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Short Report

Total Synthesis of (−)-Basiliskamide A and NMR Studies on the Conversion of Basiliskamide A to Basiliskamide B

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Descrevemos neste trabalho nossa rota sintética para obtenção do policetídeo antifúngico (−)-basiliskamida A, assim como estudos de RMN de ^{1}H relacionados a migração da cadeia lateral cinamoíla da basiliskamida A para formar a basiliskamida B em $CDCl_3$.

We describe herein our approach to the total synthesis of the antifungal polyketide (−)-basiliskamide A, as well as ^{1}H NMR studies on the migration of the cinnamoyl side chain of basiliskamide A to form basiliskamide B in $CDCl_3$ solution.

Keywords: antifungal polyketides, Stille cross-coupling, aldol reaction, NMR studies

Introduction

The polyketides basiliskamides A (**1**) and B (**2**) were isolated from the marine bacterium PNG-276 from the coast of Papua New Guinea (Figure 1).[1,2] These antifungal polyketides show potent *in vitro* activity against *Candida albicans* and *Aspergillus fumigatus*,[1] as well as at least 4-fold less cytotoxicity for normal human fibroblast cells when compared to amphotericin B.[1,3] The relative configurations of basiliskamides A (**1**) and B (**2**) were proposed by Andersen and co-workers[1] and the absolute configurations have been confirmed by total synthesis.[4]

We have recently concluded the total synthesis of basiliskamide B.[5] As the natural supply of basiliskamide A is restricted, and attracted by its potent cytotoxicity, we initiated a project directed towards an efficient and flexible total synthesis, in order to provide further material for more extensive biological studies, along with access to novel analogs.[6]

Results and Discussion

Our approach for the preparation of (−)-basiliskamide A (**1**) began with the synthesis of vinyl iodide **4**, prepared in 7 steps and 19.1% overall yield from ethylketone **3** (Scheme 1).[5,7]

The next step involved a Stille cross-coupling reaction between *Z*-vinylstannane **5**[8] and *E*-vinyl iodide **4** (Scheme 2). This was accomplished by treatment of **4** and **5** in DMF with catalytic amounts of $Pd(MeCN)_2Cl_2$ at 50 °C, providing **6** in 60% yield after purification by silica-gel column chromatography. At this point only four synthetic operations remained to conclude the total synthesis of (−)-basiliskamide A. Removal of the isopropylidene acetal protecting group in **6** with 80% AcOH provided diol **7**. Selective protection of the less hindered oxygen with TES chloride in the presence of pyridine gave alcohol **8** (67% yield, 2 steps).[9] Treatment of secondary alcohol

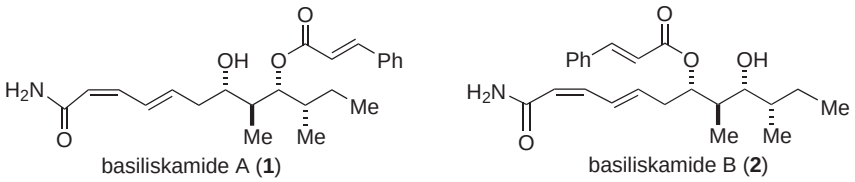

Figure 1. Basiliskamides A and B.

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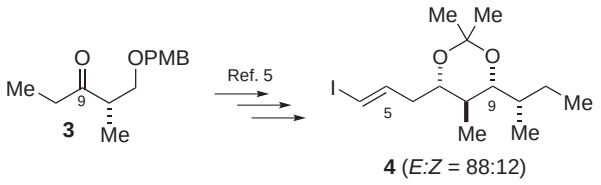


Scheme 1. Synthesis of vinyl iodide **4** from of ethylketone **3**.

8 with *E*-cinnamoyl chloride in the presence of DMAP and Et_3N gave ester **9**, which, after treatment with HF in acetonitrile, provided (–)-basiliskamide A in 42% for the four-step sequence.

The spectroscopic and physical data (^1H and ^{13}C NMR, IR, $[\alpha]^D$, R_f) for synthetic (–)-basiliskamide A were identical in all respects with the published data for the natural product.[1,4]

NMR studies

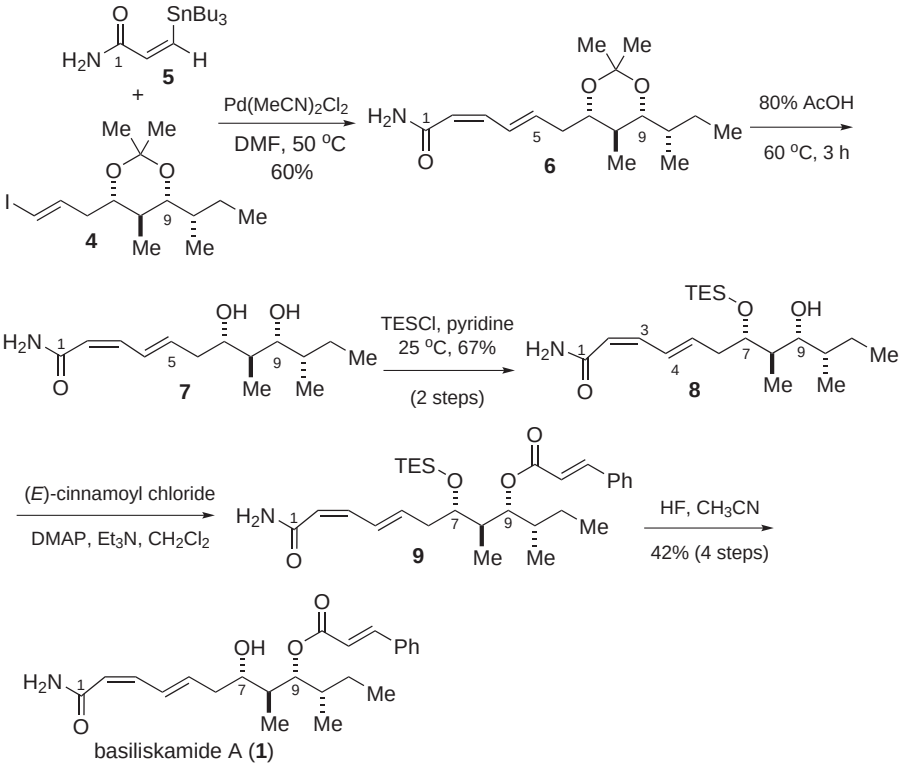
At this point, we decided to investigate the possibility of basiliskamide B being produced by cinnamoyl side chain migration from basiliskamide A. To this end, we did an NMR study to verify whether the conversion of basiliskamide A to basiliskamide B in mild acidic $CDCl_3$ solution was possible or not (Scheme 3). This conversion would occur through migration of the cinnamoyl side chain from the more hindered oxygen at C9 in basiliskamide A to the less hindered oxygen at C7.

