

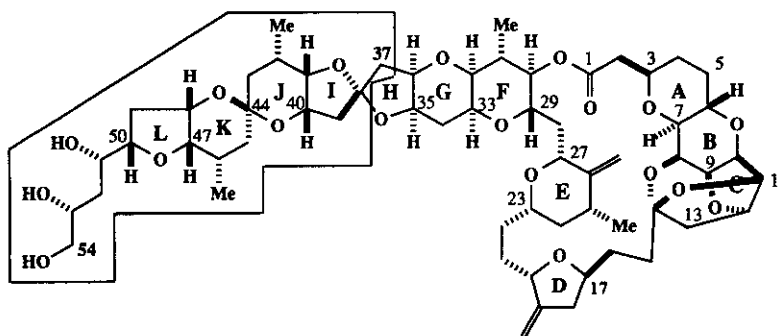
**SYNTHETIC STUDIES OF HALICHONDRIIN B, AN
ANTITUMOR POLYETHER MACROLIDE ISOLATED
FROM A MARINE SPONGE 5. A HIGHLY CONCISE
AND EFFICIENT SYNTHESIS OF THE C₃₇~C₅₄
TRICYCLIC JKL-RING PART**

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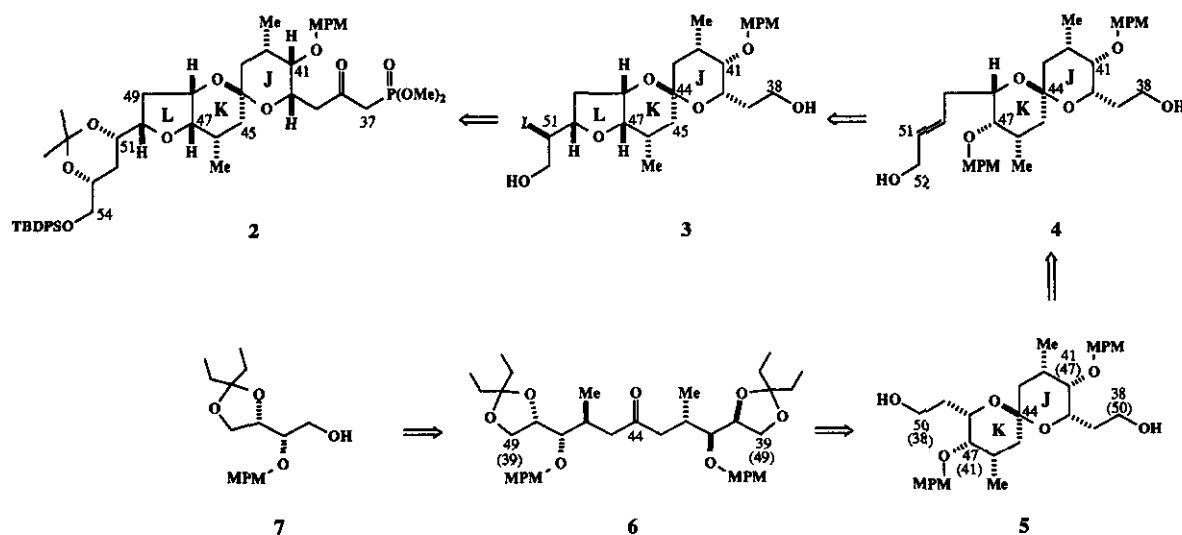
Abstract - A concise and efficient synthesis of C₃₇~C₅₄ tricyclic
JKL-ring unit (**2**) of halichondrin B (**1**) utilizing C₂-symmetric
spiroketal derivative (**5**) as a synthetic key intermediate, easily
provided from dimethyl L-(+)-tartrate, is reported.

Halichondrin B (**1**) is a representative compound of the antitumor polyether macrolides in the halichondrin family, isolated from a marine sponge *Halichondria okadai* Kadota by Uemura, Hirata and co-workers in 1985.¹ Synthetic challenges toward a total synthesis of halichondrins by synthetic organic chemists² have been reported due to the highly complex chemical structure as well as important biological activities, the first total synthesis of halichondrin B (**1**) and norhalichondrin B was achieved by Kishi and co-workers in 1992.^{2f} In connection with our synthetic program of **1**, we reported the stereoselective syntheses of four convenient synthetic subunits.³ In this paper, we describe a highly efficient, concise and stereoselective synthesis of the C₃₇~C₅₄ tricyclic (JKL-rings) unit (**2**) from dimethyl L-(+)-tartrate.



