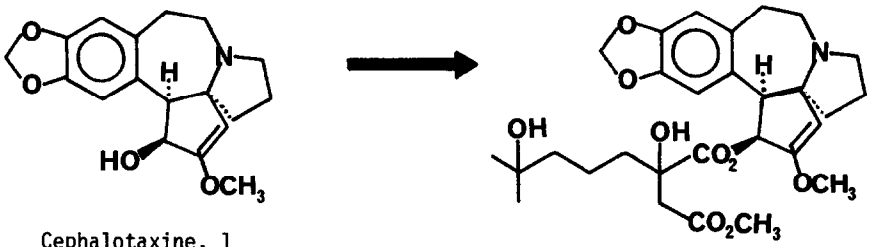
Tetrahedron Letters,Vol.23,No.34,pp 3431-3434,1982 0040-4039/82/343431-04$03.00/0
Printed in Great Britain

SYNTHESIS OF HOMOHARRINGTONINE AND ITS DERIVATIVE BY PARTIAL ESTERIFICATION OF CEPHALOTAXINE.

S. Hiranuma and T. Hudlicky*[1,8]
Department of Chemistry
Illinois Institute of Technology
Chicago, Illinois 60616

Abstract: Homoharringtonine 2 and dehydrodesoxy homoharringtonine 4 were synthesized by partial esterification of cephalotaxine.

The alkaloid ester homoharringtonine 2 eluded chemical synthesis[2] for a number of years although reasonably facile routes exist to its desoxy derivative as well as to the homologs of this alkaloid.[3] To further test the steric limits of the partial esterification of cephalotaxine 1 and to provide a potentially useful derivative of 2 for medicinal purposes we prepared the ester 4 anticipating its convertibility to homoharringtonine.



Cephalotaxine, 1 Homoharringtonine, 2

The side chain acid 7 was prepared from methyl cyclopropanecarboxylate in the following way: Cyclopropane 5 was converted to its dimethyl carbinol (92%) and treated with aqueous HBr to give the olefinic bromide 6 (83%). Following a literature report[2] we were able to produce acid 7 by the interaction of Grignard reagent derived from 6 with diethyl oxalate (28% after hydrolysis). When the acid chloride of 7 was stirred with cephalotaxine[4] (CH_2Cl_2, pyridine, 12 hrs) at room temperature a 70% yield of pyruvate 3 was attained. The Reformatsky reaction of this ester with methyl bromoacetate gave a good yield of 4 (mixture of two diastereomers separable by preparative TLC).[5,6]

In view of the ease of formation of 4 it appeared that homoharringtonine may be accessible by either a similar partial esterification of a suitably protected side chain

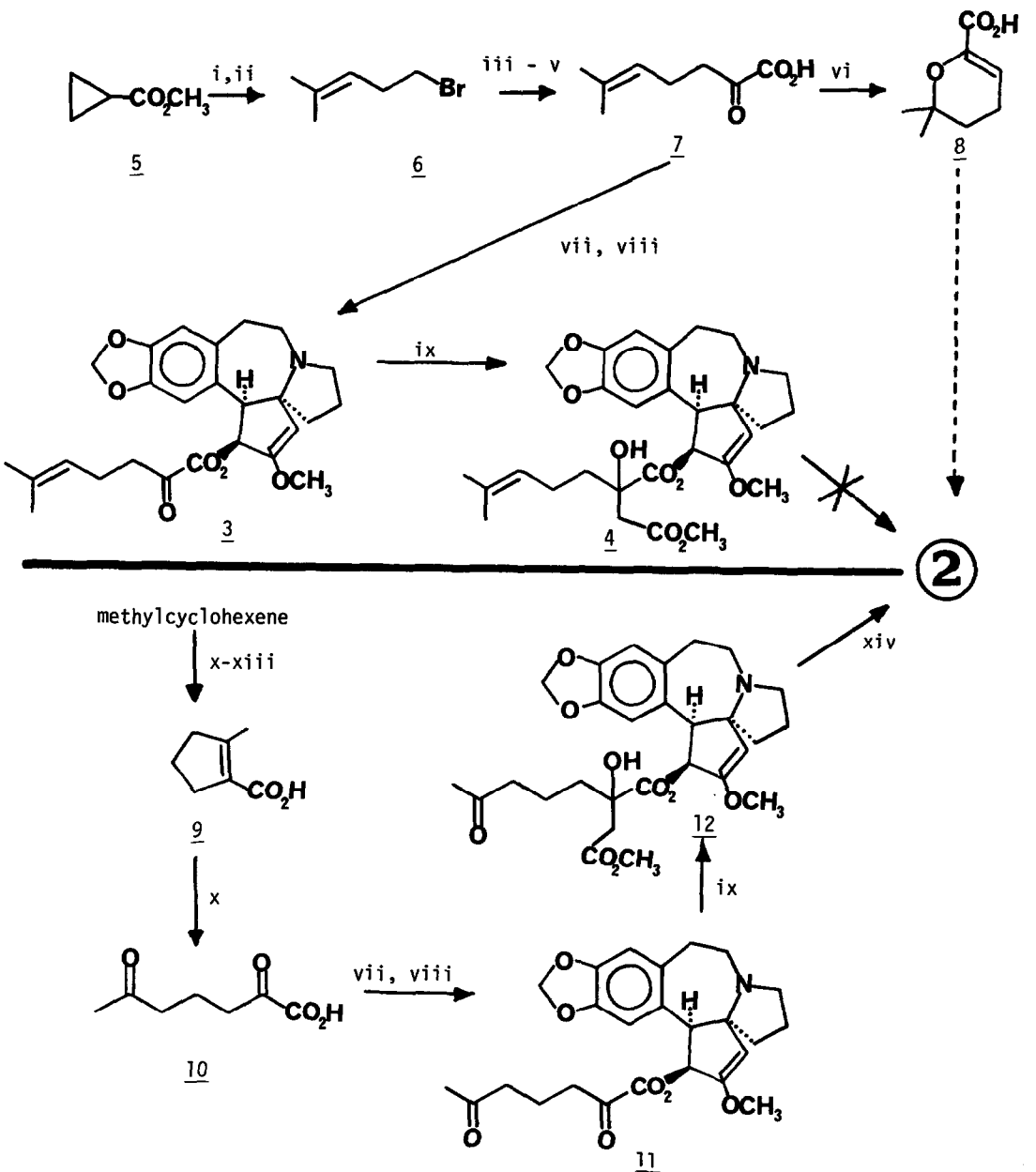
or by functionalization of the olefin in 4. Although we were able to epoxidize the olefin of 4 in the presence of the enol-ether moiety of cephalotaxine we did not succeed in generating the tertiary alcohol from the epoxide. Similarly the epoxide of acid 7 could not be transformed into the necessary hydroxy-acid. Although the acid 7 resisted hydration by conventional methods it gave (under forcing conditions using formic acid[7] followed by base hydrolysis) dihydropyrane 8 in high yield, but it was not clear how this compound could be carried through to 2 without introducing many additional steps. We then turned to an alternate approach utilizing ketoacid 10 and hoping for the vast difference in the reactivity of the two carbonyls as means of synthesis of 2.