In the ^1H NMR spectrum of basiliskamide A (**1**), the signal at δ 3.63 ppm (dt, *J* 3.5 and 10.0 Hz) is attributed to the hydrogen H7. In the ^1H NMR spectrum of basiliskamide B the signal at δ 3.35 ppm (dd, *J* 2.5 and 9.5 Hz) refers to the hydrogen H9 (Figure 2).

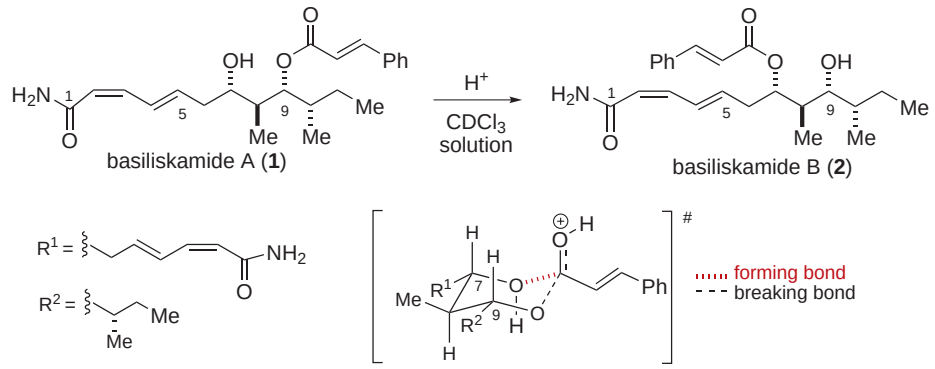
After 24 h, the ^1H NMR spectrum of basiliskamide A (**1**) shows a new signal at δ 3.35 ppm, which corresponds to the hydrogen H9 of basiliskamide B (Figure 3). After 20 days, we can observe that the signal at δ 3.35 ppm increases leading to a 1.00:0.45 ratio of basiliskamide A (**1**) and basiliskamide B (**2**), respectively. This clearly shows that the migration of the cinnamoyl side chain is occurring and that it is possible that basiliskamide B is an artifact of basiliskamide A.[10]

Conclusions

In summary, a highly convergent and efficient total synthesis of (–)-basiliskamide A has been accomplished. The synthesis required 15 steps from ethylketone **3** and produced the desired product in 3.2% overall yield. This approach compares very well with the published routes to (–)-basiliskamide A[4] and the synthetic strategy presented here is, in principle, readily applicable for the preparation of additional analogues.



Scheme 2. Total synthesis of (–)-basiliskamide A.



Scheme 3. Cinnamoyl side chain migration of basiliskamide A.

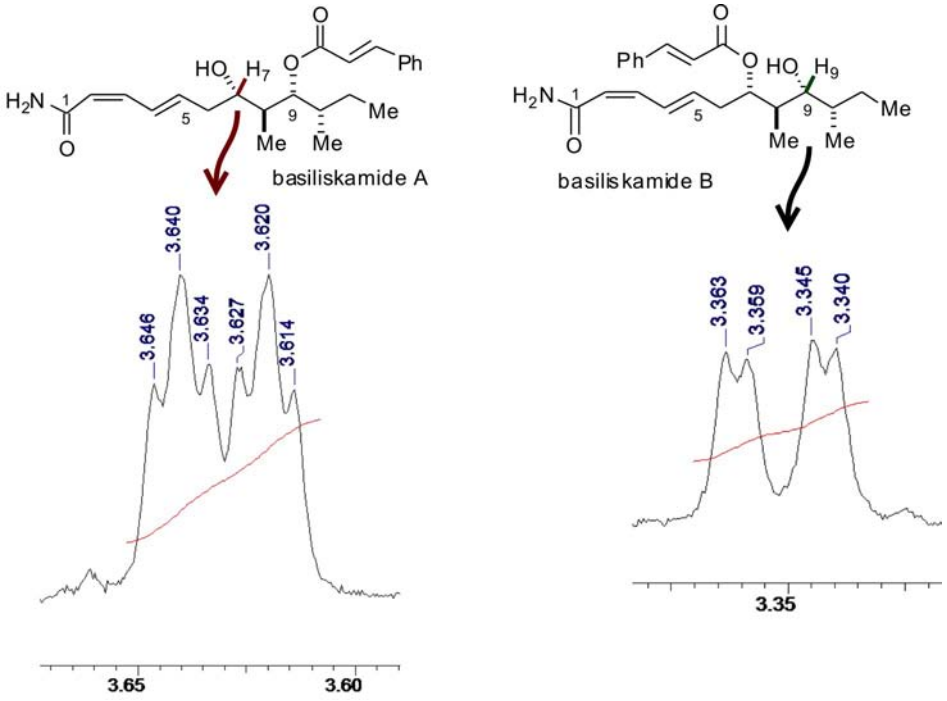


Figure 2. Chemical shifts in the ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of H7 in basiliskamide A (**1**) and H9 in basiliskamide B (**2**).

