Synthetic studies directed towards (–)-Chrysanthone A: Facile synthesis of a tricyclic lactone intermediate

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(–)-Chrysanthones A is a novel keto-ol compound belong to one relatively small but interesting class of natural products exhibiting many different potent and notable bioactivities like high antiangiogenic and anti-tumoral activity. Here, we have reported the synthetic studies directed for the synthesis of (–)-Chrysanthone A through the high yielding, step economic facile synthesis of appropriate tricyclic lactone derivative.

Keywords: Chrysanthone A, isoquinolines, natural product, organic synthesis, lactone.

Introduction

Around 1990, the benzoisoquinoline alkaloid (–)-Chrysanthone A (**1**) and the benzoisochromene compounds Chrysanthones B (**2**) and C (**3**) were isolated from *Ascochyta chrysanthemi*, the agent of the so-called ray blight disease of chrysanthemum species[1–4]. The structures and absolute configuration of these secondary metabolites were determined by X-ray crystallography, NMR spectroscopy, and chemical correlations. In contrast, the stereochemistry of the C-3 center in compound **3** could not be determined by NMR and NOEs spectroscopy most likely due to rapid equilibrium between the open (keto) and the closed (acetalic) form.

One may see the similarity of (–)-Chrysanthone A (**1**) with the 2-aza-anthraquinones **4** and **5** (Fig. 1). Although anthraquinones represent a large class of natural products, their aza-analogues are rarely found in nature; so far, only Bostrycoidin (**4**)[5] and its 6-*O*-methyl derivative **5**[6] have been isolated. Bostrycoidin (**4**) has been isolated from *Fusarium bostrycoides* and *F. solani*, it shown to possess antibiotic activity against the tubercle bacillus *in vitro*. Alike to (–)-Chrysanthone A (**1**), another natural product (–)-Heliophenanthrone (**6**) (Fig. 1) was isolated from aerial part of the herbaceous plant *Heliotropium ovalifolium* in 2003[7]. (–)-Chrysanthone A (**1**) and (–)-Heliophenanthrone (**6**) closely resemble each other because of the presence of a sensitive
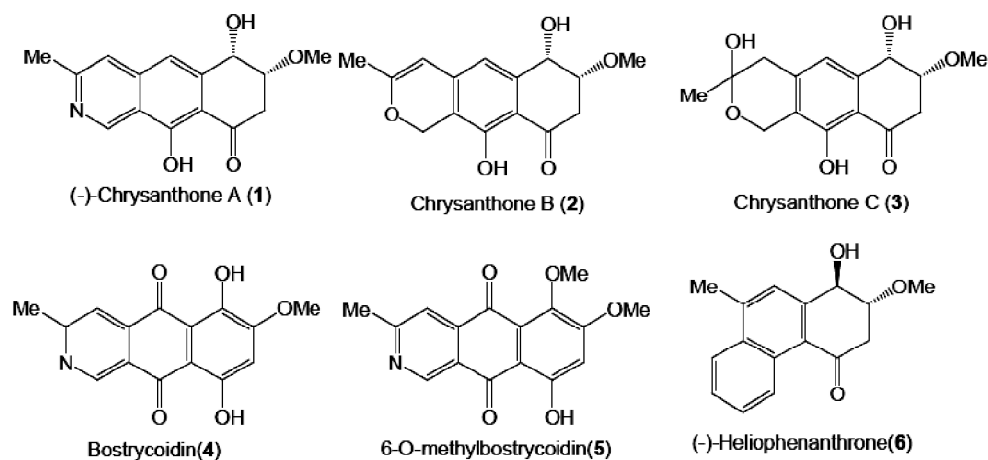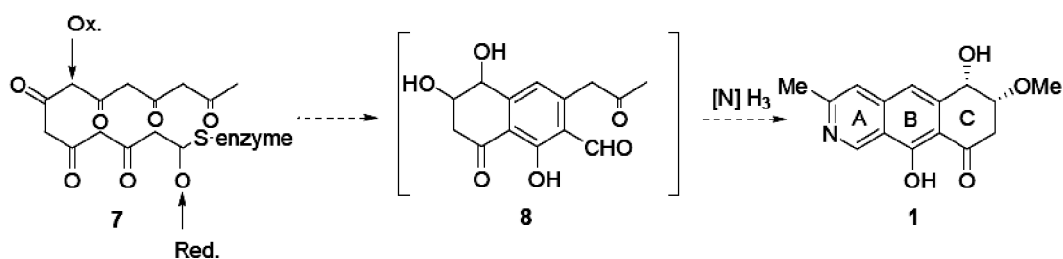

Fig. 1

monomethyl ether protected keto-diol motif. Recently, Dyker and Hildebrandt[8] have reported a racemic synthesis of Heliophenanthrone (6) using a transition metal mediated domino reaction in the key step of their synthesis.

