Spongistatins, Cynachyrolides, or Altohyrtins? Marine Macrolides in Cancer Therapy

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Isolation and Structure Determination

Marine organisms have been a rich source for new drugs during the last decades. Though only an infinitely small fraction of all marine species has been explored, a plethora of new and diverse structures and structural features with, in some cases, fascinating physiological properties could be isolated.[1, 2] Cytotoxic, antineoplastic compounds are of special interest; this field of research has been followed systematically with great commitment and success—also thanks to the intensive efforts of the American National Cancer Institute (NCI)—for over 30 years.[2] The bioactive macrolides are particularly promising.[3]

In 1993 three independant research groups reported a new class of remarkably cytotoxic marine macrolides, the spongipyrans, from marine sponges for the first time (see Table 1).[4] The research was guided by bioassays and led to the identification and structure determination of spongistatins 1–9 (Pettit et al.[4a, 5]) from *Spongia sp.* and *Spirastrella spinispirulifera*, cinachyrolide A (Fusetani et al.[4b]) from *Cinachyra*, and altohyrtins A–C as well as 5-desacetylaltohyrtin A (Kitagawa et al.[4c, 6]) from *Hyrtios* (Figure 1). The achievement of the three groups is especially noteworthy, since only trace amounts (0.5–13.8 mg) of these extremely potent, physiologically active compounds could be isolated for extensive NMR experiments after laborious extractions and multiple chromatographic purifications. The relationship of all substances is clear: Apart from the 42-membered macrolactone ring (longest carbon chain) there are two spiroketals (*AB* and *CD* rings) and one bis(tetrahydropyran) fragment (*EF* rings) as prominent structural features. Variations (spongistatins 5, 7–9) exhibit an additional five-membered ring (*G* ring). However, there are evidently differences; the proposed relative configurations of the spiroketal units (*AB*/*CD*), the (*E*)-tetrahydropyran ring as well as the stereogenic centers C14–16 and C47 diverge from each other. The absolute configurations were only determined for the altohyrtins, whose structures were postulated by Kitagawa et al.[6b, c] It was tempting to think that all macrolides, apart from the substituents at C50, only differ in their degree of acetylation. First total syntheses from Evans et al. (altohyrtin C)[7] and Kishi et al. (altohyrtin A)[8]—both from Harvard University—confirmed this. In the following these syntheses and different synthetic approaches from Heathcock,[9] Paquette,[10] Paterson,[11] and Smith[12] will be presented.

Studies Towards the Total Synthesis

There are strategic features that all approaches to the total synthesis have in common, namely, the late macrolactonization—in all reported cases Yamaguchi conditions (2,4,6-trichlorobenzoyl chloride, trialkylamine, then 4-dimethylaminopyridine) were applied—and a proposed coupling of the "northern hemisphere" **1** to the "southern hemisphere" of the spongipyrans by a Wittig reaction (aldehyde C28) to furnish double bond C28–C29 (Scheme 1). The side chain (C44–C51) can be incorporated before the lactonization either completely (Kishi et al.[8b]), partly (Smith et al.[12a] and Paterson et al.[11b]), or not at all (Evans et al.[7c]) in the southern hemisphere. However, because of the different substituents at C50 of the various altohyrtins, an introduction at the latest possible moment seems to be advantageous. In both total syntheses allylstannanes were used for a ring opening of an epoxypyran to join the resulting chain with the *EF* ring system. The strategy for the bis(tetrahydropyran) unit was similar (the numbering of the carbons atoms in the synthetic building blocks is already based on the final molecule): After separate synthesis of the *E* and *F* rings, a coupling of a C37-lithiated species to an aldehyde (C38) was anticipated. Evans et al. applied an anomeric sulfone (C37) as carbanion-stabilizing group, whereas Kishi et al. utilized an 1-iodo enolether. For the northern hemisphere different approaches were followed. While the Evans group made use of a selective aldol addition (aldehyde C15 and (*E*)-boron enolate C16) as the key step for the coupling of the spiroketal units, the Kishi group carried out the formation of a C17–C18 bond by the Ni^{2+}/Cr^{2+}-mediated addition of a vinyl iodide (C18) to an aldehyde (C17). After oxidation to a ketone (C17) the reaction sequence was completed with an intramolecular hetero-Michael cyclization to form the *C* ring with concomitant formation of the *CD* spiroketal unit.

The synthesis (Evans) of spiroketals *AB* and *CD* including the coupling to compound **1** is outlined in Scheme 2. Starting

