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ASYMMETRIC TOTAL SYNTHESIS OF THE ANTILEUKAEMIC LIGNAN PRECURSOR (-)STEGANONE AND REVISION OF ITS ABSOLUTE CONFIGURATION

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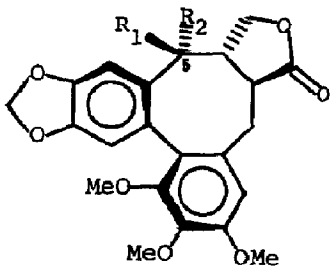
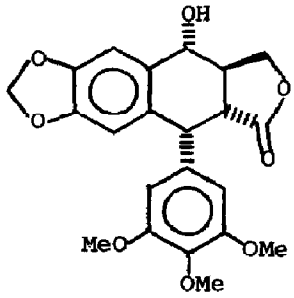
Summary : A total synthesis of (-)steganone, correlating it with L-glutamic acid, shows it to have the opposite configuration to that assigned by Kupchan.

In 1973, the late Morris KUPCHAN and his co-workers (1) isolated new antileukaemic lignans from Steganotaenia araliacea Hochst, namely steganone 1a, steganol 1b, steganacin 1c and steganangin 1d, which all have the novel bisbenzocyclooctadiene lactone skeleton. These compounds, which are closely related to the well-known antimitotic lignan podophyllotoxin 2, were assigned the absolute configuration represented on the structure 1, on the basis of X-ray diffraction studies performed on episteganol 1e, using a direct method without heavy atom (1).



1



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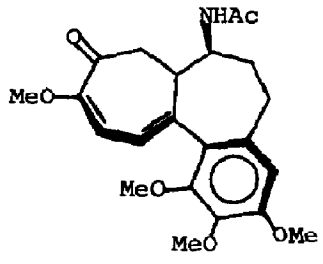


