Epoxidation–alcoholysis of cyclic enol ethers catalyzed by $Ti(O^iPr)_4$ or Venturello's peroxophosphotungstate complex

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Venturello's peroxophosphotungstate compound and $Ti(O^iPr)_4$ were successfully used as catalysts for the epoxidation–alcoholysis of various dihydropyrans and dihydrofuran using H_2O_2 as the oxidant. Different alcohols can be used as solvents and nucleophiles, resulting in hydroxy ether products with varying alkoxy groups. The Venturello compound can also be used as catalyst in a biphasic conversion of dihydropyran, in which long chain alcohols or fatty acids are incorporated in the hydroxy ether products with high yield and (stereo)selectivity.

Introduction

Natural product chemistry is a rich source of inspiration for biological investigations and medical discoveries. The development of clean and reliable organic methodologies, including catalytic procedures, is an essential tool for advancing the synthesis and modification of natural products. New catalytic reactions for the fine chemical industry are often developed using model substrates. Such molecules contain a motif that is shared by many relevant potential substrates. This approach is well exemplified by glycosylation chemistry, in which unsaturated sugars or glycals are pivotal intermediates for the synthesis of an increasingly large group of drug molecules or drug precursors.[1] The cyclic enol ether motif of glycals is also found in 3,4-dihydro-2*H*-pyran (DHP), which can accordingly be used as a model, for instance in studying oxidation of the enol ether.[2] Enol ethers are frequently transformed *via* epoxidation, followed by opening of the epoxide with an alcohol or an acid. The epoxidation–alcoholysis is not only relevant for glycal chemistry; DHP and the derived hydroxy ether products are also used in the study and synthesis of polycyclic ether frameworks.[3] The latter are known as the backbones of several naturally occurring toxins such as ciguatoxins, maitotoxins and brevetoxins.

We here present new epoxidation–alcoholysis protocols for various dihydropyrans and dihydrofuran. While some methodologies for oxidative glycal transformation have been reported,[4–8] the epoxidation–alcoholysis of DHP has only rarely been investigated.[9,10] Moreover, in several of these reports, organic oxidants are used, such as 2,6-dichloropyridine *N*-oxide in combination with a Ru catalyst,[4] iodosylbenzene in combination with a Mn catalyst,[9] the urea adduct of hydrogen peroxide in combination with CH_3ReO_3 as a catalyst,[5] *m*-chloroperbenzoic acid,[6,10] or the explosive dimethyldioxirane.[7,8] As all these organic oxidants result in additional waste, the main aim of the present work is to use a clean and safe oxidant such as aqueous H_2O_2. The objective is to reach high conversion of the cyclic enol ether model compounds with high (stereo)selectivity within short reaction times. Moreover, it is desirable to use as large a variety of alcohols or nucleophiles as possible, since this expands the applicability of the new method.

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Results and discussion

Catalyst screening

Using H_2O_2 as the oxidant, the epoxidation–alcoholysis of 3,4-dihydro-2*H*-pyran (DHP) was attempted using a variety of catalysts, including the W-based catalysts $Na_2WO_4{\cdot}2H_2O$, Q_2WO_4, $Q_2W_2O_{11}$,[11] $Q_3PW_4O_{24}$,[12,13] and $Q_4[\gamma\text{-}SiW_{10}(H_2O)_2O_{34}]^{4-}$ [14] (Q = quaternary ammonium), Mo catalysts such as $Mo(CO)_6$ and $Q_3PMo_{12}O_{40}$,[15] and a selection of metal alkoxides including $Mo(O^iPr)_5$, $Ti(O^iPr)_4$, $VO(O^iPr)_3$ and $Zr(OEt)_4$. From this screening, the Venturello peroxo compound $Q_3PW_4O_{24}$ and $Ti(O^iPr)_4$ emerged as superior catalysts. Although titanium is commonly used for epoxidations, *e.g.* in the Sharpless epoxidation,[16] the results with the Ti-catalyst are quite remarkable, as $Ti(O^iPr)_4$ is generally used with ^{t}BuOOH, rather than with aqueous hydrogen peroxide.[17] For both catalysts a short optimization was undertaken to find the best reaction conditions.

Optimization of reaction conditions for $Q_3PW_4O_{24}$ and $Ti(O^iPr)_4$

For reactions with the Venturello compound, it was found that addition of a base, such as an alkaline zeolite is necessary in order to suppress acid-catalyzed alcohol addition on the double bond. Therefore 10 mg of NaA zeolite was added per 20 ml of reaction mixture in all further tests. Other parameters considered were the nature of the quaternary ammonium salt and the composition of the solvent–nucleophile mixture (Table 1). Clearly, the Venturello catalyst can be applied in a range of alcoholic solvents. The highest activity and selectivity are achieved in ethanol (entries 2 and 3). As the reaction is rather slow in pure methanol (entry 1), there is a need for a co-solvent that is miscible with methanol but lacks nucleophilic properties. Use of acetonitrile (entry 5) led to high conversion of the starting enol ether, but the desired products were not formed. Satisfactory conversion and selectivity are obtained in

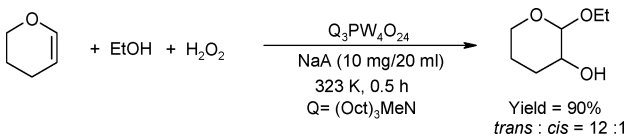
Table 1 Venturello-compound catalyzed epoxidation–alcoholysis of DHP: optimization of reaction conditions[a]

