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Lipase-catalyzed resolution of 5-acetoxy-1,2-dihydroxy-1,2,3,4-tetrahydronaphthalene. Application to the synthesis of (+)-(3*R*,4*S*)-*cis*-4-hydroxy-6-deoxyscytalone, a metabolite isolated from *Colletotrichum acutatum*

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ABSTRACT

(+)-*cis*-4-Hydroxy-6-deoxyscytalone, a natural product bio-synthesized by *Colletotrichum* sp., has been prepared and its absolute configuration confirmed as 3*R*,4*S*, the key step being a kinetic racemic resolution of a *cis*-diol easily obtained from commercial 1,2,3,4-tetrahydronaphthalen-1,5-diol. Four lipases and different reaction conditions were tested in order to obtain the best yield and enantiomeric excess. Confirmation of absolute configuration was made by NMR using a single-derivatization low-temperature procedure and MPA as the auxiliary reagent.

1. Introduction

The phytopathogen genus *Colletotrichum* (teleomorph *Glomerella*), is an important post-harvest pathogen. This is a widespread pathogen that causes anthracnose disease. *Colletotrichum* can affect a wide variety of tropical and subtropical plants such as avocado, strawberry, tomato, cereals, legumes, vegetables, etc. The fungi not only affect plants, but also stored fruit and plant materials. The symptoms of anthracnose are stunted growth and chlorosis and the appearance of dark and necrotic spots and yellow-orange masses of spores on plant tissue. The fungi affect leaves, petioles, crowns, rots, flowers, blight, fruits, and buds, ultimately killing the plant.[1] This pathogen can be found in many areas around the whole world. *Colletotrichum* is the cause of important losses in France,[2] Australia, southern Europe, Spain,[3] Norway,[4] and Finland[5] and *C. acutatum* has also been detected in Israel[6] and California.[7] Moreover legal issues are involved as *Colletotrichum acutatum* is a quarantine organism on strawberries in the EU (EC Directive 77/93).

Colletotrichum species produce phytotoxic metabolites, which induce symptoms similar to those of the pathogens themselves.[8] In the course of our search for bioactive compounds from the phytopathogen fungus *C. acutatum*, the metabolite 4-hydroxy-6-deoxyscytalone (**1**) was isolated.[9] This metabolite, also named 3,4-dihydro-3,4,8-trihydroxy-1(2*H*)-naphthalenone and *cis*-3,4,8-trihydroxytetralone, is a phytotoxic substance, which was first isolated from *Pyricularia oryzae* by Iwasaki et al. in 1972.[10,11] This substance stunts the growth of rice seedlings at high concentrations but can also stimulate the growth of seedlings at low concentrations after 24 h. 3,4,8-Trihydroxytetralone was also isolated from *Ceratocystis fimbriata coffe*[12] in 1996 and *Fusidium* sp.[13] in 2002 and from endophytic *Colletotrichum gloeosporioides* by Inácio et al. in 2006.[14] The antifungal activity displayed by **1** was similar to that exhibited by the positive control nystatin.[14]

4-Hydroxy-6-deoxyscytalone is an important melanin biosynthetic intermediate in fungi. Several studies involving melanin-deficient mutants and inhibitors (i.e., tricyclazole) have shown that melanin plays an important role in fungi virulence.[15] Melanin-deficient mutant strains were less aggressive than their wild counterparts.

The configuration of (+)-**1** was proposed as 3*R*,4*S* by comparing the rotation sign with those of (+)-isosclerone whose configuration was assigned as *S* by interpretation of the optical rotatory dispersion of isosclerone dibenzoate.[16] However, the validity of that assignment has been called into question even by its own authors.[13] The great deal of confusion found in the bibliography about the stereochemistry of **1** where we found (−)-*cis*-4-hydroxy-6-deoxyscytalone represented as 3*R*,4*S*[14] prompted us to address the problem of obtaining it from an easily available compound. In this

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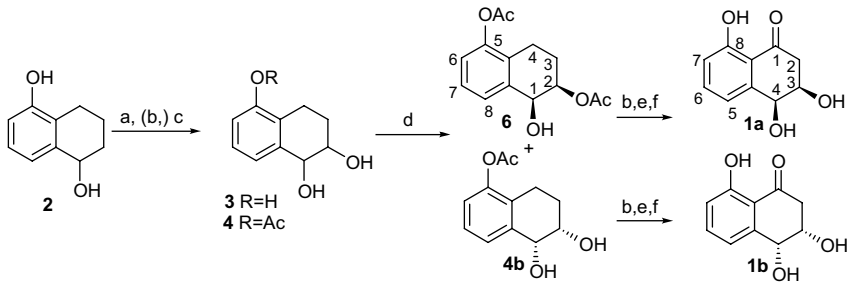


