3-18-2004

Efforts toward the First Enantioselective Total Synthesis of Praziquantel and Synthetic Model Studies on Ecteinascidin 743 by Novel Aromatic C-H Insertion Methodology

Chiliu Chen

University of South Florida

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Efforts toward the First Enantioselective Total Synthesis of Praziquantel and Synthetic Model Studies on Ecteinascidin 743 by Novel Aromatic C-H Insertion Methodology

by

Chiliu Chen

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science
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Date of Approval:
March 18, 2004

Keywords: Praziquantel, Ecteinascidin, Isoquinolone, Heterocycle, Tetrahydroisoquinoline

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Dedication

I would like to dedicate this thesis to my wife Yu Chen, for her love and support.
Acknowledgments

I would like to take this opportunity to express my eternal gratitude to my Advisor professor Kyung Woon Jung. As a brilliant organic chemist, he transformed the structures of a lot of compounds; as an inspirational mentor, he also transformed the lives of a lot of students. I am lucky and proud to be one of them. I enjoyed my organic chemistry study and research under Dr. Jung’s firm leadership and nimble guidance.

I would also like to thank all my committee members: Dr. Bill Baker, Dr. Kirpal Bisht, and Dr. Edward Turos for their kind support, critical comments, and valuable suggestions. In addition, I would also want to thank Dr. Yoon, Advait Nagle, David Flanigan, and Young Chun Jung for sharing their valuable knowledge and providing me with encouragement and support during so many ups and downs in my chemistry odyssey. Finally, I would also like to express my appreciation to my fellow graduate students and colleagues Sung Wook Yi, Robert Huigens, Dr. Yoo, and Ki Soo Park for the help and advice they constantly rendered. These invaluable and rewarding experiences will always enrich my life and be etched into my memory.
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Efforts toward the First Enantioselective Total Synthesis of Praziquantel and Synthetic Model Studies on Ecteinascidin 743 by Novel Aromatic C-H Insertion Methodology

Chiliu Chen

ABSTRACT

The thesis is composed of three chapters. The aim of this thesis is to apply the novel dirhodium perfluorobutyrate-catalyzed intramolecular aromatic C-H insertion methodology to the enantioselective total synthesis of praziquantel and synthetic model studies on ecteinascidin 743, which belongs to the important tetrahydroisoquinoline family.

The first introductory chapter deals with the biological significance and previous synthetic methodologies. Our novel methodology is based on dirhodium perfluorobutyrate-catalyzed intramolecular aromatic C-H insertion reaction, which is crucial in the pivotal carbon-carbon bond formation when constructing isoquinolone moiety, which is ubiquitous in numerous natural products of significant biological and pharmacological activities.

The second chapter takes on the first enantioselective total synthesis of praziquantel, an antihelmintic drug. Praziquantel is used worldwide to treat schistosomiasis, which has tremendous impact on the global fight on this disease affecting 150 million people. We believe this is the first asymmetric total synthesis to date, which is distinct from previous racemic syntheses reported. We also shed light on
the mechanistic aspect of this key reaction to rationalize the superb regioselectivity and stereoselectivity achieved.

The third chapter explores the synthetic model studies on ecteinascidin 743, a tetrahydroisoquinolone family natural product with significant antitumor and antimicrobial activities. Several different synthetic routes were attempted, including the $N$-Methyl and the $N$-Boc routes, and the results achieved contributed significantly to our final synthetic plan of the target molecule.
List of Abbreviations and Acronyms

ABSA  \( \text{4-Acetamido benzenesulfonyl azide} \)

Ar  \( \text{aryl} \)

Bn  \( \text{benzyl} \)

BnBr  \( \text{benzyl bromide} \)

Boc  \( \text{t-Butyloxycarbonyl} \)

CDCl \(_3\)  \( \text{deuterated chloroform} \)

CH\(_2\)Cl\(_2\)  \( \text{dichloromethane} \)

CH\(_3\)CN  \( \text{acetonitrile} \)

DBU  \( \text{1, 8-diazabicyclo[5.4.0]undec-7-ene} \)

DMAP  \( \text{4-dimethylaminopyridine} \)

DMF  \( \text{N, N-dimethylformamide} \)

EDCI  \( \text{1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride} \)

EtOAc  \( \text{ethyl acetate} \)

EtOH  \( \text{ethanol} \)

HOBT  \( \text{1-hydroxybenzotriazole hydrate} \)

LiAlH\(_4\)  \( \text{lithium aluminum hydride} \)

Me  \( \text{methyl} \)

MeI  \( \text{iodomethane} \)

MeOH  \( \text{methanol} \)
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>MPMCl</td>
<td>3-methoxybenzyl chloride</td>
</tr>
<tr>
<td>Ms</td>
<td>methanesulfonyl</td>
</tr>
<tr>
<td>NaOH</td>
<td>sodium hydroxide</td>
</tr>
<tr>
<td>Pd/C</td>
<td>palladium on carbon</td>
</tr>
<tr>
<td>pfb</td>
<td>perfluorobutyric acid</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>Rh$_2$(OAc)$_4$</td>
<td>dirhodium acetate</td>
</tr>
<tr>
<td>Rh$_2$(pfb)$_4$</td>
<td>dirhodium perfluorobutyrate</td>
</tr>
<tr>
<td>TBDMS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TEA</td>
<td>triethylamine</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>TFAA</td>
<td>trifluoroacetic anhydride</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
</tbody>
</table>
Chapter One

Introduction

The antitumor antibiotics belonging to the tetrahydroisoquinoline family have been investigated thoroughly over the past 25 years starting with the isolation of naphthyridinomycin in 1974. To date, 55 natural products in this family have been isolated\(^1\). Due to their stereochemically intricate structure, potent antitumor, antimicrobial activities, and enormous potential as promising drug candidates, they have become one of the most sought-after synthetic targets of a number of research groups. Figure 1-01 shows various natural products possessing tetrahydroisoquinoline moiety.

Figure 1-01: Various Natural Products

Although the syntheses of tetrahydroisoquinolines have been known for almost a century, chiral syntheses of tetrahydroisoquinolines have been rarely reported, and still remain a daunting challenge to organic chemists.

