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Enantioselective synthesis of α-hydroxy γ-butyrolactones from an ephedrine-derived morpholine-dione

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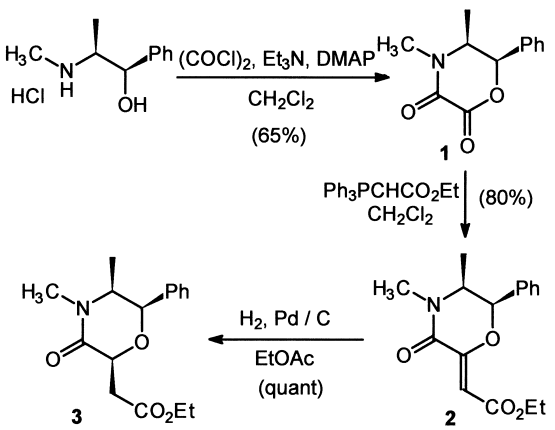
Abstract—An ephedrine-derived morpholine dione is employed in the enantioselective synthesis of (*S*)-α-hydroxy γ,γ-dimethyl-γ-butyrolactone and (*S*)-α-hydroxy γ-butyrolactone. A one-pot alkylation/allylation protocol for the stereoselective conversion of the dione to 2-alkyl-2-allyl morpholinones, key intermediates for α-alkyl-α-hydroxy-γ-butyrolactones, is described.

The enantioselective synthesis of α-hydroxy acids and esters[1] and their derivatives such as α-hydroxy γ-butyrolactones[2] has been the subject of several recent investigations. A number of these lactones are natural products, which has spurred interest in their total synthesis.[3] Herein, we describe the application of an ephedrine-derived morpholine-dione in the stereoselective synthesis of α-hydroxy butyramides and the corresponding butyrolactones.

The reaction of ephedrine with oxalyl chloride generates the morpholine-dione **1** in 65% yield.[4] Initially, we investigated chemoselective reactions of **1** with nucleophilic reagents. Treatment of **1** with (carbethoxymethylene) triphenylphosphorane in dichloromethane at ambient temperature generates the alkylidene morpholinone **2** (80%, *Z*/*E*=20/1, Scheme 1). The stereochemical assignment is based on the chemical shift of the olefinic methine proton (δ 6.22 in *Z*-**2**) as compared to the upfield shift[5] in the *E*-isomer (δ 5.83).

Hydrogenation of the alkylidene ester **2** (H_2, Pd/C, 1 atm) provides **3** as a single diastereomer in quantitative yield (Scheme 1). The stereochemistry of reduction is based on the observed diastereoselectivity for allylation and reduction on the ephedrine-derived template.[6,7] It is noteworthy that **3** is a fully protected and chemically differentiated malic acid derivative that is a valuable precursor to α-hydroxy butyrolactones. To this effect, chemoselective transformations at the ester carbonyl in **3** were investigated. Selective ester reduction in **3** to give alcohol **4** (Scheme 2) proved to be unexpectedly difficult. Heating **3** with excess LAH results in concomitant partial



Scheme 1.

reduction of the amide carbonyl and reduction at ambient temperature is capricious, often giving poor yield of the alcohol. Although hydrolysis of **3** followed by reduction of the acid with BH_3 in THF is also inefficient, reduction of the acid chloride with a combination of $TiCl_4/NaBH_4$[8] in dioxane is the procedure of choice and provides the alcohol **4** in 70% yield. Subsequent protection with ethylvinyl ether followed by removal of the ephedrine portion with dissolving metal reduction (Na/NH_3, −78°C) generates the partially unmasked butyramide **5** (65% yield over two steps, Scheme 2).

The ester group in **3** also serves as a useful tool for further functionalization of the embedded α-alkoxy succinate moiety. The potential of **3** as a common precursor to the α-hydroxy butyrolactone scaffold was demonstrated with the synthesis of (*S*)-γ,γ-dimethyl-α-hydroxy-γ-butyrolactone. The (*R*) enantiomer of this lactone, which is a valuable intermediate in the synthesis of bark beetle

Keywords: asymmetric synthesis; lactones; Wittig reaction; allylation; diastereoselectivity.

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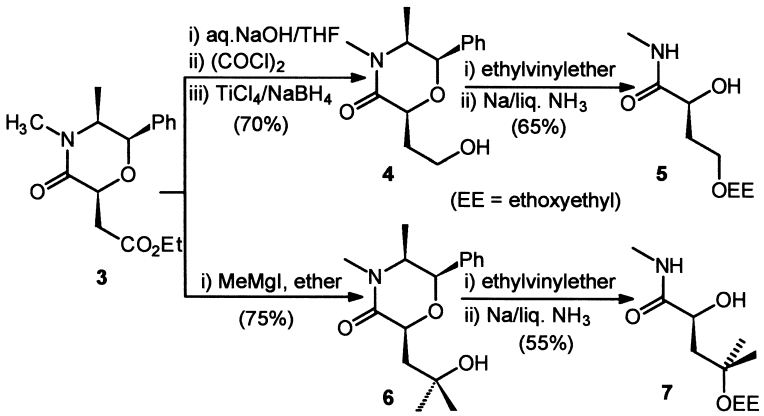


Scheme 2.

pheromones,[9] should also be readily available by the present methodology since 1*S*,2*R* ephedrine is commercially available as well. Related γ,γ-dialkyl α-hydroxy butyrolactones have been employed as components of chiral dopants in liquid crystals.[10]

Treatment of **3** with excess MeMgI yields the tertiary alcohol **6** in 75% yield. The conversion of **6** to the hydroxy amide **7** is achieved as described for the primary alcohol **4**. Protection of **6** as the ethoxyethyl ether followed by reductive cleavage generates the substituted dihydroxy butyramide **7** (55% yield over two steps (Scheme 2)).

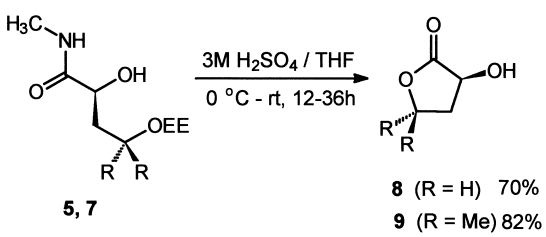
The deprotection of **5** and **7** with aqueous acid proceeds with concomitant lactonization to generate α-hydroxy γ-butyrolactones **8** (70%, 96% ee)[11a] and **9** (82%, 98% ee)[11b] respectively. This facile lactonization probably proceeds via an acyl group transfer from nitrogen to oxygen under acidic conditions (Scheme 3). The synthesis of **5**, **7**, **8** and **9** highlights the utility of the dione **1** as a general precursor for various α-hydroxy butyrates.

