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Total Synthesis and Structure Determination of Mycapolyol E Using Iterative Homologation of Boronic Esters

*Sheenagh G. Aiken[+], Dylan Rigby[+], Daniele Fiorito, Malcolm R. P. George, Simon Wübbolt, Adam Noble, and Varinder K. Aggarwal**

Editorial Summary: Mycapolyol E is a complex cytotoxic polyketide/peptide metabolite, originally isolated in 2005 from the marine sponge *Mycale izuensis*. Its stereochemistry could not be unambiguously resolved upon isolation. This study reports the first total synthesis of Mycapolyol E showcasing the effectiveness of iterative boronic ester homologation combined with platinum-catalyzed terminal alkene diboration delivering remarkable efficiency. The Scientific Advisory Committee of *Angewandte Chemie Novit* recognizes the methodology as a creative and elegant strategy for constructing structurally complex polyol scaffolds against the problem of stereochemical uncertainty.

Abstract: Mycapolyol E is a cytotoxic polyketide synthase/nonribosomal peptide synthetase (PKS/NRPS) metabolite isolated from a marine sponge containing an extended polyacetate motif, terminal formamide moiety, and tetramic acid-derived headgroup, whose structure could not be fully elucidated upon isolation. A modular approach was employed and the ten 1,3-related hydroxy-substituted stereocenters were installed through iterative diboration/homologation reactions. Furthermore, the stereochemistry of the unassigned methyl stereocenter at C5 was elucidated through partial synthesis and nuclear magnetic resonance (NMR) analysis, and the uncertainty surrounding the relative stereochemistry of the 1,3-polyol was resolved. The stereochemistry and structure of mycapolyol E was confirmed through total synthesis, which was completed in 20 steps longest linear sequence (LLS).

Mycapolyol E (**1**) is an unusual natural product of mixed biogenesis (PKS/NRPS metabolite) isolated in 2005 from the marine sponge *Mycale izuensis*, together with five other homologues bearing shorter or longer polyols (Figure 1a).[1] It exhibited cytotoxicity against HeLa cells with an IC_{50} value of 0.43 μM. This complex polyacetate possesses 10 contiguous, skipped, hydroxy-substituted stereocenters, a methyl-bearing stereocenter at C5, a trisubstituted *Z*-alkene, as well as formamide and tetramic acid-derived groups. The stereochemistry of the acyclic 1,3-polyol motif was deduced through Kishi's NMR database, but there was some uncertainty about the relative stereochemistry of the C13 and C31 hydroxy

