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Diastereo- and enantioselective synthesis of 2,8-dioxabicyclo[3.3.0]octan-3-one derivatives

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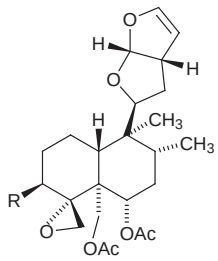
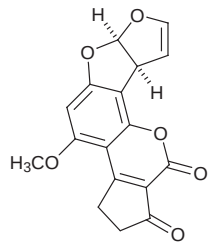
An efficient asymmetric synthesis of 4-substituted (1*S*,4*S*,5*R*)-2,8-dioxabicyclo[3.3.0]octan-3-one derivatives (de ⩾98%, ee = 80– > 98%) in good overall yields is reported by a stepwise Michael addition–α-alkylation and subsequent hydrolytic domino reaction protocol employing formaldehyde SAMP-hydrazone as a neutral formyl anion equivalent and 5,6-dihydro-2*H*-pyran-2-one as a Michael acceptor.

Many insect antifeedant clerodanes, such as clerodin (R = H) and caryoptin (R = OAc) **A** or mycotoxins like aflatoxin B_1 **B**,



A

clerodin (R = H)
caryoptin (R = OAc)



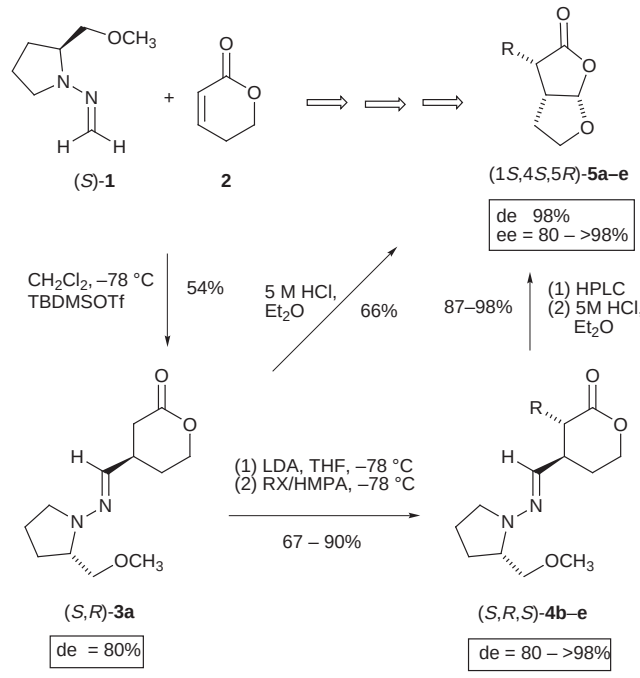
B

aflatoxin B_1

contain furo[2,3-*b*]furan moieties in various oxidation levels.[1] Although many synthetic methods for accessing such furofurans have been reported during the last decade,[2] there is still a need for enantioselective procedures suitable for structural variations and, for instance, their incorporation into the clerodane framework. Since it has been reported that this and other clerodane subunits may be crucial for insect antifeedant activity,[3,4] the development of novel asymmetric syntheses is an important goal in this context.

We describe here the asymmetric synthesis of diastereomerically pure and highly enantiomerically enriched derivates of the title perhydrofuro[2,3-*b*]furan lactone system based on the Michael addition of formaldehyde SAMP-hydrazone[5] **1** to 5,6-dihydro-2*H*-pyran-2-one **2** as the key step (Scheme 1).[6] The 1,4-adduct **3** was obtained under Lewis acid activation with TBDMSOTf (1.2 equiv.) in acceptable yield (54%) and good diastereomeric excess (de = 80%). Because the mixture of diastereoisomers of **3** was only separable by HPLC on chiral stationary phase, this mixture was directly used in the subsequent deprotonation–α-alkylations. The use of LDA at −78 °C, followed by addition of HMPA and finally the requisite alkylating agent afforded the 4-substituted lactone hydrazones **4** in good to excellent yields (67–90%) and diastereomeric excesses (de = 80– > 98%). The *trans* configuration of the disubstituted lactones **4** was determined by ^{1}H NMR spectroscopy through the *trans*-diaxial coupling constants (9.5–10.7 Hz) of the protons at the new stereogenic centres. This was confirmed by NOE experiments on compound **4b** (R = Me).† The absolute configuration of the minor diastereoisomer (*R*,*R*)-**4b** was determined by X-ray structure analysis,‡ the absolute configuration of the major diastereoisomer therefore being (3*S*,4*R*). Fortunately, in some cases the diastereoisomers of the lactone hydrazones **4** are separable by flash chromatography (**4b**) or by HPLC (**4c**,**d**) and it was possible to use the diastereomerically enriched hydrazones in the following key step.

