A Macrosphelide Library

A Combinatorial Synthesis of a Macrosphelide Library Utilizing a Palladium-Catalyzed Carbonylation on a Polymer Support**

Takashi Takahashi, Shin-ichi Kusaka, Takayuki Doi, Toshiaki Sunazuka, and Satoshi Ōmura*

The combinatorial synthesis of natural products is being developed to explore the analogues of lead compounds for drug discovery and recently for the construction of important chemical probes for use in the fields of chemical genetics, genomics, and proteomics.[1–3] Therefore, it is necessary to develop strategies for the high-speed synthesis of natural-product libraries that are more efficient than those traditionally used for the synthesis of a single final product.[4,5]

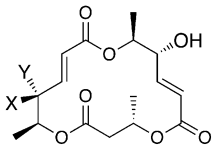
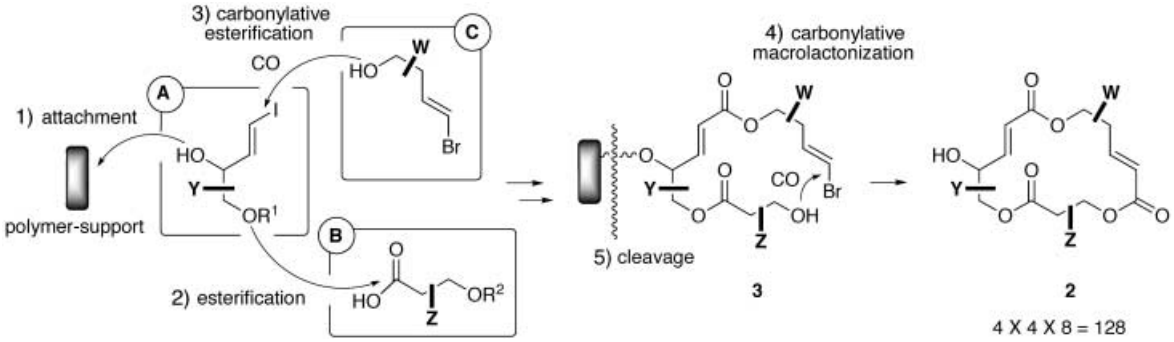


Figure 1. **1a**: X = H, Y = OH; **1b**: X = Y = O.

Macrosphelides A (**1a**) and B (**1b**, Figure 1), isolated from the culture medium of *Macrospaeropsis sp.* FO-5050 by the Omura group,[6] strongly inhibit the adhesion of human leukemia HL-60 cells to human-umbilical-vein endothelial cells (HUVEC) in a dose-dependent fashion.[7] They have received much attention as a lead compound for the development of new anti-cancer drugs and although the total syntheses of macrosphelides have been reported,[8–11] a strategy for the high-speed synthesis of a variety of these analogues is still required. Herein we report a highly convergent synthesis of a library of macrosphelide analogues on a solid support by utilizing a palladium-catalyzed chemoselective carbonylation of vinyl halides.

In considering an efficient strategy for the combinatorial synthesis of macrosphelide analogues **2**, we chose a solid-phase synthesis utilizing the three synthetic building blocks **A, B**, and **C** as illustrated in Scheme 1. The process involves: 1) attachment of the secondary alcohol in block **A** to a polymer-support, 2) esterification with block **B**, 3) chemoselective carbonylation[12] of the vinyl iodide in unit **A** with alcohol **C** containing a vinyl bromide moiety, 4) carbonylative macrolactonization[13] of the polymer-supported **3** by exploiting the rather less reactive vinyl bromide unit, and 5) cleavage from the polymer-support. We planned a 128-member natural product-like library, consisting of blocks **A** (four), **B** (four), and **C** (eight) summarized in Figure 2.



Scheme 1. Strategy for a combinatorial synthesis of macrosphelide analogues **2**.

