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Efficient synthesis of karrikinolide via Cu(II)-catalyzed lactonization

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ABSTRACT

The efficient total synthesis of karrikinolide (KAR_1), a potent plant growth regulator discovered in smoke from burning plant material, is described. 3-Hydroxy-4-pyranone, prepared from D-xylose, was subjected to a Cu(II)-catalyzed transesterification–Wittig lactonization to afford the dihydrofuropyran in good yield. Finally, radical bromination, followed by olefin formation, provided KAR_1 in acceptable yield.

1. Introduction

Karrikinolide, 3-methyl-2*H*-furo[2,3-*c*]pyran-2-one (**1**), and analogous compounds have been isolated from plant-derived smoke and are responsible for promoting seed germination of a wide range of plant species at extraordinarily low concentrations, some as low as nanomolar (Fig. 1).[1] Although the role of smoke in germination and its potential applications have been reviewed and the relationship between karrikinolides and storigolactone has been discussed, the mechanistic details of the bioactivity have not yet been elucidated.[2] Since smoke contains only a small amount of karrikinolide, this compound has to be supplied by organic synthesis for studies. So far, several reports on the total synthesis of karrikinolides have appeared in the literature, including the following:[3] Flematti et al. synthesized **1** via the intramolecular Wittig reaction with thioketone in poor yield;[3a] Goddard-Boger et al. utilized D-xylose as a carbon source to prepare KAR_2, which led to KAR_1;[3b] Xu et al. synthesized KAR_2 from a butenolide that led to KAR_1; Tanabe et al. prepared the butenolide via Ti-crossed aldol addition (Scheme 1). Since the direct lactonization of 2-hydroxy-4-pyrone seems to be difficult, efficient construction of the lactone would be a point. These efforts motivated us to find a more efficient synthetic method to provide an adequate supply of KAR_1 for an SAR study.[4]

Recently, we have developed a catalytic transesterificaiton–Wittig lactonization reaction forming a butenolide in one pot (Scheme 2),[5] which is expected to be very useful for the synthesis of the karrikinolides. Herein, we report an efficient synthesis of karrikinolide (KAR_1) (**1**) using our new lactonization reaction as the key step.

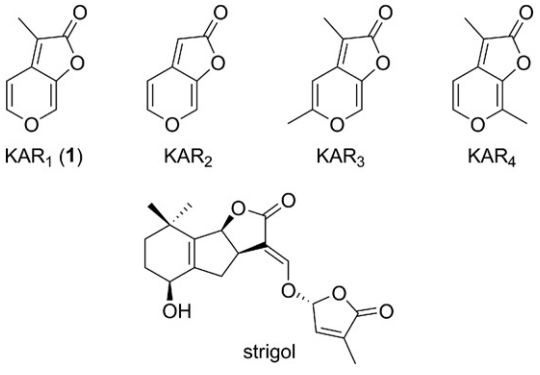

Fig. 1. Karrikinolides and strigol.

2. Results and discussion

First, we attempted the lactonization of the acyloin **3**, easily prepared from kojic acid (**2**),[6] using the Wittig reagent **5** and the Cu (II) salt **4** as the catalyst in the presence of Oxone and molecular sieves 4 Å under air. However, the reaction did not proceed at all even at higher temperature, probably due to the low nucleophilicity of the enol in **3** (Scheme 3).[7] In the initial transesterification between **5a** and **3**, the nucleophilic hydroxyl must be a more reactive alcoholic hydroxyl group.

We then decided to use the α-hydroxy enone **11** as the substrate for the lactonization (Scheme 4). 3,4-Di-*O*-acetyl-D-xylal (**9**), prepared from D-xylose in three steps,[8] was subjected to methanolysis to give the diol **10**. Its allylic alcohol was selectively oxidized with PDC in the presence of acetic acid to afford **11** in moderate yield.[9] The Cu(II) catalyzed Wittig lactonization of **11** in the presence of Oxone was carried out at 60 °C under air to provide the lactone **12** in good yield. Attempts to oxidize **12** by allylic radical bromination, followed by elimination, resulted in low

