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Lewis Acid Catalyzed Enlargement of Cyclic β-Alkoxyenals and One-Pot Synthesis of Polyfunctional Enoxysilanes Derived from Aucubin with Trimethylsilyldiazomethane

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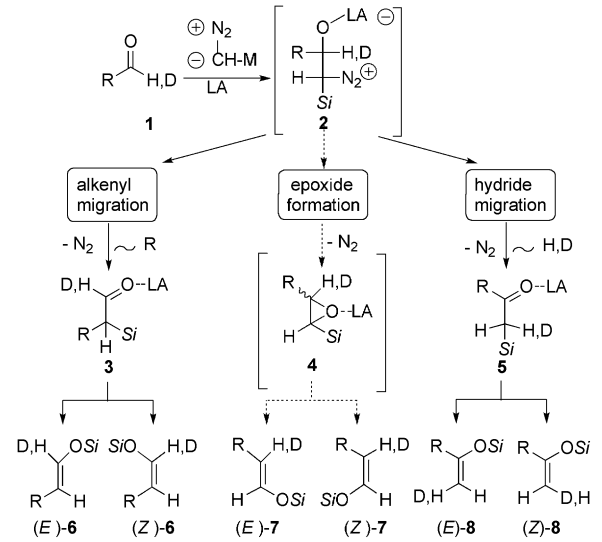
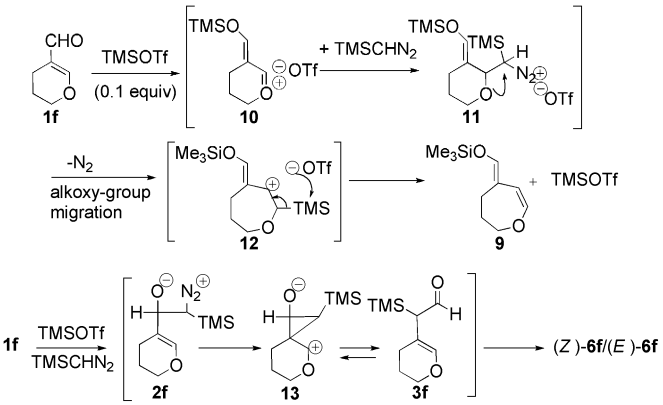
In memory of Professor François Tillequin

Aldehyde and ketone homologations, such as the Tiffeneau–Demjanov–Tchoubar rearrangement with diazomethane are well studied reactions and lead to various products depending on the nature of substrates and reaction conditions.[1] Employment of trimethylsilyldiazomethane (TMSDM)[2] instead of CH_2N_2 makes the reactions safer and allows us to capitalize on the rearrangement of the resulting β-silylcarbonyl compounds.[3] These reactions require nonprotic anhydrous conditions to avoid protolysis of the targeted enoxysilanes. Efforts to find methodologies to convert aldehydes and ketones into homologated enoxysilanes of type **6** and **8** by using TMSDM or TMSC(Li)N_2 in one-step protocols, have been presented (Scheme 1).[4] In the case of aldehydes reacting with TMSDM, the product distribution **6** versus **8** depends on the relative rates of alkyl, aryl, and alkenyl group migration **2**→**3** versus hydride migration **2**→**5** and epoxide formation **2**→**4** (Scheme 1). However, the reactions between TMSDM and cyclic aldehydes have been poorly studied. When enones were reacted, 1,4-addition of TMSDM and subsequent trimethylsilylcyclopropanation were observed.[5]

In this work, we disclose an unusual reaction of TMSDM with β-alkoxyenals. When cyclic β-alkoxyenals are employed (Scheme 2), ring enlargement might compete with the classical aldehyde homologations (Scheme 1) and with suitable Lewis acids may become the major process. This procedure has been applied to carbaldehydes derived from aucubin and it opens a new avenue for the one-pot conversion of these scaffolds into complicated polyfunctional enoxysilanes and their exploitation in semi-synthesis. To our knowledge this methodology represents the first ring expansion from β-alkoxyenals by using TMSDM in one step.



Scheme 1. Expected reactions of TMSDM with aldehydes RCHO and RCDO.



