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# Synthesis of α,β-unsaturated dioxanes, dioxolanes and dioxepanes by *trans*-acetalisation of dimethylacetals with *meso* or $C_2$-symmetrical 1,2-, 1,3- and 1,4-diols

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**Abstract**—Several *o*-dibenzylic diols were prepared reacting organometallics with *o*-phthalaldehyde at room temperature in ether. The identity of the *meso* and $C_2$-symmetrical (D,L) isomers as well as their ratio were determined by chiral gas chromatography. The *meso* and $C_2$ (racemic) stereoisomeric diols were easily separated by flash chromatography on silica gel. A set of 18 α,β-unsaturated acetals were then prepared reacting those, as well as commercially available 1,2, 1,3 and 1,4 diols, with the corresponding methylacetals in acidic medium. A *trans*-acetalisation procedure adapted to the cases of fragile allylic alcohols or unfavorable 1,6 diols-derived dioxonanes based on a Dean–Stark trapping of methanol was also employed.


## 1. Introduction

The intramolecular Diels–Alder (IMDA) cycloaddition is a remarkably efficient tool for the convergent and stereocontrolled synthesis of functionalized polycyclic systems.[1–3] Classically, the direct-demand version of this reaction relies on trienes featuring an electron-rich dienic moiety and an electron-deficient dienophile. Therefore, research aimed at simple and versatile accesses to such substrates remains of synthetic importance.[4–6] We have previously described a new route to a set of such trienes taking advantage of the sensitivity of α,β-unsaturated cyclic acetals such as dioxolanes or dioxanes to the base-induced conjugate-elimination (Fig. 1).[7,8] The final IMDA step showed this approach could open a relatively efficient route to medium-ring lactones. However, the yield and the stereoselectivity of this reaction is largely depending on the exact structure of the tether connecting the diene to the dienophile, and therefore to the nature of the 'embedded' diol.

To pursue our work on this class of trienes, we thought a detailed investigation on a general access to this sensitive class of reagents would deserve a separate investigation. In particular, our previous study did not address the central problem of the control of the stereogenic centers newly created by the IMDA. Introducing the asymmetry through the diols was a relatively simple way of tackling this problem, provided the chiral elements borne by the tether after ring fission were able to secure the diastereocontrol of the cycloaddition step. In this perspective, one could rely either on the ring fission of chiral cyclic acetals (derived from either non-symmetrical or $C_2$-symmetrical diols), or on the opening of achiral acetals (derived this time from *meso* diols). The alcohol resulting from the action of an achiral base on acetals derived from $C_2$-symmetrical chiral diols will necessarily be chiral while the opening of the *meso* derivatives will require the use of chiral bases to eventually escape their achiral origin (Fig. 2).

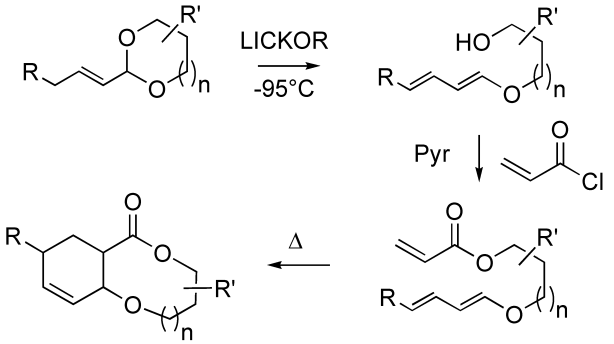


**Figure 1.** From diox(ol)anes to medium-ring lactones (LICKOR=*n*-BuLi+*t*-BuOK).

The aim of this paper is twofold. It first gathers results

*Keywords*: Diols; $C_2$-Symmetry; *meso* Compounds; Acetals.
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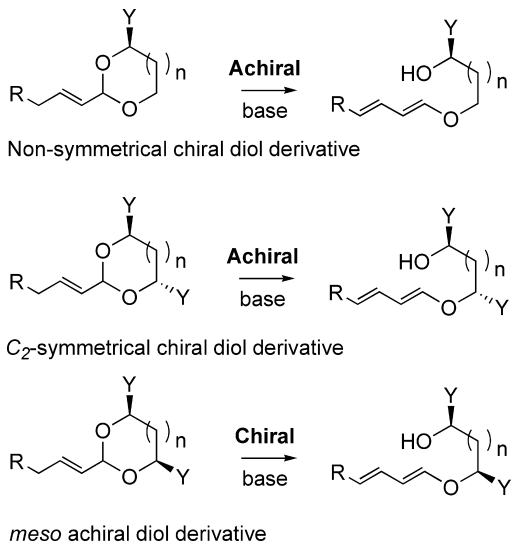
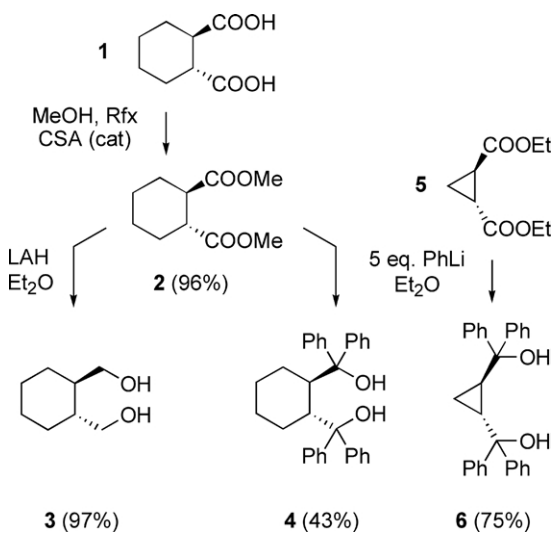



**Figure 2.** Opening acetal derived from $C_2$-symmetrical or *meso* diols.

regarding new 1,4-diols (including a family of dibenzylic diols prepared from *o*-phthalaldehyde) that are good precursors for acetals fitting one or the other of the above categories. It is then centered on the access to α,β-unsaturated cyclic acetals of various sizes through adapted *trans*-acetalisation processes.

## 2. Results and discussion

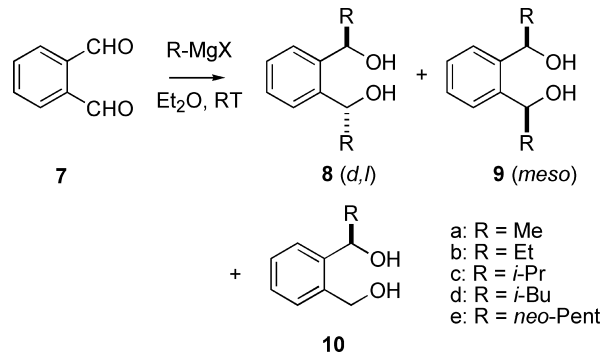
*Synthesis of diols*. A relatively large variety of chiral and achiral 1,2-, 1,3- and 1,4-diols is commercially available and was used directly in the *trans*-acetalisation experiments presented in the next paragraph. In addition, a set of racemic 1,4 diols was prepared in-house by various methods. The *anti*-cyclohexanedimethanol **3** was synthesized from commercially available racemic *anti*-1,2-cyclohexane-dicarboxylic acid **1** (Scheme 1) following a described procedure.[9,10] The addition of an excess of phenyllithium on the intermediate diester **2** led to known[11] dibenzhydrilic diol **4**, following Seebach et al. procedure.[12] Similarly, the cyclopropylic diol **6** was readily prepared from the




**Scheme 1.**

corresponding commercially available diethyl ester **5** (Scheme 1).

For the sake of an easy final deprotection, dibenzylic 1,4-diols **8**, **9** were also considered (Scheme 2). Those were initially prepared as racemic mixtures by direct addition of an excess of alkyl Grignard reagents to *o*-phthalaldehyde **7** by Weyerstahl et al.[13] A stereoselective synthesis of **8b** (R=Et) was later studied by Shibata and colleagues who obtained disappointing results reacting diethyl zinc with **7** in the presence of Ti(*i*-PrO)$_4$ and 1*S*,2*R*-PHONE, a chiral thiophosphoramidate.[14] Simultaneously, Brown et al. described an efficient access to chiral **8f** (R=allyl: d.e.=98%, e.e.≥98%) adding allyldiisopinocampheyl borane also to *o*-phthalaldehyde **7**.[15] This procedure was, however, restricted to allyl derivatives. Very recently, van Koten et al. have obtained high **8/9** ratios and good enantioselectivities reacting **7** in a two-step, one-pot procedure involving first complexation between a chiral aminothiolate and organozincs then Grignard reagents.[16]




**Scheme 2.**

We chose to resort to the convenient Weyerstahl's procedure[12] since racemic $C_2$-symmetrical diols were fully sufficient to later evaluate the IMDA step. However, the diastereoselectivities of the alkylmagnesium reagents addition to *o*-phthalaldehyde, not given in the original paper, remained to be determined. Reacting commercial or home-made solutions of methyllithium or organo-magnesium compounds with **7** in diethyl ether, either following a direct (organometallic added to the dialdehyde) or inverse (vice versa) procedure at room temperature led to the results displayed in Table 1. The D,L and *meso* diastereomers were conveniently identified by a single gas chromatography run on a chiral Supelco β-Dex column, leading to the separation of the diastereomers as well as to the 50:50 splitting of the D,L signal (Fig. 3).

The results in Table 1 call for several comments. First, the amount of diols **10**, a side-product resulting from a single nucleophilic addition and a reduction, seemed related to the bulkiness of the organometallic reagent employed (entries 1–10). Obviously, this remark did not apply to nucleophiles devoid of β-protons such as neo-pentylmagnesium bromide or bulky such as *t*-butylmagnesium chloride (entries 11 and 12). Interestingly in this latter case, a lactol resulting from a single addition and analogous to that isolated by van Koten from organozinc reagents, was obtained in good yield in ether (but not in THF, following a direct or an inverse procedure). Note also that neither the solvent (diethylether

**Table 1**. Addition of organometallics to *o*-phthalaldehyde at room temperature (Scheme 1)

| Entry | Reagent | Solvent | Addition[a] | Yield (%)[b] | **8/9/10** |
|---|---|---|---|---|---|
| 1 | MeLi | $Et_2O$ | Inverse | 92 | 39:61:0 |
| 2 | EtMgBr | $Et_2O$ | Direct | 63 | 62:21:17 |
| 3 | *i*-PrMgCl | $Et_2O$ | Direct | 72 | 59:10:31 |
| 4 | *i*-PrMgCl | THF | Direct | 68 | 70:8:22 |
| 5 | *i*-PrMgCl | $Et_2O$ | Inverse | 67 | 48:15:37 |
| 6 | *i*-PrMgBr | $Et_2O$ | Inverse | 66 | 41:10:49 |
| 7 | *i*-PrMgBr | THF | Inverse | 51 | 65:14:21 |
| 8 | *i*-BuMgCl | $Et_2O$ | Inverse | 84 | 24:10:66 |
| 9 | *i*-BuMgCl | $Et_2O$ | Inverse | 68 | 23:14:63 |
| 10 | *i*-BuMgBr | THF | Inverse | 61 | 26:8:66 |
| 11 | *neo*-Pent-MgBr | $Et_2O$ | Direct | 16[c] | 100:0:0 |
| 12 | *t*-BuMgCl | $Et_2O$ | Direct | 83[d] | 0:0:0 |

[a] The organometallic was added to the aldehyde solution (direct) or vice versa (inverse).
[b] Overall yield calculated for **8**+**9**+**10**.
[c] Only diol **8e** was isolated from the crude reaction mixture.
[d] Only lactol B (Fig. 4, R=*t*-Bu) was obtained in this case.