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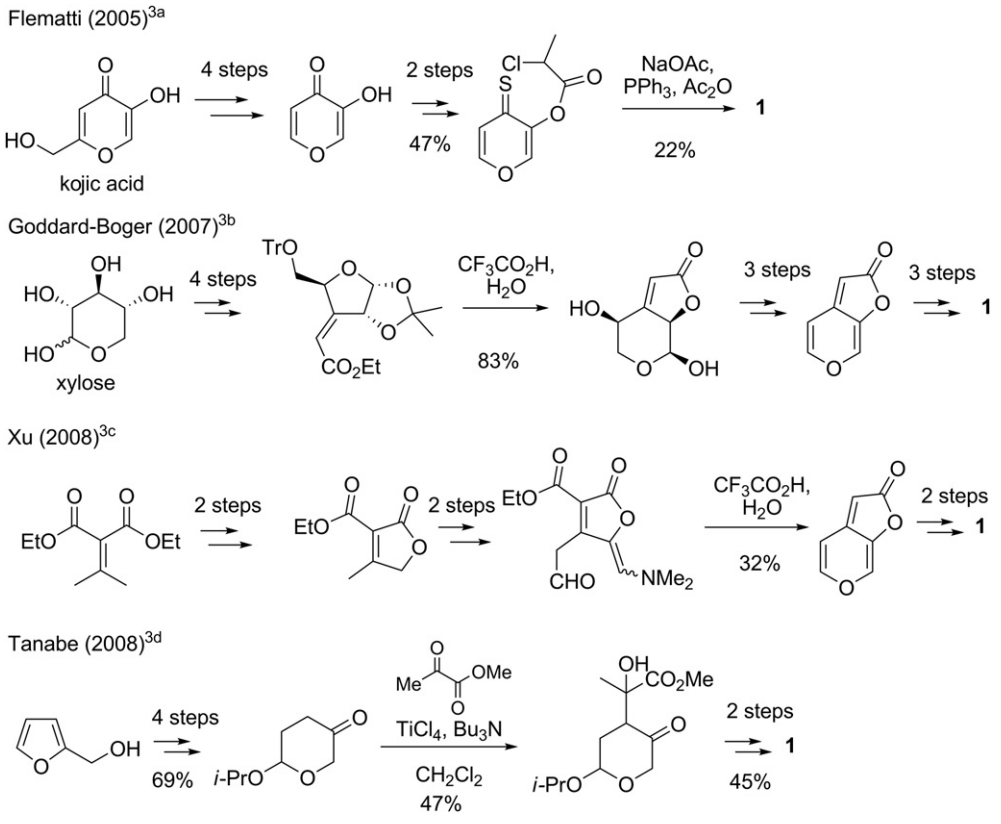
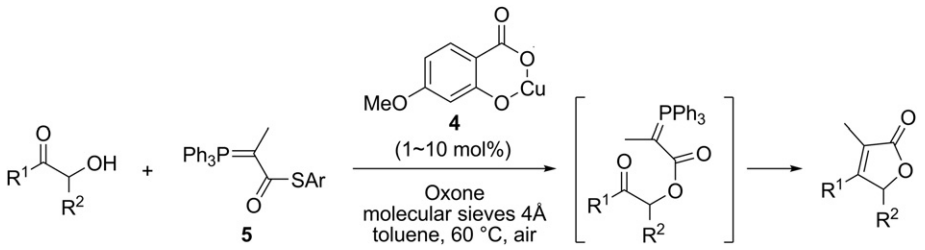
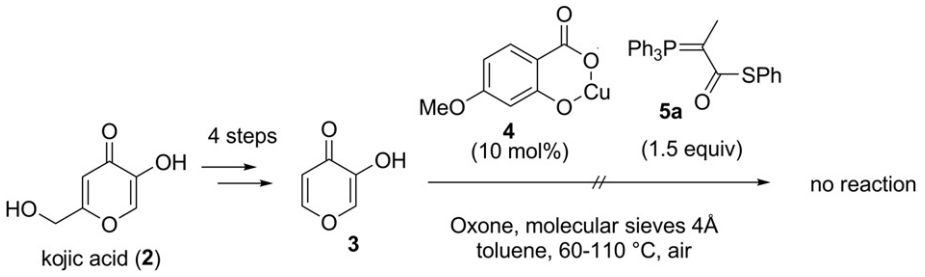


Scheme 1.