Scheme 2. Proposed mechanism for the ring expansion of β-oxyenal **1f** into **9**.

We explored the reaction of TMSDM with benzaldehydes **1a–c**, cyclohexanecarbaldehyde (**1d**), furfural (**1e**), and 3,4-dihydro-2*H*-pyran-3-carbaldehyde (**1f**; Table 1) to establish

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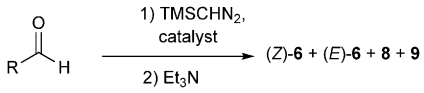
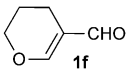
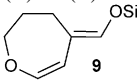
Table 1. One-step homologation of aldehydes to enoxysilanes.



Entry	Substrate	Catalyst	T [°C]	Ratio of (*Z*)-**6**/(*E*)-**6**/**8**/**9**	Yield [%]
1	benzaldehyde (**1a**)	TMSOTf (10%)[a]	−78	(*Z*)-**6a**/(*E*)-**6a**/**8a**, 84:12:4[c]	98[c]
2	*p*-nitrobenzaldehyde (**1b**)	TMSOTf (30%)[a]	−30	(*Z*)-**6b**/(*E*)-**6b**/**8b**, 62:8:30[d]	73[d]
3	*p*-methoxybenzaldehyde (**1c**)	TMSOTf (10%)[a]	−78	(*Z*)-**6c**/(*E*)-**6c**/**8c**, 85:15:0[c]	99[c]
4	*c*-C_6H_{11}-CHO (**1d**)[e]	TMSOTf (30%)[b]	−30	(*Z*)-**6d**/(*E*)-**6d**/**8d**, 24:0:76[c]	55[c]
5	*c*-C_6H_{11}-CHO (**1d**)[e]	$AlCl_3$ (30%)[a]	−30	(*Z*)-**6d**/(*E*)-**6d**/**8d**, 16:3:81[d]	95[d]
6	furfural (**1e**)	TMSOTf (10%)[a]	−78	(*Z*)-**6e**/(*E*)-**6e**/**8e**, 64:36:0[d]	93[d]
7	 **1f**	TMSOTf (10%)[a]	−78	 **9**	90[d]

[a] CH_2Cl_2. [b] CH_3CN. Yields were evaluated by ^1H NMR spectroscopic experiments in the presence of toluene. [c] Yields were evaluated by ^1H NMR spectroscopic experiments in the presence of dimethoxybenzene. [d] As an internal reference. [e] Without Et_3N.

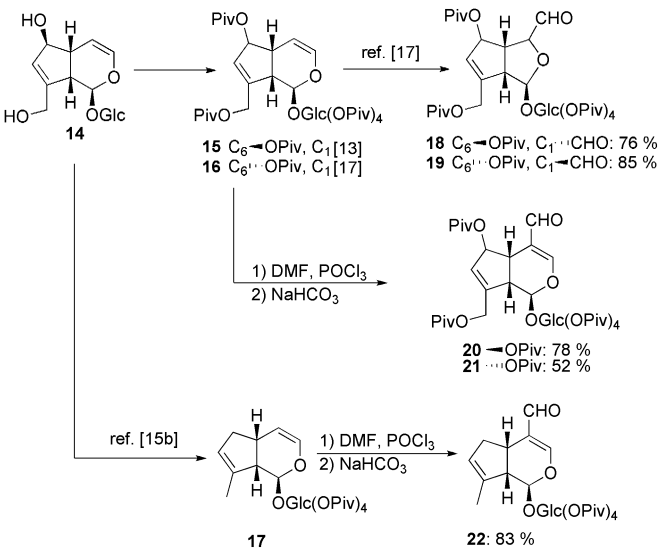
the suitable conditions for one-step homologation of aldehydes into enoxysilanes. As shown in Table 1, trimethylsilyl trifluoromethanesulfonate (TMSOTf) and $AlCl_3$ were active catalysts for these transformations at low temperature. For the aldehydes chosen, the formation of the epoxides of type **4** was not observed, although the latter might be intermediate in the formation of enoxysilanes of type (*E*)-**7** and (*Z*)-**7** by the route **2**→**4**→**7** (Scheme 1).[4f]

The concurrent formation of the 2-substituted enoxysilane of type **8** is the major process for cyclohexanecarbaldehyde (**1d**),[6] whereas it was not observed for the reaction of TMSDM with electron-rich *p*-methoxybenzaldehyde (**1c**). This was expected as the migratory ability of the electron-rich aryl group is significantly facilitated relative to the migratory ability of the hydride in pinacolic-type rearrangements,[7] **2**→**3** versus **2**→**5**. This feature is obvious also when comparing the reaction of **1b** with that of **1c** (Table 1, entries 2 and 3).

