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# Synthesis of model southern rim structures of photosynthetic tetrapyrroles and phyllobilins†

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The photosynthetic tetrapyrroles and their catabolic products (phyllobilins) share similar structural features in the southern rim encompassing rings C–E with variation in the degree of saturation including a dihydrodipyrrin (chlorophyll *a* and bacteriochlorophyll *a*), a dipyrromethane (phylloleucobilin), and a dipyrrin (chlorophyll *c*). Here, a direct, two-step route to southern rim structures was examined. The Knoevenagel condensation of a pyrrole bearing a β-ketoester at the 3-position with a pyrrole-2-carboxaldehyde formed the dipyrrole-substituted propenone, which upon Nazarov cyclization gave the dipyrromethane-type southern rim containing the annulated, isocyclic ring. In this manner, three southern rim structures (51–80%) were obtained that vary in the nature of the pyrrole substituents (H, methyl, carbomethoxy). Characterization by $^{1}$H NMR spectroscopy in each case revealed an expected mixture of *trans*/*cis* isomers (~9 : 1 ratio). Several derivatization processes (pyrrole acylation with trichloroacetic anhydride, ketone reduction with borohydrides) were examined. Analysis of one southern rim compound by single-crystal X-ray diffraction showed the *trans* configuration for the expected pair of enantiomers in the unit cell; a second compound gave the *trans* enantiomers as a conglomerate. The Knoevenagel–Nazarov route from relatively accessible pyrroles may provide new scaffolds for constructing tetrapyrrole architectures.

## Introduction

Photosynthetic tetrapyrroles harvest sunlight and thereby channel the energy that drives the biosphere. Each year an estimated $10^{15}$ g of chlorophyll is produced globally.[1] Until recently, the catabolites from this vast quantity of natural products were unknown. The pioneering work of Hörtensteiner, Kräutler, Moser, and coworkers has revealed the formation of a number of such species, termed phyllobilins, which originate from oxidative ring-opening of the chlorophyll macrocycle.[2–5] The metabolic breakdown products of other photosynthetic tetrapyrroles have been little investigated. Representative structures of photosynthetic tetrapyrroles and phyllobilins are provided in Chart 1. The structures include chlorophyll $c_1$, a light-harvesting pigment in algae; chlorophyll *a* of oxygenic photosynthesis in plants and cyanobacteria; and bacteriochlorophyll *a* of anoxygenic photosynthesis.[6] Also shown is a phylloleucobilin, one of the growing number of open-chain tetrapyrroles (phyllobilins) derived from chlorophyll *a*.[7]

A common feature to all the structures is the presence of ring E, also termed the isocyclic ring or the exocyclic ring, which contains an embedded β-ketoester motif. Examination of the various pigments shown in Chart 1 reveals the structural similarities and subtle differences of the southern rim, defined as the structure encompassing rings C, D, and E of the macrocycles. Phyllobilins are labeled differently, wherein the southern rim encompasses rings B, C, and E. For a porphyrin (chlorophyll $c_1$), the core motif is a dipyrrin. For a chlorin or bacteriochlorin (chlorophyll *a* or bacteriochlorophyll *a*), the core motif is a dihydrodipyrrin. For selected phyllobilins, the core motif is a dipyrromethane. Thus, for the respective macrocycles or phylloleucobilin, in each case the rightmost ring (C or B) is fully unsaturated whereas the leftmost ring (D or C) and the central carbon (flanked by the two pyrrolic units) vary in the degree of saturation.[7]

The photosynthetic tetrapyrroles and phyllobilins have generally not drawn the attention of the organic chemistry community.[8] A deep understanding of the functional roles of the former, and the ecological disposition of the latter, could benefit from the availability of incisive methods for chemical synthesis. A major challenge in the synthesis of native photosynthetic tetrapyrroles and analogues has been the synthesis of the isocyclic ring.[9]

We have been working to develop routes to native chlorophylls and bacteriochlorophylls. The synthetic route relies on

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† Electronic supplementary information (ESI) available: $^{1}$H NMR and $^{13}$C{$^{1}$H} NMR data for all new compounds; single-crystal X-ray diffraction data. CCDC 2266091 (**4-Es**), CCDC 2266093 (**6-HH**), CCDC 2266094 (**7**, 5*R*,3$^{2}$*S* isomer), CCDC 2266097 (**7**, 5*S*,3$^{2}$*R* isomer). For ESI and crystallographic data in CIF or other electronic format see DOI: **https://doi.org/10.1039/d3nj02515b**

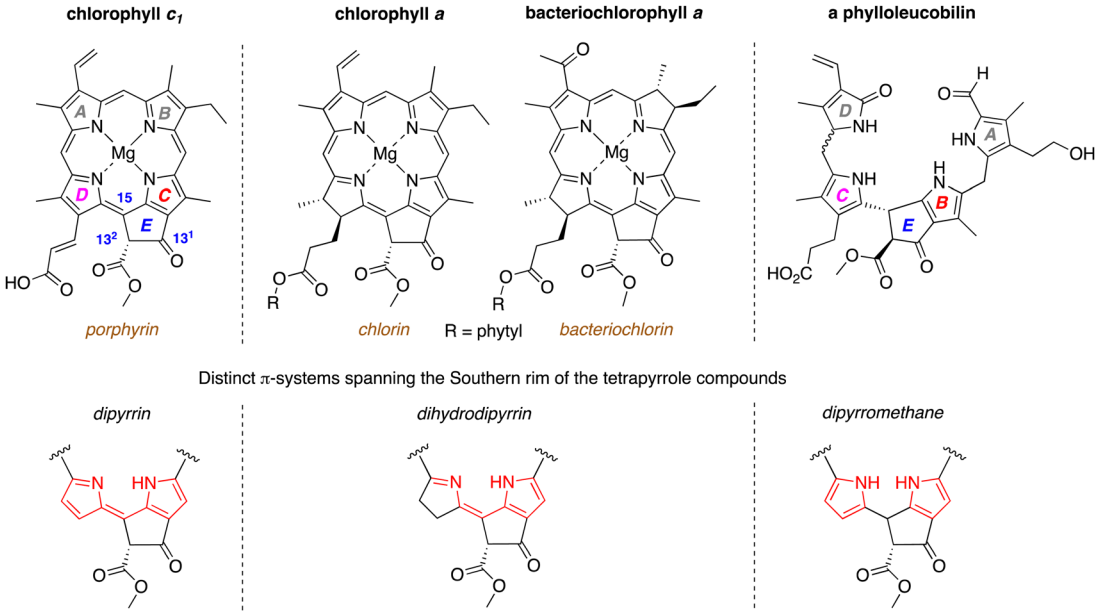
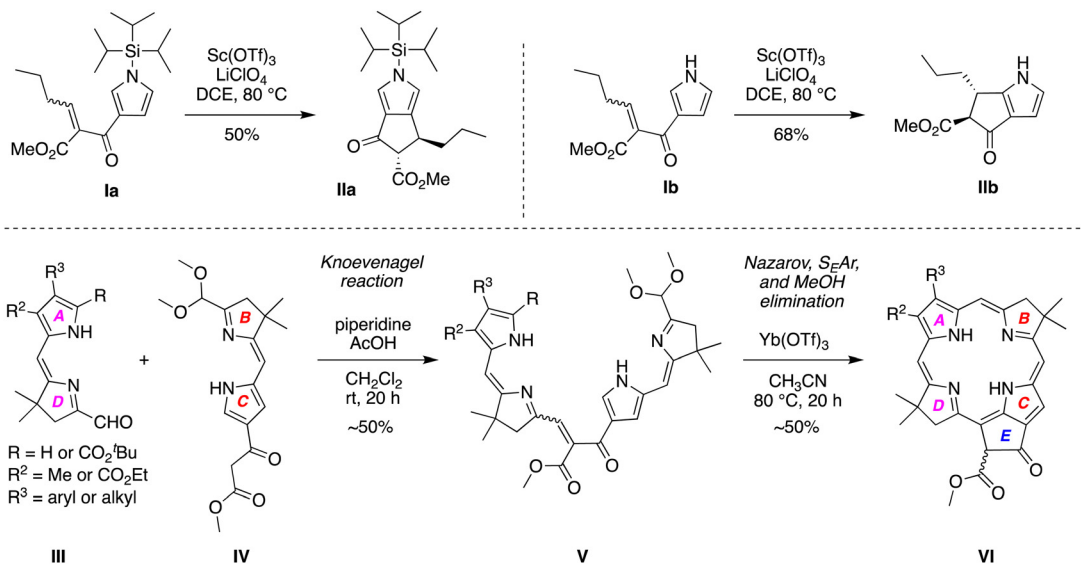



Chart 1 Representative photosynthetic tetrapyrroles and one phyllobilin (top). The numbering system applies to the macrocycles (top). Corresponding southern rim structures units with substituents omitted for clarity (bottom).

