Total Synthesis of Bioactive Natural Products
Possessing Highly Oxidized Structure

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Research of Bioactive Substances Science
Major in Applied Chemistry, Faculty of Science and Engineering,
Waseda University

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Introduction

Natural products provides research opportunities deriving from its biological properties. Some efforts direct toward the synthesis of agents regarding the structure of the natural product, of which structure has served as the basis for the design of several new classes of drugs saving thousands of lives not only humans also animals.

Needless to say, natural products have complicated structure, including members of aminoglycoside, macrolide, tetracycline, and β-lactam antibiotics. In addition to such antibiotics, all natural products have beautiful and attractive structure. In the past century, their structure have been assigned by nuclear magnetic resonance (NMR), infrared spectroscopy (IR), and mass spectrometry (MASS). Recently, spectroscopic abilities have developed and they contribute structural elucidation in any cases, of course, mistakes are still a common occurrence despite the present advantages. On the contrary, it is amazing just how many complicated natural products have been assigned correctly, especially when only limited material was available or the natural substance in question was unlike any other ever observed.

Highly oxidized structures have been observed in nature such as (–)-tetrodecamycin, (+)-actinopyrone A, TMC-264, and they would be also led to new class of drugs. Thus, their structure should be guaranteed to use as chemotherapeutic agents. Generally, highly oxidized and highly substituted products have less information to analyze by 1H-NMR and would be faced to difficulty of structural determination. Sometimes 13C-NMR or X-ray crystallographic analysis make up for the lack of 1H-NMR information. In addition, their high reactivity causes decomposition of themselves.

This dissertation would like to present the total synthesis and structural determination of these three significant natural products. Natural products whose originally proposed structures have been guaranteed by total synthesis, considering certain stereocenter and clear construction of their structure. Thus, the total synthesis is efficient tool to guarantee the structure of natural products. Indeed, structural determination clearly provide opportunities for synthetic chemists to make discoveries through total synthesis, and certainly show that there is still adventure to be had in the process of structure assignment. Moreover, the total synthesis of natural products has served as the flagship of chemical synthesis and the principal driving force for discovering new chemical reactivity, evaluating physical organic theories, testing the power of existing synthetic methods, and enabling biology and medicine.

In chapter 1, I describe the first total synthesis of (–)-tetrodecamycin, isolated in the course of screening program for novel antimicrobial antibiotics against Pasteurella piscicida, causing fish diseases known as pasteurellosis. The synthesis of structurally complex (–)-tetrodecamycin has required numerous examination to construct the tetracyclic core especially 7-membered ring and following tetronic acid core. Thus, this research have lasted twelve years in our laboratory. (–)-Tetrodecamycin has been synthesized from D-(–)-mannitol through stereoselective Michael addition, aldol reaction, 1,4-reduction, Sml2-mediated pinacol cyclization, and newly developed deoxygenation.
In chapter 2, I describe the first total synthesis of (+)-actinopyrone A, isolated as a relatively unstable compound possessing coronary vasodilating activity and antimicrobial activity. Later, it was found to exhibit potent anti-\textit{Helicobacter pylori} activity. The half value period of (+)-actinopyrone A is 2 weeks at 4 °C in non-solvent and wet solvent, and the unstability would be caused by the deconjugated structure. (+)-Actinopyrone A has been synthesized by using our developed remote stereoinduction, Kocienski olefination, Horner–Wadsworth–Emmons olefination, and reductive de-conjugation of the vinylpyrone. A concise method has also been established by O-methylation to obtain the γ-pyrone.

In chapter 3, I describe the first total synthesis of TMC-264, an inhibitor of IL-4 signal transduction, isolated from the fermentation broth of a fungus \textit{Phoma} sp. TC 1674 and represented a new class of antiallergic agents. The fully substituted quinol core of TMC-264 has less \textsuperscript{1}H-NMR information to define the structure. TMC-264 has been synthesized through regioselective bromination, selective protection of catechol, and biaryl coupling.
## Abbreviation

<table>
<thead>
<tr>
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<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>aq.</td>
<td>aqueous</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoyl</td>
</tr>
<tr>
<td>cat.</td>
<td>calculated</td>
</tr>
<tr>
<td>COD</td>
<td>1,5-cyclooctadiene</td>
</tr>
<tr>
<td>CSA</td>
<td>10-camphorsulfonic acid</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DEAD</td>
<td>diethylazodicarboxylate</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DME</td>
<td>dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>HMDS</td>
<td>hexamethyldisilazide</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramid</td>
</tr>
<tr>
<td>IBX</td>
<td>o-iodoxybenzoic acid</td>
</tr>
<tr>
<td>IP</td>
<td>isopropylidene</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>m-chloroperbenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NCS</td>
<td>N-chlorosuccinimide</td>
</tr>
<tr>
<td>NIS</td>
<td>N-iodosuccinimide</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium p-toluenesulfonate</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>Py</td>
<td>pyridine</td>
</tr>
<tr>
<td>quant.</td>
<td>quantitative</td>
</tr>
<tr>
<td>TBAC</td>
<td>tetra-n-butylammonium chloride</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetra-n-butylammonium fluoride</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Tr</td>
<td>triphenylmethyl</td>
</tr>
<tr>
<td>WSCI</td>
<td>1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide (water soluble carbodiimide)</td>
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1.1. Introduction

Recently, cultivation of many kinds of fishes is being undertaken extensively worldwide to ensure steady fish catches. Fish diseases are among the biggest concerns in fish farming. The fish disease caused by a bacterial septicemia, pasteurellosis (pseudotuberculosis), has become a considerable economic problem worldwide, inflicting significant losses in the farming industry of fishes such as yellowtail, sea bass and sea bream. Prevention of this disease is therefore considered an important aspect for the successful culture of fishes. As far as intensive fish culture goes, a large amount of fish food and antibiotics have been used to increase production and to protect fish from diseases. Consequently, a large portion of feeds and antibiotics enters the water as wastes, causing water pollution. There exists great concern over the widespread use of antibiotics in aquaculture, which may result in residue of antibiotics in water and mud. Therefore it is significant task to provide novel agents which has little toxicity. *Photobacterium damselae* subsp. *piscicida* is well known as the causative agent of the fish disease pasteurellosis, although the organism and the fish disease have also been described as *Pasteurella piscicida* and pseudotuberculosis, respectively.

In the course of a screening program for novel antimicrobial antibiotics against *Pasteurella piscicida*, the Institute of Microbial Chemistry group has isolated an antibiotic, (−)-tetrodecamycin (1), from a culture broth of *Streptomyces* sp. MJ885-mF8 (Figure 1). (−)-Tetrodecamycin (1) has been reported to show strong antimicrobial activities especially against *Pasteurella piscicida*, but no toxicity in mice at a dose of 100 mg/kg when administered intraperitoneally.

Various chemotherapeutic agents such as derivatives of tetracycline (2), oxolinic acid (3), florfenicol (4), and bicozamycin (5) have been used to treat bacterial infections in cultivated fishes, but extensive use has led to an increase in drug-resistant strains among pasteurellosis. Therefore (−)-tetrodecamycin (1), which has different structure compared with existing antibiotics, would be expected to new classes of antibacterial agent with novel mechanism. Novel mechanisms of action are urgently needed, due to the worldwide emergence of infections caused by multidrug resistant bacteria.

![Figure 1](image_url)
The structure of (–)-tetrodecamycin (1) was elucidated by nuclear magnetic resonance (NMR) studies and X-ray crystallographic analysis to be distinguished by a tetronic acid-containing tetracyclic skeleton, the one cyclohexane ring of which is fully and diversely substituted. Moreover, the quaternary carbons are located at C-7 and C-13. The imposing structure and potential medicinal importance of this molecule have attracted a great deal of attention from other researchers since the disclosure of the structure, although the total synthesis had not been reported until our total synthesis.

Paintner reported the asymmetric synthesis of key building block, which contains four of the six stereogenic centres inherent in (–)-tetrodecamycin (1) (Scheme 1). In addition, Paintner also has attempted acid catalyzed cyclization of allylic alcohol. Barriault challenged to synthesize the derivatives which had trans-decaline core. They reported the interesting method, in which intermediate was rapidly constructed via cascade oxy-Cope/ene/Claisen rearrangement of allylic ether to give the trans-decalin core. Baldwin and Tchabanenko reported an unusual silyl enol ether isomerisation followed by an intramolecular Diels–Alder cycloaddition. But all they have not achieved to the total synthesis of (–)-tetrodecamycin (1).

Scheme 1. Toward the total synthesis of (–)-tetrodecamycin (1).
1.2. Retrosynthetic Analysis

From the retrosynthetic perspective, we envisioned that the tetronic acid-containing 7-5-membered core of (–)-tetrodecamycin (1) would be accessible from the aldehyde 6 by a cyclization of 7-membered ring followed by lactonization (Scheme 2). We planned an efficient construction of 6 through the formation of the cis-diol by the SmI$_2$-mediated pinacol cyclization of the keto aldehyde 7, which would be stereospecifically derived from lactone 9 through the quaternary compound 8. Lactone 9, the starting material such as a cochleamycin synthesised in our laboratory, is derived from D-(–)-mannitol (10).

Scheme 2. Retrosynthetic analysis of (–)-tetrodecamycin (1).
1.3. Stereoselective Construction of trans-Decaline

The synthesis was initiated with establishment of the efficient root to construct trans-decaline, which would be the starting material to investigate several conditions for the first total synthesis of (−)-tetrodecamycin. Silica gel column chromatography should be avoided to perform the procedure in multi gram scale. Therefore, the procedure to prepare the lactone 9, which was well known compound as useful starting material, was improved (Scheme 3).

In previous our experience, the diacetonide 11 from D-(−)-mannitol (10) was purified by silica gel column chromatography. Alternatively, after the reaction was neutralized, only the removal of solvent and subsequent oxidative cleavage gave the aldehyde 12. The aldehyde 12 was distillated because of unstability on silica gel and low boiling point. Wittig reaction to give α,β-unsaturated ester 13 was undertaken in MeOH. After removal of MeOH, hexane and Et₂O was poured into the residue. The α,β-unsaturated ester 13 was soluble in the mixed solvent and Ph₃P=O, which was generated by Wittig reaction, was almost insoluble. The solid was removed by filtration, and the filtrate was concentrated under reduced pressure. This operation was repeated several times. After that, a mixture of α,β-unsaturated ester 13 in hydrochloric methanol was followed de-isopropylidenation and subsequent lactonization gave the α,β-unsaturated lactone 14. Tritylation of the α,β-unsaturated lactone 14 was achieved by TrCl and NH₄NO₃ in DMF. When the reaction was completed, the reaction mixture was poured into ice water, which dissolved the reagents and DMF. Insoluble syrup was left at flask by decantation, thus we avoided the extraction which needed a large amount of solvent. It was the first time to purify a compound by silica gel column chromatography and lactone 9 was obtained from D-(−)-mannitol (10) in high efficiency (32% in 5 steps).

![Scheme 3](image)
The quaternary product 8 was stereoselectively synthesized from the lactone 9, having S-configuration (Scheme 4). The lactone 9 was converted into the 2,3-dimethyl derivative 16 by Michael addition and following methylation.\(^{13,14}\) Although diastereomeric compounds were obtained, the single lithium enolate was prepared to react stereoselectively with cyclohexanone and subsequent dehydration gave the quaternary product 8. The structure was confirmed by X-ray crystallographic analysis (Figure 2, \(R\) factor = 0.0665).

\[
\begin{align*}
7 \quad a) \quad & \text{MeMgBr, CuBr·SMe}_2, \text{TMSCl, HMPA/THF, −78 °C, 20 minutes, 88%} \\
& \text{b) MeI, LDA/THF, −78 °C, 20 minutes} \\
& \text{c) Cyclohexanone, LDA/THF, −78 °C, 10 minutes} \\
& \text{d) SOCl}_2/\text{Py, 0 °C, 1 hour, 82% (3 steps)}
\end{align*}
\]

Scheme 4.

Figure 2. X-ray structure of 8.
The first stage of the progression of 8 to (–)-tetrodecamycin (1) involved the further development of stereoselective reaction and constructed carbon atom at C-8 (Scheme 5). High stereoselectivity was observed by epoxidation with m-CPBA or hydroboration with BH₃·THF from 8, although the stereochemistry was not defined. Reductive opening of the epoxide 18 was not reacted smoothly. Additionally, selective protection of the triol 20 was required several steps. Thus, the synthetic route was changed because desired compounds were not synthesized efficiently in subsequent step.

![Diagram of the synthetic route](image)

**Scheme 5.**

a) m-CPBA/CHCl₃, rt, 6 hours, 80% (6:1, diastereomer mixture)
b) BH₃·THF/THF, rt, 2 hours, then aq. NaOH, aq. H₂O₂, rt, 17 hours, 75% (7:1, diastereomer mixture)
c) LiBH₄/THF, 65 °C, 38 hours, 67%
The second route, the triol 20 was also tried to obtain from 8 via the α,β-unsaturated ketone 22, however, the route gave 22 in low yield and the selective protection of triol was found to be difficult (Scheme 6). Thus, the construction of carbon atom at C-8 should be constructed after selective protections.

![Scheme 6](image)
a) SeO\textsubscript{2}/ClCH\textsubscript{2}CH\textsubscript{2}Cl, 50 °C, 14 hours, 44%

Hydride reduction of 8 to the diol 23 with LiBH\textsubscript{4} was successively followed by selective protection as the benzyl ether and the tert-butyldimethylsilyl ether to give 24 (Scheme 7).

![Scheme 7](image)
a) LiBH\textsubscript{4}/THF, 65 °C, 38 hours
b) BnBr, K\textsubscript{2}CO\textsubscript{3}, 18-crown-6-ether/MeCN, 50 °C, 8 hours
c) TBSCl, DBU, MeCN, 65 °C, 20 hours, 88% (3 steps)
The obtained cyclohexene 24 was investigated to construct carbon atom at C-8 with introduction of the hydroxy group to C-13 by hydroboration, however, the stereoselectivity was unsatisfactory (Scheme 8).

Regioselective oxidation of 24 with SeO$_2$ gave the $\alpha,\beta$-unsaturated cyclohexenone 27 as a single product in 86% yield. The 1,4-reduction of 27 was achieved with NaBH$_4$ in the presence of NiCl$_2$•6H$_2$O to give a diastereomeric mixture of 28 and 29 in 77% and 15%,$^{15}$ respectively. The undesired 29 was recycled by epimerization to the desired 28 in alkaline MeOH. The structure of 28 was also determined by the X-ray analysis (Figure 3, R factor = 0.0357).

- [Image of chemical structures]

a) BH$_3$•THF/THF, 40 °C, 38 hours, then aq. NaOH, aq. H$_2$O$_2$, rt, 38 hours, 22% (25), 65% (26)
b) SeO$_2$/aq. dioxane, 90 °C, 17 hours, 76%
c) NaBH$_4$, NiCl$_2$•6H$_2$O/MeOH-CH$_2$Cl$_2$, 0 °C, 10 minutes, 77% (28), 15% (29)
d) KOH/MeOH, 60 °C, 60%

Scheme 8.

Figure 3. X-ray structure of 28.
The stereoselectivity was explained as below. The allylic strain of the $\alpha,\beta$-unsaturated cyclohexenone 27 would contribute the desired stereoselectivity to construct the C-8 stereochemistry and considering the cyclohexene 24 the stereoselectivity was observed conversely (Figure 4).

![Figure 4. Allylic strain of $\alpha,\beta$-unsaturated cyclohexenone 27 and cyclohexene 24.](image)

Several reducing conditions were examined as described in Table 1. General conditions were favored to generate 1,2-reduced form or concomitant 1,2 and 1,4-reduced form. These results suggested that combination of NaBH₄ and NiCl₂・6H₂O reacted as other mechanism compared with general hydride reduction. The active catalyst NiB₂ was generated with NiCl₂・6H₂O and NaBH₄ under a nitrogen atmosphere. The excess NaBH₄ was used to generate hydrogen in MeOH. The immediate formation of a black granular precipitate indicated that the catalyst formed.

<table>
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<th>Entry</th>
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<th>Reagent</th>
<th>Solvent</th>
<th>Additive</th>
<th>1,2-reduced form : 1,2-and 1,4-reduced form</th>
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<tr>
<td>1</td>
<td>NaBH₄</td>
<td>MeOH</td>
<td>None</td>
<td>0 : 0 : 0 : 1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>Py</td>
<td>&quot;</td>
<td>Multiple compounds</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>MeOH-THF</td>
<td>CoCl₂</td>
<td>1 : 0 : 10 : 0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>LiAlH₄</td>
<td>THF</td>
<td>None</td>
<td>1 : 1 : 2 : 0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>&quot;</td>
<td>&quot;</td>
<td>CuI</td>
<td>0 : 0 : 1 : 0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>LiEt₃BH</td>
<td>&quot;</td>
<td>None</td>
<td>1 : 1 : 0 : 2</td>
<td></td>
</tr>
</tbody>
</table>

Table 1.
Selective removal of the triphenylmethyl group of 28 was achieved by Et₂AlCl (Scheme 9). Under the general conditions of de-protection such as 90% aq. AcOH and BF₃·Et₂O in aq. MeCN were observed the silyl migration to primary alcohol. Thus, aluminum protected the primary hydroxide in situ under these conditions using Et₂AlCl. Subsequent PCC oxidation gave the keto-aldehyde 7.

![Scheme 9](image)

Scheme 9.

The final stage was settled on the stereoselective construction of trans-decaline. Proposed transition states of pinacol cyclization from the keto-aldehyde 7 were illustrated in Figure 5. A would be more preferred transition state than B in which the two carbonyl groups was faced contrary. C and D would be unstable because of 1,3-diaxial repulsion with cyclohexane ring and methyl. Other conformers might be also unstable by 1,3-diaxial repulsion with CH₂OBn and OTBS.

![Figure 5](image)

Figure 5. Transition states of pinacol cyclization from keto-aldehyde 7.
And the keto-aldehyde 7 gave the requisite cis-diol 31 with SmI$_2$ and t-BuOH as a single product resulting from the most stable transition state of the chelation-controlled reaction (Scheme 10).$^{16}$

*Trans*-decaline was established and all stereochemistry would be defined in this stage. Therefore, 31 was converted into acetonide 34 via 33. Crystalline 34 was obtained by recrystallization from EtOAc. The configuration of 34 was confirmed by the X-ray crystallographic analysis as shown in Figure 6 and the $R$ factor was 0.0408.

a) SmI$_2$, t-BuOH/THF, $-78$ °C, 0.5 hours, quant.
b) 2-methoxypropene, PPTS/ClCH$_2$CH$_2$Cl, 40 °C, 8 hours
c) TBAF/THF, 50 °C, 15 hours, 71% (2 steps)

Scheme 10.

Figure 6. X-ray structure of 34.
1.4. Construction of 7-Membered Ring

Progression toward synthesis of (−)-tetrodecamycin was required to two key steps, which were acylation at C-6 and oxy-Michael addition to C-3 (Scheme 11). Two routes were envisioned to construct 7-membered ring, conveniently named route A, which was acylation and subsequent oxy-Michael addition, and route B, which was oxy-Michael addition and subsequent acylation.

Scheme 11.

Synthesis of (−)-tetrodecamycin was first attempted by route A, and several conditions were examined with the acylated 35 (Scheme 12). Under these conditions 1,2-addition and subsequent acetal formation followed by dehydration occurred.

Scheme 12.

Next, we examined route B, which was shown in following page.
Di-O-methoxymethylation and de-O-silylation of 31 proceeded to give the alcohol 38 (Scheme 13). Oxy-Michael addition to α,β-unsaturated acetylene derivative with Me₃P afforded the enol ether 39. This oxy-Michael addition was achieved in high yield, and 39 was lead to various derivatives to investigate the construction of 7-membered ring. However, the desired tricyclic compound 41 or tetracyclic compound 43 were not obtained (Scheme 13 and 14). Although exact structure was not determined, a compound reacted at γ-position was observed. Thus, exo-methylene group should be introduced and following cyclization.

Scheme 13.

Scheme 14.

---
After the introduction of exo-methylene group, various conditions were examined with 44. However, our efforts resulted in disappointment and not to generate the desired tetracyclic compound 45 (Scheme 15).

\[\text{OMOM} \quad \text{O} \quad \text{Me} \quad \text{Me} \quad \text{H} \quad \text{MOM} \quad \text{O} \quad \text{O} \]

44

\[\text{OMOM} \quad \text{O} \quad \text{Me} \quad \text{Me} \quad \text{H} \quad \text{MOM} \quad \text{O} \quad \text{O} \]

45

\[\text{CHO} \quad \text{a} \quad \text{CH}_2=\text{N}^+\text{Me}_2\text{I}^{-}, \text{LHMDS/THF, } -78 \degree \text{C, 1 hour then MeI, rt, 12 hours, 44\%} \]

Scheme 15.
After numerous examinations, it was realized that the maleate derivative 46 was converted smoothly into the desired 7-membered ring (Scheme 16).

