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Total Synthesis of (6*R*,8*S*)-*cis*-Trikentrin B, (6*R*,8*R*)-*trans*-Trikentrin B, and (6*R*,8*R*)-*iso-trans*-Trikentrin B. Determination of the Absolute Structures of the Natural Trikentrins B

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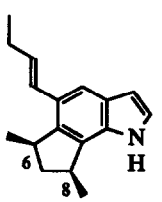
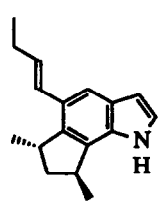
Abstract: The absolute structures of cis-trikentrin B, trans-trikentrin B, and iso-trans-trikentrin B were established to be 1, 2, and 3 by synthesizing the titled trikentrins 1, 18b, and 25 in an enantiospecific manner from a chirality-defined Diels-Alder adduct 7.

Some time ago, we reported on the chiral synthesis of enantiomers of marine sponge constituents,[1] herbindole A (**6a**), herbindole B (**6b**), and herbindole C (**6c**), using the key intermediate, (3*R*,5*S*)-dimethylcyclopentenecarboxylate **8**, derived from the known Diels-Alder adduct **7**.[2] Principles of the methodology involved in this total synthesis have now been applied to a synthesis of (6*R*,8*S*)-*cis*-trikentrin B (**1**), (6*R*,8*R*)-*trans*-trikentrin B (**18b**), and (6*R*,8*R*)-*iso-trans*-trikentrin B (**25**); comparison of their optical properties with those of the natural products established the absolute structures of natural *cis*-trikentrin B, *trans*-trikentrin B, and *iso-trans*-trikentrin B to be expressed as **1**, **2**, and **3**. These were isolated from another marine sponge, *Trikentrion flabelliforme*, together with *cis*-trikentrin A (**4**) and *trans*-trikentrin A (**5**).[3,4] The absolute structures of both trikentrins A have been already determined.[4b]

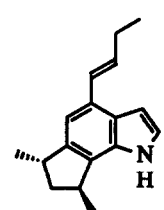
To begin with, an unsatisfactory step in the previous synthesis was improved. Instead of directly reducing



