Stereocontrolled Total Synthesis of Natural Products with Characteristic Molecular Structures and Biological Activities

Kozo Shishido

Graduate School of Pharmaceutical Sciences, The University of Tokushima;
1–78–1 Sho-machi, Tokushima 770–8505, Japan.

Received May 28, 2013

Total synthetic studies on natural products with promising biological profiles, coupled with their intriguing structural features, are described. The target molecules dealt with in this article are five helianane-type sesquiterpenes (heliannuols A, D and K and heliespirones A and C) and three meroterpenes (breviones A, B and C) with allelopathic activity, as well as four cytotoxic polyketides (lasonolide A and aspergillides A, B and C) and two pyrrolidinoindoline alkaloids (physostigmine and psychotrimine) with acetylcholine esterase inhibitory and antibacterial activities.

Key words total synthesis; natural product; allelopathy; sesquiterpene; meroterpene; pyrrolidinoindoline alkaloid

1. Introduction

Organic synthesis is a powerful tool in several disciplines, including biology, physics, material sciences and medicine. Target oriented synthesis is one of the most important areas in organic synthesis and plays an important role in medicinal, agricultural, and natural product chemistries. Of these, total synthetic studies directed toward biologically active naturally occurring substances have attracted much attention from organic and medicinal chemical societies, due mainly to the development of new drugs and the challenging nature of scientific work. For the realization of natural product synthesis, stereo-control (diastereo- and enantio-), regio- and chemo-controls are significant issues, and the development of highly efficient synthetic routes for target molecules would be strongly required. During the course of our total synthetic studies, which would contribute to an advancement of medicinal and agricultural chemistries, we focused on natural products with characteristic structural features and significant biological profiles. In this review, stereocontrolled total syntheses of five sesquiterpenes, three meroterpenes, four polyketides and formal syntheses of two alkaloids are introduced.

2. Synthesis of Natural Products with Allelopathic Activity

Allelopathy has been defined as the biochemical interaction among plants, algae and microorganisms by the intervention of chemical substances, which have been called allelochemicals. Sunflower species are native to North America and many examples of their allelopathic activity in wild and agricultural ecosystems have been reported. Sunflowers (Helianthus annuus) have great allelopathic potential, and inhibit the seedling growth of weeds, including velvet leaf, thorn apple, morning glory and wild mustard, among others. Chemical studies of Helianthus annuus have shown that this species is a rich source of terpenes, and particularly of sesquiterpenes, e.g., heliananes (1–13) and sundiversifolide (14), with a wide spectrum of biological activities, including potential allelopathic activity. The ionone-type bisnorsesquiterpenes (15, 16) have been isolated from rattail fescue (Vulpia myuros) and identified as allelochemicals (11) and the meroterpenes breviones (17–19), isolated from Penicillium brevicompactum Dierckw, have also been identified as allelochemicals (12,13). Characteristic phytotoxic activity, coupled with their unique structural features, has made these natural substances desirable synthetic targets, and we have successfully accomplished the total syntheses of these allelochemicals, as shown in Fig. 1. Among these, we present the enantioselective syntheses of heliannuols A (1), K (2), D (4), and heliespirones A (9) and C (10).

2.1. Syntheses of Helianane Sesquiterpenes Our general strategy for the syntheses of heliananes is based on the use of three chiral building blocks, 21, 23 and 25, with a benzylic tertiary stereogenic center, which is a common structural feature, as our starting materials. These three chiral building blocks can be prepared via a lipase-mediated desymmetrization of $\sigma$-symmetrical diol (20) a diastereoselective conjugate addition of a methyl group to (22), and Lewis acid (LA)-mediated diastereoselective Claisen rearrangement of (24), respectively, and have been converted successfully to helianane allelochemicals (Chart 1).
2.1.1. First Enantioselective Total Syntheses of Heliannuols A and D

Helianane type sesquiterpenes heliannuols A (1) and D (4) were isolated from the extracts of cultivated sunflowers (*Helianthus annuus* L. SH-222), and are believed to be involved in the allelopathic action of sunflowers. Our synthetic strategy, which is based on the proposed biogenetic pathway shown in Chart 2, required the preparation of the key configurationally defined enantiopure epoxide 26, the intramolecular aryl ether-forming reaction of which would provide heliannuol D (4) and/or heliannuol A (1) via a [7-exo] (route a) and/or [8-endo] (route b) mode of cyclization, respectively.

Dr. Kozo Shishido was born in Miyagi, Japan in 1946. He received his Ph.D. degree from Tohoku University in 1976 under the direction of the late Professor Tetsuji Kametani. From 1978 to 1980, he carried out postdoctoral research with the late Professor A. I. Scott (Texas A&M University) and Professor M. E. Jung (UCLA). In 1972, he was appointed as Assistant Professor at Tohoku University and then moved to the University of Tokushima as Associate Professor in 1989. Since 1994, he has been a Full Professor in the Graduate School of Pharmaceutical Sciences at the University of Tokushima. In 2012, he retired from the University and currently is an Emeritus Professor at the University of Tokushima. He received the Kametani Award (2010), Tokushima Shimbun Scientific Award (2011) and the Pharmaceutical Society of Japan Award (2013). His main research interests are the total synthesis of biologically active natural products and the development of new preparative methods.
Treatment of 29, prepared by the Heck reaction between the aryl iodide 27 and the dioxepine 28 under ozonolytic cleavage conditions, followed by a reductive work up with NaBH₄, provided the prochiral 1,3-diol 30 in 93% yield. Porcine pancreatic lipase (PPL)-mediated transesterification with vinyl acetate as an acetyl donor produced the optically active acetate 31 in 34% yield. The enantiomeric excess (ee) was 84%, as determined by HPLC. On the other hand, the enantiomer 32 was obtained by a reaction using Candida antarctica lipase (CAL) in 87% yield in an enantiomerically pure form (>99% ee). The absolute configurations of the stereogenic center in 31 and 32 could not be determined at this stage, and they were established by the following conversion of 32 to (S)-(−)-curcuhydroquinone (36).37) The hydroxyl moiety in 32 was removed by the three-step conversion to give 33. Sequential Hata reaction and oxidation with m-chloroperbenzoic acid (mCPBA) gave the sulfone 34, which was subjected to prenylation and reduction with Na–Hg, producing 35. Oxidation with cerium ammonium nitrate (CAN) and reduction with Na₂S₂O₄ provided 36, the sign of optical rotation of which was opposite to the natural (R)-(−)-curcuhydroquinone. From this result, the absolute configuration at the benzylic stereogenic center in 36 was established to be S. Then the di-tert-butyldimethylsilyl (TBS) ether of 36 was subjected to asymmetric dihydroxylation employing AD-mix-α to give the diol 37 in 99% yield for the two steps. The diastereomeric excess was 94% as determined by 1H-NMR analysis of its (R)-2-methoxy-2-trifluoromethylphenylacetic acid (MTPA) ester derivative. The absolute configuration of the newly generated stereogenic center was confirmed to be S by means of the Kusumi–Mosher method.38) Sequential mesylation, basic treatment, methoxymethylation and desilylation provided an inseparable 4:1 mixture of the monophenolic epoxides, 38 and 39. Treatment of the mixture with 5% aqueous NaOH solution provided an easily separable mixture of the 7- and 8-membered cyclic ethers, 40 and 41, in 54% and 4% yield, respectively. Finally, acidic hydrolysis of each produced heliannuol D (4), [α]D −20.1, and heliannuol A (1), [α]D +61.0, the spectral properties of which were identical with those of the natural products, except for the sign of the optical rotations: for natural 4, [α]D +16.0; for natural 1, [α]D −55.4. Thus, the first enantiocontrolled total syntheses of two allelopathic sesquiterpenes, heliannuol D and heliannuol A, have been accomplished, and the absolute configurations were found to be the enantiomers of those shown in Chart 2, as seen in Chart 4.

