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Natural Products

Total Synthesis of (+/−)-Frondosin B and (+/−)-5-*epi*-Liphagal by Using a Concise (4+3) Cycloaddition Approach

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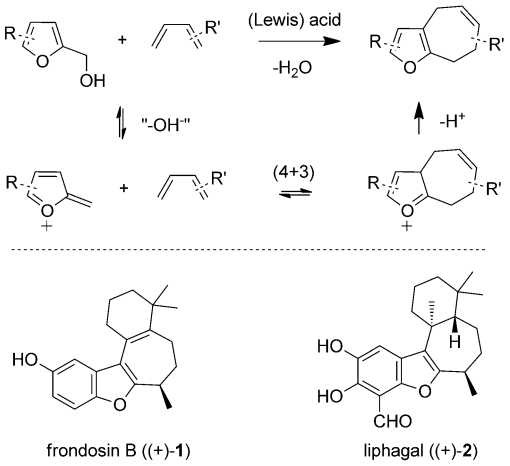
Dedicated to Prof. Dr. Pierre De Clercq on the occasion of his retirement and his 65th birthday

Abstract: A recently developed (4+3) cycloaddition between dienes and furfuryl alcohols, as precursors of oxyallyl-type cations, has been used as a key step in the racemic syntheses of two natural products: frondosin B and liphagal. This work demonstrates the synthetic potential of this cycloaddition reaction, and offers a short synthetic route to an interesting family of natural products. A full account of these synthetic studies is presented, further illustrating the mechanism, scope, and limitations of this straightforward synthetic method for seven-membered rings.

Introduction

Cycloadditions are privileged synthetic methods that allow the rapid elaboration of stereochemically complex carbocyclic structures. This is exemplified by the Diels–Alder reaction, which has had an enormous impact on the science of chemical synthesis.[1] Indeed, an important step in planning the synthesis of any target molecule that incorporates a cyclohexane substructure, is giving due consideration to all possible (4+2) cycloaddition routes. For the synthesis of seven-membered rings, the situation is somewhat less straightforward.[2] Although many useful synthetic methods have been developed that allow the assembly of cycloheptenes through a (4+3) cycloaddition of a conjugated diene and a suitable three-carbon dienophile (e.g. oxyallyl cations),[3] these methods suffer from a rather narrow reactant/substrate scope and require reaction partners (or precursors thereof) that are synthetically quite challenging. Their use in the total synthesis of natural products has thus been limited,[4] especially in the later stages of multistep syntheses; that is, the convergent assembly of two relatively advanced intermediates.

Some time ago, we reported a novel (4+3) cycloaddition that uses plain furfuryl alcohols as precursors for furfuryl cations, which were shown to be excellent three-carbon dienophiles for a relatively wide range of dienes (Scheme 1).[5] Pattenden and Winne had originally observed this transformation during synthetic studies towards the polycyclic diterpene ra-



Scheme 1. The dehydrative (4+3) cycloaddition between furfuryl alcohols and conjugated dienes and two cyclohepta[b]furan-containing natural products.

meswaralide.[6,7] Interestingly, Ivanova et al. independently found a similar transformation by starting from 2-furyl-cyclopropane-1,1-dicarboxylates as furfuryl cation precursors.[8] Recently, Wu and co-workers developed a very elegant three-component coupling process which expands the scope of this reaction to indole-3-carbinols, giving access to valuable synthetic intermediates.[9] Similarly, benzofuran-3-carbinols have also been shown to be viable substrates in this (4+3) cycloaddition.[10]

As this new cycloaddition reaction affords products incorporating a furan-fused cycloheptene, our attention was drawn to the natural products frondosin B (**1**)[11] and liphagal (**2**),[12] which both contain this cyclohepta[b]furan substructure (Scheme 1). Moreover, these tetracyclic meroterpenoids have been popular targets for total syntheses.[13,14] Especially for liphagal, this synthetic interest has been spurred by reports of a remarkable biological activity, as it selectively inhibits one isoform of the phosphatidylinositide 3-kinase (PI3K) enzyme

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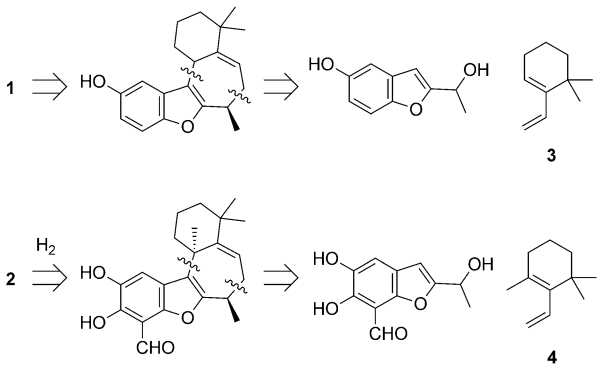
family.[12] PI3K signaling has been implicated in many important cellular functions, which makes liphagal an attractive lead structure to develop novel therapeutics. In fact, after our initial report of the (4+3) cycloaddition of furfuryl cations, a preliminary communication by Xue, Li and co-workers[13(l)] reported the total synthesis of frondosin B, together with the synthesis of an advanced intermediate for the synthesis of 5-*epi*-liphagal, using this new reaction as a key step. Herein, we present a full account of our own independent synthetic studies for these interesting natural products, which have offered further insight into the scope and limitations of the (4+3) cycloaddition reaction of furfuryl cations, illustrating its usefulness in total synthesis.

Results and Discussion

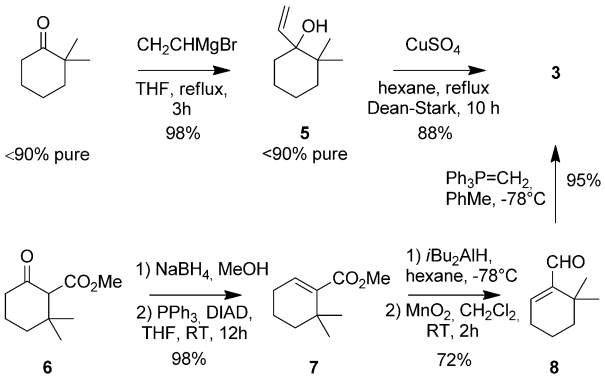
The (4+3) cycloaddition of furfuryl cations was found to be a remarkably efficient reaction.[5–7] These cations can be generated from straightforward synthetic intermediates and, in contrast to most oxyallyl-type cations, furfuryl cations show a relatively wide scope of possible diene reaction partners, giving synthetically useful yields and selectivities. For the synthesis of the skeletal types of the title natural products (see retrosynthesis in Scheme 2), we were encouraged by the fact that we had



Scheme 2. Retrosynthesis for frondosin B and liphagal by using the (4+3) cycloaddition of furfuryl alcohols gives straightforward fragments.

already shown the known vinyl cyclohexene **4** to react with a simple furfuryl alcohol under standard conditions, giving only the desired regioisomer.[5] The isolated yield was rather low in this case (45%), but we have found that for most substrate combinations the efficiency of the (4+3) cycloaddition reaction can be optimized to satisfactory levels by changing the reaction conditions and the type of (Lewis) acid promotor used. We thus set out to prepare the diene and furfuryl alcohol precursors required for the assembly of frondosin B (**1**) and liphagal (**2**).

