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CONFIGURATIONAL ASSIGNMENT AT C-2' OF SOME STRIGOL ANALOGUES

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Abstract- Configurational assignment at C-2' of several strigol analogues by (i) X-ray analysis, (ii) chemical correlation, and (iii) circular dichroism is described.

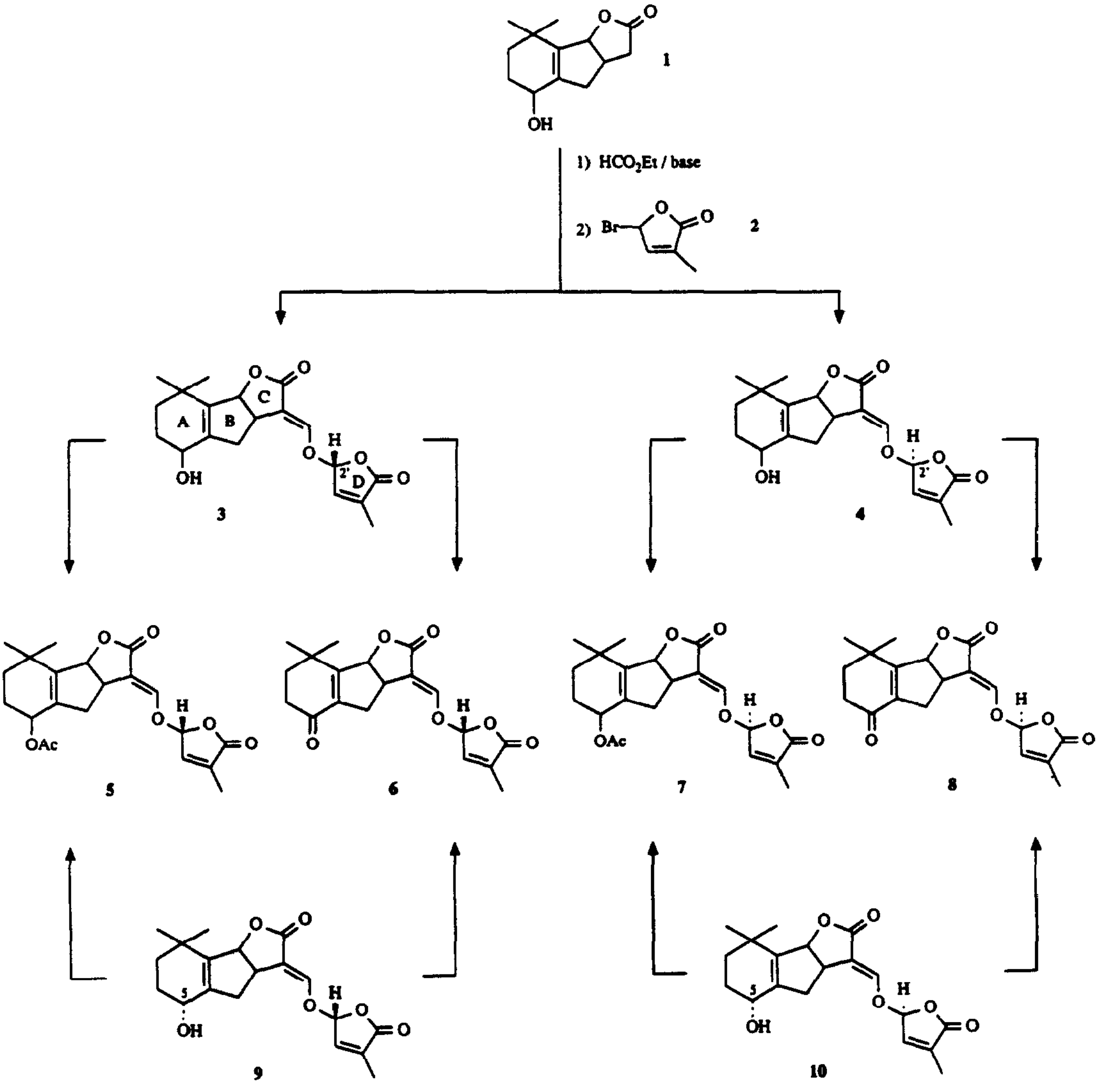
Introduction

Germination of the seeds of root parasitic flowering plants of the genera Striga, Alectra (Scrophulariaceae), and Orobanche (Orobanchaceae) is stimulated by substances exuded from their host plants. (+)-Strigol (**3**), its acetate (**5**) (both isolated from cotton[1]), and the related sorgolactone (isolated from Sorghum bicolor[2]) are highly active seed germination stimulants. Their mode of action is poorly understood. Even structure-activity relations are not particularly well-established.[3] It seems clear, however, that both the correct absolute configuration[4,5,6] and the relative configuration at C-2' [5,6,7,8,9] are prerequisites of full biological activity. Recently, we had occasion to prepare a whole set of strigol analogues and to test their biological activity in collaboration with Prof.Wegmann (Tübingen). The results thus obtained also show the intimate connection of the relative configuration at C-2' and the germination inducing power.