Supplementary Material

A STRAIGHTFORWARD AND FACILE SYNTHESIS OF A BIOACTIVE COMPONENT FROM ZINGIBER CASSUMUNAR ROXB.

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1. General procedure for synthesis of dienophiles, (S)-3-acryloyl-4-phenyloxazolidin-2-one (1a) and (S)-3-acryloyl-4-isopropyloxazolidin-2-one (1b)

a) (S)-3-Acryloyl-4-phenyloxazolidin-2-one (**1a**): To a solution of acrylic acid (0.86 g, 12 mmol) and Et₃N (2.32 g, 23 mmol) in THF (50 mL) was added pivaloyl chloride (1.30 g, 11 mmol) at -20°C. The mixture was stirred at -20°C for 2 h. LiCl (0.47 g, 11 mmol) was added, followed by the oxazolidinone (1.5 g, 9.2 mmol). The mixture was warmed to r.t. and stirred for 4 h. The reaction was quenched by saturated NH₄Cl (10 mL) and extracted with EtOAc (2 × 50 mL). The organic layer was washed with saturated NaHCO₃ (20 mL) and brine (20 mL), dried over MgSO₄, filtered and evaporated. The residue was purified by column chromatography (hexane-EtOAc, 5:1) to give **1a** (1.8 g, 86%) as a white solid. Mp. 84-86°C; [α]_D²⁰ +142.5 (c 1.1, CHCl₃), {lit.^[12] mp. 85°C; [α]_D²⁵ +143.1 (c 1.1, CHCl₃)}. ¹H-NMR (300 MHz, CDCl₃): δ = 7.53 (dd, *J* = 17.0, 10.4 Hz, 1H, CH=CH₂), 7.45-7.30 (m, 5H, ArH), 6.50 (dd, *J* = 17.0, 1.8 Hz, 1H, CH=CHH), 5.90 (dd, *J* = 10.4, 1.8 Hz, 1H, CH=CHH), 5.50 (dd, *J* = 8.7, 3.9 Hz, 1H, H-4), 4.73 (t, *J* = 8.7 Hz, 1H, H-5), 4.31 (dd, *J* = 8.7, 3.9 Hz, 1H, H-5).

b) (S)-3-Acryloyl-4-isopropyloxazolidin-2-one (**1b**): Following a similar procedure **1b** was obtained as a white solid (56%). Mp. 42-44°C; [α]_D¹⁴ +163.3 (c 0.1, CHCl₃), {lit.^[5] mp. 44-45°C; [α]_D²⁵ +110 (c 1.1, CHCl₃)}. ¹H-NMR (300 MHz, CDCl₃): δ = 7.53 (dd, *J* = 17.0, 10.4 Hz, 1H, CH=CH₂), 6.55 (dd, *J* = 17.0, 1.8 Hz, 1H, CH=CHH), 5.90 (dd, *J* = 10.4, 1.8 Hz, 1H, CH=CHH), 4.51 (m, 1H, H-4), 4.28 (m, 2H, H-5), 2.42 (m, 1H, CHMe₂), 0.90 (d, *J* = 7.0 Hz, 3H, CH₃), 0.94 (d, *J* = 7.0 Hz, 3H, CH₃).

2. General procedure for synthesis of the diene, 1-(4-hydroxy-3-methoxyphenyl)butadiene (2)

To a solution of vanillin (3.0 g, 19.7 mmol) in THF (15 mL) was added subsequently allyl bromide (7.2 g, 59.2 mmol), saturated NH₄Cl solution (75 mL) and zinc dust (7.7 g, 118.5 mmol) at

