (cf. 11), of the tertiary alcohol at

At the outset, it is interesting to note : ketone 19, obtained from 8 by acid hy- lysis (methanol, 3 N HCl, 30 min; 73 % d) was not epimerized by further pro- longed treatment (3 days) in the same medium.

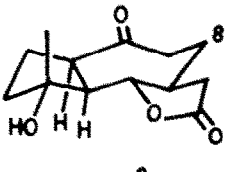


19 12

In retrospect, this result is not surprising in view of the severe nonbonded interaction between the C-4 methyl group and the α-oriented oxygen at C-6, that is present in the TC_{1-} form of the cis-fused isomer 12 that one would expect to be favored[11]. Relief of this nonbonded interaction is realized in e.g. the less stable C^8 conformation. On the other hand, an essentially strain-free conformation (i.e., TC_{9-}) is available for the trans-fused isomer 19.

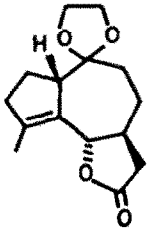


12, TC_{1-}



12, C^8

We therefore focused first on the dehydratation of 8, since the corresponding $\Delta^{3,4}$ olefins would be expected to be free of similar nonbonded interactions. Again, and in accord with literature precedents, dehydratation at C-4 proved troublesome[12]. Classical methods (thionyl chloride in pyridine or high temperature treatment in HMPT) proved unsuccessful. Reaction with Burgess reagent, however, yielded after purification on silica two fractions, one of which proved to be homogeneous in 20 (17 % yield), the other fraction consisted of a 3:1 mixture of olefins 21 and 22 (61 % yield).



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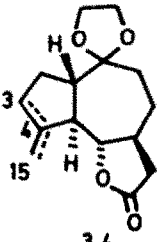
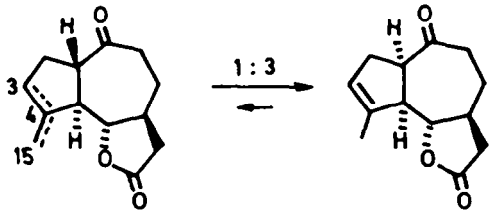


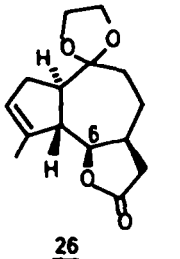
21 $\Delta^{3,4}$
22 $\Delta^{4,15}$

Acid hydrolysis of the mixture of 21 and 22 (methanol, 3 N hydrochloric acid, 30 min) yielded the same 3:1 ratio of endo- and exocyclic olefins 23 and 24, respectively. Prolonged treatment under the same conditions (3 days) eventually led to an equilibrium mixture of 25, 23 and 24 (ratio 12:3:1), clearly indicating a double bond migration (exo → endo) under the acidic conditions[13]. From this mixture 25 is obtained via HPLC purification (60 % yield from 21/22). Comparison of the ^{1}H NMR spectral data shows a large shift difference for H-1 in the cis- and trans-fused compounds : 3.55 ppm and 3.14 ppm for 25 and 23, respectively.



23 $\Delta^{3,4}$
24 $\Delta^{4,15}$
25

At this point it is interesting to note that dehydratation of 9 with Burgess reagent afforded the trisubstituted olefin 26 in 62 % yield. The coupling patterns observed for H-11, i.e., 9.0 and 1.0 Hz, indicate a lactone envelope conformation with C-7 up, in line with the preferred TC_{6-} form for the seven-membered ring[11].



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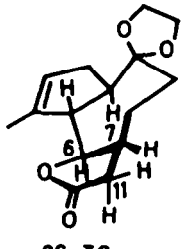
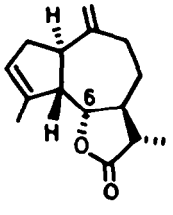


26 TC_{6-}



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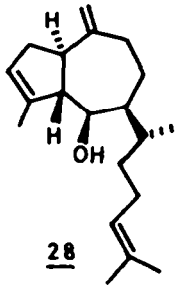
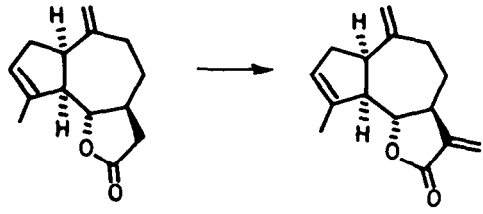


28

The small J value found for H-6/H-7, i.e., 6 Hz, is also noteworthy. In view of its structure, 26 can be regarded as a possible intermediate for the synthesis of (±)-pachydictyol-A (28). Greene recently described the partial synthesis of 28, which involved as an intermediate the lactone 27, epimeric at C-6 when compared to 26 and 28[14].



