Tetrahedron Letters No. 38, pp 3613 - 3616. 0040-4039/78/0915-3613$02.00/0

A NEW ROUTE TO THE BIS-BENZOCYCLOOCTADIENE LIGNAN SKELETON : TOTAL SYNTHESES OF (±) PICROSTEGANE, (±) ISOPICROSTEGANE AND (±) ISOSTEGANE

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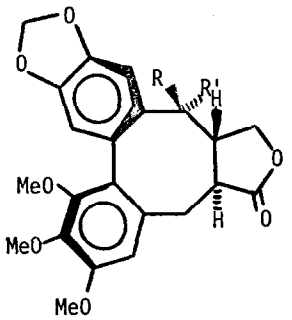
The interesting structural features of steganacin 1, as well as its pronounced antileukemic activity in mice (1,2) has aroused a growing interest in the total syntheses of this compound and its analogues (steganol 2 and steganone 3). At about the same time as RAPHAEL (3) published his ingenious synthesis of steganone 3, other syntheses of bis-benzocyclooctadiene lignans were described by other teams (4,5,6).

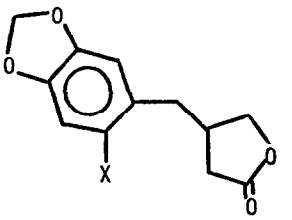
Our present approach to naturally occurring bis-benzocyclooctadienes involves, at the key steps, an ULLMANN reaction with two hindered aryl halides (7), followed by an intramolecular α-hydroxyalkylation of a γ-butyrolactone with an aromatic aldehyde (8).



1, R = OAc ; R' = H

2, R = OH ; R' = H

3, R,R' = O



4, X = H

5, X = I

6, X = (6-formyl 2,3,4-trimethoxy) phenyl

Treatment of the piperonyl lactone 4 (8) with I_2/CF_3CO_2Ag ($CHCl_3$) afforded the iodide 5, m.p. 105-107°C, in 89 % yield. The latter was mixed in the melt with 1 equ. of 2-bromo 3,4,5-trimethoxybenzaldehyde (7), and to the resulting oil was added a large excess of copper powder (inactivated), according to the technique we have already described (7). The mixture was heated at 195°C for 20 mn, and then extracted with $CHCl_3$. The soluble residue was crystallized from C_6H_6/Et_2O, thus affording the diphenyl 6, m.p. 160,5-162°C, in 42-48 % yield.

The diphenyl 6 was cyclised using lithium hexamethyl disilyl amide (4 equ.) in C_6H_6/hexane at 25°C for 1 mn, and the mixture was hydrolysed with 30 % HCl at -25°C (8). After working up in the usual way, the mixture of 8 β-hydroxy picrostegane 7 (9) and 8 α-hydroxy isopicrostegane 8 was obtained in 99 % yield (crude), and was subsequently separated by column chromatography on silica gel using CH_2Cl_2. Compound 7 (head fraction, 38 %) has m.p. 193.5-194.5°C (needles from EtOH). IR ($CHCl_3$) cm^{-1} : 3500, 1752, 1600. NMR ($CDCl_3$), δ (ppm) : 4.6 (J ∿ 10 Hz) (carbinolic H at C_8). Compound 8 (tail fraction, 34 %) has m.p. 195-196°C (prisms from EtOH/$CHCl_3$). IR ($CHCl_3$) cm^{-1} : 3530, (1754) 1600. NMR ($CDCl_3$), δ (ppm) : 4.71 (J ∿ 9 Hz) (carbinolic H at C_8).

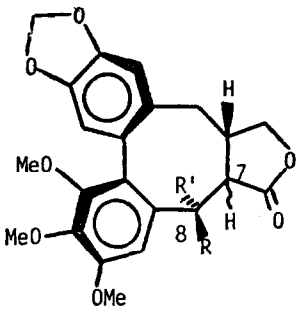
By heating without solvent at 205°C under argon for 10 mn, compound 8 gave a mixture of 8 (ca 85 %) and 8 α-hydroxy picrostegane 9 (ca 15 %), together with trace amounts of the retrocondensation product 6. Compound 9 was isolated by HPLC (CH_2Cl_2/hexane), and has m.p. 213-218°C (plates from CH_2Cl_2/EtOH). IR ($CHCl_3$) cm^{-1} : 3540, 3400 (broad and flat), 1765. NMR ($CDCl_3$), δ (ppm) : 5.32 (J ∿ 2 Hz) (carbinolic H at C_8).

Under the same conditions, compound 7 afforded an equilibrated mixture of 7 (ca 90 %) and presumably 10 (ca 10 %) which could not be separated by chromatography.