The vinylcyclohexene **4**, required for the liphagal synthesis (Scheme 2), is a known compound and can be obtained in one step from commercial β-cyclocitral by using a Wittig methylenation.[15] Similarly, the related vinylcyclohexene **3**, containing one methyl substituent less, is a known compound that can be prepared in two steps from commercially available 2,2-dimethylcyclohexanone.[16] The previously described vinylmagnesium bromide addition and subsequent dehydration reaction proceeded smoothly (Scheme 3), but we found that the ob-



Scheme 3. Alternative syntheses explored for vinylcyclohexene **3**. DIAD = diisopropyl azodicarboxylate.

tained vinylcyclohexene **3** contained considerable amounts of inseparable impurities (>10%). These were traced back to regioisomeric products in the starting material (which is only available in ~90% purity from commercial sources). These regioisomeric ketones could not be separated and our own attempts at preparing the dimethylcyclohexanone as a pure regioisomer, by controlled methylation of 2-methylcyclohexanone, did not give better results. We soon found that the presence of these impurities was quite problematic for our study of the planned cycloadditions, as they gave rise to additional reaction products, which were hard to separate from the desired compounds. As furfuryl cation cycloadditions sometimes require an excess of the diene reactant, we also observed cases in which these regioisomers were actually enriched in the isolated mixtures of cycloadducts, further complicating reaction analyses and purification. Therefore, we explored an alternative synthesis for the diene **3**, which we expected to give an isomerically pure final product without problems (Scheme 3, bottom route). Thus, starting from the known cyclic β-ketoester **6**, easily obtained from very cheap 6-methyl-5-hepten-2-one,[17] a sodium borohydride reduction and Mitsunobu-type dehydration gave the cyclic enoate ester **7**. Next, a two-step redox adjustment gave the corresponding cyclohexene–carbaldehyde **8** and, finally, a Wittig methylenation gave the desired vinylcyclohexene **3** in high overall yield and in very high purity. We later found that careful chromatography over argentated silica gel of the previously obtained diene **3**, contaminated with a mixture of regioisomers, also gave the compound **3** in quite pure form (>95%), albeit in a relatively low recovered yield (~35%). For large-scale (multigram) preparation, we still prefer the longer route, as this requires very little and straightforward purification steps, and uses inexpensive starting materials and reagents.

In our initial exploration of the key cycloaddition required for the total synthesis of frondosin B, we had rapidly achieved a promising model reaction. The reaction between the simple

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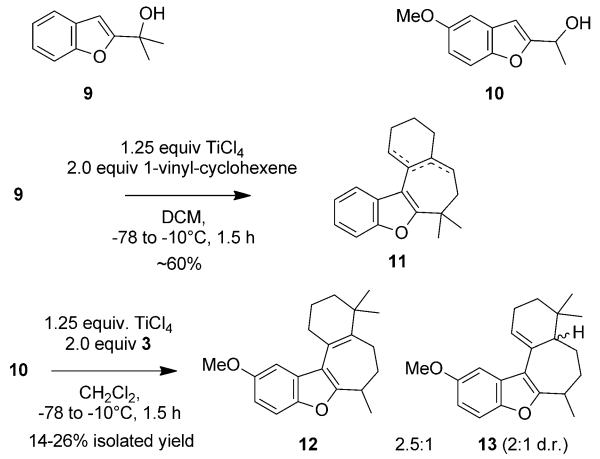
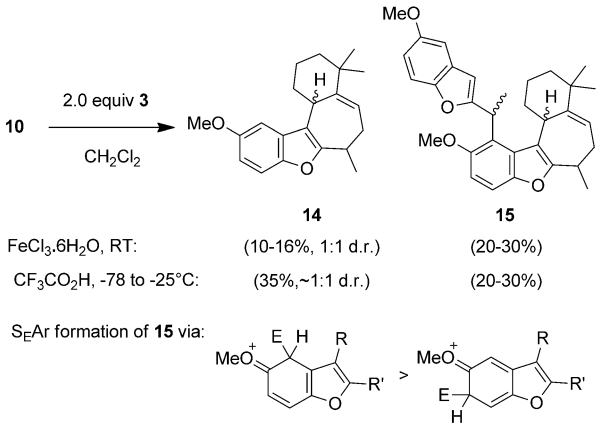
benzofuran **9**[18] and 1-vinyl-cyclohexene under our standard conditions using stoichiometric amounts of titanium chloride gave the expected polycyclic core in reasonable yield (**11**, Scheme 4). The tetracycle **11** was obtained as an inseparable



Scheme 4. Investigation of the key cycloaddition step for the assembly of the frondosin B polycyclic skeleton by using a model benzofuran substrate **9** and with the fully functionalized substrates **10** and **3**.

dicated most of the undesired reaction products seemed to be furfuryl oligomerization products (rather than the more usual and easily removed diene oligomers). Switching to the milder Lewis acid iron(III)chloride hexahydrate (Scheme 5), a reagent



Scheme 5. Optimization of the key cycloaddition step for frondosin B by using milder Lewis acids and identification and mechanistic rationalization of side products.

mixture of regioisomeric olefins, and in rather low purity (even after removal of oligomeric material by filtration over a small plug of Florisil). This low purity was attributed to the harsh reaction conditions. Although the titanium(IV)chloride reagent has been found to be the most reliable and generally applicable for a wide range of substrates,[5] this strong Lewis acid can indeed be expected to give rise to various acid-catalyzed side reactions. Nevertheless, this result clearly demonstrated the overall feasibility of the required transformation.

In contrast to the results obtained with benzofuran **9**, and somewhat unexpectedly, only terribly complex reaction mixtures were obtained when the fully functionalized benzofuran alcohol **10**[19] was used. Reaction analyses indicated only minor amounts of the expected cycloadducts were formed. However, careful chromatography of the highly complex reaction mixture obtained from the reaction with diene **3** (when used in its highly pure form), gave a small but relatively clean isolated fraction. This was found to contain a mixture of only three isomeric products, comprising (+/−)-*O*-methyl frondosin B **12** as the major product next to two minor positional alkene isomers (**13**). Interestingly, this exact mixture has been obtained in three previous total syntheses of frondosin B, reported by the groups of Danishefsky,[13a,b] Trauner,[13c,e] and MacMillan.[13j] This mixture of **12** and **13** has previously been converted to frondosin B by demethylation with boron tribromide.[13(a,b)] Thus, a formal total synthesis of frondosin B was achieved in our first attempt at the key cycloaddition.

Unfortunately, the titanium(IV)chloride-promoted reaction between diene **3** and benzofuran–carbinol **10** was not only quite low yielding, but proved to be hard to control, as a large variation in the isolated yield was observed. The reaction complexity (as judged by TLC analysis and proton NMR spectra), in-

which we have found to be useful and sometimes superior in these (4+3) cycloadditions, a much cleaner reaction mixture was obtained. After chromatography, the *O*-methyl frondosin B isomer **14** was isolated as a 1:1 mixture of C-11 epimers. Interestingly, another isolated fraction was found to contain the bis(adduct) structure **15** (obtained as a mixture of isomers). Thus, our suspicion of a Friedel–Crafts-type benzofuran–carbinol oligomerization as the major competing reaction pathway in this system was confirmed, implicating the methoxy-substituent as the promotor of this electrophilic aromatic susbstitution reaction. Finally, we found that a modest but reproducible yield of the desired cycloadducts **14** could be obtained by using trifluoroacetic acid as the cation-generating reagent (35% isolated yield).[20] This reaction has been optimized by Xue, Li, and co-workers up to a yield of 50% in their independent studies by using camphorsulfonic acid as a reagent.[13l,21]

Our total synthesis of (+/−)-frondosin B was then completed by following the literature procedure and subjecting the cycloadducts **12**/**13** or **14** to the action of boron tribromide in dichloromethane, giving deprotection of the methyl ether, and—in the case of **14**—concomittant isomerization of the C5,C6-double bond to C5,C11-position, along with a small amount of the positional isomer (cf. **13**). Thus, a convergent four-step racemic total synthesis of frondosin B was achieved, which should be amenable to skeletal diversifications and analogue synthesis around this unique natural product scaffold.

