ORGANIC LETTERS

2002
Vol. 4, No. 6
897−900

A Biosynthetic Proposal for Ring Formation in the Antitumor Agent Halichomycin. Asymmetric Synthesis of the AB-Carbon Backbone of Halichomycin

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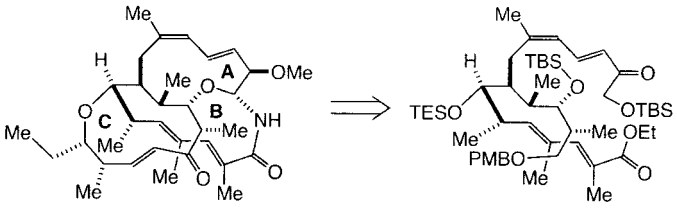
Received December 19, 2001

ABSTRACT



A biosynthetic proposal for ring formation in the antitumor agent halichomycin is presented in which macrocyclization of the putative prehalichomycin intermediate 1 is the first step. Compound 2 then undergoes dehydration to the α-keto *N*-acylimine 3 followed by tandem nucleophilic addition of the C(16)-hydroxyl to form the hemimacrolactam. A stereospecific Michael ring closure and enol protonation complete C-ring assembly. So far, synthetic efforts toward 1 have resulted in 8.

Halichomycin is a structurally unprecedented tricyclic hemimacrolactam produced by a strain of *Streptomyces hygroscopicus*, obtained from the gastrointestinal tract of *Halichoeres bleekeri*, a well-known marine fish.[1] Halichomycin displays powerful antitumor effects in vitro, exhibiting an ED_{50} of 0.13 μg/mL against a murine P388 lymphocytic leukemia cell line. As such, it is of potential interest for the future treatment of human cancer.

The extraordinary molecular complexity of halichomycin naturally raises questions about its biosynthesis. While much of its skeleton looks propionate- and acetate-derived, it is not at all clear how the bonds adjacent to the C(8)−C(9)-bond are formed by such a pathway. It is also not readily apparent how nature closes the three intersecting ring systems that are present, which include a fully functionalized 11-membered ether ring and a structurally unique 13/11-membered bicyclic hemimacrolactam. These combined conceptual difficulties recently led Kobayashi and Ishibashi to comment that the biosynthetic provenance of halichomycin "appeared to be strange".[2] Our biosynthetic proposal for ring assembly in halichomycin invokes the branched precursor **1**

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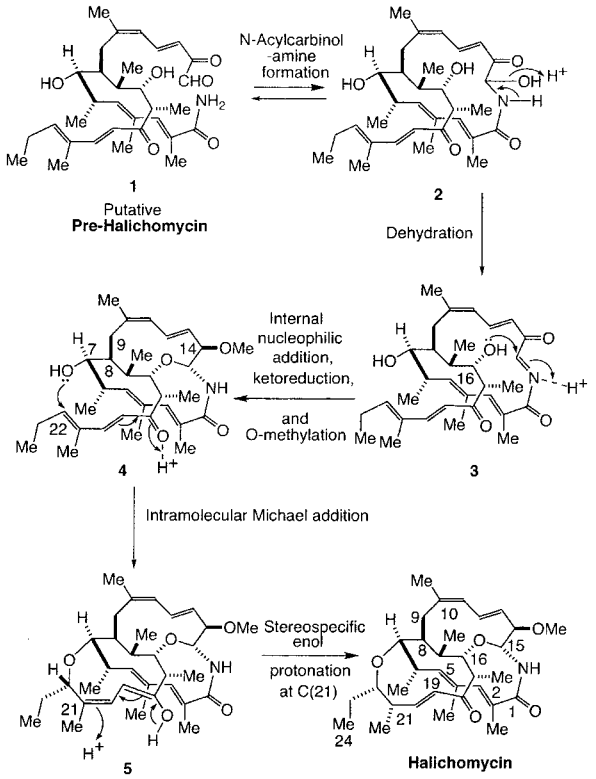
(1) Takahashi, C.; Takada, T.; Yamada, T. Minoura, K.; Uchida, K.; Matsumura, E.; Numata, A. *Tetrahedron Lett.* **1994**, *35*, 5013.