Surprisingly, the reaction conducted with aldehyde **1f** gave the product of ring enlargement **9** as the major product in 75% yield. In this case, the products of aldehyde homologation arising from homoalkylcarbinyl-rearrangement (**2f**→**3f**→**6f**) are minor (Scheme 2),[8] whereas products of type **8** obtained by a hydride migration pathway were not observed. The proposed mechanism for the formation of **9** is described in Scheme 2. Activation of β-oxyenal **1f** with TMSOTf catalyst generates intermediate **10**, which possess a strong cationic character on the β-carbon center. The 1,4-addition of TMSDM is favored leading to adduct **11**. A fast 1,2-shift of the electron-rich alkoxy group produces ion-pair **12**, which eliminates an equivalent of TMSOTf to form **9**.

Our research program involves the discovery of new medicinal chemical leads from plant secondary metabolites. By using abundant natural compounds, we deliberately created new chiral scaffolds or building blocks for the synthesis of chemical libraries to screen their biological activities. Among them, a natural iridoid glycoside, aucubin (**14**), is particularly suitable to be used as a starting material as it is easily extracted in large amounts from the fresh aerial parts of *Aucuba japonica* Thunb. (Cornaceae).[9] Through partial syntheses, **14** permitted[10] access to various biologically active chiral compounds including insect antifeedants,[11] carbocyclic nucleoside analogues,[12] aminocyclopentitol glycosidase inhibitors,[13] several prostaglandins,[14] cytotoxic cyclopentenone glucosides series,[15] and also polyaminoiridoids, the structures of which can be related to the aminoside antibiotics.[16] Furthermore, **14** was used for the syntheses of chiral rigid γ-amino acid glucosides.[17]

In this context, we have been interested in exploiting carboxaldehyde scaffolds **18**–**22** (Scheme 3) easily obtained in a few synthetic steps from **14**. By a parallel synthesis approach and by following described



Scheme 3. Syntheses of aucubin-derived carbaldehydes **18**–**22**.

procedures,[15b,18] we have prepared the (6*S*)-*per*pivalolylaucubin (**15**), the (6*R*)-*per*pivalolyl*epi*aucubin (**16**), and the 6,10-dideoxyaucubin (**17**). Epimeric iridoids **15** and **16** were converted to cyclopenta[*c*]furan heterosidic aldehydes **18** and **19**, respectively.[18b] Vilsmeier reaction allowed the introduction of a carbonyl group at C-4 of **15**–**17** producing the cyclopentano[*c*]pyran heterosidic aldehydes **20**–**22**.[14,15b]

Firstly, we used aldehydes **20**–**22**, for the one-pot conversion into polyfunctional enoxysilanes by applying our ring-enlargement reaction (Table 2). This allowed the formation of the expected enoxysilanes **23** (52%) and **25** (12%) produced by hydrolysis of enoxysilane **24**.[19] When the experiment was performed with molecular sieves (Table 2, entry 2), **23** was formed exclusively (98%). The structure of