The preparation of the building blocks including the various diastereomers of (*E*)-vinyl halides for blocks **A** and **C** is shown in Scheme 2. Commercially available methyl (*S*)-lactate **4** was converted into ynone (*S*)-**5** in three steps. The ynone **5** is a key intermediate to prepare a variety of vinyl halides. Chelation-controlled reduction of **5** with Me_2AlCl/Bu_3SnH provided **6** (> 95 % selectivity),[14] while Felkin–Ahn

[*] Prof. Dr. T. Takahashi, S.-i. Kusaka, Prof. Dr. T. Doi
Department of Applied Chemistry
Tokyo Institute of Technology
2-12-1 Ookayama, Meguro, Tokyo 152-8552 (Japan)
Fax: (+81) 3-5734-2884
E-mail: ttak@apc.titech.ac.jp
Prof. Dr. T. Sunazuka, Prof. Dr. S. Ōmura
The Kitasato Institute for Life Science, and
School of Pharmaceutical Science,
Kitasato University and The Kitasato Institute
Shirokane, Minatoku, Tokyo 108-8641 (Japan)

[**] This work was supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology, Japan (No. 14103013).

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

  DOI: 10.1002/ange.200352229

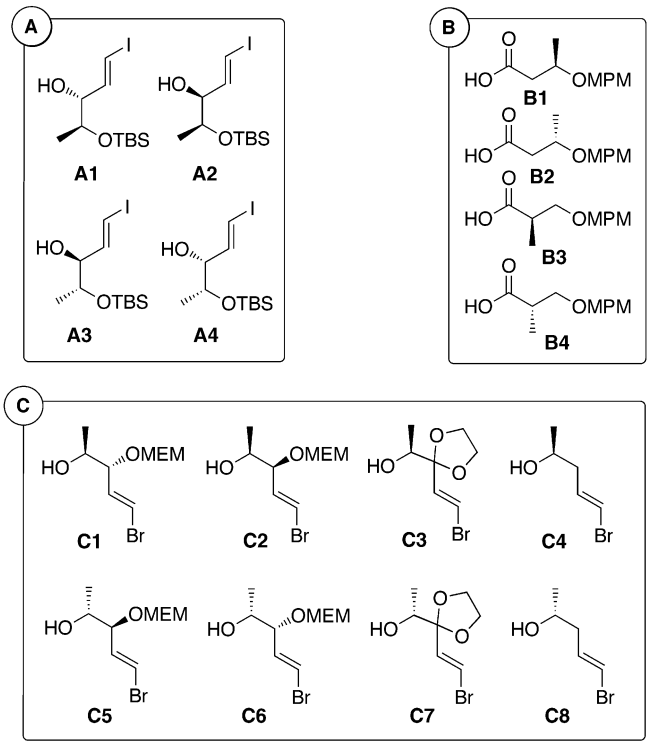
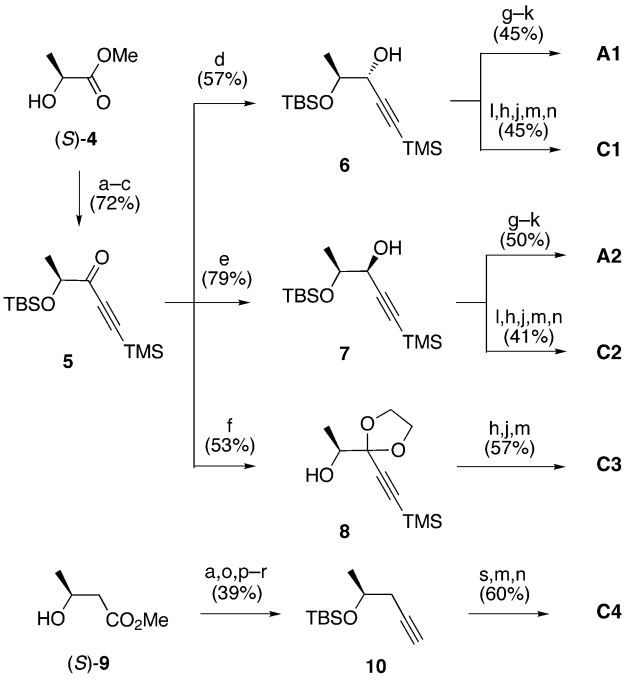


Figure 2. The building blocks **A, B**, and **C** for the synthesis of a combinatorial library of macrosphelide analogues **2**.

