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Direct Imine Acylation for Molecular Diversity in Heterocyclic Synthesis

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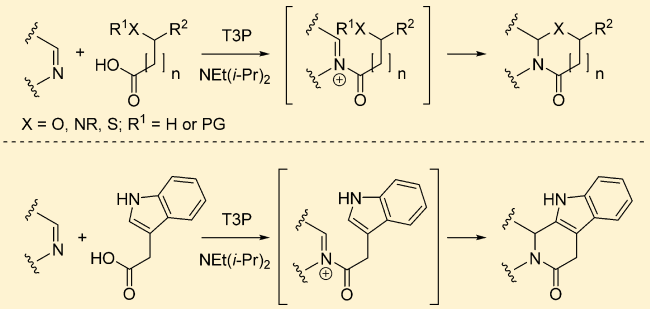
Supporting Information

ABSTRACT: Imines and carboxylic acids have been directly coupled using propylphosphonic acid anhydride and NEt(i-Pr)$_2$ to give N-acyliminium ions, which were intramolecularly trapped with oxygen, nitrogen, sulfur, and carbon nucleophiles to provide a wide range of structurally diverse heterocycles.



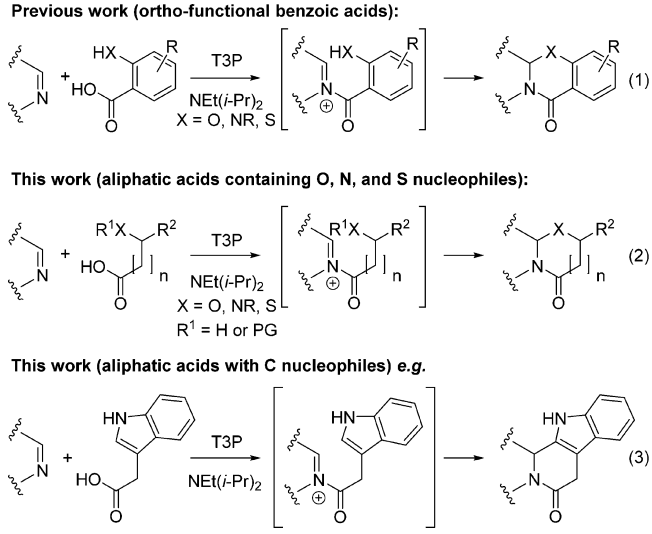
INTRODUCTION

Heterocycles are important structures in the pharmaceutical, agrochemical, and fine chemical industries.[1,2] Much recent attention has focused on diversity-oriented synthesis[3−5] to expand the variety of structures, including heterocycles, populating unexplored "chemical space" to aid the discovery of novel lead compounds.[6]

The chemistry of N-acyliminium ions is well established,[7−9] and the formation of N-acyliminium ions by the direct acylation of imines with acid halides[10−21] and anhydrides[22−24] has some precedent. However, apart from a single example,[25] previous to our recent disclosures,[26,27] the direct acylation of imines with carboxylic acids was not known. We reported[26] that imines can be coupled, using propylphosphonic acid anhydride (T3P) and NEt(i-Pr)$_2$,[28] to benzoic acids in a direct imine acylation (DIA) reaction to generate N-acyliminium ions, which were then trapped intramolecularly with a range of nucleophilic ortho substituents on the benzoic acids (Scheme 1, eq 1). This provided a range of polycyclic heterocycles, and the methodology was applied to the synthesis of the natural product evodiamine. However, this methodology was limited to benzoic acids containing nucleophilic heteroatoms in the ortho position. To date, only a single example of DIA using an aliphatic carboxylic acid has been reported.[27] We considered that the direct coupling of imines and aliphatic carboxylic acids containing nucleophiles, or pronucleophiles, would allow access to a far greater variety of heterocyclic structures using this simple coupling procedure.

Herein we report results which establish that DIA methodology has an extremely wide scope and is applicable to aliphatic carboxylic acids containing oxygen, nitrogen, and sulfur nucleophiles (Scheme 1, eq 2). Of particular note is the use of aliphatic acids containing carbon pronucleophiles such as active methylenes, aromatic groups, and alkenes, enabling structural diversity to be generated via carbon−carbon bond formation (Scheme 1, eq 3).

Scheme 1. Direct Imine Acylation (DIA)



RESULTS AND DISCUSSION

To establish the validity of the DIA protocol with aliphatic acids, we investigated the reaction of imine **1a** with hydroxy acid **2a** and its TBDMS-protected analogue **2b** (Scheme 2). The reaction of hydroxy acid **2a** led to the formation of the desired heterocycle **3a**, but in low yield. This appeared to be due to competing O-acylation of the hydroxy acid; note that this was not a problem in our previous work, when ortho-

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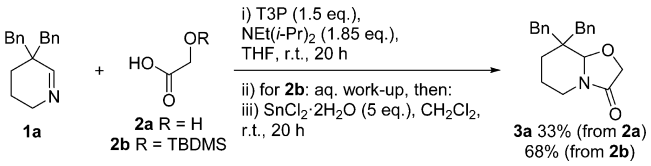
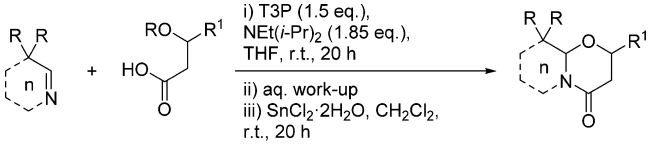
Scheme 2. DIA with Aliphatic Carboxylic Acids



substituted benzoic acids were used due to their reduced nucleophilicity. To avoid *O*-acylation, the silyl-protected acid **2b** was coupled with **1a** and following aqueous workup a mixture of products was obtained, presumably arising from the reaction of the *N*-acyliminium ion with water in the workup. The unpurified product mixture was then treated with $SnCl_2 \cdot 2H_2O$[29,30] in CH_2Cl_2 at room temperature, which resulted in concomitant silyl cleavage and cyclization, affording product **3a** in 68% yield, a significant improvement over the unprotected variant.

The scope of this improved protocol was then explored (Table 1). The coupling of imine **1a** with TBDMS-protected 3-hydroxypropanoic acid **2c** and methyl-substituted acid **2d** provided the required heterocycles in good yield (Table 1, entries 1 and 2). We also investigated the range of imines tolerated in the DIA reaction (Table 1). The majority of the imines tested as DIA substrates are stable, nonenolizable imines; however, unsubstituted imine **1b** (which exists largely as a trimer[31]) was a suitable substrate (entry 3), showing that imines which are prone to oligomerization are compatible. The five-membered-ring imine **1c** and tetrahydroisoquinoline derivative **1d** both reacted successfully, giving products **3e,f** (entries 4 and 5). Precedent for *N*-acyliminium chemistry using acyclic precursors is extremely sparse due to their propensity to hydrolyze.[11] However, the use of DIA conditions allowed the acyclic imine **1e** to be effectively employed (entry 6); in this case, the use of anhydrous triflic acid, rather than $SnCl_2 \cdot 2H_2O$, reduced unwanted hydrolysis, promoting a one-pot deprotection and cyclization. In this example, chloroform, rather than CH_2Cl_2, was used to effect cyclization because it has a higher reflux temperature and the analogous process in CH_2Cl_2 (either at room temperature or 45 °C) was low yielding. The *N*-acylation was also performed in chloroform, to avoid having to perform a solvent switch. It is noteworthy that the T3P coupling can be performed in a number of solvents with little impact on the efficiency of the process; high-yielding DIA reactions performed in toluene, CH_2Cl_2, chloroform, and THF have all been reported, previously[26,27] and herein. This flexibility in terms of the solvent for the *N*-acylation is important in examples in which additional reagents are required to effect cyclization (e.g. Table 4), as the solvent that is most compatible with the requisite additives can be used. Either CH_2Cl_2 or chloroform was used in the majority of subsequent examples for reasons of convenience, as they could be used as obtained commercially with no additional drying. The stereochemical assignments of the major diastereoisomers shown are based on NMR analysis, on literature precedent, and by analogy to our previous work.[27,29,32,33] This direct imine acylation with aliphatic carboxylic acids gives rise to a range of previously unreported structures, the core of which is present in compounds which have recently found use as herbicides.[34]

Table 1. DIA and Intramolecular Cyclization with Oxygen Nucleophiles[b]



Entry	Imine	Acid	Product	Yield (%)
1	1a	2c	3b	86
2	1a	2d	3c (d.r. = 2:1)	82
3	1b	2d	3d (d.r. = 8:1)	60
4	1c	2d	3e (d.r. = 6:1)	62
5	1d	2d	3f (d.r. = 20:1)	73[a]
6	1e	2d	3g (d.r. = 12:1)	65[b]

[a]No intermediate workup carried out. [b]The following reaction conditions were used in this reaction: (i) T3P, $NEt(i\text{-}Pr)_2$, $CHCl_3$, 70 °C, 1 h; (ii) TfOH, room temperature, 1 h (one pot).

The analogous DIA process using amine-containing coupling partners was investigated next (Table 2). Three imines were reacted with commercially available *N*-Boc or *N*-Cbz-protected amino acids. As with the oxygen variant, following the T3P coupling, an aqueous workup was carried out. This was followed by cleavage of the *N*-protecting group (using TFA in CH_2Cl_2 for Boc cleavage or $H_2/Pd(OH)_2$ in MeOH for Cbz cleavage), resulting in cyclization and formation of the expected nitrogen-containing heterocycles in excellent yields. Both α- and β-amino acids were suitable substrates (entries 1 and 2), and substitution on the amino acid was fully compatible (entry 3). It was found that secondary amines were effective nucleophiles, as evidenced by the use of *N*-Boc-(*S*)-proline (entry 4). Other imines were compatible with the procedure, including β-carboline **1f** (entry 5). Note that, in all of these examples, the *N*-acylation was performed at reflux, rather than at room temperature. This is not because the *N*-acylation is slower in this system but because the higher temperature also promotes partial cyclization before protecting group cleavage. It was found that this higher temperature led to higher overall yields for the two-step sequence in comparison to the case where the coupling was carried out at room temperature. The assigned syn stereochemistry of the major diastereoisomers of **5c,d** is based on analogy with the work of Liebscher[35] and, for **5d**, a NOESY correlation.

