Synthesis of Erythronolide A *via* Direct Macrolactonization of a Conformationally Controlled Seco-acid with the Yamaguchi Reagent in the Presence of Dimethylaminopyridine[1,2]

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Direct macrolactonization of 3,5-*O*-(3,4-dimethoxybenzylidene)-9,11-*O*-(2,4,6-trimethylbenzylidene)-(9*S*)-9-dihydroerythronolide A seco-acid (3) with several reagents was examined under various conditions, and the Yamaguchi reagent (8) was found to be the most reactive and effective; treatment of 3 with 8 in the presence of a small amount of 4-dimethylaminopyridine and a large excess of triethylamine at room temperature gave almost quantitatively the corresponding 14-membered erythronolide A derivative (5).

Keywords erythronolide A; macrolactonization; Yamaguchi reagent; 4-dimethylaminopyridine; acylation; macrolide

In a multi-step synthesis of complex natural products, there are usually a few important steps which hold the key to whether a total synthesis is achieved or not. Macrolactonization has undoubtedly been the crucial step in the synthesis of macrolide antibiotics having multiple chiral centers, and hence many methods aiming at efficient cyclization have been reported, such as the Mukaiyama–Corey,[3] Mitsunobu,[4] Yamaguchi,[5] and Keck[6] methods. Nevertheless the macrolactonization still remains as the most troublesome step, requiring elaborate conditions such as the so-called high dilution technique, which is usually essential for the cyclization of activated seco-acid derivatives into complex macrolactones such as 9-dihydroerythronolide A derivatives.

Recently we reported a highly stereoselective synthesis of erythronolide A (**1**) *via* an efficient macrolactonization of Yamaguchi's mixed anhydride (**4**) of the seco-acid (**3**) into the corresponding 14-membered lactone (**5**) in the presence of a high concentration of 4-dimethylaminopyridine (DMAP),[7] the role of which has been explained in terms of transformation of the initially formed mixed anhydride (**4**) into a much reactive acylpyridinium salt (**6**).[7,8] This macrolactonization without using the high dilution technique, ascribed to a favorable conformation and high activation of **3**, is extremely efficient, but requires prior preparation of **4** from **3**, which takes much time, usually 2 d. In order to establish a more convenient and efficient method, in this work we examined direct macrolactonization of **3** with sevaral well-known reagents, *i.e.*, 2,4,6-trichlorobenzoyl chloride (the Yamaguchi reagent) (**8**),[5] mesitylenesulfonyl chloride (**9**),[9] 1,3-dicyclohexylcarbodiimide (DCC) (**10**),[6] and 2-chloro-1-methylpyridinium iodide (**11**),[10] under various conditions, and the results are summarized in Table I.[11]

Nuclear magnetic resonance (NMR) analysis of the seco-acid (**3**) revealed the reason why its mixed anhydride (**4**) cyclized very efficiently, that is, **3** exists mainly in a conformation particularly favorable to lactonization, since the vicinal coupling constants of **3** in its ^{1}H-NMR spectrum are quite similar to those of the cyclization product (**5**).[7] This conformational analysis was supported by the MMP2-CONFLEX3 calculation.[12] Therefore **3** was expected to lactonize with various reagents without prior preparation of mixed anhydrides and active esters. When a xylene solution of **3** and 1.5 eq of the Yamaguchi reagent (**8**) was treated with excess triethylamine (TEA) and DMAP at room temperature, a very rapid lactonization occurred and was completed within only 5 min to give **5** in 86% isolation yield (Table I, entry 1). The lactonization of **3** also proceeded in dichloromethane, though rather slowly (entry 2). Acylation of hydroxy groups usually takes place with an acylation agent in the presence of a catalytic amount of DMAP and a large excess of TEA. Even under such conditions **3** readily gave **5** in excellent yield; namely, **3** was

