Pergamon

Tetrahedron Vol. 50, No. 31, pp. 9487-9494, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00541-9

Indole Alkaloids. A Combined Chemical and Enzymatic Route for Eburnane Ring Construction : Formal Synthesis of (-)-Eburnamonine[§]

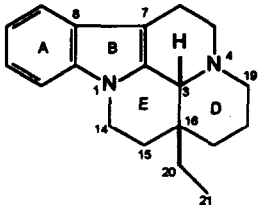
Giovanni Palmisano,* Paolo D'Anniballe, and Marco Santagostino

Dipartimento di Chimica Organica e Industriale, Facoltà di Scienze, Università degli Studi di Milano, Centro CNR per lo Studio delle Sostanze Organiche Naturali, Via Venezian 21, 20133 Milano, Italy

Abstract: A stereocontrolled formal synthesis of (-)-eburnamonine **1**, a tetracyclic indole alkaloid used as antihypertensive drug, has been achieved through the use of [3,3]-sigmatropic rearrangement (Claisen rearrangement) of the enantiopure β–alkoxy acrylate **4**, available from *rac*-3-ethyl-cyclohexenol **3** *via* lipase-catalyzed transesterification

[§] Dedicated to the memory of the late Professor L. Canonica.

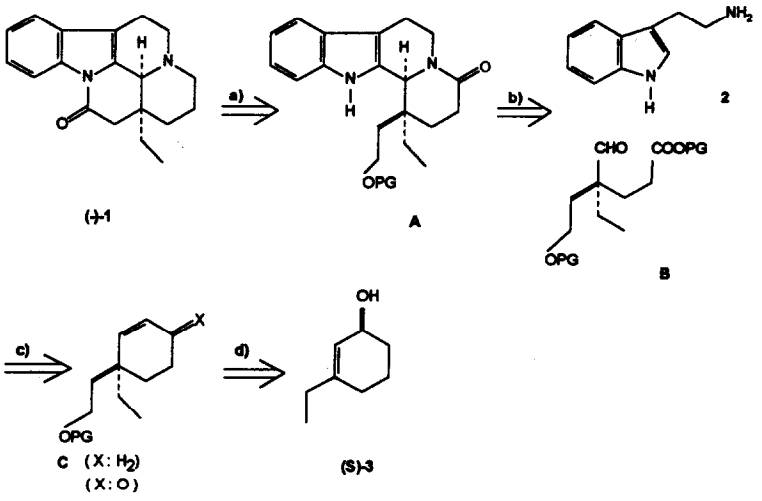
Indole alkaloids represent a formidable scenario for their rich structural diversity and close biogenetic relationship. Among the various structural arrays present in them, a small subgroup that shares the tetracyclic eburnane-core has attracted wide interest as synthetic targets and medicinal agents.[1] Our interest in this area was stimulated by the prospect of designing an enantioselective entry to this class of alkaloids, exemplified by (-)-eburnamonine **1**. The total synthesis of *rac*-**1** has been completed by several different groups[1] however, the asymmetric synthetic routes to (-)-**1** have only recently been reported mainly through the innovative and elegant work of Takano[2a] and Fuji.[2b] According to the strategy outlined in retrosynthetic format depicted in Scheme I, we envisioned an acid-promoted condensation of **B** with tryptamine **2** (Pictet-Spengler reaction) to provide tetracyclic lactam **A**. The homochiral **B** would be available from enone C(X:O).and, hence, from cyclohexene C(X:H_2) which, in turn, would be produced upon [3,3]-allyl vinyl ether-type rearrangement (Claisen reaction)[3] of alcohol *(S)*-**3**. This strategy inherently permits control of the stereochemistry at C(3)[4] and C(16) in the target molecule. By virtue of the [π2s+π2s+σ2s] nature of this process,the two-carbon pendant C(14)-C(15) is transferred suprafacially so that the stereochemistry at C(16)[5] in C(X:H_2) will be dictated by the configuration of the starting material **3**.