The sulfur variant of this DIA sequence is extremely efficient, affording *S*-containing heterocycles in high yields in a one-pot procedure with no protecting group required on the thiol (Table 3). The reactions proceeded at room temperature and

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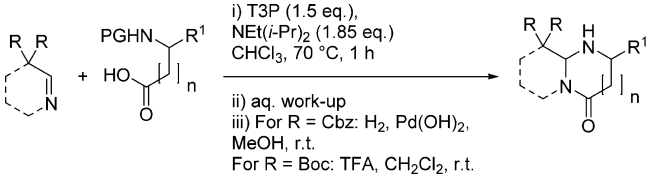
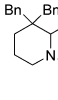
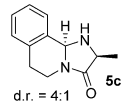
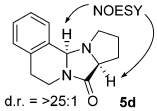
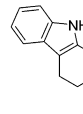
Table 2. DIA and Intramolecular Cyclization with Nitrogen Nucleophiles

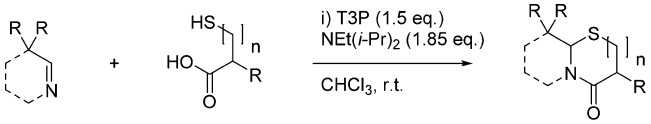


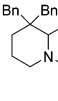
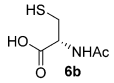
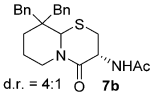
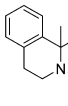
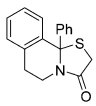
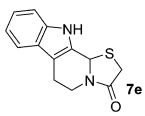
Entry	Imine	Acid	Product	Yield (%)
1	 **1a**	 **4a**	 **5a**	86
2	 **1a**	 **4b**	 **5b**	76
3	 **1d**	 **4c**	 d.r. = 4:1 **5c**	90
4	 **1d**	 **4d**	 d.r. = >25:1 **5d**	75
5	 **1f**	 **4a**	 **5e**	85

are both reliable and high-yielding in comparison with known syntheses of related heterocyclic systems.[36] Variation in the sulfur-containing carboxylic acid is tolerated, as 3-mercaptopropionic acid **6a**, *N*-acetyl-L-cysteine **6b**, and thioglycolic acid **6c** (entries 1−4) were suitable substrates. The reactions of ketone-derived imines **1g,h** (entries 3 and 4) are particularly noteworthy, as these imines do not undergo DIA in any of the other reaction systems tested (i.e. carboxylic acids bearing *O*-, *N*-, or *C*-nucleophiles). This suggests that an alternative mechanism, which was proposed in our previous communication,[26] is likely to operate, whereby the nucleophilic thiol attacks the imine before *N*-acylation in these examples. 3,4-Dihydro-*β*-carboline **1f** (entry 5) was also a suitable imine substrate, as was the acyclic imine *N*-benzylidenemethylamine **1e**, which gave the adduct **7f** in 93% yield (entry 6). The thiazolidinone scaffold is important in medicinal chemistry and present in numerous biologically active compounds,[37] and this DIA methodology allows ready access to structurally diverse thiazolidinone-containing substructures.

The value of this methodology is further enhanced by the ability to form C−C bonds by trapping the *N*-acyliminium ion with various carbon-centered nucleophiles (Table 4). In these reactions a one-pot process was achieved by using a Lewis acid to effect cyclization after the coupling (Table 4). Carboxylic acids tethered to a diester or diketone (entries 1 and 2) were used to generate an *N*-acyliminium ion, which cyclized upon the addition of $AlCl_3$. Keen to extend the scope of carbon nucleophiles, we investigated electron-rich aromatic systems, including 3,4-dimethoxyphenyl, indole, pyrrole, and dimethoxynaphthyl systems (entries 3−6). These substrates also

Table 3. DIA and Intramolecular Cyclization with Sulfur Nucleophiles



Entry	Imine	Acid	Product	Yield (%)
1	 **1a**	 **6a**	 **7a**	90
2	 **1a**	 **6b**	 d.r. = 4:1 **7b**	89
3	 **1g**	 **6a**	 **7c**	89
4	 **1h**	 **6c**	 **7d**	93
5	 **1f**	 **6c**	 **7e**	97
6	 **1e**	 **6c**	 **7f**	93

provided the expected products in good to excellent yields, with $BF_3{\cdot}OEt_2$ used to effect cyclization.

Finally, we explored the possibility that carboxylic acids containing olefins could be successfully utilized and were pleased to find that an alkene (entry 7) and an allylsilane (entry 8) were compatible, using either TFA or $BF_3{\cdot}OEt_2$ as the activating agent. The core substructures of **9a−c** are prevalent in a number of natural products,[38−40] and the heterocyclic core of **9e** is present in aldose reductase inhibitors.[41] Thus, DIA of imines with aliphatic carboxylic acids, and subsequent cyclization, can be considered to be of high importance in the synthesis of medicinally important frameworks.

In conclusion, we have demonstrated that a range of imines can be directly coupled with carboxylic acids using T3P and NEt(*i*-Pr)$_2$ to give *N*-acyliminium ions which can be intramolecularly trapped with oxygen, nitrogen, sulfur, and carbon nucleophiles. These reactions enable a range of diverse heterocyclic structures to be generated. Investigations into asymmetric variants are ongoing, as are applications in target synthesis.

EXPERIMENTAL SECTION

Preparation of Substrates for the DIA Reactions. The following substrates were commercially available and used as supplied: *N*-benzylidenemethylamine **1e**, the amino acids **4a−d**, the thioacids **6a−c**, (3,4-dimethoxyphenyl)acetic acid **8c**, 3-indoleacetic acid **8d**, and 4,7-dimethoxy-1-naphthoic acid **8f**. The following substrates were prepared according to literature procedures: imines **1a−d**,[26] Me-isoquinoline imine **1g**,[42] Ph-isoquinoline imine **1h**,[43] TBDMS-

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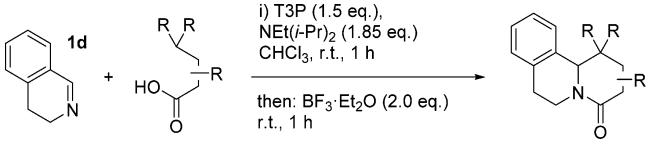
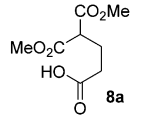
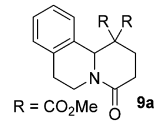
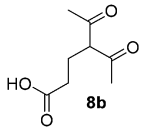
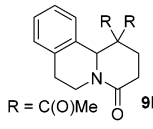
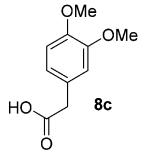
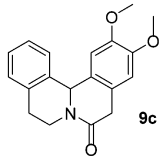
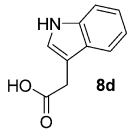
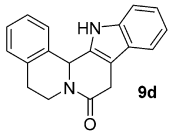
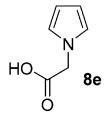
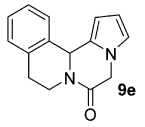
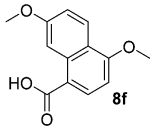
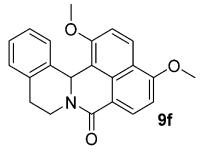
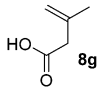
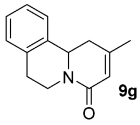
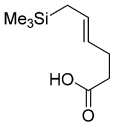
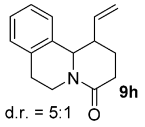
Table 4. DIA and Intramolecular Cyclization with Carbon Nucleophiles



Entry	Acid	Product	Yield (%)
1	 8a	 R = CO_2Me 9a	76[a]
2	 8b	 R = C(O)Me 9b	65[a]
3	 8c	 9c	90
4	 8d	 9d	80
5	 8e	 9e	77
6	 8f	 9f	89[b]
7	 8g	 9g	78[c]
8	 8h	 d.r. = 5:1 9h	70

[a]$AlCl_3$ (2.0 equiv) used instead of $BF_3{\cdot}OEt_2$ and reaction run at 70 °C. [b]Toluene used in place of $CHCl_3$, coupling time 20 min and cyclization time 20 h. [c]CH_2Cl_2 used in place of $CHCl_3$, TFA used in place of $BF_3{\cdot}OEt_2$, and reaction run at 45 °C.

protected 3-hydroxypropanoic acid **2b**,[44] TBDMS-protected 4-hydroxybutanoic acid **2c**, TBDMS-protected 3-hydroxybutanoic acid **2d**,[45] 2-(methoxycarbonyl)pentanedioic acid 1-methyl ester **8a**,[46] and 3-methyl-3-butenonic acid **8g**.[47]

4-Acetyl-5-oxohexanoic Acid (8b). The title compound was prepared by modified literature procedures. According to the procedure of Shrout and Lightner,[48] ethyl acrylate (2.00 g, 2.16 mL, 20.0 mmol), 2,4-pentanedione (8.00 g, 8.22 mL, 79.9 mmol), and K_2CO_3 (1.38 g, 9.99 mmol) were stirred together at 37 °C for 20 h. The mixture was filtered through a sintered-glass funnel, and the solids were washed with CH_2Cl_2 (2 × 10 mL). The filtrate was concentrated in vacuo until excess 2,4-pentanedione was removed (judged by TLC). This provided ethyl 4-acetyl-5-oxohexanoate (3.18 g, 79%) as a pale yellow liquid: R_f 0.80 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 2984, 2940, 1727, 1699, 1608, 1421, 1359, 1249, 1182, 1152, 1027; δ_H (400 MHz, $CDCl_3$) data for keto form 3.74 (1H, t, J = 6.9), 4.14 (2H, q, J = 7.0), 2.33−2.27 (2H, m), 2.21 (6H, s), 2.19−2.12 (2H, m), 1.26 (3H, t, J = 7.0), data for enol form 16.78 (1H, s), 4.15 (2H, q, J = 7.2), 2.63−2.57 (2H, m), 2.42−2.36 (2H, m), 2.17 (6H, s), 1.27 (3H, t, J = 7.2); HRMS (ESI) m/z calcd 201.1121 for $C_{10}H_{17}O_4$ (MH^+), found 201.1113. Ethyl 4-acetyl-5-oxohexanoate (500 mg, 2.50 mmol) was dissolved in THF/H_2O (1/1, 10 mL) and stirred at room temperature. Concentrated H_2SO_4 (1.25 mL) was added and the reaction mixture stirred at room temperature for 14 h. The reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated to give the crude material. Purification by column chromatography (1/1 petroleum ether/ethyl acetate) gave 4-acetyl-5-oxohexanoic acid (**8b**; 224 mg, 52%) as a clear, colorless oil: R_f 0.25 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) data for keto form 3.76 (1H, t, J = 7.0), 2.41−2.35 (2H, m), 2.22 (6H, s), 2.19−2.12 (2H, m), data for enol form 16.78 (1H, s), 2.66−2.59 (2H, m), 2.50−2.43 (2H, m), 2.18 (6H, s); HRMS (ESI) m/z calcd 173.0808 for $C_8H_{13}O_4$ (MH^+), found 173.0812.

