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SYNTHESIS OF THE NAPHTHALENECARBOXYLIC ACID DERIVATIVE OBTAINED FROM NEOCARZINOSTATIN (NCS): A STRUCTURE REVISION

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Summary: The structure of the naphthalenecarboxylic acid derivative obtained from neocarzinostatin (NCS) was revised as methyl 2-hydroxy-7-methoxy-5-methyl-1-naphthalenecarboxylate (**2a**) by its synthesis.

The antitumor antibiotic neocarzinostatin (NCS), isolated from the culture filtrate of *Streptomyces carzinostaticus var.* F-41, has been shown to be a 1:1 complex of a highly unsaturated nonprotein component (NPC) and an acidic protein.[1] The isolated NPC possesses all of the biological activity of NCS and is very unstable. An improved partial structure of NPC proposed by Goldberg *et al*[1a] is shown in Fig. 1. Edo *et al*[2] isolated a methyl naphthalenecarboxylate from the methanolysis products of NCS and NPC and proposed **1a** as its structure. As part of a series of studies on natural antitumor agents, we synthesized compound **1a**.[3] However, the reported data for the degradation product and its derivatives were markedly different from those of our samples (**1a-c**)[4] synthesized by the unequivocal route outlined in Scheme 1. Table 1 summarizes NMR spectral data on **1a-c** with those reported for natural naphthalene derivatives. We reinterpreted the reported spectral data in comparison with ours, and concluded that the naphthalenecarboxylate obtained from NCS and NPC is the regioisomer of **1a** and has the structure **2a**. In this communication, we revise the structure of the naphthalenecarboxylic acid derivatives to **2a-c**, on the basis of the total synthesis outlined in Scheme 2.[4]

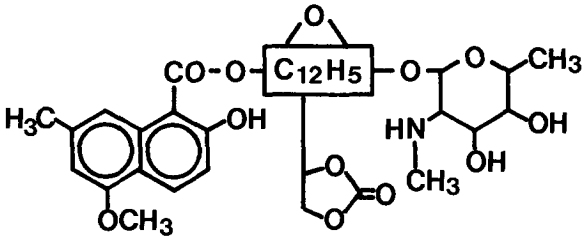
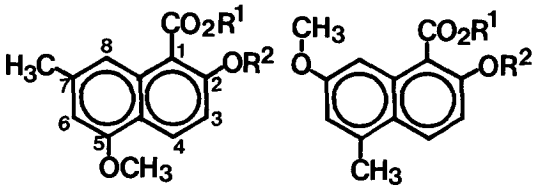


Fig. 1. Proposed partial structure of NPC (I. H. Goldberg *et al*)[1a]

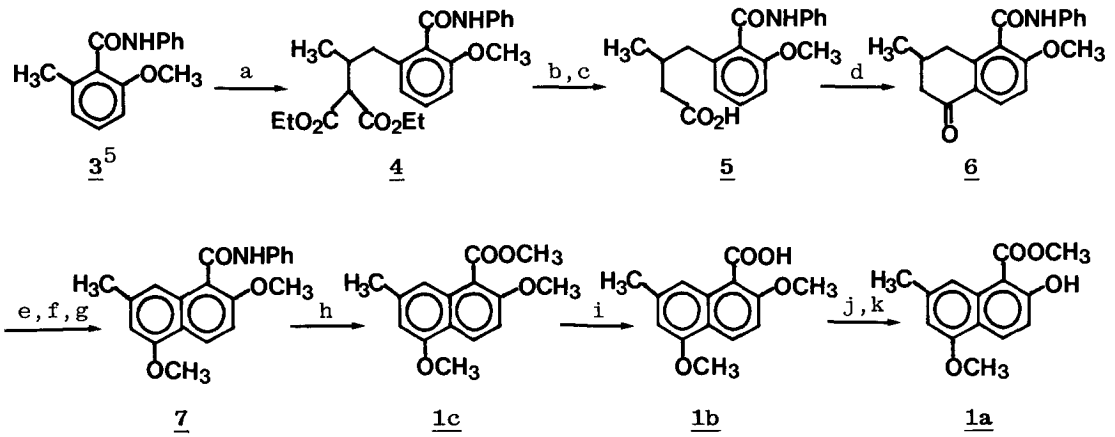


1a R^1=CH_3, R^2=H **2a** R^1=CH_3, R^2=H
1b R^1=H, R^2=CH_3 **2b** R^1=H, R^2=CH_3
1c R^1=R^2=CH_3 **2c** R^1=R^2=CH_3

Table 1. NMR spectral data on 1a-c[*1]