	Solvent	Nucleophile	*t*/h	Yield (%)	*trans* : *cis*
1	MeOH	—	24	81	17 : 1
2	EtOH	—	0.5	85	9 : 1
3[b]	EtOH	—	0.5	88	12 : 1
4	n-PrOH	—	0.25	81	8 : 1
5	MeCN	EtOH[c]	1	0[d]	—
6	1,4-Dioxane	MeOH[e]	3	78	8 : 1
7	1,4-Dioxane	MeOH[f]	0.5	70	8 : 1
8	1,4-Dioxane	EtOH[e]	0.5	45	5 : 1
9	1,4-Dioxane	4-Penten-1-ol[g]	0.5	47	9 : 1

[a] General conditions: 4 mmol DHP, 0.04 mmol $Q_3PW_4O_{24}$ (Q = $(Bu)_4N$), 20 ml solvent, 8 mmol H_2O_2, 10 mg NaA, 323 K. [b] Q = $(Oct)_3MeN$. [c] Equimolar amounts of nucleophile and substrate (0.2 M). [d] Conversion was very high but no desired products were obtained. [e] Dioxane : alcohol = 1 : 1. [f] Dioxane : MeOH = 4 : 1. [g] Dioxane : 4-penten-1-ol = 7 : 3.

a 1 : 1 mixture of methanol and 1,4-dioxane (entry 6). If a higher ratio of dioxane : MeOH is used (entry 7) the selectivity drops because of more diol formation. This is presumably due to the fact that dioxane enhances the nucleophilicity of both methanol and water present in the reaction.[18]

Attempts to incorporate more complex alcohols as nucleophiles in 1,4-dioxane were less successful. In the case of 4-penten-1-ol (entry 9) a significant amount of 5-hydroxy-1,2-epoxypentane was detected, indicating that the reactivity of the enol ether and terminal olefin were not sufficiently differentiated. Finally, the influence of the quaternary ammonium species used as counter ion in the Venturello compound was assessed by comparing the tetrabutylammonium and trioctylmethylammonium (Aliquat® 336) ions in ethanol (entries 2 and 3). With the latter ion, the yield is similar but the stereoselectivity in the epoxide opening is improved. Optimal reaction conditions are summarized in Scheme 1.



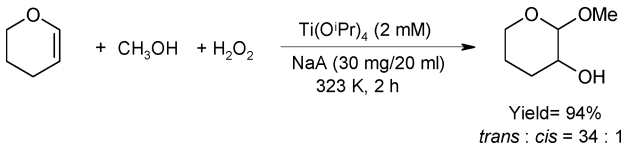
Scheme 1

For $Ti(O^iPr)_4$ as well, a thorough investigation of catalyst concentration, base, solvent–nucleophile system and temperature was performed, and a selection of the data is presented in Table 2. For optimal catalyst solubility, the $Ti(O^iPr)_4$ concentration was set at 2 mM. Among the different bases tested in methanol (entries 2–4), zeolite 4A (entry 4) gave the optimum combination of high reaction rate, selectivity and stereoselectivity. The use of triethylamine (entry 3) led to almost complete *trans* selectivity in the products, but with rather low yield. The solvent choice is limited due to the poor solubility of $Ti(O^iPr)_4$ in alcohols other than methanol, with consequent poor conversion and selectivity in ethanol and propanol (entries 4–6). Addition of dioxane as co-solvent (entry 7) resulted in drastic lowering of the activity and selectivity. The reaction rate can be increased by performing the reaction at 323 K; addition of a larger amount of NaA at this temperature (30 mg per 20 ml, entries 9 *vs.* 10) resulted in a high yield with a significantly improved selectivity for the *trans* product. These experiments led to the proposed optimized reaction conditions of Scheme 2.

Table 2 $Ti(O^iPr)_4$ catalyzed epoxidation–alcoholysis of DHP[a]

	Base	Solvent	*T*/K	*t*/h	Yield (%)	*trans* : *cis*
1	—	MeOH	303	6	73	10 : 1
2	$CaCO_3$	MeOH	″	3	88	11 : 1
3	Et_3N	MeOH	″	24	37	115 : 1
4	NaA	MeOH	″	3	94	20 : 1
5	NaA	EtOH	″	2	33	2.5 : 1
6	NaA	n-PrOH	″	2	23	3 : 1
7	NaA	Dioxane[b]	″	65	81	5.5 : 1
8	NaA	MeOH	313	2	87	20 : 1
9	NaA	MeOH	323	1	86	19 : 1
10	NaA[c]	MeOH	″	2	94	34 : 1

[a] General conditions: 4 mmol DHP, 0.04 mmol $Ti(O^iPr)_4$, 20 ml solvent, 8 mmol H_2O_2, 10 mg base. [b] + 4 mmol MeOH. [c] 30 mg.



