152. Synthesis of *cis* and *trans* Whisky and Cognac Lactones by the Regiocontrolled Alkylation of 2-(Trimethylsiloxy)furan

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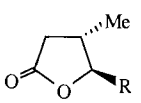
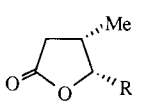
(25.VII.89)

The racemic *cis*- and *trans*-5-butyltetrahydro-4-methylfuran-2-ones (= whisky lactones) and their higher homologues tetrahydro-4-methyl-5-pentylfuran-2-ones (= cognac lactones) have been prepared in 2–3 steps from 2-(trimethylsiloxy)furan. Regioselective alkylation of the latter afforded the 5-butyl- and 5-pentylfuran-2(5*H*)-ones which served as precursors for the stereocontrolled construction of either diastereoisomer of the beverage lactones. The structure and tautomerization of the diazomethane adducts of these 5-alkylfuran-2(5*H*)-ones are also described.

Introduction. – The *trans*- and *cis*-5-butyltetrahydro-4-methylfuran-2-ones (= 3-methyloctan-4-olides; **1a** and **2a**, respectively) have been identified as aroma components of aged alcoholic beverages such as whisky, brandy, and wine [1] [2]. Since these substances are extracted by whisky or other spirits from oak barrels in which they are kept for maturing, they are whimsically known as 'whisky', 'oak', or 'quercus' lactones. More recently, tetrahydro-4-methyl-5-pentylfuran-2-one (= 3-methylnonan-4-olide) of the presumed *trans* configuration, **1b**, has been detected in cognac and so referred to as 'cognac' lactone [3]. In view of the importance of these substances as flavors and the need for stereoselective routes to 4,5-disubstituted tetrahydrofuran-2-ones [4], their structures have become popular for testing new synthetic methodology[1]).



1a R = Bu
b R = pentyl



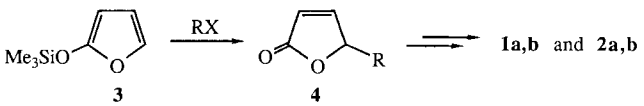
2a R = Bu
b R = pentyl

We have previously demonstrated that furan-2-olates [10–12], on prenylation or aldolization, provide practical access to a wide variety of biologically active lactones such as eldanolide [10], cavernosine [13], and bromobeckerelide [14]. We now report a simple and versatile synthesis of racemic *trans* and *cis* whisky and cognac lactones by using 2-(trimethylsiloxy)furan (**3**) at the latent butenolide entity.

[1]) For other syntheses of racemic whisky and/or cognac lactones, see [5–7]; their enantiomers have also been prepared [7–9].

Results. – Our plan entails the regioselective alkylation of **3** to generate the butenolides **4** substituted at the C(4) position[2]). Subsequently, the Me group is introduced at C(3) either directly or indirectly in two steps to give the *trans*- and *cis*-γ-lactones **1** and **2** *(Scheme 1)*.