From a biogenetic point of view, it is interesting to observe that (–)-Chrysanthone A (1) is a member of the fusarubin-javanacin family[9] however ring C is in reduced form. The acid or its biological equivalent 7, derived by the acetate-mevalonate pathway, may undergo stepwise reduction to yield the intermediate aldehyde 8 and successively (–)-Chrysanthone A (1) (Scheme 1).

Results and discussion

One may look upon (–)-Chrysanthone A (1) as a molecule containing two biologically significant fragments such as 9 and 10 juxtaposed on one another (Fig. 2). Although there are many methodologies for the construction of various isoquinoline motifs[11], the approach to 8-hydroxy-isoquinoline moiety (cf. 9) is infrequent. Recently, we have developed an LDA mediated tandem Michael-Dickman-Peterson approach for the synthesis of 5-hydroxyquinolines and 8-hydroxyisoquinolines using azaphthalides and vinyl silane derivatives[12]. The other fragment, that is 3,4,8-trihy-droxy-1-tetralone 10 itself and various congeners thereof are

Scheme 1. Biogenetic synthesis.

Chrysanthones A, B, and C were tested for their cytotoxicity properties on endothelial cells (EC) and two different tumor cell lines and for their ability to inhibit EC migration. Structure-function relationship considerations suggest that the methyl-isoquinolinic moiety is vital for the cytotoxic activity, whereas the methyl-isochromene moiety confers an endothelial selectivity to the structures. In general, compared to the activity of known anti-proliferative and anti-angiogenic compounds, Chrysanthones showed weaker activities. Although not active as known reference compounds, it is believed that Chrysanthone structures may serve as leads for the synthesis of new derivatives with potential antiangiogenic and anti-tumoral activity.

This consideration prompted us to undertake a comprehensive synthetic program in this area and, as a first target, (–)-Chrysanthone A (1) was selected. The delights and difficulties of this work are presented in details in the following sections. Surprisingly, no synthetic studies on Chrysanthone A (1) have appeared in the literature till date, although synthesis of the structurally similar Bostrycoidin (4) has been reported in the year of 1999[10].

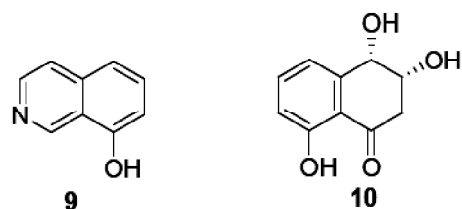themselves naturally occurring biomolecules displaying interesting biological profile[13–15].

Fig. 2

Recently, Sarkar et al. successfully developed a methodology for the preparation of cis-dihydroarenediols via a Barrett asymmetric allylation[16] and ring closing metathesis reaction[17] and they converted it into the corresponding keto-diols using completely regioselective bay-region Wacker oxidation of internal cyclic olefins[18]. Later they have developed a strategy for the synthesis of stereochemically diverse monomethyl ether protected keto-diol compounds. The heteroatom directed Wacker oxidation is the key step for the synthesis of aforemention compounds. They also used their strategy for the asymmetric synthesis of monomethyl keto-diol natural product (–)-Heliophenanthrone (6)[19]. It was found

that they have generally employ lactones a suitable precursor for the synthesis of vinyl aldehyde derivatives, which were necessary intermediates for the synthesis of both the *cis*-dihydroarenediols and monomethyl keto-ols. The vinyl aldehydes were prepared through selective reduction of lactones to lactols using DIBAL-H mediated reduction and followed by Wittig olefination of that prepared lactols. This strategy believes to be applicable for the synthesis of (–)-Chrysanthone A (1) from tricyclic lactone 13.