Scheme 2

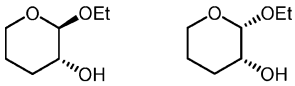
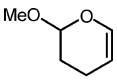
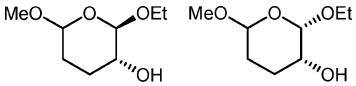
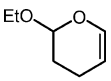
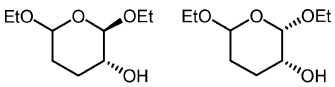
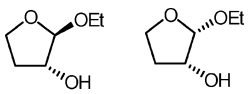
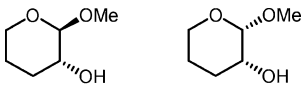
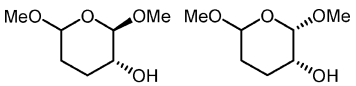
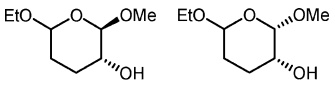
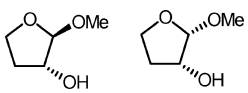
Epoxidation–alcoholysis of various cyclic enol ethers

Both catalysts were tested in optimized conditions with a selection of dihydropyrans and dihydrofuran. The results of the reactions with the Venturello catalyst in ethanol (method A) and with $Ti(O^iPr)_4$ in methanol (method B) are shown in Table 3. Similar patterns of reactivity emerge for both catalytic systems, even if differences are more pronounced with $Ti(O^iPr)_4$ than with the Venturello compound. 2,3-Dihydrofuran (entries 4 and 8) is the most reactive compound due to the high electron density in the double bond of its five-membered ring structure. Of the six-membered ring compounds, unsubstituted 3,4-dihydro-2*H*-pyran is more reactive than the related methyl and ethyl acetals. For these acetals the stereoselectivity of the reactions is somewhat lower (entries 2, 3, 6 and 7).

Comparison of both catalytic systems shows that with $Ti(O^iPr)_4$ in methanol, slightly higher yields as well as higher stereoselectivities are obtained. On the other hand, the Venturello compound is more active on a molar base, as expressed in higher turn-over-frequency (TOF/h^{-1}, measured at the initial reaction stage) values. The TOF value measured for 2,3-dihydrofuran with $Ti(O^iPr)_4$ is almost 4 times higher than the TOF value for 3,4-dihydro-2*H*-pyran (entries 5 and 8); with the Venturello compound (entries 1 and 4) the TOF for 2,3-dihydrofuran is only slightly higher than for 3,4-dihydro-2*H*-pyran. This suggests that $Ti(O^iPr)_4$ is more sensitive to changes in electron density of the double bond.

To confirm this point, relative reactivities of cyclohexene and dihydropyran were measured for both catalysts in competitive experiments (Table 4). In both cases cyclohexene, with the less electron-rich double bond proved to be significantly less reactive than the enol ether; the difference in reactivity is indeed more marked in the case of $Ti(O^iPr)_4$.

Table 3 Epoxidation–alcoholysis of dihydropyrans and dihydrofuran with the Venturello catalyst and with $Ti(O^iPr)_4$

	Substrate	Method	*t*/h	Products	Yield *trans* + *cis* (%)	TOF	*trans* : *cis*
1	 **1**	A	0.5	 **5**	88	320	12 : 1
2	 **2**	A	2	 **6**	86	148	7 : 2
3	 **3**	A	1	 **7**	75	168	7 : 2
4	 **4**	A	0.5	 **8**	89	360	9 : 1
5	**1**	B	2.5	 **9**	94	≥80	34 : 1
6	**2**	B	6	 **10**	94	22	9 : 2
7	**3**	B	5	 **11**	84	35	4 : 1
8	**4**	B	0.3	 **12**	98	300	70 : 1

[a] Conditions: Method A: 4 mmol olefin, 0.04 mmol $Q_3PW_4O_{24}$, 8 mmol 60% aq. H_2O_2, 10 mg NaA, 20 ml EtOH, 323 K. Method B: 4 mmol olefin, 0.04 mmol $Ti(O^iPr)_4$, 8 mmol 60% aq. H_2O_2, 30 mg NaA, 20 ml MeOH, 323 K. Values for TOF were measured after 10–15 minutes of reactions.

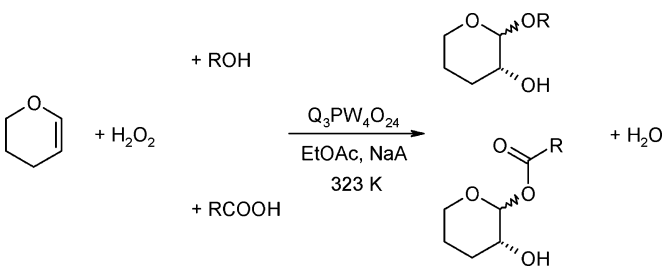
Table 4 Relative reactivities of 3,4-dihydro-2*H*-pyran and cyclohexene with the Venturello compound and with $Ti(O^iPr)_4$

Catalyst	Reactivity ratio 3,4-dihydro-2*H*-pyran : cyclohexene
$Q_3PW_4O_2$	12 : 1
$Ti(O^iPr)_4$	23 : 1

Conditions:[a] As in Table 1, entry 3. [b] As in Table 2, entry 4. As substrates, an equimolar mixture of cyclohexene and DHP was used. Reactivity ratios were determined at low conversions.

Biphasic epoxidation–alcoholysis of 3,4-dihydro-2*H*-pyran with long alcohols or fatty acids

Apolar, long chain nucleophiles are only poorly soluble in the water-containing alcoholic reaction mixtures of Schemes 1 and 2. Therefore reactions were performed in the biphasic conditions specified in Scheme 3, with DHP (0.2 M) and the Venturello catalyst (2 mM, 1%). As nucleophiles, 1-octanol, 1-dodecanol, 1-octadecanol, benzyl alcohol, L-menthol or palmitic acid were



Scheme 3

Table 5 Incorporation of long chain alcohols and a fatty acid in 3,4-dihydro-2*H*-pyran with the Venturello compound in biphasic conditions[a]

	Nucleophile	*t*/h	Product	Yield (%)	*trans* : *cis*
1	Octanol	3	**13**	93	14 : 1
2	Dodecanol	4	**14**	>90	12 : 1
3	Octadecanol	2	**15**	>90	13 : 1
4	Benzyl alcohol	2	**16**	>90	>25 : 1
5	L-Menthol	2	**17**	>90	1 : 1
6	Palmitic acid	2	**18**	85[b]	13 : 1