EBURNANE RING SYSTEM

Secondly, step b (Scheme I) is based on Fuji's earlier observation[2b] that a lactam A would equilibrate to give the desired stereochemistry at C(16) under thermodynamic control. Accordingly, the preparation of enantiopure (-)-1 required setting the stereochemistry of 3 in the (*S*)-configuration and this was efficiently achieved by kinetic resolution via enzyme-catalyzed transesterification of *rac*-3[6] under neutral conditions (Scheme II).

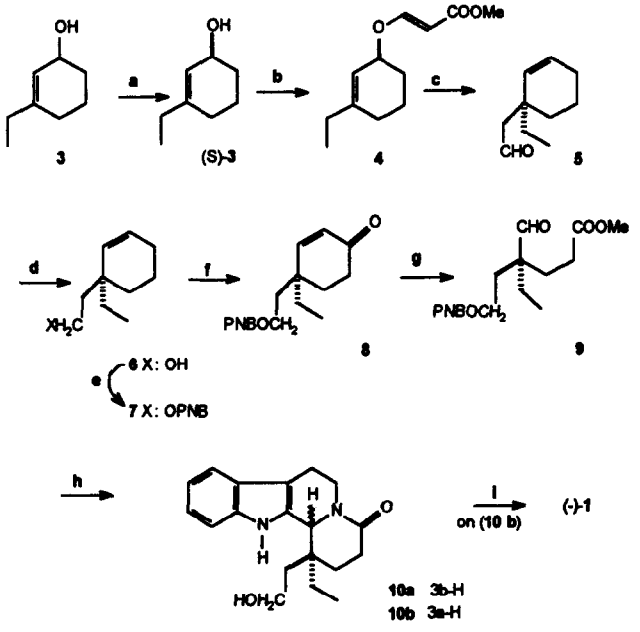
SCHEME I



The highest enantiodiscrimination (E=69)[7] was attained with immobilized *Pseudomonas cepacia* lipase in neat vinyl acetate at 45°C. After 1h, at 54% conversion, residual *(S)*-3 was recovered by silica gel filtration in 43% yield and 99.5% ee[8] (checked by GLC on a CP-cyclodextrin β - 2,3,6-M-19 column). The indicated absolute configuration assignment was based on the circular dichroic excitonic chirality method[9] on its *p*-nitrobenzoate and confirmed by ^{1}H NMR correlation of the diastereomeric esters with (*S*)-(+)-O-methylmandelyl chloride according to Trost.[10] With an adequate supply of (*S*)-3 in hand , the task of appending C(14)-C(15) fragment was undertaken, but attempts at Claisen rearrangement of the derived vinyl ether of 3 as well as orthoacetate (Claisen)-Johnson procedure gave disappointing results.[3,11] Finally,we found that exposure of (*S*)-3 to methyl propiolate in the presence of *N*-methylmorpholine (ether,rt) followed by tandem decarboxylation-rearrangement [LiI, DMF, 160°C, sealed tube, 2.5 h][12] of the resulting acrylate 4 afforded aldehyde 5, albeit in erratic yields (30-50%). Owing to the volatility of 5, it proved to be both more expeditious and efficient in practice to subject the crude reaction mixture to reduction with $NaBH_4$, affording directly the alcohol 6 in 76% overall yield from (*S*)-3. The enantiomeric purity of 6 was estimated to be 96% ee by GLC analysis on a permethylated β-cyclodextrin column. The 1,3-transfer of chirality in the Claisen rearrangement must therefore have taken place in a satisfactory manner. Conversion of the hydroxy group of 6