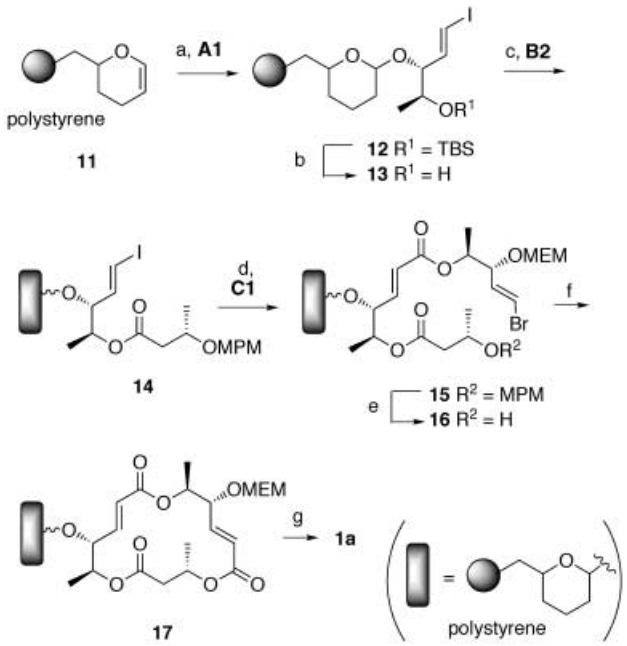


Scheme 2. Preparation of the vinyl halides, the blocks **A** and **C**: a) TBSCl, imidazole, CH_2Cl_2, RT, 6 h; b) Me(OMe)NH·HCl, *i*PrMgCl, THF, 0 °C, 30 min; c) trimethylsilylacethylene, BuLi, −78 °C, THF, 2 h; d) Me_2AlCl, Bu_3SnH, CH_2Cl_2, −78 °C, 3 h; e) L-selectride, THF, −78 °C, 1 h; f) $Sc(OTf)_3$, $CH(OMe)_3$, ethylene glycol, CH_3CN, RT→60 °C, 24 h; g) EVE, CSA, CH_2Cl_2, RT, 6 h; h) 5% KOH in MeOH, RT, 30 min; i) PPTS, MeOH, RT, 3 h; j) $[PdCl_2(PPh_3)_2]$, Bu_3SnH, THF, 0 °C, 1 h; k) NIS, THF, 0 °C, 30 min; l) MEMCl, *i*Pr_2NEt, RT, 24 h; m) NBS, THF, RT, 30 min; n) TBAF, THF, RT, 6 h; o) DIBAL-H, CH_2Cl_2, −78 °C, 30 min; p) SO_3·Py, Et_3N, CH_2Cl_2, RT, 2 h; q) CBr_4, PPh_3, THF, 0 °C, 1 h; r) BuLi, THF, −78 °C, 1 h; s) $[PdCl_2(MeCN)_2]$, PCy_3, Bu_3SnH, THF, 0 °C, 2 h. TBSCl = chlorodimethyl-1,1-dimethylethyl silane, TMS = trimethylsilane, Tf = trifluoromethanesulfonate, EVE = ethyl vinyl ether, CSA = camphorsulfonic acid, PPTS = pyridinium *p*-toluenesulfonate, NIS = *N*-iodosuccinimide, MEM = methoxyethoxymethyl, NBS = *N*-bromosuccinimide, TBAF = tetrabutylammonium fluoride, DIBAL-H = bis(2-methylpropyl)aluminium hydride, Py = pyridine.

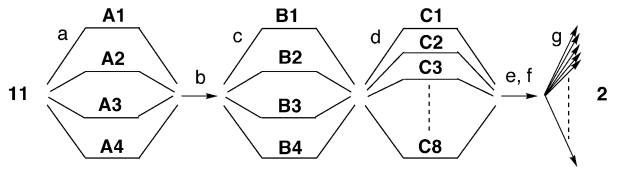
type reduction with L-selectride yielded **7** (> 95% selectivity).[15] Acetal formation of **5** with ethylene glycol afforded **8**. After removal of TMS, the alkyne was converted into the desired (*E*)-vinyl halides **A1** and **A2** and **C1**–**C3** by regioselective hydrostannylation (cat. $[PdCl_2(PPh_3)_2]/Bu_3SnH$),[16] followed by either iodination with NIS or bromination with NBS. Their enantiomers **A3** and **A4** and **C5**–**C7** were prepared from methyl (*R*)-lactate **4** by the same method. The vinyl bromides **C4** and **C8** were prepared from methyl (*S*)- and (*R*)-3-hydroxybutyrates **9**, respectively, through the regioselective hydrostannylation of **10** (cat. $[PdCl_2(MeCN)_2]/PCy_3/Bu_3SnH$), followed by bromination.

