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Asymmetric synthesis of α-alkyl-α-hydroxy-γ-butyrolactones

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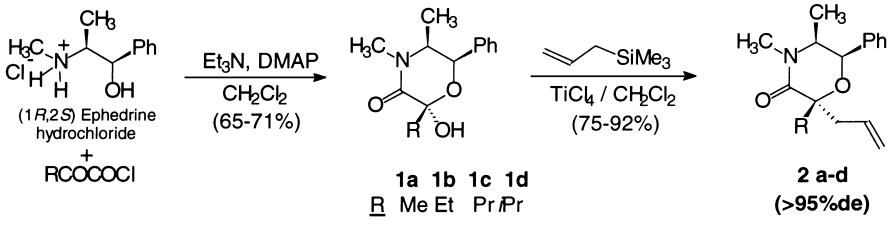
Abstract

A new enantioselective approach to α-alkyl-α-hydroxy-γ-butyrolactones employing (1*R*,2*S*)-ephedrine-derived chiral allyl morpholinones as starting materials is described.

The asymmetric synthesis of α-hydroxy-γ-butyrolactones, with or without alkyl substituents in the ring,[1–7] continues to be actively investigated due to their utility as chiral building blocks for the synthesis of natural products and biologically active molecules such as (1*S*,2*R*)-(−)-frontalin and (*R*)-(−)-mevalonolactone.[8] Similarly, the synthesis of racemic α-alkyl-α-hydroxy-γ-butyrolactones has also been examined and their application in the preparation of α,β-butenolides and furans has been demonstrated.[9]

As part of an ongoing program into the asymmetric functionalization of α-keto carboxylic acids using (1*R*,2*S*)-ephedrine as a chiral controller,[10,11] we decided to explore the possibility of functionalization of ephedrine-based allyl morpholinones[10] and their subsequent conversion to α-alkyl-α-hydroxy-γ-butyrolactones. Herein we describe an enantioselective approach to α-alkyl-α,γ-dihydroxy butyramides and their conversion to the corresponding butyrolactones. To the best of our knowledge, an asymmetric approach to enantiomerically enriched α-alkyl-α-hydroxy-γ-butyrolactones involving stereoselective functionalization of α-keto acids has not been examined.

Acylation of (1*R*,2*S*)-ephedrine hydrochloride with a variety of aliphatic α-keto acid chlorides generates the hemiacetals **1** in good yield (65–71%). Allylation of **1** with allyltrimethylsilane/$TiCl_4$ proceeds with excellent diastereoselectivity (>95/5) at −40°C, to generate the 2-alkyl-2-allyl-morpholinones **2** in good yield (75–92%)[10] (Scheme 1). These served as starting materials for this study.



Scheme 1.

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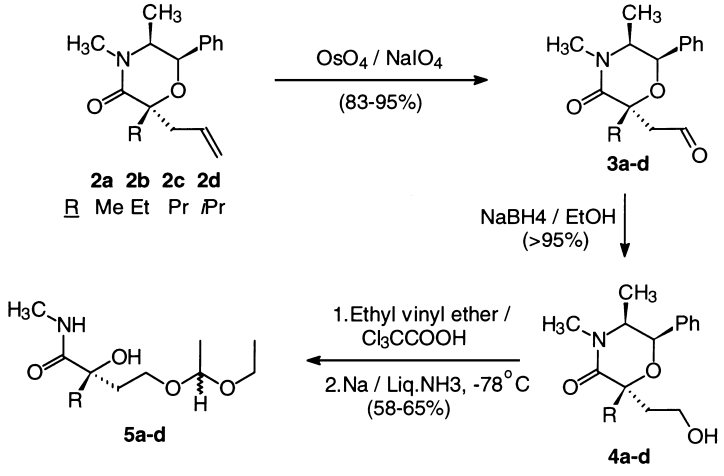
Oxidative cleavage of the allylic double bond in **2a–d** with $OsO_4/NaIO_4$[12] in THF/water at ambient temperature cleanly generates the aldehydes **3a–d** (83–95% yield)† which are quantitatively converted to the corresponding alcohols **4a–d** by reduction with $NaBH_4$ in ethanol. Treatment of **4a** with Na in liq. NH_3 at −78°C resulted in a complex mixture, presumably due to the presence of the free hydroxyl group. Conversion of **4** to the ethoxyethyl ether was beneficial and dissolving metal reduction of protected **4** proceeded smoothly at −78°C to generate the α-hydroxy amides **5a–d** in 58–65% yield over two steps. It is noteworthy that the crude alcohols **4** and the corresponding ethoxy ethyl ethers may be directly used in the Na/liq. NH_3 reduction. The overall transformation is shown in Scheme 2.

