ORGANIC LETTERS

2000
Vol. 2, No. 5
679−682

A Modular Approach to Marine Macrolide Construction. 3. Enantioselective Synthesis of the C1–C28 Sector of Spongistatin 1 (Altohyrtin A)

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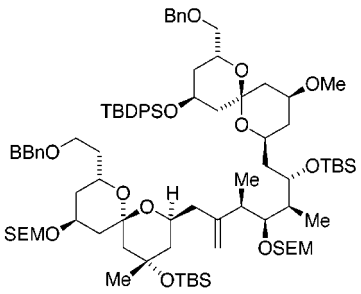
Received January 5, 2000

ABSTRACT



A completely stereocontrolled approach to assembly of the major C1–C28 subunit of spongistatin 1 (altohyrtin A) is described. Key steps included the control of two asymmetric aldols by means of Fujita–Nagao (chiral *N*-acyl-1,3-thiazolidine-2-thione auxiliary) and Mukaiyama (BF_3·OEt_2-promoted enolsilane coupling) protocols in complex settings.

The spongipyran marine macrolides, designated as the spongistatins,[1] altohyrtins,[2] and cinachyrolides[3] by their independent discoverers, are currently the most potent antineoplastic agents identified. The remarkable subnanomolar cytotoxicity exhibited by these sponge metabolites against several cancer cell lines,[4] in combination with their very limited supply, has prompted several groups to undertake synthetic activity in this area.[5−18] Our early efforts have culminated in the concise stereocontrolled construction of both the C1−C12 (AB)[19] and C17−C28 (CD) spiroacetal sectors.[20] We now describe an efficient means for tethering

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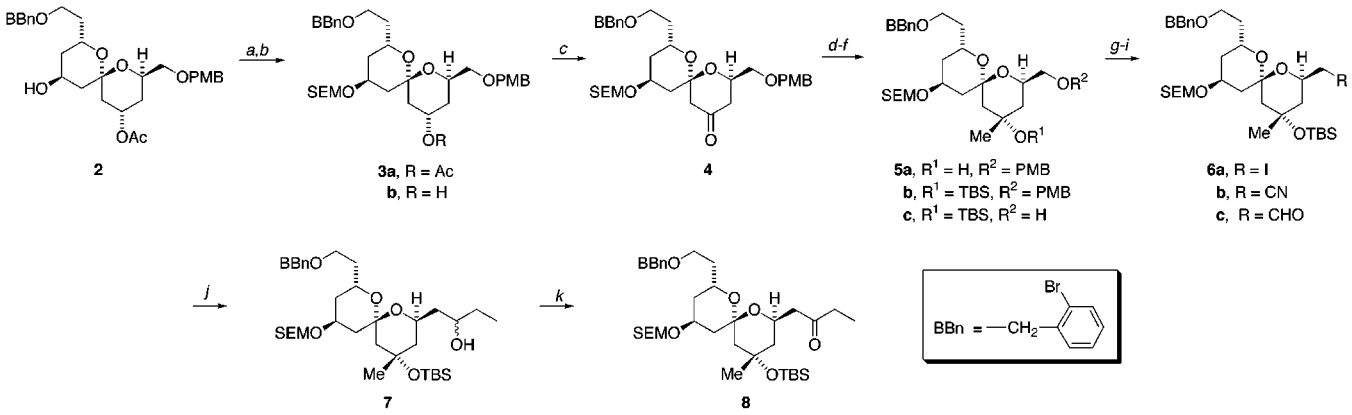
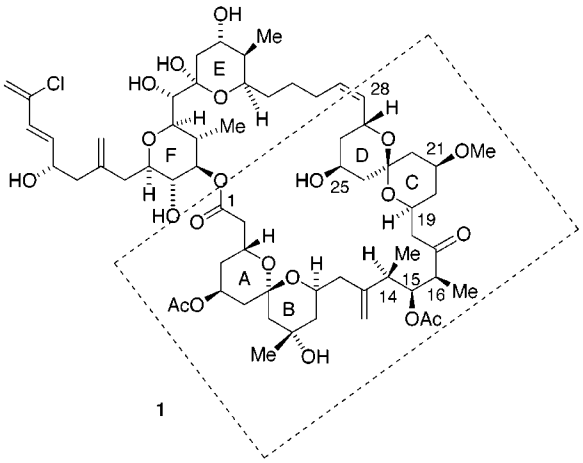
10.1021/ol0000049 CCC: $19.00
Published on Web 02/03/2000

