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Article

Natural Product-Derived Chiral Pyrrolidine-2,5-diones, Their Molecular Structures and Conversion to Pharmacologically Important Skeletons

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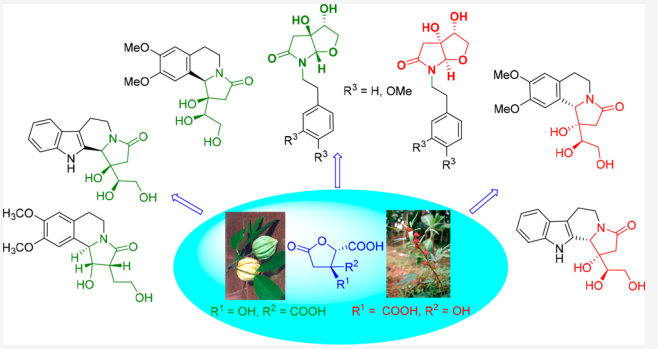
ABSTRACT: The versatility of the natural products (2*S*,3*S*)- and (2*S*,3*R*)-3-hydroxy-5-oxotetrahydrofuran-2,3-dicarboxylic acids (**1** and **2**), isolated in large amounts from tropical plant sources, has been demonstrated by the construction of 3-substituted and 3,4-disubstituted chiral pyrrolidine-2,5-diones. The absolute configurations of chiral pyrrolidine-2,5-diones have been ascertained using chiroptical spectroscopic methods and/or single-crystal XRD data. A combination of different reaction strategies delivering a diverse matrix of fused heterocyclic ring systems is presented. The pyrrolo[2,1-*a*]isoquinoline alkaloid (+)-crispine A possesses a wide range of pharmacological activities including antidepressant, antiplatelet, antileukemic, and anticancer activities. The analogues of indolizino[8,7-*b*]indole alkaloids (+)- and (−)-harmicine show strong antileishmanial, antinociceptive, PDE5-inhibitory, antimalarial, and antiviral activities. The bicyclic furo[2,3-*b*]pyrrolo skeleton is present in many natural products. Thus, the uniqueness of relatively cheap, naturally occurring chiral 2-hydroxycitric acid lactones as chirons has been demonstrated by the construction of some important molecular skeletons that are otherwise difficult to synthesize.



Chiral molecules, either obtained directly from nature or through chemical modification of the naturally occurring molecules, play a vital role in the pursuit of pharmaceutical and synthetic organic chemistry. The structure−activity studies have taken organic synthesis to the domain of enantiopure synthesis.[1] About 80% of small-molecule drugs approved by the Food and Drug Administration (FDA) are chiral, and 75% are used as a single enantiomer.[2,3] Among various strategies toward the synthesis of enantiopure compounds, the chiral pool approach is extremely attractive due to assured optical purity of the target molecule and economic viability. Several tropical plants are rich sources of structurally simple chiral 2-hydroxycitric acids.[4] Out of the four possible optical isomers, the (2*S*,3*S*)-diastereomer garcinia acid (**1**) and the (2*S*,3*R*)-diastereomer hibiscus acid (**2**) have been isolated as their γ-lactones in optically pure form in kilogram quantities (Figure 1).[5]

Among these, lactone **1** has been used extensively for the preparation of antiobesity formulations.[6,7] The two stereogenic centers in these γ-butyrolactones have structural and stereochemical features that relate to several small bioactive molecules of synthetic or natural origin.[8] Accordingly, **1** and **2** are expected to be added to the existing list of the privileged

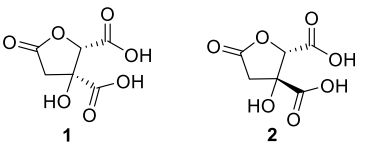


Figure 1. Structures of diastereomeric garcinia and hibiscus acids.

class of three and four carbon skeletal chiral hydroxy acids, namely, lactic, malic, mandelic, and tartaric acids. However, using the molecules having a three- or four-carbon framework, synthesis of target molecules with a basic skeleton having more than four carbons inevitably involves lengthy synthetic sequences.[9−11] Therefore, the chiral lactones **1** and **2**, bearing chemically amenable functional groups, could be an ideal choice for the construction of several bioactive molecules

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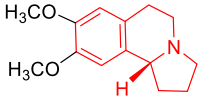
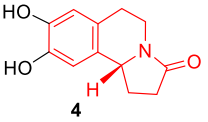
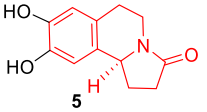
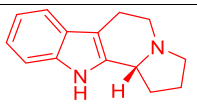
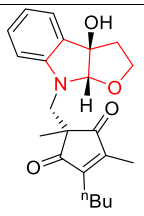
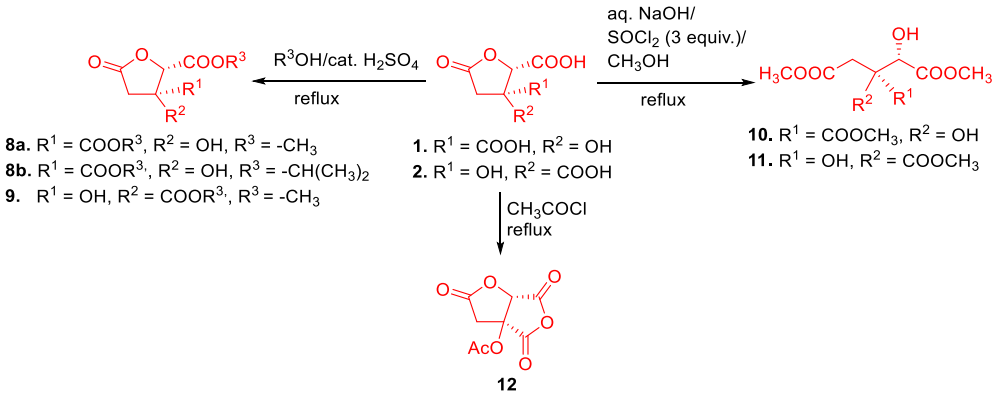
Table 1. Representative Biologically Active Molecules Synthetically Related to 1 and 2[13−24]

Bioactive molecule	Biological property	Core structure
 **3** (*R*)-(+)-crispine A	Cytotoxic activity against SKOV3, KB, HeLa Human cancer cell lines,[13] antidepressant,[14] antiplatelet,[15] and antileukemic activity[16]	Hexahydropyrrolo [2,1-*a*] isoquinoline
 **4** (*R*)-(+)-oleracine E	DPPH radical scavenger[13,17]	Tetrahydropyrrolo [2,1-*a*] isoquinolinone
 **5** (*S*)-(-)-trolline	Antibacterial activity against respiratory bacteria *Staphylococcus aureus*[16,18]	Tetrahydropyrrolo [2,1-*a*] isoquinolinone
 **6** (*R*)-(+)-harmicine	Antileishmanial,[19] antinociceptive activities,[20] PDE5 inhibitor,[21] antimalarial[22] and antiviral activity[23]	Hexahydroindoliz ino [8,7-*b*]indole
 **7** (+)-madindoline A	Selective inhibition of ILR activity in MH60[24]	Furo[2,3-*b*]pyrrole

Scheme 1. Conversion of 1 and 2 into 8, 9, 10, 11, and 12



having six-carbon structural skeletons. Moreover, the intrinsic stereogenic center steers the stereospecific generation of the new stereogenic center in the target structures.[12] Hence, taking advantage of the stereochemistry and functional group flexibility, molecules **1** and **2** serve as ideal choices for the construction of diverse structural skeletons of a variety of biologically active molecules of natural and synthetic origin. Some of the bioactive molecules that can be related to these skeletal buildups are given in Table 1.

With a goal toward the discovery of novel small molecules with biological activities, we report the successful and diversity-oriented construction of chiral skeletons, namely, tetrahydropyrrolo[2,1-*a*]isoquinolinones (**15** and **17**), hexahydroindolizino[8,7-*b*]indolones (**19** and **21**), and furo-[2,3-*b*]pyrroles (**16** and **18**), mostly in just one or two steps

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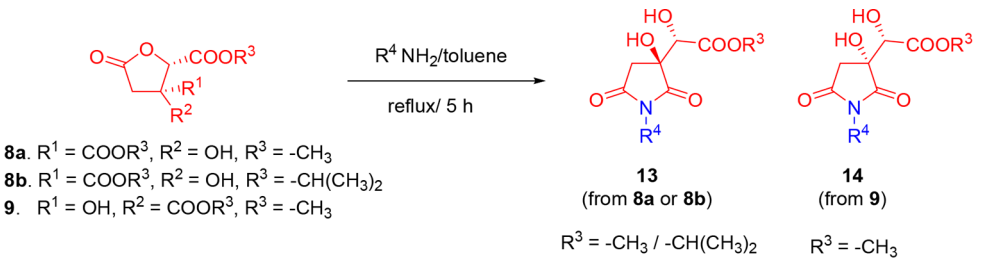
Scheme 2. Preparation of 3-Substituted Pyrrolidine-2,5-diones 13a–e and 14a–b from Monocyclic Diesters 8a, 8b, and 9



13a. R^4 = -$CH_2C_6H_5$[34] 90%[c]
R^3 = -CH_3

13b. R^4 = -$CH_2CH_2CH(CH_3)_2$ 80%[c]
R^3 = -$CH(CH_3)_2$

13c. R^4 = -$CH_2CH_2C_6H_3(OCH_3)_2$[34], 92%[c]
R^3 = -CH_3

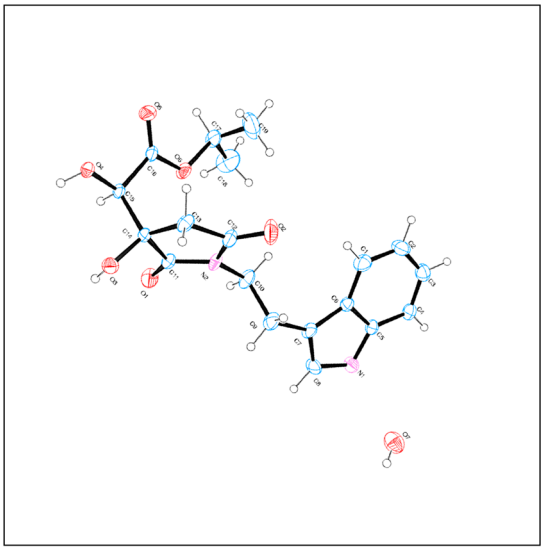
13d. R^4 = -$CH_2CH_2C_2H_2NC_6H_4$, 78%[c]
R^3 = -$CH(CH_3)_2$

