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OXIDATIVE CLEAVAGE REACTION OF SUBSTITUTED INDOLES CATALYZED BY PLANT CELL CULTURES

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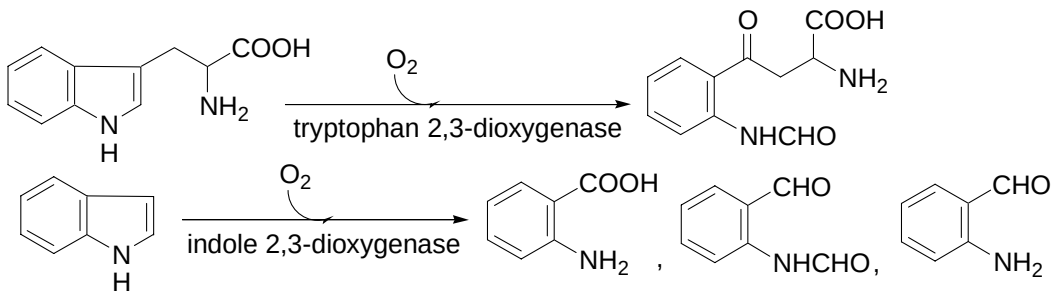
Abstract – We have developed a novel method for the oxidative cleavage of indole carbon double bonds in the presence of H_2O_2 using plant cell cultures as peroxidase. The oxidative method has some advantage, as features such as mild reactions, good yields, easy work-up and safety.

INTRODUCTION

Oxidative cleavage of a carbon-carbon double bond is a widely used essential method for the preparation of carboxylic acids and ketones in organic synthesis.[1] A number of different reagents for this reaction have been developed such as ozone,[2] potassium permanganate,[3] ruthenium tetraoxide,[4] sodium periodate,[5] sodium dichromate in acid,[6] nitrous acid[7] and molecular oxygen with copper ion systems.[8,9] On the other hand, the development of enzymes for oxidation reactions aimed at green chemistry is very important. The biocatalytic oxidative cleavage of a carbon-carbon double bond is preferable, because it takes advantage of the mild conditions. Two dioxygenases are known so far: (1) L-tryptophan 2,3-dioxygenase,[10] (2) indole 2,3-dioxygenase.[11] L-tryptophan 2,3-dioxygenase is a heme-containing dioxygenase which catalyzes the insertion of molecular oxygen into the pyrrole ring of L-tryptophan to give L-formylkynurenine. Indole 2,3-dioxygenase catalyzes the conversion of indole to anthranilic acid. Formylaminobenzaldehyde and *o*-aminobenzaldehyde were detected as intermediates during the overall conversion.



Recently, there has been interest in singlet molecular oxygen following the demonstration that it is the active species in dye-sensitized photooxygenation. Electron-rich alkenes are known to react readily with

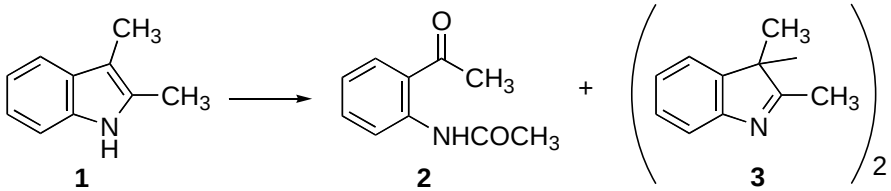
singlet oxygen to yield unstable dioxetanes, which can subsequently be cleaved to two carbonyl fragments.[12] Photooxidation of 1,3-dimethylindole at rt gives the cleaved products in nearly quantitative yield.[13] The coupled oxygenation with peroxidase in the presence of H_2O_2 is analogous to the reaction of singlet oxygen.[14] We have found that plant cell cultures is an efficient source of peroxidase enzymes as 'reagents' in organic synthesis and a substantial amount of H_2O_2 is produced in plant cell cultures by the addition of foreign substrates.[15] Very recently, we found 2,3-dimethylindole (**1**) was converted to *o*-acetylaminoacetophenone (**2**) with oxidative cleavage of the carbon-carbon double bonds.[16] In further studies, it was of interest to ascertain whether functionality other than that present in **1** could be tolerated by plant cell cultures. Then, we studied the biocatalytic cleavage of substituted indoles with a plant cell culture-H_2O_2 system.

