Amphotericin B: 50 Years of Chemistry and Biochemistry

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Abstract: The last century has seen the isolation and synthesis of a multitude of molecules with remarkable biological activity. Some of them represent milestones in chemical space and points of reference in the various disciplines of chemical synthesis, medicine, and biology that they beneficially impact. The notable history of natural products as antibiotics dates back to the 18th century. They continue to play an indispensable role in the advances that have been seen in the quality of life for the general population. This has come about because of the rich dialog that can be found at the interfaces between chemistry, biochemistry, biology, and medicine. In this review we examine amphotericin B as an important representative of antibiotics with a long rich history. Its impact continues to be felt today in its use in the clinic to combat fungal infections. In the first part, we review the biochemical efforts aimed at the explanation of amphotericin B’s mechanisms of action; in the second part, we take a look at the impact amphotericin B has had on the chemical community in the last two decades. The continuous interest aroused by amphotericin B reveals how much we still do not know about this space.

1 Introduction

The search for antibiotics has traditionally relied on the screening of microorganisms since the time of Fleming. Concerns have, however, arisen. In fact, the well-established screening approaches not only reveal new structure classes with difficulty, but also lead to the rediscovery of known compounds. This state of affairs is alarming, especially if we consider the surge of antibiotic resistance. Solutions to this problem translate into discovering new microbial targets and charting into new regions of chemical space.

The traditional approach of medicinal chemistry to developing new drugs by modifying natural products is now assisted by the flanking new paradigms of combinatorial chemistry. This approach relies either on building blocks or on organic scaffolds ‘decorated’ with a variety of functional groups. In both cases, combinations are used in order to generate vast libraries of compounds which are then tested using high-throughput screening techniques. New trends in the preparation of libraries include the use of multicomponent reactions and of DNA. The former helps the fast assembly of complex molecular scaffolds; the latter, relying on DNA as a templating structure and as an information component, leads to the rapid identification of the active compound.

Compounds generated using combinatorial chemistry are used to dissect biological pathways and to screen for specific biological activities (i.e. no longer just for their bactericidal and bacteriostatic activities). This approach is sometimes referred to as diversity-oriented synthesis to distinguish it from the classical target-oriented synthesis. Although aimed at discovering unexplored chemical space, the structural complexity of these libraries rarely approaches the diversity found in natural products; indeed, nearly half of all drugs on the market are natural products, or are based on natural product leads.

Other approaches have therefore been explored. Understanding how nature produces its different compounds could lead, in principle, to new products after manipulation of the biochemical machinery. Indeed, this concept was tested twenty years ago. After some initial improvements, this so-called combinatorial biosynthesis appears to be a promising alternative to pure chemical approaches.

Efforts to exploit biological systems to find new compounds were rendered possible by comprehensive genome sequencing projects. Other consequences of these
projects are the discovery of new potential biological targets, and, in combination with DNA microarray technology, the identification of ‘off-target’ effects, i.e. those effects arising from interactions between the tested compound and targets other than the desired one.

2 Amphotericin B from Isolation to Structure–Activity Relationship Studies

2.1 Amphotericin B in the Context of Antibiotic Research

Amphotericin B (1, Figure 1) was isolated half a century ago along the Orinoco River in Tembladora (Venezuela) from the Streptomyces culture S. nodosus Trejo. By examining its history, one sees how amphotericin B has been a player in the evolution that has been outlined and that is shaping many research fields from medicine to synthetic chemistry.

Amphotericin B (1) was first noticed for its selective antibiotic activity against yeasts and fungi over bacteria. Interestingly, the new antifungal agent was investigated for its mechanism of action even before its structure was fully elucidated by X-ray analysis of its amide derivative 2 in 1971.

Biographical Sketches

Erick M. Carreira (born in Havana, Cuba in 1963) obtained his B.A. at University of Illinois at Urbana-Champaign in 1984 and his Ph.D. in chemistry at Harvard University in 1990 with David A. Evans. In 1992, after postdoctoral studies at California Institute of Technology with Peter Dervan, he continued his independent research as an assistant professor at the same institution. In 1996 he was promoted to Associate Professor and in 1997 to Full Professor. Since 1998, he has been Full Professor for organic chemistry at ETH Zürich. In recognition of his many contributions, Professor Carreira has received numerous awards: American Chemical Society Award in Pure Chemistry, Nobel Laureate Signature Award, Fresenius Award, a David and Lucile Packard Foundation Fellowship in Science, Alfred P. Sloan Fellowship, Camille and Henry Dreyfus Teacher Scholar Award, Merck Young Investigator Award, Eli Lilly Young Investigator Award, Pfizer Research Award, National Science Foundation CAREER Award, Arnold and Mabel Beckman Young Investigator Award, Camille and Henry Dreyfus New Faculty Award, the Associated Students of the California Institute of Technology Annual Award in Teaching, and a Richard M. Badger Award in Teaching.

Damiano M. Cereghetti (born in Mendrisio, Switzerland, in 1976) completed his biochemical studies at the Eidgenössische Technische Hochschule in Zürich in 2000. He recently finished his Ph.D. in the group of Professor Carreira working on the synthesis of amphotericin B analogues. He is currently a postdoc at Stanford University where he investigates the biochemistry of celiac disease under the supervision of Professor Chaitan Khosla and Professor Peter P. Lee.
today in three formulations containing lipid carriers which help by suppressing or mitigating some toxic side effects (e.g., nephrotoxicity) observed with the first formulation available (amphotericin B deoxycholate). It is complemented by other antifungal drugs such as the synthetic azoles and the allylamines.

Amphotericin B has a broad range of activity and is active against most pathogenic fungi. It remains the drug of choice for many serious systemic fungal infections which, owing to AIDS and the increased use of immunosuppressor drugs in organ transplantation, are becoming tragically frequent in immune-compromised individuals.

Amphotericin B belongs to the macrolide class of antibiotics as well as mass spectrometric studies and, by 1970, led to the full structural elucidation of the antibiotic. The absolute stereochemical configuration was established one year later using single-crystal analysis of the N-iodoacetyl derivative of amphotericin B.

Amphotericin B belongs to the macrolide class of antibiotics, a name introduced by Woodward to designate macrocyclic lactones. Macrolides consist of a polyketide which may be linked to saccharide(s). The term polyketide was coined to refer to natural products containing multiple carbonyl and/or hydroxyl groups, each separated by a methylene or methine spacer unit, a characteristic functionalization pattern that betrays the biosynthetic origins. Because amphotericin includes a polyene subunit, it is also referred to as polyene macrolide.

All these names highlight a particular feature of this functionally complex molecule. It comprises a 38-membered macrolactone ring which is β-glycosylated with the amino sugar mycosamine at the C-19 hydroxyl group. The lactone contains a six-membered ketal ring formed from the ketone at C-13 and the hydroxyl group at C-17, seven hydroxyl groups (at C-3, C-5, C-8, C-9, C-11, C-15 and C-35), one carboxyl group at C-16, and seven conjugated double bonds extending from C-20 to C-33.

In the resulting three-dimensional structure, the lactone ring atoms lie practically in a plane. Another peculiarity in the distribution of the different functional groups is that they are arranged so as to form two physically well-distinguished subunits: one hydrophobic (encompassing the polyene) and one hydrophilic (containing the polyol segment). This aspect is important for the physicochemical properties of amphotericin B, and it has been critical in determining the way of thinking about amphotericin B’s mode of action.

The X-ray crystal structure of amphotericin B derivative was one (though decisive) of several pieces of evidence which led Finkelstein and co-workers to eventually propose in 1973 the first concrete model of how amphotericin B induces cell death.

2.2.2 Mechanism of Action of Amphotericin B

Many of the initial studies on amphotericin B must be understood in the more general context of experiments aimed at the production of vesicles whose membranes displayed similar behavior to that of biological membranes. Addition of steroids, ionophores, polynenes, anesthetics, and lytic agents to vesicles had the common goal of inducing leakage in these vesicles. In fact, during this time experiments started to reveal how signal transduction at cell membranes was taking place. Moreover, in 1972, Singer and Nicolson published a paper in Science, further corroborating their hypothesis of the fluid mosaic model of biological membranes.

Since 1958, it has been known from the work of Gottlieb and Carter that steroids could inhibit the damaging effects of polyene antibiotics on fungal cells. Three years later, independent work by Gottlieb and Lampen using permeability studies showed that the polynenes were acting at membranes. In 1962, both Lampen and Kinsky separately showed a close correlation between the ability of biomembranes to take up nystatin (4) and their ergosterol content.

In 1966, Kinsky tentatively proposed a polyene-induced sterol reorientation via a domino-like mechanism which would lead to water-filled pores. The hypothesis was based on measurements of surface pressure variations of lipid monolayers by addition of polynenes and electron microscopy. A clearer picture of these events was advanced two years later by Andreoli and co-workers. Based on permeability studies, these workers hypothesized a membrane-bound unit of general formula (PnCm)q
(P = polyene, C = cholesterol). One year later they provided evidence for a structure compatible with either an aqueous channel or a pore.36b

In 1973, Finkelstein and co-workers attempted to generate a model to explain the different pieces of information.37 In all cases, the polar groups are enclosed in a lipophilic hydrocarbon coat, which is soluble in the lipid layer. However, the mechanism of action of amphotericin B was already known to be different. The dependence of membrane conductance on valinomycin concentration shows a linear relationship, whereas in the case of nystatin the conductance is proportional to the drug concentration raised to the $n^{th}$ power.38

The authors proposed a pore composed of two halves in order to span the entire membrane bilayer. This requirement is due to the length of amphotericin B (21 Å) which is approximately the length of a lecithin molecule. Half-pores would then float independently in a sea of lipid, consistent with the fluid mosaic model.37c The assembly of two half-pores into a channel would be favored by hydrogen bonding between the facing hydroxyl groups at C-35.