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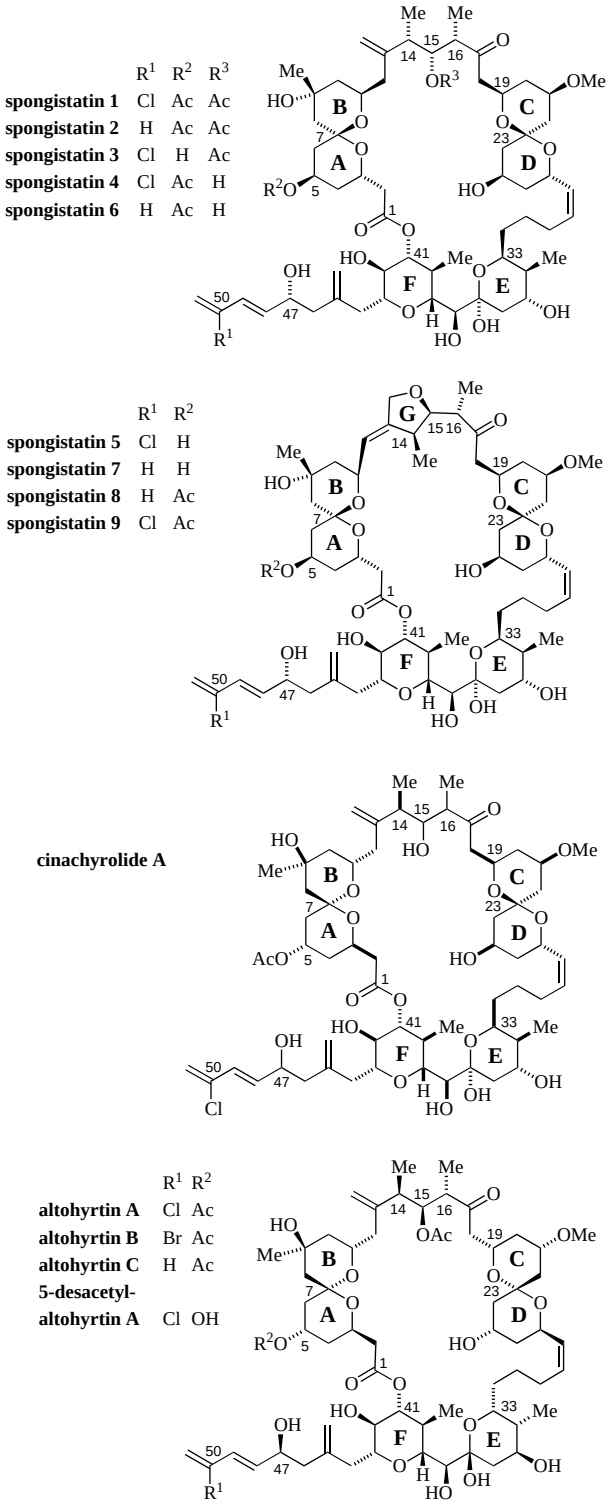
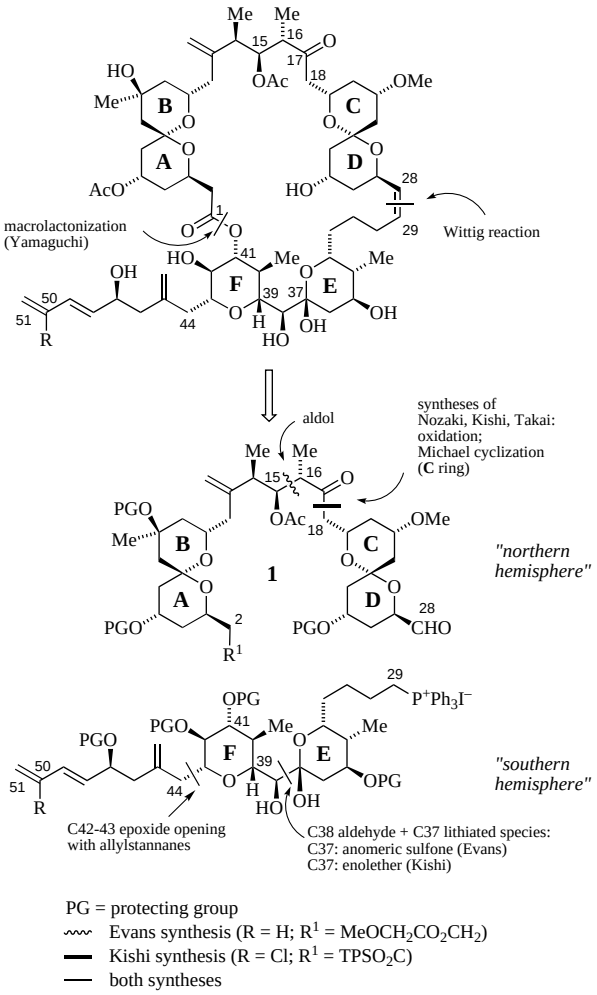


Figure 1. Structures originally proposed for the marine macrolides spongistatin 1 – 9,[4a, 5] cinachyrolide A,[4b] altohyrtin A – C, and 5-desacetylaltohyrtin A.[4c, 6]



Scheme 1. Retrosynthesis of altohyrtin A and C. TPS = *tert*-butyldiphenylsilyl.

from chiral building block **2**—which is readily available by selective opening of a protected 3-hydroxyglutamic acid anhydride with a chiral alcohol (1-(2-naphthyl)ethanol)—the convergent construction of the carbon skeleton C1 – C15 began. Reduction and Wittig reaction yielded the hydroxamic acid derivative **3**. The newly formed stereogenic center at C5 was then introduced with a highly diastereoselective, intramolecular Michael addition (1,3-*syn*) of a hemiacetal (from **3**, PhCHO, KO*t*Bu) to the α,β-unsaturated carbonyl compound. Reduction with diisobutylaluminium hydride (DIBALH) furnished aldehyde **4** in a high overall yield. The second building block (C8 – C15) was synthesized from oxazolidinone **6**. Through a nice sequence first the allylsilane **7** was formed, which in turn was selectively (1,4-*syn*) added to the suitably protected aldehyde. The right configuration at C11 was obtained after Mitsunobu inversion. Aldol addition of a boron enolate obtained from ketone **8** to aldehyde **4** gave the *AB* fragment in the open-chain form; after oxidation of the alcohol (C7) and acidic liberation of the hydroxyl groups at C1, C3, C5, and C11, a spontaneous spiroketalization occured. In this case the thermodynamically favored "axial – axial" anomer was isolated (anomeric stabilization; equatorial substituents at C3 and C11; the axial hydroxyl groups at C5 can further stabilize this product through formation of hydrogen bonds to ring oxygen atoms).

