Formaldehyde SAMP-Hydrazone as a Neutral Formyl Anion Equivalent: Asymmetric Synthesis of Substituted β-Formyl δ-Lactones and Furofuran Lactones

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Dedicated to Professor Günther Wulff on the occasion of his 65th birthday

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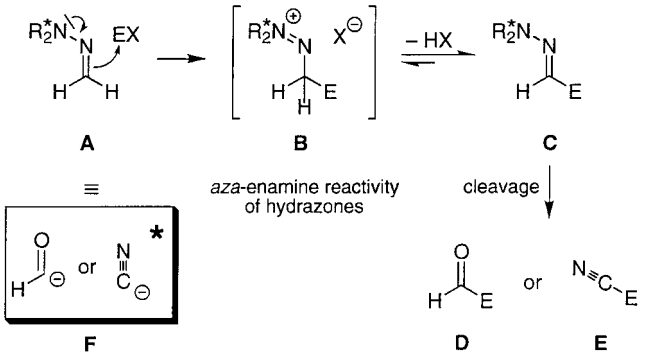
An efficient asymmetric synthesis of α-substituted β-formyl δ-lactones **5** (de ≥ 98%, *ee* = 80–95%) and 4-substituted furofuran lactones **6** (*de* ≥ 98%, *ee* = 80–>98%) in acceptable overall yields is reported. Key steps of the new procedure are an asymmetric Michael addition of formaldehyde SAMP-hydrazone (**1**) to 5,6-dihydro-2*H*-pyran-2-one (**2**) under neutral conditions, followed by *trans*-selective α-alkylation and subsequent cleavage of the auxiliary by ozonolysis or a hydrolytic domino reaction protocol, respectively. The absolute configurations given for the title compounds are based on three X-ray structure analyses and NOE measurements.

Introduction

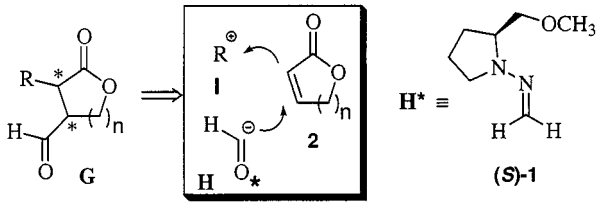
Nucleophilic formylation is an important C–C bond-forming process in synthetic chemistry and a variety of reagents, including asymmetric analogues, have been developed in recent years.[1] In the late1960's, Brehme et al.[2] recognized that formaldehyde *N*,*N*-dialkylhydrazones **A** can be regarded as azaenamines and reported electrophilic substitutions at the aldehyde hydrazone carbon on treatment with reactive electrophiles (**A B C**). After transformation of the hydrazone group to the aldehyde (**C D**) or nitrile function (**C E**), the overall result is a nucleophilic formylation or cyanation under neutral conditions. Thus, formaldehyde hydrazones **A** are indeed synthetic equivalents of the formyl and cyanide anion synthons **F** (Scheme 1).[3]



Scheme 1. Formaldehyde *N*,*N*-dialkylhydrazones as neutral formyl anion and cyanide equivalents

The commercially available formaldehyde SAMP-hydrazone [(*S*)-**1**][3] has been successfully employed as a chiral formyl-d[1] reagent in the nucleophilic asymmetric formylation and cyanation of a variety of electrophilic substrates, including nitroalkenes,[4] sugar aldehydes,[5] α,β-unsaturated ketones,[6] and trifluoromethyl ketones.[7] Because this methodology allows introduction of the versatile aldehyde or nitrile functionality with a high level of stereoselectivity, it has great synthetic potential as a tool for asymmetric carbon–carbon bond formation in the construction of complex organic molecules.

This neutral chiral equivalent of the formyl anion **H** should allow stereoselective introduction of the formyl group at the β-position of lactones **2** through 1,4-addition (Scheme 2). Moreover, subsequent alkylation with alkyl halides **I** should generate a second stereogenic centre with the introduction of further groups α to the carbonyl group. Therefore, a Michael addition/α-alkylation protocol should allow a vicinal difunctionalization of lactone frameworks, as indicated in the retrosynthetic analysis of Scheme 2.



Scheme 2. Retrosynthetic analysis of β-formyl γ- and δ-lactones

There have been several precedents for the vicinal difunctionalization of 2-butenolide (**2a**), which have been directed towards the synthesis of lignans.[8] Of note are the processes involving the use of metallated dithianes,[9] *O*-silylcyanohydrins,[10] and α-aminonitriles[11] as nucleophiles and subsequent trapping with various electrophiles. However, very little has been reported on such processes employing unsaturated six-membered lactones as Michael acceptors.[12]

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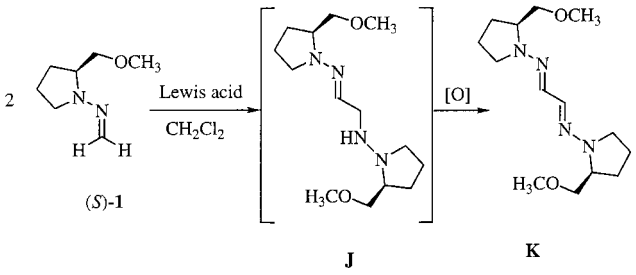
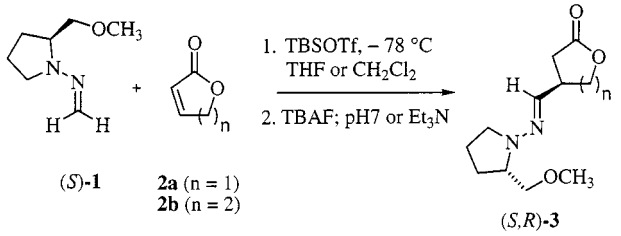
Lactones[13] and their derivatives constitute important subunits in many natural products, such as sesquiterpenes,[14] α-methylene lactones,[15] and macrolides.[16] Moreover, many exhibit important biological properties, for example as semiochemicals, as flavours and fragrances, or as antibiotics or cytostatics. Therefore, the efficient and versatile asymmetric synthesis of lactone building blocks is of great interest.[17] With this in mind, we decided to extend the already well-established formaldehyde SAMP-hydrazone methodology to α,β-unsaturated lactones.[18]



Scheme 4. Self-condensation of (*S*)-**1** in the presence of Lewis acids

Results and Discussion

We wish to describe here in detail our protocol for the stepwise Michael addition/α-alkylation of (*S*)-**1** to lactones **2** (Scheme 3 and 5). The use of a Lewis acid proved necessary in order to activate the α,β-unsaturated lactones **2** towards attack by formaldehyde SAMP-hydrazone. Various Lewis acids ($AlCl_3$, BF_3Et_2O, $TiCl_4$, $ZnCl_2$, etc.) were tested, but as has previously been observed with enones,[6] only the use of trialkylsilyl triflates (TBS or TMS) as promoters led to formation of the desired Michael adduct (*S,R*)-**3**, the best results being obtained with TBS triflate. These reactions were found to be very dependent on the lactone ring size and hence it was not possible to establish a general method for both lactones (**2a**,**b**). In the case of 5-hydro-2*H*-furan-2-one (**2a**), the best results were achieved when the hydrazone (*S*)-**1** was slowly added to a solution of the preformed trialkylsilyl lactone complex at −78 °C (see Experimental Section). Under these conditions, although the Michael product could only be obtained in poor yield (20%), it was formed with an excellent diastereoisomeric excess (*de* >95%). In the case of 5,6-dihydro-2*H*-pyran-2-one (**2b**), the best results were achieved by slow addition of the promoter to the mixture of reactants (see Experimental Section).