RESULTS AND DISCUSSION

Oxidative cleavage reactions were performed with a plant cell culture-H_2O_2 system at rt. In this work, we used suspension-cultured cells which had originally been isolated from *Nicotiana* (*N.*) *tabacum* "Bright Yellow-2", *Daucus* (*D.*) carota, *Camellia* (*C.*) *sinensis* and *Catharanthus* (*C.*) *roseus*. These cell cultures (*N. tabacum, D. carota, C. roseus* and *C. sinensis*) were prepared as described in our previous papers.[17-20] The oxidative cleavage reactions were performed by the methods with freely suspended plant cells which had the highest peroxidase activity (POD) in the stationary phase after incubation (*C. sinensis* 18 days 15.5 U/mL, *N. tabacum* 22 days 9.6 U/mL, *D. carota* 12 days 8.0 U/mL, *C. roseus* 8 days 0.5 U/mL). A substrate (1 mmol) was added to the freely suspended *C. roseus* (B-5 medium[21], pH 5.5), *N. tabacum* "Bright Yellow-2" (MS medium[22], pH 5.8), *D. carota* (MS medium, pH 5.8), and *C.sinensis* (B-5 medium, pH 5.8) in the presence of H_2O_2 as a cofactor. The mixture was shaken at rt in a rotary shaker (110 rpm) in the dark. The first substrate to be studied was 2,3-dimethylindole (**1**) as shown in Table 1.

$NaIO_4$ has been used to cleave the indolic double bond of several 2,3-disubstituted indoles to give the corresponding ketoamides.[23] For comparison with such plant cell systems, chemical reagents[24] were also examined. Among the procedures examined, *C. roseus* in the presence of H_2O_2 showed the highest yield of **2** (Entry 6). The reaction proceeded much faster with *C. sinensis*, *N. tabacum* or *C. roseus* in the presence of H_2O_2 than with $FeCl_3$, $K_3Fe(CN)_6$ or *D. carota*. In the absence of plant cell cultures, longer reaction time was required with H_2O_2 to complete the reaction (Entry 8). In B5 or MS medium, reaction does not proceed (Entry 9, 10). Though reaction with $FeCl_3$ or $K_3Fe(CN)_6$ also gave **2** and **3**, the plant cell culture and sodium periodate gave no other products than compound **2** (Entry 3-7). Thus, *C. roseus*, *C. sinensis* and *N. tabacum* were proven to be effective catalysts for oxidative cleavage of **1** in satisfactory yields without any side-products in short reaction time. The structures of **2**[24] and **3**[24] were confirmed by a comparison of the proton nuclear magnetic resonance (^{1}H-NMR) data with those reported.

Table 1. Oxidative cleavage of **1** with plant cell cultures or chemical reagents