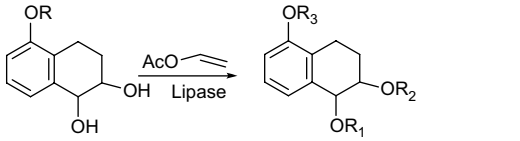
Scheme 1. Synthetic route to (+)- and (−)-*cis*-4-hydroxy-6-deoxyscytalone. (a) Benzene–TsOH, Δ; (b) Ac_2O–Py; (c) OsO_4–NMO–$^tBuO_2H$–H_2O–Py, 110 °C; (d) vinyl acetate–TBME–PSL; (e) CrO_3–Py; (f) K_2CO_3–MeOH.

article we report on its preparation using a biocatalytic racemic resolution of a *cis*-diol, easily obtained from a commercial 1,2,3,4-tetrahydronaphthalen-1,5-diol and the confirmation of its absolute configuration by NMR.

2. Results and discussion

Our initial approach to the preparation of **1** was based on the synthetic route shown in Scheme 1. (±)-*cis*-1,2,5-Trihydroxy-1,2,3,4-tetrahydronaphthalene (**3**) and (±)-*cis*-5-acetoxy-1,2-dihydroxy-1,2,3,4-tetrahydronaphthalene (**4**) were prepared from commercially available 1,2,3,4-tetrahydronaphthalene-1,5-diol (**2**), by elimination of the hydroxyl group using *p*-TsOH, acetylation (only for the synthesis of **4**) and then dihydroxylation under standard conditions (catalytic OsO_4–NMO). The lipase mediated kinetic resolution of **3** and **4** was then studied by testing different lipases, substrates, and reaction conditions.

Four lipases: PS (PSL) and AK Amano, *Candida rugosa* (CRL) and porcine pancreas lipases (PPL), and two different substrates **3** and **4** were tested (Scheme 2).



3 R=H
4 R=Ac

5 R_1=R_3=Ac, R_2=H
6 R_1=H, R_2= R_3=Ac
6a R_1=(*R*)-MPA, R_2= R_3=Ac
6b R_1=(*S*)-MPA, R_2= R_3=Ac
7 R_1=R_2=R_3=Ac
8 R_1=R_3=H, R_2=Ac
8a R_1=(*R*)-MPA, R_2=Ac, R_3=H

Scheme 2. Kinetic resolution of **3** and **4**.

PPL was rejected as a possible catalyst due to the slow conversion observed. Results obtained with the other three enzymes are shown in Table 1. Enantiomeric excess (ee) were measured by HPLC fitted with a chiral column.

The best results were obtained with PSL, which was highly selective under the initial testing conditions. Different results were obtained depending on the substrate and the lipase used. CRL was not completely regioselective on substrate **4** leading to compounds **5** and **6** in low yields while lipases AK and PS showed different regioselectivity yielding **5** and **6**, respectively. Although the yield obtained using PSL was lower than that obtained with lipase AK, stereoselectivity was significantly better.

Similar behavior was observed with the three enzymes starting from triol **3**. The same regioselectivity was observed in all cases yielding in majority the product of acetylation in both the phenol and the hydroxyl group on C-2 position ranging from low enantioselectivities (44%) when CRL was used to very high (99.96%) with

Table 1
Results of lipase mediated acetylation at room temperature for 48 h

Sub	Lipase	Products				Residual alcohol		*E*
		6		**5**				
		ee (%)	Yield[a] (%)	ee (%)	Yield[a] (%)	ee (%)	Yield[a] (%)	
4	CRL	44	11	15	1	19	20	3.4[b]
	AK			32	36	95	34	6.2
	PSL	100	19			70	37	>400
		6		**8**				
3	CRL	44	11			57	15	4.8
	AK	89	8	93	7	53	23	30[b]
	PSL	>99	12	>99	6	39	48	81.7[b]

[a] Isolated yield.
[b] Calculated considering ee of compound **6** as eep.

