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An Alternative Stereoselective Synthesis of Protected Trans-5-Alkyl-4-Hydroxy-2-Pyrrolidinones

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AN ALTERNATIVE STEREOSELECTIVE SYNTHESIS OF PROTECTED *TRANS*-5-ALKYL-4-HYDROXY-2-PYRROLIDINONES

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Abstract: A flexible approach to protected *trans*-5-alkyl-4-hydroxy-2-pyrrolidinones was described. The key step involved the α-amidoalkylation of benzenesulfone derived from (S)-malic acid, with organozinc reagents generated *in situ* from Grignard reagents and anhydrous $ZnCl_2 \cdot OEt_2$.

Trans-5-alkyl-4-hydroxy-2-pyrrolidinones are versatile intermediates particularly for the synthesis of bioactive pyrrolidine derivatives[1-3] and substituted *anti*-β-hydroxy γ-amino acids.[4] Of particular interests reside on the presence of such *anti*-β-hydroxy γ-amino acid residues in many antitumor or cytotoxic natural products of different origin. For example, (3S, 4R, 5S)-isostatine **1** and (2S, 3S, 4R)-4-amino-3-hydroxy-2-methylpentanoic acid (AHMPA) **2** are components of antiviral cytotoxic didemnins A~C[5] and antitumor antibiotic bleomycins[6] / phleomycins[6a] respectively; (3R, 4S, 5S)-*N, O*-dimethylisostatine **3** is presence in both dolastatin 10 [7] and simplostatin 1,[8] (3R, 4S)-4-amino-3-hydroxy-2-phenylpentanoic acid (AHPPA) **4** is found in hapalosin, a cyclodepsipeptide possessing MDR-reversing activities.[9] It has been shown that such unusual amino acids are essential to the

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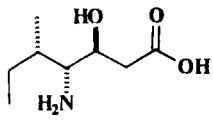
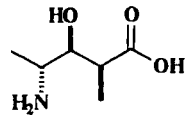
bioactivity of the natural products.[6c] As a result, several methods have been reported for the asymmetric synthesis[1-3,10] of 5-*trans*-alkyl-4-hydroxy-2-pyrrolidinones including a reductive-alkylation approach reported from this laboratory[3]. We now wish to communicate an alternative method to this class of compound based on an asymmetric α-amidoalkylation.



1.(3S,4R,5S)-isostatine



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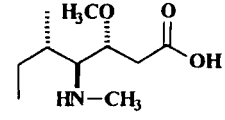
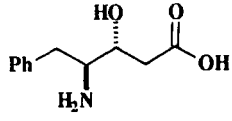
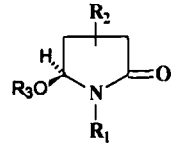


3.(3R,4S,5S)-*N*,*O*-dimethylisostatine



4. (3R,4S)-AHPPA



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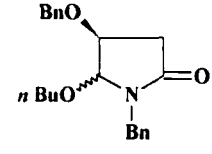

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The α-amidoalkylation have been shown to be a powerful method for the synthesis of nitrogen containing compounds[1,2,11], however, attempt α-amidoalkylation of tertiary cyclic amide (e.g. **5**) with general nucleophiles such as Grignard reagents or organocopper reagents,[3a,12] were generally unsuccessful. We were interested in the sulfone-based α-amidoalkylation[13,14] initially developed by Ley[13]. To this end, the requisite (S)-*N*,*O*-dibenzylmalimide **7** was prepared according to a procedure recently reported from this laboratory[3]. Regio and stereoselective reduction of **7** gave a mixture of two diastereomeric hydroxylactams **8** which after recrystallization gave pure *cis*-isomer **8** in good yield (86.1%). In the presence of anhydrous calcium chloride, the reaction of **8** with benzenesulfinic acid in dichloromethane gave a diastereomeric mixture of sulfone *cis*,*trans*-**9** (yield, 75.3%). We were delight to found that the separation of the two diastereomers is not necessary, since *cis*-isomer epimerized slowly but spontaneously to pure

