Influence of solvents and catalysts on the formation and hydrolysis of polyfunctional enoxysilanes derived from aucubin

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Dedicated to Professor Pierre Vogel on the occasion of his 70th anniversary

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Abstract
Aucubin, a natural iridoid widely extracted from *Aucuba japonica* presents a strong interest as semisynthetic raw substantial, thanks to its numerous features. In this study, we describe an unprecedented reaction between trimethylsilyldiazomethane and the aldehyde-derived aucubin (**3a**) leading to different original non-natural skeletons exemplified by the tricyclic compounds **6** and **9** (Figure 1). The influence of catalysts, solvents and temperature on the formation of the products together with the hydrolysis of enoxysilane **4** will be presented.

Keywords: Trimethylsilyldiazomethane, ring enlargement, aucubin, catalyst

Introduction

Aucubin (**1**) is one of the most common and widespread iridoids of the plant kingdom. It has been isolated from many species belonging to more than ten plant families.[1] It is very abundant in *Aucuba japonica* (Cornaceae), a common plant easily growing in temperate climate. It has been the first iridoid glucoside isolated in 1902 by E. Bourquelot at the "Ecole de Pharmacie de Paris".[2] After its structural elucidation by H. Uda[3] and by J. Grimshaw in 1960,[4] this naturally occurring material devoid of cytotoxic activity,[5-7] is used for several decades by organic chemists for the synthesis of chiral building blocks or scaffolds.[8-16] Aucubin permitted the synthesis of various classes of biologically interesting chiral compounds: insect antifeedants,[17] carbocyclic nucleoside analogues,[18-19] aminocyclopentitol glycosidase inhibitors,[14] prostaglandins,[20]

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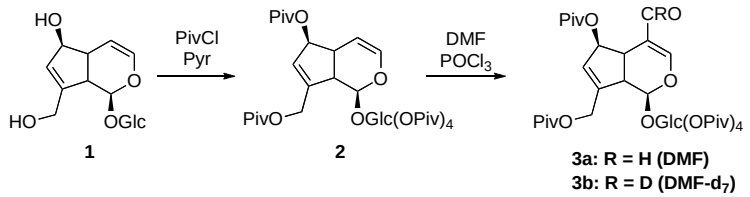
cytotoxic cyclopentenone glucosides,[21-22] chiral rigid *γ*-amino acid glucosides[23] and polyaminoiridoids whose have similar polarity with aminoside antibiotics.[24]

For those syntheses, functional or skeletal modifications were applied to aucubin and sometimes with an innovative chemistry. In a recent work, we showed, for the first time, that the use of trimethylsilyldiazomethane (TMSDM) with *β*-alkoxyenals allowed unexpectedly to a ring enlargement in one step of 3,4-dihydro-2*H*-pyran-5-carbaldehydes into trimethyl[(4*E*)-4,5,6,7-tetrahydrooxepin-4-ylidenemethoxy]silanes.[16] This methodology has been then applied to aldehydes derived from aucubin, which has been isolated from *Aucuba japonica* aqueous extract.[2]



Scheme 1. Synthesis of perpivaloyltarennoside **3a** from natural aucubin (**1**).

Herein, in continuation of our work concerning the reaction between iridoids skeletons and TMSDM, we describe the influence of various process parameters as solvent, catalyst or temperature on the nature of the products. The best conditions to form original non-natural heterotricyclic skeletons **6** and **9** (Figure 1) obtained from perpivaloyltarennoside (**3a**) derived from aucubin are reported.

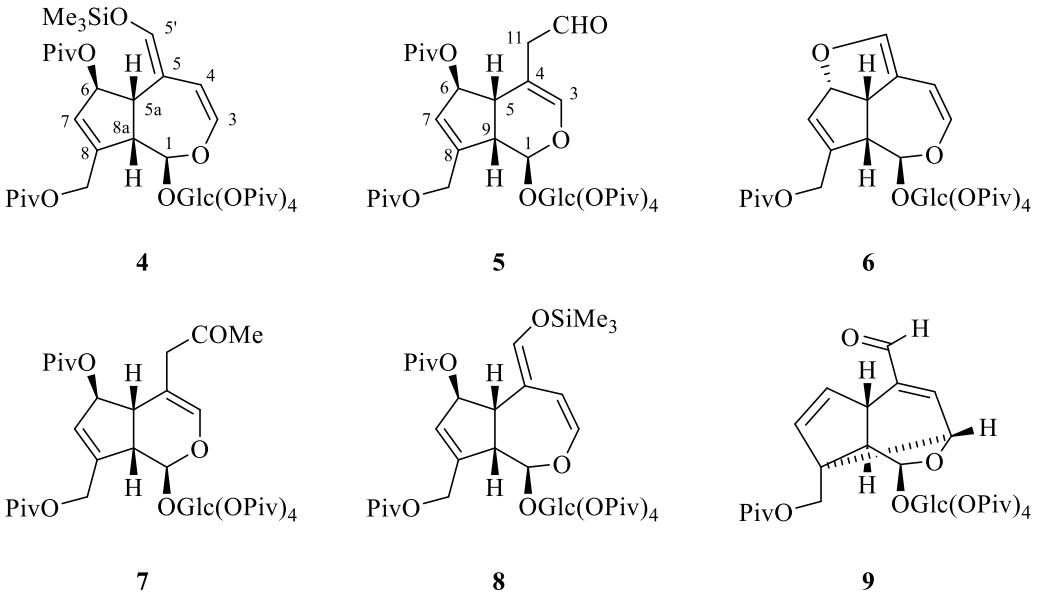


Figure 1. List of the compounds obtained from the reaction between **3a** and TMSDM.

