Synthesis of $\text{C}_5$-$\text{C}_{18}$ \textit{ansa}-Chain Intermediate
Toward the
Total Synthesis of Kendomycin

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C500 Report

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Introduction

Kendomycin (1) is a natural product that has been isolated from the mycelium of *Streptomyces violaceoruber*. It is an antibiotic that has been shown to be a significant anti-tumor agent with activity greater than that of cisplatin and potency similar to doxorubicin when tested against stomach adenocarcinoma (HM02), hepatocelluar carcinoma (HEPG2), and breast adenocarcinoma (MCF7) cell lines. It is also a potent endothelin receptor antagonist and antiosteoprotic agent. Kendomycin has shown antibacterial activity against *Staphylococcus aureus* (MRSA) strains and other Gram-positive and Gram-negative organisms. Some of the unique features of the structure include an 18-membered *ansa*-bridged ring and multiple, and in some cases, contiguous stereocenters which pose interesting synthetic challenges. There are currently no reports of proposed synthesis of kendomycin.
Objective

With the ultimate goal of total synthesis of kendomycin, the following retro-synthetic plan has been proposed (Scheme 1).

Scheme 1. Retro-synthetic plan for kendomycin.
The objective of this project will be to synthesize the important C₅-C₁₈ ansa-chain intermediate 2 to be used in the total synthesis of kendomycin. The following reaction scheme shows the proposed pathway toward producing intermediate 2 (Scheme 2).

The synthesis of the ansa-chain will be based on aspects of William's asymmetric conjugate addition methodology. Swern oxidation of 3, followed by use of Acyl-DAMP will yield 4. Transmetallation of 4 following precedents from Lipshutz and Wipf followed by conjugate addition of 5 will lead to product 6. Aldol reaction with 7 and 8 will produce product 9. Deprotection of 10, followed by substitution of phenylthioether for benzyloxy will lead to the desired intermediate 2.
Scheme 2. Synthesis of the C5-C18 ansa-chain.

In addition to the synthesis of intermediate 2, the following zirconation reaction will be explored using various alkynyl substrates (Scheme 3).

Scheme 3. Conjugate Addition involving vinylic organometalic and organocopper reagent.
Scheme 3 proceeds through the following mechanism (Scheme 4).

Completed Work

The first aspect of research that was completed was to synthesize the oxazolidinone intermediate. The synthesis began with the reduction of phenyl glycine\textsuperscript{10} to the corresponding alcohol (12, Scheme 5). The alcohol was heated with potassium carbonate and diethyl carbonate at 135°C to distill off ethanol and form the chiral auxiliary \textsuperscript{11}. The oxazolidinone intermediate 15 was made by coupling the chiral auxiliary with \textit{trans}-crotonyl chloride\textsuperscript{12}.

\begin{equation}
\text{H}_2\text{NCHOH} \xrightarrow{\text{NaBH}_4, I_2, \text{THF}} \text{H}_2\text{NCH(OH)Ph} \xrightarrow{K_2\text{CO}_3, \text{EtO}_2\text{OEt}} \text{NH} \xrightarrow{135^\circ\text{C}} \text{O} \xrightarrow{n\text{BuLi}, \text{THF}} \text{O} \xrightarrow{\text{ClISOCH}_3, \text{THF}} \text{O} \xrightarrow{\text{Cl}^-CH_3, \text{THF}} \text{O}
\end{equation}

Scheme 5. Synthesis of oxazolidinone.

The next phase of the synthesis was to produce a benzyl protected bromide reagent that could later be used to make a Grignard reagent. The synthesis began with a benzyl protection of alcohol 16 (Scheme 6), using benzyl-2,2,2-trichloroacetamidate and triflic acid\textsuperscript{13}. The methyl ester 17 was then reduced to alcohol 18\textsuperscript{14} using lithium aluminum hydride. Finally, the bromide 19 was prepared using triphenyl phospine and N-bromosuccinimide\textsuperscript{14}.
The bromide was used to form a Grignard Reagent (Scheme 7) using magnesium metal followed by formation of a cuprate using copper bromide-dimethyl sulfide at -78°C\(^2\). After addition of boron trifloride etherate at -78°C, a conjugate addition of the cuprate and the oxazolidinone 15 was carried out to form intermediate 20. The chiral auxiliary was removed\(^1\) with lithium borohydride to yield alcohol 21. Finally, the alcohol was oxidized to the aldehyde 22 using a Parikh-Doering oxidation\(^1\). The first procedure that was tried was a Swern oxidation; however, the reaction did not go to
completion.