[a] Conditions: 10 ml ethyl acetate, 2 mmol DHP, 0.02 mmol $Q_3PW_4O_{24}$, 4 mmol nucleophile, 4 mmol H_2O_2, 323 K. [b] 5–10% of the product mixture was the protected DHP of the acid-catalyzed side reaction.

added. The results (Table 5) show that the desired hydroxy ether products are obtained in high yields and within short times. This confirms that high TOF values can be achieved with the Venturello compound. For reactions with long aliphatic alcohols as the nucleophiles, the *trans* : *cis* ratios of the hydroxy ether products are between 12 : 1 and 14 : 1 (entries 1–3). These *trans* preferences in biphasic conditions are even slightly higher than with pure short-chain alcohols in a monophasic system (Table 3).

The reaction with benzyl alcohol gives a surprisingly high stereoselectivity, with more than 96% selectivity for the *trans* isomer (entry 4). In this 2-*O*-benzylated product, the C-3 ^{13}C signal is strongly shifted in comparison to the C-3 of the products containing linear alkoxy groups, likely because of the aromatic nature of the phenyl moiety. With the secondary alcohol menthol (entry 5), an almost 1 : 1 mixture of *cis* and *trans* ring-opened products is obtained. This suggests that with this sterically encumbered alcohol, the ring opening may proceed in a non-concerted fashion. Finally, with palmitic acid as the nucleophile (entry 6), an 85% yield of the desired hydroxy ester is formed; direct, Brønsted acid-catalyzed attack of the acid on DHP to form the protected acid accounts for only 5% of the total products formed. The same protocol was also applied with some thiols and amines, but due to the easy oxidation of these nucleophiles no epoxide-opened products were detected.

Concluding remarks

Lewis acid catalysts for epoxidation such as Ti and W compounds transfer an electrophilic oxygen atom to a double bond. The present data show that a cyclic enol ether is highly reactive towards this electrophilic oxygen atom, even more than a regular olefin such as cyclohexene. The only side reaction at this stage is the Brønsted-acid catalyzed ether formation. Therefore, the use of the isolated peroxophosphotungstate catalyst is to be preferred over procedures in which the catalyst is formed *in situ* from the condensation of tungstic and phosphoric acid.[12] In the latter approach, strong Brønsted acidity would have been introduced in the reaction, lowering the yields of the epoxide and products derived from it. By adding bases, the etherification reaction could be effectively suppressed, without affecting the high epoxidation activity of the W or Ti Lewis acids. The activity of the homogeneous $Ti(O^iPr)_4$ in combination with H_2O_2 is remarkable, since the reactions of the heterogeneous Ti-zeolite TS-1 represent up to now the only successful example of Ti-catalyzed epoxidation with H_2O_2.[19]

While the electron-rich nature of dihydropyran and related substrates results in a facile epoxidation, the challenge is to control the fate of the highly reactive epoxide product. At least three nucleophiles may attack the epoxide: water, which is the side product of the reaction, H_2O_2, especially if used in a large excess, and the desired alcohol reagent. In the case of W oxidation catalysis, the *in situ* opening of the epoxide to the diol, or its further transformation to carboxylic acids have even been exploited for their synthetic utility.[20,21] In the present work, we have succeeded in obtaining yields well over 80% of the alcohol-opened products. This could be realized *via* adapted concentrations of the alcohol, and *via* careful control of reaction temperature and medium acidity. It is remarkable that even the excess of H_2O_2, which is helpful in maintaining a sufficient reaction rate, does not give rise to an appreciable over oxidation. The scope of the $Ti(O^iPr)_4$ based procedure is rather small, since it is limited to methanol as the sole alcoholic solvent. However, the Venturello compound proved to be a very versatile system. As it can be used in monophasic or biphasic conditions, with a broad range of alcohols and even acids as nucleophiles, it holds great promise for future applications in the preparation of fine chemicals.

Experimental

All chemicals were of the highest grade commercially available. The peroxophosphotungstate compound $Q_3PW_4O_{24}$, with Q = Bu_4N^+, was prepared according to a literature procedure.[12,13]

Epoxidation–alcoholysis of enol ethers using the Venturello compound

A typical reaction mixture for the epoxidation–alcoholysis of a dihydropyran or dihydrofuran with the Venturello compound contains 20 ml of solvent, 4 mmol of enol ether, 0.04 mmol $Q_3PW_4O_{24}$, 8 mmol H_2O_2 (60 wt% in H_2O) and 10 mg of powdered NaA, which was pre-dried overnight at 350 °C. The mixture was stirred at 323 K. Reaction progress was monitored by GC-analysis. Conversions, selectivities, yields, turnover numbers (TON, moles of product per mole of catalyst) and *cis* : *trans* ratios were based on GC and GC-MS data.

Titanium-catalyzed epoxidation–alcoholysis of enol ethers

A similar procedure was adopted, using methanol as the solvent, 0.04 mmol $Ti(O^iPr)_4$ as the catalyst, and 30 mg dry powdered NaA.

