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Total Syntheses of (+)- and (−)-Pestalotiopsin A

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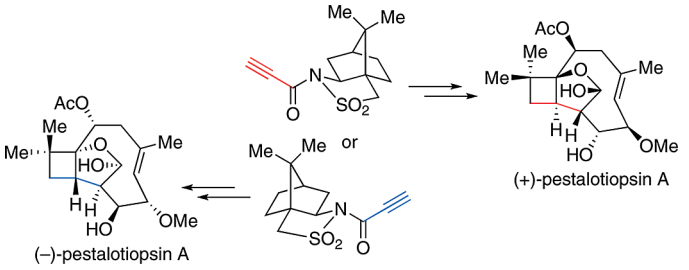

An enantioselective total synthesis of both enantiomers of caryophyllene-type sesquiterpenoid pestalotiopsin A has been achieved, thereby establishing the absolute stereochemistry of natural (+)-pestalotiopsin A. Highlights of the synthesis include a [2 + 2] cycloaddition of *N*-propioloyl Oppolzer's camphorsultam and ketene dialkyl acetal and subsequent highly stereoselective 1,4-hydride addition/protonation, an aldol reaction of functionalized bicyclic lactone with aldehyde, an efficient intramolecular Nozaki−Hiyama−Kishi (NHK) reaction for the construction of the highly strained (*E*)-cyclononene ring, and a palladium-catalyzed reduction of allylic mesylate with retention of the *E* configuration.

Introduction

The secondary metabolites of endophytic microorganisms have attracted considerable attention in the scientific community since the paclitaxel (Taxol)-producing fungus was isolated as an endophyte from the Pacific yew (*Taxus brevifolia*).[1] In 1996, Sugawara and co-workers reported the isolation and structural determination of two new caryophyllene-type sesquiterpenoids, (+)-pestalotiopsin A (**1**) and (−)-pestalotiopsin B (**2**) (Figure 1), from *Pestalotiopsis* sp., an endophytic fungus associated with the bark and leaves of *Taxus brevifolia*.[2] Later, (+)-pestalotiopsin C (**3**), a congener of **1** and **2**, was also isolated from the same fungus.[3] The structures of **1**−**3** were determined mainly by the analysis of 1D and 2D NMR data and FAB-MS. The relative stereochemistries and conformations of **1** and **2** were elucidated through single-crystal X-ray diffraction analysis. The unveiled structure of **1** is the hitherto unknown oxatricyclic skeleton that is composed of a cyclobutane ring fused with both an (*E*)-cyclononene ring and a γ-lactol unit. From the biological perspective, compound **1** shows immunosuppressive activity in the mixed lymphocyte reaction and cytotoxicity,[2] but the details have not been reported. In 2003, structurally related natural products pestalotiopsolide A (**4**), taedolidol (**5**), and 6-epitaedolidol (**6**) were discovered in cultures of *Pestalotiopsis* sp. obtained from a

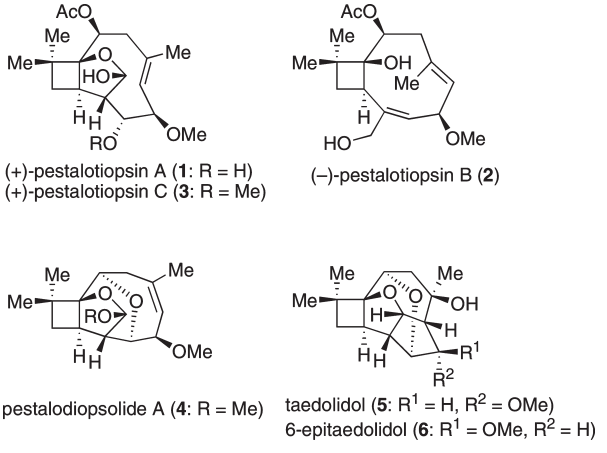

FIGURE 1. Structures of (+)-pestalotiopsin A and related compounds.

(1) Stierle, A.; Strobel, G.; Stierle, D. *Science* **1993**, *260*, 214–216.
(2) Pulici, M.; Sugawara, F.; Koshino, H.; Uzawa, J.; Yoshida, S.; Lobkovsky, E.; Clardy, J. *J. Org. Chem.* **1996**, *61*, 2122−2124. Correction: *J. Org. Chem.* **1997**, *62*, 1564.
(3) Pulici, M.; Sugawara, F.; Koshino, H.; Okada, G.; Esumi, Y.; Uzawa, J.; Yoshida, S. *Phytochemistry* **1997**, *46*, 313–319.

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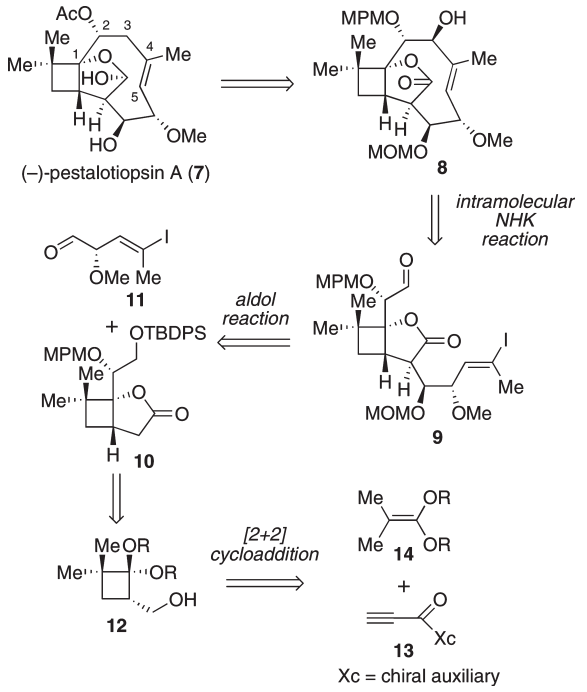
SCHEME 1. Retrosynthetic Analysis



Pinaceae plant, *Pinus taeda*.[4] They could be biosynthesized from a precursor, such as pestalotiopsins. In the context described above, the research groups of Procter,[5] Paquette,[6] and Markó,[7] in addition to our group,[8] have been interested in pestalotiopsin A (**1**) as a synthetic target, especially due to its formidable structure. Recently, we reported the first total synthesis of (−)-pestalotiopsin A (**7**, Scheme 1), thereby establishing the absolute stereochemistry of natural **1**.[9] Herein, we describe a full account of the total synthesis of pestalotiopsin A, unnatural **7**, and finally, natural enantiomer **1**. The evaluation of their biological activities is also presented.

Results and Discussion

Synthetic Strategy. In the landmark total synthesis of (±)-caryophyllene by Corey and co-workers,[10] the strained (*E*)-cyclononene framework was constructed by Grob fragmentation. Ohtsuka, Oishi, and co-workers achieved the total synthesis of (±)-caryophyllene by using a ring-contraction of 13-membered lactam sulfoxide for the construction of the (*E*)-cyclononene.[11] More recently, an intramolecular Tsuji−Trost reaction was employed for the synthesis of the structural relative caryophyllene, (−)-antheliolide A, in the laboratory of Corey.[12] To develop new synthetic methods and strategies for the caryophyllenes, we have focused on two subjects in studies directed toward the total synthesis of pestalotiopsin A, i.e., (1) an efficient formation of the highly oxygenated (*E*)-cyclononene skeleton and (2) an asymmetric synthesis of the multisubstituted cyclobutane derivatives. Our retrosynthetic analysis of pestalotiopsin A is shown in Scheme 1. As the absolute stereochemistry was undetermined at the outset of our work on pestalotiopsin A, enantiomer **7** was arbitrarily selected as the target. Since embarking on this research, we have investigated an efficient method for the direct closure of the (*E*)-cyclononene skeleton of pestalotiopsin A. However, the following early attempts were unsuccessful: (a) intramolecular pinacol coupling reaction for C1−C2 or C4−C5 bond formation, (b) Dieckmann condensation, intramolecular SmI_2-mediated reductive cyclization, and intramolecular α-sulfonyl anion or protected cyanohydrin anion cyclization for C2−C3 bond formation, and (c) ring-closing metathesis for C4−C5 double-bond formation.[13] After these experiments, we assumed that a Nozaki−Hiyama−Kishi (NHK) reaction approach[14] would enable efficient (*E*)-cyclononene ring formation. Therefore, we designed a synthetic intermediate **8** carrying a hydroxy group at C3, which would be synthesized by using the intramolecular NHK reaction of aldehyde/alkenyl iodide **9**. Deoxygenation of the hydroxy group at C3 in **8** was considered to be involved in the end game. The assembly of **9** could be achieved by the aldol reaction of functionalized bicyclic lactone **10** and γ-iodo-β,γ-unsaturated aldehyde **11**. The bicyclic lactone structure of **10** would offer potential advantages in terms of stereoselectivity in the aldol reaction. This bicyclic lactone **10**, in turn, would be prepared from a multisubstituted cyclobutane **12**. For the preparation of intermediary cyclobutane derivative **12** in an enantioenriched form, a program was launched to develop a new methodology for the asymmetric synthesis of cyclobutane compounds,[15] featuring the [2 + 2] cycloaddition of chiral propiolate **13** and ketene acetal **14**.

