Microbial Hydroxylation of Cedrol and Cedrene

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Dedicated to Professor Helmut Simon on the occasion of his 60th birthday

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Biotransformation of cedrol with 5 different strains afforded 8 previously undescribed hydroxycedrols. The attack came from a hemisphere centered at C-12 approximately. At two positions epimeric pairs were formed, which could be avoided by using different strains. Contrary to previous studies of other groups we found the 2- and 12-hydroxylations as main reactions. Cedrene needed prolonged fermentation and gave lower yields than cedrol. Apart from allylic hydroxylations the oxidation pattern by *Corynespora cassiicola* DSM 62474 of cedrene and cedrol was the same. The structures of the metabolites were elucidated by 2D NMR techniques.

Introduction

To date a wealth of natural products containing tricyclic sesquiterpene skeletons are known. Many of them are biologically active, only to mention α-santalol, patchoulol, or the illudines. Total or partial syntheses of these compounds are difficult, even chemical derivatization of the natural products is often not possible. This is a challenge for biotransformation of compounds which are available in larger quantities to come to known or previously undescribed derivatives [1].

1972 Wang and coworker [2] made a biotransformation of cedrol with *Aspergillus niger* ATCC 9142 and isolated 3β-hydroxy-cedrol as the main product. Two years ago we reported on the biotransformation of isolongifolene [3] and investigated later the transformation of further sesquiterpene hydrocarbons. Microbial oxidation of humulene and caryophyllene gave slowly many products in low to moderate yields whereas oxygen-bearing compounds which are more soluble in water reacted faster and gave higher yields with fewer side products [4]. With this experience we decided to use the alcohol cedrol (**1**) instead of the hydrocarbon cedrene (**11**).

Experimental

The microorganisms were precultivated at 27 °C and 100 rpm in five 100 ml EM flasks containing 20 ml of the following medium: 1% of glucose, 1% of universalpeptone (Merck), 2% of malt extract and 0.3% of yeast extract. After 48 h (*C. cassiicola* after 96 h) the cultures were passed into five 2 liter flasks filled with 400 ml of the medium and incubated for another period of 24 h (*C. cassiicola* 48 h). The substrate (0.3 g/flask solved in 0.4 ml DMF) was added then aseptically. After 24, 48, and 72 h samples were taken and analyzed as follows: To 1 ml of culture broth 0.2 ml ethylacetate was added and shaken for 2 min prior to centrifugation. 10 µl of the extract were developed on HPTLC plates with dichloromethane–acetone 9:1 [5]. The spots were made visible by spraying with anisaldehyde-sulfuric acid in acetic acid and heating to 110 °C for 1 min.

Extraction and purification: Culture medium and mycelia were separated by filtration and both extracted three times with ethylacetate. The solvent was evaporated and the crude extract separated on Si-60 columns with a *n*-hexane/ethylacetate gradient (changing from 19:1 to 1:1). When necessary the collected fractions were purified further by preparative TLC.

Instruments used: NMR: The ^{1}H NMR spectra were obtained at 400 MHz on a Bruker WM 400 spectrometer and the ^{13}C NMR spectra at 75.5 MHz on a Bruker AM 300 spectrometer, $CDCl_3$ was the solvent and TMS the internal standard. IR: spectra were measured in chloroform on a IR Spectral-Photometer 297, Perkin Elmer. Mass spectra were recorded on a AEI 902S mass spectrometer with 70 eV. Melting points are uncorrected and were obtained at Büchi 510 melting point apparatus. Optical rotation: Perkin-Elmer Polarimeter 241.

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Biotransformation of 0.9 g cedrol with *Rhizopus stolonifer* CBS 38252 gave after 24 h 203 mg **1**, 173 mg **2**, and 8 mg **9**.

Biotransformation of 1.5 g cedrol with *Streptomyces bikiniensis* IFO 13350 gave after 72 h 250 mg **1**, 15 mg **5**, 7 mg **3**, and 4 mg **8**.

