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IPy_2BF_4-Mediated Rearrangements of 1,2-Difunctionalized Compounds and Olefins

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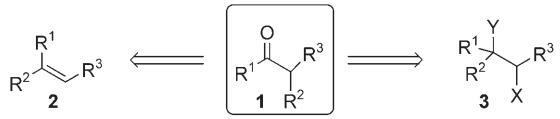
Abstract: Acetal derivatives are easily obtained from 1,2-difunctionalized compounds by a new reaction mediated by IPy_2BF_4 with a mechanism based on a 1,2-migration of aryl or alkyl groups. A new oxidative rearrangement reaction of olefins is also described. Moreover, when this metal-free protocol is applied to cyclic olefins, interesting ring-contraction reactions are observed. The new methodologies described here are a clean and efficient alternative to known strategies that make use of potentially toxic metallic complexes.

Keywords: 1,2-migration reactions · alkenes · rearrangement · ring contraction · synthetic methods.

Introduction

Carbon skeletal rearrangement reactions in which a group (H, alkyl, aryl) migrates to the adjacent position are powerful synthetic tools that give access to carbon frames not easily available by other procedures.[1] These reactions, when applied to cyclic compounds, lead to ring contraction or expansion products.[2] These atom-economical processes occur, in most cases, with very high selectivity, and therefore they have been widely used in the total synthesis of many natural products.[3] Although the variety of rearrangement reactions of this type published in the few last years is very broad, probably the most interesting processes are those which imply the formation of a carbonyl compound such as **1** (Scheme 1). Depending on the starting material, these reactions can be divided into two main groups: 1) oxidative rearrangement of olefins **2**,[4] and 2) rearrangement of 1,2-difunctionalized compounds **3** (Scheme 1).[5]



Scheme 1. Synthesis of carbonyl compounds **1** from either olefins **2** or 1,2-difunctionalized compounds **3** by rearrangement reactions.

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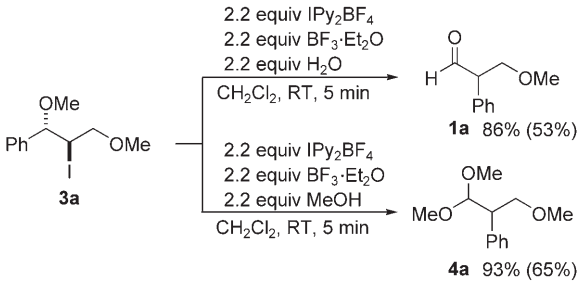
The reagent bis(pyridine)iodonium(I) tetrafluoroborate (IPy_2BF_4)[6] has been shown to be a versatile reagent in organic synthesis as it effects many useful and unique transformations.[7] During our investigations on the reactivity of this reagent with 1,2-difunctionalized compounds we observed that compounds such as **3** (X = I, Y = OMe) react with IPy_2BF_4, under certain conditions, by a rearrangement reaction to give products **1** (Scheme 1). Taking into account that compounds **3** (X = I, Y = OMe) are easily available from a well-established iodofunctionalization reaction of olefins **2** with IPy_2BF_4, we thought that compounds **1** should be directly obtainable from simple alkenes **2** by a tandem iodofunctionalization/rearrangement process mediated by IPy_2BF_4. This prompted us to initiate a deeper investigation of the ability of IPy_2BF_4 to perform these unusual rearrangement reactions. On this basis, we describe here the results of these studies which have culminated in the development of a new method for the formation of carbonylic derivatives **1**, or derivatives, from both 1,2-difunctionalized derivatives **3** (X = I, Y = OMe) and olefins **2**. An interesting ring-contraction reaction promoted by IPy_2BF_4 is also reported.

Results and Discussion

IPy_2BF_4-mediated rearrangement reactions of 1,2-difunctionalized compounds: 1,2-migration of aryl groups: As mentioned above, our investigation began with the study of the reactivity of the reagent IPy_2BF_4 with 1,2-difunctionalized compounds. Thus, (1*S**,2*R**)-2-iodo-1,3-dimethoxy-1-phenylpropane (**3a**) was chosen as a model compound to investigate all the factors that play a role in the course of the

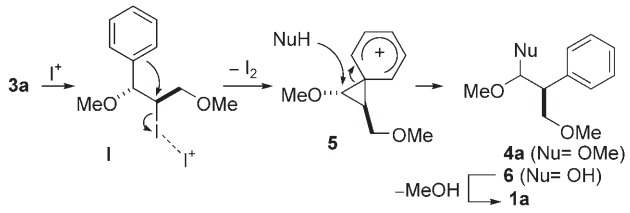
reaction. After careful optimization studies we observed that compound **3a** reacts with 2.2 equivalents of IPy_2BF_4, 2.2 equivalents of $BF_3{\cdot}OEt_2$,[8] and 2.2 equivalents of H_2O, in dry dichloromethane at room temperature, in five minutes, to afford the aldehyde **1a** in 86% yield (Scheme 2).[9] This



Scheme 2. Rearrangement reactions mediated by IPy_2BF_4 on model compound **3a**. Yields of the reaction performed using only one equivalent of IPy_2BF_4 and one equivalent of $BF_3{\cdot}OEt_2$ are given in parentheses (see reference [8]).

transformation implies the migration of the phenyl group to the adjacent position and the incorporation of a molecule of water.[9,10] Moreover, when this reaction was performed under the same reaction conditions but with 2.2 equivalents of MeOH instead of H_2O, dimethyl acetal **4a** was obtained in 93% yield (Scheme 2).[8] In this case the final product incorporates a molecule of methanol instead of a molecule of water.

A plausible mechanism that explains the formation of compounds **1a** and **4a** is depicted in Scheme 3. First, we believe that the iodonium ion generated from the mixture of

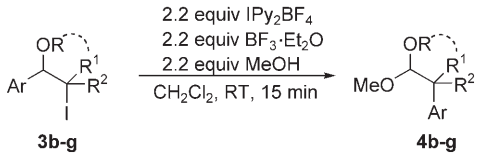


Scheme 3. Proposed mechanism for the IPy_2BF_4-mediated rearrangement reaction.

