A Concise Route for the Synthesis of Biologically Interesting Pyranocoumarins – Seselin, (±)-*cis*-Khellactone, (±)-Quianhucoumarin D, and the (±)-5-Deoxyprotobruceol-I Regioisomer

Yong Rok Lee,*[a] Won Kyong Lee,[a] Seok Kyun Noh,[a] Won Seok Lyoo[b]

[a] School of Chemical Engineering and Technology, Yeungnam University, Gyeongsan 712-749, Korea

[b] School of Textiles, Yeungnam University, Gyeongsan 712-749, Korea
Fax +82(53)8104631; E-mail: yrlee@yu.ac.kr

Received 20 July 2005; revised 12 September 2005

Abstract: An efficient synthesis of pyranocoumarins is achieved starting from 2*H*-pyrans. This process provides naturally occurring seselin, *cis*-khellactone, quianhucoumarin D, and the 5-deoxyprotobruceol-I regioisomer.

Key words: ring-opening, epoxides, nucleophiles, formylations, pyranocoumarin derivatives

Pyranocoumarins are widely distributed in nature in both linear and angular forms (Figure 1).[1] Members of both groups have a variety of interesting biological properties and potential pharmacological activities such as antimalarial,[2] antibacterial,[3] antifungal,[4] antiulcer,[5] calcium antagonistic,[6] and anti-HIV activities.[7] They show great promise in cancer therapy[8] and are used to promote smooth muscle relaxation.[9] They have also shown potent acetylcholinesterase (AChE) inhibitory activity.[10] They have been found in traditional medicines, examples include Bai-Hua Qian-Hu, which was used for the treatment of certain respiratory diseases and pulmonary hypertension in China;[9] *Aegle marmelos* Correa, an Indian medicinal plant, was used to treat various ailments;[5] and *Angellica gigas* Nakai was used not only used to treat anemia, but also as a sedative, an anodyne, and a tonic agent in Korea.[11] Pyranocoumarins, seselin (**1**), and 5-methoxyseselin (**2**) are primarily isolated from *Plumbago zeylanica*,[12] *Naucleopsis caloneura*,[13] *Carum roxburghianum*,[14] and *Citrus grandis*.[15] Clinically they are used as photoactive drugs in skin photochemotheraphy, to treat vitiligo and to prevent sun-burning.[16] Also they have been reported to act as DNA-damaging agents[17] and have been used as starting materials for the synthesis of various naturally occurring compounds.[18] (+)-*cis*-Khellactone (**5**) and its derivatives **6**–**11** are isolated from *Prionosciadium watsoni*.[19] They are known to act as a potent anti-AIDS agent in H9 lymphocytes.[7] This range of important biological properties and activities has stimulated interest in the synthesis of naturally occurring seselin, *cis*-khellactone, and their derivatives. Although several synthetic approaches to pyranocoumarin derivatives including seselin and *cis*-khellactone have been reported from resorcinol,[7c,16,20] there is still a demand for general methods which can efficiently provide variously substituted pyranocoumarin derivatives. In particular, no convergent synthetic routes to pyranocoumarin derivatives starting from 2*H*-pyrans are known.

We have recently reported that $Yb(OTf)_3$- or $InCl_3$-catalyzed reactions of 1,3-dicarbonyls with enals provide a rapid route to 2*H*-pyrans.[21] 2*H*-Pyrans seemed an ideal starting material for the synthesis of naturally occurring pyranocoumarin derivatives. We report herein a convenient and efficient synthesis of seselin, (±)-*cis*-khellactone, and their derivatives, as well as the first total synthesis of the 5-deoxyprotobruceol-I regioisomer.

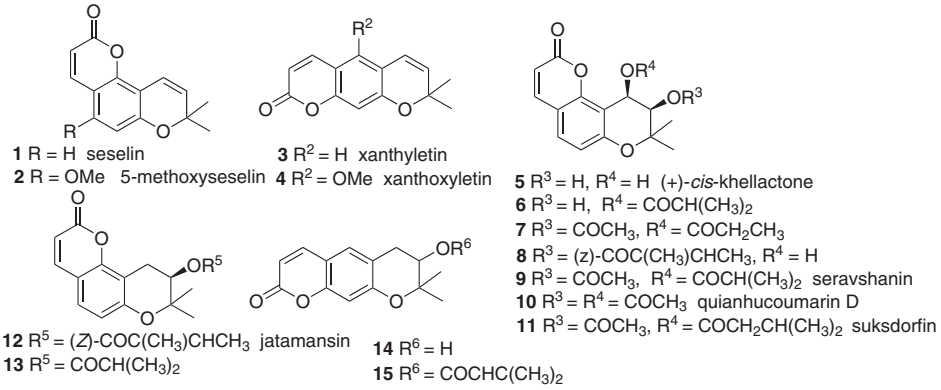
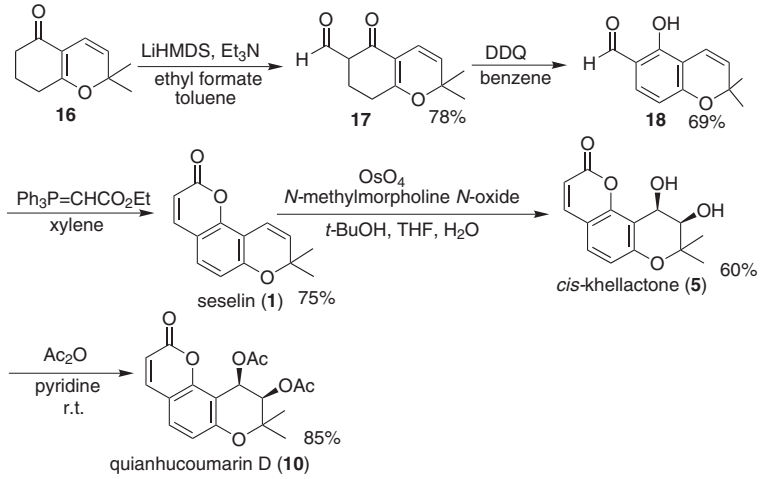


