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# Synthesis and structure–activity relationships of radicicol derivatives and WNT-5A expression inhibitory activity

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ABSTRACT

WNT-5A, a secretory glycoprotein, is related to the proliferation of dermal papilla cells. To develop a hair-growth stimulant, we have been searching for inhibitors of WNT-5A expression. We identified radicicol (**1**) as an active compound, and synthesized several radicicol derivatives. Among them, 6,7-dihydro-10α-hydroxy radicicol (**31**) was found to function as a new potent WNT-5A expression inhibitor with relatively low toxicity and excellent stability.



## 1. Introduction

Hair loss or hair thinning is a common complaint of people living in today's stressful world.[1] Some drugs such as minoxidil[2,3] and finasteride,[4] that counter hair loss have been developed, but their therapeutic effects are limited. Consequently, a new drug is required that induces hair-growth through a new mechanism. Human hair follicles are made up of epithelial and mesenchymal dermal cells such as keratinocytes, dermal papilla cells, fibroblasts, and sebaceous cells; and the hair-growth cycle (hair cycle) is controlled through interactions among these cells. The hair shaft is formed by the proliferation and differentiation (keratinization) of follicular keratinocytes. Dermal papillae regulate the proliferation, differentiation, and apoptosis of these follicular keratinocytes, which play a key role in controlling the hair cycle.[5] Wingless-type mouse mammary tumor virus integration-site family, member 5A (WNT-5A) is a secretory glycoprotein that belongs to the WNT family. WNTs are important intercellular signaling molecules that regulate axis formation and organ formation during the fetal stage.[6,7] We have been studying molecules that regulate the proliferation of dermal papilla cells to develop a hair-growth stimulant and recently found that WNT-5A was highly expressed in the dermal papillae of depilated skin. A WNT-5A expression inhibitor promotes the proliferation of dermal papilla cells,[8] and by using such an inhibitor against WNT-5A expression as a guide for bioassay, we obtained radicicol (**1**)[9–12] as a potently active compound. We have isolated 10 new radicicol analogues and 10 known radicicol analogues from a culture broth of the fungus *Pochonia chlamydosporia var. chlamydosporia* and reported the structures and WNT-5A expression inhibitory activity of these compounds.[13,14] In this study, we report the synthesis of the derivatives of radicicol and monocillin (radicicol dechlorinated analogue),[15,16] their WNT-5A expression inhibitory activity, the structure–activity relationships (SARs), cytotoxicity of the compounds against dermal papilla cells, and their chemical stability.

## 2. Results and discussion

### 2.1. Chemistry

To obtain radicicol (**1**) and monocillins [monicillin I (**3**), II (**5**), and III (**4**)] as starting materials (Fig. 1), we cultured the strain TF-0480, identified as *Pochonia chlamydosporia*, and purified the resulting compounds using silica gel column chromatography, preparative TLC and recrystallization.[14]

To study the SARs of the radicicol derivatives and their WNT-5A expression inhibitory activity, some of the moieties in **1** were altered; (i) the phenolic hydroxyl groups at C-14 and C-16, (ii) the epoxide ring at C4–C5, (iii) the double bond at C6–C9, (iv) the carbonyl group at C-10, and (v) the halogen substituent at C-13 (Fig. 1). The reactions used for the transformation are shown in Schemes 1–3.

Methylation and acetylation of the phenolic hydroxyl groups (C-14 and C-16) in **1** produced dimethyl- (6) and diacetyl-derivatives (7), respectively.

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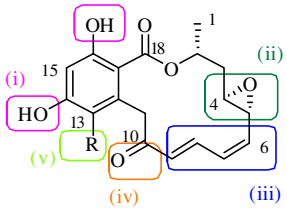
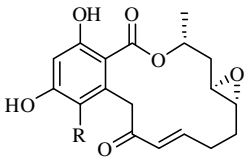
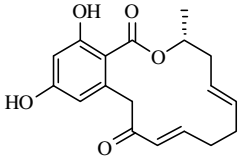



**1**: R=Cl (radicicol)
**3**: R=H (monocillin I)




**2**: R=Cl (pochonin A)
**4**: R=H (monocillin III)




**5**: (monocillin II)

**Figure 1.** Radicicol analogues (**1**–**5**) and conversion plan of radicicol.

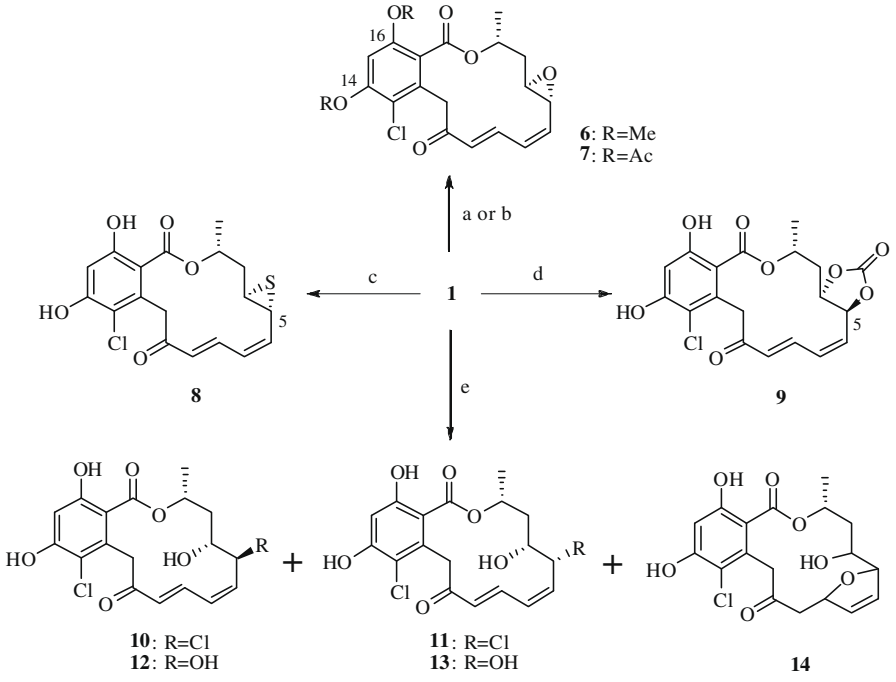
The epoxide ring at position C4–C5 was replaced with a thioxirane (**8**) and a cyclic carbonate (**9**) rings, respectively. The thioxirane-derivative (**8**) was obtained by treating **1** with potassium thiocyanate in the presence of indium(III) bromide in acetonitrile (MeCN).[17] The *E*-stereochemistry at the 4,5-thioxirane ring was assigned based on a $^1H$–$^1H$ coupling constants (**8**: $J_{4,5}$ = 5.4 Hz, **1**: $J_{4,5}$ = 3.0 Hz) and NOESY data. The NOE correlations between H-2/H-4, H-4/H-8, H-3b/H-5, and H-5/H-8 indicated the relative configuration of **8** at C4-C5, together with the conformation of **1**. The cyclic carbonate-derivative (**9**) was obtained by treating 1 with chlorosulfonyl isocyanate.[18] The stereochemistry around the new ring was determined by the NOESY spectrum exhibiting NOE cross peaks between $H_3$-1/H-4, H-4/H-6, and H-2/H-8.

Treatment of **1** with 1 M hydrochloric acid in DMF produced two chlorohydrin stereoisomers (**10**, **11**) and two diol-derivatives (**12**, **13**) at the epoxide moiety of **1**, as well as an unexpected product (**14**) with a new dihydro-furan ring formed between C-5 and C-8. The relative stereochemistries of these compounds (**10**–**13**) were compared with known chlorohydrin derivative[19] and assigned based on $^1H$–$^1H$ coupling constants (**10**: $J_{4,5}$ = 5.8 Hz, **12**: $J_{4,5}$ = 6.1 Hz, **11**: $J_{4,5}$ = 3.0 Hz, **13**: $J_{4,5}$ = 3.0 Hz) and NOESY correlations (**10** and **12**: H-5/H-6 and H-5/H-8, **11** and **13**: H-4/H-5 and H-5/H-9) for the NMR spectra of **10**–**13**.

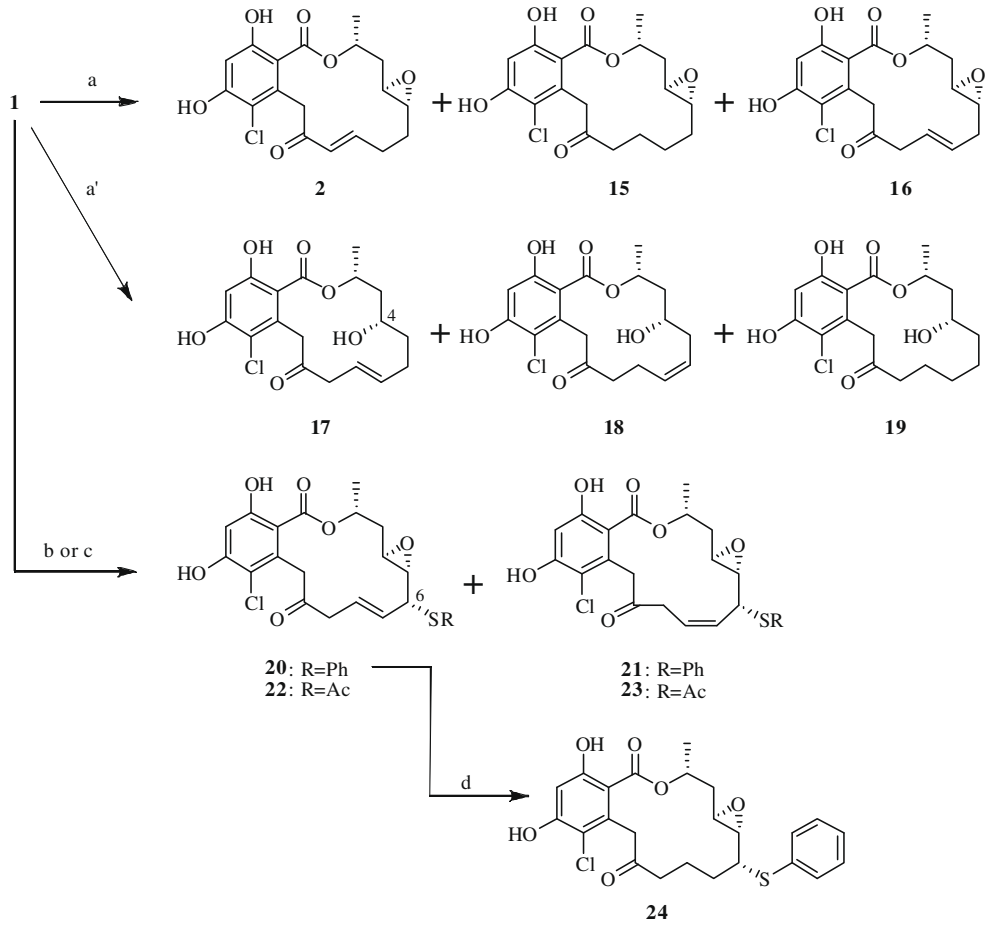
(iii) Hydrogenation of **1** produced two dihydro-derivatives and one tetrahydro-derivative (**15**) and three secondary alcohol derivatives (**17**–**19**) were converted from the epoxide. The two dihydro-derivatives were identified as 7,8-dihydo-derivative (**2**) and 6,9-dihydro-derivative (**16**) based on their 2D NMR spectra. Recently, compound **2** was reported as pochonin A, a natural product.[20] 6,7,8,9-Tetrahydro-13-dechloro derivatives **37** and **38** were synthesized from **4** and **5** in the same manner.

The Michael addition of the α,β,γ,δ-conjugated carbonyl moieties to **1** by treatment with thiophenol[21] or thioacetic acid[22] produced 1,6-adducts (**20**–**23**) that transferred the double bond at the β,γ-position and formed a *Z*- or *E*-configuration (Scheme 2). The stereochemistry of 1,6-adduct at the C-6 position was deduced using the $^1H$–$^1H$ coupling constants (**20**: $J_{4,5}$ = 2.4 Hz, $J_{5,6}$ = 8.5 Hz, **22**: $J_{4,5}$ = 1.8 Hz, $J_{5,6}$ = 7.9 Hz) and NOESY correlations (**20** and **22**: H-2/H-4, H-4/H-6, H-6/H-7, H-6/H-8, and H-5/H-6) for the NMR spectra of **20** and **22**.

To examine the influence of substituent at C-6 on WNT-5A activity, we investigated hydrogenation of the Michael addition derivative (**20**). Hydrogenation of **20** was attempted using several




**Scheme 1.** Reagents and conditions: (a) MeI, $K_2CO_3$, DMF, rt, 6.5 h, 75% (**6**); (b) $Ac_2O$, pyridine, rt, 6.5 h, 98% (**7**); (c) KSCN, $InBr_3$, MeCN, 60 °C, 8 h, 3% (**8**); (d) $ClSO_2NCO$, $CH_2Cl_2$, rt, 6 h, 20% (**9**); (e) 1 M HCl, 1,4-dioxane, rt, 0.5 h, 12% (**10**), 2% (**11**), 2% (**12**), 2% (**13**), 11% (**14**).




**Scheme 2.** Reagents and conditions: (a) $H_2$, 5% Pd–C (PH, wet-type), AcOEt, rt, 3 h, 38% (**2**), 31% (**15**), 0.2% (**16**); (a′) same condition of (a), 1% (**17**), 4% (**18**), 29% (**19**); (b) PhSH, TEA, DMF, 0 °C, 3 h, 72% (**20**), 8% (**21**); (c) AcSH, TEA, DMF, 0 °C, 16 h, 11% (**22**), 3% (**23**); (d) $H_2$, Wilkinson's catalyst, EtOH, rt, 34 h, 8% (**24**).

metal catalysts[23] including palladium, platinum, nickel, and rhodium; As a result, hydrogenation was obtained using palladium(II) acetate, platinum(IV) oxide, and Wilkinson's catalyst.[24,25] Hydrogenation with palladium carbon, palladium 2 wt % on strontium carbonate,[26] Lindlar catalyst,[27] and rhodium carbon was unsuccessful. Treatment with Raney nickel[28] resulted in an overreaction that progressed to dehydrogenation and dechlorination. Moreover, a dihydro-derivative was not observed during LC–MS analysis. Hydrogenation of **20** by treatment with Wilkinson's catalyst produced fewer byproducts than treatment with the other catalysts (palladium[II] acetate and platinum[IV] oxide) and produced a dihydro-derivative (**24**).

(iv) To examine the influence of the carbonyl group at the C-10 position on WNT-5A expression inhibitory activity, compound **1** was treated with hydroxylamine hydrochloride[19] to produce a stereoisomer mixture of a 10-oxime derivative (**25**) (*Z*:*E* = 1:0.7, as calculated by integrating the $^1$H NMR signals) (Scheme 3). The stereochemistry of **25** at C-10 was determined based on the results of $^{13}$C NMR chemical shifts at C-11 (*E*-oxime exhibited a high-field shift at about $\delta_C$ 29 [*E*-oxime], 36 ppm [*Z*-oxime])[29,30] and a NOESY experiment. Furthermore, we synthesized *O*-benzyloxime- and *O*-methyloxime-derivatives and separated them using $C_{18}$ HPLC to produce *Z*-isomers (**26** and **28**) and *E*-isomers (**27** and **29**), respectively.

A Luche reduction[31,32] of compounds **1**, **2**, and **15** produced mainly 1,2-reductive derivatives at C-10 (Scheme 3). The production ratio of the stereoisomers were controlled by the presence of the double bond (rigidity). The ratios of the two stereoisomers derived from **1**, **2**, and **15** were 10:0, 9:1, and 4:6, respectively.

Two stereoisomers were separated using $C_{18}$ HPLC; the compounds eluted earlier, possessed good crystallinity, and the crystals of **31** and **33** were grown in methanol.

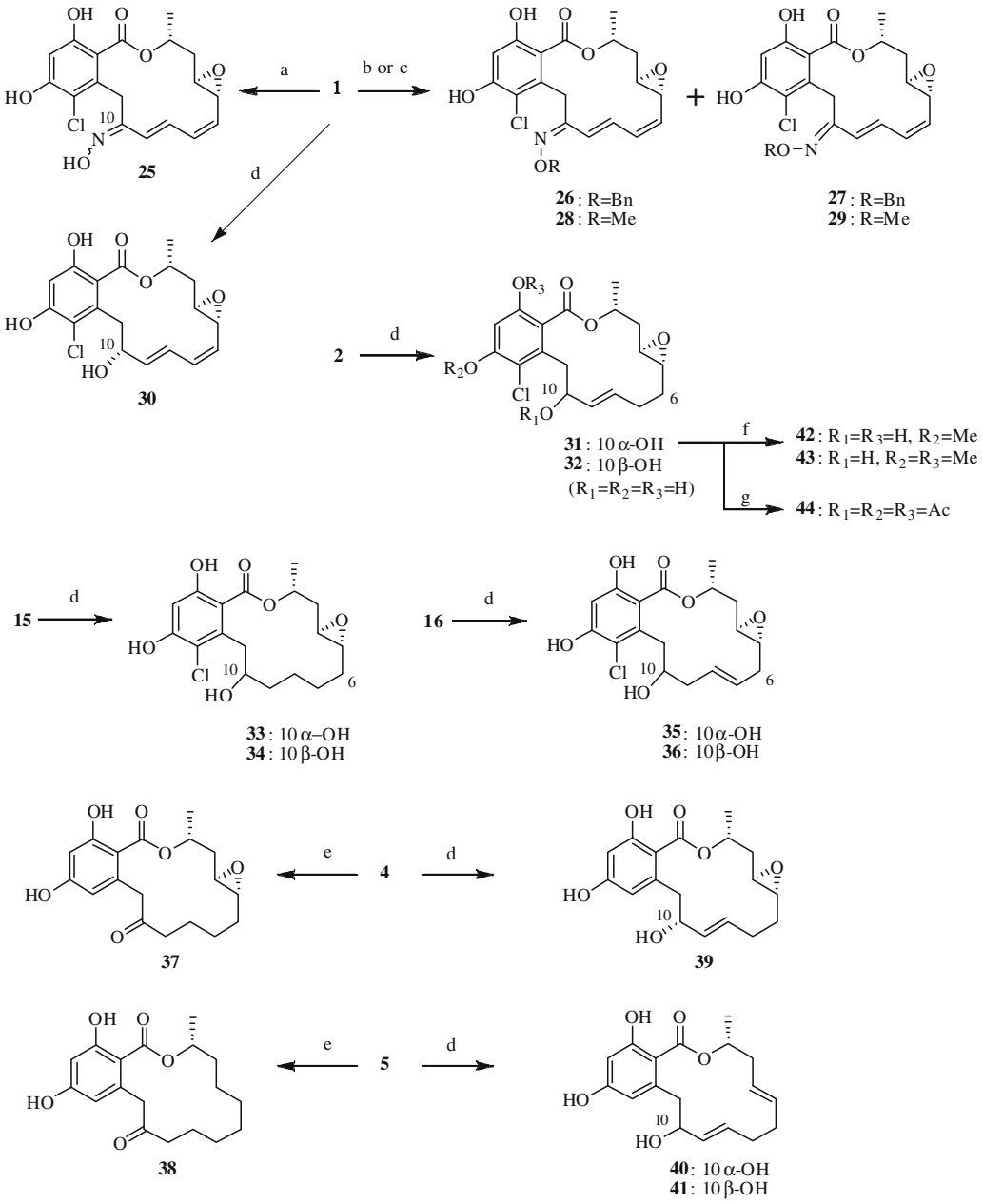
X-ray diffraction analyses of **31** and **33** were performed, and the crystal structure with the absolute configuration of **31** is shown in Figure 2. The absolute stereochemistry of **31** was 1*R*, 4*R*, 5*R*, and 10*R*, and the hydroxyl group at C-10 in both compounds was in the α-configuration.

