Tetrahedron Letters,Vol.24,No.27,pp 2783-2786,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

AN EFFICIENT TOTAL SYNTHESIS OF (±)-DECALINE AND (±)-VERTALINE

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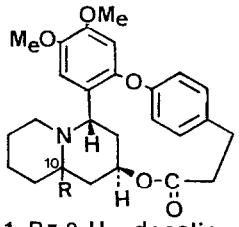
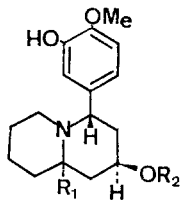
Summary: An efficient total synthesis of the Lythraceae alkaloids decaline and vertaline *via* the intermolecular [3+2]cycloaddition is described.

Two isomeric quinolizidine alkaloids[1] decaline(1) and vertaline(2), differing in the configuration of the C-10, were isolated by Ferris from Decodon verticillatus[2]. They have a unique 14-membered biphenyl ether macrolide structure. Although both alkaloids have been synthesized separately[3], there are no efficient routes which lead to the formation of both 1 and 2 from a single precursor.

In the previous paper[4], one of the authors showed a general synthetic approach to the quinolizidine alkaloids *via* [3+2]cycloaddition[5] and synthesized two naturally occurring arylquinolizidinols(3,4)[4] and the ester alkaloid abresoline (5)[6].



1 R= β-H decaline
2 R= α-H vertaline



3 R_1=β-H, R_2=H
4 R_1=α-H, R_2=H
5 R_1=β-H,
R_2= -C(=O)-CH=CH-C6H3(OH)(OMe)

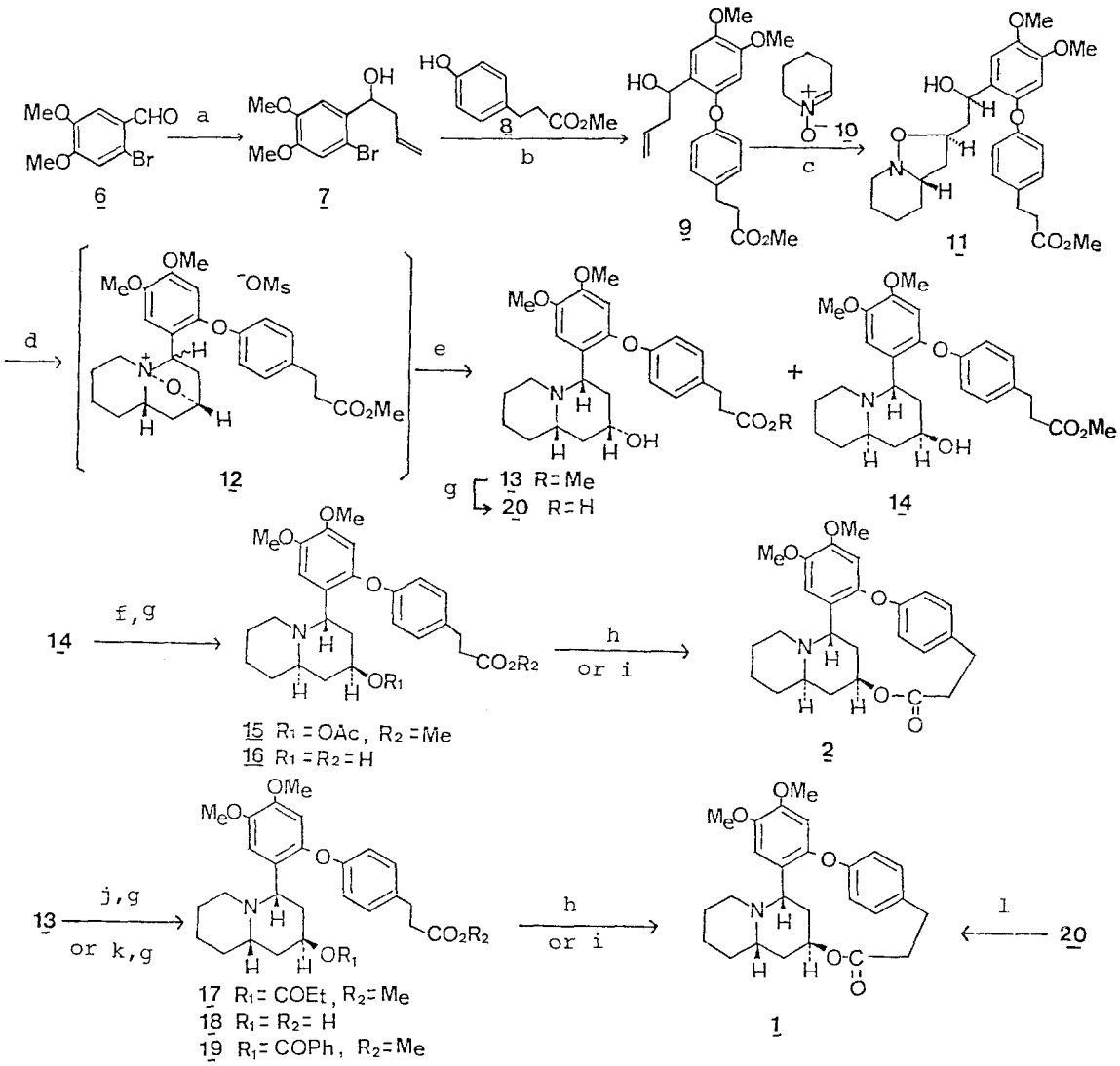
In connection with our interest in the synthesis of the Lythraceae alkaloids using this methodology, we now report here an efficient total synthesis of both decaline(1) and vertaline(2) from a single precursor(11).