	CO_2CH_3	C_2-OCH_3	C_3-H	C_4-H	C_5-OCH_3	C_6-H	C_7-CH_3	C_8-H
1a	4.07	———	7.04, d J=9.2	8.35, d J=9.2	3.94	6.57, d J=1.1	2.50, m	8.07, m
	(4.10)	———	(7.01)	(8.01)	(3.92)	(6.90)	(2.63)	(8.09)
1b	———	4.01[*2]	7.16, d J=9.5	8.32, dd J=0.7,9.5	3.96[*2]	6.55, d J=1.0	2.50, m	7.57, m
	———	(4.06)[*2]	(7.12)	(8.02)	(3.90)[*2]	(6.90)	(2.63)	(7.74)
1c	3.97	3.91[*2]	7.07, d J=9.5	8.17, dd J=0.7,9.5	3.93[*2]	6.43, d J=1.0	2.44, m	6.95, m
	(3.89)	(3.65)	(6.91)	(7.77)	(3.82)	(6.73)	(2.57)	(6.73)

*1. Determined with a JEOL JNM-FX200 instrument in $CDCl_3$(1a,b) and $CCl_4/CDCl_3$(3:1)(1c) at sample concentrations of 4% w/v. Reported chemical shifts[2] for the corresponding natural products are shown in parentheses. *2. Assignments may be reversed.



Scheme 1

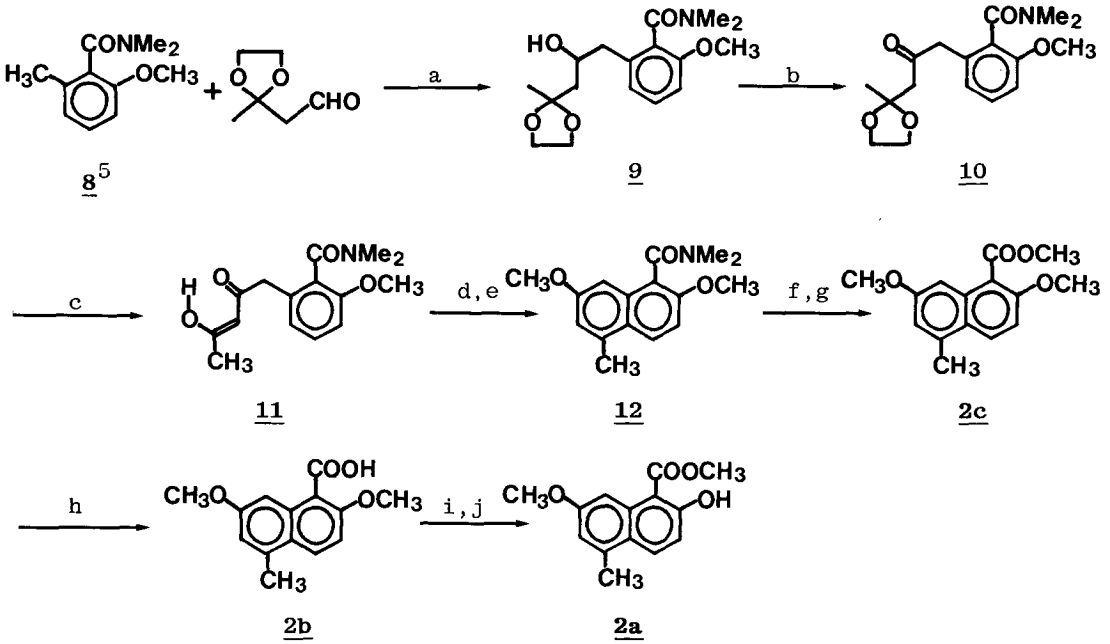
a. 2.1 equiv n-butyllithium/TMEDA/diethyl ethylidenemalonate/THF/-78°/86%. b. 5% aq.NaOH/90°/1h/95%. c. 140-150°/1h/98%. d. 2 equiv $(CF_3CO)_2O$/benzene/reflux/5min/92%. e. 2 equiv $CuBr_2$/AcOEt-$CHCl_3$(1:1)/reflux/2h/99%. f. K_2CO_3/acetone/reflux/95%. g. K_2CO_3/1.3 equiv $(CH_3O)_2SO_2$/cat.$(C_4H_9)_4NHSO_4$/reflux/1h/88%. h. 20% BF_3-MeOH/110-120°/3h/72%. i. 10% NaOH in H_2O-DMSO(1:1)/120°/99%. j. 4 equiv BCl_3/CH_2Cl_2/-78°→0°/0.5h/93%. k. CH_2N_2/ether/89%.