The key cycloaddition for the assembly of the liphagal-skeleton from diene **4** (cf. Scheme 2) was initially found to be a lot less straightforward. Although we had previously used vinyl cyclohexene **4** in reactions with various furfuryl alcohols, giving the expected cycloadducts in modest yields,[5] we could only observe the formation of traces of these cycloadducts when the bis(methoxy)-substituted benzofuran–carbinol **16** was used

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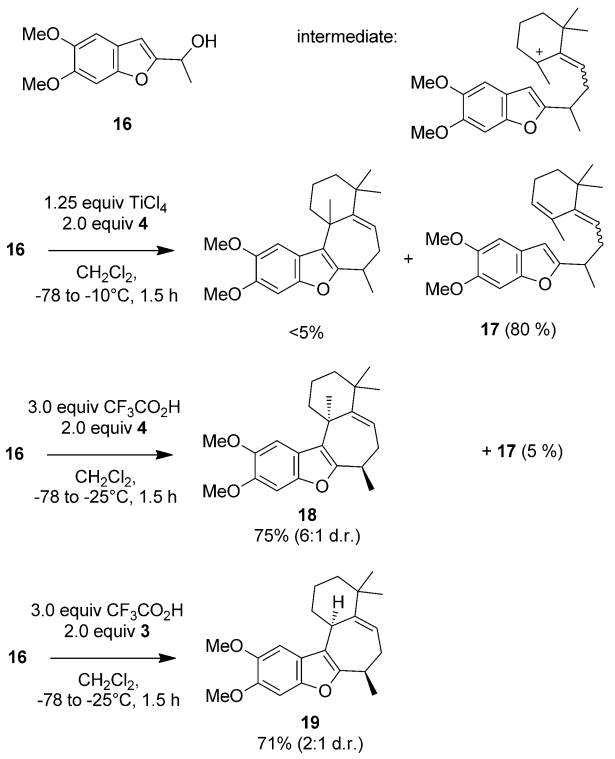


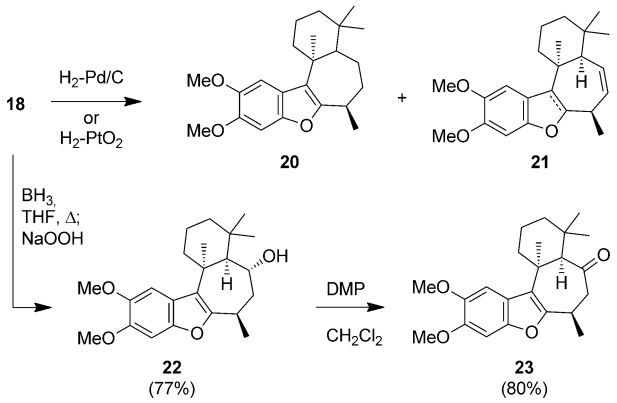
Scheme 6. Key cycloaddition step for the assembly of the liphagal polycyclic skeleton (the relative stereochemistry for the major isomer is shown), and synthesis of a frondosin B–liphagal hybrid analogue by using diene **3**.

(Scheme 6). In fact, the major reaction products under our standard conditions (using titanium(IV)chloride) were shown to be noncyclized adducts of the diene and the benzofuran, obtained as a mixture of stereoisomeric dienes (**17**). We rationalized this disappointing result in light of the two-step mechanism we proposed for this reaction, which was also confirmed by DFT calculations.[5] Clearly, these linear adducts arise from an irreversible proton elimination from the initially formed allylic cation intermediate (shown in Scheme 6). This can be explained by a slower second step (intramolecular electrophilic aromatic addition), affected by the increased steric demand around the receiving carbocationic center, and the altered nucleophilicity of the aromatic system. We then reasoned that using a protic acid rather than a Lewis acid as a reaction promotor, would allow a reversible proton elimination of the intermediate allylic cation, giving a better chance to the full cycloaddition pathway. In fact, using trifluoroacetic acid as the cation-generating reagent, gave a remarkably improved yield of the desired cycloadduct **18**. To our delight, this reaction proved to be highly stereoselective,[22] giving a major isomer showing the relative configuration of the target natural product (+/−)-**2**, even on a decagram scale.

The high efficiency of the cycloaddition giving the liphagal-type adduct **18** is somewhat surprising, considering our results for the synthesis of (+/−)-frondosin B (vide supra). In fact, no trace of Friedel–Crafts-type benzofuran oligomers could be detected in any of the reactions between substrates **4** and **16**. This can be rationalized by the decreased electrophilicity of the bis(methoxy)–benzofurfuryl cation, relative to the monomethoxy benzofurfuryl cation. This explanation was further supported by the successful synthesis of tetracycle **19**. This 'hybrid' frondosin B–liphagal structure **19** was formed in good yield, without apparent benzofuran oligomerization, albeit with lower stereoselectivity. As expected, reactions of diene **4** with the benzofuran–carbinol **10** only gave complex mixtures of mostly oligomeric material.

The cycloadduct **18** could be separated to some extent from the noncyclized adducts (**17**) by careful chromatography over silica gel. On a multigram scale; however, it was found to be more practical to perform a simple radical hydrothiolation with mercaptoethanol on the crude cycloaddition reaction mixture. This reaction was serendipitously found to selectively transform the conjugated dienes (**17**) into more polar mercaptoethanol addition products, which facilitated their removal by filtration over a plug of silica.

Upon establishing a stereoselective route for the tetracyclic alkene **18** (of which more than 10 grams were prepared in a single batch), we next explored the hydrogenation of the trisubstituted olefin to get the saturated fused cyclohexane–cycloheptane system present in liphagal **2** (Scheme 7). This



Scheme 7. Attempted hydrogenation and functionalization of polycyclic alkene **18**. DMP = Dess–Martin periodinane.

simple transformation proved to be highly problematic. The palladium or platinum(IV) oxide catalyzed hydrogenations were unusually slow, and mostly gave alkene rearrangement to the disubstituted C6,C7-alkene **21**. This rearranged alkene **21** proved highly resistant to hydrogenation and more forcing conditions resulted mainly in benzofuran hydrogenation. This alkene rearrangement could be minimized in alcohols as the solvent, but upon forcing a complete hydrogenation of the slowly reacting trisubstituted alkene, we were again unable to avoid significant concommittant hydrogenation of the benzofuran moiety. Furthermore, comparison of the proton NMR spectra of the complex hydrogenation mixtures (and isolated HPLC fractions), with those reported in the literature for the *trans*-fused liphagal-type tetracycles, revealed that in all cases we obtained major formation of the unnatural *cis*-fused ring system (**20**), and not even a trace of the desired liphagal-type relative stereochemistry could be observed.[23]

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A possible explanation for the problems in the hydrogenation reactions described above was found in the bis(methoxy)-substituted benzofuran. This very electron-rich π-system could act as a catalyst poison and its coordination to the catalyst surface might even influence the highly selective addition of hydrogen from the convex side of the polycyclic scaffold. We explored several alternatives to achieve the desired transformation, such as diazene reduction, cationic hydrogenation (TFA-Et_3SiH) or a radical hydrothiolation–hydrodesulfurization, but the hindered alkene survived all of these reactions. In fact, one of the few reactions that could be performed efficiently on this unreactive alkene was a hydroboration. This gave the corresponding secondary alcohol **22**, obtained as a single diastereomer in high yield. However, again an exclusive formation of the unnatural ring fusion stereochemistry resulted. Nevertheless, the X-ray diffraction analysis of this crystalline intermediate did allow the confirmation of the initially made NMR spectra based assignments of the relative stereochemistry in these systems (Figure 1).[24] Oxidation of the secondary hydroxyl to the corresponding ketone **23** then gave an opportunity to epimerize the carbonyl α-position by enolization. However, no trace of the epimerized *trans*-fused isomer could be detected after prolonged heating in the presence of a catalytic base.

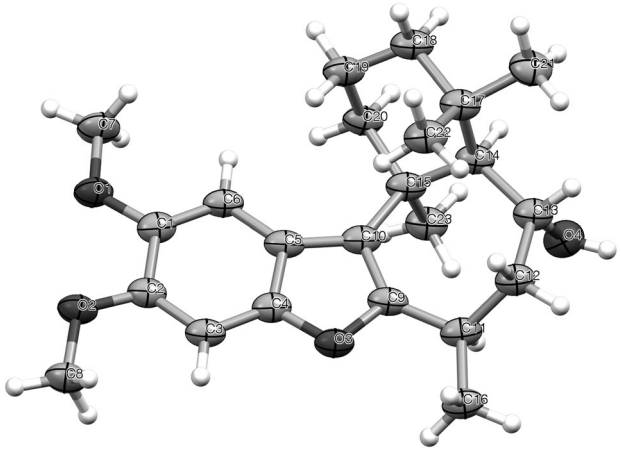
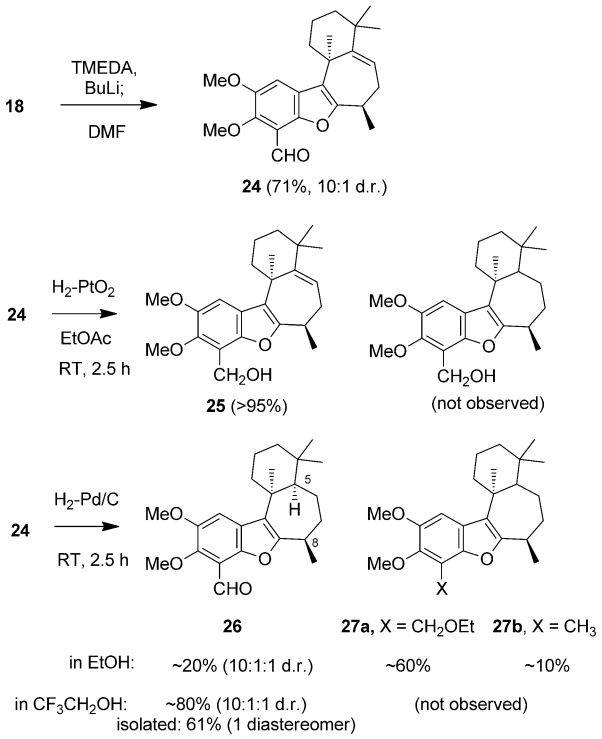