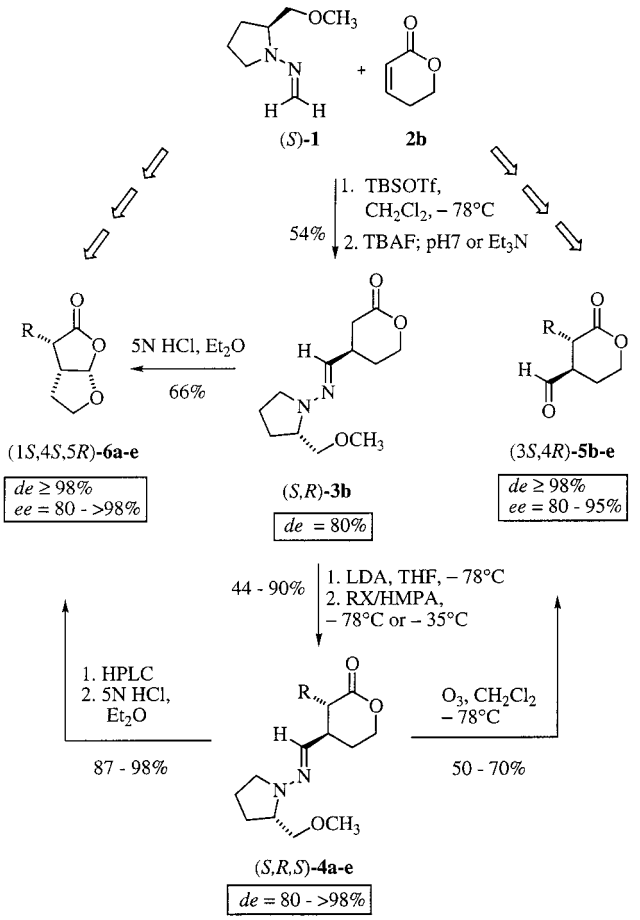
Scheme 3. Asymmetric Michael addition of (*S*)-**1** to α,β-unsaturated lactones

These reactions not only proved dependent on the order of addition of reactants, but were also found to be strongly dependent on the solvent used. In the case of 2-butenolide (**2a**), it proved necessary to carry out the reaction in tetrahydrofuran, since in dichloromethane the dimer **K**[19] was formed, owing to self-condensation of formaldehyde SAMP-hydrazone via the intermediate **J** (Scheme 4). In this case, (*S*)-**1** reacts both as a nucleophilic and as an electrophilic species. A similar outcome was observed in the addition of formaldehyde 1-aminopyrrolidine hydrazone to aldehydes.[20]

On the other hand, in the case of 2-pentenolide (**2b**) the use of dichloromethane proved necessary as THF was found to favour the formation of by-products, again arising from the dual electrophilic and nucleophilic nature of formaldehyde SAMP-hydrazone. Furthermore, it also proved necessary to carry out the reaction under dilute conditions to avoid the formation of these by-products. Under optimized conditions, it was possible to obtain the desired Michael product **3** ($n = 2$) in acceptable yield (54%) and with good diastereomeric excess (*de* = 80%). The corresponding intermediate silyl ketene acetal was found to be unstable to purification by chromatography, which obviated the need for subsequent treatment of the Michael adduct with tetrabutylammonium fluoride (TBAF). The reaction was therefore quenched with pH 7 buffer or Et_3N to neutralize the triflic acid generated. The diastereomeric excess of the Michael adduct **3** was determined by ^{13}C- or ^{1}H-NMR spectroscopy.

Although initially the reaction proceeded quite quickly (35% yield after 3 h), its rate decreased dramatically after the first 3 h (40% after 8 h) and no improvement in the yield was observed beyond 30 h (54% yield after 30 h and after 48 h). Since scaling up of the reaction with 2-butenolide did not allow the synthesis of reasonable amounts of γ-lactones **3** ($n = 1$), it was decided to use only the Michael product **3** ($n = 2$) obtained from the pentenolide. Unfortunately, it was found that the mixture of β-epimers **3** could only be separated by HPLC on chiral stationary phases. This mixture was therefore used directly in the subsequent deprotonation/α-alkylation step. Attempts to trap the silyl ketene acetal intermediate using different alkyl halides were unsuccessful.

A screening of various bases (lithium tetramethylpiperidide, *tert*-butyllithium, and lithium diisopropylamide) showed that LDA gave significantly better results compared to the other bases. Accordingly, lactone **3b** was deprotonated using LDA[21] at −78 °C, hexamethylphosphoramide (HMPA, 2.5–5 equiv.) was added, and subsequent addition of the requisite alkylating agent afforded the α-substituted lactone hydrazones **4** (Scheme 5, Table 1) in moderate to excellent yields (44–90%) and with satisfactory diastereomeric excesses (*de* = 80–>98%). However, the reaction did not take place in the absence of the HMPA



Scheme 5. Asymmetric synthesis of substituted β-formyl δ-lactones and furofuran lactones

additive. In order to prevent self-condensation,[22] a THF solution of the lactone (cooled to –78 °C) was slowly added to a solution of the lithium amide base. Various experiments indicated that an increase in the reaction temperature led to decreases in both the *de* and the yield. Posner et al. observed a similar reduction in yield at temperatures in excess of –30 °C.[21a] Therefore, by maintaining the reaction temperature at –78 °C in the case of more reactive electrophiles and warming to –35 °C in the case of less reactive electrophiles, the partial decomposition of the anion was minimized. After several hours, TLC control indicated total consumption of the starting materials in the case of more reactive electrophiles (Table 1, entries **a**, **b**, **e**). However, in the other cases (entries **c**, **d**) requiring longer reaction times, a certain amount of starting material (2–5%) persisted. Initial reaction temperatures of –100 °C with subsequent warming to –78 °C or –35 °C had little effect on the results obtained previously. The only exception was in the case of methyl iodide, where the *de* value of the alkylation increased by 10%. Although optimal conditions involved the use of relatively large quantities of HMPA (2.5–5 equivalents), both the yield and the *de* value were found to increase by up to 20%. The use of 5–10 equivalents of DMPU instead of HMPA led to similar results. Under the optimized alkylation conditions, dialkylation (6%) was only observed in the case of propyl iodide. Dialkylation also occurred using allyl and benzyl bromides, when the reaction mixtures were slowly allowed to warm to 0 °C.

Unfortunately, employing potassium diisopropylamide (KDA) the use of additives could not be avoided and lower yields were achieved. Interestingly, however, the use of this base had an effect on the ratio of the *trans*/*cis*-alkylated products in each case (see Table 2). The most drastic effect was observed in the case of methyl iodide, where the *cis*-configured lactone product became the major isomer. The addition of tetrabutylammonium iodide to exchange the counterion did not increase the ratio of the *cis*/*trans* products.

The relative *trans*-configuration of the α,β-disubstituted lactones **4** was determined by ^{1}H-NMR spectroscopy based

Table 2. α-Alkylation of lactone (*S*,*R*)-**3b** using LDA or KDA as base

entry	RX	ratio *trans*/*cis*[a] (HMPA/LDA)	ratio *trans*/*cis*[a] (DMPU/KDA)
a	MeI	13 : 1	1 : 2.5
b	*n*PrI	4.9 : 1	4.6 : 1
c	AllylBr	61 : 1	7 : 1
d	BnBr	>99 : 1	10 : 1

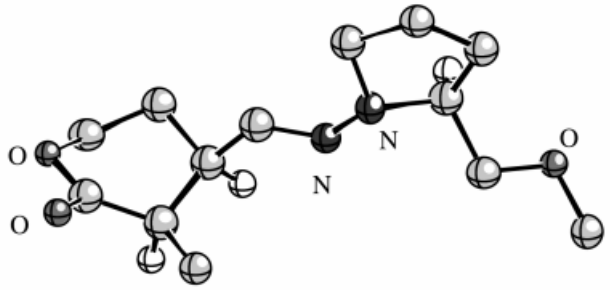
[a] Determined by HPLC on chiral stationary phases [chiralpak AD (4.6 × 250 mm), (*S*,*S*)-Whelk-O 1 (4 × 250 mm), chiralcel OJ (4.6 × 250 mm)].