[6] Unfortunately, until now the relative configuration at C-2' cannot be controlled by synthesis. In all reported instances, unit D was connected to the rest of the molecule as indicated in Scheme 1 (**1** —> **3** + **4**), i.e. by a substitution process with racemic bromo lactone rac-**2** as electrophilic reagent.[10] This route requires, that after formation and separation of the final products (cf. **3** and **4**) the configuration at C-2' has to be determined, a task that is hampered by the fact that the ^1H and ^{13}C NMR spectra of the two C-2' stereoisomers are virtually identical.[9,11,12] In this article we describe three approaches that have proven suitable for the configurational assignment at C-2' of strigol analogues.

X-ray analysis

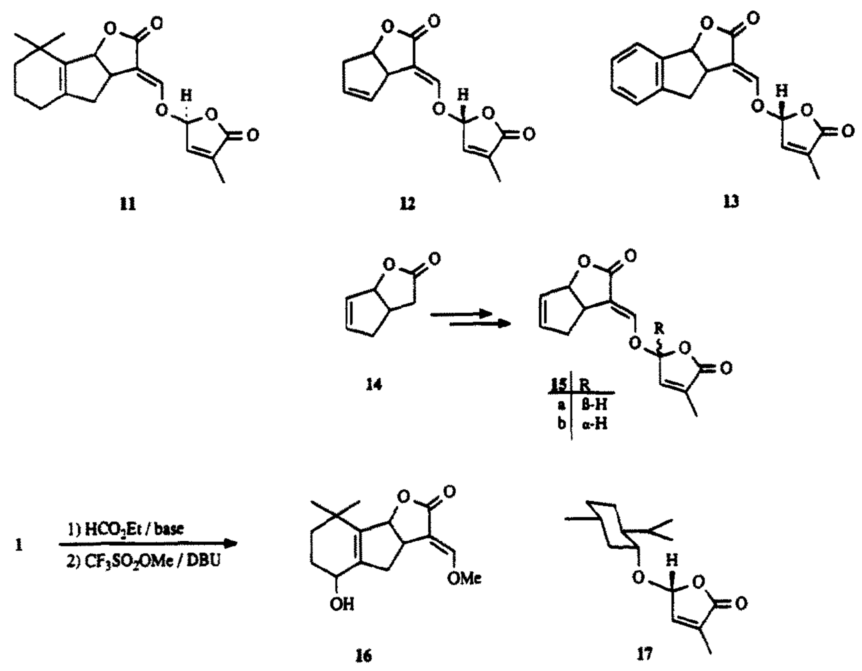
Until now, X-ray structures of (+)-strigol[13,14] and its 5-deoxy derivative rac-**11**,[11] have been reported. In the present publication we disclose the crystal structure of the 5-epimer of strigol (rac-**9**, m.p.150-151°C), prepared together with rac-**10** (m.p.188-189°C) as described recently[11] (see Figure 1).