Experimental

*(–)-Basiliskamide A (**1**)*

The diene **6** (68.5 mg, 0.23 mmol) was dissolved in 80% acetic acid (5 mL). The reaction was protected from light and stirred at 60 °C for 3 h. The reaction was then allowed to reach ambient temperature and adjusted to pH 7.0 with NH_4OH. The aqueous phase was extracted with EtOAc (2 × 10 mL), the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the corresponding diol **7**. R_f = 0.15 (hexane:EtOAc, 50:50). $[\alpha]_D^{25}$ = +15 (*c* = 0.35, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 250 MHz): δ 0.69 (d, 3H, *J* 7.0 Hz); 0.73 (d, 3H, *J* 6.3 Hz); 0.84 (t, 3H, *J* 7.3 Hz); 1.35 (m, 3H), 1.61 (m, 1H); 2.05 (m, 1H); 2.28 (m, 1H); 3.24 (m, 1H); 3.81 (m, 1H); 4.49 (d, 1H, *J* 5.3 Hz); 4.7 (d, 1H, *J* 4.7 Hz); 5.58 (d, 1H, *J* 5.6 Hz); 6.03 (dt, 1H, *J* 6.0 Hz); 6.37 (t, 1H, *J* 11.5 Hz); 6.86 (brs, 1H); 7.37 (brs, 1H);7.45 (dd, 1H, *J* 11.5 e 15.5 Hz). ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 11.3; 12.4; 12.5; 27.22; 35.9; 36.8; 41.9; 71.9; 74.8; 119.6; 128.5; 141.2; 141.3; 168.1. IR (film) ν_{max}/cm^{-1}: 3350, 2964, 2930, 2871, 1666, 1454, 1327. HRMS: [$C_{14}H_{26}NO_3^+$]: expected: 256.1907; observed: 256.1913.

A solution of the corresponding crude diol **7** obtained before (44.8 mg; 0.18 mmol) in pyridine (3 mL) was treated with TESCl (0.033 mL; 0.19 mmol) at 0 °C, and stirred at 25 °C for 2 h. The reaction was quenched with aqueous saturated $NaHCO_3$ solution and extracted with EtOAc providing alcohol **8**. R_f = 0.4 (hexane:EtOAc, 50:50). ^{1}H NMR (C_6D_6, 250 MHz): δ 0.73 (q, 6H, *J* 8 Hz); 0.84 (d, 3H, *J* 6.8 Hz); 1.01 (m, 6H); 1.12 (t, 9H, *J* 8 Hz); 1.49 (m, 3H); 2.02 (m, 1H); 2.43 (t, 2H, *J* 6.3 Hz); 2.67 (brd,

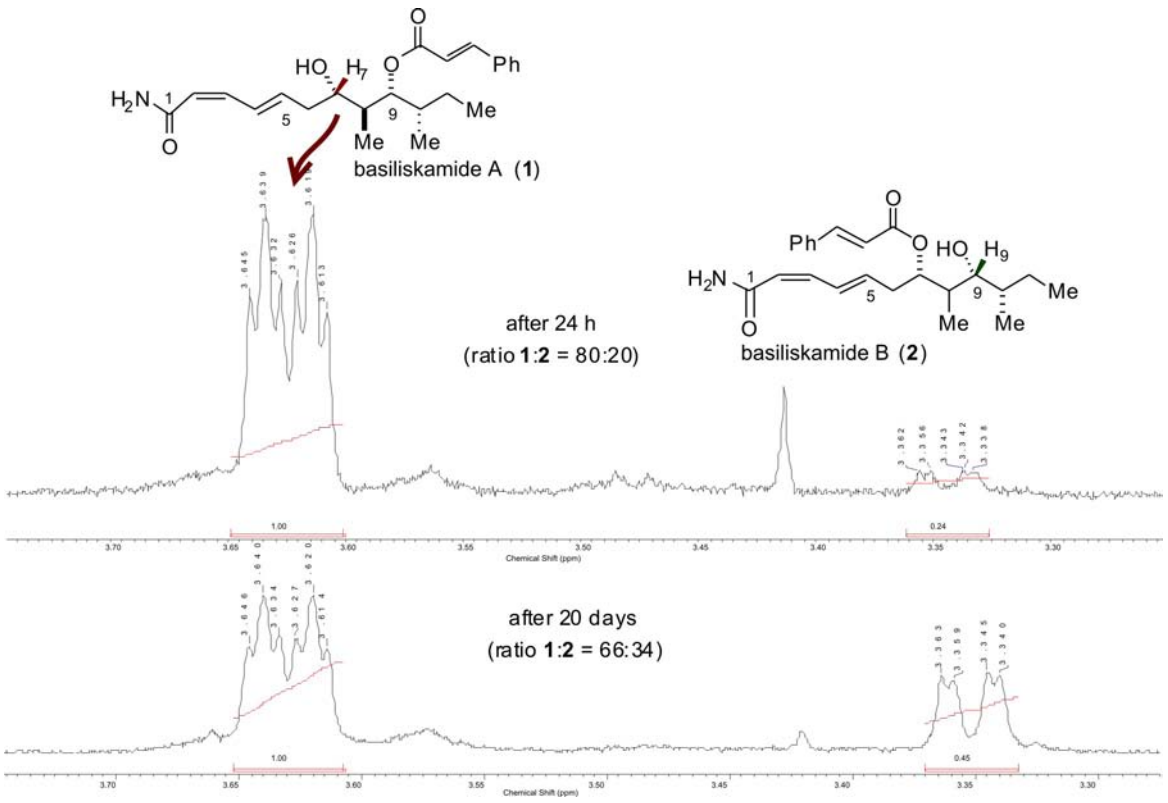


Figure 3. Partial ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) showing the migration of the cinnamoyl side chain after 24 h and after 20 days.

1H, *J* 3.3 Hz); 3.44 (brd, 1H, *J* 8.5 Hz); 4.23 (q, 1H, *J* 5.3 Hz); 4.72 (brs, 1H); 5.19 (d, 1H, *J* 11.3 Hz); 5.59 (brs, 1H); 6.25 (dt, 1H, *J* 7.3 e 15.5 Hz); 6.39 (t, 1H, *J* 11.3 Hz); 8.17 (dd, 1H, *J* 11.5 e 15.3 Hz). ^{13}C NMR (C_6D_6, 62.5 MHz): δ 5.5; 7.2; 11.3; 11.8; 12.4; 27.6; 36.8; 37.2; 42.1; 75.2; 75.6; 118.2; 129.6; 141.1; 142.6; 168.1.