Morpholine-dione **1** also reacts chemoselectively with a variety of alkyl metal reagents to generate the hemiacetals **10**[6] (Scheme 4). In particular, the reaction of **1** with Grignard reagents in ether at −20°C provides hemiacetals **10** in excellent yield and good diastereoselectivity[6] (ds≥10/1 by ^{1}H NMR). We have previously demonstrated the synthesis of these hemiacetals from ephedrine and α-keto acids and also the stereoselective allylation of these hemiacetals in a separate, subsequent step.[6] In the present study, a one-pot reaction protocol that combines the hemiacetal synthesis and the allylation step was developed. The procedure involves addition of the alkyl metal reagent to the dione followed by allylation of the resulting salt of the hemiacetal **10** (R′=MgX) with allyl trimethylsilane/$TiCl_4$ (Scheme 4).

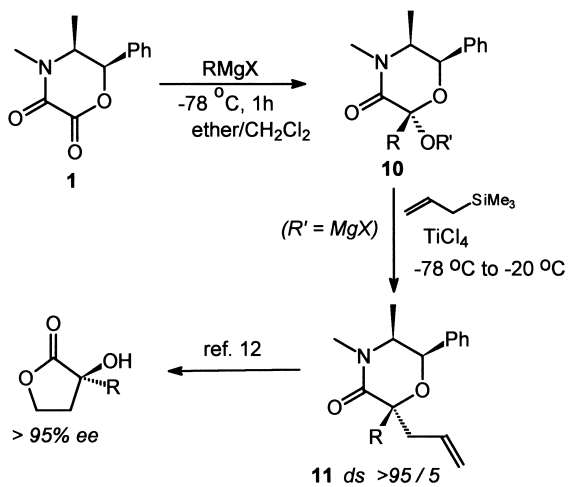
Thus, reaction of **1** with an alkyl Grignard reagent in ether at −78°C followed by allylation (−78 to −20°C for 6 h, or gradual warming to ambient temperature overnight) furnished morpholinones **11**[6] (Scheme 4) as single diastereomers (^{1}H NMR) in 50–60% yield.

Allyl morpholinones **11** are important intermediates in the synthesis of α-hydroxy acids[6] and more notably, they are readily converted α-hydroxy α-alkyl-γ-butyrolactones (Scheme 4).[12] The above one-pot procedure has a significant advantage over the earlier, α-keto acid based method for synthesis of the hemiacetals from ephedrine. The present method does not require α-keto acids and it should now be possible to prepare any hemiacetal by reaction of **1** and the appropriate organometallic reagent. In addition, isolation and purification of the hemiacetal is not required. A selection of hemiacetals and allyl morpholinones prepared by the one-pot protocol is shown in Fig. 1.

In conclusion, we have developed a novel, stereoselective route to α-hydroxy γ-butyrolactones by functionalization of a readily available ephedrine derivative. The morpholinone **3** holds great potential as a common intermediate for a



Scheme 3.



Scheme 4.

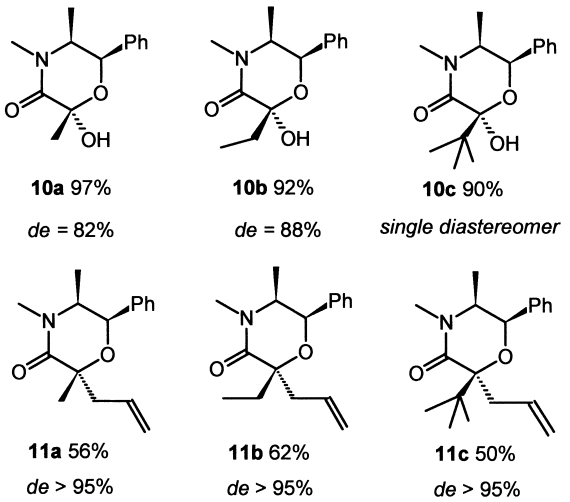


Figure 1. Hemiacetals **10** and allyl morpholinones **11** prepared from **1**.

variety of functionalized α-hydroxy acids and α-hydroxy γ-butyrolactones. The one-pot alkylation/allylation protocol with morpholine-dione **1** significantly improves the scope of the hemiacetal approach to α-hydroxy γ-butyrolactones and other α-hydroxy acid derivatives. Current efforts focus on other reactions of **1**.

1. Experimental

1.1. General

All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried (120°C) glassware. Ether, THF and dioxane were distilled from sodium and benzophenone. Dichloromethane and triethylamine were distilled from calcium hydride. Solvents for chromatography were distilled at their respective constant boiling points. Petroleum ether refers to the fraction in the 60–80°C range. Commercially available $TiCl_4$ was distilled and used. Grignard reagents were freshly prepared. Commercially available oxalyl chloride and $NaBH_4$ were used. ^1H and ^{13}C NMR spectra were recorded on Bruker MSL-300 or AC-200 instruments. IR spectra were recorded on a Shimadzu FTIR-8400 instrument. Optical rotations were measured at the sodium D line on JASCO P-1020 polarimeter. Mass spectra (EI) were recorded on a Finnigan-Mat 1020C mass spectrometer at an ionization potential of 70 eV. High resolution mass spectra were recorded on a Jeol JMS-SX-102 spectrometer. All melting points are uncorrected. Elemental analyses were performed by the microanalysis facility at NCL, Pune.

1.1.1. 5*S*,6*R*-4,5-Dimethyl-6-phenyl-morpholin-2,3-dione (1). To a stirred suspension of ephedrine hydrochloride (2 g, 9.9 mmol) and DMAP (60 mg, 0.49 mmol) in dichloromethane (200 mL) at 0°C was added triethylamine (5.5 mL, 39.6 mmol). The mixture was stirred for 10 min and a solution of oxalyl chloride (1.3 mL, 14.9 mmol) in dichloromethane (100 mL) was added dropwise over a period of 4 h at 0°C. The mixture was further stirred at 0°C for 1 h and ice was added. The mixture was warmed to ambient temperature and the biphase was separated. The dichloromethane layer was washed with water (70 mL), dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (1/3 petroleum ether/ethyl acetate) to furnish 1.42 g (65%) of **1** as a white solid.

