Tetrahedron Letters,Vol.30,No.17,pp 2221-2224,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

TOTAL SYNTHESES OF (-)-TRACHELOGENIN, (-)-NORTRACHELOGENIN AND (+)-WIKSTROMOL

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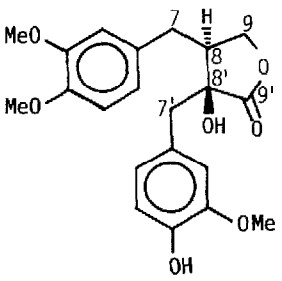
Summary : The title compounds were obtained by α-hydroxylation of the corresponding α,β-dibenzyl-γ-butyrolactones (lignans of synthetic origin), and were correlated to (±)-methyltrachelogenin **9** whose relative structure was definitely established by X-ray cristallography. (-)-Trachelogenin **1** and (-)-nortrachelogenin **12** thus have the (8S,8'S) absolute configuration, whereas (+)-nortrachelogenin **20** (or wikstromol) has the (8R,8'R) absolute configuration.

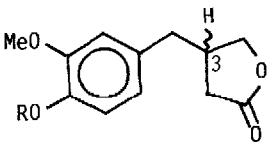
A few lignans of the trans-α,β-dibenzyl-γ-butyrolactone series typically bear a hydroxyl in the α position, as exemplified by (-)-trachelogenin **1**. As a continuation of our work on the total syntheses of various optically active natural trans-α,β-dibenzyl-γ-butyrolactones[1-3], we investigated the α-hydroxylation of such types of compounds in order to obtain lignans of the trachelogenin group. Belletire's recent disclosure[4] of the synthesis of racemic nortrachelogenin **20** (wikstromol) prompts us to describe here our latest results which also provide the definitive proof for the absolute configurations of the title compounds.

Synthetic (±)-dimethylmataires inol **6**[1], deriving from the lactone (±)-**2**, was treated with 1.5 equivalent of lithium hexamethyldisilazide (LHDS) and 0.1 equivalent of 12-crown-4 in benzene at room temperature, and dry oxygen was bubbled through the reaction mixture for 3 h. After treatment with aqueous sodium sulfite, and then with dilute hydrochloric acid, the mixture was worked-up and the reaction products were isolated by column chromatography over silica gel using 99:1 CH_2Cl_2/ether for the elution. This afforded approximately equimolecular amounts of the α-hydroxylated 8'-epimers (±)-**9** (36% yield), m.p. 146-147°C (MeOH/ether) and (±)-**13** (36% yield), m.p. 145.5-147.5°C (CH_2Cl_2/ether). The structure of (±)-methyltrachelogenin **9** was ascribed to the former compound since its 90 MHz ^{1}H-NMR and ^{13}C-NMR data were identical with those reported for the enantiomer deriving from natural sources.[5,6] The main significant difference in the ^{1}H-NMR spectra of the 8'-epimers (±)-**9** and (±)-**13** was provided by the H-9 protons which gave a doublet at δ 4.07 ppm for (±)-**9** and at δ 4.30 ppm for (±)-**13**. On the other hand, the main difference in the ^{13}C-NMR spectra of the same epimers concerned the β effect of the tertiary hydroxyl : the C-7' and C-8 carbons produced signals at δ 41.9 ppm and δ 43.7 ppm respectively, for (±)-**9**, and at δ 38.3 ppm and δ 48.1 ppm respectively, for the α-epimer (±)-**13**. The relative configuration of our racemic compound (±)-**9** was confirmed by X-ray cristallography.[7]

(-)-O-Benzyl arctigenin **7**,[8,9] deriving from the lactone (R)-(+)-**2**,[9] was treated with dry oxygen in alkaline conditions in the same way as for the racemic analogue **6**, and afforded after chromatography (-)-O-benzyltrachelogenin **10**,[9] m.p. 76-78°C (ether) in 24% yield, together with its 8'-epimer **14**,[9] m.p. 145-146°C (CH_2Cl_2/ether) in 21% yield. The NMR signals of the H-9 protons appeared at δ 4.06 ppm (d) for **10** and at δ 4.21 ppm (m) for **14**. Catalytic hydrogenolysis of the benzyl ether group of **10** was carried out in EtOH 95°/ AcOEt (1/1), in the presence of 10% Pd-C at room temperature for 3 h, thus quantitatively

