Synthesis of Bicyclic Pyroglutamic Acid Featuring the Ugi Reaction and a Unique Stereoisomerization at the Angular Position by Grob Fragmentation Followed by a Transannular Ketene [2+2] Cycloaddition Reaction

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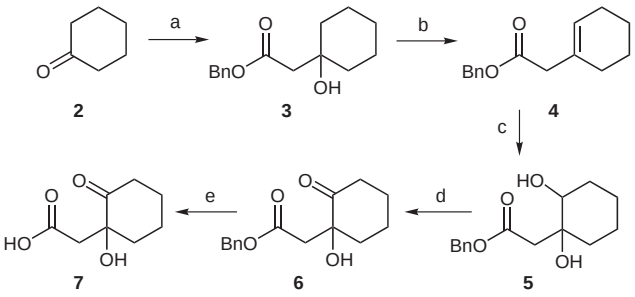
This paper is dedicated to Professor K.C. Nicolaou on the occasion of his 60th birthday.

Abstract: A stereoisomerization at the angular position of *N*-acylindoles during basic hydrolysis was discovered to give only the *syn*-bicyclic pyroglutamic acid, proceeding through a transannular [2+2] cycloaddition of a ketene–ketone intermediate generated by a Grob fragmentation.

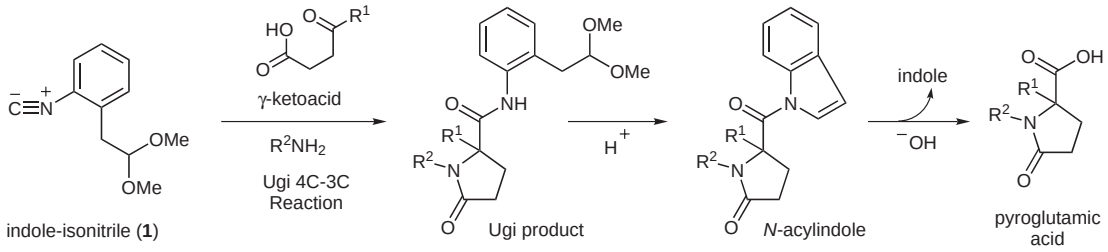
Key words: isonitrile, Ugi reaction, pyroglutamic acid, diastereoselectivity, lactams

The Ugi four-component condensation reaction represents a powerful method to quickly build in one-pot *N*-acyl amino acid amides.[1] Our lab has been interested in applying this methodology to the synthesis of natural products containing the pyroglutamic acid moiety, using γ-ketoacids. Salinosporamide A,[2] lactacystin,[3] and oxazolomycin A[4] incorporate this functional group and each shows promising anticancer activity. Many convertible isonitriles (isocyanides), which allow for mild hydrolysis of the C-terminal amide of the Ugi adduct, are known.[5] Unfortunately, it was not possible to hydrolyze sterically hindered pyroglutamic acid amides in Ugi adducts incorporating known isonitriles. We introduced a novel convertible isonitrile, 1-isocyano-2-(2,2-dimethoxyethyl)benzene (**1**).[6] This so-called indole–isonitrile (**1**) is easily cleaved even in bulky substrates via an *N*-acylindole intermediate (Scheme 1).

A key focus for our group has been to develop the Ugi four-center, three-component reaction (4C-3CR)[7] into a diastereoselective one by use of a chiral γ-ketoacid.[8] We recently reported a diastereoselective Ugi 4C-3CR in the synthesis of omuralide.[6a] Herein we describe the synthesis of a unique bicyclic pyroglutamic acid derivative which is fully substituted at the angular positions. The synthesis features quick access to the bicyclic pyroglutamic acid core using the Ugi 4C-3CR, and an unexpected stereoisomerization at the angular positions of the bicyclic structure from basic hydrolysis of the C-terminal amide to give only the *syn*-pyroglutamic acid.



