## A Synthetic Approach to Furanocembranolides<sup>1</sup>)

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The furanccembranoid skeleton of lophotoxin-type has been constructed efficiently by a method utilizing the formation reaction of a furan ring for the macrocyclization.

Cembranolide diterpenes represent a large group of marine natural products<sup>2</sup>) and have received a current attention as the target of synthetic studies.<sup>3</sup>) Among them lophotoxin  $1^{4}$  and the related compounds<sup>5</sup>) are structurally notable in that these diterpenes are highly oxygenated and have trisubstituted furan rings. Lophotoxin is also prominent by its unique neuromuscular blocking activity.<sup>6</sup>) We report here an approach for the construction of the macro ring system characteristic for a group of the furanocembranolide diterpenes.



Our strategy is the utilization of the trisubstituted furan ring synthesis developed by Williams et al.<sup>7</sup>) and to effect the furan ring formation and the macrocyclization at the same time. This plan has been explored on a model system as shown in Scheme 1.

For the preparation of acyclic precursor 3 we envisaged first the condensation of aldehyde 6 with dianion derived from 7 (5, Z = H). The left-hand segment 6 was synthesized as a diastereomeric mixture (1:1) from 2-methyl-4-pentenoic acid by eight steps procedure (Scheme 2) and right-hand segment 7 was produced readily from methyl hydrogen heptanedioate by the application of Yonemitsu's procedure.<sup>8</sup>) The reaction of 6 with the dianion of 7 prepared by two equivalents of lithium diisopropylamide (LDA) in THF/HMPA at -78 °C afforded the aldol product 8, which



Scheme 1.



Scheme 2. Reagents: i, LiAlH<sub>4</sub>, Et<sub>2</sub>O; ii, Swern oxidation; iii, Ph<sub>3</sub>P=CHCO<sub>2</sub>Me; iv, DIBAH, CH<sub>2</sub>Cl<sub>2</sub>; v, <u>t</u>-BuOOH, VO(acac)<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>; vi, <u>t</u>-BuMe<sub>2</sub>SiCl, imidazole, DMF; vii, (Sia)<sub>2</sub>BH, THF, then H<sub>2</sub>O<sub>2</sub>, NaOH



Scheme 3. Reagents: i, SOCl<sub>2</sub>, then Meldrum's acid, pyridine, CH<sub>2</sub>Cl<sub>2</sub>; ii, MeOH,  $\Delta$ ; iii, HC(OMe)<sub>3</sub>, MeOH, CSA; iv, (MeO)<sub>2</sub>P(O)CH<sub>2</sub>CO<sub>2</sub>Me or (CF<sub>3</sub>CH<sub>2</sub>O)<sub>2</sub>P(O)CH<sub>2</sub>CO<sub>2</sub>Me, NaH

was dehydrated and desilylated. After purification by silica gel chromatography an olefinic product was obtained as a mixture of  $\underline{Z}$  and  $\underline{E}$  isomers (9/10 = 1:8) in 54% overall yield from 6. In the <sup>1</sup>H NMR spectra they exhibited the signals due to the olefinic protons at  $\delta$  5.88 (t,  $\underline{J}$  = 7.5 Hz) and  $\delta$  6.69 (t,  $\underline{J}$  = 7.5 Hz) respectively. To get the  $\underline{Z}$  isomer in a predominant amount the application of Horner-Emmons procedure was investigated. The requisite phosphonate esters 12 and 13<sup>9</sup>) were prepared from 5-iodopentanoic acid <u>via</u> 11 efficiently (Scheme 3). The reaction of



the aldehyde 6 with 12 and 13 gave the mixtures of  $\underline{Z}$  and  $\underline{E}$  isomers 15 and 16 in the ratios of 4:5 and 4:1 respectively, which were seperable by chromatography (SiO<sub>2</sub>).

Next the macrocyclization was carried out with both  $\underline{Z}$  and  $\underline{E}$  isomers. When a 0.003 M acetic acid solution of the epoxy aldehyde 14 obtained by pyridinium chlorochromate (PCC) oxidation of 10 was allowed to react at 50 °C in the presence of a catalytic amount of piperidine, the cyclization products 17 and the corresponding acetates 18 (2:1 ratio) were obtained as mixtures of diastereomers in 55% yield. The structure of the products was substantiated by the inspection of <sup>1</sup>H NMR spectra. For instance the alcohol mixture 17 exhibited pairs of the signals at  $\delta$  4.45 and 5.02 (both d,  $\underline{J}$  = 8 and 4 Hz, respectively) for the protons at the hydroxyl-bearing carbon and at  $\delta$  6.50 and 6.53 (both s) for the furan ring protons.





