Tetrahedron Letters, Vol.31, No.19, pp 2705-2706, 1990
Printed in Great Britain

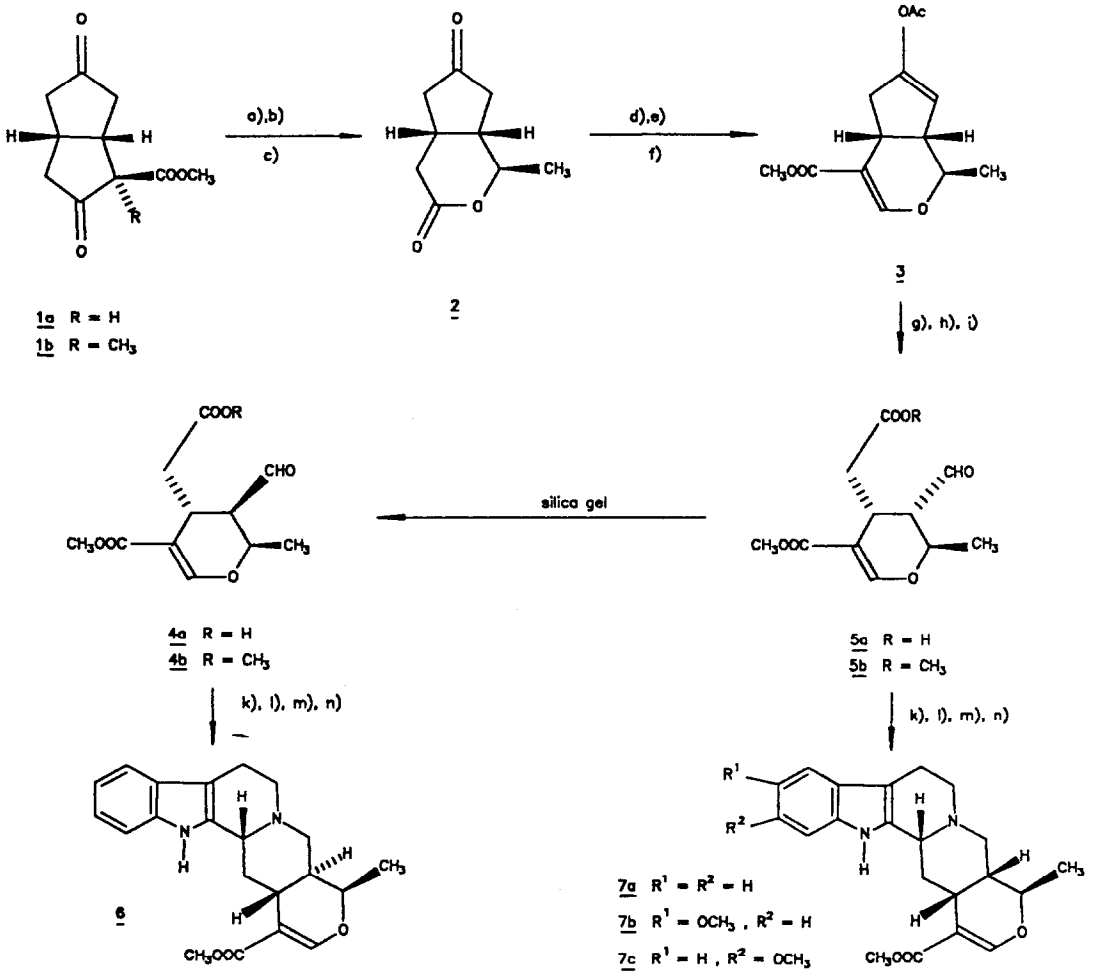
0040-4039/90 $3.00 + .00
Pergamon Press plc

ENANTIOSELECTIVE TOTAL SYNTHESIS OF (+)-TETRAHYDROALSTONINE, (+)-ACRICINE, AND (+)-RESERPININE[1]

Peter Hölscher, Hans-Joachim Knölker, and Ekkehard Winterfeldt*
Institut für Organische Chemie der Universität Hannover,
Schneiderberg 1B, D-3000 Hannover 1, F.R.G.

Summary: Starting from (-)-β-ketoester **1a** the preparation of (+)-elenoic acid **4a** and (+)-isoelenoic acid **5a** is described. Standard operations transform **5a** into (+)-tetrahydroalstonine **7a**, (+)-acricine **7b**, and (+)-reserpinine **7c**.

The elenoic acid esters **4b** and **5b** represent the synthetic chemists best substitute for secologanine which owing to its high tendency to end up in the vallesiachotamine structure is only of limited value for total synthesis[2,3]. As a simple entrance[4] and a number of regioselective and stereoselective transformations had been elaborated in our laboratory we a few years ago prepared diketoester **1b** and studied its Baeyer-Villiger oxidation as well as the subsequent decarboxylation to form lactone **2**[5].



