New Polyol Syntheses

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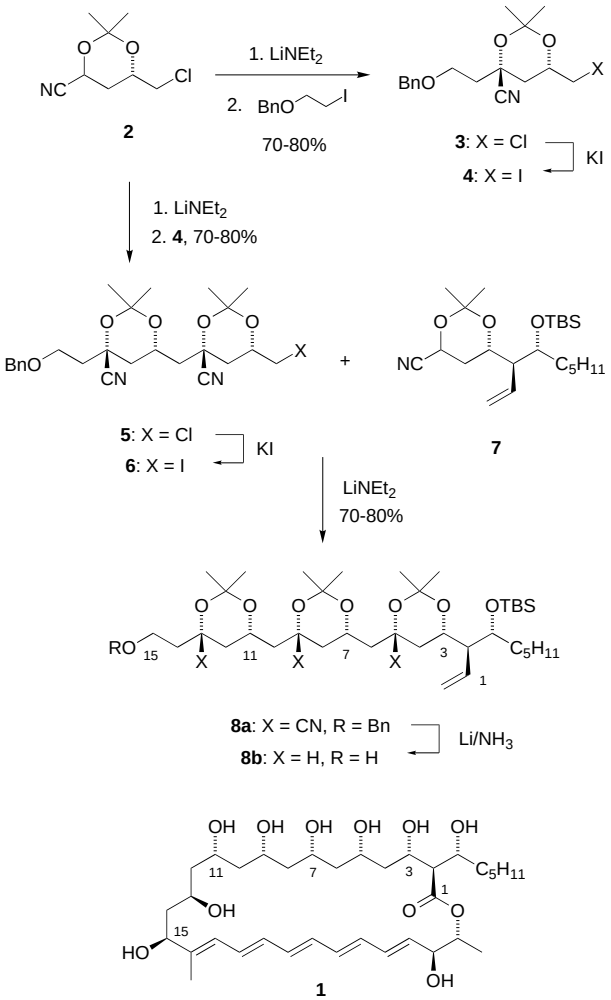
Owing to their biological action and chemical structure, certain natural products have always fascinated biologists and chemists. In addition to the cytotoxic epothilones and taxol and the antihypercholesterolemic squalestatins (zaragossic acids), the highly fungicidal polyene macrolides are attracting increasing attention.[1] More than 200 polyene macrolides have been identified, but the constitution and configuration of many have only been partially elucidated. Best known are probably amphotericin B and nystatin, which are used clinically for the treatment of systemic fungal infections. Their biological activity rests on their ability to damage cytoplasmic membranes of eukaryontic cells by various mechanisms with consequent loss of ions, amino acids, and carbohydrates. Structurally they consist of a polyene moiety with up to seven, mostly conjugated double bonds and a polyol moiety with nine secondary, mainly 1,3-orientated hydroxy groups. New strategies for the stereoselective synthesis of the polyol structures are of great interest to synthetic chemists.

Rychnovsky and his group have recently developed new synthetic methods that lead to the total syntheses of the polyene macrolides roxaticin,[2] roflamycoin,[3] and filipin III.[4] The polyol chains of all three natural products were constructed by iterative, stereoselective alkylation of lithiated cyanohydrin acetonides and subsequent reductive decyanation, illustrated here by the synthesis of the polyol framework of filipin III (**1**) (Scheme 1). The bifunctional cyanohydrin acetonide **2**, prepared by ruthenium/BINAP catalyzed enantioselective hydrogenation of the corresponding β-keto ester (BINAP = [1,1′-binaphthyl]-2,2′-diylbis(diphenylphosphane)), is deprotonated with $LiNEt_2$ and alkylated with 2-benzyloxy-1-iodoethane. The alkylation product **3** is converted by a Finkelstein reaction into the iodide **4**, which is used to alkylate a second molecule of **2**. After a second Finkelstein reaction, the protected tetraol **6** is coupled with the lithiated cyanohydrin acetonide **7** in a third alkylation to form the complete polyol segment **8** of filipin III.

Each alkylation step proceeds in good yield (70–80%), and the 1,3-dioxanes **9**, in which the "slim" cyano group assumes the axial position, are formed with high stereoselectivity. Once they have fulfilled their role for the alkylations, the three cyano groups are removed with Li/NH_3 with retention of configuration to afford the 1,3-*syn*-diol acetonides **11** (Scheme 2). Control experiments revealed, however, that the reductive decyanation always gives 1,3-*syn* configured diol acetonides irrespective of the cyanohydrin acetonide configuration. The reason is that the intermediate radical **10** prefers a configuration in which the unpaired electron assumes the axial position at the anomeric center. The carbanion formed by the next electron transfer is protonated at this position so the H atom is also in an axial position.



