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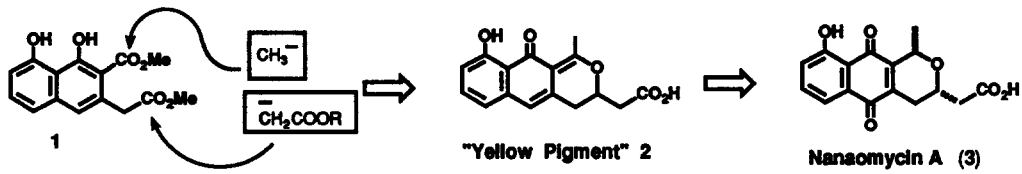
A BIOMIMETIC SYNTHESIS OF (±)-NANAOMYCIN A

Masahiko YAMAGUCHI,* Shigeo NAKAMURA, Tadashi OKUMA, and Toru MINAMI
Department of Applied Chemistry, Kyushu Institute of Technology,
Sensui-cho, Tobata, Kitakyushu 804, JAPAN

Abstract: A biosynthetic intermediate of isochromanequinone antibiotics was synthesized, and biomimetically converted to (±)-nanaomycin A. A novel synthetic method of methyl ketones from esters was also developed.

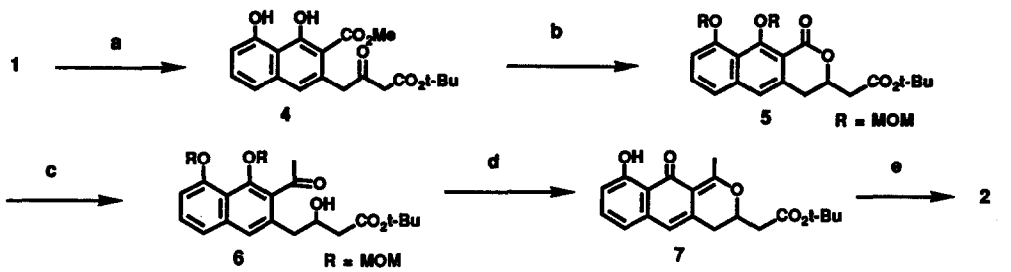
"Yellow Pigment" **2** was recently isolated as an intermediate of the biosynthesis of isochromanequinone antibiotics such as actinorhodin, kalafungin, and possibly nanaomycins.[1] During our studies on the synthesis of aromatic natural products of the polyketide-origin,[2] we were interested in the synthesis and the chemical behaviors of **2**, and our results are noted here. A novel synthetic method of methyl ketones from esters was also developed.

Naphthalenediol **1**[2], which can be readily prepared from β-hydroxyglutarate and acetoacetate, was employed as the starting material in the present synthesis. The synthetic strategy is based on the differentiation of two ester groups of **1**: Introduction of a methyl group to the aromatic carboxylate, and an acetate to the aliphatic carboxylate (Scheme 1).



Scheme 1

The selective extension of an acetate unit from the aliphatic carboxylate was carried out by the Claisen condensation of lithiated t-butyl acetate with **1** in high yield. The phenolic hydroxy groups must be unprotected, otherwise a mixture of several products was obtained from the corresponding dimethyl ether. Reduction, lactonization, and protection converted ketoester **4** to lactone **5**. Although methylation of the aromatic carboxylate of **5** with various organometallic reagents failed, the Claisen condensation of lithiated acetate was found to proceed regioselectively. Since the use of t-butyl acetate suffered from low yields at the next decarboxylation reactions,[3] 2-methyl-3-buten-2-yl ester was newly introduced. The alkoxycarbonyl group was removed by Pd catalyzed reaction[4] giving the methyl ketone **6** in high yield. The acid treatment of **6** under anhydrous conditions resulted in the removal of MOM group and dehydration to **7** (Mp 126-7 °C). t-Butyl gruop was removed, and the spectra of the resulted carboxylic acid **2** agreed with the reported values[1] (Scheme 2).