0°C. After stirring for 0.5 h the reaction mixture was filtered and washed with EtOAc (100 mL). The filtrate was washed with brine (40 mL), dried over Na₂SO₄, filtered and evaporated to give a crude alcohol (3.8 g, 99%). The crude oil was dissolved in toluene (150 mL) and catalytic amount of *p*TSA (60 mg) was added. The mixture was refluxed for 1 h, cooled down to r.t., washed with saturated NaHCO₃ (25 mL) and brine (25 mL), dried over MgSO₄, filtered and evaporated. The residue was purified by column chromatography (hexane-EtOAc, 10:1) to give **2** (1.8 g, 52%) as a colorless oil. ¹H-NMR (300 MHz, CDCl₃): δ = 6.95-6.80 (m, 3H, ArH), 6.70-6.40 (m, 3H, H-1, H-2, H-3), 5.63 (s, 1H, OH), 5.28 (dd, *J* = 17.0, 1.5 Hz, 1H, H-4), 5.12 (dd, *J* = 10.0, 1.5 Hz, 1H, H-4), 3.92 (s, 3H, OCH₃).

3. General procedure for Diels-Alder reactions

a) (*S*)-3-((*1R,2S*)-2-(4-Hydroxy-3-methoxyphenyl)cyclohex-3-enecarbonyl)-4-phenyloxazolidin-2-one (**3a**): To a solution of **1a** (0.15 g, 0.69 mmol) in CH₂Cl₂ (7 mL) was added Et₂AlCl (0.69 mL, 1 M in CH₂Cl₂) dropwise and **2** (0.16 g, 0.91 mmol) in CH₂Cl₂ (3 mL) at -78°C. The reaction was stirred for 5 h, then warmed to 0°C, quenched with 1N HCl (2 mL) and extracted with CH₂Cl₂ (30 mL). The organic layer was washed with saturated NaHCO₃ (10 mL) and brine (10 mL), dried over MgSO₄, filtered and evaporated. The residue was purified by column chromatography (hexane-Acetone, 4:1) to give **3a** (0.16 g, 60%) as a white solid. Mp. 148-150°C; [α]_D¹⁴ +278.1 (*c* 0.1, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ = 7.35-7.10 (m, 5H, phenyl), 6.52 (d, *J* = 1.9 Hz, 1H, ArH), 6.26 (d, *J* = 8.1 Hz, 1H, ArH), 6.15 (dd, *J* = 8.1, 1.9 Hz, 1H, ArH), 5.88 (m, 1H, vinyl), 5.70 (m, 1H, vinyl), 5.37 (s, 1H, OH), 5.32 (dd, *J* = 8.8, 3.8 Hz, 1H, H-4), 4.63 (t, *J* = 8.8 Hz, 1H, H-5), 4.32 (dd, *J* = 8.8, 3.8 Hz, 1H, H-5), 4.12-3.97 (m, 2H, CHCHC=O), 3.62 (s, 3H, OCH₃), 2.30-1.70 (m, 4H, CH₂CH₂). ¹³C-NMR (100 MHz,

CDCl₃): δ = 173.8, 153.9, 146.2, 144.5, 139.0, 132.4, 129.3, 129.2, 128.9, 127.4, 127.1, 122.4, 114.0, 112.0, 70.3, 58.2, 56.1, 44.0, 42.0, 24.3, 21.2. MS (MALDI-TOF): m/z [M + Na]⁺ 416.1546.

Following a similar procedure using TiCl₄ as Lewis acid at -20°C **3a** was obtained as a white solid (92%). [α]_D¹⁴ +403.2 (*c* 0.1, CHCl₃).

b) (*S*)-3-((*1R,2S*)-2-(4-Hydroxy-3-methoxyphenyl)cyclohex-3-enecarbonyl)-4-isopropylloxazolidin-2-one (**3b**): Following a similar procedure but using TiCl₄ as Lewis acid at -20°C, **3b** was obtained as a white solid (95%). Mp. 210-212°C; [α]_D¹⁴ +433.5 (*c* 0.1, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ = 6.63-6.78 (m, 3H, ArH), 5.92 (m, 1H, vinyl), 5.75 (m, 1H, vinyl), 5.51 (s, 1H, OH), 4.32-3.99 (m, 5H, CHCHC=O, H-4, H-5), 3.86 (m, 3H, OCH₃), 2.30-1.65 (m, 5H, CH₂CH₂, CHMe₂), 0.80 (d, *J* = 4.5 Hz, 3H, CH₃), 0.77 (d, *J* = 4.5 Hz, 3H, CH₃). ¹³C-NMR (100 MHz, CDCl₃): δ = 174.1, 154.4, 146.5, 145.1, 133.2, 129.2, 127.4, 122.5, 114.0, 112.4, 63.6, 59.0, 56.3, 43.9, 42.3, 28.9, 24.3, 21.3, 18.7, 15.0. MS (MALDI-TOF): m/z [M + Na]⁺ 382.1647.

