Synthesis of Functionalized Pyroglutamic Acids, Part 1: The Synthetic Utility of *N*-Acylindole and the Ugi Reaction with a Chiral Levulinic Acid

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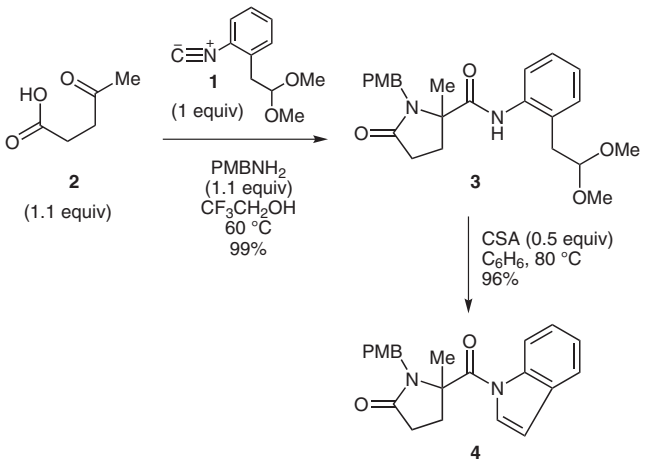
Abstract: A variety of pyroglutamic acid derivatives are readily synthesized via *N*-acylindole intermediates obtained by the Ugi reaction. For the preparation of functionalized pyroglutamic acid derivatives, the diastereoselectivity of the Ugi 4-center 3-component condensation reaction with a chiral γ-keto acid and convertible isocyanide is described.

Key words: pyroglutamic acid, Ugi reaction, convertible isocyanide, diastereoselectivity, β-lactone

In 1997, the Ugi 4-center 3-component condensation (4C-3C) reaction of levulinic acid (4-oxopentanoic acid) was reported to afford a 2-methylpyroglutamic acid amide.[1] Interestingly, the Passerini reaction, which provides the corresponding γ-lactone, had been reported in 1923, just two years after the discovery of the Passerini reaction in 1921.[2] Thanks to the mild nature of the reaction conditions and high chemical yield, the Ugi reaction with γ-keto acid derivatives could be an efficient method to obtain pyroglutamic acid derivatives. Nevertheless, in our opinion, there were two major obstacles to overcome to apply the reaction in complex natural product synthesis. First is the difficulty of hydrolysis of the sterically hindered C-terminal amide, which derives from an isocyanide.[3] Second is the diastereoselectivity in the reaction when a chiral substrate is used. Because of these difficulties, the application in the total synthesis of natural products has only been reported recently.[4] It appears that the Ugi reaction of γ-keto acids for the synthesis of pyroglutamic acid derivatives has been underestimated among synthetic organic chemists due to these problems.

In the course of synthetic studies on the proteasome inhibitor omuralide in our laboratory, a novel convertible isocyanide, 1-isocyano-2-(2,2-dimethoxyethyl)benzene (**1**), was introduced for the facile synthesis of pyroglutamic acids by use of the Ugi reaction of γ-keto acids.[4a] The hydrolysis of the resulting C-terminal anilide was facilitated by conversion to the corresponding *N*-acylindole. In this paper, we report the extended utility of *N*-acylindole as a coupling agent and our initial investigation on stereoselectivity in the Ugi 4C-3C reaction with chiral γ-keto acids.



Scheme 1 Ugi 4C-3C reaction of levulinic acid (**2**) with convertible isocyanide **1** reported in 2007

In 2007, we reported convertible isocyanide **1** and demonstrated the applicability in the synthesis of pyroglutamic acid (Scheme 1).[4a] The condensation of levulinic acid (**2**), $PMBNH_2$, and isocyanide **1** in trifluoroethanol at 60 °C afforded pyroglutamic acid anilide **3** in excellent yield.[5] The resulting sterically hindered anilide **3** was activated to *N*-acylindole **4** for facile hydrolysis. Indeed, the hydrolysis of **4** to a carboxylic acid **5a** was achieved by treatment with Cs_2CO_3 in aqueous DMF (Table 1, entry 1).