1*H*-Pyrrol-1-ylacetic Acid (8e). The title compound was prepared using a modified procedure of Mitchell and co-workers;[49] glycine ethyl ester hydrochloride (2.50 g, 17.9 mmol) and sodium acetate (2.45 g, 29.9 mmol) were placed in a round-bottomed flask. Water (12.5 mL) and acetic acid (25 mL) were then added, followed by 2,5-dimethoxytetrahydrofuran (2.37 g, 2.32 mmol, 17.9 mmol). The resulting mixture was stirred at 100 °C for 4 h and then cooled. The reaction mixture was poured into water (50 mL) and washed with EtOAc (30 mL). The aqueous phase was neutralized with solid Na_2CO_3 and extracted with EtOAc (2 × 30 mL). The combined organic phases were washed with water (50 mL) before being dried ($MgSO_4$), filtered, and concentrated to give a crude material which was purified by column chromatography (4/1 petroleum ether/ethyl acetate) to give ethyl 1*H*-pyrrol-1-ylacetate (1.79 g, 65%) as a brown oil: R_f 0.56 (4/1 petroleum ether/ethyl acetate); ν_{max} (thin film)/cm^{-1} 2985, 2939, 1748, 1500, 1297, 1188, 1091, 1025, 722; δ_H (400 MHz, $CDCl_3$) 6.68 (2H, t, J = 2.1), 6.22 (2H, t, J = 2.1), 4.64 (2H, s), 4.24 (2H, q, J = 7.1), 1.3 (3H, t, J = 7.1); δ_C (100 MHz, $CDCl_3$) 168.7 (C═O), 121.7 (2 × CH), 109.0 (2 × CH), 61.5 (CH_2), 51.8 (CH_2), 14.1 (CH_3); MS (ESI) m/z 154.09 (MH^+) and 176.07 (MNa^+). Ethyl 1*H*-pyrrol-1-ylacetate (1.0 g, 6.528 mmol) was dissolved in THF/H_2O (20 mL) and cooled to 0 °C. NaOH (1.31 g, 32.6 mmol) was added and the reaction mixture stirred at 0 °C for 30 min before being washed with CH_2Cl_2 (20 mL). The aqueous phase was acidified with concentrated HCl and extracted with CH_2Cl_2 (3 × 20 mL) before being dried ($MgSO_4$), filtered, and concentrated to give 1*H*-pyrrol-1-ylacetic acid (**8e**; 775 mg, 95%), as brown solids: R_f 0.26 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 3074 (br), 2968, 2935, 1726, 1505, 1390, 1297, 1092, 727; δ_H (400 MHz, $CDCl_3$) 9.31 (1H, br s), 6.67 (2H, t, J = 2.1), 6.24 (2H, t, J = 2.1), 4.71 (3H, s); δ_C (100 MHz, $CDCl_3$) 174.9 (C═O), 121.8 (2 × CH), 109.3 (2 × CH), 50.3 (CH_2); MS (ESI) m/z 126.06 (MH^+) and 148.04 (MNa^+).

(*E*)-/(*Z*)-6-(Trimethylsilyl)hex-4-enoic Acid (8h). The title compound was prepared using a modified procedure of Wardrop;[50] 4-pentenoic acid (500 mg, 510 μL, 4.99 mmol) and allyltrimethylsilane (1.71 g, 2.38 mL, 1.50 mmol) were dissolved in CH_2Cl_2 (10 mL). Hoveyda-Grubbs II catalyst (78.2 mg, 0.125 mmol) was added and the resulting solution stirred at reflux for 5 h. The reaction mixture was filtered through Celite and the filtrate concentrated to provide the crude product. Purification by column chromatography (4/1

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petroleum ether/Et_2O) gave the acid **8h** (461 mg, 50%) as a clear, colorless oil, as an approximately 2.8:1 mixture of isomers: R_f 0.2 (4/1 petroleum ether/Et_2O); ν_{max} (thin film)/cm^{-1} 2954, 1709, 1412, 1247, 1153, 966, 837; δ_H (400 MHz, $CDCl_3$) data for major isomer 5.53−5.43 (1H, m), 5.30−5.20 (1H, m), 2.44−2.37 (2H, m), 2.37−2.27 (2H, m), 1.41 (2H, dd, J = 7.9 0.9), −0.02 (9H, s), data for minor isomer 5.53−5.43 (1H, m), 5.30−5.20 (1H, m), 2.44−2.37 (2H, m), 2.37−2.27 (2H, m), 1.50 (2H, dd, J = 8.8, 1.2), 0.01 (9H, s); δ_C (100 MHz, $CDCl_3$) data for major isomer 179.9 (C═O), 128.1 (CH), 125.9 (CH), 34.6 (CH_2), 27.9 (CH_2), 22.7 (CH_2), −2.1 (3 × CH_3), data for minor isomer 179.9 (C═O), 127.4 (CH), 124.6 (CH), 34.2 (CH_2), 22.3 (CH_2), 18.5 (CH_2), −1.8 (3 × CH_3); HRMS (ESI) m/z calcd 209.0968 for $C_9H_{18}NaO_2Si$ (MNa^+), found 209.0962.

General Procedures for the DIA Reactions. *General DIA Procedure A (Table 1).* To a solution of imine (1 mmol) and TBDMS-protected carboxylic acid (1.2 mmol) in THF (10 mL) were added sequentially NEt(*i*-Pr)$_2$ (1.85 mmol) and then T3P (1.5 mmol, 50% solution in THF). The resulting solution was stirred at room temperature for 20 h, before it was poured into saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 30 mL), washed with water (30 mL), and concentrated in vacuo. The crude residue was then dissolved in CH_2Cl_2 (10 mL), $SnCl_2 \cdot 2H_2O$ (5 mmol) was added, and the mixture was stirred at room temperature for 20 h. The reaction was quenched by the addition of excess solid K_2CO_3, and the mixture was then stirred for 5 min, filtered, and concentrated in vacuo. Purification by column chromatography (see individual entries for the solvents used for chromatography) afforded the *N*,*O*-acetal product.

General DIA Procedure B (Table 2, Entries 1, 3, and 5). To a solution of imine (1 mmol) and Cbz-protected amino acid (1.2 mmol) in $CHCl_3$ (10 mL) were added sequentially NEt(*i*-Pr)$_2$ (1.85 mmol) and then T3P (1.5 mmol, 50% solution in THF). The resulting solution was stirred at 70 °C for 1 h, before it was cooled to room temperature and poured into saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), washed with water (30 mL), concentrated in vacuo, and passed through a short silica column, with 1/1 petroleum ether/ethyl acetate as eluent. The crude residue was then dissolved in methanol (10 mL) in a round-bottomed flask that was purged with argon. Palladium hydroxide on carbon (70 mg/mmol of imine, 20 wt %, 50% water) was then added and the flask evacuated and back-filled with hydrogen several times. The mixture was stirred under a small positive pressure of hydrogen (balloon) for 1 h, before the hydrogen was evacuated and the reaction flask back-filled with argon. The reaction mixture was then filtered through Celite, rinsed with methanol, and concentrated in vacuo, which afforded the product without the need for further purification.

General DIA Procedure C (Table 2, Entries 2 and 4). To a solution of imine (1 mmol) and Boc-protected amino acid (1.2 mmol) in $CHCl_3$ (10 mL) were added sequentially NEt(*i*-Pr)$_2$ (1.85 mmol) and then T3P (1.5 mmol, 50% solution in THF). The resulting solution was stirred at 70 °C for 1 h, before it was cooled to room temperature and poured into saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), washed with water (30 mL), and concentrated in vacuo. The crude residue was then dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C, and TFA (5 mL) was added. The reaction mixture was warmed to room temperature and stirred for 15 min, before the solvent and TFA were removed in vacuo. The residue was dissolved in CH_2Cl_2 (50 mL), and the solution was washed with saturated aqueous $NaHCO_3$ (25 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by column chromatography (see individual entries for the solvents used for chromatography) afforded the product.

General DIA Procedure D (Table 3). To a solution of imine (1 mmol) and thiol-carboxylic acid (1.2 mmol) in $CHCl_3$ (10 mL) were added sequentially NEt(*i*-Pr)$_2$ (1.85 mmol) and then T3P (1.5 mmol, 50% solution in THF). The resulting solution was stirred at room temperature for 1 h, before it was poured into 10% aqueous K_2CO_3 (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the extract was washed with water (30 mL) and concentrated in vacuo. Purification by column chromatography (see individual entries for the solvents used for chromatography) afforded the product.

General DIA Procedure E (Table 4). Imine **1d** (100 mg, 0.762 mmol) and the appropriate carboxylic acid (0.915 mmol) were dissolved in $CHCl_3$ (4 mL) in a microwave vial and stirred at room temperature. NEt(*i*-Pr)$_2$ (182 mg, 246 μL, 1.410 mmol) and T3P (364 mg, 1.14 mmol, 728 mg of a 50% solution in THF) were added via syringe. The reaction mixture was stirred at room temperature, 45 °C, or 70 °C for 1 h. The appropriate acid or Lewis acid (1.525 mmol) was added and the reaction mixture stirred at room temperature, 45 °C, or 70 °C for a further 1 h. The reaction was quenched with saturated $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated to give the crude material, which was purified by column chromatography (see individual entries for the solvents used for chromatography).

