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The First Total Synthesis of (−) and (+)-2-Hydroxy-24-oxooctacosanolide Using an Effective Lactonization

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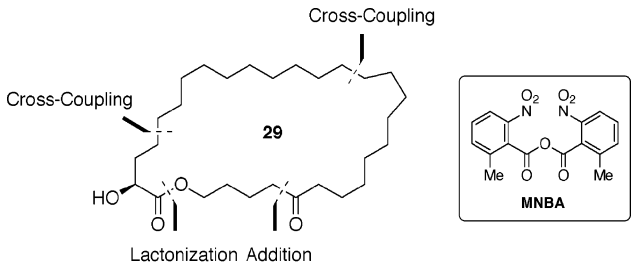
ABSTRACT



Rapid Lactonization Using **MNBA** with **DMAPO**

An effective method for the total synthesis of 2-hydroxy-24-oxooctacosanolide, a defensive salivary secretion of the African termite *Pseudacanthotermes spiniger*, has been developed. The key lactonization to form a 29-membered ring lactone core is performed using 2-methyl-6-nitrobenzoic anhydride with a catalytic amount of 4-(dimethylamino)pyridine *N*-oxide.

Some diterpenes, such as cubitene (**1**) and trinervitanes (**2**), isolated from the frontal gland secretion of a termite soldier are reported as typical defensive substances of termites against predators (Figure 1).[1,2] Related biosynthetic and chemical synthetic studies on the cyclic terpenoids have progressed over the past several decades as reported in excellent articles.[1−3] On the other hand, macrocyclic molecules, such as **3**, **4**, and **5**, were also extracted from the salivary defensive secretion of soldier termites.[4,5]

These compounds involve peculiar very large-size macrocyclic lactone moieties, however, and there are only a few reports on the chemical production of this type of giant-sized lactone to the best of our knowledge.

Recently, we developed a new and rapid lactonization of ω-hydroxycarboxylic acids using symmetrically substituted benzoic anhydrides, such as 2-methyl-6-nitrobenzoic anhydride (MNBA) as a condensation reagent.[6−15]

(1) Cubitene and related compounds. Isolation: (a) Prestwich, G. D.; Wiemer, D. F.; Meinwald, J.; Clardy, J. *J. Am. Chem. Soc.* **1978**, *100*, 2560−2561. (b) Wiemer, D. F.; Meinwald, J.; Prestwich, G. D.; Miura, I. *J. Org. Chem.* **1979**, *44*, 3950−3952. (c) Wiemer, D. F.; Meinwald, J.; Prestwich, G. D.; Solheim, B. A.; Clardy, J. *J. Org. Chem.* **1980**, *45*, 191−192. (d) Tempesta, M. S.; Pawlak, J. K.; Iwashita, T.; Naya, Y.; Nakanishi, K. *J. Org. Chem.* **1984**, *49*, 2077−2079. Synthesis: (e) Shimada, K.; Kodama, M.; Ito, S. *Tetrahedron Lett.* **1981**, *22*, 4275−4276. (f) Kodama, M.; Takahashi, T.; Kojima, T.; Ito, S. *Tetrahedron Lett.* **1982**, *23*, 3397−3400. (g) Mori, K.; Waku, M. *Tetrahedron* **1984**, *40*, 305−309. (h) Parker, K. A.; Farmar, J. G. *J. Org. Chem.* **1986**, *51*, 4023−4028. (i) Paknikar, S. K.; Greene, A. E. *J. Nat. Prod.* **1988**, *51*, 326−327.

(2) Trinervitane and related compounds. Isolation: (a) Prestwich, G. D.; Tanis, S. P.; Springer, J. P.; Clardy, J. *J. Am. Chem. Soc.* **1976**, *98*, 6061−6062. (b) Prestwich, G. D.; Tanis, S. P.; Pilkiewicz, F. G.; Miura, I.; Nakanishi, K. *J. Am. Chem. Soc.* **1976**, *98*, 6062−6064. (c) Vrkoc, J.; Budesinsky, M.; Sedmera, P. *Collect. Czech. Chem. Commun.* **1978**, *43*, 2478−2485. Synthesis: (d) Kato, T.; Tanaka, M.; Hoshikawa, M.; Yagi, M. *Tetrahedron Lett.* **1998**, *39*, 7553−7556. (e) Kato, T.; Ebihara, S.; Furukawa, T.; Tanahashi, H.; Hoshikawa, M. *Tetrahedron: Asymmetry* **1999**, *10*, 3691−3700. (f) Hoshikawa, M.; Hayashi, K.; Yagi, M.; Kato, T. *Chem. Commun.* **2001**, 623−624. (g) Kodama, M.; Matsushita, M.; Yoshio, S.; Tanimoto, K.; Noda, E.; Hioki, H.; Fukuyama, Y. The 39th Symposium on Natural Products, Sapporo, Japan 1997; Vol. 39, p 289.