The authors also claimed that the wedge between each pair of amphotericin molecules could accommodate a sterol molecule. The internal pore radius was estimated to be about 7 Å. On the basis of previous results obtained with permeability studies in thin lipid membranes, the number of polyene molecules constituting the pore was approximated to be between 4 and 8. The pore would exist in a dynamic equilibrium.

At about the same time, Hsuchen and Feingold raised some doubts about the absolute need for sterols for polyene efficiency. In their work, they stressed the importance of the fatty acid composition of the phospholipid.39 Specifically, when egg lecithin liposomes were used, the usual relation between the amount of cholesterol and polyene-induced leakage was observed. However, in the case of dipalmitoyl lecithin liposomes, the effect was reversed: leakage was observed in the absence of cholesterol, and inhibition in the presence of the sterol. The susceptibility of membranes to polyenes would relate to the overall state of membrane organization (an idea reminiscent of Kinsky’s first proposal). Also based on these observations, Finkelstein, together with Marty, refined his first hypothesis.37b In this case, the polyene would self-associate into pores and the sterols would have a role only in ordering.

In 1974, a series of three papers appeared in Biochimica et Biophysica Acta authored by the group of De Kruijff.40 This independent research was conducted on both liposomes and Acholeplasma laidlawii cells.41 and confirmed the results obtained by Finkelstein and co-workers. With the aid of a space-filling model, the pore structure was estimated to have the formula $(\cdot P \cdot C \cdot)_8$ (P = polyene, C = cholesterol). In this case the pore radius was estimated to be about 8 Å.

In their first article,40a De Kruijff and collaborators addressed the nature of the sterol.42 Incorporation of cholesterol, cholestanol or ergosterol into the membranes of A. laidlawii rendered the organism sensitive to amphotericin B or filipin. It was deduced that the minimal requirements for a sterol to induce polyene sensitivity were: a 3β-OH group, a planar ring system, and a hydrophobic side chain at the C-17 position.

The same group later43 tested the double half-pore model by varying the lipid length in the liposome and by adding the polyene either from both sides of the bilayer or from one side only (a similar experiment was also proposed by Finkelstein37b,44). One reason for skepticism towards the double half-pore model was the supposed low probability of two half-pores being located opposite each other (given also the rapid turnover of the half-pore). The experiment showed two things: 1) a half-pore model was sustainable; and 2) exchange of amphotericin B between membranes was taking place.

This last point was also confirmed in 1981 by the Bolard group using circular dichroism spectroscopy and permeability measurements. Ten years later,45 they presented a refined model which accounted for the different interactions of amphotericin B with cholesterol and ergosterol, respectively.

Emblematic of the intriguing complexity of amphotericin B’s mechanism of action is a report by the Hartsel group which appeared in 1991.46 They suggested the formation of ion-conducting membrane defects at the antibiotic–lipid interface.

A detailed study on the correlation between membrane composition and amphotericin B-induced K+ efflux by Carreira and collaborators47 has recently appeared. These authors used POPC LUVET100 with different amounts of admixed sterols38 and showed that amphotericin B monomers interact preferentially with an intermediate membrane phase between the liquid-disordered state and the liquid-ordered state. Moreover, only the amphotericin B monomer is able to distinguish between ergosterol- and cholesterol-containing membrane vesicles.

Despite having also been the subject of computer modeling studies,50 the channel hypothesis with all its variations has been questioned. For example, it has been shown that amphotericin B’s activity is enhanced by superoxide radicals51 and, interestingly, that the antibiotic loses its efficacy under hypoxic conditions.52 Also, a stimulatory action on innate immune cells has been documented, an observation that cannot be easily explained in the frame of the channel hypothesis.53

2.2.3 Structure–Activity Relationship Studies, Part I

The studies outlined thus far focused on the structural properties of sterols and the bilayer. Manipulation of amphotericin B was initially pursued in the context of its structural elucidation in the pioneering studies of Borowski and collaborators.54,25b,c

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In 1988, a paper by Borowski and co-workers appeared dealing with the correlation between amphotericin B derivatives and their biological activity. Modifications of amphotericin B at the carboxyl- and amino-termini were correlated with activity for: 1) yeasts (S. cerevisiae, C. albicans) growth inhibition; 2) potassium release from yeasts and erythrocytes; and 3) haemolysis of erythrocytes. These results confirmed previous experiments: 1) a positively charged nitrogen atom is necessary for activity; 2) the lack of a negative charge at the carboxyl group leads to improved selectivity for ergosterol versus cholesterol; 3) shifting the positive charge via N-aminoacylation while retaining the zwitterionic character also leads to improved selectivity. We note, however, that compound 2 was also reported to be biologically active.

Subsequently, modifications of amphotericin B were investigated by a group at SmithKline Beecham. They showed that functionalization of amphotericin B at the C-13 hemiketal position leads to a minimal decrease in activity (two-fold less active than amphotericin B). However, these analogues displayed improved selectivity (Candida spp. being more sensitized than mammalian erythrocytes). Functionalization at C-14 of a C-13,14 vinyl ether derivative (formed through dehydration of the ketal ring) also led to compounds with in vitro antifungal activity and less nephrotoxicity.

More recently, Carreira and collaborators showed that the amphotericin B–fluorescein conjugate 5 (Figure 3) could be used to test amphotericin B’s distribution in S. cerevisiae FY250 and Jurkat human T cells. This compound proved to induce rapid K⁺ efflux from liposomes over a wide range of concentrations (up to 500 µM). Intriguingly, flow cytometry studies revealed that both yeast and Jurkat cells recruit 5, and epifluorescence microscopy showed that while the conjugate is localized at the membrane in yeast, it is taken up by lymphocytes.

2.2.4 Degradation Studies

Since the beginning of the 1980s, amphotericin B has caught the interest of the synthetic community. The combination of intriguing biological properties and the chemical complexity provided the impetus for synthetic efforts.

In 1986 the Nicolaou group reported degradation studies encompassing the entire amphotericin B skeleton (Scheme 1). The sequence started by applying a modified procedure by Mechlinski and Schaffner, in which amphotericin B (1) was dissolved in dimethylsulfoxide and methanol and reacted at 0 °C with acetic anhydride. The acetamide was converted into its methyl ester (CH₂N₂). Addition of diethyl ether and filtration of the resulting yellow precipitate afforded a material of sufficient purity for subsequent manipulations.

In this report, the hydroxyl groups were left unprotected and the ester 6 was reduced in hot methanol with sodium borohydride. The primary alcohol was then selectively silylated and the polyene was oxidized and removed ozonolytically. Reductive workup with triphenyl phosphine yielded a dialdehyde intermediate which was immediately reduced with sodium borohydride to the corresponding pentaol 7.

After saponification to remove the six-carbon-long appendage 9, the glycosylated glycol 8 was subjected to a series of manipulations involving Grieco selenation which led to the ester 10. Deglycosidation of this fragment was effected with potassium carbonate in methanol. The protected polyol 11 served as starting material to test the macrolactonization step in the total synthesis.

In Scheme 1, intermediate 6 is represented as a single compound. In reality, as pointed out by Masamune in 1988, it consists of a mixture of two diacetonides, 6a and 6b (Figure 4). In a subsequent article, an alternative and more efficient protocol for performing the deglycosidation was described.
scribed. $N$-Acylamphotericin B methyl ester (12) was per-
silylated with trimethylsilyl trifluoroacetate and then
oxidatively deglycosidated with $N$-bromosuccinimide in
carbon tetrachloride (Scheme 2). The amphoteronolide
derivative 14 could be isolated in 20–25% yield.

Interestingly, when the group at SmithKline Beecham attempted to reproduce the persilylation of 12 with tri-
 methylsilyl trifluoroacetate, the only isolable product was
the unstable dihydropyrane 15 (Scheme 3). This substrate
was used to synthesize the amphotericin B derivatives dis-
cussed in the previous section.

The problem could be circumvented by first methylating
the acetal moiety of $N$-Fmoc-amphotericin B and then re-
placing trimethylsilyl with triethylsilyl for protection. The
triethylsilyl group exhibited increased stability dur-
ing the synthesis; and these groups could be subsequently
removed under mild conditions (in contrast, tert-bu-
tyldimethylsilyl is difficult to remove under the necessary
mild conditions). By carrying out the reaction in hexane at
room temperature over 16–24 hours, the authors were able
to isolate the desired product 17 in 69% yield (Scheme 3).

In 1988, a series of four articles by Nicolaou and co-work-
ers appeared in *The Journal of the American Chemical So-
ciety* detailing their total synthesis of amphotericin B. The
first article contained a summary of the degradation
studies on amphotericin B. The variations introduced con-
cern largely the protecting-group strategy.

The group of Masamune reported a degradation study in
which the mycosamine could be cleaved under either re-
ducing conditions or oxidative conditions (Scheme 4). In
the first case, the partially protected amphotericin B de-
rivative 6 was converted into deglycosidated 19 upon re-
duction of the polyene system and double-bond migration. The
compound obtained was then degraded further to 20.