Scheme 1



[a] SEMCl, (*i*-Pr)$_2$NEt, Bu$_4$NI, THF, rt, 24 h (95%). [b] (*i*-Bu)$_2$AlH, CH_2Cl_2, −78 °C, 45 min (98%). [c] TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 1 h (96%). [d] MeMgBr, THF, Et_2O, −78 to 0 °C, 2.5 h (93%). [e] TBSOTf, (*i*-Pr)$_2$NEt, CH_2Cl_2, −40 to 0 °C (93%). [f] DDQ, CH_2Cl_2−H_2O (16:1), rt, 1 h (90%). [g] I_2, PPh_3, imidazole, benzene, rt, 1.5 h (82%). [h] KCN, DMF, 65 °C, 36 h (quant). [i] (*i*-Pr)$_2$AlH, CH_2Cl_2, −78 °C, 20 min. [j] EtMgBr, Et_2O, −78 to 0 °C, 3 h (74% for two steps). [k] TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 9 h (99%).

these structurally complex building blocks via an enantioselective scheme designed to ultimately access spongistatin 1 (**1**, corresponds to altohyrtin A).



1

One phase of the convergent assembly began with **2**, an alcohol readily obtained via the thermodynamically controlled spirocyclization described previously[19] (Scheme 1). The remaining hydroxyl group was transformed into its SEM ether[21]in advance of Dibal-H reduction to give **3b**. Subsequent perruthenate oxidation[22] gave ketone **4**, which responded to the action of methylmagnesium bromide very predominantly by way of equatorial attack to furnish **5a** in 93% yield. The resulting axial disposition and tertiary nature of the OH substituent in this intermediate required recourse to *tert*-butyldimethylsilyl triflate[23] for protection purposes. With **5b** in hand, the acquisition of alcohol **5c** proceeded without event. Homologation of the side chain in **5c** began with cyanide ion displacement on iodide **6a**. To skirt potential complications arising from β-elimination within **6b**, this nitrile was directly transformed into ethyl ketone **8** by sequential low-temperature Dibal-H reduction, 1,2-addition

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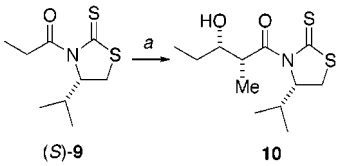
of ethylmagnesium bromide to the resulting aldehyde, and perruthenate oxidation.

Chiral *N*-acyl-1,3-thiazolidine-2-thiones have seen limited use for controlling asymmetric induction in aldol condensations.[24] When employed with tin(II) triflate and *N*-ethylpiperidine as promoters, *Z*-enolates are generated,[25] chelated transition states are kinetically favored,[26] and syn products appear to be formed with excellent diastereoselectivity.[25] To gauge the applicability of the Fujita−Nagao protocol in the present context, (*S*)-**9** was condensed with propionaldehyde and afforded **10** in 95% yield (Scheme 2). The absolute

Scheme 2



(*S*)-**9** **10**

[a] $Sn(OTf)_2$, *N*-ethylpiperidine, CH_2Cl_2, −78 °C, 2 h; CH_3CH_2CHO, −78 °C, 1 h (95%).

configuration of **10** was ascertained by X-ray crystallographic analysis (Figure 1).