(3) A review for defensive compounds of insects: Laurent, P.; Braekman, J.-C.; Daloze, D.; Pasteels, J. *Eur. J. Org. Chem.* **2003**, 2733−2743.

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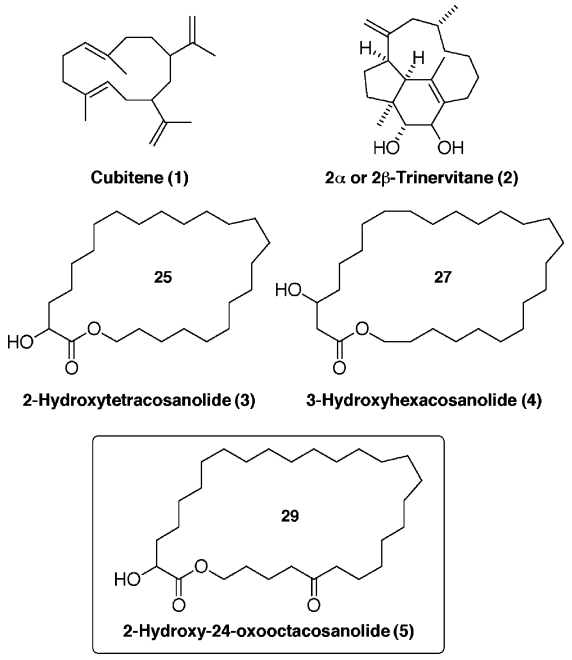


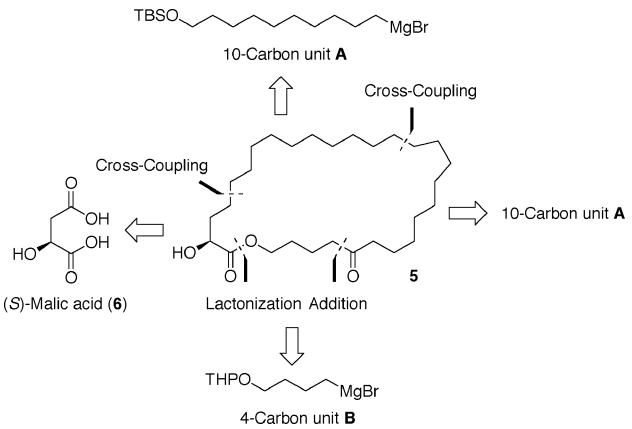
Figure 1. Some defensive substances of termite soldiers.

This protocol could be performed using a very simple procedure, and the desired lactones are obtained within a very short time under mild conditions since the reaction quickly proceeds in the presence of a catalytic amount of basic catalysts, such as DMAP or its *N*-oxide (DMAPO).

In this paper, we now report an effective synthesis of 2-hydroxy-24-oxooctacosanolide (**5**), the defensive secretion of the African termite *Pseudacanthotermes spiniger*,[5] using MNBA lactonization protocol as part of our continuous efforts to apply new synthetic methodology to produce biologically active macrolactones.

Scheme 1 illustrates the retrosynthetic route to the desired lactone **5**, in which three kinds of segments, (*S*)-malic acid (**6**), 10-carbon unit **A**, and 4-carbon unit **B**, are involved.

Scheme 1. Synthesis of 29-Membered Lactone Using Benzoic Anhydride Method



After assembling these fragments to form the corresponding seco-acid, we planned to apply our effective monomer-selective lactone formation to the seco-acid to generate the desired 29-membered ring backbone.

First, (*S*)-malic acid (**6**) was converted into the corresponding triol by the reduction with $BH_3 \cdot SMe_2$ in the presence of $B(OMe)_3$ according to the literature method (Scheme 2).[16] The triol was protected as its PMP acetal, and the resulting primary alcohol was transformed into the TBDPS ether **7**. Reductive cleavage of the PMP acetal moiety of **7** with DIBAL regioselectively produced a primary alcohol **8**, and then the hydroxyl group in **8** was replaced with iodine. Next, cross coupling between the iodide **9** with Grignard reagent **A** was examined under various reaction conditions. After several experimental trials combining metal salts with ligands, it was found that a complex generated from CuI with 2,2′-bipyridyl functions as the best promoter of the coupling reaction to produce the desired 14-carbon segment **10** in high yield.[17] Deprotection of the TBS group of **10**, substitution of the hydroxy group with iodine to transform iodide **11**, and successive cross coupling of **11** with Grignard reagent **A** were repeated in the presence of the copper complex to afford the 24-carbon segment **12**.

