ARTICLE

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Ring fission of chiral cyclic acetals plus intramolecular [4 + 2] cycloaddition: a sequential access to medium-size lactones. Application to the synthesis of carbasugars

Loïc Lemiègre,[a] Richard L. Stevens,[b] Jean-Claude Combret[c] and Jacques Maddaluno*[a]

[a] *Laboratoire des Fonctions Azotées & Oxygénées Complexes, IRCOF, UMR 6014 CNRS, Université de Rouen, 76821, Mont St Aignan Cedex, France. E-mail: jmaddalu@crihan.fr; Fax: (33)235 522 971; Tel: (33)235 522 446*

[b] *Pasarow Mass Spectrometry Laboratory, Department of Chemistry & Biochemistry, UCLA, Los Angeles, CA, 90095, USA*

[c] *Laboratoire des Sciences et Méthodes Séparatives, IRCOF, Université de Rouen, 76821, Mont St Aignan Cedex, France*

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A set of α,β-unsaturated cyclic acetals were reacted with *t*-butyllithium in THF. A conjugate elimination took place, triggering a ketal ring cleavage when two eq. of TMEDA were added to the medium. The lithium alcoholate thus obtained could be trapped *in situ* by 2,2,2-trifluoroethyl acrylate. The resulting acryloyl (1*Z*,3*E*)-dienyl ether was then submitted to an intramolecular Diels–Alder cycloaddition under high pressure (12 kbar, 50 °C). Depending on the structure of the linkage between the diene and the acrylate, the expected ("fused") lactones were obtained with total *endo*- or *exo*-selectivities and high to complete diastereoselectivities. A remarkable inversion of selectivity, from *endo* to *exo*, with respect to the stereochemical elements of the tether could be observed in these cases. A five step diastereoselective transformation of two of the resulting nine-membered ring lactones into modified carbasugars was finally achieved in 23% overall yield.

Introduction

The intramolecular version of the Diels–Alder cycloaddition (IMDA) is an excellent tool for the stereocontrolled construction of functionalized bicyclic skeletons.[1] The success of this reaction relies on the appropriate choice of both the diene and dienophile which, in the best cases, allows a simple and very convergent assembling of sophisticated skeletons. The tether joining these partners also plays a major role in the chemical and stereochemical outcome of the reaction. There is evidence that an ester linkage, which provides a favorable electron-withdrawing effect to the dienophile when a direct-demand cycloaddition is considered, has a deleterious effect on the kinetics of the ring-closure.[2] This phenomenon, proposed to be related to the relatively high *s-trans* to *s-cis* interconversion barrier in esters, can be overcome in some cases by utilizing highly polar solvents[3] or harsh thermal conditions.[4] The length of the tether also plays a significant role on the rate of the cycloaddition *i.e.*, the longer the link the more sluggish the IMDA.[5] These unfavorable characteristics explain why the use of IMDA in the synthesis of large bicycles ([*n*.4.0] with $n > 4$) has been restricted to a few cases.[6]

A sub-class of these trienes can be conveniently obtained from α,β-unsaturated cyclic acetals such as dioxolanes or dioxanes. We have shown, in collaboration with Venturello's group, that the basic treatment of diox(ol)anes triggered an efficient ring-cleavage through a conjugate elimination, providing alcohols that were, in a separate step, esterified into the corresponding acrylates. Their cyclisations, under thermal conditions, provided the cycloadducts in reasonable yields and selectivities.[7] This general and efficient ring cleavage of the diox(ol)ane nucleus was rather unexpected considering the relative robustness of this type of acetal.[8] However, in our earlier papers we did not address two important problems *viz*., i) the access to more useful 1,4-disubstituted dienes by this route and ii) the control of the stereogenic centers generated by the IMDA. Our previous experiences with acyclic acetals supported the notion that the first point could be approached using conditions similar to those described before, while the acetal appendage (which became the tether) could be regarded as a suitable tool to control the stereochemistry of the cycloadducts. A few functionalization steps from the cycloadducts would give access to attractive targets, such as carbasugars (Fig. 1).

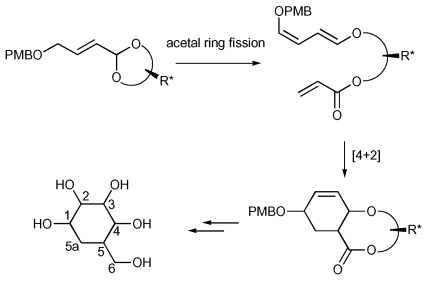

Fig. 1 From cyclic acetals to carbasugars.

We present in this paper the effects of, i) the introduction of a *p*-methoxybenzylether (PMB), an appropriate precursor for alcohols, on the elimination reaction and on its stereoselectivity and ii) the variations of the length of the linker and of the structure of the stereochemical elements on the IMDA reaction.

We expected these alterations to provide us with trienes which would afford functionalized seven- or nine-membered lactones, targets of interest *en route* to carbasugars and other natural products.[9]

Results and discussion

The conjugate elimination reaction has been relatively neglected in its synthetic applications. The *syn*-character of this reaction was first proposed by Cristol,[10] then established by the groups of Rickborn and Bock[11] who simultaneously elucidated its E1cb mechanism. Recent theoretical results obtained from a

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sophisticated level of calculations by Bickelhaupt *et al.* have confirmed this hypothesis.[12] Interestingly, under enzymatic conditions, the conjugate elimination can become *anti*.[13]

From a synthetic point of view, the application of this reaction to unsaturated ethers was first examined by Everhardus *et al.*,[14] who also studied its stereoselectivity. It was later applied to unsaturated acetals[15] and carbamates,[16] before being extended to various heterocycles.[17] Simultaneously, Venturello showed that bimetallic superbases trigger the elimination on crotonaldehyde acetals at low temperature and that an excess of base gave access to α-metallated dienol ethers, which can be efficiently trapped by many different electrophiles.[18] Our laboratory has focused on γ-functionalized α,β-unsaturated acetals. The elimination reaction provides 1,4-disubstituted dienes that can be potent synthons in Diels–Alder type cycloadditions (Fig. 2).[19]

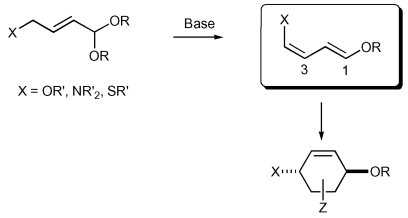
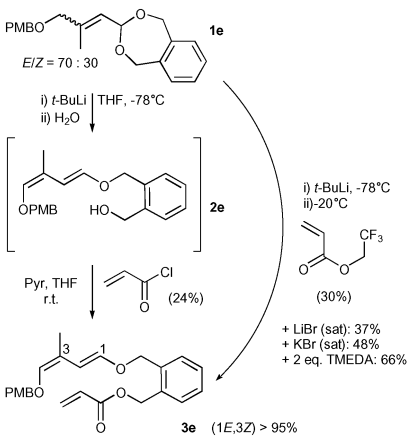


Fig. 2 From α,β-unsaturated acetals to 1,4-disubstituted dienes.

It has been shown that the stereoselectivity of the elimination is strongly dependent on the terminal substituent X and is hardly affected by the configuration of the original double bond,[19] which is in sharp contrast to the results with unsaturated ethers.[20] The X = OR case is of particular interest since it yields dienol 1,4-diethers that are attractive synthons. Prepared as above (Fig. 2), the corresponding dienes are obtained mainly in a (1*E*,3*Z*)-configuration (≥90%), a selectivity that could at first sight appear detrimental to their reactivity in cycloaddition. On the contrary, these dienes have been shown to behave as highly regio- and *endo*-selective entities in both the normal[19] and heteronuclear[21] versions of the Diels–Alder reaction. Thus, the conflicting donor mesomeric effects due to the 1,4-disubstitution, known to undermine the reactivity with respect to 1,3-disubstituted-1,3-dienes (such as Danishefsky's dienes),[22] are partly counter-balanced in the (*E*,*Z*)-dialkoxydienes. Bearing all this in mind, we reacted a set of acetals **1**, prepared in most cases by a simple acidic transacetalization of the corresponding dimethylacetal,[23] with strong bases.

Base-induced acetal ring cleavage

The base chosen was *t*-BuLi as it has been shown to promote clean eliminations at low temperature.[17a,21] Our first experiments were run using dioxepane **1e** in THF at −78 °C (Scheme 1). Under these conditions, alcohol **2e**, resulting from the ring cleavage, was observed (following water quenching) in the crude



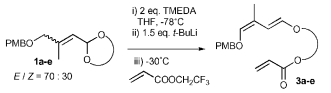
Scheme 1 Optimisation of the elimination conditions.

reaction mixture but unfortunately decomposed on silica gel. Subsequently, the crude mixture was directly dissolved in ether before adding pyridine followed by acryloyl chloride, providing the expected acrylate **3e** in a disappointingly low yield (24%) but with almost total (1*E*,3*Z*)-control[24] of the double bonds. Comparable yields (30%) and selectivities (*EZ* : *EE* > 95 : 5) were obtained by *in situ* trapping of the intermediate alkoxide with 2,2,2-trifluoroethyl (or phenyl) acrylate.

As lithium salts are known to form mixed aggregates with organolithium species,[25] we repeated the latter experiment in a saturated solution of LiBr or KBr in THF, which had a slightly positive effect, bringing the yield of **3e** up to 37% and 48%, respectively. A final improvement was achieved replacing the salts with tetramethylethylenediamine (TMEDA). By adding two eq. of this diamine to the medium before the base, led to 66% of **3e** after water quenching and flash-chromatography. The *EZ* : *EE* > 95 : 5 selectivity remained unchanged.

These conditions turned out to be rather general and applied well to dioxolanes and dioxepanes **3a–m** which gave the expected acrylates in 66–98% yields (Table 1, Table 2 and Experimental Section). The crude reaction mixtures were relatively clean but attempts to purify these fragile trienes by flash-chromatography purification worsened the situation, even after adding 0.5–1% triethylamine to the eluant. A rapid filtration on a silica gel pad appeared to be the best compromise. In all but the five test cases (shown in Table 1) the trienes were directly employed in the cycloaddition step. We also tried to apply this methodology to the opening of two dioxanes, however the disappointing results obtained discouraged us from pursuing this direction.

Table 1 Synthesis of trienes **3** by an acetal opening/*in situ* trapping sequence



Entry	Acetal **1**	Yield (%)	(1*E*,3*Z*) : (1*E*,3*E*)
1	 **1a**	67	> 95 : 5
2	 **1b**	67	> 95 : 5
3	 **1c**	73	> 95 : 5
4	 **1d**	98	> 95 : 5
5	 **1e**	66	> 95 : 5

We propose the consistent double bond stereocontrol observed for **3** stems from an intramolecular coordination of the intermediate allyllithium derivative which would partly localize the anion[26] and account for the (3*Z*)-configuration (Fig. 3). The final β-elimination of the leaving oxy group would then proceed through an *anti*-mechanism, explaining the (1*E*)-configuration.

A complementary experiment was carried out to shed light on the origin of the influence of TMEDA on the elimination. Two eq. of TMEDA added to dioxolane **1c** after the *t*-BuLi and before trifluoroethyl acrylate led to triene **3c** in 36% yield, instead of 73% from the inverse addition of the reagents (Scheme 2). This suggested that this diamine is more crucial for the deprotonation than for the acrylation.

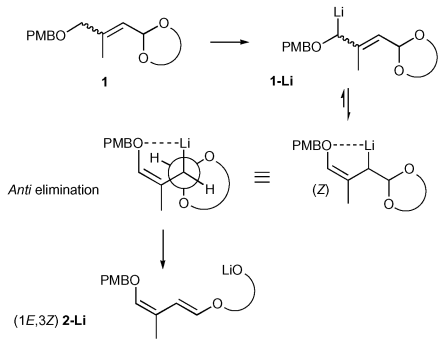
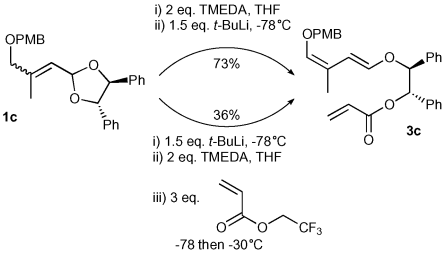
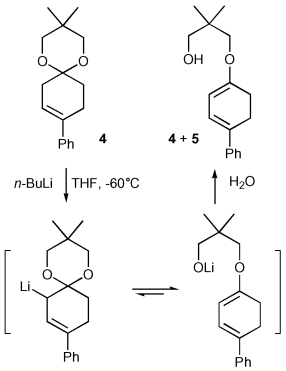


Fig. 3 A chelated model accounting for the elimination of cyclic acetals.