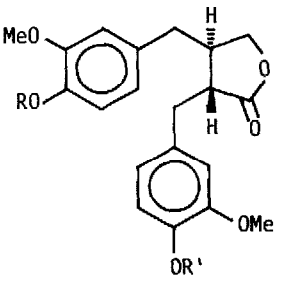


1 (-)-Trachelogenin

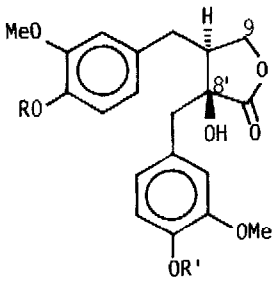


2 R = Me ; H-3α
3 R = Bn ; H-3α
4 R = H ; H-3β
5 R = Bn ; H-3β

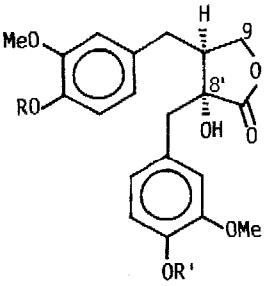
Bn = Ph-CH_2



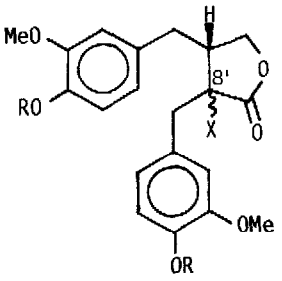
6 R = R' = Me
7 R = Me ; R' = Bn
8 R = R' = Bn



9 R = R' = Me
10 R = Me ; R' = Bn
11 R = R' = Bn
12 R = R' = H
(-)-Nortrachelogenin



13 R = R' = Me
14 R = Me ; R' = Bn
15 R = R' = Bn
16 R = R' = H



17 R = Bn ; X = H-8'α
18 R = Bn ; X = OH-8'α
19 R = Bn ; X = OH-8'β
20 R = H ; X = OH-8'α
(+)-Wikstromol
21 R = H ; X = OH-8'β

Reaction Scheme

(±)-2 ⟶ (±)-6 ⟶ (±)-9 + (±)-13

(R)-(+)-2 ⟶ 7 ⟶ 10 + 14 10 ⟶ (-)-1 ⟶ (-)-9

(R)-(+)-3 ⟶ 8 ⟶ 11 + 15 11 ⟶ 12 15 ⟶ 16

(S)-(-)-4 ⟶ (S)-(-)-5 ⟶ 17 ⟶ 18 + 19 18 ⟶ 20 19 ⟶ 21

yielding (-)-trachelogenin **1**,[9] m.p. 139.3-140.5°C (CH_2Cl_2/ether) and $[\alpha]_D$ -44°. Lit.[5] m.p. 139-141°C, $[\alpha]_D$ -43.3° (EtOH). The IR and ^{1}H-NMR data of synthetic **1** were in agreement with the data reported for the natural compound.[5] Moreover, the ^{13}C-NMR spectrum of synthetic (-)-**1** was identical with the spectrum described by Agrawal[10] for natural (-)-trachelogenin. Compound **1** in MeOH was treated with excess diazomethane in ether at room temperature for 48 h, thus giving a 66% yield of (-)-methyltrachelogenin **9**,[9] $[\alpha]_D$ -43°. Lit.[5] m.p. 97-98.5°C , $[\alpha]_D$ -45.9° (EtOH). The ^{1}H-NMR spectrum of (-)-**9** was identical with the spectrum of the racemic compound.

Synthetic (-)-O-dibenzylmatairesinol **8**,[2,9] deriving from the lactone (R)-(+)-**3**, was treated with dry oxygen in alkaline conditions in a similar fashion as for the racemic analogue **6**, and this furnished chromatographically pure (-)-O-dibenzylnortrachelogenin **11**,[9] m.p. 106.3-109.4°C (ether/pet. ether) in 24% yield, together with the 8'-epimer **15**,[9] m.p. 119-121°C (CH_2Cl_2/ether) in 23% yield. The NMR signals of the H-9 protons appeared at δ 4.07 ppm (d) for **11** and at δ 4.24 ppm (m) for **15**. Catalytic hydrogenolysis (EtOH/AcOEt 2/1), 10% Pd-C, 3 bars, 3 h at room temperature) of the benzyl groups of (-)-O-dibenzylnortrachelogenin **11** gave amorphous (-)-nortrachelogenin **12**,[9] $[\alpha]_D$ -43° in 97% yield. Lit. $[\alpha]_D$ -16.8° (c 0.178, EtOH),[11] and $[\alpha]_D$ -25° (c 1.5, EtOH).[12] The ^{13}C-NMR data of (±)-nortrachelogenin **12** (synthesized in the same fashion as the levorotary enantiomer) were in agreement with the data reported by Achenbach and coworkers[12] for natural (-)-nortrachelogenin **12**. As for the analogous compounds **9**, **10** and **11**, the H-9 protons of (±)-**12** appeared as a doublet at δ 4.09 ppm. Catalytic hydrogenolysis of the benzyl groups of the compound **15** afforded amorphous (-)-8'-epinortrachelogenin **16**,[9] m.p. 170-171.5°C in 98% yield. As we already observed for the analogous compounds **13**, **14** and **15**, the H-9 protons of **16** appeared as a multiplet at δ 4.20 ppm.

(-)-Nortrachelogenin **12** in MeOH was treated with excess diazomethane in ether and gave (-)-methyltrachelogenin **9**,[9] which was identical with the compound obtained above by O-methylation of (-)-trachelogenin **1**.

