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Enantiodifferentiation in taste perception of isovanillic derivatives

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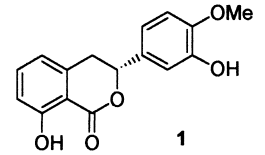
Abstract

Both the enantiomers of three isovanillic chiral 1,3-oxathianes and one 1,3-dithiane were obtained as pure compounds by asymmetric synthesis or chiral HPLC resolution. The absolute configuration was established using X-ray, CD spectra or NMR NOE experiments. The relationships between the structure and the sweet taste of the enantiomeric compounds are discussed.

1. Introduction

Isovanillic derivatives are a class of organic compounds structurally related to the natural dihydroisocoumarin phyllodulcin **1**,[1] a sweet compound extracted from the leaves of *Hydrangea macrophylla* var. Thumbergii Sieboldi, which has been used to prepare a sweet infusion. Another important member of this family is the commercial semisynthetic sweetener neohesperidindihydrochalcone (NHDC) **2**.[2]



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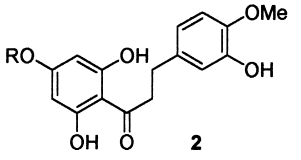

2

R = 2-O-α-L-rhamnosyl-β-D-glucopyranoside

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The intensity of their sweet taste was estimated, respectively, as 400–800 and 650× with respect to sucrose. The isovanillic moiety seems to be essential for the eliciting of the sweet taste, but a very important role also seems to be played by other molecular fragments, particularly by the heterocyclic ring *b*.

Several analogues of these compounds have been synthesised in the past.[3–7] Our interest for the synthesis in these molecules is aimed at the development of structure–activity relationships in order to explain the mechanism of the sweet taste. A strict relationship between configuration and taste has been evidenced, since the role of stereochemistry is important in defining the three-dimensional structure of the putative receptor protein which is supposed to bind the sweet ligands.[8] As in the case of other sweet compounds such as aminoacids, peptides or guanidinic derivatives, only one enantiomer, *R*-(+)-phyllodulcin, is in fact sweet, the other isomer being tasteless.[9]

Among the isovanillic derivatives several mono- or disubstituted heterocycles have been synthesized and tasted.[10–13] The sweetest compounds of the series are the 1,3-diheterosubstituted compounds, which are generally one order of magnitude sweeter than the corresponding 1,4- or mono-substituted analogues. This suggests an important role of the acetalic fragment in the interaction with the taste receptor. Therefore, the synthesis of acetallic derivatives in optically active form is an important goal.

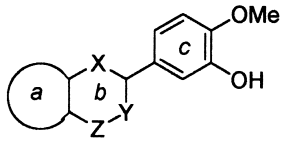
1,3-Oxathianes and dithianes are generally more stable to hydrolysis than 1,3-dioxanes, and therefore less prone to racemisation at least in neutral or basic conditions. Moreover, these compounds are quite rigid from the conformational point of view, a feature that was successfully applied to diastereoselective syntheses.[14,15] A general method for the enantioselective synthesis of 1,3-benzodioxanes, benzoxathianes or benzodithianes bearing a substituent at C2, i.e. at the acetallic position, is not described in the literature. A preliminary result has been obtained by some of us[16] using the well-known ability of homochiral tricarbonyl(η^6-arene)chromium complexes to induce stereoselective reactions at the benzylic position. A similar approach has been also used for the synthesis of optically active acetals of arylaldehydes.[17]

In this paper we describe some optically active isovanillic heterocyclic derivatives, obtained either by asymmetric synthesis or by direct chromatographic resolution of the racemates. The absolute stereochemistry of the new derivatives, which is important in structure–taste relationships, is also discussed.

2. Results and discussion

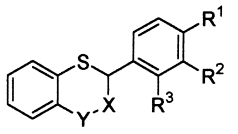
The general formula of isovanillic heterocycles is shown schematically in Fig. 1.

The taste potency is particularly high in the case of 1,3-disubstituted six-membered ring heterocycles, such as (±)-**3** (9000×) and (±)-**4** (10 000×) which are the sweetest of the series.[12]



X, Y, Z = $(CH_2)_n$, O, S; n = 0,1,2

Figure 1. The schematic representation of isovanillic sweet derivatives



	X	Y	R1	R2	R3
3	S	CH_2	OMe	OH	H
4	O	CH_2	OMe	OH	H
5	O	CH_2	H	H	OMe
6	CH_2	O	OMe	OH	H

For these two acetallic compounds, an asymmetric synthesis has not yet been developed. The analogues (+)- and (–)-(2′-methoxyphenyl)-1,3-benzoxathiane **5** have previously been prepared by some of us,[16] but the extension of that method to derivatives **3** and **4** proved to be complicated by the difficulty in finding a suitable protecting group for the phenolic substituent, which interferes with the chromium carbonyl moiety.