Figure 1. Asymmetric unit of the crystal structure of alcohol **22**, which shows thermal displacement ellipsoids at the 50% probability level and atom labeling scheme of the non-hydrogen atoms. Both methoxy groups are found to be almost planar with the benzene ring (torsion angles C6-C1-O1-C7 and C3-C2-O2-C8 of −2.9(3)° and 6.1(3)°, respectively). The six-membered ring adopts a typical chair conformation with the C-22 methyl and the furan ring as syndiaxial substituents. The configuration of the chiral carbon atoms of the asymmetric unit was established as C11(R), C13(R), C14(R) and C15(S), which confirms the relative orientation of the two methyl groups on the seven-membered ring (corresponding to that found in liphagal **2**). The presence of both enantiomers of **22** in the crystal structure is obvious from the centrosymmetric space group (*C*2/*c*).

As the selective hydrogenation the C5,C6-alkene in cycloadduct **18** proved to be highly problematic (vide supra); therefore, we decided to first install the C18 carbaldehyde group to establish the full carbon framework of the target natural product (Scheme 8). The desired tetracyclic aldehyde **24** was obtained in a single step through *ortho*-lithiation and in situ formylation, applying a procedure used by George et al. in their synthesis of (+)-liphagal.[14b] As this final substituent alters the electron density of the aromatic system, we expected this to affect the hydrogenation reaction and reduce the aforementioned assumed catalyst poisoning. Indeed, we obtained quite different results in this case. With platinum(IV)oxide as a hydrogenation catalyst, the aldehyde **24** was quickly reduced to the corresponding alcohol **25**, which did not undergo any further reaction. The reactions using palladium on carbon as a catalyst proved more interesting. Working in ethanol as a solvent, a complex but interesting reaction mixture was obtained. Examination of the olefinic region of the crude NMR spectrum indicated a fast and quite clean hydrogenation of the C5,C6-alkene bond, apart from the formation of a small amount of rearranged C6,C7-alkene (cf. compound **21**, Scheme 7). The benzofuran system remained intact, but we found that the reaction invariably gave major amounts of the products **27a** and **27b**, implicating the solvent-assisted formation of hemiacetal intermediates and their fast hydrogenolysis. This aldehyde side reaction was hard to control, but the resulting less polar products were easily separated from the reaction mixture, leaving a quite clean mixture of products consisting mainly of three diastereomers of compound **26** in a ~10:1:1 ratio (major stereochemistry shown).[23] In contrast with the reactions of alkene **18**, we could now clearly observe the formation of the natural *trans*-ring fused stereochemistry in one of the minor diastereomers. Furthermore, by switching to the less nucleophilic solvent 2,2,2-trifluoroethanol, the solvent-assisted hydrogenolysis side reaction could be completely avoided, resulting



Scheme 8. Synthesis and hydrogenation of *O*,*O*-dimethyl-5,6-dehydroliphagal **24** (shown yields and d.r.'s for the hydrogenation products are based on NMR spectroscopic integration, except when mentioned otherwise). TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

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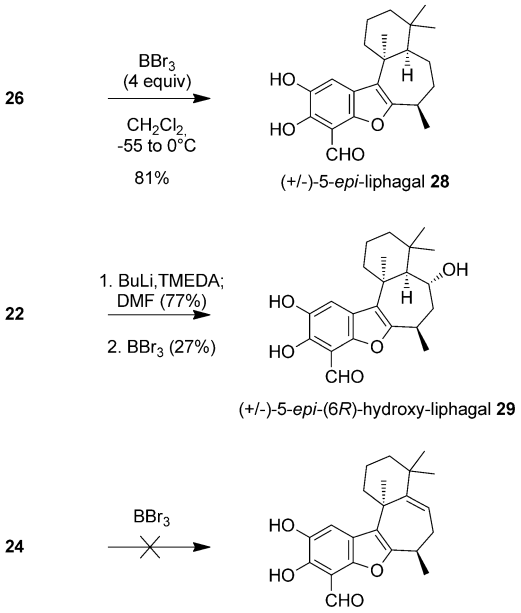
in a clean hydrogenation of the C5,C6-double bond, without affecting the benzofuran–carbaldehyde system. Despite some effort, we were unable to change the stereoselectivity more in favor of the natural product *trans*-fused stereochemistry (at best, a ~10% conversion of **24** to 5-*epi*-**26** could be obtained). Furthermore, separation and unambiguous identification of the minor isomer 5-*epi*-**26** was complicated by the presence of another minor isomer of aldehyde **26** (presumably 8-*epi*-**26**) which was formed in comparable amounts to the liphagal-type 5-*epi*-**26** diastereomer. However, semi-preparative reversed-phase HPLC gave a sufficiently pure sample of 5-*epi*-**26** to establish its identity with the known final intermediate in two previous liphagal total syntheses.[12,14(d)] Thus, a formal total synthesis of (+/−)-liphagal was completed.

The 5-*epi*-liphagal dimethyl ether (**26**) could be obtained from the hydrogenation mixture as a single diastereomer after flash chromatography (61% isolated yield). Removal of the catechol methyl ethers proceeded smoothly with boron tribromide (Scheme 9), completing a seven-step stereoselective synthesis of (+/−)-5-*epi*-liphagal (**28**) in 11% overall yield (26% from the benzofuran-carbinol **16**). Similarly, intermediate **22** was converted to (+/−)-5-*epi*-(6*R*)-hydroxy-liphagal (**30**) by *ortho*-lithiation, formylation and methyl ether deprotection. Unfortunately, this final step also gave rise to significant decomposition, which decreased the isolated yield. Surprisingly, all attempts at the deprotection of 5,6-dehydroliphagal dimethyl ether (**24**) resulted only in complete decomposition of this compound.



Scheme 9. Synthesis of 5-*epi*-liphagal, 5-*epi*-(6*R*)-hydroxy-liphagal, and attempted synthesis of 5,6-dehydroliphagal.

Conclusion

It has been argued that the true test of any novel synthetic methodology is its successful application in the total synthesis of a complex natural product. Here, we have shown that the (4+3) cycloaddition of furfuryl cations can be used to prepare two particularly challenging natural products in a straightforward way. Although our route for liphagal suffers from a late-stage unfavorable stereoselectivity, which may be difficult to circumvent efficiently, we believe the overall conciseness and convergent nature of the approach to these tetracyclic scaffolds should be quite useful for the rapid and stereoselective generation of collections of molecules inspired by the biologically interesting liphagal/frondosin B framework. Furthermore, due to the fact that furans are versatile synthetic intermediates,[25] which can be transformed into a wide range of different skeletal structures (e.g. through cycloadditions, oxidative ring openings and acid hydrolysis or rearrangements), this methodology should be applicable for the synthesis of a wide range of interesting scaffolds that contain a seven-membered ring.

Experimental Section

General: For general details, and for the experimental details for the synthetic procedures leading to compounds **3**, **4**, **10**, **16**, **25**, and **29**, see the Supporting Information. This file also contains general details and a further discussion of the crystallographic analysis of intermediate **22**. Also, images of the original NMR spectra of final compounds and intermediates are provided.