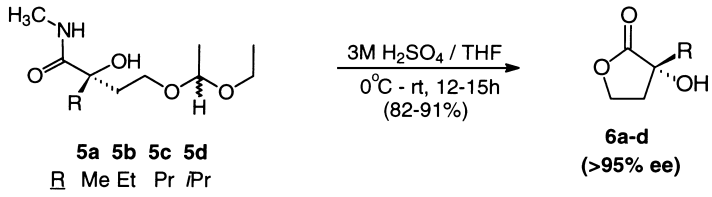


Scheme 2.

The conversion of the α-hydroxy amides **5** to the target lactones **6** was achieved under remarkably mild conditions. Unmasking of the primary alcohol in **5** is readily achieved by treatment with 3 M H_2SO_4/THF at ambient temperature and proceeds with concomitant lactonization, presumably due to a very facile intramolecular acyl transfer from nitrogen to oxygen[13] to generate the desired α-alkyl-α-hydroxy-γ-butyrolactones **6a–d** in 82–91% yield (Scheme 3).‡

† Oxidative cleavage of **2d** with $OsO_4/NaIO_4$: To the stirred solution of **2d** (0.92 g, 3.2 mmol) in THF (12 mL) and H_2O (4 mL) at ambient temperature was added OsO_4 (0.5 M in toluene, 0.07 mL, 0.04 mmol) at which point the colorless solution turned dark brown. To this was added solid $NaIO_4$ (1.64 g, 7.7 mmol) in portions over 20 min and the reaction mixture was stirred for 4 h. Brine (20 mL) was added followed by ethyl acetate (40 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2×20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give 0.99 g of crude **3d**. Purification by flash chromatography on silica gel (ethyl acetate:petroleum ether, 40:60) furnished 774 mg (83%) of **3d**. IR ($CHCl_3$): 2972, 2877, 1715, 1636, 1452, 1401, 1383, 1338, 1316, 1289, 1206, 1180, 1143, 1098, 1070, 1038 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.85 (dd, 1H, *J*=2.5, 3.4, C*H*O), 7.5–7.1 (m, 5H, Ar*H*), 5.15 (d, 1H, *J*=3.4, C*H*Ph), 3.54 (dq, 1H, *J*=3.4, 6.8, CH_3CH), 3.05 (s, 3H, NCH_3), 2.95 (dd, 1H, *J*=3.4, 15.1, CH_2CHO), 2.80 (dd, 1H, *J*=2.5, 15.1, CH_2CHO), 2.44 (sept, 1H, *J*=6.8, Me_2CH), 1.16 (d, 3H, *J*=6.8, $(CH_3)_2CH$), 1.06 (d, 3H, *J*=6.8, $(CH_3)_2CH$), 0.98 (d, 3H, *J*=6.8, $CHCH_3$); MS (70 eV) m/z 58 (51), 69 (11), 77 (11), 91 (29), 97 (32), 105 (14), 118 (100), 125 (6), 133 (8), 148 (33), 156 (4), 184 (39), 218 (6), 246 (6), 260 (11), 289 (M^+, 30).