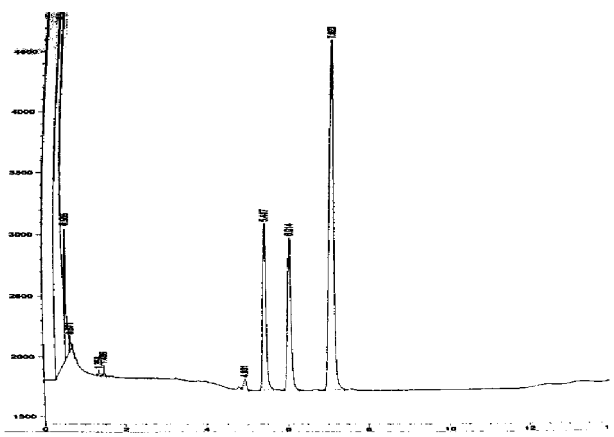


**Figure 3.** GC chromatograms of a mixture of diols D,L **8a** and *meso* **9a** on a Supelco β-Dex chiral column.

versus THF, entries 3 and 4), the Grignard counterion (chloride or bromine, entries 5 and 6 or 9 and 10) nor the order of the introduction of the reagents (direct versus inverse, entries 3 and 5) seem to have a significant influence neither on the yields nor on the selectivities.

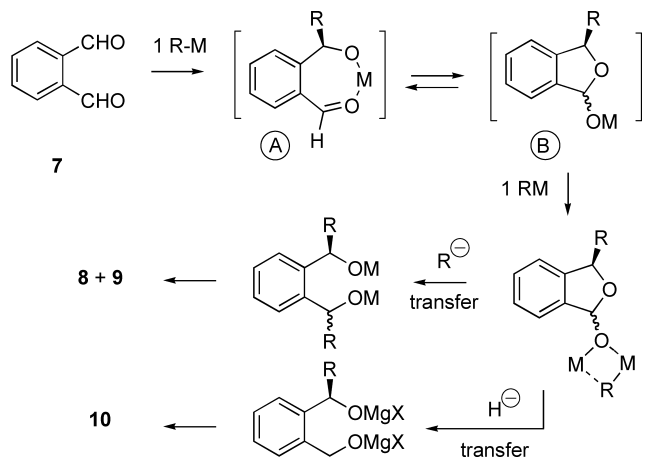


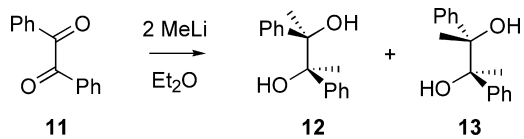

**Figure 4.** Proposed mechanism for the addition of Grignard reagents to *o*-phthalaldehyde **7**.

These data provide hints on the mechanism of this reaction (Fig. 4). The alcoholate resulting from the first addition can be regarded either as an aldehyde undergoing an intramolecular Lewis acid activation (form A) or, more likely, as a lactolate (form B). This later can probably further aggregate with a second equivalent of the organometallic leading

- to the expected $SN_2$ type substitution with smaller nucleophiles, opening the temporary 5-membered heterocycle and yielding diols **8** and **9** (on structure B) or to the nucleophilic addition on the aldehyde (on form A), in ratios obviously depending on the size of R.
- to a β-hydride transfer with cumbersome reagents (such as *i*-propyl or *i*-butyl magnesium chloride), triggering the second aldehyde reduction and thus leading to diols **10** plus the corresponding olefin.

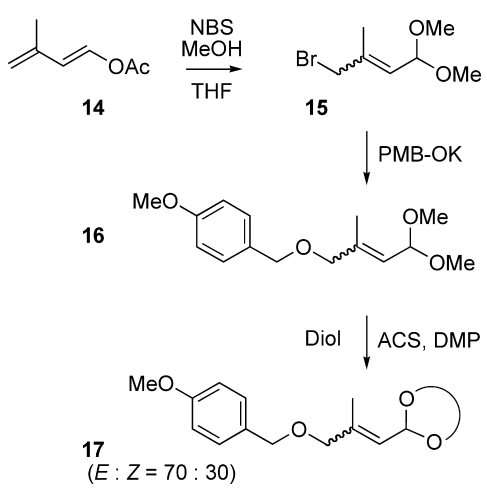
This mechanism fits the various observations in Table 1. Similar side-product and steric effects, such as a diastereoselectivity increase in favor of the D,L isomer induced by the bulky nucleophiles, have also been underlined by van Koten.[15]

Finally, benzil **11** was treated with 2 equiv. methyllithium in ether (Scheme 3). The expected diols **12** and **13** were obtained in 64% yield and 84% d.e. (in favor of *meso* **13**), in perfect agreement with the literature results, obtained in THF.[17]




**Scheme 3.**

*Synthesis of cyclic acetals*. We have recently reported[18] that dimethylacetal **16** can be prepared (as a *E*/*Z* mixture ≈70:30) in very high yields from isoprenyl acetate **14** following the efficient method of Venturello and colleagues[19] (Scheme 4). The poor control of the double bond configuration in **15** and **16** is meaningless here since we have shown in similar situations that this parameter has




**Scheme 4.**

little, if any, effect on the stereocontrol of the diene resulting from the elimination reaction.[20] Also, we retained a *p*-methoxybenzyl (PMB) ether substituent as an easily removable protecting group from the perspective of possible applications of these synthons to sugars and carbasugars synthesis.

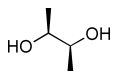
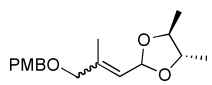
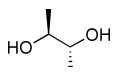
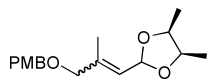
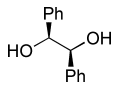
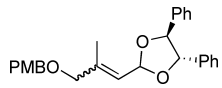
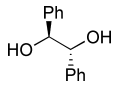
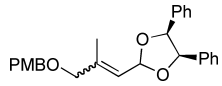
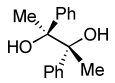
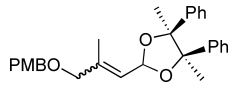
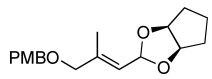
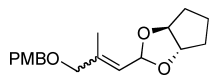
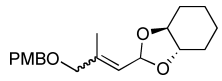
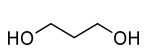
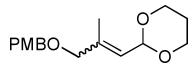
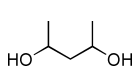
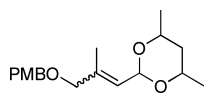
In Venturello's procedure, the reacting alcohol (methanol) is introduced as a co-solvent to THF. This can be a drawback when it comes to heavy (or expensive) diols that, if used in large excess, render the purification stage tedious or the experiment exceedingly costly. We, therefore, resorted to a *trans*-acetalisation procedure expected to favor the transformation of acyclic **16** to cyclic ketals **17**. Practically, this was achieved in most cases by simply adding 1.2–2.2 equiv. of diol to acetals **16** in the presence of trace amounts of dry camphorsulfonic acid (CSA) and 2,2-dimethoxypropane.[21] A few alterations to this general procedure turned out to be necessary for some diols, and they are presented below.

Three different families of chiral (racemic) or achiral 5, 6 and 7-membered cyclic acetals (dioxolanes, dioxanes and dioxepanes) were thus prepared, as well as one example of nine-membered acetal (dioxonane), from either commercially available diols or those described above (Tables 2 and 4).

The results in Table 2 deserve some comments. First, the yields were in general relatively good, and in all cases the configuration of the double bond remained unchanged. All the acetals derived from *meso* diols were obtained as a mixture of stereoisomers, the acetalic proton being oriented *cis* or *trans* to the two *syn* X substituents of the heterocycle (Fig. 5). The acetalic carbon is in this case pseudo-asymmetric (it bears two identical substituents but one is *R* and the other *S*) and can be defined as *r* or *s*,[22] keeping in mind that the *R* center has priority over the *S* one. The proportions between these pseudo-diasteromers as well as the configuration of the major one could be determined in a few cases through NOESY experiments (Table 3). Obviously, acetals derived from *anti* diols do not exhibit this pseudo-asymmetry feature.

Entries 7 and 8 of Table 2 show that the *trans*-relationship in 1,2-diols borne by five or six-membered rings is not compatible with the dioxolane ring closure. The strain generated by such *trans* ring-junctions is probably at the

**Table 2**. Chiral (racemic) and *meso* diox(ol)anes prepared from acetal **16** (Scheme 4)

| Entry | Diol | Equiv. | Acetal | Compound no. | Yield (%) |
|---|---|---|---|---|---|
| 1 |  | 1.5 |  | **17a** | 100 |
| 2 |  | 1.2 |  | **17b** | 59 |
| 3 |  | 1.2 |  | **17c** | 70 |
| 4 |  | 1.2 |  | **17d** | 53 |
| 5 |  | 1.2 |  | **17e** | 43 |
| 6[a] |  | 1.5 |  | **17f** | 64 |
| 7 |  | 1.5 |  | **17g** | 0 |
| 8 |  | 1.7 |  | **17h** | 0 |
| 9 |  | 2.2 |  | **17i** | 80 |
| 10 |  | 1.3 |  | **17j** | 73 |

[a] The *trans*-acetalisation was run on pure (*E*)-**16** in this case.

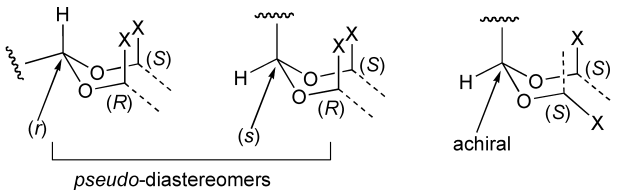



**Figure 5.** Symmetry elements in acetals derived from *meso* (left) or $C_2$-symmetrical (right) diols.

**Table 3**. *cis*/*trans* Ratios in acetals **17** derived from *meso* diols

| Entry | Acetal | *cis*/*trans* |
|---|---|---|
| 1 | **17b** | 77:23 |
| 2 | **17k** | 50:50 |
| 3 | **17p** | 80:20 |
| 4 | **17u** | 66:33 (*E*)<br>50:50 (*Z*) |

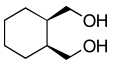
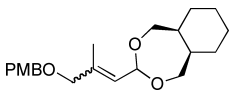
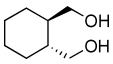
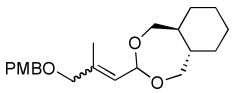
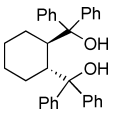
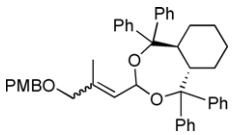
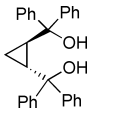
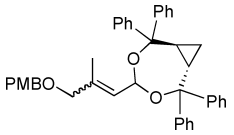
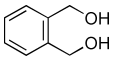
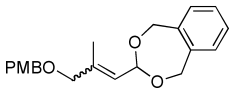
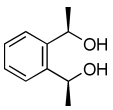
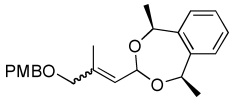
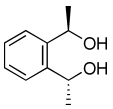
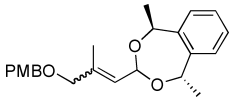
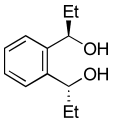
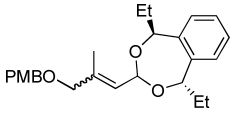
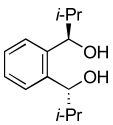
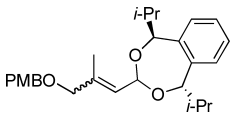
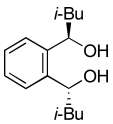
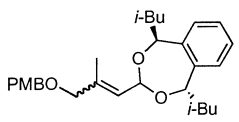
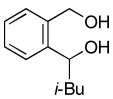
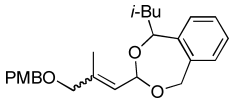
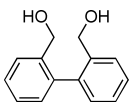
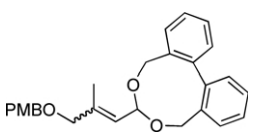
origin of this failure, as inferred from a semiempirical (AM1) study.[23]

