# A modular and organocatalytic approach to γ-butyrolactone autoregulators from Streptomycetes†

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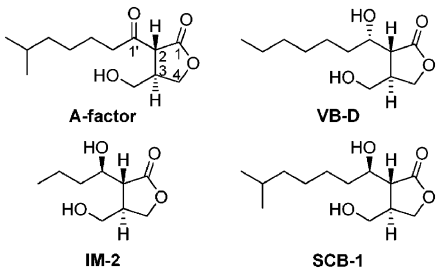
*Received (in Cambridge, UK) 23rd July 2008, Accepted 1st September 2008*
*First published as an Advance Article on the web 3rd October 2008*
**DOI: 10.1039/b812698d**

**A general synthesis of optically active γ-butyrolactone autoregulators is developed by a two-step sequence to assemble 2,3-*trans*-disubstituted butyrolactones in high yields and enantioselectivities; the scope of this reaction was elaborated by setting up a library of alkyl-substituted butyrolactones and the synthesis of the autoregulators IM-2 and VB-D.**

*Streptomyces* is a genus of Gram-positive filamentous bacteria that is known for its ability to produce secondary metabolites, including more than 70% of the commercially significant antibiotics.[1] Pioneered by the work of Khokhlov *et al.*,[2] small signalling molecules, the γ-butyrolactone autoregulators, have been identified to control the production of antibiotics in *Streptomyces* species. To date, fourteen 2,3-disubstituted γ-butyrolactones arising from seven different *Streptomyces* species have been identified, distinguishable by length, branching and stereochemistry of their fatty acid side-chain.[3] Based on the morphology of that side-chain, γ-butyrolactone autoregulators are classified into three groups (Scheme 1), the A-factor- (with a 1′-keto group), VB- (with a 1′-(*S*)-hydroxy group) and IM-2 types (with a 1′-(*R*)-hydroxy group) (see ESI for an overview of autoregulators†).

The first asymmetric synthesis of an autoregulator was accomplished for A-factor by Mori *et al.* starting from (*S*)-paraconic acid, which was obtained by resolution of the racemate.[4] Later a chiral auxiliary mediated synthesis of (*S*)-paraconic acid and its transformation to the A-factor was reported.[5,6] Autoregulators with a C-1′ hydroxyl group were first isolated by Gräfe *et al.*[7] and Yanagimoto *et al.* (VB-A–D).[8] The absolute configuration of these compounds were elucidated step by step by Mori *et al.*[9] and Yamada *et al.*[10,11] through total synthesis and NOE-experiments.

Interestingly, there is no reported general and catalytic asymmetric approach to these important compounds. We envisaged that ketolactone **A** would be a general chiral building block to synthesize all classes of γ-butyrolactone autoregulators (Scheme 2).

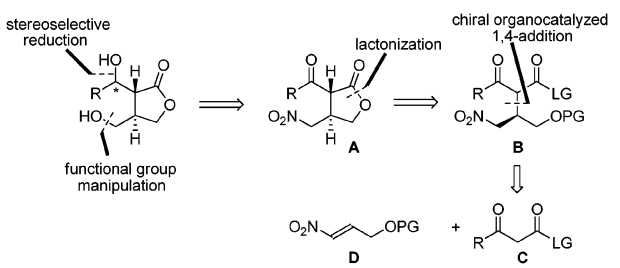



**Scheme 1** Classification of γ-butyrolactone autoregulators.

To access ketolactone **A**, our strategy included the C–C bond formation by an organocatalytic asymmetric 1,4-addition of β-keto carbonyl compounds **C** to nitroalkenes **D** and a subsequent one-pot deprotection–cyclization step of addition products **B**. In this way, a variety of *trans*-2,3-disubstituted butyrolactones of type **A** will be available in a modular fashion. Furthermore, the syntheses of optically active autoregulators IM-2 and VB-D were accomplished in a three-step sequence without the use of protective groups.

Based on a screening process we decided to focus on the *Cinchona* alkaloid-based thiourea catalysts **3a–d** since they are easily available in gram quantities and are effective for the enantioselective 1,4-addition to nitroalkenes.[12–14] Despite a good enantioselectivity, the issue of the screening was to identify suitable β-keto carbonyl compounds **1** (Table 1) that are reactive enough to undergo addition to nitroalkene **2** and facilitate the consecutive lactonization step.

