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SYNTHETIC STUDIES ON CARZINOPHILIN A. SYNTHESIS OF THE OPTICALLY ACTIVE C.1-C.18 SEGMENT

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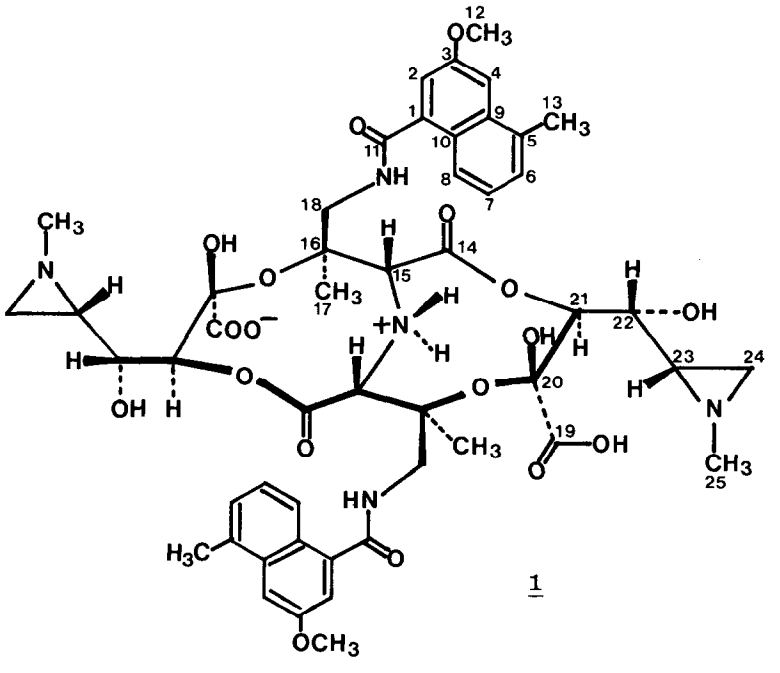
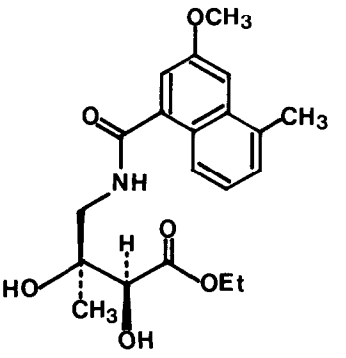
Summary: A synthetic route to compound 2, the optically active C.1-C.18 segment of carzinophilin A, is described.

Carzinophilin A (CZ), produced by *Streptomyces sahachiroi*, is the first natural intercalative bisalkylator with notable antitumor antibiotic activity.[1] The first isolation of CZ by Hata and his co-workers in 1954[2] and several other pioneering investigations[3] were followed by the structure elucidation of some degradation products.[4] The complete structure (1) of CZ was proposed recently by Lown *et al* from the 400-MHz ^{1}H and ^{13}C NMR spectra together with NOE experiments.[5] Elegance of the structure and expected proficiency of its action on DNA prompted us to synthesize CZ and its related compounds for studying their chemical and physiological properties. Our strategy for the total synthesis of CZ (1), which possesses a dimeric structure with 2-fold symmetry, is to connect the optically active C.1-C.18 segment and C.19-C.25 segment through ester, hemiacetal, and amino linkage. We now report the synthesis of a key intermediate 2, which is equivalent to the aforementioned C.1-C.18 segment.