![Chemical structure](image)

Scheme 7. Conjugate addition and synthesis of aldehyde.

For future work, the synthesis of intermediate 2 will continue as previously described by Scheme 2.

**Experimental Procedures**

**General**

All Nuclear Magnetic Resonance spectra were collected on either a Varian GEM-300 or Varian Inova-400 NMR spectrometer. The spectra are described in parts per million (δ) downfield. Deuterated chloroform was used as the solvent for all spectra, and was used as an internal standard (δ 7.26). Thin layer chromatography was done using precoated, glass-backed silica gel plates (0.25 mm thick, EM SCIENCE), and stained with either ethanolic para-anisealdehyde or ethanolic potassium permanganate. Kieselgel-60 (230-400 mesh) silica gel (E. Merck) was used for all flash chromatography. Dichloromethane (CH₂Cl₂) was distilled from calcium hydride under dry air. Tetrahydrofuran (THF) and diethyl ether (Et₂O) were distilled from sodium.
benzophenone ketyl under nitrogen. All reactions were carried out in flame dried
glassware under argon except where indicated.

(R)-2-amino-2-phenylethanol 12
To a mixture of phynyl glycine (50 g, 331 mmol) in THF (450 mL) was added NaBH₄
(30 g, 794 mmol). The mixture was cooled to 0°C and a solution of I₂ (84 g, 331 mmol)
in THF (210 mL) was added dropwise over 1.5 h. The ice bath was removed and mixture
was heated to 42°C until evolution of gas was complete. The mixture was heated to
reflux for 18 h. The reaction was cooled to rt and quenched with MeOH (250 mL). After
evolution of gas, mixture was concentrated to a white paste. KOH (20% by mass) was
added to mixture and stirred overnight. Mixture was extracted with CH₂Cl₂ (4 x 500
mL), dried over Na₂SO₄, filtered, and concentrated. The solid was recrystallized from
hot toluene to form white crystals: yield:16.69 g (36.8%); ¹H NMR (400 MHz, CDCl₃) δ
7.23 (m, 5H), 3.97 (dd, J=4.3 Hz, 1 H), 3.67 (dd, A of ABX, Jₐₓ=10.7 Hz, Jₓₙ=8.51 Hz, 1H),
3.47 (B of ABX, Jₐₖ₉=10.7 Hz, Jₓₙ₉=8.51 Hz, 1H), 1.66 (br s, 2H)

(S)-4-phynyloxazolidin-2-one 13
To a dry 250 mL round bottom w/ stirbar, alcohol 12 (7.76 g, 56.6 mmol) was added.
The K₂CO₃ (0.78 g, 5.66 mmol) was added in one portion. The diethyl carbonate (14.12
mL, 116.59 mmol) was poured from a dry graduated cylinder. A six inch Vigreaux column was attached. A condenser with 100 mL rb collection flask was attached in a 0°C ice bath. The reaction mixture was taken to 135°C via oil bath. After cessation of ethanol distillation, the mixture was cooled to rt, diluted with CH₂Cl₂, and washed with H₂O. The aqueous layer was back-extracted with CH₂Cl₂ (2 x 200 mL). The combined organic layers were dried with MgSO₄, filtered, and concentrated to an off-white solid. The flask was placed under vacuum overnight. The solid was transferred to 500 mL Erlenmeyer flask and recrystallized from hot 2:1 EtOAc: Hexanes: yield 6.04 g (65.4%); ¹H NMR (400 MHz, CDCl₃) δ 7.42-7.26 (m, 5H), 5.34 (2, 1H), 4.96 (dd, A of ABX, Jₐᵦ=7.7, Jₐₓ=7.8 Hz, 1H), 4.75 (t, J=8.6, 1H), 4.20 (dd, B of ABX, Jₐᵦ=8.1, Jₐₓ=7.1, 1H)

(S,E)-3-but-2-enoyl-4-phenyloxazolidin-2-one

Oxazolidinone 13 (1.00 g, 6.13 mmol) was taken in THF and cooled to -78°C. nBuLi (2.5 M in hexanes, 2.94 mL, 7.35 mmol) was added dropwise over 10 min. The reaction mixture turned yellow and was stirred for 30 min. Crotonyl chloride was added dropwise over 15 min. Reaction mixture stirred for 1 h at -78°C and warmed gradually to rt. After 5 h, reaction was quenched with sat. aq. NH₄Cl and diluted with Et₂O. Water was added and layers were separated. Aqueous layers were extracted with Et₂O. Organic layers were combined, dried over MgSO₄, filtered, and concentrated. Purification by column chromatography yielded 15: yield 1.01 g (71%); ¹H NMR (300 MHz, CDCl₃) δ 7.62-7.46 (m, 6H), 7.36-7.24 (m, 1H), 5.69 (dd, A of ABX, Jₐᵦ=8.7, Jₐₓ=3.85 Hz, 1H), 4.91 (t,
J=8.79 Hz, 1H), 4.48 (dd, B of ABX, J<sub>AB</sub>=8.7, J<sub>BX</sub>=3.92 Hz, 1 H), 2.14 (dd, J=6.9, 1.5 Hz, 3H)