13e. R^4 = -$CH_2CH_2C_6H_5$[34] 83%[c]
R^3 = -CH_3

14a. R^4 = -$CH_2CH_2C_6H_3(OCH_3)_2$, 90%[c]
R^3 = -CH_3

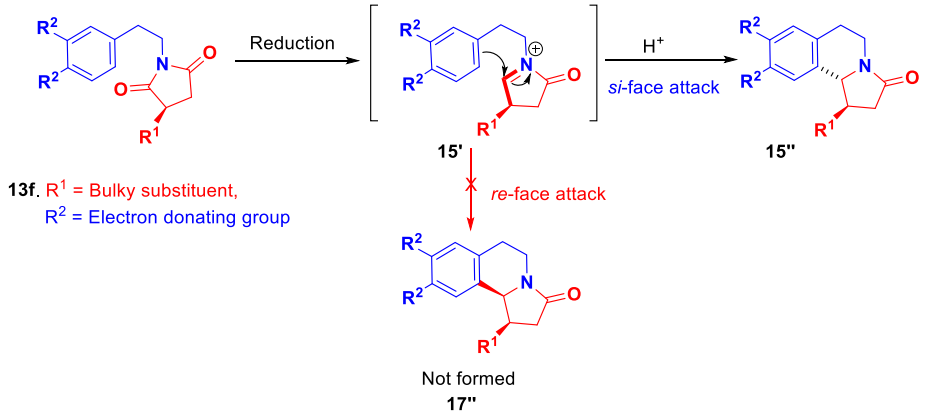
14b. R^4 = -$CH_2CH_2C_2H_2NC_6H_4$, 71%[c]
R^3 = -CH_3

[c]Isolated yields



ORTEP of 13d

Scheme 3. *N*-Acyliminium Cyclization Involving Unsymmetrical Pyrrolidine-2,5-dione 13f



using the 3-substituted (**13a–e**, **14a,b**) and 3,4-disubstituted (**23a–e**, **24a–f**) chiral pyrrolidine-2,5-diones prepared from **1** and **2**. These skeletons are related to naturally occurring (*R*)-(+)-crispine A (**3**), (*R*)-(+)-oleracine E (**4**), (*S*)-(−)-trolline (**5**), (*R*)-(+)-harmicine (**6**), and (+)-madindoline A (**7**), respectively (Table 1).

The absolute configurations (ACs) of chiral compounds can be determined from X-ray structures when good-quality crystals are available. In situations where this is not possible, chiroptical spectroscopic methods provide useful approaches to establish the AC. It is necessary to establish the reliability of chiroptical spectroscopic methods for determining the ACs of substituted pyrrolidine-2,5-diones. For this purpose, we have also undertaken chiroptical spectroscopic measurements and analyses for two representative pyrrolidine-2,5-diones and verified the derived AC with those obtained from either synthetic schemes and/or X-ray structures.

RESULTS AND DISCUSSION

For the construction of various structural skeletons (Table 1), the starting monocyclic diesters **8a**, **8b**, and **9**,[5] acyclic triesters **10** and **11**, bicyclic anhydride **12**[25] (Scheme 1), 3-substituted pyrrolidine-2,5-diones (Scheme 2), and 3,4-disubstituted pyrrolidine-2,5-diones (Scheme 6) were prepared from **1** and **2**. The pyrrolidine-2,5-diones **13a–e** are ideal starting molecules for the construction of tetrahydropyrrolo[2,1-*a*]

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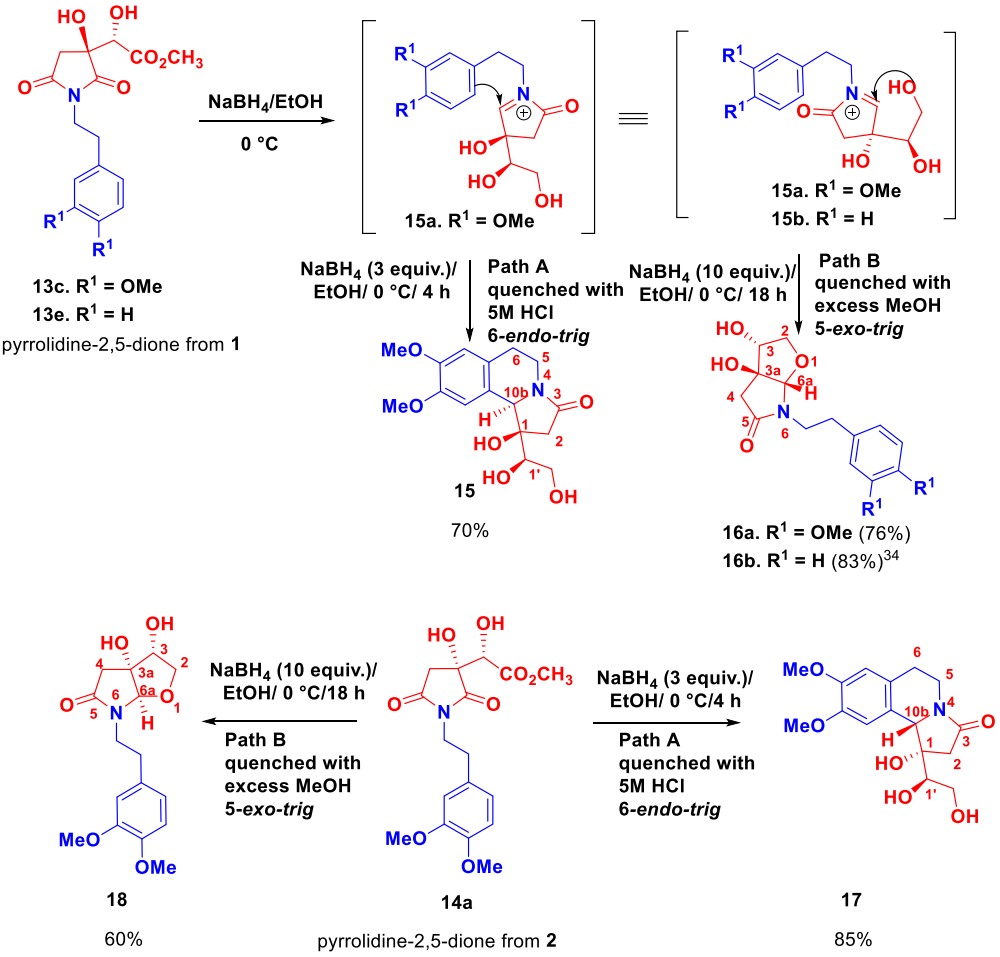
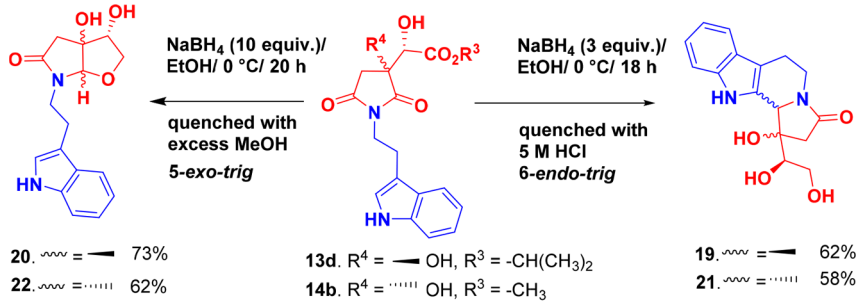
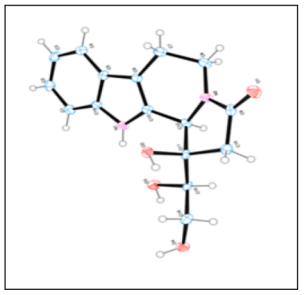
Scheme 4. Synthesis of Tetrahydropyrrolo[2,1-*a*]isoquinones 15 and 17 and Furo[2,3-*b*]pyrroles 16a, 16b,[34] and 18

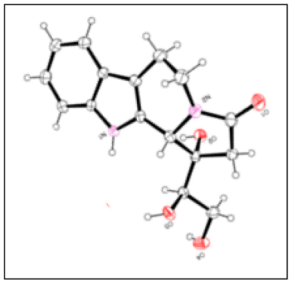


Scheme 5. Synthesis of Hexahydroindolizino[8,7-*b*]indolones 19 and 21 and Furo[2,3-*b*] pyrroles 20 and 22





ORTEP of **19**



ORTEP of **21**

isoquinolinones **15** and **17**, furo[2,3-*b*]pyrroles **16a**, **16b**, **18**, **20**, and **22**, (−)-hexahydroindolizino[8,7-*b*]indolones **19** and **21** (Schemes 4 and 5), and pyrroloisoquinolinone **25** (Scheme 6) in one step.

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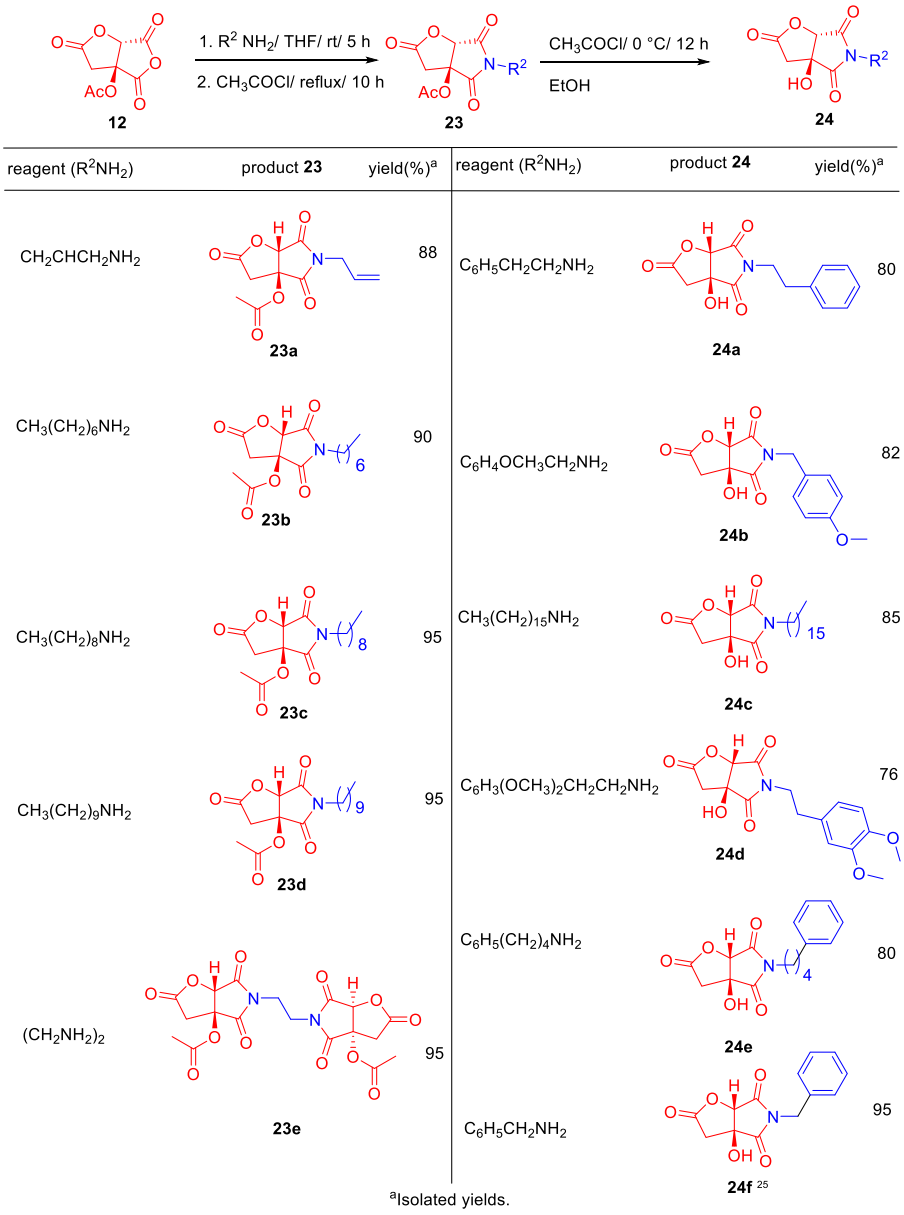
Scheme 6. Synthesis of 3,4-Disubstituted Pyrrolidine-2,5-diones 23a−e and 24a−f from Bicyclic Anhydride 12



Preparation of the Diastereomeric 3-Substituted Pyrrolidine-2,5-diones (13 and 14). The diastereomeric 3-substituted pyrrolidine-2,5-diones **13** and **14** were prepared in promising yield (71% to 90%) (Scheme 2) from **1** and **2** and are well characterized. These 3-substituted pyrrolidine-2,5-diones have an inherent appendage of diversity arising from different substituents attached to the imido nitrogen and judiciously used for the preparation of various enantiopure fused poly-heterocyclic ring systems.