Table 1. Stepwise Michael addition/α-alkylation of (*S*)-**1** to 2-pentenolide **2** and subsequent hydrazone cleavage to β-formyl δ-lactones **5**

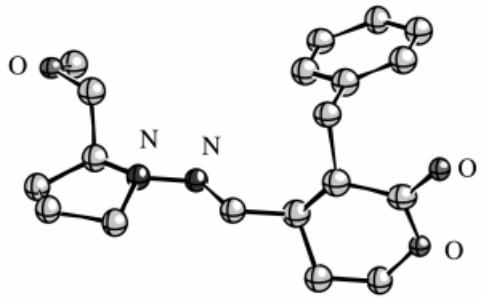
4,**5**	RX	yield[a] (%)	$[\alpha]_D^{RT}$ (*c*, $CHCl_3$)	*de*[b] (%)	yield **5** (%)	$[\alpha]_D^{RT}$ (*c*, $CHCl_3$)	*ee* (%)
a	AllylBr	90	−158.5 (1.20)	>98 (98)	[c]	–	–
b	MeI	89	−126.4 (2.88)	80[d,e] (88)	70	+36.4 (1.11)	82[f]
c	*n*PrI	67	−132.6 (1.44)	88 (74)	68	+21.5 (0.78)	89[g]
d	$TBSO(CH_2)_2I$	44	−99.7 (1.30)	94 (59)	50	−1.3 (0.77)	95[h]
e	BnBr	77	−155.7 (0.97)	80[e] (>98)	59	−9.0 (0.89)	80[i]

[a] Yield after flash chromatography. – [b] Determined by HPLC on chiral stationary phases [chiralpak AD (4.6 × 250 mm), (*S*,*S*)-Whelk-O 1 (4 × 250 mm), chiralcel OJ (4.6 × 250 mm)] after HPLC separation. Figures in brackets refer to the *de* values of the alkylation reactions. – [c] **5a** decomposes during ozonolysis. – [d] After flasch chromatography. – [e] Dieastereoisomers were not separable by HPLC. – [f] Determined from the *de* of the corresponding acetal derived from (*R*,*R*)-2,3-butanediol by GC on a chiral stationary phase (Lipodex E 25 m). – [g] Determined by shift experiments using (*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol as co-solvent. – [h] Determined as *de* of the corresponding hydrazone **4**. – [i] Determined as *de* of the corresponding acetal by HPLC on chiral stationary phases [(*S*,*S*)-Whelk-O 1 (4 × 250 mm)].

on the *trans*-diaxial coupling constants (9.5–10.7 Hz) of the protons at the new stereogenic centres.[23] The absolute configuration of the major diastereoisomer (3*S*,4*R*)-**4e** was determined by X-ray crystal structure analysis. X-ray analysis of **4e** indicated that the lactone ring adopts a chair-like conformation with the C-3 and C-4 substituents adopting a *trans*-diequatorial orientation (Figure 1). On the other hand, the X-ray analysis of the minor diastereoisomer (3*R*,4*R*)-**4b** revealed a boat-like conformation, similar to that observed by Posner (Figure 1).[24]



(2′*S*,3*R*,4*R*)-**4b**



(2′*S*,3*S*,4*R*)-**4e**

Figure 1. Crystal structures of (2′*S*,3*R*,4*R*)-**4b** and (2′*S*,3*S*,4*R*)-**4c**

Assuming a uniform reaction pathway in all cases, the relative chair-like transition-state geometry for the nucleophilic attack of (*S*)-**1** on the α,β-unsaturated δ-lactone **2** can be explained in the same way as previously described for 1,4-additions to enones.[6] Fortunately, in some cases the diastereoisomers of the lactone hydrazones **4** were found to be separable by flash chromatography (**4b**) or by HPLC (**4a**,**c**,**d**) and it was therefore possible to perform the cleavage of the chiral auxiliary using diastereomerically enriched hydrazones.

Cleavage of the Hydrazone Moiety

Finally, in order to confirm the previously demonstrated equivalence of formaldehyde SAMP-hydrazone to the formyl anion, diastereomerically enriched compounds **4** were converted in acceptable yields (50–70%) and with high diastereo- and enantiomeric excesses (*de* ≥ 98%, *ee* = 80–95%, Table 3) to their corresponding α-substituted β-formyl δ-lactones **5** by ozonolysis at –78 °C (Scheme 5).[25] These formyl δ-lactones **5** proved to be relatively unstable and their purification required the use of silica gel of particle size 0.063–0.100 mm to avoid partial decomposition upon chromatography.

Table 3. Asymmetric synthesis of (1*S*,5*R*)-2,8-dioxabicyclo[3.3.0]octan-3-one derivatives **6**

6	R	yield[a] (%)	m.p.[b] (°C)	$[\alpha]_D^{RT}$ (*c*, $CHCl_3$)	*ee*[c] (%)
a	H	66	oil	+29.5 (0.96)	85
b	Me	98 (75)[d]	78–80	+49.8 (0.95)	80 (>98)[d]
c	*n*Pr	97	oil	+76.8 (0.80)	88
d	Allyl	87	52–54	+75.6 (0.80)	>98
e	Bn	90	oil	+104.4 (0.91)	80

[a] Yield after flash chromatography (silica gel, Et_2O/pentane). – [b] Uncorrected, measured on a Büchi apparatus. – [c] Determined by GC on a chiral stationary phase (Chirasil dex 25 m). – [d] Figures in parentheses indicate values after recrystallization of the final product.

The enantiomeric purities of the δ-lactones were determined from the *de* values of the corresponding (*R*,*R*)-dimethylbutanediol acetals,[26] as measured by GC or HPLC on chiral stationary phases (**5b**,**e**), by ^{1}H-NMR shift experiments using (*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol as cosolvent (**5c**), or from the *de* value of the corresponding hydrazone **4** (**5d**). In all cases, it was demonstrated that the ozonolysis proceeds without racemization under the conditions used.[27]

Decomposition of the aldehydes was observed upon prolonged standing, hence it was necessary to store these compounds as their corresponding chemically and optically stable acetals or to prepare them directly prior to use in further reactions.

δ-Lactones **5** are interesting polyfunctional molecules, which may be used as building blocks in the synthesis of more complex compounds. One example of the potential use of these materials may be seen from their behaviour upon hydrolysis.[28] Acidic hydrolysis using 5 N HCl in a two-phase system rapidly initiated a domino reaction and afforded furofuran lactone derivatives **6** in excellent yields (87–98%) and with high stereoisomeric purities (*de* ≥ 98%, *ee* = 80–98%, Table 3, reaction times 20–35 min.). Only in the case of the unsubstituted compound **6a** was the yield lower, probably due to its sensitivity under the reaction conditions. The final cascade steps involve cleavage of the hydrazone moiety, opening of the lactone ring, and formation of the furofuran lactone system through the corresponding hemiacetal intermediate. This final step has previously been described by Yoshikoshi et al.,[29] who obtained 7-methylfurofuran lactones by hydrolysis of 6-methyl-2-oxotetrahydro-2*H*-pyran-4-carbaldehyde in the presence of *p*-toluenesulfonic acid.

These furofuran lactones **6** are particularly interesting because a number of insect antifeedant clerodanes,[30] such as clerodin (R = H) and caryoptin (R = OAc) **L** or mycotoxins such as aflatoxin B_1 **M** (Figure 2), contain furo[2,3-*b*]furan moieties at various levels of oxidation.

Because the bicyclic lactone acetal **6a** could easily be transformed into the alcohol and the 2,3-dihydrofurofu-

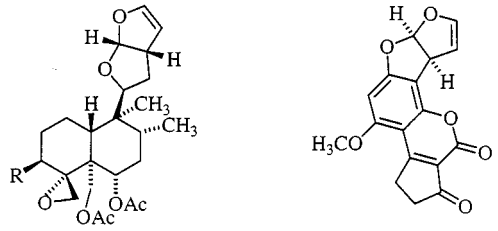


Figure 2. Insect antifeedants and mycotoxins with furo[2,3-*b*]furan moieties

ran[31] derivatives, substructures encountered in the clerodane family, these furofuran lactones may represent valuable chiral building blocks for the synthesis of clerodane derivatives. To the best of our knowledge, only a few methods exist that allow access to furofuran lactones[32] or the furo-[2,3-*b*]furan moiety[33] in such a short sequence.