Thus with a view to synthesizing (–)-Chrysanthone A (1), we therefore, chalked out our *retro*-synthetic analysis as presented in Scheme 2. We envisaged that conversion of aldehyde 14 into *syn*-alkoxyhomoallyl alcohol 15 can easily be achieved in a single step using Brown's protocol[20]. It will then involve in a three-step sequence namely the conversion of *syn*-diastereoisomer 15 to the anti-diastereoisomer 16, ring closing metathesis (RCM, 16 → 17) followed by Wacker oxidation to furnish the requisite motif for (–)-Chrysanthone A (1).

nulation and *in situ* Peterson olefination. Therefore our initial objectives are to the synthesis of tricyclic lactone 13 and then it will be used for the synthesis of (–)-Chrysanthone (1).

Basically, we envisaged a tandem Sammes-type annulation[21] of 20 with the silylated γ-crotonolactone 19 and *in situ* Peterson olefination of the product to yield 21 in one-pot. Since 2,6-dichloropyridine is user-friendly due to lesser basicity/nucleophilicity compared to pyridine itself[20]. Thus, we reframed our approach to tricyclic lactone 22 from azaphthalide 20 with the hope of introducing the lone methyl group on the pyridine nucleus {*cf.* (–)-Chrysanthone A (1)} by a regioselective displacement with a dimethylcuprate reagent (Me$_2$CuLi) followed by reductive elimination of the other chloro group at some suitable stage of the synthetic sequence. Therefore, as mentioned before (Scheme 2), our approach to tricyclic lactone 22 is summarized by disconnective analysis shown in Scheme 3.

Since azaphthalide 20 was already prepared previously from our laboratory, we then focused our attention to the syn-
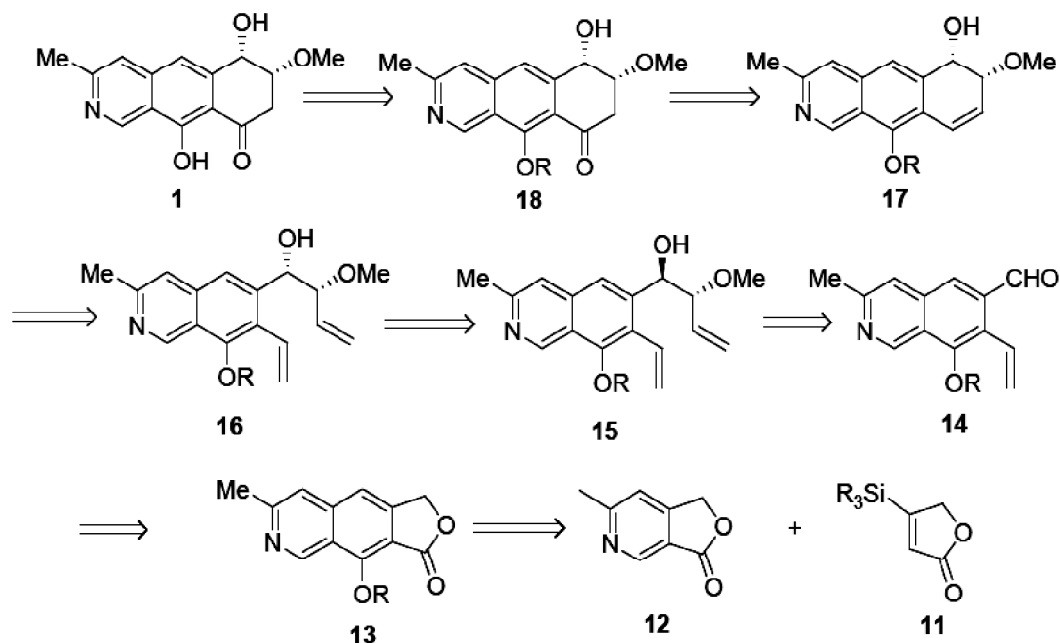
Scheme 2. Retrosynthetic pathway for the compound 1.