Halichondrin B (1)

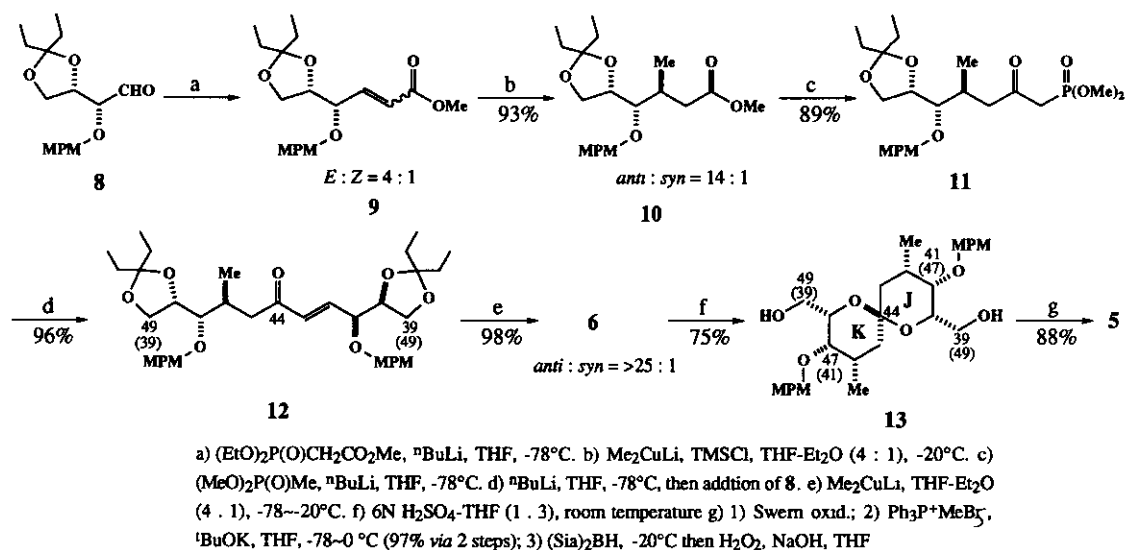
Our synthetic analysis is summarized in Scheme 1. The most significant point to this analysis is utilizing the C₂-symmetric spirocyclic diol (**5**),⁴ easily derived from dimethyl L-(+)-tartrate *via* the C₂-symmetric ketone (**6**), as a synthetic key compound. Furthermore, the tricyclic iodohydrin (**3**), which has a suitable configuration for the introduction of the C₅₁ oxygenated asymmetric center by epoxidation, could be expected to be efficiently and stereoselectively prepared from the allyl alcohol (**4**) by an iodoetherification reaction after conversion of **5** to **4** *via* a monoprotection step of the two hydroxyl groups.



Scheme 1

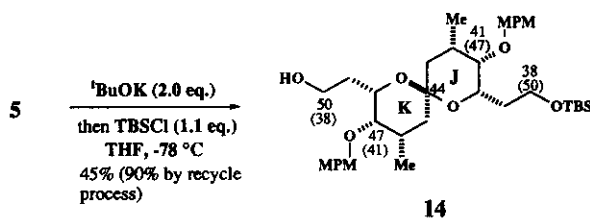
The key spirocyclic diol (**5**) was concisely prepared from the known alcohol (**7**),⁵ derived from dimethyl L-(+)-tartrate, by using two stereocontrolled conjugate additions of Me₂CuLi to γ -alkoxy- α,β -unsaturated carbonyl compounds⁶ in order to introduce two methyl groups at the C₄₂ and C₄₆ positions,⁷ as shown in Scheme 2. The first conjugate addition to the γ -(4-methoxy)phenylmethoxy- α,β -unsaturated ester (**9**), converted from **7** *via* two steps, proceeded successfully and stereoselectively to afford the desired adduct (**10**) with 3,4-*anti* stereochemistry⁸ in a 14 : 1 ratio according to Hannessian's procedure.^{6g} A more electrophilic γ -(*p*-methoxy)benzyloxy- α,β -unsaturated ketone (**12**) was prepared by Horner-Emmons coupling reaction of the aldehyde (**8**) and the β -ketophosphonate (**11**), obtained by treatment of the ester (**10**) with LiCH₂P(O)(OMe)₂ in THF at -78 °C.⁹ The second conjugate addition of Me₂CuLi to **12** without Me₃SiCl also proceeded cleanly and stereoselectively to give the desired ketone (**6**) with a high selectivity of more than 25 : 1 in 98% yield. When **6** was exposed to 6N H₂SO₄ in THF at room temperature, removal of the pentyldene groups and subsequent spiroketalization gradually proceeded to produce a pure C₂-symmetrical spiroketal derivative (**13**) as a single diastereomer. One carbon homologation of **13** *via* Swern oxidation¹⁰ and Wittig reaction with