Asymmetric Synthesis of Cyclobutane 17. It has been reported that some propiolic acid esters feasibly undergo [2 + 2] cycloaddition with ketene silyl acetals to provide cyclobutene derivatives, which were reduced to cyclobutane derivatives.[16] We anticipated that asymmetric induction in

(4) Magnani, R. F.; Rodrigues-Fo, E.; Daolio, C.; Ferreira, A. G.; de Souza, A. Q. L. *Z. Naturforsch., C: J. Biosci.* **2003**, *58c*, 319–324.

(5) (a) Johnston, D.; Francon, N.; Edmonds, D. J.; Procter, D. J. *Org. Lett.* **2001**, *3*, 2001–2004. (b) Johnston, D.; Couché, E.; Edmonds, D. J.; Muir, K. W.; Procter, D. J. *Org. Biomol. Chem.* **2003**, *1*, 328–337. (c) Edmonds, D. J.; Muir, K. W.; Procter, D. J. *J. Org. Chem.* **2003**, *68*, 3190–3198. (d) Baker, T. M.; Edmonds, D. J.; Hamilton, D.; O'Brien, C. J.; Procter, D. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 5631–5633.

(6) (a) Paquette, L. A.; Cunière, N. *Org. Lett.* **2002**, *4*, 1927–1929. (b) Paquette, L. A.; Kang, H.-J. *Tetrahedron* **2004**, *60*, 1353–1358. (c) Paquette, L. A.; Parker, G. D.; Tei, T.; Dong, S. *J. Org. Chem.* **2007**, *72*, 7125−7134. Correction: *J. Org. Chem.* **2009**, *74*, 1812. (d) Paquette, L. A.; Dong, S.; Parker, G. D. *J. Org. Chem.* **2007**, *72*, 7135–7147. (e) Dong, S.; Paquette, L. A. *Heterocycles* **2007**, *72*, 111–114.

(7) Maulide, N.; Markó, I. E. *Chem. Commun.* **2006**, 1200–1202.

(8) Takao, K.; Saegusa, H.; Tsujita, T.; Washizawa, T.; Tadano, K. *Tetrahedron Lett.* **2005**, *46*, 5815–5818.

(9) Takao, K.; Hayakawa, N.; Yamada, R.; Yamaguchi, T.; Morita, U.; Kawasaki, S.; Tadano, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3426–3429.

(10) (a) Corey, E. J.; Mitra, R. B.; Uda, H. *J. Am. Chem. Soc.* **1963**, *85*, 362–363. (b) Corey, E. J.; Mitra, R. B.; Uda, H. *J. Am. Chem. Soc.* **1964**, *86*, 485–492. (c) Recently, the enantioselective total synthesis of (−)-caryophyllene was also achieved. See: Larionov, O. V.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 2954–2955.

(11) Ohtsuka, Y.; Niitsuma, S.; Tadokoro, H.; Hayashi, T.; Oishi, T. *J. Org. Chem.* **1984**, *49*, 2326–2332.

(12) Mushti, C. S.; Kim, J.-H.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 14050–14052.

(13) The Paquette group also reported that construction of the (*E*)-cyclononene of pestalotiopsin A via ring-closing metathesis proved to be difficult. See ref 6d.

(14) For recent reviews on the synthetic utility of the NHK reaction, see: (a) Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1–36. (b) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991–1045.

(15) For reviews on the synthesis of optically active cyclobutane derivatives, see: (a) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449–1483. (b) Butenschön, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 3492–3495. For a review on the application of cyclobutane derivatives in organic synthesis, see: (c) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485–1537.

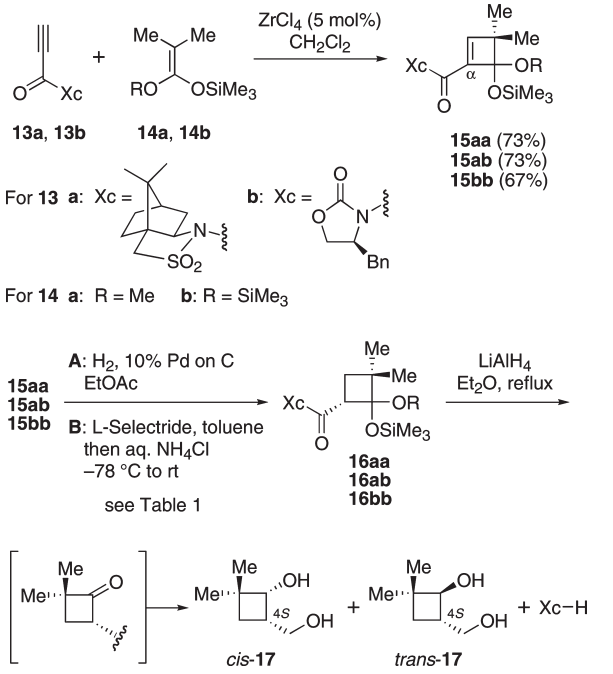
(16) (a) Quendo, A.; Rousseau, G. *Tetrahedron Lett.* **1988**, *29*, 6443–6446. (b) Mitani, M.; Sudoh, T.; Koyama, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1683–1687. (c) Miesch, M.; Wendling, F. *Eur. J. Org. Chem.* **2000**, 3381–3392.

TABLE 1. Reduction of Cyclobutenes 15 Followed by Removal of the Chiral Auxiliary

entry	cyclo-butene	conditions[a]	yields[b] (%) *cis*-**17**	yields[b] (%) *trans*-**17**	yields[b] (%) Xc-H	ee (%) of **17**[c]	config of **17**[d]
1	**15aa**	**A**	36	14	63	20	*R*
2	**15aa**	**B**	33	20	69	32	*R*
3	**15ab**	**A**	51	20	80	50	*R*
4	**15ab**	**B**	54	38	100	98	*S*
5	**15bb**	**B**	38	37	28	13	*S*

[a]See Scheme 2. [b]Isolated yields from **15aa**, **15ab**, or **15bb**. [c]Determined by chiral HPLC analysis after conversion of *cis*-**17** into the corresponding monotosylate *cis*-**18**. In entry 4, the ee of *trans*-**17** was also determined by chiral HPLC analysis and confirmed to be identical to the ee of *cis*-**17**. [d]Absolute configuration of C4 in the major enantiomer.

SCHEME 2. Asymmetric Synthesis of Cyclobutanols, *cis*-17 and *trans*-17



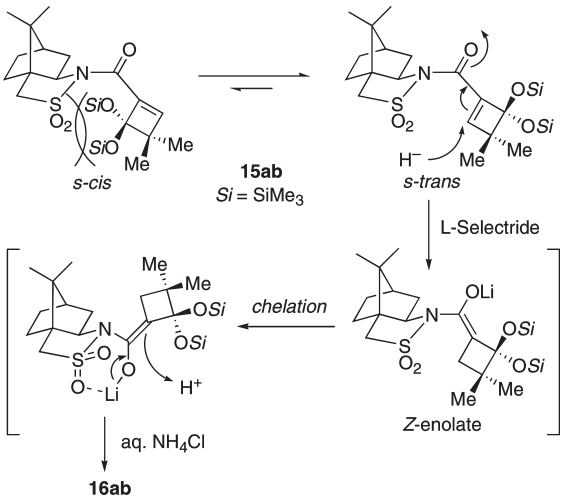
these reaction sequences would be realized by using a chiral auxiliary strategy. Therefore, two chiral propiolic acid derivatives, Oppolzer's (1*S*)-camphorsultam **13a** and Evans' oxazolidinone **13b**, both incorporating an *N*-propioloyl group, were prepared according to the procedure described in the literature[17] (Scheme 2). Rousseau and Quendo reported that ethyl propiolate reacted with dimethylketene methyl trimethylsilyl acetal (**14a**) in the presence of a catalytic amount of $ZrCl_4$ in dichloromethane to provide a cyclobutene derivative as a result of [2 + 2] cycloaddition.[16a] Under the same conditions, the reaction of **13a** with ketene silyl acetal **14a** proceeded to produce cyclobutene **15aa** as a mixture of diastereomers (ca. 3:2). Asymmetric induction at C(α) in the reduction of a C−C double bond of the resulting cyclobutenecarbonyl amide **15aa** was examined by the addition of hydrogen in the presence of palladium on carbon (conditions **A**)[18] or 1,4-hydride addition with lithium tri-*sec*-butyl borohydride (L-Selectride) in toluene and subsequent protonation of the resulting enolate (conditions **B**).[19] In the cases of **15aa** under conditions **A** and **B**, unsatisfactory stereoselectivities of the obtained cyclobutane **16aa** were observed (Table 1, entries 1 and 2). Due to a concern that the asymmetric center at the acetal carbon in **15aa** might cause low stereoselectivity, we next used a symmetrical ketene, such as bis(trimethylsilyl) acetal **14b**,[20] as a partner in the [2 + 2] cycloaddition. The reaction of **13a** and bis-silyl acetal **14b** gave the sole adduct **15ab**. Although the hydrogenation (conditions **A**) of **15ab** showed a moderate stereoinduction (entry 3), the 1,4-hydride addition/protonation (conditions **B**) realized an excellent level to provide cyclobutane **16ab** in an almost diastereomerically single form (entry 4). In contrast, the use of Evans' oxazolidinone as the chiral auxiliary gave a lower level of asymmetric induction. The cycloadduct **15bb** was reduced under conditions B to cyclobutane **16bb** with only 13% de (entry 5). To obtain the cyclobutane derivative **12** in Scheme 1, the chiral auxiliaries in **16aa**, **16ab**, or **16bb** were removed with lithium aluminum hydride. These reactions, however, induced the simultaneous cleavage of the silyl acetal and the subsequent reduction of the resulting cyclobutanone. In the case of entry 4, two diastereomers of cyclobutanols, *cis*-**17** and *trans*-**17**, were obtained with 98% ee.[21] Oppolzer's camphorsultam (Xc-H) was quantitatively recovered.

