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Synthetic Studies of Halichondrin B, an Antitumor Polyether Macrolide Isolated from a Marine Sponge. 8. Synthesis of the Lactone Part (C1-C36) via Horner-Emmons Coupling Between C1-C15 and C16-C36 Fragments and Yamaguchi Lactonization.

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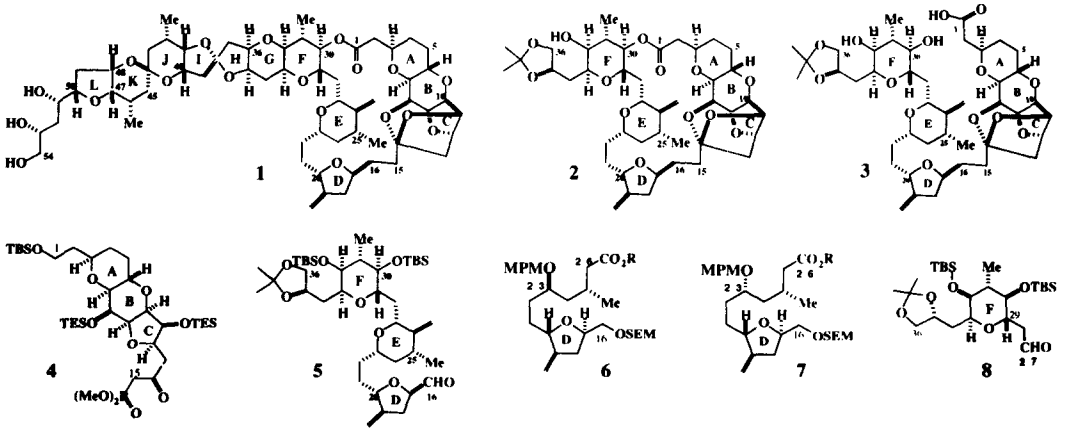
Abstract: The lactone part (**2**) of halichondrin B (**1**) was synthesized by Yamaguchi macrolactonization of the seco-acid (**3**), which was synthesized via coupling of C1-C15(**4**) with C16-C36 (**5**), prepared through stereoselective construction of the E ring starting from C16-C26 (**7**) and C27-C36 (**8**).

Halichondrin B (**1**), a representative member of the antitumor polyether macrolides in the halichondrin family, was isolated from a marine sponge *Halichondria okadai* Kadota and its structure was established by Uemura and Hirata in 1985.[1] Because of its highly complex structure and invaluable biological activity, many synthetic efforts have been made,[2] and Kishi et al. completed the first total synthesis of **1** in 1992.[3] As part of our synthetic studies of **1** we report here the synthesis of the lactone part (C1-C36) (**2**) via Yamaguchi macrolactonization of the seco-acid (**3**) prepared by a coupling of the C1-C15 fragment (**4**),[2p] already prepared by a completely stereoselective construction of the A, B and C rings starting from D-acetoneglucose, with the C16-36 fragment (**5**).

