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Article

Solvent-free Catalysed Synthesis of Tetrahydropyran Odorants: the Role of SiO_2/*p*-TSA Catalyst on the Prins-Cyclization Reaction

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Foi desenvolvido um procedimento eficiente e ecologicamente amigável para a promoção da ciclização de Prins em ausência de solventes orgânicos baseado na maceração de um aldeído e um álcool alílico em presença de quantidade catalítica de *p*-TSA disperso em sílica gel. Por esse procedimento foram sintetizadas as fragrâncias comerciais Florol® e Clarycet®, em uma e duas etapas sintéticas respectivamente.

An efficient, green and solvent-free catalysed Prins-cyclization reaction based on the simple grinding of an aldehyde and a homoallylic alcohol in the presence of catalytic amount of *p*-TSA on silica gel is reported. By this protocol were synthesized tetrahydropyran odorants including commercial Florol® and Clarycet®, in one and two steps respectively.

Keywords: Prins-cyclisation, solvent-free catalysis, green chemistry, tetrahydropyrans, fragrances

Introduction

The Prins-cyclization reaction is one of the most efficient strategies to construct the tetrahydropyran core,[1] which is present in several natural products.[2] Some non-natural compounds possessing this functionality were found to be of commercial interest by the perfume industry. Clarycet® (commercialized by IFF) and Florol® (commercialized by Firmenich) are floral odorants handled in the industry as a racemic diastereoisomeric mixture which can be used in a large number of fragrances and formulations conferring floral scents without changing the olfactory character of the perfume.[3,4] So far as we know, there are only two works in the literature describing the synthesis of both, Clarycet®[4] and Florol®. In one of these works, racemic Florol® was synthesized in 44% overall yield from geraniol/nerol mixture in 5 sequential steps. All enantioenriched stereoisomers of both odorants were prepared by an enzymatic approach in 6 sequential steps in very low yields.[4]

With the recent increase of environmental awareness and subsequent development of "green-chemistry" principles, several guidelines for the production of chemicals by cleaner and benign procedures are being established as crucial for the modern chemical industry processes. One of the most important requirements in this context is the development of alternative synthetic routes aimed at minimizing or substituting mineral solvents by more benign solvents such as water, acetone, ethanol, ethyl acetate, etc.[5] Further, emerging solvent-free processes and the utilization of solid matrices that can act as dispersing agents or as catalysts that is attracting attention.[6]

In this work, a one-pot procedure for the construction of the tetrahydropyran core of the floral odorants, Clarycet®, Florol® and other two not yet commercially utilized octahydro-*2H*-chromen-4-ols[7] using a solvent-free solid phase catalysed Prins-cyclization reaction is presented.

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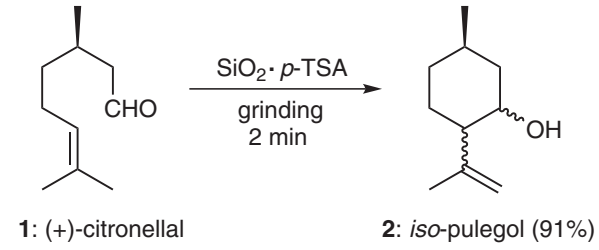
Results and Discussion

This proposition was based on previous work related to the solvent-free solid phase catalysed tetrahydropyranylation of alcohols and thiols.[8] Earlier, it was observed that citronellal can be converted, in 91% isolated yield, into *iso*-pulegol within 2 min by an intramolecular *ene*-type reaction. The reaction proceeds by grinding it in a mixture of silica gel with catalytic amount of *p*-toluenosulfonic acid (*p*-TSA) according to Scheme 1.



Scheme 1. Synthesis of *iso*-pulegol by catalytic system.

This result stimulated the application of similar reaction conditions in the preparation of tetrahydropyran derivatives by the intermolecular version of the Prins-cyclization reaction and studies related of conformational features of three tetrahydropyrans.[9] A detailed stoichiometric screen showed that a physical mixture of *p*-TSA (0.29 mmol) in silica gel (0.5 g) was the best dispersant/catalyst system in the conversion of 3-methyl-but-3-en-1-ol (**3**, 1 mmol) and benzaldehyde (**4**, 1.1 mmol) in the corresponding Prins adduct **5**, (*syn*:*anti,* 63:37) in 88% isolated yield, after 5 min grinding as presented in Scheme 2.

Scheme 2. Synthesis of model compound **5.**

In order to investigate the role of the SiO_2/*p*-TSA mixture, both components of this catalytic system, SiO_2 and *p*-TSA, were investigated separately in the reaction of **3** with **4**. SiO_2 only did not display any catalytic behaviour even at long reaction times. On the other hand when sub-stoichiometric amount of *p*-TSA was put together with **3** and **4** in absence of solvents, a very vigorous and exothermic reaction took place accompanied by partial carbonization of the components of the mixture, evidenced by the formation of a black colour and the title compound was produced in low yield among many other by-products. Other solid matrices (neutral, acid and basic aluminium oxide, Celite® as well Montmorillonite K10) were also investigated as partners of *p*-TSA in the reaction of **3** with **4** and failed to produce **5** in good yields and synthetic useful reaction time in comparison with SiO_2. These experiments allow us to conclude that SiO_2 in association with *p*-TSA acts as catalyst and not only as a dispersant agent. In this way, were adopted the reaction conditions presented in Scheme 2, as the ideal system for the preparation of the Prins adducts by a solvent-free protocol in the reaction of the alcohol **3** with other aldehydes as presented in Scheme 3 and summarized in Table 1.

In all cases the tetrahydropyran derivatives were formed, as a diastereoisomeric mixture, in reasonable to good yields by the simple grinding of the reagents in a mixture of silica gel and catalytic amount of *p*-TSA. While aldehydes **6a**, **6c** and **6g**, as well as benzaldehyde **4**, were converted to the corresponding products in good yields in only 5 min of reaction (entries 1, 3, 7 and Scheme 2), the aromatic **6b**, **6d,** cycloalkyl **6f** and alkenyl **6h** aldehydes required a longer reaction time for conversion to the corresponding products (entries 2, 4, 6 and 8). Aldehyde **6e** required 25 min to be converted into the product **7e** in 69% yield (entry 5).

The structure of the tetrahydropyran derivative **7f** (major diastereoisomer) was subsequently confirmed to have the *syn* relation, by a single-crystal X-ray structure determination, as shown in Figure 1.[10]

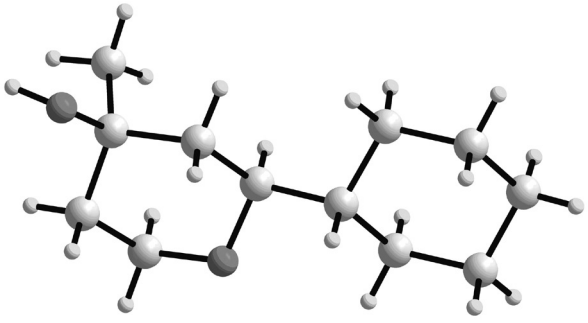
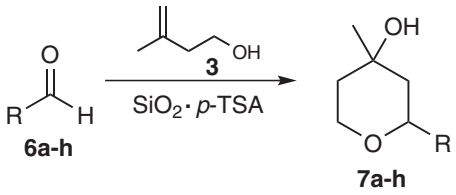


Figure 1. Molecular structure of **7f** determined by X-ray crystallography.