2.1.2. Efficient and Enantioselective Syntheses of Heliannuols A and K

As described above, we achieved the first total synthesis of (S)-(−)-heliannuol A (1), the unnatural enantiomer, and after that the second-generation synthesis of the natural enantiomer (R)-1, which was completed in seventeen steps from 2,5-dimethoxy-4-methyliodobenzene with an overall yield of 5%. An obvious challenge was to improve both the low yield and many required reaction steps. Herein we describe the efficient and enantioselective total syntheses of heliannuols A (1) and K (2).39) Our retrosynthetic analysis of 1 and 2 is shown in Chart 5. For the synthesis of 1, we chose the dihydrobenzoxocine 42 with a stereogenic center at C7 as the key compound, because it has been converted efficiently...
to 1 by a three-step sequence in good overall yield. The methoxymethyl (MOM) protected heliannuol A, the penultimate intermediate of 1, would be transformed to heliannuol K (2) by a simple two-step sequence: oxidation followed by deprotection. An eight-membered heterocycle fused to the aryl ring can be assembled by ring-closing metathesis of the diene 44, which would be prepared from the phenol 46. For the key construction of the tertiary stereogenic center at the benzylic position, we planned to use a substrate-controlled chirality transfer in the Claisen rearrangement of the allyl aryl ether 45 prepared from the phenol 46 and S-(E)-1-(benzylxy)pent-3-en-2-ol (47) by Mitsunobu coupling (Chart 5).

The Mitsunobu reaction between 46 and 47 in the presence of 1,1-(azodicarbonyl)dipiperidine (ADDP) and Bu3P provided a chromatographically separable mixture of the requisite ether 45 (>99%ee; by HPLC analysis) and the regioisomer 48, derived via the Sn2' process, in 81% and 7% yield, respectively. The key Claisen rearrangement of 45 was conducted with 3 eq of Me3Al in hexane at room temperature for 0.5 h; the requisite 44 was obtained in 85% yield (>99%ee), together with 49 (4%). On exposure of 44 to hydrogenation conditions, the phenolic alcohol was obtained quantitatively and it was then treated with the mixed carbonate 50 in the presence of catalytic (Ph3P)4Pd (1 mol%) to provide the alcohol 51 in 84% yield. This was exposed to the dehydration protocol of Nishizawa–Grieco to give the diene 43 in 91% yield, which was then treated with Grubbs’ second-generation catalyst (0.5 mol%) in refluxing methylene chloride to give the dihydrobenzoxocine 42 in 93% yield. Attempts at a substrate-controlled diastereoselective epoxidation of 52 using mCPBA provided a lower yield (73%) of the product 52. However, reaction with methyltrifluoromethyl)dioxirane provided the epoxide 52 in 83% yield. The stereochemistry was confirmed by nuclear Overhauser effect (NOE) experiments. LiAlH4 reduction of the epoxide occurred at the sterically less congested carbon (C9), regioselectively, to give the alcohol 53 in 91% yield as a single product. Finally, acidic hydrolysis of the MOM ether produced heliannuol A (1), whose spectroscopic (1H- and 13C-NMR) properties, as well as optical rotation, were identical with those of the natural product. Thus, the third-generation enantioselective total synthesis of heliannuol A (1) was accomplished in a longest linear sequence of nine steps in 25% yield from the phenol 46. For the synthesis of heliannuol K (2), alcohol 53 was oxidized with Dess–Martin periodinane (DMF) to give the corresponding ketone 54, which was exposed to acidic hydrolysis conditions, producing 2 in 99% yield for the two steps. The spectroscopic properties (1H- and 13C-NMR) of the synthetic 2 were identical with those of the natural heliannuol K. However, the optical rotation of the synthetic 2, [α]D = 90.0 (c=0.71), was completely different from that reported for the natural product [lit.59] [α]D +90.0 (c=0.1). To confirm its structure, the synthetic 2 was converted to the crystalline carbamate by treatment with 4-bromo-phenyl isocyanate and Et3N, and its X-ray crystallographic analysis revealed that our synthetic material was found to possess the structure shown in Fig. 1. Thus, the first enantioselective total synthesis of heliannuol K (2) was accomplished in a longest linear sequence of ten steps in 26% yield from 46.

During the synthetic studies, we were able to establish an alternative and highly efficient synthetic route for heliannuol K (2). We chose as the starting material the benzyl protected 55, the substrate for the Claisen rearrangement. Treatment of 55 with a catalytic amount of Eu(fod)3 provided 56 in a yield of 91%, along with 56’ (8%). The phenol 56 was then reacted with ethyl 2-bromo-2-methylpropanoate and K2CO3 to give the ester 57 in 95% yield, which was converted to the diene 58 via the Weinreb amide, quantitatively. This was then subjected
to the ring-closing metathesis to afford the eight-membered enone 59 in 80% yield. Catalytic hydrogenation of 59 with Raney nickel (W-2) in EtOH at room temperature provided heliannuol K (2) in 84% yield with >99%ee. Thus, total synthesis has been accomplished in a longest linear sequence of seven steps in a greatly improved yield of 47% from 4-benzylxy-3-methylphenol.

