EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201501002

A Stereoselective Synthesis of (+)-Piscidic Acid and Cimicifugic Acid L

Vanessa Miranda,[a] Christopher D. Maycock,[a,b] and M. Rita Ventura*[a]

Keywords: Total synthesis / Asymmetric synthesis / Chiral pool / Alkylation / Natural products

Alkylation of the lithium enolate of (2*S*,3*S*,5*S*,6*S*)-dimethoxy-2,3-dimethyl-1,4-dioxane-5,6-dithiocarboxylate using 4-benzyloxybenzyl bromide stereoselectively gave two new stereogenic centres with the carboxylate groups in a *cis* relationship. Hydrolytic deprotection of this intermediate produced the natural product (+)-piscidic acid. Installation of a cinnamic acid ester at the secondary hydroxy group was followed by selective deprotection to give a mixture of *cis*/*trans* cinnamates in a 3:1 ratio. Finally, the natural product cimicifugic acid L was obtained.

Introduction

(+)-Piscidic acid (**1**) is one of the constituents of hypnotic and narcotic extracts from *Piscidea erythrina* L. (Jamaica dogwood),[1] and is also an active constituent of *Dioscorea nippoinica*, a medicinal plant used to treat chronic bronchitis[2,3] (Figure 1). Piscidic acid has also been isolated from *Cimicifuga simplex*[4] and *Narcissus poeticus*.[5] It has been identified in the cactus Opuntia,[6,7] which comprises about 200–300 cactus species that grow in arid and semi-arid zones. Traditionally, Opuntia cactus plants serve as sources of fruit and vegetables, and are also used for medicinal and cosmetic purposes. Additionally, piscidic acid (**1**) and *O*-methylpiscidic acid have been shown to be linked to phosphorus uptake in pigeon peas, *Cajanus cajan* L. Millsp., an important crop in India.[3,8,9]

Closely related cimicifugic acids have been isolated from several *Cimicifuga* species.[10,11] Cimicifugic acid L (**2**), which consists of a piscidic acid moiety esterified with 3,4-dimethoxycinnamic acid at the secondary alcohol, was isolated from the aerial parts of *Cimicifuga simplex* and *Cimicifuga japonica*.[12] Cimicifugic acid G (**3**) was isolated from an extract of the rhizomes and roots of black cohosh (*Actaea racemosa* L. or *Cimicifuga racemosa*),[13] which is a native North American plant belonging to the Ranunculaceae family. The rhizomes and roots of this plant have been used by Native Americans to treat malaise, gynecological disorders, diarrhoea, sore throats, and rheumatism. It is also used as a botanical supplement for the treatment of menopausal symptoms in the US and Europe. *C. racemosa* extracts have shown anticancer, anti-inflammatory, and antioxidant activities.[13] Cimicifugic acid G (**3**) has also been isolated from a prepared mixture of the rhizomes of *C. dahurica* and *C. heracleifolia* (ratio about 1:9).[14] These two *Cimicifuga* species and *C. simplex* are described as source plants of "Cimicifugae rhizome" in the Japanese and Chinese Pharmacopoeia. "Cimicifugae rhizome" is used for its anti-inflammatory, analgesic, and antipyretic properties in Chinese and Japanese traditional medicine. The *cis* isomer of cimicifugic acid G, known as cimicifugic acid N (**4**),

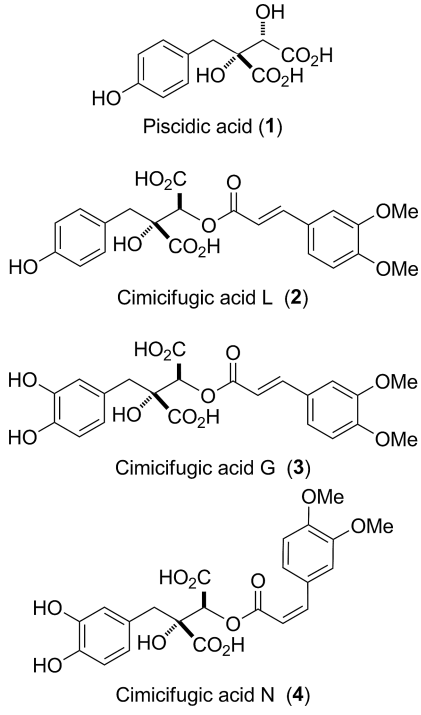


Figure 1. Piscidic acid (**1**) and cimicifugic acids L (**2**), G (**3**), and N (**4**).