Scheme 1

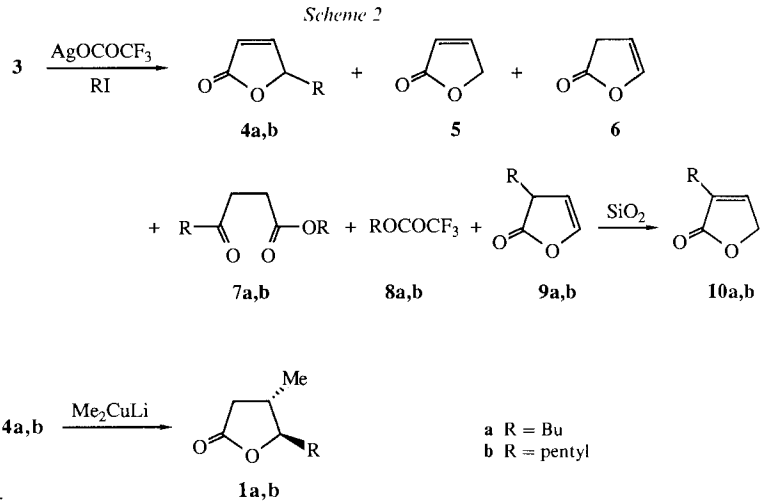


3 **4**

The alkylation of 2-(trimethylsiloxy)furan (**3**) required an appropriate choice of conditions and alkyl halide. Treatment of **3** with BuI in the presence of the usual *Lewis* acids such as $ZnCl_2$, $ZnBr_2$, $SnCl_4$, and $TiCl_4$ was ineffective. Either no reaction occurred, other than hydrolysis of **3** to the isomeric furanones **5** and **6**, or polymeric products were formed. Fortunately, silver salts proved to be the reagents of choice for bringing about the desired alkylation. High regioselectivity at the C(5) position was observed together with high efficiency. Among the salts tried, silver trifluoroacetate, heptafluorobutyrate, and trifluoromethanesulfonate were the best, giving **4a** in yields of 76, 73, and 58%, respectively. Examination of the reaction with $AgOCOCF_3$ revealed that several minor by-products were formed. Furanone **5**, occasionally accompanied by its isomer **6**, as well as traces of the γ-keto ester **7a** [17] were observed *(Scheme 2)*. In addition, butyl trifluoroacetate (**8a**) was formed [18] [19], but also a small amount of 2-alkylbutenolide **9a**. Typically, the ratio **4a**/**9a** was 10:1. The latter was hard to detect in the reaction mixture as its ^{1}H-NMR spectrum overlapped with that of **6**, but on chromatography over silica gel, **9a** was converted to its isomer **10a** [20], the NMR spectrum of which was easily distinguishable *(Scheme 2)*.

As $AgOCOCF_3$ is hygroscopic, experiments were performed incorporating molecular sieves as a precautionary measure against adventitious moisture. With this modification,

Scheme 2

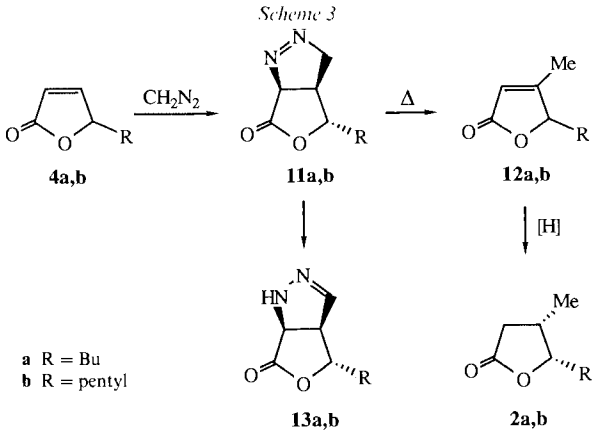


[2]) For a preliminary account of the alkylation of **3**, see [15].

the formation of **7a** which arises by hydrolysis [15] was prevented, but the yield of **4a** was essentially the same (77%) as was the regioselectivity observed. The same procedure using pentyl iodide and **3** gave **4b** [21] in 78% yield and displayed similar C(3) *vs.* C(5) regioselectivity (**4b**/**9b** ≈ 10:1).

Having supplies of **4a** and **4b** in hand, all that remained was their transformation to **1a** and **1b**. Methylation with lithium dimethylcuprate [10] directly converted **4a,b** to the *trans* lactones **1a,b** *(Scheme 2)*. Introduction of a *cis*-disposed methyl group was not so straightforward. The method chosen [22–24] exploited the 1,3-dipolar addition of diazomethane to **4a,b**. The adducts **11a,b** were thermolyzed without purification to produce the corresponding 4,5-dialkylfuran-2(5*H*)-ones **12a** [25] and **12b** in 81 and 75% yields, respectively *(Scheme 3)*.

Scheme 3



Although not essential for the purpose of our synthesis, we decided to determine the structure of **11a,b**. They were prepared in a separate experiment and were sufficiently stable to be isolated by chromatography over silica gel. Inspection of these adducts by ^{1}H- and ^{13}C-NMR revealed that they are formed as single stereoisomers in which the *cis*-fused dihydropyrazole ring is *trans* to the alkyl side chain of the lactone moiety. Since coupling constants are of little value for configurational assignments in five-membered rings [26], their relative configuration was deduced by means of NOE difference experiments on **11a**

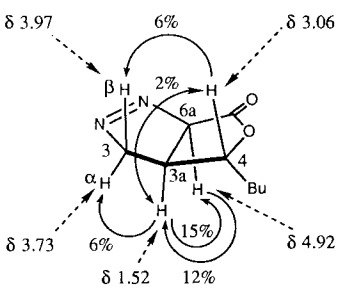


Figure. *NOE enhancements* [%] *in* **11a**.

(see *Fig.*). Irradiation of H–C(6a) had no effect on H–C(4), H–C(4), H_α–C(3), or H_β–C(3), whereas an NOE enhancement of 12% was observed for H–C(3a). Saturation of H–C(3a) caused a positive NOE on H–C(6a) (15%), H–C(4) (2%), and H_α–C(3) (6%), while irradiation of H–C(4) enhanced the signals of H–C(3a) (2%) and H_β–C(3) (6%). Furthermore, it was found that **11a,b** readily tautomerize to **13a,b** upon standing in $CDCl_3$. The ^{1}H- and ^{13}C-NMR shifts of 6.76 and *ca.* 142.5 ppm observed for the imino methine group in **13** confirm the structure [27].

