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Complex Biohopanoids Synthesis: Efficient Anchoring of Ribosyl Subunits onto a C_{30} Hopane

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Abstract: Bacteriohopanoids represent a particularly important series of triterpenoids, widely distributed in bacteria. One of the common features of these pentacyclic hopanepolyols is the presence of an extended non-terpenoid and polyhydroxylated side chain attached to the triterpenic moiety through a C–C bond. The biological function of biohopanoids also has to be addressed when one considers the broad diversity in both structures and functionalities found in the side chain. Moreover, the stereochemistries of some biohopanoids are still unconfirmed, due to the lack of synthetic methods to prepare them. In this study we describe an efficient methodology for the formation of the C–C bond between the C_{30}-hopane component and C_5-polyhydroxylated carbohydrates through the use of a hopanyllithium intermediate, which has enabled us to synthesize several biohopanoid derivatives. We also report the first synthesis of hopanepentol bearing an additional hydroxy group at position C31.

Keywords: biosynthesis · organocuprates · organolithium · steroids · terpenoids

Introduction

Biohopanoids are triterpenoids of the hopane series that are widespread in a broad range of taxonomically different strains of eubacteria.[1–9] In microorganisms the major biohopanoids are the C_{35} bacteriohopanepolyol derivatives, which surprisingly possess an additional C_5 non-terpenoid unit connected by a carbon–carbon bond to the C30 position of the hopane skeleton.[10–12]

The absolute configuration of the additional polyhydroxy C_5 side chain has been characterized by several analytical and synthetic methods,[13] with the same D-ribitol configurations having been found in the side chains of the glycoside **1** and the cyclopentyl ether **2**, present in *Zymomonas mobilis* (Figure 1),[14] as well as bacteriohopanetetrol (**3**), aminobacteriohopanetriol (**4**),[15] and adenosylhopane (**6**).[16] Biohopanoids that are hydroxylated at position 31, some of them also bearing the cyclopentyl ether functionality (compounds **7**–**12**, Figure 2), have also been isolated.[17–20]

It is assumed that bacteriohopanetetrol (**3**) and some of its polyol analogues would play the role of membrane stabilizers, although—in view of the remarkable diversity of functional groups bound to the C_5 side chain—the biohopanoid family may also serve other biological functions.[21] Moreover, the biosynthesis of some of these structures themselves also addresses challenging questions.[22–24]

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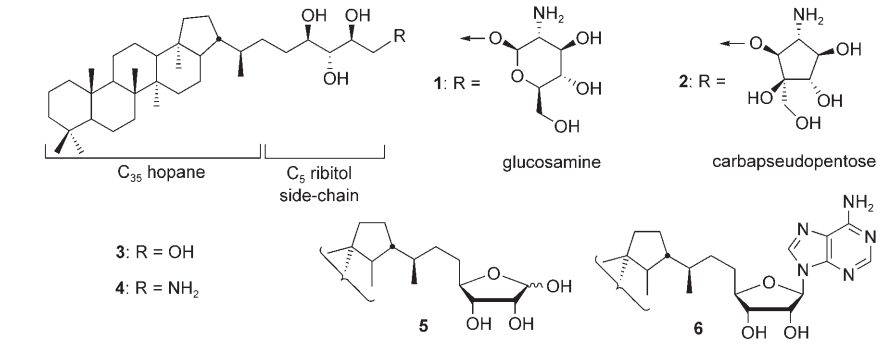

Figure 1. Biohopanoids.

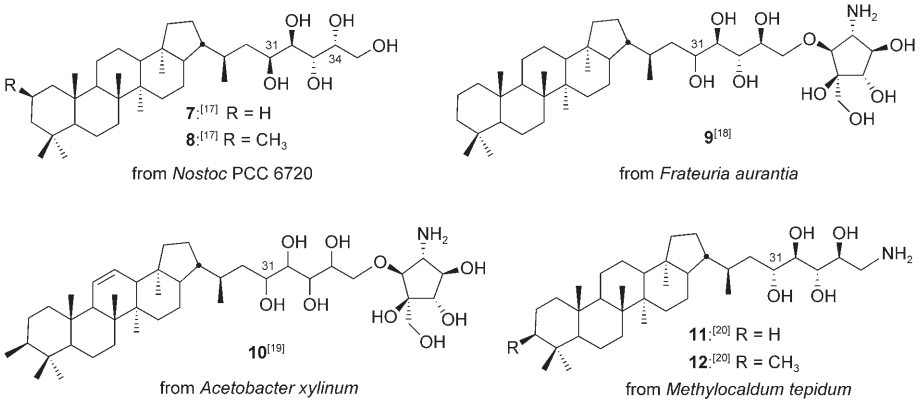

Figure 2. Biohopanoids hydroxylated at position C31.

A preliminary feeding experiment using deuterated 6,6′-[D_2]-GlcNAc showed that the glycoside **1** and the ether **2** share the same GlcNAc-derived biosynthetic pathway,[24] and so it was suggested that the biosynthesis of ether **2** should involve an unprecedented enzymatic ring contraction, transforming acetal **1** into ether **2**. Such an enzymatic reaction might also be invoked for the so far unknown biosynthetic pathways of such polyhydroxylated cyclopentyl ethers as calditol,[25] crasserides,[26a] isocrasserides,[26b] and keruffarides.[27]

Both for the investigation of the biological functions of biohopanoids and for the study of their biosynthesis it is necessary that they are obtained in pure form and sufficient quantity. Since most of them can only be isolated in trace amounts from natural sources, a general synthetic approach would be of great interest.

The chemical synthesis of such complex hopanoids had been attempted earlier,[13,28,29] but many synthetic difficulties were encountered, and only partially resolved. To date, there is no general synthetic strategy to achieve the preparation of the whole biohopanoid family.

Biosynthetically, it is believed that all these structures arise from the coupling of the C_{30} hopanic skeleton to an appropriate side chain such as a D-ribose derivative.[23] We therefore focused on a convenient and potentially biomimetic route to the synthesis of hopanoids through a (C_{30}+C_5) coupling for the construction of the key intermediate: bacteriohopanetetrol (**3**)[14] or ribosylhopane (**5**). In a preliminary communication we recently presented the direct halogen/copper exchange on bromohopane **16** that ultimately led us to complete the synthesis of glucosamine–hopanoid **1**.[14]

Here we present a more general metallation strategy for the hopane skeleton: a lithiation of phenylsulfide **14** (Scheme 1) that resulted in the formation of hopanyllithium and hopanyl cuprates. This novel methodology allowed us to synthesize polyols **1**, **3**, **5**, and **31** (Figure 1) in a flexible way.

Results and Discussion

Many efforts have already been invested in order to synthesize ribosylhopane **5** (Scheme 4) and other naturally occurring C_{35} hopanepolyols. The key coupling step has usually been achieved through Wittig-type reactions between the C_{30} hopane skeleton and an appropriate chiral building block for the C_5 side chain, but the Wittig couplings with D-ribosides have always given poor yields (8–36%),[13,28,30] the poor efficiencies of the couplings having been ascribed to the steric hindrance of the bulky hopane skeleton. To date, the best methodology for preparing bacteriohopanetetrol (**3**) is a multistep (C_{30}+C_2+C_3) sequence involving the asymmetric construction of the ribitol subunit.[29]

To the best of our knowledge, no strategy based on the use of nonstabilized organometallic hopane derivatives for

Abstract in Chinese:

摘要 —
细菌源何帕烷是一类广泛存在于细菌中的特别重要的三萜类化合物。这些含有五环三萜结构的何帕烷多醇类化合物的一个共同特征是都拥有一个非萜类结构的含多羟基结构的侧链，这个侧链通过碳－碳键的方式连接到五环三萜部分上。这些生物源何帕烷三萜的生物活性是一个仍然有待于进一步阐明的问题，对于这一点人们可以从此类化合物侧链上结构和官能团的多样性得到理解。另一方面，现阶段仍有一些生物源何帕烷三萜的立体化学结构没能得到阐明，主要是由于缺少合适的手段来合成它们。在本研究中，我们提出了一个非常有代表性的方法——
通过一个将何帕烷高效地活化为其金属锂中间体从而便于含30个碳原子的何帕烷三萜和含5个碳原子的多羟基糖衍生物之间以碳－碳键形式的连接。这个全新的方法使得我们能够顺利的合成出一系列过去非常难合成的天然何帕烷三萜类化合物。我们也同时报道了一个在其侧链的碳－31位置上含有一个额外羟基的何帕烷五醇化合物的首次人工合成。
关键词 — 甾体，生物合成，金属有机锂化合物，金属有机铜复合物，何帕烷。

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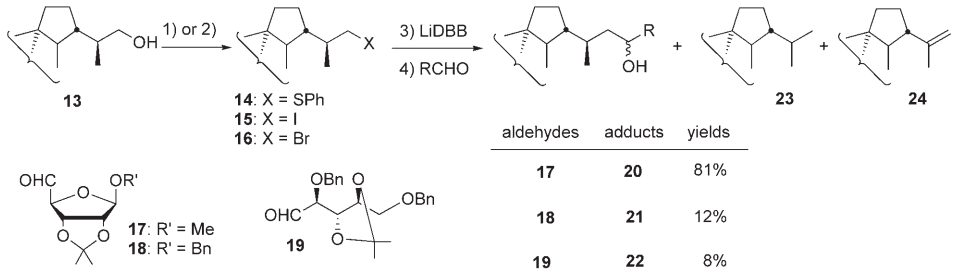


Scheme 1. 1) PhSSPh, PBu_3 (90%). 2) I_2, PPh_3 (quant.). 3) and 4) see Table 1.

carbon–carbon bond formation in the synthesis of ribosylhopane **5** or bacteriohopanetetrol **3** and their derivatives has ever been explored. In fact, organometallic reagents are usually more efficient than Wittig reagents or sulfonyl derivatives for reactions with aldehydes or epoxides, due to their higher reactivities and lower steric demands in relation to ylides. We therefore investigated the application of an organometal-mediated cross-coupling strategy to enable a direct (C_{30}+C_5) route to C_{35} hopanepolyols and their derivatives.