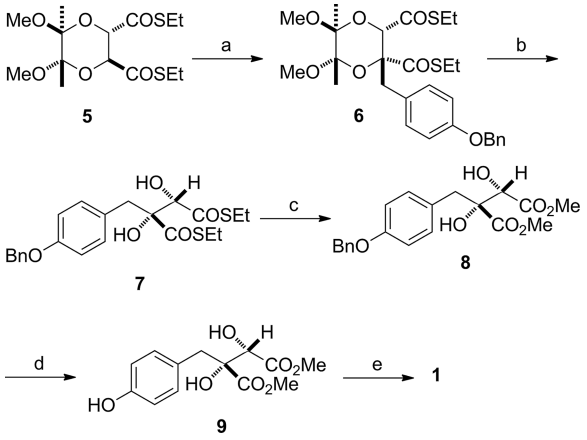
[a] Instituto de Tecnologia Química e Biológica António Xavier, Universidade Nova de Lisboa, EAN,
2780-157 Oeiras, Portugal
E-mail: rventura@itqb.unl.pt
http://www.itqb.unl.pt/
[b] Faculdade de Ciências da Universidade de Lisboa, Departamento de Química e Bioquímica,
1749-016 Lisboa, Portugal
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/ejoc.201501002.

 © 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

was isolated from the aerial parts of *C. simplex* and *C. japonica* along with **2**[12] (Figure 1).

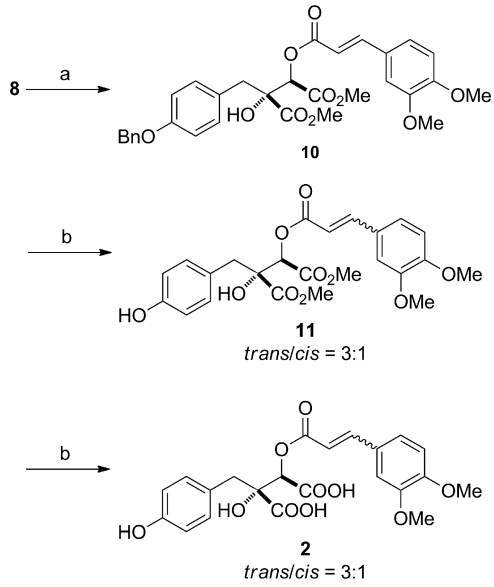
Results and Discussion

(+)-Piscidic acid (**1**) can be regarded as an alkylated tartaric acid derivative, and several syntheses of this compound have been reported.[3,8,15] Seebach reported an approach that is notable for its conciseness,[15] but the piscidic acid (**1**) obtained did not have the correct stereochemistry for the natural compound. Previously, we have described the synthesis of (+)-*O*-methylpiscidic acid dimethyl ester, and the formal synthesis of natural analogues, starting from D-tartaric acid.[16] The natural abundance of tartaric acid in both of its enantiomeric forms is an advantage, and it is often used as a small chiral building block for the asymmetric synthesis of other natural products.[17,18] In our previous work, the lithium enolate of dithioester **5**, readily available from tartaric acid,[18–20] underwent stereoselective mono- and dialkylations to form new stereogenic centres, where the acetal provided a chiral memory. The alkylation reaction of **5**, derived from D-tartaric acid, with 4-methoxybenzyl bromide was the key step in a short synthesis of 4′-*O*-methylpiscidic acid dimethyl ester.[16] In this paper, we describe the use of the same efficient strategy to create the stereochemistry necessary to synthesise natural piscidic acid (**1**; Scheme 1). Cimicifugic acid L (**2**) was obtained by further esterification of the secondary alcohol of tartrate intermediate **8** with 3,4-dimethoxycinnamoyl chloride (Scheme 2). To the best of our knowledge, none of the cimicifugic acids have been previously synthesised.



Scheme 1. Synthesis of (+)-piscidic acid (**1**). (a) LDA (lithium diisopropylamide), 4-benzyloxybenzyl bromide, HMPA (hexamethylphosphoramide), THF, –78 °C, 86%; (b) TFA (trifluoroacetic acid), CH_2Cl_2, H_2O, reflux, 92%; (c) NaOMe, MeOH, room temp., 88%; (d) H_2, Pd/C (10%), EtOAc, 50 psi, 100%. (e) H_2O, KOH (2 M), reflux, 81%.

