© 1985 The Chemical Society of Japan

SYNTHESIS OF A (\pm) -3 β -TRINORTAXANE DERIVATIVE

Tsutomu KOJIMA, Yoshinobu INOUYE,* and Hiroshi KAKISAWA Department of Chemistry, University of Tsukuba, Sakura-mura, Niihari-gun, Ibaraki 305

Intramolecular photo[2+2]cycloaddition of 4-(3-methyl-2cyclohexenyl)methoxybicyclo[3.3.1]non-3-en-2-one, followed by oxidation with RuO₄ and by alkaline hydrolysis, gave 8-methyltricyclo[9.3.1.0^{3,8}]pentadecane-2,10-dione-4-carboxylic acid, a ($^{\pm}$)-3 $_{\beta}$ -trinortaxane derivative.

A number of achievements have been successively appearing in the literature as concerned with the total syntheses of natural products with various ring systems. The taxane skeleton $(\underline{1})$,¹⁾ however, is one of the remaining synthetic targets in this field, though various approaches to this unique skeleton were reported.^{2,3)} Five groups have recently reported the syntheses of pentanortaxane,^{2a)} bisnortaxane,^{2b)} homotaxane,^{2c)} tetranortaxane,^{2d)} and nortaxane,^{2e)} respectively; all have a common tricyclo[9.3.1.0^{3,8}] pentadecane system.



In the present paper, we wish to report an alternative synthetic approach to the tricyclo[9.3.1.0^{3,8}]pentadecane derivative <u>9</u>, a (<u>+</u>)-3 β -trinortaxane skeleton.

The characteristic features of <u>1</u> are that i) the ring system is a less common tricyclo[9.3.1.0^{3,8}]pentadecane, in which an 8-membered ring is contained and ii) the bridge carbon (C-15) and the methyl group at C-8 is <u>syn</u> each other. Our basic

strategy is that the 8-membered ring is created by the cleavage of a 6-4 ring system that could be easily prepared by photo[2+2]cycloaddition of a cyclohexenone and an olefin. We chose bicylic enone $\underline{6}$ as a model compound.⁴⁾

Unreported bicyclo[3.3.1]nonane-2,4-dione (5) was prepared as shown in Scheme 1.



Scheme 1. Preparation of 5.

 α,β -Unsaturated ketone (2)^{5,6} was treated with thiophenol and ethylene glycol in the presence of TsOH to give 2,2-ethylenedioxy-4-phenylthiobicyclo[3.3.1]nonane (3), mp 107.5-108.5 °C.⁷) When 3 was subjected to oxidation with NCS, vinyl sulfide 4 was obtained in 89% yield. The presence of the ethylenedioxy group is essential to the reaction; otherwise, the reaction became complicated. Hydrolysis of 4 was achieved in high yield under basic or acidic conditions to obtain 5, mp 136-138 °C. The present method is more efficient for the preparation of the bicyclic 1,3-dione in comparison with the palladium-catalyzed rearrangement of α,β -epoxyketones⁸ or the palladium-catalyzed direct oxidation of α,β -unsaturated ketones.⁹

The bicyclic 1,3-dione 5 was condensed with 3-methyl-2-cyclohexenylmethanol¹⁰ in the presence of TsOH to afford an epimeric mixture (1:1) of enol ethers <u>6</u> [IR (CCl₄): 1655 cm⁻¹; ¹H NMR(CCl₄): 3.69 (2H/2, br d, J=6 Hz), 3.73 (2H/2, br d, J=6 Hz),



5.38(1H, m), and 5.51(1H, s)]. A 0.1% solution of the epimeric mixture <u>6</u> in hexane was irradiated with a high-pressure mercury arc lamp (400 W) for 2 h to give mainly an oily single cycloadduct <u>7</u> in 30 - 40% yield. Only one isomer (δ at 3.69) in the mixture <u>6</u> could be converted into <u>7</u> and the other (δ at 3.73) was recovered unreacted. The structure of <u>7</u> was confirmed by its spectroscopic evidence [IR(CCl₄): 1695 cm⁻¹; ¹H NMR(360 MHz, C₆D₆): 0.98(3H, s), 1.80(1H, dm, J=14 Hz, Hc), 1.87(1H, br d, J=10 Hz, Hi), 2.07(1H, m, Hh), 2.25-2.38(2H, m, Hb and He), 2.60(1H, br s, Ha), 3.56(1H, dd, J=9 and 3.5 Hz, Hf), and 3.68(1H, ddd, J=9, 7, and 1 Hz, Hg); ¹³C NMR(C₆D₆): 85.1(s) and 76.8(t)]. The stereochemistry was deduced from COSY NMR and NOE studies¹¹⁾ as shown in <u>A</u>.