The primary pathway employed in the past of synthesizing this family of compounds is via Pictet-Spengler approach and its variants, as shown in Figure 1-02.
One of the most serious drawbacks arising from the intermolecular Pictet-Spengler reaction is its nonstereoselectivity, usually resulting in different diastereomers even under mild conditions. For instance, A1, which possesses one stereogenic center, would be converted into different diastereomers A2 and A3 under the intermolecular Pictet-Spengler approach. Also shown in Figure 1-02, alternatively, E.J.Corey achieved stereoselectivity, converting A4 to a single stereoisomer A5 of tetrahydroisoquinoline via intramolecular Pictet-Spengler approach, but regioselectivity was compromised.

Figure 1-02: Pictet-Spengler Approach

Aromatic C-H insertion has been investigated by numerous research groups with mediocre results. The main hurdle encountered was the formation of side product cycloheptatriene A7, when aromatic C-H insertion was carried out with diazo precursor A6. Formation of cycloheptatriene can be explained by cyclopropanation followed by
ring expansion, as shown in Figure 1-03.

**Figure 1-03: Formation of Cycloheptatriene**

Employing diazo precursors, electrophilic aromatic substitution is another general route to gain access to the heterocyclic compounds. For example, in the presence of nafion-H (an acid), electrophilic aromatic substitution of diazo precursors such as A8 gives rise to the formation of indole A9, along with β-lactam A10.5

**Figure 1-04: Formation of Indole via Electrophilic Aromatic Substitution**

Isoquinolone formation via electrophilic aromatic substitution of diazo precursors such as A11 is also known, as shown in Figure 1-05. However, the harsh conditions employed and concomitant regioisomer formations often pose serious problems.6
The drawbacks of previous methodologies were tackled by our investigation of novel Rh (II) catalyzed formal aromatic C-H insertion methodology and its applications to the first enantioselective synthesis of praziquantel and synthetic model studies on Ecteinascidin 743.
References

1) For a comprehensive account of the chemistry and biology of these compounds, see:
       1999, 121, 8401.
       53, 4295.
       3712.
       2039.


Chapter Two

Efforts toward the First Enantioselective Total Synthesis of Praziquantel

Introduction

Praziquantel is a well-known effective antihelmintic drug, used worldwide in the treatment of schistosomiasis. Current statistics suggest that 150 million people are infected with schistosomiasis, and praziquantel plays a crucial role in curbing this disease.

Although several synthetic strategies have emerged in literature, the results are still a far cry from being ideal, as shown in Figure 2-01. Original synthesis of praziquantel was achieved by the formation of piperazine ring from 1-aminomethyl-tetrahydroisoquinoline ring B2, the main disadvantage of this synthetic strategy was the requirement of a catalytic hydrogenation step with high pressure (ca. 100 atm) to construct the tetrahydroisoquinoline B2 from isoquinoline. Another strategy employed hydroxypiperazinones B3, which were prepared by the partial reduction of piperazine-2, 6-dione, to form an isoquinoline ring system, however, multi-step synthetic sequences or vigorous reaction conditions were required.
Predicated on our investigation of Rh (II) catalyzed intramolecular C-H insertion leading to regioselective and stereoselective formation of $\gamma$-lactams,$^6$ we decided to expand this methodology to the construction of isoquinolones, in which crucial C-C bond formation would involve intramolecular aromatic C-H insertion.
Results and Discussion

Our synthetic strategy of chiral praziquantel took advantage of diazo precursor that can be easily obtained from chiral L-alpha-phenylglycine B4, as shown in figure 2-02. We expected that the electrophilic metallocarbenoid derived from diazo precursor would lead to the intramolecular aromatic C-H insertion product B6 by virtue of being less reactive, due to the elegant installation of α-phenylsulfonyl group which fine-tunes the reactivity of the metallocarbenoid center. In addition, N, O-ketal ring would provide the requisite rigidity to the system so as to prevent the formation of regioisomers. The key reactions in our novel synthesis of chiral praziquantel include: intramolecular aromatic C-H insertion of diazo precursor B5, coupling of secondary amine B7 with 2-(Cyclohexylcarbonylamino) acetic acid, and final intramolecular cyclization.

Figure 2-02: Retrosynthetic Analysis of Chiral Praziquantel
Isoquinolone formation by Intramolecular Aromatic C-H Insertion

We launched our synthesis of praziquantel with chiral L-alpha-phenylglycine. Reduction of L-alpha-phenylglycine $\textbf{B10}$ by LAH in THF afforded L-alpha-phenylglycinol $\textbf{B11}$, followed by ketalization to give N, O-ketal $\textbf{B12}$. N-acylation of secondary amine with $\alpha$-bromoacetyl bromide followed by the treatment with benzenesulfinic acid sodium salt afforded $\alpha$-phenylsulfonylacetamide $\textbf{B13}$. Diazo transfer by $p$-ABSA and DBU yielded $\alpha$-diazo-$\alpha$-phenylsulfonylacetamide $\textbf{B14}$, which underwent intramolecular aromatic C-H insertion smoothly with the assistance of catalyst dirhodium perfluorobutyrate in refluxing dichloromethane to give isoquinolone $\textbf{B15}$ as a single diastereomer, as shown in figure 2-03. The stereochemistry of the newly formed stereogenic center was unequivocally determined by X-ray crystallography.
One of the important issues of this novel methodology is the mechanism of the reaction. In order to rule out the possibility that the reaction proceeds via electrophilic aromatic substitution, reactions were carried out using different protic acids, also the electron-donating 3-OMe group was installed to further enhance the electron density of the aromatic ring. Use of 10 mol% protic acid at higher temperature led to the formation of isoquinolone in small amount, but it was accompanied by considerable product decomposition (entry 1). However, the reaction did not proceed at all in low boiling solvents like dichloromethane (entry 2). Furthermore, the reaction did not go to completion when a smaller amount of catalyst was used (entry 3), as shown in Table 2-01.
Table 2-01: Effect of Protic Acids

