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Stereoselective Synthesis of (–)-Chloramphenicol, (+)-Thiamphenicol and (+)-Sphinganine via Chiral Tricyclic Iminolactone†

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The stereoselective syntheses of (–)-chloramphenicol, (+)-thiamphenicol and (+)-sphinganine are described. The two continuous chiral centers within three target molecules were constructed through aldol reaction of chiral tricyclic iminolactone and aldehyde.

Keywords *β*-hydroxy-*α*-amino alcohol, tricyclic iminolactone, total synthesis

Introduction

Optically active amino alcohols with vicinal stereocenters are important intermediates of drugs and natural products.[1,2] Bioactive molecules (–)-chloramphenicol (**A**), (+)-thiamphenicol (**B**) and (+)-sphinganine (**C**) all contain an *β*-hydroxy-*α*-amino alcohol fragment (Figure 1). The pharmacological utility demonstrated by these compounds themselves or as subunits in larger structures has stimulated the search for better methods to achieve their syntheses.[3]

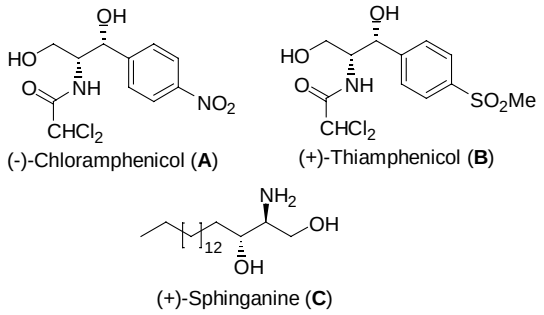

Figure 1 Representative bioactive molecules containing an amino alcohol fragment.

(–)-Chloramphenicol (**A**) is a natural antibiotic with a relatively broad spectrum of antimicrobial activity.[4,5] First isolated from *Streptomyces venezuelae* in 1947,[6] it was the first antibiotic that was produced in optically pure and active form by chemical synthesis rather than by traditional fermentation techniques. It is used clinically as a broad spectrum antibiotic and is particularly useful for the treatment of salmonella, typhi, rickettsia, and meningeal infections.[7] (+)-Thiamphenicol (**B**), an analogue of **A**, is bacteriostatic for Gram-positive aerobes, Gram-negative aerobes and for some anaerobes.[8]

Recently, interest in glycosphingolipids has increased due to the recognition that they modulate immune responses.[9-11] For example, the *β*-galactosyl ceramide, plakoside A, isolated from the marine sponge *Plakortis simplex*, was found to be a noncytotoxic immunosuppressant.[12,13] On the other hand, KRN7000, an *R*-galactosyl ceramide identified from SAR studies at Kirin Brewery, has been shown to be a potent activator of the immune system.[14,15] However, it is not an easy task to synthesize glycosphingolipids for extensive research purpose. One of the most challenging aspects of synthesizing glycosphingolipids is the preparation of the sphingoid base. (+)-Sphinganine (**C**) is an important part of symbioramide, a new type of bioactive ceramide, which is known for increasing sarcoplasmic reticulum Ca^{2+}-ATPase activity.[16]

Owing to the potential bioactive activities of these three compounds, a number of synthesis methods have been described.[17-27] As part of our continuous work on the stereoselective synthesis of *α*-amino acid using chiral tricyclic iminolactone which is derived from natural (1*R*)-(+)-camphor,[28-37] we successfully developed a concise and effective methodology to synthesize optically pure *β*-hydroxy-*α*-amino acid.[16] Structurally, **A**, **B** and **C** all have a chiral *β*-hydroxy-*α*-amino alcohol fragment which can be prepared by simple reduction of