To explain the observed high level of stereoselection in the tandem 1,4-hydride addition/protonation in the case of **15ab**, we reasoned from the well-recognized transition states argument by Oppolzer et al.[22] (Scheme 3). In the more favorable conformation of **15ab**, the carbonyl group directs *anti* to the SO_2 group and adopts *s-trans* conformation to the α,β-unsaturated bond as depicted to avoid a steric repulsion occurring between bis(trimethylsilyloxy) and the SO_2 groups in the *s-cis* conformer. Then, the 1,4-hydride addition to the *s-trans* conformer generates the *Z*-enolate intermediate, which is reorganized to the more stable lithium-chelated conformer as depicted. A proton approaches predominantly from the side opposite the bulky auxiliary (from the front side), giving **16ab** almost exclusively.

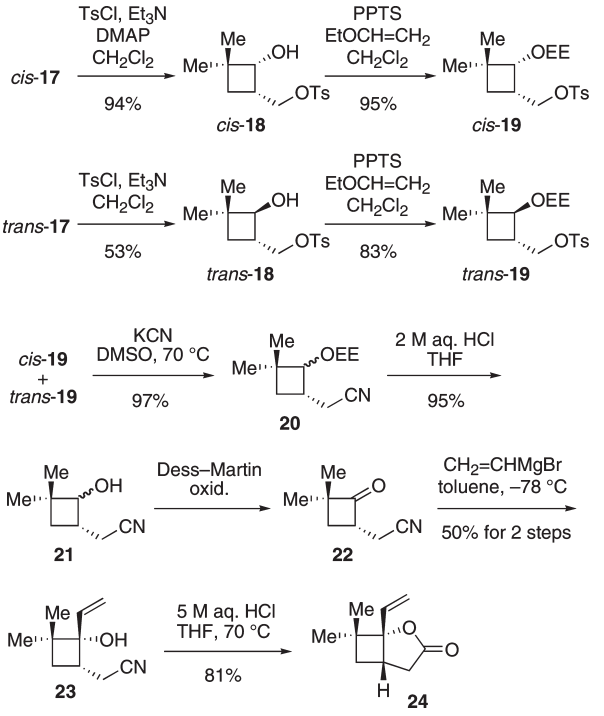
First-Generation Synthesis of Bicyclic Lactone 24. Having established the method for the asymmetric synthesis of the multisubstituted cyclobutanes *cis*-**17** and *trans*-**17**, we turned our attention to the construction of the bicyclic lactone **24** (Scheme 4). Toward this end, we examined one-carbon homologation of the hydroxymethyl group at C4 in *cis*-**17**

(17) Fonquerna, S.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron: Asymmetry* **1997**, *8*, 1685–1691.
(18) Oppolzer, W.; Mills, R. J.; Réglier, M. *Tetrahedron Lett*. **1986**, *27*, 183–186.
(19) Oppolzer, W.; Poli, G. *Tetrahedron Lett*. **1986**, *27*, 4717–4720.
(20) (a) Ainsworth, C.; Kuo, Y.-N. *J. Organomet. Chem*. **1972**, *46*, 73–87. (b) Schulz, W. J., Jr.; Speier, J. L. *Synthesis* **1989**, 163–166.
(21) For assignment of the absolute stereochemistry at C4 in the enantioenriched (98% ee) *cis*-**17** and *trans*-**17**, see the Supporting Information.
(22) Oppolzer, W.; Poli, G.; Starkemann, C.; Bernardinelli, G. *Tetrahedron Lett*. **1988**, *29*, 3559–3562.

SCHEME 3. Plausible Mechanism for the 1,4-Hydride Addition/Protonation of 15ab



SCHEME 4. First-Generation Synthesis of Bicyclic Lactone 24



and *trans*-**17**. Selective tosylation of the primary hydroxy group in *cis*-**17** was easily achieved, whereas the selectivity on *trans*-**17** was modest. Treatment of monotosylate *cis*-**18** or *trans*-**18** with potassium cyanide in hot dimethyl sulfoxide unexpectedly caused a ring-opening reaction involving the elimination of the tosyloxy group, i.e., a Grob fragmentation, to form 2,2-dimethylpent-4-en-1-al, which was attacked by a cyanide ion to produce the corresponding cyanohydrin in significant yields of 30−40%. Therefore, the secondary hydroxy group in *cis*-**18** and *trans*-**18** was temporally protected as ethoxyethyl (EE) ether. The resulting *cis*-**19** and *trans*-**19** were mixed at this stage and moved forward together. The tosyloxy group in the mixture **19** was replaced by a cyano group to provide nitrile **20**. Brief exposure of **20** to hydrochloric acid hydrolyzed the ethoxyethyl ether to regenerate secondary alcohol **21**, which was oxidized with Dess−Martin periodinane[23] to cyclobutanone **22**. The Grignard reaction of **22** with vinylmagnesium bromide in toluene occurred as anticipated from the more accessible β-face to provide vinyl-adduct **23** as a single isomer. Acid hydrolysis of the nitrile group accompanied by γ-lactone formation provided bicyclic lactone **24**. The synthesis arrived at bicyclic lactone **24**, but our first-generation synthetic route was, rather, a multistep process including (1) the formation of the *two* diastereomers *cis*-**17** and trans-**17** and (2) the protection of the secondary hydroxy group in *cis*-**18** and *trans*-**18** for the homologation. These disadvantages were originally caused by the high reactivity of the bis(trimethylsilyl) acetal moiety in **16ab** to $LiAlH_4$ under the conditions used for the removal of the camphorsultam.

Second-Generation Strategy. To circumvent a long synthesis, an improved protocol was developed by using ketene dialkyl acetal **14c** as the partner for the [2 + 2] cycloaddition of **13a** (Scheme 5). Compound **14c** was prepared in batches of 25 g from methacrolein diethyl acetal (**25**) by olefin isomerization with lithium/ethylenediamine.[24] The Lewis acid-catalyzed [2 + 2] cycloaddition of **13a** with **14c** afforded a single regioisomeric adduct **26** in a slightly higher yield (85%). The 1,4-hydride addition/protonation of cyclobutene **26** with L-Selectride showed extremely high stereoselectivity again, providing cyclobutane derivative **27** quantitatively. Treatment of **27** with lithium aluminum hydride provided cyclobutanemethanol **12** (R = Et in Scheme 1) in 94% yield for two steps with an excellent enantiomeric excess of >95%,[25] and camphorsultam was recovered efficiently in a multigram-scale experiment. Conversion of **12** into nitrile **28** through the tosylate and subsequent acid hydrolysis of the dialkyl acetal moiety in **28** provided cyclobutanone **22**, which was subjected to the same two-step sequence with the first-generation synthesis to arrive at bicyclic lactone **24**. The second-generation approach enables more convenient access to the key intermediate **24** (29% overall yield for 8 steps from **13a**) than the previous approach (16% overall yield for 12 steps).