The major diastereoisomer of **7h** was submitted to nOe experiment and the *syn* relation was confirmed, as show in Figure 2.

The strong 1D nOe for methyl group and carbinolic hydrogen provided unquestionable proof for the assigned *syn* relation. On the basis of nOe experiment acquired for compound **7h**, the relation of the others tetrahydropyrans **5**, **7a**-**g** was similarly assigned.

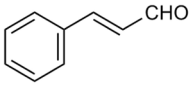
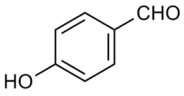
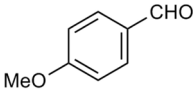
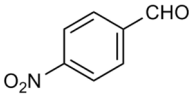
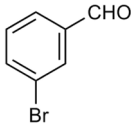
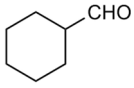
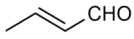
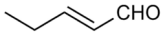
With the reaction conditions established, this method was applied to the synthesis of Florol® (**11**, in a one-pot procedure 87%, 15 min) and Clarycet® (**12**) by reacting alcohol **3** with the appropriate aldehydes (**8** and **9**, respectively), and two other odorants of commercial interest[5] (**15** and **16**) by reacting *iso*-pulegol **2** with aldehydes **13** and **14**, respectively (Scheme 4).



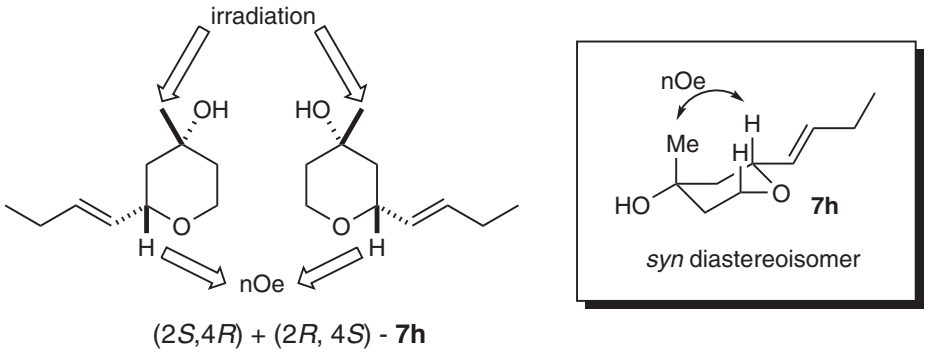
Scheme 3. Reaction of different aldehydes with compound **3.**

Despite the low yield of **15** (49%), due the high volatility of aldehyde **13**, since the reactions were conduced by grinding the reagents in an open mortar, the synthesis can be considered attractive since it can be performed in a single step and by a solvent-free procedure.

Table 1. Prins-cyclization reaction of **3** with aldehydes **6a-h**

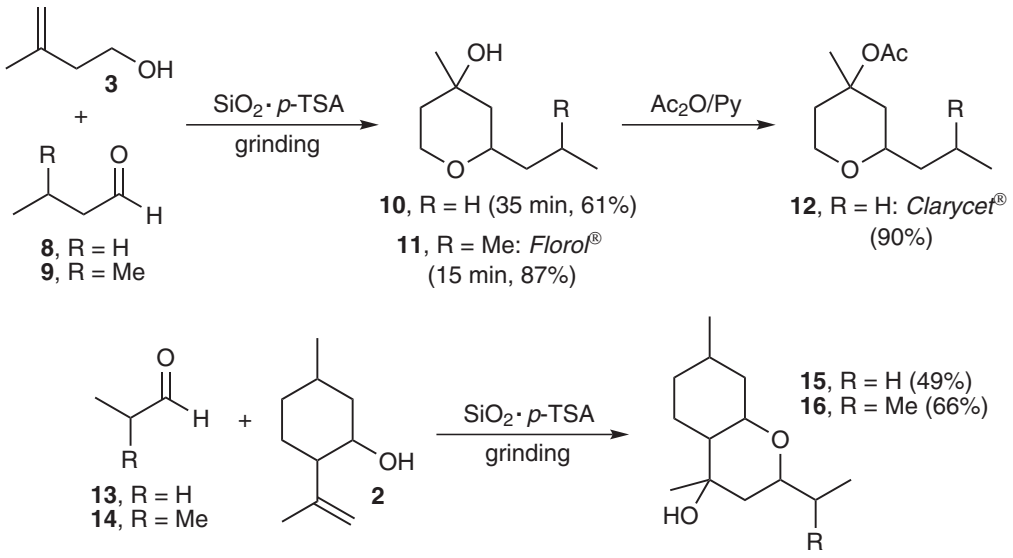
Entry	Aldehyde Structure	Compounds	Products[a]	time (min)[b]	Yield %[c] (*syn*:*anti*)[d]
1		**6a**	**7a**	5	91 (64:36)
2		**6b**	**7b**	10	67 (20:80)
3		**6c**	**7c**	5	89 (30:70)
4		**6d**	**7d**	40	70 (55:45)
5		**6e**	**7e**	25	69 (60:40)
6		**6f**	**7f**	60	71 (62:38)
7		**6g**	**7g**	5	62 (40:60)
8		**6h**	**7h**	10	58 (71:29)

[a]Compounds **7a**-**h** as well a **5**, were formed as a diastereisomeric mixture; [b]total grinding time; [c]isolated yields; [d]GC-FID and nOe experiments were used to determine the *syn*:*anti* ratio.



(2*S*,4*R*) + (2*R*, 4*S*) - **7h**

Figure 2. Relative stereochemistry of **7h** determined by nOe experiments.



Scheme 4. Application of SiO_2,*p*-TSA system on synthesis of odorants with commercial interest.

Conclusion

In conclusion, a one-pot strategy has been developed and applied to the synthesis of three important odorants: Florol® and compounds **15** and **16**. The synthesis of Clarycet® was accomplished by a usual acetylation of the Prins adduct **10**, with 55% overall yield. The great appeal of this procedure is found in its operational practicality, since the simple mixture of the reagents in a mortar allows the preparation of the target compounds in a few minutes. Currently, some variants of this protocol are under investigation aimed towards the total synthesis of industrially important compounds.

Experimental

General

The following includes general experimental procedures, specific details for representative reaction, and isolation and spectroscopic information for the new compounds prepared. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 400 MHz. Infrared spectra were recorded on a FT-IR Bomem-Hartman & Braun MB-102. Low resolution mass spectra were obtained on a GC-17A Shimadzu, equipped with HP-5MS column (5% phenyl / 95% dimethyl polysiloxane, 30 m × 0.25 mm × 0.25 μm), coupled with a GCMS-QP5000 Shimadzu (70 eV).