Mp: 182°C; ^1H NMR (200 MHz, $CDCl_3$): δ 7.50–7.28 (m, 5H, Ar*H*), 5.90 (d, 1H, *J*=2.9 Hz, C*H*Ph), 3.77–3.66 (dq, 1H, *J*=2.9, 6.8 Hz, C*H*CH_3), 3.19 (s, 3H, NCH_3), 1.12 (d, 3H, *J*=6.8 Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 156.4 (O*C*=*O*), 153.0 (N*C*=*O*), 133.8 (ArC_{ipso}), 128.6 (Ar*C*), 128.0 (Ar*C*), 125.3 (Ar*C*), 79.3 (Ph*C*H), 58.1 (CH_3*C*H), 33.2 (N*C*H_3), 11.8 (*C*H_3); IR ($CHCl_3$): 3018, 1771, 1693, 1406, 1292, 1215, 1186, 1009 cm^{-1}; MS (EI, 70 eV): *m/z* 57 (90), 77 (45), 91 (35), 105 (25), 117 (100), 147 (3), 176 (3), 219 (M^+, 12); Analysis for $C_{12}H_{13}NO_3$: calcd: C, 65.74; H, 5.97; N, 6.38; Found: C, 65.35; H, 6.09, N, 6.36; $[\alpha]_D^{25}=-184.3$ (*c*=0.8, $CHCl_3$).

1.1.2. (*Z*)-5*S*,6*R*-2-Carbethoxymethylidene-4,5-dimethyl-6-phenyl-morpholin-3-one (2). To a solution of **1** (219 mg, 1 mmol) in dichloromethane (3 mL) at room temperature was added carbethoxymethylene triphenylphosphorane (418 mg, 1.2 mmol) and the mixture was stirred at ambient temperature for 48 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (6/4 petroleum ether/ethyl acetate) to furnish 231 mg (80%) of **2** as a white solid.

Mp: 161–162°C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.55–7.3 (m, 5H, Ar*H*), 6.22 (s, 1H, vinylic), 5.47 (d, 1H, *J*=2.9 Hz, PhC*H*), 4.27–4.18 (m, 2H, OCH_2C), 3.73–3.62 (dq, 1H, *J*=2.9, 6.6 Hz, CH_3C*H*), 3.15 (s, 3H, NCH_3), 1.32 (t, 3H, *J*=7.3 Hz, CH_3CH_2), 1.02 (d, 3H, *J*=6.6 Hz, CH_3CH); ^{13}C NMR: (50 MHz, $CDCl_3$): δ 164.6 (O*C*=*O*), 157.7 (N*C*=*O*), 153.5 (*C*=CH), 135.5 (ArC_{ipso}), 128.4 (Ar*C*), 128 (Ar*C*), 125.2 (Ar*C*), 101 (C=*C*H), 77.9 (Ph*C*H), 59.7 (O*C*H_2), 57.9 (N*C*H), 33.6 (N*C*H_3), 14.0 (CH_2*C*H_3), 11.4 (*C*H_3CH); IR ($CHCl_3$): 3018, 2983, 1701, 1668, 1637, 1338, 1285, 1258, 1215, 1194, 1034, 908 cm^{-1}; MS (EI, 70 eV): *m/z* 69 (32), 77 (19), 91 (44), 107 (53), 117 (75), 135 (100), 147 (89), 154 (32), 174 (28), 244 (38), 289 (M^+, 62); Analysis for $C_{16}H_{19}NO_4$: calcd: C, 66.42; H, 6.62; N, 4.84; Found: C, 66.11; H, 6.75, N, 4.73; $[\alpha]_D^{25}=-238.1$ (*c*=0.6, $CHCl_3$).

1.1.3. 2*S*,5*S*,6*R*-2-Carbethoxymethyl-4,5-dimethyl-6-phenyl-morpholin-3-one (3). To a solution of **2** (289 mg, 1 mmol) in ethyl acetate (10 mL) was added Pd/C (5%, 25 mg) and the mixture was stirred under an atmosphere of hydrogen (1 atm) for 12 h. The mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure to give 291 mg (100%) of **3** as a clear colorless gum.

^1H NMR (200 MHz, $CDCl_3$): δ 7.46–7.22 (m, 5H, Ar*H*), 5.06 (d, 1H, *J*=2.9 Hz, PhC*H*), 4.66 (t, 1H, *J*=5.4 Hz, C*H*CH_2), 4.3–4.12 (q, 2H, *J*=6.8 Hz, OCH_2), 3.61–3.44 (dq, 1H, *J*=2.9, 6.4 Hz, CH_3C*H*), 3.15–2.88 (m, 2H, CH_2CO_2Et), 3.04 (s, 3H, NCH_3), 1.29 (t, 3H, *J*=6.8 Hz, CH_3CH_2), 0.99 (d, 3H, *J*=6.4 Hz, CH_3C*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.0 (O*C*=O), 167.5 (N*C*=O), 137 (ArC_{ipso}), 128 (Ar*C*), 127.3 (Ar*C*), 125.1 (Ar*C*), 76.4

(Ph*C*H), 74.6 (*C*HCO), 60.2 (O*C*H_2), 58.4 (N–*C*H), 37.3 (*C*H_2CO_2Et), 33.1 (N*C*H_3), 13.9 (CH_2*C*H_3), 12.3 (CH_3*C*H); IR ($CHCl_3$): 2982, 2937, 1738, 1653, 1497, 1489, 1456, 1400, 1378, 1270, 1182, 1148, 1109, 1027 cm^{-1}. HRMS for $C_{16}H_{21}NO_4$: calcd: 291.1471; Found: 291.1474; $[\alpha]_D^{25}=-114.0$ (c=1.1, $CHCl_3$).

1.1.4. 2*S*,5*S*,6*R*-2-(2-Hydroxyethyl)-4,5-dimethyl-6-phenyl-morpholin-3-one (4). To the solution of **3** (580 mg, 2 mmol) in THF (8 mL) was added aqueous NaOH (1 M, 8 mL) and the mixture was stirred at ambient temperature for 6–7 h. The aqueous layer was acidified with conc. HCl and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (25 mL). The bicarbonate extract was acidified with conc. HCl and the solution was extracted with ethyl acetate (3×20 mL). The combined ethyl acetate extracts were dried (Na_2SO_4) and concentrated to give 502 mg (96%) of the carboxylic acid.

To a solution of the carboxylic acid (502 mg, 1.91 mmol) in dichloromethane (6 mL) was added oxalyl chloride (0.83 mL, 9.54 mmol) dropwise and the mixture was stirred at ambient temperature for 2 h. The solvent and excess oxalyl chloride were removed under reduced pressure and the residue was dissolved in dioxane (6 mL). The dioxane solution was added to a stirred suspension of sodium borohydride (722 mg, 19.1 mmol) in dioxane (6 mL) followed by addition of $TiCl_4$ (1.05 mL, 9.55 mmol). The resulting mixture was heated to 90°C for 8 h and then cooled to 0°C. Saturated aqueous bicarbonate was added and the resulting mixture was extracted with ethyl acetate (3×20 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (ethyl acetate) to furnish 332 mg of alcohol **4** (70%) as a white solid.

