Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 3711–3725

TETRAHEDRON: *ASYMMETRY*

First total syntheses and configurational assignments of cytotoxic trichodenones A–C

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Received 26 July 2000; accepted 17 August 2000

Abstract

Total syntheses of cytotoxic trichodenones A–C, produced by a strain of *Trichoderma harzianum* from the sponge *Halichondria okadai*, have been achieved, and the natural trichodenones B and C have been established to have (4*R*,1′*R*)- and (1′*R*)-configurations, respectively. From this synthesis and chiral HPLC analysis, it was deduced that the major molecule with *R*-configuration coexists with its enantiomer in natural trichodenone A.

1. Introduction

As part of our ongoing search for new antitumor metabolites from marine microorganisms, we have previously isolated trichodenones A–C **1**–**3** as novel cytotoxic compounds from a strain of *Trichoderma harzianum* OUPS-N115 which was isolated from the sponge *Halichondria okadai*.[1] Their planar structures were established based on spectral analyses and extensive 2D NMR experiments. These techniques, however, did not provide the information necessary for the assignment of the stereochemistry of these molecules. In order to determine their stereochemistry, we decided to synthesize these compounds in an enantiometrically pure form. We describe herein the asymmetric total syntheses of **1**–**3** in detail, which have been briefly reported in a preliminary form.[2] The key step involves the high diastereoselectivity of two nucleophilic additions to the cyclopentenone **7** and improvement of diastereoselectivity for the reduction of the ketone **8**, a key intermediate for the synthesis of **2** and **3**. These syntheses allowed assignments of the absolute configuration of trichodenones A **1**–B **3** and also clarified that trichodenone A **1** occurs as a scalemic mixture in nature.

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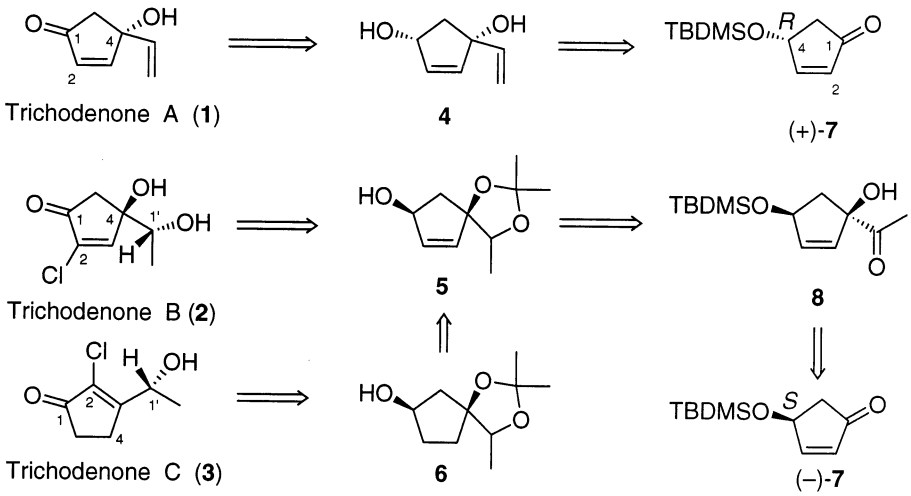
0957-4166/00/$ - see front matter
PII: S0957-4166(00)00329-3

2. Results and discussion

2.1. Synthetic strategy

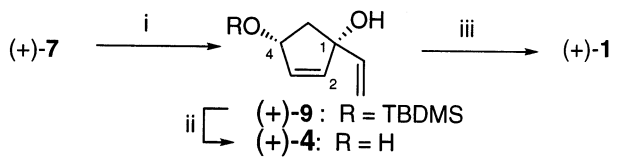
Since the stereochemistry of trichodenones A **1**–C **3** had not been elucidated, we had to devise syntheses of all the enantiomers and diastereoisomers related to them. Retrosynthetic analysis (Scheme 1) suggested that trichodenone A **1** and its enantiomer could be easily derived from 4-*tert*-butyldimethylsilyloxy(TBDMSO)-2-cyclopentenone **7**[3] or its enantiomer by a Grignard reaction. Though trichodenones B **2** and C **3** could be synthesized via **1**, it was considered that **1** is not suitable as an intermediate for their synthesis because of its volatility. Therefore, we planned to synthesize them by a C_2-unit elongation of the cyclopentenone **7** or its enantiomer using Umpolung methodology.[4] Compounds **2** and **3** and their enantiomers could be derived from the acetonide **5** of the diol obtained by reduction of the ketone **8**.



Scheme 1.

2.2. Synthesis of trichodenone A *1* and its enantiomer

Optically active cyclopentenones (+)- and (–)-**7** were used as starting materials for the synthesis of trichodenone A **1** (Scheme 2). In the presence of vinyl magnesium bromide, (+)-**7** underwent a highly diastereoselective carbonyl addition to afford the sole adduct **9** in a quantitative yield, in which the newly produced hydroxy group was established to be oriented *cis* to the TBDMSO group by the observation of an NOE of the vinyl methine proton (δ 5.91) and the C-4 methine proton (δ 4.73). Treatment of **9** with tetrabutylammonium fluoride (Bu_4NF)



Scheme 2. Reagents and conditions: (i) CH_2=CHMgBr, Et_2O, 0°C; (ii) Bu_4NF, THF, rt; (iii) PDC, CH_2Cl_2, rt

gave the diol **4** in 79% yield. Oxidation of **4** with PDC furnished (+)-(4*R*)-**1**, one of the desired molecules, in 7% yield. One cause of the low yield is its volatility. The same procedure as above with the starting material (−)-**7** gave (−)-(4*S*)-**1**. The specific rotation of the resulting (4*R*)-**1** and (4*S*)-**1** was +141.6 and −145.4, respectively. The former had the same sign of specific rotation as that of the natural product **1**, but the value was larger than that of the natural product (+56.3) reported previously.[1] This result suggested the possibility that the natural trichodenone A **1** is a scalemic mixture.

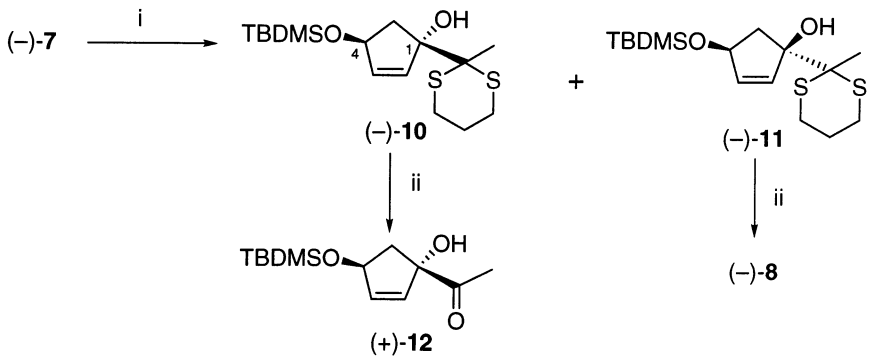
2.3. Chiral HPLC analysis of natural trichodenone A *1*

In order to investigate the enantiomeric purity of natural trichodenone A **1**, conditions for chiral HPLC analysis were examined using the synthetic compounds. The use of CHIRALPACK AS column (DAICEL) and 5% isopropyl alcohol in *n*-hexane as the eluent gave better separation of the enantiomers even though it was not enough for quantitative determination. On the other hand, a strain of *T. harzianum* was cultured anew according to the method reported previously.[1] Three samples of trichodenone A **1** isolated from the broth of three separate fermentations showed specific rotations of 0, +41 and +8.5, respectively. These samples were applied to the chiral HPLC analysis. All the samples showed the two peaks of (4*R*)- and (4*S*)-**1**, the former being a major component in the two last cases, and the roughly estimated ratios of the two peaks nearly corresponded to their specific rotations. This result showed that the major molecule with the (*R*)-configuration coexists with its enantiomer in natural trichodenone A and the ratio of the two enantiomers differed on each fermentation. Kitagawa et al.[5] have reported that there are some enantiomeric mixtures in various ratios among natural products. As described above, trichodenone A **1** is one such example.