4. Procedure for (+)-*trans*-3-(4-hydroxy-3-methoxyphenyl)-4-((*E*)-3,4-dimethoxystyryl)cyclohex-1-ene (A) from the Diels-Alder adduct (3a)

a) (*1R,2S*)-2-(4-Hydroxy-3-methoxyphenyl)cyclohex-3-enecarbaldehyde (**4**): To a solution of **3a**/TiCl₄ (1.2 g, 3.1 mmol) in CH₂Cl₂ (20 mL) was added DIBAL-H (6.2 mL, 1 M in hexane) dropwisely at -78°C under N₂. The reaction was stirred for 2h at this temperature. Then the reaction was quenched with MeOH/saturated aqueous NH₄Cl (1:5, 20 mL), extracted with CH₂Cl₂ (2 × 50 mL), washed with brine (30 mL), dried over MgSO₄, filtered and evaporated. The residue was purified by column chromatography (hexane-Acetone, 6:1) to afford **4** (0.52 g, 74%) as a colorless oil. [α]_D¹⁴ +332.3 (*c* 0.1, CHCl₃). ¹H-NMR (300 MHz, CDCl₃): δ = 9.50 (d, *J* = 2.0 Hz, 1H, CHO), 6.84 (d, *J* = 8.1 Hz, 1H,

ArH), 6.74-6.71 (dd, $J = 1.9, 8.1$ Hz 1H, ArH), 6.69 (d, $J = 1.9$ Hz, 1H, ArH), 5.98 (m, 1H, vinyl), 5.81 (m, 1H, vinyl), 5.54 (s, 1H, OH), 3.91 (m, 1H, H-2), 3.86 (s, 3H, OCH₃), 2.74 (m, 1H, H-1), 2.28 (m, 1H, H-5), 2.20-2.10 (m, 1H, H-5), 1.86 (m, 2H, H-6). ¹³C-NMR (100 MHz, CDCl₃): $\delta = 205.4, 146.7, 145.1, 132.3, 128.8, 128.5, 122.5, 114.6, 112.2, 56.3, 51.3, 41.5, 24.0, 19.2$. MS (MALDI-TOF): m/z [M + Na]⁺ 255.0919.

b) (+)-*trans*-3-(4-Hydroxy-3-methoxyphenyl)-4-((*E*)-3,4-dimethoxystyryl)cyclohex-1-ene (**A**): To a solution of (3,4-dimethoxybenzyl)triphenylphosphonium bromide (0.59 g, 1.2 mmol) in toluene (10 mL) was added *n*-BuLi (0.48 mL, 2.5 M in hexane) dropwisely at -20°C. The solution was stirred for 30 min at this temperature, then **4** (0.23 g, 1.0 mmol) in toluene (5 mL) was added dropwisely. The reaction mixture was heated to reflux and stirred for 3h, quenched with saturated aqueous NH₄Cl (5 mL), extracted with EtOAc (2 × 50 mL), washed with saturated NaHCO₃ (20 mL) and brine (20 mL), dried over MgSO₄, filtered and evaporated. The residue was purified by column chromatography (hexane-Acetone, 5:1) to afford **A** (0.14 g, 41%) as light yellow oil. $[\alpha]_D^{25} +243.3$ (c 0.1, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): $\delta = 6.84$ -6.75 (m, 4H, ArH), 6.71-6.66 (m, 2H, ArH), 6.10 (d, $J = 16$ Hz, 1H, *phCH=CH*), 6.03 (dd, $J = 16$ Hz, 6.8 Hz, 1H, *phCH=CH*), 5.90 (m, 1H, H-1), 5.67 (m, 1H, H-2), 3.88-3.81 (s, 3H × 3, OCH₃), 3.16 (m, 1H, H-3), 2.14 (m, 1H, H-4), 2.21 (m, 2H, H-6), 1.92 (m, 1H, H-5), 1.69 (m, 1H, H-5). ¹³C-NMR (100 MHz, CDCl₃): $\delta = 149.4, 148.7, 146.6, 144.3, 137.3, 132.6, 131.4, 130.7, 129.3, 127.9, 121.6, 119.2, 114.3, 111.6, 111.4, 109.2, 56.3, 56.3, 56.2, 48.5, 45.8, 28.2, 24.9$. MS (MALDI-TOF): m/z [M + Na]⁺ 389.1879.