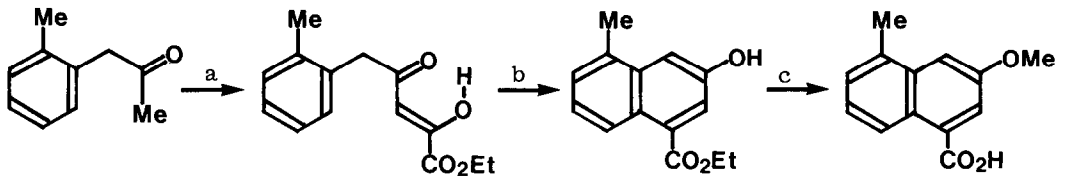
1



2

The synthesis of the naphthalenecarboxylic acid **6**, which has been obtained previously by alkaline hydrolysis of CZ by Onda *et al*,[4] is outlined in Scheme 1. Condensation of 1-(2-methylphenyl)-2-propanone **3**[6,7] with diethyl oxalate gave the enol **4** as a single product in 82 % yield. Exclusive regioselectivity of this acylation can be attributed to the steric and electronic influence of the methyl group on benzene ring.[8] After several unsuccessful attempts for cyclization of **4** (polyphosphoric acid, HBr/AcOH, neat H_2SO_4, *etc.*), the naphthol **5**, mp 113-116°, was obtained in 70 % yield by the two phase reaction of **4** with conc. sulfuric acid in chloroform. The naphthol **5** was converted into the desired naphthalenecarboxylic acid **6**, mp 179-180°, in 92 % yield; the spectroscopic data of which were identical with those reported in the literature.[4]

Scheme 1



3 **4** **5** **6**

Reagents: a. $(CO_2Et)_2$/EtONa/ether/RT. b. conc. H_2SO_4/$CHCl_3$/-78°→0°.
c. $(CH_3O)_2SO_2$/aq. NaOH/0°→RT→reflux.

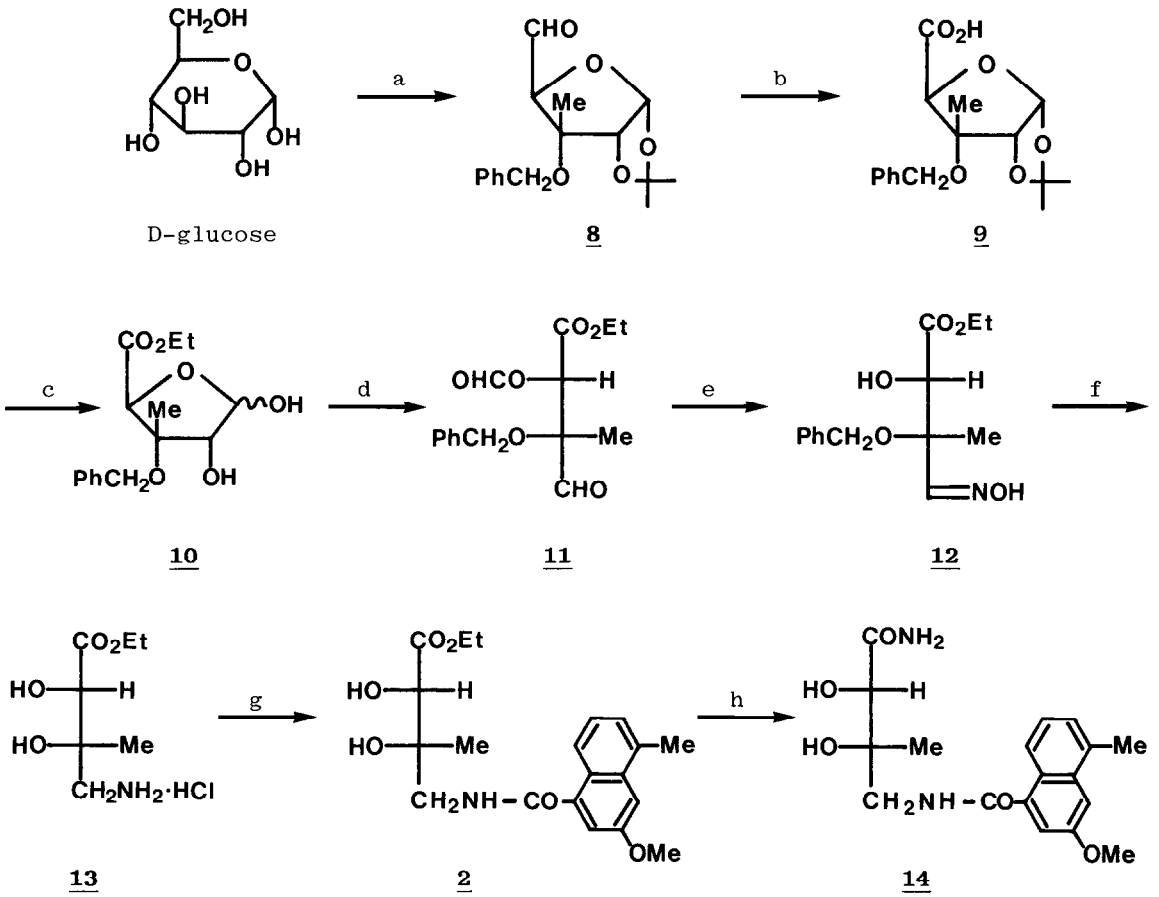
The synthesis of the key intermediate **2** is summarized in Scheme 2. The aldehyde **8**, prepared from D-glucose in 6 steps according to the established procedure,[9] was converted into the carboxylic acid **9**, mp 117-118°, by Jones' oxidation in 87 % yield. Esterification of **9** and successive partial hydrolysis with 70 % acetic acid without purification of the intermediate gave an anomeric mixture of the diol **10** in nearly quantitative yield. Periodate oxidation of **10** gave the aldehyde **11**, which was in turn treated with hydroxylamine hydrochloride in pyridine. The resulting mixture of the corresponding oxime and the de-formylated product **12** was treated with catalytic hydrogen chloride in ethanol to afford pure **12** in 94-96 % yield based on **10**.