Compound **30**, derived from **1**, was identified as a 10-α-hydroxy radicicol by comparing its NMR data with that of **31**–**34**. Compounds **32** and **34** were identified as 10β-hydroxy-derivatives based on the difference in their NMR chemical shifts around C-10, compared with those of **31** and **33**.

To obtain several 10-hydroxy derivatives, compounds **35** and **36** were derived from **16** by Luche reduction (ratio, 4:6). Dechloro derivatives **39**, **40**, and **41** were synthesized from **4** and **5** in the same manner. Methylation of **31** produced monomethyl- (**42**) and dimethyl-derivatives (**43**) at the phenolic hydroxyl groups. Acetylation of **31** produced a triacetyl-derivative (**44**) (Scheme 3).

## 2.2. WNT-5A expression inhibitory activity and structure–activity relationship

The inhibition of WNT-5A expression was measured using the QuantiGene assay (Panomics), which is a signal amplification nucleic acid probe assay used for direct quantification of cellular mRNA.[33] Cytotoxicity against dermal papilla cells was measured using the Alamar Blue™ assay (Biotium). The WNT-5A expression




**Scheme 3.** Reagents and conditions: (a) $HONH_2$·HCl, pyridine, 40 °C, 2.5 h, 18% (**25**); (b) $BnONH_2$·HCl, pyridine, 40 °C, 5.5 h, 3% (**26**), 2% (**27**); (c) $MeONH_2$·HCl, pyridine, 40 °C, 5.5 h, 6% (**28**), 5% (**29**); (d) $NaBH_4$, $CeCl_3·7H_2O$, MeOH, 0 °C, 5 min, 30% (**30**), 24% (**31**), 2% (**32**), 21% (**33**), 33% (**34**), 7% (**35**), 13% (**36**), 71% (**39**), 79% (**40**), 21% (**41**); (e) $H_2$, 5% Pd–C (PH, wet-type), AcOEt, rt, 1.5 h, 87% (**37**), 75% (**38**); (f) MeI, $K_2CO_3$, DMF, rt, 4.5 h, 18% (**42**), 40% (**43**); (g) $Ac_2O$, pyridine, rt, 17 h, 88% (**44**).

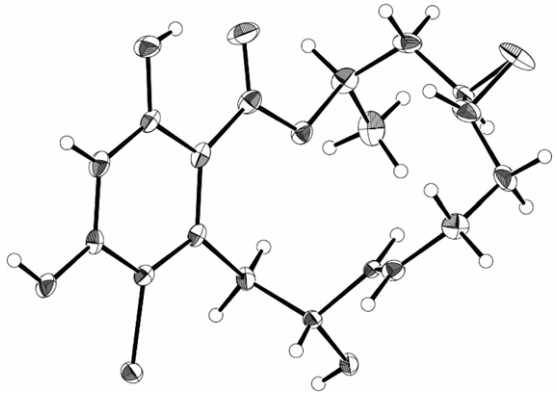


**Figure 2.** ORTEP structural plot of **31**.

inhibitory activity and cytotoxicity against dermal papilla cells of the radicicol derivatives are summarized in Table 1. The SARs of the radicicol derivatives and their WNT-5A expression inhibitory activity and cytotoxicity were as follows (Fig. 3):

Most of the derivatives (**11**–**14**) were inactivated when the epoxide ring was opened. Chlorohydrin (**10**) exhibited WNT-5A activity, but reverted to radicicol (**1**) in the assay medium (phosphate buffer, pH 7.4). Compared with other ring-formed derivatives, such as **8** and **9**, the epoxide ring appeared to exhibit an appropriate rigidity for a 14-membered macrolactone.

The Michael addition derivatives in the assay medium also reverted to radicicol, similar to chlorohydrin (**10**). To prevent this retro reaction, Michael addition derivative (**20**) was reduced to produce the 6α-thiophenyl-7,8,9-trihydro-derivative (**24**), which was inactive. However, 6,7,8,9-tetrahydro-radicicol (**15**) exhibited WNT-5A activity. Therefore, we suspect that not only the 14-mem-

**Table 1**
WNT-5A expression inhibitory activities and cytotoxicities against dermal papilla cells of radicicol (**1**) and radicicol derivatives (**2**–**44**)

| Compound | $IC_{50}$ (μM) WNT-5A | $TC_{50}$[a] (μM) | Compound | $IC_{50}$ (μM) WNT-5A | $TC_{50}$[a] (μM) |
|---|---|---|---|---|---|
| **1** | 0.19 | 15.35 | **23** | 0.50 | >100 |
| **2** | 2.64 | 57.32 | **24** | >50 | >50 |
| **3** | 1.93 | 2.90 | **25** | 0.26 | 89.45 |
| **4** | 9.43 | 28.87 | **26** | 0.51 | 65.61 |
| **5** | 7.36 | 17.62 | **27** | 0.06 | 42.13 |
| **6** | 3.76 | 8.40 | **28** | 0.15 | >100 |
| **7** | 0.30 | 29.09 | **29** | 1.22 | >100 |
| **8** | 9.13 | 28.23 | **30** | 2.07 | >100 |
| **9** | 15.71 | 28.11 | **31** | 1.89 | >100 |
| **10** | 13.28 | 41.98 | **32** | >100 | >100 |
| **11** | >50 | N.T. | **33** | 5.89 | >100 |
| **12** | >50 | N.T. | **34** | >100 | >100 |
| **13** | >50 | N.T. | **35** | >50 | N.T. |
| **14** | >50 | N.T. | **36** | >50 | N.T. |
| **15** | 2.24 | >100 | **37** | 14.95 | N.T. |
| **16** | 7.69 | >100 | **38** | >50 | N.T. |
| **17** | >50 | N.T. | **39** | 13.24 | >100 |
| **18** | >50 | N.T. | **40** | >50 | N.T. |
| **19** | >50 | N.T. | **41** | >50 | N.T. |
| **20** | 0.13 | 53.36 | **42** | >100 | N.T. |
| **21** | 0.27 | >50 | **43** | >100 | N.T. |
| **22** | 2.34 | >100 | **44** | >100 | N.T. |

N.T.: not tested.
[a] $TC_{50}$: half maximal toxic concentration.

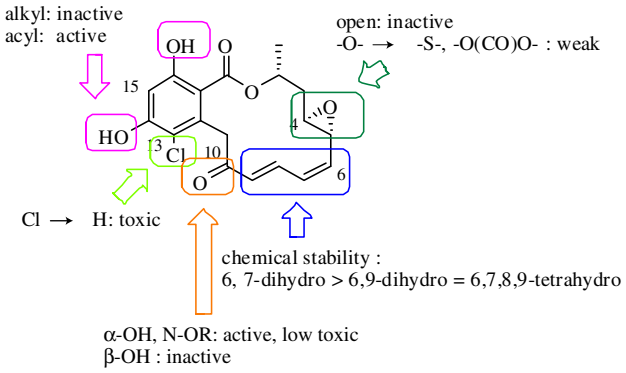



**Figure 3.** Structure–activity relationships (SARs) of radicicol derivatives and WNT-5A expression inhibitory activity.

bered macrolactone conformation formed from a double bond (C6–C9) and epoxide (C4–C5) but also the presence or size of the substituents in the macrolactone contributed to the inhibition of WNT-5A expression.

The chemical stabilities of hydrogenated radicicol derivatives (**2**, **15**, and **16**) differed; compound **2** was stable under acidic and in long-term storage conditions, but **15** and **16** were unstable under these conditions. These results indicated that the conjugation between the carbonyl at C-10 and the double bond is important for WNT-5A expression inhibitory activity and chemical stability.

10-Oxime derivatives (**25**–**29**) retained their ability to inhibit WNT-5A expression and exhibited lower cytotoxicity against dermal papilla cells. In case of the *O*-benzyloxime-derivative, the *E*-isomer (**27**) was more potent than the *Z*-isomer (**26**); however, the *Z*-isomer (**28**) of the *O*-methyloxime-derivative was more potent than the *E*-isomer (**29**).

10α-Hydroxy-derivatives (**30**, **31**, and **33**) exhibited inhibitory activity and no cytotoxicity, however, 10β-hydroxy-derivatives did not inhibit WNT-5A expression. The 10α-hydroxy-derivatives **31** and **39** differed in the presence of a Cl atom at C-13, and compound **31** was 7-fold more active than **39**. These results suggested that the Cl atom at the C-13 and C-10 substituents were very close and that the influence of these two substituents on conformation is important for WNT-5A expression inhibitory activity. The chemical stabilities of the 10α-hydroxy-derivatives **30**, **31**, **33**, and **35** differed. Compound **31** was more stable than **30**, **33**, and **35** under acidic (pH 2) or neutral conditions (pH 7.4 in phosphate buffer saline) (data not shown).

The 10α-hydroxy-derivatives were new compounds with a good balance between WNT-5A activity and cytotoxicity. The crystallinity, solubility and chemical stability of 10α-hydroxy-derivative (**31**) make it a promising compound. Therefore, we believe that the radicicol substituent at C-10 and the adjacent olefins are important regions for WNT-5A activity and chemical stability.

Radicicol (monorden) exhibits antibiotic,[9] antitumor,[34] and antimalarial[35] activities. Recently, radicicol oxime derivatives have been reported as antitumor medications, based on their inhibitory actions on tyrosine kinase and heat shock protein 90 (HSP90).[19,36] Oxime derivatives is stable and efficacious in vivo for improving the instability that caused by the presence of the epoxide and α,β,γ,δ-conjugated carbonyl moieties.

Yang et al.[37] synthesized cycloproparadicicol, in which the epoxide at C4–C5 was replaced with cyclopropyl, to improve the chemical stability, and this compound inhibited HSP90 ($IC_{50}$ 160 nM).

Pochonin A, a naturally occurring 6,7-dihydro-radicicol,[20] also exhibited HSP90 affinity ($IC_{50}$ 90 nM) and was more stable than radicicol (**1**).[38]

Turbyville et al.[39] reported that the structure–activity relationship (SAR) and chemical stability of radicicol derivatives and HSP90 inhibitory activity indicate that an $sp^2$-hybridized carbon at C-10, steric strain substituents at C4–C5 (oxirane, cyclopropyl, and double bond) and a macrocyclic system were important factors for activity, however, the Cl atom at C-13 was not essential for HSP90 activity and enhanced cytotoxicity. Hellwig et al.[20] reported the SARs of radicicol and radicicol analogues, including pochonins A–F, and antiviral activity. The epoxide ring at C4–C5 is important for antiviral activity, but a double bond at the same position produces an inactive compound and the Cl atom at C-13 is not essential. Compared with the SARs necessary for inhibition of WNT-5A expression, these SARs are similar to that of WNT-5A expression inhibitory activity except for importance of the Cl atom at C-13.

## 3. Conclusion

To develop a hair-growth stimulant, we have been searching for radicicol analogues or derivatives for a new inhibitor against WNT-5A expression. As a result, we synthesized and selected the 6,7-dihydro-10α-hydroxy derivative **31** from amongst the radicicol derivatives, which exhibited moderate inhibition against WNT-5A expression and no cytotoxicity against dermal papilla cells. We confirmed that active compounds with an inhibiting effect on WNT-5A expression also exerted dermal papilla cell proliferation activity (data report in another article). 10-Oxime- or 10α-hydroxy-radicicol derivatives exhibited a good active profile in vitro. The new radicicol derivative **31** exhibits a moderate solubility and chemical stability. Therefore, in future, we plan to perform a sequential study on the in vivo trichogenous activity of **31** and will report the results of this study in another article.

## 4. Experimental

### 4.1. General experimental procedures

$^1H$ and $^{13}C$ nuclear magnetic resonance (NMR) spectra were recorded at 500 MHz using a JEOL Alpha 500 or Lambda 500 or ECA 500 spectrometer. The coupling constants (*J*) are given in hertz (Hz), and the abbreviations s, d, t, q, br, and m refer to singlet, doublet, triplet, quartet, broad, and multiplet peaks, respectively. All

assignments were based on $^1H$–$^1H$ correlation spectroscopy (COSY), heteronuclear single- or multiple-quantum coherence (HSQC or HMQC, respectively), heteronuclear multiple-bond correlation (HMBC), and nuclear overhauser effect spectroscopy (NOESY) methods. Chemical shifts are reported in parts per million (ppm), with the solvent peaks used as an internal standard. Electron impact (EI) and electrospray ionization (ESI) mass spectra were obtained using a JEOL JMS-SX102 spectrometer and Micromass Platform LC mass spectrometer, respectively. Melting points were determined using a MP-500D micro-melting point apparatus (Yanaco). Optical rotations were measured using an AUTOPOL V digital polarimeter (Rudolph Research Analytical). UV spectra were recorded using a V-520 UV/Vis spectrophotometer (JASCO). IR spectra were measured using a Spectrum One FT-IR spectrometer (PerkinElmer). The reactions monitored by TLC and HPLC analysis (system 1). For TLC analysis, we used Merck Silica Gel $60F_{254}$ thin-layer plates, UV light as the visualizing agent and 10% methanolic phosphomolybdic acid and heat as the developing method. The HPLC analysis system (system 1); LC1100 (Agilent) was operated with the following conditions: column, YMC-Pack ODS-AM, 3 μm, 4.6 × 100 mm (YMC Co.); eluent A, $H_2O$ + 0.001% trifluoroacetic acid (TFA); eluent B, acetonitrile (MeCN); gradient, 15–85% B, 30 min; flow rate, 1.0 mL/min; temperature, 40 °C. LC–MS system (system 2): LC/MSD (Agilent) was operated in the ESI positive and negative mode with the following conditions: column, YMC-Pack ODS-AM, 3 μm, 4.6 × 100 mm (YMC Co.); eluent A, $H_2O$ + 5 mM $HCOONH_4$ + 5 mM HCOOH; eluent B, MeCN + 5 mM HCOOH; gradient, 15–85% B, 30 min; flow rate, 1.0 mL/min; temperature, 40 °C. MS parameters: scan range, 100–1200; capillary voltage, 3000 V; fragmentor voltage, 100 V. The following materials were used to separate the compounds: silica gel column chromatography, Wako Pure Chemical C-200; preparative thin layer chromatography, Merck silica gel plate $60F_{254}$ (layer thickness; 0.5 mm); gel filtration, Sephadex LH-20 (Pharmacia Co.). Preparative HPLC was performed using a Waters M600 system as follows: preparative HPLC system, Waters M600; column, YMC-Pack Pro $C_{18}$ AS-343, 5 μm, 20 × 250 mm; flow rate, 10 mL/min; UV detection, 254 nm; temperature, 40 °C; eluent, MeCN/$H_2O$ (+0.25% acetic acid).

### 4.2. Biological assays

#### 4.2.1. Inhibition of WNT-5A expression (quantification of mRNA using the QuantiGene method)

Human dermal papilla cells, which were a gift from Dr. S. Arase (University of Tokushima Faculty of Medicine), were cultured in MEM (Invitrogen) containing 12% fetal bovine serum (FBS). The dermal papilla cells in the fifth subculture generation were sowed in a 96-well plate at a density of $1 \times 10^4$ cells/well and cultured overnight. The medium was then replaced with one that contained the test compounds or one that did not contain any test compounds, and was cultured for an additional 24 h. After 24 h, the amount of WNT-5A mRNA was measured using a QuantiGene High Volume Kit (Bayer Medical) by the branched DNA (bDNA) signal amplification method.[33] In accordance with the manufacturer's protocol, the cells were lysed with a lysis mixture and the lysis solution was added to the capture plate.

Next, a set of probes specific to WNT-5A[8] was added and the reaction was allowed to proceed at 53 °C for 20 h. After the plate was washed using 0.1 × SSC (3.0 M NaCl and 0.3 M sodium citrate) containing 0.03% lauryl sulfate, an amplification probe that contained bDNA was added and allowed to react at 46 °C for 1 h. After the plate was washed, a probe labeled with alkaline phosphatase was added and allowed to react at 46 °C for 1 h. After the plate was washed, the Lumi-Phos Plus substrate was added and the reaction was allowed to proceed at 46 °C for 30 min. Luminescence was measured using a WALLAC 1420 ARVOsx.

#### 4.2.2. Cytotoxicity against dermal papilla cells

Dermal papilla cells were sowed in a 96-well plate to yield a density of $5 \times 10^3$ cells/well and cultured 16 h in MEM containing 12% FBS. The medium was then replaced with a medium to which no compounds had been added or a medium that contained the test compounds and was cultured for an additional 24 h. The medium was then replaced with a medium containing 10% Alamar Blue™ (Wako Pure Chemical Industries) and the culture was continued for an additional 4 h. Finally, the fluorescence intensity (Ex 544 nm, Em 590 nm) was measured using a WALLAC 1420 ARVOsx.

