protecting group, treatment of **22** with dimethyldioxirane generates presumably an epoxide of type **9** (X = H, OPiv; see Scheme 1). Following suitable bond reorganizations, passing through presumed diketone type **10**, the pyranose derivative **23** was in hand. The predicted stereoselective nucleophilic methylation of the keto function was achieved with methyllithium, giving rise to **24**. On treatment of the latter compound with acetic anhydride, we took advantage of the fact that the masked secondary alcohol at C8 could be selectively acetylated. This paved the way for cyclization of the tertiary alcohol (corresponding to C7 of the future eleutheside) into the carbonyl group of the enone of the open form, leading to formation of compound **25**. All structural assignments asserted thus far, were corroborated by an X-ray crystallographic determination of **25** (Figure 1).[12] Compound **25** has been

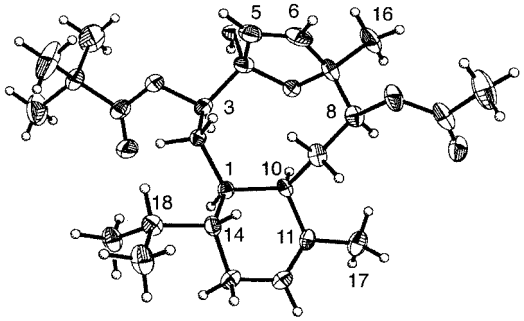

Figure 1. Crystal structure of **25**.

advanced in several directions, including the generation of the flexible platform compound, ketone **26**.

In summary, the novel chemical steps of particular interest are: 1. the elongation and fragmentation of cyclobutanone **14**, 2. the viability of 2-lithio-5-bromofuran as a readily available and functionally differentiated furano nucleophile **7**, 3. the Nozaki–Kishi reaction creating a highly strained cyclophane (**19** → **20**), and 4. the oxidative and ring–chain tautomerism manipulations leading to the differentiated eleutheside **25**. Preparations of the natural products and congeners for SAR purposes are well underway.[13,14]

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[1] D. J. Faulkner *Nat. Prod. Rep.* **1996**, *13*, 75.
[2] a) W. H. Fenical, P. R. Jensen, T. Lindel (UC), US Patent No. 5473057, **1995** [*Chem. Abstr.* **1996**, *102*, 194297z]; b) T. Lindel, W. H. Fenical, P. R. Jensen, B. H. Long, A. M. Casazza, J. Carboni, C. R. Fairchild, *J. Am. Chem. Soc.* **1997**, *119*, 8744.
[3] a) M. D'Ambrosio, A. Guerriero, F. Pietra, *Helv. Chim. Acta* **1987**, *70*, 2019; b) *ibid.* **1988**, *71*, 964.
[4] a) O. Kennard, D. G. Watson, *Tetrahedron Lett.* **1968**, 2879; b) Y. Lin, C. A. Bowley, D. J. Faulkner, *Tetrahedron* **1993**, *49*, 7977.
[5] D. T. Hung, T. F. Jamison, S. L. Schreiber, *Chem. Biol.* **1996**, *3*, 623.
[6] (*R*)-(−)-α-Phellandrene **4** is available from Fluka Chemical Corp.
[7] For preparation see: M. A. Keegstra, A. J. A. Klomp, L. Brandsma, *Synth. Commun.* **1990**, *20*, 3371. For use see: U. Wellmar, *J. Heterocycl. Chem.* **1995**, *32*, 1159. For 2-iodo-5-(iodomagnesium) furan see: H. Gilman, G. F. Wright, *J. Am. Chem. Soc.* **1933**, *55*, 3302. For 2-bromo-5-lithiothiophene see: M.-J. Shiao, L.-H. Shih, W.-L. Chia, T.-Y. Chau, *Heterocycles* **1991**, *32*, 2111.
[8] For a ketene cycloaddition with a cyclohexadiene see the following: a) M. L. Greenlee, *J. Am. Chem. Soc.* **1981**, *103*, 2425. For a diastereoselective ketene cycloaddition see: A. Kanazawa, P. Delair, M. Pourashraf, A. E. Greene, *J. Chem. Soc. Perkin Trans. 1* **1997**, 1911.
[9] B. M. Trost, M. Preckel, L. M. Leichter, *J. Am. Chem. Soc.* **1975**, *97*, 2224.
[10] Compound **17a** (in contrast to the desired **17**) undergoes partial lactonization during workup. This lactone can be converted back to **17a**. Epimer **17a** can be recycled to the synthetic mainstream by oxidation, followed by reduction of the common ketone. These adjustments to the main synthetic stream will be reported in the full paper.
[11] For a review of the Nozaki–Kishi reaction see: P. Cintas, *Synthesis* **1992**, 248. See also: M. Eckhardt, R. Brückner, *Liebigs Ann.* **1996**, 473.
[12] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-100974. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ (fax: int. code +(44) 1223 336-033; e-mail: deposit@ccdc.cam.ac.uk). No claims, regarding absolute stereochemistry, are based on this data.
[13] Sarcodictyin and eleutherobin were recently synthesized: K. C. Nicolaou, J.-Y. Xu, S. Kim, T. Ohshima, S. Hosokawa, J. Pfefferkorn, *J. Am. Chem. Soc.* **1997**, *119*, 11353; K. C. Nicolaou, F. van Delft, T. Ohshima, D. Vourloumis, J. Xu, S. Hosokawa, J. Pfefferkorn, S. Kim, T. Li, *Angew. Chem.* **1997**, *109*, 2630; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2520.
[14] Note added in proof: We have recently completed a synthesis of eleutherobin: X.-T. Chen, B. Zhou, S. K. Bhattacharya, C. E. Gutteridge, T. R. R. Pettus, S. J. Danishefsky, *Angew. Chem.* and *Angew. Chem. Int. Ed.*, in press.