The homoallylic alcohol(7), readily derived from 6-bromoveratraldehyde(6) with allylmagnesium bromide, was heated with methyl 3-(4-hydroxyphenyl)propionate(8)[7] in pyridine at 120-150° for 5 h in the presence of copper(II) oxide and a catalytic amount of tetra-n-butylammonium bromide to give the biphenyl ether(9) in 52% yield. In this Ullmann reaction, it was found that the presence of a phase-transfer catalyst[8] enhanced the yield of the biphenyl ether(9) (35% yield without PTC). On heating 9 with 3,4,5,6-tetrahydropyridine 1-oxide(10)[9] in toluene under reflux for 2 h, the adduct(11) was obtained in 99% yield as a mixture of inseparable diastereomer[10]. The adduct(11) was then treated with methanesulfonyl chloride in CH_2Cl_2 in the presence of triethylamine followed by

a Zn-50% aq. acetic acid in one-pot operation to give the expected two alcohols (13) [IR($CHCl_3$)cm^{-1}:3600(OH), 2790, 2750(Bohlmann bands), 1735(CO); MS(m/z):469 (M^+)] and (14) [IR($CHCl_3$)cm^{-1}:3600(OH), 1740(CO); MS(m/z):469(M^+)] through the quaternary salt(12) in 43.9% and 50.7% yield, respectively. The structure of the cis-quinolizidinol(14) was confirmed by the conversion to the known acetate (15) [IR($CHCl_3$)cm^{-1}:1730(CO); NMR(δ in $CDCl_3$, 100MHz):1.85(3H,s), 3.65, 3.76, 3.90 (each 3H,s), 4.54(1H,t,J=6 Hz), 5.10(1H,m); MS(m/z):511(M^+)] which was identical with the reported spectral data[3e]. The acetate(15) was converted into (±)-vertaline(2), which was identical(mixed mp, TLC, IR, and 100 MHz NMR) with an authentic sample of (±)-2, by successive hydrolysis and lactonization developed by Corey[11] in 58.9% yield. The alternative macrolide formation, which was reported by Masamune[12], was also examined. Thus, treatment of the hydroxy acid(16) with diphenyl phosphochrolidate and triethylamine followed by a stirring in warm benzene containing 4-dimethylaminopyridine resorting to a high dilution technique gave 2 in 54.1% yield.