Scheme 2 Synthesis of precursor **7** to the Ugi and Passerini multicomponent condensation reactions. *Reagents and conditions*: (a) Zn (4 equiv), CuCl (0.4 equiv), benzyl bromoacetate (1 equiv), THF, 95%; (b) CSA (4.5 equiv), PhH, reflux, 24 h, 79% (7:1 β,γ:α,β); (c) OsO_4 (3 mol%), NMO (3 equiv), DABCO (5 mol%), THF–H_2O (10:1), 93% (11:1 β,γ:α,β); (d) IBX (1.5 equiv), EtOAc, 90 °C, 6 h, 88%; (e) Pd–C, H_2, MeOH, 23 °C, 5 h, quant.



Scheme 1 Utility of indole–isonitrile (**1**) through derivatization of *N*-acylindole

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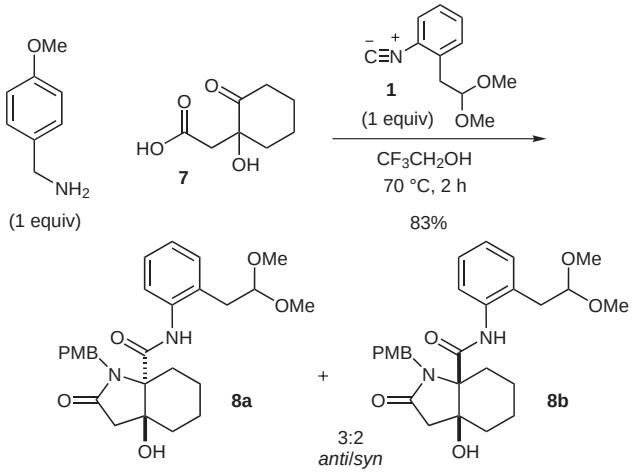
The synthesis of the Ugi precursor **7** began with the Reformatsky reaction of benzyl 2-bromoacetate and cyclohexanone (**2**) as shown in Scheme 2.[9] Acid-mediated dehydration of the resulting tertiary alcohol **3** led to regioselective formation of the desired *endo*-olefin isomer **4** in a 7:1 ratio over the *exo*-isomer. The *exo*-isomer may have been predicted to be the thermodynamically favored product due to conjugation of the double bond with the carbonyl group.[10] However, due to greater torsional strain present in the *exo*-isomer from eclipsing C=C and C–H bonds, as well as 1,3-allylic strain, we observe a preference for the *endo*-isomer.[11] Osmium tetroxide catalyzed *syn*-dihydroxylation of **4** gave the diol **5** cleanly. We anticipated that lactone formation via loss of benzyl alcohol could be a problem; however, this side product was not detected. Oxidation of **5** using IBX[12] proceeded well and it was at this stage that the minor regioisomer could be removed, thanks to the relatively high polarity of the 1,2-dicarbonyl compound. Simple catalytic hydrogenation of benzyl ester **6**[13] furnished the desired γ-ketoacid **7**[14] to be exploited in the Ugi reaction.



Scheme 3 Stereoselectivity in the Ugi Reaction of γ-ketoacid **7** with indole–isonitrile **1**

As shown in Scheme 3, the Ugi reaction was used with γ-ketoacid **7**,[15] indole–isonitrile **1** and PMB-NH_2.[16] The yield for the reaction was good; however, the diastereomeric ratio was only 3:2 and the two diastereomers of **8** were not easily separated by column chromatography. X-ray crystallography of the less polar **8a**[17] (**8a**: R_f = 0.17, **8b**: R_f = 0.12, SiO_2, hexane–EtOAc, 1:2) showed that it was the *anti*-Ugi adduct, as seen in Figure 2.[18]

With the Ugi product **8** in hand, we next subjected the indole precursor to acidic conditions, which induced the cyclization–dehydration sequence to give *N*-acylindole **9ab** (**9a**:[19] R_f = 0.35, **9b**: R_f = 0.29, SiO_2, hexane–EtOAc, 1:1) (Scheme 4). Quantitative conversion was observed, but at the expense of a significant amount of the *syn*-isomer **8b**. Two diastereomers of the propellane *N*,*O*-acetal **9cd** (**9c**:[20] R_f = 0.24, **9d**:[21] R_f = 0.12, SiO_2, hexane–EtOAc, 1:1) resulting from trapping by the tertiary alcohol of the transient iminium species following dehydration were