Michael addition of 34 to diethyl acetylenedicarboxylate gave a mixture of 46 and 47 in 75% and 15% yield, respectively, the stereochemistry of which was determined by NMR studies, especially by the chemical shifts of the olefin protons. Reductive removal of the benzyl group of the desired olefin 46 gave the alcohol, which was oxidized to the aldehyde 6. Treatment of 6 with NaHMDS constructed the 7-membered ring to afford a 5:1 diastereomeric mixture of the alcohols 48, which was oxidized to a single product 49 by IBX oxidation.

The diastereomeric 48 were separated by silica gel column chromatography and the major product was confirmed the structure by HMBC as shown in Figure 7. Correlations between H-6 and C-7, H-15 and C-7, H-6 and C-3, H-15 and C-3 were observed.

![Diagram](image_url)
1.5. Total Synthesis of (–)-Tetrodecamycin

In the diester 49, the C-2 ester is anticipated to be less reactive than the C-3 ester to submit reduction because of the tautomerization with the ring oxygen atom. Initial investigations contemplated hydride reduction to furnish lactone 50 by reduction and subsequent lactonization. However, either ketone or olefin of the diester 49 was reduced, and the desired 50 was not obtained (Scheme 17).

![Scheme 17](image)

We then turned to access saponification which might eventually lead more reactive compound, such as the acid chloride 52 or activated ester 53 (Scheme 18). As expected, 49 was selectively hydrolyzed to the mono-acid 51. However, several attempts were not directed toward generation of 50. The reduction of ketone or olefin were also preferred.

![Scheme 18](image)

a) Na₂CO₃/50% aq. THF, rt, 15 hours, 91%
Our effort reached an implementable solution. The acid 51 was transformed to the thioester 54, which was reduced under Fukuyama conditions with Et₃SiH to the aldehyde with concomitant cyclization to the diastereomeric acetal 55 (Scheme 19).  

![Diagram of the transformation process from 51 to 55](image)

a) EtSH, WSCI-HCl, Py/CH₂Cl₂, rt, 1 hour, 74%
b) Et₃SiH, Lindlar cat./Acetone, rt, 0.5 hours, 80%

Scheme 19.

General procedures were attempted to deoxygenate the acetal 55 under a variety conditions. Two carbonyl substituents influenced to afford multiple compounds under acidic conditions or by radical reduction. Neutral and mild condition was recommended to convert 55 into lactone ring.

On the other hand, indirect deoxygencation would be anticipated with the acetal 55 and bromination was attempted to furnish 57 and subsequent debromination to generate the desired lactone 50 (Scheme 20). And fortunately this was lead to our newly developed procedures.

![Diagram of the indirect deoxygenation process from 55 to 50](image)

Scheme 20.
Deoxygenation of the acetal 55 was effected in one operation using CBr₄ and PPh₃ to furnish the lactone 50 by bromination¹⁹ followed by debromination²⁰ with PPh₃ and subsequent protonation (Scheme 21). Deacetonation of 50 with 70% aq. TFA afforded the diol 59, which, upon treatment with N,N-dimethylmethyleneammonium iodide (CH₂=N⁺Me₂I),²¹ underwent introduction of an exo-methylene group to give (−)-tetrodecamycin (1).

![Chemical Structure](image)

This was identical in all respects with the natural product, including spectroscopic characteristics (¹H and ¹³C-NMR spectra, and mass spectra) and optical rotation [synthetic 1: [α]₀²⁶ −6.0 (c 0.42, MeOH); natural product: [α]₀²³ −6.0 (c 0.50, MeOH)], completing the stereoselective total synthesis to confirm the absolute structure.

In conclusion, trans-decaline was synthesized from D-(−)-mannitol through stereoselective Michael addition, aldol reaction, 1,4-reduction, and SmI₂-mediated pinacol cyclization. Construction of 7-membered ring was achieved through enol etherification and subsequent acylation. Tetronic acid core was established by regioselective hydrolysis, thio esterification, silane reduction, and our newly developed deoxygenation effected in one operation using CBr₄ and PPh₃. Subsequent introduction of exo-methylene group gave (−)-tetrodecamycin (1).
2. Total Synthesis and Structural Determination of (+)-Actinopyrone A

2.1. Introduction

(+)-Actinopyrone A (60) was isolated from *Streptomyces pactum* S12538 as a relatively unstable compound possessing coronary vasodilating activity and antimicrobial activity.\(^{22,23}\) Later, it was found to exhibit potent anti-\textit{Helicobacter pylori} (\textit{H. pylori}) activity (Figure 8).\(^{24}\) (+)-Actinopyrone A (60) exhibited potent anti- \textit{H. pylori} activity with MIC value of 0.0001 (\(\mu\text{g/ml}\)).

Many recent studies have shown that peptic ulcer diseases are mainly caused by \textit{H. pylori} infection.\(^{25,26}\) Eradiation of this bacterium dramatically decreases the recurrence rate in peptic ulcer patients. Treatment regiments including a proton pump inhibitor and antimicrobial agents such as amoxicillin (61) and macrolide compound are recommended. Recently some agents are proposed such as tatridin-A (62) and CJ-12,954 (63). However, these therapies have problems including side effects, build-up of drug resistance, and poor compliance. Therefore the development of a new class of anti-\textit{H. pylori} agents is needed. The instability of (+)-actinopyrone A (60) makes it difficult to promote further research. The half value period of actinopyrone A is 2 weeks at 4 °C in non-solvent and wet solvent, and the unstability would be caused by the deconjugated structure. Thus, (+)-actinopyrone A (60) has been required to be established the total synthesis. And multi-bioactivity and little toxicity makes 60 to be an attractive candidate of a drug for chemotherapy.

![Chemical Structures](image-url)
The absolute structure of (+)-actinopyrone A (60), especially stereochemistry of C-14 and C-15, has not been disclosed yet. Thus, we also aim to define the absolute structure by total synthesis.

The side chain of (+)-actinopyrone A (60) is similar to piericidin A1 (72), which has been synthesized by Boger and co-workers.\textsuperscript{27} They examined several methods to synthesize the aldehyde 71, the key intermediate of the side chain, and their best result is shown in Scheme 22. The aldehyde 71 was obtained from the oxazolidone 64 in 7 steps and over all yield is 27%. Thus, we would investigate to construct the aldehyde 71 by concise method.

\begin{center}
\includegraphics[width=\textwidth]{scheme22.png}
\end{center}

Piericidin A1 (72)

\begin{itemize}
\item[a)] Bu₂BOTf, i-Pr₂NET/CH₂Cl₂, \(-78^\circ\mathrm{C}\), 2 hours, 67%
\item[b)] MeNHOMe \cdot HCl/THF, Me₃Al, rt, 18 hours
\item[c)] TBSCl, imidazole/DMF, rt, 18 hours, 66% (2 steps)
\item[d)] DIBAL/THF, \(-78^\circ\mathrm{C}\), 1.5 hours, 86%
\item[e)] NaH/THF, rt, 18 hours
\item[f)] DIBAL/CH₂Cl₂, \(-78^\circ\mathrm{C}\), 1 hour, 72% (2 steps)
\item[g)] (COCl)₂, DMSO, Et₃N/CH₂Cl₂, \(-78^\circ\mathrm{C}\), 99%
\end{itemize}

Scheme 22. The total synthesis of piericidin A1 (72).
2.2. Retrosynthetic Analysis

Our previous efforts revealed that any allyl pyrones were unstable, thus 74 and 75 were not obtained from 73 (Scheme 23). Therefore, de-conjugated products were recommended to be constructed in the final steps.

Scheme 23. Our previous synthetic strategy.

The synthetic plan possessed two significant steps (Scheme 24). They were de-conjugation of vinyl pyrone and stereoselective construction of C-14 and C-15 positions. To avoid instability of (+)-actinopyrone A (60), the conjugated pyrone 76 was set up as the precursor. The precursor 76 would be subjected to the reductive de-conjugation of the vinyl pyrone moiety in the final stage of the synthesis. The conjugated pyrone 76 might be synthesized by connection of the compounds 69 and 77-79. The chiral C-14 and C-15 positions should be constructed by the remote stereocontrol methodology developed in our laboratory using the chiral vinylketene 77, which was prepared from D-valine.28

Scheme 24. Retrosynthetic analysis of actinopyrone A (60).
2.3. Synthesis of Significant Segments

The epoxy-sulfone 78 was synthesized in 2 steps from the commercially available 80 (Scheme 25). The alcohol 80 was converted to the tetrazole 82 under Mitsunobu conditions. Both olefin and sulfide of 82 were oxidized to give the epoxy-sulfone 78 by treatment with $m$-CPBA in the presence of NaHCO$_3$.

\[ \text{Ph} \quad \text{SH} \]
\[ \text{N} \quad \text{N} \]
\[ \text{HO} \quad \text{Me} \]
\[ \text{Me} \quad \text{S} \]
\[ \text{N} \quad \text{N} \quad \text{Ph} \quad \text{O} \quad \text{N} \quad \text{N} \]

\[ \text{a) DEAD, PPh}_3/\text{THF, rt, 2 hours, 92\%} \]
\[ \text{b) } m\text{-CPBA, NaHCO}_3/\text{CH}_2\text{Cl}_2, 0 \, ^\circ\text{C, 4 days, 87\%} \]

Scheme 25.

During the synthesis of the $\gamma$-pyrone moiety 79, we found a concise and economical method of O-methylation to convert 4-hydroxy-2-pyrone to 2-methoxy-4-pyrone (Scheme 26). Treatment of the known $\alpha$-pyrone 83 with CaCO$_3$ and Me$_2$SO$_4$ in acetone at 50 $^\circ$C promoted 2-O-methylation to give the $\gamma$-pyrone 73 as a major product. The regioselectivity of the O-methylation was 2-O-methylation/4-O-methylation = 3/1. The isolated yield of the $\gamma$-pyrone 73 (56\%) is comparable to the yield under conditions with MeSO$_3$F (53\%).\textsuperscript{29} The regioselective chlorination of $\gamma$-pyrone 73 to obtain the chloromethylpyrone 84 was realized with LHMDS and NCS, which was followed by substitution with P(OEt)$_3$ to afford the phosphonate 79.

\[ \text{Me} \quad \text{O} \quad \text{Me} \]
\[ \text{Me} \quad \text{O} \quad \text{Me} \]
\[ \text{Cl} \quad \text{Me} \quad \text{O} \quad \text{Me} \]
\[ \text{P(O)(OEt)$_2$} \]

\[ \text{a) } \text{Me}_2\text{SO}_4, \text{CaCO}_3/\text{acetone, 50 } ^\circ\text{C, 3 days, 56\%} \]
\[ \text{b) LHMDS, NCS/THF, 0 } ^\circ\text{C, 1 hour, 67\%} \]
\[ \text{c) P(OEt)$_3$, 140 } ^\circ\text{C, 6.5 hours, 80\%} \]

Scheme 26.
Stereoselective construction from C-11 to C-18 unit 71 was achieved by our remote stereocontrol methodology (Scheme 27). Coupling of the silyl dienolate 77 and tiglic aldehyde 65 in the presence of TiCl₄ gave C-14 and C-15 anti-adduct 86 as a single isomer. Protection of 86 as the TBS ether afforded the crystalline 87, of which stereochemistry was determined to be the (14R,15R)-isomer by X-ray crystallography as expected (Figure 9, R factor = 0.0641). The chiral auxiliary of 87 was removed to give the aldehyde 71 by treatment with DIBAL at –78 °C.

Consequently, the aldehyde 71 was obtained from the oxazolidone derivative 85 in 4 steps and over all yield was 47%. Thus, our remote stereocontrol methodology was more efficient to prepare 71, compared with known methods illustrated in Scheme 21.

Figure 9. X-ray structure of 87.

Scheme 27.

<table>
<thead>
<tr>
<th>Step</th>
<th>Reaction Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a)</td>
<td>TBSCI, NaHMDS/THF, –78 °C, 0.5 hours, 89%</td>
<td></td>
</tr>
<tr>
<td>b)</td>
<td>TiCl₄/CH₂Cl₂, –60 °C, 4 days, 82%</td>
<td></td>
</tr>
<tr>
<td>c)</td>
<td>TBSOTf, 2,6-lutidine/CH₂Cl₂, 0 °C, 1.5 hours, 93%</td>
<td></td>
</tr>
<tr>
<td>d)</td>
<td>DIBAL/CH₂Cl₂, –78 °C, 1 hour, 68%</td>
<td></td>
</tr>
</tbody>
</table>
2.4. Total Synthesis of (+)-Actinopyrone A

The aldehyde 71 was converted to the triene 88 (10,11-E/10,11-Z = 93/7) by Kocienski’s method using the sulfone 78 (Scheme 28).^30^ The triene 88 was transformed under the acidic conditions to the primary alcohol 90, which was separated from 10,11-Z-isomer by silica gel column chromatography. The alcohol 89 was submitted to oxidation to afford the aldehyde 90. The pyrone moiety was introduced by Horner–Wadsworth–Emmons reaction of 90 with the phosphonate 79 to afford the stable vinylpyrone 91.

![Chemical structures and reactions](image)

Scheme 28.

---

a) NaHMDS/DME, −60 °C to 0°C, 18 hours
b) CSA/MeOH, 0 °C, 1 hour, 67% (2 steps)
c) SO3・Py, DMSO, Et3N, rt, 30 min, 94%
d) LHMDS/THF, −78 °C to 0°C, 5.5 hours, 96%
De-O-silylation of 91 under the acidic conditions proceeded in good yield to provide 76 (Scheme 29). The final and key step was settled. Treatment of the vinylpyrone 76 with SmI$_2$ in the presence of iso-propanol promoted the reductive de-conjugation to give (+)-actinopyrone A (60). In the presence of methanol, alternated with iso-propanol, the methyl ether 95 was obtained as byproduct from 93 by protonation without removal of methoxide. The generated 60 was accompanied with the 7,8-Z-isomer (60/7,8-Z-isomer = 88/12). The isomer were easily separated by silica gel column chromatography to isolate 60 in 70% yield.

\[ \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \]
\[ \text{OTBS} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{O} \]
\[ \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{O} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{O} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{O} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{O} \]
\[ a) \quad \text{CSA/MeOH, rt, 18 hours, 70\%} \]
\[ b) \quad \text{SmI}_2, \text{i-PrOH/THF, \text{--78 °C to --20 °C, 0.5 hours, 70\%}} \]

Scheme 29.

The synthetic 60 was identical in all respects with the natural product, including spectroscopic characteristics ($^1$H and $^{13}$C-NMR spectra, and mass spectra) and optical rotation [synthetic 60: $[\alpha]_D^{25} +31.3$ (c 0.43, CH$_2$Cl$_2$), natural product: $[\alpha]_D^{26} +30.8$ (c 0.42, CH$_2$Cl$_2$)]. Thus, the absolute structure of (+)-actinopyrone A (60) was determined to be (14R,15R)-configuration.

In conclusion, (+)-actinopyrone A (60) was synthesized from silyl dienolate 77 in 9 steps including the remote stereoinduction, Kocienski olefination, Horner–Wadsworth–Emmons olefination, and reductive de-conjugation with SmI$_2$ and iso-propanol. A concise method has also been established by O-methylation to obtain the γ-pyrone. We also synthesized the enantiomer of 60 showing the opposite optical rotation $[\alpha]_D^{23} -31.7$ (c 0.43, CH$_2$Cl$_2$) by starting from the enantiomer of 77 derived from L-valine.
3. Total Synthesis of TMC-264, an Inhibitor of IL-4 Signal Transduction

3.1. Introduction

Interleukin (IL)-4 is known to be a cytokine which plays a central role in the regulation of immune response. Binding of IL-4 to its receptor on B cells leads to the activation of the janus kinase (JAK)-signal transducer and activator transcription 6 (STAT6) pathway. In this pathway, the receptor associated JAK1 and 3 phosphorylates tyrosine residue of STAT6. Then STAT6 forms dimers, translocates to the nucleus, binds the specific elements in the promoters of target genes, and transcriptionally activates these genes. As a result, B cells raise expression of CD23 and class switching to IgE. Production of IgE causes the release of various chemical mediators such as histamine, leukotriene, prostaglandin and so on. Therefore, inhibitors of IL-4 signal transduction are expected to prevent allergic diseases. During the course of screening of microbial extracts for inhibitor of IL-4 signal transduction using an IL-4 driven luciferase assay system, a novel compound, TMC-264 (96), was discovered from the fermentation broth of a fungus Phoma sp. TC 1674 (Figure 10). And the structure is determined to be 2-chloro-4,6-dihydro-1,7-dihydroxy-3,9-dimethoxy-1-methyl-1H-dibenzo[b,d]pyran-4,6-dione. TMC-264 (96) is the first compound possessing 4,6-dione or possessing 1-hydroxy group on 1-methyl-dibenzo[b,d]-pyran.

Deacetylravidomycin (97) showed the same bioactivity. Known antiallergic agents, such as olopatadine hydrochloride (98), ketotifen (99) and sodium cromoglicate (100), elicited their antiallergic effects by mainly antagonizing histamine H1 receptors or worked by inhibiting release of chemical mediators. Thus TMC-264 (96) and deacetylravidomycin (97) represented a new class of antiallergic agents.

We hope the total synthesis of TMC-264 (96) would assist the elucidation of the novel bioactive system.
3.2. Retrosynthetic Analysis

Scheme 30 illustrates our retrosynthetic analysis of TMC-264 (96). Our strategy is based on the synthesis of racemic TMC-264 through oxidation which was followed by biaryl coupling reaction and acylation of 101 and 103. The highly substituted phenol 101 and benzoic acid 103 were synthesized from commercially available 102 and 104, respectively. Thus, we examined the three significant steps including regioselective halogenation, selective protection of catechol segment, and biaryl coupling reaction to construct tricyclic compound as the priorities.

Scheme 30. Retrosynthetic analysis of TMC-264 (96).
3.3. Synthesis of Highly Substituted Phenol and Benzoic acid

The first matter of concern was regioselective halogenation. After deprotection of the trimethoxy compound \textbf{102} by BBr$_3$ affording \textbf{105}, halogenation of \textbf{105} was examined under several conditions (Scheme 31, Table 6). Finally, the best result was realized bromination of \textbf{105} by NBS in CCl$_4$ at 0 °C generated the bromide \textbf{106} in high yield, accompanied with byproduct including \textbf{107} (Table 6, Entry 3). The structure of \textbf{106} was determined by NOE (Figure 11).

![Scheme 31.](image1)

\begin{align*}
\text{Me} & \quad \text{OMe} \\
\text{OMe} & \quad \text{Me} \\
\text{OMe} & \quad \text{OH} \\
\text{OH} & \quad \text{OH} \\
\text{OMe} & \quad \text{Br} \\
\end{align*}

\text{102} \quad \text{105} \quad \text{106} \quad \text{107}

\begin{align*}
a) & \quad \text{BBr}_3/\text{CH}_2\text{Cl}_2, \quad 0 \, ^\circ\text{C}, \quad 5 \text{ minutes, } 88\% \\
b) & \quad \text{NBS/CCl}_4, \quad 0 \, ^\circ\text{C}, \quad 1 \text{ day, } 80\% (\textbf{106}), \quad 8\% (\textbf{107})
\end{align*}

Scheme 31.

\begin{align*}
\text{Me} & \quad \text{OMe} \\
\text{OMe} & \quad \text{Me} \\
\text{OMe} & \quad \text{OH} \\
\text{OH} & \quad \text{OH} \\
\text{OMe} & \quad \text{H} \\
\text{Br} & \quad \text{OH} \\
\text{OH} & \quad \text{Br} \\
\end{align*}

\text{106}

\begin{align*}
5.0\% & \quad 8.3\%
\end{align*}

Figure 11. NOE of \textbf{106}. 
After the protection of the diol \textbf{105} affording \textbf{108}, several conditions were also examined to halogenate (Scheme 32). Under some conditions illustrated in Table 2, the desired compound was obtained in high regioselectivity (Entry 7 or 10). However, this route required extra 2 steps, which was protection and deprotection. Thus, we progressed the synthesis with using the bromide \textbf{106}.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme32.png}
\caption{Scheme 32.}
\end{figure}

\begin{table}[h]
\begin{tabular}{cccccccc}
Entry & Substitution & Condition & Ratio & \\
\hline
1 & Cl & H & NCS & CCl\textsubscript{4} & None & rt & 1 : 1 : 0.7 : 0.5 \\
2 & Br & H & NBS & MeCN & None & 0 °C & 0 : 20 : 1 : 7 \\
3 & Br & H & NBS & CCl\textsubscript{4} & None & 0 °C & 1 : 20 : 2 : 1.7 \\
4 & Br & H & NBS & PhMe & None & 0 °C & 1 : 13 : 0 : 2 \\
5 & I & H & NIS & CCl\textsubscript{4} & None & rt & 1 : 0.5 : 0 : 0 \\
\hline
6 & Cl & Ac & NCS & MeCN & None & 50 °C & 0 : 12 : 1 : 1 \\
7 & Br & Ac & NBS & MeCN & None & 70 °C & 0 : 1 : 0 : 0 \\
\hline
8 & Cl & TBS & NCS & MeCN & None & 80 °C & 0 : 0.8 : 1 : 0 \\
9 & Br & TBS & NBS & MeCN & None & 50 °C & 0 : 6 : 1 : 0.2 \\
10 & Br & TBS & NBS & CCl\textsubscript{4} & None & 50 °C & 0 : 13 : 1 : 0 \\
11 & I & TBS & NIS & MeCN & None & 60 °C & 40 : 3 : 1 : 0 \\
12 & I & TBS & NIS & MeCN & AIBN & 60 °C & 14 : 3.5 : 1 : 0 \\
\end{tabular}
\caption{Table 2.}
\end{table}

\textit{a)} AcCl, \(\text{t-Pr}_2\)NEt/THF, rt, 1 hour, quant.
\textit{or TBSCl, imidazole/MeCN, 40 °C, 4 hours, 79%}
After chlorination of 106, protection of the catechol 111 with methoxymethyl ether afforded the three compounds including 112-114 under general conditions (Scheme 33).

\[
\begin{align*}
\text{Me} & \quad \text{OMe} \\
\text{Br} & \quad \text{OH} \\
106 & \quad \text{Cl} & \quad \text{OMe} \\
\text{Br} & \quad \text{OH} \\
111 & \quad \text{Cl} & \quad \text{OMe} \\
\text{Br} & \quad \text{OH} \\
112 & \quad \text{Cl} & \quad \text{OMe} \\
\text{Br} & \quad \text{OH} \\
113 & \quad \text{Cl} & \quad \text{OMe} \\
\text{Br} & \quad \text{OH} \\
114
\end{align*}
\]

- a) NCS/THF, rt, 1 hour, 61%
- b) MOMCl, i-Pr₂NEt/CH₂Cl₂, −40 °C, 15 minutes, 24% (112), 20% (113), 30% (114)

Scheme 33.