The addition of β-ketoester **1a** to TBDMS-protected nitroalkene **2** (several silyl-based protecting groups were tested, and TBDMS = *tert*-butyldimethylsilyl) was found to give the best results. Table 1 shows that all four catalysts gave full conversion after 18 h at −20 °C in $CH_2Cl_2$ (entries 1–4).




**Scheme 2** Retrosynthetic analysis to target 2,3-*trans*-disubstituted butyrolactones (LG = leaving group, PG = protecting group).

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† Electronic supplementary information (ESI) available: Full experimental details. CCDC reference number 688507. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b812698d

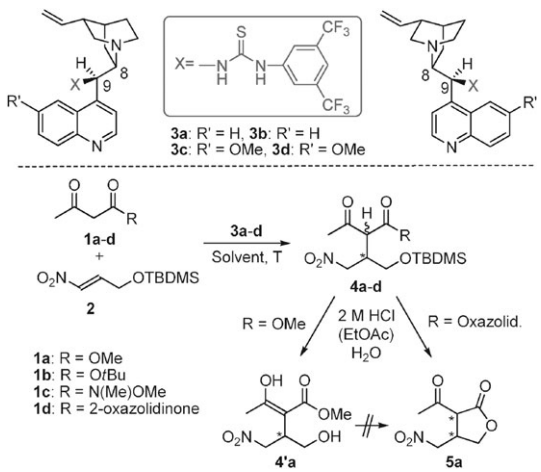
**Table 1** Screening of reaction conditions for the addition of 1,3-dicarbonyl compounds to nitroalkene **2**[a]

| Entry | Cat. | Nuc. | $T$/°C | [**2**]/M | Conv. (%)[b] | Ee (%)[c] |
|---|---|---|---|---|---|---|
| 1 | **3a** | **1a** | −20 | 1.0[d] | >95 | 80-(+)[f] |
| 2 | **3b** | **1a** | −20 | 1.0[d] | >95 | 82-(−)[f] |
| 3 | **3c** | **1a** | −20 | 1.0[d] | >95 | 81-(+)[f] |
| 4 | **3d** | **1a** | −20 | 1.0[d] | >95 | 83-(−)[f] |
| 5 | **3a** | **1a** | −20/rt | 0.2[d] | >95 | 81-(+)[f] |
| 6 | **3a** | **1b** | −20 | 1.0[d] | >95 | 76-(+)[f] |
| 7 | **3a** | **1a** | −20 | 1.0[e] | >95 | 81-(+)[f] |
| 8 | **3d** | **1c** | −20/rt | 1.0[e] | n.r. | — |
| 9 | **3d** | **1d** | −20/rt | 0.5[e] | >95[h] | 84-(−)[g] |
| 10 | **3d** | **1d** | rt | 0.5[e] | >95[i] | 84-(−)[g] |

[a] Reaction performed with 0.60 mmol of **1**, 0.20 mmol of **2**, and 10 mol% of **3**. [b] Determined by $^1$H NMR spectroscopy. [c] Ee determined by HPLC using a chiral-stationary phase or GC. [d] Performed in $CH_2Cl_2$. [e] Performed in toluene. [f] Ee determined after deprotection of the addition product (see ESI†); the sign of optical rotation is given in parentheses. [g] Ee determined after deprotection/lactonization of the addition product (see ESI†). [h] 84% isolated yield. [i] 50% isolated yield.

Both enantiomers of the addition products were obtained in good enantioselectivities ranging from 80–83% ee. A higher dilution (entry 5), as well as switching to toluene as solvent (entry 7) had no significant effect on the enantioselectivity. Increasing the size of the ester moiety in the nucleophile (**1b**) resulted in slightly lower enantioselectivity (entry 6).

