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A concise synthesis of 3,4-fused spiro[isobenzofuran-3-ones], spiro[furo[3,4-*b*]pyridin-5(7*H*)-ones], 3-aryl-, and alkylphthalides

Jeffrey T. Kuethe *, Kevin M. Maloney *

Department of Process Research, Merck & Co., Inc., P.O. Box 2000, Rahway, NJ 07065, USA

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ABSTRACT

A synthetically useful protocol has been developed for the preparation of highly functionalized 3,4-fused spiro[isobenzofuran-3-ones], spiro[furo[3,4-*b*]pyridin-5(7*H*)-ones], 3-aryl-, and alkylphthalides. Reaction of 2-iodobenzoate esters and 2-iodopyridine carboxylate esters with *i*-PrMgCl·LiCl in the presence of cyclic ketones under standard Barbier reaction conditions affords 3,4-fused spiro[isobenzofuran-3-ones] and spiro[furo[3,4-*b*]pyridin-5(7*H*)-ones] in good to excellent yields. Step-wise addition of *i*-PrMgCl·LiCl to 2-iodobenzoate esters followed by trapping with various aldehydes yields 3-aryl and 3-alkylphthalides; whereas, under similar conditions access to 3-aryl and 3-alylazaphthalides is also possible. Extension of this methodology toward the preparation of 3-*n*-butylphthalide and chrycolide, a natural product isolated from the leaves and stems of *Chrysanthemum coronarium*, is also described.

1. Introduction

Spiro isobenzofurans **1** and furopyridines **2**, and their dihydro-counterparts,[1] constitute the central pharmacophore of an emerging class of heterocyclic compounds possessing a range of biological activities (Fig. 1). In particular, spiropiperidines of general structure **3** are a common structural motif utilized in drug discovery[2] and have been classified as 'privileged structures' due to their rigid structure and ability to direct functional groups in well-defined spaces.[3] The closely related phthalides **4** are found in abundance in nature[4] as well as in many biologically active compounds[5] and are also utilized extensively in medicinal chemistry. Interestingly, azaphthalides of type **5** have remained relatively unexplored and access to these structurally intriguing molecules has not been fully reported.

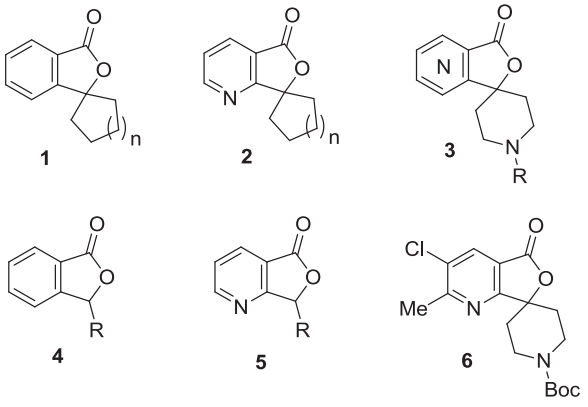

Fig. 1. 3,4-Fused spiro[isobenzofuran-3-ones], spiro[furo[3,4-*b*]pyridin-5(7*H*)-ones], 3-aryl- and alkylphthalides.

The most commonly employed method for the preparation of compounds **1**–**3** involve metal–halogen exchange of 2-(2-bromophenyl)-4,4′-dimethyloxazolines (Meyers method),[6] 2-bromobenzamides,[7] 2-bromobenzoic acid,[8] or 2-bromopyridine-3-carboxylic acids.[9] While suitable for the preparation of simple substrates, the use of butyllithium in conjunction with other sensitive functionalities render these protocols limited in scope. A three step sequence involving a Suzuki coupling, iodolactonization, and reduction for the preparation of variously substituted furopyridines **3** has been disclosed.[10] Mild synthetic methods that allow for assembly of these heterocycles and tolerate a wide range of functional groups continue to offer significant advantages. Recently we required significant quantities of compound **6** to support development of a drug candidate and needed to develop a practical procedure for its preparation on larger scale. It was envisioned that a suitably functionalized *ortho*-iodopyridyl ester or nitrile **8a**/**b** would allow for Grignard formation in the presence of ketone **7** followed by intramolecular cyclization leading to **6**, potentially in a one-pot manner (Scheme 1). In this paper, we document a complete account of our work in this area, including the preparation of

* Corresponding authors. E-mail addresses: Jeffrey_Kuethe@merck.com (J.T. Kuethe), Kevin_Maloney@merck.com (K.M. Maloney).

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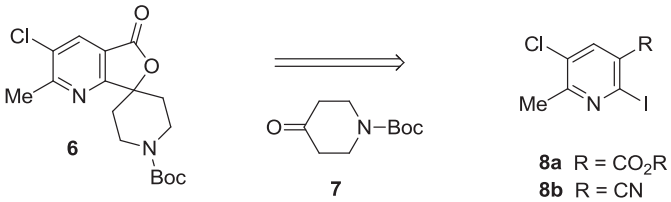
compounds of general type **1**–**5** and highlight the methodology with the efficient preparation of natural products 3-*n*-butylphthalide and chrycolide, a plant growth inhibitor isolated from *Chrysanthemum coronarium.*



Scheme 1.

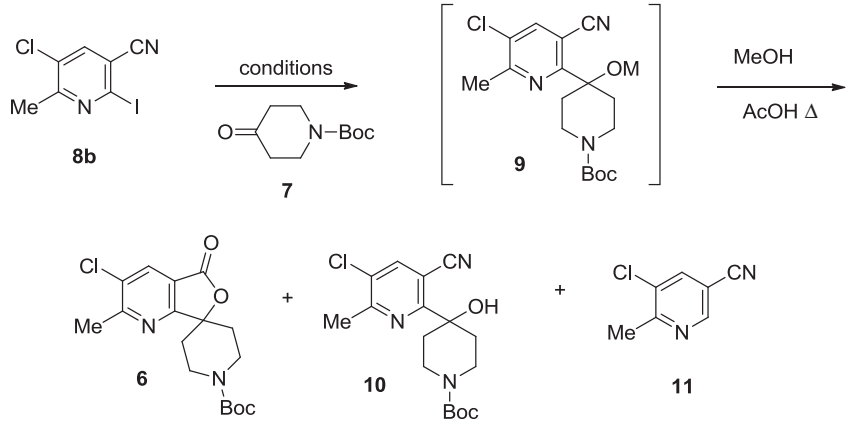
2. Results and discussion

2.1. Preparation of 3,4-fused spiro[isobenzofuran-3-ones] and spiro[furo[3,4-*b*]pyridin-5(7*H*)-ones]

Our investigations began by examining the reaction between iodide **8b**[11] and ketone **7** (Scheme 2). Initial efforts were focused on metal–halogen exchange employing *n*-BuLi at low temperature (−78 °C) followed by quenching with **7** and warming to room temperature. Examination of the crude reaction mixture by HPLC and LC/MS showed that the major product was alcohol **10** (~50%). Also detected in the crude reaction mixture was desiodopyridine **11** (27%) and the desired product **6** in 7% yield together with a number of by-products that were not identified. Direct addition of an excess of MeOH and AcOH to the crude reaction mixture followed by warming to 60 °C resulted in cyclization of **10** to give **6** in 38% isolated yield. We also examined the use of Bu_2Mg and a combination of *n*-BuLi/Bu_2MgCl.[12] In each case the reaction profile was similar to that when *n*-BuLi was employed and the isolated yields of **6** never exceeded 40%. The formation of **11** as a major reaction by-product under these conditions suggested that competitive deprotonation of **7** was taking place leading to diminished yields of the desired product (vide infra).

ketone **7** and subsequent hydrolysis with MeOH/AcOH furnished lactone **6** in 57% isolated yield. Analysis of the crude reaction mixture prior to isolation of **6** revealed the presence of **11** (~35%). The use of *i*-PrMgCl·LiCl was next examined and was found to give higher yields of **6** (up to 65%) with a corresponding reduction in the amount of **11** (~25%) being formed during the reaction. Finally, we discovered that conducting the reaction under Barbier conditions further improved the reaction yield by decreasing the level of **11** to ca. 10% (Scheme 3). The final optimized procedure for the preparation of **6** involved treatment of a mixture of **8b** and ketone **7** (1.4 equiv) with *i*-PrMgCl·LiCl (1.4 equiv) in THF at −50 °C followed by warming to room temperature and quenching with 1:1 MeOH/AcOH (7 equiv) (Scheme 3). After heating to 50 °C to affect cyclization and an aqueous workup, spirolactone **6** was isolated by crystallization from aqueous IPA in 79% yield. The mass balance of the reaction was **11**, which proved to be unavoidable due to competitive deprotonation of **7**. Attempts to use $CeCl_3$ or $LnCl_3$ to activate ketone **7** toward 1,2 addition and further suppress enolization (formation of **11**) were completely unsuccessful.[15] Given the simplicity with which the reaction was conducted and the structural complexity achieved, the optimized yield of **6** was deemed acceptable.

