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Synthesis of a proposed 1,3,4-trisubstituted isoquinoline

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ABSTRACT

The isoquinoline ring system is a reoccurring structural motif in alkaloids[1] and pharmaceuticals.[2] Consequently, the synthesis and functionalization of isoquinolines have attracted considerable attention from the synthetic community.[3] We previously reported a facile synthesis of 1,3,4-trisubstituted isoquinolines from commercially available 1,3-dichloroisoquinoline **1** (Scheme 1).[4] A key step in the process is the direct lithiation of **1** at C4. The resulting lithium species **2** was trapped with a variety of electrophiles to produce 4-substituted-1,3-dichloroisoquinoline **3**, which was further elaborated to give1,3,4-trisubstituted isoquinoline **4** by exploiting the different reactivity of C1–Cl and C3–Cl bonds under Pd-catalysis.

In connection with an internal structure-based drug design program targeting protein–protein interactions, we proposed two isoquinolines, **5** and **6**, shown in Figure 1. The structures of compounds **5** and **6** present significant challenges for synthesis, notably a 1,3,4-trisubstituted isoquinoline which is also a part of an unprecedented 6–6–5–5 tetracyclic ring system. In our retrosynthetic analysis, we envisioned compound **7** as a key intermediate for constructing the challenging tetracyclic core in **5** and **6**. In the forward direction, an aldol (R = H in **7**) or a Dieckmann condensation (R = OCH_3 in **7**) would install the key cyclopentane ring. Compound **7** could be prepared from isoquinoline **8,** which in turn could be obtained from 1,3-dichloroisoquinoline **1** utilizing the chemistry we previously described. Herein, we report our efforts along this line which culminates in a total synthesis of **5**.

Our initial effort to install a 5*H*-furan-2-one ring directly onto the C4 position of **1** from either the lithium intermediate **2** or iodide **9** met with little success (Scheme 2). For example, transmetallation of **2** from lithium to copper (CuI) followed by the addition of 5*H*-furan-2-one **10** and TMSCl gave a complex mixture. In addition, we also prepared a zinc reagent from **2** and $ZnCl_2$ (1 equiv) and explored the Rh-catalyzed conjugate addition reaction with **10** (5 mol % $[RhCl(COD)]_2$, THF, TMSCl).[5] Once again, a complex mixture was obtained. The iodide **9** has been shown to be an effective partner in Suzuki cross-coupling reactions.[4] Unfortunately, it is ineffective in the Heck reaction with **10** under a variety of conditions we examined, leading to recovered starting material and/or de-iodination product **1**. The difficulties were attributed to the poor reactivity of 4-functionalized-1,3-dichloroisoquinolines as nucleophiles and the tendency of **10** to undergo isomerization to give 2-hydroxyfuran. We reasoned that the siloxyfuran in **14** is a masked dihydrofuranone moiety**,** therefore, the synthesis of **14** was pursued. We were pleased to see that the Negishi cross-coupling reaction between iodide **9** and zinc reagent **13** afforded furan **14**, albeit in a low yield (7%, unoptimized). Monoselective cyanation went smoothly with concomitant removal of the labile TIPS group to give 5*H*-furan-2-one **15** in good yield (53%). The remaining C3–Cl bond underwent efficient carbonylation to give methyl ester **16**. Unfortunately, all our attempts to selectively hydrogenate the double bond in **15** or **16** failed,[6] resulting in either no reaction or hydrogenation of the isoquinoline ring under forcing conditions.

To understand the difficulties associated with the hydrogenation step, we carried out a conformation analysis of compound **15**.[7] It was found that **15** exists in one conformation, in which the furanone ring is orthogonal to the isoquinoline (Fig. 2). The hydrogen at C5 and the chlorine at C3 effectively blocked both face of the double bond, rendering it inaccessible for hydrogenation/reduction.

Installation of a dihydrofuranone moiety at C4 was eventually accomplished via a step-wise route (Scheme 3). Starting from 4-allyl-1,3-dichloroisoquinoline **18**, methyl ester **19** was obtained in a 3-step sequence of ozonolysis, oxidation, and esterification. Allylation of **19** provided compound **20,** which set the stage for the dihydrofuranone formation. Reduction of the methyl ester group with $LiBH_4$ went smoothly without noticeable reduction of either isoquinoline C–Cl bond. This was followed by ozonolysis and PCC oxidation to give **8**, which was prepared on gram quantities by this route.