To the memory of Günther Snatzke



Scheme 1.

It is known, that strigol analogues with simplified structures also exhibit germination inducing activity.[3] Here too, the activity seems to depend on the correct stereochemistry.[3,5] In this context we prepared, following a sequence first published by Johnson (see Scheme 2),[15] the truncated analogues rac-**15a** and rac-**15b** (GR 28) and separated the diastereoisomers for the first time. The higher-melting isomer (m.p. 158-159°C) is rac-**15b** according to a crystal structure analysis (see Figure 2). Recently, the configuration of two other strigol



Scheme 2.

analogues, rac-**13** (one of the GR 24 stereoisomers)[9] and (+)-**12** (one of the GR 7 stereoisomers)[16] was determined. Thus, for quite a number of strigol analogues the configuration at C-2' has now been secured by X-ray analysis, and sound correlations between the configuration at this stereogenic centre and the germination stimulant activity are thus possible.

Chemical Correlations

With many reference compounds of known relative configuration now available configurational assignment by chemical correlation becomes a feasible approach. Recently, we determined the configuration at C-2' of rac-**9** and rac-**10** as summarized in Scheme 1. Thus, rac-**9** and rac-**10** were converted to rac-**5** and rac-**7**, respectively, using the Mitsunobu procedure and were shown to be identical with reference samples obtained from rac-**3** and rac-**4**, respectively, by acetylation.[11] Unfortunately, in our publication[11] we changed by mistake the melting points of rac-**9** and rac-**10**. Rac-**9** is the lower-melting (150-151°C), and rac-**10** the higher-melting isomer (188-189°C).[17] We apologize for any inconvenience caused by our mistake. The correlation of rac-**9** with rac-**3** has now been secured by oxidation of both compounds to 5-oxo-derivative rac-**6**. Similarly, both rac-**4** and rac-**10** have been converted to rac-**8**. These correlations served at the same time to establish the relative configuration of the new compounds rac-**6** and rac-**8**.

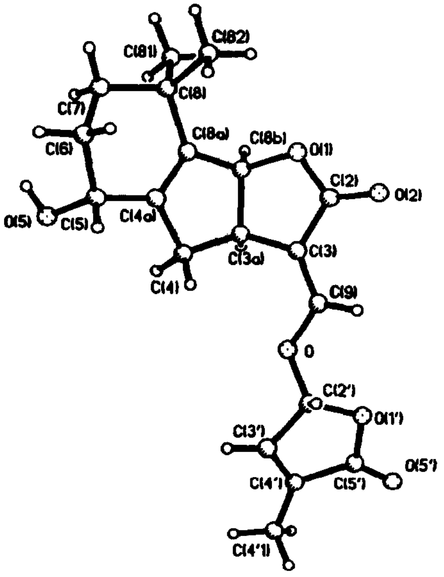


Figure 1. X-ray crystal structure of rac-**9**.

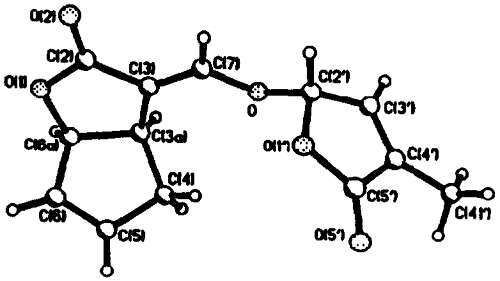


Figure 2. X-ray crystal structure of rac-**15b**.