Generation of Hopanyllithium: We first attempted numerous standard methods for the generation of the organometallic species—organolithium, -magnesium, and -zinc reagents—most commonly used to activate the bulky C_{30} hopane skeleton. To assess whether the metalated hopane had been formed, we used aldehydes **17**,[31] **18**,[32] and **19**,[1] derived from D-ribose (Scheme 1), for the cross-coupling reactions. Unfortunately though, classical Grignard or Barbier halogen/metal exchanges with Mg, Zn, or Li failed to give the desired hopanyl–metal species from iodohopane **15** or bromohopane **16**, which could be easily prepared from known hopanol **13** (Scheme 1).[29] If the halogenides **15** and **16** were used for the metallation, the only product we were able to detect and isolate was the protonation product **23**, and so we reasoned that the metallated hopane intermediate was probably unstable and would have to be generated by a quick and efficient procedure and then engaged in a coupling reaction as quickly as possible.

We considered that the generation of a hopanyllithium species was a key issue for this project, since: i) the excellent nucleophilicity of organolithiums towards aldehydes should allow us to synthesize all biohopanoids shown in Figures 1 and 2, and ii) organolithium species can be transformed into organocuprates and then coupled to epoxides to generate (in this instance) hopanetetrol (**3**), a key (bio)synthetic intermediate for a wide range of biohopanoids.

Halogen/metal exchange having been unsuccessful, we investigated arene-mediated reductive lithiation procedures using LiDBB (lithium 4,4′-di-*tert*-butylbiphenylide).[33,34]

The most significant application of LiDBB is for the cleavage of C–S bonds in phenyl sulfides, which is extremely efficient and has proven very useful for the syntheses of complex natural products such as erythromycin.[35,36]

Reductive lithiation of the hopane derivatives: We therefore investigated the reductive lithiation of 29-phenylthiohopane **14** or iodohopane **15** and their coupling with riboside **17** according to Cohen's procedure (Scheme 1).[34]

Application of the published procedure gave the desired coupling products **20**, but in disappointing low yield, the experiments resulting either in the incomplete reduction of the phenylsulfide to give hopanyllithium or in the total protonation of the generated hopanyllithium to give hopane **23** (Scheme 1). Through the use of larger amounts of DBB and Li the yields were improved to 40 and 24% (Table 1, entries 1 and 4), starting from sulfide **14** and iodide **15**, respectively. In all cases we isolated 50–60% of the protonation byproduct **23** when the addition sequence proposed by Cohen et al.[34] was followed.

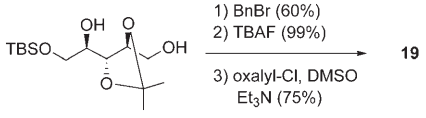
Much to our delight, though, an excellent yield of the desired coupling product was finally obtained when the addition order of the reactants was reversed (Table 1, entries 2

Table 1. Coupling experiments involving a LiDBB-promoted lithiation of sulphide **14** and iodide **15** (see Scheme 1).

Entry	Substrate	RCHO [equiv][a]	DBB (equiv)	Li [equiv]	*t* [h]	Yield [%][b]	Side product [%][c]	Procedure[d]
1	**14**	**17** (3)	6	4	2.5	40	60	N
2	**14**	**17** (2)	4	3	0.5	70	25	I
3	**14**	**17** (2)	6	6	1	81	19	I
4	**15**	**17** (4)	6	4	0.7	24	47[e]	N
5	**15**	**17** (3)	6	4	0.7	40	24[e]	I
6	**14**	**18** (2.5)	6	6	2	12	86	I
7	**14**	**19** (2)	5	5	2.5	8	90	I

[a] Numbers of equivalents were calculated on the basis of starting hopanoid **14** or **15**. [b] Isolated yields. [c] From sulfide **14** the only competing reaction is a protonation yielding **23**. [d] N (normal addition sequence): sulfide **14** was added to the LiDBB solution. I (inversed addition sequence): LiDBB was slowly added to sulfide **14** or iodide **15**. [e] From iodide **15** two side products were observed: **23**, from a protonation, and **24**, from an elimination (in both cases, the ratio **23**/**24** 4:1 was observed).

[1] Aldehyde **19** was prepared from a known ribitol derivative[14] by standard procedures.



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and 3): Instead of the addition of phenylsulfide **14** into a THF solution of LiDBB radical anion, the freshly prepared LiDBB was added dropwise to the solution of phenylsulfide **14** in dry THF at −78 °C. Coupling yields of up to 81 % were reproducibly obtained (Table 1, entry 3).

In the same optimized procedure, hopane halides **15** and **16** gave significantly lower yields: no more than 40 % of the desired alcohol **20**, together with large amounts of hopane **23** and diploptene **24** as byproducts (Table 1, entry 5).

Surprisingly, the use of other aldehydes such as **18** and **19** under the same optimized conditions also resulted only in very low yields (Table 1, entries 6 and 7).

Determination of the absolute configurations: The two resulting epimeric alcohols (*R*)-**20** and (*S*)-**20**, obtained in a ratio of 7:1 (determined by ^{1}H NMR), could easily be separated as benzoates **25** and **26** (Scheme 2). Removal of the benzoyl groups gave back the two pure diastereoisomers (*R*)-**20** and (*S*)-**20** (Scheme 2).

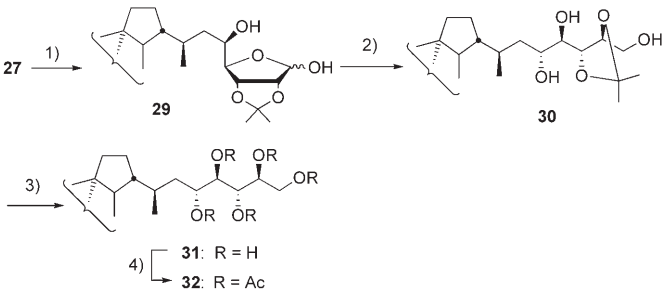
It was anticipated that it might be possible to engage the newly formed secondary alcohol in an intramolecular acetalation, giving rise to a pyranoside. NMR data of pyranosides are very characteristic and well documented, thus potentially allowing us, by comparison, to determine the relative and absolute configurations of newly formed stereogenic centers.

Indeed, compound (*R*)-**20** was hydrolyzed under acidic conditions to afford (after peracetylation) the pyranoside **28** (Scheme 2). Depending on the configuration at C31, the hopane–pyranoside **28** might exhibit either a D-allose or an L-talose stereochemical pattern, and this could be easily differentiated by analyzing the coupling constants between protons H31 and H32. The ^{1}H NMR spectrum of **28** gave a $J_{H31,H32}$ coupling constant of 10.2 Hz, which unambiguously demonstrated that these two protons were in a 1,2-*trans*-diaxial relationship and implying that peracetate **28** possesses the same configurations as D-allose, which could be confirmed by comparison with the NMR data for D-allose peracetate.[37] Since NMR data proved that the two diastereoisomers are epimeric at position C31, the additional hydroxy group in (*R*)-**20** is *R*-configured, while that in (*S*)-**20** is *S*-configured (Scheme 2).

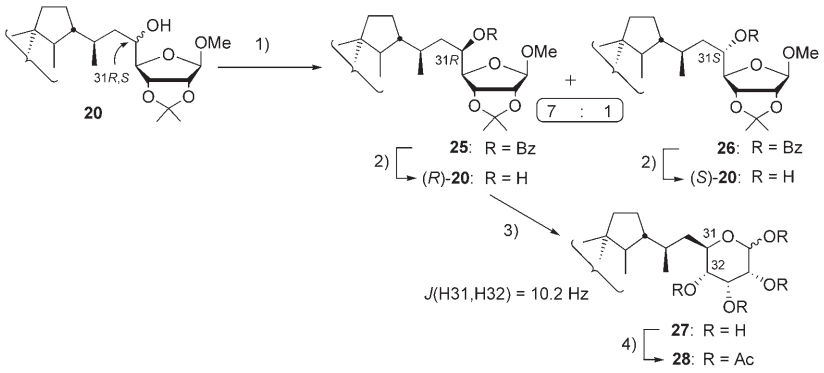
It was essential for us to establish this absolute configuration, since this protected ribosylhopane **20** can potentially be converted into naturally occurring biohopanoids possessing an additional hydroxy group at C31, such as the hopanepentols **7** or **8** or the aminobacteriohopanetetrols **11** or **12** (Figure 2).

Synthesis of hopanepentol: Natural bacteriohopanepentols have been detected in eubacteria: Zhao et al.,[17] for instance, reported the isolation and tentative structural determination of the two bacteriohopanepentols **7** and **8** from *Nostoc* PCC 6720 (Figure 2), while bacteriohopanepentols have also been found as subunits linked to polyhydroxylated cyclopentitol moieties (compounds **9** and **10**),[18,19] although the stereochemical patterns of the side chains have not been clearly established in the latter two cases. Most of the polyols that have been investigated up to now probably possess the same configuration as bacteriohopanetetrol **3**, but with an additional stereochemical center at positions C31 or even C30. Consequently, the synthesis of these hopanepentols should demonstrate their absolute configurations and provide new tools for the investigation of their biosynthesis and their biological functions.

