Chapter 2
Results and Discussion

2.1 Introduction

Plakortide E (85) and plakortone B (87) were first isolated from the Jamaican marine sponge *Plakortis halichondrioides* along with plakortones A, C, D in 1996 by Patil and coworkers (Figs. 2.1, 2.2) [1]. In 1999, plakortone B (87) was also isolated from the Caribbean sponge *Plakortis simplex* along with plakortones C–F by Fattorusso and coworkers [2]. In their continuing program to identify compounds with antifungal properties, Wright and coworkers also isolated a molecule identified as plakortide E (85) from the sponge *Plakortis halichondrioides* in 2002 [3].

Plakortide E (85), \( [\alpha]_{D}^{20} = 63.9 (c = 2.0, \text{CHCl}_3) \), isolated as a low melting solid, was first characterized in 1996 by Patil and coworkers [1]. The molecular formula of plakortide E (85) was determined as C\(_{22}\)H\(_{36}\)O\(_4\) from the LRESIMS 351(M + H)+. The basic skeleton was determined by interpretation of the IR, \(^1\)H NMR (Table 2.1), \(^{13}\)C NMR (Table 2.1), COSY, and HMBC spectra. In the IR spectrum, a sharp and intense absorption at 1,690 cm\(^{-1}\) indicated that the carbonyl was an \(\alpha,\beta\)-unsaturated acid. Treatment of 85 with diazomethane furnished methyl ester 86, confirming the presence of an acid group in 85. The data of methyl ester 86 is summarized in Table 2.2. The NMR spectra indicated that plakortide E (85) contained five methyl groups and two double bonds. The methyl group was at C-8 in the side chain. The coupling constants of the double bond (15.8 Hz) suggested *trans* stereochemistry. Additionally, the NMR data indicated that the remaining oxygen in 85 must be attached via a peroxide functionality in the form of a 1,2-dioxolane. A combination of COSY, and HMBC spectra confirmed that plakortide E (85) contained a *tetra*-substituted *cis*-1,2-dioxolane, whose oxygen atoms were linked to two tertiary C4 and C6 centers. However, only the relative configuration was established. The absolute configuration at C4, C6 and C10 were not revealed in the initial structure elucidation.
In 2002, Wright and coworkers [3] also characterized plakortide E (85), however, the absolute configurations of C4, C6 and C10 were still unknown. The NMR and specific rotation data, depicted in Table 2.3, were nearly identical to those reported by Patil and coworkers. However, a chemical shift difference at C3 was observed in both the $^1$H NMR and $^{13}$C NMR spectra, although both samples were measured in CDCl$_3$ (Tables 2.1, 2.3). The proton and carbon signals were observed at $\delta$ 6.69 (d, $J$ = 15.8 Hz) and 146.9 respectively by Patil and coworkers. While the proton and carbon were observed at $\delta$ 6.93 (d, $J$ = 15 Hz) and 152.07 respectively by Wright and coworkers. The isolation procedures used in both isolations were similar. Wright and coworkers have not given any explanations on the differences of the chemical shift at C3 in the NMR spectra. They thought that some form of tautomerism was occurring, and it was possible that their isolation was of the sodium or other salt [3].

So far, the absolute configuration of plakortide E has not been determined. Based on the stereochemical data of the isolation papers, we can conclude that plakortide E had four possible configurations (Fig. 2.3).

Plakortone B (87), $[\alpha]_{D}^{20} = -9.2$ (c = 0.72, CHCl$_3$), isolated as a colorless oil, was first characterized in 1996 by Patil and coworkers. The molecular formula of plakortone B (87) was determined as C$_{21}$H$_{34}$O$_3$ by 335.2586 (M + H)$^+$. The basic skeleton was established by NMR methods (Table 2.4). NOE difference data provided the relative configuration. Many similarities were observed between the $^1$H NMR spectra of plakortone B (87) and plakortide E (85). However, the absolute configurations of their stereocenters were not revealed in the initial structure elucidation [1].

According to the stereochemical data, there are four possible structures for plakortone B (Fig. 2.4). In 2006, the absolute configuration of plakortone B was established as 87a by total synthesis [4]. Recently, our group has reported the total syntheses and stereochemical assignments of all four isomers of plakortone B [5].

The novel structural features of plakortide E (85) as well as its potential bioactivities have stimulated our considerable interest in the quest for its total synthesis. Our first plan was to synthesize all four possible isomers of plakortide E (Fig. 2.3) and to realize the determination of the absolute configuration of plakortide E. We were also intrigued by the biosynthesis of plakortone B (87). So our second plan was to convert plakortide E to plakortone B, which would support the hypothesis that plakortide E was the precursor of plakortone B in nature.
Table 2.1 The data of plakortide E (85) reported by Patil and coworkers

<table>
<thead>
<tr>
<th>Source</th>
<th>Reference</th>
<th>Assigned structure</th>
</tr>
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<tbody>
<tr>
<td>Natural product [1]</td>
<td>[1]</td>
<td>[1]</td>
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<table>
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<tr>
<th>EIHRMS</th>
<th>m/z [M + H]⁺: 351</th>
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<tr>
<td>[α]D₁₀</td>
<td>[α]D₃₀ = 63.9 (c = 2.0, CHCl₃)</td>
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<tr>
<td>NMR (CDCl₃)</td>
<td>1H (ppm)</td>
</tr>
<tr>
<td>Equipment</td>
<td>Bruker AMX-400 spectrometer</td>
</tr>
</tbody>
</table>

| H-1                     | C-1               | 173.0              |
| H-2                     | 5.98 (1 H, d, 15.8)| C-2                | 123.9 |
| H-3                     | 6.69 (1 H, d, 15.8)| C-3                | 146.9 |
| H-4                     |                   | C-4                | 87.2  |
| H-5                     | 2.53 β (1 H, d, 12.0)| C-5               | 55.8  |
|                         | 2.42 α (1 H, d, 12.0)|                    |
| H-6                     |                   | C-6                | 89.1  |
| H-7                     | 5.12 (1 H, m)     | C-7                | 126.9 |
| H-8                     |                   | C-8                | 136.5 |
| H-9                     | 2.00 (1 H, m)     | C-9                | 46.6  |
|                         | 1.85 (1 H, m)     |                    |       |
| H-10                    | 2.00 (1 H, m)     | C-10               | 42.6  |
| H-11                    | 5.05 (1 H, ddt, 15.2, 8.3, 1.4)| C-11  | 132.8 |
| H-12                    | 5.34 (1 H, dt, 6.3, 15.2)| C-12               | 131.9 |
| H-13                    | 1.98 (2 H, m)     | C-13               | 25.6  |
| H-14                    | 0.93 (3 H, t, 7.4)| C-14               | 14.0  |
| H-15                    | 1.85 (1 H, m)     | C-15               | 32.1  |
|                         | 1.63 (1 H, m)     |                    |       |
| H-16                    | 0.87 (3 H, t, 7.4)| C-16               | 8.8   |
| H-17                    | 1.77 (2 H, m)     | C-17               | 31.0  |
| H-18                    | 0.87 (3 H, t, 7.4)| C-18               | 8.9   |
| H-19                    | 1.61 (3 H, d, 1.0)| C-19               | 17.7  |
| H-20                    | 1.35 (1 H, m)     | C-20               | 27.6  |
|                         | 1.11 (1 H, m)     |                    |       |
| H-21                    | 0.80 (3 H, t, 7.4)| C-21               | 11.6  |

Fig. 2.2 Plakortide E (85) and plakortone B (87)
2.2 Retrosynthesis

Our studies of the total synthesis of plakortide E (85) began as early as 2002. Initially, in consideration of the instability of the cyclic peroxide, we planned to construct the cyclic peroxide ring in the final step. We designed the model substrate 88 to investigate the Feldman reaction (Scheme 2.1). However, to our disappointment, the starting material decomposed, but no desired product 89 was obtained [6]. Assuming that the failure resulted from the steric hindrance in 88, we designed an alternative convergent strategy.

Table 2.2 The data of plakortide E methyl ester (86) reported by Patil and coworkers

<table>
<thead>
<tr>
<th>Source</th>
<th>Natural product [1]</th>
</tr>
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<tbody>
<tr>
<td>Reference</td>
<td>[1]</td>
</tr>
<tr>
<td>Assigned structure</td>
<td></td>
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</tbody>
</table>

EIHRMS  

$m/z$ [M + H]$^+$: calcd for C$_{22}$H$_{37}$O$_4$: 365.2692, found: 365.2681

$[\alpha]_D^{20}$  

$[\alpha]_D^{20} = 75.1 (c = 2.23, \text{CHCl}_3)$

NMR (CDCl$_3$)  

$^1$H (ppm)  

<table>
<thead>
<tr>
<th>Equipment</th>
<th>Bruker AMX-400 spectrometer</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-1</td>
<td>6.07 (1 H, d, 15.8) C-2 119.9</td>
</tr>
<tr>
<td>H-2</td>
<td>6.85 (1 H, d, 15.8) C-3 149.6</td>
</tr>
<tr>
<td>H-3</td>
<td>2.54 $\beta$ (1 H, d, 12.0) C-5 55.9</td>
</tr>
<tr>
<td>H-4</td>
<td>2.44 $\alpha$ (1 H, d, 12.0)</td>
</tr>
<tr>
<td>H-5</td>
<td>5.11 (1 H, q, 1.3) C-7 126.7</td>
</tr>
<tr>
<td>H-6</td>
<td>2.00 (1 H, m); 1.85 (1 H, m) C-9 46.5</td>
</tr>
<tr>
<td>H-7</td>
<td>2.00 (1 H, m) C-10 42.5</td>
</tr>
<tr>
<td>H-8</td>
<td>5.05 (1 H, ddt, 1.5, 8.4, 15.3) C-11 132.7</td>
</tr>
<tr>
<td>H-9</td>
<td>5.34 (1 H, dt, 6.43, 15.3) C-12 131.9</td>
</tr>
<tr>
<td>H-10</td>
<td>1.97 (2 H, m) C-13 25.5</td>
</tr>
<tr>
<td>H-11</td>
<td>0.93 (3 H, t, 7.4) C-14 14.0</td>
</tr>
<tr>
<td>H-12</td>
<td>1.86 (1 H, m); 1.64 (1 H, m) C-15 32.1</td>
</tr>
<tr>
<td>H-13</td>
<td>0.88 (3 H, t, 7.4) C-16 8.8</td>
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<tr>
<td>H-14</td>
<td>1.78 (2 H, m) C-17 30.8</td>
</tr>
<tr>
<td>H-15</td>
<td>0.90 (3 H, t, 7.4) C-18 8.8</td>
</tr>
<tr>
<td>H-16</td>
<td>1.61 (3 H, d, 1.3) C-19 17.7</td>
</tr>
<tr>
<td>H-17</td>
<td>1.35 (1 H, m); 1.10 (1 H, m) C-20 27.6</td>
</tr>
<tr>
<td>H-18</td>
<td>0.80 (3 H, t, 7.4) C-21 11.5</td>
</tr>
<tr>
<td>H-19</td>
<td>3.73 (3 H, s, OCH$_3$) 51.1</td>
</tr>
</tbody>
</table>