Circular dichroism

Figure 3 exhibits the CD curves of (+)-strigol (**3**), (+)-2'-epistrigol (**4**) and their enantiomers. The curves are, of course, sum curves of the different chromophors present in **3** and its stereoisomers. But, for example, in the difference spectrum of (+)-strigol and (+)-2'-epistrigol the contributions of the ABC chromophor should cancel each other, and twice the CD of the ring D chromophor should remain.[18] In Figure 4 the difference curve is depicted. It may be concluded that the ring D chromophore with the (2'R) configuration should have a positive Cotton effect around 220 nm and a negative Cotton effect in the 260 nm band. This kind of treatment necessitates, however, that there is neither an electronic interaction between the two chromophoric systems nor that the different configuration at C-2' causes the two compounds to have different conformations.[19] To put the procedure on a more firm basis we prepared **16** and ent-**16** as indicated in Scheme 2, as well as Feringa's compounds **17** and ent-**17**[20] as reference compounds for the ABC and D part, respectively, of (+)-strigol and its stereoisomers. The CD spectra of these compounds are depicted in Figures 5 and 6. In principle, the CD sum curve of **16** and **17** should equal the CD curve of (+)-strigol (**3**). As Figure 7 demonstrates, there is indeed a good correlation between the two curves as far as the wavelength and the sign of the CD maxima is concerned. The Δε values of the two curves vary, however, to some extent, indicating some interaction of the two systems in **3**. The same conclusion is reached by comparing the sum curve of **16** and ent-**17** with the CD curve of **4** (Figure 8) and the difference curve of **4** and **3** with twice the CD effects of ent-**17** (Figure 4). The origin of the deviation from additivity has not been investigated. As has already been mentioned, from NMR spectra no indication of different conformations of the 2'-epimers is obtained.[9,11,12] In any case, it appears that the difference curve of **3** and **4** bears so much resemblance to (twice) the Cotton effect of **17** that it is justified to base the configurational assignment on this kind of treatment.

A comparison of the CD spectra **16** and **17** (Figures 5 and 6) reveals that the λ ≈ 250 nm CD band of **17** extends to a longer wavelength than that of **16**. This difference can also be made use of for the configurational assignment at C-2'. Figures 9 and 10 (difference curves of **3** and **16**, and **4** and **16**, respectively) indicate that there is a relation between the sign of the Cotton effect above 270 nm and the configuration at C-2', a negative CD corresponding to (2'R) configuration. In the range of 270 nm the difference curves exhibit practically the same Δε values as the model compounds **17** and ent-**17**, respectively. Therefore, it seems justified to correlate the C-2' configuration *directly* with the sign of the CD around 270 nm. And indeed, as Figure 3 demonstrates, the two (2'R) compounds **3** and ent-**4** have a negative CD around 270 nm whereas the CD of the two (2'S) compounds ent-**3** and **4** is positive at this wavelength.

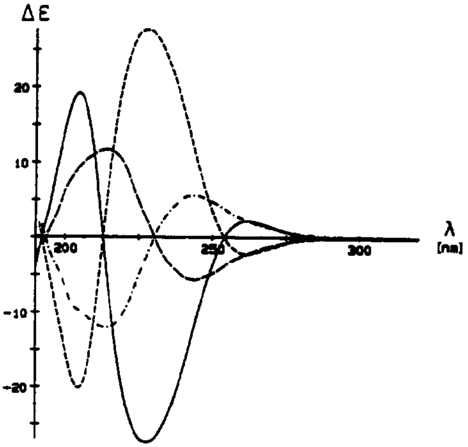


Figure 3. CD spectra of **3** (- - - -), **4** (-.-.-.-), ent-**3** (———), and ent-**4** (— —).

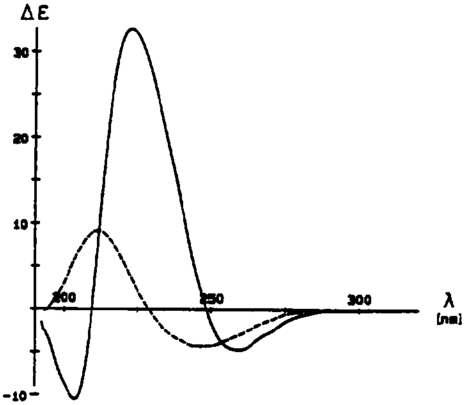


Figure 4. Difference curve of the spectra of **3** and **4** (———) and CD spectrum of **17** (Δε values multiplied by 2 (- - - -)).