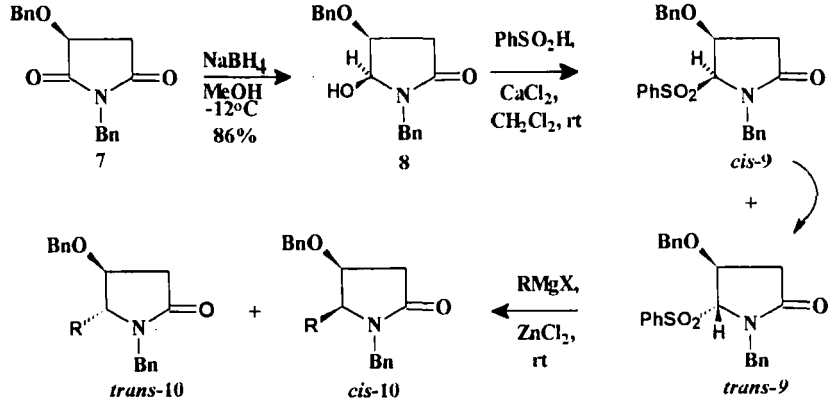
crystalline *trans*-**9** upon standing the *cis/trans* isomeric mixture at low temperature. The key α-amidoalkylation of sulfone *trans*-**9** was achieved by treating **9** with zinc species *in situ* generated from methyl magnesium iodide and $ZnCl_2$ (1.0M solution in Et_2O). The reaction proceed smoothly at room temperature yielding the desired methylated lactams *trans*-(4S, 5R)-**10a** and *cis*-(4S, 5S)-**10a** in a ratio of 3:1 (combined yield, 89%, **Table 1**, Entry 1).

The *cis trans* stereochemistry of compounds **10a** was assigned according to the observed vicinal coupling constants ($J_{4,5}$=5.9Hz for *cis*-**10a** and $J_{4,5}$=1.0Hz for *trans*-**10a**) as reported[3] previously. Other Grignard reagents reacted similarly and gave the same order of diasteroselectivity as showed in the **Table**. It is important to note that the α-amidoalkylation reaction is highly depended on the zinc salts used. The use of purchased anhydrous $ZnBr_2$ as promoter led unexpectedly to a HPLC unseparable diastereomeric mixture of ether **6** (*cis/trans*=61:39) in good yield, while when using commercially available anhydrous $ZnCl_2$ in CH_2Cl_2, a mixture of **6** and **10** were obtained. It is also worth mentioning that compounds *trans*-**10a** and *trans*-**10e** prepared by present method showed higher optical rotation values than those obtained by the reductive alkylation method[3a]. This might indicate that no notable racemization occurred in present reaction sequence.

In summary, an alternative stereoselective approach to *trans*-5-alkyl-4-hydroxy-2-pyrrolidinones was worked out. The use of Grignard reagents as alkylating agents made this approach both versatile and flexible.

Experimental

The thermometer was uncorrected. Optical rotations were measured on a Perkin-Elmer 341MC polarimeter. IR spectra were obtained on a Nicholet Avatar 360 FT-IR spectrometer. ^{1}H-NMR spectra were taken at a Varian Unity +500 spectrometer. Mass spectra were recorded on a Finnigan MAT-GCQ (direct injection, EI).