(2) Kobayashi, J.; Ishibashi, M. *Comprehensive Natural Product Chemistry*; Barton D., Nakanishi, K., Meth-Cohn, O., Eds.; Pergamon: Oxford, 1999; Vol. 8, Chapter 8.07, p 416.

10.1021/ol017266a CCC: $22.00
Published on Web 02/22/2002

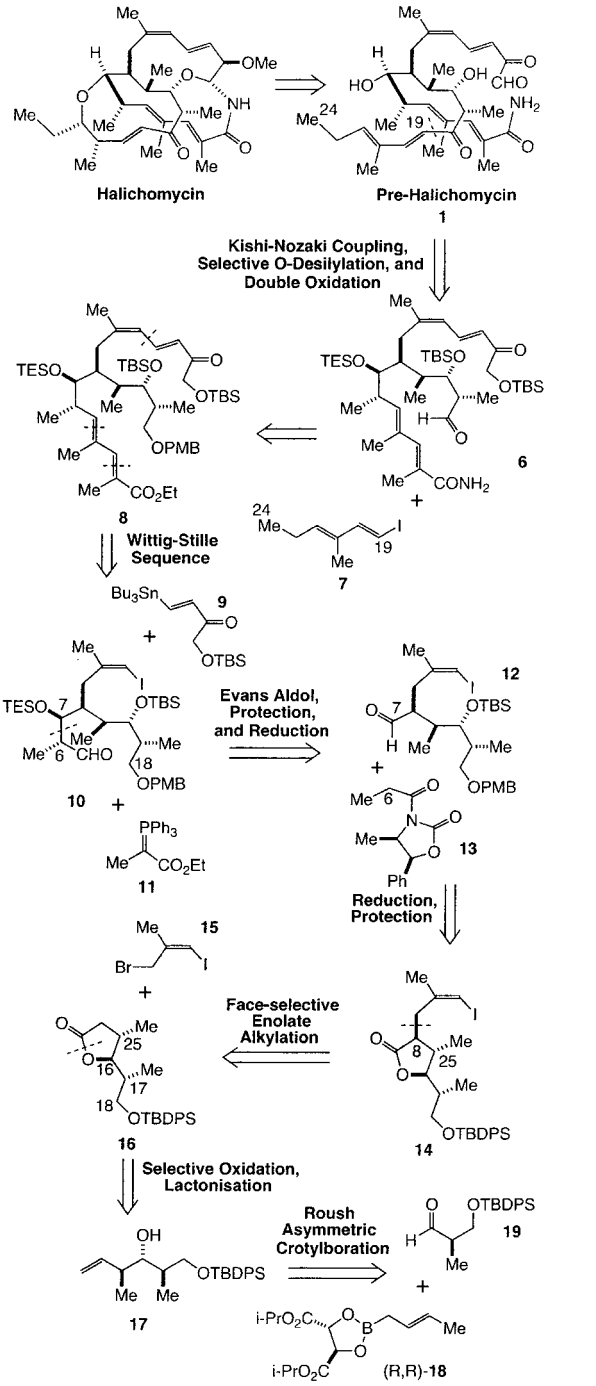
as an intermediate and postulates internal macrocyclic *N*-acylcarbinolamine formation[3] as the first step in ring formation (Scheme 1). Intermediate **2** is then thought to undergo dehydration to the α-keto-*N*-acylimine **3**. Molecular models of **3** show that it can adopt a conformation appropriate for stereospecific internal attack of the C(16)-hydroxyl upon the *N*-acylimine carbon,[4] which would lead to the hemimacrolactam **4** after C(14)-ketone reduction and *O*-methylation with *S*-adenosylmethionine. Models further show that the C(7)-hydroxyl of **4** can readily approach the C(22)-position of the dienone by a trajectory suitable for acid-catalyzed Michael ring closure, a process that could later be followed by stereospecific enol protonation at C(21). To experimentally test this simple biogenetic hypothesis, by both chemical and biological means, we embarked on an asymmetric total synthesis of the putative halichomycin precursor **1**, and now report a synthetic strategy for the key AB-carbon backbone intermediate **8** needed for this venture.

