ABCD bis(spiroketal) and the completion of the althoytin C synthesis is described in the following communication.[22]

Received: October 22, 1997 [ZL10661E]
German version: Angew. Chem. 1997, 109, 2954–2957

Keywords: althoytin - antitumor agents - natural products - spongistatin - total synthesis

[4] Abbreviations: dr = diastereomer ratio; TBS = tert-butyldimethylsilyl; TES = trimethylsilyl; TMS = trimethylsilyl; DBAL = diisobutylaluminum hydride; Tr = triethyl; TIP = trifluoromethansulfonic anhydride; BN = benzyl; PPTS = pyridinium p-toluenesulfonate; CSA = camphorsulfonic acid; LDBB = di-tert-butyldibenzylidithiophosphate; DMAP = 4dimethylaminopyridine; 9-BBN = 9-borabicyclo[3.3.1]nonane; mCPBA = m-chloroperbenzoic acid; LDA = lithium diisopropylamide; HMPA = hexamethylphosphoramide trimide.
[8] S. Hanesian, Y. Quinon, Carbohydr. Res. 1989, 186, C3–C6. Addition of Bu3Sn to Cu(I) was found to be unnecessary for this transformation.
[a] Use of ethyl-1-propanol ether prevented decomposition of the acid-sensitive dihydropropyrone.
[19] The two anomers of 25 underwent methanolysis at different rates. The mixture of anomers was subjected to Zn/H2O/EtOH at room temperature, which converted the major anomer into 26 (>95:5). The minor anomer of 25 was then separated and treated with MgBr2/Et2O in refluxing MeOH to provide additional 26 (2:1). The major side product in this reaction was the enone product of sulfone elimination: D. S. Brown, S. V. Ley, S. Vile, M. Thompson, Tetrahedron 1991, 47, 1329–1342.
[20] The authors wish to thank Kevin R. Campos for performing the X-ray analysis of 27.

Enantioselective Synthesis of Althoytin C (Spongistatin 2): Fragment Assembly and Revision of the Spongistatin 2 Stereochemical Assignment**

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Dedicated to Professor Dieter Seebach and Professor Yoshio Kishi on the occasion of their 60th birthdays

With convergent syntheses of the AB[11] CD[1] and EF[2] spongipyran fragments in hand, the assembly of these subunits to the althoytin C skeleton was addressed (Figure 1). While the C4–C5 side chain had been successfully

Figure 1. Assembly of the althoytin subunits. (See ref. [4] for abbreviations.)

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[**] Financial support has been provided by the National Institutes of Health (NIH) and the National Science Foundation (NSF). The NIH BRS Shared Instrumentation Grant Program 1-S10-RR04870 and the NSF (CHE 88-14019) are acknowledged for providing NRQ facilities.
incorporated into the isolated EF bis(pyran),\textsuperscript{[3]} we planned to delay the introduction of this fragment until later in the assembly process. Since data obtained for the altolythins and spongistatin s reveal that the identity of the side-chain substituent X exhibits a significant influence on the cytotoxic potency of these molecules,\textsuperscript{[3]} we intend to develop syntheses of other side-chain analogues of these macrolides in forthcoming investigations. We report here the completion of the total synthesis of altolythrin C (spongistatin 2), which employs a diasteroselective aldol union of the AB- and CD-spiroketal subunits, a Wittig coupling of the ABCD and EF fragments, a late-stage addition of the C\textsubscript{26}–C\textsubscript{29} side chain to the fully elaborated ABCDEF system, and a regioselective macro lactonization, which exhibits fortuitous discrimination between the unprotected C\textsubscript{31} and C\textsubscript{31} diol functionalities of the F ring.

