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Tetrahedron 60 (2004) 993–999
Tetrahedron

$LiClO_4$-Activated stereo- and regioselective alkylation of aldehydes

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Received 23 July 2003; revised 3 October 2003; accepted 7 November 2003

Abstract—Aldehydes undergo an unusual and very mild alkylation by $LiClO_4$-activation in the presence of acids. This new methodology enables the inclusion of a broad range of aldehydes as well as tertiary alcohols. Regio- and stereoselectivity observed during this reaction will be discussed.

1. Introduction

C–C bond formation processes are of great interest, in particular regio- and stereoselective transformations. The catalytic execution of these reactions are the focus of attention. The simple alkylation of carbonyl compounds mediated by $LiClO_4$ is not described so far.

Recently we described an unusual addition of aldehydes to tertiary titanium(IV)-alkoxides in the presence of α-hydroxy acids by activation of $LiClO_4$.[1] During our ongoing studies in this field we were able to obtain suitable crystals for X-ray structure analysis of compounds **1d**, **2b** and **4g** (Table 1).[2] Careful comparison of NMR data of these compounds (chemical shifts, coupling constants and NOE-experiments) with the NMR data of other compounds obtained during this work, resulted in a revision of the proposed structure to surprisingly appear as substituted tetrahydropyranols **1**–**4** (Table 1) in contrast to the earlier proposals (*syn*- and *anti*-triols **1a**–**c** and **2a**–**c** in Ref. 1). In addition, the previously described diols **5**[1] were also observed.

2. Results and discussion

In order to explore the scope and limitation of substrates in these reactions, a series of tertiary titanium(IV)-alkoxides (**Tia**–**h**, entries 1–8 in Table 1) were reacted with benzaldehyde using standard conditions (10 equiv. of aldehyde, 10 equiv. dry $LiClO_4$, 1 equiv. tartaric acid, 1 equiv. titanium(IV)-alkoxide). The distribution of products observed in this reaction is given in Table 1.

A high regioselectivity is observed during this reaction by using unsymmetrical substituted tertiary titanium(IV)-alkoxides. The attack of the aldehyde takes place at the highest substituted β-carbon atom of the titanium(IV)-alkoxide used (entries 2, 3 and 6, Table 1). One exception represents the formation of tetrahydropyranols **2e** and **4e** and diol **5e** (entry 5, Table 1). This product arose from an alkylation at the methyl group instead at the expected benzylic carbon atom.

The substituents at C-2 and C-6 are *syn*-configured (diequatorial) in every tetrahydropyranol isolated. They differ only in the configuration at C-4, the tertiary carbon atom. The observed rigid *syn*-configuration of the substituents and the high regioselectivity of the attack of the aldehydes are the sources for the formation of *meso*-configurated tetrahydropyranols during this transformation.

In the reactions of aldehydes with titanium(IV)-alkoxides bearing three or two equivalent substituents the attack of the aldehydes may occur at two equivalent α-carbon atoms. *meso*-Configurated compounds can be formed. This is true for substituted tetrahydropyranols in the a, c, g, and i series (entries 1, 3 (**1c**, **2c**), 7, 9, 11 (**1c**, **2c**), 13 and 15 in Table 1). Diols **5a**, **5b**, **5e** and **5g** were isolated with a high degree of *anti*-selectivity. *syn*-Configurated diols could not be detected.

During our studies we observed this described reaction even when using tertiary alcohols instead of the corresponding tertiary titanium(IV)-alkoxides (**Ha**–**h**, entries 9–15 in Table 1). A comparison of product distribution of these two procedures is shown in Table 1 (entries 1–8 titanium(IV)-

Keywords: Alkylation; Aldehydes; C–C coupling; Regioselectivity; Diastereoselectivity.
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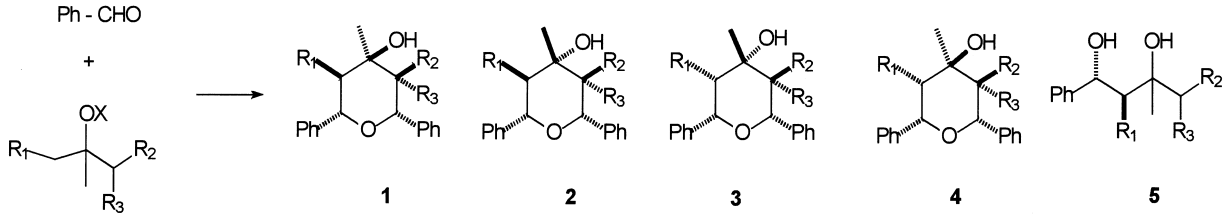
doi:10.1016/j.tet.2003.11.039

Table 1. Product distribution (in %) in reactions of benzaldehyde with titanium(IV)-alkoxides, respectively tertiary alcohols in the presence of 1 equiv. $LiClO_4$ and 10 mol% *p*-toluenesulfonate

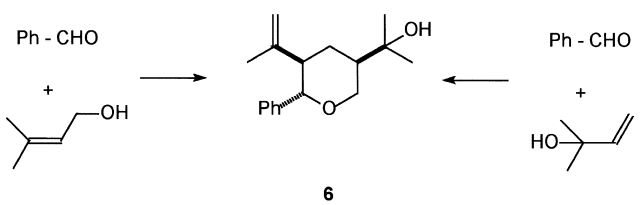


Entry	Compound	X	R_1	R_2	R_3	Overall-yield (%)	**1**	**2**	**3**	**4**	**5**
1	**a**	Ti	H	H	H	46	17	50	—	—	33
2	**b**	Ti	Me	H	H	55	32	17	17	17	17
3	**c**	Ti	Me	Me	H	77	21	32	42	5	—
4	**d**	Ti	H	Me	Me	76	83	17	—	—	—
5	**e**	Ti	H	Ph	H	52	—	8	—	32	60
6	**f**	Ti	*i*Pr	H	H	22	—	100	—	—	—
7	**g**	Ti		H	[a]	58	—	—	33	33	34
8	**h**	Ti	Cl	H	H	—	—	—	—	—	—
9	**a**	H	H	H	H	58	50	50	—	—	—
10	**b**	H	Me	H	H	62	17	66	17	—	—
11	**c**	H	Me	Me	H	61	40	10	20	30	—
12	**e**	H	H	Ph	H	48	—	33	—	67	—
13	**g**	H		H	[a]	53	—	—	40	60	—
14	**h**	H	Cl	H	H	38	—	100	—	—	—
15	**i**	H		H	[b]	46	—	—	100	—	—