A solid-phase synthesis of **1a** was initially investigated (Scheme 3). The block **A1** was attached to a PS-DHP resin **11** (0.96 mmol g^{-1} PS = polystyrene, DHP = dihydropyran[17] using PPTS. Selective deprotection of the TBS group with TBAF and esterification of the polymer-supported alcohol **13** with acid **B2**[18] provided **14**. Palladium-catalyzed carbonylation of the vinyl iodide **14** with alcohol **C1** was carried out.[19] The reaction proceeded at room temperature under 30 atm of carbon monoxide utilizing $[PdCl_2(MeCN)_2]$ as a catalyst.[20,21] The product **15** was cleaved from the resin (0.1M TsOH/MeOH, THF; Ts = 4-methylphenylsulfonyl) and its purity was determined to be 71% by HPLC analysis. The vinyl bromide moiety remained intact under the above reaction conditions. The 4-methoxyphenylmethyl (MPM) group in **15** was removed with DDQ to afford polymer-supported cyclization precursor **16**.[22] The palladium-catalyzed carbonylation of **16** was achieved at 80 °C utilizing $[Pd_2(dba)_3]$/dppf to provide macrolactone **17**.[23] Finally, treatment of **17** with 4N HCl in dioxane at room temperature released the desired macrosphelide **1a** in 68% purity. Purification by preparative HPLC provided **1a** in 38% overall yield from **11** (7 steps). The synthetic **1a** exhibited ^1H and ^{13}C NMR spectral data as well as optical rotation identical to those published for the natural product.[6b,24]

On the basis of the above solid-phase strategy, we constructed a macrosphelide combinatorial library utilizing radiofrequency encoded combinatorial (REC) chemistry by a split-and-pool method (Scheme 4).[4,25] The 128 microreactors each containing 30 mg of PS-DHP resin **11** were encoded and split into four flasks. After attachment of block **A** (**A1**–**A4**) to the resin, the microreactors were pooled together for washing and drying. After deprotection of the TBS group, the microreactors were decoded and split, followed by esterification with block **B** (**B1**–**B4**)[18] in separate flasks. The microreactors were subsequently pooled for washing and drying. The microreactors were again decoded and split, followed by palladium-catalyzed carbonylative esterification of vinyl iodides with block **C** (**C1**–**C8**) in separate autoclaves. The microreactors were again pooled for washing and drying.



Scheme 3. Solid-phase synthesis of macrosphelide A (**1a**): a) PPTS (0.05 M), CH_2Cl_2, RT, 24 h; b) TBAF (0.3 M), THF, RT, 24 h; c) DIC (0.1 M), DMAP (0.001 M), CH_2Cl_2, RT, 24 h; d) $[PdCl_2(MeCN)_2]$ (0.03 M), CO (30 atm), NEt_3 (0.2 M), DMAP (0.03 M), DMF, RT, 12 h; e) DDQ (0.3 M), aq.$NaHCO_3$ (0.3 M), CH_2Cl_2:H_2O (1:1), RT, 5 h; f) $[Pd_2(dba)_3]$/dppf (0.03 M), CO (30 atm), NEt_3 (0.2 M), DMAP (0.03 M), DMF, 80 °C, 12 h; g) 4 N HCl in dioxane, RT, 5 h; TBS = dimethyl-1,1-dimethylethyl silane, DIC = diisopropylcarbodiimide, DMAP = (4-dimethylamino)pyridine, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, dba = dibenzylideneacetone, dppf = bis(diphenylphosphanyl)ferrocene.



Scheme 4. A combinatorial synthesis of macrosphelide analogues **2** utilizing a split-and-pool method: Reagents and conditions a)–g) are the same as shown in Scheme 3.