As several attempts of the direct cleavage of the cyclobutane ring in $\underline{7}$ under acidic or neutral conditions¹² were unsuccessful, two-step conversion to the tricyclo[9.3.1.0^{3,8}]pentadecane system was then tried. Oxidation of $\underline{7}$ with RuO₄ gave a γ -lactone $\underline{8}$, mp 112-113 °C; IR(CCl₄): 1765 and 1695 cm⁻¹, and hydrolysis of $\underline{8}$ with 10% KOH in H₂O-DMSO(1:1)¹² afforded a diketo-acid $\underline{9}$ in 80% yield. Its methyl ester $\underline{10}$, mp 128.5-129.5 °C, showed following spectroscopic data: IR(CHCl₃): 1730 and 1715 cm⁻¹; ¹H NMR(CDCl₃): 1.16(3H, s), 1.94(1H, d, J=12 Hz, Ha), 2.75(1H, dt, J=13 and 5 Hz, Hh), 3.03(1H, d, J=12 Hz, Ha'), 3.10(1H, dt, J=15 and 3 Hz, Hc), 3.30 (1H, d, J=5 Hz, Hi), and 3.58(3H, s); ¹³C NMR(CDCl₃): 213.8(s), 210.3(s), and 175.3 (s). The stereochemistry of <u>10</u> is shown in <u>B</u>; the large down-field shifts of Hc and Hi in ¹H NMR is due to the steric compression.¹³)





The compound <u>9</u> has a 3β -trinortaxane framework with a correct stereochemical relationship between the bridge methylene and the methyl group at C-8. The work along the present route to a complete taxane framework is now in progress.

References

- 1) For a review, see R. W. Miller, J. Nat. Prod. (Lloydia), 43, 425(1980).
- a) S. F. Martin, J. B. White, and R. Wagner, J. Org. Chem., <u>47</u>, 3190(1982);
 - b) K. J. Shea and P. D. Davis, Angew. Chem. Suppl., 1983, 564;
 - c) K. Sakan and B. M. Craven, J. Am. Chem. Soc., 105, 3732(1983);
 - d) P. A. Brown, P. R. Jenkins, J. Fawcett, and D. R. Russell, J. Chem. Soc., Chem. Commun., 1984, 253;
 - e) R. A. Holton, J. Am. Chem. Soc., <u>106</u>, 5731(1984).
- 3) a) A. S. Kende, M. Benechie, D. P. Curran, and P. Fludzinski, Tetrahedron Lett.,
 20, 4513(1979);
 - b) Y. Inouye, C. Fukaya, and H. Kakisawa, Bull. Chem. Soc. Jpn., 54, 1117(1981);
 - c) H. Shibuya, S. Tsujii, Y. Yamamoto, K. Murakawa, K. Takagi, N. Kurokawa, and
 I. Kitagawa, 24th Symposium on the Chemistry of Natural Products, Osaka,
 October(1981), Abstr., p 340.
 - d) T. Kumagai, F. Ise, T. Uyehara, and T. Kato, Chem. Lett., 1981, 25;
 - e) B. M. Trost and H. Hiemstra, J. Am. Chem. Soc., 104, 886(1982);
 - f) R. C. Gadwood and R. M. Lett, J. Org. Chem., 47, 2268(1982);
 - g) C. S. Swindell and S. J. deSolms, Tetrahedron Lett., 25, 3801(1984).
- 4) A similar approach using an N-analogue was recently reported. See ref. 3g.
- 5) J. P. Schaefer, J. C. Lark, C. A. Flegal, and L. M. Honig, J. Org. Chem., <u>32</u>, 1372(1967).
- 6) We prepared 2 by a procedure different from ref. 5.

$$\underbrace{\bigwedge_{\text{Hg (OAc)}_{2}}^{\text{Hg (OAc)}_{2}}}_{\text{H_2O-dioxane}} (61\%) \underbrace{\bigwedge_{2}^{\text{O}} \underbrace{\text{i) Ph (CH_3)}_{3} \text{NBr}_{3} / \text{THF (0°)}}_{\text{ii) Li}_{2} \text{CO}_{3} - \text{LiBr} / \text{DMF } (\Delta)} (88\%) \underline{2}$$

- 7) Satisfactory elemental analyses were obtained for all new compounds.
- 8) M. Suzuki, A. Watanabe, and R. Noyori, J. Am. Chem. Soc., <u>102</u>, 2095(1980).
- 9) J. Tsuji, H. Nagashima, and K. Hori, Chem. Lett., 1980, 257.
- 10) T. Umehara, Y. Inouye, H. Kakisawa, Bull. Chem. Soc. Jpn., 54, 3492(1981).
- 11) We are deeply indebted to Dr. Takashi Iwashita, Suntory Institute for Bioorganic Research, for measurements of COSY and NOE spectra of 7.
- 12) T. Kojima, Y. Inouye, and H. Kakisawa, Bull. Chem. Soc. Jpn., in preparation.
- 13) S. Winstein, P. Carter, F. A. L. Anet, and A. J. R. Bourn, J. Am. Chem. Soc., <u>87</u>, 5247(1965). (Received December 18, 1984)