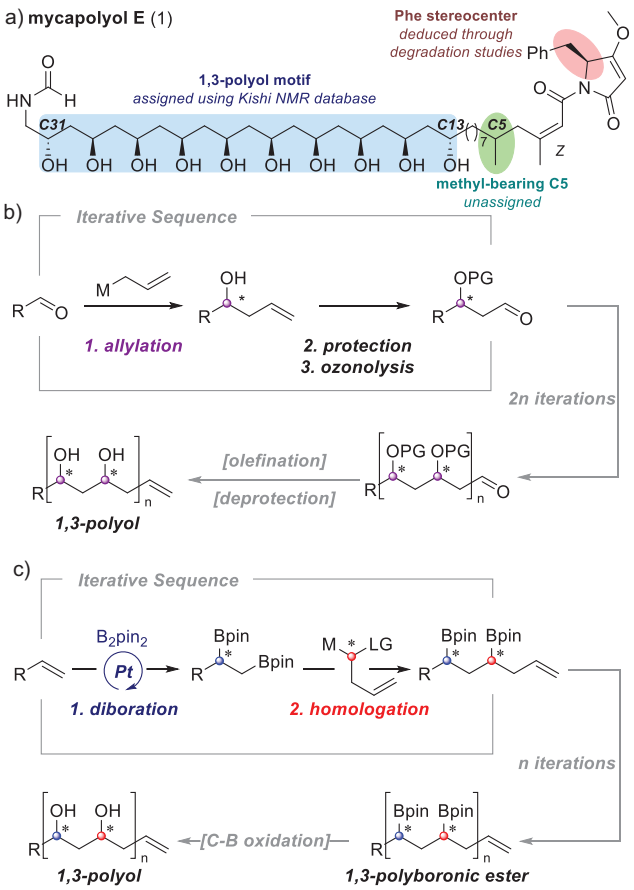


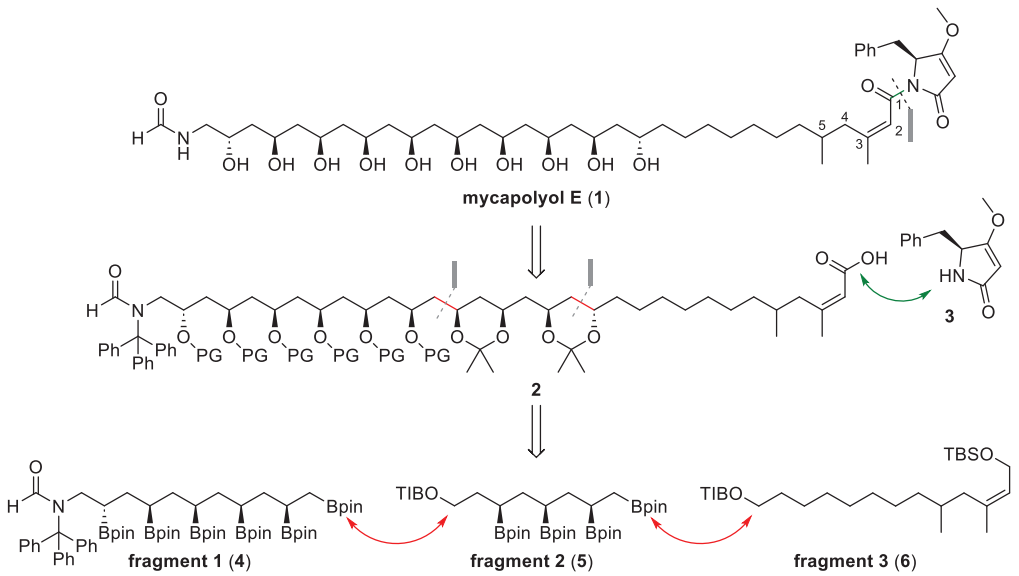
Figure 1. a) Reported structure of mycapolyol E. b) Traditional iterative strategy toward 1,3-polyols. c) Current iterative polyboron strategy toward the stereocontrolled synthesis of 1,3-polyols. M = metal; LG = leaving group; PG = protecting group.

[*] Dr. S. G. Aiken[+], D. Rigby[+], Dr. D. Fiorito, M. R. P. George, Dr. A. Noble, Prof. V. K. Aggarwal
School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, UK
E-mail: v.aggarwal@bristol.ac.uk

Dr. S. Wübbolt
Vertex Pharmaceuticals (Europe) Ltd., 86–88 Jubilee Avenue, Milton Park, Abingdon, Oxfordshire OX14 4RW, UK

[+] Both authors contributed equally to this work.

Additional supporting information can be found online in the Supporting Information section



Scheme 1. Retrosynthetic analysis of mycapolyol E. Bpin = boronic acid pinacol ester; OTIB = 2,4,6-triisopropyl benzoyl; TBS = *tert*-butyldimethylsilyl.

groups. According to Kishi's method, the hydroxy groups located between C15 and C29 were all syn, while C13/C15 and C29/C31 were anti (as drawn).[2] However, on the basis of proton signals flanked by methoxy ethers as described by Mynderse and Moore, the C13/C15 and C29/C31 were syn.[3] The relative configuration of C5 was not determined, while the absolute configuration of the phenylalanine stereocenter present on the tetramic acid head-group was deduced through degradation studies. Therefore, the uncertainty surrounding the stereochemistry of this challenging natural product called for a structure elucidation campaign through the synergy of total synthesis and NMR analysis.[4]