Chiroptical Spectroscopic Analysis of Methyl (*S*)-2-[(*S*)-1-Benzyl-3-hydroxy-2,5-dioxopyrrolidin-3-yl]-2-hydroxyacetate (13a). As a representative case for the series of 3-substituted pyrrolidine-2,5-diones with (*S*,*S*) configuration (**13**), vibrational absorption (VA), vibrational circular dichroism (VCD), electronic absorption (EA), electronic circular dichroism (ECD), and discrete wavelength optical rotatory dispersion (ORD) measurements and corresponding quantum chemical calculations were undertaken for **13a**. The solvent influence was incorporated into the calculations using the polarizable continuum model (PCM). The four lowest energy conformers of **13a** identified at the B3LYP/aug-cc-pVDZ/PCM(CH_3CN) level are shown in Figure 2.

The VA and VCD spectra are shown in Figure 3. The experimental VCD spectrum shows negative and positive bands, associated with corresponding absorption bands, at 1747 and 1716 cm^{-1}, respectively. These two VCD features are correctly reproduced in the B3LYP/aug-cc-pVDZ/PCM-(CH_3CN) predicted spectra at 1756 and 1719 cm^{-1}. The VCD bands in the experimental spectrum at 1396, 1315, and 1257 cm^{-1} are also reproduced in the predicted spectrum at 1412, 1333, and 1267 cm^{-1}.

The EA and ECD spectra are shown in Figure 4. The experimental electronic spectra show one resolved absorption band at 203 nm and a broad low-amplitude negative ECD Cotton effect stretching from 270 to 230 nm, with a peak at 252 nm, followed by a broad positive ECD Cotton effect stretching from 230 nm and extending beyond 195 nm, with a peak at 205 nm. The predicted electronic spectra at the

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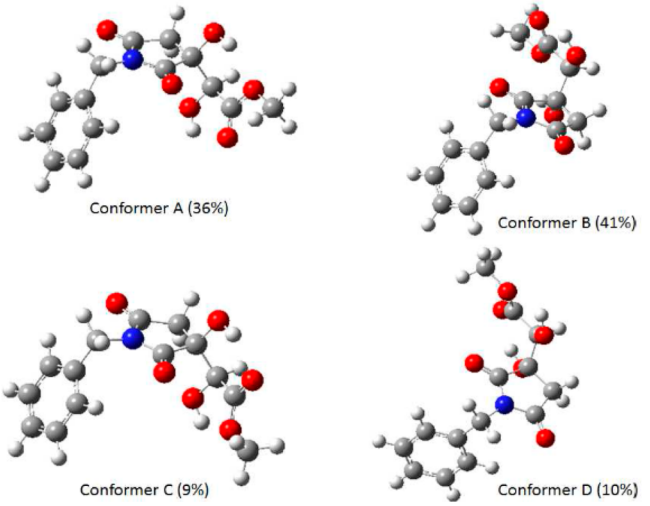

Figure 2. Four lowest energy conformers of **13a** identified at B3LYP/aug-cc-pVDZ/PCM(CH_3CN) level.

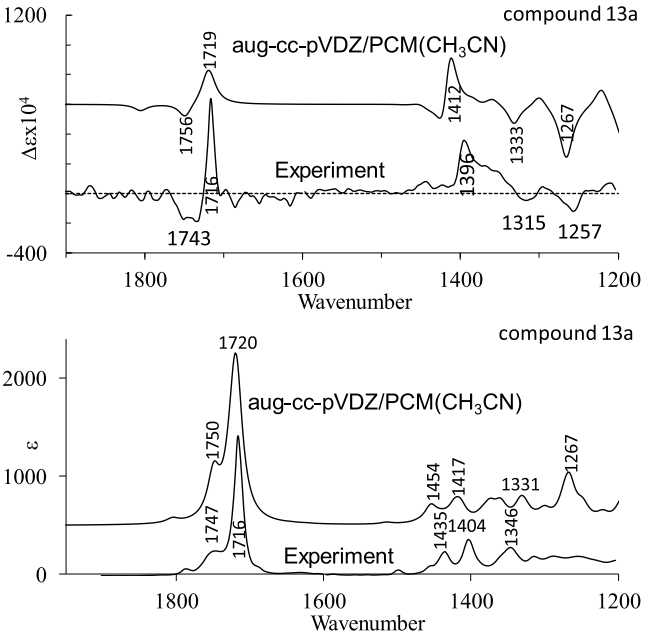

Figure 3. Experimental and quantum chemical VA (bottom panel) and VCD (top panel) spectra of compound **13a**.

B3LYP/aug-cc-pVDZ/PCM(CH_3CN) level indicate an absorption maximum at 193 nm, a broad negative ECD Cotton effect stretching from 295 to 235 nm, and a positive ECD Cotton effect stretching from 235 nm and extending beyond 195 nm.

The ORD data are shown in Figure 5. The experimental specific rotation (SR) is positive at all six wavelengths measured, with increasing magnitudes toward shorter wavelengths. However, the magnitudes of observed SRs are quite small. The predicted ORD at the B3LYP/aug-cc-pVDZ/PCM(CH_3CN) level indicates decreasing magnitudes of SR at shorter wavelengths. Since the reliability of predicted SRs is generally higher when the magnitudes are larger, the differences from the trend in experimental SRs at shorter wavelengths could be attributed to the small magnitudes of SRs for this molecule.

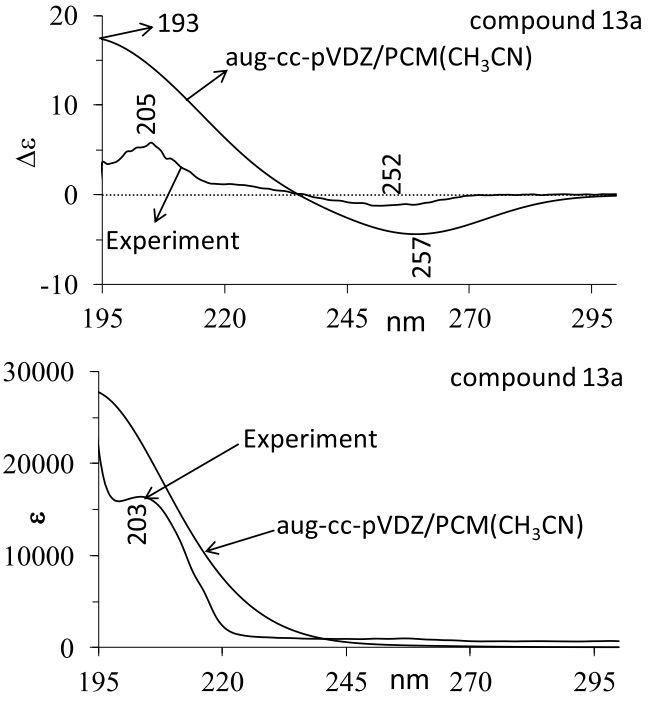

Figure 4. Experimental and quantum chemical EA (bottom panel) and ECD (top panel) spectra of compound **13a**.

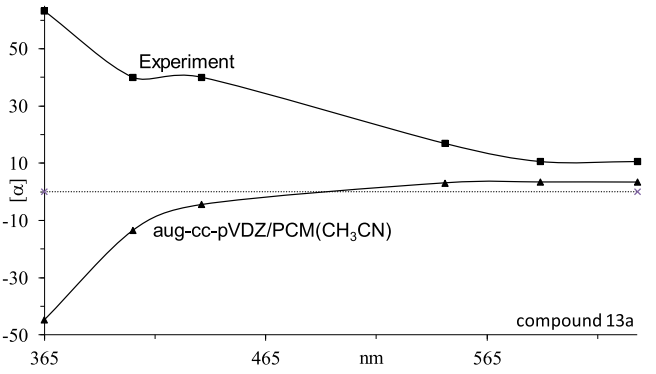

Figure 5. Experimental and quantum chemical discrete wavelength ORD spectra of compound **13a**.

Based on the current data and analysis, it is clear that the experimental VCD, ECD, and long-wavelength ORD spectra of **13a** have been reproduced very well by the quantum chemical predictions at the B3LYP/aug-cc-pVDZ/PCM-(CH_3CN) level. Thus, chiroptical spectroscopy provides a valuable approach for deducing the absolute configurations of the 3-substituted pyrrolidine-2,5-dione series with (*S*,*S*) configuration.

Chiroptical Spectroscopic Analysis of Methyl (*S*)-2-[(*R*)-1-(3,4-Dimethoxyphenethyl)-3-hydroxy-2,5-dioxopyrrolidin-3-yl]-2-hydroxyacetate (14a). Compounds **13** and **14** have diastereomeric configurations, differing in the AC of C-3 of the pyrrolidine-2,5-dione ring. We could not measure the experimental spectroscopic data, but VA, VCD, EA, ECD, and ORD calculations were undertaken for **14a**, to investigate if the diastereomeric configurations yield sufficiently different spectroscopic signatures for their identification. The predicted data for **14a** are presented in the Supporting Information. A comparison of VCD, ECD, and ORD data of **14a** with those of **13a** reveals that diastereomeric configurations have distinctly

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different spectroscopic signatures. For **14a**, the VCD bands associated with the C=O stretching bands at around 1700 cm^{-1} are of opposite signs and of different pattern in the 1400−1200 cm^{-1} region, compared to those for **13a**; starting from long-wavelength side, a positive−negative−positive−negative ECD spectroscopic pattern predicted for **14a** is different from the negative−positive pattern predicted for **13a**; ORD is negative at all wavelengths for **14a**, unlike that for **13a**. These observations enumerate the importance of chiroptical spectroscopy in discriminating the diastereomeric configurations of 3-substituted pyrrolidine-2,5-diones.