Next, stereocontrolled reduction of **12a,b** was needed to produce the *cis*-lactones **2a,b**. Although several related *cis*-dialkylbutanolides have been prepared this way [24] [28] [29], there appears to be no record of any study on the effect of the reducing agent on stereoselectivity[3]). Consequently, a brief search for the best conditions for reduction was undertaken (see the *Table*). Hydrogenation of **12a** by heterogeneous and homogeneous

Table. *Reduction of* **12a** *to* cis *and* trans *Whisky Lactones* (**2a** and **1a**, resp.)

Entry	Reaction conditions[a])	*cis*/*trans* Ratio[b])
1	H_2, Rh/Al_2O_3, MeOH, 3 h	6.1:1
2	H_2, Rh/Al_2O_3, MeOH, 10% HCl soln., 3 h	6.7:1
3	H_2, Rh/Al_2O_3, THF, 3 h	5.7:1
4	H_2, Rh/Al_2O_3, AcOEt, 3 h	5.7:1
5	H_2, Pd/Al_2O_3, AcOEt, 3 h	3.6:1
6	H_2, PtO_2, AcOEt, 8 h	3.0:1
7	H_2, Pt/C, AcOEt, 6 h	1.9:1
8	H_2, *Raney* Ni, EtOH, 3 h[c])	9.0:1
9	H_2, $(Ph_3P)_3RhCl$, C_6H_6, 16 h	1.2:1
10	$NaBH_4$, $NiCl_2 \cdot 6\,H_2O$, MeOH, 1.5 h	6.1:1
11	$LiBH_4$, $NiCl_2 \cdot 6\,H_2O$, MeOH, 1.5 h	2.6:1

[a]) All hydrogenations, except *Entry 8*, were performed at 24° using 10% (wt./wt.) of catalyst to substrate (*Entries 1–9*). Hydride reductions were carried out at 0° for 1 h, then at 24° for 0.5 h, *cf.* [29] (*Entries 10* and *11*).

[b]) Ratios and yields were determined by ^{1}H-NMR (360 MHz) of the crude mixture of products after workup. Yields were $\geq$ 94% in all cases except for *Entries 7* and *9* where only *ca.* 50 and 80% conversion was effected.

[c]) Slightly basic *Raney* Ni was used at *ca.* 1:1 (wt./wt.) ratio to substrate.

catalysis (*Entries 1–9*) as well as hydride reduction (*Entries 10* and *11*) were all successful to various degrees. Even so, the highest selectivity (**2a**/**1a** = 9:1) was conferred by hydrogenation in the presence of *Raney* nickel (*Entry 8*). Separation of the resulting mixture by column chromatography furnished **2a** and **1a** [7] in 81 and 5% yields, respectively. Similarly, **12b** was transformed to **2b** and **1b** [6] (ratio 10:1) in 83 and 4% yields, after purification.

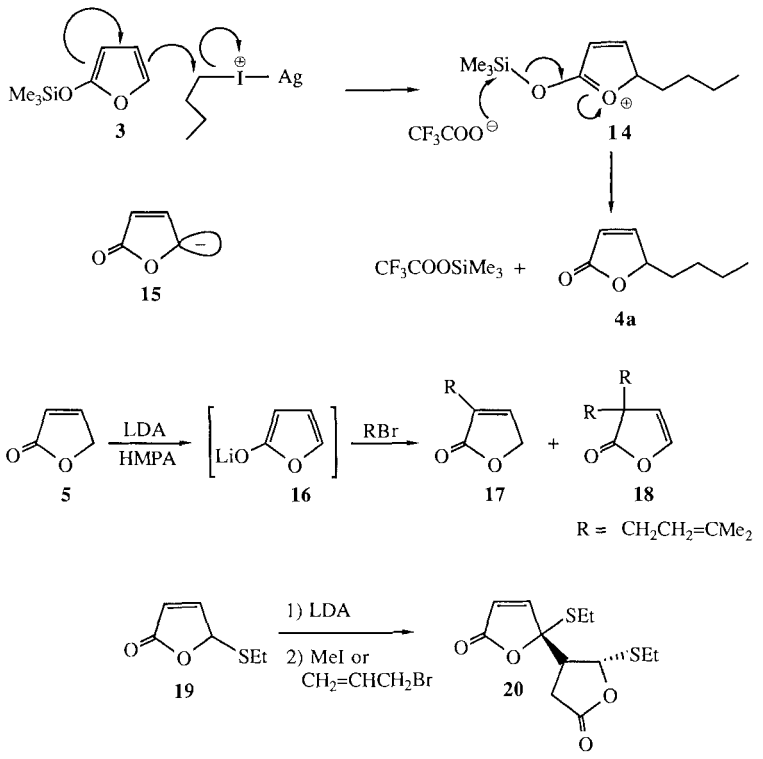
Discussion. – A noteworthy feature of the above synthesis is the simple one-step assembly of the butenolides **4a** and **4b**[4]). At first sight, the transformation of **3** to **4** appears unremarkable. It is nevertheless a fact that in general butyl iodide and S_N1-unreactive halides fail to alkylate silyl enol ethers and silyl ketene acetals under *Lewis*-acid

[3]) For the effect of reaction conditions on the stereochemistry of hydrogenation of some α,β-unsaturated ketones, see [30].