2.1.3. Syntheses of Heliespirones A and C

Heliespiron A, the first member of a new class of bioactive sesquiterpenes, was isolated from cultivar sunflowers var. SH-222 (*Helianthus annuus* L.)

![Image](https://example.com/image)

**Chart 7. Improved Route to Heliannuol K**

![Diagram](https://example.com/diagram)

**Fig. 2. Structure of Heliespirones A and C**

catalyst, furnished Z-alkene, the secondary hydroxyl function of which was protected to give the acetate (±)-65. This was then oxidized with CAN to give the quinones (±)-66 in 97% yield. With the substrates in hand, we next examined the intramolecular Hosomi–Sakurai reaction. When the reaction was carried out with tert-butylmethylsilyl trifluoromethanesulfonate (TBSOTf) in isobutyronitrile at −10°C, the expected acetylheliespiron A (the acetate of 60) was not obtained, but rather a mixture of two products, (±)-67 (60%, 7:1 mixture of two diastereoisomers), presumably generated through a Lewis acid mediated addition-elimination sequence. The stereochemistries of the two stereogenic centers in the major diastereoisomer were determined to be (3S,5R*) by its conversion to 10-epi-heliannuol E (C10 epimer of 6) (2)

The phenol 62 was treated with the mixed carbonate 50 in the presence of (Ph$_3$P)$_4$Pd$^{43}$ in tetrahydrofuran (THF) to give 63 in 93% yield. Epoxidation of 63 resulted in decomposition under any of the attempted conditions (mCPBA, dioxirane, and methyl trifluoromethyl dioxirane, etc.). Hence, the epoxide (±)-64 was prepared via a three-step sequence: dihydroxylation, selective tosylation, and basic treatment of the monotosylate produced the epoxide. Nucleophilic cleavage of the epoxide with the anion of trimethyl(prop-2-ynyl)silane in the presence of BF$_3$·OEt$_2$, followed by semi-hydrogenation with the Lindlar
transformed, via a three-step sequence, to (3S,5R)-(−)-68. This was exposed to Cs₂CO₃ in CH₂Cl₂ at room temperature for 20 min to give (−)-heliespirone A (9) and (+)-heliespirone C (10) in 34% and 42% yield, respectively. Thus, an enantioselective total synthesis of the natural enantiomers of heliespirones A and C was successfully accomplished.

2.2. Syntheses of Breviones A, B and C

The breviones A–C (17–19), the first diterpene/polyketide hybrid natural products also called meroterpenoids, were first isolated from Penicillium brevicompactum Dierckx. Their structures were elucidated by chemical transformations and extensive 2D-NMR studies. These compounds contain unprecedented penta-cyclic basic carbon frameworks that include a characteristic oxygen-containing spiro CD ring, and they inhibit etiolated wheat coleoptile growth. Here we describe the first enantioselective total synthesis of brevione C (19) and the highly efficient enantioselective total syntheses of breviones A and B (17, 18), employing a regioselective 7-endo acyl radical cyclization for assembling the seven membered A-ring (for brevione C) and a diastereoselective oxidative coupling of the exocyclic olefin and the α-pyrone for the construction of the spiro ring as the key steps. For the initial target, we chose brevione C (19). We reasoned that if a synthetic route to brevione C could be established, it would then be easier to prepare breviones A and B.

Our strategies are illustrated in Chart 11. For the synthesis of 19, we chose the pentacyclic compound 70 as the key intermediate, which would be converted to 19 by oxidation. It was thought that the penultimate intermediate 70 could be constructed by the oxidative coupling of the tricyclic compound 71, a diterpene moiety, with the α-pyrone 72, a polyketide unit. The seven-membered A ring would be assembled using a highly regioselective 7-endo-trig mode of cyclization of the acyl radical 73, a cyclization previously developed in

Chart 8. Retrosynthetic Analysis

Chart 9. Syntheses of (±)-Heliespirones A and C

Chart 10. Enantioselective Syntheses of Heliespirones A and C

Fig. 3. Plausible Transition State for Diastereoselection
our laboratory. The aldehyde 74, a precursor of the acyl radical, would in turn be prepared from the optically active Wieland–Miescher ketone derivative 76 via the tricyclic compound 75. For the synthesis of breviones A (17) and B (18), it was thought that 75 could serve as the common intermediate, which would be converted to the diene 77, which would then be coupled with 72 to produce 18. Finally, it could be dehydrogenated to give 17.

The Wieland–Miescher ketone derivative 76 (>99% ee) was converted via a 4-step sequence to the optically pure tricyclic alcohol 75. Acidic hydrolysis followed by hydrogenation afforded the keto alcohol 78, which was subjected to the Baeyer–Villiger oxidation to give the lactone 79. It was treated with p-toluenesulfonic acid in MeOH to produce the alkenyl ester 80 in excellent yield. 2-Iodoxybenzoic acid (IBX) oxidation gave the enone 81, which was converted to the aldehyde 74 by sequential treatment with DIBAH and DMP.

With the acyl radical precursor in hand, we next investigated the 7-endo-trig cyclization in order to assemble a seven-membered ketone, the A-ring of 19. Treatment of the aldehyde 74 with tert-dodecanethiol (t-C12H25SH) (3 eq) and the radical initiator V-40 [1,1′-azobis(cyclohexane)-1-carbonitrile] (3 eq) in refluxing toluene produced the requisite 82 in 82% yield as a single product through the 7-endo-trig cyclization of the acyl radical intermediate 73. The configuration of the newly generated tertiary stereogenic center in 82 was deduced to be S, based on the previous results. It should be emphasized that the reaction proceeded selectively even in the presence of an enone moiety. After protection of the A-ring ketone, an iodide was introduced at the α-carbon of the enone to give 83, which was methylated by Stille coupling to provide 84. Attempted direct methylation of 84 by a variety of methods failed to afford the carbonyl protected 71. Therefore it was treated with methyllithium and the resulting tertiary alcohol 85 was dehydrated under thermal conditions to produce in good yield the tricyclic diene 71 with exo-cyclic olefin, the diterpene segment.

Next we examined the synthesis of the α-pyrones 72, a compound previously described in literature. However, the procedure described resulted in low yields of the product and was not reproducible. Consequently, we set out to develop a more general and efficient method. After several attempts, sequential carbomethoxylation of the dianion generated from the β-diketone 86, and cyclization of the resulting diketo ester 87 using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing benzene, provided 72 efficiently.