The aldol coupling of CD-spiroketal ethyl ketone \textbf{1}\textsuperscript{[1]} with AB-spiroketal aldehyde \textbf{2}\textsuperscript{[1]} was first addressed (Scheme 1).\textsuperscript{[4]}

\begin{equation}
\textbf{2a} \quad \text{dr} = 97 : 3
\end{equation}

An investigation of the intrinsic diastereofacial bias of the E boron enolate derived from \textbf{1} indicated that remote chirality on \textbf{1} would not significantly influence the stereochemical outcome of the proposed aldol union.\textsuperscript{[9]} In contrast, treatment of model aldehyde \textbf{2a} with the E boron enolate of 3-pentanone gave the corresponding Felkin \textit{anti} aldol adduct in 97:3 diastereoselectivity [Eq. (1)]; the \textit{dr} value gives the ratio of the given isomer to all other isomers.\textsuperscript{[7]} Control experiments demonstrate that \textit{E} substituted boron enolates [Eq. (2)] exhibit enhanced Felkin selectivities in additions to chiral \textit{\alpha}-substituted aldehydes relative to their unsubstituted counterparts [Eq. (3)]. This increased selectivity can be attributed to destabilization of the Felkin \textit{anti} transition state by a developing syn pentane interaction [Eq. (4)].\textsuperscript{[8]}

\begin{equation}
\textbf{2a} \quad \text{dr} = 97 : 3
\end{equation}

Ample precedent exists for establishment of the 1,2-\textit{anti} relationship between C\textsubscript{3} and C\textsubscript{16} through the use of E boron enolates,\textsuperscript{[3]} however, control of the incipient C\textsubscript{15}-hydroxyl configuration was a concern. Because each reacting partner in this proposed aldol reaction has stereocenters that can potentially influence the stereochemical outcome of the reaction, the stereochemical preferences of each fragment were separately examined.

In the event, selective formation of the \textit{E} boron enolate of ethyl ketone \textbf{1} with dicyclohexylchloroborane,\textsuperscript{[9]} followed by the addition of aldehyde \textbf{2}\textsuperscript{[10]} afforded a 9:1 mixture of product diastereomers (Scheme 1) favoring the desired Felkin adduct \textbf{3a} (70%). At this point in the synthesis, incorporation of the C\textsubscript{3} and C\textsubscript{15} acetate residues present in the altolythrin structure was addressed. Selective desilylation of \textbf{3a} at C\textsubscript{3} and C\textsubscript{15} with buffered HF·pyridine proceeded in good yield to give tril \textbf{3b} (78%).\textsuperscript{[11]} Selective monoacetylation at the C\textsubscript{15}-hydroxyl with methoxyacetic anhydride was followed by bis(acylation) at C\textsubscript{3} and C\textsubscript{15} with acetic anhydride to afford \textbf{4} (89%). The selection of the methoxyacetyl residue for interim protection of the C\textsubscript{3} (carboxyl) terminus was made after difficulties were encountered in the selective hydrolysis of the corresponding C\textsubscript{3} acetate, which required extended reaction times. Under these conditions significant \(\beta\)-elimination of the C\textsubscript{15} acetate residue was noted.

Scheme 1. AB/CD aldol fragment coupling. a) (\textit{t}Hex\textsubscript{3})\textsubscript{B}Cl, Et\textsubscript{3}N, pentane, 0°C, 90 min, then –78°C, addition of 2; b) HF·pyridine, THF, 0°C; c) MeOCH\textsubscript{2}CO\textsubscript{2}O, iPr\textsubscript{2}EtN, CH\textsubscript{2}Cl\textsubscript{2}; d) Ac\textsubscript{2}O, DMAP, pyridine, 22°C; e) Me\textsubscript{3}Al, CH\textsubscript{2}Cl\textsubscript{2}, –78°C; f) Dess-Martin periodinane, CH\textsubscript{2}Cl\textsubscript{2}. (See ref. [4] for abbreviations.)

In general, the overall strategy involves a combination of Felkin-Ab conformations for the C3-4 and C15-16 hydroxyl groups, with C3 and C15 acetate residues installed in the AB and CD fragments, respectively. The central core of the altolythrin structure is then built up in a stepwise manner, with the introduction of the remaining functional groups and stereochemical elements.
Refunctionalization of the C₁₋₂₈ bis(spiroketal) 4 in preparation for the Wittig reaction was then undertaken. Removal of the C₂₈ trityl ether with Me₂AlCl[¹²] under carefully controlled conditions afforded the corresponding alcohol,[¹³] which was oxidized with the Dess–Martin periodinane to give aldehyde 5, the substrate required for the projected Wittig reaction. The requisite phosphonium salt 7 was prepared from EF-bis(pyran) benzyl ether 6[⁵] (Scheme 2) by successive debenzylation (LDBB, 96 %), mesylation (MsCl, Et₃N, 99 %), sodium iodide displacement (NaI, acetone, 94 %), and displacement by triphenylphosphine (PPh₃, MeCN, 91 %). Deprotonation of 7 (1.26 equiv) with LiHMDS followed by addition of aldehyde 5 provided the desired Wittig product 8 in 64 % yield (> 95:5 Z: E).[¹⁴] Removal of the methoxyacetate C₁ protecting group was accomplished with NH₂/MeOH in 82 % yield. While hydrolysis of the secondary acetates at C₁ and C₁₅ was not observed, a minor by-product resulting from β-elimination of the C₁₅