[4]) For alternative syntheses of 4-alkylbutenolides, see refs. cit. in [15].

catalysis [31–33]. Clearly, to bring about such an alkylation, the halide must be activated without damaging the acid-sensitive furan. In the present instance, silver salts, unlike the commonly used *Lewis* acids typified by $ZnBr_2$ and $SnCl_4$ [33], are 'soft' electrophiles and complex with the 'soft' iodide, thereby engendering attack by **3** in an S_N2 fashion to produce the stable cation **14** as the primary event. Subsequent desilylation by trifluoroacetate unmasks the alkylbutenolide **4** *(Scheme 4)*.

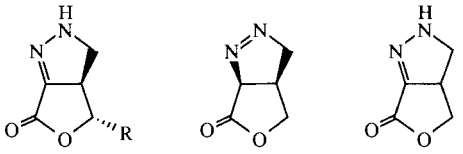
Scheme 4



Since **3** furnishes the 4-monoalkylated butenolides with high regioselectivity and under exceptionally mild conditions, it may be considered as the synthetic equivalent of the γ anion **15** of furan-2(5*H*)-one [34]. In contrast to **3**, lithium furan-2-olate (**16**) is alkylated exclusively at the 3-position. For example, when **16** is generated *in situ* from furan-2(5*H*)-one (**5**) with lithium diisopropylamide (LDA) and hexamethylphosphoramide (HMPA), its reaction with prenyl bromide gives a mixture of the mono- and disubstituted butenolides **17** and **18** in *ca.* 30% yield *(Scheme 4)* [35]. A recent attempt to alkylate 5-(ethylthio)furan-2(5*H*)-one (**19**) *via* its lithium furanolate resulted in self-condensation to the *Michael* adduct **20** *(Scheme 4)* [36]. These findings dramatically underscore the net difference in reactivities exhibited between the silicon and lithium reagents.

The tautomerization of **11** to **13** deserves further comment. It is well established that most 4,5-dihydro-3*H*-pyrazoles readily rearrange to the more stable 4,5-dihydro-1*H*-pyrazoles [27] [37], but little is known about the behavior of bicyclic derivatives like **11**

[38]. In principle, **11** could tautomerize either to **13** or **21**. Calculation[5]) of the heats of formation of **11a**, **13a**, and **21** (R = Bu) using the AM1 semi-empirical quantum chemical method [39] gave values of −57.4, −50.2, and −37.7 kcal/mol, respectively. Accordingly, the absence of the apparently conjugated tautomer **21** is explained as it is predicted to be the least stable. These results also cast doubt on a report [38] that the parent adduct **22** isomerized exclusively to **23**.



21 **22** **23**

Conclusion. – The regiocontrolled alkylation of 2-(trimethylsiloxy)furan (**3**) affords a remarkably short route to racemic *cis* and *trans* whisky and cognac lactones. Moreover, the present approach to **12** from **3** is valuable synthetically in its own right since the methods available for constructing 4,5-dialkylfuran-2(5*H*)-ones are limited in number and scope [25] [40]. The application of this new furanolate-based methodology to the synthesis of more complex natural products is presently under investigation, and the results will be disclosed in due course.

We are indebted to the *Swiss National Science Foundation* (grant No. 2.632-0.87) for support of this work. We thank Prof. *J. M. J. Tronchet* for the AM1 calculations.

Experimental Part

1. *General.* All solvents were distilled prior to use. Diazomethane was prepared from *N*-methyl-*N*-nitroso-4-toluenesulfamide [41]. Commercial *(Fluka) Raney* Ni 'ready for use' was washed successively with aq. 1M NaOH and EtOH before use. TLC: silica gel *60* F_{254} (*Merck*, layer thickness 0.20 mm). Column chromatography: *Merck* silica gel *60* (230–400 mesh). IR: *Perkin-Elmer-681* spectrometer. ^{1}H- and ^{13}C-NMR: *Bruker-FT-360* (360 MHz) and *Varian-XL-200* (50 MHz) spectrometer, resp.; chemical shifts (δ) in ppm relative to internal TMS (= 0 ppm), coupling constants (J) in Hz; commercial $CDCl_3$ was used without further purification unless otherwise indicated; ^{13}C-NMR spectra are recorded using APT [42] and are assigned an o (odd) for C-atoms with 1 or 3 attached H-atoms and e (even) for C-atoms with no or 2 attached H-atoms. MS: *m/z* (intensities in % rel. to base peak); *Finnigan GC/MS-4023* instrument using the *INCOS* data system; electron impact, 70 eV. Elemental analyses were carried out by Dr. *H. J. Eder*, Service de Microbiochimie, Institute de Chimie Pharmaceutique, Université de Genève.