Common repeating motifs, such as the 1,3-polyol of mycapolyol E, often emerge from iterative coupling of small building blocks during the biosynthesis of polyketide-derived natural products.[5] Echoing *Nature*, a number of iterative strategies in the synthesis of polyketides have also been developed. In the case of polyacetates, strategies based on iterative acetate aldols and allylations have dominated (Figure 1b).[6–15] We recently reported a two-step iterative strategy to access enantioenriched 1,3-polyboronic esters which upon stereospecific oxidation provide the corresponding 1,3-polyol motif (Figure 1c).[16,17] Our approach, which harnesses asymmetric alkene diboration and regio- and stereoselective homologation, provides a step change in efficiency and versatility in the synthesis of polyacetates.[18–20] While traditional methods require three steps for every hydroxy group that is introduced, our method requires only one step and, furthermore, is able to incorporate any stereoisomer at will. We now report the total synthesis of mycapolyol E in just 20 steps (LLS), constructing the stereodefined 1,3-polyol, one of the longest 1,3-polyols ever constructed,[21] in high diastereomeric ratio (dr) through the stereocontrolled iterative homologation of boronic esters. In addition, we have assigned the stereochemistry of the unknown C5 stereocenter and resolved the uncertainty surrounding the relative stereochemistry of the 1,3-polyol region.

Our retrosynthetic analysis (Scheme 1) involved late-stage installation of the sensitive tetramic acid-derived head-group, and then disconnection of the carbon chain into three building blocks, which could be coupled together using metalation-borylation. Not only does the coupling assemble the fragments but it also controls the alcohol stereochemistry. Fragments 1 and 2 would be assembled by our iterative diboration/homologation strategy. Fragment 3 would be accessed through iterative homologation and downstream boronic ester olefination.

Synthetic work commenced with the preparation of both enantiomers of fragment 3 (**6**) in order to establish the C5 stereochemistry, which is sufficiently remote to be unaffected by the stereochemistry of the polyol region (Scheme 2). Indeed, the C1 to C5 region of all mycapolyols A-F showed very similar chemical shifts in the ^{13}C and ^{1}H NMR.[1] Hydroboration of triisopropyl benzoyl (TIB) ester **7** gave primary boronic ester **8** in almost quantitative yield, which was homologated first with lithiated carbenoid **9** or ***ent*-9**, and subsequently with chloro-methyllithium, to provide **10** and ***ent*-10** in 90% and 87% yield over two steps, respectively.[22,23] Boronic esters **10** and ***ent*-10** were subjected to modified Zweifel olefination reaction conditions with alkenyl-lithium reagent **11**, derived from the corresponding bromide through lithium–bromine exchange.[24,25] Standard Zweifel olefination using I_2 gave a 93:7 Z/E ratio of alkenes but using phenylselenyl chloride provided **6** (fragment 3) and ***ent*-6** in 75% and 72% yield, respectively, with Z/E = 98:2. The low selectivity for the desired Z-alkene observed with I_2 may reflect competing syn elimination during the Zweifel olefination, a process that is retarded with the poorer leaving-group ability of a phenylselenide. With **6** and ***ent*-6** in hand, both enantiomers were subjected to an early iteration of the end-game series of steps both to investigate optimum conditions on a truncated component of mycapolyol E and to determine the C5 stereochemistry (Scheme 2). This entailed silyl-deprotection, two-step oxidation of the resultant allylic

