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Nucleophilic additions on acetyldioxanes derived from (−)-(1*R*)-myrtenal used as chiral auxiliaries: substituent effects on the stereochemical outcome

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Dedicated to the memory of Dr. Howard Flack

ABSTRACT

The synthesis of acetyldioxanes **4** and **9a** starting from (−)-(1*R*)-myrtenal is described. The products were treated with a representative series of nucleophilic reagents (RMgX, RLi, $NaBH_4$ and $LiAlH_4$) to assess the effect of the substituent at C-3 on the stereochemical outcome. It was observed that the nucleophiles preferred the *re*-face of the C=O group when the equatorial substituent at C-3 was a methyl group, whereas a phenyl group at the same position induced the addition through the *si*-face, thus allowing access to either desired stereochemistry of a final product. This behavior suggests that the formation of the expected Cram-chelated coordination complex takes a coplanar orientation with the C-3 equatorial substituent. Moreover, Grignard reagents were the most stereoselective nucleophiles. The stereochemistry of the addition was established by X-ray diffraction and chemical correlation.

1. Introduction

Despite the great progress that organocatalysis has shown in recent years,[1–3] chiral auxiliaries are still a very effective and widely used tool to prepare non-racemic chiral compounds.[4,5] In this context, we have already described the synthesis of several chiral auxiliary derivatives of (−)-(1*R*)-myrtenal,[6a–d] which have proven to be particularly useful for the preparation of chiral α-hydroxycarbonyl and 1,2-diol derivatives in high diastereomeric ratios. Among these, 3-substituted-5-acyl-4,6-dioxanes **1**–**4** are noteworthy since they showed a clear dependence of both the nature and position of the substituent at C-3 on their ability to induce diastereoselective nucleophilic additions when using organometallic reagents (Scheme 1).[6d]

It was demonstrated[6d] that an axial substituent at C-3 in acyldioxane **2** does not affect the stereochemical course of the nucleophilic addition, thus yielding practically the same diastereomeric ratio (*dr*) as when using acyldioxane **1**, unsubstituted at the C-3 position, as can be observed through carbinols **6a**:**6b** and **5a**:**5b**, respectively. In turn, acyldioxanes **3** and **4**, both bearing an equatorial methyl group at C-3, gave adducts **7a**:**7b** and **8a**:**8b**, respectively, thus displaying lower diastereoselectivity than that shown by acyldioxanes **1** and **2** (Scheme 1).[6d] These results clearly showed that an equatorial substituent at C-3 plays a crucial role in the diastereofacial nucleophilic additions. It should be noted that in both acyldioxanes, the nucleophilic additions took place mainly onto the *re*-face of the carbonyl group.

Encouraged by these results, we herein extend the assessment of diastereoselective additions of organometallic reagents on acetyldioxanes **4** and **9a**. Acetyldioxane **9a** bears an equatorial phenyl group at C-3 instead of the equatorial methyl group found in acyldioxanes **3** and **4**, and thus allows insight into the influence of the substituent at this position on the stereochemical control of the nucleophilic additions.

2. Results and discussion

The synthesis of **4** was achieved according to the procedure described by Becerra et al.,[6d] while preparation of acetyldioxane **9a** was done following a similar procedure (Scheme 2).

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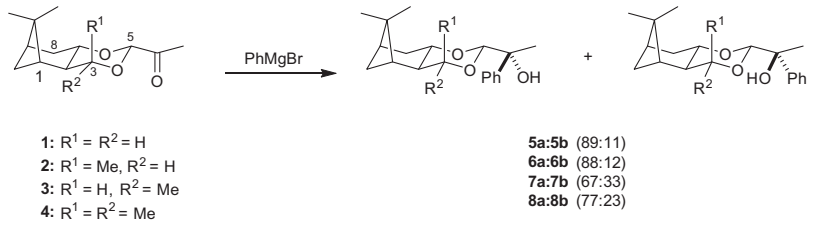
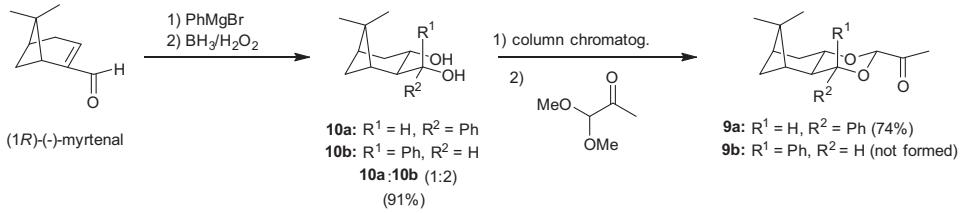


Scheme 1.



Scheme 2.

Thus, treatment of (−)-(1*R*)-myrtenal with PhMgBr in THF gave an epimeric mixture of 10-phenylmyrtenols in 98% yield, which without further purification was immediately treated with BH_3/H_2O_2 to afford an epimeric mixture of 3,10-pinanediols **10a**:**10b** (1:2, 91%). This mixture was separated by column chromatography to yield the corresponding epimeric diols **10a** and **10b**. Pinanediol **10a** was reacted with piruvaldehyde dimethyl acetal in benzene, using *p*-TsOH as the catalyst at −78 °C for 8 h, to afford acetyldioxane **9a** in 74% yield. In contrast, pinanediol **10b** did not yield acetyldioxane **9b** when treated under the protocol used for the preparation of **9a**, most likely due to the strong 1,3-diaxial interaction between the phenyl group at C-3 and the hydrogen atoms at C-5 and C-7, which would be present in the latter acetyldioxane. The single crystal X-ray diffraction PLUTO projection of pinanediol **10b** is shown in Figure 1.

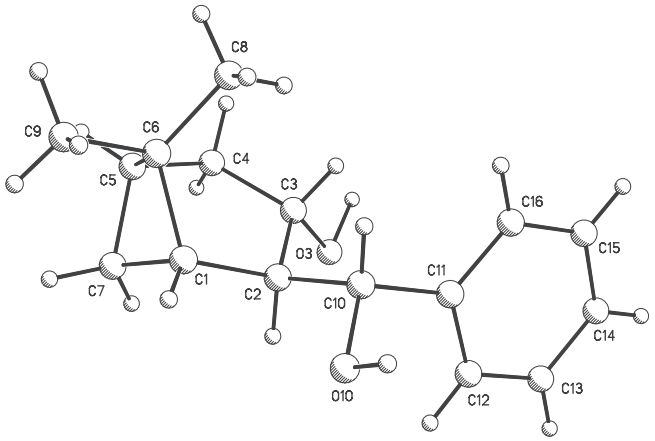


Figure 1. Single crystal X-ray PLUTO plot of pinanediol **10b**.

The stereochemical arrangement of acetyldioxane **9a** was corroborated by *nOe* difference experiments, in which the acetyl and phenyl groups were shown to have the equatorial configuration, since the respective ^{1}H NMR signals H-3ax (5.4%) and H-7 (10.2%) were enhanced upon irradiation of the H-5 acetal hydrogen.

With acetyldioxanes **4** and **9a** in hand, they were then subjected to a representative series of nucleophilic additions to gather information on the key factors controlling the stereochemical course of the reaction; the results obtained with acetyldioxane **4** are summarized in Table 1. As can be observed, nucleophilic additions proceeded in good to excellent chemical yields. Regarding the stereoselectivity, the additions of EtMgBr and PhMgBr exhibited the best diastereoisomeric ratios (entries 1 and 4), followed by the additions of H_2C═CHMgBr and *i*-PrMgBr (entries 5 and 2, respectively). In contrast, the addition of CH_3C≡CMgBr (entry 6) showed the same behavior as that observed in the reactions with $LiAlH_4$, $NaBH_4$ and PhLi (entries 7, 8 and 9) where no stereoselectivity was observed. The absence of stereoselectivity in entry 6 is likely due to the minimal steric interactions between the nucleophile possessing a rod-like geometry and the methyl group at C-3. Under these circumstances, coordination could occur between CH_3C≡CMgBr, the carbonyl group and either oxygen of the dioxane ring, and therefore the incoming nucleophile could attack either from the *re*- or the *si*-face of the carbonyl group.