$\text{Ph}_3\text{P}=\text{CH}_2$ followed by hydroboration with $(\text{Sia})_2\text{BH}$ afforded **5**.¹¹



Scheme 2

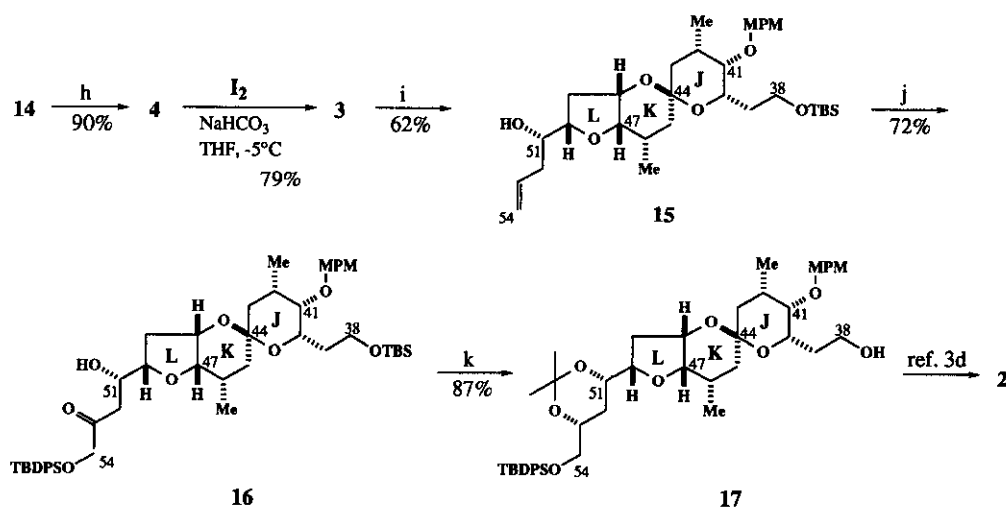
The next step in our synthetic program was to break the C_2 -symmetry of **5** by protecting only one of the two primary hydroxyl groups with TBSCl, as shown in Scheme 3. Due to the failure of many efforts¹² to produce **14** effectively, we tried to find a novel reaction condition. When the dipotassium salt of **5**, generated with $^t\text{BuOK}$ (2 eq.) in THF at -78°C , was trapped with TBSCl (1.1 eq.), the desired monoprotected silyl ether (**14**) was obtained in 45% yield with a trace of the disilyl ether. The unreacted starting diol (**5**) was easily recovered by silica gel column chromatography since the polarity of the diol (**5**) and monosilyl ether (**14**) was remarkably different.¹³ An effective conversion of **5** to **14** was achieved by repeating this recycling process three times.



Scheme 3

Finally, the synthesis of **17** from **14** was carried out via a highly stereoselective construction of the L-ring and the introduction of the two asymmetric centers at the C_{51} and C_{53} positions as shown in Scheme 4. When the allyl alcohol (**4**), converted from **14** via three conventional steps, was treated with iodine in THF at -5°C in the presence of NaHCO_3 , an iodoetherification reaction stereoselectively and smoothly occurred to give the desired tricyclic iodohydrin (**3**) as a single diastereomer. Transformation of **3** to the corresponding epoxide by

treatment with t BuOK in THF at -20°C , followed by addition of the vinylmagnesium bromide in the presence of CuI afforded allyl alcohol (**15**), which was led to **17** via a stereoselective reduction of the β -hydroxy ketone (**16**) with NaBH_4 in the presence of MeOBEt_2 in MeOH and THF.¹⁴ Since the conversion of **17** to **2** was already reported^{3d}, we were able to establish a concise and efficient synthetic route for the $\text{C}_{37}\text{--C}_{54}$ subunit (**2**) from dimethyl L-(+)-tartrate. Recently, we succeeded in synthesizing the $\text{C}_1\text{--C}_{37}$ macrolactone and the $\text{C}_{28}\text{--C}_{54}$ polyether portions by efficiently connecting our four synthetic subunits. These results will be reported soon.



h) 1) Swern oxid.; 2) $(i\text{PrO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$, t BuOK, THF, -78°C (91% via 2 steps); 3) DIBALH, CH_2Cl_2 , -78°C (99%). i) 1) t BuOK, THF, -20°C (82%); 2) vinylMgBr, CuI, Et_2O (76%); j) 1) TSCl, imidazole, CH_2Cl_2 (95%); 2) OsO_4 , NMO, H_2O -acetone (1 : 10) (95%); 3) TBDPSCl, imidazole, CH_2Cl_2 , room temperature (95%); 4) Swern oxid. (91%); 5) 1N HCl-THF (1 : 4) (91%). k) 1) Et_2BOMe , NaBH_4 , MeOH-THF (1 : 2); 2) CSA, $\text{Me}_2\text{C}(\text{OMe})_2$, benzene (87% via 2 steps)