High resolution mass spectra were obtained on a LC-MS Bruker Daltonics MicroTOF Ic by direct infusion. Analytical thin-layer chromatography (TLC) was performed on glass plates coated with 0.50 mm 230-400 mesh silica gel containing a fluorescent indicator (Merck). TLC plates were visualized by exposure to ultraviolet light (254 nm) and/or by immersion in an acidic staining solution of *p*-anisaldehyde followed by heating on a hot plate. Organic solutions were concentrated by rotary evaporation at *ca.* 30-100 mmHg. Flash column chromatography was performed on Fluka silica gel 60 (220-440 mesh).[10] Solvents used were of commercial grade and were previously treated according to the literature.[11]

General Procedure

In a mortar containg silica gel (200-400 mesh) (0.5 g, 8.33 mmol) and *p*-toluenesulfonic acid (0.05 g, 0.29 mmol) was added the aldehyde (1 mmol) and homoallylic alcohol (1.1 mmol). The resulting mixture was ground for the appropriate time and the reaction was monitored by thin layer chromatography. The reaction media was directly purified by column chromatography by elution with appropriate mixture of solvents.

*(5R)-5-Methyl-2-(prop-1-en-2-yl)cyclohexanol (**2**)*

The product was analysed by CG-FID and compared with commercial standard of *iso*-pulegol purchased from Aldrich Chemical Company (Milwaukee, Wisconsin, USA) (CAS 628693-74-3).

*4-Methyl-2-phenyltetrahydro-2H-pyran-4-ol (**5**)*

Syn diastereoisomer: Eluent: hexane/ethyl acetate (1:1), Rf 0.66; colorless oil, yield 55%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 3H), 1.66 (s, OH), 1.68 (dq, J_1 12.94 Hz, J_2 2.39 Hz, 1H), 1.72-1.86 (m, 2H), 1.89 (dt, J_1 12.94 Hz, J_2 2.39 Hz, 1H), 3.62 (td, J_1 12.48 Hz, J_2 2.31 Hz, 1H), 4.13 (ddd, J_1 11.86 Hz, J_2 5.24 Hz, J_3 1.69 Hz, 1H), 4.36 (dd,

J_1 11.86 Hz, J_2 2.31 Hz, 1H), 7.23-7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 40.1, 48.4, 66.0, 69.2, 77.7, 125.9, 127.6, 128.5, 142.1. (CAS 63500-72-1).

Anti diastereoisomer: Eluent: hexane/ethyl acetate (1:1), Rf 0.81; colorless oil, yield 33%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 3H), 1.49-1.56 (m, 2H), 1.64 (dd, J_1 13.71 Hz, J_2 11.71 Hz, 1H), 1.73-1.83 (m, 2H), 3.90-4.03 (m, 2H), 4.70 (dd, J_1 11.71 Hz, J_2 2.31 Hz, 1H), 7.21-7.43 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.8, 38.5, 46.6, 64.1, 68.1, 75.2, 125.9, 127.4, 128.4, 142.8. (CAS 63500-72-1).

*(E)-4-Methyl-2-styryltetrahydro-2H-pyran-4-ol (**7a**)*

Syn diastereoisomer: Eluent: hexane/ethyl acetate (1:1), Rf 0.56; colorless oil, yield 58%; IR ν_{max}/cm^{-1} 3431, 2969, 2935, 2851, 1713, 1599, 1494, 1449, 1377, 1250, 1174, 1104, 965, 935, 880, 818, 753, 738, 693 (film); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 3H), 1.60 (t, J 12.87 Hz, 1H), 1.64 (dq, J_1 12.87 Hz, J_2 2.22 Hz, 1H), 1.77 (td, J_1 12.87 Hz, J_2 5.08 Hz, 1H), 1.81 (dt, J_1 12.87 Hz, J_2 2.22 Hz, 1H), 2.05 (s, OH), 3.55 (td, J_1 12.23 Hz, J_2 2.38 Hz, 1H), 4.02 (ddq, J_1 12.23 Hz, J_2 5.88 Hz, J_3 1.43 Hz, 1H), 4.06 (ddd, J_1 12.23 Hz, J_2 5.08 Hz, J_3 2.22 Hz, 1H), 6.19 (dd, J_1 16.05 Hz, J_2 5.88 Hz, 1H), 6.61 (dd, J_1 16.05 Hz, J_2 1.43 Hz, 1H), 7.20-7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 40.3, 46.5, 65.3, 68.8, 75.8, 126.5, 127.7, 128.6, 129.7, 130.5, 136.7; MS: *m/z* 218 (M$^+$, 34%), 204 (2), 200 (38), 185 (57), 171 (2), 148 (19), 147 (100), 129 (65), 115 (57), 104 (44), 91 (57), 71 (72), 55 (27); HRMS [M–Na$^+$] Found: 241.1199. Calc. for $C_{14}H_{18}O_2$: 241.1204.

Anti diastereoisomer: Eluent: hexane/ethyl acetate (1:1), Rf 0.73; colorless oil, yield 33%; IR ν_{max}/cm^{-1} 3430, 2943, 2919, 2855, 1674, 1603, 1518, 1458, 1381, 1281, 1124, 1088, 1035, 935, 886, 818, 741, 637 (film); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 3H), 1.49 (dq, J_1 12.94 Hz, J_2 2.31 Hz, 1H), 1.51 (dd, J_1 13.56 Hz, J_2 11.51 Hz, 1H), 1.66-1.76 (m, 2H), 1.89 (s, OH), 3.89 (td, J_1 11.40 Hz, J_2 2.15 Hz, 1H), 3.90 (dd, J_1 7.24 Hz, J_2 1.85 Hz, 1H), 4.35 (ddq, J_1 11.40 Hz, J_2 6.01 Hz, J_3 1.54 Hz, 1H), 6.17 (dd, J_1 16.02 Hz, J_2 6.01 Hz, 1H), 6.61 (dd, J_1 16.02 Hz, J_2 1.54 Hz, 1H), 7.18-7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.7, 38.3, 44.7, 63.5, 67.7, 73.4, 126.3, 127.4, 128.4, 130.1, 130.2, 136.9; MS: *m/z* 218 (M$^+$, 20%), 207 (3), 200 (24), 185 (42), 171 (3), 148 (19), 147 (100), 129 (85), 115 (60), 104 (43), 91 (63), 71 (82), 55 (49); HRMS [M–Na$^+$] Found: 241.1200. Calc. for $C_{14}H_{18}O_2$: 241.1204.