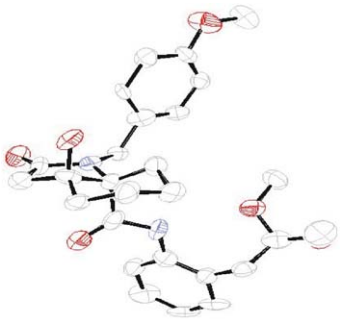
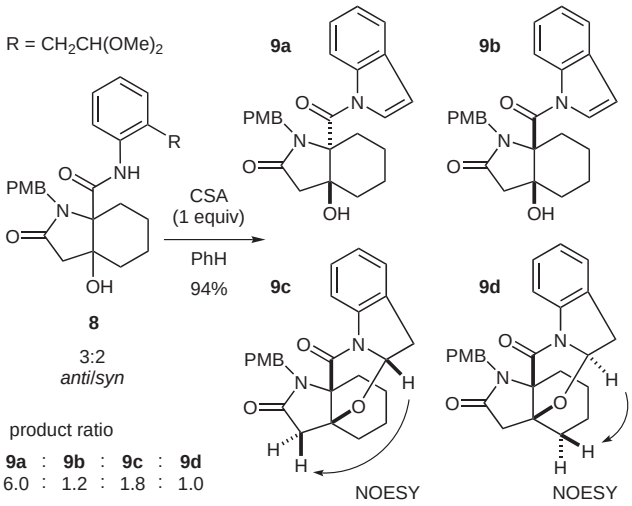


Figure 1 ORTEP representation of the *anti*-Ugi product **8a**

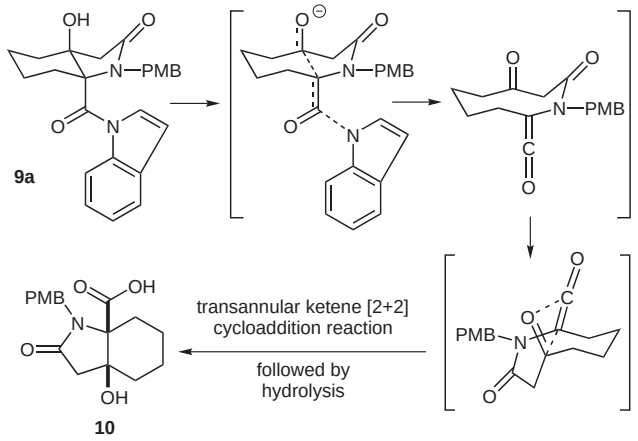
isolated. 1D NOESY studies revealed a strong NOE effect between the *N*,*O*-acetal hydrogen (**9c**: 5.60 ppm, **9d**: 5.85 ppm) and the α-hydrogen (2.65 ppm) of the lactam of **9c** and the cyclohexyl hydrogen (2.04 ppm) of **9d**, thus establishing the relative stereochemistry of each. It was observed that the *N*,*O*-acetal was surprisingly stable to both acidic and basic conditions, as we were not able to convert it to the *N*-acylindole.



Scheme 4 Attempted *N*-acylindole formation from **8** with acid

Although the separation of **8a** and **8b** was difficult, we were able to isolate small amounts of the enriched samples, which were treated with the same acidic conditions as above. It was found that **8a** gave only *anti*-*N*-acylindole **9a**, while **8b** gave a 1:2 ratio of *syn*-*N*-acylindole **9b** to *N*,*O*-acetal (**9c** + **9d**). This result was to be expected since the *anti*-Ugi adduct **8a** cannot give *N*,*O*-acetal and the more polar **8b** gave a majority of *N*,*O*-acetal.