After removal of the MPM group, the palladium-catalyzed carbonylative macrolactonization of vinyl bromides was performed. Finally, the microreactors were decoded and treated with acid in parallel for removal of the MPM group and cleavage from the polymer support to afford crude **2**. Purification by preparative HPLC (silica gel) provided 122 macrosphelide analogues **2** (0.2–1.5 mg) from 128 trials, isolated in good purities (Table 1).[26,27]

We have demonstrated the combinatorial synthesis of a natural product-like library based on macrosphelide. The combinatorial synthesis of a 122-member macrosphelide library including macrosphelides A, C, E, and F has been achieved based on a unique strategy for a three-component coupling utilizing a palladium-catalyzed chemoselective carbonylation and an unprecedented macrolactonization on a polymer support.

Received: June 26, 2003 [Z52229]

Keywords: chemoselectivity · combinatorial chemistry · macrosphelides · palladium · solid-phase synthesis

Table 1: A combinatorial library of macrosphelide analogues **2**.

Entry	A	B	C	Yield [mg][a]	Purity [%][b]	R_t [min][c]	Entry	A	B	C	Yield [mg][a]	Purity [%][b]	R_t [min][c]
1[d]	1	1	1	1.2	80	5.78	65	3	1	1	0.9	99	5.67
2	1	1	2	1.1	99	5.43	66	3	1	2	1.5	98	5.79
3	1	1	3	0.3	99	7.01	67	3	1	3	0.9	95	7.10
4[e]	1	1	4	1.1	81	6.83	68	3	1	4	0.7	97	6.94
5	1	1	5	0.6	72	5.52	69	3	1	5	1.1	97	5.97
6	1	1	6	< 0.1	–	–	70	3	1	6	0.2	78	5.43
7	1	1	7	0.5	83	6.89	71	3	1	7	0.6	96	7.16
8	1	1	8	0.3	91	6.73	72	3	1	8	0.5	88	7.14
9[f]	1	2	1	0.5	99	6.06	73	3	2	1	0.5	88	5.61
10	1	2	2	1.3	99	5.44	74	3	2	2	1.4	65	5.31
11	1	2	3	1.3	93	7.18	75	3	2	3	0.5	77	6.89
12[g]	1	2	4	0.8	96	7.14	76	3	2	4	1.0	86	6.74
13	1	2	5	0.5	91	5.59	77	3	2	5	1.0	91	5.70
14	1	2	6	0.5	99	5.87	78	2	2	6	< 0.1	–	–
15	1	2	7	1.3	98	7.10	79	3	2	7	0.9	95	7.02
16	1	2	8	0.3	97	6.93	80	3	2	8	0.5	82	6.82
17	1	3	1	0.8	90	5.76	81	3	3	1	0.6	99	5.99
18	1	3	2	0.7	73	5.34	82	3	3	2	1.6	95	5.81
19	1	3	3	0.7	78	7.02	83	3	3	3	0.5	73	7.22
20	1	3	4	0.6	94	6.94	84	3	3	4	1.7	88	7.05
21	1	3	5	0.3	80	5.64	85	3	3	5	1.2	81	6.11
22	1	3	6	< 0.1	–	–	86	3	3	6	0.5	82	5.90
23	1	3	7	0.4	85	6.98	87	3	3	7	0.7	84	7.34
24	1	3	8	0.2	95	6.78	88	3	3	8	0.4	59	7.19
25	1	4	1	1.2	98	6.20	89	3	4	1	1.2	99	5.64
26	1	4	2	1.6	84	5.91	90	3	4	2	1.5	94	5.55
27	1	4	3	0.1	54	7.35	91	3	4	3	0.8	70	6.98

Table 1: (Continued)