The nucleophilic additions using acyldioxane **9a** are summarized in Table 2. As can be observed, the preparation of carbinol series **13** and **14** generally proceeded very well. Regarding the stereoselectivity, the obtained carbinols showed inverse diastereomeric ratios as compared to the acyldioxanes previously described,[6d] since the nucheophilic attack mainly proceeded through the *si*-face of the C═O group, thus clearly showing strong evidence that in this case, the phenyl group at C-3 modulates the stereochemical course of the nucleophiles. The stereoselectivity order is very similar to those shown by acyloxathianes and acyldioxanes, in which Grignard reagents are the most stereoselective, followed by lithium alkyls, with hydrides being the least stereoselective ones.[6a–c] Thus, the aliphatic Grignard reagents (entries 1 and 2) furnished only one diastereoisomer, whereas the remaining Grignard reagents showed good stereoselectivity (entries 3–6). Furthermore, the diastereoselectivities of organolithium reagents, such as PhLi and EtLi (entries 7 and 8), were significantly lower in comparison to those of their Grignard reagent counterparts (entries 6 and 1, respectively), but higher than the adduct obtained after addition of PhLi to acyldioxane **4** (entry 9, Table 1). In cases where the reduction was carried out using $LiAlH_4$ and $NaBH_4$ (entry 9–10), the reactions showed lack of diastereoselectivity, similar to that observed in acyloxathianes and acyldioxanes.[6a–d]

The course of the addition of nucleophiles to acyldioxanes can be explained by considering a Cram-type chelated transition state

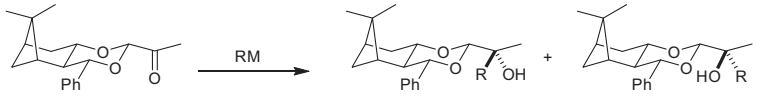
Table 1
Chemical yields and diastereomeric ratios of carbinols **11**:**12** obtained by the addition of organometallic reagents to acetyldioxane **4**

4 **11** **12**

Entry	RM	R	Yield (%)[a]	Ratio[b] (**11**:**12**)
1	EtMgBr	Et	75	84:16 (**11a:12a**)
2	*i*-PrMgBr	*i*-Pr	80	62:38 (**11b:12b**)
3	*i*-BuMgBr	*i*-Bu	89	60:40 (**11c:12c**)
4	PhMgBr	Ph	90	77:23 (**11d:12d**)
5	H_2C═CHMgBr	H_2C═CH	96	65:35 (**11e:12e**)
6	CH_3C≡CMgBr	H_3CC≡C	93	50:50 (**11f:12f**)
7	$LiAlH_4$	H	94	50:50 (**11g:12g**)
8	$NaBH_4$	H	95	50:50 (**11g:12g**)
9	PhLi	Ph	92	50:50 (**11d:12d**)

[a] Estimated, after column chromatography purification, as a **11** and **12** mixture.
[b] Determined by ^{1}H NMR integration of H-5 in the crude reaction mixture.

Table 2
Chemical yields and diastereomeric ratios of carbinols **13**:**14** obtained by the addition of organometallic reagents to acetyldioxane **9a**



9a **13** **14**

Entry	RM	R	Yield (%)[a]	Ratio[b] (**13**:**14**)
1	EtMgBr	Et	95	01:>99 (**13a:14a)**
2	BuMgBr	Bu	90	01:>99 (**13b:14b)**
3	*i*-PrMgBr	*i*-Pr	88	17:83 (**13c:14c)**
4	H_2C═CHMgBr	H_2C═CH	96	13:87 (**13d:14d)**
5	CH_3C≡CMgBr	H_3CC≡C	89	15:85 (**13e:14e)**
6	PhMgBr	Ph	84	07:93 (**13f:14f)**
7	PhLi	Ph	78	30:70 (**13f:14f)**
8	EtLi	Et	95	38:62 (**13a:14a)**
9	$LiAlH_4$	H	98	50:50 (**13g:14g)**
10	$NaBH_4$	H	96	50:50 (**13g:14g)**

[a] Estimated after column chromatography purification of the **13** and **14** mixture.
[b] Determined by ^{1}H NMR integration of H-5 of the crude reaction mixture.

(TS),[7] as proposed for acyldioxane **4** through **TS-A(Me)**[6 d] and by Bailey et al.[8] In acetyldioxane **9a**, the metal prefers to be coordinated with the carbonyl group and O-6 (**TS-B)** away from the phenyl group (Fig. 2), avoiding coordination with O-4 due to the steric hindrance as is shown in **TS-A(Ph)**. With this feature in hand, it is possible to argue that the methyl or hydrogen at C-3 does not exert a significant steric factor, as compared to the phenyl group, to avoid coordination between the metal and O-4, **TS-A(Me)**, particularly with Grignard reagents. The lack of diastereoselectivity shown by RLi, $LiAlH_4$ and $NaBH_4$ is in agreement with the well-known low affinity to form chelated complexes.

The diastereofacial preference of the nucleophile was confirmed by hydrolyzing the epimeric mixtures of carbinols **13b**:**14b** and **13f**:**14f**, obtained by the addition of BuMgBr and PhMgBr, respectively (Table 2; entries 1 and 6), with *p*-TsOH. The hydrolysis provided the corresponding α-hydroxyaldehydes **15a** and **15b**, which were easily reduced to the more stable 1,2-diols (Scheme 3) using $NaBH_4$. Subsequently, the crude reaction outcome was separated by column chromatography to give (−)-(*S*)-**16a** $[\alpha]_D^{23} = -3.1$ (*c* 1.27, $CHCl_3$), {literature[9] $[\alpha]_D^{23} = +4.4$ (*c* 1.0, $CHCl_3$) for the (*R*)-enantiomer}, and (−)-(*R*)-**16b** $[\alpha]_D^{23} = -5.0$ (*c* 1.02, EtOH), {literature[10] $[\alpha]_D^{23} = -5.8$ (*c* 0.12, EtOH)} as the major enantiomers.

Additional evidence for the stereochemical outcome of the nucleophilic additions was obtained from the X-ray structure of the major diastereoisomer formed by the addition of EtMgBr to acyldioxane **9a**, in which the (*S*) configuration at the new carbinol center can be observed, thus revealing that the nucleophile was added from the *si*-face of the carbonyl group (Fig. 3).

3. Conclusion

The already known series of carbinol derivatives **11**:**12** prepared from acyldioxane **4** has been expanded. Furthermore, the preparation of the new 3-phenyl-5-acetyldioxane **9a** allowed us to gain insight on the reactivity of acyldioxane systems derived from (−)-(1*R*)-myrtenal, thus providing new alternatives to control the stereochemical outcome**.** In comparison with acetyldioxane **4**, nucleophilic additions carried out on **9a** using Grignard reagents showed higher diastereoselectivity, even when organolithium reagents were used. Based on diols obtained by hydrolysis of

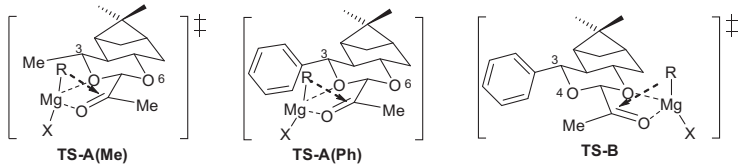
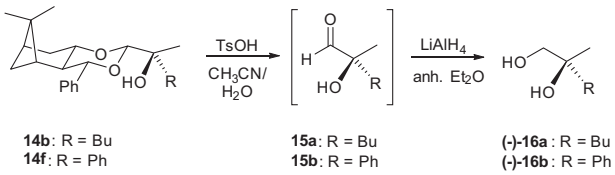


Figure 2. Cram-type chelated transition states, **TS-A(Me)**, **TS-A(Ph)** and **TS-B** showing coordination sites of Grignard reagents on acetyldioxanes **4** and **9a**. It can be observed that while **TS-A(Me)** is favored for acetyldioxane **4**, the similar arrangement **TS-A(Ph)** is disfavored for **9a**. **TS-B** shows the favored *si* face attack on the carbonyl group for acetyldioxane **9a**.



Scheme 3. Hydrolysis of the epimeric mixtures of carbinols **13b**:**14b** and **13f**:**14f** to be correlated with 1,2-diols (−)-(*S*)-**16a** and (−)-(*S*)-**16b**, respectively, of known absolute configuration (For simplicity, only the major stereoisomers are shown).

carbinols **13**:**14** and X-ray data of diastereoisomer **14a**, nucleophilic attacks on **9a** took place on the *si*-face of the carbonyl group, giving the opposite absolute configuration at the carbinol center as compared with the same center formed in the **11**:**12** series. It is noteworthy that hydrolysis of carbinolic dioxanes **11**–**14** proceeds under milder reaction conditions than the structural analogues carbinolic oxathianes.[6a–d] Thus, the present results provide the possibility to obtain either enantiomers of chiral 1,2-diols with good to excellent stereoselectivities *via* a chiral auxiliary protocol, using either acyldioxanes **1** or **9a**, according to the desired stereochemistry at the carbinol center. In some cases, it also avoids the use of odourous sulfur molecules required for the preparation of oxathianes.

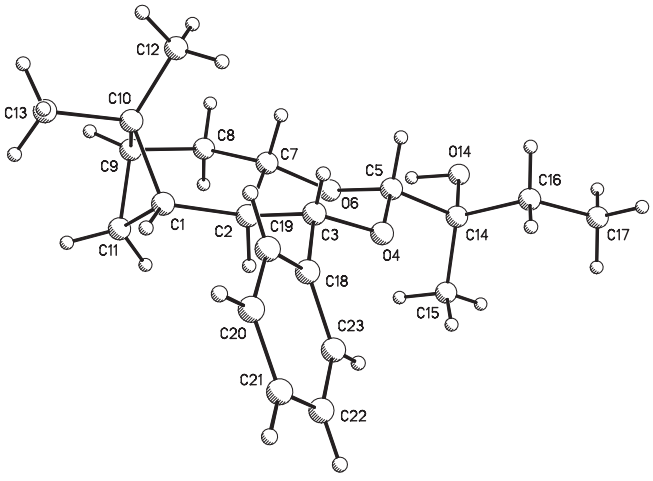


Figure 3. Single crystal X-ray PLUTO plot of **14a**.

4. Experimental

4.1. General

Melting points were determined on an Electrothermal capillary melting point apparatus and are uncorrected. Optical rotations were measured at 589 nm using a 1 dm cell on a JASCO DIP-370 polarimeter. Infrared spectra were recorded on a Perkin–Elmer Spectrum 2000 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 spectrometer using $CDCl_3$ solutions with TMS as the internal standard. Chemical shifts are reported in parts per million (δ) downfield from TMS for ^{1}H and relative to the central line of the triplet of $CDCl_3$ at 77.00 ppm for ^{13}C. The low-resolution mass spectra (LRMS) were recorded on a Varian Saturn 2000 GC/Ion Trap Detector, using either EI (70 eV) or CI, as specified. The high-resolution electron impact mass spectra (HREIMS) were recorded on a VG 7070 high-resolution mass spectrometer at the UCR Mass Spectrometry Facility, University of California, Riverside, CA. Thin-layer chromatograms were done on precoated TLC sheets of silica gel 60 F254 (E. Merck). Flash chromatography was carried out using Merck silica gel (230–400 mesh). THF used in the nucleophilic addition reactions was distilled from Na immediately prior to use, while all other reagents were used as received.