[a] R_1=R_3: $-(CH_2)_3-$.
[b] R_1=R_3: $-(CH_2)_2-$.

alkoxides **Tia**–**h** and entries 9–15 tertiary alcohols **Ha**–**h**). Higher stereoselectivities were observed by using tertiary titanium(IV)-alkoxides in these reactions. α-Halogen substituted tertiary alcohols react with aldehydes to give the tetrahydropyranole **2h**. In contrast to that the corresponding titanium(IV)-alkoxide does not react with benzaldehyde under the described conditions (compare entries 8 and 14, Table 1).

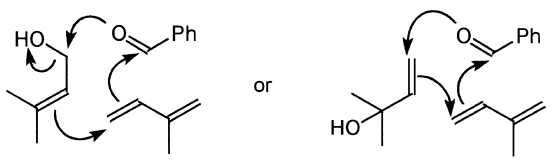
Allyl alcohols react with benzaldehyde under these standard conditions as well. 1-Hydroxy-3-methyl-2-butene and the tertiary alcohol 2-hydroxy-2-methyl-3-butene were transformed into the tetrahydropyranol **6** by a stereoselective and convergent synthesis (Scheme 1).



Scheme 1. *Reaction conditions*: tartaric acid, $LiClO_4$, rt.

There are two explanations for this unexpected result at that time. The formation of isoprene (the elimination product of the two isomeric allyl alcohols) and the subsequent alkylation lead to the product **6** (Scheme 2). Alternatively, a rearrangement of the two isomeric allyl alcohols during this transformation could explain these identical results.

The yields of the products obtained by using these standard conditions (10 equiv. of aldehyde, 10 equiv. dry $LiClO_4$, 1 equiv. tartaric acid, 1 equiv. titanium(IV)-alkoxide) are

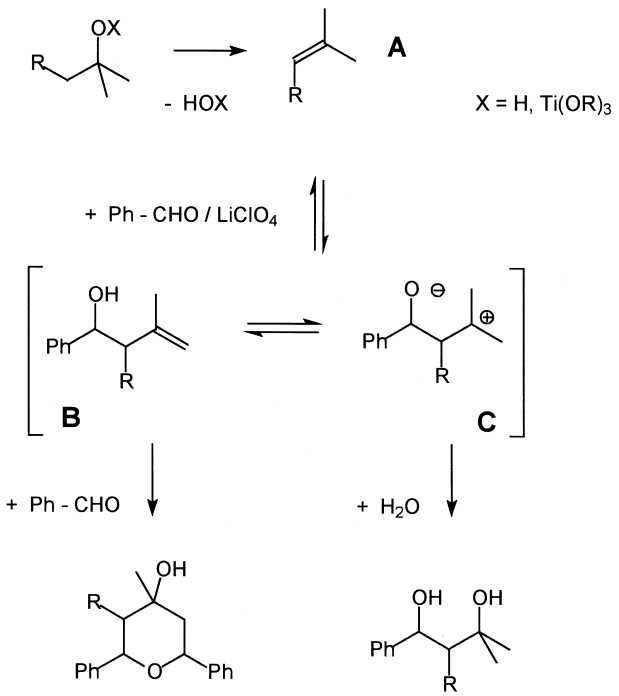


Scheme 2.

low (15–30%). Further investigations in this field led us to a more powerful and catalytic reagent system. Same regio- and stereoselectivities of products were found by using $LiClO_4$ in the presence of 10 mol% ethyl *p*-toluenesulfonate. Under these conditions the products of reaction of tertiary alcohols with aldehydes were isolated in good yields (50–70%, Table 1). It is assumed that under these reactions conditions hydrolysis occurs and toluenesulfonic acid acts as the real agent, as comparative reactions with toluenesulfonic acid showed.

Based on these results, an elimination–addition reaction mechanism can be assumed. This consideration involves an electrophilic attack by a $LiClO_4$-activated aldehyde onto an olefin formed intermediately by elimination from tertiary titanium(IV)-alkoxides or tertiary alcohols. The suggestion of such a *Prins*-type mechanism[7] was supported by the comparative reaction of isobutene (the elimination product of tertiary butanol) with benzaldehyde in the presence of $LiClO_4$ and α-hydroxy acids. The same compounds were isolated as in the corresponding reaction of benzaldehyde with $Ti(OtBu)_4$. A proposed reaction mechanism based on these results is shown in Scheme 3.

Two main products are possible. The one, which predominates, depends on the olefin and the reaction conditions.



Scheme 3. Proposed reaction mechanism.

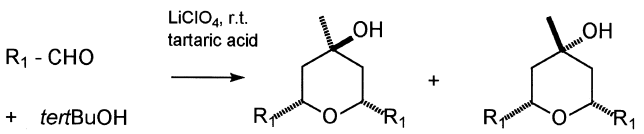
Zwitterionic structure **C** is starting point for a further alkylation of the olefin **B** resulting in the formation of the substituted tetrahydro pyranoles. Diols **5** were formed by hydration of structure **C**.

