Natural Products

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Total Synthesis of (−)-Pestalotiopsin A**

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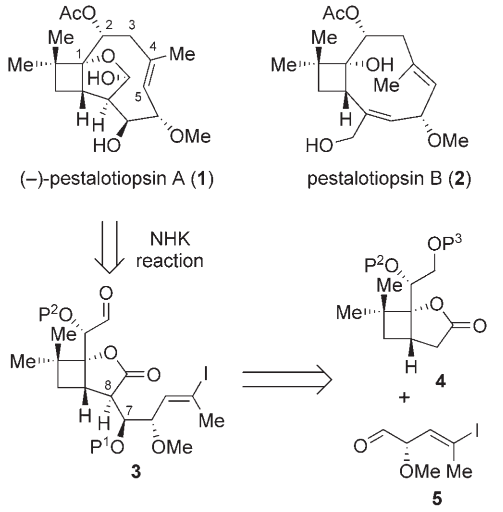
In 1996 two highly oxygenated caryophyllene sesquiterpenoids, pestalotiopsins A (**1**) and B (**2**) (Scheme 1), were isolated by Sugawara and co-workers from *Pestalotiopsis* sp., an endophytic fungus associated with the bark and leaves of *Taxus brevifolia* (the Pacific yew).[1] Later, several related natural products were found from the species of *Pestalotiopsis*.[2] Among them, pestalotiopsin A showed cytotoxicity and immunosuppressive activity in the mixed lymphocyte reaction. The structures of the pestalotiopsins were determined by extensive spectroscopic studies and finally confirmed by X-ray crystallographic analysis; however, the absolute stereochemistry remained unclear. Pestalotiopsin A (**1**) consists of an unprecedented oxatricyclic structure bearing seven stereogenic centers and it is comprised of a cyclobutane ring fused with both an (E)-cyclononene ring and a γ-lactol unit. In contrast, bicyclic pestalotiopsin B (**2**) exists as a mixture of two atropisomers at the C4=C5 carbon–carbon double bond. The synthetically formidable structure of **1** has attracted considerable attention among chemists concerned with natural product synthesis. The research groups of Procter,[3] Paquette,[4] and Markó,[5] in addition to our group,[6] have reported a number of synthetic studies of **1**. Herein, we describe the first total synthesis of (−)-pestalotiopsin A (**1**) and the assignment of its absolute configuration as the antipode of natural pestalotiopsin A.



Scheme 1. Structures of pestalotiopsins A (**1**) and B (**2**) and retrosynthetic analysis of **1**. P = protecting group.

Since embarking on this research we have devoted our efforts to the efficient formation of the strained (E)-cyclononene moiety in **1**. Although early attempts were unsuccessful,[7] we envisioned that a Nozaki–Hiyama–Kishi (NHK) reaction approach[8] would enable efficient (E)-cyclononene ring formation. As shown in Scheme 1, we considered **1** could be synthesized by using the intramolecular NHK reaction of aldehyde/alkenyl iodide **3** as a key step and subsequent deoxygenation of the newly formed hydroxy group at C3. The formation of **3** would, in turn, be achieved by the aldol reaction of functionalized bicyclic lactone **4** and γ-iodo-β,γ-unsaturated aldehyde **5**, both in high enantioenriched forms. We expected that stereogenic centers at C7 and C8 of **3** would be introduced stereoselectively as desired in the aldol process by taking advantage of the 2-oxabicyclo[3.2.0]heptan-3-one structure of **4**. This bicyclic γ-lactone **4**, in turn, would be prepared from a highly enantioenriched cyclobutane derivative analogous to that described in our preliminary report.[6]

Earlier we reported[6] the asymmetric synthesis of functionalized cyclobutanes which featured the [2+2] cycloaddition of the *N*-propioloyl derivative of Oppolzer's camphorsultam (**6**) (Scheme 2) and ketene bis(trimethylsilyl) acetal. However, the bis(trimethylsilyl) acetal moiety was not stable under the conditions used for the removal of the camphorsultam, and it gave rise to some additional steps for the conversion of the cyclobutane derivativeinto the bicyclic lactone intermediate. To overcome this disadvantage, ketene dialkyl acetal **7**[9] was examined as a partner in the [2+2] cycloaddition of **6**. The reaction of **6** with **7** proceeded under the $ZrCl_4$-catalyzed conditions to afford a single regioisomeric adduct (**8**). The 1,4-hydride addition to **8** with L-Selectride and subsequent protonation of the resulting enolate proceeded with extremely high stereoselectivity to provide cyclobutane derivative **9** in almost diastereomerically pure form. Reductive removal of the chiral auxiliary from **9** provided cyclobutanemethanol **10** with excellent enantioselectivity (> 95% *ee*),[10] and camphorsultam was efficiently recovered on a multigram scale experiment. Tosylation of the hydroxy group in **10** and subsequent displacement by a cyano