Scheme 1

Table The $ZnCl_2 \cdot OEt_2$ promoted α-amidoalkylation of benzenesulfone *trans*-9

Entry	RMgX (equiv.)	$ZnCl_2 \cdot OEt_2$ (equiv.)	*trans*/*cis* ratio of Products **10**	Yields (%)
1	MeMgBr (1.8)	1.1	75:25[a] **(10a)**	89.0
2	MeMgI (1.5)	1.1	64:36[a] **(10a)**	50.0
3	MeMgI (2.0)	1.2	50:50[a] **(10a)**	76.2
4	EtMgBr (2.0)	1.2	83:17[b] **(10b)**	81.6
5	*n*-PrMgBr (3.0)	2.0	67:33[b] **(10c)**	82.6
6	*n*-C_7H_{15}MgBr (2.0)	1.2	71:29[a] **(10d)**	71.3
7	$PhCH_2MgCl$ (2.3)	1.3	83:17[a] **(10e)**	62.0

a. ratio determined by chromatographic separation; *b*. ratio determined by ^{1}HNMR.

Column chromatography was performed on silica gel H (Qingdao, 400 Mesh). Dichloromethane was distilled over calcium hydride. The anhydrous 1M solution of $ZnCl_2$ in Et_2O was purchased from Aldrich Chemical Co., Inc.

(-)-(4S, 5R)-1-Benzyl-4-benzyloxy-5-hydroxy-2-pyrrolidinone 8. To a solution of **7** (1.037g, 3.52mmol) in 110mL of MeOH was added at -15°C, $NaBH_4$ (1.448g,

11.8mmol) in one portion. The resulting suspension was stirred at the same temperature for 25min. 25mL of chilled saturated aqueous solution of $NaHCO_3$ and 10mL of chilled brine were added. The resulting mixture was extracted with CH_2Cl_2 (4 × 60mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo* to give **8** (1.087g) as a white solid. Recrystallization gave **8** as colorless needles (899mg, yield 86.1%). m.p. 130~130.5°C. $[\alpha]_D^{20}$+20.6°(*c* 1.2, $CHCl_3$). IR(KBr)ν_{max}: 3115, 1640, 1450, 1400, 1340, 1330, 1260, 1140, 1095, 1060, 1020, 900, 725cm^{-1}. ^{1}H-NMR(500MHz)δ : 2.58(d, J=6.0Hz, 2H, H-3), 3.62(br, 1H, OH), 4.08(dt, J=5.5, 6.0Hz, 1H, H-4), 4.16(d, J=14.6Hz, 1H, PhCHN), 4.57(d, J=11.8Hz, 1H, PhCHO), 4.60(d, J=11.8Hz, 1H, PhCHO), 4.91(d, J=14.6Hz, 1H, PhCHN), 4.98(br, 1H, H-5), 7.25~7.40(m, 10H, $2C_6H_5$)ppm. MS EI (m/z): 297(M^+, 3.3), 280(M^+-OH, 0.83), 234(6.7), 206(4.2), 73(6.3), 164(6.7), 136(11.5), 106(5.8), 91(100), 65(10.8). HRMS for $C_{18}H_{19}NO_3$: calcd : 297.1365; Found: 297.1367.

(-)-(4S, 5R)-1-Benzyl-4-benzyloxy-5-sulfonyl-2-pyrrolidinone (9). A mixture of 1-benzyl-4-benzyloxy-5-hydroxy-2-pyrrolidinone **8** (999mg, 3.36mmol), freshly prepared benzenesulfinic acid (2.563g, 18.0mmol), and anhydrous calcium chloride (2.138g, 19.3mmol) in dry dichloromethane (100mL) was stirred at room temperature for 2 hours under nitrogen. The reaction mixture was quenched with water and extracted with dichloromethane. The combined extracts were washed with saturated aqueous $NaHCO_3$, dried and concentrated in *vacuo*. Purification by chromatography (eluent: ethyl acetate: petroleum ether(60-90°C), 1:3.5~1:3~1:2 gave a diastereomeric mixture of **9** as a pale yellow oil (1.066g, yield 75.3%), which, upon standing at -20°C for several weeks epimerized to give crystalline *trans*-**9** as a single epimer. m.p. 86~87°C. $[\alpha]_D^{20}$ +14.3°(*c* 1.2, $CHCl_3$). IR(film)ν_{max}: 3025, 2900, 1700, 1580, 1492, 1444, 1330, 1300, 1200, 1135, 1070, 840, 745, 690cm^{-1}. ^{1}H-NMR(500MHz)δ: 2.16(dd, J=6.2, 17.8Hz, 1H, H-3), 2.33(d, J=17.8Hz, 1H, H-3), 3.97(d, J=16.9Hz, 1H, PhCHN), 4.30(d, J=11.7, 1H,