The crude alcohol **8** (0.029 mmol) in CH_2Cl_2 (0.7 mL) was treated with Et_3N (0.034 mL; 0.24 mmol) and DMAP (1.7 mg, 0.014 mmol) and cooled to 0 °C. The solution was treated with (*E*)-cinnamoyl chloride (0.02 g; 0.12 mmol). The reaction was protected from light and stirred at ambient temperature for 18 h, and the reaction was then quenched with water. The aqueous phase was extracted with CH_2Cl_2 and the solvent was removed under reduced pressure to provide ester **9**. R_f = 0.55 (EtOAc:CH_2Cl_2, 40:10). $[\alpha]_D^{25}$ = −77 (*c* 0.26, MeOH). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.83 (d, 3H, *J* 7.0 Hz); 0.84 (d, 3H, *J* 7.0 Hz); 0.87 (t, 3H, *J* 7.5 Hz); 0.90 (d, 3H, *J* 7.0 Hz); 1.11 (m, 1H) 1.25 (m, 1H); 1.67 (m, 1H); 1.99 (m, 1H); 2.06 (m, 1H); 2.28 (m, 1H); 3.49 (m, 1H); 4.57 (d, 1H, *J* 5.0 Hz); 4.92 (dd, 1H; *J* 2.0 e 9.5 Hz); 5.55 (d, 1H, *J* 11.0 Hz); 5.91 (dt, 1H, *J* 7.0 e 15.0 Hz); 6.31 (brt, 1H, *J* 11.0 Hz); 6.61 (d, 1H, *J* 16.0 Hz); 6.83 (s, 1H); 7.31 (s, 1H); 7.40 (dd, 1H, *J* 11.0 e 15.0 Hz); 7.41 (m, 2H); 7.65 (d, 1H, *J* 16.0 Hz); 7.71 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 10.1; 11.6; 12.8; 26.4; 34.7; 35.5; 40.8; 69.7; 76.3; 118.0; 119.3; 128.2; 128.4; 128.9; 130.4; 134.0; 140.56; 140.58; 144.6; 166.1; 167.5. IR (film) ν_{max}/cm^{-1}: 3367, 2966, 2936, 1701, 1670, 1588.

The crude compound **9** (0.029 mmol) was treated with 0.4 mL of a solution of HF (40% aqueous solution): CH_3CN (1:18). After 10 min at r.t. the reaction was quenched with $NaHCO_3$ (4 mg) and stirred for 10 min, filtered and concentrated *in vacuo*. Purification by flash column chromatography (EtOAc:CH_2Cl_2, 4:2) afforded (−)-basiliskamide A (**1**) (4.6 mg, 42% yield, 4 steps). R_f = 0.6 (EtOAc:CH_2Cl_2, 40:10). ^{1}H NMR (DMSO-d_6, 5000 MHz): δ 7.72 (2H, m); 7.66 (1H, d, 16.0 Hz); 7.41 (3H, m); 7.41 (3H, m); 7.39 (1H, m); 7.33 (1H, brs); 6.84 (1H, brs); 6.62 (1H, d, 16.0 Hz); 6.31 (1H, apt, 11.5 Hz); 5.91 (1H, dt, 7.4 and 14.9 Hz); 5.55 (1H, d, 11.5 Hz); 4.92 (1H, dd, 2.6 and 9.5 Hz); 4.58 (1H, d, 5.4 Hz); 3.48 (1H, m); 2.28 (1H, m); 2.02 (1H, m); 2.02 (1H, m), 1.67 (1H, m); 1.25 (1H, m); 1.11 (1H, m); 0.89 (3H, d, 6.6 Hz); 0.87 (3H, t, 7.7 Hz); 0.84 (3H, d, 7.1 Hz) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 167.5; 166.1; 144.6; 140.56; 140.51; 134.0; 130.4; 128.9; 128.4; 128.3; 119.4; 118.0; 76.3; 69.7; 40.8; 35.5; 34.7; 26.4; 12.8; 11.7; 10.1 ppm.

Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br, as a PDF file.

Acknowledgments

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10. When submitting (–)-basiliskamide B to the same experiment we can not observe the signal at δ 3.63 ppm (dt, *J* 3.5 and 10.0 Hz) that corresponds to hydrogen H7 of basiliskamide A. However, the formation of another compound that shows three well defined signals (δ 3.65, 4.94 and 5.04 ppm) was observed.

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Total Synthesis of (−)-Basiliskamide A and NMR Studies on the Conversion of Basiliskamide A to Basiliskamide B

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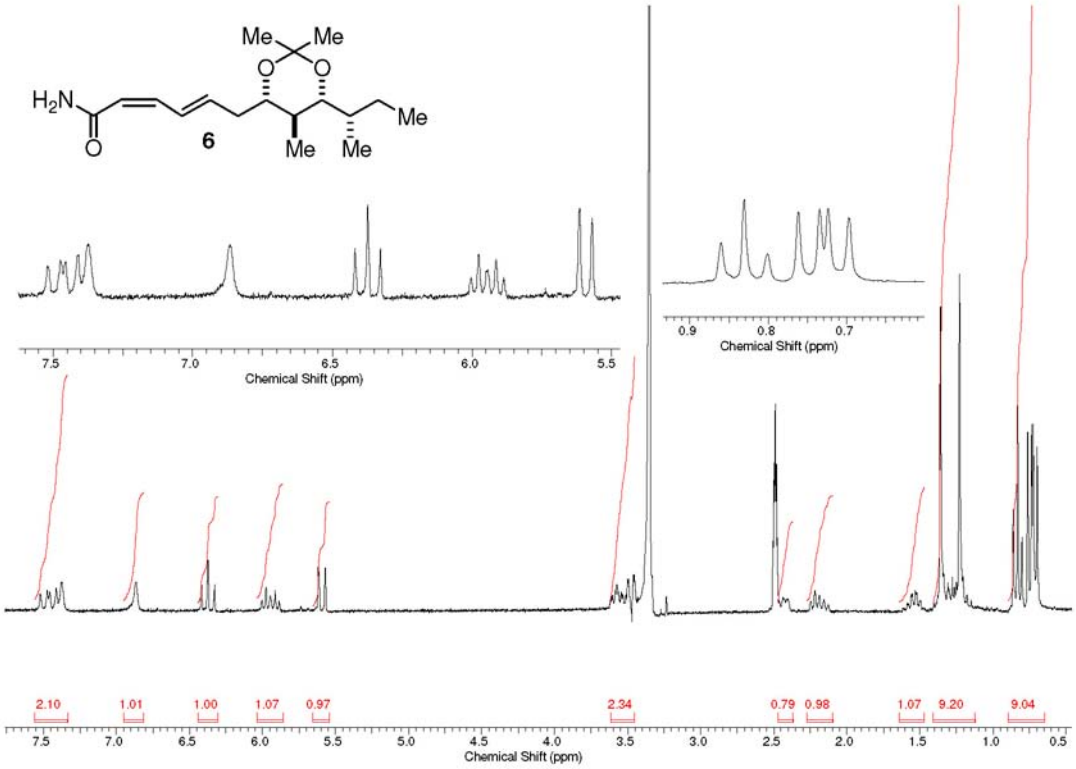

Figure S1. ^{1}H NMR of acetonide **6** (DMSO-d_6, 250 MHz).