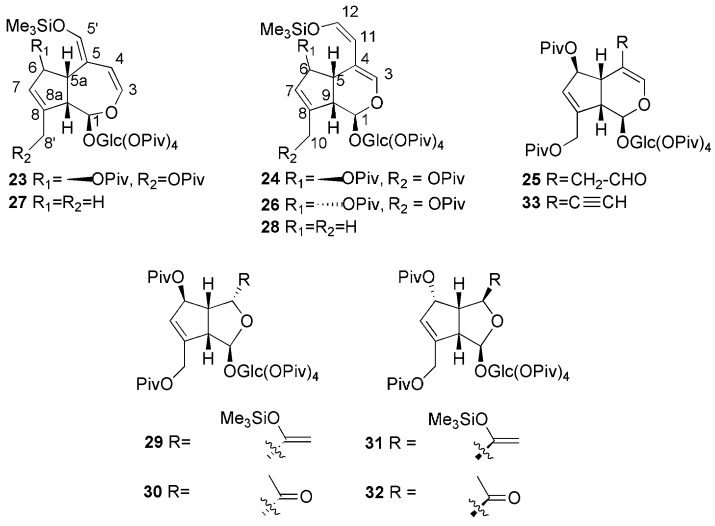


Table 2. Lewis acid catalyzed formation of enoxysilanes and enones **23**–**32** from aucubin-derived carbaldehydes **18**–**22**.

Entry	Substrate	Lewis acid[a]	T [°C]/t [h]	Product (yield [%])[c]
1	**20**	TMSOTf (10%)	−40/4	**23** (52)/**25** (12)
2	**20**	TMSOTf (10%)[b]	−40/2	**23** (98)
3	**20**	$AlCl_3$ (30%)	−40/2	**23** (31)
4	**21**	TMSOTf (10%)[b]	−40/2	**26** (60)
5	**22**	TMSOTf (10%)[b]	−40/2	**28** (56)/**27** (44)
6	**18**	TMSOTf (10%)	−78/44	**29** (21)/**30** (68)
7	**18**	TMSOTf (10%)[b]	−10/3	**29** (11)/**30** (66)
8	**18**	$AlCl_3$ (30%)[b]	−40/2	**29** (100)
9	**19**	$AlCl_3$ (30%)[b]	−40/2	**31** (98)/**32** (12)

[a] Solvent CH_2Cl_2. [b] Molecular sieves 4 Å. [c] Yields are given after chromatography over silica gel.

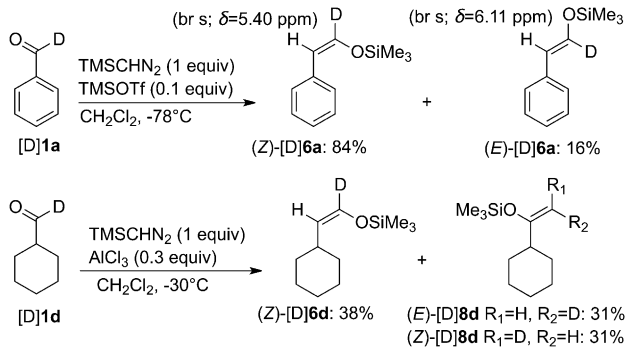
23 was deduced from NOE's by ^{1}H NMR spectroscopy. The NOESY correlations between H-1 and H-8′, H-5a and H-8a showed that the configurations of C-5a, C-8a, and C-1 did not change during the rearrangement and NOE's between H-4 and H-5′ defined the configuration of the enoxysilane moiety of **23**.

The (*Z*)-enoxysilane **26** which conserved the cyclopentano[*c*]pyran skeleton was obtained from the (6*S*)-aldehyde **21** in 60% isolated yield (Table 2, entry 4). For the reaction of iridoid derivative **22**, the cyclopentene part of the aglycon is responsible for the lower regioselectivity and provides two enoxysilanes, **27** (65%) and **28** (35%; entry 5). Thus the regioselectivity of the formation of enoxysilanes **26**–**28** depends on stereoelectronic factors induced by the cyclopentano[*c*]pyran skeleton and the nature of substituent on C-6 and its configuration.

To distinguish the structure of enoxysilane isomers **9**, **23**, **27**, **6f**, **26**, and **28**, NMR spectroscopic studies were performed. Significant differences in chemical shifts, coupling constants, and HMBC correlations were observed. Enoxysilane **9** and major constituents **23** and **27** were nonambiguously established by HMBC correlations. Notably, the correlations exist between the doublet of ethylenic proton H-3 (^3J(H-3/H-4) = 7.5 Hz) and C-1 and between H-1 and C-3. Whereas for **26** and **28**, the ^{1}H NMR spectra disclose a correlation between the ethylenic proton H-3 (doublet, ^3J (H-3/H-5) = 1.5 Hz) with C-1 and the reciprocal correlation H-1/C-3. The coupling constants between vicinal H-3/H-4 (J_{cis} = 7.5 Hz) of **23** and **27** are larger than the corresponding coupling constants of the H-11/H-12 (J_{cis} = 6.5 Hz) of **26** and **28**. Ethylenic protons H-3, H-4, and H-5 of (*Z*)-**6f**, (*E*)-**6f**, and **9** show similar values.