Scheme 1. A Biosynthetic Proposal for Ring Formation in the Antitumor Agent Halichomycin



We envisaged constructing the C(18)−C(24) dienone sector of **1** through a Kishi−Nozaki−Hiyama−Takai coupling[5] between **6** and **7**, followed by oxidation (Scheme 2).

Scheme 2. Retrosynthetic Planning for Halichomycin



Aldehyde **6** would be derived from **8** by ammonolysis, *O*-debenzylation, and primary alcohol oxidation. A double

(3) It is well-known that primary amides add reversibly to the carbonyl group of aldehydes and ketones in acidic, neutral, or basic media. In fact, for many aldehydes, the resulting *N*-acylcarbinolamines are quite stable and isolable. According to Weinreb, the equilibria of such additions usually lies toward the *N*-acylcarbinolamine to the extent of 5 kcal/mol. See: Auerbach, J.; Zamore, M.; Weinreb, S. M. *J. Org. Chem.* **1976**, *41*, 725. For reviews on this topic, see: (a) Challis, B. C.; Challis, J. A. *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon: Oxford, 1979; Vol. 2, Chapter 9.9, p 957. (b) Zaugg, H. E.; Martin, W. B. *Org. React.* **1965**, *14*, 52. For other pertinent papers on this topic, see: (a) Vail, S. L.; Moran, C. M.; Barker R. H. *J. Org. Chem.* **1965**, *30*, 1195. (b) Feuer, H.; Lynch, U. E. *J. Am. Chem. Soc.* **1953**, *75*, 5027. (c) Overkleeft, H. S.; van Wittenberg, J.; Pandit, U. K. *Tetrahedron* **1994**, *50*, 4215.

(4) The addition of alcohols to *N*-acylimines derived from *N*-acylcarbinolamines is well precedented in the chemical literature. See: Zaugg, H. E.; Martin, W. B. *Org. React.* **1965**, *14*, 52.

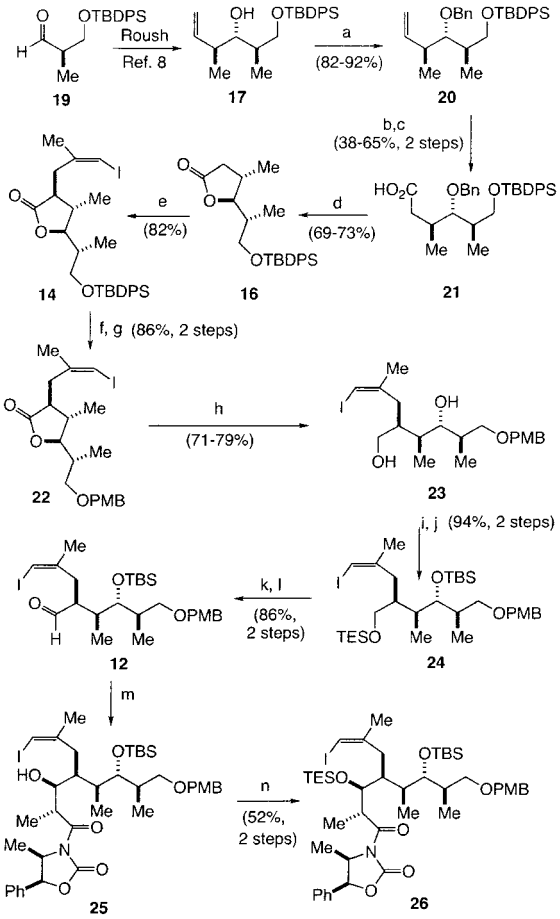
(5) Review: Cintas, P. *Synthesis* **1992**, 248.