Synthesis of Tetrahydropyrrolo[2,1-*a*]-isoquinolinones 15 and 17, Hexahydroindolizino[8,7-*b*]indolones 19 and 21, and Furo[2,3-*b*]pyrroles 16 and 18. Several molecules with pyrroloisoquinoline[18,26−28] and indolizinoindolone[12,13,16,26] ring systems are widely present in the folk medicines of tropical and subtropical regions.[29,30] Given their attractive biological activities, much attention has been focused on efficient synthetic methods for these *N*-fused heterocyclic alkaloids, bearing pyrroloisoquinoline and indolizinoindolone structural frameworks, from simple starting materials.[16,28,31] For the synthesis of these fused heterocyclic systems, *N*-acyliminium ion cyclization has become the most propitious methodology.[27,28,32] The synthetic strategy involves the preparation of the required chiral *N*-acyliminium ions, via the reduction of chiral unsymmetrical pyrrolidine-2,5-diones **13c**, **13d**, **14a**, and **14b**, which undergo diastereoselective *N*-acyliminium cyclization, leading to the formation of tetrahydropyrrolo[2,1-*a*]isoquinoline **15** and **17** and hexahydroindolizino[8,7-*b*]indolone **19** and **21** ring systems. The regioselectivity of reduction of unsymmetrical pyrrolidine-2,5-diones occurs at the more substituted carbonyl.[33] It is known that the *N*-acyliminium cyclization produces only a single diastereomer resulting from a diastereospecific attack of the nucleophilic aryl ring at the least hindered side of the acyliminium ion (Scheme 3).[12]

The tetrahydropyrrolo[2,1-*a*]isoquinone derivatives **15** and **17**, furo[2,3-*b*]pyrroles **16**, **18**, **20**, and **22**, and hexahydroindolizino[8,7-*b*]indolones **19** and **21** were prepared in enantiomerically pure form in good yield from chiral 3-substituted pyrrolidine-2,5-diones **13** and **14** (Schemes 4 and 5).

Compounds **13** and **14** are *N*-alkyl imides. It is possible that the proximal hydroxy groups are directing the regioselective reductions here. The reduction products of **13** and **14** could be folded to obtain either five- or six-membered fused heterocyclic ring systems depending on the conditions of workup and electronic status of the aromatic ring (Schemes 4 and 5). In continuation of our preliminary work on the reductive 5-*exo-trig* cyclization of 3-substituted pyrrolidine-2,5-diones,[34] we have extended the scope of the work to pyrrolidine-2,5-diones with different electronic characteristics (Schemes 4 and 5). The pyrrolidine-2,5-diones **13c,d** and **14a,b** upon reduction with $NaBH_4$ (3 equiv) followed by workup under acidic conditions (5 M HCl) (path A) furnished tetrahydropyrrolo[2,1-*a*]isoquinones **15** and **17** and hexahydroindolizino[8,7-*b*]indolones **19** and **21** diastereoselectively, via a 6-*endo-trig* cyclization involving the aromatic ring as the nucleophilic entity (Schemes 4 and 5). The chiroptical studies of the (−)-crispine A analogue (1*R*,10*bR*)-1-[(*R*)-1,2-dihydroxyethyl]-1-hydroxy-8,9-dimethoxy-1,5,6,10*b*-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (**15**) was recently reported.[29] However, the reduction of **13c−e** and **14a,b** with excess $NaBH_4$ (10 equiv) followed by quenching with excess MeOH (path B) resulted in the formation of the furo[2,3-*b*]pyrroles **16a**, **16b**, **18**, **20**, and **22** diastereospecifically, via a 5-*exo-trig* cyclization involving the hydroxy group of the reduced ester group as the nucleophilic entity. The basic reaction mixture generated by the excess (10 equiv) of $NaBH_4$ allowed the isolation of furo[2,3-*b*]pyrroles **16a**, **16b**, and **18** as the *O*−*N* acetals stable under the isolation conditions.

Accordingly, compound **15**, an analogue of naturally occurring (−)-crispine A (Scheme 4), and **19**, an analogue of naturally occurring (−)-harmicine (Scheme 5), were synthesized from **13c** and **13d**, respectively, as single diastereomers. Similarly, synthesis of compounds **17** and **21**, analogues of (+)-crispine A and (+)-harmicine, respectively, was achieved using **14a** and **14b**, the diastereomers of **13c** and **13d**, respectively. The structure and configurations of these molecules were established with all spectroscopic data including single-crystal XRD. The absolute configurations of the final molecules were defined by relating to the known absolute configurations of the starting molecules. The diastereoselective outcome can be explained on the basis of the favored conformation of intermediate **15a**, so that intramolecular cyclization of **13c** leads to **15** *via* a *re*-face attack of the aryl group. Similarly, *si*-face cyclization of **14a** resulted in the formation of **17**. The diastereoselective attack of the nucleophilic aryl ring occurs at the least hindered side of the *N*-acyliminium ion.[12,35,36]

When the pyrrolidine-2,5-dione **13e** was used, a 5-*exo-trig* cyclization occurred in the *N*-acyliminium ion, using 10 equiv of $NaBH_4$ in EtOH, followed by acidic workup (5 M HCl), resulting in the exclusive formation of furo[2,3-*b*]pyrrole **16b**.[34] However, when the aryl ring bears electron-donating groups, it competes with the hydroxy group acting as a nucleophile for the *N*-acyliminium cyclization. Thus, the pyrrolidine-2,5-diones **13c** and **14a** furnished tetrahydropyrrolo[2,1-*a*]isoquinolinones **15** and **17** *via* a 6-*endo-trig* Pictet−Spengler cyclization in excellent yield. Thus, by judiciously tuning the electron density of the aryl ring of the pyrrolidine-2,5-diones, cyclization can be switched to either furo[2,3-*b*]pyrroles or pyrrolo[2,1-*a*]isoquinolines.

The 3,4-disubstituted pyrrolidine-2,5-diones (**23a−e**) were prepared, from the anhydride **12** and using appropriate amines under refluxing conditions in the presence of acetyl chloride, in excellent yield (Scheme 6).[25] The deacetylation of corresponding pyrrolidine-2,5-diones **23** using acidic EtOH furnished **24a−e** in good yield (Scheme 6).

Chiroptical Spectroscopic Analysis of (3a*S*,6a*S*)-5-Benzyl-3a-hydroxydihydro-2*H*-furo[2,3-*c*]pyrrole-2,4,6-(3*H*,5*H*)-trione (24f). As a representative case for the series of 3,4-disubstituted pyrrolidine-2,5-diones **23a−e** and **24a−f**, VA, VCD, EA, ECD, and discrete wavelength ORD measurements and corresponding quantum chemical calculations were undertaken for **24f**. The conformers of **24f** optimized at the B3LYP/aug-cc-pVDZ/PCM(CH_3CN) level are shown in Figure 6.

The VA and VCD spectra are shown in Figure 7. The experimental VCD spectrum shows large negative and positive bands associated with corresponding absorption bands at 1751 and 1732 cm^{-1}, respectively. These large VCD features are correctly reproduced in the B3LYP/aug-cc-pVDZ/PCM-(CH_3CN) predicted spectra at 1761 and 1736 cm^{-1}. The VCD bands in the experimental spectrum at 1801, 1335, 1288,

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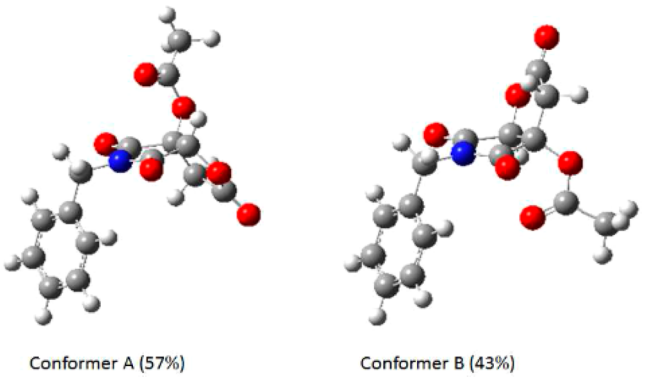

Figure 6. Two lowest energy conformers of **24f** obtained at the B3LYP/aug-cc-pVDZ/PCM(CH_3CN) level.

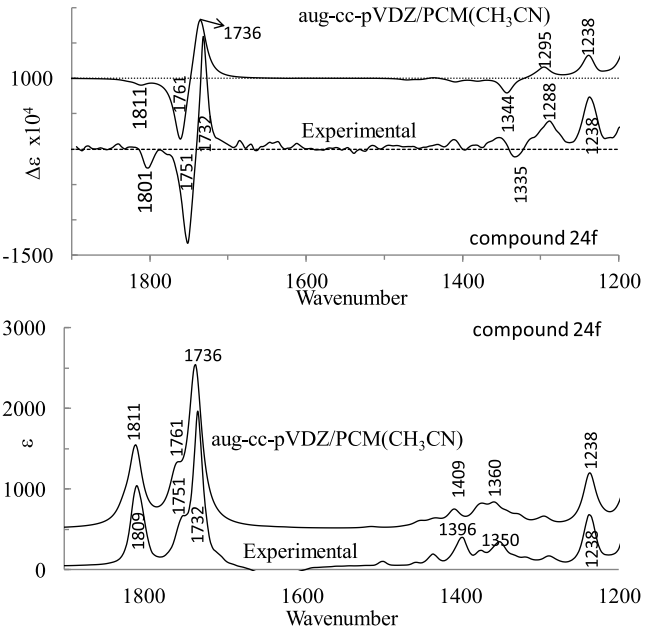

Figure 7. Experimental and quantum chemical VA (bottom panel) and VCD (top panel) spectra of **24f**.

and 1238 cm^{-1} are also reproduced in the predicted spectrum at 1811, 1344, 1295, and 1238 cm^{-1}.

The EA and ECD spectra are shown in Figure 8. The experimental electronic spectra show one resolved absorption band at 205 nm and a broad negative ECD Cotton effect stretching from 245 to 195 nm, with a peak at 209 nm. The predicted electronic spectra at the B3LYP/aug-cc-pVDZ/PCM(CH_3CN) level indicate an absorption maximum at 192 nm with an associated negative ECD Cotton effect at 193 nm. The predicted spectrum also shows a broad negative ECD Cotton effect around 240 nm, whose corresponding feature may be hidden in the broad experimental ECD Cotton effect.

Comparison of the experimental and predicted ORD for **24f** is shown in Figure 9. The experimental SR is negative at all six wavelengths measured, with increasing magnitudes toward shorter wavelengths. The same pattern is seen in the predicted ORD at the B3LYP/aug-cc-pVDZ/PCM(CH_3CN) level with predicted magnitudes in much better agreement with the corresponding experimental magnitudes.