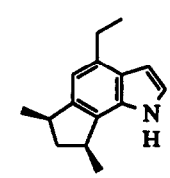
1 *cis*-Trikentrin B



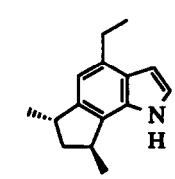
2 *trans*-Trikentrin B



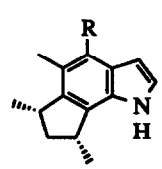
3 *iso-trans*-Trikentrin B



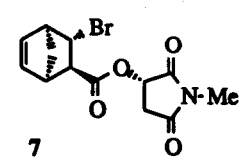
4 *cis*-Trikentrin A



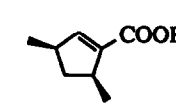
5 *trans*-Trikentrin A



6a R = Me Herbindole A
6b R = Et Herbindole B
6c R = Herbindole C

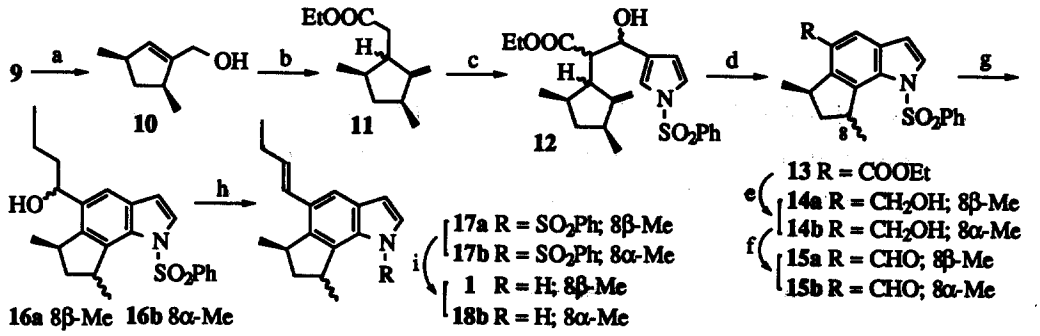


7



8 R = *t*-Bu **9** R = Me

Scheme 1



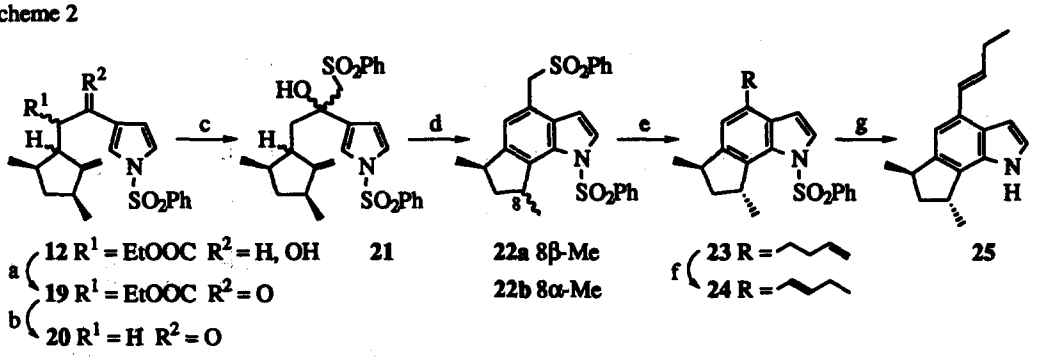
a: DIBALH, 96%. b: $MeC(OEt)_3$, *t*-$BuCO_2H$, 87%. c: LDA; 3-formyl-1-(phenylsulfonyl)pyrrole, 99%. d: i) cat. OsO_4, $NaIO_4$; ii) *p*-TsOH, PhSH, 41%. e: $LiAlH_4$, **14a**: 73%, **14b**: 17%. f: MnO_2, **15a**: 89%, **15b**: 87%. g: PrMgBr, **16a**: 88%, **16b**: 81%. h: *p*-TsOH, **17a**: 94%, **17b**: 84%. i: 20% KOH, **1**: 89%, **18b**: 91%.

the *t*-butyl ester **8** with DIBALH,[2] **8** was first converted into the methyl ester **9** by refluxing it in 1% H_2SO_4-MeOH in 91% yield. The reduction of **9** with DIBALH at -65 – -60°C was found to preferentially afford the required allyl alcohol **10** in 96% yield (Scheme 1). The usual Claisen rearrangement[5] of **10** produced **11**, whose Li salt was allowed to react with 3-formyl-1-(phenylsulfonyl)pyrrole to give the condesation product **12**. The *exo*-methylene group in **12** was cleaved to the ketone group with $NaIO_4$ in the presence of a catalytic amount of OsO_4. The resulting ketone compound was immediately subjected to the indole cyclization reaction[2] by refluxing in chlorobenzene in the presence of *p*-TsOH (1 eq.) and thiophenol (8 eq.) to form **13** as an inseparable mixture of two epimers. The methyl group adjacent to the ketone function at the intermediary compound was partially epimerized during the acid treatment, but separation of the two isomers was effected at the stage when $LiAlH_4$ yielded the reduction products **14a** and **14b**.