Synthesis of (+/−)-*O*-methyl-frondosin B (12): A solution of benzofuran–carbinol **32** (19.8 mg, 0.103 mmol) and 6,6-dimethyl-1-vinylcyclohex-1-ene **3** (28.1 mg, 0.206 mmol; 2 equiv) in dichloromethane (0.50 mL) was cooled to −78 °C. The reaction mixture was stirred vigorously at this temperature and then a solution of titanium(IV)chloride (13 μL, 1.1 equiv) in dichlorormethane (0.30 mL) was added dropwise over 1 min. The resulting mixture was allowed to warm slowly to −10 °C over a 90 min period, and then a saturated aqueous sodium bicarbonate solution (0.5 mL) was added all at once. The resulting mixture was warmed to room temperature and methyl *tert*-butyl ether (5 mL) and water (1 mL) was added. The layers were separated and the aqueous phase was extracted with methyl *tert*-butyl ether (3 × 1 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue is purified by flash chromatography over silica gel, eluting with a gradient of 0 through to 5% of methyl *tert*-butyl ether in petroleum ether (b.p. 40–60 °C). After discarding a highly apolar fraction, eluting in pure petroleum ether, a slightly more polar fraction eluted upon increasing the solvent polarity, giving *O*-methyl-frondosin B (**12**) (8.6 mg, 26%, isolated as a 2.5:1 mixture with the isomers **13**). This mixture showed a proton NMR spectrum that corresponded to that reported in the literature for the same mixture of compounds.[13a,b,c,e,j] Careful analysis of the resonances of the minor isomer further revealed a 2:1 ratio of diastereomers. All later eluting (more polar) fractions showed similar proton NMR resonances, but as broad and/or heavily splitted bands, with extra peaks in the aromatic regions.

*Compounds **12** and **13***: ^{1}H NMR (300 MHz, $CDCl_3$): the main isomer **12** was identified by its characteristic resonances, corresponding to those reported in the literature:[13a,b] $\delta = 7.25$ (1H, d, $J = 8.8$ Hz;

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ArH), 7.12 (1H, d, $J=2.5$ Hz; ArH), 6.79 (1H, dd, $J=8.8$, 2.5 Hz; –O–C(=CH–)CH=CH), 3.81 (3H, s; O–CH_3), 3.15 (1H, q, $J=8.5$ Hz; CH), 2.54 (2H, t, $J=5,9$ Hz; CH_2-C=C-CH_2); the minor isomer **13** showed two closely related diastereomers; the major diastereomer (integrating for 66%) showed $\delta=7.24$ (1H, d, $J=8,8$ Hz; ArH), 7.05 (1H, d, 2,5 Hz; ArH), 6.772 (1H, dd, $J=8.8$, 2.5 Hz; ArH), 5.99 (1H, t, $J=3.5$ Hz; C=CH–CH_2), 3.815 (3H, s; CH_3O–), 3.10–2.95 (1H, m; Fur-CH); and the minor diastereomer (integrating for 33%) showed: $\delta=7.23$ (1H, d, $J=8.8$ Hz; ArH), 7.03 (1H, d, 2.5 Hz; ArH), 6.764 (1H, dd, $J=8.8$, 2.5 Hz; ArH), 5.98 (1H, t, $J=3.5$ Hz; C=CH-CH_2), 3.813 (3H, s; CH_3O–), 3.10–2.95 ppm (1H, m; Fur-CH); GCMS (EI): for **12**: *m/z*: 310 (70) [$M^{\bullet+}$], 295 (100) [$M^{\bullet+}-CH_3$]; for **13**: *m/z*: 310 (73) [$M^{\bullet+}$]; 295 (100) [$M^{\bullet+}-CH_3$].

Synthesis of (+/−)-*O*-methyl-frondosin B alkene isomer (14): A solution of benzofuran–carbinol **32** (25 mg, 0.13 mmol) and vinyl cyclohexene **3** (36 mg, 0.26 mmol) in dichloromethane (0.30 mL) was cooled to −78 °C. At this temperature, a solution of trifluoroacetic acid (0.030 mL, 0.39 mmol) in dichloromethane (0.30 mL) was added and the resulting mixture was allowed to warm slowly to −25 °C over 1 h. While stirring the reaction mixture at −25 °C, a saturated aqueous sodium bicarbonate solution (5 mL) was added all at once, followed by dichloromethane (5 mL). The resulting mixture was warmed to room temperature, the layers were separated and the aqueous phase was extracted with dichloromethane (3×15 mL). The combined organic phase was washed with brine, dried on magnesium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel, eluting with a gradient of 0.5% through to 10% of ethyl acetate in petroleum ether (b.p. 40–60 °C). This gave the cycloadduct **14** (14.1 mg, 35%), obtained as an almost 1:1 mixture of epimers, and the derived Friedel–Crafts adducts **15** (6 mg, 10%), obtained as a complex mixture of diastereomers.

*Cycloadduct **14**:* The interpretation and assignment of split epimer resonances (with half integrations) in the proton NMR spectra was guided by comparison with literature data for these known intermediates.[13j] ^{1}H NMR (300 MHz, $CDCl_3$): 7.27 (d, 0.5H, $J=8.8$ Hz; ArH), 7.26 (d, 0.5H, $J=8.8$ Hz; ArH), 6.87 (d, 1H, $J=2.5$ Hz; ArH), 6.79 (dd, 1H, $J=8.9$, 2.5 Hz; ArH), 5.62 (app. brt, 0.5H, $J=6.0$ Hz; C=CH-CH_2), 5.58 (dd, 0.5H, $J=7.7$, 4.2 Hz; C=CH–CH_2), 3.86 (s, 3H; –OCH_3), 3.70 (brd, 1H, $J=12.2$ Hz; Fur-CH-C=CH), 3.29–3.09 (m, 1H; –CHCH_3), 2.62–2.37 (m, 1H; CHH), 2.36–2.13 (band, 2H), 1.97–1.79 (m, 1H), 1.73 (band, 2H), 1.60–1.55 (band, 2H), 1.35 (d, 3H, $J=6.8$ Hz; –CHCH_3), 1.20 (s, 3H; –C$CH_3$$CH_3$), 1.15 (s, 1.5H; C$CH_3$$CH_3$), 1.13 ppm (s, 1.5H; C$CH_3$$CH_3$); HRMS (ESI): *m/z*: calcd for $C_{22}H_{26}O_2$: 311.2001 [*M*+H]$^+$; found: 311.2006.

*Friedel–Crafts adduct **15***: Most diastereomers show closely overlapping resonances, allowing interpretation of the spectrum, guided by the similarity with those obtained for compound **14**. The observed chemical shifts and partial multiplicities of the aromatic proton resonances are consistent with alkylation on the frondosin C17-position, as shown in Scheme 5. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=$ 7.29–7.23 (m, 1H; ArH), 7.17–7.12 (m, 1H; ArH), 6.99–6.95 (m, 1H; ArH), 6.88–6.86 (m, 1H; ArH), 6.82–6.76 (m, 1H; ArH), 6.45–6.36 (m, 1H; FurH), 5.64–5.55 (m, 1H; C=CH-CH_2-), 4.79 (q, 1H, $J=7.0$ Hz; –Ar–CHMe–Fur), 3.93 (s, 3H; –OCH_3), 3.83 (s, 3H; –OCH_3), 3.77–3.68 (m, 1H; Fur–CH–C=CH), 3.26–3.05 (m, 1H; FurCHMe), 2.61–2.12 (band, 3H), 2.00–1.81 (m, 1H), 1.76–1.69 (m, 1H); 1.67–1.13 ppm (band, 15H; including 4×CH_3); HRMS (ESI): *m/z*: calcd for $C_{32}H_{37}O_4$: 485.2686 [*M*+H]$^+$; found: 485.2668.

