DIASTEREOSELECTIVE APPROACH TO cis-4-METHYL/THIOL-PIPECOLIC ESTERS BASED ON RCM REACTION AND CONJUGATE MICHAEL ADDITION

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GRAPHICAL ABSTRACT

Abstract A synthetic route for the access to enantiopure cis-4-methyl/thiol-pipecolic esters is presented. It is based on the ring-closing metathesis reaction to build the α,β-unsaturated piperidin-2-one derived from (S)-(−)-phenylethylamine, followed by either diastereoselective conjugate addition of methylorganocuprate allowing access to cis-4-methyl pipecolic ester or by tandem diastereoselective hydrosulforization–thionization reaction providing access to cis-4-thiol pipecolic ethyl esters.

Keywords Diastereoselective Michael addition; hydrosulforization; pipecolic esters; ring-closing metathesis

INTRODUCTION

Cyclic α-amino acids are present in many biologically important compounds.[1] Specifically, 4-substituted pipecolic acids (4-substituted piperidine-2-carboxylic acid) and their derivatives are key fragments of compounds of pharmacological interest.
For example, argatroban, an important anticoagulant, is a small molecule direct thrombin inhibitor. Sulfur-containing amino acids include pulcherrimine, from the ovaries of the sea urchin Hemicentrotus pulcherrimus. Consequently, enantiopure 4-substituted-pipecolic esters, their acids, and their salts are, in general, important synthetic intermediates (Scheme 1).

In this sense, approaches toward the synthesis of racemic or cis-trans-4-substituted mixture are known, and several methodologies to the synthesis of trans-4-substituted pipecolic acids and processes for the synthesis of cis-4-substituted pipecolic acid have been also disclosed.

In this article, we describe a diastereoselective synthetic route to cis-4-methyl/thiol pipecolic ethyl esters based on the ring-closing metathesis reaction followed by either diastereoespecific conjugate addition of methylorganocuprate or by tandem diastereospecific hydrosulfurization/thionization reaction. Interestingly, the presence of the ester function located at C-6 on the piperidine ring directs the nucleophilic attack on the Michael addition reaction.

**DISCUSSION**

The separable diastereomeric mixture of the \( \alpha,\beta \)-unsaturated piperidin-2-ones \( 7a + 7b \) in six steps was prepared. First, \((S)-(-)-\)phenylethylamine was treated with ethyl 2-bromoacetate, giving the corresponding chiral glycine \( 2 \), which was treated with di-\text{tert}-butyl dicarbonate, affording the N-Boc protected glycine \( 3 \). Next, the compound \( 3 \) was reacted with lithium diisopropylamide (LDA) and allyl iodide at \(-78 \, ^\circ C \) providing the unseparable diastereomeric mixture of alkylated adducts \( 4(a+b) \), which was reacted with trifluoroacetic acid (TFA) to deliver the deprotected diastereomeric mixture \( 5(a+b) \). These compounds were condensed with acryloyl chloride affording the unsaturated mixture \( 6(a+b) \). Finally, \( 6(a+b) \) were subjected to a ring-closing metathesis reaction giving access to \( \alpha,\beta \)-unsaturated diastereomeric mixture of \( 7a + 7b \) in 70:30 dr, determined by \( ^1H \) NMR from the crude reaction mixture (Scheme 2).

The diastereomeric mixture of \( 7(a+b) \) was separated, and then \( 7a \) and \( 7b \) were crystallized. The absolute configuration at C-6 was determined by X-ray diffraction analysis as \((R)\) and \((S)\) respectively (Fig. 1).
With the \( \alpha,\beta \)-unsaturated piperidin-2-one in our hands, we started to explore the conjugate addition of methylcuprate to the \( \alpha,\beta \)-unsaturated lactam 7a. In this sense, Hanessian\[^10\] reported that the conjugate addition of organocuprates to \( N \)-Boc unsaturated lactams delivers a mixture of cis and trans diastereoisomers. After testing various reaction conditions, the best result was obtained by the use of chlorotrimethylsilane (TMSCl), which accelerates copper-mediated conjugate addition reaction in THF.\[^{11}\] This procedure afforded the desired 4-methyl piperidin-2-one 8a as a major diastereoisomer (determined direct from the \(^1H\) NMR spectra of the crude reaction mixture), in 80% yield. The analysis of two-dimensional nuclear Overhauser spectroscopy (2D-NOESY) experiments of lactam 8a indicates that both substituents are cis-oriented for the lactam ring (Scheme 3). It is worth noting that Antoni et al.\[^{12}\] reported a highly diastereoselective conjugate addition of methylorganocuprate to enantiopure \( N \)-Boc pipecolic \( \alpha,\beta \)-unsaturated esters; however, in this case only the trans-4-methyl pipecolic ester was obtained.