The pentaacetylbacteriohopanepentol **32** (Scheme 3) thus became one of our synthetic targets, as it could reasonably be derived from (*R*)-**20**. The direct reduction of **27** to the corresponding pentitol **31**, followed by a peracetylation, resulted in an unsatisfactory yield. Interestingly, though, acetalation of glycolipid **27** regioselectively gave the monoprotected acetonide **29**, which was readily reduced to the triol **30** in high yield. This triol was readily deprotected and peracetylated to give the desired pentaacetate **32** in 22 % overall yield in 10 steps from a commercially available hopanone (Scheme 3). This compound should also serve as a key tool to demonstrate the absolute



Scheme 3. 1) H_2SO_4, acetone, 0 °C→RT (92 %). 2) $NaBH_4$, THF/EtOH, RT (96 %). 3) HCl (conc.), THF/MeOH, RT. 4) pyr, Ac_2O (90 %, two steps).



Scheme 2. 1) BzCl, py (96 %). 2) MeONa/MeOH (quant.). 3) HCl, THF/dioxane, 70 °C. 4) Ac_2O, pyr (95 %, two steps).

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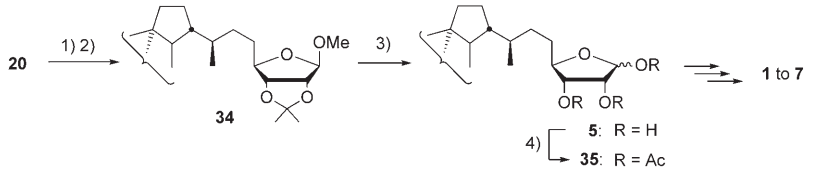
configurations of natural hopanepolyols such as **9** and **10** (Figure 2).

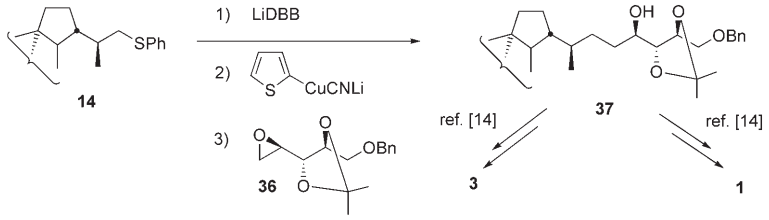
Deoxygenation and reduction of 20: For the preparation of ribosylhopane (**5**) or derivatives such as bacteriohopanetetrol (**3**), aminotriol **4**, or glycoside **1**, the epimeric mixture **20** was deoxygenated at position 31 (Scheme 4) via the xanthate **33**. Subsequent homolytic reduction afforded the desired deoxygenated product **34** in 95% yield.



Scheme 4. 1) CS_2, LiHMDS, then MeI (xanthate **33**). 2) $n$$Bu_3SnH$ (95%, two steps). 3) HCl, THF/dioxane. 4) pyr, Ac_2O (92%, two steps).

After optimization, triacetate **35** was obtained in 92% yield from methyl riboside **34** and was found to be analytically identical to the previously synthesized compound.[28,29] This is a key target compound as it can easily be transformed into ribosylhopane (**5**), which is regarded as a potential biosynthetic intermediate for biohopanoids such as **1**, **3**, **4**, or **6** (Figure 1).[21,38] In this work, the triacetate **35** has been obtained in nine steps and in 30% overall yield from a natural hopanone, having previously been synthesized in much lower overall yields through Wittig-type coupling reactions. The analytical data for triacetate **35** were identical to those previously described by Rohmer et al.[16,28,29,38][2]

Hopanylcuprate–ribose coupling: For the synthesis of biohopanoids that are not hydroxylated at position 31 (all compounds represented in Figure 1), the most straightforward strategy is coupling between a hopanecopper species and an epoxide derived from ribitol, such as **36** (Scheme 5).



Scheme 5.

In a previous work we had described the direct transformation of bromide **16** into an organocopper species[3] and its coupling to epoxide **36** (Scheme 5).[14]

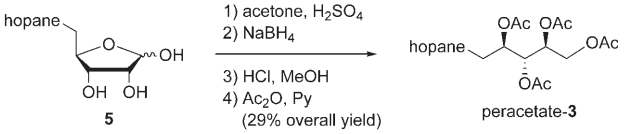
The previously described LiDBB reductive lithiation of phenylsulfide **14** offered us the opportunity to generate hopanyl cuprates. Instead of homocuprates (dialkyl cuprates), we developed a procedure for the preparation of a hopanylthienyl mixed cuprate based on Lipshutz's methodology.[39,40] Thienylalkyl cuprates are readily prepared from 2-thienyllithium and copper(I) cyanide and they only transfer the alkyl group: in our case, one equivalent of hopane phenylsulfide **14** was therefore necessary. Moreover, mixed cuprates are inherently more stable than dialkyl cuprates and their reactivities towards other substrates are similar to those of other cuprates.

After optimization, coupling of the cuprate derived from sulfide **14** and epoxide **36**[14] gave **37** in 55% yield. In comparison with the methodology implying a "zero-valent"[41] organocopper intermediate, this procedure appeared more convenient and easier to scale up. As demonstrated previously, hopanoid **37** could be transformed into bacteriohopanetetrol (**4**) and glycoside **1**.[14] Another advantage of the coupling via an organocuprate is that it requires only a two-equivalent excess of epoxide, while the coupling through a "zero-valent" organocopper species requires a minimum of three equivalents of epoxide **36**.

Conclusions

In summary, we have developed a (C_{30}+C_5) methodology based on the metallation of hopanyl sulfide **14** and its efficient coupling either to an aldehyde or to an epoxide, both derived from D-ribose. Since the metallated hopane was found to undergo rapid protonation or degradation, the key parameter for efficient coupling between the bulky hopane skeleton and the electrophile was the rapid generation of a hopanyllithium intermediate through a LiDBB reductive lithiation. This novel strategy greatly improved the yield of the hopane–ribose coupling reaction, which was regarded as

[2] To provide further structural corroboration, we transformed the precursor of triacetate **35** into the peracetate of bacteriohopanetetrol **3**, which has been very well characterized in the literature, and compared it with the natural compound.[13,29]



[3] These organocopper species have been termed "zero-valent" in the literature,[41] although their chemical nature has never been clearly demonstrated.

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the most concise sequence for the syntheses of biohopanoids.

Thanks to this procedure, we achieved an efficient synthesis of ribosylhopane **5** in an overall yield of 28% in nine steps from a commercial hopanone. We also showed that natural hopane pentol derivatives (Figure 2) could also be prepared by this sequence. Finally, we showed that the hopanyllithium intermediate could also be efficiently transformed into a mixed cuprate, thus allowing an even more direct synthesis of biohopanoids that are not hydroxylated at position C31 (Figure 1).

We have already taken advantage of this sequence to prepare natural hopanoids **1**,[14] **3**,[14] and **5** (Scheme 4) in sufficient amounts to explore both their biosyntheses and their biological functions.

It is now possible to envision the synthesis of various bacteriohopanepolyols, both naturally occurring and modified, with potential biological applications.

Experimental Section

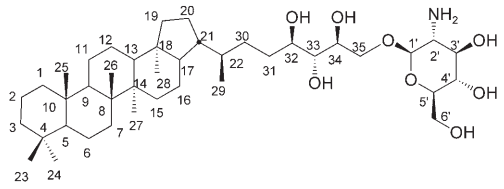
Materials and procedure: All chemicals were purchased from Acros, Sigma, Aldrich, or Fluka and were used without further purification. Tetrahydrofuran, diethyl ether, and toluene were freshly distilled over sodium benzophenone, dichloromethane over P_2O_5. ^1H and ^{13}C NMR spectra were recorded with Bruker AC 250 and DRX 400 spectrometers. All compounds were characterized by ^1H and ^{13}C NMR, as well as by ^1H–^1H and ^1H–^{13}C correlation experiments. ^{13}C shift values of the carbon atoms in the hopanoid skeleton did not significantly depend on the natures of the side chains. Mass spectra were recorded in the electron impact (EI), chemical ionization (CI), or Fast Atom Bombardment (FAB) modes on a JMS-700 spectrometer. Specific optical rotations were measured with a Perkin–Elmer 241 polarimeter in a 1 dm cell. Melting points were determined with a Büchi B-535 apparatus. Column chromatography was performed on silica gel (Kieselgel Si 60) (40–63 μm). Alcohol **13** was prepared from the commercially available Dammar resin (Sigma–Aldrich), in four steps, by known procedures.[29]

Moisture-sensitive ribosyl–hopane coupling reactions: All the coupling reactions were conducted under argon in flame- or oven-dried glass, cooled under a stream of argon or in a dessicator in the presence of P_2O_5. Solvents were dried just before their use. All transfers (reagents in solution and solvents) were carried out with oven-dried needle or cannula. Argon was dried by passing it successively through a tube filled with $CaCl_2$ and a gas drying bottle filled with KOH.

LiDBB preparation: Freshly prepared Li (20.0 mg, 2.9 mmol) and DBB (480.0 mg, 1.8 mmol) were added under argon to freshly distilled THF (5 mL). The flask was then clamped in an ultrasonic bath at a maximum energy position and the irradiation was continued for 2 min at 0 °C to afford a blue solution. The reaction mixture was stirred for 10 min at 0 °C and was then sonicated again for 2 min. This procedure was repeated four times over 1 h to generate a dark blue solution of LiDBB.