The unsaturated aldehyde 14 will be available from phthalide 13 by three-step sequences involving DIBAL-H reduction, Wittig olefination, and oxidation. The compound 13 may be obtainable from 12 and 11 via Sammes-type an-

thesis of silylated γ-crotonolactone 19 and the later is required for the synthesis of the isoquinoline lactone 21 which upon methylation will afford lactone 22. In this context, our strategy for the preparation of the silylated γ-crotonolactone
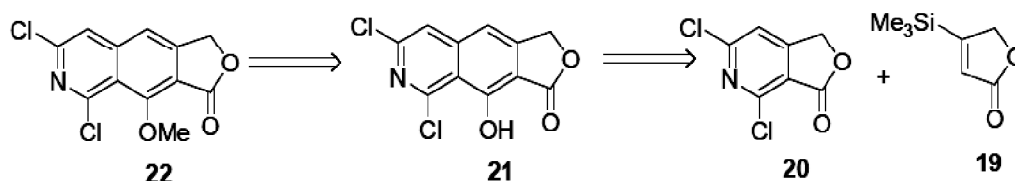
Scheme 3. Retrosynthetic pathway for the compound **22**.
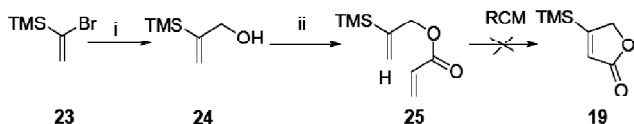
Scheme 4. Attempt to synthesis of compound **19**. *Reagents and conditions*: (i) Mg/THF, 70°C, 2.5 h; (HCHO)$_n$, 55–60°C, 6 h, 62%; (ii) acrolyl chloride, Et$_3$N, CH$_2$Cl$_2$, 70%; (iii) Grubbs' catalyst (1st and 2nd generation).

19 is depicted in Scheme 4.

α-Bromovinyl trimethylsilane (**23**) was conveniently converted to the corresponding Grignard reagent, and the addition of paraformaldehyde provided the alcohol **24** in 62% yield[23]. The alcohol **24** was then treated with acryloyl chloride, Et$_3$N, DMAP (cat.) in CH$_2$Cl$_2$ to furnish **25** in good yield. We found that the RCM of **25** using standard conditions, 5–10 mol% of Grubbs I catalyst in CH$_2$Cl$_2$ did not give the desired silylated γ-crotonolactone **19** even after 48 h of reflux. Next, we tried to initiate the reaction using 15 mol% Grubbs I catalyst and then added a further 5 mol% catalyst after 24 h. Even this condition failed after a total of 48 h of heating at reflux in CH$_2$Cl$_2$. The diene **25**, even, on treatment with Grubbs II catalyst following the similar procedure, mainly gave back the starting material.

In view of these difficulties, we used the commercially available lactone **26** to explore the crucial annulation reaction with aza-phthalide **20**. Exposure of **20** to LDA in THF at –60°C produced the lithiated derivative (deep orange colour)

which was treated with **26**. After overnight stirring at ambient temperature indicate the formation of Michael addition product **27** and **28** an inseparable mixture having without formation of the expected Michael-Dickman product even in trace (Scheme 5). It is not clear to us that why Dickman cyclization reaction did not occur in this case.

To overcome the above difficulties, we altered the strategy and the *retro*-synthetic analysis of the new approach that was adopted by us is shown in the following Scheme 6.

As per the above scheme, lactone **22** may available by DIBAL-H mediated selective reduction of ester **29**. Compound **29** will be obtainable via diazomethane mediated methylation of 8-hydroxy isoquinoline derivatives **30**. Compound **30** is to be prepared by oxidation of **31** using 2,3-dicyano-5,6-dichloro-parabenzoquinone (DDQ). On the other hand, compound **31** may be available from **32** and **33** via tandem Micheal-Dickmann cyclization reaction in the presence of LDA.

