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TOTAL SYNTHESIS OF A MACROCYCLIC SPERMIDINE ALKALOID, CODONOCARPINE

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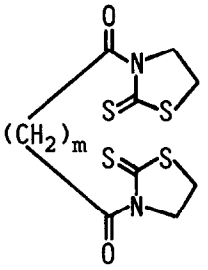
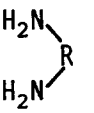
Summary: Total synthesis of codonocarpine (5) and its regio-isomer (15) utilizing a new cyclization procedure is described.

Very recently, we developed a new synthesis of macrocyclic diamide 4 by aminolysis of dicarboxylic acid thiazolidine-2-thione diamide 1 with diamines 2 or spermidine (3).[1,2]

A macrocyclic spermidine alkaloid, codonocarpine (5) was isolated from *Codonocarpus australis* A. Cunn. (Phytolaccaceae) by Doskotch and co-workers.[3] Its 24-membered macrocyclic diamide structure consists of spermidine and oxygenated cinnamoid biphenylether moiety. We attempted to synthesize codonocarpine (5) utilizing our new aminolysis method.[2] Unnatural tetrahydrocodonocarpine had been synthesized by C. Poupat.[4] However, we have never encountered any paper on the synthesis of codonocarpine itself.

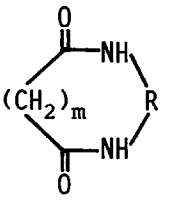


m = 2,4,8,12
(1)

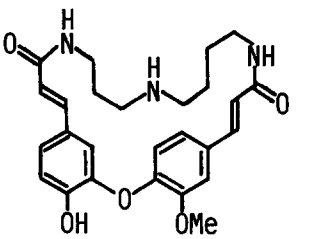


(2) R = $-(CH_2)_n-$
n = 2,3,4,6

(3) R = $-(CH_2)_3$ NH $-(CH_2)_4$



(4)

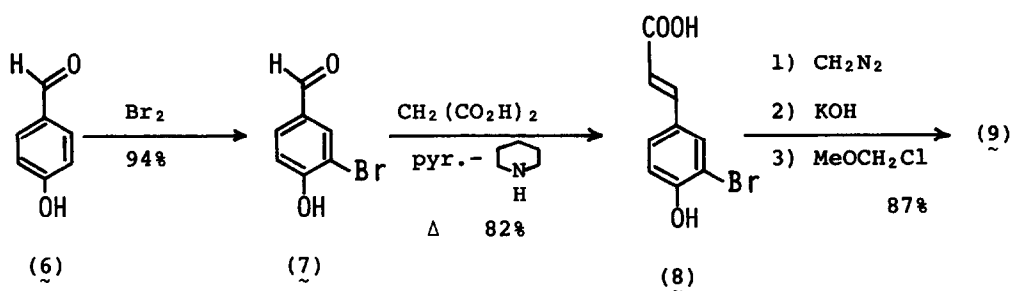


(5)