Scheme 1. Synthesis of the C_1–C_{15} polyol fragment **8b** of filipin III (**1**) according to Rychnovsky et al. Bn = benzyl, TBS = *tert*-butyldimethylsilyl.

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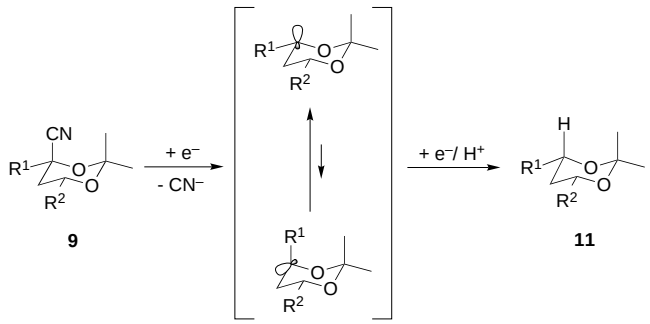
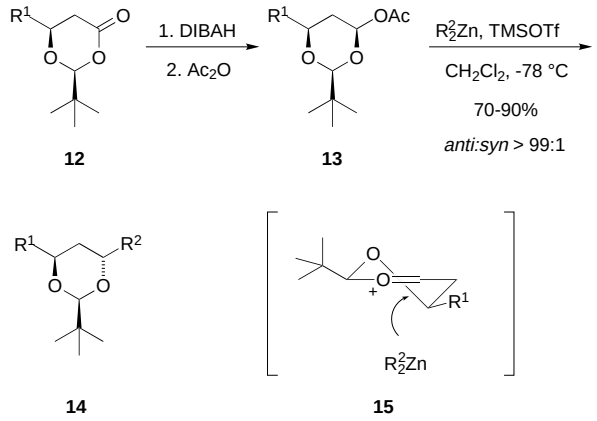


Scheme 2. Reductive decyanation of the cyanohydrin acetonide **9** according to Rychnovsky et al.

Protected 1,3-*anti*-diols **14** are accessible by the highly stereoselective Lewis acid promoted addition of dialkylzinc compounds to 4-acetoxy-1,3-dioxanes **13** (Scheme 3).[5] The

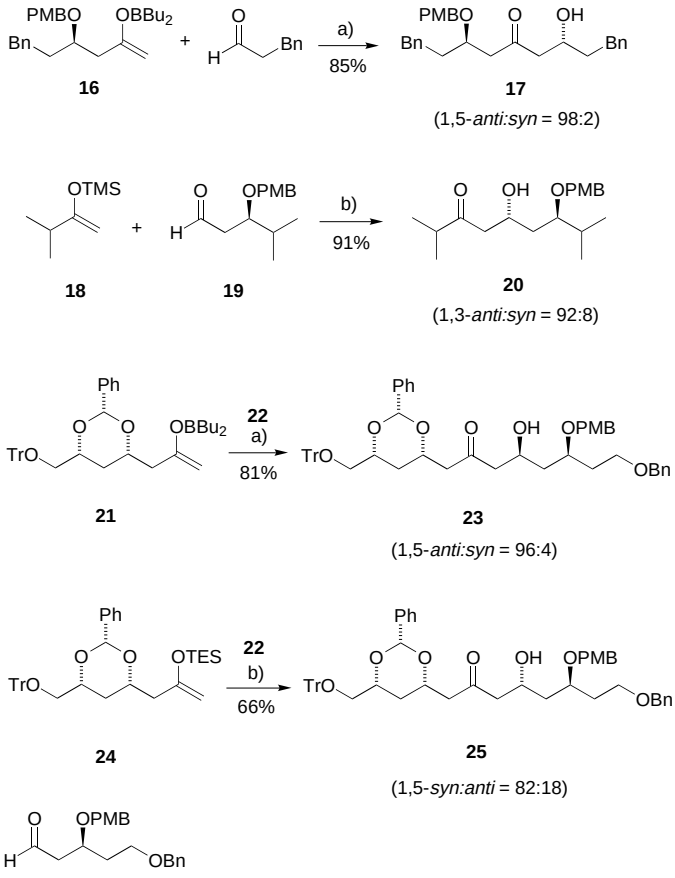


Scheme 3. Preparation of the 1,3-*anti*-diol acetal **14** by dialkylzinc addition to 4-acetoxy-1,3-dioxanes **13** according to Rychnovsky et al. TMSOTf = trimethylsilyltrifluoromethyl sulfonate.

