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Enantioselective synthesis of β,β-dialkyl α-hydroxy γ-butyrolactones

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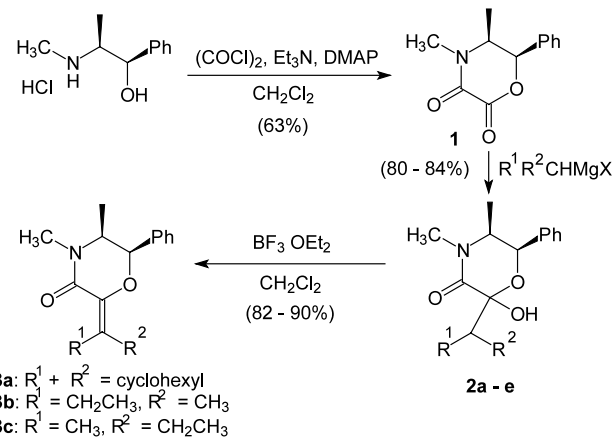
Abstract—An ephedrine-derived morpholine dione is employed in the synthesis of chiral alkylidene morpholinones that are efficiently converted to β-substituted α,γ-dihydroxy butyramides, precursors of the corresponding butyrolactones. Enantioselective synthesis of a spiro analog of pantolactone as well as a naturally occurring pantolactone homolog is achieved with this protocol.

The enantioselective synthesis of α-hydroxy γ-butyrolactones[1] has been the subject of several recent investigations. A number of these lactones are natural products and this has spurred interest in their total synthesis.[2] β,β-Dialkyl α-hydroxy γ-butyrolactones have recently been employed as components of interleukin inhibitors.[3] This particular class of butyrolactones and the parent hydroxy acids are also of interest due to their structural similarity to pantolactone[4] and the potential for application as pantothenic acid analogs in biologically relevant molecules.[5] Herein, we describe the application of an ephedrine-derived morpholine-dione in a general, stereoselective synthesis of β,β-disubstituted α-hydroxy butyramides and the corresponding butyrolactones.

The reaction of ephedrine and oxalyl chloride at ambient temperature generates the morpholine-dione **1** in 63% yield. Dione **1** reacts readily with a variety of Grignard and organolithium reagents[6] at the lactone carbonyl to generate the corresponding hemiacetals **2** (Scheme 1). Thus, treatment of **1** with cyclohexyl magnesium bromide generates **2a** (80%, ds = 2.5/1) and reaction with *sec*-butyl magnesium chloride gives a mixture of diastereomers **2b–e** (84%, dr = 3/3/1/1). The stereochemistry at the hemiacetal carbon and the *sec*-butyl carbon for **2b–e** has not been established. Dehydration of the hemiacetals is best achieved by treatment with BF_3 etherate at ambient temperature and the cyclohexylidene morpholinone **3a** is obtained in 82% from **2a**. Dehydration of the **2b–e** mixture gives **3b**/**3c** (90%, 1/1 mixture of *E*/*Z* isomers, Scheme 1). The stereochemistry of **3b** and **3c** is based on the downfield shift of the methylene hydrogens in **3b** (δ 2.6–2.8) as compared to **3c** (δ 2.2–2.4).[7] Olefins **3b** and **3c** are separable by chromatography and further reactions were conducted on isomerically homogeneous material.

We next investigated the synthesis of a spiro analog of pantolactone. The Prins reaction[8] ($(CH_2O)_n$, acetic acid, cat. H_2SO_4, 85°C) of the cyclohexylidene morpholinone **3a** efficiently generates the spiro bis-acetal **4a** (90%, Scheme 2) as a single diastereomer. This remarkably rapid reaction is complete within 2 min. Prolonged heating results in decomposition of **4a**. The alkylidene morpholinones **3b** and **3c** are converted to the spiro bis-acetals **4b** and **4c** in an analogous manner. The stereochemistry at the spiro acetal stereocenter in **4a–c**



Scheme 1.