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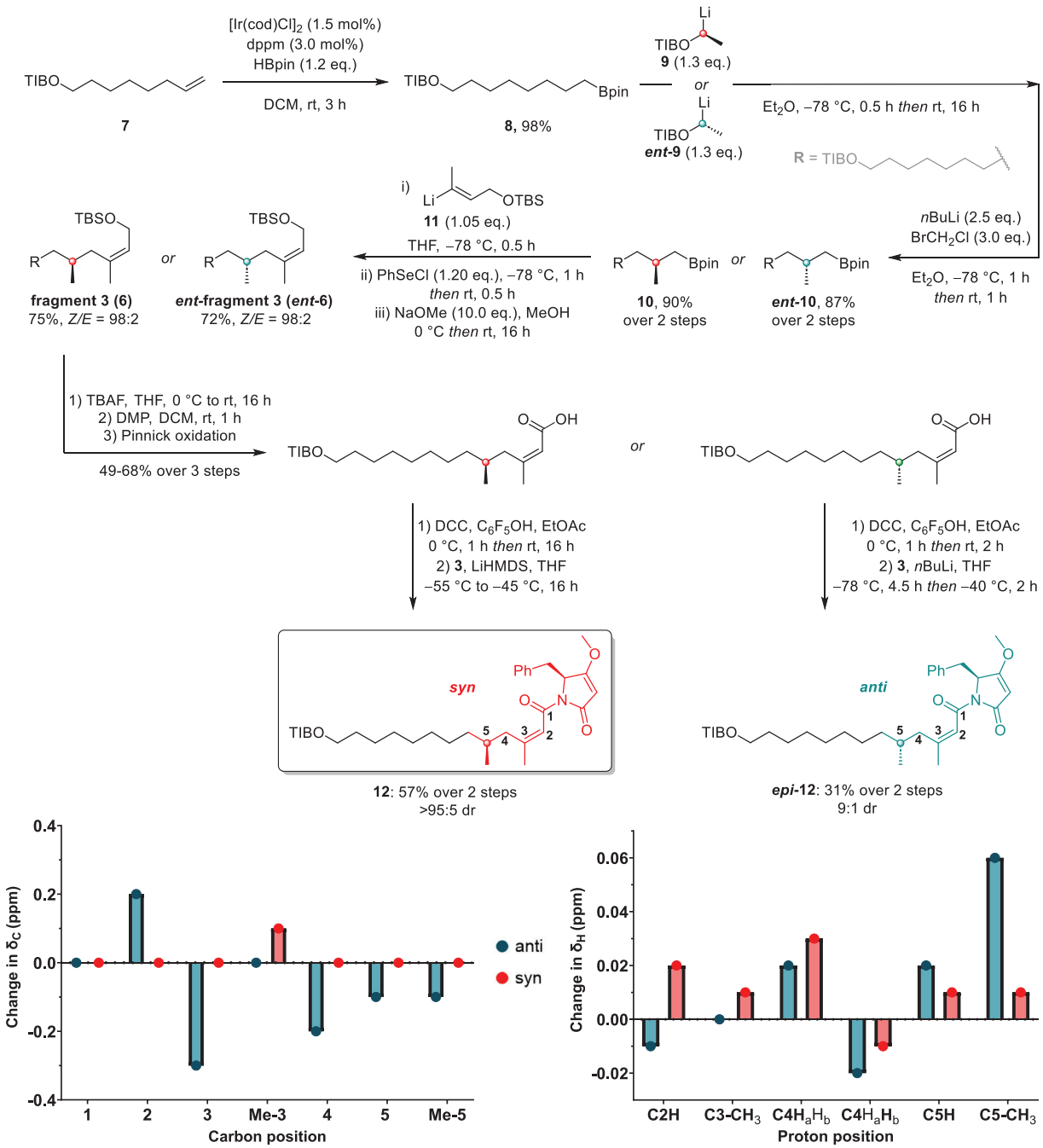
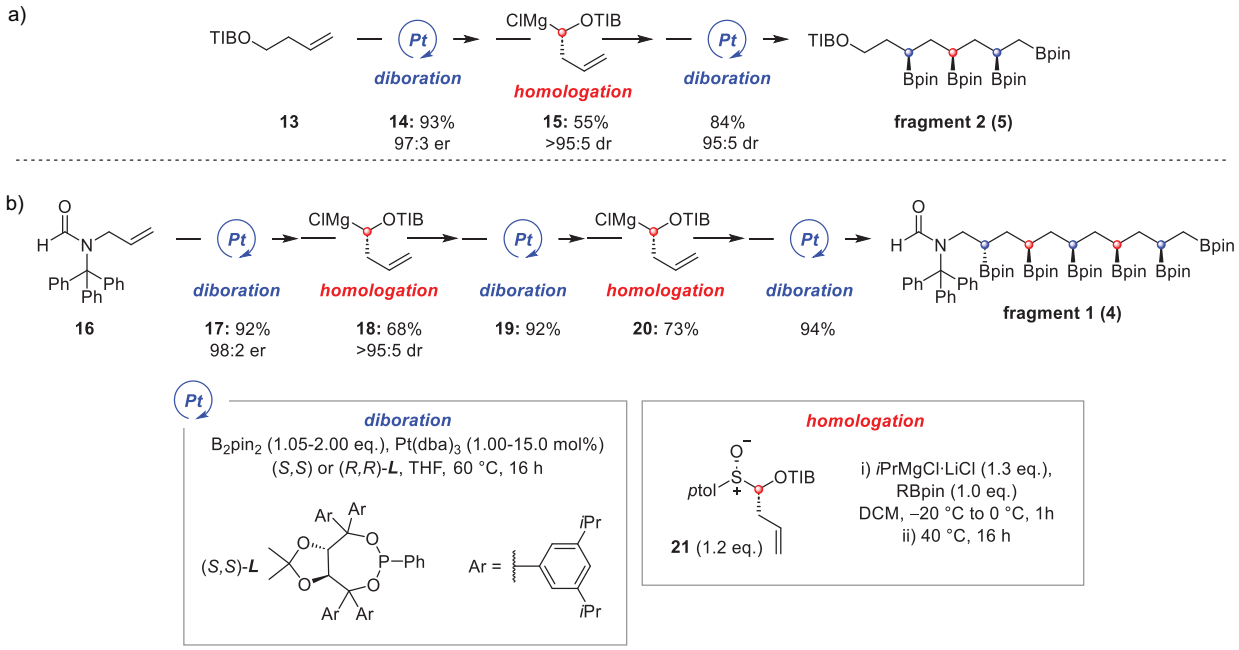