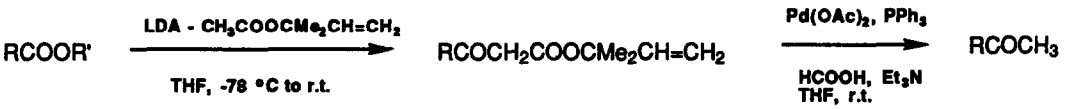


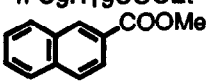
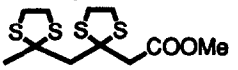
a LDA-$CH_3COOtBu$ (8 eq.), THF; -78 °C to r.t. (96%). **b** i) $NaBH_4$, EtOH; -45 °C, 2 h. ii) Et_3N (12 eq.), CH_2Cl_2; 0 °C, 3 h. (98% in two steps). iii) MOMCl, iPr_2NEt; CH_2Cl_2, r.t., overnight (90%). **c** i) LDA-$CH_3COOCMe_2CH{=}CH_2$ (6 eq.), THF; -78 °C, 1 h. ii) $Pd(OAc)_2$, Ph_3P, Et_3N, HCOOH, THF; refl., 30 min (92% in two steps). **d** HCl (2 eq.), MeOH; 0 °C, 1 h (97%). **e** TFA, CH_2Cl_2; r.t., 5 h (90%).

Scheme 2

Since a novel synthesis of a methyl ketone from an ester utilizing Pd chemistry worked efficiently in the above synthesis, the method was applied to other substrates. As shown in Table 1, the reaction proceeded under mild reaction conditions, and methyl ketones were obtained in good yields.

Table 1. Synthesis of Methyl Ketones from Esters.



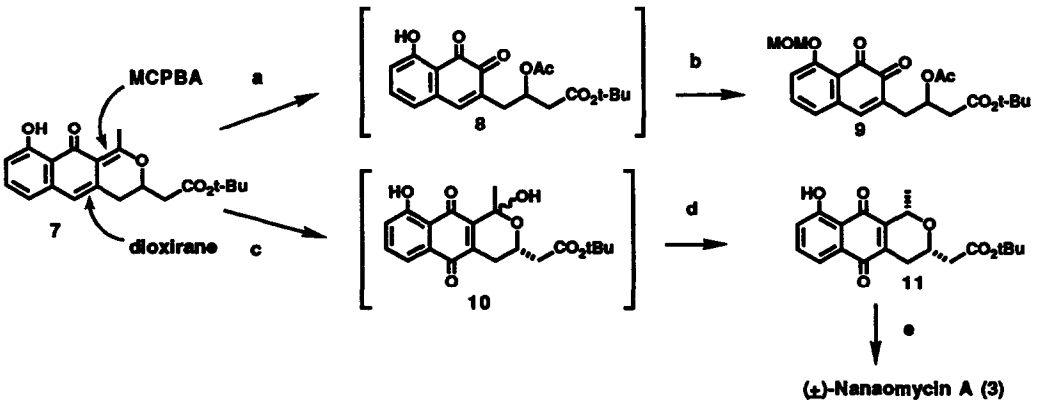
RCOOR'	Yield(%) ketoester[a]	Yield(%) methylketone
n-$C_9H_{19}COOEt$	83	72, 94[b]
	66	86, 94[c]
	78	91

a) An excess amount (3 to 6 eq.) of enolate was used.

b) Thermal decarboxylation was conducted: i) TFA,CH_2Cl_2; r.t., 1 h, ii) benzene; refl., 40 min.

c) $Pd_2(dba)_3$ was used as the catalyst.

Next, chemical behaviors of the 4,10-dihydro-3*H*-naphtho[2,3-*c*]pyran-10-one structure, especially oxidation reactions, were examined, and a novel biomimetic route to (±)-nanaomycin A (**3**)[5,6] was discovered. When **7** was treated with MCPBA, a bond cleavage occurred at 1-10*a* position, and unstable *ortho*-quinone **8** was formed, which was isolated as MOM ether **9**. The oxidation with 1,2-dioxirane[7], however, gave the *para*-quinone **10** presumably *via* an epoxide at 4*a*-5 position. The lactol **10**, without isolation, was reduced to *cis*-pyran **11** by Kraus's method,[6p] and was finally converted to (±)-nanaomycin A (**3**).[6m] Since we encountered many difficulties in the direct oxidation of **1** to quinones,[8] the above observations suggest that a related quinone formation process is operating in the biosynthesis of **3** and its derivatives.



a MCPBA (5 eq.), CH_2Cl_2; -25 °C, 20 min. **b** MOMCl, iPr_2NEt, CH_2Cl_2; r.t., 2 h (46% in two steps). **c** 3,3-dimethyldioxirane (15 eq.), benzene, buffer (pH 8), 18-crown-6; 6 °C, 2 h. **d** TFA (8.5 eq.), Et_3SiH (8.5 eq.), CH_2Cl_2; -78 °C to r.t., 2 h (54% in two steps). **e** catalytic conc H_2SO_4, benzene; r.t., 30 min (83%).

