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HIGH YIELD STEREOSPECIFIC TOTAL SYNTHESES
OF EBURNAMONINE AND EBURNAMINE

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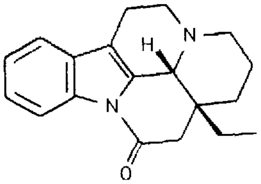
Eburnamonine (1) and eburnamine (2) are pentacyclic indole alkaloids isolated from *Hunteria eburnea* Pichon (Apocyanaceae) [1] Eburnamonine is useful as a cerebrovascular agent,[2] and therefore, is of interest with respect to efficient total synthesis [3] Herein, we describe a regiospecific alkylation of the tricyclic lactam 3[4] which facilitates construction of *dl*-eburnamonine and *dl*-eburnamine in overall yields of 67% and 53% respectively



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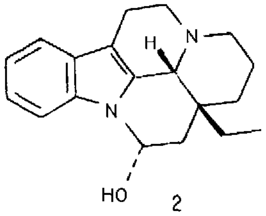

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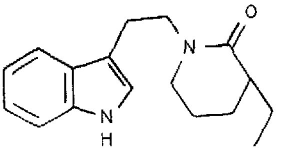

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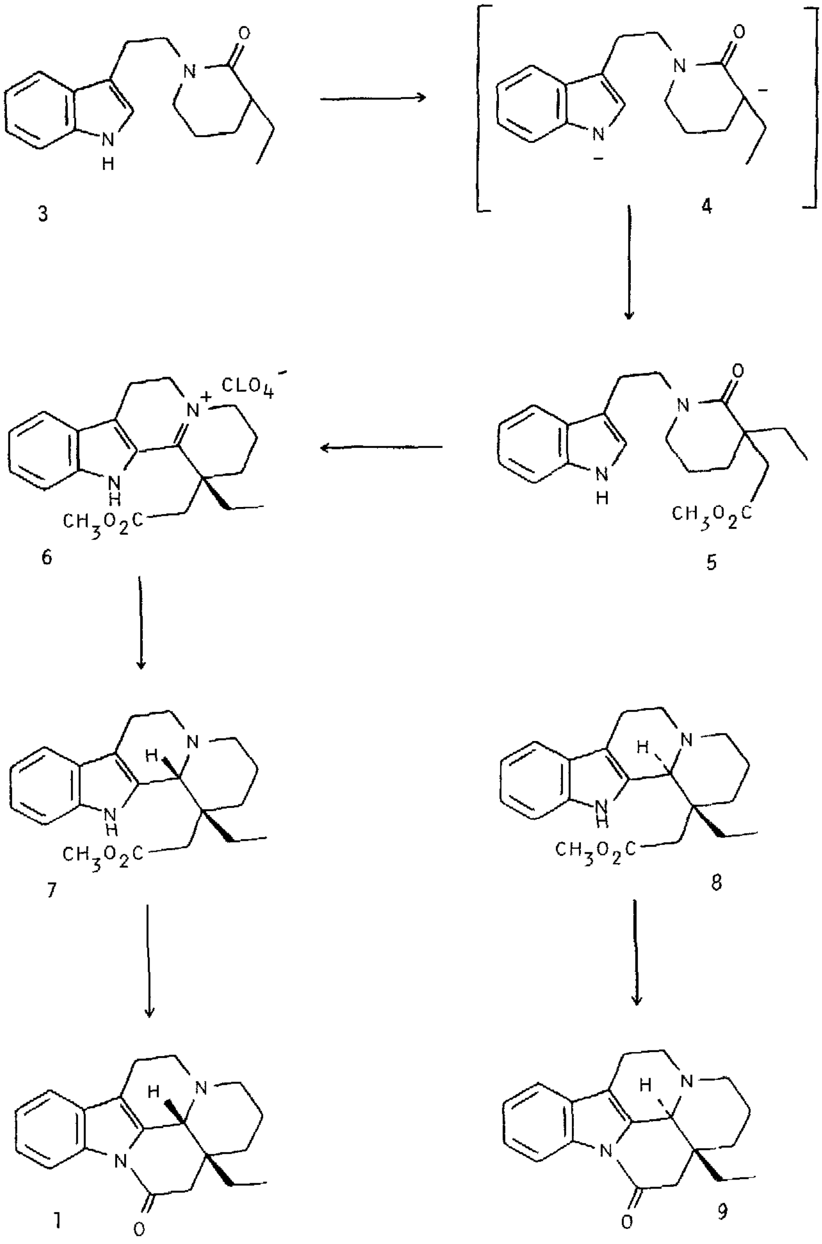
3
4
5
6
7
8
1
9
CLO4⁻
CH3O2C

