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Total synthesis of (±)-gusanlung D

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Abstract

A new approach to the core structure of protoberberine alkaloid was described. Total synthesis of (±)-gusanlung D (**2**) was reported.

1. Introduction

Polycyclic nitrogen containing heterocycles form the basic skeleton of various alkaloids and physiologically active drugs.[1,2] Protoberberines are naturally occurring tetracyclic isoquinoline alkaloids. The Bischler–Napieralski process,[3] Pictet–Spengler sequence,[4] and Pomeranz–Fritsch reaction[5] were the major approaches for the synthesis of protoberberine ring system **1** (Fig. 1).[6] (−)-Gusanlung D isolated from *Acangelisia gusanlung* H.S. Lo, by Zhang et al.[7] in 1995 is the first optically active natural protoberberine alkaloid unoxygenated at ring D. A number of elegant approaches to (±)-gusanlung D (**2**) have been reported.[8–11]

Recently, we developed a new approach to isoquinolinone skeleton **4** from 2-pyridones **3** and further applied to the synthesis of oxyisoterihanine **5** (Fig. 2).[12] To extend these results, a new route to the core structure of protoberberine was investigated. In contrast to the existing synthetic approaches for **1**, ring D was built up in the last stage. Total synthesis of (±)-gusanlung D was also reported.

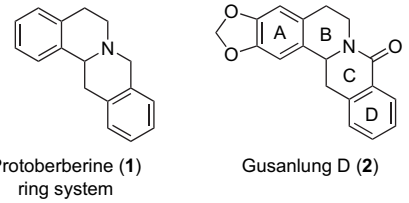

Figure 1. The core structure of protoberberine alkaloids.

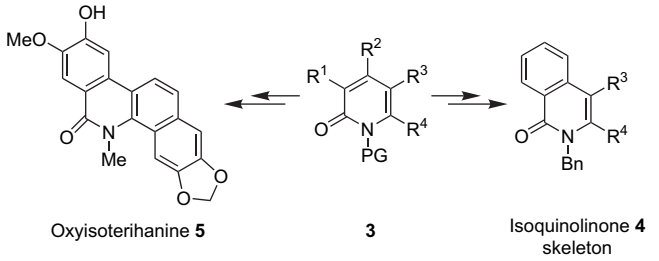

Figure 2. The application of 2-pyridones **3** to oxyisoterihanine **5** and isoquinolinone **4**.

2. Results and discussion

2.1. Retrosynthesis of (±)-gusanlung D (2)

Our strategy for the synthesis of (±)-gusanlung D (**2**) was shown in Scheme 1. The core structure of **2** was envisaged to arise from tricyclic pyridone derivative **6**. Pyridone **6** was anticipated to derive from [3+3] annulation adduct **7**.

2.2. Preparation of a key intermediate, tricyclic pyridone derivative 6

As shown in Scheme 2, glutarimide **7** was easily prepared via stepwise [3+3] annulation[13] of α-sulfonyl acetamide **8**