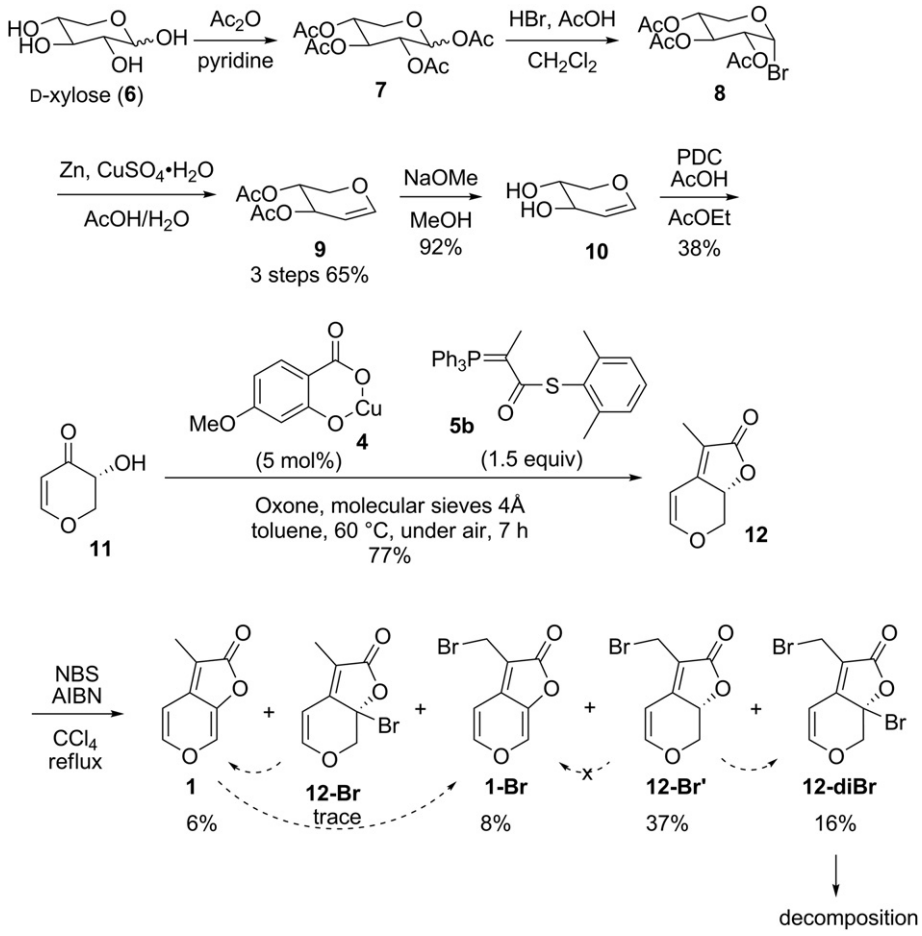
Scheme 2.



Scheme 3.

yields, because considerable amounts of byproducts (**12-Br**, **1-Br**, **12-Br′**, and **12-diBr**) were formed via allylic bromination at the terminal methyl group. Since the terminal methylene radical **12a′** would be highly stabilized by the conjugated dienyl group compared to the *endo*-radical **12b′**, these byproducts were preferentially generated (Fig. 2). We also tried dehydrobromination of **12-diBr** to result in decomposition. Therefore, the desired product **1**, which would be generated from **12-Br**, was converted into **1-Br**, while **12-diBr** would be formed from **12-Br′**. Dehydrogenation of **12** with Pd–C did not work at all.

Since it seems to be very difficult to obtain **1** from **12** in good yield, we then decided to use another type of ketone as a precursor of the lactonization. To prevent the generation of the terminal methylene radical, we prepared an unconjugated acyloin **13** as the substrate by the Michael addition of thiophenol to **11** (Scheme 5).[10] Due to its instability, the acyloin **13** was subjected to lactonization



Scheme 4.