In addition, the utility of *N*-acylindole **4** as a coupling agent was investigated. The direct conversion of the *N*-acylindole to an ester, amide and aldehyde was smoothly carried out under mild conditions. *N*-Acylindole **4** was converted in good yields into the corresponding benzyl ester **5b** (entry 2) or butyl thioester **5c** (entry 3) with a stoichiometric amount of benzyl alcohol or butanethiol, respectively. Overall a transamidation process, secondary amide formation occurred smoothly from **4** by heating the *N*-acylindole with a primary amine. The amide **5d** was obtained by treatment with excess *p*-methoxybenzylamine (entry 4). Although primary alcohols, thiols, and amines reacted with the *N*-acylindole, secondary alcohols (isopropanol) and amines (morpholine) failed to react, presumably due to steric hindrance.

An interesting two-step, one-pot sequence was employed to convert the *N*-acylindole moiety directly into an aldehyde **5e** (entry 5). Reduction of the *N*-acylindole with

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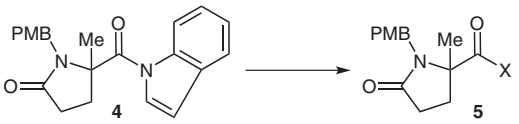
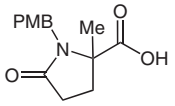
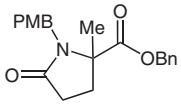
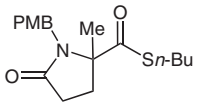
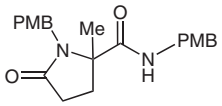
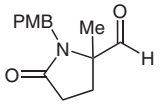
Table 1 Synthetic Utility of *N*-Acylindole **4** as a Coupling Agent



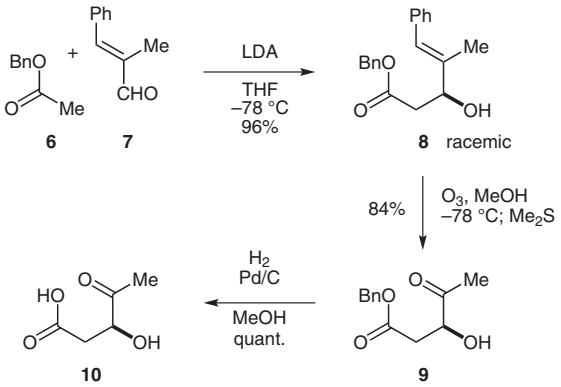
Entry	Conditions	Products	Yield
1	Cs_2CO_3 (1.0 equiv) DMF–H_2O (1:1) r.t.	 **5a**	97%
2	Cs_2CO_3 (1.4 equiv) BnOH (1.2 equiv) DMF, r.t.	 **5b**	79%
3	Cs_2CO_3 (1.5 equiv) *n*-BuSH (1.5 equiv) DMF, r.t.	 **5c**	86%
4	$PMBNH_2$ (10 equiv) THF, reflux	 **5d**	81%
5	$NaBH_4$ (1.0 equiv) MeOH; aq NaOH, THF r.t.	 **5e**	69%

$NaBH_4$ provides an *N*,*O*-hemiacetal intermediate which is stable until treated with aqueous NaOH.[6] Deprotonation to form the alkoxide of the hemiacetal hydroxy group causes concurrent expulsion of indole and aldehyde formation.

As shown in Table 1, the *N*-acylindole **4** is a versatile synthetic intermediate, which can be directly converted to a variety of acid derivatives as well as an aldehyde. Due to the steric hindrance in particular, the formation of the *N*-acylindole is a convenient method to activate the *exo* amide derived from the isocyanide, instead of sequential manipulations; hydrolysis to a carboxylic acid followed by condensation with a coupling agent like DCC.

Next, we were interested in investigating a substrate-controlled stereoselective Ugi 4C-3C reaction with a chiral γ-keto acid. We envisioned that stereocenters on the carbon backbone connecting the carboxyl group and the carbonyl group might affect the stereochemistry at the α-carbon of the resulting amino acid. Based on the reaction mechanism, the stereodetermining step is the addition of an isocyanide toward a putative iminium ion. Therefore, a stereocenter at the α-position of the carbonyl group could be the most effective to achieve the stereoselective addition of an isocyanide. We chose an unprotected hydroxy group as our chiral substituent, as this was the most intriguing for us. We expected a chelation of unprotected hydroxy group with a putative imine to enhance the selectivity[7] and a creation of diversity by a post-Ugi modification of the hydroxy group.