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Results and Discussion

Previously, we published that the reaction of **3a**, obtained by Vilsmeier procedure from perpivaloylaucubin **2** (Scheme 1),[23, 25] with TMSDM in presence of TMSOTf and molecular sieves in dichloromethane at -40°C led to a quantitative homologation of the pyran ring to oxepin forming the enoxysilane **4** (Table 1, Entry 1). The impact of process parameters has been showed and the role of molecular sieves has been described. Indeed, the lack of molecular sieves drove a significant decrease of the enoxysilane yield along with the formation of the minor product **5**, resulting in the homologation on C-11 of the starting material.[16]

With the goal to demonstrate that the experimental conditions control the products of the reaction, we studied at first the influence of the solvent polarity. As shown in Table 1, the use of non-polar solvents without sieves did not significantly affect the yield of the formation of **4** and **5** (Table 1, Entries 2-5). In a protic solvent as MeOH, **3a** does not react (Table 1, Entry 6). Surprisingly, in a more polar solvent such as acetonitrile, the reaction does not stop to the formation of **4**, because an original tricyclic glucoside **6** was isolated with an acceptable yield (60%) (Table 1, Entry 7). With this solvent, the use of sieves does not seem to have a clear effect on the formation of the tricyclic compound (Table 1, Entry 8). Regarding the ^{1}H NMR spectrum, the structure of **6** was deduced from the loss of the pivaloyl group in position 6. This allegation has been confirmed by the molecular ion at *m/z* $[M + Na]^+$ 813.4013 in the HR-ESI-MS. The important correlation on the HMBC spectrum between H-5' and C-6 justified the formation of the dihydrofuran ring 5-5'-O-6-5a. Furthermore, the broad doublet at 5.50 ppm is in good agreement with a proton H-6 up to the plan and characteristic of the configuration. On the NOESY spectrum, examination of correlations between H-6 and H-5a, and between H-6 and H-8a ensured this affirmation.

Table 1. Influence of solvent and sieves for the reaction of **3a** with TMSDM and TMSOTf

3a $\xrightarrow[\textbf{Solvent}]{\text{TMSDM (1equiv) TMSOTf (0.3 equiv)}}$ **4** **5** **6**

Entry	Solvent	T(°C)	Time (h)	Sieves (4Å)	Yield (%)		
1	CH_2Cl_2	-40	2	Yes	98[16]		
2	CH_2Cl_2	-40	4	No	52	12	
3	Et_2O	-40	2	No	55	9	
4	Toluene	-40	2	No	38	8	
5	$CHCl_3$	-40	2	No	43	7	
6	MeOH	-40	24	No	No reaction !		
7	CH_3CN	-10	3	No			60
8	CH_3CN	-10	3	Yes			58

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The second part of the study concerned the influence of the catalyst. As described before, the reaction of **3a** with TMSDM in presence of TMSOTf has led specifically to the enoxysilane **4** having the oxepin ring with high yield compared to the experience with $AlCl_3$ (Table 2, Entry 1).[16] Using a catalytic amount of a solution of $Yb(OTf)_3$ in THF, the stereoselectivity of the formation of enoxysilanes has been lost because **4** and **8** were formed with equal ratio (Table 2, Entry 2). Enoxysilanes **4** and **8** presented a structural analogy. They differed by the stereochemistry of the double bond C-5-C-5' which was deduced thanks to NOESY spectrum. For **4,** a H-5'- H-4 correlation was observed while that for **8,** a H-5'- H-5a correlation was displayed. It must be noted that with those two latter catalysts, no homologation of the formyl group at position C-11 and no formation of tricycle **6** have been observed. Various catalysts which were defined previously to react with TMSDM and carbonyls,[26] have also been tested. No reaction occurred with $AlMe_3$ and $MgBr_2$ while the use of $BF_3.Et_2O$ generated the homologated methylketone **7**.

To explain the formation of **5**, a proton source is required. The hypothesis that TMSOTf is able to generate triflic acid (TfOH) without molecular sieves was formulated. So, we sought to optimize the process to obtain **5** by using a Brønsted acid as catalyst. With Tf_2NH, a mixture of enoxysilane **4** and aldehyde **5** has been obtained in a poor yield (Table 2, Entry 6). Trifluoroacetic acid failed to react with **3a** (Table 2, Entry 7) while the acidity of TfOH has been proved efficient in a stoichiometric amount. These latter conditions lead to the unique aldehyde **5** in 55% of yield (Table 2, Entry 8).

Table 2. Influence of catalysts for the reaction of **3a** with TMSDM

3a $\xrightarrow[\text{-40°C, } CH_2Cl_2]{\text{TMSDM (1equiv.) } \textbf{Catalyst}}$ **4** **5** **6** **7** **8**

Entry	Catalyst	Equiv.	Time (h)	Yield (%)*				
1	$AlCl_3$	0.3	2	31[16]				
2	$Yb(OTf)_3$**	0.3	24	25				22
3	$AlMe_3$	0.3	24		No reaction !			
4	$MgBr_2$	0.3	24		No reaction !			
5	$BF_3.Et_2O$***	0.3	2				43	
6	Tf_2NH	1	2	37	11			
7	CF_3COOH	1	24		No reaction !			
8	TfOH	1	2		55			

*After flash column chromatography. ** Solubilized in the THF. *** To have a total reaction of **3a**, 2 equiv. of TMSDM and 1.5 equiv. of $BF_3.Et_2O$ were used.

In order to have a better understanding of the mechanism of formations of **5** and **7**, the deuteriated aldehyde **3b**[16] has been engaged in similar processes (Scheme 2). We first