2.2 Results and Discussion
2.2 Retrosynthesis

Table 2.3: The data of plakortide E (85) reported by Wright and coworkers

<table>
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<tr>
<th>Source</th>
<th>Natural product [3]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>[3]</td>
</tr>
<tr>
<td>Assigned structure</td>
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Retrosynthetic analysis. According to the convergent synthetic strategy as shown in Scheme 2.2, we envisioned that the assembly of the target molecule 86 can be achieved by coupling the corresponding central core 90 with the side chain 91. Formation of the C8–C9 single bond is realized by a metal-catalyzed $sp^2$–$sp^3$ coupling reaction [7–10]. Realization of the trans double bond, in turn, can be accomplished by a Horner–Wadsworth–Emmons olefination reaction [11–13]. Variations in the structure of central core 90 and the side chain 91 would provide the four possible absolute configurations of plakortide E. In our synthetic strategy,
Fig. 2.3 Four possible isomers of plakortide E

Table 2.4 The data of plakortone B (87) reported by Patil and coworkers

<table>
<thead>
<tr>
<th>Source</th>
<th>Natural product [1]</th>
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<tbody>
<tr>
<td>Reference</td>
<td>[1]</td>
</tr>
<tr>
<td>Assigned structure</td>
<td></td>
</tr>
<tr>
<td>[2]I_D</td>
<td>[2]I_D = -9.2 (c = 0.72, CHCl₃)</td>
</tr>
<tr>
<td>EIHRMS</td>
<td>m/z [M + H]⁺: calcd for C₂₁H₃₅O₃: 335.2586, found: 335.2541</td>
</tr>
<tr>
<td>NMR (CDCl₃) H-1 C-1</td>
<td>175.6</td>
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</table>
lipase-catalyzed kinetic resolution of racemic 1,2-dioxolane would be employed to generate the two enantiomerically pure central cores [14, 15]. The racemic 1,2-dioxolane would be prepared from vinylcyclopropane. When the four possible isomers of plakortide E are obtained, we plan to convert them into the four possible isomers of plakortone B (87), whose total synthesis has been reported by us recently [5]. This conversion will not only provide a biomimetic synthesis towards plakortone B, but will also help to confirm the absolute configuration of plakortide E (Scheme 2.2).

2.3 Synthesis of cis-1,2-Dioxolane

2.3.1 Syntheses of 1,2-Dioxolanes by the Feldman Reaction

In 1986, Feldman developed a convenient method for the synthesis of 1,2-dioxolanes. In this reaction, vinylcyclopropanes react with molecular oxygen via a radical-mediated [3 + 2] addition to form 1,2-dioxolanes (Scheme 2.3). The experimental results support the notion that cis-1,2-dioxolanes should predominate [16–19].

The mechanism of the Feldman reaction is depicted in Scheme 2.4. The free radical PhSe• is produced by using AIBN as an initiator, which reacts with the...
double bond of vinylcyclopropane 95, leading to cyclopropylcarbinyl radical 96. Then cyclopropylcarbinyl radical 96 opens to the homoallylic radical 97, which is trapped by oxygen to generate 5-hexenylperoxy 98. Cyclization of the intermediate 98 leads to 99. Finally, expulsion of PhSe\textperiodcentered radical from peroxyl radical 99.
results in the formation of 1,2-dioxolane 100. The rate-determining step is the irreversible cyclization of 5-hexenylperoxy 98 to peroxyl radical 99 [16–19].

**Our previous research.** Our preliminary synthetic efforts towards plakortide E were recorded in 2007 [20], in which Zhao studied the application of the Feldman reaction to synthesize highly substituted 1,2-dioxolanes. Initially, substrate 101d was prepared and used to investigate the Feldman reaction. Irradiation with a 300 W sunlamp at 0 °C under an atmosphere of oxygen and in the presence of catalytic amounts of Ph$_2$Se$_2$ and AIBN furnished 1,2-dioxolane in 88% yield and as a 1/7 mixture of diastereomers, as determined by $^1$H NMR and HPLC. The major product was determined to have trans configuration based upon nOe studies. A subsequent study applied the same peroxidation to a series of vinyl cyclopropanes. The results are depicted in Table 2.5.

In studies on less substituted vinylcyclopropane substrates, Feldman found that cis-1,2-dioxolanes predominated [16–19]. Weinreb and Feldman [19] utilized ab initio computation methods at the MP2/6-31G*/UHF/6-31G* level to probe the predicted energies between these species (5-hexenylperoxy 98 and peroxyl radical 99 in Scheme 2.4) in order to explain the cis/trans ratio in the product. Their results indicate that a chair-like transition state is always favorable, and an electron-withdrawing group would prefer an axial disposition that leads to a trans-product. On the other hand, an electron-donating group will occupy an equatorial position to give a cis-product (Scheme 2.5).

In the less substituted substrates, both experimental and computational results support the notion that cis-1,2-dioxolanes should predominate [16–19]. However, to our disappointment, during our construction of 3,5-tetrasubstituted-1,2-dioxolanes, we observed that the Feldman reaction predominantly furnished the
trans-stereoisomer when both oxygen atoms were on tertiary carbons (Table 2.5) [20]. Even substrate 92a, which had an electron-rich styrenyl substituent, under Feldman reaction conditions as described above furnished the trans-product (cis/trans = 1:2.8) as the major product. These results were different from the traditional results as reported by Feldman and coworkers.

To explain our experimental results, we reinvestigate the transition states for cyclization of the hexenyl peroxyl radical which were developed by Feldman and coworkers to interpret the stereochemistry of 1,2-dioxolane formation [17]. After the equilibration studies with 1,2-dioxolanes and a trapping experiment with 1,2-dioxolane, Feldman and coworkers had predicted that the cyclization was irreversible and that the stereoselectivity reflected kinetic control. In the cyclization of 5-hexenylperoxy radical 108, there were four transition states, the chair-like

### Table 2.5 Investigations of Feldman reaction

| Entry | Substrate | Yield (%) | cis/trans
<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>101a</td>
<td>Quant</td>
<td>trans</td>
</tr>
<tr>
<td>2</td>
<td>101b</td>
<td>75</td>
<td>1/22</td>
</tr>
<tr>
<td>3</td>
<td>101c</td>
<td>Quant</td>
<td>1/13</td>
</tr>
<tr>
<td>4</td>
<td>101d</td>
<td>88</td>
<td>1/7</td>
</tr>
<tr>
<td>5</td>
<td>92a</td>
<td>82</td>
<td>1/2.8</td>
</tr>
</tbody>
</table>

*a Determined by $^1$H NMR analysis

### Scheme 2.5 Chair-like transition states in Feldman reaction
transition state \textit{108a} featuring a pseudoequatorial substituent \(R^3\), a boat-like transition state \textit{108b} with pseudoaxial \(R^3\), the chair-like transition state \textit{108c} featuring a pseudoaxial substituent \(R^3\) and a boat-like transition state \textit{108d} with pseudoequatorial \(R^3\) (Scheme 2.6). Reaction is believed to proceed through the more stable chair-like transition states \textit{108a} or \textit{108c} to generate the \textit{cis}-product or \textit{trans}-product respectively. When \(R^1 = R^2 = H\), the reaction mainly proceeded through conformer \textit{108a} to furnish the \textit{cis}-1,2-dioxolane as the major product. However, when \(R^1 = R^2 = \text{Et}\), the two Et groups would suffer from a 1,3-diaxial interaction in \textit{108a}. As a result, cyclizations of substrates with \(R^1 = R^2 = R^3 = \text{alkyl}\) proceed mainly via conformer \textit{108c}, leading to the \textit{trans}-1,2-dioxolane as the major product.

We also have studied this issue by employing DFT computational methods (courtesy of Dr. Yu-Xue Li, Shanghai Institute of Organic Chemistry, The Chinese Academy of Science). As expected, UB3LYP/6-31G* level computations indicated that the chair-like transition state going towards tertiary \textit{trans}-peroxide was about 0.2 kcal/mol more stable in energy than those leading to \textit{cis}-products.

Comparing the \textit{cis/trans} ratio of the peroxides in Table 2.5, we found that the substrate 92a gave the best value (\textit{cis/trans} = 1:2.8). We envisioned that \textit{cis/trans} ratio can be improved with a benzyl group. This result might suggest that the aryl group plays an important role in the stereocontrol process. We presumed that a \(\pi-\pi\) stacking interaction might be a crucial factor to control \textit{cis}-selectivity (Fig. 2.5). To address this issue, we planned to reinvestigate the Feldman reaction with a series of divinylcyclopropanes containing a range of arene substituents on the alkenes. It was anticipated that the realization of \textit{cis}-1,2-dioxolane could be accomplished by this strategy.

\textbf{Syntheses of \textit{trans}-divinyl cyclopropanes.} The key intermediate 113 was prepared according to McCoy’s procedure [21–23]. As depicted in Scheme 2.7,
ethyl α-chlorobutyrate (111) and ethyl α-ethylacrylate (112) underwent tandem Michael/alkylation for the generation of diethyl 1,2-diethyl-1,2-cyclopropanedicarboxylate (113). Ethyl α-chlorobutyrate (111) [24–26] was prepared from butyric acid (114) (Scheme 2.8) and ethyl α-ethylacrylate (112) [27] was formed from diethyl 1,2-ethylmalonate (116) (Scheme 2.9).

Our previous studies towards plakortide E showed that the cis-divinyl cyclopropane might undergo Cope rearrangement to furnish cycloheptadiene [20]. Therefore, we resorted to the use of the trans-divinyl cyclopropane as a precursor for our investigation of the Feldman reaction (Scheme 2.10). Reduction of diester 113 gave diol 118 in 93% yield by employing LiAlH₄ [6, 20].