29 30

Further transformation of ketone 25 to (±)-estafiatin (11) proceeded via Wittig reaction to diolefin 29 (75 % yield) and high yield introduction of the α-methylene moiety on the lactone using Grieco's method (78 % yield)[15]. The spectral data and TLC behavior of triene 30 were identical with those of a sample obtained by Crabbé and coworkers en route to natural estafiatin from α-santonin[7a,16]. Selective epoxidation (m-chloroperbenzoic acid, $CHCl_3$, -5°C) yielded (±)-estafiatin (69 %) next to minor amounts of the isomeric β-epoxide (ca 2 % compound to the 20 % previously reported for the same epoxidation)[7a]. ^{1}H NMR data (360 MHz) and TLC behavior of the synthetic material were identical with (-)-estafiatin obtained by Crabbé and co-workers[7a,16]. It should be noted that the α-orientation of the epoxide in the natural product now seems well established[7b].

EXPERIMENTAL SECTION

The m.ps. are uncorrected. IR spectra were recorded on a Perkin-Elmer 337 spectrometer, mass spectra on a AEI MS-50 spectrometer. The ^{1}H NMR spectra were recorded at 90 MHz (Varian EM-390) or at 360 MHz (WH-Brucker) in $CDCl_3$ unless otherwise stated with TMS as internal standard. Chemical shifts (δ) are expressed in ppm. Rf values are quoted for Merck silicagel 60 GF_{254} TLC plates of thickness 0.25 mm.

Reaction products were isolated by the addition of water and extraction with the specified solvent. The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed from the filtered solution on a rotary evaporator. Column chromatographic separations were performed on silica gel with EtOAc-isooctane (ratio given between brackets) as eluent unless otherwise stated.

9α-Hydroxy-9β-methyl-3aα,4,5,7,8,9,9aα,9bβ-tahydroazuleno|4,5-b|furan-2(3H),6(6aαH)-ne (12).

oln of ketal 6 (123 mg; 0.44 mmol) in ace-ie (20 ml) containing dil. H_2SO_4 (5 drops) stirred for 4 hrs. $NaHCO_3$ (0.1 g) and er (0.5 ml) were then added. Work-up with CH_2Cl_2 and chromatography (isooctane-ether,) gave ketone 12 (73 mg) in 76 % yield. (ether) 0.09; m.p. 150°-152°C; IR 3580, 15, 1720 cm^{-1}; NMR 3.92 (1H, dd, J = 9.5, 3 Hz), 3.50 (1H, dt, J = 12.5, 8.75 Hz), 2 (1H, ABX, J = 17.5, 17.8 Hz), ∿2.56 , m), 2.48 (1H, dd, J = 11.3, 12.5 Hz), 0 (1H, ABX, J = 17, 11.8 Hz), 1.28 (3H, s); m/z 238 (M^+, 11), 181 (60), 43 (100).

9α-Hydroxy-9β-methyl-6-methylene-3aα,,6,6aα,7,8,9,9aα,9bβ-decahydroazuleno|4,5-b|an-2(3H)-one (13).

uspension of methylenetriphenylphosphorane om methyltriphenylphosphonium bromide (620 1.74 mmol) and n-BuLi (0.87 ml of a 2 M n in hexane)| and ketone 12 (70 mg; 0.29 l) in THF (5 ml) was stirred for 20 min at C. The mixture was poured into a satd Cl soln (10 ml). Extractive work-up with er and $CHCl_3$, followed by purification on ica gel (hexane-ether, 2:3) gave olefin 13 mg) in 55 % yield.

(ether) 0.33; IR 3450, 1790, 1270, 1100, 0 cm^{-1}; NMR 4.98 (1H, br s), 4.95 (1H, br s), 2 (1H, dd, J = 9.3, 11.3 Hz), 3.00 (1H, br J = 12, 8.5 Hz), 2.11 (1H, dq, J = 13, 3.3 , 1.30 (3H, s); MS m/z 236 (M^+, 0.5), 221 , 218 (4), 43 (100).