The resolution of the enantiomers of isovanillic compounds by derivatisation with chiral auxiliaries has proven troublesome. Several diastereomeric derivatives have been synthesised using the phenolic function as an anchoring group. Diastereomeric esters and carbamates were

Table 1
Absolute configuration, enantiomeric excess, $[\alpha]_D$ and taste of compounds prepared in this paper

Cpd.	e.e	taste† (RS)	$[\alpha]_D$	c (EtOH)	Cotton eff. λ =297 nm	Absolute configuration
(+)-**1**		s (400-800x)				*R*
(-)-**1**		t				*S*
(+)-**3**	98	s (18000x)	+155	0.080	-	*R*
(-)-**3**	98	t	-154	0.080	+	*S*
(+)-**4**	92	s (20000x)	+295	0.010	-	*R*
(-)-**4**	98	t	-196	0.004	+	*S*
(+)-**5**			+139	0.076*	-	*R*
(-)-**5**			-92	0.110*	+	*S*
(+)-**6**	90	s (1500x)	+18	0.087		
(-)-**6**	90	s (750x)	-15	0.098		
(+)-**9**	>95	s (150x)	+80	0.143		2*S*, 4a*R*, 7*S*, 8a*S*
(-)-**9**	>95	t	-86	0.143		2*R*, 4a*S*, 7*R*, 8a*R*
(+)-**10**	>95	-				2*R*, 4a*R*, 7*S*, 8a*R*
(-)-**10**	>95	s (100x)	-12	0.180		2*S*, 4a*S*, 7*R*, 8a*S*

† t= tasteless; s= sweet; RS = relative sweetness respect to 3% sucrose.

* = $CHCl_3$

easily formed, but none of them was easily separated by chromatography or by selective crystallisation.

2.1. Chromatographic resolution

A convenient and rapid method for obtaining small amounts of enantiomerically pure compounds is the direct chromatographic resolution by HPLC on a chiral column. The separation conditions for isovanillic derivatives were checked using β-cyclodextrin, cellulose triacetate (CTA) and the bonded cellulose tris-(3,5-dimethylphenyl)carbamate on silica (Chiralcel OD) as stationary phases. While the first two phases gave no or poor resolution, with the last column the resolution was so good that an analytical column could be used for semi-preparative purposes without losing the required separation between the two peaks of the enantiomers, which were collected and recovered as pure compounds by evaporation of the solvent. With this method, compounds **3**, **4** and **6** were resolved (Table 1).

2.2. Asymmetric synthesis

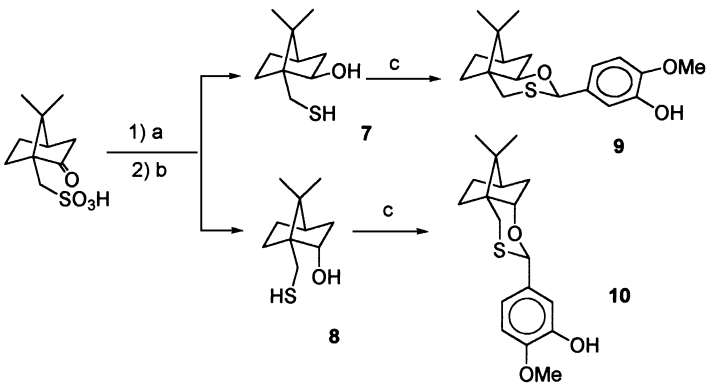
An alternative source of optically active isovanillic derivatives was found by substituting the simple aromatic ring *c* with an aliphatic ring containing one or more stereogenic centres with fixed configuration. Following this strategy isovanillin is reacted with an optically active 1,3-hydroxythiol or dithiol which should work as a chiral synthon during the generation of the new acetallic stereogenic carbon atom, leading to two diastereoisomeric acetallic derivatives, which can be reduced to one if the reaction is diastereoselective.