Oxidative cleavage of the double bond in **11**,[20] best accomplished under Lemieux−Johnson conditions,[27] furnished aldehyde **12** (Scheme 3). Union of **12** with (*S*)-**9** led to highly stereocontrolled introduction of two new stereogenic centers under the absolute control of the 1,3-thiazolidine-2-thione as previously demonstrated. The transformation of **13** into the Weinreb amide[28] occurred in 97% yield without any detectable epimerization. Following formation of the TBS ether, reduction to give aldehyde **14** proceeded quantitatively upon treatment with Dibal-H in THF at −78 °C. At this juncture, recourse was made to a second aldol reaction, now involving **14**, to establish absolute configuration properly at C14 and C15. To this end, ketone **8** was first converted to its *Z*-enolsilane according to the Masamune protocol.[29] This regio- and stereoselective transformation led to **15** (Scheme 4). Our expectation was that coupling of **14**

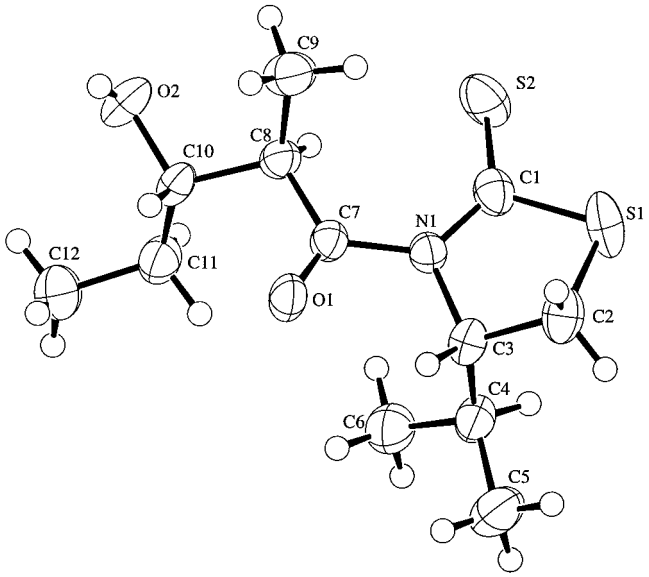
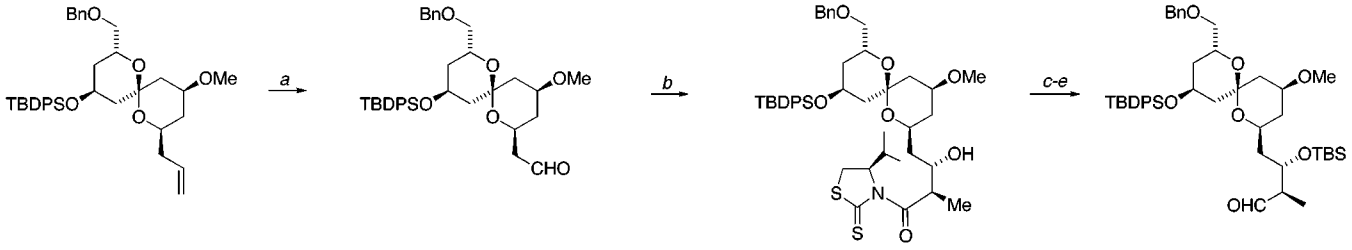


Figure 1. ORTEP diagram of **10**.

to **15** under catalysis by boron trifluoride etherate at low temperature would proceed in a *syn*-stereoselective manner to set the substituents at C15 and C16 into an anti arrangement. Related processes are recognized to exhibit a tendency to afford anti-Felkin products predominantly via synclinal transition states.[30] In the present instance, the Mukaiyama aldol reaction proceeded in a highly controlled manner to deliver **16** as the only detectable product. The assignment of stereochemistry was addressed by spectroscopic analysis of **16** in C_6D_6 solution at 500 MHz. The syn relationship between H14 (δ 2.88) and H15 (δ 4.22) was readily deduced on the basis of the low magnitude (2.8 Hz) of the corresponding coupling constant. Similarly, the significant spin−spin interaction between H15 and H16 (9.2 Hz) unequivocally defined their anti relationship. The ensuing olefination[31] of ketone **17** with the Tebbe reagent[32] conveniently provided the targeted molecule **18**.