After reduction with LiAlH₄, mono-protection of alcohol group was necessary. Diol 118 was treated with Et₃N and t-BuMe₂SiCl to afford the desired mono-protected product 119 as a colorless oil in 80% yield (Scheme 2.10) [6, 20].
The mono-protected alcohol $\text{119}$ was then subjected to Swern oxidation to generate aldehyde $\text{120}$ as a colorless oil. Subsequently, aldehyde $\text{120}$ was used directly for the Wittig reaction affording vinylcyclopropane $\text{121}$ as a colorless oil in 65% yield (Scheme 2.10) [6, 20].

Then $p$-TsOH mediated desilylation of $\text{121}$ furnished the free hydroxyl intermediate $\text{122}$ as a colorless oil in 98% yield. Then the alcohol was subjected to Swern oxidation as above to furnish aldehyde $\text{123}$ a colorless oil. Subsequently, Wittig reaction was performed, and the desired product divinylcyclopropane $\text{92a}$ was prepared in 70% yield (two steps) (Scheme 2.10) [6, 20].
Starting from the 1,2-diethyl-2-vinyl-cyclopropanecarbaldehyde (123), three other aryl-substituted divinylcyclopropanes were prepared by Wittig reactions in a similar manner (Scheme 2.11) [6, 20].

Syntheses of 1,2-dioxolanes by the Feldman reaction. With the desired substrates in hand, we began our studies on the effect of aryl π–π stacking interaction in the Feldman reaction. The reactions were performed under standard Feldman reaction conditions. All the experimental results are summarized in Table 2.6. However, to our disappointment, we found that there was no significant improvement to the cis/trans ratio when various substrates were used. The best value in the table was cis/trans = 1:2.6, when the substrate 92c was used. However, the major product was still the trans-1,2-dioxolane. The natural product plakortide E [1] was a cis-tetrasubstituted peroxide, so we sought to develop a complementary approach to synthesize the cis-tetrasubstituted 1,2-dioxolanes.

### Table 2.6 Syntheses of 1,2-dioxolanes by Feldman reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Yield (%)</th>
<th>cis/trans&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>1</td>
<td>92a</td>
<td>72</td>
<td>1:3.1</td>
</tr>
<tr>
<td>2</td>
<td>92b</td>
<td>75</td>
<td>1:4</td>
</tr>
<tr>
<td>3</td>
<td>92c</td>
<td>84</td>
<td>1:2.6</td>
</tr>
<tr>
<td>4</td>
<td>92d</td>
<td>62</td>
<td>1:2.5</td>
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</table>

<sup>a</sup> Determined by 1H NMR analysis

2.3.2 Palladium-Catalyzed Approach Towards 1,2-Dioxolanes

Ru-catalyzed oxidation of amides with tert-butyl hydroperoxide to give the corresponding tert-butylidioxy amides has been reported [28]. A Co-mediated peroxidation of alkenes in the presence of oxygen and triethylsilane was also known [29–34]. To the best of our knowledge, only two examples of Pd-catalyzed reaction resulting in peroxide-containing products have been reported [35, 36].
Corey’s method only furnished allylic tert-butylperoxy ethers as the major products (Scheme 2.12) [35]. Woerpel reported a palladium-catalyzed intramolecular cyclization of unsaturated hydroperoxides for the formation six-membered cyclic peroxides [36]. However, yields of this method were reportedly low (30–35%). Furthermore, this method has not been known to afford 1,2-dioxolanes (Scheme 2.13).

Our initial studies involved the use of 92a [20] as a substrate. Thus, under O2 (oxygen balloon), we examined a number of catalysts to identify the optimal catalytic system. Our results are summarized in Table 2.7. As can be seen, Pd(PPh3)4 was found to give the best result. In the absence of the catalyst, the reaction did not take place. In the presence of the CuSO4, or Pd2+ [Pd(OAc)2,
Pd(PCy3)2Cl2 and PdCl2], no 1,2-dioxolane was resulted. In the presence of the Pd(0) catalyst, the desired product was obtained, and the ratio of the cis/trans is 1:1. When Pd(PPh3)4 was used as the catalyst, the yield of the reaction was found to be higher than that of Pd2(dba)3.

For further optimization, we examined the reaction in a variety of solvents. All results are summarized in Table 2.8. In DMSO or MeNO2, there was no reaction. When MeCN was used as the solvent, the reaction gave a higher yield than in other solvents.

In the syntheses of peroxides, H2O2 is a widely used reagent. For further screening of reaction conditions for the oxidation of 92a, aqueous H2O2 (30%) was used instead of oxygen balloon. The reaction was performed at room temperature in the presence of various catalysts with aqueous H2O2 solution in MeCN. The results are shown in Table 2.9. To our delight, in the presence of Pd (0) catalyst, substrate 92a reacted with aqueous H2O2 solution, leading to the desired 1,2-dioxolane. However, the yields were not good. In the presence of 20 mol% Pd(PCy3)2Cl2 and PdCl2], no 1,2-dioxolane was resulted. In the presence of the Pd(0) catalyst, the desired product was obtained, and the ratio of the cis/trans is 1:1. When Pd(PPh3)4 was used as the catalyst, the yield of the reaction was found to be higher than that of Pd2(dba)3.
Pd(PPh₃)₄, the mixture of 1,2-dioxolanes (cis/trans = 1:1.5) was obtained in 26% yield (Table 2.9).

Consideration of the effect of water in the reaction, urea hydrogen peroxide (UHP), a white crystalline solid, was used instead of aqueous H₂O₂. The reaction was performed at room temperature in the presence of Pd(PPh₃)₄ with urea hydrogen peroxide in dry organic solvents. The experimental results are summarized in Table 2.10. In these studies, we observed that the reaction with urea peroxide led to a better result (yield = 33%, cis/trans = 1:1.5) than that with aqueous H₂O₂ solution (yield = 15%, cis/trans = 1:1.5). By increasing the Pd(PPh₃)₄ catalyst loading from 10 mol% to 20 mol%, an isolated yield of 57% was realized. We also screened other solvents (THF and benzene), but it was found that MeCN was the best solvent for this reaction.

Table 2.10  Optimizations for the Pd-catalyzed approach towards 1,2-dioxolane

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>H₂O₂ (equiv)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>cis/trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh₃)₄ (10)</td>
<td>2.0</td>
<td>MeCN</td>
<td>12</td>
<td>33</td>
<td>1:1.5</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh₃)₄ (20)</td>
<td>2.0</td>
<td>MeCN</td>
<td>12</td>
<td>53</td>
<td>1:1.5</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh₃)₄ (20)</td>
<td>2.0</td>
<td>Benzene</td>
<td>36</td>
<td>46</td>
<td>1:1.9</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh₃)₄ (20)</td>
<td>2.0</td>
<td>THF</td>
<td>12</td>
<td>17</td>
<td>1:1.2</td>
</tr>
<tr>
<td>5</td>
<td>Pd(PPh₃)₄ (20)</td>
<td>3.0</td>
<td>MeCN</td>
<td>12</td>
<td>57</td>
<td>1:1.5</td>
</tr>
</tbody>
</table>

a Determined by ¹H NMR analysis

Table 2.11  Palladium-catalyzed approach towards 1,2-dioxolanes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Yield (%)</th>
<th>cis/trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>57</td>
<td>1:1.5</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>70</td>
<td>1:1.4</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>40</td>
<td>1:1.6</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>67</td>
<td>1:1.8</td>
</tr>
<tr>
<td>5</td>
<td>e</td>
<td>NR</td>
<td>–</td>
</tr>
</tbody>
</table>

a Determined by ¹H NMR analysis, b NR No product formed

Pd(PPh₃)₄, the mixture of 1,2-dioxolanes (cis/trans = 1:1.5) was obtained in 26% yield (Table 2.9).

Consideration of the effect of water in the reaction, urea hydrogen peroxide (UHP), a white crystalline solid, was used instead of aqueous H₂O₂. The reaction was performed at room temperature in the presence of Pd(PPh₃)₄ with urea hydrogen peroxide in dry organic solvents. The experimental results are summarized in Table 2.10. In these studies, we observed that the reaction with urea peroxide led to a better result (yield = 33%, cis/trans = 1:1.5) than that with aqueous H₂O₂ solution (yield = 15%, cis/trans = 1:1.5). By increasing the Pd(PPh₃)₄ catalyst loading from 10 mol% to 20 mol%, an isolated yield of 57% was realized. We also screened other solvents (THF and benzene), but it was found that MeCN was the best solvent for this reaction.
The application of this palladium-catalyzed approach towards various 1,2-dioxolanes under the optimized condition is shown in Table 2.11. We have still not been able to obtain exclusively cis-1,2-dioxolanes by this method although the cis/trans ratio of this palladium approach (cis/trans = 1:1.4) is much better than that of the Feldman reaction (cis/trans = 1:2.8) [20]. Further optimization and search for asymmetric versions of this palladium-catalyzed process towards 1,2-dioxolanes are in progress.

An attempt to gain insight into the mechanism of this reaction was carried out. A radical scavenger, 2,6-di-tert-butyl-4-methylphenol (BHT), was used in the reaction between 92a and urea peroxide. Despite the presence of a radical scavenger, the desired product was still obtained in 42% yield. This result implies that the reaction is not expected to proceed through a free radical process. As illustrated in Scheme 2.14a, a mechanism is proposed in light of other palladium-catalyzed reactions involving vinylcyclopropanes [37]. Divinylcyclopropane 92a may react with Pd(0) to generate a π-allylpalladium complex 131b, which can attack the monopalladium(II) dioxide [O₂PdII] [38] to form 132. Ring closure by an intramolecular attack therefore yields 133, which undergoes reductive elimination to yield the 1,2-dioxolane 124a and regenerate the Pd(0) catalyst.

\[ \text{Scheme 2.14a} \quad \text{Proposed mechanism for a palladium-catalyzed approach towards 1,2-dioxolane} \]

2.3.3 Synthesis of cis-1,2-Dioxolane

The mixture of cis/trans 1,2-dioxolanes 124a was subjected to ozonolysis, which on reductive workup with NaBH₄ gave two chromatographically separable diols trans-134 and cis-135. (Scheme 2.14b) [20]. Peroxide cis-135 was isolated as a
colorless solid, whose stereochemistry was confirmed by an X-ray crystallographic analysis (Fig. 2.6). Peroxides *trans*-*134* and *cis*-135 were monoprotected with *t*-BuMe₂SiCl to give *trans*-136 and *cis*-137, respectively.