Alkylation of the lithium dienolate of **5** with 4-benzyloxybenzyl bromide gave monoalkylated product **6** exclusively in 86% yield.[16] Removal of the dioxane acetal with TFA in dichloromethane/water gave diol **7** in excellent yield (92%). Transesterification gave dimethyl ester **8**, and, after

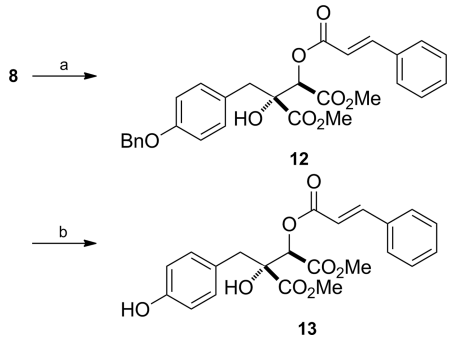


Scheme 2. Synthesis of cimicifugic acid L (**2**). (a) 3,4-Dimethoxycinnamoyl chloride, Et_3N, CH_2Cl_2, 0 °C to room temp., 95%; (b) $FeCl_3$, CH_2Cl_2, 0 °C, 53%, *trans*/*cis* = 3:1; (c) LiI, pyridine, 125 °C, without light, 60%, *trans*/*cis* = 3:1.

hydrogenation, compound **9** was obtained quantitatively. Hydrolysis of the methyl esters gave piscidic acid (**1**) in 81% yield, $[\alpha]_D^{20}$ = +45.5 (*c* = 1.16, MeOH) {ref.[21] $[\alpha]_D$ = +42.8 (*c* = 0.80, MeOH); ref.[5] $[\alpha]_D^{28}$ = +48.88 (*c* = 2.6, H_2O); ref.[1] $[\alpha]_D^{20}$ = +41.03 (*c* = 2.6, H_2O); ref.[3] $[\alpha]_D^{22}$ = +32.3 (*c* = 1.35, H_2O)}. From 4-benzyloxypiscidic acid dimethyl ester (**8**), cimicifugic acid L (**2**) was synthesised in three steps (Scheme 2).

Cinnamate ester **10** was obtained in excellent yield (95%) by selective esterification of the secondary hydroxy group of diol **8** with 3,4-dimethoxycinnamoyl chloride and Et_3N. In order to preserve the double bond of the cinnamate, the benzyl group could not be removed using catalytic hydrogenolysis. Acid-catalysed removal of the this group with $FeCl_3$[22,23] gave the desired compound **11** in 53% yield; however, a 3:1 mixture of the *trans*/*cis* isomers was obtained. The same reaction was carried out with cinnamate ester **12**, and, interestingly, only the *trans* product, phenol **13**, was obtained (Scheme 3). We believe that, although the $FeCl_3$ probably facilitated this isomerisation, without the necessary methoxy groups the stabilising hydrogen bond does not form. Optimised 3D structures of *trans*-**11** and *cis*-**11** (Figure 2) indicated that a hydrogen bond could be established between the free phenolic hydroxy group and the 3-OMe group of the cinnamic acid moiety in both cases. However, in the *trans* isomer, the two aromatic rings are perpendicular, while in the *cis* isomer these rings are parallel. In the formation of **11**, the *trans* isomer was the major isomer of the product; this shows that it is the more stable isomer, and the fact that the *trans*/*cis* isomers were formed in a 3:1 ratio shows that there is not a significant energy difference between the two isomers. The presence of the energetically favourable hydrogen bond helps to decrease the expected energy difference.

 © 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 3. Synthesis of compound **13**. (a) Cinnamoyl chloride, Et_3N, CH_2Cl_2, 0 °C, 74%; (b) $FeCl_3$, CH_2Cl_2, 0 °C, 37%.

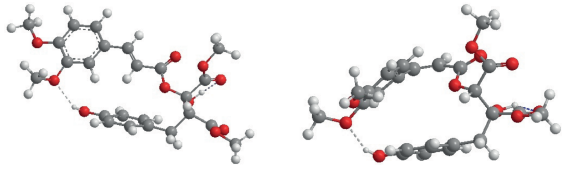


Figure 2. 3D structures of *trans*-**11** (left) and *cis*-**11** (right) [PBE1PBE/6-311G(d,p) optimisation method].

Selective cleavage of the methyl esters in the presence of the cinnamate group was accomplished using LiI,[24] and cimicifugic acid L (**2**) was obtained in 60% yield as a mixture of *trans*/*cis* isomers (3:1). Cimicifugic acid L (**2**) was isolated as the *trans* isomer. However, cimicifugic acid N (**4**), which is the *cis* isomer of **3**, has already been identified (Figure 1); thus, *cis* isomers of the other cimicifugic acids may also be present in natural sources.

Conclusions

An efficient and rapid route has been developed for the synthesis of piscidic acid (**1**) and cimicifugic acid L. This synthetic strategy could be useful for the synthesis of other cimicifugic acids by varying the aryl alkylating reagent and the substituents on the cinnamoyl chloride.

Experimental Section

General Methods: ^{1}H NMR spectra were obtained at 400 MHz in $CDCl_3$; chemical shift values (δ) are given in ppm downfield from tetramethylsilane. ^{13}C NMR spectra were obtained at 100.61 MHz in $CDCl_3$. Assignments are supported by 2D correlation NMR spectroscopic studies. Medium-pressure preparative column chromatography: silica gel Merck 60 H. Analytical TLC: aluminium-backed silica gel Merck 60 F254. Reagents and solvents were purified and dried according to ref.[25] Specific rotations ($[\alpha]_D^{20}$) were measured with a Perkin–Elmer D241 automatic polarimeter. All reactions were carried out under argon.