Mp: 135–136°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.55–7.2 (m, 5H, Ar*H*), 5.03 (d, 1H, J=2.9 Hz, PhC*H*), 4.47 (t, 1H, J=6.3 Hz, C*H*CO), 3.89 (t, 2H, J=6.4 Hz, CH_2OH), 3.58–3.43 (dq, 1H, J=2.9, 6.3 Hz, C*H*CH_3), 3.05 (s, 3H, NCH_3), 2.42–2.10 (m, 2H, CH_2CH), 1.00 (d, 3H, J=6.3 Hz, CH_3CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.9 (N*C*=O), 137.1 (ArC_{ipso}), 127.7 (Ar*C*), 126.9 (Ar*C*), 124.8 (Ar*C*), 75.8 (Ph*C*H), 75.4 (*C*HCO), 58.4 (*C*H_2OH), 57.9 (N*C*H), 35 (*C*H_2CH_2OH), 32.9 (N*C*H_3), 12.2 (*C*H_3CH); IR ($CHCl_3$): 3404, 3013, 2980, 2928, 2860, 1641, 1634, 1497, 1452, 1404, 1381, 1250, 1215, 1148, 1109, 1065 cm^{-1}; MS (EI, 70 eV): m/z 58 (100), 69 (7), 77 (20), 84 (24), 105 (14), 115 (39), 143 (27), 205 (15), 249 (M^+, 5); Analysis for $C_{14}H_{19}NO_3$: calcd: C, 67.45; H, 7.68; N, 5.62; Found: C, 67.50; H, 7.83; N, 5.24; $[\alpha]_D^{25}=-177.7$ (c=0.5, $CHCl_3$).

1.1.5. 2*S*-2-Hydroxy-4-ethoxyethyl-butanoic acid *N*-methyl amide (5). To the solution of **4** (168 mg, 0.67 mmol) in chloroform (3 mL) was added ethyl vinyl ether (0.52 mL, 5.4 mmol) and trichloroacetic acid (a few crystals). The resulting mixture was stirred at ambient temperature for 12 h. Saturated aqueous $NaHCO_3$ was added and the organic layer was separated. The bicarbonate layer was extracted with chloroform (3×5 mL) and all the $CHCl_3$ layers were combined, dried (Na_2SO_4) and concentrated to give the ethoxyethyl derivative of **4** that was used further without purification.

The above derivative was dissolved in anhydrous THF (2 mL) and added to a mixture of anhydrous liquid ammonia (7 mL, distilled over sodium) and sodium (154 mg, 6.7 mmol) at −78°C. The mixture was stirred at −78°C for 3 min and methanol (6 mL) was added. The mixture was warmed to ambient temperature to remove ammonia and the methanol was removed under reduced pressure. The residue was taken up in water and the mixture was saturated with sodium chloride. The aqueous phase was extracted with ethyl acetate and the combined extracts were concentrated. The residue was purified by rapid filtration through a short silica gel column (ethyl acetate) to furnish 90 mg (65%) of **5** which was immediately used further.

^{1}H NMR (200 MHz, $CDCl_3$): Major diastereomer: δ 6.95 (br s, 1H, NH), 4.7–4.6 (m, 1H, OC*H*O), 4.25 (br dd, 1H, 2.9, 8.3, C*H*OH), 3.9–3.36 (m, 4H, 2×OCH_2), 2.81 (d, 3H, J=5.0 Hz, NCH_3), 2.25 (br t, 1H, 7.0, CH_2), 1.86 (br t, 1H, J=7.3 Hz, CH_2), 1.28 (d, 3H, J=5.3 Hz, CHCH_3), 1.17 (t, 3H, J=7.0 Hz, CH_2CH_3). Minor diastereomer: δ 6.0 (br s, N*H*), 4.7–4.6 (m, 1H, OC*H*O), 4.25 (br dd, 1H, C*H*OH), 3.9–3.36 (m, 4H, 2×OCH_2), 2.76 (d, 3H, J=5.0 Hz, NCH_3), 2.19–2.08 (m, 1H, CH_2), 1.98–1.79 (m, 1H, CH_2), 1.25 (d, 3H, J=5.4 Hz, CHCH_3), 1.16 (t, 3H, J=7.0 Hz, CH_2CH_3); IR (neat): 3355, 2976, 2933, 2882, 1658, 1547, 1410, 1381, 1131, 1099, 1058 cm^{-1}.

The dihydroxy amide obtained by deprotection of **5** was characterized. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.03 (b, 1H, N*H*), 4.58 (b, 1H, O*H*), 4.38–4.25 (dd, 1H, J=3.5, 7.9 Hz, C*H*OH), 3.95–3.84 (m, 2H, CH_2OH), 2.85 (d, 3H, J=5.4 Hz, NHCH_3), 2.23–2.0 (m, 1H, CH_2CHOH), 1.98–1.73 (m, 1H, CH_2CHOH); HRMS for $C_5H_{11}NO_3$: calcd: 133.0925; Found: 133.0921; $[\alpha]_D^{25}=-31.8$ (c=0.4, $CHCl_3$).

1.1.6. 2*S*,5*S*,6*R*-2-(2-Hydroxy-2-methyl-propyl)-4,5-dimethyl-6-phenyl-morpholin-3-one (6). To a solution of **3** (160 mg, 0.55 mmol) in benzene (3 mL) was added MeMgI in ether (5.5 mmol) at 10–15°C and the mixture was stirred for 2 h at ambient temperature. Saturated aqueous NH_4Cl was added and the mixture was extracted with ethyl acetate (3×15 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (4/6 petroleum ether/ethyl acetate) to furnish 115 mg (75%) of **6** as a white solid.