Then, compound 7b (minor diastereoisomer) was treated with methylcuprate following the optimized conditions described. 4-Methyl piperidin-2-one 8b was obtained in 80% yield. The relative configuration at C-4 as (S) was confirmed from the X-ray analysis diffraction of compound 8b (Fig. 2).\[^{13}\]

Next, diastereoisomers 8a and 8b were treated with \( \text{BH}_3 \text{SMe}_2 \) giving the corresponding piperidines 9a and 9b in 95% yield, which were subject to hydrogenolysis.

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**Scheme 2.** Reagents and conditions: (i) ethyl 2-bromoacetate, \( \text{K}_2\text{CO}_3 \) (2 eq), \( \text{CH}_2\text{CN} \), rt, 1.45 h, 90%. (ii) \((\text{Boc})_2\text{O}\) (1.5 eq), \( \text{H}_2\text{O} \), rt, 5 h, 98%. (iii) \( \text{LDA} \) (1.5 eq), THF, \(-78^\circ\)C, 3 h, then allyl iodide, \(-20^\circ\)C 8 h. (iv) TFA (5 eq), \( \text{CH}_2\text{Cl}_2 \), rt, 2 h. (v) Acryloyl chloride, \( \text{K}_2\text{CO}_3 \) (2 eq), \( \text{CH}_2\text{Cl}_2/\text{H}_2\text{O} \) 70% after three steps. (vi) Grubbs’s second-generation (5 mol%), \( \text{CH}_2\text{Cl}_2 \), rt, 6 h, quantitative.

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**Figure 1.** X-ray ORTEP diagram of compounds 7a and 7b.
in the presence of di-tert-butyl dicarbonate to give the N-Boc-protected piperidines 10a and 10b. The comparison of its optical rotation confirmed that 10a and 10b are enantiomers and as a correlation compound 8a have the (R) configuration at C-4 (Scheme 4).

We then oriented our attention to the reactivity of 7a (major diastereoisomer) toward Lawesson’s reagent (LR), taking into account our previous report. When compound 7a was treated with 0.5 equivalents of LR in boiling toluene, the expected unsaturated thioamide 11a was obtained in 70% yield. Interestingly, the treatment of 7a with an equimolar amount of LR gave a mixture of compound 11a and the unexpected 4-mercapto-substituted thioamide 12a as a single diastereoisomer. The use of 2 equivalents of LR resulted in exclusive formation of compound 12a in 73% yield. Finally, compound 7b showed the same behavior toward LR (Scheme 5).

Scheme 4. Reagents and conditions: (i) BH$_3$SMe$_2$, THF, 25°C, 95%. (ii) H$_2$, (Boc)$_2$O, Pd(OH)$_2$, AcOEt, 25°C, 90%.
Compounds 12a and 12b were crystallized and the absolute configuration at C-4 was determined by x-ray analysis diffraction as (R) for 12a and (S) for 12b, and the presence of the thiol function was also confirmed (Fig. 3).[15]

To obtain the corresponding piperolic ethyl ester, compound 12b was treated with BH₃ SMe₂, affording the desired reduced compound 13b in 95% yield. Debenzylation of 13b was performed under Birch conditions to give the desired piperidine 14b in 43% yield (Scheme 6).

In conclusion, an efficient method for the diastereoselective synthesis of cis-4-methyl/thiol-pipelicolic ethyl esters from (S)-phenylethylamine has been developed. The stereochemical outcome showed that the conjugate addition occurs from the same side of the ester function located at C-6 on the piperidine ring. Expansion of the protocol scope and application of this methodology to the total synthesis are currently under way in our group.