### 4.3. Preparation and characteristics of starting materials: radicicol (1), monocillin I (3), monocillin III (4), and monocillin II (5)

These compounds were obtained by fungal fermentation in our laboratory,[14] and their structures were confirmed using spectral data described in the previous studies.[11,16,20]

#### 4.3.1. Radicicol (1)

Colorless crystal; mp 181–183 °C, lit.:[10] 195 °C; $[\alpha]_D^{20}$ +194.6 (*c* 1.00, chloroform), lit.:[10] $[\alpha]_D$ +216 (*c* 1.00, chloroform); UV (methanol) $\lambda_{max}$ (log $\varepsilon$) 215 (4.58), 266 (4.34), and 308 sh (3.92) nm; IR (KBr) $\nu_{max}$ 3418, 2988, 1706, 1655, 1607, 1438, 1360, 1306, 1244, 1110, 1043, 982, 925, 848, 732, 712, 670, 602 $cm^{-1}$; HPLC, $t_R$ 8.10 min (system 1); $^1H$ NMR (chloroform-*d*/methanol-$d_4$, 500 MHz) $\delta$ 7.48 (1H, dd, *J* = 15.9, 9.8 Hz, H-8), 6.45 (1H, s, H-15), 6.15 (1H, t, *J* = 9.8 Hz, H-7), 6.05 (1H, d, *J* = 15.9 Hz, H-9), 5.78 (1H, dd, *J* = 9.8, 3.0 Hz, H-6), 5.41 (1H, ddq, *J* = 3.7, 3.7, 6.7 Hz, H-2), 4.51 (1H, d, *J* = 16.5 Hz, H-11a), 3.86 (1H, d, *J* = 16.5 Hz, H-11b), 3.19 (1H, br s, H-5), 2.94 (1H, dt, *J* = 9.6, 3.0 Hz, H-4), 2.33 (1H, dt, *J* = 15.3, 3.7 Hz, H-3a), 1.83 (1H, ddd, *J* = 15.3, 9.6, 3.7 Hz, H-3b), 1.48 (3H, d, *J* = 6.7 Hz, $H_3$-1); $^{13}C$ NMR (chloroform-*d*/methanol-$d_4$, 125 MHz) $\delta$ 199.1 (s, C-10), 168.9 (s, C-18), 161.2 (s, C-16), 158.2 (s, C-14), 139.6 (d, C-8), 135.7 (s, C-12), 135.0 (d, C-6), 130.5 (d, C-9), 130.1 (d, C-7), 116.1 (s, C-13), 108.0 (s, C-17), 103.4 (d, C-15), 71.2 (d, C-2), 56.1 (d, C-4), 55.8 (d, C-5), 46.3 (t, C-11), 36.3 (t, C-3), 18.5 (q, C-1); ESI-MS (neg.) *m/z* (%) 363.0 (100, $[M-H]^-$), 365.0 (40); HRESI-MS *m/z* 363.0647 (calcd for $C_{18}H_{16}Cl_1O_6$ $[M-H]^-$, 363.0635, $\Delta$ +1.2 mmu).

#### 4.3.2. Monocillin I (3)

Colorless oil; $[\alpha]_D^{20}$ +6.9 (*c* 1.00, acetone); UV (methanol) $\lambda_{max}$ (log $\varepsilon$) 217 (4.13), 262 (3.98), and 294 sh (3.67) nm; IR (KBr) $\nu_{max}$ 3388, 2980, 2941, 1708, 1651, 1625, 1588, 1504, 1451, 1384, 1346, 1311, 1262, 1209, 1169, 1121, 1099, 1044, 1027, 993, 924, 850, 802, 754, 718, 693, 667, 618, 520 $cm^{-1}$; HPLC, $t_R$ 8.34 min (system 1); $^1H$ NMR (acetone-$d_6$, 500 MHz) $\delta$ 10.94 (1H, br s, 16-OH), 9.16 (1H, br s, 14-OH), 7.83 (1H, dd, *J* = 16.1, 11.3 Hz, H-8), 6.30 (1H, dd, *J* = 11.3, 10.7 Hz, H-7), 6.29 (1H, d, *J* = 2.7 Hz, H-15), 6.28 (1H, d, *J* = 2.7 Hz, H-13), 5.97 (1H, d, *J* = 16.1 Hz, H-9), 5.83 (1H, dd, *J* = 10.7, 2.7 Hz, H-6), 5.49 (1H, ddq, *J* = 3.7, 3.7, 6.7 Hz, H-2), 4.97 (1H, d, *J* = 14.0 Hz, H-11a), 3.56 (1H, d, *J* = 14.0 Hz, H-11b), 3.32 (1H, q, *J* = 2.7 Hz, H-5), 3.12 (1H, dt, *J* = 8.5, 2.7 Hz, H-4), 2.44 (1H, ddd, *J* = 14.9, 3.7, 2.7 Hz, H-3a), 1.85 (1H, ddd, *J* = 14.9, 8.5, 3.7 Hz, H-3b), 1.60 (3H, d, *J* = 6.7 Hz, $H_3$-1); $^{13}C$ NMR (acetone-$d_6$, 125 MHz) $\delta$ 198.9 (s, C-10), 170.4 (s, C-18), 165.5 (s, C-16), 162.9 (s, C-14), 141.6 (d, C-8), 140.3 (s, C-12), 137.2 (d, C-6), 131.7 (d, C-9), 130.6 (d, C-7), 110.1 (d, C-13), 106.0 (a, C-17), 102.8 (d, C-15), 72.0 (d, C-2), 56.0 (d, C-4), 55.7 (d, C-5), 43.9 (t, C-11), 36.9 (t, C-3), 18.9 (q, C-1); ESI-MS (neg.) *m/z* (%) 329.1 (100, $[M-H]^-$), 330.1 (20); HRESI-MS *m/z* 329.1016 (calcd for $C_{18}H_{17}O_6$ $[M-H]^-$, 329.1025, $\Delta$ −0.9 mmu).

#### 4.3.3. Monocillin III (4)

Colorless crystal; mp 197–200 °C, lit.:[16] 204–205 °C; $[\alpha]_D^{20}$ −0.8 (*c* 1.00, acetone); UV (methanol) $\lambda_{max}$ (log $\varepsilon$) 217 (4.49), 264 (4.00), and 304 (3.72) nm; IR (KBr) $\nu_{max}$ 3613, 3418, 2985, 1674, 1643, 1621, 1584, 1493, 1464, 1440, 1418, 1389, 1358, 1342, 1312, 1260, 1217, 1196, 1175, 1143, 1100, 1078, 1059, 1036, 1021, 986, 922, 896, 879, 850, 805, 738, 585, 556, 502 $cm^{-1}$; HPLC, $t_R$ 7.51 min (system 1); $^1H$ NMR (acetone-$d_6$, 500 MHz) $\delta$ 11.91 (1H, br s, 16-OH), 9.23 (1H, br s, 14-OH), 6.91 (1H, ddd, *J* = 15.8, 11.0, 4.6 Hz, H-8), 6.27 (1H, d, *J* = 2.4 Hz, H-15), 6.24 (1H, d, *J* = 2.4 Hz, H-13), 6.02 (1H, d, *J* = 15.8 Hz, H-9), 5.18 (1H, m, H-2), 4.65 (1H, d, *J* = 17.7 Hz, H-11a), 3.65 (1H, d, *J* = 17.7 Hz, H-11b), 2.80 (1H, ddd, *J* = 5.5, 4.0, 2.7 Hz, H-4), 2.51 (1H, dt, *J* = 9.4, 2.7 Hz, H-5), 2.47 (1H, dd, *J* = 8.8, 4.6 Hz, H-7a), 2.29 (1H, m, H-7b), 2.27 (1H, m, H-6a), 2.06 (1H, dt, *J* = 16.1, 4.0 Hz, H-3a), 1.63 (1H, ddd, *J* = 16.1, 5.5, 4.0 Hz, H-3b), 1.37 (3H, d, *J* = 6.7 Hz, $H_3$-1), 1.19 (1H, m, H-6b); $^{13}C$ NMR (acetone-$d_6$, 125 MHz) $\delta$ 196.9 (s, C-10), 171.9 (s, C-18), 167.1 (s, C-16), 163.4 (s, C-14), 148.6 (d, C-8), 141.3 (s, C-12), 131.9 (d, C-9), 113.9 (d, C-13), 105.9 (s, C-17), 102.8 (d, C-15), 72.5 (d, C-2), 57.0 (d, C-5), 55.7 (d, C-4), 48.2 (t, C-11), 37.0 (t, C-3), 31.8 (t, C-6), 29.8 (t, C-7), 18.1 (q, C-1); ESI-MS (neg.) *m/z* (%) 331.0 (100, $[M-H]^-$), 332.0 (20); HRESI-MS *m/z* 331.1188 (calcd for $C_{18}H_{19}O_6$ $[M-H]^-$, 331.1182, $\Delta$ +0.6 mmu).

#### 4.3.4. Monocillin II (5)

Colorless crystal; mp 188–191 °C, lit.:[16] 198–200 °C; $[\alpha]_D^{20}$ +23.7 (*c* 0.43, acetone); UV (methanol) $\lambda_{max}$ (log $\varepsilon$) 224 (4.60), 262 (4.18), and 302 (3.90) nm; IR (KBr) $\nu_{max}$ 3313, 2944, 1674, 1646, 1612, 1594, 1498, 1485, 1460, 1442, 1414, 1366, 1332, 1317, 1258, 1216, 1173, 1140, 1108, 1036, 979, 924, 892, 860, 823, 790, 728, 691, 625, 544 $cm^{-1}$; HPLC, $t_R$ 11.71 min (system 1); $^1H$ NMR (DMSO-$d_6$, 500 MHz) $\delta$ 10.27 (1H, br s, 16-OH), 9.92 (1H, br s, 14-OH), 6.64 (1H, ddd, *J* = 16.1, 7.6, 6.4 Hz, H-8), 6.20 (1H, d, *J* = 2.4 Hz, H-15), 6.09 (1H, d, *J* = 2.4 Hz, H-13), 5.86 (1H, d, *J* = 16.1 Hz, H-9), 5.31 (1H, ddd, *J* = 15.2, 7.6, 3.0 Hz, H-4), 5.29 (1H, ddd, *J* = 15.2, 7.0, 4.3 Hz, H-5), 5.09 (1H, m, H-2), 3.90 (1H, d, *J* = 15.2 Hz, H-11a), 3.50 (1H, d, *J* = 15.2 Hz, H-11b), 2.39 (1H, dt, *J* = 14.0, 3.0 Hz, H-3a), 2.25–2.13 (3H, m, H-3b, H-6a and H-7a), 2.12 (1H, m, H-7b), 2.04 (1H, m, H-6b), 1.23 (3H, d, *J* = 6.4 Hz, $H_3$-1); $^{13}C$ NMR (DMSO-$d_6$, 125 MHz) $\delta$ 196.6 (s, C-10), 168.4 (s, C-18), 160.2 (s, C-16), 159.5 (s, C-14), 148.2 (d, C-8), 136.6 (s, C-12), 131.2 (d, C-5), 129.7 (d, C-9), 128.3 (d, C-4), 110.3 (s, C-17), 108.8 (d, C-13), 101.4 (d, C-15), 71.0 (d, C-2), 45.2 (t, C-11), 37.9 (t, C-3), 30.4 (t, C-6), 30.3 (t, C-7), 19.2 (q, C-1); ESI-MS (neg.) *m/z* (%) 315.1 (100, $[M-H]^-$), 316.1 (20); HRESI-MS *m/z* 315.1228 (calcd for $C_{18}H_{19}O_5$ $[M-H]^-$, 315.1232, $\Delta$ −0.4 mmu).

### 4.4. Preparation and characteristics of radicicol derivatives

#### 4.4.1. Radicicol dimethyl ether (6)

Potassium carbonate (3 mg, 0.022 mmol) and methyl iodide (4 mL, 64.2 mmol) were added to a solution of radicicol (**1**) (19.0 mg, 0.052 mmol) in *N*,*N*-dimethylformamide (1 mL), and the mixture was stirred for 6.5 h at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, evaporated in vacuo and purified using preparative TLC (developing solvent, chloroform–methanol = 95:5) to produce compound **6** (15.3 mg, 74.8%). Compound **6**: colorless oil; HPLC, $t_R$ 11.27 min (system 1); $^1H$ NMR (chloroform-*d*, 500 MHz) $\delta$ 7.48 (1H, dd, *J* = 15.9, 10.4 Hz, H-8), 6.45 (1H, s, H-15), 6.12 (1H, t, *J* = 10.4 Hz, H-7), 6.07 (1H, d, *J* = 15.9 Hz, H-9), 5.69 (1H, dd, *J* = 10.4, 4.3 Hz, H-6), 5.35 (1H, m, H-2), 3.95 (1H, d, *J* = 15.9 Hz, H-11a), 3.89 (3H, s, 16-O*Me*), 3.83 (3H, s, 14-O*Me*), 3.75 (1H, d, *J* = 15.9 Hz, H-11b), 3.40 (1H, dd, *J* = 4.3, 1.8 Hz, H-5), 3.02 (1H, dt, *J* = 8.6, 1.8 Hz, H-4), 2.40 (1H, ddd, *J* = 14.6, 3.7, 1.8 Hz, H-3a), 1.61 (1H, ddd, *J* = 14.6, 8.6, 3.7 Hz, H-3b), 1.50 (3H, d, *J* = 6.7 Hz, $H_3$-1); $^{13}C$ NMR (chloroform-*d*, 125 MHz) $\delta$ 196.4 (s, C-10), 166.0 (s, C-18), 156.9 (s, C-16), 156.3 (s, C-14), 138.6 (d, C-8), 135.6 (d, C-6), 132.4 (s, C-12), 131.0 (d, C-9), 130.2 (d, C-7), 117.9 (s, C-17), 115.5 (s, C-13), 95.5 (d, C-15), 70.2 (d, C-2), 56.4 (q, 14-O*Me*), 56.3 (q, 16-O*Me*), 55.6 (d, C-4), 55.5 (d, C-5), 45.2 (t, C-11), 37.3 (t, C-3), 18.6 (q, C-1); ESI-MS *m/z* 415 $[M+Na]^+$ as $C_{20}H_{21}ClO_6Na$.

#### 4.4.2. Radicicol diacetate (7)

Acetic anhydride (4 mL) was added to a solution of **1** (15.3 mg, 0.042 mmol) in pyridine (1.5 mL), and the mixture was stirred for 6.5 h at room temperature. The reaction mixture was poured over ice water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, evaporated in vacuo and purified using preparative TLC (developing solvent, chloroform–methanol = 95:5) to produce compound **7** (18.5 mg, 98.4%). Compound **7**: colorless oil; HPLC, $t_R$ 11.35 min (system 1); $^1H$ NMR (chloroform-*d*, 500 MHz) $\delta$ 7.45 (1H, dd, *J* = 16.5, 11.0 Hz, H-8), 7.02 (1H, s, H-15), 6.12 (1H, t, *J* = 11.0 Hz, H-7), 6.03 (1H, d, *J* = 16.5 Hz, H-9), 5.74 (1H, dd, *J* = 11.0, 3.0 Hz, H-6), 5.37 (1H, m, H-2), 4.04 (1H, d, *J* = 15.9 Hz, H-11a), 3.91 (1H, d, *J* = 15.9 Hz, H-11b), 3.49 (1H, dd, *J* = 3.7, 3.0 Hz, H-5), 2.99 (1H, dt, *J* = 8.5, 3.7 Hz, H-4), 2.38 (1H, ddd, *J* = 14.6, 3.7, 3.0 Hz, H-3a), 2.31 (3H, s, 16-OCO*Me*), 2.24 (3H, s, 14-OCO*Me*), 1.54 (1H, ddd, *J* = 14.6, 8.5, 3.7 Hz, H-3b), 1.51 (3H, d, *J* = 6.7 Hz, $H_3$-1); $^{13}C$ NMR (chloroform-*d*, 125 MHz) $\delta$ 195.6 (s, C-10), 168.1 (s, C-18), 167.5 (s, 14-OCOMe), 163.8 (s, 16-OCOMe), 148.7 (s, C-16), 146.6 (s, C-14), 139.1 (d, C-8), 136.1 (d, C-6), 133.6 (s, C-12), 130.6 (d, C-9), 129.9 (d, C-7), 126.5 (s, C-15), 126.3 (s, C-13), 117.8 (d, C-15), 70.9 (d, C-2), 55.4 (d, C-4), 55.0 (d, C-5), 45.1 (t, C-11), 37.1 (t, C-3), 20.7 (q, 14-OCO*Me*), 20.6 (q, 16-OCO*Me*), 18.6 (q, C-1); ESI-MS *m/z* 471 $[M+Na]^+$ as $C_{22}H_{21}ClO_8Na$.

#### 4.4.3. 4,5-Thioxirane radicicol derivative (8)

Indium(III) bromide (48 mg, 0.14 mmol, 0.1 equiv) and potassium thiocyanate (125 mg, 1.29 mmol, 1.3 equiv) were added to a solution of **1** (366 mg, 1.00 mmol) in MeCN (12 mL) at room temperature. The mixture was stirred for 8 h at 60 °C and then cooled to room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, evaporated in vacuo and purified using preparative HPLC (eluent, MeCN–$H_2O$ = 40:60), and was further purified using preparative TLC (developing solvent, chloroform–methanol = 9:1) to produce compound **8** (12.2 mg, 3.0%). Compound **8**: colorless oil; HPLC, $t_R$ 11.68 min (system 1); $^1H$ NMR (acetone-$d_6$, 500 MHz) $\delta$ 7.42 (1H, dd, *J* = 16.0, 9.2 Hz, H-8), 6.57 (1H, s, H-15), 6.15 (1H, dd, *J* = 10.7, 9.2 Hz, H-7), 6.10 (1H, d, *J* = 16.0 Hz, H-9), 5.91 (1H, dd, *J* = 10.7, 4.6 Hz, H-6), 5.36 (1H, m, H-2), 4.45 (1H, d, *J* = 16.0 Hz, H-11a), 4.40 (1H, d, *J* = 16.0 Hz, H-11b), 3.55 (1H, dd, *J* = 5.4, 4.6 Hz, H-5), 3.29 (1H, dt, *J* = 7.6, 5.4 Hz, H-4), 2.46 (1H, ddd, *J* = 15.3, 5.4, 2.3 Hz, H-3a), 2.11 (1H, ddd, *J* = 15.3, 7.6, 6.9 Hz, H-3b), 1.46 (3H, d, *J* = 6.1 Hz, $H_3$-1); $^{13}C$ NMR (acetone-$d_6$, 125 MHz) $\delta$ 195.7 (s, C-10), 169.3 (s, C-18), 159.8 (s, C-16), 157.7 (s, C-14), 138.8 (d, C-8), 136.6 (d, C-6), 135.9 (s, C-12), 132.6 (d, C-9), 128.8 (d, C-7), 116.5 (s, C-17), 111.1 (s, C-13), 103.5 (d, C-15), 74.1 (d, C-2), 43.6 (t, C-11), 43.2 (t, C-3), 40.5 (d, C-4), 40.4 (d, C-5), 20.2 (q, C-1); ESI-MS *m/z* 379 $[M-H]^-$ as $C_{18}H_{16}ClO_5S$.