Hydrogenolysis of the benzylic alcohols 7 and 8 could be effected only in fairly drastic conditions : $CF_3CO_2H/HClO_4$, 5 % Pd/C (1 weight part) at 60°C under 3 atm ; reaction time : 48 h for 7 and 72 h for 8. Thus 7 gave picrostegane 11 (83 %), m.p. 185.5 - 187°C (needles from Et_2O). IR ($CHCl_3$) cm^{-1} : 1769. NMR (C_6D_6), δ (ppm) : 6.82 (1H, s) ; 6.48 (1H, s) ; 6.23 (1H, s) ; 5.49 - 5.41 (2H) ; 3.80 (3H, s) ; 3.44 (3H, s) ; 3.38 (3H, s) ; 2.80 - 2.0 (6H). M^+ 398.1372 ($C_{22}H_{22}O_7$). Similarly, compound 8 afforded isopicrostegane 12 (55 %), m.p. 179-181.5°C (clusters of needles from Et_2O). IR ($CHCl_3$) cm^{-1} : 1769.
NMR (C_6D_6), δ (ppm) : 7.38 (1H, s) ; 6.98 (1H, s) : 6.53 (1H, s) ; 5.52 - 5.47 (2H) ; 3.74 (3H, s) ; 3. 67 (3H, s) ; 3.51 (3H, s) ; 3.28 - 2.90 (1H) ; 2.45 - 1.78 (4H). M^+ 398.1372 ($C_{22}H_{22}O_7$).

By heating at 185°C for 1 mn, the compounds 11 or 12 were interconverted (10), to give an equilibrated mixture containing ca 33 % of 11 and ca 66 % of 12.

In the same way as that described in the podophyllotoxin series (11), we next tried to isomerise compounds 11 and 12 into the corresponding compounds having a trans lactone junction, i.e., stegane 13 and isostegane 14, respectively. Thus 11 and 12 were separa-

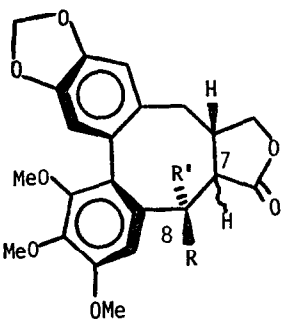


7, R = OH ; R' = H ; 7 β-H

9, R = H ; R' = OH ; 7β -H

11, R = R' = H ; 7 β-H

13, R = R' = H ; 7 α-H

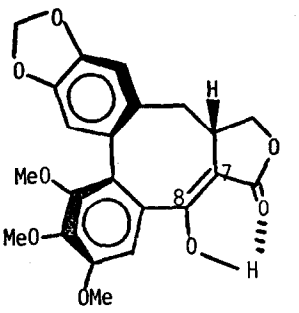


8, R = H ; R' = OH ; 7 β- H

10, R = OH ; R' = H ; 7 β- H

12, R = R' = H ; 7 β- H

14, R = R' = H ; 7 α- H



15

tely treated with 3 % NaOH in aqueous EtOH at 25°C for 24 h (to open the lactone ring and isomerise the resulting γ-hydroxy acid), and subsequently treated with HCl or dicyclohexyl carbodiimide (to reform the lactone ring). Under these conditions, picrostegane 11 was recovered unchanged, the formation of stegane 13 not being observed. But on the other hand, isopicrostegane 12 gave an isomeric compound, which was identified as isostegane 14, by comparison with an authentic sample. Our compound 14 has m.p. 172-174°C (Et_2O/hexane), Lit. (5) m.p. 172-172.5°C IR ($CHCl_3$) cm^{-1} : 1777. NMR (C_6D_6), δ (ppm) : 6.71 (1H, s) ; 6.49 (1H, s) ; 6.41 (1H, s) ; 5.48-5.42 (2H) ; 3.83 (3H, s) ; 3.49 (3H, s) ; 3.42 (3H, s).

Finally steg-7-en-8-ol 15 was obtained by JONES's oxidation (1 h at room temperature) of 7 and 8, in 62 % and 78 % yields respectively. Compound 15 has m.p. 207-209°C (C_6H_6) and gives a positive $FeCl_3$ test. IR (CH_2Cl_2) cm^{-1} : 1698, 1647. NMR ($CDCl_3$), δ(ppm) 11.28 (1H, s) ; 6.97 (1H, s) ; 6.78 (1H, s) ; 6.68 (1H, s) ; 6.06 (2H) ; 4.70 - 4.0 (3H) ; 3.97 (6H, s) ; 3.61 (3H, s) ; 2.87 (1H) ; 2.38 (1H). M^+ 412.1158 ($C_{22}H_{20}O_8$). Molecular model examination has revealed that the only possible configuration of steg-7-en-8-ol is that of structure 15 ("normal" configuration).

Conclusion.

The thermal interconversion of 11 into 12 and the alkaline isomerisation of 12 into 14 provide good evidence for the structures we propose for 11 and 12. These findings, as well as other chemical correlations already mentioned above, confirm the structures we assigned to compounds 7, 8, 9 and 10. In the latter compounds, the stereochemistry of the hydroxyl

at C_8 was ascertained by comparing the chemical shifts and the coupling constants of the carbinolic H at C_8, using DREIDING models, and by comparison with the NMR signals described for the carbinolic H of podorhizol and epipodorhizol (12).

The approach to bis-benzocyclooctadienes described by SCHLESSINGER (5), led to isostegane 14 and not to stegane 13. The present results confirm SCHLESSINGER's observations, inasmuch as we were equally unable to obtain stegane 13, even under supposedly equilibrating conditions. Therefore stegane 13, the parent compound of steganacin 1, steganol 2 and steganone 3, remains as yet unknown.

Aknowledgements

We are very grateful to Dr. R.H. SCHLESSINGER, Rochester, N.Y., for a generous gift of (±) isostegane.

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(Received in UK 10 July 1978; accepted for publication 21 July 1978)