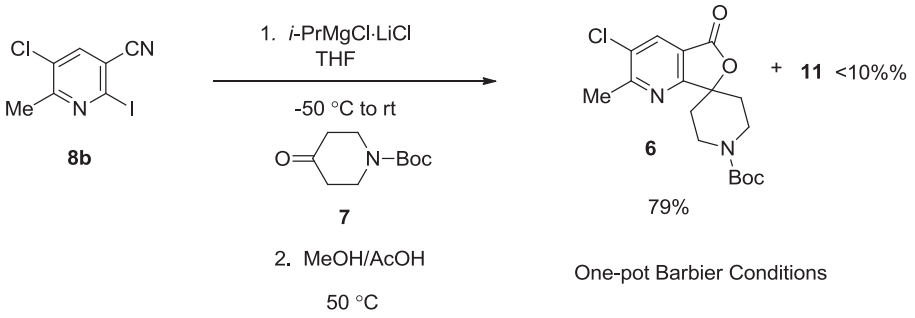
In order to understand the mechanistic aspects of the formation of **11** under the optimal conditions, a series of experiments were devised to probe whether enolization was indeed occurring or if the formation of **11** was a result of quenching of the intermediate Grignard reagent upon workup (Scheme 4). For example, treatment of **12** with *i*-PrMgCl·LiCl (1.4 equiv) in THF at −50 °C followed by addition of piperidone **13** and warming the reaction to room temperature lead to the formation of **14** (67%). The reaction mixture was then quenched with D_2O and the crude organic layer was analyzed by GC–MS, which indicated almost the exclusive formation of **15** and only trace amounts (<3%) of **16** (Scheme 4). Further analysis of the crude reaction mixture by ^1H NMR did not reveal any deuterium incorporation into **13**. To further demonstrate that competitive enolization of **13** (and **7** above) was the source of the formation of **15**, the reaction was repeated under the identical reaction conditions using perdeuterated piperidone **17**.[16] Analysis of



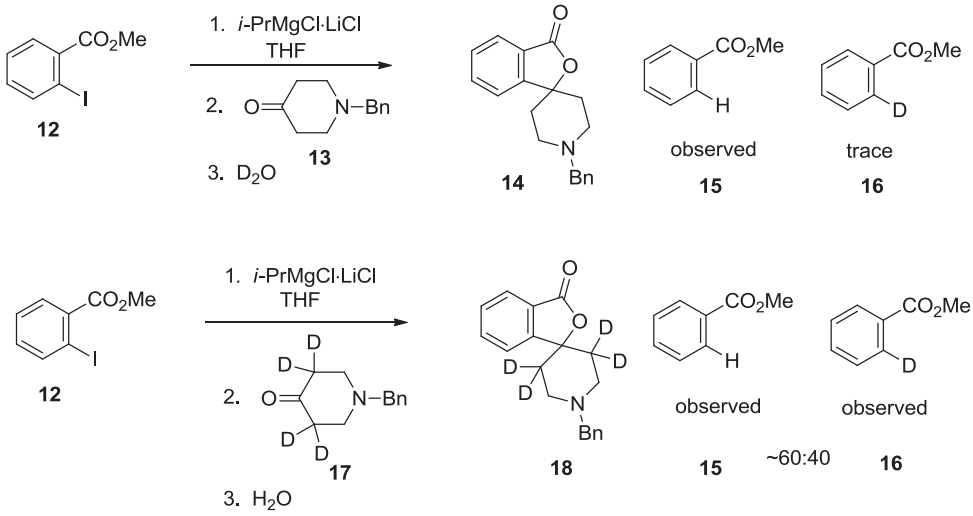
Scheme 2.

The pioneering work by Knochel and co-workers has demonstrated that under particularly mild reaction conditions, halogen–magnesium exchange is facile and tolerant of a wealth of functional groups.[13] Typically *i*-PrMgCl is utilized for halogen–magnesium exchange; however, due to its magnesiate character and enhanced reactivity, *i*-PrMgCl·LiCl often proves to be the superior reagent.[14] We set out to explore the use of these reagents in an attempt to improve the reaction profile and yield of **6**. Treatment of **8b** with *i*-PrMgCl at −50 °C in THF followed by trapping with

the crude reaction mixture by GC–MS revealed both the formation of **15** and **16** in an approximated 3:2 ratio. Compound **18** was obtained in 71% isolated yield after chromatography. The formation of **15** was not completely surprising as the isotopic purity of **17** employed in the experiment existed as 66:27:6.4:0.5:0.1 ratio of D_4:D_3:D_2:D_1:D_0 as determined by LC–MS. Due to the kinetic isotope effect of deuterium, it would be expected that proton extraction from D_3–D_1 containing **17** would be faster than deuterium extraction leading the formation of observed **15**. Therefore, it is



Scheme 3.



Scheme 4.

reasonable to conclude that proton extraction of **7**, **13**, and **17** is a competitive process leading to slightly diminished yields of the products.

Having established a productive synthesis of **6**, which was successfully applied on kilogram scale, we set out to explore the application of this methodology in the preparation of other 3,4-fused spiro[isobenzofuran-3-ones] and spiro[furo[3,4-*b*]pyridin-5(7*H*)-ones. The results are highlighted in Table 1. For example, reaction of iodoester **12** with either ketone **7** or **20** in THF and in the presence of *i*-PrMgCl·LiCl under Barbier conditions lead to excellent yields of the expected spirolactones **19** and **21**. In similar fashion, reaction of **12** with cyclohexanone and cyclopentanone afforded **23** and **25** in 83% and 57% yields, respectively. Grignard addition to ketone **26** followed by cyclization proceeds in exceptionally good yield to give **27** in 90% isolated yield. Interestingly, reaction of **28** with *i*-PrMgCl·LiCl in the presence of ketone **7** did not give any of the expected cyclization product **29** and dehalogenation of **28** was the only observed reaction. We speculate that the intermediate Grignard is particularly stable and addition to **7** does not take place (entry 6). Instead, proton extraction from **7** was the predominate reaction pathway. On the other hand, reaction of **30** with **7** in the presence of *n*-BuLi was successful and, after hydrolysis of the intermediate addition products with MeOH/AcOH, spirolactone **29** was obtained in 51% yield. Iodoindole **31** also served as a useful substrate leading to the formation of the novel and highly functionalized spiro-indolelactones **32** (63%) and **33** (67%). It should be noted in all cases, except entry 7, that upon addition of *i*-PrMgCl·LiCl and warming to room temperature, cyclization to the corresponding spirolactones occurred without the need for a secondary acid-mediated cyclization step. Furthermore, the mass balance of each reaction was dehalogenation via competitive proton extraction from the ketones.

2.2. Preparation of 3-aryl and alkylphthalides

As a further extension, we investigated the formation of both 3-aryl- and alkylphthalides. While there are a number of methods reported for the preparation of 3-substituted phthalides,[17] reactions of 2-iodoesters and nitriles with *i*-PrMgCl·LiCl and aldehydes for the preparation of these important pharmacophores has been relegated to a few isolated reports.[14,18] Our investigations began with the treatment of **12** with *i*-PrMgCl·LiCl at −60 °C for 15 min followed by the addition of **34** and warming the reaction mixture to room temperature (Scheme 5). After an aqueous workup, phthalide **35** was obtained in 91% yield. An alternative preparation of **35** was also investigated. Reaction of **36** with *i*-PrMgCl·LiCl at −60 °C for 15 min followed by addition of **37** and warming to room temperature gave **35** in 64% yield. The application of this process for the preparation of a range of phthalides is shown in Table 2. The yields of these phthalides were uniformly high and provided access to functionalized intermediates bearing suitable handles for further manipulation (entries 2–5). Entry 5 demonstrates the high iodide selectivity during the halogen–magnesium exchange reaction of **46** giving rise to phthalide **48** after quenching with aldehyde **47**. Even alkyl aldehydes are suitable substrates as demonstrated by the preparation of 3-alkylphthalide **50** (entry 6). Extracted from celery seed oil,[19] 3-*n*-butylphthalide **52** is an active ingredient in Chinese folk medicine that has been approved by the State Food and Drug Administration (SFDA) of China for the treatment of ischemic stroke.[20] It has also been used in flavoring and

Table 1
3,4-Fused spiro[isobenzofuran-3-ones] and spiro[3,4-*b*]pyridine-5(7*H*)-ones

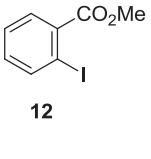
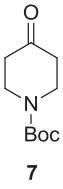
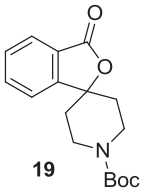
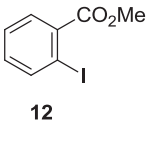
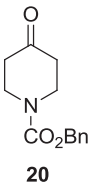
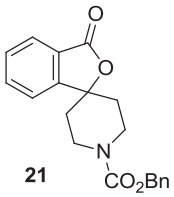
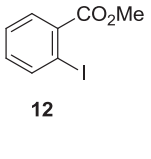
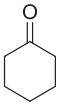
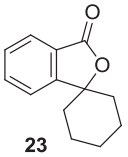
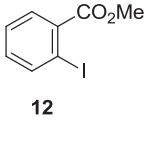
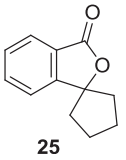
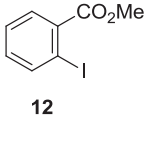
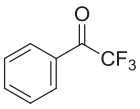
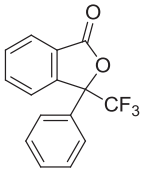
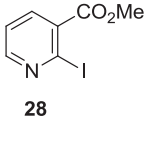
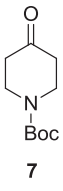
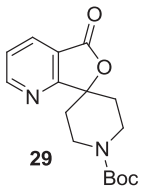
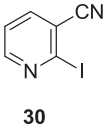
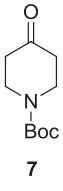
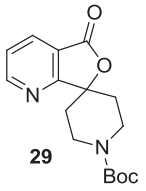
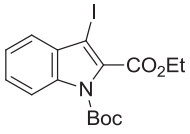
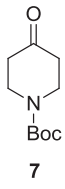
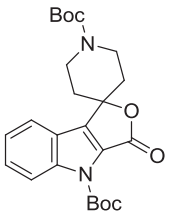
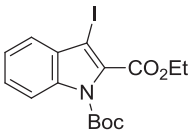
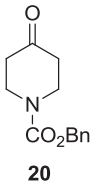
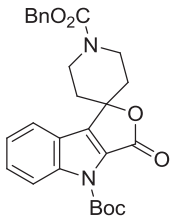
Entry	Iodide	Electrophile	Product	Yield
1	 **12**	 **7**	 **19**	84%
2	 **12**	 **20**	 **21**	75%
3	 **12**	 **22**	 **23**	83%
4	 **12**	 **24**	 **25**	57%
5	 **12**	 **26**	 **27**	90%
6	 **28**	 **7**	 **29**	0%
7	 **30**	 **7**	 **29**	51%