The (S)-(-)-lactone **4**[2,9] was treated with benzyl chloride in acetone (K_2CO_3/KI, reflux, 18 h), thus leading to the hitherto unknown O-benzyl derivative **5**,[9] m.p. 81-82°C (CH_2Cl_2/ether) in 81% yield. The lithium enolate of the latter was generated with LHDS in THF and was alkylated at -78°C with O-benzylvanillyl bromide.[2] This gave (+)-O-dibenzylmatairesinol **17**[9] as a viscous oil, in 97% yield. The compound **17** was treated with dry oxygen in alkaline conditions in a similar fashion as for the racemic analogue **6**, and afforded chromatographically pure (+)-O-dibenzyl wikstromol **18**,[9] in 32% yield, together with the 8'-epimer **19**,[9] in 15% yield. The IR and ^{1}H-NMR spectra of **18** and **19** were identical with those of their levorotary enantiomers **11** and **15**, respectively. Catalytic hydrogenolysis of the benzyl groups of **18** was carried out as above and quantitatively yielded (+)-wikstromol **20** as an amorphous solid, $[\alpha]_D$ +43° (EtOH) and $[\alpha]_D$ +34° ($CHCl_3$). Lit. $[\alpha]_D$ +72° (c 0.37, $CHCl_3$)[13], $[\alpha]_D$ +41° ($CHCl_3$)[14] for (+)-wikstromol and lit. $[\alpha]_D$ +15.4° (c 0.52, $CHCl_3$) for (+)-nortrachelogenin.[6] The IR and ^{1}H-NMR data of **20** were in agreement with those reported in the literature for the natural compound called wikstromol[12] or (+)-nortrachelogenin.[6] These data were also identical with those we observed for synthetic levorotary nortrachelogenin **12**. The hydrogenolysis of the benzyl groups of compound **19** quantitatively afforded (+)-8'-epiwikstromol **21**,[9] m.p. 170-172.5°C, whose IR and ^{1}H-NMR data were identical with those of the levorotary enantiomer **16**.

The fact that the compounds **1**, **9**, **11**, **12** and **20** indeed have the same relative configuration was confirmed by the examination of their ^{13}C-NMR spectra which exhibited almost identical data for the aliphatic parts of their molecules, as shown by the following table.

Moreover, it can be seen that the above data significantly differ from those displayed by the α-epimers, such as **13**.

	(-)-Trachelogenin **1**	(±)-Methyl-trachelogenin **9**	(±)-Dibenzyl-nortrachelogenin (±)-**11** or (±)-**18**	(±)-Nortra-chelogenin (±)-**12** or (±)-**20**	(±)-Epi methyl-trachelogenin **13**
C-7	31.55	31.52	31.48	31.62	32.07
C-7'	42.00	41.90	41.83	42.02	38.29
C-8	43.79	43.75	43.63	43.82	48.11
C-8'	76.55	76.48	76.40	76.53	75.94
C-9	70.34	70.31	70.29	70.35	69.40
C-9'	178.71	178.69	178.64	178.75	177.92

Good microanalytical data were obtained for the new compounds (±)-**9**, **11**, (±)-**11**, (±)-**12**, (±)-**13**, **15**, **16**, **18**, **19** and **21** as well as for (-)-nortrachelogenin **12** and (+)-wikstromol **20**.

Conclusion

We have synthesized (-)-trachelogenin **1**, (-)-nortrachelogenin **12** and (+)-nortrachelogenin **20** (wikstromol) which displayed IR, ^{1}H- and ^{13}C-NMR data identical with those described in the literature for the same compounds of natural origin. These three compounds have been correlated to (±)-methyltrachelogenin **9** whose relative configuration has been definitely established by X-ray cristallographic studies.[7] We thus confirm that (-)-trachelogenin **1** and (-)-nortrachelogenin **12** have the (8S, 8'S) absolute configuration, whereas (+)-wikstromol **20** has the (8R, 8'R) absolute configuration.

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9. Observed specific rotations $[\alpha]_D$: **1**, -44° (c 0.9, EtOH) ; (R)-(+)-**2**, +7° (c 2, $CHCl_3$) ; (R)-(+)-**3**, +4° (c 1.7, $CHCl_3$) ; (S)-(-)-**4**, -8° (c 0.5, MeOH) ; **5**, -4° (c 1.6, $CHCl_3$) ; **7**, -26° (c 4.6, $CHCl_3$); **8**, -15° (c 1.6, $CHCl_3$) ; **9**, -43° (c 1.1, EtOH) and -47° (c 1.4, EtOH) ; **10**, -24° (c 1.3, $CHCl_3$) ; **11**, -26° (c 1.0, $CHCl_3$); **12**, -43° (c 0.44, EtOH) ; **14**, -15° (c 1, $CHCl_3$) ; **15**, -13° (c 1.0, $CHCl_3$) ; **16**, -9° (c 0.96, EtOH) ; **17**, +16° (c 1.6, $CHCl_3$) ; **18**, +23° (c 6.22, EtOH); **19**, +11° (c 0.9, $CHCl_3$) ; **20**, +43° (c 2.32, EtOH) and +34° (c 2.32, $CHCl_3$) ; **21**, +4° (c 0.82, $CHCl_3$) and +10° (c 0.82, EtOH).
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(Received in France 6 February 1989)