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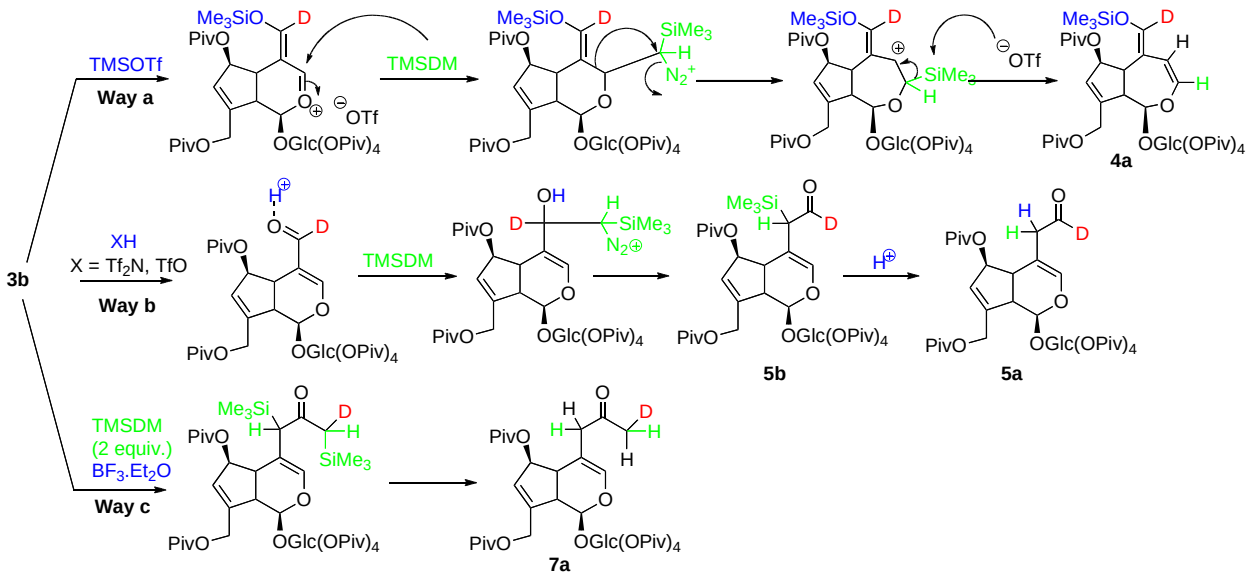
demonstrated that ring-enlargement products exemplified by enoxysilane **4a** proceeded by the 1,4-addition of TMSDM (**way a**). In accordance to the Table 2 (Entries 6 and 8), the protonic catalysis to form **5a** suggests an activation of the aldehyde followed by the exclusive attack of TMSDM on the carbonyl group. Then the hydride migrates to furnish ketosilane **5b** which was hydrolyzed to **5a** (**way b**). Otherwise, we found that the use of $BF_3.Et_2O$ as catalyst promotes the methylketone **7a** formation. In that event, TMSDM reacts on the carbonyl giving a double homologation. Although the first steps of formation of compounds **5a** and **7a** are similar, for **7a**, $BF_3.Et_2O$ also participated to the hydrolysis of the trimethylsilyl group.[29] Once the intermediate **5a** formed, TMSDM reacts again with the carbonyl activated by $BF_3.Et_2O$ (**way c**). Thereby, to have a total reaction of the starting material and optimize the results, two equivalents of TMSDM were required in this case.



Scheme 2. Proposed mechanism of ring expansion and homologation of **3b**.

The formation of tricyclic product was also thoroughly studied. The preferred configuration of enoxysilane observed for **4** suggests that **6** was obtained from a rearrangement of this latter. In order to support this hypothesis, we carried out the acid catalysis of **4** with TMSOTf, Tf_2NH, $AlCl_3$, $Yb(OTf)_3$ and $BF_3.Et_2O$. Regarding the results presented in Table 3, we observed an undeniable influence of the nature of the catalyst on the formation of tricyclic compound. Thus, using 10% of TMSOTf in dichloromethane at -78°C the original tricyclic compound **6** was obtained quantitatively in an instant way (Table 3, Entry 1). With Tf_2NH, 20% of catalyst has been necessary to have a total reaction of **4** and the tricycle **6** has been formed in a lower yield (Table 3, Entry 2). $AlCl_3$ has not allowed the rearrangement of the enoxysilane even at room temperature by using a stoichiometric quantity of catalyst (Table 3, Entry 3). **4** did not react at low temperature with $Yb(OTf)_3$ and $BF_3.Et_2O$. Nevertheless, at room temperature, an unexpected rearrangement occurred (Table 3, Entries 4 and 5) and an original heterotricyclic heteroside

aldehyde **9** produced. The nature of this skeleton has been established from several NMR experiments. In addition to the loss of one pivaloyl group, a quaternary carbon at 63.4 ppm was attributed to C-8 by a ^{3}J-HMBC correlation with H-1. The presence of the double bond Δ6-7 was shown firstly by the ^{13}C NMR chemical shifts at δ 145.1 and 130.2 ppm together with COSY correlation between H-7 at δ 5.66 ppm and H-6 at δ 6.51 ppm. Moreover HMBC correlations H-7/C-8', H-7/C-5a, H-6/C-8 and H-6/C-5a confirmed the insaturation's position. These data considered, the tricyclic skeleton was deduced on one hand from the HMBC correlations between the aldehydic signal at δ 9.41 ppm and the ethylenic carbons C-4, C-5 and also the carbon sp^3 C-5a and on other hand by the ^{3}J correlations H-3/C-8a and H-8a/C-3.

Table 3. Acid catalysis of enoxysilane **4**

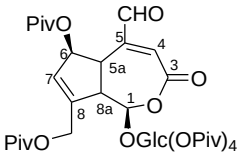
4 $\xrightarrow[CH_2Cl_2]{Catalyst}$ **6** **9**

Entry	Catalyst	Equiv.	T (°C)	Time	Yield (%)	
1	TMSOTf	0.1	-78	1 min	100	
2	Tf_2NH	0.2	-78	20 min	50	
3	$AlCl_3$	1	RT	24 h	No reaction !	
4	$Yb(OTf)_3$	1	RT	20 h		15
5	$BF_3.Et_2O$	1	RT	3 h		60

The final part of this study concerned the hydrolysis of enoxysilane **4** by cleavage of the trimethylsilyl group following three different methods that are TBAF in THF, a hydromethanolic mixture or a combination of acetic acid, THF, water. Whatever the conditions used, an unselective oxydative addition at C-3 or C-5 has furnished, in low yield, two original compounds **10** and **11** possessing an aldehyde function in C-5. Although the mechanism of formation of these latter is still obscure, it could be also explained by the presence of dioxygen during the reaction which has not been carried out under inert atmosphere.