With bicyclic lactone **24** in hand, we turned to the dihydroxylation of the vinyl group. We initially assumed that Sharpless asymmetric dihydroxylation[26] of **24** would provide the desired (*R*)-diastereomer (Scheme 6). However, treatment of **24** with AD-mix-α preferentially produced the undesired (*S*)-isomer. After selective *O*-silylation of the primary hydroxy group in the dihydroxylation products, the diastereomeric products **29** and **30** were obtained in a ratio of 1:4. This stereochemical propensity was also observed in the case of using AD-mix-β (**29**:**30** = 1:2) or achiral reagents OsO_4/NMO (**29**:**30** = 1:4). We, therefore, explored

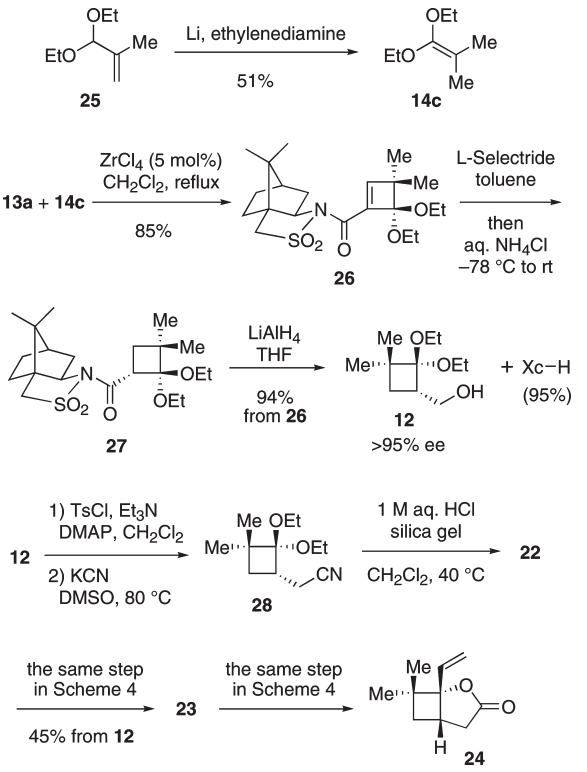
(23) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287. (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(24) For the conventional method for the synthesis of **14c** from triethyl orthoisobutyrate, see: McElvain, S. M.; Davie, W. R. *J. Am. Chem. Soc.* **1951**, *73*, 1400–1402.

(25) The ee of **12** was determined by ^1H NMR analysis of the Mosher esters derived from **12**.

(26) For a review on Sharpless asymmetric dihydroxylation, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.

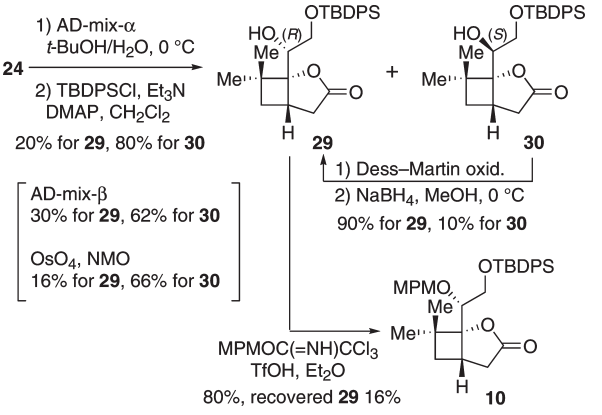
SCHEME 5. Second-Generation Synthesis of Bicyclic Lactone 24



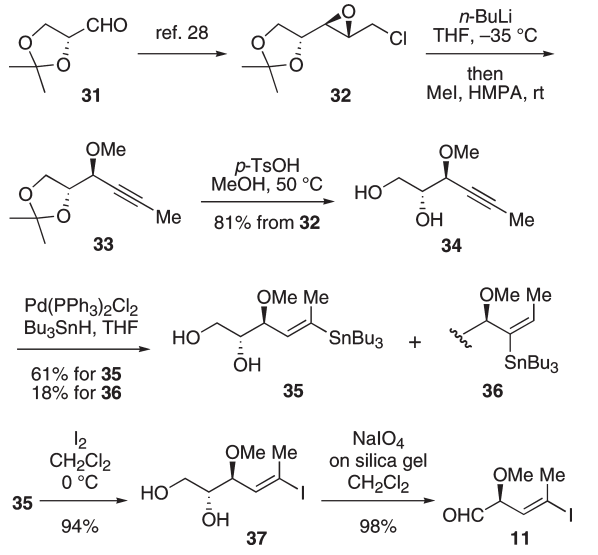
a method for the reversal of the stereochemistry in the major isomer **30**. Fortunately, (*S*)-isomer **30** was converted into the desired **29** by an oxidation/reduction strategy. Thus, the Dess–Martin oxidation of **30**, followed by the sodium borohydride reduction of the resulting ketone, provided (*R*)-isomer **29** in a high overall yield of 90%. The substrate for the planned aldol was protected with (4-methoxyphenyl)-methyl (MPM) imidate to provide the functionalized bicyclic lactone **10**.

Synthesis of (*E*)-Cyclononene Skeleton. The γ-iodo-β,γ-unsaturated aldehyde **11**, the coupling partner for the aldol reaction of **10**, was synthesized from D-glyceradehyde acetonide (**31**) (Scheme 7). Although the additions of metal acetylide reagents to **31** have been studied,[27] stereochemical control is still difficult. Therefore, we adopted Takano's protocol[28] to prepare the chiral propargylic alcohol. Treatment of the known epoxy chloride **32** prepared from **31** with 3 equiv of *n*-butyllithium resulted in the formation of the intermediary dianion, which was trapped with iodomethane in the presence of hexamethylphosphoramide (HMPA) to afford the *C*,*O*-methylated propargyl alcohol **33**. Hydrolysis of the acetonide group in **33**, followed by a palladium-catalyzed hydrostannation of the resulting diol **34** using $Bu_3SnH/Pd(PPh_3)_2Cl_2$,[29] gave the terminally stannylated olefin **35** and its regioisomer **36** in ratio of 3.4:1. The

SCHEME 6. Synthesis of Lactone 10



SCHEME 7. Synthesis of Aldehyde 11



regioselectivity of **35**:**36** has now been greatly improved by the stannylcupration methodology identified in a later experiment for the synthesis of **1** (vide infra). The metal–halogen exchange of **35** with iodine provided alkenyl iodide **37**, which was subjected to an oxidative cleavage using silica gel-supported sodium metaperiodate[30] to provide essentially pure aldehyde **11** in a good yield.

With bicyclic lactone **10** and aldehyde **11** in hand, we next focused on the coupling of these partners by an aldol reaction (Scheme 8). On the basis of our previous experiment performed by using structurally analogous coupling partners,[8] the aldol reaction of **10** with **11** was examined by use of sodium bis(trimethylsilyl)amide (NaHMDS) as a base. As expected, this reaction provided the *anti*-aldol **38** predominantly (**38**:**39** = 3:1), securing the two contiguous stereogenic centers required for the target molecule. The approach of aldehyde **11** occurred exclusively from the convex face of the bicyclic skeleton of **10**. Other bases were screened for the generation of the enolate (LiHMDS and KHMDS), but no better result was found.

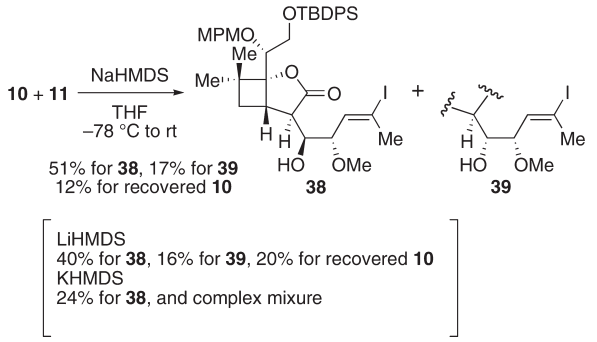
(27) (a) Mulzer, J.; Greifenberg, S.; Beckstett, A.; Gottwald, M. *Liebigs Ann. Chem.* **1992**, 1131–1135. (b) Mulzer, J.; Funk, G. *Synthesis* **1995**, 101–112.

(28) Takano, S.; Samizu, K.; Sugihara, T.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1344–1345.

(29) (a) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857–1867. (b) For a review on the metal-catalyzed hydrostannation, see: Smith, N. D.; Mancuso, J.; Lautens, M. *Chem. Rev.* **2000**, *100*, 3257–3282.

(30) Zhong, Y.-L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622–2624.