On the other hand, tetrasubstituted benzoic acid 117 and 103 was synthesised from commercially available 115 and 104 in 2 steps, respectively (Scheme 34). Regioselective halogenation was followed by halogen-metalexchange to react with carbon dioxide to yield desired carboxylic acid.

\[
\begin{align*}
\text{MeO} & \quad \text{Br} \\
\text{OMe} & \quad \text{MeO} \\
115 & \quad \text{Br} & \quad \text{MeO} \\
\text{OMe} & \quad \text{MeO} \\
116 & \quad \text{Br} & \quad \text{MeO} \\
\text{OMe} & \quad \text{MeO} \\
117
\end{align*}
\]

- a) NIS/CICH₂CH₂Cl, 50 °C, 8.5 hours, 78%
- b) s-BuLi/PhMe, −78 °C, 10 minutes, then CO₂ gas, rt, 2 hours, 97%

\[
\begin{align*}
\text{MeO} & \quad \text{Cl} \\
\text{OMe} & \quad \text{Cl} \\
104 & \quad \text{Cl} & \quad \text{OMe} \\
\text{OMe} & \quad \text{Cl} \\
118 & \quad \text{Cl} & \quad \text{OMe} \\
\text{OMe} & \quad \text{Cl} \\
103
\end{align*}
\]

- a) NBS/CCl₄, 60 °C, 5 hours, 80%
- b) s-BuLi/PhMe, −78 °C, 10 minutes, then CO₂ gas, rt, 2 hours, 97%

Scheme 34.
According to the synthetic route to protect the diol 105 in Scheme 32, it was observed that silyl and acyl group migrated in the two hydroxy (Figure 12).

Thus, 111 would be acylated with 119 to afford 121 and 122, migrated to each other, which were expected to react under the condition of biaryl coupling reaction when the benzoyl moiety was acylated at C-4a (Scheme 35). However, the reaction was resulted in the disappointment and multiple compounds were obtained.

\[
\begin{align*}
111 & \xrightarrow{a} 121 \quad \text{Br, Et}_{3}N/\text{THF, } 60^\circ\text{C, 10 hours, 82\% (121+122)} \\
123 & 
\end{align*}
\]

Scheme 35.
We concerned the methodology of the protection which was utilized to synthesis of kanamycin derivatives. After numerous examinations, selective protection of catechol was realized that treatment of the catechol $\text{111}$ with $\text{ZnCl}_2$ and $\text{i-Pr}_2\text{NEt}$ in DMF, and subsequent MOMCl afforded $\text{112}$ in high yield (Scheme 36, Table 3, Entry 11). We confirmed the structure of both mono methoxymethylated products, $\text{112}$ and $\text{113}$, by NOE (Figure 13).

![Scheme 36](image)

Figure 13. NOE of $\text{112}$ and $\text{113}$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Condition</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chloride</td>
<td>Base</td>
</tr>
<tr>
<td>1</td>
<td>MOMCl</td>
<td>$\text{i-Pr}_2\text{NEt}$</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>4</td>
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<tr>
<td>5</td>
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<td>6</td>
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</tr>
<tr>
<td>12</td>
<td>&quot;</td>
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</tr>
</tbody>
</table>

Table 3.
3.4. Total Synthesis of TMC-264

Our attention was turned to intramolecular coupling reaction. The Stille reaction and the Suzuki reaction were useful palladium-catalyzed carbon-carbon bond-forming reaction (Figure 14). The Heck reaction was also applied as a palladium-catalyzed coupling of aryl halides.\(^{36}\)

![Reaction Scheme](image)

\(124 : X \text{ or } Y = \text{H, Cl, Br, I, B(OR)}_2, \text{SnR}_3\)

Figure 14.

The desired organotin or organoboron compounds were not obtained, on the other hand, the precursor 126 was prepared from the benzoic acid 125 to examine the Heck reaction (Scheme 37).

![Reaction Scheme](image)

\(125 \xrightarrow{\text{a, b}} 126 \xrightarrow{\text{Heck reaction}} 127\)

\(a) (\text{COCl})_2, \text{DMF/CH}_2\text{Cl}_2, 40 \degree \text{C, 4 hours}\)

\(b) 112/\text{Py, 50 \degree \text{C, 10 hours, 82\% (2 steps)}}\)

Scheme 37.
The oxidative addition to 126 was not underwent smoothly and starting material was recovered under the mild condition (Scheme 38). Several conditions were attempted with Pd(OAc)$_2$ or Pd(PPh$_3$)$_2$Cl$_2$. Some base (Et$_3$N, K$_2$CO$_3$, NaOAc, AgNO$_3$) and additive (TBAC, PPh$_3$) were added to generate desired compound. However, multiple compounds were afforded, including the hydrogenated compound 130 at C-10b, simultaneously deacylated when heated. Additionally, the iodinated compound at C-10b instead of the bromide compound 126 was also reached same result.

Scheme 38.
Synthetic procedures for the preparation of biaryls by the classical Ullmann-type reaction had, in recent years, been supplanted by the use of zerovalent nickel to effect the reductive coupling of aryl halides under homogeneous conditions.\textsuperscript{37} We prepared the precursor \textit{132} from the benzoic acid \textit{117} through the acid chloride \textit{131} (Scheme 39). And fortunatelly, treatment of \textit{132} with Ni(COD)\textsubscript{2} in DMF was underwent to generate the tricyclic compound \textit{127} and hydrogenated \textit{126}.

This result suggested that oxidative addition at C-10a was faster than at C-10b. And the oxidative addition affording \textit{134} was competed with affording \textit{126} (Scheme 40).
Thus we prepared the precursor 136, possessing chlorine at C-10a position, from 103 through acid chloride 135 (Scheme 41). We meant to suppress the first oxidative addition at C-10a and second oxidative addition at C-10b would be occurred. Cyclization of 136 with Ni(COD)$_2$ and EtAlCl$_2$ in DMF gave the corresponding 127.

![Scheme 41.](image)

a) (COCl)$_2$, DMF/CH$_2$Cl$_2$, 40 $^\circ$C, 4 hours
b) 112/Py, 50 $^\circ$C, 10 hours, 82% (2 steps)
c) Ni(COD)$_2$, EtAlCl$_2$/DMF, 40 $^\circ$C, 10 hours, 85%

Scheme 41.
Mechanism of the cyclization was illustrated in Scheme 42 by nickel-catalyzed coupling of aryl halide. The mechanism initiated with oxidative addition of aryl chloride and aryl bromide to zero-valent nickel afforded 138, followed by methathesis to diarylnickel(II) species 139 accompanied nickel(II) halide, which would not be underwent any more. Thus, this reaction consumed stoichiometric amount of Ni(COD)$_2$. And reductive elimination from diarylnickel(II) species 139 gave cyclic 127 and regenerates zero-valent nickel. However, the formation of diarylnickel(II) species via methathesis had not been demonstrated in detail and was still controversial.\textsuperscript{38} 

Scheme 42.
Final step is illustrated in Scheme 43. Selective deprotection was achieved by BCl$_3$ according to carbonyl function and the phenol 141 was afforded. Oxidation of para-substituted phenol is generally slower and provides a more complex mixture of products. Ortho oxidized products and hydroperoxidated products would be obtained. Oxidation of the phenol 141 with oxygen activated by [bis-(salicylidene) ethylenediamine]cobalt (salcomine) generated racemic TMC-264 (96) in 60% yield.

![Scheme 43.](image)

The synthetic TMC-264 (96) was identical in spectroscopic characteristics (\textsuperscript{1}H and \textsuperscript{13}C-NMR spectra, MASS spectrum and IR spectrum) with the natural product. Thus, the structure of TMC-264 (96) was confirmed.

In conclusion, highly substituted two segments were synthesized regioselectively. Especially, selective protection of catechol was achieved by methoxymethylation with MOMCl and ZnCl$_2$. Biaryl coupling reaction was underwent by zero-valent nickel catalyzed cyclization. Subsequent oxidation generated TMC-264.
Summary

This dissertation was summarized as below.


1-1. Stereoselective Construction of trans-Decaline

Trans-decaline including the one cyclohexane ring of which was fully and diversely substituted was synthesized from D-(–)-mannitol through stereoselective Michael addition, aldol reaction, 1,4-reduction, SmI₂-mediated pinacol cyclization.

1-2. Construction of 7-Membered Ring

Construction of 7-membered ring was achieved through the two critical steps, enol etherification and subsequent acylation. In addition, it was realized that the reaction order proceeded the successful cyclization.

1-3. Total Synthesis of (–)-Tetrodecamycin

Tetracyclic core was established by regioselective hydrolysis, thio esterification, silane reduction and our newly developed deoxygenation, effected in one operation using CBr₄ and PPh₃. Subsequent steps including introduction of exo-methylene group gave (–)-tetrodecamycin, which was identical all respects with the natural product, and completed the first stereoselective total synthesis to confirm the absolute structure.

2. Total Synthesis and Structural Determination of (+)-Actinopyrone A

2-1. Synthesis of Significant Segments

The chiral C-14 and C-15 were constructed by Hosokawa's methodology using the chiral vinylketene, which was prepared from D-valine. And a concise method has also been established by O-methylation to obtain the γ-pyrone.

2-2. Total Synthesis of (+)-Actinopyrone A

(+)-Actinopyrone A was obtained from silyl dienolate in 9 steps including the remote stereoinduction, Kocienski olefination, Horner–Wadsworth–Emmons olefination, and reductive deconjugation with SmI₂ and iso-propanol afforded actinopyrone A, which was identical all respects with the natural product. The first stereoselective total synthesis was completed and confirmed (+)-actinopyrone A to be (14R,15R)-configuration. We also synthesized the enantiomer of actinopyrone A showing the opposite optical rotation by starting from L-valine.
3. Total Synthesis of TMC-264, an inhibitor of IL-4 signal transduction

3-1. Synthesis of Highly Substituted Phenol and Benzoic acid

Selective protection of catechool was achieved by methoxymethylation with MOMCl and ZnCl$_2$. And highly substituted two segments were synthesized regioselectively.

3-2. Total Synthesis of TMC-264

Biaryl coupling reaction was underwent by zero-valent nickel catalyzed cyclization. Subsequent oxidation generated TMC-264, which was identical in spectroscopic characteristics ($^1$H and $^{13}$C-NMR spectra, MASS spectrum and IR spectrum) with the natural product, and completed the first total synthesis to confirm the structure.
Experimental Section

General procedure

1. Thin layer chromatography

All reactions were monitored by thin-layer chromatography using E. Merck silica gel 60F-254 pre-coated plates (0.25 mm).

2. Silica gel column chromatography

Chromatography was performed with indicated solvents using Fuji Siria Chemical silica gel BW-820MH and Kanto Chemical silica gel 60N.

Instrument

1. Optical rotation

Optical rotations were obtained on a JASCO DIP-360.

2. Melting point

Melting points were obtained on a Yanako MP-S3 and are uncorrected.

3. MASS spectrum

Mass spectra were acquired on a JEOL JMS-SX102A Mass spectrometer and JEOL JMS-GCMATE II.

4. $^1$H-NMR spectrum

$^1$H-NMR spectra were recorded on BRUKER AVANCE 600, JEOL AL 400 and JEOL AL 300. Chemical shifts were shown in parts per million from internal tetramethylsilane on the δ scale and are referenced from the residual protium in the solvent (CHCl$_3$: δ 7.27). Data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant in Hertz, assignment.

5. $^{13}$C-NMR spectrum

$^{13}$C-NMR spectra were recorded on BRUKER AVANCE 600, JEOL AL 400 and JEOL AL 300. Chemical shifts were shown in parts per million from internal tetramethylsilane on the δ scale and are referenced from the carbon resonances of the solvent (CDCl$_3$: δ 77.0).

6. Infrared spectrum

Infrared spectra were recorded on a JEOL JIR-WINSPEC 50 by KBr.

7. X-ray crystallographic analysis

Diffractometer was Rigaku RAXIS-RAPID.

\[
(1S,2S)-1,2-Bis((R)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol (11)
\]

A mixture of D-(−)-mannitol (10) (57.9 g, 318 mmol) and camphorsulfonic acid (7.39 g, 31.8 mmol) in dimethylformamide (900 ml) was added dropwise over 12 hours acetone dimethylacetal (82.4 ml, 668 mmol) at 0 °C under nitrogen atmosphere. Sodium hydride (55%, 1.39 g, 31.8 mmol) was added, and the resulting mixture was concentrated under reduced pressure to afford crude diacetone 11 (83.4 g, 318 mmol).

\[ R_f \text{ value: } 0.32 \text{ (PhMe : EtOAc = 1 : 2).} \]

\[ ^1H-NMR (600MHz, CDCl}_3): \delta 1.35 (6H, s, IP), 1.41 (6H, s, IP), 2.64 (2H, br, OH-16), 3.74 (2H, m, H-16), 3.97 (2H, dd, J = 8.0, 5.0Hz, H-14), 4.12 (2H, dd, J = 8.0, 6.0Hz, H-14'), 4.18 (2H, ddd, J = 6.0, 6.0, 5.0Hz, H-15). \]

\[ ^13C-NMR (150MHz, CDCl}_3): \delta 25.17, 26.69, 66.71, 71.18, 76.24, 109.37. \]

\[
(R)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde (12)
\]

To a vigorously stirred mixture of diacetone 11 (83.4 g, 318 mmol) in dichloromethane (830 ml) and saturated aqueous sodium bicarbonate (42 ml) was added sodium periodate (88.4 g, 413 mmol) at 10 °C. The resulting mixture was stirred at room temperature for 6 hours, and then filtered. The filtrate was distilled to remove dichloromethane at atmospheric pressure, and then distilled to afford aldehyde 12 (37.1 g, 284 mmol) under reduced pressure.

\[ R_f \text{ value: } 0.50 \text{ (hexane : EtOAc = 1 : 1).} \]

\[
(Z)-Methyl 3-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (13)
\]

\[
(S)-5-(Hydroxymethyl)furan-2(5H)-one (14)
\]

A solution of aldehyde 12 (37.1g, 284 mmol) in methanol (740 ml) was added triphenylphosphoranylidene acetic acid methylester (Ph₃P=CHCO₂Me, 143 g, 426 mmol) under nitrogen atmosphere, and left at room temperature for 14 hours. The mixture was concentrated under reduced pressure to give a residue, which was added a mixture of hexane-diethyl ether (2:1, 500 ml). The resulting mixture was filtered, and the filtrate was concentrated under reduced pressure to afford crude α,β-unsaturated ester 13 until triphenylphosphine oxide and excess Ph₃P=CHCO₂Me were removed. The α,β-unsaturated ester 13 was dissolved in 0.1M hydrochloric acid methanol, which was prepared by acetyl chloride (37.1 g, 284 mmol) and methanol (300 ml), and left at room temperature for 20 minutes. The solution was concentrated under reduced pressure to afford crude α,β-unsaturated lactone 14 (24.6 g, 215 mmol).
$R_f$ value of 13: 0.43 (hexane : EtOAc = 3 : 1).

$^1$H-NMR (400MHz, Acetone-$_d_6$): $\delta$ 1.40 (3H, s, IP), 1.46 (3H, s, IP), 3.62 (1H, dd, $J = 7.5, 6.0$Hz, H-14), 3.73 (3H, s, CO$_2$Me), 4.39 (1H, dd, $J = 7.5, 6.0$Hz, H-14'), 5.50 (1H, dddd, $J = 6.0, 6.0, 6.0, 1.5$Hz, H-15), 5.86 (1H, dd, $J = 11.0, 1.5$Hz, H-7), 6.38 (1H, dd, $J = 11.0, 6.0$Hz, H-16).

$R_f$ value of 14: 0.36 (EtOAc only).

$^1$H-NMR (600MHz, Acetone-$_d_6$): $\delta$ 2.46 (1H, dd, $J = 12.0, 3.5$Hz, H-14), 2.62 (1H, dd, $J = 12.0, 2.0$Hz, H-14'), 3.91 (1H, m, H-15), 4.93 (1H, d, $J = 5.0$Hz, H-7), 6.40 (1H, dd, $J = 5.0, 0.5$Hz, H-16).

$^{13}$C-NMR (150MHz, CDCl$_3$): $\delta$ 59.79, 83.68, 120.44, 154.04, 173.12.

To a stirred mixture of $\alpha,\beta$-unsaturated lactone 14 (24.6 g, 215 mmol) and triphenylmethyl chloride (71.7 g, 257 mmol) in N,N-dimethylformamide (500 ml) at room temperature was added ammonium nitrate (68.2 g, 852 mmol) under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 15 hours, and poured into ice water to give a gum. The residue was purified on silica gel column chromatography (BW820-MH 1200 g, PhMe : EtOAc = 30 : 1) to afford trityloxy 9 (70.6 g, 198 mmol, 32% in 5 steps).

$R_f$ value: 0.28 (hexane : EtOAc = 3 : 1).

[α]$_D^{26}$–95.3° (c 1.87, CHCl$_3$).

HRFAB-MS (m/z): 356.1382 [M+H]$^+$; calcd for C$_{24}$H$_{20}$O$_3$: 356.1413.

$^1$H-NMR (600MHz, CDCl$_3$): $\delta$ 3.36 (1H, dd, $J = 9.5, 4.5$Hz, H-14), 3.40 (1H, dd, $J = 9.5, 4.5$Hz, H-14'), 5.05 (1H, dddd, $J = 4.5, 4.5, 2.0, 1.0$Hz, H-15), 6.15 (1H, dd, $J = 5.5, 2.0$Hz, H-7), 7.38 (1H, dd, $J = 5.5, 1.0$Hz, H-16).

$^{13}$C-NMR (150MHz, CDCl$_3$): $\delta$ 63.36, 82.10, 86.92, 122.35, 127.22, 127.34, 127.76, 127.91, 128.03, 128.13, 128.25, 128.32, 128.47, 128.65, 143.20, 154.18, 172.84.

A mixture of copper(I)bridedimethylsulfidecomplex (3.05 g, 14.6 mmol) and hexamethylphosphoramid (26.0 ml, 149 mmol) in tetrahydrofuran (250 ml) was cooled to –78 °C under nitrogen atmosphere. The mixtue was added 3.0M methylmagnesium bromide (61.0 ml, 183 mmol), trimethylsilylchloride (26.0 ml, 149 mmol) and a solution of trityloxy 9 (25.0 g, 70.1 mmol) in tetrahydrofuran (150 ml), and the temperature was spontaneously increased slowoly to –50 °C 1 hour. Saturated aqueous ammonium chloride was added, and the resulting mixture was concentrated. Ethyl acetate (300 ml) was added and the layers were separated. The aqueous solution was extracted twice with ethyl acetate (300 ml×2), and the combined organic extracts were concentrated. The residue which was purified on silica gel column chromatography (BW820-MH 750 g, hexane : EtOAc = 3 : 1) to afford monomethyl 15 (23.0 g, 61.8 mmol, 88%).
$R_f$ value: 0.37 (hexane : EtOAc = 3 : 1).
$[\alpha]_D^{23} +32.3^\circ$ (c 0.98, CHCl$_3$).

HRFAB-MS (m/z): 467.2592 [M+H]$^+$; calcd for C$_{32}$H$_{35}$O$_3$: 467.2588.

$^1$H-NMR (600MHz, CDCl$_3$): $\delta$ 0.74 (3H, d, $J = 6.5$Hz, Me-18), 1.19 (3H, s, Me-17), 1.48-1.56 (1H, m), 1.60-1.74 (3H, m), 1.97-2.19 (4H, m), 2.66 (1H, dq, $J = 10.0$, 6.5Hz, H-16), 3.17 (1H, dd, $J = 10.5$, 4.0Hz, H-14$'$), 3.50 (1H, dd, $J = 10.5$, 3.0Hz, H-14$'$), 4.08 (1H, ddd, $J = 10.0$, 4.0, 3.0Hz, H-15), 5.65 (1H, m, H-9), 7.21-7.35 (9H, m), 7.44-7.51 (6H, m).