The addition product **4a** derived from β-ketoester **1a** was deprotected with 2 M HCl in EtOAc or $H_2O$ to afford the hydroxyester **4′a** (Table 1). However, it also became evident that no further cyclization occurred under these reaction conditions. Applying TBAF as the deprotection agent led to decomposition of the addition product. Various other Brønsted and Lewis acids were tested to cyclize **4′a** but none of them gave considerable conversion to lactone **5a**. Consequently, we sought for an R-group in **1** that would enhance the reactivity of the addition product **4** towards ring-closure. Weinreb amide **1c** was not reactive enough to undergo addition to nitroalkene **2** (entry 8), but the reaction with oxazolidinone **1d** proceeded smoothly at −20 °C in toluene and the addition product **4d** showed 84% ee (entry 9). $CH_2Cl_2$ was also an effective solvent with respect to reactivity and enantioselectivity, but the yield was lower compared to the reactions in toluene (entry 10).




We were further delighted to see that the addition product **4d** could be deprotected and cyclized in a one-pot reaction using 2 M HCl in EtOAc and 5 equiv. of $H_2O$. The presence of a defined amount of $H_2O$ was crucial, since lactone **5a** was not formed when the reaction was conducted under anhydrous acidic conditions or in an aqueous acidic media. Under the optimized conditions, **5a** was isolated in 70% yield as a single diastereoisomer (keto : enol ratio = 2.5 : 1).

Next we investigated the scope of this transformation by using different alkyl-substituted oxazolidinones **1** (Table 2). Nucleophile **1e** with an *n*-propyl substituent reacted smoothly at −20 °C to give the addition product in 89% yield and the subsequent lactone **5b** in 71% yield and 90% ee (entry 2). Conducting the same reaction with catalyst **3c** gave access to the other enantiomer of **5b** in comparable yields and with 86% ee (entry 3). When moving to longer alkyl chains, we observed a decrease in reactivity at −20 °C. Adjusting the reaction temperature to 4 °C or rt for nucleophiles **1f–j**, respectively, gave in all cases full conversion after 48 h of reaction time. Addition products **4f–j** and the corresponding lactones **5c–g** were isolated in good yields and with 82–88% ee (entries 4–8). The results for lactones **5a, b, d** were also reproduced when performing the reactions on a 2 mmol scale.

In general, addition products **4** were obtained as diastereomeric mixtures in the range of 3 : 1 to 4 : 1. However, the ketolactones **5** were obtained as *single* diastereoisomers consisting up to 10% of the enol-form (for dr of **4a–j** and keto/enol ratios of **5a–g** see ESI†). The relative configuration of **5** was determined to be *trans* by analogy with the X-ray analysis of compound **5f** (see ESI†).

Table 2 shows that various autoregulators should be available from the 2,3-disubstituted γ-butyrolactones **5**. To exemplify this, we synthesized two autoregulators with opposite stereochemistry in the side chain, IM-2 **8** and VB-D **10**.

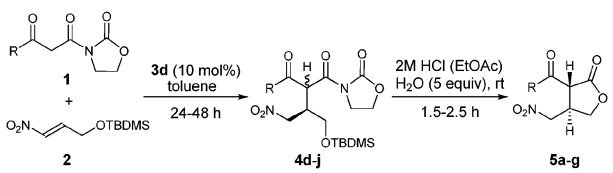
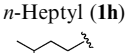
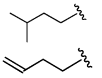
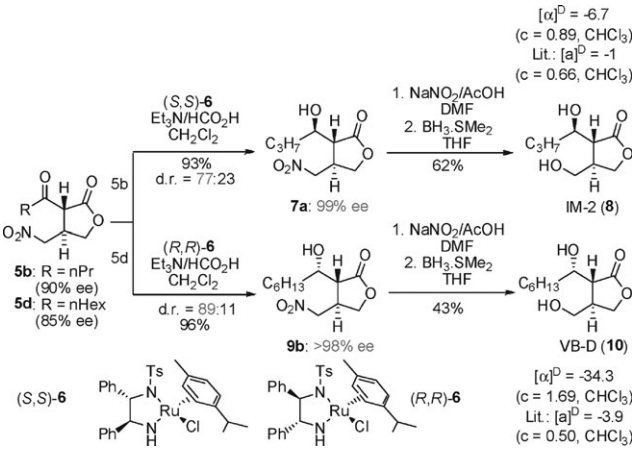