*2-(4-Hydroxyphenyl)-4-methyltetrahydro-2H-pyran-4-ol (**7b**)*

Syn diastereoisomer: Eluent: hexane/ethyl acetate (1:1), Rf 0.22; colorless oil, yield 13%; IR ν_{max}/cm^{-1} 3363, 2940, 2861, 1614, 1518, 1443, 1377, 1250, 1225, 1170, 1143, 1080, 1047, 1013, 939, 899, 506 (film); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 3H), 1.56-1.86 (m, 4H), 3.63 (td, J_1 12.07 Hz, J_2 2.25 Hz, 1H), 4.01 (ddd, J_1 12.07 Hz, J_2 5.30 Hz, J_3 2.25 Hz, 1H), 4.31 (dd, J_1 12.07 Hz, J_2 2.25 Hz, 1H), 6.74 (dt, J_1 8.59 Hz, J_2 1.95 Hz, 2H), 7.16 (dt, J_1 8.59 Hz, J_2 1.95 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2, 41.1, 49.1, 66.8, 69.5, 78.8, 116.1, 128.5, 134.6, 158.0; MS: *m/z* 208 (M$^+$, 2%), 190 (8), 175 (29), 161 (1), 137 (3), 121 (70), 119 (28), 91 (32), 77 (38), 71 (75), 58 (100); HRMS [M–Na$^+$] Found: 231.0992. Calc. for $C_{12}H_{16}O_3$: 231.0997.

Anti diastereoisomer: Eluent: hexane/ethyl acetate (1:1), Rf 0.49; white solid, yield 54%, m.p. 194 °C; IR ν_{max}/cm^{-1} 3467, 2920, 2899, 2855, 1671, 1615, 1518, 1466, 1373, 1261, 1084, 1039, 1007, 902, 830, 737 (KBr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.52 (dq, J_1 13.84 Hz, J_2 1.69 Hz, 1H), 1.62 (dd, J_1 13.70 Hz, J_2 11.30 Hz, 1H), 1.65-1.74 (m, 3H), 3.86 (ddd, J_1 11.30 Hz, J_2 5.22 Hz, J_3 1.13 Hz, 1H), 3.94 (td, J_1 11.30 Hz, J_2 2.40 Hz, 1H), 4.61 (dd, J_1 11.30 Hz, J_2 2.40 Hz, 1H), 4.86 (s, OH), 6.74 (dt, J_1 8.61 Hz, J_2 1.97 Hz, 2H), 7.16 (dt, J_1 8.61 Hz, J_2 1.97 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.6, 39.1, 47.1, 65.2, 68.5, 76.6, 116.1, 128.6, 134.8, 157.9; MS: *m/z* 208 (M$^+$, 11%), 190 (36), 176 (12), 175 (100), 161 (2), 137 (5), 121 (81), 119 (22), 91 (19), 71 (37), 58 (43); HRMS [M–Na$^+$] Found: 231.0991. Calc. for $C_{12}H_{16}O_3$: 231.0997.

*2-(4-Methoxyphenyl)-4-methyltetrahydro-2H-pyran-4-ol (**7c**)*

Syn diastereoisomer: Eluent: hexane/ethyl acetate (2:1), Rf 0.31; colorless oil, yield 27%; IR ν_{max}/cm^{-1} 3426, 2948, 2915, 2847, 1614, 1587, 1518, 1470, 1377, 1249, 1176, 1080, 1031, 942, 898, 830, 770, 737, 605 (film); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 3H), 1.66 (qd, J_1 12.87 Hz, J_2 2.38 Hz, 1H), 1.70-1.88 (m, 4H), 1.95 (s, OH), 3.61 (td, J_1 12.87 Hz, J_2 1.74 Hz, 1H), 3.79 (s, 3H), 4.10 (ddd, J_1 12.08 Hz, J_2 5.24 Hz, J_3 1.74 Hz, 1H), 4.30 (dd, J_1 12.08 Hz, J_2 1.74 Hz, 1H), 6.87 (dt, J_1 8.74 Hz, J_2 2.06 Hz, 2H), 7.27 (dt, J_1 8.74 Hz, J_2 2.06 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2, 40.3, 48.1, 55.2, 65.8, 69.1, 77.2, 113.7, 127.2, 134.2, 159.0; MS: *m/z* 222 (M$^+$, 16%), 204 (30), 190 (13), 189 (100), 173 (5), 151 (6), 135 (95), 133 (23), 119 (18), 92 (10), 91 (26), 71 (46), 58 (31); HRMS [M–Na$^+$] Found: 245.1152. Calc. for $C_{13}H_{18}O_3$: 245.1154.

Anti diastereoisomer: Eluent: hexane/ethyl acetate (2:1), Rf 0.46; white solid, yield 62%, m.p. 82 °C; IR ν_{max}/cm^{-1} 3422, 2947, 2919, 2843, 1611, 1518, 1462, 1377, 1249, 1176, 1144, 1084, 1035, 943, 898, 830, 766, 605 (film); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.50 (dq, J_1 13.82 Hz, J_2 2.22 Hz, 1H), 1.59-1.81 (m, 4H), 3.78 (s, 3H), 3.92-3.98 (m, 2H), 4.64 (dd, J_1 11.44 Hz, J_2 2.54 Hz, 1H), 6.86 (dt, J_1 8.74 Hz, J_2 2.06 Hz, 2H), 7.26 (dt,

J_1 8.74 Hz, J_2 2.06 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.8, 38.4, 46.4, 55.3, 64.1, 68.1, 74.9, 113.9, 127.5, 135.0, 159.1; MS: *m/z* 222 (M^+, 15%), 204 (29), 190 (13), 189 (100), 173 (4), 151 (5), 135 (86), 133 (23), 109 (15), 92 (9), 91 (21), 71 (37), 58 (27); HRMS [M–Na^+] Found: 245.1156. Calc. for $C_{13}H_{18}O_3$: 245.1154.

*4-Methyl-2-(4-nitrophenyl)tetrahydro-2H-pyran-4-ol (**7d**)*

Syn diastereoisomer: Eluent: hexane/ethyl acetate (1:1), Rf 0.42; colorless oil, yield 38%; IR ν_{max}/cm^{-1} 3418, 2972, 2939, 2859, 1604, 1519, 1347, 1252, 1093, 1045, 1014, 940, 809, 738, 697, 595 (film); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 3H), 1.63 (t, J_1 12.23 Hz, 1H), 1.71 (dq, J_1 12.87 Hz, J_2 2.22 Hz, 1H), 1.82 (s, OH), 1.85 (td, J_1 12.39 Hz, J_2 5.24 Hz, 1H), 1.91 (dt, J_1 12.87 Hz, J_2 2.22 Hz, 1H), 3.64 (td, J_1 12.87 Hz, J_2 2.22 Hz, 1H), 4.17 (ddd, J_1 12.39 Hz, J_2 5.24 Hz, J_3 2.22 Hz, 1H), 4.47 (dd, J_1 12.23 Hz, J_2 2.22 Hz, 1H), 7.51 (dt, J_1 8.90 Hz, J_2 2.22 Hz, 2H), 8.19 (dt, J_1 8.90 Hz, J_2 2.22 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 40.1, 48.4, 65.9, 68.9, 76.5, 123.7, 126.5, 147.3, 149.6; MS: *m/z* 219 (M^+-18, 30%), 204 (82), 188 (4), 174 (15), 152 (34), 135 (3), 120 (21), 107 (35), 103 (16), 91 (22), 71 (55), 58 (100); HRMS [M–Na^+] Found: 260.0894. Calc. for $C_{12}H_{15}NO_4$: 260.0899.