$^{13}$C-NMR (150MHz, CDCl$_3$): $\delta$ 10.36, 15.15, 22.17, 22.99, 25.41, 25.87, 38.03, 52.41, 62.55, 82.57, 86.73, 124.46, 127.12, 127.88, 128.64, 135.77, 143.60, 180.14.

![TrO](3R,4S,5S)-Dihydro-3,4-dimethyl-5-((triphenylmethyloxy)methyl)furan-2(3H)-one (16)

A stirred solution of diisopropylamine (18 ml, 126 mmol) in tetrahydrofuran (122 ml) was added 2.66M solution of n-butyllithium in hexane (41 ml, 108 mmol) at 0°C under nitrogen atmosphere, and cooled to –78°C. A solution of monomethyl 15 (33.6 g, 90.1 mmol) in tetrahydrofuran (330 ml) was added, and followed by methyl iodide (34 ml, 541 mmol). Acetic acid (13 ml, 234 mmol) was added and the resulting mixture was concentrated. Water (150 ml) and ethyl acetate (500 ml) were added, and the layers were separated. The aqueous solution was extracted twice with ethyl acetate (500 ml×2), and the combined organic extracts were concentrated to afford dimethyl 16 (32.7 g, 84.7 mmol).

$R_f$ value: 0.40 (hexane : EtOAc = 4 : 1).
$[\alpha]_D^{25} +31.6^\circ$ (c 0.93, CHCl$_3$).

HRFAB-MS (m/z): 467.2592 [M+H]$^+$; calcd for C$_{32}$H$_{35}$O$_3$: 467.2588.

$^1$H-NMR (600MHz, CDCl$_3$): $\delta$ 0.74 (3H, d, $J = 6.5$Hz, Me-18), 1.19 (3H, s, Me-17), 1.48-1.56 (1H, m), 1.60-1.74 (3H, m), 1.97-2.19 (4H, m), 2.66 (1H, dq, $J = 10.0$, 6.5Hz, H-16), 3.17 (1H, dd, $J = 10.5$, 4.0Hz, H-14$'$), 3.50 (1H, dd, $J = 10.5$, 3.0Hz, H-14$'$), 4.08 (1H, ddd, $J = 10.0$, 4.0, 3.0Hz, H-15), 5.65 (1H, m, H-9), 7.21-7.35 (9H, m), 7.44-7.51 (6H, m).

$^{13}$C-NMR (150MHz, CDCl$_3$): $\delta$ 10.36, 15.15, 22.17, 22.99, 25.41, 25.87, 38.03, 52.41, 62.55, 82.57, 86.73, 124.46, 127.12, 127.88, 128.64, 135.77, 143.60, 180.14.
A stirred solution of diisopropylamine (57 ml, 406 mmol) in tetrahydrofuran (350 ml) was added 2.66M solution of n-butyllithium in hexane (145 ml, 386 mmol) at 0 °C under nitrogen atmosphere, and cooled to −78 °C. A solution of dimethyl 16 (32.7 g, 84.7 mmol) in tetrahydrofuran (300 ml) was added, and followed by cyclohexanone (30 ml, 290 mmol). Acetic acid (45 ml, 792 mmol) was added and the mixture was concentrated. Water (150 ml) and ethyl acetate (500 ml) were added, and the layers were separated. The aqueous solution was extracted twice with ethyl acetate (500 ml×2), and the combined organic extracts were concentrated under reduced pressure to afforded aldol adduct compound 17 (38.8 g, 80.1 mmol).

Rf value: 0.24 (PhMe : EtOAc = 20 : 1).

A stirred solution of aldol adduct compound 17 (38.8 g, 80.1 mmol) in pyridine (600 ml) was added thionyl chloride (42 ml, 580 mmol) at 0 °C and stirred for 30 minutes under nitrogen atmosphere. The mixture was poured into ice water, and then ethyl acetate (600 ml) was added. The layers were separated, and the aqueous solution was extracted twice with ethyl acetate (600 ml×2). The combined organic extracts were concentrated, and the residue was purified on silica gel column chromatography (BW820-MH 1600 g, hexane : EtOAc = 6 : 1) to afford cyclohexene 8 (33.1 g, 71.0 mmol, 79% in 3 steps).

Rf value: 0.45 (PhMe : EtOAc = 20 : 1).

needles recrystallized from iso-propanol; m.p. 153.5 °C.

[α]D28 +21.8° (c 0.95, CHCl3).


1H-NMR (600MHz, CDCl3): δ 0.74 (3H, d, J = 6.5Hz, Me-18), 1.19 (3H, s, Me-17), 1.48-1.56 (1H, m), 1.60-1.74 (3H, m), 1.97-2.19 (4H, m), 2.66 (1H, dq, J = 10.0, 6.5Hz, H-16), 3.17 (1H, dd, J = 10.5, 4.0Hz, H-14), 3.50 (1H, dd, J = 10.5, 3.0Hz, H-14'), 4.08 (1H, ddd, J = 10.0, 4.0, 3.0Hz, H-15), 5.65 (1H, m, H-9), 7.21-7.35 (9H, m), 7.44-7.51 (6H, m).

13C-NMR (150MHz, CDCl3): δ 10.36, 15.15, 22.17, 22.99, 25.41, 25.87, 38.03, 52.41, 62.55, 82.57, 86.73, 124.46, 127.12, 127.88, 128.64, 135.77, 143.60, 180.14.
A mixture of lithium bromide (15.6 g, 180 mmol) in tetrahydrofuran (200 ml) was added sodium borohydride (6.5 g, 171 mmol) at 0 °C under nitrogen atmosphere, and the mixture was stirred at 65 °C for 12 hours. A solution of cyclohexene 8 (20.0 g, 42.9 mmol) was added and stirred continued for 3 hours. Acetic acid (137 ml, 792 mmol) and methanol (200 ml) was added then concentrated under reduced pressure. Water (200 ml) and ethyl acetate (600 ml) was added and the layers were separated. The aqueous solution was extracted twice with ethyl acetate (600 ml×2). The combined organic extracts were concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 600 g, hexane : EtOAc = 3 : 1) to afford diol 23 (20.0 g, 42.5 mmol).

Rf value: 0.30 (hexane : EtOAc = 3 : 1).

1H-NMR (600MHz, CDCl3): δ 0.44 (3H, d, J = 6.5Hz, Me-18), 0.86 (3H, s, Me-17), 1.44-1.62 (4H, m), 1.81-1.89 (1H, m), 1.89 (1H, dd, J = 8.5, 6.5Hz, H-16), 1.99-2.09 (3H, m), 3.06 (1H, dd, J = 8.5, 8.5Hz, H-14'), 3.24-3.43 (1H, br, OH), 3.38 (1H, dd, J = 8.5, 2.5Hz, H-14'), 3.49 (1H, d, J = 10.5Hz, H-6), 3.60 (1H, d, J = 10.5Hz, H-6'), 3.63 (1H, d, J = 8.5, 8.5, 2.5Hz, H-15), 5.49 (1H, m, H-9), 7.24-7.29 (3H, m), 7.30-7.36 (3H, m), 7.42-7.48 (3H, m).

13C-NMR (150MHz, CDCl3): δ 11.48, 15.24, 22.38, 23.38, 24.91, 25.61, 38.84, 47.53, 66.96, 70.22, 71.38, 87.14, 121.88, 127.21, 127.92, 128.54, 141.84, 143.69, 143.84.

(2S,3S,4R)-4-((Benzylxy)methyl)-4-cyclohexenyl-3-methyl-1-(triphenylmethyloxy)pentan-2-ol

A mixture of diol 23 (20.0 g, 42.5 mmol), 18-crown-6-ether (5.6 g, 21.3 mmol) and potassium carbonate (17.6 g, 127 mmol) in acetonitrile (400 ml) was added benzyl bromide (7.6 ml, 63.7 mmol) under nitrogen atmosphere, and stirred at 50 °C for 8 hours. Acetic acid (137 ml, 792 mmol) was added then concentrated under reduced pressure. Water (200 ml) and ethyl acetate (600 ml) was added and the layers were separated. The aqueous solution was extracted twice with ethyl acetate (600 ml×2), and the combined organic extracts were concentrated to afford crude benzyl compound (20.1 g, 37.7 mmol).

Rf value: 0.41 (hexane : EtOAc = 8 : 1).

1H-NMR (600MHz, CDCl3): δ 0.47 (3H, d, J = 6.5Hz, Me-18), 0.94 (3H, s, Me-17), 1.47-1.64 (4H, m), 1.83-1.93 (1H, m), 1.97-2.07 (4H, m), 3.01 (1H, dd, J = 8.5, 5.5Hz, H-14), 3.31 (1H, dd, J = 8.5, 2.5Hz, H-14'), 3.46 (1H, d, J = 8.5Hz, H-6), 3.46 (1H, d, J = 3.0Hz, H-15), 3.55 (1H, d, J = 8.5Hz, H-6'), 3.55 (1H, d, J = 8.5, 2.5Hz, H-15), 4.44 (1H, d, J = 11.5Hz, OCH2Ph), 4.50 (1H, d, J = 11.5Hz, OCH2Ph), 5.45 (1H, m, H-9), 7.21-7.39 (14H, m), 7.43-7.49 (6H, m).
A solution of crude benzyl compound (20.0 g, 42.5 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (5.6 ml, 21.3 mmol) in acetonitrile (400 ml) was added tert-butyldimethylsilyl chloride (17.6 g, 127 mmol) under nitrogen atmosphere, and left at 65 °C for 20 hours. The resulting solution was concentrated under reduced pressure. The residue was purified on silica gel column chromatography (BW820-MH 600 g, hexane : EtOAc = 15 : 1) to afford silyl compound 24 (24.1 g, 35.8 mmol, 85% in 3 steps).

$R_f$ value: 0.38 (hexane : EtOAc = 20 : 1).

$[\alpha]_D^{23}$ -3.8° (c 1.16, MeOH).

HRFAB-MS (m/z): 697.4030 [M+Na]$^+$; calcd for C$_{45}$H$_{58}$O$_3$SiNa: 697.4053.

$^1$H-NMR (600MHz, CDCl$_3$): δ 0.10 (3H, s, SiMe), 0.18 (3H, s, SiMe), 0.58 (3H, d, $J = 7.0$Hz, Me-18), 0.76 (3H, s, Me-17), 0.93 (9H, s, Si$^t$Bu), 1.44-1.56 (4H, m), 1.73-1.87 (3H, m), 1.92-2.06 (2H, m), 2.96 (1H, dd, $J = 10.0$, 2.0Hz, H-14), 3.10 (1H, dd, $J = 10.0$, 8.0Hz, H-14'), 4.07 (1H, ddd, $J = 8.0$, 2.0, 2.0Hz, H-15), 4.36 (2H, s, OCH$_2$Ph), 5.28 (1H, m, H-9), 7.19-7.32 (14H, m), 7.44-7.50 (6H, m).

$^{13}$C-NMR (150MHz, CDCl$_3$): δ –4.45, –4.11, 9.62, 18.06, 19.13, 22.53, 22.65, 25.98, 26.56, 40.20, 42.40, 45.04, 67.57, 73.06, 73.19, 76.02, 84.44, 126.74, 127.22, 127.32, 127.59, 128.13, 128.90, 138.84, 142.37, 144.35, 145.73, 199.37.

A solution of silyl compound 24 (1.10 g, 1.63 mmol) in 97% aqueous dioxane (33 ml) was added selenium dioxide (608 mg, 5.48 mmol), and left at 90 °C for 17 hours. The mixture was concentrated under reduced pressure. The residue was purified on silica gel column chromatography (BW820-MH 55 g, hexane : EtOAc = 5 : 1) to afford α,β-unsaturated ketone 27 (24.1 g, 35.8 mmol, 86%).

$R_f$ value: 0.33 (hexane : EtOAc = 20 : 1).

$[\alpha]_D^{27}$ -4.0° (c 1.18, MeOH).

HRFAB-MS (m/z): 711.3839 [M+Na]$^+$; calcd for C$_{45}$H$_{56}$O$_4$SiNa: 711.3846.

$^1$H-NMR (600MHz, CDCl$_3$): δ 0.19 (3H, s, SiMe), 0.20 (3H, s, SiMe), 0.50 (3H, d, $J = 7.0$Hz, Me-18), 0.74 (3H, s, Me-17), 0.95 (9H, s, Si$^t$Bu), 1.81-1.92 (2H, m), 2.24-2.39 (4H, m), 2.52 (1H, dq, $J = 7.0$, 2.0Hz, H-16), 2.94 (1H, dd, $J = 9.5$, 1.5Hz, H-14), 3.13 (1H, dd, $J = 9.5$, 7.5Hz, H-14'), 3.44 (1H, d, $J = 8.0$Hz, H-6), 3.92 (1H, d, $J = 8.0$Hz, H-6'), 4.01 (1H, ddd, $J = 7.5$, 2.0, 1.5Hz, H-15), 4.33 (2H, s, OCH$_2$Ph), 6.43 (1H, dd, $J = 4.0$, 4.0Hz, H-9), 7.18-7.32 (14H, m), 7.44-7.51 (6H, m).

$^{13}$C-NMR (150MHz, CDCl$_3$): δ –4.45, –4.11, 9.62, 18.06, 19.13, 22.53, 22.65, 25.98, 26.56, 40.20, 42.40, 45.04, 67.57, 73.06, 73.19, 76.02, 84.44, 126.74, 127.22, 127.32, 127.59, 128.13, 128.90, 138.84, 142.37, 144.35, 145.73, 199.37.
2,3-Dideoxy-4-O-((1,1-dimethylethylsilyl)-2,3-dimethyl-2-((1S)-2-oxocyclohexyl)-1-O-(phenylmethyl)-5-O-(triphenylmethyl)-(2R)-D-erythro-pentitol (28)
2,3-Dideoxy-4-O-((1,1-dimethylethlysilyl)-2,3-dimethyl-2-((1R)-2-oxocyclohexyl)-1-O-(phenylmethyl)-5-O-(triphenylmethyl)-(2R)-D-erythro-pentitol (29)

A solution of α,β-unsaturated ketone 27 (166 mg, 242 μmol) in dichloromethane (0.9 ml) and methanol (4.1 ml) was added nickel chloride hexahydrate (33.2 mg, 140 μmol) under nitrogen atmosphere, and cooled to 0 °C. Sodium borohydride (46.8 mg, 1.24 μmol) was added, then stirred for 10 minutes. The mixture was concentrated under reduced pressure, and the resulting residue was purified on silica gel column chromatography (BW820-MH 10 g, PhMe : cyclohexane = 5 : 1) to afford desired stereochemical compound 28 (128 mg, 185 μmol, 82%) and undesired stereochemical compound 29 (16.7 mg, 24.2 μmol, 10%).

Rf value of 28: 0.51 (PhMe : cyclohexane = 3 : 1).
needles recrystallized from methanol; m.p. 114.6 °C.

[α]D23 +4.0° (c 0.82, CHCl₃), [α]D25 +7.9° (c 0.16, MeOH).

HRFAB-MS (m/z): 713.4010 [M+Na]⁺; calcd for C₄₅H₅₈O₄SiNa: 713.4004.

¹H-NMR (600MHz, CDCl₃): δ 0.10 (3H, s, SiMe), 0.16 (3H, s, SiMe), 0.62 (3H, s, Me-17), 0.70 (3H, d, J = 8.0Hz, Me-18), 0.93 (9H, s, Si'tBu), 1.44-1.56 (2H, m), 1.59-1.68 (1H, m), 1.79-1.86 (1H, m), 1.92-1.98 (1H, m), 1.99-2.05 (1H, m), 2.20 (1H, dq, J = 3.0, 8.0Hz, H-16), 2.25-2.33 (2H, m), 2.51 (1H, dd, J = 12.0, 4.5Hz, H-8), 3.11 (1H, dd, J = 10.0, 8.0Hz, H-15), 4.08 (1H, d, J = 12.0Hz, OCH₂Ph), 4.17 (1H, d, J = 12.0Hz, OCH₂Ph), 7.15-7.31 (14H, m), 7.43-7.50 (6H, m).

¹³C-NMR (150MHz, CDCl₃): δ –4.58, –4.17, 8.92, 17.97, 18.09, 25.82, 26.01, 26.35, 28.60, 30.09, 40.67, 42.47, 44.39, 55.24, 67.12, 72.83, 73.21, 86.42, 126.71, 127.32, 127.55, 127.90, 128.13, 128.95, 138.43, 144.47, 213.22.

Rf value of 29: 0.46 (PhMe : cyclohexane = 3 : 1).
needles recrystallized from methanol; m.p. 93.6 °C.

[α]D25 +24° (c 1.34, CHCl₃), [α]D26 +29° (c 0.41, MeOH).

HRFAB-MS (m/z): 713.4010 [M+Na]⁺; calcd for C₄₅H₅₈O₄SiNa: 713.4004.

¹H-NMR (600MHz, CDCl₃): δ 0.16 (3H, s, SiMe), 0.19 (3H, s, SiMe), 0.62 (3H, s, Me-17), 0.66 (3H, d, J = 7.0Hz, Me-18), 0.94 (9H, s, Si'tBu), 1.40-1.57 (2H, m), 1.58-1.67 (1H, m), 1.79-1.87 (1H, m), 1.95-2.06 (3H, m), 2.18-2.19 (2H, m), 2.52 (1H, dd, J = 12.0, 4.5Hz, H-8), 3.06 (1H, dd, J = 10.0, 1.5Hz, H-14), 3.17 (1H, dd, J = 10.0, 7.5Hz, H-14'), 3.28 (1H, d, J = 9.5Hz, H-6, 3.51 (1H, d, J = 9.5Hz, H-6'), 4.08 (1H, d, J = 11.0Hz, OCH₂Ph), 4.12 (1H, d, J = 11.0Hz, OCH₂Ph), 4.25 (1H, ddd, J = 7.5, 2.0, 1.5Hz, H-15), 7.16-7.29 (14H, m), 7.42-7.49 (6H, m).

¹³C-NMR (150MHz, CDCl₃): δ –4.58, –3.90, 9.10, 17.95, 18.09, 25.99, 26.12, 28.69, 30.02, 40.95, 44.01, 44.18, 55.19, 67.26, 72.71, 72.86, 73.30, 86.40, 126.70, 127.11, 127.36, 127.51, 128.07, 129.01, 138.69, 144.37, 213.02.
Epimerization of 29 to afford 28

A solution of undesired stereochemical compound 29 (5.33 g, 7.72 mmol) in methanol (110 ml) was added potassium hydroxide (650 mg, 11.7 mmol), and left at 60 °C for 2 hours. The mixture was cooled to room temperature, causing the product to crystallize. The mixture was filtered, and the crystals were washed twice with methanol (50 ml×2) and dried to afford desired stereochemical compound 28 (1.15 g, 1.67 mmol). The filtrate was concentrated under reduced pressure. The resulting residue was purified on silica gel column chromatography (BW820-MH 25 g, PhMe : cyclohexane = 5 : 1) to afford desired stereochemical compound 28 (2.05 g, 2.97 mmol, combined yield 82%).

\[
\text{2,3-Dideoxy-4-O-((1,1-dimethylethylsilyl)-2,3-dimethyl-2-((1S)-2-oxocyclohexyl)-1-O-(phenylmethyl)-(2R)-D-erythro-pentitol (30)}
\]

A solution of desired stereochemical compound 28 (1.15 g, 1.67 mmol) in dichloromethane (23 ml) was added 0.92M solution of diethyl aluminium chloride in hexane (7.3 ml, 6.72 mmol) at 0 °C under nitrogen atmosphere and stirred for 2 hours. Triethylamine (3.7 ml, 26.7 mmol) and water (600 μl, 33.3 mmol) was added, and the resulting mixture was filtered and washed twice with dichloromethane (23 ml×2). The filtrate was concentrated under reduced pressure to afford crude primary alcohol 30 (747 mg, 1.67 mmol).

\[
R_f \ \text{value: 0.19 (hexane : EtOAc = 9 : 1).}
\]

\[
\text{3,4-Dideoxy-2-O-((1,1-dimethylethylsilyl)-2,3-dimethyl-4-((1S)-2-oxocyclohexyl)-5-O-(phenylmethyl)-(4R)-L-erythro-pentose (7)}
\]

A mixture of crude primary alcohol 30 (747 mg, 1.67 mmol) and neutral alumini (1.07 g) in dichloromethane (15 ml) was added pyridinium chlorochromate (634 mg, 2.94 mmol) under nitrogen atmosphere, and stirred at room temperature for 6 hours. The mixture was filtered through celite and washed twice with dichloromethane (15 ml×2). The filtrate was concentrated under reduced pressure to afford crude keto-aldehyde 7 (747 mg, 1.67 mmol).

\[
R_f \ \text{value: 0.42 (PhMe only).}
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\[
[\alpha]_{D}^{26} +21^\circ \ (c \ 1.29, \ \text{MeOH})
\]

HRFAB-MS (m/z): 445.2779 [M-H]+; calcd for C_{26}H_{41}O_{4}Si: 445.2774.
1H-NMR (600MHz, CDCl₃): δ -0.01 (3H, s, SiMe), 0.00 (3H, s, SiMe), 0.87 (9H, s, Si′Bu), 0.97 (3H, s, Me-17), 1.05 (3H, d, J = 7.5Hz, Me-18), 1.45-1.55 (1H, m), 1.56-1.71 (2H, m), 1.80-1.88 (1H, m), 1.93-2.00 (1H, m), 2.02-2.10 (1H, m), 2.26-2.33 (1H, m), 2.33-2.40 (1H, m), 2.58 (1H, dq, J = 3.5, 7.5Hz, H-16), 2.82 (1H, dd, J = 12.5, 5.0Hz, H-8), 3.30 (2H, s, H-6), 3.95 (1H, dd, J = 3.5, 3.0Hz, H-15), 4.26 (1H, d, J = 12.0Hz, OCH₂Ph), 4.40 (1H, d, J = 12.0Hz, OCH₂Ph), 7.24-7.30 (3H, m), 7.31-7.37 (2H, m), 9.43 (1H, d, J = 3.0Hz, H-14).