2.4. Synthesis of the key intermediate *5* toward trichodenones B *2* and C *3*

2.4.1. Stereoselective C_2-unit elongation of the cyclopentenone *7*

Treatment of (−)-**7** with 2-lithio-2-methyl-1,3-dithiane yielded quantitatively the adducts **10** and **11** as a 1:10 mixture of diastereoisomers, which could be separated by silica gel column chromatography (Scheme 3). The thioketals **10** and **11** were deprotected with $HgCl_2$[6] to give the ketones (+)-**12** and (−)-**8**, respectively. Their relative stereochemistries were determined by



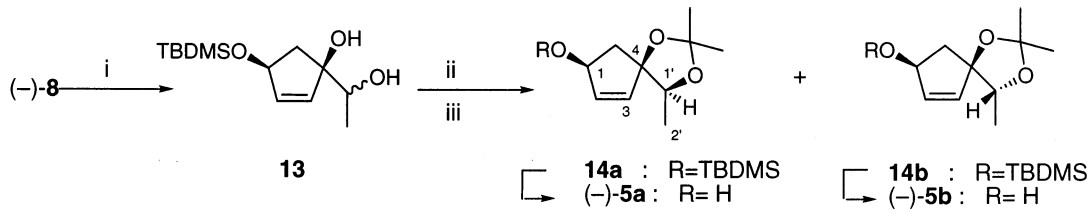
Scheme 3. Reagents and conditions: (i) 2-lithio-2-methyl-1,3-dithiane, THF, −78°C; (ii) $HgCl_2$, $CaCO_3$, CH_3CN–H_2O (4:1), rt

NOESY analysis. An NOE (1%) between H-4 and acetyl protons was observed in **8**, but not in **12**.

The ketones (−)-**12** and (+)-**8** were synthesized from (+)-**7**, using the same procedure as above with (−)-**7**.

*2.4.2. Diastereoselectivity in reduction of the ketone **8***

Reduction of the ketone (−)-**8** with $NaBH_4$ in MeOH at 0°C followed by acetonide formation afforded an approximately 1:1 mixture of the acetonide **14a** and its C2′-diastereoisomer, **14b**, of the diastereomeric diols **13** (Scheme 4), of which the formation ratio was deduced by ^1H NMR spectral analysis. The mixture of the diastereomeric acetonides was treated with Bu_4NF for deprotection of the TBDMS group to give a mixture of the alcohols (−)-**5a** and (−)-**5b**, which could be separated by silica gel column chromatography. Their relative stereochemistry was established by NOESY analysis. NOEs between H-3 and H-2′ in (−)-**5a**, and between H-3 and H-1′ in (−)-**5b** indicated the C-1′ configuration of both compounds as shown in Scheme 4. Observation of NOEs (1.8% each) between H-1 and H-2′ in **5a** and **5b** confirmed the relative chemistry of C-1 and C-4.



Scheme 4. Reagents and conditions: (i) reducing reagent; (ii) 2-methoxypropene, cat. PPTS; (iii) Bu_4NF

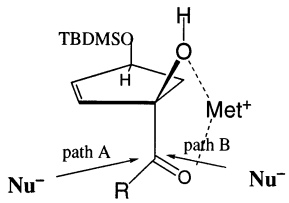
Both compounds **5a** and **5b** are useful as intermediates for the synthesis of trichodenones B and C in view of their stereochemical flexibility. Nevertheless, it seemed worthwhile to examine the diastereoselectivity in the reduction of **8**. The experiment was carried out using racemic substrates, and the results are summarized in Table 1. The ratio of the diastereomeric diols **13**

Table 1
Nucleophilic addition to compounds (±)-**8** and (±)-**15**

Run	Substrate	Method[a]	Reagent	Solvent	Reaction temperature (°C)	Overall yield	Product ratio
						14a+**14b**, %	**14a**:**14b**
1	**8**	A	$NaBH_4$	MeOH	rt	79	44:56
2	**8**	A	$NaBH_4$	MeOH	−78	78	33:67
3	**8**	A	$LiAlH_4$	Et_2O	0	79	47:53
4	**8**	A	$LiAlH_4$	Et_2O	−78	92	43:57
5	**8**	A	$LiAlH(t\text{-}BuO)_3$	THF	−78	29	43:57
6	**8**	B	Red-Al	THF	−78	64	43:57
7	**8**	B	DIBAL	THF	−20	54	33:65
8	**8**	B	DIBAL	THF	−78	93	25:75
9	**8**	B	DIBAL	Et_2O	−78	65	23:77
10	**15**	B	MeMgBr	Et_2O	0	87	64:36

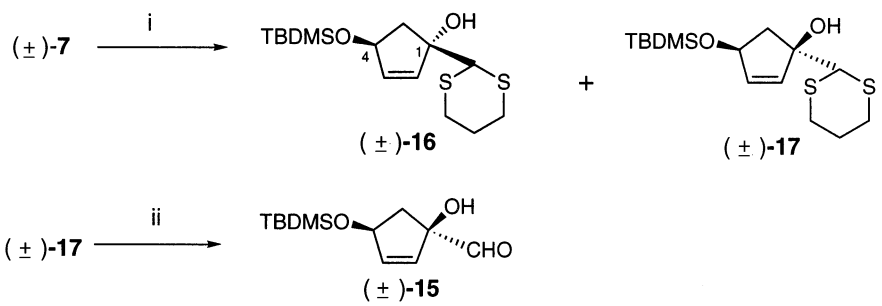
[a] Method A: a solution of substrate was added to a suspension of reducing reagent in the solvent. Method B: a solution of nucleophilic reagent was added to a solution of substrate.

formed by the reduction was determined by ^{1}H NMR spectra of the acetonide **14** derived from them. When (±)-**8** was reduced with $NaBH_4$ or DIBAL at −78°C, the acetonide (±)-**14b** was preferentially formed. This result suggested that an attack of a nucleophilic reagent (H^-) to a carbonyl group chelated with a metal[7] through path B (Fig. 1) is prevented by the C-5 methylene at low temperature, and the attack through A prevails. This consideration was supported by the fact that the acetonide **14a** was preferentially produced on addition of methylmagnesium bromide to 4-TBDMSO-1-formyl-2-cyclopenten-1-ol **15** followed by acetonide formation. The aldehyde **15** was prepared from (±)-**7** according to the procedure described for (−)-**8** (Scheme 5). Treatment of (±)-**7** with 2-lithio-1,3-dithiane afforded quantitatively the adducts **16** and **17** as a 1:14 mixture of diastereoisomers. After separation by silica gel column chromatography, **17** was deprotected with $HgCl_2$ to give the aldehyde **15**. The relative stereochemistry was determined by observation of an NOE (2.4%) between H-4 and the aldehydic proton. The preferential formation of **14b**, and consequently **5b**, by the reduction of **8** was favorable for synthesis of the natural trichodenones B and C, though this fact was revealed later. Based on these results, optically active **5a** and **5b** were prepared using DAIBAL as reducing reagent.



8: R = CH_3, Nu = H^-
15: R = H, Nu = CH_3^-

Fig. 1.

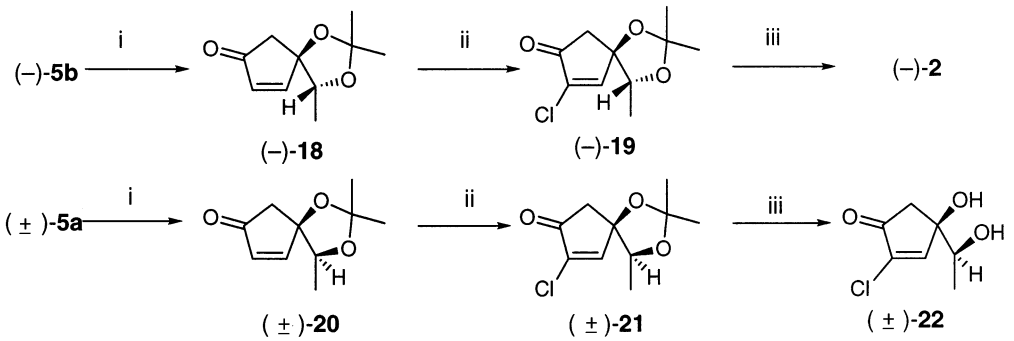


Scheme 5. Reagent and conditions: (i) 2-lithio-1,3-dithiane, THF, −78°C; (ii) $HgCl_2$, $CaCO_3$, CH_3CN–H_2O (4:1), rt

2.5. Synthesis of trichodenone B 2 and its enantiomer

Synthesis of trichodenone B **2** was achieved as shown in Scheme 6. Oxidation of (−)-**5b** with PDC afforded the enone **18**, to which the addition of chlorine followed by dehydrohalogenation with triethylamine[8] gave the haloenone **19** in 58% overall yield. Deprotection of **19** afforded the desired (−)-(4*R*,1′*R*)-**2** in 67% yield. The spectral data and specific rotation value ($[\alpha]_D^{24}$ −29.2; lit.[1] −30.4) of this compound were entirely in agreement with those of the natural product.[†]

[†] A part of IR and ^{1}H NMR spectral data for trichodenones B and C was incorrectly described in the literature reported previously.[1] The correct data should be as in Section 4 of this paper.