Thus, the asymmetric Michael addition of **1** to pent-2-enolide **2** and subsequent α-alkylations enabled us to synthesize the appropriate precursors with the desired carbon skeleton for the formation of the title compounds. Finally, a domino reaction was initiated by acidic hydrolysis in a two-phase system and afforded the desired furofuran lactones derivatives **5**[7] in excellent yields (87–98%) and stereoisomeric purity (de ⩾ 98%, ee = 80–98%) (Table 1). Only in the case of the unsubstituted compound **5a** is the yield lower probably due to its sensitivity under the reaction conditions. The final cascade



Scheme 1

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

5	R	Yield[a] (%)	Mp[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	Pr^n	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. [b] Uncorrected, measured on a Büchi apparatus. [c] Determined by GC on chiral stationary phases. [d] Figures in parentheses indicate values after recrystallization of the final product.

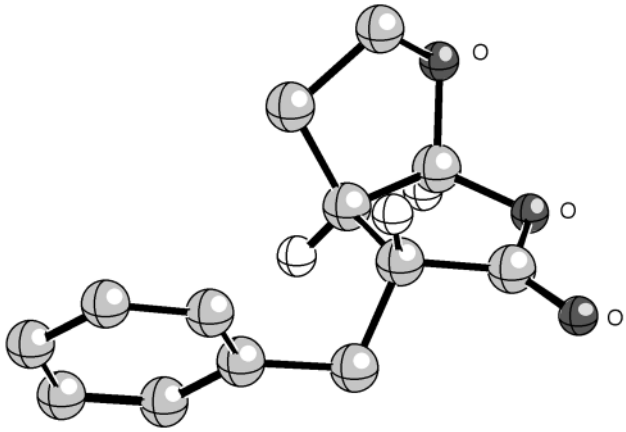


Fig. 1 X-Ray structure of furofuran lactone (1*S*,4*R*,5*R*)-**5e**.

steps involve the cleavage of the hydrazone moiety, opening of the lactone ring and, finally, formation of the furofuran lactone system through the corresponding hemiacetal intermediate.

The relative configuration of the perhydrofurofuran lactones **5** was confirmed by NOE experiments on (1*S*,4*S*,5*R*)-**5e**§ and the absolute configuration of this compound was determined by X-ray structure analysis of its minor diastereoisomer (1*S*,4*R*,5*R*)-**5e**, which was separable from the major one by HPLC (Fig. 1).¶ Assuming uniform reactions pathways, the absolute configuration of **5a**–**d** were assigned by analogy with **5e**.

The enantiomeric purity of all compounds was determined by GC on chiral stationary phases indicating the absence of racemization during our procedure. Some of the substituted derivatives of (1*S*,5*R*)-2,8-dioxabicyclo[3.3.0]octan-3-one **5a** were solids and enabled us to increase the ee of the final furofuran lactones by simple recrystallization.

The bicyclic lactone acetal **5a**, which constitutes a valuable chiral building block for the synthesis of clerodane derivatives, could be easily transformed to the alcohol and to the 2,3-dihydrofurofuran[8] derivatives widely encountered in the clerodane family.

In conclusion, our new procedure *via* asymmetric Michael addition of formaldehyde SAMP-hydrazone to pent-2-enolide followed by α-alkylations, and subsequent cleavage of the hydrazones using acidic hydrolysis in a two-phase system affords the desired 4-substituted furofuran lactone derivatives in acceptable overall yields (32–47%) and high diastereo- and enantiomeric purity (de ⩾98%, ee = 80–98%). In addition, pentenolides with different substituents in position 6 could allow access to a library of potential insect antifeedants. The extension of this methodology is currently under study in our laboratory.