Scheme 4

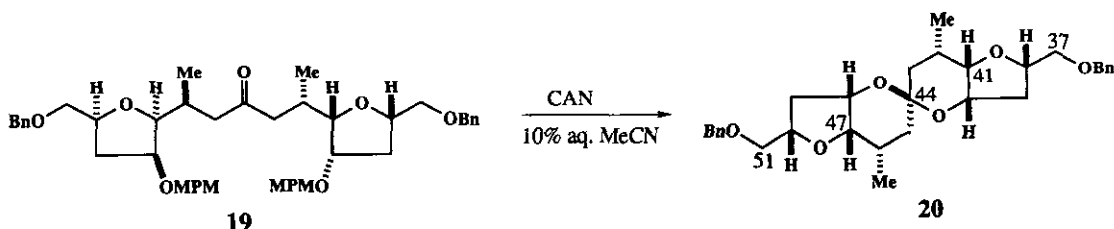
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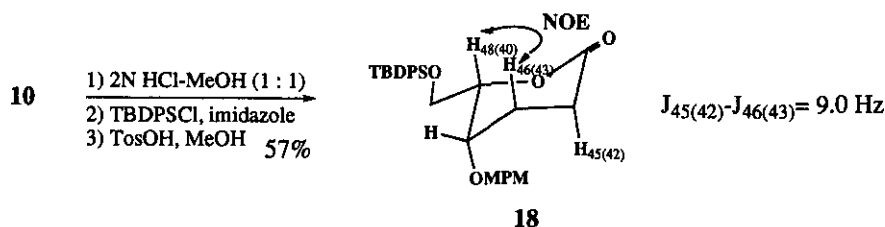
- 4 Salomon and co-workers have independently synthesized C₂-symmetrical spirotricyclic compound (20) from ketone (19), derived from D-mannitol by using two conjugate addition reactions of Me₂Cu(CN)Li₂ in the presence of TMSCl in THF at -75 °C to a γ -alkoxy- α,β -unsaturated acylsilane and a ketone, as a model compound corresponding to the C₃₇-C₅₁ portion of halichondrin B (1).^{2J}



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- 7 Unless otherwise noted, numbering is based on those of halichondrin B (1).
- 8 The stereochemistry of methyl ester (10) was assigned on the basis of the ^1H -nmr data (J -value between $\text{H}_{45(43)}$ axial proton and $\text{H}_{46(42)}$ proton, and ^1H -NOESY) after conversion of 10 to the six membered lactone (18) via the conventional 3 steps, as shown below.



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- 11 5: $[\alpha]_{\text{D}}^{23} -90^\circ$ ($c=0.68$, CHCl_3); ^1H -nmr (500 MHz, CDCl_3) δ 0.94 (6H, d, $J=7.0$ Hz), 1.52~1.42 (2H, m), 1.50 (2H, dd, $J=4.0, 13.0$ Hz), 1.59 (2H, t, $J=13.0$ Hz), 2.18 (2H, dddd, $J=2.0, 4.5, 10.0, 11.0$ Hz), 2.11~2.20 (2H, m), 2.20~2.34 (2H, m), 3.19 (2H, s), 3.65 (2H, dt, $J=11.0, 4.5$ Hz), 3.76~3.81 (2H, m), 3.79 (6H, s), 3.82 (2H, dd, $J=1.0, 11.0$ Hz), 4.51 (2H, d, $J=11.5$ Hz), 4.55 (2H, d, $J=11.5$ Hz), 6.85 (4H, d, $J=8.5$ Hz), 7.26 (4H, d, $J=8.5$ Hz). ^{13}C -Nmr (500 MHz, CDCl_3); δ 18.16, 30.93, 35.24, 37.94, 55.34, 58.83, 68.52, 74.99, 78.60, 96.84, 113.66, 129.86, 130.92, 159.25.
- 12 For example: (a) A usual silylation using imidazole and TBSCl in CH_2Cl_2 or DMF at a low temperature (even as low as -20°C) gave predominantly a disilyl ether. (b) When $^n\text{BuLi}$ was used as a base instead of $^t\text{BuOK}$, the silylation reaction didn't proceed at all.
- 13 Rf value: (5) 0.01, (14) 0.60, disilyl ether of (5) 0.95 ($\text{AcOEt} : ^n\text{hexane}=1 : 2$).
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