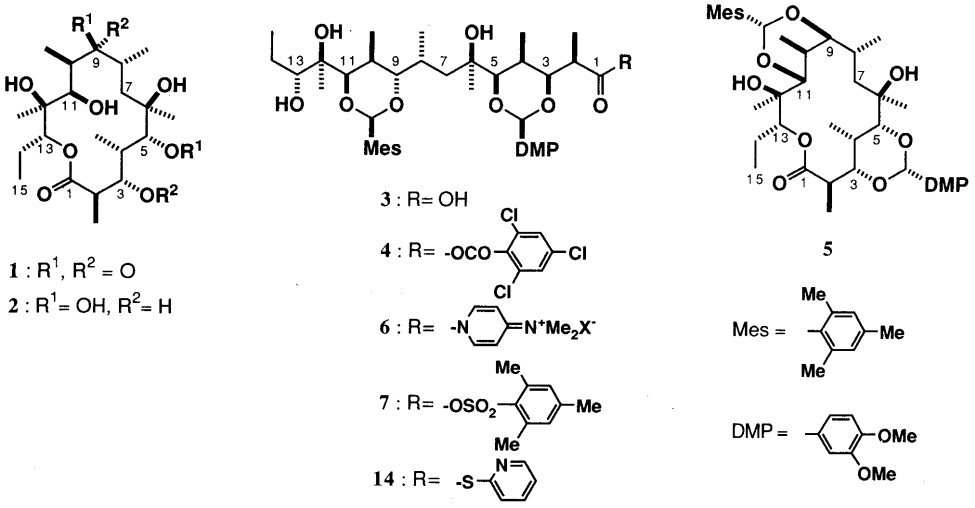

Fig. 1

TABLE I. Direct Macrolactonization of the Seco-acid (**3**) into the Lactone (**5**)[a]

Entry	Reagent (eq)	Et_3N (eq)	DMAP (eq)	Solvent	Time	Yield (%)
1	**8** (1.5)	1.5	2.0	Xylene	5 min	86
2	**8** (1.5)	1.5	2.0	CH_2Cl_2	30 min	80
3	**8** (1.1)	5.0	0.1	Xylene	30 min	82
4	**8** (1.1)	5.0	0.1	Benzene	1 h	98
5	**9** (1.1)	1.2	2.0	Xylene	24 h, 4 h[b]	77
6	**9** (1.5)	1.5	2.0	Xylene	40 min	76
7	**9** (1.1)	5.0	0.1	Xylene	2 h	82
8	**10** (1.5)	—	2.0[c]	CH_2Cl_2	1.5 h	73
9	**10** (3.0)	—	2.0[c]	CH_2Cl_2	8 h	85
10	**10** (3.0)	5.0	0.1[c]	CH_2Cl_2	24 h	25
11	**11** (1.5)	1.5	2.0	CH_2Cl_2	1 h	76
12	**11** (1.1)	5.0	0.1	CH_2Cl_2	24 h	41
13	**12** (1.5)	—	2.0[d]	Toluene	24 h	0[e]
14	**13** (1.5)	—	2.0[d]	Toluene	24 h	0

a) Lactonization of a 10 mM solution of **3** with a reagent was carried out at room temperature. *b*) Treatment of **3** with **9** in the presence of Et_3N for 24 h gave the mixed anhydride (**7**), which was treated with DMAP for 4 h to give **5**. *c*) In the presence of 1.0 eq of *dl*-10-camphorsulfonic acid (CSA). *d*) In the presence of 4.0 eq of tri-*n*-butylphosphine. *e*) The pyridylthio ester (**14**) was isolated in 61% yield.

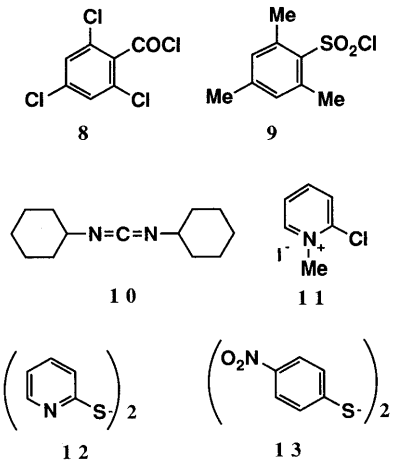

Fig. 2

treated with a slight excess of **8** in the presence of 10 mol percent of DMAP and a large excess of TEA at room temperature, and after 1 h **5** was isolated almost quantitatively (entries 3 and 4).

Mesitylenesulfonyl chloride (**9**) was expected to be more reactive than **8** as an acylation reagent, but contrary to our expectation, the lactonization of **3** with **9** proceeded more slowly and less efficiently than that with **8**, similarly to that descirbed above[11] (entries 6 and 7).