8,8-Dibenzyltetrahydro-2*H*-oxazolo[3,2-*a*]pyridin-3(5*H*)-one (3a; Scheme 1). The compound was synthesized using general DIA procedure A from imine **1a** (24.9 mg, 0.0963 mmol) and acid **2b** (22.0 mg, 0.116 mmol). Purification by column chromatography (4/1 petroleum ether/ethyl acetate) afforded the title compound **3a** as a colorless oil (21.0 mg, 68%): R_f 0.60 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 1713, 1445, 1287, 1084, 703; δ_H (400 MHz, $CDCl_3$) 7.34−7.18 (8H, m), 7.08−7.04 (2H, m), 4.81 (1H, s), 4.37 (1H, d, J = 15.5) and 4.33 (1H, d, J = 15.5, AB system), 4.15−4.10 (1H, m), 2.96 (1H, d, J = 13.5), 2.92 (1H, d, J = 13.5), 2.72 (1H, d, J = 13.5), 2.60−2.51 (1H, m), 2.38 (1H, d, J = 13.5), 2.04−1.92 (1H, m), 1.60−1.53 (2H, m), 1.28−1.18 (2H, m); δ_C (100 MHz, $CDCl_3$) 168.2 (C), 137.1 (C), 136.4 (C), 131.1 (CH), 130.8 (CH), 128.2 (CH), 128.0 (CH), 126.4 (CH), 126.4 (CH), 91.7 (CH), 68.3 (CH_2), 41.9 (C), 41.3 (CH_2), 38.8 (CH_2), 34.0 (CH_2), 26.8 (CH_2), 19.6 (CH_2); HRMS (ESI^+): m/z calc. 344.1621 for $C_{21}H_{23}NNaO_2$ (MNa^+), found 344.1630.

9,9-Dibenzylhexahydropyrido[2,1-*b*][1,3]oxazin-4(6*H*)-one (3b; Table 1, Entry 1). The compound was synthesized using general DIA procedure A from imine **1a** (53.0 mg, 0.201 mmol) and acid **2c** (49.2 mg, 0.241 mmol). Purification by column chromatography (4/1 → 2/1 petroleum ether/ethyl acetate) afforded the title compound **3b** as a colorless oil (58.0 mg, 86%): R_f 0.65 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 2898, 1625, 1471, 1422, 1391, 1261, 1114, 1015, 720; δ_H (400 MHz, $CDCl_3$) 7.33−7.18 (8H, m), 7.10−7.06 (2H, m), 4.74−4.67 (1H, m), 4.33 (1H, s), 4.25 (1H, dd, J = 11.0, 6.4), 3.76−3.69 (1H, m), 3.08 (1H, d, J = 13.1), 3.00 (1H, d, J = 13.5), 2.86 (1H, d, J = 13.5), 2.77−2.68 (1H, m), 2.38−2.20 (3H, m), 2.05−1.89 (1H, m), 1.54−1.46 (2H, m), 1.35−1.25 (1H, m); δ_C (100 MHz, $CDCl_3$) 167.3 (C), 137.7 (C), 137.0 (C), 130.9 (CH), 130.9 (CH), 128.0 (CH), 127.9 (CH), 126.2 (CH), 126.2 (CH), 88.9 (CH), 62.3 (CH_2), 41.7 (CH_2), 41.4 (C), 40.1 (CH_2), 35.2 (CH_2), 33.1 (CH_2), 27.8 (CH_2), 20.2 (CH_2); HRMS (ESI^+) m/z calcd 336.1958 for $C_{22}H_{26}NO_2$ (MH^+), found 336.1953.

9,9-Dibenzyl-2-methylhexahydropyrido[2,1-*b*][1,3]oxazin-4(6*H*)-one (3c; Table 1, Entry 2). The compound was synthesized using general DIA procedure A from imine **1a** (65.0 mg, 0.247 mmol) and acid **2d** (64.6 mg, 0.296 mmol). Purification by column chromatography (2/1 → 1/1 petroleum ether/ethyl acetate) afforded the title compound **3c** as a colorless oil (71.0 mg, 82%) as a 2/1 (A/B) mixture of diastereoisomers: R_f 0.55 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 2941, 1658, 1463, 1451, 1358, 1280, 1142, 703; δ_H (400 MHz, $CDCl_3$) 7.33−7.16 and 7.14−7.05 (20H, m, 10 from A and 10 from B), 4.76−4.64 (2H, m, A and B), 4.36 (1H, s, A), 4.32 (1H, s, B), 3.85−3.77 (1H, m, B), 3.10 (1H, d, J = 13.2, B), 3.05−2.94 (3H, m, 2 from A and B), 2.89−2.77 (3H, m, 2 from A and B), 2.40−2.18 (7H, m, 3 from A and 4 from B), 2.01−1.89 (2H, m, A and B), 1.55−1.45 (4H, m, A and B), 1.42 (3H, d, J = 6.2, B), 1.38−1.28 (2H, m, A and B), 1.25 (3H, d, J = 6.6, A); δ_C (100 MHz, $CDCl_3$) 167.6 (C, B), 166.4 (C, A), 137.9 (C, A and B), 137.2 (C, B), 137.0 (C, A), 131.1 (CH, A), 131.0 (CH, B), 131.0 (CH, A), 130.9 (CH, B), 128.0 (CH, A), 128.0 (CH, B), 127.9 (CH, B), 127.8 (CH, A), 126.3 (CH, A), 126.2 (CH, B), 126.2 (CH, A and B), 88.6 (CH, B), 83.4 (CH, A), 68.8 (CH, B), 67.1 (CH, A), 41.7 (C, A), 41.6 (C, B), 41.5 (CH_2, B), 41.3 (CH_2, A), 40.2 (CH_2, B), 40.1 (CH_2, B), 39.8 (CH_2, A), 37.9 (CH_2,

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A), 35.3 (CH_2, B), 35.2 (CH_2, A), 28.0 (CH_2, A), 27.9 (CH_2, B), 21.1 (CH_2, B), 20.4 (CH_2, A), 20.2 (CH_2, B), 17.2 (CH_2, A); HRMS (ESI^+) m/z calcd 350.2115 for $C_{23}H_{28}NO_2$ (MH^+), found 350.2104.

2-Methylhexahydropyrido[2,1-*b*][1,3]oxazin-4(6*H*)-one (3d; Table 1, Entry 3). The compound was synthesized using general DIA procedure A from dodecahydro-4a,8a,12a-triazatriphenylene (the trimer of imine **1b**; 50.0 mg, 0.201 mmol) and acid **2d** (131 mg, 0.603 mmol). Purification by column chromatography (2/1 → 1/1 petroleum ether/ethyl acetate → ethyl acetate) afforded the title compound **3d** as a pale yellow oil (61.0 mg, 60%) as an 8/1 (A/B) mixture of diastereoisomers: R_f 0.20 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 4.77−4.70 (1H, m, B), 4.70−4.66 (2H, m, A and B), 4.62−4.57 (1H, m, A), 4.26−4.18 (1H, m, B), 3.91−3.82 (1H, m, A), 2.55−2.18 (6H, m, 3 from A and 3 from B), 2.04−1.64 (6H, m, 3 from A and 3 from B), 1.55−1.30 (6H, m, 3 from A and 3 from B), 1.27 (6H, d, J = 6.2, 3 from A and 3 from B); δ_C (100 MHz, $CDCl_3$) 166.8 (C, A and B), 88.2 (CH, A), 83.9 (CH, B), 69.5 (CH, A), 65.8 (CH, B), 41.1 (CH_2, B), 40.1 (CH_2, A), 39.8 (CH_2, A), 39.1 (CH_2, B), 32.8 (CH_2, A), 32.0 (CH_2, B), 24.8 (CH_2, B), 24.5 (CH_2, A), 23.4 (CH_2, B), 22.6 (CH_2, A), 21.0 (CH_3, A), 19.8 (CH_3, B). Spectral data are in accord with those reported in the literature.[11]

8,8-Dibenzyl-2-methyltetrahydro-2*H*-pyrrolo[2,1-*b*][1,3]-oxazin-4(3*H*)-one (3e; Table 1, Entry 4). The compound was synthesized using general DIA procedure A from imine **1c** (50.0 mg, 0.201 mmol) and acid **2d** (48.2 mg, 0.221 mmol). Purification by column chromatography (2/1 → 1/1 petroleum ether/ethyl acetate) afforded the title compound **3e** as a colorless oil (42.0 mg, 62%) as a 6/1 (A/B) mixture of diastereoisomers: R_f 0.40 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 2930, 1644, 1455, 1391, 1126, 757, 703; δ_H (400 MHz, $CDCl_3$) 7.34−7.16 (16H, m, 8 from A and 8 from B), 7.08−7.03 (4H, m, 2 from A and 2 from B), 4.74 (1H, s, B), 4.64 (1H, s, A), 4.52−4.47 (1H, m, B), 3.95−3.87 (1H, m, A), 3.60−3.43 (2H, m, A and B), 3.30−3.19 (2H, m, A and B), 2.91 (1H, d, J = 13.7, A), 2.86 (1H, d, J = 13.7, B), 2.79−2.61 (7H, m, 3 from A and 4 from B), 2.39 (1H, dd, J = 17.6, 4.0, A), 2.26−2.09 (2H, m, A and B), 1.77−1.67 (2H, m, A and B), 1.57−1.45 (2H, m, A and B), 1.42 (3H, d, J = 6.0, A), 1.34 (3H, d, J = 6.6, B); δ_C (100 MHz, $CDCl_3$) 166.7 (C, A and B), 137.6 (C, B), 137.5 (C, A), 136.7 (C, A), 136.6 (C, B), 130.9 (CH, B), 130.8 (CH, A), 128.2 (CH, A and B), 128.1 (CH, A and B), 126.6 (CH, B), 126.5 (CH, A), 126.5 (CH, A and B), 90.4 (CH, A), 84.0 (CH, B), 72.0 (CH, A), 69.1 (CH, B), 47.4 (C, B), 47.1 (C, A), 40.7 (CH_2, B), 40.4 (CH_2, A and B), 39.9 (CH_2, A), 38.6 (CH_2, A), 37.3 (CH_2, A and B), 37.0 (CH_2, B), 24.9 (CH_2, B), 24.7 (CH_2, A), 21.4 (CH_3, A), 19.7 (CH_3, B); HRMS (ESI^+) m/z calcd 336.1958 for $C_{22}H_{26}NO_2$ (MH^+), found 336.1958.