two *cis*-orientated alkyl substituents at C2 and C6 fix the carboxonium ion **15** in the half chair conformation, which undergoes preferential axial attack by the dialkylzinc under stereoelectronic control. The 4-acetoxy-1,3-dioxanes **13** may be synthesized from the Seebach 1,3-dioxan-4-ones **12** by reduction with diisobutylaluminium hydride (DIBAH) and acetylation. Since dialkylzinc compounds are now readily available and are compatible with many functional groups, this method should be widely applicable to the preparation of 1,3-*anti*-diols.

The most direct method for the preparation of polyol frameworks is without doubt the aldol reaction. The diastereofacial selectivity of the reaction can be controlled by β-alkoxy groups in both the methylketone enolate and the aldehyde. As investigations by Evans[6] and Paterson[7] and their groups have demonstrated, the correct selection of enolization conditions and the protective group for the β-hydroxy group are important for the stereocontrol of the reaction.

Boron-aldol reactions of the *p*-methoxybenzyl(PMB)-protected methylketone **16** proceeds with excellent 1,5-*anti*-selectivity (Scheme 4). The asymmetric induction may be



Scheme 4. Stereocontrolled aldol reaction according to Evans et al. a) Et_2O, $-115^\circ C$; b) $BF_3 \cdot OEt_2$, CH_2Cl_2, $-78^\circ C$. TES = triethylsilyl, TMS = trimethylsilyl, Tr = triphenylmethyl.

improved by a double stereodifferential aldol reaction with chiral boron ligands.[7] The reason for this high stereoselectivity is currently unknown. Ab initio calculations suggest the involvement of twisted boat structures rather than chair transition states.[6]

If the chiral information is contained within the aldehyde, a Mukaiyama aldol reaction is the method of choice.[8] The BF_3-catalyzed addition of the silyl enol ether **18** to the chiral aldehyde **19** affords the 1,3-*anti* product **20** in high yield and stereoselectivity. Evans has developed a modified Felkin–Anh model as a working hypothesis in which repulsive interactions between the carbonyl group and the β-alkoxy group, and steric interactions between the carbonyl group and the β-alkyl group are minimized. The complementary reaction conditions permit selective product formation in a double stereodifferential aldol reaction of a chiral ketone and a chiral aldehyde, even in the mismatched situation.[6] Thus the boron enolate **21** adds to the aldehyde **22** with excellent stereoselectivity and forms almost exclusively the 1,5-*anti* product **23** (enolate control). In the Mukaiyama reaction of the corresponding silyl enol ether **24**, however, the aldehyde **22** exercises stereochemical control, and the 1,5-*syn* product **25** is the main product. The ketone carbonyl function of the aldol products can be reduced with high diastereoselectivity to the 1,3-*syn*-diols with $Et_2BOMe/NaBH_4$[9] and DIBAH,[10] and to the 1,3-*anti*-diols with $Me_4NBH(OAc)_3$[11] and SmI_2/RCHO.[12]

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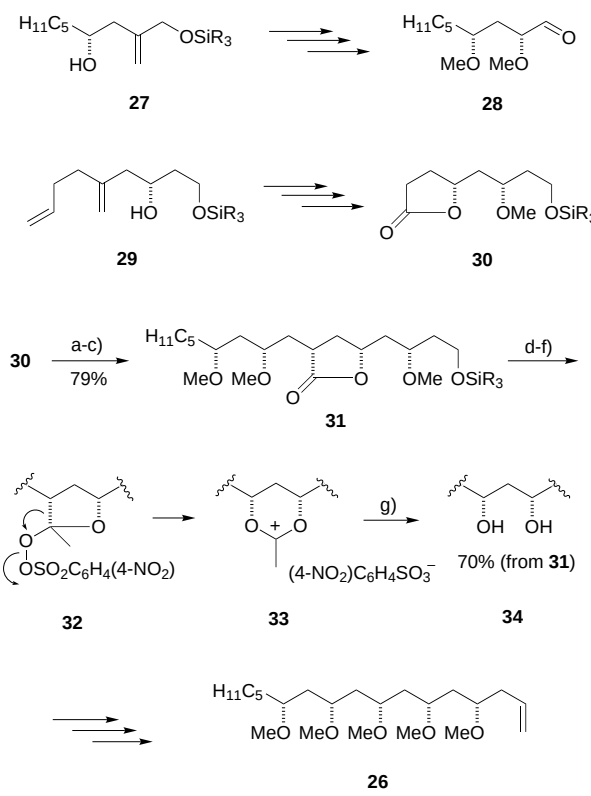
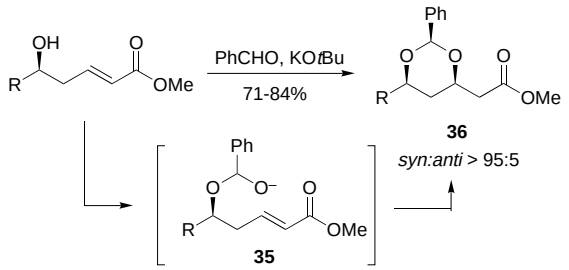
Brückner et al. use the oxidative degradation of butyrolactones by a Criegee rearrangement as the key step in the synthesis of different polyol systems (Scheme 5).[13] In