**EXPERIMENTAL**

(R)-Ethyl-1,2,3,6-tetrahydro-6-oxo-1-((S)-1-phenylethyl)pyridine-2-carboxylate, 7a

[α]D²⁰ = +18.45 (c 1.0, CH₂Cl₂); bp = 96–98 °C. IR (film) 2964, 2924, 1738, 1659, 1429, 1018, 809, 707, 536 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.25 (t, J = 7.2 Hz, 3H), 1.45 (d, J = 7.2 Hz, 3H), 2.50 (AB, J = 1.6, 6.0, 2.3, 2.9, 7.0, 18.1 Hz, 2H), 3.86
(S)-Ethyl-1,2,3,6-tetrahydro-6-oxo-1-((S)-1-phenylethyl)pyridine-2-carboxylate, 7b

$[\alpha]_{D}^{20} = -55.73$ (c 1.0, CH$_2$Cl$_2$); bp = 58–60°C; IR (film) 2978, 2932, 1744, 1665, 1609, 1433, 1390, 1084, 1033, 813, 702 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.93 (t, $J = 7.1$ Hz, 3H), 1.55 (d, $J = 7.1$ Hz, 3H), 2.60 (ddd, $J = 1.0$, 6.1, 18.1 Hz, 1H), 2.72 (m, 1H), 3.54 (m, 1H), 3.70 (m, 1H), 4.11 (d, $J = 7.4$ Hz, 1H), 6.03 (dd, $J = 3.0$, 9.8 Hz, 1H), 6.06 (q, $J = 7.1$ Hz, 1H), 6.29 (m, 1H), 7.26 (m, 5H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 13.7, 17.3, 28.7, 50.4, 52.6, 61.0, 126.7–138.2, 163.5, 170.9. HRMS (FAB): calcd. for C$_{17}$H$_{23}$NO$_3$: 289.1678. Found: 289.1680.

**General Procedure for Conjugate Michael Addition of Organocuprate**

Methyl lithium (0.5 M in Et$_2$O, 5 eq) was added to a suspension of CuBr SMe$_2$ (5 eq) in Et$_2$O at $-15^\circ$C. The resulting yellow suspension was stirred for 45 min at $-15^\circ$C, and then 7a (0.100 g, 0.183 mmol, 1 eq) in 6 mL of Et$_2$O and TMSCl (0.148 mL, 0.585 mmol, 3.2 equiv) were successively added. The mixture was warmed to 0°C and stirred for 18 h. After quenching at 0°C with saturated NH$_4$Cl, a few drops of saturated NH$_4$OH were added until the aqueous layer remained colorless. The organic layer was separated, dried over anhydrous MgSO$_4$, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography to afford the expected product 8a as a white solid in 80% yield.

(2R,4R)-Ethyl-4-methyl-6-oxo-1-((S)-1-phenylethyl)piperidine-2-carboxylate, 8a

$[\alpha]_{D}^{20} = -15.1$ (c 1.0, CH$_2$Cl$_2$). IR (film) 2950, 2938, 1741, 1654, 1434, 1198, 1029, 922, 732, 691 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.97 (d, $J = 6.4$ Hz, 3H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.45 (d, $J = 7.2$ Hz, 3H), 1.51 (m, 1H), 1.97 (m, 2H), 2.15 (dd, $J = 12$, 15.6 Hz, 1H), 2.50 (ddd, $J = 1.8$, 4.4, 15.6 Hz, 1H), 3.74 (dd, $J = 4$, 8.7 Hz, 1H), 4.16 (q, $J = 7.1$ Hz, 2H), 5.98 (q, $J = 7.1$ Hz, 1H), 7.29 (m, 5H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 14.0, 15.7, 21.7, 26.2, 34.1, 40.4, 50.7, 53.4, 61.4, 127.3–128.4, 133.9, 140.1, 172.2, 173.4. HRMS (FAB): calcd. for C$_{17}$H$_{23}$NO$_3$: 289.1678. Found: 289.1680.

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**Scheme 6.** Reagents and conditions: (i) BH$_3$ SMe$_2$, THF, 25°C, 95%. (ii) Na/NH$_3$, $-78^\circ$C, 43%.
(2S,4S)-Ethyl-4-methyl-6-oxo-1-((S)-1-phenylethyl)piperidine-2-carboxylate, 8b. \[\delta^1H_{D} = -152 \text{ (c 1.0, CH}_2\text{Cl}_2); \text{ bp} = 68-70^\circ\text{C. IR (film) 2949, 2935, 1742, 1436, 1187, 1029, 733, 701 cm}^{-1}; 1^H \text{ NMR (400 MHz, CDCl}_3\text{)} \delta 0.96 (d, J = 6.6 Hz, 3H), 1.0 (t, J = 7.1 Hz, 3H), 1.48 (m, 1H), 1.54 (d, J = 7.1 Hz, 3H), 1.94 (m, 1H), 2.15 (dd, J = 12.1, 15.8 Hz, 1H), 2.26 (m, 1H), 2.48 (ddd, J = 2.0, 4.5, 15.8 Hz, 1H), 3.60 (m, 2H), 4.08 (dd, J = 5.4, 8.6 Hz, 1H), 5.8 (q, J = 7.1 Hz, 1H), 7.25 (m, 5H); 13C NMR (100 MHz, CDCl}_3\text{)} \delta 13.7, 16.1, 21.4, 26.3, 34.7, 40.8, 51.7, 54.7, 61.0, 127.5-128.5, 139.2, 171.8, 172.3. HRMS (FAB): Calcd. for C\textsubscript{17}H\textsubscript{23}NO\textsubscript{3}: 289.1678. Found: 289.1681.