the Nazarov cyclization to construct ring E. In this regard, Frontier and coworkers reported the Nazarov cyclization of an enone (**Ia**) derived from pyrrole bearing a 3-methoxy-1,3-dioxopropyl unit at the β-position (Scheme 1, top).[10] With a TIPS-substituted pyrrole (**Ia**), the cyclization occurred across the pyrrole 3,4-positions to give Nazarov product **IIa**, whereas in the absence of the steric congestion presented by the TIPS group, cyclization of **Ib** occurred across the pyrrole 2,3-positions to give Nazarov product **IIb**. We also have employed the Nazarov cyclization in a similar guise as part of a *de novo* synthesis of bacteriochlorophyll model compounds beginning with AD and BC halves **III** and **IV** (Scheme 1, bottom).[11] In the latter synthesis, the Nazarov cyclization of enone **V** is accompanied or followed by electrophilic aromatic substitution and elimination of methanol to create the macrocycle **VI**. The route was first developed with use of a gem-dimethyl group in the pyrroline ring, and was recently shown to be compatible with *trans*-dialkyl substituents as required for synthesis of the native photosynthetic pigments.[12,13]

In this paper, we report an initial set of studies aimed at establishing the foundation for gaining access to phyllobilins. A long-term objective is to synthesize diverse phyllobilins for fundamental chemical, ecological, and nutritional studies. The synthesis of the key pyrroles is described first followed by focus




Scheme 1 Nazarov cyclizations with pyrroles (top) and route to bacteriochlorophyll model compounds (bottom).

on the Knoevenagel condensation and Nazarov cyclization to form the southern rim compounds. The products have been examined by absorption spectroscopy, $^1$H NMR spectroscopy, and single-crystal X-ray diffraction. The southern rim compounds reported herein are dipyrromethanes (which are invaluable constituents in tetrapyrrole chemistry[14–16]) that are equipped with an annulated ring characteristic of the native macrocycles. Of the 73 phyllobilins and analogues described in a recent review, 51 contain a dipyrromethane southern rim.[7] The present work identifies opportunities and constraints in key reactions that could support the synthesis of phyllobilin and other tetrapyrrole model compounds.

## Results and discussion

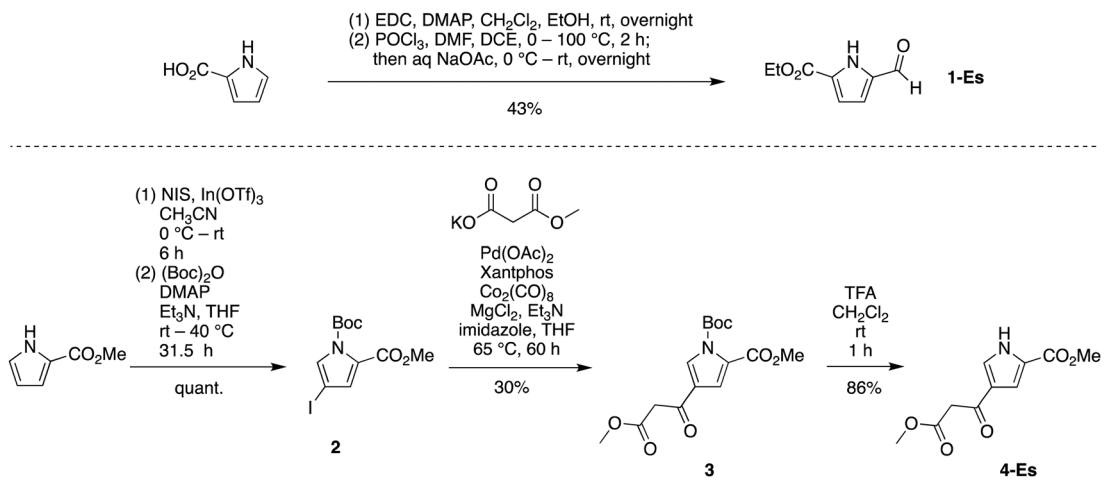
### Synthesis of pyrrole precursors

To examine the Nazarov cyclizations of several substituted pyrroles, two pyrrole precursors were prepared. Pyrrole-2-carboxylic acid was subjected to esterification[17] with ethanol in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and 4-dimethylaminopyridine (DMAP). Subsequent Vilsmeier–Haack formylation[18] afforded ethyl 5-formylpyrrole-2-carboxylate (**1-Es**) in 43% yield over two steps (Scheme 2, top). We subsequently found a recent procedure to prepare **1-Es** in 99% yield.[19] Iodination[20] of methyl pyrrole-2-carboxylate was carried out with *N*-iodosuccinimide (NIS) and $In(OTf)_3$. Protection of the pyrrolic nitrogen atom by reaction with di-*tert*-butyl dicarbonate $[(Boc)_2O]$[21] in the presence of DMAP and $Et_3N$[22] afforded the intermediate **2** in quantitative yield over the two steps. The installation of the β-ketoester relies on the known reaction of an aryl halide and potassium monomethyl malonate.[23] The carbonylation has been applied with pyrroles.[11,18,24–26] The reaction of **2** and potassium monomethyl malonate was carried out in tetrahydrofuran (THF) with the addition of $Pd(OAc)_2$, Xantphos, $Co_2(CO)_8$, $MgCl_2$, $Et_3N$, and imidazole for 60 hours at 65 °C. In this manner, the intermediate **3** was obtained in 30% yield. Finally, cleavage of the Boc group[25] was carried out with trifluoroacetic acid (TFA) to give the target pyrrole **4-Es** as a pale yellow solid in 86% yield (Scheme 2, bottom). In a separate implementation under ostensibly the same conditions, the Pd-mediated reaction of **2** and potassium monomethyl malonate afforded **4-Es** directly in 29% yield. The "Es" suffix is appended for comparison purposes (*vide infra*). Single-crystal X-ray diffraction validated the structure of **4-Es** (see the ESI†).

### Formation of southern rim compounds

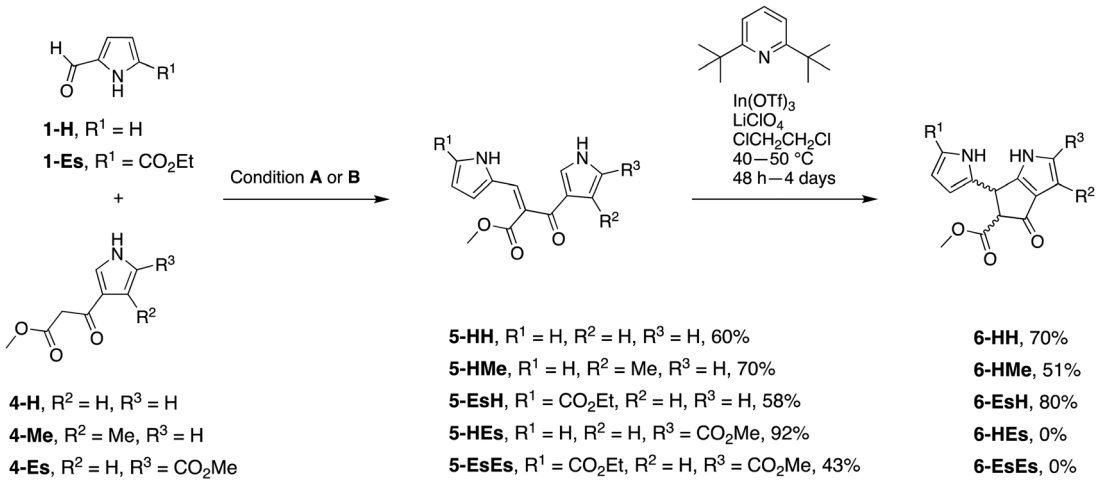
The availability of two pyrrole–carboxaldehydes (**1-H**, **1-Es**) and three pyrrole-β-ketoesters (**4-H**, **4-Me**, **4-Es**) enabled study of the effects of simple substituents on the yields of the Knoevenagel and Nazarov reactions (Scheme 3). The Knoevenagel reaction[27] of pyrrole-2-carboxaldehyde (**1-H**) and pyrrole-β-ketoester **4-H**[26] was carried out in the presence of acetic acid, piperidine, and molecular sieves (4 Å) in dichloromethane at 40 °C for 20 h. The product **5-HH** was obtained as a brown solid in 60% yield. Under the same condition, the reaction of pyrrole-2-carboxaldehyde **1-H** and 4-methylpyrrole-β-ketoester **4-Me** gave the product **5-HMe** in 70% yield. Modified conditions[28] that lack molecular sieves (condition B) also were examined. Thus, the Knoevenagel reaction of **1-Es** and **4-H** (in methanol containing piperidine at 45 °C for 48 h) afforded the resulting enone **5-EsH** in 58% yield. The Knoevenagel reaction of **1-H** and **4-Es** under condition B gave **5-HEs** as a yellow oil in 92% yield, whereas the analogous reaction of **1-Es** and **4-Es** gave product **5-EsEs** as a pale yellow solid in 43% yield (Scheme 3).