The real role of $LiClO_4$ is not clear up to now. This reaction is observed only in the presence of dry $LiClO_4$. No reactions were observed with the use of other metal salts and perchlorates (e.g., $NaClO_4$, $Mg(ClO_4)_2$, $Al(ClO_4)_3$, $KClO_4$, Et_4NClO_4). On the other hand $LiClO_4$ does not act as a dehydrating agent only. This alkylation is not observed in comparative experiments with other dehydrating reagents (molecular sieves, Drierite, Na_2SO_4 etc.). No reactions were observed by using $LiClO_4 \cdot 10H_2O$ in these reactions.

In order to demonstrate the broad applicability of this new and promising transformation, aliphatic aldehydes were reacted with *tert*-butanol and 1-methyl-cyclopentanol. The expected tetrahydropyranols **7**, **8** and **9** were isolated in lower yields in comparison with reactions of benzaldehyde. An overview of products observed during these reactions is given in Table 2 and Scheme 4.

Herein we described a very simple and effective alkylation of aldehydes by $LiClO_4$-activation. Nevertheless, there still are several questions remaining, e.g. the role of $LiClO_4$, the enantioselective execution of this reaction, or the extension of this reaction to secondary alcohols. In any event, we are convinced that this extremely mild and easy alkylation is a useful method for the preparation of tertiary alcohols.[8,9]

Table 2. Product distribution in reactions of aliphatic aldehydes with *tert*butanol



7 **8**

Entry	R_1	Compound	Overall-yield (%)	**7**	**8**
1	Me	**a**	36	—	100
2	Et	**b**	26	—	100
3	*n*Pr	**c**	35	50	50
4	*iso*Pr	**d**	36	—	100

3. Experimental

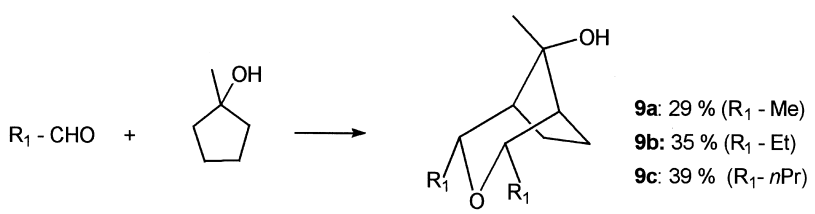
3.1. General procedures

All reactions were performed using oven-dried glassware under an atmosphere of dry argon. Toluene was distilled, dried and stored over molecular sieve (3A). $Ti(OiPr)_4$ purchased from Merck chemical company was used without prior purification. Aldehydes were distilled before use. Purification of products was accomplished using flash chromatography according to the method of Still.[10] $LiClO_4$ was dried at 120 °C in vacuo for 10 h.

^1H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz in $CDCl_3$, respectively using a AC-300 spectrometer. Chemical shifts are given in ppm. Thin layer chromatography was performed out using Merck Silica Gel 60 F_{254} TLC plates.

The stereodescriptors a (axial) and e (equatorial) were used for the characterization of configuration. The description of configuration by CIP-rules is not sufficient for the characterization of the *meso*-configurated tetrahydro pyranols.

Yields are related to the amount of titanium(IV)-alkoxides or alcohols used and are not optimized.



Scheme 4. *Reaction conditions*: *p*-toluenesulfonate, $LiClO_4$, rt.

3.2. Preparation of titanium(IV)-alkoxides (Tia–Tih)

The titanium(IV)-alkoxides were prepared by a procedure given in Ref. 11. 100 mmol of the corresponding alcohol were dissolved under inert conditions in 50 ml of anhydrous toluene. 7.5 ml (25 mmol) of $Ti(OiPr)_4$ were carefully added at room temperature. The resulting solution was heated and *iso*propanol was removed by azeotropic distillation of toluene. Resulting residue was dried in vacuo at room temperature and was used without further purification. Using this procedure, the ^1H NMR spectra do not contain any typical signals of the starting $Ti(OiPr)_4$.

3.3. General procedure of alkylation

Procedure A. Alkylation of aldehydes with titanium(IV)-alkoxides (**Tia**–**Tih**): 1.1 g $LiClO_4$ (10 mmol) were dissolved in 1.0 ml benzaldehyde (10 mmol). 1.0 mmol of the corresponding titanium(IV)-alkoxide was added after 10 min stirring at rt. 200 mg ethyl *p*-toluenesulfonate (1 mmol) were added. The reactions were monitored by thin layer chromatography. At the end of the reaction the resulting mixtures were stirred for 24 h at rt and then extracted by diethylether and successively by saturated aq. NH_4Cl- and $NaHCO_3$-solution. The organic layers were separated, dried (Na_2SO_4) and the solvent was removed in vacuo. The residue was purified by column chromatography.

Procedure B. Alcohols (**Ha**–**Hi**): The same procedure as described for titanium(IV)-alkoxides was used with 4 mmol of the corresponding alcohol.

3.3.1. 4e-Methyl-2e,6e-diphenyl-tetrahydropyran-4a-ol (1a). 93 mg **1a** (8.7%) as a colourless oil (procedure A); IR (neat) ν_{max} 3498, 2908, 1454, 1379, 1211, 1137, 1050, 1012 cm^{-1}; ^1H NMR δ=7.41–7.12 (10H, m, CH_{Ph}), 4.88 (2H, dd, *J*=1.9, 11.7 Hz, H2, H6), 1.78 (2H, dd, *J*=1.9, 13.5 Hz, H3, H5), 1.70 (2H, dd, *J*=11.7, 13.5 Hz, H3, H5), 1.21 (3H, s, $-CH_3$); ^{13}C NMR δ=143.0, 128.3, 127.3, 125.9, (C_{Ph}), 75.3, 69.0, (C2, 4, 6), 46.6, (C3, 5), 31.6, ($-CH_3$); HRMS: *m*/*z* calcd for $C_{18}H_{20}O_2$ 268.1463. Found: 268.1463.