A convenient, highly enantioselective route to a major portion of **1** has been brought to successful fruition. Our

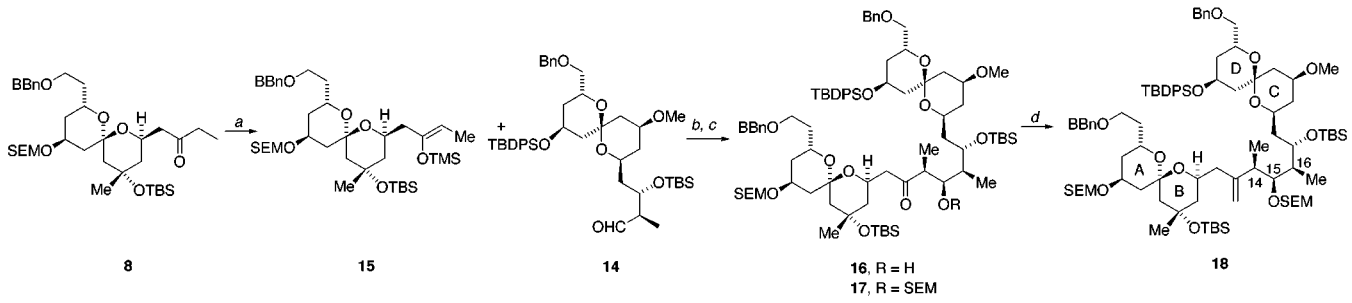
Scheme 3



11 **12** **13** **14**

[a] OsO_4, NMO, THF, H_2O, rt, 50 min; $NaIO_4$, rt, 1.5 h (87%). [b] (*S*)-9, $Sn(OTf)_2$, *N*-ethylpiperidine, CH_2Cl_2, −78 °C, 2 h 15 min; **12**, −78 °C, 1 h (96%). [c] Me_3Al in hexanes, MeNH(OMe)·HCl, CH_2Cl_2, THF, −5 °C, 1 h 50 min (95%). [d] TBSOTf, 2,6-lutidine, CH_2Cl_2, −20 °C, 1 h 15 min (88%). [e] $(i\text{-Bu})_2AlH$, THF, −78 °C, 15 min (quant).

Scheme 4



8 **15** **14** **16**, R = H; **17**, R = SEM **18**

[a] $(PhMe_2Si)_2NLi$, THF, −78 °C, 1 h; TMSCl, −78 °C to rt, 6 h (35%; 100% based on recovered **8**). [b] $BF_3{\cdot}Et_2O$, toluene, −78 °C, 1.5 h (67%). [c] SEMCl, $(i\text{-}Pr)_2NEt$, Bu_4NI, THF, rt, 2 days (53%). [d] $Cp_2Ti(Cl)CH_2AlMe_2$, THF, −78 °C to rt, 6 h (23%, 88% based on recovered **17**).

synthetic pathway exploits the very utilitarian capability of tin enolates derived from *N*-acyl-1,3-thiazolidine-2-thiones to control aldol stereoselectivity with minimal regard for matched/mismatched pairing, as well as the many advantages associated with Lewis acid-promoted C−C bond formation between aldehydes and stereodefined enolsilanes. Completion of the synthesis of **1** is being actively pursued.[33]

Acknowledgment. We thank the Eli Lilly Company for financial support.

Supporting Information Available: Tables of X-ray crystal data, bond lengths and angles, and positional and anisotropic displacement parameters for **10**. This material is available free of charge via the Internet at http://pubs.acs.org. This information can also be obtained on request from The Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

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