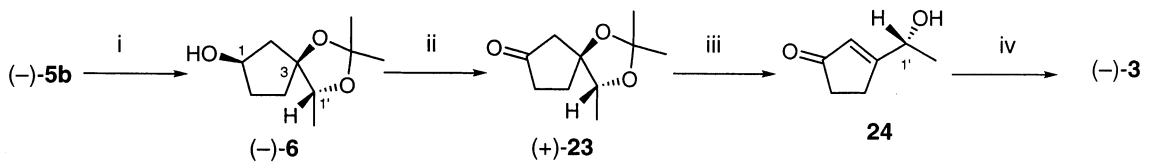


Scheme 6. Reagents and conditions: (i) PDC; (ii) Cl_2, Et_2O, Et_3N; (iii) 5% HCl–H_2O, ethylene glycol

Based on this fact, the absolute configuration of natural trichodenone B **2** was assigned to be (4*R*) and (1′*R*).

The enantiomer (+)-**2** of trichodenone B was synthesized from (+)-**5b**, using the same procedure as above with (–)-**5b**.

On the other hand, the epimer **22** of **2** at C-1′ was synthesized as a racemate from (±)-**5a** via the enone **20** and the haloenone **21**, using the same procedure as above with (–)-**5b** (Scheme 6). As expected, the resulting (±)-**22** was spectroscopically different from the natural product **2**. In this case, the addition of chlorine to the enone **20** did not often proceed smoothly in contrast of the addition to **18**. A similar phenomenon was also observed in hydrogenation of **5a** for synthesis of the enantiomer of **3** as described below (Scheme 7). Compound **5a** was not hydrogenated under the same conditions as the case of **5b**. These results imply that the addition reaction can occur from the α-side in the case of **18** or **5b**, whereas the addition reaction from both the α- and β-sides is disturbed by both one methyl group of the acetonide and the C-2′ methyl group in the case of **20** and **5a** (Fig. 2).



Scheme 7. Reagents and conditions: (i) 10% H_2/Pd–C; (ii) PDC; (iii) 5% HCl–H_2O; (iv) Cl_2, Et_2O, Et_3N

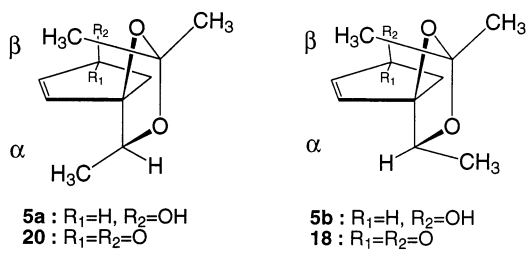


Fig. 2.

2.6. Synthesis of trichodenone C **3** and its enantiomer

Total synthesis of **3** was completed as shown in Scheme 7. Hydrogenation of (−)-**5b** followed by oxidation of the resulting cyclopentanol **6** with PDC first gave the ketone **23** in 74% overall yield. When the acetonide in **23** was next deprotected by acid, dehydration simultaneously occurred to give the enone **24** in 70% yield. Finally, addition of chlorine to **24** followed by dehydrochlorination with a base afforded (−)-(1′*R*)-**3** in 41% overall yield.

This synthetic material showed identical NMR spectroscopic and other data to those of the natural trichodenone C **3**.[†] Although the specific rotation value (−12.4) seemed to be in agreement with the literature value (−10.8)[1] within experimental error, the natural product **3** was subjected to a chiral HPLC analysis using CHIRALCEL OBH to confirm its enantiomeric purity. The result mentioned above allowed assignment of the absolute configuration for trichodenone C.

The enantiomer of **3** should be obtained from (−)-**5a** using the same method as above. However, hydrogenation of **5a** did not proceed as mentioned above. It seemed likely that hydrogenation of **5a** was disturbed by steric hindrance of the C-2′ methyl group in addition to one of two methyl groups of the acetonide. Consequently, the enantiomer of **3** was synthesized from the enantiomer (+)-**5b**, using the same procedure as above with (−)-**5b**.

3. Conclusion

We have completed the first enantioselective synthesis of trichodenones A **1**–C **3**, their enantiomers and the diastereomer (±)-**22** of trichodenone B, using (+)-**7**, its enantiomer or racemate as the starting material. From these syntheses, it was deduced that trichodenone A exists in a scalemic mixture of two enantiomers, (4*R*)- and (4*S*)-**1**, the former being predominant in nature, and that the absolute stererostructures of natural trichodenones B and C are depicted as (4*R*,1′*R*)-**2** and (1′*R*)-**3**, respectively. Biogenetically, it is interesting that the C-4 configuration of the major component of trichodenone A is opposite to that of **2** produced by the same microorganism. The synthetic process includes some key features such as the high diastereoselectivity for the addition of a Grignard reagent and 2-methyl-1,3-dithiane anion to **7** and improvement of diastereoselectivity for the reduction of the ketone **8**.

4. Experimental

4.1. General remarks

IR spectra were obtained with Perkin–Elmer FTIR spectrometer 1720X. EIMS was determined using a Hitachi 4000H mass spectrometer. NMR spectra were recorded at 27°C on Varian UNITY INOVA-500 and XL-300 spectrometers in $CDCl_3$ with tetramethylsilane (TMS) as an internal reference. Melting points were determined on Yanagimoto micromelting point apparatus and are uncorrected. Chiral HPLC was run on a Waters 600E instrument equipped with a photodiode array detector (Waters 990J). Liquid column chromatography was conducted over silica gel (Nakarai, silica gel 60, mesh 70–230 or 230–400). Analytical TLC was performed on precoated Merck aluminium sheets (DC-Alufolien Kieselgel 60 F254), and compounds were

viewed by spraying with an aqueous 10% H_2SO_4 or an ethanol solution of phosphomolybdic acid followed by heating. Dry ether and THF were distilled over sodium–benzophenone ketyl under an argon atmosphere.

4.2. (1R,4R)-tert-Butyldimethylsilyloxy-1-vinyl-2-cyclopenten-1-ol (+)-9

To a solution of (4*R*)-4-*tert*-butyldimethylsilyloxy-2-cyclopenten-1-one (+)-**7** (424 mg, 2.0 mmol) in diethyl ether (5 ml) was added dropwise at 0°C a 1 M solution (2.5 ml) of vinyl magnesium bromide in THF under argon atmosphere. After stirring for 30 min at room temperature, the reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by silica gel chromatography using MeOH–CH_2Cl_2 (1:99) as the eluent afforded (+)-**9** (464.5 mg, 97%) as an oil, $[\alpha]_D^{28}$ +95.8 (*c* 1.065, $CHCl_3$). IR (liquid film): ν_{max} 3415 (OH), 1641 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.09 (6H, s, $SiMe_2$), 0.90 (9H, s, ^{t}Bu), 1.83 (1H, dd, $J=13.6$, 4.0 Hz, H-5_A), 2.46 (1H, dd, $J=13.6$, 6.5 Hz, H-5_B), 4.74 (1H, m, H-4), 5.05 (1H, dd, $J=10.5$, 1.4 Hz, –CH=C$H_A(H_B)$), 5.23 (1H, dd, $J=17.4$, 1.4 Hz, –CH=C(H_A)H_B), 5.81 (1H, dd, $J=5.5$, 0.9 Hz, H-2), 5.89 (1H, dd, $J=5.5$, 2.1 Hz, H-3), 5.90 (1H, dd, $J=17.4$, 10.5 Hz, –C*H*=CH_2); ^{13}C NMR ($CDCl_3$): δ −4.7 (2×, q), 18.1 (s), 25.8 (3×, q), 49.9 (t), 75.4 (d), 83.4 (s), 112.2 (t), 136.2 (d), 137.9 (d), 141.7 (d); HRMS: *m*/*z* calcd for $C_{13}H_{24}O_2Si$ (M^+) 240.1544, found 240.1547.