***S*,*S*-Diethyl (2*R*,3*S*,5*S*,6*S*)-2-[4-(Benzyloxy)benzyl]-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2,3-dicarbothioate (6):** LDA was prepared by adding BuLi (1.6 M in hexane; 1.56 mL, 2.50 mmol) to a solution of diisopropylamine (0.42 mL, 2.95 mmol) in dry THF (4 mL) at 0 °C. The solution was stirred at 0 °C for 15 min, and then it was cooled to –78 °C. A solution of **5** (0.400 g, 1.13 mmol) in dry THF (3 mL) was added to the LDA solution, and the mixture was stirred at –78 °C for 45 min. A solution of bromide **4** (0.472 g, 1.70 mmol) in HMPA (1.17 mL) was then added to the dienolate solution. The reaction mixture was stirred at –78 °C for 1 h, and then the reaction was quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with ethyl acetate (3× 20 mL), then the combined organic phases were dried with $MgSO_4$, and concentrated. Purification of the residue by flash column chromatography (hexane/ethyl acetate, 95:5 and 90:10) gave **6** (0.520 g, 83%) as a viscous colourless oil. $[\alpha]_D^{20}$ = +35.9 (*c* = 1.35, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 7.37 (m, 7 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 5.05 (s, 2 H), 3.99 (s, 1 H), 3.32 (s, 3 H), 3.32 (d, *J* = 14.3 Hz, 1 H), 3.19 (d, *J* = 14.3 Hz, 1 H), 2.95–2.74 (m, 4 H), 2.85 (s, 3 H), 1.33 (s, 3 H), 1.30 (s, 3 H), 1.27 (t, *J* = 7.4 Hz, 3 H), 1.26 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 199.3, 198.9, 157.7, 137.2, 132.0, 128.5, 128.4, 127.9, 127.4, 114.1, 100.3, 99.6, 83.0, 73.2, 69.9, 51.7, 48.0, 42.5, 22.9, 22.1, 17.6, 17.5, 14.5, 14.1 ppm. FTIR: $\tilde{\nu}$ = 1679 (C=O) cm^{-1}. $C_{28}H_{36}O_7S_2$ (548.71124): calcd. C 61.29, H 6.61, S 11.69; found C 61.29, H 6.61, S 11.69.

***S*,*S*-Diethyl (2*R*,3*S*)-2-[4-(Benzyloxy)benzyl]-2,3-dihydroxybutanebis(thioate) (7):** Trifluoroacetic acid (0.35 mL, 4.50 mmol) and a catalytic amount of H_2O were added to a solution of **6** (0.350 g, 0.64 mmol) in CH_2Cl_2 (3 mL). The mixture was heated at reflux for 3 h, then it was concentrated. The residue was purified by flash column chromatography (hexane/ethyl acetate, 80:20) to give diol **7** (0.254 g, 92%) as a white solid. $[\alpha]_D^{20}$ = –23.7 (*c* = 0.9, CH_2Cl_2). m.p. 82–83 °C. ^{1}H NMR ($CDCl_3$): δ = 7.37 (m, 5 H), 7.12 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 5.02 (s, 2 H), 4.43 (s, 1 H), 3.21 (d, *J* = 13.9 Hz, 1 H), 3.13 (d, *J* = 13.9 Hz, 1 H), 2.88 (m, 2 H), 2.80 (m, 2 H), 1.24 (t, *J* = 7.4 Hz, 3 H), 1.17 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 204.2, 201.5, 158.1, 137.0, 131.8, 128.6, 128.0, 127.5, 126.1, 114.1, 84.3, 79.7, 69.9, 40.6, 23.3, 23.2, 14.3, 14.1 ppm. FTIR (neat): $\tilde{\nu}$ = 3440–3241 (OH), 1668 (C=O) cm^{-1}. $C_{22}H_{26}O_5S_2$ (434.56884): calcd. C 60.80, H 6.03, S 14.76; found C 60.80, H 6.02, S 14.65.