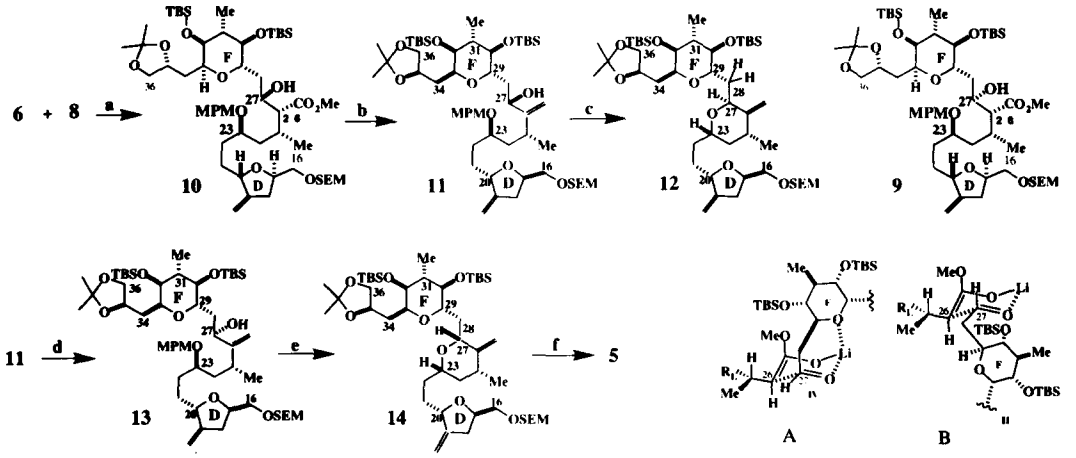


Synthesis of 5 via Syn-selective Aldol Reaction and Stereoselective E Ring Construction For the synthesis of **5** stereoselective construction of the E ring was predicted to be crucial, thus requiring particular attention. An aldol condensation of a C16-C26 ester (**6** or **7**)[2i] with the C27-C36 aldehyde (**8**)[2j-q] followed by an S$_N$2 type cyclization to construct the E ring was planned. Although the stereochemistry of aldol reaction is now well

documented, the stereoselectivity of the reaction between such highly functionalized esters and aldehydes is quite difficult to predict. Therefore, we prepared two C23 epimeric C16-C26 esters, **6** and **7**, in which the C23 hydroxy groups are used as a leaving group and an attacking group, respectively, for the construction of the E ring.[4]

Aldol reaction between a simple ester-enolate and an aldehyde under kinetical conditions usually proceeds via a six-membered transition state to give a 2,3-anti substituted ester, although high selectivity is not necessarily expectable.[5] If this is also the case for the reaction between **6** and **8**, the main product should be **9**. When **6** was converted to its ester enolate with LDA at -78°C and allowed to react with **8**, a completely stereoselective reaction proceeded and completed within 10 min to give a single coupling product, which was not the expected **9**, but a 2,3-syn substituted ester (**10**), whose structure was proved after conversion to **12** via **11** by eight conventional reactions. In the NMR spectrum of **12** ^{1}H-NOESY correlation between C23-H and C28-H, not between C23-H and C27-H, was observed. Therefore, the most probable transition structure to give **10** is depicted as A, in which Li chelates not only to the aldehyde oxygen to form the usual six-membered transition state (B), but also to the F ring oxygen.

In order to construct the E ring (C23,27-cis) starting from **10**, inversion of the C27 hydroxy group was required. Again **10** was transformed to **11** followed by a Dess-Martin oxidation[6] to give the C27 ketone, which was reduced with LiI-$LiAlH_4$,[7] and the expected C27 epimeric alcohol (**13**) was mainly obtained, although in a 4:1 mixture with **11**. Conversion of **13** to the expected **14** proceeded smoothly by a series of conventional reactions. Configurations of the E ring were confirmed by NOESY measurements, in which clear correlations among the C23-, C25- and C27-protons were observed. Compound **14** was easily transformed to the C16-C36 fragment (**5**), although a detour was required due to difficult selective deprotection of the SEM group. Thus, the synthesis of **5** was completed, but the overall yield for the sixteen steps from **8** to **5** was only 6.1%.