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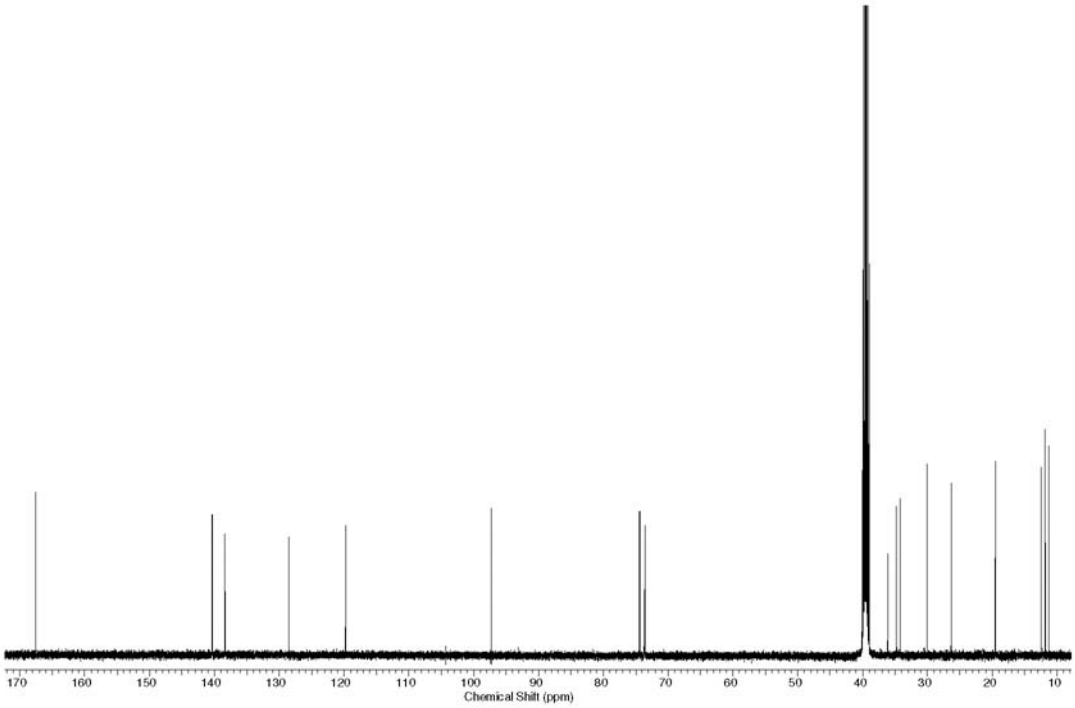

Figure S2. ^{13}C NMR of acetonide **6** (DMSO-d_6, 62.5 MHz).

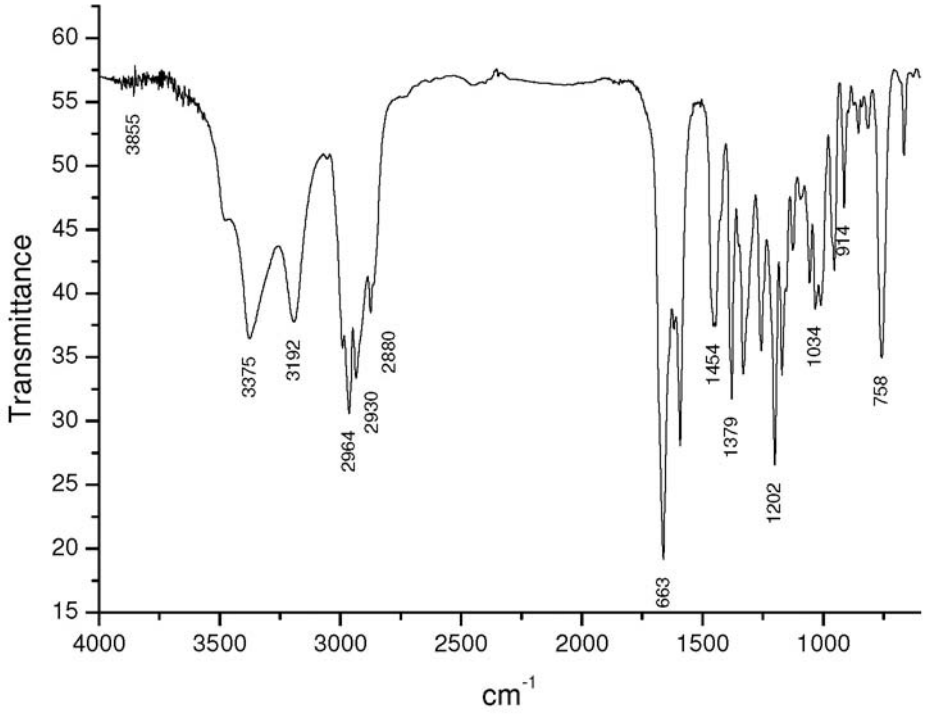

Figure S3. IR of acetonide **6**.