SCHEME 8. Aldol Reaction of Lactone 10 and Aldehyde 11

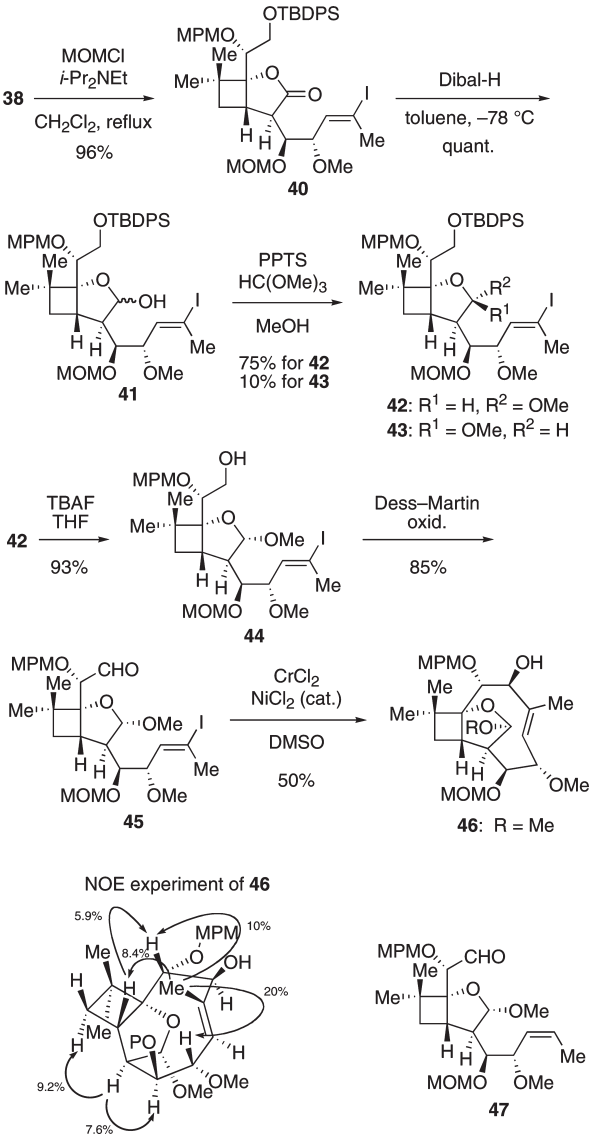


The next stage was to construct the formidable (*E*)-cyclononene ring. The initial route was designed to form the γ-lactol moiety prior to the NHK reaction (Scheme 9). Protection of the secondary alcohol **38** as methoxymethyl (MOM) ether, followed by reduction of the resulting **40** with diisobutylaluminum hydride (DIBAL-H), provided γ-lactol **41** as an anomeric mixture (ca. 2:1). Acetalization of **41** with trimethyl orthoformate and a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) in methanol gave α-isomer **42** and β-isomer **43** in 75% and 10% yields, respectively. The predominantly obtained isomer **42** was treated with tetrabutylammonium fluoride (TBAF) to provide the desilylated alcohol **44**, which was oxidized to aldehyde **45** with Dess–Martin periodinane. Treatment of a 0.005 M solution of **45** in dimethyl sulfoxide with $CrCl_2$ and catalytic $NiCl_2$ effected an intramolecular NHK reaction that provided the cyclized product **46** in 50% yield as a single diastereomer. The yield of the cyclized product **46** was moderate because the intermediary metalated olefin underwent competitive protonation during the NHK reaction, thereby forming an uncyclized product **47** in 26% yield. The stereochemistry and conformation of **46** were determined by NOE experiments as shown. The NOE relations suggest that compound **46** exists in solution as a $\beta\alpha$-conformer,[31] similarly to the natural product **1**. The $\beta\beta$-conformational isomer was not observed in NMR analysis of **46** at room temperature.

In an effort to optimize the ring closure process, we next examined the intramolecular NHK reaction of the γ-lactone corresponding to **45** (Scheme 10). The requisite substrate for the reaction, aldehyde/alkenyl iodide **9**, was available via a desilylation of **40** and subsequent oxidation of the resulting **48**. We were pleased to find that the intramolecular NHK reaction of **9** provided the cyclized product **8** in 92% yield as a single diastereomer and as a single atropisomer ($\beta\alpha$-conformer), as determined by NOE analysis. Considering the highly strained structure of (*E*)-cyclononene, the high yield of **8** was remarkable.

Completion of the Synthesis of (−)-Pestalotiopsin A (7). The final stage of the synthesis required the removal of the extra hydroxy group introduced in **8**. Preliminarily, we attempted the radical-induced deoxygenation of **8** utilizing the Barton method.[32] The anticipated product was not

SCHEME 9. Intramolecular NHK Reaction of 45



obtained; the geometrical isomerization of the trisubstituted (*E*)-olefin moiety occurred. For example, when the methyl xanthate ester of **8** was treated with tributyltin hydride in refluxing toluene, the desired deoxygenation proceeded, accompanied by a complete isomerization of the olefin geometry, resulting in the quantitative formation of the *Z*-isomer. Moreover, the MOM group at C7−OH was difficult to remove under acidic conditions in the final step.[33] We were, therefore, forced to explore an alternative strategy that could avoid the isomerization of the (*E*)-olefin moiety as well as an easily removable protecting group on C7−OH. These encountered difficulties were solved by using a palladium-catalyzed reduction strategy[34] and by switching the MOM group to the triethylsilyl (TES) group, as shown in Scheme 11. Leaving group investigation in the palladium-catalyzed reduction, a mesylate was found to be suitable in

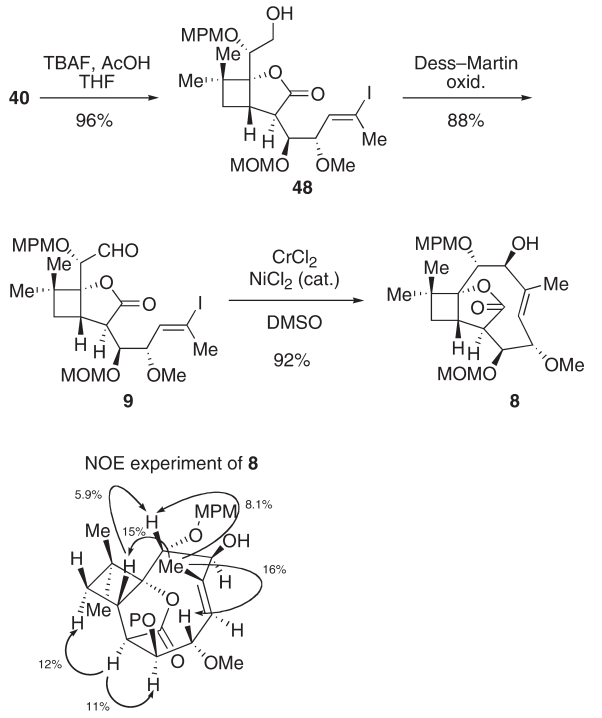
(31) Using the terminology of Shirahama et al., see: Shirahama, H.; Osawa, E.; Chhabra, B. R.; Shimokawa, T.; Yokono, T.; Kanaiwa, T.; Amiya, T.; Matsumoto, T. *Tetrahedron Lett*. **1981**, *22*, 1527–1528.

(32) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574–1585. (b) For a review on the radical deoxygenation of alcohols, see: Hartwig, W. *Tetrahedron* **1983**, *39*, 2609–2645.

(33) It was reported that the caryophyllene skeleton is somewhat sensitive to acids: Collado, I. G.; Hanson, J. R.; Macías-Sánchez, A. J. *Nat. Prod. Rep.* **1998**, *15*, 187–204.

(34) For a review on palladium-catalyzed hydrogenolysis, see: Tsuji, J.; Mandai, T. *Synthesis* **1996**, 1–24.

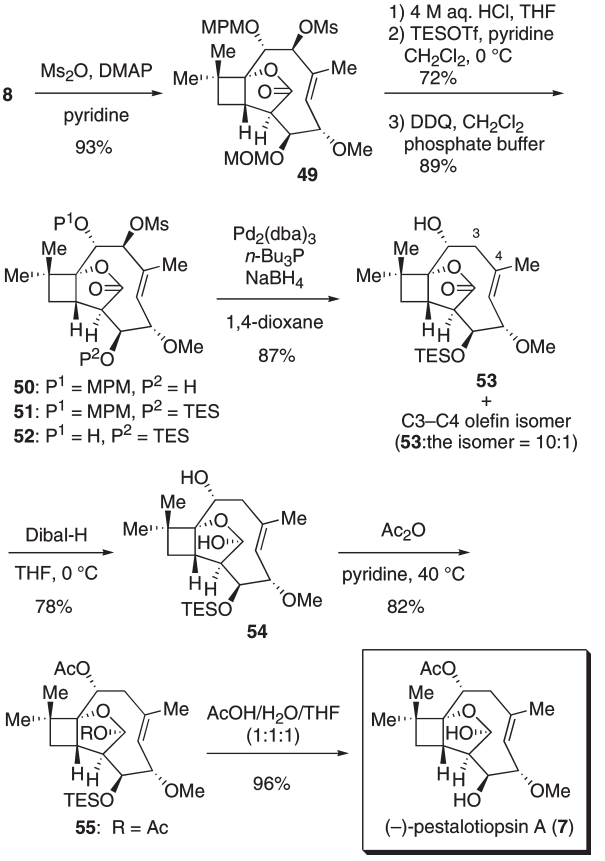
SCHEME 10. Intramolecular NHK Reaction of 9