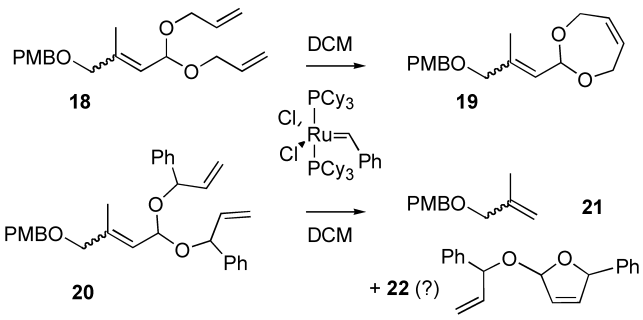
When it comes to dioxepanes and dioxonanes (Table 4), the same protocol can be followed, albeit the use of dimethoxypropane is not recommended in entries 6, 7, 10, and 11 since it reacts with the corresponding diols, yielding an entangled mixture of acetals. The *trans*-acetalisation with the two TADDOL-like diols (entries 3 and 4) failed, probably because of the high stabilization of the triply-benzylic intermediate cations. Entries 6–10 rely on dibenzylic diols **8** and **9** described above. The *trans*-acetalisation yields tended to decrease with the increasing size of the benzylic substituents. One unsymmetrical acetal (**17u**, entry 11) and one dioxonane (**17v**, entry 12) were also prepared, respectively, from mono-alkylated diol **10d** or from commercially available 2,2′-biphenyldimethanol, a model for biarylic diols featuring a chiral axis. With **10d**, the standard *trans*-acetalisation procedure proved efficient, while it did not yield any identified product in the case of biphenyldimethanol. The classical sulfuric acid catalysis and Dean–Stark trapping at reflux of benzene[24] also proved too harsh for **16**. Actually, only a few syntheses of such acetals have been reported. Finally, a methanol/dichloromethane azeotropic distillation in presence of trace amounts of acetic acid,[25] afforded **17v** in 51% yield. The very fragile allylic acetals **18** and **20** were obtained following this same procedure in 53 and 60% conversion, respectively. Actually, **18** was prepared in an attempt to access dioxepine **19** by a ring closing metathesis (RCM). We resorted for this step to the use of a ruthenium carbene complex (Grubb's catalyst)[26] that has previous been reported to perform RCM of other acid sensitive substrates.[25] Unfortunately, it led here to a partial or total failure (Scheme 5). Dioxepine **19** was indeed obtained, but in only 27% after 12 h at room temperature.

Its dibenzylic analogue **20** led to a complex mixture out of which only olefin **21** could be characterized. This by-product suggests that the RCM takes place rather between the trisubstituted inner double bond and one of the terminal allyl groups than between the two acetalic appendages. The complementary cyclic mixed-acetal **22** should therefore be obtained as well, although we did not isolate this fragile looking compound.

The origin of this unexpected difficulty probably stems from the strong preference for a five-membered ring closing over a seven-membered one. A comparable competition, leading

**Table 4**. Chiral (racemic) and *meso* dioxepanes and dioxonane prepared from acetal **16** (Scheme 4)

| Entry | Diol | Equiv. | Acetal | No. | Yield (%) |
|---|---|---|---|---|---|
| 1 |  | 1.5 |  | **17k** | 61 |
| 2 |  | 1.3 |  | **17l** | 54 |
| 3 |  | 1.3 |  | **17m** | 0 |
| 4 |  | 1.2 |  | **17n** | 0 |
| 5 |  | 1.2 |  | **17o** | 70 |
| 6 |  | 1.5 |  | **17p** | 81 |
| 7 |  | 1.5 |  | **17q** | 60 |
| 8 |  | 1.5 |  | **17r** | 67 |
| 9 |  | 1.5 |  | **17s** | 50 |
| 10 |  | 1.5 |  | **17t** | 52 |
| 11 |  | 1.5 |  | **17u** | 68 |
| 12 |  | 2.0 |  | **17v** | 51 |




**Scheme 5.**

to a similar conclusion, has been published by Harrity and colleagues lately.[25]

## 3. Conclusion

The results presented in this paper describe a family of dibenzylic diols prepared by double addition of alkylmagnesium reagents onto *o*-phthalaldehyde. This procedure provided, in most cases, the D,L diastereomers as the major products. These compounds, together with a set of homemade or commercially available 1,2, 1,3 or 1,4 diols were reacted with α,β-unsaturated dimethyl acetal **16**. A standard acidic *trans*-acetalisation procedure provided the expected dioxolanes, dioxanes and dioxepanes in medium to good yields. For dioxonane or allylic acetals, an azeotropic trapping of methanol was found necessary. An attempt to cyclize the latter allylic acetals using Grubb's catalyst turned out unsuccessful. Despite this final failure, 18 different cyclic acetals were prepared that are potential substrates for the base-induced conjugated ring-fission, the transformation of the corresponding alcoholates into trienic substrates as well as the thermal and hyperbaric IMDA final step. These results will be reported in a near future.

## 4. Experimental

### 4.1. General remarks

$^1$H NMR spectra were recorded at 300 MHz and $^{13}$C NMR spectra at 75 MHz; chemical shift ($\delta$) are given in parts per million (ppm) and the coupling constants ($J$) in Hertz. The solvent was deuterochloroform or deuterobenzene. IR spectra were recorded by transmission. Gas chromatography analysis were performed on high resolution DB-1 or HP-5MS columns (30 m×0.25 mm×0.25 μm). GC/MS analysis were performed on instruments equipped with the same columns. The chiral gas chromatography runs were performed on a Supelco β-Dex column (15 m× 0.25 mm×0.25 μm). 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.

**4.1.1. *anti*-Cyclohexane dimethanol (3).** A solution of diester **2** (2.00 g, 1 equiv., 9.99 mmol, prepared refluxing commercial *anti*-cyclohexane-1,2-dicarboxylic acid in methanol containing camphorsulfonic acid) in ether (50 mL) was added to a dispersion of LAH (1.52 g, 3.6 equiv., 36.3 mmol) in ether (20 mL). After 2 h, $H_2O$ (2 mL), NaOH 4 M (2 mL) and $H_2O$ (6 mL) were added successively into the reaction mixture. The aqueous phase was extracted by ether (3×15 mL), the combined organic phases were dried ($Na_2SO_4$) and evaporated under reduce pressure to afford 1.38 g (96%) of diol **3** as a white solid (mp=60 °C) pure enough to be used as such. $\nu_{max}$ (film)/cm$^{-1}$ 3301, 2914, 2848, 1428, 1020. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.00 (m, 2H), 1.23 (m, 4H), 1.58 (d, $J$=13.6 Hz, 2H), 1.71 (m, 2H), 3.47 (dd, $J$=6.4, 10.7 Hz, 2H), 3.57 (d, $J$=10.7 Hz, 2H), 4.09 (s, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=26.5, 30.2, 45.2, 68.1. EIMS (70 eV) *m/z* 144 ($M^{+\cdot}$, 0.3), 126 ($M^{+\cdot}-18$, 11), 108 (8), 96 (100), 81 (67). Anal. Calcd for $C_8H_{16}O_2$: C, 66.63%; H, 11.18%. Found: C, 66.58%; H, 11.26%.

**4.1.2. 1,2-Bis(1-hydroxyethyl)benzene (8a, 9a).** A solution of *o*-phthalaldehyde (4.0 g, 1 equiv., 29.8 mmol) in ether (30 mL), was added, at room temperature, to a solution of MeLi (65 mL, 3.5 equiv., 1.6 mol L$^{-1}$, 104.3 mmol) in ether (30 mL). The reaction mixture was stirred for 3 h, before $H_2O$ (10 mL) then HCl 1 N (20 mL) were added carefully. The pH of the aqueous phase was brought to 5 then extracted with ether (3×20 mL) and the combined organic phases were dried ($Na_2SO_4$) and evaporated under reduce pressure. The ratio **8a/9a/10a** was found to be, in the crude mixture, 40:60:0 according to GC. Most of the *syn* isomer was selectively precipitated out of a 60:40, heptane/AcOEt mixture. The two isomers in the residual liquor were separated by flash chromatography (eluting with heptane/AcOEt, 40:60). The total amount in diols (**8a**+**9a**) was 4.5 g (92%), the *syn* isomer being isolated as a white solid (mp=90 °C) and the *anti* one as a colorless oil.

$\nu_{max}$ (film)/cm$^{-1}$ 3354, 2974, 2928, 1448, 1372, 1068, 734. *syn* Isomer **8a**. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.54 (d, $J$=6.6 Hz, 6H), 2.53 (bs, 2H), 5.25 (q, $J$=6.6 Hz, 2H), 7.32 (m, 2H), 7.50 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=23.7, 65.9, 125.7, 128.4, 142.4. *anti* Isomer **9a**. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.55 (d, $J$=6.4 Hz, 6H), 2.16 (bs, 2H), 5.25 (q, $J$=6.4 Hz, 2H), 7.29 (m, 2H), 7.47 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=24.8, 67.5, 126.5, 128.1, 142.6. EIMS (70 eV) *m/z* 148 ($M^{+\cdot}-18$, 32), 133 (100), 105 (58), 77 (54). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26%; H, 8.49%. Found: C, 72.14%; H, 8.85%.

**4.1.3. 1,2-Bis(1-hydroxypropyl)benzene (8b, 9b).** *Direct procedure*. A solution of ethylmagnesium bromide (1.8 mL, 3 M, 3.5 equiv., 5.2 mmol) in ether was added dropwise, at room temperature, to a solution of *o*-phthalaldehyde (0.20 g, 1 equiv., 1.5 mmol) also in ether (3 mL). The reaction mixture was stirred for 1 h and 30 min. Then $H_2O$ (2 mL) and HCl 1 N (4 mL) were added carefully. The pH of the aqueous phase was brought to 5 and extracted with ether (3×5 mL). The resulting organic phase was dried ($Na_2SO_4$) and evaporated under reduce pressure. The ratio **8b/9b/10b** was found to be, in the crude mixture, 62:21:17 according to GC. A flash chromatography afforded the pure *anti* isomer **8b** as a white solid (mp=77 °C) The others diols were not

separated and a total of 0.18 g **8b**+**9b**+**10b** was recovered (63%).

*Compound* **8b**. $\nu_{max}$ (film)/cm$^{-1}$ 3286, 2964, 1456, 1326, 972, 754. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=0.95 (t, $J$=7.5 Hz, 6H), 1.81 (m, 4H), 2.40 (s, 2H), 4.88 (t, $J$=5.8 Hz, 2H), 7.26 (m, 2H), 7.39 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=11.1, 31.8, 72.9, 126.8, 128.1, 141.8. EIMS (70 eV) $m/z$ 176 ($M^{+\cdot}-18$, 4), 165 (24), 147 (100), 129 (69), 91 (39). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19%; H, 9.34%. Found: C, 74.21%; H, 9.39%.

*Compound* **9b**. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=0.89 (t, $J$=7.4 Hz, 6H), 1.72 (m, 4H), 2.69 (s, 2H), 4.74 (t, $J$=6.0 Hz, 2H), 7.23 (m, 4H).

*Compound* **10b**. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=0.91 (t, $J$=9.0 Hz, 6H), 1.69 (s, 1H), 1.82 (m, 2H), 2.62 (s, 1H), 4.60 (d, $J$=12.1 Hz, 1H), 4.71 (d, $J$=12.1 Hz, 1H), 4.78 (t, $J$=7.1 Hz, 1H), 7.20 (m, 4H).

**4.1.4. 1,2-Bis(1-hydroxy-2-methylpropyl)benzene (8c, 9c) and 1-(2-hydroxymethyl-phenyl)-2-methyl-propan-1-ol (10c).** These compounds were prepared as above following either a direct or inverse procedure, in ether or THF and with *i*-propylmagnesium chloride or bromide (See Table 1).