Abstract in Spanish: *La reacción de compuestos 1,2-difuncionalizados con IPy_2BF_4 da lugar a acetales a través de un proceso basado en una reacción de migración 1,2 de un grupo arilo o alquilo. También se describe una nueva reacción de reagrupamiento oxidativo de olefinas promovida por IPy_2BF_4. Cuando este protocolo se aplica a olefinas cíclicas se obtienen interesantes productos procedentes de una reacción de contracción de anillo. Las nuevas metodologías aquí descritas suponen una alternativa limpia y eficiente a los conocidos métodos que utilizan complejos metálicos potencialmente contaminantes.*

IPy_2BF_4 and $BF_3{\cdot}OEt_2$ coordinates to the iodine atom of the starting compound **3a**, as shown in **I**. Subsequent elimination of a molecule of iodine assisted by the vicinal phenyl group leads to the phenonium ion intermediate **5**.[11] Attack of the nucleophile present in the reaction medium (H_2O or MeOH) then occurs at the carbon bound to the methoxy group to form the corresponding acetal derivative **4a** or the hemiacetal derivative **6**. Hemiacetal **6** evolves into the aldehyde **1a** by losing a molecule of MeOH (Scheme 3).

Once we had found the optimum conditions to obtain the aldehyde **1a** or the acetal **4a**, we decided to investigate the scope of the reaction. Thus, we carried out a set of experiments, under those optimized conditions, starting from the aryl-substituted 1,2-difunctionalized compounds **3b–g** (Scheme 4). Although aldehydes analogous to **1a** are easily



Scheme 4. Synthesis of acetals **4b–g** from 1,2-difunctionalized compounds **3b–g** by 1,2-migration reactions of aryl groups.

available following the procedure described above, in some cases their isolation was found to be difficult. For this reason, and taking into account that these aldehydes are easily available from the corresponding dimethyl acetals, we decided to perform all the reactions in the presence of MeOH. Under these conditions, the acetals **4b–g** were easily obtained in high yields (Scheme 4).

The most interesting results are highlighted in Table 1. A phenyl group (Table 1, entries 1, 4, and 5) and also electron-rich (Table 1, entry 2) and, surprisingly, electron-poor aryl groups (Table 1, entry 3) undergo the 1,2-migration reaction. Moreover, the aryl group can migrate to primary, secondary, or tertiary carbons (Table 1, entries 1, 4, and 5). The result shown in Table 1, entry 6 is noteworthy as it supposes that the reaction proceeds when cyclic ethers such as **3g** [(2*S**,3*R**)-diastereoisomer] are used. Interestingly, this reaction is totally diastereoselective, as only the formation of

Table 1. Synthesis of acetals **4b–g** from 1,2-difunctionalized compounds **3b–g**.

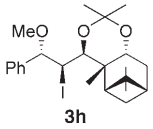
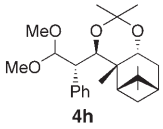
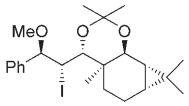
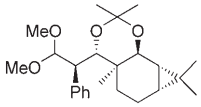
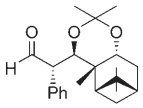
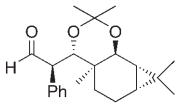
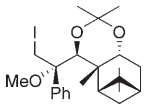
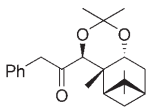
Entry	Starting material	Ar	R	R^1	R^2 [%][a]	Product	Yield
1	**3b**	Ph	Me	H	H	**4b**	96
2	**3c**	4-MeC_6H_4	Me	H	H	**4c**[b]	90
3	**3d**	4-BrC_6H_4	Me	H	H	**4d**[c]	87
4	**3e**	Ph	Me	Me	H	**4e**	91
5	**3f**	Ph	Me	Me	Me	**4f**[b]	86
6	**3g**[d]	Ph	-$(CH_2)_2$-		H	**4g**[b,e]	81

[a] Yield based on starting iodide **3**. [b] The reaction was performed at −10°C. [c] The reaction required 1 h to complete. [d] (2*S**,3*R**)-diastereoisomer. [e] The (2*S**,3*R**)-diastereoisomer was formed exclusively.

diastereoisomer **4g** [(2*S**,3*R**)-diastereoisomer] was observed.

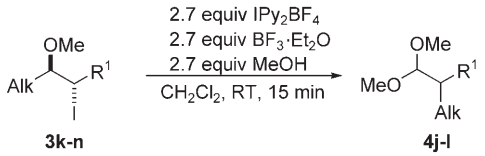
Taking advantage of our experience in the synthesis of terpene derivatives such as **3h–j** (Table 2),[12] we decided to try the rearrangement reaction with these substrates. The objectives of these studies were, on the one hand, to transform the initial terpene derivatives into others with a different substitution pattern,[13] and, on the other hand, as the initial terpene derivatives **3h–j** are enantiomerically pure, this investigation could give us some information about the stereochemical outcome of the rearrangement reaction. Thus, terpene derivatives **3h–j**, under the same reaction conditions as those previously mentioned, gave the new terpene-derived acetals **4h**,**i** or aldehydes/ketones **1b–d** in very high yield and as single enantiomers in all cases (Table 2). The structure of these compounds was determined by NMR spectroscopy and confirmed by X-ray crystal-structure analysis in the case of **4h**. The stereochemical outcome of the reaction can be explained by a model similar to that shown in Scheme 3.

Table 2. Synthesis of terpene-derived acetals **4h**,**i** and aldehydes or ketones **1b–d** from the corresponding 1,2-difunctionalized terpene derivative **3h–j**.

Entry	Starting material	Additional nucleophile	Product	Yield [%][a]
1	 **3h**	MeOH	 **4h**	96
2	***ent*-3h**	MeOH	***ent*-4h**	98
3	 **3i**	MeOH	 **4i**	92
4	**3h**	H_2O	 **1b**	83
5	**3i**	H_2O	 **1c**	86
6	 **3j**	H_2O	 **1d**	43[b]

[a] Yield based on starting iodide **3**. [b] 49% of the starting material was recovered.

IPy_2BF_4-mediated rearrangement reactions of 1,2-difunctionalized compounds: 1,2-migration of alkyl groups and ring-contraction reactions: Once the 1,2-migration reaction of aryl groups had been perfectly established, we decided to investigate the 1,2-migration of alkyl groups. As shown in Scheme 5, the reaction was carried out as described before except that larger amounts of IPy_2BF_4 and $BF_3{\cdot}EtO_2$ (2.7 equiv) were required to achieve complete conversion.