Biotransformation of 1.5 g cedrol with *Verticillium tenerum* DSM 63545 gave after 72 h 100 mg **2**, 40 mg **7**, 37 mg **1**, 25 mg **6**, 12 mg **5**, and 3 mg **10**.

Biotransformation of 0.9 g cedrol with *Streptoverticillium reticuli* DSM 40776 gave after 72 h 155 mg **1** and 5 mg **5**.

Biotransformation of 1.5 g cedrol with *Corynespora cassiicola* DSM 62474 gave after 72 h 105 mg **9**, 70 mg **1**, 30 mg **3**, and 10 mg **4**.

Biotransformation of 1.8 g cedrene with *Corynespora cassiicola* DSM 62474 gave after 72 h 83 mg **11**, 25 mg **13**, 5 mg **14**, and 3 mg **12**.

*2-Hydroxy-cedrol (**2**):* Colorless cristals, m.p. 137 °C. ^{1}H NMR: s 1.29, s 1.28, s 1.18, s 1.04 (12-H, 13-H, 14-H, 15-H). ^{13}C NMR data are listed in Table I.

$$\alpha = \frac{589\,\text{nm} \quad 578\,\text{nm} \quad 546\,\text{nm} \quad 436\,\text{nm} \quad 365\,\text{nm}}{+10.6^\circ \quad +11.2^\circ \quad +12.9^\circ \quad +23.4^\circ \quad +39.2^\circ} (c = 1.00).$$

*3β-Hydroxy-cedrol (**3**):* ^{1}H NMR: ddd 3.61 (J = 10, 10, 5; 3-H), d 0.96 (J = 7; 12-H), s 1.26 (13-H), s 1.02 (14-H), s 1.34 (15-H).

Irradiation at δ = 0.96 gave an NOE enhancement at δ = 3.61. ^{13}C NMR data are listed in Table I.

$$\alpha = \frac{589\,\text{nm} \quad 578\,\text{nm} \quad 546\,\text{nm} \quad 436\,\text{nm}}{+12.3^\circ \quad +13.0^\circ \quad +14.7^\circ \quad +23.5^\circ} (c = 1.00).$$

*3α-Hydroxy-cedrol (**4**):* Colorless cristals, m.p. 158 °C. ^{1}H NMR: qd 1.76 (J = 7.5, 4.5; 2-H), dt 4.28 (J = 5, 4; 3-H), m 1.62 (4-H), t 2.15 (J = 9; 5-H), d 0.91 (J = 7.5; 12-H), s 1.34 (13-H), s 1.01 (14-H), s 1.26 (15-H). ^{13}C NMR data are listed in Table I. MS *(m/e):* $M^+ - CH_3$ 223.1693 (223.1698 calculated for $C_{14}H_{23}O_2$).

$$\alpha = \frac{589\,\text{nm} \quad 578\,\text{nm} \quad 546\,\text{nm} \quad 436\,\text{nm} \quad 365\,\text{nm}}{+2.1^\circ \quad +2.2^\circ \quad +2.6^\circ \quad +5.0^\circ \quad +8.9^\circ} (c = 1.00).$$

*4β-Hydroxy-cedrol (**5**):* Colorless cristals, m.p. 118 °C. ^{1}H NMR: m 2.15 (2-H), ddd 1.90 (J = 12, 6, 3; 3-H), m 1.52 (3′-H), ddd 4.34 (J = 6, 4, 3; 4-H), d(br) 1.75 (J = 6; 5-H), d(br) 1.64 (J = 5; 7-H), m 1.86 (9α-H), m 1.38 (9β-H), m 1.8 (10-H), d(br) 1.51 (J = 13; 11-H), m 1.76 (11′-H), d 0.90 (J = 7; 12-H), s 1.42 (13-H), s 1.34 (14-H), s 1.27 (15-H), long-range couplings between 5-H and 11-H, 9α-H and 15-H, 3-H and 12-H, 3′-H and 12-H from COSY. ^{13}C NMR data are listed in Table I. MS *(m/e):* M^+ 238.1928 (238.1933 calculated for $C_{15}H_{26}O_2$).

