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Absolute configuration of phytocassanes as proposed on the basis of the CD spectrum of synthetic (+)-2-deoxyphytocassane A

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Abstract

Phytocassane A–E possess *ent*-cassane skeleton because synthetic (+)-2-deoxyphytocassane A with cassane skeleton showed the Cotton effects positive at 369 nm (due to the ring-C dienone chromophore) and negative at 289 nm (due to the ring-A carbonyl group), while the natural phytocassane A exhibited the opposite Cotton effects.

Keywords: circular dichroism; configuration; phytoalexins; terpenes; terpenoids.

Phytoalexins are antifungal and defensive metabolites playing an important role in plant chemical ecology, and are biosynthesized in plant cells after their exposure to pathogens. Phytocassanes A–E were isolated as the phytoalexins produced by rice plants (*Oryza sativa*) infected with *Magnaporthe grisea* (old name: *Pyricularia oryzae*), *Rhizoctonia solani* and *Phytophthora infesta*.[1,2] Their structures as cassane diterpenes were proposed as **1**–**5** (Scheme 1) on the basis of extensive spectroscopic analysis.[1,2] Their absolute configuration, however, remained unknown even after their CD measurements.

This paper describes a synthesis of (+)-2-deoxyphytocassane A (**6**) with depicted absolute configuration. Comparison of its CD spectrum in a longer wave length region (>300 nm) with those of phytocassans enabled us to propose **1′** as the absolute configuration of phytocassane A. Phytocassanes belong to *ent*-series of diterpenoids like the gibberellins and (+)-oryzalexin A (**7**), another phytoalexin produced by rice plants,[3] whose synthesis was previously reported by Mori and Waku.[4]

Scheme 2 summarizes our synthesis of (+)-2-deoxyphytocassane A (**6**). (*S*)-(+)-Wieland–Miescher ketone[5] was selected as the starting material, because it gave enantiomerically pure **8** by simple yeast reduction with *Torulaspora delbrueckii* IFO 10921.[6] Conversion of **8** to **9** was executed according to Smith and Mewshaw.[7] Removal of the THP protective group of **9** was followed by acetalization of the C-3 carbonyl group and Swern oxidation of the C-9 hydroxy group to give ketone **10**.[8] Formylation of **10** was followed by Robinson annelation (methyl vinyl ketone) with concomitant removal of the formyl

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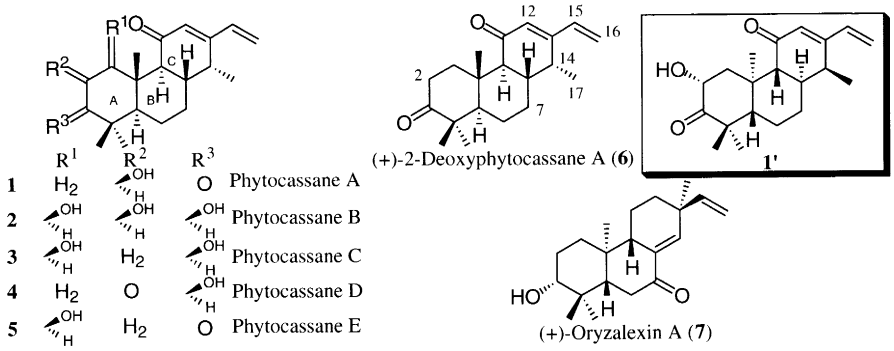


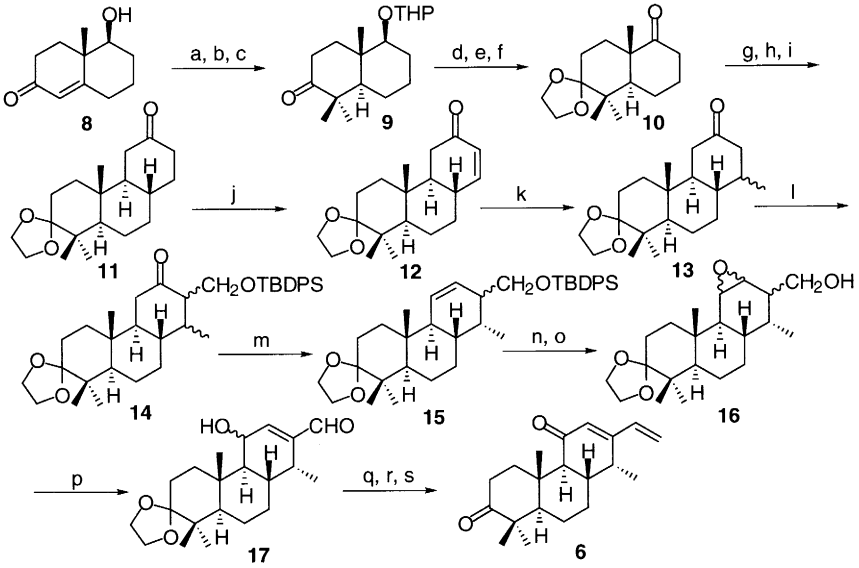
Scheme 1. Structures of phytoalexins produced by rice plants

group (cf. Ref. 9). Birch reduction of the resulting tricyclic enone yielded the saturated ketone **11** after reoxidation with PCC. For the introduction of the axial methyl group at C-14, the ketone **11** was first converted to the enone **12**. Accordingly, **11** was thiophenylated by the method of Trost and Massiot,[10] and the resulting phenylthio ether was oxidized with dimethyldioxirane[11] to give the corresponding phenyl sulfoxide, whose thermolysis furnished **12**. Conjugate addition of lithium dimethylcuprate to **12** afforded **13** as a mixture of the desired α- and axially methylated one at C-14 and its equatorial isomer. In the ^{1}H NMR spectrum of **13**, the axial methyl group at C-14 absorbed at δ=0.79 (d, *J*=7.4 Hz) due to the shielding effect caused by the ring-C,[9] while the equatorial one showed a doublet at δ=0.99 (d, *J*=6.4 Hz). The ratio of these two isomers was axial-methyl:equatorial-methyl=1:2. Different conditions for the introduction of the methyl group were examined with no improved results. Unfortunately, the two isomers could not be separated at this stage, and, therefore, the mixture **13** was employed as such in the next step to attach a hydroxymethyl group at C-13 by the method of Corey and Smith.[12] Protection of the newly generated primary hydroxy group as TBDPS ether gave **14**.

In order to introduce an oxygen function at C-11, the ketone **14** was subjected to the Shapiro olefination reaction[13] to give **15** after chromatographic purification. Fortunately at this stage, the undesired β-methyl isomers at C-14 could be eliminated and what we obtained was a diastereomeric mixture (**15**) at C-13 with the correct stereochemistry at C-14, exhibiting ^{1}H NMR signals at δ=0.63 and 0.81 (d, *J*=7 Hz, total 3H). The reason for this unexpected disappearance of the β-methyl isomers at C-14 was unclear. Deprotection of the TBDPS protective group of **15** was followed by epoxidation of the resulting olefinic alcohol with MCPBA to give **16**. Dess–Martin oxidation of **16** afforded the corresponding epoxy aldehyde, which was treated with pyrrolidine to give γ-hydroxy-α,β-unsaturated aldehyde **17**. This aldehyde **17** was subjected to Wittig methylenation, TPAP oxidation[14] and deacetalization to give (+)-2-deoxyphytocassane A (**6**), $[\alpha]_D^{26}$=+5.8 (*c* 0.1, $CHCl_3$).[15] The overall yield of (+)-**6** was 0.04% based on (*S*)-**8** (27 steps).

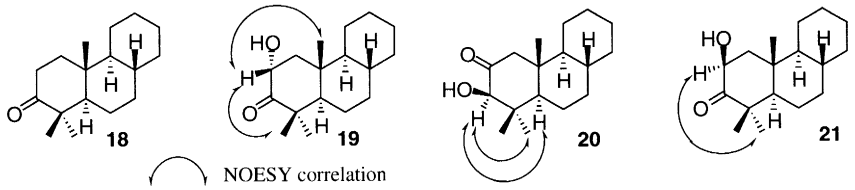
The CD spectrum of (+)-**6** showed a positive Cotton effect at 369 nm (Δε=+1.63) due to the $n\rightarrow\pi^*$ transition of the ring-C carbonyl group,[16] while all of the natural phytocassanes A–E showed negative Cotton effects at the wave length between 345 and 369 nm [λext nm (Δε): **A**, 369 (−2.78); **B**, 345 (−5.36); **C**, 349 (−5.17); **D**, 368 (−3.27); **E**, 348 (−4.47)]. The absolute configuration of the natural phytocassane A was therefore proposed as depicted in **1′**.

To further support this conclusion, we decided to synthesize some model compounds **18**–**21**[17] with different ring-A functionalities without any functional group on ring-C, and compared their CD with those of the natural and synthetic phytocassanes (Scheme 3). As expected, the ketones **18**–**21** with no ring-C functionality showed no CD absorption around 369 nm. Accordingly, the strong CD absorption at 369 nm of (+)-2-deoxyphytocassane A (**6**) must be due to the chirality of the ring-C. The ketones **18**–**21** exhibited CD absorption around 290 nm due to the $n\rightarrow\pi^*$ transition of the ring-A carbonyl group



Scheme 2. Reagents: (a) DHP, TsOH, CH_2Cl_2 (91%); (b) PhSH, HCHO aq., Et_3N, EtOH, reflux (79%); (c) Li, H_2O, liq. NH_3, THF then MeI, THF (79%); (d) TsOH, MeOH, H_2O (99%); (e) ethylene glycol, PPTS, benzene, 80°C (94%); (f) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2 (92%); (g) (1) HCO_2Et, NaH, THF, toluene; (2) methyl vinyl ketone, Et_3N; (3) MeONa, MeOH (76%, three steps); (h) Li, EtOH, liq. NH_3, THF; (i) PCC, MS 3A, CH_2Cl_2 (76%, two steps); (j) (1) LDA, $PhSSO_2Ph$, THF, −78°C; (2) dimethyldioxirane, CH_2Cl_2, −78°C; (3) $CaCO_3$, toluene, 110°C (83%, three steps based on recovered **11**); (k) Me_2CuLi, Et_2O, 0°C (quant.); (l) (1) NaH, HCO_2Et, MeOH; (2) NaH, Red-Al, THF, −30°C; (3) TBDPSCl, imidazole, DMF; (m) (1) $TsNHNH_2$, $MgSO_4$, THF; (2) excess LDA, THF, quenched with NH_4Cl aq. then SiO_2 chromatog. (8%, from **13**); (n) TBAF, THF (74%); (o) MCPBA, $NaHCO_3$, $CHCl_3$ (72%); (p) (1) Dess–Martin periodinane, CH_2Cl_2; (2) pyrrolidine, Et_2O (85%, two steps); (q) $Ph_3P{=}CH_2$, THF (77%); (r) TPAP, MS 3A, CH_2Cl_2, MeCN (91%); (s) 1N HCl, THF (64%)

[λext nm (Δε): **18**, 309 (−0.38); **19**, 284 (−0.61); **20**, 288 (+0.97); **21**, 289 (+0.04)]. The ketone **21** with the same ketol system as that of phytocassane A showed a positive Cotton effect at 289 nm, while phytocassane A exhibited a negative Cotton effect at 289 nm (Δε −8.74).[1] The opposite signs of the CD absorptions at 369 nm of **6** and also at 289 nm of **21** in comparison to those of phytocassane A led us to the conclusion that phytocassanes possess *ent*-cassane skeleton, and belong to the same stereochemical families of diterpenoids as the gibberellins and oryzalexins.



Scheme 3. Structures of the ring-A model compounds

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15. (+)-2-Deoxyphytocassane A (**6**): colorless gum; CD (EtOH) λ_{ext}: 369 nm ($\Delta\varepsilon$ +1.63), 279 nm ($\Delta\varepsilon$ −1.20); IR ($CHCl_3$) ν_{max} (cm^{-1})=2980 (s, C–H), 2870 (m, C–H), 1700 (s, C=O), 1650 (s, C=O), 1460 (m), 1385 (m), 1230 (w), 1110 (m); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06 (s, 3H, 20-CH_3), 1.08 (s, 3H, 18-CH_3), 1.09 (d, *J*=7 Hz, 3H, 17-CH_3), 1.11 (s, 3H, 19–CH_3), 1.42 (br, dd, *J*=3, 12 Hz, 1H, 5-H), 1.52 (m, 2H, 6β,7α-H), 1.66 (m, 2H, 1α,6α-H), 1.77 (m, 1H, 7β-H), 1.97 (d, *J*=13.2 Hz, 1H, 9-H), 2.22 (m, 1H, 8-H), 2.38 (ddd, *J*=4, 5.8, 14 Hz, 1H, 2α-H), 2.64 (m, 2H, 1β,14-H), 3.23 (ddd, *J*=4, 6.5, 14 Hz, 1H, 2β-H), 5.49 (d, *J*=10.9 Hz, 1H, 16-C*H*H), 5.67 (d, *J*=17.7 Hz, 1H, 16-CH*H*), 5.76 (s, 1H, 12-H), 6.35 (dd, *J*=10.9, 17.7 Hz, 1H, 15-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.3 (C-17), 14.2 (C-18), 21.7 (C-20), 22.2 (C-6), 26.2 (C-19), 31.1 (C-7), 33.3 (C-14), 34.5 (C-1), 37.9 (C-8), 37.9 (C-8), 38.4 (C-2), 38.4 (C-10), 48.1 (C-4), 55.7 (C-5), 55.9 (C-9), 120.6 (C-16), 128.6 (C-15), 136.3 (C-12), 160.7 (C-13), 201.1 (C-11), 216.8 (C-3); HRMS: $C_{20}H_{28}O_2$: calcd 300.2088; found: 300.2094. The protons of C-17 methyl group attached at C-14 of **6** absorbed at δ=1.06, while the same methyl group at C-14 of **15** appeared at δ=0.63 and 0.81. This may be due to the fact that C-17 methyl group of **6** is located near the conjugated dienone system and thereby much more deshielded in comparison to the methyl group of **15**.
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