Biphasic epoxidation–alcoholysis

0.02 mmol of $Q_3PW_4O_{24}$ is weighed in a small reaction flask and 10 ml of ethyl acetate is added. 2 mmol of DHP is added to this solution, followed by 5 mg zeolite 4A and 2 equivalents of a nucleophile. 4 mmol H_2O_2 (50 wt% solution in H_2O) is added to this mixture which is kept at 323 K in a flask with condenser. The reaction is monitored by TLC. When the reaction is completed, the mixture is filtered and the filtrate is taken up in CH_2Cl_2 and washed 3 times with water. The organic phase is dried with $MgSO_4$, filtered

and concentrated *in vacuo*, followed by acetylation. Products and their stereochemistry ratios are determined by ^{1}H, ^{13}C-NMR, COSY, HSQC and DEPT analysis. When necessary purification was done by separation on a silica gel column.

Characterization data

The names of compounds **5–18** correspond to the acetylated derivatives.

2-Ethyl-3-acetyl-2,3-dihydroxypyran (5). Yellowish oil, R_f: 0.45 (*trans*), 0.42 (*cis*) (2 : 8 EtOAc : Petr. Ether), MS (non-acetylated): 146 *m*/*z*, Anal. calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 58.06; H, 8.77%.

trans. ^{1}H-NMR: (300 MHz, $CDCl_3$) δ ppm 4.62 (td, $J = 4.79$, 3.22, 3.22 Hz, 1H, H-2), 4.49 (d, $J = 2.96$ Hz, 1H, H-1), 3.83–3.63 (m, 2H, H-5 & OCH_2CH$_3$), 3.52–3.37 (m, 2H, H-5′ & OCH_2CH$_3$), 2.02 (s, 3H, CH$_3$ acetyl), 1.99–1.91 (m, 1H, H-3′), 1.89–1.73 (m, 1H, H-4), 1.68–1.56 (m, 1H, H-3′), 1.42–1.31 (m, 1H, H-4′). ^{13}C-NMR: (75 MHz, $CDCl_3$) δ ppm 170.17 (C=O), 97.43 (C-1), 68.91 (C-2), 63.07 (O*C*H$_2$CH$_3$), 60.55 (C-5), 23.97 (C-3), 21.07 (OCO*C*H$_3$), 20.99 (C-4), 14.96 (OCH$_2$*C*H$_3$).

cis. ^{13}C-NMR: (75 MHz, $CDCl_3$) δ ppm 95.71 (C-1), 70.33 (C-2), 62.99 (O*C*H$_2$CH$_3$), 59.16 (C-5), 24.30, 23.16 (C-3, C-4), 14.92 (OCH$_2$*C*H$_3$).

5-Methyl-2-ethyl-3-acetyl-2,3,5-trihydroxypyran (6). Yellowish oil, R_f: 0.32 (2 : 8 EtOAc : Petr. Ether), MS (non-acetylated): 174.9 *m*/*z*.

trans. ^{1}H NMR: (400 MHz, $CDCl_3$) δ ppm 4.66–4.59 (m, 1H, H-2), 4.50 (dd, $J = 6.43$, 3.15 Hz, 1H, H-5), 4.48 (d, $J = 5.17$ Hz, 1H, H-1), 3.87–3.75 (m, 2H, OCH_2CH$_3$), 3.56–3.46 (m, 2H, OCH_2CH$_3$), 3.40 (s, 3H, OMe), 2.60–2.43 (m, 1H, H-3), 1.99 (s, 3H, CH$_3$ acetyl), 1.90–1.81 (m, 1H, H-4), 1.63–1.50 (m, 1H, H-4′), 1.49–1.36 (m, 1H, H-3′), 1.15 (t, 3H, OCH$_2$CH_3). ^{13}C-NMR: (100 MHz, $CDCl_3$) δ ppm 170.3 (C=O), 99.86 (C-5), 98.90 (C-1), 70.03 (C-2), 64.35 (O*C*H$_2$CH$_3$), 55.94 (OMe), 27.33 (C-4), 22.39 (C-3), 21.11 (OCO*C*H$_3$), 15.10 (OCH$_2$*C*H$_3$).

cis. ^{1}H NMR: (400 MHz, $CDCl_3$) δ ppm 4.73 (d, $J = 4.23$ Hz, 1H, H-1), 3.39 (s, 3H, OMe). ^{13}C-NMR: (100 MHz, $CDCl_3$) δ ppm 97.88 (C-5), 97.65 (C-1), 68.88 (C-2), 63.83 (O*C*H$_2$CH$_3$), 55.60 (OMe), 26.81 (C-4), 22.95 (C-3), 20.40 (OCO*C*H$_3$).

5-Ethyl-2-ethyl-3-acetyl-2,3,5-trihydroxypyran (7). Yellowish oil, R_f: 0.37 (2 : 8 EtOAc : Petr. Ether), MS (non-acetylated): 189 *m*/*z*, Anal. calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 57.10; H, 8.32%.

trans. ^{1}H NMR: (400 MHz, $CDCl_3$) δ ppm 4.64–4.57 (m, 2H, H-2, H-5), 4.46 (d, $J = 5.72$ Hz, 1H, H-1), 3.89–3.73 (m, 2H, C$_1$-OCH_2CH$_3$, C$_5$-OCH_2CH$_3$), 3.55–3.40 (m, 2H, C$_1$-OCH_2CH$_3$, C$_5$-OCH_2CH$_3$), 2.19–2.08 (m, 1H, H-3), 1.99 (s, 3H, CH$_3$ acetyl), 1.88–1.79 (m, 1H, H-4), 1.67–1.54 (m, 1H, H-4′), 1.47–1.37 (m, 1H, H-3′), 1.19–1.12 (m, 6H, OCH$_2$CH_3). ^{13}C-NMR: (100 MHz, $CDCl_3$) δ ppm 170.03 (C=O), 99.07 (C-1), 98.62 (C-5), 70.20 (C-2), 64.21 and 64.01 (O*C*H$_2$CH$_3$), 28.01 (C-4), 23.11 (C-3), 21.08 (OCO*C*H$_3$), 15.08 (OCH$_2$*C*H$_3$).

