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Asymmetric synthesis of 5-(1-hydroxyalkyl)-5-methyl-5*H*-furan-2-ones

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Abstract—The reactivity of 5-methyl-4-(pyrrolidin-1-yl)-5*H*-furan-2-one with aldehydes and with acyl chlorides followed by reduction was studied. The aldol condensation gave predominantly the *anti* aldol product when the acylation–reduction sequence led exclusively to the *syn* product. The use of a chiral pyrrolidine, (*S*)-2-methoxymethylpyrrolidine (SMP), allowed the synthesis of enantio-enriched compounds, the acylation–reduction leading to the (*R*,*R*) addition product.

1. Introduction

Over the last decade, a great number of new natural products have been isolated from marine organisms.[1,2] A lot of these marine natural products contain α,α′-disubstituted 5-membered oxygenated heterocycles in their structures and exhibit various biological activities. Some examples of these compounds are shown in Figure 1: the cytotoxic macrolides oscillariolide[3] and pectenotoxin-2,[4] clavidol,[5] a novel marine polyether and valdivone A[6] which presents anti-inflammatory activity.

Eleutherobin **1** (Fig. 2), isolated from soft coral, possesses very interesting cytotoxic activity with a mechanism of action similar to paclitaxel.[7] In an approach of the total synthesis of eleutherobin and analogues, we have conducted a model study in the aim of preparing 5,5-disubstituted-5*H*-furan-2-ones. In this paper, we describe the results of this study which represents a method to synthesize 5-(1-hydroxyalkyl)-5-methyl-5*H*-furan-2-one of type **2** with the control of relative and absolute configurations.

2. Results and discussion

Reactivity of 5*H*-furan-2-one and particularly of its

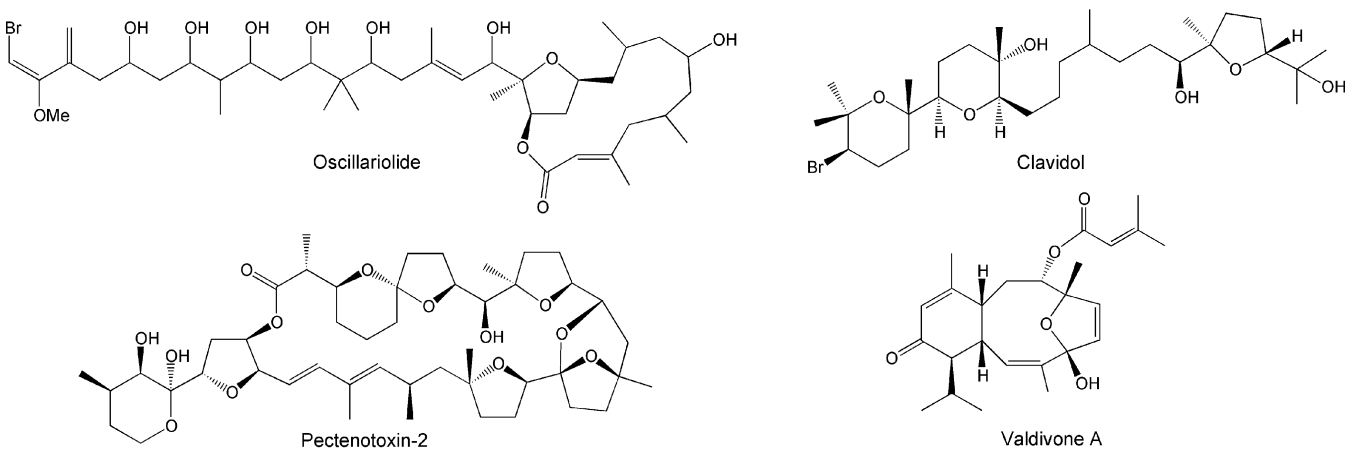

Figure 1.

Keywords: aldol reaction; acylation; furanones; stereoselectivity.
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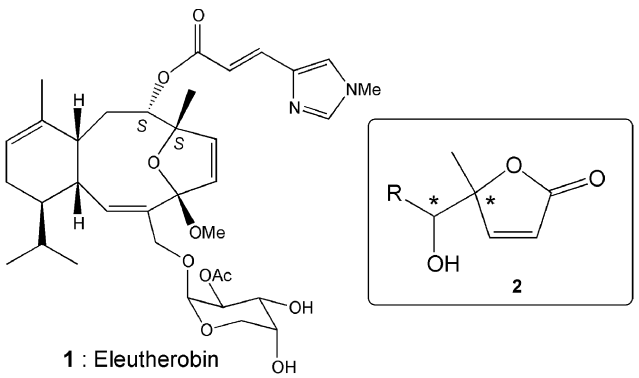
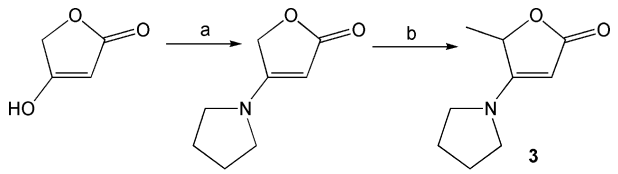


Figure 2.

2-silyloxyfuran derivatives towards aldol-type addition has been largely used in organic synthesis and reviewed in the literature.[8–11] The silyloxyfurans are known to afford only C5 adducts under Mukaiyama conditions.[9] However, a recent study of the reactivity of 5-methyl-2-silyloxyfuran in Mukaiyama-aldol condensation[12] showed that the C5 adducts cannot be obtained in satisfactory yields due to the competitive reaction at C3. On the other hand, it has been reported in the literature[13] that the presence of an electron-releasing group, such as an alkylamine, at the C4 position of 5*H*-furan-2-one favors the formation of C5 substituted derivatives. A pyrrolidinyl group at C4 not only favors C5 addition but can also be a chiral auxiliary by using asymmetric derivatives which could be easily removed to afford α,β-unsaturated γ-lactone.[14–18]

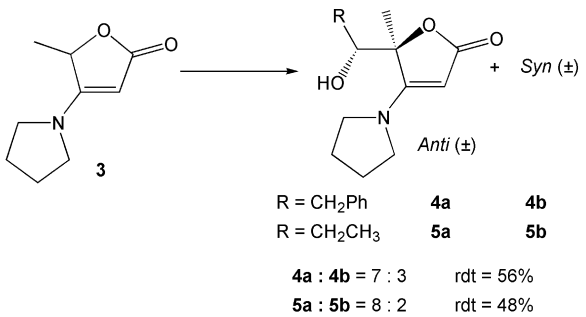
Taking these results into account, we decided to use 5-methyl-4-(pyrrolidin-1-yl)-5*H*-furan-2-one (**3**) as starting material to study the *syn*–*anti* diastereoselectivity of the addition reaction. This compound is obtained in two steps from tetronic acid (Scheme 1) according to a protocol described with (*S*)-2-methoxymethylpyrrolidine.[19]



Scheme 1. *Reagents and conditions*: (a) pyrrolidine, *p*TsOH, benzene, reflux, 24 h; (b) *t*-BuLi, THF, −78°C then MeI, 89% (two steps).