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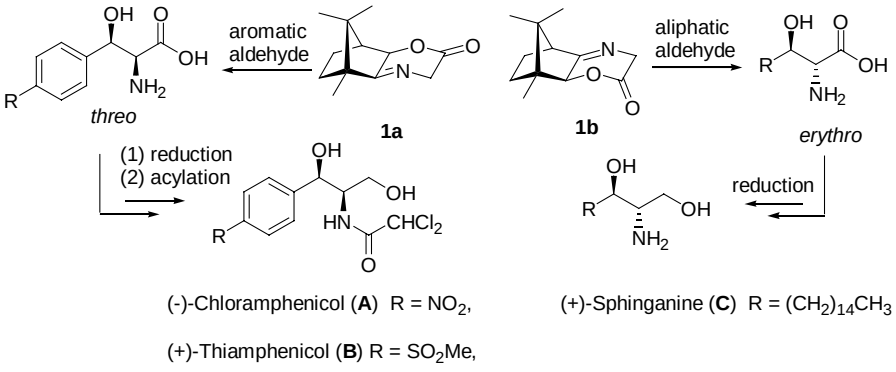
β-hydroxy-*α*-amino acid. Herein, we report a novel and more efficient method to synthesize these three bioactive compounds using our methodology.

Results and Discussion

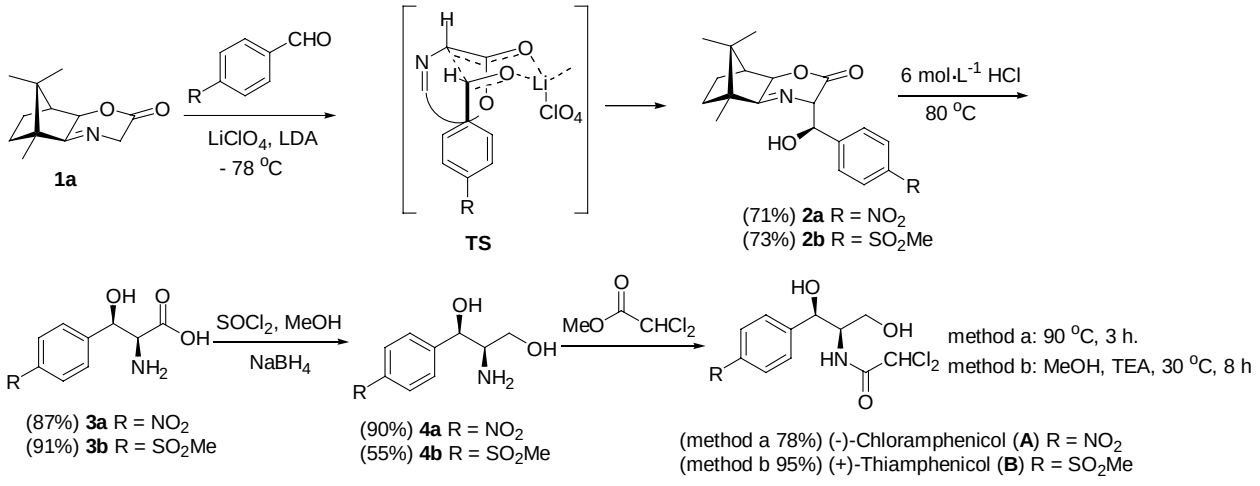
From our previous work (Scheme 1),[36] we know that when chiral tricyclic iminolactone **1a** reacts with an aromatic aldehyde, we mainly obtained *threo*-*β*-hydroxy-*α*-amino acid which has *S*, *R*-configuration, which is the same as that of the (–)-chloramphenicol and (+)-thiamphenicol. From the amino acid, only two more steps are needed to synthesize **A** and **B**. On the other hand, when tricyclic iminolactone **1b** reacts with an aliphatic aldehyde, the *erythro*-*β*-hydroxy-*α*-amino acid will be the major product. In this case, the chiral amino acid has *R*,*R*-configuration, which is the same as that of (+)-sphinganine, and only one more step is needed to synthesize **C** from the amino acid. Therefore, from chiral tricyclic iminolactone, the stereocenters of all the three target molecules can be constructed by one-step reaction and a concise and more efficient strategy for the synthesis of all the three bioactive molecules is developed.