Table 1 (*continued*)

Entry	Iodide	Electrophile	Product	Yield
8	 **31**	 **7**	 **32**	63%
9	 **31**	 **20**	 **33**	67%

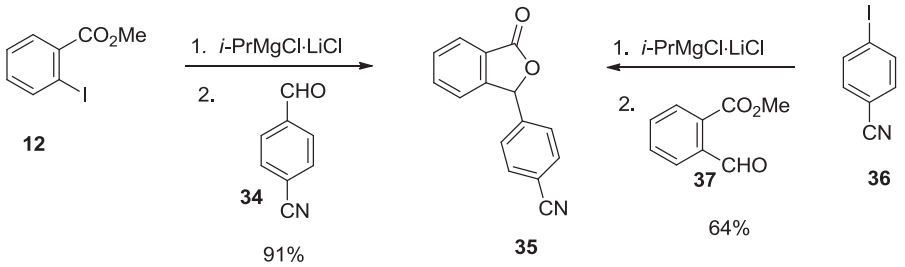
seasoning. In addition, 3-*n*-butylphthalide **52** has been shown to increase the duration of anesthesia,[21] to have anticonvulsant action,[22] may have neuroprotective affects,[23] and has been studied for the treatment of hypertension.[24] There have been a number of syntheses reported including asymmetric syntheses.[25] We envisioned a one-pot single step synthesis of **52** starting from iodide **12** and readily available valeraldehyde **51** (Table 2, entry 7). Reaction of **12** with *i*-PrMgCl·LiCl in THF at −60 °C for 15 min followed by quenching with **51** and warming to room temperature gave racemic 3-*n*-butylphalide **52** in 82% yield after purification by silica gel chromatography. Nitriles may also be employed (entry 8), but require hydrolysis with MeOH/AcOH to effect cyclization to lactone **54**. In the case of iodoindole **31** did cyclization prove problematic and only secondary alcohol **55** was isolated in 90% yield. All attempts to close the lactone ring (MeOH/AcOH or NaH) proved unsuccessful and did not afford the desired product.

2.3. Preparation of 3-aryl and alkylazaphthalides

We next turned our attention to synthesis of relatively unknown azaphthalides (Scheme 6).[26] For example, reaction of **28** with *i*-PrMgCl·LiCl at −60 °C followed by quenching with piperonal **38** and warming the reaction mixture to room temperature resulted in the exclusive formation of intermediate **56**, which could be isolated after an aqueous workup in 90% yield.[27] There was no evidence of further cyclization to azaphthalide **57** observed in both the crude ^{1}H NMR or by HPLC analysis. Unlike the reaction of **28** in the presence of ketones where no reaction occurs (Table 1, entry 6), addition of the Grignard of **28** to aldehyde **38** is facile leading to **56**. Cyclization to **57** was accomplished by direct addition of MeOH/AcOH (7 equiv each) to the crude reaction mixture and heating to 60 °C for several hours to drive the reaction to completion, which gave **57** in 83% yield for the one-pot process. In like fashion, azaphthalides **58**, **59**, **61**, and **63** were prepared in good to excellent yield (Table 3) providing access to aryl (entries 1–3) and alkylazaphthalides (entry 4).

2.4. Application to natural product synthesis

Having established the synthetic utility of the process, we highlighted the synthetic protocol toward natural product synthesis. Isolated from leaves and stem of a popular vegetable (*C.*



Scheme 5.

coronarium, Japanese name: shugiku) in China and Japan, chrycolide **70** has been shown to have plant growth inhibiting activity.[28] To date there have been no reported total synthesis of chrycolide **70** and the absolute configuration has yet to be established. Our first attempted synthesis of chrycolide **70** began with iodofluoroester **64** (Scheme 7). Treatment of **64** with *i*-PrMgCl·LiCl in THF at −70 °C for 15 min followed by quenching with 2-thiophenecarboxaldehyde **66** and warming to room temperature gave thienylphthalide **66** in 78% isolated yield. Attempted nucleophilic aromatic displacement of the fluoride atom in **66** with various alcohols was unsuccessful forcing us to explore an alternative route. The second route started with iodonitrile **68**. Treatment of **68** with *i*-PrMgCl·LiCl in THF at −70 °C for 15 min followed by quenching with 2-thiophenecarboxaldehyde **65** and warming to room temperature gave alcohol **69** in 86% isolated yield. Unfortunately, all attempts to cyclize **69** with acid or base to give **67** resulted in complete decomposition. The thienylphthalide moiety of **66** and **69** is particularly sensitive to any strong acid and leads to significant degradation of the molecule.[29]

The successful synthesis of chrycolide began with acid **71** (Scheme 8). Protection of **71** as its *tert*-butylester proceeded smoothly and gave **72** in near quantitative yield. Surprisingly, displacement of the aryl fluoride atom with potassium *tert*-butoxide in THF occurred smoothly at room temperature to give **73** in 88% yield. Removal of the *tert*-butyl protecting groups with TFA and re-esterification afforded **74** in 90% overall yield for the two steps. Initially, we believed that protection of the phenol was required prior to formation of the phthalide ring system. Therefore, reaction of **74** with TBDMS-Cl and treatment with *i*-PrMgCl·LiCl and quenching with 2-thiophenecarboxaldehyde **65** afforded the expected product in good overall yield. Finally, removal of the silyl protecting group with TBAF gave chrycolide **70** in 82% yield from **74**. With a synthetic route in place, we set out to shorten the synthesis by looking at the direct conversion of **74** to chrycolide **70**. Much to our delight, reaction of **74** with 1 equiv of sodium hydride followed by 1 equiv of *i*-PrMgCl·LiCl in THF at −70 °C and trapping the intermediate with **65** furnished **70** in 92% yield for the single step process thus eliminating two steps from the sequence. The five step total synthesis of (±)-chrycolide proceeded in 71% overall yield from iodoacid **71**. The ^{1}H and ^{13}C NMR, melting point, and UV of our synthetic chrycolide were in complete agreement with that reported for natural chrycolide and thus this represents the first total synthesis of this natural product.

3. Conclusion

In conclusion, we have outlined an effective strategy for the preparation of highly functionalized 3,4-fused spiro[isobenzofuran-3-ones] and spiro[furo[3,4-*b*]pyridin-5-(7*H*)-ones] via a one-pot Barbier reaction between 2-iodoesters or nitriles with ketones or aldehydes in the presence of *i*-PrMgCl·LiCl. The methodology was extended to the synthesis of highly functionalized 3-aryl and alkylphthalides including the azaphthalides. The reaction conditions are mild and tolerant of a range of functionality leading to increasing molecular complexity in a single chemical transformation. Finally, the synthetic protocol was highlighted by the one-pot synthesis of 3-*n*-butylphthalide and the first reported total synthesis of chrycolide.

4. Experimental section

4.1. General

Commercial grade reagents and solvents were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were measured with a 400 MHz spectrometer. ^{1}H NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the $CHCl_3$ peak at 7.27 ppm used as a standard). ^{13}C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of $CHCl_3$ at 77.23 ppm used as a standard). Purifications were carried out by flash column chromatography on a Teledyne Isco CombiFlash R_f using a gradient elution of 0–100% EtOAc/hexanes unless otherwise specified.

4.2. General procedure A

A three-necked, round-bottomed flask equipped with a septum, nitrogen inlet adapter, and thermocouple was charged with the iodopyridine (1 equiv), ketone (1.0–1.1 equiv), and THF (15 mL per 1 g of iodopyridine). The reaction mixture was cooled at −50 to −70 °C while a solution of isopropylmagnesium chloride–lithium chloride (1.3 M, 1.1–1.2 equiv) or *n*-butyllithium (2.5 M, 1.1 equiv) was added rapidly via syringe and the reaction mixture was warmed to room temperature. MeOH (7 equiv) and AcOH (7 equiv) were added and the resulting reaction mixture was stirred at 60 °C for 2–17 h. After complete cyclization, the reaction mixture was concentrated and then diluted with EtOAc and satd $NaHCO_3$. The resulting aqueous layer was separated and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (EtOAc/hexanes) to give the desired product.