Scheme 5. Synthesis of acetals **4j–l** from 1,2-difunctionalized compounds **3k–n** by 1,2-migration reactions of alkyl groups.

The most interesting results are collected in Table 3. First of all, it should be noted that the reaction only proceeded in those cases in which the carbon containing the iodine atom was substituted. In contrast, when the R^1 substituent was a hydrogen atom (i.e., the carbon containing the iodine atom was primary), the reaction did not work under any of the different conditions attempted and the starting material was recovered unchanged. Also remarkable are those examples where a 1,2-migration reaction of a hydrogen atom was observed (Table 3, entries 3 and 4). Although the main product obtained when starting from compound **3m** was that coming from the 1,2-migration reaction of a methyl group (**4k**), a small amount (17% yield) of 2-octanone was also isolated. This minor product is thought to come from the 1,2-migration reaction of a hydrogen atom. This latter reaction was the only one observed when the reaction was performed with compound **3n** (Table 3, entry 4).

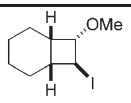
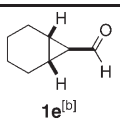
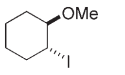
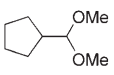
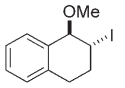
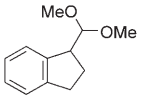
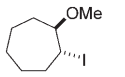
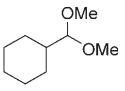
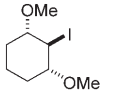
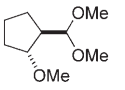
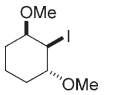
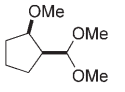
Table 3. Synthesis of acetals **4j–l** from 1,2-difunctionalized compounds **3k–n**.

Entry	Starting material	Alk	R^1	Product	Yield [%][a]
1	**3k**	Pr	Pr	**4j**	90
2	**3l**	Pent	Me	**4k**	85
3	**3m**	Me	pentyl	**4k**	61[b]
4	**3n**	H	cyclohexyl	**4l**	88

[a] Yield based on starting iodide **3**. [b] 17% of 2-octanone was also isolated.

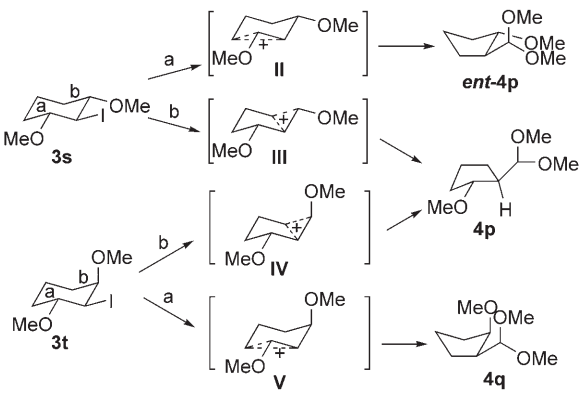
Although the 1,2-migration reactions of alkyl groups described here are a significant achievement, probably the most interesting results were those obtained when using cyclic compounds as starting materials. Thus, the treatment of cyclic compounds **3o–t** with IPy_2BF_4 under the conditions described in Scheme 5 led to the new cyclic compounds **1e** or **4m–q** (Table 4). This transformation supposes an unprecedented ring-contraction reaction mediated by IPy_2BF_4. Thus, four-, six-, and seven-membered rings have been transformed into the corresponding three-, five-, and six-membered rings, respectively (Table 4, entries 1–4). However, the reaction did not proceed when it was attempted with five- and eight-membered rings; in these cases the starting material was recovered unchanged.[14]

Table 4. Synthesis of cyclic compounds **1e** and **4m–q** by ring-contraction reactions.

Entry	Starting material	Product	Yield [%][a]
1	 **3o**	 **1e**[b]	68
2	 **3p**	 **4m**	62
3	 **3q**	 **4n**	70
4	 **3r**	 **4o**	86
5	 **3s**	 **4p**	81
6	 **3t**	 **4q**[d]	76[e]

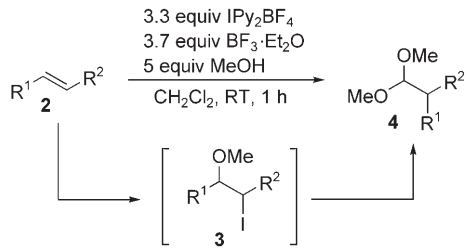
[a] Yield based on starting iodide **3**. [b] The expected dimethyl acetal was not observed, and under these reaction conditions the aldehyde **1e** was isolated. [c] Reaction performed at −40 °C. [d] The reaction was performed at −40 °C for 90 min. The ^{1}H NMR spectrum of the crude reaction mixture shows a 15:1 mixture of **4q** and **4p**. [e] Yield of the major diastereoisomer **4q** based on **3t**.

Interesting results from both a synthetic and mechanistic point of view were observed from the reaction of the trisubstituted cyclohexane derivatives **3s** and **3t**. As reflected in entries 5 and 6 of Table 4, these two diastereoisomers led to two different disubstituted cyclopentane derivatives **4p** and **4q**, respectively. These observations can be rationalized according to Scheme 6. Thus, starting from compound **3s** we suppose an initial coordination of the iodonium ion to the iodine atom of **3s** to give an intermediate analogous to **I** (see Scheme 3). At this point, the elimination of the molecule of iodine can be assisted by one of two sections (a or b) of the cyclohexane skeleton that lead, via intermediates **II** or **III**, to the same diastereoisomer of the final product (**4p**, or ***ent*-4p**). In contrast, starting from **3t**, the migration of the two possible branches (a or b) does not lead to the same diastereoisomer. Migration of branch b leads, via intermediate **IV**, to diastereoisomer **4p**, which is the minor isomer observed in the reaction, whereas migration of branch a leads, via intermediate **V**, to diastereoisomer **4q**, which is the major isomer observed in the reaction. Although we do not have a clear justification for this, it is clear that migration of the branch that contains the methoxy group in an equatorial position (branch a, leading to **4q**) is much more favored than the migration of the branch that contains the methoxy group in an axial position (branch b).



Scheme 6. Proposed mechanism for the evolution of diastereoisomeric compounds **3s** and **3t**.