Using the same procedure as above with (+)-**7**, (−)-**7** (424 mg) afforded (−)-**9** (475.6 mg, 99%), $[\alpha]_D^{28}$ −97.0 (*c* 1.207, $CHCl_3$).

4.3. (1R,4R)-1-Vinyl-2-cyclopentene-1,4-diol (+)-4

To a solution of (+)-**9** (464.5 mg) in dry CH_2Cl_2 (1 ml) was added dropwise at room temperature a 1 M solution (5 ml) of Bu_4NF in THF, and then stirred overnight. The reaction mixture was poured into Na_2CO_3 aq. and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and then evaporated.

Purification by silica gel column chromatography using MeOH–CH_2Cl_2 (3:97) as the eluent gave (+)-**4** (186.7 mg, 79%). $[\alpha]_D^{27}$ +109.8 (*c* 1.0, $CHCl_3$); IR (liquid film): ν_{max} 3305 (OH), 1641 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.86 (1H, dd, $J=14.4$, 3.4 Hz, H-5_A), 2.53 (1H, dd, $J=14.4$, 7.1 Hz, H-5_B), 4.72 (1H, m, H-4), 5.04 (1H, dd, $J=10.8$, 1.2 Hz, –CH=C$H_A(H_B)$), 5.21 (1H, dd, $J=17.2$, 1.2 Hz, –CH=C(H_A)H_B), 5.82 (1H, dd, $J=5.5$, 0.9 Hz, H-2), 5.90 (1H, dd, $J=17.2$, 10.8 Hz, –C*H*=CH_2), 5.98 (1H, dd, $J=5.5$, 2.1 Hz, H-3); ^{13}C NMR ($CDCl_3$): δ 48.8 (t), 75.1 (d), 83.6 (s), 112.2 (t), 135.7 (d), 138.5 (d), 142.0 (d); HRMS: *m*/*z* calcd for $C_7H_{10}O_2$ (M^+) 126.0680, found 126.0679.

Using the same procedure as above with (+)-**9,** (−)-**9** (475.6 mg) gave (−)-**4** (205.7 mg, 85%), $[\alpha]_D^{28}$ −112.5 (*c* 1.0, $CHCl_3$).

4.4. (4R)-4-Hydroxy-4-vinyl-2-cyclopenten-1-one (+)-1, (4R)-trichodenone A

PDC (995.5 mg, 2.0 eq.) and Celite (ca. 300 mg) were added to a solution (3 ml) of (+)-**4** (166.7 mg) in CH_2Cl_2. After stirring for 4 h at room temperature, the reaction mixture was concentrated to give a residue, which was put on silica gel column directly, and eluted with MeOH–CH_2Cl_2 (1:99) to afford (+)-**1** (14.2 mg, 8.6%) as a colorless oil, $[\alpha]_D^{27}$ +141.6 (*c* 0.9, $CHCl_3$). IR (liquid film): ν_{max} 3406 (OH), 1717 (C=O), 1683, 1652, 1588 (C=C) cm^{-1}; ^1H NMR

($CDCl_3$): δ 2.60 (1H, d, $J=18.6$ Hz, H-5_A), 2.63 (1H, d, $J=18.6$ Hz, H-5_B), 5.22 (1H, d, $J=10.6$ Hz, –CH=CH_A(H_B)), 5.33 (1H, d, $J=17.3$ Hz, –CH=C(H_A)H_B), 6.00 (1H, dd, $J=17.3$, 10.6 Hz, –CH=CH_2), 6.17 (1H, d, $J=5.6$ Hz, H-2), 7.35 (1H, d, $J=5.5$ Hz, H-3); ^{13}C NMR ($CDCl_3$): δ 49.6 (C-5), 78.9 (C-4), 114.5 (CH=CH$_2$), 133.7 (C-2), 140.2 (CH=CH$_2$), 164.1 (C-3), 206.3 (C-1); HRMS: m/z calcd for $C_7H_8O_2$ (M^+) 124.0524, found 124.0526.

Using the same procedure as above with (+)-**4,** (–)-**4** (185.4 mg) afforded (–)-**1** (15.4 mg, 8.5%), $[\alpha]_D^{26}$ –145.4 (c 1.1, $CHCl_3$).

*4.5. (1*S,*4*S*)-4-*tert-*Butyldimethylsilyloxy-1-(1,1-trimethylenedithio)ethyl-2-cyclopenten-1-ol (–)-**10** and (1*R,*4*S*)-4-*tert-*butyldimethylsilyloxy-1-(1,1-trimethylenedithio)-ethyl-2-cyclopenten-1-ol (–)-**11***

To a solution (5 ml) of 2-methyl-1,3-dithiane (445 mg) in THF was added a 1.6 M solution (2 ml) of n-BuLi in hexane at −78°C under argon atmosphere. The solution was warmed to −15°C, stirred for 1.5 h, and then cooled to −78°C again. A solution of (–)-**7** (424 mg, 2 mmol) in THF (5 ml) was added dropwise at −78°C to the solution. After stirring for 30 min, the mixture was quenched by addition of H_2O, and extracted three times with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography using a CH_2Cl_2–MeOH gradient as the eluent. The first and second CH_2Cl_2 eluate gave the recovered reagent and (–)-**10** (69.9 mg, 10%), respectively. The MeOH–CH_2Cl_2 (1:99) eluate afforded (–)-**11** (617.6 mg, 89%). (–)-**10**: a colorless oil, $[\alpha]_D^{26}$ −51.2 (c 0.82, $CHCl_3$); IR (liquid film): ν_{max} 3463 (OH), 1591 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ (6H, s, $SiMe_2$), 0.89 (9H, s, ^{t}Bu), 1.77 (3H, s, CH_3), 1.91, 2.05 (1H each, m, $CH_2CH_2CH_2$), 2.18 (1H, dd, $J=14.1$, 4.3 Hz, H-5_A), 2.30 (1H, dd, $J=14.1$, 6.9 Hz, H-5_B), 2.87–3.31 (4H, m, 2× SCH_2), 5.06 (1H, m, H-4), 5.94 (1H, dd, $J=5.7$, 1.8 Hz, H-3), 6.06 (1H, dd, $J=5.7$, 1.4 Hz, H-2); ^{13}C NMR ($CDCl_3$): δ −4.9 (2×, q), 17.8 (s), 24.6 (t), 24.9 (q), 25.6 (3×, q), 26.4 (t), 26.5 (t), 44.6 (t), 57.3 (s), 75.5 (d), 90.7 (s), 133.7 (d), 138.5 (d); HRMS, m/z calcd for $C_{16}H_{30}O_2S_2Si$ (M^+) 346.1455, found 346.1452. (–)-**11**: colorless needles, mp 41–44°C; $[\alpha]_D^{26}$ −48.0 (c 0.81, $CHCl_3$); IR (KBr): ν_{max} 3369 (OH), 1652 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.09 (6H, s, $SiMe_2$), 0.89 (9H, s, ^{t}Bu), 1.72 (3H, s, CH_3), 1.76 (1H, dd, $J=14.2$, 3.7 Hz, H-5_A), 1.91, 2.03 (1H each, m, $CH_2CH_2CH_2$), 2.87–2.95 (5H, m, H-5_B, 2× SCH_2), 4.76 (1H, m, H-4), 5.96 (1H, dd, $J=5.5$, 1.8 Hz, H-3), 6.10 (1H, d, $J=5.5$ Hz, H-2); ^{13}C NMR ($CDCl_3$): δ −4.7 (2×, q), 18.1 (s), 24.6 (q), 25.0 (t), 25.8 (3×, q), 26.8 (t), 26.9 (t), 45.8 (t), 56.7 (s), 75.6 (d), 91.1 (s), 135.5 (d), 137.7 (s); HRMS: m/z calcd for $C_{16}H_{30}O_2S_2Si$ (M^+) 346.1455, found 346.1459.

Using the same procedure as above with (–)-**7**, (+)-**7** (424 mg) afforded (+)-**10** (36.7 mg), $[\alpha]_D^{26}$ +49.4 (c 0.24, $CHCl_3$), and (+)-**11** (562.8 mg), $[\alpha]_D^{26}$ +50.3 (c 0.96, $CHCl_3$).