Scheme 2 Influence of the order of introduction of the reagents on the chemical yields.

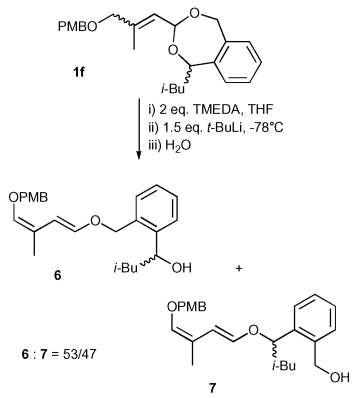
It is possible that the TMEDA is involved in the direct solvation of the deprotonated intermediates **1-Li** (Fig. 3) and facilitate the elimination. Previous observations also suggest that the diamine could stabilize the lithium alkoxide and prevent its readdition onto the newly formed diene. In a relatively comparable case, an inefficient β-elimination with the spirodioxane **4** (Scheme 3)[27] seems to be related to the reversible character of the reaction, as inferred from the deprotonation of pure alcohol **5** by *n*-BuLi leading back, upon hydrolysis, to a mixture of **4** and **5**. These interpretations are however of limited value in the absence of complementary experiments. The role of TMEDA is still an object of debate.[28]



Scheme 3 Partial reversibility of the elimination process.

The case of unsymmetrical dioxepane **1f** deserves special comment. The ring cleavage using the above conditions was not regioselective and led to a 53 : 47 mixture of alcohols **6** and **7** (Scheme 4). This disappointing result appears to prohibit the use of acetals bearing a chirality other than a C_2-axis in this strategy. It also points out that resorting to chiral bases could be of interest to desymmetrize *meso*-acetals. This point will be discussed in a future paper.[29]

Let us finally underline that the conjugate elimination can be competitive with a [1,2]-Wittig rearrangement that has been observed for several dioxanes and dioxolanes. This side-reaction can even become the major pathway when the temperature is raised up to 20 °C.[30]



Scheme 4 Low regioselectivity during the elimination of unsymmetrical dioxepane 1f.

Intramolecular cycloadditions

We next examined the key cyclisation step. The unfavorable influence of a carboxylate moiety in the tether has not deterred research using trienic esters in an IMDA key step, leading to complex natural products such as stenin[31] or securinin.[32] Our own results in comparable intermolecular examples prompted us to consider high pressure as a mild activation mode for the cycloaddition of the fragile dienol diethers **3**.[19,21] A few cases of hyperbaric IMDA have been described, where the results show a limited but consistent increase of the diastereoselectivities.[33]

The isolated trienes **3a–d**, derived from dioxolanes **1a–d** (Table 1), were first tested under several classical cycloaddition conditions, including thermal (140 °C in a sealed-tube of toluene), hyperbaric (12 kbar, 50 °C) and catalytic ($MgCl_2$ or $Yb(OTf)_3$)[34] conditions. However, all experiments with these compounds failed, providing either starting or polymerized material, presumably due to the unfavorable seven-membered lactonization process and the sensitivity of dienol diethers to harsh or acidic conditions. Note that analogue trienes exhibiting a 1,3-disubstituted diene cyclise under thermal conditions.[7a]

Next, the simple triene **3e**, derived from dioxepane **1e**, was tested in various conditions as a prototypical achiral substrate with a seven-atom bridge. Under thermal activation (Table 2, entries 1 and 2) the expected adduct **7e** was obtained regioselectively in low yield in toluene or THF (sluggish), but with high *endo*-selectivity (as deduced from ^{1}H NMR spectra). Comparable results were obtained under 12 kbar at 50 °C (entry 3). The slight heating was required to keep the reaction medium relatively fluid while limiting the triene polymerization. We thus retained these conditions for the rest of our study. The relative success obtained with **1e** prompted us to examine in greater detail a set of dioxepanes we had prepared in a previous work,[23] so that we may evaluate the influence of the appendage on the chiral benzylic position.

We first employed the *meso*-dioxepane **1g**. In this case, as in all the following ones, the "crude" corresponding triene **3g** (a quick filtration on a silica gel pad to remove the TMEDA was found to be necessary) was placed under a high pressure. After 60 h, lactone **7g** was obtained in 36% isolated yield for the three steps and with complete *endo*- and diastereoselectivity (Table 2, entry 4). This encouraging result obtained with a *meso*-derivative prompted us to consider the case of the dioxepane derived from the corresponding C_2-symmetrical diol, an appealing chiral auxiliary with a view to applications to asymmetric synthesis.[35] Thus, acetal **1h** was employed which led, in both THF and toluene, to an unexpected reversal of selectivity in favor of the *exo*-adduct (Table 2, entries 5 and 6). Interestingly, the diastereomeric excess associated to the major *exo*-isomer was low (de = 37 and 20%, respectively) while it remains high to very high (de = 90 and 98%, respectively) for the minor *endo*-compound.

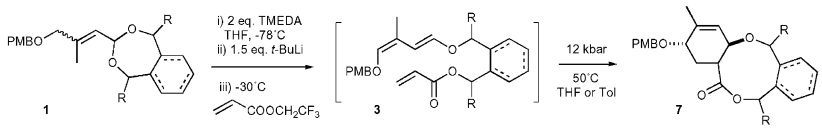
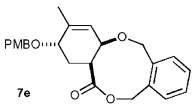
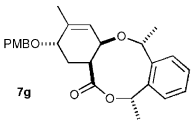
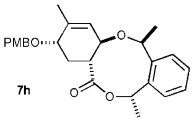
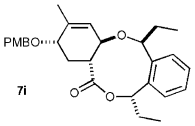
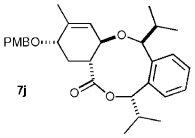
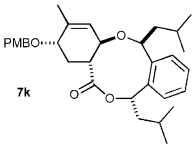
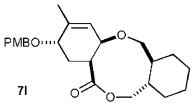
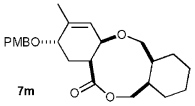


Table 2 Synthesis of lactones **7** by a dioxepane opening/*in situ* trapping/IMDA sequence

Entry	Acetal	R (conf.)[a]	IMDA conditions	Cycloadduct **7**	Overall yield (%)[b]	*endo* : *exo*[c]	de[c,d]
1	**1e**	H[e]	110 °C, toluene, 50 h		33	85 : 15	—
2			105 °C,[g] THF, 120 h		18	100 : 0	—
3			HP,[f] THF, 48 h		24	100 : 0	—
4	**1g**	Me (*syn*)	HP,[f] THF, 60 h		36	100 : 0	100%
5	**1h**	Me (*anti*)	HP,[f] THF, 48 h		50	38 : 62	*endo*: 90% *exo*: 37%
6			HP,[f] toluene, 48 h		34	25 : 75	*endo*: >98% *exo*: 20%
7	**1i**	Et (*anti*)	HP,[f] THF, 48 h		< 20	0 : 100	20%
8			HP,[f] toluene, 48 h		48	0 : 100	50%
9	**1j**	*i*-Pr (*anti*)	HP,[f] THF, 48 h		< 26	0 : 100	50%
10			HP,[f] toluene, 48 h		47	0 : 100	75%
11	**1k**	*i*-Bu (*anti*)	HP,[f] toluene, 48 h		41	0 : 100	50%
12	**1l**	H (*anti*)	110 °C,[g] THF, 120 h		25	100 : 0	34%
13			HP,[f] THF, 72 h		34	100 : 0	50%
14	**1m**	H (*syn*)	HP,[f] toluene, 72 h		30	100 : 0	40%
15			HP,[f] THF, 72 h		25	100 : 0	—
16			110 °C,[g] THF, 120 h		40	100 : 0	—

[a] Relative configuration between either Rs of benzylic tethers or protons at the ring junction of cyclohexanic tethers. [b] Isolated yields in lactones **7** calculated from acetals **1** (three steps). [c] Determined by ^{1}H NMR on crude material. [d] Control of the newly created asymmetric centers with respect to the chiral tether. [e] Yield calculated from isolated triene **3e**. [f] HP: high pressure (12 kbar, 50 °C). [g] In sealed tube.

Three other benzylic substituents were then considered and the results are displayed in entries 7–11 of Table 2. Replacing the methyl moiety by an ethyl (**1i**), *i*-propyl (**1j**) or *i*-butyl (**1k**) group gave exclusively the *exo*-product. On the other hand, the associated de increased when going from methyl to ethyl and isopropyl (from 20% to 50% and 75%, respectively, in toluene) but decreased to 50% with the *i*-butyl derivative.

Finally, two supplementary derivatives **1l** and **1m** were considered (Table 2, entries 12–16). They were prepared from commercially or readily available *syn*- and *anti*-1,2-cyclohexanedimethanol.[23] When submitted to the conditions of reaction described above, they provided the expected adducts **7l** and **7m** in comparable yields and with complete *endo*-selectivity. The stereocontrol imposed by the chiral auxiliary on the newly created asymmetric centers was determined in the case of **7l** only and was found in the range of 40–50%.

All the selectivities discussed above were determined on the basis of ^{1}H NMR coupling constant measurements. The compounds **7g–h** (*endo*-isomer) adopt exclusively the conformation A (Fig. 4), as indicated by the very large H^a–H^c diaxial coupling value (>13 Hz), and probably due to the unfavourable $A^{1,2}$ allylic

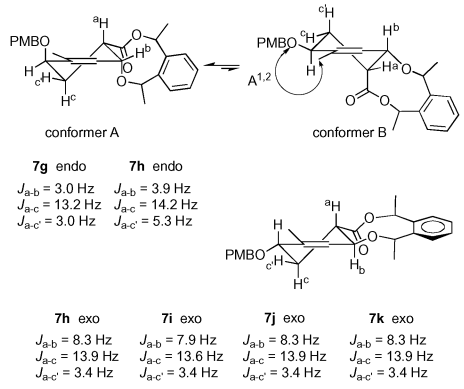


Fig. 4 ^{1}H NMR constant coupling analysis of cycloadducts **7g–k**.

interaction.[36] The *endo*-character is illustrated by a $J_{a-b} < 4$ Hz, in accord with an axial-equatorial relationship. On these basis, the *exo*-isomers of compounds **7h–k** exhibit consistently large J_{a-b} values ($\approx$ 8 Hz) that can hardly be reached if H^a and H^b were not in a *trans*-diaxial relationship.

The *endo*-selectivity for **7g** was also determined by an X-ray analysis[37] of alcohol **8g**, prepared *via* cleavage of the PMB group of lactone **7g** (Fig. 5)†. This result also shows the relative orientation of the stereogenic carbons borne by the cyclohexene with respect to the benzylic methyl groups.

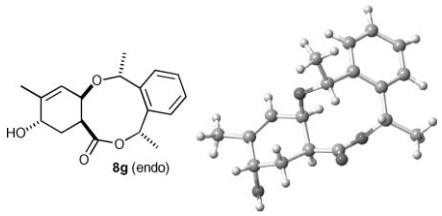


Fig. 5 Representation of alcohol **8g** X-ray structure.

In conclusion, it appears that a synthetic scheme consisting of a deprotonation/ring-cleavage/acrylation/cycloaddition sequence is relatively efficient when carried out with dioxepanes under well-defined conditions. The yields obtained, for the three step process were in the a range of 24–50% (60–80% yield per step). However, the cycloadducts derived from dioxolanes could never be obtained, showing that the length of the tether probably affects the cycloaddition reaction because of its lack of flexibility. From a stereochemical point of view, it appears that either an *endo*- or *exo*-selective process can be secured, depending on the *syn*-/*anti*-relationship between the substituents attached to the benzylic tether. However, good diastereoselectivity can only be obtained in the case of the *endo*-adducts.

Application to the synthesis of modified carbasugars

To illustrate the possible interest this strategy for the synthesis of biologically interesting molecules, we transformed two adducts obtained from this route into carbasugars. In general, such compounds exhibit interesting properties as antibiotic, antifungal and antiviral agents.[38] Numerous synthetic efforts, following the pioneering work of McCasland *et al.*,[39] have been dedicated to accessing this chemical family.[40] Our approach required four transformations to convert the lactones **7** into unusual methylated carbasugars. The four steps are the cleavage of the two benzylic ethers, reduction of the ester and dihydroxylation of the cyclohexene double bond (Fig. 6). However, the relative order of these steps was important to the overall stereoselectivity, as previously established in similar situations.[21]

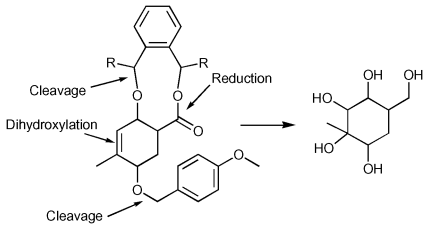
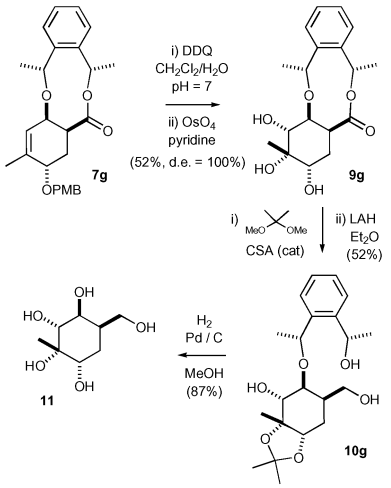


Fig. 6 Transformation of lactones **7** in carbasugars.

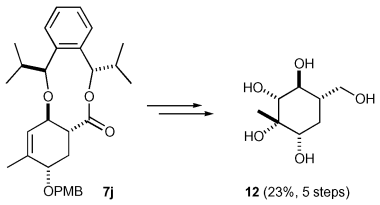
We decided to follow the sequence beginning with the PMB cleavage, then the dihydroxylation, followed by the ester reduction and ended with the benzylic tether removal. The *endo*-lactone **7g** was first selected as a starting substrate. The PMB deprotection was performed following the classical dichlorodicyanoquinone (DDQ) procedure in a buffered DCM–water solution. The dihydroxylation of the trisubstituted double bond was then achieved by addition of a stoichiometric amount of osmium tetroxide in pyridine (Scheme 5).



Scheme 5 Conversion of lactone **7g** into 2-methyl-5*a*-carba-α-DL-glucopyranose **11**.

To avoid the problems due to the high water solubility of polyhydroxylated compounds, we chose to protect triol **9g** as its acetonide. Fortunately, treating **9g** with 2,2-dimethoxypropane in the presence of trace amounts of camphorsulfonic acid in DCM led to a single regioisomer of the expected ketal. The LAH reduction using standard conditions afforded triol **10g** in acceptable yields. The final hydrogenolysis of the benzylic auxiliary was accomplished using catalytic palladium in methanol. The deprotection of the acetonide group occurred simultaneously, providing directly the target 2-methyl-5*a*-carba-α-DL-gulopyranose **11** (Scheme 5). The overall yield for this five step sequence was 23%.

The same sequence of reactions was then applied to the major diastereomer of *exo*-lactone **7j** (Scheme 6). Comparable results were obtained with the exception of a lower diastereoselectivity for the dihydroxylation step (de = 88%). However, the two isomeric triols were easily separated by flash chromatography on silica gel. The corresponding 2-methyl-5*a*-carba-β-DL-mannopyranose **12** was also obtained in 23% yield over the five steps.



Scheme 6 Conversion of lactone **7j** into 2-methyl-5*a*-carba-β-DL-mannopyranose **12**.

The conformation of these two modified carbasugars in solution in methanol has been studied by high-field NMR. The results indicate that both products adopt a similar chair conformation, with the three secondary alcohols in an equatorial and the tertiary alcohol in an axial position. However, the hydroxymethyl group resides in an axial (**11**) or in an equatorial (**12**) position, related respectively to the *endo*- or *exo*-cycloadducts (Fig. 7).

The conversion of these two lactones into two diastereomeric 2-methylated carbasugars demonstrates that they can serve as precursors for a relatively short and efficient synthesis of these sugar mimetics. The overall yields to transform acetal **1g** and **1j**

† CCDC reference numbers 208104. See http://www.rsc.org/suppdata/ob/b4/b419381d/ for crystallographic data in .cif or other electronic format.

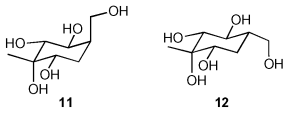


Fig. 7 Conformation of carbasugars **11** and **12** in d_4-methanol.

into **11** and **12** are 8.3 and 10.8%, respectively, for an eight step procedure.

This strategy is likely to be relatively versatile since the order of the four transformations needed to convert **7** into carbasugars is expected to have a major influence on the stereoselectivity of the dihydroxylation step. Thus, and as demonstrated before for regular sugars,[21] diastereomeric carbasugars are probably within reach utilising this approach.

Conclusion

This paper details a synthesis of methylated carbasugars through an intramolecular Diels–Alder route that relies on trienic precursors, easily prepared from dioxepanes by a base-induced acetal ring cleavage. The conjugate elimination remains remarkably efficient despite the known sensitivity of comparable reactions to the heterocycle size[8a] and substitution.[8b] This part of the study suggests that dioxanes are inappropriate precursors since the derived trienes do not cyclise in our conditions. By contrast, dioxepanes are well-suited. From a stereochemical point of view, a strategy resorting to dioxepanes derived from *meso*-diols should be preferred over another based on chiral C_2-symmetrical diols. Transforming an achiral *meso*-derivative **1** into a chiral triene **3** could eventually be performed with a chiral base. However, such a desymmetrization, which would be an appropriate way to introduce the asymmetry in this reaction scheme, has never been described to our knowledge.[27,41] It should be noted that the introduction of a PMBO group on the terminal allylic position of the acetal does not inhibit the deprotonation and provides an almost fully controlled 1,4-disubstituted (1*Z*,3*E*)-dienic appendage.

The second part of our study shows that the intramolecular Diels–Alder cycloadditions of these trienes can be efficient and diastereoselective. This occurs as long as the activation conditions and the benzylic substituents on the tether are choosen with care. The combination of a high pressure and mild heating seems to be particularly appropriate. In these conditions, and depending on the size of the benzylic substituents, complete *endo*- or *exo*-selectivities were observed, with diastereocontrol varying from 20 to 100%.

A five step procedure allowed the final conversion of the resulting lactones into carbasugar derivatives, which were obtained in decent overall yields.

Experimental

General aspects

^{1}H NMR spectra were recorded at 300, 500 or 600 MHz and ^{13}C NMR spectra at 75 MHz; chemical shift (δ) are given in parts per million (ppm) and the coupling constants (J) in Hertz. The solvent was deuterochloroform or deuteromethanol. IR spectra were recorded on a Perkin-Elmer 16 PC FT-IR. Gas chromatography analysis were performed on a high resolution DB-1 type column (30 m, 0.25 mm i.d., 0.25 μ coating). GC/MS analysis were performed on an instrument equipped with the same column. The mass spectra under electron impact conditions (EI) were recorded at 70 eV ionizing potential; methane (CH_4), isobutane (*t*-BuH) or ammonia (NH_3) were used for chemical ionization (CI). The silica gel used for flash chromatography was 230–400 mesh. All reagents were of reagent grade and were used as such or distilled prior to use.

1,2-*anti*-(1′*E*,3′*Z*)-2-[3-Methyl-4-(*p*-methoxy-benzyloxy)-buta-1,3-dienyloxy]-1-methyl-propyl acrylate 3a. Under an argon atmosphere, at −78 °C, TMEDA (516 μL, 2 eq., 3.42 mmol) was added to a solution of dioxolane **1a** (500 mg, 1eq., 1.71 mmol) in dry THF (8 mL). Then at the same temperature, *t*-BuLi in pentane (1.86 mL, 1.6 eq., 1.5 M, 2.74 mmol) was added into the reaction mixture. After 15 min, 2,2,2-trifluoroethyl acrylate (653 μL, 3 eq., 5.15 mmol) was added and the reaction mixture was allowed to warm at −40 °C over 3 h. A solution of $NaHCO_3$ (3 mL) was added and the aqueous phase was extracted by ether (2 × 8 mL). The combined organic phases were dried ($MgSO_4$) and evaporated under a reduced pressure. Flash chromatography on silica gel (heptane–AcOEt–Et_3N, 70 : 30 : 3 as eluant) afforded 396 mg (67%) of triene **3a** (colorless oil) as a 1*E*,3*Z* : 1*E*,3*E* > 95 : 5 mixture.

ν_{max} (film)/cm^{-1} 2938, 2838, 1722, 1614, 1514, 1248, 1172, 810. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.16 (3 H, d, J = 6.8 Hz), 1.20 (3H, d, J = 6.4 Hz), 1.49 (3H, s), 3.71 (3H, s), 3.89 (1H, m), 4.61 (2H, s), 4.92 (1H, m), 5.74 (1H, dd, J = 1.5, 10.6 Hz), 5.76 (1H, s), 6.04 (1H, dd, J = 10.6, 17.3 Hz), 6.08 (1H, d, J = 12.8 Hz), 6.21 (1H, d, J = 12.8 Hz), 6.32 (1H, dd, J = 1.5, 17.3 Hz), 6.80 (2H, d, J = 6.4 Hz), 7.18 (2H, d, J = 6.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 15.0, 15.1, 16.7, 55.7, 73.4, 73.8, 78.5, 104.9, 110.4, 114.2, 129.1, 129.5, 130.2, 131.3, 140.7, 145.7, 159.7, 165.9. EIMS (70 eV) m/z 346 (M^+, 9), 345 (20), 218 (6), 121 (100).

1,2-*syn*-(1′*E*,3′*Z*)-2-[3-Methyl-4-(*p*-methoxy-benzyloxy)-buta-1,3-dienyloxy]-1-methyl-propyl acrylate 3b. This compound was prepared as above, starting with dioxolane **1b** (500 mg, 1eq., 1.71 mmol) and TMEDA (516 μL, 2 eq., 3.42 mmol). 1.86 mL (1.6 eq., 1.5 M, 2.74 mmol) was added at −78 °C, 653 μL (3 eq., 5.15 mmol) of 2,2,2-trifluoroethyl acrylate and 3 mL of a saturated solution of $NaHCO_3$ was added for quenching. Flash chromatography on silica gel (heptane–AcOEt–Et_3N, 70 : 30 : 3 as eluant) afforded 396 mg (67%) of triene **3b** (colorless oil) as a 1*E*,3*Z* : 1*E*,3*E* > 95 : 5 mixture.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.23 (3H, d, J = 6.4 Hz), 1.27 (3H, d, J = 6.4 Hz), 1.56 (3H, s), 3.79 (3H, s), 3.96 (1H, dq, J = 3.8, 6.4 Hz), 4.69 (2H, s), 4.98 (1H, dq, J = 3.8, 6.4 Hz), 5.81 (1H, dd, J = 1.5, 10.6 Hz), 5.82 (1H, s), 6.11 (1H, dd, J = 10.6, 17.3 Hz), 6.15 (1H, d, J = 12.6 Hz), 6.28 (1H, d, J = 12.6 Hz), 6.39 (1H, dd, J = 1.5, 17.3 Hz), 6.86 (2H, d, J = 6.4 Hz), 7.25 (2H, d, J = 6.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 14.5, 14.6, 16.1, 55.2, 72.8, 73.3, 78.0, 104.3, 109.9, 113.7, 128.6, 129.0, 129.7, 130.8, 140.2, 145.2, 159.2, 165.4.

1,2-*anti*-(1′*E*,3′*Z*)-2-[4-(4-Methoxy-benzyloxy)-3-methylbuta-1,3-dienyloxy]-1,2-diphenyl-ethyl acrylate 3c. This compound was prepared as above, starting with acetal **1c** (100 mg, 1 eq., 0.240 mmol) and TMEDA (72 μL, 2 eq., 0.481 mmol). 0.24 mL (1.5 eq., 1.5 M, 0.361 mmol) of *t*-BuLi in pentane was added at −78 °C, 91 μL (3 eq., 0.721 mmol) of 2,2,2-trifluoroethyl acrylate and 2 mL of a saturated solution of $NaHCO_3$ was added for quenching. Flash chromatography on silica gel (heptane–AcOEt–Et_3N, 70 : 30 : 3 as eluant) afforded 83 mg (73%) of triene **3c** (colorless oil) as a 1*E*,3*Z* : 1*E*,3*E* > 95 : 5 mixture.

ν_{max} (film)/cm^{-1} 3062, 3032, 2933, 1725, 1614, 1513, 1249, 1174, 808, 700. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.47 (3H, s), 3.80 (3H, s), 4.63 (1H, d, J = 12.1 Hz), 4.68 (1H, d, J = 12.1 Hz), 5.01 (1H, d, J = 7.0 Hz), 5.78 (1H, s), 5.84 (1H, dd, J = 1.5, 10.6 Hz), 6.10 (1H, d, J = 7.0 Hz), 6.16 (1H, d, J = 12.8 Hz), 6.19 (1H, dd, J = 10.2, 17.3 Hz), 6.31 (1H, d, J = 12.8 Hz), 6.45 (1H, dd, J = 1.5, 17.3 Hz), 6.87 (2H, d, J = 8.3 Hz), 7.05–7.25 (12H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 14.9, 55.7, 73.7, 78.4, 84.6, 105.8, 110.4, 114.2, 128.01, 128.03, 128.39, 128.45, 128.50, 128.55, 128.8, 129.4, 130.2, 131.6, 136.8, 137.3, 140.9, 145.2, 159.7, 165.4. FAB + MS m/z 471 (MH^+, 1), 470 (M^+, 1), 251 (22), 195 (25), 121 (100).

(1′*E*,3′*Z*)-2-[4-(4-Methoxy-benzyloxy)-3-methylbuta-1,3-dienyloxy]-cyclopentyl acrylate 3d. This compound was prepared as above, starting with acetal **1d** (200 mg, 1 eq., 0.751 mmol) and TMEDA (230 μL, 2 eq., 3.42 mmol). 0.85 mL (1.7 eq., 1.5 M, 2.74 mmol) of *t*-BuLi in pentane was added at −78 °C, 286 μL (3 eq., 2.26 mmol) of 2,2,2-trifluoroethyl acrylate and 2 mL of a saturated solution of $NaHCO_3$ was added for quenching. Flash chromatography on silica gel (heptane–AcOEt–Et_3N, 70 : 30 : 3 as eluant) afforded 264 mg (98%) of triene **3d** (off yellow oil) as a 1*E*,3*Z* : 1*E*,3*E* > 95 : 5 mixture.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.15 (2H, m), 1.56 (3H, s), 1.62 (1H, m), 1.87 (3H, m), 3.80 (3H, s), 4.32 (1H, m), 4.68 (2H, s), 5.08 (1H, m), 5.79 (1H, d, $J = 10.4$ Hz), 5.81 (1H, s), 6.11 (1H, d, $J = 12.7$ Hz), 6.12 (1H, dd, $J = 10.4$, 17.3 Hz), 6.26 (1H, d, $J = 12.7$ Hz), 6.39 (1H, dd, $J = 1.5$, 17.3 Hz), 6.87 (2H, d, $J = 8.7$ Hz), 7.25 (2H, d, $J = 8.7$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 15.0, 19.4, 28.2, 29.2, 55.7, 73.8, 75.9, 80.3, 104.6, 110.5, 114.2, 128.8, 129.4, 130.2, 131.3, 140.6, 145.7, 159.7, 165.9.

(1′*E*,3′*Z*)-2-[4-(4-Methoxy-benzyloxy)-3-methylbuta-1,3-dienyloxymethyl]-benzyl acrylate 3e. This compound was prepared as above, starting with acetal **1e** (500 mg, 1 eq., 1.47 mmol) and TMEDA (380 μL, 1.7 eq., 2.50 mmol). 1.90 mL (1.7 eq., 1.3 M, 2.74 mmol) of *t*-BuLi in pentane, 560 μL (3 eq., 4.41 mmol) of 2,2,2-trifluoroethyl acrylate was used and 3 mL of a saturated solution of $NaHCO_3$ was added for quenching. Flash chromatography on silica gel (heptane–AcOEt–Et_3N: 70 : 30 : 3 as eluant) afforded 381 mg (66%) of triene **3e** (colorless oil) as a 1*E*,3*Z* : 1*E*,3*E* > 95 : 5 mixture.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.51 (3H, d, $J = 1.1$ Hz), 3.71 (3H, s), 4.63 (2H, s), 4.80 (2H, s), 5.19 (2H, s), 5.73 (1H, dd, $J = 1.5$, 10.2 Hz), 5.78 (1H, s), 6.06 (1H, dd, $J = 10.2$, 17.3 Hz), 6.11 (1H, d, $J = 13.2$ Hz), 6.35 (1H, $J = 1.5$, 17.3 Hz), 6.42 (1H, d, $J = 13.2$ Hz), 6.80 (2H, d, $J = 8.7$ Hz), 7.18 (2H, d, $J = 8.7$ Hz), 7.25 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 15.1, 55.7, 64.2, 69.6, 73.9, 103.7, 110.3, 114.3, 128.6, 128.8, 129.0, 129.5, 129.6, 129.9, 130.2, 131.6, 134.7, 135.9, 140.9, 146.1, 159.7, 166.3.

2-(4-Methoxy-benzyloxy)-3-methyl-1,2,4*a*,13*a*-tetrahydro-5,12-dioxa-dibenzo[*a*,*e*]cyclononan-13-one 7e. A solution of isolated triene **3e** in THF (8 mL) was placed under 12 kbar at 50 °C for 48 h. After decompression, the solvent was removed to give crude product, which showed only the *endo*-diastereomer (^{1}H NMR). The purification could be achieved easily by precipitation in ether to afforded 36 mg (24%) of titled product as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.68 (3H, s), 1.64 (1H, m), 2.16 (1H, dt, $J = 2.6$, 14.7 Hz), 3.06 (1H, dt, $J = 4.5$, 14.3 Hz), 3.62 (1H, t, $J = 2.6$ Hz), 3.72 (3H, s), 4.27 (1H, d, $J = 11.3$ Hz), 4.44 (1H, t, $J = 4.5$ Hz), 4.51 (1H, d, $J = 11.3$ Hz), 4.75 (2H, s), 5.29 (1H, d, $J = 13.4$ Hz), 5.47 (1H, d, $J = 13.4$ Hz), 5.66 (1H, d, $J = 4.9$ Hz), 6.79 (2H, d, $J = 8.6$ Hz), 7.20 (6H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.9, 23.6, 40.4, 55.7, 67.2, 71.7, 73.8, 77.4, 78.4, 114.2, 124.8, 128.37, 128.42, 129.1, 130.0, 130.7, 133.1, 136.6, 136.9, 138.6, 159.7, 173.9. CIMS (*i*-but) *m*/*z* 395 (MH^+, 2), 257 (10), 223 (5), 121 (100). HRMS (CI, *i*-butane): calcd for $C_{24}H_{27}O_5$: 395.1859; found: MH^+ 395.1858. Anal. calcd for $C_{24}H_{26}O_5$: C, 73.08%; H, 6.64%; found: C, 72.89%; H, 6.65%.

2-(4-Methoxy-benzyloxy)-3,6,11-trimethyl-1,2,4*a*,13*a*-tetrahydro-5,12-dioxa-dibenzo[*a*,*e*]cyclononan-13-one 7g. Under an inert atmosphere, TMEDA (0.49 mL, 2.0 eq., 3.26 mmol) was added to a solution of dioxepane **1g** (600 mg, 1eq., 1.63 mmol) in THF (8 mL), then *t*-BuLi in pentane (1.63 mL, 1.5 eq., 1.5M, 2.45 mmol) was added dropwise at −78 °C. After 15 min, 2,2,2-trifluoroethyl acrylate (0.62 mL, 3.0 eq., 4.89 mmol) was added and the solution was allowed to warm to −30 °C over 1.5 h and then stirred for other 3.5 h at this temperature. A saturated solution of $NaHCO_3$ (3 mL) was added to the reaction mixture and the aqueous phase was extracted by ether (2 × 10 mL). The resulting organic phase was dried ($MgSO_4$) and evaporated under a reduced pressure. TMEDA was removed by filtration on silica gel (heptane–AcOEt–Et_3N, 70 : 30 : 4 as eluant) to afforded crude triene. The latter was rapidly used for the next step, dissolved in THF (8 mL) and then set under 12 kbar at 50 °C for 60 h. After decompression, the reaction mixture was evaporated. Flash chromatography on silica gel (dichloromethane as eluant) afforded 251 mg (36%, three steps) of a single diastereomer (*endo* = 100%, de = 100%, determined by ^{1}H NMR from the crude mixture) as a colorless oil.

ν_{max} (film)/cm^{-1} 2978, 2934, 2858, 1732, 1612, 1513, 1248, 1169, 1043, 825, 731. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.42 (3H, d, $J = 6.2$ Hz), 1.70 (3H, s), 1.80 (3H, d, $J = 6.6$ Hz), 2.06 (1H, dt, $J = 3.8$, 13.8 Hz), 2.30 (1H, d, $J = 13.8$ Hz), 2.75 (1H, dt, $J = 3.0$, 13.2 Hz), 3.78 (4H, s), 4.06 (1H, bs), 4.35 (1H, d, $J = 10.9$ Hz), 4.58 (1H, d, $J = 10.9$ Hz), 4.83 (1H, q, $J = 6.2$ Hz), 5.48 (1H, d, $J = 5.7$ Hz), 6.12 (1H, q, $J = 6.6$ Hz), 6.85 (2H, d, $J = 8.7$ Hz), 7.24 (2H, d, $J = 8.7$ Hz), 7.35 (3H, m), 7.52 (1H, d, $J = 6.5$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 18.6, 21.6, 22.3, 24.1, 39.8, 55.7, 68.9, 71.6, 72.2 (2C), 74.8, 114.2, 124.6, 125.9, 128.2, 128.4, 129.1, 130.0, 130.8, 139.1, 140.9, 141.0, 159.7, 177.9. EIMS (70 eV) *m*/*z* 422 (M^+, 3), 391 (31), 279 (26), 167 (47), 149 (80), 121 (100). HRMS (EI): calcd for $C_{26}H_{30}O_5$: 422.2093; found: M^+ 422.2095.

2-(4-Methoxy-benzyloxy)-3,6,11-trimethyl-1,2,4*a*,13*a*-tetrahydro-5,12-dioxa-dibenzo[*a*,*e*]cyclononan-13-one 7h. The triene **3h** was prepared as above from dioxepane **1h** (400 mg, 1 eq., 1.09 mmol) and used rapidly for the next step, dissolved in THF (8 mL) or toluene (8 mL) and set under 12 kbar at 50 °C for 48 h. After decompression, the reaction mixture was evaporated to provide a mixture of four diastereomers (see Table 2). Flash chromatography on silica gel (heptane–AcOEt, 70 : 30 as eluant) afforded 230 mg (50% in THF, three steps) or 157 mg (34% in toluene, three steps) of combined diastereomers as a colorless oil. Only the main *endo*-diastereomer was isolated.

ν_{max} (film)/cm^{-1} 2975, 2932, 2866, 1737, 1612, 1513, 1249, 1074, 821, 761. *Endo*-Isomer (major diastereomer): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.61 (3H, d, $J = 6.8$ Hz), 1.63 (1H, m), 1.64 (3H, d, $J = 6.8$ Hz), 1.75 (3H, s), 2.22 (1H, dt, $J = 2.8$, 14.2 Hz), 3.14 (1H, ddd, $J = 3.9$, 5.3, 14.2 Hz), 3.67 (1H, s), 3.78 (3H, s), 4.32 (1H, d, $J = 11.3$ Hz), 4.50 (1H, m), 4.55 (1H, d, $J = 11.3$ Hz), 5.32 (1H, q, $J = 6.8$ Hz), 5.65 (1H, d, $J = 3.4$ Hz), 5.90 (1H, q, $J = 6.8$ Hz), 6.85 (2H, d, $J = 8.7$ Hz), 7.22 (5H, m), 7.42 (1H, $J = 6.4$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 19.1, 20.5, 22.1, 22.3, 38.6, 54.2, 70.3, 72.4, 74.5, 75.9, 77.0, 112.8, 124.3, 125.5, 126.5, 127.2, 128.6 (2C), 129.4, 136.8, 137.1, 139.8, 158.2, 172.0. *Exo*-Isomer (major diastereomer): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.50 (3H, d, $J = 6.4$ Hz), 1.64 (3H, d, $J = 6.8$ Hz), 1.70 (1H, m), 1.75 (3H, s), 2.12 (1H, dt, $J = 4.0$, 13.4 Hz), 2.85 (1H, ddd, $J = 3.4$, 8.3, 13.9 Hz), 3.62 (1H, d, $J = 8.0$ Hz), 3.78 (3H, s), 3.97 (1H, d, $J = 10.6$ Hz), 4.37 (1H, d, $J = 11.3$ Hz), 4.50 (1H, d, $J = 11.3$ Hz), 5.26 (1H, s), 5.84 (1H, q, $J = 6.8$ Hz), 6.20 (1H, q, $J = 6.4$ Hz), 6.85 (2H, d, $J = 8.3$ Hz), 7.21 (6H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 19.5, 22.7, 23.9, 30.2, 48.2, 55.7, 69.3, 70.6, 72.9, 74.8, 78.0, 114.2, 126.4, 128.4, 128.7, 129.2, 129.6 (2C), 130.9, 137.4, 140.2, 142.7, 159.5, 177.8. *Exo*-Isomer (minor diastereomer): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.50 (3H, d, $J = 6.4$ Hz), 1.64 (3H, d, $J = 6.8$ Hz), 1.70 (1H, m), 1.69 (3H, s), 2.12 (1H, dt, $J = 3.4$, 13.4 Hz), 3.11 (1H, ddd, $J = 3.4$, 8.3, 13.9 Hz), 3.53 (2H, m), 3.79 (3H, s), 4.37 (1H, d, $J = 11.3$ Hz), 4.55 (1H, d, $J = 11.3$ Hz), 5.32 (1H, s), 5.84 (1H, q, $J = 6.8$ Hz), 6.21 (1H, q, $J = 6.4$ Hz), 6.86 (2H, d, $J = 8.3$ Hz), 7.21 (6H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.5, 22.7, 23.9, 27.8, 43.6, 55.7, 69.3, 72.0, 72.5, 73.4, 78.0, 114.2, 126.4, 128.4, 128.7, 129.2, 129.6 (2C), 130.9, 135.6, 137.8, 142.7, 159.5, 179.2. EIMS (70 eV) *m*/*z* 422 (M^+, 1), 203 (14), 149 (23), 132 (100), 121 (55). HRMS (EI): calcd for $C_{26}H_{30}O_5$: 422.2093; found: M^+ 422.2095.

6,11-Diethyl-2-(4-methoxy-benzyloxy)-3-methyl-1,2,4*a*,13*a*-tetrahydro-5,12-dioxa-dibenzo[*a*,*e*]cyclononan-13-one 7i. The triene **3i** was prepared as above from the dioxepane **1i** (200 mg, 1 eq., 0.505 mmol) and used rapidly for the next step, dissolved in toluene (8 mL) and set under 12 kbar at 50 °C for 48 h. After decompression, the reaction mixture was evaporated. Flash chromatography on silica gel (heptane–AcOEt, 70 : 30 as eluant) afforded 109 mg (48%, three steps) of two *exo*-diastereomers (*exo* = 100%, de = 50%, determined by ^{1}H NMR from the crude mixture) as a colorless oil. Only the main *exo*-diastereomer was isolated, while the minor *exo*-isomer (detected on the NMR spectra of the crude mixture) was not isolated.

Exo-Isomer (major diastereomer): ν_{max} (film)/cm^{-1} 2964, 2936, 2875, 1737, 1612, 1513, 1171, 822, 760. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.75 (3H, t, J = 7.5 Hz), 1.04 (3H, t, J = 7.5 Hz), 1.65–2.17 (6H, m), 1.79 (3H, s), 2.84 (1H, ddd, J = 3.4, 7.9, 13.6 Hz), 3.65 (1H, d, J = 7.9 Hz), 3.78 (3H, s), 3.98 (1H, d, J = 10.5 Hz), 4.37 (1H, d, J = 11.5 Hz), 4.46 (1H, d, J = 11.5 Hz), 5.24 (1H, s), 5.58 (1H, dd, J = 6.8, 8.7 Hz), 5.85 (1H, dd, J = 5.6, 8.6 Hz), 6.85 (2H, d, J = 8.7 Hz), 7.15–7.32 (5H, m), 7.42 (1H, d, J = 6.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 11.1, 11.2, 19.4, 30.2, 30.4, 30.7, 48.3, 55.7, 71.8, 72.5, 74.8, 75.2, 83.7, 114.1, 126.6, 128.2, 128.7, 129.4, 129.6, 129.9, 130.4, 136.8, 139.2, 142.6, 159.5, 178.1. EIMS (70 eV) m/z 450.2 (M$^+$, 1), 231 (11), 175 (30), 160 (75), 129 (100), 121 (70). HRMS (EI): calcd for $C_{28}H_{34}O_5$: 450.2406; found: M$^+$ 450.2412.

6,11-Diisopropyl-2-(4-methoxy-benzyloxy)-3-methyl-1,2,4*a*,13*a*-tetrahydro-5,12-dioxa-dibenzo[*a*,*e*]cyclononan-13-one 7j. The triene **3j** was prepared as above from the dioxepane **1j** (700 mg, 1 eq., 1.77 mmol) and used rapidly for the next step, dissolved in toluene (8 mL) and set under 12 kbar at 50 °C for 60 h. After decompression, the reaction mixture was evaporated. Flash chromatography on silica gel (DCM–pentane, 90 : 10 as eluant) afforded 398 mg (47%, three steps) of two diastereomers (*exo* 100%, de = 75%, determined by ^{1}H NMR from the crude mixture) as a colorless oil. Only the main *exo*-diastereomer was isolated.

ν_{max} (film)/cm^{-1} 2958, 2870, 1738, 1612, 1514, 1250, 1172, 822, 734. *Exo*-Isomer (major diastereomer): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.54 (3H, d, J = 6.8 Hz), 0.81 (3H, d, J = 6.8 Hz), 1.19 (6H, d, J = 6.4 Hz), 1.70 (1H, m), 1.74 (3H, s), 2.12 (3H, m), 2.79 (1H, ddd, J = 3.4, 8.3, 13.9 Hz), 3.59 (1H, d, J = 7.9 Hz), 3.78 (3H, s), 3.97 (1H, d, J = 8.7 Hz), 4.36 (1H, d, J = 11.5 Hz), 4.50 (1H, d, J = 11.5 Hz), 5.18 (1H, d, J = 10.6 Hz), 5.23 (1H, s), 5.40 (1H, d, J = 9.8 Hz), 6.85 (2H, d, J = 8.3 Hz), 7.13 (1H, d, J = 7.5 Hz), 7.15–7.30 (4H, m), 7.37 (1H, d, J = 6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 19.4, 19.6, 20.0, 20.8, 21.3, 30.1, 34.0, 35.4, 48.3, 55.7, 70.3, 72.6, 74.8, 79.7, 88.4, 114.1, 127.3, 127.5, 128.6, 129.5, 129.7, 131.0, 131.5, 136.9, 138.8, 141.6, 159.5, 178.2. HRMS (EI): calcd for $C_{30}H_{38}O_5$: 478.2719; found: M$^+$ 478.2713.

6,11-Diisobutyl-2-(4-methoxy-benzyloxy)-3-methyl-1,2,4*a*,13*a*-tetrahydro-5,12-dioxa-dibenzo[*a*,*e*]cyclononan-13-one 7k. The triene **3k** was prepared as above from the dioxepane **1k** (200 mg, 1 eq., 0.442 mmol) and used rapidly for the next step, dissolved in toluene (8 mL) and set under 12 kbar at 50 °C for 48 h. After decompression, the reaction mixture was evaporated. Flash chromatography on silica gel (DCM–pentane, 90 : 10 as eluant) afforded 92 mg (41%, three steps) of two diastereomers (*exo* 100%, de = 50%, determined by ^{1}H NMR from the crude mixture) as a colorless oil. Only the main diastereomer (*exo*) was isolated.

ν_{max} (film)/cm^{-1} 2953, 2867, 1739, 1612, 1513, 1249, 1149, 1074, 822, 757. *Exo*-Isomer (major diastereomer): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.88 (3H, d, J = 6.4 Hz), 0.95 (3H, d, J = 6.8 Hz), 0.97 (3H, d, J = 6.8 Hz), 1.01 (3H, d, J = 6.4 Hz), 1.35–2.05 (7H, m), 1.74 (3H, s), 2.13 (1H, dt, J = 3.8, 13.2 Hz), 2.82 (1H, ddd, J = 3.4, 8.3, 13.9 Hz), 3.62 (1H, d, J = 7.9 Hz), 3.78 (3H, s), 3.97 (1H, d, J = 9.0 Hz), 4.37 (1H, d, J = 11.3 Hz), 4.50 (1H, d, J = 11.3 Hz), 5.23 (1H, s), 5.76 (1H, dd, J = 5.3, 9.8 Hz), 6.04 (1H, dd, J = 5.6, 7.9 Hz), 6.85 (2H, d, J = 8.7 Hz), 7.1–7.3 (5H, m), 7.43 (1H, d, J = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 19.4, 22.4, 22.8, 23.5, 24.2, 25.2, 25.3, 30.1, 45.5, 47.5, 48.4, 55.7, 70.5, 71.6, 72.6, 74.7, 80.4, 114.2, 126.9, 128.2, 128.5, 129.5, 129.7, 129.9, 131.0, 137.4, 139.4, 142.4, 159.5, 178.1. *Exo*-Isomer (minor diastereomer): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.95 (12H, m), 1.35–2.05 (8H, m), 1.68 (3H, s), 3.03 (1H, m), 3.54 (2H, s), 3.80 (3H, s), 4.35 (1H, d, J = 11.3 Hz), 4.58 (1H, d, J = 11.3 Hz), 5.30 (1H, s), 5.74 (1H, dd, J = 5.3, 9.8 Hz), 6.08 (1H, dd, J = 5.6, 7.9 Hz), 6.87 (2H, d, J = 8.7 Hz), 7.1–7.3 (5H, m), 7.43 (1H, d, J = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.4, 22.4, 22.7, 23.5, 24.2, 25.1, 25.2, 27.8, 43.7, 45.5, 47.7, 55.7, 71.3, 71.8, 72.4, 73.1, 80.4, 114.2, 126.4, 127.99, 128.04, 128.4, 129.4, 129.9, 131.0, 134.5, 137.8, 142.5, 159.6, 179.6. EIMS (70 eV) m/z 506 (M$^+$, 1), 492 (1), 330 (6), 215 (20), 159 (45), 121 (100).

5,12-*anti*-2-(4-Methoxy-benzyloxy)-3-methyl-1,2,4*a*,6,6*a*,7,8,9,10,10*a*,11,13*a*-dodecahydro-5,12-dioxa-dibenzo[*a*,*e*]cyclononen-13-one 7l. The triene **3l** was prepared as above from the dioxepane **1l** (120 mg, 1 eq., 0.347 mmol) and used rapidly for the next step, dissolved in THF (8 mL) or toluene (8 mL) and set under 12 kbar at 50 °C for 72 h. After decompression, the reaction mixture was evaporated and provided a mixture of two diastereomers (*endo*). Flash chromatography on silica gel (DCM–pentane, 90 : 10 as eluant) afforded 47 mg (34%, three steps, de = 50%, determined by ^{1}H NMR from the crude mixture) from the experiment run in THF or 42 mg (30%, three steps, de = 40%, determined by ^{1}H NMR from the crude mixture) in toluene of the *endo*-isomers as a colorless oil.

ν_{max} (film)/cm^{-1} 2923, 2854, 1741, 1513, 1248, 1172, 1071, 821. Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.85 (2H, m), 1.17 (4H, m), 1.70 (5H, m), 1.75 (3H, s), 2.29 (1H, dt, J = 3.0, 13.3 Hz), 3.14 (1H, ddd, J = 3.8, 6.0, 12.4 Hz), 3.32 (1H, dd, J = 7.5, 10.9 Hz), 3.79 (5H, m), 3.90 (1H, d, J = 10.9 Hz), 4.02 (1H, m), 4.36 (1H, d, J = 11.3 Hz), 4.57 (1H, d, J = 11.3 Hz), 4.64 (1H, m), 5.63 (1H, d, J = 4.5 Hz), 6.86 (2H, d, J = 8.6 Hz), 7.24 (2H, d, J = 8.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.8, 25.7, 26.0, 26.5, 29.2, 31.4, 40.1, 44.1, 45.0, 55.7, 70.4, 71.6, 73.7, 78.0, 84.1, 114.2, 124.4, 130.0, 130.8, 138.0, 159.7, 175.2. EIMS (70 eV) m/z 400 (M$^+$, 3), 345 (20), 270 (5), 121 (100).

5,12-*syn*-2-(4-Methoxy-benzyloxy)-3-methyl-1,2,4*a*,6,6*a*,7,8,9,10,10*a*,11,13*a*-dodecahydro-5,12-dioxa-dibenzo[*a*,*e*]cyclononen-13-one 7m. The triene **3m** was prepared as above from the dioxepane **1m** (150 mg, 1 eq., 0.439 mmol) and used rapidly for the next step, dissolved in THF (8 mL) and then heated at 110 °C in a sealed tube for 5 days. The reaction mixture was evaporated. Flash chromatography on silica gel (DCM–pentane: 90 : 10 as eluant) afforded 47 mg (40%, three steps) of product as a colorless oil. One diastereomer was isolated (*endo*) but diastereoselectivities could not be determined because of the complexity of the crude mixture.

ν_{max} (film)/cm^{-1} 2938, 2852, 1742, 1513, 1248, 1156, 1058, 820. One *endo*-diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.1–1.9 (10H, m), 1.75 (3H, s), 2.34 (1H, dt, J = 3.4, 14.3 Hz), 2.45 (1H, bs) 3.09 (1H, ddd, J = 4.2, 6.0, 13.4 Hz), 3.47 (1H, t, J = 11.4 Hz), 3.79 (4H, m), 4.01 (2H, m), 4.15 (1H, t, J = 11.2 Hz), 4.36 (1H, d, J = 11.3 Hz), 4.58 (1H, d, J = 11.3 Hz), 4.64 (1H, dd, J = 3.0, 11.3 Hz), 5.64 (1H, d, J = 4.5 Hz), 6.86 (2H, d, J = 8.7 Hz), 7.24 (2H, d, J = 8.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.8, 23.1, 24.8, 25.9, 28.7 (2C), 39.7 (3C), 55.7, 67.4, 71.6, 73.8, 77.0, 79.4, 114.2, 124.7, 130.0, 130.8, 137.9, 159.7, 175.5. EIMS (70 eV) m/z 400.2 (M$^+$, 1), 135 (22), 121 (100). HRMS (EI): calcd for $C_{24}H_{32}O_5$: 400.2250; found: M$^+$ 400.2255.

2-Hydroxy-3-methyl-1,2,4*a*,13*a*-tetrahydro-5,12-dioxa-dibenzo[*a*,*e*]cyclononan-13-one 8e. To a solution of adduct **7e** (46 mg,

1 eq., 0.116 mmol) in CH_2Cl_2 (15 mL), were added water (1 mL) and buffer (pH = 7, 1 mL). At room temperature, under agitation dichlorodicyanoquinone (DDQ) (80 mg, 3 eq., 0.348 mmol) was added in one portion, the reaction was followed by TLC and, after 4 h, water (3 mL) was added. The aqueous phase was extracted by DCM (3 × 30 mL), the combined organic phases were dried (Na_2SO_4) and evaporated under a reduced pressure. Flash chromatography on silica gel (heptane–AcOEt, 30 : 70 as eluant) afforded 19.1 mg (56%) of alcohol **8e** as a off white gum.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.69 (1H, bs), 1.83 (3H, s), 1.93 (2H, m), 3.10 (1H, dt, J = 4.5, 12.8 Hz), 4.02 (1H, t, J = 2.8 Hz), 4.50 (1H, t, J = 4.5 Hz), 4.78 (1H, d, J = 10.9 Hz), 4.82 (1H, d, J = 10.9 Hz), 5.37 (1H, d, J = 13.6 Hz), 5.50 (1H, d, J = 13.6 Hz), 5.71 (1H, d, J = 4.0 Hz), 7.24 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.7, 28.6, 40.0, 67.30, 67.32, 76.8, 78.1, 124.4, 128.5, 128.6, 129.1, 133.1, 136.5, 136.9, 139.5, 173.7. EIMS (70 eV) m/z 274 (M^+, 1), 256 ($M^+ - H_2O$, 1), 175 (6), 165 (11), 104 (100). Anal. calcd for $C_{16}H_{18}O_4$: C, 70.06%; H, 6.61%; found: C, 70.05%; H, 6.71%.

2-Hydroxy-3,6,11-trimethyl-1,2,4*a*,13*a*-tetrahydro-5,12-dioxa-dibenzo[*a*,*e*]cyclononan-13-one 8g. The alcohol **8g** was prepared as above from adduct **7g** (200 mg, 1 eq., 0.473 mmol) in CH_2Cl_2 (20 mL) with 2 mL of water and 1.5 mL of buffer (pH = 7). 301 mg (2.8 eq., 1.32 mmol) of DDQ were used and the reaction was stirred during 3 h. After the same treatment, flash chromatography (heptane–AcOEt, 60 : 40 as eluant) afforded 114 mg (80%) of product as a off white gum.

ν_{max} (film)/cm^{-1} 3440, 2980, 2932, 1736, 1170, 1042, 732. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.42 (3H, d, J = 6.2 Hz), 1.56 (1H, s), 1.80 (3H, s), 1.80 (3H, d, J = 6.6 Hz), 2.05 (1H, d, J = 14.3 Hz), 2.25 (1H, dt, J = 4.1, 13.2 Hz), 2.72 (1H, dt, J = 2.6, 13.2 Hz), 4.08 (1H, s), 4.14 (1H, s), 4.84 (1H, q, J = 6.2 Hz), 5.49 (1H, d, J = 5.6 Hz), 6.12 (1H, q, J = 6.6 Hz), 7.34 (3H, m), 7.55 (1H, d, J = 6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 18.5, 21.5, 24.0, 27.4, 39.4, 68.4, 68.7, 69.0, 72.1, 124.6, 125.6, 128.1, 128.5, 129.2, 139.7, 140.9 (2C), 177.4. EIMS (70 eV) m/z 302.2 (M^+, 1), 203 (15), 148 (25), 131 (100). HRMS (EI): calcd for $C_{18}H_{22}O_4$: 302.1518; found: M^+ 302.1512.

2-Hydroxy-6,11-diisopropyl-3-methyl-1,2,4*a*,13*a*-tetrahydro-5,12-dioxa-dibenzo[*a*,*e*]cyclononan-13-one 8j. The alcohol **8j** was prepared as above from adduct **7j** (223 mg, 1 eq., 0.466 mmol) in CH_2Cl_2 (50 mL) with 4 mL of water and 4 mL of buffer (pH = 7). 212 mg (2.0 eq., 0.932 mmol) of DDQ were used and the reaction was stirred during 4 h. After the same treatment, flash chromatography (heptane–AcOEt, 70 : 30 as eluant) afforded 105.4 mg (63%) of product as a off white gum.

ν_{max} (film)/cm^{-1} 3434, 2959, 2871, 1739, 1449, 1172, 760. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.54 (3H, d, J = 6.8 Hz), 0.80 (3H, d, J = 6.8 Hz), 1.18 (6H, d. J = 6.4 Hz), 1.59 (1H, bs), 1.61 (1H, m), 1.76 (3H, s), 2.1 (3H, m), 2.84 (1H, ddd, J = 3.4, 8.3, 13.6 Hz), 3.56 (1H, d, J = 7.8 Hz), 4.17 (1H, bs), 5.17 (1H, d, J = 10.9 Hz), 5.21 (1H, s), 5.38 (1H, d, J = 9.8 Hz), 7.12 (1H, dd, J = 1.5, 7.5 Hz), 7.21 (1H, dt, J = 1.5, 7.5 Hz), 7.28 (1H, dt, J = 1.5, 7.5 Hz), 7.39 (1H, dd, J = 1.5, 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 18.9, 19.6, 19.9, 20.8, 21.3, 34.0, 34.1, 35.4, 48.4, 68.8, 72.5, 79.7, 88.5, 126.9, 127.6, 128.6, 129.5, 131.5, 136.9, 139.3, 141.6, 178.1. EIMS (70 eV) m/z 358 (M^+, 2), 259 (5), 187 (78), 145 (100), 91 (72).

2,3,4-Trihydroxy-3,6,11-trimethyl-1,2,3,4,4*a*,13*a*-hexahydro-5,12-dioxa-dibenzo[*a*,*e*]cyclononan-13-one 9g. To a solution of alcohol **8g** (100 mg, 1 eq., 0.331 mmol) in distillated pyridine (5 mL), was added a solution of OsO_4 in pyridine (0.74 mL, 1.1 eq., 0.364 mmol, 0.492 mmol L^{-1}). After 2.5 h, at room temperature, 1 mL of saturated $NaHSO_3$ was added followed by 1 mL of water. The aqueous phase was extracted by ethyl acetate and the resulting organic phase was dried (Na_2SO_4) and evaporated under a reduced pressure. The ^{1}H NMR spectra of the crude mixture showed only one diastereomer. Flash chromatography on silica gel (heptane–AcOEt, 20 : 80 as eluant) afforded 72 mg (65%) of triol **9g** (off white gum).

ν_{max} (film)/cm^{-1} 3416, 3070, 2981, 2936, 1731, 1453, 1042, 911, 733. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.28 (3H, s), 1.38 (3H, d, J = 6.0 Hz), 1.78 (3H, d, J = 6.6 Hz), 2.08 (2H, m), 2.89 (1H, m), 3.40 (1H, s), 3.72 (4H, bs), 4.00 (1H, s), 4.76 (1H, q, J = 6.0 Hz), 6.06 (1H, q, J = 6.6 Hz), 7.33 (3H, m), 7.52 (1H, d, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 18.5, 23.6, 24.1, 26.2, 35.6, 68.7, 71.6, 72.4, 75.1, 76.2, 78.1, 124.5, 128.2, 128.5, 129.3, 140.4, 140.8, 178.3.

2,3,4-Trihydroxy-6,11-diisopropyl-3-methyl-1,2,3,4,4*a*,13*a*-hexahydro-5,12-dioxa-dibenzo[*a*,*e*]cyclononan-13-one 9j. The triol **9j** was prepared as above starting from alcohol **8j** (75 mg, 1 eq., 0.209 mmol) in 3 mL of pyridine. 0.37 mL (1.15 eq., 0.242 mmol, 0.655 mmol.L^{-1}) of OsO_4 in pyridine were used and the reaction was quenched after 2 h with 1 mL of saturated $NaHSO_3$ and 1 mL of water. After the same treatment, flash chromatography (heptane–AcOEt, 30 : 70 as eluant) afforded 50 mg of triol **9j** as a single diastereomer and 14 mg of a mixture of two diastereomers for a total of 64 mg (78%, de = 88%, determined by ^{1}H NMR from the crude mixture) as a off white gum.

ν_{max} (film)/cm^{-1} 3447, 2921, 2867, 1737, 1157, 1014, 731. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.53 (3H, d, J = 6.8 Hz), 0.82 (3H, d, J = 6.8 Hz), 1.18 (3H, d. J = 6.4 Hz), 1.19 (3H, d. J = 6.4 Hz), 1.36 (3H, s), 1.7–2.3 (6H, m), 2.64 (1H, ddd, J = 4.9, 9.4, 14.3 Hz), 2.97 (1H, bs), 3.18 (1H, dd, J = 9.0, 8.7 Hz), 3.30 (1H, dd, J = 1.5, 8.5 Hz), 3.34 (1H, m), 5.17 (1H, d, J = 10.9 Hz), 5.44 (1H, d, J = 9.8 Hz), 7.1–7.4 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 19.6, 19.9, 20.8, 21.2, 23.0, 30.3, 33.7, 35.4, 45.4, 71.9, 73.4, 76.6, 78.7, 80.1, 88.5, 127.9, 128.7, 129.4, 131.8, 135.5, 141.9, 176.7. EIMS (70 eV) m/z 392 (M^+, 8), 249 (10), 161 (100), 143 (75), 84 (95).

2,3-Acetonide-4-hydroxy-6,11,3-trimethyl-1,2,3,4,4*a*,13*a*-hexahydro-5,12-dioxa-dibenzo[*a*,*e*]cyclononan-13-one (acetonide of 9g). Under an argon atmosphere, triol **9g** (70 mg, 1eq., 0.208 mmol) was dissolved in anhydrous CH_2Cl_2 (5 mL), then 2,2-dimethoxypropane (1 mL) was added followed by a catalytic amount of camphorsulfonic acid. After 4 h, a saturated solution of $NaHCO_3$ (2 mL) was added. The aqueous phase was extracted by DCM (3 × 5 mL) and the resulting organic phase was dried (Na_2SO_4) and evaporated under a reduced pressure to afford 70 mg (90%) of pure titled product as a colorless oil. The regioselectivity was determined by NOESY experiment in which a correlation was observed between the secondary alcohol and the methyl on the benzylic position.

ν_{max} (film)/cm^{-1} 3528, 2982, 2933, 1730, 1169, 1071, 734. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.31 (3H, s), 1.40 (9H, m), 1.78 (3H, d, J = 6.5 Hz), 2.13 (1H, dt, J = 4.1, 13.4 Hz), 2.34 (1H, d, J = 13.4 Hz), 2.78 (1H, bs), 2.97 (1H, d, J = 13.2 Hz), 3.30 (1H, d, J = 3.4 Hz), 4.08 (1H, bs), 4.17 (1H, bs), 4.64 (1H, q, J = 6.0 Hz), 6.00 (1H, q, J = 6.5 Hz), 7.31 (3H, m), 7.50 (1H, d, J = 6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 18.7, 21.9, 23.4, 26.3, 26.7, 35.3, 68.6, 73.0, 74.0, 74.6, 78.9, 79.4, 108.3, 124.6, 128.2, 128.5, 129.2, 140.5, 140.6, 179.2. CIMS (CH_4) m/z 377 (MH^+, 1), 362 (3), 213 (4), 131 (100).

1,2-Acetonide-3-hydroxy-4{1-[2-(1-hydroxyethyl)-phenyl]-ethoxy}-5-hydroymethyl-2-methyl-cyclohexane 10g. A solution of the prior acetonide (70 mg, 1eq., 0.186 mmol) in anhydrous ether (5 mL) was added, at 0 °C, to a solution of $LiAlH_4$ (0.410 mL, 2.2 eq., 1 M in toluene, 0.410 mmol) diluted in ether (5 mL). After the addition, the reaction mixture was stirred at room temperature for 2 h. Then 0.05 mL of water, 0.1 mL of NaOH 4 M and 0.2 mL of water were added successively. The aqueous phase was extracted by ethyl acetate (2 × 10 mL) and the combined organic phases were dried (Na_2SO_4) and evaporated under a reduced pressure. Flash chromatography

on silica gel (heptane–AcOEt, 20 : 80 as eluant) afforded 41 mg (58%) of triol **10g** as a off white gum.

ν_{max} (film)/cm^{-1} 3419, 3064, 2975, 2930, 1372, 1070, 762, 733. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.29 (3H, s), 1.32 (3H, s), 1.35 (3H, s), 1.40 (3H, d, $J = 6.4$ Hz), 1.41 (3H, d, $J = 6.4$ Hz), 1.78 (2H, m), 2.23 (2H, m), 2.80 (1H, s), 3.03 (1H, bs), 3.20 (1H, d, $J = 5.3$ Hz), 3.56 (1H, m), 3.66 (1H, dd, $J = 4.9$, 11.3 Hz), 3.79 (1H, dd, $J = 3.8$, 5.3 Hz), 4.05 (1H, s), 5.05 (1H, q, $J = 6.4$ Hz), 5.24 (1H, q, $J = 6.4$ Hz), 7.26 (2H, m), 7.41 (1H, m), 7.51 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 23.8, 23.9, 24.8, 26.0, 26.3, 26.7, 32.6, 63.9, 65.2, 72.7, 73.3, 74.6, 79.0, 80.2, 108.3, 125.4, 126.8, 127.9, 128.2, 140.7, 143.1. EIMS (70 ev) m/z 362 ($M^+ - H_2O$, 2), 215 (5), 131 (100).

2,3-Acetonide-4-hydroxy-6,11-diisopropyl-3-methyl-1,2,3,4,4*a*, 13*a*-hexahydro-5,12-dioxa-dibenzo[*a*,*e*]cyclononan-13-one (acetonide fo 9j). Under an argon atmosphere, triol **9j** (45 mg, 1eq., 0.115 mmol) was dissolved in anhydrous CH_2Cl_2 (DCM) (5 mL), then 2,2-dimethoxypropane (1 mL) was added followed by a catalytic amount of camphorsulfonic acid. After 4 h, a saturated solution of $NaHCO_3$ (2 mL) was added. The aqueous phase was extracted by DCM (3 × 4 mL) and the resulting organic phase was dried (Na_2SO_4) and evaporated under a reduced pressure. Flash chromatography on silica gel (heptane–AcOEt, 30 : 70 as eluant) afforded 45 mg (90%) of titled product as a colorless oil (90 : 10 mixture of two regioisomers). The regioselectivity was determined by a NOESY experiment in which a correlation was observed between the secondary alcohol and the *i*-Pr protons for the major regioisomer and between the acetonide and the same *i*-Pr group for the minor isomer.

ν_{max} (film)/cm^{-1} 3552, 2975, 2872, 1747, 1167, 732. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.54 (3H, d, $J = 6.8$ Hz), 0.73 (3H, d, $J = 6.8$ Hz), 0.85 (3H, s), 1.14 (6H, m), 1.22 (3H, s), 1.33 (3H, s), 1.71 (1H, ddd, $J = 4.1$, 7.5, 14.7 Hz), 2.14 (3H, m), 2.73 (1H, m), 2.79 (1H, s), 3.20 (1H, t, $J = 7.5$ Hz), 3.30 (1H, dd, $J = 1.1$, 7.2 Hz), 3.91 (1H, dd, $J = 3.8$, 5.3 Hz), 5.17 (1H, d, $J = 10.5$ Hz), 5.38 (1H, d, $J = 9.8$ Hz), 7.10 (1H, d, $J = 6.4$ Hz), 7.16 (1H, d, $J = 6.4$ Hz), 7.28 (1H, d, $J = 6.4$ Hz), 7.40 (1H, d, $J = 6.4$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 19.7, 20.0, 20.7, 21.1, 23.6, 25.3, 25.8, 26.8, 34.2, 34.3, 45.5, 72.8, 76.0, 79.1, 80.6, 80.8, 87.6, 108.4, 127.8, 129.1, 129.6, 131.2, 136.1, 141.4, 176.6. CIMS (CH_4) m/z 417 (10), 247 (6), 187 (84), 131 (51), 59 (100).

1,2-Acetonide-3-hydroxy-5-hydroymethyl-4-{1-[2-(1-hydroxy-2-methyl-propyl)-phenyl]-2-methyl-propyloxy}-2-methyl-cyclohexane 10j. A solution of acetonide (40 mg, 1eq., 0.093 mmol) in anhydrous ether (4 mL) was added, at 0 °C, to a solution of $LiAlH_4$ (0.204 mL, 2.2 eq., 1 M in toluene, 0.204 mmol) diluted in ether (5 mL). After the addition, the reaction mixture was stirred at room temperature for 2 h. Then 0.05 mL of water, 0.1 mL of NaOH 4 M and 0.2 mL of water were added successively. The aqueous phase was extracted by ethyl acetate (2 × 10 mL) and the combined organic phases were dried (Na_2SO_4) and evaporated under a reduced pressure. Flash chromatography on silica gel (heptane–AcOEt, 30 : 70 as eluant) afforded 30 mg (75%) of triol **10j** as a colorless oil.

ν_{max} (film)/cm^{-1} 3419, 2962, 2874, 1463, 1379, 1210, 1059, 733. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.63 (3H, d, $J = 6.4$ Hz), 0.71 (3H, d, $J = 6.8$ Hz), 1.16 (3H, d, $J = 6.4$ Hz), 1.17 (3H, d, $J = 6.4$ Hz), 1.27 (3H, s), 1.30 (3H, s), 1.33 (3H, s), 1.87 (1H, d, $J = 15.8$ Hz), 1.97–2.22 (6H, m), 3.12 (1H, bs), 3.17 (1H, d, $J = 9.4$ Hz), 3.55 (1H, dd, $J = 7.9$, 9.4 Hz), 3.63 (1H, dd, $J = 2.3$, 11.3 Hz), 4.01 (3H, m), 4.84 (1H, d, $J = 7.1$ Hz), 7.12 (2H, m), 7.26 (1H, m), 7.51 (1H, d, $J = 7.9$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 20.0, 20.2, 20.5, 26.1, 26.9, 27.4, 34.8, 35.5 (2C), 65.3, 75.1 (2C), 75.2 (2C), 78.8, 81.8, 109.0, 126.8 (2C), 128.6 (2C), 139.8 (2C).

2-Methyl-5*a*-carba-α-DL-gulopyranose 11. The triol **10g** (30 mg, 1eq., 78.9 μmol) was dissolved in methanol (5 mL) and Pd/C 10% (5 mg) was added. The suspension was stirred under a hydrogen atmosphere for 24 h. The reaction mixture was filtered trough a pad of celite and the resulting filtrate was evaporated under a reduced pressure. Flash chromatography (CH_2Cl_2–MeOH, 60 : 40 as eluant) afforded 13.1 mg (87%) of carbasugar **11** as a off white gum.

ν_{max} (film)/cm^{-1} 3381, 2933, 1650, 1037. ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 1.39 (3H, s), 1.85 (1H, m), 1.95 (1H, dt, $J = 4.6$, 13.4 Hz), 2.29 (1H, m), 3.41 (1H, d, $J = 8.4$ Hz), 3.64 (2H, m), 3.93 (1H, dd, $J = 6.2$, 10.9 Hz), 4.01 (1H, dd, $J = 5.2$, 8.4 Hz). ^{13}C NMR (75 MHz, CD_3OD) 23.7, 30.5, 42.5, 62.2, 72.6, 73.2, 75.5, 77.0. EIMS (70 ev) m/z 174 (M − 18, 5), 157 (20), 138 (100), 119 (85).

2-Methyl-5*a*-carba-β-DL-mannopyranose 12. The triol **10j** (30 mg, 1eq., 68.8 μmol) was dissolved in methanol (5 mL) and Pd/C 10% (10 mg) was added. The suspension was stirred under a hydrogen atmosphere for 22 h. The reaction mixture was filtered trough a pad of celite and the resulting filtrate was evaporated under a reduced pressure. Flash chromatography (CH_2Cl_2–MeOH, 90 : 10, then 50 : 50 as gradient of eluant) afforded 5.1 mg of pure carbasugar **12** as a off white gum and 8.6 mg of a partially hydrogenolyzed derivative (see below for analysis). Total: 48.9 μmol (71%).

ν_{max} (film)/cm^{-1} 3359, 2931, 2885, 1407, 1017. ^{1}H NMR (600 MHz, CD_3OD) δ (ppm) 1.34 (3H, s), 1.51 (1H, m), 1.60 (1H, q, $J = 12.5$ Hz), 1.81 (1H, dt, $J = 4.3$, 12.5 Hz), 3.06 (1H, d, $J = 9.2$ Hz), 3.40 (1H, dd, $J = 4.3$, 12.4 Hz), 3.47 (1H, dd, $J = 8.7$, 9.0 Hz), 3.58 (1H, dd, $J = 6.3$, 10.7 Hz), 3.81 (1H, dd, $J = 3.9$, 10.7 Hz). ^{13}C NMR (75 MHz, CD_3OD) δ (ppm) 23.2, 32.5, 42.5, 65.4, 73.8, 74.6, 76.2, 80.3. CIMS (CH_4) m/z 193 (MH^+, 7), 175 (6), 157 (37), 139 (100).

1,2,3-Hydroxy-5-hydroymethyl-4-[1-(2-isobutyl-phenyl)-2-methyl-propoxy]-2-methyl-cyclohexane (partially hydrogenolyzed derivative). ν_{max} (film)/cm^{-1} 3545, 3417, 2955, 2928, 2869, 1465, 1056, 1017, 733. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.78 (3H, d, $J = 6.4$ Hz), 0.92 (3H, d, $J = 6.4$ Hz), 1.00 (3H, d, $J = 6.4$ Hz), 1.14 (3H, d, $J = 6.4$ Hz), 1.28 (3H, s), 1.76 (2H, m), 1.95 (2H, m), 2.10 (1H, m), 2.25 (1H, bs), 2.37 (3H, bs), 2.52 (1H, dd, $J = 8.3$, 13.9 Hz), 2.73 (1H, dd, $J = 6.4$, 13.9 Hz), 3.19 (1H, d, $J = 7.9$ Hz), 3.44 (2H, m), 3.85 (1H, d, $J = 10.6$ Hz), 3.96 (1H, d, $J = 7.9$ Hz), 4.60 (1H, d, $J = 7.5$ Hz), 7.15 (1H, dd, $J = 1.7$, 7.3 Hz), 7.20–7.30 (2H, m), 7.43 (1H, d, $J = 7.5$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 19.8, 22.6, 23.3, 23.8, 29.9, 32.1, 35.5, 40.5, 41.9, 64.0, 73.2 (2C), 74.1, 77.4, 78.8, 126.4, 127.3, 127.9, 131.2, 140.4, 141.1. EIMS (70 eV) m/z 381.3 (MH^+, 3), 337 (M − (*i*-Pr), 62), 190 (100), 175 (60). HRMS (EI): calcd for $C_{22}H_{36}O_5$: 381.2641; found: MH^+ 381.2632.

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References

1 General reviews on IMDA: (*a*) E. Ciganek, *Org. React.*, 1984, **32**, 1; (*b*) D. Craig, *Chem. Soc. Rev.*, 1987, **16**, 187; (*c*) A. G. Fallis, *Acc. Chem. Res.*, 1999, **32**, 464.

2 M. E. Jung and J. Gervay, *J. Am. Chem. Soc.*, 1991, **113**, 224.

3 (*a*) M. E. Jung and M. Kiankarimi, *J. Org. Chem.*, 1998, **63**, 2968; (*b*) C. Giessner-Prettre, S. Hückel, J. Maddaluno and M. E. Jung, *J. Org. Chem.*, 1997, **62**, 1439; (*c*) D. J. Tantillo, K. N. Houk and M. E. Jung, *J. Org. Chem.*, 2001, **66**, 1938.

4 (*a*) K. J. Shea, W. M. Fruscella, R. C. Carr, L. D. Burke and D. K. Cooper, *J. Am. Chem. Soc.*, 1987, **109**, 447; (*b*) M. J. Batchelor and J. M. Mellor, *J. Chem. Soc., Perkin Trans. 1*, 1989, 985; (*c*) J. D. White, F. W. J. Demnitz, H. Oda, C. Hassler and J. P. Snyder, *Org. Lett.*, 2000, **2**, 3313; (*d*) T. Honda, H. Namiki, M. Kudoh, N. Watanabe, H. Nagase and H. Mizutani, *Tetrahedron Lett.*, 2000, **41**, 5927.

5 (*a*) D. A. Smith, K. Sakan and K. N. Houk, *Tetrahedron Lett.*, 1986, **27**, 4877; (*b*) M. K. Diedrich, F.-G. Klärner, B. R. Beno, K. N. Houk, H. Senerowitz and W. C. Still, *J. Am. Chem. Soc.*, 1997, **119**, 10256.

6 See for instance: (*a*) Y.-F. Lu and A. G. Fallis, *Tetrahedron Lett.*, 1993, **34**, 3367; (*b*) P. J. Ainsworth, D. Craig, J. C. Reader, A. M. Z. Slawin, A. J. P. White and D. J. Williams, *Tetrahedron*, 1995, **51**, 11601; (*c*) P. C. Bulman Page, D. C. Jennens and H. McFarland, *Tetrahedron Lett.*, 1997, **38**, 6913.

7 (*a*) M. Deagostino, J. Maddaluno, C. Prandi and P. Venturello, *J. Org. Chem.*, 1996, **61**, 7597; (*b*) A. M. Deagostino, J. Maddaluno, M. Mella, C. Prandi and P. Venturello, *J. Chem. Soc., Perkin Trans. 1*, 1998, 881.

8 (*a*) R. Ballini, G. Bosica, S. Cossu, O. De Lucchi and P. Peluso, *Tetrahedron*, 2001, **57**, 4461; (*b*) M. Caballero, M. Garcia-Valverde, R. Pedrosa and M. Vicente, *Tetrahedron: Asymmetry*, 1996, **7**, 2.

9 For recent exemples of natural products featuring 8-membered-ring lactones see: (*a*) C. M. Kao, M. McPherson, R. N. McDaniel, H. Fu, D. E. Cane and C. Khosla, *J. Am. Chem. Soc.*, 1997, **119**, 11339; (*b*) J. A. Marco, J. F. Sanz-Cervera, A. Yuste and J. Jakupovic, *J. Nat. Prod.*, 1999, **62**, 110; (*c*) H. Shigemori, S. Shimamoto, M. Sekiguchi, A. Ohsaki and J. Kobayashi, *J. Nat. Prod.*, 2002, **65**, 82; (*d*) K. R. Buszek, N. Sato and Y. Jeong, *Tetrahedron Lett.*, 2002, **43**, 181; (*e*) For 9-membered-ring lactones: K. Iguchi, K. Kajiyama, H. Miyaoka and Y. Yamada, *J. Org. Chem.*, 1996, **61**, 5998; (*f*) D. J. Critcher, S. Connolly and M. Wills, *J. Org. Chem.*, 1997, **62**, 6638; (*g*) M. Gill, A. Gimenez, A. G. Jhingran, N. M. Milanovic and A. R. Palfreyman, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3431.

10 S. Cristol, *Acc. Chem. Res.*, 1971, **4**, 393.

11 (*a*) R. K. Hill and M. G. Bock, *J. Am. Chem. Soc.*, 1978, **100**, 637; (*b*) R. J. Moss and B. J. Rickborn, *Org. Chem.*, 1986, **51**, 1992.

12 F. M. Bickelhaupt, G. J. H. Buisman, L. J. Koning, N. M. M. Nibbering and E. J. Baerends, *J. Am. Chem. Soc.*, 1995, **117**, 9889.

13 S. Handa and H. G. Floss, *Chem. Commun.*, 1997, 153.

14 R. H. Everhardus, A. Peterse, P. Vermeer, L. Brandsma and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, 1974, **93**, 90.

15 (*a*) J. Paust, W. Reif and H. Schumacher, *Liebigs Ann. Chem.*, 1976, 2194; (*b*) C. Mioskowski, S. Manna and J. R. Falck, *Tetrahedron Lett.*, 1984, **25**, 519.

16 P. H. Mason and N. D. Emslie, *Tetrahedron*, 1995, **51**, 2673.

17 (*a*) F. Cominetti, A. Deagostino, C. Prandi and P. Venturello, *Tetrahedron*, 1998, **54**, 14603; (*b*) D. Lançois and J. Maddaluno, *Tetrahedron Lett.*, 1998, **39**, 2335; (*c*) F. Acquadro, H. Oulyadi, P. Venturello and J. Maddaluno, *Tetrahedron Lett.*, 2002, **43**, 8759.

18 P. Venturello, *J. Chem. Soc., Chem. Commun.*, 1992, 1032.

19 A. Guillam, L. Toupet and J. Maddaluno, *J. Org. Chem.*, 1998, **63**, 5110.

20 C. Margot, H. Matsuda and M. Schlosser, *Tetrahedron*, 1990, **46**, 2425.

21 C. Bataille, G. Bégin, A. Guillam, L. Lemiègre, C. Lys and J. Maddaluno, *J. Org. Chem.*, 2002, **67**, 8054.

22 This has been checked for instance with (*E*,*E*)-1,4-diacetoxybutadiene. See: R. R. Schmidt, *Acc. Chem. Res.*, 1986, **19**, 250 and references therein.

23 L. Lemiègre, F. Lesetre, J.-C. Combret and J. Maddaluno, *Tetrahedron*, 2004, **60**, 415.

24 As established by coupling constant measurements as well as NOE experiments on the ethylenic protons.

25 F. E. Romesberg and D. B. Collum, *J. Am. Chem. Soc.*, 1994, **116**, 9187.

26 G. Fraenkel, A. Chow, R. Fleischer and H. Liu, *J. Am. Chem. Soc.*, 2004, **126**, 3983.

27 C. Martin, PhD thesis, University of Rouen, France, 2000.

28 See for an in-depth discussion on this topic: (*a*) D. B. Collum, *Acc. Chem. Res.*, 1992, **25**, 448; (*b*) See also: J. L. Rutherford, D. Hoffmann and D. B. Collum, *J. Am. Chem. Soc.*, 2002, **124**, 264 and references therein.

29 T. Regnier, L. Lemiègre, P. Cardinael, J. Maddaluno, manuscript in preparation.

30 L. Lemiègre, T. Regnier, J.-C. Combret and J. Maddaluno, *Tetrahedron Lett.*, 2003, **44**, 373.

31 (*a*) S. K. Bur, S. M. Lynch and A. Padwa, *Org. Lett.*, 2002, **4**, 473; (*b*) J. D. Ginn and A. Padwa, *Org. Lett.*, 2002, **4**, 1515.

32 T. Honda, H. Namiki, M. Kudoh, N. Watanabe, H. Nagase and H. Mizutani, *Tetrahedron Lett.*, 2000, **41**, 5927.

33 (*a*) Y. Araki and T. Konoike, *J. Org. Chem.*, 1997, **62**, 5299; (*b*) T. Butz and J. Sauer, *Tetrahedron: Asymmetry*, 1997, **8**, 703; (*c*) S. Jarosz, E. Kozlowska and A. Jezewski, *Tetrahedron*, 1997, **53**, 10775; (*d*) B. Plietker, D. Seng, R. Frölich and P. Metz, *Tetrahedron*, 2000, **56**, 873.

34 For a general overview on Lewis acids in cycloadditions see: *Lewis acids in organic synthesis*, ed. H. Yamamoto, Wiley-VCH, Weinheim, 2000. For an efficient application of $Yb(OTf)_3$ as a catalyst of Diels–Alder cycloaddition, see: A. C. Kinsman and M. A. Kerr, *Org. Lett.*, 2000, **2**, 3517.

35 Note that the dioxepane derived from a *meso*-diol remains *meso*, while that derived from a C_2-symmetrical diol is C_1.

36 F. Johnson, *Chem. Rev.*, 1968, **68**, 375.

37 Crystal data†: $C_{18}H_{22}O_4$, $M = 302.36$, monoclinic $P2_1$, $a = 10.004$ Å, $b = 27.001$ Å, $c = 12.181$ Å, $\beta = 95.15°$, $V = 3276.9$ Å^3. $Z = 2$, $\mu = 0.086$ mm^{-1}. Total number of reflections: 26 441, independent reflections: 13 096. $R_{int} = 0.0224$, Final $R = 0.0581$.

38 For reviews, see: (*a*) T. Suami, *Top. Curr. Chem.*, 1990, **154**, 257; (*b*) P. Sears and C.-H. Wong, *Angew. Chem., Int. Ed.*, 1999, **38**, 2300; (*c*) V. H. Lillelund, H. H. Jensen, X. Liang and M. Bols, *Chem. Rev.*, 2002, **102**, 515.

39 G. E. Mc Casland, S. Furuta and L. J. Durham, *J. Org. Chem.*, 1966, **31**, 1516.

40 Reviews: (*a*) T. Suami and S. Ogawa, *Adv. Carbohydr. Chem. Biochem.*, 1990, **48**, 21; (*b*) Among recent papers see: G. Rassu, L. Auzzas, V. Zambrano, P. Burreddu, L. Pinna, L. Battistini, F. Zanardi and G. Casiraghi, *J. Org. Chem.*, 2004, **69**, 1625; (*c*) A. M. Gómez, E. Moreno, S. Valverde and J. C. López, *Eur. J. Org. Chem.*, 2004, 1830.

41 T. Regnier, *DEA report*, Université de Rouen, France, 2003.