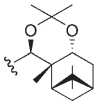
IPy_2BF_4-mediated rearrangement reactions of olefins: tandem iodofunctionalization/rearrangement reactions: Bearing in mind that all the alkoxy-substituted iodides used as starting materials in the previous sections can be easily obtained from olefins by the well-established iodofunctionalization reaction mediated by the reagent IPy_2BF_4,[15] we believed that we could develop a tandem iodofunctionalization/rearrangement method to transform olefins into acetals directly. The scope of the reactions described previously in this paper would be considerably extended if this tandem process could be achieved. As shown in Scheme 7, the reagent IPy_2BF_4 would play a dual role in this process: firstly it would act as an iodinating agent to favor the functionalization of the olefin **2** to form intermediate **3**, and secondly it would mediate the 1,2-migration reaction that leads to the final rearranged product **4**.



Scheme 7. Synthesis of acetals **4** from olefins **2** by a tandem iodofunctionalization/rearrangement process.

After some initial studies focused on finding the best reaction conditions, we realized that the treatment of olefins **2** with 3.3 equivalents of IPy_2BF_4 and 3.7 equivalents of $BF_3{\cdot}EtO_2$ in dichloromethane, in the presence of five equivalents of methanol, at room temperature for one hour, led to the formation of acetals **4** in very high yields in most cases (Scheme 7 and Table 5). The reaction was found to be general and both styrene- (Table 5, entries 1–6) and alkyl-substituted olefins (Table 5, entries 7 and 8) can be used as starting materials. Highly functionalized olefins, such as the

Table 5. Synthesis of acetals **4** from olefins **2**.

Entry	Olefin	R^1	R^2	Product	Yield [%][a]
1	**2a**	Ph	CH_2OMe	**4a**	84
2	**2b**	Ph	H	**4b**	91
3	**2c**	4-MeC_6H_4	H	**4c**	89
4	**2d**	4-BrC_6H_4	H	**4d**	93
5	**2e**	Ph	Me	**4e**	82
6	**2f**	Ph		**4h**	93
7	**2g**	Pr	Pr	**4j**	88
8	**2h**	pentyl	Me	**4k**	66[b]
9	 **2i**			**1e**[c]	71
10	 **2j**			**4n**	67
11	OMe  **2k**			**4p/4q**	55/32
12	 **2l**			**4o**	88

[a] Yield based on starting olefin **2**. [b] 12% of 2-octanone was also isolated. [c] The expected dimethyl acetal was not observed, and under these reaction conditions the aldehyde **1e** was isolated.

terpene derivative **2f**, also reacted without any problem (entry 6). Interestingly, in this case the reaction was found to be highly selective, leading to a single isomer of the rearranged final product **4h**. Finally, it should be noted that cyclic alkenes **2i–l** cleanly underwent ring-contraction reactions to give compounds **1e** and **4m–q** (Table 5, entries 9–12).

Conclusion

We have developed a novel reaction with the reagent IPy_2BF_4 that widens even further the synthetic possibilities of this reagent. Following the protocol described here, it is possible to synthesize aldehydes (or derivatives) from alkoxy-substituted iodides by a 1,2-migration reaction of aryl or alkyl groups. Moreover, a new oxidative rearrangement reaction of olefins to give aldehyde/ketone derivatives has been studied. Novel ring-contraction reactions are observed when the process is applied to cyclic compounds. The metal-free strategy described here represents a clean and synthetically competitive alternative to the already established use of metal complexes and it is likely to find many applications in organic synthesis.

Experimental Section

General: Unless noted, all reactions were carried out under nitrogen in oven-dried glassware. Temperatures are reported as bath temperatures; baths were prepared by cooling ethanol, 2-propanol, or acetone with liquid nitrogen. Dichloromethane was continuously refluxed and freshly distilled from calcium hydride under nitrogen. Solvents used in extraction and purification (CH_2Cl_2, hexane, Et_2O, AcOEt) were purchased from Scharlau and used without further purification. $BF_3{\cdot}OEt_2$ used to obtain the acetals was dried by standard methods and stored under nitrogen.[9] Compounds were visualized on analytical thin-layer chromatograms (TLC) by UV light (254 nm) and/or by staining with an *o*-phosphomolybdic acid solution (prepared by dissolving *o*-phosphomolybdic acid (5 g) in ethanol (100 mL) and subsequent heating. Silica gel (230–240 mesh) was used for flash chromatography. ^{1}H NMR (200, 300, 400 MHz) and ^{13}C NMR (50.5, 75.5, 100 MHz) spectra were measured at room temperature on Bruker AC-200, AC-300, and AMX-400 instruments, respectively, with tetramethylsilane ($\delta = 0.0$ ppm, ^{1}H NMR) or $CDCl_3$ ($\delta = 77.00$ ppm, ^{13}C NMR) as internal standard. Carbon multiplicities were assigned by DEPT techniques. High-resolution mass spectra (HRMS) were determined on a Finnigan MAT 95 spectrometer. Elemental analyses were carried out on a Perkin-Elmer 2400 microanalyzer. A Perkin Elmer 241 polarimeter was used to measure optical rotations (sodium lamp).

1,2-Difunctionalized compounds **3** were synthesized as reported previously.[12,15]

General procedure for the rearrangement reaction of 1,2-difunctionalized compounds 3 to give aldehydes or ketones 1: A solution of IPy_2BF_4 (0.41 g, 1.1 mmol) in dry CH_2Cl_2 (2.5 mL) was prepared under nitrogen and treated with dry $BF_3{\cdot}OEt_2$ (3 mL of a 0.4 M solution in CH_2Cl_2, 1.1 mmol) and H_2O (20 μL, 1.1 mmol) at room temperature. A solution of the corresponding compound **3** (0.5 mmol) in dry CH_2Cl_2 (2 mL) was then added at the same temperature. A change in the color of the solution (red to violet) was observed immediately. The reaction was monitored by TLC and quenched with a 5% solution of $Na_2S_2O_3{\cdot}5H_2O$ (10 mL) when complete. Extraction with CH_2Cl_2 (2×10 mL) was performed immediately, and the combined organic layers were washed with water (2×10 mL) and dried with anhydrous sodium sulfate. The solvents were carefully removed and the residue was purified by flash chromatography (SiO_2, hexane/diethyl ether, 40:1) to obtain pure aldehydes or ketones **1**.