Table 4. Hydrolysis of enoxysilane **4**

4 $\xrightarrow{\textbf{Hydrolysis}}$



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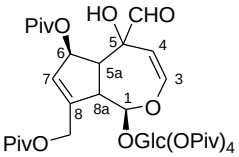

11

Entry	Hydrolysis conditions	Yield (%)	
1	TBAF (1equiv.), THF, RT	18	31
2	$MeOH/H_2O$ (5/1), RT	11	16
3	$AcOH/THF/H_2O$ (3/1/1), RT	14	36

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Conclusions

Different works done until now on the semisynthesis from aucubin led to develop contraction of pyran ring to furan or cyclopropane[14] or homologation in C-4.[23, 25] We described here for the first time a novel semisynthesis method to obtain in only few steps, ring expansion from aucubin, providing various unprecedented skeletons. The exploitation of these building blocks opens great prospects both in chemical and biological area.

Experimental Section

General. Optical rotations were measured (*c*: g/100 mL) with a *Perkin-Elmer 241* polarimeter. The IR spectra were obtained on a *Nicolet 510-FT-IR* instrument. NMR spectra were recorded on *Bruker Avance-400* and/or *Bruker AC-300* spectrometers, chemical shifts are expressed in ppm downfield to TMS. The melting points were determined on a hot stage *Leica* microscope and are not corrected. When necessary, the structures of the novel compounds were insured and the signals unambiguously assigned by 2D NMR techniques: ^{1}H-^{1}H COSY, ^{1}H-^{1}H NOESY, ^{1}H-^{13}C HMQC, and ^{1}H-^{13}C HMBC. These experiments were performed using standard Bruker microprograms. ESI-MS and HR-ESI-MS were determined on a *Waters Micromass Q-TOF* apparatus equipped with a ESI-Z spray source. TLC were performed on *Merck Silica gel 60 F254* aluminium sheets, using vanillin/H_2SO_4 as spray reagent. Column chromatographies were conducted using silica gel *Merck* [6-35 μm, 20-45 μm, or 35-70 μm (flash)] with an overpressure of 300 mbar. THF was distilled over sodium-benzophenone. DMF and pyridine were stored on molecular sieves (4 Å). Dichloromethane, toluene and triethylamine were distilled over calcium hydride and methanol in presence of magnesium and iodide. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise noted. Usual nomenclature of iridoids was employed. Trimethylsilydiazomethane was purchased from Sigma Aldrich as a 2M solution in diethyl ether.

Perpivaloylaucubin (**2**). **2** was isolated as a white amorphous powder (yield: 76%) according to the procedure described before.[14] NMR and MS spectra were identical to the reported data.

6(*R*)-Perpivaloyl-6-hydroxytarennoside (**3a**). **3a** was isolated as colorless crystals (yield: 78%) according to the procedure described before.[16] NMR and MS spectra were identical to the reported data.

6(*R*)-Perpivaloyl-6-hydroxy(11-^{2}H)tarennoside (**3b**): **3b** was isolated as white powder (yield: 71%) according to the procedure described before.[16] NMR and MS spectra were identical to the reported data.

Enoxysilane 4. 4 was isolated as white powder (yield: 98%) according to the procedure described before.[16] NMR and MS spectra were identical to the reported data.

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Aldehyde 5. To a solution of 300 mg of aldehyde **3a** (0.34 mmol) in dichloromethane (10 mL) at -40 °C was added 30 µL of TfOH (0.34 mmol) dissolved in dichloromethane (C = 0.1 M). 171 µL of trimethylsilyldiazomethane has then added. The reaction was stirred for 2h. After the complete conversion of the aldehyde the mixture was warmed to rt, washed with 2 x 10 mL of distillated iced water. Then the organic phase was dried on $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography over silica gel (20-45 µM, cyclohexane/EtOAc: 98/2) to afford corresponding aldehyde **5** as white amorphous solid (yield: 55%). Spectral data of **5** were consistent with the literature.[16]