$$\alpha = \frac{589\,\text{nm} \quad 578\,\text{nm} \quad 546\,\text{nm} \quad 436\,\text{nm} \quad 365\,\text{nm}}{+5.9^\circ \quad +6.0^\circ \quad +7.2^\circ \quad +14.0^\circ \quad +26.0^\circ} (c = 1.00).$$

*9β-Hydroxy-cedrol (**6**):* ^{1}H NMR: m 1.72 (2-H), m 1.87 (3-H), m 1.28 (3′-H), m 1.39 (4-H), m 1.54 (4′-H), t 1.75 (J = 6; 5-H), d 1.67 (J = 3.5; 7-H), dd 4.08 (J = 11, 7; 9-H), m 1.85 (10-H), dd 1.21 (J = 11, 7; 10′-H), ddd 1.62 (J = 9, 2, 2; 11-H), d 1.38 (J = 9; 11′-H), d 0.86 (J = 6; 12-H), s 1.28 (13-H), s 0.99 (14-H), s 1.22 (15-H), long-range couplings between 5α-H and 11α-H, 10α-H and 11β-H, 13-H and 14-H from COSY. ^{13}C NMR data are listed in Table I. MS *(m/e):* M^+ 238.1928 (238.1933 calc. for $C_{15}H_{26}O_2$).

$$\alpha = \frac{589\,\text{nm} \quad 578\,\text{nm} \quad 546\,\text{nm} \quad 436\,\text{nm}}{+0.2^\circ \quad +0.4^\circ \quad +0.9^\circ \quad +1.6^\circ} (c = 1.00).$$

*10β-Hydroxy-cedrol (**7**):* Colorless cristals, m.p. 88 °C. ^{1}H NMR: m 1.87 (2-H), m 1.9 (3-H), m 1.6 (4-H), d(br) 1.60 (J = 4; 7-H), dd 2.00 (J = 14, 4; 9α-H), ddd 1.77 (J = 14, 2, 2; 9β-H), ddd 3.96 (J = 4, 2, 2; 10-H), d(br) 1.92 (J = 12; 11-H), ddd 1.52 (J = 12, 5, 2; 11′-H), d 0.92 (J = 7; 12-H), s 1.03 (13-H), s 1.28 (14-H), s 1.45 (15-H), long-range couplings between 5-H and 11-H, 9α-H and 15-H, 7-H and 14-H, 7-H and 9β-H, 11α-H and 14-H, 13-H and 14-H from COSY. ^{13}C NMR data are listed in Table I. MS *(m/e):* M^+ 238.1928 (238.1933 calculated for $C_{15}H_{26}O_2$).

$$\alpha = \frac{589\,\text{nm} \quad 578\,\text{nm} \quad 546\,\text{nm} \quad 436\,\text{nm} \quad 365\,\text{nm}}{-9.8^\circ \quad -10.1^\circ \quad -11.3^\circ \quad -17.8^\circ \quad -24.5^\circ} (c = 1.00).$$

*10α-Hydroxy-cedrol (**8**):* ^{1}H NMR: dd 3.78 (J = 10, 6; 10-H), d 1.14 (J = 7; 12-H), s 1.04 (13-H), s 1.26 (14-H), s 1.34 (15-H). ^{13}C NMR data are listed in Table I. MS *(m/e):* $M^+ - CH_3$ 223.1691 (223.1698 calculated for $C_{14}H_{23}O_2$).

$$\alpha = \frac{589\,\text{nm} \quad 578\,\text{nm} \quad 546\,\text{nm} \quad 436\,\text{nm}}{+4.7^\circ \quad +4.8^\circ \quad +5.7^\circ \quad +9.9^\circ} (c = 1.00).$$