3-Methoxy-2-phenylpropanal (1a): Colorless oil. $R_f = 0.35$ (hexane/ethyl acetate, 5:1); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 9.78$ (d, $J = 1.6$ Hz, 1H; CHO), 7.50–7.10 (m, 5H; ArH), 4.06 (dd, $J = 8.9$, 7.2 Hz, 1H; C*H*HOMe), 3.88 (apparent td, $J = 7.2$, 5.5, 1.6 Hz, 1H; PhCH), 3.74 (dd, $J = 8.9$, 5.5 Hz, 1H; CH*H*OMe), 3.39 (s, 3H; OMe) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 199.6$, 133.8, 129.0, 128.8, 127.8, 71.7, 59.1, 58.7 ppm; HRMS (70 eV, EI): calcd for $C_{10}H_{12}O_2$ ($[M]^+$): 164.0837; found 164.0840; elemental analysis calcd (%) for $C_{10}H_{12}O_2$: C 73.15, H 7.37; found: C 73.28, H 7.49.

(1*S*,2*S*,3*R*,7*R*,9*S*)-3-[(*S*)-Formylphenylmethyl]-2,5,5,10,10-pentamethyl-4,6-dioxatricyclo[7.1.1.0^{2,7}]undecane (1b): Colorless oil. $R_f = 0.37$ (hexane/ethyl acetate, 10:1); $[\alpha]_D^{20} = +17.6$ ($c = 2.0$, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 9.71$ (d, $J = 4.3$ Hz, 1H; HC=O), 7.50–7.10 (m, 5H; ArH), 4.60 (d, $J = 8.6$ Hz, 1H; OC*H*CHPh), 3.74 (d, $J = 8.2$ Hz, 1H; OC*H*CH$_2$), 2.50–2.30 (m, 1H; aliphatic ring), 1.90–0.80 (m, 5H; aliphatic ring), 1.42, 1.38, 1.20, 0.95, 0.85 (5s, 15H; 5×Me) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 199.2$, 135.0, 128.9, 128.8, 127.6, 100.7, 73.0, 71.1, 58.3, 48.6, 46.0, 39.2, 39.0, 34.7, 27.7, 26.6, 25.9, 24.0, 22.7, 20.4 ppm; HRMS (FAB): calcd for $C_{22}H_{31}O_3$ ($[M+1]^+$): 343.2273; found 343.2277; elemental analysis calcd (%) for $C_{22}H_{30}O_3$: C 77.16, H 8.83; found: C 77.31, H 8.99.

(1*S*,2*S*,4*R*,7*R*,8*S*)-8-[(*R*)-Formylphenylmethyl]-3,3,7,10,10-pentamethyl-9,11-dioxatricyclo[5.4.0.0^{2,4}]undecane (1c): Colorless oil. $R_f = 0.48$ (hexane/ethyl acetate, 5:1); $[\alpha]_D^{20} = -30.8$ ($c = 3.0$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.73$ (d, $J = 4.3$ Hz, 1H; HC=O), 7.40–7.20 (m, 5H; ArH), 4.50 (d, $J = 7.4$ Hz, 1H; OC*H*CHPh), 3.64 (dd, $J = 7.4$, 4.3 Hz, 1H; PhC*H*), 3.39 (d, $J = 2.0$ Hz, 1H; OC*H*CH), 1.70–0.50 (m, 6H; aliphatic ring), 1.51, 1.44, 1.05, 1.01, 0.91 (5s, 15H; 5×Me) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 199.4$, 135.5, 129.0, 128.9, 127.7, 100.0, 75.0, 72.8, 58.4, 37.6, 31.5, 29.2, 25.9, 25.6, 25.2, 21.0, 20.1, 16.2, 15.3, 14.9 ppm; HRMS (FAB): calcd for $C_{22}H_{31}O_3$ ($[M+1]^+$): 343.2273; found 343.2274; elemental analysis calcd (%) for $C_{22}H_{30}O_3$: C 77.16, H 8.83; found: C 77.32, H 9.02.

(1*S*,2*S*,3*S*,7*R*,9*S*)-3,3,7,10,10-Pentamethyl-3-(phenylacetyl)-9,11-dioxatricyclo[5.4.0.0^{2,4}]undecane (1d): Colorless oil. R_f=0.38 (hexane/ethyl acetate, 10:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.40–7.10 (m, 5H; ArH), 4.17 (s, 1H; OC*H*C=O), 3.95 (d, J=16.4 Hz, 1H; PhC*H*H), 3.80 (d, J=16.4 Hz, 1H; PhCH*H*), 3.78 (d, J=7.8 Hz, 1H; OC*H*CH_2), 2.50–0.80 (m, 6H; aliphatic ring), 1.47, 1.32, 1.24, 1.15, 0.92 (5s, 15H; 5×Me) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ=209.8, 134.1, 129.8, 128.2, 126.5, 100.8, 77.7, 70.9, 47.6, 47.4, 47.4, 39.5, 39.0, 34.4, 27.9, 26.2, 25.4, 24.1, 23.0, 20.3 ppm; HRMS (70 eV, EI): calcd for $C_{22}H_{30}O_3$ ([M]$^+$): 342.2195; found 342.2198; elemental analysis calcd (%) for $C_{22}H_{30}O_3$: C 77.16, H 8.83; found: C 77.28, H 8.69.

General procedure for the rearrangement reaction of 1,2-difunctionalized compounds 3 to give acetals 4 or aldehyde 1e: A solution of IPy_2BF_4 (0.41 g, 1.1 mmol) in dry CH_2Cl_2 (2.5 mL) was prepared under nitrogen and treated with dry $BF_3{\cdot}OEt_2$ (3 mL of a 0.4 M solution in the same solvent, 1.1 mmol) and methanol (46 μL, 1.1 mmol) at room temperature. A solution of the corresponding compound **3** (0.5 mmol) in CH_2Cl_2 (2 mL) was then added at the same temperature. A change in the color of the solution (red to violet) was observed immediately. The reaction was monitored by TLC and quenched with a 5% solution of $Na_2S_2O_3{\cdot}5H_2O$ (10 mL) when complete. Extraction with CH_2Cl_2 (2×10 mL) was performed immediately, and the combined organic layers were washed with water (2×10 mL) and dried with anhydrous sodium sulfate. Solvents were carefully removed and the residue was purified by flash chromatography (SiO_2, hexane/diethyl ether, 40:1) to give pure acetals **4** or aldehyde **1e**.