Tricycle 6. To a solution of enoxysilane **4** (100 mg, 0.11 mmol) in 5 mL of dichloromethane at -78°C, 2 µL of TMSOTf dissolved in dichloromethane (0.011 mmol) were added dropwise. After 1 min, the catalyst was neutralized with 1.6 µL of Et_3N (0.011 mmol) dissolved in dichloromethane. After at room temperature, 3 mL of pentane was introduced to precipitate the formed salts. The 1h30 stirring solution was then filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography over silica gel (20-45 µM, cyclohexane/EtOAc: 9/1) to afford tricycle **6** as white powder, yield 98%, 85 mg, $[\alpha]_D^{20}$ -100 (*c* 0.1, CH_2Cl_2); IR (ν_{max}, cm^{-1}): 1651 and 1596 (C=C-C=C), 1237 (C-O-C); UV λ (log ε): 275 nm (3.12 L. mol^{-1}. cm^{-1}), ^1H NMR (300 MHz, $CDCl_3$): δ_H 6.28 (d, 1H, $^3J_{3\text{-}4}$ 7 Hz, H_3), 6.16 (d, 1H, $^4J_{5'\text{-}5a}$ 1.5 Hz, $H_{5'}$), 5.67 (m, 1H, H_7), 5.50 (*br*.d, 1H, $^3J_{6\text{-}5a}$ 8 Hz, H_6), 5.44 (d, 1H, $^3J_{4\text{-}3}$ 7 Hz, H_4), 5.37 (t, 1H, $^3J_{3''\text{-}2''} = {}^3J_{3''\text{-}4''}$ 9 Hz, $H_{3''}$), 5.15 (t, 1H, $^3J_{4''\text{-}3''} = {}^3J_{4''\text{-}5''}$ 9.5 Hz, $H_{4''}$), 5.11 (d, 1H, $^3J_{1\text{-}8a}$ 9 Hz, H_1), 5.08 (dd, 1H, $^3J_{2''\text{-}3''}$ 9.5 Hz, $^3J_{2''\text{-}1''}$ 8 Hz, $H_{2''}$), 4.82 (d, 1H, $^3J_{1''\text{-}2''}$ 8 Hz, $H_{1''}$), 4.79 (*br*.d, 1H, $^2J_{8'a\text{-}8'b}$ 15 Hz, $H_{8'a}$), 4.72 (*br*.d, 1H, $^2J_{8'b\text{-}8'a}$ 15 Hz, $H_{8'b}$), 4.18 (dd, 1H, $^2J_{6''a\text{-}6''b}$ 12 Hz, $^3J_{6''a\text{-}5''}$ 2 Hz, $H_{6''a}$), 4.10 (dd, 1H, $^2J_{6''a\text{-}6''b}$ 12 Hz, $^3J_{6''b\text{-}5''}$ 5.5 Hz, $H_{6''b}$), 3.91 (m, 1H, H_{5a}), 3.76 (ddd, 1H, $^3J_{5''\text{-}4''}$ 9.5 Hz, $^3J_{5''\text{-}6''b}$ 5.5 Hz, $^3J_{5''\text{-}6''a}$ 2 Hz, $H_{5''}$), 3.30 (m, 1H, H_{8a}), 1.10-1.27 (5s, 45H, $COC(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 178.0, 177.4, 177.2, 176.5, 176.4 ($COC(CH_3)_3$), 143.6 (C_3), 143.5 (C_8), 140.3 ($C_{5'}$), 125.9 (C_7), 111.6 (C_5), 105.1 (C_4), 103.4 (C_1), 96.3 ($C_{1''}$), 88.8 (C_6), 72.6 ($C_{3''}$), 72.0 ($C_{5''}$), 70.6 ($C_{2''}$), 67.9 ($C_{4''}$), 62.0 ($C_{6''}$), 61.8 ($C_{8'}$), 55.3 (C_{8a}), 46.8 (C_{5a}), 38.9, 38.8, 38.7 ($COC(CH_3)_3$), 27.3, 27.2, 27.1, 27.0, 26.9 ($COC(CH_3)_3$). ESI-MS, *m/z* = 813 $[M + Na]^+$, HRMS calcd for $C_{42}H_{62}O_{14}$: *m/z* = 813.4037 $(M + Na)^+$, found: *m/z* = 813.4013 $(M + Na)^+$.

Methylketone 7. To a solution of 200 mg of aldehyde **3a** (0.23 mmol) in dichloromethane (10 mL) at -40 °C was added 228 µL of trimethylsilyldiazomethane (0.46 mmol) and 28 µL of $BF_3.Et_2O$ dissolved in dichloromethane (C = 0.1 M). The reaction was stirred for 2h. After the complete conversion of the aldehyde the mixture was warmed to rt, washed with 2 x 10 mL of distillated iced water. Then the organic phase was dried on $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography over silica gel (20-45 µM, cyclohexane/EtOAc: 98/2) to afford corresponding methylketone **7** as an amorphous white solid, yield 42%, 165.6 mg, $[\alpha]_D^{20}$ - 60.4 (*c* 0.065, CH_2Cl_2); IR (ν_{max}, cm^{-1}): 1666 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ_H 6.22 (*br*.d, 1H, $^4J_{3\text{-}5}$ 1.5 Hz, H_3), 5.69 (m, 1H, H_7), 5.4 (*br*.ddd, 1H, $^5J_{6\text{-}10}$ 2 Hz, $^3J_{6\text{-}7}$ 4 Hz, $^3J_{6\text{-}5}$ 6 Hz, H_6), 5.35 (t, 1H, $^3J_{3'\text{-}4'} = {}^3J_{3'\text{-}2'}$ 9.5 Hz, $H_{3'}$), 5.14 (t, 1H, $^3J_{4'\text{-}5'} = {}^3J_{4'\text{-}3'}$ 9.5 Hz, $H_{4'}$), 5.06 (dd, 1H, $^3J_{2'\text{-}1'}$ 8 Hz, $^3J_{2'\text{-}3'}$ 9.5 Hz, $H_{2'}$), 4.93 (d, 1H, $^3J_{1'\text{-}2'}$

8 Hz, $H_{1'}$), 4.75 (*br*.s, 2H, H_{10}), 4.60 (d, 1H, $^3J_{1\text{-}9}$ 8.5 Hz, H_1), 4.19 (dd, 1H, $^2J_{6'a\text{-}6'b}$ 12 Hz, $^3J_{6'a\text{-}5'}$ 2 Hz, $H_{6'a}$), 4.05 (dd, 1H, $^2J_{6'b\text{-}6'a}$ 12 Hz, $^3J_{6'b\text{-}5'}$ 5.5 Hz, $H_{6'b}$), 3.74 (ddd, 1H, $^3J_{5'\text{-}4'}$ 9.5 Hz, $^3J_{5'\text{-}6'b}$ 5.5 Hz, $^3J_{5'\text{-}6'a}$ 2 Hz, $H_{5'}$), 3.09 (*br*.s, 2H, H_{11}), 2.96 (*br*.ddd, 1H, $J_{5\text{-}3}$ 1.5 Hz, $J_{5\text{-}6}$ 6 Hz, $J_{5\text{-}9}$ 8 Hz, H_5), 2.93 (m, 1H, H_9), 2.15 (s, 3H, C*H*$_3$), 1.25-1.0 (6s, 54H, COC(C*H*$_3$)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 205.7 (C_{12}), 178.2, 177.9, 177.5, 177.2, 176.4 (6C, *C*OC(CH_3)$_3$), 144.1 (C_8), 139.9 (C_3), 127.0 (C_7), 109.2 (C_4), 97.7 (C_1), 97.0 ($C_{1'}$), 82.5 (C_6), 72.4 ($C_{5'}$), 72.0 ($C_{3'}$), 70.6 ($C_{2'}$), 67.8 ($C_{4'}$), 61.7 ($C_{6'}$), 61.6 (C_{10}), 46.8 (C_9), 44.8 (C_{11}), 44.3 (C_5), 38.9, 38.8, 38.7, 38.6 (6C, CO*C*(CH_3)$_3$), 29.3 (CO*C*H_3), 27.2, 27.15, 27.1, 27.0, 26.9 (18C, COC(*C*H_3)$_3$). ESI-MS, *m/z* = 813 (M + Na)$^+$, HRMS calcd for $C_{48}H_{74}O_{16}$: *m/z* = 929.4875 (M + Na)$^+$, found: *m/z* = 929.4887 (M + Na)$^+$.