Figure 1 Naturally occurring pyranocoumarins

SYNTHESIS 2006, No. 5, pp 0853–0859
Advanced online publication: 07.02.2006
DOI: 10.1055/s-2006-926329; Art ID: F12305SS

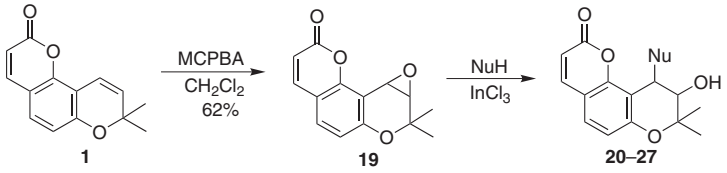


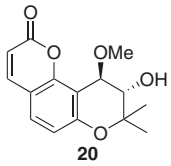
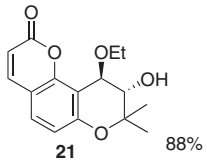
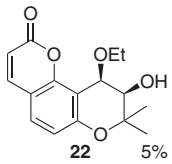
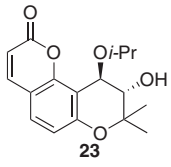
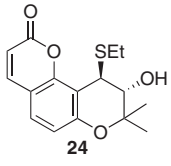
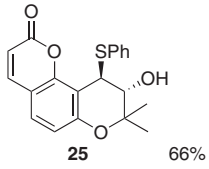
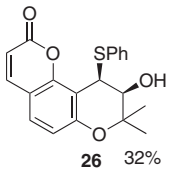
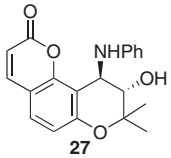
Scheme 1

The total syntheses of seselin (**1**), (±)-*cis*-khellactone (**5**), and (±)-quianhucoumarin D (**10**) was recently examined (Scheme 1). Formylation of 2*H*-pyran **16**[21b] with ethyl formate was attempted under basic conditions. Reaction of **16** with ethyl formate in the presence of LDA in THF was extremely slow, with only a 20% yield of the desired product **17** after a reaction time of 12 hours at –78 °C. The yield was improved to 35% when the mixture was stirred in the presence of LiHMDS in THF at –78 °C for 12 hours. Very recently, it was found that the LiHMDS and triethylamine-mediated reaction of the ketone can accelerate enolization via a dimer-based mechanism.[22] As expected, a much faster reaction was observed when **16** was treated with ethyl formate in the presence of LiHMDS and triethylamine in toluene. After only three hours at –78 °C, compound **17** was isolated in 78% yield. The structure of **17** was assigned to be predominantly the enol form by ^{1}H NMR spectral analysis. Oxidation of **17** by DDQ in refluxing benzene for three hours afforded compound **18** in 69% yield. In order to build the pyrone ring, we attempted the condensation of aldehyde **18** with the Horner–Emmons reagent, triethyl phosphonoacetate and a base, however, this reaction was unsuccessful, probably because of the presence of the acidic phenol group. Fortunately, we were able to introduce the pyrone ring by the one-pot Wittig reaction followed by intramolecular cyclization.[23] Treatment of **18** with (carbethoxymethylene)triphenylphosphorane in refluxing xylene for ten hours afforded seselin (**1**) in 75% yield. The physical and spectroscopic properties of our synthetic material **1** was in good agreement with those reported in the literature.[20a] Conversion of seselin to (±)-*cis*-khellactone (**5**) was carried out by catalytic osmium oxidation using NMO in 60% yield.[18b] The spectral data of our synthetic material **5** was in good agreement with those reported in the literature.[18b] Treatment of **5** with excess acetic anhydride in pyridine afforded (±)-quianhucoumarin D (**10**) in 85% yield. The spectral data of **10** were in agreement with those reported in the literature.[18d] These synthetic routes provide a rapid entry to the synthesis of pyranocoumarin derivatives with *cis*-substituents on the dihydropyran ring.

Further conversion of seselin (**1**) to a variety of pyranocoumarin derivatives with *trans*-substituents on the dihydropyran ring was carried out by the ring-opening of epoxide **19** with several nucleophiles promoted by a Lewis acid catalyst (Table 1). Treatment of **1** with MCPBA at 0 °C for 12 hours gave epoxide **19** in 62% yield. The epoxide **19** was then reacted with an oxygen, nitrogen, or sulfur nucleophile at room temperature, either neat or in a suitable solvent. Reaction of **19** with methanol in the presence of 10 mol% $InCl_3$ at room temperature for two hours afforded *trans*-product **20** as the sole product in 92% yield, whereas treatment with ethanol at room temperature for two hours afforded both *trans*-product **21** and *cis*-product **22** in 88% and 5% yields, respectively (Table 1, entries 1 and 2). Compound **20** was identified as the *trans*-product by spectroscopic analysis and by comparison with the literature.[24] Compounds **21** and **22** were easily separated by silica gel column chromatography and their structures were assigned on the basis of their spectral data. The ^{1}H NMR spectrum of *trans*-adduct **21** showed two characteristic methine signals on the pyran ring at 4.61 (1 H, d, J = 3.3 Hz) and 3.88 (1 H, d, J = 3.3 Hz) ppm. The *cis*-adduct **22** showed two methine protons at 4.79 (1 H, d, J = 5.0 Hz) and 3.83 (1 H, d, J = 5.0 Hz) ppm. With isopropanol, *trans*-product **23** was produced in 94% yield (Table 1, entry 3). To further expand the utility of this reaction, other nucleophiles were investigated in the presence of 10 mol% $InCl_3$. When **19** was treated with ethanethiol at room temperature for one hour, product **24** was obtained in 92% yield (Table 1, entry 4). Finally, an aromatic thiol and amine were investigated. Treatment of **19** with thiophenol at room temperature for two hours in dichloromethane resulted in products **25** and **26** in 66% and 32% yields, respectively (Table 1, entry 5). In this case, the *trans*-product was obtained as the major component. On the other hand, reaction with aniline in dichloromethane afforded the corresponding product **27** in 87% yield (Table 1, entry 6). In view of this result, $InCl_3$-cata-