Entry	A	B	C	Yield [mg][a]	Purity [%][b]	R_t [min][c]	Entry	A	B	C	Yield [mg][a]	Purity [%][b]	R_t [min][c]
28	**1**	**4**	**4**	1.1	40	7.20	92	**3**	**4**	**4**	1.6	88	6.79
29	**1**	**4**	**5**	0.9	80	5.98	93	**3**	**4**	**5**	0.3	94	5.76
30	**1**	**4**	**6**	0.4	82	5.81	94	**3**	**4**	**6**	<0.1	–	–
31	**1**	**4**	**7**	0.5	91	7.22	95	**3**	**4**	**7**	0.6	80	7.02
32	**1**	**4**	**8**	0.5	85	5.72	96	**3**	**4**	**8**	0.2	91	6.93
33	**2**	**1**	**1**	1.2	96	5.78	97	**4**	**1**	**1**	0.8	93	5.60
34	**2**	**1**	**2**	1.0	97	5.61	98	**4**	**1**	**2**	1.3	95	5.37
35	**2**	**1**	**3**	0.2	74	7.12	99	**4**	**1**	**3**	0.1	96	6.87
36	**2**	**1**	**4**	1.9	66	6.86	100	**4**	**1**	**4**	0.9	94	6.65
37	**2**	**1**	**5**	0.5	95	5.74	101	**4**	**1**	**5**	1.0	95	5.60
38	**2**	**1**	**6**	0.2	84	5.40	102	**4**	**1**	**6**	0.9	60	5.16
39	**2**	**1**	**7**	1.4	83	7.02	103	**3**	**1**	**7**	0.6	84	6.81
40	**2**	**1**	**8**	0.7	69	6.92	104	**4**	**1**	**8**	0.4	69	6.67
41	**2**	**2**	**1**	0.1	94	5.61	105	**4**	**2**	**1**	0.8	99	5.75
42	**2**	**2**	**2**	<0.1	–	–	106	**3**	**2**	**2**	1.5	86	5.31
43	**2**	**2**	**3**	0.4	99	6.81	107	**4**	**2**	**3**	0.5	82	6.98
44	**2**	**2**	**4**	1.5	97	6.71	108	**4**	**2**	**4**	1.3	72	6.93
45	**2**	**2**	**5**	0.1	99	5.60	109	**4**	**2**	**5**	0.8	84	5.69
46	**2**	**2**	**6**	0.5	75	5.35	110	**4**	**2**	**6**	<0.1	–	–
47	**2**	**2**	**7**	0.4	89	6.87	111	**4**	**2**	**7**	0.6	92	7.12
48	**2**	**2**	**8**	0.3	93	6.64	112	**4**	**2**	**8**	0.2	81	6.85
49	**2**	**3**	**1**	0.6	89	5.81	113	**4**	**3**	**1**	0.6	96	5.74
50	**2**	**3**	**2**	0.7	99	5.52	114	**4**	**3**	**2**	1.1	98	5.35
51	**2**	**3**	**3**	0.7	80	6.93	115	**4**	**3**	**3**	1.1	88	6.92
52	**2**	**3**	**4**	1.8	92	6.78	116	**4**	**3**	**4**	1.5	88	6.79
53	**2**	**3**	**5**	0.2	93	5.74	117	**4**	**3**	**5**	0.6	80	5.72
54	**2**	**3**	**6**	0.4	95	5.35	118	**4**	**3**	**6**	0.5	66	5.61
55	**2**	**3**	**7**	0.2	84	7.00	119	**4**	**3**	**7**	0.4	91	6.99
56	**2**	**3**	**8**	0.3	90	6.78	120	**4**	**3**	**8**	0.4	97	6.79
57	**2**	**4**	**1**	0.6	98	5.81	121	**4**	**4**	**1**	0.3	90	5.74
58	**2**	**4**	**2**	0.8	95	5.52	122	**4**	**4**	**2**	1.5	99	5.34
59	**2**	**4**	**3**	0.5	94	7.00	123	**4**	**4**	**3**	0.2	81	7.00
60	**2**	**4**	**4**	0.5	93	6.80	124	**4**	**4**	**4**	1.5	64	6.79
61	**2**	**4**	**5**	0.2	81	5.65	125	**4**	**4**	**5**	0.5	50	5.74
62	**2**	**4**	**6**	<0.1	–	–	126	**4**	**4**	**6**	0.2	71	5.53
63	**2**	**4**	**7**	0.5	91	6.92	127	**4**	**4**	**7**	0.2	70	6.92
64	**2**	**4**	**8**	0.3	91	6.78	128	**4**	**4**	**8**	0.2	94	6.77