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>solvent</th>
<th>time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 mol% pfb</td>
<td>C\textsubscript{6}H\textsubscript{6}</td>
<td>1 h</td>
<td>25%</td>
</tr>
<tr>
<td>2</td>
<td>10 mol% pfb</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>24 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>2 mol% Rh\textsubscript{2}(OAc)\textsubscript{4}</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>0.75 h</td>
<td>68%</td>
</tr>
<tr>
<td>4</td>
<td>2 mol% Rh\textsubscript{2}(OAc)\textsubscript{4}, 5 mol% pfb</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>0.5 h</td>
<td>63%</td>
</tr>
<tr>
<td>5</td>
<td>2 mol% Rh\textsubscript{2}(OAc)\textsubscript{4}, 5 mol% AcOH</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>0.5 h</td>
<td>92%</td>
</tr>
</tbody>
</table>

Based on these results, we postulated that the reaction proceeded via formation of electrophilic rhodium carbenoid B\textbf{19}, which was then attacked by the electron-rich aromatic ring. The phenylsulfonyl group then rearranged itself into a more thermodynamically stable position, so as to make C-H and C-Rh bond syn-periplanar to each other, and hence facilitating hydrogen transfer, as shown in Figure 2-04.
**Figure 2-04: Mechanism of Formal Aromatic C-H Insertion**

![Mechanism of Formal Aromatic C-H Insertion](image)

**Coupling with 2-(Cyclohexylcarbonylamino) Acetic Acid**

Dephenylsulfonylation followed by deketalization of isoquinolone B23 afforded acetate B25. Amido acetate was then completely reduced to give amino alcohol B26. In order to set the stage for the crucial coupling with 2-(cyclohexylcarbonylamino) acetic acid, the hydroxyl group of the amino alcohol has to be selectively protected over the amino group. In the course of our synthesis, we first tried to protect the hydroxyl group with TBDMSCl and imidazole, only a trace amount of desired product was observed. The use of a more reactive silylating agent TBDMS triflate resulted in the protection of both amino and hydroxyl groups. The selective protection problem was circumvented by fine-tuning the reactivity of the silylating agent. Selective protection of the hydroxyl group was achieved by employing TBDMSCl in the presence of TEA to give the protected amino alcohol B27. Finally, the crucial coupling of the protected amino
alcohol B27 with 2-(cyclohexylcarbonylamino) acetic acid was accomplished on treatment with HOBT, EDCI, and TEA, as shown in Figure 2-05.

**Figure 2-05: Coupling with 2-(Cyclohexylcarbonylamino) Acetic Acid**

![Diagram showing the coupling process with 2-(Cyclohexylcarbonylamino) acetic acid]

**Intramolecular Cyclization**

TBDMS deprotection of the coupling product B28 by TBAF afforded alcohol B29, we were poised to explore the final intramolecular cyclization. We considered that two competing factors would come into play to effect the final outcome of the intramolecular cyclization: the tendency to form six-membered ring would be the favorable factor, and the weak nucleophilicity of the amide nitrogen would be the unfavorable factor. We tried to cyclize B29 by using methanesulfonyl chloride and TEA, but it failed to afford the desired intramolecular cyclization product praziquantel, as shown in Figure 2-06. Efforts to clear the final hurdle of cyclization will be continued in
our research group.

**Figure 2-06: Intramolecular Cyclization**
Conclusion

In conclusion, we have developed a novel and efficient methodology for the synthesis of isoquinolones via intramolecular aromatic C-H insertion. The isoquinolone was obtained as a single regio- and diastereomer. This methodology can be applied to construct various chiral isoquinolones, and these isoquinolones can be further functionalized to synthesize a slew of biologically important natural products.
Experimental Section

General Methods

All experiments were performed under nitrogen atmosphere, using glassware dried by oven or flame. All reagents were purchased from ACROS and Aldrich chemical Co. Dichloromethane was distilled over calcium hydride prior to use. Analytical thin-layer chromatography (TLC) was performed on precoated glass-backed 60 Å silica gel (0.25 mm thickness) and visualized with a 254 nm UV light. TLC plates were further visualized with I$_2$ and/or ninhydrin solution (0.4 gm in 100 ml n-butanol + 1 ml acetic acid). All reactions were worked up after the complete consumption of starting materials unless specified otherwise. Flash chromatography was carried out using silica gel 60Å (particle size 200 mesh). Unless otherwise stated, all NMR spectra were recorded on 250 or 360 MHz Bruker spectrometers, using CHCl$_3$ ($\delta_H = 7.26$ ppm) or $\delta_C = 77.00$ ppm) as an internal standard.
Formation of $\alpha$-Diazo-$\alpha$-(phenylsulfonyl)acetamide B14.

Into a solution of 2-benzenesulfonyl-1-(2,2-dimethyl-4-phenyl-oxazolidin-3-yl)ethanone (359 mg, 1.00 mmol) in acetonitrile (5.00 ml, 0.2 M) were added successively ABSA (360 mg, 1.5 mmol, 1.5 eq.) and DBU (0.38 ml, 2.5 mmol., 2.5 eq.) and stirred under nitrogen atmosphere for 1.5 hrs at 0 °C. At the end of the reaction, the solvent was removed under reduced pressure and the residue was dissolved in diethyl ether. The organic layer was successively washed with 1 N NaOH followed by water. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude diazo compound was subjected to flash column chromatography to yield analytically pure diazo compound B14 (300 mg, 78%) as a yellow solid. $^1$H NMR (250 MHz) δ 1.50 (s, 3 H), 1.68 (s, 3 H), 3.67 (t, $J = 8.5$ Hz, 1 H), 4.22 (t, $J = 7.1$ Hz, 1 H), 4.71 (t, $J = 6.2$ Hz, 1 H), 7.40 (m, 10 H). $^{13}$C NMR (62 MHz) δ 24.36, 61.48, 72.12, 74.43, 97.38, 125.31, 127.63, 128.38, 128.81, 129.06, 133.48, 137.95, 141.67, 154.86.
Formation of Isoquinolone B15 via Intramolecular Aromatic C-H Insertion of α-Diazo-α-(phenylsulfonyl)acetamide B14.