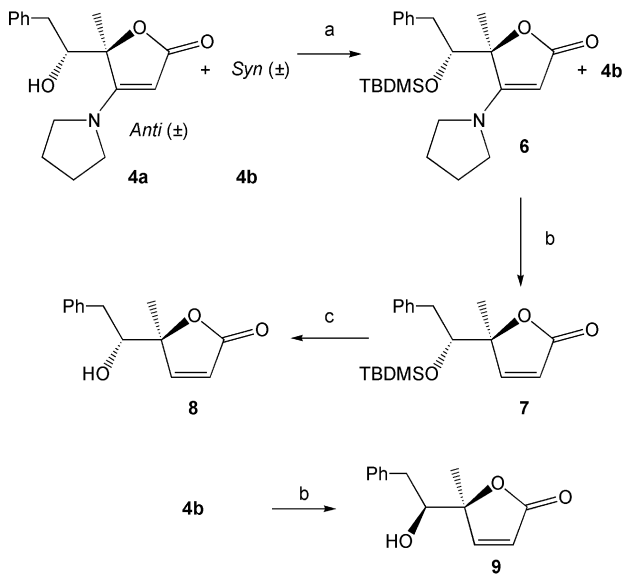
We chose to conduct the addition reaction with the lithium dienolate of **3** obtained by treatment with *tert*-butyllithium. We studied the aldol condensation in THF at −78°C with two different aldehydes: phenylacetaldehyde and propionaldehyde (Scheme 2). Under these conditions, the addition was totally regioselective since only C5 adducts **4** and **5** were formed in 56 and 48% yields with phenylacetaldehyde and propionaldehyde, respectively. A fair diastereoselectivity was observed (de=40% for **4** and de=60% for **5** determined by NMR) in favor of the diastereomers **4a** and **5a**.

In order to determine the relative configuration of the major diastereomer, the **4a**:**4b** mixture was subjected to a silylation reaction. Under standard conditions, only the isomer **4a** was silylated which greatly facilitated the

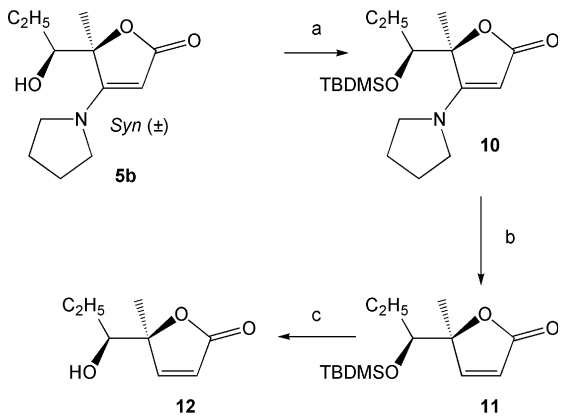


Scheme 2. *Reagents and conditions*: *t*-BuLi, THF, then RCHO, −78°C.

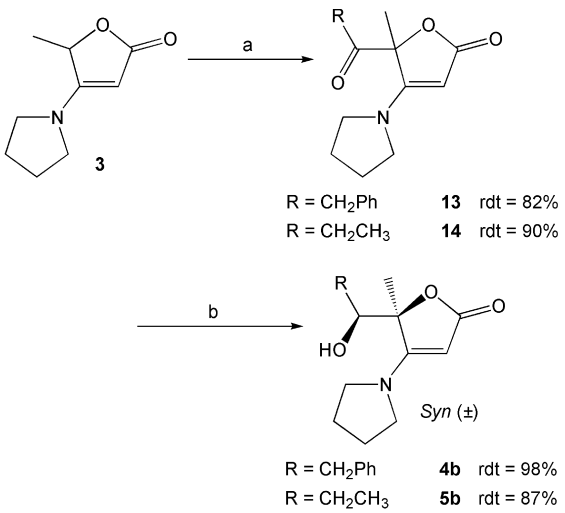
separation of the two diastereomers. This diastereoselective protection of the *anti* aldol adduct has already been reported.[17] However, to confirm this assignement, the pyrrolidinyl group was removed from **6** (Scheme 3) via a two-step Borch reduction–Cope elimination[16] and the alcohol function of **7** deprotected under acidic conditions to give product **8**. The spectral data of **8** were in agreement with the *anti* product described by Redero et al.[12] Elimination of the pyrrolidinyl group from compound **4b**



Scheme 3. *Reagents and conditions*: (a) 2,6-lutidine, TBDMSOTf, CH_2Cl_2, 18 h, 74%; (b) (i) $NaBH_3CN$, AcOH; (ii) *m*CPBA, CH_2Cl_2, aq. $NaHCO_3$, 30% (two steps); (c) TFA–H_2O, THF, quant.



Scheme 4. *Reagents and conditions*: (a) 2,6-lutidine, DMAP, TBDMSOTf, CH_2Cl_2, 42 h, 95%; (b) (i) $NaBH_3CN$, AcOH; (ii) *m*CPBA, CH_2Cl_2, aq. $NaHCO_3$, 94% (two steps); (c) TFA–H_2O, THF, quant.



Scheme 5. *Reagents and conditions:* (a) *t*-BuLi, TMSCl, THF, then RCOCl, −78°C; (b) $NaBH_4$, $CeCl_3$, MeOH, 0°C.

gave the *syn* product **9**[20] (Scheme 3). The yields obtained for the reduction–elimination procedure of enamine **6** or **4b** were not optimized. When the same sequence of reaction was applied to compound **5b**, with more drastic silylation conditions,[21] *syn*-5-(1-hydroxypropyl)-5-methyl-5*H*-furan-2-one (**12**) was obtained with an overall yield of 89% (Scheme 4).

Direct elimination of pyrrolidinyl group from compound **5b** with the free hydroxyl was possible but the yield in desired compound **12** was not satisfactory.

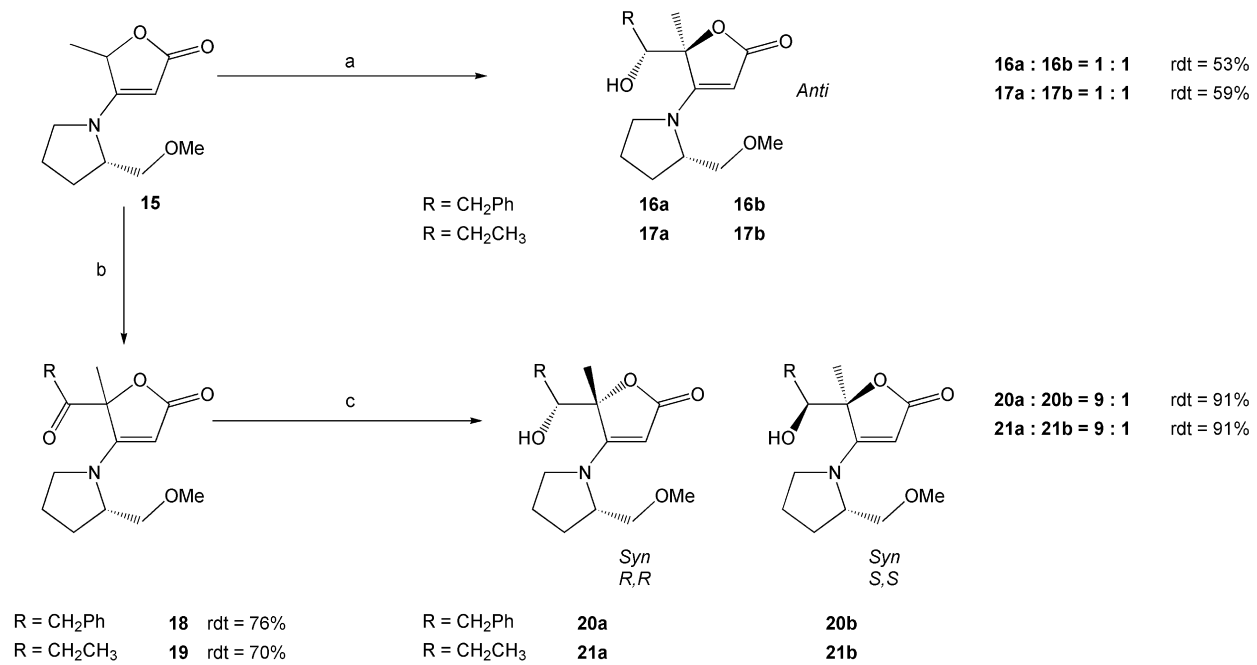
We also studied another route to obtain 5-(1-hydroxyalkyl)-5-methyl-5*H*-furan-2-one, still using the 5-methyl-4-(pyrrolidin-1-yl)-5*H*-furan-2-one (**3**) as starting material. Compound **3** was deprotonated with *tert*-butyllithium and treated with chlorotrimethylsilane and then with either phenylacetyl or propionyl chloride. Ketones **13** and **14** were obtained in 82 and 90% yields, respectively (Scheme 5). Reduction of these ketones under Luche conditions[22] provided diastereoselectively the *syn* addition products **4b** and **5b** in 98 and 87%, respectively. Reduction without $CeCl_3$ furnished a mixture of diastereoisomers with a de=40%.