Only at this stage was the tertiary center C9 formed; the nucleophilic attack (with methyllithium/cerium trichloride) occurred diastereoselectively from the lower face. For the synthesis of the *CD* spiroketal very similar building blocks

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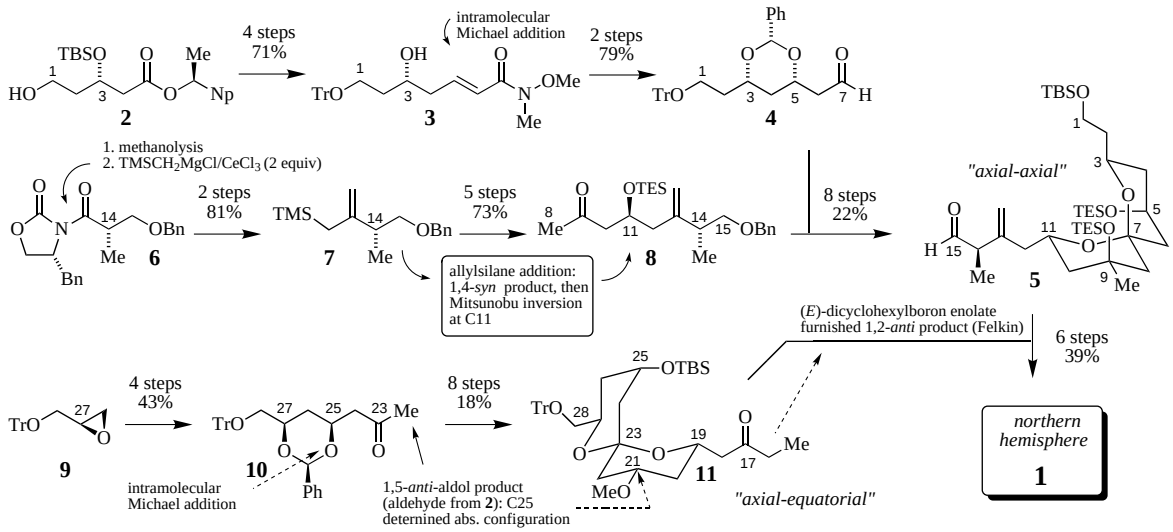
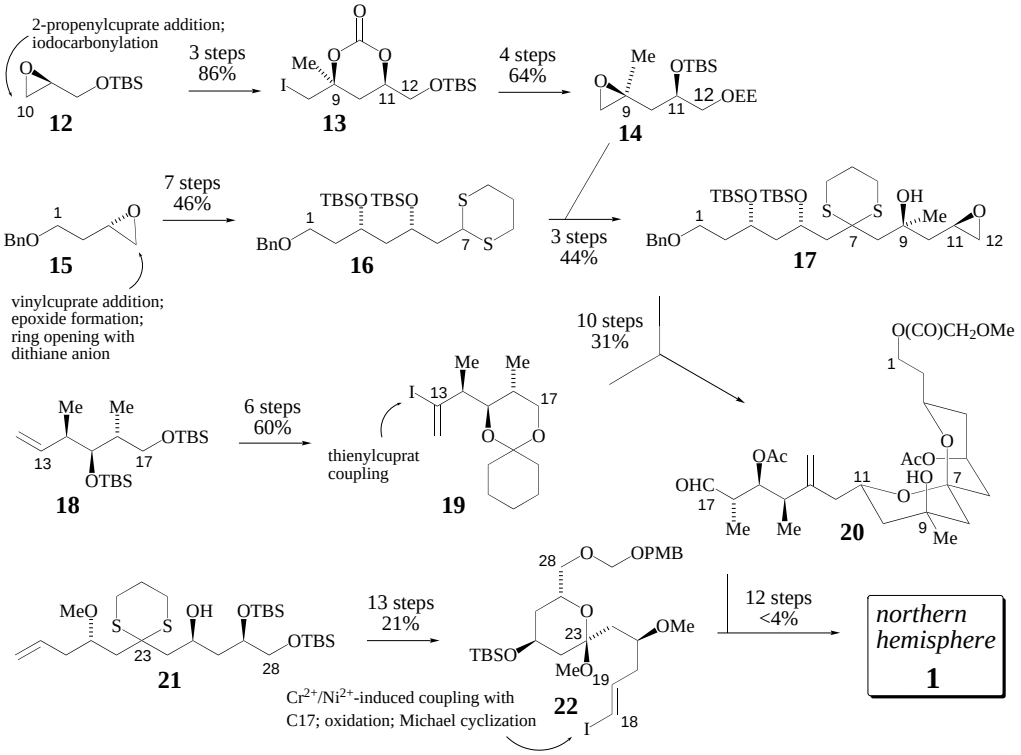


Scheme 2. Synthesis of the northern hemisphere of altohyrtin C according to Evans et al.[7a, c] Bn = benzyl, Np = 2-naphthyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, TMS = trimethylsilyl, Tr = trityl = triphenylmethyl.

and concepts were used. Again, key steps were the well-established intramolecular Michael addition (chain extension of epoxide **9**, then 1,3-*syn* addition of a hemiacetal to the α,β-unsaturated compound) and a 1,5-*anti* aldol addition of ketone **10** to an aldehyde, which is, for instance, available from **2** through oxidation. The configuration at C21 was exclusively determined by the configuration at C25; that at C19 had no influence at all. The spiroketalization proved problematic since in this case the axial – equatorial product **11** was needed. After equilibration with $Mg(O_2CCF_3)_2$ in CF_3CO_2H/CH_2Cl_2 the desired spiro product could be obtained in a 2.2:1 ratio. The synthesis of the northern hemisphere **1** was completed after the selective aldol addition of the (*E*)-dicyclohexylboron enolate derived from keton **11** to the C1 – C15 fragment **5**. Ingenious manipulations of the protecting groups enabled, among others, the acetylation of the hydroxyl group at C5.