cis. ^{1}H NMR: (400 MHz, $CDCl_3$) δ ppm 4.85–4.77 (m, 2H, H-2, H-5), 4.73 (d, $J = 3.88$ Hz, 1H, H-1), 2.00 (CH$_3$ acetyl). ^{13}C-NMR: (100 MHz, $CDCl_3$) δ ppm 97.70 (C-1), 96.35 (C-5), 68.78 (C-2), 63.71 and 63.66 (O*C*H$_2$CH$_3$), 26.90 (C-4), 22.99 (C-3), 21.13 (OCO*C*H$_3$), 15.05 (OCH$_2$*C*H$_3$).

2-Ethyl-3-acetyl-2,3-dihydroxyfuran (*trans*) (8). Yellowish oil, R_f: 0.57 (*trans*), 0.47 (*cis*) (2 : 8 EtOAc : Petr. Ether), MS (non-acetylated): 132.9 *m*/*z*.

trans. ^{1}H-NMR: (400 MHz, $CDCl_3$) δ ppm 5.00 (dd, $J = 6.00$, 1.57 Hz, 1H, H-2), 4.93 (s, 1H, H-1), 4.02–3.88 (m, 2H, H-4, H-4′), 3.68–3.58 (m, 1H, OCH_2CH$_3$), 3.46–3.37 (m, 1H, OCH_2CH$_3$), 2.34–2.24 (m, 1H, H-3), 1.99 (s, 3H, CH$_3$ acetyl), 1.87–1.79 (m, 1H, H-3′), 1.12 (t, $J = 7.07$, 7.07 Hz, 3H, OCH$_2$CH_3). ^{13}C-NMR: (100 MHz, $CDCl_3$) δ ppm 170.32 (C=O), 105.38 (C-1), 77.83 (C-2), 66.27 (C-4), 62.69 (O*C*H$_2$CH$_3$), 29.81 (C-3), 21.00 (OCO*C*H$_3$), 15.06 (OCH$_2$*C*H$_3$).

2-Methyl-3-acetyl-2,3-dihydroxypyran (*trans*) (9)[22,23]. Yellowish oil, R_f: 0.37 (*trans*), 0.30 (*cis*) (2 : 8 EtOAc : Petr. Ether), MS (non-acetylated): 132 *m*/*z* ^{1}H-NMR: (400 MHz, $CDCl_3$) δ ppm 4.63 (td, $J = 4.69$, 3.23, 3.23 Hz, 1H, H-2), 4.39 (d, $J = 2.89$ Hz, 1H, H-1), 3.76 (dt, $J = 10.80$, 10.71, 3.06 Hz, 1H, H-5), 3.49 (dtd, $J = 11.23$, 4.14, 4.08, 0.96 Hz, 1H, H-5′), 3.34 (s, 3H, OCH_3), 2.03 (s, 3H, CH$_3$ acetyl), 2.00–1.90 (m, 1H, H-3), 1.88–1.76 (m, 1H, H-4), 1.67–1.58 (m, 1H, H-3′), 1.42–1.33 (m, 1H, H-4′). ^{13}C-NMR: (100 MHz, $CDCl_3$) δ ppm 170.30 (C=O), 98.88 (C-1), 68.76 (C-2), 60.57 (C-5), 55.09 (O*C*H$_3$), 24.00 (C-3), 21.19 (OCO*C*H$_3$), 20.99 (C-4).

5-Methyl-2-methyl-3-acetyl-2,3,5-trihydroxypyran (10). Yellowish oil, R_f: 0.28 (2 : 8 EtOAc : Petr. Ether), MS (non-acetylated): 161 *m*/*z*.

trans. ^{1}H NMR: (300 MHz, $CDCl_3$) δ ppm 4.68 (dd, $J = 6.11$, 3.16 Hz, 1H, H-5), 4.65–4.59 (m, 1H, H-2), 4.63 (d, $J = 2.28$ Hz, 1H, H-1), 3.40 (s, 3H, OMe), 3.39 (s, 3H, OMe), 2.60–2.40, 2.01 (s, 3H, CH$_3$ acetyl), 1.95–1.83, 1.80–1.65, 1.60–1.50 (4 × m, 4H, H-3, H-3′, H-4, H-4′). ^{13}C NMR: (75 MHz, $CDCl_3$) δ ppm 170.2 (C=O), 98.87 (C-1), 97.74 (C-5), 68.58 (C-2), 55.58 (OMe), 52.69 (OMe), 26.86 (C-4), 22.86 (C-3), 21.11 (OCO*C*H$_3$).

cis. ^{13}C NMR: (75 MHz, $CDCl_3$) δ ppm 104.45 (C-1), 104.17 (C-5), 55.43 (OMe), 52.66 (OMe).

5-Ethyl-2-methyl-3-acetyl-2,3,5-trihydroxypyran (*trans*) (11). Yellowish oil, R_f: 0.27 (2 : 8 EtOAc : Petr. Ether). MS (non-acetylated): 175 *m*/*z*.

^{13}C NMR: (75 MHz, $CDCl_3$) δ ppm 99.09, 98.87 (C-1, C-5), 68.52 (C-2), 63.79 (O*C*H$_2$CH$_3$), 51.43 (OMe), 26.89 (C-4), 22.87 (C-3), 21.14 (OCO*C*H$_3$), 15.08 (OCH$_2$*C*H$_3$).