The acyclic substrate 3 with Z double bond was synthesized from 15 by a sequence of reactions: (i) Bu4NF, (ii) Swern oxidation, and (iii) p-toluenesulfonic acid, acetone. The reaction of 3 at the same condition as the case of 14 gave a rather complex mixture of products which were acetylated. Separation by preparative TLC (silica gel) afforded two cyclization products 19 and 20 (1:1 ratio) epimeric with respects to the configuration of the acetoxyl groups in approximately 10% yield. In the <sup>1</sup>H NMR spectra **19** and **20** shows the signals due to the protons attached to the acetoxyl-bearing carbon atoms at  $\delta$  4.95 (d, <u>J</u> = 9 Hz) and 5.40 (d,  $\underline{J}$  = 3 Hz ), and the olefinic proton singlets at  $\delta$  7.13 and 7.00 respectively. The disappearance of the olefinic proton signals due to the the  $\alpha,\beta$ -unsaturated ester system in 3 as well as the absence of those due to the furan ring suggested that 19 and 20 would be the products formed by the intramolecular Diels-Alder reaction of the cyclized intermediate 2. The structures of 19 and 20 have been confirmed by the single crystal X-ray analysis on the p-bromobenzoate 21 derived from 19.

Crystal data of 21:  $C_{26}H_{29}O_7Br$ ,  $\underline{M} = 533.4$ ,  $P_{21}/\underline{c}$ ,  $\underline{a} = 10.552(3)$ ,  $\underline{b} = 22.321(4)$ ,  $\underline{c} = 18.341(6)$  Å,  $\beta = 146.23(1)^{\circ}$ ,  $\underline{U} = 2401(1)$  Å<sup>3</sup>,  $\underline{Z} = 4$ ,  $\underline{D}_{c} = 1.476$  g/cm<sup>3</sup>,  $\underline{R} = 0.050$ , No. of unique reflections = 4078. Three-dimensional intensity data within  $\theta = 65^{\circ}$  were collected on a Rigaku AFC-5 diffractometer equipped with a graphite monochromator using Cu Ka radiation ( $\lambda = 1.54178$  Å). Intensities of 3686 reflections with  $|\underline{F}_{O}| > 3\sigma(\underline{F}_{O})$  were observed. Lorentz and polarization corrections were applied, but not absorption correction. The structure was solved by conventional

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heavy atom method, and refined by blockdiagonal least-squares technique. The molecular structure is shown in Fig. 1.

In conclusion the novel macrocyclization approach is demonstrated to be feasible for the construction of the furanocembranolide framework although the efficiency was less satisfactory for the  $\underline{Z}$  precursor with the requisite configuration for the synthesis of the natural products. However in view of the possible delicate conformational effects exerted by the substituents,<sup>10</sup>) e.g. the presence of a lactone ring, to the



Fig. 1.

ease of the cyclization, our method described above may provide a potent access to the lophotoxin and related furanocembranolides, and the studies in this direction are now on progress.

References

- Synthetic Studies on Terpenic Compounds XXI. Part XIX, H. Iio, K. Asao, and T. Tokoroyama, J. Chem. Soc., Chem. Commun., <u>1985</u>, 774; Part XX, H. Iio, M. Monden, K. Okada, and T. Tokoroyama, ibid., <u>1987</u>, 358.
- 2) A. J. Weinheimer, C. W. J. Chang, and J. A. Matson, Fortsch. Chem. Org. Naturst., <u>36</u>, 286(1979); <u>49</u>, 151(1986).
- 3) J. A. Marshall and B. S. DeHoff, Tetrahedron Lett., <u>27</u>, 4873(1986); J. A. Marshall and R. C. Andrews, ibid., 5197; J. A. Marshall, T. M. Jenson, and B. S. DeHoff, J. Org. Chem., <u>51</u>, 4316(1986); M. A. Tius, and A. Fauq, J. Am. Chem. Soc., 108, 6389(1986) and references cited therein.
- 4) W. Fenical, R. K. Okuda, M. M. Bandurraga, P. Culver, and R. S. Jacobs, Science (Washington, D.C.), <u>212</u>, 1512(1981).
- 5) M. G. Missakian, B. J. Burreson, and P. J. Scheuer, Tetrahedron, <u>31</u>, 2513(1975) ; M. B. Ksebati, L. S. Ciererszko, and F. J. Schmitz, J. Nat. Prod., <u>47</u>, 1009 (1984). For the furanocembranolides of another type, see M. M. Bandurraga, W. Fenical, S. F. Donovan, and J. Clardy, J. Am. Chem. Soc., <u>104</u>, 6463(1982); S. A. Look, M. T. Burch, W. Fenical, Z. Qi-tai, and J. Clardy, ibid., <u>50</u>, 5741(1985); D. Williams, R. J. Andersen, G. D. van Duyne, and J. Clardy, J. Org. Chem., <u>52</u>, 332(1987).
- 6) R. S. Jacobs, P. Culver, R. Langdon, T. O'Brien, and S. White, Tetrahedron, <u>41</u>, 981(1985).
- 7) P. H. Williams, G. B. Pavne, W. J. Sullivan, and P. R. van Ess, J. Am. Chem. Soc., <u>82</u>, 4883(1960).
- 8) Y. Oikawa, K. Sugano, and O. Yonemitsu, J. Org. Chem., <u>43</u>, 2087(1978).
- 9) W. C. Still and C. Gennari, Tetrahedron Lett., 24, 4405(1983).
- 10) A. J. Kirby, Adv. Phys. Org. Chem., <u>17</u>, 183(1980); P. Delongchamps, Aldrichimica Acta, <u>17</u>, 59(1984).

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