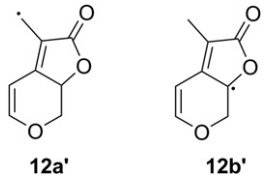
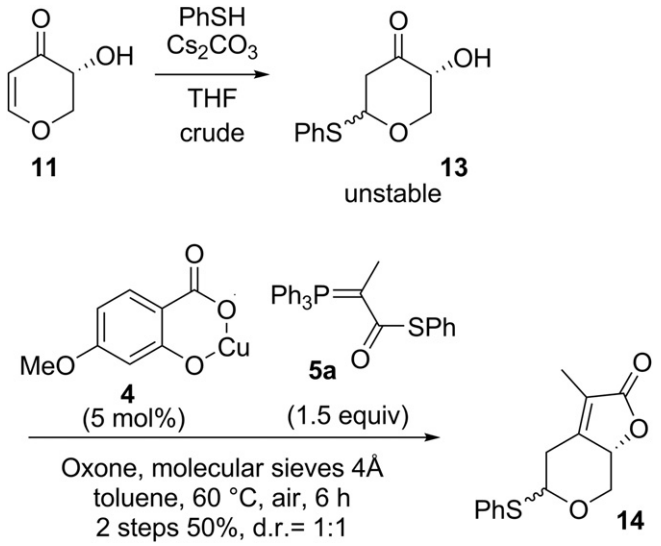


Fig. 2. Possible radical intermediates.



Scheme 5.

without purification to afford the butenolide **14** as a diastereomeric mixture in 50% yield for the two steps. The structure of one diastereomer (trans form) was confirmed by the X-ray crystallographic analysis (Fig. 3).

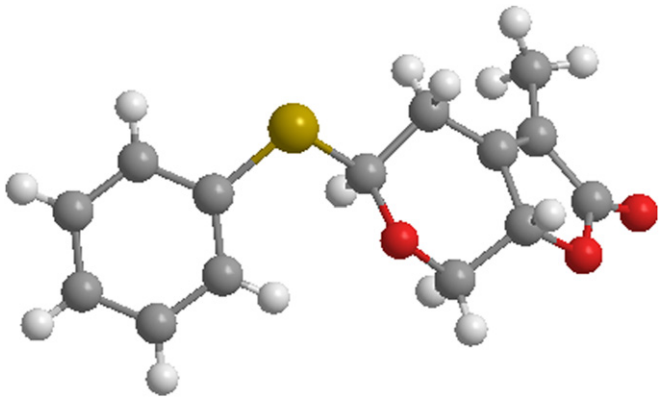
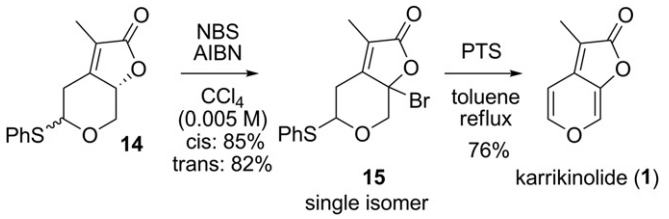


Fig. 3. X-ray crystal structure of *trans*-**14**.

The radical allylic bromination of **14** with NBS initiated by AIBN in CCl_4 under high dilution successfully afforded the *endo*-brominated product **15** in good yield as a single isomer. Both the cis and trans isomers of **14** were converted into the same isomer of **15**, the stereochemistry of which is not known. Finally, **15** was treated with *p*-TsOH in toluene under reflux to furnish karrikinolide (KAR_1) (**1**) in 76% yield (Scheme 6).



Scheme 6.

3. Conclusion

We have achieved an efficient synthesis of karrikinolide (KAR_1) by using the Wittig lactonization in 7.3% overall yield in nine steps in which purification was performed in only six steps. SAR studies for the potential plant growth regulator are now in progress.