Now for the commencement of the synthesis, compound **32** was first lithiated with LDA in THF at –78°C and when a deep burgundy colour was formed dimethyl maleate was added to it. After completion of reaction, it provides **31** in good yield (84%). Treatment of **31** with DDQ in benzene under refluxing condition led to an inseparable mixture of **30** admixed with starting material **31** and quinol derivatives generated from DDQ (Scheme 7).
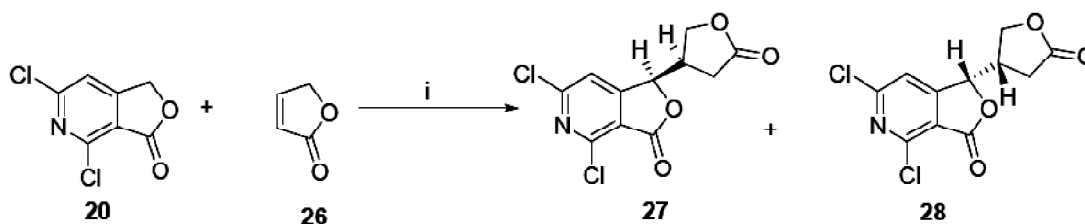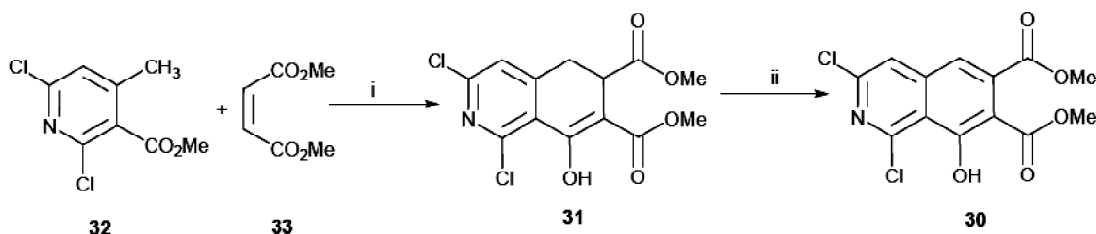

Scheme 5. Reaction of lactone **20** with lactone **26**. *Reagents and conditions*: (i) LDA, –60°C, → r.t, 12 h, 78%.
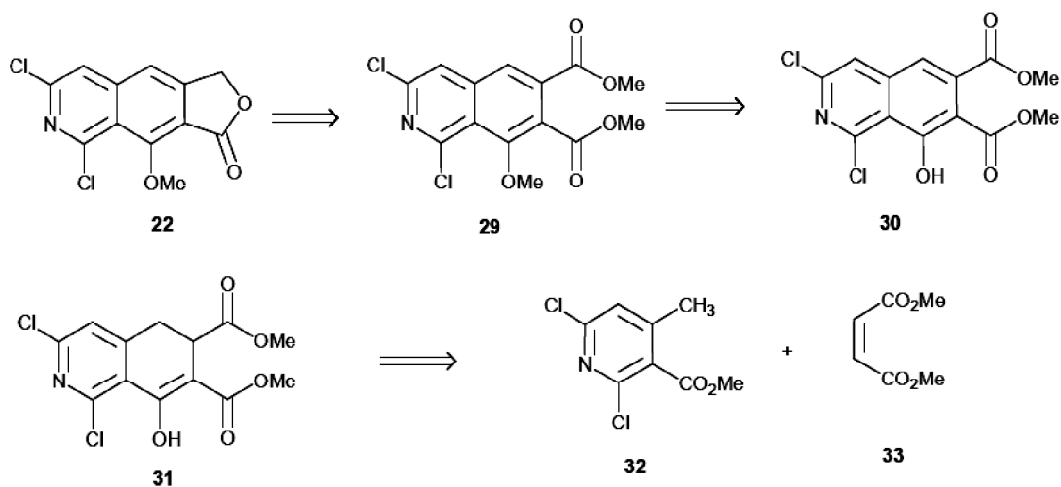
Scheme 6. Revised retrosynthetic pathway for the compound **22**.

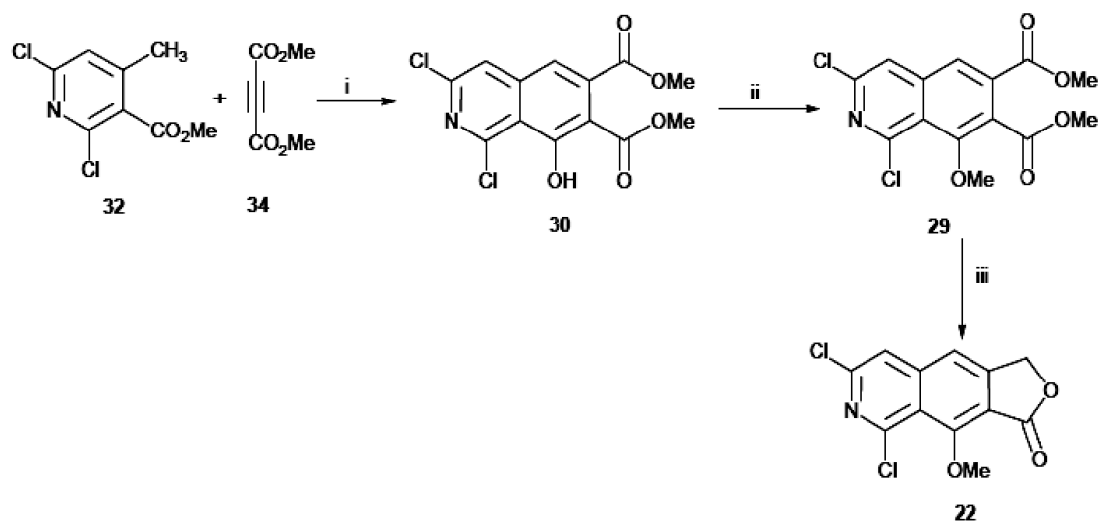**Scheme 7.** Synthetic pathway for the compound **30**. *Reagents and conditions*: (i) LDA, THF, –78°C, 45 min, then **33**, THF, –78°C → r.t, 12 h, 84%; (ii) DDQ, benzene, reflux, 3 h.