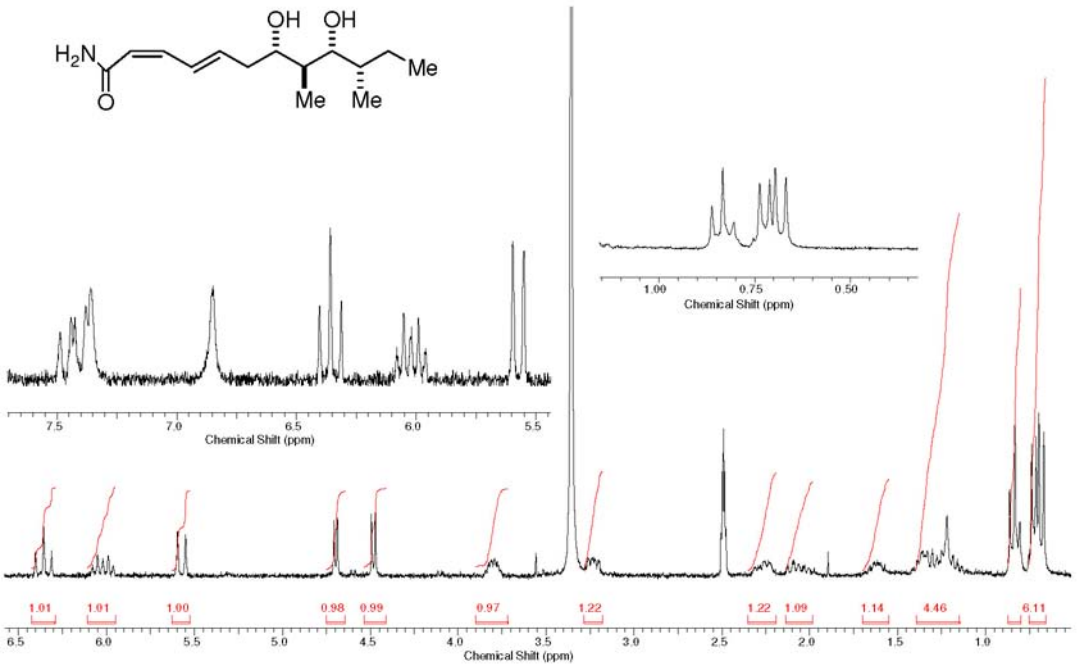

Figure S4. [1]H NMR of diol **7** (DMSO-d_6, 250 MHz).

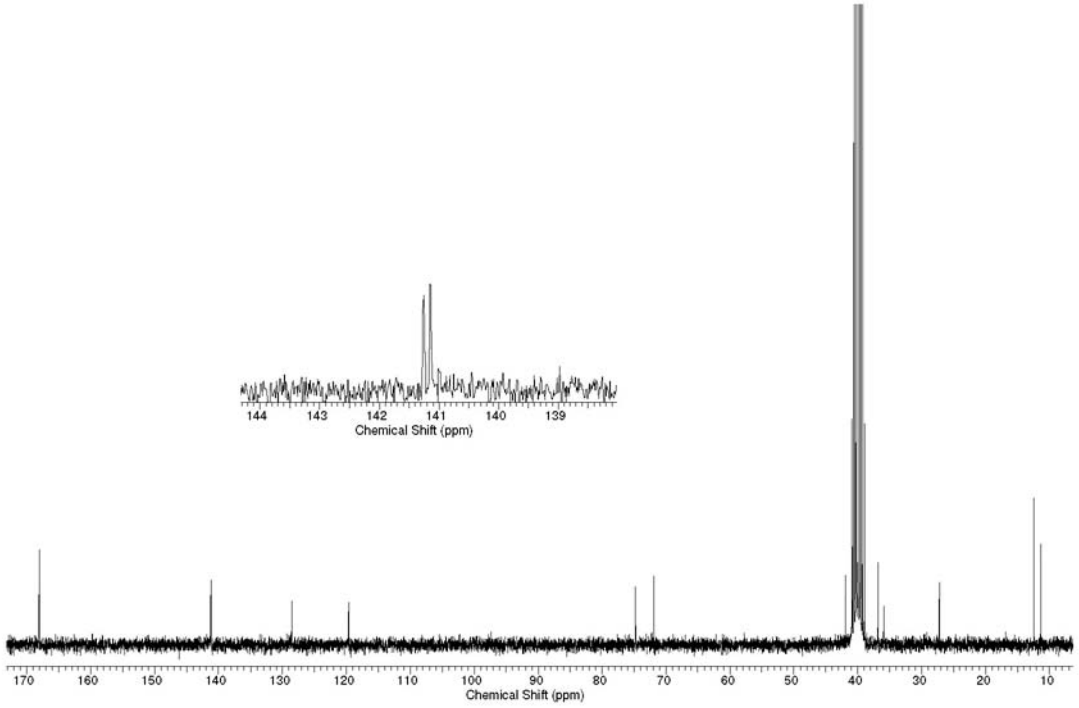

Figure S5. [13]C NMR of diol **7** (DMSO-d_6, 62.5 MHz).

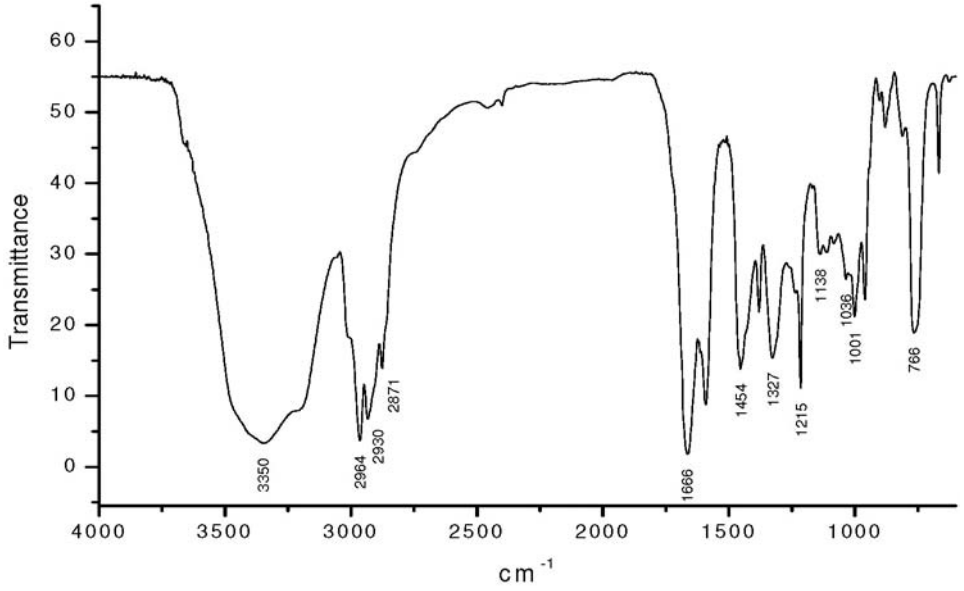

Figure S6. IR of diol **7**.