#### 4.4.4. 4,5-Carbonate radicicol derivative (9)

Chlorosulfonyl isocyanate (0.5 mL, 5.74 mmol, 2.2 equiv) was added to a solution of **1** (930 mg, 2.55 mmol) in dichloromethane (35 mL), and the mixture was stirred for 6 h at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, evaporated in vacuo and purified using preparative

TLC (developing solvent, *n*-hexane–acetone = 1:1), and was further purified using preparative HPLC (eluent, MeCN–$H_2O$ = 45:55) to produce compound **9** (189.8 mg, 19.5%). Compound **9**: colorless oil; HPLC, $t_R$ 8.04 min (system 1); $^1$H NMR (acetone-$d_6$, 500 MHz) $\delta$ 9.98 (1H, br s, 16-OH), 9.60 (1H, br s, 14-OH), 7.53 (1H, dd, $J$ = 15.9, 10.4 Hz, H-8), 6.58 (1H, s, H-15), 6.44 (1H, dd, $J$ = 11.0, 10.4 Hz, H-7), 6.13 (1H, d, $J$ = 15.9 Hz, H-9), 5.98 (1H, dd, $J$ = 11.0, 7.3 Hz, H-6), 5.59 (1H, m, H-5), 5.56 (1H, m, H-2), 4.75 (1H, dt, $J$ = 6.7, 3.7 Hz, H-4), 4.36 (1H, d, $J$ = 16.5 Hz, H-11a), 4.01 (1H, d, $J$ = 16.5 Hz, H-11b), 2.42 (1H, ddd, $J$ = 16.5, 6.7, 3.0 Hz, H-3a), 2.30 (1H, ddd, $J$ = 16.5, 6.1, 3.7 Hz, H-3b), 1.54 (3H, d, $J$ = 6.1 Hz); $^{13}$C NMR (acetone-$d_6$, 125 MHz) $\delta$ 196.9 (s, C-10), 168.3 (s, C-18), 160.0 (s, C-16), 157.9 (s, C-14), 154.3 (s, C-1′; –O–*C*O–O–), 138.3 (d, C-8), 136.2 (s, C-12), 134.6 (d, C-6), 133.2 (d, C-9), 131.1 (d, C-7), 115.5 (s, C-13), 111.1 (s, C-17), 103.9 (d, C-15), 80.1 (d, C-4), 77.7 (d, C-5), 70.4 (d, C-2), 45.6 (t, C-11), 36.5 (t, C-3), 19.8 (q, C-1); ESI-MS $m/z$ 407 $[M-H]^-$ as $C_{19}H_{16}ClO_8$.

#### 4.4.5. Chlorohydrin (10), (11) and diol (12), (13) derivatives

One-molar hydrochloric acid (2 mL) was added to a solution of **1** (611 mg, 1.67 mmol) in 1,4-dioxane (8 mL), and the mixture was stirred for 30 min at room temperature. The reaction mixture was neutralized with 1 M sodium hydroxide, evaporated in vacuo and purified using preparative HPLC (eluent, MeCN–$H_2O$ = 35:65) to produce compounds **10** (83.2 mg, 12.4%), **11** (10.4 mg, 1.5%), **12** (10.7 mg, 1.7%), and **13** (9.9 mg, 1.5%).

**4.4.5.1. Chlorohydrin derivative (10) (pochonin C;[20] synthetic).** Colorless oil; HPLC, $t_R$ 5.72 min (system 1); $^1$H NMR (methanol-$d_4$, 500 MHz) $\delta$ 7.21 (1H, dd, $J$ = 16.1, 11.3 Hz, H-8), 6.46 (1H, s, H-15), 6.17 (1H, dd, $J$ = 11.3, 10.0 Hz, H-7), 5.95 (1H, d, $J$ = 16.1 Hz, H-9), 5.75 (1H, t, $J$ = 10.0 Hz, H-6), 5.38 (1H, m, H-2), 5.12 (1H, dd, $J$ = 10.0, 5.8 Hz, H-5), 4.21 (1H, d, $J$ = 16.2 Hz, H-11a), 3.99 (1H, ddd, $J$ = 9.1, 5.8, 2.4 Hz, H-4), 3.66 (1H, d, $J$ = 16.2 Hz, H-11b), 2.03 (1H, ddd, $J$ = 15.2, 7.0, 2.4 Hz, H-3a), 1.89 (1H, ddd, $J$ = 15.2, 9.1, 3.4 Hz, H-3b), 1.42 (3H, d, $J$ = 6.4 Hz, $H_3$-1); $^{13}$C NMR (methanol-$d_4$, 125 MHz) $\delta$ 199.8 (s, C-10), 168.1 (s, C-18), 157.0 (s, C-16), 156.9 (s, C-14), 141.1 (d, C-8), 138.1 (d, C-6), 134.6 (s, C-12), 132.6 (d, C-9), 130.9 (d, C-7), 116.3 (s, C-17), 114.3 (s, C-13), 103.9 (d, C-15), 72.6 (d, C-4), 70.9 (d, C-2), 60.6 (d, C-5), 45.7 (t, C-11), 38.2 (t, C-3), 19.3 (q, C-1); ESI-MS $m/z$ 399 $[M-H]^-$; HRESI-MS $m/z$ 423.0736 (calcd for $C_{18}H_{18}Cl_2O_6Na$ $[M+Na]^+$, 423.0378, $\Delta$ −0.2 mmu).

**4.4.5.2. Chlorohydrin derivative (11).** Colorless oil; HPLC, $t_R$ 7.22 min (system 1); $^1$H NMR (methanol-$d_4$, 500 MHz) $\delta$ 7.18 (1H, dd, $J$ = 15.9, 9.8 Hz, H-8), 6.46 (1H, s, H-15), 6.14 (1H, t, $J$ = 9.8 Hz, H-7), 6.02 (1H, t, $J$ = 9.8 Hz, H-6), 6.00 (1H, d, $J$ = 15.9 Hz, H-9), 5.27 (1H, m, H-2), 5.00 (1H, dd, $J$ = 9.8, 3.0 Hz, H-5), 4.73 (1H, d, $J$ = 15.3 Hz, H-11a), 3.88 (1H, dt, $J$ = 9.8, 3.0 Hz, H-4), 3.76 (1H, d, $J$ = 15.3 Hz, H-11b), 2.12 (1H, ddd, $J$ = 14.0, 9.8, 3.0 Hz, H-3a), 1.96 (1H, ddd, $J$ = 14.0, 10.4, 3.0 Hz, H-3b), 1.46 (3H, d, $J$ = 6.1 Hz, $H_3$-1); $^{13}$C NMR (methanol-$d_4$, 125 MHz) $\delta$ 198.7 (s, C-10), 168.5 (s, C-18), 158.6 (s, C-16), 157.8 (s, C-14), 139.1 (d, C-6), 138.6 (d, C-8), 135.4 (s, C-12), 131.7 (d, C-9), 127.6 (d, C-7), 115.7 (s, C-17), 113.8 (s, C-13), 104.1 (d, C-15), 72.1 (d, C-4), 71.0 (d, C-2), 60.4 (d, C-5), 44.5 (t, C-11), 40.6 (t, C-3), 20.8 (q, C-1); ESI-MS $m/z$ 399 $[M-H]^-$ as $C_{18}H_{17}Cl_2O_6$.

**4.4.5.3. 4,5-Diol derivative (12).** Colorless oil; HPLC, $t_R$ 3.71 min (system 1); $^1$H NMR (methanol-$d_4$, 500 MHz) $\delta$ 7.30 (1H, dd, $J$ = 15.9, 11.0 Hz, H-8), 6.41 (1H, s, H-15), 6.14 (1H, t, $J$ = 11.0 Hz, H-7), 5.90 (1H, d, $J$ = 15.9 Hz, H-9), 5.73 (1H, dd, $J$ = 11.0, 8.5 Hz, H-6), 5.40 (1H, m, H-2), 4.78 (1H, dd, $J$ = 8.5, 6.1 Hz, H-5), 4.18 (1H, d, $J$ = 15.9 Hz, H-11a), 3.80 (1H, m, H-4), 3.63 (1H, d, $J$ = 15.9 Hz, H-11b), 1.95 (1H, ddd, $J$ = 15.3, 6.7, 1.8 Hz, H-3a), 1.87 (1H, ddd, $J$ = 15.3, 9.2, 3.7 Hz, H-3b), 1.42 (3H, d, $J$ = 6.7 Hz, $H_3$-1); $^{13}$C NMR (methanol-$d_4$, 125 MHz) $\delta$ 200.2 (s, C-10), 168.4 (s, C-18), 156.9 (s, C-16), 156.7 (s, C-14), 142.9 (d, C-8), 142.4 (d, C-6), 134.7 (s, C-12), 131.5 (d, C-9), 130.0 (d, C-7), 116.6 (s, C-17), 114.3 (s, C-13), 103.8 (d, C-15), 72.0 (d, C-5), 71.9 (d, C-4), 71.2 (d, C-2), 45.8 (t, C-11), 37.8 (t, C-3), 19.4 (q, C-1); ESI-MS $m/z$ 381 $[M-H]^-$ as $C_{18}H_{18}ClO_7$.

**4.4.5.4. 4,5-Diol derivative (13).** Colorless oil; HPLC, $t_R$ 4.57 min (system 1); $^1$H NMR (methanol-$d_4$, 500 MHz) $\delta$ 7.36 (1H, dd, $J$ = 15.9, 10.4 Hz, H-8), 6.44 (1H, s, H-15), 6.12 (1H, t, $J$ = 10.4 Hz, H-7), 5.96 (1H, d, $J$ = 15.9 Hz, H-9), 5.94 (1H, dd, $J$ = 10.4, 7.3 Hz, H-6), 5.45 (1H, m, H-2), 4.56 (1H, m, H-5), 4.53 (1H, d, $J$ = 15.9 Hz, H-11a), 3.87 (1H, d, $J$ = 15.9 Hz, H-11b), 3.64 (1H, dt, $J$ = 9.8, 3.0 Hz, H-4), 2.10 (1H, ddd, $J$ = 14.6, 9.2, 3.0 Hz, H-3a), 1.83 (1H, ddd, $J$ = 14.6, 9.8, 3.0 Hz, H-3b), 1.44 (3H, d, $J$ = 6.1 Hz, $H_3$-1); $^{13}$C NMR (methanol-$d_4$, 125 MHz) $\delta$ 199.5 (s, C-10), 168.7 (s, C-18), 158.9 (s, C-16), 158.2 (s, C-14), 143.7 (d, C-6), 140.6 (d, C-8), 135.8 (s, C-12), 131.3 (d, C-9), 127.2 (d, C-7), 115.9 (s, C-17), 113.0 (s, C-13), 104.0 (d, C-15), 72.7 (d, C-4), 71.2 (d, C-2), 69.5 (d, C-5), 44.5 (t, C-11), 39.3 (t, C-3), 21.0 (q, C-1); ESI-MS $m/z$ 381 $[M-H]^-$ as $C_{18}H_{18}ClO_7$.

#### 4.4.6. Compound (14)

One-molar hydrochloric acid (12 mL) was added to a solution of **1** (930 mg, 2.55 mmol) in 1,4-dioxane (14 mL), and the mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and concentrated to produce a colorless oil. The crude oil was purified using preparative TLC (developing solvent, chloroform–methanol–*n*-hexane = 5:1:5), and was further purified using preparative HPLC (eluent, MeCN–$H_2O$ = 30:70 to 40:60, gradient) to produce compound **14** (103.7 mg, 10.6%). Compound **14**: colorless oil; HPLC, $t_R$ 5.21 min (system 1); $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 10.47 (1H, br s, 16-OH), 9.97 (1H, s, 14-OH), 6.50 (1H, s, H-15), 6.00 (1H, dt, $J$ = 6.1, 1.8 Hz, H-6), 5.89 (1H, dt, $J$ = 6.1, 1.8 Hz, H-7), 5.20 (1H, m, H-2), 5.01 (1H, m, H-8), 4.88 (1H, d, $J$ = 6.7 Hz, OH-4), 4.21 (1H, dt, $J$ = 9.8, 1.8 Hz, H-5), 3.90 (1H, d, $J$ = 18.3 Hz, H-11a), 3.71 (1H, d, $J$ = 18.3 Hz, H-11b), 3.20 (1H, m, H-4), 2.76 (1H, dd, $J$ = 14.6, 4.9 Hz, H-9a), 2.37 (1H, dd, $J$ = 14.6, 5.5 Hz, H-9b), 2.16 (1H, m, H-3a), 1.44 (1H, ddd, $J$ = 14.6, 7.9, 3.0 Hz, H-3b), 1.26 (3H, d, $J$ = 6.7 Hz, $H_3$-1); $^{13}$C NMR (DMSO-$d_6$, 125 MHz) $\delta$ 203.8 (s, C-10), 166.4 (s, C-18), 154.7 (s, C-16), 154.4 (s, C-14), 130.2 (s, C-12), 130.0 (d, C-7), 129.3 (d, C-6), 115.3 (s, C-13), 111.7 (s, C-17), 102.4 (d, C-15), 88.4 (d, C-5), 83.3 (d, C-8), 70.3 (d, C-4), 69.7 (d, C-2), 48.3 (t, C-11), 45.1 (t, C-9), 37.6 (t, C-3), 19.2 (q, C-1); ESI-MS $m/z$ 381 $[M-H]^-$; HREI-MS $m/z$ 382.0813 (calcd for $C_{18}H_{18}Cl_1O_7$ $[M]^+$, 382.0819, $\Delta$ −0.6 mmu).

#### 4.4.7. Hydrogenation of radicicol (1) (i)

Five-percent palladium–carbon (PH, wet-type, Kawaken Fine Chemicals Co.) (255 mg) was added to a solution of **1** (10.8 g, 29.6 mmol) in ethyl acetate (140 mL). After hydrogenation for 3 h at room temperature under atmospheric pressure, the catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residue was purified using silica gel column chromatography (eluent, *n*-hexane–ethyl acetate = 3:2) to produce compounds **15** (3.43 g, 31.4%), **2** (4.14 g, 38.1%) and a semi-pure fraction (500 mg) containing compound **2**. The semi-pure fraction was purified using preparative HPLC (eluent, MeCN–$H_2O$ = 38:62) to produce compound **2** (177.8 mg, 1.7%) and **16** (20.7 mg, 0.2%).

**4.4.7.1. 6,7,8,9-Tetrahydroradicicol (15).** Colorless solid; mp 153–155 °C; UV (methanol) $\lambda_{max}$ (log $\varepsilon$) 215 (4.40), 259 (3.89), and 310 (3.83) nm; IR (KBr) $\nu_{max}$ 3120, 2940, 1714, 1665, 1609, 1578,

1487, 1467, 1436, 1417, 1370, 1354, 1340, 1309, 1264, 1228, 1177, 1146, 1115, 1070, 1053, 1036, 1023, 974, 930, 874, 837, 782, 695, 669, 632, 606, 549 $cm^{-1}$; HPLC, $t_R$ 8.57 min (system 1); $^1H$ NMR (chloroform-*d*/methanol-$d_4$, 500 MHz) $\delta$ 6.37 (1H, s, H-15), 5.15 (1H, m, H-2), 4.25 (1H, d, $J$ = 18.3 Hz, H-11a), 4.02 (1H, d, $J$ = 18.3 Hz, H-11b), 2.68 (1H, m, H-4), 2.53 (1H, dt, $J$ = 8.8, 3.0 Hz, -5), 2.34 (2H, m, $H_2$-9), 2.04 (1H, ddd, $J$ = 15.5, 5.5, 4.3 Hz, H-3), 1.92 (1H, ddd, $J$ = 14.0, 7.0, 3.0 Hz, H-6a), 1.77 (1H, ddd, $J$ = 15.5, 6.4, 3.0 Hz, H-3b), 1.64 (1H, m, H-8a), 1.41 (2H, m, H-7a and H-8b), 1.36 (1H, m, H-7b), 1.32 (3H, d, $J$ = 6.4 Hz, $H_3$-1), 1.02 (1H, m, H-6b); $^{13}C$ NMR (chloroform-*d*/methanol-$d_4$, 125 MHz) $\delta$ 208.0 (s, C-10), 169.6 (s, C-18), 162.2 (s, C-16), 158.2 (s, C-14), 135.6 (s, C-12), 115.6 (s, C-13), 106.4 (s, C-17), 103.1 (d, C-15), 70.9 (d, C-2), 57.6 (d, C-5), 54.8 (d, C-4), 46.5 (t, C-11), 40.3 (t, C-9), 36.1 (t, C-3), 30.8 (t, C-6), 23.2 (t, C-7), 22.1 (t, C-8), 18.6 (q, C-1); ESI-MS *m/z* 367 $[M-H]^-$; HREI-MS *m/z* 368.1021 (calcd for $C_{18}H_{21}Cl_1O_6$ $[M]^+$, 368.1027, $\Delta$ −0.6 mmu).

**4.4.7.2. 6,7-Dihydroradicicol (2) (pochonin A;[20] synthetic).** Colorless crystal; mp 208–210 °C; $[\alpha]_D^{20}$ −15.3 (*c* 1.00, chloroform); UV (methanol) $\lambda_{max}$ (log $\varepsilon$) 220 (4.58), 261 (3.97), and 315 (3.95) nm; IR (KBr) $\nu_{max}$ 3409, 2986, 2936, 1703, 1648, 1601, 1580, 1490, 1450, 1423, 1382, 1355, 1311, 1245, 1147, 1104, 1036, 969, 886, 847, 803, 784, 705, 670, 639 $cm^{-1}$; HPLC, $t_R$ 7.87 min (system 1); $^1H$ NMR (chloroform-*d*/methanol-$d_4$, 500 MHz) $\delta$ 6.85 (1H, ddd, $J$ = 15.9, 11.0, 4.3 Hz, H-8), 6.48 (1H, s, H-15), 6.05 (1H, d, $J$ = 15.9 Hz, H-9), 5.21 (1H, m, H-2), 4.40 (1H, d, $J$ = 18.3 Hz, H-11a), 4.27 (1H, d, $J$ = 18.3 Hz, H-11b), 2.74 (1H, dt, $J$ = 4.3, 2.4 Hz, H-4), 2.52 (1H, dt, $J$ = 9.8, 2.4 Hz, H-5), 2.48 (1H, m, H-7a), 2.35 (1H, ddd, $J$ = 14.0, 7.3, 2.4 Hz, H-6a), 2.23 (1H, m, H-7b), 1.97 (1H, ddd, $J$ = 15.9, 4.9, 2.4 Hz, H-3a), 1.81 (1H, dt, $J$ = 15.9, 4.3 Hz, H-3b), 1.21 (1H, m, H-6b), 1.41 (3H, d, $J$ = 6.1 Hz, $H_3$-1); $^{13}C$ NMR (chloroform-*d*/methanol-$d_4$, 125 MHz) $\delta$ 197.0 (s, C-10), 170.3 (s, C-18), 163.4 (s, C-16), 158.8 (s, C-14), 148.0 (d, C-8), 136.1 (s, C-12), 130.1 (d, C-9), 116.3 (s, C-13), 106.3 (s, C-17), 103.5 (d, C-15), 72.1 (d, C-2), 57.6 (d, C-5), 56.0 (d, C-4), 45.1 (t, C-11), 36.5 (t, C-3), 30.9 (t, C-6), 29.2 (t, C-7), 17.8 (q, C-1); ESI-MS *m/z* 365 $[M-H]^-$; HRESI-MS *m/z* 365.0789 (calcd for $C_{18}H_{18}Cl_1O_6$ $[M-H]^-$, 365.0792, $\Delta$ −0.3 mmu).

