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A REGIOCONTROLLED SYNTHESIS OF CODONOCARPINE

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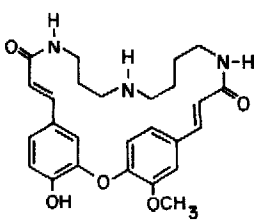
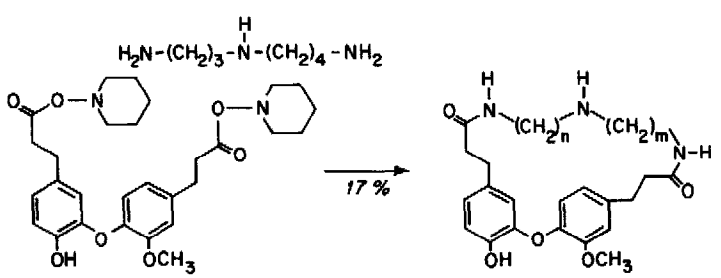
Abstract. The total synthesis of the Lunaria alkaloid codonocarpine is described. Regiospecific formation of the macrocycle is achieved by the use of a properly protected spermidine unit.

The bark of Codonocarpus australis has afforded the Lunaria alkaloid, codonocarpine (1), as a yellow crystalline solid.[1] Its structure was deduced by a series of chemical transformations and spectroscopic studies,[2] and contains a spermidine unit incorporated into an unsymmetrical 24-membered lactam. Although the synthesis of codonocarpine has not been achieved, a tetrahydro derivative 2 has been reported.[3] The synthesis of 2 was designed (Scheme 1) to introduce the spermidine unit intact in the last step, a measure which fails to establish the orientation of the triamine within the macrocycle.



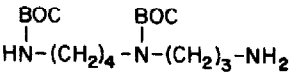
1. codonocarpine



2. n=3, m=4
n=4, m=3

SCHEME 1.

Retrosynthetic analysis of 1 suggested that such regiochemical control would require that a properly protected spermidine unit be acylated by a differentially functionalized biscinnamoyl derivative, e.g. 7. The previously reported selectively protected spermidine 3 appeared to be a useful reagent for this goal.[4] The condensation of 3 and 7 insures the



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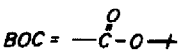


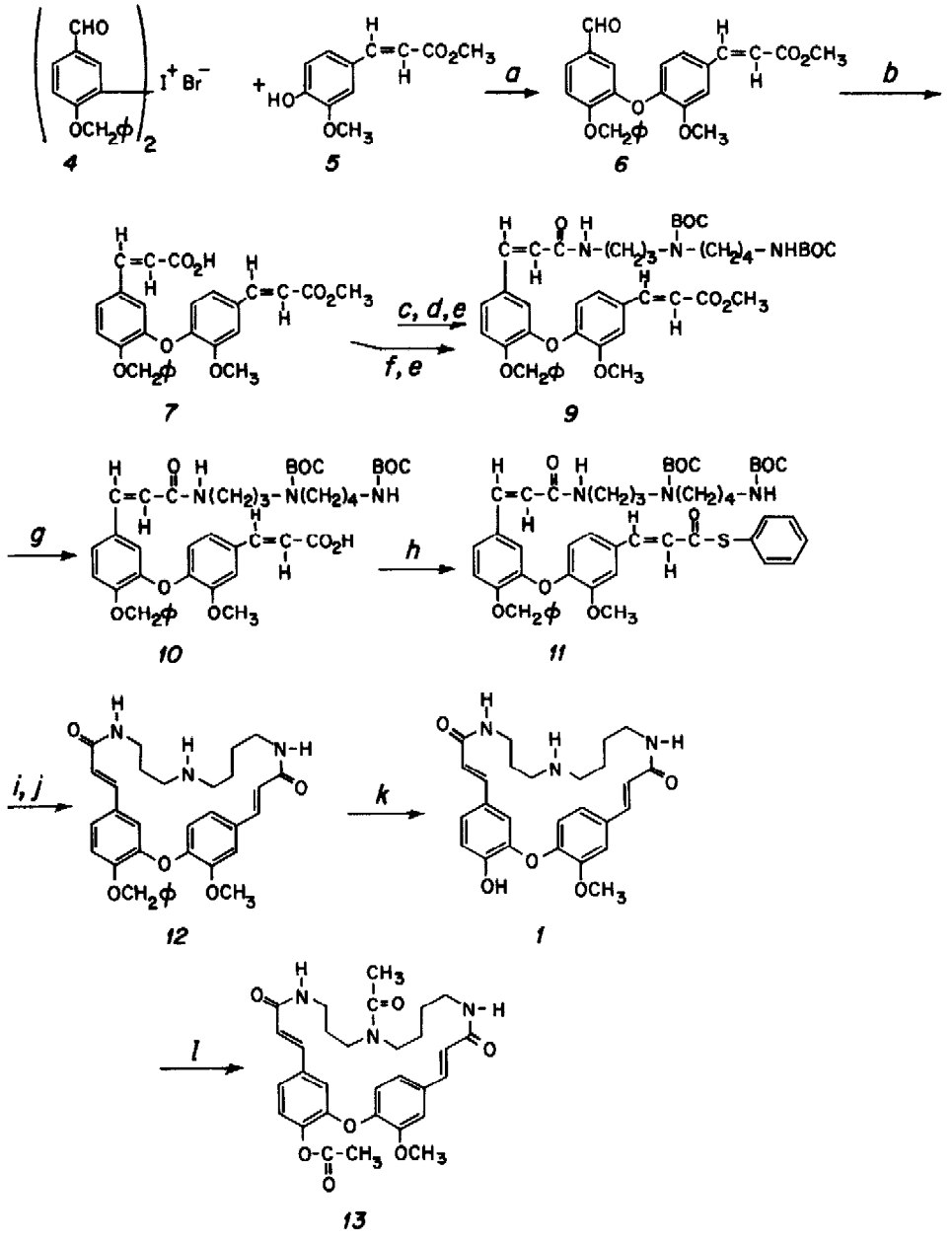
correct regiochemistry in 9; the remaining crucial step is the formation of the macrocyclic lactam.