Atom and position numberings: We systematically numbered the C_{30} pentacyclic hopane skeleton and the C_5 ribitol side chain according to literature data.[42,43]

30-Phenylthiohopane (14): Tri-*n*-butylphosphine (82.4 μL, 0.3 mmol) was added under argon to a solution of hopan-30-ol **13**[29] (11.0 mg, 0.03 mmol) in dry pyridine (1 mL), followed by phenyl disulfide (33.6 mg, 0.2 mmol), and the reaction mixture was stirred overnight at room temperature. The mixture was then diluted with excess CH_2Cl_2 and washed with aqueous HCl (1 M), NaOH (3 M), and brine, the combined organic phases were dried over $MgSO_4$ and filtered through cotton, and the solvents were concentrated to dryness to afford a crude yellow oil, which



was purified by FCC (2,2,4-trimethylpentane/EtOAc 15:1) to give **14** as a white powder (12.0 mg, 90%). R_f = 0.75 (cyclohexane/EtOAc 3:1); m.p. 203.5–204 °C; $[\alpha]_D^{23}$ = +93 (*c* = 1.0 in CH_3Cl); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.17 (m, 5H; H arom.), 3.20 (ABX, *J*(22,30b) = 2.6, *J*(30a,30b) = 12.2 Hz, 1H; H30b), 2.61 (ABX, *J*(22,30a) = 8.8, *J*(30a,30b) = 12.2 Hz, 1H; H30a), 1.18 (d, *J*(22,29) = 6.2 Hz, 3H; 22-Me), 1.00, 0.98 (2×s, 6H; 8β- and 14α-Me), 0.89 (s, 3H; 4α-Me), 0.86 (s, 3H; 10β-Me), 0.84 (s, 3H; 4β-Me), 0.70 (s, 3H; 18α-Me), 1.13–1.95 (m, 25H; H hopane), 0.73–0.97 ppm (m, 3H; H hopane); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.8, 129.0, 128.7, 125.5, 56.1 (C5), 54.5 (C17), 50.4 (C9), 49.3 (C13), 45.7 (C21), 44.3 (C18), 42.1 (C3), 41.8 (C14), 41.6 (C8), 41.5 (C19), 41.2 (C30), 40.3 (C1), 37.41 (C22), 37.4 (C10), 33.6 (C15), 33.4 (C24), 33.3, 33.2 (C4, C7), 27.8 (C20), 24.0 (C12), 22.8 (C16), 21.6 (C23), 20.9 (C11), 20.2 (C29), 18.7 (C2, C6), 16.6, 16.5 (C26, C27), 15.9 (C25), 15.7 ppm (C28); MS (DCI-NH_3): *m*/*z*: 521 $[M+H]^+$; HRMS: *m*/*z*: calcd for $C_{36}H_{57}S$: 521.4181; found: 521.4175.

30-Iodohopane (15): Compound **13**[29] (300 mg, 0.7 mmol) was dissolved under argon in anhydrous toluene (30 mL), PPh_3 (1.83 g, 7.0 mmol), imidazole (476 mg, 7.0 mmol), and I_2 (1.42 g, 5.6 mmol) were then successively added to the reaction mixture, and it was then stirred at 80 °C for 2 h. The resulting mixture was allowed to cool to room temperature, after which it was treated with saturated aqueous $Na_2S_2O_3$ solution (40 mL). The aqueous phase was then extracted twice with excess CH_2Cl_2 and the combined organic phases were washed with brine, dried over $MgSO_4$, and filtered through cotton. The solvents were evaporated under reduced pressure, and subsequent FCC purification (2,2,4-trimethylpentane) afforded **15** as a white powder (377 mg, quantitative yield). R_f = 0.60 (2,2,4-trimethylpentane); m.p. 220–221 °C; $[\alpha]_D^{23}$ = +67 (*c* = 0.9 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.36 (ABX, *J*(22,30b) = 2.5, *J*(30a,30b) = 9.5 Hz, 1H; H30b), 3.24 (ABX, *J*(22,30a) = 5.7, *J*(30a,30b) = 9.5 Hz, 1H; H30a), 1.08 (d, *J*(22,29) = 6.2 Hz, 3H; 22-Me), 0.99 (s, 6H; 8β-, 14α-Me), 0.89 (s, 3H; 4α-Me), 0.86 (s, 3H; 10β-Me), 0.83 (s, 3H; 4β-Me), 0.74 (s, 3H; 18α-Me), 1.11–1.98 (m, 25H; H hopane), 0.73–1.01 ppm (m, 3H; H hopane); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 56.2 (C5), 54.2 (C17), 50.5 (C9), 49.3 (C13), 44.6 (C18), 44.2 (C21), 43.5 (C30), 42.1 (C3), 41.7 (C14), 41.8 (C8), 41.5 (C19), 40.4 (C1), 37.8 (C22), 37.4 (C10), 33.6 (C15), 33.4 (C24), 33.3 (C4, C7), 27.3 (C20), 24.0 (C12), 22.9 (C16), 21.6 (C23), 20.9 (C11), 21.0 (C29), 18.7 (C2, C6), 16.6, 16.5 (C26, C27), 15.9 (C25), 15.8 ppm (C28); MS (CI-CH_4): *m*/*z* (%): 411 (100) $[M-I]$.

30-Bromohopane (16): Compound **13**[29] (129 mg, 0.3 mmol) was dissolved under argon in anhydrous toluene (20 mL), PPh_3 (782 mg, 3.0 mmol), imidazole (204 mg, 3.0 mmol), and Br_2 (1.62 g, 1.8 mmol) were then successively added to the reaction mixture, and it was stirred at 80 °C for 2 h. The resulting mixture was allowed to cool to room temperature, after which it was treated with saturated aqueous $Na_2S_2O_3$ solution (30 mL). The aqueous phase was then extracted twice with excess CH_2Cl_2, the combined organic phased were washed with brine, dried over $MgSO_4$, and filtered through cotton, and the solvents were evaporated under reduced pressure. FCC purification (2,2,4-trimethylpentane) afforded **16** as a white powder (143 mg, 97%). R_f = 0.55 (2,2,4-trimethylpentane); m.p. 214.5–216 °C; $[\alpha]_D^{23}$ = +55 (*c* = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.52 (ABX, *J*(22,30b) = 2.5, *J*(30a,30b) = 9.8 Hz, 1H; H30b), 3.43 (ABX, *J*(22,30a) = 6.9, *J*(30a,30b) = 9.8 Hz, 1H; H30a), 1.14 (d, *J*(22,29) = 6.2 Hz, 3H; 22-Me), 0.99 (s, 6H; 8β-, 14α-Me), 0.89 (s, 3H; 4α-Me), 0.86 (s, 3H; 10β-Me), 0.83 (s, 3H; 4β-Me), 0.75 (s, 3H; 18α-Me), 1.13–1.98 (m, 25H; H hopane), 0.73–1.02 ppm (m, 3H; H hopane); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 56.1 (C5), 54.1 (C17), 50.4 (C9), 49.2 (C13), 44.5 (C18), 44.0 (C21), 43.3 (C30), 42.1 (C3), 41.8 (C14), 41.6 (C8), 41.5 (C19), 40.3 (C1), 38.6 (C22), 37.4 (C10), 33.6

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(C15), 33.4 (C24), 33.2 (C4, C7), 27.3 (C20), 23.9 (C12), 22.7 (C16), 21.6 (C23), 20.9 (C11), 19.9 (C29), 18.7 (C2, C6), 16.6, 16.5 (C26, C27), 15.9 (C25), 15.8 ppm (C28); MS (EI): *m/z* (%): 490 (10) $[M]^+$, 492 (10) $[M]^+$, 369 (15) [cleavage between C21 and C22], 269, 271 (60) [*M*−rings A, B, and C], 191 (100) [rings A and B], cleavage; HRMS: *m/z*: calcd for $C_{30}H_{51}Br$: 490.3171; found: 490.3174.