Wittig sequence involving aldehyde **10** and ylide **11** was envisioned for stereospecific elaboration of the dienoate array in **8**, while a Stille reaction[6] with β-stannylenone **9** was planned for fashioning the dienone perimeter. The *syn*-relationship between the C(6) and C(7) stereocenters of **10** could potentially be controlled through an Evans asymmetric aldol reaction[7] between **12** and **13**, while a face-selective alkylation reaction between **15** and **16** could set the C(8) stereocenter. We imagined deriving lactone **16** from the known homoallylic alcohol **17**, which would be available from the Roush asymmetric crotylboration of **19** with (*R*,*R*)-**18**.[8]

The synthesis of vinyl iodide **26** is shown in Scheme 3. *O*-Benzylation of the *anti*-alcohol **17** with *O*-benzyl trichloroacetimidate and catalytic TfOH[9] procured the doubly protected alkene **20**, which was converted to the primary alcohol by rhodium-catalyzed hydroboration[10] and oxidation. Further oxidation to acid **21** was accomplished with PDC in DMF. Hydrogenation of acid **21** over a 20% $Pd(OH)_2$ on carbon catalyst effected a clean, but rather slow, deprotection of the *O*-benzyl ether to permit in situ butyrolactonization. The stereospecific *C*-alkylation of butyrolactone **16** was achieved by low-temperature enolization with LDA and addition of the allylic bromide **15**.[11] The total stereocontrol observed in this reaction is attributable to the stereodirecting influence of the C(25)-Me group (which hinders *syn*-approach of the bulky electrophile to the enolate) and preservation of the reaction temperature at −78 °C throughout. In this regard, premature warming markedly lowered the selectivity levels that could be attained. The configuration of the newly induced stereocenter in **14** was verified by NOE analysis. An OPMB for OTBDPS protecting group interchange was now effected to permit C(19)−C(24) side-chain elaboration later on in the synthesis; this delivered the PMB-ether **22**.

Having fulfilled its role in stereospecific attachment of the C(8)-methallyl unit, the butyrolactone ring of **22** was reductively ring-opened with lithium borohydride and diol **23** differentially *O*-silylated to obtain **24**. Selective cleavage of the primary OTES group now permitted oxidation to the aldehyde **12** with TPAP/NMO.[12] The Evans aldol addition between **12** and **13** required the use of a significant excess of the propionimide enolate (4 equiv) to drive the reaction to completion, which made the purification of **25** exceedingly difficult. The subsequent *O*-triethylsilylation reaction remedied this situation, allowing the protected aldol adduct **26** to be isolated pure by simple flash chromatography. Significantly, no other aldol adducts were observed in the above addition. The structure of **26** was verified by X-ray crystallography.

Scheme 3. Synthesis of Vinyl Iodide **26**[a]



[a] Reagents and conditions: (a) $BnOC(NH)CCl_3$ (1 equiv), TfOH (0.05 equiv), CH_2Cl_2 (0.4 M), rt, 3.5 h; (b) catecholborane (1.1 equiv), $(Ph_3P)_3RhCl$ (0.05 equiv), THF (0.2 M), 0 °C for 5 min, then rt for 14 h; 27.5% H_2O_2/MeOH/2N NaOH, 0 °C, 2 h; (c) PDC (7 equiv), DMF (0.3 M), rt, 48 h; (d) H_2, 20% $Pd(OH)_2$/C, MeOH (0.4 M), 3−7 d; (e) **16**, $LiN(Pr\text{-}i)_2$ (1.3 equiv), THF−HMPA (10:1) (0.2 M), −78 °C, 1 h, then add **15** (1.2 equiv) in THF at −78 °C dropwise and stir at −78 °C for 2 h; (f) 40% aqueous HF/THF/MeCN (1:2:1) (concentration of **14** ca. 0.09 M), rt, 24−27 h; (g) $PMBOC(NH)CCl_3$ (2 equiv), PPTS (0.5 equiv), CH_2Cl_2 (0.1 M), rt, 7 h; (h) $LiBH_4$ (10 equiv), THF/MeOH (100:1) (0.2 M), Δ, 3 h; (i) **23**, Imid (2.2 equiv), DMF (concentration of **23**, ca. 0.1 M), 0 °C, add Et_3SiCl (1.2 equiv) over 5 min, then stir at 0 °C for 1.5 h; (j) 2,6-lutidine (20 equiv), CH_2Cl_2, −50 °C, add TBSOTf (3 equiv) over 5 min, then stir for 0.5 h; (k) 2% aqueous HF, THF/MeCN (1:1), rt, 1.5 h; (l) TPAP (0.05 equiv), NMO (2 equiv), CH_2Cl_2 (0.01 M), 4A MS, rt, 40 min; (m) **13** (4 equiv), $(n\text{-}Bu)_2BOTf$ (4 equiv), Et_3N (4.2 equiv), CH_2Cl_2, 0 °C, 0.5 h, then cool to −78 °C, add **12** (1 equiv) in CH_2Cl_2, stir for 35 min, then warm to rt for 1 h; (n) add Et_3SiOTf (5 equiv) over 5 min to **25** in CH_2Cl_2 (0.02M), 2,6-lutidine (20 equiv), at −50 °C, then warm to rt for 45 min.