Scheme 2. Fragment 3 (**6**) synthesis and assignment of the C5 methyl stereocenter by comparison of ^{1}H and ^{13}C NMR chemical shifts with the average of mycapolyols A–F. dppm = methane-1,1-diylbis(diphenylphosphane), $[Ir(cod)Cl]_2$ = bis(1,5-cyclooctadiene)diiridium(I) dichloride. DMP = Dess–Martin periodinane. Pinnick oxidation = $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH, THF/H_2O, 0 °C to rt, 16–48 h. DCC = *N*,*N*′-dicyclohexylcarbodiimide.

alcohol and then carboxylic acid activation with pentafluorophenol, prior to reaction with lithiated pyrrolidinone **29** (derived from lithiation of **3**) to provide **12** and ***epi*-12**.[26,27] Since mycapolyols A–F all share the same head-group and C1 to C13 component, we decided to compare the ^{1}H and ^{13}C NMR chemical shifts in d_6-DMSO of **12** and ***epi*-12** with the average of all of the mycapolyols. Although the spectra of **12** and ***epi*-12** were very similar, it was clear that the signals for the C1 to C5 portion in **12** matched much more closely than ***epi*-12**, which led us to conclude that the C5 stereochemistry was (*S*). Following this analysis, the synthesis of the correct enantiomer of fragment 3 (**6**) was successfully scaled-up to gram-scale with an overall yield of 66% over five steps from **7** and 98:2 *Z*/*E*.

Attention then turned toward the construction of the polyol motif, which would be installed through our iterative diboration/homologation strategy (Scheme 3). The synthesis of fragment 2 (**5**) commenced with Pt-catalyzed diboration of



Scheme 3. a) Synthesis of fragment 2 (**5**). b) Synthesis of fragment 1 (**4**). $Pt(dba)_3$ = tris(dibenzylideneacetone)dipalladium(0).