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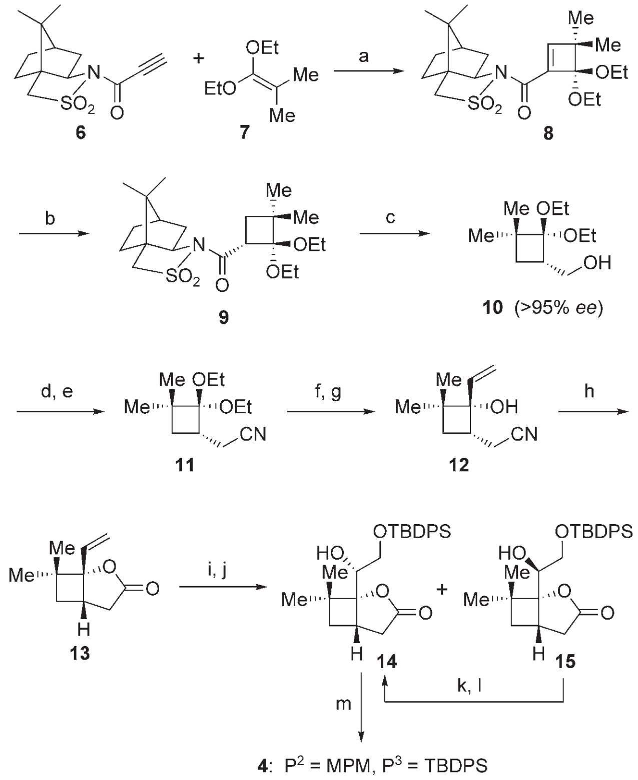
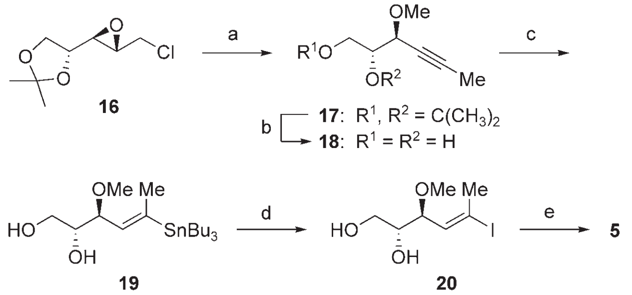


Scheme 2. Synthesis of bicyclic lactone **4**: a) $ZrCl_4$, CH_2Cl_2, reflux, 6 d, 85 %; b) L-Selectride, toluene, −78 °C, 30 min, then aq. NH_4Cl, warming from −78 to 0 °C, 4 h, quant.; c) $LiAlH_4$, THF, RT, 12 h, 94 % for **10**, 95 % for the camphorsultam; d) TsCl, Et_3N, DMAP, CH_2Cl_2, RT, 3 h; e) KCN, DMSO, 80 °C, 12 h, quant.; f) 1 M aq. HCl, silica gel, CH_2Cl_2, 40 °C, 6 h; g) $CH_2{=}CHMgBr$, toluene, −78 °C, 5 min, 45 % from **10**; h) 5 M aq. HCl, THF, 70 °C, 41 h, 81 %; i) AD-mix-α, tBuOH/H_2O, 0 °C, 5 h; j) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, RT, 10 h, 20 % for **14**, 80 % for **15**; k) DMP, CH_2Cl_2, RT, 3 h; l) $NaBH_4$, MeOH, 0 °C, 25 min, 90 % for **14**, 10 % for **15**; m) MPMOC(NH)CCl_3, TfOH, Et_2O, RT, 50 min, 80 % for **4**, 16 % for recovered **14**. L-Selectride = lithium tri-*s*-butylborohydride; Ts = *p*-toluenesulfonyl; DMAP = 4-(dimethylamino)pyridine; DMSO = dimethyl sulfoxide; TBDPS = *tert*-butyldiphenylsilyl; DMP = Dess–Martin periodinane; MPM = (4-methoxyphenyl)methyl; Tf = trifluoromethanesulfonyl.