5. Procedure for conversion of Diels-Alder Adducts to their alcohols/acetates

a) 4-((*1S,6R*)-6-(Hydroxymethyl)cyclohex-2-enyl)-2-methoxyphenol (**5**): To a suspension of LiAlH₄

(0.11 g, 3.0 mmol) in THF (10 mL) was added dropwisely the solution of **3a**/Et₂AlCl (0.39 g, 1.0 mmol) in THF (10 mL) at 0°C. The reaction mixture was stirred at r.t. for 4 h, quenched with MeOH (5 mL) and saturated NH₄Cl (20 mL), and filtered. The filtrate was extracted with EtOAc (2 × 40 mL). The combined organic layer was washed with brine (30 mL), dried over MgSO₄, and concentrated. The residue was purified by column chromatography (hexane-EtOAc, 3:1) to give **5** (0.16 g, 68%) as a white solid. Mp. 122-124°C; [α]_D¹⁴ +262.0 (c 0.2, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ = 6.87-6.70 (m, 3H, ArH), 5.92 (m, 1H, vinyl), 5.75 (m, 1H, vinyl), 5.53 (s, 1H, *phOH*), 3.87 (s, 3H, OCH₃), 3.57 (m, 1H, H-1'), 3.28 (m, 2H, CH₂OH), 2.22-2.00 (m, 3H, H-4', H-6'), 1.58-1.40 (m, 2H, H-5'), 1.08 (brs, 1H, CH₂OH). ¹³C-NMR (100 MHz, CDCl₃): δ = 146.6, 144.7, 133.4, 129.7, 128.2, 122.7, 114.3, 122.7, 65.6, 56.3, 42.6, 41.3, 25.2, 21.1. MS (MALDI-TOF): *m/z* [M + H]⁺ 234.1260.

Following a similar procedure using **3b** as starting material, **5** was obtained as a white solid. [α]_D¹⁴ +278.2 (c 0.2, CHCl₃).

Following a similar procedure using **3a** /TiCl₄ as starting material, **5** was obtained as a white solid. [α]_D¹⁴ +291.3 (c 0.2, CHCl₃).

b) ((*1R,2S*)-2-(4-Acetoxy-3-methoxyphenyl)cyclohex-3-enyl)methyl acetate (**6**): To a solution of **5** (0.14 g, 0.6 mmol) from the reaction with Et₂AlCl was added Ac₂O (0.3 mL, 3.0 mmol) and pyridine (0.08 mL, 1.0 mmol) at 0°C. The reaction was stirred at r.t. for 2 h, diluted with CH₂Cl₂ (40 mL), and washed sequentially with 1N HCl (10 mL), saturated NaHCO₃ (10 mL) and brine (10 mL), dried over MgSO₄, filtered and evaporated. The residue was purified by column chromatography (hexane-EtOAc, 8:1) to give **6** as a colorless oil (0.16 g, 83%). [α]_D¹⁴ +196.2 (c 0.2, CHCl₃). ¹H-NMR (300 MHz, CDCl₃): δ = 6.97-6.75 (m, 3H, ArH), 5.94 (m, 1H, vinyl), 5.74 (m, 1H, vinyl), 3.82-3.55 (m, 6H, OCH₃, AcOCH₂, H-3'), 2.35-2.12 (m, 6H, CH₃C=O, H-4', H-6'), 2.02 (s, 3H, CH₃C=O), 1.58-1.45 (m, 2H,