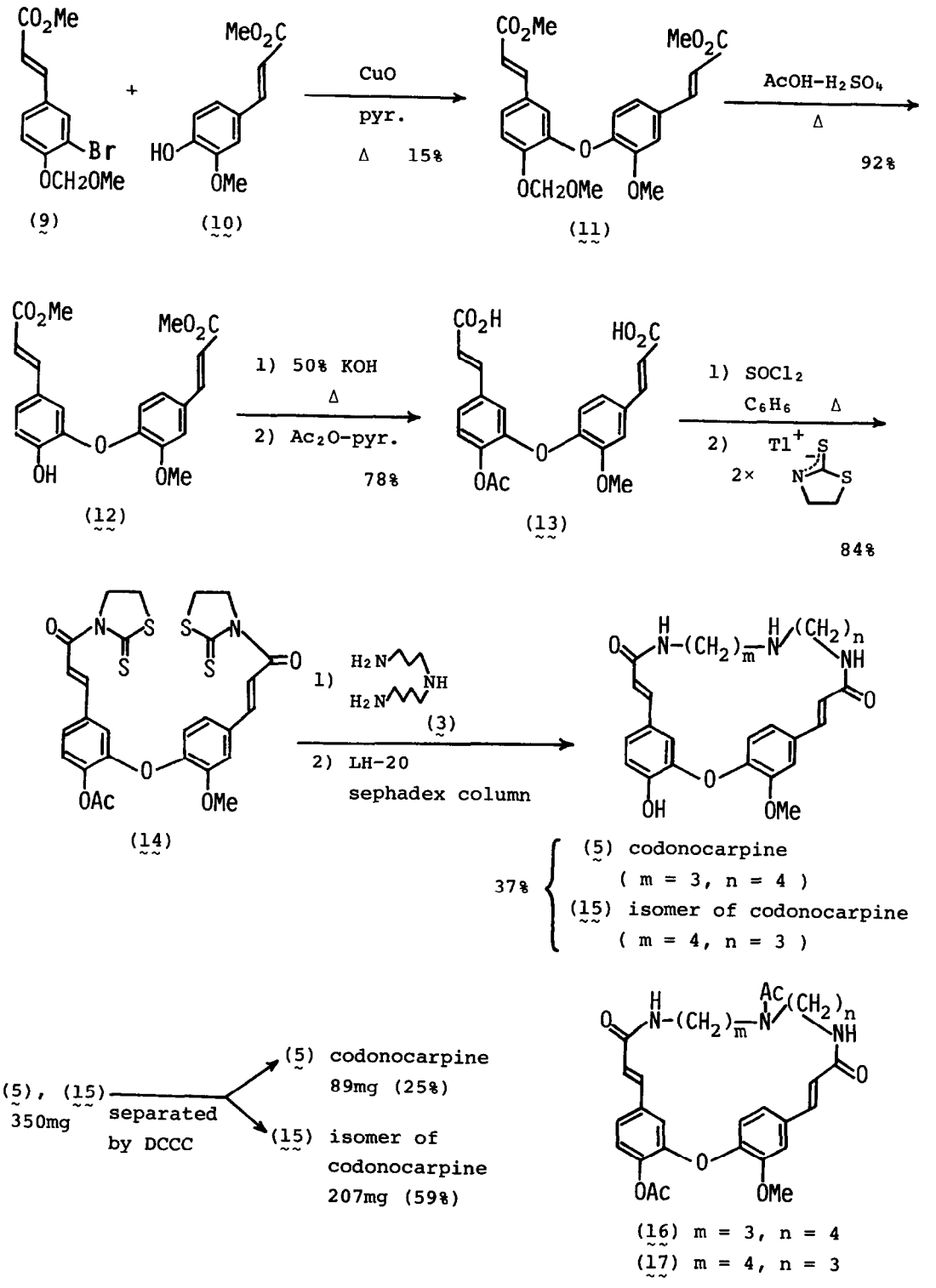
We now wish to describe the first total synthesis of codonocarpine (5). Bromination of *p*-hydroxybenzaldehyde (6), Knoevenagel condensation of product 7 with malonic acid, selecteve methylation of carboxyl group of product 8 followed by methoxymethylation of phenol transformed 6 into compound 9 in high yield. Ullmann condensation between 9 and methyl ferulate (10) was performed in hot pyridine in the presence of CuO under the argon atmosphere to give the desired biphenylether 11 : IR ($CHCl_3$) 1705 cm^{-1}; NMR ($CDCl_3$) δ 3.40 (3 H, s), 3.74 (3 H, s), 3.78 (3 H, s), 3.90 (3 H, s), 5.20 (2 H, s), 6.24, 7.57 (each

