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Total Synthesis of (+)-Herbindole A, (+)-Herbindole B, and (+)-Herbindole C. Determination of the Absolute Configuration of the Natural Herbindoles

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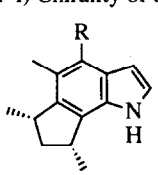
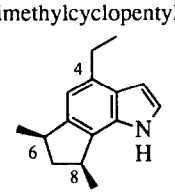
Abstract: *(6R, 8S)-(+)-Herbindoles A (**3a**), B (**3b**), and C (**3c**) were synthesized from the chirality-definite Diels-Alder adduct **7** using an acid-induced indole cyclization reaction of **4** to **5**, as well as novel reactions of the $PhSO_2$ group of **24** with Mg in MeOH, Me_3Al, and a combination of allyltrimethylsilane and $EtAlCl_2$. The absolute structure of natural herbindole A was determined to be **1a**, and those of natural herbindoles B and C were assumed to be **1b** and **1c**.*

Herbindoles A (**1a**), B (**1b**), and C (**1c**) are ingredients of an orange-colored sponge, *Axinella* sp., collected in the Gulf of Exmouth, Western Australia; they exhibit both cytotoxic activity against KB cells and antifeedant activity aginst generalist fish.[1] Their chemical structures, except for the absolute stereochemistry, are clarified mainly on the basis of NMR studies, showing that they belong to a group of biogenetically unique polyalkylcyclopentindoles, whose representative, cis-trikentrin A (**2**), has been isolated from another marine sponge, *Trikentrion flabelliforme*.[2] The absolute structure of **2** was determined by us to be (6*R*, 8*S*)-6,8-dimethyl-4-ethyl-1,6,7,8-tetrahydrocyclopent[*g*]indole.[3] In this communication, we report the first total synthesis of (+)-herbindoles A (**3a**), (+)-B (**3b**), and (+)-C (**3c**) in the enantio-definite manner. Comparison of the optical behavior of the synthetic **3a** with natural herbindole A (**1a**) revealed the absolute configuration of **1a** to be 6*S*, 8*R*, and therefore the absolute structures of herbindoles B (**1b**) and C (**1c**) were estimated as shown.

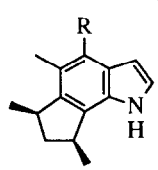
The key reaction of the present synthesis of (+)-herbindoles A – C (**3a** – **3c**) was an acid-induced indole cyclization reaction of 3-substituted pyrrole derivative **4** having a dimethylcyclopentanone moiety of the correct absolute stereochemistry at the side chain to form the *N*-protected indole derivative **5**, based upon our previous finding concerning an efficient synthetic method for 4-alkylindoles.[4] In these compounds **4** and **5**, we selected the $PhSO_2CH_2$ group for the substituent R as a common precursor function, instead of individually introducing Me or Et groups, *etc*. Then we devised novel procedures for elaborating this to the requisite 4-alkyl and alkenyl substituents involved in **3a** – **3c**. Our synthetic plan for leading to **4** (R = CH_2SO_2Ph) was composed of three ideas. i) Chirality of the cis-dimethylcyclopentyl unit was created from a [2.2.1]-bicycloheptene system such as



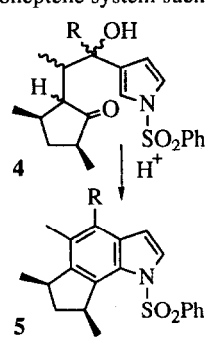
1a R = Me Herbindole A
1b R = Et Herbindole B
1c R =  Herbindole C