**Table 2** Scope of the organocatalytic synthesis of 2,3-disubstituted γ-lactones[a]

| Entry | R (**1**) | **4** (yield (%))[b] | **5** (yield (%))[b] | Ee (%)[c] | Target |
|---|---|---|---|---|---|
| 1 | Methyl (**1d**) | **4d** (84) | **5a** (70) | 84 | — |
| 2 | *n*-Propyl (**1e**) | **4e** (89) | **5b** (71) | 90 | IM-2 |
| 3[d] | *n*-Propyl (**1e**) | *ent*-**4e** (92) | *ent*-**5b** (68) | 86 | ent-IM-2 |
| 4[e] | *n*-Pentyl (**1f**) | **4f** (62) | **5c** (76) | 83 | VB-C |
| 5[e] | *n*-Hexyl (**1g**) | **4g** (77) | **5d** (80) | 85 | VB-D |
| 6[f] | *n*-Heptyl (**1h**) | **4h** (72) | **5e** (75) | 84 | SCB2 |
| 7[e] |  | **4i** (66) | **5f** (55) | 82 | VB-E |
| 8[f] |  | **4j** (84) | **5g** (68) | 88 | — |

[a] Reaction performed with 0.60 mmol of **1** (1.0 M in toluene), 0.20 mmol of **2** and 10 mol% of **3d** at −20 °C. [b] Isolated yields after column chromatography. [c] Ee determined by chiral stationary phase HPLC or GC. [d] Catalyst **3c** was used. [e] Reaction performed at rt and with a 0.5 M concentration of **2**. [f] Reaction performed at 4 °C with a 1.0 M concentration of **2**.




**Scheme 3** Synthesis of autoregulators IM-2 (8) and VB-D (10).

An efficient way of transforming primary nitroalkanes into the carboxylic acids has been developed by Mioskowski *et al.*[15] However, preliminary results with ketolactone **5a** showed that transformation of the keto group early in the sequence was decisive, since **5a** decomposed under the reported conditions, whereas the corresponding hydroxylactone gave clean conversion to the carboxylic acid. It has also been reported that $NaBH_4$-reduction of the keto group with the hydroxymethyl side-chain already installed led to considerable racemization.[9] Consequently, we first elaborated conditions for the reduction of the keto group of **5b** (see ESI†). The best results were obtained when **5b** was reacted under transfer hydrogenation conditions with Noyori's Ru-catalyst (*S*,*S*)-**6** (dr = 77 : 23) or (*R*,*R*)-**6** (dr = 13 : 87) favouring the formation of desired 1′-(*R*)-hydroxylactone **7a** in the first case (see Scheme 3). Due to *double stereoselection* the major diastereomer was enantiomerically enriched. For the synthesis of VB-D ketolactone **5d** was reduced with Ru-catalyst (*R*,*R*)-**6** furnishing 1′-(*S*)-hydroxylactone **9b** with high diastereo- and enantioselectivity.

To conclude the synthesis of autoregulator IM-2 **8**, hydroxylactone **7a** was reacted with $NaNO_2$ and AcOH in DMF at 35 °C. After acidic aqueous work-up and removal of DMF, the crude carboxylic acid was reduced with $BH_3$ $SMe_2$ in THF at 0 °C to give IM-2 in 62% yield (Scheme 3). The spectroscopic data and the sign of rotation were in agreement with the literature data.[11b]

Applying the conditions described above for the transformation of the nitro group to hydroxylactone **9b** gave autoregulator VB-D **10** in 43% yield, with spectroscopic data and sign of rotation matching the literature data.[8b,9] The discrepancy of the absolute values for the optical rotations of compounds **8** and **10** compared to the literature underlines the necessity for a synthetic sequence that installs the free hydroxymethyl unit in the last part of the synthesis in order to avoid racemization of the compounds. A similar observation was made by Takabe *et al.* when preparing autoregulator VB-C.[16]

In conclusion, we have developed a general and efficient way to synthesize optically active γ-butyrolactone autoregulators. 1,3-Dicarbonyl compounds containing the oxazolidinone motif have been proven to be very effective nucleophiles in the chiral *Cinchona* alkaloid–thiourea catalyzed 1,4-addition to alkyl-substituted nitroalkenes to assemble 2,3-*trans*-disubstituted butyrolactones in high yields and enantioselectivities. The scope of this reaction was elaborated by setting up a library of different alkyl-substituted butyrolactones targeting thereby naturally occurring autoregulators and the applicability was outlined by a three-step sequence to synthesize autoregulators IM-2 and VB-D.

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