Based on the current data and analysis, it is clear that the experimental VCD, ECD, and ORD of **24f** have been reproduced very well by the quantum chemical predictions at

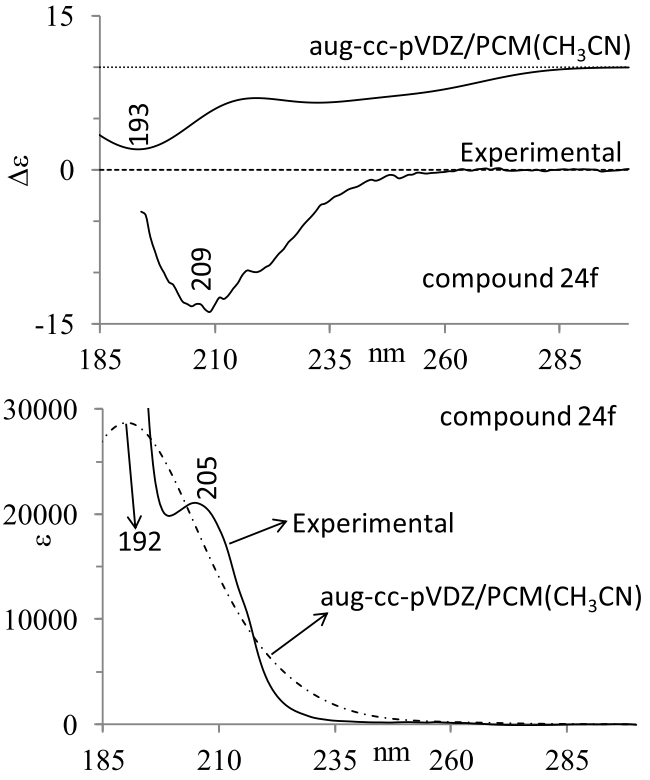

Figure 8. Experimental and calculated EA (bottom panel) and ECD (top panel) spectra of **24f**.

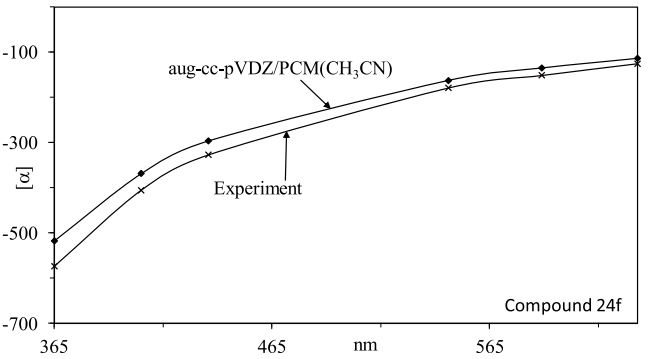

Figure 9. Experimental and quantum chemical discrete wavelength ORD spectra of **24f**.

the B3LYP/aug-cc-pVDZ/PCM(CH_3CN) level. Thus, chiroptical spectroscopy provides a practically useful approach for deducing the absolute configurations of 3,4-disubstituted pyrrolidine-2,5-diones.

Synthesis of Pyrroloisoquinolinone 25 from Bicyclic Anhydride 12. The reaction between **24d** and excess $NaBH_4$ (10 equiv), followed by acidic workup,[28,33] resulted in the formation of 2,3-disubstituted pyrrolo[2,1-*a*]isoquinolinone **25** (Scheme 7). As in the case of pyrrolidine-2,5-diones **13** and **14**, the steric crowding at C-3[12] of **24d** directs the reducing agent to selectively reduce the C-2 carbonyl group. Reduction of the carbonyl on the more hindered side reduces the overall steric crowding, whereas there is no such gain if the carbonyl is reduced at the less hindered side. The resulting *N*-acyliminium ion undergoes Pictet−Spengler cyclization to furnish **25** instead of the anticipated **25a**. A plausible explanation for the formation of **25** can be offered on assuming the formation

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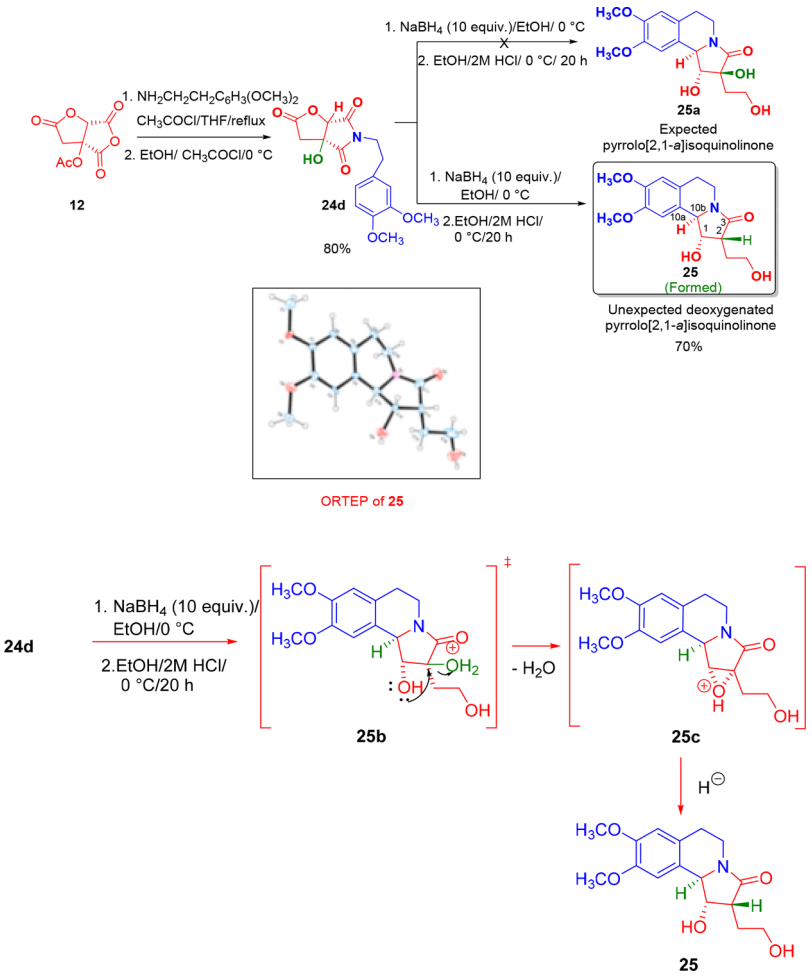
Scheme 7. Synthesis of Pyrroloisoquinolinone 25 from Bicyclic Anhydride 12



of the epoxide **25c** by an intramolecular substitution of the tertiary hydroxy group of **25b** followed by a hydride transfer to exclusively form **25** (Scheme 7).

The structure of **25** was confirmed on the basis of ^{1}H NMR, ^{13}C NMR, DEPT 90, DEPT 135, and HRMS data. The relative configuration and structure were established from single-crystal X-ray crystallography.

EXPERIMENTAL SECTION

General Experimental Procedures. All commercial solvents were distilled prior to use. Dry solvents and reagents were prepared by following the procedures described in *Purification of Laboratory Chemicals* by Perrin, D. D., and Armarego, W. L. F. (3rd ed., Pergamon Press, 1988). Melting points were determined on a "Sunbim" electrically heated melting point apparatus and are uncorrected. IR spectra were recorded using a Shimadzu IR 470 spectrophotometer as thin films (liquids), PerkinElmer Spectrum-400 FTIR spectrophotometer, and ThermoFisher Is 10 FTIR spectrometer equipped with an ATR unit. Selected characteristic peaks are reported in cm^{-1}. ^{1}H and ^{13}C NMR were recorded on a Bruker AVANCE III spectrometer. The chemical shifts are given in parts per million (ppm) on the δ scale. Data are reported as follows: s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; dd = doublet of doublets; dt = doublet of triplets; br = broad. High-resolution mass spectrometry (HRMS) was recorded on a QTOF mass spectrometer. Optical rotations were recorded using a Rudolph Autopol IV polarimeter.

Chiroptical Spectroscopic Measurements and Calculations[37,38] for 13a. VA and VCD measurements were carried out in CD_3CN at 1.1 and 3.0 mg/mL using a 100 μm cell with BaF_2 windows. EA and ECD spectra were obtained in CH_3CN at 1.2 mg/400 μL and 0.6 mg/400 μL using a 0.1 mm cell. ORD measurements were made at six discrete wavelengths, 633, 589, 546, 436, 405, and 365 nm, at 1.9 mg/2 mL in CH_3CN solvent using a 0.5 dm cell. The crystal structure was used as the starting point for conformational searching with the CONFLEX program.[39] Ninety-one conformers were found within a 20 kcal/mol energy window. The first 20 conformers, in the 6 kcal/mol range, were optimized at the B3LYP/6-31G* level using the Gaussian 09 program.[40] The resulting lowest energy conformers in a 2 kcal/mol energy window were reoptimized at the B3LYP/aug-cc-pVDZ and B3LYP/aug-cc-pVDZ/PCM-(CH_3CN) levels. ORD, ECD, and VCD calculations were undertaken for the lowest energy conformations at the B3LYP/6-31G*, B3LYP/aug-cc-pVDZ, and B3LYP/aug-cc-pVDZ/PCM(CH_3CN) levels using respective optimized geometries. This discussion is restricted to the results obtained at the B3LYP/aug-cc-pVDZ/PCM(CH_3CN) level.

Chiroptical Spectroscopic Predictions for 14a. The details are provided in the Supporting Information.

Chiroptical Spectroscopic Measurements and Calculations for 24f. The EA and ECD spectra were measured in CH_3CN at 1.66 mg/mL using a 0.1 mm cell, and solvent spectra were subtracted. ORD measurements at six discrete wavelengths, 633, 589, 546, 436, 405, and 365 nm, were measured at 1.1 mg/mL in CH_3CN using a 0.5 dm cell. VCD measurements were made in CD_3CN at 1.3 and 4.7 mg/mL using a 100 μm cell with BaF_2 windows. A molecular model of compound **24f** was built starting from the structure of acetylated garcinia acid anhydride. This structure was used as input for conformational searching with the CONFLEX program.[39] Thirteen conformers were found. These 13 conformations were optimized at

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the B3LYP/6-31G* level using the Gaussian 09 program.[40] The two lowest energy conformers were found to be within 2 kcal/mol energy. These two conformers were reoptimized at the B3LYP/aug-cc-pVDZ and B3LYP/aug-cc-pVDZ/PCM(CH_3CN) levels, and ORD, ECD, and VCD calculations were undertaken using respective optimized geometries. This discussion is restricted to the results obtained at the B3LYP/aug-cc-pVDZ/PCM(CH_3CN) level.

General Procedure for the Synthesis of 3-Substituted Pyrrolidine-2,5-diones 13a−e and 14a,b from Monocyclic Diesters 8a, 8b, and 9. To a stirred solution of **8a** (1.0 g, 4.6 mmol, 1 equiv)/**8b** (1.0 g, 3.64 mmol, 1 equiv)/**9** (1.0 g, 4.6 mmol, 1 equiv) in toluene (10 mL) was added the amine (1 equiv), and the reaction flask was equipped with a reflux condenser. The resulting mixture was refluxed. After 5 h, the reaction mixture was concentrated under reduced pressure and the crude residue was purified by column chromatography on silica gel 60−120 mesh (20% EtOAc/*n*-hexane) to afford pyrrolidine-2,5-diones **13a−e** and **14a,b**.