PSL. Also, mono-acetylated and fully acetylated compounds **8** and **7** were obtained with AK and PSL.

Based on the best value of selectivity obtained (E>400), we chose **4** as the starting material and lipase PS to carry out a reaction conditions' study with the aim of attaining the best yield with the highest enantioselectivity possible.

Temperature, time, and the effect of *tert*-butylmethyl ether (TBME) as a solvent on the enantiomeric excesses and conversion were evaluated. The reaction was carried out at room temperature (rt) and at 48 °C, which is the optimum reaction temperature for PSL, and with and without TBME for 72 h. The results shown in Table 2 indicate that temperature accelerates the kinetics of enzymes yielding di- and triacetylated compound in excellent ee.

In view of the results shown in Tables 1 and 2, the best enantiomeric excess was obtained under the initial conditions but in a poor yield. So we used initial conditions to obtain enantiomerically pure **6** and **8** in order to determine its absolute configuration and chose 48 °C, 72 h, and TBME as the best conditions for continuing the synthetic route. Under these conditions we obtained di- and triacetylated compounds with an overall yield of 46% and excellent enantiomeric excess and recovered starting material enriched in 95% ee.

In accordance with the Kazlauskas empirical rule for secondary alcohols,[17] 1*S*,2*R*-**6** and **7** along with unreacted alcohol **4** highly enriched in enantiomer 1*R*,2*S* should be obtained. All attempts to

Table 2
Results of PSL-mediated acetylation of diol **4** for 72 h

	Residual alcohol		**6**			**7**		
	ee (%)	Yield[a] (%)	ee (%)	Yield[a] (%)	E_1	ee (%)	Yield[a] (%)	E_2
rt, TBME	84	30	98	29	>400	—	—	
48 °C, TBME	95	37	91	38	90.5	>99	8	>400
rt, solvent free	38	47	87	39	1.9	—	—	
48 °C, solvent free	88	35	70	33	16.3	99	11	>400

[a] Isolated yield.

assign the absolute configuration of compound **6** were unsuccessful. Treatment of **6** with *R* (−) and *S* (+)-MPA led to the securing of the corresponding *R* and *S*-MPA esters **6a** and **6b**, respectively. ^{1}H NMR spectra of both compounds were compared but the signals of neighboring protons to the ester group in the diastereoisomeric derivatives were too close to be distinguished (small $\Delta\delta^{RS}$) and we therefore decided to use the single-derivatization low-temperature procedure.[18] The NMR spectrum of **6a** was recorded at −70 °C and compared with that recorded at 25 °C but the signals were again to close to be distinguished. Confirmation of absolute configuration was finally made using single-derivatization low-temperature procedure on compound **8**. Compound **8** was treated with *R* (−)-MPA leading to the corresponding *R*-MPA ester **8a**. Comparison of the chemical shifts in ^{1}H NMR spectra taken both at 25 °C and at −70 °C showed that $\Delta\delta^{T1T2}$ value for H2, H-3a, and H-3b was 0.08, 0.11, and 0.09 ppm, respectively, while the $\Delta\delta^{T1T2}$ for H-7 and H8 was −0.08 and −0.06 ppm. Application of Riguera's rule[18] showed a 1*S*,2*R* configuration for esterified product **8a** and hence for compound **8**. This stereochemistry coincides with that predicted by the Kazlauskas' rule for transesterification reactions catalyzed by lipases.

Compound **6** and residual alcohol **4**, highly enriched in enantiomer 1*R*,2*S*, were acetylated under standard conditions (Ac_2O, Py). Triacetylated compounds were oxidized in position 1 with CrO_3 and acetic acid. Deprotection with K_2CO_3 and ethanol gave a very poor yield, leading to the two enantiomers of *cis*-4-hydroxy-6-deoxyscytalone. Comparison of specific rotations of natural and synthetic triacetylated derivative of **1** allows us to confirm the absolute configuration for (+)-*cis*-4-hydroxy-6-deoxyscytalone as 3*R*,4*S*.

3. Conclusions

Preparation of enantiomerically pure (+) and (−)-*cis*-4-hydroxy-6-deoxyscytalone allowed us to confirm the absolute stereochemistry of (+)-*cis*-4-hydroxy-6-deoxyscytalone proposed by Krohn et al.[13] for natural product obtained from *Colletotrichum* sp. The absolute stereochemistry was established via the transesterification kinetic resolution of racemic diol (±)-**4** and confirmed by NMR using a single-derivatization low-temperature procedure. The optimal conditions for kinetic racemic resolution have been established.