Metallation of the *o*-toluamide 8[5] with LDA followed by quenching with 2-methyl-2-(2-oxoethyl)-1,3-dioxolane[6] provided the amide alcohol 9.[7] Oxidation of 9 with the chromium trioxide-pyridine complex and acetic anhydride[8] gave the keto amide 10, which was hydrolyzed in acidic conditions to afford the enolated β-diketone 11. Cyclization of 11 with conc. sulfuric acid provided the naphthol, which upon methylation with potassium carbonate and dimethylsulfate

in acetone afforded the dimethyl ether **12**. After several unsuccessful attempts to hydrolyze **12** [(a) 50% KOH, H_2O/DMSO, 170°, 12h, (b) 60% $HClO_4$, 130°, 12h, *etc.*], the methyl ester **2c** was obtained in 31% yield (66% recovery of **12**) by methylation with methyl fluorosulfonate followed by alkaline hydrolysis of the intermediate imidate salt.[9] Alkaline hydrolysis of the ester **2c** afforded the carboxylic acid **2b** in good yield. Selective demethylation of **2b** with boron trichloride produced the hydroxy acid which was methylated with diazomethane to afford the hydroxy ester **2a**. Compound **2a** was found to be identical with the degradation product of NCS by direct comparison (mp, ^1H NMR, IR, MS, TLC). Compounds **2b** and **2c** were also identical spectroscopically with the derivatives of the above ester from NCS.[2]

Thus, the structure of the naphthalenecarboxylic acid derivative from NCS and NPC was concluded to be methyl 2-hydroxy-7-methoxy-5-methyl-1-naphthalenecarboxylate (**2a**). The partial structure of NPC proposed by Goldberg *et al*[1a] should be revised. It is noteworthy that the carbon skeleton of **2a** is the same as that of the naphthalene chromophore of the antitumor antibiotic carzinophilin.[10,11]

Acknowledgement: The authors are grateful to Dr. Kusano, Tohoku University, for a gift of the naphthalenecarboxylic acid derivative **2a** and spectroscopic data on **2a-c**.



Scheme 2

a. 1.5 equiv LDA/THF/-78°/0.5h/98%. b. 4 equiv CrO_3/8 equiv pyr./4 equiv Ac_2O/CH_2Cl_2/RT/2h/83%. c. 10% aq. HCl/acetone/RT/3h/88%. d. conc H_2SO_4/RT/12h/45%. e. K_2CO_3/1.3 equiv $(CH_3O)_2SO_2$/cat. $(C_4H_9)_4NHSO_4$/reflux/1h/92%. f. FSO_3CH_3/RT/1h/100%. g. 1N NaOH/CH_3CN/50°/10min/31%(66% recovery of **12**). h. 10% NaOH in H_2O-DMSO (1:1)/120°/1h/99%. i. 4 equiv BCl_3/CH_2Cl_2/-78→0°/0.5h/87%. j. CH_2N_2/ether/55%.