*4.6. (1*R,*4*S*)-1-Acetyl-4-*tert-*butyldimethylsilyloxy-2-cyclopenten-1-ol [(–)-**8**]*

To a vigorously stirred solution of (–)-**11** (640.8 mg, 1.8 mmol) in CH_3CN–H_2O (4:1) (30 ml) were added gradually at room temperature $CaCO_3$ (1.98 g) and $HgCl_2$ (2.44 g). After 30 min, an equivalent weight of $Na_2S{\cdot}9H_2O$ was added to the resulting suspension. The reaction mixture was extracted with EtOAc, and the organic layer was dried over $MgSO_4$, filtered and concentrated to give a crude residue. Purification by silica gel flash chromatography using MeOH–CH_2Cl_2 (1:99) as the eluent afforded (–)-**8** (336.6 mg, 75%) as an oil, $[\alpha]_D^{26}$ −264.9 (c 1.976,

$CHCl_3$). IR (liquid film): ν_{max} 3465 (OH), 1713 (C=O), 1619 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.10 (3H, s, SiMe), 0.11 (3H, s, SiMe), 0.91 (9H, s, ^{t}Bu), 1.88 (1H, dd, $J=14.4$, 5.5 Hz, H-5_A), 2.09 (3H, s, $COCH_3$), 2.70 (1H, dd, $J=14.4$, 7.3 Hz, H-5_B), 4.91 (1H, dddd, $J=7.3$, 5.5, 1.8, 1.6 Hz, H-4), 5.66 (1H, dd, $J=5.5$, 1.6 Hz, H-2), 6.11 (1H, dd, $J=5.5$, 1.8 Hz, H-3); ^{13}C NMR ($CDCl_3$): δ −4.64 (q), −4.60 (q), 18.1 (s), 22.9 (q), 25.9 (3×, q), 46.9 (t), 75.9 (s), 89.1 (s), 133.8 (d), 140.0 (d), 209.2 (s); HRMS: m/z calcd for $C_{13}H_{23}O_3Si$ ($(M-H)^+$) 255.1415, found 255.1412. Using the same procedure as above with (−)-**11**, (+)-**11** (600.5 mg) afforded (+)-**8** (311.5 mg) as a colorless oil, $[\alpha]_D^{26}$ +264.5 (*c* 1.79, $CHCl_3$).

*4.7. (1*S,*4*S*)-1-Acetyl-4-*tert*-butyldimethylsilyloxy-2-cyclopenten-1-ol (+)-**12***

According to the procedure described for (−)-**8**, (−)-**10** (193.6 mg) afforded (+)-**12** (108.4 mg, 74%) as a colorless oil, $[\alpha]_D^{26}$ +71.2 (*c* 0.76, $CHCl_3$). IR (liquid film): ν_{max} 3468(OH), 1713 (C=O), 1623 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.10 (3H, s, SiMe), 0.11 (3H, s, SiMe), 0.90 (9H, s, ^{t}Bu), 2.09 (1H, dd, $J=14.8$, 2.3 Hz, H-5_A), 2.27 (1H, dd, $J=14.8$, 7.1 Hz, H-5_B), 2.33 (3H, s, $COCH_3$), 4.28 (1H, s, OH), 5.19 (1H, br d, $J=7.1$ Hz, H-4), 5.67 (1H, dd, $J=5.5$, 0.9 Hz, H-2), 6.13 (1H, dd, $J=5.5$, 2.3 Hz, H-3); ^{13}C NMR ($CDCl_3$): δ −4.9 (q), −4.7 (q), 18.0 (s), 23.7 (q), 25.7 (3×, q), 46.1 (t), 76.6 (d), 89.4 (s), 134.9 (d), 138.1 (d), 210.2 (s); HRMS: m/z calcd for $C_{13}H_{25}O_3Si$ ($[M+H]^+$) 257.1572, found 257.1567. Using the same procedure as above with (−)-**10**, (+)-**10** (200.8 mg) afforded (−)-**12** (93.9 mg) as a colorless oil, $[\alpha]_D^{26}$ −70.6 (*c* 1.33, $CHCl_3$).

*4.8. (1*S*,*4*S*)-4-*tert*-Butyldimethylsilyloxy-1-(1,1-trimethylenedithio)methyl-2-cyclopenten-1-ol(±)-**16** and (1*R*,*4*S*)-4-*tert*-butyldimethylsilyloxy-1-(1,1-trimethylenedithio)methyl-2-cyclopenten-1-ol (±)-**17***

According to the procedure described for (−)-**10** and (−)-**11**, (±)-**7** (430 mg) was treated with 2-lithio-1,3-dithiane to yield (±)-**16** (42.9 mg) and (±)-**17** (605 mg). (±)-**16**: a colorless oil; IR (liquid film): ν_{max} 3420 (OH), 1654 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.08 (6H, s, $SiMe_2$), 0.90 (9H, s, ^{t}Bu), 1.92, 2.12 (1H each, m, $CH_2CH_2CH_2$), 2.15 (1H, dd, $J=13.7$, 4. 4 Hz, H-5_A), 2.29 (1H, dd, $J=13.7$, 6.6 Hz, H-5_B), 2.84–2.95 (4H, m, 2× SCH_2), 4.37 (1H, s, SCHS), 5.02 (1H, m, H-4), 5.95 (1H, dd, $J=5.5$, 1.9 Hz, H-3), 6.01 (1H, dd, $J=5.5$, 1.5 Hz, H-2); HRMS: m/z calcd for $C_{15}H_{28}O_2S_2Si$ (M^+) 332.1299, found 332.1288. (±)-**17**: a colorless oil; IR (liquid film): ν_{max} 3426 (OH), 1643, 1613 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.09 (6H, s, $SiMe_2$), 0.91 (9H, s, ^{t}Bu), 1.81 (1H, dd, $J=14.8$, 2.7 Hz, H-5_A), 1.87, 2.10 (1H, m, $CH_2CH_2CH_2$), 2.85 (1H, dd, $J=14.8$, 7.3 Hz, H-5_B), 2.80–2.98 (4H, m, 2× SCH_2), 4.28 (1H, s, SCHS), 4.75 (1H, m, H-4), 5.97 (1H, dd, $J=5.5$, 0.7 Hz, H-2), 6.03 (1H, dd, $J=5.5$, 2.1 Hz, H-3); ^{13}C NMR ($CDCl_3$): δ −3.6 (2×, q), 17.9 (s), 25.6 (3×, q), 25.6 (t), 30.1 (t), 30.3 (t), 45.8 (t), 56.8 (d), 75.0 (d), 86.2 (s), 136.6 (d), 137.0 (d); HRMS: m/z calcd for $C_{15}H_{28}O_2S_2Si$ (M^+) 332.1299, found 332.1294.

*4.9. (1*R*,*4*S*)-4-*tert*-Butyldimethylsilyloxy-1-formyl-2-cyclopenten-1-ol (±)-**15***

According to the procedure described for (−)-**8**, (±)-**17** (62.7 mg) afforded (±)-**15** (19.6 mg, 33%) as a colorless oil. IR (liquid film): ν_{max} 3388 (OH), 1727 (C=O), 1632 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.12 (3H, s, SiMe), 0.13 (3H, s, SiMe), 0.93 (9H, s, ^{t}Bu), 1.93 (1H, dd, $J=14.0$, 5.5 Hz, H-5_A), 2.75 (1H, dd, $J=14.0$, 7.1 Hz, H-5_B), 4.88 (1H, dddd, $J=7.1$, 5.5, 1.8, 1.4 Hz, H-4), 5.62 (1H, dd, $J=5.5$, 1.4 Hz, H-2), 6.19 (1H, dd, $J=5.5$, 1.8Hz, H-3), 9.25 (1H, s, CHO); ^{13}C

NMR ($CDCl_3$): δ −4.7 (q), −4.6 (q), 18.1 (s), 25.8 (3×, q), 44.7 (t), 74.8 (d), 88.7 (s), 131.0 (d), 141.7 (d), 199.1 (d); HRMS; m/z calcd for $C_{12}H_{23}O_3Si$ ($[M+H]^+$) 243.1415, found 243.1417.

