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First Synthesis of a Strained 14-Membered Biaryl Ether Lactone by Macrolactonization

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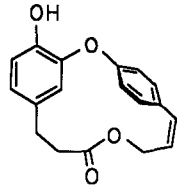
Summary: The synthesis of biaryl ether lactone **3** by macrolactonization of hydroxy acid **8** under defined Mitsunobu conditions is described. In accord with the literature, attempts to cyclize **8** *via* carboxyl activation failed.

Macrocyclic lactones and lactams which incorporate a biaryl ether moiety in their ring occur as subunits in several natural products.[1,2] Attempts to obtain these compounds by macrolactonization or macrolactamization methods have so far been unsuccessful. Thus, Boger *et al.* observed the formation of cyclodimers when using this approach for the synthesis of combretastatin D-2 (**1**)[3] and lactam[4] **2** and overcame this obstacle by taking advantage of an intramolecular Ullmann aryl ether coupling. During our studies on the total synthesis of retipolide A[2] we became interested in the preparation of **3**, the lactone analogue of **2**. In the following letter we describe an effective method for the synthesis of this compound by macrolactonization of the corresponding hydroxy acid **8**.



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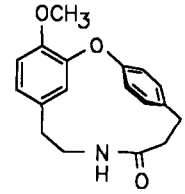

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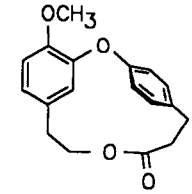

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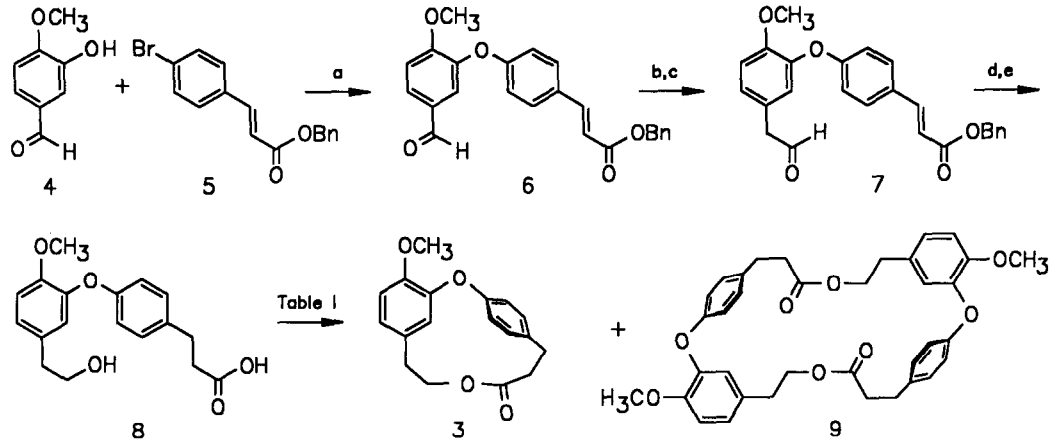
Compound **8** was synthesized as shown in Scheme I. Ullmann coupling[5] of isovanillin (**4**) with benzyl (*E*)-4-bromocinnamate (**5**) yielded the biaryl ether[6] **6** which was transformed into the aldehyde[6] **7** by homologization with methoxymethyltriphenylphosphonium chloride.[7] Subsequent reduction with sodium borohydride followed by catalytic hydrogenation afforded the hydroxy acid[6] **8** which served to examine the viability of different macrocyclization methods[8] as detailed in Table I.

Scheme I



(a) **4** (1.0 equiv), **5** (1.0 equiv), CuO (2.5 equiv), K_2CO_3 (2.0 equiv), pyridine, 140°C, 18 h, 65%; (b) $Ph_3P^+CH_2OCH_3\ Cl^-$ (1.8 equiv), KO*t*-Bu (1.7 equiv), THF, -78°C to 25°C, 3 d; (c) p-TsOH (0.2 equiv), dioxane/H_2O (5:1), 4 h, 43% (from **6**); (d) $NaBH_4$, (0.5 equiv), EtOH, 25°C, 1 h; (e) 10% Pd/C, H_2 (3 atm), EtOAc, 25°C, 3 h, 69% (from **7**).