*12-Hydroxy-cedrol (**9**):* Colorless cristals, m.p. 126 °C. ^{1}H NMR: m 1.77 (2-H), m 1.89 (3-H), m 1.39 (3′-H), m 1.52 (4-H), m 1.41 (4′-H), t 1.82 (J = 8; 5-H), d 1.58 (J = 5; 7-H), m 1.84 (9-H), m 1.68 (9′-H), ddd 1.53 (J = 12, 12, 5; 10-H), m 1.44 (10′-H), m 1.69 (11-H), d 1.46 (J = 13; 11′-H), dd 3.67 (J = 10, 7; 12-H), dd 3.48 (J = 10, 8; 12′-H),

s 1.31 (13-H), s 1.00 (14-H), s 1.25 (15-H), long-range couplings between 7-H and 13-H, 9-H and 15-H, 11′-H and 13-H, 13-H and 14-H from COSY. ^{13}C NMR data are listed in Table I.

$$\alpha = \frac{589\,\text{nm} \quad 578\,\text{nm} \quad 546\,\text{nm} \quad 436\,\text{nm} \quad 365\,\text{nm}}{+7.3^\circ \quad +7.6^\circ \quad +8.4^\circ \quad +14.1^\circ \quad +22.2^\circ} (c = 1.00).$$

2,10β-Dihydroxy-cedrol (***10***): ^{1}H NMR: m 4.05 (10-H), s 1.28 (12-H), s 1.08 (13-H), s 1.31 (14-H), s 1.45 (15-H). ^{13}C NMR data are listed in Table I. MS *(m/e)*: M^+ 254.1877 (254.1882 calculated for $C_{15}H_{26}O_3$).

$$\alpha = \frac{589\,\text{nm} \quad 578\,\text{nm} \quad 546\,\text{nm} \quad 436\,\text{nm}}{-6.3^\circ \quad -6.7^\circ \quad -7.6^\circ \quad -12.0^\circ} (c = 1.00).$$

3α,15-Dihydroxy-cedrene (***12***): ^{1}H NMR: qd 1.87 (J = 7.5, 4.5; 2-H), ddd 4.35 (J = 5, 5, 5; 3-H), m 1.62 (4-H), m 1.64 (4′-H), d(br) 1.99 (J = 4; 7-H), s(br) 5.52 (9-H), d(br) 2.29 (J = 11; 10-H), m 1.96 (10′-H), ddd 1.73 (J = 11, 4, 1; 11-H), d 1.48 (J = 11; 11′-H), d 0.92 (J = 7.5; 12-H), s 1.02 (13-H), s 0.98 (14-H), d 4.06 (J = 13; 15-H), d 3.96 (J = 13; 15′-H). MS *(m/e)*: M^+ 236.1775 (236.1776 calculated for $C_{15}H_{26}O_2$).

$$\alpha = \frac{589\,\text{nm} \quad 578\,\text{nm} \quad 546\,\text{nm} \quad 436\,\text{nm} \quad 365\,\text{nm}}{-36.5^\circ \quad -38.2^\circ \quad -44.0^\circ \quad -83.9^\circ \quad -148.0^\circ} (c = 0.25).$$

12,15-Dihydroxy-cedrene (***13***): ^{1}H NMR: s(br) 5.46 (9-H), dd 3.67 (J = 10, 7; 12-H), dd 3.49 (J = 10, 8; 12′-H), s 1.01 (13-H), s 0.99 (14-H), d 4.02 (J = 12; 15-H), d 3.93 (J = 12; 15′-H). ^{13}C NMR data are listed in Table I. MS *(m/e)*: M^+ 236.1770 (236.1776 calculated for $C_{15}H_{26}O_2$).

$$\alpha = \frac{589\,\text{nm} \quad 578\,\text{nm} \quad 546\,\text{nm} \quad 436\,\text{nm}}{-60.3^\circ \quad -63.2^\circ \quad -72.8^\circ \quad -137.0^\circ} (c = 1.00).$$