group yielded nitrile **11**. Acid hydrolysis of the dialkyl acetal moiety in **11** provided a cyclobutanone, which was subjected to a Grignard reaction with vinylmagnesium bromide to furnish adduct **12** as a single diastereomer. The addition of the Grignard reagent occurred exclusively from the *Si* face of the ketone carbonyl group. Acid hydrolysis of the nitrile group accompanied by γ-lactone formation provided bicyclic lactone **13**. This new approach enables more convenient access to key intermediate **13** when compared to the previous approach. We then examined the Sharpless asymmetric dihydroxylation[11] of the vinyl group in **13**. After selective O silylation of the primary hydroxy group in the dihydroxylation products obtained by using AD-mix-α or AD-mix-β, diastereomeric products **14** and **15** were obtained in ratios of 1:4 and 1:2, respectively. Both dihydroxylation conditions preferentially produced the undesired diol, which was converted into **15**. To our delight, we found that the undesired **15** was efficiently converted into the desired **14** by an oxidation/reduction strategy. Thus, Dess–Martin oxidation[12] of **15** and subsequent sodium borohydride reduction of the resulting ketone provided **14** in a high overall yield of 90 %. Protection of the hydroxy group in **14** with (4-methoxyphenyl)methyl (MPM) imidate provided **4**, the substrate for the planned aldol reaction.

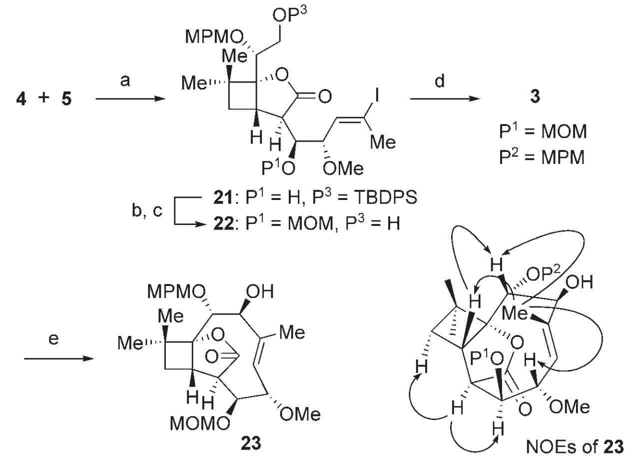
Chiral aldehyde **5**, the coupling partner for the aldol reaction, was prepared from known compound **16**,[13] which was in turn prepared from D-glyceradehyde acetonide (Scheme 3). The epoxy chloride **16** was exposed to three equivalents of *n*-butyllithium[13,14] and trapping the intermediary α-alkoxylated acetylenic dianion with iodomethane led to the C,O-methylated propargyl alcohol **17**. The acetonide group in **17** was hydrolyzed to diol **18**, which was then subjected to a palladium-catalyzed hydrostannation by using $Bu_3SnH/Pd(PPh_3)_2Cl_2$[15] to provide terminally stannylated olefin **19** preferentially. Aldehyde **5** was obtained after metal/halogen exchange of **19** and subsequent oxidative cleavage of resulting diol **20**.



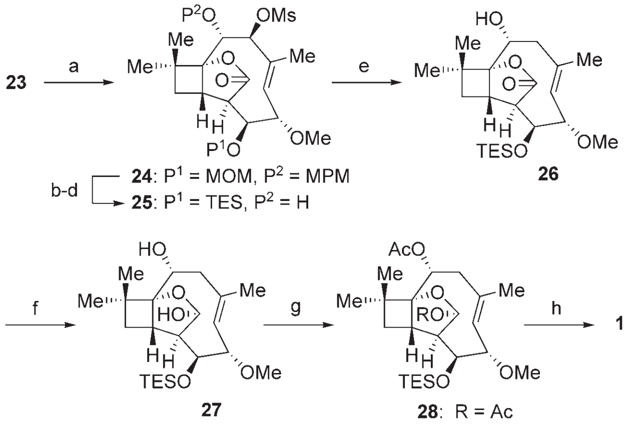
Scheme 3. Synthesis of γ-iodo-β,γ-unsaturated aldehyde **5**: a) *n*BuLi, THF, −35 °C, 1 h, then MeI, HMPA, RT, 1 h; b) TsOH, MeOH, 40 °C, 62 h, 81 % from **16**; c) Bu_3SnH, $Pd(PPh_3)_2Cl_2$, THF, RT, 15 min, 61 % for **19**, 18 % for the regioisomer; d) I_2, CH_2Cl_2, 0 °C, 15 min, 94 %; e) silica gel supported $NaIO_4$, CH_2Cl_2, RT, 15 min, 98 %. HMPA = hexamethylphosphoramide.

