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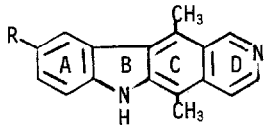
# A REGIOSPECIFIC TOTAL SYNTHESIS OF ELLIPTICINE *VIA* NITRENE INSERTION

R. Bryan Miller* and Sundeep Dugar
Department of Chemistry, University of California, Davis, CA 95616

Abstract. Ellipticine, a 6H-pyrido[4,3-b]carbazole alkaloid, has been regiospecifically synthesized by a general route which should allow for the preparation of a number of derivatives. The approach employs a versatile coupling reaction between phenylboronic acid and a substituted bromoisoquinoline followed by carbazole ring formation *via* a nitrene insertion reaction to give ellipticine.

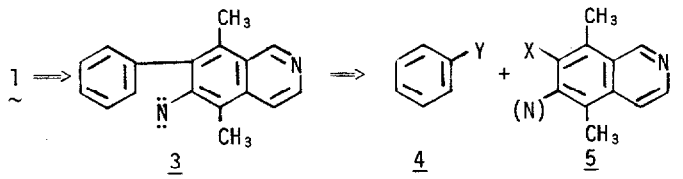
Members of the 6H-pyrido[4,3-b]carbazole class of alkaloids, particularly ellipticine (1) and 9-methoxyellipticine (2), have attracted considerable interest due to their significant anticancer activity.[1-3] As a result a general synthetic approach to this class of alkaloids has become highly desirable and considerable effort has been directed towards such a goal[3-5] including two reports from our laboratory.[6]




1 : R = H
2 : R = $OCH_3$

To achieve a general and regiospecific synthesis of these pyridocarbazole alkaloids, which would allow maximum versatility, we chose to keep the isoquinoline (rings C and D) and benzene (ring A) portions of the molecule separate until the latter stages of the synthesis and to form the pyrrole ring (B) in the last step by a nitrene insertion reaction. This paper describes the successful completion of such a route which is shown retrosynthetically in Scheme I. There are three major stages involved in this approach: (i) synthesis of an

Scheme I

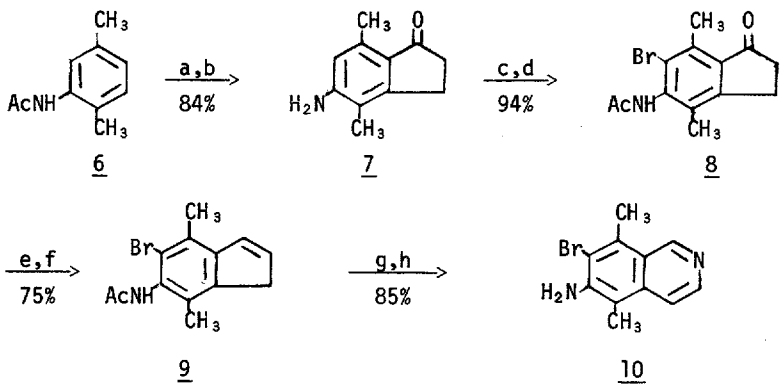



3 4 5

appropriately substituted isoquinoline moiety (5); (ii) formation of the crucial C-C bond to yield the corresponding 7-phenylisoquinoline derivative, the precursor of 3; and (iii) generation of the nitrene 3 to give ellipticine following C-H insertion.

The isoquinoline required for our purpose was 6-amino-7-bromo-5,8-dimethylisoquinoline (10) whose synthesis is shown in Scheme II. Acylation-alkylation of 2,5-dimethylacetanilide (6, prepared by acetylation of 2,5-dimethylaniline) with β-chloropropionyl chloride gave a mixture of free and acetylated aminoindanones which was hydrolyzed to give 5-amino-4,7-dimethylindan-1-one (7)[7]. The hydrolysis was favored over reacetylation of the amino group at this stage because the subsequent bromination of the aromatic nucleus was easier and gave a better yield with 7 than with the corresponding acetamidoindanone. Bromination in methylene chloride with a catalytic amount of iodine was found to be very selective with no detectable amounts of product(s) resulting from bromination α to the carbonyl. The amino