9β,3β-Dimethyl-9α-hydroxy-6-methylene-3aα,,6,6aα,7,8,9,9aα,9bβ-decahydroazuleno|4,5-b|an-2(3H)-one (15) and (±)-compressanolide (

a soln of olefin 13 (30 mg; 0.127 mmol) in Cl_2 (10 ml) was added TMSCl (30 µl, 0.127 l), Et_3N (50 µl, 0.127 mmol) and DMAP (3 mg). er stirring for 2 hrs further Et_3N (0.15 ml) TMSCl (80 µl) were added, followed by the ition of Et_3N (0.15 ml) and TMSCl (50 µl) er 4 hrs. After 8 hrs the mixture was con-trated in vacuo and directly purified on ica gel (isooctane-EtOAc, 7:3) to give 14 mg) in 80 % yield.

(EtOAc-isooctane, 1:4) 0.23; IR 1775, 1245, 0, 1020 cm^{-1}; NMR 4.91 (2H, br s), 4.02 (1H, J = 9.3, 11 Hz), 2.98 (1H, br dt, J = 11, 8 ; MS m/z 308 (M^+, 0.5), 293 (24), 143 (91), (100).

a soln of LDA (0.156 mmol) in THF (0.2 ml) added dropwise a soln of the lactone 14 mg; 0.123 mmol) in THF(0.5 ml) at -78°C. er stirring for 20 min at -78°C a soln of (9.3 µl) in HMPA (28 µl) was added at once. soln was warmed to -45°C and stirred for /2 hrs. After pouring into dil HCl-ether %, 1 ml) stirring was continued for 1 hr. ractive work-up, ether and $CHCl_3$, followed chromatography (isooctane-EtOAc, 3:2), e (±)-compressanolide (5 mg) and its epi-15 (19.4 mg) in 16 % and 63 % yield, pectively.

a soln of LDA (0.152 mmol) in THF (0.5 ml) added dropwise (10 min) a soln of 15 5 mg, 0.038 mmol) in THF (0.5 ml) at -78°C. er stirring for 1 hr, the soln was poured o a satd NH_4Cl soln (1 ml). After extrac-e work-up with ether and chromatography ooctane-ether, 2:3) (±)-compressanolide 11 5 mg) and its epimer 15 (7 mg) were ob-ned in 27 % and 73 % yield, respectively.

(±)-compressanolide (10) : Rf (ether-iso-ane, 2:1) 0.17; IR 1785 cm^{-1}; NMR 4.98 (1H, s), 4.95 (1H, br s), 4.05 (1H, dd, J = 9.5, 11.3 Hz), 2.99 (1H, dt, J = 12, 8.5 Hz), 2.65 (1H, dt, J = 12.8, 3.8 Hz), 2.27 (1H, dd, J = 12, 11.3 Hz), 2.22 (1H, dq, J = 11.8, 7 Hz), 2.13 (1H, dq, J = 13, 3.5 Hz), 1.30 (3H, s), 1.24 (3H, d, J = 7.0 Hz).

For lactone 15 : Rf (ether-isooctane, 2:1) 0.08; m.p. 86°-87°C; IR 1790 cm^{-1}; NMR 4.96 (1H, br s), 4.93 (1H, br s), 4.17 (1H, dd, J = 10, 11 Hz), 2.99 (1H, dt, J = 12, 9 Hz), 2.67 (1H, quint, J = 8 Hz), 2.65 (1H, dt, J = 12.5, 3.8 Hz), 2.33 (1H, m), 2.28 (1H, dd, J = 11, 12 Hz), 1.36 (1H, dq, 4.5, 12.5 Hz), 1.31 (3H, s), 1.19 (3H, d, J = 7.3 Hz); MS m/z 250 (M^+, 2), 235 (8), 232 (32), 43 (100).

9α-Hydroxy-9β-methyl-3aα,4,5,7,8,9,9aα,9bβ-octahydroazuleno|4,5-b|furan-2(3H),6(6aα)-dione (19).

A soln of ketal 8 (0.1 g; 0.35 mmol) in 10 % 3 N HCl-MeOH (5 ml) was stirred at 0°C for 1 hr. After concentration in vacuo ice-water was added. Extractive work-up with ether and chromatography (EtOAc-isooctane, 4:1) gave ketone 19 (0.06 g) in 73 % yield.