### 2.4 Studies on the Model Reactions

*cis*-1,2-Dioxolane 137 is the key synthetic precursor towards the total synthesis of plakortide E, while the *trans*-product 136 is useful for model studies. Due to the weak O–O bond dissociation energy (37 ± 1 kcal mol⁻¹) [39], the functionalization of the 1,2-dioxolanes are expectedly difficult. Generally, it is widely believed that peroxides are unstable compounds. Metals and metal ions such as Co and Pd, Sn(II), Fe(II) and Zn(II) are able to function as single- or two electron donors or Lewis acids to decompose peroxides. Strong bases, strong acids and high...
temperature are all detrimental to peroxides [39, 40]. According to these facts, it goes without saying that the studies on the model reactions for the total synthesis are by no means trivial.

2.4.1 Construction of \textit{trans}-Double Bond

In 1958, Horner developed a modified Wittig reaction between aldehydes or ketones $^{138}$ and stabilized phosphonate $^{139}$ (Scheme 2.15) [11–13, 41]. Compared to phosphonium ylides, phosphonate-stabilized carbanions are more nucleophilic and more basic. Wadsworth and Emmons did further studies on this reaction [12]. The stereoselectivity of Horner–Wadsworth–Emmons reaction is usually pretty high, which favors the formation of $E$-alkenes. Another advantage is that the phosphate by-product can be washed away by aqueous solution of $p$H.

Encouraged by the success of the Horner–Wadsworth–Emmons olefination, we next investigated the application of a Wittig olefination for introduction of tri-substituted alkene adjacent to the 1,2-dioxolane. The model reaction is shown in Scheme 2.17. Although two kinds of Wittig reactions have been tried, we failed to obtain the desired product (Table 2.12). In both cases, no obvious product spot

\textbf{Scheme 2.15} Horner–Wadsworth–Emmons reaction

\begin{center}
\begin{tikzpicture}
  \node[anchor=west] at (0,0) {\textbf{Scheme 2.15} Horner–Wadsworth–Emmons reaction};
  \node at (0,0) {\includegraphics[width=\textwidth]{scheme15.png}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 2.16} Construction of \textit{trans}-double bond. \textbf{Reagents and conditions:} (a) Dess–Martin periodinane (1.5 equiv), $\text{CH}_2\text{Cl}_2$; (b) (EtO)$_2$P(O)CH$_2$CO$_2$Et (3.0 equiv), NaH (2.8 equiv), THF, 0 °C, 79% (2 steps)
was observed on TLC, although all starting material was consumed. We presumed that the steric hindrance between the 1,2-dioxolane-containing aldehyde 141 and the side chain 144 [6] or 145 [6] led to the failure of these coupling reactions. When the desired Wittig reaction did not take place, the unstable 1,2-dioxolane-containing aldehyde decomposed under these conditions. For this reason, we abandoned this Wittig reaction approach. Next, we place our focus on the Pd-catalyzed cross-coupling reaction, which has been widely used in carbon–carbon bond-forming reactions.

### 2.4.2 Synthesis of Alkenyl Iodide

In our retrosynthesis of plakortide E, 1,2-dioxolane-containing-alkenyl iodide 90 was an important key precursor. To prepare for the synthesis of the cis-1,2-dioxolane-containing alkenyl iodide 90, we intended to initially model the
synthetic steps on the \textit{trans} isomer, \textbf{146}. As shown in Scheme 2.18, starting from the \textit{trans}-1,2-dioxolane-containing-aldehyde \textbf{141} to prepare the \textit{trans}-1,2-dioxolane-containing-alkenyl iodide \textbf{146}, we need as the first step to prepare the intermediate terminal alkyne \textbf{148}. With terminal alkyne \textbf{148} in hand, subsequent methylation afforded the alkyne \textbf{147}. The conversion of an alkyne to an alkenyl iodide has been reported in the literature \cite{4, 5, 42}.

\textbf{Preparation of terminal alkyne \textbf{148}.} The one-pot conversion of ketones or aldehydes to the corresponding internal or terminal alkynes by using diazophosphonates under basic conditions is called Seyferth–Gilbert homologation (Scheme 2.19). In 1973, Colvin and coworkers reported that aryl ketone \textbf{149} (or aldehyde) reacted with dimethyl (diazomethyl)phosphonate \textbf{150} in the presence of a base to give substituted alkynes \textbf{151} \cite{43, 44}. Dimethyl (diazomethyl)phosphonate \textbf{150} was often called the Seyferth–Gilbert reagent \cite{45}, which was first synthesized by Seyferth. In 1979 Gilbert and coworkers improved the procedure of the reaction, and extended its scope \cite{46, 47}. Ohira and Bestmann made a further modification of this reaction based upon generation of the dimethyl(diazomethyl)phosphonate in situ from dimethyl(1-diazo-2-oxopropyl)phosphonate (\textbf{153}), which was called Ohira–Bestmann reagent (Scheme 2.20) \cite{48, 49}. The Ohira–Bestmann procedure is now widely used in organic syntheses. The mild reaction conditions are tolerant most functional groups and various aldehydes can be homologated in excellent yields.

In the light of the advantages of the Ohira–Bestmann procedure and its wide synthetic applications, we planned to use this reaction to introduce the terminal alkyne to our 1,2-dioxolane-containing substrate. As shown in Scheme 2.21, freshly prepared aldehyde \textbf{141} was subjected to the standard Ohira–Bestmann procedure \cite{48, 49}. To our disappointment, none of the desired terminal alkyne \textbf{148} was obtained, although the TLC showed that all starting material was
consumed. We presumed that the 1,2-dioxolane-containing aldehyde 141 decomposed under the basic conditions due to its instability. Due to the fact that a one-pot conversion of the 1,2-dioxolane-containing aldehyde 141 to terminal alkyne 148 failed, we planned to convert the 1,2-dioxolane-containing aldehyde 141 to the 1,1-dibromoalkene 155, which can be treated with n-BuLi to generate the desired terminal alkyne 148 (Scheme 2.22).

The Corey–Fuchs reaction [50] included two sequential reactions, the formation of the 1,1-dibromoolefin and the formation of the terminal alkyne. Starting from aldehyde 156, and through these two sequential transformations, a terminal alkyne 158 was obtained (Scheme 2.23). The formation of 1,1-dibromoolefins via phosphine-dibromomethane was originally developed by Desai and McKelvie [51].

In consideration of the good functional group tolerance of the Corey–Fuchs reaction, we intended to employ it in our preparation of the terminal alkyne 148. Freshly prepared aldehyde 141 was used to investigate the Corey–Fuchs reaction. The reaction was performed under standard Corey–Fuchs reaction conditions [50].

| Table 2.13 Reaction conditions for the preparation of 1,1-dibromoalkene 155 |
|---|---|---|
| Entry | Reaction conditions | Results |
| 1 | CBr4, Ph3P, CH2Cl2 (Corey–Fuchs reaction) | Decomposed |
| 2 | CBr2HPPh3Br, t-BuOK | 79% (2 steps) |

We presumed that the 1,2-dioxolane-containing aldehyde 141 decomposed under the basic conditions due to its instability. Due to the fact that a one-pot conversion of the 1,2-dioxolane-containing aldehyde 141 to terminal alkyne 148 failed, we planned to convert the 1,2-dioxolane-containing aldehyde 141 to the 1,1-dibromoalkene 155, which can be treated with n-BuLi to generate the desired terminal alkyne 148 (Scheme 2.22).

The Corey–Fuchs reaction [50] included two sequential reactions, the formation of the 1,1-dibromoolefin and the formation of the terminal alkyne. Starting from aldehyde 156, and through these two sequential transformations, a terminal alkyne 158 was obtained (Scheme 2.23). The formation of 1,1-dibromoolefins via phosphine-dibromomethane was originally developed by Desai and McKelvie [51].

In consideration of the good functional group tolerance of the Corey–Fuchs reaction, we intended to employ it in our preparation of the terminal alkyne 148. Freshly prepared aldehyde 141 was used to investigate the Corey–Fuchs reaction. The reaction was performed under standard Corey–Fuchs reaction conditions [50].
However, to our disappointment, we failed to obtain the desired 1,1-dibromoalkene (Table 2.13). Under these reaction conditions, no obvious spot was observed on TLC although all starting material was consumed. We thought that the 1,2-dioxolane-containing aldehyde decomposed during the reaction.

Then we adopted the Rassat’s procedure which has also been widely used in total synthesis [52]. Thus to a slurry of freshly prepared Ph₃P-CHBr₃ (2.5 equiv) in THF at 0°C, t-BuOK (2.4 equiv) was added. The bright yellow slurry was stirred for 15 min and the temperature was allowed to warm to room temperature. Then the solution of the aldehyde (1.0 equiv) in THF was added to the mixture and stirred for 30 min, the reaction was complete as monitored by TLC. To our delight, the desired 1,1-dibromoalkene was prepared in 79% yield starting from the 1,2-dioxolane-containing alcohol (two steps). It was necessary to warm the reaction system after the addition of t-BuOK. If the reaction were kept at 0°C, an inseparable side product was formed along with the 1,1-dibromoalkene. The reaction time for the Wittig salt Ph₃P-CHBr₃ and t-BuOK were also important. It is essential to allow a complete consumption of the base t-BuOK; otherwise, the base would decompose 1,2-dioxolane-containing aldehyde.

Preparation of the alkyne 147. With dibromoalkene in hand, we treated it with n-BuLi (2.2 equiv) at −78°C to provide the terminal alkyne 148 in 95% yield. Then the terminal alkyne 148 was deprotonated with n-BuLi (1.2 equiv) at −78°C, followed by methylation to afford trans-1,2-dioxolane-containing alkyne 147 in 70% yield (Scheme 2.24) [4, 5].