4. Experimental

4.1. General procedures

^{1}H NMR and ^{13}C NMR were measured in $CDCl_3$ solution using a JEOL JNM AL-400 (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz) and a JNM ECA-600 spectrometer (^{1}H NMR at 600 MHz, ^{13}C NMR at 150 MHz) with the reference standards (^{1}H NMR at 0.00 ppm (TMS), ^{13}C NMR at 77.03 ppm ($CDCl_3$)) unless otherwise noted. Chemical shifts are reported in parts per million. Peak multiplicities are indicated with the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. IR spectra were recorded on Shimazu FT/IR-8300 spectrometers. Mass spectra and high resolution mass spectra were obtained on a JEOL JMS-700. Elemental analyses were performed with a YANACO 026 CHN analyzer. Melting points were measured with an SRS Opti Melt MPA 100 apparatus and are uncorrected. Analytical TLC was performed on precoated plates (0.25 mm, silica gel Merck 60 F_{254}). Column chromatography was performed on silica gel (Kanto Chemical Co., Inc.). Preparative HPLC was performed on Kanto Mightysil Si60, with a system utilizing a JASCO PU-2087 *plus* Intelligent Pump with Dynamic Mixer MX-2080.32, UV-2075 *plus* Intelligent UV/vis Detector, and RI-2031 *plus* Intelligent RI Detector. All reactions were performed under an air atmosphere unless otherwise noted, and dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), and tetrahydrofuran (THF) were purchased from Kanto Chemical Co., Inc.; all other solvents were distilled. Unless otherwise noted, reagents were obtained from chemical sources and used without further purification.

*4.1.1. 3,4-Di-O-acetyl-D-xylal (**9**)*[7]. D-Xylose (106.6 mmol, 16.0 g) was acetylated with acetic anhydride (80 mL) and pyridine (133 mL) at room temperature for 6 h. Methanol was added to the mixture and then removed in vacuo. Toluene was added to the residue, and the mixture was evaporated. The residue was dissolved in dichloromethane (427 mL), and HBr (30% in acetic acid, 97 mL) was added at 0 °C. After 3 h at 0 °C, the mixture was diluted with chloroform, washed with water, saturated aqueous $NaHCO_3$, and brine, dried with $MgSO_4$, and concentrated in vacuo. The resulting bromide **8** was dissolved in acetic acid (350 mL) and was added to the suspension of Zn dust (1.06 mmol, 69.3 g) and $CuSO_4$–H_2O (21.3 mmol, 5.3 g) in water (71 mL) with stirring. After 2.5 h at 0 °C, the mixture was filtered through Celite. The filtrate was poured into saturated aqueous $NaHCO_3$ and extracted with chloroform. The combined organic phases were washed with saturated aqueous $NaHCO_3$ and brine, then dried, and concentrated. The residue was purified by silica-gel column chromatography (20% EtOAc–hexane) to give **5** (13.8 g, 65% for three steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.07 (s, 3H), 2.10 (s, 3H), 3.96 (dd, J=12.0, 1.2 Hz, 1H), 4.20 (ddd, J=12.0, 3.2, 1.2 Hz, 1H), 4.95–5.00 (m, 3H), 6.60 (d, J=5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.9 (q), 21.1 (q), 63.4 (d), 63.6 (t), 67.2 (d), 97.4 (d), 148.0 (d), 169.8 (s), 169.9 (s); IR (neat): 2968, 1732, 1645, 1373, 1224, 1095 cm^{-1}; MS (FAB) m/z: 201 ([M+H]$^+$); HRMS (FAB) calcd for $C_9H_{13}O_5$ ([M+H]$^+$): 201.0763, found: 201.0761.

*4.1.2. D-Xylal (**10**).* A solution of the acetate **9** (0.4 g, 2.0 mmol) in MeOH (10 mL) was treated with MeONa (11.0 mg, 0.2 mmol) and the reaction mixture was stirred for 4 h at room temperature. After the mixture was evaporated, the residue was purified by silica-gel column chromatography (80% EtOAc–hexane) to give **10** (0.21 g, 92% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.73 (d, J=5.6 Hz, 1H), 1.93 (d, J=4.0 Hz, 1H), 3.79–3.84 (m, 1H), 3.97 (dd, J=8.4, 4.4 Hz, 1H), 4.01–4.03 (m, 2H), 4.92 (ddd, J=6.0, 4.4, 1.6 Hz, 1H), 6.52 (d, 1.73, J=6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 64.8 (d), 65.9 (t), 68.5 (d), 101.0 (d), 146.5 (d); IR (neat): 3352, 2924, 1651, 1454, 1242, 1084, 1033, 995 cm^{-1}; MS (EI) m/z: 116 (M$^+$), 73 (100%); HRMS (EI) calcd for $C_5H_8O_3$ (M$^+$): 116.0473, found: 116.0478.