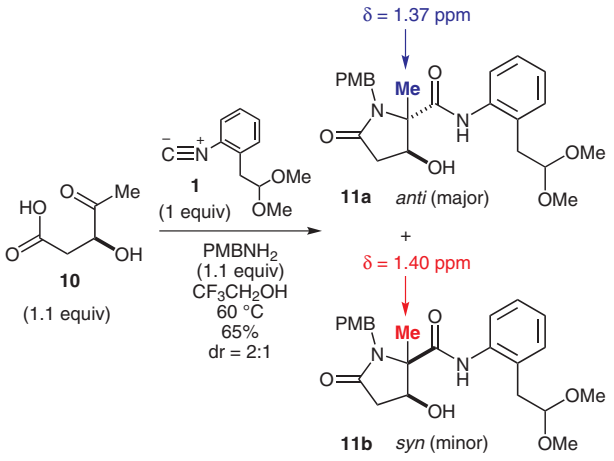
We synthesized racemic 3-hydroxy-4-oxopentanoic acid (**10**), as shown in Scheme 2, to determine first its feasibility in the Ugi reaction with an α-hydroxyketone, and second the resulting diastereoselectivity. The literature revealed a single report of the synthesis of **10**[8] but, unfortunately, the sequence was inefficient and low yielding. Our own strategy for the synthesis of 3-hydroxy-4-oxopentanoic acid (**10**) began with aldol reaction of the lithium enolate of benzyl acetate (**6**) and α-methylcinnamaldehyde (**7**), which afforded aldol product **8** in 96% yield (Scheme 1). Use of the enal allows for immediate installation of the carbonyl group at the γ-position. Ozonolysis of **8** conveniently provided β-hydroxy-γ-ketoester **9** in 84% yield. Lastly, carboxylic acid **10** was formed in quantitative yield via hydrogenolysis of **9**. Hydrogenolysis of the benzyl ester generated the carboxylic acid without elimination of the hydroxy group. This strategy could be a general procedure established to obtain a series of chiral β-hydroxy-γ-keto acid (3-hydroxy-4-oxopentanoic acid) derivatives when stereoselective aldol reactions are applied with enals.



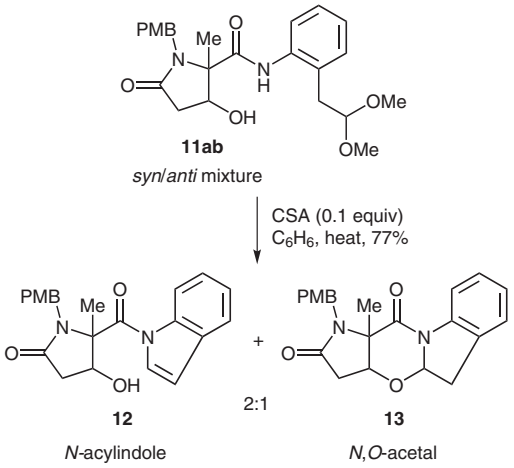
Scheme 2 Synthesis of racemic 3-hydroxy-4-oxopentanoic acid (**10**)

With the chiral substrate in hand, we set out to investigate the diastereoselectivity in the Ugi 4C-3C reaction. Our concerns were a potential side reaction from α-hydroxylimine to α-amino carbonyl compound, known as Amadori rearrangement,[9] and *N*-acylindole formation in the presence of the unprotected hydroxy group at the β-position, in addition to the stereoselective outcome of the reaction.

Ugi reaction of 3-hydroxy-4-oxopentanoic acid (**10**) with isocyanide **1** and *p*-methoxybenzylamine in trifluoroethanol provided an inseparable 2:1 diastereomeric mixture of anilides **11a** and **11b** in 65% yield (Scheme 3).[10] The chemical shifts of the methyl group of **11** were at δ = 1.37 ppm for the major isomer and at δ = 1.40 ppm for the minor. Fortunately, a side product resulting from an Amadori rearrangement was not observed with this substrate. The relative stereochemistry of the minor diastereomer was assigned as *syn* as shown in Scheme 3. That assignment was established by comparison of the ^1H NMR



Scheme 3 Ugi 4C-3C reaction of 3-hydroxy-4-oxopentanoic acid (**10**) with convertible isocyanide **1**