Next, the further conversion of the 24-carbon linear segment **12** to an elongated 28-carbon seco-acid **17** was tried as follows: the TBS group of **12** was cleaved with hydrochloric acid, and the formed primary alcohol was oxidized with PCC to yield an aldehyde **13**. Elongation of the 4-carbon unit onto **13** was attained by the addition of Grignard reagent **B** to **13** as shown in Scheme 2. The resulting secondary alcohol **14** was protected as its THP ether. Deprotection of the terminal TBDPS group of **15** by the treatment with a mixture of TBAF and acetic acid smoothly occurred to give the corresponding primary alcohol **16**, which was directly oxidized to form a carboxylic acid.

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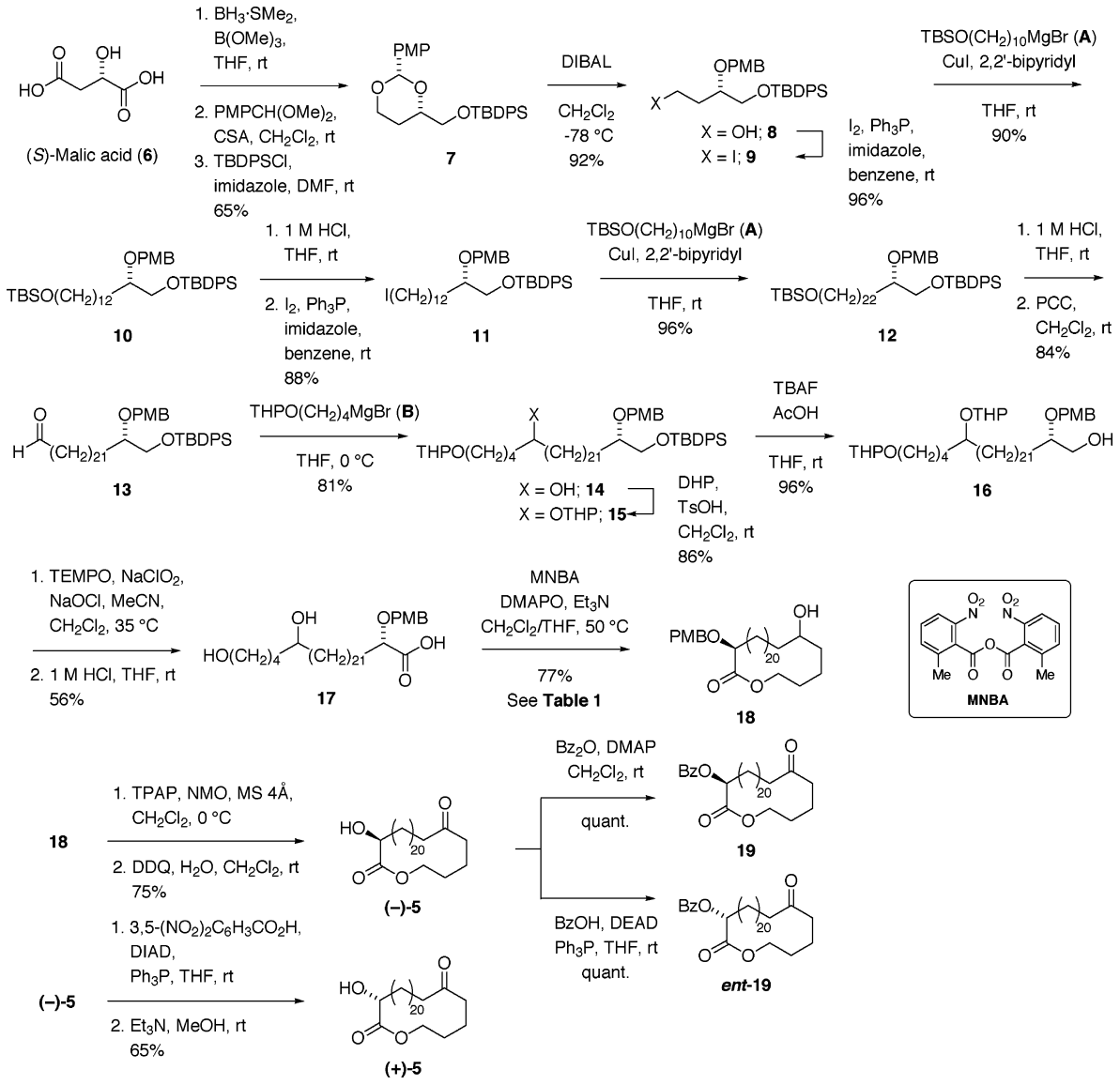
(16) Toshima, H.; Maru, K.; Saito, M.; Ichikawa, A. *Tetrahedron* **1999**, *55*, 5793−5808.

(17) Ito, M.; Kibayashi, C. *Tetrahedron* **1991**, *47*, 9329−9350.