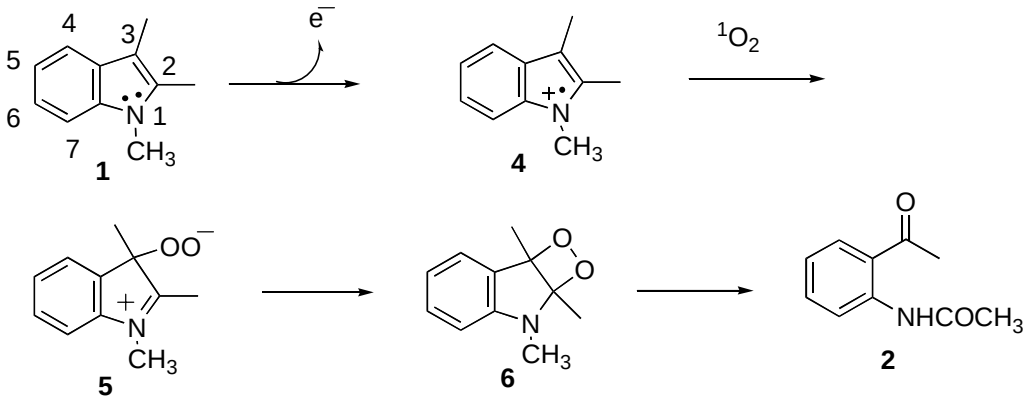


Entry	Method	Medium	Time (h)	**2**[a] Y. (%)	**3**[a] Y. (%)
1	$FeCl_3$	EtOH	24	8	4
2	$K_3Fe(CN)_6$	H_2O-acetone	24	19	2
3	$NaIO_4$	H_2O-CH_3OH	0.5	85	0
4	*C. sinensis,* H_2O_2	B5 medium	0.5	49	0
5	*N. tabacum,* H_2O_2	MS medium	0.5	53	0
6	*C. roseus,* H_2O_2	B5 medium	0.5	95	0
7	*D. carota,* H_2O_2	MS medium	168	53	0
8	H_2O_2	MS medium	168	16	0
9		B5 medium	168	0	0
10		MS medium	168	0	0

[a]All are isolated yields. Entries 8-10 are control experiments.

Although the mechanisms are not clear at present, the following mechanism seems likely in the case of (**1)** as shown in Chart 1. At first, one-electron oxidation of indole (**1**) by peroxidase gives rise to a radical cation (**4)**, which reacts readily with singlet oxygen to yield unstable dioxetane (**6)** via zwitter ion (**5)** as intermediate. **6** can subsequently give the corresponding C2-C3 ring cleavage product (**2)**. We could not trap the zwitter ionic peroxide intermediates proposed theoretically, but it is well known that cleavage of dioxetane produces chemiluminescence. Actually, chemiluminescence was produced in this oxidative cleavage of indoles. From these observations, the mechanism may be proposed.

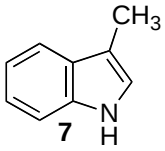
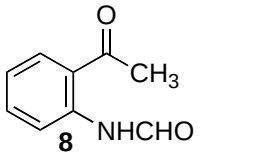
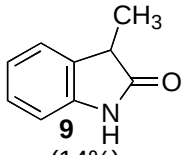
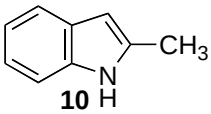
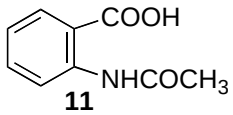
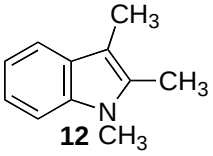
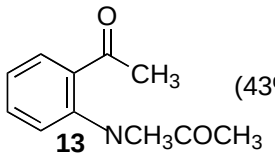
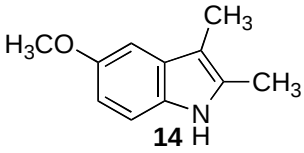
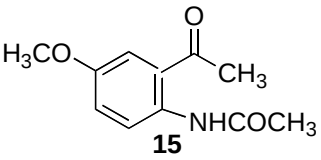
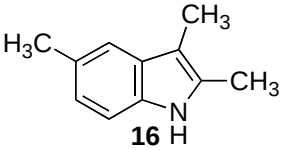
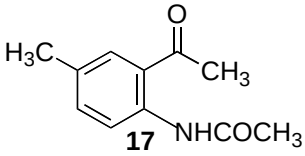
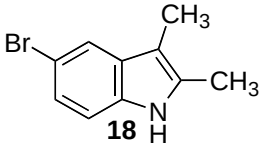
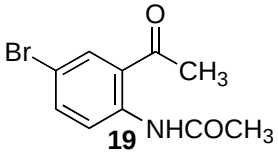
Chart 1. Proposed mechanism



In further studies, it was of interest to ascertain whether functionality other than that present in **1** could be tolerated by plant cell cultures. For this purpose, indoles (**7**, **10**, **12**, **14**, **16**, **18**, and **20**-**25**) were selected as

the next substrate. Indoles (**7**, **10**, **21**, and **22**) are commercially available samples. Indoles (**12**) and (**16**) were prepared according to the method of ref. [25, 26] Indoles (**14**, **18**, **20**, **23**, **24**, and **25**) were synthesized as shown in Experimental. The structures of (**14**,[27] **20**,[28] **23**,[27] **24**,[29] and **25**[30]) were confirmed by a comparison of the proton nuclear magnetic resonance (^{1}H-NMR) data with those reported. These results of oxidative cleavage are shown in Table 2.

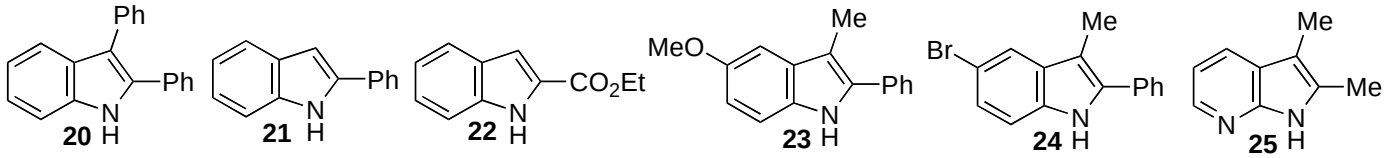
Table 2. Oxidative cleavage of indoles with plant cell cultures

Entry	Indole	Plant[a]	Time (h)	Product (Y. %)[b, c]	
1	 **7**	*C. sinensis* (H_2O_2)	24	 **8** (37%) (47%, 18 h)[c]	 **9** (14%)
2	 **10**	*C. roseus* (H_2O_2)	24	 **11**	(51%) (16%, 18 h)[c]
3	 **12**	*C. roseus* (H_2O_2)	18	 **13**	(43%) (52%, 18 h)[c]
4	 **14**	*N. tabacum* (H_2O_2)	1	 **15**	(87%) (68%, 2 h)[c]
5	 **16**	*C. roseus* (H_2O_2)	1	 **17**	(64%) (65%, 2h)[c]
6	 **18**	*D. carota* (H_2O_2)	18	 **19**	(61%) (38%, 18 h)[c]

a: 30% H_2O_2 was added to the freely suspended plant cell cultures (Entries 1-3, 5-9). b: All are isolated yields.
c: Yields and reaction time with $NaIO_4$

The carbon-carbon double bonds of indoles (**7**, **10**, **12**, **14**, **16**, and **18**) were cleaved to give the corresponding amides in the presence of H_2O_2. For comparison with such plant cell cultures-H_2O_2 system, $NaIO_4$[23] was also examined. The yields with $NaIO_4$ decreased in the case of highly reactive indoles having an electron-donating substituent in the indole ring (e.g., compounds **10**, **14**, **18**), but the yields with the plant cell culture were much higher than that with $NaIO_4$ (Entries 2, 4, 6). Although indoles (**20**—**25**) were subjected to plant cell cultures in the presence of H_2O_2, no oxidative cleavage products were given. But, the

reaction of **20** and **24** with $NaIO_4$ afforded oxidative cleavage products [*N*-(2-benzoylphenyl)benzamide: 4.5%, 24 h, 2'-acetyl-4'-bromobenzanilide: 14%, 18h).



The structures of **2**,[24] **3**,[24] **8**,[31] **9**,[32] **15**,[34] **13**,[33] **19**[35] were confirmed by a comparison of the proton nuclear magnetic resonance (^{1}H NMR) data with those reported. The product (**11)** was confirmed by a comparison of ^{1}H-NMR data, mp and TLC with a commercially available sample.

In summary, a novel oxidative cleavage of substituted indoles was developed by using plant cell cultures of *C. roseus*, *C. sinensis*, *D. carota* and *N. tabacum* in the presence of H_2O_2. This procedure has some advantageous features such as mild reactions, good yields, easy work-up and safety; therefore, it is a valuable alternative to the cleavage of indoles by $NaIO_4$.

EXPERIMENTAL

General experimental procedures. ^{1}H-NMR spectra were measured at 270 MHz on a JEOL JNM-EX 270 FT NMR spectrometer. Chemical shifts are quoted in ppm with tetramethylsilane as an internal standard, and coupling constants (*J*) are given in Hz. Melting points were determined on a micro-melting point apparatus (Yanagimoto) and are uncorrected.

Preparation of 2,3-dimethyl-5-methoxyindole (14)

To a stirred solution of 2-butanone (180 mg, 2.5 mmol) in AcOH (5 mL) was added 4-methoxyphenylhydrazine hydrochloride (200 mg, 1.1 mmol). The solution was refluxed for 1.5 h while stirring with a mechanical stirrer. The reaction mixture was cooled to rt. The reaction mixture was added to AcOEt (20 mL), washed with brine (2 x 50 mL) and $NaHCO_3$ aq. (1 x 50 mL), dried over $MgSO_4$, filtered, and evaporated *in vacuo* to yield **14** (200 mg, quant.). mp 109-113℃ (lit.,[27] mp 108-112℃).