Keto-aldehyde 7 (570 mg, 1.28 mmol) and t-butanol (520 μl, 5.10 mmol) were dissolved in tetrahydrofuran (40 ml) under argon atmosphere at room temperature, and added 0.1M solution of samarium iodide in tetrahydrofuran (38.3 ml, 3.83 mmol) at –78 °C. The mixture was warmed to 0 °C, and added saturated aqueous sodiumbicarbonate and 20% aqueous sodium thiosulfate (6 ml). The mixture was filtered, and washed twice with ethyl acetate (6 ml×2). The filtrate was concentrated under reduced pressure. The resulting residue was purified on silica gel column chromatography (BW820-MH 50 g, PhMe only) to afford diol 31 (462 mg, 1.03 mmol, 62% in 3 steps).

Rf value: 0.40 (PhMe only).
[α]D²⁵ +30° (c 1.07, MeOH).
HRFAB-MS (m/z): 471.2913 [M+H]+; calcd for C₂₆H₄₆O₄Si: 471.2907.

1H-NMR (600MHz, CDCl₃): δ 0.11 (3H, s, SiMe), 0.12 (3H, s, SiMe), 0.91 (3H, d, J = 7.0 Hz, Me-18), 0.93 (9H, s, Si′Bu), 1.18 (3H, s, Me-17), 1.12-1.15 (2H, m), 1.31 (1H, m), 1.41 (1H, dd, J = 12.0, 2.5 Hz, H-8), 1.51 (1H, m), 1.58 (1H, dddd, J = 12.5, 12.5, 12.5, 3.5 Hz), 1.64 (1H, ddddd, J = 13.5, 13.5, 13.5, 4.0, 4.0 Hz), 1.75 (1H, m), 1.91-1.98 (2H, m), 1.95 (1H, dq, J = 7.0, 4.5 Hz, H-16), 2.31 (1H, m), 3.16 (1H, d, J = 8.5 Hz, H-6), 3.20 (1H, d, J = 8.5 Hz, H-6′), 3.31 (1H, d, J = 9.5 Hz, H-14), 4.07 (1H, dd, J = 9.5, 4.5 Hz, H-15), 4.44 (1H, d, J = 11.5 Hz, OCH₂Ph), 4.47 (1H, d, J = 11.5 Hz, OCH₂Ph), 7.24-7.37 (5H, m).

13C-NMR (150MHz, CDCl₃): δ –4.82, –4.23, 7.84, 18.09, 20.27, 20.91, 21.45, 25.86, 26.52, 37.46, 40.50, 41.66, 43.08, 71.84, 73.13, 73.56, 74.98, 77.71, 127.21, 127.28, 128.05, 128.22, 138.90.
A mixture of diol 31 (142 mg, 327 μmol) and 2-methoxypropene (700 μl, 7.31 mmol) in 1,2-dichloromethane (2.8 ml) was added pyridinium-\textit{p}-toluenesulfonic acid (16 mg, 63.5 μmol) under nitrogen atmosphere, and left at room temperature for 8 hours. Triethylamine (885 μl, 6.35 mmol) was added and concentrated under reduced pressure. The residue was purified on silica gel column chromatography (BW820-MH 7 g, hexane : \textit{i}Pr\textsubscript{2}O = 20 : 1) to afford acetonide 33 (115 mg, 234 μmol, 74%).

\[ R_f \text{ value: 0.39 (hexane : \textit{i}Pr\textsubscript{2}O = 20 : 1).} \]

Acetonide 33 (109 mg, 224 μmol) was dissolved in tetrahydrofuran (2.0 ml), and added 1.0M solution of tetra-\textit{n}-butylammonium fluoride in tetrahydrofuran (670 μl, 670 μmol) under nitrogen atmosphere. The solution was left at 50 °C for 15 hours, and concentrated under reduced pressure. The residue was purified on silica gel column chromatography (BW820-MH 5 g, hexane : EtOAc = 5 : 1) to afford secondary alcohol 34 (80.4 mg, 215 μmol, 96%).

\[ R_f \text{ value: 0.21 (hexane : EtOAc = 6 : 1).} \]

needles recrystallized from ethyl acetate; m.p. 134.6 °C.

[\alpha]_{D}^{28} +26° (c 1.57, MeOH).

HRFAB-MS (m/z): 375.2532 [M+H]⁺; calcd for C\textsubscript{23}H\textsubscript{34}O\textsubscript{4}Si: 375.2535.

\( ^{1}H\)-NMR (600MHz, CDCl\textsubscript{3}): \delta 0.86 (3H, s, Me-17), 1.10 (3H, d, J = 6.5 Hz, Me-18), 1.21 (1H, ddd, J = 12.5, 12.5, 12.5, 3.0, 3.0 Hz), 1.42 (1H, m), 1.41 (3H, s, IP), 1.45 (3H, s, IP), 1.52-1.60 (2H, m), 1.65 (1H, ddd, J = 13.0, 13.0, 13.0, 3.0, 3.0 Hz), 1.76 (1H, m), 1.90 (1H, dd, J = 12.0, 3.0 Hz), 2.08 (1H, ddd, J = 13.5, 4.0, 2.5 Hz), 2.15 (1H, dq, J = 7.5, 1.5 Hz, H-16), 3.48 (1H, br, H-15), 3.89 (1H, d, J = 2.5 Hz, H-14), 4.47 (1H, d, J = 12.0 Hz, OCH\textsubscript{2}Ph), 4.57 (1H, br, OH-15), 4.61 (1H, d, J = 12.0 Hz, OCH\textsubscript{2}Ph), 7.28-7.33 (3H, m), 7.34-7.38 (2H, m).

\( ^{13}C\)-NMR (150MHz, CDCl\textsubscript{3}): \delta 12.95, 19.93, 22.18, 23.59, 26.59, 28.64, 28.85, 36.46, 38.41, 39.83, 41.77, 72.20, 73.23, 73.36, 82.27, 83.97, 108.53, 127.96, 128.11, 128.57.
Secondary alcohol 34 (246 mg, 657 µmol) was dissolved in 1,2-dichloroethane (5.0 ml), and added potassium fluoride (1.6 g, 11.8 mmol) at 0 °C under argon atmosphere. Diethylester acetylene (530 µl, 3.28 mmol) was added, and the resulting mixture was stirred at 75 °C for 6 hours. Acetic acid (940 µl, 16.4 mmol) and water (5 ml) was added at 0 °C. The layers were separated, and the aqueous solution was extracted twice with dichloromethane (15 ml×2). The combined organic extracts were concentrated under reduced pressure, and the resulting residue was purified on silica gel column chromatography (BW820-MH 12 g, PhMe : Et₂O = 20 : 1) to afford desired compound 46 (267 mg, 491 µmol, 75%) and undesired compound 47 (267 mg, 491 µmol, 15%).

Rf value of 46: 0.45 (PhMe:iPr₂O = 6 : 1).

[α]D²⁶ +40° (c 1.15, MeOH).

HRFAB-MS (m/z): 545.3084 [M+H]+; calcld for C₃₁H₄₄O₈: 545.3114.

1H-NMR (600MHz, CDCl₃): δ 0.92 (3H, d, J = 7.0 Hz, Me-18), 1.18 (3H, s, Me-17), 1.23-1.31 (2H, m), 1.26 (3H, t, J = 7.0 Hz, CO₂CH₂CH₃), 1.35 (3H, t, J = 7.5 Hz, CO₂CH₂CH₃), 1.46 (3H, s, IP), 1.49-1.74 (5H, m), 1.52 (3H, s, IP), 1.79 (1H, m), 2.29 (1H, dq, J = 7.0, 4.0 Hz, H-16), 3.22 (2H, s, H-6), 3.95 (1H, d, J = 6.5 Hz, H-14), 4.15 (2H, q, J = 7.0 Hz, CO₂CH₂CH₃), 4.31 (1H, dq, J = 10.5, 7.0 Hz, CO₂CH₂CH₃), 4.33 (1H, dq, J = 10.5, 7.0 Hz, CO₂CH₂CH₃), 4.42 (1H, d, J = 12.5 Hz, OCH₂Ph), 4.46 (1H, d, J = 12.5 Hz, OCH₂Ph), 5.23 (1H, s, H-2), 7.27-7.37 (5H, m).

13C-NMR (150MHz, CDCl₃): δ 13.88, 14.21, 19.36, 21.29, 23.23, 26.38, 29.51, 29.77, 36.92, 38.55, 39.14, 42.84, 60.32, 62.04, 73.27, 76.79, 79.90, 81.18, 83.45, 94.38, 108.93, 127.40, 127.43, 128.28, 138.56, 141.16, 163.61, 166.08.

Rf value of 47: 0.57 (PhMe:iPr₂O = 6 : 1).

[α]D²⁷ +25° (c 0.79, MeOH).

HRFAB-MS (m/z): 545.3119 [M+H]+; calcld for C₃₁H₄₄O₈: 545.3114.

1H-NMR (600MHz, CDCl₃): δ 1.01 (3H, d, J = 7.0 Hz, Me-18), 1.18 (3H, s, Me-17), 1.22-1.35 (2H, m), 1.28 (3H, t, J = 7.0 Hz, CO₂CH₂CH₃), 1.33 (3H, t, J = 7.0 Hz, CO₂CH₂CH₃), 1.42 (6H, s, IP), 1.46 (1H, m), 1.52 (1H, m), 1.57-1.73 (3H, m), 2.10 (1H, m), 2.30 (1H, dq, J = 7.0, 4.5 Hz, H-16), 3.26 (1H, d, J = 10.0 Hz, H-6), 3.27 (1H, d, J = 10.0 Hz, H-6'), 4.05 (1H, d, J = 7.5 Hz, H-14), 4.19 (2H, q, J = 7.0 Hz, CO₂CH₂CH₃), 4.23 (1H, dq, J = 10.0, 7.0 Hz, CO₂CH₂CH₃), 4.28 (1H, dq, J = 10.0, 7.0 Hz, CO₂CH₂CH₃), 4.43 (1H, d, J = 12.0 Hz, OCH₂Ph), 4.49 (1H, d, J = 12.0 Hz, OCH₂Ph), 4.87 (1H, dd, J = 7.5, 4.5 Hz, H-15), 6.10 (1H, s, H-2), 7.24-7.36 (5H, m).

13C-NMR (150MHz, CDCl₃): δ 13.88, 14.21, 19.36, 21.29, 23.23, 26.38, 29.51, 29.77, 36.92, 38.55, 39.14, 42.84, 60.32, 62.04, 73.27, 76.79, 79.90, 81.18, 83.45, 94.38, 108.93, 127.40, 127.43, 128.28, 138.56, 141.16, 163.61, 166.08.
Diethyl 2-((3aR,4S,5S,6R,6aS,10aS)-octahydro-6-(hydroxymethyl)-2,2,5,6-tetramethyl-3aH-naphtho[1-d][1,3]dioxol-4-yl)oxy)fumarate

A solution of desired compound 46 (248 mg, 456 μmol) in ethanol (4 ml) was added 5% palladium on activated carbon (48 mg). The mixture was vigorously stirred for 2 hours under hydrogen atmosphere. The mixture was filtered and the filtrate was concentrated under reduced pressure to afford crude primatay alcohol (223 mg, 456 μmol).

Rf value: 0.30 (PhMe : Pr2O = 3 : 1).
[α]D26 +25° (c 1.54, MeOH).
HRFAB-MS (m/z): 455.2637 [M+H]+; calcd for C24H38O8: 455.2645.

1H-NMR (600MHz, CDCl3): δ 0.97 (3H, s, Me-17), 1.08 (3H, d, J = 7.0 Hz, Me-18), 1.27 (3H, s, IP), 1.30-1.39 (2H, m), 1.35 (3H, t, J = 7.0 Hz, CO2CH2CH3), 1.46 (3H, s, IP), 1.49 (3H, s, IP), 1.53-1.72 (4H, m), 1.76-1.89 (2H, m), 2.01 (1H, br), 2.11 (1H, m), 2.26 (1H, dq, J = 7.0, 2.0 Hz, H-16), 3.28 (1H, dd, J = 10.5, 6.0 Hz, H-6), 3.37 (1H, d, J = 10.5 Hz, H-6'), 3.96 (1H, d, J = 3.0 Hz, H-14), 4.11 (1H, br, H-15), 4.17 (2H, q, J = 7.0 Hz, CO2CH2CH3), 4.33 (1H, dq, J = 10.0, 7.0 Hz, CO2CH2CH3), 4.35 (1H, dq, J = 10.0, 7.0 Hz, CO2CH2CH3), 5.41 (1H, s, H-2).

13C-NMR (150MHz, CDCl3): δ 13.84, 14.14, 20.34, 21.80, 23.50, 26.27, 29.08, 35.60, 39.45, 60.69, 62.43, 78.98, 81.96, 83.11, 96.88, 109.70, 162.83, 165.58.

Diethyl 2-[(3aR,4S,5S,6R,6aS,10aS)-6-formyloctahydro-2,2,5,6-tetramethyl-5H-naphtho[1,8a-d]-1,3-dioxol-4-yl]oxy)fumarate (6)

A mixture of primary alcohol (223 mg, 456 μmol) and neutral aluminu (292 mg) in dichloromethane (4.4 ml) was added pyridinium chlorochromate (147 mg, 682 μmol) under nitrogen atmosphere, and stirred at room temperature for 6 hours. The mixture was filtered through celite and washed twice with dichloromethane (2 ml×2). The filtrate was concentrated under reduced pressure, and the resulting residue was purified on silica gel column chromatography (BW820-MH 12 g, PhMe : EtOAc = 20 : 1) to afford aldehyde 6 (158 mg, 349 μmol, 77%).

Rf value: 0.54 (PhMe : Et2O = 3 : 1).
[α]D24 +23° (c 0.73, MeOH).

1H-NMR (600MHz, CDCl3): δ 0.99 (3H, d, J = 7.0 Hz, Me-18), 1.13 (3H, s, Me-17), 1.17 (1H, m), 1.27 (1H, m), 1.28 (3H, t, J = 7.0 Hz, CO2CH2CH3), 1.36 (3H, t, J = 7.0 Hz, CO2CH2CH3), 1.43 (1H, ddd, J = 13.5, 13.5, 2.5 Hz, H-12), 1.46 (3H, s, IP), 1.49 (3H, s, IP), 1.52-1.71 (3H, m), 1.76 (1H, m), 2.02 (1H, dd, J = 12.5, 3.0 Hz, H-8), 2.14 (1H, ddd, J = 13.5, 4.5, 3.0 Hz, H-12), 2.20 (1H, dq, J = 7.0, 1.5 Hz, H-16), 4.11 (1H, d, J = 2.5 Hz, H-14), 4.15 (1H, dd, J = 2.5, 1.5 Hz, H-15), 4.17 (2H, q, J = 7.0 Hz, CO2CH2CH3), 4.35 (1H, dq, J = 10.0, 7.0 Hz, CO2CH2CH3), 4.37 (1H, dq, J = 10.0, 7.0 Hz, CO2CH2CH3), 5.39 (1H, s, H-2), 9.42 (1H, s, H-6).

13C-NMR (150MHz, CDCl3): δ 13.12, 13.94, 14.16, 16.51, 21.82, 24.31, 26.09, 28.55, 28.72, 34.81, 38.71, 41.15, 50.51, 60.61, 62.29, 78.28, 80.49, 81.62, 95.55, 110.27, 160.07, 163.11, 165.57, 205.18.
Aldehyde 6 (100 mg, 221 μmol) was dissolved in tetrahydrofuran (7 ml) under argon atmosphere, and added 1.0 M solution of sodiumbis(trimethylsilyl)amide in tetrahydrofuran (330 μl, 330 μmol) at −78 °C. The mixture was stirred for 10 minutes, and then acetic acid (19 μl, 330 μmol) was added. The resulting mixture was concentrated under reduced pressure. Water (2.0 ml) and ethyl acetate (0.5 ml) was added and the layers were separated. The aqueous solution was extracted twice with ethyl acetate (2.0 ml×2). The combined organic extracts were concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 600 g, PhMe : ’BuOMe = 6 : 1) to diastereomeric alcohol 48 (88.1 mg, 195 μmol, 88%).

Less polar of 48.

Rf value: 0.40 (PhMe : ’BuOMe = 6 : 1).

1H-NMR (600MHz, CDCl3): δ 1.12 (3H, s, Me-17), 1.28 (3H, t, J = 6.5 Hz, CO2CH2CH3), 1.32 (3H, t, J = 6.5 Hz, CO2CH2CH3), 1.35 (3H, d, J = 7.0 Hz, Me-18), 1.41 (1H, m), 1.46 (3H, s, IP), 1.46 (3H, s, IP), 1.55 (1H, m), 1.61-1.69 (2H, m), 1.74 (1H, m), 1.81 (1H, m), 2.11 (1H, m), 2.20 (1H, dq, J = 7.0, 0.5 Hz, H-16), 4.01 (1H, d, J = 2.5 Hz, H-14), 4.20 (2H, m), 4.24 (2H, m), 4.28 (1H, dd, J = 2.5, 0.5 Hz, H-15), 4.46 (1H, s, H-16).

13C-NMR (150MHz, CDCl3): δ 13.90, 13.94, 16.82, 19.86, 21.72, 24.55, 26.38, 28.78, 29.18, 34.10, 39.78, 41.14, 43.34, 61.44, 61.79, 75.75, 82.01, 82.47, 87.55, 110.04, 113.46, 150.99, 164.59, 168.58.

More polar of 48.

Rf value of diastereomer: 0.28 (PhMe : ’BuOMe = 6 : 1).

1H-NMR (600MHz, CDCl3): δ 1.09 (3H, d, J = 7.5 Hz, Me-18), 1.25 (3H, s, Me-17), 1.27 (3H, t, J = 6.5 Hz, CO2CH2CH3), 1.31 (3H, t, J = 6.5 Hz, CO2CH2CH3), 1.32-1.45 (2H, m), 1.44 (3H, s, IP), 1.47 (3H, s, IP), 1.53 (1H, m), 1.60-1.73 (3H, m), 1.80 (1H, dd, J = 11.5, 2.5 Hz, H-8), 2.07 (1H, m), 2.20 (1H, m), 2.37 (1H, dq, J = 7.5, 0.0 Hz, H-16), 3.29 (1H, d, J = 4.0 Hz, OH-6), 3.97 (1H, d, J = 2.5 Hz, H-14), 4.10 (1H, dd, J = 2.5, 0.0 Hz, H-15), 4.19 (2H, m), 4.21 (1H, d, J = 4.0 Hz, H-6), 4.23 (2H, m).

13C-NMR (150MHz, CDCl3): δ 13.86, 14.59, 20.95, 22.07, 26.29, 27.24, 28.83, 29.11, 29.19, 33.18, 39.24, 41.59, 42.11, 61.55, 61.72, 77.53, 81.74, 83.36, 85.79, 109.53, 114.84, 150.83, 164.54, 168.68.
A solution of diastereomeric alcohol 48 (88.1 mg, 195 μmol) in toluene (1.7 ml) was added a solution of 0.45M solution of o-iodoxybenzoyl acid in dimethylsulfoxide (870 μl, 390 μmol) under argon atmosphere, and left at room temperature for 3 hours. 20% aqueous sodium thiosulfate (500 μl) was added, and the resulting layers were separated. The aqueous solution was extracted twice with toluene (1.5 ml×2). The combined organic extracts were concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 4.4 g, PhMe : EtOAc = 9 : 1) to ketone 49 (81.0 mg, 180 μmol, 73%).

$\text{R}_f$ value: 0.40 (PhMe : EtOAc = 9 : 1).

[α]D$^2$ +51° (c 0.84, MeOH).

HRFAB-MS (m/z): 451.2319 [M+H]$^+$; calcld for C$_{24}$H$_{34}$O$_8$: 451.2332.