In order to obtain some new thioacetallic derivatives structurally related to **3** and **4**, chiral 1,3-hydroxythiols or dithiols were needed. Despite the potential applications of these compounds as chiral auxiliaries in organic chemistry, only a few compounds of this class are described in the literature[18–21] and none of them are commercially available in optically active form. However, 10-mercaptoisoborneol **7** and 10-mercaptoborneol **8** are easily obtained by reduction of 1*S*-(+)-camphor-10-sulfonic acid chloride,[14,22] and the corresponding enantiomers are obtained as well from the enantiomeric starting material. The use of (+)- and (–)-**7** and of other optically active 1,3-hydroxythiols as precursors of conformationally blocked 1,3-oxathianes has found several applications in the literature.[15,23–27] In the reduction reaction, the *endo*-isomer **8** is obtained in small amounts and is purified with difficulty. In our hands, every attempt to obtain **8** in greater amounts from the reduction of the corresponding camphorsulfonyl chloride, by varying the reaction temperature or prolonging the reaction time with respect to the conditions which are described in the literature,[15,23] failed. Also, the isolation of this product by flash chromatography was difficult since **8** is generally eluted in a mixture with the most abundant isomer **7**.

The reaction of isovanillin with optically pure **7** and **8** was completely diastereoselective to give the acetal derivatives shown in Scheme 1.

In both cases, only one product was formed in the reaction. The reaction of isovanillin with (+)- and (–)-**7** gave the corresponding 1,3-oxathianes (+)- and (–)-**9** with the expected stereochemistry. The reaction of isovanillin with (+)- and (–)-**8** gave very poor yields of product and was generally non-reproducible; therefore, after many attempts, only compound (–)-**10** was isolated in sufficient amount and purity to be tasted.

The chemical purity and enantiomeric excess of each compound was tested by HPLC before tasting trials.



Scheme 1. Synthesis of compounds (+)- and (–)-**9** and **10**. (a) $SOCl_2$; (b) $LiAlH_4$; (c) isovanillin, CH_2Cl_2, BF_3 or HCl gas, 0°C

2.3. Attribution of the absolute configuration

The absolute configuration of compounds (+)- and (–)-**3** was assigned on the basis of their circular dichroism spectra (Fig. 2).

The UV and CD spectra for compound (+)-**3** are very similar to those of the analogous 1,3-benzoxathiane (+)-**5**, whose absolute configuration has been previously assigned.[16] Thus, the absolute configuration of compound (+)-**3** must be *R*. The comparison of the CD spectra of compounds **3** and **4** is shown in Fig. 3.

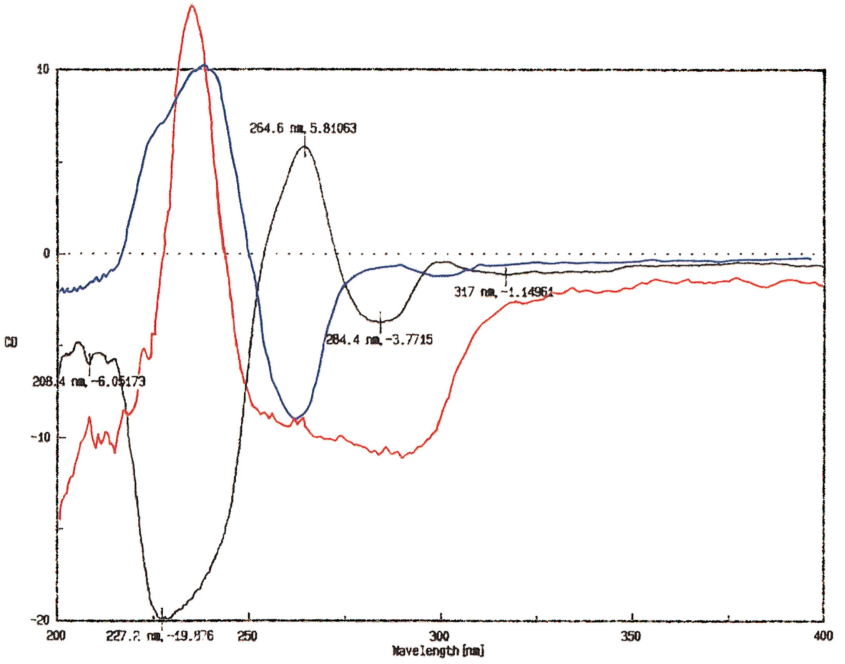


Figure 2. The circular dichroism spectra of compounds (+)-**3** (blue), (–)-**3** (black) and *R*-(+)-**5** (red)

In the region from 275 to 325 nm the curves are very similar and the sign of the Cotton effect allows to assign the absolute *R* configuration to the (+)-**4** enantiomer.