Preparation of 5-bromo-2,3-dimethylindole (18)

To a stirred solution of 2-butanone (225 mg, 3.1 mmol) in AcOH (5 mL) was added 4-bromophenylhydrazine hydrochloride (220 mg, 1.0 mmol). The solution was refluxed for 2 h while stirring with a mechanical stirrer. The reaction mixture was cooled to rt. The reaction mixture was added to AcOEt (20 mL), washed with brine (2 x 50 mL) and $NaHCO_3$ aq. (1 x 50 mL), dried over $MgSO_4$, filtered, and evaporated *in vacuo* to yield **18** (180 mg, 80%). **18**: mp 136-137℃ (lit.,[36] mp 138℃).

18: ^{1}H-NMR ($CDCl_3$) δ: 2.17 (3H, s), 2.34 (3H, s), 7.08 (1H, d, *J*=8.6 Hz), 7.15 (1H, d, *J*=8.6 Hz), 7.56

(1H, s), 7.67 (1H, br s).

Preparation of 2,3-diphenylindole (20)

To a stirred solution of 1-phenylacetophenone (915 mg, 4.7 mmol) in AcOH (10 mL) was added phenylhydrazine (500 mg, 4.7 mmol) and $BF_3 \cdot Et_2O$ (664 mg, 4.7 mmol). The solution was refluxed for 2 h while stirring with a mechanical stirrer. The reaction mixture was cooled to rt. The reaction mixture was added to AcOEt (20 mL), washed with brine (2 x 50 mL) and $NaHCO_3$ aq. (1 x 50 mL), dried over $MgSO_4$, filtered, and evaporated *in vacuo.* The residue was subjected to silica gel column chromatography using hexane–AcOEt (6:1) to afford **20** (1.1 g, 88%). **20**: mp 124-126°C (lit.,[37] mp 124.5-125.5°C).

Preparation of 5-methoxy-3-methyl-2-phenylindole (23)

To a stirred solution of propiophenone (800 mg, 6.0 mmol) in AcOH (5 mL) was added 4-methoxyphenylhydrazine hydrochloride (1.0 g, 5.9 mmol). The solution was refluxed for 2 h while stirring with a mechanical stirrer. The reaction mixture was cooled to rt. The reaction mixture was added to AcOEt (20 mL), washed with brine (2 x 50 mL) and $NaHCO_3$ aq. (1 x 50 mL), dried over $MgSO_4$, filtered, and evaporated *in vacuo.* The residue was subjected to silica gel column chromatography using hexane–AcOEt (5:1) to afford **23** (775 mg, 57%). **23**: mp 114-116°C (lit.,[27] mp 114-116°C).

Preparation of 5-bromo-3-methyl-2-phenylindole (24)

To a stirred solution of propiophenone (260 mg, 2.0 mmol) in AcOH (5 mL) was added 4-bromophenylhydrazine hydrochloride (450 mg, 2.0 mmol). The solution was refluxed for 2 h while stirring with a mechanical stirrer. The reaction mixture was cooled to rt. The reaction mixture was added to AcOEt (20 mL), washed with brine (2 x 50 mL) and $NaHCO_3$ aq. (1 x 50 mL), dried over $MgSO_4$, filtered, and evaporated *in vacuo.* The residue was subjected to silica gel column chromatography using hexane–AcOEt (5:1) to afford **24** (452 mg, 79%). mp 138-140°C (lit.,[29] mp 141°C).

Preparation of 2,3-dimethyl-1H-pyrrolo[2.3-b]pyridine (25)

To a stirred solution of 2-butanone (1.44 g, 2.0 mmol) in AcOH (10 mL) was added 2-hydrazinopyridine (1.09 g, 10 mmol). The solution was refluxed for 2 h while stirring with a mechanical stirrer. The reaction mixture was cooled to rt. The reaction mixture was added to AcOEt (20 mL), washed with brine (2 x 50 mL) and $NaHCO_3$ aq. (1 x 50 mL), dried over $MgSO_4$, filtered, and evaporated *in vacuo.* To the residue was added polyphosphoric acid (5 g). The residue was heated at 160°C for 0.5 h. The residue was cooled to rt. The reaction mixture was added to AcOEt (20 mL), washed with brine (2 x 50 mL) and $NaHCO_3$ aq. (1 x 50 mL), dried over $MgSO_4$, filtered, and evaporated *in vacuo* to yield **26** (630 mg, 43%). mp 136-138°C (lit.,[30] mp 137-138°C).