Ozonolysis of methylcylohexene (CH_2Cl_2, -78°, Me_2S) gave a good yield of ketoaldehyde which was cyclized in 82% yield (piperidine, HOAc) and oxidized to acid 9. Ozonolysis of this compound gave the ketopyruvate 10 in excellent yield. The formation of ester 11 was accomplished using 2 eq. of the acid chloride of 10. Although the yield of this esterification compared to that of 3, the material was difficult to purify by chromatography decomposing to cephalotaxine and the side chain acid.

The addition of zinc reagent derived from methyl bromoacetate took place at the pyruvate carbonyl to furnish 12 in good yield. Addition of MeLi (2 eq.) to 12 gave homoharringtonine (the ^{1}H-NMR of which was identical to the spectrum of natural material) and some cephalotaxine resulting from the cleavage of the side chain ester. Compound 12 (and/or its cyclic hemi-ketal) has been claimed as an intermediate in the reported synthesis of 2[2]. In our experience both 11 or 12 proved extremely labile materials; this observation places some doubt on the reported hydrolysis of ethylene glycol ketal of 12.

The yield of homoharringtomine from cephalotaxine is only modest due to the fast decomposition of 11. We believe this yield will improve considerably when a method of purification of 11 is unearthed.

Acknowledgments: We are grateful to the National Cancer Institute (grant #CA-25375) for the support of this work. We also acknowledge the Developmental Therapeutics Program, Chemotheraphy, NCI, for a generous gift of synthetic cephalotaxine. For a similar gift of homoharringtonine, cephalotaxine, drupacine and hydroxycephalotaxine together with their spectra we thank Richard Powell of the Northern Regional Agricultural Institute, U.S. D.A.



Reagents: i. CH_3MgBr/THF; ii. 48% HBr/Et_2O; iii. $Mg/THF/\Delta$; iv. $(CO_2Et)_2$; v. $KOH/CH_3OH/H_2O$; vi. HCO_2H/Δ; vii. $(COCl)_2$benzene; viii. CH_2Cl_2/pyridine/1; ix. $ZnCl_2/K/THF$ $BrCH_2CO_2Me$; x. $O_3/-78°Me_2S$; xi. piperidine/Et_2O; xii. $HOAc/Et_2O$; xiii. Ag_2O; xiv. MeLi or MeMgBr/-20°C.

Peoria Illinois. Our appreciations are also extended to Prof. S.M. Weinreb, Penn State University for a gift of a cephalotaxine precursor and an updated experimental of his work in this area. To both gentlemen go our heartfelt thanks for the interest they showed in our research.

References:

1. Fellow of the Alfred P. Sloan Foundation, 1981-3.

2. A report appeared describing the synthesis of 2 by partial esterification: Wang Yong-Keng, Li Yulin, Pan Xinfu, Li Shaobai and H. Wenkeui, Kexue Tongbao, 25, 576 (1980) cf: CA: 94: 103628f, CA: 94: 103627e, 1981. We have tried unsuccessfully to reproduce portions of this work and must await the appearance of experimental description.

3. See for example: T.R. Kelly, R.W. McNutt, Jr., M. Montury, N.P. Tosches, K.K. Mikolajczak, C.R. Smith, Jr. and D. Wiesleder, J. Org. Chem., 44, 63 (1979), for the synthesis of harringtonine and the references within for the preparations of homologs of 2.

4. J. Auerbach and S.M. Wienreb, J. Am. Chem. Soc., 94, 7172 (1972). We have prepared a quantity of cephalotaxine by this method and its updated version and found the work readily reproducible.

5. All compounds were characterized by ^{1}H-NMR, IR and ^{13}C-NMR. The ^{1}H-NMR spectra of the diastereomers of 3 were recorded on Nicolet 300 instrument. We are grateful to the National Institutes of Health (grant #GM-26071) for the purchase of this instrument.

6. K.L. Milolajczak and C.R. Smith, Jr., J. Org. Chem., 43, 4762 (1978).

7. H.B. Knight, R.E. Koos and D. Swern, J. Am. Chem. Soc., 75, 6212 (1953).

8. Address correspondence to this author at: Chemistry Department, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 26460.

(Received in USA 26 February 1982)