Having obtained a method to diastereoselectively synthesize *syn*-5-(1-hydroxyalkyl)-5-methyl-5*H*-furan-2-one, we further investigated the reaction in order to access to enantio-enriched compounds. For this purpose, we introduced a chiral pyrrolidine, (*S*)-2-methoxymethylpyrrolidine (SMP), via tetronic acid and methylated the intermediate to obtain **15** as a mixture of diastereomers (de=40%) as described in the literature.[19]

Compound **15** reacted with the same aldehydes and acyl chlorides and according to the same protocols used in the previous racemic series. The results obtained with SMP derivative are resumed in Scheme 6.

The aldolisation furnished a mixture of two *anti* products **16a** and **16b** with phenylacetaldehyde and **17a** and **17b** with propionaldehyde in a 1:1 ratio in both cases (determined by NMR of the reaction mixtures). Under these conditions, no diastereofacial selectivity was observed. The couple of diastereomers could not be separated using standard chromatography technique. Trace amounts of the *syn* products could not be detected in the NMR spectra.

As in the racemic series, the two-step procedure of acylation–reduction was much more stereoselective. In both examples, ketones **18** and **19** (Scheme 6) were obtained from the acylation reaction in 76 and 70% yields respectively as an unseparable mixture of two diastereomers. The HPLC analyses of these mixtures show a de=80%. After reduction, compounds **20** and **21** were obtained in 91% yield each. NMR analysis of alcohols **20** and **21** showed that they both consisted of a 9:1



Scheme 6. *Reagents and conditions*: (a) *t*-BuLi, THF, then RCHO, −78°C; (b) *t*-BuLi, TMSCl, THF, then RCOCl, −78°C; (c) $NaBH_4$, $CeCl_3$, MeOH, 0°C.

diastereomeric mixture indicating that the reduction step is totally diastereoselective. This diastereoselectivity was confirmed after elimination of the chiral auxiliary from **20** using a slightly modified procedure:[23] only one diastereomer exhibiting the same NMR data than **9** was obtained.

In order to determine the absolute configuration of the major isomer **20a**, the latter was separated from the mixture by chromatography on silica gel. Compound **20a** could be crystallized and submitted to single crystal X-ray analysis. This allowed us to confirm the *syn* relative configuration of **20a** and to assign a (*R*,*R*) absolute configuration (Fig. 3) for the two stereogenic centers created during the reaction sequence.

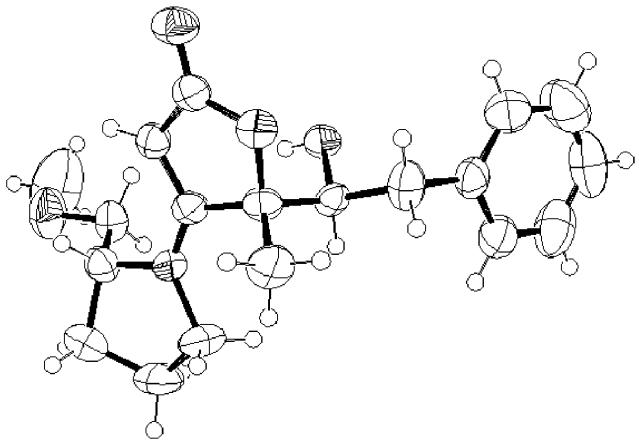


Figure 3. X-Ray structure of compound **20a**.[24]

3. Conclusion

To summarize, the introduction of a pyrrolidinyl group at the C4 position of 5*H*-furan-2-one allowed the regioselective double addition at the C5 position. With 5-methyl-4-(pyrrolidin-1-yl)-5*H*-furan-2-one (**3**), the aldolisation reaction furnished the *anti* product while the acylation–reduction sequence gave exclusively the *syn* product. The introduction of the SMP, as a chiral auxiliary, allowed a diastereofacial selectivity in the acylation–reduction which led to the (*R*,*R*) *syn* addition products **20a** and **21a** in good yields, providing an efficient asymmetric method to synthesize 5-(1-hydroxyalkyl)-5-methyl-5*H*-furan-2-ones.

4. Experimental

General directions: Tetrahydrofuran (THF) was distilled from sodium-benzophenone and dichloromethane (CH_2Cl_2) from CaH_2. IR spectra were recorded on a Nicolet 205-FT infrared spectrophotometer. Only noteworthy IR absorptions are listed. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 300 or Bruker 400 Avance. Chemical shifts are reported in δ (ppm). Specific rotations were measured on a Perkin Elmer 241C polarimeter with sodium (589 nm) lamp. CIMS were recorded on Nermag R10-10C and HRMS on Q-Tof 1 Micromass by the Laboratoire de Spectrométrie de Masse de la Faculté de Pharmacie, Paris V. Elementary analyses were performed at the Microanalysis Laboratory, Paris VI. All reactions were carried out under argon or nitrogen atmosphere, and were monitored by thin-layer chromatography with Merck 60F-254 precoated silica (0.2 mm) on aluminium. Flash chromatography was performed with SDS Silicagel 60 (35–70 μm); the solvent systems were given v/v. Spectroscopic (^1H and ^{13}C NMR, MS) and/or analytical data were obtained using chromatographically homogeneous samples.

4.1. 5-Methyl-4-(pyrrolidin-1-yl)-5*H*-furan-2-one (3)

To a solution of 4-(pyrrolidin-1-yl)-5*H*-furan-2-one[25] (3.1 g, 20 mmol) in anhydrous THF (100 mL) at −78°C was added dropwise *t*-BuLi (1.7 M in pentane, 14.2 mL, 24 mmol) and the solution was stirred for 1 h. Methyl iodide (5.0 mL, 80 mmol) was slowly added. After 3 h stirring at −78°C, saturated ammonium chloride solution (100 mL) was added to the reaction mixture. The resulting mixture was extracted with Et_2O (3×200 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness. Compound **3** (3.0 g, 89%) was obtained as a tan solid. A sample was purified by column chromatography (CH_2Cl_2/MeOH, 98:2): R_f 0.31 (EtOAc); mp 88°C; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.52 (d, ^3J=6.7 Hz, 3H, CH_3), 1.8–2.2 (m, 4H, CH_{2Pyr}), 3.0–3.6 (m, 4H, CH_{2Pyr}), 4.47 (s, 1H, CH═C), 4.93 (q, ^3J=6.5 Hz, 1H, C*H*CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.8 (CH_3), 24.7, 26.1, 48.3, 49.9 (CH_{2Pyr}), 74.5 (*C*HCH_3), 80.8 (*C*H═C), 170.6 (CqN), 174.41 (C═O); CIMS (NH_3) *m*/*z* (%): 185 (MNH_4^+, 100), 168 (MH^+, 55); Anal. calcd for $C_9H_{13}NO_2$: C, 64.65, H, 7.84, N, 8.38; found: C, 64.61, H, 7.96, N, 8.27.