Scheme 2. Final assembly: a) LDBB, THF, −78 °C; b) MsCl, Et₃N, CH₂Cl₂; c) NaI, NaHCO₃, Na₂SO₃, acetone; d) PPh₃, CH₃CN; e) LiHMDS, THF, −78 °C, then 5, −20 °C; f) NH₂, MeOH; g) Dess–Martin periodinane, pyridine, CH₂Cl₂; h) NaClO₃, 2-methyl-2-butene, ethyl-1-proplyl ether, tBuOH, pH 5.5; i) TIPSCI, Et₃N, THF; j) dimethyldioxirane, acetone, CH₂Cl₂; k) 16 equiv of 10, 2 equiv of Bu₃SnOTf, −78 °C; l) HF, pyridine, pyridine, THF, 0 °C; m) TESCl, imidazole, CH₂Cl₂, 0 °C (61 % from 11); n) 2,4,6-trichlorobenzoyl chloride, iPr₂NEt, benzene, then DMAP, benzene, reflux; o) HF, H₂O, MeCN. (See ref. [4] for abbreviations.)
ester was isolated. Dess–Martin oxidation (92%) followed by buffered Kraus oxidation[2] and silyl protection (TIPSCI, Et3N) provided TIPS ester 9 (72%, two steps).

At this stage, introduction of the Cα−Cβ side chain was undertaken. Epoxidation of the C42=C43 dihydropyran was accomplished with complete chemo- and stereoselectivity (as judged by 1H NMR analysis) by addition of approximately 1.5 equivalents of dimethyltetrine. Immediate treatment of the resulting epoxide with allylstannane 10[3] (16 equiv) and tributylstannyln triflate (2 equiv) afforded the desired adduct 11, comprising the full aldehytin carbon skeleton, in 80–94% yield of isolated product as a single diastereomer. The excess allylstannane was recovered in quantitative yield after column chromatography.

As a prelude to macrocycle formation, a complex series of silyl deprotection operations on ester 11 was implemented. Treatment of this intermediate with buffered HF•pyridine (THF, 0°C), afforded selective deprotection of the TIPS ester at the C-terminus, the C17 TMS ether, and the C18 TES ether,[15] while retaining the four silyl protecting groups at C9, C39, C52, and C58 (Scheme 2). Subjection of acid triol 12 to Yamaguchi macrocyclization conditions (2,4,6-trichlorobenzoyl chloride, IP2,NET3, DMAP)[16] provided a product tentatively identified as the desired cyclization product bearing a trichlorobenzoyl group at the C9 oxygen. Accordingly, selective protection of acid triol 12 at the C42 hydroxyl was performed prior to macrocyclization to give TES ether 13 (TESCI, imidazole, 0°C, 61% from 11).[17]

Exposure of 13 to Yamaguchi conditions provided a single regioisomeric lactone 14 in 86% yield. Deprotection (HF/ 
H2O/MeCN) provided the desired natural product, which was isolated in 85% yield after reverse phase HPLC. The regiochemical outcome of the macrocyclization was unambiguously established by observation of the coupling patterns among the Cα−Cβ protons in the COSY spectrum of the deprotected compound ([d3]JDMSo). This allowed an unambiguous assignment of resonances of hydrogen atoms at the C42 and C43 atoms; both the diagnostic downfield shift of the C9H resonance (δ = 4.68 for C9H, 3.04 for C9H) and the presence of a C43H−C42OH coupling verified that macrocyclization had occurred at the C42,hydroxyl group. Our observation that the sec acid 13, carrying an unprotected hydroxyl function at C42, may be cyclized directly to the macrocycle 14 simplifies the later stages of the synthesis plan. The motivation for attempting this cyclization as part of the original plan was based on the conviction that any protecting group appended to the C42-hydroxyl would add sufficient steric hindrance to the C43-hydroxyl group to impair the macrocyclization process.