Scheme 2. Synthesis of 2-Hydroxy-24-oxooctacosanolide (**5**)



Finally, deprotection of two THP groups of the carboxylic acid was simultaneously achieved using hydrochloric acid to afford the diol **17**, the desired seco-acid, in good yield.

Optimization of the reaction conditions for the lactonization of **17** was carried out as shown in Table 1. When a solution of **17** in THF was slowly added to the reaction mixture of 1.2 equiv of MNBA and 3.0 equiv of DMAP in dichloromethane over a 12 h period at 50 °C (bath temp), the corresponding monomeric lactone **18** was obtained in 69% yield (entry 1). Further examination to decrease the amount of DMAP to 20 mol % using an excess amount of triethylamine (3.0 equiv) afforded a somewhat lower yield (64%) of the desired lactone **18** (entry 2). On the other hand, when DMAPO, an *N*-oxide of DMAP, was employed together with MNBA, the desired monomeric lactone **18** was obtained in low yield (38%) as shown in entry 3. Although the catalytic use of DMAPO with an excess amount of triethylamine at room temperature unfortunately afforded a poor result (entry 4), the yield of the 29-membered lactone **18** remarkably increased to 77% when the same reaction was carried out at 50 °C as described in entry 5. Thus, it was shown that the combination of MNBA with a catalytic amount of DMAPO at a relatively high temperature was the most effective conditions for lactonization of seco-acid **17** to produce the desired 29-membered lactone **18**.

To compare the efficiency of this procedure for the key lactonization forming the 29-membered ring with that of other generally effective protocols, two additional lactonizations were carried out. When the *S*-pyridyl ester method was applied to the cyclization of seco-acid **17** using $(PyS)_2$ and Ph_3P followed by addition to gently refluxing toluene over 12 h under the standard reaction conditions (2.0 mM),[18] the desired lactone **18** was prepared in low yield (35%). Furthermore, Yamaguchi lactonization also afforded the

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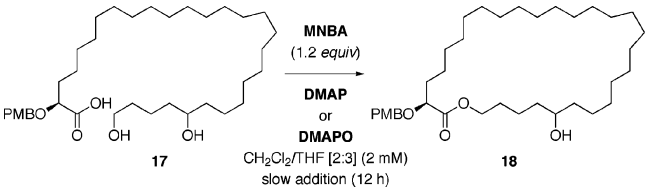
Table 1. Synthesis of 29-Membered Lactone **18** from **17** Using MNBA



entry	catalyst	co-base	temp (°C)	yield (%)
1	DMAP (3.0 equiv)	none	50	69
2	DMAP (0.2 equiv)	Et_3N (3.0 equiv)	50	64
3	DMAPO (3.0 equiv)	none	50	38
4	DMAPO (0.2 equiv)	Et_3N (3.0 equiv)	rt	29
5	DMAPO (0.2 equiv)	Et_3N (3.0 equiv)	50	77

lactone **18** in 29% yield via the generation of the mixed anhydride using 2,4,6-trichlorobenzoyl chloride with triethylamine, although favorable conditions were employed for the ring closing reaction of the mixed anhydride by addition to a solution of DMAP (3.0 equiv) in gently refluxing toluene over 12 h under highly dilute concentration (2.0 mM).[19]

The facile oxidation of **18** with TPAP/NMO was then carried out to produce a keto lactone, which was in turn converted to the final target lactone (−)-**5** by deprotection of the PMB group with DDQ/H_2O. All spectral data, including the ^1H and ^{13}C NMR chemical shifts, IR absorption, and mass spectra of the synthetic (−)-**5**, correspond to those of the natural 29-membered lactone.[5] The produced (−)-**5** was further converted into its benzoate **19** to determine the optical purity. The Mitsunobu inversion of (−)-**5** using benzoic acid in the presence of DEAD and Ph_3P produced the corresponding antipode ester *ent*-**19** in good yield. An HPLC analysis of the pair of enantiomers (**19** and *ent*-**19**) showed that these esters have a very high enantiopurity (>99% ee). This result revealed that the synthetic **5** and all the other intermediates described in Scheme 2 have very high optical purities. Furthermore, (+)-**5**, an enantiomer of (−)-**5**, was also produced via Mitsunobu inversion at the C2 position followed by selective cleavage of the benzoate group.

Thus, the substituted benzoic anhydride method was successfully applied to the formation of the 29-membered lactone **18** in good yield under mild reaction conditions. The combination of MNBA, a powerful dehydrating reagent, with DMAPO, a novel basic catalyst, functions as a very effective promoter for the intramolecular dehydration condensation to form the giant cyclic skeleton of **5**. Through the total synthesis, the unusual 29-membered ring of **5** proposed by Braekman et al. has been unambiguously confirmed. Further investigations on the absolute stereochemistry of natural macrocyclic molecules are now in progress in this laboratory.

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Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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