Rf (ether) 0.04; IR 3590, 1800, 1725 cm^{-1}; NMR 4.09 (1H, t, J = 10.3 Hz), 2.83 (1H, ddd, J = 6.5, 9.5, 12 Hz), 1.31 (3H, s); MS m/z 238 (M^+, 2), 181 (52), 44 (100).

Dehydratation of alcohol 8.

To a soln of 8 (1.0 g; 3.54 mmol) in benzene (20 ml) was added dropwise a soln of Burgess reagent (2.38 g; 10 mmol) in benzene (4 ml). After stirring for 2 hrs at 50°C, the reaction mixture was poured into a satd NH_4Cl soln. Extractive work-up with ether and column chromatography (ether, isooctane, 1:1) gave 21 and 22 (0.57 g) as a mixture of isomers (ratio 3:1, respectively) in 61 % yield, next to tetrasubstituted olefin 20 (0.16 g; 17 %).

For 21 and 22 : Rf (ether) 0.57; IR 2950, 1785, 1350, 900 cm^{-1}; NMR 5.36 (1H, 21; br s), 5.34 (1H, 22; m), 4.92 (1H, 22; m), 3.78 (1H, 21; t, J = 10 Hz), 2.93 (1H, 21; br t, 10 Hz), 1.82 (3H, s); MS m/z 264 (M^+, 13), 249 (6), 164 (10), 99 (100).

For 20 : Rf (ether) 0.62; IR 2950, 1780, 1420, 1200, 900 cm^{-1}; NMR 4.81 (1H, br d, J = 10 Hz), ∿3.86 (4H, m), 3.00 (1H, m), 2.62 (1H, ABX, J = 16, 6.5 Hz), 2.33 (1H, m), 2.27 (1H, ABX, J = 16, 12.8 Hz), ∿2.16 (2H, m), 1.98 (1H, ddt, J = 1, 12.5, 7 Hz), 1.84 (3H, s); MS m/z 264 (M^+, 13), 249 (6), 164 (10), 99 (100).

9-Methyl-3aα,4,5,7,9aα,9bβ-hexahydroazuleno|4,5-b|furan-2(3H),6(6aα)-dione (25).

To a soln of 21 and 22 (0.5 g; 18.9 mmol) in MeOH (40 ml) was added a 3 N soln of HCl (5 ml). After stirring for 30 min at room temperature the soln was concentrated in vacuo and a satd $NaHCO_3$ soln was added to the residue. Extractive work-up with CH_2Cl_2 gave a 3:1 mixture of olefins 23 and 24 (0.41 g; 100 %) not separable by chromatography.

Rf (ether) 0.21; IR 2950, 1720, 1460, 900 cm^{-1}; NMR 5.43 (1H, 23; br s), 5.37 (1H, 24; q, J = 2.3 Hz), 5.05 (1H, 24, q, J = 2.3 Hz), 4.07 (1H, 24; t, J = 10 Hz), 4.0 (1H, 23; t, J = 10 Hz), 3.14 (1H, 23; dt, J = 7.8, 10.3 Hz), 1.83 (3H, s); MS m/z 220 (M^+, 100), 205 (13), 177 (23), 79 (98).

To a soln of 23 and 24 (0.41 g, 18.6 mmol) in MeOH (40 ml) was added a soln of 3 N HCl (5 ml). After stirring for 3 days at room temperature, the mixture was poured into a satn $NaHCO_3$ soln and the waterphase extracted with CH_2Cl_2 (6 x). Work-up and purification by HPLC (EtOAc-hexane, 1:9) gave, next to starting material 23/24 (0.105 g, 26 %), pure ketone 25 (0.245 g) in 60 % yield.

Rf (ether) 0.22; IR 3000, 1780, 1460, 1100, 900 cm^{-1}; NMR 5.51 (1H, br s), 3.82 (1H, t,

J = 10 Hz), 3.55 (1H, dt, J = 6, 8.9 Hz), 3.08 (1H, br t, J = 10 Hz), 2.81 (1H, m), 2.68 (1H, ABX, J = 16.5, 7.5 Hz), 2.7-2.4 (3H, m), 2.34 (1H, m), 2.27 (1H, ABX, J ∿ 16.5, 12 Hz), 2.18 (1H, dq, J = 13.5, 4.2 Hz), 1.84 (3H, br s), 1.53 (1H, m); MS m/z 220 (M^+, 88), 150 (15), 80 (100).