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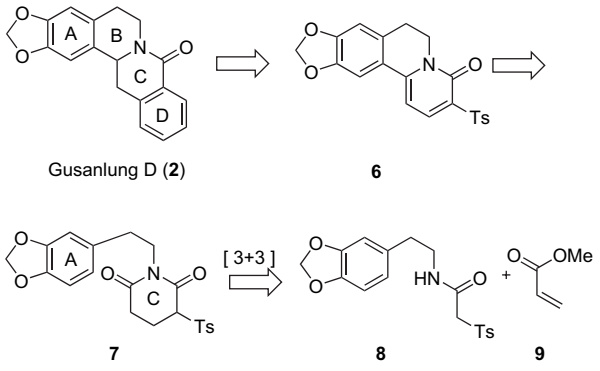
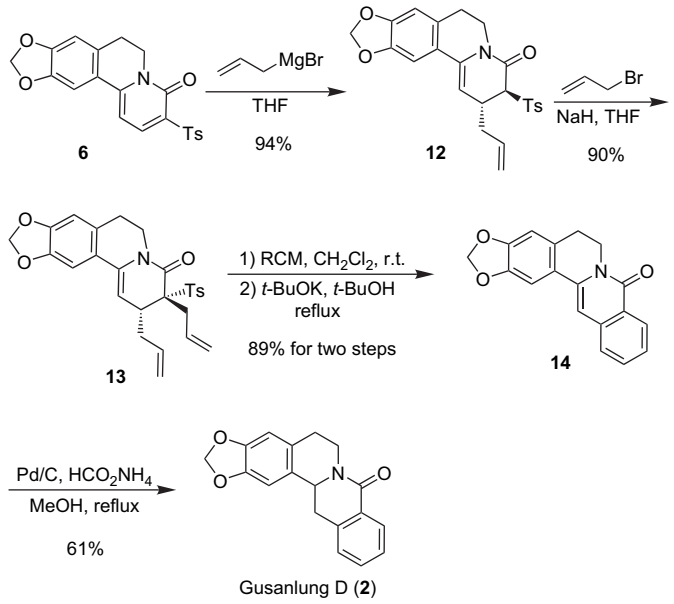


Scheme 1. Retrosynthesis of (±)-gusanlung D (**2**).

with methyl acrylate **9**. Regioselective reduction of C6 carbonyl in **7** provided hydroxylactam **10**.[14] Without purification, **10** was converted to tricyclic product **11** in the presence of $BF_3 \cdot OEt_2$. Bromination and dehydrobromination of **11** with NBS and excessive amount of sodium methoxide furnished an α,β-unsaturated lactam, which was then further oxidized with DDQ[15] to yield the corresponding tricyclic pyridone **6**.

2.3. Total synthesis of (±)-gusanlung D (2)

With the key intermediate **6** in hand, we then focused our attention on the construction of ring D in (±)-gusanlung D (**2**) (Scheme 3). Treatment of **6** with allylmagnesium bromide provided 1,4-addition adduct **12**,[16] which was further allylated with sodium hydride and allyl bromide to produce the diallyl enlactam **13**.[16] Performing RCM reaction on **13** with first generation Grubbs catalyst followed by dehydrosulfonation produced protoberberine derivative **14**. Presumably, after sequential RCM reaction and dehydrosulfonation of **13**, a spontaneous oxidation arises to form **14**. Finally, protoberberine derivative **14** was treated with HCO_2NH_4 in the presence of Pd–C in MeOH,[17] and the desired reduced adduct (±)-gusanlung D (**2**) was obtained in 61% yield. The spectral data of **2** were in agreement with those reported in the literature.[7–11]



Scheme 3. Completion of the total synthesis of (±)-gusanlung D (**2**).