Addition of 3[4] (1 equiv) at -78° to a solution of lithium diisopropylamide (2 1 equiv, 1 M in THF) gave rise to the dianion 4 (tan suspension) Alkylation of the dianion with methyl bromoacetate (1 5 equiv) followed by stirring at -78° for 30 min afforded the lactam ester 5 (oil) in 95% yield Cyclization of 5 (1 equiv) was carried out for 14 hrs in refluxing acetonitrile (0 1 M) containing phosphorus oxychloride (30 equiv) The crude reaction mixture was treated with lithium perchlorate (2 equiv) in water to give the immonium perchlorate 6 (mp 102-110°, 90% yield from 5)

Hydrogenation of 6 with 10% palladium on charcoal (30% by weight relative to 6) in methanol solution (0 5 M containing a trace of 70% perchloric acid) gave a mixture of methyl eburnamoninate 7 and methyl epieburnamoniate 8 in quantitative yield This mixture of esters was cyclized at 22° for 12 hours using sodium methoxide (1 equiv) in methanol solution (0 1 M) The resulting reaction mixture was filtered through silica gel to give *dl*-epieburnamonine 9 (mp 133-136°,[5] 13% yield from 6) and *dl*-eburnamonine 1 (mp 200-202°,[5] 78% yield from 6)[6]

Lithium aluminum hydride reduction of synthetic eburnamonine in THF solution at 5° gave a 1 1 mixture of *dl*-eburnamine 2 and *dl*-isoeburnamine 10 in quantitative yield

This mixture was epimerized by treatment with sodium methoxide (1 equiv) in methanol (1 M) at 70° for 12 hrs After thick layer chromatography, *dl*-eburnamine (mp 178-181°)[5] was isolated in 80% overall yield from 1

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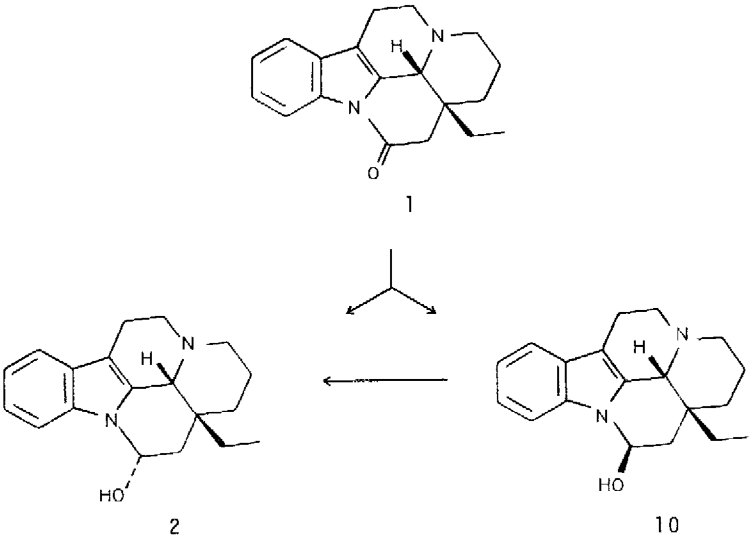

REFERENCES

1 M F Bartlett, W I Taylor, and Raymond-Hamet, *C R Acad Sci* , Paris <u>249</u> 1259 (1959)

2 J Martel and G Costerousse, *Fr Demande,* 2,179,620 (1973)

3 Syntheses of eburnamonine have been described by (a) M F Bartlett and W I Taylor, *J Amer Chem Soc* , <u>82</u>, 5941 (1960), (b) E Wenkert and B Wickberg, *ibid* , <u>87</u>, 1580 (1965)

4 J L Herrmann, R J Cregge, J E Richman, C L Semmelhack, and R H Schlessinger, *ibid* , <u>96</u>, 3702 (1974), also see reference 3b

5 M F Bartlett, R Sklar, A F Smith, and W I Taylor, *J Org Chem.,* <u>28</u>, 2197 (1963)

6 Compounds 1 and 9 are readily separated by one crystallization from methylene chloride