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**Scheme 1** Nicolaou’s first degradation approach. *Reagents, conditions, and yields:* a) Ac<sub>2</sub>O, DMSO–MeOH (1:1), 0 °C, then CH<sub>2</sub>Cl<sub>2</sub>–Et<sub>2</sub>O, 0 °C; b) CSA cat., Me<sub>3</sub>C(O)Me–MeOH (1:3), 66% over 2 steps; c) NaBH<sub>4</sub>, MeOH, 40 °C, 85%; d) TBDPSCl, imid, DMF, 0 °C, 80%; e) O<sub>3</sub>, MeOH–CH<sub>2</sub>Cl<sub>2</sub> (1:4), then PPh<sub>3</sub>, 0–25 °C, 83%; f) NaBH<sub>4</sub>, 25 °C, 85%; g) K<sub>2</sub>CO<sub>3</sub>, MeOH, 25 °C, (8): 79%, (9): 74%; h) $o$-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>SeCN, Bu<sub>3</sub>P, THF–py (2:1), 0 °C, 85%; i) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, –78 °C, then (i-Pr)<sub>2</sub>NH, benzene, reflux, 70%; j) LiOH, THF–H<sub>2</sub>O (2:1), 0–25 °C; k) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, –78 °C, then PPh<sub>3</sub>, 0–25 °C, 57% over 2 steps; l) K<sub>2</sub>CO<sub>3</sub>, MeOH, 25 °C, 79%.

**Scheme 2** Nicolaou’s oxidative deglycosidation. *Reagents, conditions, and yields:* a) TMSOTf, 2,6-lutidine, 0 °C, CH<sub>2</sub>Cl<sub>2</sub>, 90%; b) NBS, CaCO<sub>3</sub>, CCl<sub>4</sub>, 25 °C, 5–8 h, 20–25%.

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using conditions analogous to those reported by Nicolaou. The alternative path used the fully protected amphotericin B derivative 21 and yielded the polyenone system 22 in 50% yield after treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

Since Fmoc proved to be unstable to Grignard reagents, it was replaced by the trifluoroacetyl group (25, Scheme 5). With this protecting group, C-16 ketone analogues were prepared.68 Although the chemists at SmithKline Beecham relied on the work of Nicolaou and collaborators (Scheme 2), they made use of a different protecting group for the amine. Inspired by the previous work of Wright et al.,59d where N-Fmoc-protected amino acids were coupled to the amino group of amphotericin B, they decided to use Carpino’s Fmoc protecting group70 due to its lability to mild base (Scheme 5).71 The N-Fmoc-protected amphotericin B methyl ester 23 could be reduced to alcohol 24, which in turn served for the preparation of different amphotericin B analogues containing unsaturated chains at C-16.72

2.2.5 Structure–Activity Relationship Studies, Part II
The approach of the Nicolaou and SmithKline Beecham groups was later implemented by the Rychnovsky group73 in their studies aimed at evaluating the importance of the amphotericin B polyene moiety for its antibiotic activity.74 The degradation and subsequent reconstitution of the modified macrolactone is depicted in Scheme 6. After protection of the amino functionality with N-Fmoc-succinimide and the carboxylic acid with diazomethane, per-silylation with chlorotriethylsilane led to the fully protected macrolide 26. One may note that under these conditions, the ketal undergoes opening to the corresponding ketone (this can be contrasted with 13 in Scheme 2).

Scheme 3 Degradation studies at Smith-Kline. Reagents, conditions, and yields: a) TMSOTf, 2,6-lutidine, 0 °C, CH₂Cl₂; b) TESOTf, 2,6-lutidine, 0 °C, CH₂Cl₂, (17): 31%, (18): 24%; c) TESOTf, 2,6-lutidine, 0 °C, hexane, (17): 69%, (18): 0%.62

Scheme 4 Masamune’s degradation studies. Reagents, conditions, and yields: a) Al(Hg), THF, 2% H₂O, 25 °C, 45%; b) DDQ, THF, 25 °C, 50%.66
The dialdehyde resulting from ozonolytic cleavage of the polyene 26 was converted into the divinyliodide 28 by the method of Takai. Sonogashira cross-coupling was then used to reconstitute the macrolactone. In the event, biaryl 29 was reacted with 28 in the presence of catalytic amounts of Pd(II) and Cu(I) and piperidine as base to yield the macrocycle 30 in 6% yield. After desilylation and N-Fmoc deprotection, the methyl ester derivative 31 was obtained. Substrate 32 was also used to form the open polyketide derivative 34. In this case, phenylacetylene was used as coupling partner (Scheme 6).

The cyclic analogue 31 showed measurable, but poor, biological activity against \( C.\) albicans and Cryptococcus neoformans (the minimum inhibitory concentration being about three orders of magnitude higher than for amphotericin B). The acyclic analogue 34 was devoid of activity. These experiments underscore the vital importance of the polyene in the recognition process.

2.2.6 Biosynthesis of Deoxyamphotericins

In 1998, the Rawlings group published the incorporation of isotopically labeled sodium acetate and sodium propionate into amphotericin B. The authors showed that: 1) amphotericin B is made up of sixteen ‘C2’ acetate and three ‘C3’ propionate units; 2) the hydroxyl group at C-8 is inserted after cleavage of the antibiotic precursor from the PKS; and 3) the carboxylic acid is formed by oxidation of the methyl group at C-41.

Three years later, the Caffrey group was able to clone a large polyketide synthase gene cluster from total cellular DNA of \( S.\) nodosus. The six genes (amphA, B, C, I, J, and K) code for one loading module and eighteen elongation modules. Within the same gene cluster are also encoded the enzymes that assemble the mycosamine sugar, the glycosyl transferase to attach the sugar to the ring, and two cytochrome P450 monooxygenases probably responsible for hydroxylation at C-8 and oxidation of the C-16 methyl branch to a carboxyl group. Taking advantage of this, the Caffrey group was able to manipulate the biosynthetic pathway of amphotericin B and obtain 8-deoxyamphotericolides. These displayed reduced water solubility and diminished antifungal activity. 8-Deoxyamphotericins were also obtained which showed reduced water solubility, but they retained activity as antifungal drugs. Subsequently, they were able to form a derivative with a contracted macrolactone ring, missing two double bonds.

3 Studies toward the Total Synthesis of Amphotericin B

The last review of the literature concerning the synthetic studies of amphotericin included work through 1990. The rapid pace of developments in synthetic methodology, and specifically its application to the synthesis of amphotericin B, permits us to integrate in this review the literature through 2004. We focus on two specific aspects (macrolactone formation and stereoselective synthesis), situating them within a historical perspective.
3.1 Synthesis of Macrolides at the Beginning of the 1980s

By the end of the 1970s, synthetic chemists had developed methods to synthesize important groups of natural products such as steroids, terpenes, and alkaloids. In the area of antibiotics, syntheses for penicillins, cephalosporins, and tetracyclins had been disclosed, while the macrolides still presented a major challenge.

In reviewing the state of the art in macrolide synthesis in those years, both Masamune\textsuperscript{82} and Nicolaou\textsuperscript{83} noted two major problems: 1) formation of the macrocyclic ring; and 2) assembly of the polyol subunits. It goes without saying that significant progress in asymmetric bond construction had been made since Woodward’s statement concerning erythromycin in 1956: ‘It looks at present quite hopelessly complex, particularly in view of its plethora of asymmetric centers.’\textsuperscript{84} Indeed, by 1978, the Corey group had accomplished the first total synthesis of erythronolide B.\textsuperscript{85}

Scheme 6  Rychnovsky’s studies on the polyene portion of amphotericin B (1). Reagents, conditions, and yields: a) N-Fmoc-succinimide, py, DMF–MeOH, r.t.; b) CH\textsubscript{2}N\textsubscript{2}, r.t., 73% over 2 steps; c) TESCl, imid, DMF, r.t., 87%; d) O\textsubscript{3}, –78 °C, CH\textsubscript{2}Cl\textsubscript{2}–MeOH, then PPh\textsubscript{3}, –78 °C to r.t., 87%; e) CrCl\textsubscript{2}, CHI\textsubscript{3}, THF–dioxane, r.t., 62%; f) either: 29, PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2}, CuI, THF, r.t., piperidine, (30): 6%; or: 32, PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2}, CuI, THF, r.t., piperidine, (33): 88%; g) HF–py, 97% from 30, 66% from 33; h) piperidine, (31): yield not reported; (34): 87%.\textsuperscript{74}
3.1.1 Macrocyclization Reactions

A brief look into the historical development of macrocyclization reactions is a worthwhile undertaking. After Perkin\textsuperscript{86} and others had demonstrated that rings containing fewer than six carbon atoms could be prepared, considerable additional work was required to demonstrate that larger cycles could be prepared and isolated. The research of Ruzicka was directed toward this latter goal.

In a series of 25 publications in \textit{Helvetica Chimica Acta} between 1926 and 1933 Ruzicka\textsuperscript{87} demonstrated the occurrence in nature of rings larger than the six-membered ones (such as muscone 35\textsuperscript{87a,87b} and zibetone 37,\textsuperscript{87a} see Figure 5). Ruzicka also succeeded in the preparation of many of these cyclic compounds by optimizing the intramolecular condensation of diacids salts.\textsuperscript{87b–d} In particular, thorium salts proved to be superior in efficiency to the usually employed calcium salts. Subjection of these cyclic ketones to the oxidative conditions developed by Baeyer and Villiger\textsuperscript{88} allowed Ruzicka and collaborators to prepare medium-sized lactones (Scheme 7, \textit{39}→\textit{38}).\textsuperscript{87i}

Subsequently, Ziegler\textsuperscript{89} showed that these cyclic ketones were attainable in superior yields via an ingenious modification of the Dieckmann condensation. While Ruggli\textsuperscript{90} used high-dilution conditions to favor the unimolecular cyclization over oligomerization side reactions, Ziegler and co-workers kept the starting material concentration low by adding it over a long period of time. Other tricks can be found in the detailed report by Ziegler et al.\textsuperscript{89}

Kinetic studies were pursued by Stoll\textsuperscript{91} and others\textsuperscript{92} in order to better understand the cyclization mechanism. For instance, reactions under investigation involved lactonization of \(\omega\)-hydroxyacids in refluxing benzene\textsuperscript{91a} or lactonization of the potassium salt of \(\omega\)-bromoacids (Scheme 7, path B).\textsuperscript{91c,92b} In the mid 1970s, a series of papers by Baldwin\textsuperscript{93} appeared, stating some empirical rules for ring-closure reactions.