Having established a robust synthesis of dihydrofuranone **8**, we next focused on installation of the central cyclopentane ring in **5** and **6** (Scheme 4). Bis-methyl ester **21**, a precursor for the planned Dieckmann condensation, was prepared by biscarbonylation of **8** without any incident. However, under a variety of conditions,[8] no desired product **22** was obtained. In many cases, upon addition of a strong base, such as lithium tetramethylpiperidine (LHMDS)

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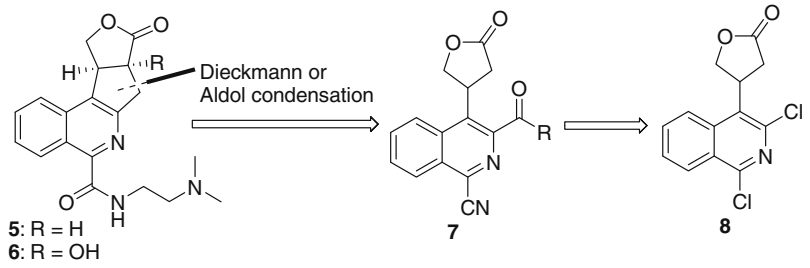
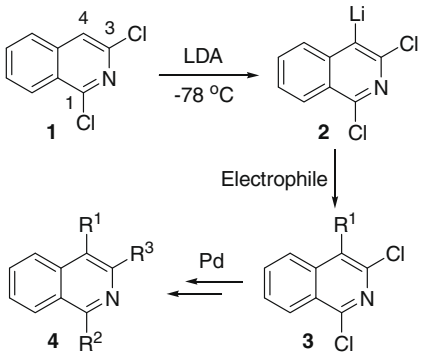


Figure 1. Two proposed isoquinolines and key retrosynthetic analysis.



Scheme 1.

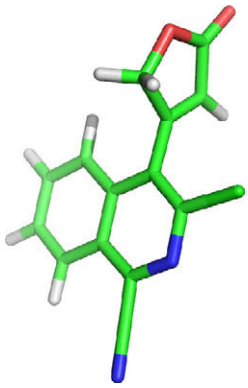
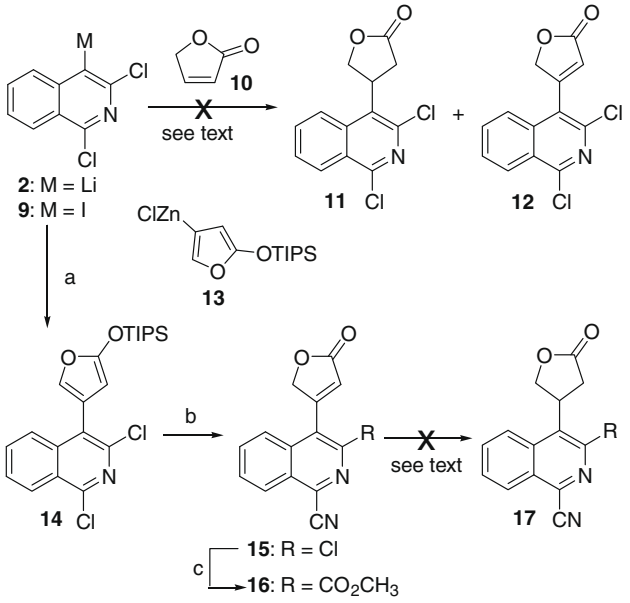


Figure 2. Lowest energy conformation of **15** by molecular modeling. The carbons and chlorine are colored in green. The nitrogens are in blue. The hydrogens are in white. The oxygens are in red.



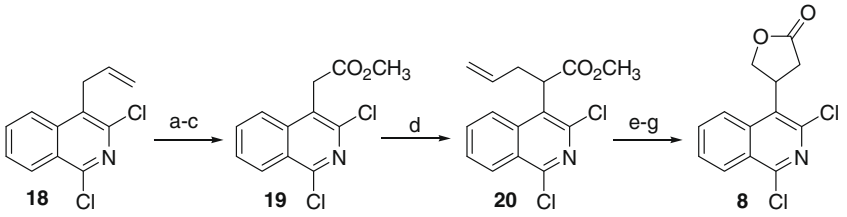
Scheme 2. Reagents and conditions: (a) $Pd(PPPh_3)_4$ (10 mol %), **9**, **13**, THF, 60 °C, 8 h, 7%; (b) $Pd(PPh_3)_4$, DMF/H_2O, $Zn(CN)_2$, 85 °C, 6 h, microwave, 53%; (c) $Pd(PPh_3)_4$, CO, $DMF/CH_3OH/Et_3N$, 100 °C, quant.