Table I: Cyclization of hydroxy acid **8**

entry	reaction conditions	final concentration (M)	yield (%)	
			3	**9**
1	**8** and 2,2′-dipyridyl disulfide (1.5 equiv) in p-xylene, 25°C, 18 h, then added dropwise to refluxing p-xylene over a period of 46 h	0.0026	0	25
2	**8**, 2,2′-bis(4-*t*-butyl-*N*-isopropyl)imidazolyl disulfide (1.5 equiv), toluene, 0°C, 1.5 h, then added dropwise to toluene (80°C, bath) over a period of 19 h	0.0031	0	59
3	**8** added dropwise to a refluxing solution of *N*-methyl-2-chloropyridinium iodide (4.0 equiv) and Et^iPr_2N (8.0 equiv) in CH_3CN over a period of 42 h	0.0011	0	0
4	**8** added dropwise to a refluxing solution of *N*-methyl-2-chloropyridinium iodide (5.0 equiv) and Et^iPr_2N (10.0 equiv) in CH_2Cl_2 over a period of 70 h	0.0013	0	0
5	**8** added dropwise with DMAP (3.0 equiv) to a refluxing solution of DCC (11.0 equiv) and DMAP·HCl (7.0 equiv) in $CHCl_3$ over a period of 40 h	0.0005	0	32
6	**8**, 2,4,6-trichlorobenzoyl chloride (1.0 equiv), Et_3N (1.1 equiv), THF, 25°C, 2 h, then added to a refluxing solution of DMAP (6.0 equiv) in toluene over 12 h	0.0004	0	39
7	**8** added dropwise to a solution of DEAD (7.7 equiv) and PPh_3 (7.5 equiv) in toluene over a period of 10 h at 25°C	0.0015	59	<1
8	**8**, DEAD (5.0 equiv) and PPh_3 (5.0 equiv) in toluene, 25°C, 18 h	0.0006	2	40

The Corey-Nicolaou double-activation method using 2,2´-dipyridyl disulfide[9] (entry 1) or 2,2´-bis(4-*t*-butyl-*N*-isopropyl)imidazolyl disulfide[10] (entry 2) failed to provide any of the lactone **3** and yielded only the diolide[6] **9**. Treatment of **8** by the Mukaiyama protocol[11] resulted in intractable mixtures containing neither **3** nor **9** (entries 3 and 4). Keck´s variant[12] of the DCC/DMAP method (entry 5) and Yamaguchi´s procedure[13] (entry 6) yielded only **9**. Surprisingly, dropwise addition of the hydroxy acid **8** over a period of 10 h to a mixture of diethyl azodicarboxylate (DEAD) and triphenylphosphine afforded the desired lactone **3** in 59% yield (entry 7).[14] Under the usual Mitsunobu cyclization conditions[15,16] only traces of **3** were formed, and the diolide **9** was obtained in 40% yield (entry 8).

In accord with Boger´s results,[3,4] all of those cyclization methods which proceed *via* carboxyl activation lead exclusively to the cyclic diolide **9**. In contrast, ring closure under special Mitsunobu conditions affords the desired lactone **3** presumably by S_N2 reaction of the carboxylate ion with an intermediate alkoxytriphenylphosphonium salt.[15] Obviously, attack by the hydroxy group at the activated carbonyl group is sterically inhibited whereas the intramolecular nucleophilic substitution can still take place. It is crucial for the success of this lactonization, however, that the hydroxy acid **8** is added slowly to the preformed Mitsunobu reagent to avoid higher stationary concentrations of **8**. Application of this macrocyclization protocol to the total synthesis of retipolide A is in progress and will be reported in due course.