Table 1 Ring-Opening of Epoxide **19** with Nucleophiles



Entry	NuH	Time (h)	Solvent	Product (yield)
1	MeOH	2	MeOH	 92% **20**
2	EtOH	2	EtOH	 88% **21**  5% **22**
3	*i*-PrOH	2	*i*-PrOH	 94% **23**
4	EtSH	1	EtSH	 92% **24**
5	PhSH	2	CH_2Cl_2	 66% **25**  32% **26**
6	Aniline	2	CH_2Cl_2	 87% **27**

lyzed reactions of epoxide **19** with several nucleophiles provided *trans*-adducts as the major component. The stereochemistry of **23**–**27** was determined by comparison with reported data.[20b] These transformations provided a rapid entry to the synthesis of biologically interesting pyranocoumarin derivatives with *trans*-substituents on the dihydropyran rings.

This methodology was applied to the first total synthesis of naturally occurring 5-deoxyprotobruceol-I regioisomer **28**. The 5-deoxyprotobruceol-I regioisomer **28**, 5-deoxyprotobruceol-II hydroperoxide regioisomer **29**, and 5-deoxyprotobruceol-III hydroperoxide regioisomer **30**

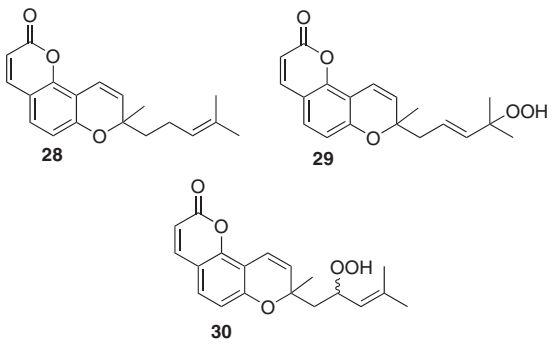


Figure 2 Natural products isolated from *Boronia lanceolata*

were isolated from *Boronia lanceolata*, a tall shrub with tomentose branches found in Australia (Figure 2).[25] Starting material **31** was readily prepared from 1,3-cyclohexanedione and citral in the presence of 10 mol% ethylenediamine diacetate in 66% yield.[26] The formylation of **31** by ethyl formate with LiHMDS and triethylamine at –78 °C gave product **32** in 79% yield after three hours.[22] Compound **32** also exists primarily in the enol form. Oxidation of **32** with DDQ in refluxing benzene for five hours afforded the aromatic compound **33** in 67% yield. Reaction of **33** with (carbethoxymethylene)triphenylphosphorane in refluxing xylene gave **28** in 76% yield (Scheme 2).[23] The spectral data of our synthetic material **28** agreed well with those reported in the literature.[25]

In conclusion, a new synthetic route to pyranocoumarins has been accomplished from 2*H*-pyrans, which were prepared by the methodology developed by our group. The process afforded a rapid synthetic route to naturally occurring seselin, *cis*-khellactone, and quianhucoumarin D. This synthetic route also provided the biologically interesting *cis*- or *trans*-khellactone derivatives and the 5-deoxyprotobruceol-I regioisomer.

All experiments were carried out under a nitrogen atmosphere. Merck precoated silica gel plates (Art. 5554) with a fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). Mps were determined with microcover glasses on a Fisher-Johns apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Model ARX (300 MHz) spectrometer. ^{13}C NMR spectra were recorded on a Bruker Model ARX (75 MHz) spectrometer in $CDCl_3$ referenced to the solvent peak at 77.0 ppm. IR spectra were recorded on a JASCO FTIR 5300 spectrophotometer. HRMS were obtained with a JEOL JMS-700 spectrometer at the Korea Basic Science Institute.

2,2-Dimethyl-5-oxo-5,6,7,8-tetrahydro-2*H*-chromene-6-carbaldehyde (17)

To a stirred solution of HMDS (1.162 g, 7.2 mmol) in anhyd toluene (30 mL) was added a solution of *n*-BuLi (2.5 M, 2.6 mL) in hexane at –78 °C. After stirring at the same temperature for 30 min, compound **16** (0.570 g, 3.2 mmol) in toluene (2 mL) and Et_3N (3.290 g, 32.5 mmol) were added via cannula. The reaction mixture was stirred at the same temperature for 3 h, warmed to r.t., quenched by the addition of an aq solution of NH_4Cl (40 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane–EtOAc, 5:1) to give **17** (0.515 g, 78%).

IR (neat): 2978, 1637, 1586, 1433, 1358, 1273, 1225, 1208, 1134, 1088, 972, 899 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 13.78 (1 H, d, *J* = 11.0 Hz), 7.12 (1 H, d, *J* = 11.0 Hz), 6.40 (1 H, d, *J* = 10.0 Hz), 5.27 (1 H, d, *J* = 10.0 Hz), 2.57–2.35 (4 H, m), 1.40 (6 H, s).

HRMS: *m*/*z* calcd for $C_{12}H_{14}O_3$ (M^+): 206.0943; found: 206.0941.

5-Hydroxy-2,2-dimethyl-2*H*-chromene-6-carbaldehyde (18)

A mixture of **17** (0.455 g, 2.2 mmol) and DDQ (0.749 g, 3.3 mmol) in benzene (30 mL) was heated under reflux for 3 h. The resulting mixture was cooled in an ice-bath and the solids were removed by filtration through Celite. The filtrate was concentrated under reduced pressure and purified by flash column chromatography (hexane–EtOAc, 10:1) to give **18** (0.310 g, 69%) as a solid; mp 45–47 °C.