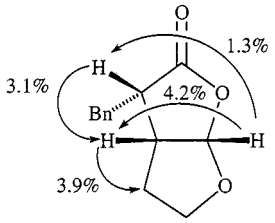


Figure 3. NOE connectivity in (1*S*,4*S*,5*R*)-**6d**

The relative configuration of the perhydrofurofuran lactones **6** was confirmed by NOE experiments on (1*S*,4*S*,5*R*)-**6e** (Figure 3) and the absolute configuration of this compound was determined by the X-ray structure analysis of its minor diastereoisomer (1*S*,4*R*,5*R*)-**6e**,[28] which could be separated from the major isomer by HPLC. The absolute configuration of the furofuran lactone **6a** was confirmed by comparison of its optical rotation value with literature data.[34] Assuming uniform reaction pathways, the absolute configurations of **6b**,**c** and **d** were assigned by analogy with **6e** and **6a**.

The enantiomeric purities of all the compounds were determined by gas chromatography on chiral stationary phases, which indicated that no racemization took place during this transformation. It was found that the enantiomeric purity of **6b** could be increased by simple recrystallization. Finally, we wish to mention that the use of vanadium(II) chloride or chromium(II) acetate also led to the formation of furofuran lactones **6** from **3b**, albeit in poor yields.

It has been shown that perhydrofuro[2,3-*b*]furan derivatives exhibit antifeedant activity even in the absence of the *trans*-decalin system, although this activity is between 10 and 20 times lower than that of clerodin itself.[35] Taking this into account, pentenolides with different substituents at C-6 could allow access to potential insect antifeedants. Extension of this methodology is currently under study in our laboratory.

Conclusion

In summary, our Michael addition/α-alkylation protocol employing formaldehyde SAMP-hydrazone **1** as a neutral chiral formyl anion equivalent in 1,4-additions to 2-pentenolide extends the palette of electrophiles that may be used for C–C bond formation with **1**. The new procedure has allowed an efficient and stereoselective synthesis of (4*R*)-2-oxotetrahydro-2*H*-pyran-4-carbaldehyde and (1*S*,5*R*)-2,8-dioxabicyclo[3.3.0]octan-3-one derivatives in acceptable overall yields and with high diastereo- and enantiomeric purities, the outcome being dependent on the hydrazone cleavage method used. Both types of compound represent useful building blocks in the asymmetric synthesis of bioactive compounds, of which the corresponding enantiomers would be obtained by employing the enantiomeric auxiliary RAMP.

Experimental Section

General: All solvents were dried and purified prior to use. – Column chromatography: Merck silica gel 60, 0.040–0.063 mm (230–400 mesh). – Optical rotation values: Perkin–Elmer P 241 (254 nm); solvents Merck Uvasol quality. – IR: Perkin–Elmer FT-IR 1750. – NMR: Varian VXR 300 and Gemini 300; TMS as internal standard. – MS: Finnigan MAT 212 and Finnigan SSQ 7000 (70 eV). – Microanalyses: Elementar vario EL. – Crystallographic data (excluding structure factors) for the structures **4b** and **4e** (Figure 1) reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-115168 and 115169, respectively. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [Fax: (internat.) +44 (0)1223 336033; E-mail: deposit@ccdc.cam.ac.uk]. – THF was dried by distillation from K/benzophenone under Ar. CH_2Cl_2 was dried by distillation from CaH_2 under Ar. All other reagents were purchased and used as received. The diastereoisomeric excesses of δ-lactones (*S*,*R*,*S*)-**4** were determined by HPLC for **4a**, and by HPLC on chiral stationary phases [chiralpak AD (4.6 × 250 mm) for compounds **4c**, (*S*,*S*)-Whelk-O 1 (4 × 250 mm) for compounds **4d**,**e**, and chiralcel OJ (4.6 × 250 mm) for compound **4b**]. The enantiomeric excesses of α-substituted β-formyl δ-lactones **5** were determined in the case of **5b** from the *de* of the corresponding acetal by GC on a chiral stationary phase (Lipodex E 25m) and in the case of **5e** from the *de* of the corresponding acetal by HPLC on a chiral stationary phase [(*S*,*S*)-Whelk-O 1 (4 × 250 mm)]. The enantiomeric excesses of furofuran lactones **6** were determined by GC on a chiral stationary phase (Chirasil dex 25m). The title reagent, formaldehyde SAMP-hydrazone (*S*)-**1**, may be purchased from Merck-Schuchardt, Hohenbrunn, Germany.

(4*R*)-4({[2*S*-(Methoxymethyl)tetrahydro-1*H*-1-pyrrolyl]imino}-methyl)tetrahydro-2*H*-2-furanone [3a (*n* = 1)]: To a cooled (−78 °C) solution of 2-butenolide (**2a**) (1 mmol) in dry THF (1 mL) under argon were sequentially added TBSOTf (0.25 mL, 1.1 mmol) and precooled (−78 °C) formaldehyde SAMP-hydrazone [(*S*)-**1**] (0.18 mL, 1.25 mmol). After 3 h, the mixture was neutralized by addition of pH 7 buffer at –78 °C and then allowed to warm to room temperature. The resulting mixture was diluted with CH_2Cl_2 and washed with water. The organic layer was dried ($MgSO_4$), concentrated, and the residue was purified by flash chromatography

(SiO_2, Et_2O/CH_2Cl_2/pentane, 2:2:3) to give **3a** (n = 1) as a yellow oil. – Yield: 46 mg (20%). – IR (film): ν = 2957, 2927, 2857, 1780, 1745, 1670, 1461, 1407, 1379, 1341, 1300, 1283, 1256, 1170, 1118, 1017, 916, 838 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 1.80–2.01 (m, 4 H, 3′-H, 4′-H), 2.66 (dd, J = 3.7 Hz, J = 8.1 Hz, 2 H, 3-H), 2.71–2.82 (m, 1 H, 2′-H), 3.37 (s, 3 H, OMe), 3.29–3.55 (m, 5 H, 4-H, 5′-H, CH_2OMe), 4.26 (dd, J = 6.9 Hz, J = 9.1 Hz, J = 1 Hz, 1 H, 5b-H), 4.46 (dd, J = 7.7 Hz, J = 9.1 Hz, 1 H, 5a-H), 6.45 (d, J = 4.9 Hz, 1 H, HC=N). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.7, 27.1 (C-3′, C-4′), 33.5 (C-5′), 39.3 (C-4), 50.1 (C-3), 59.8 (C-2′), 63.7 (OMe), 72.1 (CH_2OMe), 75.0 (C-5), 132.0 (HC=N), 177.0 (C-2). – MS (EI, 70 eV): *m/z* (%): 226 [M^+] (15), 181 (100), 123 (7), 97 (2), 80 (4), 70 (13), 55 (3). – It was not possible to obtain a correct combustion analysis.