Synthesis of (+/−)-frondosin B (1): A solution of (+/−)-*O*-methyl frondosin B (**12**) (3.2 mg, 0.010 mmol) in dichloromethane (1.0 mL) was cooled to −55 °C. Then, a solution of boron tribromide (0.033 mL, 1 M in dichloromethane, 0.033 mmol) was added dropwise at −55 °C. The reaction was slowly warmed to 0 °C over 45 min. After stirring for 30 min at 0 °C, a mixture of water and acetonitrile (0.5/3.0 mL) was added all at once. The volatiles were removed by using reduced pressure and the resulting residue was filtered over a plug of silica, using a 1:10 ethyl acetate/hexane mixture. Flash chromatography over silica gel, eluting with 6% ethyl acetate in hexane gave (+/−)-frondosin B (**1**) (2.3 mg, ~75%, d.r. 3:1 with the positional isomer cf. **13**) as a yellow oil. This showed a proton NMR spectrum corresponding to that reported in the literature for the same mixture of diastereomers.[12a,b]

Synthesis of the liphagal-precursor cycloadduct (18): A solution of benzofuran–carbinol **16** (10.1 g, 45.5 mmol) and vinyl cyclohexene **4** (13.65 g, 91.0 mmol, 2 equiv) in dichloromethane (300 mL) was cooled to −78 °C. At this temperature, trifluoroacetic acid (10.5 mL, 137 mmol) was added dropwise and the resulting mixture was allowed to warm slowly to −25 °C over 2 h. While stirring the reaction mixture at −25 °C, a saturated aqueous sodium bicarbonate solution (150 mL) was added all at once. The resulting layers were separated and the aqueous phase was extracted with dichloromethane (3×500 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified over a plug of silica gel, eluting with a gradient of 0.5 to 10% of ethyl acetate in petroleum ether (b.p. 40–60 °C). This gave the cycloadduct **18** (12.94 g, 80.3%), contaminated with a small amount of noncyclized adducts **17** (~5% by ^{1}H NMR spectroscopic integration). These noncyclized adducts were removed by first boiling a solution of this mixture in ethanol (200 mL) and 2-mercaptoethanol (10 mL, 143 mmol) in the presence of azobisisobutyronitrile (250 mg, 1.5 mmol) for 2 h under reflux conditions. Removal of the volatiles under reduced pressure, followed by filtration over a plug of silica gel, washing with 8% ethyl acetate in petroleum ether (b.p. 40–60 °C) gave cycloadduct **18** (12.08 g, 75%, d.r. 6:1) as a viscous colorless oil.

*Cycloadduct **18***: IR $\tilde{\nu}=2958$, 2866, 1623, 1485 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): for the major isomer: $\delta=7.14$ (s, 1H; ArH), 6.93 (s, 1H; ArH), 5.95 (dd, 1H, $J=9.7$, 5.8 Hz; C=CHCH$_2$), 3.91 (s, 3H; OCH_3), 3.88 (s, 3H; OCH_3), 3.13 (dqd, 1H, $J=10.6$, 6.8, 3.8 Hz; –CHMe), 2.70–2.64 (m, 1H; –CMe$_2$CH$_2$CH$_2$CHH), 2.65 (ddd, 1H, $J=$ 13.6, 5.8, 3.2 Hz; =CHCHH), 2.19 (ddd, 1H, $J=13.6$, 9.7, 4.0 Hz; = CHCHH), 1.89–1.79 (band, 2H), 1.67–1.64 (m, 1H; CHH), 1.62 (s, 3H; O–C=C-CCH_3), 1.57–1.53 (m, 1H; CHH), 1.46–1.40 (m, 1H; CHH), 1.30 (d, 3H, $J=7.0$ Hz; CHCH_3), 1.24 (s, 3H; C$CH_3$$CH_3$), 1.21 (s, 3H; C$CH_3$$CH_3$); the minor isomer showed the following major resonances: 7.15 (s, 1H; ArH), 6.95 (s, 1H; ArH), 6.05 (dd, 1H, $J=10.0$, 6.0 Hz; C=CHCH$_2$), 3.92 (s, 3H; –OCH_3), 3.90 (s, 3H; –OCH_3), 2.97 (dqd, 1H, $J=11.6$, 7.4, 2.6 Hz; FurCHMe), 2.32 (ddd, 1H, $J=13.8$, 7.7, 6.0 Hz; C=CHCHH), 1.59 (s, 3H; O–C=C-CCH_3), 1.32 (d, 3H, $J=$ 7.2 Hz; FurCHCH_3), 1.22 (s, 3H; C$CH_3$$CH_3$), 1.15 ppm (s, 3H; C$CH_3$$CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): for the major isomer: $\delta=156.7$ (C), 155.9 (C), 154.0 (C), 153.3 (C), 148.0 (C), 146.8 (C), 144.7 (C), 121.1 (CH), 106.0 (CH), 94.9 (CH), 57.0 (CH_3), 56.0 (CH_3), 40.3 (C), 38.2 (CH_2), 37.5 (CH_2), 34.8 (C), 33.7 (CH_3), 33.5 (CH_3), 33.2 (CH), 31.4 (CH_2), 26.9 (CH_3), 18.4 (CH_3), 18.1 ppm (CH_2); an analytical sample of the minor epimer could not be obtained, hampering the direct structural assignment through NOE-correlations. However, the assignment was obvious through analogy and remarkable similarity to known synthetic intermediates. Conclusive proof was obtained in the synthesis of intermediate **22** and of the final compound liphagal (**2**). HRMS (ESI): *m/z*: calcd for $C_{23}H_{31}O_3$: 355.2268 [*M*+H]$^+$; found: 355.2268.

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Synthesis of the liphagal–frondosin hybrid cycloadduct (19): A solution of benzofuran–carbinol **16** (25 mg, 0.113 mmol) and vinyl cyclohexene **3** (30 mg, 0.226 mmol) in dichloromethane (0.3 mL) was cooled to −78 °C. At this temperature, a solution of trifluoroacetic acid (25 μL, 0.34 mmol) in dichloromethane (0.2 mL) was added dropwise and the resulting mixture was allowed to warm slowly to −25 °C over 1 h. Then, a saturated aqueous sodium bicarbonate solution (2 mL) was added all at once, followed by dichloromethane (10 mL). The resulting layers were separated and the aqueous phase was extracted with dichloromethane (3× 10 mL). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure The residue was purified by flash chromatography over silica gel, eluting with a gradient of 0.5 to 10% of ethyl acetate in petroleum ether (b.p. 40–60 °C). This gave the cycloadduct **19** (19.5 mg, 51%, d.r. 2:1) as a viscous colorless oil.

*Cycloadduct **19***: ^{1}H NMR (300 MHz, $CDCl_3$): for the major isomer: $\delta = 6.99$ (s, 1H; Ar*H*), 6.84 (s, 1H; Ar*H*), 5.62 (app.t, 1H, $J = 6.0$ Hz; C=C*H*CH_2), 3.94 (s, 3H; OCH_3), 3.89 (s, 3H; OCH_3), 3.69 (brd, 1H, $J = 12.1$ Hz; Fur-C*H*-C=CH), 3.19 (dqd, 1H, $J = 11.7$, 7.0, 3.8 Hz; C*H*Me), 2.41 (ddd, 1H, $J = 15.2$, 7.0, 3.0 Hz; $CMe_2CH_2CH_2CH$*H*), 2.34–2.12 (band, 2H; C=CHCH_2), 1.98–1.79 (m, 1H), 1.75–1.36 (band, 4H; CH_2CH_2), 1.33 (d, 3H, $J = 7.0$ Hz; CHCH_3), 1.21 (s, 3H; CCH_3CH_3), 1.13 ppm (s, 3H; CCH_3CH_3); the minor isomer showed: $\delta = 6.97$ (s, 1H; Ar*H*), 6.84 (s, 1H; Ar*H*), 5.58 (dd, 1H, $J = 7.5$, 4.5 Hz; C=C*H*CH_2), 3.16 (dqd, 1H, $J = 11.7$, 7.0, 3.0 Hz; C*H*Me), 2.60–2.50 ppm (m, 1H); HRMS (ESI): *m/z*: calcd for $C_{22}H_{29}O_3$: 341.2111 $[M+H]^+$; found: 341.2114.

Synthesis of the tetracyclic alcohol 22: A solution of borane in THF (1.0 M, 6.75 mL, 6.75 mmol) was slowly added to a stirring solution of cycloadduct **18** (0.80 g, 2.15 mmol, 6:1 d.r.) in THF (30 mL), kept at 0 °C. The reaction was heated and boiled under reflux for 1 h. After cooling to 0 °C, an aqueous solution of sodium hydroxide (15%, 24 mL) was added to the reaction mixture and stirring was continued for 5 min at 0 °C. Then an aqueous solution of hydrogen peroxide (10%, 32 mL) was added and stirring was continued for 1 h at 0 °C. Finally, a saturated sodium thiosulfate solution (10 mL) was added and stirring was continued for 5 min before removing the bulk of the THF under reduced pressure. The aqueous residue was extracted with ethyl acetate (3×150 mL) and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel, eluting with 30% ethyl acetate in hexane. This gave the tetracyclic alcohol **22** (630 mg, 77%) in diastereomerically pure form as a white crystalline solid. The expected other diastereomer (cf. d.r. starting material) was not isolated or detected. Recrystallization from hexane/ethyl acetate gave a single crystal suitable for X-ray analysis.