9-Methyl-3aα,4,5,7,9aß,9bα-hexahydroazuleno|4,5-b|furan-2(3H),6(6aα)-dione 6-ethylene ketal (26).

A soln of the alcohol 9 (0.227 g; 0.8 mmol) and Burgess reagent (0.571 g; 2.4 mmol) in benzene (30 ml) was stirred for 2 1/2 hrs at 60°C. The reaction mixture was poured into water (100 ml) and the aqueous phase extracted with CH_2Cl_2. Work-up of the combined organic phases, followed by chromatography (ether-hexane, 1:1) gave olefin 26 (130 mg) in 61 % yield.
Rf (EtOAc-hexane, 1:1) 0.4; IR 1800 cm^{-1}; NMR 5.34 (1H, m), 4.43 (1H, dd, J = 6, 9.75 Hz), ∿4 (4H, m), 3.05 (1H, br t, J = 9.5 Hz), 2.88 (1H, dd, J = 9, 17.5 Hz), 2.56 (1H, tddd, J = 1.25, 6, 9, 12 Hz), 2.22 (1H, dd, J = 1, 17.5 Hz), 2.06 (1H, ddd, J = 1.5, 6, 14 Hz), 1.79 (3H, s), 1.51 (1H, ddd, J = 2.3, 13, 14 Hz), 1.32 (1H, ddt, J = 6, 14.5, 1.8 Hz); MS m/z 264 (M^+, 9), 202 (20), 151 (100).

9-Methyl-6-methylene-3aα,4,5,6,6aα,7,9aα,9bß-octahydroazuleno|4,5-b|furan-2(3H)-one (29).

To a suspension of methylenetriphenylphosphorane |from methyltriphenylphosphonium bromide (0.66 g; 1.86 mmol) and a 1 M soln of sodium t-amylate in toluene (1.8 ml; 1.8 mmol)| in toluene (10 ml) was added a soln of ketone 25 (0.1 g; 0.4 mmol) in toluene (2 ml) at room temperature over 1 hr. After stirring for 30 min, the reaction mixture was poured into a satd NH_4Cl soln. Extractive work-up with ether and chromatography (ether-isooctane 1:9) gave olefin 29 (0.074 g) in 75 % yield.
Rf (ether, isooctane, 1:4) = 0.09; IR 3095, 1790, 1660, 950 cm^{-1}; NMR 5.54 (1H, br s), 4.87 (1H, br s), 4.84 (1H, br s), 4.07 (1H, t, J = 10 Hz), 3.11 (1H, br dt, J = 5.5, 8.3 Hz), 2.83 (1H, br t, J = 9 Hz), 2.62 (1H, ABX, J = 16.5, 7.5 Hz), 2.5-2.3 (4H, m), 2.23 (1H, ABX, J = 16.5, 12 Hz), 2.12 (1H, dq, J = 13, 4.3 Hz), 2.01 (1H, m), 1.81 (3H, br s), 1.77 (1H, ddt, J = 4.5, 13, 11.3 Hz); MS m/z 218 (M^+, 30), 159 (65), 158 (77), 138 (100).

3,6-Dimethylene-9-methyl-3aα,4,5,6,6aα,7,9aα,9bß-octahydroazuleno|4,5-b|furan-2(3H)-one (30).