4.2. (5*S* *,1′*R* *)-5-(1′-Hydroxy-2′-phenylethyl)-5-methyl-4-(pyrrolidin-1-yl)-5*H*-furan-2-one (4a)

To a solution of 5-methyl-4-(pyrrolidin-1-yl)-5*H*-furan-2-one (**3**) (0.20 g, 1.20 mmol) in anhydrous THF (2.2 mL) at −78°C was added dropwise *t*-BuLi (1.7 M in pentane, 1.05 mL, 1.79 mmol) and the solution was stirred for 1 h at −78°C. Phenylacetaldehyde (0.17 mL, 1.43 mmol) was added dropwise. After stirring for 1 h at −78°C and 3 h at 0°C, the volatiles were removed under reduced pressure and chromatography of the residue (EtOAc) afforded aldols **4a** and **4b** as a 7:3 mixture (0.19 g, 56%). The following spectroscopic properties for the major isomer **4a** are given: R_f 0.26 (EtOAc); IR (neat): ν 3320 (OH), 1718 (C═O), 1588 (C═C) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.70 (s, 3H, CH_3), 1.7–2.1 (m, 4H, CH_{2Pyr}), 2.41 (bd, ^3J=10.6 Hz, 1H, OH), 2.76 (d, ^3J=6.3 Hz, 2H, CH_2Ph), 3.1–3.6 (m, 4H, CH_{2Pyr}), 4.10 (dt, ^3J=10.4, 6.3 Hz, 1H, C*H*OH), 4.45 (s, 1H, CH═C), 7.1–7.4 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7 (CH_3), 26.0 (CH_{2Pyr}), 38.8 (*C*H_2Ph), 49.7 (CH_{2Pyr}), 75.2 (CHOH), 83.3 (*C*H═C), 86.0 (*C*qCH_3), 126.6, 128.5, 129.4 (CH_{arom}), 137.9 (Cq_{arom}), 170.1 (CqN), 173.2 (C═O); CIMS (NH_3) *m*/*z* (%): 288 (MH^+, 100), 168 (13), 72 (10); HRMS calcd for $C_{17}H_{21}NO_3$ (MH^+) 288.1600; found: 288.1588.

4.3. (5*S* *,1′*R* *)-5-(1′-Hydroxypropyl)-5-methyl-4-(pyrrolidin-1-yl)-5*H*-furan-2-one (5a)

The above protocol for **4a** was used with propionaldehyde (81 μL, 1.11 mmol) and 5-methyl-4-(pyrrolidin-1-yl)-5*H*-furan-2-one (**3**) (0.15 g, 0.93 mmol). Chromatography of

the residue (cyclohexane/EtOAc, 1:9) afforded aldols **5a** and **5b** as a 8:2 mixture (0.10 g, 48%). The following spectroscopic properties for the major isomer **5a** are given: R_f 0.15 (EtOAc). IR (neat): ν 3322 (OH), 1700 (C=O), 1594 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.94 (t, ^3J=7.4 Hz, 3H, CH_2CH_3), 1.2–1.5 (m, 2H, CH_2CH_3), 1.64 (s, 3H, CH_3Cq), 1.8–2.0 (m, 4H, CH_{2Pyr}), 3.2–3.5 (m, 4H, CH_{2Pyr}), 3.67 (bd, ^3J=5.9 Hz, 1H, CHOH), 4.38 (s, 1H, CH=C); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.3 (CH_2CH_3), 20.7 (CH_3Cq), 24.5 (CH_2CH_3), 25.2, 49.6 (CH_{2Pyr}), 75.3 (CHOH), 83.1 (CH=C), 86.5 ($CqCH_3$), 170.4 (CqN), 173.3 (C=O); CIMS (NH_3) *m/z* (%): 226 (MH^+, 100); HRMS calcd for $C_{12}H_{19}NO_3$+Na 248.1263; found: 248.1260.

4.4. (5*S* *,1′*R* *)-5-[1′-(*tert*-Butyldimethylsilanyloxy)-2′-phenylethyl]-5-methyl-4-(pyrrolidin-1-yl)-5*H*-furan-2-one (6)

To a cooled (0°C) solution of 7:3 mixture of alcohols **4a** and **4b** (100 mg, 0.35 mmol) in anhydrous CH_2Cl_2 (3.5 mL) was added dropwise 2,6-lutidine (250 μL, 2.12 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (122 μL, 0.53 mmol). The reaction mixture was warmed to room temperature and stirred overnight. Water was added and the layers were separated. The aqueous solution was extracted with Et_2O (3×5 mL) and the combined organic extracts were dried over $MgSO_4$. The volatiles were removed under reduced pressure and chromatography of the residue (EtOAc) yielded silyl ether **6** (104 mg, 74%) as an oil and unreacted alcohol **4b** (15 mg, 11%). **6**: R_f 0.44 (EtOAc); ^1H NMR ($CDCl_3$, 400 MHz) δ −0.11, −0.03 (2 s, 6H, $SiCH_3$), 0.89 (s, 9H, $SiC(CH_3)_3$), 1.5–1.7 (m, 7H, containing at 1.55 (s, 3H, CH_3) and CH_{2Pyr}), 2.77 (dd, ^2J=14.5 Hz, ^3J=4.3 Hz, 1H, CH_2Ph), 2.86 (dd, ^2J=14.5 Hz, ^3J=7.7 Hz, 1H, CH_2Ph), 2.9–3.1 (m, 4H, CH_{2Pyr}), 4.2–4.4 (m, 2H, containing at 4.28 (s, 1H, CH=C) and CHOTBS), 7.0–7.3 (m, 5H, CH_{arom}); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −3.7 ($SiCH_3$), 18.3 (CqSi), 21.8 (CH_3Cq), 25.2 (CH_{2Pyr}), 26.0 ($C(CH_3)_3$), 39.3 (CH_2Ph), 49.2 (CH_{2Pyr}), 75.6 (CHOTBS), 84.4 (CH=C), 86.3 ($CqCH_3$), 126.4, 128.2, 129.8 (CH_{arom}), 138.5 (Cq_{arom}), 169.9 (CqN), 174.1 (C=O); HRMS calcd for $C_{23}H_{35}NO_3Si$+Na 424.2284; found: 424.2292.

4.5. (5*S* *,1′*R* *)-5-[1′-(*tert*-Butyldimethylsilanyloxy)-2′-phenylethyl]-5-methyl-5*H*-furan-2-one (7)

To a solution of lactone **6** (104 mg, 0.26 mmol) in glacial acetic acid (3 mL), was added sodium cyanoborohydride (330 mg, 5.2 mmol) in portions over 2 h. Aqueous NaOH (25 mL of a 2 M solution) was added slowly at 0°C and the solution was extracted with Et_2O (4×30 mL). The combined organic extracts were dried over $MgSO_4$ and the volatiles were removed under reduced pressure. Purification on a short pad of silica gel (cyclohexane/EtOAc, 1:1) furnished unreacted lactone **6** (65 mg) and saturated lactone which was dissolved in CH_2Cl_2 (1 mL). Then *m*-CPBA (60% w/w, 30 mg, 0.11 mmol) was added. The reaction mixture was stirred for 10 min, then sat. aq. $NaHCO_3$ (2 mL) was added at 0°C and stirring was continued for 20 min. The solution was extracted with CH_2Cl_2 (3×5 mL) and the combined organic extracts were dried over $MgSO_4$. The volatiles were removed under reduced pressure and chromatography of the residue (cyclohexane/EtOAc, 1:1) afforded α,β-unsaturated lactone **7** (26 mg, 30%) as a clear colorless oil: R_f 0.37 (cyclohexane/EtOAc, 8:2); ^1H NMR ($CDCl_3$, 300 MHz) δ −0.64, −0.05 (2 s, 6H, $SiCH_3$), 0.81 (s, 9H, $SiC(CH_3)_3$), 1.50 (s, 3H, CH_3), 2.67 (dd, ^2J=13.8 Hz, ^3J=8.6 Hz, 1H, CH_2Ph), 3.13 (dd, ^2J=13.6 Hz, ^3J=2.5 Hz, 1H, CH_2Ph), 3.93 (dd, ^3J=8.6, 2.9 Hz, 1H, CHOTBS), 6.00 (d, ^3J=5.7 Hz, 1H, CHC=O), 7.1–7.4 (m, 6H, containing at 7.27 (d, ^3J=5.7 Hz, 1H, CH=CHC=O) and CH_{arom}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −3.7 ($SiCH_3$), 17.8 (CqSi), 19.5 (CH_3Cq), 25.7 ($C(CH_3)_3$), 40.0 (CH_2Ph), 76.4 (CHOTBS), 90.9 ($CqCH_3$), 121.2 (CHC=O), 126.6, 128.3, 129.8 (CH_{arom}), 137.8 (Cq_{arom}), 158.6 (CH=CHC=O), 173.5 (C=O).