Enoxysilane 8. To a stirred mixture of aldehyde **3a** (50 mg, 0.06 mmol) and molecular sieves 4Å (100 mg) in anhydrous dichloromethane (5 mL) under an Ar atmosphere at -40 °C was added a solution of trimethylsilyldiazomethane (30 µL, 0.06 mmol). A solution of 11 mg of Yb(OTf)$_3$ (0.034 mmol, C = 0.1 M) in THF was added dropwise carefully. After 2h stirring, the mixture was filtered and the solvents were removed under reduced pressure. The crude product was purified by column chromatography over silica gel (20-45 µM, cyclohexane/EtOAc: 9/1) to afford enoxysilane **4** (22%) accompanied by enoxysilane **8** (25%) as an amorphous yellow solid, yield 25%, 14 mg, $[\alpha]_D^{20}$ - 83 (*c* 0.11, CH_2Cl_2) ; IR (ν_{max}, cm^{-1}): 1654 and 1609 (C=C-C=C), 1143 (OSi). UV λ (log ε): 243 nm (3.46 L. mol^{-1}. cm^{-1}). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 6.29 (q, 1H, $^4J_{5'\text{-}3}$ = $^4J_{5'\text{-}4}$ 1 Hz, $H_{5'}$), 6.24 (dd, 1H, $^5J_{3\text{-}5'}$ 1Hz, $^3J_{3\text{-}4}$ 7 Hz, H_3), 6.17 (m, 1H, H_7), 6.14 (m, 1H, H_6), 6.01 (dd, 1H, $^4J_{4\text{-}5'}$ 1Hz, $^3J_{4\text{-}3}$ 7 Hz, H_4), 5.52 (d, 1H, $^3J_{1\text{-}8a}$ 6.5 Hz, H_1), 5.5 (t, 1H, $^3J_{3''\text{-}2''}$ = $^3J_{3''\text{-}4''}$ 9 Hz, $H_{3''}$), 5.42 (dd, 1H, $^3J_{2''\text{-}3''}$ 9 Hz, $^3J_{2''\text{-}1''}$ 8 Hz, $H_{2''}$), 5.27 (dd, 1H, $^3J_{4''\text{-}3''}$ 9 Hz, $^3J_{4''\text{-}5''}$ 9.5 Hz, $H_{4''}$), 5.09 (*br*.d, 1H , $^2J_{8'a\text{-}8'b}$ 15 Hz, $H_{8'a}$), 4.98 (*br*.d, 1H, $^2J_{8'b\text{-}8'a}$ = 15 Hz, $H_{8'b}$), 4.62 (d, 1H, $^3J_{1''\text{-}2''}$ 8 Hz, $H_{1''}$), 4.17 (dd, 1H, $^2J_{6''a\text{-}6''b}$ 12 Hz, $^3J_{6''a\text{-}5''}$ 1.5 Hz, $H_{6''a}$), 4.05 (dd, 1H, $^2J_{6''a\text{-}6''b}$ 12 Hz, $^3J_{6''b\text{-}5''}$ 5 Hz, $H_{6''b}$), 3.65 (m, 1H, $^3J_{8a\text{-}5a}$ 7 Hz, H_{8a}), 3.4 (ddd, 1H, $^3J_{5a\text{-}8a}$ 7 Hz, $^3J_{5a\text{-}6}$ 4 Hz, $^4J_{5a\text{-}7}$ 1 Hz, H_{5a}), 3.07 (ddd, 1H, $^3J_{5''\text{-}4''}$ 9.5 Hz, $^3J_{5''\text{-}6''b}$ 5 Hz, $^3J_{5''\text{-}6''a}$ 1.5 Hz, $H_{5''}$), 1.10-1.45 (6s, 54H, COC(C*H*$_3$)$_3$), 0.20 (s, 9H, Si(C*H*$_3$)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 177.9, 176.9, 175.9, (6C, *C*OC(CH_3)$_3$), 145.3 (C_8), 140.1 (C_3), 136.5 ($C_{5'}$), 127.1 (C_7), 114.8 (C_5), 106.5 (C_4), 100.8 (C_1), 96.8 ($C_{1''}$), 80.5 (C_6), 72.5 ($C_{3''}$), 72.4 ($C_{5''}$), 70.9 ($C_{2''}$), 67.9 ($C_{4''}$), 61.9 ($C_{8'}$), 61.4 ($C_{6''}$), 54.4 (C_{8a}), 49.3 (C_{5a}), 38.75, 38.7, 38.6 (6C, COC(*C*H_3)$_3$), 27.3, 27.1, 27.0, 26.9 (18C, COC(*C*H_3)$_3$, -0.71(3C, Si(*C*H_3)$_3$). ESI-MS, *m/z* = 987 [M$^+$ + Na], HRMS calcd for $C_{50}H_{80}O_{16}$: *m/z* = 987.5114 (M + Na)$^+$, found: *m/z* = 987.5112 (M + Na)$^+$.