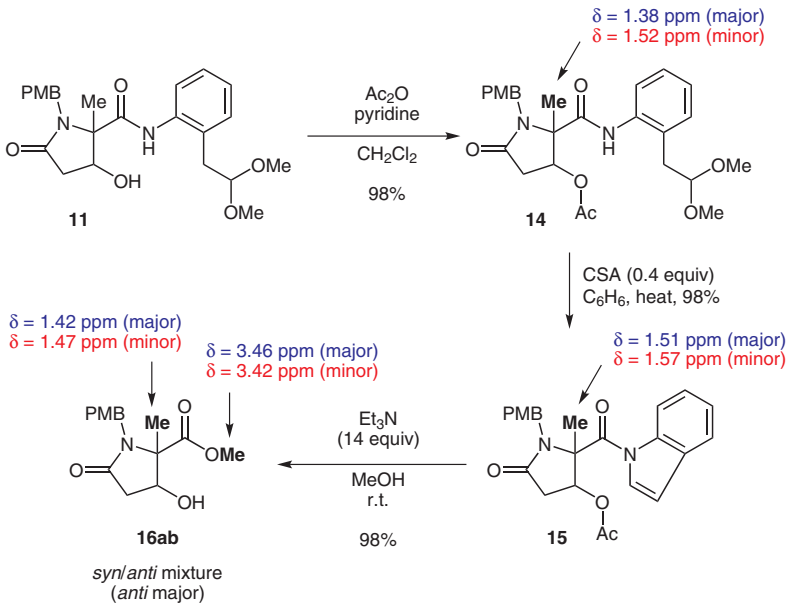


Scheme 4 Attempted *N*-acylindole formation from **11ab**

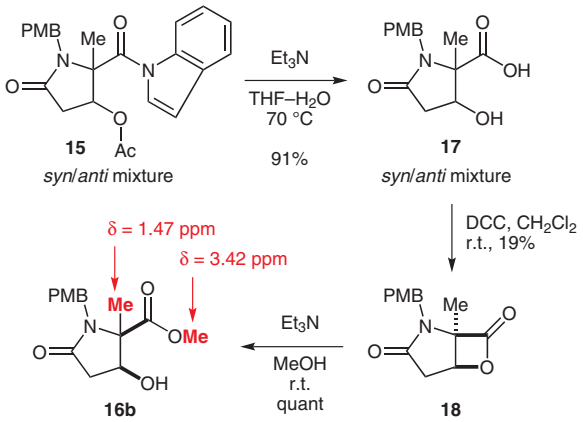
chemical shifts after conversion of the Ugi product mixture to the corresponding methyl esters. The selective formation of *syn* methyl ester was achieved via methanolysis of the β-lactone (vide infra).

For the assignment of the relative stereochemistry, methanolysis of the Ugi product anilide **11** via *N*-acylindole formation was attempted (Scheme 4). Unfortunately, exclusive formation of *N*-acylindole **12** was not successful like the sequence with levulinic acid. When anilide **11** was subjected to acidic conditions, *N*,*O*-acetal **13** was obtained as a 1:1 mixture of two diastereomers (unknown stereochemistry),[11] in addition to two diastereomers (dr = 5:1) of *N*-acylindole **12** (**12**/**13** = 2:1). The acetal was stable and could not be converted to *N*-acylindole **12** under any conditions we attempted. As we foresaw, during the *N*-acylindole formation the hydroxy group intercepted the putative *N*-acyliminium ion to form the acetal before the isomerization to indole. However, such a side reaction could be avoided by protection of the hydroxy group.

The secondary alcohol of the diastereomeric mixture of anilide **11** was acetylated to afford **14** (dr = 2:1) before the formation of the *N*-acylindole (Scheme 5). Protection of the alcohol prevents side product formation of *N*,*O*-acetal during the *N*-acylindole formation step as described below. Treatment of the acetate **14** with CSA in benzene at reflux afforded *N*-acylindole **15** (dr = 2:1) in excellent yield. Concomitant methanolysis of the *N*-acylindole and the acetate was achieved successfully to afford ester **16ab** (dr = 2:1) by treatment with excess Et_3N in MeOH at room temperature. The diastereomeric mixture of anilide **11** was converted to the corresponding methyl ester **16ab** in 94% overall yield in three steps, and the ^{1}H NMR chemical shifts of the *syn*/*anti* mixture of methyl ester **16ab** were measured (see below). The major isomer showed two singlet peaks at δ = 1.42 and 3.46 ppm, while the minor at δ = 1.47 and 3.42 ppm.