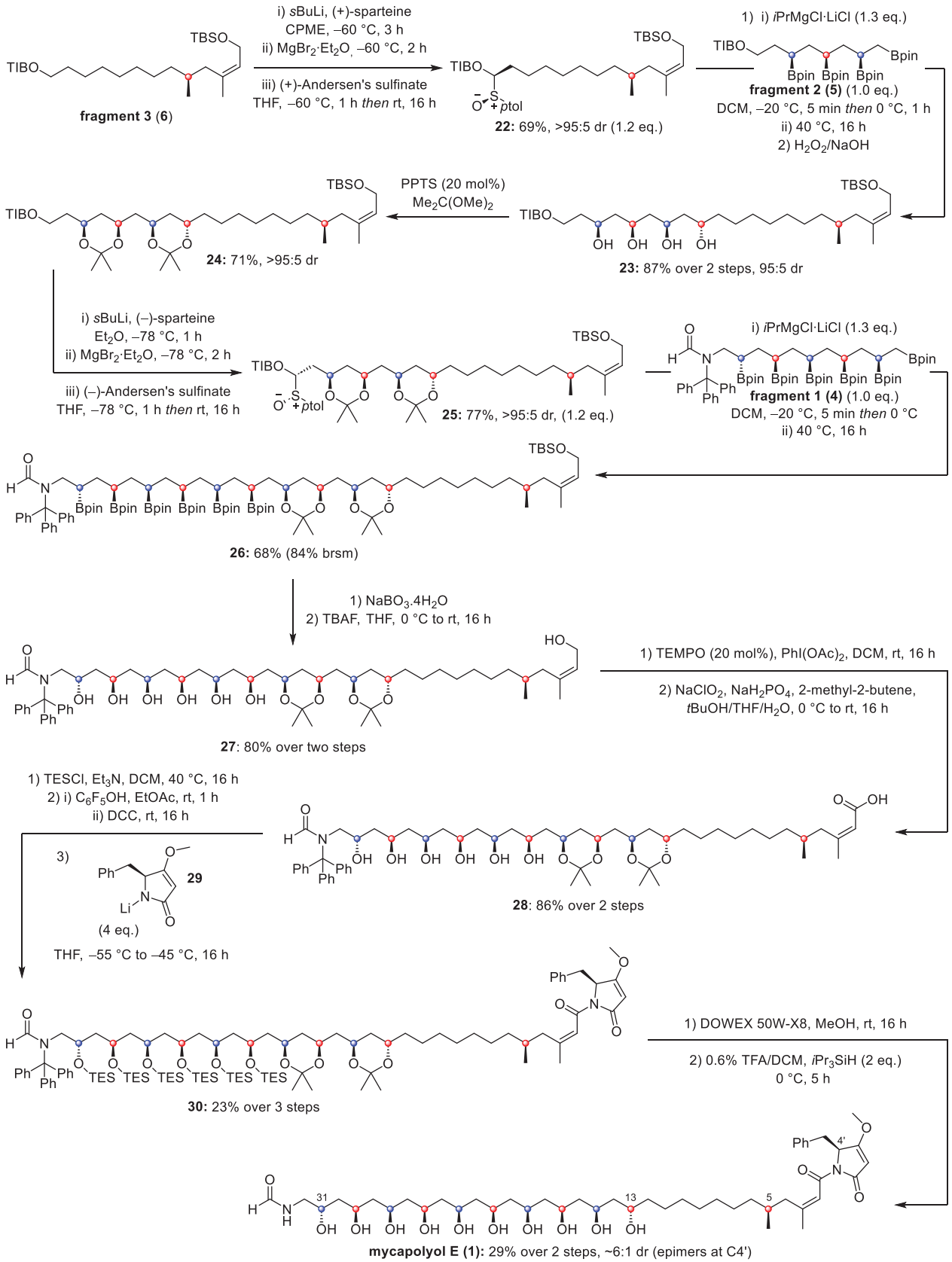
homoallylic TIB ester **13**, to give 1,2-bis(boronic ester) **14** in 93% yield and 98:2 er (Scheme 3a). Subsequent regioselective homologation with the magnesiated carbenoid derived from sulfoxide **21** provided the desired 1,3-bis(boronic ester) **15** as a single diastereomer by ^{13}C NMR analysis in 55% yield. A final enantioselective alkene diboration of **15** provided tetraboronic ester **5** in an overall yield of 42% over four steps on multi-gram scale. Fragment 2 (**5**) serves as the linchpin reagent in our modular strategy, since it possesses both TIB ester and primary boronic ester functionality, and therefore the potential for chain-elongation from either terminus.

We next addressed the synthesis of fragment 1 (**4**) (Scheme 3b). Careful consideration was given to the protecting group strategy for the nitrogen functionality. Since a formamide group was required in the natural product, we were keen to incorporate it at the outset to limit protecting group manipulations. Cognizant of the potential for nucleophilic attack on the formamide under the homologation conditions, we selected the bulky trityl (Tr, triphenylmethyl) group. *N*-Trityl formamide **16** was prepared in two steps from allylamine,[28,29] and subjected to iterative diboration/homologation providing hexaboronic ester **4** on gram-scale in an overall yield of 27% over seven steps with high dr. HPLC and ^{13}C NMR analysis of the hexaol derived from **4** indicated that it had been formed in an 84:5:11 ratio of isomers (see Supporting Information). No discernible undesired reaction at the formamide functionality was observed during the iterative homologation sequence, validating our choice of protecting group.