(R)-methyl 3-(benzyloxy)-2-methylpropanoate 17

To a rt solution of alcohol 16 (5.00g, 42.3 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (90 mL) was added benzyl-2,2,2-trichloroacetamidate (28.3 mL, 63.5 mmol) and triflic acid (224.1 µL, 1.27 mmol). The reaction mixture was stirred for 15 min at rt. The mixture was quenched with 200 mL NaHCO<sub>3</sub>, and stirred for 30 min. The layers were separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 150 mL). The organic layer was dried with MgSO<sub>4</sub>, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel column. Elution with 5% EtOAc in Hexanes yielded 17: yield 7.63 g (86.6%); silica gel TLC (33% EtOAc in Hex); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.28-7.20 (m, 5H), 5.24, (s, 2H), 3.63 (s, 3H), 3.61 (dd, A of ABX, J<sub>AB</sub>=13.2, J<sub>AX</sub>=8.4, 1H), 3.44 (dd, B of ABX, J<sub>AB</sub>=13.7, J<sub>BX</sub>=5.8, 1H), 2.79-2.62 (m, 2H), 1.12 (d, J=7.1 Hz, 3H)

(S)-3-(benzyloxy)-2-methylpropan-1-ol 18

To Et<sub>2</sub>O (60 mL) at 0°C was added LAH (1.67 g, 43.97 mmol). A solution of propionate 17 (7.63 g, 36.64 mmol) in Et<sub>2</sub>O (60 mL) was then added dropwise to the 0°C LAH
suspension. After stirring for 30 min at 0°C, TLC indicated no starting material remaining. Reaction was quenched at 0°C with H$_2$O (5 mL) and stirred for 5 min. Reaction mixture was warmed to rt and stirred with Na$_2$SO$_4$ for 1 hr. Solids were filtered via sintered glass funnel, and filtrate was concentrated. The crude product was purified via flash chromatography on silica gel column. Elution with 20% EtOAc in hexanes gave 18: yield 5.21 g (78.9%); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.27-7.18 (m, 5H), 4.45 (s, 2H), 3.59-3.46 (m, 3H), 3.36 (t, J=8.3 Hz, 1H), 1.51 (d, J=13.7 Hz, 1H), 1.19 (t, J=7.1 Hz, 1H), 0.79 (d, J=7.0 Hz, 3H)

$\text{H}_3\text{C}-\text{O}$\text{Bn} $\rightarrow$ \text{BnO-CH}$_3$\text{Br} 

(R)-((3-bromo-2-methylpropoxy)methyl)benzene 19

To a solution of alcohol 18 (4.62 g, 25.63 mmol) in CH$_2$Cl$_2$ (51.26 mL) was added PPh$_3$ (7.06 g, 26.91 mmol). The solution was cooled to 0°C and NBS (4.79 g, 26.91 mmol) was added in four portions over 10 min. The clear yellow solution was warmed to rt, covered with foil, and stirred overnight. Solution was washed with 5% aq. NaHCO$_3$ (100 mL) and concentrated to a blue solid. The solid was treated with hexanes (250 mL) and H$_2$O (250 mL) and stirred at rt for 20 min. The solid was filtered and washed with hexanes. The organic layer was separated from the aqueous later, dried with MgSO$_4$, filtered, and concentrated. The crude product was purified via flash chromatography on silica gel column. Elution with 1% Et$_2$O in hexanes gave 19: yield 5.56 g (89.2%); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.28-7.20 (m, 5H), 4.50 (s, 2H), 3.43 (dd, A of ABX,
$J_{AB}=23.6, J_{AB}=5.5 \text{ Hz, 1H}, 3.43 \text{ (dd, A of ABX, } J_{AB}=5.5, J_{AX}=3.88 \text{ Hz, 1H}}, 3.34 \text{ (dd, B of ABX, } J_{AB}=23.3, J_{BX}=6.0 \text{ Hz, 1H}}, 3.34 \text{ (B of ABX, } J_{AB}=4.88, J_{BX}=3.9 \text{ Hz, 1H}), 2.10-2.01 \text{ (m, 1H), 1.02 (d, J=6.8 Hz, 3H)}$

\[(S)-3-((3S,5S)-6-(benzyloxy)-3,5-dimethylhexanoyl)-4-phenyloxazolidin-2-one 20\]