Treatment of the 5:1 *anti–syn* mixture of **9ab** with excess Et_3N in THF–H_2O (3:1) at 70 °C gave the pyroglutamic acid **10**[22] in quantitative yield and 56% over three steps from **7** (Scheme 5). Surprisingly, **10** was isolated as a single diastereomer which was clearly discernable by ^1H NMR. In order to explain this convergence to a single isomer under basic conditions, we proposed a Grob fragmentation[23] followed by a transannular ketene–ketone [2+2] cycloaddition to give the β-lactone,[24] which



Scheme 5 Grob fragmentation followed by transannular ketene [2+2] under basic conditions

was then hydrolyzed to **10**. As can be seen in the ORTEP diagram in Figure 2, there is a good antiperiplanar relationship between the cleaved C–C angular bond and the indole C–N amide bond for *anti*-*N*-acylindole **9a**, allowing for the Grob fragmentation to generate the ketene intermediate.[25] To our knowledge, this is the first example of a Grob fragmentation proceeding through a ketene intermediate.

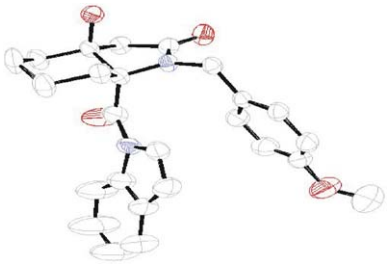


Figure 2 ORTEP representation of *N*-acylindole **9a**

As shown in Figure 3, X-ray analysis of the pyroglutamic acid **10** unambiguously assigned it as the *syn*-isomer.[26] Thus, hydrolysis of the *anti–syn* mixture **9** gives only the *syn*-isomer of pyroglutamic acid **10**. This observation could be useful in an enantioselective synthesis if a resolution, via diastereomeric salt formation with a chiral amine, could be performed on the racemic *syn*-acid **10**. One issue that remains to be addressed is suppression of *N*,*O*-acetal formation from the *syn*-Ugi product **8b**. We envision that protection of the tertiary alcohol in γ-ketoacid **7** would serve that purpose as well as act as a possible vehicle for diastereoselectivity in the Ugi reaction.

To explore the stereoselectivity of the related Passerini reaction, γ-ketoacid **7** was reacted with indole–isonitrile **1** to yield **11** in 74% yield as a 5.5:1 *anti–syn* mixture (Scheme 6). Treatment of **11** with CSA led to a 79% yield of a 17:2:1 mixture of *anti*-*N*-acylindole **12**:*N*,*O*-acetal **12a** (*vide infra*)[27]:*syn*-*N*-acylindole. Based on the low relative yield of the *N*,*O*-acetal, we concluded that the *syn*-isomer was the minor product in the Passerini reaction.

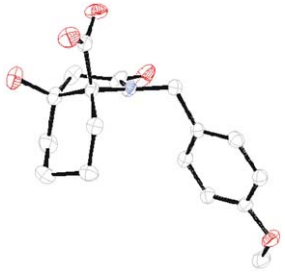
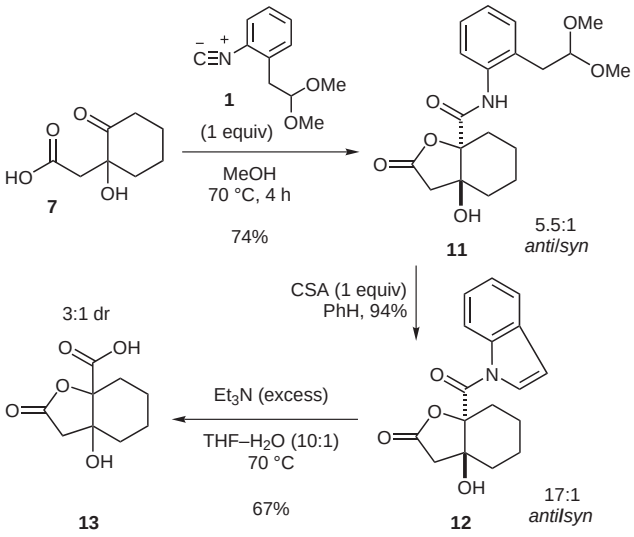