4.2. General procedure for the addition of Grignard reagents to acyldioxanes 4 and 9a

4.2.1. Method 1

To a solution of acetyldioxanes **4** or **9a** (1 equiv) in anhydrous THF, the Grignard reagent (3 equiv) was added at −78 °C under an N_2 atmosphere. After stirring for 3 h at the same temperature, the reaction mixture was allowed to warm up to the room temperature and then stirred for 1 h. The reaction mixture was quenched with 10 mL of a saturated solution of ammonium chloride; the THF was eliminated by evaporation under reduced pressure, and the remaining emulsion was extracted with ethyl ether. The organic layer was washed with a saturated solution of ammonium chloride, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness to give the corresponding mixture of carbinols as colorless oils. Column chromatography separation was unsuccessful due to the very similar R_f of the diastereoisomers in the mixture and therefore specific rotations are not reported. Only the spectroscopic data of the major diastereoisomers **11a-g** and **14a-g**, obtained from the spectra of the corresponding mixture, are described.

4.2.2. Method 2

Into an oven-dried two-necked 100 mL round-bottom flask equipped with a magnetic stirring bar were added magnesium (3 equiv) and the alkyl halide (3 equiv) in 10 mL of anhydrous THF. The resulting mixture was stirred at room temperature for 30 min. The mixture was then cooled to −78 °C and a solution of acetyldioxane **4** or **9a** (1 equiv) in 5 mL of anhydrous ether was added and stirring was continued at the same temperature for a further 3 h. The reaction mixture was quenched with 10 mL of a saturated solution of ammonium chloride, the THF was eliminated by evaporation under reduced pressure, and the remaining emulsion was extracted with ethyl ether. The organic layer was washed with a saturated solution of ammonium chloride, dried over anhydrous Na_2SO_4, filtered, and evaporated to give the corresponding mixture of carbinols as colorless oils.

4.3. (1*S*,2*R*,5*R*,7*S*,9*R*,1′*R*)-5-(2′-Hydroxybut-2′-yl)-3,3,10,10-tetramethyl-4,6-dioxatricyclo[7.1.1.0^{2,7}]undecane 11a

4.3.1. Obtained using method 2

Compound **4** (80 mg, 0.31 mmol) in anhydrous ethyl ether (10 mL) was treated with 0.07 mL (1 mmol) of EtBr and 24 mg (1 mmol) of magnesium. After work-up, 67 mg (75%) of a diastereoisomeric mixture of carbinols **11a:12a** (84:16) were obtained as a colorless syrup. (R_f 0.48, hexanes-AcOEt 9:1). ^{1}H NMR ($CDCl_3$): δ 4.69 (1H, s, H-5), 4.49 (1H, dd, J = 8.7 Hz, H-7), 2.64 (1H, m, H-11eq), 2.34 (1H, m, H-8eq), 2.24 (1H, bs, OH), 2.09 (2H, m, H-2, H-9), 1.94 (1H, t, J = 6 Hz, H-1), 1.70 (1H, m, H-8ax), 1.56 (2H, m, H-3′), 1.26 (3H, s, Me-1′), 1.24 (3H, s, Me-15), 1.20 (3H, s, Me-13), 1.13 (3H, s, Me-14), 1.08 (3H, s, Me-12), 1.05 (1H, d, J = 9.6 Hz, H-11ax), 0.92 (3H, t, J = 7.6 Hz, Me-4′). ^{13}C NMR ($CDCl_3$): δ 100.1 (C-5), 76.7 (C-3), 73.4 (C-2′), 70.8 (C-7), 58.1 (C-2), 43.5 (C-1), 43.3 (C-9), 41.5 (C-11), 39.5 (C-10), 33.1 (C-8), 30.2 (C-1′), 29.5 (C-13), 29.3 (C-3′), 25.7 (C-12), 21.5 (C-14), 19.4 (C-15), 7.5 (C-4′). IR ($CHCl_3$): 3586, 2975, 1457, 1379, 1155, 1095 cm^{-1}. MS m/z (rel. int.): 281 (M^+−1, 0.3), 163 (15), 121 (22), 107 (34), 91 (22), 79 (100), 67 (66), 55 (29), 43 (53), 41 (48), 39 (25).

4.4. (1*S*,2*R*,5*R*,7*S*,9*R*,1′*R*)-5-(2′-Hydroxybut-3-en-2′-yl)-3,3,10,10-tetramethyl-4,6-dioxatricyclo[7.1.1.0^{2,7}]undecane 11b

4.4.1. Obtained using method 1

Obtained using method 1: Compound **4** (90 mg, 0.35 mmol) in anhydrous THF (10 mL) was treated with 1.0 M *i*-PrMgBr (0.90 mL, 0.90 mmol) in ether. After work-up, 85 mg (80%) of a diastereoisomeric mixture of carbinols **11b:12b** (62:38) were obtained as a colorless syrup. (R_f 0.45, hexanes-AcOEt 98:2). ^{1}H NMR ($CDCl_3$): δ 4.67 (1H, s, H-5), 4.48 (1H, dd, J = 8.7 Hz, H-7), 2.63 (1H, m, H-11eq), 2.35 (1H, m, H-8eq), 2.22 (1H, s, –OH), 2.10 (2H, m, H-2, H-9), 1.97 (1H, c, J = 6.9 Hz, H-3′), 1.95 (1H, t, J = 6.0 Hz, H-1), 1.71 (1H, m, H-8ax), 1.25 (3H, s, Me-1′), 1.22 (3H, s, Me-15), 1.18 (3H, s, Me-13), 1,11 (3H, s, Me-14), 1.08 (3H, s, Me-12), 1.05 (1H, d, J = 9.6 Hz, H-11ax), 0.95 (3H, d, J = 6.6 Hz, Me-5′), 0.92 (3H, d, J = 6.9 Hz, Me-4′). ^{13}C NMR ($CDCl_3$): δ 100.2 (C-5), 76.5 (C-3), 73.3 (C-2′), 70.9 (C-7), 58.3 (C-2), 43.2 (C-1), 43.4 (C-9), 41.5 (C-11), 39.4 (C-10), 33.4 (C-3′), 33.6 (C-8), 30.2 (C-1′), 29.5 (C-13), 25.5 (C-12), 21.4 (C-14), 19.4 (C-15), 17.7 (C-4′), 17.1 (C-5′). IR ($CHCl_3$): 2953, 1457, 1356, 1150, 1085 cm^{-1}. MS m/z (rel. int.): 297 (M^++1, 2), 279 (1), 253 (3), 209 (37), 181 (8), 163 (98), 135 (41), 121 (52), 109 (100), 95 (22), 43 (25).

4.5. (1*S*,2*R*,5*R*,7*S*,9*R*,1′*R*)-5-(4′-Methyl-2′-hydroxypent-2′-yl)-3,3,10,10-tetramethyl-4,6-dioxatricyclo[7.1.1.0^{2,7}]undecane 11b

4.5.1. Obtained using method 1

Compound **4** (100 mg, 0.39 mmol) in anhydrous THF (10 mL) was treated with 1.0 M *i*-BuMgBr (0.96 mL, 0.96 mmol) in ether. After work-up, 110 mg (89%) of a diastereoisomeric mixture of carbinols **11c:12c** (60:40) were obtained as a colorless syrup. (R_f 0.45, hexanes-AcOEt 98:2). ^{1}H NMR ($CDCl_3$): δ 4.69 (1H, s, H-5), 4.49 (1H, dd, J = 8.7 Hz, H-7), 2.64 (1H, m, H-11eq), 2.34 (1H, m, H-8eq), 2.24 (1H, bs, –OH), 2.09 (2H, m, H-2, H-9), 1.94 (1H, t, J = 6.0 Hz, H-1), 1.82 (m, 1H, H-4′), 1.70 (1H, m, H-8ax), 1.45 (m, 2H, H-3′), 1.26 (3H, s, Me-1′), 1.24 (3H, s, Me-15), 1.20 (3H, s, Me-13), 1.13 (3H, s, Me-14), 1.08 (3H, s, Me-12), 1.05 (1H, d, J = 9.6 Hz, H-11ax), 0.98 (d, 3H, J = 6.6 Hz, CH3-5′), 0.95 (d, 3H, J = 6.7 Hz, CH3-6′). ^{13}C NMR ($CDCl_3$): δ 100.3 (C-5), 76.4 (C-3), 73.1 (C-2′), 70.7 (C-7), 58.4 (C-2), 44.7 (C-3′), 43.5 (C-1), 43.1 (C-9), 41.6 (C-11), 39.4 (C-10), 33.0 (C-8), 30.1 (C-1′), 29.4 (C-13), 25.6 (C-12), 25.2 (C-6′), 24.5 (C-5′), 23.3 (C-4′), 21.5 (C-14), 19.4 (C-15). IR (CHCl3): 3587, 2952, 1464, 1369, 1095, 964 cm^{-1}. MS m/z (rel. int.): 309 (M^+−1, 3), 209 (41), 163 (100), 135 (41), 121 (48), 110 (76), 108 (39), 98 (13), 85 (10), 71 (13).