Tricycle 9. To a solution of enoxysilane **4** (100 mg, 0.11 mmol) in 5 mL of dichloromethane at room temperature, 6.4 µL of $BF_3.Et_2O$ dissolved in dichloromethane (0.05 mmol) was added dropwise. After 1h stirring, the mixture was washed with 2 x 10 mL of distillated iced water. Then the organic phase was dried on $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography over silica gel (20-45 µM, cyclohexane/EtOAc: 9/1) to afford corresponding tricycle **9** as white crystalline powder, yield: 60%, 52.2 mg, mp: 218°C; IR (ν_{max}, cm^{-1}): 1723 (CHO), 1674 (C=C). UV λ (log ε): 229.5 nm (3.43 L. mol^{-1}. cm^{-1}). $[\alpha]^{20}_D$ +35 (*c* 0.02, CH_2Cl_2), RMN ^{1}H (300 MHz, $CDCl_3$): δ_H 9.41 (s, 1H,

$H_{5'}$), 6.51(dd, 1H, $^3J_{6\text{-}7}$ 6 Hz, $^3J_{6\text{-}5a}$ 3 Hz, H_6), 6.33 (d, 1H, $^3J_{4\text{-}3}$ 5 Hz, H_4), 5.66 (d, 1H, $^3J_{7\text{-}6}$ 6 Hz, H_7), 5.40 (d, 1H,$^3J_{1\text{-}8a}$ 5.5 Hz, H_1), 5.31 (t, 1H, $^3J_{3''\text{-}2''} = {}^3J_{3''\text{-}4''}$ 9.5 Hz, $H_{3''}$), 5.08 (t, 1H, $^3J_{4''\text{-}3''} = {}^3J_{4''\text{-}5''}$ 9,5 Hz, $H_{4''}$), 4.92 (dd, 1H, $^3J_{2''\text{-}3''}$ 9.5 Hz, $^3J_{2''\text{-}1''}$ 8 Hz, $H_{2''}$), 4.64 (d, 1H, $^3J_{1''\text{-}2''}$ 8 Hz, $H_{1''}$), 4.50 (d, 1H, $^2J_{8'a\text{-}8'b}$ 11 Hz, $H_{8'a}$), 4.40 (d, 1H, $^3J_{3\text{-}4}$ 5 Hz, H_3), 4.20 (*br*.d, 2H, $^2J_{8'b\text{-}8'a}$ 11 Hz, $H_{8'a}$ and $H_{6''b}$), 4.03 (dd, 1H, $^2J_{6''b\text{-}6''a}$ 12.5 Hz, $^3J_{6''b\text{-}5''}$ 5.5 Hz, $H_{6''b}$), 3.70 (ddd, 1H, $^3J_{5''\text{-}4''}$ 9.5 Hz, $^3J_{5''\text{-}6''b}$ 5.5 Hz, $^3J_{5''\text{-}6''a}$ 2 Hz, $H_{5''}$), 3.51 (m, 1H, H_{5a}), 3.27 (m, 1H, H_{8a}), 1.10-1.27 (5s, 45H, COC(C*H*$_3$)$_3$). RMN ^{13}C (75 MHz, $CDCl_3$): δ_C 190.9 ($C_{5'}$), 178.0, 177.1, 176.4 (5C, *C*OC(CH_3)$_3$), 152.1 (C_5), 145.1 (C_6), 140.7 (C_4), 130.2 (C_7), 102.1 (C_1), 99.9 ($C_{1''}$), 72.7 (C_3), 72.2 ($C_{3''}$), 72.0 ($C_{5''}$), 70.9 ($C_{2''}$), 67.8 ($C_{4''}$), 64.1 ($C_{8'}$), 63.4 (C_8), 62.5 (C_{8a}), 61.8 ($C_{6'}$), 40.7 (C_{5a}), 38.9, 38.8, 38.7, 38.6 (5C, CO*C*(CH_3)$_3$), 27.2, 27.1, 27.0, 26.9 (15C, COC(*C*H$_3$)$_3$). ESI-MS *m/z* = 813.6 [M^+ + Na]. Anal. Calcd. for $C_{42}H_{62}O_{14}$ (790.6): C, 63.78; H, 7.90% found: C, 59.77; H, 7.63%.

Aldehydes 10 and 11: Method A: A solution of 120 mg of 4 (0.12 mmol) in 10 mL of a mixture of AcOH/THF/H_2O (3/1/1, V/V/V) was stirred during 3h. The mixture was then extracted with 3 x 10 mL of AcOEt and the organic phase was dried on $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography over silica gel (20-45 µM, cyclohexane/EtOAc: 9/1) to afford corresponding 15.5 mg of **10** (14%) and 40.5 mg of **11** (36%).

Method B: A solution of 150 mg of **4** (0.15 mmol) in 6 mL of a mixture of MeOH/H_2O (5/1, V/V) was stirred during 1h. The solvent was then evaporated under reduced pressure. The residue was purified by column chromatography over silica gel (20-45 µM, cyclohexane/EtOAc: 9/1) to afford corresponding 14.7 mg of **10** (11%) and 17.2 mg of **11** (16%).

Method C: To a solution of 100 mg of **4** (0.10 mmol) in 5 mL of THF was added 30 µL of TBAF dropwise. After 1h stirring, 10 mL of saturated aqueous solution of NH_4Cl were added and the mixture was washed with 2 x 10 mL of AcOEt. The organic phase was then dried over $MgSO_4$, evaporated under reduced pressure and the residue was purified by column chromatography over silica gel (20-45 µM, cyclohexane/EtOAc: 9/1) to afford corresponding 16.3 mg of **10** (18%) and 28.1 mg of **11** (31%).