Figure 3 ORTEP representation of acid **10**

Subsequent hydrolysis with excess Et_3N in THF–H_2O (3:1) at 70 °C gave the 2-hydroxyglutaric acid γ-lactone **13** in 67% yield as a 3:1 mixture of diastereomers (major isomer unknown). Because of this partial stereoisomerization (dr = 17:1 to 3:1), we can conclude that at least some of the hydrolysis product **13** results from a similar mechanism to that for the pyroglutamic acid **10**. However, this result for the lactone **12** is in contrast to that for the lactam **9** which gave only the *syn*-isomer upon hydrolysis. The chemoselectivity of the hydrolysis should be noted, as the amide was hydrolyzed in the presence of the lactone.



Scheme 6 Stereoselectivity in the Passerini reaction of γ-ketoacid **7** with indole–isonitrile **1**

We have shown that ready access to bicyclic pyroglutamic acid derivatives via the Ugi reaction is available with indole–isonitrile **1** and γ-ketoacid **7**. Also, the related Passerini reaction with **7** allows construction of a 2-hydroxyglutaric acid γ-lactone with moderate diastereoselectivity. Interestingly, a Grob fragmentation followed by transannular ketene–ketone [2+2] reaction proceeded upon hydrolysis of *N*-acylindole compound **9a**. This is unusual given that typically the Grob fragmentation is observed when the displaced group has strong leaving group ability (such as a tosylate), and indole does not fit into that category. The pyroglutamic acid structures generated by this strategy have possible applications as polydentate ligands in asymmetric organometallic reactions.

Acknowledgment

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(14) γ-Ketoacid **7** has been made from a different ketone starting material and is known to exist in the hemi-ketal form **7a** (Figure 4): Mondon, A.; Menz, H.; Zander, J. *Chem. Ber.* **1963**, *96*, 826.

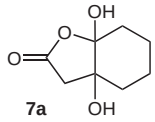

Figure 4

(15) Although **7** is known to exist as the hemi-ketal **7a**, presumably under equilibrium in the Ugi reaction conditions, that did not prevent it from reacting in the Ugi 4C-3CR.

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(17) **8a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.03 (s, 1 H), 7.65 (d, *J* = 8.0 Hz, 1 H), 7.27 (d, *J* = 8.3 Hz, 2 H), 7.26 (d, *J* = 7.3 Hz, 1 H), 7.19, (d, *J* = 5.7 Hz, 1 H), 7.13 (d, *J* = 7.6 Hz, 1 H), 6.80 (d, *J* = 8.8 Hz, 2 H), 4.96 (d, *J* = 15.6 Hz, 1 H), 4.47 (t, *J* = 5.2 Hz, 1 H), 3.75 (s, 1 H), 3.63 (d, *J* = 16.0 Hz, 1 H), 3.42 (s, 3 H), 3.39 (s, 3 H), 2.92 (dd, *J* = 5.6, 14.0 Hz, 1 H), 2.83 (dd, *J* = 5.6, 14.0 Hz, 1 H), 2.32 (d, *J* = 16.0 Hz, 1 H), 2.19 (td, *J* = 4.0, 12.8 Hz, 1 H), 1.81 (m, 5 H), 1.58 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.7, 169.0, 158.7, 136.0, 131.1, 130.0, 128.6, 128.3, 127.5, 125.5, 124.7, 113.9, 107.1, 77.1, 73.7, 55.4, 54.6, 54.5, 45.5, 43.1, 37.2, 29.3, 25.6, 21.8, 19.9; HRMS: *m*/*z* calcd for $C_{27}H_{34}N_2O_6$: 482.2411; found: 482.2405.