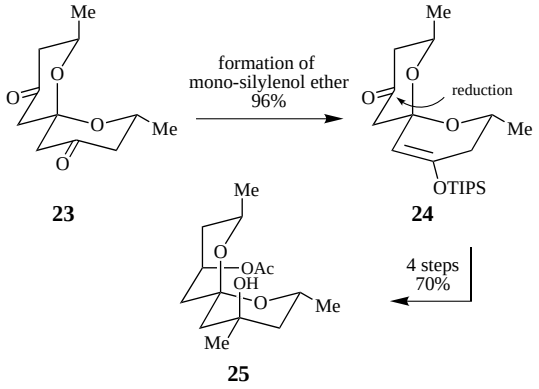
The Kishi group followed a different approach (Scheme 3). Starting from epoxides **12** and **15** the carbon skeleton C1 – C12 was obtained after repeated dithiane coupling. In the second step the dithiane adduct **16** was added to epoxide **14**. With this, oxirane **17** was synthesized, and the C1 – C17 fragment was furnished after a cuprate coupling with vinyl iodide **19** (obtained from alkene **18**). Manipulation of the protecting groups and spiroketalization (*N*-iodosuccinimide-induced dithiane cleavage) to the *AB* spiroketal proved unproblematic. Finally, Dess – Martin periodinane oxidation led to aldehyde **20**. For the synthesis of the C18 – C28 fragment, the group again relied on the dithiane method. Compound **21** is readily available from the corresponding enantiomerically pure epoxides. However, the spiroketal was not directly synthesized from this intermediate; instead only



Scheme 3. Synthesis the northern hemisphere of altohyrtin A according to Kishi et al.[8a] EE = ethoxyethyl, PMB = *p*-methoxybenzyl.

the *D* ring of altohyrtin A with a suitable vinyl iodide grouping in the side chain (**22**) was formed. As described above, an interesting sequence followed, starting with the transition metal induced coupling of vinyl iodide **22** to aldehyde **20**. Oxidation to the ketone (C17) and intramolecular Michael cyclization yielded only one of the four possible diastereomers. Whereas the configuration at C19 proved to be correct, the spiro center was wrongly configured. After epimerization the desired spiroketal was obtained in 50% yield. Further manipulation of the protecting group and selective oxidations of the side-chains provided the suitably protected northern hemisphere **1**.

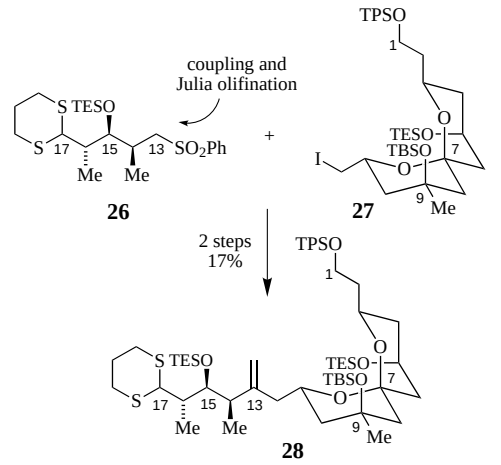
Similar strategies for the formation of the spiroketals were followed by other groups as well.[9, 10, 11a, c, d, 12b, c] In a model study Heathcock and co-workers[9a] have established an efficient entry to the *AB* ring system (Scheme 4). Startin



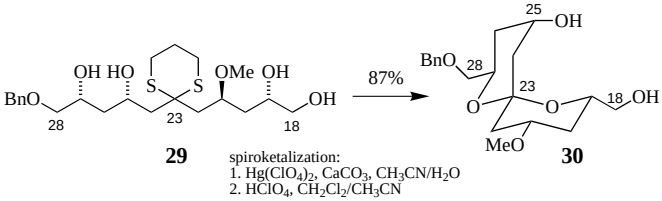
Scheme 4. Synthesis of the *AB* model spiroketal **25** according to Heathcock et al.[9a] TIPS = triisopropyl.

gfrom the readily available C_2-symmetric spiro diketone **23** a diastereoselective functionalization via the monosilyl enolether **24** to product **25** could be achieved. The one-pot dithiane method for the synthesis of acyclic precursors of the spiroketals has been intensively used by the Smith group. To introduce the C13–C17 side chain, this research group proposed a nice variation that unfortunately led to product formation in relatively unsatisfactory yield:[12c] Alkylation of sulfone **26** (C13) with iodide **27** was followed by a Julia olefination and thus the formation of the exocyclic double bond at C13 (**28**, Scheme 5). One problem for both reported total syntheses is the unusual configuration at C23 of the *CD* spiroketal. Smith and co-workers showed that the presence of calcium ions can play a critical, constructive role. Presumably, they promote the selective, acid-catalyzed spiroketalization of dithiane **29** to the desired product **30** (Scheme 6).[12b] Surprisingly, Paquette et al. observed no complications with this reaction. Silylation of alcohol **31** and deprotection of the hydroxyl groups at C19 and C27 were reported to spontaneously yield spiroketal **32** (Scheme 7).[10b]

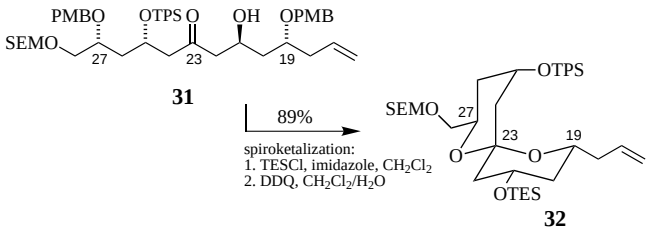
The synthesis of the southern hemisphere from Evans et al. is summarized in Scheme 8.[7b] The *E* ring was synthesized from the readily available hydroxamic acid derivative **33**. The stereogenic center at C35 of thioester **34** was formed by a Felkin-selective aldol addition of a thioketene acetal to an



Scheme 5. Sulfone strategy for the coupling of the side chain to the *AB* ring system according to Smith et al.[12c]



Scheme 6. Calcium ion induced selective spiroketalization according to Smith et al.[12b]