As in our previous experiments performed by using structurally analogous coupling partners,[6] the aldol reaction of **4** with **5** proceeded stereoselectively with NaHMDS as the base (Scheme 4). As expected, this reaction provided *anti*-aldol product **21** predominantly, securing the two contiguous stereogenic centers required for the target molecule.[16] At this stage, all the skeletal carbons of **1** were introduced. The next task was to construct the formidable (*E*)-cyclononene ring, and this was efficiently accomplished as described. After a two-step protecting group manipulation of **21** and subsequent oxidation of resulting **22**, substrate **3** was obtained for use in the intramolecular NHK reaction. We were pleased to find that the intramolecular NHK reaction of **3** proceeded smoothly with the use of $CrCl_2/NiCl_2$ in DMSO to provide cyclized product **23** in 92 % yield as a single diastereomer and as a single atropisomer. Considering the highly strained structure of (*E*)-cyclononene, the high yield of **23** was remarkable.[17] The stereochemistry and conformation of **23** were determined by NOE experiments as shown.

The final stage of the total synthesis was the removal of the extra hydroxy group introduced in **23**. The Barton radical-



Scheme 4. Construction of the (*E*)-cyclononene ring: a) NaHMDS, THF, −78 °C, 15 min, then to RT, 5 min, 51 % for **21**, 17 % for the diastereomer, 12 % for recovered **4**; b) MOMCl, iPr$_2$NEt, CH$_2$Cl$_2$, reflux, 17 h, 96 %; c) nBu$_4$NF, AcOH, THF, RT, 19 h, 96 %; d) DMP, CH$_2$Cl$_2$, RT, 3.5 h, 88 %; e) CrCl$_2$, NiCl$_2$, DMSO, RT, 19 h, 92 %. NaHMDS = sodium bis(trimethylsilyl)amide, MOM = methoxymethyl.



Scheme 5. Completion of the total synthesis of (−)-pestalotiopsin A (**1**): a) Ms$_2$O, DMAP, pyridine, RT, 4 h, 93 %; b) 4 M aq. HCl, THF, RT, 3.5 h; c) TESOTf, pyridine, CH$_2$Cl$_2$, 0 °C, 30 min, 72 % from **24**; d) DDQ, CH$_2$Cl$_2$, phosphate buffer, RT, 17 h, 89 %; e) Pd$_2$(dba)$_3$, nBu$_3$P, NaBH$_4$, 1,4-dioxane, RT, 6 h, 87 % as a mixture (10:1) of **26** and the C3−C4 olefin isomer; f) Dibal-H, THF, 0 °C, 1 h, 78 %; g) Ac$_2$O, pyridine, 40 °C, 22 h, 82 %; h) AcOH/H$_2$O/THF (1:1:1), RT, 3 h, 96 %. Ms = methanesulfonyl; TES = triethylsilyl; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; dba = dibenzylideneacetone; Dibal-H = diisobutylaluminum hydride.