1,1,3-Trimethoxy-2-phenylpropane (4a): Colorless oil. R_f=0.31 (hexane/ethyl acetate, 5:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.40–7.20 (m, 5H; ArH), 4.61 (d, J=6.6 Hz, 1H; C*H*$(OMe)_2$), 3.74 (d, J=5.8 Hz, 2H; CH_2OMe), 3.44 (s, 3H; OMe), 3.32 (s, 6H; 2×OMe), 3.19 (dd, J=6.6, 5.8 Hz, 1H; PhC*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ=139.0, 128.6, 127.9, 126.4, 105.8, 73.0, 58.7, 54.6, 54.5, 49.0 ppm; HRMS (70 eV, EI): calcd for $C_{12}H_{18}O_3$ ([M]$^+$): 210.1256; found 210.1254; elemental analysis calcd (%) for $C_{12}H_{18}O_3$: C 68.54, H 8.63; found: C 68.68, H 8.54.

1,1-Dimethoxy-2-phenylethane (4b): Colorless oil. R_f=0.34 (hexane/ethyl acetate, 20:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.40–7.20 (m, 5H; ArH), 4.58 (t, J=5.5 Hz, 1H; C*H*$(OMe)_2$), 3.37 (s, 6H; 2×OMe), 2.94 (d, J=5.5 Hz, 2H; CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ=137.0, 129.3, 128.2, 126.3, 105.2, 53.2, 39.6 ppm; HRMS (70 eV, EI): calcd for $C_{10}H_{14}O_2$ ([M]$^+$): 166.0994; found 166.0997; elemental analysis calcd (%) for $C_{10}H_{14}O_2$: C 72.26, H 8.49; found: C 72.37, H 8.58

1,1-Dimethoxy-2-(4-methylphenyl)ethane (4c): Colorless oil. R_f=0.31 (hexane/ethyl acetate, 20:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.20–7.00 (m, 4H; ArH), 4.54 (t, J=5.7 Hz, 1H; C*H*$(OMe)_2$), 3.35 (s, 6H; 2×OMe), 2.89 (d, J=5.7 Hz, 2H; CH_2), 2.33 (s, 3H; Me) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ=135.6, 133.8, 129.1, 128.9, 105.2, 53.1, 39.0, 20.9 ppm; HRMS (70 eV, EI): calcd for $C_{11}H_{16}O_2$ ([M]$^+$): 180.1150; found 180.1146; elemental analysis calcd (%) for $C_{11}H_{16}O_2$: C 73.30, H 8.95; found: C 73.46, H 8.81.

2-(4-Bromophenyl)-1,1-dimethoxyethane (4d): Colorless oil. R_f=0.24 (hexane/ethyl acetate, 20:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.40 (d, J=8.3 Hz, 2H; ArH), 7.10 (d, J=8.3 Hz, 2H; ArH), 4.49 (t, J=5.4 Hz, 1H; C*H*$(OMe)_2$), 3.33 (s, 6H; 2×OMe), 2.85 (d, J=5.4 Hz, 2H; CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ=135.8, 131.2, 131.1, 120.2, 104.9, 53.3, 39.0 ppm; HRMS (70 eV, EI): calcd for $C_9H_{10}BrO$ ([M−31]$^+$): 212.9915; found 212.9910; elemental analysis calcd (%) for $C_{10}H_{13}BrO_2$: C 49.00, H 5.35; found: C 49.23, H 5.26.

1,1-Dimethoxy-2-phenylpropane (4e): Colorless oil. R_f=0.30 (hexane/ethyl acetate, 20:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.50–7.10 (m, 5H; ArH), 4.40 (d, J=7.0 Hz, 1H; C*H*$(OMe)_2$), 3.41, 3.28 (2s, 6H; 2×OMe), 3.05 (q, J=7.0 Hz, 1H; PhC*H*), 1.31 (d, J=7.0 Hz, 3H; Me) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ=142.9, 128.1, 127.8, 126.2, 108.4, 54.2, 53.8, 42.8, 16.6 ppm; HRMS (70 eV, EI): calcd for $C_{11}H_{16}O_2$ ([M]$^+$): 180.1150; found 180.1153; elemental analysis calcd (%) for $C_{11}H_{16}O_2$: C 73.30, H 8.95; found: C 73.51, H 9.15.

1,1-Dimethoxy-2-methyl-2-phenylpropane (4f): Colorless oil. R_f=0.34 (hexane/ethyl acetate, 20:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.50 (d, J=8.0 Hz, 2H; ArH), 7.37 (t, J=8.0 Hz, 2H; ArH), 7.27 (m, 1H; ArH), 4.20 (s, 1H; C*H*$(OMe)_2$), 3.38 (s, 6H; 2×OMe), 1.41 (s, 6H; 2×Me) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ=146., 127.7, 126.7, 125.8, 113.6, 58.2, 43.4, 23.1 ppm; HRMS (70 eV, EI): calcd for $C_{12}H_{18}O_2$ ([M]$^+$): 194.1307; found 194.1312; elemental analysis calcd (%) for $C_{12}H_{18}O_2$: C 74.19, H 9.34; found: C 74.35, H 9.22.

(2*S,3*R**)-2-Methoxy-3-phenyltetrahydrofuran (4g)**: Colorless oil. R_f=0.37 (hexane/ethyl acetate, 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.40–7.20 (m, 5H; ArH), 4.94 (d, J=2.0 Hz, 1H; C*H*$(OMe)_2$), 4.14 (m, 1H; C*H*HO), 4.06 (m, 1H; CH*H*O), 3.37 (s, 3H; OMe), 3.33 (m, 1H; C*H*Ph), 2.47 (m, 1H; C*H*HCHPh), 2.05–1.90 (m, 1H; CH*H*CHPh) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ=142.3, 128.5, 127.2, 126.5, 110.5, 67.2, 54.8, 51.3, 26.9 ppm; HRMS (70 eV, EI): calcd for $C_{11}H_{14}O_2$ ([M]$^+$): 178.0994; found 178.0997; elemental analysis calcd (%) for $C_{11}H_{14}O_2$: C 74.13, H 7.92; found: C 74.27, H 7.83.