Total Synthesis of Altohyrtin A (Spongistatin 1): Part 1**

Jiasheng Guo, Kevin J. Duffy, Kirk L. Stevens, Peter I. Dalko, Rebecca M. Roth, Matthew M. Hayward, and Yoshito Kishi*

In 1993 three groups independently reported the isolation and structural elucidation of a new class of macrolides (spongipyran) derived from marine sponges of the genus *Spongia*[1] and *Spirastrella*[2] (spongistatins 1 through 9), *Cinachyra*[3] (cinachyrolide A), and *Hyrtios*[4] (altohyrtins A–C). These compounds displayed extraordinarily potent cytotoxicity against a wide variety of cancer cell lines.[5, 6] Structurally, spongistatin 1 appeared to be identical to altohyrtin A and spongistatin 4 to cinachyrolide A, although no definitive proof had been previously presented. The Kitagawa group has proposed the complete structure of altohyrtin A[4c] to be that shown in structure **1**. However, this structure is in conflict with the relative configuration proposed by the Pettit[2b] and Fusetani[3] groups. In this and the following communication, we report the first total synthesis of altohyr-

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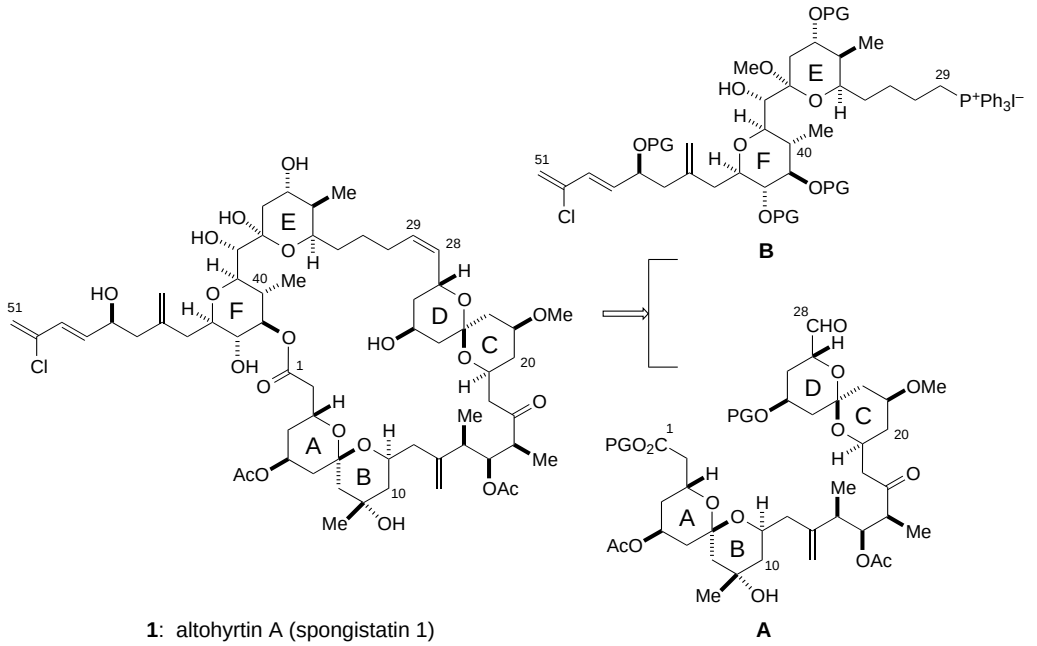