The Nazarov cyclization has been performed under a variety of conditions.[29,30] The literature reports often employ a trivalent Lewis acid in conjunction with an added salt, generally $LiClO_4$. The rationale for the Lewis acid is to facilitate formation of the pentadienyl cation as required for the 4π-electrocyclization.[31] During the reaction, the Lewis acid forms a bidentate complex with the oxygen atoms of the β-ketoester, while the anion of the added salt (e.g., perchlorate) is regarded as undergoing exchange with the anion of the Lewis acid thereby enhancing catalytic activity.[32] The *E* and *Z* isomers of enones are known to interconvert under the conditions of the Nazarov reaction,[10,12,33–36]




Scheme 2 Synthesis of target pyrroles.




Scheme 3 Synthesis of southern rim compounds. Condition A: piperidine, AcOH, MS 4 Å, $CH_2Cl_2$, 40 °C, 20 h; condition B: piperidine, MeOH, 50 °C, 24 or 48 h.

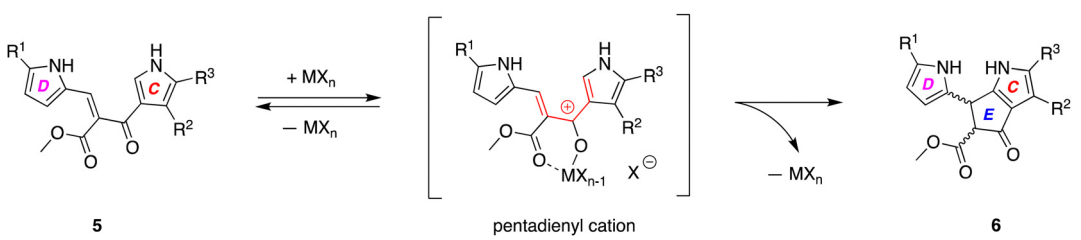
hence no effort was made to separate the *E* and *Z* isomers of the Knoevenagel enones for independent use in the subsequent Nazarov cyclizations.

Prior studies showed that the Nazarov cyclization products (**VI**, Scheme 1) were obtained in good yield upon treatment of the Knoevenagel enone (**V**) with $Yb(OTf)_3$ in $CH_3CN$ at 80 °C for 20 hours.[11] A lengthy survey of analogues of **V** did not reveal any acid superior to $Yb(OTf)_3$.[13] The prior studies employed a dilute solution (0.2 mM) of the Knoevenagel enone (**V**) because the Nazarov cyclization was only one of several transformations required in the one-flask process to yield the bacteriochlorin macrocycle (**VI**).[11] Here, compound **5-HH** was subjected to the same conditions as well as at increased concentration along with use of the proton scavenger[37] 2,6-di-*tert*-butylpyridine. In both of the latter cases, only a trace of the Nazarov product **6-HH** was detected (by TLC analysis). A short survey of acids ($AlCl_3$,[38] $TiCl_4$,[39] $FeCl_3$[40] or methanesulfonic acid[41]) did not give the desired product **6-HH**. On the other hand, $Sc(OTf)_3$ and $In(OTf)_3$ worked well in 1,2-dichloroethane (a solvent found effective by Frontier and coworkers[10]), and further increases in yield were observed upon inclusion of $LiClO_4$. Ultimately, the use of $In(OTf)_3$, $LiClO_4$, and 2,6-di-*tert*-butylpyridine in 1,2-dichloroethane at 40 °C under an argon atmosphere was found to be the most effective. While a more systematic survey of reaction conditions is warranted, application of this condition at the 1.0 mmol scale provided the desired product **6-HH** in 70% isolated yield (Scheme 3).

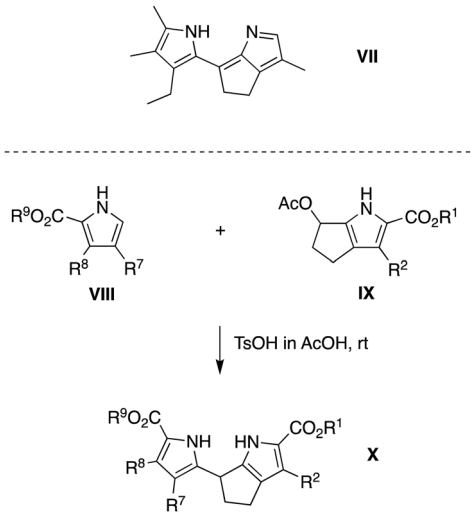
Under the best condition for **5-HH** with the use of $In(OTf)_3$ along with addition of $LiClO_4$ in 1,2-dichloroethane at 40 °C, a small-scale reaction (168 mg) of enone **5-HMe** was conducted, which afforded **6-HMe** in 51% yield. The origin of the lower yield with the more electron-rich pyrrole is not clear, particularly since a single methyl group is known to substantially potentiate the reactivity of pyrroles toward electrophiles.[42,43] The enone **5-EsH** was treated to the same conditions for the Nazarov cyclization to afford **6-EsH** in 80% yield. On the other hand, under the same conditions neither **5-HEs** nor **5-EsEs** gave the desired cyclization product. The Nazarov reaction is known to be highly dependent on electronic effects given the intermediacy of the pentadienyl cation (Scheme 4).[34] An electron-rich ring C or an electron-deficient ring D (macrocycle nomenclature) is expected to accelerate the cyclization.[44] Our limited results show that the southern rim can be prepared bearing an ester at the α-position of ring D but not ring C. The *cis–trans* stereochemistry of the isolated southern rim products (**6-HH**, **6-HMe**, **6-EsH**) is described in the Characterization section (*vide infra*).

## Comparison of synthetic routes

The synthesis of the southern rim compounds can be compared with prior work in this general regard. An annulated dipyrrolic compound (**VII**) was displayed 55 years ago by Flaugh and Rapoport (Scheme 5, top),[45] but to our knowledge, no synthesis was ever reported. Pioneering and extensive work by Lash and coworkers[46,47] has afforded a general synthesis (Scheme 5, bottom) whereby a 2-unsubstituted pyrrole (**VIII**) reacts with an annulated pyrrole bearing an acetoxy group at the α-methylene




Scheme 4 Proposed Nazarov cyclization mechanism.

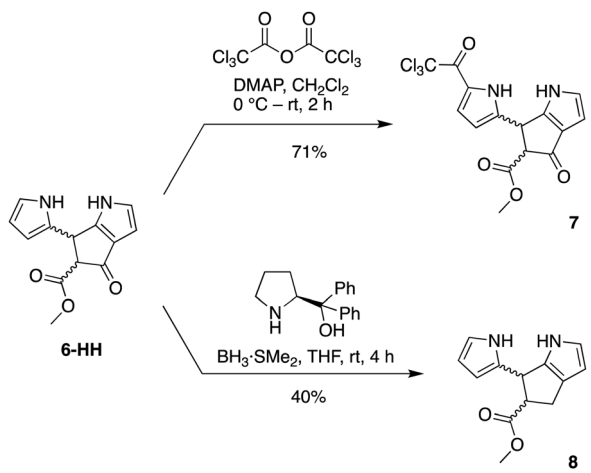



Scheme 5 Prior synthetic analogues of the southern rim.

site (**IX**). The Lash synthesis[48,49] builds the annulated ring first, generally during formation of the pyrrole itself, then creates the annulated dipyrromethane (**X**), to be contrasted with the synthesis herein where the annulated ring is formed concomitant with the dipyrromethane. The Lash structures (**X**) would correspond to derivatives of the native southern rim where in both desmethoxycarbonylation and deoxygenation have occurred. Such structures may also prove beneficial as phyllobilin model compounds.

### Derivatization of a southern rim compound

Elaboration of the southern rim compounds provides an attractive means of accessing open-chain structures such as phyllobilins. Pyrrole has long been known to react with trichloroacetic anhydride to give the 2-(trichloroacetyl)pyrrole, which can then undergo substitution with a variety of nucleophiles.[50] Typical derivatization includes formation of the benzylester,[51] amide,[52] and carboxylic acid[53] moieties. Here, the Nazarov product **6-HH** was treated with trichloroacetic anhydride[54] to give the trichloroacetyl product **7**, which was isolated by simple filtration in 71% yield (Scheme 6, top). The trichloroacetylation occurs selectively at the α-position of the unsubstituted pyrrole rather than the α-position of the annulated pyrrole, as the latter is deactivated by the β-keto substituent. Reduction of the ketone on the exocyclic ring was explored as a mean to increase the reactivity of the annulated pyrrole (Scheme 6, bottom). Treatment of **6-HH** with $NaBH_4$ resulted in decomposition, but Corey–Bakshi–Shibata (CBS) reduction with the *in situ* prepared CBS catalyst[55] afforded the desoxo derivative **8** in 40% yield.




Scheme 6 Derivatization of a southern rim model compound.