(1*S*,2*S*,3*R*,7*R*,9*S*)-3-[(1*S*)-2,2-Dimethoxy-1-phenylethyl]-2,5,5,10,10-pentamethyl-4,6-dioxatricyclo[7.1.1.0^{2,7}]undecane (4h): Colorless solid. M.p. 156.2–156.4 °C (cold pentane); $[\alpha]_D^{20}$=+1.6 (c=2.7, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.30–7.15 (m, 5H; ArH), 4.70 (d, J=3.1 Hz, 1H; C*H*$(OMe)_2$), 4.42 (d, J=11.0 Hz, 1H; OC*H*CHPh), 3.66 (d, J=8.2 Hz, 1H; OC*H*CH_2), 3.45 (s, 3H; OMe), 3.39 (s, 3H; OMe), 3.01 (dd, J=11.0, 3.1 Hz, 1H; PhC*H*), 2.42–2.28 (m, 1H; aliphatic ring), 1.80–0.30 (m, 5H; aliphatic ring), 1.44, 1.39, 1.14, 0.78, 0.78 (5s, 15H; 5×Me) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ=137.7, 130.4, 127.4, 126.7, 106.7, 100.2, 71.7, 71.5, 56.6, 56.3, 48.7, 48.6, 46.4, 38.8, 38.6, 35.0, 27.7, 26.3, 26.0, 24.0, 23.0, 20.0 ppm; HRMS (FAB): calcd for $C_{24}H_{37}O_4$ ([M+1]$^+$): 389.2692; found 389.2684; elemental analysis calcd (%) for $C_{24}H_{36}O_4$: C 74.19, H 9.34; found: C 74.07, H 9.12.

(1*R*,2*R*,3*S*,7*S*,9*R*)-3-[(1*R*)-2,2-Dimethoxy-1-phenylethyl]-2,5,5,10,10-pentamethyl-4,6-dioxatricyclo[7.1.1.0^{2,7}]undecane (*ent*-4h): Colorless solid. The spectroscopic data for ***ent*-4h** were identical to those of **4h**. $[\alpha]_D^{20}$=−1.6 (c=5.2, CH_2Cl_2).

(1*S*,2*S*,4*R*,7*R*,8*S*)-8-[(1*R*)-2,2-Dimethoxy-1-phenylethyl]-3,3,7,10,10-pentamethyl-9,11-dioxatricyclo[5.4.0.0^{2,4}]undecane (4i): Colorless oil. R_f=0.42 (hexane/ethyl acetate, 5:1); $[\alpha]_D^{20}$=−3.4 (c=1.0, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.45–7.15 (m, 5H; ArH), 4.70 (d, J=3.1 Hz, 1H; C*H*$(OMe)_2$), 4.27 (d, J=10.0 Hz, 1H; OC*H*CHPh), 3.44 (s, 3H; OMe), 3.36 (s, 3H; OMe), 3.29 (d, J=1.7 Hz, 1H; OC*H*CH), 3.06 (dd, J=10.0, 3.1 Hz, 1H; PhC*H*), 1.70–0.50 (m, 6H; aliphatic ring), 1.50, 1.44, 0.98, 0.96, 0.87 (5s, 15H; 5×Me) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ=138.0, 130.7, 127.6, 126.8, 106.7, 99.7, 73.6, 72.4, 56.8, 56.2, 49.3, 38.5, 31.6, 29.2, 25.5, 25.4, 21.0, 19.4, 15.9, 15.5, 14.9 ppm; HRMS (FAB): calcd for $C_{24}H_{37}O_4$ ([M+1]$^+$): 389.2692; found 389.2690; elemental analysis calcd (%) for $C_{24}H_{36}O_4$: C 74.19, H 9.34; found: C 74.26, H 9.40.

4-(Dimethoxymethyl)heptane (4j): Colorless oil. R_f=0.43 (hexane/ethyl acetate, 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.10 (d, J=6.0 Hz, 1H; C*H*$(OMe)_2$), 3.31 (s, 6H; 2×OMe), 1.65–1.10 (m, 9H; $CH(CH_2CH_2)_2$), 0.85 (t, J=6.7 Hz, 6H; 2×Me) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ=107.8, 54.2, 39.8, 31.1, 19.9, 14.4 ppm; HRMS (70 eV, EI): calcd for $C_{10}H_{22}O_2$ ([M]$^+$): 174.1620; found 174.1625; elemental analysis calcd (%) for $C_{10}H_{22}O_2$: C 68.92, H 12.72; found: C 69.04, H 12.65.

2-(Dimethoxymethyl)heptane (4k): Colorless oil. R_f=0.36 (hexane/ethyl acetate, 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.01 (d, J=6.6 Hz, 1H; C*H*$(OMe)_2$), 3.34 (s, 6H; 2×OMe), 2.45–2.35 (m, 1H; C*H*$CH(OMe)_2$), 1.45–1.20 (m, 8H; 4×CH_2), 1.00–0.80 (m, 6H; 2×Me) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ=108.9, 53.9, 53.7, 35.6, 32.0, 31.5, 26.5, 22.5, 14.2, 13.9 ppm; HRMS (70 eV, EI): calcd for $C_{10}H_{22}O_2$ ([M]$^+$): 174.1620; found 174.1618; elemental analysis calcd (%) for $C_{10}H_{22}O_2$: C 68.92, H 12.72; found: C 69.02, H 12.58.

2-Cyclohexyl-1,1-dimethoxyethane (4l): Colorless oil. R_f=0.37 (hexane/ethyl acetate, 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.45 (t, J=5.7 Hz, 1H; C*H*$(OMe)_2$), 3.28 (s, 6H; 2×OMe), 1.76–0.80 (m, 13H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ=102.6, 52.2, 39.8, 33.6, 33.4, 26.4, 26.1 ppm; HRMS (70 eV, EI): calcd for $C_{10}H_{20}O_2$ ([M]$^+$): 172.1463; found 172.1467; elemental analysis calcd (%) for $C_{10}H_{20}O_2$: C 69.72, H 11.70; found: C 69.79, H 11.56.

***exo*-Bicyclo[4.1.0]heptane-7-carbaldehyde (1e)**: Colorless oil. R_f=0.30 (hexane/ethyl acetate, 10:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.99 (d, J=

5.5 Hz, 1H; HC=O), 2.10–0.80 (m, 11H; bicyclic moiety) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 201.4, 36.4, 22.4, 22.1, 20.7 ppm; HRMS (70 eV, EI): calcd for $C_8H_{12}O$ ($[M]^+$): 124.0888; found 124.0892; elemental analysis calcd (%) for $C_8H_{12}O$: C 77.38, H 9.74; found: C 77.49, H 9.60.