Anti diastereoisomer: Eluent: hexane/ethyl acetate (1:1), Rf 0.60; colorless oil, yield 32%; IR ν_{max}/cm^{-1} 3474, 2968, 2923, 2875, 1605, 1530, 1349, 1257, 1144, 1013, 985, 906, 803, 749, 697, 596 (film); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.54 (dd, J_1 13.51 Hz, J_2 11.76 Hz, 1H), 1.58 (dq, J_1 13.51 Hz, J_2 2.22 Hz, 1H), 1.74 (s, OH), 1.80 (td, J_1 13.66 Hz, J_2 6.51 Hz, 1H), 1.83 (dt, J_1 13.66 Hz, J_2 2.22 Hz, 1H), 3.99 (td, J_1 11.76 Hz, J_2 2.22 Hz, 1H), 4.03 (ddd, J_1 11.76 Hz, J_2 6.51 Hz, J_3 2.22 Hz, 1H), 4.84 (dd, J_1 11.76 Hz, J_2 2.22 Hz, 1H), 7.52 (dt, J_1 8.90 Hz, J_2 2.22 Hz, 2H), 8.18 (dt, J_1 8.90 Hz, J_2 2.22 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.7, 38.2, 46.7, 64.0, 67.9, 74.2, 123.5, 126.4, 147.0, 150.5; MS: *m/z* 219 (M^+–18, 36%), 204 (100), 202 (3), 188 (2), 174 (3), 152 (30), 144 (1), 120 (4), 103 (8), 91 (8), 71 (29), 58 (51); HRMS [M–Na^+] Found: 260.0901. Calc. for $C_{12}H_{15}NO_4$: 260.0899.

*2-(3-Bromophenyl)-tetrahydro-4-methyl-2H-pyran-4-ol (**7e**)*

Syn diastereoisomer: Eluent: hexane/ethyl acetate (3:1), Rf 0.22; colorless oil, yield 41%; IR ν_{max}/cm^{-1} 3422, 2964, 2939, 2855, 1716, 1595, 1569, 1474, 1337, 1252, 1092, 1045, 996, 942, 868, 822, 784, 747, 693, 598; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 3H), 1.62 (d, J_1 12.33 Hz, 1H), 1.65 (dq, J_1 12.79 Hz, J_2 2.46 Hz, 1H), 1.80 (td, J_1 12.79 Hz, J_2 5.24 Hz, 1H), 1.84 (dt, J_1 12.79, J_2 2.46 Hz, 1H), 1.23 (s, OH), 3.58 (td, J_1 12.33 Hz, J_2 2.31 Hz, 1H), 4.10 (ddd, J_1 12.02 Hz, J_2 5.24 Hz, J_3 1.54 Hz, 1H), 4.31 (dd, J_1 12.02 Hz, J_2 1.54 Hz, 1H), 7.18 (t, J_1 7.70 Hz, 1H), 7.24 (dt, J_1 7.70 Hz, J_2 1.54 Hz, 1H), 7.38 (dt, J_1 7.70 Hz, J_2 1.54 Hz, 1H), 7.50 (t, J_1 1.54 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2, 40.1, 48.3, 65.8, 69.0, 76.8, 122.5, 124.4, 129.0, 129.9, 130.6, 144.4; MS: *m/z* 272 (M^++2, 2%), 254 (22), 237 (49), 227 (2), 209 (1), 199 (1), 185 (35), 173 (6), 157 (13), 145 (6), 128 (7), 115 (5), 103 (37), 78 (16), 71 (90), 58 (100); HRMS [M–Na^+] Found: 293.0146. Calc. for $C_{12}H_{15}BrO_2$: 293.0153.

Anti diastereoisomer: Eluent: hexane/ethyl acetate (3:1), Rf 0.28; colorless oil, yield 28%; IR ν_{max}/cm^{-1} 3467, 3067, 2969, 2919, 2873, 1713, 1596, 1568, 1477, 1361, 1261, 1044, 984, 925, 864, 816, 783, 739, 692 (film); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.49 (dq, J_1 13.84 Hz, J_2 1.29 Hz, 1H), 1.55 (dd, J_1 13.84 Hz, J_2 11.80 Hz, 1H), 1.68-1.78 (m, 2H), 1.84 (s, OH), 3.58 (td, J_1 11.53 Hz, J_2 2.14 Hz, 1H), 4.66 (ddd, J_1 11.53 Hz, J_2 6.24 Hz, J_3 1.29 Hz, 1H), 4.31 (dd, J_1 11.53 Hz, J_2 2.14 Hz, 1H), 7.16 (t, J_1 7.76 Hz, 1H), 7.23 (d, J_1 7.76 Hz, 1H), 7.36 (dt, J_1 7.76 Hz, J_2 1.54 Hz, 1H), 7.51 (t, J_1 1.54 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.6, 38.3, 46.4, 64.0, 67.8, 74.4, 122.4, 124.5, 128.9, 129.8, 130.3, 145.0; MS: *m/z* 272 (M^++2, 2%), 237 (66), 209 (1), 200 (3), 185 (41), 173(7), 157 (15), 145 (6), 128 (6), 115 (5), 103 (31), 78 (16), 71 (82), 58 (100); HRMS [M–Na^+] Found: 293.0152. Calc. for $C_{12}H_{15}BrO_2$: 293.0153.

*2-Cyclohexyl-4-methyltetrahydro-2H-pyran-4-ol (**7f**)*

Syn diastereoisomer: Eluent: hexane/ethyl acetate (3:1), Rf 0.62; white solid, yield 44%, m.p. 90 °C; IR ν_{max}/cm^{-1} 3414, 2920, 2855, 1708, 1450, 1381, 1333, 1216, 1172, 1146, 939, 862, 826, 741, 649 (KBr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.72-2.04 (m, 15H), 1.31 (s, 3H), 2.47 (s, OH), 3.03 (ddd, J_1 11.27 Hz, J_2 6.18 Hz, J_3 2.09 Hz, 1H), 3.40 (td, J_1 11.86 Hz, J_2 2.89 Hz, 1H), 3.96 (ddd, J_1 11.86 Hz, J_2 6.18 Hz, J_3 2.09 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 26.2, 26.6, 28.7, 28.9, 29.0, 40.8, 43.0, 43.5, 65.5, 69.3, 79.8; MS: *m/z* 180 (M^+–18, 2%), 135 (1), 115 (46), 95 (10), 81 (7), 71 (100), 55 (22); HRMS [M–Na^+] Found: 221.1519. Calc. for $C_{12}H_{22}O_2$: 221.1517.