2. *Alkylation of 2-(Trimethylsiloxy)furan* (**3**). To a stirred suspension of $AgOCOCF_3$ (574 mg, 2.6 mmol) in CH_2Cl_2 (5 ml), **3** (313 mg, 2.0 mmol) and BuI (478 mg, 2.6 mmol) were added under Ar at −78°. The temp. was increased to 10° within 4 h, and the mixture was filtered through *Celite* and evaporated. Examination of the resulting yellow oil (365 mg) by ^{1}H-NMR ($CDCl_3$) revealed that the main product *5-butylfuran-2(5H)-one* (**4a**) was accompanied by traces of *3-butylfuran-2(3H)-one* (**9a**), *butyl 4-oxooctanoate* (**7a**), *butyl trifluoroacetate* (**8a**), and the *furan-2(5H)-* and *-2(3H)-ones* (**5** and **6**, resp.). The signals due to **9a** at 3.20, 5.46, and 6.79 ppm are in agreement with those of related furan-2(3*H*)-ones [43]. Compounds **4a** and **7a** were isolated by column chromatography (AcOEt/hexane 1:2).

4a: 213 mg (76%). Colorless oil [16]. R_f 0.29 (AcOEt/hexane 1:2). ^{1}H-NMR ($CDCl_3$): 0.91 (*t*, *J* = 7.3, 3 H); 1.27–1.86 (*m*, 6 H); 5.05 (*m*, 1 H); 6.10 (*dd*, *J* = 5.6, 1.8, 1 H); 7.46 (*dd*, *J* = 5.6, 1.5, 1 H). ^{13}C-NMR ($CDCl_3$): 13.8 (o); 22.4 (e); 27.0 (e); 32.8 (e); 83.4 (o); 121.5 (o); 156.4 (o); 173.2 (e). Data in agreement with [16]. Traces (*ca.* 4%) of *3-butylfuran-2(5H)-one* (**10a**) [20] were seen in the ^{1}H-NMR.

7a: 8 mg (3%). Pale yellow oil. R_f 0.57 (AcOEt/hexane 1:2). IR (CCl_4): 1741*s*, 1724*s*. ^{1}H-NMR ($CDCl_3$): 0.89 (*t*, *J* = 7.5, 3 H); 0.91 (*t*, *J* = 7.3, 3 H); 1.20–1.46 (*m*, 6 H); 1.53–1.67 (*m*, 2 H); 2.47 (*t*, *J* = 7.4, 2 H); 2.60 (*t*, *J* = 6.5,

[5]) Calculations were performed on a *Silicon Graphics 4D70GT* workstation using the AMPAC program (QCPE No. 527) in its UNIX implementation (QUANTA™) as developed by the *Polygen Corporation*.

2 H); 2.74 (*t*, *J* = 6.5, 2 H); 4.09 (*t*, *J* = 6.7, 2 H). ^{13}C-NMR ($CDCl_3$): 13.7 (o); 13.9 (o); 19.1 (e); 22.3 (e); 25.9 (e); 28.0 (e); 30.6 (e); 37.0 (e); 42.5 (e); 64.5 (e); 173.0 (e); 209.2 (e). MS: 214 (0, M^+), 172 (37), 141 (48), 101 (100), 98 (80), 85 (83), 57 (98). For the fragmentation of related keto esters, see [44].

Repetition of this experiment using $AgOCOCF_2CF_2CF_3$ or $AgOSO_2CF_3$ instead of $AgOCOCF_3$ gave **4a** in yields of 73 and 58%, resp.

3. *Alkylation of* **3** *in the Presence of Molecular Sieves. Procedure 2* was repeated by using a suspension of freshly dried 4-Å molecular sieves (0.5 g) and $AgOCOCF_3$ (574 mg, 2.6 mmol) in CH_2Cl_2 (5 ml), prior to the addition of **3** (313 mg, 2.0 mmol) and BuI (478 mg, 2.6 mmol). Yield of **4a**, 77% (215 mg).

Using this procedure with pentyl iodide (515 mg, 2.6 mmol) instead of BuI, *5-pentylfuran-2(5*H*)-one* (**4b**; 239 mg, 78%) was obtained as a colorless oil, R_f 0.31 (AcOEt/hexane 1:2). ^{1}H-NMR ($CDCl_3$): 0.89 (*t*, *J* = 7.3, 3 H); 1.18–1.50 (*m*, 6 H); 1.60–1.80 (*m*, 2 H); 5.04 (*m*, 1 H); 6.09 (*dd*, *J* = 5.7, 1.8, 1 H); 7.46 (*dd*, *J* = 5.7, 1.5, 1 H). ^{13}C-NMR ($CDCl_3$): 13.9 (o); 22.4 (e); 24.6 (e); 31.4 (e); 33.1 (e); 83.5 (o); 121.4 (o); 156.4 (o); 173.2 (e). Data in agreement with [21]. *Ca.* 3% of *3-pentylfuran-2(5*H*)-one* (**10b**) [45] was seen in the ^{1}H-NMR.