4.6. (5*S* *,1′*R* *)-5-(1′-Hydroxy-2′-phenylethyl)-5-methyl-5*H*-furan-2-one (8)

The silyl ether **7** (26 mg, 0.08 mmol) was dissolved in TFA/H_2O/THF (9:1:1) (3 mL). After stirring for 2 h at room temperature, the solvents were evaporated to dryness and the residue was purified by chromatography to afford 5-(1-hydroxy-2-phenylethyl)-5-methyl-5*H*-furan-2-one **8** (17 mg, quant.) as a clear colorless oil: R_f 0.38 (cyclohexane/EtOAc, 1:1); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.55 (s, 3H, CH_3), 2.65 (dd, ^2J=13.7 Hz, ^3J=10.4 Hz, 1H, CH_2Ph), 3.02 (dd, ^2J=13.8 Hz, ^3J=2.4 Hz, 1H, CH_2Ph), 3.78 (dd, ^3J=10.4, 2.3 Hz, 1H, CHOH), 6.08 (d, ^3J=5.7 Hz, 1H, CHC=O), 7.1–7.4 (m, 5H, CH_{arom}), 7.52 (d, ^3J=5.7 Hz, 1H, CH=CHC=O); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.9 (CH_3Cq), 38.5 (CH_2Ph), 76.1 (CHOH), 90.1 ($CqCH_3$), 121.0 (CHC=O), 126.8, 128.6, 129.2 (CH_{arom}), 137.3 (Cq_{arom}), 159.1 (CH=CHC=O), 172.3 (C=O); HRMS calcd for $C_{13}H_{14}O_3$+Na 241.0841; found: 241.0844.

4.7. (5*S* *,1′*S* *)-5-(1′-Hydroxy-2′-phenylethyl)-5-methyl-5*H*-furan-2-one (9)

The protocol described for compound **7** was applied to alcohol **4b** to afford **9**:[20] R_f 0.34 (cyclohexane/EtOAc, 1:1); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.59 (s, 3H, CH_3), 1.99 (d, ^3J=3.3 Hz, 1H, OH), 2.55 (dd, ^2J=13.7 Hz, ^3J=10.2 Hz, 1H, CH_2Ph), 2.91 (dd, ^2J=13.7 Hz, ^3J=3.0 Hz, 1H, CH_2Ph), 3.93 (dt, ^3J=10.2, 2.9 Hz, 1H, CHOH), 6.11 (d, ^3J=5.7 Hz, 1H, CHC=O), 7.1–7.4 (m, 5H, CH_{arom}), 7.40 (d, ^3J=5.7 Hz, 1H, CH=CHC=O); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.2 (CH_3), 37.9 (CH_2Ph), 76.3 (CHOH), 90.5 ($CqCH_3$), 121.6 (CHC=O), 127.0, 128.8, 129.2 (CH_{arom}), 137.2 (Cq_{arom}), 158.2 (CH=CHC=O), 172.0 (C=O); HRMS calcd for $C_{13}H_{14}O_3$+Na 241.0841; found: 241.0842.

4.8. (5*S* *,1′*S* *)-5-[1′-(*tert*-Butyldimethylsilanyloxy)-propyl]-5-methyl-4-(pyrrolidin-1-yl)-5*H*-furan-2-one (10)

To a cooled (0°C) solution of alcohol **5b** (1.85 g, 8.22 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise 2,6-lutidine (5.75 mL, 49.3 mmol), DMAP (0.5 g, 4.11 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (3.8 mL, 16.44 mmol). The reaction mixture was warmed to room temperature and stirred overnight. DMAP (0.5 g, 4.11 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.89 mL, 8.22 mmol) were added again. After 18 h stirring, water was added and the layers were separated. The aqueous

solution was extracted with Et_2O (3×50 mL) and the combined organic extracts were dried over $MgSO_4$. The volatiles were removed under reduced pressure and chromatography of the residue (cyclohexane/EtOAc, 1:9) yielded silyl ether **10** (2.68 g, 95%) as an oil: R_f 0.46 (EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.06, 0.07 (2 s, 6H, $SiCH_3$), 0.7–1.0 (m, 12H, $SiC(CH_3)_3$ and CH_2CH_3), 1.39 (dq, ^2J=14.3 Hz, ^3J=7.2 Hz, 1H, CH_2CH_3), 1.5–1.7 (m, 4H, containing at 1.53 (s, 3H, CH_3Cq) and CH_2CH_3), 1.8–2.1 (m, 4H, CH_{2Pyr}), 3.1–3.4 (m, 4H, CH_{2Pyr}), 3.85 (t, ^3J=5.0 Hz, 1H, CHOTBS), 4.38 (s, 1H, CH=C); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.1 ($SiCH_3$), 10.2 (CH_2CH_3), 18.3 (CqSi), 21.9 (CH_3Cq), 24.9 (CH_{2Pyr}), 25.5 ($C(CH_3)_3$), 29.8 (CH_2CH_3), 50.2 (CH_{2Pyr}), 76.8 (CHOTBS), 83.7 (CH=C), 87.1 ($CqCH_3$), 170.7 (CqN), 173.2 (C=O); CIMS (NH_3) *m/z* (%): 340 (MH^+, 100), 300 (35), 282 (10); Anal. calcd for $C_{18}H_{33}NO_3Si$: C, 63.67, H, 9.80, N, 4.13; found: C, 63.57, H, 9.87, N, 3.94.

4.9. (5*S* *,1′*S* *)-5-[1′-(*tert*-Butyldimethylsilanyloxy)-propyl]-5-methyl-5*H*-furan-2-one (11)

To a solution of lactone **10** (950 mg, 2.75 mmol) in glacial acetic acid (27 mL), was added sodium cyanoborohydride (3.46 g, 55 mmol) in portions over 2 h. Aqueous NaOH (250 mL of a 2 M solution) was slowly added at 0°C and the solution was extracted with Et_2O (4×250 mL). The combined organic extracts were dried over $MgSO_4$ and the volatiles were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (6 mL), then *m*-CPBA (60% w/w, 1.05 g, 3.57 mmol) was added. The reaction mixture was stirred for 10 min, then sat. aq. $NaHCO_3$ (17 mL) was added at 0°C and stirring was continued for 20 min. The solution was extracted with CH_2Cl_2 (3×50 mL) and the combined organic extracts were dried over $MgSO_4$. The volatiles were removed under reduced pressure and chromatography of the residue (cyclohexane/EtOAc, 1:1) afforded α,β-unsaturated lactone **11** (700 mg, 94%) as a clear colorless oil: R_f 0.43 (cyclohexane/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.04, 0.09 (2 s, 6H, $SiCH_3$), 0.7–1.0 (m, 12H, $SiC(CH_3)_3$ and CH_2CH_3), 1.4–1.7 (m, 5H, containing at 1.39 (s, 3H, CH_3Cq) and CH_2CH_3), 3.53 (dd, ^3J=7.5, 3.9 Hz, 1H, CHOTBS), 6.00 (d, ^3J=5.6 Hz, 1H, CHC=O), 7.34 (d, ^3J=5.6 Hz, 1H, CH=CHC=O); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.1 ($SiCH_3$), 11.0 (CH_2CH_3), 18.3 (CqSi), 20.2 (CH_3Cq), 26.0 ($C(CH_3)_3$), 26.3 (CH_2CH_3), 78.1 (CHOTBS), 91.7 ($CqCH_3$), 121.6 (CHC=O), 159.1 (CH=CHC=O), 173.2 (C=O); CIMS (NH_3) *m/z* (%): 288 (MNH_4^+, 100), 271 (MH^+, 22), 186 (33); Anal. calcd for $C_{14}H_{26}O_3Si$: C, 62.18, H, 9.69; found: C, 62.16, H, 9.78.