4.3. General procedure B

A three-necked, round-bottomed flask equipped with a septum, nitrogen inlet adapter, and thermocouple was charged with the iodopyridine (1 equiv) and THF (15 mL per 1 g of iodopyridine). The reaction mixture was cooled at −50 to −70 °C while a solution of isopropylmagnesium chloride–lithium chloride (1.3 M, 1.1–1.3 equiv) was added and the reaction mixture stirred for 30 min. The aldehyde or ketone (1.0–1.3 equiv) was added in one portion and the reaction mixture was warmed to room

Table 2
3-aryl- and alkylphthalides

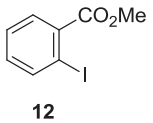
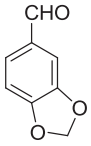
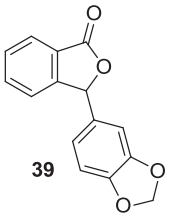
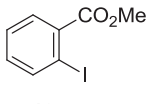
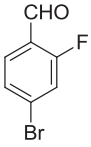
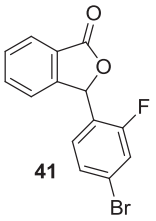
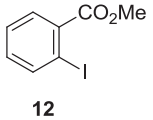
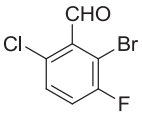
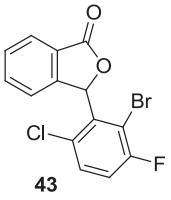
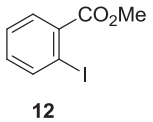
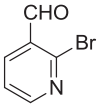
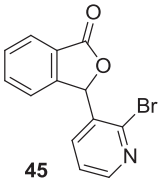
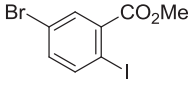
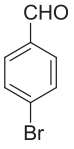
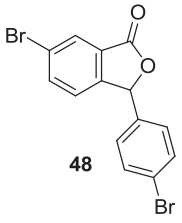
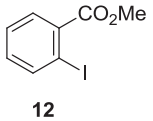
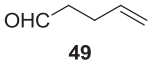
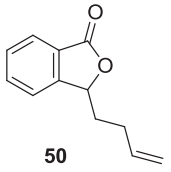
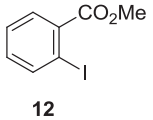
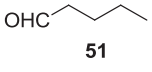
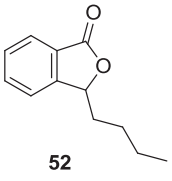
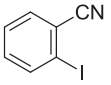
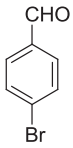
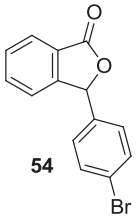
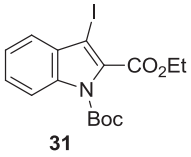
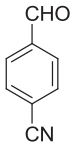
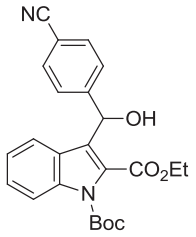
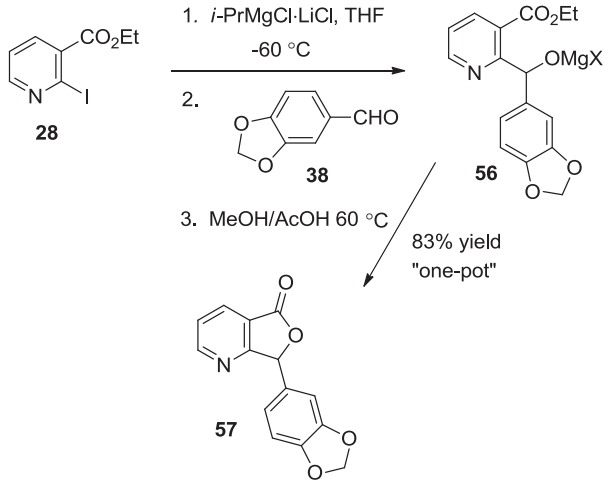
Entry	Iodide	Aldehyde	Phthalide	Yield
1	 **12**	 **38**	 **39**	89%
2	 **12**	 **40**	 **41**	77%
3	 **12**	 **42**	 **43**	82%
4	 **12**	 **44**	 **45**	90%
5	 **46**	 **47**	 **48**	70%
6	 **12**	 **49**	 **50**	95%
7	 **12**	 **51**	 **52**	82%

Table 2 (*continued*)

Entry	Iodide	Aldehyde	Phthalide	Yield
8	 **53**	 **47**	 **54**	78%
9	 **31**	 **34**	 **55**	90%



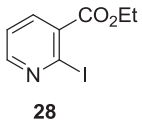
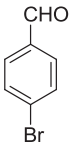
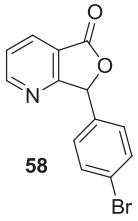
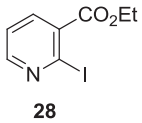
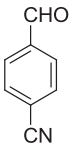
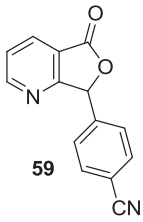
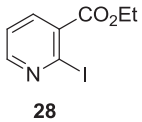
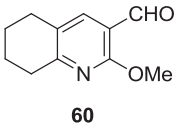
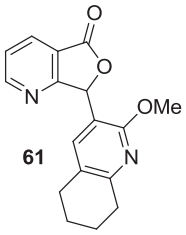
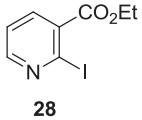
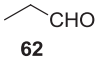
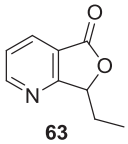
Scheme 6.

temperature. After complete cyclization, water was added and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (EtOAc/hexanes) to give the desired product.

4.4. General procedure C

A three-necked, round-bottomed flask equipped with a septum, nitrogen inlet adapter, and thermocouple was charged with the iodopyridine (1 equiv) and THF (15 mL per 1 g of iodopyridine). The reaction mixture was cooled at −50 to −70 °C and a solution of isopropylmagnesium chloride–lithium chloride (1.3 M, 1.1–1.2 equiv) was added and the reaction mixture was stirred for 30 min. The aldehyde or ketone (1.0–1.1 equiv) was added in one portion and the reaction mixture was warmed to room temperature. MeOH (7 equiv) and AcOH (7 equiv) were added in one portion and the resulting reaction mixture was stirred at 60 °C for 2–17 h. After complete cyclization, the reaction mixture was

Table 3
3-aryl- and alkylazaphthalides

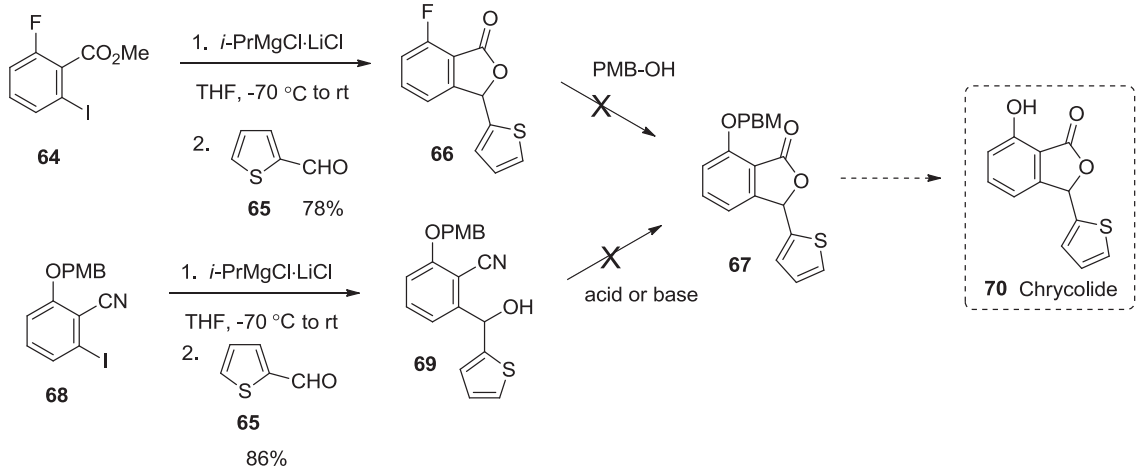
Entry	Iodide	Aldehyde	Phthalide	Yield
1	 **28**	 **47**	 **58**	70%
2	 **28**	 **29**	 **59**	70%
3	 **28**	 **60**	 **61**	67%
4	 **28**	 **62**	 **63**	60%

*4.4.1. tert-Butyl 3-chloro-2-methyl-5-oxo-5H-spiro[furo[3,4-b]pyridine-7,4′-piperidine]-1′-carboxylate (**6**).* According to general procedure A, treatment of 2.00 g (7.18 mmol) of iodopyridine **8b** and 1.57 g (7.90 mmol) of ketone **7** with 6.63 mL (8.62 mmol) of a 1.3 M solution of *i*-PrMgCl–LiCl afforded 2.01 g (79%) of **6** as light yellow crystals: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51 (s, 9H), 1.67 (d, 2H, J=12.9 Hz), 2.25 (td, 2H, J=13.8, 4.9 Hz), 2.77 (s, 3H), 3.31 (s, 2H), 4.21 (s, 2H), 8.09 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.8, 28.5, 33.9, 40.3, 80.0, 85.4, 118.3, 132.7, 133.8, 154.5, 163.6, 166.5, 168.6. Anal. Calcd for $C_{17}H_{21}ClN_2O_4$: C, 57.87; N, 7.94, H, 6.00. Found: C, 57.86; N, 7.95; H, 6.02.