DCC (**10**) is the most common esterification reagent, and was also effective, though less reactive than **8**, for the lactonization of **3** (entries 8 and 9). Poor results were obtained from the reaction in the presence of catalytic DMAP (entry 10). In these lactonizations, addition of an acid was required to lower the basicity of DMAP in order to avoid side reactions.[6] The lactonization proceeded with the chloropyridinium salt (**11**) only in dichloromethane because **11** was insoluble in aromatic hydrocarbons, and therefore we obtained only less satisfactory results, particularly in the reaction with a catalytic amount of DMAP (entries 11 and 12). Finally, because the Mukaiyama–Corey method[3] is the most popular for lactonization, we tried to use **12** as a direct lactonization reagent in the presence of DMAP and tri-*n*-butylphosphine, but only negative results have so far been obtained (entry 13). Less reactive **13** was also ineffective (entry 14).

In conclusion, the Yamaguchi reagent (**8**) is surprisingly effective for the lactonization of **3** directly to give **5** in almost quantitative yield under usual acylation conditions. The lactone (**5**) was readily converted to erythronolide A (**1**).[7,13]

Experimental

Lactonization of 3,5-*O*-(3,4-Dimethoxybenzylidene)-9,11-*O*-(2,4,6-trimethylbenzylidene)-(9*S*)-9-dihydroerythronolide A Seco-acid (3). 1) With 2,4,6-Trichlorobenzoyl Chloride (8) a) In the Presence of Excess DMAP: Et_3N (5.8 μl, 41.6 μmol) and then **8** (6.4 μl, 41.7 μmol) were added to a stirred solution of **3** (20.0 mg, 27.8 μmol) and DMAP (6.8 mg, 55.6 μmol) in dry xylene (2.8 ml) at room temperature under argon. After 5 min, the solvent was evaporated off *in vacuo* and the residue was chromatographed on a silica gel column with EtOAc–hexane (1 : 3) as the eluant to give 3,5-*O*-(3,4-dimethoxybenzylidene)-9,11-*O*-(2,4,6-trimethylbenzylidene)-(9*S*)-9-dihydroerythronolide A (**5**) (16.8 mg, 86%) as an amorphous powder, mp 140—143 °C.[7]

b) In the Presence of a Catalytic Amount of DMAP: Et_3N (9.7 μl, 69.6 μmol), DMAP (0.17 mg, 1.4 μmol), and **8** (2.3 μl 15.0 μmol) were successively added to a stirred solution of **3** (10.0 mg, 13.9 μmol) in dry benzene (1.4 ml) at room temperature under argon. After 1 h, the reaction mixture was worked up as described above to give **5** (9.6 mg, 98%).

2) With Mesitylenesulfonyl Chloride (9) a) In the Presence of Excess DMAP: Compound **3** (20.0 mg, 27.8 μmol), **9** (9.2 mg, 42.0 μmol), and DMAP (6.8 mg, 55.6 μmol) were successively dissolved in dry xylene (2.8 ml). To this solution was added Et_3N (5.8 μl, 41.6 μmol), and the reaction mixture was stirred for 40 min and then worked up to give **5** (14.7 mg, 76%).

b) In the Presence of Catalytic DMAP: Compound **5** (16.0 mg, 82%) was obtained from the reaction mixture of **3** (20.0 mg, 27.8 μmol), **9** (6.7 mg, 30.6 μmol), DMAP (0.4 mg, 3.2 μmol), and Et_3N (19.4 μl, 139.2 μmol) for 2 h.

3) With DCC (10) a) In the Presence of Excess DMAP: A solution of **3** (20.0 mg, 27.8 μmol), **10** (8.6 mg, 41.6 μmol), DMAP (6.8 mg, 55.6 μmol), and *dl*-10-camphorsulfonic acid (CSA) (7.1 mg, 30.5 μmol) in dry CH_2Cl_2 (2.8 ml) was stirred for 1.5 h at room temperature under argon. Work-up as described above gave **5** (14.2 mg, 73%).

b) In the Presence of Catalytic DMAP: A solution of **3** (20.0 mg, 27.8 μmol), **10** (17.3 mg, 83.8 μmol), DMAP (0.4 mg, 3.2 μmol), and CSA (6.5 mg, 27.9 μmol) in dry CH_2Cl_2 (2.8 ml) was stirred for 24 h at room temperature to give **5** (4.9 mg, 25%).