4. Experimental section

4.1. General

IR spectra were recorded on a Perkin–Elmer FT-IR System Spectrum BX spectrophotometer. ^{1}H and ^{13}C NMR spectra were taken with an Inova-400 MHz instrument and mass spectra were determined with a Voyager (Termoquest) spectrometer. Air sensitive reactions were run under an argon atmosphere. Solvents were distilled by normal methods (THF was dried over sodium–benzophenone, CH_2Cl_2 was dried over $CaCl_2$). TLC was performed on Merck Kieselgel 60 F_{254}, 0.2 mm thick Silica gel 60PF_{254} (60–100 mesh, Merck) was used for column chromatography. HPLC was performed with a Hitachi/Merck L-6270 apparatus equipped with a UV–vis detector (L 4250) and a differential refractometer detector (RI-71) using a silica gel column (Hibar 60, 7 m, 1 cm wide, 25 cm long). Chemical products were obtained from Fluka or Aldrich. All solvents used were freshly distilled. Enantiomeric excesses were determined by means of HPLC analyses on a chiral column (Chiralcel OD, Daicel, Japan).

4.1.1. 7,8-Dihydronaphthalen-1-ol

1,2,3,4-Tetrahydronaphthalene-1,5-diol (1 g, 6 mmol) and *p*-toluene sulfonic acid (420 mg, 2.2 mmol) were dissolved in dry benzene (187.5 mL). The mixture was stirred for 12 h at room temperature under nitrogen atmosphere. The mixture was then washed with distilled water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in a rotary evaporator. The residue was purified by column chromatography using EtOAC–hexane (30%) as an eluent to give 7,8-dihydronaphthalen-1-ol in 82.82% yield. IR (film): ν_{max} 3390.18, 1574.03, 1463.49, 1279.80, 808.17 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.17 (2H, m), 2.67 (2H, t, *J*=8.3 Hz), 5.86 (1H, m), 6.28 (1H, ddd, *J*=1.6, 3.3, 9.5 Hz), 6.46 (1H, d, *J*=7.4 Hz), 6.58 (1H, d, *J*=7.9 Hz), 6.84 (1H, t, *J*=8.2 Hz), 7.15 (1H, s, OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 19.5 (1C, t), 22.5 (1C, t), 114.5 (1C, d), 118.9 (1C, d), 120.6 (1C, s), 126.7 (1C, d), 127.6 (1C, d), 128.5 (1C, d), 135.3 (1C, s), 152.2 (1C, s); EIMS *m*/*z*: 146 (M^+, 73), 144 (100), 126 (90), 115 (85).

4.1.2. 1-Acetoxy-7,8-dihydronaphthalene

7,8-Dihydronaphthalen-1-ol (86.2 mg, 0.59 mmol) and acetic anhydride (60 mg, 0.59 mmol, 55 μL) were dissolved in dry pyridine (330 μL) and the mixture was stirred for 26 h at room temperature. The excess of acetic anhydride was then eliminated with cyclohexane and acetone and evaporated in a rotary evaporator. The residue was purified by column chromatography using EtOAC–hexane (10%) as an eluent to give 1-acetoxy-7,8-dihydronaphthalene in 89.83% yield. IR (film): ν_{max} 2929.78, 1763.94, 1206.90 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.30 (3H, s), 2.30 (2H, m), 2.65 (2H, t, *J*=8.2 Hz), 6.05 (1H, dt, *J*=4.7, 9.7 Hz), 6.48 (1H, d, *J*=9.7 Hz), 6.88 (1H, dd, *J*=1.2, 8.2 Hz), 6.92 (1H, d, *J*=7.4 Hz), 7.15 (1H, dd, *J*=7.4, 8.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 20.5 (1C, t), 20.6 (1C, q), 22.2 (1C, t), 120.5 (1C, d), 123.7 (1C, d), 126.7 (1C, d), 126.9 (1C, s), 127.2 (1C, d), 128.9 (1C, d), 135.6 (1C, s), 147.7 (1C, s), 169.1 (1C, s); EIMS *m*/*z*: 164 (M^+, 78), 122 (85), 43 (100).