$PhCH_2O$), 4.33(d, J=11.7Hz, 1H, $PhCH_2O$), 4.36(d, J=6.2Hz, 1H, H-4), 4.52(s, 1H, H-5), 5.29(d, J=16.9Hz, 1H, PhCHN), 6.94~7.14, 7.24~7.32, 7.60~7.84(6m, 15H, ArH)ppm. MS EI (m/z): 422(MH^+, 0.77), 370(1.51), 280 (31.9), 188(11.2), 174(8.6), 91(100), 77(82), 65(86), 55(10.6). Anal. calcd for $C_{24}H_{23}NOS$: C 68.36; H 5.51; N 3.32; Found: C 68.21; N 5.36; H 3.12.

Typical Procedure for α-amidoalkylation of sulfone *trans*-9 with Grignard Reagents. To a solution of anhydrous zinc chloride (1.0 mol/L in diethyl ether, 0.43ml, 0.43mmol) in dichloromethane (0.5mL) was added dropwise an Et_2O solution of the Grignard reagent (0.72mmol). The mixture was stirred at room temperature under nitrogen for 30 minutes. A solution of the sulfone *trans*-9 (0.36mmol) in dry dichloromethane (1.5 mL) was added and stirring continued at r.t. for 14-16hs. The reaction was quenched with saturated aqueous NH_4Cl and extracted with dichloromethane (3 × 30mL), the combined extracts were dried and concentrated in vacuo. Products were purified by chromatography using ethyl acetate: petroleum ether (1:3-1:1).

(-)-(4S, 5R)-1-Benzyl-4-benzyloxy-5-methyl-2-pyrrolidinone (10a). Yield, 89.0% (for *trans*/*cis* ratio, see **Table**). ***trans*-10a** (major isomer). Colorless oil. $[\alpha]_D^{22}$ +80.5°(*c* 1.1, $CHCl_3$) [Lit.[3a] $[\alpha]_D^{22}$ +77.6° (*c* 0.35, $CHCl_3$)]. Identical with the product obtained by reductive alkylation method[3a] by I.R., ^{1}H-NMR, mass spectroscopy and HRMS. ***cis*-10a** (minor): colorless oil. $[\alpha]_D^{20}$-28.1°(*c* 0.5, $CHCl_3$). IR(film)ν_{max}: 3502, 2976, 2360, 1690, 1604, 1496, 1453, 1418, 1354, 1263, 1065, 735, 698cm^{-1}. ^{1}H-NMR(500Hz)δ: 1.20(d, J=6.5Hz, 3H, CH_3), 2.59(dd, J=6.5, 17.3Hz, 1H, H-3), 2.61(dd, J=6.5, 17.3Hz, 1H, H-3), 3.65(dq, J=6.5, 6.5Hz, 1H, H-5), 3.96(d, J=15.08Hz, 1H, PhCHN), 4.11(dt, J=6.5, 6.5Hz, 1H, H-4), 4.45(d, J=11.83Hz, 1H, PhCHO), 4.54(d, J=11.83Hz, 1H, PhCHO), 5.02(d, J=15.08Hz, 1H, PhCHN), 7.10~7.40(m, 10H, $2C_6H_5$)ppm. MS EI (m/z): 295(M^+, 40), 280(2), 189(18), 132(25), 91(100). HRFABMS calcd for $[C_{19}H_{21}NO_2+H]^+$ 296.1645; Found: 296.1641.