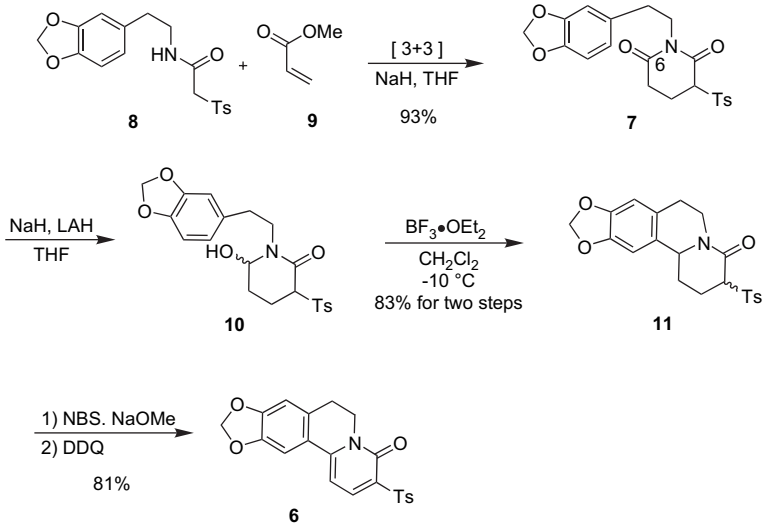
3. Conclusion

In summary, we have developed a new route to the tetracyclic protoberberine ring system. The characteristic feature of this approach is the construction of ring D at the final stage. By changing the substituents on allyl group, this process has the potential to produce protoberberine derivatives with various substituents on ring D. The application of this method to the synthesis of protoberberine alkaloids corytenchirine and ophiocarpine is currently underway in our laboratory and will be reported in future.

4. Experimental

4.1. General

Melting points were determined with melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR were recorded



Scheme 2. Synthesis of tricyclic pyridone **6**.

on Varian VRX 500 spectrometer. NMR spectra were recorded in $CDCl_3$ (^1H at 500 MHz and ^{13}C at 125 MHz), and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si.

Tetrahydrofuran was distilled prior to use. All other reagents and solvents were obtained from commercial sources and were used without any further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Solutions of products in organic solvents were dried with anhydrous magnesium sulfate before concentration under vacuum.

4.2. Preparation of a key intermediate, tricyclic pyridone derivative **6**

4.2.1. 1-(2-Benzo[1,3]dioxol-5-yl-ethyl)-3-(4-toluenesulfonyl)piperidine-2,6-dione (**7**)

A solution of α-toluenesulfonyl acetamide **8** (5.0 g, 13.8 mmol) in dry THF (100 mL) was added to a rapidly stirred suspension of sodium hydride (1.7 g, 41.4 mmol, 60%) in dry THF (20 mL). After the reaction mixture was stirred at room temperature for 30 min, a solution of α,β-unsaturated ester **9** (1.3 g, 15.2 mmol) in dry THF (80 mL) was slowly added over 4 h. The resulting mixture was stirred for another 4 h, quenched with saturated ammonium chloride solution (25 mL) in an ice bath, and concentrated under reduced pressure. The residue was diluted with water (25 mL) and extracted with ethyl acetate (3×70 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Purification on silica gel (*n*-hexane/ethyl acetate=4:1−2:1) produced glutarimide **7** (5.35 g, 93%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J=8.0 Hz, 2H), 7.40 (d, J=8.0 Hz, 2H), 6.73−6.72 (m, 1H), 6.71 (s, 1H), 6.66−6.64 (m, 1H), 5.92 (s, 2H), 4.08 (t, J=4.0 Hz, 1H), 3.95 (t, J=7.0 Hz, 2H), 3.24−3.17 (m, 1H), 2.79−2.69 (m, 4H), 2.48 (s, 3H), 2.34−2.27 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 164.8, 147.6, 146.1, 145.8, 134.9, 131.9, 129.9 (2C), 129.0 (2C), 121.8, 109.4, 108.2, 100.8, 65.6, 41.6, 33.4, 29.2, 21.8, 17.8; IR ($CHCl_3$, cm^{-1}): 1728, 1677; HRMS (ESI, M^++1) calcd for $C_{21}H_{22}NO_6S$ 416.1168, found 416.1166.

4.2.2. 3-(4-Toluenesulfonyl)-1,2,3,6,7,12b-hexahydro-[1,3]-dioxolo[4,5-g]pyrido[2,1-a]isoquinolin-4-one (**11**)