(4*R*)-4-({[(2*S*)-(Methoxymethyl)tetrahydro-1*H*-1-pyrrolyl]imino}-methyl)tetrahydro-2*H*-pyran-2-one [(*S*,*R*)-3b]: To a cooled (–78 °C) solution of 2-pentenolide (**2b**) (10 mmol) and (*S*)-**1** (20 mmol) in CH_2Cl_2 (80 mL), TBSOTf (12 mmol) precooled at –30 °C was added dropwise. The mixture was stirred for 30 h, then neutralized with Et_3N at –78 °C, and allowed to warm to 0 °C. The resulting mixture was washed with water, dried ($MgSO_4$), and purified by flash chromatography (SiO_2, Et_2O/pentane, 3:1, Et_2O) to give (*S,R*)-**3b** as a yellow oil. – Yield: 1.3 g (54%). – IR (film): ν = 3490, 2925, 2829, 1737, 1600, 1475, 1461, 1449, 1402, 1340, 1253, 1199, 1156, 1120, 1078, 972 cm^{-1}. – ^1H NMR (500 MHz, C_6D_6): δ = 1.17–1.25 (m, 1 H, 5a-H), 1.32–1.39 (m, 1 H, 5b-H), 1.46–1.55 (m, 1 H, 4′a-H), 1.66–1.75 (m, 3 H, 4′b-H, 3′-H), 2.27–2.34 (m, 1 H, 4-H), 2.40 (ddd, J = 1 Hz, J = 6.3 Hz, J = 17.0 Hz, 1 H, 3a-H), 2.40–2.48 (m, 1 H, 5′a-H), 2.53 (ddd, J = 0.5 Hz, J = 8.0 Hz, J = 17.0 Hz, 1 H, 3b-H), 2.87–2.94 (m, 1 H, 5′b-H), 3.16 (s, 3 H, OMe), 3.41 (dd, J = 6.8 Hz, J = 9.0 Hz, 1 H, CH_2OMe), 3.46–3.51 (m, 1 H, 1′-H), 3.58 (dd, J = 3.3 Hz, J = 9.0 Hz, 1 H, CH_2OMe), 3.64 (ddd, J = 4.2 Hz, J = 8.0 Hz, 11.3 Hz, 1 H, 6a-H), 3.84 (ddd, J = 4.4 Hz, J = 6.6 Hz, J = 11.3 Hz, 1 H, 6b-H), 5.98 (d, J = 3.9 Hz, 1 H, 1-H). – ^{13}C NMR (125 MHz, C_6D_6): δ = 22.2 (C-4′), 27.1 (C-3′), 27.3 (C-5), 34.1 (C-3), 34.4 (C-4), 49.1 (C-5′), 58.9 (OMe), 63.3 (C-1′), 66.8 (C-6), 75.1 (CH_2OMe), 133.8 (C-1), 169.3 (C-2). – MS (EI, 70 eV): *m/z* (%) = 241 [M^+ + 1] (2), 240 [M^+] (10), 195 (100), 110 (7), 70 (13), 68 (10), 55 (7). – $C_{12}H_{20}O_3N_2$ (240.31): calcd. C 59.98, H 8.39, N 11.66; found C 59.66, H 8.53, N 11.74.

General Procedure for the α-Alkylation of δ-Lactone [(*S*,*R*)-3b] (GP1): At –78 °C, a solution of (*S*,*R*)-**3b** (2 mmol) in THF (4 mL) was treated with a precooled solution of LDA (2.2 mmol) in THF (4 mL). After stirring for 3 h, HMPA (0.87 mL or 1.74 mL) was added dropwise. The mixture was then treated with the appropriate alkyl halide (2.6 mmol) and kept at –78 °C or allowed to warm to –35 °C until TLC indicated consumption of the starting material [the most reactive electrophiles required about 8 h (**4a**,**b**,**e**) and the less reactive required 24 h (**4c**) and 48 h (**4d**)]. After hydrolysis with saturated aqueous NH_4Cl solution, the aqueous phase was extracted with Et_2O and the combined organic phases were extracted with water and dried ($MgSO_4$). The crude material was purified by flash chromatography as indicated below.

(3*S*,4*R*)-3-Allyl-4-({[2*S*-(methoxymethyl)tetrahydro-1*H*-1-pyrrolyl]-imino}methyl)tetrahydro-2*H*-pyran-2-one (4a): According to GP1, **4a** was obtained as a yellow oil after purification by column chromatography (SiO_2, Et_2O/pentane, 3:1). – Yield: 0.51 g (90%). This mixture of diastereoisomers was separated by HPLC and the major isomer was used in the next step. – $[\alpha]_D^{25}$ = –158.5 (c = 1.20, $CHCl_3$). – IR (film): ν = 3438, 3076, 2925, 2829, 1731, 1640, 1598, 1442, 1403, 1386, 1341, 1302, 1260, 1196, 1164, 1120, 1003, 973, 958, 919, 876, 803 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 1.81–2.03 (m, 6 H, 3′-H, 4′-H, 5-H), 2.41–2.51 (m, 1 H, 8a-H), 2.57–2.68 (m, 1 H, 8b-H), 2.70–2.80 (m, 2 H, 4-H, 2′-H), 2.86 (dt, J = 5.4 Hz, J = 8.8 Hz, 1 H, 3-H), 3.30–3.43 (m, 2 H, 5′a-H), 3.38 (s, 3 H, OMe), 3.48 (dd, J = 5.8 Hz, J = 9.1 Hz, 1 H, 5′a-H), 3.54 (dd, J = 3.8 Hz, J = 9.1 Hz, 1 H, 5′b-H), 4.26 (m, 1 H, 6a-H), 4.35 (m, 1 H, 6b-H), 5.08–5.14 (m, 2 H, CH_2=), 5.81–5.84 (m, 1 H, CH=), 6.49 (d, J = 5.0 Hz, 1 H, CH=N). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.6, 27.0, 28.0, 34.6 (C-3′, C-4′, C-5, C-8), 38.6, 43.8 (C-4, C-3), 50.2 (C-4′), 59.8 (C-1′), 63.9 (OMe), 67.7, 74.9 (C-6, C-5′), 118.6 (CH_2=), 135.6, 136.0 (HC=N, CH=), 174.0 (C-2). – MS (EI, 70 eV): *m/z* (%) = 280 [M^+] (5), 235 (100), 207 (3), 123 (7), 70 (25), 55 (8). – HRMS: calcd. 280.17855; found 280.17843. – $C_{15}H_{24}O_3N_2$ (280.37): calcd. C 64.26, H 8.63, N 9.99; found C 63.42, H 8.69, N 10.04.

(3*S*,4*R*)-4({[2*S*-(Methoxymethyl)tetrahydro-1*H*-1-pyrrolyl]imino}-methyl)-3-methyltetrahydro-2*H*-pyran-2-one (4b): According to GP1, **4b** was obtained as a colourless oil after purification by column chromatography (SiO_2, Et_2O/pentane, 3:1). Yield: 0.51 g (89%). The *trans* diastereoisomers (74%) were eluted first, followed by the *cis* diastereoisomers (15%). – $[\alpha]_D^{25}$ = –126.4 (c = 2.88, $CHCl_3$). – IR (film): ν = 3447, 2972, 2931, 2878, 2828, 1739, 1458, 1402, 1383, 1340, 1304, 1285, 1252, 1220, 1188, 1162, 1110, 1037, 991, 973 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 1.30 (d, J = 6.9 Hz, 3 H, 8-H), 1.80–2.12 (m, 6 H, 3′-H, 4′-H, 5-H), 2.45–2.55 (m, 1 H, 4-H), 2.70 (dt, J = 6.9 Hz, J = 9.6 Hz, 1 H, 3-H), 2.75–2.83 (m, 1 H, 1′-H), 3.30–3.56 (m, 4 H, 5′-H, CH_2OMe), 3.37 (s, 3 H, OMe), 4.24–4.41 (m, 2 H, 6-H), 6.51 (d, J = 5.3 Hz, 1 H, CH=N). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.0 (C-8), 22.7, 27.0, 28.2 (C-3′, C-4′, C-5), 39.1 (C-3), 42.1 (C-4), 50.3 (C-5′), 59.8 (OMe), 63.8 (C-2′), 67.5 (C-6), 74.4 (CH_2OMe), 136.3 (CH=N), 175.3 (C-2). – MS (EI, 70 eV): *m/z* (%): 254 [M^+] (9), 213 (13), 209 (100), 70 (17), 68 (13), 41 (14). – $C_{13}H_{22}O_3N_2$ (254.33): calcd. C 61.39, H 8.72, N 11.01; found C 61.32, H 8.86, N 10.83.