Reaction of 1 with $FeCl_3$

To a stirred solution of $FeCl_3$ (487 mg) in EtOH (10 mL) was added **1** (146 mg, 1 mmol) in EtOH (5 mL). The solution was stirred for 24 h with a mechanical stirrer. The solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL) and the solution was washed with brine (10 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography using hexane–AcOEt (3:1) to afford **2** (14.5 mg, 8%) and **3** (11.5 mg, 4%).

Reaction of 1 with $K_3[Fe(CN)_6]$

To a stirred solution of $K_3[Fe(CN)_6]$ (659 mg) in water (10 mL) was added **1** (146 mg, 1 mmol) in acetone (5 mL). The solution was stirred for 24 h with a mechanical stirrer. The solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL) and the solution was washed with brine (10 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography using hexane–AcOEt (3:1) to afford **2** (34.4 mg, 19%) and **3** (5.8 mg, 2%).

Reaction of 1 with H_2O_2

To a stirred MS medium (30 mL) was added **1** (146 mg, 1 mmol) in EtOH (5 mL). After 5 min, 30% H_2O_2 (4.8 mL) was added. The solution was stirred for 168 h with a mechanical stirrer. The reaction mixture was extracted with AcOEt (20 mL). The AcOEt extract was washed with brine (10 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography using hexane–AcOEt (3:1) to afford **2** (28.9 mg, 16%).

Reaction of 1 with $NaIO_4$

To a stirred solution of **1** (300 mg, 2.1 mmol) in MeOH (10 mL) was added $NaIO_4$ (1.3 g) in water (10 mL) at 0°C. The solution was stirred for 2 h at rt. The reaction mixture was extracted with AcOEt (20 mL). The AcOEt extract was washed with brine (10 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography using hexane–AcOEt (3:1) to afford **2** (292 mg, 80%).

Reaction of 1 with MS or B5 medium

To a stirred MS medium (200 mL) or B5 medium (200 mL) was added **1** (145 mg, 1 mmol) in EtOH (5 mL). The solution was shaken at 25°C on a rotary shaker (110 rpm) in the dark for 168 h. The reaction mixture was extracted with AcOEt (50 mL). The AcOEt extract was washed with brine (30 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography using hexane–AcOEt (3:1) to afford **1** (MS medium: 130 mg, 90%, B5 medium: 125 mg, 86%).

Cultivation of *C. roseus* cells

Suspension cells of *C. roseus* were subcultured every 7 days by transferring a 1-week culture (8 mL) into B5 medium (80 mL) containing 2,4-dichlorophenoxyacetic acid (2,4-D) (1 mg/L) and 2% sucrose (pH 5.5) on a rotary shaker (110 rpm) at 25°C in the dark.

Cultivation of *D. carota* cells

Suspension cells of *D. carota* were subcultured every 7 days by transferring a 1-week culture (8 mL) into MS medium (80 mL) containing 2,4-D (2 mg/L) and 3% sucrose (pH 5.8) on a rotary shaker (110 rpm) at 25°C in the dark.

Cultivation of *N. tabacum* cells

Suspension cells of *N. tabacum* were subcultured every 7 days by transferring a 1-week culture (1.3 mL) into MS medium (80 mL) containing 2,4-D (2 mg/L) and 3% sucrose (pH 5.8) on a rotary shaker (110 rpm) at 25°C in the dark.

Cultivation of *C. sinensis* cells

Suspension cells of *C. sinensis* were subcultured every 10 days by transferring a 1-week culture (10 mL) into B5 medium (80 mL) containing 2,4-D (1.25 mg/L) and 5% sucrose (pH 5.8) on a rotary shaker (110 rpm) at 25°C in the dark.