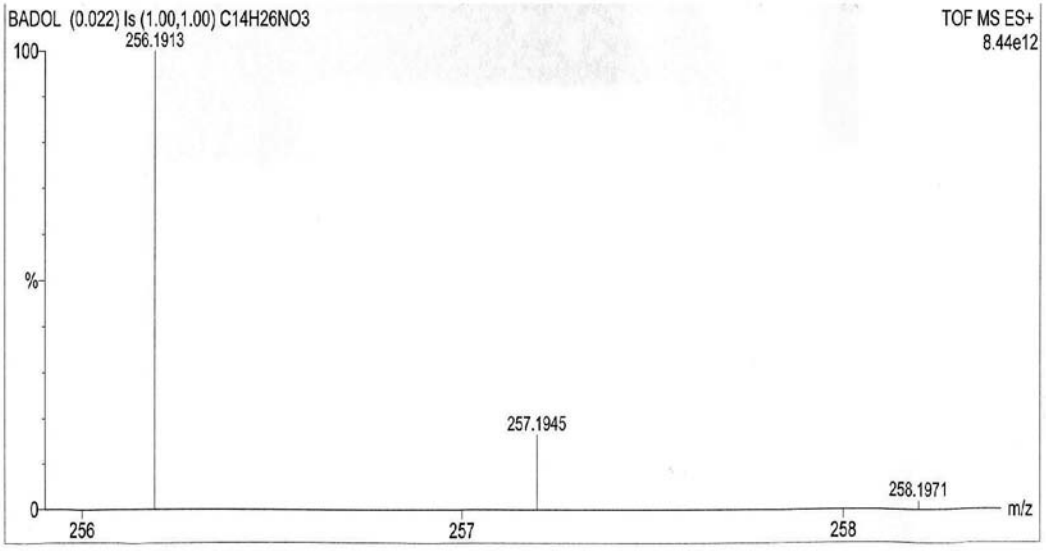

Figure S7. HRMS of diol **7**.

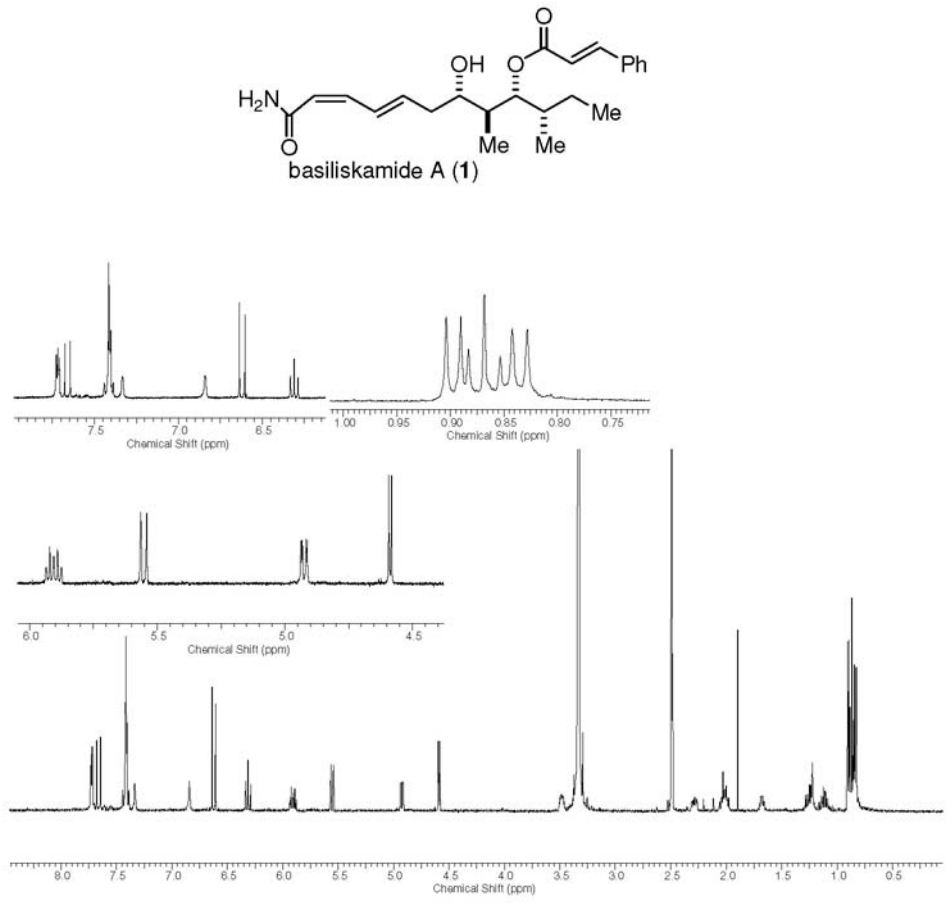

Figure S8. ^{1}H NMR of basiliskamide A (**1**), (DMSO-d_6, 500 MHz).