2-Methyl-2,3,6,7-tetrahydro[1,3]oxazino[2,3-*a*]isoquinolin-4(11b*H*)-one (3f; Table 1, Entry 5). To a solution of imine **1d** (210 mg, 1.60 mmol) and TBDMS-protected carboxylic acid **2d** (419 mg, 1.92 mmol) in CH_2Cl_2 (11.1 mL) were added sequentially $NEt(i\text{-}Pr)_2$ (0.520 mL, 2.96 mmol) and then T3P (1.53 g, 2.40 mmol, 50% solution in THF). The resulting solution was stirred at room temperature for 20 h. $SnCl_2{\cdot}2H_2O$ (2.49 mmol, 11.2 mmol) was then added directly to the reaction mixture, which was stirred at room temperature for a further 24 h. The reaction was quenched by the addition of 10% aqueous K_2CO_3, and the mixture was diluted with water (50 mL), extracted with CH_2Cl_2 (3 × 50 mL), washed with water (50 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by column chromatography (1/1 petroleum ether/ethyl acetate) afforded the title compound **3f** as a colorless oil (254 mg, 73%) as a 20/1 (A/B) mixture of diastereoisomers: R_f 0.40 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 2800, 1650, 1463, 1391, 1374, 1307, 1166, 1123, 747; δ_H (400 MHz, $CDCl_3$; data for the major diastereoisomer A only) 7.51−7.47 (1H, m), 7.28−7.22 (2H, m), 7.14−7.09 (1H, m), 5.86 (1H, s), 4.67−4.60 (1H, m), 4.20−4.10 (1H, m), 3.09−2.92 (1H, m), 2.73−2.67 (1H, m), 2.52 (1H, dd, J = 17.2, 3.7), 2.37 (1H, dd, J = 17.2, 11.4), 1.37 (3H, d, J = 6.2); δ_C (100 MHz, $CDCl_3$) 166.2 (C), 134.8 (C), 133.5 (C), 128.3 (CH), 128.2 (CH), 126.6 (CH), 126.0 (CH), 84.1 (CH), 70.3 (CH), 39.3 (CH_2), 37.4 (CH_2), 27.8 (CH_2), 21.1 (CH_3); HRMS (ESI^+) m/z calcd 240.0995 for $C_{13}H_{15}NNaO_2$ (MNa^+), found 240.0991.

Characteristic NMR data for the minor diastereoisomer B: δ_H (400 MHz, $CDCl_3$) 5.98 (1H, s); δ_C (100 MHz, $CDCl_3$) 82.3 (CH).

3,6-Dimethyl-2-phenyl-1,3-oxazinan-4-one (3g; Table 1, Entry 6). To a solution of imine **1e** (98.0 μL, 0.795 mmol) and TBDMS-protected carboxylic acid **2d** (208 mg, 0.954 mmol) in chloroform (5.5 mL) were added sequentially DIPEA (0.260 mL, 1.47 mmol) and then T3P (1759 mg, 1.19 mmol, 50% solution in THF). The resulting solution was heated to reflux for 1 h and then cooled to 0 °C. Triflic acid (0.700 mL, 7.95 mmol) was then added directly to the reaction mixture, which was warmed to room temperature and stirred for a further 1 h. The reaction was quenched by the addition of 1 M aqueous NaOH (25 mL), extracted with CH_2Cl_2 (3 × 50 mL), washed with water (50 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by column chromatography (1/1 petroleum ether/ethyl acetate) afforded the title compound **3g** as a colorless oil (106 mg, 65%) as a 12/1 (A/B) mixture of diastereoisomers: R_f 0.25 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 3432, 1643, 1456, 1389, 1350, 1301, 1152, 755, 701; δ_H (400 MHz, $CDCl_3$) 7.42−7.35 (10H, m, 5 from A and 5 from B), 5.81 (1H, s, B), 5.58 (1H, s, A), 4.14−4.05 (1H, m, A), 3.93−3.85 (1H, m, B), 2.87 (3H, s, B), 2.58 (3H, s, A), 2.55−2.51 (4H, m, 2 from A and 2 from B), 1.32 (3H, d, J = 6.1, A), 1.15 (3H, d, J = 6.1, B); δ_C (100 MHz, $CDCl_3$; data for the major diastereoisomer A only) 167.9 (C), 137.5 (C), 129.8 (CH), 128.9 (CH), 127.5 (CH), 90.9 (CH), 70.7 (CH), 40.0 (CH_2), 29.8 (CH_3), 21.1 (CH_3); HRMS (ESI^+) m/z calcd 206.1176 for $C_{12}H_{16}NO_2$ (MH^+), found 206.1176.

8,8-Dibenzylhexahydroimidazo[1,2-*a*]pyridin-3(5*H*)-one (5a; Table 2, Entry 1). Synthesis using general DIA procedure B from imine **1a** (27.0 mg, 0.103 mmol) and protected amino acid **4a** (25.9 mg, 0.124 mmol) afforded the title compound **5a** as a colorless oil (28.5 mg, 86%): R_f 0.25 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 3344 (br), 2940, 1680, 1452, 1293, 910; δ_H (400 MHz, $CDCl_3$) 7.34−7.10 (8H, m), 7.08−6.98 (2H, m), 4.30 (1H, s), 4.15 (1H, dd, J = 12.8, 4.8), 3.69 (1H, d, J = 15.8), 3.55 (1H, d, J = 15.8), 2.99 (1H, d, J = 13.5), 2.86 (1H, d, J = 13.0), 2.79 (1H, d, J = 13.0), 2.57−2.48 (1H, m), 2.37 (1H, d, J = 13.5), 2.05−1.90 (1H, m), 1.63−1.50 (2H, m), 1.35−1.20 (1H, m); δ_C (100 MHz, $CDCl_3$) 182.5 (C), 137.4 (C), 137.1 (C), 131.0 (CH), 130.9 (CH), 128.3 (CH), 128.3 (CH), 126.6 (CH), 126.5 (CH), 76.7 (CH), 49.3 (CH_2), 43.0 (C), 41.8 (CH_2), 39.5 (CH_2), 34.1 (CH_2), 27.9 (CH_2), 20.1 (CH_2); HRMS (ESI^+) m/z calcd 321.1961 for $C_{21}H_{25}N_2O$ (MH^+), found 321.1955.

9,9-Dibenzylhexahydro-1*H*-pyrido[1,2-*a*]pyrimidin-4(6*H*)-one (5b; Table 2, Entry 2). The compound was synthesized using general DIA procedure C from imine **1a** (53.0 mg, 0.201 mmol) and acid **4b** (49.2 mg, 0.241 mmol). Purification by column chromatography (1/1 petroleum ether/ethyl acetate → ethyl acetate) afforded the title compound **5b** as a pale yellow solid (82.0 mg, 76%): R_f 0.65 (ethyl acetate); mp 102−104 °C; ν_{max} (thin film)/cm^{-1} 3344 (br), 2943, 1632, 1454, 1360, 1280, 910; δ_H (400 MHz, $CDCl_3$) 7.34−7.17 (10H, m), 4.78−4.72 (1H, m), 3.92 (1H, s), 3.30−3.24 (1H, m), 3.17 (1H, d, J = 13.1), 3.01 (1H, d, J = 13.1), 2.86−2.79 (1H, m), 2.62 (1H, d, J = 13.1), 2.44−2.36 (3H, m), 2.27−2.17 (1H, m), 1.98−1.85 (1H, m), 1.53−1.40 (2H, m), 1.36−1.25 (1H, m); δ_C (100 MHz, $CDCl_3$) 169.8 (C), 137.2 (C), 137.1 (C), 131.0 (CH), 130.9 (CH), 128.2 (CH), 127.8 (CH), 126.5 (CH), 126.3 (CH), 75.2 (CH), 42.0 (CH_2), 41.2 (C), 40.8 (CH_2), 40.1 (CH_2), 36.4 (CH_2), 34.6 (CH_2), 29.6 (CH_2), 20.4 (CH_2); HRMS (ESI^+) m/z calcd 335.2118 for $C_{22}H_{27}N_2O$ (MH^+), found 335.2107.

(2*S*)-2-Methyl-1,2,5,6-tetrahydroimidazo[2,1-*a*]isoquinolin-3(10b*H*)-one (5c; Table 2, Entry 3). Synthesis using general DIA procedure B from imine **1d** (57.0 mg, 0.434 mmol) and protected amino acid **4c** (116 mg, 0.521 mmol) afforded the title compound **5c** as a colorless oil (79 mg, 90%) as a 4/1 (A/B) mixture of diastereoisomers: R_f 0.10 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 3406 (br), 1682, 1439, 1354, 1306, 737; δ_H (400 MHz, $CDCl_3$) 7.51−7.14 (8H, m, 4 from A and 4 from B), 5.70 (1H, s, B), 5.57 (1H, s, A), 4.20−4.13 (2H, m, A and B), 3.75−3.64 (2H, m, A and B), 3.27−3.14 (2H, m, A and B), 3.03−2.92 (2H, m, A and B), 2.84−2.73 (2H, m, A and B), 1.44 (3H, d, J = 6.8, B), 1.37 (3H, d, J = 6.8, A); δ_C (100 MHz, $CDCl_3$) 173.4 (C, A and B), 134.2 (C, B), 134.0 (C, A), 133.8 (C, A and B), 129.2 (CH, A), 129.1 (CH, B), 128.6 (CH, B), 128.4 (CH, A),

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127.2 (CH, A), 127.1 (CH, B), 125.4 (CH, A), 125.4 (CH, B), 69.7 (CH, B), 69.6 (CH, A), 56.4 (CH, A), 55.9 (CH, B), 37.2 (CH_2, B), 36.8 (CH_2, A), 28.3 (CH_2, A), 27.9 (CH_2, B), 16.4 (CH_3, B), 15.9 (CH_2, A); HRMS (ESI^+) m/z calcd 203.1179 for $C_{12}H_{15}N_2O$ (MH^+), found 203.1174.