### Characterization

**Absorption spectroscopy.** The absorption spectra of the five Knoevenagel enones (**5-HH**, **5-HMe**, **5-EsH**, **5-HEs**, and **5-EsEs**) are shown in Fig. 1 panel A, and the absorption spectra of the three southern rim compounds (**6-HH**, **6-HMe**, and **6-EsH**) are

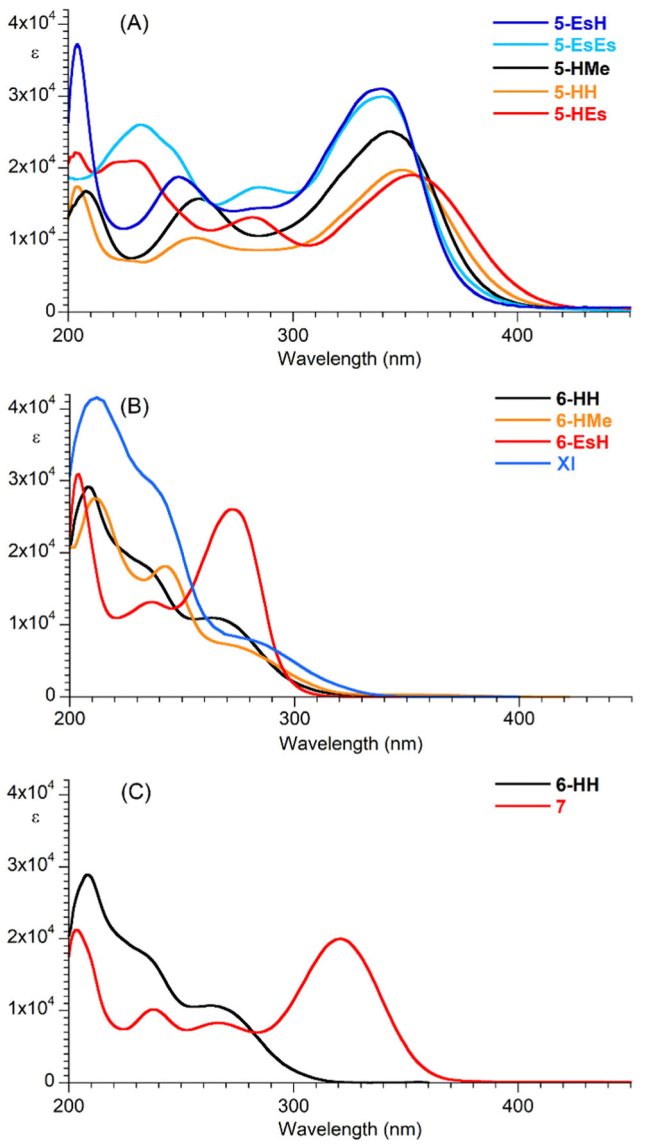



Fig. 1 Absorption spectra in methanol at room temperature of (A) Knoevenagel products; (B) southern rim compounds and a native phylloleucobilin (**XI**); and (C) **6-HH** and trichloroacetyl derivative **7**.

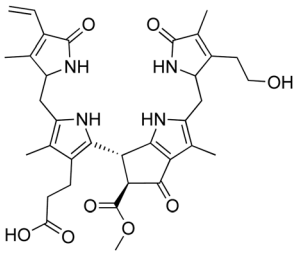


Chart 2 A phylloleucobilin (**XI**).[7,56]

shown in Fig. 1 panel B. All the Knoevenagel products (yellow-brown samples) show an absorption maximum at ~350 nm, which is attributed to the presence of the extended conjugated system. After Nazarov cyclization, the absorption band at ~350 nm disappears due to the disrupted conjugated system. The absorption spectra of two of the southern rim compounds (**6-HH** and **6-HMe**) closely resemble that of typical phylloleucobilins, as exemplified by the overlaid absorption spectrum of **XI** (Chart 2).[7,56] On the other hand, the trichloroacetyl derivative **7** gives a long-wavelength absorption at 321 nm as shown in Fig. 1 panel C. The position of the long-wavelength absorption band in the trichloroacetyl derivative **7** (321 nm) can be compared with that of the ester derivative **6-EsH** (272 nm), illustrating the profoundly distinct effects of the respective auxochromic groups.

**$^1$H NMR spectroscopic analyses.** The $^1$H NMR spectrum of each southern rim compound (**6-HH**, **6-HMe**, and **6-EsH**) shows two distinct, dominant N–H resonances in the region 8.0–9.5 ppm, consistent with the presence or absence of the attached keto group (Fig. 2). The region from 3.8–5.1 ppm is diagnostic for identifying the *trans* and *cis* isomers. For compound **6-HH**, the resonances at 3.88 and 4.97 ppm have small $J$ values (3.3 Hz) corresponding to a *trans*-configuration, while two much weaker resonances at 4.24 (not shown) and 4.94 ppm have larger $J$ values (7.5 Hz) corresponding to a *cis*-configuration. This result coheres with proton–proton coupling data in benchmark, five-membered, rigid-ring systems (hexachlorobicyclo[2.2.1]heptenes).[57] The southern rim compounds **6-HMe** and **6-EsH** also exhibited the same trend, with small coupling constants (3.2, 3.3 Hz) observed for the *trans* isomer and large vicinal coupling constants (7.5, 7.7 Hz) for the *cis* isomer. The ratio of *trans* to *cis* isomer on the basis of peak integration was ~9 : 1 in each case. The data are summarized in Table 1. For each compound, COSY spectra (700 MHz) showed the expected correlations among resonances corresponding to protons in the *cis* isomer as well as in the *trans* isomer (see the ESI†).

The greater yield of the *trans versus cis* isomer is generally expected in the Nazarov cyclization on simple structural considerations. On the other hand, the quantity of *cis* isomer is not negligible given that the groups about the constrained bond are not grossly dissimilar in size. The Newman projections sighting along the 3$^2$–5 carbon–carbon bond are shown in Fig. 3. Note that the 3$^2$-position can equally be termed the 5$^1$-position, but we retain the 3$^1$,3$^2$ terminology for coherence with the 13$^1$,13$^2$-labels of the structurally related native photosynthetic tetrapyrroles (Chart 1). Both *cis* and *trans* stereoisomers are observed in native photosynthetic tetrapyrroles. Indeed, the two 13$^2$-epimers of chlorophyll *a* and bacteriochlorophyll *a* are found *in vivo* in photosynthetic systems.[58] The ratio of the two 13$^2$-epimers of bacteriochlorophyll *a* has been reported to be 7 : 3,[59] 3 : 1,[60] and >10 : 1.[61]

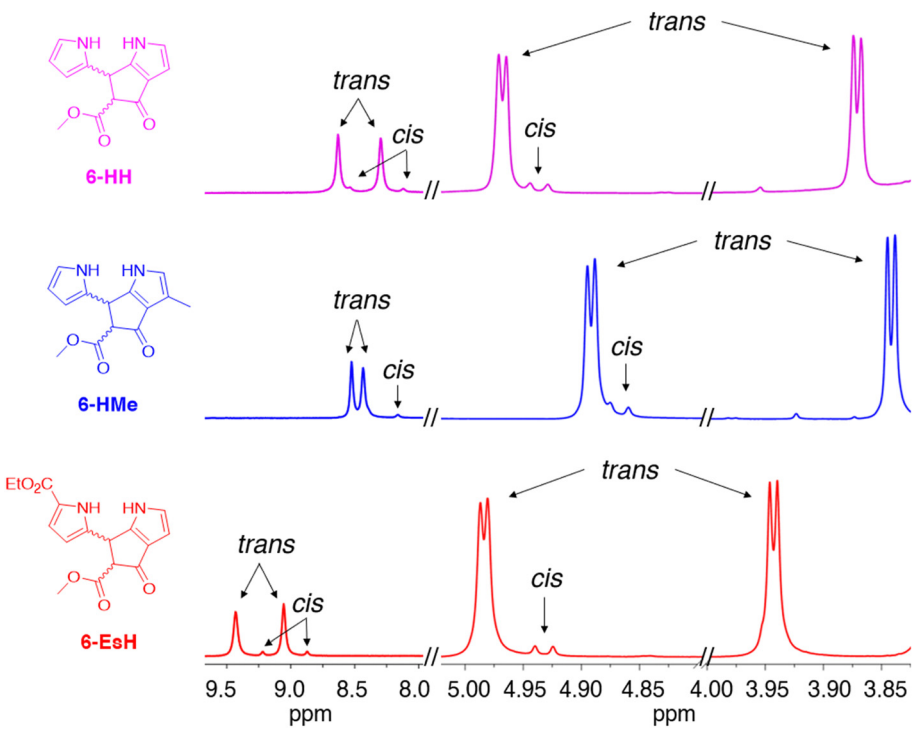



Fig. 2 Chemical shifts (measured in $CDCl_3$) of N–H protons (8.0–9.5 ppm) and methine protons (3.8–5.0 ppm).