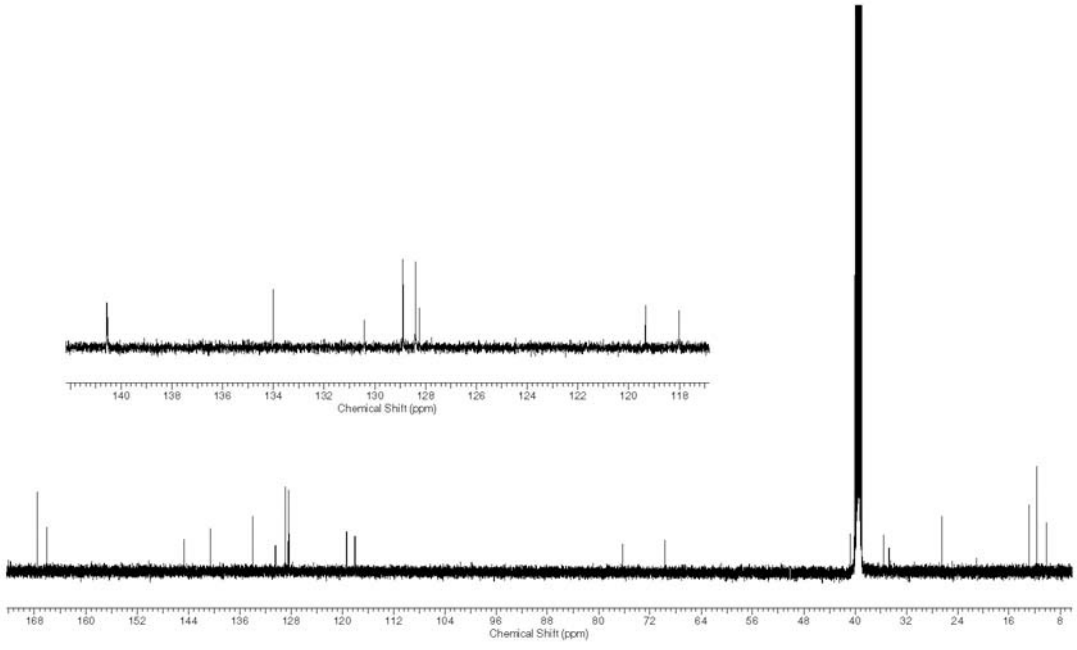

Figure S9. ^{13}C NMR of basiliskamide A (**1**), (DMSO-d_6, 125 MHz).

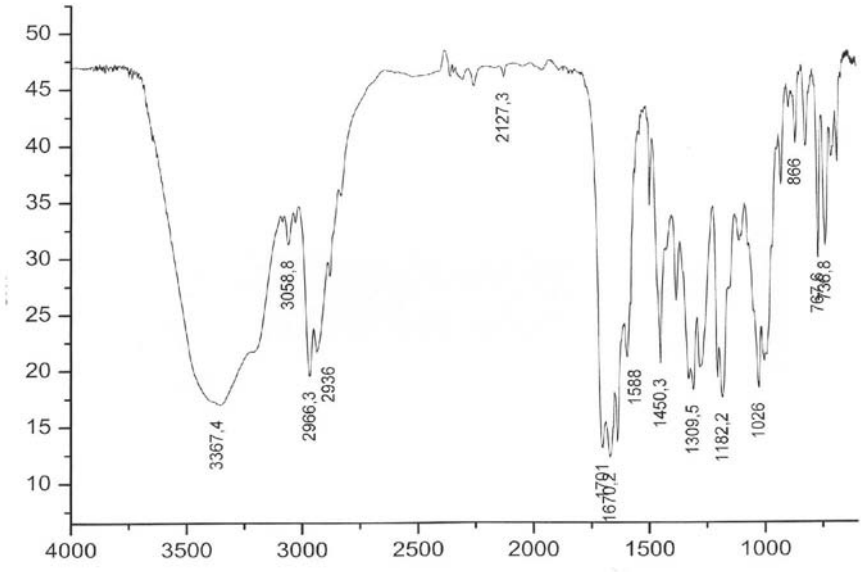

Figure S10. IR of basiliskamide A (**1**).

Table 1. Comparison of ^{1}H and ^{13}C NMR data for natural[1] and our synthetic basiliskamide A (DMSO-d_6)

^{1}H NMR (400 MHz) δ/ppm (number of hydrogens, multiplicity, coupling constant) Natural	^{1}H NMR (500 MHz) δ/ppm (number of hydrogens, multiplicity, coupling constant) Synthetic	^{13}C NMR (100 MHz)[1] δ (ppm) Natural	^{13}C NMR (125 MHz)[1] δ (ppm) Synthetic
0.84 (3H, d, 7.0 Hz)	0.84 (3H, d, 7.1 Hz)	10.1	10.1
0.87 (3H, t, 7.5 Hz)	0.87 (3H, t, 7.7 Hz)	11.6	11.7
0.90 (3H, d, 7.0 Hz)	0.89 (3H, d, 6.6 Hz)	12.8	12.8
1.11 (1H, m)	1.11 (1H, m)	26.4	26.4
1.25 (1H, m)	1.25 (1H, m)	34.7	34.7
1.67 (1H, m)	1.67 (1H, m)	35.5	35.5
1.99 (1H, m)	2.02 (1H, m)	40.7	40.8
2.06 (1H, m)	2.04 (1H, m)	69.6	69.7
2.28 (1H, m)	2.28 (1H, m)	76.3	76.3
3.49 (1H, m)	3.48 (1H, m)	118.0	118.0
4.57 (1H, d, 5.0 Hz)	4.58 (1H, d, 5.4 Hz)	119.3	119.4
4.92 (1H, dd, 2.0 and 9.5 Hz)	4.92 (1H, dd, 2.6 and 9.5 Hz)	128.2	128.3
5.55 (1H, d, 11.0 Hz)	5.55 (1H, d, 11.5 Hz)	128.4	128.4
5.91 (1H, dt, 7.0 and 15.0 Hz)	5.91 (1H, dt, 7.4 and 14.9 Hz)	128.9	128.9
6.31 (1H, dd, 11.0 and 11.0 Hz)	6.31 (1H, apt, 11.3 Hz)	130.4	130.4
6.61 (1H, d, 16.0 Hz)	6.62 (1H, d, 15.9 Hz)	134.0	134.0
6.83 (1H, s)	6.84 (1H, brs)	140.5	140.51
7.31 (1H, s)	7.33 (1H, brs)	-	140.56
7.40 (1H, dd, 11.0 and 15.0 Hz)	7.39 (1H, m)	144.6	144.6
7.40 (1H, m)	7.41 (3H, m)	166.0	166.1
7.41 (2H, m)	-	167.4	167.5
7.65 (1H, d, 16.0 Hz)	7.66 (1H, d, 16.0 Hz)	-	-
7.71 (2H, m)	7.72 (2H, m)	-	-

1. Barsby, T.; Kelly, M. T.; Andersen R. J.; *J. Nat. Prod.* **2002**, *65*, 1447; Kelly, M. T.; Anderson, R. J.; Barsby, T.; *US Patent 2005/0277779 A1*, **2005**.