*Direct procedure in ether with isopropylmagnesium chloride*. To a solution of *o*-phthalaldehyde (0.20 g, 1 equiv., 1.5 mmol) in ether (4 mL) was added, dropwise and at room temperature, a solution of isopropylmagnesium chloride (2.8 mL, 3.5 equiv., 2.0 M, 5.2 mmol). After 1.5 h of reaction and the same treatment, a GC analysis of the crude mixture led to a **8c/9c/10c** ratio=59:10:31. A flash chromatography (eluting with heptane/AcOEt, 60:40) afforded 23 mg of alcohol **10c**, as a yellowish oil, 94 mg of diol *anti* **8c**, as a colorless oil and 10 mg of its *syn* isomer **9c**, as a white solid (mp=70 °C). Total amount of products: 1.1 mmol (72%).

*Inverse procedure in THF with isopropylmagnesium bromide*. The isopropylmagnesium bromide was prepared from 2-bromopropane (0.55 g, 3 equiv., 4.5 mmol) in THF (3 mL) and 0.11 g of magnesium shaves (3 equiv., 4.5 mmol) in THF (1 mL). After 1 h of stirring at room temperature, a solution of *o*-phthalaldehyde (0.20 g, 1 equiv., 1.5 mmol) in THF (3 mL) was added dropwise. The same work-up and analysis led to a **8c/9c/10c** ratio=65:14:21 in an overall yield of 51%.

*Compound* **8c/9c**. $\nu_{max}$ (film)/cm$^{-1}$ 3420, 3064, 2958, 2872, 1468, 1002, 760. *anti* Isomer **8c**. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=0.79 (d, $J$=6.8 Hz, 6H), 1.07 (d, $J$=6.4 Hz, 6H), 1.98 (s, 2H), 2.02 (m, 2H), 4.64 (d, $J$=7.9 Hz, 2H), 7.27 (m, 2H), 7.40 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=19.0, 20.0, 35.4, 76.6, 127.0, 127.9, 141.5. *syn* Isomer **9c**. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=0.75 (d, $J$=6.8 Hz, 6H), 1.10 (d, $J$=6.4 Hz, 6H), 2.10 (m, 2H), 2.15 (s, 2H), 4.61 (d, $J$=8.3 Hz, 2H), 7.28 (m, 2H), 7.41 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=19.3, 20.3, 34.5, 75.7, 127.1, 128.2, 141.6. CIMS ($CH_4$) $m/z$ 205 ($MH^+-18$, 39), 187 (15), 161 (46), 143 (55), 91 (100). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63%; H, 9.97%. Found: C, 75.76%; H, 10.09%.

*Compound* **10c**. $\nu_{max}$ (film)/cm$^{-1}$ 3453, 3064, 2958, 1468, 1013, 759. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=0.76 (d, $J$=6.8 Hz, 3H), 1.11 (d, $J$=6.4 Hz, 3H), 2.11 (m, 1H), 2.49 (s, 2H), 4.53 (d, $J$=8.3 Hz, 1H), 4.73 (s, 2H), 7.33 (m, 4H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=19.6, 20.0, 34.4, 63.4, 77.7, 127.9, 128.0, 128.5, 129.9, 138.3, 142.3. CIMS ($CH_4$) $m/z$ 162 ($M^{+\cdot}-18$, 29), 161 (76), 143 (33), 119 (87), 91 (100). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30%; H, 8.95%. Found: C, 73.25%; H, 9.49%.

**4.1.5. 1,2-Bis(1-hydroxy-3-methylbutyl)benzene (8d, 9d) and 1-(2-hydroxymethyl-phenyl)-3-methyl-butan-1-ol (10d).** *Inverse procedure*. A solution of *o*-phthalaldehyde (2.00 g, 1 equiv., 14.9 mmol) in ether (30 mL) was added to a solution of isobutylmagnesium chloride (30 mL, 4 equiv., 2.0 mol L$^{-1}$, 60.0 mmol) in the same solvent (20 mL). After 1.5 h of reaction, a work-up and analysis as above led to a **8c/9c/10c** ratio=24:10:66. A flash chromatography (eluting with heptane/AcOEt, 60:40) afforded 1.60 g of **10d**, as a white solid (mp=85 °C), 750 mg of diol *anti* **8d**, as a white solid (mp=79 °C) and 340 mg of diol *syn* **9d**, also as a white solid (mp=51 °C) in an overall yield of 84%.

*Compound* **8d/9d**. $\nu_{max}$ (film)/cm$^{-1}$ 3317, 3061, 2952, 2867, 1462, 1054, 760. *anti* Isomer **8d**. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=0.97 (d, $J$=6.4 Hz, 6H), 0.99 (d, $J$=7.1 Hz, 6H), 1.51 (m, 2H), 1.78 (m, 2H), 1.84 (m, 2H), 1.96 (d, $J$=3.4 Hz, 2H), 5.08 (dt, $J$=3.4, 9.0 Hz, 2H), 7.27 (m, 2H), 7.44 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=22.3, 23.9, 25.5, 48.5, 69.3, 126.4, 128.1, 142.1. *syn* Isomer **9d**. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=0.97 (d, $J$=6.4 Hz, 6H), 0.99 (d, $J$=7.1 Hz, 6H), 1.46 (m, 2H), 1.83 (m, 4H), 1.95 (d, $J$=3.4 Hz, 2H), 5.16 (dt, $J$=3.4, 9.2 Hz, 2H), 7.30 (m, 2H), 7.48 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=22.3, 24.0, 25.5, 48.5, 67.9, 126.2, 128.3, 142.2. CIMS ($CH_4$) $m/z$ 233 ($MH^+-18$, 9), 231 (21), 215 (83), 175 (82), 159 (100), 147 (59). Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75%; H, 10.47%. Found: C, 77.21%; H, 10.57%.

*Compound* **10d**. $\nu_{max}$ (film)/cm$^{-1}$ 3295, 2954, 2866, 1463, 1041, 763. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=0.97 (d, $J$=6.4 Hz, 3H), 0.98 (d, $J$=6.4 Hz, 3H), 1.61 (m, 1H), 1.83 (m, 2H), 2.47 (bs, 1H), 2.53 (bs, 1H), 4.70 (dd, $J$=4.5, 12.1 Hz, 1H), 4.80 (dd, $J$=3.8, 12.1 Hz, 1H), 5.03 (bs, 1H), 7.3–7.5 (m, 4H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=22.5, 23.8, 25.5, 46.6, 64.3, 70.0, 126.9, 128.2, 128.9, 130.2, 138.4, 143.3. CIMS ($CH_4$) $m/z$ 191 (10), 175 (21), 159 ($MH^+-36$, 100), 119 (37). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19%; H, 9.34%. Found: C, 74.24%; H, 9.52%.

**4.1.6. 1,2-Bis(1-hydroxy-3,3-dimethylbutyl)benzene (8e).** *Inverse procedure*. The neopentylmagnesium bromide was prepared from 1-bromo-3,3-dimethyl-butane (10.1 g, 3 equiv., 66.9 mmol) in ether (20 mL) and 1.63 g of magnesium shaves (3 equiv., 67.1 mmol) in THF (20 mL). After 1 h of stirring at room temperature, a solution of *o*-phthalaldehyde (3.00 g, 1 equiv., 22.4 mmol) in ether (20 mL) was added dropwise. After 2 h, the reaction was

quenched by 50 mL of saturated ammonium chloride; the rest of the work-up was as above and led to a complex mixture out of which a flash chromatography on silica gel (eluting with cyclohexane/AcOEt, 60:40 mixture) afforded 1.00 g *anti* diol **8e** as a colorless oil (16%). $\nu_{max}$ (film)/cm$^{-1}$ 3418, 2952, 2868, 1476, 1364, 1058, 734. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.04 (m, 18H), 1.61 (dd, $J$=2.6, 14.7 Hz, 2H), 1.81 (dd, $J$=9.0, 14.7 Hz, 2H), 1.98 (s, 2H), 5.18 (d, $J$=9.0 Hz, 2H), 7.26 (m, 2H), 7.44 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=30.7, 31.3, 52.8, 69.2, 126.7, 128.0, 142.9. CIMS ($CH_4$) $m/z$ 261 ($MH^+-18$, 5), 243 ($MH^+-36$, 11), 189 (100), 173 (21), 161 (18), 133 (28).

**4.1.7. 3-*t*-Butyl-1,3-dihydro-isobenzofuran-1-ol (B with R=*t*-Bu and M=H).** *Inverse procedure*. A solution of *o*-phthalaldehyde (0.20 g, 1 equiv., 1.5 mmol) in ether (3 mL) was added dropwise and at room temperature, to a solution of *t*-butylmagnesium chloride (2.6 mL, 2 M, 3.5 equiv., 5.2 mmol) in ether. After 1.5 h of reaction, a work-up and analysis as above led to a yellow oil that was purified by flash chromatography on silica gel (eluting with cyclohexane/AcOEt, 70:30 mixture). A pale yellow oil (235 mg), identified as an unseparable mixture (75:25) of the *syn* and *anti* diastereomers of lactol **B**, was recovered in an overall yield of 83%.

*syn Isomer*. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=0.89 (s, 9H), 3.00 (d, $J$=8.7 Hz, 1H), 4.98 (d, $J$=2.3 Hz, 1H), 6.40 (dd, $J$=8.7, 2.3 Hz, 1H), 7.20 (m, 4H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=26.0, 36.5, 91.5, 101.0, 123.0 -141.0 unidentified aromatic peaks together with isomer *anti*.

*anti Isomer*. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=0.98 (s, 9H), 2.99 (d, $J$=8.3 Hz, 1H), 4.80 (s, 1H), 6.31 (d, $J$=8.3 Hz, 1H), 7.22 (m, 4H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=26.4, 35.0, 92.2, 100.0, 123.0–141.0 unidentified aromatic peaks together with isomer *syn*.

**4.1.8. 2,3-Diphenyl-butane-2,3-diol (12 and 13).** To a solution of 1,2-diphenyl-ethane-1,2-dione (benzil, 2.5 g, 1 equiv., 11.9 mmol) in ether (20 mL), were added 20 mL of a solution of MeLi/LiBr (1:1) in ether at 0 °C. The reaction mixture was then stirred at room temperature for 2 h and 30 min. Next, 20 mL of HCl (3 M) were added and the resulting aqueous phase was extracted by ether (3×15 mL). The combined organic solutions were dried ($Na_2SO_4$) and evaporated under reduce pressure. The residue was precipitated in heptane/ether (80:20) to afford 1.85 g (64%) of a mixture of diols **12** and **13** as a white solid (mp=111 °C) and with a *syn*/*anti*: 92:8 ratio as determined by NMR. $\nu_{max}$ (film)/cm$^{-1}$ 3508, 3058, 2982, 1598, 1445, 900. *syn* Isomer **12**. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.58 (s, 6H), 2.27 (bs, 2H), 7.23 (m, 10H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=25.5, 79.0, 127.3, 127.7, 127.8, 144.2. *anti* Isomer **13**. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.50 (s, 6H), 2.27 (bs, 2H), 7.23 (m, 10H). EIMS (70 eV) $m/z$ 224 ($M^{+\cdot}-18$, 4), 206 ($M^+-36$, 11), 181 (73), 165 (15), 121 (100), 105 (32). Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31%; H, 7.49%. Found: C, 79.13%; H, 7.61%.

### 4.2. General procedure for cyclic acetals 17

To a solution of dimethylacetal **16** in dichloromethane, were added 1.2–1.5 equiv. of appropriate diol in the presence of a catalytic amount of camphorsulfonic acid (CSA) and of 2,2-dimethoxypropane (when precised). The reaction mixture was stirred at room temperature for 2 h and a saturated solution of sodium bicarbonate was added. The aqueous phase was extracted with dichloromethane and the resulting organic solution was dried ($MgSO_4$) and evaporated under reduce pressure to afford the crude product. A flash chromatography on silica gel (eluting with an AcOEt/heptane, 30:70 mixture) afforded the pure cyclic acetals. The *E*/*Z* ratio of the double bond remained unchanged under these conditions.