Now to conquer the difficulties for the synthesis of phenolic compound **30**, we turned to the alternate synthetic route shown in Scheme 8, using dimethyl but-2-ynedioate **34** instead of **33** and this modification will avoid DDQ oxidation step. Now as expected, the reaction of compound **32** with **34** in presence of strong base LDA at –78°C gives **30** in 81% isolated yield. It was found that the yield of this reaction is very sensitive to the reaction conditions; as the solvent should be anhydrous diethyl ether instead of tetrahydrofuran and quick addition of **34** instead of slow addition provide the desired product in best yield. Probably decreasing the solvent polarity from THF to Et$_2$O, product **30** was precipitated from the reaction media. Similarly, the quick addition may reduce the side-product formation via decomposition of product **30** in highly basic medium. Expectedly, compound **30** was methylated using the ethereal solution of diazomethane to afford compound **29** in excellent yield. The DIBAL-H reduction

of methyl ether **29** yielded tricyclic lactone **22** as a white solid in 92% isolated yield.

After successful synthesis of dichlorotricyclic lactone **22**, our next goal was to the synthesis of required methylchloro tricyclic lactone **35** for the synthesis of (–)-Chrysanthone A (**1**). The LDA mediated reaction of methyl ester **36** with **34** at –78°C offers the desired phenolic compound **37** in 78% yield. This compound was methylated using the ethereal solution of diazomethane which gave compound **38** in 96% yield. Now the DIBAL-H reduction of diester **38** at –78°C provides the desired tricyclic lactone **35**. Thus we have successfully synthesized the required tricyclic lactone in 69% overall yields in three steps. Currently, the synthesis of (–)-Chrysanthone A (**1**) is underway in our laboratory using prepared tricyclic lactone **35** and this work will be published elsewhere in future.

Scheme 8. Synthetic pathway for the compound **22**. *Reagents and conditions*: (i) LDA, Et$_2$O, −78°C, 20 min, then **34**, −78°C (5 min), −78°C to rt, 1 h, 81%; (ii) CH$_2$N$_2$, Et$_2$O, 0°C, overnight, rt, 96%; (iii) DIBAL-H, CH$_2$Cl$_2$, −78°C, 1 h, 92%.
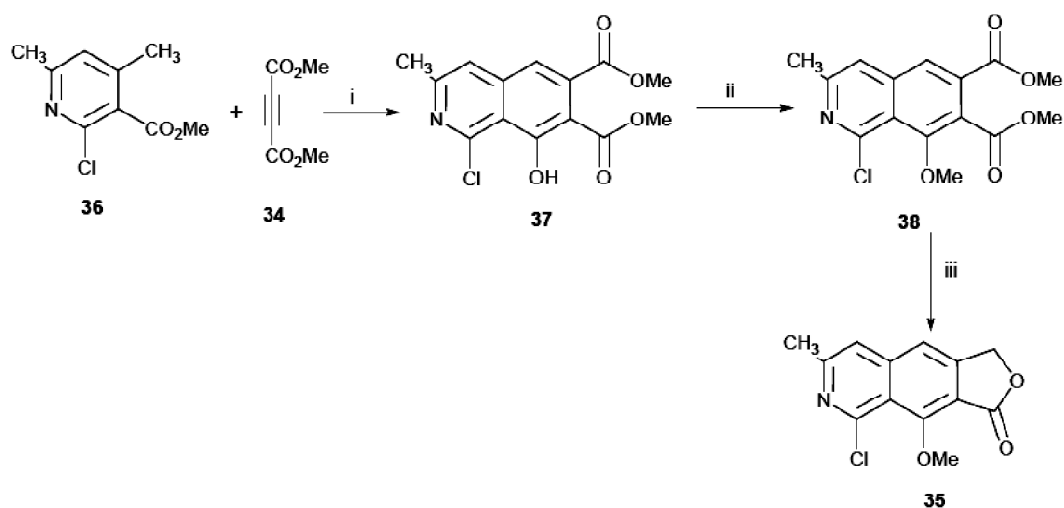
Scheme 9. Synthetic pathway for the compound **35**. *Reagents and conditions*: (i) LDA, Et$_2$O, −78°C, 20 min, then **34**, −78°C (5 min), − 78°C to rt, 1 h, 78%; (ii) CH$_2$N$_2$, Et$_2$O, 0°C, overnight, rt, 96%; (iii) DIBAL-H, CH$_2$Cl$_2$, −78°C, 1 h, 93%.