3

1a, R_1, R_2 = O

1b, R_1 = OH, R_2 = H

1c, R_1 = OAc, R_2 = H

1d, R_1 =angelate, R_2=H

1e, R_1 = H, R_2 = OH

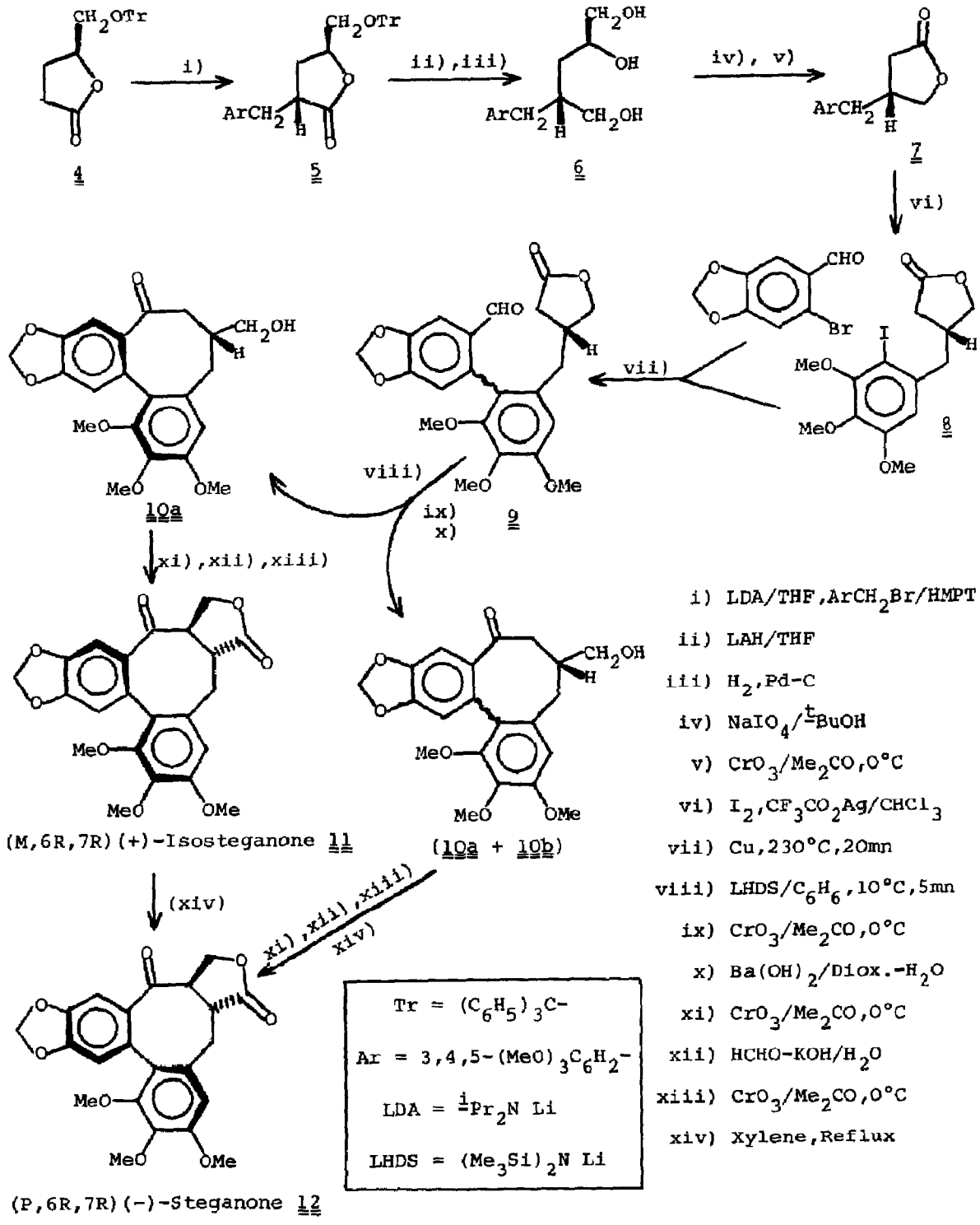
	yield (%)	m.p.(Solvent)	$[\alpha]_D^{20}$
5	78	133.5°(ether)	+25.4°,C= 0.86$CHCl_3$
6	91	liquid	-5.7°,C= 0.95$CHCl_3$
7	91	101-103°(ether)	+6.6°,C= 0.76$CHCl_3$
8	100	85° (ether)	+2.3°,C= 0.87$CHCl_3$
9	59	142-145°(ether)	+3.5°, C = 1 $CHCl_3$

Later on, KUPCHAN and co-workers found (2) that steganacin 1c inhibited the in vitro polymerization of tubulin, in a competitive manner with colchicine 3, and in the same way as podophyllotoxin 2 does. One of us (JPR) has already pointed out (3,4) that since steganacin 1c, podophyllotoxin 2 and colchicine 3 competitively bind to the same site of the tubulin protein, they must have similar overall geometries, which implies for steganacin 1c an absolute configuration opposite to that allotted by KUPCHAN and co-workers.

In order to clear up this point, the asymmetric total synthesis of steganone 1a was carried out in the following manner, using the optically active precursor 4 which we prepared from L-glutamic acid, after improvement of the litterature procedure (5).

Optically active (R)-3-(3,4,5-trimethoxybenzyl)-4-butanolide 7 was obtained in five steps (see scheme) from compound (S)(+) - 4 [m.p. = 148.5-149.5° (C_6H_6), $[\alpha]_D^{20}$ = + 30.5° (C=1, EtOH)] using the so-called "self-immolative" technique described by KOGA (5) for the asymmetric synthesis of 3-alkyl 4-butanolides. Alkylation of the lithium enolate of 4 with 3,4,5-trimethoxybenzyl bromide afforded 5 as a single, sharp-melting, compound. In contrast with the described piperonyl analogue (5), compound 5 could be easily purified by recrystallization. Compound (3R)-7 was submitted to the same reaction sequence we used with the corresponding racemic mixture in our total synthesis of (±) steganone 1a (6) (see scheme). All the present yields (see table) were close to those we observed in our racemic synthesis, and the various optically active intermediates we obtained had IR and NMR data identical to those of their racemates.