or KO*t*-Bu, to a solution of **21** in either THF or DMF, a thick and dark suspension resulted. We attributed this phenomenon to single electron transfer processes occurring between the electron-deficient isoquinoline and the base. Therefore, avoiding strong bases could be the key for a successful ring closure. Toward this end, compound **8** was elaborated to aldehyde **23** in three steps (cyanation, Stille cross-coupling, and ozonolysis). Rewardingly, subjecting **23** to a mild aldol condition employing a combination of a Lewis acid (TBSOTf) and a mild base (*i*-Pr_2NEt) gave tetracycle **24** in good yield (78%).[9] The 1:1 diastereomeric mixture of **24** could be separated by preparative thin-layer chromatography (TLC), but it is usually used without separation. The TBS in **24** was then deprotected with HF·pyridine to give alcohol **25**.

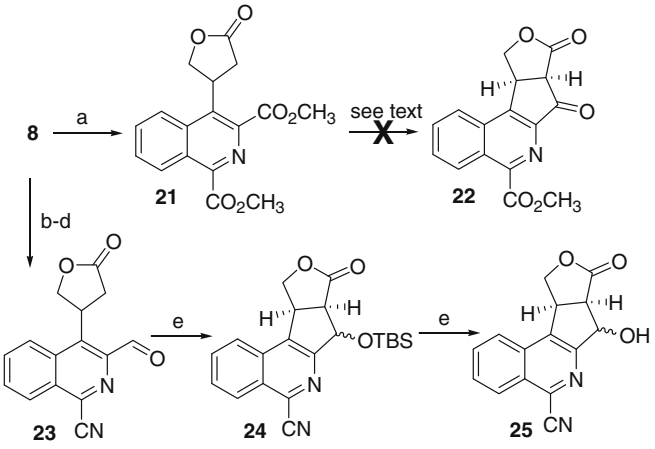
Structural assignment of the two diastereomers, **24a** and **24b**, was initially based on coupling constants from HNMR. The literature compounds, **26** and **27**, have been reported (Fig. 3).[10] The H_a in **26** appeared as a dd with $J = 8.0$ and 7.0 Hz while the H_a in **27** showed a very similar pattern and coupling constants as those of **26**. This observation led us to conclude that the coupling constant between H_a and H_b (*cis*-relationship) is about 8 Hz while the coupling constant between H_a and H_c (*trans*-relationship) is close to 7 Hz. Therefore, one of the diastereomers of **24** was assigned as **24a** based on the fact that H_a appeared as a dd with coupling constant of 8.8 and 7.3 Hz. In the other diastereomer **24b**, H_a appeared as a d with a coupling constant of 7.9 Hz, presumably due to the lack of coupling between H_a and H_c in a *cis*-relationship.

Further support of the *cis*-fused 5–5 ring can be obtained from analysis of the transition states required for the product formation. There are two possible transition states, **A** and **B** (Fig. 4). Both are nearly equal in energy due to the small size of H and O of the aldehyde and presumably react at similar rates under the reaction conditions, leading to a 1:1 mixture of **24a** and **24b** (Fig. 4). On the other hand, transition states required for the *trans*-fused 5–5 ring cannot be achieved.

All attempts to effect deoxygenation of either TBS ether **24** or alcohol **25** were not successful. However, deoxygenation of thionocarbonate **28** (Bu_3SnH, AIBN) afforded tetracycle **29** in a satisfactory 77% yield. Hydrolysis of the nitrile group at C1 accompanied with a concomitant lactone hydrolysis, which readily relactonized to give acid **30** (Scheme 5). Finally, coupling of **30** with *N*,*N*-dimethylethylenediamine under standard conditions yielded target **5**[11] in 20% over two steps. It is noted that the low yield in the last two steps is presumably due to aqueous solubility and



Scheme 3. Reagents and conditions: (a) O_3, CH_2Cl_2/MeOH (1:1), −78 °C, then Me_2S; (b) $NaClO_2$, *t*-BuOH, 2-methyl-2-butene, NaH_2PO_4; (c) MeOH, TsOH·H_2O, 50 °C, 80% over three steps; (d) **19**, LDA, THF, −78 °C; then allyl iodide, 92%; (e) $LiBH_4$, THF, rt, 61%; (f) O_3, EtOAc, −78 °C, then Me_2S, 78%; (g) pyridinium chlorochromate, CH_2Cl_2, 4 Å molecular sieves, rt, 72%.