$^1$H-NMR (600MHz, CDCl$_3$): δ 1.06 (3H, d, J = 7.5 Hz, Me-18), 1.21 (3H, s, Me-17), 1.22-1.38 (2H, m), 1.31 (3H, t, J = 7.0 Hz, CO$_2$CH$_2$CH$_3$), 1.42 (1H, m), 1.48 (3H, s, IP), 1.52-1.68 (4H, m), 1.75 (1H, m), 2.16 (1H, m), 2.46 (1H, dq, J = 7.5, 0.5 Hz, H-16), 4.18 (1H, d, J = 2.5 Hz, H-14), 4.28 (1H, dq, J = 10.5, 7.0 Hz, CO$_2$CH$_2$CH$_3$), 4.48 (1H, dq, J = 10.5, 7.0 Hz, CO$_2$CH$_2$CH$_3$)

$^{13}$C-NMR (150MHz, CDCl$_3$): δ 13.88, 13.93, 14.87, 17.05, 21.58, 24.28, 25.96, 28.73, 29.07, 31.13, 40.98, 41.07, 53.08, 61.69, 62.81, 80.71, 82.21, 85.27, 110.64, 120.22, 150.79, 163.11, 165.85, 198.72.

A mixture of ketone 49 (81.0 mg, 180 μmol) in 50% aqueous tetrahydrofuran (2.7 ml) was added sodium carbonate (72.8 mg, 687 μmol), and stirred at room temperature for 3 hours. The mixture was concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 4.0 g, n-butanol : EtOH : CHCl$_3$ = 8 : 1 : 1) to hydrolysis 51 (70.0 mg, 166 μmol, 93%).

$R_f$ value: 0.46 (n-butanol : EtOH : CHCl$_3$ = 8 : 1 : 1).

$^1$H-NMR (600MHz, CDCl$_3$): δ 0.93 (3H, d, J = 7.5 Hz, Me-18), 1.02 (1H, m), 1.20 (3H, t, J = 7.0 Hz, CO$_2$CH$_2$CH$_3$), 1.26 (3H, s, IP), 1.29 (3H, s, IP), 1.36 (3H, s, Me-17), 1.49-1.58 (2H, m), 1.63 (1H, m), 1.76 (1H, m), 1.85 (1H, m), 2.40 (1H, dq, J = 7.0, 0.0 Hz, H-16), 3.96 (1H, m, H-14), 4.33 (1H, dd, J = 2.5, 0.5 Hz, H-15), 4.39 (1H, m, CO$_2$CH$_2$CH$_3$).
A mixture of hydolysis 51 (30.0 mg, 71.1 μmol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (41.0 mg, 213 μmol) and pyridine (17 μl, 213 μmol) in dichloromethane (900 μl) was added ethanethiol (26 μl, 355 μmol) under argon atmosphere, and left at room temperature for 1 hour. The mixture was concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 1.5 g, PhMe : iPr2O = 7 : 1) to thioester 54 (21.9 mg, 46.9 μmol, 66%).

$R_f$ value: 0.41 (PhMe : iPr2O = 6 : 1).

$[\alpha]_{D}^{22} = -2.0^\circ$ (c 1.47, MeOH).

HRFAB-MS ($m/z$): 467.2098 [M+H]$^+$; calcld for C$_{24}$H$_{34}$O$_7$S: 467.2104.

$^1$H-NMR (600MHz, CDCl$_3$): δ 1.08 (3H, d, $J$ = 7.5 Hz, Me-18), 1.21 (3H, s, Me-17), 1.32 (1H, m), 1.28 (3H, t, $J$ = 7.0 Hz, SCH$_2$CH$_3$), 1.35 (1H, dddd, $J$ = 13.5, 13.5, 13.5, 3.5 Hz), 1.42 (1H, m), 1.49 (3H, s, IP), 1.50 (3H, s, IP), 1.56 (1H, m), 1.58-1.69 (3H, m), 1.75 (1H, m), 2.17 (1H, m), 4.21 (1H, d, $J$ = 2.5 Hz, H-15).

$R_f$ value: 0.20 (CHCl$_3$ : methyl ethyl ketone = 4 : 1).

HRFAB-MS ($m/z$): 379.1764 [M+H]$^+$; calcld for C$_{20}$H$_{26}$O$_7$: 379.1757.

$^1$H-NMR (600MHz, CDCl$_3$): δ 1.00 (3H, d, $J$ = 7.5 Hz, Me-18), 1.03 (3H, d, $J$ = 7.5Hz, Me-18), 1.56 (1H, m), 1.21 (6H, s, Me-17), 1.23-1.32 (2H, m), 1.35-1.48 (4H, m), 1.49 (12H, s, IP), 1.53-1.72 (7H, m), 1.75 (1H, m), 1.89 (1H, m), 2.19 (1H, m), 2.23 (1H, m), 2.49 (1H, dq, $J$ = 7.5, 1.5 Hz, H-16), 2.50 (1H, dq, $J$ = 7.5, 1.5 Hz, H-16), 4.23 (1H, d, $J$ = 1.5 Hz, H-14), 4.29 (1H, d, $J$ = 1.5 Hz, H-14), 4.66 (1H, dd, $J$ = 1.5, 1.5 Hz, H-15), 4.73 (1H, dd, $J$ = 1.5, 1.5 Hz, H-15), 5.81 (2H, br), 5.90 (1H, s, H-4), 5.95 (1H, s, H-4).
\(^{13}\)C-NMR (150MHz, CDCl\(_3\)): \(\delta\) 13.79, 14.18, 16.76, 21.31, 21.35, 24.58, 25.53, 25.95, 29.01, 29.06, 29.14, 30.90, 30.95, 40.65, 40.94, 42.26, 43.14, 53.23, 53.28, 79.71, 79.90, 82.52, 82.56, 87.77, 87.93, 92.86, 92.92, 100.80, 100.81, 110.86, 111.03, 168.44, 168.60, 176.70, 176.76, 195.10, 195.20.

\(\text{Diastereomeric lactol 55 (5.1 mg, 13.5 \text{ \(\mu\)mol) was dissolved 0.28M solution of triphenylphosphine in dichloromethane (193 \text{ \(\mu\)l, 54.0 \text{ \(\mu\)mol) under argon atmosphere. 0.21M solution of carbon tetrabromide in dichloromethane (193 \text{ \(\mu\)l, 40.5 \text{ \(\mu\)mol) was added, and the resulting solution was left at 0 \(^\circ\)C for 30 minutes. The solution was concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 510 mg, PhMe : methyl ethyl ketone = 4 : 1) to lactone 50 (3.7 mg, 10.2 \text{ \(\mu\)mol, 76%).}

\[R_f\text{ value: 0.50 (CHCl}_3 : \text{methyl ethyl ketone = 4 : 1).}\]

\([\alpha]_D^{27} +120^\circ\ (c 0.76, \text{MeOH}).\]

HRFAB-MS (m/z): 363.1808 [M+H]\(^+\); calcd for C\(_{20}\)H\(_{26}\)O\(_6\): 363.1807.

\(^1\)H-NMR (600MHz, CDCl\(_3\)): \(\delta\) 1.01 (3H, d, \(J = 7.5\) Hz, Me-18), .14 (1H, ddddd, \(J = 12.5, 12.5, 12.5, 3.5, 3.5\) Hz), 1.23 (3H, s, Me-17), 1.27 (1H, ddd, \(J = 13.5, 13.5, 3.5\) Hz), 1.45 (1H, m), 1.50 (6H, s, IP), 1.56 (1H, m), 1.59-1.70 (3H, m), 1.77 (1H, m), 2.23 (1H, ddd, \(J = 14.0, 4.0, 2.5\) Hz), 2.51 (1H, dq, \(J = 7.5, 1.5\) Hz, H-16), 4.19 (1H, d, \(J = 1.5\) Hz, H-14), 4.60 (1H, d, \(J = 16.5\) Hz, H-4), 4.61 (1H, dd, \(J = 1.5, 1.5\) Hz, H-15), 4.66 (1H, d, \(J = 16.5\) Hz, H-4').

\(^{13}\)C-NMR (150MHz, CDCl\(_3\)): \(\delta\) 14.20, 16.77, 21.37, 24.48, 26.00, 29.02, 29.13, 30.94, 41.05, 43.12, 53.06, 65.80, 79.84, 82.64, 87.59, 101.01, 111.02, 169.01, 178.69, 193.90.

\(\text{Lactone 50 (2.8 mg, 7.7 \text{ \(\mu\)mol) was added 70% aqueous trifluoroacetic acid (300 \text{ \(\mu\)l) and left at 50 \(^\circ\)C for 13 hours. The solution was concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 560 mg, CHCl\(_3 : \text{methyl ethyl ketone = 1 : 1) to di-ol 59 (1.7 mg, 5.3 \text{ \(\mu\)mol, 69%).}

\[R_f\text{ value: 0.16 (CHCl}_3 : \text{methyl ethyl ketone = 2 : 1).}\]

\([\alpha]_D^{27} +97^\circ\ (c 0.43, \text{MeOH}).\]

HRFAB-MS (m/z): 323.1490[M+H]\(^+\); calcd for C\(_{17}\)H\(_{22}\)O\(_6\): 323.1495.
1H-NMR (600MHz, Acetone-d6): $\delta$ 0.96 (3H, d, $J = 7.0$ Hz, Me-18), 1.10 (1H, ddddd, $J = 12.5$, 12.5, 12.5, 3.0, 3.0 Hz), 1.17 (3H, s, Me-17), 1.22 (1H, ddd, $J = 13.0$, 13.0, 3.5 Hz), 1.29 (1H, m), 1.43 (1H, m), 1.52-1.73 (4H, m), 2.03-2.08 (2H, m), 2.75 (1H, dq, $J = 7.0$, 3.0 Hz, H-16), 3.36 (1H, s, OH-13), 3.70 (1H, d, $J = 6.5$ Hz, H-14), 4.63 (1H, d, $J = 16.0$ Hz, H-4), 4.66 (1H, d, $J = 16.0$ Hz, H-4'), 4.80 (1H, d, $J = 3.0$ Hz, H-15), 5.02 (1H, d, $J = 6.5$ Hz, OH-14).

13C-NMR (150MHz, Acetone-d6): $\delta$ 13.44, 17.91, 21.66, 24.47, 26.74, 33.33, 39.98, 43.17, 53.58, 66.45, 69.24, 79.24, 93.43, 101.32, 178.73, 194.84.

(5S,6R,6aS,10aS,11R,13S)-Octahydro-6,6a-dihydroxy-11,13-dimethyl-3-methylene-5,11-dimethano-furo[3,4-d][3]benzoxonin-1,12(3H,5H)-dione, 

(−)-tetrodecamycin (1)

Di-ol 59 (2.1 mg, 6.5 μmol) was dissolved 0.46M solution of diisopropylethylamine in dioxane (100 μl, 46.0 μmol) under argon atmosphere, and added Eschenmoser's salt (3.8 mg, 20.5 μmol). The mixture was stirred at room temperature for 10 hours. 2.6M solution of methyl iodide in dioxane (50 μl, 130 μmol) was added and stirred at room temperature for 11 hours. The mixture was concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 420 mg, PhMe : EtOAc = 1 : 1) to (−)-tetrodecamycin (1) (1.1 mg, 3.3 μmol, 50%).

Rf value: 0.46 (PhMe : EtOAc = 1 : 2).

[α]D$^26$ −6.0 (c 0.42, MeOH) [natural [α]D$^{23}$ −6.0 (c 0.50, MeOH)].


1H-NMR (600MHz, CDCl3): $\delta$ 1.01 (3H, d, $J = 7.5$ Hz, Me-18), 1.12 (1H, ddddd, $J = 13.0$, 13.0, 13.0, 3.0, 3.0 Hz, H-10), 1.25 (3H, s, Me-17), 1.25 (1H, d, $J = 12.5$, 4.0 Hz, H-8), 1.43 (1H, ddddd, $J = 13.0$, 13.0, 13.0, 3.0, 3.0 Hz, H-11), 1.50 (1H, m, H-9 & H-11), 1.79 (1H, m, H-10), 2.04 (1H, s, OH-13), 2.09 (1H, ddd, $J = 14.0$, 5.0, 2.5 Hz, H-12), 2.65 (1H, dq, $J = 7.5$, 3.0 Hz, H-16), 3.08-3.16 (1H, brs, OH-14), 3.61 (1H, brs, H-14), 4.81 (1H, dd, $J = 3.0$, 0.5 Hz, H-15), 5.27 (1H, d, $J = 2.5$ Hz, H-5'), 5.37 (1H, d, $J = 2.5$ Hz, H-5).

13C-NMR (150MHz, CDCl3): $\delta$ 13.6, 17.56, 20.87, 23.52, 25.73, 32.72, 39.70, 42.84, 53.10, 69.01, 78.57, 92.00, 96.40, 100.79, 148.39, 164.64, 164.64, 194.53.
$^1$H-NMR spectrum of 9 (600MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of 9 (150MHz, CDCl$_3$)
$^1$H-NMR spectrum of 15 (600MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of 15 (150MHz, CDCl$_3$)
$^1\text{H-NMR}$ spectrum of 16 (600MHz, CDCl$_3$)

$^{13}\text{C-NMR}$ spectrum of 16 (150MHz, CDCl$_3$)
$^1$H-NMR spectrum of 8 (600MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of 8 (150MHz, CDCl$_3$)
$^1$H-NMR spectrum of 23 (600MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of 23 (150MHz, CDCl$_3$)
$^1$H-NMR spectrum of benzyl compound (600MHz, CDCl$_3$)
$^1$H-NMR spectrum of 24 (600MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of 24 (150MHz, CDCl$_3$)
$^1$H-NMR spectrum of **27** (600MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of **27** (150MHz, CDCl$_3$)
$^1$H-NMR spectrum of 28 (600MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of 28 (150MHz, CDCl$_3$)
$^1$H-NMR spectrum of 29 (600MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of 29 (150MHz, CDCl$_3$)
$^1$H-NMR spectrum of 7 (600MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of 7 (150MHz, CDCl$_3$)
$^1$H-NMR spectrum of 31 (600MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of 31 (150MHz, CDCl$_3$)
1H-NMR spectrum of 34 (600MHz, CDCl₃)

13C-NMR spectrum of 34 (150MHz, CDCl₃)
$^1$H-NMR spectrum of 46 (600MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of 46 (150MHz, CDCl$_3$)
H-NMR spectrum of 47 (600MHz, CDCl₃)

13C-NMR spectrum of 47 (150MHz, CDCl₃)
$^1$H-NMR spectrum of primary alcohol from 46 (600MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of primary alcohol from 46 (150MHz, CDCl$_3$)
The NMR spectra of compound 6 are shown below:

- **$^1$H-NMR spectrum of 6 (600MHz, CDCl$_3$)**

- **$^{13}$C-NMR spectrum of 6 (150MHz, CDCl$_3$)**
$^1$H-NMR spectrum of 48 (600MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of 48 (150MHz, CDCl$_3$)
HMBC of 48 (600MHz, CDCl₃)
H-NMR spectrum of 48' (600MHz, CDCl₃)

^1^H-NMR spectrum of 48' (600MHz, CDCl₃)

'13C-NMR spectrum of 48' (150MHz, CDCl₃)
$^1$H-NMR spectrum of 49 (600MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of 49 (150MHz, CDCl$_3$)
$^1$H-NMR spectrum of 51 (600MHz, CDCl$_3$)
\( ^1\text{H-NMR spectrum of 54} \ (600\text{MHz, CDCl}_3) \)

\( ^{13}\text{C-NMR spectrum of 54} \ (150\text{MHz, CDCl}_3) \)
$^1$H-NMR spectrum of 55 (600MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of 55 (150MHz, CDCl$_3$)
$^1$H-NMR spectrum of 50 (600MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of 50 (150MHz, CDCl$_3$)
$^1$H-NMR spectrum of 59 (600MHz, Acetone-$d_6$)

$^{13}$C-NMR spectrum of 59 (150MHz, Acetone-$d_6$)
H-NMR spectrum of synthetic (–)-tetrodecamycin (1) (600MHz, CDCl₃)

H-NMR spectrum of synthetic (–)-tetrodecamycin (1) (600MHz, CDCl₃)
$^{13}$C-NMR spectrum of synthetic (–)-tetrodecamycin (1) (150MHz, CDCl$_3$)

MASS spectrum of synthetic (–)-tetrodecamycin (1) (FAB+)
$^1$H-NMR spectrum of natural (−)-tetrodecamycin (1) (600MHz, CDCl$_3$)
2. Total Synthesis and Structural Determination of Actinopyrone A

\[ \text{S} \]
\[ \text{N} \]
\[ \text{N} \]
\[ \text{Ph} \]
\[ \text{O} \]
\[ \text{O} \]
\[ \text{O} \]
\[ \text{Me} \]

5-(3-Methylbut-3-enylthio)-1-phenyl-1\( H \)-tetrazole (82)

A mixture of 3-methyl-3-butene-1-ol (80) (131 µl, 1.30 mmol), 1-phenyl-1\( H \)-tetra-5-thiol (81) (178 mg, 1.00 mmol) and triphenylphosphine (341 mg, 1.30 mmol) in tetrahydrofuran (2.7 ml) was added 2.2M solution of diethyl azodicarboxylate in toluene (590 µl, 1.30 mmol) at 0 °C under argon atmosphere, and stirred for 2 hours. The mixture was concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 20 g, hexane : EtOAc = 6 : 1) to thioether 82 (226 mg, 917 µmol, 92%).

R\(_ f\) value: 0.28 (hexane : EtOAc = 6 : 1).

\(^1\)H-NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.77 (3H, s, Me-8), 2.54 (2H, t, \( J \)=13.0 Hz, H-9), 3.54 (2H, t, \( J \)=13.0 Hz, H-10), 4.78 (1H, m, H-7), 4.84 (1H, m, H-7'), 7.51-7.64 (5H, m, Ph).

\(^13\)C-NMR (100 MHz, CDCl\(_3\)) \( \delta \) 22.0, 31.4, 36.8, 77.2, 112.4, 123.8, 129.8, 130.1, 133.7, 142.5, 154.3.

A mixture of thioether 82 (2.52 g, 10.1 mmol) and sodium bicarbonate (3.04 g, 36.2 mmol) in dichloromethane (25 ml) was added \( m \)-chloroperbenzoic acid (6.12 g, 35.5 mmol) which was dissolved in dichloromethane (75 ml) at 0 °C under argon atmosphere, and stirred for 1 hour. Sodium bicarbonate (0.85 g, 10.1 mmol) and \( m \)-chloroperbenzoic acid (1.75 g, 10.1 mmol) which was dissolved in dichloromethane (20 ml) was added. The mixture was warmed to room temperature and stirred for 71 hours. Dichloromethane (100 ml) was added and washed with 1.0M aqueous sodium thiosulfate (45 ml), 1.0M aqueous sodium carbonate (45 ml), water (40 ml) and brine (40 ml), subsequently. The resulting mixture was concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 200 g, hexane : EtOAc = 2 : 1) to epoxide 78 (2.54 g, 8.63 mmol, 86%).

R\(_ f\) value: 0.24 (hexane : EtOAc = 2 : 1).

\(^1\)H-NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.40 (3H, s, Me-8), 2.21 (1H, ddd, \( J \)=14.4, 10.8, 5.4 Hz, H-9), 2.32 (1H, ddd, \( J \)=14.4, 10.8, 5.6 Hz, H-9'), 2.66 (1H, d, \( J \)=4.0 Hz, H-7), 2.71 (1H, d, \( J \)=4.0 Hz, H-7'), 3.75 (1H, ddd, \( J \)=14.8, 10.8, 5.4 Hz, H-10), 3.83 (1H, ddd, \( J \)=14.8, 10.8, 5.6 Hz, H-10'), 7.56-7.64 (3H, m, Ph), 7.65-7.73 (2H, m, Ph).

\(^13\)C-NMR (100 MHz, CDCl\(_3\)) \( \delta \) 21.0, 28.9, 52.1, 53.3, 54.8, 125.1, 129.8, 131.5, 133.0, 153.3.


IR (KBr) 3072, 3056, 2981, 2967, 2927, 1949, 1348, 1324, 1155, 894, 765, 694.
2-(Chloromethyl)-6-methoxy-3,5-dimethyl-4H-pyran-4-one (84)

A solution of 2-methoxy-γ-pyrone (73) (320 mg, 2.50 mmol) in tetrahydrofuran (8.4 ml) was added 1.06M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (3.07 ml, 3.25 mmol) at −78 °C under argon atmosphere. N-Chlorosuccinimide (0.85 g, 10.1 mmol) which was dissolved in tetrahydrofuran (20 ml) was added, and the resulting mixture was stirred for 1 hour. The mixture was concentrated, then ethyl acetate (300 ml) and water (10 ml) was added. The layers were separated, and the aqueous solution was extracted twice with ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium bicarbonate (10 ml×2) and brine (10 ml), subsequently. The organic extracts were concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 50 g, hexane : EtOAc = 1 : 1) to chloride 84 (338 mg, 1.67mmol, 67%).

R<sub>f</sub> value: 0.19 (hexane : EtOAc = 1 : 1).

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ 1.86 (3H, s, Me), 2.04 (3H, s, Me), 4.01 (3H, s, OMe), 4.45 (2H, s, H-6).

<sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ 7.0, 9.8, 39.4, 55.6, 100.4, 121.4, 151.7, 162.2, 180.2.