Though limited to ‘simple’ systems, these experiments were decisive in demonstrating the existence and accessibility of large rings.\textsuperscript{87i} However, the isolation of more functionalized molecules required the development of milder and more sophisticated synthetic methods.

In the 1950s and 1960s, fragmentation reactions\textsuperscript{94} proved to be powerful tools to access medium-sized rings. Reports by Eschenmoser,\textsuperscript{95} Grob,\textsuperscript{96} Stork,\textsuperscript{97} Wharton,\textsuperscript{98} Marshall,\textsuperscript{99} and Corey\textsuperscript{100} experimentally demonstrated the concept. The Borowitz group\textsuperscript{101} made use of the fragmentation of enol ethers in the presence of MCPBA with the purpose of preparing medium-size lactones. The fragmentation approach proved to be a powerful tool for constructing medium-sized rings and was also extended to multiple fragmentations to access even larger rings.\textsuperscript{102}

The simplest access to macrolides would involve cyclization of an acyclic precursor (Scheme 8). This is exactly what Stoll did when he lactonized \(\omega\)-hydroxyacids in refluxing benzene in the presence of a Bronsted acid.\textsuperscript{91a} However, the conditions were prohibitive for complex molecules. In 1968, a group at Merck\textsuperscript{103} reported the activation of the acid moiety with trifluoroacetic acid anhydride in the form of a mixed anhydride. The method was used to form the macrolactone ring of zearalenone.

In 1972, Colvin et al.\textsuperscript{104} synthesized racemic pyrenophorin by effecting the ring closure via lactonization (Scheme 8). The acid was activated as an imidazolide following the procedure of Staab.\textsuperscript{105} In a similar fashion: 1) Corey\textsuperscript{106} activated the acid as an \(\beta\)-(2-pyridyl) thioate following the procedure of Mukaiyama;\textsuperscript{107} 2) Masamune\textsuperscript{108} (in the context of the methymycin synthesis\textsuperscript{109}) used thioesters which were then activated with Hg(II); and 3) Mukaiyama\textsuperscript{110} activated the acid in situ by using 1-methyl-2-chloropyridinium iodide. In their total synthesis of nonactin, the Gerlach group\textsuperscript{111} made use of a modification of the Masamune macrolactonization which also allowed for the exploitation of metal templation.\textsuperscript{112} Nowadays, the method of choice is the one introduced by Yamaguchi, where the acid is activated as an anhydride with 2,4,6-trichlorobenzoyl chloride (Scheme 8).

Concurrently, alternative approaches were tested, leading to macrolides via carbon–carbon double-bond formation (Scheme 9). For instance, Corey used tetracarboxylic acid (0) to close the diallyl bromide termini of an ester-containing acyclic precursor (Scheme 9, \textit{50} → \textit{49}).\textsuperscript{114} This strategy was used in the synthesis of humulene.\textsuperscript{115}

Figure 5 Some musk-smelling compounds.
The Wittig reaction and derivatives thereof were also used for this purpose (Scheme 9, path B). After a first report by Masamune,\textsuperscript{82} this disconnection was also exploited by Burri\textsuperscript{116} in the synthesis of vermiculine, and by Stork\textsuperscript{117} and Nicolaou\textsuperscript{118} in the synthesis of \textit{rac}-muscone. In the context of amphotericin B, this method was first applied by Floyd and Fritz\textsuperscript{119} at Squibb towards polyene macrolide mimics. More recently, ring-closing metathesis has complemented the Horner–Wadsworth–Emmons reaction as a macrocyclization technique (Scheme 9, path C).\textsuperscript{120}

### Equation 1

1,3-Polyols through substrate-controlled diastereoselective reduction of $\beta$-hydroxy ketone.

\[
\begin{align*}
\text{Equation 1} & \quad 1,3\text{-Polyols through substrate-controlled diastereoselective reduction of $\beta$-hydroxy ketone.}
\end{align*}
\]

A \textit{syn} reduction was first reported by Narasaka\textsuperscript{122} using tributylborane in THF and a catalytic amount of air to form dibutylboronic ester at room temperature. The reducing agent (NaBH$_4$) was subsequently added at $-78$ °C. The procedure was later improved with the use of methanol.\textsuperscript{123} Subsequent work by Evans\textsuperscript{124} disclosed a procedure to afford the \textit{anti} relationship. In the event, tetramethylammonium triacetoxylborohydride participates in an exchange process involving the substrate hydroxyl group, which results in intramolecular delivery of the hydride.

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**Scheme 9** Possible disconnections of a hypothetical macrolactone 38.
β-Hydroxy ketones can be accessed through the well-established aldol reaction. It is worth noting, however, that no use of this reaction has been made to generate the 1,3-polyol pattern of amphotericin B. The reason is that aldol reactions of methyl ketones usually yield poor asymmetric induction. The problem was solved only relatively recently by using chiral boron enolates and via catalytic, asymmetric methods.

Alkylation of β-hydroxy esters has found use in the construction of the propionate moiety of amphotericin B. Commercially available (S)-hydroxybutyric acid ethyl ester represents a common building block.

Of major interest for our discussion on amphotericin B are methods relying on epoxide chemistry (Equation 2). In 1982, Kishi, Masamune and Sharpless, and Nicolaou reported exploiting epoxides as building blocks for 1,3-polyhydroxylated systems. After having installed the desired stereochemistry by means of the Katsuki–Sharpless epoxidation, the authors were able to stalled the desired stereochemistry by means of the Katsu-

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The first disconnection on amphotericin B (Equation 4) with notation referring to amphotericin B. Reagents, conditions, and yields: a) HONO, 85%; b) BH₃·SMe₂, 72%; c) TBDPSCI, py, DMAP, CH₂Cl₂, 85%; d) TBDPSCI, py, DMAP, CH₂Cl₂, 85%; e) TBDPSCI, py, DMAP, CH₂Cl₂, 85%; f) TBDPSCI, py, DMAP, CH₂Cl₂, 85%; g) TBDPSCI, py, DMAP, CH₂Cl₂, 85%; h) TBDPSCI, py, DMAP, CH₂Cl₂, 85%; i) TBDPSCI, py, DMAP, CH₂Cl₂, 85%; j) TBDPSCI, py, DMAP, CH₂Cl₂, 85%; k) TBDPSCI, py, DMAP, CH₂Cl₂, 85%; l) TBDPSCI, py, DMAP, CH₂Cl₂, 85%; m) TBDPSCI, py, DMAP, CH₂Cl₂, 85%; n) TBDPSCI, py, DMAP, CH₂Cl₂, 85%; o) TBDPSCI, py, DMAP, CH₂Cl₂, 85%; p) TBDPSCI, py, DMAP, CH₂Cl₂, 85%; q) TBDPSCI, py, DMAP, CH₂Cl₂, 85%; r) TBDPSCI, py, DMAP, CH₂Cl₂, 85%; s) TBDPSCI, py, DMAP, CH₂Cl₂, 85%; t) TBDPSCI, py, DMAP, CH₂Cl₂, 85%; u) TBDPSCI, py, DMAP, CH₂Cl₂, 85%; v) TBDPSCI, py, DMAP, CH₂Cl₂, 85%; w) TBDPSCI, py, DMAP, CH₂Cl₂, 85%; x) TBDPSCI, py, DMAP, CH₂Cl₂, 85%; y) TBDPSCI, py, DMAP, CH₂Cl₂, 85%; z) TBDPSCI, py, DMAP, CH₂Cl₂, 85%.

McGarvey made use of aspartic acid 72 to derive 2-phenyloxazolines such as 75 which served as a rigid equivalent to β-dicarbonyl fragments (Scheme 11). 2-Phenyloxazole 75 was used in the context of McGarvey’s synthetic studies on amphotericin B.

The Lipshutz group also addressed the polycarbonate problem. They opened an epoxide with (vinyl)₂Cu(CN)Li₂ to yield an allylic alcohol which could be oxidized to an extended epoxide. Iteration of the sequence led to all-

syn 1,3-polyols.

Equation 2 Access to 1,3-polyols via epoxidation of allylic alcohols and opening of oxirane with Red-Al.

Equation 3 Preparation of 1,3-polyols through iteration of an allyl-
cation/epoxidation–oxidation sequence.

Also of interest is the recognition that isoxazolines represent aldol surrogates (Equation 4). This method has recently been developed into a powerful tool to access polypropionate and polyacetate compounds. Other strategies involving olefin oxidation and cyclization directed by the hydroxyl group have also been reported.

The chiral pool is a valuable source of functionalized, optically active fragments. As shown by the work of Barton, deoxygenation of secondary alcohols to methylene units constitutes an efficient way to convert natural compounds, such as sugars, into advanced complex mole-

Equation 4 Synthesis of β-hydroxy ketones via nitrile oxide cy-
claddition to olefins.
along with the dipropionate unit C33–C37 (A2). The B segment contains three polyhydroxylated fragments B1, B2 and B3. In addition to the 1,3-polyol motifs, B2 contains a syn-1,2-diol (C8–C9) and B3 is functionalized with a carboxylic acid at C-16.