(8a*S*)-5,6,8a,9,10,11-Hexahydropyrrolo[1′,2′:3,4]imidazo-[2,1-*a*]isoquinolin-8(12a*H*)-one (5d; Table 2, Entry 4). The compound was synthesized using general DIA procedure C from imine **1d** (57.0 mg, 0.434 mmol) and acid **4d** (106 mg, 0.521 mmol). Purification by column chromatography (100/1 → 50/1 ethyl acetate/methanol) afforded the title compound **5d** as a colorless oil (74.0 mg, 75%): R_f 0.10 (100/1 ethyl acetate/methanol); ν_{max} (thin film)/cm^{-1} 3442, 2967, 1694, 1650, 1433, 1368, 1303, 1199, 1057, 748; δ_H (400 MHz, $CDCl_3$) 7.44 (1H, d, J = 7.5), 7.31−7.23 (2H, m), 7.14 (1H, d, J = 7.3), 5.82 (1H, s), 4.25 (1H, ddd, J = 13.2, 5.7, 1.5), 3.94 (1H, dd, J = 8.6, 4.6), 3.11−3.02 (1H, m), 2.92−2.74 (2H, m), 2.59−2.53 (1H, m), 2.23−2.07 (2H, m), 1.95−1.87 (1H, m), 1.76−1.67 (2H, m); δ_C (100 MHz, $CDCl_3$) 174.6 (C), 134.8 (C), 131.7 (C), 129.2 (CH), 127.9 (CH), 127.3 (CH), 127.0 (CH), 73.4 (CH), 66.4 (CH), 48.1 (CH_2), 36.9 (CH_2), 29.0 (CH_2), 25.4 (CH_2), 24.3 (CH_2); HRMS (ESI^+) m/z calcd 229.1335 for $C_{14}H_{17}N_2O$ (MH^+), found 229.1335; $[\alpha]_D^{22}$ −21.0° (c 0.9, $CHCl_3$).

5,6,11,11b-Tetrahydro-1*H*-imidazo[1′,2′:1,2]pyrido[3,4-*b*]-indol-3(2*H*)-one (5e; Table 2, Entry 5). The compound was synthesized using general DIA procedure B from imine **1f** (35.0 mg, 0.206 mmol) and protected amino acid **4a** (51.7 mg, 0.247 mmol), affording the title compound **5e** as a colorless oil (40 mg, 85%): R_f 0.10 (100/1 ethyl acetate/methanol); ν_{max} (thin film)/cm^{-1} 3141 (br), 1643, 1424, 1285, 734; δ_H (400 MHz, d_6-DMSO) 11.09 (1H, br s), 7.39 (1H, d, J = 7.9), 7.31 (1H, d, J = 7.9), 7.05 (1H, dd, J = 7.9, 6.7), 6.95 (1H, dd, J = 7.9, 6.7), 5.71 (1H, s), 4.19−4.13 (1H, m), 3.42 (1H, d, J = 15.8), 3.20−3.08 (2H, m), 2.73−2.65 (1H, m); δ_C (100 MHz, d_6-DMSO) 173.1 (C), 136.3 (C), 132.8 (C), 126.2 (C), 121.5 (CH), 118.6 (CH), 118.2 (CH), 111.5 (CH), 107.7 (C), 69.6 (CH), 49.6 (CH_2), 37.4 (CH_2), 20.4 (CH_2); HRMS (ESI^+) m/z calcd 228.1131 for $C_{13}H_{14}N_3O$ (MH^+), found 228.1134.

9,9-Dibenzylhexahydropyrido[2,1-*b*][1,3]thiazin-4(6*H*)-one (7a; Table 3, Entry 1). The compound was synthesized using general DIA procedure D from imine **1a** (25.0 mg, 0.0950 mmol) and thioacid **6a** (9.9 μL, 0.247 mmol). Purification by column chromatography (1/1 petroleum ether/ethyl acetate) afforded the title compound **7a** as a colorless oil (30 mg, 90%): R_f 0.60 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 2941, 1642, 1454, 1360, 1327, 1185, 912; δ_H (400 MHz, $CDCl_3$) 7.34−7.16 (10H, m), 5.00−4.94 (1H, m), 4.40 (1H, s), 3.10−2.91 (4H, m), 2.88−2.74 (3H, m), 2.40 (1H, d, J = 14.0), 2.28−2.18 (1H, m), 2.06−1.94 (1H, m), 1.62−1.49 (2H, m), 1.40−1.30 (1H, m); δ_C (100 MHz, $CDCl_3$) 169.6 (C), 137.4 (C), 136.4 (C), 131.0 (CH), 130.9 (CH), 128.1 (CH), 128.0 (CH), 126.5 (CH), 126.4 (CH), 64.9 (CH), 44.8 (CH_2), 44.3 (C), 42.0 (CH_2), 36.6 (CH_2), 35.5 (CH_2), 29.9 (CH_2), 23.0 (CH_2), 20.1 (CH_2); HRMS (ESI^+) m/z calcd 352.1730 for $C_{22}H_{26}NOS$ (MH^+), found 352.1728.

***N*-((3*R*)-9,9-Dibenzyl-4-oxooctahydropyrido[2,1-*b*][1,3]-thiazin-3-yl)acetamide (7b; Table 3, Entry 2).** The compound was synthesized using general DIA procedure D from imine **1a** (34 mg, 0.129 mmol) and thioacid **6b** (25.3 mg, 0.155 mmol). Purification by column chromatography (1/1 petroleum ether/ethyl acetate) afforded the title compound **7b** as a colorless oil (47 mg, 89%) as a 4/1 (A/B) mixture of diastereoisomers: R_f 0.2 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 3260, 2894, 1608, 1419, 720; δ_H (400 MHz, $CDCl_3$) 7.35−7.15 (18H, m, 8 from A and 10 from B), 7.05 (2H, d, J = 6.6, A), 6.94−6.91 (1H, m, B, NH), 6.78−6.75 (1H, m, A, NH), 4.89−4.82 (2H, m, A and B), 4.64−4.52 (2H, m, A and B), 4.49 (1H, s, B), 4.16 (1H, s, A), 3.49−3.40 (2H, m, A and B), 3.24−3.18 (2H, m, A and B), 3.05−2.97 (3H, m, A), 2.96−2.82 (2H, m, B), 2.67−2.60 (1H, m, B), 2.42−2.30 (4H, m, 2 from A and 2 from B), 2.02 (3H, s, B), 2.01 (3H, s, A), 2.00−1.90 (2H, m, A and B), 1.64−1.52 (4H, m, 2 from A and 2 from B), 1.45−1.35 (1H, m, A), 1.35−1.25 (1H, m, B); δ_C (100 MHz, $CDCl_3$) 170.6 (C, A), 170.4 (C, B), 169.0 (C, B), 168.2 (C, A), 137.2 (C, B), 136.7 (C, A), 136.3 (C, A), 135.9 (C, B), 131.0 (CH, A and B), 130.9 (CH, A and B), 128.2 (CH, 2 from A and 1 from B), 128.0 (CH, B), 126.6 (CH, A), 126.5 (CH, B), 65.0 (CH, B), 63.5 (CH, A), 53.3 (CH, B), 52.3 (CH, A), 46.5 (CH_2, A), 46.2 (C, A), 45.5 (CH_2, B), 43.3 (C, B), 42.1 (CH_2, A), 41.1 (CH_2, B), 37.0 (CH_2, A), 36.2 (CH_2, B), 29.7 (CH_2, A), 29.6 (CH_2, B), 28.1 (CH_2, A), 26.9 (CH_2, B), 23.3 (CH_3, A), 23.2 (CH_3, B), 21.2 (CH_2, A), 21.0 (CH_2, B); HRMS (ESI^+) m/z calcd 409.1944 for $C_{24}H_{29}N_2O_2S$ (MH^+), found 409.1945.

11b-Methyl-2,3,6,7-tetrahydro[1,3]thiazino[2,3-*a*]-isoquinolin-4(11b*H*)-one (7c; Table 3, Entry 3). The compound was synthesized using general DIA procedure D from imine **1g** (57.0 mg, 0.393 mmol) and thioacid **6a** (41.0 μL, 0.471 mmol). Purification by column chromatography (1/1 → 1/2 petroleum ether/ethyl acetate) afforded the title compound **7c** as a colorless oil (82 mg, 89%): R_f 0.10 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 1607, 1372, 1330, 1067, 751; δ_H (400 MHz, $CDCl_3$) 7.43 (1H, d, J = 7.5), 7.26−7.17 (2H, m), 7.12 (1H, d, J = 7.3), 5.10 (1H, ddd, J = 13.0, 4.9, 1.7), 3.24 (1H, ddd, J = 15.6, 9.9, 5.1), 3.03−2.93 (1H, m), 2.87−2.67 (4H, m), 2.04 (3H, s); δ_C (100 MHz, $CDCl_3$) 168.0 (C), 139.1 (C), 134.1 (C), 129.1 (CH), 127.4 (CH), 126.7 (CH), 126.1 (CH), 65.3 (C), 36.7 (CH_2), 33.8 (CH_2), 30.5 (CH_3), 29.1 (CH_2), 22.5 (CH_2); HRMS (ESI^+) m/z calcd 234.0947 for $C_{13}H_{16}NOS$ (MH^+), found 234.0948.

10b-Phenyl-5,6-dihydro-2*H*-thiazolo[2,3-*a*]isoquinolin-3-(10b*H*)-one (7d; Table 3, Entry 4). The compound was synthesized using general DIA procedure D from imine **1h** (58.0 mg, 0.280 mmol) and thioacid **6c** (23.3 μL, 0.336 mmol). Purification by column chromatography (3/1 petroleum ether/ethyl acetate) afforded the title compound **7d** as a colorless oil (73 mg, 93%): R_f 0.30 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 1653, 1380, 1271, 1157, 739; δ_H (400 MHz, $CDCl_3$) 7.50−7.46 (1H, m), 7.33−7.13 (8H, m), 4.12 (1H, ddd, J = 13.0, 7.0, 4.6), 3.98 (1H, d, J = 15.5), 3.73 (1H, d, J = 15.5), 3.17 (1H, ddd, J = 13.0, 9.0, 6.0), 3.06−3.00 (1H, m), 2.64 (1H, ddd, J = 16.3, 6.0, 4.6); δ_C (100 MHz, $CDCl_3$) 169.8 (C), 144.0 (C), 138.8 (C), 133.4 (C), 128.8 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.6 (CH), 126.8 (CH), 126.4 (CH), 73.4 (C), 38.1 (CH_2), 34.3 (CH_2), 27.1 (CH_3); HRMS (ESI^+) m/z calcd 282.0947 for $C_{17}H_{16}NOS$ (MH^+), found 282.0954.