A solution of glutarimides **7** (1.5 g, 3.6 mmol) in dry THF (60 mL) was added to a rapidly stirred suspension of sodium hydride (220 mg, 5.4 mmol, 60%) in dry THF (10 mL). After the reaction mixture was stirred at room temperature for 15 min, lithium aluminum hydride (160 mg, 4.0 mmol) was slowly added in an ice bath. After the reaction mixture was stirred for 2 h, quenched with saturated ammonium chloride solution (10 mL) at the same temperature, filtered and then concentrated under reduced pressure. The residue was diluted with water (40 mL) and extracted with ethyl acetate (3×60 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Without purification, a solution of above crude product in dry dichloromethane (20 mL) was treated with $BF_3\cdot OEt_2$ (0.5 mL, 3.6 mmol) at −10 °C. After 15 h, the resulting mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with dichloromethane (2×20 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Purification on silica gel (*n*-hexane/ethyl acetate=2:1−1:1) produced **11** (1.2 g, 83% for two steps), which was recrystallized from *n*-hexane/ethyl acetate as a white solid. ^1H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, J=8.5 Hz, 2H), 7.35 (d, J=8.5 Hz, 2H), 6.64 (s, 1H), 6.56 (s, 1H), 5.92 (s, 2H), 4.68 (dd, J=4.0, 10.5 Hz, 1H), 4.61 (dt, J=4.0, 12.5 Hz, 1H), 4.04 (t, J=8.5 Hz, 1H), 2.90−2.85 (m, 1H), 2.78−2.72 (m, 1H), 2.65−2.49 (m, 4H), 2.44 (s, 3H), 1.74−1.66 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5, 146.6, 146.5, 144.6, 136.7, 129.4 (2C), 129.1 (2C), 129.0, 128.2, 108.6, 105.0, 101.1, 65.5, 56.5, 40.5, 29.3, 28.6, 21.7, 19.9; IR ($CHCl_3$, cm^{-1}): 1632; HRMS (ESI) calcd for $C_{21}H_{22}NO_5S$ (M^++1) 400.1219, found 400.1220; mp: 89.4−91.3 °C.

4.2.3. 3-(4-Toluenesulfonyl)-6,7-dihydro[1,3]dioxolo[4,5-g]-pyrido[2,1-a]isoquinolin-4-one (**6**)

To a solution of **11** (1.2 g, 3.0 mmol) in CH_3CN (30 mL) was added sequentially sodium methoxide (340 mg, 6.3 mmol) and *N*-bromosuccinimide (590 mg, 3.3 mmol). The resulting mixture was stirred for 6 h at that temperature. The reaction mixture was filtered and the organic solvents were removed under reduced pressure. The residue was diluted with water (30 mL) and extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Without further purification, the solution of the residue in toluene (40 mL) was added DDQ (1.0 g, 4.5 mmol). The resulting mixture was refluxed for 1 day. After removal of the precipitates by filtration, a large amount of 5% NaOH was added to the filtrate and the mixture was extracted with dichloromethane (3×50 mL). The combined organic layers were washed with 5% NaOH, dried over anhydrous $MgSO_4$, filtered, and evaporated. Purification on silica gel (dichloromethane/methanol=200:1−100:1) produced pyridone derivative **6** (960 mg, 81% for two steps) as a yellow solid. ^1H NMR (500 MHz, $CDCl_3$): δ 8.38 (d, J=8.0 Hz, 1H), 8.02 (d, J=8.0 Hz, 2H), 7.31 (d, J=8.0 Hz, 2H), 7.17 (s, 1H), 6.72 (s, 1H), 6.63 (d, J=8.0 Hz, 1H), 6.05 (s, 2H), 4.18 (t, J=6.5 Hz, 2H), 2.84 (t, J=6.5 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.1, 150.9, 149.5, 147.8, 144.0, 141.6, 137.1, 132.1, 129.2 (2C), 129.0 (2C), 126.4, 121.6, 108.1, 105.8, 102.0, 100.7, 39.2, 27.5, 21.6; IR ($CHCl_3$, cm^{-1}): 1656; HRMS (ESI) calcd for $C_{21}H_{18}NO_5S$ (M^++1) 396.0906, found 396.0907; mp: 181.1−182.8 °C. Anal. Calcd for $C_{21}H_{17}NO_5S$: C, 63.79; H, 4.33; N, 3.54. Found: C, 63.78; H, 4.24; N, 3.61.