Mp: 104–105°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45–7.17 (m, 5H, Ar*H*), 5.04 (d, 1H, J=2.5 Hz, PhC*H*), 4.66–4.5 (dd, 1H, J=4.9, 7.8 Hz, C*H*CO), 4.25–4.05 (b, 1H, O*H*), 3.58–3.4 (dq, 1H, J=2.5, 6.3 Hz, C*H*CH_3), 3.04 (s, 3H, NCH_3), 2.39–2.15 (dd, 1H, J=4.9, 14.6 Hz, CH_2CHO), 2.14–1.9 (dd, 1H, J=7.8, 14.6 Hz, CH_2CHO), 1.33 (s, 6H, (CH_3)$_2$C), 1.0 (d, 3H, J=6.3 Hz, CH_3CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.6 (N*C*=O), 137.2 (ArC_{ipso}), 128.4 (Ar*C*), 127.8 (Ar*C*), 125.4 (Ar*C*), 77.2 (Ph*C*H), 76.4 (*C*HCO), 69.4 (*C*–OH), 58.7 (N*C*H), 45.13 (*C*H_2CH), 33.7 (N*C*H_3), 29.7 ((*C*H_3)$_2$C), 29.5 ((*C*H_3)$_2$), 13 (*C*H_3CH); IR (film): 3417, 2972, 2932, 1633, 1497, 1452, 1402, 1379, 1210, 1149, 1104 cm^{-1}; MS (EI, 70 eV): m/z 58 (100), 77 (10), 91 (12),

112 (48), 148 (8), 171 (12), 265 (25), 277 (M^+, 2); HRMS for $C_{16}H_{23}NO_3$: calcd: 277.1679; Found: 277.1680; $[\alpha]_D^{25}=-163.2$ (c=0.6, $CHCl_3$).

1.1.7. 2*S*-2-Hydroxy-4-ethoxyethyl-4-methyl-pentanoic acid *N*-methyl amide (7). To the solution of **6** (327 mg, 1.18 mmol) in chloroform (3 mL) was added ethyl vinyl ether (0.9 mL, 9.40 mmol) and trichloroacetic acid (a few crystals). The resulting mixture was stirred at ambient temperature for 18–20 h. Solid sodium bicarbonate was added and the chloroform was removed under reduced pressure. Attempted isolation of the product by conventional partitioning techniques results in decomposition to the starting material and the crude ethoxyethyl ether was therefore used further without any treatment or purification.

The crude ethoxyethyl ether was dissolved in THF (2 mL) and the solution was added to the mixture of anhydrous liquid ammonia (10 mL, distilled over sodium) and sodium (270 mg, 11.8 mmol) at −78°C. The reaction mixture was stirred at −78°C for 3 min, methanol was added and the mixture was warmed to ambient temperature to remove ammonia. The methanol was removed under reduced pressure and the residue was taken up in water. The mixture was saturated with solid NaCl and extracted with ethyl acetate (3×15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by rapid filtration through a short silica gel column (ethyl acetate) to furnish 151 mg (55%) of **7** which was immediately used further.

^{1}H NMR (200 MHz, $CDCl_3$): Major diastereomer: δ 7.04 (br s, 1H, N*H*), 5.04 (br s, 1H, O*H*), 5.0–4.8 (m, 1H, OC*H*O), 4.46–4.28 (br t, 1H, J=10.7 Hz, C*H*OH), 3.77–3.37 (m, 2H, OCH_2), 2.84 (d, 3H, J=4.9 Hz, NCH_3), 2.14–1.70 (m, 2H, CH_2CH), 1.5–1.05 (m, 12H, (CH_3)$_2$C, CH_3CH, CH_3CH$_2$). Minor diastereomer: δ 6.12 (br s, 1H, N*H*), 5.7 (br s, 1H, O*H*), 5.0–4.8 (m, 1H, OC*H*O), 4.46–4.28 (t, 1H, J=10.7 Hz, C*H*OH), 3.77–3.37 (m, 2H, OCH_2), 2.79 (d, 3H, J=4.8 Hz, NCH_3), 2.6–2.25 (m, 2H, CH_2CH), 1.5–1.05 (m, 12H, (CH_3)$_2$C, CH_3CH, CH_3CH$_2$); IR (neat): 3360, 2972, 2937, 1659, 1651, 1549, 1470, 1452, 1412, 1385, 1371, 1167, 1109, 1070, 966, 906 cm^{-1}.

The dihydroxy amide obtained by deprotection of **7** was characterized. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.0 (b, 1H, N*H*), 5.15 (b, 1H, O*H*), 4.46–4.28 (dd, 1H, J=2.9, 10.3 Hz, C*H*OH), 2.81 (d, 3H, J=4.9 Hz, CH_3NH), 2.1–1.93 (dd, 1H, J=2.9, 14.7 Hz, CH_2CH), 1.84–1.62 (dd, 1H, J=10.3, 14.7 Hz, CH_2CH), 1.34 (s, 3H, CH_3C), 1.28 (s, 3H, CH_3C); ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.9 (N*C*=O), 72.1 (*C*HOH), 70.5 ((CH$_3$)$_2$*C*), 44.8 (*C*H$_2$CH), 31.4 (NH*C*H$_3$), 27.6 (*C*H$_3$), 25.7 (*C*H$_3$); IR ($CHCl_3$): 3348, 2967, 2953, 2913, 1651, 1556, 1478, 1417, 1371, 1325, 1153 cm^{-1}; HRMS for $C_7H_{15}NO_3$: calcd: 161.1052; Found: 161.1051; $[\alpha]_D^{25}=-25.9$ (c=1.5, $CHCl_3$).

1.1.8. *S*-3-Hydroxy-dihydro-2-(3*H*)-furanone (8).[10] To a stirred solution of **5** (280 mg, 1.40 mmol) in THF (1.5 mL) at 0°C was added H_2SO_4 (3 M, 0.5 mL) dropwise over a period of 3 min. The resulting solution was warmed to ambient temperature stirred for 48 h. The mixture was then diluted with ether and neutralized with excess solid $NaHCO_3$. The organic layer was separated, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (4/6 petroleum ether/ethyl acetate followed by ethyl acetate) to furnish 98 mg (70%) of **8** as a clear, colorless gum.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.62–4.37 (m, 2H, CH_2O), 4.25 (ddd, 1H, J=6.0, 9.0, 10.0 Hz, C*H*OH), 3.58 (bs, 1H, O*H*), 2.72–2.52 (m, 1H, CH_2CH$_2$O), 2.43–2.16 (m, 1H, CH_2CH$_2$O); ^{13}C NMR (50 MHz, $CDCl_3$): δ 177.7 (O*C*=O), 67.44 (*C*HOH), 65.09 (*C*H$_2$O), 30.91 (*C*H$_2$CH$_2$O); IR ($CHCl_3$): 3441, 3020, 2920, 1776, 1626, 1454, 1375, 1323, 1217, 1178, 1126, 1087, 1018 cm^{-1}; $[\alpha]_D^{25}=-66$ (c=1, $CHCl_3$).