to its *p*-nitrobenzoate **7**, followed by allylic oxidation according to the Pearson protocol [$Cr(CO)_6$, *tert*-BuOOH, refluxing MeCN, 36 h][13] gave the enone **8** [63% (86% after correction for recovered **7**)]. The next step served to set up the 1,5-dicarbonyl function in **B** (Scheme I) which unmasks the terpenoid moiety in the eburnane skeleton. Since selective excision of extra-carbon in **8** *via* direct ozonolytic cleavage proved troublesome, an indirect route was chosen. Accordingly, osmylation [OsO_4(cat.), *N*-methylmorpholine *N*-oxide (NMNO), acetone-water,rt ,72 h][14] of **8** followed by glycol cleavage [$Pb(OAc)_4$, benzene-MeOH,0°C, 30 min][15] produced the expected aldehydo ester **9** in 72% yield. Ring closure of **9** to the tetracyclic lactams **10a,10b** (as a nearly 1:1 mixture) proceeded in good yield (83%) by refluxing **9** (48 h) with tryptamine **2** in AcOH, followed by alkaline hydrolysis.[16] The unwanted diastereomer **10a** was separated by careful silica gel chromatography, so that the desired **10b** was recovered in 61% total yield, after re-equilibration of the 3-*epi* compound **10a** using BF_3 etherate in CH_2Cl_2 at 40°C for 10 h.[2b]

SCHEME II



Key: (a) immobilized *Pseudomonas cepacia* lipase/vinyl acetate; (b) methyl propiolate/ NMM/Et_2O; (c) LiI/DMF; (d) $NaBH_4$/ MeOH; (e) *p*-nitrobenzoyl chloride/ Py; (f) $Cr(CO)_6$ / 90% *t*-BuOOH/ MeCN; (g) OsO_4 (cat.)/ NMNO/ Me_2CO-H_2O ; then, $Pb(OAc)_4$/ Bz-MeOH; (h) tryptamine **2**/ AcOH, then 10% NaOH, MeOH; (i) Ref. 2b

This highly enantioenriched material, mp 261-2°C, $[\alpha]_D$ -193.2°(MeOH), was shown to be identical by all available analytical procedures with an authentic sample of lactam **10b** kindly provided by Prof. K. Fuji. Considering that any racemization at the quaternary stereocenter C(16) was highly improbable in each step of

the sequence **6-10b**, it can be assumed that the ee of **10b** is at least 96%. Since this has been transformed previously into (-)-**1**, the present approach to **10b** completes the formal synthesis of (-)-eburnamonine.[2b]

In summary, the strategy outlined in Scheme I represents an alternative method for constructing the pentacyclic skeleton common to eburnane alkaloids. In addition, the potential to incorporate functionality in the D and E ring systems suggests that this approach might be applicable for enantiocontrolled generation of more highly functionalized substrates (*e.g.*, cuanzine[17] and larutensine[18]) in this subgroup of indole alkaloids.

EXPERIMENTAL SECTION

General Methods. Melting points (uncorrected) were taken with a hot-stage microscope apparatus. IR spectra were recorded (unless otherwise stated) for solutions in chloroform with a Perkin Elmer 681 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra with a CPX-300 for solutions in $CDCl_3$ (unless otherwise stated) (TMS as internal standard). Optical rotations were obtained for solutions in chloroform (unless stated otherwise) at room temperature (23° C) on a Perkin Elmer 241 polarimeter and CD measurements were carried out on a Jobin-Yvon Dicrograph III. EIMS (70 eV) and HRMS (R=5000) were recorded on a VG 7070EQ instrument. GC analyses were performed on a quartz column (OV-101, 5 m, Ø 2.5 mm) and H_2 as gas vector: retention time (in min ;t_R) and column temperature are reported. Thin-layer (TLC) was performed with silica gel plates and the spots were detected under UV light or phosphomolybdic acid-$Ce(SO_4)_2$ solution followed by charring on a hot plate. Analytical samples were dried *in vacuo* at 78°C or in the presence of P_2O_5 at room temperature for at least 12 h. Elemental analyses were provided by Laboratorio di Microanalisi in our Department.