On the other hand, to complete the synthesis of decaline(1), it is necessary to lactonize with S_N2 inversion at the hydroxy-bearing carbon atom(C-2) in 13. Treatment of the hydroxy acid(20) with Mitsunobu condition[13] or Kellog method[14] has proven ineffective. Only in the use of N,N-dimethylformamide dineopentyl acetal[15], (±)-decaline(1) was obtained in 10% yield. To improve the yield of the final step, the intermolecular S_N2 inversion at C-2 was investigated by two different methods. Formation of the mesylate of 13 followed by treatment with cesium propionate[16] in DMF at 90° for 42 h gave the inverted propionate(17) [IR ($CHCl_3$)cm^{-1}:2800, 2780(Bohlmann bands), 1730(CO); NMR(δ in $CDCl_3$, 100 MHz):0.92 (3H,t,J=8 Hz), 2.06(2H,q,J=8 Hz), 4.92(1H,m); High resolution MS(m/z):Calcd for $C_{30}H_{39}NO_7$:525.2725. Found:525.2703] in 41.5% yield from 13. The second we examined is the method using Mitsunobu reaction[13]. Thus, 13 was treated with diethyl azodicarboxylate and triphenylphosphine in the presence of benzoic acid gave the benzoate(19) [IR($CHCl_3$)cm^{-1}:2800, 2770(Bohlmann bands), 1720(CO); NMR (δ in $CDCl_3$, 100 MHz):5.15(1H,m); High resolution MS(m/z):Calcd for $C_{34}H_{39}NO_7$: 573.2726. Found:573.2729] in 86.2% yield. Finally, the hydrolysis of 19 followed by the lactonization of the resulting hydroxy acid(18) under the same conditions as described for vertaline synthesis gave (±)-decaline(1), which was identical (mixed mp, TLC, IR, and 100 MHz NMR) with an authentic (±)-1, in 57.4% and 45.0% yield, respectively.

Acknowledgement: We are grateful to Professor M. Hanaoka, Kanazawa University, for providing a generous authentic samples and their spectral data(IR and ^{1}HNMR) of (±)-decaline and (±)-vertaline.



(a) Allyl bromide, Mg, THF, 87.7% (b) pyridine, CuO, $^{n}Bu_4NBr$(0.09 eq.), 120-150°, 52% (c) toluene, reflux, 99% (d) CH_3SO_2Cl, NEt_3, CH_2Cl_2, 0°-RT (e) Zn powder, 50% aq. AcOH, RT, 43.9% of 13, 50.7% of 14 (f) Ac_2O, pyridine, RT, 83.6% (g) 5% NaOH, MeOH, reflux: or LiOH, aq. MeOH, RT (h) 2,2'-dipyridyl disulfide, Ph_3P, CH_2Cl_2, RT; xylene, reflux, 58.9% for (±)-2, 57.4% for (±)-1 (i) $(PhO)_2POCl$, NEt_3, THF, 0°; DMAP, benzene, 80°-reflux, 54.1% for (±)-2, 45.0% for (±)-1 (j) CH_3SO_2Cl, NEt_3, CH_2Cl_2, 0°-RT; $EtCO_2Cs$, DMF, 90°, 41.5% (k) diethyl azodicarboxylate, Ph_3P, benzoic acid, THF, RT, 86.2% (l) N,N-dimethylformamide dineopentyl acetal, toluene, reflux, 10%.

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8) We examined two types of phase-transfer catalysts such as quaternary ammonium salts and crown ethers. Both catalysts showed almost the same effectiveness in the yield of the biphenyl ether formation, and furthermore it was revealed that the ammonium salts are superior to the crown ethers in the less formation of the debrominated by-product.

9) The nitrone(10) was prepared in situ by the reaction of 1-hydroxypiperidine with HgO(yellow) in CH_2Cl_2 at 0 - 10°.

10) The structure and stereochemistry of the adduct(11) was firmly established by its eventual conversion to both decaline and vertaline.

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(Received in Japan 22 March 1983)