General Procedure for Thionation of \(\alpha,\beta\)-Unsaturated Lactams 7a and 7b

Lawesson’s reagent (1.024 mmol, 2.0 eq) was added to a solution of 7a (0.140 g, 0.512 mmol, 1.0 eq) in 10 mL of dry toluene. The resulting mixture was stirred for 4 h at reflux temperature and then concentrated under reduced pressure. The residue was purified by column chromatography using 80:20 petroleum ether/AcOEt as the eluent to give the compound 12a as a white solid in 60\% yield.

(2R,4R)-Ethyl-4-mercapto-1-((S)-1-phenylethyl)-6-thioxopiperidine-2-carboxylate, 12a. \[\delta^1H_{D} = -207.4 \text{ (c 1.0, CH}_2\text{Cl}_2\text{)}; \text{ IR (film) 2976, 2926, 1740, 1465, 1311, 1197, 1085, 1023, 801, 700 cm}^{-1}; 1^H \text{ NMR (500 MHz, CDCl}_3\text{)} \delta 1.31 (t, J = 7.1 Hz, 3H), 1.54 (d, J = 7.1 Hz, 3H), 1.84 (d, J = 6.5 Hz, 1H), 2.12 (m, 2H), 2.81 (dd, J = 11.6, 15.8 Hz, 1H), 3.15 (m, 1H), 3.64 (dd, J = 5.5, 15.7 Hz, 1H), 3.98 (dd, J = 2.7, 7.4 Hz, 1H), 4.25, (m, 2H), 7.13 (q, J = 7.1 Hz, 1H), 7.34 (m, 5H); 13C NMR (125 MHz, CDCl}_3\text{)} \delta 14.0, 14.4, 29.4, 36.3, 52.4, 55.3, 58.1, 62.4, 127.0-128.8, 138.4, 170.3, 201.0. HRMS (FAB): calcd. for C\textsubscript{16}H\textsubscript{21}NO\textsubscript{2}S\textsubscript{2}: 323.1014. Found: 323.1016.

(2S,4S)-Ethyl-4-mercapto-1-((S)-1-phenylethyl)-6-thioxopiperidine-2-carboxylate, 12b. \[\delta^1H_{D} = -348.9 \text{ (c 1.0, CH}_2\text{Cl}_2\text{)}; \text{ IR (film) 2975, 2930, 1736, 1466, 1313, 1199, 1073, 910, 730, 691 cm}^{-1}; 1^H \text{ NMR (500 MHz, CDCl}_3\text{)} \delta 0.98 (t, J = 7.1 Hz, 3H), 1.52 (d, J = 7.0 Hz, 3H), 1.81 (d, J = 6.6 Hz, 1H), 2.15 (ddd, J = 2.3, 5.9, 14.7 Hz, 1H), 2.56 (m, 1H), 2.96 (dd, J = 11.3, 15.6 Hz, 1H), 3.18 (m, 1H), 3.63 (ddd, J = 0.8, 5.6, 15.6 Hz, 1H), 3.73, (m, 2H), 4.2 (dd, J = 2.3, 8.3 Hz, 1H), 7.14 (q, J = 7.1 Hz, 1H), 7.30 (m, 5H); 13C NMR (125 MHz, CDCl}_3\text{)} \delta 13.7, 14.4, 29.7, 37.2, 52.3, 55.3, 58.1, 61.7, 128.2-128.9, 136.8, 169.4, 200.7. HRMS (FAB): Calcd. for C\textsubscript{16}H\textsubscript{21}NO\textsubscript{2}S\textsubscript{2}: 323.1014. Found: 323.1017.

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**SUPPORTING INFORMATION**

Full experimental details and 1H and 13C NMR spectra for this article can be accessed on the publisher’s website.
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