1,4-Bis-*O*-benzyl-2,3-*O*-isopropylidene-5-aldehydo-D-ribitol (19): To a solution of 5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribitol[14] (226.0 mg, 0.737 mmol) in dry DMF (6 mL) was added NaH (60%, 53.1 mg, 2.21 mmol) in portions under argon at −78°C. The suspension was stirred at this temperature for 30 min, before BnBr (220 μL, 1.85 mmol) was added. The reaction mixture was allowed to gradually warm up to −20°C and was then quenched at this temperature with MeOH (1 mL), diluted with brine, and extracted with excess diethyl ether. The combined organic phases were washed with brine, dried ($MgSO_4$), and filtered. After evaporation under reduced pressure, the resulting crude product was purified by FCC purification (cyclohexane/EtOAc 10:1) to yield the dibenzylated ribitol as a light yellow oil (245.1 mg, 69% yield). To a solution of this dibenzyl ether (132 mg, 0.271 mmol) in THF (8 mL) under argon was added TBAF (1 M, 136 μL, 0.136 mmol) portionwise at room temperature. The reaction was stirred overnight at this temperature and concentrated to dryness under reduced pressure. The residue was purified by FCC purification (cyclohexane/EtOAc 2:1) yielding the primary alcohol as a white solid (96 mg, 95% yield). This alcohol was directly engaged in a Swern oxidation. Thus, oxalyl chloride (26.5 μL, 0.31 mmol) was added to a stirred solution of dry DMSO (45.6 μL, 0.643 mmol) in freshly distilled CH_2Cl_2 (3 mL) under argon at −78°C. The resulting mixture was stirred for 10 min. A solution of the alcohol (96 mg, 0.257 mmol) in distilled CH_2Cl_2 (3 mL) was then added under argon. After 15 min at −78°C, the reaction was quenched with dry Et_3N (180 μL, 1.28 mmol) and the mixture was allowed to gradually warm up to room temperature. Water (5 mL) was added, and the mixture was extracted three times with CH_2Cl_2. The combined organic extracts were washed successively with HCl (1 M), saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. After filtration, the solvents were evaporated under reduced pressure and the residue was purified by FCC purification (cyclohexane/EtOAc 5:1) yielding aldehyde **19** as a white solid (88.6 mg, 93%). R_f = 0.45 (cyclohexane/EtOAc 3:1); m.p. 100-101°C; $[\alpha]_D^{20}$ = +2 (*c* = 0.61 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.68 (d, *J*(4,5) = 2.7 Hz, 1H; H5), 7.33 (m, 10H; H arom.), 4.41–4.63 (m, 4H; $BnCH_2$), 4.48 (m, 1H; H2), 4.40 (dd, *J*(2,3) = 7.5, *J*(3,4) = 6.5 Hz, 1H; H3), 3.97 (dd, *J*(3,4) = 6.5, *J*(4,5) = 2.7 Hz, 1H; H5b), 3.79 (dd, *J*(1b,2) = 4.2 Hz, *J*(1a,1b) = 10.3 Hz, 1H; H1b), 3.55 (dd, *J*(1a,2) = 6.9 Hz, *J*(1a,1b) = 10.3 Hz, 1H; H1a), 1.52, 1.50 ppm (2× s, 6H; acetal-Me); ^{13}C NMR (101 MHz): δ = 200.4 (C5), 137.7, 136.6, 128.5, 128.4, 128.3, 128.2, 127.8, 127.7, 109.6 (C^q acetal), 81.4 (C4), 76.4 (C2), 75.4 (C3), 73.5, 72.8 ppm ($PhCH_2$), 68.1 (C1), 27.4, 25.2 ppm (acetal-Me); MS (DCI-NH_3): *m/z*: 388 $[M+NH_4]^+$; HRMS: *m/z*: calcd for $C_{22}H_{30}O_5N$: 388.2124; found: 388.2118.

31-Hydroxy-ribosylhopane (20): The LiDBB solution was prepared by the general procedure (Li 2.9 mmol; DBB 1.9 mmol; THF 5 mL) and was slowly transferred (over 20 minutes) by glass syringe into a solution of phenylthiohopane 14 (238.0 mg, 0.5 mmol) in freshly distilled THF (11 mL) under argon at −78°C. After this time the dark blue color of the reaction mixture remained unchanged. The mixture was stirred at −78°C for 3 min, and a solution of aldehyde 17[31] (220.0 mg, 1.1 mmol) in anhydrous THF (1 mL) was then added dropwise at −78°C over a period of 5 min. After stirring at −78°C for 10 min, the reaction mixture was allowed to warm up gradually to room temperature and stirring was continued overnight. The reaction mixture was quenched with aqueous NH_4Cl solution, the aqueous phase was extracted three times with CH_2Cl_2, the combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered through cotton, and the solvents were evaporated under reduced pressure. The resulting crude product was purified by FCC (cyclohexane/EtOAc 15:1) to yield 20 as a 7:1 mixture of the two epimers (R)-20 and (S)-20 (225.0 mg, 81% overall yield); R_f = 0.42 (cyclohexane/EtOAc 6:1); and hopane 23 (36.0 mg, 19%); R_f = 0.81 (n-pentane). The analyses of pure (R)-20 and (S)-20 are described below.

(31*R*)-Hydroxyribosylhopane [(*R*)-20]: A solution of MeONa (4 mL, 0.1 M in dry MeOH) was added under argon to a solution of benzoate **25** (42.0 mg, 0.06 mmol) in anhydrous CH_2Cl_2 (1 mL). The reaction mixture was stirred overnight at room temperature and the mixture was neutralized with Amberlyst A-120 resin (H^+ form) and filtered through cotton. The filtrates were concentrated to dryness, and the residue was purified by FCC (cyclohexane/EtOAc 20:1) to afford (*R*)-**20** as a white solid (34.0 mg, 95%). R_f = 0.47 (cyclohexane/EtOAc 6:1); m.p. 183–184°C; $[\alpha]_D^{21}$ = +24 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.99 (s, 1H; H35), 4.88 (d, *J* = 6.0 Hz, 1H; H34), 4.61 (d, *J* = 6.0 Hz, 1H; H33), 4.17 (d, *J* = 1.5 Hz, 1H; H32), 3.78 (m, 1H; H31), 3.55 (d, *J*(31,31-OH) = 1.3 Hz, 1H; OH-31), 3.46 (s, 3H; OMe), 1.51, 1.36 (2×s, 6H; acetal-Me), 1.02 (d, *J*(22,29) = 5.6 Hz, 3H; 22-Me), 0.98 (s, 6H; 8β- and 14α-Me), 0.87 (s, 3H; 4α-Me), 0.84 (s, 3H; 10β-Me), 0.82 (s, 3H; 4β-Me), 0.77 (s, 3H; 18α-Me), 1.10–1.90 (m, 27H; H hopane), 0.71–0.98 ppm (m, 3H; H hopane); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 111.9 (C^q acetal), 109.9 (C35), 92.9 (C32), 85.9 (C33), 80.1 (C34), 69.4 (C31), 56.1 (C5), 55.6 (OMe), 54.6 (C17), 50.4 (C9), 49.3 (C13), 46.7 (C21), 44.2 (C18), 42.1 (C3), 41.7 (C14), 41.6 (C8), 41.55 (C19), 40.3 (C1), 39.2 (C30), 37.3 (C10), 34.0 (C22), 33.7 (C15), 33.4 (C24), 33.2 (C4, C7), 28.1 (C20), 26.3, 24.7 (acetal-Me), 23.9 (C12), 23.0 (C16), 21.6 (C23), 20.9 (C11), 19.8 (C29), 18.6 (C2, C6), 16.5, 16.4 (C26, C27), 15.9 (C28), 15.86 ppm (C25); MS (DCI-NH_3): *m/z*: 632 $[M+NH_4]^+$; HRMS(DCI): *m/z*: calcd for $C_{39}H_{70}O_5N$: 632.5254; found: 632.5250.

(31*S*)-Hydroxyribosylhopane [(*S*)-20]: Ribosylhopane (*S*)-**20** was prepared from **26** by the preceding method (93%). R_f = 0.45 (cyclohexane/EtOAc 6:1); m.p. 221–222.5°C; $[\alpha]_D^{22}$ = +19 (*c* = 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.99 (s, 1H; H35), 4.88 (d, *J* = 6.0 Hz, 1H; H34), 4.62 (d, *J* = 6.0 Hz, 1H; H33), 4.43 (d, *J* = 2.4 Hz, 1H; H32), 3.86 (m, 1H; H31), 3.49 (s, 3H; OMe), 3.32 (d, *J*(31,31-OH) = 11.7 Hz, 1H; OH-31), 1.53, 1.35 (2×s, 6H; acetal-Me), 1.02 (d, *J*(22,29) = 5.6 Hz, 3H; 22-Me), 0.99 (s, 6H; 8β-, 14α-Me), 0.88 (s, 3H; 4α-Me), 0.85 (s, 3H; 10β-Me), 0.83 (s, 3H; 4β-Me), 0.77 (s, 3H; 18α-Me), 1.13–1.90 (m, 27H; H hopane), 0.73–0.97 ppm (m, 3H; H hopane); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 111.9 (C^q acetal), 110.5 (C35), 89.0 (C32), 85.7 (C33), 82.8 (C34), 70.4 (C31), 56.1 (C5), 55.9 (OMe), 54.5 (C17), 50.4 (C9), 49.3 (C13), 46.9 (C21), 44.3 (C18), 42.1 (C3), 41.8 (C14), 41.7 (C8), 41.6 (C19), 40.6 (C30), 40.3 (C1), 37.4 (C10), 34.7 (C22), 33.7 (C15), 33.4 (C24), 33.3, 33.2 (C4, C7), 27.9 (C20), 26.3, 24.6 (acetal-Me), 24.0 (C12), 22.9 (C16), 21.6 (C23), 21.0 (C11), 20.4 (C29), 18.7 (C2, C6), 16.6, 16.5 (C26, C27), 16.0 (C28), 15.9 ppm (C25); MS (DCI-NH_3): *m/z*: 632 $[M+NH_4]^+$; HRMS: *m/z*: calcd for $C_{39}H_{70}O_5N$: 632.5254; found: 632.5240.

Benzoates 25 and 26: Benzoyl chloride (45.5 μL, 0.4 mmol) was added dropwise under argon at 0°C to a solution of the mixture of (*R*)-**20** and (*S*)-**20** (30.0 mg, 0.05 mmol) in dry pyridine (3 mL). The reaction mixture was stirred at room temperature for 24 h, quenched with saturated aqueous $NaHCO_3$, and extracted three times with CH_2Cl_2, the combined extracts were washed with brine and dried ($MgSO_4$), and the solvents were removed to dryness under reduced pressure. The resulting mixture was separated by FCC (cyclohexane/EtOAc 20:1) to yield **25** (29.4 mg, 85%); R_f = 0.32 (cyclohexane/EtOAc 15:1); and **26** (4.0 mg, 11%); R_f = 0.37 (cyclohexane/EtOAc 15:1).