The next transformation involves a deprotection, reduction of the hydroxyimino group, and acylation of the resulting amino group. Catalytic hydrogenation of **12** with Pd-C in the presence of ethanolic hydrogen chloride at high pressure gave the amino ester hydrochloride **13**.[10] It is interesting to note that the alternative method by using PtO_2 as a catalyst in acetic acid resulted in a hydrogenation of benzene ring to afford the cyclohexylmethyl derivative of **13** exclusively.[11] The amino ester **13** was treated with the acid chloride **7** obtained from the naphthalenecarboxylic acid **6** (PCl_5/ether/reflux) to yield the amide **2**, mp 66-68°, in 91 % yield based on **12**. Compound **2** was converted into the diamide **14**, which was found to be identical with the degradation product **14**[4b] of CZ by direct comparison of spectroscopic data (^{1}H-NMR, IR, MS).

The above work completes the construction of C.1-C.18 segment of CZ and work is in progress toward the synthesis of another segment (C.19-C.25).[12]

Acknowledgement: The author is grateful to Professor Onda, Kitasato University, for spectroscopic data of degradation product **14**.

Scheme 2



Reagents: a. See reference 9. b. Jones' reagent/acetone/0°. c. (i) HCl(cat.)/EtOH/RT. (ii) 70% AcOH-H_2O/gentle reflux. d. 2 equiv $NaIO_4$/50% MeOH-H_2O/0°. e. (i) 2 equiv NH_2OH·HCl/pyridine/RT, (ii) HCl(cat.)/EtOH/RT. f. H_2(130 kg/cm^2)/10% Pd-C/EtOH-HCl(1.5 equiv HCl)/RT. g. 7 (acid chloride of 6)/NEt_3/CH_2Cl_2/-78°→RT. h. NH_3(sat.)/50% EtOH-H_2O/NH_4Cl(cat.)/RT.

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4. (a) M. Onda, Y. Konda, A. Noguchi, S. Omura, and T. Hata, *J. Antibiot.*, 22, 42 (1969); (b) M. Onda, Y. Konda, S. Omura, and T. Hata, *Chem. Pharm. Bull.*, 19, 2013 (1971).
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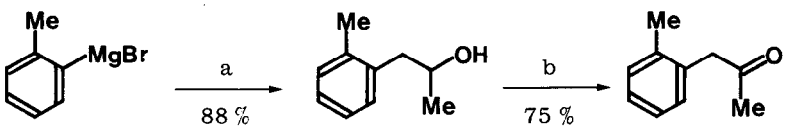
6. Y. Ogata and K. Takagi, *J. Org. Chem.*, 39, 1385 (1974); S. Goszczynski, D. R-Roszak, and M. Lozynski, *Pol. J. Chem.*, 53, 849 (1979); R. Knorr, A. Weiss, P. Löw, and E. Räpple, *Chem. Ber.*, 113, 2462 (1980).
7. Compound 3 was prepared alternatively by the following method which is more practical and suitable for a large scale experiment.