Having made the two segments, we next examined the key oxidative coupling. The results are shown in Table 1. Treatment of the tricyclic diene 71 with the α-pyrone 72 using CAN in acetonitrile (MeCN) at 0°C gave the desired pentacyclic compound 70 as a separable 10:1 diastereomeric mixture in 65% yield. The X-ray crystallographic analysis of the major diastereoisomer revealed it to be the desired pentacycle. To improve the chemical yield, we examined many oxidizing agents, e.g., Mn(OAc)3 (entry 2), Mn(pic)3, Ag2CO3/Celite, etc., as well as various reaction conditions, and found that using a mixture of CAN and Cu(OAc)2 (2:1) resulted in a dramatic improvement of the yield, namely 84%, with the same diastereoselectivity of 10:1 (entry 3). As for the diastereoselectivity, the addition of an ionic liquid, [bdmin]BF4, as a solvent elicited a dramatic improvement in annulation efficiency, affording 70 exclusively, but the yield remained at 45% (entry 4). However, excellent results, the formation of 70 exclusively in 81% yield, were obtained when the reaction was conducted with CAN/Cu(OAc)2 in a mixture of the ionic liquid.
Comparable diastereoselectivity and yields were obtained even when using only CAN (entry 6).

The diastereoselective formation of the CD spiro ring can be explained by considering the conformation of the intermediate carbocation \(^89\), which would be generated from the initially formed allyl radical intermediate \(^88\) by oxidation. The hydroxyl oxygen atom on the \(\alpha\)-pyrone in \(^89\) would attack from the sterically less hindered bottom face of the molecule to give \(^70\), with the \(S\)-configuration at the spiro stereogenic center, preferentially.

The pentacyclic ketone \(^70\) thus prepared was treated with IBX in dimethyl sulfoxide (DMSO) \(^58\) at 80°C to provide brevione C (19), along with the enone \(^90\), in 44% and 54% yield, respectively. \(^25\) The semi-oxidized enone \(^90\) was converted to brevione A (17) in \(84\)% yield. The spectral properties and optical rotations of both compounds were identical with those for the natural breviones A and B.

### 3. Synthesis of Natural Products with Cytotoxic Activity

Enantioselective synthetic efforts directed toward natural products with cytotoxic activities are important to the studies of medicinal chemistry and chemical biology. Here we would like to introduce the enantioselective total syntheses of two naturally occurring poliketides, lasonolide A and Aspergil-lides.

#### 3.1. Synthesis of Lasonolide A \(^59\)

[\(\text{[bmin]}\text{BF}_4\) and \(\text{CH}_2\text{Cl}_2\) (entry 5)]. Comparable diastereoselectivity and yields were obtained even when using only CAN (entry 6).

The diastereoselective formation of the CD spiro ring can be explained by considering the conformation of the intermediate carbocation \(^89\), which would be generated from the initially formed allyl radical intermediate \(^88\) by oxidation. The hydroxyl oxygen atom on the \(\alpha\)-pyrone in \(^89\) would attack from the sterically less hindered bottom face of the molecule to give \(^70\), with the \(S\)-configuration at the spiro stereogenic center, preferentially.

The pentacyclic ketone \(^70\) thus prepared was treated with IBX in dimethyl sulfoxide (DMSO) \(^58\) at 80°C to provide the enone \(^92\). It was likewise transformed to the 1,3-diene \(^77\) in 2 steps. Oxidative coupling of \(^77\) and \(^72\) with CAN in a mixture of \([\text{bmin}]\text{BF}_4/\text{CH}_2\text{Cl}_2\) (1/5) gave brevione B (18) in 99% yield as a single product. Brevione B thus obtained was treated with IBX in DMSO to give brevione A (17) in 84% yield. The spectral properties and optical rotations of both compounds were identical with those for the natural breviones A and B.

### Table 1. Oxidative Coupling of \(^71\) and \(^72\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Time (h)</th>
<th>Yield (%)(^a)</th>
<th>(d)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CAN, MeCN, 0°C</td>
<td>1.2</td>
<td>65</td>
<td>10:1</td>
</tr>
<tr>
<td>2</td>
<td>Mn(OAc)(_2\cdot2\text{H}_2\text{O}), benzene, reflux</td>
<td>21</td>
<td>Decomp.</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>CAN, Cu(OAc)(_2), MeCN, 0°C</td>
<td>1.3</td>
<td>84</td>
<td>10:1</td>
</tr>
<tr>
<td>4</td>
<td>CAN, ([\text{bmin}]\text{BF}_4/\text{CH}_2\text{Cl}_2) (1/5), 0°C–rt</td>
<td>4.8</td>
<td>45</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>5</td>
<td>CAN, Cu(OAc)(_2\cdot2\text{H}_2\text{O}), ([\text{bmin}]\text{BF}_4/\text{CH}_2\text{Cl}_2) (1/5), 0°C–rt</td>
<td>4</td>
<td>81</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>6</td>
<td>CAN, ([\text{bmin}]\text{BF}_4/\text{CH}_2\text{Cl}_2) (1/5), 0°C–rt</td>
<td>3</td>
<td>78</td>
<td>&gt;20:1</td>
</tr>
</tbody>
</table>

\(a\) Isolated yield. \(b\) Determined by \(^1\)H-NMR analysis of the crude product.
to inhibit the \textit{in vitro} proliferation of A-549 human lung carcinoma cells, as well as cell adhesion, in a newly developed whole cell assay that detects signal transduction agents. We show a novel strategy towards the synthesis of (+)-lasonolide A that is characterized by an efficient assembly of the 20-membered polyene macrolide core through sequential cross metathesis and macrolactonization. Our synthetic strategy was based on the retrosynthetic degradation of \( \text{93} \) into the three segments \( \text{94–96} \). Since the introduction of the C26–C35 side chain by Wittig reaction of the ylide generated from \( \text{96} \) in the final stage of the total synthesis has been established, the assembly of the 20-membered polyene macrolide core should be crucial. We envisioned that it would be constructed by a sequence consisting of the cross metathesis between the C5–C17 and C18–C25 segments (\( \text{94 and 95} \)), carbon chain elongation and macrolactonization. The key segment \( \text{95} \) would be addressed from a chiral building block \( \text{97} \) by taking advantage of the convex nature of the molecule for the stereochemical control of the C21 and C22, particularly the C22 quaternary center, on the pyran ring.