The (*E*)-butenyl side chains of final trikentrins B **1** and **18b** were constructed from the carbinol functions of **14a** and **14b**. The carbinols **14a** and **14b** were oxidized with MnO_2 to the aldehydes **15a** and **15b** respectively and each was reacted with *n*-propylmagnesium bromide for the three carbon elongation. Dehydration of the resulting secondary alcohols **16a** and **16b** with a catalytic amount of *p*-TsOH in refluxing benzene selectively afforded (*E*)-olefin compounds **17a** and **17b**, whose indole-protecting group was removed by hydrolysis with caustic alkali to afford (6*R*,8*S*)-*cis*-trikentrin B (**1**), $[\alpha]_D^{24}$ +102° (*c* = 0.18, $CHCl_3$) and (6*R*,8*R*)-*trans*-trikentrin B (**18b**), $[\alpha]_D^{24}$ +24° (*c* = 0.078, $CHCl_3$). The specific rotational value of natural *trans*-trikentrin B has been reported to be $[\alpha]_D$ –13° (*c* = 1.97, $CHCl_3$),[3] which allows the conclusion that the absolute structure of natural *trans*-trikentrin B is the (6*S*,8*S*) derivative **2**. As for *cis*-trikentrin B, the natural product was obtained as an inseparable mixture with *iso-trans*-trikentrin B. Therefore the synthesis of the latter compound was performed as follows, and their absolute structure were estimated by means of CD spectra.

The condensation product **12** was converted into the ketone derivative **20** by way of the β-ketoester **19** (Scheme 2). Removal of the ethoxycarbonyl group of **19** was best carried out by a simple treatment with caustic alkali, which accompanied spontaneous decarboxylation and hydrolysis of the phenylsulfonyl group. The resulting product was sulfonylated again to give **20** in a better yield than the direct deethoxycarbonylation by heating of **19** with LiCl in HMPA-H_2O (50% yield) or with $MgCl_2$ in HMPA (33% yield). (Phenylsulfonyl)-methyllithium was reacted on **20**, and indole cyclization from **21** was carried out by the successive reactions stated above, namely the oxidative cleavage of the *exo*-methylene group, followed by treatment of the resulting

Scheme 2



ketone with *p*-TsOH in the presence of benzylthiol this time to furnish **22a** and **22b**. Synthesis of **24** was achieved from **22b** according to our previous procedures[2] by replacement of the side chain phenylsulfone group of **22b** with an allyl group, employing allyltrimethylsilane and dichloroethylaluminium to afford 3-butenyl derivative **23**, followed by migration of the double bond by refluxing an EtOH solution of **23** with a catalytic amount of $RhCl_3$. Alkaline hydrolysis of the protecting group finally yielded (6*R*,8*R*)-*iso-trans*-trikentrin B (**25**), $[\alpha]_D^{24}$ *ca.* 0° (*c* = 0.11, $CHCl_3$).

Our plan for the absolute structural determination of *cis*-trikentrin B and *iso-trans*-trikentrin B was to make a comparison of the CD spectral curve of the natural mixture of these trikentrins (Figure 1) with calculated curves of **1**+**25** (Figure 4), **1**+*ent*-**25** (Figure 5), *ent*-**1**+**25** (Figure 6), and *ent*-**1**+*ent*-**25** (Figure 7), which were drawn from the measured CD curves of synthesized (6*R*,8*S*)-*cis*-trikentrin B (**1**) (Figure 2) and (6*R*,8*R*)-*iso-trans*-trikentrin B (**25**) (Figure 3).[6,7] The curve obtained from the combination of **1**+*ent*-**25** (Figure 5) only resembled that of the natural mixture (Figure 1). Therefore, the absolute structures of natural *cis*-trikentrin B and *iso-trans*-trikentrin B are expressed as **1** and **3** (= *ent*-**25**).

In conclusion, a series of chiral syntheses, reported so far utilizing our indole cyclization reaction, has made clear the absolute structures of all eight indole alkaloids, trikentrins and herbindoles **1** – **6c**, isolated from the marine sponges.