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6) **6**: Colourless oil; ^{1}H-NMR ($CDCl_3$): δ 3.83 (s, 3 H), 5.23 (s, 2 H), 6.37 (d, J = 16 Hz, 1 H), 6.90 - 7.90 (m, 13 H), 9.88 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ 56.2, 66.3, 112.3, 116.6, 117.4 (2 C), 121.2, 128.2 (3 C), 128.6 (2 C), 128.9, 129.3, 129.8 (2 C), 130.3, 136.1, 144.3, 144.8, 156.6, 159.2, 166.9, 190.1. **7**: yellow oil; ^{1}H-NMR ($CDCl_3$): δ 3.53 (d, J = 2 Hz, 2 H), 3.72 (s, 3 H), 5.15 (s, 2 H), 6.28 (d, J = 16 Hz, 1 H), 6.70 - 7.00 (m, 5 H), 7.10 - 7.50 (m, 7 H), 7.60 (d, J = 16 Hz, 1 H), 9.67 (t, J = 2 Hz, 1 H); ^{13}C-NMR ($CDCl_3$): δ 49.3, 55.9, 66.1, 113.2, 116.0, 116.7 (2 C), 123.1, 124.8, 126.8, 128.2, 128.2 (2 C), 128.5 (2 H), 129.7,

129.7 (2 C), 136.1, 143.8, 144.5, 150.8, 159.8, 166.9, 199.0. **8**: mp 127°C; ^{1}H-NMR (acetone-d_6): δ 2.40 - 3.00 (m, 6 H), 3.71 (s, 3 H), 3.72 (t, J = 7 Hz, 2 H), 6.30 (s, br, 2 H), 6.70 - 7.30 (m, 7 H); ^{13}C-NMR (acetone-d_6): δ 30.6, 36.1, 39.1, 56.1, 63.7, 113.9, 116.8 (2 C), 123.2, 126.4, 130.1 (2 C), 133.4, 135.3, 144.8, 151.0, 157.7, 174.3. **9**: mp 191°C; ^{1}H-NMR ($CDCl_3$): δ 2.35 - 2.45 (m, 4 H), 2.65 - 2.75 (m, 4 H), 2.81 (t, J = 7 Hz, 4 H), 3.62 (s, 6 H), 4.26 (t, J = 7 Hz, 4 H), 6.80 - 6.97 (m, 14 H); ^{13}C-NMR ($CDCl_3$): δ 30.2, 34.3, 36.3, 56.2, 65.1, 113.0, 117.5 (2 C), 121.8, 124.6, 129.3 (2 C), 131.7, 134.6, 144.9, 150.0, 156.3, 172.6.

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14) *Preparation of lactone 3*: To a solution of triphenylphosphine (3.24 g, 12.4 mmol, 5.0 equiv) in dry, deaerated toluene (1.5 l) at ambient temperature under argon was added diethyl azodicarboxylate (DEAD) (2.19 g, 12.6 mmol, 5.1 equiv) and the mixture was stirred for 2 min. A solution of **8** (783 mg, 2.47 mmol, 1.0 equiv, pre-dissolved in 10 ml of dry tetrahydrofuran) in toluene (120 ml) was added dropwise from a precision dropping funnel to the vigorously stirring reaction mixture at 25°C. When half of the solution of **8** had been added (5 h), the mixture was treated again with triphenylphosphine (1.61 g, 6.2 mmol, 2.5 equiv) and diethyl azodicarboxylate (1.10 g, 6.3 mmol, 2.6 equiv) before the addition of **8** was continued. When the addition of **8** was complete (5 h), the reaction mixture was concentrated in vacuo (< 35°C) to afford a red oil. Coulumn chromatography (three successive coulumns: 5 x 10 cm, 5 x 25 cm and 3 x 50 cm, silica gel, eluent: dichloromethane/acetone 100:1) yielded **3** (437 mg, 59%) as a colourless, crystalline solid: mp 173°C; R_f 0.50 (dichloromethane/acetone 100:1); ^{1}H-NMR ($CDCl_3$): δ 2.49 (m, 2 H), 2.73 (m, 2 H), 3.03 (m, 2 H), 3.93 (s, 3 H), 3.98 (m, 2 H), 4.88 (d, J = 2.2 Hz, 1 H), 6.57 (ddt, J = 8.1, 2.2, 0.8 Hz, 1 H), 6.73 (d, J = 8.1 Hz), 7.03 - 7.30 (m, 4 H); ^{13}C-NMR ($CDCl_3$): δ 31.5, 32.4, 39.6, 56.1, 66.4, 111.2, 115.3, 120.8, 125.0 (2 C), 130.6 (2 C), 132.7, 138.5, 146.3, 152.8, 157.2, 173.1.

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