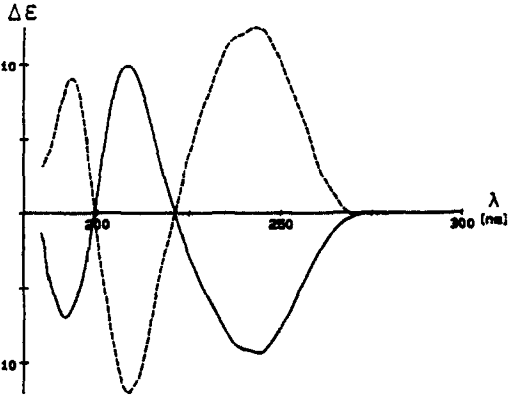


Figure 5. CD spectra of **16** (- - - -) and ent-**16** (———).

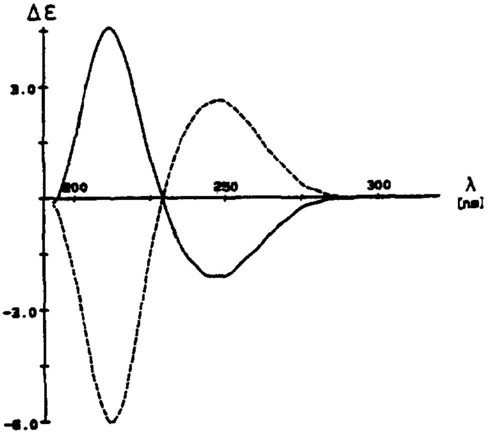


Figure 6. CD spectra of **17** (———) and ent-**17** (- - - -).

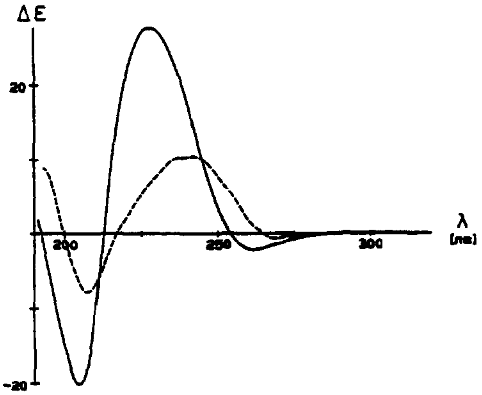


Figure 7. CD spectrum of **3** (———) and sum curve of **16** and **17** (- - - -).

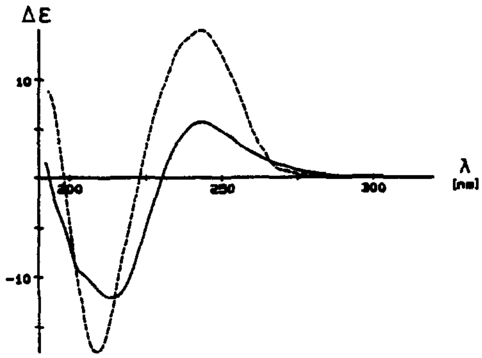


Figure 8. CD spectrum of **4** (———) and sum curve of **16** and ent-**17** (- - - -).

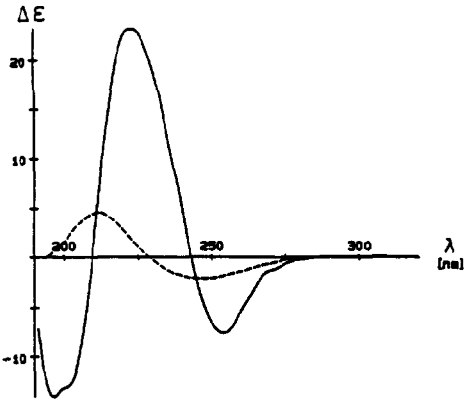


Figure 9. CD spectrum of **17** (- - - -) and difference curve of **3** and **16** (———).