2
cis-Trikentrin A



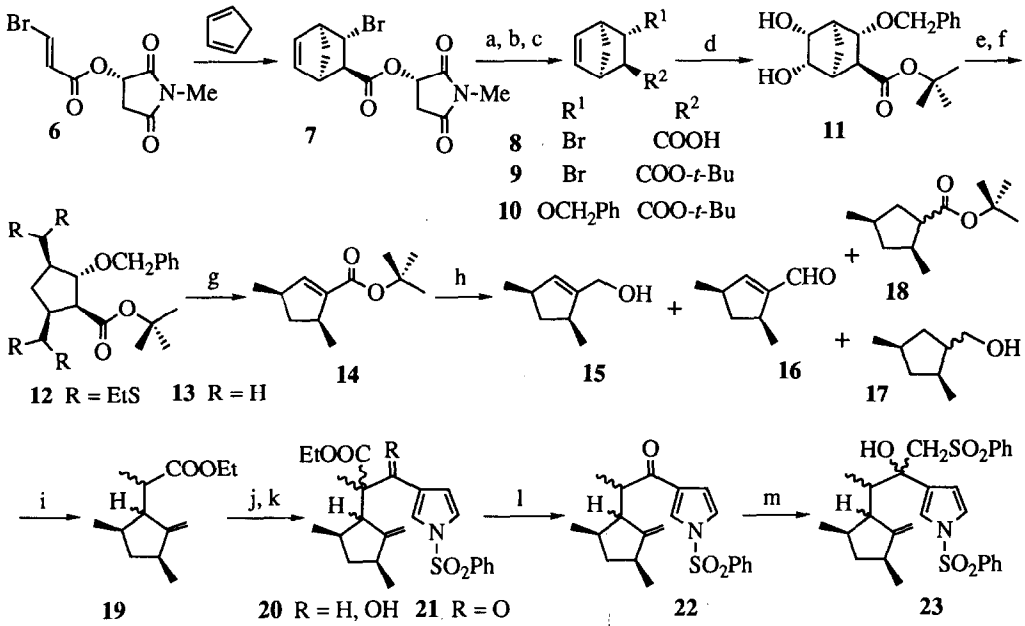
3a R = Me (+)-Herbindole A
3b R = Et (+)-Herbindole B
3c R =  (+)-Herbindole C



7, which carries one hetero atom as well as one carbon function so as to be transformed into (3*R*, 5*S*)-3,5-dimethyl-1-cyclopentenylmethanol (**15**) (Scheme 1). ii) The allyl alcohol part in **15** was utilized to elongate the necessary side chain by applying the Claisen procedure to afford **19**, which was condensed with 3-formyl-1-(phenylsulfonyl)pyrrole producing **20**. iii) The exo-methylene group in **19** – **23** served as a masked ketone function up to the stage just before submission to the indole cyclization.

The actual synthesis was intiated from the known Diels-Alder adduct **7** between cyclopentadiene and (*S*, *E*)-3-bromoacrylate (**6**), whose absolute stereochemistry had been unequivocally established.[5] Referring to the methods described in the literature,[5, 6] the adduct **7** was converted into **10**[7] in 52% overall yield by way of **8** and **9** {$[\alpha]_D^{24}$ +121.2° (*c* 2.88, $CHCl_3$)}. For cleavage of the double bond in **10**, direct methods such as the Lemieux-Johnson protocol were inapplicable here. The nearness of the two aldehyde and the ester groups probably produced a complex interaction among these through the intervention of a hydrate form of the aldehyde. If there was an oxidation cycle due to a combination of OsO_4 and $NaIO_4$, possible forms of hemiacetal and hemilactol might be oxidized further to result in the formation of a variety of by-products. To avoid this complication, it was necessary to once isolate the diol derivative **11**[7] in 96% yield; this was treated with periodate, and the resulting dialdehyde product was transformed without any purification into a bisdithioacetal compound **12**[7] in 76% yield.[8] Desulfurization of **12** was carried out as usual, and the subsequent treatment of **13**[7] with *t*-BuOK provided an α, β-unsaturated ester **14** {$[\alpha]_D^{22}$ +85.7° (*c* 3.12, $CHCl_3$)}as a single compound in 76% yield.[9]

The next step, the reduction of the *t*-Bu ester function to the carbinol group, proved to be most crucial in