Scheme 5. Synthesis of the *Tolypothrix* pentamethyl ether **26** according to Brückner et al. a) 2 equiv LDA, 1 equiv $MePh_2SiCl$, $-78^\circ C \rightarrow RT$; b) **28**, $-78^\circ C \rightarrow RT$; c) $Rh/C/H_2$; d) MeLi, $-78^\circ C$; e) H_2O_2, PPTS; f) $(4\text{-}NO_2)C_6H_4SO_2Cl$, NEt_3; g) H_2O, K_2CO_3, MeOH. LDA = lithium diisopropylamide, PPTS = pyridinium toluene-4-sulfonate.

their convergent route to the pentamethyl ether **26** from *Tolypothrix conglutinata* they synthesize the homoallylic alcohols **27** and **29** by catalytic, enantioselective allylstannane additions and convert them into the two central building blocks **28** and **30** by ozonolysis and *syn*-selective ketone reduction. Coupling of these two fragments to form the complete carbon framework **31** of the polyol chain is achieved by Peterson olefination and stereoselective hydrogenation of the conjugated double bond. The butyrolactone **31** is now converted into the peroxosulfonate **32** by addition of MeLi, oxidation with H_2O_2, and reaction with *p*-nitrobenzenesulfonyl chloride. This sulfonate undergoes a Criegee rearrangement at room temperature to form the resonance-stabilized, cyclic carboxonium ion **33** by cleavage of the unstable peroxo compound and stereospecific migration of the neighboring carbon atom. Alkaline hydrolysis yields the *syn*-diol **34**, and standard methods then give the natural product in a few steps.

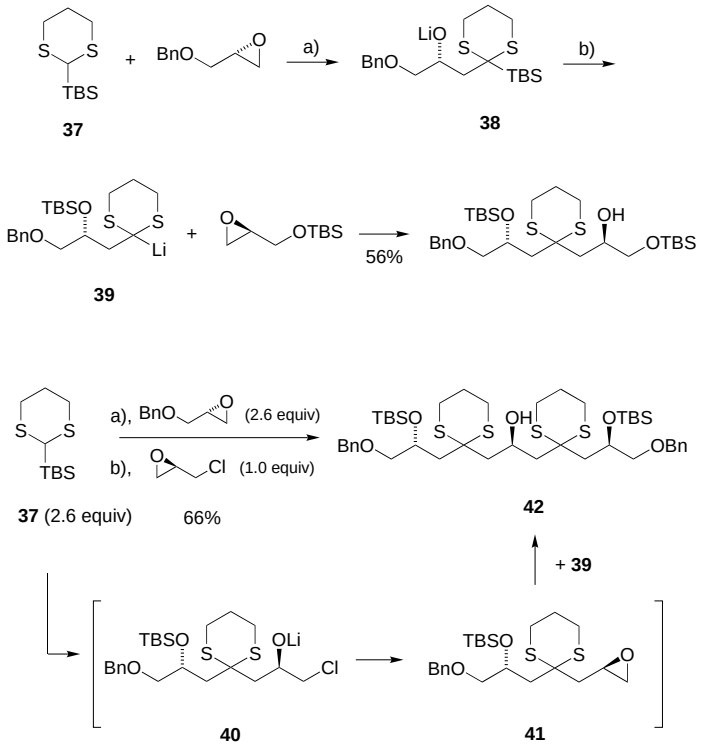
α,β-unsaturated δ-hydroxy esters and amides are excellent starting materials for the synthesis of 1,3-diols. Protected 1,3-*syn*-diols may be prepared with high stereoselectivity by intramolecular Michael addition of the hemiacetal alkoxides **35** derived from them (Scheme 6).[14] The thermodynamically controlled reaction gives almost exclusively the all-equato-