Scheme 3

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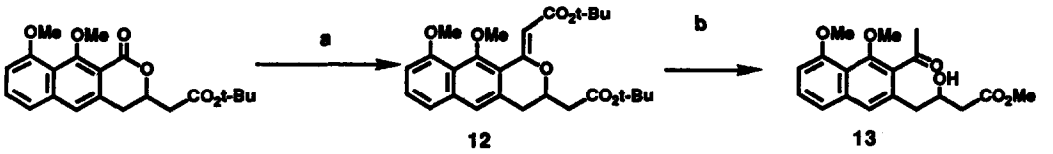
2) M. Yamaguchi, K. Hasebe, H. Higashi, M. Uchida, A. Irie, and T. Minami, *J. Org. Chem.*, **55**, 1611 (1990); and references cited therein.
3) Although the t-butyl ester **12** also gave a methyl ketone **13**, the yield was moderate. What is more, the acidic conditions to remove t-butyl ester did not allow the use of MOM group as the protecting group (Scheme 4).



12 13

a LDA - $CH_3COOtBu$ (6 eq.); THF, -78 °C, 30 min (quant.). **b** i) TFA, CH_2Cl_2; r.t., 3 h. ii) catalytic CH_3SO_3H, THF-H_2O; refl., 2.5 h. iii) CH_2N_2, ether; 0 °C, 1 h (42% in 3 steps).

Scheme 4

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6) Synthesis: a) T. Li and R. H. Ellison, *J. Am. Chem. Soc.*, **100**, 6263 (1978); b) A. Ichihara, M. Ubukata, H. Oikawa, K. Murakami, and S. Sakamura, *Tetrahedron Lett.*, **1980**, 4469; c) T. Kometani, Y. Takeuchi, and E. Yoshii, *J. Chem. Soc., Perkin I*, **1981**, 1197; d) Y. Naruta, H. Uno, and K. Maruyama, *Chem. Lett.*, **1982**, 609; e) M. F. Semmelhack, J. J. Bozell, T. Sato, W. Wulff, E. Spiess, and A. Zask, *J. Am. Chem. Soc.*, **104**, 5850 (1982); f) M. F. Semmelhack, L. Keller, T. Sato, and E. Spiess, *J. Org. Chem.*, **47**, 4382 (1982); g) T. Kometani, Y. Takeuchi, and E. Yoshii, *J. Org. Chem.*, **48**, 2630 (1983); h) M. F. Semmelhack and A. Zask, *J. Am. Chem. Soc.*, **105**, 2034 (1983); i) E. Yoshii, T. Kometani, K. Nomura, Y. Takeuchi, S. Odake, and Y. Nagata, *Chem. Pharm. Bull.*, **32**, 4779 (1984); j) M. S. South and L. S. Liebeskind, *J. Am. Chem. Soc.*, **106**, 4181 (1984); k) M. F. Semmelhack, J. J. Bozell, L. Keller, T. Sato, E. J. Spiess, W. Wulff, and A. Zask, *Tetrahedron*, **41**, 5803 (1985); l) M. F. Semmelhack, L. Keller, T. Sato, E. J. Spiess, and W. Wulff, *J. Org. Chem.*, **50**, 5566 (1985); m) K. Tatsuta, K. Akimoto, M. Annaka, Y. Ohno, and M. Kinoshita, *Bull. Chem. Soc. Jpn.*, **58**, 1699 (1985); n) H. Uno, *J. Org. Chem.*, **51**, 350 (1986); o) G. A. Kraus, M. T. Molina, and J. A. Walling, *J. Chem. Soc., Chem. Commun.*, **1986**, 1568; p) G. A. Kraus, M. T. Molina, and J. A. Walling, *J. Org. Chem.*, **52**, 1273 (1987); q) O. H. W. Decker and H. W. Moore, *ibid.*, **52**, 1174 (1987).

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8) Although the direct oxidation of **1** was tried employing various oxidation reagents such as CAN, CrO_3, Fremy's salt, AgO, etc., none of the methods gave the corresponding quinone.

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