Scheme 7. Selective formation of the *CD* spiroketal **32** according to Paquette et al.[10b] SEM = 2-(trimethylsilyl)ethoxymethyl.

aldehyde, which had been synthesized by reduction of **33** with DIBALH. Mild reduction utilizing Fukuyama conditions (Lindlar catalyst, Et_3SiH, 1-hexene, acetone) followed by acidic hydrolysis of the silyl protecting group and concomitant cyclization furnished, after silylation, the methyl pyranoside **35**. The anomeric sulfone **36** was synthesized in four steps from **35**. A similar route was possible for synthesizing the *F* ring (**37** → **38**). The hemiacetal **39** was formed after desilylation, Ag^I mediated lactonization, DIBALH reduction, and silylation. Elimination to form the enolether and oxidation at C38 furnished, after debenzylation, an aldehyde that should have been a suitable coupling partner for sulfone **36**. However, all attempts failed, and the desired product was obtained only after use of the activated benzotriazolylamide **40**. The sulfone group was then transformed to the methyl pyranoside and, after reduction ($KBHEt_3$) to the alcohol (C38), building block **41** was isolated. This compound was successfully coupled with the northern hemisphere by a Wittig reaction (C29); diastereoselective epoxidation with dimethyl dioxirane

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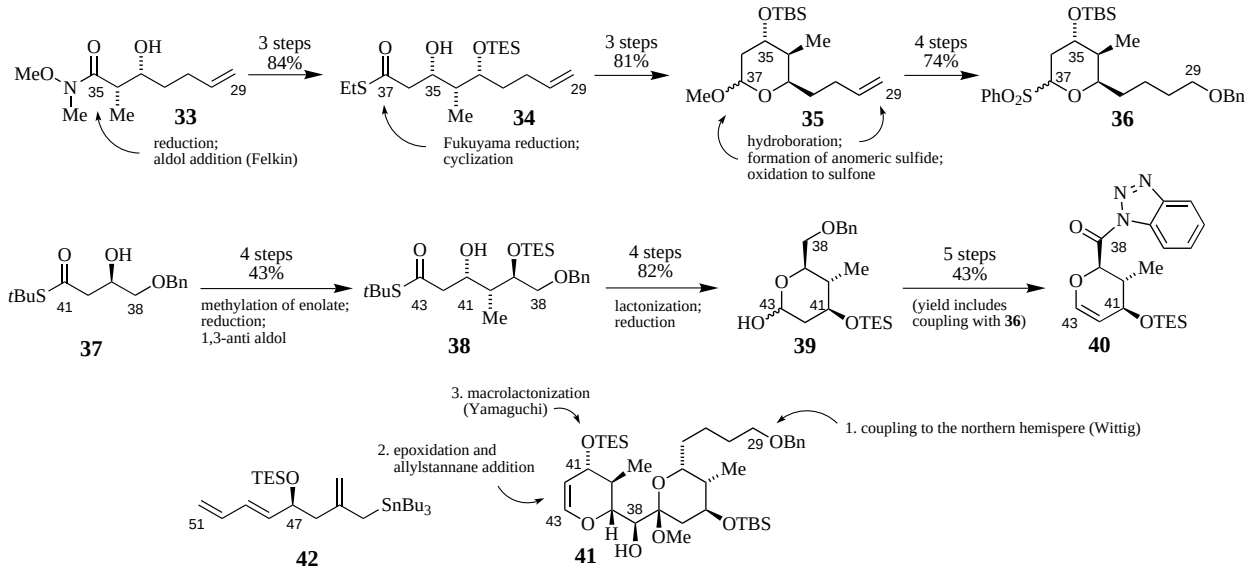
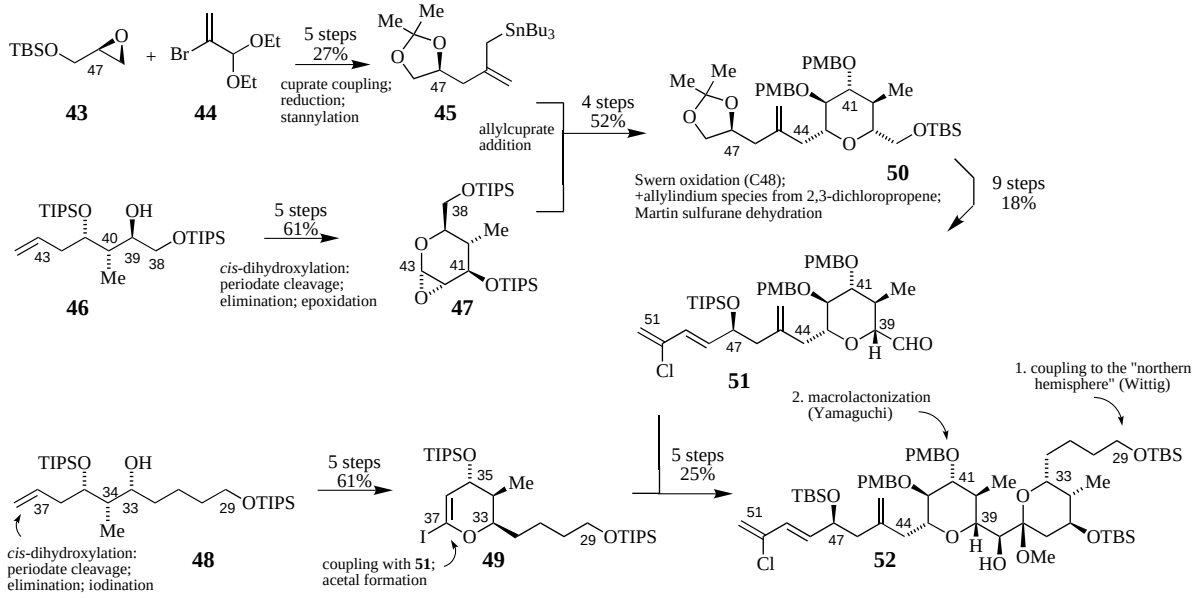