Compound 25: $[\alpha]_D^{21}$ = −23 (*c* = 1.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08–7.46 (m, 5H; H arom.), 5.38 (m, 1H; H31), 4.99 (s, 1H; H35), 4.77 (d, *J* = 6.0 Hz, 1H; H33), 4.65 (d, *J* = 6.0 Hz, 1H; H34), 4.22 (d, *J* = 8.4 Hz, 1H; H32), 3.36 (s, 3H; OMe), 1.51, 1.32 (2×s, 6H; acetal-Me), 1.04 (d, *J*(22,29) = 6.6 Hz, 3H; 22-Me), 0.96, 0.88 (2×s, 6H; 8β-, 14α-Me), 0.87 (s, 3H; 4α-Me), 0.83 (s, 3H; 10β-Me), 0.81 (s, 3H; 4β-Me), 0.49 (s, 3H; 18α-Me), 1.08–1.90 (m, 27H; H hopane), 0.69–0.95 ppm (m, 3H; H hopane); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.2 (PhC=O), 133.0, 130.1, 129.6, 128.3, 112.3 (C^q acetal), 110.1 (C35), 88.8 (C32), 85.3 (C34), 81.4 (C33), 71.9 (C31), 56.1 (C5), 55.8 (OMe), 54.5 (C17), 50.4 (C9), 49.3 (C13), 46.4 (C21), 44.2 (C18), 42.1 (C3), 41.7 (C14), 41.6 (C8), 41.5 (C19), 40.3 (C1), 38.8 (C30), 37.3 (C10), 33.7 (C15), 33.6 (C22), 33.4 (C24), 33.2 (C4, C7), 28.2 (C20), 26.5, 25.0 (acetal-Me), 24.0 (C12), 22.8 (C16), 21.6 (C23), 20.9 (C11), 20.0 (C29), 18.6 (C2, C6), 16.5, 16.3 (C26,

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C27), 15.9 (C25), 15.6 ppm (C28); MS (DCI-NH_3): m/z: 736 $[M+NH_4]^+$; HRMS: m/z: calcd for $C_{46}H_{74}O_6N$: 736.5516; found: 736.5515.

Compound 26: $[\alpha]_D^{21} = -9$ (c = 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23–7.49 (m, 5H; H arom.), 5.30 (m, 1H; H31), 5.09 (s, 1H; H35), 4.66 (dd, J(32,33) = 1.0, J(33,34) = 6.0 Hz, 1H; H33), 4.60 (d, J(33,34) = 6.0 Hz, 1H; H34), 4.49 (dd, J(31,32) = 3.8, J(32,33) = 1.0 Hz, 1H; H32), 3.47 (s, 3H; OMe), 1.54, 1.31 (2×s, 6H; acetal-Me), 1.12 (d, J(22,29) = 6.2 Hz, 3H; 22-Me), 0.98 (2×s, 6H; 8β-, 14α-Me), 0.88 (s, 3H; 4α-Me), 0.85 (s, 3H; 10β-Me), 0.83 (s, 3H; 4β-Me), 0.78 (s, 3H; 18α-Me), 1.15–1.90 (m, 27H; H hopane), 0.72–0.97 ppm (m, 3H; H hopane); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.0 (Ph*C*=O), 133.0, 130.4, 129.9, 128.4, 112.4 (C^q acetal), 110.6 (C35), 86.6 (C32), 85.9 (C34), 82.1 (C33), 73.9 (C31), 56.1 (C5), 55.3 (OMe), 54.5 (C17), 50.4 (C9), 49.3 (C13), 46.9 (C21), 44.3 (C18), 42.1 (C3), 41.8 (C14), 41.7 (C8), 41.5 (C19), 40.3 (C1), 37.4 (C10), 36.9 (C30), 34.4 (C22), 33.7 (C15), 33.4 (C24), 33.2, 32.9 (C4, C7), 27.9 (C20), 26.7, 25.0 (acetal-Me), 24.0 (C12), 22.8 (C16), 21.6 (C23), 21.0 (C11), 20.5 (C29), 18.7 (C2, C6), 16.6, 16.5 (C26, C27), 15.94 (C25), 15.89 ppm (C28); MS (DCI-NH_3): m/z: 736 $[M+NH_4]^+$; HRMS: m/z: calcd for $C_{46}H_{74}O_6N$: 736.5516; found: 736.5518.

32,33,34,35-Tetra-*O*-acetyl-D-allopyranosylhopane (28): A solution of (*R*)-**20** (45.0 mg, 0.07 mmol) in a mixture of THF (1 mL), dioxane (1 mL), and HCl (1 M, 1 mL) was heated at reflux at 70 °C for 4.5 h. The reaction mixture was then quenched with pyridine at 70 °C and concentrated to dryness to afford the crude tetrol, which was acetylated (1 mL Ac_2O/pyr, 1:2) overnight at room temperature and purified by FCC (cyclohexane/acetone 20:1) to yield **28**β (34.0 mg, 64% yield, R_f 0.36 with cyclohexane/acetone 5:1) and **28**α as a white solid (13.0 mg, 24%). R_f = 0.35 (cyclohexane/acetone 5:1).

Compound 28β: m.p. 239–240 °C; $[\alpha]_D^{22} = +59$ (c = 1.7 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.93 (d, J(34,35) = 8.7 Hz, 1H; H35), 5.69 (t, J(32,33) = J(33,34) = 3.0 Hz, 1H; H33), 4.98 (dd, J(33,34) = 3.0, J(34,35) = 8.7 Hz, 1H; H34), 4.73 (dd, J(31,32) = 10.2, J(32,33) = 3.0 Hz, 1H; H32), 3.98 (dt, J(30a,31) = 1.6, J(30b,31) = J(31,32) = 10.2 Hz, 1H; H31), 2.20, 2.13, 2.05, 2.04 (4×s, 12H; AcO), 1.00 (d, J(22,29) = 5.3 Hz, 3H; 22-Me), 0.98 (s, 6H; 8β-, 14α-Me), 0.88 (s, 3H; 4α-Me), 0.84 (s, 3H; 10β-Me), 0.82 (s, 3H; 4β-Me), 0.70 (s, 3H; 18α-Me), 1.01–1.80 (m, 27H; H hopane), 0.71–0.93 ppm (m, 3H; H hopane); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.0, 169.4, 169.3, 169.1 (4×CH_3C=O), 90.1 (C35), 70.6 (C31), 70.0 (C32), 68.6 (C33), 68.4 (C34), 56.1 (C5), 54.5 (C17), 50.4 (C9), 49.3 (C13), 46.3 (C21), 44.2 (C18), 42.1 (C3), 41.8 (C14), 41.6 (C8), 41.5 (C19), 40.3 (C1), 37.7 (C30), 37.4 (C10), 33.7 (C15), 33.4 (C24), 33.26, 33.22 (C4, C7), 33.1 (C22), 27.9 (C20), 23.9 (C12), 22.9 (C16), 21.6 (C23), 20.9 (C11), 20.87, 20.7, 20.6, 20.5 (4×CH_3C=O), 20.3 (C29), 18.7 (C2, C6), 16.6, 16.5 (C26, C27), 15.9 (C25), 15.6 ppm (C28); MS (DCI-NH_3): m/z: 746 $[M+NH_4]^+$; HRMS: m/z: calcd for $C_{43}H_{72}O_9N$: 746.5207; found: 746.5194.

Compound 28α: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.23 (d, J(34,35) = 4.0 Hz, 1H; H35), 5.65 (t, J = 3.1 Hz, 1H; H33), 5.12 (dd, J(33,34) = 3.0, J(34,35) = 4.0 Hz, 1H; H34), 4.78 (dd, J(31,32) = 10.1, J(32,33) = 3.1 Hz, 1H; H32), 4.23 (dt, J(30a,31) = 1.8, J(30b,31) = J(31,32) = 10.1 Hz, 1H; H31), 2.20, 2.17, 2.06, 2.04 (4×s, 12H; AcO), 0.99 (2×s, 6H; 8β-, 14α-Me), 0.96 (d, J(22,29) = 5.6 Hz, 3H; 22-Me), 0.88 (s, 3H; 4α-Me), 0.85 (s, 3H; 10β-Me), 0.83 (s, 3H; 4β-Me), 0.73 (s, 3H; 18α-Me), 1.00–1.80 (m, 27H; H hopane), 0.69–0.95 ppm (m, 3H; H hopane); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.2, 169.4, 169.3, 169.1 (4×CH_3C=O), 88.4 (C35), 69.7 (C31), 67.3 (C32), 66.3 (C33), 64.6 (C34), 56.1 (C5), 54.6 (C17), 50.4 (C9), 49.3 (C13), 46.6 (C21), 44.3 (C18), 42.1 (C3), 41.8 (C14), 41.7 (C8), 41.5 (C19), 40.3 (C1), 37.4 (C10), 36.9 (C30), 33.7 (C15), 33.4 (C24), 33.3, 33.2 (C4, C7), 32.6 (C22), 27.6 (C20), 24.0 (C12), 22.9 (C16), 21.6 (C23), 20.94 (C11), 20.92, 20.8, 20.7, 20.5 (4×CH_3C=O), 19.5 (C29), 18.7 (C2, C6), 16.6, 16.5 (C26, C27), 15.9 (C25), 15.8 ppm (C28); MS (DCI-NH_3): m/z: 746 $[M+NH_4]^+$; HRMS: m/z: calcd for $C_{43}H_{72}O_9N$: 746.5207; found: 746.5201.