Figure 1. Retrosynthesis of altohyrtin A (spongistatin 1). PG = protecting group.

tin A (spongistatin 1), which firmly establishes the relative and absolute configuration proposed by Kitagawa.

All of the members in this class of natural products contain a 51-carbon chain, 6 pyran rings, and a 42-membered lactone ring. In addition, the most potent congeners (spongistatins 1, 4, 5, and 9)[5, 6] contain the novel chlorodiene functionality, which had neither been seen in a natural product nor synthesized before. We chose altohyrtin A (spongistatin 1) as our synthetic target, due to its historical position in this class of natural products, the availability of spectroscopic data from two independent research groups, and finally its position as the most cytotoxic congener. Several synthetic approaches to the spongipyran class of natural products have been reported,[7] and most recently a beautiful total synthesis of altohyrtin C (spongistatin 2) has been completed by Evans et al.[8]

Upon close examination of the spectroscopic data on spongipyrans disclosed by the three groups, it became evident that the correct relative and absolute configuration of altohyrtin A was most likely that proposed by Kitagawa,[4c] and thus we chose altohyrtin A (**1**) as the target for our total synthesis.[9] In the retrosynthetic analysis, **1** was dissected into the two segments **A** and **B** which could be joined by Wittig olefination of the C29 phosphonium salt with the C28 aldehyde and subsequent macrolactonization of the C1 carboxylic acid with the C41 alcohol (Figure 1). It might be expected that, to effect the proposed macrolactonization selectively, the C41 alcohol must be differentiated from the remaining alcohols, particularly the C42 alcohol. However, we recognized the possibility that such macrolactonization might take place preferentially at the C41 alcohol under controlled conditions. Therefore, we chose to leave the C41 and C42 alcohols undifferentiated for synthetic simplicity.

Based on the precedents gained in the halichondrins[10] and the polyether antibiotic (−)-A23187[11] syntheses, **A** was envisioned to arise from the intramolecular Michael addition of enone **C** (Figure 2). Enone **C** could be realized from the

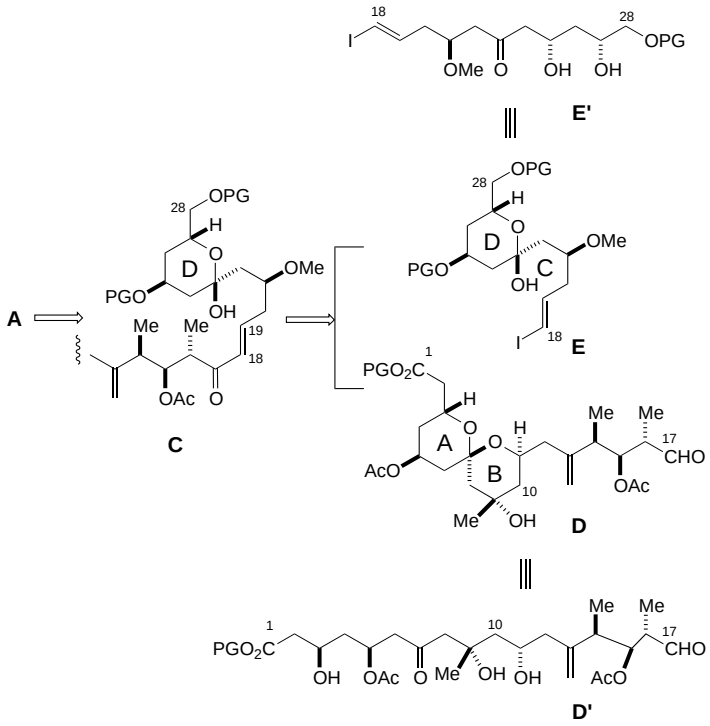

Figure 2. Retrosynthesis of the C1 – C28 fragment.