4.1.3. (±)-cis-5-Acetoxy-1,2-dihydroxy-1,2,3,4-tetrahydronaphthalene (**4**)

1-Acetoxy-7,8-dihydronaphthalene (100.6 mg, 0.53 mmol), trimethylamine-*N*-oxide (82.35 mg, 0.74 mmol), pyridine (100 μL), and osmium tetroxide 2.5 wt% solution in 2-methyl-2-propanol (45 μL) were dissolved in H_2O–^{t}BuOH 1:1 (2 mL) in a 5 mL flask. The mixture was refluxed at 100 °C and stirred for 48 h. The mixture was then diluted with 10 mL of 10% $NaHSO_3$ and stirred at room temperature for 1 h. The crude was extracted with AcOEt and the organic layers were dried over anhydrous Na_2SO_4 and concentrated in a rotary evaporator. The residue was purified by column chromatography using AcOEt–hexane (30%) as an eluent to give (±)-**4** in 51.84% yield. IR (film): ν_{max} 3385.6, 2936.8, 1735.5, 1215.13 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.89 (1H, m), 2.00 (1H, m), 2.30 (3H, s), 2.52 (1H, ddd, *J*=17.5, 8.8, 6.5 Hz), 2.79 (1H, dt, *J*=17.5, 5.8 Hz), 3.98 (1H, dt, *J*=9.8, 3.7 Hz), 4.67 (1H, d, *J*=3.7 Hz), 6.96 (1H, dd, *J*=1.4, 8.0 Hz), 7.25 (1H, t, *J*=7.8 Hz), 7.36 (1H, d, *J*=7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 20.8 (1C, q), 21.0 (1C, t), 25.3 (1C, t), 68.9 (1C, d), 69.6 (1C, d), 121.5 (1C, d), 127.2 (1C, d), 127.6 (1C, d), 128.7 (1C, s), 138.4 (1C, s), 148.4 (1C, s), 169.4 (1C, s); EIMS *m*/*z*: 222 (M^+, 0.01), 204 (12), 180 (36), 162 (91), 136 (97), 43 (100).

4.1.4. (±)-cis-1,2,3,4-Tetrahydronaphthalene-1,2,5-triol (**3**)

Following the procedure described above for dihydroxylation, 7,8-dihydronaphthalen-1-ol was treated with osmium tetroxide–trimethylamine-*N*-oxide yielding **3** in 73.5% yield. IR (film): ν_{max} 3385.65, 1215.33, 1057.18 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.27 (1H, m), 1.47 (1H, m), 1.99 (1H, m), 2.32 (1H, dt, *J*=17.5, 5.6 Hz), 2.90 (2H, s, OH), 3.35 (1H, dt, *J*=2.3, 10.2 Hz), 4.02 (1H, d, *J*=3.9 Hz), 6.14 (1H, br d, *J*=7.8 Hz), 6.34 (1H, d, *J*=7.8 Hz), 6.41 (1H, t, *J*=7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 21.5 (1C, t), 25.9 (1C, t), 69.5 (1C, d), 70.2 (1C, d), 113.7 (1C, d), 121.4 (1C, d), 123.8 (1C, s), 126. 7 (1C, d, C-7), 139.2 (1C, s, C-8a), 154.6 (1C, s, C-5); EIMS *m*/*z*: 162 (M^+−18, 61), 131 (12), 120 (100), 91 (21), 69 (21).

4.2. General procedure for lipase-catalyzed kinetic resolution at room temperature

Starting material (0.255 mmol), the lipase (68.04 mg), vinyl acetate (813 mg, 9.4 mmol, 870 μL), and TBME (1.3 mL) were mixed and stirred for the period of time detailed in Table 2 at room temperature or 48 °C. TBME was omitted in solvent-free reactions.

The lipase was then filtered and the solvent evaporated in a rotary evaporator. The residue was purified by column chromatography using AcOEt–hexane (30%) as an eluent to give the diacetylated product. The yields are summarized in Table 2.