Diethyl (6-methoxy-3,5-dimethyl-4-oxo-4H-pyran-2-yl)methylphosphonate (79)

Chloride 84 (141 mg, 695 μmol) was dissolved in triethoxy phosphate (2.1 ml, 12.2 mmol) under argon atmosphere, and stirred at 140 ºC for 6.5 hours. The mixture was concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 20 g, PhMe : acetone = 3 : 2) to phosphine 79 (169 mg, 555 μmol, 80%).

R<sub>f</sub> value: 0.19 (PhMe : acetone = 1 : 1).

prisms recrystallized from PrO, mp 70.0-70.4 ºC.

HRFAB-MS (m/z): 305.1158 [M+H]<sup>+</sup>; calcd for C<sub>13</sub>H<sub>22</sub>O<sub>6</sub>P: 305.1154.

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ 1.32 (6H, t, J=7.1 Hz), 1.85 (3H, s), 1.98 (3H, d, J=3.7 Hz), 3.14 (2H, d, J=22.0 Hz), 3.99 (3H, s), 4.08-4.17 (4H, m).

<sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ 6.9, 10.4 (d, J=3 Hz), 16.5 (d, J=6 Hz), 30.1 (d, J=140 Hz), 55.7, 62.6 (d, J=6 Hz), 99.8, 120.8 (d, J=9 Hz), 149.4 (d, J=12 Hz), 162.3, 180.4 (d, J=3 Hz).

IR (KBr) 2985, 2967, 2927, 1672, 1602, 1463, 1328, 1253, 1238, 1020, 977, 792.

—92—
A mixture of oxazolidone 77 (5.26 g, 15.5 mmol) and trans-2-methyl-2-butenal (65) (2.24 ml, 23.2 mmol) in dichloromethane (50 ml) was added titanium tetrachloride (1.78 ml, 16.3 mmol) which was dissolved in dichloromethane (152 ml) at –78 °C under argon atmosphere. The resulting mixture was stirred at –60 °C for 17 hours. Pyridine (1.3 ml, mmol) was added at 0 °C, and the resulting mixture was poured into saturated aqueous sodium bicarbonate (100 ml). The mixture was filtered through Celite, and the filtrate was separated. The aqueous solution was extracted with chloroform (50 ml) and the combined organic extracts were washed with brine (30 ml). The organic extracts were concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 500 g, hexane : EtOAc = 3 : 1) to anti-adduct 86 (3.89 g, 12.6 mmol, 82%).

Rf value: 0.23 (hexane : EtOAc = 2 : 1).

\[ \alpha_d^{25} +16.5^\circ \text{ (c 1.16, CH}_2\text{Cl}_2) \].

\[ ^1\text{H-NMR (400 MHz, CDCl}_3 \] \( \delta \) 0.82 (3H, d, J=6.6 Hz, Me-14), 0.92 (3H, d, J=7.1 Hz, 'Pr), 0.93 (3H, d, J=7.1 Hz, 'Pr), 1.63 (3H, d, J=6.6 Hz, Me-18), 1.66 (3H, d, J=1.2 Hz, Me-16), 1.97 (3H, d, J=1.2 Hz, Me-12), 2.34 (1H, dqq, J=7.1, 7.1, 4.7 Hz, 'Pr), 2.74 (1H, ddq, J=10.3, 9.3, 6.6 Hz, H-14), 3.31 (1H, d, J=1.7 Hz, OH-15), 3.66 (1H, dd, J=9.3, 1.7 Hz, H-15), 4.18 (1H, dd, J=9.0, 5.6 Hz), 4.34 (1H, dd, J=9.0, 9.0 Hz), 4.57 (1H, dd, J=9.0, 5.6, 4.7 Hz), 5.47 (1H, q, J=6.6 Hz, H-17), 5.78 (1H, dd, J=10.3, 1.2 Hz, H-13).

\[ ^13\text{C-NMR (100 MHz, CDCl}_3 \] \( \delta \) 10.4, 13.1, 14.0, 15.2, 16.1, 17.8, 28.4, 37.8, 58.1, 63.4, 77.2, 82.2, 123.6, 131.7, 134.8, 142.0, 154.5, 171.5.

A mixture of anti-adduct 86 (3.01 g, 9.78 mmol) and 2,6-lutidine (1.71 ml, 14.7 mmol) in dichloromethane (60 ml) was added t-butyldimethylsilyl trifluoromethanesulfonyl (2.23 ml, 12.7 mmol) at 0 °C under argon atmosphere, and the resulting mixture was stirred for 1 hour. t-Butyldimethylsilyl trifluoromethanesulfonyl (171 µl, 977 µmol) was added, and the mixture was stirred for 30 minutes. Water (20 ml) was added at 0 °C, and the layer of mixture was separated. The aqueous solution was extracted with dichloromethane (20 ml) and the combined organic extracts were washed with brine (20 ml). The organic extracts were concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 120 g, hexane : EtOAc = 10 : 1) to silyl compound 87 (3.85 g, 9.12 mmol, 93%).
$R_f$ value: 0.55 (hexane : EtOAc = 3 : 1).

$[\alpha]_D^{22} +14.5^\circ$ (c 1.16, CH$_2$Cl$_2$).

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ –0.06 (3H, s, SiMe), 0.01 (3H, s, SiMe), 0.84 (9H, s, Si'Bu), 0.84 (3H, d, $J$=7.5 Hz, Me-14), 0.89 (3H, d, $J$=7.5 Hz, 'Pr), 0.91 (3H, d, $J$=7.5 Hz, 'Pr), 1.56 (3H, s, Me-16), 1.59 (3H, d, $J$=6.7 Hz, Me-18), 1.92 (3H, d, $J$=1.8 Hz, Me-12), 2.39 (1H, dq, $J$=7.5, 7.5, 4.7 Hz, 'Pr), 2.64 (1H, ddq, $J$=10.1, 7.5, 7.5 Hz, H-14), 3.76 (1H, d, $J$=7.5 Hz, H-15), 4.17 (1H, dd, $J$=9.2, 9.2 Hz), 4.17 (1H, ddd, $J$=9.2, 4.7, 4.7 Hz), 5.36 (1H, q, $J$=6.7 Hz, H-17), 5.93 (1H, dd, $J$=10.1, 1.8 Hz, H-13).

$^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ –5.1, –4.8, 11.0, 12.9, 14.2, 14.9, 16.5, 17.9, 18.1, 25.8, 28.2, 37.8, 58.4, 63.4, 82.7, 121.7, 130.8, 136.7, 142.3, 153.4, 171.8.

A solution of silyl compound 87 (1.41 g, 2.70 mmol) in dichloromethane (23 ml) was added to a 0.99M solution of diisopropylaluminium hydride in toluene (4.09 ml, 4.05 mmol) dissolved in dichloromethane (123 ml) at –78 °C under argon atmosphere. The resulting mixture was stirred for 2 hours. Methanol (3.0 ml) and sodium sulfate decahydrate were added, and the mixture was stirred for 1 hour. The mixture was filtered through Celite, and the filtrate was concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 50 g, hexane : EtOAc = 10 : 1) to aldehyde 71 (545 mg, 1.84 mmol, 68%).

$R_f$ value: 0.44 (hexane : EtOAc = 10 : 1).

$[\alpha]_D^{23} +9.60^\circ$ (c 0.50, CH$_2$Cl$_2$).

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ –0.07 (3H, s, SiMe), –0.03 (3H, s, SiMe), 0.81 (9H, s, Si'tBu), 0.89 (3H, d, $J$=6.7 Hz, Me-14), 1.57 (3H, s, Me-16), 1.60 (3H, d, $J$=6.7 Hz, Me-18), 1.75 (3H, d, $J$=1.3 Hz, Me-12), 2.85 (1H, ddq, $J$=10.1, 8.0, 6.7 Hz, H-14), 3.81 (1H, d, $J$=8.0 Hz, H-15), 5.40 (1H, q, $J$=6.7 Hz, H-17), 6.36 (1H, dd, $J$=10.1, 1.3 Hz, H-13), 9.40 (1H, s, H-11).

$^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ –5.1, –4.7, 9.5, 10.9, 13.0, 16.5, 18.1, 25.7, 38.4, 82.8, 122.3, 136.3, 139.0, 158.8, 195.6.

A solution of epoxide 78 (83.6 mg, 284 μmol) in dimethoxyethane (420 μl) was added to a 0.99M sodiumbis(trimethylsilyl)amide in tetrahydrofuran (273 μl, 270 μmol) at –78 °C under argon atmosphere, and the resulting mixture was stirred at –60 °C for 30 minutes. Aldehyde 71 (42.1 mg, 142 μmol) which was dissolved in dimethoxyethane (600 μl) was added, and the stirring mixture was warmed to room temperature over 4.5 hours. Ethyl acetate (5.0 ml) and water (2.5 ml) was added, and the layer was separated. The aqueous solution was extracted with ethyl acetate (3.0 ml) and the combined organic extracts were washed with brine (2.5 ml). The organic extracts were concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 9 g, hexane : EtOAc = 25 : 1) to triene 88 (43.1 mg, 118 μmol).
$R_f$ value: 0.48 (hexane : EtOAc = 10 : 1).

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ −0.09 (3H, SiMe), −0.07 (3H, SiMe), 0.76 (3H, d, $J=6.8$ Hz, Me-14), 0.80 (9H, s, SiBu), 1.31 (3H, d, $J=2.0$ Hz, Me-14), 1.55 (3H, s, Me-12), 1.58 (3H, d, $J=6.8$ Hz, Me-18), 1.73 (3H, s, Me-16), 2.30 (1H, dd, $J=14.4$, 7.2 Hz, H-9), 2.41 (1H, dd, $J=14.4$, 8.0 Hz, H-9'), 2.60 (1H, d, $J=4.8$ Hz, H-7), 2.62 (1H, dd, $J=8.0$, 2.0 Hz, H-14), 2.65 (1H, d, $J=4.8$ Hz, H-7), 3.63 (1H, d, $J=8.0$ Hz, H-15), 5.21 (1H, d, $J=8.0$ Hz, H-13), 5.31 (1H, q, $J=6.8$ Hz, H-17), 5.45 (1H, ddd, $J=14.6$, 8.0, 7.2 Hz, H-10), 6.50 (1H, d, $J=14.6$ Hz, H-11).

$\text{CHO}$

(4E,6Z,8R,9R,10E)-9-(((1,1-Dimethylethyl)dimethylsilyl)oxy)-2-Methoxy-2,6,8,10-tetramethyldodeca-4,6,10-triene-1-ol (89)

A solution of triene 88 (43.1 mg, 118 μmol) in methanol (800 μl) was added camphorsulfonic acid (1.4 mg, 5.9 μmol) at 0 °C under argon atmosphere, and stirred for 1 hour. Triethylamine (5 μl, 36.5 μmol) was added and the resulting mixture was concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 10 g, hexane : EtOAc = 8 : 1) to primary alchole 89 (38.0 mg, 95.8 μmol, 67% in 2 steps).

$R_f$ value: 0.09 (hexane : EtOAc = 8 : 1).

$\left[\alpha\right]_{D}^{25}$ $-2.93^\circ$ (c 1.00, CH$_2$Cl$_2$).

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ −0.09 (3H, s, SiMe), −0.07 (3H, s, SiMe), 0.75 (3H, d, $J=6.7$ Hz, Me-14), 0.80 (9H, s, SiBu), 1.12 (3H, s, Me-8), 1.55 (3H, s, Me-12), 1.58 (3H, d, $J=6.7$ Hz, Me-18), 1.73 (3H, s, Me-16), 1.86 (1H, t, $J=6.0$ Hz, OH-7), 2.22-2.41 (2H, m, H-9), 2.61 (1H, ddq, $J=9.6$, 8.0, 6.7 Hz, H-14), 3.26 (3H, s, OMe), 3.42 (1H, ddq, $J=11.2$, 6.1 Hz, H-7), 3.48 (1H, dd, $J=11.2$, 6.1 Hz, H-7), 3.62 (1H, d, $J=8.0$ Hz, H-15), 5.19 (1H, d, $J=9.6$ Hz, H-13), 5.32 (1H, q, $J=6.6$ Hz, H-17), 5.46 (1H, dt, $J=15.5$, 7.7 Hz, H-10), 6.09 (1H, d, $J=15.5$ Hz, H-11).

$^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ −5.1, −4.8, 10.8, 10.8, 12.9, 13.1, 17.5, 18.1, 19.0, 19.1, 25.7, 37.2, 38.5, 49.3, 49.4, 66.8, 66.8, 77.2, 77.3, 77.4, 83.6, 83.6, 121.1, 121.3, 132.9, 132.9, 136.1, 136.2, 137.2, 138.7, 138.7.

$\text{CHO}$

(4E,6Z,8R,9R,10E)-9-(((1,1-Dimethylethyl)dimethylsilyl)oxy)-2-Methoxy-2,6,8,10-tetramethyldodeca-4,6,10-trienal (90)

A mixture of primary alchole 89 (225 mg, 566 μmol) and triethylamine (1.58 ml, 11.3 mmol) in dimethoxyethane (3.9 ml) was added sulfur trioxide pyridine complex (895 mg, 5.62 mmol) at room temperature under argon atmosphere, and the resulting mixture was stirred for 30 minutes. Toluene (12 ml) and water (4.0 ml) were added, and the layer was separated. The aqueous solution was extracted with toluene (12 ml) and the combined organic extracts were washed twice with brine (3.0 ml×2). The organic extracts were concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 28 g, hexane : EtOAc = 25 : 1) to aldehyde 90 (211 mg, 535 μmol, 94%).
$R_t$ value: 0.48 (hexane : EtOAc = 10 : 1).

$[\alpha]_D^{20} -3.30^\circ$ (c 1.11, CH$_2$Cl$_2$).

HRFAB-MS (m/z): 393.3827 [M-H]$^+$; calced for C$_{23}$H$_{41}$O$_3$Si$_1$: 393.2825.

$^1$H-NMR (400 MHz, CDCl$_3$): (the value in bracket is data of the isomer at C8 position): $\delta$ –0.09 (3H, s, SiMe), –0.07 (3H, s, SiMe), 0.75 (3H, d, $J$=6.9 Hz, Me-14), 0.80 (9H, s, Si' Bu), 1.21 [1.22] (3H, s, Me-8), 1.55 (3H, s, Me-12), 1.58 (3H, d, $J$=6.4 Hz, Me-18), 1.71 (3H, s, Me-16), 2.33-2.52 (2H, m, H-9), 2.59 (1H, ddq, $J$=10.1, 8.0, 6.9 Hz, H-14), 3.32 (3H, s, OMe), 3.62 (1H, d, $J$=8.0 Hz, H-15), 5.20 (1H, d, $J$=8.0 Hz, H-15), 5.31 (1H, q, $J$=6.4 Hz, H-17), 5.41 (1H, dt, $J$=17.9, 7.5 Hz, H-10), 6.09 (1H, d, $J$=17.9 Hz, H-11), 6.58 [6.59] (1H, s, H-7).

$^13$C-NMR (100 MHz, CDCl$_3$) $\delta$ –5.1, –4.8, 10.8 [10.8], 12.9 [13.0], 17.4, 17.5 [17.5], 18.1, 25.7, 37.3, 38.0 [38.2], 51.9 [51.9], 82.4 [82.4], 83.5 [83.6], 118.9, 121.3 [121.3], 132.7, 136.7 [136.7], 137.1, 139.5 [139.6], 205.0 [205.1].

IR (KBr) 3031, 2956, 2929, 2856, 2829, 2800, 2701, 1737, 1471, 1461, 1247, 1079, 1056, 860, 836, 773.

![Chemical structure](image)

2-((1E,5E,7E,9R,10R,11E)-10(((1,1-Dimethylethyl)dimethylsilyl)oxy)-3-methoxy-3,7,9,11-tetramethyltrideca-1,5,7,11-tetraenyl)-6-methoxy-3,5-dimethyl-4H-pyran-4-one (91)

A solution of phosphine 79 (183 mg, 600 μmol) in tetrahydrofuran (5.7 ml) was added 1.0M lithiumbis(trimethylsilyl)amide in tetrahydrofuran (576 μl, 576 μmol) at –78 °C under argon atmosphere, and the resulting mixture was stirred at –60 °C for 1 hour. Aldehyde 90 (189 mg, 480 μmol) which was dissolved in tetrahydrofuran (3.7 ml) was added, and the mixture was stirred for 1 hour. The mixture was warmed to 0 °C over 2.5 hours and stirred for 2 hours. Acetic acid was added and the resulting mixture was concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 30 g, hexane : EtOAc = 3 : 1) to γ-pyrone 91 (250 mg, 459 μmol, 96%).

$R_t$ value: 0.10 (hexane : EtOAc = 4 : 1).

$[\alpha]_D^{20} -0.99^\circ$ (c 1.15, CH$_2$Cl$_2$).

$^1$H-NMR (400 MHz, CDCl$_3$): (the value in bracket is data of the isomer at C-8 position): $\delta$ –0.12 (3H, s, SiMe), –0.10 (3H, s, SiMe), 0.75 (3H, d, $J$=6.9 Hz, Me-14), 0.78 [0.79] (9H, s, Si' Bu), 1.33 [1.34] (3H, s, Me-8), 1.54 (3H, s, Me-12), 1.58 (3H, d, $J$=6.7 Hz, Me-18), 1.71 [1.72] (3H, s, Me-2), 1.87 (3H, s, Me-16), 2.04 (3H, s, Me-4), 2.43 (2H, m, H-9), 2.60 (1H, s, H-15), 2.40 (3H, s, OMe), 3.62 (1H, d, $J$=8.3 Hz, H-12), 4.00 (3H, s, OMe-1), 5.19 (1H, d, $J$=10.1 Hz, H-13), 5.31 (1H, q, $J$=6.9 Hz, H-17), 5.41-5.52 (1H, m, H-10), 6.08 [6.10] (1H, d, $J$=15.2 Hz, H-11), 6.36 (1H, d, $J$=16.6 Hz, H-6), 6.48 [6.49] (1H, d, $J$=16.6, 2.4 Hz, H-7).

$^13$C-NMR (100 MHz, CDCl$_3$) $\delta$ –5.1, –4.8, 6.9, 9.7, 10.8 [10.8], 12.9 [13.1], 17.5 [18.1], 21.9 [22.3], 25.7, 37.3, 43.4 [43.6], 50.5 [50.6], 55.3 [55.3], 77.2 [77.5], 83.5, 99.6 [99.6], 119.0 [119.0], 119.3 [119.5], 120.7 [120.8], 121.3 [121.3], 132.8 [132.8], 136.3 [136.4], 137.1 [137.1], 138.9 [139.0], 140.3 [140.4], 151.3 [151.3], 161.7, 181.0.
2-((1E,5E,7E,9R,10R,11E)-10-Hydroxy-3-methoxy-3,7,9,11-tetramethyltrideca-1,5,7,11-tetraenyl)-6-methoxy-3,5-dimethyl-4H-pyran-4-one (76)

A solution of γ-pyrone 91 (31.1 mg, 57.1 μmol) in methanol (1.6 ml) was added camphorsulfonic acid (13.3 mg, 57.1 μmol) which was dissolved in methanol (400 μl) at room temperature under argon atmosphere, and left for 18 hours. Triethylamine was added at 0 °C, and the resulting mixture was concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 9.6 g, hexane : EtOAc = 1 : 1) to secondary alcohol 76 (17.2 mg, 39.9 μmol, 70%).

Rf value: 0.19 (hexane : EtOAc = 1 : 1).

[α]D25 +3.64° (c 1.28, CH2Cl2).

HRFAB-MS (m/z): 431.2769 [M+H]+; calcd for C26H39O5: 431.2797.

1H-NMR (400 MHz, CDCl3): (the value in bracket is data of the isomer at C8 position): δ 0.81 (3H, d, J=6.9 Hz, Me-14), 1.35 (3H, s, Me-8), 1.63 (3H, d, J=5.1 Hz, Me-18), 1.64 (3H, s, Me-12), 1.80 (3H, s, Me-2), 1.87 (3H, s, Me-16), 2.05 (3H, s, Me-4), 2.44 (2H, d, J=7.2 Hz, H-9), 2.69 (1H, ddq, J=9.6, 9.1, 6.5 Hz, H-14), 3.25 [3.25] (3H, s, OMe), 3.63 (1H, d, J=9.1 Hz, H-13), 5.00 [4.00] (3H, s, OMe-1), 5.26 (1H, d, J=9.6 Hz, H-13), 5.49 (1H, q, J=6.2 Hz, H-17), 5.53-5.63 (1H, m, H-10), 6.13 [6.14] (1H, d, J=16.3 Hz, H-11), 6.36 (1H, d, J=16.3 Hz, H-6), 6.50 [6.51] (1H, d, J=16.3 Hz, H-7).

13C-NMR (100 MHz, CDCl3) δ 6.9, 9.6, 10.5, 13.1 [13.1], 17.4, 22.2 [22.2], 36.8, 43.5 [43.6], 50.5, 55.3, 77.2 [77.2], 82.8, 99.6, 119.1, 119.5 [119.5], 122.4 [122.5], 123.6, 134.1 [134.1], 135.5 [135.5], 135.6, 138.0 [138.1], 140.0, 151.2, 161.7, 181.0.

IR (KBr) 3423, 3029, 2971, 2925, 2863, 2829, 2683, 1666, 1631, 1602, 1577, 1465, 1417, 1376, 1336, 1259, 1168, 968.