(18) Crystal data for **8a**: $C_{27}H_{34}N_2O_6$, M_r = 482.56, triclinic, space group P1, *a* = 9.899 (3) Å, *b* = 12.169 (4) Å, *c* = 13.444 (4) Å, *α* = 79.540 (4)°, *β* = 80.366 (4)°, *γ* = 69.755 (4)°, *V* = 1484.6 (7) Å^3, *Z* = 2, ρ_{calc} = 1.080 Mg/m^3, *F*(000) = 516, *λ* = 0.71073 Å, *T* = 200 (2) K, *μ*(MoKa) = 0.076 mm^{-1}. Of the 16570 measured reflections, 11473 were independent [*R*(int) = 0.0283]. The final refinement converged at *R*1 = 0.0629 for $I > 2\sigma(I)$, *wR*2 = 0.1654 for all data. The data for **8a, 9a** and **10** were collected on a Bruker diffractometer with an APEX CCD detector, the structure was solved by direct methods (SHELXL-97) and refined with all data by full matrix least squares on F^2. CCDC 634645 contains the supplementary crystallographic data of **8a**. The data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax:+44 (1223)336033 or deposit@ccdc.cam.ac.uk.

(19) **9a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.34 (d, *J* = 8.5 Hz, 1 H), 7.55 (d, *J* = 7.5 Hz, 1 H), 7.59 (d, *J* = 4.0 Hz, 1 H), 7.35 (t, 8.0 Hz, 1 H), 7.29 (t, *J* = 7.5 Hz, 1 H), 7.23 (d, *J* = 8.5 Hz, 2 H), 6.81 (d, *J* = 8.5 Hz, 2 H), 6.56 (d, *J* = 4.0 Hz, 1 H), 5.02 (d, *J* = 16.0 Hz, 1 H), 4.21 (d, *J* = 16.5 Hz, 1 H), 3.76 (s, 3 H), 3.62 (d, *J* = 16.0 Hz, 1 H), 2.59 (td, *J* = 5.5, 13.5 Hz, 1 H), 2.50 (br s, 1 H, OH), 2.40 (d, *J* = 16.0 Hz, 1 H), 2.31 (td, *J* = 3.5, 14.0 Hz, 1 H), 2.20 (m, 1 H), 1.82 (m, 3 H), 1.64 (m, 1 H), 1.54 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.8, 170.8, 159.1, 137.2, 129.6, 129.1, 128.8, 125.4, 124.7, 124.2, 121.0, 117.2, 114.2, 109.1, 79.0, 76.3, 55.4, 45.2, 44.6, 29.8, 26.4, 21.7, 19.8; HRMS: *m*/*z* calcd for $C_{25}H_{26}N_2O_4$: 418.1887; found: 418.1883.

(20) **9c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.5 Hz, 1 H), 7.24 (d, *J* = 8.0 Hz, 2 H), 7.19 (t, *J* = 7.5 Hz, 1 H), 7.08 (d, *J* = 7.0 Hz, 1 H), 7.01 (t, *J* = 7.5 Hz, 1 H), 6.57 (d, *J* = 9.0 Hz, 2 H), 5.60 (t, *J* = 7.0 Hz, 1 H), 4.59 (d, *J* = 14.5 Hz, 1 H), 4.17 (d, *J* = 14.5 Hz, 1 H), 3.53 (s, 3 H), 3.15 (dd, *J* = 8.0, 16.5 Hz, 1 H), 2.95 (dd, *J* = 5.5, 16.0 Hz, 1 H), 2.82 (d, *J* = 17.5 Hz, 1 H), 2.65 (d, *J* = 17.5 Hz, 1 H), 2.00 (dd, *J* = 4.0, 14.0 Hz, 1 H), 1.65 (m, 1 H), 1.58 (m, 2 H), 1.29 (m, 2 H), 1.11 (m, 1 H); HRMS: *m*/*z* calcd for $C_{25}H_{26}N_2O_4$: 418.1887; found: 418.1893.