10,12,15-Trihydroxy-cedrene (***14***): ^{1}H NMR: m 2.32 (2-H), dddd 1.88 (J = 12, 5.5, 5.5, 5.5; 3-H), dddd 1.58 (J = 12, 12, 10, 5.5; 3′-H), dddd 1.75 (J = 12.5, 12, 12, 5.5; 4-H), m 2.11 (4′-H), ddd 1.48 (J = 12, 5.5, 1.5; 5-H), d(br) 2.06 (J = 4; 7-H), dt 5.84 (J = 3, 1.5; 9-H), dt 3.64 (J = 3, 1.5; 10-H), dd 1.66 (J = 11, 4; 11-H), d 1.34 (J = 11; 11′-H), dd 4.26 (J = 9.5, 8.5; 12-H), dd 3.50 (J = 9.5, 7.5; 12′-H), s 1.05 (13-H), s 0.99 (14-H), dt 4.12 (J = 14.5, 1.5; 15-H), dt 4.06 (J = 14.5, 1.5; 15′-H).

$$\alpha = \frac{589\,\text{nm} \quad 578\,\text{nm} \quad 546\,\text{nm} \quad 436\,\text{nm}}{-59.1^\circ \quad -61.1^\circ \quad -72.4^\circ \quad -209.0^\circ} (c = 0.25).$$

Results

After a screen of 47 microorganisms the following strains were selected for biotransformation of cedrol in preparative scale: *Rhizopus stolonifer* CBS 38252, *Streptomyces bikiniensis* IFO 13350, *Verticillium tenerum* DSM 63545, *Streptoverticillium reticuli* DSM 40776, *Corynespora cassiicola* DSM 62474.

From these transformations 9 different products were isolated all being hydroxylation products of cedrol. Their structures were elucidated mainly by ^{1}H and ^{13}C NMR spectroscopy. Here the problem occurred that some cedrols exhibited only few re-

Table. ^{13}C NMR data of **1**–**10** and **13** (75.5 MHz, $CDCl_3$, TMS as internal standard).

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**13**
C-1	s 54.1	s 57.6	s 50.9	s 52.7	s 53.1	s 54.2	s 60.1	s 58.4?	s 53.5	s 60.4	s 53.2
C-2	d 41.5	s 79.5	d 50.2	d 46.0	d 38.0	d 41.2	d 38.0	d 44.7	d 50.6	s 76.5	d 50.9
C-3	t 37.0	t 36.6	d 81.5	d 79.9	t 46.5	t 36.8	t 34.3	t 40.2	t 32.3	t 39.7	t 31.7
C-4	t 25.3	t 21.5	t 32.2	t 32.8	d 73.3	t 25.6	t 24.0	t 26.4	t 26.0	t 21.5	t 25.5
C-5	d 61.1	d 59.2[a]	d 52.8	d 54.3	d 61.2	d 57.4	d 53.7	d 52.7	d 57.7	d 52.2	d 60.6
C-6	s 43.4	s 44.9	s 42.7	s 42.9	s 45.1	s 43.2	s 44.2	s 43.2	s 43.3	s 44.7	s 48.0
C-7	d 56.5	d 53.7[a]	d 61.0	d 61.5	d 62.9	d 60.9	d 59.8	d 61.2	d 61.5	d 59.0	d 50.7
C-8	s 75.0	s 74.8	s 74.9	s 74.9	s 74.9	s 78.6	s 74.7	s 74.6	s 75.2	s 74.3	s 144.3
C-9	t 35.3	t 35.6	t 35.4	t 35.0	t 34.9	d 74.5	t 43.7	t 45.5	t 35.2	t 43.5	d 119.7
C-10	t 31.6	t 30.1	t 34.3	t 33.9	t 31.5	t 41.4	d 71.6	d 72.2	t 31.2	d 72.0	t 38.1
C-11	t 42.0	t 41.3	t 43.2	t 42.4	t 42.9	t 40.1	t 34.7	t 40.3	t 42.8	t 31.0	t 41.3
C-12	q 15.5	q 24.3	q 12.4	q 9.7	q 15.1	q 15.7	q 15.5	q 14.7	t 63.9	q 23.9	t 63.4
C-13	q 27.6	q 28.4	q 29.6	q 29.1	q 30.1	q 29.1	q 28.5	q 29.4	q 27.7	q 28.9	q 27.6
C-14	q 28.9	q 27.5	q 27.4	q 27.5	q 28.9	q 27.9	q 29.2	q 27.4	q 29.2	q 28.8	q 25.7
C-15	q 30.2	q 30.4	q 30.2	q 30.2	q 30.3	q 24.1	q 32.5	q 31.6	q 30.5	q 32.6	t 67.1

