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Polycyclic Compounds by Ugi−Pictet−Spengler Sequence

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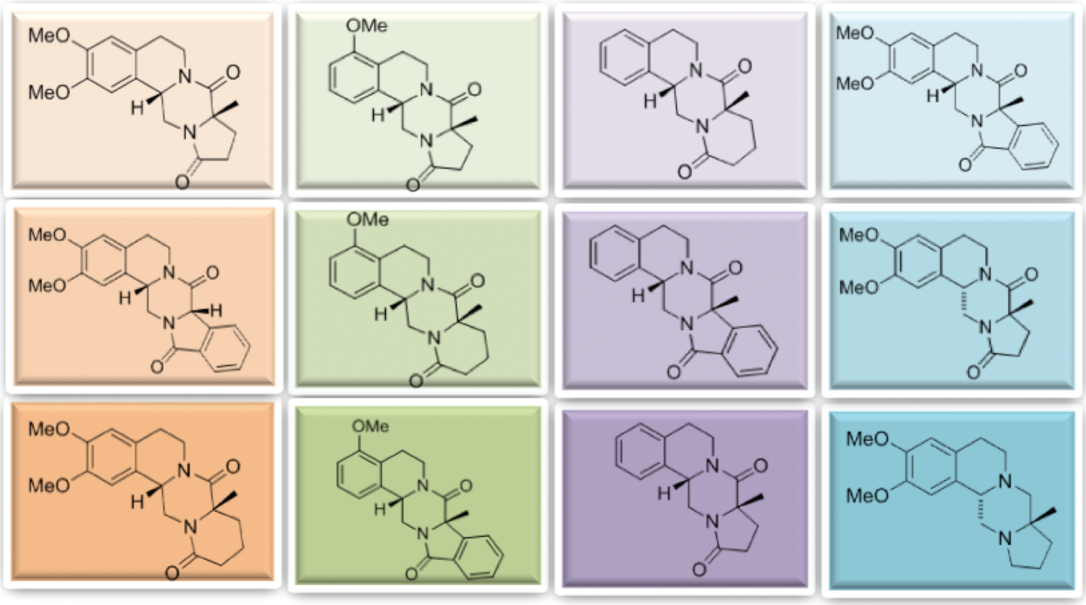
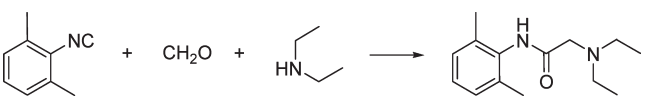


A general approach to architecturally stimulating polycyclic structures is described by a concise, two-step procedure including a Ugi MCR (multicomponent reaction) and a subsequent Pictet−Spengler reaction starting from phenylethylamine-derived isocyanides. Ten compounds are described in full experimental detail, and yields range from medium to very good. Some of the reactions run with a high degree of stereoselectivity. The compound structures resemble steroid hormones and alkaloid classes of natural products. Exemplary products have been fully reduced to their tertiary amines. As such they could potentially become interesting biological probes.

Introduction

2010 is the 50th anniversary of the discovery of the Ugi multicomponent reactions.[1] Ivar Ugi was a visionary scientist and immediately recognized the huge potential of his then discovered unusual chemical transformations for the synthesis of drugs. He prepared "collections of compounds" using the U-4CR and variations, nowadays called libraries, decades before the ascent of combinatorial chemistry. Today, combinatorial chemistry plays a major role in filling the screening decks of pharmaceutical companies as they form the basis of high-throughput screening, the major process to find medicinal chemistry starting points for new targets for unmet medical needs. Although MCRs are among the first

SCHEME 1. Ugi's Famous One-Pot Xylocain Synthesis



(1) Ugi, I.; Steinbrückner, C. *Angew. Chem.* **1960**, *72*, 267–268.

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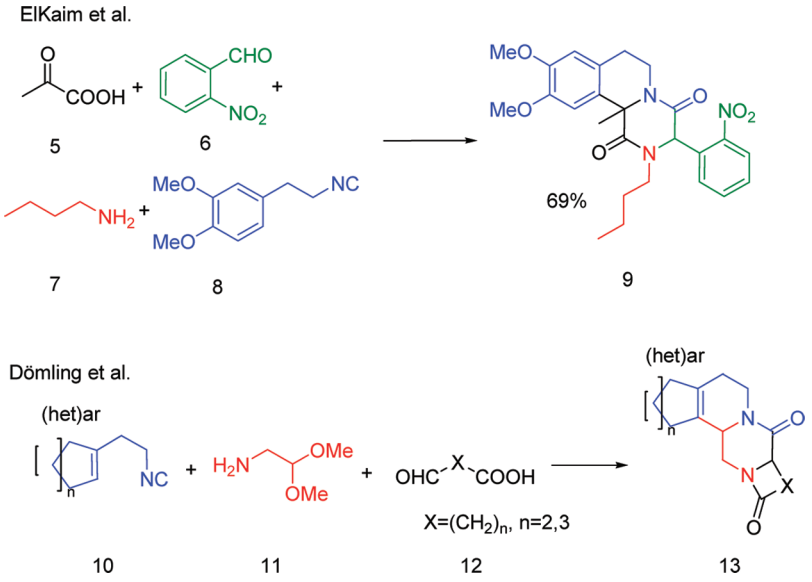
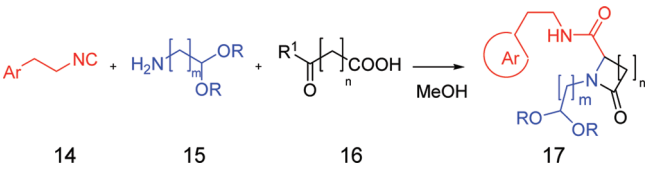
SCHEME 2. Two Conceptually Different Approaches of Using the Ugi−Pictet−Spengler Sequence for the Assembly of Polycyclic Products



SCHEME 3. Ugi Reaction of Bifunctional Oxocarboxylic Acids, Aminoacetaldehyde Dimethyl Acetal, and Phenylethyl Isocyanides



reactions of organic chemistry (e.g., Strecker synthesis, 1849) the potential of MCR for applied chemistry was only fully recognized by Ivar Ugi.[2] For example, one of the first applications of the Ugi reaction was the one-pot synthesis of the popular local anesthetic xylocain and several related compounds (Scheme 1).[3] Today, MCR chemistry is a major instrument for drug discovery.[4] The mature state of this large group of reactions and their use in the discovery and synthesis of biologically active compounds are reflected in the numerous preclinical and development compounds, e.g., almorexant (first-in-class orexin 1 antagonist, sleeping disorders) and retosiban (oxytocin receptor antagonist, preterm birth), or in the recently discovered HCV protease inhibitors, just to name a few.[5] The advantages of MCR chemistry can be summarized as follows: (1) MCRs are one-pot reactions; currently most of the chemical products on the market are made by a sequential multistep synthesis. If a structurally elaborated compound can be synthesized in one (or a few) step(s) this is advantageous in terms of effort, cost, and time. (2) MCR products are assembled by three or more starting materials; therefore, the complexity of the resulting products is higher than in a typical two-component process; the complexity of organic compounds plays an important role in the selective and potent recognition of biological matter. (3) MCRs typically rely on a set of starting materials which are commercially available; the consequence is that a very large chemical space can be accessed; thus, Ivar Ugi mentioned in his monography *Isonitrile Chemistry* from 1970, "If for example, 40 each of the different components are reacted with one another (in the Ugi-4CR), the result is 40^4 = 2,560,000 reaction products, which is quite a high figure considering that it is of the same order of magnitude as the total number of chemical compounds described to date."[6] To date, hundreds of MCRs have been described leading to a great diversity of scaffolds.[7]

Polycyclic compounds have been of special interest to synthetic organic chemists. We and others recently recognized the value of combining the Ugi and Pictet-Spengler reactions in the synthesis of complex polycyclic products (Scheme 2).[8] EI Kaïm et al. used α-ketocarboxylic acids (**5**) together with phenylethyl isocyanides (**8**), primary amines (**7**), and aldehydes (**6**) to yield polycyclic products (**9**) in two steps and overall satisfactory yields. We recently introduced electron-rich indolethylamine-derived isocyanides for the reaction with

(2) (a) Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 8–21. (b) Ugi, I.; Dömling, A.; Horl, W. *Endeavour* **1994**, *18*, 115–122. (c) Ugi, I.; Dömling, A.; Gruber, B.; Almstetter, M. *Croat. Chem. Acta* **1997**, *70*, 631–647.