**4.2.1. 2-[2-Methyl-3-(*p*-methoxy-benzyloxy)-prop-2-enyl]-4,5-*anti*-dimethyl-[1,3]dioxolane (17a).** The above procedure was applied to 500 mg (1 equiv., 1.88 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 250 mg (1.5 equiv., 2.77 mmol) of *anti*-butane-2,3-diol in dichloromethane (10 mL) in presence of 0.1 mL of 2,2-dimethoxypropane. The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (3 mL) was added. After flash chromatography, 550 mg (100%) of dioxolane **17a** were obtained as a colorless oil (*E*/*Z*, 70:30). $\nu_{max}$ (film)/cm$^{-1}$ 2972, 2864, 1680, 1612, 1512, 1248, 1080, 820. *E* isomer. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.12–1.32 (m, 6H), 1.77 (s, 3H), 3.62 (m, 2H), 3.77 (s, 3H), 3.88 (s, 2H), 4.37 (s, 2H), 5.52 (d, $J$=7.3 Hz, 1H), 5.69 (d, $J$=7.3 Hz, 1H), 6.84 (d, $J$=8.8 Hz, 2H), 7.23 (d, $J$=8.8 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=14.5, 17.3, 17.6, 55.6, 71.7, 74.7, 78.6, 80.2, 99.5, 114.1, 124.5, 129.7, 130.5, 140.8, 159.6. *Z* isomer. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.12–1.32 (m, 6H), 1.81 (s, 3H), 3.62 (m, 2H), 3.77 (s, 3H), 4.05 (s, 2H), 4.37 (s, 2H), 5.43 (d, $J$=7.3 Hz, 1H), 5.63 (d, $J$=7.3 Hz, 1H), 6.84 (d, $J$=8.8 Hz, 2H), 7.23 (d, $J$=8.8 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=17.5, 21.8, 55.6, 68.0, 71.7, 78.6, 80.2, 98.1, 114.1, 126.7, 129.7, 130.5, 141.2, 159.6. EIMS (70 eV) $m/z$ 292 ($M^{+\cdot}$, 1.8), 121 (100). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84%; H, 8.27%. Found: C, 69.98%; H, 8.83%.

**4.2.2. 2-[2-Methyl-3-(*p*-methoxy-benzyloxy)-prop-2-enyl]-4,5-*syn*-dimethyl-[1,3]dioxolane (17b).** The above procedure was applied to 2.0 g (1 equiv., 7.51 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 813 mg (1.2 equiv., 9.03 mmol) of *syn*-butane-2,3-diol in dichloromethane (20 mL) in presence of 0.2 mL of 2,2-dimethoxypropane. The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (4 mL) was added. After flash chromatography, 1.30 g (59%) of dioxolane **17b** were obtained as a colorless oil (*E*/*Z*, 70:30) as two epimers. For the *E* isomer, a *syn*/*anti* ratio=73:27 was measured. $\nu_{max}$ (film)/cm$^{-1}$ 2976, 2908, 1684, 1612, 1514, 1248, 1084, 820. *E anti* isomer. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.17 (d, $J$=6.0 Hz, 6H), 1.77 (d, $J$=1.0 Hz, 3H), 3.79 (s, 3H), 3.88 (s, 2H), 4.14 (m, 2H), 4.39 (s, 2H), 5.51 (dd, $J$=7.5, 1.0 Hz, 1H), 5.57 (d, $J$=7.5 Hz, 1H), 6.86 (d, $J$=8.6 Hz, 2H), 7.25 (d, $J$=8.6 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=14.6, 15.9, 55.7, 71.9, 74.9, 75.0, 98.9, 114.1, 124.4, 129.7, 130.8, 141.0, 159.5. Other isomers: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.1–1.3 (6H), 1.7–1.9 (3H), 3.79 (s, 3H), 3.8–4.0 (2H), 4.1–4.3 (2H), 4.39 (s, 2H), 5.4–5.6 (1H), 6.86 (d, $J$=8.6 Hz, 2H), 7.25 (d, $J$=8.6 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=14.5–21.8,

15.9, 52.7–55.7, 71.9, 68.1–74.9, 75.0, 98.1–98.9, 114.1, 124–128, 129.7, 130.8, 139–141, 159.5. EIMS (70 eV) *m/z* 292 ($M^{+\cdot}$, 1), 219 (2), 155 (23), 121 (100). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84%; H, 8.27%. Found: C, 69.73%; H, 8.54%.

**4.2.3. 2-[2-Methyl-3-(*p*-methoxy-benzyloxy)-prop-2-enyl]-4,5-*anti*-diphenyl-[1,3]dioxolane (17c).** The above procedure was applied to 1.0 g (1 equiv., 3.75 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 965 mg (1.2 equiv., 4.50 mmol) of *anti*-1,2-diphenylethane-1,2-diol in dichloromethane (10 mL) in presence of 0.1 mL of 2,2-dimethoxypropane. The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (4 mL) was added. After flash chromatography, 1.11 g (70%) of dioxolane **17c** were obtained as a colorless oil (*E*/*Z*, 70:30). $\nu_{max}$ (film)/$cm^{-1}$ 3032, 2918, 1684, 1612, 1512, 1248, 1068, 820. *E* isomer. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.95 (s, 3H), 3.82 (s, 3H), 4.04 (s, 2H), 4.52 (s, 2H), 4.87 (s, 2H), 5.92 (d, *J*=7.2 Hz, 1H), 6.27 (d, *J*=7.2 Hz, 1H), 6.95 (d, *J*=8.7 Hz, 2H), 7.34 (m, 12H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=14.9, 55.7, 72.1, 74.8, 85.3, 87.2, 101.5, 114.3, 123.7, 126.8, 127.4, 128.6, 128.96, 129.04, 129.8, 130.8, 137.3, 138.9, 141.4, 159.7. *Z* isomer. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.99 (s, 3H), 3.82 (s, 3H), 4.24 (s, 2H), 4.52 (s, 2H), 4.81 (d, *J*=7.5 Hz, 1H), 4.86 (d, *J*=7.5 Hz, 1H), 5.81 (d, *J*=7.2 Hz, 1H), 6.20 (d, *J*=7.2 Hz, 1H), 6.95 (d, *J*=8.7 Hz, 2H), 7.34 (m, 12H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=22.1, 55.7, 68.5, 71.9, 85.3, 87.2, 100.7, 114.3, 126.2, 126.8, 127.4, 128.6, 128.96, 129.04, 129.9, 130.8, 137.3, 138.9, 141.6, 159.7. CIMS (*i*-BuH) *m/z* 417 ($MH^+$, 9), 197 (12), 121 (100). Anal. Calcd for $C_{27}H_{28}O_4$: C, 77.86%; H, 6.78%. Found: C, 77.92%; H, 6.94%.

**4.2.4. 2-[2-Methyl-3-(*p*-methoxy-benzyloxy)-prop-2-enyl]-4,5-*syn*-diphenyl-[1,3]dioxolane (17d).** The above procedure was applied to 2.0 g (1 equiv., 7.51 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 1.93 g (1.2 equiv., 9.01 mmol) of *syn*-1,2-diphenylethane-1,2-diol in dichloromethane (20 mL) in presence of 0.2 mL of 2,2-dimethoxypropane. The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (4 mL) was added. After flash chromatography, 1.65 g (53%) of dioxolane **17d** were obtained as a colorless oil (*E*/*Z*, 70:30) as two epimers (90:10). Only the major isomer could be isolated. $\nu_{max}$ (film)/$cm^{-1}$ 3030, 2914, 1686, 1612, 1512, 1248, 1066, 820. *E* isomer. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.92 (s, 3H), 3.82 (s, 3H), 4.04 (s, 2H), 4.52 (s, 2H), 5.37 (s, 2H), 6.01 (s, 2H), 6.93 (d, *J*=8.6 Hz, 2H), 7.05 (m, 10H), 7.35 (d, *J*=8.6 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=15.0, 55.7, 72.1, 74.8, 82.8, 100.4, 114.3, 122.6, 127.4, 127.8, 128.0, 130.1, 130.7, 137.6, 142.4, 159.7. *Z* isomer. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=2.00 (s, 3H), 3.81 (s, 3H), 4.21 (s, 2H), 4.48 (s, 2H), 5.47 (s, 2H), 5.92 (s, 2H), 6.93 (d, *J*=8.6 Hz, 2H), 7.05 (m, 10H), 7.35 (d, *J*=8.6 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=22.0, 55.7, 67.5, 71.9, 81.7, 99.6, 114.3, 124.6, 127.2, 127.8, 128.1, 129.8, 130.7, 137.6, 142.4, 159.7. CIMS ($NH_3$) *m/z* 434 ($M+NH_4^+$, 16), 238 (47), 121 (100). Anal. Calcd for $C_{27}H_{28}O_4$: C, 77.86%; H, 6.78%. Found: C, 77.78%; H, 7.04%.

**4.2.5. 2-[3-(4-Methoxy-benzyloxy)-2-methyl-propenyl]-4,5-*syn*-dimethyl-4,5-diphenyl-[1,3]dioxolane (17e).** The above procedure was applied to 1.0 g (1 equiv., 3.76 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 1.2 g (1.3 equiv., 4.96 mmol)of *syn*-1,2-diphenyl-1,2-dimethylethane-1,2-diol in dichloromethane (20 mL). The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (4 mL) was added. After flash chromatography, 720 mg (43%) of dioxolane **17e** were obtained as a colorless oil (*E*/*Z*, 70:30) and as a single (undetermined) epimer. $\nu_{max}$ (film)/$cm^{-1}$ 3058, 2994, 2922, 2854, 1612, 1514, 1248, 1072, 820, 698. *E* isomer. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.81 (s, 6H), 1.94 (d, *J*=1.1 Hz, 3H), 3.82 (s, 3H), 4.04 (s, 2H), 4.51 (s, 2H), 6.04 (d, *J*=7.2 Hz, 1H), 6.24 (d, *J*=7.2 Hz, 1H), 6.91 (d, *J*=8.7 Hz, 2H), 7.00 (m, 10H), 7.32 (d, *J*=8.7 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=15.0, 22.9, 55.7, 71.9, 74.9, 87.8, 97.1, 114.2, 123.9, 126.4, 126.8, 127.5, 129.8, 130.8, 141.6, 143.8, 159.6. *Z* isomer. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.74 (s, 6H), 1.99 (d, *J*=1.1 Hz, 3H), 3.80 (s, 3H), 4.22 (s, 2H), 4.47 (s, 2H), 5.94 (d, *J*=6.8 Hz, 1H), 6.13 (d, *J*=6.8 Hz, 1H), 6.91 (d, *J*=8.7 Hz, 2H), 7.00 (m, 10H), 7.32 (d, *J*=8.7 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=22.0, 22.9, 55.7, 68.4, 71.7, 87.8, 96.4, 114.2, 125.9, 126.4, 126.8, 127.5, 129.8, 130.8, 141.6, 143.8, 159.6.

**4.2.6. 2-[3-(4-Methoxy-benzyloxy)-2-methyl-propenyl]-tetrahydro-cyclopenta[1,3]dioxolane (17f).** The above procedure was applied to 1.0 g (1 equiv., 3.76 mmol) of pure *E* dimethylacetal **16** and 575 mg (1.5 equiv., 5.63 mmol) of *syn*-1,2-cyclopentanediol in dichloromethane (15 mL) in the presence of 0.1 mL of 2,2-dimethoxypropane. The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (4 mL) was added. After flash chromatography, 730 mg (64%) of dioxolane **17f** were obtained as a colorless oil. Two epimers were detected (88:12) but only the major isomer could be isolated. $\nu_{max}$ (film)/$cm^{-1}$ 2926, 1686, 1612, 1514, 1248, 1040, 820. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.39 (m, 2H), 1.56 (m, 1H), 1.76 (m, 1H), 1.77 (s, 3H), 1.93 (dd, *J*=6.0, 13.6 Hz, 2H), 3.79 (s, 3H), 3.90 (s, 2H), 4.39 (s, 2H), 4.53 (d, *J*=4.5 Hz, 2H), 5.41 (d, *J*=7.1 Hz, 1H), 5.54 (d, *J*=7.1 Hz, 1H), 6.86 (d, *J*=8.7 Hz, 2H), 7.24 (d, *J*=8.7 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=14.8, 22.7, 33.5, 55.7, 72.0, 74.9, 82.0, 99.6, 114.2, 122.8, 129.7, 130.8, 141.6, 159.7. CIMS (*i*-BuH) *m/z* 305 ($MH^+$, 15), 203 (3), 121 (100).