[a] Assignments may be interchanged.

solved protons so their ^{13}C NMR spectra were used to elucidate the structure. For this purpose 2D NMR techniques were applied for the assignments of the carbons [6]. The protons of 12-hydroxy-cedrol (**9**) were identified *via* homonuclear double resonance or 2D chemical shift correlation ("COSY"). Important informations concerning the relative configuration of the molecule were obtained from the long-range couplings, especially "W"-couplings (Fig. 1).

Once the ^{1}H NMR data had been assigned, the carbons can be identified by heteronuclear double resonance ($^{1}H/^{13}C$) (Fig. 2). This procedure was also applied for 4β- and 10β-hydroxy-cedrol (**5**) and (**7**). These data were used to assign the ^{13}C NMR data of the remaining compounds. By comparison of the ^{13}C shifts the relative configuration of the additional hydroxy group could also be deduced. So 10α- and 10β-hydroxy-cedrol (**8**) and (**7**) were distinguished by different shifts caused by the γ-effect at C-11 and the δ-effect at C-3 and C-15. The differences of these effects were not so pronounced with 3α- and 3β-hydroxy-cedrol (**4**) and (**3**), so nuclear Overhauser enhancement difference ^{1}H NMR spectra were also used to elucidate the configurations.

The biotransformation products are shown in Fig. 3. The different yields reveal that the main attack occurred at C-2 and C-12. 3- and 10-hydroxy-cedrols were formed in epimeric pairs. Their formation could be avoided by using different strains. So *Streptomyces bikiniensis* formed 10α-hydroxy-cedrol (**8**), while *Verticillium tenerum* gave only 10β-hydroxy-cedrol (**7**).

For comparison cedrene was transformed by *Corynespora cassiicola* DSM 62474, too. Even prolonged fermentation gave a much lower yield than that of cedrol. Beside hydroxylation at allylic positions the 12-hydroxylation was again the main reaction (Fig. 4). Because the overall yield was very low, it must be assumed that the total degradation is the favoured pathway.