4.6. (1*S*,2*R*,5*R*,7*S*,9*R*,1′*R*)-5-(1′-Hydroxy-1′-phenyleth-1′-yl)-3,3,10,10-tetramethyl-4,6-dioxatricyclo[7.1.1.0^{2,7}]undecane 11d

4.6.1. Method 3

A well-stirred cooled (−78 °C) solution of 84 mg (0.33 mmol) of acetyldioxane **4** in 10 mL of anhydrous THF was treated with 0.55 mL (0.99 mmol) of 1.8 M PhLi in cyclohexane and stirred under an N_2 atmosphere for 3 h. The mixture was quenched with 1.5 mL of a saturated solution of ammonium chloride and allowed to warm up to room temperature. The THF was evaporated and the residue was extracted with 50 mL of ethyl ether. The organic layer was washed with 5% aq HCl (3 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by column chromatography using silica gel and a mixture of hexanes-AcOEt as eluent to give 101 mg (92%) of carbinols **11d:12d** (50:50) as a colorless syrup.

4.6.2. Obtained using method 1

Compound **4** (72 mg, 0.28 mmol) in anhydrous THF (10 mL) was treated with 1 M PhMgBr (0.86 mL, 86 mmol) in ether. After work-up, 85 mg (90%) of a diastereoisomeric mixture of carbinols **11d:12d** (77:23) was obtained as a colorless syrup. (R_f 0.34, hexanes-AcOEt 98:2). ^{1}H NMR ($CDCl_3$): δ 7.54 (2H, d, J = 8.5 Hz, H-*ortho*), 7.31 (2H, dd, J = 7.2, 8.5 Hz, H-*meta*), 7.24 (1H, d, J = 7.2 Hz, H-*para*), 4.92 (1H, s, H-5), 4.47 (1H, bt, J = 8.7 Hz, H-7), 3.07 (1H, bs, OH), 2.62 (1H, m, H-11eq), 2.30 (1H, m, H-8eq), 2.09 (2H, m, H-2, H-9), 1.92 (1H, t, J = 6.9 Hz, H-1), 1.78 (1H, m, H-8ax), 1.52 (3H, s, Me-2′), 1.24 (3H, s, Me-15), 1.19 (6H, s, Me-13,14), 1.05 (1H, d, J = 9.5 Hz, H-11ax), 1.04 (3H, s, Me-12). ^{13}C NMR ($CDCl_3$): δ 145.2 (C-*ipso*), 127.9 (C-*meta*), 126.8 (C-*para*), 126.2 (C-*ortho*), 100.5 (C-5), 77.5 (C-3), 74.9 (C-1′), 71.1 (C-7), 58.1 (C-2), 43.6 (C-1), 43.5 (C-9), 41.7 (C-11), 39.6 (C-10), 33.2 (C-8), 30.3 (C-15), 29.6 (C-13), 25.9 (C-12), 24.6 (C-2′), 19.6 (C-14). IR ($CHCl_3$): 3566, 2976, 1493, 1447, 1379, 1153, 1093 cm^{-1}. MS m/z (rel. int.): 330 (M^+, 0.3), 163 (146), 135 (16), 121 (51), 107 (72), 91 (68), 79 (100), 67 (48).

4.7. (1*S*,2*R*,5*R*,7*S*,9*R*,1′*R*)-5-(2′-Hydroxy-3′-buten-2′-yl)-3,3,10,10-tetramethyl-4,6-dioxatricyclo[7.1.1.0^{2,7}]undecane 11e

4.7.1. Obtained using method 1

Compound **4** (60 mg, 0.23 mmol) in anhydrous THF (10 mL) was treated with 2 M CH_2=CHMgBr (0.35 mL, 0.71 mmol) in ether. After work-up, 64 mg (96%) of a diastereoisomeric mixture of carbinols **11e:12e** (65:35) were obtained as a colorless syrup (R_f 0.4, hexanes-AcOEt 9:1). ^{1}H NMR ($CDCl_3$): δ 6.03 (1H, dd, J = 10.8, 17.4 Hz, H-3′), 5.36 (1H, dd, J = 1.7, 17.4 Hz, H-4′a), 5.12 (1H, dd, J = 1.7, 10.8 Hz, H-4′b), 4.70 (1H, s, H-5), 4.49 (1H, dd, J = 8.7 Hz, H-7), 2.63 (1H, m, H-11eq), 2.53 (1H, m, H-2), 2.33 (1H, m, H-8eq), 2.08 (1H, m, H-9), 1.93 (1H, t, J = 6.0 Hz, H-1), 1.77 (1H, m, H-8ax), 1.26 (3H, s, Me-1′), 1.25 (3H, s, Me-15), 1.24 (3H, s, Me-13), 1.21 (3H, s, Me-14), 1.07 (3H, s, Me-12), 1.06 (1H, d, J = 8.4 Hz, H-11ax). ^{13}C NMR δ 141.6 (C-3′), 113.3 (C-4′), 100.4 (C-5), 77.2 (C-3), 74.0 (C-2′), 71.0 (C-7), 58.1 (C-2), 43.6 (C-1), 43.4 (C-9), 41.5 (C-11), 39.6 (C-10), 33.1 (C-8), 30.3 (C-15), 29.6 (C-13), 25.9 (C-12), 22.7 (C-1′), 19.6 (C-14). IR ($CHCl_3$): 3580, 2976, 1646, 1456, 1379, 1155, 1093 cm^{-1}. MS m/z (rel. int.): 279 (M^+−1, 0.2), 181 (15), 163 (100), 121 (13), 107 (28), 79 (54), 67 (40), 55 (18), 43 (73), 41 (45), 39 (27).

4.8. (1*S*,2*R*,5*R*,7*S*,9*R*,1′*R*)-5-(2′-Hydroxy-3′-pentin-2′-yl)-3,3,10,10-tetramethyl-4,6-dioxatricyclo[7.1.1.0^{2,7}]undecane 11f

4.8.1. Obtained using method 1

Compound **4** (85 mg, 0.34 mmol) in anhydrous THF (10 mL) was treated with 0.5 M C_3H_3MgBr (0.2 mL, 1 mmol) in ether. After work-up 92 mg (93%) of a diastereoisomeric mixture of carbinols **11f:12f** (50:50) were obtained as a colorless syrup. (R_f 0.2, hexanes-AcOEt 98:2). ^{1}H NMR ($CDCl_3$): δ 4.76 (1H, s, H-5), 4.55 (1H, bt, J = 8.9 Hz, H-7), 2.80 (1H, s, OH), 2.64 (1H, m, H-11eq), 2.37 (1H, m, H-8eq), 2.11 (2H, m, H-2, H-9), 1.95 (1H, t, J = 7 Hz, H-1), 1.85 (3H, s, Me-5′), 1.84 (1H, m, H-8ax), 1.43 (3H, s, Me-1′), 1.27 (3H, s, Me-15), 1.26 (3H, s Me-13), 1.24 (3H, s, Me-14), 1.08 (3H, s, Me-12), 1.07 (1H, d, J = 9.7 Hz, H-11ax). ^{13}C NMR ($CDCl_3$): δ 99.5 (C-5), 80.7 (C-3′), 80.6 (C-4′), 77.5 (C-3), 71.1 (C-7), 69.5 (C-2′), 57.9 (C-2), 43.6 (C-1), 43.5 (C-9), 41.6 (C-11), 39.6 (C-10), 33.1 (C-8), 30.3 (C-15), 29.6 (C-14), 25.9 (C-12), 24.4 (C-1′), 19.6 (C-13), 4.7 (C-5′). IR ($CHCl_3$): 3565, 2977, 1455, 1379, 1154, 1097 cm^{-1}. MS m/z (rel. int.): 292 (M$^+$, 0.1), 121 (12), 107 (32), 91 (23), 79 (100), 67 (67), 55 (16), 43 (64), 41 (47), 39 (27).

4.9. (1*S*,2*R*,5*R*,7*S*,9*R*,1′*R*)-5-(1′-Hydroxy-eth-1′-yl)-3,3,10,10-tetramethyl-4,6-dioxatricyclo[7.1.1.0^{2,7}]undecane 11g

4.9.1. Method 4

To a cooled (−78 °C) suspension of 27 mg (0.713 mmol) of $LiAlH_4$ in 5 mL of anhydrous THF under an N_2 atmosphere, a solution of 60 mg (0.237 mmol) of dioxane **4** in 5 mL of anhydrous THF was added. The resulting mixture was stirred at the same temperature for 3 h. Next, 10 mL of a saturated solution of ammonium chloride were added, after which THF was evaporated and the crude reaction mixture was extracted (3 × 30 mL) with ethyl ether. The organic layer was washed with brine, dried with anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by column chromatography using alkalinized silica gel and a mixture of hexanes-AcOEt 95:5 as eluent, yielding 57 mg (94%) of carbinols **11g**:**12g** (50:50) as colorless syrups.