Biotransformation of indoles (1, 7, 10, 12, 14, 16, 18, and **20-25) with plant cell cultures**

A substrate (**1, 7, 10, 12, 14, 16, 18,** and **20-25**) (1 mmol) was added to the freely suspended *C. roseus* (30 g of cells and 120 ml broth, B-5 medium, pH 5.5, 8 d old), *N. tabacum* ‘ Bright Yellow-2’ (30 g of cells and 120 mL broth, MS medium, pH 5.8, 22 d old), *D. carota* (30 g of cells and 120 ml broth, MS medium, pH 5.8, 12 d old), and *C. sinensis* (30 g of cells and 120 ml broth, B-5 medium, pH 5.8, 18 d old). After 5 min, 30% H_2O_2 (1 mL) was added to the reaction mixture. The mixture was shaken at 25°C on a rotary shaker (110 rpm) in the dark. At the termination of the reaction, the incubation mixture was filtered, and the filtered cells were washed with AcOEt. The filtrates and washings were combined and extracted with AcOEt. The AcOEt layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*.

In the case of indoles (**1**, **7**, **10**, **12**, **14**, **16** and **18**), the residue was subjected to silica gel column chromatography using CH_2Cl_2–MeOH (50:1) to afford oxidative cleavage products (**2**, **3**, **8**, **9**, **11**, **13**, **15**, **17** and **19**). The reaction time and the chemical yield are listed in Table 1 and Table 2. In the case of indoles (**20-25**), reaction time was 18 h and the starting materials were recovered. **20**: (*C. roseus* cell):

recovered **20** (70%), (*N. tabacum* cell): recovered **20** (70%), (*D. carota* cell): recovered **20** (90%), (C. sinensis cell): recovered **20** (75%). **21**: (*C. roseus* cell): recovered **21** (68%), (*N. tabacum* cell): recovered **21** (72%), (*D. carota* cell): recovered **21** (70%), (C. sinensis cell): recovered **21** (75%). **22**: (*C. roseus* cell): recovered **22** (71%), (*N. tabacum* cell): recovered **22** (70%), (*D. carota* cell): recovered **22** (69%), (C. sinensis cell): recovered **22** (74%). **23**: (*C. roseus* cell): recovered **23** (62%), (*N. tabacum* cell): recovered **23** (71%), (*D. carota* cell): recovered **23** (76%), (C. sinensis cell): recovered **23** (80%). **24**: (*C. roseus* cell): recovered **24** (73%), (*N. tabacum* cell): recovered **24** (72%), (*D. carota* cell): recovered **24** (74%), (C. sinensis cell): recovered **24** (76%). **25**: (*C. roseus* cell): recovered **25** (70%), (*N. tabacum* cell): recovered **25** (77%), (*D. carota* cell): recovered **25** (73%), (C. sinensis cell): recovered **25** (72%).

17: ^{1}H-NMR ($CDCl_3$) δ: 2.21 (3H, s), 2.36 (3H, s), 2.71 (3H, s), 7.36 (1H, dd, *J*=8.6, 1.4 Hz), 7.67 (1H, d, *J*=1.4 Hz), 8.51 (1H, d, *J*=8.2 Hz), 11.57 (1H, br s). mp 123-124°C (lit.[38] mp 123.5-124.5°C).

Reaction of Indoles (7, 10, 12, 14, 16, 18 and **20-25) with $NaIO_4$**

To a stirred solution of indoles (**7**, **10**, **12**, **14**, **16**, **18**, and **20-25)** (2.1 mmol) in MeOH (10 mL) was added $NaIO_4$ (1.3 g) in water (10 mL) at 0°C. The solution was stirred for at rt. The reaction mixture was extracted with AcOEt (20 ml). The AcOEt extract was washed with brine (10 ml), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography using CH_2Cl_2–MeOH (50:1) to afford oxidative cleavage products (**8**, **11**, **13**, **15**, **17**, and **19**), *N*-(2-benzoylphenyl)benzamide[39] [mp 89-90°C (lit.,[38] mp 89-90°C)] and 2'-acetyl-4'-bromobenzanilide[40] [^{1}H-NMR ($CDCl_3$) δ: 2.55 (3H, s), 7.08-7.65 (8H, m), 8.63(1H, br s)]. The reaction time and the chemical yield of indoles (**7**, **10**, **12**, **14**, **16**, and **18**) are listed in Table 2.

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