Table 1 Listed chemical shifts of two methine protons (measured in $CDCl_3$)

| | *trans* isomer | | *cis* isomer | | |
|---|---|---|---|---|---|
| Cmpd | $\delta$, ppm | $J_{trans}$, Hz | $\delta$, ppm | $J_{cis}$, Hz | *trans*:*cis* ratio[a] |
| **6-HH** | 3.88, 4.97 | 3.3 | 4.24, 4.94 | 7.5 | 91:9 |
| **6-HMe** | 3.86, 4.89 | 3.2 | 4.17, 4.88 | 7.5 | 90:10 |
| **6-EsH** | 3.92, 4.99 | 3.3 | 4.93[b] | 7.7[b] | 87:13 |

[a] Calculated on the basis of $^1$H NMR spectroscopy. [b] The resonance of the other proton overlaps with another peak in the $^1$H NMR spectrum.

**Single-crystal X-ray diffraction (XRD) analyses.** Compound **6-HH**, which is comprised of *cis* and *trans* isomers, was crystallized by slow evaporation in acetonitrile. Examination by XRD of a single crystal showed the *trans*-configuration about the single bond joining the two pyrroles on one carbon and the carbomethoxy group on the other (Fig. 4). The two enantiomers were observed in the unit cell as is common for racemic compounds.[62] The structure shows the essential coplanarity of the annulated pyrrole and isocyclic rings.

The trichloroacetylated southern rim compound 7 was crystallized by slow evaporation in $CDCl_3$. Of five crystals examined, each was of the *trans* isomer and each was homochiral; four were identified as the 5*R*,3$^2$*S* isomer and one was the 5*S*,3$^2$*R* enantiomer. On the basis of data in the Cambridge Crystallographic Date Centre, it has been estimated that only ~10%[62] (or more recently, 9.5%)[63] of crystallized racemates are obtained as conglomerates. The ORTEP diagram of each enantiomer is shown in Fig. 5. Regardless of the collection of homochiral crystals in this conglomerate, the structures prove that the trichloroacetylation occurred selectively at the α-position of the unsubstituted, and hence more reactive, pyrrole.

## Outlook

Photosynthetic tetrapyrroles and their catabolites the phyllobilins share a common southern rim structure, with variation only in the saturation state (dihydrodipyrrin, dipyrromethane, or dipyrrin). A route toward synthetic dipyrromethane southern rim analogues has been developed by Knoevenagel condensation of a pyrrole-2-carboxaldehyde and a 3-(3-methoxy-3-oxopropanoyl)pyrrole followed by Nazarov cyclization. The Knoevenagel reactions gave reasonable yields in all cases (43–92%). The scope of the Nazarov cyclization encompasses a carbomethoxy group in the pyrrole-2-carboxaldehyde but not the 3-(3-methoxy-3-oxopropanoyl)pyrrole; the latter failure is consistent with the necessary participation of the β-substituted pyrrole in forming the intermediate pentadienyl cation that undergoes 4π-electrocyclization. Each southern rim product was obtained as a mixture of *trans* and *cis* isomers (~9:1 ratio). The synthetic work provides a glimmer of an entrée for further studies related to the chemistry of phyllobilins, which ultimately impinges on the fields of plant biology, nutrition, ecology, and agricultural sciences.

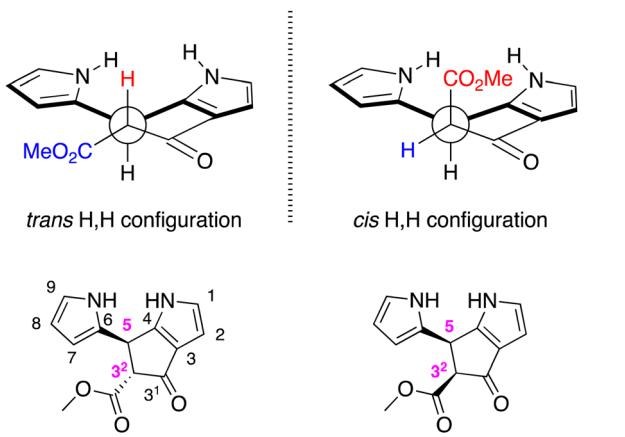



Fig. 3 Newman projections down the 3$^2$–5 bond of the *trans*/*cis* diastereomers of the southern rim compounds (top). Corresponding line drawings of *trans*/*cis* diastereomers, and southern rim position numbering (bottom).

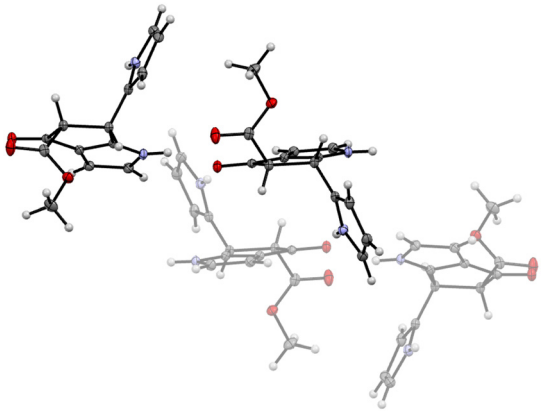


Fig. 4 ORTEP diagram of compound **6-HH** (*trans* isomer only) showing the presence of two enantiomers in the unit cell. Thermal ellipsoids drawn at the 50% probability level.

# Experimental section

## General methods

$^1$H NMR and $^{13}$C{$^1$H} NMR spectra were collected at room temperature in $CDCl_3$ unless noted otherwise. COSY spectra were collected at 700 MHz at room temperature in $CDCl_3$. Absorption spectra were collected in 1 cm pathlength quartz cuvettes in methanol at room temperature. Electrospray ionization mass spectrometry (ESI-MS) data are reported for the molecular ion or protonated molecular ion. Molecular sieves (4 Å, powder) were heated (>120 °C) overnight prior to use. Silica (40 μm average particle size) was used for column chromatography. THF used in all reactions was freshly distilled from Na/benzophenone ketyl unless noted otherwise. THF (HPLC-grade) was used as received. All commercially available compounds were used as received. Known compounds **1-Es**,[19] **4-H**,[26] and **4-Me**[24] were prepared as described in the literature or by routes described herein. Reaction mixtures that were heated were done so in an oil bath at the stated temperature. Solutions that were concentrated were done so under reduced presssure using a rotary evaporator.

## Synthesis and characterization

**Ethyl 5-formyl-1*H*-pyrrole-2-carboxylate (1-Es).** Following a reported procedure[17] with modification, a solution of pyrrole-2-

carboxylic acid (11.2 g, 0.101 mol) in anhydrous $CH_2Cl_2$ (300 mL) under argon was added to a mixture of DMAP (1.5 g, 0.012 mol) and EDC (18.6 g, 0.120 mol). The solution was stirred at room temperature for 5 minutes. Then, ethanol (70 mL) was added, and the mixture was stirred overnight at room temperature. The reaction was quenched by the addition of a saturated aqueous solution of $NH_4Cl$ (300 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic extract was dried ($Na_2SO_4$) and concentrated to a white solid. The crude ethyl ester product was carried onto the next step without further purification. Following a reported procedure[18] to prepare the Vilsmeier–Haack reagent *in situ*, anhydrous DMF (12 mL) under argon was cooled to 0 °C in a 500 mL round bottom flask. $POCl_3$ (12 mL, 0.12 mol) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 15 minutes, then at room temperature for 30 min, to form a white solid. Anhydrous 1,2-dichloroethane (20 mL) was added to the solid. The resulting solution was cooled to 0 °C and treated with a solution of the ethyl ester, obtained from the previous step, in 1,2-dichloroethane (50 mL). The mixture was then stirred at 100 °C under argon. After 2 h, a saturated aqueous solution of NaOAc (100 mL) was added, and the mixture was stirred overnight at room temperature. The suspension was extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic extract was dried ($Na_2SO_4$), concentrated, and chromatographed [silica, hexanes/ethyl acetate (1 : 1)] to obtain a light-yellow solid (7.22 g, 43%): mp 65–67 °C; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 10.06 (s, 1H), 9.66 (s, 1H), 6.93–6.94 (m, 2H), 4.35–4.40 (q, 2H, $J$ = 7 Hz), 1.36–1.39 (t, 3H, $J$ = 7 Hz); $^{13}$C{$^1$H} NMR ($CDCl_3$, 126 MHz) $\delta$ 180.5, 160.5, 134.5, 128.7, 119.9, 115.7, 61.5, 14.4.