The bromide 19 (1.00 g, 4.11 mmol) was azeotroped, via rotary evaporator, with toluene (2 x 1.5 mL). To Mg turnings (0.999 g, 41.12 mmol, crushed and flame dried) was added THF (1.06 mL) and 1 drop of dibromoethane followed by the bromide in THF (6 mL) slowly enough to maintain a gentle reflux. Mixture was stirred at reflux for 30 min and then cooled to rt. Grignard solution was added via canula to a solution of CuBr-DMS (0.8453 g, 4.11 mmol) in THF (4.5 mL) at -78°C. DMS (1 mL) was added to reaction mixture at -78°C. The mixture was warmed to -30°C, stirred for 30 min, then cooled to -78°C (solution turned yellowish brown). BF$_3$OEt$_2$ (0.521 mL, 4.11 mmol) was added, solution was stirred for 5 min, then oxazolidinone (0.475 g, 2.06 mmol) in THF (4.5 mL) was added. The mixture was stirred for 3 h at -78°C, and placed in -20°C freezer overnight. The reaction was quenched with sat. NH$_4$Cl (25 mL) and diluted with Et$_2$O. The aqueous layer was extracted with Et$_2$O (3 x 25 mL). The combined organic layers were washed with H$_2$O (25 mL) and brine (25 mL), dried over MgSO$_4$, filtered, and concentrated. The crude compound was purified using flash chromatography on silica gel column. Elution with 20% EtOAc in hexanes gave compound 20: yield 0.397 g
(48.8%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.33-7.24 (m, 10H), 5.43 (dd, A of ABX, $J_{AB}$=8.6, $J_{AX}$=3.6 Hz, 1H), 4.68 (t, $J$=9.3 Hz, 1H), 4.47 (s, 2H), 4.27 (dd, B of ABX, $J_{AB}$=8.8, $J_{BX}$=3.39 Hz, 1H), 3.27-3.18 (m, 2H), 2.95 (dd, A of ABX, $J_{AB}$=16.1, $J_{AX}$=5.18 Hz, 1H), 2.73 (dd, B of ABX, $J_{AB}$=16.4, $J_{BX}$=8.5 Hz, 1H), 2.09 (m, 1H), 1.85-1.80 (m, 1H), 0.853 (dd, $J$=6.8, 2.9 Hz, 6H)

![Chemical Structure](image)

(3S,5S)-6-(benzyloxy)-3,5-dimethylhexan-1-ol 21

To a solution 0°C solution of oxazolidinone 20 (0.846 g, 2.18 mmol) in Et$_2$O (10.9 mL) was added MeOH (0.177 mL, 4.37 mmol) and LiBH$_4$ (0.0952 g, 4.37 mmol). The reaction mixture was stirred at 0°C for 10 min. Reaction was quenched with NaHCO$_3$ and warmed to rt. The mixture was diluted with Et$_2$O and washed with NaHCO$_3$. Organic layer was dried over anhyd. Na$_2$SO$_4$, filtered, and concentrated. The crude product was purified using flash chromatography on a silica gel column. Elution in 25% EtOAc in hexanes gave product 21: yield 0.225 g (44%)

![Chemical Structure](image)

(3S,5S)-6-(benzyloxy)-3,5-dimethylhexanal 22

Alcohol 21 (0.0272 g, 1.15 mmol) was dissolved in CH$_2$Cl$_2$ (0.408 mL) in a flame dried flask. In separate flask, SO$_3$·Pyr (0.0549 g, 3.45 mmol) was dissolved in DMSO (0.108 mL). The alcohol was cooled to 0°C and Hunig’s base (0.0583 mL, 3.45 mmol) was added. The solution of SO$_3$·Pyr was then added slowly. The reaction mixture was stirred
for 15 min at 0°C. The solution was diluted with CH₂Cl₂ and washed with brine, NaHCO₃, H₂O, and sat. CuSO₄. The organic layer was dried over MgSO₄, filtered, and concentrated to give a pale yellow liquid. The crude compound was purified by flash chromatography using silica gel column. Elution with 20% EtOAc in hexanes gave compound 22.
References