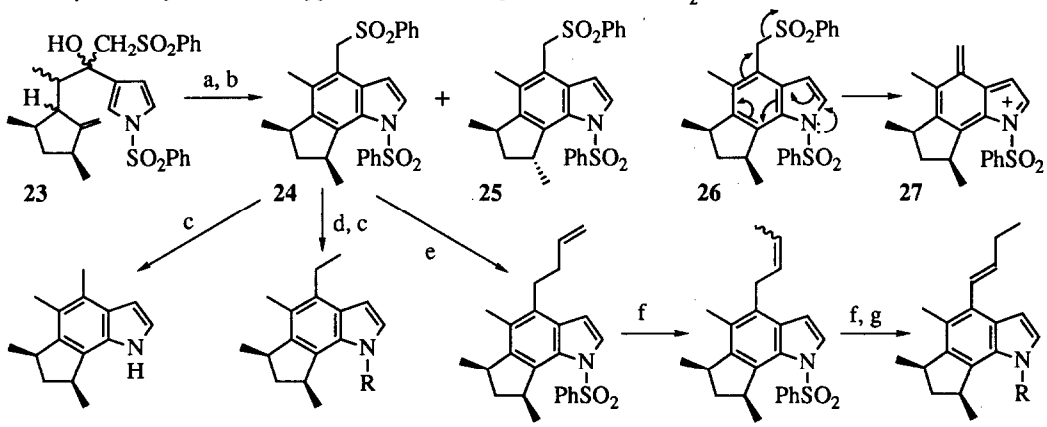
a: *ca.* 2% NaOH in DME-MeOH-H_2O, 0°C, 1 h. b: isobutene, H_2SO_4, CH_2Cl_2, -20 – 23°C, 48 h. c: NaH, $PhCH_2OH$, THF, 0°C, 3 h. d: cat. OsO_4, $Me_3N{\rightarrow}O$, acetone-H_2O, 20°C, 15 h. e: i) $NaIO_4$, THF-H_2O, 0°C, 1 h; ii) EtSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0°C, 18 h. f: Raney Ni (W-2), EtOH-DME, reflux, 2 h. g: *t*-BuOK, THF, 0°C, 1 h. h: DIBAL, hexane-PhMe, -85 – -77°C, 2 h. i: i) $NaBH_4$, EtOH, 0°C, 10 min; ii) $EtC(OEt)_3$, *t*-BuCOOH, PhMe, reflux, 3 h. j: LDA, THF, -65°C, 40 min; 3-formyl-1-(phenylsulfonyl)pyrrole, -78°C, 40 min. k: MnO_2, CH_2Cl_2, reflux, 2 h. l: LiCl, HMPA-H_2O, 130°C, 24 h. m: $LiCH_2SO_2Ph$, THF, -75 – -70°C, 50 min.

Scheme 1

this synthesis, because the simple reduction of **14** with $LiAlH_4$ afforded predominantly the over-reduction product **17**. Therefore the ester **14** was reduced with DIBAL to a mixture containing **15**, **16**, **17**, and **18** (2 : 1: 0.7 : trace amount),[10a] which was reduced further with $NaBH_4$ to effect the reduction of **16** to **15** (**15** : **17** : **18** = 4.5 : 1 : trace).[10a] Without separation, the mixture was submitted to the Johnson modification of the Claisen rearrangement using $EtC(OEt)_3$,[11] and the resulting mixture was separated to furnish finally the left half compound **19** in 51% overall yield as a mixture of two diastereomers of unknown stereochemistry.[10b] This was condensed with the right half molecule, 3-formyl-1-(phenylsulfonyl)pyrrole,[12, 13] to lead to **20** in 94% yield, calculated from the pyrrole derivative. The condensation product **20** was oxidized with MnO_2 to the ketoester **21** in 81% yield, whose COOEt group was eliminated only by heating with LiCl in aqueous HMPA[14] to give **22** in 70% yield. This compound **22** was reacted with a carbanion derived from $PhSO_2Me$ and n-BuLi to produce in 92% yield the precursor molecule **23** for preparation of the ketone derivative **4** (R = CH_2SO_2Ph).