4.10. (5*S* *,1′*S* *)-5-(1′-Hydroxypropyl)-5-methyl-5*H*-furan-2-one (12)

The silyl ether **11** (27 mg, 0.1 mmol) was dissolved in TFA/H_2O/THF (9:1:1) (3 mL). After 2 h stirring, the solvents were evaporated to dryness and the residue was purified by chromatography to afford 5-(1-hydroxypropyl)-5-methyl-5*H*-furan-2-one (**12**) (15 mg, quant.) as a clear colorless oil: R_f 0.26 (cyclohexane/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.03 (t, ^3J=7.3 Hz, 3H, CH_2CH_3), 1.39 (dqd, ^2J=14.3 Hz, ^3J=7.2, 2.9 Hz, 1H, CH_2CH_3), 1.49 (s, 3H, CH_3Cq), 1.58 (dqd, ^2J=14.5 Hz, ^3J=7.4, 2.5 Hz, 1H, CH_2CH_3), 2.12 (bs, 1H, OH), 3.53 (dd, ^3J=10.2, 2.2 Hz, 1H, CHOH), 6.08 (d, ^3J=5.7 Hz, 1H, CHC=O), 7.41 (d, ^3J=5.7 Hz, 1H, CH=CHC=O); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.6 (CH_2CH_3), 19.0 (CH_3Cq), 24.6 (CH_2CH_3), 77.1 (CHOH), 91.4 ($CqCH_3$), 121.5 (CHC=O), 158.5 (CH=CHC=O), 172.2 (C=O); HRMS calcd for $C_8H_{12}O_3$+Na 179.0684; found: 179.0691.

4.11. 5-Methyl-5-phenylacetyl-4-(pyrrolidin-1-yl)-5*H*-furan-2-one (13)

To a solution of 5-methyl-4-(pyrrolidin-1-yl)-5*H*-furan-2-one (**3**) (0.30 g, 1.80 mmol) in anhydrous THF (3.3 mL) at −78°C was added dropwise *t*-BuLi (1.7 M in pentane, 1.58 mL, 2.69 mmol) and the solution was stirred for 1 h at −78°C. Chlorotrimethylsilane (0.27 mL, 2.15 mmol) was added dropwise. The reaction mixture was stirred at −78°C for 30 min and at 0°C for 30 min. After recooling to −78°C, phenylacetyl chloride (0.28 mL, 2.15 mmol) was added dropwise. After stirring for 1 h at −78°C and 3 h at 0°C, the volatiles were removed under reduced pressure and chromatography of the residue (cyclohexane/EtOAc, 3:7) afforded ketone **10** (0.42 g, 82%): R_f 0.34 (cyclohexane/EtOAc, 3:7); IR (neat): ν 1725 (C=O), 1602 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.65 (s, 3H, CH_3), 1.7–1.9 (m, 4H, CH_{2Pyr}), 2.8–3.3 (m, 4H, CH_{2Pyr}), 3.69 (d, ^2J=14.7 Hz, 1H, CH_2Ph), 3.91 (d, ^2J=14.7 Hz, 1H, CH_2Ph), 4.55 (s, 1H, CH=C), 7.1–7.3 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.9 (CH_3), 24.1, 25.9 (CH_{2Pyr}), 42.2 (CH_2Ph), 47.6, 50.7 (CH_{2Pyr}), 82.9 (CH=C), 86.9 ($CqCH_3$), 127.2, 128.5, 129.5 (CH_{arom}), 133.3 (Cq_{arom}), 167.1 (CqN), 173.3 (OC=O), 202.5 (CH_2C=O); CIMS (NH_3) *m/z* (%): 286 (MH^+, 100), 244 (36), 168 (6), 72 (14); Anal. calcd for $C_{17}H_{19}NO_3$: C, 71.56, H, 6.71, N, 4.91; found: C, 71.98, H, 6.60, N, 4.53.

4.12. 5-Methyl-5-propionyl-4-(pyrrolidin-1-yl)-5*H*-furan-2-one (14)

The above protocol for **13** was reproduced with propionyl chloride (63 μL, 0.72 mmol) and 5-methyl-4-(pyrrolidin-1-yl)-5*H*-furan-2-one (**3**) (0.10 g, 0.60 mmol). Chromatography of the residue (EtOAc) afforded ketone **14** (0.11 g, 82%): R_f 0.44 (EtOAc); IR (neat): ν 1727 (C=O), 1602 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.00 (t, ^3J=7.0 Hz, 3H, CH_2CH_3), 1.67 (s, 3H, CH_3Cq), 1.8–2.0 (m, 4H, CH_{2Pyr}), 2.43 (dq, ^2J=18.6 Hz, ^3J=6.9 Hz, 1H, CH_2CH_3), 2.74 (dq, ^2J=18.7 Hz, ^3J=7.0 Hz, 1H, CH_2CH_3), 3.1–3.5 (m, 4H, CH_{2Pyr}), 4.53 (s, 1H, CH=C); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 7.6 (CH_3CH_2), 19.1 (CH_3Cq), 24.2, 26.3 (CH_{2Pyr}), 28.9 (CH_2CH_3), 47.9, 51.0 (CH_{2Pyr}), 82.2 (CH=C), 87.1 ($CqCH_3$), 167.5 (CqN), 173.3 (OC=O), 208.2 (CH_2C=O); CIMS (NH_3) *m/z* (%): 224 (MH^+, 100); Anal. calcd for $C_{12}H_{17}NO_3$: C, 64.55, H, 7.67, N, 6.27; found: C, 64.71, H, 7.84, N, 6.07.

4.13. (5*S* *,1′*S* *)-5-(1′-Hydroxy-2′-phenylethyl)-5-methyl-4-(pyrrolidin-1-yl)-5*H*-furan-2-one (4b)

To a solution of 5-methyl-5-phenylacetyl-4-(pyrrolidin-1-yl)-5*H*-furan-2-one (**13**) (0.30 g, 1.05 mmol) in MeOH (7.6 mL) at 0°C was added cerium(III) chloride (0.39 g, 1.58 mmol). Sodium borohydride (0.16 g, 4.21 mmol) was

added portionwise. The reaction mixture was stirred at room temperature to completion. The volatiles were removed under reduced pressure and filtration of the residue over silica gel (EtOAc) afforded alcohol **4b** (0.30 g, 98%) as a light yellow solid: R_f 0.24 (EtOAc); mp 144°C; IR (neat): ν 3283 (OH), 1686 (C═O), 1584 (C═C) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.62 (s, 3H, CH_3), 1.8–2.0 (m, 4H, CH_{2Pyr}), 2.4–2.5 (m, 1H, OH), 2.74 (dd, ^2J=14.1 Hz, ^3J= 10.2 Hz, 1H, CH_2Ph), 3.03 (dd, ^2J=14.1 Hz, ^3J=2.1 Hz, 1H, CH_2Ph), 3.3–3.6 (m, 4H, CH_{2Pyr}), 4.03 (bd, ^3J=9.5 Hz, 1H, C*H*OH), 4.44 (s, 1H, CH═C), 7.1–7.3 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.2 (CH_3), 25.3 (CH_{2Pyr}), 38.1 (*C*H_2Ph), 49.6 (CH_{2Pyr}), 75.0 (CHOH), 83.2 (*C*H═C), 86.5 (*C*qCH_3), 126.6, 128.6, 129.4 (CH_{arom}), 138.2 (Cq_{arom}), 170.8 (CqN), 173.6 (C═O); CIMS (NH_3) *m/z* (%): 288 (MH^+, 100), 168 (10); HRMS calcd for $C_{17}H_{21}NO_3$+Na 310.1419; found: 310.1418.