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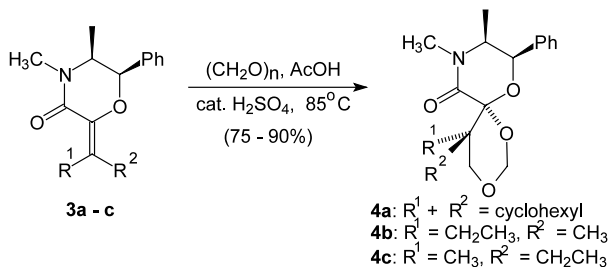
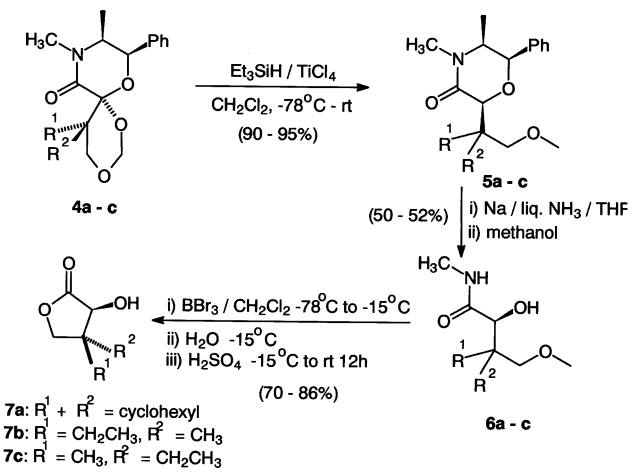
is assigned by analogy to other reactions of the oxocarbenium ion intermediate in the ephedrine-derived template.[9] At this stage, the stereochemistry at the quaternary carbon (bearing the methyl and ethyl groups) in **4b** and **4c** was tentatively assigned as shown (Scheme 2). The assignment was later confirmed by synthesis of the derived lactones and by correlation.

Morpholinones **4** incorporate all the required carbons for the target α-hydroxy butyrates and possess a spiro acetal stereocenter that is subject to stereoselective reduction with silanes. Accordingly, treatment of **4a–c** with excess $TiCl_4$/triethylsilane efficiently generates the morpholinones **5a–c** as single diastereomers resulting from axial reduction of the intermediate oxocarbenium ion under stereoelectronic control (Scheme 3). Morpholinones **5a–c** are protected versions of the requisite α,γ-dihydroxy butyric acid precursors of the target lactones. Dissolving metal reduction of **5a–c** generates the α-hydroxy γ-methoxy butyramides **6a–c** (50–52%). Conversion of **6** to the lactones **7** was readily achieved by a one-pot reaction sequence. Liberation of the primary hydroxyl group in **6** by demethylation (BBr_3) and subsequent acid catalyzed lactonization (H_2SO_4/H_2O, −15°C to rt) generates the lactones **7a–c** in good yield (70–86%, Scheme 3).[10]

This constitutes the first asymmetric synthesis of the spiro lactone (*S*)-**7a** (98% e.e. by chiral GC analysis).[11] One of the pantolactone homologs **7** is a natural product isolated from *Marshallia tenuifolia*,[12] the absolute configuration of which has been unambiguously established as 3*S*,4*S* by synthesis from D-glucose.[13] A synthesis from (*S*)-malic acid has also been reported recently.[14] The specific rotation and spectroscopic data of **7b** (97% e.e.) obtained from our study are in agreement with those of the natural product[15] and **7b** therefore has the 3*S*,4*S* configuration. Since the stereochemistry of the α-hydroxy bearing carbon has been established as '*S*' in the present as well as other related systems,[4b] and **7b** and **7c** are diastereomers, it follows that **7c** (97% e.e.) has the 3*S*,4*R* configuration. The Prins reaction of the alkylidene morpholinones **3** is therefore stereospecific and proceeds with retention of the olefin geometry. Thus, the *E*-isomer **3b** generates **4b** whereas the *Z*-isomer **3c** generates **4c**.



Scheme 2.



Scheme 3.

In conclusion, the ephedrine derived morpholine dione **1** is a convenient precursor for chiral alkylidene morpholinones that are key substrates in a highly stereoselective Prins reaction/acetal reduction protocol. A general, enantioselective route to β,β-disubstituted α-hydroxy butyrolactones has been established. Current efforts focus on other applications of the dione **1** in the enantioselective synthesis of α-hydroxy acids and derivatives.

Acknowledgements

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11. The enantiomeric excess of the lactones was determined by GC analysis with a HP Chiral (20% permethylated β-cyclodextrin) column (30 m×0.320 mm×0.25 μm).
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15. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.2 (d, 1H, $J=9.3$, CH_2O), 4.16 (s, 1H, $CHOH$), 3.87 (d, 1H, $J=9.3$, CH_2O), 3.0 (br, 1H, OH), 1.61–1.39 (m, 2H, CH_2CH_3), 1.19 (s, 3H, CH_3), 0.92 (t, 3H, $J=7.3$, CH_2CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 177.6 (C=O), 76.0 (CHOH), 73.7 (CH_2O), 43.6 ($C_{quat.}$), 24.2 (CH_2CH_3), 21.0 (CH_3), 8.2 (CH_2CH_3); $[\alpha]_D^{25}=+4.5$ (c 0.25, $CHCl_3$) for **7b** and $[\alpha]_D^{20}=+4.7$ (c 0.26, $CHCl_3$) for the natural product.