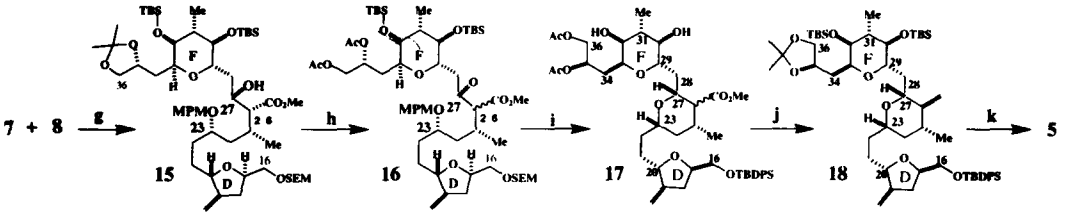


(a) LDA, THF ,-78°C, 79%. (b) 1) $LiAlH_4$, THF, 81%; 2) Ts-Cl, pyridine, CH_2Cl_2, 90%; 3) NaI, $NaHCO_3$, DBU, THF, 75%. (c) 1) TMS-imidazole, CH_2Cl_2, 96%; 2) DDQ, CH_2Cl_2, H_2O, 75%; 3) Ms_2O, TEA, CH_2Cl_2, 74%; 4) PPTS, THF:MeOH (1:1), 82%; 5) KH, DME, 39%. (d) 1) Dess-Martin oxid, 78%; 2) LiI-$LiAlH_4$, Et_2O, 64%. (e) 1) TMS-imidazole, CH_2Cl_2; DDQ, benzene-H_2O, 89%; 2) Ms_2O, TEA, CH_2Cl_2; PPTS, THF-MeOH, 90%; 3) KH, DME, 69%. (f) 1) TBAF, HMPA-THF; BzCl, pyridine, CH_2Cl_2, 72%; 2) TBSOTf, 2,6-lutidine, CH_2Cl_2, 93%; 3) K_2CO_3, MeOH, 92%; 4) Swern oxid, 83%.

Another route starting from **7** and **8** was next examined. The aldol reaction between **7** and **8** again proceeded via the A-type transition state to give another 2,3-syn substituted ester (**15**). If the C27 hydroxy group can be used as a leaving group, a direct construction of the E ring and a concise synthesis of **5** were expected. However, all attempts to convert the C27 hydroxy group to a mesyloxy group in several compounds such as C26 carbomethoxy, benzoyloxymethyl and methylene compounds were unfortunately unsuccessful.

Reductive deoxygenation of six-membered lactols with Et_3SiH and BF_3·Et_2O readily gave the corresponding tetrahydropyrans,[8] and Kishi et al. synthesized selectively 2,6-cis disubstituted compounds (C-glycosides) by

this reaction.[9] If a lactol is formed from **15** by oxidation of the C27 hydroxy group and deprotection of the C23-OMPM group, this reduction method should be applicable to the E ring construction. Dess-Martin oxidation of **15** followed by exchange of the isopropylidene protection to a diacetyl group[10] gave **16** (1:1 mixture at C26). When **16** was treated with Et_3SiH and $BF_3{\cdot}Et_2O$, deprotection of the MPM group and subsequent deoxygenation of the lactol rapidly occurred to give the expected **17** within 5 min in 87% yield.[11] After the diacetyl group was replaced again to the isopropylidene group, the C26 ester was converted to a methylene group to give **18**, which corresponds to **14** and led to **5** as described above. The overall yield for sixteen steps from **8** to **5** was 20%.

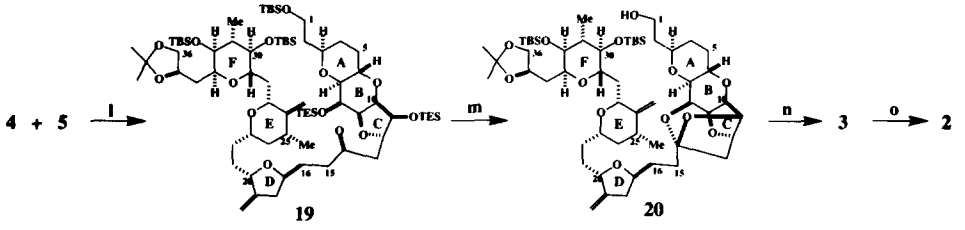


(g) LDA, THF, -78°C, 76%. (h) 1) Dess-Martin oxid, 100%; 2) PPTS, MeOH; Ac_2O, TEA, DMAP, CH_2Cl_2, 77%. (i) Et_2SiH, BF_3Et_2O, MeCN, 0°C, 5min; TBDPSCl, imidazole, CH_2Cl_2, 87%. (j) 1) K_2CO_3, MeOH; $Me_2C(OMe)_2$, CSA, benzene, 92%; 2) TBSOTf, 2,6-lutidine, CH_2Cl_2, 89%; 3) DIBAH, toluene, 86%; 4) TsCl, TEA, DMAP, 100%; 5) NaI, $NaHCO_3$, DBU, THF, 83%. (k) 1) TBAF, THF; BzCl, pyridine, CH_2Cl_2, 97%; 2) TBSOTf, 2,6-lutidine, CH_2Cl_2, 91%; 3) K_2CO_3, MeOH, 93%; 4) Swern oxid, 83%.