The synthesis of the C5–C17 segment \( \text{94} \) was initiated by the introduction of a skipped triene appendage at C11 of the lactone \( \text{99} \), which was prepared from \( \text{98} \) diastereoselectively via Evans’ aldol reaction, according to the previous paper. After protection of the secondary hydroxyl group using TBS ether, the addition of benzyloxymethyl anion, followed by reduction of the resulting lactol with boron trifluoride etherate and triethylsilane, provided \( \text{100} \) as a single diastereomer. Debenzylation followed by Dess–Martin oxidation gave an aldehyde, which was treated with ethyl 2-[(\( \text{o} \)-isopropylphenyl)phosphono]propionate in the presence of DBU and sodium iodide to produce \( \text{101} \) with the Z-geometry and the stereochemistries on the pyran ring, as established by nuclear Overhauser effect spectroscopy (NOESY) experiments. Carbon chain elongation to furnish the dienylchloride \( \text{102} \) was carried out via a conventional 5-step sequence of reactions. Construction of the skipped triene employing the Stille coupling was successfully realized by treatment of \( \text{102} \) with tributylvinyltin in the presence of \( \text{PD}_{3}(\text{dba})_{2} \cdot \text{CHCl}_{3} \) and (\( \text{o} \)-tolyl)\( \text{P} \) to provide in 90\% yield of the triene, whose primary tert-butylidiphenylsilyl (TBDPS) ether was selectively cleaved to give the C5–C17 segment \( \text{94} \) in a highly diastereoselective fashion. The optically pure enone \( \text{97} \) with a bicyclo[3.2.1]octane framework served as the starting material for the synthesis of the C18–C25 segment \( \text{95} \). The reaction of \( \text{97} \) with methyl-lithium in the presence of CuBr·SMe\(_{2}\) and chlorotrimethylsilane (TMSCl), followed by oxidation of the resulting silyl enol ether, gave the enone \( \text{103} \) which upon subsequent 1,4-addition of the vinyl group, the ketone \( \text{104} \) was obtained diastereoselectively, having a crucial quaternary stereogenic center at the C22. Conversion of \( \text{104} \) to \( \text{105} \) was achieved by a 5-step sequence involving ozonolysis, selective protection of a primary alcohol moiety and oxidation. The ketone thus obtained was then treated with \( \text{p} \)-toluenesulfonylhydrazine to give a hydrazone, which was subjected to the Bamford–Stevens reaction to afford cleanly \( \text{105} \) in 79\% yield, for a total of 5 steps. Although the epoxidation of \( \text{105} \) with \( \text{mCPBA} \) resulted in the formation of the requisite epoxide only in only 46\% yield, the use of methyl(trifluoromethyl)dioxirane \( \text{106} \) in aqueous acetonitrile provided \( \text{107} \) in 92\% yield with 90\% de after debenzylation. The optically and diastereomerically pure \( \text{107} \), purified by a recrystallization, was iodinated and reduced by zinc in refluxing ethanol to produce \( \text{108} \). Introduction of the two-carbon unit into the C23 position with an R configuration was carried out efficiently by treatment of \( \text{108} \) with triethyl phosphonoacetate in the presence of potassium hydride as a base in 1,2-dimethoxyethane (DME) to provide \( \text{109} \) as a chromatographically separable mixture of diastereoisomers in a ratio of 14:1 in 87\% yield. The configuration at C23 of the major isomer proved to be the desired R by the NOESY
experiment. Reduction of 109 with lithium aluminum hydride furnished the triol, whose 1,3-diol and primary alcohol moieties were sequentially protected as acetonide and TBDBPS ether to give the C18–C25 segment 95.

The C26–C35 segment 96 was prepared from 5-methylhexan-1-ol by Swern oxidation followed by one-pot methylation and immediate DIBAH reduction to give 110. This was reacted with 111, prepared from (S)-(−)-malic acid, in the presence of sodium bis(trimethylsilyl)amide (NaHMDS) to give 112, which was converted to the C26–C35 segment 96 in four steps.

With the desired three segments in hand, the stage was now set for crucial construction of the 20-membered polyene macrolide core. The key installation of the C17–C18 E-olefin by cross metathesis between 92 and 93 proved to be difficult. However, after numerous trials, it was found that sequential treatment of a mixture of 92 and 93 with the Grubbs’ type I catalyst in CH2Cl2 for 24 h under argon gas bubbling, and then with Grubbs’ type II catalyst for an additional 24 h, provided the desired coupled product 113 with C17–C18 E-olefin (from 1H-NMR), and the homodimer 114, in 70% and 19% yield, respectively. The dimer can be converted to 113 by treatment with 93 in the presence of Grubbs’ type II catalyst in a yield of 27% (57% based on the recovered 114). Oxidation of the primary hydroxy group in 113, followed by the vinylogous Horner–Emmons reaction, gave the ester 115, which was subjected to sequential deacetalization, alkaline hydrolysis and selective protection of a primary alcohol to afford the hydroxy carboxylic acid 116. The macro-lactonization was achieved by employing the procedure of Yamaguchi to provide 117 in 58% yield. Selective desilylation, followed by oxidation of the resulting primary alcohol, afforded the aldehyde 118. Finally, Wittig reaction between the ylide prepared from 96 with potassium bis(trimethylsilyl)amide (KHMD) and the aldehyde 118 led to (+)-lasonolide A (93) after subsequent TBS deprotection. Spectroscopic properties and the optical rotation of the synthetic 93 were identical to those reported for the natural product.

3.2. Syntheses of Aspergillides A, B and C Based on Transannular Oxy-Michael Strategy

The aspergillides A, B and C (119, 120, and 121) comprise a novel class of fourteen-membered macrolides, isolated by Kusumi and colleagues from the marine-derived fungus Aspergillus ostianus strain 01F313 that was cultured in a medium composed of bromine-modified artificial sea water. Their structures were elucidated by extensive spectroscopic studies, and their absolute configurations were determined by the Kusumi–Mosher method and X-ray crystallographic analyses of the corresponding m-bromobenzoates for aspergillides A and B. These compounds 119–121 contain tri-substituted tetrahydro- and dihydropyrans, and exhibit cytotoxicity against mouse lymphocytic leukemia cells (L1210). We herein describe our synthetic approaches toward the aspergillides, focusing mainly on a biomimetic transannular oxy-Michael (TAOM) strategy.