5,6,11,11b-Tetrahydrothiazolo[3′,2′:1,2]pyrido[3,4-*b*]indol-3(2*H*)-one (7e; Table 3, Entry 5). The compound was synthesized using general DIA procedure D from imine **1f** (35.0 mg, 0.206 mmol) and thioacid **6c** (17.2 μL, 0.247 mmol). Purification by column chromatography (1/1 petroleum ether/ethyl acetate) afforded the title compound **7e** as a colorless oil (49 mg, 97%): R_f 0.35 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 3168, 1624, 1420, 1302, 1214, 885; δ_H (400 MHz, d_6-DMSO) 11.51 (1H, br s), 7.40 (1H, d, J = 7.7), 7.29 (1H, d, J = 8.1), 7.07−7.03 (1H, m), 6.98−6.94 (1H, m), 6.22 (1H, s), 4.34 (1H, dd, J = 13.2, 4.4), 3.81 (1H, d, J = 15.2), 3.57 (1H, d, J = 15.2), 3.19−3.11 (1H, m), 2.78−2.62 (2H, m); δ_C (100 MHz, d_6-DMSO) 170.1 (C), 137.0 (C), 132.6 (C), 126.5 (C), 122.3 (CH), 119.5 (CH), 118.9 (CH), 112.0 (CH), 107.8 (C), 56.1 (CH), 40.9 (CH_2), 33.5 (CH_2), 21.2 (CH_3); HRMS (ESI^+) m/z calcd 245.0743 for $C_{13}H_{13}N_2OS$ (MH^+), found 245.0753.

3-Methyl-2-phenylthiazolidin-4-one (7f; Table 3, Entry 6). The compound was synthesized using general DIA procedure D from imine **1e** (90.8 mg, 0.726 mmol) and thioacid **6c** (84.3 mg, 63.8 μL, 0.915 mmol). Purification by column chromatography (1/1 petroleum ether/ethyl acetate) afforded the title compound **7f** as a colorless oil (173 mg, 93%): R_f 0.35 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 3031, 2922, 1670, 1389, 697; δ_H (400 MHz, $CDCl_3$) 7.44−7.34 (3H, m), 7.33−7.28 (2H, m), 5.52 (1H, d, J = 2.1), 3.84 (1H, dd, J = 15.4, 2.1), 3.72 (1H, d, J = 15.4), 2.74 (3H, s); δ_C (100 MHz, $CHCl_3$) 171.13 (C═O), 139.12 (C), 129.1 (2 × CH), 129.0 (2 × CH), 126.8 (CH), 65.3 (CH), 32.9 (CH_2), 30.1 (CH_3); HRMS (ESI^+) m/z calcd 194.0634 for $C_{10}H_{12}NOS$ (MH^+), found 194.0630. These data were consistent with those reported in the literature.[12]

Dimethyl 4-Oxo-3,4,6,7-tetrahydro-1*H*-pyrido[2,1-*a*]-isoquinoline-1,1(2*H*,11b*H*)-dicarboxylate (9a, Table 4, entry 1). Imine **1d** (50 mg, 0.381 mmol) and carboxylic acid **8a** (93 mg, 0.457 mmol) were dissolved in $CHCl_3$ (2 mL) in a microwave vial. $NEt(i\text{-}Pr)_2$ (91.1 mg, 123 μL, 0.705 mmol) and T3P (182 mg, 0.572 mmol, 364 mg of a 50% solution in THF) were added via syringe. The

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reaction mixture was stirred at 70 °C for 1 h. $AlCl_3$ (102 mg, 0.762 mmol) was added and the reaction mixture stirred at 70 °C for 1 h. The reaction mixture was quenched with saturated $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated to give the crude material. Purification by column chromatography (ethyl acetate) gave the title compound **9a** (92 mg, 76%) as a yellow solid: mp 130−133 °C (from $CHCl_3$); R_f 0.48 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 2952, 2874, 1741, 1713, 1668, 1399, 1276, 1159, 1078, 759; δ_H (400 MHz, $CDCl_3$) 7.27−7.12 (4H, m), 5.49 (1H, m), 4.67−4.55 (1H, m), 3.82 (3H, s), 3.36 (3H, s), 2.94−2.83 (2H, m), 2.77−2.65 (1H, m), 2.66−2.43 (4 H, m); δ_C (100 MHz, $CDCl_3$) 171.2 (C═O), 170.9 (C═O), 169.1 (C═O), 137.5 (C), 132.9 (C), 128.3 (CH), 127.4 (CH), 126.5 (CH), 126.1 (CH), 60.1 (C), 59.0 (CH), 53.1 (CH_3), 52.5 (CH_3), 39.7 (CH_2), 29.5 (CH_2), 28.7 (CH_2), 28.7 (CH_2); HRMS (ESI) m/z calcd 318.1336 for $C_{17}H_{20}NO_5$ (MH^+), found 318.1335.

1,1′-(4-Oxo-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinoline-1,1-diyl)diethanone (9b; Table 4, Entry 2). The compound was synthesized using general DIA procedure E (at 70 °C and with $AlCl_3$ as the Lewis acid) from imine **1d** (100 mg, 0.762 mmol) and carboxylic acid **8b** (158 mg, 0.915 mmol). Purification by column chromatography (ethyl acetate) gave the *title compound* **9b** (141 mg, 65%) as a colorless solid: mp 146−147 °C (from petroleum ether/EtOAc); R_f 0.25 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 3014, 2947, 2921, 1687, 1660, 1464, 1402, 1356, 1186, 1136, 759; δ_H (400 MHz, $CDCl_3$) 7.26−7.20 (1H, m), 7.20−7.14 (2H, m), 7.09−7.04 (1H, m), 5.67 (1H, s), 4.36 (1H, dt, J = 12.7, 5.8), 3.18−3.09 (1H, m), 2.87 (2H, *app* t, J = 6.6), 2.59−2.40 (3H, m), 2.38−2.29 (1H, m), 2.28 (3H, s), 1.82 (3H, s); δ_C (100 MHz, $CDCl_3$) 204.2 (C═O), 203.8 (C═O), 170.3 (C═O), 137.2 (C), 133.8 (C), 129.0 (CH), 127.9 (CH), 126.6 (CH), 125.5 (CH), 71.2 (C), 56.2 (CH), 40.3 (CH_2), 29.1 (CH_2), 28.2 (CH_3), 28.0 (CH_2), 26.8 (CH_3), 24.2 (CH_2); HRMS (ESI) m/z calcd 286.1438 for $C_{17}H_{20}NO_3$ (MH^+), found 286.1430.

2,3-Dimethoxy-8,9-dihydro-5*H*-isoquinolino[1,2-*a*]isoquinolin-6(13b*H*)-one (9c; Table 4, Entry 3). The compound was synthesized using general DIA procedure E (at room temperature and with $BF_3{\cdot}OEt_2$ as the Lewis acid) from imine **1d** (100 mg, 0.762 mmol) and carboxylic acid **8c** (179 mg, 0.915 mmol). Purification by column chromatography (ethyl acetate) gave the title compound **9c** (212 mg, 90%) as a yellow solid: mp 175−177 °C (from EtOAc/MeOH) (lit.[13] mp 141−142 °C (from EtOH/petroleum ether)); R_f 0.30 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 2932, 1629, 1520, 1461, 1251, 758, 601; δ_H (400 MHz, $CDCl_3$) 7.31−7.28 (3H, m), 7.03 (1H, d, J = 7.3), 6.73 (1H, s), 6.57 (1H, s), 5.64 (1H, s), 4.61 (1H, ddd, J = 13.0, 6.2, 5.2), 3.91 (3H, s), 3.80 (3H, s), 3.60 (1H, d, J = 18.9), 3.51 (1H, d, J = 18.9), 3.29 (1H, ddd, J = 13.0, 8.8, 5.2), 3.03 (1H, ddd, J = 15.4, 8.8, 6.2), 2.91 (1H, app dt, J = 15.9, 5.2); δ_C (100 MHz, $CDCl_3$) 169.5 (C═O), 148.7 (C), 147.4 (C), 136.0 (C), 135.7 (C), 128.8 (CH), 127.6 (CH), 126.1 (CH), 125.8 (CH), 125.3 (C), 125.2 (C), 110.3 (CH), 109.7 (CH), 59.0 (CH), 56.0 (CH_3), 56.0 (CH_3), 40.9 (CH_2), 37.3 (CH_2), 28.1 (CH_2); HRMS (ESI) m/z calcd 310.1438 for $C_{19}H_{20}NO_3$ (MH^+), found 310.1437.

5,6,14,14b-Tetrahydroindolo[2′,3′:3,4]pyrido[2,1-*a*]isoquinolin-8(9*H*)-one (9d; Table 4, Entry 4). The compound was synthesized using general DIA procedure E (at room temperature and with $BF_3{\cdot}OEt_2$ as the Lewis acid) from imine **1d** (100 mg, 0.762 mmol) and carboxylic acid **8d** (160 mg, 0.915 mmol). Purification by column chromatography (ethyl acetate) gave the title compound **9d** (176 mg, 80%) as a light brown solid: mp decomposition noted at 205 °C (from EtOAc/MeOH); R_f 0.51 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 3063, 2953, 1603, 1454, 1226, 1216, 756, 738, 710; δ_H (400 MHz, $CDCl_3$) 11.51 (1H, s), 7.50−7.43 (2H, m), 7.30−7.13 (5H, m), 7.04 (1H, ddd, J = 7.9, 7.0, 0.9), 6.02 (1H, s), 4.25 (1H, *app* dt, J = 12.8, 6.4), 3.67 (1H, dd, J = 20.7, 2.4), 3.47 (1H, dd, J = 20.7, 2.4), 3.48−3.39 (1H, m), 3.13−2.94 (2H, m); δ_C (100 MHz, $CDCl_3$) 167.1 (C═O), 137.7 (C), 137.0 (C), 135.4 (C), 128.5 (CH), 128.3 (C), 127.6 (CH), 126.2 (CH), 125.5 (C), 124.3 (CH), 121.8 (CH), 118.9 (CH), 118.3 (CH), 111.4 (CH), 105.0 (C), 54.9 (CH), 41.9 (CH_2), 29.2 (CH_2), 27.1 (CH_2); HRMS (ESI) m/z calcd 289.1335 for $C_{19}H_{17}N_2O$ (MH^+), found 289.1334.