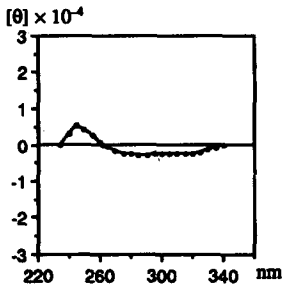


Figure 1
CD Spectrum of the Mixture of Natural *cis*-Trikentrin B and *iso-trans*-Trikentrin B

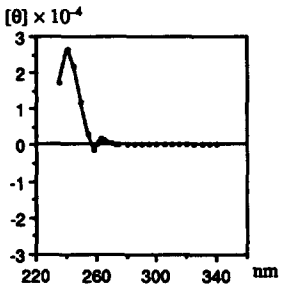


Figure 2
CD Spectrum of (6*R*,8*S*)-*cis*-Trikentrin B (**1**)

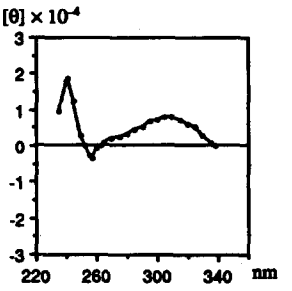


Figure 3
CD Spectrum of (6*R*,8*R*)-*iso-trans*-Trikentrin B (**25**)

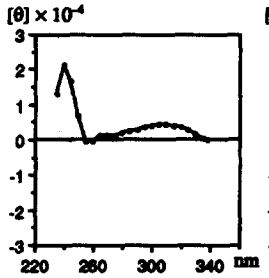


Figure 4
CD Curve of
1 + 25

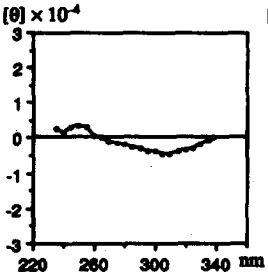


Figure 5
CD Curve of
1 + *ent*-25

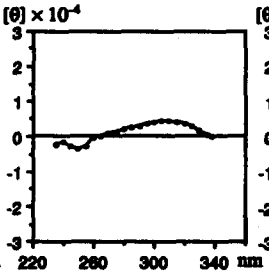


Figure 6
CD Curve of
ent-1 + 25

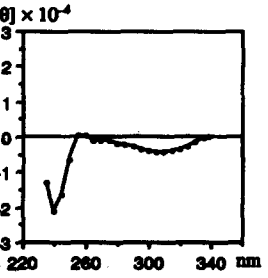


Figure 7
CD Curve of
ent-1 + *ent*-25

ACKNOWLEDGMENT

We are much indebted to Dr. R. J. Capon of the University of Melbourne for a precious sample containing *cis*-trikentrin B and *iso-trans*-trikentrin B. We also thank Professor S. Sakai and Dr. H. Takayama of Chiba University for the CD measurement. This work was supported by a Grant-in-Aid from the Ministry of Education, Science and Culture, which is acknowledged with appreciation.

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6. For the additive rule concerning [θ]'s, see: Velluz, L.; Legrand, M. *Angew. Chem.* **1961**, *73*, 603-611 (especially pp. 609-610).
7. CD curves of Figures 4, 5, 6, and 7 were obtained as follows. At first the content ratio (44:56) of natural *cis*-trikentrin B and *iso-trans*-trikentrin B in the inseparable mixture, supplied by Dr. Capon, was determined from integrated values of well-resolved olefinic protons at the C-2 position of the 1-butenyl side chain. Then the CD curves of *ent*-1 and *ent*-25 were estimated by making mirror image curves of Figures 2 and 3. Thirdly, in all curves of 1, 25, *ent*-1, and *ent*-25, the [θ] value was measured at every 5 nm from 235 nm until 340 nm. Finally, at each wave-length of 235 nm, 240 nm and so forth, the sum of the [θ] values, for instance, $0.44 \times \{[\theta]_{235}$ of 1$\} + 0.56 \times \{[\theta]_{235}$ of 25$\}$, taking into consideration the 44:56 ratio of the natural mixture, was calculated in every combination of 1+25 , 1+*ent*-25 , *ent*-1+25, and *ent*-1+*ent*-25, and plotted to draw the CD curves of Figures 4, 5, 6, and 7.

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