We separated the crude mixture of β-hydroxymethylketones 10 into 10a (amorphous) alone and the atropoisomeric mixture of (10a + 10b) in 67 % yield, by chromatography on silica gel using a CH_2Cl_2/MeOH gradient. Compound 10a was treated according to the sequence we already described (JONES's oxidation, HCHO/KOH hydroxymethylation, lactonization, oxidation of the alcohols resulting from a cross-CANNIZZARO reaction), to give pure (M, 6R, 7R) (+)-isosteganone 11 (7), m.p. 107-109° (ether), $[\alpha]_D^{20}$ = + 118° (C=1.16, $CHCl_3$) ; $\nu_{(CO)}$ = 1710 cm^{-1}, in 57 % yield from 10a. Similar treatment of the mixture of (10a + 10b), followed by thermal isomerization, afforded the thermodynamically favoured (P, 6R, 7R) (-)-steganone 12, m.p. = 154-156°C (ether), $[\alpha]_D^{20}$ = -140° (C=1.16, $CHCl_3$), $\nu_{(CO)}$ = 1668 cm^{-1}, in 52 % yield from (10a + 10b).


CH2OTr
i)
ArCH2
ii),iii)
CH2OH
OH
iv), v)
O
4
5
6
7
vi)
CHO
Br
I
MeO
OMe
8
vii)
9
viii)
ix)
x)
10a
xi),xii),xiii)
(M,6R,7R)(+)-Isosteganone 11
(10a + 10b)
(xiv)
xi),xii),xiii)
xiv)
(P,6R,7R)(-)-Steganone 12
Tr = (C6H5)3C-
Ar = 3,4,5-(MeO)3C6H2-
LDA = iPr2N Li
LHDS = (Me3Si)2N Li
i) LDA/THF,ArCH2Br/HMPT
ii) LAH/THF
iii) H2,Pd-C
iv) NaIO4/tBuOH
v) CrO3/Me2CO,0°C
vi) I2,CF3CO2Ag/CHCl3
vii) Cu,230°C,20mn
viii) LHDS/C6H6,10°C,5mn
ix) CrO3/Me2CO,0°C
x) Ba(OH)2/Diox.-H2O
xi) CrO3/Me2CO,0°C
xii) HCHO-KOH/H2O
xiii) CrO3/Me2CO,0°C
xiv) Xylene,Reflux

The literature (1) gives m.p. = 155-156°C and $[\alpha]_D^{20} = -202°$ for natural steganone. Racemic steganone has a m.p. = 231-233°C (6). We could not obtain a sample of natural (-) steganone to estimate the optical purity of our synthetic compound using our own polarimeter.

Conclusion

We have described an asymmetric total synthesis of (-)steganone 11, following an unambiguous scheme which shows that this natural compound has indeed an absolute configuration opposite to that assigned by KUPCHAN (1,8). Therefore, the absolute configuration (P, 6R, 7R) of (-)steganone 11 is similar to those of podophyllotoxin 2 and colchicine 3. The present reaction scheme, which is of preparative value, is being applied in our laboratory to the syntheses of various potentially useful anticancer analogues of bisbenzocyclooctadiene lactone lignans.

Aknowledgements

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References

(1) S.M. KUPCHAN, R.W. BRITTON, M.F. ZIEGLER, C.J. GILMORE, R.J. RESTIVO and R.F. BRYAN, J. Amer. Chem. Soc., 95, 1335 (1973).

(2) R.W.J. WANG, L.I. REBBUN and S.M. KUPCHAN, Cancer Res., 37, 3071 (1977).

(3) J.P. ROBIN, Thèse d'Etat, LE MANS, 1979 and ref. cit.

(4) F. ZAVALA, D. GUENARD, J.P. ROBIN and E. BROWN, J. Med. Chem., (April 1980), in the press.

(5) K. TOMIOKA and K. KOGA, Tetrahedron Letters, 3315 (1979).

(6) E. BROWN, R. DHAL and J.P. ROBIN, Tetrahedron Letters, 733 (1979).

(7) We prefer using CAHN, INGOLD and PRELOG's rule of helicity in the case of bridged biphenyls (P,M convention), because the (R, S) denomination can be ambiguous in the present case (R.F. CAHN, C. INGOLD, V. PRELOG, Angew. Chem. internat. Edit., 5, 385 (1966).

We keep the prefix iso to describe the (M, 6R, 7R) or (P, 6S, 7S) configuration, the adjective normal referring to the (P, 6R, 7R) or (M, 6S, 7S) configurations.

(8) Confirmation of our assertion by X-ray diffraction using a heavy atom is in progress.

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