Anti diastereoisomer: Eluent: hexane/ethyl acetate (3:1), Rf 0.40; colorless oil, yield 27%; IR ν_{max}/cm^{-1} 3402, 2919, 2843, 1703, 1478, 1450, 1398, 1096, 1007, 863, 826, 733, 645 (film); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91-1.98 (m, 15H), 1.26 (s, 3H), 3.12 (s, OH), 3.36 (ddd, J_1 11.40 Hz, J_2 6.31 Hz, J_3 1.54 Hz, 1H), 3.73 (td, J_1 11.40 Hz, J_2 1.54 Hz, 1H), 3.84 (dd, J_1 11.40 Hz, J_2 6.31 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1, 26.2, 26.5, 28.5, 28.9, 31.9, 38.8, 41.4, 42.4, 63.7, 67.9, 77.1; MS: *m/z* 180 (M^+–18, 11%), 165 (3), 135 (2), 125 (6), 115 (78), 95 (28), 83 (17),

69 (100), 55 (41); HRMS [M–Na$^+$] Found: 221.1513. Calc. for $C_{12}H_{22}O_2$: 221.1517.

*(E)-4-Methyl-2-(prop-1-enyl)tetrahydro-2H-pyran-4-ol (**7g**)*

Syn diastereoisomer: Eluent: hexane/ethyl acetate (2:1), Rf 0.60; colorless oil, yield 25%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.43-1.62 (m, 5H), 1.70 (dq, J_1 6.55 Hz, J_2 0.80 Hz, 3H), 3.48 (td, J_1 12.19 Hz, J_2 2.46 Hz, 1H), 3.78 (ddq, J_1 11.33 Hz, J_2 6.38 Hz, J_3 1.06 Hz, 1H), 3.99 (ddd, J_1 11.95 Hz, J_2 5.11 Hz, J_3 1.99 Hz, 1H), 5.49 (ddq, J_1 15.38 Hz, J_2 6.43 Hz, J_3 1.63 Hz, 1H), 5.72 (ddq, J_1 15.38 Hz, J_2 6.49 Hz, J_3 1.05 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 27.7, 39.7, 46.4, 58.4, 73.2, 75.1, 128.0, 133.9; (CAS 69359-03-1).

Anti diastereoisomer: Eluent: hexane/ethyl acetate (2:1), Rf 0.73; colorless oil, yield 37%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.40-1.60 (m, 5H), 1.69 (dq, J_1 6.46 Hz, J_2 0.84 Hz, 3H), 3.82 (td, J_1 11.50 Hz, J_2 2.28 Hz, 1H), 3.85 (dd, J_1 6.35 Hz, J_2 1.46 Hz, 1H), 4.10 (ddq, J_1 11.50 Hz, J_2 6.46 Hz, J_3 0.84 Hz, 1H), 5.46 (ddq, J_1 15.35 Hz, J_2 6.56 Hz, J_3 1.46 Hz, 1H), 5.72 (ddq, J_1 15.35 Hz, J_2 6.48 Hz, J_3 1.09 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 31.8, 38.4, 44.7, 63.5, 67.8, 73.5, 127.2, 131.9; (CAS 69359-03-1).

*(E)-2-(But-1-enyl)-4-methyltetrahydro-2H-pyran-4-ol (**7h**)*

Syn diastereoisomer: Eluent: hexane/ethyl acetate (3:1), Rf 0.28; colorless oil, yield 41%; IR ν_{max}/cm^{-1} 3418, 2964, 2931, 2859, 1675, 1462, 1381, 1337, 1253, 1081, 971, 830 (film); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, J_1 7.49 Hz, 3H), 1.35 (s, 3H), 1.51 (t, J_1 11.83 Hz, 1H), 1.60 (dq, J_1 12.89 Hz, J_2 2.23 Hz, 1H), 1.70 (dt, J_1 12.76 Hz, J_2 2.36 Hz, 2H), 2.05 (qt, J_1 7.36 Hz, 2H), 3.49 (td, J_1 12.10 Hz, J_2 2.49 Hz, 1H), 3.80 (ddq, J_1 11.18 Hz, J_2 6.31 Hz, J_3 1.18 Hz, 1H), 4.00 (ddd, J_1 11.83 Hz, J_2 5.13 Hz, J_3 1.84 Hz, 1H), 5.46 (ddt, J_1 15.52 Hz, J_2 6.31 Hz, J_3 1.57 Hz, 1H), 5.75 (dtd, J_1 15.52 Hz, J_2 6.18 Hz, J_3 1.05 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 25.3, 25.4, 40.4, 46.6, 65.3, 68.9, 76.0, 129.3, 134.4; MS: *m/z* 170 (M$^+$, 1%), 155 (4), 141 (25), 123 (3), 107 (2), 99 (4), 83 (10), 71 (100), 55 (18); HRMS [M–Na$^+$] Found: 193.1204. Calc. for $C_{10}H_{18}O_2$: 193.1204.

Anti diastereoisomer: Eluent: hexane/ethyl acetate (3:1), Rf 0.20; colorless oil, yield 17%; IR ν_{max}/cm^{-1} 3434, 2964, 2927, 2875, 1623, 1466, 1381, 1264, 1080, 971, 908, 735, 650 (film); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, J_1 7.39 Hz, 3H), 1.27 (s, 3H), 1.45 (dd, J_1 13.71 Hz, J_2 11.40 Hz, 1H), 1.59 (dt, J_1 13.71 Hz, J_2 2.46 Hz, 2H), 1.68 (dq, J_1 13.87 Hz, J_2 6.16 Hz, 1H), 2.05 (qt, J_1 7.24 Hz, 2H), 3.83 (td, J_1 11.56 Hz, J_2 2.31, 1H), 3.84-3.90 (m, 1H), 4.12 (ddd, J_1 10.48 Hz, J_2 6.62 Hz, J_3 1.38 Hz, 1H), 5.44 (ddt, J_1 15.41 Hz, J_2 6.47 Hz, J_3 1.54 Hz, 1H), 5.76 (dtd, J_1 15.56 Hz, J_2 6.31 Hz, J_3 1.07 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 25.3, 31.8, 38.4, 44.8, 63.5, 67.9, 73.6, 129.6, 134.1; MS: *m/z* 170 (M$^+$, 2%), 152 (3), 141 (22), 123 (6), 113 (2), 99 (3), 83 (13), 71 (100), 55 (21); HRMS [M–Na$^+$] Found: 193.1202. Calc. for $C_{10}H_{18}O_2$: 193.1204.

*4-Methyl-2-propyltetrahydro-2H-pyran-4-ol (**10**)*

Syn diastereoisomer: Eluent: hexane/ethyl acetate (3:1), Rf 0.28; colorless oil, yield 21%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J_1 6.88 Hz, 3H), 1.32 (s, 3H), 1.34-1.88 (m, 9H), 3.21-3.34 (m, 1H), 3.42 (td, J_1 11.96 Hz, J_2 2.99 Hz, 1H), 3.96 (ddd, J_1 11.96 Hz, J_2 4.98 Hz, J_3 2.99 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 18.7, 25.4, 38.4, 40.7, 46.6, 65.4, 68.9, 75.2; (CAS 723340-91-8).

Anti diastereoisomer: Eluent: hexane/ethyl acetate (3:1), Rf 0.46; colorless oil, yield 40%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J_1 6.98 Hz, 3H), 1.25 (s, 3H), 1.27-1.76 (m, 8H), 1.95 (s, OH), 3.53-3.89 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 18.5, 31.7, 38.2, 38.6, 44.6, 63.5, 67.7, 72.6; (CAS 723340-91-8).