(3) Ugi, I.; Steinbrueckner, C. (Aktiebolaget Astra Apotekarnes Kemiska Fabriker) Patent Application DE1103337, 1961

(4) (a) Akritopoulou-Zanze, I. *Curr. Opin. Chem. Biol.* **2008**, *12*, 324–331. (b) Dömling, A.; Wang, K.; Wang, W. *Chem. Rev.* **2010**, submitted.

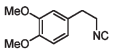
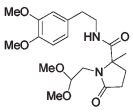
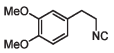
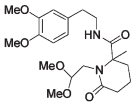
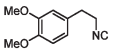
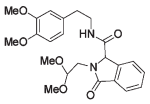
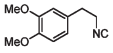
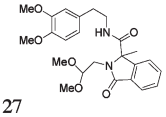
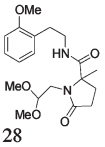
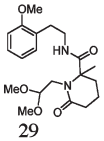
(5) (a) Aissaoui, H.; Cappi, M.; Clozel, M.; Fischli, W.; Koberstein, R. (Actelion Pharmaceuticals Ltd., Switzerland) Patent Application WO2001068609, 2001. (b) Liddle, J.; Allen, M. J.; Borthwick, A. D.; Brooks, D. P.; Davies, D. E.; Edwards, R. M.; Exall, A. M.; Hamlett, C.; Irving, W. R.; Mason, A. M.; McCafferty, G. P.; Nerozzi, F.; Peace, S.; Philp, J.; Pollard, D.; Pullen, M. A.; Shabbir, S. S.; Sollis, S. L.; Westfall, T. D.; Woollard, P. M.; Wu, C.; Hickey, D. M. B. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 90–94. (c) Prongay, A. J.; Guo, Z.; Yao, N.; Pichardo, J.; Fischmann, T.; Strickland, C.; Myers, J.; Weber, P. C.; Beyer, B. M.; Ingram, R.; Hong, Z.; Prosise, W. W.; Ramanathan, L.; Taremi, S. S.; Yarosh-Tomaine, T.; Zhang, R.; Senior, M.; Yang, R.-S.; Malcolm, B.; Arasappan, A.; Bennett, F.; Bogen, S. L.; Chen, K.; Jao, E.; Liu, Y.-T.; Lovey, R. G.; Saksena, A. K.; Venkatraman, S.; Girijavallabhan, V.; Njoroge, F. G.; Madison, V. *J. Med. Chem.* **2007**, *50*, 2310–2318.

(6) Ugi, I. *Isonitrile Chemistry*; Academic Press: New York, 1971.

(7) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89.

(8) (a) El Kaim, L.; Gageat, M.; Gaultier, L.; Grimaud, L. *Synlett* **2007**, 500–502. (b) Liu, H.; Dömling, A. *J. Org. Chem.* **2009**, *74*, 6895–6898. (c) Wang, W.; Herdtweck, E.; Dömling, A. *Chem. Commun.* **2010**, *46*, 770–772. (d) Sapi, J.; Laronze, J.-Y. *ARKIVOC* **2004**, 208–222. (e) Znabet, A.; Zonneveld, J.; Janssen, E.; De Kanter, F. J. J.; Helliwell, M.; Turner, N. J.; Ruijter, E.; Orru, R. V. A. *Chem. Commun.* **2010**, *46*, 7706–7708.

TABLE 1. Products and Yields of the Primary Ugi Reaction

Oxocarboxylic acid	Isocyanide	Product	Yield[a]
			62%
18	8	24	
			40%
19	8	25	
			50%
20	8	26	
			55%
21	8	27	
			60%
18	22	28	
			57%
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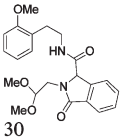
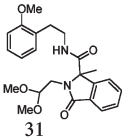
			45%
20	22	30	
			45%
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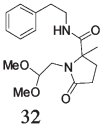
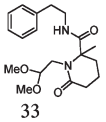
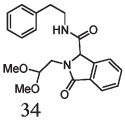
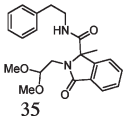
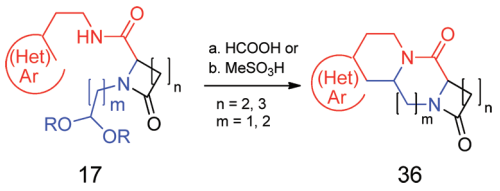
			60%
18	23	32	
			32%
19	23	33	
			38%
20	23	34	
			54%
21	23	35	

[a]Isolated yields after column chromatography.

SCHEME 4. Pictet–Spengler Reaction of the Ugi Intermediates



17 36

aminoacetaldehyde (**11**), carboxylic acids, and aldehydes in the two-step sequence Ugi–Pictet–Spengler reactions.[8c] Both syntheses naturally yield different scaffolds with different substitution patterns. Here we elaborate on our previous reaction sequence and describe the synthesis of a small focused library of polycyclic products based on phenylethylamine-derived isocyanides in full experimental detail. The resulting polyheterocycles are different from our previously described indole polyheterocyles by their structure but also by their presumably different biological activities. Moreover, the reaction conditions and stereochemical outcome for the Pictet–Spengler reaction are different from the previous indole chemistry and therefore deserve detailed description.

Results and Discussion

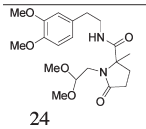
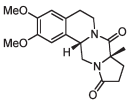
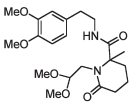
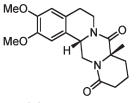
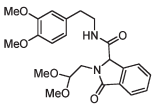
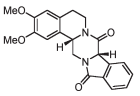
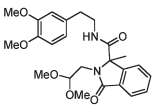
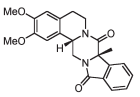
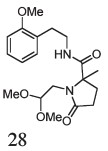
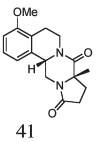
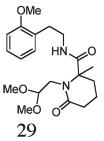
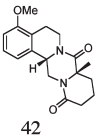
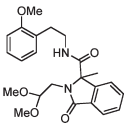
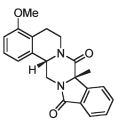
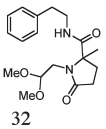
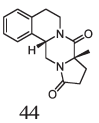
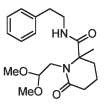
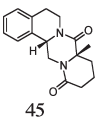
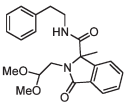
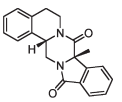
The first step toward accessing the herein described polycyclic compounds is a Ugi-3CR of a phenylethylamine-derived isocyanide (**14**) and aminoacetaldehyde dimethyl acetal (**15**) with a suitable bifunctional oxocarboxylic acid (**16**) (Scheme 3, Table 1). For the investigation on scope and limitation of this two step-procedure we used electronically neutral phenylethyl isocyanide (**23**) as well as electron-rich 3,4-dimethoxy- and 2-methoxyphenylethyl isocyanide (**8**, **22**), which can be easily accessed from their primary amine precursors in multigram amounts either via Ugi's two-step procedure (formylation, dehydration) or in one step via Hoffmann's procedure.[9] The Ugi reaction gives medium yields of **17** ranging from 38 to 62%. It is noteworthy that aliphatic oxocarboxylic acids **18** and **19** reacted similarly satisfactorily toward 5- and 6-membered rings and aromatic *o*-formylbenzoic acid and 2-carboxyacetophenone **20** and **21**, despite their different electronical and sterical features (Table 1). Interestingly, no systematic reactivity difference between aromatic acetophenone (**21**) and benzaldehyde (**20**) and aliphatic ketones **18** and **19** was observed, despite the formation of a quaternary and tertiary carbon center, respectively. In fact, all oxocarboxylic acids (**16**) reacted satisfactorily.

The next step involves a Pictet–Spengler reaction of the dimethyl acetal protected Ugi intermediates **24**–**35** (Scheme 4).[10] The conditions for this ring closure are formic acid or methanesulfonic acid and have been chosen according to previous optimizations of this reaction sequence, albeit using different isocyanide inputs.[8c] The formic acid ring-forming condition at room temperature is good for the more reactive dimethoxyphenyl Ugi products **24**–**27**. For the less reactive monomethoxy phenyl or

(9) (a) Ugi, I.; Fetzer, U.; Eholzer, U.; Knupfer, H.; Offermann, K. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 472–484. (b) Weber, W. P.; Gokel, G. W.; Ugi, I. K. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 530–531.