*4.10. General procedure for the reduction of (±)-**8** followed by acetonide formation—{(1S*,4R*,1′S*)-1-*O*-tert-butyldimethylsilyl-4-(1′-hydroxyethyl)-4,1′-O-isopropylidene-2-cyclopentene-1,4-diol (±)-**14a** and (1S*,4R*,1′R*)-1-*O*-tert-butyldimethylsilyl-4-(1′-hydroxyethyl)-4,1′-O-isopropylidene-2-cyclopentene-1,4-diol (±)-**14b**} (Table 1)*

Method A: A solution of (±)-**8** (ca. 50 mg) in the solvent (1 ml) mentioned in Table 1 was added to a stirred suspension of 1 equivalent of reducing reagent in the same solvent (5 ml) under argon atmosphere. Method B: To a stirred solution of (±)-**8** or (±)-**15** (ca. 50 mg) in the solvent (5 ml) mentioned in Table 1 was added under an argon atmosphere a solution of 1 equivalent of nucleophilic reagent (Red-Al, DIBAL or MeMgBr) in toluene, hexane or ether. After stirring for 30 min, the reaction mixture was quenched with water, and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude diol (±)-**13** was dissolved in dry CH_2Cl_2 (5 ml) and 2-methoxypropene (1 ml) and a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) were added at room temperature under an argon atmosphere. After stirring for 30 min, the reaction mixture was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography using MeOH–CH_2Cl_2 (1:99) as the eluent. Fractions including acetonides were collected, and used to determine the ratio of (±)-**14a** and (±)-**14b** by means of ^{1}H NMR spectrum. Column chromatography using CH_2Cl_2 as the eluent could separate the two diastereomeric acetonides although the efficiency was not enough. (±)-**14a**: IR (liquid film): ν_{max} 3436 (OH), 1641 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.04 (3H, s, SiMe), 0.05 (3H, s, SiMe), 0.86 (9H, s, ^{t}Bu), 1.01 (3H, d, J=6.2 Hz, H-2′), 1.36 (3H, s, acetonide-CH_3), 1.43 (3H, s, acetonide-CH_3), 2.01 (1H, dd, J=14.0, 4.8 Hz, H-5$_A$), 2.31 (1H, dd, J=14.0, 7.1 Hz, H-5$_B$), 4.04 (1H, q, J=6.2 Hz, H-1), 4.61 (1H, m, H-1), 5.75 (1H, dd, J=5.6, 1.4 Hz, H-3), 5.85 (1H, dd, J=5.6, 1.8 Hz, H-2); HRMS: m/z calcd for $C_{16}H_{31}O_3Si$ ($[M+H]^+$) 299.2041, found 299.2034.

(±)-**14b**: IR (liquid film): ν_{max} 3446 (OH), 1646 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.053 (3H, s, SiMe), 0.057 (3H, s, SiMe), 0.87 (9H, s, ^{t}Bu), 1.07 (3H, d, J=6.2 Hz, H-2′), 1.35 (3H, s, acetonide-CH_3), 1.38 (3H, s, acetonide-CH_3), 1.57 (1H, dd, J=13.5, 6.2 Hz, H-5$_A$), 2.63 (1H, dd, J=13.5, 6.6 Hz, H-5$_B$), 3.91 (1H, q, J=6.2 Hz, H-1′), 4.56 (1H, m, H-1), 5.63 (1H, dd, J=5.7, 1.4 Hz, H-3), 5.88 (1H, dd, J=5.7, 1.7 Hz, H-2); HRMS: m/z calcd for $C_{16}H_{31}O_3Si$ ($[M+H]^+$) 299.2041, found 299.2029.

*4.11. (1S,4R,1′S)-4-(1′-Hydroxyethyl)-4,1′-O-isopropylidene-2-cyclopentene-1,4-diol (−)-**5a** and (1S,4R,1′R)-4-(1′-hydroxyethyl)-4,1′-O-isopropylidene-2-cyclopentene-1,4-diol (−)-**5b***

According to the procedure described for (±)-**14a** and (±)-**14b**, (−)-**8** (929 mg, 2.7 mmol) was treated with DIBAL followed by 2-methoxypropene to yield a mixture of the diastereomeric acetonides (1*S*,4*R*,1′*S*)-**14a** and (1*S*,4*R*,1′*R*)-**14b** (701 mg) as an oil.

To a solution of the mixture in THF (5 ml) was added at room temperature a solution of 2 equivalents of Bu_4NF in THF. After stirring overnight, the reaction mixture was poured into aqueous Na_2CO_3 and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to give crude product. Repeated medium-pressure silica gel chromatography using MeOH–CH_2Cl_2 (3:97) as the eluent afforded (−)-**5a** (39.4 mg) and

(−)-**5b** (271.2 mg). (−)-**5a**: a colorless oil, $[\alpha]_D^{24}$ −51.2 (*c* 0.978, $CHCl_3$); IR (liquid film): ν_{max} 3415 (OH), 1642 (C=C) cm^{-1}: ^1H NMR ($CDCl_3$): δ 1.08 (3H d, $J=6.4$ Hz, H-2′), 1.39 (3H, d, $J=0.5$ Hz, acetonide-CH_3), 1.45 (3H, d, $J=0.5$ Hz, acetonide-CH_3), 1.96 (1H, dd, $J=14.9$, 3.0 Hz, H-5_A), 2.33 (1H, dd, $J=14.9$, 6.9 Hz, H-5_B), 4.11 (1H, q, $J=6.4$ Hz, H-1′), 4.61 (1H, dddd, $J=6.9$, 3.0, 2.2, 0.9 Hz, H-1), 5.90 (1H, dd, $J=5.6$, 0.9 Hz, H-3), 6.02 (1H, dd, $J=5.6$, 2.2 Hz, H-2); ^{13}C NMR ($CDCl_3$): δ 14.2 (q), 26.4 (q), 28.5 (q), 43.9 (t), 74.1 (d), 77.2 (d), 92.8 (s), 107.6 (s), 134.8 (d), 136.7 (d); HRMS: *m*/*z* calcd for $C_{10}H_{15}O_3([M-H]^+)$ 183.1020, found 183.1016. (−)-**5b**: a colorless oil [(±)-**5b**, colorless needles, mp 97–100°C], $[\alpha]_D^{24}$ −105.8 (*c* 0.34, $CHCl_3$); IR (liquid film): ν_{max} 3454 (OH), 1649, 1600 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.11 (3H, d, $J=6.4$ Hz, H-2′), 1.38 (3H, d, $J=0.5$ Hz, acetonide-CH_3), 1.42 (3H, d, $J=0.5$ Hz, acetonide-CH_3), 1.54 (1H, ddd, $J=13.7$, 5.7, 0.5 Hz, H-5_A), 1.97 (1H, d, $J=8.5$ Hz, –OH), 2.77 (1H, dd, $J=13.7$, 6.9 Hz, H-5_B), 3.99 (1H, q, $J=6.4$ Hz, H-1′), 4.60 (1H, m, H-1), 5.74 (1H, dd, $J=5.6$, 1.4 Hz, H-3), 6.03 (1H, dd, $J=5.6$, 1.8 Hz, H-2); ^{13}C NMR ($CDCl_3$): δ 13.3 (q), 26.5 (q), 28.1 (q), 43.0 (t), 74.9 (d), 76.1 (d), 91.6 (s), 107.8 (s), 134.6 (d), 138.3 (d); HRMS: *m*/*z* calcd for $C_{10}H_{17}O_3$ ($[M+H]^+$) 185.1177, found 177.1173.

Using the same procedure as above with (−)-**8**, (+)-**8** (507.7 mg) afforded (+)-**5a** (24.2 mg), $[\alpha]_D^{24}$ +53.7 (*c* 0.35, $CHCl_3$, and (+)-**5b** (125.8 mg), $[\alpha]_D^{24}$ +103.1 (*c* 0.32, $CHCl_3$).

*4.12. (4*R,*1′*R*)-4-Hydroxy-4-(1′-hydroxyethyl)-4,1′-*O*-isopropylidene-2-cyclopenten-1-one (−)-**18***

PDC (120.6 mg) and Celite (ca. 100 mg) were added to a solution of (−)-**5b** (29.8 mg) in CH_2Cl_2 (3 ml). After stirring overnight at room temperature, the reaction mixture was filtered, and then concentrated under reduced pressure. The residue was purified by silica gel chromatography using MeOH–CH_2Cl_2 (1:99) as the eluent to yield (−)-**18** (24.5 mg, 83%) as a colorless oil, $[\alpha]_D^{26}$ −99.7 (*c* 1.30, $CHCl_3$). IR (liquid film): ν_{max} 1728 (C=O), 1593 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.17 (3H, d, $J=6.4$ Hz, H-2′), 1.43 (3H, s, acetonide-CH_3), 1.52 (3H, s, acetonide-CH_3), 2.41 (1H, d, $J=18.5$ Hz, H-5_A), 2.70 (1H, d, $J=18.5$ Hz, H-5_B), 4.29 (1H, q, $J=6.4$ Hz, H-1′), 6.20 (1H, d, $J=5.9$ Hz, H-2), 7.42 (1H, d, $J=5.9$ Hz, H-3); ^{13}C NMR ($CDCl_3$): δ 14.2 (q), 26.2 (q), 28.5 (q), 43.6 (t), 77.0 (d), 87.4 (s), 108.5 (s), 134.6 (d), 161.0 (d), 205.1 (s); HRMS: *m*/*z* calcd for $C_{10}H_{14}O_3$ (M^+) 182.0942, found 182.0942.