33,34-*O*-Isopropylidene-D-allopyranosylhopane (29): A solution of (*R*)-**20** (22.0 mg, 0.03 mmol) in a mixture of THF (1.2 mL), dioxane (0.75 mL), and HCl (1 M, 0.75 mL) was heated at reflux at 70 °C for 5 h. The reaction mixture was then quenched with pyridine at 70 °C, and concentrated to dryness to afford the crude pyranosylhopanetetrol **27**. The resulting mixture was dried overnight under vacuum before being suspended at room temperature in a mixture of dry acetone (3 mL) and THF (3 mL) containing a catalytic amount of concentrated sulfuric acid (10 μL). The reaction mixture was stirred at room temperature for 16 h, neutralized with solid $NaHCO_3$, and filtered through cotton. The filtrates were concentrated to dryness and the residue was purified by FCC (cyclohexane/EtOAc 4:1) to afford **29** as a syrup (18.2 mg, 92%). R_f = 0.52 (cyclohexane/EtOAc 2:1). Compound **29** was characterized as its peracetate.

31,35-Di-*O*-acetyl-D-ribosylhopane (peracetate-29): Ac_2O (1 mL) was added to a solution of **29** (18.2 mg, 0.03 mmol) in pyridine (2 mL). The reaction mixture was stirred overnight at room temperature, after which it was poured into a mixture of ice/water. The resulting mixture was then extracted three times with CH_2Cl_2, and the combined organic phases were washed with brine, dried ($MgSO_4$), and filtered through cotton. The solvents were removed under reduced pressure and the resulting residue was purified by FCC (cyclohexane/EtOAc 6:1) to yield the peracetate of **29** as a white powder (20.4 mg, 97%). R_f = 0.53 (cyclohexane/EtOAc 2:1); $[\alpha]_D^{18} = +13$ (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.22 (s, 1H; H35), 5.09 (ddd, J(30a,31) = 1.7, J(30b,31) = 9.8, J(31,32) = 8.2 Hz, 1H; H31), 4.73 (d, J(33,34) = 6.0 Hz, 1H; H34), 4.70 (d, J(33,34) = 6.0 Hz, 1H; H33), 4.16 (d, J(31,32) = 8.1 Hz, 1H; H32), 2.12, 2.09 (2×s, 6H; 2 Ac), 1.52, 1.36 (2×s, 6H; acetal-Me), 0.98 (d, J(22,29) = 5.9 Hz, 3H; 22-Me), 0.97 (2×s, 6H; 8β-, 14α-Me), 0.88 (s, 3H; 4α-Me), 0.84 (s, 3H; 10β-Me), 0.81 (s, 3H; 4β-Me), 0.70 (s, 3H; 18α-Me), 1.11–1.90 (m, 27H; hopane), 0.72–0.98 ppm (m, 3H; hopane); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.7, 169.4 (2×CH_3C=O), 113.0 (C^q acetal), 102.5 (C35), 89.4 (C32), 85.2 (C34), 81.3 (C33), 71.0 (C31), 56.1 (C5), 54.4 (C17), 50.4 (C9), 49.3 (C13), 46.2 (C21), 44.3 (C18), 42.1 (C3), 41.8 (C14), 41.6 (C8), 41.5 (C19), 40.3 (C1), 38.3 (C30), 37.4 (C10), 33.7 (C15), 33.2 (C22), 33.4 (C24), 33.2 (C4, C7), 28.1 (C20), 26.5, 25.1 (acetal-Me), 23.9 (C12), 22.9 (C16), 21.6 (C23), 21.2, 21.0 (2×CH_3C=O), 20.9 (C11), 20.0 (C29), 18.7 (C2, C6), 16.5, 16.4 (C26, C27), 15.9 ppm (C25, C28); MS (DCI-NH_3): m/z: 702 $[M+NH_4]^+$; HRMS: m/z: calcd for $C_{42}H_{72}O_7N$: 702.5309; found: 702.5311.

33,34-*O*-Isopropylidene-hopanepentol (30): $NaBH_4$ (1.5 mg, 0.04 mmol) was added to a solution of **29** (16.0 mg, 0.03 mmol) in a mixture of THF (1 mL) and EtOH (1 mL) and the mixture was stirred overnight at room temperature, quenched with acetone (0.5 mL), and concentrated to dryness to afford **30** as a white solid (15.7 mg, 96%). R_f = 0.15 (cyclohexane/EtOAc 2:1). Compound **30** was characterized as its peracetate.

33,34-*O*-Isopropylidene-31,32,35-tri-*O*-acetyl-hopanepentol (peracetate-30): Triol **30** (19.0 mg, 0.03 mmol) was acetylated overnight at room temperature in Ac_2O/pyr (1:1, 2 mL), the crude mixture was concentrated to dryness under reduced pressure, and the resulting product was purified by FCC (cyclohexane/acetone 20:1) to afford the triacetate as a colorless syrup (21.8 mg, 95%). R_f = 0.51 (cyclohexane/acetone 5:1); $[\alpha]_D^{25} = +32$ (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.28 (m, 1H; H31), 5.24 (dd, J(31,32) = 2.6, J(32,33) = 9.4 Hz, 1H; H32), 4.34 (m, 1H; H34), 4.31 (ABX, J(34,35b) = 3.9, J(35a,35b) = 13.3 Hz, 1H; H35b), 4.22 (dd, J(32,33) = 9.4, J(33,34) = 5.4 Hz, 1H; H33), 3.96 (m, 1H; H35a), 2.12, 2.11, 2.03 (3×s, 9H; 3×Ac), 1.57, 1.40 (2×s, 6H; acetal-Me), 0.99 (s, 6H; 8β-, 14α-Me), 0.97 (d, J(22,29) = 4.3 Hz, 3H; 22-Me), 0.88 (s, 3H; 4α-Me), 0.85 (s, 3H; 10β-Me), 0.83 (s, 3H; 4β-Me), 0.73 (s, 3H; 18α-Me), 1.08–1.96 (m, 27H; H hopane), 0.73–0.97 ppm (m, 3H; H hopane); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.71, 170.68, 169.7 (3×CH_3C=O), 109.6 (C^q acetal), 75.5 (C34), 74.3 (C33), 71.2 (C31), 70.5 (C32), 62.1 (C35), 56.1 (C5), 54.5 (C17), 50.4 (C9), 49.3 (C13), 46.4 (C21), 44.3 (C18), 42.1 (C3), 41.8 (C14), 41.7 (C8), 41.5 (C19), 40.3 (C1), 37.4 (C10), 33.9 (C30), 33.7 (C22), 33.6 (C15), 33.4 (C24), 33.3, 33.2 (C4, C7), 27.9 (C20), 27.8, 25.7 (acetal-Me), 24.0 (C12), 22.8 (C16), 21.6 (C23), 20.93 (C11), 21.0, 20.89, 20.83 (3×CH_3C=O), 19.9 (C29), 18.7 (C2, C6), 16.6, 16.5 (C26, C27), 15.9, 15.8 ppm (C25, C28); MS (DCI-NH_3): m/z: 746 $[M+NH_4]^+$; HRMS(DCI): m/z: calcd for $C_{44}H_{76}O_8N$: 746.5571; found: 746.5558.

(31*R*,32*R*,33*S*,34*S*)-31,32,33,34,35-Penta-*O*-acetyl-hopanepentol (32): 33,34-*O*-Isopropylidene-hopanepentol (**30**, 15.7 mg, 0.03 mmol) was dissolved at 0 °C in THF/MeOH (1:1, 2 mL) containing a catalytic amount

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of concentrated aqueous HCl (37%, 12 μL). The resulting mixture was vigorously stirred overnight at room temperature and then neutralized with solid $NaHCO_3$ and filtered through cotton, and the filtrates were concentrated. The resulting crude pentol **31** was acetylated overnight at room temperature in Ac_2O/pyr (1:1, 2 mL) and the resulting mixture was purified by FCC (cyclohexane/EtOAc 4:1) to provide the hopanepentol pentacetate **32** as a white solid (18.1 mg, 90% yield in two steps from **30**). M.p. 158–159°C; $[\alpha]_D^{19} = +24$ ($c = 0.8$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.38–5.32 (m, 2H; H33, H34), 5.26 (dd, J(31,32) = 3.7, J(32,33) = 6.6 Hz, 1H; H32), 5.14 (ddd, J(30a,31) = 1.5, J(30b,31) = 11.3, J(31,32) = 3.7 Hz, 1H; H31), 4.40 (ABX, J(34,35b) = 3.2, J(35a,35b) = 12.2 Hz, 1H; H35b), 4.16 (ABX, J(34,35a) = 7.2, J(35a,35b) = 12.2 Hz, 1H; H35a), 2.15, 2.13, 2.11, 2.08, 2.06 (5×s, 15H; 5 Ac), 0.98, 0.96 (2×s, 6H; 8β-, 14α-Me), 0.94 (d, J(22,29) = 6.3 Hz, 3H; 22-Me), 0.88 (s, 3H; 4α-Me), 0.84 (s, 3H; 10β-Me), 0.82 (s, 3H; 4β-Me), 0.70 (s, 3H; 18α-Me), 1.00–1.90 (m, 27H; H hopane), 0.72–0.90 ppm (m, 3H; H hopane); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.6, 170.5, 170.0, 169.7, 169.5 (5×CH_3C=O), 71.6 (C32), 70.0 (C34), 69.8 (C31), 69.4 (C33), 61.7 (C35), 56.1 (C5), 54.4 (C17), 50.4 (C9), 49.3 (C13), 46.2 (C21), 44.3 (C18), 42.1 (C3), 41.8 (C14), 41.6 (C8), 41.5 (C19), 40.3 (C1), 37.4 (C10), 35.5 (C30), 33.69 (C22), 33.66 (C15), 33.4 (C24), 33.2 (C4, C7), 28.0 (C20), 23.9 (C12), 22.9 (C16), 21.6 (C23), 20.9 (C11), 20.8, 20.7, 20.6 (5×CH_3C=O), 19.9 (C29), 18.7 (C2, C6), 16.5, 16.4 (C26, C27), 15.9 (C25), 15.8 ppm (C28); MS (DCI-NH_3): m/z: 790 $[M+NH_4]^+$; HRMS: m/z: calcd for $C_{45}H_{76}O_{10}N$: 790.5469; found: 790.5472.