(+)-Actinopyrone A (60)

2-((2Z,5E,7Z,9R,10R,11E)-10-Hydroxy-3,7,9,11-tetramethyltrideca-2,5,7,11-tetraenyl)-6-methoxy-3,5-dimethyl-4H-pyran-4-one, (+)-actinopyrone A (60)

A mixture of secondary alcohol 76 (6.3 mg, 14.6 μmol) and iso-propanol (11 μl, 14.6 μmol) in tetrahydrofuran (630 μl) was added 0.1M samarium iodide in tetrahydrofuran (438 μl, 43.8 μmol) at −78 °C under argon atmosphere, and the resulting mixture was stirred at −20 °C for 30 minutes. Air was bubbled, then ethyl acetate (1.0 ml), saturated aqueous sodium bicarbonate (0.5 ml) and water (0.5 ml) was added, and the layer was separated. The aqueous solution was extracted with ethyl acetate (0.5 ml) and the combined organic extracts were concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 1.3 g, hexane : EtOAc = 1 : 1) to (+)-actinopyrone A (60) (4.7 mg, 11.7 μmol, 80%).
$R_f$ value: 0.24 (hexane : EtOAc = 1 : 1).
synthetic: $\left[\alpha\right]_D^{25}$ +31.3 (c 0.43, CH$_2$Cl$_2$) [natural $\left[\alpha\right]_D^{26}$ +30.8 (c 0.42, CH$_2$Cl$_2$)].
HRFAB-MS ($m/z$): 401.2673 [M+H]$^+$; calcd for C$_{25}$H$_{37}$O$_4$: 401.2692.
$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 0.81 (3H, d, $J$=6.9 Hz, Me-14), 1.63 (3H, d, $J$=6.0 Hz, Me-17), 1.64 (3H, s, Me-12), 1.67 (1H, br, OH-15), 1.73 (3H, s, Me-16), 1.81 (3H, s, Me-8), 1.84 (3H, s, Me-2), 1.96 (3H, s, Me-4), 2.68 (1H, ddq, $J$=9.6, 9.1, 6.9 Hz, H-14), 2.80 (2H, d, $J$=6.9 Hz, H-9), 3.31 (2H, d, $J$=7.3 Hz, H-6), 3.63 (1H, d, $J$=9.1 Hz, H-15), 3.92 (3H, s, OMe), 5.24 (1H, d, $J$=9.6 Hz, H-13), 5.26 (1H, t, $J$=7.3 Hz, H-7), 5.49 (1H, q, $J$=6.0 Hz, H-17), 5.56 (1H, dt, $J$=15.5, 6.9 Hz, H-10), 6.10 (1H, d, $J$=15.5 Hz, H-11).
$^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 6.9, 9.9, 10.5, 13.1, 13.2, 16.6, 17.4, 30.0, 36.9, 42.9, 55.2, 82.8, 99.3, 118.0, 118.1, 123.6, 125.6, 133.8, 135.57, 135.61, 136.4, 138.0, 156.9, 162.1, 181.0.
IR (KBr) 3407, 3023, 2958, 2923, 2863, 1666, 1587, 1463, 1378, 1326, 1251, 1164.
IR spectrum of 61 (100MHz, CDCl₃)
\( ^1 \text{H-NMR spectrum of } \alpha \text{-pyrone (400MHz, CDCl}_3 \text{)} \)

IR spectrum of \( \alpha \)-pyrone (100MHz, CDCl\(_3\))
$^1$H-NMR spectrum of 82 (400MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of 82 (100MHz, CDCl$_3$)
**$^1$H-NMR spectrum of 78 (400MHz, CDCl$_3$)**

**IR spectrum of 78**
$^1$H-NMR spectrum of 84 (400MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of 84 (100MHz, CDCl$_3$)
$^1$H-NMR spectrum of 79 (400MHz, CDCl$_3$)
$^{1}$H-NMR spectrum of 86 (400MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of 86 (100MHz, CDCl$_3$)
$^1$H-NMR spectrum of 87 (400MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of 87 (100MHz, CDCl$_3$)
$^1$H-NMR spectrum of 71 (400MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of 71 (100MHz, CDCl$_3$)
$^1$H-NMR spectrum of 88 (400MHz, CDCl$_3$)
$^1$H-NMR spectrum of 89 (400MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of 89 (100MHz, CDCl$_3$)
$^1$H-NMR spectrum of 90 (400MHz, CDCl$_3$)

IR spectrum of 90
$^1$H-NMR spectrum of 91 (400MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of 91 (100MHz, CDCl$_3$)
$^1$H-NMR spectrum of 76 (400MHz, CDCl$_3$)

IR spectrum of 76
$^1$H-NMR spectrum of synthetic actinopyrone A (60) (400MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of synthetic actinopyrone A (60) (100MHz, CDCl$_3$)
IR spectrum of synthetic actinopyrone A (60)
$^1$H-NMR spectrum of Z-isomer actinopyrone A (60) (400MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of Z-isomer actinopyrone A (60) (100MHz, CDCl$_3$)
$^1$H-NMR spectrum of natural actinopyrone A (60) (400MHz, CDCl$_3$)
3. Total Synthesis of TMC-264, an Inhibitor of IL-4 Signal Transduction

A solution of 1,2,3-trimethoxy-5-methylbenzene (102) (17.0 ml, 101 mmol) in dichloromethane (170 ml) was added 1.0M solution of boron tribromide in dichloromethane (101 ml, 101 mmol) at 0 °C under argon atmosphere, and stirred for 1 hour. The mixture was added 3.0M aqueous sodium hydroxide, and warmed to room temperature. After addition of 1.0M aqueous hydrochloride, the layers were separated, and the aqueous solution was extracted three times with chloroform. The combined organic extracts were concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 200 g, hexane : EtOAc = 2 : 1) to diol 105 (13.4 g, 86.9 mmol, 87%).

A solution of diol 105 (512 mg, 3.32 mmol) in carbon tetrachloride (52 ml) was added N-bromosuccinimide (611 mg, 3.49 mmol) at 0 °C under argon atmosphere, and stirred for 24 hours. Water (30 ml), 1.0M aqueous hydrochloride (16 ml) and carbon tetrachloride (90 ml) was added. The layers were separated, and the aqueous solution was extracted with carbon tetrachloride. The combined extracts were concentrated to afford the residue which was recrystallized by ethyl acetate to afford bromide 106 (610 mg, 2.62 mmol, 80%).

\[ R_f \text{ value: 0.41 (CHCl}_3 : \text{EtOAc = 4} : 1). \]

plates recrystallized from EtOAc; m.p. 142.0 °C (decomposed).

HRFAB-MS (m/z): 231.9760 [M]; calcd for C\textsubscript{8}H\textsubscript{9}O\textsubscript{3}Br: 231.9735.

\[ ^1\text{H-NMR (400MHz, CDCl}_3): \delta 2.33 (3H, s, Me-1), 3.86 (3H, s, OMe-3), 5.36 \text{(1H, s, OH-4)}, 5.61 \text{(1H, s, OH-4a)}, 6.43 \text{(1H, s, H-2)}. \]

\[ ^{13}\text{C-NMR (100MHz, CDCl}_3): \delta 22.6, 56.2, 104.1, 105.2, 128.6, 131.1, 140.7, 145.9. \]
A solution of bromide 106 (61.4 mg, 263 μmol) in tetrahydrofuran (1.2 ml) was added N-chlorosuccinimide (42.1 mg, 315 μmol) at room temperature under argon atmosphere, and stirred for 2 hours. The resulting mixture was added silica gel (700 mg), and concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 7.0 g, PhMe : acetone = 7 : 1) to chloride 111 (42.9 mg, 160 μmol, 61%).

*RF value: 0.29 (hexane : EtOAc = 2 : 1).

plates recrystallized from EtOAc; m.p. 94.7 °C.

HRFAB-MS (m/z): 267.9325 [M]; calcd for C_{8}H_{8}O_{3}BrCl: 267.9323.

1^H-NMR (400MHz, CDCl_{3}): δ 2.45 (3H, s, Me-1), 3.91 (3H, s, OMe-3), 5.60-5.76 (2H, br, OH-4, OH-4a).

13C-NMR (100MHz, CDCl_{3}): δ 20.0, 60.9, 107.7, 119.5, 127.1, 135.7, 140.2, 143.0.

A mixture of chloride 111 (444 mg, 1.66 mmol) and diisopropylethylamine (870 μl, 4.98 mmol) in N,N-dimethylformamide (18 ml) was added 1.0M solution of zinc dichloride in diethylether (1.7 ml, 1.7 mmol) at 0 °C under argon atmosphere, and stirred for 1.5 hours. The resulting mixture was cooled to –40 °C, and added chloromethylmethylether (140 μl, 1.82 mmol). The mixture was stirred for 1.5 hours and added methanol (1.8 ml), then concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 25 g, CHCl_{3} : hexane : EtOAc = 40 : 20 : 1) to desired compound 112 (427 mg, 1.37 mmol, 83%) and undesired compound 113 (66.0 mg, 212 μmol, 13%).

*RF value of 112: 0.30 (hexane : EtOAc = 5 : 1).

needles recrystallized from MeOH; m.p. 113.8 °C.

HRFAB-MS (m/z): 309.9617 [M]; calcd for C_{10}H_{12}O_{4}BrCl: 309.9607.

1^H-NMR (400MHz, CDCl_{3}): δ 2.49 (3H, s, Me-1), 3.60 (3H, s, CH_{2}OMe), 3.86 (3H, s, OMe-3), 5.14 (2H, s, CH_{2}OMe), 6.88 (1H, s, OH-4a).

13C-NMR (100MHz, CDCl_{3}): δ 20.6, 57.7, 60.9, 99.8, 108.0, 119.9, 132.6, 137.2, 146.1, 148.5.

*RF value of 113: 0.28 (hexane : EtOAc = 5 : 1).

needles recrystallized from hexane; m.p. 104.6 °C.

HRFAB-MS (m/z): 309.9628 [M]; calcd for C_{10}H_{12}O_{4}BrCl: 309.9607.

1^H-NMR (400MHz, CDCl_{3}): δ 2.47 (3H, s, Me-1), 3.65 (3H, s, CH_{2}OMe), 3.91 (3H, s, OMe-3), 5.12 (2H, s, CH_{2}OMe), 6.90 (1H, s, OH-4).

13C-NMR (100MHz, CDCl_{3}): δ 20.4, 57.8, 60.7, 99.8, 114.9, 124.7, 127.4, 141.9, 142.3, 144.1.
A solution of 1-chloro-3,5-dimethoxybenzene (104) (2.46 g, 14.3 mmol) in dichloroethane (50 ml) was added N-bromosuccinimide (2.66 g, 14.9 mmol) under nitrogen atmosphere, and stirred at 60 °C for 5 hours. The resulting mixture was added silica gel (10 g), and concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 100 g, hexane : EtOAc = 6 : 1) to bromide 118 (3.20 g, 12.7 mmol, 90%).

Rf value: 0.34 (hexane : EtOAc = 10 : 1). plates recrystallized from EtOAc; m.p. 78.5 °C.
HRFAB-MS (m/z): 251.9366 [M]; calcd for C8H8O2BrCl: 251.9376.
1H-NMR (400MHz, CDCl3): δ 3.79 (3H, s, OMe-9), 3.86 (3H, s, OMe-7), 6.38 (1H, s, H-8), 6.64 (1H, s, H-10).
13C-NMR (100MHz, CDCl3): δ 55.7, 56.5, 98.4, 103.7, 106.7, 135.8, 157.8, 159.7.

A mixture of 1.00M s-butyl lithium in cyclohexane (640 μl, 640 μmol) and toluene (20 ml) was added bromide 118 (153 mg, 610 μmol) in toluene (1.0 ml) at –78 °C under argon atmosphere, then the resulting mixture was stirred under carbondioxide atmosphere and warmed to room temperature. 1.0M aqueous hyrdrochloride (1.0 ml, 1.0 mmol) was added, then the layers were separated, and the aqueous solution was extracted three times with ethyl acetate. The combined extracts were concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 5.4 g, hexane : EtOAc = 3 : 4) to benzoic acid 103 (119 mg, 548 μmol, 90%).

Rf value: 0.25 (hexane : EtOAc = 3 : 4). plates recrystallized from EtOAc; m.p. 155.0 °C.
HRFAB-MS (m/z): 216.0168 [M]; calcd for C9H9O4Cl: 216.0189.
1H-NMR (400MHz, CDCl3): δ 3.82 (3H, s, OMe-9), 3.86 (3H, s, OMe-7), 6.40 (1H, d, J = 2.0Hz, H-8), 6.56 (1H, d, J = 2.0Hz, H-10).
13C-NMR (100MHz, CDCl3): δ 55.7, 56.3, 97.6, 106.6, 115.0, 133.6, 158.8, 162.0, 169.4.
A mixture of benzoic acid 103 (193 mg, 892 μmol) and N,N-dimethylformamide (5.0 ml, 65.0 μmol) in dichloromethane (6.0 ml) was added oxalylchloride (230 μl, 2.68 mmol) under argon atmosphere. The resulting mixture was left at 40 °C for 5 hours. The mixture was concentrated to afford acid chloride 135, and which was dissolved in pyridine (3.0 ml). The solution was added desired mono methoxymethyl compound 112 (280 mg, 899 μmol) in pyridine (3.0 ml) at room temperature and left at 50 °C for 16 hours. The resulting solution was concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 9.0 g, hexane : EtOAc = 3 : 1) to condensate 136 (372 mg, 729 μmol, 82%).

Spectrum data of 135:

1H-NMR (400MHz, CDCl3): δ 3.82 (3H, s, OMe), 3.86 (3H, s, OMe), 6.38 (1H, d, J = 2.0Hz, H-8), 6.52 (1H, d, J = 2.0Hz, H-10).

13C-NMR (100MHz, CDCl3): δ 55.8, 56.3, 97.6, 106.2, 121.1, 131.3, 157.5, 162.5, 165.4.

Rf value of 136: 0.33 (hexane : EtOAc = 3 : 1).

plates recrystallized from acetone; m.p. 119.9 °C.

HRFAB-MS (m/z): 510.9718 [M]; calcd for C_{19}H_{19}O_{7}BrCl_{2}: 510.1131.

1H-NMR (400MHz, CDCl3): δ 2.55 (3H, s, Me-1), 3.55 (3H, s, CH_{2}OMe), 3.84 (3H, s, OMe), 3.88 (3H, s, OMe), 3.92 (3H, s, OMe), 5.15 (2H, s, CH_{2}OMe), 6.43 (1H, d, J = 2.0Hz, H-8), 6.59 (1H, d, J = 2.0Hz, H-10).

13C-NMR (100MHz, CDCl3): δ 20.9, 55.7, 56.0, 57.6, 61.1, 97.6, 99.3, 106.6, 114.9, 127.2, 132.8, 133.9, 141.4, 142.0, 149.6, 159.4, 162.2, 162.4.
A mixture of condensate \textbf{136} (4.5 mg, 8.82 \( \mu \text{mol} \)) and bis(1,5-cyclooctadiene)nickel(0) (24.5 mg, 89.1 \( \mu \text{mol} \)) in dimethylformamide (4.5 ml) was added 1.00M dichloroethylaluminum in \( n \)-hexane (93 \( \mu \text{l}, 89.1 \mu \text{mol} \)) at –78 °C under argon atmosphere. The resulting mixture was sonicated at 40 °C for 10 hours. The mixture was concentrated and added aqueous hydrochloride and ethyl acetate, then extracted three times with ethyl acetate. The combined organic layers were concentrated to afford cyclization \textbf{127}, and which was dissolved in dichloromethane (352 \( \mu \text{l} \)). The solution was added 1.00M boron tribromide in \( n \)-hexane (22.0 \( \mu \text{l}, 22.0 \mu \text{mol} \)) at –15 °C and stirred for 20 minutes. The mixture was added 3.0M aqueous sodium hydroxide, and warmed to room temperature. The layers were separated, and the aqueous solution was extracted three times with chloroform (2 ml). The combined organic extracts were added silica gel and concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 0.5 g, PhMe : EtOAc = 8 : 1) to diol \textbf{141} (2.3 mg, 6.83 \( \mu \text{mol}, 75\% \)).

\( R_f \) value of \textbf{141} : 0.38 (PhMe : EtOAc = 8 : 1). plates recrystallized from MeOH; m.p. 229.7 °C.

HRFAB-MS (\textit{m/z}): 33.0516 \([\text{M}+\text{H}]^+\); calcld for \( \text{C}_{16}\text{H}_{13}\text{O}_6\text{Cl} \): 336.0400.

\textsuperscript{1}H-NMR (400MHz, Acetone-\( d_6 \)): \( \delta \) 2.83 (3H, s, Me-1), 3.96 (3H, s, OMe-3), 4.00 (3H, s, OMe-9), 6.67 (1H, d, \( J = 2.0 \text{Hz}, \text{H-8} \)), 7.32 (1H, d, \( J = 2.0 \text{Hz}, \text{H-10} \)), 8.99 (1H, s, OH-4), 11.75 (1H, s, OH-7).

\textsuperscript{13}C-NMR (100MHz, Acetone-\( d_6 \)): \( \delta \) 20.6, 56.4, 61.0, 100.6, 101.1, 106.7, 116.0, 125.0, 127.1, 138.0, 138.4, 140.8, 145.9, 165.0, 165.8, 167.4.
2-Chloro-1,7-dihydroxy-3,9-dimethoxy-1-methyl-1H-benzo[c]chromene-4,6-dione, TMC-264 (96)

A mixture of diol 133 (30.0 mg, 89.1 μmol) and salcomine (62.9 mg, 91.5 μmol) in acetonitrile (6.0 ml) was stirred under oxygen atmosphere for 2.5 hours. Methanol was added and the resulting mixture was stirred for 0.5 hours. The mixture was decantated and concentrated to afford the residue which was purified on silica gel column chromatography (BW820-MH 1.6 g, PhMe : Acetone : AcOH = 10 : 1 : 0.05) to racemic TMC-264 (96) (18.2 mg, 51.6 μmol, 58%).

R_f value: 0.38 (PhMe : EtOAc = 8 : 1).
HRFAB-MS (m/z): 353.0430 [M+H]^+; calcd for C_{16}H_{14}O_7Cl: 352.0350.
\[ ^1\text{H-NMR} (400\text{MHz}, \text{CDCl}_3): \delta 1.94 (3\text{H, s, Me-1}), 2.76 (1\text{H, s, OH-1}), 3.92 (3\text{H, s, OMe-3}), 3.97 (3\text{H, s, OMe-9}), 6.66 (1\text{H, d, } J = 2.0\text{Hz, H-8}), 7.32 (1\text{H, d, } J = 2.0\text{Hz, H-10}), 11.34 (1\text{H, s, OH-7}). \]
\[ ^{13}\text{C-NMR} (100\text{MHz}, \text{CDCl}_3): \delta 29.5, 55.9, 60.5, 72.5, 101.5, 103.3, 107.0, 128.3, 134.3, 141.8, 144.5, 146.8, 163.6, 164.8, 166.8, 171.8. \]
$^1$H-NMR spectrum of 106 (400MHz, CDCl$_3$)

NOE spectrum of 106 (400MHz, CDCl$_3$)
$\text{H-NMR spectrum of } 111 \quad (400\text{MHz, CDCl}_3)$

$\text{C-NMR spectrum of } 111 \quad (100\text{MHz, CDCl}_3)$
$^1$H-NMR spectrum of 112 (400MHz, CDCl₃)
\( ^1\text{H-NMR spectrum of 113 (400MHz, CDCl}_3\text{)} \)

\( \text{NOE spectrum of 113 (400MHz, CDCl}_3\text{)} \)
$^1$H-NMR spectrum of 118 (400MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of 118 (100MHz, CDCl$_3$)
$^1$H-NMR spectrum of 103 (400MHz, CDCl$_3$)

IR spectrum of 103
$^{1}H$-NMR spectrum of $^{135}$ (400MHz, CDCl$_3$)

IR spectrum of $^{135}$
$^1$H-NMR spectrum of 136 (400MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of 136 (100MHz, CDCl$_3$)
\(^1\)H-NMR spectrum of 141 (400MHz, CDCl\(_3\))

\(^{13}\)C-NMR spectrum of 141 (100MHz, CDCl\(_3\))
$^1$H-NMR spectrum of TMC-264 (96) (400MHz, CDCl$_3$)
$^{13}$C-NMR spectrum of TMC-264 (96) (100MHz, CDCl₃)

MASS spectrum of TMC-264 (96)
IR spectrum of TMC-264 (96)
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References


Achievement for this dissertation

Paper
1) The first total synthesis of a tetracyclic antibiotic, (−)-tetrodecamycin
   Kuniaki Tatsuta, Yasuaki Suzuki, Akiho Furuyama, Hiroshi Ikegami

2) The first total synthesis and structural determination of actinopyrone A
   Seijiro Hosokawa, Kazuya Yokota, Keisuke Imamura, Yasuaki Suzuki,
   Masataka Kawarasaki, Kuniaki Tatsuta

Presentation
1) The first total synthesis of a pyranonaphthoquinone antitumor, BE-54238B
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   Tokyo, December, 2004
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