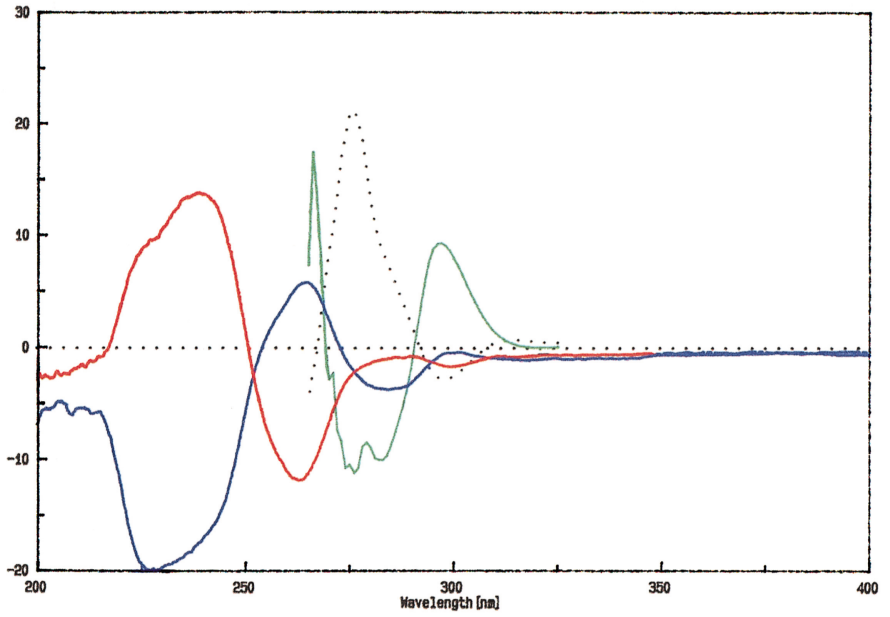


Figure 3. The circular dichroism spectra of compounds (+)-**4** (black), (–)-**4** (green), (+)-**3** (red) and (–)-**3** (blue)

The absolute configuration of compounds (+)- and (–)-**6** could not be assigned on the basis of their CD spectra. In fact, the electronic spectrum of this 1,4-oxathiane derivative is quite different from those of the 1,3-disubstituted compounds **3** and **4**, and no analogous optically active reference derivative could be found in the literature. The absolute configuration of compound (–)-**9** has been determined by X-ray analysis (Fig. 4).

The configuration of the acetalic carbon is 2*R*, as expected from the analogous cyclisation reactions described in the literature, which give stereoselectively the acetal having the bulky substituent equatorial.[15]

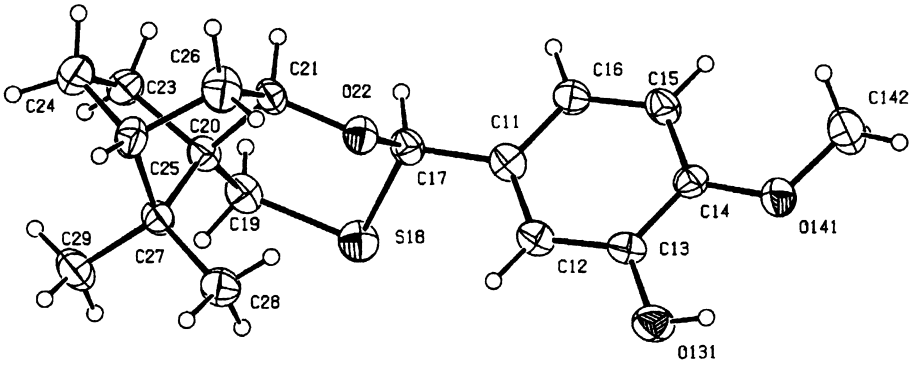
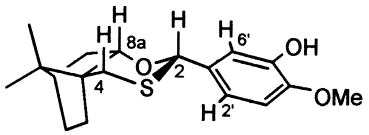


Figure 4. The structure of (–)-**9** with ellipsoid shown at 30% probability

It was impossible to crystallise compound (–)-**10** in a form suitable for X-ray analysis. The absolute configuration of this compound was therefore determined by NMR NOE experiments. Fig. 5 shows the minimum energy conformation for compound (2*S*)(–)-**10** calculated with a MM2 molecular mechanics program.[28] This configuration is that expected from the stereochemical outcome of the cyclisation reaction, both by analogy with compound **9** and by the fact that this stereoisomer has the isovanillic substituent equatorial.