Scheme 4. Reagents and conditions: (a) $PdCl_2$(BINAP), MeOH/Et_3N, CO (30 psi), 100 °C, 74%; (b) $Pd(PPh_3)_4$ (10 mol %), $Zn(CN)_2$ (2 equiv), DMF/H_2O (99:1), 85 °C, 4 h, 41% (97% BRSM); (c) $Pd(PPPh_3)_4$ (10 mol %), tributylvinyltin (1 equiv), 100 °C, 67%; (d) O_3, EtOAc, −78 °C; then Me_2S, −78 °C to rt; (e) TBSOTf (4 equiv), *i*-Pr_2NEt (4 equiv), CH_2Cl_2, rt, 78%, 1:1 dr; (f) HF·pyridine, THF, rt, quant.

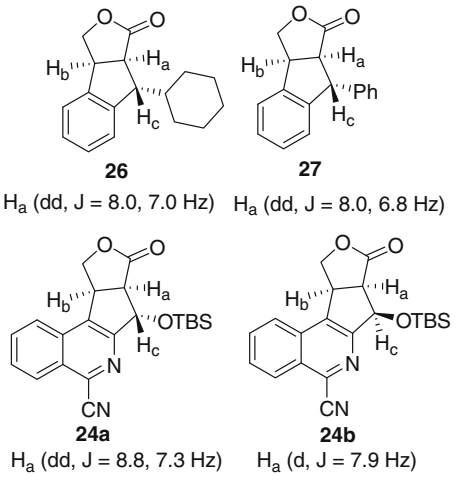


Figure 3. Coupling constant analysis.

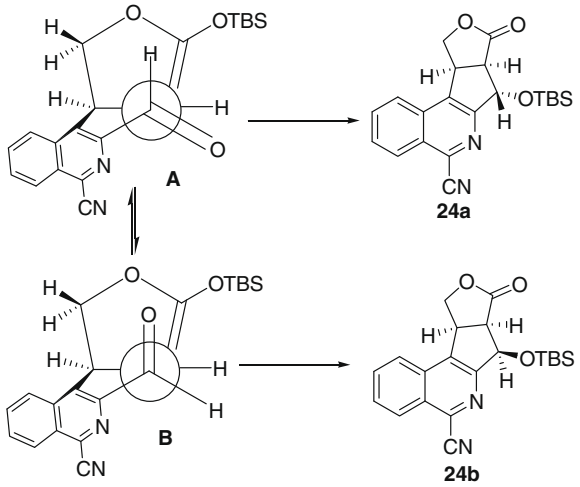
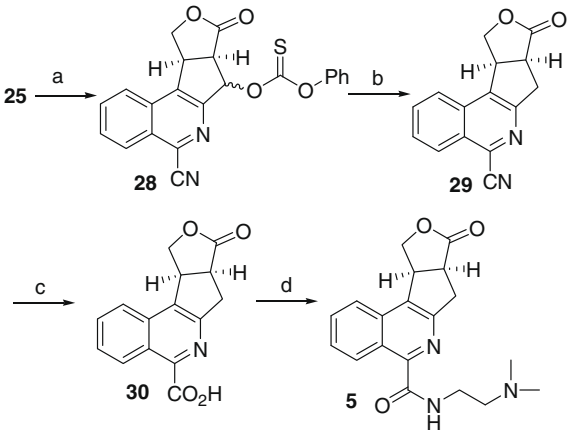


Figure 4. Transition states leading to **24a** and **24b**.



Scheme 5. Reagents and conditions: (a) DMAP (3 equiv), CH_2Cl_2, *O*-phenyl chlorothionoformate (1.2 equiv), 72%; (b) Bu_3SnH (1.3 equiv.), AIBN (30 mol %), toluene, reflux, 77%; (c) 4 N KOH, H_2O, 60 °C, 6 h; then 20 wt % NaHSO4; (d) benzotriazolyloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), Et_3N, DMF, *N*,*N*-dimethylethylenediamine, 20% yield over two steps.

polarity of the intermediates since the liquid chromatography–mass spectrometry (LC–MS) profiles of both reactions are quite clean.