*Methyl (S)-2-[(S)-1-benzyl-3-hydroxy-2,5-dioxopyrrolidin-3-yl]-2-hydroxyacetate (**13a**).*[34] Colorless needles ($CHCl_3$); mp 106−107 °C; $[\alpha]_D^{25}$+11 (*c* 0.1, $CHCl_3$); IR (KBr) ν_{max} 3432, 2949, 1775, 1743, 1695 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 7.34−7.26 (m, 5H), 4.70−4.62 (m, 2H, CH_2), 4.31 (s, 1H), 4.10 (br s, 1H), 3.87 (s, 3H, OCH_3), 3.21 (br s, 1H) 3.16 (d, *J* = 18.0 Hz, 1H), 2.76 (d, 1H, *J* = 18.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 176.8 (C═O), 173.5 (C═O), 171.8 ($COOCH_3$), 135.1, 128.7, 128.5, 128.0, 76.2, 72.1, 53.8, 42.6, 39.7; HRESIMS *m*/*z* 294.0970 [M + H^+] (calcd for $C_{14}H_{16}NO_6$ 294.0978).

*Isopropyl (S)-2-hydroxy-2-[(S)-3-hydroxy-1-isopentyl-2,5-dioxopyrrolidin-3-yl]acetate (**13b**).* Pale yellow oil; $[\alpha]_D^{25}$ −11 (*c* 0.3, $CHCl_3$); IR (KBr) ν_{max}3438, 1781, 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 5.06 (m, 1H), 4.28 (s, 1H), 3.38 (m, 2H), 2.95 (d, *J* = 18.4 Hz, 1H), 2.59 (d, *J* = 18.4 Hz, 1H), 1.44 (m, 1H), 1.34 (m, 2H), 1.20 (s, 6H, $CH(CH_3)_2$), 0.80 (d, *J* = 6.4 Hz, 6H, $CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$,100 MHz) 177.0 (C═O), 174.3 (C═O), 170.4 (COOCH-$(CH_3)_2$), 75.9, 72.5, 71.2, 39.5, 37.4, 36.0, 25.7, 22.2, 22.1, 21.5, 21.4; HRESIMS *m*/*z* 324.1420 [M + Na]$^+$ (calcd for $C_{14}H_{23}NNaO_6$324.1418).

*Methyl (S)-2-[(S)-1-(3,4-dimethoxyphenethyl)-3-hydroxy-2,5-dioxopyrrolidin-3-yl]-2-hydroxyacetate (**13c**).* Colorless needles ($CHCl_3$); mp 120−122 °C; $[\alpha]_D^{25}$ +17 (*c* 0.2, acetone); IR (KBr) ν_{max} 3466, 2952, 1790, 1739, 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 6.75 (m, 3H), 4.26 (s, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H, OCH_3), 3.72 (m, 2H), 3.11 (d, *J* = 18 Hz, 1H), 2.83 (m, 2H), 2.69 (d, *J* = 18 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 177.1 (C═O), 173.8 (C═O), 171.7 ($COOCH_3$), 148.9, 147.8, 130.0, 120.9, 112.1, 111.2, 76.1, 72.1, 55.9, 55.8, 53.7, 40.2, 39.6, 32.8; HRESIMS *m*/*z* 368.1333 [M + H^+] (calcd for $C_{17}H_{22}NO_8$368.1345) (CCDC 1852020).

*Isopropyl (S)-2-{(S)-1-[2-(1H-indol-3-yl)ethyl]-3-hydroxy-2,5-dioxopyrrolidin-3-yl}-2-hydroxyacetate (**13d**).* Colorless needles ($CHCl_3$); mp 90−92 °C; $[\alpha]_D^{25}$ +55 (*c* 0.1, CH_3OH); IR (KBr) ν_{max} 3465, 2984, 1731, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 8.09 (s, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.18 (m, 2H), 7.02 (s, 1H), 5.27 (m, 1H), 4.14 (s, 1H), 3.81 (m, 2H), 3.11 (s, 1H), 3.05 (m, 3H), 2.68 (d, *J* = 18.0 Hz, 1H), 1.36 (m, 6H, $CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) 177.0 (C═O), 174.0 (C═O), 170.8 [$COOCH(CH_3)_2$], 136.2, 127.4, 122.3, 122.1, 119.6, 118.8, 111.9, 111.1, 76.7, 76.0, 72.2, 72.0, 39.8, 39.5, 23.2, 21.7; HRESIMS *m*/*z* 375.1550 [M + H^+] (calcd for $C_{19}H_{23}N_2O_6$375.155) (CCDC 1852019).

*Methyl (S)-2-[(R)-1-(3,4-dimethoxyphenethyl)-3-hydroxy-2,5-dioxopyrrolidin-3-yl]-2-hydroxyacetate (**14a**).* Colorless crystal ($CHCl_3$); mp 133−134 °C; $[\alpha]_D^{25}$ −38 (*c* 0.1, acetone); IR (KBr) ν_{max} 3453, 2933, 1789, 1747, 1703 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 6.75 (m, 3H), 4.42 (d, *J* = 6.8 Hz, 1H), 3.87 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.76 (s, 1H), 3.73 (m, 2H), 3.29 (d, *J* = 6.8 Hz, 1H), 2.99 (d, *J* = 18.4 Hz, 1H), 2.82 (m, 2H), 2.66 (d, *J* = 18.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 176.8 (C═O), 173.4 (C═O), 171.6 ($COOCH_3$), 149.0, 147.9, 130.0, 120.9, 112.1, 111.4, 77.2, 75.4, 72.7, 55.9, 53.3, 40.4, 38.2, 33.0; HRESIMS *m*/*z* 368.1333 [M + H^+] (calcd for $C_{17}H_{22}NO_8$368.1345).

*Methyl (S)-2-[(R)-1-(2-(1H-indol-3-yl)ethyl)-3-hydroxy-2,5-dioxopyrrolidin-3-yl]-2-hydroxyacetate (**14b**).* Colorless crystals ($CHCl_3$); mp 85−86 °C; $[\alpha]_D^{25}$−37 (*c* 0.1, CH_3OH); IR (KBr) ν_{max} 3405, 2980, 1747, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 8.01 (s, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.17 (m, 2H), 7.06 (s, 1H), 4.39 (s, 1H), 3.83 (m, 3H), 3.79 (s, 3H), 3.04 (m, 3H), 2.96 (s, 1H), 2.68 (d, *J* = 18 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 176.5 (C═O), 173.4 (C═O), 171.8 [$COOCH(CH_3)_2$], 136.2, 127.4, 122.4, 122.1, 119.6, 118.7, 112.0, 111.2, 75.4, 72.8, 53.3, 39.6, 38.4, 23.3; HRESIMS *m*/*z* 369.1081 [M + Na]$^+$ (calcd for $C_{17}H_{18}N_2NaO_6$369.1063).

General Procedure for the Preparation of Furopyrrolone Analogues 16, 18, 20, and 22. To a stirred solution of pyrrolidine-2,5-dione **13c**/**13d**/**14a**/**14b** (1 mmol, 1 equiv) in absolute EtOH (10 mL) precooled to 0 °C was added excess $NaBH_4$ (10 equiv) with stirring. After 20 h, the reaction was quenched with excess MeOH, and then a saturated aqueous $NaHCO_3$ solution was added. The excess MeOH was concentrated under reduced pressure. The aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography on silica gel 60−120 mesh (20% *n*-hexane/EtOAc) to afford **16a**, **18**, **20**, and **22**.

*(3R,3aS,6aS)-6-(3,4-Dimethoxyphenethyl)-3,3a-dihydroxytetrahydro-2H-furo[2,3-b]pyrrol-5(3H)-one (**16a**).* Yellow oil; $[\alpha]_D^{25}$ −157 (*c* 0.1, CH_3OH); IR (KBr) ν_{max} 3330, 2932, 1662 cm^{-1}; ^1H NMR (methanol-d_4, 400 MHz) 6.87 (m, 2H), 6.78 (d, *J* = 8.0 Hz,1H), 5.02 (s, 1H), 4.19 (m, 1H), 4.06 (m, 1H), 3.84 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.62 (m, 1H), 3.38 (m, 3H), 3.13 (d, *J* = 18.0 Hz, 1H), 2.82 (m, 2H), 2.28 (d, *J* = 18.0 Hz, 1H); ^{13}C NMR (methanol-d_4, 100 MHz) 173.5 (C═O), 149.1, 147.7, 131.6, 120.8, 112.3, 111.8, 98.6, 81.6, 76.8, 70.6, 55.1, 55.0, 41.6, 37.6, 32.9; HRESIMS *m*/*z* 324.1446 [M + H^+] (calcd for $C_{16}H_{22}NO_6$324.1447).

*(3R,3aR,6aR)-6-[3,4-Dimethoxyphenethyl]-3,3a-dihydroxytetrahydro-2H-furo[2,3-b]pyrrol-5(3H)-one (**18**).* Colorless crystals ($CHCl_3$); mp 114−116 °C; $[\alpha]_D^{25}$ −45 (*c* 0.1, acetone); IR (KBr) ν_{max} 3387, 2946, 1676 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) 6.87 (m, 2H), 6.77 (m,1H), 5.04 (s, 1H), 4.93 (br s, 1H), 4.63 (br s, 1H), 3.99 (s, 1H), 3.86 (s, 2H), 3.81 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.58 (m, 1H), 3.36 (m, 1H), 2.81 (m, 2H), 2.60 (d, *J* = 18.0 Hz, 1H), 2.49 (d, *J* = 18.0 Hz, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) 172.1 (C═O), 150.4, 149.0, 132.7, 121.5, 113.6, 113.0, 98.5, 81.3, 76.3, 73.3, 56.1, 56.0, 43.0, 42.7, 34.3; HRESIMS *m*/*z* 346.1259 [M + Na]$^+$ (calcd for $C_{16}H_{21}NO_6Na$346.1267) (CCDC 1852023).

*(3R,3aS,6aS)-6[(2-(1H-Indol-3-yl)ethyl]-3,3a-dihydroxytetrahydro-2H-furo[2,3-b]pyrrol-5(3H)-one (**20**).* Yellow oil; $[\alpha]_D^{25}$ −45 (*c* 0.1, acetone); IR (KBr) ν_{max} 3362, 2934, 1669 cm^{-1}; ^1H NMR (methanol-d_4, 400 MHz) 7.61 (d, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.10 (m, 2H), 7.02 (m, 1H), 5.08 (s, 1H), 4.19 (dd, *J* = 14.4 Hz, 6.3 Hz, 1H), 4.08 (dd, *J* = 6.4 Hz, 2.8 Hz, 1H), 3.69 (m, 1H), 3.51 (m, 1H), 3.39 (m, 1H), 3.18 (d, *J* = 18.0 Hz, 1H), 3.04 (m, 2H), 2.32 (d, *J* = 18.0 Hz, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) 173.5 (C═O), 136.8, 127.3, 122.0, 120.9, 118.3, 117.8, 111.4, 110.8, 98.7, 81.6, 76.9, 70.5, 40.8, 37.7, 23.1; HRESIMS *m*/*z* 303.1351 [M + H^+] (calcd for $C_{16}H_{19}N_2O_4$303.1339).