Dimethyl (2*R*,3*S*)-2-[4-(Benzyloxy)benzyl]-2,3-dihydroxysuccinate (8): Sodium methoxide (0.020 g, 0.366 mmol) was added to a solution of **7** (0.053 g, 0.12 mmol) in dry methanol (3 mL) at 0 °C, and the reaction mixture was stirred for 30 min. The reaction was then quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with ethyl acetate (3× 10 mL), and the combined organic phases were dried with $MgSO_4$, and concentrated. Purification of the residue by preparative chromatography (hexane/ethyl acetate, 50:50) gave **8** (0.040 g, 88%) as a white solid. $[\alpha]_D^{20}$ = +47.5 (*c* = 0.125, CH_2Cl_2). m.p. 101–102 °C. ^{1}H NMR ($CDCl_3$): δ = 7.38 (m, 5 H), 7.08 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 5.02 (s, 2 H), 4.55 (d, *J* = 8.5 Hz, 1 H), 3.76 (s, 3 H), 3.74 (s, 3 H), 3.29 (d, *J* = 13.9 Hz, 1 H), 3.05 (d, *J* = 13.9 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 173.3, 171.7, 158.0, 137.0, 131.1, 128.6, 128.0, 127.5, 127.2, 114.7, 80.1, 75.1, 69.9, 52.9, 52.8, 40.6 ppm. FTIR (neat): $\tilde{\nu}$ = 3488–3374 (OH), 1639 (C=O) cm^{-1}. $C_{20}H_{22}O_7$ (374.38448): calcd. C 64.16, H 5.92; found C 64.40, H 5.85.

Dimethyl (2*R*,3*S*)-2,3-Dihydroxy-2-(4-hydroxybenzyl)succinate (9): Diol **8** (0.040 g, 0.110 mmol) in ethyl acetate (5 mL) was hydrogenated at 50 psi in the presence of Pd/C (10%; 0.25 equiv.). After 4 h, the reaction mixture was filtered, and the solvent was evaporated to give diol **9** (0.030 g, 100%) as a white solid. $[\alpha]_D^{20}$ = +52.0 (*c* = 0.25, CH_2Cl_2). m.p. 64–65 °C. ^{1}H NMR ($CDCl_3$): δ = 7.00 (d, *J* = 8.5 Hz, 2 H), 6.69 (d, *J* = 8.5 Hz, 2 H), 4.56 (s, 1 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.26 (d, *J* = 14.0 Hz, 1 H), 3.04 (d, *J* = 14.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 173.4, 171.7, 155.0, 131.2, 126.6, 115.3, 80.3, 75.2, 52.9, 40.6 ppm. FTIR (neat): $\tilde{\nu}$ = 3440–3262

 © 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

(OH), 1739 (C=O) cm^{-1}. $C_{13}H_{16}O_7$ (284.27): calcd. C 54.93, H 5.67; found C 55.10, H 5.64.

(+)-Piscidic Acid (1): Diol **9** (0.053 g, 0.120 mmol) was dissolved in H_2O (3 mL), and an aqueous solution of KOH (2 M; 0.11 mL, 0.210 mmol) was added. The mixture was heated at reflux for 12 h, after which time all of the starting material had been consumed. The pH was adjusted to 1–2 by the addition of Dowex-H^+. The reaction mixture was filtered, and the solvent was evaporated to give (+)-piscidic acid (**1**; 0.026 g, 91%) as a yellowish viscous oil. $[\alpha]_D^{20}$ = +45.5 (*c* = 1.16, MeOH) {ref.[21] $[\alpha]_D$ = +42.8 (*c* = 0.80, MeOH); ref.[5] $[\alpha]_D^{28}$ = +48.88 (*c* = 2.6, H_2O); ref.[1] $[\alpha]_D^{20}$ = +41.03 (*c* = 2.6, H_2O); ref.[3] $[\alpha]_D^{22}$ = +32.3 (*c* = 1.35, H_2O)}. ^1H NMR ($CDCl_3$): δ = 6.99 (d, *J* = 8.6 Hz, 2 H), 6.67 (d, *J* = 8.6 Hz, 2 H), 4.55 (s, 1 H), 2.98 (d, *J* = 14.0 Hz, 1 H), 2.93 (d, *J* = 14.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 175.6, 174.2, 154.5, 131.5, 126.9, 115.1, 80.6, 74.7, 40.4 ppm. FTIR (neat): $\tilde{\nu}$ = 3424–3262 (OH), 1725 (C=O) cm^{-1}. HRMS: calcd. for $C_{11}H_{12}O_7Na^+$ $[M + Na]^+$ 279.0475; found 279.0478.