Experimental

All melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature at 400 and 200 MHz and 100 and 50 MHz, respectively. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Unless otherwise noted, all reactions were carried out under an inert atmo-

sphere in flame-dried flasks. All reagents were commercially obtained and, where appropriate, purified before use unless specified otherwise. Solvents were dried as follows: THF, toluene, and Et$_2$O from sodium benzophenone ketyl; CH$_2$Cl$_2$ from P$_2$O$_5$ and Et$_3$N from solid KOH. After drying, organic extracts were evaporated under reduced pressure and the residue was chromatographed on silica gel (Rankem, 230–400 mesh) using EtOAc, petroleum ether (60–80°C) mixture as eluent. TLC was recorded using precoated plate (Merck, silica gel 60 F254).

Dimethyl 1-chloro-8-hydroxy-3-methylisoquinoline-6,7-dicarboxylate (37):

A solution of n-butyllithium (1.6 *M*, 2.6 ml, 4.2 mmol) and diisopropylamine (590 mg, 4.2 mmol) in dry ether (20 ml) was stirred under a nitrogen atmosphere at 0°C for 15 min. The resulting solution was cooled to –78°C, followed by addition of 30 ml of a diethyl ether solution of **36** (1 g, 5 mmol). The reaction mixture was stirred for 20 min. Dimethyl but-2-ynedioate **34** (0.71 mg, 5 mmol) dissolved in diethyl ether (10 ml) was added dropwise over a 5 min period. The reaction mixture was warmed slowly to room temperature and then quenched by the addition of a saturated aqueous ammonium chloride solution (30 ml). The organic layer was separated and the aqueous layer was extracted with ether (40 ml, 3 times). The combined organic layers were washed with aqueous brine (80 ml) and then dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel to afford the product **37**, 1.21 g (78%).

M.p. 154–155°C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 12.81 (s, 1H), 7.33 (s, 1H), 7.23 (s, 1H), 3.97 (s, 3H), 3.93 (s, 3H), 2.66 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.9, 168.5, 162.4, 155.3, 149.5, 142.9, 135.8, 119.1, 117.2, 116.7, 105.4, 53.3, 52.9, 50.2; HRMS (FAB-TOF) *m/z* for C$_{14}$H$_{13}$ClNO$_5$ (M+H)$^+$ Calcd. 310.0482, Found 310.0481.

Dimethyl 1-chloro-8-methoxy-3-methylisoquinoline-6,7-dicarboxylate (38):

Diazomethane solution prepared from *N*-nitroso *N*-methyl urea (2.36 g, 22.9 mmol) and 40% aqueous KOH in diethyl ether was added to **37** (620 mg, 2 mmol) at 0°C. After vigorous hand stirring, the ice bath was removed and the reaction mixture was left at room temperature for overnight. Diethyl ether was removed under reduced pressure and the residue was flash chromatographed on silica gel to yield a white solid **38** in 622 mg (96%).