this case. Thus, the cyclized product **8** was converted into allylic mesyl ester **49**. Deprotection of the MOM group in **49** was proved successful by use of standard acidic hydrolysis conditions. Silylation of the resulting alcohol **50**, followed by cleavage of the MPM ether in **51**, afforded the TES ether **52**. Treatment of **52** with a combination system of $Pd_2(dba)_3$/n-Bu_3P and $NaBH_4$[35] provided the desired deoxygenated product **53** in a practical manner,[36] accompanied by a small amount (ca. 8%) of the C3−C4 olefin isomer. Use of HCO_2NH_4[37] as a hydride source in place of $NaBH_4$ in this reaction resulted in the preferential formation of the undesired C3−C4 olefin isomer. DIBAL-H reduction of **53** provided γ-lactol **54** as a sole α-anomer, while the C3−C4 olefinic isomer obtained in the former reaction was removed at this stage. Acetylation of **54** provided diacetate **55**, and the mild acid hydrolysis allowed clean deprotection of the TES group and the acetyl group in the γ-lactol moiety to provide (−)-pestalotiopsin A (**7**). The synthetic sample was identical in all respects (mp, TLC, IR, ^1H and ^{13}C NMR, and HRMS) to those of natural pestalotiopsin A, except for the sign of optical rotation [$[\alpha]^{21}_D$ −74.7 (*c* 0.535, MeOH) for **7**; lit.[2] $[\alpha]^{22}_D$ +76.8 (*c* 1, MeOH) for the natural sample]. This fact verified that we had synthesized the antipode of natural pestalotiopsin A.

Synthesis of 2-*epi*-Pestalotiopsin A (64). We next directed our efforts to the synthesis of the unnatural congener

SCHEME 11. Completion of the Synthesis of (−)-Pestalotiopsin A (7)



2-*epi*-pestalotiopsin A (**64**) (Scheme 12). As described in Scheme 6, diastereomer **30** was obtained as the major isomer in the step for the dihydroxylation of **24**. We considered that a similar reaction sequence used for the total synthesis of **7** would lead to **64** starting with compound **30**. This was eventually accomplished as shown in Scheme 12. The aldol reaction of the bicyclic lactone **56** derived from **30** and the aforementioned aldehyde **11** using NaHMDS provided a diastereomeric mixture of aldol adducts, which were protected as the MOM ether to afford *anti*-isomer **57** and *syn*-isomer in a ratio of 2:1. Removal of the silyl group in **57** and subsequent oxidation led to aldehyde/alkenyl iodide **58**. The intramolecular NHK reaction of **58** required heating at 50 °C to effect complete conversion. In this case, two diastereomers, **59** and **60**, were obtained as cyclized products in 73% and 14% yields, respectively.[38] The major isomer **59** was converted into allylic mesylate **61**, which was subjected to the palladium-catalyzed reduction to provide the deoxygenated product **62**. DIBAL-H reduction of **62** showed low conversion, but the unreacted **62** was recovered well as a reusable material. After acetylation, diacetate **63** was obtained in 83% yield based on the recovered starting material. Unlike the previous synthesis for **7**, attempted deprotection of **63** failed under acidic hydrolysis conditions. We therefore turned to a two-step sequence for the final deprotection. In the first step, the TES group was removed with TBAF, and subsequent

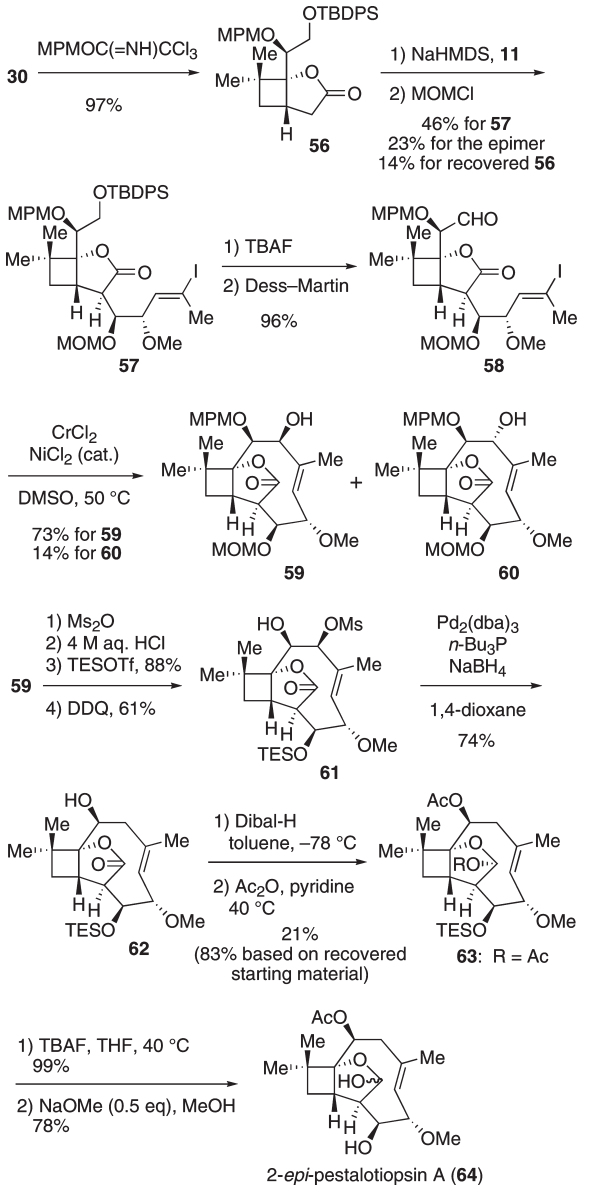
(35) Hutchins, R. O.; Learn, K.; Fulton, R. P. *Tetrahedron Lett*. **1980**, *21*, 27–30.

(36) Deoxygenation of **51** under the same conditions used for **52** provided a complex mixture. The hydroxy group at C2 in **52** might play an important role in the observed high regioselectivity of the hydride attack. For similar assistance of the neighboring hydroxy group in the palladium-catalyzed displacement of allylic substrates by hydride, see: (a) Oshima, M.; Yamazaki, H.; Shimizu, I.; Nisar, M.; Tsuji, J. *J. Am. Chem. Soc*. **1989**, *111*, 6280–6287. (b) Ono, N.; Hamamoto, I.; Kamimura, A.; Kaji, A. *J. Org. Chem*. **1986**, *51*, 3734–3736.

(37) Takahashi, T.; Nakagawa, N.; Minoshima, T.; Yamada, H.; Tsuji, J. *Tetrahedron Lett*. **1990**, *31*, 4333–4336.

(38) The stereochemistries of **59** and **60** were determined by NOE experiments; see: Supporting Information.

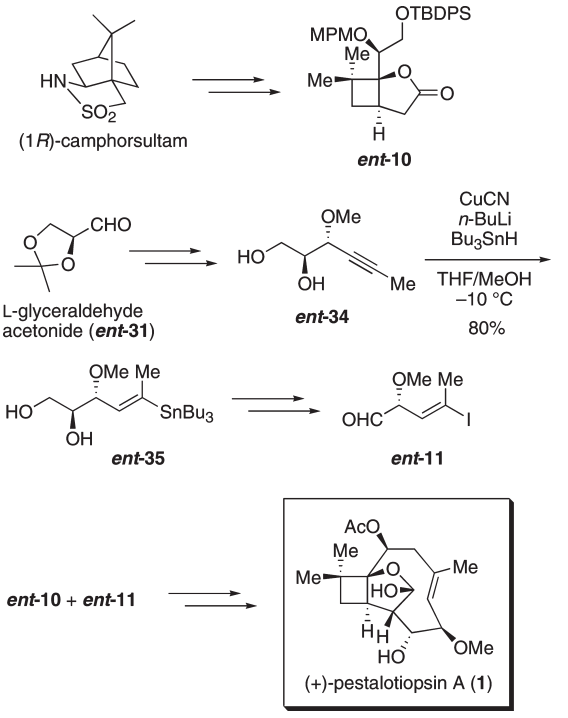
SCHEME 12. Synthesis of 2-*epi*-Pestalotiopsin A (64)



treatment with 0.5 equiv of sodium methoxide in methanol provided 2-*epi*-pestalotiopsin A (**64**) as an anomeric mixture of 5:1; the compound had a specific rotation of $[\alpha]^{24}_{D}$ +14 (*c* 0.35, MeOH) and showed spectroscopic data (^{1}H and ^{13}C NMR) that were distinguishable from those of pestalotiopsin A.