Dimethyl (2*R*,3*R*)-2-[4-(Benzyloxy)benzyl]-3-{[*trans*-3-(3,4-dimethoxyphenyl)acryloyl]oxy}-2-hydroxysuccinate (10): Triethylamine (24 μL, 0.176 mmol) and 3,4-dimethoxycinnamoyl chloride (40 mg, 0.176 mmol) were added to a solution of compound **8** (0.044 g, 0.118 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C. After 1.5 h at 0 °C and 30 min at room temperature, the reaction was quenched with saturated aqueous NH_4Cl solution (5 mL). The aqueous phase was extracted with ethyl acetate (3 × 10 mL), and the combined organic phases were dried with $MgSO_4$ and concentrated. Purification of the residue by preparative chromatography (ethyl acetate/hexane/dichloromethane, 10:20:20) gave **10** (0.070 g, 95%) as a colourless viscous oil. $[\alpha]_D^{20}$ = +37.9 (*c* = 1.09, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ = 7.79 (d, *J* = 15.9 Hz, 1 H), 7.42–7.34 (m, 5 H), 7.16–7.09 (m, 4 H), 6.89–6.87 (m, 3 H), 6.54 (d, *J* = 15.9 Hz, 1 H), 5.84 (s, 1 H), 5.02 (s, 2 H), 3.94 (s, 3 H), 3.93 (s, 3 H), 3.80 (s, 3 H), 3.75 (s, 3 H), 3.20 (d, *J* = 13.8 Hz, 1 H), 2.97 (d, *J* = 13.7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 172.6, 167.7, 166.2, 158.1, 151.6, 149.4, 148.5, 137.0, 131.1, 128.6, 128.0, 127.5, 127.1, 126.6, 123.3, 114.7, 114.1, 111.0, 109.5, 78.9, 75.6, 70.0, 56.0, 55.9, 53.2, 52.7, 40.6 ppm. FTIR (neat): $\tilde{\nu}$ = 1715 and 1742 (C=O), 1628 (C=C alkene) cm^{-1}.

Dimethyl (2*R*,3*R*)-3-{[*trans*/*cis*-3-(3,4-Dimethoxyphenyl)acryloyl]-oxy}-2-hydroxy-2-(4-hydroxybenzyl)succinate (11): $FeCl_3$ (0.017 g, 0.11 mmol) was added to a solution of ester **10** (0.020 g, 0.035 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C.[23] After 25 min at 0 °C, the reaction was quenched with water (5 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried with anhydrous $MgSO_4$ and concentrated. Purification of the residue by preparative chromatography (hexane/ethyl acetate, 50:50) gave **11** (0.009 g, 53%, *trans*/*cis* = 3:1) as a colourless viscous oil. ^1H NMR ($CDCl_3$): δ = 7.79 (d, *J* = 15.6 Hz, *trans* isomer), 7.72 (d, *J* = 2.0 Hz, *cis* isomer), 7.16–6.71 (m), 6.53 (d, *J* = 16.0 Hz, *trans* isomer), 6.40 (d, *J* = 15.8 Hz, *cis* isomer), 5.84 (s, 1 H, *trans* isomer), 5.70 (s, *cis* isomer), 3.94 (s, 3 H, *trans* isomer), 3.93 (s, 3 H, *trans* isomer), 3.92 (s, *cis* isomer), 3.90 (s, *cis* isomer), 3.80 (s, 3 H, *trans* isomer), 3.77 (s, *cis* isomer), 3.75 (s, 3 H, *trans* isomer), 3.73 (s, *cis* isomer), 3.56 (s, 1 H, *trans* isomer), 3.19 (d, *J* = 13.8 Hz, 1 H, *trans* isomer), 3.08 (d, *J* = 13.8 Hz, *cis* isomer), 2.95 (d, *J* = 13.8 Hz, 1 H, *trans* isomer), 2.88 (d, *J* = 13.8 Hz, *cis* isomer) ppm. ^{13}C NMR ($CDCl_3$): δ = 172.6, 167.7, 167.6 (*cis* isomer), 166.3, 154.9, 151.6, 149.3, 146.9, 146.6 (*cis* isomer), 131.3, 127.1, 126.4, 125.2 (*cis* isomer), 123.3, 115.3, 115.2 (*cis* isomer), 114.1, 113.5 (*cis* isomer), 111.0, 110.3 (*cis* isomer), 109.5, 78.9, 78.8 (*cis* isomer), 75.6, 56.0, 55.9, 55.8 (*cis* isomer), 53.2, 53.1 (*cis* isomer), 52.7, 52.6 (*cis* isomer), 40.5, 40.4 (*cis* isomer) ppm. FTIR (neat): $\tilde{\nu}$ = 1715 and 1742 (C=O), 1628 (C=C alkene) cm^{-1}.