4.9.2. Method 5

To a cooled (−78 °C) solution of 93 mg (0.37 mmol) of acetyldioxane **4** in 10 mL of MeOH were added 42 mg (1.11 mmol) of $NaBH_4$ and the resulting mixture was stirred for 3 h. The reaction was quenched with 10 mL of a saturated solution of NH_4Cl, stirred for 30 min, and then the solvent was evaporated. The crude reaction mixture was extracted with Et_2O (3 × 50 mL) and the solution washed with water. The organic layer was dried with anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by column chromatography using hexanes-AcOEt (99:1) as eluent, giving 89 mg (95%) of carbinols **11g**:**12g** (50:50) as a colorless syrup. (R_f 0.14, hexanes-AcOEt 98:2). ^{1}H NMR ($CDCl_3$): δ 4.71 (1H, s, H-5), 4.52 (1H, bq, J = 8.3 Hz, H-7), 3.68 (1H, m, H-1′), 2.53 (1H, m, H-11eq), 2.39 (2H, m, OH, H-8eq), 2.13 (2H, m, H-2, H-9), 1.97 (1H, m, H-1), 1.78 (1H, m, H-8ax), 1.27 (6H, s, Me-15, Me-13), 1.26 (3H, s, Me-14), 1.21 (3H, d, J = 6.3 Hz, Me-2′), 1.07 (3H, s, Me-12), 1.05 (1H, d, J = 9.6 Hz, H-11ax). ^{13}C NMR ($CDCl_3$): δ 99.8 (C-5), 77.5 (C-3), 70.9 (C-7), 69.3 (C-1′), 58.0 (C-2), 43.8 (C-1), 43.8 (C-9), 41.9 (C-11), 39.8 (C-10), 33.5 (C-8), 30.2 (C-15), 29.9 (C-13), 26.0 (C-12), 19.9 (C-14), 18.8 (C-2′). IR ($CHCl_3$): 3736, 2924, 1455, 1379, 1154, 1092 cm^{-1}. MS m/z (rel. int.): 254 (M$^+$, 0.1), 181 (10), 163 (59), 107 (29), 91 (16), 79 (88), 67 (66), 55 (28), 43 (100), 41 (76), 39 (37).

4.10. (1*R*)-10-*epi*-Phenylmyrtenol

To a cooled solution (−78 °C) of 7.43 g (49.5 mmol) of (1*R*)-myrtenal in 50 mL of anhydrous THF, 1.5 equiv of PhMgBr were added and the resulting mixture was stirred at the same temperature for 5 h under an N_2 atmosphere. The crude reaction mixture was poured into ice-water and extracted (3 × 100 mL) with ether, washed with brine, dried with anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by column chromatography (hexanes-EtOAc 98:2) giving 11.8 g (98%) of 10-*epi*-phenylmyrtenol as colorless syrup. (R_f 0.37, hexanes-AcOEt 9:1). ^{1}H NMR ($CDCl_3$): δ 7.26 (5H, m, H-Ar), 5.56 (1H, m, H-3), 5.05 (1H, bs, H-10), 2.29 (3H, m, H-4, H-7eq), 2.18 (1H, s, –OH), 2.05 (2H, m, H-1, H-5), 1.17 (3H, s, Me-9), 1.07 (1H, d, J = 8.5 Hz, H-7ax), 0.71 (3H, s, Me-8). ^{13}C NMR ($CDCl_3$): δ 149.7 (C-*ipso*), 141.9 (C-2), 128.3 (C-*ortho*), 126.9 (C-*para*), 126.6 (C-*meta*), 119.0 (C-3), 76.7 (C-10), 42.5 (C-1), 40.9 (C-5), 37.9 (C-6), 32.1 (C-4), 31.5 (C-7), 26.2 (C-9), 21.5 (C-8). IR ($CHCl_3$): 3392, 3028, 2989, 2915, 2831, 1636, 1450, 1365, 1267, 1079, 1047, 1017, 753, 700 cm^{-1}. MS m/z (rel. int.): 228 (M$^+$, 3), 228 (30), 211 (100), 210 (58), 195 (12), 184 (12), 168 (15), 167 (32), 155 (11), 141 (11), 107 (12), 105 (20), 91 (16), 79 (19). HRFABMS calcd for $C_{16}H_{20}O$ 228.1514. Found 228.1521.

4.11. (1*S*,2*S*,3*S*,5*R*)-2-((*S*)-Hydroxy(phenyl)methyl)-6,6-dimethylbicyclo[3.1.1]heptan-3-ol 10a and (1*S*,2*S*,3*S*,5*R*)-2-((*R*)-hydroxy(phenyl)methyl)-6,6-dimethylbicyclo[3.1.1]heptan-3-ol 10b

A 500-mL oven-dried two-necked round bottom flask, equipped with a pressure-equalizing addition funnel, was cooled in an ice-water bath and loaded with 100 mL of anhydrous THF and 15.4 g (67.47 mmol) of 10-*epi*-phenylmyrtenol under a nitrogen atmosphere. A solution of 26.9 mL (269.9 mmol) of 10–10.2 M BH_3SMe_2 in 30 ml of THF was then added dropwise through the addition funnel for 1 h. The resulting mixture was stirred at 0–4 °C for 3 h and then for 24 h at room temperature. The mixture was cooled again in an ice-water bath and 10 mL of water were added dropwise over 30 min, and stirring was continued for 1 h at the same temperature. Next, 45 mL of 3 M NaOH were added at once, followed by the dropwise addition of 30 mL of 30% H_2O_2 over 30 min; the mixture was stirred for an additional 1 h. Excess THF was eliminated in a rotary evaporator, and the residue was extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The solid residue was washed with hexanes (3 × 50 mL) and dissolved in 250 mL of a mixture of hexanes-CH_2Cl_2 (3:1). The organic layer was washed with water (5 × 40 mL), dried with anhydrous Na_2SO_4, and evaporated to dryness yielding an epimeric mixture of **10a** and **10b**. The solid was recrystallized from hexanes-$CHCl_3$.

4.11.1. (1*S*,2*S*,3*S*,5*R*)-2-((*S*)-Hydroxy(phenyl)methyl)-6,6-dimethylbicyclo[3.1.1]heptan-3-ol 10a

Obtained in 40% yield after column chromatography from the epimeric mixture of **10a** and **10b** as colorless needles, mp 104–108 °C. (R_f = 014, hexanes-AcOEt 8:2). $[\alpha]_D^{21}$ = +14.8 (0.32, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.32 (5H, m, H-Ar), 4.62 (2H, m, H-3, H-10), 3.03 (1H, bs, OH), 2.78 (1H, bs, OH), 2.53 (1H, m, H-4eq), 2.24 (1H, m, H-7eq), 2.11 (1H, m, H-2), 1.94 (1H, m, H-5), 1.76 (1H, m, H-4ax), 1.38 (1H, m, H-1), 1.11 (3H, s, Me-9), 1.04 (3H, s, Me-8), 0.98 (1H, d, J = 9.9 Hz, H-7ax). ^{13}C NMR ($CDCl_3$): δ 143.7 (C-*ipso*), 128.6 (C-*ortho*), 128.0 (C-*para*), 127.2 (C-*meta*), 79.3 (C-10), 69.0 (C-3), 60.3 (C-2), 42.9 (C-1), 42.0 (C-5), 38.2 (C-6), 37.0 (C-4), 34.5 (C-7), 27.8 (C-9), 24.7 (C-8). IR ($CHCl_3$): 3495, 3308, 2912, 1457, 1384, 1284, 1200, 1116, 1030, 853, 760, 699, 554 cm^{-1}. MS m/z (rel. int.): 245 (M$^+$−1, 1), 211 (38), 210 (17), 185 (14), 167 (11), 159 (16), 143 (35), 131 (36), 130 (31), 129 (31), 128 (16), 122 (12), 115 (12), 108 (12), 107 (34), 105 (34), 95 (13), 91 (70), 80 (10), 79 (100), 78 (41), 77 (36), 67 (11), 41 (14). HRFABMS calcd for $C_{16}H_{22}O_2$+NH_4 246.1856. Found 246.1862.

4.11.2. (1*S*,2*S*,3*S*,5*R*)-2-((*R*)-Hydroxy(phenyl)methyl)-6,6-dimethylbicyclo[3.1.1]heptan-3-ol 10b

Obtained in 35% yield after column chromatography from the epimeric mixture of **10a** and **10b** as colorless crystals, mp = 90–92 °C. (R_f = 014, hexane-AcOEt 8:2). $[\alpha]_D^{21} = -27.9$ (1.14, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): d 7.34 (5H, m) H-Ar; 4.58 (1H, dd, J = 3 y 10 Hz) H-10; 3.97 (1H, m) H-3; 2.45 (2H, m) H-1, H-7*e*; 2.38 (1H, m) H-4*e*; 2.22 (1H, m) H-2; 2.14 (1H, s) OH; 1.97 (1H, m) H-5; 1.65 (1H, m) H-4*a*; 1.27 (3H, s) Me-9; 1.09 (1H, m) H-7*a*; 0.96 (3H, s) Me-8; 0.84 (1H, m) –OH. ^{13}C NMR (300 MHz, $CDCl_3$): δ 143.7 (C-*ipso*); 129.2 (C-*ortho*); 128.6 (C-*para*); 127.1 (C-*meta*); 76.8 (C-10); 65.1 (C-3); 60.8 (C-2); 42.7 (C-1); 41.8 (C-5); 38.3 (C-6); 37.2 (C-4); 33.5 (C-7); 27.0 (C-9); 23.9, (C-8). IR (ν, cm^{-1}); 3561; 3421; 2923; 2886; 1457; 1361; 1287; 1047; 1019; 765; 707; 641; 552. EM (70 eV) *m*/*z* (rel. int.): 244 (M^+−2, 1); 211 (30); 210 (14); 185 (13); 184 (12); 169 (15); 167 (18); 159 (10); 143 (14); 131 (14); 130 (14); 129 (14); 122 (13); 108 (24); 107 (44); 105 (29); 95 (13); 91 (33); 79 (100); 78 (34). HRFABMS calcd for $C_{16}H_{22}O_2$ – H 245.1542. Found 245.1522.