IR (KBr): 2974, 1657, 1580, 1489, 1433, 1375, 1335, 1300, 1256, 1217, 1181, 1111, 1088, 974, 937, 900, 845 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.63 (1 H, s), 9.64 (1 H, s), 7.27 (1 H, d, *J* = 8.5 Hz), 6.67 (1 H, d, *J* = 10. 1 Hz), 6.40 (1 H, d, *J* = 8.5 Hz), 5.59 (1 H, d, *J* = 10.0 Hz), 1.54 (3 H, s), 1.44 (3 H, s).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.9, 161.0, 159.1, 135.1, 129.0, 115.6, 115.5, 109.8, 109.2, 78.6, 29.8, 28.8.

HRMS: *m*/*z* calcd for $C_{12}H_{12}O_3$ (M^+): 204.0786; found: 204.0788.

Seselin (1)

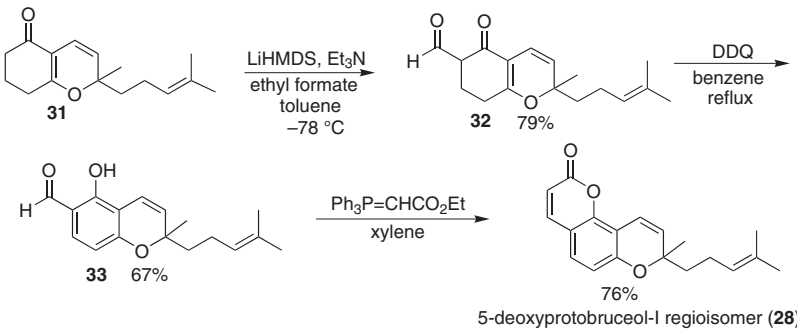
To aldehyde **18** (0.408 g, 2.0 mmol) in anhyd xylene (10 mL) was added carbethoxymethylenetriphenylphosphorane (0.836 g, 2.4 mmol) and the mixture was heated under reflux for 10 h. The mixture was concentrated and purified by silica gel column chromatography (hexane–EtOAc, 5:1)to give **1** (0.342 g, 75%).

IR (neat): 2978, 1736, 1639, 1597, 1485, 1404, 1373, 1292, 1260, 1213, 1157, 1115, 1076, 1011, 837 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (1 H, d, *J* = 9.5 Hz), 7.19 (1 H, d, *J* = 8.5 Hz), 6.86 (1 H, d, *J* = 10.0 Hz), 6.70 (1 H, d, *J* = 8.5 Hz), 6.21 (1 H, d, *J* = 9.5 Hz), 5.71 (1 H, d, *J* = 10.0 Hz), 1.45 (6 H, s).

***cis*-Khellactone (5)**

Seselin (**1**) (0.115 g, 0.5 mmol) was added to a solution of OsO_4 (10 mg, 0.04 mmol) and NMO (0.07 g, 0.6 mmol) in *t*-BuOH–THF–H_2O (10:3:1, 10 mL) and the reaction mixture was stirred at r.t. for 24 h. A sat. solution of $NaHSO_3$ (30 mL) was added and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column



Scheme 2

chromatography (hexane–EtOAc, 1:1) to give **5** (0.079 g, 60%) as a solid; mp 158–160 °C.

IR (KBr): 3400, 3001, 2928, 2820, 1720, 1680, 1600, 1223, 1020 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.64 (1 H, d, *J* = 10.0 Hz), 7.29 (1 H, d, *J* = 8.5 Hz), 6.77 (1 H, d, *J* = 8.5 Hz), 6.22 (1 H, d, *J* = 10.0 Hz), 5.16 (1 H, d, *J* = 5.0 Hz), 3.88 (1 H, d, *J* = 5.0 Hz), 1.46 (3 H, s), 1.42 (3 H, s).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.2, 155.6, 153.8, 144.4, 128.7, 113.8, 111.7, 111.6, 111.2, 78.8, 71.0, 60.1, 26.8, 21.1.

Quianhucoumarin D (10)

To a solution of seselin (**1**) (0.072 g, 0.3 mmol) in anhyd pyridine (2 mL) was added Ac_2O (2 mL, 21.2 mmol). The reaction mixture was stirred for 20 h at r.t., H_2O (30 mL) was added, and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with HCl (2 N, 30 mL), H_2O (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane–EtOAc, 3:1) to give **10** (0.093 g, 85%).

IR (neat): 3096, 2979, 1745, 1605, 1224, 1022 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.57 (1 H, d, *J* = 9.5 Hz), 7.31 (1 H, d, *J* = 8.5 Hz), 6.73 (1 H, d, *J* = 8.5 Hz), 6.45 (1 H, d, *J* = 5.0 Hz), 6.15 (1 H, d, *J* = 9.5 Hz), 5.22 (1 H, d, *J* = 5.0 Hz), 2.07 (3 H, s), 2.05 (3 H, s), 1.38 (3 H, s), 1.34 (3 H, s).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8, 169.7, 159.8, 156.4, 153.7, 143.3, 129.1, 114.3, 112.9, 112.3, 106.5, 77.3, 70.0, 60.7, 24.6, 22.4, 20.5, 20.4.

Epoxide 19

To a solution of **1** (0.456 g, 2 mmol) in anhyd CH_2Cl_2 (20 mL) was added MCPBA (77%; 0.493 g, 2.2 mmol) and $NaHCO_3$ (0.840 g, 10 mmol) at 0 °C. After stirring at r.t. for 5 h, an aq solution of Na_2CO_3 (5%; 30 mL) was added, and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane–EtOAc, 5:1) to give **19** (0.303 g, 62%) as a solid; mp 116–118 °C.