3.2.1. Syntheses of Aspergillides A and B

In our strategy for the synthesis of the aspergillides A (119) and B (120), illustrated in Chart 23, we propose the formation of a tri-substituted tetrahydro- and dihydropyrans, and exhibit cytotoxicity against mouse lymphocytic leukemia cells (L1210). We herein describe our synthetic approaches toward the aspergillides, focusing mainly on a biomimetic transannular oxy-Michael (TAOM) strategy.
of the alcohol moiety as the TBS ether. It was hydrogenated to give 127, which was transformed to the hemiacetal 123 (as a 1.5:1 mixture of diastereomers at the acetal carbon). Its conversion to 128 was realized by sequential reduction, selective pivaloylation of the primary alcohol, silylation and reductive deprotection. Cross metathesis (98%, E-selective), followed by Dess–Martin oxidation of the resulting 129, gave the corresponding aldehyde which was subjected to the intramolecular HWE reaction to provide the macrolide 130 in 78% yield in two steps. Desilylation using HF·pyridine gave 122, a substrate for the TAOM reaction, in 93% yield.

With the macrolactone in hand, we next investigated the crucial TAOM reaction (Table 2). Treatment of 122 with DBU (10 eq) and LiCl (10 eq) in MeCN at room temperature for 1 h provided aspergillide A (119) quantitatively (entry 1). In an attempt to make the reaction catalytic, treatment of 122 with 5 mol% of DBU and LiCl in acetonitrile at room temperature for 36 h produced 119 in 84% yield (entry 2). This result can be explained by invoking the lithium-chelated transition state (TS), in which the conformation is quite similar to the crystal structure of the m-bromobenzoate of aspergillide A 131,70 as shown in Chart 25. We next sought to obtain aspergillide B (120), and found that treatment of 122 with KH (2 eq) in the presence of 18-Crown-6 (5 eq) in THF at 0°C for 1 h produced 120 exclusively in 95% yield (entry 3). The catalytic version of the reaction was also realized (entry 4). Attempted cycloaddition with tetrabutylammonium fluoride (TBAF) (5 mol%) as the base resulted in the formation of 120 in 83% yield (entry 5). Thus, we were able to demonstrate that the diastereoselectivity of the cycloaddition could be altered completely by changing the reaction conditions, and we accomplished the total syntheses of aspergillides A (119) and B (120) in a longest linear sequence of sixteen steps in 33% and 32% yield, respectively, from the readily accessible bicyclic chiral building block 97.

Based on the results in Table 2, we examined the conversion of 119 to 120 to prove thermodynamic preference (Table 3). Exposure of 119 to the conditions of entries 1 and 2 provided 120 in good yield; on the other hand, treatment of 120 with DBU and LiCl in refluxing MeCN for 5 h resulted in 95% recovery of starting material. From these observations, the anti-isomer aspergillide B was found to be thermodynamically favored. This was supported by the calculation shown in Table 3. The use of TBAF (2 eq) at 50°C for 12 h provided 120 in 89% yield (entry 3), and decreasing the amount of TBAF (20 mol%) at a higher temperature resulted in yield of 91% (entry 4). In addition, exposure of 119 to isolation conditions (SiO₂ in MeOH/CHCl₃=1/3 at room temperature)⁷⁷ did not produce 120 at all, which indicated that aspergillide B is not an artifact.
3.2.2. Synthesis of Aspergillide C\(^ {73} \) For the synthesis of aspergillide C (121), the [6-exo-trig] TAOM reaction was also used as the key step. The pivotal transannular cyclization of 132 to afford the dihydropyran incorporated in the natural product could have been challenging. Two interesting aspects had to be taken into consideration, the rate and the diastereoselectivity of the key cyclization due to the presence of a Z-olefin. In our strategy for the synthesis of aspergillide C (121), illustrated in Chart 26, the macrolide 132, the precursor of the key cyclization, would be assembled sequentially by i) cross metathesis of the dihydropyran 133, which could be derived from 126, with (S)-hept-6-en-2-yl acetate (134),\(^ {74} \) ii) a Wittig reaction, and iii) a macrolactonization.

To preserve the double bond, the future C5–C6 unsaturated linkage, debenzylation of the optically pure 126 was conducted with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to give 135 in 94% yield. It was converted to the hemiacetal 133 in 92% yield as a 2.7 : 1 mixture of diastereoisomers at the acetal carbon. The cross metathesis with 134, prepared from (S)-propylene oxide via a two-step sequence using Grubbs’ second-generation catalyst (5 mol %), gave 136 with the E-olefin in 84% yield. The Wittig reaction afforded a chromatographically separable 8 : 1 (E:Z) mixture of the enoate 137 (94%), which was converted to the seco-acid 138 via standard manipulations in two steps. Attempted macrolactonization using the Yamaguchi protocol furnished the requisite 140 in 56% yield for the two steps. After several attempts, it was found that the Shiina procedure\(^ {75,76} \) gave excellent results. Thus, treatment of a solution of 138 in CH\(_2\)Cl\(_2\) with 2-methyl-6-nitrobenzoic acid anhydride (139) and 4-dimethylaminopyridine (4-DMAP) at room temperature produced 140 in 92% yield. Desilylation with HF·pyridine afforded the lactone diol 132, which is a substrate for the key cyclization.

With the macrolactone in hand, we next investigated the TAOM reaction. Treatment of 132 with KH (2 eq) and 18-Crown-6 (5 eq) in THF at 0°C for 10 min provided aspergillide C (1) quantitatively (Table 4, entry 1). Under the reaction conditions using a catalytic KH and 18-Crown-6 (5 mol%) each at room temperature for 2 h, a 9 : 1 mixture of 121 and 3-epi-aspergillide C (141) was obtained in 55% yield (entry 2). Use of 2 eq or catalytic (5 mol%) amounts of TBAF resulted in the selective formation of 121 in 92% and 81% yield, respectively (entries 3 and 4). When the reaction was carried out with DBU (10 eq) and LiCl (10 eq) in MeCN at room temperature for 15 min, 141 was generated in 97% yield exclusively (entry 5). An efficient preparation of 141 was realized under catalytic conditions (entry 6). This result can also be explained by invoking the lithium-chelated transition state, in which the conformation is quite similar to the before mentioned transition state in Chart 25. Thus, we have accomplished the enantioselective total synthesis of aspergillide C (121), as well as the first enantioselective synthesis of 3-epi-aspergillide C (141).