To a soln of lithium diisopropylamide (0.37 mmol) in THF (4 ml) was added at -78°C a soln of lactone 29 (0.05 g; 0.23 mmol) in THF (3 ml). After stirring for 45 min at -78°C the soln was brought to -30°C over a period of 30 min. At this temperature, formaldehyde was led through the mixture via a dry nitrogen stream. After 20 min a satd NH_4Cl soln was added via syringe. Extractive work-up with ether and chromatography (EtOAc-isooctane, 2:3) gave the intermediate alcohol (0.045 g) in 80 % yield.
Rf (EtOAc-isooctane, 2:3) 0.15; IR 3650-3450, 1780, 1655, 1640 cm^{-1}; NMR 5.54 (1H, m), 4.88 (1H, s), 4.84 (1H, s), 1.83 (3H, s).
To a soln of this alcohol (0.02 g; 0.08 mmol) in CH_2Cl_2 (1 ml) were added at 0°C mesylchloride (0.037 ml, 0.39 mmol) and triethylamine (0.067 ml; 0.48 mmol). The reaction mixture was stirred for 1 hr at 0°C and warmed to room temperature. After 2 hrs 1,5-diazabicyclo|5.4.0|undec-5-ene (0.16 ml; 1.6 mmol) was added and the mixture further stirred for 2 hrs at room temperature. After pouring into water, the mixture was worked-up with CH_2Cl_2. Chromatography (ether-hexane, 1:4) gave olefin 30 (18 mg) in 97 % yield.
Rf (ether-hexane, 1:4) 0.2; IR 3050, 1775, 1650, 1640 cm^{-1}; NMR 6.2 (1H, d, J = 3.3 Hz), 5.54 (1H, d, J = 3.3 Hz), 4.89 (1H, s), 4.86 (1H, s), 4.05 (1H, ∿t, J = 9 Hz), 3.15 (1H, ∿dt, J = 5,8 Hz), 1.86 (3H, s); MS m/z 230 (M^+, 13), 150 (65), 91 (100).

(±)Estafiatin (11).

To a soln of olefin 30 (15 mg; 0.065 mmol) in $CHCl_3$ (2 ml) was added at -10°C m-chloroperbenzoic acid (38.5 mg; 0.19 mmol). The reaction mixture was warmed to 5°C over 3 hrs and then poured into a satd NH_4Cl soln. Extractive work-up with CH_2Cl_2 and chromatography (EtOAc-hexane, 1:9) gave (±)-estafiatin (11 mg) in 69 % yield.
Rf (ether-hexane, 1:1) 0.19; m.p. 92°-93°C; IR 3075, 1770, 1660, 1640 cm^{-1}; NMR 6.21 (1H, d; J = 3.5 Hz), 5.48 (1H, d; J = 3.5 Hz), 4.95 (1H, s), 4.86 (1H, s), 4.07 (1H, dd, J = 8.5, 11 Hz), 3.37 (1H, s), 2.98 (1H, ∿dt, J = 10.5, 7.5 Hz), 2.87 (1H, m), 1.62 (3H, s).

References

1. Research Associate of the National Fund for Scientific Research (Belgium).
2. N.H. Fischer, P.J. Olivier, H.D. Fischer, Fortschr. Chem. Org. Naturst. 38, 47 (1979).
3. C.H. Heathcock, S.L. Graham, M.C. Pirrung, F. Navac, C.T. White, in "The Total Synthesis of Natural Products", vol. 5, J.W. ApSimon, Ed., Wiley, New York, 1982.
4. M. Ogura, G.A. Cordell, N.R. Fainsworth, Phytochemistry, 17, 957 (1978).
5. F. Sanchez-Viesca, J. Romo, Tetrahedron Lett. 1285 (1963); F. Bohlmann, H. Bornowski, C. Arndt, Chem. Ber. 99, 2828 (1966).
6. A.A. Devreese, P.J. De Clercq, M. Vandewalle, Tetrahedron Lett. 21, 4767 (1980).
7. (a) M.T. Edgar, A.E. Greene, P.J. Crabbé, J. Org. Chem., 44, 159 (1979); (b) L.A. Maçaira, F. Welbaneide, L. Machado, M. Garcia, J.A. Rabi, Tetrahedron Lett., 21, 773 (1980).
8. M. Demuynck, A.A. Devreese, P.J. De Clercq, M. Vandewalle, Tetrahedron Lett. 23, 2501 (1982).
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10. J.P. Declercq, G. Germain, M. Van Meerssche, A. Devreese, P. De Clercq, M. Vandewalle, Bull. Soc. Chim. Belges, 90, 167 (1981).
11. P.J. De Clercq, J. Org. Chem. 46, 667 (1981).
12. E. Piers, K.F. Cheng, Can. J. Chem. 48, 2234 (1970); R.O. Hutchins, M.G. Hutchins, C.A. Milewski, J. Org. Chem. 37, 4190 (1972).
13. L.A. Maçaira, M. Garcia, J.A. Rabi; J. Org. Chem. 42, 4207 (1977).
14. A.E. Greene, Tetrahedron Lett. 851 (1978); J. Am. Chem. Soc. 102, 5337 (1980).
15. P.A. Grieco, K. Hiroi, J. Chem. Soc., Chem. Commun. 1317 (1972).
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