IR (KBr): 2982, 1732, 1606, 1495, 1464, 1406, 1290, 1256, 1206, 1161, 1121, 1078, 1039, 1011, 943, 916 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.61 (1 H, d, *J* = 9.5 Hz), 7.30 (1 H, d, *J* = 8.6 Hz), 6.72 (1 H, d, *J* = 8.6 Hz), 6.26 (1 H, d, *J* = 9.5 Hz), 4.60 (1 H, d, *J* = 4.5 Hz), 3.55 (1 H, d, *J* = 4.5 Hz), 1.59 (3 H, s), 1.30 (3 H, s).

HRMS: *m*/*z* calcd for $C_{14}H_{12}O$ (M^+): 244.0736; found: 244.0733.

Ring-Opening of Epoxide 19 with Nucleophiles; General Procedure

To a solution of epoxide **19** (0.09 g, 0.4 mmol) and nucleophile neat or in CH_2Cl_2 (3 mL) was added $InCl_3$ (9 mg, 0.04 mmol). The reaction mixture was stirred at r.t. for 1–2 h and then concentrated under reduced pressure. The residue was purified by column chromatography (hexane–EtOAc, 2:1).

***trans*-9-Hydroxy-10-methoxy-8,8-dimethyl-9,10-dihydro-8*H*-pyrano[2,3-*f*]chromen-2-one (20)**

Reaction of **19** (0.09 g, 0.4 mmol) with MeOH (3 mL) catalyzed by $InCl_3$ afforded **20** (0.094 g, 92%) as a solid; mp 202–203 °C.

IR (KBr): 3405, 2928, 2820, 1705, 1607, 1491, 1410, 1364, 1246, 1142, 1126, 1092, 1063, 968 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.59 (1 H, d, *J* = 9.5 Hz), 7.30 (1 H, d, *J* = 8.6 Hz), 6.76 (1 H, d, *J* = 8.6 Hz), 6.24 (1 H, d, *J* = 9.5 Hz), 4.53 (1 H, d, *J* = 3.2 Hz), 3.90 (1 H, d, *J* = 3.2 Hz), 3.73 (3 H, s), 1.47 (3 H, s), 1.42 (3 H, s).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.3, 156.5, 155.5, 144.0, 129.0, 115.0, 113.2, 112.9, 109.3, 78.8, 74.5, 71.1, 59.1, 24.5, 23.8.

HRMS: *m*/*z* calcd for $C_{15}H_{16}O_5$ (M^+): 276.0998; found: 276.0997.

***trans*-10-Ethoxy-9-hydroxy-8,8-dimethyl-9,10-dihydro-8*H*-pyrano[2,3-*f*]chromen-2-one (21) and *cis*-10-Ethoxy-9-hydroxy-8,8-dimethyl-9,10-dihydro-8*H*-pyrano[2,3-*f*]chromen-2-one (22)**

Reaction of **19** (0.09 g, 0.4 mmol) with EtOH (3 mL) catalyzed by $InCl_3$ afforded **21** (0.094 g, 88%) and **22** (5 mg, 5%).

21

Mp 160–162 °C.

IR (KBr): 3472, 1730, 1604, 1489, 1466, 1404, 1372, 1246, 1117, 910 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.59 (1 H, d, *J* = 9.5 Hz), 7.29 (1 H, d, *J* = 8.6 Hz), 6.75 (1 H, d, *J* = 8.6 Hz), 6.23 (1 H, d, *J* = 9.5 Hz), 4.61 (1 H, d, *J* = 3.3 Hz), 4.11–3.89 (2 H, m), 3.88 (1 H, d, *J* = 3.3 Hz), 1.46 (3 H, s), 1.44 (3 H, s), 1.28 (3 H, t, *J* = 7.0 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.3, 156.6, 155.4, 144.1, 128.9, 115.0, 113.1, 113.0, 109.6, 78.8, 73.0, 71.7, 67.1, 24.5, 24.1, 16.1.

HRMS: *m*/*z* calcd for $C_{16}H_{18}O_5$ (M^+): 290.1154; found: 290.1155.

22

Mp 149–151 °C.

IR (KBr): 3468, 2924, 2855, 1715, 1605, 1406, 1281, 1240, 1117, 1063, 839 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.60 (1 H, d, *J* = 9.5 Hz), 7.28 (1 H, d, *J* = 8.6 Hz), 6.74 (1 H, d, *J* = 8.6 Hz), 6.23 (1 H, d, *J* = 9.5 Hz), 4.79 (1 H, d, *J* = 5.0 Hz), 4.30–4.10 (2 H, m), 3.83 (1 H, d, *J* = 5.0 Hz), 1.44 (3 H, s), 1.37 (3 H, s), 1.27 (3 H, t, *J* = 7.0 Hz).

HRMS: *m*/*z* calcd for $C_{16}H_{18}O_5$ (M^+): 290.1154; found: 290.1157.

***trans*-9-Hydroxy-10-isopropoxy-8,8-dimethyl-9,10-dihydro-8*H*-pyrano[2,3-*f*]chromen-2-one (23)**

Reaction of **19** (0.09 g, 0.4 mmol) with *i*-PrOH (3 mL) catalyzed by $InCl_3$ afforded **23** (0.105 g, 94%) as a solid; mp 134–136 °C.

IR (KBr): 3449, 2976, 2932, 1707, 1607, 1491, 1408, 1360, 1292, 1242, 1123, 1051, 941, 833 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.57 (1 H, d, *J* = 9.5 Hz), 7.27 (1 H, d, *J* = 8.6 Hz), 6.74 (1 H, d, *J* = 8.6 Hz), 6.20 (1 H, d, *J* = 9.5 Hz), 4.70 (1 H, d, *J* = 2.6 Hz), 4.23–4.15 (1 H, m), 3.82 (1 H, dd, *J* = 7.2, 2.6 Hz), 1.49 (3 H, s), 1.43 (3 H, s), 1.38 (3 H, d, *J* = 6.1 Hz), 1.22 (3 H, d, *J* = 6.1 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.4, 156.7, 155.5, 144.1, 128.8, 115.1, 113.0, 112.9, 109.4, 78.5, 72.8, 71.8, 70.8, 25.5, 24.0, 23.8, 22.8.