Preparation of the alkenyl iodide 146. In 1970, Wailes and Weigold first prepared zirconocene hydrochloride (Cp₂ZrHCl) by the reduction of Cp₂ZrCl₂ [54], and then Schwartz examined the reactions of Cp₂ZrHCl with a wide range of substrates and developed it to become a useful reagent for organic synthesis (Fig. 2.7) [42, 55]. Zirconocene hydrochloride reacts with alkenes or alkynes to form alkenylzirconium or alkylzirconium compounds and this reaction is called
Schwartz hydrozirconation. Zirconocene hydrochloride (Cp₂ZrHCl) is called the Schwartz reagent. Generally, the addition of the Zr–H proceeds with syn-addition [56].

To prepare the alkenyl iodide 146, we attempted to employ the Schwartz reagent in our transformation. Hydrozirconation of the alkyne 147 should lead to the formation of the alkenylzirconium 160, iodination of which affords the desired alkenyl iodide 146 (Scheme 2.25).

The Schwartz hydrozirconation reaction of the alkyne 147 was performed under standard reaction conditions reported in the literature [42, 55, 57]. To a suspension of Cp₂Zr(H)Cl in THF at 0 °C was added a solution of the alkyne 147 in benzene under nitrogen. The temperature was allowed to warm to room temperature. The reaction was examined by ¹H NMR. Although the reaction mixture was stirred for 24 h, no reaction took place (Table 2.14). Then the reaction was performed at 50 °C, and was monitored by ¹H NMR. To our disappointment, no desired product 160 resulted. However, the starting material was consumed. Decomposition of the starting material made the reaction very messy.

After the failure of the Schwartz hydrozirconation reaction, we sought to employ a milder reaction to prepare the 1,2-dioxolane-containing alkenyl iodide 146. This time, we resorted to the palladium-catalyzed hydrostannylation of alkynes. Compared to other methods, the palladium-catalyzed hydrostannylation offers these advantages: (1) mild reaction conditions; (2) good functional group tolerance; (3) good stereoselectivity (cis-addition) [58, 59]; (4) wide application in total synthesis. It was recently reported that hexane minimized the competitive stannane dimerization in palladium-catalyzed hydrostannylation [60]. In light of these findings, our synthetic route was designed in Scheme 2.26. The palladium-catalyzed hydrostannylation of the alkyne 147 regiospecifically furnished 161. Then subsequent iodination of 161 cleanly led to the 1,2-dioxolane-containing alkenyl iodide 146.

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**Scheme 2.25** Preparation of *trans*-1,2-dioxolane-containing alkenyl iodide 23 by Schwartz hydrozirconation

**Table 2.14** Reaction conditions for Schwartz hydrozirconation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cp₂Zr(H)Cl, benzene, THF, 0 °C to rt</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>Cp₂Zr(H)Cl, benzene, THF, 50 °C</td>
<td>Complicated</td>
</tr>
</tbody>
</table>

---

**Table 2.14** Reaction conditions for Schwartz hydrozirconation

Schwartz hydrozirconation. Zirconocene hydrochloride (Cp₂ZrHCl) is called the Schwartz reagent. Generally, the addition of the Zr–H proceeds with syn-addition [56].

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After the failure of the Schwartz hydrozirconation reaction, we sought to employ a milder reaction to prepare the 1,2-dioxolane-containing alkenyl iodide 146. This time, we resorted to the palladium-catalyzed hydrostannylation of alkynes. Compared to other methods, the palladium-catalyzed hydrostannylation offers these advantages: (1) mild reaction conditions; (2) good functional group tolerance; (3) good stereoselectivity (cis-addition) [58, 59]; (4) wide application in total synthesis. It was recently reported that hexane minimized the competitive stannane dimerization in palladium-catalyzed hydrostannylation [60]. In light of these findings, our synthetic route was designed in Scheme 2.26. The palladium-catalyzed hydrostannylation of the alkyne 147 regiospecifically furnished 161. Then subsequent iodination of 161 cleanly led to the 1,2-dioxolane-containing alkenyl iodide 146.
Employing alkyne 147 as the substrate, we studied the palladium-catalyzed hydrostannylation of 1,2-dioxolane-containing alkyne. To a solution of Pd(PPh₃)₂Cl₂ (10 mol%), n-Bu₃SnH (3.0 equiv), THF, tributyltin hydride was added dropwise at room temperature. The dark brown reaction mixture was stirred for 1 h, and the reaction was monitored by TLC. The starting material alkyne 147 was completely consumed. After flash column chromatography, both 161 and 162 were obtained in 66% yield, and the 161/162 ratio is 1:1. Although we obtained our desired product 161, the regioselectivity was not acceptable. We optimized the reactions by screening several palladium catalysts, ligands and solvents. All the results are summarized in Table 2.15. Gratifyingly, we found the best reaction conditions. In the presence of Pd(PPh₃)₂Cl₂ (10 mol%), alkyne 147 reacted with tributyltin hydride in hexane, and regioselectively resulted in the desired product in 84% yield. With the intermediate 161 in hand, its iodination led to 1,2-dioxolane-containing alkenyl iodide 146 in 86% yield.
2.4.3 Synthesis of the Racemic Side Chain

To continue our basic model study, the racemic side chain needed to be prepared. The route is shown in Scheme 2.28. The synthetic paradigm was step-economical and starting material was commercially available and cheap.

As shown in Scheme 2.28, Julia olefination was used to construct the trans-double bond of the side chain. We first prepared the Julia reagent \(165\) by literature reported methods (Scheme 2.27) [6]. Commercially available \(n\)-propyl bromide \(163\) was allowed to react with 1-phenyl-1H-tetrazole-5-thiol (Hspt) in THF in the presence of NaH furnishing the intermediate thioether \(164\) in 96% yield, which was in turn oxidized to the sulfone \(165\) with \(H_2O_2\) in the presence of a catalytic amounts of \((NH_4)_6Mo_7O_{24} \cdot 4H_2O\) in 92% yield.

We next prepared the aldehyde substrate for the Julia olefination. Commercially available ethyl diethyl malonate \((116)\) was reduced to diol \(166\) in 60% yield by using LiAlH\(_4\). Diol \(166\) was then treated with \(n\)-BuLi and \(t\)-BuMe\(_2\)SiCl at \(-78\) °C to afford the desired mono-protected product \(167\) as a colorless oil in excellent...
yield [61]. The mono-protected alcohol 167 was then subjected to Swern oxidation. After oxidation, a colorless oil of aldehyde 168 was obtained and was directly used for the Julia olefination (Scheme 2.28).

When we used Julia olefination to construct the trans-double bond, we found that the stereoselectivity of the reaction was problematic. We found that the trans/cis ratio was affected by the base. Initially, LDA was used, the trans/cis ratio is 10:1.2 as determined by 1H NMR spectrometry. Then we optimized the reaction by screening bases and solvents. The results are summarized in Table 2.16. When KHMDS was used as a base, the desired 1,2-disubstituted olefin 169 was obtained in 89% yield (two steps). The trans/cis ratio of the 1,2-disubstituted olefin 169 obtained under these reaction conditions was also acceptable (trans/cis = 25:1).

The 1,2-disubstituted alkene 169 underwent p-TsOH mediated desilylation to furnish the free hydroxy intermediate 170 as a colorless oil in 86% yield. Alcohol 170 was converted to (+)-91 in 86% yield with PPh3/I2/imidazole (Scheme 2.28) [4, 5].

2.4.4 Pd-Catalyzed sp²–sp³ Coupling

In studying the evolution of organic chemistry and grasping its essence, one comes quickly to the conclusion that no other type of reaction plays as large a role in shaping this domain of science than carbon–carbon bond-forming reactions.—K. C. Nicolaou [62]

In the last quarter of the 20th century, transition metal-catalyzed cross coupling reactions have been greatly developed. Nowadays, these types of cross coupling reactions have become the most powerful and useful C–C formation reactions in synthetic organic chemistry. Amongst them, the palladium-catalyzed cross coupling reactions are the most visible. It is only natural that Pd-catalyzed coupling has been used as a pivotal reaction in many total syntheses [63, 64].

Palladium-catalyzed cross-coupling reactions in total synthesis have been comprehensively reviewed by Nicolaou and coworkers [65]. Below, I have provided some examples relevant to our total synthesis of plakortide E.
These beautiful applications of palladium-catalyzed cross-coupling reactions in total synthesis have shed light on our own program in the quest for plakortide E.

In 2006, Semmelhack and coworkers reported the synthesis of plakortone B (87) and analogs [4]. The connection of the side chain (S)-91 to the core structure 172 was achieved by a palladium-catalyzed Suzuki reaction (Scheme 2.29).

Recently, starting from D-mannitol (174), our group accomplished the total syntheses of all four possible isomers of plakortone B [5]. And one of these molecules, 87, was found to be identical with the natural plakortone B on the basis of 1H, 13C NMR spectra and specific rotation, demonstrating that absolute configuration of the natural plakortone B is (3S,4S,6R,10R). In our synthesis, a Suzuki reaction was also used to connect the central core 175 and side chain (S)-91 (Scheme 2.30).

In 1977, Negishi and coworkers developed a new carbon–carbon bond formation reaction, which was used to couple organozinc reagents and organic halides [65]. The synthesis of β-carotene demonstrates the utility of this reaction both as a $sp-sp^2$ and $sp^2-sp^2$ coupling method [66]. Generally, diorganozinc species ($R_2Zn$) and organozinc halides ($RZnX$) can be employed in the Negishi reaction. Organozinc halides ($RZnX$), typically prepared either by the direct insertion of zinc (zinc dust) into organic halides or by transmetalation from other
organometallic species, are widely used in organic synthesis [67, 68]. Alkylzinc reagents were used in the cross coupling process, which have greatly expanded the scope of the Negishi reaction beyond standard C(sp2)–C(sp2) couplings. Smith and coworkers reported a gram-scale synthesis of discodermolide (180), which was a clinically relevant microtubule-stabilizing agent. In their total synthesis, the Negishi coupling reaction was beautifully utilized to achieve the coupling of two fragments (Scheme 2.31). This application was a good example of the use of alkylzinc reagents in the process of sp2–sp3 carbon–carbon bond-formation [8, 9].

In this approach, the two fragments 176 and 178 were coupled to form the C14–C15 bond of the target product. Significantly, it was found that 3 equivalents of t-BuLi were needed in the initial lithium–halogen exchange process after the optimization. If the customary 2 equivalents were used, the product was a 1:1 mixture of the iodide starting material 176 and the expected product 179.

To explain such modified Negishi protocol, they speculated that the mixed tert-butyl-alkyl zinc intermediate (177) was in fact the reactive alkyl donor in the coupling process (Scheme 2.31) [8, 9].