Synthesis of 7 via the Ulmann synthesis was not successful despite numerous attempts. A suitably functionalized biphenyl ether 6 was eventually prepared utilizing the diaryliodonium salt method of Beringer.[5] Thus diphenyliodonium bromide 4, secured from 4-benzyloxybenzaldehyde following the procedure of Doskotch,[2] was coupled with methyl ferulate to afford the cinnamate 6 in 50% yield. Knoevenagel condensation of 6 with malonic acid gave the trans-cinnamic acid derivative 7 in 96% yield.

Two procedures were utilized to couple the protected spermidine 3 with carboxylic acid 7. The activated ester was prepared in 60% yield by sequential treatment of 7 with oxalyl chloride and N-hydroxypiperidine. Acylation of 3 with the activated ester by treatment in tetrahydrofuran at room temperature for 14 days afforded 9 in 90% yield. A more expedient procedure was to condense the mixed anhydride (isobutyl chloroformate, -10°C, 20 min) with 3 at -10°C for 10 min to afford a 79% yield of 9. The methyl ester 9 was quantitatively hydrolyzed to acid 10.

N-Hydroxypiperidine esters have been shown to selectively acylate primary amines in the presence of less reactive amines.[6] However, attempts to prepare the N-hydroxypiperidine ester of 10, by first transforming the acid to an acid chloride using either thionyl chloride or oxalyl chloride with an acid scavenger, resulted in cleavage of the BOC groups. Treatment of 10 with isobutyl chloroformate afforded a mixed anhydride which could be isolated but did not readily acylate N-hydroxypiperidine and was unstable to the acid conditions required to remove the BOC groups. Eventually, thio ester 11 was secured by treatment of 10 with one equivalent each of thiophenol, dicyclohexylcarbodiimide and pyridine.

Removal of the BOC groups of 11 with trifluoroacetic acid (methylene chloride, 23°C, 18 min) and concentration of the solvent in vacuo afforded an amine salt which was not isolated. Following the procedure of Blout,[7] an anhydrous dimethylformamide solution of the amine salt was slowly added to pyridine at 90°C to produce a 0.001 M solution. The reaction mixture was heated an additional 4 hr at 90°C followed by 12 hr at room temperature to afford, after chromatographic purification, a 60% yield of O-benzylcodonocarpine 12. The structure of 12 was fully supported by spectral data and ultimately confirmed by its transformation to codonocarpine and N,O-diacetylcodonocarpine. Removal of the O-benzyl group of 12 to yield 1



a) Cu, Et_3N, MeOH. b) malonic acid, pyr., piperidine. c) oxalyl chloride. d) N-hydroxypiperidine. e) 3. f) isobutylchloroformate. g) KOH, H_2O, MeOH. h) PhSH, pyr., i) TFA, CH_2Cl_2. j) DMF, pyr., 90°C. k) TFA or TMSI. DCC l) Ac_2O

was achieved either by treatment with trifluoroacetic acid[8] for 10 hr or trimethylsilyl iodide,[9] generated in situ by reaction of hexamethyldisilane[10] and iodine. Treatment of codonocarpine with acetic anhydride gave N,O-diacetylcodonocarpine 13 which was identical in all respects (NMR, IR, MS, UV, mp, tlc) with a sample provided by Professor Doskotch.[11]

Acknowledgement. The authors wish to thank Professor Doskotch for a sample of 13 and NMR and IR spectra of 1 and 13. They are also indebted to Mr. Joel Kandel for obtaining 270 MHz NMR spectra (facilities funded by Research Grants NS-12007 and NS-15343) and to NICHDS and the Petroleum Research Fund, sponsored by the American Chemical Society, for providing financial support.

References and Notes

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