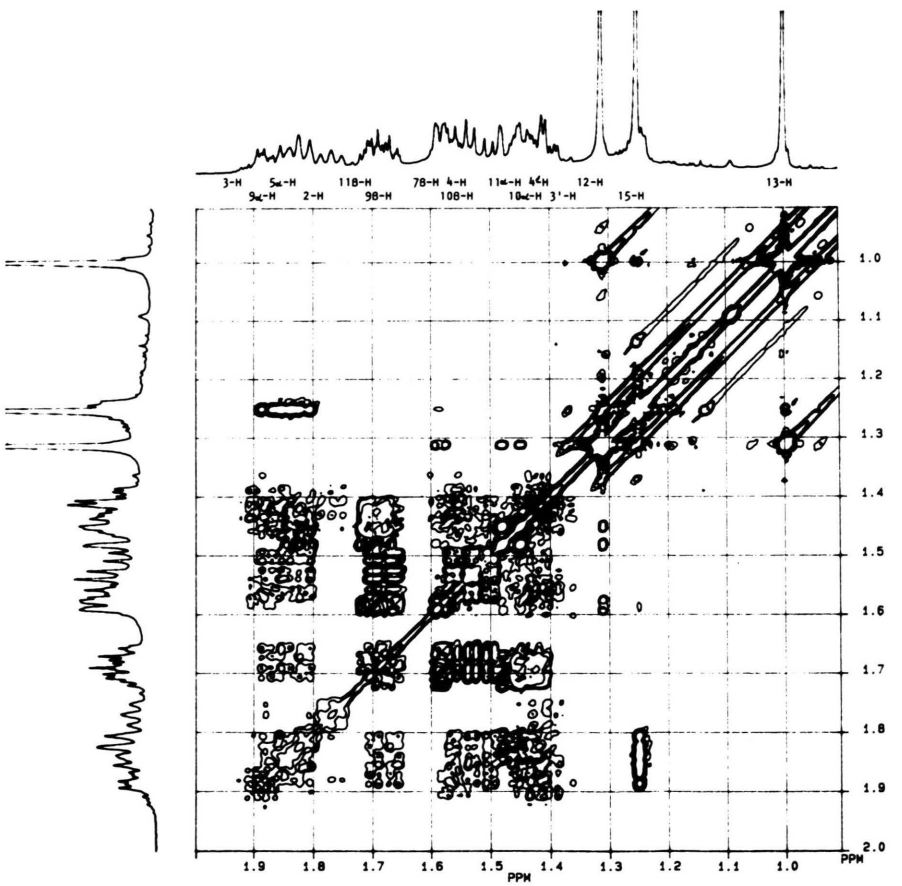

Fig. 1. "COSY" NMR spectrum of 12-hydroxy-cedrol (**9**). (Resonances of 12-H not shown.)

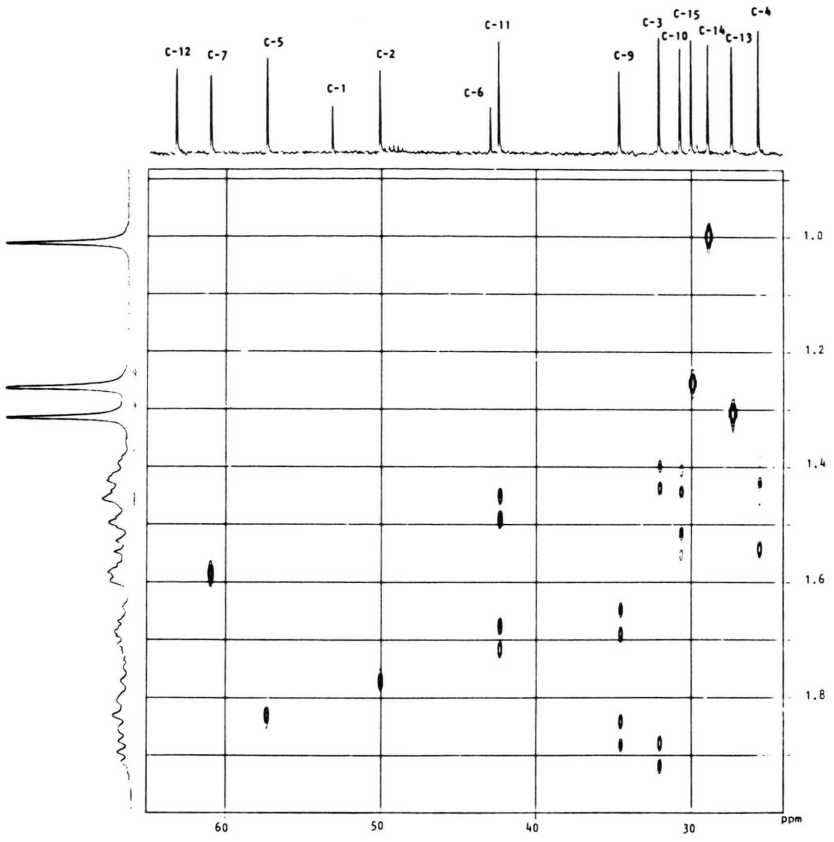

Fig. 2. $^{1}H/^{13}C-2D$ NMR spectrum of 12-hydroxy-cedrol (**9**). (Resonances of C-8 and 12-H not shown.)