4.12. (1*S*,2*R*,3*S*,5*R*,7*S*,9*R*)-5-Acetyl-10,10-dimethyl-3-phenyl-4,6-dioxatricyclo[7.1.1.0^{2,7}]undecane 9a

A 100 mL oven-dried two-necked round-bottom flask equipped with a Dean Stark trap and a magnetic stirring bar, containing a solution of 208 mg (0.84 mmol) of diol **10a** and 20 mg of *p*-TsOH in 50 mL of anhydrous benzene, was placed in an oil bath and warmed to 78 °C. Then 0.40 mL (3.38 mmol) of α,α-dialkoxyacetal was added dropwise, and the resulting mixture was stirred at the same temperature under a nitrogen atmosphere for 8 h. The reaction mixture was allowed to reach the room temperature and 50 mL of hexanes were added. The organic layer was washed with 10 mL of a 5% aqueous solution of $NaHCO_3$, dried with anhydrous Na_2SO_4, filtered, and evaporated at 40–45 °C under a reduced pressure. The oil residue was purified by column chromatography using silica gel alkalinized with Et_3N and a mixture of hexanes-AcOEt (98:2) to give 186.7 mg (74%) of acetyldioxane **9a** as a colorless syrup (R_f = 0.42, hexanes-AcOEt 9:1). $[\alpha]_D^{21} = -28.2$ (*c* 0.97, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.34 (5H, m, H-Ar), 5.18 (1H, s, H-5), 4.72 (1H, d, *J* = 10.4 Hz, H-3), 4.62 (1H, c, *J* = 9, 18.3 Hz, H-7), 2.47 (2H, m, H-8eq, H-11eq), 2.32 (3H, s, Me-2′), 2.27 (1H, t, *J* = 9.8 Hz, H-2), 2.12 (1H, c, *J* = 5.7, 10.8 Hz, H-9), 1.94 (1H, dd, *J* = 9.6, 12.7 Hz, H-8ax), 1.60 (1H, t, *J* = 6 Hz, H-1), 1.21 (6H, s, Me-12, Me-13), 0.96 (1H, d, *J* = 9.6 Hz, H-11ax). ^{13}C NMR ($CDCl_3$): δ 202.1 (C-1′), 138.7 (C-*ipso*), 128.6 (C-*ortho*), 128.5 (C-*para*), 127.3 (C-*meta*), 102.4 (C-5), 85.8 (C-3), 77.5 (C-7), 55.5 (C-2), 43.3 (C-9), 42.9 (C-1), 40.2 (C-11), 39.1 (C-10), 33.3 (C-8), 30.0 (C-2′), 25.6 (C-13), 25.4 (C-12). IR ($CHCl_3$): 3365, 2935, 1642, 1577, 1446, 1420, 1366, 1315, 1268, 1178, 1114, 1026, 861, 784, 718 cm^{-1}. MS *m*/*z* (rel. int.): 212 (40), 169 (27), 151 (19), 143 (22), 141 (17), 131 (13), 130 (23), 129 (21), 128 (16), 122 (43), 121 (13), 119 (11), 115 (23), 107 (43), 105 (23), 93 (13), 91 (78), 83 (30), 80 (12), 79 (95), 78 (100), 77 (40), 67 (17). HRFABMS calcd for $C_{19}H_{24}O_3$+NH_4 318.2069. Found 318.2067.

4.13. (1*S*,2*R*,3*S*,5*R*,7*S*,9*R*,1′*S*)-5-(2′-Hydroxybut-2′-yl)-10,10-dimethyl-3-phenyl-4,6-dioxatricyclo[7.1.1.0^{2,7}]undecane 14a

4.13.1. Using method 2

Compound **9a** (270 mg, 0.89 mmol) in anhydrous ethyl ether (10 mL) was treated with 0.2 mL (2.68 mmol) of EtBr and 65.1 mg (2.68 mmol) of magnesium. After work-up, 282.2 mg (95%) of a diastereoisomeric mixture of carbinols **13a:14a** (1:>99) were obtained as a colorless syrup.

4.13.2. Using method 3

Compound **9a** (281.4 mg, 0.93 mmol) in anhydrous THF (10 mL) was treated with 0.5 M EtLi (5.62 mL, 2.8 mmol) in ether. After work-up, 294.6 mg (95%) of a diastereoisomeric mixture of carbinols **13a:14a** (38:62) was obtained as colorless syrup. Data for major diastereoisomer **14a**. Colorless crystals, mp = 115–117 °C. (R_f 0.25, hexanes-AcOEt 9:1). $[\alpha]_D^{21} = -10.2$ (*c* 1.08, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.30 (5H, m, H-Ar), 4.78 (1H, s, H-5), 4.62 (1H, d, *J* = 10.2 Hz, H-3), 4.53 (1H, bq, *J* = 9.2 Hz, H-7), 2.41 (2H, m, H-8eq, H-11eq), 3.30 (1H, bs, OH), 2.82 (2H, m, H-2, H-9), 1.86 (1H, m, H-8ax), 1.61 (3H, m, H-1, H-3′), 1.24 (3H, s, Me-1′), 1.21 (3H, s, Me-13), 0.99 (3H, s, Me-12), 0.94 (3H, t, *J* = 7 Hz, H-4′), 0.88 (1H, d, *J* = 9 Hz, 11ax). ^{13}C NMR ($CDCl_3$): δ 139.7 (C-*ipso*), 128.4 (C-*ortho*), 128.1 (C-*para*), 127.2 (C-*meta*), 106.4 (C-5), 84.9 (C-3), 76.9 (C-7), 73.8 (C-2′), 55.8 (C-2), 43.3 (C-9), 42.8 (C-1), 40.2 (C-11), 39.1 (C-10), 33.4 (C-8), 30.1 (C-1′), 29.6 (C-3′) 25.6 (C-13), 21.6 (C-12), 7.7 (C-4′). IR ($CHCl_3$): 3529, 2927, 1456, 1376, 1175, 1095, 1017, 909, 761, 702 cm^{-1}. MS *m*/*z* (rel. int.): 331 (M^++1) (3), 229 (30), 211 (88), 185 (17), 169 (18), 155 (18), 141 (20), 130 (25), 122 (42), 107 (34), 91 (68), 79 (98), 78 (100), 77 (9). HRFABMS calcd for $C_{21}H_{30}O_3$+H 331.2272. Found 331.2262.

4.14. (1*S*,2*R*,3*S*,5*R*,7*S*,9*R*,1′*S*)-5-(2′-Hydroxy-hex-2′-yl)-10,10-dimethyl-3-phenyl-4,6-dioxatricyclo[7.1.1.0^{2,7}]undecane 14b

4.14.1. Obtained using method 2

Compound **9a** (270 mg, 0.89 mmol) in anhydrous ethyl ether (10 mL) was treated with 0.27 mL (2.52 mmol) of BuBr and 63.1 mg (2.52 mmol) of magnesium. After work-up, 289.1 mg (90%) of a diastereoisomeric mixture of carbinols **13b:14b** (1:>99) was obtained as colorless syrup. (R_f 0.42, hexanes-AcOEt 9:1). $[\alpha]_D^{21} = -12.4$ (*c* 0.58, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.31 (5H, m, H-Ar), 4.76 (1H, s, H-5), 4.62 (1H, d, *J* = 10 Hz, H-3), 4.53 (1H, bq, *J* = 9.2 Hz, H-7), 2.41 (2H, m, H-8eq, H-11eq), 2.28 (1H, bs, OH), 2.08 (2H, m, H-2, H-9), 1.86 (1H, m, H-8ax), 1.59 (3H, m, H-1, H-3′), 1.35 (4H, m, H-4′, H-5′), 1.25 (3H, s, Me-13), 1.21 (6H, s, Me-12, Me-13), 0.88 (4H, m, 11ax, Me-6′). ^{13}C NMR ($CDCl_3$): δ 139.7 (C-*ipso*), 128.4 (C-*ortho*), 128.0 (C-*para*), 127.2 (C-*meta*), 100.5 (C-5), 84.9 (C-3), 76.9 (C-7), 73.7 (C-2′), 55.8 (C-2), 43.3 (C-9), 42.8 (C-1), 40.2 (C-11), 39.1 (C-10), 36.8 (C-3′), 33.4 (C-8), 30.1 (C-13) 25.6 (C-12), 25.4 (C-5′), 23.6 (C-4′), 22.1 (C-1′), 14.4 (C-6′). IR ($CHCl_3$): 3584, 2928, 2878, 1455, 1380, 1136, 1094, 1078, 1015, 758, 699 cm^{-1}. MS *m*/*z* (rel. int.): 257 (M^+−1, 2), 229 (73), 212 (27), 211 (100), 185 (15), 122 (19), 91 (15), 79 (12), 78 (12). HRFABMS calcd for $C_{23}H_{34}O_3$+H 359.2586. Found 359.2572.