Rh₂(pfb)₄ (22 mg, 5 mol%) was added to a solution of α-diazo-α-(phenylsulfonyl)acetamide B14 (0.15 g, 0.41 mmol) in dry dichloromethane (17 mL, C = 0.025 M). The mixture was refluxed for 8 hrs under N₂, cooled to r.t., and concentrated. The residue was chromatographed to give isoquinolone B15 as a white crystal. (144 mg, 90%). ¹H NMR (250 MHz) δ 1.45 (s, 3 H), 1.62 (s, 3 H), 3.74 (ABX, J_AB = 9.2 Hz, J_AX = 8.4 Hz, 1 H), 4.53 (J_ABX, J_AB = 9.2 Hz, J_BX = 6.3 Hz, 1 H), 4.86 (s, 1 H), 4.98 (dd, J₁ = 6.2 Hz, J₂ = 10.1 Hz, 1 H), 6.98 (m, 1 H), 7–7.77 (m, 8 H). ¹³C NMR (62 MHz) δ 23.21, 25.08, 58.16, 68.19, 74.49, 95.73, 123.96, 125.44, 128.32, 129.04, 129.23, 129.69, 130.94, 134.97, 137.11, 157.69.
Formation of Dephenylsulfonated Isoquinolone B24

S.M. B23 was dissolved in THF (C=0.2 M) at 0°C, then 6.0 eq. of activated zinc was added to the solution, followed by the addition of 2.0 eq. of titanium tetrachloride in 1M dichloromethane solution, kept vigorously stirring at 0°C for 30 min, and the ice bath was removed, and kept stirring at room temperature under nitrogen atmosphere for 4 h. At the end of the reaction, a small amount of water was added to the reaction mixture, then extracted three times with dichloromethane, the organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude mixture was subjected to flash column chromatography to give the dephenylsulfonated isoquinolone B24 (95%) as a green solid. $^1$H NMR (250 MHz) $\delta$ 1.48 (s, 3 H), 1.67 (s, 3 H), 3.51 (q, J= 18.3 Hz, 2 H), 3.88 (t, J = 8.7 Hz, 1 H), 4.56 (t, J= 6.4 Hz, 1 H), 4.78 (m, 1 H), 6.92-7.43 (m, 4 H). $^{13}$C NMR (62 MHz) $\delta$ 23.50, 25.40, 39.62, 57.60, 67.60, 77.24, 94.71, 123.12, 126.68, 127.09, 127.85, 132.95, 133.17, 165.50.
Formation of Acetate B25 via Deketalization of the N, O-Ketal Ring

Into S.M. B24, was added hydrobromic acid with acetic acid, kept vigorously stirring at room temperature for 8 h. At the end of the reaction, air-blew most of the hydrobromic acid. Then the brown reaction mixture was kept at 0°C, into which saturated sodium bicarbonate solution was added cautiously, and when the reaction mixture solution turned into weakly basic, extracted with ethyl acetate three times. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude mixture was then subjected to flash column chromatography to give the pure acetate B25 (70%) as a brown solid. $^1$H NMR (250 MHz) δ 2.06 (s, 3 H), 3.55 (m, 2 H), 4.11 (m, 1 H), 4.33 (dd, $J_1$=3.8 Hz, $J_2$=11.1Hz, 1 H), 4.73 (m, 1 H), 6.93-8.05 (m, 4 H). $^{13}$C NMR (62 MHz) δ 20.66, 35.59, 54.91, 67.90, 76.91, 125.98, 126.74, 127.96, 130.07, 131.61, 170.52, 171.63.
Formation of Complete Reduction Product Amino Alcohol B26

Acetate B25 was dissolved in THF (C=0.4 M) at 0°C, and then 4.0 eq. of lithium aluminum hydride was added to the solution, kept vigorously stirring at 0°C for 30 min, and then the ice bath was removed, and kept refluxing for 8h. Let the reaction mixture cool down to room temperature, and then kept at 0°C, small amount of sodium sulfate decahydrate was added to quench the reaction. The resulting reaction mixture was filtered by vacuum filtration, and the solid was washed three times with THF, the organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting mixture was subjected to flash column chromatography to give the amino alcohol B26 (85%) as a light yellow oil. ¹H NMR (250 MHz) δ 2.74-2.79 (m, 2 H), 3.05-3.10 (m, 2 H), 3.59-3.81 (m, 2 H), 4.01-4.05 (m, 1 H), 7.06-7.33 (m, 4 H).
Formation of TBDMS Protected Amino Alcohol B27

Amino alcohol B26 was dissolved in anhydrous dichloromethane, 2.5 eq. of TEA was added, then 1.2 eq. of t-butyl-dimethylchlorosilane and catalytic amount of DMAP was added, and kept vigorously stirring at room temperature for 24 h. At the end of the reaction, a small amount of water was added into the reaction mixture, and extracted with dichloromethane three times. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure, then the crude mixture was subjected to flash column chromatography to give the TBDMS protected amino alcohol B27 (80%) as a light yellow solid. $^1$H NMR (250 MHz) $\delta$ 0.048 (d, J=7.6 Hz, 6 H), 0.88 (s, 9 H), 2.65-2.81 (m, 2 H), 2.88-2.97 (m, 1 H), 3.16-3.20 (m, 1 H), 3.70-3.85 (m, 2 H), 4.03-4.05 (m, 1 H), 7.10-7.56 (m, 4 H).
Formation of the Coupled Product B28 via Coupling Reaction of the TBDMS Protected Amino Alcohol with 2-(Cyclohexylcarbonylamino) Acetic Acid

1.2 eq. of 2-(Cyclohexylcarbonylamino) acetic acid was dissolved in DMF (C=0.2 M), then 1.44 eq. of HOBT was added, followed by addition of 1.44 eq. of TEA, then addition of 1.44 eq. of EDCI, kept vigorously stirring for 1h, finally, the solution of TBDMS protected amino alcohol B27 (dissolved in small amount of DMF) was added to the reaction mixture. The reaction mixture was kept vigorously stirring for 4h. At the end of the reaction, a small amount of water was added, and extracted with ethyl acetate three times, the organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure, then the crude mixture was subjected to flash column chromatography to give the coupling product B28 as a white solid. $^1$H NMR (250 MHz) δ -0.15 (d, J=8.3 Hz, 6 H), -0.03 (d, J=10.6 Hz, 6 H), 0.68 (s, 9 H), 0.80 (s, 9 H), 1.22-2.15 (m, 11 H), 2.85 (s, 2 H), 2.92 (s, 2 H), 3.52-4.38 (m, 5 H), 4.81-4.95 (m, 2 H), 7.06-7.97 (m, 4 H).
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Chapter Three