In this conformation, the distance between the acetallic H-2 hydrogen and the other hydrogens is shown in Table 2.

By irradiation of the H-2 proton of compound (–)-**10**, it is possible to observe an NOE effect on H-8a (11.6%) and H-4β (2.4%) while H-4α is too far (4.04 Å) to give an NOE effect. An NOE effect, mediated by the free rotation of the isovanillyl group around the C2–C1′ bond, is also observed on aromatic hydrogens H-2′ and H-6′. These NOE effects are therefore consistent with the calculated conformation and suggest that the configuration of the acetallic carbon is 2*S* as expected.



2*S*, 4a*S*, 7*R*, 8a*S*-(-)-**10**

Figure 5. The minimum energy conformation calculated for compound (–)-**10**

Table 2
Calculated distances and observed NOE effects for compound (–)-**10**

		Calc. distance (Å)	Irrad.		NOE (%)
H-2	H-8a	2.27	H-2	H-8a	11.6
	H-4β	2.83		H-4β	2.4
	H-4α	4.04		H-4α	-
	H-2'	2.60		H-2'	5.7
	H-6'	3.69		H-6'	5.9

2.4. Structure–activity relationships

All the new derivatives have been submitted to the sensory analysis following the 'sip and spit' standard procedures[11,12] and the results are shown in Table 1.

In each case, the taste of the two enantiomers was different. In the thioacetalic derivatives **3** and **4**, only one of the enantiomers is sweet, the other being tasteless. The absolute stereochemistry of the sweet enantiomer is the same of sweet (*R*)-(+)-phyllodulcin. Compound (*R*)-(+)-**4**, having a relative sweetness of 20 000× with respect to sucrose, is the sweetest known compound in this series. Both the enantiomers of compound **6** are sweet, but with different taste potencies. It is not possible to say anything about structure–activity relationships without knowing the absolute stereochemistry of these compounds. Also, in the terpene-based derivatives, compounds (–)-**10** and (+)-**9** resulted as being sweet, while (–)-**9** was tasteless.

Therefore, the enantiodifferentiation in taste properties of isovanillic derivatives seems to be a general outcome. As in other cases, this effect is usually related to geometric factors. This was in fact first observed in our previous QSARs studies on isovanillic derivatives,[29] where we already evidenced the importance of steric factors in affecting the active conformation and therefore the taste of this class of compounds, showing that these parameters are also straightforward in explaining the different tastes of different enantiomers.

As a further general remark, we observe that the changing of the structure of ring *c* from aromatic to aliphatic seems to have a striking negative effect on the taste of isovanillic derivatives. One of the reasons could be a type of 'synergistic effect' exerted by the combination of the acetalic moiety and the aromatic benzocondensed ring on the interaction with the receptor, possibly related to electronic or stereoelectronic parameters which are currently under investigation.

3. Conclusions

The isolation of new optically active isovanillic compounds confirmed the importance of configuration in structure–taste relationships. In this family, optically active 1,3-benzoxathianes and dithianes are the most active compounds; some of them were obtained on a small scale and with high enantiomeric excess by direct chromatographic resolution on chiral columns. The stereoselective introduction of a substituent on an acetallic carbon atom in these heterocycles could be better obtained starting from alkyl chiral building blocks such as camphor derivatives. The terpene-based sovanillic derivatives obtained by this approach are also sweet, but the sweet taste potency is decreased in respect to their benzocondensed analogues.

4. Experimental

Melting points are uncorrected. Flash column chromatography was performed on Merck 60 silica gel (230–400 mesh STM). NMR spectra were recorded with a Bruker AMX 300 instrument (300 MHz) using TMS as internal standard. Chemical shift values are in δ (ppm) and coupling constant values (J) are given in hertz. EI Mass spectra were recorded with a Finnigan-MAT TSQ70 spectrometer. Optical rotation was measured with a Perkin–Elmer polarimeter. HPLC separations were done with a Hewlett–Packard instrument, UV detector at 254 nm.