4.15. (1*S*,2*R*,3*S*,5*R*,7*S*,9*R*,1′*S*)-5-(3′-Methyl-2′-hydroxybut-2′-yl)-10,10-dimethyl-3-phenyl-4,6-dioxatricyclo[7.1.1.0^{2,7}]undecane 14c

4.15.1. Obtained using method 2

Compound **9a** (306.0 mg, 1.01 mmol) in anhydrous ethyl ether (10 mL) was treated with 0.4 mL (5.08 mol) of 2-bromopropane and 123.5 mg (5.08 mmol) of magnesium. After work-up, 308.7 mg (89%) of a diastereoisomeric mixture of carbinols **13c:14c** (17:83) were obtained as colorless syrup. (R_f 0.34, hexanes-AcOEt 9:1). $[\alpha]_D^{21} = +31.0$ (*c* 0.78, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.31 (5H, m, H-Ar), 4.87 (1H, s, H-5), 4.63 (1H, d, *J* = 9.9 Hz, H-3), 4.53 (1H, m, H-7), 2.41 (2H, m, H-8eq, H-11eq), 2.30 (1H, bs, OH), 2.09 (2H, m, H-2, H-9), 1.99 (1H, c, *J* = 6.9 Hz, H-3′), 1.88 (1H, dd, *J* = 10.2, 12.9 Hz, H-8ax), 1.59 (1H, m, *J* = 6 Hz, H-1), 1.21 (6H, s, Me-12, Me-13), 1.19 (3H, s, Me-1′), 0.96 (3H, d, *J* = 6.6 Hz, Me-5′), 0.93 (3H, d, *J* = 6.9 Hz, Me-4′), 0.92 (1H, d, *J* = 9.6 Hz, H-11ax). ^{13}C NMR ($CDCl_3$): δ 139.7 (C-*ipso*), 128.4 (C-*ortho*), 128.0 (C-*para*), 127.1 (C-*meta*), 105.3 (C-5), 85.0 (C-3), 76.9 (C-7), 75.5 (C-2′), 55.8

(C-2), 43.3 (C-9), 42.8 (C-1), 40.2 (C-11), 39.1 (C-10), 33.4 (C-8), 33.1 (C-3′), 30.1 (C-13), 25.6 (C-12), 19.1 (C-1′), 17.7 (C-4′), 17.1 (C-5′). IR ($CHCl_3$): 3583, 3497, 2928, 1456, 1366, 1213, 1180, 1140, 1091, 1001, 926, 870, 837 cm^{-1}. MS *m*/*z* (rel. int.): 229 (9), 212 (19), 211 (80), 185 (17), 169 (43),155 (22), 143 (30), 141 (23), 131 (16), 130 (38), 129 (26), 128 (25), 122 (53), 121 (16), 119 (11), 117 (19), 115 (25), 108 (16), 107 (51), 105 (28), 95 (15) 93 (14), 87 (15), 79 (100), 78 (97), 77 (31), 69 (19), 45 (11), 43 (26), 41 (35), 39 (27). HRFABMS calcd for $C_{22}H_{32}O_3$+Na 367.2249. Found 367.2247.

4.16. (1*S*,2*R*,3*S*,5*R*,7*S*,9*R*,1′*S*)-5-(2′-Hydroxybut-3-en-2′-yl)-10,10-dimethyl-3-phenyl-4,6-dioxatricyclo[7.1.1.$0^{2,7}$]undecane 14d

4.16.1. Obtained using method 1

Compound **9a** (237 mg, 0.79 mmol) in anhydrous THF (10 mL) was treated with 0.5 M C_2H_3MgBr (3.65 mL, 1.83 mmol) in ether. After work-up 249 mg (96%) of a diastereoisomeric mixture of carbinols **13d**:**14d** (13:83) was obtained as a colorless syrup (Rf 0.44, hexane-AcOEt 9:1). ^{1}H NMR (CDCl3): δ 7.36 (5H, m, H-Ar), 6.03 (1H, dd, *J* = 10.8, 17.4 Hz, H-3′), 5.36 (1H, dd, *J* = 1.6, 17.4 Hz, H-4′), 5.12 (1H, dd, *J* = 1.8, 10.8 Hz, H-4′), 4.83 (1H, s, H-5), 4.67 (1H, d, *J* = 9.9 Hz, H-3), 4.54 (1H, c, *J* = 9.3 Hz, H-7), 2.80 (1H, s, –OH), 2.45 (2H, m, H-8eq, H-11eq), 2.11 (2H, m, H-2, H-9), 1.90 (1H, m, H-8ax), 1.57 (1H, t, *J* = 6 Hz, H-1), 1.50 (3H, s, Me-1′), 1.22 (6H, s, Me-12, Me-13), 0.95 (1H, d, *J* = 9.6 Hz, H-11ax). ^{13}C NMR (CDCl3): δ 141.4 (C-3′), 139.3 (C-ipso), 128.1 (C-*ortho*), 128.0 (C-*para*), 127.5 (C-*meta*), 113.4 (C-4′), 105.1 (C-5), 84.8 (C-3), 55.6 (C-2), 43.3 (C-9), 42.6 (C-1), 40.2 (C-11), 39.3 (C-10), 33.2 (C-8), 30.0 (C-13), 25.3 (C-12), 24.9 (C-1′). IR ($CHCl_3$): 3500, 2920, 2869, 3501, 2930, 1456, 1368, 1140, 1091 cm^{-1}. MS *m*/*z* (rel. Int.): 328 (M^+, 1), 210 (1), 257 (11), 212 (12), 211 (100), 183 (73), 151 (75), 166 (90), 143 (86), 131 (35), 43 (55), 41 (40), 39 (39).

4.17. (1*S*,2*R*,3*S*,5*R*,7*S*,9*R*,1′*S*)-5-(2′-Hydroxy-3-penten-2′-yl)-10,10-dimethyl-3-phenyl-4,6-dioxatricyclo[7.1.1.$0^{2,7}$]undecane 14d

4.17.1. Obtained using method 1

Compound **9a** (301 mg, 1.0 mmol) in anhydrous THF (10 mL) was treated with 0.5 M C_3H_3MgBr (6.0 mL, 3 mmol) in ether. After work-up, 303.6 mg (89%) of a diastereoisomeric mixture of carbinols **13d:14d** (15:85) was obtained as colorless syrup (R_f 0.34, hexanes-AcOEt 9:1). $[\alpha]_D^{21}$ = −18.7 (*c* 0.88, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.38 (5H, m, H-Ar), 4.84 (1H, s, H-5), 4.68 (1H, d, *J* = 9.9 Hz, H-3), 4.58 (1H, m, H-7), 2.81 (1H, bs, OH), 2.44 (2H, m, H-8eq, H-11eq), 2.12 (2H, m, H-2, H-9), 1.92 (1H, m, H-8ax), 1.87 (3H, s, Me-5′), 1.59 (1H, t, *J* = 6 Hz, H-1), 1.51 (3H, s, Me-1′), 1.21 (6H, s, Me-12, Me-13), 0.93 (1H, d, *J* = 9.6 Hz, H-11ax). ^{13}C NMR ($CDCl_3$): δ 139.4 (C-*ipso*), 128.4 (C-*ortho*), 128.1 (C-*para*), 127.3 (C-*meta*), 105.0 (C-5), 84.9 (C-3), 80.5 (C-4′), 80.3 (C-3′), 55.5 (C-2), 43.3 (C-9), 42.7 (C-1), 40.1 (C-11), 39.1 (C-10), 33.2 (C-8), 30.0 (C-13), 25.5 (C-12), 24.9 (C-1′). IR ($CHCl_3$): 3500, 2920, 2869, 1455, 1368, 1329, 1254, 1215, 1140, 1092, 1054, 1008, 963, 872, 839, 727, 669, 530 cm^{-1}. MS *m*/*z* (rel. int.): 340 (M^++1, 1), 211 (15), 210 (11), 169 (53), 167 (12), 156 (13), 155 (78),153 (10), 143 (34), 142 (14), 141 (60), 133 (13), 131 (22), 130 (40), 129 (42), 128 (23), 122 (72), 121 (13), 119 (30), 117 (22), 115 (21), 113 (12), 108 (25), 107 (81), 105 (30), 95 (39), 93 (21), 91 (88), 81 (12), 79 (58), 78 (100), 43(13). HRFABMS calcd for $C_{22}H_{28}O_3$+Na 363.1936. Found 363.1936.

4.18. (1*S*,2*R*,3*S*,5*R*,7*S*,9*R*,1′*S*)-5-(1′-Hydroxy-1′-phenyleth-2′-yl)-10,10-dimethyl-3-phenyl-4,6-dioxatricyclo[7.1.1.$0^{2,7}$]undecane 14e

4.18.1. Obtained using method 2

Compound **9a** (431.2 mg, 1.43 mmol) in anhydrous ethyl ether (10 mL) was treated with 0.45 mL (4.30 mol) of PhBr and 103.3 mg (4.30 mmol) of magnesium. After work-up, 454.7 mg (84%) of a diastereoisomeric mixture of carbinols **13e:14e** (07:93) were obtained as a colorless syrup. (R_f 0.28, hexanes-AcOEt 9:1). $[\alpha]_D^{21}$ = −23.4 (*c* 0.69, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.38 (10H, m, H-Ar), 4.97 (1H, s, H-5), 4.59 (1H, d, *J* = 10.2 Hz, H-3), 4.52 (1H, bq, *J* = 9.1 Hz, H-7), 3.03 (1H, bs, OH), 2.38 (2H, m, H-8eq, H-11eq), 2.05 (2H, m, H-2, H-9), 1.84 (1H, m, H-8ax), 1.65 (3H, s, Me-2′), 1.57 (1H, t, *J* = 6.3 Hz, H-1), 1.19 (3H, s, Me-13), 1.17 (3H, s, Me-12), 0.88 (1H, d, *J* = 9.6 Hz, H-11ax). ^{13}C NMR ($CDCl_3$): δ 144.4 (C-*ipso*), 139.0 (C-*ipso*′), 106.3 (C-5), 84.5 (C-3), 76.8 (C-7), 74.9 (C-1′), 55.8 (C-2), 43.3 (C-9), 42.8 (C-1), 40.2 (C-11), 39.1 (C-10), 33.4 (C-8), 30.1 (C-13), 25.5 (C-12), 24.8 (C-2′). IR ($CHCl_3$): 3391, 3028, 2915, 2831, 1492, 1450, 1365, 1264, 1047, 1015, 966, 883, 785, 753 cm^{-1}. MS *m*/*z* (rel. int.): 229 (4), 212 (46), 211 (53), 170 (12), 169 (78), 155 (30), 143 (25), 141 (29), 130 (21), 129 (18), 128 (22), 122 (17), 121 (99), 117 (11), 115 (21),108 (30), 107 (33), 105 (43), 103 (10), 95 (27), 93 (20), 91 (98), 79 (75), 78 (46), 77 (48), 51 (18), 43 (100), 41 (15), 39 (18). HRFABMS calcd for $C_{25}H_{30}O_3$+Na 401.2093. Found 401.2094.