Scheme 8. First total synthesis of altohyrtin C according to Evans et al.[7b, c]

(C42 – C43) and Lewis acid catalyzed ring opening with allylstannane **42** introduced the C44 – C51 side chain. The Yamaguchi macrolactonization was surprisingly very selective: Although both the hydroxyl groups at C41 and C42 were not protected, this reaction gave a single product in high yield (86 %). Final manipulation of the protecting groups led to the isolation of altohyrtin C, a compound that, after comparison of all spectral data, proved to be identical with spongistatin 2.[7c]

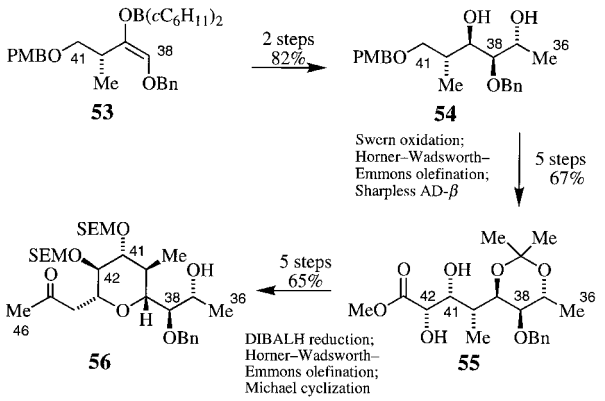
The alternative approach to the southern hemisphere from Kishi and co-workers is described in Scheme 9.[8b] As mentioned above, the side chain C44 – C51 was brought in at an early stage; the stereogenic center at C47 was already present in the starting oxirane **43**, which was obtained by Sharpless epoxidation. Cuprate coupling with vinyl bromide **44** and introduction of the tributylstannyl group yielded intermediate **45**. The *F* ring was formed starting from protected triol **46**. A typical sequence consists of a *cis*-dihydroxylation of the alkene and periodate cleavage to the aldehyde with spontaneous formation of the hemiacetal. After elimination and treatment of the enolether with dimethyl dioxirane, epoxide **47** was obtained. A similar sequence was used for the *E* ring fragment (**48** →**49**). The starting materials **46** and **48** were also accessible by reliable methods: In each case addition of Brown crotylboranes to the appropriate achiral aldehydes (C39 or C33) resulted in the formation of two new stereogenic centers (C39, C40 and C33, C34, respectively), and the corresponding enantiomerically pure alkenes were isolated. Degradation of the double bonds to the aldehydes and repeated addition of allylborane furnished **46** and **48**. After coupling of the allyl compound **45** (transmetalation to the



Scheme 9. First total synthesis of altohyrtin A according to Kishi et al.[8b]

cuprate) with epoxide **47**, the synthesis of the side chain was completed in nine steps (**50** →**51**). The aldehyde obtained was directly suitable for the finishing synthesis of the southern hemisphere. It must be pointed out that at this stage, with the addition of the allylindium species derived from 2,3-dichloropropene, the decision for the synthesis of either altohyrtin A, B, or C was made. The final steps to the C29 – C51 building block **52** were initiated by direct reaction of the C37-lithiated species **49** ($MgBr_2$ additive) with aldehyde **51**; the detour via the activated ester was in this case not necessary. The formation of the methyl pyranoside (C37) was accomplished by iodomethanolysis and reductive dehalogenation in the presence of bromobenzene (to prevent reaction of the vinyl chloride). After preparation of the Wittig salt (C29) and coupling with the northern hemisphere the synthesis was successfully completed by the macrolactonization. Spectroscopic analysis proved that the compound formed, altohyrtin A, and spongistatin 1 were identical.

Further synthetic work on the southern hemisphere was reported by Smith and co-workers[12a]—who very effectively used dithiane methodology and Julia olefination (methylenation at C45) to synthesize the entire building block—and Paterson et al. (Scheme 10).[11b] The latter group approached



Scheme 10. Synthesis of the *F* ring of the southern hemisphere according to Paterson et al.[11b]

the synthesis of the *EF* ring in a completely different way. Whereas all the other groups coupled the rings to form the C37 – C38 bond, Paterson and co-workers synthesized the carbon chain C36 – C41 at an early stage by aldol addition of boron enolate **53** to acetaldehyde (→**54**). Two more stereogenic centers (C41 and C42) were introduced by selective asymmetric Sharpless dihydroxylation after chain extension (Swern oxidation, Horner – Wadsworth – Emmons olefination). The ester **55** was subsequently transformed to the substituted *F* Ring **56**. It might be advantageous that the stereochemistry at C38 was determined at an early step, whereas the side chain C47 – C51 could be coupled at a later stage and with high flexibility. The future will show whether this synthetic plan is effective.

Biological Aspects

To sum up the first two successful total syntheses by the research groups of Evans and Kishi, it should be noted that the spectial merit of the approach of Evans et al. lies not only in the efficient application of methods developed in the group, but also in the convergence and flexibility (longest linear chain: 32 steps starting from **6**, ≈0.7% yield; synthesis by Kishi: 37 steps, ≈0.01% total yield starting from **12**). In the future the physiological activity and the potential application in cancer therapy will be at the center of interest. The outstanding GI values (Table 1) are certainly impressive, but reports on the selectivity for tumor cells and other cells are still lacking. In vitro tests proved that spongistatins efficiently inhibit mitosis by binding to tubilin and blocking microtubule assembly. It was found that at least three different, characteristic binding sites to the tubulin dimer must be present.[5f] First investigations of structure – activity relationships by Hamel

Table 1. Data of the macrolides spongistatin 1 – 9,[a] cinachyrolide A, altohyrtin A – C, and 5-desacetylaltohyrtin A