(*S,E*)-Methyl 3-(3-ethyl-cyclohex-2-enyloxy)acrylate (4). To a solution of methyl propiolate (5.46 mL,65 mmol) in dry ether (20 mL) at 0°C was added *N*-methylmorpholine (5.5 mL, 50 mmol). The mixture was stirred for 20 min at 0°C, and then alcohol (*S*)-**3**[8] (6.30 g, 50 mmol) in ether (30 mL) was added and the mixture was allowed to stir for 20 h at rt. The solvent was removed *in vacuo*, and the residue was extracted with EtOAc (3 x 25 mL) and thoroughly washed with water. Evaporation of the dried solvent afforded a pale yellow oil which was subjected to silica gel filtration (hexane-EtOAc,4:1) to give **4** (8.61 g, 82%): t_R 7.02 (120°C), R_f(hexane-EtOAc,4:1) 0.37, IR 1715 cm^{-1}(ester); ^{1}H NMR 1.02(t, J=7.1 Hz,3H, *Me*CH_2), 2.01(q, J=7.1 Hz, 2H, MeC*H*$_2$), 3.65(s, 3H, OMe), 4.48(m, 1H, C*H*-O), 5.28 & 7.60(AB syst, J=12.5 Hz, 2H), 5.48(br s, 1H, H-2); $[\alpha]_D$ -231.8°(*c* 4.95). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.40; H, 8.51.

(*S*)-(1-Ethyl-cyclohex-2-enyl)acetaldehyde (5). To a 150 mL thick-walled glass vessel was added acrylate **4** (1.54 g, 7.33 mmol), lithium iodide (5.0 g, 37.1 mmol) and DMF (50 mL). This was sealed under nitrogen and was heated at 160°C with stirring for 2.5 h. The the dark solution was then cooled , diluted with water (150 mL) and extracted with hexane (2 x 50 mL). The organic phases were combined, washed with brine and dried.

Removal of the solvent *in vacuo* at rt afforded the rather pure aldehyde **5** (501 mg, 45%) as a colourless oil. A small amount was distilled (Kugelrohr):t_R 4.38 (70°C), Rf (hexane-EtOAc, 9:1) 0.38, IR 1710 cm^{-1} (carbonyl); ^1H NMR 0.85(t, J=7.5 Hz, *Me*CH_2), 1.40-1.70(m,4H), 1.47(q, J=7.5 Hz, 2H, MeC*H*$_2$), 2.32(d, J= 3.6 Hz, C*H*$_2$CHO), 5.54(dt; J= 10.2 Hz, 1.6 Hz; 1H), 5.73(dt; J =10.2 Hz, 3.6 Hz; C*H*O). Anal. Calcd for $C_{10}H_{16}O$. C, 78.90; H, 10.59. Found: C, 78.53; H, 10.78.

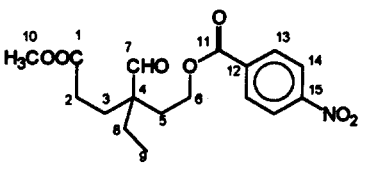
(*S*)- 2-(1-Ethyl-cyclohex-2-enyl)ethanol (6). On the same scale above, after opening of the glass vessel , the chilled crude reaction mixture was thoroughly extracted with pentane (2 x 50 mL). To the combined pentane extracts was the added $NaBH_4$ (3 g) in EtOH (10 mL) and the mixture was stirred at rt for 15 min, at which time no aldehyde **5** was detectable by TLC. The reaction mixture was evaporated *in vacuo* at rt, diluted with water and extracted with ether (3 x 15 mL). Removal of dried combined organic phases afforded pure alcohol **6** (858 mg, 76%) as colourless thick oil. This was further distilled (Kugelrohr): t_R 7.75(120°C), Rf (hexane-EtOAc, 1:1) 0.58, ^1H NMR 0.84(t, J= 7.4 Hz, 3H, *Me*CH_2), 1.35 & 1.38(2 x q, J=7.4 Hz, 2H, diastereotopic $MeCH_aH_b$), 1.40-1.50(m, 2H), 1.63(t, J= 7.2 Hz, 2H,C*H*$_2$CH$_2$OH), 3.71(t, J=7.2 Hz, 2H, C*H*$_2$OH), 5.48(dt; J= 10.6 Hz,1.7 Hz; 1H), 5.60(dt; J =10.6 Hz, 3.2 Hz; 1H); $[\alpha]_D$ +0.33°(*c* 3.2).Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76.Found: C, 77.58; H, 10.96.

(S)-2-(1-ethyl-cyclohex-2-enyl)-1-(4-nitrobenzoyloxy)ethane (7). To a solution of **6** (750 mg, 4.87 mmol) in dry pyridine (5 mL) at rt was added 4-nitrobenzoyl chloride (990 mg, 5.35 mmol). After 5 h, the reaction mixture was poured into aq $CuSO_4$ solution, extracted with chloroform (3 x 35 mL), dried and evaporated to dryness giving the pure ester 7 (1.370 g, 93%) as a low-melting glass: Rf (hexane-EtOAc, 19:1) 0.47; IR 1720, 1605, 1450 cm^{-1}; ^1H NMR 0.84(t, J= 7.1 Hz, 3H, *Me*CH_2), 1.43(q, J =7.1 Hz, 2H, MeC*H*$_2$), 1.81(t, J 7.5 Hz, 2H,C*H*$_2$CH$_2$O), 4.39(t, J= 7.5 Hz, 2H, C*H*$_2$O), 5.41(dt; J= 10.2 Hz, 1.6 Hz; 1H,H-2), 5.72(dt; J= 10.2 Hz, 3.6 Hz; 1H, H-1), $[\alpha]_D$ +44.2°(*c* 4.85). Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.02; H, 6.55; N, 4.99.

(*S*)-Ethyl 2(1-ethyl-4-oxocyclohex-2-enyl)-4-nitrobenzoate (8). 90% *tert*-Butyl hydroperoxide (1.13 mL, 7.0 mmol) was added to a stirred mixture of compound 7 (1.060 g, 3.5 mmol) and chromium hexacarbonyl (385 mg, 1.75 mmol) in acetonitrile (50 mL) under nitrogen. The resulting mixture was then refluxed for 36 h and cooled to rt. The reaction mixture was diluted with ether (100 mL) and washed with sodium metabisulphite, water, and brine. After removal of the solvents under reduced pressure, flash chromatography[19] (hexane-EtOAc,2:1) of the residue gave the starting material 7 (287 mg) and the pure enone **8** (699 mg, 63%) as a nicely crystalline solid: mp 106-7°C (ether-dichloromethane), Rf (hexane-EtOAc, 1:1) 0.44; IR 1710 (ester), 1670 (enone) cm^{-1}; ^1H NMR 0.92 (t, J= 7.1 Hz, 3H, *Me*CH_2), 1.63 (q, J =7.1 Hz, 2H, MeC*H*$_2$), 2.01(t, J= 7.0 Hz, 2H, C*H*$_2$CH$_2$O), 2.48(t, J =7.1 Hz, 2H, C*H*$_2$CO), 4.45(t, J =7.0 Hz, 2H, C*H*$_2$O), 5.94(d, J =10.5 Hz,

1H, H-2), 6.74(d, J =10.5 Hz, 1H, H-3); $[\alpha]_D$ +73.7° (*c* 2.87).Anal.Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.39; H, 6.05; N, 4.49.

(*S*)-Methyl 4-ethyl-4-formyl-6(4-nitrobenzoyloxy)hexanoate (9). A solution of *N*-methylmorpholine-*N*-oxide (82 mg, 0.70 mmol) in a mixture of water (2 mL) and acetone (4 mL) was added to a solution of OsO_4 (0.04M in *tert*-BuOH; 17.5 mL) in *tert*-BuOH: To this solution was added a solution of **8** (150 mg, 0.47 mmol) in acetone (10 mL). The reaction mixture was stirred at rt for 72 h, then $Na_2S_2O_4$ (100 mg) was added, and the reaction mixture was stirred for 15 min, diluted with EtOAc (25 mL) , and dried.



The dried solution was filtered through a short pad of Florisil. The solvent was evaporated to give the crude diol (as a diastereomeric mixture) (150 mg) which was used in the next reaction without purification. To a solution of the crude glycol (150 mg, 0.427 mmol) in benzene (5 mL) and methanol (5 mL) was added freshly recrystallized $Pb(OAc)_4$ (220 mg, 0.50 mmol) at 0°C. The reaction mixture turned to a bright orange, and the solution was stirred for 30 min at 0°C. The solvent was removed, dichloromethane (20 mL) and water (20 mL) were added, filtered and evaporated. The residue was purified by flash chromatography (hexane-EtOAc, 2:1) to give **9** (108 mg, 72%) as an oil, Rf(hexane-EtOAc, 1:1); IR 1735, 1720 cm^{-1}; ^1H NMR 0.82(t, J = 7.8 Hz, 3H, H-9), 1.65(q, J= 7.8 Hz, 2H, H-8), 1.93 & 1.96(2 x t, J= 6.8 Hz, diastereotopic H-3), 2.02(t, J =7.0 Hz, 2H, H-5), 2.25 & 2.27(2 x dd; J= 9.5 Hz, 6.8 Hz; diastereotopic H-2), 3.66(s, 3H, H-10), 4.36(t, J= 7.0 Hz, 2H, H-6), 8.0-8.3(AA'XX' system, 4H, aromatic Hs). ^{13}C NMR 7.6(C-9), 24.3(C-8), 26.3(C-7), 28.3(C-2), 30.0(C-5),50.5(C-4), 51.7(C-6), 61.6(C-7), 123.5(C-13&C-15), 130.8(C-12&C-16), 135.1(C-11), 150.5(C-14), 165.1(C-10), 173.2(C-1), 204.5(C-7).EIMS 351($M^{+\cdot}$,15%), 320(37), 185(100).Anal. Calcd for $C_{17}H_{21}NO_7$: C, 58.11; H, 6.02; N, 3.99. Found: C, 58.54; H, 6.19; N, 4.11. $[\alpha]_D$ + 6.9° (*c* 2.51).

(3*R*, 16*S*)-14, 15-Dihydro-14-hydroxy-1,14-secoeburnamenin-19-one (10a) and **(3*S*, 16*S*)-14, 15-dihydro-14-hydroxy-1, 14-secoeburnamenin-19-one (10b).** A solution of **9** (100 mg, 0.28 mmol) in AcOH (5 mL) and tryptamine **2** (48 mg, 0.3 mmol) was stirred at reflux for 48 h under a N_2 atmosphere. The solvent was removed *in vacuo*, and the residue, dissolved in 10% NaOH in MeOH (10 mL) was kept at rt for 24 h. After addition of water (20 mL) the resulting solution was extracted with dichloromethane (2 x 10 mL). The dried extracts, washed with water and brine, were dried and evaporated. The residue was subjected to silica gel chromatography and by elution with hexanes-EtOAc (6 : 1) lactams **10a** (35 mg, 40 %) and **10b** (38 mg, 44 %) were sequentially obtained. **10a**: mp 104-6°C(aqueous EtOH) ; IR (KBr) 3250 (NH), 1620 (amide) cm^{-1}; ^1H NMR (DMSO-d_6).0.65(t, J=7.5 Hz, 3H, *Me*CH_2), 0.81(m, 1H, H-20), 1.30(m, 1H, H-20), 3.75(m, 1H, H-14), 3.65(m, 1H, H-14), 4.92(m,1H, H-5eq),5.08(s, 1H, H-3), 6.95(t, J=7.2 Hz, 1H, H-11), 7.05(t, J=7.2