REFERENCES AND NOTES

1. (a) Chemical structure: O. D. Hensens, R. S. Dewey, J. M. Liesch, M. A. Napier, R. A. Reamer, J. L. Smith, G. A. Schönberg, I. H. Goldberg, *Biochem. Biophys. Res. Commun.*, 113, 538 (1983), and references cited therein, (b) biological activity: M. A. Napier and I. H. Goldberg, *Molecular Pharmacology*, 23, 500 (1983) and references cited therein.
2. K. Edo, S. Katamine, F. Kitame, N. Ishida, Y. Koide, G. Kusano, and S. Nozoe, *J. Antibiot.*, 33, 347 (1980).
3. Satisfactory analytical data were obtained for all new compounds.
4. Selected data, **4**: mp 84-85°; $\nu(CHCl_3)$ 3420, 1745(sh), 1725, 1675, and 1598 cm^{-1}. **5**: mp 155-156°; $\nu(CHCl_3)$ 3420, 1715, 1675, and 1598 cm^{-1}. **6**: mp 219-220°; $\nu(CHCl_3)$ 3420, 1678, and 1587 cm^{-1}; $\delta(CDCl_3$, 100 MHz) 1.09 (3H, d, J=5.5), 2.00-3.20 (5H, m), 3.87 (3H, s), 6.95 (1H, d, J=9), 7.00-7.85 (5H, m), 8.05 (1H, d, J=9), and 10.02 (1H, br.). **7**: mp 213-214°; $\nu(CHCl_3)$ 3420, 1675, and 1598 cm^{-1}; $\delta(DMSO\text{-}d_6$, 100 MHz) 2.37, 3.85, 3.91 (3X3H, s), 6.66, 7.02 (2X1H, m), 6.90-7.90 (5H, m), 7.35 (1H, d, J=9.5), 8.16 (1H, d, J=9.5), and 10.41 (1H, br.). **1c**: mp 118-119°; $\nu(CHCl_3)$ 1723, 1679, 1583, and 1270 cm^{-1}. **1b**: mp 141-142°; $\nu(CHCl_3)$ 1722, 1628, 1597, and 1583 cm^{-1}. **1a**: mp 113-114°; $\nu(CHCl_3)$ 1657(sh), 1648, 1623, and 1272 cm^{-1}. **10**: $\nu(CHCl_3)$ 1712 and 1622 cm^{-1}; $\delta(CDCl_3$, 100 MHz) 1.40 (3H, s), 2.78 (2H+3H, s), 3.05 (3H, s), 3.79 (3H, s), 3.95 (4H, s), 3.70 (1H, d, J=17), 3.90 (1H, d, J=17), 6.77 (1H, d, J = 7.5), 6.79 (1H, d, J=9), and 7.23 (1H, dd, J=7.5 and 9). **11**: $\nu(CHCl_3)$ 1624 cm^{-1}; $\delta(CDCl_3$, 100 MHz) 2.00, 2.72, 3.03, 3.76 (4X3H, s), 3.42 (1H, d, J=15), 3.63 (1H, d, J=15), 5.48 (1H, s), 6.78 (1H, d, J=7.5), 6.85 (1H, d, J=7.5), and 7.25 (1H, t, J=7.5). **12**: mp 132-134°; $\nu(CHCl_3)$ 1623 cm^{-1}; $\delta(CDCl_3$, 100 MHz) 2.57, 2.75, 3.20, 3.81, 3.88 (5X3H, s), 6.71 (1H, m), 6.84 (1H, m), 7.06 (1H, d, J=9.5), and 7.85 (1H, d, J=9.5). **2c**: mp 147-148° (lit.,[2] 151-151.5°). **2b**: mp 159-160° (lit.,[2] 133-134°). **2a**: mp 104-105° (lit.,[2] 104-105°); $\delta(CDCl_3$, 200 MHz) 2.60, 3.90, 4.08 (3X3H, s), 6.87 (1H, dd, J=0.7 and 2.6), 7.01 (1H, d, J=9.2), 8.00 (1H, d, J=9.2), 8.05 (1H, d, J=2.6), and 12.13 (1H, s); Edo *et al*[2] reported that there was a nuclear Overhauser effect (18%) between the methoxyl group and the paramagnetically shifted member of the *ortho* coupled hydrogens. Our results were as follows. Irradiation of the methoxyl peak (δ 3.90) resulted in 25% increase in the intensity for C_8-H (δ 8.05) and 7% increase in that for C_6-H (δ 6.87), but no increase for C_4-H (δ 8.00).
5. The *o*-toluamides **3** and **8** were synthesized from 2-methoxy-6-methylbenzoic acid (F. M. Hauser and S. A. Pogany, *Synthesis*, 1980, 814) in two steps [(i) $SOCl_2$, 80°, 1h, (ii) RR'NH, RT, CH_2Cl_2 or H_2O].
6. M. Bertrand, G. Leandri, and A. Meou, *Tetrahedron*, 37, 1703 (1981).
7. In the NMR spectrum of **9**, a set of signals of the two conformational isomers, arising from restricted rotation about the amide bond, was observed. These two isomers could not be isolated, but two spots were observed on TLC at room temperature.
8. P. J. Garegg and B. Samuelsson, *Carbohydrate Research*, 67, 267 (1978).
9. The complete transformation of **12** to the imidate salt was confirmed by TLC. Unfortunately, the ester **2c** could not be obtained predominantly by hydrolysis of the imidate salt under various conditions. *c.f.* P. Deslongchamps and R. J. Taillefer, *Can. J. Chem.*, 53, 3029 (1975).
10. M. Onda, Y. Konda, A. Hatano, T. Hata, and S. Ōmura, *J. Amer. Chem. Soc.*, 105, 6311 (1983).
11. M. Shibuya, *Tetrahedron Letters*, 24, 1175 (1983).

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