Our synthesis of **A** (Scheme 2) started with tricyclic iminolactone **1a**. Our previous work demonstrated that when enolate of **1a** reacted with aromatic aldehydes (*e.g.* benzaldehyde, *o*-fluorobenzaldehyde, *o*-chlorobenzaldehyde and *o*-methoxybenzaldehyde) in the presence of 6 equiv. of LiCl, the aldol adducts were obtained in good yield (up to 80%) and high diastereoselectivity (up to >25∶1 *dr*). However, low stereoselectivity was observed when **1a** reacted with *p*-nitrobenzaldehyde under the same condition due to the high activity of *p*-nitrobenzaldehyde and the strong electron withdrawing effect of nitro group. Gratifyingly it was found that 1.3 equiv. of $LiClO_4$ as the additive gave the significant selectivity (*dr*=4∶1). Using more or less than 1.3 equiv of $LiClO_4$ resulted in no improvement of diastereoselectivity. With 1.3 equiv. $LiClO_4$ as the additive, treatment of **1a** with LDA at –40 ℃ generated the corresponding anion which reacted with *p*-nitrobenzaldehyde at –78 ℃ to form compound (*S*,*R*)-**2a** at the yield of 71%. The reaction proceeds through the transition state outlined in Scheme 2. If benzene ring is paralleled with the iminoloactone ring, it would enforce a π-π interaction between the benzene ring and the π system of the iminolactone. Therefore this pathway is favoured and the compound **2a** was obtained with the expected configuration. The hydrolysis of **2a** in 6 mol•L^{-1} HCl solution at 80 ℃ afforded the corresponding *threo*-*β*-hydroxy-*α*-amino acid **3a** in 87% yield. The transformation of amino acid **3a** to amino alcohol **4a** was accomplished by esterification of **3** with $SOCl_2$ in MeOH

Scheme 1 Strategy in the synthesis of **A**, **B** and **C**



Scheme 2 Total synthesis of chloramphenicol and thiamphenicol



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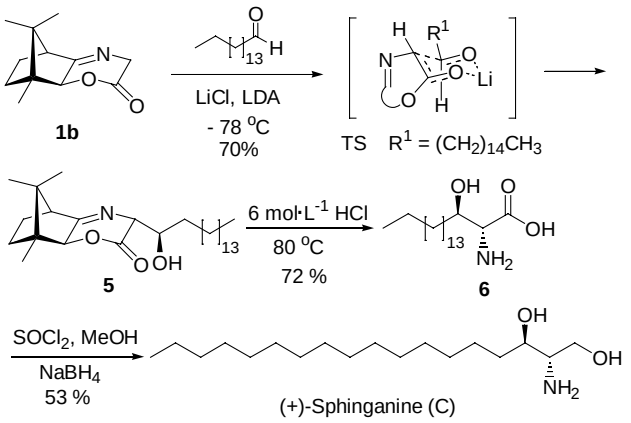
followed by reduction with $NaBH_4$ in the same pot in high yield. Finally, amino alcohol **4a** was added to methyl dichloroacetate and heated at 90 ℃ for 3 h to produce (−)-chloramphenicol in 78% yield (Scheme 2).[17]

Similarly, the synthesis of **B** (Scheme 2) started with the aldol reaction of tricyclic iminolactone **1a** with *p*-methylsulfonylbenzaldehyde in the presence of 1.3 equiv. of $LiClO_4$ as the additive and LDA as the base. Subsequent hydrolysis of **2b** in 6 mol•L^{-1} HCl solution at 80 ℃ afforded the corresponding *threo*-*β*-hydroxy-*α*-amino acid **3b** in 91% yield. Then the amino acid **3b** was reduced to amino alcohol **4b** using the same protocol as described above. Finally, amino alcohol **4b** was successfully transformed to **B** following a literature procedure.[18] As a summary, through our novel synthetic routes, we not only successfully synthesized (−)-chloramphenicol and (+)-thiamphenicol, but also extended the spectrum of substrates. In our previous work, we mainly discussed about the electron-rich or weak electron-deficient benzaldehydes, herein we extended the range of the substrates to strong electron-deficient benzaldehydes (*p*-nitro- and *p*-(methylsulfonyl)-benzaldehyde).