*4.1.3. (R)-3-Hydroxy-2H-pyran-4-one (**11**).* PDC (0.66 g, 1.7 mmol) was added to a solution of the diol **10** (163 mg, 1.4 mmol) in EtOAc (18 mL) and anhydrous AcOH (0.37 mL). The mixture was stirred vigorously for 16 h at room temperature and filtered through a pad of Celite, and the residue was washed with EtOAc. After evaporation of the filtrate, the residue was purified by silica-gel column chromatography (35% EtOAc–hexane) to give **11** (60.7 mg, 38%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.55 (s, 1H), 4.04 (dd, J=14.4, 10.8 Hz, 1H), 4.37 (dd, J=14.4, 6.4 Hz, 1H), 4.65 (dd, J=10.8, 6.4 Hz, 1H), 5.46 (d, J=6.0 Hz, 1H), 7.38 (d, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 67.3 (d), 71.3 (t), 103.7 (d), 164.9 (d), 193.8 (s); IR (neat): 3352, 2883, 1681, 1593, 1415, 1265, 1199, 1122, 1033, 1003, 922, 887, 848 cm^{-1}; MS (EI) m/z: 114 (M$^+$), 71 (100%); HRMS (EI) calcd for $C_5H_6O_3$ (M$^+$): 114.0317, found: 114.0314.

*4.1.4. 3-Methyl-5-(phenylthio)-4,5,7,7a-tetrahydro-2H-furo[2,3-c]pyran-2-one (**14**).* To a dry THF solution (100 mL) of **11** (1.14 g, 10 mmol) at 0 °C, was added Cs_2CO_3 (3.9 g, 12 mmol), followed by the addition of PhSH (3.08 mL, 30 mmol) under an Ar atmosphere. The reaction was monitored by thin-layer chromatography (TLC) until the starting material disappeared. After 30 min, the reaction was quenched with water and extracted with CH_2Cl_2. The solvent was evaporated under reduced pressure to give **13**. To a solution of the crude product **13** in toluene (100 mL) was added the Cu(II) catalyst **4** (210 mg, 0.5 mmol), the Wittig reagent **5a** (6.33 g, 15 mmol), molecular sieves 4 Å (5.0 g), and Oxone (9.2 g, 30 mmol). The mixture was stirred at 60 °C for 6 h under air. The resulting mixture was filtered through a pad of Celite, and the solvent was evaporated under reduced pressure. The residue was purified with column chromatography (5–15–25% EtOAc–hexane) to give **14a** (0.63 g, 24% for two steps) and **14b** (0.67 g, 26% for two steps) as colorless needles.

trans Isomer **14a**: colorless needles (EtOAc–hexane): mp 93–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.86 (s, 3H), 2.62 (d, J=12.0 Hz, 1H), 3.10–3.16 (m, 2H), 4.57–4.60 (m, 2H), 4.73 (br t, J=7.8 Hz, 1H), 7.26–7.35 (m, 3H), 7.51–7.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.5 (q), 34.0 (t), 72.0 (t), 74.9 (d), 84.7 (d), 121.7 (s), 128.3 (d), 129.1 (d), 132.39 (s), 132.44 (d), 157.4 (s), 173.8 (s); IR (KBr): 1763, 1747, 1693, 1477, 1039 cm^{-1}; MS (FAB) m/z: 263 ([M+H]$^+$); HRMS (FAB) calcd for $C_{14}H_{15}O_3S$ ([M+H]$^+$): 263.0742, found: 263.0743. The stereochemistry was determined by X-ray crystal structure analysis: CCDC 793254 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223 336 033; or deposit@ccdc.cam.ac.uk.

cis Isomer **14b**: colorless needles (EtOAc–hexane): mp 98–99 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.92 (t, J=1.8 Hz, 3H), 3.04 (dddd, J=14.4, 7.2, 1.8, 1.8 Hz, 1H), 3.15 (d, J=14.4 Hz, 1H), 3.97 (dd,