Synthetic Model Studies on Ecteinascidin 743

Introduction

Ecteinascidin 743 is an extremely potent antitumor agent isolated from a marine tunicate, Ecteinascidia turbinate. 1 The isolation of the ecteinascidins was first reported by Rinehart et al. in 1990. Ecteinascidin 743 is currently undergoing phase II clinical trials and attracting considerable attention due to its remarkable biological activities. The mechanism of action of the ecteinascidins has been studied by several groups. It has been shown that Ecteinascidin 743 has a similar structure to that of saframycin S, indicating that DNA alkylation should be indeed possible. 2 The alkylation takes place in the minor groove, as does alkylation with the saframycins. The alkylated DNA substrate exhibits a bend or widening of the minor groove, presumably due to the C-subunit of the ecteinascidins. The C-subunit, which is perpendicular to the rest of the molecule, makes the ecteinascidins unique from the saframycins, which are fairly flat. It has been postulated that this bend in DNA disrupts DNA-protein binding and may be, in part, the source of the enhanced biological activities of the ecteinascidins. The novelty of its structure, the meager availability from natural sources, and the unique mechanism of action 3 has made Ecteinascidin 743 a very attractive and important synthetic target, as shown in Figure 3-01.
The first total synthesis of Ecteinascidin 743[^4] was accomplished by E. J. Corey in 1996 employing the coupling of two optically active fragments as seen in their saframycin A synthesis. Starting with hexacycle C1, a selective hydroxylation was accomplished using phenylselenic anhydride. Removal of the silyl ether followed by esterification with a diprotected cysteine derivative provided C2. Elimination of the tertiary alcohol under Swern conditions allowed for cyclization of the thiol to form C3. Removal of the Alloc carbamate followed by transamination afforded \( \alpha \)-keto lactone C4. The final three steps to Ecteinascidin 743 were the condensation of the homobenzylic amine C5 on the ketone followed by removal of the MOM group with TFA and finally conversion of the aminonitrile to the carbinolamine using silver nitrate and water, as shown in Figure 3-02.
Carmen Cuevas’ group \(^5\) was able to synthesize Ecteinascidin 743 in a semisynthetic fashion starting from cyanosafracin B \(^6\), which is an antibiotic of bacterial origin, available through fermentation of the bacterial Pseudomonas fluorescens \(^7\). Optimization of the fermentation process has allowed for the synthesis of cyanosafracin B on a kilogram scale, providing a robust, sophisticated, and cheap starting material for the synthesis of Ecteinascidin compounds, as shown in Figure 3-03.
In 2002, Tohru Fukuyama’s group accomplished an enantioselective total synthesis of Ecteinascidin 743. Their synthesis features Ugi’s four-component condensation for a ready access to diketopiperazine C9, and the intramolecular Heck reaction of the cyclic enamide C10 to give tricycle C11, as shown in Figure 3-04.
Figure 3-04: Fukuyama’s Synthesis of Ecteinascidin 743

1) MeOH, reflux (90%)
2) TBAF, THF, r.t. (89%)
3) Ac₂O, pyridine, DMAP, r.t. (93%)
4) TFA, anisole, CH₂Cl₂, r.t.
5) EtOAc, reflux (87% in two steps)

Pd₂(dba)₃ (5mol%)
P(o-tol)₃ (20mol%)
TEA, CH₃CN, reflux (83%)

Ecteinascidin 743
Results and Discussion

Despite some progress made in the total synthesis of ecteinascidin 743, there is still of vast interest to find a more efficient synthesis, and we have felt that a convergent synthetic strategy may become a more practical solution. Efficient synthesis of chiral building blocks is crucial for a convergent synthetic strategy to succeed, and we are ambitious to apply our novel intramolecular aromatic C-H insertion methodology to serve this aim. Ecteinascidin 743 is composed of three tetrahydroisoquinoline moieties, which resemble the three building blocks designed in our synthetic strategy, the three fragments C12, C13, and C14 will be prepared in an asymmetric manner, and coupled in the order of (C12 + C13) + C14 to secure the Ecteinascidin 743 skeleton, as depicted in Figure 3-05.

Figure 3-05: Jung’s Synthetic Strategy of Ecteinascidin 743

One of the strategies we are currently pursuing is the late stage cyclization of
diazo precursor. In order to achieve this goal, we have coupled pyroglutamic acid derivative to phenylglycine methyl ester. Currently, we are investigating various diazo transfer conditions as well as different pyroglutamic acid derivatives to achieve optimum conditions for fused ring system.

The first route attempted in our synthetic model studies on Ecteinascidin 743 was with the N-methyl derivative of pyroglutamic acid, as shown in Figure 3-06.

**Figure 3-06: N-Methyl Derivatives of Pyroglutamic Acid**
Esterification of L-2-pyrrolidone-5-carboxylic acid with benzyl bromide afforded benzyl ester \( \text{C13} \). \( N \)-methylation of pyrrolidone with iodomethane afforded the \( N \)-methylated benzyl ester \( \text{C14} \), hydrogenolysis of the benzyl ester with palladium on carbon afforded the resulting carboxylic acid \( \text{C15} \). Generation of acid chloride in situ, followed by coupling with (S)-(+)\-2-phenylglycine methyl ester hydrochloride, afforded the coupled methyl ester \( \text{C16} \). Selective reduction of the coupled methyl ester with sodium borohydride: lithium chloride (1:1) afforded the alcohol \( \text{C17} \). Then we were poised to do the intramolecular cyclization to install the crucial oxazoline skeleton. Treatment of the alcohol \( \text{C17} \) with methanesulfonyl chloride and TEA, followed by refluxing in sodium hydroxide in ethanol afforded the oxazoline \( \text{C19} \) smoothly. Next three steps were mainly functional group manipulations to install the phenylsulfonyl group to the oxazoline ring nitrogen, so as to set the stage for diazo transfer. \( N \)-Acylation and in situ reduction of the resulting \( N \)-acylium ion with sodium borohydride afforded the reduced oxazoline \( \text{C20} \) with \( N \)-(\( \alpha \)-chloro)-acetyl group at the proper position. The primary chloride \( \text{C20} \) was treated with sodium iodide in acetone, namely, Finkelstein reaction, followed by treatment with benzenesulfinic acid sodium salt, afforded the phenylsulfone \( \text{C22} \). Frustratingly, several diazo transfer conditions failed to obtain the desired diazo transfer product \( \text{C23} \), which was the requisite precursor for our next intramolecular C-H insertion, as shown in Figure 3-07.
Figure 3-07: Failure of Diazo Transfer