3.3.2. 4a-Methyl-2e,6e-diphenyl-tetrahydropyran-4e-ol (2a).[3] 225 mg **2a** (20.1%) as a colourless solid (procedure A); IR (neat) ν_{max} 3483, 2914, 1495, 1455, 1382, 1212, 1115, 1056, 986 cm^{-1}; ^1H NMR δ=7.41–7.18 (10H, m, CH_{Ph}), 4.53 (2H, dd, *J*=1.9, 11.6 Hz, H2, H6), 1.96 (2H, dd, *J*=1.9, 10.5 Hz, H3, H5), 1.70 (2H, dd, *J*=10.5, 11.6 Hz, H3, H5), 1.51 (3H, s, $-CH_3$); ^{13}C NMR δ=142.2, 128.4, 127.5, 125.9, (C_{Ph}), 77.5, 69.8, (C2, C4, C6), 48.2, (C3, C5), 25.8, ($-CH_3$); HRMS: *m*/*z* calcd for $C_{18}H_{20}O_2$ 268.1463. Found: 268.1463.

3.3.3. 3-Methyl-1-phenyl-butan-1,3-diol (5a).[4] 125 mg **5a** (17.3%) as a colourless oil (procedure A); ^1H NMR δ=7.50–7.23 (5H, m, CH_{Ph}), 5.09 (1H, dd, *J*=2.3, 11.3 Hz, H1), 1.99 (1H, dd, *J*=11.3, 14.7 Hz, H2), 1.70 (1H, dd, *J*=2.3, 14.7 Hz, H2), 1.47 (3H, s, $-CH_3$), 1.32 (3H, s, $-CH_3$); ^{13}C NMR δ=144.7, 128.5, 127.5, 125.7, (C_{Ph}), 72.3, 71.7, (C2, C4, C6), 50.4, (C3, C5), 31.9, 27.6 (2×$-CH_3$).

3.3.4. 3e,4e-Dimethyl-2e,6e-diphenyl-tetrahydropyran-4a-ol (1b). 200 mg **1b** (17.7%) as a colourless oil (procedure A); IR (neat) ν_{max} 3788, 3639, 1654, 1544, 1458, 1378, 1217, 1079 cm^{-1}; ^1H NMR δ=7.40–7.10 (10H, m, CH_{Ph}), 4.90 (1H, dd, *J*=2.6, 11.3 Hz, H2), 4.45 (1H, d, *J*=10.2 Hz, H6), 1.89 (1H, dd, *J*=2.6, 13.9 Hz, H5), 1.77 (1H, dd, *J*=11.3, 13.9 Hz, H5), 1.70 (1H, dq, *J*=10.17, 6.8 Hz, H3), 1.23 (3H, s, C(OH)CH_3), 0.68 (3H, d, *J*=6.8 Hz, $-CH_3$); ^{13}C NMR δ=142.8, 141.5, 128.2, 128.2, 128.1, 127.6, 127.6, 125.8, (CH_{Ph}), 81.7, 75.0, 70.4, (C2, C4, C6), 48.2, 45.1, (C3, C5), 29.0, 9.6, (2×$-CH_3$); HRMS: calcd for $C_{19}H_{22}O_2$: 282.1620. Found: 282.1620.

3.3.5. 3e,4a-Dimethyl-2e,6e-diphenyl-tetrahydropyran-4e-ol (2b). 100 mg **2b** (8.9%) as colourless crystals (procedure A); mp 102–103 °C (hexane/ethylacetate); IR (neat) ν_{max} 3413, 2973, 1718, 1603, 1495, 1450, 1381, 1271, 1210, 1100, 1069, 1021 cm^{-1}; ^1H NMR δ=7.40–7.10 (10H, m, CH_{Ph}), 4.56 (1H, dd, *J*=2.3, 10.7 Hz, H6), 4.12 (1H, d, *J*=10.2 Hz, H2), 1.98 (1H, dd, *J*=2.3, 12.8 Hz, H5), 1.83 (1H, dd, *J*=10.7, 12.8 Hz, H5), 1.78 (1H, dq, *J*=6.8, 10.2 Hz, H3), 1.50 (3H, s, $-CH_3$), 0.80 (3H, d, *J*=6.8 Hz, $-CH_3$); ^{13}C NMR δ=140.9, 140.7, 128.4, 128.3, 127.9, 127.5 127.4, 125.9, (CH_{Ph}), 83.7, 77.3, 71.7, (C2, C4, C6), 50.3, 47.8, (C3, C5), 20.7, 10.1, (2×$-CH_3$); HRMS: calcd for $C_{19}H_{22}O_2$ 282.1620. Found: 282.1620.

3.3.6. 3a,4a-Dimethyl-2e,6e-diphenyl-tetrahydropyran-4e-ol (3b). 110 mg **3b** (9.8%) as a colourless oil (procedure A); IR (neat) ν_{max} 3117, 3028, 2971, 2804, 1726, 1398, 1106, 1069 cm^{-1}; ^1H NMR δ=7.40–7.10 (10H, m, CH_{Ph}), 4.83 (1H, d, *J*=2.3 Hz, H2), 4.55 (1H, dd, *J*=3.0, 12.1 Hz, H6), 1.88 (1H, dq, *J*=2.3, 7.2 Hz, H3), 1.84 (1H, dd, *J*=12.1, 13.6 Hz, H5), 1.71 (1H, dd, *J*=3.0, 13.6 Hz, H5), 1.60 (3H, s, $-CH_3$), 0.72 (3H, d, *J*=7.2 Hz, $-CH_3$); ^{13}C NMR δ=142.5, 141.4, 128.3, 128.0, 127.4, 126.6, 125.7, 125.3, (CH_{Ph}), 78.7, 77.6, (C2, C4, C6), 45.5, 42.8, (C3, C5), 27.2, 7.5, (2×$-CH_3$); HRMS: calcd for $C_{19}H_{22}O_2$ 282.1620. Found: 282.1620.