2-Methyl-3-acetyl-2,3-dihydroxyfuran (*trans*) (12)[23]. Yellowish oil, R_f: 0.37 (*trans*), 0.29 (*cis*) (2 : 8 EtOAc : Petr. Ether), MS (non-acetylated): 118 *m*/*z*. ^{1}H-NMR: (400 MHz, $CDCl_3$) δ ppm 5.00 (dd, $J = 6.01$, 1.46 Hz, 1H, H-2), 4.82 (s, 1H, H-1), 4.00 (dd, $J = 15.36$, 7.89 Hz, 1H, H-4), 3.91 (dt, $J = 8.59$, 8.46, 4.93 Hz, 1H, H-4′), 3.27 (s, 3H, OCH_3), 2.34–2.21 (m, 1H, H-3), 1.99 (s, 3H, CH$_3$ acetyl), 1.88–1.79 (m, 1H, H-3′). ^{13}C-NMR: (100 MHz, $CDCl_3$) δ ppm 170.3 (C=O), 106.67 (C-1), 77.63 (C-2), 66.38 (C-4), 54.49 (O*C*H$_3$), 29.34 (C-3), 20.99 (OCO*C*H$_3$).

2-Octyl-3-acetyl-2,3-dihydroxypyran (*trans*) (13). Yellowish oil, R_f: 0.58 (2 : 8 EtOAc : Petr. Ether), MS (non-acetylated): 230 *m*/*z*. ^{1}H NMR: (400 MHz, $CDCl_3$) δ ppm 4.70 (td, $J = 4.72$, 3.27, 3.27 Hz, 1H, H-2), 4.53 (d, $J = 2.97$ Hz, 1H, H-1), 3.84 (dt, $J = 10.81$, 10.77, 3.03 Hz, 1H, H-3), 3.72 (td, $J = 9.59$, 6.73, 6.73 Hz, 1H, H-5), 3.54 (dtd, $J = 11.12$, 4.12, 4.10, 1.02 Hz, 1H, H-3′), 3.41 (td, $J = 9.61$, 6.53, 6.53 Hz, 1H, H-5′), 2.09 (s, 3H, CH$_3$

acetyl), 2.06–1.99 and 1.76–1.65 (m, 2H, H-4, H-4′), 1.94–1.81, 1.63–1.56 and 1.48–1.20 (m, 14H, CH_2 octyl), 0.88 (t, 3H, CH_3 octyl). ^{13}C NMR: (100 MHz, $CDCl_3$) ppm 169.9 (C=O), 97.77 (C-1), 69.01 (C-2), 67.89 (C-5), 60.68 (C-3), 31.80 (O*C*H_2), 29.55, 29.35, 29.21, 26.12, 22.61, 21.17 (6C, CH_2 octyl), 24.09 (C-4), 14.02 (CH_3, octyl).

2-Dodecyl-3-acetyl-2,3-dihydroxypyran (*trans*) (14). Yellowish oil, R_f: 0.60 (2 : 8 EtOAc : Petr. Ether), MS (non-acetylated): 286 *m*/*z*. ^{1}H NMR: (300 MHz, $CDCl_3$) δ ppm 4.69 (td, $J = 4.63, 3.19, 3.19$ Hz, 1H, H-2), 4.53 (d, $J = 2.96$ Hz, 1H, H-1), 3.84 (dt, $J = 10.73, 10.65, 2.99$ Hz, 1H, H-3), 3.71 (td, $J = 9.55, 6.75, 6.75$ Hz, 1H, H-5), 3.54 (dtd, $J = 11.18, 4.09, 4.06, 1.08$ Hz, 1H, H-3′), 3.41 (td, $J = 9.68, 6.63, 6.63$ Hz, 1H, H-5′), 2.08 (s, 3H, CH_3 acetyl), 1.95–1.80 and 1.49–1.37 (m, 2H, H-4, H-4′), 1.74–1.51, 1.37–1.15 (m, 22H, CH_2 dodecyl), 0.88 (t, 3H, CH_3 dodecyl). ^{13}C NMR: (75 MHz, $CDCl_3$) δ ppm 170.294 (C=O), 97.75 (C-1), 69.01 (C-2), 67.90 (C-5), 60.67 (C-3), 31.90 (O*C*H_2), 29.65, 29.62, 29.60, 29.59, 29.57, 26.14, 25.90, 22.66, 21.20, 21.09 (10C, CH_2 dodecyl), 24.09 (C-4), 21.09 ($OCOCH_3$), 14.02 (CH_3, dodecyl).

2-Octadecyl-3-acetyl-2,3-dihydroxypyran (*trans*) (15). Yellowish oil, R_f: 0.63 (2 : 8 EtOAc : Petr. Ether). ^{1}H NMR: (300 MHz, $CDCl_3$) δ ppm 4.70 (td, $J = 4.85, 3.20, 3.20$ Hz, 1H, H-2), 4.53 (d, $J = 2.92$ Hz, 1H, H-1), 3.84 (dt, $J = 10.72, 10.61, 3.01$ Hz, 1H, H-3), 3.72 (td, $J = 9.58, 6.70, 6.70$ Hz, 1H, H-5), 3.54 (dtd, $J = 11.09, 4.09, 4.05, 1.19$ Hz, 1H, H-3′), 3.41 (td, $J = 9.60, 6.54, 6.54$ Hz, 1H, H-5′), 2.09 (s, 3H, $OCOCH_3$), 1.96–1.80 (m, 1H, H-4), 1.50–1.38 (m, 1H, H-4′), 1.74–1.50 and 1.38–1.12 (m, 34H, octadecanyl), 0.88 (t, 3H, CH_3-octadecanyl). ^{13}C NMR: (75 MHz, $CDCl_3$) δ ppm 170.41 (C=O), 97.75 (1C, CH, C-1), 69.01 (1C, CH, C-2), 67.90 (1C, CH_2, C-5), 60.67 (1C, CH_2, C-3), 31.90 (1C, OCH_2), 29.71–29.29, 26.13, 22.66 and 21.08 (16C, octadecanyl), 24.08 (1C, CH_2, C-4), 21.19 (1C, $OCOCH_3$), 14.07 (1C, CH_3 octadecanyl).