Since a large number of classical procedures using TMSCl and organic bases have failed to form enoxysilane **29** from ketone **30**, this single-step procedure has been very useful to transform the iridoids derivatives **18**–**19** to enoxysilanes **29** and **31**. In contrast to the ring expansion of cyclic β-alkoxyenals by TMSDM, employment of a lithiated form $TMSC(Li)N_2$[4f] with **20** provided the expected compound **33**.

To determine the mechanistic pathway for the formation of enoxysilanes by the reaction of TMSDM with aldehydes **1** (Scheme 1), we employed the deuterated benzaldehyde (PhDCO = [D]**1a**). The same conditions as for the reaction of TMSDM with **1a** resulted in a mixture of 84:16 of (*Z*)-[D]**6a** and (*E*)-[D]**6a**, accompanied with less than 1% of [D]**8a** (Table 1, entry 1). The proportion of **8a**/[D]**8a** (4%/≪1%) is consistent with a rate-determining step involving hydride/deuteride migrations and it might be characterized as a primary kinetic isotopic effect ($k_H/k_D \gg 2$; Scheme 4).

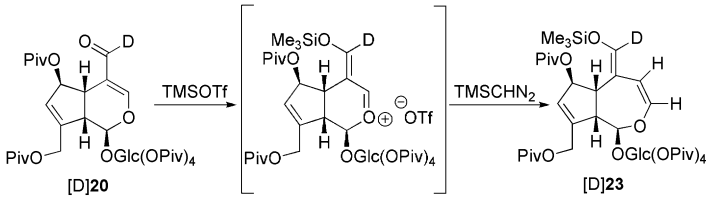


Scheme 4. Ratios of enoxysilanes derived from the reaction of RCDO with TMSDM.

The observation that product ratios (*Z*)-**6a**/(*E*)-**6a** (84:12) and (*Z*)-[D]**6a**/(*E*)-[D]**6a** (84:16) are nearly the same, is in agreement with the reaction pathway by the rearrangement **3**→**6**, for which no kinetic isotopic effect is expected. Importantly, the absence of the isotopomeric compounds (*E*)-[D]**7a** and (*Z*)-[D]**7a** demonstrates that the route through **1**→**2**→**4**→**7** is not followed. The above observation is also in agreement with the reaction of TMSDM with deuterated cyclohexanecarbaldehyde (*c*-C_6H_{11}-CDO = ([D]**1d**)) and **1d** (Table 1, entry 5). Under the same conditions ($AlCl_3$/CH_2Cl_2, −30°C), the reaction of nondeuterated aldehyde **1d** forms a 16:3:81 mixture of (*Z*)-**6d**/(*E*)-**6d**/**8d** and its deuterated isotopomer [D]**1d** gives a 38:≪1:31:31 mixture of (*Z*)-[D]**6d**/(*E*)-[D]**6d**/(*Z*)-[D]**8d**/(*E*)-[D]**8d** (Scheme 3). These

results also show that the deuteride migration is slower than the hydride migration. Interestingly, the absence of the formation of the enoxysilanes (*Z*)-[D]**7d** and (*E*)-[D]**7d** excludes the pathway via **1**→**2**→**4**→**7**. The observation of a 1:1 ratio for enoxysilanes (*Z*)-[D]**8d** and (*E*)-[D]**8d** is consistent with a rearrangement via [D]**1d**→[D]**5d**→[D]**8d** that cannot be affected by a kinetic deuterium isotopic effect (no. *E* vs. *Z* stereoselectivity).[20]

To further validate the mechanisms proposed in Scheme 4, we examined the stereochemistry and regioselectivity of the ring expansion with deuterated aldehyde [D]**20**. Formation of enoxysilane [D]**23** deuterated at 5′ supports the mechanism involving the migration of the carbon–oxygen bond (Scheme 5). The participation of the oxygen



Scheme 5. Ring expansion of deuterated aldehyde [D]**20**.

atom in the pyran ring facilitates the activation of the carbonyl moiety by TMSOTf and thus favors a conjugate addition of TMSDM.