Using the same procedure as above with (−)-**5b**, (+)-**5b** (48.1 mg) afforded (+)-**18** (41 mg), $[\alpha]_D^{26}$ +99.7 (*c* 0.90, $CHCl_3$).

*4.13. (4*R,*1′*R*)-2-Chloro-4-hydroxy-4-(1′-hydroxyethyl)-4,1′-*O*-isopropylidene-2-cyclopenten-1-one (−)-**19***

Chlorine was bubbled into a solution of (−)-**18** (22.2 mg) in ether (50 ml). After standing overnight at room temperature, the mixture was concentrated to remove the solvent and excess chlorine. The resulting crude dichloride was dissolved in 5 ml ether again, and then triethylamine (0.1 ml) added. After stirring at room temperature for 3 h, the reaction mixture was treated with dil. HCl and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography using MeOH–CH_2Cl_2 (1:99) as the eluent to yield (−)-**19** (18.5 mg, 70%) as colorless needles (CH_2Cl_2), mp 84–86.5°C, $[\alpha]_D^{26}$ −70.1 (*c* 0.23, $CHCl_3$). IR (KBr): ν_{max} 1726 (C=O), 1599 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.19 (3H, d, $J=6.4$ Hz, H-2′), 1.44 (3H, s, acetonide-CH_3), 1.56 (3H, s, acetonide-CH_3), 2.44 (1H, dd, $J=18.5$, 0.5 Hz, H-5_A), 2.90 (1H, d, $J=18.5$ Hz, H-5_B), 4.20 (1H, qd,

$J=6.4$, 0.5 Hz, H-1′), 7.21 (1H, s, H-3); ^{13}C NMR ($CDCl_3$): δ 13.7 (q), 26.4 (q), 27.8 (q), 42.7 (t), 76.4 (d), 84.0 (s), 109.2 (s), 138.0 (d), 154.0 (d), 196.9 (s); HRMS: m/z calcd for $C_{10}H_{13}O_3Cl$ (M^+) 216.0553, found 216.0542. Using the same procedure as above with (−)-**18**, (+)-**18** (41 mg) afforded (+)-**19** (41 mg), $[\alpha]_D^{26}$ +69.8 (*c* 0.36, $CHCl_3$).

*4.14. (4*R,*1′*R*)-2-Chloro-4-hydroxy-4-(1′-hydroxyethyl)-2-cyclopenten-1-one(−)-**2**, (4*R,*1′*R*)-trichodenone B*

Ethylene glycol (0.1 ml) and 5% aqueous HCl (1 ml) was added to (−)-**19** (9.9 mg). After stirring overnight at room temperature, the reaction mixture was diluted with H_2O (10 ml) and extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated to give a crude product, which was purified by silica gel chromatography using MeOH–CH_2Cl_2 (3:97) as the eluent to afford (−)-**2** (4.8 mg, 59%) as a colorless oil, $[\alpha]_D^{24}$ −29.2 (*c* 0.48, $CHCl_3$). IR (liquid film): ν_{max} 3419 (OH), 1729 (C=O), 1683 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.23 (3H, d, $J=6.4$ Hz, H-2′), 2.48 (1H, d, $J=18.7$ Hz, H-5$_A$), 2.75 (1H, d, $J=18.7$ Hz, H-5$_B$), 3.89 (1H, q, $J=6.4$ Hz, H-1′), 7.45 (1H, s, H-3); ^{13}C NMR ($CDCl_3$): δ 17.8 (C-2′), 43.9 (C-5), 71.7 (C-1′), 78.8 (C-4), 137.2 (C-2), 156.4 (C-3), 197.9 (C-1); HRMS: m/z, calcd for $C_7H_{10}O_3$ Cl ([M+H]$^+$) 177.0318, found 177.0322. Using the same procedure as above with (−)-**19**, (+)-**19** (27.2 mg) afforded (+)-**2** (14.9 mg), $[\alpha]_D^{24}$ +27.0 (*c* 1.25, $CHCl_3$).

*4.15. (4*R*,*1′*S*)-4-Hydroxy-4-(1′-hydroxyethyl)-4,1′-*O*-isopropylidene-2-cyclopenten-1-one (±)-**20***

According to the procedure described for (−)-**18**, (±)-**5a** (45.5 mg) was treated with PDC to yield (±)-**20** (44.7 mg, 83%) as a colorless oil. IR (liquid film): ν_{max} 1724 (C=O), 1591 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.16 (3H, d, $J=6.4$ Hz, H-2′), 1.43 (3H, s, acetonide-CH_3), 1.44 (3H, s, acetonide-CH_3), 2.29 (1H, dd, $J=18.3$, 0.5 Hz, H-5$_A$), 2.73 (1H, d, $J=18.3$ Hz, H-5$_B$), 4.18 (1H, q, $J=6.4$ Hz, H-1′), 6.25 (1H, d, $J=5.7$ Hz, H-2), 7.29 (1H, d, $J=5.7$ Hz, H-3); ^{13}C NMR ($CDCl_3$): δ 13.4 (q), 26.5 (q), 27.7 (q), 43.2 (t), 76.4 (d), 86.9 (s), 108.9 (s), 136.0 (d), 161.1 (d), 205.3 (s); HRMS: m/z calcd for $C_{10}H_{14}O_3$ (M^+) 182.0942, found 182.0945.

*4.16. (4*R*,*1′*S*)-2-Chloro-4-hydroxy-4-(1′-hydroxyethyl)-4,1′-*O*-isopropylidene-2-cyclopenten-1-one (±)-**21***

According to the procedure described for (−)-**19**, (±)-**20** (5 mg) was treated with chlorine followed by triethylamine to afford (±)-**21** (3 mg, 83%) as a colorless oil. IR (liquid film): ν_{max} 1738 (C=O), 1600 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.19 (3H, d, $J=6.4$ Hz, H-2′), 1.43 (3H, s, acetonide-CH_3), 1.51 (3H, s, acetonide-CH_3), 2.68 (1H, d, $J=18.8$ Hz, H-5$_A$), 2.83 (1H, d, $J=18.8$ Hz, H-5$_B$), 4.26 (1H, q, $J=6.4$ Hz, H-1′), 7.33 (1H, s, H-3); ^{13}C NMR ($CDCl_3$): δ 14.1 (q), 26.1 (q), 28.5 (q), 42.7 (t), 76.4 (d), 84.5 (s), 108.8 (s), 132.5 (d), 154.0 (d), 196.6 (s); HRMS: m/z calcd for $C_{10}H_{13}O_3Cl$ (M^+) 216.0552, found 216.0543.

*4.17. (4*R*,*1′*S*)-2-Chloro-4-hydroxy-4-(1′-hydroxyethyl)-2-cyclopenten-1-one (±)-**22***

According to the procedure described for (−)-**2**, (±)-**21** (2.5 mg) was deprotected to afford (±)-**22** (1.7 mg) as a colorless oil. IR (liquid film): ν_{max} 3436 (OH), 1728 (C=O), 1601 (C=C) cm^{-1};

^{1}H NMR ($CDCl_3$): δ 1.19 (3H, d, $J=6.4$ Hz, H-2′), 2.57 (1H, d, $J=18.6$ Hz, H-5_A), 2.72 (1H, d, $J=18.6$ Hz, H-5_B), 3.98 (1H, br q, $J=6.4$ Hz, H-1′), 7.39 (1H, s, H-3); ^{13}C NMR ($CDCl_3$): δ 17.8 (q), 45.3 (t), 72.0 (d), 78.9 (s), 137.8 (d), 155.0 (d), 197.2 (s); HRMS: m/z calcd for $C_7H_{10}O_3Cl$ ($(M+H)^+$) 177.0318, found 177.0314.