Figure 6 Retrosynthetic analysis of amphotericin B (I). In the polyene portion (A1), other disconnections are possible, but only one is shown. Adapted from ref. 81.

3.2.2 Synthetic Studies on the B1 and B2 Fragments

To join the two subunits B1 and B2 (Figure 6) two strategies have been devised (Figure 4): 1) C–C bond formation between C-7 and C-8; and 2) coupling between C-6 and C-7. The latter approach does not generate any new stereogenic center, while the former does (at C-8). Though synthetically more efficient, the latter strategy is not without complications, such as poor stereocontrol. In their synthesis, Masamune and co-workers discovered only at a late stage that the product of their addition was actually a carboxylic acid at C-16.

Masamune was the only investigator to have examined both approaches (Figure 7). Allylic alcohol 77 (derived in five steps from malic acid, 75) was oxidized stereospecifically to 78 by means of Sharpless asymmetric epoxidation (Scheme 12). Red-Al mediated opening of oxirane 78 afforded 1,3-diol 79 which, after some protecting group manipulations, was converted into triflate 80. The latter served as electrophile for coupling with sulfoxide 85. Alternatively, displacement of the activated alcohol with lithiated p-tolylmethylsulfoxide followed by sulfide oxidation afforded sulfoxide 81.

Functionlization of the primary alcohol in epoxide 78 as the benzyl carbonate 82 led, after treatment with AlCl3, to debenzylation and cyclization to a five-membered ring carbonate via opening of the epoxide at C-8 (Scheme 13). After saponification of the resulting carbonate, glycol 83 was either degraded and oxidized with NaIO4 to afford aldehyde 86, or processed into epoxide 84. Thiolyte attack on the less hindered carbon opened oxirane 84 to give, after oxidation, sulfoxide 85.

In this way, Masamune and co-workers were able to examine both the C6–C7 and the C7–C8 disconnection (Scheme 14). Sulfoxide 81 and aldehyde 86 gave a 15:1 mixture of epimers. Only towards the end of the synthesis and after comparison with a sample of degraded amphotericin B66 did the authors discover that the major diastereomer resulting from the addition corresponded to the wrong epimer (see later).

The Sharpless asymmetric epoxidation is also a key feature of Nicolaou’s route to the C1–C13 fragment (Scheme 15, Scheme 16, Scheme 17). Stereoselective epoxidation of the allylic alcohol 89, followed by two-carbon chain extension and reduction, led to a new aliphatic alcohol 91 which was subjected to a second asym-
metric epoxidation (Scheme 15). A sequence of protecting group manipulations led to epoxide 92. A similar sequence of reactions was used to prepare the enantiomer, ent-92, starting from allylic alcohol 89 (Scheme 16). Opening of ent-92 with Red-Al afforded triol ent-93, whose primary alcohol was then selectively silylated and the 1,3-diol protected as the acetonide. Debenzylation of 95 and oxidation of the resulting primary alcohol gave methyl ester 96 which was allowed to react with lithiated dimethyl methylphosphonate to yield β-ketophosphonate 97 in 71% yield over three steps.

Scheme 13 Masamune’s approach to the C7–C12 and C8–C12 fragments. Reagents, conditions, and yields: a) CICO₂CH₂Ph, py, THF, –40 °C, 100%; b) AlCl₃, Et₂O, –20 °C, 64%; c) 1% H₂SO₄, MeOH, r.t., 92%; d) TBSCl, imid, THF, –20 °C, 74%; e) Me₂C(OMe)₂, cat. CSA, r.t., 95%; f) K₂CO₃, MeOH, r.t., 100%; g) NaIO₄, MeOH–H₂O, r.t., 96%; h) PhCOCN, Et₃N, CH₃CN, –10 °C, 77%; i) TsOH, acetone, r.t., 92%; j) Bu₄NOH, Et₂O, MeOH (trace), r.t., 91%; k) PhSH, 0.5 M NaOH, THF, 0 °C to r.t., 91%; l) NaIO₄, MeOH–H₂O, 0 °C, 87%.144

Scheme 14 Masamune’s approach to the C1–C12 fragment. Reagents, conditions, and yields: a) BuLi, THF, HMPA, –30 °C, then 80, –30 °C to –20 °C, 30%; b) Ra-Ni, acetone, r.t., 86%; c) LDA, THF, –60 °C, then 86, –78 °C, 90%, dr 1:15 in favor of the undesired epimer, epi-88.144

Scheme 15 Nicolaou’s approach to the C1–C6 fragment. Reagents, conditions, and yields: a) Ti(O-Pr)₄, (+)-DET, t-BuOOH, CH₂Cl₂, –20 °C, 75%; b) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, –78 °C, 98%; c) Ph₂P=CHCO₂Me, benzene, r.t., 77%; d) DIBAL·H, CH₂Cl₂–hexane, –78 °C, 82%; e) PivCl, py, 0 °C, 95%; f) TBDPSCI, imid, DMF, 96%; g) DIBAL·H, CH₂Cl₂–hexane, –78 °C, 87–91%; h) Ti(Oi-Pr)₄, (+)-DET, t-BuOOH, CH₂Cl₂–20 °C, dr 9:1, 60%; i) Red-Al, THF, r.t., 85%; j) SO₃, py, Et₃N, DMSO–CH₂Cl₂ 2:1, r.t., 92%.131,145

Scheme 16 Nicolaou’s approach to the C7–C13 fragment. Reagents, conditions, and yields: a) Red-Al, THF, r.t., 85%; b) TBSCI, imid, DMF, r.t., 90%; c) Me₂C(OMe)₂, cat. CSA, r.t., 95%; d) H₂, 20% Pd/C, EtOH, r.t., 100%; e) NaIO₄, cat. RuO₄, CH₃CN–CCl₄–H₂O (2:2:3), r.t., then CH₃N₂, 76%; f) LiCH₂P(O)(OMe)₂, THF, –78 °C to r.t., 96%.131,145

The coupling between the two units (94 and 97) was easily performed with a Horner–Wadsworth–Emmons reaction. Enone 98 was then reduced in two steps to alcohol 99. Reduction with L-selectride yielded the desired epimer as the only product. After protection of the hydroxyl group at C-8, the primary alcohol at C-13 was converted into a phosphonate which upon deprotonation was converted into a 1:1 mixture of epimeric sulfides (100).

In his approach, McGarvey146 used the 2-phenyloxazoline 75 (Scheme 11) as a key launching point. Aldehyde 101, obtained by DIBAL·H reduction of thioster 75, was treated with allyltrimethylaluminate to afford the 1,3-aminooalcohol 102 in 84:16 antilsyn diastereoselectivity (Scheme 18). After silylation of the free hydroxyl group, followed by reduction and opening of the oxazoline system, the resulting aminooalcohol was converted into the masked epoxide 103 by treatment with dichlorocarbene.143 Oxirane 103 served as a common starting material for both the C1–C7 and the C8–C13 fragments.
Opening of epoxide 103 with phenylthiolate was followed by acidic cleavage of the TBS group with concomitant acetoneide formation (Scheme 20). The sulfide obtained was oxidized and subjected to Pummerer rearrangement in refluxing acetic anhydride. The resulting thioacetal was converted into aldehyde 108 under basic conditions.

Scheme 20 McGarvey’s approach to the C8–C13 fragment.

The coupling of 106 and 108 (via I–I exchange) proved to be more efficient than the addition of lithiated sulfoxide 107 to aldehyde 108. In either case, the alcohol obtained was oxidized to ketone 110 and reduced diastereoselectively to the desired epimer. Protection of the resulting alcohol and oxidation of the terminal olefin yielded aldehyde 112 (Scheme 21).

Hanessian and co-workers were able to derive 1,3-polyol units from the common precursor 71 (Scheme 10). This methodology was employed in the construction of the C2–C12 fragment of amphotericin B (Scheme 22). Hydroxylactone 71 was converted into acetone 113, which served as common intermediate for alkyne 114 and aldehyde 115. The lithioacetylide derivative of 114 underwent addition to the carbonyl in 115 in an anti-Cram fashion (dr 12:1), a result which is similar to that reported by Masam-

Scheme 19 McGarvey’s approach to the C1–C7 fragment.

Reagents and conditions: a) PPh₃, I₂, imid, CH₂Cl₂; b) PhSSPh, Bu₃P, t-BuOH, NaOH; c) 3% HCl–MeOH, Me₂C(OMe)₂; d) Ac₂O, NaOAc, reflux; e) K₂CO₃, MeOH.¹⁴⁶b

Scheme 21 McGarvey’s approach to the C1–C13 fragment.

Reagents and conditions: a) LDA, THF, –78 °C; b) DMP; c) t-BuLi, Et₂O, –78 °C; d) AIBN, Bu₃SnH, toluene, reflux; e) LiHB(t-Bu)₃, THF, –110 °C; f) TBSOTf, 2,6-lutidine, CH₂Cl₂; g) OsO₄, NMO, t-BuOH–H₂O; h) NaO₂, aq EtOH.¹⁴²b
Solladié applied his methodology\(^{134}\) to the preparation of the C1–C12 portion of amphotericin B (Scheme 23).\(^{149}\)

The strategy makes extensive use of 2-metallo-1,3-dithiane 126. The stereocenter at C-8 was set diastereoselectively through the use of metallated dithiane 126b. The resulting stereoselectivity was as predicted from Cram’s chelation model.