Scheme 5 Hydrolysis of anilide **11** via *N*-acylindole **15** and diagnostic chemical shifts of ^{1}H NMR spectra



Scheme 6 Selective formation of *syn* methyl ester **16b** via methanolysis of β-lactone **18**

The ^{1}H NMR spectrum of the pure *syn* methyl ester derived from Ugi product **11** was obtained as follows (Scheme 6). Because the separation of the *syn* and *anti* isomers was difficult at any stage, we decided to use to our advantage a unique structural property of fused γ-lactam-β-lactone heterobicyclic ring systems. The *syn*/*anti* mixture of the *N*-acylindole **15** was hydrolyzed and the resulting carboxylic acid **17** was converted into γ-lactam-β-lactone bicycle **18**. At this point, only the *syn* isomer could form the β-lactone, while the *anti* isomer formed oligomers by intermolecular esterification.[12] Methanolysis of the β-lactone exclusively gave *syn* methyl ester **16b**. The ^{1}H NMR spectrum of *syn* methyl ester **16b** showed two singlet peaks at δ = 1.47 and 3.42 ppm. It was compared to a spectrum containing the 2:1 mixture of methyl ester diastereomers **16ab**, obtained from methanolysis of the *N*-acylindole derived from mixture of Ugi products **11**. We determined by comparison of ^{1}H NMR chemical shifts that the minor isomer of **11** is the *syn* diastereomer.[13]

In conclusion, we have shown the synthetic utility of an *N*-acylindole derivative of a pyroglutamic acid as a coupling agent to afford the corresponding carboxylic acid, ester, thioester, amide and aldehyde. We also disclosed the stereoselective outcome of the Ugi reaction of 3-hydroxy-4-oxopentanoic acid. The relative stereochemistry of the Ugi product was established via chemoselective transformation of the *syn* isomer to a β-lactone. In the following Letter, to further explore the utility of the Ugi reaction in the synthesis of functionalized pyroglutamic acids, we describe a general method for the synthesis of a series of levulinic acid derivatives and their use in the stereoselective Ugi 4C-3C reaction.[14]

Acknowledgment

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References and Notes

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(5) Ammonium acetate or HMDS could be used to prepare unprotected γ-lactams: (a) Isaacson, J.; Loo, M.; Kobayashi, Y. *Org. Lett.* **2008**, *10*, 1461. (b) Isaacson, J.; Gilley, C. B.; Kobayshi, Y. *J. Org. Chem.* **2007**, *72*, 3913.

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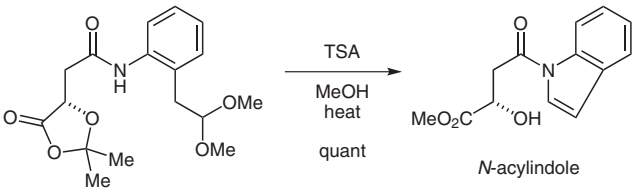
(10) Solvent effects in the stereoselective Ugi 4C-3C reaction of 4-oxopentanoic acid(**10**), $PMBNH_2$, and isocyanide **1** was examined in H_2O, MeOH, *i*-PrOH, CH_2Cl_2, MeCN, THF, EtOAc and dioxane. No Ugi product **11** was observed by the reaction in those solvents; instead, *N*-(4-methoxybenzyl)-acetamide was isolated as a product (28–52%). The reaction in hexafluoroisopropanol, $(CF_3)_2CHOH$, furnished the desired Ugi products **11a** and **11b** in 70% yield as 1.2:1 diastereomixture.

(11) The formation of the *N*,*O*-acetal **13** was enhanced and the stability was increased by the γ-lactam. For example, the linear anilide was converted into *N*-acylindole without formation of *N*,*O*-acetal as shown in Scheme 7.



Scheme 7

(12) The formation of 3-mer, 4-mer and 5-mer of the *anti* isomer shown in Figure 1 were detected by mass spectrometry.