Attention now shifted toward stereospecific elaboration of the two diene arrays present within **8** (Scheme 4).

(6) (a) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1998**, *50*, 1.

(7) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

(8) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6355.

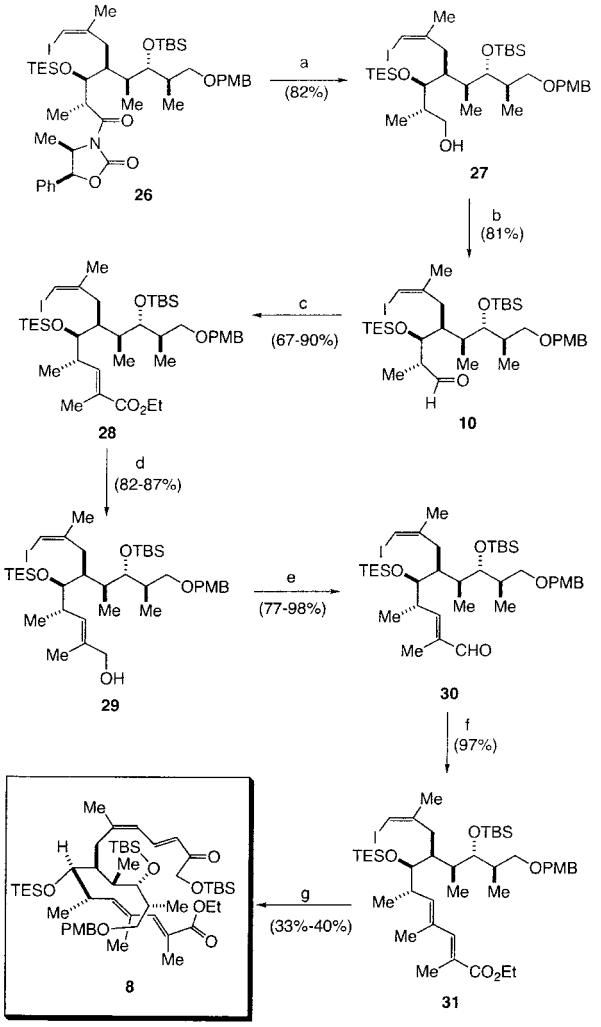
(9) Wessel, H.-P.; Iverson, T.; Bundle, D. R. *J. Chem. Soc., Perkin. Trans. 1* **1985**, 2247.

(10) (a) Mannig, D.; Noth, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 878. (b) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 6917. (c) Evans, D. A.; Fu, G. *J. Org. Chem.* **1990**, *55*, 2280.

(11) Bromide **15** was synthesized in 72% yield from (*Z*)-3-iodo-2-methylpropen-1-ol (prepared according to Rayner, C. M.; Astles, P. C.; Paquette, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 3926) after treatment with Ph_3P (1.5 equiv) and NBS (1.3 equiv) in CH_2Cl_2 (0.2 M) at 0 °C for 1.5 h.