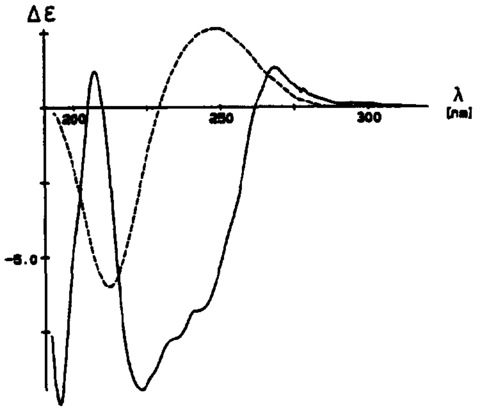


Figure 10. CD spectrum of ent-**17** (- - - -) and difference curve of **4** and **16** (———).

Experimental

For general methods, instrumentation, and abbreviations, see ref.[21] For nomenclature, see ref.[22]

CD data of **16** and ent-**16**

Solvent: acetonitrile.

16	(0.724 mmol/l): λ_{max} ($\Delta\varepsilon$) =	243.1 (12.46), 238.4 (11.89), 208.5 (-11.96), 193.1 (9.05)
ent-**16**	(0.659 mmol/l): λ_{max} ($\Delta\varepsilon$) =	244.2 (-9.39), 239.6 (-9.08), 208.4 (9.92), 191.2 (-6.94)

(3aR)-5t-Hydroxy-8,8-dimethyl-3-(methoxymethylene)-(3ar,8bc)-3,3a,4,5,6,7,8,8b-octahydro-indeno[1,2-b]furan-2-one (**16**).

(+)-**1**[10] was formylated with ethyl formate and sodium hydride as described by Brooks et al..[23] A solution of the formylated product (19.5 mg, 0.08 mmol), DBU (13.5 µl, 0.09 mmol), and methyl triflate (48.0 µl, 0.43 mmol) in dichloromethane (4 mL), was stirred at 20°C for 1 h. Triethylamine (0.2 mL) was added and the reaction mixture was stirred for 10 min. Solvent evaporation and LC (SiO_2 (15 g), petrol - ethyl acetate 1 : 1) gave **16** (16.9 mg, 82%).- M.p.: 160 - 162°C (petrol - ethyl acetate).- IR ($CHCl_3$): 3600 - 3300, 1740, 1670 cm^{-1}.- ^1H NMR (400 MHz, $CDCl_3$): δ = 1.07 (s, 3H, 8-CH_3), 1.15 (s, 3H, 8-CH_3), 1.38 - 1.47 (ddd, 1H, 7-H), 1.50 - 1.73 (m, 3H, 6-H, 7-H', OH), 1.90 - 2.00 (m, 1H, 6-H'), 2.63 - 2.69 (m, 2H, CH_2-4), 3.55 - 3.63 (m, 1H, 3a-H), 3.85 (s, 3H, OCH_3), 4.06 - 4.13 (m, 1H, 5-H), 5.42 - 5.49 (m, 1H, 8b-H), 7.20 - 7.24 (d, 1H, 9-H); $J_{7,7'}$= 14.0 Hz, $J_{3a,9}$= 2.5 Hz.- MS: m/z (%) = 264 (77, M^+), 246 (47), 231 (78), 218 (54), 208 (100), 176 (62), 105 (71), 91 (85), 77 (64), 55 (72), 41 (100), 39 (61).- Found C, 68.26; H, 7.61 $C_{15}H_{20}O_4$ 264.3 requires C, 68.16; H, 7.63.

(3aS)-5t-Hydroxy-8,8-dimethyl-3-(methoxymethylene)-(3ar,8bc)-3,3a,4,5,6,7,8,8b-octahydro-indeno[1,2-b]furan-2-one (ent-16).

Ent-**16** was prepared in 47% yield from (-)-**1** as described for **16**.- IR ($CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$), MS: these spectra are superimposible with those obtained from **16**.- Found C, 68.13; H, 7.55. $C_{15}H_{20}O_4$ 264.3 requires C, 68.16; H, 7.63.