*4.2.1. (+)-2,5-Diacetoxy-1-hydroxy-1,2,3,4-tetrahydronaphthalene (**6**)*

$[\alpha]_D^{23}$ +23.94 (*c* 1.697, $CHCl_3$); IR (film): ν_{max} 3368.6, 2947.94, 1734.9, 1718.15, 1260.06 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.94 (1H, m), 2.11 (3H, s), 2.26 (1H, m), 2.30 (3H, s), 2.63 (1H, dt, *J*=7.2, 17.6 Hz), 2.77 (1H, dt, *J*=6.2, 17.6 Hz), 4.85 (1H, br s), 5.18 (1H, dt, *J*=3.1, 9.6 Hz), 6.99 (1H, dd, *J*=1.2, 7.8 Hz), 7.26 (1H, t, *J*=7.8 Hz), 7.38 (1H, d, *J*=7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 20.8 (1C, q), 20.9 (1C, t), 21.2 (1C, q), 22.3 (1C, t), 68.9 (1C, d), 72.2 (1C, d), 121.6 (1C, d), 127.0 (1C, d), 127.2 (1C, d), 128.3 (1C, s), 138.0 (1C, s), 148.4 (1C, s), 169.1 (1C, s), 170.6 (1C, s); EIMS *m*/*z*: 264 (M^+, 0.02), 246 (3), 204 (18), 162 (100), 144 (71), 133 (66), 77 (29), 43 (75).

*4.2.2. (+)-2-Acetoxy-1,5-dihydroxy–1,2,3,4-tetrahydronaphthalene (**8**)*

$[\alpha]_D^{23}$ +14.15 (*c* 1.75, $CHCl_3$); IR (film): ν_{max} 3450.32, 2935.56, 1736.21, 1214.40 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.95 (1H, m), 2.11 (3H, s), 2.28 (1H, m), 2.68 (1H, m), 2.86 (1H, dt, *J*=17.4, 5.8 Hz), 4.81 (1H, d, *J*=3.1 Hz), 5.16 (1H, dt, *J*=9.9, 3.1 Hz), 6.70 (1H, d, *J*=7.8 Hz), 7.02 (1H, d, *J*=7.81 Hz), 7.10 (1H, t, *J*=7.81 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 20.7 (1C, t), 21.3 (1C, q), 22.2 (1C, t), 22.2 (1C, q), 68.6 (1C, d), 72.6 (1C, d), 114.3 (1C, d), 121.5 (1C, d), 122.6 (1C, s), 127.2 (1C, d), 137.5 (1C, s), 153.0 (1C, s), 170.8 (2C, s); EIMS *m*/*z*: 222 (M^+, 1), 204 (0.5), 162 (100), 144 (74), 133 (71),43 (79).

*4.2.3. 1,2,5-Triacetoxy-1,2,3,4-tetrahydronaphthalene (**7**)*

2,5-Diacetoxy-1-hydroxy-1,2,3,4-tetrahydronaphthalene (**6**) (100 mg, 0.38 mmol) and acetic anhydride (38.64 mg, 0.38 mmol, 35 μL) were dissolved in dry pyridine (212 μL) and the mixture was stirred for 26 h at room temperature. The excess of acetic anhydride was then eliminated with cyclohexane and acetone and evaporated in a rotary evaporator. The residue did not need any purification and **7** was obtained in 100% yield. 1,2,5-Triacetoxy-1,2,3,4-tetrahydronaphthalene ((+)-**7**): $[\alpha]_D^{23}$ +119 (*c* 1.025, $CHCl_3$); IR (film): ν_{max} 2949.40, 1742.8, 1370.36, 1248.9, 1217.10, 1202.28 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.94 (1H, m), 2.00 (3H, s), 2.05 (3H, s), 2.15 (1H, m), 2.28 (3H, s), 2.63 (1H, ddd, *J*=6.8, 9.6, 17.6 Hz), 2.84 (1H, ddd, *J*=4.7, 5.8, 17.6 Hz), 5.19 (1H, dt, *J*=3.1, 10.9 Hz), 6.13 (1H, d, *J*=3.1 Hz), 6.98 (1H, dd, *J*=1.3, 7.8 Hz), 7.14 (1H, d, *J*=7.8 Hz), 7.18 (1H, t, *J*=7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 20.7 (1C, q), 20.9 (2C, q), 21.5 (1C, t), 22.4 (1C, t), 68.8 (1C, d), 69.5 (1C, d), 122.3 (1C, d), 127.2 (1C, d), 127.6 (1C, d), 129.0 (1C, s), 134.6 (1C, s), 148.6 (1C, s), 169.0 (1C, s), 170.3 (1C, s), 170,43 (1C, s); EIMS *m*/*z*: 306 (0.01), 204 (38), 162 (100), 144 (100), 133 (80), 43 (72).