‡ 2-(1-Methylethyl)-2-hydroxy-γ-butyrolactone (**6d**): To the stirred solution of **5d** (0.1 g, 0.4 mmol) in THF (2.5 mL) at 0°C was added 3 M H_2SO_4 (2.5 mL) dropwise over 3 min. The resulting solution was warmed to and stirred at ambient temperature for 12 h. It was then diluted with ether (20 mL) and neutralized with excess solid $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with ether (3×10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give 53 mg of crude **6d**. Purification by flash chromatography on silica gel (ethyl acetate:petroleum ether, 30:70) furnished 48 mg (82%) of **6d** as a clear colorless oil. $[\alpha]_D^{25}$=+75.6 (*c* 3.2, $CHCl_3$); IR (neat): 3445, 2968, 2924, 2880, 1759, 1472, 1373, 1300, 1136, 1107, 1013, 984, 961, 943 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.5–4.3 (m, 1H, CH_2O), 4.3–4.15 (m, 1H, CH_2O),



Scheme 3.

The absolute configuration and enantiomeric excesses of compounds **6** are based on those of the precursors **2** since epimerization of the newly generated stereocenter in **2** during conversion of **2** to **3**, **3** to **5** and **5** to **6** is unlikely. Thus, lactones **6a**–**c** are assigned *R* configuration and **6d** the *S* configuration. The configurational assignment was further confirmed by conversion of **6a** (R=CH_3) to its benzoate derivative (PhCOCl, Et_3N, DMAP, CH_2Cl_2, 90%) and comparison of the sign of the optical rotation of the benzoate with the literature value.[8] The overall conversion of the allyl morpholinones **2** to the lactones **6** constitutes a new approach to these important intermediates that involves asymmetric functionalization of readily available α-keto carboxylic acids as the key step. The results are summarized in Table 1.

Table 1
Conversion of allyl morpholinones **2** to aldehydes **3**; **3** to hydroxy amides **5**; and **5** to α-alkyl-α-hydroxy-γ-butyrolactones **6**

Substrate	%yield 3	% yield 5[a]	%yield 6	$[\alpha]_D$ 6	%ee 6[b]	Configuration 6[c]
2a	95	64	91[d]	+17.6[e]	>95	*R*
2b	85	60	80	+59	>95	*R*
2c	84	65	82	+50.7	>95	*R*
2d	83	58	82	+75.6	>95	*S*

a: from crude **4** over two steps b: based on de of **2** c: based on the absolute configuration of **2** d: yield of crude product which was pure by ^{1}H NMR e: benzoate derivative, lit.[8] $[\alpha]_D$ = +18.9 (*c* 3.8, $CHCl_3$).

In conclusion, an asymmetric synthesis of α-alkyl-α-hydroxy-γ-butyrolactones has been achieved from (1*R*,2*S*)-ephedrine-derived allyl morpholinones. The methodology developed has been successfully applied for the synthesis of 2-methyl-2-hydroxy-γ-butyrolactone which serves as a key precursor in the synthesis of (1*S*,2*R*)-(−)-frontalin and (*R*)-(−)-mevalonolactone.[8] Since (1*S*,2*R*)-ephedrine is also commercially available, the enantiomeric series of α-alkyl-α-hydroxy-γ-butyrolactones should also be available by this methodology. Current efforts focus on other reactions of allyl morpholinones **2**.

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2.8–2.45 (b, 1H, O*H*), 2.45–2.10 (m, 2H, CH_2), 2.05 (sept, 1H, *J*=6.8, Me_2CH), 1.05 (d, 3H, *J*=6.8, CHCH_3), 0.95 (d, 3H, *J*=6.8, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7 (*C*=O), 78.0 (*C*-OH), 65.4 (CH_2-O), 33.8 (*C*H), 30.8 (CH_2-C), 17.2 (CH_3), 15.8 (CH_3); MS (70 eV) m/z 57 (65), 67 (26), 71 (100), 85 (99), 102 (82), 126 (1), 144 (M^+, 1).

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