Recently, Aggarwal and coworkers reported the total synthesis of (+)-faranal. Remarkably, this synthesis was completed in only six steps from propyne, which was quite step-economical. The key reaction in the total synthesis was the coupling of the two fragments 182 and 181 from Negishi coupling. Zinc bromide was used to generate the alkyl-zinc intermediate from the corresponding organolithium (Scheme 2.32). This application was also an example of sp2–sp3 carbon–carbon bond-formation achieved by Negishi cross-coupling [10].
In 1998, Dussault and coworkers reported their studies on the application of palladium-mediated carbon–carbon bond forming reactions to functionalized peroxides [69]. They found that the peroxides are compatible with a series of Pd-catalyzed cross coupling reactions. In that paper, they used acyclic peroxides in Stille (Scheme 2.33), Heck (Scheme 2.34), and Pd-catalyzed carbonylation reactions of vinyl iodides (Scheme 2.35). These examples demonstrated that peroxides

**Scheme 2.31** Application of the Negishi reaction in the total synthesis of discodermolide

**Scheme 2.32** Application of Negishi reaction in the total synthesis of (+)-faranal

In 1998, Dussault and coworker reported their studies on the application of palladium-mediated carbon–carbon bond forming reactions to functionalized peroxides [69]. They found that the peroxides are compatible with a series of Pd-catalyzed cross coupling reactions. In that paper, they used acyclic peroxides in Stille (Scheme 2.33), Heck (Scheme 2.34), and Pd-catalyzed carbonylation reactions of vinyl iodides (Scheme 2.35). These examples demonstrated that peroxides
are stable to the conditions for a series of palladium-catalyzed carbon–carbon bond formation reactions.

Dussault and coworkers observed that acyclic peroxides were reduced under the conditions of the Sonogashira reaction. However, in the syntheses of polyunsaturated peroxides peroxyacarnoate A (203) and peroxyacarnoate D (204) [70], the Sonogashira reaction was successfully employed for the key coupling reactions (Scheme 2.36). Taken together, these results encouraged us in our planned use of Pd-catalyzed cross coupling reactions in our total synthesis of plakortide E.
In our retrosynthetic analysis of the total synthesis of plakortide E, the coupling of the side chain 91 with the cyclic peroxide containing central core 90 is one of the challenging issues (Scheme 2.37). Side chain 91 is an alkyl iodide, and the centre core is an 1,2-dioxolane-containing alkenyl iodide. So the C7–C8 bond formation is in fact an issue concerning C(sp²)–C(sp³) coupling.

The organozinc reagents mentioned before show only moderate reactivity towards many organic electrophiles. However, they are among the most reactive of nucleophilic species in palladium-catalyzed cross-coupling reactions. This is due to the fact that in contrast to other organometallic reagents, organozinc reagents undergo rapid transmetalation with transition-metal salts, most notably those of palladium [62]. Based on these facts, we thought the Negishi cross-coupling reaction was suitable for application to the peroxide-containing substrate, because the moderate nucleophility of organozinc reagents would decrease their reactivity towards organic peroxides.

Scheme 2.36 Syntheses of polyunsaturated peroxides

Scheme 2.37 The coupling of the side chain 91 and the central core 90

In our retrosynthetic analysis of the total synthesis of plakortide E, the coupling of the side chain 91 with the cyclic peroxide containing central core 90 is one of the challenging issues (Scheme 2.37). Side chain 91 is an alkyl iodide, and the centre core is an 1,2-dioxolane-containing alkenyl iodide. So the C7–C8 bond formation is in fact an issue concerning C(sp²)–C(sp³) coupling.

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We proceeded to test this reaction with a model study. With the side chain (±)-91 and trans-1,2-dioxolane-containing alkenyl iodide 146 in hand, we attempted to couple the two components together. The modified Negishi coupling protocol developed by Smith’s group was demonstrated as an efficient method for C(sp²)–C(sp³) bond formation in their gram-scale synthesis of discodermolide [8, 9]. Inspired by their success, we directly employed the modified Negishi coupling protocol to our model reaction (Scheme 2.38). To a solution of iodide (±)-91 (1.2 equiv) and ZnCl₂ (1.2 equiv) in Et₂O at -78 °C, t-BuLi (3.6 equiv) was added, and was followed by warming the reaction mixture to room temperature. Then alkenyl iodide 146 (1.0 equiv) and Pd(PPh₃)₄ (10 mol%) in THF were added to the reaction mixture. The reaction mixture was stirred at room temperature for 16 h. After work-up and flash column chromatography, a colorless oil was obtained. The ¹H NMR spectrum indicated that a 4:1 mixture of our expected coupling product 206 and an unknown side product was furnished. Unfortunately the side product cannot be removed by column chromatography.

To obtain the pure coupling product 206, we optimized the Negishi cross-coupling reaction. The side chain was easily prepared by reported methods [5, 61]. However, the 1,2-dioxolane-containing alkenyl iodide was not readily available. Due to the above facts, we considered to use an excess of the side chain in order to improve the yield and the purity of the expected coupling product. In accordance with the literature, ZnBr₂ was used instead of ZnCl₂ [10]. The reaction was then performed under the improved conditions (Scheme 1.3). To a solution of iodide (±)-91 (1.0 equiv) and ZnBr₂ (1.3 equiv) in Et₂O, t-BuLi (2.0 equiv) was added at -78 °C. The mixture was stirred at -78 °C for 30 min. Then the temperature was allowed to warm to room temperature and the reaction mixture was stirred for 1 h. Subsequently, alkenyl iodide 146 (0.4 equiv) and Pd(PPh₃)₄ (4 mol%) in THF were added to the above reaction mixture. The reaction mixture was stirred at
room temperature for 16 h (Scheme 2.39). After flash column chromatography, the desired coupling product was obtained in good yield (>80%) as the only product. No side product was found by ¹H NMR spectroscopy.

After we successfully obtained the crossing coupling product 206, we continued to study the total synthesis of plakortide E. To our delight, the successive conversions were achieved smoothly (Scheme 2.40). The crossing coupling product 206 was subjected to a p-TsOH mediated desilylation to give the free hydroxy intermediate 208 in 89% yield [20]. Dess–Martin oxidation of 208 afforded an aldehyde 209, whose Horner–Wadsworth–Emmons olefination with triethyl phosphonoacetate gave 210 in a good yield [11–13]. The coupling constant between H-2 and H-3 of 210 was found to be 15.8 Hz, indicating trans stereochemistry of the C2–C3 disubstituted double bond (Scheme 1.6). Until now, all fundamental reactions related to the total synthesis of plakortide E were well 
studied. The successful completion of this model sequence was very helpful to our total synthesis of plakortide E.

2.5 Synthesis of Chiral Side Chains

In our project, the four possible structures of plakortide E will be synthesized. For this reason, both chiral side chains \((R)-91\) and \((S)-91\) were needed (Fig. 2.8). The syntheses of these two compounds have been reported in the literature (Scheme 2.41) [4, 5, 71–75].

Commercially available l-phenylalanine (211) was reduced by LiAlH₄ to give amino alcohol 212 in good yield, which was converted to \((S)-4\)-benzyl-2-oxazolidinone (213) with potassium dicarbonate/diethyl carbonate [75]. Then the Evans reagent 213 was treated with \(n\)-BuLi/butyryl chloride to furnish imide 214 [74]. The subsequent reaction of 214 with (benzoyloxy)methyl chloride (BOMCl) in the presence of TiCl₄ and Et₃N at 0 °C produced imide 215 as a single stereoisomer in 77% yield. Hydrogenolysis of 215, followed by protection of the resulting alcohol 216 with \(t\)-BuMe₂Si group, quantitatively provided 217 (Scheme 2.41) [73]. Reduction of 217 with LiBH₄ furnished \((S)-167\) in 85% yield [73].

As shown in Scheme 2.41, 7 steps were needed in the synthesis of the chiral intermediate \((S)-167\), starting from the commercial available l-phenylalanine (211). The synthesis of its enantiomer of \((R)-167\) also should involve similar steps. In consideration of a step-economic synthetic strategy, we sought to develop an alternative synthetic route to realize the chiral side chain \((R)-91\) and \((S)-91\) (Scheme 2.42). In our model studies for the synthesis of the racemic side chain, the racemic-167 as the intermediate was easily prepared in only two steps from commercially available ethyl diethyl malonate (116). The lipase catalyzed kinetic resolution of racemic-167 was employed in the total synthesis of rutamycin B and oligomycin C, and showed excellent enantiomeric excess [61]. We envisioned to use this method to prepare the optically pure \((S)-167\) and \((R)-167\) in only one step. If we employed the synthetic route described in Scheme 2.41, there were totally 14 steps required to prepare \((S)-167\) and \((R)-167\). According to the literature, the kinetic resolution of racemic 167 was performed. To a solution of racemic 167 in pentane, the lipase extract and vinyl acetate were added. The reaction mixture was stirred vigorously for 24 h. Then the reaction mixture was filtered to remove the lipase catalyst. Purification by column chromatography furnished acetate \((R)-218\) in 47% yield and alcohol \((S)-167\) in 46% yield. On the other hand, hydrolysis of acetate \((R)-218\) gave the enantiomeric alcohol \((R)-167\) (Scheme 2.42). A comparison of the specific rotation with literature values is shown in Table 2.17 [76, 77].

We also assessed the enantiomeric purity of \((S)-167\) and \((R)-167\) by analyses of the \(^1\text{H}\) NMR and \(^{13}\text{C}\) NMR spectra of the diastereomeric derivative 220. Our synthetic chiral compound \((R)-167\) reacted with optically pure \(N\)-Boc protected l-phenylalanine (219) to afford the diastereomeric derivative 220 [78], which was
analyzed by the $^1$H NMR and $^{13}$C NMR spectroscopy (Scheme 2.43). The NMR spectra indicated that compound 220 was very pure, with virtually no trace of the diastereoisomer (dr $\geq 95\%$).