M.p. 142–143°C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.22 (s, 1H), 7.50 (s, 1H), 4.00 (s, 3H), 3.98 (s, 3H), 3.96 (s, 3H), 2.68 (s, 3H); HRMS (FAB-TOF) *m/z* for C$_{15}$H$_{15}$ClNO$_5$ (M+H)$^+$ Calcd. 324.0639, Found 324.0642.

5-Chloro-4-methoxy-7-methyl-1H-furo[3,4-g]isoquinolin-3-one (35):

To a stirred solution of **38** (3.67 g, 11.36 mmol) in 100 ml of dry toluene cooled to –78°C has added 24 mL of DIBAL-H

(1.0 *M* solution in toluene) dropwise under argon atmosphere. The resulting mixture was stirred for 1 h at the same temperature and then allowed to warm to room temperature over 2 h. It was then cooled to 0°C and quenched with saturated aqueous NH$_4$Cl solution. This mixture was stirred for one hour at 0°C and then acidified with 1 (*M*) HCl. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic fractions were washed with saturated aqueous solution of NaHCO$_3$ and brine. The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography (silica gel, EtOAc:petroleum ether, 1:9) to give tricyclic lactone **35** as a white crystalline solid (2.78, 93% yield).

M.p. 164–166°C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.47 (s, 1H), 7.43 (s, 1H), 5.40 (s, 2H), 4.32 (s, 3H), 2.69 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 167.4, 159.6, 153.7, 149.4, 146.9, 144.4, 119.7, 118.7, 114.7, 114.2, 68.3, 64.4, 23.7; HRMS (FAB-TOF) *m/z* for C$_{13}$H$_{11}$ClNO$_3$ (M+H)$^+$ Calcd. 264.0427, Found 264.0429.

5,7-Dichloro-4-methoxy-1H-furo[3,4-g]isoquinolin-3-one (22):

M.p. 173–174°C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.05 (s, 1H), 7.26 (s, 1H), 5.39 (s, 2H), 4.35 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 166.3, 158.6, 151.1, 147.6, 145.6, 142.1, 121.7, 117.5, 115.8, 115.7, 67.7, 64.8; HRMS (FAB-TOF) *m/z* for C$_{12}$H$_8$Cl$_2$NO$_3$ (M+H)$^+$ Calcd. 283.9881, Found 283.9883.

4,6-Dichloro-1-(5-oxo-tetrahydro-furan-3-yl)-1H-furo[3,4-c]pyridin-3-one(S,R) (27) and 4,6-Dichloro-1-(5-oxo-tetrahydro-furan-3-yl)-1H-furo[3,4-c]pyridin-3-one (R,R)(28):

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.41(s, 1H), 7.39 (s, 1H), 5.50–5.47 (m, 2H), 4.62 (t, *J* 8.8 Hz, 1H), 4.43–4.36 (m, 2H), 4.14–4.10 (m, 1H), 3.21–3.19 (m, 1H), 3.08–3.04 (m, 1H), 2.89–2.83 (m, 1H), 2.76–2.69 (m, 1H), 2.49–2.43 (m, 1H), 2.31–2.25 (m, 1H); HRMS (FAB-TOF) *m/z* for C$_{11}$H$_8$Cl$_2$NO$_4$ (M+H)$^+$ Calcd. 287.9830, Found 287.9833.

1,3-Dichloro-8-hydroxy-isoquinoline-6,7-dicarboxylic acid dimethyl ester (30):

M.p. 163–164°C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 12.92 (s, 1H), 7.54 (s, 1H), 7.24 (s, 1H), 3.98 (s, 3H), 3.93 (s, 3H); HRMS (FAB-TOF) *m/z* for C$_{13}$H$_{10}$Cl$_2$NO$_5$ (M+H)$^+$ Calcd. 329.9936, Found 329.9938.

Conclusion

In conclusion, we have successfully prepared the necessary intermediate tricyclic lactone for the synthesis of biologically active natural product (–)-Chrysanthone A. The tandem Michael-Dickman cyclization of pyridine containing *ortho*-methyl esters with activated alkynes are promising synthetic strategy for isoquinoline derivatives. The high yielding, step economic synthetic strategy for the synthesis of various heterocyclic compounds believes to be helpful to the chemical community. Future work in this area will entail total synthesis of (–)-Chrysanthone A using tricyclic lactone intermediate and will be published elsewhere.

Acknowledgements

Supporting information

NMR spectra of all new compounds.

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