H-5'). ¹³C-NMR (100 MHz, CDCl₃): δ = 171.3, 169.5, 150.9, 139.8, 138.8, 128.9, 128.6, 122.5, 122.3, 114.3, 66.7, 56.2, 42.8, 37.6, 24.8, 21.3, 21.1. MS (MALDI-TOF): *m/z* [M + K]⁺ 357.1152.

6. General conditions for determination of enatiomeric excesses

The ee was determined to be 93.8% by HPLC (CHIRACEL OD, hexane/EtOH/*i*-PrOH/*t*-BuOH=480/2/1/1, 0.5 mL/min, 254 nm, major 60.6 min and minor 74.9).

Following the same procedure using **5** from **3b** as starting material, **6** was obtained as a colorless oil. [α]

_D¹⁴ +217.1 (*c* 0.2, CHCl₃); The ee was determined to be 97.1%.

Following the same procedure using **5** from **3a**/TiCl₄ as starting material, **6** was obtained as a colorless

oil. [α]_D¹⁴ +234.4 (*c* 0.2, CHCl₃); The ee was determined to be 99.9%.

7. Analytical data for compounds

- S1. ¹H-NMR spectrum of **1a**
- S2. ¹H-NMR spectrum of **1b**
- S3. ¹H-NMR spectrum of **2**
- S4. ¹H-NMR spectrum of **3a**
- S5. ¹³C-NMR spectrum of **3a**
- S6. Mass spectrum of **3a**
- S7. ¹H-NMR spectrum of **3b**
- S8. ¹³C-NMR spectrum of **3b**
- S9. Mass spectrum of **3b**
- S10. ¹H-NMR spectrum of **4**
- S11. ¹³C-NMR spectrum of **4**
- S12. Mass spectrum of **4**
- S13. ¹H-NMR spectrum of **A**
- S14. ¹³C-NMR spectrum of **A**
- S15. Mass spectrum of **A**
- S16. ¹H-NMR spectrum of **5a**
- S17. ¹³C-NMR spectrum of **5a**
- S18. Mass spectrum of **5a**
- S19. ¹H-NMR spectrum of **6a**
- S20. ¹³C-NMR spectrum of **6a**
- S21. Mass spectrum of **6a**
- S22. HPLC trace of (±)-**6**

S25. HPLC trace of **6a'**

S1. ¹H-NMR spectrum of **1a**

S3. ¹H-NMR spectrum of **2**

S4. ¹H-NMR spectrum of **3a**

S5. ^{13}C -NMR spectrum of **3a**

S6. Mass spectrum of **3a**

Voyager Spec #1=>NF1.0=>NR(2.00)=>SM5=>CT[BP = 416.2, 17487]

S7. ¹H-NMR spectrum of **3b**

S8. ^{13}C -NMR spectrum of **3b**

S9. Mass spectrum of **3b**

S10. ¹H-NMR spectrum of **4**

S11. ^{13}C -NMR spectrum of **4**

S12. Mass spectrum of **4**

S15. Mass spectrum of A

S16. ¹H-NMR spectrum of **5a**

Y2-PhOH

Chemical structure of Y2-PhOH:

COc1ccc(O)cc1[C@H]2C=CC(=C(C=C2)O)C3=CC=CC=C3

¹H NMR spectrum (DMSO-d₆) showing chemical shifts (ppm) and integration values:

Chemical Shift (ppm)	Integration
7.17, 7.02, 6.95, 6.82, 6.71, 6.54	1.00, 1.00, 1.00, 1.00, 1.00, 1.00
6.54	0.54
5.87, 5.80	1.00, 1.00
3.80	3.00
10.50	1.00

Current Data Parameters:

Date_	20050615
F40	12.26
FID100	1.00
INSTRUM	5 mm QNP 1H/1
PROBHD	5 mm QNP 1H/1
PULPROG	zgpg30
TD	65536
SOLVENT	DMSO
NS	2048
DS	4
SWH	32847.133 Hz
FIDRES	0.400000 Hz
AQ	1.000000 sec
RG	364.1
NUC1	15 N 100.626 MHz
DE	5.00 umol
TE	300.2 K
SI	2.0000000 sec
RG1	0.0000000 sec
DELTA	1.0000000 sec
RGRES1	0.0000000 sec
RGW	0.0100000 sec

===== CHANNEL F1 =====

NUC1	15 N
FL1	10.000 MHz
PL1	-1.00 dB
PR1	100.000 MHz

===== CHANNEL F2 =====

OPROG2	zgpg30
NUC2	1H
PCPD2	100.000 MHz
PL2	-2.00 dB
PL12	18.00 dB
PL13	15.00 dB
PR12	400.000 MHz

F2 - Processing parameters:

SI	32768
SW	100.617700 MHz
NUC	1H
NUC2	15 N
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters:

CA	30.00 Hz
CT	20.00 Hz
FID1	210.000 Hz
F2	210.000 Hz
F3	-5.000 Hz
F4	-5.000 Hz
PR1	1.000 Hz
PR2	1.000 Hz

Voyager Spec #1=>NF1.0=>NR(2.00)=>BC=>CT[BP = 155.0, 4677]

Chemical Structure: COc1ccc(cc1)[C@H](O)Cc2ccccc2

Mass Spectrum Data (Peak m/z values):

Peak m/z	Approximate % Intensity
185	2
198.9923	15
221.0419	10
233.1169	35
234.1260	100
248	5
273.0440	75
274.0492	15
311	10
331.0485	35
332.3369	40
333.3383	25
374	5
422.5	100
437	5
467	15
500	2

S19. ¹H-NMR spectrum of **6a**

S20. ^{13}C -NMR spectrum of **6a**

S21. Mass spectrum of **6a**

S22. HPLC trace of (±)-6

Operator: FYYLC Software, Version 1.65.

Object name: FYY-OAc-RIS_Ch2 - Created: 14-11-2011, 21:10

Object type: Curve

Path: >DemoBase>FYY

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S23. HPLC trace of **6a**

Operator: FYYLC Software, Version 1.65.

Object name: FYY-OAc-PhOX2S_Chn2 - Created: 14-11-2011, 15:21

Object type: Curve

Path: >DemoBase>FYY

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S24. HPLC trace of **6b**

Operator: FYYLC Software. Version 1.65.

Object name: FYY-OAc-iPOX1S_Ch2 - Created: 14-11-2011, 18:23

Object type: Curve

Path: >DemoBase>FYY

	Time hh:mm:ss	IV	Flow ml/min	Valve %A	Valve %B	D.In
1	000:00:00		0.500	100	0	0---
2	000:00:02		0.500	100	0	1---
3	000:10:00		0.500	100	0	1---

	et.tim	Start [min]	End [min]	Height [mAU]	Area [mAU*min]	% Area	Compound
1	1.283	51.64	68.81	11.7775	51.4058	98.5500	
2	8.767	73.77	83.84	0.166891	0.756361	1.4500

S25. HPLC trace of **6a'**

Operator: FYYPLC Software, Version 1.65.

Object name: FYY-OAc-PhOXTi2S_Chn2 - Created: 18-11-2011, 21:17

Object type: Curve

Path: >DemoBase>FYY

	Time hh:mm:ss	IV	Flow ml/min	Valve %A	Valve %B	D.In
1	000:00:00		0.500	100	0	0---
2	000:00:02		0.500	100	0	1---
3	000:10:00		0.500	100	0	1---

	et.tim	Start [min]	End [min]	Height [mAU]	Area [mAU*min]	% Area	Compound
1	7.767	60.87	73.93	23.2119	90.0862	100.0000

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