In summary, the total synthesis of a proposed 1,3,4-trisubstituted isoquinoline **5** with an unprecedented 6–6–5–5 tetracyclic ring system is described.[12] One of the key steps is an intramolecular aldol reaction with a combination of a Lewis acid (TBDMSOTf) and a mild base (*i*-Pr_2NEt) to construct the central cyclopentane ring. During the course of this work, the scope of our previously reported 1,3-dichloroisoquinoline chemistry was further examined. The synthesis of target **6** and the biological evaluation of related synthetic analogous are currently in progress.

References and notes

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6. *Selected reactions*: (1) compound **15**, Et_3SiH, TMSOTf, CH_2Cl_2, rt, no reaction; (2) compound **15**, Pd/C, EtOAc, H_2, 55 psi, hydrogenation of the isoquinoline ring; (3) compound **16**, $[(Ph_3P)CuH]_6$, benzene, H_2O, rt, multiple spots.
7. The conformation analysis was carried out with an internal program developed based on Omega (v2.3.2) from OpenEye Scientific. For additional information, see: www.eyesopen.com.
8. Bases used for the attempted Dieckmann condensation include LDA, LHMDS, NaH, CH_3ONa, and k*O*t-Bu with THF or DMF as solvents.
9. (a) Rassu, G.; Auzzas, L.; Pinna, L.; Zambrano, V.; Zanardi, F.; Battistini, L.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2002**, *67*, 5338–5342; (b) Rassu, G.; Auzzas, L.; Pinna, L.; Zambrano, V.; Zanardi, F.; Battistini, L.; Gaetani, E.; Curti, C.; Casiraghi, G. *J. Org. Chem.* **2003**, *68*, 5881–5884.
10. Muraoka, O.; Tanabe, G.; Sano, K.; Minematsu, T.; Momose, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1833–1845.
11. Efforts to confirm the *cis*-configuration at the two five-membered ring junction in **5** by coupling constant analysis was not successful due to the broad shape of the proton α to the lactone carbonyl. However, the well-known strain associated with *trans*-fused 5–5 ring in general coupled with the fact that all indenofuranones in the literature exemplified by **26** and **27** possess a *cis*-configuration at the ring junction provide strong support for our structural assignment of **5**.
12. *Selected spectroscopic data*: *Compound* **8**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.45 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.89 (t, *J* = 6.7 Hz, 1H), 7.77 (t, *J* = 6.7 Hz, 1H), 4.98–4.88 (m, 1H), 4.80–4.72 (m, 2H), 3.15 (dd, *J* = 10, 18.6 Hz, 1H), 3.04 (dd, *J* = 11.4, 18.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz): δ 175.9, 150.7, 143.2, 137.3, 132.8, 128.7, 128.3, 126.4, 122.4, 70.8, 33.4, 33.1; mp 202–203 °C; IR (KBr film) 3432, 1772, 1614, 1551, 1498, 1319, 1251, 1176, 1159, 1144, 1076, 1032, 968, 855, 836, 783, 770, 714, 626, 617 cm^{-1}; Anal. Calcd for $C_{13}H_9Cl_2NO_2$: C, 55.35; H, 25.13; N, 4.96. Found: C, 54.96; H, 3.07; N, 4.92. *Compound* **5**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.59 (d, *J* = 1.1 Hz, 1H), 8.56–8.45 (br m, 1H), 7.80–7.75 (m, 1H), 7.69–7.64 (m, 2H), 4.92 (dd, *J* = 7.9, 9.4 Hz, 1H), 4.69 (dd, *J* = 2.3, 9.3 Hz, 1H), 4.65–4.55 (m, 1H), 3.76 (q, *J* = 6.1 Hz, 2H), 3.69–3.60 (m, 3H), 2.86 (t, *J* = 6.3 Hz, 2H), 2.52 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 Hz): δ 179.4, 166.3, 152.9, 149.9, 134.1, 131.9, 131.5, 129.3, 127.9, 126.3, 122.1, 71.6, 57.8, 44.8, 43.6, 40.5, 37.5, 36.5; IR (KBr film) 3382, 1760, 1653, 1516, 1178, 1020 cm^{-1}; HRMS calcd for $C_{19}H_{22}N_3O_3$ $[M+H]^+$: 340.1661. Found: 340.1669.