(21) **9d**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.0 Hz, 1 H), 7.14 (t, *J* = 7.5 Hz, 1 H), 7.12 (d, *J* = 8.5 Hz, 2 H), 7.12 (behind peak), 7.03 (t, *J* = 7.5 Hz, 1 H), 6.44 (d, *J* = 9.0 Hz, 2 H), 5.85 (t, *J* = 7.5 Hz, 1 H), 4.70 (d, *J* = 15.5 Hz, 1 H), 4.30 (d, *J* = 15.0 Hz, 1 H), 3.54 (s, 3 H), 3.10 (dd, *J* = 7.0, 15.0 Hz, 1 H), 2.93 (dd, *J* = 9.0, 15.0 Hz, 1 H), 2.93 (behind

peak), 2.79 (d, *J* = 16.5 Hz, 1 H), 2.47 (d, *J* = 16.5 Hz, 1 H), 2.04 (td, *J* = 4.5, 14.0 Hz, 1 H), 1.84 (m, 2 H), 1.47 (m, 2 H), 1.29 (td, *J* = 3.0, 12.5 Hz, 1 H), 1.10 (m, 1 H); HRMS: *m*/*z* calcd for $C_{25}H_{26}N_2O_4$: 418.1887; found: 418.1889.

(22) **10**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.5 Hz, 2 H), 6.80 (d, *J* = 8.0 Hz, 2 H), 4.66 (d, *J* = 15.5 Hz, 1 H), 4.24 (d, *J* = 15.5 Hz, 1 H), 3.78 (s, 3 H), 3.20 (br s, 1 H, OH), 2.77 (d, *J* = 16.0 Hz, 1 H), 2.46 (d, *J* = 16.5 Hz, 1 H), 2.14 (m, 2 H), 1.81 (tt, *J* = 4.5, 19.0 Hz, 2 H), 1.67 (td, *J* = 4.0, 14.5 Hz, 1 H), 1.53 (m, 1 H), 1.41 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.9, 175.6, 159.0, 130.2, 129.4, 114.0, 74.3, 72.3, 55.4, 44.5, 44.4, 36.0, 27.9, 20.5, 20.3; HRMS: *m*/*z* calcd for $C_{17}H_{21}NO_5$: 319.1414; found: 319.1417.

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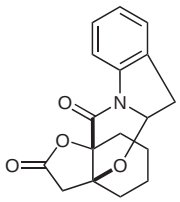
(25) Crystal data for **9a**: $C_{25}H_{26}N_2O_4$, M_r = 418.48, monoclinic, space group *P*2(1)/*c*, *a* = 17.172 (6) Å, *b* = 27.378 (11) Å, *c* = 13.501 (5) Å, *α* = 90°, *β* = 100.125 (5)°, *γ* = 90°, *V* = 6248 (4) Å^3, *Z* = 12, ρ_{calc} = 1.335 Mg/m^3, *F*(000) = 2664, *λ* = 0.71073 Å, *T* = 100 (2) K, *μ*(MoKa) = 0.091 mm^{-1}. Of the 50332 measured reflections, 13977 were independent [*R*(int) = 0.0772]. The final refinement converged at *R*1 = 0.2393 for *I* > 2σ(*I*), *wR*2 = 0.5894 for all data. CCDC 634643 contains the supplementary crystallographic data of **9a**.

(26) Crystal data for **10**: $C_{17}H_{21}NO_5$, M_r = 319.35, orthorhombic, space group Pccn, *a* = 31.323 (2) Å, *b* = 9.3197 (6) Å, *c* = 10.4743 (6) Å, *α* = 90°, *β* = 90°, *γ* = 90°, *V* = 3057.6 (3) Å^3, *Z* = 8, ρ_{calc} = 1.387 Mg/m^3, *F*(000) = 1360, *λ* = 1.54178 Å, *T* = 100 (2) K, *μ*(MoKa) = 0.846 mm^{-1}. Of the 12336 measured reflections, 2763 were independent [*R*(int) = 0.0266]. The final refinement converged at *R*1 = 0.0472 for *I* > 2σ(*I*), *wR*2 = 0.1227 for all data. CCDC 634647 contains the supplementary crystallographic data of **10**.

(27) A single diastereomer of the *N*,*O*-acetal **12a** (Figure 5), the relative stereochemistry of which was not determined, was formed.



12a

Figure 5

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