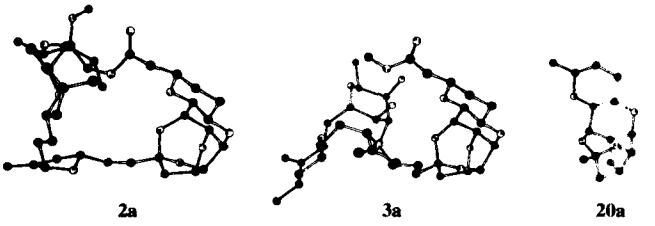
Synthesis of 2 via Horner-Emmons Coupling of 5 with 4 and Yamaguchi Macrolactonization

A Horner-Emmons coupling of **5** with the Li-salt of **4** readily gave the enone, which was treated with the copper (I) hydride cluster under Stryker's conditions.[12] A conjugate reduction of the C14-16 enone group proceeded smoothly to give **19.** In order to deprotect selectively two TES groups and the TBS group of C1 primary alcohol, **19** was carefully treated with dil-HCl at room temperature to give the triol, which, on treatment with PPTS, was transformed to **20**. Because of the completely fixed conformation of the C2-C15 part of **20** (**20a**) due to ketal formation at C14,[13] we may expect that the molecule is folded at around C15-C20, and consequently C1 and C30-O are brought close together favorably to macrolactonization of the corresponding seco-acid.[15] In macrolide synthesis, the design of a seco-acid suitable for lactonization is crucial.[16]

Desss-Martin oxidation of **20** followed by $NaClO_2$ oxidation and TBAF treatment gave the seco-acid (**3**), which was converted to Yamaguchi's mixed-anhydride[17] and then treated with a large excess of DMAP at room temperature[16] to give the title compound (**2**),[18,19] although the yield is still unsatisfactory.



(l) 1) nBuLi, THF, rt, 74%; 2) Ph_3PCuH, benzene-H_2O, rt, 90%. (m) 1N-HCl, THF, rt; PPTS, THF-MeOH, 80%. (n) Dess-Martin oxid; $NaClO_2$, NaH_2PO_4, $Me_2C{=}CMe_2$; TBAF, THF, 70%. (o) $Cl_3C_6H_2COCl$, TEA, THF; DMAP, benzene, rt, 35%



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10. Under the reduction conditions, the isopropylidene group is also deprotected.
11. Since under the reduction conditions, deprotection of the MPM group occurred very rapidly, the deprotection prior to the reduction was fortunately unnecessary.
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13. Molecular mechanics calculation using MacroModel[14] revealed that the C2-C15 part (**20a**) exists as a single conformer with 100% population.
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15. The most stable conformers of **2** and **3** are depicted as **2a** and **3a**, respectively, according to calculations of model compounds. Model **3a** has a folded structue, in which the distances from C1 to C30-O and C32-O are 3.6 and 4.9Å, respectively.
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18. $[\alpha]_D$+3.8° (*C*=0.144, $CHCl_3$). ^{1}H-NMR 0.70-1.10 (3H,m), 0.87 (3H,d,*J*=6.5Hz), 0.91 (3H,d,*J*=6.5Hz), 0.99 (3H,s), 1.01 (3H,s), 1.13-1.95 (12H,m), 2.02-2.25 (12H,m), 2.42 (1H,ddd,*J*=5.0,10.0,15.0Hz), 2.45-2.60 (3H,m), 3.35-3.43 (1H,m), 3.44-3.48 (1H,m), 3.52-3.58 (1H,m), 3.64 (1H,t,*J*=7.5Hz), 3.78 (1H,dd,*J*=4.0,6.5Hz), 3.94-3.99 (3H,m), 3.98 (1H,dd,*J*=6.0,8.0Hz), 4.03 (1H, dd,*J*=6.0,8.0Hz), 4.15-4.22 (4H,m), 4.23-4.31 (2H,m), 4.32-4.43 (2H,m), 4.51-4.53 (1H,m), 4.53-4.59 (2H,m), 4.64-4.67 (1H,m), 4.83 (1H,d,*J*=2.5Hz), 4.88 (1H,dt,*J*=2.0,2.5Hz), 4.98 (2H,s), 5.26 (1H,dd,*J*=5.5,8.5Hz). HR-MS (FAB) Calcd for $C_{43}H_{63}O_{13}$(M+H) 787.4273. Found 787.4297.
19. A downfield shift (5.26 ppm) of the C30-H signal [for **3**: 3.26 (1H,t,*J*=9.5Hz)] was observed.

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