2-Benzyl-3-acetyl-2,3-dihydroxypyran (*trans*) (16)[24]. Yellowish oil, R_f: 0.39 (2 : 8 EtOAc : Petr. Ether), Anal. calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.75; H, 6.86%. ^{1}H NMR: (300 MHz, $CDCl_3$) δ ppm 7.37–7.33 (m, 5H, phenyl), 4.78 (d, $J = 11.99$, 1H, CH_2-benzyl), 4.78 (m, 1H, H-2), 4.66 (d, $J = 2.82$ Hz, 1H, H-1), 4.53 (d, $J = 11.98$, 1H, CH_2-benzyl), 3.90 (dt, $J = 3.00, 10.92, 10.91$ Hz, 1H, H-5), 3.59 (m, 1H, H-5′), 2.08 (s, 3H, $COCH_3$), 2.14–2.05 (m, 1H, H-3), 1.99–1.83 (m, 1H, H-4), 1.77–1.66 (m, 1H, H-3′), 1.51–1.39 (m, 1H, H-4′). ^{13}C NMR: (75 MHz, $CDCl_3$) δ ppm 170.21 (C=O), 137.614 (1C, Ph-A), 128.32 and 127.67 (5C, Ph), 96.87 (1C, CH, C-1), 68.96 (1C, CH_2Ph), 68.77 (1C, CH, C-2), 60.71 (1C, CH_2, C-5), 23.90 (1C, CH_2, C-3), 21.12 (1C, $OCOCH_3$), 20.88 (1C, CH_2, C-4).

2-Menthyl-3-acetyl-2,3-dihydroxypyran (17). Yellowish oil, R_f: 0.59 (2 : 8 EtOAc : Petr. Ether).

trans. ^{1}H NMR: (300 MHz, $CDCl_3$) δ ppm 4.69–4.61 (m, 1H, H-2), 4.57 (d, $J = 3.92$ Hz, 1H, H-1), 2.09 (s, 3H, $OCOCH_3$). ^{13}C NMR: (75 MHz, $CDCl_3$) δ ppm 170.36 (C=O), 100.41 (1C, CH, C-1), 81.10 (1C, CH, C-2), 69.80 (1C, CH, C-1-menthyl), 61.78 (1C, CH_2, C-5), 48.74, 43.22, 34.51, 31.70, 25.65–21.20, 16.13 (12C, 9C menthyl, C-3, C-4, $OCOCH_3$).

cis. ^{1}H NMR: (300 MHz, $CDCl_3$) δ ppm 4.73 (d, $J = 2.78$ Hz, 1H, H-1), 4.69–4.61 (m, 1H, H-2), 2.07 (s, 3H, $OCOCH_3$). ^{13}C NMR: (75 MHz, $CDCl_3$) δ ppm 170.27 (C=O), 94.04 (1C, CH, C-1), 75.35 (1C, CH, C-2), 69.68 (1C, CH, C-1-menthyl), 60.92 (1C, CH_2, C-5), 48.08, 40.00, 34.37, 31.42, 25.65–21.20, 15.58 (12C, 9C menthyl, C-3, C-4, $OCOCH_3$).

2-Palmitoyl-3-acetyl-2,3-dihydroxypyran (*trans*) (18). White crystals, R_f: 0.49 (2 : 8 EtOAc : Petr. Ether), mp: 54–55 °C (from chloroform), Anal. calcd for $C_{23}H_{42}O_5$: C, 69.31; H, 10.62. Found: C, 69.73; H, 10.81%. ^{1}H NMR: (400 MHz, $CDCl_3$) δ ppm 5.83 (d, $J = 3.62$, 1H, H-1), 4.74 (td, $J = 5.23, 3.67, 3.67$, 1H, H-2), 3.88 (ddd, $J = 3.21, 9.69, 11.63$, 1H, H-5), 3.73–3.66 (m, 1H, H-5′), 2.35 (t, 2H, $OCOCH_2$), 2.09 (s, 3H, $OCOCH_3$), 2.08–2.01 and 1.84–1.74 (m, 2H, H-3, H-3′), 1.98–1.87 and 1.55–1.49 (m, 2H, H-4, H-4′), 1.69–1.59 and 1.38–1.20 (m, 26H, -CH_2-), 0.88 (t, 3H, –CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 171.92 (C=O), 170.00 (C=O), 91.33 (1C, CH, C-1), 67.83 (1C, CH, C-2), 62.84 (1C, CH, C-5), 34.38 (1C, CH_2, $OCOCH_2$), 31.96, 29.85–29.05, 24.83 and 22.71 (13C, CH_2, palmitic), 24.44 (1C, CH_2, C-3), 21.07 (1C, $OCOCH_3$), 20.95 (1C, CH_2, C-4), 14.12 (1C, CH_3 palmitic).

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