**4.4.7.3. 6,9-Dihydroradicicol (16).** Colorless oil; HPLC, $t_R$ 7.40 min (system 1); $^1H$ NMR (chloroform-*d*/methanol-$d_4$, 500 MHz) $\delta$ 6.38 (1H, s, H-15), 5.40 (1H, ddd, $J$ = 15.3, 7.9, 7.3 Hz, H-8), 5.28 (1H, ddd, $J$ = 15.3, 7.3, 3.7 Hz, H-7), 5.18 (1H, m, H-2), 4.22 (1H, d, $J$ = 18.3 Hz, H-11a), 4.06 (1H, d, $J$ = 18.3 Hz, H-11b), 3.14 (1H, dd, $J$ = 12.2, 7.9 Hz, H-9a), 2.81 (1H, dd, $J$ = 12.2, 7.3 Hz, H-9b), 2.69 (1H, dt, $J$ = 9.2, 3.0 Hz, H-4), 2.60 (1H, dt, $J$ = 7.9, 3.0 Hz, H-5), 2.53 (1H, ddd, $J$ = 14.0, 7.9, 3.7 Hz, H-6a), 2.10 (1H, ddd, $J$ = 14.6, 4.9, 3.0 Hz, H-3a), 1.66 (2H, m, H-3b and 6b), 1.31 (3H, d, $J$ = 6.7 Hz, $H_3$-1); $^{13}C$ NMR (chloroform-*d*/methanol-$d_4$, 125 MHz) $\delta$ 205.6 (s, C-10), 169.1 (s, C-18), 161.0 (s, C-16), 157.8 (s, C-14), 135.2 (s, C-12), 129.2 (d, C-7), 125.9 (d, C-8), 115.6 (s, C-13), 107.6 (s, C-17), 103.1 (d, C-15), 71.5 (d, C-2), 58.2 (d, C-5), 53.7 (d, C-4), 45.8 (t, C-9), 45.4 (t, C-11), 36.2 (t, C-3), 33.8 (t, C-6), 18.9 (q, C-1); ESI-MS *m/z* 365 $[M-H]^-$ as $C_{18}H_{18}ClO_6$.

### 4.4.8. Hydrogenation of radicicol (1) (ii)

Five-percent palladium–carbon (PH, wet-type) was added to a solution of **1** (11.9 g, 32.6 mmol) in ethyl acetate (160 mL). After hydrogenation for 3 h at room temperature under atmospheric pressure, the catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residue was purified using silica gel column chromatography (eluent, *n*-hexane–ethyl acetate = 3:2 to 1:1) to produce compounds **15**, **2**, and a semi-pure fraction (936 mg). The semi-pure fraction was purified using preparative HPLC (eluent, MeCN–$H_2O$ = 34:66) to produce compounds **17** (17.4 mg, 1.4%), **18** (49.4 mg, 4.1%), and **19** (347.4 mg, 28.7%).

**4.4.8.1. 5,6,9-Trihydro-4α-hydroxyradicicol (17).** Colorless oil; HPLC, $t_R$ 6.37 min (system 1); $^1H$ NMR (chloroform-*d*, 500 MHz) $\delta$ 6.53 (1H, s, H-15), 5.60 (1H, ddd, $J$ = 15.2, 7.6, 7.0 Hz, H-7), 5.47 (1H, dt, $J$ = 15.2, 7.6 Hz, H-8), 5.33 (1H, m, H-2), 4.59 (1H, d, $J$ = 18.3 Hz, H-11a), 4.48 (1H, d, $J$ = 18.3 Hz, H-11b), 3.78 (1H, ddd, $J$ = 6.7, 6.4, 5.2 Hz, H-4), 3.16 (1H, dd, $J$ = 12.5, 7.6 Hz, H-9a), 3.04 (1H, dd, $J$ = 12.5, 7.6 Hz, H-9b), 2.20 (2H, m, $H_2$-6), 1.89 (1H, ddd, $J$ = 14.9, 7.6, 6.4 Hz, H-3a), 1.79 (1H, ddd, $J$ = 14.9, 6.7, 3.0 Hz, H-3b), 1.63 (2H, m, $H_2$-5), 1.40 (3H, d, $J$ = 6.4 Hz, $H_3$-1); $^{13}C$ NMR (chloroform-*d*, 125 MHz) $\delta$ 205.0 (s, C-10), 168.0 (s, C-18), 161.2 (s, C-16), 156.0 (s, C-14), 135.8 (s, C-12), 135.2 (d, C-7), 123.5 (d, C-8), 115.2 (s, C-13), 108.5 (s, C-17), 103.7 (d, C-15), 71.7 (d, C-2), 66.4 (d, C-4), 46.4 (t, C-9), 45.1 (t, C-11), 42.1 (t, C-3), 35.3 (t, C-5), 28.0 (t, C-6), 20.6 (q, C-1); ESI-MS *m/z* 367 $[M-H]^-$ as $C_{18}H_{20}ClO_6$.

**4.4.8.2. 5,8,9-Trihydro-4α-hydroxyradicicol (18).** Colorless oil; HPLC, $t_R$ 6.62 min (system 1); $^1H$ NMR (chloroform-*d*, 500 MHz) $\delta$ 6.50 (1H, s, H-15), 5.50–5.41 (3H, m; small coupling, H-2, H-6 and H-7), 4.38 (1H, d, $J$ = 17.7 Hz, H-11a), 4.24 (1H, d, $J$ = 17.7 Hz, H-11b), 3.60 (1H, ddd, $J$ = 6.7, 6.4, 5.8 Hz, H-4), 2.73 (1H, ddd, $J$ = 13.4, 8.8, 3.0 Hz, H-9a), 2.40 (1H, m, H-8a), 2.32 (1H, m, H-9b), 2.29 (1H, m, H-5a), 2.20 (1H, m, H-8b), 2.04 (1H, m, H-5b), 1.86 (2H, m, $H_2$-3), 1.42 (3H, d, $J$ = 6.4 Hz, $H_3$-1); $^{13}C$ NMR (chloroform-*d*, 125 MHz) $\delta$ 207.8 (s, C-10), 168.8 (s, C-18), 161.9 (s, C-16), 156.7 (s, C-14), 136.1 (s, C-12), 131.1 (d, C-7), 126.5 (d, C-6), 115.1 (s, C-13), 107.8 (s, C-17), 103.8 (d, C-15), 71.2 (d, C-2), 69.3 (d, C-4), 47.4 (t, C-11), 41.4 (t, C-9), 41.1 (t, C-3), 34.6 (t, C-5), 22.4 (t, C-8), 20.3 (q, C-1); ESI-MS *m/z* 367 $[M-H]^-$ as $C_{18}H_{20}ClO_6$.

**4.4.8.3. 5,6,7,8,9-Pentahydro-4α-hydroxyradicicol (19).** Colorless oil; HPLC, $t_R$ 7.03 min (system 1); $^1H$ NMR (chloroform-*d*, 500 MHz) $\delta$ 6.54 (1H, s, H-15), 5.47 (1H, m, H-2), 4.51 (1H, d, $J$ = 17.7 Hz, H-11a), 4.33 (1H, d, $J$ = 17.7 Hz, H-11b), 3.71 (1H, ddd, $J$ = 6.7, 6.1, 5.5 Hz, H-4), 2.58 (1H, ddd, $J$ = 15.9, 8.5, 3.0 Hz, H-9a), 2.32 (1H, ddd, $J$ = 15.9, 9.2, 3.7 Hz, H-9b), 1.95 (1H, ddd, $J$ = 15.3, 7.3, 5.5 Hz, H-3a), 1.84 (1H, ddd, $J$ = 15.3, 6.7, 3.0 Hz, H-3b), 1.69 (1H, m, H-8a), 1.60 (2H, m, H-5a and H-8b), 1.46 (2H, m, H-6a and H-7a), 1.44 (3H, d, $J$ = 6.7 Hz, $H_3$-1), 1.32 (1H, m, H-5b), 1.24 (2H, m, H-6b and H-7b); $^{13}C$ NMR (chloroform-*d*, 125 MHz) $\delta$ 207.9 (s, C-10), 168.3 (s, C-18), 161.7 (s, C-16), 156.3 (s, C-14), 136.2 (s, C-12), 115.3 (s, C-13), 107.9 (s, C-17), 103.8 (d, C-15), 71.4 (d, C-2), 66.4 (d, C-4), 46.5 (t, C-11), 42.3 (t, C-3), 40.6 (t, C-9), 34.9 (t, C-5), 25.2 (t, C-7), 22.8 (t, C-6), 22.0 (t, C-8), 20.3 (q, C-1); ESI-MS *m/z* 369 $[M-H]^-$ as $C_{18}H_{22}ClO_6$.

### 4.4.9. Michael addition of radicicol (1) (i)

Triethylamine (220 μL, 1.57 mmol) and thiophenol (500 mg, 4.54 mmol, 1.39 equiv) were added to a solution of **1** (1190 mg, 3.26 mmol) in *N*,*N*-dimethylformamide (10 mL), and the solution was stirred for 3 h at 0 °C. The reaction mixture was diluted with dilute hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, evaporated in vacuo and purified using preparative HPLC (eluent, MeCN–$H_2O$ = 58:42) to produce compounds **20** (1109.2 mg, 71.6%) and **21** (126.9 mg, 8.2%).

**4.4.9.1. 7,8-(*Z*)-9-Hydro-6α-thiophenylradicicol (20).** Colorless solid; mp 219–222 °C; HPLC, $t_R$ 13.00 min (system 1); $^1H$ NMR (DMSO-$d_6$, 500 MHz) $\delta$ 10.39 (1H, s, 16-OH), 9.91 (1H, s, 14-OH), 7.40 (2H, t, $J$ = 7.3 Hz, H-2′), 7.31 (2H, t, $J$ = 7.3 Hz, H-3′), 7.25 (1H, t, $J$ = 7.3 Hz, H-4′), 6.48 (1H, s, H-15), 5.84 (1H, dt, $J$ = 15.3, 7.9 Hz,

H-8), 5.55 (1H, dd, $J$ = 15.3, 8.5 Hz, H-7), 5.08 (1H, m, H-2), 3.84 (2H, m, $H_2$-11), 3.61 (1H, t, $J$ = 8.5 Hz, H-6), 3.05 (1H, dd, $J$ = 8.5, 2.4 Hz, H-5), 2.99 (2H, m, $H_2$-9), 2.94 (1H, ddd, $J$ = 8.5, 4.3, 2.4 Hz, H-4), 2.24 (1H, ddd, $J$ = 14.0, 9.8, 4.3 Hz, H-3a), 1.31 (1H, ddd, $J$ = 14.0, 8.5, 2.4 Hz, H-3b), 1.22 (3H, d, $J$ = 6.7 Hz, $H_3$-1); $^{13}$C NMR (DMSO-$d_6$, 125 MHz) $\delta$ 203.1 (s, C-10), 166.9 (s, C-18), 154.6 (s, C-16), 154.0 (s, C-14), 133.5 (s, C-1′), 132.0 (s, C-12), 131.2 (2d, C-2′), 130.6 (d, C-7), 128.9 (2d, C-3′), 127.2 (d, C-8), 126.9 (d, C-4′), 115.0 (s, C-13), 112.0 (s, C-15), 102.2 (d, C-15), 70.3 (d, C-2), 59.3 (d, C-5), 54.6 (d, C-4), 52.2 (d, C-6), 45.1 (t, C-9), 43.5 (t, C-11), 37.3 (t, C-3), 20.0 (q, C-1); ESI-MS $m/z$ 473 $[M-H]^-$ as $C_{24}H_{22}ClO_6S$.

**4.4.9.2. 7,8-(*E*)-9-Hydro-6α-thiophenylradicicol (21).** Colorless oil; HPLC, $t_R$ 13.19 min (system 1); $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 10.36 (1H, br s, 16-OH), 9.90 (1H, s, 14-OH), 7.43 (2H, d, $J$ =7.3 Hz, H-2′), 7.31 (2H, m, H-3′), 7.29 (1H, m, H-4′), 6.48 (1H, s, H-15), 5.62 (1H, dt, $J$ = 10.4, 6.7 Hz, H-8), 5.58 (1H, t, $J$ = 10.4 Hz, H-7), 4.90 (1H, m, H-2), 3.92 (2H, m, $H_2$-11), 3.78 (1H, dd, $J$ = 10.4, 8.8 Hz, H-6), 3.06 (1H, dd, $J$ = 18.3, 10.4 Hz, H-9a), 2.97 (1H, dd, $J$ = 8.8, 1.8 Hz, H-5), 2.85 (1H, dd, $J$ = 18.3, 6.7 Hz, H-9b), 2.76 (1H, m, H-4), 2.16 (ddd, $J$ = 14.3, 11.3, 3.0 Hz, H-3a), 1.22 (1H, m, H-3b), 1.20 (3H, d, $J$ = 6.1 Hz, $H_3$-1); $^{13}$C NMR (DMSO-$d_6$, 125 MHz) $\delta$ 202.5 (s, C-10), 166.8 (s, C-18), 154.7 (s, C-16), 154.0 (s, C-14), 133.4 (2d, C-2′), 132.6 (s, C-1′), 131.3 (s, C-12), 130.1 (d, C-7), 129.1 (2d, C-3′), 128.0 (d, C-4′), 124.0 (d, C-8), 115.5 (s, C-13), 111.9 (s, C-17), 102.4 (d, C-15), 70.6 (d, C-2), 58.6 (d, C-5), 56.2 (d, C-4), 49.0 (d, C-6), 43.2 (t, C-11), 42.3 (t, C-9), 37.6 (t, C-3), 20.3 (q, C-1); ESI-MS $m/z$ 473 $[M-H]^-$ as $C_{24}H_{22}ClO_6S$.

**4.4.10. Michael addition of radicicol (1) (ii)**

Triethylamine (56 μL, 0.40 mmol) and thioacetic acid (163 mg, 2.14 mmol, 2.06 equiv) were added to a solution of **1** (378 mg, 1.04 mmol) in *N*,*N*-dimethylformamide (6 mL), and the solution was stirred for 16 h at 0 °C. The reaction mixture was diluted with dilute hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, evaporated in vacuo and purified using preparative HPLC (eluent, MeCN–$H_2O$ = 35:65) to produce compounds **22** (49.0 mg, 10.7%) and **23** (15.7 mg, 3.4%).

**4.4.10.1. 7,8-(*Z*)-9-Hydro-6α-thioacetylradicicol (22).** Colorless oil; HPLC, $t_R$ 10.46 min (system 1); $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 10.37 (1H, s, 16-OH), 9.91 (1H, s, 14-OH), 6.48 (1H, s, H-15), 5.91 (1H, ddd, $J$ = 15.3, 7.9, 7.3 Hz, H-8), 5.63 (1H, dd, $J$ = 15.3, 7.9 Hz, H-7), 5.10 (1H, m, H-2), 3.87 (2H, m, $H_2$-11), 3.76 (1H, t, $J$ = 7.9 Hz, H-6), 3.11 (1H, dd, $J$ = 7.9, 1.8 Hz, H-5), 3.07 (1H, dd, $J$ = 15.3, 7.3 Hz, H-9a), 3.00 (2H, m, H-4 and H-9b), 2.35 (3H, s, $H_3$-2′), 2.23 (1H, ddd, $J$ = 14.6, 10.4, 3.7 Hz, H-3a), 1.30 (1H, ddd, $J$ = 14.6, 8.5, 2.3 Hz, H-3b), 1.22 (3H, d, $J$ = 6.1 Hz, $H_3$-1); $^{13}$C NMR (DMSO-$d_6$, 125 MHz) $\delta$ 203.0 (s, C-10), 193.6 (s, C-1′), 166.9 (s, C-18), 154.6 (s, C-16), 153.9 (s, C-14), 132.0 (s, C-12), 130.0 (d, C-7), 127.2 (d, C-8), 115.0 (s, C-13), 112.1 (s, C-17), 102.2 (d, C-15), 70.2 (d, C-2), 58.0 (d, C-5), 55.3 (d, C-4), 48.1 (d, C-6), 45.2 (t, C-9), 43.4 (t, C-11), 37.3 (t, C-3), 30.6 (q, C-2′), 20.1 (q, C-1); ESI-MS $m/z$ 439 $[M-H]^-$ as $C_{20}H_{20}ClO_7S$.

**4.4.10.2. 7,8-(*E*)-9-Hydro-6α-thioacetylradicicol (23).** Colorless oil; HPLC, $t_R$ 10.79 min (system 1); $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 10.39 (1H, s, 16-OH), 9.87 (1H, s, 14-OH), 6.49 (1H, s, H-15), 5.67 (1H, dt, $J$ = 11.0, 4.9 Hz, H-8), 5.17 (1H, dd, $J$ = 11.0, 10.4 Hz, H-7), 5.13 (1H, m, H-2), 4.80 (1H, d, $J$ = 10.4 Hz, H-6), 3.98 (2H, m, $H_2$-11), 3.71 (1H, dd, $J$ = 18.3, 11.0 Hz, H-9a), 3.20 (1H, dd, $J$ = 18.3, 4.9 Hz, H-9b), 3.06 (1H, br s, H-5), 2.58 (1H, m, H-4), 2.38 (3H, s, $H_3$-2′), 2.08 (1H, m, H-3a), 1.30 (1H, m, H-3b), 1.22 (3H, d, $J$ = 6.1 Hz, $H_3$-1); $^{13}$C NMR (DMSO-$d_6$, 125 MHz) $\delta$ 203.8 (s, C-10), 193.9 (s, C-1′), 167.2 (s, C-18), 154.7 (s, C-16), 154.4 (s, C-14), 132.5 (s, C-12), 126.7 (d, C-8), 126.1 (d, C-7), 114.6 (s, C-13), 112.0 (s, C-17), 102.3 (d, C-15), 70.2 (d, C-2), 58.8 (d, C-5), 52.9 (d, C-4), 44.2 (t, C-11), 40.9 (d, C-6), 40.4 (t, C-9), 37.8 (t, C-3), 30.6 (q, C-2′), 20.3 (q, C-1); ESI-MS $m/z$ 439 $[M-H]^-$ as $C_{20}H_{20}ClO_7S$.

**4.4.11. Dehydrogenation of compound 20**

Wilkinson's catalyst (chlorotris [triphenylphosphine rhodium (I)]) (453 mg, 0.48 mmol, 0.20 equiv) was added to a solution of **20** (1090 mg, 2.29 mmol) in ethanol (40 mL). After hydrogenation for 34 h at room temperature under atmospheric pressure, the catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residue was purified using silica gel column chromatography (eluent, *n*-hexane–ethyl acetate = 4:1), then further purified using preparative HPLC (eluent, MeCN–$H_2O$ = 60:40) to produce compound **24** (84.0 mg, 7.7%).

**4.4.11.1. 7,8,9-Trihydro-6α-thiophenylradicicol (24).** Colorless solid; mp 169–172 °C; HPLC, $t_R$ 13.62 min (system 1); $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 10.46 (1H, br s, 16-OH), 10.00 (1H, br s, 14-OH), 7.45 (2H, d, $J$ = 7.3 Hz, H-2′), 7.32 (2H, t, $J$ = 7.3 Hz, H-3′), 7.26 (1H, t, $J$ = 7.3 Hz, H-4′), 6.50 (1H, s, H-15), 5.07 (1H, m, H-2), 4.05 (1H, d, $J$ = 18.6 Hz, H-11a), 3.90 (1H, d, $J$ = 18.6 Hz, H-11b), 2.86 (1H, br s, H-4), 2.85 (1H, br s, H-5), 2.76 (1H, dt, $J$ = 8.8, 5.2 Hz, H-6), 2.42 (2H, m, $H_2$-9), 2.21 (1H, ddd, $J$ = 14.0, 10.4, 3.6 Hz, H-3a), 1.78 (1H, m, H-8a), 1.70 (1H, m, H-8b), 1.62 (1H, m, H-7a), 1.41 (1H, m, H-7b), 1.31 (1H, ddd, $J$ = 14.0, 8.5, 2.4 Hz, H-3b), 1.24 (3H, d, $J$ = 6.1 Hz, $H_3$-1); $^{13}$C NMR (DMSO-$d_6$, 125 MHz) $\delta$ 206.7 (s, C-10), 167.4 (s, C-18), 155.1 (s, C-16), 154.9 (s, C-14), 133.7 (s, C-1′), 132.3 (s, C-12), 132.2 (2d, C-2′), 129.1 (2d, C-3′), 127.3 (d, C-4′), 114.8 (s, C-13), 112.1 (s, C-17), 102.5 (d, C-15), 70.7 (d, C-2), 60.8 (d, C-5), 56.2 (d, C-4), 49.3 (d, C-6), 44.9 (t, C-11), 39.9 (t, C-9), 37.2 (t, C-3), 30.3 (t, C-7), 21.3 (t, C-8), 20.1 (q, C-1); ESI-MS $m/z$ 475 $[M-H]^-$ as $C_{24}H_{24}ClO_6S$.

**4.4.12. 10-Oxime radicicol (25)**

Hydroxylamine hydrochloride (180 mg, 2.59 mmol, 4.46 equiv) was added to a solution of **1** (210 mg, 0.58 mmol) in pyridine (4 mL). The mixture was stirred for 2.5 h at 40 °C and cooled to room temperature. The mixture was diluted with water, extracted with ethyl acetate, dried over sodium sulfate and concentrated to produce a yellowish residue. The residue was purified using preparative TLC (developing solvent, chloroform–methanol = 90:10) to produce compound **25** (40.0 mg, 18.3%, *Z*-isomer: *E*-isomer = 1:0.7). Compound **25**: colorless oil; HPLC, $t_R$ 5.86 min (system 1); $^1$H NMR (methanol-$d_4$, 500 MHz) (major isomer) $\delta$ 7.22 (1H, dd, $J$ = 15.9, 11.0 Hz, H-8), 6.83 (1H, d, $J$ = 15.9 Hz, H-9), 6.43 (1H, s, H-15), 6.16 (1H, m, H-7), 5.56 (1H, dd, $J$ = 10.4, 3.0 Hz, H-6), 5.29 (1H, m, H-2), 3.90 (1H, d, $J$ = 15.9 Hz, H-11a), 3.79 (1H, d, $J$ = 15.9 Hz, H-11b), 3.34 (1H, m, H-5), 3.01 (1H, ddd, $J$ = 9.2, 3.7, 1.8 Hz, H-4), 2.41 (1H, m, H-3a), 1.57 (1H, m, H-3b), 1.52 (3H, d, $J$ = 6.7 Hz, $H_3$-1); $^{13}$C NMR (methanol-$d_4$, 125 MHz) $\delta$ 169.0 (s, C-18), 157.1 (s, C-16), 156.7 (s, C-14), 154.8 (s, C-10), 135.5 (s, C-12), 132.8 (2d, C-6 and C-8), 132.5 (d, C-7), 121.9 (d, C-9), 116.2 (s, C-13), 114.6 (s, C-17), 103.4 (d, C-15), 72.3 (d, C-2), 57.0 (d, C-4), 56.6 (d, C-5), 38.1 (t, C-3), 36.2 (t, C-11), 18.6 (q, C-1); ESI-MS $m/z$ 378 $[M-H]^-$; HRESI-MS $m/z$ 402.0725 (calcd for $C_{18}H_{18}Cl_1N_1O_6Na$ $[M+Na]^+$, 402.0720, $\Delta$ +0.5 mmu).

**4.4.13. Preparation of 10-*O*-benzyloxime radicicol**

*O*-Benzylhydroxylamine hydrochloride (1338 mg, 8.70 mmol, 2.36 equiv) was added to a solution of **1** (1344 mg, 3.69 mmol) in pyridine (10 mL). The mixture was stirred for 5.5 h at 40 °C and cooled to room temperature. The mixture was diluted with water, extracted with ethyl acetate, dried over sodium sulfate and con-

centrated to produce a colorless oil. The residue was purified using preparative HPLC (eluent, MeCN–$H_2O$ = 55:45) to produce compounds **26** (538.6 mg, 31.2%) and **27** (271.2 mg, 15.1%).

**4.4.13.1. 10-(*Z*)-*O*-benzyloxime radicicol (26).** Colorless oil; HPLC, $t_R$ 13.52 min (system 1); $^1$H NMR (acetone-$d_6$, 500 MHz) $\delta$ 9.73 (1H, s, 16-OH), 9.12 (1H, s, 14-OH), 7.41 (2H, d, $J$ = 6.9 Hz, H-3′), 7.34 (2H, dd, $J$ = 7.6, 6.9 Hz, H-4′), 7.29 (1H, d, $J$ = 7.6 Hz, H-5′), 7.25 (1H, dd, $J$ = 16.0, 11.5 Hz, H-8), 6.78 (1H, d, $J$ = 16.0 Hz, H-9), 6.54 (1H, s, H-15), 6.20 (1H, dd, $J$ = 11.5, 10.7 Hz, H-7), 5.58 (1H, dd, $J$ = 10.7, 3.8 Hz, H-6), 5.35 (1H, m, H-2), 5.17 (2H, s, $H_2$-1′), 4.13 (1H, d, $J$ = 16.0 Hz, H-11a), 4.00 (1H, brd, $J$ = 16.0 Hz, H-11b), 3.29 (1H, br s, H-5), 3.02 (1H, dt, $J$ = 8.4, 2.3 Hz, H-4), 2.44 (1H, ddd, $J$ = 14.5, 3.8, 2.3 Hz, H-3a), 1.65 (1H, ddd, $J$ = 14.5, 8.4, 3.8 Hz, H-3b), 1.55 (3H, d, $J$ = 6.1 Hz, $H_3$-1); $^{13}$C NMR (acetone-$d_6$, 125 MHz) $\delta$ 168.1 (s, C-18), 158.2 (s, C-16), 157.1 (s, C-14), 154.4 (s, C-10), 139.4 (s, C-2′), 136.6 (s, C-12), 132.9 (2d, C-6 and C-8), 132.1 (d, C-7), 129.0 (2d, C-4′), 128.8 (2d, C-3′), 128.4 (d, C-5′), 121.8 (d, C-9), 115.2 (s, C-13), 113.9 (s, C-17), 103.5 (d, C-15), 76.6 (t, C-1′), 71.9 (d, C-2), 56.0 (d, C-4), 55.6 (d, C-5), 37.4 (t, C-3), 35.7 (t, C-11), 18.7 (q, C-1); ESI-MS $m/z$ 468 $[M-H]^-$ as $C_{25}H_{23}ClNO_6$.

**4.4.13.2. 10-(*E*)-*O*-benzyloxime radicicol (27).** Colorless oil; HPLC, $t_R$ 13.71 min (system 1); $^1$H NMR (acetone-$d_6$, 500 MHz) $\delta$ 9.88 (1H, s, 16-OH), 9.21 (1H, s, 14-OH), 7.45 (2H, d, $J$ = 6.9 Hz, H-3′), 7.36 (2H, dd, $J$ = 7.6, 6.9 Hz, H-4′), 7.30 (1H, t, $J$ = 7.6 Hz, H-5′), 7.14 (1H, dd, $J$ = 16.0, 10.7 Hz, H-8), 6.54 (1H, s, H-15), 6.17 (1H, d, $J$ = 16.0 Hz, H-9), 6.15 (1H, t, $J$ = 10.7 Hz, H-7), 5.47 (1H, dd, $J$ = 10.7, 3.8 Hz, H-6), 5.35 (1H, m, H-2), 5.22 (2H, s, $H_2$-1′), 4.65 (1H, d, $J$ = 16.0 Hz, H-11a), 3.76 (1H, d, $J$ = 16.0 Hz, H-11b), 3.22(1H, m, H-5), 2.94 (1H, m, H-4), 2.42 (1H, dt, $J$ = 14.5, 3.8 Hz, H-3a), 1.62 (1H, ddd, $J$ = 14.5, 9.9, 4.6 Hz, H-3b), 1.53 (3H, d, $J$ = 6.1 Hz, $H_3$-1); $^{13}$C NMR (acetone-$d_6$, 125 MHz) $\delta$ 168.4 (s, C-18), 158.6 (s, C-16), 157.1 (s, C-14), 155.4 (s, C-10), 138.9 (s, C-2′), 137.0 (s, C-12), 132.0 (d, C-7), 131.5 (d, C-8), 130.6 (d, C-6), 130.0 (d, C-9), 129.1 (2d, C-3′), 129.0 (2d, C-4′), 128.6 (d, C-5′), 114.3 (s, C-13), 113.8 (s, C-17), 103.4 (d, C-15), 77.1 (t, C-1′), 72.0 (d, C-2), 56.1 (d, C-4), 55.9 (d, C-5), 37.4 (t, C-3), 28.8 (t, C-11), 18.4 (q, C-1); ESI-MS $m/z$ 468 $[M-H]^-$ as $C_{25}H_{23}ClNO_6$.

### 4.4.14. Preparation of 10-*O*-methyloxime radicicol

*O*-Methylhydroxylamine hydrochloride (1338 mg, 16.02 mmol, 8.52 equiv) was added to a solution of **1** (685 mg, 1.88 mmol) in pyridine (6 mL). The mixture was stirred for 5.5 h at 40 °C and cooled to room temperature. The mixture was diluted with water, extracted with ethyl acetate, dried over sodium sulfate and concentrated to produce a colorless oil. The residue was purified using preparative HPLC (eluent, MeCN–$H_2O$ = 40:60) to produce compounds **28** (144.6 mg, 19.9%) and **29** (107.1 mg, 14.4%).

**4.4.14.1. 10-(*Z*)-*O*-methyloxime radicicol (28).** Colorless oil; HPLC, $t_R$ 10.65 min (system 1); $^1$H NMR (acetone-$d_6$, 500 MHz) $\delta$ 9.65 (1H, br s, 16-OH), 9.10 (1H, br s, 14-OH), 7.19 (1H, dd, $J$ = 16.0, 11.5 Hz, H-8), 6.65 (1H, d, $J$ = 16.0 Hz, H-9), 6.51 (1H, s, H-15), 6.15 (1H, dd, $J$ = 11.5, 10.7 Hz, H-7), 5.54 (1H, dd, $J$ = 10.7, 3.8 Hz, H-6), 5.32 (1H, m, H-2), 4.06 (1H, d, $J$ = 16.0 Hz, H-11a), 3.95 (1H, d, $J$ = 16.0 Hz, H-11b), 3.84 (3H, s, OMe), 3.26 (1H, dd, $J$ = 3.8, 1.5 Hz, H-5), 2.98 (1H, ddd, $J$ = 8.4, 3.0, 1.5 Hz, H-4), 2.43 (1H, ddd, $J$ = 14.5, 3.8, 3.0 Hz, H-3a), 1.62 (1H, ddd, $J$ = 14.5, 8.4, 3.8 Hz, H-3b), 1.53 (3H, d, $J$ = 6.1 Hz, $H_3$-1); $^{13}$C NMR (acetone-$d_6$, 125 MHz) $\delta$ 168.0 (s, C-18), 158.1 (s, C-16), 157.0 (s, C-14), 153.8 (s, C-10), 136.6 (s, C-12), 132.8 (d, C-8), 132.7 (d, C-6), 132.1 (d, C-7), 121.6 (d, C-9), 115.1 (s, C-13), 114.0 (s, C-17), 103.5 (d, C-15), 71.9 (d, C-2), 62.0 (q, OMe), 56.0 (d, C-4), 55.6 (d, C-5), 37.4 (t, C-3), 35.7 (t, C-11), 18.7 (q, C-1); ESI-MS $m/z$ 392 $[M-H]^-$ as $C_{19}H_{19}ClNO_6$.

**4.4.14.2. 10-(*E*)-*O*-methyloxime radicicol (29).** Colorless oil; HPLC, $t_R$ 10.98 min (system 1); $^1$H NMR (acetone-$d_6$, 500 MHz) $\delta$ 9.82 (1H, br s, 16-OH), 9.18 (1H, br s, 14-OH), 7.14 (1H, dd, $J$ = 16.0, 10.7 Hz, H-8), 6.55 (1H, s, H-15), 6.16 (1H, d, $J$ = 16.0 Hz, H-9), 6.15 (1H, t, $J$ = 10.7 Hz, H-7), 5.47 (1H, dd, $J$ = 10.7, 3.0 Hz, H-6), 5.35 (1H, m, H-2), 4.58 (1H, d, $J$ = 16.0 Hz, H-11a), 3.95 (3H, s, OMe), 3.70 (1H, d, $J$ = 16.0 Hz, H-11b), 3.22 (1H, br s, H-5), 2.95 (1H, ddd, $J$ = 9.2, 3.0, 1.5 Hz, H-4), 2.43 (1H, dt, $J$ = 14.5, 3.0 Hz, H-3a), 1.62 (1H, ddd, $J$ = 14.5, 9.2, 3.8 Hz, H-3b), 1.54 (3H, d, $J$ = 6.1 Hz, $H_3$-1); $^{13}$C NMR (acetone-$d_6$, 125 MHz) $\delta$ 168.3 (s, C-18), 158.4 (s, C-16), 157.2 (s, C-14), 155.0 (s, C-10), 137.0 (s, C-12), 132.0 (d, C-7), 131.3 (d, C-8), 130.5 (d, C-6), 130.0 (d, C-9), 114.0 (s, C-13), 113.9 (s, C-17), 103.4 (d, C-15), 72.0 (d, C-2), 62.3 (q, OMe), 56.1 (d, C-4), 55.9 (d, C-5), 37.4 (t, C-3), 28.4 (t, C-11), 18.4 (q, C-1); ESI-MS $m/z$ 392 $[M-H]^-$ as $C_{19}H_{19}ClNO_6$.

### 4.4.15. Luche reduction of radicicol (1)

A mixture of **1** (91.5 mg, 0.25 mmol) and cerium(III) chloride heptahydrate (88 mg, 0.24 mmol, 0.96 equiv) in methanol (5 mL) was stirred for 10 min at room temperature. Sodium borohydride (60 mg, 1.59 mmol, 6.36 equiv) was added and the reaction mixture was stirred for 5 min at 0 °C. After stirring, the reaction mixture was diluted with water and extracted with ethyl acetate and the organic layer was dried over sodium sulfate and concentrated to produce a colorless oil. The crude oil was purified using preparative TLC (developing solvent, chloroform–methanol = 90:10) to produce compound **30** (27.2 mg, 29.6%).

**4.4.15.1. 10α-Hydroxyradicicol (30).** Colorless oil; HPLC, $t_R$ 6.43 min (system 1); $^1$H NMR (methanol-$d_4$, 500 MHz) $\delta$ 6.35 (1H, s, H-15), 5.90-5.78 (3H, m, H-7, H-8 and H-9), 5.31 (1H, dd, $J$ = 11.3, 4.9 Hz, H-6), 5.21 (1H, m, H-2), 4.52 (1H, ddd, $J$ = 10.4, 5.5, 4.0 Hz, H-10), 3.73 (1H, dd, $J$ = 12.8, 10.4 Hz, H-11a), 3.28 (1H, m, H-5), 3.18 (1H, dd, $J$ = 12.8, 4.0 Hz, H-11b), 2.97 (1H, dt, $J$ = 7.6, 3.0 Hz, H-4), 2.50 (1H, ddd, $J$ = 16.1, 7.6, 3.0 Hz, H-3a), 1.95 (1H, ddd, $J$ = 16.1, 5.5, 3.0 Hz, H-3b), 1.41 (3H, d, $J$ = 6.7 Hz, $H_3$-1); $^{13}$C NMR (methanol-$d_4$, 125 MHz) $\delta$ 171.2 (s, C-18), 162.8 (s, C-16), 159.0 (s, C-14), 139.1 (d, C-8), 139.1 (s, C-12), 130.7 (d, C-7), 129.3 (d, C-6), 127.4 (d, C-9), 115.9 (s, C-13), 108.6 (s, C-17), 103.5 (d, C-15), 72.7 (d, C-10), 70.3 (d, C-2), 57.2 (d, C-4), 56.0 (d, C-5), 40.0 (t, C-11), 36.0 (t, C-3), 20.1 (q, C-1); ESI-MS $m/z$ 731 [2 M-H]$^-$; HRESI-MS $m/z$ 389.0757 (calcd for $C_{18}H_{19}Cl_1O_6Na$ $[M+Na]^+$, 389.0768, $\Delta$ −1.1 mmu).

### 4.4.16. Luche reduction of compound 2

A mixture of **2** (602 mg, 1.64 mmol) and cerium(III) chloride heptahydrate (2.14 g, 5.74 mmol, 3.5 equiv) in methanol (13 mL) was stirred for 30 min at room temperature. Sodium borohydride (180 mg, 4.76 mmol, 2.9 equiv) was added and the reaction mixture was stirred for 5 min at 0 °C. After stirring, the reaction mixture was diluted with water, extracted with ethyl acetate and the organic layer was dried over sodium sulfate and concentrated to produce a colorless oil. The crude oil was purified using preparative TLC (developing solvent, chloroform–methanol = 93:7) and further purified using preparative HPLC (eluent; MeCN–$H_2O$ = 35:65) to produce compounds **31** (144.9 mg, 24.0%) and **32** (13.8 mg, 2.3%).

**4.4.16.1. 6,7-Dihydro-10α-hydroxyradicicol (31).** Colorless crystal; mp 210–213 °C; $[\alpha]_D^{20}$ −109.8 ($c$ 1.00, acetone); UV (methanol) $\lambda_{max}$ (log $\varepsilon$) 221 (4.45), 264 (3.93), and 314 (3.79) nm; IR (KBr) $\nu_{max}$ 3414, 3166, 2983, 2933, 1678, 1645, 1604, 1579, 1490, 1455, 1439, 1414, 1385, 1364, 1342, 1310, 1246, 1198, 1119, 1109, 1078, 1017, 978, 919, 876, 845, 810, 785, 705, 672, 634, 619 cm$^{-1}$; HPLC, $t_R$ 6.46 min (system 1); $^1$H NMR (methanol-$d_4$, 500 MHz) $\delta$ 6.32 (1H, s, H-15), 5.38 (1H, ddd, $J$ = 15.5, 12.8, 4.9 Hz, H-8), 5.28 (1H, dd, $J$ = 15.5, 5.2 Hz, H-9), 5.07 (1H, m, H-2), 4.33 (1H, m, H-10),

3.63 (1H, dd, $J$ = 12.5, 9.4 Hz, H-11a), 3.23 (1H, dd, $J$ = 12.5, 5.5 Hz, H-11b), 2.85 (1H, dt, $J$ = 6.7, 3.0 Hz, H-4), 2.50 (1H, dt, $J$ = 9.1, 3.0 Hz, H-5), 2.27 (1H, ddd, $J$ = 15.5, 6.7, 3.0 Hz, H-3a), 2.16 (1H, m, H-7a), 2.01 (1H, m, H-6a), 1.95 (1H, m, H-7b), 1.85 (1H, ddd, $J$ = 15.5, 5.5, 2.4 Hz, H-3b), 1.35 (3H, d, $J$ = 6.7 Hz, $H_3$-1), 1.19 (1H, m, H-6b); $^{13}$C NMR (methanol-$d_4$, 125 MHz) $\delta$ 171.8 (s, C-18), 163.0 (s, C-16), 159.2 (s, C-14), 140.0 (s, C-12), 133.2 (d, C-9), 129.1 (d, C-8), 115.9 (s, C-13), 109.3 (s, C-17), 103.4 (d, C-15), 71.8 (d, C-10), 70.9 (d, C-2), 59.6 (d, C-5), 58.3 (d, C-4), 40.2 (t, C-11), 37.0 (t, C-3), 31.3 (t, C-6), 29.5 (t, C-7), 20.2 (q, C-1); ESI-MS $m/z$ 367 $[M-H]^-$; HRESI-MS $m/z$ 367.0952 (calcd for $C_{18}H_{20}Cl_1O_6$ $[M-H]^-$, 367.0948, $\Delta$ +0.4 mmu).

**4.4.16.2. 6,7-Dihydro-10β-hydroxyradicicol (32).** Colorless oil; HPLC, $t_R$ 6.11 min (system 1); $^1$H NMR (methanol-$d_4$, 500 MHz) $\delta$ 6.41 (1H, s, H-15), 5.64 (1H, dt, $J$ = 15.5, 6.1 Hz, H-8), 5.37 (1H, dd, $J$ = 15.5, 4.0 Hz, H-9), 4.93 (1H, m, H-2), 4.43 (1H, m, H-10), 3.30 (1H, dd, $J$ = 12.8, 9.8 Hz, H-11a), 3.25 (1H, dd, $J$ = 12.8, 5.5 Hz, H-11b), 2.92 (1H, dt, $J$ = 8.5, 3.0 Hz, H-5), 2.86 (1H, dd, $J$ = 5.8, 3.0 Hz, H-4), 2.20 (1H, m, H-7a), 2.17 (1H, m, H-3a), 2.05 (1H, m, H-3b), 2.03 (1H, m, H-6a), 2.02 (1H, m, H-7b), 1.35 (3H, d, $J$ = 6.1 Hz, $H_3$-1), 1.27 (1H, m, H-6b); $^{13}$C NMR (methanol-$d_4$, 125 MHz) $\delta$ 169.5 (s, C-18), 158.2 (s, C-16), 157.3 (s, C-14), 138.5 (s, C-12), 133.4 (d, C-9), 129.7 (d, C-8), 114.9 (s, C-13), 114.7 (s, C-17), 103.3 (d, C-15), 70.6 (d, C-10), 69.5 (d, C-2), 57.6 (d, C-5), 56.8 (d, C-4), 39.7 (t, C-11), 36.8 (t, C-3), 31.2 (t, C-6), 28.8 (t, C-7), 20.4 (q, C-1); ESI-MS $m/z$ 367 $[M-H]^-$; HRESI-MS $m/z$ 391.0932 (calcd for $C_{18}H_{21}Cl_1O_6Na$ $[M+Na]^+$, 391.0924, $\Delta$ +0.8 mmu).

### 4.4.17. Luche reduction of compound 15

A mixture of **15** (26.5 mg, 0.072 mmol) and cerium(III) chloride heptahydrate (100 mg, 0.27 mmol, 3.8 equiv) in methanol (5 mL) was stirred for 30 min at room temperature. Sodium borohydride (60 mg, 1.59 mmol, 22.0 equiv) was added and the reaction mixture was stirred for 5 min at 0 °C. After stirring, the reaction mixture was diluted with water, extracted with ethyl acetate and the organic layer was dried over sodium sulfate and concentrated to produce a colorless oil. The crude oil was purified using preparative TLC (developing solvent, chloroform–methanol = 94:6) to produce compounds **33** (5.7 mg, 21.2%) and **34** (8.8 mg, 32.7%).

**4.4.17.1. 6,7,8,9-Tetrahydro-10α-hydroxyradicicol (33).** Colorless solid; mp 173–175 °C; IR (KBr) $\nu_{max}$ 3503, 3146, 2982, 2940, 1639, 1608, 1598, 1530, 1495, 1455, 1421, 1376, 1356, 1312, 1288, 1264, 1240, 1196, 1178, 1145, 1107, 1062, 1040, 1026, 927, 902, 855, 801, 774, 747, 735, 701, 672, 636, 608 cm$^{-1}$; HPLC, $t_R$ 6.87 min (system 1); $^1$H NMR (methanol-$d_4$, 500 MHz) $\delta$ 6.38 (1H, s, H-15), 5.20 (1H, m, H-2), 3.88 (1H, m, H-10), 3.21 (2H, m, $H_2$-11), 3.03 (1H, dt, $J$ = 7.3, 2.4 Hz, H-4), 2.71 (1H, dt, $J$ = 9.4, 2.4 Hz, H-5), 2.36 (1H, ddd, $J$ = 15.5, 7.3, 2.4 Hz, H-3a), 2.09 (1H, ddd, $J$ = 14.3, 4.3, 2.4 Hz, H-6a), 1.74 (1H, ddd, $J$ = 15.5, 7.3, 2.4 Hz, H-3b), 1.57 (1H, m, H-9a), 1.52 (2H, m, $H_2$-7), 1.48 (1H, m, H-9b), 1.45 (3H, d, $J$ = 6.4 Hz, $H_3$-1), 1.43 (2H, m, $H_2$-8), 1.11 (1H, m, H-6b); $^{13}$C NMR (methanol-$d_4$, 125 MHz) $\delta$ 171.1 (s, C-18), 160.1 (s, C-16), 158.0 (s, C-14), 139.7 (s, C-12), 115.3 (s, C-13), 112.3 (s, C-17), 103.0 (d, C-15), 72.8 (d, C-10), 71.4 (d, C-2), 60.5 (d, C-5), 58.2 (d, C-4), 39.9 (t, C-11), 38.0 (t, C-3), 36.8 (t, C-9), 32.2 (t, C-6), 25.8 (t, C-8), 25.2 (t, C-7), 20.0 (q, C-1); ESI-MS $m/z$ 369 $[M-H]^-$ as $C_{18}H_{22}ClO_6$.

**4.4.17.2. 6,7,8,9-Tetrahydro-10β-hydroxyradicicol (34).** Colorless oil; HPLC, $t_R$ 6.07 min (system 1); $^1$H NMR (methanol-$d_4$, 500 MHz) $\delta$ 6.39 (1H, s, H-15), 5.12 (1H, m, H-2), 3.82 (1H, m, H-10), 3.15 (1H, dd, $J$ = 13.4, 7.2 Hz, H-11a), 2.98 (1H, dd, $J$ = 13.4, 5.5 Hz, H-11b), 2.88 (1H, dt, $J$ = 7.3, 2.4 Hz, H-4), 2.81 (1H, dt, $J$ = 7.3, 2.4 Hz, H-5), 2.37 (1H, ddd, $J$ = 14.0, 7.3, 3.7 Hz, H-3a), 1.94 (1H, m, H-6a), 1.57 (1H, m, H-7a), 1.50 (1H, m, H-8a), 1.40 (3H, d, $J$ = 6.1 Hz, $H_3$-1), 1.38 (2H, m, H-3b and H-9a), 1.35 (2H, m, H-7b and H-8b), 1.29 (1H, m, H-6b); $^{13}$C NMR (methanol-$d_4$, 125 MHz) $\delta$ 169.8 (s, C-18), 156.8 (s, C-16), 156.6 (s, C-14), 138.5 (s, C-12), 115.9 (s, C-13), 114.6 (s, C-17), 102.9 (d, C-15), 72.3 (d, C-10), 72.2 (d, C-2), 59.1 (d, C-5), 57.1 (d, C-4), 39.2 (t, C-3), 37.8 (t, C-11), 35.1 (t, C-9), 30.2 (t, C-6), 24.6 (t, C-7), 23.5 (t, C-8), 20.5 (q, C-1); ESI-MS $m/z$ 369 $[M-H]^-$ as $C_{18}H_{22}ClO_6$.

### 4.4.18. Luche reduction of compound 16

A mixture of **16** (153 mg, 0.42 mmol) and cerium(III) chloride heptahydrate (213 mg, 0.57 mmol, 1.36 equiv) in methanol (6 mL)/THF (2 mL) was stirred for 30 min at room temperature. Sodium borohydride (79 mg, 2.1 mmol, 4.97 equiv) was added, and the reaction mixture was stirred for 5 min at 0 °C. After stirring, the reaction mixture was diluted with water, extracted with ethyl acetate and the organic layer was dried over sodium sulfate and concentrated to produce a colorless oil. The crude oil was purified using silica gel column chromatography (eluent, $n$-hexane–ethyl acetate = 3:2) and further purified using preparative HPLC (eluent, MeCN–$H_2O$ = 35:65) to produce compounds **35** (11.3 mg, 7.3%) and **36** (19.8 mg, 12.9%).

**4.4.18.1. 6,9-Dihydro-10α-hydroxyradicicol (35).** Colorless oil; HPLC, $t_R$ 7.06 min (system 1); $^1$H NMR (chloroform-$d$/methanol-$d_4$, 500 MHz) $\delta$ 6.26 (1H, s, H-15), 5.52 (1H, dt, $J$ = 15.3, 7.9 Hz, H-8), 5.35 (1H, dt, $J$ = 15.3, 7.3 Hz, H-7), 5.22 (1H, m, H-2), 3.93 (1H, m, H-10), 3.23 (1H, dd, $J$ = 14.0, 10.4 Hz, H-11a), 3.01 (1H, dt, $J$ = 9.2, 2.4 Hz, H-4), 2.85 (1H, ddd, $J$ = 5.5, 3.0, 2.4 Hz, H-5), 2.79 (1H, dd, $J$ = 14.0, 3.0 Hz, H-11b), 2.50 (1H, ddd, $J$ = 14.0, 7.3, 3.0 Hz, H-6a), 2.19 (1H, m, H-3a), 2.16 (2H, m, $H_2$-9), 2.01 (1H, m, H-6b), 1.37 (1H, ddd, $J$ = 14.6, 9.2, 2.4 Hz, H-3b), 1.29 (3H, d, $J$ = 6.7 Hz, $H_3$-1); $^{13}$C NMR (chloroform-$d$/methanol-$d_4$, 125 MHz) $\delta$ 169.4 (s, C-18), 157.7 (s, C-16), 155.8 (s, C-14), 138.1 (s, C-12), 129.8 (d, C-8), 127.6 (d, C-7), 113.7 (s, C-13), 111.8 (s, C-17), 102.0 (d, C-15), 70.5 (d, C-2), 70.1 (d, C-10), 59.4 (d, C-5), 54.6 (d, C-4), 39.4 (t, C-9), 37.1 (t, C-3), 36.4 (t, C-11), 33.1 (t, C-6), 19.3 (q, C-1); ESI-MS $m/z$ 367 $[M-H]^-$ as $C_{18}H_{20}ClO_6$.

**4.4.18.2. 6,9-Dihydro-10β-hydroxyradicicol (36).** Colorless oil; HPLC, $t_R$ 6.51 min (system 1); $^1$H NMR (chloroform-$d$/methanol-$d_4$, 500 MHz) $\delta$ 6.21 (1H, s, H-15), 5.53 (1H, ddd, $J$ = 15.3, 10.4, 4.9 Hz, H-8), 5.25 (1H, m, H-2), 5.17 (1H, ddd, $J$ = 15.3, 9.8, 4.9 Hz, H-7), 4.05 (1H, m, H-10), 2.88 (1H, dd, $J$ = 4.3, 2.4 Hz, H-5), 2.83 (1H, dt, $J$ = 14.0, 2.4 Hz, H-11a), 2.81 (1H, m, H-4), 2.66 (1H, dd, $J$ = 14.0, 11.0 Hz, H-11b), 2.45 (1H, m, H-6a), 2.40 (2H, m, H-6b and H-9a), 2.07 (1H, ddd, $J$ = 14.0, 10.4, 3.0 Hz, H-3a), 1.90 (1H, m, H-9b), 1.27 (1H, ddd, $J$ = 14.0, 6.7, 1.8 Hz, H-3b), 1.22 (3H, d, $J$ = 6.7 Hz, $H_3$-1); $^{13}$C NMR (chloroform-$d$/methanol-$d_4$, 125 MHz) $\delta$ 169.8 (s, C-18), 155.1 (s, C-16), 154.9 (s, C-14), 136.1 (s, C-12), 129.8 (d, C-8), 127.5 (d, C-7), 114.4 (s, C-13), 112.7 (s, C-17), 102.0 (d, C-15), 69.9 (d, C-2), 67.7 (d, C-10), 59.4 (d, C-5), 54.4 (d, C-4), 38.8 (t, C-9), 38.2 (t, C-3), 37.0 (t, C-11), 32.7 (t, C-6), 20.1 (q, C-1); ESI-MS $m/z$ 367 $[M-H]^-$ as $C_{18}H_{20}ClO_6$.

### 4.4.19. Hydrogenation of monocillin III (4)

Five-percent palladium–carbon (PH, wet-type) (30 mg) was added to a solution of **4** (154 mg, 0.46 mmol) in ethyl acetate (5 mL). After hydrogenation for 1.5 h at room temperature under atmospheric pressure, the catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residue was purified using preparative TLC (developing solvent, chloroform–methanol = 95:5) to produce compound **37** (monocillin V[16]) (134.8 mg, 87.0%).

*Monocillin V (**37**) (synthetic):* colorless oil; HPLC, $t_R$ 7.65 min (system 1); $^1$H NMR (acetone-$d_6$, 500 MHz) $\delta$ 6.28 (1H, d,

$J$ = 2.4 Hz, H-15), 6.24 (1H, d, $J$ = 2.4 Hz, H-13), 5.21 (1H, m, H-2), 4.32 (1H, d, $J$ = 17.4 Hz, H-11a), 3.70 (1H, d, $J$ = 17.4 Hz, H-11b), 2.78 (1H, ddd, $J$ = 5.8, 4.0, 2.4 Hz, H-4), 2.59 (1H, dt, $J$ = 9.1, 2.4 Hz, H-5), 2.49 (2H, m, $H_2$-9), 2.14 (1H, ddd, $J$ = 15.5, 5.8, 2.4 Hz, H-3a), 1.96 (1H, m, H-6a), 1.87 (1H, ddd, $J$ = 15.5, 4.0, 2.4 Hz, H-3b), 1.62 (1H, m, H-8a), 1.52 (1H, m, H-8b), 1.49 (2H, m, $H_2$-7), 1.40 (3H, d, $J$ = 6.4 Hz, $H_3$-1), 1.08 (1H, m, H-6b); $^{13}$C NMR (acetone-$d_6$, 125 MHz) $\delta$ 207.7 (s, C-10), 171.5 (s, C-18), 166.1 (s, C-16), 163.2 (s, C-14), 140.7 (s, C-12), 113.6 (d, C-13), 106.4 (s, C-17), 102.8 (d, C-15), 71.2 (d, C-2), 57.7 (d, C-5), 55.4 (d, C-4), 50.5 (t, C-11), 40.8 (t, C-9), 37.0 (t, C-3), 31.8 (t, C-6), 24.2 (t, C-7), 22.9 (t, C-8), 19.4 (q, C-1); ESI-MS $m/z$ 333 $[M-H]^-$; HRESI-MS $m/z$ 357.1324 (calcd for $C_{18}H_{22}O_6Na$ $[M+Na]^+$, 357.1314, $\Delta$ +1.0 mmu).

#### 4.4.20. Hydrogenation of monocillin II (5)

Five-percent palladium–carbon (PH, wet-type) (42 mg) was added to a solution of **5** (211 mg, 0.67 mmol) in ethyl acetate (11 mL). After hydrogenation for 1.5 h at room temperature under atmospheric pressure, the catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residue was purified using preparative TLC (developing solvent, chloroform–methanol = 95:5) to produce compound **38** (nordinone[15]) (159.7 mg, 74.7%).

*Nordinone* (***38***) (synthetic): colorless oil; HPLC, $t_R$ 13.00 min (system 1); $^1$H NMR (acetone-$d_6$, 500 MHz) $\delta$ 6.30 (1H, d, $J$ = 2.4 Hz, H-15), 6.19 (1H, d, $J$ = 2.4 Hz, H-13), 5.15 (1H, m, H-2), 4.61 (1H, d, $J$ = 17.7 Hz, H-11a), 3.79 (1H, d, $J$ = 17.7 Hz, H-11b), 2.77 (1H, ddd, $J$ = 18.3, 11.0, 3.7 Hz, H-9a), 2.54 (1H, ddd, $J$ = 18.3, 5.5, 3.7 Hz, H-9b), 1.85 (1H, m, H-3a), 1.80 (1H, m, H-8a), 1.53 (1H, ddd, $J$ = 9.2, 7.3, 2.4 Hz, H-3b), 1.43 (1H, m, H-7a), 1.35–1.32 (7H, m, H-4a, $H_2$-5, $H_2$-6, H-7b and H-8b), 1.33 (3H, d, $J$ = 6.7 Hz, $H_3$-1), 1.31 (1H, m, H-4b); $^{13}$C NMR (acetone-$d_6$, 125 MHz) $\delta$ 207.0 (s, C-10), 172.2 (s, C-18), 166.4 (s, C-16), 163.0 (s, C-14), 140.9 (s, C-12), 113.8 (d, C-13), 106.3 (s, C-17), 102.6 (d, C-15), 74.4 (d, C-2), 50.5 (t, C-11), 39.4 (t, C-9), 35.2 (t, C-3), 27.4 (t, C-5), 24.6 (t, C-7), 23.8 (t, C-6), 23.3 (t, C-4), 22.4 (t, C-8), 21.2 (q, C-1); ESI-MS $m/z$ 319 $[M-H]^-$; HRESI-MS $m/z$ 343.1520 (calcd for $C_{18}H_{24}O_5Na$ $[M+Na]^+$, 343.1521, $\Delta$ −0.1 mmu).

#### 4.4.21. Luche reduction of monocillin III (4)

A mixture of **4** (191 mg, 0.57 mmol) and cerium(III) chloride heptahydrate (641 mg, 1.72 mmol, 3.02 equiv) in methanol (10 mL)/THF (4 mL) was stirred for 10 min at room temperature. Sodium borohydride (216 mg, 5.71 mmol, 10.02 equiv) was added, and the reaction mixture was stirred for 5 min at 0 °C. After stirring, the reaction mixture was diluted with water, extracted with ethyl acetate and the organic layer was dried over sodium sulfate and concentrated to produce a colorless oil. The crude oil was purified using preparative HPLC (eluent, MeCN–$H_2O$ = 30:70) to produce compound **39** (137.3 mg, 71.4%).

**4.4.21.1. 10α-Hydroxymonocillin III (39) .** Colorless oil; HPLC, $t_R$ 6.25 min (system 1); $^1$H NMR (methanol-$d_4$, 500 MHz) $\delta$ 6.30 (1H, d, $J$ = 2.4 Hz, H-13), 6.20 (1H, d, $J$ = 2.4 Hz, H-15), 5.54 (1H, ddd, $J$ = 15.9, 4.9, 1.2 Hz, H-8), 5.43 (1H, dd, $J$ = 15.9, 4.9 Hz, H-9), 5.16 (1H, m, H-2), 4.13 (1H, m H-10), 3.77 (1H, dd, $J$ = 12.2, 7.9 Hz, H-11a), 2.91 (1H, ddd, $J$ = 6.1, 3.7, 2.4 Hz, H-4), 2.74 (1H, dd, $J$ = 12.2, 6.7 Hz, H-11b), 2.57 (1H, dt, $J$ = 9.2, 2.4 Hz, H-5), 2.25 (1H, m, H-7a), 2.13 (1H, m, H-6a), 2.11 (2H, m, $H_2$-3), 2.05 (1H, m, H-7b), 1.40 (3H, d, $J$ = 6.1 Hz, $H_3$-1), 1.23 (1H, ddt, $J$ = 14.0, 9.2, 3.7 Hz, H-6b); $^{13}$C NMR (methanol-$d_4$, 125 MHz) $\delta$ 172.6 (s, C-18), 166.4 (s, C-16), 163.5 (s, C-14), 144.6 (s, C-12), 133.3 (d, C-9), 129.7 (d, C-8), 113.3 (d, C-13), 106.2 (s, C-17), 102.5 (d, C-15), 74.9 (d, C-10), 70.5 (d, C-2), 58.9 (d, C-5), 58.3 (d, C-4), 43.2 (t, C-11), 36.9 (t, C-3), 31.8 (t, C-6), 29.4 (t, C-7), 19.9 (q, C-1); ESI-MS $m/z$ 333 $[M-H]^-$ as $C_{18}H_{21}O_6$.

#### 4.4.22. Luche reduction of monocillin II (5)

A mixture of **5** (233 mg, 0.74 mmol) and cerium(III) chloride heptahydrate (754 mg, 2.02 mmol, 2.73 equiv) in methanol (5 mL)/THF (2 mL) was stirred for 10 min at room temperature. Sodium borohydride (236 mg, 6.24 mmol, 8.43 equiv) was added, and the reaction mixture was stirred for 5 min at 0 °C. After stirring, the reaction mixture was diluted with water, extracted with ethyl acetate and the organic layer was dried over sodium sulfate and concentrated to produce a colorless oil. The crude oil was purified using preparative HPLC (eluent, MeCN–$H_2O$ = 45:55) to produce compounds **40** (184.6 mg, 78.7%) and **41** (49.3 mg, 21.0%).

**4.4.22.1. 10α-Hydroxymonocillin II (40).** Colorless oil; HPLC, $t_R$ 10.37 min (system 1); $^1$H NMR (acetone-$d_6$, 500 MHz) $\delta$ 6.50 (1H, d, $J$ = 2.4 Hz, H-13), 6.23 (1H, d, $J$ = 2.4 Hz, H-15), 5.43 (1H, ddd, $J$ = 15.3, 9.2, 7.3 Hz, H-4), 5.35 (1H, ddd, $J$ = 15.3, 11.0, 5.5 Hz, H-8), 5.33 (1H, dd, $J$ = 15.3, 4.3 Hz, H-9), 5.22 (1H, m, H-2), 5.20 (1H, ddd, $J$ = 15.3, 6.1, 3.7 Hz, H-5), 4.17 (1H, m, H-10), 3.72 (1H, dd, $J$ = 13.4, 7.3 Hz, H-11a), 2.85 (1H, dd, $J$ = 13.4, 6.1 Hz, H-11b), 2.67 (1H, ddd, $J$ = 15.3, 7.3, 3.7 Hz, H-3a), 2.29 (1H, ddd, $J$ = 15.3, 9.2, 6.7 Hz, H-3b), 2.12 (2H, m, $H_2$-6), 2.09 (1H, m, H-7a), 1.94 (1H, m, H-7b), 1.39 (3H, d, $J$ = 6.7 Hz, $H_3$-1); $^{13}$C NMR (acetone-$d_6$, 125 MHz) $\delta$ 172.4 (s, C-18), 166.3 (s, C-16), 162.8 (s, C-14), 145.5 (s, C-12), 135.0 (d, C-9), 133.9 (d, C-5), 128.3 (d, C-8), 126.4 (d, C-4), 112.1 (d, C-13), 105.9 (s, C-17), 102.0 (d, C-15), 75.0 (d, C-10), 73.3 (d, C-2), 43.4 (t, C-11), 37.9 (t, C-3), 31.9 (t, C-6), 31.0 (t, C-7), 19.5 (q, C-1); ESI-MS $m/z$ 317 $[M-H]^-$; HRESI-MS $m/z$ 341.1378 (calcd for $C_{18}H_{22}O_5Na$ $[M+Na]^+$, 341.1365, $\Delta$ +1.3 mmu).

**4.4.22.2. 10β-Hydroxymonocillin II (41).** Colorless oil; HPLC, $t_R$ 9.55 min (system 1); $^1$H NMR (acetone-$d_6$, 500 MHz) $\delta$ 6.53 (1H, d, $J$ = 2.4 Hz, H-13), 6.24 (1H, d, $J$ = 2.4 Hz, H-15), 5.43 (1H, ddd, $J$ = 15.9, 7.3, 6.7 Hz, H-8), 5.39 (1H, ddd, $J$ = 15.9, 7.3, 6.1 Hz, H-4), 5.28 (1H, ddd, $J$ = 15.9, 8.5, 6.1 Hz, H-5), 5.27 (1H, m, H-9), 5.23 (1H, m, H-2), 4.25 (1H, m, H-10), 3.25 (1H, dd, $J$ = 15.3, 5.5 Hz, H-11a), 3.23 (1H, dd, $J$ = 15.3, 5.5 Hz, H-11b), 2.56 (1H, ddd, $J$ = 14.0, 6.1, 3.7 Hz, H-3a), 2.29 (1H, ddd, $J$ = 14.0, 7.3, 6.1 Hz, H-3b), 2.12 (2H, m, $H_2$-6), 2.02 (2H, m, $H_2$-7), 1.37 (3H, d, $J$ = 6.1 Hz, $H_3$-1); $^{13}$C NMR (acetone-$d_6$, 125 MHz) $\delta$ 171.2 (s, C-18), 164.6 (s, C-16), 162.2 (s, C-14), 144.4 (s, C-12), 134.5 (d, C-9), 133.3 (d, C-5), 130.6 (d, C-8), 127.0 (d, C-4), 112.6 (d, C-13), 107.4 (s, C-17), 102.0 (d, C-15), 73.4 (d, C-10), 72.8 (d, C-2), 42.4 (t, C-11), 38.3 (t, C-3), 32.2 (t, C-6), 31.1 (t, C-7), 19.5 (q, C-1); ESI-MS $m/z$ 317 $[M-H]^-$; HRESI-MS $m/z$ 341.1362 (calcd for $C_{18}H_{22}O_5Na$ $[M+Na]^+$, 341.1365, $\Delta$ −0.3 mmu).

#### 4.4.23. Methylation of compound 31

Potassium carbonate (3 mg, 0.022 mmol) and methyl iodide (0.5 mL, 8.0 mmol) were added to a solution of **31** (34 mg, 0.09 mmol) in *N*,*N*-dimethylformamide (2 mL), and the mixture was stirred for 4.5 h at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, evaporated in vacuo and purified using preparative HPLC (eluent, MeCN–$H_2O$ = 38:62) to produce compounds **42** (6.4 mg, 18.1%) and **43** (14.5 mg, 39.6%).

**4.4.23.1. 6,7-Dihydro-10α-hydroxyradicicol monomethyl ether (42).** Colorless oil; HPLC, $t_R$ 9.90 min (system 1); $^1$H NMR (acetone-$d_6$, 500 MHz) $\delta$ 6.58 (1H, s, H-15), 5.53 (1H, dddd, $J$ = 15.2, 6.7, 4.3, 1.8 Hz, H-8), 5.36 (1H, dd, $J$ = 15.2, 4.3 Hz, H-9), 5.16 (1H, m, H-2), 4.43 (1H, m), 3.94 (3H, s, 14-O*Me*), 3.89 (1H, dd, $J$ = 12.5, 9.8 Hz, H-11a), 3.35 (1H, dd, $J$ = 12.5, 6.1 Hz, H-11b), 2.83 (1H, m, H-4), 2.50 (1H, dt, $J$ = 2.4, 1.8 Hz, H-5), 2.33 (1H, ddd, $J$ = 15.8, 7.0, 3.0 Hz, H-3a), 2.21 (1H, m, H-7a), 2.06 (1H, m,

H-6a), 2.00 (1H, m, H-7b), 1.98 (1H, m, H-3b), 1.43 (3H, d, $J$ = 6.7 Hz, $H_3$-1), 1.22 (1H, dt, $J$ = 17.0, 9.1 Hz, H-6b); $^{13}$C NMR (acetone-$d_6$, 125 MHz) $\delta$ 171.8 (s, C-18), 164.5 (s, C-16), 160.4 (s, C-14), 140.4 (s, C-12), 133.4 (d, C-9), 127.9 (d, C-8), 116.4 (s, C-13), 108.0 (s, C-17), 100.2 (d, C-15), 70.7 (d, C-2), 70.6 (d, C-10), 58.3 (d, C-5), 57.2 (d, C-4), 56.9 (q, 14-O*Me*), 40.3 (t, C-11), 36.5 (t, C-3), 31.1 (t, C-6), 29.3 (t, C-7), 20.2 (q, C-1); ESI-MS $m/z$ 405 $[M+Na]^+$; HRESIMS $m/z$ 405.1098 (calcd for $C_{19}H_{23}Cl_1O_6Na$ $[M+Na]^+$, 405.1081, $\Delta$ +1.7 mmu).

**4.4.23.2. 6,7-Dihydro-10α-hydroxyradicicol dimethyl ether (43).** Colorless oil; HPLC, $t_R$ 8.90 min (system 1); $^1$H NMR (acetone-$d_6$, 500 MHz) $\delta$ 6.75 (1H, s, H-15), 5.58 (1H, m, H-8), 5.52 (1H, dd, $J$ = 15.9, 6.7 Hz, H-9), 5.18 (1H, m, H-2), 4.49 (1H, m, *m*H-10), 3.94 (3H, s, 16-O*Me*), 3.84 (3H, s, 14-O*Me*), 3.28 (1H, dd, $J$ = 13.4, 6.7 Hz, H-11a), 2.83 (1H, ddd, $J$ = 8.6, 3.7, 1.8 Hz, H-4), 2.73 (1H, dd, $J$ = 13.4, 5.5 Hz, H-11b), 2.69 (1H, dt, $J$ = 9.2, 1.8 Hz, H-5), 2.31 (1H, ddd, $J$ = 14.6, 6.7, 3.7 Hz, H-3a), 2.20–2.10 (3H, m, H-6a and $H_2$-7), 1.46 (3H, d, $J$ = 6.7 Hz, $H_3$-1), 1.40 (1H, ddd, $J$ = 14.6, 8.6, 3.0 Hz, H-3b), 1.09 (1H, m, H-6b); $^{13}$C NMR (acetone-$d_6$, 125 MHz) $\delta$ 167.2 (s, C-18), 157.4 (s, C-16), 156.9 (s, C-14), 136.1 (s, C-12), 135.7 (d, C-9), 130.2 (d, C-8), 119.9 (s, C-17), 115.1 (s, C-13), 96.5 (d, C-15), 73.0 (d, C-10), 71.5 (d, C-2), 58.0 (d, C-5), 56.8 (q, 14-O*Me*), 56.7 (q, 16-O*Me*), 56.1 (d, C-4), 40.8 (t, C-11), 39.0 (t, C-3), 33.3 (t, C-6), 28.7 (t, C-7), 19.8 (q, C-1); ESI-MS $m/z$ 419 $[M+Na]^+$; HRESI-MS $m/z$ 419.1243 (calcd for $C_{20}H_{25}Cl_1O_6Na$ $[M+Na]^+$, 419.1237, $\Delta$ +0.6 mmu).

### 4.4.24. Acetylation of compound 31

Acetic anhydride (3 mL) was added to a solution of **31** (55 mg, 0.15 mmol) in pyridine (1 mL), and the mixture was stirred for 17 h at room temperature. The reaction mixture was poured ice water and extracted with ethyl acetate. The organic layer was washed brine, dried over sodium sulfate, evaporated in vacuo and purified using preparative HPLC (eluent, MeCN–$H_2O$ = 60:40) to produce compound **44** (64.7 mg, 87.7%).

**4.4.24.1. 6,7-Dihydro-10α-hydroxyradicicol triacetate (44).** Colorless oil; HPLC, $t_R$ 12.59 min (system 1); $^1$H NMR (acetone-$d_6$, 500 MHz) $\delta$ 7.16 (1H, s, H-15), 5.74 (1H, dt, $J$ = 14.6, 6.7 Hz, H-8), 5.55 (1H, m, H-10), 5.53 (1H, dd, $J$ = 14.6, 7.3 Hz, H-9), 5.30 (1H, m, H-2), 3.51 (1H, dd, $J$ = 14.0, 7.9 Hz, H-11a), 3.05 (1H, dd, $J$ = 14.0, 4.9 Hz, H-11b), 2.88 (1H, ddd, $J$ = 7.9, 3.7, 2.4 Hz, H-4), 2.71 (1H, dt, $J$ = 9.2, 2.4 Hz, H-5), 2.34 (3H, s, 16-OCO*Me*), 2.30 (1H, ddd, $J$ = 15.3, 7.9, 3.7 Hz, H-3a), 2.23 (3H, s, 14-OCO*Me*), 2.23–2.13 (3H, m, H-6a and $H_2$-7), 1.94 (3H, s, 10-OCO*Me*), 1.48 (1H, ddd, $J$ = 15.3, 7.9, 3.0 Hz, H-3b), 1.47 (3H, d, $J$ = 6.7 Hz, $H_3$-1), 1.15 (1H, m, H-6b); $^{13}$C NMR (acetone-$d_6$, 125 MHz) $\delta$ 169.9 (s, 10-O*C*OMe), 168.7 (s, 14-O*C*OMe), 168.4 (s, 16-O*C*OMe), 165.5 (s, C-18), 149.2 (s, C-16), 147.6 (s, C-14), 136.1 (s, C-12), 134.1 (d, C-8), 130.0 (d, C-9), 128.9 (s, C-17), 126.0 (s, C-13), 118.6 (d, C-15), 74.7 (d, C-10), 72.8 (d, C-2), 57.7 (d, C-5), 56.2 (d, C-4), 38.9 (t, C-3), 37.5 (t, C-11), 32.9 (t, C-6), 28.0 (t, C-7), 20.9 (q, 10-OCO*Me*), 20.6 (q, 14-OCO*Me*), 20.5 (q, 16-OCO*Me*), 19.8 (q, C-1); ESI-MS $m/z$ 517 $[M+Na]^+$; HRESI-MS $m/z$ 517.1254 (calcd for $C_{24}H_{27}Cl_1O_9Na$ $[M+Na]^+$, 517.1241, $\Delta$ +1.3 mmu).

## 4.5. X-ray crystal analysis of compound 31

A single crystal of **31** was grown by crystallization from methanol at room temperature. X-ray intensity data was collected on a R-AXIS RAPID II diffractometer (Rigaku Co.) equipped with graphite monochromatized Cu $K_\alpha$ radiation. The structure was solved by direct methods and refined anisotropically using the CRYSTAL STRUCTURE™ program package. Crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre (CCDC) and allocated the deposition number CCDC 724738. Copies of the data can be obtained free of charge by applying to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-[0]1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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