*Tetracyclic alcohol **22**: $R_f = 0.41$* (hexane/ethyl acetate 7:3); m.p. 163 °C (from hexane/ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.15 (s, 1H; Ar*H*), 6.97 (s, 1H; Ar*H*), 4.60 (dt, 1H, $J = 5.3$, 2.9 Hz; C*H*OH), 3.88 (brs, 6H; 2×OCH_3), 3.55 (dqd, 1H, $J = 10.6$, 7.2, 4.0 Hz; C*H*Me), 2.67 (brd, 1H, $J = 14.2$ Hz; $CMe_2CH_2CH_2CH$*H*), 2.08–1.92 (band, 3H), 1.67–1.60 (m, 1H; CH*H*), 1.57–1.53 (band, 2H, ring-fusion C*H* and CH*H*), 1.50 (s, 3H; O–C=C-CCH_3), 1.51–1.43 (m, 1H; $CMe_2CH_2CH_2CH$H), 1.44 (d, 3H, $J = 7.0$ Hz; CHCH_3), 1.39 (dd, 1H, $J = 12.8$, 3.5 Hz; CH*H*), 1.37–1.32 (m, 1H; CH*H*), 1.01 (s, 3H; CCH_3CH_3), 0.68 ppm (s, 3H; CCH_3CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 156.3$ (C), 148.1 (C), 146.5 (C), 145.3 (C), 119.8 (C), 119.3 (C), 104.7 (CH), 95.0 (CH), 70.9 (CH), 61.7 (CH), 56.6 (CH_3), 56.1 (CH_3), 45.4 (CH_2), 42.7 (CH_2), 39.5 (CH_2), 38.1 (C), 34.7 (C), 33.3 (CH_3), 33.0 (CH_3), 27.7 (CH), 24.0 (CH_3), 21.4 (CH_2), 18.4 ppm (CH_3); HRMS (ESI): *m/z*: calcd for $C_{23}H_{33}O_4$: 373.2373 $[M+H]^+$; found: 373.2373.

Synthesis of (+/−)-*O*,*O*-dimethyl-5,6-dehydroliphagal (24): A solution of *n*-butyllithium in hexanes (2.5 M, 3.39 mL, 8.47 mmol) was added dropwise to a stirring solution of cycloadduct **19** (1.0 g, 2.82 mmol) and tetramethylethylenediamine (1.27 mL, 8.47 mmol) in THF (25 mL), and the resulting mixture was cooled to 0 °C and stirred for 30 min at this temperature. Then, dimethylformamide (2.17 mL, 28.2 mmol) was added dropwise to the reaction at 0 °C. The resulting mixture was warmed to room temperature and stirred another 20 min at this temperature. Then, a saturated aqueous ammonium chloride solution (20 mL) was added and the resulting mixture was stirred vigorously for 5 min. The aqueous phase was extracted with methyl-*tert*-butylether (100 mL and 2× 50 mL) and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel, eluting with 5% ethyl acetate in petroleum ether (b.p. 40–60 °C). This gave (+/−)-*O*,*O*-dimethyl-5,6-dehydroliphagal (**24**) as a slightly yellow oil (761 mg, 71%, d.r 10:1).

*(+/−)-*O,O*-Dimethyl-5,6-dehydroliphagal (**24**)*: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 10.55$ (s, 1H; C*H*O), 7.45 (s, 1H; Ar*H*), 5.96 (dd, 1H, $J =$ 9.8, 5.8 Hz; C=C*H*-CH_2), 3.96 (s, 3H; OCH_3), 3.93 (s, 3H; OCH_3), 3.26 (dqd, 1H, $J = 10.6$, 6.8, 3.8 Hz; –C*H*Me), 2.60 (ddd, 1H, $J = 13.9$, 5.8, 3.0 Hz; C=CHC*H*H), 2.60–2.53 (m, 1H; –$CMe_2CH_2CH_2CH$*H*), 2.21 (ddd, 1H, $J = 13.9$, 9.8, 4.1 Hz; C=CHCH*H*), 1.83–1.76 (m, 1H; C*H*H), 1.83–1.77 (m, 1H; C*H*H), 1.68–163 (m, 1H; C*H*H), 1.62 (s, 3H; O–C= C-CCH_3), 1.59–1.53 (m, 1H; C*H*H), 1.44–1.37 (m, 1H; $CMe_2CH_2CH_2CH$H), 1.29 (d, 3H, $J = 7.0$ Hz; –CHCH_3), 1.24 (s, 3H; CCH_3CH_3), 1.21 ppm (s, 3H; CCH_3CH_3); the minor isomer (not isolated), integrating for about 10%, showed: $\delta = 10.56$ (s, 1H; –C*H*O), 7.47 (s, 1H; Ar*H*), 6.06 (dd, 1H, $J = 9.8$, 6.2 Hz; C=C*H*-CH_2), 3.97 (s, 3H; OCH_3), 3.93 (s, 3H; OCH_3), 3.09–2.95 (dqd, 1H, $J = 11.5$, 7.0, 3.2 Hz; C*H*Me), 1.66 (s, 3H; O–C=C-CCH_3), 1.33 (d, 3H, $J = 6.9$ Hz; –CHCH_3), 1.22 (s, 3H; CCH_3CH_3), 1.15 ppm (s, 3H; CCH_3CH_3; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 188.4$ (CH), 159.7 (C), 153.6 (C), 149.5 (C), 147.8 (C), 146.0 (C), 125.3 (C), 121.5 (CH), 121.1 (C), 114.8 (C), 113.5 (CH), 62.8 (CH_3), 57.4 (CH_3), 40.3 (C), 38.3 (CH_2), 37.7 (CH_2), 37.4 (C), 33.9 (CH_3), 33.6 (CH_3), 33.3 (CH), 31.4 (CH_2), 27.0 (CH_3), 18.4 (CH_3), 18.2 ppm (CH_2); HRMS (ESI): *m/z*: calcd for $C_{24}H_{31}O_4$: 383.2217 $[M+H]^+$; found: 383.2219.

Synthesis of (+/−)-*O*,*O*-dimethyl-5-*epi*-liphagal (26), (+/−)-*O*,*O*-dimethyl-liphagal (5-*epi*-26), and (+/−)-*O*,*O*-dimethyl-8-*epi*-liphagal (5-*epi*-8-*epi*-26): A solution of *O*,*O*-dimethyl-5,6-dehydroliphagal 24 (115 mg, 0.30 mmol, 10:1 ratio with the C8-epimer) in trifluoroethanol (10 mL) in a Schlenk flask (2 neck) was degassed and backfilled with argon three times. Palladium on carbon (10 w%, 63.6 mg, 0.06 mmol) was added while keeping a gentle positive flow of argon. The Schlenk flask was cooled down to −78 °C upon which the content solidified. The entire set-up was again degassed and backfilled with argon three times. The stop cork was swiftly replaced by a three way adapter equipped with a hydrogen filled balloon under a gentle flow of argon. The vessel was degassed and backfilled with hydrogen three times and was then allowed to warm to room temperature. The mixture was stirred vigourously for 2.5 h at room temperature. The reaction mixture was then filtered over a plug of Celite and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel, eluting with 4% ethyl acetate in hexane. This gave (+/−)-*O*,*O*-dimethyl-5-*epi*-liphagal **26** (70 mg, 61%), collected as a single diastereomer, followed by impure fractions also containing the two minor diastereomers of **26** as well as the alkene rearranged compounds (as judged by proton NMR spectroscopy, these rearranged alkenes make up 15–20% of the initial crude reaction mixture). Reversed-phase semi-preparative HPLC of the fractions

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enriched in the minor diastereomers of **26** (Luna, 4.6 mm, gradient 75 to 100% acetonitrile in water with 0.1% trifluoroacetic acid, 15 min) gave small amounts of sufficiently pure samples of these isomers, which allowed the identification of *O,O*-dimethylliphagal (5-*epi*-**26**) by comparison with the literature NMR spectroscopic data.[12] The other diastereomer of **26** was tentatively assigned as *O,O*-dimethyl-5-*epi*-8-*epi*-liphagal (8-*epi*-**26**), further supported by the fact that this isomer showed a different proton NMR spectrum than the known *O,O*-dimethyl-8-*epi*-liphagal.[12] The ratio of the major and the two minor diastereomers of **26** can be judged as ~10:1:1 based on the proton NMR spectra of the initial reaction mixture (see the Supporting Information).