4.18.2. Obtained using method 3

Compound **9a** (315 mg, 1.04 mmol) in 10 mL of anh. THF was treated with 0.49 mL (0.89 mmol) of 1.8 M PhLi in cyclohexane and was stirred at −78 °C under an N_2 atmosphere for 3 h. After usual work-up, 310 mg (78%) of a diastereoisomeric mixture of carbinols **13e:14e** (30:70) was obtained as colorless syrup.

4.19. (1*S*,2*R*,3*S*,5*R*,7*S*,9*R*,1′*S*)-5-(1′-Hydroxyeth-2′-yl)-10,10-dimethyl-3-phenyl-4,6-dioxatricyclo[7.1.1.$0^{2,7}$]undecane 14f

4.19.1. Obtained using method 4

Compound **9a** (150 mg, 0.50 mmol) in anhydrous THF (10 mL) was treated with $LiAlH_4$ (56.9 mg, 1.5 mmol). After work-up, 147.9 mg (98%) of a diastereoisomeric mixture of carbinols **13f:14f** (50:50) were obtained as a colorless syrup.

4.19.2. Using method 5

Compound **9a** (199.0 mg, 0.66 mmol) in methanol THF (10 mL) was treated with $NaBH_4$ (37.3 mg, 0.98 mmol). After work-up, 192 mg (96%) of a diastereoisomeric mixture of carbinols **13f:14f** (50:50) were obtained as a colorless syrup. (R_f 0.14, hexanes-AcOEt 8:2). ^{1}H NMR ($CDCl_3$): δ 7.31 (5H, m, H-Ar), 4.78 (1H, d, *J* = 4.8, H-5), 4.62 (1H, d, *J* = 10 Hz, H-3), 4.55 (1H, bq, *J* = 9.2 Hz, H-7), 3.85 (1H, m, H-1), 2.43 (2H, m, H-8eq, H-11eq), 2.13 SO($CDCl_3$): δ 139.2 (C-*ipso*), 128.5 (C-*ortho*), 128.3 (C-*para*), 127.4 (C-*meta*), 105.4 (C-5), 85.1 (C-3), 76.9 (C-7), 69.0 (C-1′), 55.6 (C-2), 43.3 (C-9), 42.8 (C-1), 40.2 (C-11), 39.1 (C-10), 33.2 (C-8), 30.1 (C-13), 25.6 (C-12), 17.6 (C-2′). IR ($CHCl_3$): 3467, 2945, 1454, 1366, 1263, 1136, 1115, 1093, 1076, 1018, 938, 759, 700 cm^{-1}. MS *m*/*z* (rel. int.): 301 (25), 169 (10), 155 (15), 130 (20), 122 (30), 107 (32), 91 (51), 79 (93), 78 (100), 77 (10). HRFABMS calcd for $C_{19}H_{26}O_3$+H 303.1960. Found 303.1945.

4.20. (−)-(*S*)-2-Methyl-1,2- hexanediol 16a

A diastereoisomeric mixture of 391 mg (1.09 mmol) of carbinols **13b:14b** (1:>99) in 10 mL of acetonitrile:water (4:1) was treated with 80 mg of *p*-TsOH and the resulting mixture was stirred and refluxed by 3 h. After, 5 mL of a $NaHCO_3$ saturated aq. solution was poured into the reaction mixture and stirred for 15 min, extracted with ethyl ether, washed with water, dried with anh. Na_2SO_4 and concentrated to dryness. This residue was dissolved in 5 mL of anh. ethyl ether, cooled at −78 °C and treated with a suspension of 22 mg (0.59 mmol) of $LiAlH_4$ in 10 mL of anh. ethyl ether. The reaction mixture was stirred at room temperature for 1 h and the residual $LiAlH_4$ was deactivated by slow addition of

ice chips and stirred until precipitation of a white solid. The crude reaction was extracted with ethyl ether, washed with brine, dried with anh. Na_2SO_4 and concentrated to dryness. The resulting syrup was chromatographed (silica gel) using hexane-AcOEt (9:1) as eluent, yielding 105 mg (78%) of diol **16a** as a colorless oil {$[\alpha]_D^{23} = -3.1$ (*c* 1.27, $CHCl_3$), literature[9] $[\alpha]_D^{23} = +4.4$ for the (*R*) enantiomer (*c* 1.0, $CHCl_3$)}. The mixture of eluents was changed to hexane:EtOAc (1:1) to recover 230 mg (92%) of the chiral auxiliary 10-phenyl-3,10-pinanediol **10a**.

4.21. (−)-(*S*)-2-Phenyl-1,2-propanediol 16b

Following a similar procedure as described for **16a**, after hydrolysis of a diastereoisomeric mixture of carbinols **13f:14f** (07:93), successive reduction of the resulting crude reaction and purification through column chromatography, was obtained diol **16b** ($[\alpha]_D^{23} = -5.0$ (*c* 1.02, EtOH), [literature[10] $[\alpha]_D^{23} = -5.8$ (*c* 0.12, EtOH)).

4.22. Single crystal X-ray analysis of 10b and 14a

Suitable colorless crystals of **10b** and **14a**, obtained by slow evaporation from CH_2Cl_2-hexanes solutions, were mounted on glass fibers and measurements were carried out at room temperature with graphite monocromated Cu Kα radiation ($\lambda = 1.54184$ Å) in the $\omega/2\theta$ scan mode on a Siemens P4 diffractometer equipped with a scintillation detector. Three standard reflections were monitored periodically, which showed no significant change during data collection. The unit cell parameters for **10b** were obtained from least-squares refinements of 44 reflections in the $10.94 < \theta < 28.06°$ range, while for **14a** 40 reflections in the $12.89 < \theta < 28.09°$ range were used. In the case of **10b** a crystal measuring $0.40 \times 0.40 \times 0.38$ mm, $C_{16}H_{22}O_2$, $M = 246.34$ turned out to be orthorhombic, space group $P2_12_12_1$, $a = 10.396(2)$ Å, $b = 11.083(4)$ Å, $c = 12.051(3)$ Å, $V = 1388.5(6)$ Å^3, $Z = 4$, $\rho = 1.178$ mg/mm^3, $\mu = 0.594$ mm^{-1}, total reflections 1516. unique reflections 1365 (R_{int} 0.0572, observed reflections 1322. In the case of **14a** the crystal measuring $0.6 \times 0.4 \times 0.4$ mm, $C_{21}H_{30}O_3$, $M = 330.45$ turned out to be monoclinic, space group $P2_1$, $a = 10.416(1)$ Å, $b = 10.891(2)$ Å, $c = 17.325(2)$ Å, $\beta = 92.904(8)°$, $V = 1962.9(5)$ Å^3, $Z = 4$, $\rho = 1.118$ mg/mm^3, $\mu = 0.575$ mm^{-1}, total reflections 3758, unique reflections 3125 (R_{int} 0.0979, observed reflections 2767, unique reflections 3125 (R_{int} 0.0979, observed reflections 2767. The intensities were corrected for Lorentz and polarization effects, no absorption corrections were applied to the diffraction data of **10b**, while empirical corrections (psi-scans) were applied to the data of **14a**. Either structure was solved by direct methods using the SIR-2004 program.[11] For the structural refinement, the non-hydrogen atoms were treated anisotropically, and the hydrogen atoms, included in the structure factor calculation, were refined isotropically. The final *R* indices for **10b** were $[I > 2\sigma(I)]$ $R_1 = 4.9\%$ and $wR_2 = 13.0\%$, largest difference peak and hole, 0.148 and −0.202 e.Å^3., and those for **14a** were $[I > 2\sigma(I)]$ $R_1 = 5.8\%$ and $wR_2 = 14.4\%$, largest difference peak and hole, 0.237 and −0.199 e.Å^3. The Olex2 v1.1.5 software[12] allowed calculating the Flack[13] (x) and Hooft (y) parameters.[14,15] In the case of **10b** these parameters were x = −0.4(5) and y = 0.15(16) which for the inverted structure were x = 1.3(5) and y = 0.85(16), while for **14a** they were x = 0.2(3) and y = 0.1(3) which again for the inverted structure were x = 0.1(3) and y = 01.02(2). Crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre, from where copies of the data can be obtained free of charge on application to the CCDC, Cambridge, UK. The CCDC deposition numbers for **10b** and **14a** are 1560035 and 1560037, respectively.

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