**Methyl 1-(*tert*-butoxycarbonyl)-4-iodo-1*H*-pyrrole-2-carboxylate (2).** Following a reported procedure,[20] a solution of methyl pyrrole-2-carboxylate (2.50 g, 20.0 mmol) in anhydrous acetonitrile (120 mL) was treated with NIS (4.95 g, 22.0 mmol) and $In(OTf)_3$ (1.12 g, 2.00 mmol) at 0 °C. The mixture was stirred for 5 h at 0 °C and then for 1 h at room temperature. The reaction was quenched by the addition of water (200 mL). The resulting mixture was concentrated to remove acetonitrile. The resulting mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic layer was dried ($Na_2SO_4$) and concentrated to a light-yellow solid. The crude product was carried onto the next step without further purification. Following a reported procedure,[22] a solution of the previous crude solid, $(Boc)_2O$ (5.93 g, 27.2 mmol), and DMAP (248.8 mg, 2.0363 mmol) in THF (HPLC grade, 67 mL) was treated with $Et_3N$ (3.0 mL, 22 mmol). The mixture was stirred for 30 h at room temperature. TLC analysis showed starting material remained. The mixture was heated to 40 °C. After 1 h, another batch of $(Boc)_2O$ (4.72 g, 21.6 mmol) was added, and the reaction mixture was stirred for another 30 min at 40 °C. The reaction was quenched by the addition of 1 M aqueous HCl (100 mL). The aqueous layer was extracted with ethyl acetate (3 × 150 mL). The combined organic extract was washed with saturated aqueous $NaHCO_3$ solution (3 × 200 mL) and brine (1 × 200 mL), dried ($Na_2SO_4$), and concentrated. The residue was chromatographed [silica, hexanes/ethyl acetate (5 : 1)] to obtain a yellow oil (7.48 g, quant): $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.38–7.37 (d, 1H, $J$ = 2 Hz), 6.87–6.86 (d, 1H, $J$ = 1.5 Hz), 3.84 (s, 3H), 1.57 (s, 9 H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 126 MHz) $\delta$ 160.2, 147.0, 130.8, 126.7, 126.6, 85.7, 63.2, 52.3, 27.7; HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{11}H_{14}INO_4$, 352.00403; found, 352.00354.

**Methyl 1-(*tert*-butoxycarbonyl)-4-(3-methoxy-3-oxopropanoyl)-1*H*-pyrrole-2-carboxylate (3).** Following a reported procedure,[11] a mixture of **2** (451.6 mg, 1.286 mmol), potassium monomethyl malonate (322.9 mg, 2.067 mmol), Xantphos (444.3 mg, 0.7679 mmol), $MgCl_2$ (196.5 mg, 2.064 mmol), and imidazole (173.3 mg, 2.546 mmol) in freshly distilled THF (25 mL) in a Schlenk flask was treated with $Et_3N$ (290 μL, 2.08 mmol). The resulting mixture was subjected to three cycles of freeze–pump–thaw. Then, $Pd(OAc)_2$ (349.4 mg, 1.556 mmol) and $Co_2(CO)_8$ (444.4 mg, 1.300 mmol) were added. The flask was sealed immediately and heated to 65 °C. After 60 h, the reaction mixture was diluted with ethyl acetate and filtered through Celite. The filtrate was washed with brine (2 × 100 mL) and water (3 × 100 mL), dried ($Na_2SO_4$), and concentrated. The residue was chromatographed [silica, hexanes/ethyl acetate (5 : 1)] to obtain a red solid. The red solid was further chromatographed [silica, hexanes/$CH_2Cl_2$ (1 : 2) then (0 : 100)] to obtain a white solid (116.7 mg, 30%): mp 97–99 °C;

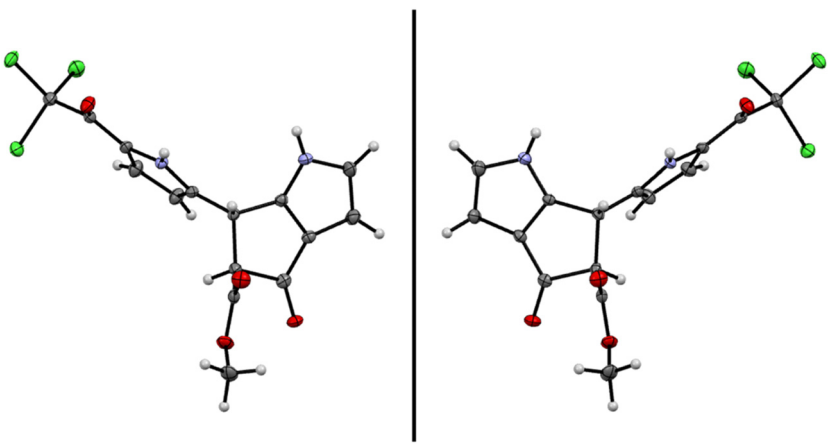


Fig. 5 ORTEP diagram of enantiomers found in two different homochiral crystals of **7** (*trans* isomer only) with thermal ellipsoids drawn at the 50% probability level.

$^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.89 (m, 1H), 7.18 (m, 1H), 3.86 (s, 3H), 3.78 (s, 2H), 3.74 (s, 3H), 1.60 (s, 9H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz) $\delta$ 186.7, 167.6, 160.7, 147.5, 130.1, 126.7, 125.0, 118.6, 86.9, 52.7, 52.5, 46.8, 27.7; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{19}NO_7$, 326.12343; found, 326.12279.

A separate reaction was performed following the above procedure but the deprotected product **4-Es** was obtained. A mixture of **2** (521.5 mg, 1.485 mmol), potassium monomethyl malonate (390.5 mg, 2.384 mmol), Xantphos (521 mg, 0.894 mmol), $MgCl_2$ (229.7 mg, 2.384 mmol), and imidazole (206.5 mg, 3.033 mmol) in freshly distilled THF (25 mL) was treated with $Et_3N$ (350. μL, 2.38 mmol). The resulting mixture was subjected to three cycles of freeze–pump–thaw. Then, $Pd(OAc)_2$ (418.7 mg, 1.865 mmol) and $Co_2(CO)_8$ (523.0 mg, 1.529 mmol) were added. The flask was sealed immediately and heated to 65 °C. After 60 h, the reaction mixture was diluted with ethyl acetate and filtered through Celite. The filtrate was washed with brine (2 × 150 mL) and water (3 × 150 mL), dried ($Na_2SO_4$), and concentrated. The residue was chromatographed [silica, $CH_2Cl_2$] to obtain a light-yellow solid (95.8 mg, 29%), which proved to be **4-Es**: $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 9.74 (s, 1H), 7.61–7.60 (m, 1H), 7.29–7.26 (m, 1H), 3.89 (s, 3H), 3.80 (s, 2H), 3.74 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz) $\delta$ 187.1, 168.0, 161.3, 127.1, 126.3, 124.4, 115.1, 52.7, 52.2, 46.9.

**Methyl 4-(3-methoxy-3-oxopropanoyl)-1*H*-pyrrole-2-carboxylate (4-Es).** Following a reported procedure,[25] a solution of **3** (116.7 mg, 0.3586 mmol) in $CH_2Cl_2$ (4 mL) was treated with TFA (500 μL) dropwise at room temperature. After 1 h, the reaction was quenched by the dropwise addition of saturated aqueous $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL). The organic extract was dried ($Na_2SO_4$) and concentrated. The residue was passed through a short silica column eluted with $CH_2Cl_2$ to obtain a light yellow solid (70.2 mg, 86%): mp 55–58 °C; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 9.67 (s, 1H), 7.60 (m, 1H), 7.29 (m, 1H), 3.89 (s, 3H), 3.80 (s, 2H), 3.74 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz) $\delta$ 187.1, 168.0, 161.2, 127.1, 126.3, 124.4, 115.1, 52.7, 52.2, 46.9; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{10}H_{11}NO_5$, 226.07100; found, 226.07063.

**Methyl (*Z*/*E*)-3-(1*H*-pyrrol-2-yl)-2-(1*H*-pyrrole-3-carbonyl)-acrylate (5-HH).** Following a reported method[11] with modification, a mixture of pyrrole-2-carboxaldehyde (25 mg, 0.26 mmol), **4-H** (40 mg, 0.24 mmol), and activated molecular sieves (4 Å, 100 mg) was placed in a dried 20 mL vial and treated with a solution of piperidine/acetic acid in $CH_2Cl_2$ (60 mM/60 mM, 1.'2 mL) under an argon atmosphere. The reaction mixture was stirred at 40 °C for 20 h and then chromatographed [silica, hexanes/ethyl acetate (1 : 1)] afforded a brown solid (35 mg, 60%): mp 119–123 °C; $^1$H NMR ($CDCl_3$, 400 MHz) major isomer $\delta$ 9.90–9.80 (b, 1H), 8.78–8.70 (b, 1H), 7.68 (s, 1H), 7.36–7.33 (m, 1H), 6.92–6.89 (m, 1H), 6.76–6.73 (m, 1H), 6.67–6.63 (m, 2H), 6.26–6.23 (m, 1H), 3.73 (s, 3H); minor isomer $\delta$ 11.94–11.86 (b, 1H), 8.78–8.70 (b, 1H), 7.36–7.33 (m, 1H), 7.21 (s, 1H), 7.12–7.09 (m, 1H), 6.81–6.78 (m, 1H), 6.64–6.61 (m, 2H), 6.34–6.31 (m, 1H), 3.75 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) $\delta$ 167.8, 135.3, 133.4, 127.4, 126.3, 125.3, 125.04, 124.99, 124.8, 121.9, 120.5, 119.6, 111.1, 111.0, 109.9, 109.5, 52.13, 52.05; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{13}H_{12}N_2O_3$ 245.09207; found 245.09193; $\lambda_{abs}$ (MeOH) 348 nm.