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Notes and references

† Representative NOE data for **4b**: $CH_3 \rightarrow H_4$ 10.2%, $CH_3 \rightarrow H_3$ 16.5%, $H_3 \rightarrow H_{6eq}$ 2.8%, $H_3 \rightarrow H_{5ax}$ 2.2%.

‡ The crystal structure of (2′*S*, 3*R*, 4*R*)-**4b** will be part of our full paper on this chemistry: D. Enders, J. Vázquez and G. Raabe, manuscript in preparation.

§ Representative NOE data for (1*S*,4*S*,5*R*)-**5e**: $H_1 \rightarrow H_5$ 4.2%, $H_1 \rightarrow H_4$ 1.3%, $H_4 \rightarrow H_5$ 3.1%, $H_5 \rightarrow H_6$ 3.9%.

¶ *Crystal data* for (1*S*,4*R*,5*R*)-**5e:** $C_{13}H_{14}O_3$, orthorhombic, a = 6.250(3), b = 9.353(1), c = 19.655(2) Å, V = 1149.0 Å^3, $P2_12_12_1$, Z = 4, μ = 6.9 cm^{-1}, no absorption correction, T = 298 K, 2378 independent and 1351 observed $I > 2\sigma(I)$] reflections, 145 parameters in final least-squares full-matrix refinement on F, terminating at R = 0.053 (R_w = 0.033, $w = \sigma^{-2}$), a goodness of fit of 1.677, and a residual electron density of −0.22/+0.24 e Å^{-3}. Refinement of the Flack parameter (ref. 9) to determine the absolute configuration of the minor isomer (1*S*,4*R*,5*R*)-**5e** resulted in a value of X = 0.01(68) for the structure shown in Fig. 1. The authors recognize that due to the high standard uncertainty the diffraction results alone do not definitely fix the absolute configuration, which, however is determined based on the X-ray structures of several hydrazone precursors, such as (2′*S*,3*R*,4*R*)-**4b** (see note ‡). CCDC 182/1195. Crystallographic data are available in CIF format from the RSC web site, see: http://www.rsc.org/suppdata/cc/1999/701/

1 For reviews see: T.A. van Beeck and Ae. de Groot, *Recl. Trav. Chim. Pays-Bas*, 1986, **105**, 513; A. T. Merritt and S. V. Ley, *Nat. Prod. Rep*., 1992, 243.
2 F. Petit and R. Furstoss, *Synthesis*, 1995, 1517; H. Bouchard, J. Soulié and J. Y. Lallemand, *Tetrahedron Lett*., 1991, **32**, 2621; J. Vader, H. Sengers and Ae. de Groot, *Tetrahedron*, 1989, **45**, 2131 and references cited therein.
3 Y. Kojima and N. Kato, *Agric. Biol. Chem*., 1980, **44**, 855.
4 S. V. Ley, N. S. Simpkins and A. J. Whittle, *J. Chem. Soc., Chem. Commun*., 1981, 1001.
5 H. Eichenauer, Dissertation, University of Giessen, 1980.
6 D. Enders and J. Vázquez, submitted. For a short review on nucleophilic formylations and cyanations with **1** see: D. Enders, M. Bolkenius, J. Vázquez, J.-M. Lassaletta and R. Fernández, *J. Prakt. Chem., Chem. Ztg.*, 1998, **340**, 281.
7 *Typical procedure*: To a cooled (0 °C) solution of hydrazone **4** (1 mmol) in Et_2O (20 ml) was added 5 M HCl (4 ml), and the mixture was vigorously stirred until TLC indicated total consumption of the starting material (*ca.* 20 min). The aqueous layer was 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.
8 M. Pezechk, A. P. Brunetiere and J. Y. Lallemand, *Tetrahedron Lett*., 1986, **27**, 3715; A. P. Brunetiere and J. Y. Lallemand, *Tetrahedron Lett*., 1988, **29**, 179; J. C. Anderson, S. V. Ley, D. Santafianos and R. N. Sheppard, *Tetrahedron*, 1991, **47**, 6813.
9 H. D. Flack, *Acta Crystallogr., Sect. A*, 1983, **39**, 876; G. Bernardinelli and H. D. Flack, *Acta Crystallogr., Sect. A*, 1985, **41**, 500.

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