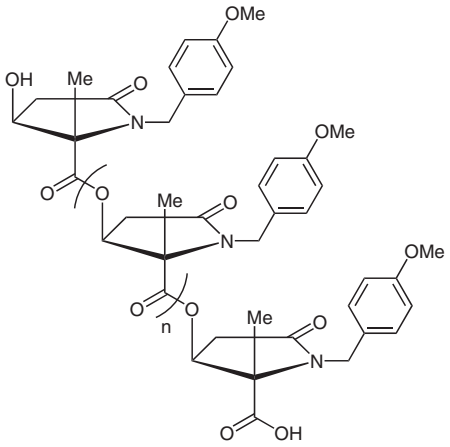


Figure 1

(13) ^{1}H NMR data of the selected compounds are shown below. Compound **5b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21–7.38 (m, 5 H), 7.17 (d, *J* = 8.7 Hz, 2 H), 6.77 (d, *J* = 9.0 Hz, 2 H), 4.97 (d, *J* = 12.3 Hz, 1 H), 4.73 (d, *J* = 12.3 Hz, 1 H), 4.46 (d, *J* = 15.3 Hz, 1 H), 4.31 (d, *J* = 15.6 Hz, 1 H), 3.75 (s, 3 H), 2.36–2.61 (m, 2 H), 2.23–2.31 (m, 1 H), 1.80–1.91 (m, 1 H), 1.43 (s, 3 H). Compound **5c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 8.4 Hz, 2 H), 6.81 (d, *J* = 8.4 Hz, 2 H), 4.96 (d, *J* = 15.3 Hz, 1 H), 3.86 (d, *J* = 15.6 Hz, 1 H), 3.77 (s, 3 H), 2.85 (t, *J* = 6.6 Hz, 2 H), 2.41–2.65 (m, 2 H), 2.21–2.29 (m, 1 H), 1.83–1.94 (m, 1 H), 1.53 (p, *J* = 7.8 Hz, 2 H), 1.39 (p, *J* = 7.2 Hz, 2 H), 1.36 (s, 3 H), 0.92 (t, *J* = 7.5 Hz, 3 H). Compound **5d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.18 (d, *J* = 8.7 Hz, 2 H), 6.99 (d, *J* = 8.4 Hz, 2 H), 6.74–6.86 (m, 4 H), 6.05 (br s, 1 H), 4.36 (q, *J* = 13.8 Hz, 2 H), 4.26 (dd, *J* = 6.3, 14.4 Hz 1 H), 3.91 (dd, *J* = 5.1, 14.4 Hz, 1 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 2.26–2.45 (m, 3 H), 1.84–2.04 (m, 1 H), 1.44 (s, 3 H). Compound **5e**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.04 (s, 1 H), 7.14 (d, *J* = 8.4 Hz, 2 H), 6.78 (d, *J* = 8.7 Hz, 2 H), 4.60 (d, *J* = 15.0 Hz, 1 H), 4.13 (d, *J* = 14.7 Hz, 1 H), 3.74 (s, 3 H), 2.47 (t, *J* = 7.5 Hz, 2 H), 2.07–2.16 (m, 1 H), 1.77 (td, *J* = 8.7, 13.8 Hz, 1 H), 1.31 (s, 3 H). Compound **8**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.21 (m, 10 H), 6.59 (s, 1 H), 5.18 (s, 2 H), 4.64 (t, *J* = 6.4 Hz, 1 H), 2.94 (br s, 1 H), 2.73 (d, *J* = 2.0 Hz, 1 H), 2.71 (s, 1 H), 1.88 (s, 3 H). Compound **9**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.39 (m, 5 H), 5.17 (d, *J* = 12.4 Hz, 1 H), 5.13 (d, *J* = 12.4 Hz, 1 H), 4.39 (q, *J* = 4.8, 10.8 Hz, 1 H), 3.77 (d, *J* = 5.2 Hz, 1 H), 2.93 (dd, *J* = 4.4, 16.8 Hz, 1 H), 2.79 (dd, *J* = 6.0, 16.4 Hz, 1 H), 2.26 (s, 3 H). Compound **10**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.61 (br s, 1 H), 4.39 (dd, *J* = 4.0, 6.4 Hz, 1 H), 2.93 (dd, *J* = 4.4, 16.8 Hz, 1 H), 2.79 (dd, *J* = 6.4, 16.8 Hz, 1 H), 2.27 (s, 3 H). Compound **11a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.96 (br s, 1 H), 7.57 (d, *J* = 7.6 Hz, 1 H), 7.10–7.24 (m, 5 H), 6.78 (d, *J* = 8.4 Hz, 2 H), 4.94 (d, *J* = 15.2 Hz, 1 H), 4.41–4.46 (m, 2 H), 4.10–4.18 (m, 1 H), 3.74 (s, 3 H), 3.38 (s, 3 H), 3.36 (s, 3 H), 2.74–2.94 (m, 3 H), 2.45 (dd, *J* = 2.8, 17.2 Hz, 1 H), 1.37 (s, 3 H). Compound **18**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.8 Hz, 2 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 4.78 (t, *J* = 4.0 Hz, 1 H), 4.72 (d, *J* = 14.8 Hz, 1 H), 4.38 (d, *J* = 15.2 Hz, 1 H), 3.78 (s, 3 H), 2.88 (d, *J* = 3.6 Hz, 2 H), 1.50 (s, 3 H).

(14) See the following paper: Gilley, C. B.; Buller, M. J.; Kobayashi, Y. *Synlett* **2008**, 2249.