Cimicifugic Acid L (2): Compound **11** (0.011 g, 0.023 mmol) was dissolved in pyridine (2 mL), and LiI (0.012 g, 0.093 mmol) was added. The reaction mixture was stirred at 125 °C for 6 h while protected from light. After 6 h, the pyridine was removed under vacuum. The residue was partitioned between HCl (10%) and ethyl acetate. The combined organic phases were dried with anhydrous $MgSO_4$ and concentrated. The residue was dissolved in water. The aqueous solution was then washed with chloroform. The aqueous phase was concentrated to give **2** (0.006 g, 60%, *trans*/*cis* = 3:1) as a colourless viscous oil. ^1H NMR (D_2O): δ = 7.68 (d, *J* = 16.1 Hz, *cis* isomer), 7.66 (d, *J* = 16.0 Hz, *trans* isomer), 7.17–6.70 (m), 6.42 (d, *J* = 16.1 Hz, *trans* isomer), 6.02 (d, *J* = 12.2 Hz, *cis* isomer), 5.54 (s, *trans* isomer), 5.39 (s, *cis* isomer), 3.79 (s, *cis* isomer), 3.76 (s, *trans* isomer), 3.75 (s, *trans* isomer), 3.71 (s, *cis* isomer), 3.00 (d, *J* = 13.7 Hz, *trans* isomer), 2.91 (d, *J* = 13.5 Hz, *trans* isomer), 2.68 (d, *J* = 15.2 Hz, *cis* isomer), 2.53 (d, *J* = 13.8 Hz, *cis* isomer) ppm. ^{13}C NMR (D_2O): δ = 168.1 (*trans* isomer), 154.5 (*trans* isomer), 151.7 (*cis* isomer), 148.2 (*trans* isomer), 147.3 (*cis* isomer), 131.6 (*trans* isomer), 127.0 (*trans* isomer), 126.7 (*trans* isomer), 123.7 (*cis* isomer), 115.0 (*trans* isomer), 113.4 (*trans* isomer), 111.4 (*trans* isomer), 110.3 (*cis* isomer), 55.6 (*trans* isomer), 55.5 (*trans* isomer), 55.5 (*cis* isomer), 40.5 (*trans* isomer) ppm. FTIR (neat): $\tilde{\nu}$ = 3357 (OH), 1645 (C=O) cm^{-1}.

Dimethyl (2*R*,3*R*)-2-[4-(Benzyloxy)benzyl]-3-(cinnamoyloxy)-2-hydroxysuccinate (12): Triethylamine (22 μL, 0.16 mmol) and cinnamoyl chloride (27 mg, 0.16 mmol) were added to a solution of compound **8** (0.040 g, 0.107 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C. After 2 h at 0 °C, the reaction was quenched with saturated aqueous NH_4Cl solution (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic phases were dried with $MgSO_4$ and concentrated. Purification of the residue by preparative chromatography (hexane/ethyl acetate, 70:30) gave **12** (0.040 g, 74%) as a colourless viscous oil. $[\alpha]_D^{20}$ = +37.3 (*c* = 0.88, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ = 7.85 (d, *J* = 16.0 Hz, 1 H), 7.58 (m, 2 H), 7.43–7.32 (m, 8 H), 7.10 (d, *J* = 8.7 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 6.66 (d, *J* = 16.0 Hz, 1 H), 5.83 (s, 1 H), 5.02 (s, 2 H), 3.80 (s, 3 H), 3.75 (s, 3 H), 3.20 (d, *J* = 13.7 Hz, 1 H), 2.97 (d, *J* = 13.7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 172.6, 167.6, 166.0, 158.1, 147.0, 137.0, 134.1, 131.1, 130.8, 129.0, 128.6, 128.4, 128.0, 127.5, 126.6, 116.5, 114.7, 78.9, 75.8, 70.0, 53.2, 52.8, 40.6 ppm. FTIR (neat): $\tilde{\nu}$ = 1742 (C=O), 1637 (C=C alkene) cm^{-1}. HRMS: calcd. for $C_{29}H_{28}O_8Na^+$ $[M + Na]^+$ 527.1676; found 527.1670.

Dimethyl (2*R*,3*R*)-3-(Cinnamoyloxy)-2-hydroxy-2-(4-hydroxybenzyl)succinate (13): $FeCl_3$ (0.019 g, 0.12 mmol) was added to a solution of ester **12** (0.020 mg, 0.04 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C. After 25 min at 0 °C, the reaction was quenched with water (5 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried with anhydrous $MgSO_4$ and concentrated. Purification of the residue by preparative chromatography (hexane/ethyl acetate, 60:40) gave **13** (0.006 g, 37%) as a colourless viscous oil. $[\alpha]_D^{20}$ = +103.9 (*c* = 0.31, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ = 7.85 (d, *J* = 16.0 Hz, 1 H), 7.58 (m, 2 H), 7.41 (m, 3 H), 7.05 (d, *J* = 8.4 Hz, 2 H), 6.73 (d, *J* = 8.4 Hz, 2 H), 6.66 (d, *J* = 16.0 Hz, 1 H), 5.83 (s, 1 H), 3.80 (s, 3 H), 3.75 (s, 3 H), 3.19 (d, *J* = 13.8 Hz, 1 H), 2.95 (d, *J* = 13.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 172.6, 167.6, 166.1, 154.9, 147.0, 134.1, 131.3, 130.8, 129.0, 128.4, 126.3, 116.5, 115.3, 78.9, 75.8, 53.2, 52.8, 40.5 ppm. FTIR (neat): $\tilde{\nu}$ = 3432–3351 (OH), 1720 (C=O), 1635 (C=C alkene) cm^{-1}. HRMS: calcd. for $C_{22}H_{22}O_8Na^+$ $[M + Na]^+$ 437.1207; found 437.1210.