(Dimethoxymethyl)cyclopentane (4m): Colorless oil. R_f = 0.25 (hexane/ethyl acetate, 20:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.10 (d, J = 7.7 Hz, 1H; C*H*(OMe)$_2$), 3.33 (s, 6H; 2×OMe), 2.20 (sextet, J = 7.7 Hz, 1H; C*H*CH(OMe)$_2$), 2.00–1.10 (m, 8H; rest of the ring) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 108.2, 52.8, 41.6, 28.1, 25.6 ppm; HRMS (70 eV, EI): calcd for $C_7H_{13}O$ ($[M-31]^+$): 113.0966; found 113.0968; elemental analysis calcd (%) for $C_8H_{16}O_2$: C 66.63, H 11.18; found: C 66.77, H 11.01

1-(Dimethoxymethyl)indane (4n): Colorless oil. R_f = 0.31 (hexane/ethyl acetate, 20:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (dd, J = 5.6, 3.0 Hz, 1H; HC=C), 7.36–7.15 (m, 3H; ArH), 4.40 (d, J = 7.4 Hz, 1H; C*H*-(OMe)$_2$), 3.60–3.40 (m, 1H; C*H*CH(OMe)$_2$), 3.50 (s, 3H; OMe), 3.44 (s, 3H; OMe), 3.10–2.85 (m, 2H; CCH_2), 2.25 (dtd, J = 13.1, 8.3, 5.3 Hz, 1H; CCH_2C*H*H), 2.03 (ddt, J = 13.1, 8.8, 7.1 Hz, 1H; CCH_2CH*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.6, 142.7, 126.7, 126.0, 125.4, 124.2, 107.0, 54.0, 52.7, 47.3, 31.2, 27.2 ppm; HRMS (70 eV, EI): calcd for $C_{12}H_{16}O_2$ ($[M]^+$): 192.1150; found 192.1156; elemental analysis calcd (%) for $C_{12}H_{16}O_2$: C 74.97, H 8.39; found: C 74.92, H 8.50

(Dimethoxymethyl)cyclohexane (4o): Colorless oil. R_f = 0.35 (hexane/ethyl acetate, 20:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.97 (d, J = 7.0 Hz, 1H; C*H*(OMe)$_2$), 3.32 (s, 6H; 2×OMe), 1.85–1.50 (m, 6H; aliphatic ring), 1.34–0.80 (m, 5H; aliphatic ring) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 108.4, 53.4, 39.9, 27.9, 26.3, 25.6 ppm; HRMS (70 eV, EI): calcd for $C_9H_{18}O_2$ ($[M]^+$): 158.1307; found 158.1313; elemental analysis calcd (%) for $C_9H_{18}O_2$: C 68.31, H 11.47; found: C 68.45, H 11.56.

(1*R,2*R**)-1-(Dimethoxymethyl)-2-methoxycyclopentane (4p)**: Colorless oil. R_f = 0.16 (hexane/ethyl acetate, 10:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.14 (d, J = 7.0 Hz, 1H; C*H*(OMe)$_2$), 3.70–3.55 (m, 1H; MeOC*H*), 3.37, 3.33, 3.29 (3s, 9H; 3xOMe), 2.30–2.10 (m, 1H; C*H*CH(OMe)$_2$), 1.90–1.30 (m, 6H; rest of the ring) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 106.3, 84.3, 56.5, 53.9, 53.1, 48.1, 31.8, 26.2, 23.5 ppm; HRMS (70 eV, EI): calcd for $C_9H_{18}O_3$ ($[M]^+$): 174.1256; found 174.1259; elemental analysis calcd (%) for $C_9H_{18}O_3$: C 62.04, H 10.41; found: C 62.15, H 10.30.

(1*S,2*R**)-1-(Dimethoxymethyl)-2-methoxycyclopentane (4q)**: Colorless oil. R_f = 0.22 (hexane/ethyl acetate, 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.46 (d, J = 8.5 Hz, 1H; C*H*(OMe)$_2$), 3.69 (t, J = 3.1 Hz, 1H; MeOC*H*), 3.39, 3.31, 3.25 (3s, 9H; 3xOMe), 2.10–1.97 (m, 1H; C*H*CH-(OMe)$_2$), 1.94–1.42 (m, 6H; rest of the ring) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 105.2, 82.9, 56.3, 54.1, 52.6, 47.8, 30.0, 25.0, 21.7 ppm; HRMS (70 eV, EI): calcd for $C_9H_{18}O_3$ ($[M]^+$): 174.1256; found 174.1254; elemental analysis calcd (%) for $C_9H_{18}O_3$: C 62.04, H 10.41; found: C 62.17, H 10.55.

General procedure for the rearrangement reaction of olefins 2 to give acetals 4 or aldehyde 1e: A solution of IPy_2BF_4 (1.23 g, 3.3 mmol) in dry CH_2Cl_2 (16 mL) was prepared under nitrogen and then treated with dry $BF_3{\cdot}OEt_2$ (0.46 mL, 3.7 mmol) and methanol (0.21 mL, 5 mmol) at room temperature. The corresponding olefin **2** (1.0 mmol) was then slowly added, the red color of the mixture turning violet. The reaction was monitored by TLC and quenched after 1 h by addition of a 5% solution of $Na_2S_2O_3{\cdot}5H_2O$ (10 mL). Extraction with CH_2Cl_2 (2×10 mL) was performed immediately and the combined organic layers washed with water (2×10 mL) and dried with anhydrous sodium sulfate. The solvents were removed carefully and the residue was purified by flash chromatography (SiO_2, hexane/diethyl ether, 40:1) to obtain pure acetals **4** or aldehyde **1e**.

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[9] In the absence of water the reaction did not proceed and the starting material was recovered unchanged. The solvent (CH_2Cl_2) and the $BF_3{\cdot}OEt_2$ were dried before use. When commercial $BF_3{\cdot}OEt_2$ was used without any previous drying treatment, 72% of aldehyde **1a** was isolated. In this case the water is thought to come from the commercial $BF_3{\cdot}OEt_2$.
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