J=10.2, 10.2 Hz, 1H), 4.25 (dd, J=10.2, 6.6 Hz, 1H), 4.77 (br t, J=8.4 Hz, 1H), 5.78 (d, J=6.6 Hz, 1H), 7.26–7.33 (m, 3H), 7.40–7.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.5 (q), 33.5 (t), 64.6 (t), 75.4 (d), 84.0 (d), 123.1 (s), 127.7 (d), 129.2 (d), 131.3 (d), 133.6 (s), 155.0 (s), 174.0 (s); IR (KBr): 1747, 1691, 1224, 1039 cm^{-1}; MS (FAB) m/z: 263 ([M+H]$^+$); HRMS (FAB) calcd for $C_{14}H_{15}O_3S$ ([M+H]$^+$): 263.0742, found: 263.0743. Anal. Calcd for $C_{14}H_{14}O_3S$: C, 64.10; H, 5.38. Found: C, 64.04; H, 5.39.

*4.1.5. 7a-Bromo-3-methyl-5-(phenylthio)-4,5,7,7a-tetrahydro-2H-furo[2,3-c]pyran-2-one (**15**).* To a solution of **14b** (cis isomer) (500 mg, 1.9 mmol) in CCl_4 (380 mL) was added *N*-bromosuccinimide (388 mg, 1.25 mmol). The mixture was refluxed for 15 min, and AIBN (6.2 mg, 38 μmol) was added. Then additional *N*-bromosuccinimide (259 mg, 0.84 mmol) was carefully added. After cooling to 0 °C, the unreacted succinimide was removed by filtration, and the filtrate was evaporated under reduced pressure. The residue was purified with column chromatography (5–10% EtOAc–hexane) to give **15** (551.3 mg, 85%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.94 (d, J=1.2 Hz, 3H), 3.06 (d, J=14.4 Hz, 1H), 3.47 (dddd, J=14.4, 6.6, 3.6, 1.8 Hz, 1H), 4.25 (d, J=12.0 Hz, 1H), 4.28 (d, J=12.0 Hz, 1H), 5.85 (d, J=6.6 Hz, 1H), 7.27–7.33 (m, 3H), 7.38–7.40 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 8.6 (q), 31.6 (t), 70.7 (t), 83.9 (d), 88.0 (s), 123.7 (s), 127.8 (d), 129.3 (d), 131.1 (d), 132.9 (s), 156.0 (s), 169.7 (s); IR ($CHCl_3$): 3018, 2359, 1782, 1689, 1440, 1273, 1224, 1207, 1080, 995, 877, 788 cm^{-1}; MS (FAB) m/z: 341 (M$^+$), 343 ([M+2]$^+$); HRMS (FAB) calcd for $C_{14}H_{14}BrO_3S$ ([M+H]$^+$): 340.9847, found: 340.9847.

*4.1.6. Karrikinolide (3-methyl-2H-furo[2,3-c]pyran-2-one) (**1**)*[3]. A solution of **15** (3 mg, 8.8 μmol) and *p*TsOH–H_2O (8.3 mg, 43.9 μmol) in toluene (176 μL) was refluxed for 1 h. The mixture was cooled to room temperature, and saturated aqueous $NaHCO_3$ was added. The mixture was extracted with EtOAc, and the combined organic phase was washed with water and brine and dried over $MgSO_4$. The residue was purified with column chromatography (5–35% EtOAc–Hex) to give **1** (1.0 mg, 76%) as pale yellow needles (EtOAc–Hex): mp 118–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.93 (s, 3H), 6.51 (s, 1H), 7.32 (s, 1H), 7.44 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 7.7, 100.4, 103.5, 126.8, 139.7, 142.3, 148.0, 171.3; IR (KBr): 3088, 1737, 1668, 1616, 1556, 1313, 1286, 1228, 1114, 1074, 991, 881, 868, 810 cm^{-1}; MS (EI) m/z: 151 ([M+H]$^+$), 151 (100%); HRMS (EI) calcd for $C_8H_6O_3$ ([M+H]$^+$): 151.0395, found: 151.0398.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.11.108. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

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