(10) (a) Pictet, A.; Spengler, T. *Chem. Ber.* **1911**, *44*, 2030–2036. (b) Whaley, W. M.; Govindachari, T. R. In *Organic Reactions*; Adams, R., Ed.; John Wiley & Sons: New York, 1951; Vol. 6, pp 151–190.

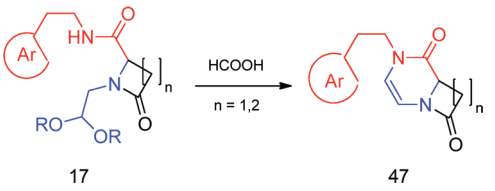
TABLE 2. Products and Yields of the Secondary Pictet–Spengler Reaction

Ugi	Pictet Spengler	Yields	Diastereomeric ratio[c]
 24	 37	62%[a]	>95:5
 25	 38	60%[a]	>95:5
 26	 39	20%[a]	>95:5
 27	 40	26%[a]	>95:5
 28	 41	68%[b]	87:13
 29	 42	80%[b]	70:30
 31	 43	25%[b]	95:5
 32	 44	64%[b]	95:5
 33	 45	75%[b]	80:20
 35	 46	26%[b]	95:5

[a]Formic acid/room temperature conditions. [b]Methanesulfonic acid/70 °C conditions.

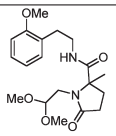
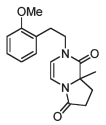
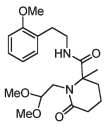
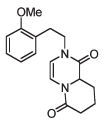
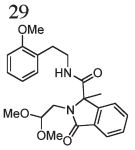
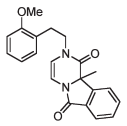
phenyl Ugi products **28**–**31**, formic acid was ineffective; however, methanesulfonic acid at 70 °C with longer reaction time was found to be effective for the cylization. The methanesulfonic acid conditions were also employed for the electron-neutral phenylethyl isocyanide derived Ugi products **32**–**35**. The crude Pictet–Spengler reactions of the aliphatic ketoacid-derived Ugi products were very clean as confirmed by reaction

SCHEME 5. Side Products Formed during Formic Acid Attempted Pictet–Spengler Reaction



17 47

TABLE 3. Products and Yields of the Primary Ugi Reaction

Ugi	Pictet-Spengler	Yields
 28	 47	60%[a]
 29	 48	54%[a]
 31	 49	72%[a]

[a]Formic acid/room temperature conditions.

NMR analysis; the separated yields after chromatography for these transformations were good to satisfactory (**37**, **38**, **41**, **42**, **44**, **45**). The yields of aromatic ketoacid-derived Ugi products, however, are rather low (**39**, **40**, **43**, **46**). TLC analysis showed the formation of additional spots pointing toward possible side reactions of the phenyl ring under the acid conditions (Table 2). The ring-closing reaction of the 2-formylbenzoic acid derived Ugi products **30** and **34** under methanesulfonic acid conditions was complex, and no product could be separated. High diasteromeric ratios (>90%) were observed for the cyclization except for **28**, **29**, and **33** (Table 2).

The 2-methoxyphenylethyl isocyanide derived Ugi products reacted to products **47**–**49** under the formic acid conditions; they are likely formed due to intramolecular condensation and didehydro diketopiperazine formation without subsequent Pictet–Spengler condensation (Scheme 5, Table 3). The structure assignment is based on the presence of olefinic protons at ~5.75 ppm as well as literature precedence.[11] The same products could also be observed under methanesulfonic acid conditions after a short reaction period. Conversely, the isolated didehydro intermediates of the formic acid conditions **48**–**50** could be cleanly converted to the final Pictet–Spengler products under enforced methanesulfonic acid conditions.

To better understand the high diastereomeric ratio during the Pictet–Spengler reaction, we elucidated the relative stereochemistry of the products. First, crystals of **37** suitable for X-ray diffraction were obtained (Supporting Information).

(11) Cheng, J.-F.; Chen, M.; Arrhenius, T.; Nadzan, A. *Tetrahedron Lett.* **2002**, *43*, 6293–6295.

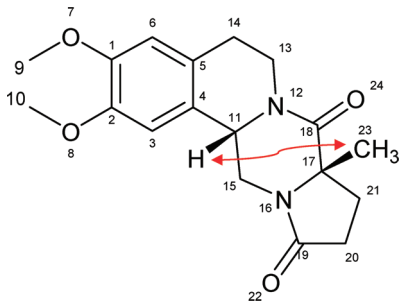


FIGURE 1. Key NOE signal for the configuration analysis of **37**.

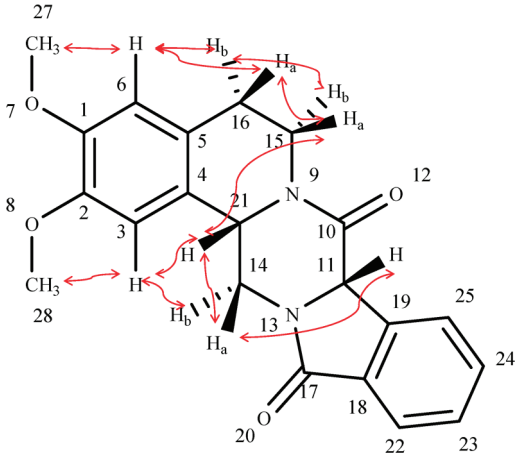
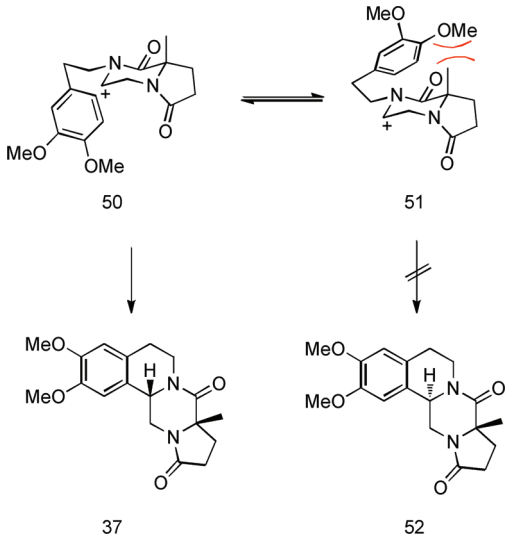


FIGURE 2. NOE analysis of compound **39**.

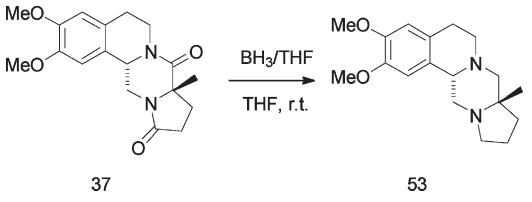
The NOE interaction signal of the proton of C11 and methyl carbon C23 (Figure 1) is consistent with the stereochemistry observed in the crystal structure. The general outcome of the stereochemistry during the Pictet−Spengler reaction could be deduced by analogous 2D NOESY NMR analysis of the same hydrogens except for compound **39**, which is lacking the methyl group (all 2D NMR are included in the Supporting Information). For compound **39**, there is no NOE signal observed between the protons of the two tertiary carbons C11 and C21 (Figure 2). More detailed NOE analysis was used to solve this stereo configuration problem. The *syn* configuration between the proton of C21 and the proton of C11 is determined through their relative configuration to Ha of C14 (full assignment of all protons in the Supporting Information).