*2-Isobutyl-4-methyltetrahydro-2H-pyran-4-ol (**11**)-Florol®*

Syn diastereoisomer: Eluent: hexane/ethyl acetate (3:1), Rf 0.48; colorless oil, yield 35%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, J_1 6.54 Hz, 6H), 1.12 (ddd, J_1 13.66 Hz, J_2 8.39 Hz, J_3 4.55, 1H), 1.25 (s, 3H), 1.28 (dd, J_1 13.66 Hz, J_2 11.52 Hz, 1H), 1.40-1.50 (m, 3H), 1.53 (dtl, J_1 13.66 Hz, J_2 2.13 Hz, 1H), 1.63 (td, J_1 13.66 Hz, J_2 5.83, 1H), 1.78 (hept, J_1 6.54 Hz, 1H), 3.19 (sl, OH), 3.65-3.84 (m, 2H), 3.76 (td, J_1 12.09 Hz, J_2 2.13 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4, 23.3, 24.3, 31.7, 38.7, 45.1, 45.4, 63.6, 67.8, 71.2; (CAS 723440-93-0).

Anti diastereoisomer: Eluent: hexane/ethyl acetate (3:1), Rf 0.22; colorless oil, yield 52%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, J_1 6.54 Hz, 6H), 1.17 (ddd, J_1 12.66 Hz, J_2 8.25 Hz, J_3 4.55 Hz, 1H), 1.32 (s, 3H), 1.37 (t, J_1 12.24 Hz, 1H), 1.49 (ddd, J_1 12.66 Hz, J_2 8.25 Hz, J_3 5.97 Hz, 1H), 1.58 (dq, J_1 12.66 Hz, J_2 2.13 Hz, 1H), 1.63 (dt, J_1 12.66 Hz, J_2 2.13 Hz, 1H), 1.71 (td, J_1 12.66 Hz, J_2 5.12 Hz, 1H), 1.77 (hept, J_1 6.54 Hz, J_2 1.56 Hz, 1H), 2.96 (s, OH), 3.32-3.37 (m, 1H), 3.41 (td, J_1 12.24 Hz, J_2 2.13 Hz, 1H), 3.95 (ddd, J_1 12.66 Hz, J_2 5.12 Hz, J_3 1.56 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 23.1, 24.3, 25.3, 40.5, 45.4, 46.9, 65.3, 68.8, 73.6; (CAS 723440-93-0).

*4-Methyl-2-propyltetrahydro-2H-pyran-4-yl acetate (**12**)-Clarycet®*

To a stirred solution of 4-methyl-2-propyltetrahydro-2*H*-pyran-4-ol (**10**) (500 mg, 3.16 mmol) in pyridine (3 mL)

are added acetic anhydride (322 mg, 3.16 mmol, 1.0 equiv). The mixture is magnetically stirred at room temperature for 7 h. After completion of acetylation, the solution is neutralized with solid $NaHCO_3$, filtered and solvent evaporated. Purification by flash column chromatography on silica gel, using a mixture of hexane/ethyl acetate (10:1) as eluent, afforded 180 mg (90%) of the title compound as colourless oil.

Syn diastereoisomer: Colorless oil, yield 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J_1 7.20 Hz, 3H), 1.54 (ddq, J_1 12.60 Hz, J_2 11.50 Hz, J_3 0.90 Hz, 1H), 1.30-1.55 (m, 4H), 1.62 (t, J_1 0.90 Hz, 3H), 1.86 (dddq, J_1 12.80 Hz, J_2 12.60 Hz, J_3 5.30 Hz, J_4 0.90 Hz, 1H), 1.97 (s, 3H), 2.03 (dddd, J_1 12.80 Hz, J_2 2.30 Hz, J_3 2.20 Hz, J_4 1.90 Hz, 1H), 2.10 (dt, J_1 12.60 Hz, J_2 2.20 Hz, 1H), 3.33 (m, 1H), 3.46 (ddd, J_1 12.60 Hz, J_2 12.10 Hz, J_3 2.30 Hz, 1H), 3.93 (ddd, J_1 12.10 Hz, J_2 5.30 Hz, J_3 1.90 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 19.1, 21.4, 24.4, 36.3, 37.8, 42.1, 58.5, 66.7, 73.9, 170.2; (CAS 723340-91-8).

Anti diastereoisomer: Colorless oil, yield 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J_1 7.20 Hz, 3H), 1.02 (dd, J_1 13.80 Hz, J_2 11.30 Hz, 1H), 1.28 (ddd, J_1 14.10 Hz, J_2 12.60 Hz, J_3 5.30 Hz, 1H), 1.25-1.60 (m, 4H), 1.68 (s, 3H), 2.05 (dddd, J_1 14.10 Hz, J_2 2.30 Hz, J_3 2.10 Hz, J_4 1.60 Hz, 1H), 2.20 (dt, J_1 13.80 Hz, J_2 2.30 Hz, 1H), 3.52 (dddd, J_1 11.40 Hz, J_2 7.40 Hz, J_3 4.60 Hz, J_4 2.30 Hz, 1H), 3.57 (ddd, J_1 12.60 Hz, J_2 11.60 Hz, J_3 2.10 Hz, 1H), 3.71 (ddd, J_1 11.60 Hz, J_2 5.30 Hz, J_3 1.60 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 18.7, 21.7, 22.5, 30.4, 37.8, 38.4, 43.5, 64.6, 74.3, 80.1, 170.3; (CAS 723340-91-8).

*2-Ethyl-4,7-dimethyloctahydro-2H-chromen-4-ol (**15**)*

Diastereoisomeric mixture: Eluent: hexane/ethyl acetate (4:1); colorless oil, yield 49%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85-1.25 (m, 15H), 1.35-1.50 (m, 3H), 1.51-1.63 (m, 2H), 1.68-1.82 (m, 5H), 1.87-1.99 (m, 3H), 3.07 (td, J_1 10.44 Hz, J_2 4.24 Hz, 1H), 3.24-3.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.9, 21.4, 22.2, 23.1, 29.1, 31.5, 34.5, 41.6, 48.0, 52.4, 70.8, 75.9, 76.9. (CAS 134869-45-7).