*(3R,3aR,6aR)-6[2-(1H-indol-3-yl)ethyl]-3,3a-dihydroxytetrahydro-2H-furo[2,3-b]pyrrol-5(3H)-one (**22**).* Yellow oil; $[\alpha]_D^{25}$ +99 (*c* 0.1, CH_3OH); IR (KBr) ν_{max} 3310, 2921, 1651 cm^{-1}; ^1H NMR (methanol-d_4, 400 MHz) 7.65 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.20 (s, 1H), 7.07 (m, 2H), 5.15 (s, 1H), 4.29 (m, 1H), 4.04 (m,1H), 3.64 (m, 1H), 3.48 (m,1H), 3.39 (m, 1H), 3.15 (m, 1H), 3.04 (m, 2H), 2.25 (m, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) 172.4 (C═O), 137.7, 128.5, 123.2, 122.1, 119.4, 119.3, 113.1, 112.2, 99.4, 82.7, 78.3, 71.2, 41.6, 38.9, 24.5; HRESIMS *m*/*z* 303.1351 [M + H^+] (calcd for $C_{16}H_{19}N_2O_4$303.1339).

General Procedure for the Preparation of Tetrahydropyrrolo[2,1-*a*]isoquinolinones 15 and 17 and Hexahydroindolizino[8,7-*b*]indolones 19 and 21. To a stirred solution of pyrrolidine-2,5-dione **13c**/**14a**/**13d**/**14b** (1 mmol) in

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EtOH was added $NaBH_4$ (3 mmol, 3 equiv) at 0 °C. After being stirred at room temperature for 4 h (**13c**/**14a**) and 18 h (**13d**/**14b**), the reaction was quenched with 5 M HCl. The reaction mixture was concentrated under reduced pressure, and the residue was extracted with MeOH. The organic layer was concentrated under reduced pressure, and the crude residue obtained was purified by column chromatography over silica gel 60−120 mesh (3% MeOH/$CHCl_3$) to afford **15**, **17**, **19**, and **21**.

*(1R,10bR)-1-[(R)-1,2-Dihydroxyethyl]-1-hydroxy-8,9-dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3(2H)-one (**15**).*[8] Colorless crystals (MeOH); mp 99−102 °C; $[\alpha]_D^{25}$ +157 (*c* 0.1, CH_3OH); IR (KBr) ν_{max} 3330, 2934, 1661 cm^{-1}; ^1H NMR (methanol-d_4, 400 MHz) 7.42 (s, 1H), 6.71 (s, 1H), 5.06 (s, 1H), 4.28 (m, 1H), 3.95 (dd, *J* = 6.8, 4.8 Hz, 1H), 3.85 (m, 1H), 3.82 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.72 (m, 1H), 2.85 (m, 3H), 2.63 (d, *J* = 14.8 Hz, 1H), 2.34 (d, *J* = 17.2 Hz, 1H); ^{13}C NMR (methanol-d_4, 100 MHz) 173.6 (C═O), 149.3, 148.7, 130.1, 125.1, 113.7, 113.3.2, 80.1, 77.4, 66.5, 64.3, 56.5, 56.4, 44.1, 39.0, 29.9; HRESIMS *m*/*z* 346.1256 $[M + Na]^+$ (calcd for $C_{16}H_{21}NO_6Na$346.1267) (CCDC 1852021).

*(1S,10bS)-1-[(R)-1,2-Dihydroxyethyl]-1-hydroxy-8,9-dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3(2H)-one (**17**).* Colorless crystals (MeOH); mp 129−131 °C; $[\alpha]_D^{25}$ +140 (*c* 0.1, CH_3OH); IR (KBr) ν_{max} 3264, 2940, 1658 cm^{-1}; ^1H NMR (methanol-d_4, 400 MHz) 6.90 (s, 1H), 6.79 (s, 1H), 5.23 (s, 1H), 4.33 (m, 1H), 4.04 (dd, *J* = 7.2, 2.7 Hz, 1H), 3.87 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.55 (dd, *J* = 11.0, 7.6 Hz, 1H), 3.03 (d, *J* = 16.4 Hz, 1H), 2.85 (m, 2H), 2.67 (m, 1H), 2.15 (d, *J* = 16.4 Hz, 1H); ^{13}C NMR (methanol-d_4, 100 MHz) 172.7 (C═O), 148.1, 147.8, 128.9, 123.1, 112.3, 110.2, 80.0, 71.9, 62.7, 62.1, 55.2, 55.0, 39.6, 37.2, 28.5; HRESIMS *m*/*z* 346.1269 $[M + Na]^+$ (calcd for $C_{16}H_{21}NO_6Na$ 346.1267).

*(1R,11bR)-1-[(R)-1,2-Dihydroxyethyl]-1-hydroxy-5,6,11,11b-tetrahydro-1H-indolizino[8,7-b]indol-3(2H)-one (**19**).* Colorless crystals (MeOH); mp 200−202 °C; $[\alpha]_D^{25}$ +118 (*c* 0.1, CH_3OH); IR (KBr) ν_{max} 3465, 2975, 1661 cm^{-1}; ^1H NMR (methanol-d_4, 400 MHz) 7.44 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.10 (t, *J* = 7.2 Hz, 1H), 7.01 (t, *J* = 7.2 Hz, 1H) 5.14 (s, 1H), 4.50 (m, 1H), 3.91 (dd, *J* = 7.0, 4.1 Hz,1H), 3.77 (m, 2H), 3.11−3.04 (m, 1H), 2.93 (s, 1H), 2.87 (m, 2H), 2.41 (d, *J* = 17.0 Hz, 1H);); ^{13}C NMR (methanol-d_4, 100 MHz) 173.4 (C═O), 137.6, 130.1, 128.3, 122.6, 119.8, 118.8, 112.2, 110.6, 78.5, 78.2, 66.2, 63.8, 44.9, 39.0, 21.9; HRESIMS *m*/*z* 303.1337 $[M + H]^+$ (calcd for $C_{16}H_{19}N_2O_4$303.1345) (CCDC 1852024).

*(1S,11bS)-1-[(R)-1,2-Dihydroxyethyl]-1-hydroxy-5,6,11,11b-tetrahydro-1H-indolizino[8,7-b]indol-3(2H)-one (**21**).* Colorless crystals (MeOH); mp 195−197 °C; $[\alpha]_D^{25}$ +99 (*c* 0.1, CH_3OH); IR (KBr) ν_{max} 3310, 2921, 1651 cm^{-1}; ^1H NMR (methanol-d_4, 400 MHz) 7.44 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1 Hz), 7.10 (m, 1H), 7.02 (m, 1 H), 5.31 (s, 1H), 4.49 (m, 1H), 4.09 (m, 1H), 3.92 (m, 1H), 3.69 (m, 1H), 3.14 (d, *J* = 17.0 Hz, 1H), 3.01 (m, 1H), 2.86 (m, 2H), 2.29 (d, *J* = 17.0 Hz, 1H); ^{13}C NMR (methanol-d_4, 100 MHz) 173.8 (C═O), 138.4, 129.9, 128.2, 122.6, 119.9, 118.7, 112.2, 111.1, 79.2, 74.2, 64.0, 62.6, 42.2, 39.0, 22.0; HRESIMS *m*/*z* 303.1360 $[M + H]^+$ (calcd for $C_{16}H_{19}N_2O_4$303.1345) (CCDC 1852025).

General Procedure for the Synthesis of Furo[2,3-*c*]pyrroles 23a−e from Bicyclic Anhydride 12. To a stirred solution of **12** (1.0 g, 4.7 mmol) in dry THF (5 mL) was added the appropriate amine at 0 °C. After being stirred at room temperature for 5 h, the mixture was concentrated under reduced pressure, and the residue was refluxed with acetyl chloride (5 mL). After 10 h, the mixture was concentrated under reduced pressure. The resulting crude residue was purified by column chromatography over silica gel 60−120 mesh (10% EtOAc/*n*-hexane) to afford crude **23a−e**.

*(3aS,6aS)-5-Allyl-2,4,6-trioxohexahydro-2H-furo[2,3-c]pyrrol-3a-yl acetate (**23a**).* White solid; $[\alpha]_D^{25}$ +160 (*c* 0.1, acetone); IR (KBr) ν_{max} 3380, 2937, 1803, 1755, 1735, 1677 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) 5.81 (m, 1H), 5.19 (m, 1H), 5.14 (s, 1H), 5.05 (m, 1H), 3.85 (m, 2H), 3.56 (d, *J* = 18.0 Hz, 1H), 2.98 (d, *J* = 18.0 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) 173.1 (C═O), 170.3 (C═O), 167.4 (C═O), 165.4 ($OCOCH_3$), 135.1, 116.4, 84.6, 82.8, 42.3, 38.2, 20.8; HRESIMS *m*/*z* 254.0669 $[M + H]^+$ (calcd for $C_{11}H_{12}NO_6$254.0665).

*(3aS,6aS)-5-Heptyl-2,4,6-trioxohexahydro-2H-furo[2,3-c]pyrrol-3a-yl acetate (**23b**).* Brown liquid; $[\alpha]_D^{25}$ −65 (*c* 0.1, $CHCl_3$); IR (KBr) ν_{max} 2930, 1807, 1726 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 5.25 (s, 1H), 3.57 (m, 2H), 3.20 (d, *J* = 19.6 Hz, 1H), 3.03 (d, *J* = 19.6 Hz, 1H), 2.21 (s, 3H), 1.61 (m, 2H), 1.29 (m, 8H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.1 (C═O), 170.5 (C═O), 170.2 (C═O), 167.7 ($OCOCH_3$), 79.6, 79.3, 39.9, 36.1, 31.6, 28.7, 27.0, 26.6, 22.5, 20.2, 14.1; HRESIMS *m*/*z* 312.1457 $[M + H]^+$ (calcd for $C_{15}H_{22}NO_6$312.1447).

*(3aS,6aS)-5-Nonyl-2,4,6-trioxohexahydro-2H-furo[2,3-c]pyrrol-3a-yl acetate (**23c**).* Brown liquid; $[\alpha]_D^{25}$ −113 (*c* 0.3, $CHCl_3$); IR (KBr) ν_{max} 2926, 2858, 1807, 1727 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 5.25 (s, 1H), 3.56 (m, 2H), 3.18 (d, *J* = 19.6 Hz, 1H), 3.05 (d, *J* = 19.6 Hz, 1H), 2.20 (s, 3H), 2.05 (s, 1H), 1.84 (m, 1H), 1.61 (m, 2H), 1.28 (m, 10H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.1(C═O), 170.6(C═O), 170.4 (C═O), 167.8 ($OCOCH_3$), 79.3, 63.7, 39.9, 36.1, 31.8, 29.4, 29,2, 29.0, 27.0, 26.6, 22.7, 20.2, 14.1; HRESIMS *m*/*z* 340.1766 $[M + H]^+$ (calcd for $C_{17}H_{26}NO_6$340.1760).

*(3aS,6aS)-5-Decyl-2,4,6-trioxohexahydro-2H-furo[2,3-c]pyrrol-3a-yl acetate (**23d**).* Brown liquid; $[\alpha]_D^{25}$ −113 (*c* 0.2, $CHCl_3$); IR (KBr) ν_{max} 2927, 2855, 1811, 1724 cm^{-1}; ^1H NMR ($CDCl_3$,400 MHz) 5.25 (s, 1H), 3.57 (m, 2H), 3.20 (d, *J* = 19.5 Hz, 1H), 3.03 (d, *J* = 19.5 Hz, 1H), 2.20 (s, 3H), 1.61 (m, 2H), 1.28 (m, 14H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.1 (C═O), 170.5 (C═O), 170.3 (C═O), 167.8 ($OCOCH_3$), 79.6, 79.3, 39.9, 36.1, 31.9, 29.5, 29.4, 29.3, 29.0, 27.1, 26.6, 22.7, 20.2, 14.1; HRESIMS *m*/*z* 354.1917 $[M + H]^+$ (calcd for $C_{18}H_{28}NO_6$354.1917).