Hz, 1H, H-10), 7.41(m, 2H, H-9 & H-12), 10.23 (s, 1H,N*H*); $[\alpha]_D$ + 87.2°(c 0.21,MeOH) (lit.[2b] $[\alpha]_D$ +88.3°); HREIMS: calcd for $C_{19}H_{24}N_2O_2$ 312.1838 , found 312..1849. **10b**: mp 262-3°C(ether-EtOH); IR(KBr) 3300(NH), 1610 (amide) cm^{-1}; ^1H NMR(DMSO-d6) 1.07(t, J=7.5 Hz, 3H, *Me*CH_2), 2.35(br t, J=6.5 Hz, 2H, H-18), 2.50-2.75(m, 3H, H-5ax&H-6), 3.22(m, 2H, H-14), 4.19(t, J=5.0 Hz, 1H, O*H*), 4.82(br s, 1H, H-3), 4.93(m, 1H, H-5eq), 6.98(t, J=7.2 Hz, 1H, H-11), 7.07(t, J=7.2 Hz, 1H, H-10), 7.41(d, J=7.1 Hz, 1H, H-12), 7.48(d, J=7.1 Hz, 1H, H-9), 10.22(br s, 1H, N*H*); $[\alpha]_D$ - 193.2°(c 0.51, MeOH) (lit.[2b] $[\alpha]_D$ - 195.5); HREIMS: calcd for $C_{19}H_{24}N_2O_2$ 312.1838 , found 312.1829.

Equilibration of 10a. Lactam **10a** (15 mg, 4.80 mmol) was heated in dichloromethane (2 mL) containing BF_3:Et_2O (0.1 mL) at 40°C for 10 h. After the reaction mixture was cooled to rt, it was poured onto $NaHCO_3$ soln: Extractive workup with chloroform, followed by preparative TLC (1.0 mm thickness) (hexane-EtOAc, 6:1) afforded the less polar epimer **10a** (5.4 mg, 36 %) and the more polar **10b** (6.8 mg,45 %).

REFERENCES AND NOTES

1. For general reviews and leading references, see: (a) Saxton, J.E., Heterocyclic Compounds, Vol. 25, Part 4, p.439 ; Saxton, J.E., Ed.; Wiley : N.Y. 1983; (b) Taylor, W.I. 'The Alkaloids' , Vol. XI , p.125 ; Manske, R.H.F., Ed.; Academic Press :N.Y.1968 (c) Döpke, W., 'The Alkaloids' Vol. XX, p. 297, Manske, R.H.F. & Rodrigo, R.G.A., Eds.; Academic Press :N.Y. 1981; (d) Lounasmaa, M.& Tolvanen, A. ' The Alkaloids', Vol. XL, Cordell, G.A.,Ed.; Academic Press: N.Y. 1992.
2. a) Takano, S., Yonaga, M.; Morimoto, M.; Ogasawara, K. *J.Chem.Soc., Perkin Trans I* **1985**, 305; b) Node, M.; Nagasawa, H.; Fuji, K. *J: Org. Chem.* **1990**, *55*, 517 and references cited therein. See also, c) Ihara, M.; Takahashi, M.; Taniguchi, N.; Yasui, K., Nitsuma, H.; Fukumoto, H. *J.Chem.Soc.,Perkin Trans I*, **1991**, 525; d) Meyers, A.I.; Romine, J.; Robichaud, A.J. *Heterocycles* **1990**, *30*,339.
3. For general reviews on the Claisen rearrangement, see: a) Ziegler, F.E. *Chem.Rev.* **1988**, *88*, 1423; b) Blechert, S. *Synthesis* **1989**, 71.
4. To avoid confusion, the eburnane positional numbering and ring letters are used throughout the discussion section of this paper. A more appropriate numbering system is used in the Experimental Section.
5. The creation of quaternary carbon center in an enantioselective manner is often a major problem in many synthetic endeavours, see: Martin, S.F. *Tetrahedron* **1980**, *36*, 419: See also: Fuji, K, *Chem.Rev.* **1993**, *93*, 2037.
6. Racemic alcohol was prepared by reduction according to Luche (Luche, J.L. *J.Am.Chem.Soc.* **1978**, *100*, 2226) of 3-ethyl-2-cyclohexen-1-one, easily available from 3-ethoxy-2-cyclohexen-1-one (Woods, F.; Griswold, P.H.; Armbrecht, B.H.; Blumenthal, D.I.; Plapinger, R. *J.Am.Chem.Soc.* **1949**, *71*, 2028).
7. Chen, C.; Fujimoto, Y.; Girdaukas, G.; Sih, C.J. *J.Am.Chem.Soc.* **1982**, *104*, 7294.