1.1.9. *S*-3-Hydroxy-5,5-dimethyl-dihydro-2-(3*H*)-furanone (9). This was prepared from **7** (72 mg, 0.31 mmol) in THF (1.5 mL) as described for **8** at ambient temperature for 12–15 h. Purification by flash chromatography on silica gel (7/3 petroleum ether/ethyl acetate) furnished 33 mg (82%) of **9** as a clear, colorless gum that solidifies below 5°C.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.78–4.58 (dd, 1H, J=8.3, 9.7 Hz, C*H*OH), 3.69 (b, 1H, O*H*), 2.63–2.45 (dd, 1H, J=8.3, 12.7 Hz, CH_2CH), 2.18–1.94 (dd, 1H, J=9.7, 12.7 Hz, CH_2CH), 1.52 (s, 3H, CH_3), 1.42 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 177.1 (*C*=O), 82.3 (*C*(CH$_3$)$_2$), 68.8 (*C*HOH), 42.9 (*C*H$_2$), 29.1 (*C*H$_3$), 27.7 (*C*H$_3$); IR ($CHCl_3$): 3431, 2980, 2937, 1770, 1456, 1391, 1377, 1306, 1197, 1154, 1105, 1033, 997 cm^{-1}; HRMS for $C_6H_{10}O_3$: calcd: 130.0630; Found: 130.0635; $[\alpha]_D^{25}=-22.2$ (c=0.7, CH_3OH).

1.2. General procedure for the preparation of hemiacetals 10 from 1

To a suspension of **1** (1 equiv.) in anhydrous ether at −20°C was added the Grignard reagent (5 equiv.) and the mixture was stirred at −20°C for 1 h. Saturated aqueous NH_4Cl was added and the reaction mixture was warmed up to ambient temperature. The precipitated solids were dissolved in water and the solution was extracted in ether. The combined ether extracts were dried (Na_2SO_4) and concentrated to give crude **10** which can be used further without purification. An analytical sample is obtained by column chromatography.

1.2.1. 2*S*,5*S*,6*R*-2,4,5-Trimethyl-2-hydroxy-6-phenyl morpholin-3-one(10a). The reaction of **1** (219 mg, 1 mmol) with MeMgI (5 mL of ~1 M solution in ether, 5 mmol) in anhydrous ether (3 mL) gave after purification by column chromatography (petroleum ether/ethyl acetate, 3/7) 228 mg (97%) of **10a** as a solid.

Mp: 79–80°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.36–7.23 (m, 5H, Ar*H*), 5.47 (d, 1H, J=2.9 Hz, PhC*H*), 4.58 (br s, 1H, O*H*), 3.43 (dq, 1H, J=2.9, 6.5 Hz, C*H*CH$_3$), 2.99 (s, 3H, NCH_3), 1.71 (s, 3H, CH_3COH), 0.93 (d, 3H, J=6.5 Hz, CHCH_3). Visible peak of minor diastereomer: δ 5.16 (d, J=2.9 Hz, PhC*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.7 (C=O), 137.4 (ArC_{ipso}), 128.1 (Ar*C*), 127.4 (Ar*C*), 125.6 (Ar*C*), 95.9 (Ar*C*), 71.2 (PH*C*H), 59.2 (N*C*H), 33.5 (N*C*H$_3$), 26.3 (*C*H$_3$O), 11.9 (*C*H$_3$CH); IR ($CHCl_3$): 3340, 2940,

1635, 1490, 1450, 1380, 1220, 1130, 1010, 940, 890, 750 cm^{-1}; MS (EI, 70 eV): *m/z* 58 (100), 77 (12), 91 (8), 100 (28), 105 (71), 118 (32), 146 (2), 235 (M^+, <1); Analysis for $C_{13}H_{17}NO_3$: calcd: C, 66.36; H, 7.28; N, 5.05; Found: C, 66.38; H, 7.43, N, 5.97; $[\alpha]_D^{25}=-107.4$ (*c*=1.1, $CHCl_3$).

1.2.2. 2*S*,5*S*,6*R*-2-Ethyl-4,5-dimethyl-2-hydroxy-6-phenyl morpholin-3-one (10b). The reaction of **1** (110 mg, 0.5 mmol) with EtMgI (2.5 mL of ~1 M solution in ether, 2.5 mmol) in anhydrous ether (2 mL) gave after purification by column chromatography (petroleum ether/ethyl acetate, 2/3) 114 mg (92%) of **10b** as a solid.

Mp: 88–89°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45–7.20 (m, 5H, Ar*H*), 5.52 (d, 1H, *J*=3.0 Hz, PhC*H*), 3.70 (br s, 1H, O*H*), 3.46 (dq, 1H, *J*=6.5, 3.0 Hz, CH_3CH), 3.03 (s, 3H, NCH_3), 2.26–2.08 (m, 1H, CH_3CH_2), 2.02–1.84 (m, 1H, CH_3CH_2), 1.06 (t, 3H, *J*=7.0 Hz, CH_3CH_2), 0.97 (d, 3H, *J*=6.5 Hz, $CHCH_3$). Visible peaks of minor diastereomer: 5.17 (d, *J*=2.9 Hz, PhC*H*), 4.05 (br s, 1H, O*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.2 (C=O), 137.5 (ArC_{ipso}), 127.9 (Ar*C*), 127.1 (Ar*C*), 125.3 (Ar*C*), 97.9 (*C*OH), 70.4 (Ph*C*H), 58.8 (CH_3CH), 33.2 (NCH_3), 32.0 (CH_2), 12.2 ($CHCH_3$), 7.9 (CH_2CH_3); IR ($CHCl_3$): 3340, 3120, 1640, 1450, 1452, 1220, 1214, 1140, 1021, 749 cm^{-1}; MS (EI, 70 eV): *m/z* 57 (43), 77 (15), 86 (35), 91 (15), 105 (8), 118 (100), 143 (7), 174 (2), 232 (2); Analysis for $C_{14}H_{19}NO_3$: calcd: C, 67.45; H, 7.68; N, 5.62; Found: C, 67.21; H, 7.75, N, 5.54; $[\alpha]_D^{25}=-110.0$ (*c*=2.3, $CHCl_3$).

1.2.3. 2*S*,5*S*,6*R*-2-*tert*-Butyl-2-hydroxy-4,5-dimethyl-6-phenyl morpholin-3-one (10c). The reaction of **1** (226 mg, 1.04 mmol) with *t*-BuMgCl (5.2 mL of ~1 M solution in ether, 5 mmol) in anhydrous ether (3 mL) gave after purification by column chromatography (petroleum ether/ethyl acetate, 1/1) 257 mg (90%) of **10c** as a solid.