1,2,3,4-Tetrahydro-1,2,5-triacetoxynaphthalene ((−)-**7**) was obtained from residual alcohol **5**, following the same procedure. $[\alpha]_D^{23}$ −121.52 (*c* 1.025, $CHCl_3$).

4.2.4. 3,4,8-Triacetoxytetralone

To a stirred solution of (+)-1,2,5-triacetoxy-1,2,3,4-tetrahydronaphthalene (**7**) (100 mg, 0.32 mmol) in glacial acetic acid (1.5 mL) at 5–10 °C in an ice bath was added dropwise over 15 min a solution of CrO_3 (95 mg, 0.96 mmol) in AcOH (1 mL). The resulting dark brown solution was stirred for 15 min at room temperature and then for another 15 min at 100 °C. The solvent was removed under reduced pressure and ice–water (10 mL) was added. The organic layers were extracted with Et_2O (3×5 mL), washed with H_2O (15 mL), dried over dry Na_2SO_4, filtered, and concentrated in a rotary evaporator providing a crude product. The residue was purified by chromatography using AcOEt–hexane 15:85 as an eluent to give (+)-3,4,8-triacetoxytetralone in 65% yield. $[\alpha]_D^{23}$ +95.30 (*c* 0.345, $CHCl_3$); IR (film): ν_{max} 3021.98, 1746.5, 1693.7, 1241.55, 1218.37, 1196.67 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.03 (3H, s), 2.10 (3H, s), 2.37 (3H, s), 2.87 (1H, ddd, *J*=0.7, 4.2, 17.4 Hz), 3.03 (1H, dd, *J*=9.2, 17.4 Hz), 5.51 (1H, ddd, *J*=2.9, 4.7, 9.2 Hz), 6.29 (1H, d, *J*=2.9 Hz), 7.13 (1H, dd, *J*=1.2, 7.8 Hz), 7.40 (1H, dd, *J*=0. 8, 7.8 Hz), 7.61 (1H, t, *J*=7.8 Hz); ^{13}C NMR ($CDCl_3$) δ: 20.8 (1C, q), 20.9 (1C, q), 21.0 (1C, q), 40.4 (1C, t), 67.9 (1C, d), 69.5 (1C, d), 124.0 (1C, s), 125.1 (1C, d), 127.2 (1C, d), 135.0 (1C, d), 139.3 (1C, s), 150.1 (1C, s), 169.6 (1C, s), 170.0 (1C, s), 170.2 (1C, s), 192.4 (1C, s); EIMS *m*/*z*: 320 (M^+, 48), 162 (84), 144 (100), 133 (79), 43 (91).

(−)-3,4,8-Triacetoxytetralone was obtained from (−)-**7**, following the same procedure. $[\alpha]_D^{23}$ −93.48 (*c* 0.525, $CHCl_3$).

*4.2.5. (+)-(3R,4S)-cis-4-Hydroxy-6-deoxyscytalone (**1**)*

3,4,8-Triacetoxytetralone (100 mg, 0.37 mmol) was dissolved in methanol (2 mL) containing a few drops of water and then K_2CO_3 (168 mg, 1.22 mmol) was added and the mixture stirred at room temperature for 2 h. The reaction mixture was concentrated to remove methanol, diluted with water (5 mL), and extracted with AcOEt (3×5 mL). The crude product was purified by column chromatography with hexane–AcOEt (30:70) as the eluent to give **1** in a very poor yield. The ^1H NMR was identical with that of the natural product.

*4.2.6. Acetylation of natural (+)-(3R,4S)-cis-4-hydroxy-6-deoxyscytalone (**1**)*

Compound **1** (4 mg, 0.0206 mmol), obtained from the fermentation broth of *C. acutatum*,[9] and acetic anhydride (6.28 mg, 0.062 mmol, 6 μL) were dissolved in dry pyridine (100 μL) and the mixture was stirred for 24 h at room temperature. The excess of acetic anhydride was eliminated with cyclohexane and acetone and evaporated in a rotary evaporator. The residue was purified by column chromatography using EtOAc–Hex (10%) as an eluent to give the fully acetylated natural product in a 92.13% yield. (+)-3,4,8-Triacetoxytetralone: $[\alpha]_D^{23}$ +97.13, the spectral data were identical with that previously described for synthetic compound.