(-)-(4S, 5R)-1-Benzyl-4-benzyloxy-5-ethyl-2-pyrrolidinone (10b). Yield, 81.6% (*trans*:*cis* = 83:17, unseparable by column chromatography). IR(film) ν_{max}: 3028, 2962, 2922, 2876, 1684, 1496, 1446, 1267, 1091, 1065, 744, 700, 612cm^{-1}. ^{1}H-NMR (500MHz)δ： :0.84(t, J=7.5Hz, 3H, CH_3, M), 1.88(t, J=7.4Hz, 3H, CH_3, m), 1.38(m, 1H, CH, M), 1.66(m, 2H, CH, M+m), 1.78(m, 1H, CH, m), 2.56(dd, J=2.2, 17.5Hz, 1H, H-3, M), 2.58(dd, J=6.5, 16.9Hz, 1H, H-3, m), 2.63(dd, J=4.6, 16.9Hz, 1H, H-3, m), 2.74(ddd, J=0.8, 6.6, 17.5Hz, 1H, H-3, M), 3.44(ddd, J=1.6, 3.1, 8.8Hz, 1H, H-5, M), 3.48(ddd, J=3.5, 6.0, 9.6Hz, 1H, H-5, m), 3.89(ddd, J=1.6, 2.2, 6.6Hz, 1H, H-4, M), 3.95(d, J=15.1Hz, 1H, PhCHN, M), 3.98(d, J=13.5Hz, 1H, PhCHN, m), 4.14(m, 1H, H-4, m), 4.41(d, J=11.7Hz, 1H, PhCHO, M), 4.42(d, J=11.6Hz, 1H, PhCHO, m), 4.44(d, J=11.7Hz, 1H, PhCHO, M), 4.59(d, J=11.6Hz, 1H, PhCHO, m), 5.01(d, J=13.5Hz, 1H, PhCHN, m), 5.03(d, J=15.1Hz, 1H, PhCHN, M), 7.20~7.40(m, 10H, $2C_6H_5$)ppm. MS EI (m/z)： 309(M^+, 76), 280(32), 218(4), 203(23), 174(36), 92(100). HRFABMS calcd for $[C_{20}H_{23}NO_2+H]^+$ 310.1801; Found: 310.1804.

(-)-(4S, 5R)-1-Benzyl-4-benzyloxy-5-propyl-2-pyrrolidinone (10c). Yield, 82.6% (*trans* / *cis* = 67:33, unseparable by column chromatography). IR(film)ν_{max}: 3063, 3030, 2958, 2929, 2871, 1685, 1496, 1454, 1354, 1309, 1260, 1070, 1028, 737, 700, 616cm^{-1} ^{1}H-NMR(500Hz)δ: 0.87(t, J=7.3Hz, 3H, CH_3, M+m), 1.14~1.36, 1.59, 1.82(3m, 4H, $2CH_2$), 2.55(dd,J=1.9, 17.6Hz, 1H, H-3, M), 2.57(dd, J=6.1, 16.9Hz, 1H, H-3, m), 2.62(dd, J=9.2, 16.9Hz, 1H, H-3, m), 2.74(dd, J=6.3, 17.6Hz, 1H, H-3, M), 3.47(m, 1H, H-5, m), 3.49(m, 1H, H-5, M), 3.52(ddd, J=1.9, 6.3, 8.9Hz, 1H, H-4, M), 3.96(d, J=15.3Hz, PhCHN, M), 3.98(d, J=15.2Hz, 1H, PhCHN, m), 4.10(ddd, J=4.5, 6.1, 9.2Hz, 1H, H-4m), 4.40(d, J=11.8Hz, 1H, PhCHO, m), 4.41(d, J=11.8Hz, 1H, PhCHO, M), 4.46(d, J=11.8Hz, 1H, PhCHO, M), 4.58(d, J=11.8Hz, 1H, PhCHO, m), 5.02(d, J=15.2Hz, 1H, PhCHN, m), 5.06(d, J=15.3Hz, PhCHN, M), 7.20~7.40(m, 10H, $2C_6H_5$)ppm. MS EI (m/z)： 323(M^+, 33), 280(15), 217(42), 174(41), 92(100). HRFABMS calcd for

$[C_{21}H_{25}NO_2+H]^+$ 324.1958; Found: 324.1962.