(3*S*,4*R*)-4-({[2*S*-(Methoxymethyl)tetrahydro-1*H*-1-pyrrolyl]imino}-methyl)-3-propyl)tetrahydro-2*H*-pyran-2-one (4c): According to GP1, **4c** was obtained as a yellow oil after purification by column chromatography (SiO_2, Et_2O/pentane, 4:1). Yield: 0.38 g (67%). This mixture of diastereoisomers was separated by HPLC and the major isomer was used in the next step. – $[\alpha]_D^{25}$ = –132.6 (c = 1.44, $CHCl_3$) – IR (film): ν = 3455, 2958, 2828, 1735, 1599, 1460, 1341, 1260, 1199, 1116 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, J = 7.1 Hz, 3 H, 9-H), 1.30–1.60 (m, 2 H, 8-H), 1.67–2.12 (m, 8 H, 3′-H, 4′-H, 5-H, 7-H), 2.61–2.82 (m, 3 H, 4-H, 5′a-H), 3.28–3.36 (m, 5 H, 2′-H, 3-H, 5′b-H, CH_2OMe), 3.37 (s, 3 H, OMe), 4.26 (ddd, J = 4.1 Hz, J = 7.1 Hz, J = 11.3 Hz, 1 H, 6a-H), 4.36 (ddd, J = 3.8 Hz, J = 7.4 Hz, J = 11.3 Hz, 1 H, 6b-H), 6.50 (d, J = 5 Hz, 1 H, CH=N). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.67 (C-9), 20.71, 22.62, 26.96, 28.05, 33.01 (C-3′, C-4′, C-5, C-7, C-8), 39.64, 43.82 (C-3, C-4), 50.22 (C-5′), 59.79 (OMe), 63.85 (C-2′), 67.38 (C-6), 74.87 (CH_2OMe), 136.44 (CH=N), 174.67 (C-2). – MS (EI, 70 eV): *m/z* (%): 282 [M^+] (8), 267 (6), 237 [M^+ – 45] (100), 193 (12), 149 (10), 99 (13), 83 (13), 70 (34), 55 (41). – $C_{15}H_{26}O_3N_2$ (283.39): calcd. C 63.80, H 9.28, N 9.92; found C 63.41, H 9.30, N 10.26.

(3*S*,4*R*)-4-({[2*S*-(Methoxymethyl)tetrahydro-1*H*-1-pyrrolyl]imino}-methyl)-3-(2-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}ethyl)tetrahydro-2*H*-pyran-2-one (4d): According to GP1, **4d** was obtained as a yellow oil after purification by column chromatography (SiO_2, Et_2O/pentane, 3:1). Yield: 0.35 g (44%). This mixture of diastereoisomers was separated by HPLC and the major isomer was used in the next step. – $[\alpha]_D^{25}$ = –99.7 (c = 1.30, $CHCl_3$). – IR (film): ν = 3346, 2928, 2856, 1739, 1682, 1471, 1463, 1387, 1255, 1198, 1103, 837

cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6 H, Me_2Si), 0.86 (s, 9 H, *t*Bu), 1.75–2.08 (m, 8 H, 3′-H, 4′-H, 5-H, 7-H), 2.64–2.78 (m, 3 H, 5′-H, 4-H), 3.26–3.31 (m, 1 H, 3-H), 3.34 (s, 3 H, OMe), 3.36–3.52 (m, 3 H, 2′-H, CH_2OMe), 3.70–3.80 (m, 2 H, 8-H), 4.25 (ddd, *J* = 4.1 Hz, *J* = 7.2 Hz, *J* = 11.2 Hz, 1 H, 6a-H), 4.33 (ddd, *J* = 3.9 Hz, *J* = 7.2 Hz, *J* = 11.2 Hz, 1 H, 6b-H), 6.47 (d, *J* = 5.0 Hz, 1 H, CH=N). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4, –5.3 (Me_2Si), 22.2, 26.6, 27.9, 32.7 (C-3′, C-4′, C-5, C-7), 26.0 (*t*Bu), 39.2, 40.2 (C-3, C-4), 49.7 (C-5′), 59.3, 63.3 (C-2′, OMe), 60.7, 66.9 (CH_2OMe, C-8), 76.8 (C-6), 135.9 (CH=N), 174.1 (C-2). – MS (EI, 70 eV): *m*/*z* (%): 398 [M^+] (1), 353 [M^+ – 45] (10), 229 (18), 228 (100), 149 (25), 128 (48), 96 (12), 91 (42), 73 (47), 57 (34). – HRMS: calcd. 353.22605; found 353.22610. – $C_{20}H_{38}O_4N_2Si$ (398.63): calcd. C 60.26, H 9.61, N 7.03; found C 59.62, H 9.76, N 7.00.

(3*S*,4*R*)-3-Benzyl-4-({[2*S*-(methoxymethyl)tetrahydro-1*H*-1-pyrrolyl]imino}methyl)tetrahydro-2*H*-pyran-2-one (4e): According to GP1, **4e** was obtained as a colourless solid after purification by column chromatography (SiO_2, Et_2O/pentane, 1:1 → 3:1). Yield: 0.51 g (77%). – m.p. 59–60 °C – $[\alpha]_D^{25}$ = –155.7 (*c* = 0.97, $CHCl_3$). – IR (film): ν = 3420, 2927, 2829, 1732, 1603, 1496, 1454, 1404, 1386, 1341, 1303, 1245, 1217, 1193, 1153, 1121, 1098, 1075, 1030, 972 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 1.83–2.02 (m, 6 H, 3′-H, 4′-H, 5-H), 2.65–2.69 (m, 2 H, 4-H, 5′a-H), 3.10–3.20 (m, 3 H, 3-H, 5′b-H, 8a-H), 3.21–3.29 (m, 1 H, 2′-H), 3.40 (s, 3 H, OMe), 3.39–3.59 (m, 3 H, CH_2OMe, CH_2Ph), 4.11 (ddd, 1 H, *J* = 3.9 Hz, *J* = 7.4 Hz, *J* = 11.2 Hz, 6a-H), 4.32 (ddd, 1 H, *J* = 3.9 Hz, *J* = 7.2 Hz, *J* = 11.2 Hz, 6b-H), 6.39 (d, 1 H, *J* = 4.7 Hz, CH=N), 7.21–7.30 (m, 5 H, Ph). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.12 (C-4′), 26.60 (C-3′), 27.61 (C-5), 35.95 (CH_2Ph), 38.25, 45.30 (C-3, C-4), 49.56 (C-5′), 59.33 (OMe), 63.26 (C-2′), 66.99 (C-6), 74.49 (CH_2OMe), 126.47, 128.44, 129.80, 139.13 (Ph), 135.34 (C-7), 173.66 (C-2). – MS (EI, 70 eV): *m*/*z* (%): 330 [M^+] (4), 286 (17), 285 [M^+ – 45] (100), 131 (7), 115 (7), 91 (41), 70 (31). – $C_{19}H_{26}O_3N_2$ (330.43): calcd. C 69.09, H 7.88, N 8.48; found C 69.12, H 7.97, N 8.76.

General Procedure for the Ozonolysis of the δ-Lactones (*S*,*R*,*S*)-4 (GP2): Ozone was bubbled through a solution of **4** (1 mmol) in dry CH_2Cl_2 (25 mL) at –78 °C until a blue colour persisted (TLC control). Me_2S (1.1 mmol) was then added, the mixture was allowed to warm to room temperature, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 0.063–0.100 mm) as indicated below.

(3*S*,4*R*)-3-Methyl-2-oxotetrahydro-2*H*-pyran-4-carbaldehyde (5b): According to GP2, **5b** was obtained as a colourless oil after purification by column chromatography (SiO_2, Et_2O/pentane, 3:1). Yield: 99 mg (70%). – $[\alpha]_D^{28}$ = +36.4 (*c* = 1.11, $CHCl_3$). – IR (film): ν = 3423, 2975, 2931, 2856, 1727, 1448, 1385, 1258, 1168, 1082, 993 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 1.31 (d, *J* = 6.8 Hz, 3 H, Me), 2.01–2.23 (m, 2 H, 5-H), 2.61–2.69 (m, 1 H, 4-H), 2.89–2.99 (m, 1 H, 3-H), 4.21 (ddd, *J* = 3.8 Hz, *J* = 9.1 Hz, *J* = 11.5 Hz, 1 H, 6a-H), 4.31 (dt, *J* = 4.9 Hz, *J* = 11.5 Hz, 1 H, 6b-H), 9.75 (d, *J* = 1.1 Hz, 1 H, CHO). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.2, 22.4 (C-5, Me), 33.0, 49.4 (C-4, C-3), 65.5 (C-6), 173.4 (C-2), 198.9 (CHO). – MS (EI, 70 eV): *m*/*z* (%): 143 [M^+ + 1] (2), 142 [M^+] (2), 114 (6), 99 (35), 86 (17), 83 (46), 69 (100), 55 (73). – HRMS: [M^+ + 1]: 143.07082 ($C_7H_{10}O_3$, calcd. [M^+ + 1]: 143.07054).

