Tetrahedron Letters,Vol.23,No.20,pp 2139-2142,1982 0040-4039/82/202139-04$03.00/0
Printed in Great Britain

IMINE-ENAMINE ANNELATION: STEREOSELECTIVE SYNTHESES OF (±)-DEPLANCHEINE

Luisella Calabi, Bruno Danieli*, Giordano Lesma and Giovanni Palmisano*

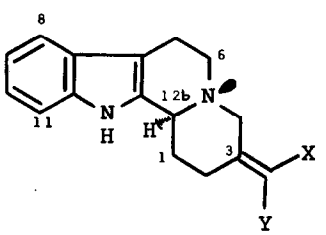
Istituto di Chimica Organica della Facoltà di Scienze - Via Venezian, 21 - 20133 Milano - Italy, Centro CNR di Studio per le Sostanze Organiche Naturali

Summary: Two new approaches to synthesis of (±)-deplancheine (1) are described which utilize the alkylation of the imine-enamine (2) as the key ring-forming step.

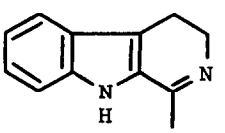
The synthesis of the simple indoloquinolizidine alkaloid deplancheine (1), isolated from a New Caledonian plant [*Alstonia deplanchei* van Heurck and Müller Arg.][1a] has attracted the attention of several research groups.[1b-d]

We report here the details of two efficient approaches to (±)-deplancheine taking advantage of the reactivity of the readily available imine-enamine (2) as ambident nucleophile *vs.* electron-deficient alkenes.[2]

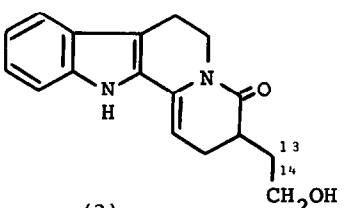
Treatment of (2) with 1.1 equiv of α-methylene-γ-butyrolactone in MeCN for 5 hr at 80° C gave an 84% yield of enaminone (3), m.p. 208° C (MeOH).[3] Reduction of this with $LiAlH_4$ in boiling THF (1 hr), followed by reductive work-up with $NaBH_4$ at 0° C (30 min) proceeded smoothly affording the alcohol (4)[4] as the sole product in 79% yield. The trisubstituted olefinic linkage in (1) was then elaborated with low selectivity in 58% overall yield from (4) *via* a three-step sequence. The alcohol (4), upon exposure to o-nitrophenyl selenocyanate[5] in THF in the presence of n-Bu_3P (3 hr, r.t.), provided the nicely crystalline selenide (5), m.p. 91° C (Et_2O)[6] whose subsequent oxidation ($NaIO_4$, MeOH, -10° C, 4 hr) and base-induced *syn*-elimination[7] (diisopropylamine work-up at r.t.) ga-



(1) X:H; Y:Me
(7) X:Me; Y:H



(2)



(3)

ve rise to the vinyl quinolizine (6).[8,9] Attempts to eliminate the hydroxy group of (4) by any of the standard methods seemed unlikely to succeed because of N_b-participation.

Finally, (6) underwent double bond migration by heating (thick-walled tube) in degassed EtOH at 120°C for 1 hr in the presence of catalytic $RhCl_3$ trihydrate.[10] Column chromatography followed by PLC on silica gel gave the desired (±)-deplancheine (1) (CH_2Cl_2-MeOH, 95:5; R_f 0.23)[11] along with its (Z)-isomer (7) (R_f 0.47)[12] and unreacted (6) (R_f 0.34) as a 6:3:1 mixture.

In an effort to render the approach to (1) more stereoselective we examined an alternative scheme, the key feature of which was projected to be the synthesis of the (E)-enamide (8) by joining the phosphonate (9) with acetaldehyde under Wittig-Horner conditions. When an equimolecular mixture of (2) and methyl 2-(diethylphosphono)acrylate[13] in MeOH-C_6H_6 (1:1) was stirred at r.t. for 24 hr, the imino-phosphonate (10)[14] was obtained. Reduction of (10) with $NaBH_4$ in MeOH (0°C, 50 min) gave, with concomitant lactonization, the amido-phosphonate (9) in 87% overall yield as a 9:1 mixture of diastereoisomers,[15] which was used directly in the next step. Generation of the phosphoryl-stabilized anion derived from (9) was carried out by addition of NaH (2.1 equiv) to a solution of (9) in DME at 0°C. After 5 min, a solution of acetaldehyde (1.5 equiv) in DME was added, warmed at r.t. and processed after 10 min. Chromatographic purification produced the pure (E)-enamide (8), m.p. 239°C (Et_2O)[16] in 83% yield [no (Z)-isomer present].