After the enantiomerically pure (R)-167 and (S)-167 were obtained, we proceeded to continue the syntheses of enantiomerically pure side chains of plakortide E. Since all related reactions have been well studied in model studies, we found it straightforward to convert the desired enantiomerically pure side chains (R)-91 and (S)-91. The synthetic route is shown in Scheme 2.44. The enantiomerically pure alcohol (R)-167 was first subjected to Swern oxidation. After oxidation, a colorless oil of aldehyde 221a was generated and was used immediately in the Julia olefination. When KHMDS was used as the base, the desired 1,2-disubstituted olefin 222a was obtained in 89% yield (two steps) [4, 5]. From 1,2-disubstituted olefin 222a, $p$-TsOH mediated desilylation helped to remove the $t$-BuMe$_2$Si group to

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**Scheme 2.41** Synthesis of side enantiomerically pure side chain

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**Fig. 2.8** Enantiomerically pure side chains

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give the free hydroxy intermediate 223a as a colorless oil in 86% yield. Alcohol 223a was converted with PPh₃/I₂/imidazole to iodide (R)-91 in 86% yield. In a similar manner, enantiomerically pure side chain (S)-91 was also synthesized [4, 5].

### 2.6 Syntheses of Enantiomerically Pure Dioxolane Cores

**Syntheses of enantiomerically pure central cores via chemical resolution.** Chemical resolution is an established method for producing optically pure compound as single enantiomers. A racemic compound is reacted with an optically
pure reagent to form a pair of diastereomers, which can be separated by conventional techniques, such as column chromatography. This method was first introduced by Louis Pasteur in 1853, who successfully resolved racemic tartaric acid with optically active (+)-cinchotoxine.

Scheme 2.43 Formation of the diastereomeric derivative 220

Scheme 2.44 Syntheses of enantiomerically pure side chains. **Reagents and conditions:** (a) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$, −78 °C; (b) KHMDS (solid), Julia reagent, THF, −78 °C to rt, 89% (2 steps); (c) p-TsOH, CH$_2$Cl$_2$/CH$_3$OH, 86%; (d) PPh$_3$, imidazole, I$_2$, CH$_2$Cl$_2$, 0 °C to rt, 86%

pure reagent to form a pair of diastereomers, which can be separated by conventional techniques, such as column chromatography. This method was first introduced by Louis Pasteur in 1853, who successfully resolved racemic tartaric acid with optically active (+)-cinchotoxine.

Scheme 2.45 illustrates the planned resolution. To prepare the optically pure cyclic peroxide, we planned to start from cis-137. Thus, oxidation of the aldehyde 224 leads to the acid 225, which is allowed to react with the chiral amine 226 to furnish a pair of diastereomers 227 and 228. Then the diastereomers are separated by column chromatography.

To our disappointment, oxidation of aldehyde 224 with NaClO$_2$ did not successfully furnish the corresponding acid 225; instead, the aldehyde decomposed. TLC indicated that the reaction was very complicated. On the other hand, attempts
to oxidize aldehyde 224 with PDC in DMF also did not lead to the desired acid 225 [79]. The results are summarized in Table 2.18.

One reason for these failures was presumably due to the sensitivity of the \( t\)-BuMe\(_2\)Si group. We therefore designed an alternate route replacing the \( t\)-BuMe\(_2\)Si protecting group with a Bn group. Another route of chemical resolution was therefore designed (Scheme 2.46). Thus, racemic \( cis\)-1,2-dioxolane alcohol 137 is protected with Bn group to give 229, whose \( t\)-BuMe\(_2\)Si group is removed to afford the free alcohol 230. Oxidation of the racemic \( cis\)-1,2-dioxolane alcohol 230 leads to the acid 231, which reacts with enantiomerically pure amine 226 to furnish the diastereomers 231 and 232. Then the diastereomers are separated by column chromatography.

However, the protection of the racemic \( cis\)-1,2-dioxolane alcohol 137 with benzyl bromide is problematic. The reaction conditions are depicted in Table 2.19 [80–82]. In all cases, TLC indicated that no expected product was produced. However, the starting material was consumed. The racemic \( cis\)-1,2-dioxolane alcohol 137 was found to decompose easily under these reaction conditions. For this reason, we had to abandon this chemical resolution route.

Due to the aforementioned failure, we had to seek other milder reactions to accomplish the resolution of racemic \( cis\)-1,2-dioxolane alcohol 137. Finally,
we found the racemic cis-1,2-dioxolane alcohol 137 reacted with N-Boc protected L-phenylalanine (219) smoothly in the presence of DMAP/DCC to furnish the diastereomers 234 and 235 (Scheme 2.47) [78]. However, their diastereomers could not be separated by column chromatography. In principle, diastereomers 234 and 235 could be converted to other derivatives that might be separable. However, this approach is not step-economical for our total synthesis of plakortide E. We therefore moved onto enzymatic resolution of the 1,2-dioxolane core.

**Syntheses of enantiomerically pure central cores by lipase-catalyzed kinetic resolution.** Enzymes are proteins that catalyze a vast number of chemical reactions [14, 15, 83, 84]. The history of enzyme is very long, which can go back to thousands of years to ancient Egypt [14, 15]. Over the last few years, more and more organic chemists have recognized the potential of biocatalysis as a viable and popular technique in organic synthesis. Compared to other catalysts, the...
advantages of enzymes are quite obvious. It is known that reactions catalyzed by enzymes are more selective and efficiently performed.

There has been a dramatic increase in the number of publications in the field of lipase-catalyzed reactions. Lipases are ubiquitous water-soluble enzymes that catalyze the hydrolysis of ester chemical bonds and can be found in animals, plants, fungi and bacteria [14, 15, 85–88]. A computer-generated image of a type of pancreatic lipase (PLRP2) from the guinea pig is showed in Fig. 2.9. Traditionally, biocatalysis are performed in aqueous medium. However, water is a poor solvent for organic chemistry, since most organic compounds are very sparingly soluble and are sometimes unstable in aqueous solutions. Side reactions such as hydrolysis, racemization, polymerization and decomposition often take place easily in water medium. As a result, chemists have developed procedures for the use of enzymes in organic solvents. Now, enzymatic catalysis in non-aqueous media has significantly benefited the chemistry of lipase catalysis [89, 90].

Scheme 2.47  Formation of diastereomeric derivatives of racemic cis-1,2-dioxolane alcohol

Fig. 2.9  A computer-generated image of a type of pancreatic lipase (PLRP2) from the guinea pig
Lipases as organocatalysts are widely used in three main types of asymmetric transformations [91]. They are (a) kinetic resolution of racemic carboxylic acids or alcohols, (b) transformations of meso dicarboxylic acids or meso diols and (c) transformations of prochiral dicarboxylic acid and diol derivatives. In kinetic resolutions, theoretical yields are limited to 50%. Through enantiotopic group differentiation of meso dicarboxylic acids or meso diols, yields of up to 100% are possible [92]. Some typical reactions catalyzed by lipases are depicted in Scheme 2.48.

According to IUPAC recommendation, kinetic resolution (KR) is defined as the achievement of partial or complete resolution by virtue of unequal rates of reaction of the enantiomers in a racemate with a chiral agent (reagent, catalyst, solvent, etc.) [92].

The enzyme catalyzed reactions and the lipase-catalyzed kinetic resolutions have been reviewed [14, 15]. The following section describes some selected examples of lipase-catalyzed resolutions.

In 1997, an efficient method [93, 94] to prepare enantiomerically pure (S)-(+)\textsuperscript{236} and (R)-(+)\textsuperscript{237} by a lipase-catalyzed kinetic resolution was reported by Sakai. Their reactions were carried out preferentially at \textdegree{}40 °C (Scheme 2.49). Recently, in their continuing program, porous ceramic (Toyonite)-immobilized lipase (PSCII) was used in the resolution of (±)-\textsuperscript{238} at low temperature, giving the
synthetically useful (2R, 3S)-238 and its acetate (2S, 3R)-239 with (2S)-selectivity ($E = 55$ at $-40 \, ^\circ\text{C}$), while a similar reaction of (±)-240 gave (2S, 3S)-240 and its acetate (2R, 3R)-241 with (2R)-selectivity ($E = 73$ at $-20 \, ^\circ\text{C}$) (Scheme 2.49).

Two special points in this example are intriguing and are worthy of mentioning. First, substrates (±)-238 and (±)-240 belong to an interesting class of primary aziridine alcohols, which feature two stereogenic centers at the β- and γ-carbons. Before this report, there were few examples of the lipase-catalyzed reaction for such 2-aziridinemethanols. Second, the substrates without N-protection were directly used in the reactions. These outcomes inspired us to use the lipase-catalyzed resolution to realize the enantiomerically pure cis-1,2-dioxolane containing alcohols, which also feature two stereogenic centers [93, 94].

Boron compounds are useful as potential enzyme inhibitors. Recently, a highly enantioselective lipase-catalyzed kinetic resolution of boron-containing alcohols was reported. It was found that aromatic, allylic, and aliphatic secondary alcohols containing a boronate ester or boronic acid group (viz. 242) were resolved by lipase from Candida antarctica (CALB). Excellent $E$ values ($E > 200$) and high enantiomeric excesses ($>99\%$) of 243 and 244 were obtained (Scheme 2.50) [95]. This example extends the scope of the lipase-catalyzed kinetic resolutions.
With the desired mono-protected alcohol (±)-cis-137 in hand, the lipase-catalyzed kinetic resolution of cis-1,2-dioxolane-containing alcohol was investigated [14, 15, 61]. Results of these studies are summarized in Table 2.20. Lipase PS from Burkholderia cepaci was found to give the best kinetic resolution outcome. We observed that prolongation of the reaction time to 29 h provided the optically pure alcohol, which showed excellent enantiomeric excess (99% ee). When the reaction was quenched after 3 h, the optically pure ester was obtained (94% ee). We were able to secure the optically pure ester in excellent enantiomeric excess (99% ee) by repeating the resolution on partially resolved material.

2.7 Total Synthesis of Four Possible Structures of Plakortide E Methyl Ester

With the enantiomerically pure 1,2-dioxolane-containing alcohol cis-137 and ester cis-245, enantiomerically pure side chain (R)-91 and (S)-91 in hand, we assembled the four possible plakortide E methyl esters structures using the chemistry worked out in our model sequences. The routes are illustrated in Scheme 2.51.