We also attempted the conversion of the syn-isomer 141 to anti-121. On exposure of 141 to KH (2 eq) and 18-Crown-6 (5 eq) in THF at 0°C for 15 min, complete conversion occurred to give 121 in 75% yield. This observation indicated that aspergillide C (121) is thermodynamically more stable than 3-epi-isomer 141, which was also supported by the theoretical calculations.


We previously reported the formal synthesis of Calabar bean alkaloid physovenine (144) employing a newly developed
intramolecular carbamoylketene–alkene [2+2] cycloaddition reaction (142→143) as the key step. This reaction can provide access to suitably functionalized tricyclic compounds 143, which would serve as versatile building blocks for the synthesis of a variety of nitrogen-containing heterocycles and alkaloids. To date, we have successfully achieved formal syntheses of physovenine (144)77) and physostigmine (145),78) and total syntheses of debromoflustramines B (146), E (147),79) folicanthine (148) and chimonanthine (149)80) based on the cycloaddition methodology, as shown in Chart 28.

### Chart 25. Presumed Mechanism and Crystal Structure of 131

intramolecular carbamoylketene–alkene [2+2] cycloaddition reaction (142→143) as the key step. This reaction can provide access to suitably functionalized tricyclic compounds 143, which would serve as versatile building blocks for the synthesis of a variety of nitrogen-containing heterocycles and alkaloids. To date, we have successfully achieved formal syntheses of physovenine (144)77) and physostigmine (145),78) and total syntheses of debromoflustramines B (146), E (147),79) folicanthine (148) and chimonanthine (149)80) based on the cycloaddition methodology, as shown in Chart 28.

### Table 2. TAOM Reaction of 128

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DBU (10 eq), LiCl (10 eq), MeCN, rt, 1 h</td>
<td>119</td>
<td>Quant.</td>
</tr>
<tr>
<td>2</td>
<td>DBU (5 mol%), LiCl (5 mol%), MeCN, rt, 36 h</td>
<td>119</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>KH (2 eq), 18-Crown-6 (5 eq), THF, 0°C, 1 h</td>
<td>120</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>KH (5 mol%), 18-Crown-6 (5 mol %), THF, rt, 6 h</td>
<td>120</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>TBAF (5 mol%), THF, 50°C, 7 h</td>
<td>120</td>
<td>83</td>
</tr>
</tbody>
</table>

### Table 3. Attempted Interconversion

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield (%) of 120</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KH (1.1 eq), 18-Crown-6 (1 eq), THF, rt, 10 min</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>KH (5 mol%), 18-Crown-6 (5 mol %), THF, 50°C, 0.5 h</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>TBAF (2 eq), THF, 50°C, 12 h</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>TBAF (20 mol%), THF, reflux, 2 h</td>
<td>91</td>
</tr>
</tbody>
</table>

Calculation: ΔE_{aspB-aspA} = −1.81 kcal/mol. Gaussian 09 [B3LYP/6-31G (d)].

### 4.1. Development of Diastereoselective Intramolecular Carbamoylketene–Alkene [2+2] Cycloaddition and Its Application to Enantioselective Syntheses of Pyrrolidinoindoline Alkaloids

In previous papers, we have described the syntheses of alkaloids with tetrahydrofuro[2,3-b]indole and hexahydropyrrolo[2,3-b]indole skeletons employing an intramolecular carbamoylketene–alkene [2+2] cycloaddition reaction as the key step.77–80) The chemical yield obtained in the cycloaddition is uniformly high, and the subsequent transformations proceed smoothly and selectively to give the alkaloids or the key intermediates as racemic forms. We thought it important to make the reaction asymmetric. Accordingly, we designed a substrate-controlled diastereoselective process. We chose the optically active substrate 150, which contains the but-3-ene-1,2-diol moiety with a tertiary stereogenic center at the allylic position (C2). The chiral auxiliary would serve to induce chirality at the newly generated benzylic quaternary stereogenic center, and we anticipated that the substituent (R at C1 in 150) would play an important role in obtaining higher diastereoselectivity in 151. In addition, the 1,2-diol functional-
It would facilitate transformation to a variety of functional groups.

Our retrosynthetic analysis of the ketene precursors 152a–d, chosen to evaluate the diastereoselection during the cycloaddition is outlined in Chart 30. The aniline derivatives 153a–d, which can be converted to 152a–d in the usual manner, would be prepared by Suzuki–Miyaura coupling 82) of the aminophenylboronates 154a, b 83) and corresponding optically active vinyl bromides 155a–d, among which 155a, c are known in the literature. 84)

The optically active dimethylated dioxolanes 155b, d were prepared as shown in Chart 31. Asymmetric dihydroxylation of 156 provided the enantiomerically pure diol 157, which was treated with cyclopentanone under acidic conditions, followed by desilylation to give the alcohol 158. On exposure to Nishizawa–Grieco conditions, 44) it afforded 159 which was converted to the vinyl bromide (R)-155d by bromination and then dehydrobromination. The (R)-155b was derived from 155d by sequential deacetalization and acetonide formation.

Preparation of the carboxylic acids 152a–d is shown in Chart 32. Thus, treatment of 154a with 155a, b in the presence of (Ph3P)4Pd and K2CO3 in aqueous THF provided 153a, b.

### Table 4. TAOM Reaction of 132

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Product(s) (ratio)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KH (2 eq), 18-Crown-6 (5 eq), THF, 0°C, 10 min</td>
<td>121</td>
<td>Quant.</td>
</tr>
<tr>
<td>2</td>
<td>KH (5 mol%), 18-Crown-6 (5 mol%), THF, rt, 2 h</td>
<td>121 + 141 (9 : 1)</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>TBAF (2 eq), THF, rt, 5 h</td>
<td>121</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>TBAF (5 mol%), THF, 50°C, 3 h</td>
<td>121</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>DBU (10 eq), LiCl (10 eq), MeCN, rt, 15 min</td>
<td>141</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td>DBU (5 mol%), LiCl (5 mol%), MeCN, rt, 5 h</td>
<td>141</td>
<td>91</td>
</tr>
</tbody>
</table>


Chart 29. Designed Substrate for Diastereoselective Cycloaddition
These were sequentially subjected to carbomethoxylation, alkylation and alkaline hydrolysis to produce (S)-152a,b. The dimethylated analogs (S)-152c,d were prepared efficiently via a sequence of reactions similar to that for the preparation of 152a,b.