10: White powder; IR (ν_{max}, cm^{-1}): 1732 (C=O), UV λ (log ε): 233.5 nm (4.07 L. mol^{-1}. cm^{-1}) $[\alpha]^{20}_D$ - 47 (*c* 0.054, CH_2Cl_2), RMN ^{1}H (300 MHz, $CDCl_3$): δ_H 9.54 (s, 1H, $H_{5'}$), 6.53 (s, 1H, H_4), 5.90 (m, 1H, H_7), 5.73 (d, 1H, $^3J_{1\text{-}8a}$ 2,5 Hz, H_1), 5.39 (m, 1H, H_6), 5.33 (t, 1H, $^3J_{3''\text{-}2''} = {}^3J_{3''\text{-}4''}$ 9.5 Hz, $H_{3''}$), 5.13 (t, 1H, $^3J_{4''\text{-}3''} = {}^3J_{4''\text{-}5''}$ 9.5 Hz, $H_{4''}$), 4.99 (dd, 1H, $^3J_{2''\text{-}3''}$ 9.5 Hz, $^3J_{2''\text{-}1''}$ 8 Hz, $H_{2''}$), 4.82 (d, 1H, $^3J_{1''\text{-}2''}$ 8 Hz, $H_{1''}$), 4.78 (*br*.d, 1H, $^2J_{8'a\text{-}8'b}$ 14 Hz, $H_{8'a}$), 4.70 (*br*.d, 1H, $^2J_{8'b\text{-}8'a}$ 14 Hz, $H_{8'b}$), 4.30 (dd, 1H, $^2J_{6''a\text{-}6''b}$ 12.5 Hz, $^3J_{6''a\text{-}5''}$ 1.5 Hz, $H_{6''a}$), 4.02 (dd, 1H, $^2J_{6''a\text{-}6''b}$ 12.5 Hz, $^3J_{6''b\text{-}5''}$ 4.5 Hz, $H_{6''b}$), 3.77 (*br*.d, 1H, $^3J_{5a\text{-}8a}$ 5 Hz, H_{5a}), 3.73 (*br*.d, 1H, $^3J_{8a\text{-}5a}$ 5 Hz, H_{8a}), 3.60 (ddd, 1H, $^3J_{5''\text{-}4''}$ 9.5 Hz, $^3J_{5''\text{-}6''b}$ 4.5 Hz, $^3J_{5''\text{-}6''a}$ 1.5 Hz, $H_{5''}$), 1.08-1.27 (6s, 54H, COC(C*H*$_3$)$_3$). RMN ^{13}C (75 MHz, $CDCl_3$): δ_C 191.7 ($C_{5'}$), 177.3, 175.9, 175.9 (6C, *C*OC(CH_3)$_3$), 163.4 (C_3), 148.4 (C_5), 141.9 (C_8), 135.9 (C_4) 131.0 (C_7), 98.9 (C_1), 97.8 ($C_{1''}$), 84.8 (C_6), 72.5 ($C_{5''}$), 72.4 ($C_{3''}$), 71.1 ($C_{2''}$), 67.4 ($C_{4''}$), 61.0 ($C_{6''}$), 60.3 ($C_{8'}$), 55.2 (C_{8a}), 41.9 (C_{5a}), 38.7, 38.6, 38.4 (6C, CO*C*(CH_3)$_3$), 27.2, 27.0, 26.9, 26.8 (18C, COC(*C*H$_3$)$_3$). ESI-MS, *m/z* = 929 [M + Na]$^+$. HRMS calcd for $C_{47}H_{70}O_{17}$: *m/z* = 929.4511 (M + Na)$^+$, found: *m/z* = 929.4515 (M + Na)$^+$.

11: White crystals; mp: 199-200°C hexane, IR (ν_{max}, cm^{-1}): 3474 (OH), 1743 (C=O), [α] -64 (*c* 0.11, CH_2Cl_2). RMN ^1H (300 MHz, $CDCl_3$): δ_H 9.56 (s, 1H, $H_{5'}$), 6.44 (d, 1H, $^3J_{3-4}$ 7 Hz, H_3), 5.77 (d, 1H, $^3J_{1-8a}$ 9Hz, H_1), 5.71 (m, 1H, H_7), 5.38 (t, 1H, $^3J_{3''-2''}$ = $^3J_{3''-4''}$ 9.5 Hz, $H_{3''}$), 5.16 (t, 1H, $^3J_{4''-3''}$ = $^3J_{4''-5''}$ 9.5 Hz, $H_{4''}$), 5.16 (m, 1H, H_6), 5.11 (dd, 1H, $^3J_{2''-3''}$ 9.5 Hz, $^3J_{2''-1''}$ 8 Hz, $H_{2''}$), 4.88 (d, 1H, $^3J_{1''-2''}$ 8 Hz, $H_{1''}$), 4.78 (*br*.s, 2H, $H_{8'}$), 4.46 (d, 1H, $^3J_{4-3}$ 7 Hz, H_4), 4.20 (dd, 1H, $^2J_{6''a-6''b}$ 12.5 Hz, $^3J_{6''a-5''}$ 2 Hz, $H_{6''a}$), 4.08 (dd, 1H, $^2J_{6''a-6''b}$ 12.5 Hz, $^3J_{6''b-5''}$ 5.5 Hz, $H_{6''b}$), 3.76 (ddd, 1H, $^3J_{5''-4''}$ 9.5 Hz, $^3J_{5''-6''b}$ 5.5 Hz, $^3J_{5''-6''a}$ 2 Hz, $H_{5''}$ and O*H*), 3.54 (*br*.t, 1H, $^3J_{8a-5a}$ 9 Hz, H_{8a}), 2.88 (*br*.dd, 1H, $^3J_{5a-8a}$ 9 Hz, $^3J_{5a-6}$ 2 Hz, H_{5a}), 1.25-1.12 (6s, 54H, COC(C*H*$_3$)$_3$). RMN ^{13}C (75 MHz, $CDCl_3$): δ_C 199.1 ($C_{5'}$), 178.5, 178.1, 177.4, 177.2, 176.4, 176.3 (6C, *C*OC(CH_3)$_3$), 147.4 (C_3), 146.0 (C_8), 125.0 (C_7) 102.4 (C_4), 100.4 (C_1), 96.9 ($C_{1''}$), 79.6 (C_6), 77.2 (C5), 72.6 ($C_{5''}$), 71.9 ($C_{3''}$), 70.5 ($C_{2''}$), 67.7 ($C_{4''}$), 62.3 ($C_{8'}$), 61.7 ($C_{6''}$), 53.2 (C_{8a}), 48.4 (C_{5a}), 38.9, 38.8, 38.7 (6C, CO*C*(CH_3)$_3$), 27.2, 27.1, 27.0, 26.9 (18C, COC(*C*H$_3$)$_3$). ESI-MS, *m/z* = 931 [M^+ + Na], HRMS calcd for $C_{47}H_{72}O_{17}$: *m/z* = 931.4667 $(M + Na)^+$, found: *m/z* = 931.4672 $(M + Na)^+$.

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