Preparation of enantiomerically pure cis-1,2-dioxolane-containing alkenyl iodide 246a and 246b. As shown in Scheme 2.52, oxidation of 137a with Dess–Martin periodinane (DMP) produced a 1,2-dioxolane-containing aldehyde. Thus, the 1,2-dioxolane-containing aldehyde was treated with freshly prepared CHBr₂PPh₃Brand t-BuOK, giving dibromoalkene 247a in good yield with
Scheme 2.51  Total synthesis of four possible structures of Plakortide E methyl ester
excellent reproducibility [52]. Preparation of terminal alkyne 248a was subsequently achieved by treatment of 247a with n-BuLi, followed by methylation to provide 249a [5]. In the presence of a catalytic amount of PdCl\(_2\)(PPh\(_3\))\(_2\), 249a underwent regiospecific hydrostannylation to furnish 250a in 84% yield. Subsequent iodination of 250a led to the formation of the key alkenyl iodide 246a. On the other hand, hydrolysis of 245 gave the enantiomeric 137b in a good yield. In a similar manner, optically pure 246b was also synthesized (Scheme 2.52).

Because all the related reactions had been well executed in the model studies, the syntheses of 246a and 246b were achieved smoothly.

**Scheme 2.52** Syntheses of enantiomerically pure 246a and 246b. Reagents and conditions:
(a) Dess–Martin periodinane (1.5 equiv), CH\(_2\)Cl\(_2\); (b) CHBr\(_2\)P\(_2\)Ph\(_3\)Br\(^-\) (2.5 equiv), t-BuOK (2.4 equiv), THF, rt, 79% (2 steps); (c) n-BuLi (2.2 equiv), THF, −78 °C, 0.5 h, 95%; (d) n-BuLi (1.2 equiv), MeOTf (1.5 equiv), THF, −78 °C, 1 h, 70%; (e) Pd(PPh\(_3\))\(_2\)Cl\(_2\) (10 mol%), n-Bu\(_3\)SnH (3.0 equiv), Hexane, 1 h, 84%; (f) I\(_2\) (1.0 equiv), CH\(_2\)Cl\(_2\), 0 °C, 86%; (g) K\(_2\)CO\(_3\) (1.0 equiv), MeOH, 94%

**Total synthesis of four possible isomers of plakortide E methyl ester.** With the central core (+)-246a and side chain (R)-91 in hand, the Negishi cross coupling reaction was carried out to join the two partners together [10], from which the desired molecule 251a was generated as the only product. Subsequent p-TsOH mediated desilylation of the t-BuMe\(_2\)Si group furnished the free hydroxy intermediate 252a in 89% yield [20]. Dess–Martin oxidation of 252a afforded an
aldehyde, whose Horner–Wadsworth–Emmons olefination with trimethyl phosphonoacetate gave 86a in a good yield [11–13]. The coupling constant between H-2 and H-3 of 86a was found to be 15.8 Hz, indicating the trans stereochemistry of the C2–C3 disubstituted double bond (Scheme 2.53).

With the two enantiomerically pure central cores (246a and 246b) and two side chains (R)-91 and (S)-91 available, the other three possible isomers of plakortide E methyl ester were synthesized through similar sequences. All reactions proceeded smoothly to give the other three isomers in good yields (Scheme 2.54).

All four possible isomers of plakortide E methyl ester were synthesized so that a comparison of their NMR spectral data with those of the natural plakortide E
methyl ester could be made [1]. All $^1$H and $^{13}$C NMR spectra and specific rotation data are included in the experimental section, with the most crucial data being summarized in Tables 2.21 and 2.22. As can be seen, the four synthetic samples can be divided into two pairs of enantiomers ($86a$ and $86d$, $86b$ and $86c$). Although the differences in their $^1$H NMR spectra are generally very small, there are considerable differences in the chemical shifts of H-5, H-7 and H-19. While the $^1$H NMR spectra of the synthetic molecules $86a$ and $86d$ show good agreement with those of the natural compound, the $^1$H NMR spectra of compounds $86b$ and $86c$ exhibit significant differences. It is therefore clear that $86b$ and $86c$ are not related to the natural product. Because the specific rotation $[\alpha]_{D}^{20}$ of the natural plakortide E methyl ester ($[\alpha]_{D}^{20} = +75.1, c = 2.23$ in CHCl$_3$) [1] was found to be in positive value, the value of $86a$ is negative ($[\alpha]_{D}^{20} = -86, c = 0.28$ in CHCl$_3$), indicating that this enantiomer can also be ruled out. It was found therefore that only the $^1$H NMR spectrum and specific rotation ($[\alpha]_{D}^{20} = +87.1, c = 0.39$ in CHCl$_3$) of $86d$ fit closely with those of the natural plakortide E methyl ester. These results confirm that $86d$ possesses an identical structure to the natural plakortide E methyl ester.

<table>
<thead>
<tr>
<th>H5</th>
<th>H7</th>
<th>H19</th>
<th>$[\alpha]_{D}^{20}$</th>
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<tbody>
<tr>
<td>2.54 (11.9)</td>
<td>5.11</td>
<td>1.61</td>
<td>−86.0</td>
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<tr>
<td>2.44 (11.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.58 (11.8)</td>
<td>5.15</td>
<td>1.59</td>
<td>−74.8</td>
</tr>
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<td>5.15</td>
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<tr>
<td>2.54 (11.9)</td>
<td>5.11 (1.3)$^a$</td>
<td>1.61 (1.3)$^a$</td>
<td>+87.0</td>
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<tr>
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<tr>
<td>2.54 (12.0)</td>
<td>5.11 (1.3)</td>
<td>1.61 (1.3)</td>
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<tr>
<td>2.44 (12.0)</td>
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$^a$ Coupling constants were measured by 2D $J$-resolved NMR experiment on an advance Bruker 600M spectrometer

<table>
<thead>
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<th>C-1</th>
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<td>136.6</td>
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<td>Plakortide E methyl ester</td>
<td>166.9</td>
<td>119.9</td>
<td>149.6</td>
<td>55.9</td>
<td>126.7</td>
<td>136.4</td>
<td>132.7</td>
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</table>
Over the past few years, the intramolecular Michael addition has become one of the most efficient and simple approaches to the synthesis of furanofuran bicyclic lactone skeleton, which has been widely applied to the total synthesis of natural products containing furanofuran bicyclic lactone skeleton. For example, Shing and coworkers [96] reported the total synthesis of (+)-goniofufurone through an intramolecular Michael addition reaction (Scheme 2.55). Thus, treatment of the butenolide with a catalytic amount of DBU in THF provided the desired lactone in 74% yield.

Our group has used intramolecular Michael addition to prepare the dioxaspiro framework in the syntheses of natural products, including the total synthesis of sphydrofuran and secosyrin (Scheme 2.56) [97].

### 2.8 Biomimetic Synthesis of Plakortone B and Determination of the Absolute Configuration of Plakortide E

Over the past few years, the intramolecular Michael addition has become one of the most efficient and simple approaches to the synthesis of furanofuran bicyclic lactone skeleton, which has been widely applied to the total synthesis of natural products containing furanofuran bicyclic lactone skeleton. For example, Shing and coworkers [96] reported the total synthesis of (+)-goniofufurone through an intramolecular Michael addition reaction (Scheme 2.55). Thus, treatment of the butenolide with a catalytic amount of DBU in THF provided the desired lactone 254 in 74% yield.

Our group has used intramolecular Michael addition to prepare the dioxaspiro framework in the syntheses of natural products, including the total synthesis of sphydrofuran and secosyrin (Scheme 2.56) [97].
Peng also applied the same protocol to realize the total syntheses of natural products pallavicinin (264) and neopallavicinin (265) (Scheme 2.57). Treatment of the butenolide mixture 261 with DBU in toluene provided a 4:1 mixture of 262 and 263 [98, 99].

Recently, our group has reported the total syntheses and configuration assignments of all four isomers of plakortone B. The synthesis of the furanofuran bicyclic lactone skeleton was achieved through a stereoselective intramolecular Michael addition (Scheme 2.58).

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conjugate addition of an alcohol to an unsaturated lactone; the transformation is chemoselective for one alcohol in the triol substrate (Scheme 2.58) [5].

In consideration that plakortone B (87a) was isolated from the same marine sponge together with plakortide E (85) [1], we reasoned that plakortide E methyl ester 86d could be converted to plakortone B (87a). In this way, the determination of the absolute configuration of plakortide E methyl ester (86d) would be achieved, and this conversion would also provide a concise biomimetic synthesis pathway to plakortone B (87a). To begin with, cleavage of the O–O bond of plakortide E methyl ester (86d) with zinc in acetic acid provided 1,3-diol 268 in an excellent yield [100]. With the 1,3-diol 268 in hand, our next objective was to

Scheme 2.59  Biomimetic synthesis of plakortone B. Reagents and conditions: (a) Zn (50 equiv), AcOH/CH2Cl2 (1:2), 0 °C to rt, 2 h, 99%; (b) DBU (0.2 equiv), toluene, reflux, overnight, 90%

Scheme 2.60  Syntheses of the other three isomers of plakortone B

 conjugate addition of an alcohol to an unsaturated lactone; the transformation is chemoselective for one alcohol in the triol substrate (Scheme 2.58) [5].

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convert it to the corresponding isomer of plakortone B. Encouraged by our recent success in the preparation of various tetrahydrofurofuranone frameworks towards the syntheses of naturally occurring molecules, an intramolecular Michael addition was employed to achieve this conversion. Thus, the 1,3-diol \( \text{268} \) was subjected to an intramolecular oxa-Michael addition/lactonization cascade reaction. To our delight, our target \( \text{87a} \) was afforded exclusively in 90% yield (Scheme 2.59) [98, 99, 101].

The other three possible isomers of plakortone B were prepared in a similar manner from the three corresponding isomers of plakortide E methyl ester, as can be seen in Scheme 2.60. A comparison of the NMR spectra and the specific rotations of the four synthetic isomers and the reported data of plakortone B (\( \text{87a} \)) and its isomers [5] confirms the absolute configurations of \( \text{86a}, \text{86b}, \text{86c} \) and \( \text{86d} \).
to be (4R,6S,10S), (4R,6S,10R), (4S,6R,10S) and (4S,6R,10R). All absolute configurations of plakortide E methyl ester and its isomers are depicted in Fig. 2.10.

2.9 Synthesis of Plakortide E

As depicted in Scheme 2.61, compound 86d was then saponified to provide the plakortide E (85a). Comparisons of the chemical shifts and coupling constants for the synthetic compound and the literature values for plakortide E are summarized in Table 2.23. Our values are identical to those reported by Wright [3]. However, our results and those of Patil [1] show some differences for the 13C NMR chemical shifts of C-1, C-2 and C-3.

References

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