4) With 2-Chloro-1-methylpyridinium Iodide (11) a) In the Presence of Excess DMAP: A solution of **3** (20.0 mg, 27.8 μmol), **11** (10.7 mg, 41.8 μmol), DMAP (6.8 mg, 55.6 μmol), and Et_3N (5.8 μl, 41.6 μmol) in dry CH_2Cl_2 (2.8 ml) was stirred for 1 h under argon at room temperature to give **5** (14.8 mg, 76%).

b) In the Presence of Catalytic DMAP: A solution of **3** (20.0 mg, 27.8 μmol), **11** (7.8 mg, 30.5 μmol), DMAP (0.4 mg, 3.2 μmol), and Et_3N (19.4 μmol, 139.2 μmol) in dry CH_2Cl_2 (2.8 ml) was stirred for 24 h at room temperature to give **5** (7.9 mg, 41%).

References and Notes

1) Chiral synthesis of polyketide-derived natural products. 38. For part 37, see: T. Matsushima, N. Nakajima, O. Yonemitsu, and T. Hata, *Tetrahedron*, **48**, 4525 (1992).
2) For a preliminary communication on this work, see: M. Hikota, Y. Sakurai, K. Horita, and O. Yonemistu, *Tetrahedron Lett.*, **31**, 6367 (1990).
3) Mukaiyama–Corey method: E. J. Corey, P. B. Hopkins, S. Kim, S. Yoo, K. P. Pambier, and J. R. Falk, *J. Am. Chem. Soc.*, **101**, 7131 (1979).
4) Mitsunobu method: *a*) O. Mitsunobu, *Synthesis*, **1981**, 1; *b*) T. Kurihara, Y. Nakajima, and O. Mitsunobu, *Tetrahedron Lett.*, **1976**, 2455.
5) Yamaguchi method: J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, **52**, 1989 (1979).
6) Keck method: E. Boden and G. E. Keck, *J. Org. Chem.*, **50**, 2394

(1985).
7) *a*) M. Hikota, H. Tone, K. Horita, and O. Yonemitsu, *J. Org. Chem.*, **55**, 5 (1990); *b*) *Idem.*, *Tetrahedron*, **46**, 4613 (1990).
8) *Cf.* G. Höfle, W. Steglich, and H. Vorbruggen, *Ang. Chem. Int. Ed. Engl.*, **17**, 569 (1978).
9) *a*) T. M. Jacob and H. G. Khorana, *J. Am. Chem. Soc.*, **86**, 1630 (1964); *b*) S. A. Norang and H. G. Khorana, *ibid.*, **87**, 2981 (1965).
10) *a*) T. Mukaiyama, M. Usui, and K. Saigo, *Chem. Lett.*, **1976**, 49; *b*) T. Mukaiyama, K. Narasaka, and K. Kikuchi, *ibid.*, **1977**, 441; *c*) K. Narasaka, T. Masui, and T. Mukaiyama, *ibid.*, **1977**, 763.
11) First the cyclization of the mixed anhydride (**7**) of **3** with mesitylenesulfonic acid was examined in order to find a more rapid reaction, because **7** was expected to be more reactive than **4**. Alternatively **7** could be converted into **6** more rapidly and/or efficiently than **4**. However, a rather slow and less efficient cyclization actually occurred under the same conditions as with **4**[7] to give **5** (entry 5), presumably because the strong counter anion, mesitylenesulfonate, is attached rather tightly to the pyridinium cation, preventing access of the C13 hydroxy group to form the lactone (**5**), although thin layer chromatography analyses of the reaction mixture clearly showed that conversion of **7** into **6** was faster than that of **4**.
12) T. Hamada, M. Hikota, O. Yonemitsu, H. Goto, and E. Osawa, *Tetrahedron Lett.*, submitted.
13) M. Kinoshita, M. Arai, K. Tomooka, and M. Nakata, *Tetrahedron Lett.*, **27**, 1815 (1986).