3.3.7. 3a,4e-Dimethyl-2e,6e-diphenyl-tetrahydropyran-4a-ol (4b). 100 mg **4b** (8.8%) as a colourless oil (procedure A); IR (neat) ν_{max} 3416, 2975, 1702, 1603, 1495, 1450, 1379, 1142, 1096, 1056, 1018 cm^{-1}; ^1H NMR δ=7.50–7.20 (10H, m, CH_{Ph}), 5.37 (1H, d, *J*=2.3 Hz, H2), 4.96 (1H, dd, *J*=3.0, 11.3 Hz, H6), 1.90 (1H, dq, *J*=2.3, 7.2 Hz, H3), 1.80 (1H, dd, *J*=11.3, 13.9 Hz, H5), 1.70 (1H, dd, *J*=3.0, 13.9 Hz, H5), 1.40 (3H, s, $-CH_3$), 0.86 (3H, d, *J*=7.2 Hz, $-CH_3$); ^{13}C NMR δ=143.2, 142.0, 128.1, 127.8, 127.0, 126.2, 125.6, 125.4, (CH_{Ph}), 76.4, 75.3, 72.0, (C2, C4, C6), 44.9, 41.9, (C3, C5), 29.4, 9.7, (2×$-CH_3$); HRMS: calcd for $C_{19}H_{22}O_2$ 282.1620. Found: 282.1620.

3.3.8. *anti*-2,3-Dimethyl-1-phenyl-butan-1,3-diol (5b).[5] 80 mg **5b** (10.3%) as a colourless oil (procedure A); ^1H NMR δ=7.30–7.10 (5H, m, CH_{Ph}), 4.47 (1H, d, *J*=10.2 Hz, H1), 1.86 (1H, dq, *J*=6.8, 10.2 Hz, H2), 1.18 (6H, s, 2×$-CH_3$), 0.42 (3H, d, *J*=6.8 Hz, $-CH_3$); ^{13}C NMR δ=143.8, 128.3, 127.6, 125.6, (CH_{Ph}), 78.9, 75.0, (C1, C3) 48.7, (C2), 30.3, 14.2, (2×$-CH_3$); HRMS: calcd for $C_{12}H_{16}O$ (M$-H_2O$) 176.1201. Found: 176.1201 (M$-H_2O$).

3.3.9. 3e,4a,5e-Trimethyl-2e,6e-diphenyl-tetrahydropyran-4e-ol (2c). 300 mg **2c** (25.3%) colourless solid (procedure A); mp 160–162 °C (hexane/ethylacetate); IR (neat) ν_{max} 3478, 2974, 2882, 1495, 1453, 1381, 1312, 1208, 1069, 1026, 984 cm^{-1}; ^1H NMR δ=7.36–7.12 (10H, m, CH_{Ph}), 4.18 (2H, d, J=10.6 Hz, H2, H6), 1.88 (2H, dq, J=7.2, 10.6 Hz, H3, H5), 1.18 (3H, s, $-CH_3$), 0.64 (6H, d, J=7.2 Hz, $-CH_3$); ^{13}C NMR δ=141.0, 128.3, 127.8, 127.3, (CH_{Ph}), 83.4, 73.9, (C2, C4, C6), 49.2, (C3, C5), 14.7, 10.4, (3×$-CH_3$); HRMS: calcd for $C_{20}H_{24}O_2$ 296.17763. Found: 296.17763.

The isomers **1c**, **3c** and **4c** could not be separated by chromatography. The ratio of these isomers was determined by integration of important signals in the ^1H and ^{13}C NMR spectra.

3.3.10. 3e,3′a,4e-Trimethyl-2e,6e-diphenyl-tetrahydropyran-4a-ol (1d). 755 g **1d** (63.7%) as colourless crystals (procedure A); mp 129–130 °C (hexane/ethylacetate); IR (neat) ν_{max} 3505, 2976, 1686, 1454, 1363, 1287, 1201, 1144, 1119, 1091, 1058, 1039, 1007 cm^{-1}; ^1H NMR δ=7.39–7.11 (10H, m, CH_{Ph}), 4.91 (1H, dd, J=2.6, 12.1 Hz, H6), 4.89 (1H, s, H2), 1.95 (1H, dd, J=12.1, 13.9 Hz, H5), 1.64 (1H, dd, J=2.6, 13.9 Hz, H5), 1.14 (3H, s, $-CH_3$), 0.85 (3H, s, $-CH_3$), 0.75 (3H, s, $-CH_3$); ^{13}C NMR δ=143.2, 139.6, 128.3, 128.2, 127.2, 127.1, 126.9, 125.6, (CH_{Ph}), 82.0, 75.4, 73.7, (C2, C4, C6), 44.4, 40.8, (C3, C5), 25.6, 18.6, 17.9, (3×$-CH_3$); HRMS: calcd for $C_{20}H_{24}O_2$ 296.1776. Found: 296.1776.

3.3.11. 3e,3′a,4a-Trimethyl-2e,6e-diphenyl-tetrahydropyran-4e-ol (3d). 150 mg **3d** (12.7%) as a colourless oil (procedure A); IR (neat) ν_{max} 3484, 2975, 1720, 1495, 1453, 1385, 1102, 1081, 1066, 1036 cm^{-1}; ^1H NMR δ=7.43–7.14 (10H, m, CH_{Ph}), 4.65 (1H, dd, J=2.6, 12.1 Hz, H6), 4.50 (1H, s, H2), 2.05 (1H, dd, J=12.1, 13.6 Hz, H5), 1.74 (1H, dd, J=2.6, 13.6 Hz, H5), 1.52 (3H, s, $-CH_3$), 0.93 (3H, s, $-CH_3$), 0.78 (3H, s, $-CH_3$); ^{13}C NMR δ=142.5, 139.1, 128.3, 128.1, 127.4, 127.3, 127.2, 125.7, (CH_{Ph}), 84.1, 77.2, 73.5, (C2, C4, C6), 45.9, 41.8, (C3, C5), 23.3, 19.6, 16.0, (3×$-CH_3$); HRMS: calcd for $C_{20}H_{24}O_2$ 296.1776. Found: 296.1776.