31-*O*-(*S*-Methyldithiocarbonyl)-ribosylhopane (33): LiHMDS (97%, 33.4 mg, 0.2 mmol) was added under argon at −78°C to a solution of (*R*)-**20** (41.0 mg, 0.07 mmol) in anhydrous THF (4 mL), followed by carbon disulfide (12 μL, 0.2 mmol). Stirring was continued at this temperature for 3 h, and methyl iodide (33.3 μL, 0.5 mmol) was then added at −78°C. The reaction mixture was stirred at this temperature for a further 30 min and then at room temperature overnight. The mixture was quenched with water (4 mL) and extracted twice with CH_2Cl_2, and the organic layer was washed with brine, dried over $MgSO_4$, filtered through cotton, and concentrated in vacuo. Further purification by FCC (cyclohexane/EtOAc 40:1) provided **33** as a white solid (54.0 mg, quantitative yield). R_f = 0.44 (toluene/EtOAc 40:1); m.p. 167–168.5°C; $[\alpha]_D^{23} = +6$ ($c = 0.8$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.02 (m, 1H; H31), 4.99 (s, 1H; H35), 4.78 (d, J = 6.0 Hz, 1H; H34), 4.62 (d, J = 6.0 Hz, 1H; H33), 4.21 (d, J = 9.0 Hz, 1H; H32), 3.40 (s, 3H; OMe), 2.60 (s, 3H; SMe), 1.51, 1.34 (2×s, 6H; acetal-Me), 1.01 (d, J(22,29) = 5.7 Hz, 3H; 22-Me), 0.97 (2×s, 6H; 8β-, 14α-Me), 0.88 (s, 3H; 4α-Me), 0.85 (s, 3H; 10β-Me), 0.82 (s, 3H; 4β-Me), 0.70 (s, 3H; 18α-Me), 1.12–1.97 (m, 27H; H hopane), 0.72–0.97 ppm (m, 3H; H hopane); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 112.4 (C^q acetal), 110.2 (C35), 88.0 (C32), 85.2 (C34), 81.2 (C33), 80.5 (C31), 56.1 (C5), 56.0 (OMe), 54.5 (C17), 50.4 (C9), 49.4 (C13), 46.4 (C21), 44.2 (C18), 42.1 (C3), 41.74 (C14), 41.68 (C8), 41.6 (C19), 40.3 (C1), 39.1 (C30), 37.4 (C10), 33.7 (C15), 33.5 (C22), 33.4 (C24), 33.3, 33.2 (C4, C7), 28.4 (C20), 26.9, 26.5, 25.1 (acetal-Me), 24.0 (C12), 22.9 (C16), 21.6 (C23), 20.9 (C11), 20.3 (C29), 19.0 (SMe), 18.7 (C2, C6), 16.6, 16.4 (C26, C27), 15.9 (C25), 15.7 ppm (C28); MS (DCI-NH_3): m/z: 722 $[M+NH_4]^+$; HRMS: m/z: calcd for $C_{41}H_{72}O_5S_2N$: 722.4852; found: 722.4871.

33,34-*O*-Isopropylidene-35-*O*-methyl-β-D-ribosylhopane (34): nBu$_3$SnH (97%, 0.3 mL, 1.1 mmol) was added under dry argon to a solution of xanthate **33** (99.0 mg, 0.14 mmol) in freshly distilled toluene (5 mL), followed by a catalytic amount of AIBN (5.0 mg), and the mixture was heated at reflux overnight at 80°C. The reaction mixture was then concentrated to dryness to afford a residue, which was purified by FCC (cyclohexane/EtOAc 20:1) to yield **34** as a white solid (83.0 mg, 98%). R_f = 0.38 (toluene/EtOAc 40:1); m.p. 179.7–180°C; $[\alpha]_D^{23} = +32$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.97 (s, 1H; H35), 4.63 (d, J = 6.0 Hz, 1H; H34), 4.54 (d, J = 6.0 Hz, 1H; H33), 4.13 (m, 1H; H32), 3.38 (s, 3H; OMe), 1.52, 1.35 (2×s, 6H; acetal-Me), 0.99 (s, 6H; 8β-, 14α-Me), 0.97 (d, J(22,29) = 6.4 Hz, 3H; 22-Me), 0.89 (s, 3H; 4α-Me), 0.86 (s, 3H; 10β-Me), 0.83 (s, 3H; 4β-Me), 0.75 (s, 3H; 18α-Me), 1.11–1.90 (m, 29H; H hopane), 0.73–0.95 ppm (m, 3H; H hopane); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 112.1 (C^q acetal), 109.4 (C35), 87.8 (C32), 85.6 (C34), 84.3 (C33), 56.2 (C5), 55.0 (OMe), 54.5 (C17), 50.5 (C9), 49.3 (C13), 46.2 (C21), 44.4 (C18), 42.1 (C3), 41.8 (C14), 41.7 (C8), 41.6 (C19), 40.3 (C1), 37.4 (C10), 36.8 (C22), 33.7 (C15), 33.4 (C24), 33.3, 33.2 (C4, C7), 32.5 (C30), 32.0 (C20), 27.8 (C31), 26.5, 25.1 (acetal-Me), 24.0 (C12), 22.9 (C16), 21.6 (C23), 21.0 (C11), 20.0 (C29), 18.7 (C2, C6), 16.6, 16.5 (C26, C27), 15.9 ppm (C25, C28); MS (DCI-NH_3): m/z: 616 $[M+NH_4]^+$; HRMS: m/z: calcd for $C_{39}H_{70}O_4N$: 616.5305; found: 616.5303.

Ribosylhopane (35): A solution of compound **34** (20.5 mg, 0.03 mmol) in a mixture of THF (1.5 mL), dioxane (0.75 mL), and HCl (1M, 0.75 mL) was heated at reflux at 75°C for 4.5 h. The reaction mixture was then quenched with pyridine at 75°C, and concentrated to dryness to afford the crude ribosylhopane **5**. To this residue was added pyridine (2 mL, followed by Ac_2O (1 mL). The reaction mixture was stirred at room temperature, after which it was poured into a mixture of ice/water and extracted three times with CH_2Cl_2, and the combined organic phases were washed with brine, dried ($MgSO_4$), and filtered through cotton. The solvents were removed under reduced pressure and the resulting residue was purified by FCC (cyclohexane/EtOAc 15:1) to yield **35**α (15.7 mg, 68%); R_f = 0.57 (cyclohexane/acetone 6:1) and **35**β (6.0 mg, 26%); R_f = 0.51 (cyclohexane/acetone 6:1). These two compounds have been described in the literature previously.[16,28,29,38]

33,34-*O*-Isopropylidene-35-*O*-benzylhopanetetrol (37)

Solution A (lithium 2-thienylcyanocuprate): nBuLi (2.5M in hexane, 0.46 mL, 1.2 mmol) was added dropwise under argon at −78°C to a solution of thiophene (92 μL, 1.2 mmol) in dry THF (2 mL). Stirring was continued at this temperature for 15 min and then at −20°C for 30 min. This solution was transferred into a slurry of CuCN (103.0 mg, 1.2 mmol) and dry THF (0.5 mL) at −78°C, and the suspended mixture was then allowed to warm to −40°C, giving a clear, light tan solution.

Solution B (LiDBB): LiDBB was prepared by the general procedure, with Li (12.0 mg, 1.7 mmol) and DBB (345.3 mg, 1.3 mmol) in THF (4 mL).

Solution C: The LiDBB solution (**B**) was slowly (over a period of 10 min) transferred under argon at −78°C into a solution of phenylthiohopane **14** (150.0 mg, 0.3 mmol) in THF (10 mL). Lithium 2-thienylcyanocuprate (1.6 mL of Solution **A**) was then added dropwise to the reaction mixture at −78°C over a period of 5 min by glass syringe, after which a solution of epoxide **36**[14] (190.0 mg, 0.7 mmol) in THF (1 mL) was added. After having been stirred at −78°C for 10 min, the reaction mixture was allowed to warm to room temperature over 1 h and the stirring was continued overnight. The reaction was quenched with aqueous NH_4Cl solution, the aqueous phase was extracted three times with excess CH_2Cl_2, the combined extracts were washed with brine, dried ($MgSO_4$), and filtered through cotton, and the solvents were evaporated under reduced pressure. The resulting crude mixture was purified by FCC (2,2,4-trimethylpentane/acetone 40:1→30:1) to yield **37** as a white powder (106.4 mg, 55%), R_f = 0.30 (2,2,4-trimethylpentane/acetone 15:1) and hopane **23** (42.0 mg, 36%), R_f = 0.81 (cyclohexane). Analytical data for **37** matched those published.[14]

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