Reagents and conditions: a) KO^{t}Bu,CH_3I,DME; b)6n HCl reflux; c)mCPBA 0.8 eq,$NaHCO_3$ in CH_2Cl_2,educt recovered;yield **1a** to 2:41%; d)NaH 4 eq, $HCOOCH_3$,then HCl reflux; e)CH_2N_2; f)KO^{t}Bu 2 eq or LDA,AcCl 2.5 eq; g)OsO_4 1mol%/NMO 1.25 eq in $CO(CH_3)_2/H_2O$;h)H_5IO_6 in Et_2O; i)CH_2N_2,yield about 40% from **2**; k)1.1 eq tryptamine,C_6H_6,rt; l)$NaBH_4$ in CH_3OH; m)$POCl_3$,CH_2Cl_2,reflux; n)$NaBH_4$ in CH_3OH.

For an enantioselective approach to (+)-heteroyohimbine alkaloids we started from enantiomerically pure β-ketoester **1a** which had been prepared by K.Petzold[7] by enzymatic hydrolysis. Conventional alkylation afforded **1b** which after transformation into (+)-**2** gave rise to **3** via Korte rearrangement[8] and highly regioselective enol acetate formation. Treatment with osmium tetroxide and N-methylmorpholine-N-oxide, cleavage with periodic acid, and esterification with diazomethane afforded epi-elenoic acid methylester **5b**. Its trans isomer **4b** was obtained by stirring **5b** with silica[9].

The well established sequence imine formation, borohydride reduction[9,10], and cyclization to the lactams, followed by a Bischler-Napieralski cyclization and a second borohydride reduction afforded (+)-tetrahydroalstonine in 44% yield from **5b**. The virtually same procedure led to (+)-acricine **7b** and (+)-reserpinine **7c** in good yields from **5b**. After isomerization to **4b**, the total synthesis of (+)-ajmalicine **6** and related compounds could be achieved as well.

REFERENCES AND NOTES

1. Reactions with indole derivatives, LVIII. For part LVII seeI.Ninomiya, T.Naito,O.Miyata, T.Shinada, E.Winterfeldt, R.Freund, I.Ishida, Heterocycles, in print.

2. R.T.Brown, C.L.Chapple, J.Chem.Soc.,Chem.Commun. **1973**, 886.
R.T.Brown, J.Leonard,S.K.Sleigh, J.Chem.Soc.,Chem.Commun. **1977**, 636.

3. P.Westekemper, U.Wieczorek, F.Gueritte, N.Langlois, Y.Langlois,P.Potier, M.H.Zenk, Planta Medica **39**, 24 (1980).

4. M.Harre, E.Winterfeldt, Chem.Ber. **115**, 1437 (1982).

5. H.-J.Knölker, E.Winterfeldt, Liebigs Ann.Chem. **1986**, 465.
Although these preparations were communicated in 1986 and the completion of this synthetic project was reported at the Fourth International Kyoto Conference on New Aspects of Organic Chemistry in 1988 and published in the proceedings (VCH **1989**, p. 157-174) this approach was republished recently by J.Leonard, D.Quali, S.K.Rahman, Tetrahedron Lett. **31**, 73 (1990).

6. R.T.Brown, C.L.Chapple, D.M.Duckworth, R.Platt, J.Chem.Soc.,Perkin Trans.I**1976**, 160.
S.Takano, S.Hatekayama, K.Saijo, Tetrahedron Lett. **26**, 865 (1985).S.F.Martin, B.Benage, J.E.Hunter, J.Am.Chem.Soc. **110**, 5925 (1988). S.Takano, S.Satoh, K.Ogasawara J.Chem.Soc.,Chem.Commun. **1988**, 59. R.M.Uskokovic, J.Gutzwiller, G.Pizzolato, J.Am.Chem.Soc. **93**, 5907 (1971). S.Sakai et al., Yakugaku Zasshi **98**, 850 (1978). E.Winterfeldt, H.Radunz, T.Korth, Chem.Ber. **101**, 3172 (1968).

7. W.Skuballa,M.Schäfer, Nachr.Chem.Techn. **37**, 584 (1989). K.Petzold, H.Dahl, W.Skuballa, Schering AG,Berlin, Eur.Pat.Appl. 271432.
We thank Dr.K.Petzold, Schering AG, Berlin, for preparation of compound **1a**.

8. K.H.Büchel, F.Korte, Angew.Chem. **71**, 709 (1959).
C.Placeway, E.E.van Tamelen, J.Am.Chem.Soc. **91**, 7359 (1969).

9. R.M.Uskokovic, E.Baggiolini, G.Pizzolato, Tetrahedron **44**, 3203 (1988) and literature cited.

10. S.Takano, S.Satoh, K.Ogasawara, Heterocycles **30**, 583 (1990). Earlier contributions see there.

(Received in Germany 9 March 1990)