[a] Purified by an automated preparative HPLC (Waters 2695) detected by UV (214 nm; Silica 60-5N, 20$\phi\times$250 mm, elution with 15% 2-propanol in hexane at 7.0 mL min^{-1} flow rate). [b] Purity was determined by reverse-phase HPLC with peak area (UV) at 214 nm. LC/MS were obtained on an AppliedBioSystems Mariner TK3500 Biospectrometry Workstation (ESI-TOF) mass spectrometery and Hewlett-Packard Series 1100 (GL Science Inc. Inertsil ODS-3, 3 μm, 4.6×75 mm with a linear gradient of 10% acetonitrile containing 0.1% formic acid/water containing 0.1% formic acid to 100% acetonitrile containing 0.1% formic acid over 9 min at 1.0 mL min^{-1} flow rate). [c] Retention time. Positive ion electrospray MS data, $[M+H]^+$ were recorded. [d] Macrosphelide E. [e] Macrosphelide F. [f] Macrosphelide A. [g] Macrosphelide C.

[1] J. Nielsen, *Curr. Opin. Chem. Biol.* **2002**, *6*, 297–305.

[2] L. A. Wessjohann, *Curr. Opin. Chem. Biol.* **2000**, *4*, 303–309.

[3] K. C. Nicolaou, J. A. Pfefferkorn, G.-Q. Cao, *Angew. Chem.* **2000**, *112*, 750–755; *Angew. Chem. Int. Ed.* **2000**, *39*, 734–739.

[4] K. C. Nicolaou, D. Vourloumis, T. Li, J. Pastor, N. Winssinger, Y. He, S. Ninkovic, F. Sarabia, H. Vallberg, F. Roschangar, N. P. King, M. R. V. Finlay, P. Giannakakou, P. Verdier-Pinard, E. Hamel, *Angew. Chem.* **1997**, *109*, 2181–2187; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2097–2103.

[5] I. Hijikuro, T. Doi, T. Takahashi, *J. Am. Chem. Soc.* **2001**, *123*, 3716–3722.

[6] a) M. Hayashi, Y.-P. Kim, H. Hiraoka, M. Natori, S. Takamatsu, T. Kawakubo, R. Masuma, K. Komiyama, S. Omura, *J. Antibiot.* **1995**, *48*, 1435–1439; b) S. Takamatsu, Y.-P. Kim, M. Hayashi, H. Hiraoka, M. Natori, K. Komiyama, S. Omura, *J. Antibiot.* **1996**, *49*, 95–98.

[7] a) T. A. Springer, *Nature* **1990**, *346*, 425–434; b) E. C. Butcher, *Cell* **1991**, *67*, 1033–1036; c) A. Fukami, K. Iijima, M. Hayashi, K. Komiyama, S. Omura, *Biochem. Biophys. Res. Commun.* **2002**, *291*, 1065–1070.

[8] T. Sunazuka, T. Hirose, Y. Harigaya, S. Takamatsu, M. Hayashi, K. Komiyama, S. Omura, P. A. Sprengeler, A. B. Smith III, *J. Am. Chem. Soc.* **1997**, *119*, 10247–10248.

[9] a) Y. Kobayashi, B. G. Kumar, T. Kurachi, *Tetrahedron Lett.* **2000**, *41*, 1559–1563; b) Y. Kobayashi, G. B. Kumar, T. Kurachi, H. P. Acharya, T. Yamazaki, T. Kitazume, *J. Org. Chem.* **2001**, *66*, 2011–2018; c) Y. Kobayashi, H. P. Acharya, *Tetrahedron Lett.* **2001**, *42*, 2817–2820; d) Y. Kobayashi, Y.-G. Wang, *Tetrahedron Lett.* **2002**, *43*, 4381–4384.

[10] a) M. Ono, H. Nakamura, F. Konno, H. Akita, *Tetrahedron: Asymmetry* **2000**, *11*, 2753–2764; b) H. Nakamura, M. Ono, Y. Shiba, H. Akita, *Tetrahedron: Asymmetry* **2002**, *13*, 705–713; c) H. Nakamura, M. Ono, M. Makino, H. Akita, *Heterocycles* **2002**, *57*, 327–336.

[11] G. V. M. Sharma, C. C. Mouli, *Tetrahedron Lett.* **2002**, *43*, 9159–9161.

[12] R. Anacardio, A. Arcadi, G. D'Anniballe, F. Marinelli, *Synthesis* **1995**, 831 – 836.