4. *Conjugate Cuprate Addition to* **4**. To a stirred suspension of CuI (762 mg, 4 mmol) in Et_2O (10 ml) at –20° under Ar was added dropwise a soln. of MeLi in Et_2O (1.6M; 5 ml, 8 mmol), and the resulting soln. of $LiCuMe_2$ was cooled to –78°. A soln. of **4** (0.8 mmol) in Et_2O (3 ml) was then added dropwise and the mixture was warmed to 0° within 2.5 h. After addition of aq. HCl soln. (1M, 10 ml), the mixture was filtered through *Celite* and extracted with Et_2O (4 × 10 ml). The combined org. layers were dried ($MgSO_4$) and evaporated to give a pale yellow oil which, on column chromatography (AcOEt/hexane 1:3→1:2), furnished **1**.

trans-*Whisky Lactone* (= trans-*5-Butyltetrahydro-4-methylfuran-2-one*) (**1a**): 84% from **4a**. Colorless oil. R_f 0.22 (petroleum ether (60–80°)/Et_2O 3:1). IR, ^{1}H- and ^{13}C-NMR, MS: as reported in [7].

trans-*Cognac Lactone* (= trans-*Tetrahydro-4-methyl-5-pentylfuran-2-one*) (**1b**): 85% from **4b**. Colorless oil. R_f 0.23 (petroleum ether (60–80°)/Et_2O 3:1). ^{1}H-NMR ($CDCl_3$): 0.87 (*t*, *J* = 7.0, 3 H); 1.13 (*d*, *J* = 6.4, 3 H); 0.98–1.75 (*m*, 8 H); 2.19 (*m*, 2 H); 2.67 (*m*, 1 H); 4.02 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$): 14.0 (o); 17.4 (o); 22.4 (e); 25.4 (e); 31.5 (e); 33.9 (e); 36.1 (o); 37.1 (e); 87.4 (o); 176.6 (e). These data agree with literature values [6] [9].

5. *One-Pot Procedure for Converting* **4** *to* **12**. To a stirred soln. of **4** (1.4 mmol, 196 mg of **4a** or 216 mg of **4b**) in Et_2O (3 ml), a soln. of CH_2N_2 (*ca.* 7 mmol) in Et_2O (25 ml) was added within 30 min at 24°. After 21 h of stirring with exclusion of light, the mixture was evaporated and the resulting crude **11** (yellow oil) heated at 150° for 30 min. Furanone **12** was isolated by column chromatography (AcOEt/hexane 1:2).

*5-Butyl-4-methylfuran-2(5*H*)-one* (**12a**): 175 mg (81%). Colorless oil. R_f 0.31 (AcOEt/hexane 1:2). IR (CCl_4): 2962*s*, 2938*s*, 2880*m*, 2863*m*, 1770*s*, 1650*m*, 1470*m*, 1440*m*, 1383*m*, 1292*m*, 1170*m*, 1155*m*, 1110*w*, 1080*w*, 980*m*. ^{1}H-NMR ($CDCl_3$): 0.85 (*t*, *J* = 7.3, 3 H); 1.28–1.60 (*m*, 5 H); 1.84–1.98 (*m*, 1 H); 2.06 (*dd*, *J* = 1.5, 0.9, 3 H); 4.80 (*m*, 1 H); 5.76 (*dq*, *J* = 1.5, 1.5, 1 H). ^{13}C-NMR ($CDCl_3$): 13.8 (o); 13.9 (o); 22.3 (e); 26.4 (e); 31.6 (e); 84.6 (o); 116.8 (o); 168.7 (e); 173.3 (e). MS: 154 (13, M^+), 125 (23), 112 (10), 98 (65), 97 (97), 85 (24), 69 (100), 57 (19).

*4-Methyl-5-pentylfuran-2(5*H*)-one* (**12b**): 176 mg, 75%. Pale yellow oil. R_f 0.28 (AcOEt/hexane 1:2). IR (CCl_4): 2960*m*, 2940*m*, 2870*w*, 1770*s*, 1650*m*, 1470*w*, 1440*w*, 1382*w*, 1295*w*, 1170*m*, 1155*m*, 1112*w*, 1080*w*, 985*w*, 950*m*. ^{1}H-NMR ($CDCl_3$): 0.84 (*t*, *J* = 7.3, 3 H); 1.20–1.52 (*m*, 7 H); 1.80–1.92 (*m*, 1 H); 2.02 (*dd*, *J* = 1.5, 0.7, 3 H); 4.79 (*m*, 1 H); 5.77 (*dq*, *J* = 1.5, 1.5, 1 H). ^{13}C-NMR ($CDCl_3$): 13.86 (o); 13.95 (o); 22.4 (e); 24.0 (e); 31.5 (e); 31.9 (e); 84.6 (o); 116.9 (o); 168.7 (e); 173.3 (e). MS: 168 (10, M^+), 139 (27), 125 (7), 112 (10), 111 (12), 99 (30), 98 (83), 97 (87), 84 (8), 71 (10), 70 (12), 69 (100), 55 (15). HR-MS: 168.1156 ($C_{10}H_{16}O_2$, calc. 168.1150).