Mp: 85–86°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.42–7.24 (m, 5H, Ar*H*), 5.41 (d, 1H, *J*=2.9 Hz, PhC*H*), 3.54–3.41 (m, 2H, O*H*, CH_3CH), 3.00 (s, 3H, NCH_3), 1.18 (s, 9H, $C(CH_3)_3$), 0.99 (d, 3H, *J*=6.4 Hz, CH_3CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.9 (*C*=O), 137.7 (ArC_{ipso}), 128.1 (Ar*C*), 127.4 (Ar*C*), 125.5 (Ar*C*), 100.3 (*C*OH), 71.0 (Ph*C*H), 59.3 (*C*HCH$_3$), 39.7 ($C_{quat}(CH_3)_3$), 33.5 (NCH_3), 25.2 ($C(CH_3)_3$), 12.2 (CH_3); IR ($CHCl_3$): 3382, 2979, 2960, 2933, 1643, 1379, 1078, 757 cm^{-1}; MS (EI, 70 eV): *m/z* 57 (20), 71 (7), 91 (14), 105 (7), 118 (100), 262 (22); Analysis for $C_{16}H_{23}NO_3$: calcd: C, 69.29; H, 8.36; N, 5.05; Found: C, 69.42; H, 8.12, N, 5.28; $[\alpha]_D^{25}=-139.0$ (*c*=1.6, $CHCl_3$).

1.3. General procedure for the one-pot alkylation/allylation of dione 1

To a suspension of the dione **1** (1 equiv.) in dichloro methane at −78°C was added the Grignard reagent (5 8 equiv.) and the mixture was stirred for 1 h at −78°C. $TiCl_4$ (5 equiv.) was added followed by allyltrimethylsilane (5–8 equiv.) and the mixture was stirred at −60°C or allowed to warm up to ambient temperature. Saturated aq. NH_4Cl was added and the precipitated solids were dissolved in water, the solution was extracted with dichloromethane and the combined extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography on silica gel.

1.3.1. 2*R*,5*S*,6*R*-2,4,5-Trimethyl-2-(1-propenyl)-6-phenyl morpholin-3-one (11a). The reaction of **1** (219 mg, 1 mmol) in anhydrous dichloromethane (2 mL) and MeMgI (1.3 mL of ~1 M solution in ether, 1.3 mmol) at −78°C for 1 h followed by $TiCl_4$ (0.60 mL, 5.35 mmol) and allyltrimethysilane (1.7 mL, 10.7 mmol), gradual warming to −20°C for 8 h gave after purification by flash chromatography on silica gel (7/3 petroleum ether/ethyl acetate) 145 mg (56%) of **11a** as colorless gum.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45–7.20 (m, 5H, Ar*H*), 5.98–5.75 (m, 1H, CH_2=C*H*), 5.20 (d, 1H, *J*=2.7 Hz, PhC*H*), 5.18–5.03 (m, 2H, CH_2=CH), 3.5 (dq, 1H, *J*=6.5, 2.7 Hz, CH_3CH), 3.04 (s, 3H, NCH_3), 2.83 (dd, 1H, *J*=14.4, 5.9 Hz, $CHCH_2$), 2.53 (dd, 1H, *J*=14.4, 8.7 Hz, $CHCH_2$), 1.50 (s, 3H, CCH_3), 0.98 (d, 3H, *J*=6.5 Hz, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4 (*C*=O), 137.7 (ArC_{ipso}), 132.6 ((Ar*C*), 127.8 (Ar*C*), 127.0 (Ar*C*), 125.1 (*C*H=CH_2), 117.6 (CH=*C*H$_2$), 78.8 (CCH_3), 71.7 (Ph*C*H), 58.7 (CH_3CH), 40.2 (CH_2), 33.2 (NCH_3), 24.8 (CCH_3), 12.1 ($CHCH_3$); IR ($CHCl_3$): 3000, 1630, 1430, 1210, 750 cm^{-1}; MS (EI, 70 eV) *m/z* 58 (53), 67 (22), 77 (19), 91 (27), 105 (18), 117 (40), 148 (100), 174 (6), 190 (27), 218 (69), 259 (8, M^+, 3); HRMS (FAB+) for $C_{16}H_{22}NO_2$ calcd: 260.1651; Found: 260.1645; $[\alpha]_D^{25}=-67.1$ (*c*=2.1, $CHCl_3$).

1.3.2. 2*R*,5*S*,6*R*-2-Ethyl-2-(1-propenyl)-4,5-dimethyl-6-phenylmorpholin-3-one (11b). The reaction of **1** (219 mg, 1 mmol) in anhydrous dichloromethane (2 mL) and EtMgI (1.3 mL of ~1 M solution in ether, 1.3 mmol) at −78°C for 1 h followed by $TiCl_4$ (0.55 mL, 5 mmol) and allyltrimethysilane (1.27 mL, 8 mmol), gradual warming to −20°C and stirring for 6 h, gave after purification by flash chromatography on silica gel (7/3 petroleum ether/ethyl-acetate) 170 mg (62%) of **11b** as colorless gum.

^{1}H NMR (200 MHz, $CDCl_3$): δ ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45–7.20 (m, 5H, Ar*H*), 5.95–5.74 (m, 1H, C*H*=CH_2), 5.25 (d, 1H, *J*=3.0 Hz, PhC*H*), 5.15–5.02 (m, 2H, CH_2=CH), 3.54 (dq, 1H, *J*=6.5, 3.0 Hz, CH_3CH), 3.05 (s, 3H, NCH_3), 2.85 (tdd, 1H, *J*=16.1, 5.8, 1.3 Hz, $CHCH_2$), 2.55 (dd, 1H, *J*=14.6, 8.5 Hz, $CHCH_2$), 2.08–1.75 (m, 2H, CH_3CH_2), 1.02 (t, 3H, *J*=6.6 Hz, CH_3CH_2), 0.98 (d, 3H, *J*=7.8 Hz, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2 (*C*=O), 138.1 (ArC_{ipso}), 133.0 (Ar*C*), 128.1 (Ar*C*), 127.3 (Ar*C*), 125.5 (*C*H=CH_2), 117.9 (CH=*C*H$_2$), 82.3 (CCH_3), 71.4 (Ph*C*H), 59.1 (CH_3CH), 40.1 (CH_2=$CHCH_2$), 33.5 (NCH_3), 30.9 (CH_3CH_2), 12.9 (CH_3), 8.7 (CH_3); IR ($CHCl_3$): 3010, 1625, 1440, 1215, 1140, 1030, 750 cm^{-1}; MS (EI, 70 eV): *m/z* 58 (100), 67 (23), 77 (21), 91 (31), 105 (12), 117 (39), 148 (90), 204 (35), 232 (78), 245 (1), 273 (6, M^+); HRMS (FAB+) for $C_{17}H_{24}NO_2$ $[M{\cdot}H]^+$: calcd: 274.1808; Found: 274.1812.