Synthesis of (+)-Pestalotiopsin A (1). With a successful synthesis of the enantiomer of the natural product completed, we finally turned to the synthesis of natural (+)-pestalotiopsin A (**1**) (Scheme 13). We repeated all of the steps of the synthesis, starting from (1*R*)-camphorsultam (in place of the 1*S*-isomer) and L-glyceraldehyde acetonide (***ent*-31**), both of which were conveniently available.[39] Upon optmization for the hydrostannation of alkyne ***ent*-34**, the

SCHEME 13. Synthesis of (+)-Pestalotiopsin A (1)



stannylcupration/protonation protocol was found to be highly efficient. Although the moderate regioselectivity of 3.4:1 was observed in our early experiment, as shown in Scheme 7, treatment of ***ent*-34** with $(n\text{-Bu})_3\text{Sn}(n\text{-Bu})\text{CuCNLi}_2$[40] in THF/MeOH exhibited a perfect regiocontrol to produce the desired ***ent*-35** exclusively. All other reaction sequences proceeded uneventfully, and we ultimately achieved the total synthesis of (+)-pestalotiopsin A (**1**) with an optical rotation [$[\alpha]^{22.5}_{D}$ +75 (*c* 0.26, MeOH)], consistent with that reported for the natural sample.

Biological Activities. We conducted biological studies with synthetic samples (+)-pestalotiopsin A (**1**), (−)-pestalotiopsin A (**7**), and 2-*epi*-pestalotiopsin A (**64**). In the assay for activity against P388 murine leukemia cells in vitro, natural **1** and unnatural **7** were both found to show cytotoxicity with IC_{50}s (μg/mL) of 1.3 for **1** and 1.6 for **7**. Compound **64** showed slightly weaker activity with an IC_{50} value of 2.7 μg/mL. These results suggest that the cyctotoxic property of pestalotiopsin A is nonenantiospecific.

Conclusions

We have achieved the enantioselective total syntheses of both (+)- and (−)-pestalotiopsin A by using the corresponding enantiomers of Oppolzer's camphorsultam. Key features of this synthetic venture include (1) a [2 + 2] cycloaddition of *N*-propioloyl camphorsultam **13a** and ketene dialkyl acetal **14c** followed by stereoselective 1,4-hydride addition/protonation to provide highly enantioenriched cyclobutane derivative **12**, (2) the aldol reaction of bicyclic lactone **10** with aldehyde **11** to assemble all the skeletal carbons, (3) the intramolecular NHK reaction of **9** for the construction of the highly strained (*E*)-cyclononene ring, and (4) the

(39) (1*R*)-Camphorsultam was prepared from (1*R*)-camphorsulfonic acid. L-Glyceraldehyde acetonide (***ent*-31**) was prepared from L-ascorbic acid; see (a) Hubschwerlen, C.; Specklin, J.-L.; Higelin, J. *Org. Synth.* **1995**, *72*, 1−5 (*Coll. Vol. IX*, **1998**, 454). (b) Jung, M. E.; Shaw, T. J. *J. Am. Chem. Soc.* **1980**, *102*, 6304–6311.

(40) Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768–7780.

palladium-catalyzed reduction of allylic mesylate **52** without destruction of the *E* configuration. This work has established the absolute stereochemistry of natural (+)-pestalotiopsin A (**1**). In addition, our synthetic venture has provided opportunities to access a related analogue and to investigate the biological activities of pestalotiopsins.

Experimental Section

[2 + 2] Cycloaddition of 13a and 14c: Synthesis of 26. To a stirred solution of **13a** (8.88 g, 33.2 mmol) in CH_2Cl_2 (120 mL) were added $ZrCl_4$ (387 mg, 1.66 mmol) and **14c** (4.8 mL, 33 mmol). The mixture was refluxed while **14c** (4.8 mL, 33 mmol) was added six times over a period of 6 days. The mixture was diluted with EtOAc (300 mL) and washed with saturated aqueous $NaHCO_3$ (200 mL × 3). The organic layer was dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:8) to provide 11.6 g (85%) of **26** as white crystals: mp 79−83 °C; TLC R_f 0.59 (EtOAc/hexane, 1:3); $[\alpha]^{24}_D$ −23.6 (*c* 0.290, $CHCl_3$); IR 2980, 1680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (s, 3H), 1.18 (t, 3H, *J* = 7.1 Hz), 1.19 (s, 3H), 1.23 (s, 3H), 1.24 (t, 3H, *J* = 7.1 Hz), 1.25 (s, 3H), 1.34−1.43 (m, 2H), 1.86−1.93 (m, 3H), 2.03−2.05 (m, 2H), 3.41 (d, 1H, *J* = 13.7 Hz), 3.51 (d, 1H, *J* = 13.7 Hz), 3.52−3.75 (m, 4H), 4.01 (t, 1H, *J* = 6.1 Hz), 7.16 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.1, 15.5, 19.8, 21.0, 21.4, 21.9, 26.4, 33.0, 38.5, 45.0, 47.6, 48.1, 53.5, 53.8, 59.1, 60.5, 65.5, 105.5, 136.6, 159.3, 161.9; HRMS (EI) calcd for $C_{21}H_{33}NO_5S$ (M^+) *m*/*z* 411.2079, found 411.2078.

Aldol Reaction of 10 and 11: Synthesis of 38 and 39. The following reaction was carried out under Ar. To a cooled (−78 °C) stirred solution of **10** (364 mg, 0.650 mmol) in THF (5 mL) was added NaHMDS (1.0 M solution in THF, 2.4 mL, 2.4 mmol). The mixture was stirred at −78 °C for 15 min, and a solution of **11** (393 mg, 1.63 mmol) in THF (4 mL) was added. After being stirred at −78 °C for 15 min, the mixture was warmed to ambient temperature over 5 min, diluted with saturated aqueous NH_4Cl (60 mL), and extracted with EtOAc (30 mL × 3). The combined extracts were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/toluene, 1:70) to provide 266 mg (51%) of **38**, 90.7 mg (17%) of **39**, and 42.6 mg (12%) of recovered **10**. Compound **38** was obtained as a colorless oil: TLC R_f 0.74 (EtOAc/toluene, 1:8); $[\alpha]^{23}_D$ −45.1 (*c* 1.35, $CHCl_3$); IR 3490, 2940, 1770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (s, 3H), 1.05 (s, 9H), 1.23 (s, 3H), 1.39 (dd, 1H, *J* = 6.8, 12.0 Hz), 1.98 (dd, 1H, *J* = 9.2, 12.0 Hz), 2.40 (br, 1H, OH), 2.65 (d, 3H, *J* = 1.3 Hz), 2.93−2.98 (m, 2H), 3.34 (s, 3H), 3.47 (br d, 1H, *J* = 9.1 Hz), 3.82 (s, 3H), 3.88 (dd, 1H, *J* = 8.3, 10.7 Hz), 3.96 (dd, 1H, *J* = 2.1, 10.7 Hz), 4.07 (dd, 1H, *J* = 2.1, 8.3 Hz), 4.30 (dd, 1H, *J* = 9.1, 9.6 Hz), 4.69 (d, 1H, *J* = 11.1 Hz), 4.98 (d, 1H, *J* = 11.1 Hz), 5.91 (qd, 1H, *J* = 1.3, 9.6 Hz), 6.88 (d, 2H, *J* = 8.5 Hz), 7.28 (d, 2H, *J* = 8.5 Hz), 7.31−7.43 (m, 6H), 7.69−7.73 (m, 4H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 19.1, 24.5, 26.1, 26.9 (3C), 29.1, 36.3, 39.0, 41.5, 50.0, 55.3, 56.5, 64.5, 73.9, 74.4, 78.7, 82.9, 92.4, 103.3, 113.5 (2C), 127.6 (2C), 127.7 (2C), 128.9 (2C), 129.5, 129.6 (2C), 131.7, 133.4, 135.7 (4C), 137.1, 158.8, 177.4; HRMS (EI) calcd for $C_{36}H_{42}O_7SiI$ ($M^+ - t$-C_4H_9) *m*/*z* 741.1745, found 741.1755. Compound **39** was obtained as a colorless oil: TLC R_f 0.54 (EtOAc/toluene, 1:8); $[\alpha]^{23.5}_D$ −9.6 (*c* 1.15, $CHCl_3$); IR 3480, 2930, 1750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (s, 3H), 1.09 (s, 9H), 1.11 (s, 3H), 1.69−1.72 (m, 2H), 2.46 (d, 3H, *J* = 1.5 Hz), 3.03−3.10 (m, 2H), 3.25 (s, 3H), 3.61 (dd, 1H, *J* = 5.5, 6.2 Hz), 3.71−3.81 (m, 3H), 3.78 (s, 3H), 3.94 (dd, 1H, *J* = 5.3, 8.8 Hz), 4.04 (d, 1H, *J* = 11.3 Hz), 4.30 (d, 1H, *J* = 11.3 Hz), 4.23 (d, 1H, *J* = 2.1 Hz), 6.00 (qd, 1H, *J* = 1.5, 8.8 Hz), 6.80 (d, 2H, *J* = 8.5 Hz), 7.04 (d, 2H, *J* = 8.5 Hz), 7.40−7.48 (m, 6H), 7.65−7.74 (m, 4H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 19.1, 23.1, 25.0, 26.9 (3C), 28.6, 34.2, 35.7, 41.0, 45.2, 55.2, 56.7, 61.5, 70.8, 71.8, 79.4, 80.5, 92.4, 99.5, 113.6 (2C), 127.9 (4C), 129.2 (2C), 130.0 (2C), 130.1, 132.5, 133.0, 135.6 (2C), 135.7 (2C), 139.2, 159.1, 180.3; HRMS (EI) calcd for $C_{36}H_{42}O_7SiI$ ($M^+ - t$-C_4H_9) *m*/*z* 741.1745, found 741.1754.