In separate experiments, *(3a*RS*,4*SR*,6a*SR*)-4-butyl-4,6a-dihydro-3*H-cis-*furo[3,4-c]pyrazol-6(3a*H*)-one* (**11a**) and *(3a*RS*,4*SR*,6a*SR*)-4-pentyl-4,6a-dihydro-3*H-cis-*furo[3,4-c]pyrazol-6(3a*H*)-one* (**11b**) were isolated by column chromatography (AcOEt/hexane 1:1).

11a: 222 mg (87%). Pale yellow oil. R_f 0.28 (AcOEt/hexane 1:1). IR (CCl_4): 2970*s*, 2935*s*, 2870*m*, 1780*s*, 1550*w*, 1470*m*, 1435*m*, 1380*w*, 1350*m*, 1288*w*, 1260*w*, 1228*m*, 1187*s*, 1027*m*, 998*m*, 978*m*, 908*m*. ^{1}H-NMR ($CDCl_3$, pretreated with basic alumina): 0.87 (*t*, *J* = 7.0, 3 H); 1.20–1.78 (*m*, 6 H); 2.65 (*m*, 1 H); 3.90 (*dt*, *J* = 7.2, 5.5, 1 H; irr. at 2.65→*t*, *J* = 5.5, no change on irr. at 4.78 and at 5.51); 4.78 (*m*, 2 H); 5.51 (*dt*, *J* = 8.8, 2.0, 1 H; irr. at 4.78→*d*, *J* = 8.8, no change on irr. at 1.65 and at 3.90). NOE: experiments performed in C_6D_6 as solvent. Data (see *Results* and the *Fig.*). ^{13}C-NMR ($CDCl_3$, pretreated with basic alumina): 13.8 (o); 22.2 (e); 26.8 (e); 36.0 (e); 37.3 (o); 85.3 (e); 86.4 (o); 94.4 (o); 168.5 (e). MS: 182 (0, M^+), 154 (6), 125 (11), 112 (8), 98 (32), 97 (100), 85 (11), 69 (52), 57 (9), 55 (7), 53 (9). Anal. calc. for $C_9H_{14}N_2O_2$ (182.22): C 59.32, H 7.74, N 15.37; found: C 59.25, H 7.69, N 15.33.

11b: 230 mg (84%). Pale yellow oil. R_f 0.39 (AcOEt/hexane 1:1). IR (CCl_4): 2955*s*, 2930*s*, 2860*m*, 1780*s*, 1550*w*, 1460*w*, 1378*w*, 1346*w*, 1282*w*, 1258*w*, 1224*m*, 1198*s*, 1177*s*, 1062*w*, 1020*w*, 998*w*, 944*w*, 901*w*. ^{1}H-NMR ($CDCl_3$, pretreated with basic alumina): 0.89 (*t*, *J* = 7.0, 3 H); 1.22–1.50 (*m*, 6 H); 1.56–1.82 (*m*, 2 H); 2.67 (*m*, 1 H); 3.93 (*dt*, *J* = 7.4, 5.3, 1 H); 4.78 (*m*, 2 H); 5.51 (*dt*, *J* = 8.8, 2.0, 1 H). ^{13}C-NMR ($CDCl_3$, pretreated with basic alumina): 13.9 (o); 22.4 (e); 24.5 (e); 31.3 (e); 36.3 (e); 37.4 (o); 85.3 (e); 86.2 (o); 94.4 (o); 168.3 (e). MS: 196 (0,

M^+), 168 (18), 140 (8), 139 (22), 112 (8), 111 (7), 99 (15), 98 (42), 97 (100), 69 (59), 55 (10), 53 (11). Anal. calc. for $C_{10}H_{16}N_2O_2$ (196.25): C 61.20, H 8.22, N 14.27; found: C 61.20, H 8.23, N 14.18.

6. *Isomerization of* **11** *to* **13**. A soln. of **11** (0.05–0.07 mmol) in commercial $CDCl_3$ (0.6 ml) was left standing for 24 h at 24°. Conversion to **13** was quantitative.