HRMS: *m*/*z* calcd for $C_{17}H_{20}O_5$ (M^+): 304.1311; found: 340.1310.

***trans*-10-Ethylsulfanyl-9-hydroxy-8,8-dimethyl-9,10-dihydro-8*H*-pyrano[2,3-*f*]chromen-2-one (24)**

Reaction of **19** (0.09 g, 0.4 mmol) with ethanethiol (3 mL) catalyzed by $InCl_3$ afforded **24** (0.104 g, 92%) as a solid; mp 166–168 °C.

IR (KBr): 3464, 2976, 2928, 1705, 1603, 1491, 1408, 1277, 1238, 1127, 1055, 941, 839 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.59 (1 H, d, *J* = 9.5 Hz), 7.24 (1 H, d, *J* = 8.6 Hz), 6.73 (1 H, d, *J* = 8.6 Hz), 6.23 (1 H, d, *J* = 9.5 Hz), 3.89 (1 H, d, *J* = 5.7 Hz), 3.83 (1 H, d, *J* = 5.7 Hz), 3.12–3.03 (2 H, m), 1.48 (3 H, s), 1.34 (3 H, d, *J* = 7.4 Hz), 1.32 (3 H, s).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.3, 156.4, 154.4, 144.1, 128.0, 115.0, 113.2, 113.1, 111.7, 78.9, 75.9, 44.1, 29.4, 26.1, 21.7, 15.6.

HRMS: *m*/*z* calcd for $C_{16}H_{18}O_4S$ (M^+): 306.0926; found: 306.0928.

trans-9-Hydroxy-8,8-dimethyl-10-phenylsulfanyl-9,10-dihydro-8*H*-pyrano[2,3-*f*]chromen-2-one (25) and _cis_-9-Hydroxy-8,8-dimethyl-10-phenylsulfanyl-9,10-dihydro-8*H*-pyrano[2,3-*f*]chromen-2-one (26)

Reaction of **19** (0.09 g, 0.4 mmol) with thiophenol (0.441 g, 4.0 mmol) catalyzed by $InCl_3$ in CH_2Cl_2 (5 mL) afforded **25** (0.086 g, 66%) and **26** (0.042 g, 32%).

25

Mp 177–179 °C.

IR (KBr): 3493, 2978, 1715, 1603, 1489, 1406, 1354, 1271, 1231, 1123, 1049, 937, 843 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62–7.58 (3 H, m), 7.31–7.23 (4 H, m), 6.74 (1 H, d, *J* = 8.6 Hz), 6.26 (1 H, d, *J* = 9.5 Hz), 4.32 (1 H, d, *J* = 5.0 Hz), 4.00 (1 H, d, *J* = 5.0 Hz), 1.54 (3 H, s), 1.35 (3 H, s).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.0, 156.9, 154.3, 144.0, 134.6, 134.2, 129.6, 128.7, 128.4, 115.1, 113.3, 113.2, 109.5, 79.1, 74.5, 47.8, 26.5, 22.5.

HRMS: *m*/*z* calcd for $C_{20}H_{18}O_4S$ (M^+): 354.0926; found: 354.0927.

26

Mp 168–170 °C.

IR (KBr): 3460, 2970, 1701, 1605, 1489, 1404, 1360, 1231, 1142, 1121, 1103, 1078, 835 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84–7.82 (2 H, m), 7.58 (1 H, d, *J* = 9.5 Hz), 7.43–7.34 (3 H, m), 7.27 (1 H, d, *J* = 8.5 Hz), 6.73 (1 H, d, *J* = 8.6 Hz), 6.21 (1 H, d, *J* = 8.6 Hz), 4.70 (1 H, d, *J* = 6.0 Hz), 4.04 (1 H, d, *J* = 6.0 Hz), 1.47 (3 H, s), 1.39 (3 H, s).

HRMS: *m*/*z* calcd for $C_{20}H_{18}O_4S$ (M^+): 354.0926; found: 354.0929.

trans-9-Hydroxy-8,8-dimethyl-10-phenylamino-9,10-dihydro-8*H*-pyrano[2,3-*f*]chromen-2-one (27)

Reaction of **19** (0.09 g, 0.4 mmol) with aniline (0.377 g, 4.0 mmol) catalyzed by $InCl_3$ in CH_2Cl_2 (5 mL) afforded **27** (0.108g, 87%) as a solid; mp 169–171 °C.

IR (KBr): 3393, 2976, 1701, 1603, 1514, 1495, 1406, 1319, 1240, 1130, 1053, 941, 837 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52 (1 H, d, *J* = 9.5 Hz), 7.27 (1 H, d, *J* = 8.6 Hz), 7.12–7.07 (2 H, m), 6.81 (1 H, d, *J* = 8.6 Hz), 6.71 (1 H, d, *J* = 7.4 Hz), 6.63 (1 H, d, *J* = 7.8 Hz), 6.13 (1 H, d, *J* = 9.5 Hz), 4.64 (1 H, d, *J* = 5.0 Hz), 6.12 (1 H, d, *J* = 5.0 Hz), 4.64 (1 H, d, *J* = 5.0 Hz), 4.12 (1 H, d, *J* = 5.0 Hz), 1.52 (3 H, s), 1.36 (3 H, s).

HRMS: *m*/*z* calcd for $C_{20}H_{19}NO_4$ (M^+): 337.1314; found: 337.1312.

2-Methyl-2-(4-methylpent-3-enyl)-5-oxo-5,6,7,8-tetrahydro-2*H*-chromene-6-carbaldehyde (32)

To a stirred solution of HMDS (1.162 g, 7.2 mmol) in anhyd toluene (30 mL) was added a solution of *n*-BuLi (2.5 M, 2.6 mL) in hexane at –78 °C. After stirring at the same temperature for 30 min, compound **31** (0.788 g, 3.2 mmol) in toluene (2 mL) and Et_3N (3.290 g, 32.5 mmol) were added via cannula. The reaction mixture was stirred at the same temperature for 3 h, warmed to r.t., quenched by the addition of an aq solution of NH_4Cl (50 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane–EtOAc, 10:1) to give **33** (0.693 g, 79%).