The exo-methylene group in **23** was cleaved in a usual manner, and the resulting ketone derivative[15] **4** (R = CH_2SO_2Ph) was treated with a catalytic amount of *p*-TsOH in refluxing toluene in the presence of PhSH[16] (Scheme 2). Although partial isomerization of the methyl group adjacent to the ketone group took place during this acid treatment, the desired indole derivative **24** {$[\alpha]_D^{21}$ +296.6° (*c* 0.95, $CHCl_3$)} was obtained in 48% yield, accompanied by the trans-dimethyl derivative **25** {$[\alpha]_D^{21}$ -484.4° (*c* 0.38, $CHCl_3$)} in 15% yield. When **24** was treated with Mg in MeOH in the presence of NH_4Cl for the purpose of removal of the *N*-protecting group,[17] facile reductive splitting of the sulfone group at the C-4 side chain was observed concurrently, producing directly in 85% yield (6*R*, 8*S*)-(+)-herbindole A (**3a**), colorless needles, mp 134-136°C (MeOH-H_2O), $[\alpha]_D^{21}$ +56.9° (*c* 0.28, $CHCl_3$), identical with natural herbindole A[18] (**1a**) {$[\alpha]_D^{21}$ –62.0° (*c* 0.07, $CHCl_3$)}, by comparison of their ^1H and ^{13}C NMR spectra, except for the antipodal characters of the optical rotation and CD curves.

The ready substitution of the side chain sulfone group might be explained by its special location as exerting pseudo-gramine character (*cf.* **26**). This nature was enhanced by an accumulated electron-donating effect of alkyl substituents, and a reactive species **27** generated as shown would be responsible for that reaction. Therefore the nucleophilic reaction was tried with the assistance of the organoaluminium compounds by taking into consideration the behavior of *N*-acyl-2-(phenylsulfonyl)piperidines.[19] A successful result was obtained when allyltrimethylsilane was applied to **24** in the presence of $EtAlCl_2$ to achieve the carbon-carbon bond



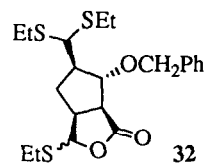
a: cat. OsO_4, $NaIO_4$, THF-H_2O (4 : 1), 21°C, 19 h. b: *p*-TsOH, PhSH, PhMe, reflux, 5 h. c: Mg, NH_4Cl, MeOH, 18-19°C, 2-3 h. d: Me_3Al in hexane, CH_2Cl_2, 0°C, 1 h. e: CH_2=$CHCH_2SiMe_3$, $EtAlCl_2$ in hexane, CH_2Cl_2, -20°C, 20 min. f: cat. $RhCl_3 \cdot 3H_2O$, EtOH, 100°C, 50 h. g: 20% KOH in DME-MeOH-H_2O (1 : 1 : 1), 85-87°C, 6 h.

Scheme 2

formation, providing compound **29**, which had a butenyl side chain in 92% yield. Based on our previous experience,[20] **29** was treated with $RhCl_3$ for migration of the double bond, and **30** and **31** {$[\alpha]_D^{22}$ +400.9° (*c* 0.35, $CHCl_3$)} were separated in 38% and 54% yields, respectively. The same treatment of **30** afforded **31** in 50% yield, accompanied by the 40% recovery of **30**. Alkaline hydrolysis of **31** furnished (6*R*, 8*S*)-(+)-herbindole C (**3c**), colorless syrup, $[\alpha]_D^{22}$ +19.9° (*c* 0.18, $CHCl_3$), in 93% yield. For the preparation of herbindole B (**3b**), Me_3Al was the reagent of choice, and **28** {$[\alpha]_D^{22}$ +504.0° (*c* 0.70, $CHCl_3$)} was produced from **24** in 92% yield. Removal of the *N*-protecting group of **28** gave, in 92% yield, (6*R*, 8*S*)-(+)-herbindole B (**3b**), colorless needles, mp 131-133°C, $[\alpha]_D^{21}$ +51.2° (*c* 0.26, $CHCl_3$) [lit.[1]: mp 118-120°C (MeOH)]. The identity of the synthetic **3b** and **3c** as natural herbindoles B (**1b**) and C (**1c**) was confirmed by comparing their ^1H and ^{13}C NMR spectral data with those reported in the literature.[1,21]