4.3. Total synthesis of (±)-gusanlung D (**2**)

4.3.1. 2-Allyl-3-(4-toluenesulfonyl)-2,3,6,7-tetrahydro-[1,3]-dioxolo[4,5-g]pyrido[2,1-a]isoquinolin-4-one (**12**)

To a solution of **6** (560 mg, 1.4 mmol) in dry THF (15 mL) was added allylmagnesium bromide (2.8 mmol) in one portion

by syringe. The resulting mixture was stirred at room temperature for 1.5 h. After the reaction was accomplished (monitored by TLC), the reaction mixture was quenched with water (15 mL) and filtered through Celite. The mixture was extracted with ethyl acetate (3×20 mL) and dried with anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel chromatography (*n*-hexane/ethyl acetate=4:1–2:1) produced **12** (582 mg, 94%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, J=8.0 Hz, 2H), 7.18 (d, J=8.0 Hz, 2H), 6.79 (s, 1H), 6.53 (s, 1H), 5.95 (d, J=8.5 Hz, 2H), 5.74–5.66 (m, 1H), 5.45 (d, J=7.0 Hz, 1H), 5.13–5.07 (m, 2H), 4.04–4.00 (m, 2H), 3.57–3.51 (m, 1H), 3.39 (m, 1H), 2.65–2.60 (m, 2H), 2.34–2.30 (m, 1H), 2.30 (s, 3H), 2.14–2.08 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.4, 147.9, 146.9, 145.1, 135.4, 134.1, 133.3, 129.3 (2C), 129.0 (2C), 128.6, 122.8, 119.1, 107.6, 104.3, 101.9, 101.2, 70.3, 39.2, 38.3, 31.9, 28.6, 21.5; IR ($CHCl_3$, cm^{-1}): 1645; HRMS (ESI) calcd for $C_{24}H_{24}NO_5S$ (M^++1) 438.1375, found 438.1376.

4.3.2. 2,3-Diallyl-3-(4-toluenesulfonyl)-2,3,6,7-tetrahydro-[1,3]dioxolo[4,5-g]pyrido[2,1-a]isoquinolin-4-one (*13*)

A solution of **12** (581 mg, 1.3 mmol) in dry THF (15 mL) was added to a rapidly stirred suspension of sodium hydride (100 mg, 2.7 mmol, 60%) in dry THF (5 mL). After the reaction mixture was stirred at room temperature for 15 min, allyl bromide (0.23 mL, 2.7 mmol) was added. The resulting mixture was stirred for 12 h, quenched with water (3 mL), and concentrated under reduced pressure. The residue was diluted with water (10 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Purification on silica gel (*n*-hexane/ethyl acetate=4:1–2:1) produced **13** (570 mg, 90%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, J=8.0 Hz, 2H), 7.14 (d, J=8.0 Hz, 2H), 6.80 (s, 1H), 6.53 (s, 1H), 5.94 (d, J=6.0 Hz, 2H), 5.78–5.70 (m, 1H), 5.66–5.57 (m, 1H), 5.42 (d, J=3.5 Hz, 1H), 5.27–5.22 (m, 2H), 5.19–5.14 (m, 2H), 4.07–4.03 (m, 1H), 3.55–3.50 (m, 1H), 3.35 (dd, J=5.0, 14.0 Hz, 1H), 3.12–3.08 (m, 1H), 2.86–2.77 (m, 3H), 2.73–2.62 (m, 2H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.5, 147.7, 146.8, 144.8, 136.1, 135.8, 133.2, 131.9, 129.7 (2C), 129.1 (2C), 128.1, 122.9, 120.5, 117.7, 107.6, 104.3, 104.1, 101.2, 73.3, 39.9, 36.0, 34.1, 32.3, 28.6, 21.5; IR ($CHCl_3$, cm^{-1}): 1647; HRMS (ESI) calcd for $C_{27}H_{28}NO_5S$ (M^++1) 478.1689, found 478.1687.