Ni^{II}/Cr^{II}-mediated coupling[12] between fragments **D** and **E**, followed by oxidation. The two building blocks **D** and **E** thus obtained should be synthetically equivalent to their open forms **D′** and **E′**. Two structural characteristics present in both **D′** and **E′** are noteworthy. A typical polypropionate structure is apparent in the C14 – C17 unit, while a 1,3-*syn*-diol structure is found repeatedly in the C3 – C5, C9 – C11, and C25 – C27 units. The synthesis of these functionalities has been studied extensively over the past few decades. We anticipated that, coupled with a well-precedented regioselective ring-opening

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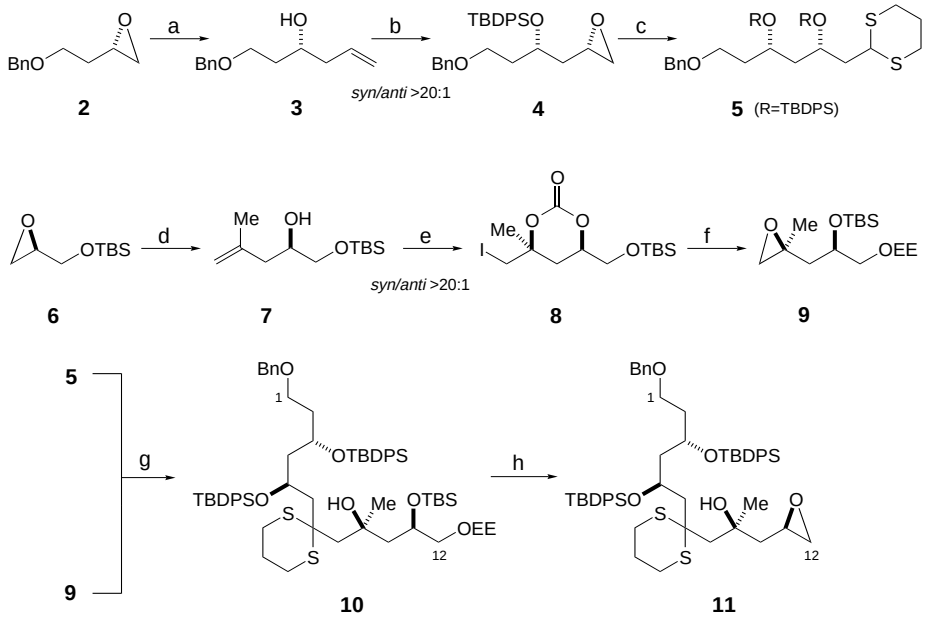
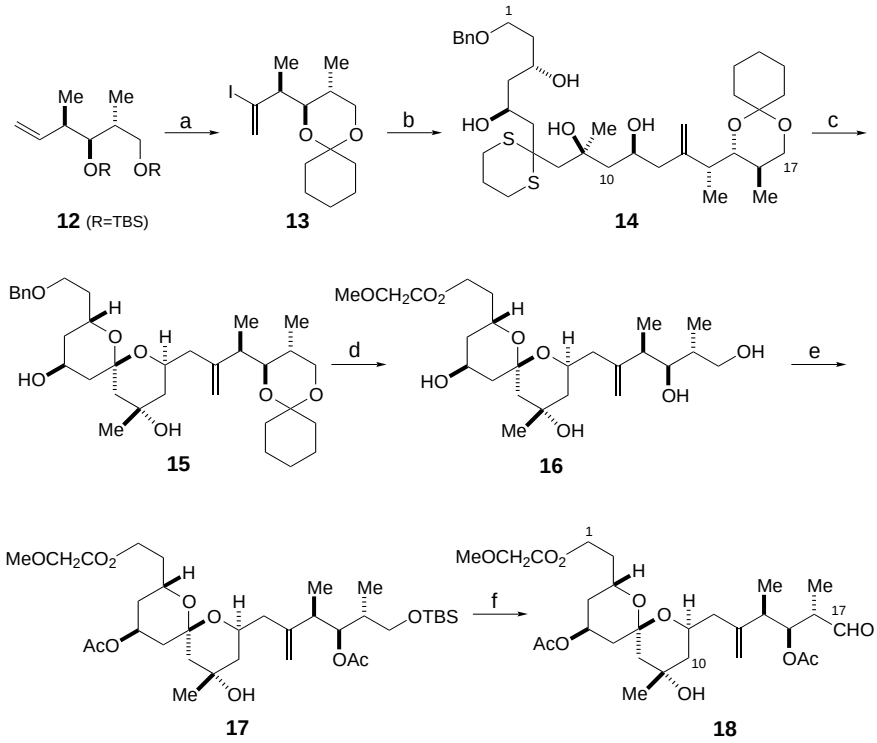
of terminal epoxides with nucleophiles, the synthesis of **D**′ and **E**′ could be achieved by a combination of these methods.