1 H, AB, J = 15.9 Hz), 6.37, 7.66 (each 1 H, AB, J = 15.9 Hz), 6.73-7.35 ppm (6 H, m); M^+ m/e=428.147. Deprotection of 11 afforded 12, which on hydrolysis followed by acetylation gave the desirable dicarboxylic acid 13. Its acid chloride was treated with thallium (I) salt[5] of thiazolidine-2-thione (4 mol equiv.) at room temperature in THF with stirring for 24 hr to afford a yellow solid 14 in overall 84% yield from dicarboxylic acid 13. Compound 14: *Anal.* Calcd for $C_{27}H_{24}O_6N_2S_4$: C, 53.98; H, 4.03; N, 4.66. Found: C, 53.63; H, 3.96; N, 4.39%, M^+ m/e=600, IR (KBr) 1765 and 1675 cm^{-1}; NMR ($CDCl_3$) δ 2.22 (3 H, s), 3.34 (2 H, t, J = 7.4 Hz), 3.37 (2 H, t, J = 7.4 Hz), 3.88 (3 H, s), 4.53 (2 H, t, J = 7.4 Hz), 4.55 (2 H, t, J = 7.4 Hz), 7.46, 7.75 (each 1 H, AB, J = 15.4 Hz), 7.59, 7.87 (each 1 H, AB, J = 15.6 Hz), 6.89-7.37 ppm (6 H, m).

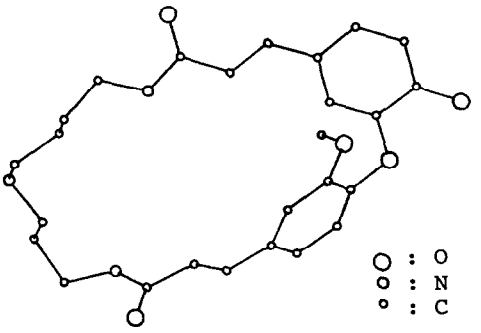
The cyclization between compound 14 and spermidine (3) was performed by the following high dilution method.[2] A yellow solution of 14 (2 mmol) in CH_2Cl_2 (200 ml) and a solution of spermidine (3) (3 mmol) in CH_2Cl_2 (200 ml) were added dropwise using two mechanically driven syringes (commercial name: microfeeder) over 5 hr into CH_2Cl_2 (1.5 l) under nitrogen with stirring at room temperature and then the mixture was stirred for further 3 hr. After evaporation of the solvent *in vacuo*, the residue was chromatographed on a column prepared from Sephadex LH-20 and MeOH using MeOH-$CHCl_3$ (7:3) to give a pale yellow substance, which was crystallized from a solution of its hydrochloride in aqueous ammonia. A crystalline mixture of codonocarpine (5) and its isomer (15) thus obtained in 37% yield was separated by droplet countercurrent chromatography (DCCC); the mixture (350 mg) was subjected repeatedly to the descending method of DCCC [$CHCl_3$: MeOH : n-PrOH : c.NH_4OH : H_2O (9:12:1:1:7)]. Thus, pure codonocarpine (5) [89 mg, mp 183-187° (decomp.)(lit.[3] mp 187° (decomp.)] and its isomer (15) [207 mg, mp 243-246° (decomp.)(from 28% ammonia); N,O-diacetate (17), colorless needles, mp 281-285° (decomp.)(from acetone)] were obtained as pale yellow prisms.



(6) (7) (8)


CO2Me
MeO2C
Br
OCH2OMe
HO
OMe
(9)
(10)
CuO
pyr.
Δ 15%
(11)
AcOH-H2SO4
Δ
92%
OH
(12)
1) 50% KOH
Δ
2) Ac2O-pyr.
78%
CO2H
HO2C
OAc
(13)
1) SOCl2
C6H6 Δ
2) Tl+
2×
84%
(14)
1)
H2N
NH
H2N
(3)
2) LH-20
sephadex column
37%
(5) codonocarpine
(m = 3, n = 4)
(15) isomer of codonocarpine
(m = 4, n = 3)
(5), (15)
350mg
separated
by DCCC
(5) codonocarpine
89mg (25%)
(15) isomer of
codonocarpine
207mg (59%)
Ac
(16) m = 3, n = 4
(17) m = 4, n = 3

The accomplishment of this total synthesis was confirmed by the identity of melting point, retention time (HPLC), and spectral data (IR, PMR, and mass spectra) between synthetic and natural codonocarpine. Further confirmation of this total synthesis also came from the identity of synthetic N,O-diacetylcodonocarpine (16) [colorless fine needles, mp 166-170° (from acetone) (lit.[3] 169-171°)] with its authentic sample.



perspective view

Figure

The structure of the regioisomer (15) of codonocarpine was established by X-ray crystallographic analysis (see Figure).

Acknowledgement

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References

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