Intramolecular NHK Reaction of 9: Synthesis of 8. The following reaction was carried out under Ar. To a stirred solution of $NiCl_2$ (2.5 mg, 0.019 mmol) and $CrCl_2$ (285 mg, 2.32 mmol) in degassed DMSO (56 mL) was added a solution of **9** (184 mg, 0.305 mmol) in degassed DMSO (5 mL). The mixture was stirred for 19 h, diluted with saturated aqueous NH_4Cl (60 mL), and extracted with EtOAc (50 mL × 3). The combined extracts were washed with H_2O (30 mL × 2) and saturated brine (20 mL), dried, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2) to provide 134 mg (92%) of **8** as a colorless oil: TLC R_f 0.28 (EtOAc:hexane, 1:1); $[\alpha]^{20}_D$ −118 (*c* 0.740, $CHCl_3$); IR 3460, 2940, 1780 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (s, 3H), 1.33 (s, 3H), 1.40 (dd, 1H, *J* = 5.1, 12.6 Hz), 1.91 (br s, 3H), 2.16 (dd, 1H, *J* = 10.2, 12.6 Hz), 2.37 (d, 1H, *J* = 1.9 Hz, OH), 2.72 (m, 1H), 2.97 (m, 1H), 3.27 (s, 3H), 3.35 (s, 3H), 3.79 (s, 3H), 3.98 (d, 1H, *J* = 9.0 Hz), 4.07 (dd, 1H, *J* = 5.6, 11.6 Hz), 4.25 (dd, 1H, *J* = 2.4, 5.6 Hz), 4.62 (br d, 1H, *J* = 9.0 Hz), 4.65 (d, 1H, *J* = 11.1 Hz), 4.72 (d, 1H, *J* = 6.8 Hz), 4.74 (d, 1H, *J* = 11.1 Hz), 4.83 (d, 1H, *J* = 6.8 Hz), 5.26 (br d, 1H, *J* = 11.6 Hz), 6.87 (d, 2H, *J* = 8.1 Hz), 7.27 (d, 2H, *J* = 8.1 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 12.9, 24.7, 27.1, 34.4, 41.8, 42.8, 54.9, 55.3, 55.6, 56.4, 69.0, 75.0, 80.2, 81.3, 84.3, 92.6, 97.0, 113.9 (2C), 123.5, 128.7 (2C), 130.6, 140.9, 159.1, 178.7; HRMS (EI) calcd for $C_{26}H_{36}O_8$ (M^+) *m*/*z* 476.2410, found 476.2412.

Palladium-Catalyzed Reduction of 52: Synthesis of 53. The following reaction was carried out under Ar. A solution of catalyst was prepared by mixing $Pd_2(dba)_3$ and *n*-Bu_3P in degassed 1,4-dioxane at 40 °C for 10 min. To a stirred solution of **52** (12.8 mg, 0.0252 mmol) in degassed 1,4-dioxane (1 mL) were added $NaBH_4$ (15.5 mg, 0.410 mmol) and a solution of the premixed catalyst (2.5 μmol for $Pd_2(dba)_3$, 11 μmol for *n*-Bu_3P) in 1,4-dioxane (0.22 mL). The mixture was stirred for 6 h, quenched with H_2O (0.1 mL), and filtered through a pad of Celite. The filtrate was diluted with saturated brine (10 mL) and extracted with EtOAc (5 mL × 3). The combined extracts were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:6) to provide 9.0 mg (87%) of an inseparable mixture (ca. 10:1) of **53** and its regioisomer as white solids: TLC R_f 0.44 (EtOAc/hexane, 1:2); IR 3390, 2960, 1760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.56−0.67 (m, 6H), 0.92−0.97 (m, 9H), 1.08 (s, 3H), 1.32 (s, 3H), 1.34 (dd, 1H, *J* = 5.7, 12.6 Hz), 1.53 (d, 1H, *J* = 11.1 Hz, OH), 1.87 (d, 3H, *J* = 1.1 Hz), 2.16 (dd, 1H, *J* = 9.6, 12.6 Hz), 2.38 (dd, 1H, *J* = 11.1, 11.2 Hz), 2.59 (dd, 1H, *J* = 5.6, 11.2 Hz), 2.66 (dd, 1H, *J* = 2.6, 2.8 Hz), 2.76 (ddd, 1H, *J* = 2.6, 5.7, 9.6 Hz), 3.21 (s, 3H), 3.78 (dd, 1H, *J* = 5.6, 11.8 Hz), 4.23 (dt, 1H, *J* = 5.6, 11.1 Hz), 4.30 (dd, 1H, *J* = 2.8, 5.6 Hz), 5.02 (qd, 1H, *J* = 1.1, 11.8 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 4.7 (3C), 6.7 (3C), 18.2, 24.6, 26.6, 33.5, 42.4, 42.7, 45.6, 56.1, 59.2, 69.7, 78.8, 83.4, 93.9, 125.2, 137.5, 178.7; HRMS (EI) calcd for $C_{22}H_{38}O_5Si$ (M^+) *m*/*z* 410.2489, found 410.2493.

Synthesis of (−)-Pestalotiopsin A (7). A solution of **55** (6.8 mg, 0.014 mmol) in THF (0.4 mL), H_2O (0.4 mL), and AcOH (0.4 mL) was stirred for 3 h. The mixture was diluted with saturated aqueous $NaHCO_3$ (8 mL) and extracted with EtOAc (4 mL × 3). The combined extracts were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 2:1) to provide 4.4 mg (96%) of **7** as white crystals: mp 204−205 °C; TLC R_f 0.16 (EtOAc/hexane, 2:1), 0.21 (MeOH:$CHCl_3$, 2:98), 0.46 (acetone:toluene, 1:1); $[\alpha]^{21}_D$ −74.7 (*c* 0.535, MeOH); IR 3370, 2940, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$/

$CD_3OD = 10/1$) δ 1.04 (s, 3H), 1.17 (s, 3H), 1.65 (dd, 1H, J = 6.4, 12.2 Hz), 1.93 (d, 3H, J = 0.9 Hz), 2.01 (dd, 1H, J = 9.6, 12.2 Hz), 2.07 (s, 3H), 2.42 (m, 1H), 2.43 (dd, 1H, J = 10.5, 10.7 Hz), 2.55 (dd, 1H, J = 5.3, 10.5 Hz), 2.63 (ddd, 1H, J = 1.5, 6.4, 9.6 Hz), 3.32 (s, 3H), 3.88 (dd, 1H, J = 6.2, 11.5 Hz), 3.96 (dd, 1H, J = 1.9, 6.2 Hz), 5.10 (br d, 1H, J = 11.5 Hz), 5.25 (dd, 1H, J = 5.3, 10.7 Hz), 5.84 (d, 1H, J = 2.8 Hz); ^{13}C NMR (68 MHz, $CDCl_3/CD_3OD = 10/1$) δ 17.6, 21.4, 23.9, 27.2, 38.4, 39.6, 41.1, 42.4, 56.1, 64.8, 73.6, 77.3, 83.0, 98.3, 108.8, 123.9, 137.8, 170.4; HRMS (EI) calcd for $C_{18}H_{28}O_6$ (M^+) m/z 340.1886, found 340.1887.

Synthesis of (+)-Pestalotiopsin A (1). As described for the preparation of **7** from **55**, compound ***ent*-55** (7.9 mg, 0.016 mmol) was converted to 5.2 mg (96%) of **1**: mp 204−205 °C; $[\alpha]^{22.5}_D$ +75 (*c* 0.26, MeOH).

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Supporting Information Available: Experimental procedures, full characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.