8. Carrea, G.; Danieli, B.; Palmisano, G.; Riva, S.; Santagostino, M. *Tetrahedron Asym.* **1992**, *3*, 775
9. The CD spectrum of *p*-nitrobenzoate showed a split Cotton effect, negative at 262 nm and positive at 195 nm. This splitting indicates a left-hand screw sense between the p-nitrobenzoate and the alkene chromophore, *i.e. (S)* [Harada, N.; Inabuchi, J.; Yokota, Y.; Uda, H.; Nakanishi, K. *J.Am.Chem.Soc.* **1981**, *103* , 5590].
10. Trost, B.M.; Belletire, J.L.; Godleski, S.; McDougal, P.G.; Balkoveck, J.M.; Baldwin, J.J.; Christy, M.E.; Ponticello, G.S.; Varga, S.L.; Springer, J.P. *J.Org.Chem.* **1986**, *51*, 2370.
11. Our attempts to prepare aldehyde **5** employing water as a solvent for the Claisen rearrangement of vinyl ether of **3** according to Grieco protocol were also unsuccessful [Grieco, P.A.; Brandes, E.B.; McCann, S.; Clark, J.D. *J.Org.Chem.* **1989**, *54*, 5849].
12. Sücrow, W.; Radecker, G. *Chem. Ber.* **1988**, *121*, 219. Preparation and rearrangement of *trans*-acrylate **4** according to Büchi protocol was tried as well but yields were significantly reduced (*ca.* 30%) [Büchi, G.; Vogel, D.E. *J.Org.Chem.* **1983**, *48*, 5408].
13. Pearson, A.J.; Chen, Y.-S.; Han, G.R.; Hsu, S.-Y.; Ray, T. *J.Chem.Soc. Perkin Trans I*, **1985**, 267.
14. Van Rheenen, V.; Kelly, R.C.; Cha, D.Y. *Tetrahedron Lett.* **1976**, 1973.
15. Danishefsky, S.; Schuda, P.F.; Kitahara, T.; Etheridge, S. *J.Am.Chem.Soc.* **1977**, *99*, 6066.
16. Treatment of **9** with **2** in refluxing AcOH resulted in partial transesterification at hydroxy group. This complication was easily bypassed by making recourse to alkaline hydrolysis of the crude reaction mixture.
17. a) Palmisano, G.; Gabetta, B.; Lesma, G.; Pilati, T.; Toma, L. *J.Org.Chem.* **1990**, *55*, 2182; b) Palmisano, G.; Danieli, B.; Lesma, G.; Passarella, D.; Toma, L. *J.Org.Chem.* **1991**, *56*, 2380.
18. a) Awang, K.; Pais, T.; Sévenet, T.; Schaller, H.; Nasir, A.M.; Hamid, A.H. *Phytochemistry* **1991**, *30*, 3164; b) Kam, T.-S.; Tan, P.-S.; Chuah, C.-H. *Phytochemistry* **1992**, *31*, 2936. For synthesis of *rac*-larutensine, see: Lounasmaa, M.; Karvinen, E. *Heterocycles* **1993**, *36*, 751.
19. Still, W.C.; Kahn, M.; Mitra, A.P. *J.Org.Chem.* **1978**, *43*, 2923.

ACKNOWLEDGMENT

We are warmly grateful to Prof. Kaoru Fuji (Kyoto University) for providing us with an authentic sample of both lactams **10a** and **10b**. We are indebted to Dr. S.Riva (Istituto degli Ormoni,CNR, Milan) for optimization of enzyme-assisted step and stimulating discussion. We thank the 'Progetto Finalizzato Chimica Fine II' for the financial support.

(*Received in UK* 12 *May* 1994; *revised* 10 *June* 1994; *accepted* 17 *June* 1994)