(3*S*,4*R*)-3-Propyl-2-oxotetrahydro-2*H*-pyran-4-carbaldehyde (5c): According to GP2, **5c** was obtained as a colourless oil after purification by column chromatography (SiO_2, Et_2O/pentane, 1:1 → 3:1). Yield: 116 mg (68%). – $[\alpha]_D^{28}$ = +21.5 (*c* = 0.78, $CHCl_3$). – IR (film): ν = 3408, 2961, 2874, 1784, 1731, 1446, 1323, 1120, 1078, 949 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.2 Hz, 3 H, 9-H), 1.20–1.88 (m, 4 H, 7-H, 8-H), 2.00–2.21 (m, 2 H, 5-H), 2.73–2.84 (m, 1 H, 3-H), 2.94–3.01 (m, 1 H, 4-H), 4.18–4.34 (m, 2 H, 6-H), 9.75 (s, 1 H, CHO). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (C-9), 20.5–22.6 (C-7, C-8), 33.1, 37.9 (C-3, C-4), 47.7 (C-5), 64.8 (C-6), 171.8 (C-2), 198.6 (CHO). – MS (EI, 70 eV): *m*/*z* (%): 171 [M^+ + 1] (1), 141 [M^+ – CHO] (3), 128 (11), 99 (100), 83 (13), 71 (10), 55 (46). – HRMS: 170.09429 ($C_9H_{14}O_3$ calcd. 170.09448).

(3*S*,4*R*)-3-(2-{[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy}ethyl)-2-oxotetrahydro-2*H*-pyran-4-carbaldehyde (5d): According to GP2, **5d** was obtained as a yellow oil after purification by column chromatography (SiO_2, Et_2O/pentane, 1:1 → 3:1). Yield: 144 mg (50%). – $[\alpha]_D^{27}$ = –1.3 (*c* = 0.77, $CHCl_3$). – IR (film): ν = 3381, 2928, 2856, 1779, 1732, 1682, 1471, 1379, 1257, 1099, 951, 837 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 6 H, Me_2Si), 0.88 (s, 9 H, *t*BuSi), 1.85–2.20 (m, 4 H, 5-H, 7-H), 2.91–3.01 (m, 1 H, 3-H), 3.07–3.14 (m, 1 H, 4-H), 3.71–3.85 (m, 2 H, 8-H), 4.20–4.36 (m, 2 H, 6-H), 9.74 (d, *J* = 1.4 Hz, 1 H, CHO). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.8 (Me_2Si), 17.9 (CMe_3), 22.9, 32.6, 35.3 (C-3, C-5, C-7), 25.6 (*t*Bu), 47.3 (C-4), 60.1, 65.6 (C-6, C-8), 172.7 (C-2), 199.2 (CHO). – MS (EI, 70 eV): *m*/*z* (%): 287 [M^+ + 1] (1), 271 [M^+ – 15] (3), 229 [M^+ – *t*Bu] (100), 199 (10), 171 (8), 109 (13), 75 (45). – HRMS: [M^+ – 15]; 271.13656 ($C_{14}H_{26}O_4Si$ calcd. 271.13669).

(3*S*,4*R*)-3-Benzyl-2-oxotetrahydro-2*H*-pyran-4-carbaldehyde (5e): According to GP2, **5e** was obtained as a yellow oil after purification by column chromatography (SiO_2, Et_2O/pentane, 1:2 → 1:1). Yield: 129 mg (59%). – $[\alpha]_D^{23}$ = –9.0 (*c* = 0.89, $CHCl_3$). – IR (film): ν = 3417, 2929, 1726, 1454, 1269, 1159, 1074, 756 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 1.91–2.13 (m, 2 H, 5-H), 2.74–2.82 (m, 1 H, 4-H), 3.06 (dd, *J* = 6.6 Hz, *J* = 14.0 Hz, 1 H, CH_aPh), 3.20 (dd, *J* = 5.7 Hz, *J* = 14.0 Hz, 1 H, CH_bPh), 3.28–3.35 (m, 1 H, 3-H), 4.12–4.25 (m, 2 H, 6-H), 7.20–7.33 (m, 5 H, Ph), 9.46 (d, *J* = 1.0 Hz, 1 H, CHO). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.1 (C-5), 36.5 (CH_2Ph), 40.5, 47.1 (C-3, C-4), 66.1 (C-6), 127.2, 128.9, 129.7, 137.7 (Ph), 172.4 (C-2), 199.1 (CHO). – MS (EI, 70 eV): *m*/*z* (%): 218 [M^+] (35), 189 [M^+ – CHO] (25), 149 (32), 131 (100), 115 (23), 103 (19), 91 (84), 70 (61). – HRMS: 218.09429 ($C_{13}H_{14}O_3$ calcd. 218.09396).

General Procedure for the Acetalation of α-Alkyl β-Formyl δ-Lactones (5) (GP3): The appropriate aldehyde **5** (1 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) at 0 °C under an atmosphere of argon. (*R*,*R*)-Butanediol bis(trimethylsilyl) ether (468 mg, 2 mmol) was then added, followed by a catalytic amount of TMSOTf (1 drop). The resulting mixture was stirred for 2 h at 0 °C, then poured into water, and extracted with CH_2Cl_2. The combined extracts were dried ($NaSO_4$) and concentrated in vacuo. The crude material was purified by column chromatography as indicated below.

(3*S*,4*R*)-4-[(4*R*,5*R*)-4,5-Dimethyl-1,3-dioxolan-2-yl]-3-methyltetrahydro-2*H*-pyran-2-one: According to GP3, the acetal derived from **5b** was obtained as a colourless solid after purification by column chromatography (SiO_2, Et_2O/pentane, 1:4 → 1:1). Yield: 172 mg (80%); m.p. 55–57 °C. – IR (film): ν = 2983, 2880, 1735, 1459, 1387, 1254, 1171, 1115, 1056, 969 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 1.23–1.36 (m, 9 H, $3CH_3$), 1.83–2.00 (m, 3 H, 4-H, 5-H), 2.63–2.72 (m, 1 H, 3-H), 3.58–3.70 (m, 2 H, 2HCO), 4.22–4.29 (m, 1 H, 6a-H), 4.34–4.42 (m, 1 H, 6b-H), 5.14 (d, *J* = 2.0 Hz, 1 H, HCO_2). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.9, 16.7, 17.5 (3 CH_3), 23.1 (C-5), 35.3, 41.1 (C-3, C-4), 67.1 (C-

6), 79.4, 79.9 (2HCO), 103.4 (HCO_2), 175.3 (C-2). – MS (EI, 70 eV): *m/z* (%): 215 [M^+ + 1] (4), 213 (3), 101 (100), 83 (7), 73 (42), 55 (50). – $C_{11}H_{18}O_4$ (214.26): calcd. C 61.66, H 8.47; found C 62.06, H 8.65.

(3*S*,4*R*)-3-Benzyl-4-[(4*R*,5*R*)-4,5-dimethyl-1,3-dioxolan-2yl]tetrahydro-2*H*-pyran-2-one: According to GP3, the acetal derived from **5e** was obtained as a colourless oil after purification by column chromatography (SiO_2, Et_2O/pentane, 1:5 1:1). Yield: 205 mg (71%). – IR (film): ν = 3028, 2924, 2854, 1771, 1732, 1497, 1454, 1384, 1260, 1160, 1083, 968, 893 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 1.15 (d, *J* = 5.7 Hz, 3 H, CH_3), 1.22 (d, *J* = 5.8 Hz, 3 H, CH_3), 1.64–1.84 (m, 1 H, 5-H), 2.00–2.11 (m, 1 H, 4-H), 2.89–2.95 (m, 1 H, 3-H), 3.02–3.19 (m, 2 H, CH_2Ph), 3.49–3.59 (m, 2 H, 2CHO), 3.83–3.91 (m, 1 H, 6a-H), 4.22–4.29 (m, 1 H, 6b-H), 4.95 (d, *J* = 3.0 Hz, 1 H, HCO_2), 7.12–7.27 (m, 5 H, Ph). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.3, 17.0 ($2CH_3$), 22.7 (C-5), 36.5 (CH_2Ph), 37.5, 41.6 (C-3, C-4), 66.8 (C-6), 78.8, 79.4 (2CHO), 103.4 (HCO_2), 126.3, 128.2, 129.3, 138.2 (Ph), 173.5 (C-2). – MS (EI, 70 eV): *m/z* (%): 290 [M^+] (11), 218 (7), 140 (17), 131 (14), 115 (14), 101 (100), 91 (47), 83 (46), 70 (55). – HRMS: 290.15181 ($C_{17}H_{22}O_4$ calcd. 290.15177).