*2-Isopropyl-4,7-dimethyloctahydro-2H-chromen-4-ol (**16**)*

Diastereoisomeric mixture: Eluent: hexane/ethyl acetate (7:1); colorless oil, yield 66%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84-1.09 (m, 14H), 1.12-1.21 (m, 4H), 1.35-1.50 (m, 2H), 1.61-1.75 (m, 5H), 1.85-1.99 (m, 3H), 3.00-3.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3 (2C), 21.0, 25.8, 26.2, 31.5, 32.5, 34.6, 36.5, 40.7, 42.3, 76.0, 78.3, 80.9. (CAS 134869-70-8)

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References

1. Olier, C.; Kaafarani, M.; Gastaldi, S.; Bertrand, M. P.; *Tetrahedron* **2010**, *66*, 413; Vascondellos, M. L. A. A.; Miranda, L. S. M. A.; *Quim. Nova* **2006**, *29*, 834; Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L.; *Org. Lett.* **2002**, *4*, 577; Hiebel, M. A.; Pelotier, B.; Piva, O.; *Tetrahedron* **2007**, *63*, 7874; Yadav, J. S.; Reddy, B. V. S.; Maity, T.; Kumar, G. G. K. S.; *Tetrahedron Lett.* **2007**, *48*, 8874; Chan, K. P.; Seow, A. H.; Loh, T. P.; *Tetrahedron Lett.* **2007**, *48*, 37; Yadav, J. S.; Reddy, B. V. S.; Maity, T.; Kumar, G. G. K. S. N.; *Tetrahedron Lett.* **2007**, *48*, 7155; Yadav, J. S.; Reddy, B. V. S.; Kumar, G. G. K. S. N.; Swamy, T.; *Tetrahedron Lett.* **2007**, *48*, 2205; Yadav, J. S.; Reddy, B. V. S.; Kumar, G. M.; Murthy, C. V. S. R.; *Tetrahedron Lett.* **2001**, *42*, 89.
2. Reddy, U. C.; Bondalapati, S.; Saikia, A. K.; *J. Org. Chem.* **2009**, *74*, 2605; Perron, F.; Albizati, K. F.; *J. Org. Chem.* **1987**, *52*, 4130; Clarke, P. A.; Santos, S.; *Eur. J. Org. Chem.* **2006**, 2045, and references cited therein; Class, Y. J.; DeShong, P.; *Chem. Rev.* **1995**, *95*, 1843; Kopecky, D. J.; Rychnovsky, S. D.; *J. Am. Chem. Soc.* **2001**, *123*, 8420; Wang, Y.; Janjic, J.; Kozmin, S. A.; *J. Am. Chem. Soc.* **2002**, *124*, 13670; Tian, X. T.; Jaber, J. J.; Rychnovsky, S. D.; *J. Org. Chem.* **2006**, *71*, 3176; Hu, Y.; Skalitzky, D. J.; Rychnovsky, S. D.; *Tetrahedron Lett.* **1996**, *37*, 8679; Arundale, E.; Mikeska, L. A.; *Chem. Rev.* **1952**, *51*, 505; Miles, R. B.; Davis, C. E.; Coates, R. M.; *J. Org. Chem.* **2006**, *71*, 1493; Yadav, J. S.; Reddy, B. V. S.; Kumar, G. G. K. S. N.; Reddy, G. M.; *Tetrahedron Lett.* **2007**, *48*, 4903.
3. Gupta, P.; Sethi, V. K.; Taneja, S. C.; Shah, B. A.; Andotra, S. S.; Koul, S.; Chimni, S. S.; Oazi, G. N.; *Helv. Chim. Acta* **2007**, *90*, 196.
4. Abate, A.; Brenna, E.; Fronza, G.; Fuganti, C.; Gatti, F. G.; Serra, S.; Zardoni, E.; *Helv. Chim. Acta* **2004**, *87*, 765.
5. Alfonsi, K.; Colberg, J.; Dunn, P. J.; Fevig, T.; Jennings, S.; Johnson, T. A.; Kleine, H. P.; Knight, C.; Nagy, M. A.; Perry, D. A.; Stefaniak, M.; *Green Chem.* **2008**, *10*, 31; Abaee, M. S.; Mojtahedi, M. M.; Forghani, S.; Ghandchi, N. M.; Forouzani, M.; Sharifi, R.; Chaharnazm, B.; *J. Braz. Chem. Soc.* **2009**, *20*, 1895; Lenardão, E. J.; Trecha, D. O.; Ferreira, P. C.; Jacob, R. G.; Perin, G.; *J. Braz. Chem. Soc.* **2009**, *20*, 93; Bueno, M. A.; Silva, L. R. S. P.; Corrêa, A. G.; *J. Braz. Chem. Soc.* **2008**, *19*, 1264; Almeida, Q. A. R.; Pereira, M. L. O.; Coelho, R. B.; Carvalho, E. M.; Kaiser, C. R.; Jones Jr., J.; Silva, F. M.; *J. Braz. Chem. Soc.* **2008**, *19*, 894.

6. Reddy, B. M.; Sreekanth, P. M.; Lakshmanan, P.; *J. Molec. Catal. A: Chem.* **2006**, *237*, 93; Bartoli, G.; Bartolacci, M.; Bosco, M.; Foglia, G.; Giuliani, A.; Marcantoni, E.; Sambri, L.; Torregiani, E.; *J. Org. Chem.* **2003**, *68*, 4594; Bartoli, G.; Bartolacci, M.; Giuliani, A.; Marcantoni, E.; Massaccesi, M.; Torregiani, E.; *J. Org. Chem.* **2005**, *70*, 169; Bartoli, G.; Bosco, M.; Giuli, S.; Giuliani, A.; Lucarelli, L.; Marcantoni, E.; Sambri, L.; Torregiani, E.; *J. Org. Chem.* **2005**, *70*, 1941; Bartoli, G.; Fernández-Bolaños, J. G.; Di Antonio, G.; Foglia, G.; Giuli, S.; Gunnella, R.; Mancinelli, M.; Marcantoni, E.; Paoletti, M.; *J. Org. Chem.* **2007**, *72*, 6029; Chen, J.-X.; Liu, M.-C.; Yang, X.-L.; Ding, J.-C.; Wu, H.-Y.; *J. Braz. Chem. Soc.* **2008**, *19*, 877; Costa, J. S.; Pisoni, D. S.; Silva, C. B.; Petzhold, C. L.; Russowsky, D.; Ceschi, M. A.; *J. Braz. Chem. Soc.* **2009**, *20*, 1448.
7. Sprecker, M. A.; Belko, R. P.; Hanna, M. R.; Beck, C. E. J.; Brucato, S. M.; *US pat. 4,999,439* **1991**. (pp. 48).
8. Dos Santos, A. A.; Brito Jr., G. A.; Archilha, M. V. L.; Bele, T. G. A.; Dos Santos, G. P.; De Mello, M. B. M.; *J. Braz. Chem. Soc.* **2009**, *20*, 42.
9. Zukerman-Schpector, J.; Dos Santos, A. A.; Macedo, A.; Wendler, E. P.; Brito Jr., G. A.; Tiekink, E. R. T.; *Z. Kristallogr.* **2008**, *223*, 471.
10. The crystals of **7f** are orthorhombic, space group $P2_12_12_1$, with a = 5.5714(10) Å, b = 11.0182(12) Å, c = 18.753(3) Å, V = 1151.2(3) Å^3, D_x = 1.144 g cm^{-3}, and Z = 4. The structure was solved by direct-methods and refined by full-matrix least-squares to final R = 0.050. Tiekink, E. R. T.; Macedo, A.; Wendler, E. P.; Dos Santos, A. A.; Zukerman-Schpector, J.; *Acta Cryst.* **2010**, *E66*, o1233.

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