*(3aS,3a′S,6aS,6a′S)-Ethane-1,2-diylbis(2,4,6-trioxohexahydro-3aH-furo[2,3-c]pyrrole-5,3a-diyl) diacetate (**23e**).* To a stirred solution of **12** (1.07 g, 5 mmol, 1 equiv) in HOAc (5 mL) was added the diamine (2.5 mmol, 0.5 equiv), and the mixture was refluxed for 5 h. The reaction mixture was cooled to room temperature and poured into water. The resulting precipitate was filtered off by suction and was recrystallized from $CHCl_3$ to afford **23e** as brown crystals; mp 226−230 °C; $[\alpha]_D^{25}$ −128 (*c* 0.1, acetone); IR (KBr) ν_{max} 2999, 1802, 1730 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) 5.54 (s, 2H), 4.02 (d, *J* = 10.0 Hz, 2H), 3.75 (d, *J* = 10.0 Hz, 2H), 3.29 (d, *J* = 19.2 Hz, 2H), 3.21 (d, *J* = 19.2 Hz, 2H), 2.15 (s, 6H); ^{13}C NMR (acetone-d_6, 100 MHz) 172.3 (C═O), 171.9 (C═O), 171.7(C═O), 169.2 ($OCOCH_3$), 80.8, 79.9, 37.6, 36.0, 20.2; HRESIMS *m*/*z* 475.0613 $[M + Na]^+$ (calcd for $C_{18}H_{16}N_2O_{12}Na$ 475.0601).

General Procedure for the Synthesis of Furo[2,3-*c*]pyrroles (24a−f) from Bicyclic Anhydride 12. To a stirred solution of **12** (1.0 g, 4.7 mmol, 1 equiv) in dry THF (5 mL) was added the appropriate amine at 0 °C. After being stirred at room temperature for 5 h, the reaction mixture was concentrated under reduced pressure, and the residue was refluxed with acetyl chloride (5 mL). After 10 h, the reaction mixture was concentrated under reduced pressure, and to a stirred solution of the residue in EtOH (10 mL) was added acetyl chloride (2 mL) at 0 °C. After 12 h, the reaction mixture was concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel 60−120 mesh (20% EtOAc/*n*-hexane) to afford **24a−f**.

*(3aS,6aS)-3a-Hydroxy-5-phenethyldihydro-2H-furo[2,3-c]-pyrrole-2,4,6(5H,6aH)-trione (**24a**).* Colorless crystals ($CHCl_3$); mp 128−130 °C; $[\alpha]_D^{25}$ −159 (*c* 0.1, $CHCl_3$); IR (KBr) ν_{max} 3427, 2941, 1816, 1797, 1776, 1726 cm^{-1}; ^1H NMR ($CDCl_3$,400 MHz) 7.26 (m, 3H), 7.13 (m, 2H), 4.92 (s, 1H), 3.85 (m, 2H), 3.00 (m, 2H), 2.74 (d, *J* = 19.2 Hz, 1H), 2.33 (d, *J* = 19.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 174.6 (C═O), 171.4 (C═O), 168.7 (C═O), 136.5, 129.0, 128.9, 127.3, 81.0, 76.8, 40.0, 39.1, 32.5; HRESIMS *m*/*z* 276.0882 $[M + H]^+$ (calcd for $C_{14}H_{14}NO_5$276.0872).

*(3aS,6aS)-3a-Hydroxy-5-(4-methoxybenzyl)dihydro-2H-furo[2,3-c]pyrrole-2,4,6(5H,6aH)-trione (**24b**).* Colorless crystals ($CHCl_3$); mp 115−117 °C; $[\alpha]_D^{25}$ −82 (*c* 0.1, $CHCl_3$); IR (KBr) ν_{max} 3407,

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2918, 2849, 1812, 1792, 1771, 1712 cm^{-1}; ^1H NMR ($CDCl_3$,400 MHz) 7.28 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H),5.00 (s, 1H), 4.63 (s, 2H), 3.79 (s, 3H), 2.94 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 174.2, 171.2, 168.2, 159.8, 130.4, 126.2, 114.4, 81.2, 76.7, 55.3, 42.8, 39.1; HRESIMS m/z 314.0648 $[M + Na]^+$ (calcd for $C_{14}H_{13}NO_6Na$ 314.0641).

*(3aS,6aS)-5-Hexadecyl-3a-hydroxydihydro-2H-furo[2,3-c]-pyrrole-2,4,6(5H,6aH)-trione (**24c**).* Colorless crystals ($CHCl_3$); mp 96−98 °C; $[\alpha]_D^{25}$ −86 (c 0.2, $CHCl_3$); IR (KBr) ν_{max} 3425, 2917, 2846, 1814, 1790, 1773, 1715, 1704 cm^{-1}; ^1H NMR ($CDCl_3$,400 MHz) 5.03 (s, 1H), 3.55 (m, 2H), 3.06 (t, J = 19.2 Hz, 2H), 1.59 (m, 2H), 1.25−1.28 (m, 27H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 174.8 (C═O), 171.5 (C═O), 168.7 (C═O), 81.3, 76.9, 39.7, 39.2, 31.9, 31.0, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 29.0, 27.4, 26.7, 22.7, 14.1; HRESIMS m/z 418.2553 $[M + Na]^+$ (calcd for $C_{22}H_{37}NO_5Na$ 418.2569).

*(3aS,6aS)-5-(3,4-Dimethoxyphenethyl)-3a-hydroxydihydro-2H-furo[2,3-c]pyrrole-2,4,6(5H,6aH)-trione (**24d**).* Colorless crystals ($CHCl_3$); mp 135−137 °C; $[\alpha]_D^{25}$ −147 (c 0.1, $CHCl_3$); IR (KBr) ν_{max} 3400, 1815, 1772, 1711 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 6.74 (d, J = 8.0 Hz, 1H), 6.67 (m, 1H), 6.60 (m, 1H), 4.90 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.77−3.94 (m, 2H), 2.94 (m, 2H), 2.76 (d, J = 19.2 Hz, 1H), 2.38 (d, J = 19.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 174.5 (C═O), 171.2 (C═O), 168.7 (C═O), 149.2, 148.3, 128.8, 121.2, 112.0, 111.4, 81.0, 76.8, 56.0, 55.9, 39.9, 39.1, 32.1; HRESIMS m/z 358.0907 $[M + Na]^+$ (calcd for $C_{16}H_{17}NO_7Na$ 358.0903).

*(3aS,6aS)-3a-Hydroxy-5-(4-phenylbutyl)dihydro-2H-furo[2,3-c]-pyrrole-2,4,6(5H,6aH)-trione (**24e**).* Colorless crystals ($CHCl_3$); mp 112−114 °C; $[\alpha]_D^{25}$ −107 (c 0.1, $CHCl_3$); IR (KBr) ν_{max} 3417, 2934, 1814, 1799, 1789, 1772, 1714 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) 7.17−7.29 (m, 5H),5.15 (s, 1H), 3.27 (d, J = 18.8 Hz, 1H), 2.74 (d, J = 18.8 Hz, 1H), 2.51 (m, 4H), 1.53 (m, 4H); ^{13}C NMR (DMSO-d_6, 100 MHz) 175.0 (C═O), 174.0 (C═O), 170.1 (C═O), 142.3, 128.8, 128.7, 126.2, 82.3, 77.0, 39.3, 38.8, 35.0, 28.6, 26.9; HRESIMS m/z 326.1011 $[M + Na]^+$ (calcd for $C_{16}H_{17}NO_5Na$ 326.1004).

*(3aS,6aS)-5-Benzyl-3a-hydroxydihydro-2H-furo[2,3-c]pyrrole-2,4,6(3H,5H)-trione (**24f**).*[25] Colorless crystals ($CHCl_3$); mp 110−112 °C; $[\alpha]_D^{25}$ −133 (c 0.1, $CHCl_3$); IR (KBr) ν_{max} 3382, 1809, 1791, 1769, 1714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.26−7.36 (m, 5H) 5.04 (s, 1H), 4.71 (s, 2H), 3.56 (s, 1H), 2.97 (s, 2H); ^{13}C NMR (CDCl3, 100 MHz) 174.3 (C═O), 171.3 (C═O), 168.3 (C═O), 134.1, 129.1, 128.9, 128.7, 81.3, 77.2, 43.3, 39.1; HRESIMS m/z 284.0545 $[M + Na]^+$ (calcd for $C_{13}H_{11}NO_5Na$ 284.0535).

Synthesis of Pyrroloisoquinolinone 25 from Bicyclic Anhydride 12. *(1S,2R,10bR)-1-Hydroxy-2-(2-hydroxyethyl)-8,9-dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3(2H)-one (**25**).* To a stirred solution of pyrrolidinedione **24d** (1.0 g, 2.98 mmol, 1 equiv) in absolute EtOH (10 mL) precooled to 0 °C was added $NaBH_4$ (1.1 g, 30 mmol, 10 equiv) with stirring. Subsequently over a 3 h period, a 2 M solution of HCl in ethanol (2 mL) was slowly added via syringe. The resulting solution was acidified to pH 1−3 by the addition of a 2 M solution of HCl in ethanol over a 15 min period with stirring. After 20 h, the reaction was quenched with saturated aqueous $NaHCO_3$ solution, and excess EtOH was concentrated under reduced pressure. The aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel 60−120 mesh (20% n-hexane/EtOAc) to afford **25** as colorless crystals ($CHCl_3$): mp 96−98 °C; $[\alpha]_D^{25}$ −72 (c 0.1, ($CHCl_3$); IR (KBr) ν_{max} 3500, 3299, 2925, 1688, 1670 cm^{-1}; ^1H NMR (methanol-d_4, 400 MHz) 7.09 (s, 1H), 6.75 (s, 1H), 4.64 (s, 1H), 4.59 (d, J = 6.0 Hz, 1H), 4.32 (m, 1H), 3.85 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.78 (t, J = 6.6 Hz, 2H), 3.06 (m, 1H), 2.81 (m, 2H), 2.65 (m, 1H), 2.14 (m, 1H), 1.87 (m, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) 174.4 (C═O),149.4, 149.3, 128.7, 126.8, 113.3, 109.8, 74.7, 63.2, 61.6, 56.2, 56.1, 47.4, 37.4, 28.8, 28.5; HRESIMS m/z 308.1500 $[M + H]^+$ (calcd for $C_{16}H_{22}NO_5$ 308.1498) (CCDC 1852026).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jnatprod.0c00211.

^1H and ^{13}C NMR spectra and HRMS for all new compounds; single-crystal XRD data of the representative examples (PDF)

X-ray data (CIF)

X-ray data (CIF)

X-ray data (CIF)

X-ray data (CIF)

X-ray data (CIF)

X-ray data (CIF)

X-ray data (CIF)

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Notes

The authors declare no competing financial interest.

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