*(3a*RS,*4*SR,*6a*SR*)-4-Butyl-4,6a-dihydro-1*H-cis-*furo[3,4-c]pyrazol-6(3a*H*)-one* (**13a**): Pale yellow oil. R_f 0.21 (AcOEt/hexane 1:1). IR ($CDCl_3$): 3350*w*, 2960*s*, 2925*s*, 2855*m*, 2245*w*, 1775*s*, 1600*w*, 1465*m*, 1380*m*, 1350*w*, 1240*m*, 1175*m*, 970*w*. ^{1}H-NMR ($CDCl_3$): 0.92 (*t*, *J* = 7.0, 3 H); 1.25–1.58 (*m*, 4 H); 1.74 (*m*, 2 H); 3.64 (*ddd*, *J* = 9.8, 1.7, 1.6, 1 H); 4.33 (*d*, *J* = 9.8, 1 H); 4.56 (*td*, *J* = 6.5, 1.7, 1 H; irr. at 3.64→*t*, *J* = 6.5); 6.20 (br., 1 H); 6.76 (*d*, *J* = 1.7, 1 H). ^{13}C-NMR ($CDCl_3$): 13.7 (o); 22.1 (e); 26.8 (e); 36.1 (e); 53.0 (o); 58.9 (o); 82.2 (o); 142.5 (o); 176.3 (e).

*(3a*RS,*4*SR,*6a*SR*)-4-Pentyl-4,6a-dihydro-1*H-cis-*furo[3,4-c]pyrazol-6(3a*H*)-one* (**13b**): Pale yellow oil. R_f 0.23 (AcOEt/hexane 1:1). IR ($CDCl_3$): 3352*w*, 2960*s*, 2935*s*, 2860*m*, 2245*m*, 1775*s*, 1590*w*, 1468*m*, 1380*m*, 1350*m*, 1272*w*, 1240*m*, 1177*s*, 1115*w*, 1045*w*, 975*w*. ^{1}H-NMR ($CDCl_3$): 0.91 (*t*, *J* = 7.0, 3 H); 1.23–1.62 (*m*, 6 H); 1.74 (*m*, 2 H); 3.65 (*ddd*, *J* = 9.9, 1.7, 1.7, 1 H); 4.34 (*d*, *J* = 9.9, 1 H); 4.56 (*td*, *J* = 6.5, 1.7, 1 H); 6.76 (*d*, *J* = 1.7, 1 H). ^{13}C-NMR ($CDCl_3$): 13.9 (o); 22.4 (e); 24.5 (e); 31.3 (e); 36.5 (e); 53.2 (o); 59.1 (o); 82.3 (o); 142.7 (o); 176.4 (e).

7. *Reduction of* **12**. A vigorously stirred soln. of **12** (0.65 mmol) in EtOH (3 ml) was hydrogenated at atmospheric pressure in the presence of *Raney* Ni (slightly basic, *ca.* 100 mg) for 3 h at 24°. The mixture was filtered through *Celite* and evaporated. Isomers **2** and **1** were isolated by column chromatography (petroleum ether (60–80°)/Et_2O 3:1).

cis-*Whisky Lactone* (= cis-*5-Butyl-tetrahydro-4-methylfuran-2-one;* **2a**): 81% from **12a**. Colorless oil. R_f 0.18 (petroleum ether (60–80°)/Et_2O 3:1). IR, ^{1}H- and ^{13}C-NMR, MS: as reported in [7]. The *trans*-isomer **1a** was also isolated in 5% yield.

cis-*Cognac Lactone* (= cis-*Tetrahydro-4-methyl-5-pentylfuran-2-one;* **2b**): 83% from **12b**. Colorless oil. R_f 0.18 (petroleum ether (60–80°)/Et_2O 3:1). IR (CCl_4): 2940*s*, 2865*m*, 1782*s*, 1460*m*, 1420*w*, 1380*w*, 1330*w*, 1290*w*, 1210*m*, 1165*s*, 1067*w*, 1008*w*, 973*w*, 930*m*. ^{1}H-NMR ($CDCl_3$): 0.87 (*t*, *J* = 6.9, 3 H); 0.97 (*d*, *J* = 7.0, 3 H); 1.20–1.68 (*m*, 8 H); 2.17 (*dd*, *J* = 16.7, 3.8, 1 H); 2.57 (*m*, 1 H); 2.67 (*dd*, *J* = 16.7, 7.8, 1 H); 4.44 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$): 13.8 (o); 14.0 (o); 22.5 (e); 25.5 (e); 29.8 (e); 31.6 (e); 33.0 (o); 37.5 (e); 83.7 (o); 176.9 (e). MS: 171 (1, $M^+ + 1$), 170 (0.8, M^+), 142 (2.5), 128 (3), 110 (6), 101 (13), 100 (7), 99 (100), 97 (8), 83 (22), 71 (31), 70 (13), 56 (14), 55 (22). Anal. calc. for $C_{10}H_{18}O_2$ (170.25): C 70.55, H 10.66; found: C 70.27, H 10.91.

Data in agreement with [6]. The *trans*-isomer **1b** was also isolated in 4% yield.

Reduction of **12a** under alternative conditions are summarized in the *Table*.

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