Compound	Yield (isolated prod.)	Bioassay (cel line)	Cytotoxicity
spongistatin 1[a]	3.5×10^{-6} % 13.8 mg[b]	P388	GI_{50} $2.5-3.5\times10^{-11}$ M[f] GI_{50} 1.3×10^{-10} M[g] IC_{50} 5.3×10^{-6} M[h] IC_{50} 3×10^{-11} M[i],[5f]
spongistatin 2[a]	1×10^{-6} % 4.34 mg[b]	P388	GI_{50} 8.51×10^{-10} M[g] IC_{50} 4.6×10^{-6} M[h] IC_{50} 2×10^{-9} M[i],[5f]
spongistatin 3	6.7×10^{-7} % 2.69 mg[b]	P388	GI_{50} 8.32×10^{-10} M[g] IC_{50} 1.3×10^{-5} M[h] IC_{50} 1×10^{-9} M[i],[5f]
spongistatin 4	4.4×10^{-7} % 10.7 mg[c]	P388	GI_{50} 1.0×10^{-10} M[g] IC_{50} 5.1×10^{-6} M[h] IC_{50} 1×10^{-10} M[i],[5f]
spongistatin 5	5.4×10^{-7} % 12.9 mg[c]	P388	GI_{50} 1.2×10^{-10} M[g] IC_{50} 6.7×10^{-6} M[h] IC_{50} 2×10^{-10} M[i],[5f]
spongistatin 6	3.5×10^{-7} % 8.4 mg[c]	P388	GI_{50} 1.1×10^{-9} M[g] IC_{50} 4.4×10^{-6} M[h] IC_{50} 8×10^{-10} M[i],[5f]
spongistatin 7	2.2×10^{-7} % 5.4 mg[c]	P388	GI_{50} 1.0×10^{-9} M[g] IC_{50} 5.3×10^{-6} M[h] IC_{50} 2×10^{-9} M[i],[5f]
spongistatin 8	7.5×10^{-8} % 1.8 mg[c]	P388	GI_{50} 2.3×10^{-10} M[g] IC_{50} 5.5×10^{-6} M[h] IC_{50} 3×10^{-9} M[i],[5f]
spongistatin 9	2.2×10^{-7} % 5.4 mg[c]	P388	GI_{50} 4.0×10^{-11} M[g] IC_{50} 4.2×10^{-6} M[h] IC_{50} 3×10^{-10} M[i],[5f]
cinachyrolide A	1.7×10^{-5} % 1.1 mg[d]	L1210	IC_{50} $<6\times10^{-10}$ g mL^{-1}[i],[4b]
altohyrtin A[a]	6.9×10^{-6} % 7.6 mg[e]	L1210 KB	IC_{50} 3×10^{-11} g mL^{-1}[i] IC_{50} 1×10^{-11} g mL^{-1}[j],[4c]
altohyrtin B	4×10^{-7} % 0.5 mg[e]	L1210 KB	IC_{50} 3×10^{-11} g mL^{-1}[i] IC_{50} 2×10^{-11} g mL^{-1}[j],[6a]
altohyrtin C[a]	4×10^{-7} % 0.5 mg[e]	L1210 KB	IC_{50} 1.3×10^{-9} g mL^{-1}[i] IC_{50} 4×10^{-10} g mL^{-1}[j],[6a]
5-desacetyl altohyrtin A	4.2×10^{-6} % 4.7 mg[e]	L1210 KB	IC_{50} 3.3×10^{-9} g mL^{-1}[i] IC_{50} 3×10^{-10} g mL^{-1}[j],[6a]

[a] Spongistatin 1 and altohyrtin A as well as spongistatin 2 and altohyrtin C are identical.[8b, 7c] [b] From 400 kg (wet weight) of *Spongia sp*.[5a] [c] From 2409 kg (wet weight) of *Spirastella spinispirulifera*.[5b–d] [d] From 6.6 kg (wet eight) of *Cinachyra sp*.[4b] [e] From 112 kg (wet weight) of *Hyrtios altum*.[4c, 6] [f] Typical values for a subgroup of especially chemoresistent tumor types in the NCI test.[4a] [g] All 60 cancer cell lines of the standard screen of the NCI were considered.[5f] [h] Inhibition of the glutamate-induced polymerization of tubuline.[5f] [i] Inhibition of the L1210 cell growth. [j] Inhibition of the KB cell growth.

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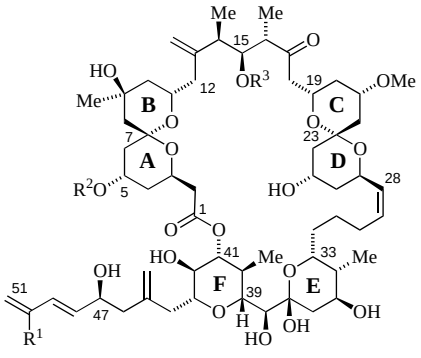
et al. with the different spongistatins provided no evidence of crucial functionalities.[5f] This result fits very well to the observation made by Kishi et al., namely, that C23-*epi*-altohyrtin A is highly cytotoxic as well.[8b] To obtain more detailed information, especially in view of in vivo tests and possible medical applications, larger quantities of these compounds are a prerequisite. This is certainly a dilemma in the case of active substances of marine origin; the isolation from tons of sponges is only partly justifiable for ecological reasons, a large-scale cultivation does not seem to be possible at present. As long as the isolation of the genes is still wishful thinking, total synthesis remains the only possibility for obtaining sufficient amounts of the desired compound for further systematic investigations—for the reported cytotoxicity a few grams should be more then enough for a start. This still remains the aim of different research groups. A comparison of the altohyrtins and spongistatins with other natural antineoplastics indicates that there is strong competition. Commercially available drugs such as taxol or taxotere are established;[13] other compounds, for example, the epothilones, are impressive not only because of their excellent cytotoxicity test results, but especially because of their very economic accessability through the cultivation of myxobacteria.[14] The bryostatins, a relatively new class of marine macrolides, are in a way the competition in the own backyard, since the first clinical tests are already underway.[2, 15] A long list of further potential candidates could be easily made (see, for instance, ref. [2, 3]).