4.14. (5*S* *,1′*S* *)-5-(1′-Hydroxypropyl)-5-methyl-4-(pyrrolidin-1-yl)-5*H*-furan-2-one (5b)

The protocol for **4b** was carried out using 5-methyl-5-propionyl-4-(pyrrolidin-1-yl)-5*H*-furan-2-one (**14**) (50 mg, 0.22 mmol). Filtration of the residue (EtOAc) afforded alcohol **5b** (44 mg, 87%): R_f 0.30 (CH_2Cl_2/MeOH, 98:2); IR (neat): ν 3306 (OH), 1694 (C═O), 1588 (C═C) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.01 (t, ^3J=7.4 Hz, 3H, CH_2CH_3), 1.50 (dqd, ^2J=14.3 Hz, ^3J=7.1, 3.0 Hz, 1H, CH_2CH$_3$), 1.53 (s, 3H, CH_3Cq), 1.73 (dqd, ^2J=14.4 Hz, ^3J=7.5, 2.5 Hz, 1H, CH_2CH$_3$), 1.9–2.1 (m, 4H, CH_{2Pyr}), 3.2–3.5 (m, 4H, CH_{2Pyr}), 3.72 (bt, ^3J=4.3 Hz, 1H, C*H*OH), 4.42 (s, 1H, CH═C); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.7 (CH_2CH_3), 20.8 (*C*H_3Cq), 24.5 (*C*H_2CH$_3$), 25.2, 49.6 (CH_{2Pyr}), 75.1 (CHOH), 83.2 (*C*H═C), 86.7 (*C*qCH_3), 171.1 (CqN), 173.7 (C═O); CIMS (NH_3) *m/z* (%): 226 (MH^+, 100), 186 (16), 166 (8); Anal. calcd for $C_{12}H_{19}NO_3$: C, 63.98, H, 8.50, N, 6.22; found: C, 63.48, H, 8.50, N, 5.81.

4.15. (5*R* *,1′*S* *,2″*S*)-5-(1′-Hydroxy-2′-phenylethyl)-4-(2″-methoxymethylpyrrolidin-1″-yl)-5-methyl-5*H*-furan-2-one (16)

The protocol for **4** was used on (2′*S*)-4-(2′-methoxymethylpyrrolidin-1′-yl)-5-methyl-5*H*-furan-2-one (**15**) (0.30 g, 1.42 mmol). Chromatography of the residue (CH_2Cl_2/MeOH, 98:2) afforded aldols **16a** and **16b** as a 1:1 mixture (0.25 g, 53%). The following spectroscopic properties for the mixture are given: R_f 0.28 (CH_2Cl_2/MeOH, 95:5); IR (neat): ν 3448 (OH), 1718 (C═O), 1584 (C═C) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.68, 1.72 (2 s, 6H, CH_3Cq), 1.8–2.2 (m, 8H, CH_{2Pyr}), 2.60 (dd, ^2J=14.0 Hz, ^3J= 10.4 Hz, 1H, CH_2Ph), 2.75 (d, ^3J=7.0 Hz, 2H, CH_2Ph), 2.79 (dd, ^2J=13.7 Hz, ^3J=2.4 Hz, 1H, CH_2Ph), 3.2–3.8 (m, 16H, containing at 3.25, 3.29 (2 s, 6H, OCH_3) and CH_{2Pyr}, CHN, CH_2O), 3.94 (bd, ^3J=9.1 Hz, 1H, C*H*OH), 4.12 (bt, ^3J=6.3 Hz, 1H, C*H*OH), 4.58 (s, 2H, CH═C), 7.1–7.3 (m, 10H, H_{arom}); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.3, 21.3 (*C*H_3Cq), 24.0, 27.7, 28.0 (CH_{2Pyr}), 37.8, 38.6 (*C*H_2Ph), 49.2, 50.0 (CH_{2Pyr}), 59.3 (OCH_3), 61.1 (CHN), 70.6 (CH_2O), 74.6, 75.7 (CHOH), 84.2 (*C*H═C), 86.8 (*C*qCH_3), 126.5, 126.6, 128.5, 129.4, 129.5 (CH_{arom}), 137.9, 138.6 (Cq_{arom}), 170.1, 170.3 (CqN), 173.4 (C═O); CIMS (NH_3) *m/z* (%): 332 (MH^+, 100), 212 (52), 138 (16).

4.16. (5*R* *,1′*S* *,2″*S*)-5-(1′-Hydroxypropyl)-4-(2″-methoxymethylpyrrolidin-1″-yl)-5-methyl-5*H*-furan-2-one (17)

The protocol for **4** was used on propionaldehyde (0.12 mL, 1.70 mmol) and (2′*S*)-4-(2′-methoxymethylpyrrolidin-1′-yl)-5-methyl-5*H*-furan-2-one (**15**) (0.30 g, 1.42 mmol). Chromatography of the residue (CH_2Cl_2/MeOH, 98:2) afforded aldols **17a** and **17b** as a 1:1 mixture (0.23 g, 59%). The following spectroscopic properties for the mixture are given: R_f 0.15 (CH_2Cl_2/MeOH, 98:2). IR (neat): ν 3424 (OH), 1707 (C═O), 1586 (C═C) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.98 (t, ^3J=7.4 Hz, 6H, CH_2CH_3), 1.3–1.8 (m, 10H, containing at 1.65, 1.68 (2 s, 6H, CH_3Cq) and CH_2CH$_3$), 1.8–2.1 (m, 8H, CH_{2Pyr}), 3.1–3.8 (m, 18H, containing at 3.29, 3.31 (2 s, 6H, OCH_3), and CH_{2Pyr}, C*H*OH, CHN, CH_2O), 4.52, 4.53 (2 s, 2H, CH═C); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.3, 10.5 (CH_2CH_3), 20.4, 21.4 (*C*H_3Cq), 24.1, 24.6 (CH_{2Pyr}), 28.0 (*C*H_2CH$_3$), 49.4, 49.7 (CH_{2Pyr}), 59.3 (OCH_3), 61.1 (CHN), 70.9 (CH_2O), 75.1, 76.0 (CHOH), 84.1 (*C*H═C), 87.1 (*C*qCH_3), 170.2, 170.7 (CqN), 173.5 (C═O); CIMS (NH_3) *m/z* (%): 270 (MH^+, 22), 116 (100), 72 (29).

4.17. (2′*S*)-4-(2′-Methoxymethylpyrrolidin-1′-yl)-5-methyl-5-phenylacetyl-5*H*-furan-2-one (18)

The protocol for **13** was carried out using phenylacetyl chloride (2.25 mL, 1.70 mmol) and (2′*S*)-4-(2′-methoxymethylpyrrolidin-1′-yl)-5-methyl-5*H*-furan-2-one (**15**) (0.30 g, 1.42 mmol). Chromatography of the residue (cyclohexane/EtOAc, 3:7) afforded ketone **18** as a 9:1 mixture of diastereoisomers (0.36 g, 73%). The following spectroscopic properties for the major isomer are given: R_f 0.49 (EtOAc); IR (neat): ν 1725 (C═O), 1594 (C═C) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.67 (s, 3H, CH_3Cq), 1.7–2.0 (m, 4H, CH_{2Pyr}), 3.1–3.3 (m, 7H, containing at 3.24 (s, 3H, OCH_3) and CH_{2Pyr}, CH_2O), 3.67 (bs, 1H, CHN), 3.81 (bs, 2H, CH_2Ph), 4.66 (s, 1H, CH═C), 7.0–7.3 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.2 (*C*H_3Cq), 24.1, 28.0 (CH_{2Pyr}), 41.9 (*C*H_2Ph), 48.8 (CH_{2Pyr}), 59.1 (OCH_3), 61.5 (CHN), 70.4 (CH_2O), 83.9 (*C*H═C), 87.7 (*C*qCH_3), 127.1, 128.5, 129.5 (CH_{arom}), 133.3 (Cq_{arom}), 167.0 (CqN), 173.3 (OC═O), 203.0 (CH_2*C*═O); CIMS (NH_3) *m/z* (%): 330 (MH^+, 100), 288 (16); Anal. calcd for $C_{14}H_{21}NO_4$: C, 62.90, H, 7.92, N, 5.24; found: C, 62.96, H, 7.98, N, 5.05.