Scheme II




6 7 8

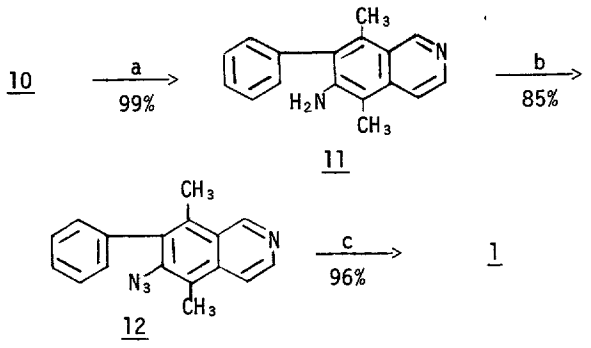
9 10

a. (i) $ClCH_2CH_2COCl$, $CS_2$, $AlCl_3$, (ii) $AlCl_3$, NaCl, 180°C; b. 2N HCl, reflux; c. $Br_2$($I_2$ cat.), $CH_2Cl_2$, r.t.; d. AcCl, $Et_3N$, THF, r.t.; e. $NaBH_4$, MeOH, 0°→r.t.; f. (i) 40% $H_2SO_4$/THF (1:4), reflux, (ii) $Ac_2O$, NaOAc; g. (i) $O_3$, MeOH/$CH_2Cl_2$(4:1), -78°C, (ii) $Me_2S$, $NaHCO_3$(s), (iii) $NH_4OH$; h. 2N HCl, reflux.

group, which is now a vinylogous amide, was protected using acetyl chloride and triethylamine; use of more standard conditions, such as acetic anhydride, were unsuccessful. Sodium borohydride reduction of the resulting 5-acetamido-6-bromo-4,7-dimethylindan-1-one (8)[7] gave the indanol which was eliminated under acidic conditions to the indene. These elimination conditions resulted in some hydrolysis of the acetamido group and thus the crude reaction mixture was treated with acetic anhydride and sodium acetate prior to work up. The purified 6-acetamido-5-bromo-4,7-dimethylindene (9)[7] was converted into the substituted isoquinoline following the procedure previously developed in our laboratories for the general synthesis of isoquinolines.[8] Hydrolysis of the acetamido group gave the desired 6-amino-7-bromo-5,8-dimethylisoquinoline (10)[7] in 50% overall yield from 6.

The key coupling reaction was carried out using the versatile methodology of Suzuki[9], which has been further extended in our laboratories[10] and others.[11] Thus, the aminobromoisoquinoline 10 was coupled with phenylboronic acid to give 6-amino-5,8-dimethyl-7-phenylisoquinoline (11)[7] in excellent yield (see Scheme III). The coupling could be carried out on the acetyl derivative of 10 as well, followed by acidic hydrolysis to yield 11. The amine 11 was converted to 6-azido-5,8-dimethyl-7-phenylisoquinoline (12)[7] by diazotization followed by treatment with sodium azide. The azidophenylisoquinoline 12, the precursor to nitrene 3, was subjected to solvent phase thermolysis in dodecane at 180°C. At the end of the reaction the

Scheme III




a. $PhB(OH)_2$, $Pd(PPh_3)_4$ (cat.), PhH, aq. 2M $Na_2CO_3$; reflux;
b. (i) $NaNO_2$, dil. HCl, 0°C, (ii) $NaN_3$; c. dodecane, 180°C.

solvent was removed by reduced pressure distillation and the crude product was purified by preparative thin layer chromatography (silica gel developed with methanol/dichloromethane: 10/90) to give ellipticine as a yellow solid in 96% yield.

The above synthetic approach to ellipticine should be quite general and, with the aminobromoisoquinoline 10 in hand, should allow the preparation of a number of ellipticine derivatives with various substituents in ring A by a three step sequence: (i) coupling with an appropriate arylboronic acid, (ii) conversion of the amino group to an azide, and (iii) thermolysis of the azide to give the ellipticine derivative.

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