(-)-(4S, 5R)-1-Benzyl-4-benzyloxy-5-heptyl-2-pyrrolidinone (10d). Yield, 71.3%(*trans* / *cis* = 71:29). ***trans*-10d** (major isomer): Colorless oil. $[\alpha]_D^{20}$ +30.6° (*c* 0.75, $CHCl_3$). IR(film) ν_{max}: 3030, 2927, 2855, 1693, 1496, 1453, 1355, 1260, 1090, 1071, 737, 699cm^{-1}. ^{1}H-NMR (500MHz) δ: 0.88(t, J=6.8Hz, 3H, CH_3), 1.22(m, 10H, $5CH_2$), 1.60(m, 1H, CH), 1.90 (m, 1H, CH), 2.55(dd, J=1.5, 17.5Hz, 1H, H-3), 2.75(dd, J=6.1, 17.5Hz, 1H, H-3), 3.47(m, 1H, H-5), 3.88(dd ,J=1.5, 6.1Hz, 1H, H-4), 3.96(d, J=15.2Hz, 1H, PhCHN), 4.40(d, J=11.7Hz, 1H, PhCHO), 4.47(d, J=11.7Hz, 1H, PhCHO), 5.05(d, J=15.2Hz, 1H, PhCHN), 7.20~7.40(m, 10H, $2C_6H_5$)ppm. MS EI (m/z): 379(M^+, 45), 288(11), 273(70), 174(56), 149(36), 91(100). HRFABMS calcd for $[C_{25}H_{33}NO_2+H]^+$ 380.2584; Found: 380.2579. ***cis*-10d** (minor isomer): colorless oil. $[\alpha]_D^{20}$ +13.2°(*c* 1.1, $CHCl_3$). IR(film)ν_{max} : 3030, 2924, 2855, 1696, 1496, 1455, 1419, 1351, 1098, 734, 700cm^{-1}. ^{1}H-NMR(500MHz)δ : 0.87(t, J=6.6Hz, 3H CH_3), 1.22(m, 10H, $5CH_2$), 1.61(m, 1H, CH), 1.73(m, 1H, CH), 2.56(dd, J=6.2, 17.0Hz, 1H, H-3), 2.65(dd, J=4.4, 17.0Hz, 1H, H-3), 3.51(ddd, 3.6, 5.1, 7.4Hz, 1H, H-5), 3.70(d J=15.1Hz, 1H, PhCHN), 4.10(ddd, J=6.2, 4.4, ca. 7.4Hz, 1H, H-4), 4.40(d, J=11.7Hz, 1H, PhCHO), 4.58(d, J=11.7Hz, 1H, PhCHO), 5.30(d, J=15.1Hz, 1H, PhCHN), 7.20~7.40(m, 10H, $2C_6H_5$)ppm. MS EI (m/z): 379(M^+, 21), 288(8), 273(64), 174(51), 91(100). HRFABMS calcd for $[C_{25}H_{33}NO_2+H]^+$ 380.2584; Found: 380.2580.

(-)-(4S, 5R)-1,5-Dibenzyl-4-benzyloxy-2-pyrrolidinone (10e). Yield, 62% (*trans* / *cis* = 83:17, ***trans*-10e** (major isomer). colorless oil. $[\alpha]_D^{20}$ +38.5°(*c* 0.3, $CHCl_3$). [Lit.[3a] $[\alpha]_D^{22}$ +36.4°(*c* 1.2, $CHCl_3$)]; Identical with the product obtained by reductive alkylation method[3a] by I.R., ^{1}H-NMR, mass spectroscopy and HRMS.

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