[13] a) T. Takahashi, T. Nagashima, J. Tsuji, *Chem. Lett.* **1980**, 369 – 372; b) T. Takahashi, H. Ikeda, J. Tsuji, *Tetrahedron Lett.* **1980**, *21*, 3885 – 3888.

[14] a) D. A. Evans, B. D. Allison, M. G. Yang, C. E. Masse, *J. Am. Chem. Soc.* **2001**, *123*, 10840 – 10852; b) D. A. Evans, B. D. Allison, M. G. Yang, *Tetrahedron Lett.* **1999**, *40*, 4457 – 4460; c) D. A. Evans, D. P. Halstead, B. D. Allison, *Tetrahedron Lett.* **1999**, *40*, 4461 – 4462.

[15] After removal of the silyl groups (HF/pyridine), the stereochemistry was determined by ^{1}H NMR compared with those reported in the literature. G. Guanti, L. Banfi, E. Narisano, *Gazz. Chim. Ital.* **1987**, *117*, 681.

[16] a) H. X. Zhang, F. Guibe, G. Balavoine, *J. Org. Chem.* **1990**, *55*, 1857 – 1867; b) N. D. Smith, J. Mancuso, M. Lautens, *Chem. Rev.* **2000**, *100*, 3257 – 3282.

[17] J. A. Ellman, L. A. Tompson, *Tetrahedron Lett.* **1994**, *35*, 9333 – 9336.

[18] Block **B** was prepared from the corresponding methyl hydroxycarboxylate (commercially available) (4-methoxyphenylmethyl 2,2,2-trichloroacetimidate/CSA(0.3 equiv)/CH_2Cl_2; NaOH/H_2O, MeOH, THF; HCl; CSA = camphorsulfonic acid).

[19] a) T. Takahashi, H. Inoue, S. Tomita, T. Doi, A. M. Bray, *Tetrahedron Lett.* **1999**, *40*, 7843 – 7846; b) T. Takahashi, H. Inoue, Y. Yamamura, T. Doi, *Angew. Chem.* **2001**, *113*, 3330 – 3333; T. Takahashi, H. Inoue, Y. Yamamura, T. Doi, *Angew. Chem.* **2001**, *113*, 3330 – 3333; *Angew. Chem. Int. Ed.* **2001**, *40*, 3230 – 3233; c) M. Hashimoto, A. Mori, H. Inoue, H. Nagamiya, T. Doi, T. Takahashi, *Tetrahedron Lett.* **2003**, *44*, 1251 – 1254.

[20] 1-Iodo-1-alken-3-ol underwent carbonylation at room temperature using [$PdCl_2(PPh_3)_2$] as a catalyst. A. Cowell, J. K. Stille, *Tetrahedron Lett.* **1979**, *20*, 133 – 136.

[21] The reaction conditions were initially optimized in solution. We found that the vinyl bromide did not react with CO at room temperature utilizing [$PdCl_2(MeCN)_2$]. However, the palladium-catalyzed carbonylation of the vinyl bromide proceeded at 80 °C using triphenylphosphane, dppf, or [(tBu)$_3$PH]BF_4 as a ligand.

[22] Removal of the MPM group was not complete using 0.15 M of DDQ. In the absence of aqueous $NaHCO_3$, **16** was cleaved from the resin. K. Horita, T. Yoshioka, T. Tanaka, Y. Oikawa, O. Yonemitsu, *Tetrahedron* **1986**, *42*, 3021 – 3028.

[23] The dimerized product was not obtained (**16**: ca. 0.6 mmol g^{-1} loading). Under the cyclization conditions, elimination of the β-acyloxy ester moiety was not observed.

[24] The spectral data are given in the Supporting Information.

[25] K. C. Nicolaou, X.-Y. Xiao, Z. Parandoosh, A. Senyei, M. P. Nova, *Angew. Chem.* **1995**, *107*, 2476 – 2479; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2289 – 2291.

[26] LC/MS spectra of the 122 products gave the corresponding [M+H]$^+$ data and the structures of 15 compounds randomly selected were determined by ^{1}H NMR spectra. The acetal of the ethylene glycol moiety in **C3** and **C7** was intact under the cleavage conditions.

[27] No other isomer was detected in LC/MS. However, as a referee pointed out, there is some uncertainty about the structure of the new lactones by the possibility of complete transesterification under acid cleavage conditions.