With the first total syntheses—and only these could at this stage prove it—the structures of the spongipyranes have been unequivocally established. The new proposed structures are summarized in Figure 2. The structures published by Kitagawa et al. have been confirmed, and the relationship to the spongistatins 1 and 2 was established. Inevitably, this leads to the (corrected) structures for the spongistatins 3, 4, and 6 and possibly for cinachyrolide A as well as spongistatins 5, and 7–9. Further total syntheses must and will follow to provide larger quantities of these fascinating substances in order to gain more insight into the clinical potential of these macrolides. Only then can the ultimate question of which route leads to sufficient amounts of a possible drug be answered.



	R^1	R^2	R^3
altohyrtin A, spongistatin 1	Cl	Ac	Ac
altohyrtin B	Br	Ac	Ac
altohyrtin C, spongistatin 2	H	Ac	Ac
5-desacetylaltohyrtin A, spongistatin 3	Cl	H	Ac
spongistatin 4, cinachyrolide A	Cl	Ac	H
spongistatin 6	H	Ac	H

Figure 2. Proposal for the new classification of the marine macrolides spongistatin 1–4, and 6, cinachyrolide A, altohyrtin A–C, and 5-desacetylaltohyrtin A.

German version: *Angew. Chem.* **1998**, *110*, 2773–2780

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New Developments in Nitrogen Fixation

Felix Tuczek* and Nicolai Lehnert

The prospect of producing ammonia from dinitrogen at room temperature and ambient pressure in analogy to nature has fascinated coordination chemists for a long time. Modeling the conditions present in the enzyme with low-molecular weight compounds, however, is extremely difficult in this case. So far, the iron–molybdenum cofactor (FeMoco), which is the center of bonding and reduction of dinitrogen in the enzyme nitrogenase,[1] has not been synthesized.[2] Furthermore, this cofactor does not bind N_2 in isolated form. It therefore appears more promising to realize a catalytic cycle based on the mono- and binuclear transition metal N_2 compounds that give NH_3 or N_2H_4 upon protonation. On the other hand, a "biomimetic" approach is important for understanding aspects of the function of the enzyme on a molecular level.[3] The results of these two different research directions, however, have always been considered as closely related.

Through coordination to one or more metal centers, the dinitrogen ligand, which is extremely inert in free form, acquires a different degree of "activation" (Figure 1).[4] In principle, systems suitable for protonation reactions are those with "moderate" to "strong" activation as well as compounds which cleave the N_2 molecule upon coordination. However, if the aim is to achieve relevance to the biological process, "mild" conditions are important. "Nonactivated" systems, although not protonable, may also provide information fundamental to an understanding of the metal–N_2 bond. Besides the two mentioned, central problems, "nitrogen fixation" also involves reactions of the dinitrogen ligand or its partly reduced, complex-bound derivatives leading to the incorporation of nitrogen from N_2 into (mostly organic) compounds. Recently, there has been important progress in each of these areas, which will be reported here in the order of increasing activation of N_2.

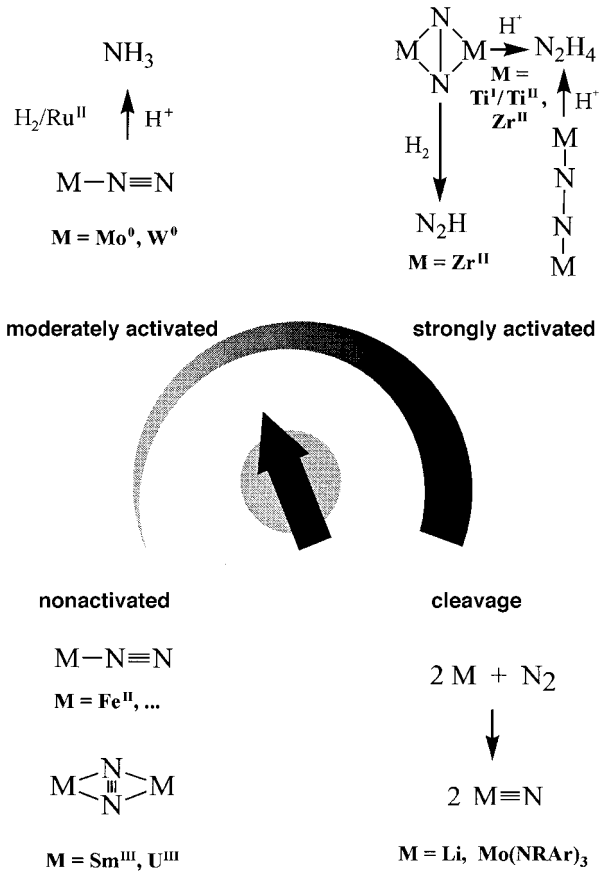

Figure 1. "Tuning" the activation of the N_2 ligand by the choice of the coordinating metal. The activation scale may be divided into four regimes; typical representatives mentioned in the text are indicated. The arrow points to the minimal degree of activation necessary for protonation.

N_2-containing systems in which the N–N distances are similar to that in free dinitrogen are termed "nonactivated" and are found among compounds exhibiting an *end-on* coordination of N_2 to transition metals, for example Fe^{II}. It appears that there is now a further bonding mode possible in this category: the nonactivating *side-on* coordination to lanthanide and actinide centers. Up to now, this bonding mode had been known only for a Sm^{III} complex.[5] The recent isolation and structural characterization of the *side-on* N_2-bridged complex $[\{U(NN_3')\}_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}N_2)]$ ($NN_3' = N(CH_2$

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