The synthetic material was identical to a sample of natural spongistatin 2[18] as judged by 1H NMR (500 MHz, CD3CN), HPLC, electrospray mass spectroscopy, and ultraviolet spectroscopy. Comparison of optical rotations confirmed that the synthetic and natural compounds possessed the same absolute stereochemistry (synthetic: [α]D +21.3° (c = 0.03 in MeOH); natural: [α]D +29.2° (c = 0.12 in MeOH)). Further, detailed comparison of one-dimensional 1H NMR and two-dimensional COSY spectra (500 MHz, [d2]DMSO) confirmed that our synthetic material was also identical to natural aldehytin C[18]. We thus conclude that spongistatin 2 and aldehytin C are identical compounds and speculate that the aldehytin stereochemical assignment can be extended to the remaining members of the spongipyran family.

The route to aldehytin C outlined here should be readily applicable to the side-chain congeners aldehytin A (spongistatin 1) and aldehytin B[3] with dihydropyran 9 serving as a common intermediate for the synthesis of these compounds and additional unnatural analogues.[20]

Received: October 22, 1997 [Z 110671E]

German version: Angew. Chem. 1997, 109, 2951–2961

Keywords: aldehytin • antitumor agents • natural products • spongistatin • total synthesis


[3] Representative IC50 values against tumor cell lines: a) M. Kobayashi, S. Aoki, K. Takata, Y. Nishino, Chem. Pharm. Bull. 1996, 44, 2142–2149; aldehytin A (X = Cl) 0.01 ng/mL; aldehytin B (X = Br) 0.02 ng/mL; aldehytin C (X = H) 0.4 ng/mL; b) R. Bai, G. F. Taylor, Z. A. Cichacz, C. L. Herald, J. A. Kepler, G. R. Pettit, E. Hamel, Biochemistry 1995, 34, 9714–9721; spongistatin 1 (X = Cl) 0.13 nm; spongistatin 2 (X = H) 0.85 nm.

[4] Abbreviations: dr−diastereomer ratio, 9-BBN = 9-borabicyclo[3.3.1]nonane, eH = ethoxy; TIPS = triisopropylsilyl, TBS = tert-butyldimethylsilyl, TES = triethylsilyl, TMS = trimethylsilyl, Tr = trityl = triphenylmethyl, TF = trifluoromethanesulfonyl, Bn = benzyl, LDBB = lithium diisopropyl-butyldiphenyl, DMAP = 4-dimethylaminopyridine, MsCl = methanesulfonyl chloride, LiHMDS = lithium hexamethyldisilazide.


[6] Reaction of the E-tert eicinolate derived from 1 with isobutylaldehyde gave low stereoconduction (2:1).


[10] Aldehyde 2 was used directly in these experiments without purification. Exposure of 2 to silica gel led to isomerization to the α,β-unsaturated aldehide.

[11] The desilylation was interrupted before completion. Some monodesilylated material (hydroxy group at C2) was recovered (15%).


[13] The use of aqueous Rochelle’s salt in the isolation was essential for removing the organoaluminum salts prior to concentration; otherwise, residual aluminum-promoted spiroketal isomerization to the undesired diaxial anomer took place.

[14] Changed aldehyde 5 (11%) was also recovered in diastereomerically pure form.

[15] The moderate yield for this transformation may be partly due to difficulties in isolating the polar acid triol on small scale. TLC analysis of the reaction suggests a clean and selective transformation.


[17] The initial product of the reaction is the corresponding C, TES ester, which is cleaved during purification on silica gel.

We thank Professor G. R. Pettit for providing a natural sample of spongistatin 2.

We thank Professor M. Kobayashi for providing copies of spectra of natural aldehytin C.

While addition of the side chain at an even later stage may be possible, preliminary investigations of an alternative route involving lactonization of the dihydropyran sec acid corresponding to 9 and subsequent side-chain addition suggest that the epoxidation/allylstannane addition sequence may be more difficult.