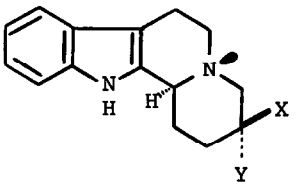
Selective reduction of carbonyl group in enamides is known to be difficult to achieve[16b] but careful reduction with $LiAlH_4$ in DME (-78°→0°C, 30 min) or with AlH_3 in Et_2O-DME (1:1) (1 hr at r.t.) yielded the target compound (1) in 65% and 69% yields respectively.

The ketone (11),[1c] a straightforward precursor of (1) and (7), was obtained in 63% overall yield by a two-step sequence which exploits the reactivity of (2) *vis* 1,3-difunctionalized propanes.[17]

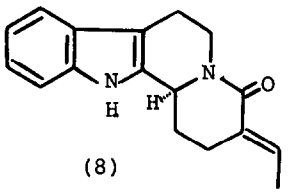
Alkylation of (2) with 1.2 equiv of 1-bromo-2,3-epoxypropane in refluxing MeCN (3 hr) in the presence of Hünig's base, followed by reductive work-up ($NaBH_4$, MeOH, r.t.) led to alcohol (12)[18] as a 1:1 diastereoisomeric mixture which was in turn oxidized (DMSO-DCC-orthophosphoric acid, r.t., 3 hr) to the sensitive ketone (11).[19]

Extension of this annelation to suitably substituted α-methylene-γ-butyrolactones and phosphonoacrylates for the synthesis of *Corynanthé* alkaloids is currently underway.

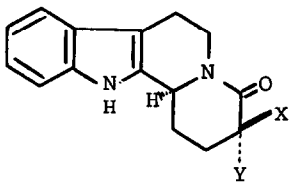
We are grateful to Dr. Joule for providing us with a generous sample of (1)+(7) mixture and the procedure for separation of these isomers.



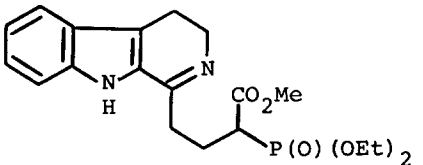
(4) X:H; Y:$(CH_2)_2OH$
(5) X:H; Y:$(CH_2)_2Se(o\text{-}NO_2)Ph$
(6) X:H; Y:$CH{=}CH_2$
(11) X,Y:O
(12a) X:H; Y:OH
(12b) X:OH; Y:H
(13) X:H; Y:C_2H_5



(8)



(9a) X:H; Y:$P(O)(OEt)_2$
(9b) X:$P(O)(OEt)_2$; Y:H



(10)

References and notes

1 *a*) R.Besselièvre, J.-P.Cosson,B.C.Das, and H.-P.Husson, Tetrahedron Letters, 63(1980); *b*) D.Thielke, J.Wegener, and E.Winterfeldt, Chem.Ber.,108,1791(1974); *c*) W.R.Ashcroft and J.A.Joule, Tetrahedron Letters,2341(1980); *d*) M.Hämeilä and M.Lounasmaa, Acta Chem.Scand.,B,35,5(1981).

2 T.Kametani, Y.Suzuki, H.Terasawa, and M.Ihara, J.C.S.Perkin I,1211(1979); B.Danieli, G.Lesma, and G.Palmisano, J.C.S.Chem.Commun.,109(1980).

3 PMR(DMSO-d_6): δ3.66(1H,dt,J 12.5Hz,H-6α),4.16(1H,t,J 6Hz,OH), 4.32(1H,dt,J 12,5Hz,H-6β), 5.74(1H,t,J 5Hz,H-1).

4 $\nu_{max}(CHCl_3)$:2850,2800,2760 cm^{-1}[Bohlmann bands(Bb)]; PMR(DMSO-d_6): δ3.54(2H, t,J 6Hz,CH_2OH), 4.46(1H,t,J 6Hz,OH).

5 P.A.Grieco, S.Gilman, and M.Nishizawa, J.Org.Chem.,41,1485(1976).

6 $\nu_{max}(CHCl_3)$:2830,2790,2740 cm^{-1}(Bb); PMR($CDCl_3$): δ7.78(1H,br s,NH), 8.38(1H, ddd,J 10,1.5,1Hz).

7 K.B.Sharpless and M.Young, J.Org.Chem.,40,947(1975).

[8] $\nu_{max}(CHCl_3)$: 2850,2800,2750(Bb),915 cm^{-1}(C=C); PMR($CDCl_3$): δ5.09(1H,dd,J 10,1Hz,H-14), 5.15(1H,dd,J 18,1Hz,H-14), 5.86(1H,ddd,J 18,10,7Hz,H-13), 7.80(1H,br s,NH).

[9] The relative stereochemistry of (4) was firmly established by reductive removal of phenylselenyl group from (5) with Bu_3SnH-azobis(isobutyronitrile) in refluxing toluene (3 hr) to give the known (3R*,12bS*)-octahydroflavopereirine (13); CMR($CDCl_3$): δ_C29.9(C_2), 30.8(C_1), 37.8(C_3), 60.3(C_4), 61.8(C_{12b}). [Cfr. E.Wenkert and B.Wickberg, J.Amer.Chem.Soc.,84,4914(1962)]

[10] J.F.Harrod and A.J.Chalk, J.Amer.Chem.Soc.,86,1776(1964).