Similarly, to the cyclohexylcarbaldehyde (**1d**), $AlCl_3$ catalyst led to higher yields than TMSOTf for the conversion of cyclopenta[*c*]furan aldehydes **18** and **19** to enoxysilanes **29** and **31**, respectively. Indeed, when the reaction of **18** was catalyzed by TMSOTf in CH_2Cl_2 at −78 °C, the desired enoxysilane **29** was obtained as a minor product (21 %) next to the corresponding methyl ketone **30** (68 %). In contrast, the reaction was quantitative in favor of **29** when $AlCl_3$ was used. A similar result was observed for the $AlCl_3$-catalyzed reaction of aldehyde **19** in CH_2Cl_2 at −40 °C leading to particularly instable enoxysilane **31** (98 %).

In conclusion, the first ring expansions of cyclic β-alkoxyenals with TMSDM were realized. The selection of an appropriate catalyst for the reaction of TMSDM with various aldehydes resulted in the formation of enoxysilanes with a high control of stereoselectivity. The migratory aptitude of aldehyde substituents and the stereoelectronic effects provided by the cyclopentene part of the iridoid aldehydes dictate the regioselectivity of alkylidene insertion. The formation of epoxides or cyclopropanes was never observed under employed condition, for all substrates investigated. Further investigations will be directed towards the synthetic utilization of this method with other complex substrates.

Experimental Section

General method for the preparation of enoxysilanes 23, [D]23, 25, 26, and 27 (exemplified for compound 23): A solution of trimethylsilyldiazomethane (57 μL, 0.11 mmol) was added to a stirred mixture of aldehyde **20** (100 mg, 0.11 mmol) and molecular sieves 4 Å (100 mg) in anhydrous dichloromethane (5 mL) under an Ar atmosphere at −40 °C. A solution of TMSOTf (6.2 μL, 0.011 mmol, 0.1 M) diluted in dichloromethane was carefully added dropwise. The reaction was stirred for 1.5 h. After the complete conversion of the aldehyde, a solution of triethylamine (48 μL, 0.011 mmol, 0.1 M) in dichloromethane was then added. After 1 h, the mixture was warmed at RT and stirred for 0.5 h. Pentane (3 mL) was added and precipitated salts were filtered after additional stirring for 0.5 h. The solvents were removed under reduced pressure. The crude product was purified by column chromatography over silica gel (35–70 μm, cyclohexane/EtOAc 9:1) to afford the corresponding enoxysilane **23** as a white powder (104 mg, 98 %).

General method for the preparation of enoxysilanes 29 and 31 (exemplified for 29): a solution of trimethylsilyldiazomethane (TMSDM; 30 μL, 0.06 mmol) was added to a stirred solution of molecular sieves 4 Å (100 mg) and $AlCl_3$ (2.3 mg, 0.017 mmol) in anhydrous dichloromethane (5 mL) under an Ar atmosphere at −40 °C. A solution of **18** (50 mg, 0.06 mmol) in dichloromethane (5 mL) was then added and the reaction was stirred for 1.5 h. After complete conversion of the aldehyde, the solution was filtered on a pad of silica and the solvent was removed under reduced pressure to give the crude enoxysilane as a yellow powder. The crude product was purified by column chromatography over silica gel (35–70 μm, cyclohexane/EtOAc 9:1) to afford the corresponding compound **29** as a white powder (50 mg, 100 %).

Acknowledgements

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Keywords: aldehydes · enals · homologation · Lewis acids · trimethylsilyldiazomethane

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[19] Under these conditions, **24** was never observed.
[20] Notably, the reaction leads to the preferential formation of (*Z*)-**6** isomers. Our results do not permit a clear explication of this observation and in silico studies are in process.

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