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Stereocontrolled Synthesis of an Indole Moiety of Sespendole and Stereochemical Assignment of the Side Chain

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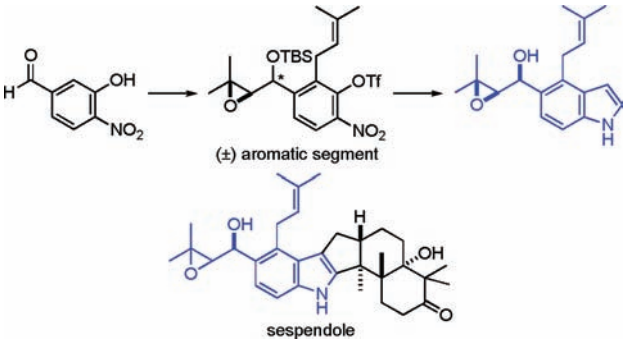
ABSTRACT



Two possible diastereomers of the indole moiety of sespendole were synthesized from 3-hydroxy-4-nitrobenzaldehyde in a highly stereoselective manner. Comparison of ^{1}H and ^{13}C NMR spectra of the two synthetic materials with those sespendole leads us to propose that the relative stereochemistry of the epoxyalcohol is *syn*.

Sespendole (**1**) was isolated from the culture broth of the fungal strain *Pseudobotrytis terrestris* FKA-25 by Tomoda and co-workers in 2004, and its structure including all absolute configurations except C-31 was elucidated by extensive spectroscopic analyses (Figure 1).[1] This new indole sesquiterpene alkaloid inhibits the synthesis of cholesteryl ester and triacylglycerol by mouse macrophages with IC_{50} values of 4.0 and 3.2 μM, respectively.[1b]

The structural complexity as well as the important biological activity prompted us to embark on the synthesis of sespendole and its related compounds.[2] Our synthetic strategy is a divergent manner based on coupling between two highly functionalized segments, aromatic segment **2** and sesquiterpene segment **3** (Figure 1). We have already reported the synthesis of the (±) sesquiterpene segment **3** possessing all requisite functions for sespendole.[3] We disclose herein the stereocontrolled synthesis of two diastereomers of the aromatic segment and construction of the indole nucleus possessing the same side chains as those of sespendole. We also compare the NMR data of these two compounds with those of sespendole for stereochemical assignment of the side chain.

Synthesis of the aromatic segment having two prenyl units began with the addition of 2-methyl-1-propenylmagnesium

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(1) (a) Yamaguchi, Y.; Masuma, R.; Kim, Y.-P.; Uchida, R.; Tomoda, H.; Ōmura, S. *Mycoscience* **2004**, *45*, 9–16. (b) Uchida, R.; Kim, Y.-P.; Namatame, I.; Tomoda, H.; Ōmura, S. *J. Antibiot.* **2006**, *59*, 93–97. (c) Uchida, R.; Tomoda, H.; Ōmura, S. *J. Antibiot.* **2006**, *59*, 298–302. (d) Uchida, R.; Kim, Y.-P.; Nagamitsu, T.; Tomoda, H.; Ōmura, S. *J. Antibiot.* **2006**, *59*, 338–344.

(2) For recent synthetic studies on indole diterpenes with a related architectural ring system, see: (a) Smith, A. B.; Davulcu, A. H.; Cho, Y. S.; Ohmoto, K.; Kürti, L.; Ishiyama, H. *J. Org. Chem.* **2007**, *72*, 4596–4610. (b) Smith, A. B.; Kürti, L.; Davulcu, A. H.; Cho, Y. S.; Ohmoto, K. *J. Org. Chem.* **2007**, *72*, 4611–4620. (c) Churruca, F.; Fousteris, M.; Ishikawa, Y.; von Wantoch Rekowski, M.; Hounsou, C.; Surrey, T.; Giannis, A. *Org. Lett.* **2010**, *12*, 2096–2099.

(3) Sugino, K.; Nakazaki, A.; Isobe, M.; Nishikawa, T. *Synlett* **2011**, 647–650.