4.3.3. 5,6-Dihydro[1,3]dioxolo[4,5-g]isoquino[3,2-a]-isoquinolin-8-one (*14*)

Diallyl compound **13** (360 mg, 0.75 mmol) in dry dichloromethane (50 mL) was added to 1st generation Grubbs catalyst $[(C_6H_{11})_3P]_2Cl_2RuC_2H_3Ph$ (62 mg, 0.075 mmol, 10 mol %), and the mixture was allowed to react for 12 h at room temperature. After the reaction was finished (monitored by TLC), the mixture was quenched with water (20 mL) and extracted with dichloromethane (2×30 mL) and dried with anhydrous $MgSO_4$, filtered, and concentrated. To the solution of the residue in *t*-BuOH (25 mL) was added *t*-BuOK (130 mg, 1.1 mmol) and then heated to reflux for 24 h. The organic solvent was evaporated under reduced pressure and the residue was extracted with water (15 mL) and ethyl acetate (3×20 mL). The combined organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel chromatography (*n*-hexane/ethyl acetate=4:1–2:1) to afford protoberberine derivative **14** (194 mg, 89% for two steps) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.42 (d, J=8.0 Hz, 1H), 7.63 (t, J=7.0 Hz, 1H), 7.55 (d, J=8.0 Hz, 1H), 7.44 (t, J=7.0 Hz, 1H), 7.27 (s, 1H), 6.85 (s, 1H), 6.73 (s, 1H), 6.03 (s, 2H), 4.35 (t, J=6.0 Hz, 2H), 2.92 (t, J=6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.1, 148.7, 147.4, 137.4, 136.7, 132.3, 130.3, 127.9, 126.3, 126.0, 124.6, 123.7, 108.0, 105.1, 101.9, 101.5, 39.7, 28.6; IR ($CHCl_3$, cm^{-1}): 1650; HRMS (ESI) calcd for $C_{18}H_{14}NO_3$ (M^++1) 292.0974, found 292.0973; mp: 183.1–184.5 °C. Anal. Calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found: C, 74.21; H, 4.54; N, 4.72.

4.3.4. 5,6,13,13a-Tetrahydro[1,3]dioxolo[4,5-g]isoquino-[3,2-a]isoquinolin-8-one (*2*)

A suspension of **14** (194 mg, 0.67 mmol) and Pd–C (10%, 10 mg) in methanol (20 mL) was vigorously stirred and a solution of HCO_2NH_4 (423 mg, 6.7 mmol) in distilled water (3 mL) was slowly added. The reaction mixture was refluxed for 5 h with stirring and then filtered on Celite. Water (20 mL) was added and the mixture extracted with dichloromethane (3×30 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. Purification on silica gel (*n*-hexane/ethyl acetate=4:1–2:1) gave gusanlung D (**2**) (119 mg, 61%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, J=8.0 Hz, 1H), 7.34–7.45 (m, 2H), 7.25 (d, J=8.0 Hz, 1H), 6.73 (s, 1H), 6.67 (s, 1H), 6.03 (s, 2H), 4.95–5.01 (m, 1H), 4.82–4.90 (m, 1H), 3.08–3.15 (m, 1H), 2.91–2.99 (m, 3H), 2.84–2.89 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.2, 146.7, 146.5, 137.2, 131.8, 129.0, 128.8, 128.6, 128.5, 127.3, 126.8, 108.6, 105.8, 101.1, 55.3, 38.7, 38.2, 29.6; IR ($CHCl_3$, cm^{-1}): 1640; HRMS (ESI) calcd for $C_{18}H_{16}NO_3$ (M^++1) 294.1131, found 294.1129; mp: 175.9–177.6 °C.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.01.119.

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