3.3.12. 4e-Methyl-2e-3e,6e-triphenyl-tetrahydropyran-4a-ol (4e). 250 mg **4e** (18.2%) as a colourless oil (procedure A); IR (neat) ν_{max} 3479, 3032, 1719, 1492, 1453, 1116, 1059, 1022 cm^{-1}; ^1H NMR δ=7.43–7.01 (15H, m, CH_{Ph}), 5.17 (1H, d, J=10.6 Hz, H2), 5.12 (1H, dd, J=2.3, 11.3 Hz, H6), 2.88 (1H, d, J=10.6 Hz, H3), 2.05 (1H, dd, J=2.3, 13.6 Hz, H5), 1.88 (1H, dd, J=11.3, 13.6 Hz, H5), 1.03 (3H, s, $-CH_3$); ^{13}C NMR δ=142.8, 141.0, 137.5, 130.6, 130.5, 128.6, 128.3, 128.2, 127.3, 127.0, 126.5, 125.9, (CH_{Ph}), 79.6, 75.1, 70.4, (C2, C4, C6), 58.5, 47.3, (C3, C5), 29.9, ($-CH_3$); HRMS: calcd for $C_{24}H_{24}O_2$ 344.1776. Found: 344.1776.

The isomer **2e** could not be separated by column chromatography. The ratio of the isomers **2e** and **4e** was determined by integration of important signals in the ^1H and ^{13}C NMR spectra.

3.3.13. *syn*-3-Methyl-1,4-diphenyl-butan-1,3-diol (5e). 350 mg **5e** (34.2%) as a colourless oil (procedure A); IR (neat) ν_{max} 2917, 1712, 1602, 1494, 1452, 1103, 1067, 1028 cm^{-1}; ^1H NMR δ=7.40–7.10 (10H, m, CH_{Ph}), 4.88 (1H, dd, J=3.0, 10.9 Hz, H1), 2.72 (2H, d, J=13.7 Hz, H4), 1.75 (1H, dd, J=3.0, 13.2 Hz, H2), 1.69 (1H, dd, J=10.9, 13.2 Hz, H2), 1.18 (3H, s, $-CH_3$); ^{13}C NMR δ=142.9, 137.7, 130.6, 128.7, 128.5, 128.2, 127.3, 126.9, (CH_{Ph}), 75.1, 70.5, (C1, C3), 50.1, 45.1, (C2, C4), 29.1($-CH_3$); HRMS: calcd for $C_{17}H_{16}$ (M-2H_2O) 220.1252. Found: 220.1252 (M−2H_2O).

3.3.14. 3e-Isopropyl-4a-methyl-2e,6e-diphenyl-tetrahydropyran-4e-ol (2f). ^1H NMR δ=7.50–7.10 (10H, m, CH_{Ph}), 4.54 (1H, dd, J=2.6, 11.3 Hz, H6), 4.45 (1H, d, J=10.9 Hz, H2), 2.17 (1H, dqq, J=7.2, 7.2, 9.4 Hz, $-CHMe_2$), 1.91 (1H, dd, J=2.6, 12.8 Hz, H5), 1.88 (1H, dd, J=11.3, 12.8 Hz, H5), 1.81 (1H, dd, J=9.4, 10.9 Hz, H3), 1.51 (3H, s, −Me), 0.88 (3H, d, J=7.2 Hz, −Me), 0.41 (3H, d, J=7.2 Hz, −Me); ^{13}C NMR δ=142.3, 141.4, 128.8, 128.3, 128.2, 128.1, 127.4, 125.9, 80.6, 77.2, 73.1 (C2, C4, C6), 56.4, 51.6 (C3, C5), 24.5, 24.4, 22.7, 18.7.

3.3.15. 9a-Methyl-2e,4e-diphenyl-3-oxa-bicyclo[3.3.1]-nonan-9e-ol (3g). 283 mg **3g** (23%) as a colourless oil (procedure A); IR (neat) ν_{max} 3454, 2960, 1738, 1372, 1215, 1141, 1050 cm^{-1}; ^1H NMR δ=7.50–7.10 (10H, m, CH_{Ph}), 5.09 (1H, m, H2, H4), 2.10–1.00 (11H, m, H1, H5, H6, H7, H8, $-CH_3$); ^{13}C NMR δ=141.8, 128.1, 126.7, 125.2, (CH_{Ph}), 79.0, 71.8, (C2, C4, C6), 45.4, (C3, C5), 26.6, 20.4, (3×$-CH_2$), 19.0 ($-CH_2$); HRMS: calcd for $C_{21}H_{24}O_2$ 308.1776. Found: 308.1776.

3.3.16. 9e-Methyl-2e,4e-diphenyl-3-oxa-bicyclo[3.3.1]-nonan-9a-ol (4g). 230 mg **4g** (18.7%) as colourless crystals (procedure A); mp 132–133 °C (hexane/ethylacetate); IR (neat) ν_{max} 3251, 2925, 1738, 1496, 1449, 1380, 1207, 1139, 1064 cm^{-1}; ^1H NMR δ=7.42–7.11 (10H, m, CH_{Ph}), 5.50 (2H, m, H2, H4), 2.09–1.13 (11H, m, H1, H5, H6, H7, H8, $-CH_3$); ^{13}C NMR δ=142.5, 127.9, 126.3, 125.2, (CH_{Ph}), 76.5, 72.4, (C2, C4, C9), 45.4, (C1, C5), 27.9, 23.0, (C6, C7, C8), 19.3, ($-CH_3$); HRMS: calcd for $C_{21}H_{24}O_2$ 308.1776. Found: 308.1776.