With our three fragments (**4**, **5**, and **6**) in hand, focus turned to the union of fragments 2 (**5**) and 3 (**6**) (Scheme 4). To achieve this with complete stereocontrol, fragment 3 (**6**) was first converted to sulfoxide **22** through (+)-sparteine-controlled lithiation/sulfinylation, since sulfoxide **22** could be isolated as a single enantiomer and diastereomer after purification. Subsequent treatment with turbo Grignard in the presence of fragment 2 (**5**) revealed the magnesiated carbenoid for the homologation reaction to give a tetraboronic ester which was directly oxidized to tetraol **23**, in 87% yield. Oxidation at this stage was necessary since the boronic esters in the coupled product are not compatible with *s*BuLi, required for deprotonation of the TIB ester. It is notable that excess fragment 3 (**6**) could be recovered following this two-step process. Tetraol **23** was protected as the bis-(acetonide) **24** in 71% isolated yield and as a single diastereomer by NMR analysis.[30] By combining fragment 2 and fragment 3, the C1 to C22 carbon-scaffold of mycapolyol E (**1**) had been assembled.

In a similar vein to the previous fragment coupling process, bis(acetonide) **24** was converted to sulfoxide **25** through (−)-sparteine-controlled lithiation/sulfinylation in 77% yield. It is worth noting that six-membered acetonides adjacent to the site of lithiation (as in **24**) impart minimal substrate-control, in contrast to five-membered acetonides.[31] To forge the complete carbon backbone of mycapolyol E, in situ sulfoxide-magnesium exchange of sulfoxide **25** provided the required magnesiated carbenoid for regioselective homologation of fragment 1 (**4**).

Remarkably, no reaction at any of the five secondary boronic esters was observed, providing hexaboronic ester **26** in 68% yield (84% brsm). Subsequent polyoxidation with sodium perborate and removal of the primary alcohol silyl protecting group afforded heptaol **27** in 80% yield over two steps. Unfortunately, neither hexaboronic ester **26** nor heptaol **27** could be progressed directly through the proposed end game synthetic sequence due to functional group incompatibility,[32] and so protection of the hydroxy groups was required. Attempts at full acetonide protection of the polyol were unsuccessful, and so we considered silyl



Scheme 4. Fragment unification and endgame in the synthesis of mycapolyol E. CPME = cyclopentyl methyl ether; DCC = *N*,*N*′-dicyclohexylcarbodiimide; PPTS = pyridinium *p*-toluenesulfonate; TBAF = tetra-*n*-butylammonium fluoride; TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy, TES = triethylsilyl; TFA = trifluoroacetic acid.

protection instead. Cognizant of the need to deprotect under mild conditions at the end, we initially selected the trimethylsilyl (TMS) group.