4.18. (2′*S*)-4-(2′-Methoxymethylpyrrolidin-1′-yl)-5-methyl-5-propionyl-5*H*-furan-2-one (19)

The protocol for **13** was carried out using propionyl chloride (0.15 mL, 1.70 mmol) and (2′*S*)-4-(2′-methoxymethylpyrrolidin-1′-yl)-5-methyl-5*H*-furan-2-one (**15**) (0.30 g, 1.42 mmol). Chromatography of the residue (cyclohexane/EtOAc, 3:7) afforded ketone **19** as a 9:1 mixture of diastereoisomers (0.27 g, 70%). The following spectroscopic properties for the major isomer are given: R_f 0.31 (cyclohexane/EtOAc, 3:7); IR (neat): ν 1724 (C═O), 1594 (C═C) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, ^3J=7.2 Hz, 3H, CH_2CH_3), 1.59 (s, 3H, CH_3Cq), 1.7–2.0 (m, 4H, CH_{2Pyr}), 2.33 (dq, ^2J=18.5 Hz, ^3J=7.2 Hz, 1H, CH_2CH$_3$), 2.60 (dq, ^2J=18.6 Hz, ^3J=7.3 Hz, 1H, CH_2CH$_3$),

3.2–3.5 (m, 7H, containing at 3.18 (s, 3H, OCH_3) and CH_{2Pyr}, CH_2O), 3.66 (bs, 1H, CHN), 4.55 (s, 1H, CH═C); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.5 (CH_2CH_3), 19.0 (CH_3Cq), 24.1 (CH_{2Pyr}), 28.1 (CH_2CH_3), 28.4, 48.8 (CH_{2Pyr}), 59.0 (OCH_3), 61.2 (CHN), 70.4 (CH_2O), 83.6 (CH═C), 87.5 ($CqCH_3$), 167.2 (CqN), 173.3 (OC═O), 206.1 (CH_2C═O); CIMS (NH_3) *m/z* (%): 268 (MH^+, 100), 226 (10); Anal. calcd for $C_{19}H_{23}NO_4$: C, 69.28, H, 7.04, N, 4.25; found: C, 69.22, H, 7.22, N, 4.18.

4.19. (5*R*,1′*R*,2″*S*)-5-(1′-Hydroxy-2′-phenylethyl)-4-(2″-methoxymethylpyrrolidin-1″-yl)-5-methyl-5*H*-furan-2-one (20a)

The protocol for **4b** was reproduced with (2′*S*)-4-(2′-methoxymethylpyrrolidin-1′-yl)-5-methyl-5-phenylacetyl-5*H*-furan-2-one (**18**) (50 mg, 0.15 mmol). Filtration of the residue (CH_2Cl_2/MeOH, 8:2) afforded alcohols **20a** and **20b** as a 9:1 mixture (46 mg, 91%). Chromatography of a sample of the mixture (CH_2Cl_2/MeOH, 98:2) allowed the separation of isomer **20a** which could be crystallized (Isopropylether): R_f 0.28 (EtOAc); mp 132°C; $[\alpha]_D^{20}$=+72.8 (*c* 0.5, $CHCl_3$); IR (neat): ν 3356 (OH), 1694 (C═O), 1575 (C═C) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.65 (s, 3H, CH_3Cq), 1.8–2.0 (m, 4H, CH_{2Pyr}), 2.50 (d, ^3J=6.1 Hz, 1H, OH), 2.70 (dd, ^2J=13.9 Hz, ^3J=10.3 Hz, 1H, CH_2Ph), 2.98 (dd, ^2J=14.0 Hz, ^3J=2.3 Hz, 1H, CH_2Ph), 3.2–3.5 (m, 6H, containing at 3.27 (s, 3H, OCH_3) and CHN, CH_2O), 3.6–3.9 (m, 2H, CH_{2Pyr}), 3.98 (ddd, ^3J=10.2, 6.1, 2.3 Hz, 1H, C*H*OH), 4.58 (s, 1H, CH═C), 7.1–7.3 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.9 (CH_3Cq), 24.2, 28.0 (CH_{2Pyr}), 37.6 (CH_2Ph), 49.5 (CH_{2Pyr}), 59.1 (OCH_3), 61.0 (CHN), 70.6 (CH_2O), 75.2 (CHOH), 85.0 (CH═C), 86.7 ($CqCH_3$), 126.6, 128.6, 129.4 (CH_{arom}), 138.4 (Cq_{arom}), 169.7 (CqN), 173.5 (C═O); CIMS (NH_3) *m/z* (%): 332 (MH^+, 100), 212 (20); Anal. calcd for $C_{19}H_{25}NO_4$: C, 68.86, H, 7.60, N, 4.23; found: C, 68.19, H, 7.65, N, 3.55.

4.20. (5*R*,1′*R*,2″*S*)-5-(1′-Hydroxypropyl)-4-(2″-methoxymethylpyrrolidin-1″-yl)-5-methyl-5*H*-furan-2-one (21a)

The above protocol for **20** was used with (2′*S*)-4-(2′-methoxymethylpyrrolidin-1′-yl)-5-methyl-5-propionyl-5*H*-furan-2-one (**19**) (50 mg, 0.19 mmol). Filtration of the residue (CH_2Cl_2/MeOH, 8:2) afforded alcohols **21a** and **21b** as a 9:1 mixture (49 mg, 91%). The following spectroscopic properties for the major isomer **21a** are given: R_f 0.31 (CH_2Cl_2/MeOH, 98:2); IR (neat): ν 3335 (OH), 1696 (C═O), 1578 (C═C) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.99 (t, ^3J=7.4 Hz, 3H, CH_2CH_3), 1.45 (dqd, ^2J=14.2 Hz, ^3J=7.3, 2.9 Hz, 1H, CH_2CH$_3$), 1.55 (s, 3H, CH_3Cq), 1.66 (dqd, ^2J=14.3 Hz, ^3J=7.5, 2.4 Hz, 1H, CH_2CH$_3$), 1.8–2.1 (m, 4H, CH_{2Pyr}), 2.50 (d, ^3J=7.8 Hz, OH), 3.2–3.5 (m, 7H, containing at 3.28 (s, 3H, OCH_3) and CH_{2Pyr}, CH_2O), 3.66 (td, ^3J=7.8, 2.3 Hz, 1H, C*H*OH), 3.76 (bs, 1H, CHN), 4.55 (s, 1H, CH═C); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.9 (CH_2CH_3), 20.6 (CH_3Cq), 24.0, 24.2 (CH_{2Pyr}), 28.0 (CH_2CH_3), 49.4 (CH_{2Pyr}), 59.1 (OCH_3), 60.9 (CHN), 70.6 (CH_2O), 75.4 (CHOH), 85.0 (CH═C), 87.0 ($CqCH_3$), 170.1 (CqN), 173.6 (C═O); CIMS (NH_3) *m/z* (%): 270 (MH^+, 100), 226 (7), 212 (13); Anal. calcd for $C_{14}H_{23}NO_4$: C, 62.43, H, 8.61, N, 5.20; found: C, 62.61, H, 8.67, N, 5.06.

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