3.3.17. *anti*-2-Hydroxybenzyl-1-methyl-cyclohexan-1-ol (5g).[6] 147 mg **5g** (16.7% yield) as a colourless oil (procedure A); ^1H NMR δ=7.30–7.10 (5H, m, CH_{Ph}), 4.46 (1H, d, J=10.2 Hz, CHOH), 1.72–0.68 (12H, m, H2, H3, H4, H5, H6, $-CH_3$); ^{13}C NMR δ=142.4, 128.3, 127.8, 127.3, (CH_{Ph}), 78.7, 74.5, (C1, CHOH), 52.1, 42.2, (C2, C6), 27.0, 25.5, 23.6, 21.0, (C3, C4, C5, $-CH_3$).

3.3.18. 3e-Chlor-4a-methyl-2e,6e-diphenyl-tetrahydropyran-4e-ol (2h). 470 mg **2h** (38.8%) as a colourless oil (procedure B); IR (neat) ν_{max} 3279, 1690, 1602, 1495, 1449, 1300, 1094, 1065, 1028 cm^{-1}; ^1H NMR δ=7.45–7.12 (10H, m, CH_{Ph}), 4.65 (1H, dd, J=2.3, 11.7 Hz, H6), 4.42 (1H, d, J=10.6 Hz, H2), 3.99 (1H, d, J=10.6 Hz, H3), 2.13 (1H, dd, J=2.3, 13.6 Hz, H5), 2.06 (1H, dd, J=11.7, 13.6 Hz, H5), 1.58 (3H, s, CH_3); ^{13}C NMR δ=140.7, 138.6, 128.6, 128.4, 128.3, 127.9, 127.7, 125.9, (CH_{Ph}), 81.7, 71.9, 71.1, (C2, C3, C4, C6), 47.7, (C5), 21.9 ($-CH_3$); HRMS: calcd for $C_{18}H_{19}ClO_2$ 302.1074. Found: 302.1072.

3.3.19. 8a-Methyl-2e,4e-diphenyl-3-oxa-bicyclo[3.2.1]-octan-8e-ol (3i). 550 mg **3i** (46.7%) as a colourless oil

(procedure B); IR (neat) ν_{max} 3304, 2873, 1495, 1330, 1292, 1120, 1108, 1002 cm^{-1}; ^1H NMR δ=7.40–7.13 (10H, m, CH_{Ph}), 5.00–4.96 (2H, m, H2, H4), 2.02–1.95 (2H, m, H1, H5), 1.73 (3H, s, $-CH_3$), 1.52–1.49 (4H, m, H6, H7); ^{13}C NMR δ=141.7, 128.0, 126.8, 125.7, (CH_{Ph}), 79.9, 77.9, (C2, C4, C8), 51.1, (C1, C5), 21.0, 20.3, (C6, C7, $-CH_3$); HRMS: calcd for $C_{20}H_{22}O_2$ 294.1619. Found: 294.1620.

3.3.20. 5e-(2-Hydroxy-isopropyl)-3e-isopropenyl-2e-phenyl-tetrahydropyran (6). 860 mg **6** (82.6%) were isolated as a colourless oil by the reaction of 1-hydroxy-3-methyl-2-buten (procedure B); IR (neat) ν_{max} 3412, 2970, 1453, 1371, 1191, 1073 cm^{-1}; ^1H NMR δ=7.33–7.12 (5H, m, CH_{Ph}), 4.56 (2H, m, CH_2), 4.17 (1H, ddd, J=2.7, 3.8, 10.9 Hz, H6), 4.03 (1H, d, J=10.2 Hz, H2), 3.38 (1H, dd, J=10.9, 11.3 Hz, H6), 2.29 (1H, ddd, J=3.4, 10.2, 10.2 Hz, H3), 1.91 (1H, ddd, J=3.4, 3.5, 12.6 Hz, H4), 1.78 (1H, dddd, J=3.4, 3.8, 11.3, 12.1 Hz, H5), 1.52 (1H, ddd, J=10.2, 12.1, 12.6 Hz, H4), 1.43 (3H, s, $-CH_3$), 1.22 (6H, s, $-CH_3$); ^{13}C NMR δ=146.0, 140.8, 128.1, 127.8, 127.3,112.3, (CH_{Ph}, C_q, CH_2), 84.2, (C2), 71.3, (–COH), 69.8, ($-CH_2O$), 50.6, 46.8, 31.6, (C3, C4, C5), 27.8, 27.3, 21.5, (3×CH_3); HRMS: calcd for $C_{17}H_{24}O_2$ 260.1776. Found: 260.1776.

3.3.21. 4e-Methyl-2e,6e-di-*n*propyl-tetrahydro-pyran-4a-ol (7c). 160 mg **7c** (20%) as a colourless oil (procedure B); IR (neat) ν_{max} 3117, 2959, 2806, 1735, 1381, 1147, 1124, 1077 cm^{-1}; ^1H NMR δ=3.21 (2H, m, H2, H6), 1.20–1.59 (12H, m, H3, H5, 4×CH_2), 1.24 (3H, s, CH_3), 0.85 (6H, dd, J=6.8, 7.2 Hz, 2×CH_3); ^{13}C NMR δ=74.7 (C2, C4), 69.5 (C4), 46.5 (C3, C5), 38.4 (2×CH_2), 26.2 ($-CH_3$), 19.0 ($-CH_2$), 14.0 (2×CH_3); HRMS: calcd for $C_{12}H_{24}O_2$ 200.1776. Found: 200.1743.

3.3.22. 2e,4a,6e-Trimethyl-tetrahydro-pyran-4e-ol (8a).[12] 210 mg **8a** (36.4%) as a colourless oil (procedure B); ^1H NMR δ=3.43 (2H, ddq, J=1.5, 6.2, 10.7 Hz, H2, H6), 1.58 (2H, dd, J=2.3, 10.7 Hz, H3, H5), 1.33 (2H, dd, J=1.5, 2.3 Hz, H3, H5), 1.25 (3H, s, CH_3), 1.15 (6H, d, J=6.2 Hz, 2×CH_3); ^{13}C NMR δ=77.2 (C2, C5), 70.9 (C4), 47.6 (C3, C5), 26.0, 22.0 (3×CH_3).