IR (neat): 2968, 2926, 2853, 1638, 1589, 1431, 1329, 1223, 1159, 1067, 970 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 13.79 (1 H, d, *J* = 9.7 Hz), 7.10 (1 H, d, *J* = 9.7 Hz), 6.43 (1 H, d, *J* = 10.1 Hz), 5.20 (1 H, d, *J* = 10.1 Hz), 5.07–5.03 (1 H, m), 2.49–2.35 (4 H, m), 2.09–1.98 (2 H, m), 1.77–1.69 (2 H, m), 1.65 (3 H, s), 1.56 (3 H, s), 1.36 (3 H, s).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 189.3, 171.8, 160.1, 132.4, 124.0, 122.5, 116.3, 109.4, 106.5, 83.6, 42.2, 28.7, 28.1, 26.1, 23.0, 22.4, 14.4.

HRMS: *m*/*z* calcd for $C_{17}H_{22}O_3$ (M^+): 274.1569; found: 274.1566.

5-Hydroxy-2-methyl-2-(4-methylpent-3-enyl)-2*H*-chromene-6-carbaldehyde (33)

A mixture of **32** (0.563 g, 2.1 mmol) and DDQ (0.699 g, 3.1 mmol) in benzene (30 mL) was heated under reflux for 3 h. The resulting mixture was cooled in an ice bath and the solids were removed by filtration through Celite. The filtrate was concentrated under reduced pressure and purified by flash column chromatography (hexane–EtOAc, 10:1) to give **33** (0.374 g, 67%).

IR (neat): 2971, 2926, 2855, 1649, 1622, 1578, 1485, 1375, 1329, 1252, 1181, 1094, 960, 908 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.6 (1 H, s), 9.6 (1 H, s), 7.25 (1 H, d, *J* = 8.6 Hz), 6.70 (1 H, d, *J* = 10.2 Hz), 6.39 (1 H, d, *J* = 8.6 Hz), 5.53 (1 H, d, *J* = 10.2 Hz), 5.09–5.03 (1 H, m), 2.11–2.03 (2 H, m), 1.81–1.71 (2 H, m), 1.63 (3 H, s), 1.54 (3 H, s), 1.40 (3 H, s).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.8, 161.3, 159.0, 135.1, 132.4, 127.8, 124.1, 116.2, 115.4, 109.6, 109.0, 81.1, 42.1, 27.7, 26.1, 23.1, 18.0.

HRMS: *m*/*z* calcd for $C_{17}H_{20}O_3$ (M^+): 272.1412; found: 272.1414.

8-Methyl-8-(4-methylpent-3-en-1-yl)-2*H*,8*H*-pyrano[2,3-*f*]chromen-2-one (28, 5-Deoxyprotobruceol-I Regioisomer)

To aldehyde **33** (0.325 g, 1.2 mmol) in anhyd xylene (10 mL) was added carbethoxymethylenetriphenylphosphorane (0.499 g, 1.4 mmol) and the mixture was heated under reflux for 10 h. The filtrate was evaporated under reduced pressure and purified by flash column chromatography (hexane–EtOAc, 5:1) to give **28** (0.269, 76%).

IR (neat): 2969, 2924, 2854, 1734, 1598, 1481, 1444, 1404, 1377, 1288, 1254, 1158, 1114, 1086, 1008, 835 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (1 H, d, *J* = 9.5 Hz), 7.17 (1 H, d, *J* = 8.5 Hz), 6.89 (1 H, d, *J* = 10.0 Hz), 6.68 (1 H, d, *J* = 8.5 Hz), 6.19 (1 H, d, *J* = 9.5 Hz), 5.66 (1 H, d, *J* = 10.0 Hz), 5.08–5.02 (1 H, m), 2.11–2.02 (2 H, m), 1.83–1.66 (2 H, m), 1.62 (3 H, s), 1.53 (3 H, s), 1.41 (3 H, s).

EIMS: *m*/*z* (%) = 296 (10), 283 (3), 253 (3), 213 (100), 185 (7), 128 (3), 69 (2).

HRMS: *m*/*z* calcd for $C_{19}H_{20}O_3$ (M^+): 296.1413; found: 296.1412.

Acknowledgment

This work was supported by grant No. RTI04-01-04 from the Regional Technology Innovation Program of the Ministry of Commerce, Industry, and Energy (MOCIE).

References

(1) Murray, R. D. H. In *Progress in the Chemistry of Organic Natural Products*, Vol. 58; Herz, W.; Kirby, G. W.; Steglich, W.; Tamm, C., Eds.; Springer-Verlag: New York, **1991**, 84–316.