4.1. Chromatographic resolution

A Chiralcel OD (Daicel) column, 4.6×250 mm was used. The separation conditions for isovanillic derivatives were set in order to obtain a resolution factor (α) of at least 1.3 on analytical scale; for compounds **3–6** this was obtained using hexane:isopropyl alcohol 9:1 (v/v) as eluent in isocratic condition, flow 1 mL/min. In these conditions, 20 μL of a solution of concentration up to 50 mg/mL of the racemate were injected in the column without losing the required resolution between the two peaks of the enantiomers, which were collected after detection and recovered as pure compounds by evaporation of solvent. About 20 injections were usually required to obtain 3–10 mg of the single enantiomers, with an enantiomeric excess higher than 95%.

4.2. Synthesis of compounds

Racemic **3**–**6** were previously synthesised in our laboratory. Compounds **7** and **8** were synthesised following literature methods.[15,23] Compounds **9** and **10** were obtained by reaction with isovanillin in dry dichloromethane at 0°C using either HCl gas or BF_3–ethyl ether as a catalyst.

4.2.1. (2R,4aS,7R,8aR)-(–)-2-(3′-Hydroxy-4′-methoxyphenyl)-9,9-dimethyltetrahydro-5H-4a,7-methano-4H-1,3-benzoxathiane (–)-9

A solution of (+)-**7** (0.20 g, 1.07 mmol) and isovanillin (0.16 g, 1.07 mmol) in dry dichloromethane (5 ml) was refrigerated at 0°C, and saturated with HCl gas. The reaction mixture was washed with aq. $NaHCO_3$, brine and water, dried over Na_2SO_4 and evaporated to dryness. After chromatography (hexane:ethyl acetate, 7:3, v/v) and crystallisation (–)-**9** was obtained as a white solid (0.12 g, 35%). Mp (cyclohexane) 111°C; $[\alpha]_D = -86.13$ (*c* 0.143, EtOH); δ_H ($CDCl_3$) 0.98 (3H, s, Me), 1.49 (3H, s, Me), 1.00–2.10 (7H, m), 2.80–3.20 (2H, AB, H-8a and H-8b, J = 13.7 5), 3.83 (1H, dd, H-2, J = 11.25 and 2.75), 3.88 (3H, s, OMe), 5.60 (2H, s, H-10 and OH), 6.80 (1H, d, H-5′, J = 8), 6.95 (1H, dd, H-6′, J = 2 and 8), 7.00 (1H, d, H-2′, J = 2); *m*/*z* (%): 320 (15), 168 (35), 152 (100).

Compound (+)-**9**, obtained from (1*R*)-(–)-**7**, has identical spectroscopic properties; $[\alpha]_D = +80$ (*c* 0.143, EtOH).

4.2.2. (2S,4aS,7R,8aS)-(–)-2-(3′-Hydroxy-4′-methoxyphenyl)-9,9-dimethyl tetrahydro-5H-4a,7-methano-4H-1,3-benzoxathiane (–)-10

(1*S*)-(+)-10-Mercaptoborneol (0.05 g, 0.27 mmol) and isovanillin (0.04 g, 0.27 mmol) gave (–)-**10** as an oil (0.04 g, 48%); $[\alpha]_D = -12$ (*c* 0.180, EtOH); δ_H ($CDCl_3$) 0.98 (6H, s, 2 Me), 1.10–1.80 (5H, m), 2.2–2.8 (2H, m), 2.50 and 3.20 (2H, AB, H-8a and H-8b, J = 13.75), 3.95 (1H, m, H-2), 3.90 (3H, s, OMe), 5.60 (1H, broad, OH), 5.70 (1H, s, H-10), 6.80 (1H, d, H-5′, J = 8), 7.00 (1H, dd, H-6′, J = 2 and 8), 7.15 (1H, d, H 2′, J = 2); *m*/*z* (%): 320 (26), 168 (54), 152 (62), 32 (100).

Compound (+)-**10** has identical spectroscopic properties.

4.3. X-Ray

Crystals were obtained from cyclohexane. Crystal data for compound (–)-**9** were collected with MoKα radiation using the MARresearch Image Plate System. The crystal was positioned at 75 mm from the Image Plate. Ninety-five frames were measured at 2° intervals with a counting time of 2 min. Data analysis was carried out with the XDS program.[30] The structure was solved using direct methods with the SHELX-86 program.[31] The non-hydrogen atoms were refined with anisotropic thermal parameters equivalent to 1.2 times those of the atom to which they were attached. The structure was refined on F^2 using SHELX-1.[32]

Acknowledgements

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