The novel synthesis method for (+)-sphinganine (**C**) was also developed using the similar strategy as for the synthesis of **A** and **B** (Scheme 3). From our previous research, we know that the adducts of **1b** with aliphatic aldehydes have *erythro*-(*R*,*R*)-configuration. Therefore, our synthesis started with the aldol reaction of tricyclic iminolactone **1b** with hexadecanal using 6 equiv. of LiCl as the additive. The aldol reaction proceeded for about 20 h because the solubility of hexadecanal was low in THF under −78 ℃. Luckily, no obvious decrease of selectivity was observed. The adduct **5** was obtained with expected configuration in 70% yield with about 10% of **1b** recovered. The reaction proceeds through the transition state outlined in Scheme 3. The stereoselectivity comes from minimization of nonbonded interaction in the form of a chairlike transition state in which the alkyl group assumes a pseudoequatorial position. Then the *erythro*-*β*-hydroxy-*α*-amino acid (**6**) was obtained through the hydrolysis of **5** in 6 mol•L^{-1} HCl at 80 ℃ in 72% yield, the synthesis was completed by reduction of *erythro*-*β*-hydroxy-*α*-amino acid (**6**) to the target molecule (+)-sphinganine in 53% yield.

Scheme 3 Total synthesis of (+)-sphinganine



Conclusions

We have developed a novel, concise and efficient strategy for the total syntheses of bioactive molecules (−)-chloramphenicol, (+)-thiamphenicol and (+)-sphinganine. The two continuous chiral centers within three target molecules are introduced in just one single step via the aldol reaction of the chiral auxiliaries with aldehydes to produce enantiomerically pure *β*-hydroxy-*α*-amino acids. For the total synthesis of chloramphenicol and thiamphenicol, only four steps are needed from the chiral auxiliary **1a**; while for the total synthesis of sphinganine**,** only three steps are needed from the chiral auxiliary **1b**.

Experimental

(1*S*,2*R*,5*S*,8*R*,1'*R*)-5-(1'-Hydroxy-*p*-nitrobenzyl)-8,11,11-trimethyl-3-oxa-6-azatricyclo [6.2.1.$0^{2,7}$] undec-6-en-4-one (2a) $LiClO_4$ (208 mg, 1.5 mmol, 1.3 equiv.) was added to a dry 50 mL long-neck flask under argon. Diisopropylamine (0.234 mL, 1.65 mmol, 1.1 equiv.) in dry THF (8 mL) was added to the long-neck flask. After the solution was cooled to –40 ℃, *n*-BuLi (2.2 mol•L^{-1}, 0.750 mL, 1.65 mmol, 1.1 equiv.) was added dropwise to the cooled solution. The reaction mixture was stirred at –40 ℃ for 30 min. Tricyclic iminolactone **1a** (310 mg, 1.5 mmol) in dry THF (10 mL) was added dropwise over a period of 10 min to the above freshly prepared LDA solution at –40 ℃ while stirring. The reaction mixture was subsequently cooled to −78 ℃ and the stirring was continued for 1 h followed by the dropwise addition of the solution of *p*-nitrobenzaldehyde (272 mg, 1.8 mmol, 1.2 equiv.) in dry THF (20 mL) over a period of 15 min with vigorous stirring. And then the well-stirred reaction was quenched by adding saturated NH_4Cl (1 mL) solution at −78 ℃. The reaction was warmed up to r.t., and the solvent was removed under reduced pressure and the residue was diluted with water and then extracted with ethyl acetate (15 mL×3), the combined organic phase was washed with water and brine, dried over $MgSO_4$ and concentrated to give the crude product. The crude product was purified by column chromatography (petrol ether/EtOAc 3∶1) to yield desired compound **2a** (381 mg, 71 %). White solid, $[\alpha]_D^{27}$ −86 (*c* 0.028, $CHCl_3$); m.p. 75−78 ℃; IR (film) *v*: 3384, 2925, 1740, 1521, 1346 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 8.2 (d, *J*= 8.8 Hz, 2H), 7.52 (d, *J*=8.4 Hz, 2H), 5.51 (t, *J*=4.0 Hz, 1H), 4.75 (d, *J*=3.6 Hz, 1H), 4.54 (s, 1H), 3.25 (d, *J*= 4.4 Hz, 1H), 2.15 (d, *J*=4.4 Hz, 1H), 2.03−1.75 (m, 1H), 1.66−1.59 (m, 1H), 1.33−1.23 (m, 1H), 0.97 (s, 3H), 0.94 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ: 184.2, 170.9, 147.1, 127.4, 123.5, 80.3, 74.9, 67.0, 53.3, 48.3, 47.7, 29.4, 26.1, 20.1, 19.5, 10.1. HRMS (ESI) calcd for $C_{19}H_{22}N_2O_5[M+H]^+$: 359.1601, found 359.1606.