[11] PMR(200MHz,$CDCl_3$): δ1.62(3H,d,J 6.5Hz,CH_3-C=), 3.06(1H,d,J 12Hz,H-4α), 3.35(1H,d,J 12Hz,H-4β), 3.42(1H,br d,J 11Hz,H-12b), 5.43(1H,q,J 6.5Hz,H-C=), 7.08 and 7.10(2H,2xt,J 8.5Hz,H-9 and H-10), 7.29(1H,t,J 8Hz,H-11), 7.44(1H,d,J 8Hz,H-8), 7.86(1H,br s,NH).

[12] PMR(200MHz,$CDCl_3$): δ1.65(3H,d,J 6.5Hz,CH_3-C=), 2.80(1H,d,J 12Hz,H-4α), 3.47(1H,br d,J 11Hz,H-12b), 3.84(1H,d,J 12Hz,H-4β), 5.33(1H,q,J 6.5Hz,H-C=), 7.86(1H,br s,NH).

[13] M.F.Semmelhack, J.C.Tomesch, M.Czarny, and S.Boettger,J.Org.Chem.,43,1259(1978).

[14] $\nu_{max}(CHCl_3)$:1720(C=O) 1040,1018,930 cm^{-1}(P=O); PMR($CDCl_3$): δ1.36(6H,t,J 7 Hz,CH_3-CH_2), 3.20(1H,dt,J 23,7Hz,H-C-P), 3.80(3H,s,CO_2CH_3), 3.84(2H,t,J 7 Hz,CH_2-N), 4.24(2H,dq,J 7Hz,CH_2-O-P), 10.36(1H,br s,NH).

[15] (9a):m.p. 236°C(MeOH); $\nu_{max}(CHCl_3)$:1625(C=O),960 cm^{-1}(P=O); PMR(200MHz,DMSO-d_6): δ1.15 and 1.26(6H,2 t,J 7Hz,CH_3-CH_2), 2.91(1H,dt,J 12,4Hz,H-6α), 4.02 and 4.06(4H,2xquint,J 7Hz,CH_3-CH_2-O-P), 4.89(1H,m,$W_{1/2}$ 12Hz,H-12b), 5.00(1H,dd,J 12,4Hz,H-6β), 7.04 and 7.13(2H,2xt,J 8.5Hz,H-9 and H-10), 7.39 and 7.48(2H,2xd,J 8.5Hz,H-8 and H-11), 10.92(1H,br s,NH). (9b); PMR($CDCl_3$): δ 1.33 and 1.35(6H,2xt,J 7Hz,CH_3-CH_2), 4.15(4H,2xquint,J 7Hz,CH_3-CH_2-O-P), 4.81(1H,ddd,J 10,5,2Hz,H-6β), 5.09(1H,dd,J 8.5,2.5Hz,H-12b), 8.44(1H,br s,NH).

[16] PMR(200MHz,DMSO-d_6):δ1.72(3H,J 8Hz,CH_3-C=), 4.86(1H,dd,J 12,2Hz,H-12b),4.95(1H,dd,J 13,2.5Hz,H-6β), 6.74(1H,q,J 8Hz,H-C=), 6.95 and 7.05(2H,2xt,J 8Hz, H-9 and H-10), 7.30 and 7.39(2H,2xd,J 8Hz,H-8 and H-11), 10.92(1H,br s,NH).

[17] B.Danieli, G.Lesma, and G.Palmisano, J.C.S.Chem.Commun.,860(1980); Tetrahedron Letters,1827(1981); Gazz.Chim.Ital.,111,257(1981).

[18] W.R.Ashcroft and J.A.Joule, Heterocycles,16,1883(1981). (12a); PMR($CDCl_3$): δ2.28(1H,t,J 10Hz,H-4α), 3.21(1H,ddd,J 10,4,2Hz,H-4β), 3.92(1H,tt,J 10,4Hz, H-3), 7.75(1H,br s,NH). (12b); PMR($CDCl_3$):δ2.60(1H,dd,J 11,2Hz,H-4α), 3.00(1H,dt,J 11,2Hz,H-4β), 3.30(1H,dd,J 10,2Hz,H-12b), 3.94(1H,br s,$W_{1/2}$8Hz,H-3).

[19] $\nu_{max}(CHCl_3)$:2845,2800,2730(Bb),1720 cm^{-1}(C=O); PMR($CDCl_3$): δ3.05(1H,d,J 14Hz, H-4α), 3.45(1H,d,J 14Hz,H-4β), 4.19(1H,dd,J 8,1Hz,H-12b), 8.11(1H,br s,NH).

(Received in UK 23 March 1982)