Allylic alcohol **27** was subjected to a two-step, primary-selective oxidation process to provide carboxylic acid **28** in 86% yield over two steps, and the hexaol was subsequently TMS-protected. During the protection of the alcohols, silylation of the acid also occurred, but it was readily hydrolyzed upon aqueous workup. Subsequent activation of carboxylic acid **28** with DCC in the presence of pentafluorophenol gave the activated acid but unfortunately significant deprotection of the TMS ethers also occurred. We therefore sought a non-acidic activating group and considered carbonyldiimidazole (CDI).[33] Treatment of carboxylic acid **30** with CDI gave the corresponding acyl imidazole (see Supporting Information), and this time without any deprotection of the TMS ethers. However, a small erosion (3–9:1) in the *Z/E* ratio of the alkene was observed during this process which reduced further (1–3:1) upon reaction with lithiated pyrrolidinone **29**. We believe that the release of imidazole is the cause of the isomerization either through a base-catalyzed or conjugate addition/elimination process.[34] Our earlier success with pentafluorophenol on the model system with no associated *E/Z* isomerization made us revisit this strategy with a more stable alcohol protecting group. Thus, treatment of carboxylic acid **28** with TESCl, and base gave the protected adduct OTES-**28** bearing TES silyl ethers and the TES ester which this time was found to be stable to aqueous workup (see Supporting Information). We reasoned that pentafluorophenol might be sufficiently acidic to deprotect the labile TES silyl ester in the presence of the silyl ethers, which was borne out in practice. Treatment of the protected adduct OTES-**28** with DCC and pentafluorophenol gave the activated ester directly, without isomerization of the alkene and minimal deprotection of the TES ethers. Subsequent reaction with lithiated pyrrolidinone **29** gave the completed skeleton of mycapolyol E (**30**). Final deprotection was best achieved in a two-step process involving overnight suspension in MeOH/DOWEX 50W-X8 which removed the acetonides and TES ethers, followed by treatment with TFA/DCM in the presence of Et_3SiH to remove the trityl group. Using TFA/DCM in the presence of Et_3SiH as a one-step method gave multiple products. Careful monitoring of the latter conditions was essential as deformylation was observed at extended reaction time. Following purification by reverse-phase preparative HPLC using $MeCN/H_2O/NH_4OH$, a synthetic sample of mycapolyol E (**1**) was isolated in 29% yield over two steps. The purified product was analyzed by ^1H NMR in CD_3OD, but this revealed that some epimerization of the stereocenter centered on the tetramic acid head-group had occurred (~6:1 dr), which increased further (~3:1 dr) after just 12 hours under neutral conditions (see Supporting Information). Surprisingly, the sample subsequently proved to be insoluble in d_6-DMSO, the solvent used in the isolation paper, even after sonication and gentle warming, making it difficult to directly compare our data with the literature at this stage. We believed that NH_4OH had complexed with the polyol through hydrogen bonding, making it insoluble in d_6-DMSO, and that upon dissolution in CD_3OD the NH_4OH caused epimerization of the sensitive tetramic acid head-group with concomitant deuterium incorporation at C4′. The same sample was therefore repurified in $MeCN/H_2O$ without NH_4OH and this time it was soluble in d_6-DMSO, validating our hypothesis. The ^1H and ^{13}C NMR data in d_6-DMSO now matched the literature report for the isolated natural product, although there were additional peaks from the C4' epimers.[35] However, the high resolution in our HSQC spectrum allowed us to distinguish the signals corresponding to the 2 epimers with confidence, and the chemical shifts for the major epimer matched the natural product very closely (difference in $\delta_C \leq 0.1$ ppm). Crucially we were also able to assign C12 to C16 and C28 to C32, confirming the relative stereochemistry of the polyol. The original uncertainty of the relative stereochemistry of the C13 and C31 hydroxy groups has therefore been resolved. Furthermore, it validates the application of Kishi's NMR database to the determination of the stereochemistry of even highly complex, extended polyol motifs. The $[\alpha]_D^{24}$ of the synthetic material (4:3 mixture of C4′ epimers) was + 95 (c = 0.084, 80% aq. MeOH) which had the same positive rotation as natural mycapolyol E {$[\alpha]_D^{21}$ = +117.7 (c 0.27, 80% aq. MeOH)}.[1] Since all the data (^1H, ^{13}C NMR chemical shifts; positive optical rotation) match the natural product, we conclude that the structure of mycopolyol E is polyol **1**, as shown in Scheme 4.

In conclusion, the first total synthesis of reported mycapolyol E (**1**) has been realized in 20 steps (LLS). This was achieved through the construction of the 1,3-polyol motif by iterative catalyst-controlled alkene diboration and regioselective boronic ester homologation reactions using enantiopure magnesiated TIB esters, both during fragment synthesis and fragment unification. Furthermore, the stereochemistry of the methyl stereocenter at C5 was elucidated through partial synthesis and NMR comparison, and the uncertainty of the relative stereochemistry of the C13 and C31 hydroxy groups was resolved. Through minor alterations, every member of the mycapolyol family of natural products, and other complex molecules bearing 1,3-polyol motifs, should be accessible through this reported synthetic strategy.

Supporting Information

The authors have cited additional references within the Supporting Information.[36–49]

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Conflict Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

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