3

Reagents: a. (i) 2 equiv propylene oxide/ether/-10°→RT, (ii) aq. NH_4Cl
b. 1 equiv Jones' reagent/acetone/0°.

8. It is known that the base-catalyzed reaction of 1-phenyl-2-propanone with aromatic aldehydes produce both possible condensation products; see, S. A. Fine and P. D. Pulaski, *J. Org. Chem.*, 38, 1747 (1973).
9. J. Yoshimura, K. Hara, M. Yamaura, K. Mikami, and H. Hashimoto, *Bull. Chem. Soc. Jpn.*, 55, 933 (1982) and references cited therein.
10. The corresponding amino acid has been synthesized by Onda *et al* in racemic form.[4b]
11. Identified as a benzyloxycarbonyl derivative.
12. Selected data, 4: ν ($CHCl_3$) 1738, 1638, and 1592 cm^{-1}; δ ($CDCl_3$) 1.32 (3H, t, J = 7), 2.25 (3H, s), 3.76 (2H, s), 4.26 (2H, q, J = 7), 6.28 (1H, s), 7.15 (4H, s), and 14.0 (1H, br., OH). 5. ν (KBr) 3350, 1677, and 1599 cm^{-1}; δ ($CDCl_3$) 1.40 (3H, t, J = 7), 2.48 (3H, s), 4.44 (2H, q, J = 7), 6.63 (1H, s, OH), 7.10-7.40 (2H, m), 7.44 (1H, dd, J = 1 and 2.5), 7.77 (1H, d, J = 2.5), and 8.52 (1H, m). 11: ν ($CHCl_3$) 1740 cm^{-1}; δ ($CDCl_3$) 1.19 (3H, t, J = 7), 1.45 (3H, s), 4.19 (2H, q, J = 7), 4.65 (2H, s), 5.48 (1H, s), 7.29 (5H, s), 8.16 (1H, s), and 9.65 (1H, s). 12: ν ($CHCl_3$) 3560, 3330, and 1735 cm^{-1}; δ ($CDCl_3$) 1.25 (3H, t, J = 7), 1.54 (3H, s), 3.57 (1H, d, J = 8, OH), 4.23 (1H, d, J = 8), 4.24 (2H, q, J = 7), 4.43 (1H, d, J = 11.5), 4.48 (1H, d, J = 11.5), 7.25 (5H, s), 7.56 (1H, s), and 8.70 (1H, s, OH). 2: ν (KBr) 3380, 3260, 1730, 1705, 1637, 1610, and 1598 cm^{-1}; δ ($CDCl_3$, 200 MHz) 1.25 (3H, s), 1.35 (3H, t, J = 7.1), 2.63 (3H, s), 3.27 (1H, dd, J = 5.4 and 14.2), 3.90 (1H, d, J = 1.5, OH), 3.92 (3H, s), 3.98 (1H, ddd, J = 1.5, 7.8, and 14.2), 4.20 (1H, d, J = 5.1), 4.32 (2H, q, J = 7.1), 4.76 (1H, d, J = 5.1, OH), 6.76 (br. q, NH), 7.24-7.34 (4H, m), and 8.04 (1H, m); ^{13}C NMR δ ($CDCl_3$, 50 MHz) 14.1 (q), 19.8 (q), 20.9 (q), 46.8 (t), 55.3 (q), 61.9 (t), 74.0 (d), 74.5 (s), 105.2 (d), 117.4 (d), 123.4 (d), 124.3 (d), 125.5 (s), 127.6 (d), 133.0 (s), 134.1 (s), 135.5 (s), 156.0 (s), 171.1 (s), and 173.2 (s); MS m/e 375.1682 (M^+), 329, 229, 228, 199; λ (EtOH) 225 nm (log ε = 4.56), 282 (3.57), 290 (3.59), 325 (3.37), and 335 (3.45); $[\alpha]_\lambda^{22}$ (c=2.18, MeOH) +20.7°(589 nm), +24.8°(550), +31.2°(500), and +61.5°(400).

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