In the synthesis of the polyl segments of amphotericin B, Fraser-Reid exploited deoxygenation reactions and hydroxyl-to-methyl conversions.\(^{150}\) In this case, the starting material was di-O-isopropylidene glucofuranose which was subjected to a sequence of deoxygenations as previously described by Barton.\(^{139}\)

More recently, Carreira and Krüger described an enantioselective addition of dienyl silyl enol ethers to aldehydes which afforded aldol adducts in up to 95% ee and in good selective addition of dienyl silyl enol ethers to aldehydes. More recently, Carreira and Krüger described an enantioselective, Cu(I)-catalyzed aldol reaction. Reagents, conditions, and yields: a) NaOH, BnOH, THF, then CH\(_2\)N\(_2\); b) (COCl\(_2\)) cat. DMF; c) imid, THF; d) LiCH\(_2\)S(O)Tol, THF, –78 °C, 95% over 3 steps; e) DIBAL-H, toluene, –78 °C, 81%; d) BuLi, THF, –78 °C, 85%; e) Ph\(_3\)P, DEAD, HCO\(_2\)H, 84%; f) H\(_2\), Pt, EtOAc, 99%.\(^{18a}\)

Scheme 22 Hanessian’s approach to the C2–C12 fragment. Reagents, conditions, and yields: a) aq LiOH, THF, then CH\(_2\)N\(_2\); b) (COCl\(_2\)) cat. DMF; c) imid, THF; d) LiCH\(_2\)S(O)Tol, THF, –78 °C, 95%; e) Ph\(_3\)P, DEAD, HCO\(_2\)H, 84%; f) H\(_2\), Pt, EtOAc, 99%.\(^{18a}\)

Scheme 23 Solladié’s approach to the C1–C12 fragment. Reagents, conditions, and yields: a) NaOH, BnOH, THF, then CH\(_2\)N\(_2\); b) (COCl\(_2\)) cat. DMF; c) imid, THF; d) LiCH\(_2\)S(O)Tol, THF, –78 °C, 95%; e) Ph\(_3\)P, DEAD, HCO\(_2\)H, 84%; f) H\(_2\), Pt, EtOAc, 99%.\(^{18a}\)

Scheme 24 Carreira’s enantioselective, Cu(I)-catalyzed aldol reaction. Reagents, conditions, and yields: a) 2% (R)-Tol-BINAP CuF\(_2\), generated in situ from (R)-Tol-BINAP, Cu(OtTf)\(_2\), and (Bu\(_4\)N)Ph\(_3\)SiF, THF, –78 °C, then CF\(_2\)CO\(_2\)H, 95%, 99% ee after recrystallization from Et\(_2\)O-hexane 3:1; b) same as a) but (S)-Tol-BINAP is used instead. The numeration follows the amphotericin B numeration.\(^{153}\)
and oxidized with Dess–Martin periodinane\(^{156}\) to give aldehyde 139.

Deprotonation of alkyne 135 with BuLi at \(-78^\circ\text{C}\) in THF followed by addition of the aldehyde 139 resulted in a 3.5:1 mixture of diastereomers in favor of the undesired C-8 epimer 140 (Scheme 27). A similar outcome was observed by Hanessian with alkyne 114 (Scheme 22). Alkyne hydrogenation followed by TPAP oxidation yielded ketone 142 which could be cleanly reduced to the 8\(R\) epimer 141, as previously shown by Nicolaou (Scheme 17).

Another approach, based on reagent-controlled asymmetric synthesis, was reported by BouzBouz and Cossy\(^{157}\) and relied on the iterative allyltitanation of aldehydes using the chiral allyltitanium species established the configuration at C-8. After oxidation at C-8 proceeded in high enantiomeric excess and the chiral allyltitanium species resulted in a 98% yield and 98% enantiomeric excess. This intermediate was then elaborated into the two subunits 158 and 159. Halogen–metal exchange followed by addition to aldehyde 159 in the presence of MgBr\(_2\) and Cul gave polyl 160 as a single diastereomer. The high stereoselective outcome can be attributed to the chelating role of Mg(II).

A last strategy was devised by Bonini and co-workers\(^{160}\) and was based on an enzyme-catalyzed desymmetrization\(^{159}\) of the \(\alpha\)-acetone 155, itself derived from racemic \(\beta\)-hydroxy keto 154 (Scheme 29). Use of \(Pseudomonas\ fluoride\) lipase (PFL) gave alcohol 156 in 98% yield and 98% enantiomeric excess. This intermediate was then elaborated into the two subunits 158 and 159. Halogen–metal exchange followed by addition to aldehyde 159 in the presence of MgBr\(_2\) and Cul gave polyl 160 as a single diastereomer. The high stereoselective outcome can be attributed to the chelating role of Mg(II).
3.2.3 Synthetic Studies on the B3 Fragment

To prepare the C13–C19 fragment, Masamune relied on the diastereoselective aldol methodology developed in his group (Scheme 30).144b,144a Aldehyde 161 was allowed to react with the chiral boron enolate derived from ketone 170 (or from 169)144b to yield the aldol product 162 in excellent diastereoselectivity. Cleavage of the chiral auxiliary with sodium periodate and extension of the resulting methyl ester 163 led to allylic alcohol 164 in six steps from 162. Sharpless asymmetric epoxidation gave oxirane 165 which was opened with Red-Al and processed to diol 166. Diol 166 was protected as the orthoester and the benzyl-protected alcohol in 167 was converted into sulfone 168 in three steps.144e

The point of departure for the Nicolaou group was (+)-diethyl-L-tartrate (172), which was protected as the orthoester and reduced (Scheme 31).145a,145b,161 The resulting diol was protected as the benzyl ether to afford 173 which, upon exposure to phosphorus pentachloride, yielded chloroformate 174. Treatment of the latter with base (K2CO3, MeOH) afforded epoxide 175.

The C2-symmetric epoxide 175 served as a common substrate for both the C14–C20 and the C33–C37 fragments (Scheme 32). Upon opening of oxirane 175 with Et3AlC=CH2OTBDPS, protection, and reduction of the propargylic moiety, allylic alcohol 176 was subjected to Sharpless asymmetric epoxidation. Epoxide opening with Red-Al followed by a sequence of protecting group manipulations yielded polyol 177 which, after hydrolysis, gave triol 178. The latter was protected as an acetal and oxidized to aldehyde 179.

McGarvey (see Scheme 43) used the same disconnections as Masamune, i.e. an enantioselective aldol reaction to connect C-16 and C-17. The difference between the two routes resides in the subsequent manipulations of the ensuing olefin. While Masamune converted the olefin into the carboxylic acid of amphotericin B, McGarvey incorporated it into the macroside ring (C-14 and C-15). The latter strategy turns out to be extremely efficient, since it: 1) obviates the need to shorten the olefin to a carboxylic derivative, and 2) extends the carboxylic moiety by two carbon units.

**Scheme 29** Bonini’s approach to the C1–C13 fragment. *Reagents, conditions, and yields:* a) MeCOCH2CO2Me, NaH, BuLi, 0 °C, 38%; b) PFL, phosphate buffer, ee >98%, 98%; c) TBSCI, imid, DMAP, CH2Cl2, 0 °C; d) Na, MeOH, r.t., 93% (over 2 steps); e) t-BuLi, Et2O, –78 °C, MgBr2, CuI, –78 °C, 70%.

**Scheme 30** Masamune’s approach to the C13–C19 fragment. *Reagents, conditions, and yields:* a) 169, (c-C5H4)2BOTf, DIPEA, CH2Cl2, –78 °C to 0 °C, then add 161, 0 °C, 93%; b) 170, (c-C5H4)2BOTf, DIPEA, CH2Cl2, –78 °C to 0 °C, then 161, 0 °C; c) 48% HF–CH2-CN (1:20 v/v); d) O3, CH2Cl2, –78 °C; e) py, hexane, 50 °C; f) NaIO4, MeOH–H2O, r.t.; then CH2N2, Et2O, 0 °C; g) TBSOTf, 2,6-lutidine, CH2Cl2, 0 °C; h) Ti(Oi-Pr)4, (–)-DET, t-BuOOH, CH2Cl2, –20 °C; i) CSA, CH2Cl2, 95%; 166

**Scheme 31** Nicolaou’s synthesis of the common intermediate 175 for the C14–C19 and C33–C37 fragments. *Reagents, conditions, and yields:* a) HCl(OEt)2, AcOH, toluene, reflux; b) LAH, THF, 0 °C; c) BnBr, NaH, THF, 0 °C to 65 °C, 87%; d) PCl5, CH2Cl2, 0 °C; e) K2CO3, MeOH, r.t., 76%.

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In Hanessian’s strategy, hydroxylated lactone 71 (Scheme 10) was exploited as the key starting point, and was converted into epoxide 181 (Scheme 33). Upon opening of the oxirane with diion 186 and subsequent ring closure, a Michael addition to the enone system of 183, which was stereospecifically oxygenated with Vedejs reagent.

The work of Brückner 162 also merits scrutiny (Scheme 34). Commencing with L-arabinose 187, sulfone 189 was prepared, which upon treatment with three equivalents of allyllithium underwent a [2,3]-Wittig rearrangement and extrusion of phenylsulfinate to yield aldehyde 190c. Nucleophilic attack by an additional equivalent of allyllithium afforded homoallylic alcohol 191 as a 1.4:1 mixture of alcohols.

3.2.4 Synthetic Studies on the A2 Fragment

The preparation of the C33–C37 fragment was approached by Masamune in a route that commences with Roche ester 194 (Scheme 35). It was known from the work of Still 163 that addition of the Gillman cuprate Me2CuLi to aldehyde 195 would lead to the anti-Cram adduct 196. A moderate degree of diastereoselectivity was obtained upon epoxidation of the allylic alcohol 197, itself obtained from reduction of the corresponding α,β-unsaturated ester. Regioselective opening of epoxide 198 with the Gillman reagent yielded the 1,3-polyol 199, which could be converted via a short sequence to aldehyde 200.