*4.2.7. 2,5-Diacetoxy-1,2,3,4-tetrahydronaphthyl 1-(R)-α-methoxyphenylacetate (**6a**)*

(+)-2,5-Diacetoxy-1-hydroxy-1,2,3,4-tetrahydronaphthalene (**6**) (5 mg, 0.033 mmol), EDC (6.5 mg, 0.036 mmol, 1.1 equiv), DAMP (catalytic amount), and *R* (−)-α-methoxyphenylacetic acid (*R*-MPA) (5 mg, 0.03 mmol) were dissolved in dry DCM (1 mL) and the mixture was stirred under Ar atmosphere for 3 h at room temperature. The solvent was then evaporated in a rotary evaporator and the residue purified by HPLC using AcOEt–hexane (20%) as an eluent to give **6a** in 76.3% yield. ^1H NMR ($CDCl_3$, 400 MHz, 25 °C) δ (ppm): 1.90 (3H, s, C_2–OAc), 1.96 (1H, m, H-3a), 2.17 (1H, m, H-3b), 2.30 (3H, s, C_5–OAc), 2.63 (1H, m, H-4a), 2.84 (1H, dt, *J*=17.4, 5.5 Hz, H-4b), 3.41 (3H, s, $C_{2'}$–OMe), 4.77 (1H, s, H-2′), 5.24 (1H, dt, *J*=10.8, 3.3 Hz, H-2), 6.14 (1H, d, *J*=3.3 Hz, H-1), 6.76 (1H, br d, *J*=7.4 Hz, H-6), 6.96 (1H, dd, *J*=8.0, 1.2 Hz, H-8), 7.07 (1H, t, *J*=7.8 Hz, H-7), 7.31 and 7.40 (2H, m and 3H, m, $C_{2'}$–Ph).

*4.2.8. 2,5-Diacetoxy-1,2,3,4-tetrahydronaphthyl 1-(S)-α-methoxyphenylacetate (**6b**)*

(+)-2,5-Diacetoxy-1-hydroxy-1,2,3,4-tetrahydronaphthalene (**6**) was treated with *S* (−)-α-methoxyphenylacetic acid (*S*-MPA) following the procedure described above for **6a** yielding **6b** in 75.8% yield. IR and ^1H NMR were almost identical to those described for **6a**.

*4.2.9. 2-Acetoxy-5-hydroxy-1,2,3,4-tetrahydronaphthyl 1-(R)-α-methoxyphenylacetate (**8a**)*

(+)-2-Acetoxy-1,5-dihydroxy-1,2,3,4-tetrahydronaphthalene (**8**) was treated with *S* (−)-α-methoxyphenylacetic acid (*S*-MPA) following the procedure described above for **6a** yielding **8a** in 51.8% yield. ^{1}H NMR (CD_2Cl_2–CS_2 (1:4), 400 MHz, 25 °C) δ (ppm): 1.780 (1H, m, H-3a), 1.942 (1H, m, H-3b), 2.24 (3H, s, C_2–OAc), 2.563 (1H, m, H-4a), 2.772 (1H, ddd, J=18.0, 3.0, 1.6 Hz, H-4b), 3.34 (3H, s, $C_{2'}$–OMe), 4.64 (1H, s, H-2′), 4.920 (1H, dt, J=11.6, 3.2 Hz, H-2), 6.07 (1H, d, J=3.2 Hz, H-1), 6.934 (1H, dd, J=8.0, 1.2 Hz, H-6), 7.067 (1H, br d, J=7.2 Hz, H-8), 7.161 (1H, t, J=7.6 Hz, H-7), 7.32 and 7.25 (2H, m and 3H, $C_{2'}$–Ph); (CD_2Cl_2–CS_2 (1:4), 400 MHz, −70 °C) δ (ppm): 1.691 (1H, m, H-3a), 1.830 (1H, m, H-3b), 2.32 (3H, s, C_2–OAc), 2.530 (1H, m, H-4a), 2.752 (1H,m, H-4b), 3.32 (3H, s, $C_{2'}$–OMe), 4.68 (1H, s, H-2′), 4.841 (1H, dt, J=12.0, 3.2 Hz, H-2), 6.08 (1H, d, J=3.2 Hz, H-1), 6.963 (1H, dd, J=8.0, 1.2 Hz, H-6), 7.130 (1H, br d, J=8.0 Hz, H-8), 7.242 (1H, t, J=8.0 Hz, H-7), 7.32 (5H, m, $C_{2'}$–Ph).

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