Unsuccessful Reaction Conditions Include:

1. p-ABSA, DBU
   CH₃CN, 0°C
2. p-ABSA, TEA
   CH₃CN, 0°C
3. TsN₃, DBU
   CH₃CN, 0°C
4. TsN₃, Pyridine
   CH₃CN, 0°C
5. MsN₃, TEA
   CH₃CN, 0°C

The second route was with the N-Boc derivative of pyroglutamic acid, as shown in Figure 3-08.
Esterification of L-2-pyrrolidone-5-carboxylic acid by thionyl chloride in methanol afforded methyl ester. N-Boc protection of pyrrolidone with di-tert-butyl dicarbonate afforded the N-Boc protected methyl ester C24. Selective reduction of the resulting N-Boc protected amide with sodium borohydride afforded the N-Boc protected amino alcohol C25, conscientious monitoring and stringent control of temperature was crucial in achieving the desired selectively reduced amino alcohol, otherwise, side products may ensue, as shown in Figure 3-09.
After we obtained the N-Boc protected amino alcohol C25, we were ready to do the elimination reaction. Treatment of the amino alcohol C25 with trifluoroacetic anhydride and TEA in dichloromethane afforded the elimination product C26, followed by hydrolysis with sodium hydroxide in methanol gave the resulting carboxylic acid. Coupling of the carboxylic acid with (S)-(+)−2-phenylglycine methyl ester hydrochloride by treatment with HOBt, EDCI, and TEA in dichloromethane afforded the coupled methyl ester C28. Selective reduction of the coupled methyl ester with sodium borohydride: lithium chloride (1:1) afforded the alcohol C29. Then we were poised to do the intramolecular cyclization to install the crucial oxazoline skeleton. Treatment of the alcohol C29 with methanesulfonyl chloride and TEA yielded the methanesulfonate C30, but the resulting intramolecular cyclization failed to give the oxazoline C31 by reluxing.
the methanesulfonate $\text{C30}$ in sodium hydroxide in ethanol.
Conclusion

In conclusion, we have developed a novel and efficient methodology for the construction of isoquinolones via intramolecular aromatic C-H insertion. Our audacious and pioneering research in this field will make huge impact on the ingenious syntheses of various natural products with tetrahydroisoquinoline skeletons, including saframycin, tetrazomine, and ecteinascidin 743, which are considered as possible anticancer drugs. The synthetic model studies on Ecteinascidin 743 helped explore new routes to apply the methodology to the fused ring system and gain insight on how to design a more suitable strategy to accomplish the total synthesis, especially when the intramolecular aromatic C-H insertion would take place in the context of a big, complicated molecule with diabolical disposition of various functional groups. We are dedicated to further refining and applying this novel methodology to the total syntheses of various natural products with tetrahydroisoquinoline skeletons.
Experimental Section

General Methods

All experiments were performed under nitrogen atmosphere, using glassware dried by oven or flame. All reagents were purchased from ACROS and Aldrich chemical Co. Dichloromethane was distilled over calcium hydride prior to use. Analytical thin-layer chromatography (TLC) was performed on precoated glass-backed 60 Å silica gel (0.25 mm thickness) and visualized with a 254 nm UV light. TLC plates were further visualized with I₂ and/or Ninhydrin solution (0.4 gm in 100 ml n-butanol + 1 ml acetic acid). All reactions were worked up after the complete consumption of starting materials unless specified otherwise. Flash chromatography was carried out using silica gel 60Å (particle size 200 mesh). Unless otherwise stated, all NMR spectra were recorded on 250 or 360 MHz Bruker spectrometers, using CHCl₃ (δ_H = 7.26 ppm) or δ_C = 77.00 ppm) as an internal standard.
**Formation of Benzyl-(2S)-1-Pyroglutamate C13**

L-2-pyrrolidone-5-carboxylic acid C12 was dissolved in acetonitrile (C=0.2 M), and 1.1 eq. of potassium carbonate was added, then 1.1 eq. of benzyl bromide was added dropwise, kept vigorously stirring under reflux for 8h. At the end of the reaction, acetonitrile was evaporated under reduced pressure, the resulting mixture was subjected to flash column chromatography to give the benzyl ester C13 (97%). $^1$H NMR (250 MHz) $\delta$ 2.17-2.44 (m, 4 H), 4.21 (dd, $J_1$=5.4 Hz, $J_2$=8.3 Hz, 1 H), 5.13 (s, 2 H), 5.93 (s, 1 H), 7.24 (m, 5 H).
Formation of Benzyl-(2S)-1-Methyl Pyroglutamate C14

Benzyl ester C13 was dissolved in THF (C=0.4 M) at 0°C, 1.2 eq. of sodium hydride was added, then 1.3 eq. of iodomethane was added dropwise, kept vigorously stirring for 2h. At the end of the reaction, THF was evaporated under reduced pressure. Into the resulting reaction mixture was added a small amount of water, and extracted with ethyl acetate three times, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The mixture was subjected to flash column chromatography to give the Benzyl-(2S)-1-Methyl Pyroglutamate C14 (65%). ¹H NMR (250 MHz) δ 2.10-2.33 (m, 4 H), 2.77 (s, 3 H), 4.07 (dd, J₁=5.4 Hz, J₂=8.3 Hz, 1 H), 5.14 (s, 2 H), 7.24 (m, 5 H).
Formation of 1-Methyl-(2S)-Pyroglutamic Acid C15