Along this line of analysis, the C1 – C12 segment was synthesized as summarized in Scheme 1.[13, 14] The two key reactions in this sequence were 1) regioselective ring-opening of terminal epoxides with vinyl cuprates and dithiane anions, and 2) stereoselective iodocarbonylation under the conditions developed by Smith et al.,[15] followed by base treatment to furnish the subsequent terminal epoxide.

The C13 – C17 segment **13** was prepared from the known alkene **12**[16] (Scheme 2). The C12 – C13 bond formation was realized by ring opening of **11** with the higher order 2-thienyl



Scheme 1. Synthesis of the C1 – C12 fragment: a) CuCN, vinyllithium, – 78°C, then **2**, – 30 →0°C, 90 %; b) *n*BuLi, Et_2O, – 78°C, BOC–ON, THF, 0 →20°C, 90 %; IBr, PhMe, – 78 →0°C; K_2CO_3, MeOH, 73 % over 2 steps; imidazole, TBDPSCl, CH_2Cl_2, 92 %; c) 1,3-dithiane, *n*BuLi, THF, – 20°C, then – 78°C, DMPU, **4**, THF, – 20°C, 97 %;[30] imidazole, TBDPSCl, CH_2Cl_2, 87 %; d) 2-bromopropene, *t*BuLi, Et_2O, – 78°C, then CuI, **6**, Et_2O, – 78 →0°C, quant.; e) *n*BuLi, Et_2O, – 78°C, BOC–ON, THF, 0 →20°C, 93 %; IBr, PhMe, – 78 →0°C, 93 %; f) HOAc/THF, 81 %; ethyl vinyl ether, CH_2Cl_2, PPTS, 96 %; K_2CO_3, 94 %; imidazole, TBSCl, 87 %; g) *t*BuONa, *n*BuLi, pentane, 0 →20°C,[31] then – 78°C, **5**, then **9**, – 78 → – 20°C, 59 %; h) PPTS, MeOH, 80 %; NaH, THF, 0°C, then Ts-im,[32] 0°C, 93 %.



Scheme 2. Synthesis of the C1 – C17 fragment: a) NMO, OsO_4,[33] acetone/H_2O; $Pb(OAc)_4$, benzene, 81 % over 2 steps; DAMP,[34] *t*BuOK, THF, – 78°C, then aldehyde, 96 %; *B*-I-9-BBN,[35] pentane, – 20°C, 88 %; HF · py, CH_3CN, 91 %; 1,1-dimethoxycyclohexane, PPTS, 97 %; b) **13**, *t*BuLi, THF, – 78°C, then lithium 2-thienylcyanocuprate, then **11**, THF, – 78 →0°C, 72 %; TBAF, 0°C, quant.; c) $CaCO_3$, NIS, CH_3CN, 0°C, then PPTS, CH_3CN, 68 %; d) Li/NH_3, THF, – 78°C, quant.; methoxyacetyl chloride, CH_2Cl_2/py, 93 %; PPTS, MeOH, 50°C, 87 %; e) Et_3N, TBSCl, DMAP, CH_2Cl_2, 94 %; py, Ac_2O, DMAP, 96 %; f) HF · py, CH_3CN, 95 %; Dess – Martin periodinane, CH_2Cl_2, 91 %.