*4.4.2. 1′-Benzyl-3H-spiro[isobenzofuran-1,4′-piperidine]-3-one (**14**).* According to general procedure B, treatment of 0.70 g (2.67 mmol) of methyl 2-iodobenzoate **12** with 2.47 mL (3.20 mmol) of a 1.3 M solution of *i*-PrMgCl–LiCl followed by trapping with 510 mg (2.67 mmol) of ketone **13** gave 525 mg (67%) of **18** as a colorless solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.71 (m, 2H), 2.23 (m, 2H), 2.56 (m, 2H), 2.92 (m, 2H), 3.64 (s, 2H), 7.23–7.39 (m, 5H), 7.42 (d, 1H, J=7.6 Hz), 7.51 (t, 1H, J=7.6 Hz), 7.66 (t, 1H, J=7.3 Hz), 7.87 (d, 1H, J=7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.7, 49.5, 63.2, 84.7, 121.1, 125.7, 125.9, 127.2, 128.3, 129.2, 134.1, 138.1, 153.9, 169.7. MS ($C_{20}H_{21}NO_2$): 308.2.0 ($M+H^+$).

*4.4.3. 1′-Benzyl-3′,3′,5′,5′-tetradeterio-3H-spiro[isobenzofuran-1,4′-piperidine]-3-one (**18**).* According to general procedure B, treatment of 0.66 g (2.52 mmol) of methyl 2-iodobenzoate **12** with 2.33 mL (3.02 mmol) of a 1.3 M solution of *i*-PrMgCl–LiCl followed by trapping with 0.49 g (2.52 mmol) of ketone **17** gave 532 mg (71%) of **18**[17a] as a colorless solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.56 (d, 2H, J=12.0 Hz), 2.92 (d, 2H, J=11.0 Hz), 3.64 (s, 2H), 7.23–7.39 (m, 5H), 7.42 (d, 1H, J=7.6 Hz), 7.51 (t, 1H, J=7.6 Hz), 7.66 (t, 1H, J=7.3 Hz), 7.87 (d, 1H, J=7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.7 (m), 49.5, 63.2, 84.7, 121.1, 125.7, 125.9, 127.2, 128.3, 129.2, 134.1, 138.1, 153.9, 169.7. MS ($C_{20}H_{17}D_4NO_2$): 312.2.0 ($M+H^+$).

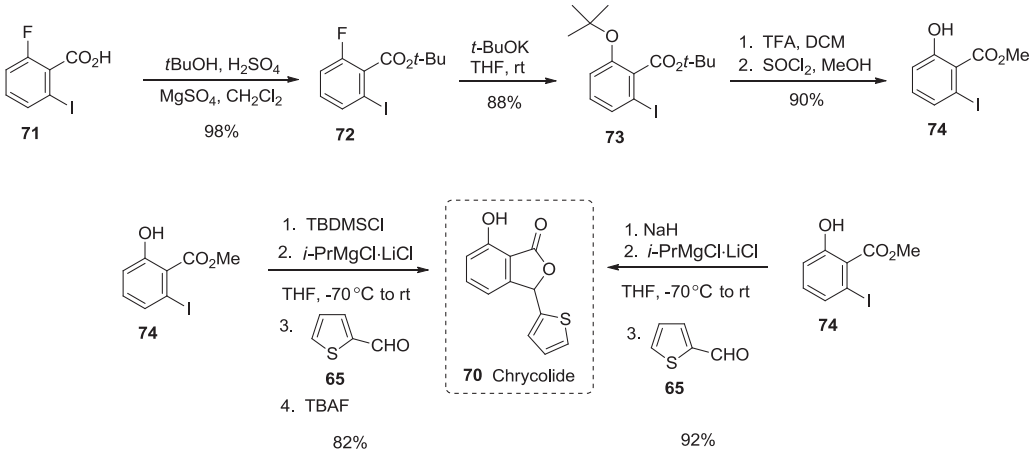
*4.4.4. tert-Butyl 3-oxo-3H-spiro[isobenzofuran-1,4′-piperidine]-1′-carboxylate (**19**).* According to general procedure B, treatment of 1.78 g (6.81 mmol) of methyl 2-iodobenzoate **12** with 6.28 mL



Scheme 7.

concentrated and then diluted with EtOAc and satd $NaHCO_3$. The resulting aqueous layer was separated and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (EtOAc/hexanes) to give the desired product.

(8.17 mmol) of a 1.3 M solution of *i*-PrMgCl–LiCl followed by trapping with 1.63 g (8.17 mmol) of ketone **7** afforded 1.73 g (84%) of **19**[30] as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51 (s, 9H), 1.69 (d, 2H, J=12.4 Hz), 2.08 (td, 2H, J=13.7, 5.0 Hz), 3.27 (s, 2H), 3.31 (s, 2H), 4.20 (s, 2H), 7.38 (dt, 1H, J=7.6, 0.9 Hz), 7.54 (td, 1H, J=7.5, 0.9 Hz), 7.69 (td, 1H, J=7.5, 1.1 Hz), 7.90 (dt, 1H, J=7.6, 0.9 Hz); ^{13}C



Scheme 8.

NMR ($CDCl_3$, 100 MHz) δ 28.4, 35.8, 40.5, 80.0, 84.6, 121.0, 125.5, 126.1, 129.5, 134.3, 153.2, 154.7, 169.4. Anal. Calcd for $C_{17}H_{21}NO_4 \cdot 0.5H_2O$: C, 65.37; N, 4.48, H, 7.10. Found: C, 65.72; N, 4.88; H, 7.49.

*4.4.5. Benzyl 3-oxo-3H-spiro[isobenzofuran-1,4′-piperidine]-1′-carboxylate (**21**).* According to general procedure B, treatment of 2.67 g (10.19 mmol) of methyl 2-iodobenzoate **12** with 8.62 mL (11.21 mmol) of a 1.3 M solution of *i*-PrMgCl–LiCl followed by trapping with 2.62 g (11.21 mmol) of ketone **20** afforded 2.58 g (75%) of **21** as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.72 (d, 2H, J=13.7 Hz), 2.10 (s, 2H), 3.36 (s, 2H), 4.31 (s, 2H), 5.20 (s, 2H), 7.34–7.41 (m, 6H), 7.55 (t, 1H, J=7.5 Hz), 7.69 (t, 1H, J=7.6 Hz), 7.91 (d, 1H, J=7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.8, 40.8, 67.5, 84.4, 121.1, 125.5, 126.2, 128.1, 128.2, 128.6, 129.7, 134.5, 136.7, 153.1, 155.3, 169.3; Anal. Calcd for $C_{20}H_{19}NO_4 \cdot 0.5H_2O$: C, 69.35; N, 4.04, H, 5.82. Found: C, 69.47; N, 4.28; H, 5.73.

*4.4.6. 3′H-Spiro[cyclohexane-1,1′-isobenzofuran]-3′-one (**23**).* According to the general procedure B, treatment of 1.50 g (5.72 mmol) of methyl 2-iodobenzoate (**12**) with 4.85 mL (6.30 mmol) of a 1.3 M solution of *i*-PrMgCl–LiCl followed by trapping with 0.618 g (6.30 mmol) of cyclohexanone (**22**) afforded 0.960 g (83%) of **23**[31] as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.71–1.86 (m, 10H), 7.38 (d, 1H, J=7.6 Hz), 7.48 (t, 1H, J=7.6 Hz), 7.63 (t, 1H, J=7.6 Hz), 7.84 (d, 1H, J=7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.3, 24.7, 36.4, 87.0, 121.0, 125.4, 125.8, 128.9, 133.9, 154.9, 170.1. Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 76.91; H, 6.67.

*4.4.7. 3′H-Spiro[cyclopentane-1,1′-isobenzofuran]-3′-one (**25**).* According to the general procedure B, treatment of 1.50 g (5.72 mmol) of methyl 2-iodobenzoate (**12**) with 4.85 mL (6.30 mmol) of a 1.3 M solution of *i*-PrMgCl–LiCl followed by trapping with 0.530 g (6.30 mmol) of cyclohexanone (**24**) afforded 0.610 g (57%) of **25**[30] as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.97 (m, 2H), 2.11 (m, 6H), 7.39 (d, 1H, J=7.6 Hz), 7.47 (t, 1H, J=7.6 Hz), 7.62 (t, 1H, J=7.6 Hz), 7.83 (d, 1H, J=7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.9, 39.6, 95.5, 121.0, 125.3, 126.0, 128.8, 134.2, 152.6, 169.8. MS ($C_{12}H_{12}O_2$): 189.3 (M+H).

*4.4.8. (±)-3-Phenyl-3-(trifluoromethyl)-2-benzofuran-1(3H)-one (**27**).* According to the general procedure B, treatment of 1.00 g (3.82 mmol) of methyl 2-iodobenzoate (**12**) with 3.23 mL (4.20 mmol) of a 1.3 M solution of *i*-PrMgCl–LiCl followed by trapping with 0.664 g (3.83 mmol) of 2,2,2-trifluoroacetophenone (**26**) afforded 0.96 g (90%) of **27** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (m, 3H), 7.69 (t, 1H, J=7.6 Hz), 7.78–7.85 (m, 3H), 7.93 (d, 1H, J=7.6 Hz), 7.99 (d, 1H, J=7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 85.6 (d, J=32 Hz), 123.22 (q, J=282 Hz), 124.2, 125.9, 126.5, 126.6, 128.9, 130.0, 131.1, 132.3, 134.9, 144.9, 167.9; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −76.3. Anal. Calcd for $C_{15}H_9F_3O_2$: C, 64.75; H, 3.26. Found: C, 64.48; H, 3.19.