(12) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

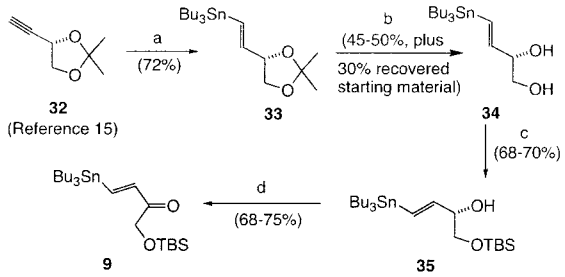
Scheme 4. Synthesis of **8**[a]



[a] Reagents and conditions: (a) add $LiBH_4$ (10 equiv) in one portion to **26** in Et_2O/H_2O (160:1) (0.02 M), at 0 °C, then warm to rt and stir for 1.5 h; (b) TPAP (0.1 equiv), NMO (2 equiv), CH_2Cl_2 (0.02 M), 4A MS, rt, 1 h 10 min; (c) **11** (10 equiv), PhMe (0.01 M), Δ, 5 h; (d) *i*-Bu_2AlH (2.2 equiv), PhMe (0.048M), −78 °C, 0.5 h; (e) MnO_2 (20 equiv), $CHCl_3$ (0.02 M), Δ, 6 h; (f) **11** (15 equiv), PhMe (0.01 M), Δ, 16 h; (g) **9** (2 equiv), $(CH_3CN)_2PdCl_2$ (0.5 equiv), *i*-Pr_2NEt (10 equiv), DMF (0.01 M), 5 h.

Reductive removal[13] of the oxazolidinone unit from **26** with $LiBH_4$ furnished the primary alcohol **27** in excellent yield (82%). A TPAP oxidation[12] converted **27** into the aldehyde **10**, which reacted readily with **11** in PhMe at reflux to give **28** with complete stereocontrol.[14] DIBAL reduction to **29** and allylic alcohol oxidation with MnO_2 generated the aldehyde **30**, which willingly engaged in a second Wittig reaction with **11**. The (*E*,*E*)-dienoate **31** was formed as a single geometrical isomer in 97% yield. The dienone unit was fashioned by a Stille coupling[6] between **31** and **9** (for the preparation of **9**, see Scheme 5). The desired tetraene **8** was isolated as a single geometrical isomer in 33−40% yield, but was formed alongside a significant quantity of the stannane homocoupling product. Work is currently underway to improve the yield of **8** and to reduce the amount of dimerization that is occurring with stannylenone **9**. Future reports will deal with the synthesis of isotopically labeled **1** from **8**, and with our chemical and biological efforts to convert **1** into halichomycin itself.

Scheme 5. Synthesis of Vinylstannane **9**[a]



[a] Reagents and conditions: (a) Bu_3SnH (1.2 equiv), AIBN (0.05 equiv), PhMe (0.3 M), Δ, 24 h; (b) PPTS (1.5 equiv), MeOH (0.3 M), rt, 24 h; (c) TBSCl (1 equiv) (0.03 M in CH_2Cl_2) added dropwise to **34** (1 equiv) and imidazole (2 equiv) in CH_2Cl_2 (concentration of **34** ca. 0.26 M) at 0 °C; stir 10 min; (d) TPAP (0.05 equiv), NMO (2.2 equiv), 4A MS, CH_2Cl_2 (0.26 M), rt, 1 h.

Acknowledgment. We thank the EPSRC (Project Grant GR/M63690), Pfizer (EPSRC INDUSTRIAL CASE QUOTA studentship to M.L.F.C.), and the BBSRC (M.F.) for financial support and the ULIRS for HRMS.

Supporting Information Available: High-resolution mass spectra, 500 MHz ^1H and 125 MHz ^{13}C NMR spectra of all new compounds, and X-ray data for **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) For an alternative synthetic strategy to the C(1)−C(7)-segment of halichomycin which also utilises ylide **11**, see: McGann, E. E.; Janes, G.; Ortsey, C.; Wood, J. L. *Tetrahedron Lett.* **1997**, *38*, 303.

(15) Jiang, B.; Ma, P. *Synth. Comm.* **1995**, *25*, 3641.