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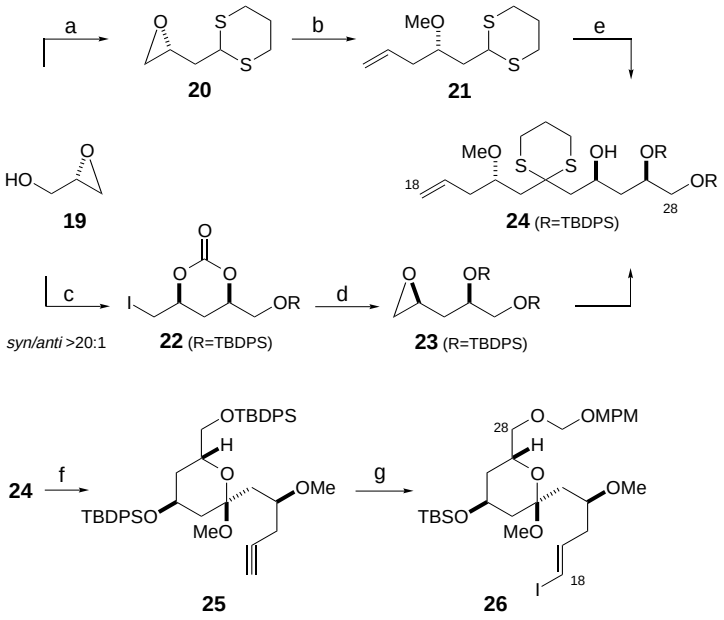
cyanocuprate[17] derived from **13**, to yield the diol. After cleavage of the silyl protecting groups, **14** was subjected to NIS-induced dithiane deprotection to form the single spiroketal **15** in good overall yield. Based on literature precedent,[18] we anticipated spiroketal formation to be stereoselective in the desired sense; indeed, NOE experiments (NOE = nuclear Overhauser enhancement) confirmed this configuration at the spirocenter. By routine synthetic operations the protecting groups of alcohols in **15** were then adjusted resulting in tetraol **16**. The protecting groups at the C1 and C17 primary alcohols were differentiated, and the C9 tertiary alcohol was left unprotected. Since the requisite C5 and C15 acetates were compatible with the remaining synthetic operations, they were installed at this juncture.[19] The C15 acetyl group was found to migrate readily to the C17 primary alcohol once the TBS protecting group was removed. Therefore, the C17 alcohol generated from **17** was immediately subjected without purification to Dess–Martin oxidation[20] to furnish aldehyde **18**.

Scheme 3 summarizes the synthesis of the *trans* vinyl iodide **26**.[21] The key reactions used in this sequence were fundamentally the same as those described for the synthesis of the C1–C17 segment. However, several comments are in order.