Benzyl-(2S)-1-Methyl Pyroglutamate C14 was dissolved in Methanol (C=0.4 M), catalytic amount of palladium on carbon was added, then put into hydrogenator and subjected to hydrogenolysis for 12 h. At the end of the reaction, the palladium on carbon was filtered out by vacuum filtration and washed with dichloromethane three times. The organic layer was concentrated under reduced pressure to give the 1-Methyl-(2S) Pyroglutamic acid C15 in quantitative yield. $^1$H NMR (250 MHz) $\delta$ 2.09-2.58 (m, 4 H), 2.88 (s, 3 H), 4.14 (dd, $J_1=1.8$ Hz, $J_2=8.2$ Hz, 1 H).
Formation of the Coupled Product C16 via Coupling Reaction of 1-Methyl-(2S)-Pyroglutamic Acid C15 with (S)-(+)2-Phenylglycine Methyl ester Hydrochloride

The carboxylic acid C15 was dissolved in anhydrous dichloromethane (C=0.2 M), and 1.1 eq. of oxalyl chloride was added, and kept vigorously stirring at room temperature for 8 h to form the acid chloride. 1.2 eq. of (S)-(+)2-phenylglycine methyl ester hydrochloride was dissolved in anhydrous dichloromethane (C=0.4 M), 3.5 eq. of TEA was added, and cooled to 0°C, followed by addition of the acid chloride mixture. The reaction mixture was kept vigorously stirring at 0°C for 4 h. At the end of the reaction, a small amount of water was added, and extracted with dichloromethane three times, the organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure, then the crude mixture was subjected to flash column chromatography to give the coupling product C16 (74%) as a white solid. \(^1\)H NMR (250 MHz) \(\delta \) 1.87-2.52 (m, 4 H), 2.68 (s, 3 H), 3.63 (s, 3 H), 4.04 (m, 1 H), 5.49 (dd, \(J_1=3.1 \) Hz, \(J_2=7.2 \) Hz, 1 H), 7.14-7.80 (m, 5 H).
Formation of the Reduction Product Phenylglycinol C17

Methyl ester C16 was dissolved in THF (C=0.4 M) at 0°C, 3.0 eq. of lithium chloride was added, and the mixture was kept stirring at 0°C for 5 mins, then 3.0 eq. of sodium borohydride was added portionwise, and equal volume of methanol was added dropwise, and the mixture was kept vigorously stirring at 0°C for 5 h. At the end of the reaction, solvents were evaporated under reduced pressure, into the white reaction mixture, a small amount of water was added, and extracted with ethyl acetate three times. The organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the reduced product phenylglycinol C17 (90%) as a white solid.
Formation of Oxazoline C19 via Intramolecular Cyclization

The phenylglycinol C17 was dissolved in anhydrous dichloromethane (C=0.4 M), then cooled to -20°C, and 5.0 eq. of TEA was added, followed by the addition of 2.3 eq. of methanesulfonyl chloride, and kept vigorously stirring for 4 h. At the end of the reaction, a small amount of water was added, and extracted with dichloromethane three times, the organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude mixture was dissolved in ethanol (C=0.4M), and 5.0 eq. of sodium hydroxide was added, then kept refluxing for 30 mins. At the end of the reaction, a small amount of water was added, and extracted with ethyl acetate three times, the organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the oxazoline C19 (quantitative yield for two steps) as a light yellow oil.

$^1$H NMR (250 MHz) δ 1.95-2.33 (m, 4 H), 2.82 (s, 3 H), 4.01-4.14 (m, 1 H), 4.26-4.31 (m, 1 H), 5.15-5.16 (m, 1 H), 7.11-7.30 (m, 5 H).
Formation of N-Iodoacetyl Oxazoline C21 via N-Acylation and Reduction, and Finkelstein Reaction

The oxazoline C19 was dissolved in anhydrous THF (C=0.3 M), then cooled to -78°C, and 1.1 eq. of chloroacetyl chloride was added, kept stirring at -78°C for 3 h, followed by portionwise addition of 3.0 eq. of sodium borohydride at -78°C, then the reaction mixture was slowly warmed up to room temperature, and kept vigorously stirring at room temperature for 45 min. At the end of the reaction, THF was evaporated under reduced pressure, and a small amount of saturated sodium bicarbonate solution was added into the reaction mixture, and extracted with ethyl acetate three times, the organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the reduced N-chloroacetylated oxazoline C20. Then C20 was dissolved in acetone (C=0.3 M), and 5.0 eq. of sodium iodide was added, refluxing for 2 h. At the end of the reaction, the reaction mixture was filtered by vacuum filtration, the organic layer was collected and concentrated under reduced pressure to give N-iodoacetyl oxazoline C21.
Formation of Phenylsulfone C22

The N-iodoacetyl oxazoline C21 was dissolved in DMF (C=0.2 M), and 1.2 eq. of benzene sulfinic acid sodium salt was added, kept vigorously stirring at room temperature for 4 h. At the end of the reaction, a small amount of water was added, and extracted with ethyl acetate three times, the organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude mixture was subjected to flash column chromatography to give the phenylsulfone C22 (80%) as a white solid. $^1$H NMR (250 MHz) $\delta$ 1.90-2.30 (m, 4 H), 2.67 (s, 3 H), 3.72-3.77 (m, 1 H), 3.99-4.04 (m, 2 H), 4.36-4.38 (d, J=5 Hz, 1 H), 4.04-4.34 (m, 1 H), 5.22-5.24 (m, 1 H), 7.19-7.75 (m, 10 H).
Formation of Methyl-(2S)-1-(tert-Butoxycarbonyl) Pyroglutamate C24