(2*S*,3*R*)-2-Amino-3-hydroxy-3-(*p*-nitrophenyl)-propanoic acid (3a) The aldol product (380 mg, 1.06 mmol) was dissolved in 6 mol•L^{-1} HCl (19 mL) in a sealed tube with a Teflon screw cap and heated at 80 ℃ for 3.5 h. After cooling to r.t., water (5 mL) was added and the mixture was extracted with diethyl ether (5 mL ×3). The aqueous layer was evaporated under reduced pressure and the residue was dissolved in anhydrous ethanol. Propylene oxide (3 mL) was then added and the mixture was stirred at r.t. for 30 min during which time light yellow solids precipitated. The precipitate was collected by centrifugation, washed successively with cold EtOAc (2 mL×2) and Et_2O (4 mL×1), and air dried to give the desired free *threo*-β-hydroxy-α-amino acid **3a** (211 mg, 87%). Light yellow solid, $[\alpha]_D^{26}$ −12 (*c* 0.044, H_2O); m.p. 184−186 ℃; ^{1}H NMR (400 MHz, D_2O) δ: 8.32 (d, *J*=8.8 Hz, 2H), 7.71 (d, *J*=8.4 Hz, 2H), 5.43 (d, *J*=4.4 Hz, 1H), 3.98 (d, *J*=4.4 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ: 171.5, 147.6, 147.0, 127.1, 124.0, 70.7, 60.5. HRMS (ESI) calcd for $C_9H_{10}N_2O_5$ $[M+H]^+$: 227.0662, found 227.0654.

(2*R*,3*R*)-2-Amino-3-hydroxy-3-(*p*-nitro-phenyl)-1-propanol (4a) The **3a** (45 mg, 0.2 mmol) was added to absolute methanol (2 mL) while stirring, then freshly distilled thionyl chloride (0.088 mL, 1.2 mmol, 6 equiv.) was added to the stirred suspension of **3a** and the mixture was heated at 40 ℃ while stirring for 2−3 d (TLC monitored). Following the completion of reaction, the excess thionyl chloride was evaporated under reduced pressure. Then absolute methanol (2 mL) and $NaBH_4$ (75 mg, 2 mmol, 10 equiv.) were added to the residue. The reaction was performed at 60 ℃ until the TLC analysis showed the reaction was complete. The crude product was purified by column chromatography (methylene chloride/methanol/aqueous ammonia 90∶9∶1 to 60∶30∶10) to yield desired compound **4a** (38 mg, 90%) as light yellow solid. ^{1}H NMR (400 MHz, D_2O) δ: 8.33 (d, *J*=8.8 Hz, 2H), 7.71 (d, *J*=8.4 Hz, 2H), 5.05 (d, *J*=3.2 Hz, 1H), 3.74 (dd, *J*=11.4, 3.4 Hz, 1H), 3.65 −3.56 (m, 2H); ^{13}C NMR (100 MHz, D_2O) δ: 150.5, 149.2, 130.4, 126.8, 72.5, 61.1, 60.4.

(1*R*,2*R*)-2-(Dichloroaceramido)-1-(*p*-nitrophenyl)-1,3-propanediol (Chloramphenicol A) A large excess of methyl dichloroacetate was added to **4a** and heated at 90 ℃ while stirring for about 3 h (TLC monitored). The excess methyl dichloroacetate was removed under reduced pressure and the crude product was purified by column chromatography (petrol ether/EtOAc 3∶7) to give Chloramphenicol A.[17] $[\alpha]_D^{26}$ −25 (*c* 0.031, EtOAc); m.p. 150−151 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.31 (d, *J*=8.8 Hz, 1H), 8.17 (d, *J*=8.4 Hz, 2H), 7.60 (d, *J*=8.8 Hz, 2H), 6.48 (s, 1H), 6.04 (d, *J*=4.4 Hz, 1H), 5.06 (dd, *J*=4.0, 2.4 Hz, 1H), 4.98 (dd, *J*=6.0, 5.2 Hz, 1H), 3.59 (dd, *J*=6.0, 2.6 Hz, 1H), 3.39−3.33 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.4, 151.2, 146.4, 127.3, 122.9, 69.0, 66.4, 60.2, 56.8.

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