induced deoxygenation strategy[18] proved to be troublesome because of the geometrical isomerization of the trisubstituted (*E*)-olefin moiety into the *Z* form, or C3−C4 olefin migration.[19] Moreover, the methoxymethyl (MOM) group was difficult to remove under acidic conditions in the final step.[20] These issues were solved by using a strategy involving palladium(0)-catalyzed reductive displacement by hydride and by switching the MOM group to a triethylsilyl (TES) group (Scheme 5). Mesylation of **23** and subsequent standard protecting group manipulations of the resulting allylic mesyl ester **24** led to TES ether **25** without event. Treatment of **25** with a combination of Pd$_2$(dba)$_3$/nBu$_3$P and NaBH$_4$[21] provided desired deoxygenated product **26** without destruction of the *E* configuration.[22] This reaction was accompanied by a small amount (ca. 8 %) of the C3−C4 olefin isomer. Dibal-H reduction of **26** provided γ-lactol **27** as the sole α anomer. The C3−C4 olefinic isomer obtained in the former reaction was removed at this stage. Acetylation of **27** provided diacetate **28** and mild acid hydrolysis uneventfully cleaved the TES group and the acetyl group in the γ-lactol moiety to provide (−)-pestalotiopsin A (**1**); the compund was identical in all respects (mp, TLC, IR, ^{1}H and ^{13}C NMR, and HRMS methods) to those of natural pestalotiopsin A,[23] except for the sign of optical rotation [$[\alpha]_D^{21} = -74.7$ ($c = 0.535$, MeOH) for **1**; lit.[1] $[\alpha]_D^{22} = +76.8$ ($c = 1$, MeOH) for the natural sample]. This fact verified that synthesized **1** is the antipode of natural pestalotiopsin A.

In conclusion, we have completed the first total synthesis of (−)-pestalotiopsin A (**1**), thereby establishing the absolute stereochemistry of natural (+)-pestalotiopsin A. The total synthesis features 1) a [2+2] cycloaddition of *N*-propioloyl derivative of Oppolzer's camphorsultam (**6**) and ketene dialkyl acetal **7** and subsequent stereoselective 1,4-hydride addition/protonation to provide a highly enantioenriched cyclobutane derivative **10**, 2) the aldol reaction of bicyclic lactone **4** with aldehyde **5** to assemble all the skeletal carbons, and 3) the intramolecular NHK reaction of **3** for the construction of the highly strained (*E*)-cyclononene ring. The synthetic strategies developed in the total synthesis will be applicable to the synthesis of related caryophyllenes.[24]

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[7] We examined the following approaches a)–f) towards (*E*)-cyclononene formation. For C1−C2 or C4−C5 bond formation: a) intramolecular pinacol coupling reactions. For C2−C3

bond formation: b) Dieckmann condensation, c) intramolecular SmI_2-mediated reductive cyclization, d) intramolecular α-sulfonyl anion cyclizations, and e) cyclization by protected cyanohydrin and allylic bromide. For C4–C5 double bond formation: f) ring-closing metathesis.

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[9] Compound **7** was prepared in batches of 25 g from methacrolein diethylacetal by olefin isomerization with lithium/ethylenediamine in 51 % yield.

[10] The *ee* value of **10** was determined by ^1H NMR analysis of the Mosher esters derived from **10**. The absolute stereochemistry of **10** was confirmed after conversion into **12**, whose specific rotation matched well with that of the sample derived by the previous approach.[6]

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[16] Stereochemistry of the newly introduced stereogenic centers in the aldol adduct **21** was confirmed after conversion into **23**.

[17] We confirmed that the γ-lactol methyl acetal corresponding to **3** also served as a substrate for the intramolecular NHK reaction, which provided the cyclized product in a lower yield of 52 %, along with 38 % yield of an uncyclized disubstituted olefinic product produced by protonation of the intermediary metallated olefin.

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[22] Deoxygenation of **24** under the same conditions used for **25** provided a complex mixture. The hydroxy group at C2 in **25** 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(0)-catalyzed displacement of allylic substrates by hydride, see: a) M. Oshima, H. Yamazaki, I. Shimizu, M. Nisar, J. Tsuji, *J. Am. Chem. Soc.* **1989**, *111*, 6280 – 6287; b) N. Ono, I. Hamamoto, A. Kamimura, A. Kaji, *J. Org. Chem.* **1986**, *51*, 3734 – 3736.

[23] The ^1H and ^{13}C NMR spectral copies of natural pestalotiopsin A, provided by Professor Sugawara, were recorded in a mixed solution of $CDCl_3$ and CD_3OD (10:1).

[24] By using exactly the same reaction sequence, natural (+)-pestalotiopsin A could be synthesized from (1*R*)-camphorsultam (in place of the 1*S* isomer used in this communication) and the α-epoxide isomer (in place of the β-epoxide **16**). For the preparation of the α epoxide, see reference [13].