*4.4.9. tert-Butyl 5-oxo-5H-spiro[furo[3,4-b]pyridine-7,4′-piperidine]-1′-carboxylate (**29**).* According to general procedure A, treatment of 2.00 g (8.70 mmol) of iodopyridine **30** and 1.91 g (9.56 mmol) of ketone **7** with 3.83 mL (9.56 mmol) of a 2.5 M solution of *n*-BuLi afforded 1.35 g (51%) of **29**[10] as white crystals: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51 (s, 9H), 1.68 (d, 2H, J=13.6 Hz), 2.27 (td, 2H, J=13.8, 4.8 Hz), 3.33 (s, 2H), 4.20 (s, 2H), 7.51 (dd, 1H, J=7.7, 4.8 Hz), 8.20 (d, 1H, J=8.7 Hz), 8.85 (d, 1H, J=4.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.4, 33.9, 40.1, 79.9, 85.6, 119.2, 124.3, 134.5, 154.5, 155.2, 167.5, 171.1. Anal. Calcd for $C_{17}H_{21}ClN_2O_4$: C, 63.14; N, 9.20, H, 6.62. Found: C, 62.74; N, 9.12; H, 6.57.

*4.4.10. 1-tert-Butyl 2-ethyl-3-iodo-1H-indole-1,2-dicarboxylate (**31**).* To a solution of 1.5 g (4.76 mmol) of ethyl 3-iodo-1*H*-indole-2-carboxylate[32] in 15 mL of CH_2Cl_2 was added 1.00 mL (7.20 mmol) of NEt_3 and 15 mg (0.123 mmol) of DMAP followed by 1.14 g (5.24 mmol) of Boc_2O. The resulting mixture was stirred at room temperature overnight and then was concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford 1.90 g (96%) of **31** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (t, 3H, J=7.3 Hz), 1.65 (s, 9H), 4.48 (q, 2H, J=7.3 Hz), 7.34 (t, 1H, J=7.6 Hz), 7.37–7.50 (m, 2H), 8.10 (d, 1H, J=8.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 27.9, 62.0, 72.1, 85.4, 115.1, 122.9, 123.9, 127.3, 130.8, 132.6, 135.9, 148.3, 162.0. Anal. Calcd for $C_{16}H_{18}INO_4$: C, 46.28; H, 4.37; N, 3.37. Found: C, 46.32; H, 4.53; N, 3.36.

*4.4.11. Di-tert-butyl 3-oxospiro[furo[3,4-b]indole-1,4′-piperidine]-1,4′-dicarboxylate (**32**).* According to general procedure B, treatment of 1.00 g (2.41 mmol) of (**31**) with 2.41 mL (3.13 mmol) of a 1.3 M solution of *i*-PrMgCl–LiCl followed by trapping with 0.48 g (2.41 mmol) of ketone **7** gave 0.674 g (63%) of **32** as a colorless foam: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51 (s, 9H), 1.67 (s, 9H), 1.79 (m, 2H), 2.24 (m, 2H), 3.31 (m, 2H), 4.21 (m, 2H), 7.34 (t, 1H, J=7.3 Hz), 7.54 (m, 2H), 8.36 (d, 1H, J=8.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.1, 28.4, 35.4, 40.1, 80.0, 80.3, 85.5, 117.3, 120.3, 120.8, 124.0, 127.6, 128.7, 142.8, 148.5, 148.7, 154.7, 159.3. Anal. Calcd for $C_{24}H_{30}N_2O_6$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.98; H, 6.73; N, 6.29.

*4.4.12. 1′-Benzyl-4-tert-butyl 3-oxospiro[furo[3,4-b]indole-1,4′-piperidine]-1′,4(3H)-dicarboxylate (**33**).* According to general procedure B, treatment of 0.28 g (0.674 mmol) of (**31**) with 0.52 mL (0.674 mmol) of a 1.3 M solution of *i*-PrMgCl–LiCl followed by trapping with 0.157 g

(0.674 mmol) of ketone **20** afforded 0.224 g (70%) of **33** as a colorless foam: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.72 (s, 9H), 1.83 (m, 2H), 2.27 (m, 2H), 3.41 (m, 2H), 4.31 (m, 2H), 5.22 (s, 2H), 7.37 (m, 6H), 7.53 (m, 2H), 8.38 (d, 1H, J=8.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.1, 35.3, 40.4, 67.4, 80.1, 85.6, 117.3, 120.2, 120.7, 124.0, 127.6, 128.1, 128.2, 128.6, 128.7, 136.6, 142.8, 148.3, 148.7, 155.2, 159.2. Anal. Calcd for $C_{27}H_{28}N_2O_6$: C, 68.05; H, 5.92; N, 5.88. Found: C, 67.81; H, 5.72; N, 5.79.

*4.4.13. (±)-4-(3-Oxo-1,3-dihydro-2-benzofuran-1-yl)benzonitrile (**35**). Method A*: According to general procedure B, treatment of 1.50 g (5.72 mmol) of methyl 2-iodobenzoate (**12**) with 4.85 mL (6.30 mmol) of a 1.3 M solution of *i*-PrMgCl–LiCl followed by trapping with 0.75 g (5.72 mmol) of 4-cyanobenzaldehyde (**34**) afforded 1.22 g (91%) of **35**[33] as a colorless solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.46 (s, 1H), 7.36 (d, 1H, J=7.6 Hz), 7.45 (d, 2H, J=8.4 Hz), 7.58 (t, 1H, J=7.6 Hz), 7.68 (m, 3H), 7.94 (d, 1H, J=7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 81.3, 113.1, 118.2, 122.7, 125.1, 126.0, 127.4, 129.9, 132.9, 134.8, 141.7, 148.6, 170.0. Anal. Calcd for $C_{15}H_9NO_2\cdot 0.2H_2O$: C, 75.43; H, 3.97; N, 5.86. Found: C, 75.74; H, 3.57; N, 5.95.

Method B: According to general procedure B, treatment of 1.50 g (6.55 mmol) of 4-iodobenzonitrile (**36**) with 5.04 mL (6.55 mmol) of a 1.3 M solution of *i*-PrMgCl–LiCl followed by trapping with 1.08 g (7.20 mmol) of methyl 2-formylbenzoate (**37**) afforded 0.99 g (64%) of **35**, which was identical to that prepared by Method A.

*4.4.14. (±)-3-(1,3-Benzodioxol-5-yl)-2-benzofuran-1(3H)-one (**34**).* According to general procedure B, treatment of 1.5 g (5.72 mmol) of methyl 2-iodobenzoate (**12**) with 4.85 mL (6.30 mmol) of a 1.3 M solution of *i*-PrMgCl–LiCl followed by trapping with 0.86 g (5.72 mmol) of piperonal (**38**) afforded 1.29 g (89%) of **39**[34] as a colorless solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.98 (m, 2H), 6.34 (s, 1H), 6.61 (s, 1H), 6.81 (d, 1H, J=7.9 Hz), 6.85 (d, 1H, J=7.9 Hz), 7.33 (d, 1H, J=7.6 Hz), 7.56 (t, 1H, J=7.5 Hz), 7.68 (t, 1H, J=7.5 Hz), 7.97 (d, 1H, J=7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 82.7, 101.4, 107.3, 108.4, 121.5, 122.9, 125.6, 125.8, 129.4, 130.0, 134.3, 148.3, 148.6, 149.6, 170.3. Anal. Calcd for $C_{15}H_{10}O_4$: C, 70.84; H, 3.96. Found: C, 70.44; H, 3.77.

*4.4.15. (±)-3-(4-Bromo-2-fluorophenyl)-2-benzofuran-1(3H)-one (**41**).* According to general procedure B, treatment of 1.5 g (5.72 mmol) of methyl 2-iodobenzoate (**12**) with 4.85 mL (6.30 mmol) of a 1.3 M solution of *i*-PrMgCl–LiCl followed by trapping with 1.16 g (5.72 mmol) of 4-bromo-2-fluorobenzaldehyde (**40**) afforded 1.35 g (77%) of **41** as a colorless solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.70 (s, 1H), 7.05 (t, 1H, J=8.0 Hz), 7.30 (dd, 1H, J=9.8, 1.9 Hz), 7.37 (dd, 1H, J=9.8, 1.9 Hz), 7.45 (d, 1H, J=7.6 Hz), 7.60 (t, 1H, J=7.6 Hz), 7.69 (t, 1H, J=7.6 Hz), 7.98 (d, 1H, J=7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 76.2, 119.7 (d, J=24 Hz), 122.7 (d, J=3.0 Hz), 123.4 (d, J=60 Hz), 123.5, 125.4, 125.9, 128.1 (d, J=30 Hz), 128.8 (d, J=3.0 Hz), 129.7, 134.7, 148.6, 160.2 (d, J=251.0 Hz), 170.0; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −115.7. Anal. Calcd for $C_{14}H_8BrFO_2$: C, 54.75; H, 2.63. Found: C, 54.66; H, 2.37.