8,9-Dihydro-5*H*-pyrrolo[2′,1′:3,4]pyrazino[2,1-*a*]isoquinolin-6(13b*H*)-one (9e; Table 4, Entry 5). The compound was synthesized using general DIA procedure E (at room temperature and with $BF_3{\cdot}OEt_2$ as the Lewis acid) from imine **1d** (100 mg, 0.762 mmol) and carboxylic acid **8e** (115 mg, 0.915 mmol). Purification by column chromatography (1/1 petroleum ether/ethyl acetate) gave the title compound **9e** (140 mg, 77%) as a brown oil: R_f 0.65 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 2944, 2897, 1651, 1448, 1427, 1317, 908, 724; δ_H (400 MHz, $CDCl_3$); 7.41−7.35 (1H, m), 7.31−7.24 (2H, m), 7.24−7.19 (1H, m), 6.70 (1H, dd, J = 2.6, 1.6), 6.23 (1H, dd, J = 3.6, 2.6), 5.99 (1H, ddd, J = 3.6, 1.6, 1.0), 5.90 (1H, s), 4.76 (1H, ddd, J = 12.6, 5.4, 3.6), 4.69 (1H, d, J = 17.1), 4.62 (1H, d, J = 17.1), 3.22−3.13 (1H, m), 3.12−3.01 (1H, m), 2.86 (1H, app dt, J = 15.8, 3.6); δ_C (100 MHz, $CDCl_3$) 165.3 (C═O), 134.8 (C), 133.5 (C), 129.0 (CH), 127.6 (CH), 126.3 (CH), 125.5 (CH), 119.2 (CH), 108.9 (CH), 105.7 (CH), 54.2 (CH), 48.9 (CH_2), 40.4 (CH_2), 28.2 (CH_2); HRMS (ESI) m/z calcd 239.1179 for $C_{15}H_{15}N_2O$ (MH^+), found 239.1179.

11,14-Dimethoxy-5,6-dihydrobenzo[*de*]isoquinolino[1,2-*a*]isoquinolin-8(14b*H*)-one (9f; Table 4, Entry 6). Imine **1d** (53.4 mg, 0.407 mmol) and carboxylic acid **8f** (113 mg, 0.489 mmol) were dissolved in toluene (2.5 mL). $NEt(i\text{-}Pr)_2$ (97.3 mg, 131 μL, 0.753 mmol) and T3P (194 mg, 0.611 mmol, 386 mg of a 50% solution in THF). The resulting solution was stirred at room temperature for 20 min. $BF_3{\cdot}Et_2O$ (0.25 mL, 2.04 mmol) was added and the reaction mixture stirred at room temperature for 20 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated to give the crude material. Purification by column chromatography (4/1 petroleum ether/ethyl acetate → 1/1 petroleum ether/ethyl acetate → EtOAc) gave the title compound **9f** (125 mg, 89%) as a pink solid: mp 242−248 °C; R_f 0.31 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 2944, 2845, 1638, 1586, 1518, 1461, 1412, 1349, 1261, 1242, 1186, 1055, 1048, 1093, 736; δ_H (400 MHz, $CDCl_3$); 8.30 (1H, d, J = 9.2), 8.24 (1H, d, J = 8.1), 7.38 (1H, d, J = 9.2), 7.20−7.12 (2H, m), 6.96 (1H, t, J = 7.8), 6.75 (1H, d, J = 8.1), 6.49 (1H, d, J = 7.8), 6.22 (1H, s), 4.70 (1H, ddd, J = 13.5, 7.1, 6.6), 4.03 (3H, s), 3.97 (3H, s), 3.61 (1H, ddd, J = 13.5, 7.1, 7.1), 3.34 (1H, ddd, J = 16.1, 7.1, 7.1), 3.07 (1H, ddd, J = 16.1, 7.1, 6.6); δ_C (100 MHz, $CDCl_3$) 163.7 (C═O), 158.5 (C), 154.4 (C), 138.0 (C), 135.6 (C), 130.7 (C), 128.9 (CH), 128.5 (CH), 127.2 (CH), 125.7 (CH), 123.9 (CH), 123.6 (CH), 119.3 (C), 116.7 (C), 113.7 (C), 111.2 (CH), 102.1 (CH), 55.9 (CH_3), 55.7 (CH), 55.6 (CH_3), 42.3 (CH_2), 27.2 (CH_2); HRMS (ESI) m/z calcd 346.1438 for $C_{22}H_{20}NO_3$ (MH^+), found 346.1440.

2-Methyl-6,7-dihydro-1*H*-pyrido[2,1-*a*]isoquinolin-4(11b*H*)-one (9g; Table 4, Entry 7). Imine **1d** (38 mg, 0.290 mmol) and 3-methylbut-3-enoic acid **8g** (34.8 mg, 0.348 mmol) were dissolved in CH_2Cl_2 (2.9 mL). $NEt(i\text{-}Pr)_2$ (69.3 mg, 93.5 μL, 0.536 mmol) and T3P (13.8 mg, 0.435 mmol, 27.7 mg of a 50% solution in THF) were added, and the reaction mixture was stirred at 45 °C for 1 h. TFA (165 mg, 111 μL, 1.449 mmol) was added and the reaction mixture stirred at 45 °C overnight. The reaction was poured into saturated aqueous $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined aqueous layers were dried ($MgSO_4$), filtered, and concentrated to give the crude material. Purification by column chromatography (2/1 petroleum ether/ethyl acetate) gave the title compound **9g** (48 mg, 78%) as a colorless oil: R_f 0.52 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 2974, 2936, 2909, 2851, 1670, 1623, 1415, 1299, 760; δ_H (400 MHz, $CDCl_3$) 7.26−7.15 (4H, m), 5.88 (1H, app dq, J = 2.6, 1.4), 4.83−4.72 (2H, m), 3.00−2.75 (3H, m), 2.59 (1H, dd, J = 17.1, 4.9), 2.43−2.31 (1H, m), 1.99 (3H, s); δ_C (100 MHz, $CDCl_3$) 165.4 (C═O), 150.2 (C), 135.9 (C), 134.9 (C), 129.0 (CH), 126.7 (CH), 126.6 (CH), 125.6 (CH), 120.7 (CH), 54.3 (CH), 38.6 (CH_2), 37.7 (CH_2), 29.5 (CH_2), 22.7 (CH_3); HRMS (ESI) m/z calcd 214.1226 for $C_{14}H_{16}NO$ (MH^+), found 214.1223.

1-Vinyl-2,3,6,7-tetrahydro-1*H*-pyrido[2,1-*a*]isoquinolin-4-(11b*H*)-one (9h; Table 4, Entry 8). The compound was synthesized using general DIA procedure E (at room temperature and with $BF_3{\cdot}OEt_2$ as the Lewis acid) from imine **1d** (100 mg, 0.762 mmol) and

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carboxylic acid **8h** (170 mg, 0.915 mmol). Purification by column chromatography (1/1 petroleum ether/ethyl acetate) gave the title compound **9h** (122 mg, 70%) as a clear, colorless oil, as a 5/1 (A/B) mixture of diastereoisomers: R_f 0.39 (ethyl acetate); ν_{max} (thin film)/cm^{-1} 2933, 2870, 1635, 1461, 1433, 1409, 1360, 1286, 1248, 916, 741; δ_H (400 MHz, $CDCl_3$) data for major diastereoisomer 7.26−7.10 (4H, m), 5.53 (1H, ddd, J = 17.6, 10.1, 7.3), 4.97 (3H, m), 4.91 (1H, d, J = 3.4), 3.17−3.11 (1H, m), 2.88−2.67 (3H, m), 2.61 (1H, ddd, J = 18.0, 11.6, 7.0), 2.53 (1H, ddd, J = 18.0, 7.3, 2.8), 2.26−2.14 (1H, m), 2.09−2.00 (1H, m), data for minor diastereoisomer 7.26−7.10 (4H, m), 6.05 (1H, ddd, J = 17.5, 10.3, 7.3), 5.26 (1H, dt, J = 17.5, 1.2), 5.24 (1H, dt, J = 10.3, 1.1), 4.56 (1H, d, J = 7.3), 4.39 (1H, dt, J = 12.6, 5.6), 3.22−3.16 (1H, m), 3.10−3.00 (1H, m), 2.88−2.67 (3H, m), 2.44−2.31 (1H, m), 1.97−1.78 (2H, m); δ_C (100 MHz, $CDCl_3$) data for major diastereoisomer 169.7 (C═O), 135.8 (C), 134.4 (CH), 128.8 (CH), 126.5 (CH), 126.3 (CH), 126.2 (CH), 118.0 (CH_2), 60.0 (CH), 42.3 (CH), 38.5 (CH_2), 29.1 (CH_2), 28.1 (CH_2), 25.7 (CH_2), one quaternary carbon signal not observed, data for minor diastereoisomer 140.2 (CH), 136.5 (C), 134.9 (C), 128.5 (CH), 127.2 (CH), 126.1 (CH), 125.0 (CH), 116.4 (CH_2), 59.6 (CH), 41.9 (CH_2), 41.7 (CH), 30.6 (CH_2), 28.5 (CH_2), 26.2 (CH_2), carbonyl signal not observed; HRMS (ESI) m/z calcd 228.1383 for $C_{15}H_{18}NO$ (MH^+), found 228.1386.

■ ASSOCIATED CONTENT

Supporting Information

Text giving general experimental details and figures giving ^{1}H and ^{13}C spectra of all novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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