(3aRS)-5-Oxo-8,8-dimethyl-3-((SR,E)-4-methyl-5-oxo-2,5-dihydro-furan-2-yloxymethylene)-(3ar,8bc)-3,3a,4,5,6,7,8,8b-octahydro-indeno[1,2-b]furan-2-one (rac-6).

a) A solution of rac-**3**[10] (100.2 mg, 0.29 mmol) in dichloromethane (1.5 mL) was added to pyridinium dichromate (PDC, 163.3 mg, 0.43 mmol). The reaction mixture was stirred at 20°C for 2 h, diluted with dry ether, and filtered. Solvent evaporation and LC (SiO_2 (12 g), petrol - ethyl acetate 1 : 1) gave rac-**6** (73.5 mg, 74%).- R_f (petrol - ethyl acetate 1 : 4): 0.46.- Mp: 165 - 167°C (petrol - ethyl acetate).- IR ($CHCl_3$): 1780, 1745, 1670 cm^{-1}.- ^1H NMR (400 MHz, ^1H, ^1H COSY, $CDCl_3$): δ = 1.27 (s, 3H, 8-CH_3), 1.30 (s, 3H, 8-CH_3), 1.82 - 1.95 (m, 2H, CH_2-7), 1.98 - 2.02 (m, 3H, 4'-CH_3), 2.40 - 2.48 (ddd, 1H, 6-H), 2.50 - 2.59 (ddd, 1H, 6-H'), 2.62 - 2.67 (ddd, 1H, 4-H), 2.86 - 2.93 (dd, 1H, 4-H'), 3.65 - 3.73 (m, 1H, 3a-H), 5.65 - 5.68 (dd, 1H, 8b-H), 6.11 - 6.15 (m, 1H, 2'-H), 6.91 - 6.95 (m, 1H, 3'-H), 7.48 - 7.52 (d, 1H, CHO); $J_{6,6'}$= 17.5 Hz, $J_{6,7}$=5.0 Hz, $J_{6,7'}$= 5.0 Hz, $J_{6',7}$= 10.5 Hz, $J_{6',7'}$= 5.5 Hz, $J_{4,4'}$= 17.0 Hz, $J_{4,3a}$= 2.5 Hz, $J_{4,8b}$= 2.5 Hz, $J_{4',3a}$= 9.0 Hz, $J_{3a,8b}$= 8.0 Hz, $J_{3a,CHO}$= 2.5 Hz.- MS: m/z (%) = 344 (M^+, 1.4), 247 (3), 230 (4), 97 (100). - Found C, 66.19; H, 5.78. $C_{19}H_{20}O_6$ 344.3 requires C, 66.27; H, 5.85.

b) Oxidation of rac-**9**[11] (42.1 mg, 0.12 mmol) with PDC (68.4 mg, 0.18 mmol) as described for rac-**3** gave rac-**6** (28.6 mg, 68%), identical (R_f value, ^1H NMR, MS, IR) with the sample obtained from rac-**3**.

(3aRS)-5-Oxo-8,8-dimethyl-3-((RS,E)-4-methyl-5-oxo-2,5-dihydro-furan-2-yloxymethylene)-(3ar,8bc)-3,3a,4,5,6,7,8,8b-octahydro-indeno[1,2-b]furan-2-one (rac-8).

a) Oxidation of rac-**4**[10] (100.0 mg, 0.29 mmol) with PDC (163.3 mg, 0.43 mmol) as described for rac-**3** gave rac-**8** (60.0 mg, 60%).- R_f (petrol : ethyl acetate 1 : 4): 0.39.- Mp : 185 - 187°C (petrol - ethyl acetate). - IR ($CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$), MS: these spectra are superimposible with those obtained from rac-**6**.- Found C, 66.28; H, 5.92. $C_{19}H_{20}O_6$ 344.3 requires C, 66.27; H, 5.85.

b) Oxidation of rac-**10**[11] (42.5 mg, 0.12 mmol) with PDC (69.3 mg, 0.18 mmol) as described for rac-**3** gave rac-**8** (28.6 mg, 68%), identical (R_f value, ^1H NMR, MS, IR) with the sample obtained from rac-**4**.