Scheme 6. Preparation of the 1,3-*syn*-diol acetals **36** by intramolecular Michael addition of a hemiacetal alkoxide according to Evans et al.

rially substituted 1,3-dioxanes **36**, which are readily deprotected by hydrogenolysis or acid hydrolysis. Evans made repeated use of this strategy that he developed in his recently completed synthesis of altohyrtin C.[15]

Smith et al. have developed a very elegant route to complex polyol structures by sequential dithiane – epoxide coupling reactions (Scheme 7).[16] Following the work of Tietze,[17]



Scheme 7. Sequential dithiane – epoxide coupling according to Smith et al. a) *t*BuLi, Et_2O, $-78^\circ C \rightarrow -45^\circ C$; b) HMPA, Et_2O, $-78^\circ C \rightarrow -25^\circ C$.

2-silyl-1,3-dithianes **37** are deprotonated with *t*BuLi in ether and converted into the stable lithium alkoxides **38** with enantiomerically pure epoxides. A fast 1,4-Brook rearrangement occurs only after the addition of 0.3 equivalents of hexamethylphosphoramide (HMPA) or 1,3-dimethylhexahydro-2-pyrimidone (DMPU) to the reaction mixture. A new lithiated dithiane **39** that can undergo nucleophilic addition to a second epoxide is formed. Thus, careful tuning of the reaction conditions allows unsymmetrical bisalkylation of dithianes with two different epoxides. The suitable selection of stoichiometric ratios and the insertion of an additional

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leaving group into the second epoxide allows a third dithiane–epoxide coupling to be achieved. The new epoxide **41** which is formed from the doubly alkylated product **40** by intramolecular S_N reaction, is opened by unreacted Brook rearrangement product **39**. Thus a C_{11}-polyol chain (**42**) with five free or protected secondary alcohol functions is formed from five components in a one pot reaction. However, this remarkable efficiency is achieved only if the complete stereochemical information of the polyol chain has already been introduced by the chiral epoxides.

Although the absolute configuration has only been established for a few polyene macrolide antibiotics, the search for new, efficient, and selective strategies for the synthesis of their polyol structures is in full swing. A number of the synthetic procedures presented here will certainly be used in future syntheses of this class of natural products.

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Keywords: aldol reactions · asymmetric syntheses · macrolides · polyenes · polyols

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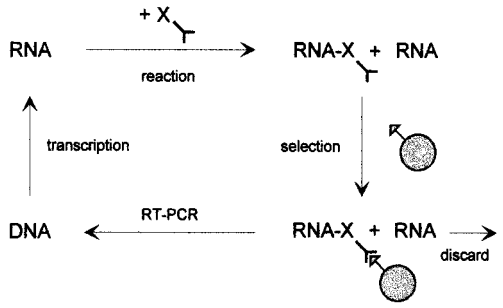
Catalysis of Organic Reactions by RNA

Christian Frauendorf and Andres Jäschke*

It has been known since the early 1980s that ribonucleic acids (RNAs) do not only participate in the flow of genetic information, but may also have catalytic properties.[1] This discovery, which was honored with the Nobel Prize in 1989, stimulated earlier hypotheses about the existence of a prebiotic "RNA world" in which both the storage of genetic information and the control of chemical reactions were carried out by RNA.[2] While the search for other naturally occurring ribozymes has not led to substantial discoveries in recent years, the use of in vitro selection and evolution techniques has provided significant contributions to the exploration of the catalytic potential of RNA.[3]

To isolate catalytically active RNA molecules, catalysis must be coupled with some other event that allows a selection. The most successful method for the selection of RNA catalysts is direct selection in which those members are selected from RNA libraries that can modify themselves in the absence of an external catalyst (Scheme 1). A combinatorial RNA pool is incubated with a substrate X, which contains an anchor group that is not present in unmodified RNA (e.g., a thiol group or biotin). After incubation, those RNAs are isolated by affinity chromatography that have been covalently linked to the anchor group. These RNA molecules are reverse transcribed into DNA and then amplified by polymerase chain reaction (PCR). The double-stranded DNA is subsequently used to generate RNA by transcription, and the next cycle starts with the incubation step. This cycle is repeated until the active RNA molecules dominate the pool.



Scheme 1. General principle of direct selection with a combinatorial RNA library.

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