With the ketene precursors 152a–d in hand, we advanced to the key [2+2] cycloaddition. Treatment of 152a with oxalyl chloride in benzene, followed by triethylamine, provided the cycloadduct 151a as an inseparable mixture of diastereoisomers in a ratio of 9:1 in 45% yield (Table 5, entry 1). However, we anticipated, and indeed found, that the cycloaddition of the alkenyl ketene generated from 152b resulted in 151b as a single product in 71% yield (entry 2). In the case of 152c,d, which possess a cyclic acetal moiety, similar diastereoselections were observed, and the cycloadducts 151c,d were obtained in higher yields of 81% and 89%, respectively (entries 3 and 4). Thus, we were able to establish a novel diastereoselective process for obtaining the optically pure tricyclic compound.

The mechanism for the exclusive formation of the cycloadducts 151b,d could be explained by considering the transition states $T_1$ and $T_2$, in which the alkenyl moiety with a chiral auxiliary would take a conformation (Ha–C3–C2–C1 is in the same plane) minimizing the allylic strain. As we expected, the bulkiness of the substituent R on the dioxolane ring played an important role in the transition state $T_2$, in which the R group significantly interacts with the ketene moiety. Therefore, the cycloadditions of the alkenyl ketenes generated from (S)-152b,d resulted in the predominant formation of 151b,d with the $(R,R,S)$ configuration (Fig. 6). The absolute configurations of the cycloadducts were confirmed by the following transformation of 151d to (−)-esermethole (164) as shown in Chart 33.

Table 5. [2+2] Cycloaddition

<table>
<thead>
<tr>
<th>Entry</th>
<th>Carboxylic acid</th>
<th>Product</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>$R^3$</th>
<th>Yield (%)</th>
<th>$d$&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>152a</td>
<td>151a</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>45</td>
<td>9:1</td>
</tr>
<tr>
<td>2</td>
<td>152b</td>
<td>151b</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>71</td>
<td>1:0</td>
</tr>
<tr>
<td>3</td>
<td>152c</td>
<td>151c</td>
<td>OMe</td>
<td>H</td>
<td>$(\text{CH}_2)_3^-$</td>
<td>81</td>
<td>5:1</td>
</tr>
<tr>
<td>4</td>
<td>152d</td>
<td>151d</td>
<td>OMe</td>
<td>$(\text{CH}_2)_3^-$</td>
<td>89</td>
<td>1:0</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by $^1$H-NMR.

To test the applicability of this methodology, and to confirm the absolute configuration of the cycloadduct, we examined the conversion of 151d to (−)-esermethole (164). Treatment of 151d with N-methylhydroxylamine hydrochloride, NaHCO<sub>3</sub> and molecular sieves 3 Å in ethanol at 50°C provided the nitroene<sup>79</sup> which, without purification, was immediately reacted with p-TsCl and 4-pyrrolidinopyridine (PPY) in refluxing chloroform to give 161. After acidic hydrolysis, the resulting diol 162 was exposed to oxidative cleavage conditions to produce the aldehyde, which was reduced with NaBH<sub>4</sub> to give the alcohol 163. Tosylation, followed by reduction with LiAlH<sub>4</sub> provided (−)-esermethole (164), whose spectral properties and optical rotation were identical with those reported in the literature. Thus, the absolute configuration of the cycloadduct obtained diastereoselectively was firmly established to be $(R,R,S)$ as we had expected.

We also applied this method to the synthesis of the alkaloid (+)-psychotrimine (165), which was isolated from Psychotria rostrata by Takayama et al. in 2004,<sup>85</sup> and which exhibits antibacterial activity against Gram-positive bacteria and acts via membrane disruption.<sup>86</sup> Several synthetic reports have been published so far, including the first enantioselective total synthesis by Takayama and colleagues,<sup>87</sup> that established the absolute structure. In Takayama’s enantioselective synthesis, the 3a-indole-substituted pyrrolidinoindoline (166) was shown to be a key intermediate, which was converted via an eight-step sequence to (+)-psychotrimine (165) uneventfully. Therefore, we attempted the transformation of (S,S,R)-167, which can be derived from (R)-168, to (−)-(3aS,8aS)-166.

The carboxylic acid (R)-168 was subjected to ketene-forming conditions to provide exclusively the (S,S,R)-167. This
was then converted to the carboxylic acid 171 via 169 and 170 through the same sequence of reactions described in Chart 33. The Shioiri–Curtius rearrangement of 171 gave the amine 172, which was exposed to indole-forming conditions 88,89) with 1-bromo-2-(2-bromovinyl)benzene (173) to furnish the indole 174. Finally, reduction followed by tert-butoxycarbonyl (Boc)-protection produced (−)-166, whose spectral properties and optical rotation were identical with those reported.

As described above, a novel and highly diastereoselective intramolecular carbamoylketene–alkene [2+2] cycloaddition has been developed, and the methodology was successfully applied to the enantioselective syntheses of (−)-esermethole and Takayama’s intermediate of (+)-psychotrimine. The diastereoselective cycloaddition methodology developed here permits access to both enantiomeric products, in which the chiral dioxolane moiety can efficiently serve for further transformations and functionalization. It could also be applied to the enantioselective synthesis of other related alkaloids with more complicated molecular structures.

5. Conclusion
In this account, our synthetic efforts toward natural products with promising biological profiles and intriguing structural features have been introduced. Enantiocontrolled total syntheses of two types of allelochemicals, helianane sesquiterpenes (heliannuols A, D and K, heliespirones A and C), and meroterpenes (breviones A, B and C), have been demonstrated. In addition, the intramolecular car-
bamoylketene–alkene [2+2] cycloaddition reaction, which has been developed in our laboratories, has evolved as a powerful methodology for the enantioselective synthesis of alkaloids, and it has been successfully applied to the formal syntheses of two pyrrolidinoindoline alkaloids, phystostigmine and psychotrinine. The strategies we have employed should have great potential in organic synthesis studies, particularly in the context of the stereoselective synthesis of biologically active target molecules in the natural product and pharmaceutical research sectors.

Acknowledgments I express my sincere gratitude to the dedicated collaborators in my group, individually acknowledged in the references, whose enthusiastic contributions, intellectual and experimental, made this work possible. This work was supported financially by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Sciences (JSPS) and a Grant-in-Aid for the Program for the Promotion of Basic and Applied Research for Innovation in the Bio-oriented industry (BRAIN).

References

54) Hagiwara H., Fujiwara N., Suzuki T., Ando M., Heterocycles, 53,