 © 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Acknowledgments

This work was supported by the Fundação para a Ciência e a Tecnologia (FCT) through grant PEst-OE/EQB/LA0004/2011. The NMR spectrometers are part of The National NMR Facility, supported by Fundação para a Ciência e a Tecnologia (RECI/BBB-BQB/0230/2012). We acknowledge Saúl Silva for the help with the 3D models.

[1] W. Bridge, F. Coleman, A. Robertson, *J. Chem. Soc.* **1948**, 257–260.
[2] J. A. Moore, S. Eng, *J. Am. Chem. Soc.* **1956**, *78*, 395–398.
[3] H. Toshima, M. Saito, T. Yoshihara, *Biosci. Biotechnol. Biochem.* **1999**, *63*, 964–967.
[4] M. Takahira, A. Kusano, M. Shibano, G. Kusano, T. Miyase, *Phytochemistry* **1998**, *49*, 2115–2119.
[5] F. S. Okumura, R. R. Smeby, F. M. Strong, *J. Am. Chem. Soc.* **1955**, *77*, 5750–5751.
[6] A. Nordal, D. Resser, *Acta Chem. Scand.* **1966**, *20*, 1431–1432.
[7] F. C. Stintzing, R. Carle, *Mol. Nutr. Food Res.* **2005**, *49*, 175–194.
[8] H. Toshima, M. Saito, T. Yoshihara, *Biosci. Biotechnol. Biochem.* **1999**, *63*, 1934–1941.
[9] W. Heller, C. Tamm, *Helv. Chim. Acta* **1974**, *57*, 1766–1784.
[10] T. Gödecke, D. Nikolic, D. C. Lankin, S.-N. Chen, S. L. Powell, B. Dietz, J. L. Bolton, R. B. van Breemen, N. R. Farnsworth, G. F. Pauli, *Phytochem. Anal.* **2009**, *20*, 120–133.
[11] A. Kusano, Y. Seyama, M. Nagai, M. Shibano, G. Kusano, *Biol. Pharm. Bull.* **2001**, *24*, 1198–1201.
[12] A. Iwanaga, G. Kusano, T. Warashina, T. Miyase, *J. Nat. Prod.* **2010**, *73*, 609–612.
[13] P. Nuntanakorn, B. Jiang, L. S. Einbond, H. Yang, F. Kronenberg, I. B. Weinstein, E. J. Kennelly, *J. Nat. Prod.* **2006**, *69*, 314–318.
[14] A. Iwanaga, G. Kusano, T. Warashina, T. Miyase, *J. Nat. Prod.* **2010**, *73*, 573–578.
[15] R. Naef, D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 1030–1031; *Angew. Chem.* **1981**, *93*, 1113.
[16] A. J. Burke, C. D. Maycock, M. R. Ventura, *Org. Biomol. Chem.* **2006**, *4*, 2361–2363.
[17] J. Gawronski, K. Gawronska, *Tartaric and Malic Acids in Synthesis* Wiley-Interscience, New York, **1999**.
[18] M. T. Barros, C. D. Maycock, M. R. Ventura, *Org. Lett.* **2003**, *5*, 4097–4099.
[19] M. T. Barros, A. J. Burke, C. D. Maycock, *Tetrahedron Lett.* **1999**, *40*, 1583–1586.
[20] D. J. Dixon, A. C. Foster, S. V. Ley, D. J. Reynolds, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1631–1633.
[21] M. Takahira, A. Kusano, M. Shibano, G. Kusano, T. Miyase, *Phytochemistry* **1998**, *49*, 2115–2119.
[22] R. Rodebaugh, J. S. Debenham, B. Fraser-Reid, *Tetrahedron Lett.* **1996**, *37*, 5477–5478.
[23] J. I. Padrón, J. T. Vázquez, *Tetrahedron: Asymmetry* **1995**, *6*, 857–858.
[24] O. Lepage, E. Kattnig, A. Fürstner, *J. Am. Chem. Soc.* **2004**, *126*, 15970–15971.
[25] W. L. F. Armarego, C. L. L. Chai, *Purification of Laboratory Chemicals*, 5th ed., Elsevier, London, **2003**.

Received: July 30, 2015
Published Online: October 23, 2015

 © 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim