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Total synthesis of macrosphelide A by way of palladium-catalyzed carbonylative esterification

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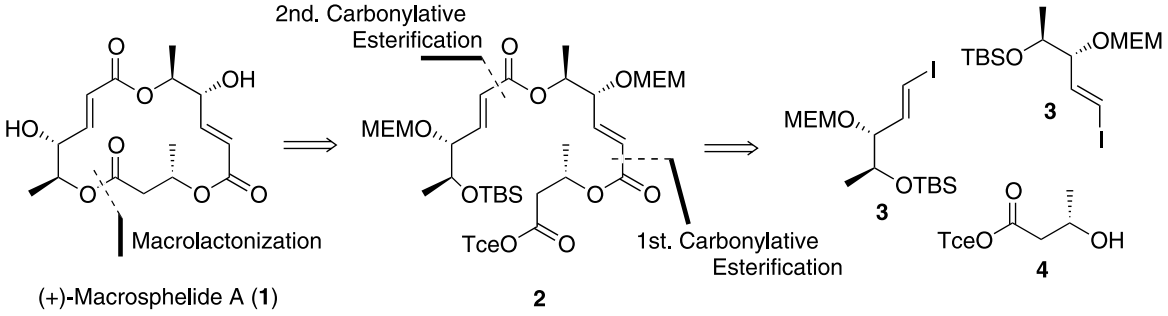
Abstract—We achieved the total synthesis of macrosphelide A, as part of a combinatorial library of its analogues. The key intermediate, the *seco*-acid derivative, was prepared from the corresponding vinyl iodide using sequential carbonylative esterification.

Macrosphelide A–L are a family of compounds isolated from two different culture medium of *Macrospaeropsis* sp. FO-5050 and/or *pericania byssoides* by the Omura[1] and Numata[2] groups. Macrosphelides are 16-membered macrolides including three ester linkages consisting of one β-hydroxybutyric acid and two 5-hydroxy-2-hexenoic acid units and strongly inhibit the adhesion of human leukemia HL-60 cells to human-umbilical-vein endothelial cell (HUVEC) in dose-dependent fashion.[1–4] In order to prepare a variety of their analogues, a simple synthetic method is required.[3,5–7] As a part of the synthesis of a macrosphelide library, we wish to report the total synthesis macrosphelide A via sequential carbonylative esterification.

An outline of the synthetic strategy is described in Scheme 1. The target molecule **1** would be synthesized through macrolactonization of *seco*-acid derivative **2**. Compound **2** can be prepared from **3** and **4**[6c] by applying alkoxycarbonylation[8,9] as the key reaction. Since palladium-catalyzed carbonylative esterification of vinyl halides can be regarded as the synthetic equivalent of the formation of an α,β-unsaturated ester, we designed the vinyl iodide **3** as a masked activated ester for this synthesis which can be repeatedly utilized in the formation of remaining two ester linkages in **1**.

The (*E*)-vinyl iodide **3** was prepared from commercially available methyl (*S*)-lactate **5**, which was converted into the ynone **6** in three steps. Chelate-controlled reduction with dimethylaluminium chloride[10] provided the *erythro*-alcohol **7** with the required stereochemistry (>95%). Deprotection of the TMS group and subsequent protection as the methoxyethoxymethyl ether gave



Scheme 1. Retrosynthetic analysis of macrosphelide A (**1**). MEM = methoxyethoxymethyl, TBS = *tert*-butyldimethylsilyl, Tce = 2,2,2-trichloroethyl.

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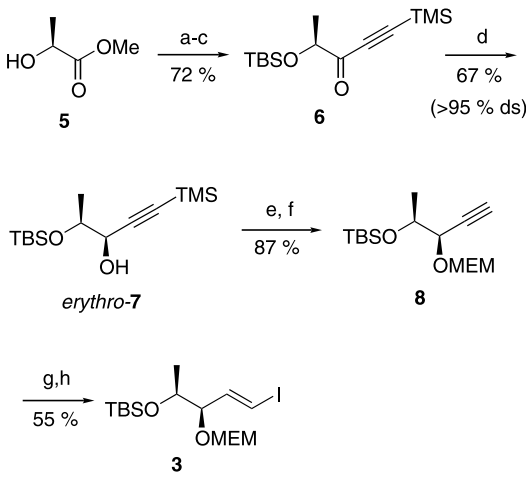
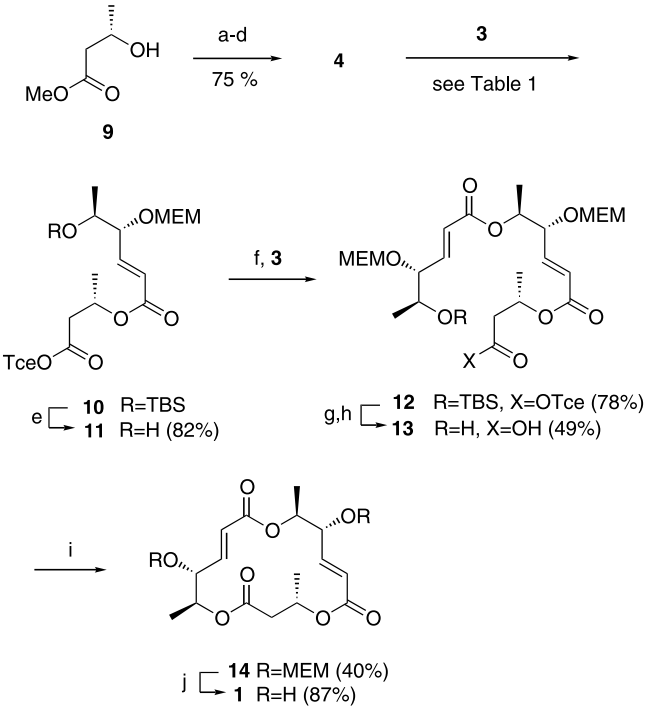


Scheme 2. Synthesis of (*E*)-vinyl iodide **3**. (a) TBSCl, imidazole, CH_2Cl_2, rt, 6 h; (b) Me(OMe)NH·HCl, *i*-PrMgCl, THF, 0°C, 30 min; (c) trimethylsilyl acetylene, BuLi, THF, −78°C, 30 min; (d) Me_2AlCl, Bu_3SnH, CH_2Cl_2, −78°C, 1 h; (e) MEMCl, *i*-Pr_2NEt, rt, 1.5 h; (f) K_2CO_3, MeOH–H_2O, rt, 24 h; (g) $PdCl_2(PPh_3)_2$, Bu_3SnH, THF, 0°C, 30 min; (h) NIS, THF, 0°C to rt, 10 min.

alkyne **8**. Treatment of **8** with tributyltinhydride in the presence of a catalytic amount $PdCl_2(PPh_3)_2$ afforded the vinyl stannane[11] which was converted to the corresponding vinyl iodide with *N*-iodosuccinimide to afford vinyl iodide **3** in 55% overall yield (Scheme 2).

Protection of methyl (*S*)-3-hydroxybutyrate **9** as its TBS ether, transformation of the methyl ester to the 2,2,2-trichloroester, followed by desilylation generated the second building block **4**. With the desired vinyl iodide **3** and alcohol **4** in hand, we next focused our attention to the palladium-catalyzed carbonylative esterification. The alkoxy carbonylation between **3** and **4** under the standard reaction conditions ($Pd(PPh_3)_4$, CO 30 atm, NEt_3, DMAP, DMF) provided moderate conversion and produced the homo dimer of **3** and the α,β-unsaturated carboxylic acid as a β-elimination product via the desired ester **10** (Entry 1). Consequently, the carbonylation reaction was extensively optimized and the results are summarized in Table 1. The best result was obtained using $PdCl_2(MeCN)_2$, as a palladium catalyst, giving the desired ester **10** as the sole product in 87% yield (Entry 6).[12]

Desilylation of **10** produced alcohol **11** in 82% yield. Palladium-catalyzed carbonylative esterification of **11** was accomplished under the above conditions except using excess amount of vinyl iodide **3** (5 equiv) to provide **12** in 78% yield. Deprotection of the TBS and Tce groups furnished the key intermediate **13** (49%). Macrolactonization of **13** under various conditions (i.e. Yamaguchi,[13a] Keck,[13b] and Mitsunobu[13c] method) yielded recovered starting material or the undesired 12-membered lactone that was formed via β-elimination



Scheme 3. Total synthesis of macrosphelide A (**1**) by carbonylation and macrolactonization. (a) TBSCl, imidazole, CH_2Cl_2, rt, 3 h; (b) 1 M NaOH in MeOH, rt, 12 h; (c) 2,2,2-trichloroethanol, DIC, DMAP, CH_2Cl_2, rt, 5 h; (d) HF·pyridine, CH_3CN, rt, 12 h; (e) TBAF, AcOH, CH_2Cl_2, rt, 24 h; (f) CO(30 atm), $PdCl_2(MeCN)_2$, Et_3N, DMAP, DMF, rt, 12 h; (g) AcOH–H_2O–THF (1:1:3), rt, 48 h; (h) Zn dust, NH_4OAc, THF–H_2O (3:1), rt, 2 h; (i) 2,2′-dipyridyl disulfide, PPh_3, toluene, rt, 1 h; AgOTf, rt, 30 min; (j) TFA, CH_2Cl_2. 6 h, rt; DIC = *N*,*N*-diisopropylcarbodiimide, DMAP = 4-(dimethylamino)pyridine, DMF = *N*,*N*-dimethylformamide, Tf = trifluoromethanesulfonyl, TFA = trifluoroacetic acid.

Table 1. Palladium-catalyzed carbonylation between vinyl iodide **3** and alcohol **4**[a]

Entry	Catalyst	**3**:**4**	DMAP (equiv.)	Temp. (°C)	Yield of **10**[b] (%)
1	$Pd(PPh_3)_4$	1:3	1.0	60	57
2	$Pd(PPh_3)_4$	1:3	None	60	0
3	$PdCl_2(PPh_3)_2$	1:3	1.0	60	60
4	$PdCl_2(MeCN)_2$	1:3	1.0	60	72
5	$PdCl_2(MeCN)_2$	1:3	1.0	rt	81
6	$PdCl_2(MeCN)_2$	1:3	0.1	rt	87
7	$PdCl_2(MeCN)_2$	3:1	0.1	rt	37

[a] Reaction was performed on a 0.5 mmol scale in DMF using 10 mol% Pd-catalyst in the presence of triethylamine for 6 h under 30 atm of carbon monoxide.

[b] Isolated yield after silica-gel column chromatography

of β-alkoxyester followed by cyclization. The Mukaiyama–Corey method[14] (2,2′-dipyridyl disulfide, PPh_3), provided the desired lactone **14**, however in disappointingly low yield. Extensive optimization of the Mukaiyama method increased the yield of the desired lactone **14** up to 40%. Addition of Ag-salt was crucial to activate the pyridinium thioester intermediate.[14] Finally, deprotection of the MEM group with TFA in CH_2Cl_2 furnished **1** in 92% yield. The synthetic **1** exhibited ^1H and ^{13}C NMR spectral data as well as optical rotation identical to those published for the natural product[1b] (Scheme 3).

In summary, the total synthesis of macrosphelide A has been achieved with a highly convergent and efficient strategy. Further refinement of the synthetic scheme toward the synthesis of combinatorial library of its analogues will be reported.

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12. Carbonylative esterification was carried out as follows: To a solution of vinyl iodide (0.50 mmol) and alcohol (1.50 mmol) in DMF (5.0 ml) was added Et_3N (0.55 mmol), DMAP (0.05 mmol), and $PdCl_2(MeCN)_2$ (0.05 mmol) under an argon. The vessel was placed in an autoclave, which was purged with CO three times before applying a pressure of 30 atm. After stirring at room temperature for 6 h, the catalyst was deposited through a short florisil plug. The filtrate was partitioned between EtOAc and 1 M HCl. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. Column chromatography on silica gel afforded the product.
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