REFERENCES AND NOTES

1. Herb, R.; Carroll, A. R.; Yoshida, W. Y.; Scheuer, P. J.; Paul, V. J. *Tetrahedron* **1990**, *46*, 3089-3092.
2. Capon, R. J.; MacLeod, J. K.; Scammells, P. J. *Tetrahedron* **1986**, *42*, 6545-6550.
3. Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1989**, *30*, 5771-5772.
4. a) Muratake, H.; Natsume, M. *Heterocycles* **1990**, *31*, 683-690. b) Fuji, M.; Muratake, H.; Natsume, M. *Chem. Pharm. Bull.*, submitted for publication.
5. Poll, T.; Abdel Hady, A. F.; Jarge, R.; Linz, G.; Weetman, J.; Helmchen, G. *Tetrahedron Lett.* **1989**, *30*, 5595-5598.
6. Linz, G.; Weetman, J.; Abdel Hady, A. F.; Helmchen, G. *Tetrahedron Lett.* **1989**, *30*, 5599-5602.
7. This compound contained about 15% of diastereoisomers with respect to the stereochemistry of benzyloxy and carboxylate groups.
8. Even with this manipulation, a by-product **32** was obtained in 5% yield.
9. The benzyloxy group at the compounds **10** – **13** was stable enough to allow the above-mentioned transformations. Other hetero functions such as bromine and methoxy groups were unsuitable due to the tendency of partial elimination to afford α, β-unsaturated ester derivatives at any stage during these transformations.



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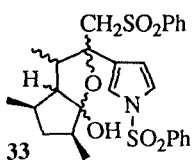
10. a) Estimated from the integrated values of the vinyl and carbinol proton signals of the ^1H NMR spectra. b) Estimated from the data of the GCMS (OV-1, 80°C).
11. Johnson, W. S.; Werthemann, L.; Barlett, W. R.; Brocksom, T. J.; Li, T. -T.; Faukner, D. J.; Pertersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.
12. Hamdan, A.; Wasley, J. W. F. *Synth. Commun.* **1983**, *13*, 741-744.
13. We developed three-step practical synthesis of this compound from 3-acetyl-1-(phenylsulfonyl)pyrrole [Rokach, J.; Hamel, P.; Kakushima, M.; Smith, G. M. *Tetrahedron Lett.* **1981**, *22*, 4901-4904] using the following operations: i) oxidation with SeO_2, ii) reduction of the intermediary ketoaldehyde with $NaBH_4$, and iii) treatment of the resulting diol with $NaIO_4$.[4b]
14. Hagiwara, H.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1988**, 815.
15. The resulting compound existed as a mixture of **4** (R = CH_2SO_2Ph) and **33**. The latter behaved the same as **4** (R = CH_2SO_2Ph) against the acid treatment, so that the mixture was submitted to the indole cyclization reaction without separation.
16. For the addition of thiol, see Abstract Papers, pp 283-286, the 22 nd Congress of Heterocyclic Chemistry, Sendai, Japan, Oct. 7-9, 1991.
17. Okabe, K.; Natsume, M. *Tetrahedron* **1991**, *47*, 7615-7624.
18. The authentic sample was kindly supplied by Professor P. J. Scheuer, to whom authors' heartiest thanks are due. It showed mp 132-134°C after recrystallization from MeOH-H_2O as colorless needles.
19. Brown, D. S.; Charreau, P.; Hansson, T.; Ley, S. V. *Tetrahedron* **1991**, *47*, 1311-1328.
20. Muratake, H.; Watanabe, M.; Goto, K.; Natsume, M. *Tetrahedron* **1990**, *46*, 4179-4192.

21. This work was supported by a Grant-in-Aid from the Ministry of Education, Science and Culture, which is much acknowledged. We are indebted to Professor S. Sakai of Chiba University for the CD measurement.



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