Conversion of rac-14 to rac-15a and rac-15b.

rac-**14**[15] (223.5 mg, 1.80 mmol) was formylated and the formyl derivative alkylated with rac-**2** as described by Brooks et al.[23] for the preparation of strigol. LC (SiO_2 (115 g), petrol - ethyl acetate 3 : 2) gave rac-**15a** (154.9 mg, 35%), rac-**15b** (65.7 mg, 15%) and a mixture of rac-**15a** and rac-**15b** (135.4 mg, 30%).

(3aRS)-3-((RS,E)-4-methyl-5-oxo-2,5-dihydrofuran-2-yloxymethylene)-(3ar,6ac)-2,3,3a,6a-tetrahydro-4H-cyclopenta[b]furan-2-one (rac-15a)

R_f (petrol - ethyl acetate 1 : 1): 0.28.- Mp: 99 - 100 °C (petrol - ethyl acetate).- IR ($CHCl_3$): 1785, 1750, 1680 cm^{-1}.- ^1H NMR (400 MHz, $CDCl_3$): δ = 1.96 - 2.03 (m, 3H, 4'-CH_3), 2.45 - 2.50 (m, 1H, 4-H), 2.80 - 2.84

(m, 1H, 4-H'), 3.63 - 3.71 (m, 1H, 3a-H), 5.50 - 5.53 (d, 1H, 6a-H), 5.81 - 5.88 (m, 1H, 5-H), 5.98 - 6.07 (m, 1H, 6-H), 6.12 - 6.17 (m, 1H, 2'-H), 7.40 - 7.45 (m, 1H, 3'-H); $J_{4,4}$= 17.5 Hz.- ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 10.99 (CH_3-4'), 37.62 (C-3a), 38.73 (C-4), 87.95 (C-6a), 100.70 (C-9), 113.88 (C-4'), 128.94 (C-5), 136.24 (C-3), 137.40 (C-3'), 141.12 (C-6), 150.65 (C-7), 170.39 (C-5'), 171.50 (C-2).- MS: m/z (%) = 248 (M^+, 1), 151 (12), 97 (100), 69 (11), 41 (33).- HRMS calcd for $C_{13}H_{12}O_5$: 248.0685, found 248.0677.

(3aRS)-3-((SR,E)-4-methyl-5-oxo-2,5-dihydrofuran-2-yloxymethylene)-(3ar,6ac)-2,3,3a,6a-terahydro-4H-cyclopenta[b]furan-2-one (rac-15b)

R_f (petrol - ethyl acetate 1 : 1): 0.20.- Mp: 158 - 159 °C (petrol - ethyl acetate).- IR ($CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$), MS: these spectra are superimposible with those obtained from rac-15a.- HRMS calcd for $C_{13}H_{12}O_5$: 248.0685, found 248.0679.

X-ray structural analysis of rac-9 and rac-15b.

Rac-9, $C_{19}H_{22}O_6$ crystallises triclinic $P\bar{1}$ with a = 7.849(2), b = 9.375(2), c = 12.251(3), α = 85.46(2), β = 79.00(2), γ = 75.08(2)°, Z = 2, D_{calc}= 1.35 g•cm^{-3}. The structure was refined to R = 0.038, wR = 0.038 for 2401 independent reflections (MoK_α, $2\Theta \le 50°$, $F_o^2 > 2\sigma(F_o^2)$). rac-15b, $C_{13}H_{12}O_5$ crystallises monoclinic $P2_1/c$, a = 13.684(5), b = 10.749(4), c = 8.340(3) Å, β = 95.66(3), Z = 4, D_{calc} = 1.35 g•cm^{-3}. The structure was refined to R = 0.037, wR = 0.036 for 1592 independent reflections (MoK_α, $2\Theta \le 50°$, $F_o^2 > 2\sigma(F_o^2)$). Further details may be obtained from Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen, upon specification of the deposition number CSD-56708, the authors and the journal reference.

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