1.3.3. 2*S*,5*S*,6*R*-2-(*tert*-Butyl)-2-(1-propenyl) 4,5-dimethyl-6-phenyl morpholin-3-one (11c). The reaction of **1** (110 mg, 0.5 mmol) in anhydrous dichloromethane (1 mL) and *t*-BuMgCl (1.5 mL of ~1 M solution in THF, 1.5 mmol) at −78°C for 1 h followed by $TiCl_4$ (0.55 mL, 5 mmol) and allyltrimethysilane (0.8 mL, 5 mmol), gradual

warming to ambient temperature and stirring overnight, gave after purification by flash chromatography on silica gel (5/1 petroleum ether/ethylacetate) 76 mg (50%) of **11c**.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.43–7.23 (m, 5H, ArH), 6.09–5.81 (m, 1H, CH_2=C*H*), 5.4 (d, 1H, *J*=3.4 Hz, PhC*H*), 5.16–4.88 (m, 2H, CH_2=CH), 3.5 (dq, 1H, *J*=3.4, 6.8 Hz, CH_3CH), 3.01 (s, 3H, NCH_3), 2.95–2.90 (m, 1H, $CHCH_2$), 2.71 (dd, 1H, *J*=8.8, 14.6 Hz, $CHCH_2$), 1.18 (s, 9H, $C(CH_3)_3$), 0.98 (d, 3H, *J*=6.8 Hz, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2 (*C*=O), 138.6 (ArC_{ipso}), 135.5 (*C*H=CH_2), 128.2 (Ar*C*), 127.3 (Ar*C*), 125.6 (Ar*C*), 116.7 (CH=CH_2), 85.5 (O*Cquat*), 72.0 (Ph*C*H), 59.2 (CH_3CH), 39.7 ($C(CH_3)_3$), 38.1 (CH_2CH=CH_2), 33.7 (NCH_3), 26.9 ($C(CH_3)_3$), 12.8 ($CHCH_3$); IR ($CHCl_3$): 3269, 2959, 1643, 1452, 1392, 1379, 1363, 1284, 1217, 1145, 1120, 1097, 1033, 914 cm^{-1}; MS (EI, 70 eV): *m/z* 57 (100), 77 (87), 91 (12), 105 (6), 118 (24), 148 (9), 260 (17), 301 (M^+, 3); HRMS for $C_{19}H_{27}NO_2$: calcd: 301.2042; Found: 301.2036; $[\alpha]_D^{25}$=−110.2 (*c*=3.4, $CHCl_3$).

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References

1. (a) Gathergood, N.; Zhuang, W.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 12517. (b) Huerta, F. F.; Santosh Lakshmi, Y. R.; Baeckvall, J.-E. *Org. Lett.* **2000**, *2*, 1037. (c) Quian, C.; Wang, L. *Tetrahedron: Asymmetry* **2000**, *11*, 2347. (d) Chen, C.-J.; Chu, Y.-Y.; Liao, Y.-Y.; Tsai, Z.-H.; Wang, C.-C.; Chen, K. *Tetrahedron Lett.* **1999**, *40*, 1141.
2. (a) Peterson, M.; Kalbermatten, G. PCT Int. Appl. WO 2001018231 A2, 2001. (b) Ueki, T.; Ichinari, D.; Yoshihara, K.; Morimoto, Y.; Kinoshita, T. *Tetrahedron Lett.* **1998**, *39*, 667. (c) Eliel, E. L.; Bai, X.; Ohwa, M. *J. Chin. Chem. Soc.* **2000**, *47*, 63. (d) Blandin, V.; Carpentier, J.-F.; Mortreaux, A. *Eur. J. Org. Chem.* **1999**, 1787.
3. (a) Sefkow, M. *J. Org. Chem.* **2001**, *66*, 2343. (b) Ichinari, D.; Ueki, T.; Yoshihara, K.; Kinoshita, T. *Chem. Commun.* **1997**, 1743.
4. Dione **1** has been prepared earlier as a proof for the reactivity of an activated oxalic acid derivative, see: Rudchenko, V. F.; Shtamburg, V. G.; Pleshkova, A. P.; Kostyanovskii, R. G. *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)* **1981**, *30*, 825. For a preparation of racemic **1** see: Drefahl, G.; Hartmann, M.; Skurk, A. *Chem. Ber.* **1963**, *96*, 1011. Synthetic applications of **1** were not described.
5. The stereochemical assignment is based on the reported trend in chemical shift for the olefinic methine protons in (*E*) and (*Z*) benzylidenecamphor derivatives, see: Kossanyi, J.; Furth, B.; Morizur, J. P. *Tetrahedron* **1970**, *26*, 395.
6. The stereochemistry at the hemiacetal centre has been confirmed in an earlier study by X-ray crystallography, see: Pansare, S. V.; Ravi, R. G.; Jain, R. P. *J. Org. Chem.* **1998**, *63*, 4120.
7. For the application of other aminoalcohol based morpholinones in the asymmetric synthesis of amino acids, see: (a) Cox, G. G.; Harwood, L. M. *Tetrahedron: Asymmetry* **1994**, *9*, 1669. (b) Sinclair, P. J.; Zhai, D.; Reibenspies, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103.
8. Kano, S.; Tanaka, Y.; Sugino, E.; Hibino, S. *Synthesis* **1980**, *9*, 695.
9. Takigawa, T.; Mori, K.; Matsuo, T. *Tetrahedron* **1979**, *35*, 933.
10. Ikemoto, K.; Sakashita, Y.; Kageyama, F.; Terada, Y.; Nakaoka, K.; Ichimura, K. Mori. *Chem. Lett.* **1992**, 567.
11. (a) Shiuey, S.-J.; Partridge, J. J.; Uskokovic, M. R. *J. Org. Chem.* **1988**, *53*, 1040. (b) The enantiomeric excess of the lactones was determined by GC analysis with a HP Chiral (20% permethylated β-cyclodextrin) column (30 m×0.32 mm×0.25 μm).
12. Pansare, S. V.; Jain, R. P.; Ravi, R. G. *Tetrahedron: Asymmetry* **1999**, *10*, 3103.