**Methyl (*Z*/*E*)-2-(4-methyl-1*H*-pyrrole-3-carbonyl)-3-(1*H*-pyrrol-2-yl) acrylate (5-HMe).** Following a procedure[11] with modification, a mixture of pyrrole-2-carboxaldehyde (**1-H**, 104.6 mg, 1.100 mmol), compound **4-Me** (181.2 mg, 1.000 mmol), and molecular sieves (4 Å, 400 mg) was treated with a solution of piperidine/acetic acid in $CH_2Cl_2$ (60 mM/60 mM, 5.00 mL, 300 μmol/300 μmol) under an argon atmosphere. The mixture was stirred at 40 °C for 20 h and then chromatographed [silica, hexanes/ethyl acetate (1 : 1)] to afford a brown solid (180.1 mg, 70%): mp 80–83 °C; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 11.92 (s, 1H), 8.47 (s, 1H), 7.18–7.17 (m, 1H), 7.12 (s, 1H), 7.09–7.08 (m, 1H), 6.60–6.58 (m, 1H), 6.32–6.30 (m, 1H), 3.76 (s, 3H), 2.34 (s, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz) $\delta$ 190.4, 168.8, 134.8, 127.4, 126.8, 124.8, 123.9, 122.3, 121.9, 121.6, 118.5, 111.1, 52.3, 11.1; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{14}H_{14}N_2O_3$, 259.10772; found, 259.10741; $\lambda_{abs}$ (MeOH) 343 nm.

**Ethyl 5-(3-methoxy-3-oxo-2-(1*H*-pyrrole-3-carbonyl)prop-1-en-1-yl)-1*H*-pyrrole-2-carboxylate (5-EsH).** Following a reported procedure[28] with modification, a mixture of **1-Es** (226.0 mg, 1.352 mmol) and **4-H** (226.0 mg, 1.352 mmol) under argon was treated with a solution of piperidine in anhydrous methanol (60 mM, 4 mL). The mixture was stirred for 2 days at 50 °C. The reaction mixture was then diluted with $CH_2Cl_2$ and filtered to obtain a light-yellow solid (249.1 mg, 58%): mp 195–200 °C; $^1$H NMR ($CD_3OD$, 500 MHz) 7.73 (s, 1H), 7.39–7.40 (m, 1H), 6.83–6.84 (m, 1H), 6.71–6.72 (m, 1H), 6.62–6.63 (m, 1H), 6.31 (m, 1H), 4.27–4.32 (q, 2H, $J$ = 7 Hz), 3.77 (s, 3H), 1.33–1.36 (t, 3H, $J$ = 7 Hz); $^{13}C\{^1H\}$ NMR ($CD_3OD$, 176 MHz) $\delta$ 192.1, 167.4, 162.0, 131.7, 131.0, 130.7, 128.4, 126.8, 125.9, 122.0, 117.6, 115.7, 109.5, 61.7, 52.8, 14.7; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{16}N_2O_5$, 317.11320; found, 317.11294; $\lambda_{abs}$ (MeOH) 339 nm.

**Methyl (*Z*/*E*)-4-(2-(methoxycarbonyl)-3-(1*H*-pyrrol-2-yl)acryloyl)-1*H*-pyrrole-2-carboxylate (5-HEs).** Following a reported procedure[28] with modification, a mixture of pyrrole-2-carboxaldehyde (**1-H**, 14.1 mg, 0.148 mmol) and **4-Es** (24.0 mg, 0.106 mmol) under argon was treated with a solution of piperidine in anhydrous methanol (60 mM, 540 μL). The reaction mixture was stirred for 24 h at 50 °C. The reaction mixture was then chromatographed [silica, hexanes then hexanes/ethyl acetate (1 : 1)] to obtain a yellow oil as a mixture of two isomers with the ratio of 2 : 1 (29.60 mg, 92%); $^1$H NMR ($CDCl_3$, 600 MHz) major isomer $\delta$ 10.09 (s, 1H), 10.01 (s, 1H), 7.73 (s, 1H), 7.50–7.49 (m, 1H), 7.22 (m, 1H), 6.96–6.95 (m, 1H), 6.67–6.66 (m, 1H), 6.28–6.27 (m, 1H), 3.86 (s, 3H), 3.74 (s, 3H); minor isomer $\delta$ 11.89 (s, 1H), 10.01 (s, 1H), 7.52–7.51 (m, 1H), 7.24 (s, 1H), 7.24–7.23 (m, 1H), 7.14–7.12 (m, 1H), 6.69–6.68 (m, 1H), 6.35–6.33 (m, 1H), 3.87 (s, 3H), 3.75 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) $\delta$ 190.7, 188.9, 168.6, 167.8, 161.6, 161.5, 136.0, 134.8, 128.1, 127.9, 127.6, 127.4, 127.4, 127.1, 125.8, 125.5, 124.1, 124.0, 122.9, 121.6, 120.7, 116.1, 115.7, 111.5, 111.5, 52.3, 52.3, 52.1; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{14}N_2O_5$, 303.09755; found, 303.09721; $\lambda_{abs}$ (MeOH) 353 nm.

**Ethyl (*Z*/*E*)-5-(3-methoxy-2-(5-(methoxycarbonyl)-1*H*-pyrrole-3-carbonyl)-3-oxoprop-1-en-1-yl)-1*H*-pyrrole-2-carboxylate (5-EsEs).** Following a reported procedure[28] with modification, a mixture of **1-Es** (25.9 mg, 0.155 mmol) and **4-Es** (33.9 mg, 0.151 mmol) under

argon was treated with a solution of piperidine in anhydrous methanol (60 mM, 600 μL). The mixture was stirred for 24 h at 50 °C. The reaction mixture was filtered. The filtered material was washed with $CH_2Cl_2$ to obtain a white solid (24.0 mg, 43%): mp 185–187 °C; $^1$H NMR ($CDCl_3$, 600 MHz) major isomer $\delta$ 10.24 (s, 1H), 9.62 (s, 1H), 7.70 (s, 1H), 7.57 (m, 1H), 7.24 (m, 1H), 6.84–6.83 (d, 1H, $J$ = 3.6 Hz), 6.55–6.54 (d, 1H, $J$ = 3.6 Hz), 4.35–4.31 (q, 2H, $J$ = 7.2 Hz), 3.88 (s, 3H), 3.78 (s, 3H), 1.37–1.34 (t, 3H, $J$ = 7.2 Hz); minor isomer $\delta$ 12.31 (s, 1H), 9.62 (s, 1H), 7.53–7.52 (m, 1H), 7.15 (s, 1H), 6.84 (m, 1H), 6.55 (m, 1H), 4.42–4.38 (q, 2H, $J$ = 7.2 Hz), 1.42–1.40 (t, 3H, $J$ = 7.2 Hz). $^{13}$C{$^1$H} NMR ($CDCl_3$, 150 MHz) $\delta$ 189.7, 188.0, 167.7, 166.6, 161.3, 161.2, 160.6, 160.5, 134.3, 132.7, 130.0, 129.9, 128.0, 127.8, 127.7, 127.3, 127.1, 127.0, 126.8, 125.6, 124.5, 124.3, 121.7, 119.5, 116.2, 115.8, 115.8, 115.6, 61.1, 61.1, 52.8, 52.6, 52.2, 14.6, 14.5; HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{18}H_{18}N_2O_7$, 375.11868; found, 375.11783; $\lambda_{abs}$ (MeOH) 340 nm.