Nicolaou’s synthesis of the C14–C19 and C33–C37 segments (Scheme 36) relies on the use of tartrate ester 172. From previous work 161 it was known that epoxide 175 could be converted into acetonide 201, which after oxidation to the aldehyde underwent an Evans aldol reaction with the chiral propionate oxazolidinone 205. Aldehyde 204 was obtained after auxiliary cleavage, deoxygenation to provide the methyl at C-37, and the usual protecting group manipulations.
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Scheme 35 Masamune’s approach to the C33–C37 fragment. Reagents, conditions, and yields: a) Me$_2$CuLi, Et$_2$O, –78 °C, 92%;
b) MCPBA, separation of diastereomers by flash chromatography, 70%; c) Me$_2$CuLi, 88%.

Scheme 36 Nicolaou’s approach to the C33–C37 fragment. Reagents, conditions, and yields: a) Me$_2$CuLi, Et$_2$O, –78 °C to 40 °C;
b) H$_2$, 10% Pd/C, EtOH, r.t., 100% over 2 steps; c) Me$_2$(OMe)$_2$, CSA, benzene, r.t.; d) MeOH, CSA, r.t., 98% over 2 steps; e) PCC, 4 Å MS, CH$_2$Cl$_2$, 94%; f) BuBOTf, DIPEA, 205, 0 °C, then add aldehyde, –78 °C, 72%.

The McGarvey group$^{146a}$ used the strategy outlined earlier in this review in Scheme 11. Oxazoline 75 was subjected to methylation and subsequently reduced to aldehyde 207, which was subjected to crotylation with crotyltrimethylaluminate to afford a mixture of the four possible diastereomers (Scheme 37). After TBS protection, the desired diastereomer 208 could be separated by column chromatography and the oxazoline moiety converted into aldehyde 209. Subsequent to addition of MeMgBr, oxidation to ketone 210, and reduction with L-selectride, alcohol 211 was obtained, and was easily protected and oxidized to yield aldehyde 212.

Scheme 37 McGarvey’s approach to the C33–C37 fragment. Reagents, conditions, and yields: a) NaN(TMS)$_2$, THF–HMPA, 0 °C then MeI, –78 °C; b) DIBAL-H, toluene, –78 °C; c) Li[Me$_3$AlCH$_2$CH=CHCH$_3$], Et$_2$O, –78 °C; d) TBSOTf, Et$_3$N, CH$_2$Cl$_2$, 30% over 4 steps, separation of diastereomers by flash chromatography; e) DIBAL-H, toluene, 0 °C; f) NaIO$_4$, Et$_2$O–H$_2$O; g) MeMgBr, THF, –78 °C; h) PCC, CH$_2$Cl$_2$, r.t.; i) L-Selectride, THF, –100 °C; j) MEMCl, DIPEA, CH$_2$Cl$_2$, r.t.; k) O$_3$, MeOH, –78 °C, Me$_2$S, r.t.

Hanessian and co-workers$^{148b}$ started from lactone 213 (Scheme 38). The strategy is very similar to the one previously discussed for the C14–C20 fragment (Scheme 33) wherein the (MeS)$_3$C group served as a bulky synthetic equivalent of a methyl group and directed the subsequent substitution on the ring (in the present case, it directs the introduction of the hydroxyl group at C-37).
In Brooks’ strategy\(^{164}\) (Scheme 39), the synthesis commenced with a Fräter–Seebach alkylation\(^{28}\) followed by protection and reduction to aldehyde 219. A substrate-controlled Masamune aldol reaction afforded the desired product 220a in moderate diastereomeric excess. The two diastereomers were separated by column chromatography after benzylation of the free alcohol.

![Scheme 39](image)

**Scheme 39** Brooks’ approach to the C33–C37 fragment. Reagents, conditions, and yields: a) LDA, THF, HMPA, MeI, –50 °C, 70%; b) TBSCI, imid, DMAP, DMF, 60 °C; c) LiBH\(_4\), THF, reflux; d) PCC, Me\(_2\)NNH\(_2\), TsOH, CH\(_2\)Cl\(_2\), r.t., 60% over 3 steps; e) [Pd\(_2\)(dba)\(_3\)] CHCl\(_3\), Bu\(_3\)P, HO\(_2\)H, Et\(_3\)N, THF, 23 °C, 93%; f) TIPSOTf, py, 0–23 °C, 92%; g) O\(_3\), CH\(_2\)Cl\(_2\), r.t., 60% over 3 steps; h) 2,6-di((tert-butyl)-4-methylpyridine, TESOTf, CH\(_2\)Cl\(_2\), 0 °C.\(^{164}\)

The synthesis of the C33–C37 portion of amphotericin B by Tholander and Carreira\(^{165}\) commenced from diene 222 (Scheme 40). The regio- and enantioselective dihydroxyl-ation of 222 using the Sharpless conditions\(^{166}\) proceeded in 68% yield (>99% ee). Conversion of the glycol into epoxide 223 was accomplished in two steps via mesylation of the less hindered hydroxyl group and intramolecular displacement by the neighboring alkoxide.

![Scheme 40](image)

**Scheme 40** Carreira’s synthesis of the C33–C37 fragment. Reagents, conditions, and yields: a) (DHQD)\(_2\)-PHAL, K\(_2\)SO\(_4\), 2H\(_2\)O, K\(_3\)CO\(_3\), K-Fer(CN)\(_3\), Me\(_2\)SO\(_2\)NH\(_2\), t-BuOK, H\(_2\)O 1:1, 0 °C, >99% ee; b) MeCl, py, CH\(_2\)Cl\(_2\), 0 °C; c) NaH, MeCN, 0–23 °C, 58% over 3 steps; d) [Pd(dbach)\(_2\)] CHCl\(_3\), Bu\(_3\)P, HO\(_2\)H, Et\(_3\)N, THF, 23 °C, 93%; e) PhCHO, t-BuOK, THF, 0 °C, 82%; f) Pd(OH)\(_2\), H\(_2\), EtOH, then 2.5% TFA-MeCN, 23 °C, 92%; g) LDA, HMPA–THF, –78 °C, 80%, >95% de; h) 2,6-di((tert-butyl)-4-methylpyridine, TESOTf, CH\(_2\)Cl\(_2\), –40 °C, 99%; i) DIBAL–H, THF, –78 °C, 93%; j) Me\(_2\)NNH\(_2\), TsOH, EtOH, reflux, 92%; k) TIPSOTf, py, 0–23 °C, 92%; l) O\(_3\), CH\(_2\)Cl\(_2\), –78 °C, then MeS, 71%.\(^{165}\)

Treatment of alcohol 224 with benzaldehyde in the presence of t-BuOK led to the desired syn-diol 225.\(^{137}\) After removal of the acetal and cyclization, lactone 226 was alkylated using the Fräter–Seebach conditions\(^{128}\) and protected as a silyl ether. The δ-lactone 227 was converted into the desired aldehyde 229 in four steps. After DIBAL–H reduction, formation of the N,N-dimethylhydrazine derivative 228 was required to drive the lactol–hydroxylaldehyde equilibrium to the open form.

### 3.2.5 Synthesis of the B Fragment (B1B2 + B3)

The coupling between the B1B2 (epi-88, Scheme 14) and the B3 (168, Scheme 30) units was accomplished by Masamune\(^{144e}\) via nucleophilic displacement of the triflate at C-12 (Scheme 41). Oxidation at C-13 yielded ketone 231 which was attacked by the hydroxyl group at C-17 by treating the orthoester with a catalytic amount of pyridinium p-toluenesulfonate (PPTS) in methanol. The subsequent steps involved installing the correct oxidation state at C-1, C-16, and C-19. The methyl ester at C-19 was reacted with lithiated dimethyl methylphosphonate to yield the β-keto phosphonate 235 which after selective saponification at C-1 afforded acid 236. The sequence from 232 to 233 was intended to reverse the configuration at C-8.

Nicolau\(^{145}\) exploited once more the efficiency and mildness of the Horner–Wadsworth–Emmons reaction to couple the advanced intermediates 100 and 179 (Scheme 42). Treatment of the vinyl sulfide 237 with a catalytic amount of PPTS and deprotection of the primary TBS-protected alcohol afforded ketal 238. Acid 236 was obtained after oxidation at C-1, C-16, and C-19.

Following Curran’s strategy\(^{135}\) of employing isoxazolines as β-hydroxy ketone equivalents, McGarvey\(^{146c}\) efficiently coupled oxime 241 (derived from aldehyde 112, see Scheme 21) and olefin 242 via a nitrile oxide [3+2]-cy cloaddition reaction (Scheme 43). Treatment of isoxazoline 243 with molybdenum hexacarbonyl in hot, aqueous acetonitrile yielded the hemiketal 244 which after the usual manipulations was converted into acid 240.

### 3.2.6 Synthesis of the A Fragment (A2 + Polyene)

At the time when the studies described in the previous paragraphs were performed, the method of choice for double-bond formation was the Wittig reaction and its variations, in particular the Horner–Wadsworth–Emmons (HWE) reaction. In 1984, in the context of the amphotericin B synthesis, Masamune reported a very mild method involving activation of a β-keto phosphonate with LiCl in acetonitrile.\(^{167}\) Deprotonation can take place with organic bases such as DBU and Hünig’s base.