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bromide to 3-hydroxy-4-nitrobenzaldehyde **4**, a commercially available starting material (Scheme 1).[4] Protection of the two hydroxy groups as TBS ethers followed by selective deprotection of the phenol TBS ether gave **5**. Copper-catalyzed alkylation of **5** with 3-chloro-3-methyl-1-butyne[5] and subsequent deprotection of the TBS group afforded allylic alcohol **6**. Epoxidation of **6** with MCPBA gave *syn*-epoxyalcohol **7*β*** as a single diastereomer, whose stereochemistry was unambiguously determined to be *syn* by single-crystal X-ray diffraction.[6] The corresponding *anti*-epoxyalcohol **7α** was synthesized by inversion of the hydroxy group at the C-30 position of **7*β***; oxidation of **7*β*** with MnO_2 afforded ketone, which was used to search conditions for stereoselective reduction. An extensive examination led us to conclude that LiAlH(O-*t*-Bu)$_3$ was the best reductant to give **7α** with a high stereoselectivity (dr = 15:1).

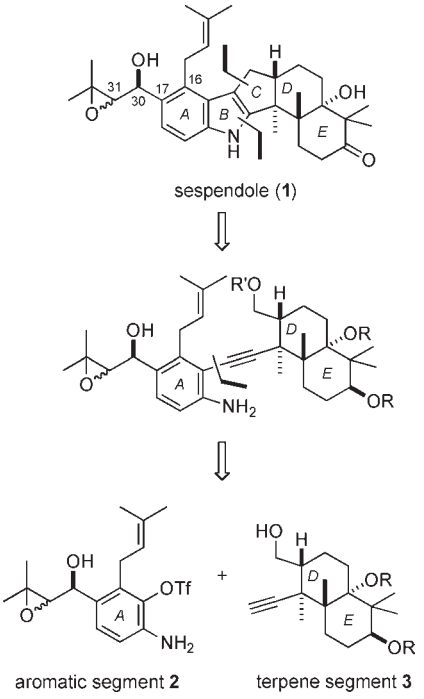
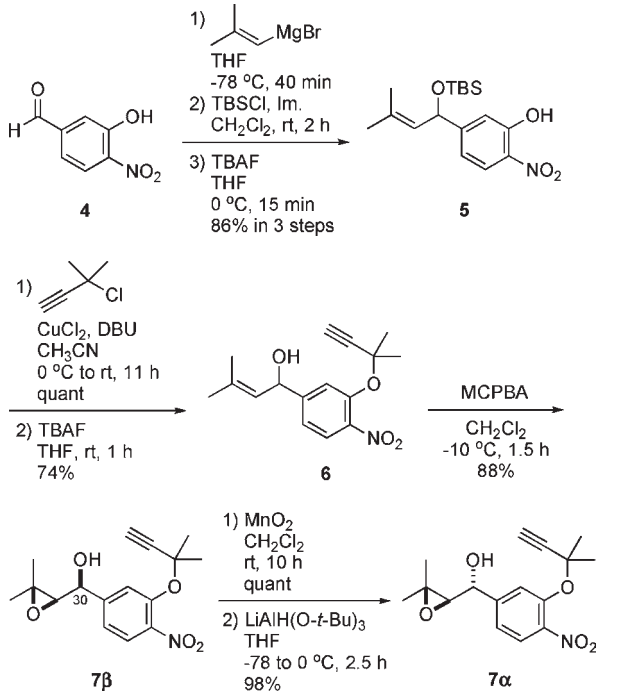


Figure 1. Structure and synthetic strategy of sespendole (**1**).

Synthesis of the aromatic segments **10*β*** and **10α** is shown in Scheme 2. Protection of the benzylic alcohol of **7*β*** as TBS ether followed by partial hydrogenation of the acetylenic moiety with Lindlar's catalyst yielded reverse prenyl ether **8*β***, a precursor for *ortho* Claisen rearrangement. For the synthesis of bis-prenylated nitrophenol **9*β***, however, the Claisen rearrangement[7] was particularly challenging because of the highly functionalized precursor **8*β***, which included an acid-sensitive epoxide. After extensive examination, we were pleased to find that the rearrangement of **8*β*** proceeded in the presence of $NaHCO_3$ at 110 °C to give the desired bis-prenylated nitrophenol **9*β*** in a moderate yield. Treatment of **9*β*** with Tf_2O afforded the aryltriflate **10*β***, an aromatic segment of sespendole. The corresponding aryltriflate **10α** having the *anti*-epoxide was synthesized from **7α** by the same procedure used for the synthesis of **10*β***.

Scheme 1. Synthesis of *syn*-Epoxyalcohol **7*β*** and *anti*-Epoxyalcohol **7α**



We next investigated the construction of the indole nucleus to validate our synthetic plan (Scheme 3). Sonogashira coupling reaction[8,9] of **10** with trimethylsilylacetylene

(4) These synthetic compounds were numbered according to sespendole.

(5) (a) Godfrey, J. D., Jr.; Mueller, R. H.; Sedergram, T. C.; Soundararajan, N.; Colandrea, V. *Tetrahedron Lett.* **1994**, *35*, 6405–6408. (b) Bell, D.; Davies, M. R.; Geen, G. R.; Mann, I. S. *Synthesis* **1995**, 707–712.

(6) CCDC 837239 (**7*β***) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(7) (a) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939–3002. (b) Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G.-Q. *Angew. Chem., Int. Ed.* **2000**, *39*, 734–739. (c) Pettus, T. R. R.; Inoue, M.; Chen, X.-T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 6160–6168.

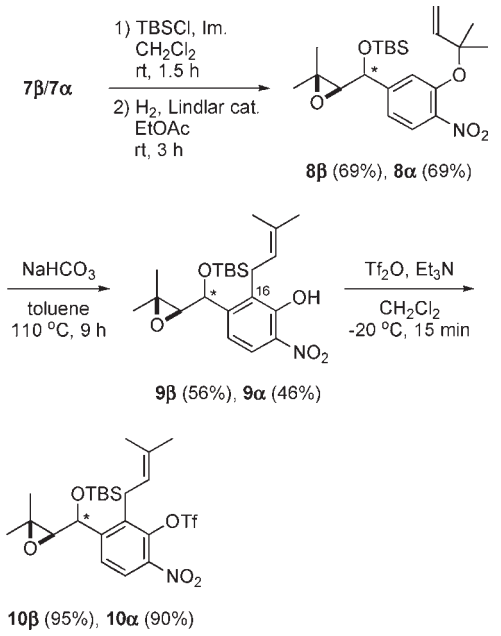
(8) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470.

(9) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874–922.

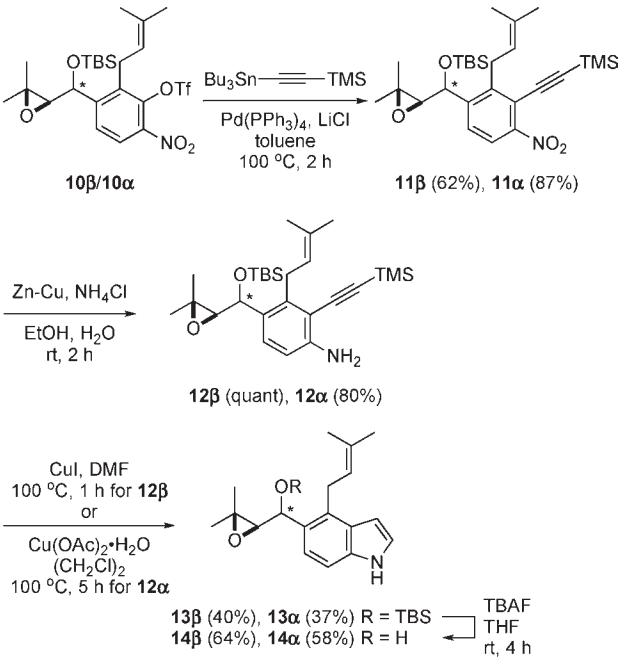
(10) (a) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630–4632. (b) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033–3040. (c) Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 301–302. (d) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524.

(11) Castro, C. E.; Gaughan, E. J.; Owsley, D. C. *J. Org. Chem.* **1966**, *31*, 4071–4078.

Scheme 2. Synthesis of Aromatic Segments **10*β*** and **10α**



Scheme 3. Synthesis of Epoxyindoles **14*β*** and **14α** by Migita–Stille Coupling and Castro-Type Indole Synthesis



provided arylacetylene **11** in a low yield, along with a significant amount of the recovered **10** and **9** as a byproduct. The reason might be due to steric hindrance around the triflate group exerted by two *ortho* substituents. In contrast, Migita–Stille coupling reaction[10] with tributyl[(trimethylsilyl)ethynyl]-stannane proceeded smoothly to afford **11** in good yield. Reduction of the nitro group with the Zn–Cu couple afforded alkynylaniline **12**. Unexpectedly, indole synthesis of **12** under the conventional conditions used for the Castro reaction[11] proved to be problematic. We reasoned that the trimethylsilylacetylene and the oxygenated prenyl groups may be unstable under these conditions. After screening conditions for the indole synthesis, we found that CuI in DMF without a base was optimal for the cyclization of *syn*-alkynylaniline **12*β***. Surprisingly, these conditions were not applicable for the diastereomer **12α**; exposure of **12α** to the same conditions gave a complex mixture of products. Finally, $Cu(OAc)_2$ in dichloroethane[12] was found to be the optimal reagent for production of the *anti*-alkynylaniline **12α**. Desilylation of **13** with TBAF furnished epoxyindole **14**.

With the two diastereomers of the indole moiety of sespendole (**1**) in hand, ^1H and ^{13}C NMR spectra of these synthetic indoles **14*β*** and **14α** were compared. The coupling constants between H-30 and H-31 of **14*β***/**14α** were very close ($J_{30,31}$ = 7.5 Hz for **14*β*** and $J_{30,31}$ = 8.0 Hz for **14α**, respectively) and in good agreement with that reported previously ($J_{30,31}$ = 8.0 Hz for sespendole). On the other hand, the chemical shifts of the synthetic compounds **14*β*** and **14α** were significantly different, which indicates

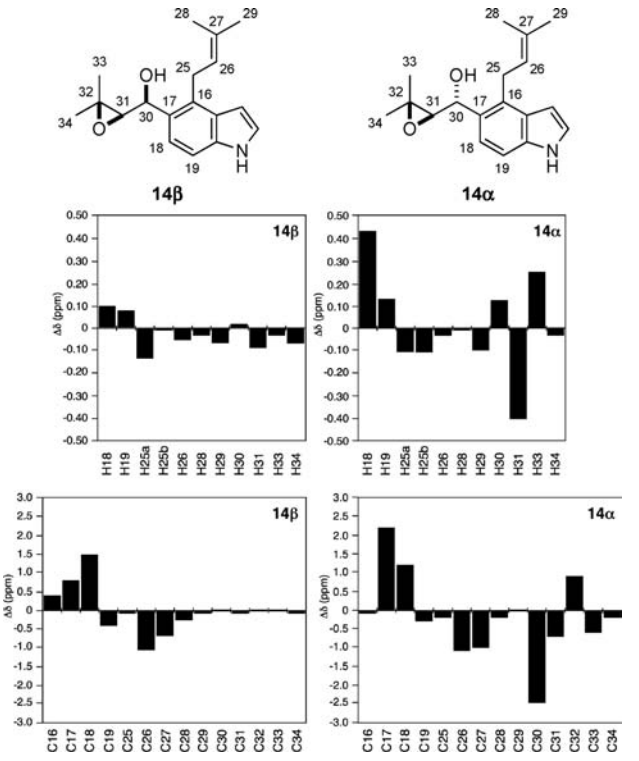


Figure 2. Chemical shift differences ($\Delta\delta$) of ^1H and ^{13}C NMR spectra for *syn*- and *anti*-epoxyindoles **14**. $\Delta\delta$ = δ(synthetic) – δ(natural). Bars represent the deviation in ppm between individual chemical shifts observed for **14** and those reported for the sespendole (**1**) (400 MHz, C_5D_5N).

(12) Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126–1136.

the possibility of stereochemical assignment of the side chain. Selected comparative ^{1}H and ^{13}C NMR data are shown in Figure 2. The resonances corresponding to the benzylic and epoxide protons at C-30 and C-31 were distinctly different in chemical shift. The *syn*-epoxyindole **14β** exhibited smaller chemical shift differences ($\Delta\delta$ = 0.02 and −0.09 ppm, respectively), whereas the *anti*-epoxyindole **14α** showed larger differences ($\Delta\delta$ = 0.12 and −0.40 ppm, respectively). In the ^{13}C NMR spectra, **14β** also exhibited smaller chemical shift differences than **14α** in the carbons of epoxyalcohol between C-30 and C-34. These results strongly suggest that the relative stereochemistry of the epoxyalcohol moiety is *syn* in sespendole (**1**).

In conclusion, we have stereoselectively synthesized two diastereomers **10β** and **10α** of the aromatic segment of sespendole (**1**), which were transformed into epoxyindoles **14β** and **14α**, respectively, according to our synthetic plan. Comparison of the ^{1}H and ^{13}C NMR spectra of these epoxyindoles with those of sespendole (**1**) leads us to propose that the epoxy group has a *syn* relationship to the hydroxyl group. Continuing efforts toward the enantioselective synthesis of the aromatic segment and the total synthesis of sespendole (**1**) are now in progress.

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Supporting Information Available. Experimental procedures, characterization data, copies of ^{1}H and ^{13}C NMR spectra for all new compounds, and crystallographic data for **7β** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.