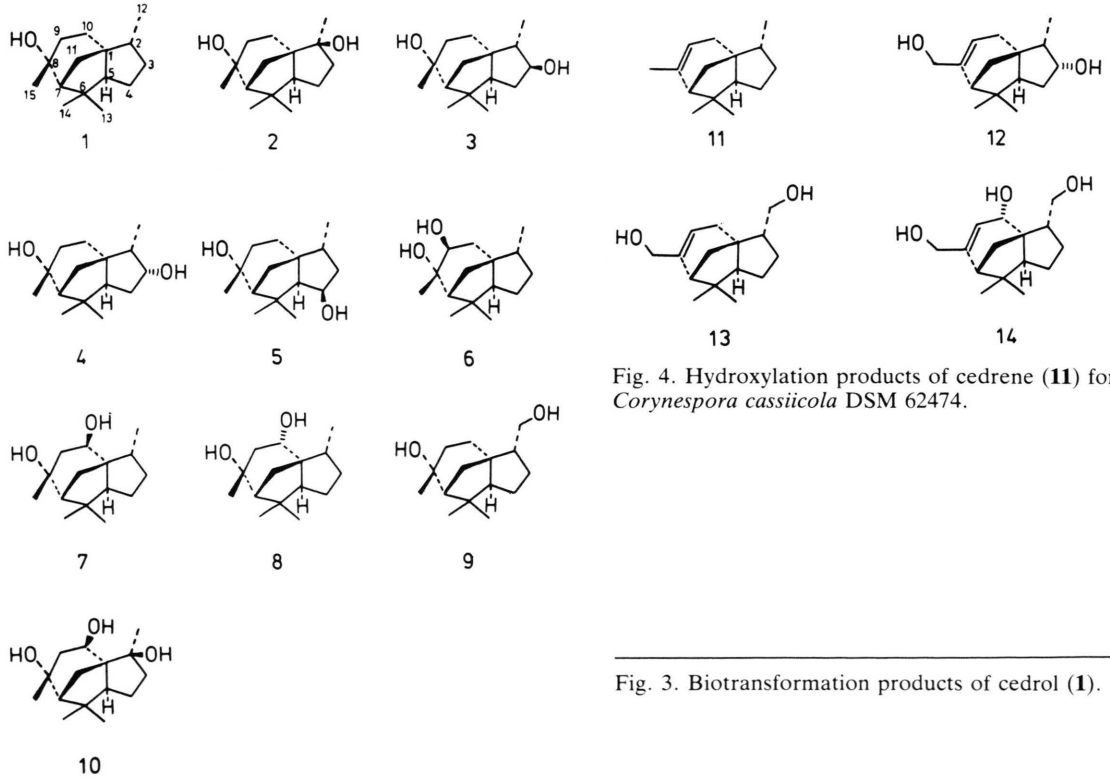

Fig. 4. Hydroxylation products of cedrene (**11**) formed by *Corynespora cassiicola* DSM 62474.

Fig. 3. Biotransformation products of cedrol (**1**).

Conclusions

Biotransformation of cedrol with 5 different strains afforded 8 previously undescribed hydroxycedrols. The attack came from one side of the molecule in a hemisphere centered at C-12 approximately. At two positions epimeric pairs were formed, which could be avoided by using different strains. Outside of this hemisphere no attack was observed, the geminal methyl groups were also not oxidized. Contrary to Wang and coworkers we found the 2- and 12-hydroxylations as the main reactions, the 3β-oxidation led only to a side product. Cedrene which was also used as substrate needed prolonged fermentation and gave lower yields than cedrol. Apart from allylic hydroxylations the oxidation pattern by *Corynespora cassiicola* DMS 62474 of cedrene and cedrol was the same.

Beside of the production of previously unknown sesquiterpenes and the study of the selectivity of the strains used, the biotransformation presented here produced valuable data for NMR spectroscopy. To date the prediction of ^{13}C NMR shifts of these complex molecules is relatively uncertain. Now the effects of additional hydroxy groups in the cedrol molecule can be deduced from the data of the cedrols described here. Thus additional data are now available to predict the shifts of related substances.

12-Hydroxy-cedrol (**9**) can easily be oxidized to give isocedrolic acid, a natural product isolated in 1976 by Kuo *et al.* [7] from *Juniperus squamata* Lamb. Some of these biotransformation products were formed in sufficient amounts for tests of their biological activity. These investigations are still in progress.

Acknowledgement

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