*4.4.16. (±)-3-(2-Bromo-6-chloro-3-fluorophenyl)isobenzofuran-1(3H)-one (**43**).* According to general procedure B, treatment of 0.40 g (1.53 mmol) of methyl 2-iodobenzoate (**12**) with 1.17 mL (1.53 mmol) of a 1.3 M solution of *i*-PrMgCl–LiCl followed by trapping with 0.362 g (1.53 mmol) of aldehyde **42**[35] afforded 0.427 g (82%) of **43** as a colorless solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.99 (s, 1H), 7.19 (dd, 1H, J=8.7, 1.6 Hz), 7.34 (dd, 1H, J=7.6, 0.6 Hz), 7.53–7.62 (m, 2H), 7.68 (dt, 1H, J=7.5, 1.0 Hz), 8.01 (d, 1H, J=7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 76.1, 108.8 (d, J=22 Hz), 122.0, 123.4 (d, J=20 Hz), 125.8, 126.1, 126.8 (d, J=4 Hz), 129.7, 133.9 (d, J=4 Hz), 134.4, 134.6, 147.5, 158.3 (d, J=254 Hz), 170.1. Anal. Calcd for $C_{14}H_7BrClFO_2$: C, 49.23; H, 2.07. Found: C, 48.91; H, 1.79.

*4.4.17. (±)-3-(2-Bromopyridin-3-yl)-2-benzofuran-1(3H)-one (**44**).* According to general procedure B, treatment of 1.5 g (5.72 mmol) of methyl 2-iodobenzoate (**12**) with 4.85 mL (6.30 mmol) of a 1.3 M solution of *i*-PrMgCl–LiCl followed by trapping with 1.065 g (5.72 mmol) of 2-bromopyridinecarboxaldehyde (**44**) afforded 1.50 g (90%) of **45** as a colorless solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.92 (s, 1H), 7.27 (dd, 1H, J=7.7, 4.7 Hz), 7.42 (dd, 1H, J=7.7, 1.9 Hz), 7.62 (m, 1H), 7.65–7.72 (m, 2H), 8.00 (d, 1H, J=7.7 Hz), 8.41 (dd, 1H, J=4.7, 1.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 79.9, 122.9, 123.4, 125.1, 130.0, 134.1, 134.8, 136.2, 141.9, 148.6, 150.5, 170.0; Anal. Calcd for $C_{13}H_8BrNO_2$: C, 53.82; H, 2.78; N, 4.83. Found: C, 53.68; H, 2.60; N, 4.69.

*4.4.18. (±)-6-Bromo-3-(4-bromophenyl)isobenzofuran-1(3H)-one (**48**).* According to general procedure B, treatment of 1.0 g (2.93 mmol) of methyl 2-iodobenzoate (**12**) with 1.76 mL (3.52 mmol) of a 1.3 M solution of *i*-PrMgCl–LiCl followed by trapping with 0.570 g (3.08 mmol) of aldehyde **47** afforded 0.750 g (70%) of **48** as a colorless solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.43 (s, 1H), 7.16 (d, 2H, J=8.4 Hz), 7.22 (d, 1H, J=8.1 Hz), 7.53 (d, 2H, J=8.5 Hz), 7.79 (dd, 1H, J=8.2, 1.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 81.8, 123.7, 123.8, 124.4, 127.6, 128.6, 128.8, 132.3, 134.8, 137.6, 147.8, 168.6; MS ($C_{14}H_8Br_2O_2$): 366.9 ($M+H^+$).

*4.4.19. (±)-3-(But-3-en-1-yl)isobenzofuran-1(3H)-one (**50**).* According to general procedure B, treatment of 2.68 g (10.21 mmol) of methyl 2-iodobenzoate (**12**) with 9.82 mL (12.77 mmol) of a 1.3 M solution of *i*-PrMgCl–LiCl followed by trapping with 1.20 g (14.30 mmol) of aldehyde **49** afforded 1.83 g (95%) of **50** as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.83–1.92 (m, 1H), 2.13–2.38 (m, 3 H), 5.05–5.14 (m, 2H), 5.53 (dd, 1H, J=8.1, 3.5 Hz), 5.81–5.92 (m, 1H), 7.47 (d, 1H, J=7.6 Hz), 7.56 (t, 1H, J=7.5 Hz), 7.70 (t, 1H, J=7.7 Hz), 7.93 (d, 1H, J=7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.1, 34.1, 80.6, 115.9, 121.8, 125.7, 126.2, 129.1, 134.0, 136.8, 149.9, 170.5; Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.01; H, 6.23.

*4.4.20. (±)-3-Butyl-2-benzofuran-1(3H)-one (**52**).* According to general procedure B, treatment of 2.00 g (7.62 mmol) of methyl 2-iodobenzoate (**12**) with 5.87 mL (7.63 mmol) of a 1.3 M solution of *i*-PrMgCl–LiCl followed by trapping with 0.986 g (11.45 mmol) of valeraldehyde (**51**) afforded 1.19 g (82%) of **52** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, 3H, J=7.1 Hz), 1.30–1.47 (m, 4H), 1.68–1.76 (m, 1H), 1.99–2.05 (m, 1H), 5.45 (m, 1H), 7.42 (d, 1H, J=7.6 Hz), 7.47 (t, 1H, J=7.6 Hz), 7.65 (t, 1H, J=7.6 Hz), 7.84 (d, 1H, J=7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 22.4, 26.8, 34.4, 81.4, 121.8, 125.5, 126.1, 129.0, 134.0, 150.1, 170.6. MS ($C_{12}H_{14}O_2$): 191.1 ($M+H^+$).

*4.4.21. (±)-3-(4-Bromophenyl)isobenzofuran-1(3H)-one (**54**).* According to general procedure B, treatment of 1.2 g (5.24 mmol) of iodonitrile (**53**) with 5.04 mL (6.55 mmol) of a 1.3 M solution of *i*-PrMgCl–LiCl followed by trapping with 1.26 g (6.81 mmol) of aldehyde **47** afforded 1.18 g (78%) of **54**[33] as a colorless solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.37 (s, 1H), 7.17 (d, 2H, J=8.4 Hz), 7.33 (d, 1H, J=7.6 Hz), 7.50 (d, 2H, J=8.5 Hz), 7.57 (t, 1H, 7.5 Hz), 7.67 (t, 1H, J=7.4 Hz), 7.95 (d, 1H, J=7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 81.9, 122.8, 123.5, 125.4, 125.8, 128.6, 129.6, 132.2, 134.5, 135.5, 149.2, 170.3; MS ($C_{14}H_{10}BrO_2$): 289.0 ($M+H^+$).

*4.4.22. (±)-1-tert-Butyl 2-ethyl 3((4-cyanophenyl)(hydroxy)methyl)-1H-indole-1,2-dicarboxylate (**55**).* According to general procedure C, treatment of 0.370 g (0.891 mmol) of **31** with 0.754 mL (0.98 mmol) of a 1.3 M solution of *i*-PrMgCl–LiCl followed by trapping with 0.117 g (0.891 mmol) of 4-cyanobenzaldehyde (**34**) afforded 0.338 g (90%) of **55** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (t, 3H, J=7.2 Hz), 1.66 (s, 9H), 3.41 (d, 1H, J=5.7 Hz), 4.34 (q, 2H, J=7.2 Hz), 6.28 (d, 1H, J=5.7 Hz), 7.22 (t, 1H, J=7.1 Hz), 7.41 (t, 1H, J=8.5 Hz), 7.54 (d, 1H, J=7.1 Hz), 7.60 (d, 2H, J=8.5 Hz), 7.64 (d, 2H, J=8.5 Hz),

8.06 (d, 1H, J=8.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 28.0, 62.2, 67.6, 85.3, 111.1, 115.2, 118.8, 121.2, 123.5, 126.2, 126.7, 127.1, 127.6, 132.1, 136.4, 147.5, 149.1, 163.1. Anal. Calcd for $C_{24}H_{24}N_2O_5$: C, 68.56; H, 5.75; N, 6.66. Found: C, 68.39; H, 5.67; N, 6.56.

*4.4.23. (±)-7-(1,3-Benzodioxol-5-yl)-furo[3,4-b]pyridine-5(7**H**)-one (**57**).* According to general procedure C, treatment of 2.00 g (7.22 mmol) of ethyl 2-iodopyridine-3-carboxylate (**28**) with 6.11 mL (7.94 mmol) of a 1.3 M solution of *i*-PrMgCl–LiCl followed by trapping with 1.19 g (7.94 mmol) of piperonal (**38**) afforded 1.52 g (83%) of **57** as a colorless solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.98 (m, 2H), 6.37 (9s, 1H), 6.75 (d, 1H, J=1.5 Hz), 6.84 (d, 1H, J=8.0 Hz), 6.96 (dd, 1H, J=8.0, 1.5 Hz), 7.52 (dd, 1H, J=7.7, 4.8 Hz), 8.27 (dd, 1H, J=7.7, 1.6 Hz), 8.89 (dd, 1H, J=4.9, 1.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 83.0, 101.4, 107.1, 108.6, 119.5, 121.3, 124.3, 128.2, 134.2, 148.2, 148.6, 155.7, 168.3. Anal. Calcd for $C_{14}H_9NO_4$: C, 65.88; H, 3.55; N, 5.49. Found: C, 65.48; H, 3.28; N, 5.33.