4.18. (1R,3S,1′R)-3-(1′-Hydroxyethyl)-3,1′-O-isopropylidene-1-cyclopentanol (−)-6

To a solution of (−)-**5b** (89.7 mg) in MeOH (5 ml) was added 10% Pd/C (5 mg), and the reaction mixture was stirred under hydrogen atmosphere (1 atm) overnight at room temperature. The catalyst was filtered off and the solvent evaporated under reduced pressure. The residue was purified by silica gel column chromatography using MeOH–CH_2Cl_2 (1:99) as the eluent to give (−)-**6** (75.5 mg, 83%) as a colorless oil, $[\alpha]_D^{26}$ −8.3 (c 0.34, $CHCl_3$). IR (liquid film): ν_{max} 3431 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.21 (3H, d, $J=6.2$ Hz, H-2′), 1.36 (3H, s, acetonide-CH_3), 1.45 (3H, s, acetonide-CH_3), 1.65 (1H, ddd, $J=15.1$, 8.2, 5.5 Hz, H-4_A), 1.67 (1H, dd, $J=13.7$, 5.3Hz, H-2_A), 1.81 (1H, dq, $J=13.7$, 1.8 Hz, H-2_B), 1.90 (1H, m, H-5_A), 1.97 (1H, m, H-4_B), 2.00 (1H, m, H-5_B), 3.01 (1H, d, $J=10.1$ Hz, OH), 4.11 (1H, q, $J=6.2$ Hz, H-1′) 4.28 (1H, m, H-1); ^{13}C NMR ($CDCl_3$): δ 14.8 (q), 26.7 (q), 28.2 (q), 33.8 (t), 33.9 (t), 41.0 (t), 73.6 (d), 75.6 (d), 92.1 (s), 107.3 (s); HRMS: m/z calcd for $C_{10}H_{18}O_3$ (M^+) 186.1255, found 186.1261. Using the same procedure as above with (−)-**5b**, (+)-**5b** (116 mg) afforded (+)-**6** (88.7 mg), $[\alpha]_D^{26}$ +8.0 (c 0.50,$CHCl_3$).

4.19. (3S,1′R)-3-Hydroxy-3-(1′-hydroxyethyl)-3,1′-O-isopropylidene-1-cyclopentanone (+)-23

According to the procedure described for (−)-**18**, (−)-**6** (67.5 mg) was treated with PDC to yield (+)-**23** (57.5 mg, 89%) as a colorless oil, $[\alpha]_D^{28}$ +70.7 (c 0.82, $CHCl_3$). IR (liquid film): ν_{max} 1747 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.27 (3H, d, $J=6.4$ Hz, H-2′), 1.39 (3H, d, $J=0.7$ Hz, acetonide-CH_3), 1.40 (3H, d, $J=0.5$ Hz, acetonide-CH_3), 2.01 (1H, ddd, $J=13.5$, 9.8, 9.4 Hz, H-4_A), 2.17 (1H, dddd, $J=13.5$, 9.4, 3.4, 1.8 Hz, H-4_B), 2.26–2.36 (3H, m, H-2_A, H-2_B and H-5_A), 2.50 (1H, m, H-5_B), 4.12 (1H, q, $J=6.4$ Hz, H-1′); ^{13}C NMR ($CDCl_3$): δ 15.3 (q), 26.7 (q), 28.1 (q), 32.8 (t), 36.7 (t), 46.2 (t), 76.7 (d), 87.4 (s), 107.7 (s), 216.1 (s); HRMS: m/z calcd for $C_{10}H_{16}O_3$ (M^+) 184.1098, found 184.1100. Using the same procedure as above with (−)-**6**, (+)-**6** (78.7 mg) afforded (−)-**23** (75.7 mg), $[\alpha]_D^{28}$ −70.4 (c 1.06, $CHCl_3$).

4.20. (1′R)-3-(1′-Hydroxyethyl)-2-cyclopenten-1-one 24

According to the procedure described for (−)-**2**, (+)-**23** (39.3 mg) was deprotected to afford (1′*R*)-**24** (18.5 mg) as a colorless oil. Specific rotation could not be determined due to the too-low value. IR (liquid film): ν_{max} 3415 (OH), 1673 (C=O), 1614 (C=C) cm^{-1}: ^{1}H NMR ($CDCl_3$): δ 1.46 (3H, d, $J=6.6$ Hz, H-2′), 2.46 (2H, m, H-5), 2.65 (2H, m, H-4), 4.67 (1H, br q, $J=6.6$ Hz, H-1′), 6.14 (1H, q, $J=1.6$ Hz, H-2); ^{13}C NMR ($CDCl_3$): δ 22.1 (q), 27.8 (t), 35.2 (t), 67.8 (d), 128.0 (d), 184.0 (s), 209.3 (s); HRMS: m/z calcd for $C_7H_{10}O_2$ (M^+) 126.0680, found 126.0679.

Using the same procedure as above with (+)-**23**, (−)-**23** (69 mg) afforded (1′*S*)-**24** (36.8 mg). Specific rotation could not be determined due to the too-low value.

4.21. (1′R)-2-Chloro-3-(1′-hydroxyethyl)-2-cyclopenten-1-one (−)-3, (1′R)-trichodenone C

According to the procedure described for (−)-**19**, (1′*R*)-**24** (7.4 mg) was treated with chlorine followed by triethylamine. Purification by silica gel column chromatography using MeOH–CH_2Cl_2 (3:97) as the eluent afforded (−)-**3** (3.9 mg, 41%) as a colorless oil, $[\alpha]_D^{28}$ −12.4 (*c* 0.45, $CHCl_3$). IR (liquid film): ν_{max} 3414 (OH), 1713 (C=O), 1620 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.44 (3H, d, $J=6.7$ Hz, H-2′), 2.54 (2H, m, H-5), 2.71 (1H, dddd, $J=19.2$, 5.5, 3.4, 1.1 Hz, H-4_A), 2.85 (1H, dddd, $J=19.2$, 5.5, 3.7, 0.7 Hz, H-4_B), 5.08 (1H, br q, $J=6.7$ Hz, H-1′); (300 MHz, $CDCl_3$): δ 1.44 (3H, d, $J=6.7$ Hz, H-2′), 2.54 (2H, t, $J=4.5$ Hz, H-5), 2.71 (1H, dt, $J=19.2$, 4.5 Hz, H-4_A), 2.86 (1H, dt, $J=19.2$, 4.5 Hz, H-4_B), 5.08 (1H, q, $J=6.7$ Hz, H-1′); ^{13}C NMR ($CDCl_3$): δ 20.6 (C-2′), 24.3 (C-4), 32.6 (C-5), 65.3 (C-1′), 129.0 (C-2), 175.0 (C-3), 201.6 (C-1); (300 MHz, $CDCl_3$): δ 20.8 (C-2′), 24.3 (C-4), 32.7 (C-5), 65.4 (C-1′), 129.2 (C-2), 174.7 (C-3), 201.4 (C-1). HRMS: *m*/*z* calcd for $C_7H_9O_2Cl$ (M^+) 160.0290, found 160.0272.

Using the same procedure as above with (1′*R*)-**24**, (1′*S*)-**24** (24.4 mg) afforded (+)-**3** (15.7 mg) as a colorless oil, $[\alpha]_D^{28}$ +11.5 (*c* 1.57, $CHCl_3$).

4.22. Chiral HPLC analyses for natural trichodenones A 1 and C 3

Chiral HPLC analyses were performed by the detection at 220 nm using Chiralpak AS and Chiralcel OBH (Daicel, 4.6×250 mm) as a column for trichodenone A **1** and trichodenone C **3**, respectively. A mixture of isopropyl alcohol and *n*-hexane (5:95) was used as the eluent. Under this operating condition, retention times for synthetic (+)- and (−)-**1,** and (+)- and (−)-**3** were 31.5, 33.0, 75.3, and 51.5 min, respectively. All the samples of natural trichodenone A **1**, isolated from the broth of three separate fermentations according to the method reported previously,[1] indicated two peaks of (+)- and (−)-**1**, while a sample of natural trichodenone C **3** showed only a peak of (−)-**3**.

Acknowledgements

We thank Drs. A. Hazato and Y. Naniwa, Teijin Co. Ltd, for providing the starting material, Mr. K. Minoura and Mrs. M. Fujitake and S. Okabe of our university for the NMR and MS measurements, respectively.

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