2.0 eq. of thionyl chloride was added dropwise to a cooled solution of L-2-pyrrolidone-5-carboxylic acid in methanol (C=0.3 M). The mixture was allowed to warm to room temperature. After vigorously stirring for 2 h, the solution was evaporated and the residue dissolved in dichloromethane, washed with saturated sodium bicarbonate solution, brine, and dried over anhydrous sodium sulfate. Evaporation of the organic layer gave methyl-(S)-pyroglutamate as a crude oil. A solution of this crude ester, 1.2 eq. of di-tert-butyl-dicarbonate, and 0.1 eq. of DMAP in acetonitrile (C=0.6M) was stirred for 1h, and the residue obtained after removal of the solvent was subjected by flash column chromatography to give Methyl-(2S)-1-(tert-Butoxycarbonyl) Pyroglutamate C24 as an oil which solidified under vacuo. $^1$H NMR (250 MHz) $\delta$ 1.37 (s, 9 H), 1.92-2.52 (m, 4 H), 3.67 (s, 3 H), 4.51 (dd, $J_1=2.5$ Hz, $J_2=9.1$ Hz, 1 H).
Formation of Methyl-(2S)-1-(tert-Butoxycarbonyl) Amino Alcohol C25

Methyl-(2S)-1-(tert-Butoxycarbonyl) Pyroglutamate C24 was dissolved in methanol (C=0.2 M), and kept at -10°C, then 10 eq. of sodium borohydride was added, kept stirring at -10°C for 1h. Then the reaction mixture was quenched by saturated sodium bicarbonate solution, and extracted with dichloromethane three times. The organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the Methyl-(2S)-1-(tert-Butoxycarbonyl) Amino Alcohol C25 as a white oil.

Conscientious monitoring and stringent control of temperature was crucial in achieving the desired selectively reduced amino alcohol, otherwise, side products may ensue.
Elimination Product C26 from Methyl-(2S)-1-(tert-Butoxycarbonyl) Amino Alcohol C25

Methyl-(2S)-1-(tert-Butoxycarbonyl) Amino Alcohol C25 was dissolved in dichloromethane (C=0.5 M), 5.0 eq. of TEA was added and kept stirring at -5°C, then 1.2 eq. of trifluoroacetic anhydride was added, kept stirring at -5°C for 2h. Then the reaction mixture was quenched by addition of a small amount of water, and extracted with dichloromethane three times. The organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude reaction mixture was subjected flash column chromatography to give the elimination product C26 as a white oil. $^1$H NMR (250 MHz) δ 1.39 (s, 6 H), 1.44 (s, 3 H), 2.63 (dd, $J_1$=14.6, $J_2$=20.2, 1 H), 2.94-3.10 (m, 1 H), 3.72 (s, 3 H), 4.51-4.65 (m, 1 H), 4.89 (d, $J$=10.2, 1 H), 6.54 (d, $J$=31.7, 1 H).
Formation of Carboxylic Acid C27 by Hydrolysis

Methyl ester C26 was dissolved in methanol (C=0.2 M), and then 1.5 eq. of 1.0 N. aqueous NaOH solution was added, kept stirring at room temperature for 5h. Then the reaction mixture was quenched by slow addition of 2.0 N. HCl, as soon as the reaction mixture turned into weakly acidic, ethyl acetate was poured into the reaction mixture, and extracted with ethyl acetate three times. The organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give carboxylic acid C27 (97%) as a white solid.
Formation of the Coupled Product C28 via Coupling Reaction of the Carboxylic Acid C27 with (S)-(+)−2-phenylglycine methyl ester hydrochloride

The carboxylic acid C27 was dissolved in anhydrous dichloromethane (C=0.4 M) at 0°C, then 1.2 eq. of HOBt was added, followed by addition of 2.4 eq. of TEA, then addition of 1.2 eq. of EDCI, kept vigorously stirring at 0°C for 1h, finally, the solution of (S)-(+)−2-phenylglycine methyl ester hydrochloride (dissolved in small amount of anhydrous dichloromethane) was added to the reaction mixture. The reaction mixture was kept vigorously stirring at 0°C for 4h. At the end of the reaction, a small amount of water was added, and extracted with ethyl acetate three times, the organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure, then the crude mixture was subjected to flash column chromatography to give the coupling product C28 as a white solid. $^1$H NMR (250 MHz) δ 1.45 (s, 9 H), 2.90 (2 H), 3.71 (s, 3 H), 4.60 (1 H), 5.02 (t, J=1.8, 1 H), 5.56 (d, J=7.2, 1 H), 6.48 (1 H), 7.32 (m, 5 H).
Formation of the Reduction Product Phenylglycinol C29

Methyl ester C28 was dissolved in THF (C=0.4 M) at 0°C, 3.0 eq. of lithium chloride was added, kept stirring at 0°C for 5 mins, then 3.0 eq. of sodium borohydride was added portionwise, and equal volume of methanol was added dropwise, kept vigorously stirring at 0°C for 5 h. At the end of the reaction, all solvents were evaporated under reduced pressure, into the white reaction mixture, a small amount of water was added, and extracted with ethyl acetate three times. The organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the reduced product phenylglycinol C29 (90%) as a white solid. $^1$H NMR (250 MHz) $\delta$ 1.48 (s, 6 H), 1.57 (s, 3H), 2.60 (m, 1 H), 3.00 (m, 2 H), 3.89 (s, 2 H), 4.70 (m, 1 H), 5.10 (t, J=6.3, 1 H), 6.48 (1 H), 7.30 (m, 5 H).
Formation of the Methanesulfonate C30

Phenylglycinol C29 was dissolved in dichloromethane (C=0.4 M) at -20°C, and 5.0 eq. of TEA was added, then 2.3 eq. of methanesulfonyl chloride was added dropwise, kept vigorously stirring at -20°C for 4h. At the end of the reaction, a small amount of water was added to quench the reaction mixture, and extracted with dichloromethane three times. The organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the product methanesulfonate C30 (90%). ¹H NMR (250 MHz) δ 1.40 (s, 9 H), 2.72 (m, 1 H), 2.96 (m, 1 H), 3.14 (s, 3 H), 4.07-4.23 (m, 2 H), 4.72-5.26 (m, 3 H), 6.47 (1 H), 7.30 (m, 5 H).
References

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Appendices
Appendix A

Selected $^1$H and $^{13}$C NMR Spectra
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