For the first HWE reaction connecting C-33 to C-32 (Scheme 44) Masamune and co-workers\(^{144d}\) used the pen tenic phosphonate 247 which was derived from the known\(^{168}\) triendial 252 (Scheme 45). The use of bulky groups on the phosphonate was required by the poor E/Z selectivity obtained with the standard ethyl or methyl sub-
Scheme 41 Masamune’s approach to the C1–C20 fragment. Reagents, conditions, and yields: a) LDA, THF, HMPA, –30 °C, 85%; b) LDA, Mo(OAr), 40%; c) CH3C(O)=CH2, MeOH, PPTS, r.t., 94%; d) TBSOTf, 2,6-di-tert-butylpyridine, CH2Cl2, 0 °C, 100%; e) O2, EtOH, Co(OEt), 87%; f) K2Cr2O7, CH2Cl2, 98%; g) LiOH, dioxane–H2O, then TMSCHN2, MeOH–benzene, 65%; h) PDC, DMF, then TMSCHN2, MeOH–benzene, 100%; i) HF py–py 1:2, 98%; j) PDC, 4 Å MS, CH2Cl2, 82%; k) LiCH2P(O)(OMe)2, THF, –95 °C, 56%; m) CrO3 py, 75%; n) LiOH, THF–H2O, NaH2PO4, r.t., then CH2N2, Et2O, 0 °C, 83%; g) H2, Pd/C, 80%; h) PDC, 4 Å MS, CH2Cl2, 75%; i) KMnO4, MeO2C–Ph, –46 °C to r.t., 88%; b) Mo(CO)6, MeCN–H2O, 70 °C, 81%; c) MeC(O)Me3, PPTS, MeOH, r.t., 90%; d) TBSOTf, Et3N, CH2Cl2, 99%; e) DDQ, CH2Cl2, 98%; f) LiOH, dioxane–H2O, then TMSCHN2, MeOH–benzene, 65%; g) PDC, DMF, then TMSCHN2, MeOH–benzene, 45%; h) H2, Pd(OH)2, MeOH; i) DMP, CH2Cl2; j) NaClO2, NaHPO4, 2-methylene-2-butene, t-BuOH, 63% over 3 steps; k) Bu4BOTf, Et3N, CH2Cl2, then 245.146c

Scheme 42 Nicolaou’s approach to the C1–C20 fragment. Reagents, conditions, and yields: a) LDA, THF, 100, –78 °C, then aldehyde, r.t.; b) TBAF, THF, r.t., 86%, over 2 steps; c) PPTS, CH2Cl2; d) 2 equiv (MeO)2P(O)CH2Li, 62% over 2 steps.148b
stirrings. Of interest is the use of DDQ as oxidant to access the hexaenal \(249\), which is similar to the oxidative deglycosidation step used in the degradation studies (see section 2.2.4). Incidentally, the exploitation of \(252\) as a polyenic phosphonate precursor has recently been used by Evans in the synthesis of (+)-roxaticin.137b Nicolaou145c accessed intermediate \(257\) (Scheme 46) in a similar fashion, the main difference being a two-fold iteration of the HWE reaction with phosphonate \(258\).

McGarvey based his polyene synthesis on the use of the Wollenberg reagent169 260. After a three-fold repetition of the three-step cycle the protected polyene \(259\) was obtained from aldehyde \(212\) (Scheme 47).146a,d

In an exploratory study towards the synthesis of the polyenic portion of amphotericin B, Hanessian 148c applied methodology introduced by Vedejs. 170 However, the method furnishes poor \(E/Z\) selectivity and the polyene must be converted into the all-

3.2.7 Assembly of the A and B Fragments and Glycosidation

The assembly of the A and B units has only been accomplished by the Nicolaou145c and Masamune144e groups to date. The latter, however, followed the procedure reported by the former.

The acid \(236\) was activated with DCC and esterified with the free alcohol of the polyene fragment \(257\) (Scheme 48). The resulting ester \(261\) was then cyclized by means of the HWE reaction. Both the Masamune protocol167 and potassium carbonate with catalytic 18-crown-6 in benzene gave the macro lactone \(262\) in 70% yield.
Amphotericin B holds a special place in the development of the molecular sciences in the second half of the last century. Unlike many other natural products, its impact has resonated across numerous disciplines in science. It is a natural product that remains in use in the clinic because of its indispensable, life-saving activity as an antifungal agent. Its unique structure and biological activity inspired a number of intriguing hypotheses in membrane biology and biophysics in order to account for its mode of action. It kindled the development of novel effective approaches for its delivery as a drug. Moreover, the constellation of functionality and stereochemical patterns found adorning the macrocycle have also stimulated the field of natural products synthesis both in the development of innovative synthetic methods and at the level of synthetic strategy. Recent work in this area suggests that additional significant discoveries and advances are on the horizon.

4 Conclusion

Amphotericin B holds a special place in the development of the molecular sciences in the second half of the last century. Unlike many other natural products, its impact has resonated across numerous disciplines in science. It is a natural product that remains in use in the clinic because of its indispensable, life-saving activity as an antifungal agent. Its unique structure and biological activity inspired a number of intriguing hypotheses in membrane biology and biophysics in order to account for its mode of action. It kindled the development of novel effective approaches for its delivery as a drug. Moreover, the constellation of functionality and stereochemical patterns found adorning the macrocycle have also stimulated the field of natural products synthesis both in the development of innovative synthetic methods and at the level of synthetic strategy. Recent work in this area suggests that additional significant discoveries and advances are on the horizon.
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References

(3) This somewhat-unfortunate name indicates an ‘n-dimensional space defined by the value of n descriptors; these descriptors can be of a chemical or biological nature and are either computed or measured’ (see ref. 6c). It seems more appropriate to call this abstract space a Q SAR- or QSPR-space where QSAR and QSPR are the more familiar (and general) acronyms for ‘quantitative structure–activity relationship’ and ‘quantitative structure–property relationship’, respectively (see ref. 56).
(b) Strausberg, R. L.; Schreiber, S. L. Science 2003, 300, 294.
(c) Hopwood, D. A. PLoS Biology 2004, 2, 166.
(15) For the strain isolation: (a) Sternberg, T. H.; Wright, E. T.; Oura, M. Antibiot. Annu. 1956, 566.
(17) Trejo, W.; Bennett, R. J. Bacteriol. 1962, 85, 436. It is worth reminding that the ability to biosynthesize a certain antibiotic is characteristic not of microbial genera, not even of species, but of strains or races within a given species. Trejo and Bennett first officially characterized S. nodosus according to the International Code of Nomenclature of Bacteria and Viruses, thus providing the full name Streptomyces nodosus Trejo (= M 4575 = ATCC 14899).
(19) Amphotericin A is biosynthesized along with amphotericin B and needs to be removed from the latter during purification.
(b) Brown, R.; Hazen, E. L.; Mason, A. Science 1953, 117, 609.
(29) Singer, S. J.; Nicolson, G. L. Science 1972, 175, 720. As stated by Singer: ‘This particular paper was the culmination of our ideas and experiments going back about 10 years’ (Citation Classics 1977, 46, 223).
(38) (a) Finkelstein, A.; Krepsi, V. J. Gen. Physiol. 1970, 56, 100. (b) Holz, R.; Finkelstein, A. J. Gen. Physiol. 1970, 56, 125; This latter paper also critically assesses the data furnished by Andreolii and co-workers in ref. 36b.

An alternative to epoxidation followed by ring-opening is the regioselective hydroboration of allylic alcohols. However, this method has not been used in the context of 1,3-polyols, but rather to access primary alcohols via hydroboration (9-BBN) of terminal olefins. See, for example: (a) Kim, H.; Choi, W. J.; Jung, J.; Kim, S.; Kim, D. J. Am. Chem. Soc. 2003, 125, 10238. (b) Buszek, K. R.; Sato, N.; Jeong, Y. Tetrahedron Lett. 2002, 43, 181. See also the hydroboration of vinyl ethers by McGarvey: (c) McGarvey, G. J.; Bajwa, J. S. Tetrahedron Lett. 1985, 26, 6297.

For a similar use of β-hydroxy esters but not in the context of alkylation, see: (d) Kraus, G. A.; Taschner, M. J. Tetrahedron Lett. 1977, 52, 4575. An alternative to epoxidation followed by ring-opening is the regioselective hydroboration of allylic alcohols. However, this method has not been used in the context of 1,3-polyols, but rather to access primary alcohols via hydroboration (9-BBN) of terminal olefins. See, for example: (a) Kim, H.; Choi, W. J.; Jung, J.; Kim, S.; Kim, D. J. Am. Chem. Soc. 2003, 125, 10238. (b) Buszek, K. R.; Sato, N.; Jeong, Y. Tetrahedron Lett. 2002, 43, 181. See also the hydroboration of vinyl ethers by McGarvey: (c) McGarvey, G. J.; Bajwa, J. S. Tetrahedron Lett. 1985, 26, 6297.

See, for example: (a) Solladié, G.; Demailly, G.; Greck, C. J. Org. Chem. 1982, 50, 1552.

In a later study, epoxide 103 was accessed from the known acetonide 104 which, in turn, could be prepared from l-malic acid dimethyl ester (Scheme 51). See ref. 146c.

Scheme 51


(161) Nicolaou, K. C.; Papahatjis, D. A.; Claremont, D. A.; Magolda, R. L.; Doole, R. E. J. Org. Chem. 1985, 50, 1440; In this synthesis (--) diethyl-t-tartrate was used.


(172) Glycoside 266 was prepared in 14 steps from the glucose derivative 268 (Scheme 52). The synthesis encompassed deoxygenation at C-5' and double inversion at C-3' in order to install the azide functionality, which after the glycosidation was reduced to the required amine. See ref. 145b.

Scheme 52