*4.4.24. (±)-7-(4-Bromophenyl)furo[3,4-b]pyridin-5(7H)-one (**58**).* According to general procedure C, treatment of 1.4 g (5.05 mmol) of 2-iodopyridine (**28**) with 5.25 mL (6.82 mmol) of a 1.3 M solution of *i*-PrMgCl–LiCl followed by trapping with 1.22 g (6.52 mmol) of aldehyde **47** afforded 1.02 g (70%) of **58** as a colorless solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.41 (s, 1H), 7.34 (d, 2H, J=8.4 Hz), 7.53 (d, 3H, J=8.6 Hz), 8.26 (d, 1H, J=7.8 Hz), 8.87 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 82.0, 119.1, 123.4, 124.4, 128.2, 132.1, 133.8, 134.3, 155.8, 168.0, 168.1; MS ($C_{13}H_8BrNO_2$): 290.0 ($M+H^+$).

*4.4.25. (±)-4-(5-Oxo-5,7-dihydrofuro[3,4-b]pyridin-7-yl)benzonitrile (**59**).* According to general procedure C, treatment of 1.00 g (3.61 mmol) of ethyl 2-iodopyridine (**28**) with 3.33 mL (4.33 mmol) of a 1.3 M solution of *i*-PrMgCl–LiCl followed by trapping with 0.473 g (3.61 mmol) of 4-cyanobenzaldehyde (**34**) afforded 0.600 g (70%) of **59** as a colorless solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.49 (s, 1H), 7.54 (dd, 1H, J=7.9, 4.9 Hz), 7.66 (d, 2H, J=8.5 Hz), 7.70 (d, 2H, J=8.5 Hz), 8.26 (dd, 1H, J=7.9, 1.6 Hz), 8.86 (dd, 1H, J=4.9, 1.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 81.1, 113.0, 118.2, 119.0, 124.7, 127.0, 132.6, 134.5, 139.9, 155.9, 167.3, 167.8. Anal. Calcd for $C_{14}H_8N_2O_2$: C, 71.18; H, 3.41; N, 11.86. Found: C, 70.99; H, 3.34; H, 11.59.

*4.4.26. (±)-7-(2-Methoxy-5,6,7,8-tetrahydroquinolin-3-yl)furo[3,4-b]pyridin-5(7H)-one (**61**).* According to general procedure C, treatment of 0.25 g (0.90 mmol) of ethyl 2-iodopyridine (**28**) with 0.833 mL (1.08 mmol) of a 1.3 M solution of *i*-PrMgCl–LiCl followed by trapping with 0.173 g (0.90 mmol) of aldehyde **60**[36] afforded 0.180 g (67%) of **61** as a colorless solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.72–1.84 (m, 4H), 2.62 (t, 2H, J=6.3 Hz), 2.76 (t, 2H, J=6.3 Hz), 3.75 (s, 3H), 6.51 (s, 1H), 7.11 (s, 1H), 7.47 (dd, 1H, J=7.7, 4.7 Hz), 8.24 (dd, 1H, J=7.7, 1.4 Hz), 8.82 (dd, 1H, J=4.7, 1.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.7, 22.9, 27.6, 32.2, 53.3, 80.1, 113.8, 120.5, 123.9, 124.7, 133.8, 139.5, 155.2, 156.3, 159.4, 168.5, 168.7. Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.92; H, 5.41; H, 9.46.

*4.4.27. (±)-7-Ethylfuro[3,4-b]pyridin-5(7H)-one (**63**).* According to general procedure C, treatment of 4.10 g (14.80 mmol) of 2-iodopyridine (**28**) with 14.23 mL (18.50 mmol) of a 1.3 M solution of *i*-PrMgCl–LiCl followed by trapping with 1.12 g (19.24 mmol) of aldehyde **62** afforded 1.45 g (60%) of **63** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.02 (t, 3H, J=7.4 Hz), 1.91–1.99 (m, 2H), 2.25–2.32 (m, 1H), 5.47 (dd, 1H, J=6.9, 4.4 Hz), 7.50 (dd, 1H, J=7.7, 4.9 Hz), 8.21 (d, 1H, J=7.7 Hz), 8.88 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.7, 26.2, 83.2, 120.2, 124.0, 134.0, 155.1, 168.7, 168.9; MS ($C_9H_9NO_2$): 164.0 ($M+H^+$).

*4.4.28. tert-Butyl 2-fluoro-6-iodobenzoate (**72**).* A 500-mL round-bottomed flask was charged with 12.7 g (105 mmol) of magnesium sulfate and 150 mL of DCM. Sulfuric acid (1.40 mL, 26.3 mmol) was added in one portion and the reaction mixture was stirred at room temperature for 30 min. Carboxylic acid **71** (7.00 g, 26.3 mmol) and *tert*-butanol (9.75 g, 132 mmol) were added in one portion and the resulting reaction mixture was stirred at room temperature overnight. The reaction mixture was then filtered and the filtrate was carefully quenched with satd $NaHCO_3$. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (EtOAc/hexanes) to give 8.3 g (98%) of **72** as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.65 (s, 9H), 7.05–7.13 (m, 2H), 7.63 (d, 1H, J=8.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.1, 83.9, 92.1 (d, J=2.9 Hz), 115.7 (d, J=21.5 Hz), 129.9 (d, J=20.2 Hz), 131.6 (d, J=8.1 Hz), 134.9 (d, J=3.6 Hz), 158.8 (d, J=253.9 Hz), 164.0. Anal. Calcd for $C_{11}H_{12}FIO_2$: C, 41.02; H, 3.75. Found: C, 41.10; H, 3.52.

*4.4.29. tert-Butyl 2-(tert-butoxy)-6-iodobenzoate (**73**).* A 200-mL round-bottomed flask was charged with iodoester **72** (4.0 g, 12.42 mmol) and 50 mL of THF. The reaction mixture was cooled at 5 °C and potassium *tert*-butoxide (1.53 g, 13.66 mmol) was added in one portion. The resulting reaction mixture was stirred at room temperature for 17 h and then cooled to room temperature and quenched with satd NH_4Cl. The aqueous layer was separated and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated to give 4.1 g (88%) of **73** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 9H), 1.65 (s, 9H), 6.96 (t, 1H, J=8.2 Hz), 7.11 (d, 1H, J=8.3 Hz), 7.45 (d, 1H, J=7.9 Hz). Anal. Calcd for $C_{15}H_{21}IO_3$: C, 47.89; H, 5.63. Found: C, 47.95; H, 5.44.

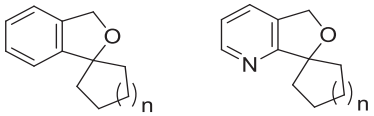
*4.4.30. Methyl 2-hydroxy-6-iodobenzoate (**74**).* A 100-mL round-bottomed flask was charged with ester **73** (1.73 g, 4.60 mmol) and 20 mL of DCM at 5 °C. TFA (0.71 mL, 9.20 mmol) was added drop wise via syringe and the resulting reaction mixture was slowly warmed to room temperature over 1 h. The reaction mixture was then diluted with water. The organic layer was separated, washed with brine, and concentrated to give 1.3 g of a white solid. The solid was dissolved in 15 mL of DCM and charged with oxalyl chloride (0.60 mL, 6.90 mmol) and cat. DMF. The reaction mixture was stirred at room temperature for 1 h and then quenched with excess MeOH. Water was then added to the reaction mixture. The organic layer was separated, washed with brine, and concentrated. The residue was purified by column chromatography (EtOAc/hexanes) to give 1.15 g (90%) of **74** as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.00 (s, 3H), 6.97–7.04 (m, 2H), 7.61 (dd, 1H, J=7.2, 1.6 Hz) 10.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.0, 93.8, 116.8, 118.2, 133.9, 135.1, 162.4, 169.0. Anal. Calcd for $C_8H_7IO_3$: C, 34.56; H, 2.54. Found: C, 34.63; H, 2.16.

*4.4.31. (±)-Chrycolide (**70**).* A 40-mL vial equipped with a nitrogen inlet needle and thermocouple was charged with iodide **74** (0.222 g, 0.798 mmol) and 3 mL of THF. The reaction mixture was cooled at 5 °C while sodium hydride (0.038 g, 0.96 mmol) was added in three portions. The resulting reaction mixture was stirred at 5 °C for 10 min and then cooled to −70 °C. A 1.3 M solution of *i*-PrMgCl–LiCl (0.921 mL, 1.20 mmol) was added drop wise via syringe over 3 min and the reaction mixture was stirred at −70 °C for 30 min. Thiophene-2-carbaldehyde (**65**) (0.224 g, 1.80 mmol) was added in one portion. The resulting reaction mixture was warmed to room temperature over 1 h and then quenched with satd NH_4Cl. The aqueous layer was separated and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated onto silica gel. The residue was purified by column chromatography (EtOAc/hexanes) to give 0.185 g (92%) of **70** as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.71 (s, 1H), 6.98–7.06 (m, 3H), 7.19 (s, 1H), 7.42 (s, 1H), 7.62

(t, 1H, J=6.2 Hz), 7.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 79.1, 111.1, 114.6, 116.2, 127.1, 127.9, 128.3, 137.2, 138.2, 148.7, 156.5, 171.3. MS ($C_{12}H_8O_3S$): 233.0 ($M+H^+$).

References and notes

1. General structures of dihydro-isobenzofurans and dihydro-furopyridines.



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