3.3.23. 2e,6e-Diethyl-4a-methyl-tetrahydro-pyran-4e-ol (8b). 180 mg **8b** (26.1%) as a colourless oil (procedure B); IR (neat) ν_{max} 3388, 2965, 2936, 1731, 1460, 1371, 1175, 1141, 1125, 1080, 1023 cm^{-1}; ^1H NMR δ=3.18–3.09 (2H, m; H2, H6), 1.64–1.14 (11H, m, H3, H5, 2×CH_2, CH_3), 0.88 (6H, t, J=7.3 Hz; 2×$-CH_3$); ^{13}C NMR δ=76.3, (C2, C6), 69.5 (C4), 46.2, (C3, C5), 29.2 (2×CH_2), 26.2 ($-CH_3$), 10.1 (2×$-CH_3$); HRMS: calcd for $C_9H_{17}O_2$ (M−CH_3) 157.122855. Found: 157.12288.

3.3.24. 4a-Methyl-2e,6e-di-*n*propyl-tetrahydro-pyran-4e-ol (8c). 120 mg **8c** (15%) as a colourless oil (procedure B); IR (neat) ν_{max} 3407, 2958, 2930, 1736, 1459, 1376, 1217, 1142, 1125, 1082 cm^{-1}; ^1H NMR δ=3.54 (2H, dddd, J=1.9, 2.3, 4.5, 15.8 Hz, H2, H6), 1.18–1.48 (12H, m, H3, H5, 4×CH_2), 1.17 (3H, s, CH_3), 0.85 (6H, dd, J=6.8, 7.2 Hz, 2×CH_3); ^{13}C NMR δ=72.6 (C2, C6), 68.8 (C4), 44.7 (C3, C5), 38.3 (2×CH_2), 31.8 (CH_3), 16.9 (2×CH_2), 14.1 (2×CH_3); HRMS: calcd for $C_{12}H_{24}O_2$: 200.1776. Found: 200.1774.

3.3.25. 2e,6e-Di-*iso*propyl-4a-methyl-tetrahydro-pyran-4e-ol (8d). 290 mg **8d** (36.2%) as a colourless oil (procedure B); IR (neat) ν_{max} 2959, 2929, 1733, 1469, 1369, 1154, 1127, 1084, 1015; ^1H NMR δ=2.86 (2H, ddd, J=2.3, 6.8, 11.7 Hz; H2, H6), 1.85–1.76 (4H, m; 2×H_3C-CH_2-CHR), 0.95 (6H, t, J=7.3 Hz; 2×H_3C-CH_2R); ^{13}C NMR δ=79.9 (C2, C4), 43.4 (C3, C5), 33.3 (2×CH), 26.3 (CH_3), 18.7, 18.6 (2×CH_3); HRMS: calcd for $C_{12}H_{23}O_2$ 199.1698. Found: 199.1700.

3.3.26. 2a,4a,8a-Trimethyl-3-oxa-bicyclo-[3.2.1]-octan-8e-ol (9a). 160 mg **9a** (28.5%) as a colourless oil (procedure B); IR (neat) ν_{max} 3317, 2971, 2917, 1738, 1464, 1371, 1348, 1297, 1130, 1089, 1069 cm^{-1}; ^1H NMR: δ=3.78 (2H, q, J=6.4 Hz, H2, H4), 1.55–1.71 (4H, m, H6, H7), 1.45 (3H, s, CH_3), 1.43 (2H, m, H1, H5), 1.03 (6H, d, J=6.4 Hz, 2×CH_3); ^{13}C NMR 80.1 (C8), 72.5 (C2, $C4_l$), 49.8 (C1, C5), 21.0 (C6, C7), 20.0 (CH_3), 19.5 (2×CH_3); HRMS: calcd for $C_{10}H_{18}O_2$ 170.1307. Found: 170.1306.

3.3.27. 2e,4e-Diethyl-8a-methyl-3-oxa-bicyclo[3.2.1]-octan-8e-ol (9b). 280 mg **9b** (35.3%) as a colourless oil (procedure B); IR (neat) ν_{max} 3307, 2970, 2919, 1738, 1365, 1217, 1127, 1070, 989 cm^{-1}; ^1H NMR δ=3.42 (2H, t, J=6.78 Hz; H2, H4), 1.69–1.14 (13H, m, H1, H5, H6, H7, 2×$-CH_2$, $-CH_3$), 0.83 (6H, t, J=7.0 Hz; 2×$-CH_3$); ^{13}C NMR δ=80.4, (C8), 76.9 (2×C2, C4), 49.0, (C1, C5), 26.3, 21.5 (2×CH_2, C6, C7), 20.1 (CH_3), 10.3 (2×CH_3); HMRS: calcd for $C_{12}H_{22}O_2$ 198.1620. Found: 198.1624.

3.3.28. 8a-Methyl-2e,4e-di-*n*propyl-3-oxa-bicyclo[3.2.1]-octan-8e-ol (9c). 350 mg **9c** (38.7%) as a colourless oil (procedure B); IR (neat) ν_{max} 3321, 2954, 2867, 1738, 1464, 1374, 1323, 1217, 1131, 1093 cm^{-1}; ^1H NMR δ=3.52 (2H, t, J=7.16 Hz; H2, H4), 1.69–1.14 (17H, m, H1, H5, H6, H7, 4×CH_2, CH_3), 0.82 (6H, t, J=7.2 Hz; 2×$-CH_3$); ^{13}C NMR δ=80.4 (C8), 78.6 (2×C2, C8), 48.3 (C1, C5), 26.3, 21.5 (2×CH_2, C6, C7), 20.1 (CH_3), 10.3 (2×CH_3); HMRS: calcd for $C_{14}H_{26}O_2$ 226.1933 Found: 226.1933.

Acknowledgements

This research was supported by the Deutsche Forschungsgemeinschaft. The authors thank B. Ziemer and P. Neubauer for performing out the X-ray analysis.

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