**Methyl 4-oxo-6-(1*H*-pyrrol-2-yl)-1,4,5,6-tetrahydrocyclopenta[*b*]-pyrrole-5-carboxylate (6-HH).** A solution of **5-HH** (244 mg, 1.0 mmol), 2,6-di-*tert*-butylpyridine (1.30 mL, 6.00 mmol), $LiClO_4$ (106 mg, 1.0 mmol), and $In(OTf)_3$ (562 mg, 1.0 mmol) in anhydrous 1,2-dichloroethane (10.0 mL) was heated to 40 °C under an argon atmosphere in a glove box. The reaction mixture was stirred for 48 h and then filtered through a silica pad (2 × 2 cm, ethyl acetate). The filtrated was concentrated. Purification by chromatography [silica, $CH_2Cl_2$/ethyl acetate (5 : 1)] afforded a pale-brown, foam-like solid as a mixture of *trans*/*cis* (91 : 9) isomers (170 mg, 70%): decomposition observed at 100 °C, $^1$H NMR ($CDCl_3$, 500 MHz) *trans* isomer (major): $\delta$ 8.73 (s, 1H), 8.40 (s, 1H), 6.92 (dd, $J$ = 3.2, 2.0 Hz, 1H), 6.74 (d, $J$ = 1.4 Hz, 1H), 6.36 (dd, $J$ = 3.2, 1.8 Hz, 1H), 6.13 (d, $J$ = 2.9 Hz, 1H), 6.00 (d, $J$ = 1.4 Hz, 1H), 4.96 (d, $J$ = 3.5 Hz, 1H) 3.88 (d, $J$ = 3.3 Hz, 1H), 3.80 (s, 3H); *cis* isomer (minor): $\delta$ 8.61 (s, 1H), 8.13 (s, 1H), 6.94 (t, $J$ = 2.8 Hz, 1H), 6.67 (td, $J$ = 2.7, 1.5 Hz, 1H), 6.41 (dd, $J$ = 3.2, 1.8 Hz, 1H), 6.10 (q, $J$ = 2.9 Hz, 1H), 6.04 (d, $J$ = 3.7 Hz, 1H), 4.23 (d, $J$ = 7.5 Hz, 1H), 3.80 (s, 3H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 126 MHz) $\delta$ 188.0, 169.7, 157.9, 129.1, 126.6, 126.0, 118.6, 108.9, 106.4, 103.7, 67.3, 53.0, 37.5; HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{13}H_{12}N_2O_3$, 245.09207; found, 245.09145; $\lambda_{abs}$ (MeOH) 263 nm, also ∼225 nm.

**Methyl 3-methyl-4-oxo-6-(1*H*-pyrrol-2-yl)-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole-5-carboxylate (6-HMe).** A solution of **5-HMe** (168 mg, 0.650 mmol), 2,6-di-*tert*-butylpyridine (0.85 mL, 3.78 mmol), $LiClO_4$ (68.9 mg, 0.650 mmol), and $In(OTf)_3$ (365.3 mg, 0.6500 mmol) in anhydrous 1,2-dichloroethane (6.5 mL) was heated to 40 °C under an argon atmosphere. The reaction mixture was stirred for 48 h and then filtered through a silica pad (2 × 2 cm, ethyl acetate). The filtrate was concentrated. Purification by chromatography [silica, $CH_2Cl_2$/ethyl acetate (5 : 1)] afforded a yellow solid (85.2 mg, 51%): mp 57–60 °C; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 8.52 (s, 1H), 8.43 (s, 1H), 6.73–6.71 (m, 1H), 6.62 (m, 1H), 6.13–6.11 (m, 1H), 6.00–5.98 (m, 1H), 4.90–4.89 (d, $J$ = 3 Hz, 1H), 3.85 (d, $J$ = 3 Hz, 1H), 3.78 (s, 3H), 2.18 (s, 3H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 126 MHz) $\delta$ 188.2, 170.0, 167.6, 157.7, 136.1, 129.3, 125.3, 123.6, 118.5, 116.1, 115.3, 108.8, 106.3, 67.2, 52.9, 37.4, 10.4; HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{14}H_{14}N_2O_3$, 259.10772; found, 259.10740; $\lambda_{abs}$ (MeOH) 242 nm, also ∼270 nm.

**Methyl 6-(5-(ethoxycarbonyl)-1*H*-pyrrol-2-yl)-4-oxo-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole-5-carboxylate (6-EsH).** A mixture of **5-EsH** (29.5 mg, 93.3 μmol), 2,6-di-*tert*-butylpyridine (120.0 μL, 555.1 μmol), $In(OTf)_3$ (52.8 mg, 94.0 μmol), and $LiClO_4$ (10.0 mg, 94.0 μmol) in anhydrous 1,2-dichloroethane (1 mL) under argon was stirred for 96 h at 45 °C. The reaction mixture was then chromatographed [silica, $CH_2Cl_2$ to $CH_2Cl_2$/ethyl acetate (3 : 1)] to obtain a white solid (23.7 mg, 80%); mp 170–175 °C; $^1$H NMR ($CDCl_3$, 500 MHz) major isomer $\delta$ 9.42 (s, 1H), 9.05 (s, 1H), 6.93–6.92 (m, 1H), 6.81–6.80 (m, 1H), 6.38–6.37 (m, 1H), 6.03–6.01 (m, 1H), 4.99–4.98 (d, 1H, $J$ = 3 Hz), 4.31–4.23 (m, 2H), 3.95–3.94 (d, 1H, $J$ = 3.5 Hz), 1.34–1.30 (m, 3H); minor isomer $\delta$ 9.21 (s, 1H), 8.86 (s, 1H), 6.97–6.96 (m, 1H), 6.81–6.78 (m, 1H), 6.44–6.43 (m, 1H), 6.05–6.01 (m, 1H), 4.93–4.92 (d, 1H, $J$ = 7.5 Hz), 4.31–4.23 (m, 2H), 1.34–1.25 (m, 3H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 126 MHz) $\delta$ 187.3, 169.4, 161.4, 156.9, 134.7, 126.9, 126.0, 123.4, 116.1, 108.5, 103.9, 66.8, 60.8, 53.2, 37.3, 14.6; HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{16}H_{16}N_2O_5$, 317.11320; found, 317.11309; $\lambda_{abs}$ (MeOH) 272 nm.

**Methyl 4-oxo-6-(5-(2,2,2-trichloroacetyl)-1*H*-pyrrol-2-yl)-1,4,5,6-tetrahydrocyclo-penta[*b*]pyrrole-5-carboxylate (7).** Following a reported procedure,[54] a solution of **6-HH** (25.0 mg, 0.102 mmol) and DMAP (3.1 mg, 0.020 mmol) in anhydrous $CH_2Cl_2$ (1 mL) at 0 °C was treated dropwise with 2,2,2-trichloroacetic anhydride (22.5 μL, 0.123 mmol). The resulting solution under argon was allowed to warm to room temperature and stirred over the course of 2 h. Then, the reaction mixture was diluted with $CH_2Cl_2$ and filtered to obtain a white solid (25.0 mg, 71%): decomposition observed at 220 °C; $^1$H NMR ($CD_3OD$, 600 MHz) $\delta$ 7.33 (d, $J$ = 4.2 Hz, 1H), 7.03 (d, $J$ = 3.6 Hz, 1H), 6.32 (d, $J$ = 3.0 Hz, 1H), 6.07 (d, $J$ = 3.6 Hz, 1H), 4.97–4.98 (d, $J$ = 3.0 Hz, 1H), 3.95–3.96 (d, $J$ = 3.0 Hz, 1H), 3.80 (s, 3H); $^{13}$C{$^1$H} NMR ($CD_3OD$, 150 MHz) $\delta$ 190.5, 173.7, 170.8, 159.7, 142.0, 128.9, 126.4, 124.0, 123.2, 110.1, 103.5, 68.3, 53.1, 49.6, 38.7; HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{15}H_{11}Cl_3N_2O_4$, 388.98572; found, 388.98558; $\lambda_{abs}$ (MeOH) 321 nm.

**Methyl 6-(1*H*-pyrrol-2-yl)-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole-5-carboxylate (8).** Following a reported procedure,[55] a solution of (*S*)-(+)-α,α-diphenyl-2-pyrrolidinemethanol (7.0 mg, 28 μmol) in freshly distilled THF (150 μL) was treated with $BH_3{\cdot}SMe_2$ (25 μL, 0.26 mmol) at room temperature under argon. The resulting solution was stirred for 1 h at room temperature. A solution of **6-HH** (31.0 mg, 127 μmol) in freshly distilled THF (300 μL) was added dropwise to the reaction mixture. The reaction mixture was monitored by TLC analysis every hour. After 4 h, aqueous 1 M HCl (5 mL) was added. The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The organic extract was dried ($Na_2SO_4$), concentrated, and chromatographed with a short column [silica, $CH_2Cl_2$] to obtain a light-yellow oil (12 mg, 40%): $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 8.57 (s, 1H), 7.97 (s, 1H), 6.76–6.75 (m, 1H), 6.74–6.73 (m, 1H), 6.15–6.13 (q, $J$ = 3 Hz, 1H), 6.03–6.02 (m, 1H), 6.01–6.00 (m, 1H), 4.70–4.68 (d, $J$ = 8 Hz, 1H), 3.76 (s, 3H), 3.58–3.53 (q, $J$ = 8 Hz, 1H), 3.13–3.08 (m, 1H), 2.91–2.86 (m, 1H); $^{13}$C{$^1$H} NMR ($CDCl_3$, 126 MHz) $\delta$ 133.9, 133.4, 124.5, 121.6, 117.5, 108.3, 104.8, 104.0, 58.1, 52.2, 40.7, 29.0; HRMS (ESI-TOF) $m/z$: $[M + H]^+$ calcd for $C_{13}H_{14}N_2O_2$, 231.11280; found, 231.11268.

## Conflicts of interest

The authors declare no competing financial interest.

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