Thus, in all cases, the formation of the *syn* diastereomer (e.g., **37**) is strongly preferred over the *anti* diastereomer (e.g., **52**) in the Pictet−Spengler cyclization. This can be possibly explained by the sterical hindrance effect exerted by the 4-methoxyphenyl while approaching from the *si*-face (Scheme 6). In line with this argument, **41** is formed in only moderate diastereoselectivity when **28** with an *o*-methoxyl group is used. When **33** reacts with **44** with a less activated phenyl, high diastereoselectivity is still observed, which currently cannot be explained by this model. Different more drastic and longer reaction conditions can lead to a more thermodynamically determined product mixture. The selectivity is also affected by the adjacent lactam structure, e.g., 6-membered vs 5-membered. There is only moderate diastereoselectivity observed during the cylization of the six-membered-ring lactam compared with all five-membered-ring lactams. In agreement with a recent finding, low diastereoselectivity was observed during the Pictet−Spengler step

SCHEME 6. Model for the Observed High Stereoselectivity during the Pictet−Spengler Reaction



SCHEME 7. Exhaustive Reduction of the Ketopiperazine Moiety to the Piperazine



in the case of indolethyl isocyanide derived Ugi products generally.[8c,e]

Finally, we were interested to perform some selective transformations of our multicyclic systems to alter physicochemical properties. An interesting transformation that occurred is the reduction of the amide groups since it leads to the formation of a bis tertiary amine and thus eventually altering the physicochemical and biological properties of the starting materials. Exhaustive reduction of the two tertiary amides using borane indeed resulted the corresponding highly substituted piperazine (**53**) in medium 45% yield (Scheme 7).

Conclusion

In conclusion, we have shown the two-step formation of condensed tetra- and pentacyclic ring systems by the application of the Ugi-3CR and a subsequent Pictet−Spengler reaction. Such ring systems are of potential interest due to their reported antifungal, antiparasital, and anticancer activities.[8e,12] Scope and limitations of the two-step procedure are discussed. Both reactions can be performed in medium to good yields. An example of a followup reaction

(12) (a) Zhou, Y.; Tang, H.; Zhu, J.; Lv, J.; Zheng, C.; Li, Y. (The Second Military Medical University, PLA, People's Repulic of China) CN101691367, 2010. (b) Tang, H.; Zheng, C.; Lv, J.; Wu, J.; Li, Y.; Yang, H.; Fu, B.; Li, C.; Zhou, Y.; Zhu, J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 979–982. (c) Boissier, J.; Cosledan, F.; Robert, A.; Meunier, B. *Antimicrob. Agents Chemother.* **2009**, *53*, 4903–4906. (d) Dong, Y.; Chollet, J.; Vargas, M.; Mansour, N. R.; Bickle, Q.; Alnouti, Y.; Huang, J.; Keiser, J.; Vennerstrom, J. L. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2481–2484. (e) Dong, G.; Sheng, C.; Wang, S.; Miao, Z.; Yao, J.; Zhang, W. *J. Med. Chem.* **2010**, *53*, 7521–7531.

leading to a bis-tertiary amine product by exhaustive reduction is shown as an outlook.

Experimental Section

General Procedure for Ugi Reaction. A 1 mmol portion of aldehyde or ketone acid was dissolved in 1 mL of MeOH, and 1 mmol of isocyanide and 1 mmol of amino acetal were added into the solution. The solution was stirred for 24 h at rt. The MeOH solvent was evaporated, and the residue was purified by SiO_2 column chromatography to give the Ugi product.

Compound 24: $C_{20}H_{30}N_2O_6$, M_w 394.45 g/mol; HRMS (ESI-TOF) *m*/*z* calcd for $C_{20}H_{29}N_2O_6Na$ 417.2002, found 417.2020; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.46 (3H, s), 1.95 (1H, m, J=4.78 Hz), 2.19 (1.0H, d, J=11.71 Hz), 2.28 (3H, m, J=5.06 Hz), 2.62 (1H, t, J=6.42 Hz), 2.77 (2H, t, J=6.97 Hz), 2.90 (1H, dd, J=6.33, 14.19 Hz), 3.36 (1H, m, J=7.37 Hz), 3.40 (3H, s), 3.42 (3H, s), 3.55 (1H, dd, J=4.52, 14.06 Hz), 3.59 (1H, dt, J=7.06, 6.77 Hz), 3.86 (3H, s), 3.88 (3H, s), 4.94 (1H, dd, J=4.77, 6.25 Hz), 6.72 (1H, d, J=7.62 Hz), 6.73 (1H, s), 6.81 (1H, d, J=7.86 Hz), 7.44 (1H, t, J=5.10 Hz); ^{13}C NMR ($CDCl_3$, 150.92 MHz) δ 22.0, 29.3, 34.0, 35.1, 41.0, 43.9, 54.9, 55.8, 55.9, 56.1, 67.9, 101.9, 111.2, 111.7, 120.6, 131.3, 147.7, 149.0, 173.7, 177.5.

Compound 25: $C_{21}H_{32}N_2O_6$, M_w 408.49 g/mol; HRMS (ESI-TOF) *m*/*z* calcd for $C_{21}H_{32}N_2O_6Na$ 431.2158, found 431.2169; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.49 (3H, s), 1.67 (1H, m), 2.18 (2H, m), 2.26 (1H, m), 2.36 (2H, m), 2.77 (2H, m), 3.00 (1H, m), 3.41 (6H, m), 3.49 (1H, m), 3.61 (2H, m), 3.86 (6H, m), 5.03 (1H, m), 6.72 (2H, m), 6.80 (1.0H, t, J=7.18 Hz), 7.44 (1H, s); ^{13}C NMR ($CDCl_3$, 150.92 MHz) δ 17.2, 24.5, 30.9, 32.7, 35.1, 36.5, 39.3, 41.1, 47.9, 53.4, 55.7, 55.8, 55.9, 56.5, 66.8, 103.0, 111.2, 111.3, 111.8, 120.6, 131.4, 147.7, 149.0, 173.0, 173.6.

Compound 26: $C_{23}H_{28}N_2O_6$, M_w 428.48 g/mol; HRMS (ESI-TOF) *m*/*z* calcd for $C_{23}H_{28}N_2O_6Na$ 451.1845, found 451.1810; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.69 (2H, m), 3.09−3.21 (1H, m), 3.27 (1.0H, m), 3.32−3.45 (6H, m), 3.75 (3H, s), 3.80 (3H, s), 4.69 (1H, t, J=5.49 Hz), 5.15 (1H, s), 6.52 (1H, d, J=7.92 Hz), 6.58 (1H, s), 6.66 (1H, d, J=8.10 Hz), 7.03 (1H, w), 7.38 (1H, t, J=7.35 Hz), 7.51 (1H, t, J=7.50 Hz), 7.57 (1H, d, J=7.50 Hz), 7.62 (1H, d, J=7.56 Hz); ^{13}C NMR ($CDCl_3$, 150.92 MHz) δ 14.2, 34.8, 40.8, 44.0, 54.5, 54.7, 55.7, 55.8, 65.7, 102.0, 111.2, 111.7, 120.6, 122.9, 123.4, 128.8, 130.3, 130.9, 132.4, 141.7, 147.6, 148.9, 167.8, 170.1.

Compound 27: $C_{24}H_{30}N_2O_6$, M_w 442.50 g/mol; HRMS (ESI-TOF) *m*/*z* calcd for $C_{24}H_{30}N_2O_6Na$ 465.2002, found 465.2023; HPLC-MS t_R 9.72, found *m*/*z* $[M + Na]^+$464.9, $[M - H]^-$ 441; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.71 (3H, s), 1.81 (3H, s), 2.36 (1H, s), 2.60−2.63 (2H, m), 3.16 (1H, dd, J=7.20, 14.10 Hz), 3.24−3.27 (1H, m), 3.31 (3.0H, s), 3.39 (3H, s), 3.46−3.48(1H, m), 3.49 (3H, s), 3.71 (1H, dd, J=4.49, 14.03 Hz), 4.39 (0.7H, t, J=5.29 Hz), 5.30−5.34 (2H, m), 6.42 (1H, dd, J=1.81, 8.04 Hz), 6.54 (1H, d, J=1.68 Hz), 6.64 (1H, d, J=8.31 Hz), 7.17 (1H, q, J=6.92 Hz), 7.26 (1H, t, J=6.84 Hz), 7.46 (1H, d, J=16.02 Hz), 7.50 (2H, dd, J=4.08, 6.72 Hz), 7.52−7.57 (2H, m), 7.68 (1H, dd, J=1.05, 7.46 Hz), 7.71 (1H, d, J=7.62 Hz), 7.78 (1H, d, J=7.44 Hz), 7.87 (1H, d, J=7.93 Hz); ^{13}C NMR ($CDCl_3$, 150.92 MHz) δ 22.1, 27.4, 34.9, 41.1, 43.3, 44.6, 53.4, 53.6, 55.3, 55.7, 55.9, 56.6, 69.9, 101.1, 102.1, 103.0, 111.1, 111.6, 120.6, 122.3, 122.6, 123.3, 125.3, 125.5, 127.8, 128.2, 128.8, 129.0, 129.3, 130.1, 131.2, 132.7, 134.3, 147.5, 147.8, 148.8, 149.4, 169.0, 170.0, 170.5.

Compound 28: $C_{19}H_{28}N_2O_5$, M_w 364.44 g/mol; HRMS (ESI-TOF) *m*/*z* calcd for $C_{19}H_{28}N_2O_5Na$ 387.1896, found 387.1914; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.45 (3H, s), 1.90 (1H, m), 2.26 (3H, m), 2.83 (2H, m, J=6.97 Hz), 2.94 (1H, dd, J=6.30, 14.16 Hz), 3.50 (1H, dd, J=4.56, 14.16 Hz), 3.59 (1H, q, J=6.54 Hz), 4.87 (1H, dd, J=4.71, 6.15 Hz), 6.86 (1H, d, J=8.22 Hz), 6.88 (1H, dt, J=0.75, 7.40 Hz), 7.10 (1H, d, J=7.32 Hz), 7.20 (1H, dt, J=1.44, 7.80 Hz); ^{13}C NMR ($CDCl_3$, 150.92 MHz) δ 22.1, 27.6, 29.3, 29.9, 33.9, 38.0, 39.8, 43.9, 53.5, 54.7, 55.4, 55.7, 60.4, 67.8, 76.9, 77.1, 77.3, 101.8, 110.4, 120.6, 127.2, 127.9, 130.4, 157.5, 173.5, 177.4.

Compound 29: $C_{20}H_{30}N_2O_5$, M_w 378.46 g/mol; HRMS (ESI-TOF) *m*/*z* calcd for $C_{20}H_{30}N_2O_5Na$ 401.2052, found 401.2081; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.49 (3H, s), 1.56−1.58 (1H, m), 1.65 (3H, m), 2.24 (1H, m), 2.37 (2H, m), 2.81 (1H, m), 2.89 (1H, m), 3.09 (1.0H, dd, J=6.09, 13.95 Hz), 3.38 (3H, s), 3.42 (3H, s), 3.62 (1H, m), 3.85 (3H, s), 5.00 (1H, d, J=11.04 Hz), 6.87 (1H, d, J=8.16 Hz), 6.90 (1H, d, J=14.76 Hz), 6.90 (1H, t, J=7.38 Hz), 7.13 (1H, dd, J=1.41, 7.35 Hz), 7.22 (1H, dt, J=1.50, 7.80 Hz), 7.30 (1H, w); ^{13}C NMR ($CDCl_3$, 150.92 MHz) δ 17.2, 24.6, 30.0, 32.7, 36.5, 39.9, 47.8, 55.4, 55.6, 56.0, 66.7, 76.8, 77.0, 77.2, 102.8, 110.4, 127.3, 127.9, 130.4, 157.6, 172.9, 173.5.

Compound 30: $C_{22}H_{26}N_2O_5$, M_w 398.45 g/mol; HRMS (ESI-TOF) *m*/*z* calcd for $C_{22}H_{26}N_2O_5Na$ 421.1739, found 421.1747; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.64−2.81 (2H, m), 3.19 (1H, s), 3.25(1H, s), 3.26(1H, s), 3.27 (2H, m), 3.37(3H, s) 3.38(3H, s), 3.44−3.48 (2H, m), 3.78 (2H, s), 3.83−3.88(2H, m), 4.73−4.78(1H, m), 5.16 (1H, s), 6.52 (1H, s), 6.79 (2H, dd, J=7.73, 15.27 Hz), 6.83−6.93 (3H, m), 7.16 (1H, d, J=17.34 Hz), 7.24 (1H, m), 7.53 (2H, dd, J=7.41, 14.91 Hz), 7.58 (2H, dt, J=1.10, 7.52 Hz), 7.68 (1H, dd, J=0.60, 7.56 Hz), 7.84 (1H, d, J=7.44 Hz); ^{13}C NMR ($CDCl_3$, 150.92 MHz) δ 29.5, 40.1, 44.0, 53.4, 55.4, 65.7, 102.0, 110.4, 120.7, 123.1, 123.6, 126.8, 128.0, 128.9, 130.5.

Compound 31: $C_{23}H_{28}N_2O_5$, M_w 412.49 g/mol; HRMS (ESI-TOF) *m*/*z* calcd for $C_{23}H_{28}N_2O_5Na$ 435.1896, found 435.1932; HPLC-MS t_R 10.39, *m*/*z* $[M + Na]^+$ 434.9, $[M - H]^-$ 411.1; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.72 (3H, s), 2.60 (1H, m), 2.76 (1H, m), 3.19 (1H, q, J=7.06 Hz), 3.27 (1H, d, J=7.14 Hz), 3.32 (1H, s), 3.36 (3H, s), 3.47 (3H, s), 3.68 (1H, dd, J=4.47, 14.07 Hz), 3.73 (3H, s), 5.25 (1H, dd, J=4.41, 7.05 Hz), 6.70 (2H, d, J=4.32 Hz), 6.75 (1H, d, J=8.16 Hz), 7.12 (1H, dd, J=4.23, 8.49 Hz), 7.50 (1H, t, J=7.77 Hz), 7.51 (1H, d, J=6.84 Hz), 7.58 (1H, t, J=7.50 Hz), 7.70 (1H, d, J=7.62 Hz), 7.81 (1H, d, J=7.50 Hz); ^{13}C NMR ($CDCl_3$, 150.92 MHz) δ 14.2, 29.7, 39.8, 44.5, 55.1, 55.2, 56.1, 60.4, 101.9, 103.0, 110.2, 120.4,122.6, 123.3, 127.0, 127.7, 128.8, 129.4, 130.1, 130.4, 132.6, 148.0, 157.3, 169.8.

Compound 32: $C_{18}H_{26}N_2O_4$, M_w 334.41 g/mol; HRMS (ESI-TOF) *m*/*z* calcd for $C_{18}H_{26}N_2O_4Na$ 357.1790, found 357.1796; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.45 (3H, s), 1.90−1.95 (1H, m), 2.23−2.29 (3H, m), 2.79−2.84 (2H, m), 2.88 (1H, dd, J=6.36, 14.16 Hz), 3.35 (3H, s), 3.40 (3H, s), 3.53 (1H, dd, J=4.55, 14.01 Hz), 3.64 (1H, dt, J=6.71, 13.51 Hz), 4.93 (1.0H, dd, J=4.59, 6.33 Hz), 7.18 (2H, d, J=6.80 Hz), 7.21 (1H, t, J=7.41 Hz), 7.30 (2H, t, J=7.53 Hz), 7.43 (1H, w); ^{13}C NMR ($CDCl_3$, 150.92 MHz) δ 22.0, 29.3, 33.9, 35.4, 40.8, 43.9, 53.5, 54.8, 56.2, 67.9, 101.8, 126.5, 128.6, 128.7, 138.9, 173.6, 177.4.

Compound 33: $C_{19}H_{28}N_2O_4$, M_w 348.44 g/mol; HRMS (ESI-TOF) *m*/*z* calcd for $C_{19}H_{28}N_2O_4Na$ 371.1946, found 371.1937; ^{1}H NMR ($CDCl_3$, 600 MHz) 1.48 (3H, s), 1.53−1.59 (1H, m), 1.63−1.67 (2H, m), 2.23−2.27 (1H, m), 2.34−2.37 (2H, m), 2.84 (2H, t, J=7.18 Hz), 2.97 (1H, dd, J=6.45, 13.98 Hz), 3.35 (3H, s), 3.36−3.39 (1H, m), 3.42 (3H, s), 3.52 (1H, dd, J=4.74, 13.98 Hz), 3.69 (1H, dt, J=6.80, 6.73 Hz), 5.04 (1H, dd, J=4.83, 6.33 Hz), 7.20 (2H, d, J=7.68 Hz), 7.23 (1H, d, J=7.20 Hz), 7.31 (2H, t, J=7.52 Hz), 7.50 (1H, s); ^{13}C NMR ($CDCl_3$, 150.92 MHz) δ 17.2, 24.4, 32.7, 35.5, 36.5, 41.0, 47.9, 55.7, 56.5, 66.8, 102.9, 126.5, 128.6, 128.7, 139.0, 173.0, 173.6.

Compound 34: $C_{21}H_{24}N_2O_4$, M_w 368.43 g/mol; HRMS (ESI-TOF) *m*/*z* calcd for $C_{21}H_{24}N_2O_4Na$ 391.1634, found 391.1646; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.69−2.78 (2H, m), 3.25 (1H, d, J=6.42 Hz), 3.37 (3H, s), 3.40 (3H, s), 3.54 (1H, ddd, J=6.43, 0.03, 13.24 Hz), 3.74 (1H, dd, J=5.31, 14.31 Hz), 4.82 (1H, t, J=5.43 Hz), 5.15 (1H, s), 6.56 (1H, w), 6.95 (2H, dd, J=1.71, 7.29 Hz), 7.18 (2H, d, J=7.14 Hz), 7.53 (1H, t, J=7.55 Hz), 7.61 (1H, dt, J=0.75, 3.75 Hz), 7.71 (1H, d, J=7.62 Hz), 7.82 (1H, d, J=7.50 Hz); ^{13}C NMR ($CDCl_3$, 150.92 MHz) δ 35.2, 40.7, 44.6,

54.7, 55.1, 65.8, 102.0, 123.2, 123.7, 126.5, 128.6, 128.7, 129.0, 130.4, 132.5, 138.3, 141.7, 167.8, 170.3.

Compound 35: $C_{22}H_{26}N_2O_4$, M_w 381.18 g/mol; HRMS (ESI-TOF) m/z calcd for $C_{22}H_{26}N_2O_4Na$ 405.1790, found 405.1767; HPLC-MS t_R 10.26, m/z $[M + Na]^+$ 405.1; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.69 (3H, s), 2.60−2.64 (2H, m), 3.17 (2H, ddd, J = 7.33, 13.58, 25.46 Hz), 3.28 (3H, s), 3.43 (3H, s), 3.53 (1H, ddd, J = 6.30, 0.20, 13.00 Hz), 3.66 (1H, dd, J = 4.47, 14.19 Hz), 5.25 (1H, dd, J = 4.46, 7.05 Hz), 5.26 (0.6H, s), 6.80−6.82 (2H, d, J = 9.06 Hz), 7.09−7.10 (3H, m), 7.47 (2H, t, J = 7.47 Hz), 7.56 (1.0H, t, J = 7.55 Hz), 7.70 (1.0H, d, J = 7.80 Hz), 7.74 (1.0H, d, J = 7.56 Hz); ^{13}C NMR ($CDCl_3$, 150.92 MHz) δ 21.9, 35.2, 41.0, 44.5, 55.1, 56.5, 70.0, 76.9, 77.2, 77.4, 102.0, 122.5, 123.3, 126.3, 128.3, 128.6, 128.8, 129.4, 132.6, 138.7, 147.8, 169.9, 170.4.

General Procedure A for Pictet−Spengler reaction. A 0.1 mmol portion of Ugi product was dissolved in 0.5 mL of HCOOH and stirred for 4 h at rt, excess HCOOH was evaporated, and the residue was purified by preparative TLC or column chromatography to give the corresponding polycyclic product.

Compound 37: $C_{18}H_{22}N_2O_4$, M_w 330.38 g/mol; HRMS (ESI-TOF) m/z calcd for $C_{18}H_{22}N_2O_4$ 330.1580, found 330.1583; HPLC-MS t_R 8.24, m/z $[M + Na]^+$ 353.1; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.56 (3H, s), 2.12 (1H, ddd, J = 1.82, 9.00, 13.02 Hz), 2.18 (1H, m, J = 6.69 Hz), 2.27 (1H, ddd, J = 1.82, 9.44, 16.85 Hz), 2.51 (1H, td, J = 9.82, 17.2 Hz), 2.62 (0.5H, t, J = 6.48 Hz), 2.73 (1.5H, m), 2.97 (1H, ddd, J = 5.81, 0.02, 16.01 Hz), 3.07 (1H, ddd, J = 4.79, 10.52, 12.77 Hz), 3.70 (1H, dd, J = 4.80, 13.56 Hz), 3.86 (3H, s), 3.90 (3H, s), 4.20 (1H, dd, J = 5.67, 12 Hz), 4.60 (1H, ddd, J = 3.55, 5.88, 12.75 Hz), 4.79 (1H, t, J = 5.25 Hz), 6.64 (1H, s), 6.82 (1H, s); ^{13}C NMR ($CDCl_3$, 150.92 MHz) δ = 23.2, 27.7, 29.4, 30.9, 39.5, 41.1, 54.4, 55.9, 56.1, 62.4, 107.5, 111.7, 125.7, 127.2, 147.7, 148.4, 172.0, 173.4.

Single-Crystal X-ray Structure Determination of Compound 37. Crystal data and details of the structure determination (see also Supporting Information) formula: $C_{18}H_{22}N_2O_4$; M_r = 330.38; crystal color and shape, colorless fragment, crystal dimensions = 0.30 × 0.36 × 0.69 mm; crystal system, monoclinic; space group $P2_1/c$ (no. 14); a = 10.2111(2) Å, b = 13.3943(3) Å, c = 12.6770(3) Å, β = 108.913(1)°; V = 1640.23(6) Å^3 ; Z = 4; μ(Cu Kα) = 0.779 mm^{-1}; ρ_{calc} = 1.338 gcm^{-3}; θ range = 4.58−66.20°; data collected, 20660; independent data [$I_o > 2\sigma(I_o)$/all data/R_{int}], 2538/2766/0.029; data/restraints/parameters, 2766/0/306; R1 [$I_o > 2\sigma(I_o)$/all data], 0.0350/0.0378; wR2 [$I_o > 2\sigma(I_o)$/all data], 0.0907/0.0941; GOF = 1.032; $\Delta\rho_{max/min}$, 0.18/−0.19 e Å^{-3}. CCDC 786934 (**37**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Compound 38: $C_{19}H_{24}N_2O_4$, M_w 344.40 g/mol; HRMS (ESI-TOF) m/z calcd for $C_{18}H_{22}N_2O_4Na$ 367.1633, found 367.1637; HPLC-MS t_R 8.41, m/z $[M + Na]^+$ 366.8; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.60 (3H, s), 1.65 (1H, dd, J = 3.45, 13.89 Hz), 1.76 (0.7H, q, J = 3.54 Hz), 1.87 (1H, m, J = 2.88 Hz), 2.18 (1H, ddd, J = 7.25, 0.11, 18.26 Hz), 2.25 (1H, d, J = 13.86 Hz), 2.41 (1H, dd, J = 6.12, 18.05 Hz), 2.73 (1H, td, J = 4.49, 16.05 Hz), 3.01 (1H, ddd, J = 6.63, 9.66, 16.17 Hz), 3.13 (1H, ddd, J = 5.37, 0.06, 12.69 Hz), 3.51 (1H, dd, J = 4.35, 14.49 Hz), 3.86 (3H, s), 3.89 (3H, s), 4.57 (1H, ddd, J = 3.66, 6.55, 12.73 Hz), 4.64 (1H, t, J = 3.78 Hz), 5.14 (1H, dd, J = 3.02, 14.35 Hz), 6.62 (1H, s), 6.97 (1H, s); ^{13}C NMR ($CDCl_3$, 150.92 MHz) δ 16.3, 23.3, 27.6, 31.0, 32.5, 37.3, 42.3, 54.8, 55.9, 56.1, 61.3, 107.6, 111.6, 126.6, 127.2, 147.4, 148.2, 169.0, 170.7.

Compound 39: $C_{21}H_{20}N_2O_4$, M_w 364.39 g/mol; HRMS (ESI-TOF) m/z calcd for $C_{21}H_{20}N_2O_4Na$ 387.1321, found 387.1331; HPLC-MS t_R 9.41, m/z $[M + H]^+$ 365.1, $[M + Na]^+$ 387.2; ^1H NMR ($CDCl_3$, 600 MHz) δ 2.70 (2H, m, J = 5.91 Hz), 2.98 (1H, m, J = 8.15 Hz), 3.29 (1H, dd, J = 10.80, 13.62 Hz), 3.88 (3H, s), 3.92 (3H, s), 4.83 (1H, dd, J = 4.39, 10.72 Hz), 4.91 (1H, ddd, J = 2.52, 4.86, 13.32 Hz), 5.04 (1H, dd, J = 4.86, 13.62 Hz), 5.22 (1H, s), 6.66 (1H, s), 6.74 (1H, s), 7.55 (1H, t, J = 7.55 Hz), 7.66 (1H, dt, J = 0.98, 3.72 Hz), 7.89 (1H, d, J = 7.56 Hz), 8.05 (1H, d, J = 7.55 Hz); ^{13}C NMR ($CDCl_3$, 150.92 MHz) δ 28.4, 39.3, 43.9, 56.0, 56.2, 56.3, 60.2, 107.8, 111.7, 123.7, 124.3, 125.0, 126.9, 129.2,131.7, 132.6, 140.5, 148.2, 148.4, 164.5, 168.3.

Compound 40: $C_{22}H_{22}N_2O_4$, M_w 378.42 g/mol; HRMS (ESI-TOF) m/z calcd for $C_{22}H_{22}N_2O_4Na$ 401.1477, found 401.1509; HPLC-MS t_R 9.32, m/z $[M + Na]^+$400.9; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.86 (3H, s), 2.69 (1.0H, td, J = 4.56, 16.08 Hz), 2.88 (1.0H, ddd, J = 6.15, 0.02, 16.07 Hz), 3.17 (1.0H, ddd, J = 5.29, 9.95, 12.83 Hz), 3.83 (2.6H, s), 3.89 (0.4H, d, J = 7.14 Hz), 3.96 (1.4H, dd, J = 5.46, 14.10 Hz), 3.99 (2.6H, s), 4.52 (1.0H, ddd, J = 4.05, 6.15, 12.93 Hz), 4.75 (0.9H, dd, J = 4.26, 14.10 Hz), 4.90 (0.9H, t, J = 4.74 Hz), 6.57 (0.9H, s), 7.06 (0.9H, s), 7.45 (0.9H, t, J = 7.55 Hz), 7.59 (1.0H, t, J = 7.18 Hz), 7.73 (0.9H, d, J = 7.85 Hz), 7.95 (0.9H, d, J = 7.55 Hz); ^{13}C NMR ($CDCl_3$, 150.92 MHz) δ 25.3, 27.5, 38.3, 41.6, 55.9, 56.0, 56.2, 64.5, 107.9, 111.6, 123.4, 124.6, 125.9, 127.2, 128.7, 130.3, 132.2, 146.3, 147.6, 148.4, 167.3.

Side Products of the Pictet−Spengler Reaction. Compound 47: $C_{17}H_{20}N_2O_3$, M_w 300.35 g/mol; HRMS (ESI-TOF) m/z calcd for $C_{17}H_{20}N_2O_3$ 300.1473, found 300.1469; ^1H NMR ($CDCl_3$, 600 MHz) δ 2.16 (1H, dd, J = 9.72, 11.82 Hz), 2.34 (1H, dd, J = 11.31, 22.29 Hz), 2.43 (1H, dd, J = 9.66, 17.04 Hz), 2.54 (1H, dd, J = 9.00 Hz), 2.86(1H, m), 2.91(1H, m), 3.76 (1H, m), 3.84 (3H, s), 5.62 (1H, d, J = 4.56 Hz), 6.24 (1H, d, J = 4.80 Hz), 6.85 (2H, t, J = 8.10 Hz), 7.07 (1H, d, J = 7.14 Hz), 7.21 (1H, t, J = 7.77 Hz); ^{13}C NMR ($CDCl_3$, 150.92 MHz) δ 20.6, 29.2, 29.6, 29.7, 46.2, 55.3, 61.8, 104.6, 110.2, 117.0, 120.4, 126.1, 128.1, 130.7, 157.6, 167.9, 171.8.

Compound 48: $C_{18}H_{22}N_2O_3$, M_w 314.38 g/mol; HRMS (ESI-TOF) m/z calcd for $C_{18}H_{22}N_2O_3Na$ 337.1528, found 337.1513; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.28 (3H, s), 1.89 (2H, m), 2.24 (1H, m), 2.39 (1.0H, m), 2.52 (1H, m), 2.87 (1H, m), 2.94 (1H, m), 3.74 (2H, m), 3.85 (3H, s), 5.64 (1H, d, J = 6.06 Hz), 6.57 (1H, d, J = 6.06 Hz), 6.86 (2H, d, J = 7.80 Hz), 6.87 (1H, d, J = 7.08 Hz), 7.09 (1H, dd, J = 1.02, 7.50 Hz), 7.23 (1H, dt, J = 1.68, 7.80 Hz); ^{13}C NMR ($CDCl_3$, 150.92 MHz) δ 16.3, 21.3, 29.6, 29.9, 31.5, 46.4, 55.3, 60.4, 107.4, 110.2, 115.5, 120.4, 126.3, 128.1,130.7, 157.6, 167.8, 168.6.

Compound 49: $C_{21}H_{20}N_2O_3$, M_w 348.40 g/mol; HRMS (ESI-TOF) m/z calcd for $C_{21}H_{20}N_2O_3Na$ $[M + Na]^+$ 371.1372, found 371.1369; HPLC-MS t_R 10.74, m/z $[M + Na]^+$370.8; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.45 (3H, s), 2.86(1H, m), 2.92 (1H, m), 3.77 (2H, m), 3.79 (3H, s), 5.75 (1H, d, J = 5.52 Hz), 6.52 (1H, d, J = 5.52 Hz), 6.84 (2H, d, J = 8.28 Hz), 6.85 (2H, t, J = 7.38 Hz), 7.08 (1H, d, J = 7.26 Hz), 7.21 (1H, t, J = 7.77 Hz), 7.53 (1H, t, J=7.50 Hz), 7.65 (1H, t, J = 7.53 Hz), 7.84 (1H, d, J = 7.56 Hz), 7.98 (1H, d, J = 7.62 Hz); ^{13}C NMR ($CDCl_3$, 150.92 MHz) δ 23.9, 29.6, 46.9, 55.3, 63.5, 105.3, 110.3,118.1, 120.6, 123.6, 124.9, 126.2, 128.2, 129.0, 129.9, 130.7, 132.5, 145.3, 157.6, 165.2, 166.2.

General Procedure B for the Pictet−Spengler Reaction. A 0.1 mmol portion of Ugi product was dissolved in 0.5 mL of methanesulfonic acid and stirred for 24 h at 70 °C. Neutralization with 1 mM Na_2CO_3, extraction with ethyl acetate, and purification by preparative TLC or column chromatography gave the corresponding polycyclic product.

Compound 41: $C_{17}H_{20}N_2O_3$, M_w 300.35 g/mol; HRMS (ESI-TOF) m/z calcd for $C_{17}H_{20}N_2O_3$ 300.1473, found 300.1475; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.27 (3H, s), 2.11 (1H, m), 2.24 (2.0H, m), 2.49 (1H, m), 2.78 (1H, m), 2.89 (1H, d, J = 19.02 Hz), 2.96 (1H, m), 3.71 (1H, dd, J = 5.07, 13.77 Hz), 3.84 (3H, s), 3.86 (0.5H, s), 4.17 (1H, dd, J = 5.76, 13.74 Hz), 4.71 (1H, m), 4.88 (0.5H, m), 6.80 (1H, d, J = 7.93 Hz), 6.92 (1H, d, J = 7.74 Hz), 7.24 (1H, t, J = 8.07 Hz).

Compound 42: $C_{18}H_{22}N_2O_3$, M_w 314.38 g/mol; HRMS (ESI-TOF) *m*/*z* calcd for $C_{18}H_{22}N_2O_3$ 314.1630, found 314.1628; ^{1}H NMR ($CDCl_3$, 600 MHz) (only the major diastereomer is interpreted here) δ 1.59 (3H, s), 1.69 (1H, dt, J = 3.60, 13.67 Hz), 1.75−1.85 (2H, m), 2.18 (1.0H, ddd, J = 7.22, 11.30, 18.26 Hz), 2.25 (1H, d, J = 13.86 Hz), 2.40 (1H, dd, J = 6.21, 18.33 Hz), 2.53 (0.2H, dd, J = 4.71, 18.33 Hz), 2.6−2.90 (1H, m),2.85(1H, m) 3.03 (1H, ddd, J = 5.94, 0.12, 12.84 Hz), 3.54 (1H, dd, J = 4.56, 14.40 Hz), 3.82 (3H, s), 4.69 (1H, ddd, J = 3.09, 0.15, 13.26 Hz), 4.72 (1H, s), 5.07 (1H, dd, J = 3.51, 14.49 Hz), 6.78 (1H, d, J = 8.16 Hz), 7.02 (1H, d, J = 8.34 Hz), 7.20 (1H, t, J = 8.10 Hz); ^{13}C NMR ($CDCl_3$, 150.92 MHz) δ 16.3, 22.3, 23.3, 30.9, 32.5, 38.1, 41.2, 41.6, 55.0, 55.4, 61.0, 109.0, 116.6, 124.0, 127.2, 135.5, 157.0, 169.2, 170.6.

Compound 43: $C_{21}H_{20}N_2O_3$, M_w 348.40 g/mol; HRMS (ESI-TOF) *m*/*z* calcd for $C_{21}H_{20}N_2O_3$ 348.1473, found 348.1469; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.84 (2.9H, s), 2.67 (1.0H, ddd, J = 6.14, 11.24, 17.28 Hz), 2.80 (1.0H, ddd, J = 3.02, 0.19, 17.00 Hz), 3.03 (1.0H, ddd, J = 4.82, 11.43, 12.94 Hz), 3.49 (0.1H, s), 3.77 (2.9H, s), 3.95 (1.0H, dd, J = 5.67, 13.97 Hz), 4.65 (1.0H, ddd, J = 2.74, 6.33, 13.12 Hz), 4.71 (1.0H, dd, J = 4.91, 13.97 Hz), 4.98 (1.0H, t, J = 5.10 Hz), 6.75 (1.0H, d, J = 7.93 Hz), 7.10 (1.0H, d, J = 7.93 Hz), 7.25 (1.9H, t, J = 7.74 Hz), 7.43 (1.0H, t, J = 7.55 Hz), 7.57 (1.0H, t, J = 7.55 Hz), 7.71 (0.9H, d, J = 7.55 Hz), 7.94 (0.9H, d, J = 7.18 Hz). ^{13}C NMR ($CDCl_3$, 150.92 MHz) δ = 22.1, 25.1, 39.0, 41.0, 55.4, 56.1, 64.4, 109.1, 116.7, 123.4, 123.9, 124.6, 127.3, 128.7, 130.3, 132.2, 134.9, 146.3, 156.9, 167.3, 168.4.

Compound 44: $C_{16}H_{18}N_2O_2$, M_w 270.14 g/mol; HRMS (ESI-TOF) *m*/*z* calcd for $C_{16}H_{18}N_2O_2$ 270.1368, found 270.1362; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.57 (3H, s), 2.10−2.13 (1H, m), 2.21−2.28 (2H, m), 2.46−2.55 (1H, m), 2.82 (1H, dd, J = 3.44, 15.93 Hz), 3.02−3.09 (2H, m), 3.71−3.74 (1H, m), 4.15−4.18 (1H, m), 4.60−4.63 (1H, m), 4.88 (1H, s), 7.17 (1H, d, J = 6.80 Hz), 7.26 (2H, m), 7.31 (1H, m); ^{13}C NMR ($CDCl_3$, 150.92 MHz) δ 23.2, 28.3, 29.4, 30.8, 40.0, 40.7, 54.4, 62.3, 124.5, 127.0, 127.8, 129.1, 133.8, 135.2, 172.0, 173.2.

Compound 45: $C_{17}H_{20}N_2O_2$, M_w 284.15 g/mol; HRMS (ESI-TOF) *m*/*z* calcd for $C_{17}H_{20}N_2O_2Na$ 307.1422, found 307.1404; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.60 (3H, s), 1.67−1.71 (1H, m), 1.78 (1H, m), 1.87−1.90 (2H, m), 2.17−2.27 (2.0H, m), 2.42 (1.0H, d, J = 26.42 Hz), 2.82−2.84 (1H, m), 3.05−3.07 (1.0H, m), 3.14−3.17 (1H, m), 3.57 (1H, dd, J = 4.38, 14.20 Hz), 4.55−4.59 (1H, m), 4.72 (1H, s), 5.07 (1H, dd, J = 3.96, 14.38 Hz), 7.15 (1H, d, J = 4.53 Hz), 7.23 (2H, t, J = 3.98 Hz), 7.40 (1H, d, J = 4.03 Hz); ^{13}C NMR ($CDCl_3$, 150.92 MHz) δ 16.3, 16.6, 23.4, 28.2, 28.8, 30.9, 31.6, 32.5, 33.3, 38.0, 39.6, 41.1, 41.9, 54.8, 55.2, 61.1, 124.3, 125.4, 126.8, 126.9, 127.3, 127.7, 128.9, 129.3, 134.5,134.8, 135.3, 169.3, 170.7.

Compound 46: $C_{20}H_{18}N_2O_2$, M_w:318.37 g/mol; HRMS (ESI-TOF) *m*/*z* calcd for $C_{20}H_{18}N_2O_2$ 318.1368, found 318.1368; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.42 (1H, t, J = 7.35 Hz), 1.86 (3H, s), 2.78 (1.0H, td, J = 4.36, 16.31 Hz), 2.93 (1H, ddd, J = 6.02, 0.09, 16.15 Hz), 3.17 (2H, ddt, J = 4.85, 2.47, 6.46 Hz), 3.99 (1H, dd, J = 5.70, 13.98 Hz), 4.55 (1H, ddd, J = 4.04, 0.02, 12.92 Hz), 4.72 (1H, dd, J = 4.89, 14.01 Hz), 5.01 (1H, t, J = 5.28 Hz), 7.10 (1H, d, J = 7.18 Hz), 7.22 (1H, t, J = 7.39 Hz), 7.30 (1H, t, J = 7.67 Hz), 7.45 (1H, t, J = 7.41 Hz), 7.52 (1H, d, J = 7.93 Hz), 7.60 (1H, t, J = 7.47 Hz), 7.74 (1H, d, J = 7.56 Hz), 7.95 (1H, d, J = 7.74 Hz); ^{13}C NMR ($CDCl_3$, 150.92 MHz) δ 8.6, 25.1, 28.1, 38.9, 41.3, 45.9, 55.9, 64.5, 123.5, 124.6, 124.6, 126.9, 127.8, 128.7, 129.0, 130.3, 132.2, 133.9, 135.1, 146.3, 167.4, 168.5.

General Procedure for Borane Reduction Reaction. A 10 mg portion of polycyclic amide was added to 2 mL of borane/THF solution and stirred overnight. The reaction was quenched with a few drops of 1 M HCl, neutralized with Na_2CO_3, extracted with ethyl acetate, evaporated, and purified by preparative TLC to give the polycyclic amine product.

Compound 53: $C_{18}H_{26}N_2O_2$, M_w 302.41 g/mol; HRMS (ESI-TOF) *m*/*z* calcd for $C_{18}H_{25}N_2O_2$ 301.1916, found 301.1905; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.19 (3H, s), 1.49−1.56 (2H, m), 1.81−1.86 (2H, m), 2.49 (2H, d, J = 12.46 Hz), 2.62−2.68 (2H, dt, J = 9.05, 5.96 Hz), 2.75 (1H, dd, J = 6.03, 10.59 Hz), 2.89 (1H, d, J = 12.24 Hz), 2.95−2.99 (2H, m), 3.27 (1H, dd, J = 2.21, 11.35 Hz), 3.46 (1H, d, J = 32.48 Hz), 3.74 (3H, s), 3.75 (3H, s), 3.95 (1H, d, J = 10.95 Hz), 6.45 (1H, s), 6.49 (1H, s); ^{13}C NMR ($CDCl_3$, 150.92 MHz) δ =29.5, 40.1, 44.0, 53.4, 55.4, 65.7, 102.0, 110.4, 120.7, 123.1, 123.6, 126.8, 128.0, 128.9, 130.5, 123.4, 123.6, 123.7, 126.9.

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Supporting Information Available: NMR spectra of the new compounds and X-ray crystallographic data of compound **37**. This material is available free of charge via the Internet at http://pubs.acs.org.