General Procedure for the Hydrolytic Cleavage of δ-Lactone (*S*,*R*)-4 (GP4): To a cooled (0 °C) solution of hydrazone **4** (1 mmol) in Et_2O (20 mL) was added 5 N HCl (4 mL) and the mixture was stirred vigorously until TLC indicated total consumption of the starting material (ca. 20 min.). The aqueous layer was then extracted with CH_2Cl_2 (3 times). The combined organic layers were neutralized ($NaHCO_3$, 0.1 g), dried ($MgSO_4$), and concentrated. The resulting residue was purified by flash chromatography as indicated below.

(1*S*,5*R*)-2,8-Dioxabicyclo[3.3.0]octan-3-one (6a): According to GP4, **6a** was obtained as a colourless oil after purification by column chromatography (SiO_2, Et_2O). Yield: 84 mg (66%). – $[\alpha]_D^{27}$ = +29.5 (*c* = 0.96, $CHCl_3$). The spectroscopic data were in accordance with previously published data.[33]

(1*S*,4*S*,5*R*)-4-Methyl-2,8-dioxabicyclo[3.3.0]octan-3-one (6b): According to GP4, **6b** was obtained as a colourless solid after purification by column chromatography (SiO_2, Et_2O/pentane, 4:1). Yield: 140 mg (98%). The solid was recrystallized from Et_2O/hexane (107 mg, 75%); m.p. 78–80 °C – $[\alpha]_D^{25}$ = +49.8 (*c* = 0.95, $CHCl_3$). – IR (film): ν = 3447, 2923, 2888, 1766, 1454, 1382, 1361, 1189, 1098, 968 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ =1.27 (d, *J* = 7.1 Hz, 1 H, CH_3), 1.83–2.08 (m, 2 H, 6-H), 2.89–2.99 (m, 1 H, 4-H), 3.09–3.19 (m, 1 H, 5-H), 3.95–4.11 (m, 2 H, 7-H), 6.00 (d, *J* = 4.9 Hz, 1 H, 1-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.2 (CH_3), 24.6 (C-6), 37.7, 43.7 (C-4, C-5), 68.5 (C-7), 106.2 (C-1), 176.7 (C-3). – MS (EI, 70 eV): *m/z* (%): 143 [M^+ + 1] (3), 98 (51), 83 (100), 68 (35), 55 (31). – $C_7H_{10}O_3$ (142.16): calcd. C 59.14, H 7.09; found C 58.92, H 7.18.

(1*S*,4*S*,5*R*)-4-Propyl-2,8-dioxabicyclo[3.3.0]octan-3-one (6c): According to GP4, **6c** was obtained as a colourless oil after purification by column chromatography (SiO_2, Et_2O/pentane, 3:1). Yield: 165 mg (97%). – $[\alpha]_D^{25}$ = +76.75 (*c* = 0.80, $CHCl_3$). – IR (film): ν = 2961, 2935, 2874, 1775, 1180, 1113, 971, 938 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 1.10 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.53–165 (m, 3 H, 9-H, 8a-H), 1.90–2.22 (m, 3 H, 8b-H, 6-H), 2.91–2.98 (m, 1 H, 4-H), 3.19–3.29 (m, 1 H, 5-H), 4.11–4.23 (m, 2 H, 7-H), 6.10 (d, *J* = 4.9 Hz, 1 H, 1-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.5 (C-10), 20.6, 24.1, 28.4 (C-6, C-8, C-9), 42.7, 43.2 (C-4, C-5), 68.6 (C-7), 106.3 (C-1), 176.0 (C-3). – MS (EI, 70 eV): *m/z* (%): 171 [M^+ + 1] (1), 126 (10), 97 (37), 83 (100), 81 (11), 67 (8), 55 (31). – $C_9H_{14}O_3$ (170.21): calcd. C 63.51, H 8.29; found C 63.22, H 8.46.

(1*S*,4*S*,5*R*)-4-Allyl-2,8-dioxabicyclo[3.3.0]octan-3-one (6d): According to GP4, **6d** was obtained as a white solid after purification by column chromatography (SiO_2, Et_2O/pentane, 1:1). Yield: 148 mg (87%); m.p. 52–54 °C. – $[\alpha]_D^{20}$ = +75.6 (*c* = 0.80, $CHCl_3$). – IR (film): ν = 2979, 2925, 1769, 1360, 1171, 1113, 971, 910 cm^{-1}. – ^1H NMR: (300 MHz, $CDCl_3$): δ = 1.81–1.93 (m, 1 H, 6b-H), 1.98–2.10 (m, 1 H, 6a-H), 2.15–2.27 (m, 1 H, 9b-H), 2.73–2.81 (m, 1 H, 9a-H), 2.91–2.99 (ddd, *J* = 4.7 Hz, *J* = 8.5 Hz, *J* = 11.0 Hz, 1 H, 4-H), 3.08–3.18 (m, 1 H, 5-H), 4.06 (t, *J* = 7.1 Hz, 2 H, 7-H), 5.10–5.18 (m, 2 H, H_2C=), 5.77–5.91 (m, 1 H, HC=), 6.00 (d, *J* = 4.7 Hz, 1 H, 1-H). – ^{13}C NMR (300 MHz, $CDCl_3$): δ = 24.4, 30.6 (C-6, C-9), 42.7, 43.1 (C-4, C-5), 68.8 (C-7), 106.4 (C-10), 116.9 (C-11), 134.4 (C-1), 175.1 (C-3). – MS (EI, 70 eV): *m/z* (%): 169 [M^+ + 1] (100), 145 (7). – $C_9H_{12}O_3$ (168.19): calcd. C 64.27, H 7.19; found C 64.24, H 7.48.

(1*S*,4*S*,5*R*)-4-Benzyl-2,8-dioxabicyclo[3.3.0]octan-3-one (6e): According to GP4, **6e** was obtained as a colourless oil after purification by column chromatography (SiO_2, Et_2O/pentane, 4:1). Yield: 197 mg (90%). – $[\alpha]_D^{25}$ = +104.4 (*c* = 0.91, $CHCl_3$). – IR (film): ν = 3028, 2960, 1769, 1497, 1454, 1316, 1184, 1116, 969, 893 cm^{-1}. – ^1H NMR: (500 MHz, $CDCl_3$): δ = 1.92–2.07 (m, 2 H, 6-H), 2.70 (dd, *J* = 11.4 Hz, *J* = 14.9 Hz, 1 H, CH_aPh), 2.92–2.98 (m, 1 H, 5-H), 3.21 (ddd, *J* = 4.2 Hz, *J* = 7.9 Hz, *J* = 11.9 Hz, 1 H, 4-H), 3.42 (dd, *J* = 4.1 Hz, *J* = 14.9 Hz, 1 H, CH_bPh), 4.02–4.07 (m, 1 H, 7a-H), 4.11–4.16 (m, 1 H, 7b-H), 5.95 (d, *J* = 4.6 Hz, 1 H, 1-H), 7.21–7.35 (m, 5 H, Ph). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.0 (C-6), 32.7 (CH_2Ph), 43.3 (C-5), 46.1 (C-4), 69.5 (C-7), 106.8 (C-1), 126.9, 128.4, 128.9, 138.5 (Ph), 175.2 (C-3). – $C_{13}H_{14}O_3$ (218.25): calcd. C 71.54, H 6.47; found C 71.31, H 6.57.

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