(2) Donnelly, D. M. X.; Molloy, D. J.; Reilly, J. P.; Finet, J.-P. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2531.
(3) Melliou, E.; Magiatis, P.; Mitaku, S.; Skaltsounis, A.-L.; Chinou, E.; Chinou, I. *J. Nat. Prod.* **2005**, *68*, 78.
(4) (a) Ahluwalia, V. K.; Kaila, N.; Bala, S. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1987**, *26*, 700. (b) Ahluwalia, V. K.; Mann, R. R. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1989**, *28*, 608. (c) Rao, C. P.; Prashant, A.; Krupadanam, G. L. D. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1994**, *33*, 593.
(5) Goel, R. K.; Maiti, R. N.; Manickam, M.; Ray, A. B. *Indian J. Exp. Biol.* **1997**, *35*, 1080.
(6) Kozawa, T.; Sakai, K.; Uchida, M.; Okuyama, T.; Shibata, S. *J. Pharm. Pharmacol.* **1981**, *33*, 317.
(7) (a) Xie, L.; Takeuchi, Y.; Cosentino, L. M.; Lee, K.-H. *J. Med. Chem.* **1999**, *42*, 2662. (b) Ishikawa, T. *Heterocycles* **2000**, *53*, 453. (c) Xie, L.; Takeuchi, Y.; Cosentino, L. M.; McPhail, A. T.; Lee, K.-H. *J. Med. Chem.* **2001**, *44*, 664.
(8) (a) Nicolaou, K. C.; Pfefferkorn, J. A.; Schuler, F.; Roecker, A. J.; Cao, G.-Q.; Casida, J. E. *Chem. Biol.* **2000**, *7*, 979. (b) Fang, N.; Casida, J. E. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 3380. (c) Fang, N.; Casida, J. E. *J. Nat. Prod.* **1999**, *62*, 205. (d) Duh, C.-Y.; Wang, S.-K.; Wu, Y.-C. *Phytochemistry* **1991**, *30*, 2812. (e) Duh, C.-Y.; Wang, S.-K.; Wu, Y.-C. *Phytochemistry* **1992**, *31*, 1829.
(9) Zao, N.-C.; Jin, W.-B.; Zhang, X.-H.; Guan, F.-L.; Sun, Y.-B.; Adachi, H.; Okuyama, T. *Bio. Pharm. Bull.* **1999**, *22*, 984.
(10) Kang, S. Y.; Lee, K. Y.; Sung, S. H.; Park, M. J.; Kim, Y. C. *J. Nat. Prod.* **2001**, *64*, 683.
(11) Ann, K.-S.; Sim, W.-S.; Kim, I.-H. *Planta Med.* **1996**, *62*, 7.
(12) Lin, L.-C.; Yang, L.-L.; Chou, C.-J. *Phytochemistry* **2003**, *62*, 619.
(13) Alvarenga, M.; Filho, R. B.; Gottlieb, O. R. *Phytochemistry* **1972**, *11*, 1184.
(14) Sattar, A.; Ashraf, M.; Bhatty, M. K.; Chisti, N. H. *Phytochemistry* **1978**, *17*, 559.
(15) Wu, T.-S.; Kuoh, C.-S.; Furukawa, H. *Phytochemistry* **1983**, *22*, 1493.
(16) Mail, R. S.; Pandhare, N. A.; Sindkhedkar, M. D. *Tetrahedron Lett.* **1995**, *36*, 7109.
(17) Gunatilaka, A. A. L.; Kingston, D. G. I. *J. Nat. Prod.* **1994**, *57*, 518.
(18) (a) Skaltsonnis, A. L.; Matare, S.; Gandel, G.; Tilleguin, F.; Koch, M. *Heterocycles* **1992**, *34*, 121. (b) Bal-Tembe, S.; Bhedi, D. N.; de Souza, N. J.; Rupp, R. H. *Heterocycles* **1987**, *26*, 1239. (c) Reisch, J.; Voerste, A. A. W. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3251. (d) Prokopios, M.; Melliou, E.; Skaltsounis, A.-L.; Mitaku, S.; Léonce, S.; Renard, P.; Pierré, A.; Atassi, G. *J. Nat. Prod.* **1998**, *61*, 982.
(19) Valencia-Islas, N.; Abbas, H.; Bye, R.; Toscano, R.; Meta, R. *J. Nat. Prod.* **2002**, *65*, 828.
(20) (a) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939. (b) Nicolaou, K. C.; Pfefferkorn, J. A.; Barluenga, S.; Mitchell, H. J.; Roecker, A. J.; Cao, G.-Q. *J. Am. Chem. Soc.* **2000**, *122*, 9968. (c) Nicolaou, K. C.; Pfefferkorn, J. A.; Mitchell, H. J.; Roecker, A. J.; Barluenga, S.; Cao, G.-Q.; Affleck, R. L.; Lillig, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 9954. (d) Craavotto, G.; Nano, G. M.; Palmisano, G.; Pilati, T.; Tagliapietra, S. *J. Heterocycl. Chem.* **2001**, *38*, 965. (e) Murray, R. D.; Zeghdi, S. *Phytochemistry* **1989**, *28*, 227.
(21) (a) Lee, Y. R.; Kweon, H. I.; Koh, W. S.; Min, K. R.; Kim, Y.; Lee, S. H. *Synthesis* **2001**, 1851. (b) Lee, Y. R.; Kim, D. H.; Shim, J.-J.; Kim, S. K.; Park, J. H.; Cha, J. S.; Lee, C.-S. *Bull. Korean Chem. Soc.* **2002**, *23*, 998.
(22) (a) McNeil, A. J.; Collum, D. B. *J. Am. Chem. Soc.* **2005**, *127*, 5655. (b) Zhao, P.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 4008. (c) Zhao, P.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 14411. (d) Zhao, P.; Lucht, B. L.; Kenkre, S. L.; Collum, D. B. *J. Org. Chem.* **2004**, *69*, 242.
(23) Ishii, H.; Kaneko, Y.; Miyazaki, H.; Harayama, T. *Chem. Pharm. Bull.* **1991**, *39*, 3100.
(24) Macías, F. A.; Massanet, G. M.; Rodríguez-Luis, F.; Salvá, J. *Magn. Reson. Chem.* **1989**, *27*, 653.
(25) Ahsan, M.; Gray, A. I.; Leach, G. G.; Waterman, P. E. *Phytochemistry* **1994**, *36*, 777.
(26) Spectral data for **31**: IR (neat): 3053, 2928, 1651, 1593, 1453, 1412, 1348, 1331, 1302, 1263, 1190, 1163, 1136, 1071, 1020, 920: 864 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.44 (1 H, d, J = 10.0 Hz), 5.16 (1 H, d, J = 10.0 Hz), 5.06 (1 H, t, J = 7.1 Hz), 2.40–2.33 (4 H, m), 2.03–1.93 (4 H, m), 1.75–1.68 (2 H, m), 1.65 (3 H, s), 1.54 (3 H, s), 1.34 (3 H, s).