**4.2.7. 2-[2-Methyl-3-(*p*-methoxy-benzyloxy)-prop-2-enyl]-[1,3]dioxane (17i).** The above procedure was applied to 500 mg (1 equiv., 1.88 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 0.30 mL (2.2 equiv., 4.15 mmol) of propanediol in dichloromethane (10 mL) in presence of 0.1 mL of 2,2-dimethoxypropane. The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (3 mL) was added. After flash chromatography, 420 mg (80%) of dioxolane **17i** were obtained as a colorless oil (*E*/*Z*, 70:30). $\nu_{max}$ (film)/$cm^{-1}$ 2958, 2850, 1666, 1612, 1514, 1248, 1092, 820. *E* isomer. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.35 (d, *J*=13.6 Hz, 1H), 1.76 (s, 3H), 2.14 (m, 1H), 3.79 (s, 3H), 3.85 (m, 4H), 4.13 (dd, *J*=4.9, 11.3 Hz, 2H), 4.37 (s, 2H), 5.24 (d, *J*=6.4 Hz, 1H), 5.55 (d, *J*=6.4 Hz, 1H), 6.85 (d, *J*=8.7 Hz, 2H), 7.24 (d, *J*=8.7 Hz, 2H). $^{13}$C

NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=15.0, 26.1, 55.7, 67.4, 71.8, 74.8, 98.9, 114.1, 124.7, 129.7, 130.8, 139.4, 159.5. *Z* isomer. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.35 (d, *J*=13.6 Hz, 1H), 1.81 (s, 3H), 2.14 (m, 1H), 3.79 (s, 3H), 3.85 (m, 4H), 4.04 (dd, *J*=4.9, 11.7 Hz, 2H), 4.39 (s, 2H), 5.14 (d, *J*=6.4 Hz, 1H), 5.45 (d, *J*=6.4 Hz, 1H), 6.85 (d, *J*=8.7 Hz, 2H), 7.24 (d, *J*=8.7 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=20.3, 26.1, 55.7, 67.4, 72.9, 74.8, 98.2, 114.8, 126.7, 129.7, 130.8, 139.4, 159.5. CIMS (*i*-BuH) *m/z* 279 ($MH^{+\cdot}$, 25), 121 (100). HRMS Calcd for $C_{16}H_{22}O_4$: 279.1596. Found: 279.1596.

**4.2.8. 2-[2-Methyl-3-(*p*-methoxy-benzyloxy)-prop-2-enyl]-3,5-*syn*-dimethyl-[1,3]dioxane (17j).** The above procedure was applied to 2.0 g (1 equiv., 7.52 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 1.08 mL (1.3 equiv., 9.85 mmol) of pentane-1,3-diol (mixture of isomers) in dichloromethane (30 mL) in presence of 0.1 mL of 2,2-dimethoxypropane. The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (5 mL) was added. After flash chromatography, 441 mg of *syn-E*-**17j**, 144 mg of *syn-Z*-**17j** and 1.09 g as a mixture of isomers. A total of 1.67 g (73%) dioxanes was recovered. $\nu_{max}$ (film)/cm$^{-1}$ 2932, 2854, 1612, 1514, 1248, 1036, 820. *E* isomer. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.26 (m, 7H), 1.53 (dt, *J*=12.3, 2.3 Hz, 1H), 1.76 (s, 3H), 3.79 (m, 5H), 3.89 (s, 2H), 4.38 (s, 2H), 5.26 (d, *J*=6.4 Hz, 1H), 5.60 (d, *J*=6.4 Hz, 1H), 6.85 (d, *J*=8.3 Hz, 2H), 7.24 (d, *J*=8.3 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)= 14.9, 22.1, 40.7, 55.7, 71.9, 72.8, 75.1, 98.1, 114.1, 124.8, 129.7, 130.9, 139.2, 159.5. *Z* isomer. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.22 (m, 7H), 1.49 (dt, *J*=2.3, 13.2 Hz, 1H), 1.81 (s, 3H), 3.71 (m, 2H), 3.80 (s, 3H), 4.05 (s, 2H), 4.39 (s, 2H), 5.18 (d, *J*=6.8 Hz, 1H), 5.51 (d, *J*=6.8 Hz, 1H), 6.87 (d, *J*=8.7 Hz, 2H), 7.26 (d, *J*=8.7 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=21.6, 22.0, 40.5, 55.7, 68.7, 71.5, 72.8, 97.3, 114.1, 126.7, 129.8, 130.9, 139.3, 159.5. CIMS ($NH_3$) *m/z* 324 ($M+NH_4^+$, 100), 307 ($MH^+$, 90), 238 (10), 121 (72). Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56%; H, 8.55%. Found: C, 70.59%; H, 8.66%.

**4.2.9. 3-[3-(4-Methoxy-benzyloxy)-2-methyl-propenyl]-hexahydro-benzo[*e*]-[1,3]dioxepane (17k).** The above procedure was applied to 2.0 g (1 equiv., 7.52 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 1.63 g (1.5 equiv., 11.3 mmol) of *syn*-1,2-cyclohexane dimethanol in dichloromethane (15 mL) in presence of 0.1 mL of 2,2-dimethoxypropane. The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (3 mL) was added. After flash chromatography, 1.60 g (61%) of dioxepane **17k** (*E*/*Z*, 70:30) were recovered as a colorless oil and as a mixture of two epimers (50:50). $\nu_{max}$ (film)/cm$^{-1}$ 2926, 2856, 1612, 1512, 1248, 1144, 820. *E* isomer (*syn*, *anti*). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.36 (m, 4H), 1.65 (m, 6H), 1.66 (s, 3H), 3.4–3.8 (m, 4H), 3.68 (s, 3H), 3.79 (s, 2H), 4.30 (s, 1H), 4.32 (s, 1H), 5.31 (d, *J*=6.4 Hz, 0.5H), 5.33 (d, *J*=6.4 Hz, 0.5H), 5.54 (d, *J*=6.4 Hz, 1H), 6.77 (d, *J*=8.5 Hz, 2H), 7.17 (d, *J*=8.5 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=14.7, 24.7, 27.2, 27.4, 40.0, 40.2, 55.6, 67.9, 71.8, 71.9, 75.0, 97.9, 98.3, 114.1, 125.0, 129.7, 130.8, 137.8, 159.6. *Z* isomer (*syn*, *anti*). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.36 (m, 4H), 1.65 (m, 6H), 1.73 (s, 3H), 3.4–3.8 (m, 4H), 3.68 (s, 3H), 3.98 (s, 2H), 4.29 (s, 1H), 4.30 (s, 1H), 5.25 (d, *J*=7.2 Hz, 0.5H), 5.27 (d, *J*=7.2 Hz, 0.5H), 5.46 (d, *J*=7.2 Hz, 1H), 6.77 (d, *J*=8.5 Hz, 2H), 7.17 (d, *J*=8.5 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=21.3, 24.7, 27.2, 27.4, 40.0, 40.2, 55.6, 67.9, 68.5, 71.8, 71.9, 97.7, 97.3, 114.1, 127.2, 129.7, 130.8, 138.1, 159.6. EIMS (70 eV) *m/z* 347.2 ($MH^+$, 15), 220 (45), 156 (56), 137 (100), 121 (85). Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73%. Found: C, 72.58%; H, 8.64%.

**4.2.10. 3-[3-(4-Methoxy-benzyloxy)-2-methyl-propenyl]-hexahydro-benzo[*e*]-[1,3]dioxepane (17l).** The above procedure was applied to 709 mg (1 equiv., 2.67 mmol) of dimethylacetal **16** *E*/*Z*, 70:30 were used with 500 mg (1.3 equiv., 3.47 mmol) of *anti*-1,2-cyclohexane dimethanol in dichloromethane (10 mL) in presence of 0.1 mL of 2,2-dimethoxypropane. The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (3 mL) was added. After flash chromatography, 500 mg (54%) of dioxepane **17l** (*E*/*Z*, 70:30) were recovered as a colorless oil. $\nu_{max}$ (film)/cm$^{-1}$ 2924, 2854, 1612, 1514, 1248, 1032, 820. *E* isomer. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=0.86 (m, 2H), 1.25 (m, 4H), 1.62 (m, 2H), 1.74 (s, 3H), 1.78 (m, 2H), 3.2–3.7 (m, 4H), 3.78 (s, 3H), 3.86 (s, 2H), 4.39 (s, 2H), 5.42 (d, *J*=6.4 Hz, 1H), 5.61 (d, *J*=6.4 Hz, 1H), 6.86 (d, *J*=8.3 Hz, 2H), 7.24 (d, *J*=8.3 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=15.7, 26.6, 28.9, 29.2, 46.6, 55.6, 67.6, 71.8, 75.0, 97.7, 114.1, 125.1, 129.7, 130.8, 137.8, 159.5. *Z* isomer. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=0.86 (m, 2H), 1.25 (m, 4H), 1.62 (m, 2H), 1.80 (s, 3H), 1.78 (m, 2H), 3.2–3.7 (m, 4H), 3.78 (s, 3H), 4.05 (s, 2H), 4.39 (s, 2H), 5.42 (d, *J*=6.4 Hz, 1H), 5.52 (d, *J*=6.4 Hz, 1H), 6.86 (d, *J*=8.3 Hz, 2H), 7.24 (d, *J*=8.3 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=21.6, 26.6, 28.9, 29.2, 46.6, 55.6, 68.5, 71.8, 72.9, 97.0, 114.1, 127.3, 129.4, 130.8, 138.1, 159.5. EIMS (70 eV) *m/z* 347.2 ($MH^+$, 7), 210 (50), 155 (47), 122 (100). HRMS Calcd for $C_{21}H_{31}O_4$ ($MH^+$) 347.2222. Found: 347.2216.

**4.2.11. 3-[3-(4-Methoxy-benzyloxy)-2-methyl-propenyl]-benzo[*e*]-[1,3]dioxepane (17o).** The above procedure was applied to 3.0 g (1 equiv., 11.3 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 2.34 g (1.5 equiv., 16.9 mmol) of (2-hydroxymethyl-phenyl)-methanol in dichloromethane (30 mL) in presence of 0.2 mL of 2,2-dimethoxypropane. The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (5 mL) was added. After flash chromatography, 2.66 g (70%) of dioxepane **17o** (*E*/*Z*, 70:30) as a colorless oil. $\nu_{max}$ (film)/cm$^{-1}$ 2954, 2852, 1612, 1512, 1248, 1088, 1032, 820. *E* isomer. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.76 (d, *J*=0.8 Hz, 3H), 3.73 (s, 3H), 3.85 (s, 2H), 4.34 (s, 2H), 4.86 (s, 4H), 5.55 (d, *J*=6.0 Hz, 1H), 5.65 (dd, *J*=6.0, 1.1 Hz, 1H), 6.80 (d, *J*=8.7 Hz, 2H), 7.1–7.3 (m, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=15.0, 55.7, 71.1, 71.9, 74.9, 103.5, 114.2, 124.5, 127.6,127.7, 129.8, 130.8, 139.3, 159.6. *Z* isomer. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.77 (s, 3H), 3.73 (s, 3H), 4.05 (s, 2H), 4.37 (s, 2H), 4.75 (d, *J*=13.9 Hz, 2H), 4.82 (d, *J*=13.9 Hz, 2H), 5.49 (d, *J*=6.4 Hz, 1H), 5.55 (d, *J*=6.4 Hz, 1H), 6.80 (d, *J*=8.7 Hz, 2H), 7.1–7.3 (m, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=21.7, 55.7, 68.8, 71.2, 71.9, 103.1, 114.2, 126.6, 127.6, 127.7, 129.8, 130.8, 139.1, 159.6. CIMS (*i*-BuH) *m/z* 341 ($MH^+$, 100), 259 (15), 121 (98). Anal.

Calcd for $C_{21}H_{24}O_4$: C, 74.09%; H, 7.11%. Found: C, 74.15%; H, 7.25%.

**4.2.12. 3-[3-(4-Methoxy-benzyloxy)-2-methyl-propenyl]-1,5-*syn*-dimethyl-benzo[*e*]-[1,3]dioxepane (17p).** The above procedure was applied to 1.41 g (1 equiv., 5.30 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 1.32 g (1.5 equiv., 7.95 mmol) of *syn*-diol **9a** in dichloromethane (20 mL). The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (4 mL) was added. After flash chromatography, 1.54 g (81%) of dioxepane **17p** (*E*/*Z*, 70:30) were obtained as a colorless oil and as a mixture of two epimers (*syn*/*anti*: 80:20). $\nu_{max}$ (film)/$cm^{-1}$ 2978, 2854, 1612, 1512, 1246, 1094, 818. *E* (*anti*) isomer. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.69 (d, *J*=6.4 Hz, 6H), 1.80 (s, 3H), 3.79 (s, 3H), 3.88 (s, 2H), 4.37 (s, 2H), 5.20 (q, *J*=6.4 Hz, 1H), 5.60 (d, *J*=6.0 Hz, 1H), 5.84 (d, *J*=6.0 Hz, 1H), 6.85 (d, *J*=8.7 Hz, 2H), 7.1–7.3 (m, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=15.0, 19.8, 55.7, 71.9, 75.2, 75.4, 105.2, 114.1, 125.4, 126.5, 128.0, 129.8, 130.9, 137.5, 142.5, 159.5. *Z* (*anti*) isomer. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.65 (d, *J*=6.4 Hz, 6H), 1.80 (s, 3H), 3.80 (s, 3H), 4.10 (s, 2H), 4.37 (s, 2H), 5.08 (q, *J*=6.4 Hz, 1H), 5.51 (d, *J*=6.0 Hz, 1H), 5.78 (d, *J*=6.0 Hz, 1H), 6.85 (d, *J*=8.7 Hz, 2H), 7.1–7.3 (m, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=19.8, 21.6, 55.7, 68.8, 71.9, 75.2, 104.4, 114.2, 125.4, 126.5, 128.0, 129.8, 130.9, 137.5, 142.5, 159.5. EIMS (70 eV) *m*/*z* 368.2 ($M^{+\cdot}$, 1), 232 (8), 220 (12), 177 (70), 132 (100), 121 (55). Anal. Calcd for $C_{23}H_{28}O_4$: C, 74.97%; H, 7.66%. Found: C, 74.63%; H, 7.84%.

**4.2.13. 3-[3-(4-Methoxy-benzyloxy)-2-methyl-propenyl]-1,5-*anti*-dimethyl-benzo[*e*]-[1,3]dioxepane (17q).** The above procedure was applied to 1.20 g (1 equiv., 4.51 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 1.10 g (1.5 equiv., 6.63 mmol) of *anti*-diol **8a** in dichloromethane (20 mL). The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (4 mL) was added. After flash chromatography, 1.00 g (60%) of dioxepane **17q** (*E*/*Z*, 70:30) was obtained as a colorless oil. $\nu_{max}$ (film)/$cm^{-1}$ 2978, 2934, 1612, 1512, 1248, 1104, 1034, 820, 754. *E* isomer. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.55 (m, 6H), 1.73 (s, 3H), 3.73 (s, 3H), 3.85 (s, 2H), 4.34 (s, 2H), 5.07, 5.26 (2q, *J*=6.8 Hz, 2H), 5.57 (d, *J*=6.0 Hz, 1H), 5.67 (d, *J*=6.0 Hz, 1H), 6.81 (d, *J*=8.7 Hz, 2H), 7.1–7.2 (m, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=15.0, 20.3, 22.1, 55.7, 68.2, 71.9, 75.1, 76.3, 97.4, 114.2, 124.9, 126.1, 126.3, 127.5, 127.6, 129.7, 130.8, 139.3, 141.2, 143.1, 159.6. *Z* isomer. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.78 (s, 3H), 3.73 (s, 3H), 4.05 (s, 2H), 4.34 (s, 2H), 4.95, 5.10 (2q, *J*=6.8 Hz, 2H), 5.56 (d, *J*=6.0 Hz, 1H), 5.67 (d, *J*=6.0 Hz, 1H), 6.80 (d, *J*=8.7 Hz, 2H), 7.1–7.3 (m, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=25.0, 55.7, 67.3, 72.9, 73.6, 76.2, 96.4, 114.2, 125.4, 126.1, 126.3, 127.5, 127.6, 129.7, 130.8, 139.3, 140.6, 142.6, 159.6. EIMS (70 eV) *m*/*z* 368.2 ($M^{+\cdot}$, 1), 220 (10), 177 (57), 131 (100), 121 (57). Anal. Calcd for $C_{23}H_{28}O_4$: C, 74.97%; H, 7.66%. Found: C, 74.48%; H, 7.93%.

**4.2.14. 3-[3-(4-Methoxy-benzyloxy)-2-methyl-propenyl]-1,5-*anti*-diethyl-benzo[*e*]-[1,3]dioxepane (17r).** The above procedure was applied to 1.50 g (1 equiv., 5.63 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 1.64 g (1.5 equiv., 8.45 mmol) of *anti*-diol **8b** in dichloromethane (15 mL) in presence of 0.1 mL of 2,2dimethoxypropane. The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (4 mL) was added. After flash chromatography, 1.50 g (67%) of dioxepane **17r** (*E*/*Z*, 70:30) were recovered as a colorless oil. $\nu_{max}$ (film)/$cm^{-1}$ 2930, 2874, 1612, 1514, 1248, 1070, 1036, 820. *E* isomer. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.04 (t, *J*=6.0 Hz, 3H), 1.07 (t, *J*=5.7 Hz, 3H), 1.79 (s, 3H), 1.93 (m, 2H), 2.13 (m, 2H), 3.80 (s, 3H), 3.91 (s, 2H), 4.41 (s, 2H), 4.90 (dd, *J*=3.8, 8.3 Hz, 1H), 5.07 (dd, *J*=4.5, 8.6 Hz, 1H), 5.64 (d, *J*=6.0 Hz, 1H), 5.74 (d, *J*=6.0 Hz, 1H), 6.87 (d, *J*=8.6 Hz, 2H), 7.1–7.3 (m, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=10.6, 11.0, 15.1, 26.3, 28.4, 55.1, 71.8, 73.7, 75.1, 81.5, 97.6, 114.3, 125.3, 126.5, 127.4, 129.7, 130.8, 138.7, 140.3, 142.0, 159.5. *Z* isomer. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.04 (t, *J*=6.0 Hz, 3H), 1.07 (t, *J*=5.7 Hz, 3H), 1.85 (s, 3H), 1.93 (m, 2H), 2.13 (m, 2H), 3.80 (s, 3H), 3.96 (d, *J*=12.2 Hz, 1H), 4.10 (d, *J*=12.2 Hz, 1H), 4.38 (s, 2H), 4.79 (dd, *J*=3.7, 8.3 Hz, 1H), 5.06 (m, 1H), 5.59 (d, *J*=6.0 Hz, 1H), 5.74 (d, *J*=6.0 Hz, 1H), 6.87 (d, *J*=8.6 Hz, 2H), 7.1–7.3 (m, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=10.6, 11.0, 21.1, 26.3, 28.4, 55.1, 68.8, 71.8, 73.7, 81.5, 95.5, 114.3, 125.3, 126.5, 127.4, 129.7, 130.8, 138.7, 140.3, 142.0, 159.5. EIMS (70 eV) *m*/*z* 396.2 ($M^{+\cdot}$, 1), 205 (7), 177 (55), 159 (100), 121 (62). Anal. Calcd for $C_{25}H_{32}O_4$: C, 75.73; H, 8.13%. Found: C, 75.86%; H, 8.11%.

**4.2.15. 3-[3-(4-Methoxy-benzyloxy)-2-methyl-propenyl]-1,5-*anti*-diisopropyl-benzo[*e*]-[1,3]dioxepane (17s).** The above procedure was applied to 1.50 g (1 equiv., 5.63 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 1.90 g (1.5 equiv., 8.56 mmol) of *anti*-diol **8c** in dichloromethane (15 mL) in presence of 0.1 mL of 2,2dimethoxypropane. The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (5 mL) was added. After flash chromatography, 1.20 g (50%) of dioxepane **17s** (*E*/*Z*, 70:30) were recovered as a colorless oil. $\nu_{max}$ (film)/$cm^{-1}$ 2960, 2872, 1612, 1514, 1248, 1076, 1034, 822. *E* isomer. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=0.88 (m, 6H), 1.03 (d, *J*=6.8 Hz, 3H), 1.11 (d, *J*=6.8 Hz, 3H), 1.80 (s, 3H), 2.4–2.6 (m, 2H), 3.80 (s, 3H), 3.92 (s, 2H), 4.42 (s, 2H), 4.81 (d, *J*=3.0 Hz, 1H), 4.91 (d, *J*=4.5 Hz, 1H), 5.56 (d, *J*=6.0 Hz, 1H), 5.74 (d, *J*=6.0 Hz, 1H), 6.87 (d, *J*=8.7 Hz, 2H), 7.2–7.3 (m, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=15.2, 16.4, 16.9, 20.6, 21.2, 29.7, 31.5, 55.7, 71.9, 75.2, 76.6, 83.9, 98.1, 114.2, 125.3, 126.9, 127.0, 129.7, 130.8, 138.6, 140.9, 141.9, 159.5. *Z* isomer. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=0.88 (m, 6H), 1.03 (d, *J*=6.8 Hz, 3H), 1.11 (d, *J*=6.8 Hz, 3H), 1.85 (s, 3H), 2.4–2.6 (m, 2H), 3.80 (s, 3H), 4.06 (d, *J*=12.8 Hz, 1H), 4.13 (d, *J*=12.8 Hz, 1H), 4.39 (s, 2H), 4.71 (d, *J*=3.4 Hz, 1H), 4.89 (m, 1H), 5.51 (d, *J*=6.4 Hz, 1H), 5.60 (d, *J*=6.4 Hz, 1H), 6.87 (d, *J*=8.7 Hz, 2H), 7.2–7.3 (m, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=16.6, 17.2, 19.4, 20.0, 21.6, 29.5, 31.8, 55.7, 68.8, 71.9, 76.6, 84.4, 97.1, 114.2, 125.3, 126.9, 127.0, 129.7, 130.8, 138.6, 140.9, 141.9, 159.5. Anal. Calcd for $C_{27}H_{36}O_4$: C, 76.38; H, 8.55%. Found: C, 76.44%; H, 8.85%.

**4.2.16. 3-[3-(4-Methoxy-benzyloxy)-2-methyl-propenyl]-1,5-*anti*-diisobutyl-benzo[*e*]-[1,3]dioxepane (17t).** The

above procedure was applied to 500 mg (1 equiv., 1.88 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 700 mg (1.5 equiv., 2.80 mmol)of *anti*-diol **8d** in dichloromethane (5 mL). The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (2 mL) was added. After flash chromatography (heptane/AcOEt, 80/20 as eluent), 446 mg (52%) of dioxepane **17t** (*E*/*Z*, 70:30) were recovered as a colorless oil. $\nu_{max}$ (film)/$cm^{-1}$ 2954, 2867, 1612, 1513, 1247, 1084, 820, 750. *E* isomer. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.00 (m, 12H), 1.7–2.0 (m, 6H), 1.77 (s, 3H), 3.80 (s, 3H), 3.91 (s, 2H), 4.41 (s, 2H), 5.09 (dd, *J*=3.6, 10.2 Hz, 1H), 5.23 (m, 1H), 5.64 (d, *J*=6.3 Hz, 1H), 5.73 (d, *J*=6.3 Hz, 1H), 6.87 (d, *J*=6.8 Hz, 2H), 7.24 (m, 6H). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=15.0, 22.2, 22.4, 24.2, 24.7, 42.8, 45.1, 55.7, 71.0, 71.9, 75.1, 78.4, 97.2, 114.2, 125.5, 126.3, 126.4, 127.5, 129.6, 130.8, 138.5, 140.4, 142.9, 159.5. *Z* isomer. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.00 (m, 12H), 1.7–2.0 (m, 6H), 3.80 (s, 3H), 4.00, 4.11 (2d, *J*=16.7 Hz, 2H), 4.38 (s, 2H), 5.01 (dd, *J*=3.6, 10.2 Hz, 1H), 5.23 (m, 1H), 5.60 (d, *J*=6.3 Hz, 1H), 5.73 (d, *J*=6.3 Hz, 1H), 6.87 (d, *J*=6.8 Hz, 2H), 7.24 (m, 6H). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=21.6, 22.2, 22.4, 24.2, 24.7, 42.8, 45.1, 55.7, 68.8, 71.0, 71.9, 78.4, 96.2, 114.2, 125.5, 126.3, 126.4, 127.5, 129.6, 130.8, 138.8, 140.4, 142.9, 159.5. EIMS (70 eV) *m*/*z* 452.3 ($M^{+\cdot}$, 1), 231 (100), 215 (80), 121 (55). Anal. Calcd for $C_{29}H_{40}O_4$: C, 76.95; H, 8.91%. Found: C, 76.55%; H, 8.96%.

**4.2.17. 5-Isobutyl-3-[3-(4-methoxy-benzyloxy)-2-methyl-propenyl]-benzo[*e*]-[1,3]dioxepane (17u).** The above procedure was applied to 1.00 g (1 equiv., 3.76 mmol) of dimethylacetal **16** (*E*/*Z*, 70:30) and 1.1 g (1.5 equiv., 5.67 mmol) of *anti*-diol **10d** in dichloromethane (15 mL). The reaction was monitored by TLC and upon completion, a solution of saturated $NaHCO_3$ (4 mL) was added. After flash chromatography (heptane/AcOEt, 75:25 as eluent), 1.01 g (68%) of dioxepane **17u** (*E*/*Z*, 70:30) were obtained as a yellowish oil, each stereoisomer being a mixture of two epimers (*E*: 33:66, *Z*, 50:50). $\nu_{max}$ (film)/$cm^{-1}$ 2953, 2865, 1611, 1512, 1247, 1086, 820, 747. Major isomer *syn* or *anti* *E*. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.00 (m, 6H), 1.81 (s, 3H), 1.7–2.1 (m, 3H), 3.79 (s, 3H), 3.90 (s, 2H), 4.39 (s, 2H), 4.8–5.1 (m, 3H), 5.74 (s, 2H), 6.86 (d, *J*=8.7 Hz, 2H), 7.1–7.4 (m, 6H). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=15.0, 22.0, 24.6, 42.5, 55.7, 71.1, 71.9, 73.7, 75.0, 104.0, 114.2, 125.5, 127.7, 128.1, 128.7, 129.71, 129.74, 130.7, 138.0, 139.3, 143.7, 159.5. Other isomers. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=0.98 (m, 6H), 1.7–2.1 (m, 6H), 3.79 (s, 3H), 4.09 (s, 2H), 4.42 (s, 2H), 4.8–5.1 (m, 3H), 5.56–5.78 (m, 2H), 6.86 (d, *J*=8.7 Hz, 2H), 7.1–7.4 (m, 6H). EIMS (70 eV) *m*/*z* 397.2 ($MH^+$, 1), 260 (8), 220 (25), 175 (77), 119 (100). Anal. Calcd for $C_{25}H_{32}O_4$: C, 75.73; H, 8.13%. Found: C, 75.52%; H, 8.51%.

**4.2.18. 2-[3-(4-Methoxy-benzyloxy)-2-methyl-propenyl]-dibenzo[*e*,*g*]-[1,3]dioxonane (17v).** A solution of dimethylacetal **16** (500 mg, 1 equiv., 1.88 mmol) in dichloromethane (25 mL) and (2′-hydroxymethyl-biphenyl-2-yl)-methanol (806 mg, 2 equiv., 3.76 mmol) were put in a flask equipped with a heavy-solvent designed Dean–Stark device. The mixture was refluxed in presence of 0.05 mL acetic acid. After 24 h, 4 mL saturated $NaHCO_3$ were added and the aqueous phase was extracted with dichloromethane (2×10 mL). The resulting organic phase was dried ($MgSO_4$) and evaporated under reduce pressure. A flash chromatography on silica gel (eluting with heptane/AcOEt, 70:30) afforded 399 mg (51%) of dioxonane **17v**. $\nu_{max}$ (film)/$cm^{-1}$ 3060, 2932, 1674, 1612, 1514, 1248, 1076, 822, 760. *E* isomer. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.63 (s, 3H), 3.79 (s, 3H), 3.86 (s, 2H), 4.05 (d, *J*=12.3 Hz, 1H), 4.29 (d, *J*=10.9 Hz, 1H), 4.39 (s, 2H), 4.53 (d, *J*=10.9 Hz, 1H), 4.74 (d, *J*=12.3 Hz, 1H), 5.01 (d, *J*=6.4 Hz, 1H), 5.63 (d, *J*=6.4 Hz, 1H), 6.86 (d, *J*=8.7 Hz, 2H), 7.15–7.45 (m, 9H). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=14.9, 55.7, 65.7, 72.0, 74.1, 75.1, 101.4, 114.2, 126.6, 128.4, 128.8, 128.9, 129.0, 129.7, 130.1, 130.2, 130.6, 131.0, 130.8, 135.6, 136.9, 137.0, 141.8, 142.0, 159.7. *Z* isomer. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm)=1.80 (s, 3H), 3.79 (s, 3H), 3.94 (d, *J*=12.4 Hz, 1H), 4.04 (s, 2H), 4.27 (d, *J*=10.9 Hz, 1H), 4.39 (s, 2H), 4.51 (d, *J*=10.9 Hz, 1H), 4.66 (d, *J*=12.4 Hz, 1H), 5.01 (d, *J*=6.4 Hz, 1H), 5.53 (d, *J*=6.4 Hz, 1H), 6.86 (d, *J*=8.7 Hz, 2H), 7.15–7.45 (m, 9H). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ (ppm)=21.7, 55.7, 65.6, 69.0, 72.0, 73.9, 100.7, 114.2, 126.6, 128.4, 128.8, 128.9, 129.0, 129.7, 130.1, 130.2, 130.6, 131.0, 130.8, 135.6, 136.9, 137.0, 141.8, 142.0, 159.7. CIMS (*i*-BuH) *m*/*z* 417 ($MH^+$, 6), 335 (4), 197 (24), 121 (100).

**4.2.19. 1,1-Diallyloxy-3-methyl-4-(*p*-methoxy-benzyloxy)-but-2-ene (18).** A solution of dimethylacetal **16** (500 mg, 1 equiv., 1.88 mmol) in dichloromethane (25 mL) and allylic alcohol (1.09 g,10 equiv., 18.8 mmol) were put in a flask equipped with a heavy-solvent designed Dean–Stark device. The reaction mixture was refluxed in presence of acetic acid (0.05 mL). After 12 h, $NaHCO_3$ (4 mL) was added and the aqueous phase extracted with dichloromethane (2×10 mL). The resulting organic phase was dried ($MgSO_4$) and evaporated under reduce pressure. A flash chromatography on silica gel (eluting with heptane/AcOEt, 70:30) afforded 320 mg (53%) of diallylacetal **18** as a colorless oil. *E* isomer. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 1.75 (s, 3H), 3.79 (s, 3H), 3.89 (s, 2H), 4.06 (m, 4H), 4.39 (s, 2H), 5.24 (m, 5H), 5.60 (d, *J*=6.8 Hz, 1H), 6.87 (d, *J*=8.7 Hz, 2H), 7.25 (d, *J*=8.7 Hz, 2H). *Z* isomer. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 1.82 (s, 3H), 3.79 (s, 3H), 4.06 (m, 4H), 4.39 (s, 2H), 5.24 (m, 5H), 5.49 (d, *J*=6.8 Hz, 1H), 6.87 (d, *J*=8.7 Hz, 2H), 7.25 (d, *J*=8.7 Hz, 2H).

**4.2.20. 2-[3-(4-Methoxy-benzyloxy)-2-methyl-propenyl]-4,7-dihydro-[1,3]dioxepine (19).** Diallyl acetal **18** (207 mg, 1 equiv., 0.651 mmol) was dissolved in 10 mL dichloromethane containing 60 mg Grubbs catalyst (0.1 equiv., 0.073 mmol) under argon and at room temperature. After 2 h, a second load of 50 mg (0.09 equiv., 0.061 mmol) catalyst was added. The reaction mixture was stirred overnight then evaporated under reduce pressure. A flash chromatography on silica gel (eluting with heptane/AcOEt, 70:30) afforded 52 mg (27%) of dioxepine **19** as a colorless oil. *E* isomer. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 1.77 (s, 3H), 3.79 (s, 3H), 3.89 (s, 2H), 4.20 (d, *J*=15.1 Hz, 2H), 4.44 (m, 4H), 5.50 (d, *J*=6.0 Hz, 1H), 5.70 (d, *J*=6.0 Hz, 1H), 5.73 (s, 2H), 6.86 (d, *J*=8.7 Hz, 2H), 7.25 (d, *J*=8.7 Hz, 2H). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) 14.9, 55.7, 65.2, 72.0, 74.9, 100.1, 114.2, 124.2, 129.7, 130.4, 130.7, 139.1, 159.6. *Z*

isomer. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 1.83 (s, 3H), 3.79 (s, 3H), 4.07 (s, 2H), 4.20 (d, $J$=15.1 Hz, 2H), 4.44 (m, 4H), 5.44 (d, $J$=6.0 Hz, 1H), 5.6 (d, $J$=6.0 Hz, 1H), 5.73 (s, 2H), 6.86 (d, $J$=8.7 Hz, 2H), 7.25 (d, $J$=8.7 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) 21.6, 55.7, 65.2, 68.7, 72.0, 99.5, 114.2, 126.4, 129.8, 130.3, 130.7, 139.3, 159.6.

**4.2.21. 1,1-Bis-[1′-phenyl-prop-2′-en-1′-yloxy]-3-methyl-4-(*p*-methoxy-benzyloxy)-but-2-ene (20).** A solution of dimethylacetal **16** (500 mg, 1 equiv., 1.88 mmol) in dichloromethane (25 mL) and 1-phenyl-prop-2-en-1-ol (1.01 g, 4 equiv., 7.52 mmol) were put in a flask equipped with a heavy-solvent designed Dean–Stark device. The reaction mixture was refluxed in presence of acetic acid (0.05 mL). After 30 h, $NaHCO_3$ (4 mL) was added and the aqueous phase extracted with dichloromethane (2×10 mL). The resulting organic phase was dried ($MgSO_4$) and evaporated under reduce pressure. A flash chromatography on silica gel (eluting with heptane/AcOEt, 70:30) afforded 509 mg (60%) of acetal **20** as an inseparable mixture of diastereoisomers. Mixture of isomers: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) 1.5 (s, 3H), 3.79 (s, 5H), 4.9–5.7 (m, 10H), 5.95 (m, 2H), 6.86 (d, $J$=8.3 Hz, 2H), 7.1–7.4 (m, 12H).

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