Scheme 3. Synthesis of the C18–C28 fragment: a) Et_3N, TBSCl, DMAP, CH_2Cl_2, 90%; 1,3-dithiane, *n*BuLi, THF, −20°C, then DMPU, then epoxide, THF, −78 → −20°C, 83%; TBAF, THF, quant.; NaH, THF, 0°C, Ts-im, 0°C, 79%; b) CuCN, vinyllithium, −78°C, then **20**, THF, −20 → 0°C, 85%; NaH, MeI, THF, 0°C, 90%; c) Et_3N, TBDPSCl, DMAP, CH_2Cl_2, 90%; CuCN, vinyllithium, −78°C, then epoxide, Et_2O, −30 → 0°C, 92%; *n*BuLi, Et_2O, BOC–ON, THF, −78 → 20°C, 96%; IBr, PhMe, −78 → 0°C, 78%; d) K_2CO_3, MeOH, 78%; imidazole, TBDPSCl, CH_2Cl_2, 91%; e) *t*BuONa, *n*BuLi, pentane, 0 → 20°C, then −78°C, **21**, THF, −78°C, then **23**, THF, −78 → −20°C, 54% and 44% recovered **23**; f) TBAF, THF, 0°C, 92%; Et_3N, TBDPSCl, DMAP, CH_2Cl_2, 72%; NIS, $CaCO_3$, MeOH, 0°C, 78%; imidazole, TBDPSCl, CH_2Cl_2, 86%; NMO, OsO_4, acetone/H_2O; $NaIO_4$, MeOH/(pH 7 phosphate buffer), 0 → 20°C; DAMP, *t*BuOK, THF, −78°C, then aldehyde, THF, −78°C, 79% over 3 steps; g) nBu_3SnH, AIBN, toluene, 105°C, 67%; $CaCO_3$, NIS, THF, quant.; TBAF, THF, 92%; iPr_2NEt, $MPMOCH_2Cl$,[36] CH_2Cl_2, 98%; TBAF, THF, quant.; imidazole, TBSCl, CH_2Cl_2, 99%.

First, while ring-opening of **20** was accomplished with the anion of TMS-acetylene allowing earlier incorporation of the alkyne moiety, clean lithiation of the resultant dithiane proved difficult. Second, deprotection of the dithiane group (step f) resulted in a single methyl ketal, whose configuration was tentatively assigned as indicated but was not established experimentally. Third, the hydrostannylation of **25**, followed by NIS treatment, yielded mainly the expected product, along with a small amount of its regio- and stereoisomers. Finally, the C25 TBDPS protecting group was required for efficient synthesis of **25** but the final deprotection to form altohyrtin A (**1**) necessitated substitution to the more labile TBS protecting group.

The completion of the synthesis of **32** is illustrated in Scheme 4. The Ni^{II}/Cr^{II}-mediated coupling[12] of **26** with **18** proceeded smoothly to yield the two expected allylic alcohols, which were oxidized to α,β-unsaturated ketone **27**. After hydrolysis to the C23 hemiketal, the crucial intramolecular Michael cyclization was effected with Triton-B to furnish spiroketal **28** with concomitant deprotection of the C1 methoxyacetate.[22] Out of four possible products, only one diastereomer was isolated. ROESY data on the C1 TBS ether of **28** clearly demonstrated the C19 stereocenter to be desired but the C23 spirostereocenter to be undesired.[23, 24] In light of recent work by Heathcock,[7b] the stereochemical outcome at this spirocenter was not surprising. This stereocenter was configurationally stable under acidic conditions with a protected C25 alcohol, but was expected to epimerize readily if the C25 alcohol was deprotected.[7b] Indeed, deprotection of **28** with HF · py in CH_3CN provided a separable 1:1 mixture of desired C23 diastereomer **30** and undesired **29**, which could be recycled efficiently under acidic conditions (HF · py/CH_3CN or CSA/CH_2Cl_2). Reprotection of the C1 and C25 alcohols with TBSOTf proceeded without compromising the integrity of C23 spiroketal stereocenter.

NMR (NOE) data on the C1 TBS-ether of **31** clearly demonstrated the desired configurations at C19 and C23.[23,24] Selective deprotection of the C1 TBS group, followed by TPAP[25] oxidation, $NaClO_2$[26] oxidation, TBDPSCl protection,[27] and finally cleavage of the C28 protecting group with DDQ[28] furnished the desired product. Interestingly, a small amount of the C23 epimeric spiroketal was isolated during the DDQ deprotection step. Finally, Dess–Martin oxidation of the C28 primary alcohol furnished **32**, the ABCD unit of the target.

Using the methods disclosed in the following communication, we completed the total synthesis of the C23 epimer of altohyrtin A from intermediate **28** with the hope that the C23 stereocenter might be equilibrated to the natural configuration. Although both altohyrtin A and its C23 epimer were relatively stable under acidic conditions (HF · py/THF, CSA/CH_2Cl_2, or HCl/$CHCl_3$), there was no evidence of inversion at the C23 stereocenter.[29] This experiment demonstrated that the macrolactone prevents epimerization at the C23 position, suggesting that the correct C23 configuration must be installed prior to macrolactonization.

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