(+/−)-O,O-*Dimethyl-5*-epi-*liphagal (**26**)*: $R_f = 0.27$ (hexane/ethyl acetate 92:8); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 10.58$ (s, 1H; −C*H*O), 7.50 (s, 1H; Ar*H*), 3.97 (s, 3H; OCH_3), 3.91 (s, 3H; OCH_3), 3.17 (dqd, 1H, $J = 11.7$, 6.9, 4.0 Hz; −C*H*Me), 2.68 (br d, 1H, $J = 14.1$ Hz; $CMe_2CH_2CH_2CH$*H*), 2.26–2.17 (m, 2H), 2.00–1.71 (band, 2H), 1.70–1.60 (band, 2H), 1.58–1.54 (m, 1H; ring fusion C*H*), 1.49 (d, 3H, $J = 6.9$ Hz; −CHCH_3), 1.37–1.20 (band, 3H), 1.30 (s, 3H; O–C=C-CCH_3), 0.97 (s, 3H; CCH_3CH$_3$), 0.64 ppm (s, 3H; CCH$_3$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 188.4$ (CH), 159.2 (C), 149.0 (C), 148.3 (C), 145.7 (C), 124.9 (C), 119.1 (C), 114.8 (C), 122.2 (CH), 62.7 (CH_3), 56.8 (CH_3), 53.9 (CH_3), 45.0 (C), 41.2 (C), 38.5 (CH_2), 35.5 (CH_2), 35.0 (CH), 32.3 (CH_3), 32.0 (CH_2), 30.4 (CH_3), 26.2 (CH_2), 25.4 (CH), 21.2 (CH_2), 18.4 ppm (CH_3); HRMS (ESI): *m/z*: calcd for $C_{24}H_{33}O_4$: 385.2373 $[M+H]^+$; found: 385.2394.

(+/−)-O,O-*Dimethyl-11*-epi-*liphagal (8*-epi-***26**)*: $R_f = 0.27$ (hexane/ethyl acetate 92:8); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 10.552$ (s, 1H; C*H*O), 7.53 (s, 1H; Ar*H*), 3.98 (s, 3H; OCH_3), 3.91 (s, 3H; OCH_3), 3.40 (app. sext, 1H, $J = 7.2$ Hz; −C*H*Me), 2.72 (br d, 1H; $J = 14.4$ Hz; $CMe_2CH_2CH_2CH$*H*), 2.32–2.17 (band, 3H), 2.00–1.93 (band, 2H), 1.77–1.71 (m, 1H), 1.66–1.62 (m, 1H), 1.50–1.40 (band, 3H), 1.39 (s, 3H; O–C=C-CCH_3), 1.37 (d, 3H, $J = 7.2$ Hz; C*H*Me), 0.97 (s, 3H; CCH_3CH$_3$), 0.67 ppm (s, 3H; CCH$_3$CH_3).

(+/−)-O,O-*Dimethylliphagal (5*-epi-***26**)*: $R_f = 0.27$ (hexane/ethyl acetate 92:8); this compound showed all resonances reported for the known literature compound:[12] ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 10.547$ (s, 1H; C*H*O), 7.46 (s, 1H; Ar*H*), 3.96 (s, 3H; OCH_3), 3.92 (s, 3H; OCH_3), 3.30 (app sext, 1H, $J = 7.2$ Hz; C*H*Me), 2.54 (br d, 1H, $J = 12.7$ Hz; $CMe_2CH_2CH_2CH$*H*), 2.21–2.16 (m, 1H), 1.85–1.81 (m, 1H), 1.75–1.70 (m, 1H), 1.63–1.47 (band, 6H), 1.45 (d, 3H, $J = 7.2$ Hz; −C*H*Me), 1.36 (s, 3H; O–C=C-CCH_3), 1.25 (m, 1H), 0.98 (s, 3H; CCH_3CH$_3$), 0.95 ppm (s, 3H, CCH$_3$CH_3).

Synthesis of (+/−)-5-*epi*-liphagal (28): A solution of boron tribromide (0.040 mL, 0.416 mmol) in dichloromethane (0.8 mL) was added dropwise to a solution of *O,O*-dimethyl-5-*epi*-liphagal (**26**) (40 mg, 0.104 mmol) in dichloromethane (15 mL), which was stirred and cooled to −55 °C. The reaction was slowly warmed to 0 °C over 30 min and then stirred for another 30 min at 0 °C. Then, a mixture of water (0.75 mL) and acetonitrile (4.50 mL) was added all at once to the reaction mixture and the volatiles were removed under reduced pressure. The resulting oily residue was filtered through a small plug of silica gel, washing with 10% ethyl acetate in hexane. Concentration of the filtrate under reduced pressure and purification of the residue by flash chromatography over silica gel, eluting with 8% ethyl acetate in hexane, gave (+/−)-5-*epi*-liphagal (**28**) (30 mg, 81.0%) as a yellow film.

5-epi-*Liphagal (**26**)*: $R_f = 0.41$ (hexane/ethyl acetate 7:3); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 11.23$ (s, 1H; HCO-C=C-O*H*), 10.46 (s, 1H; C*H*O), 7.54 (s, 1H; Ar*H*), 5.40 (s, 1H; O*H*), 3.16 (dqd, 1H, $J = 11.9$, 7.0, 3.8 Hz; C*H*Me), 2.63 (br d, 1H, $J = 14.1$ Hz; −$CMe_2CH_2CH_2CH$*H*), 2.27–2.12 (band, 2H), 1.91–1.73 (m, 2H), 1.69–1.58 (m, 2H), 1.43 (d, 3H, $J = 7.0$ Hz; −CHCH_3), 1.35–1.29 (m, 2H), 1.29 (s, 3H; O–C=C-CCH_3), 0.97 (s, 3H; CCH_3CH$_3$), 0.64 ppm (s, 3H; CCH$_3$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 192.5$ (CH), 156.9 (C), 147.5 (C), 145.2 (C), 140.0 (C), 120.2 (C), 120.0 (C), 115.6 (CH), 106.3 (C), 53.9 (CH), 45.2 (C), 40.9 (C), 38.4 (CH_2), 35.5 (CH_2), 34.9 (CH_3), 32.4 (CH_3), 32.1 (CH_2), 30.4 (CH_3), 26.2 (CH_2), 25.4 (CH), 21.2 (CH_2), 18.4 ppm (CH_3).

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[21] Using camphorsulfonic acid at elevated temperatures, as in reference [13l], also results in the formation of a 1:1 mixture of epimers, as reported in that reference.

[22] Using camphorsulfonic acid at elevated temperatures, as in reference [13l], results in an unselective formation of a 1:1 mixture of epimers, as reported in that reference.

[23] The natural C5-epimer of compound **20** is a known synthetic intermediate for which the NMR spectroscopic data are available, see references [14b,d]. The unnatural C5-epimer of **20** was also obtained in reference [13l].

[24] Crystal data for compound **22**: $C_{23}H_{32}O_4$, $M = 372.49$, monoclinic, space group $C2/c$ (No. 15), $a = 27.995(2)$, $b = 11.6489(6)$, $c = 14.1728(10)$ Å, $\beta = 120.952(10)^\circ$, $V = 3963.7(6)$ Å^3, $Z = 8$, $T = 100(2)$ K, $\rho_{calcd} = 1.248$ g cm^{-3}, $\mu(Cu_{K\alpha}) = 0.667$ mm^{-1}, $F(000) = 1616$, 16742 reflections measured, 3881 unique ($R_{int} = 0.0545$), which were used in all calculations. The final $R1$ was 0.0552 ($I > 2\sigma(I)$) and $wR2$ was 0.1535 (all data). CCDC-948989 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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