Tetrahedron Letters 52 (2011) 5245–5248

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A short microwave-assisted synthesis of tetrahydroisoquinolin-pyrrolopyridinones by a triple process: Ugi-3CR–aza Diels–Alder/S-oxidation/Pummerer

Alejandro Islas-Jácome [a], Eduardo González-Zamora [a,*], Rocío Gámez-Montaño [b,*]

[a] Departamento de Química, División de Ciencias Básicas e Ingeniería, Universidad Autónoma Metropolitana-Iztapalapa, San Rafael Atlixco 186, Col. Vicentina Iztapalapa, C.P. 09340, México D.F., Mexico
[b] Departamento de Química, Universidad de Guanajuato, Noria Alta S/N, Col. Noria Alta, C.P. 36050, Guanajuato, Gto., Mexico

ARTICLE INFO

Article history:
Received 10 June 2011
Revised 28 July 2011
Accepted 28 July 2011
Available online 5 August 2011

Keywords:
Microwave-assisted synthesis
Tetrahydroisoquinolin-pyrrolopyridinones
Ugi-3CR
Aza Diels–Alder cycloaddition
S-oxidation
Pummerer cyclization

ABSTRACT

A series of tetrahydroisoquinolin-pyrrolopyridinones were prepared from an easily accessible aldehyde, a commercially available amine, a readily isolable isonitrile, and maleic anhydride via a triple process: Ugi-3CR–aza Diels–Alder/S-oxidation/Pummerer. The combination of a multicomponent Ugi-type reaction with other post-functionalization processes provides a powerful tool for the preparation of fused polyheterocyclic compounds.

The chemistry of heterocyclic compounds has assumed an important role in recent years.[1] Nitrogenated heterocyclic compounds are an integral part of numerous drugs and natural products,[2] and the majority of these latter exhibit biological activity.[3] For these reasons, several synthetic methodologies have been developed for preparing natural products.[4] Synthetic methodologies, such as multicomponent reactions (MCR's) have been used to achieve advanced intermediates for the synthesis of compounds with biological activity.[5] In this context, a combination of multicomponent reactions[6] and an efficient post-transformation, typically involving a ring-forming process, has provided a powerful tool to the synthesis of highly functionalized heterocyclic compounds.[7] Indeed, multicomponent reactions that combine three or more reactants together during a single ordered event offer not only molecular complexity and diversity in each step, they also enable the matching of functionalities that are suitable for further transformations. The reaction times and yields of MCR's can greatly benefit from the use of microwave (MW) irradiation.[8]

Several post-transformations of Ugi products have been reported, including cyclocondensations,[9] radical cyclizations,[10] S_NAr's,[11] S_N2's,[12] cycloadditions,[13] and metathesis reactions.[14]

Recently, we focused on the preparation of compound libraries using multicomponent processes, such as Ugi-type reactions combined with other post-functionalization techniques, such as free-radical cyclizations.[15] We also focused on the preparation of synthetically nitrogenated analogs of important natural products in medicinal chemistry. In this context, one of our goals has been to develop synthetic routes to compounds with the tetrahydroisoquinolin-pyrrolopyridinone skeleton, which is an aza-analog of the tetrahydroisoquinolin-isoindolinone skeleton that may exhibit biological activity. The preparation of these compounds presents an attractive challenge.[16]

In 1997, Grigg and co-workers[17] reported the synthesis of the tetrahydroisoquinolin-pyrrolopyridinone **1** using a palladium-catalyzed cascade cyclization–Friedel–Crafts alkylation approach in 71% yield Figure 1.

In 2002, Gámez-Montaño and Zhu[18] reported a three-step synthesis of the tetrahydroisoquinolin-pyrrolopyridine **2** using a combination of multicomponent reactions and Pummerer cyclization in good overall yield. This sequence provided the first synthetic approach to tetrahydroisoquinolin-pyrrolopyridinones without a carbonyl in the pyrrole ring of the linear polyheterocyclic system, Figure 1.

In this Letter, we describe the synthesis of the new compounds **3a–c** (Fig. 1) containing the aza-tetracyclic skeleton of tetrahydroisoquinolin-pyrrolopyridinones via a combined multicomponent Ugi-type reaction, aza Diels–Alder cycloaddition, and Pummer

* Corresponding authors. Tel.: +52 55 58044913; fax: +52 55 58044666 (E.G.); tel.: +52 473 7320006x8191; fax: +52 473 7320006x8168 (R.G.).
E-mail addresses: egz@xanum.uam.mx (E. González-Zamora), rociogm@quijote.ugto.mx (R. Gámez-Montaño).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.07.134

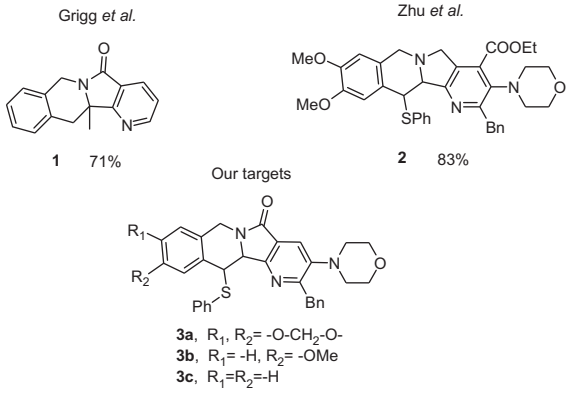
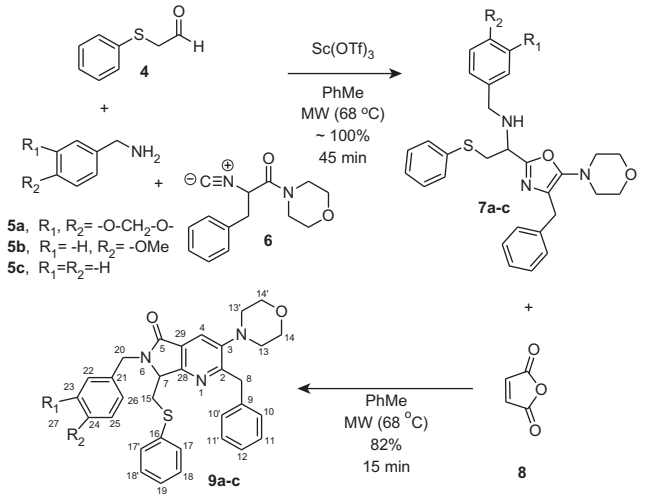


Figure 1. Compounds with the tetrahydroisoquinolin-pyrrolopyridinone skeleton.

er-type cyclization as a post-functionalization reaction performed under MW-irradiation.

Recently, our group developed a new methodology for preparing the pyrrolopyridinone skeleton using a four-component reaction.[15a] Following this methodology, the easily accessible aldehyde **4**,[19] the commercially available piperonylamine (**5a**), and the readily isolable isonitrile[20] **6** were sequentially combined in an Ugi-3CR in toluene using MW as a heat source to give, after 45 min, the corresponding 5-amino-oxazole **7a**.[21] Next, maleic anhydride (**8**)[22] was added to afford, after 15 min, the expected pyrrolo[3,4-*b*]pyridin-5-one **9a** via an aza-Diels–Alder cycloaddition[23] (Scheme 1).

In the first attempt to obtain the pyrrolo[3,4-*b*]pyridin-5-one **9a**, we used LiBr as an additive[24] to facilitate the imine formation, however, the desired compound was obtained in low yield (32%), probably due to the hygroscopic properties of this salt (Table 1, entry 1). The use of NH_4Cl to generate the iminium ion, which was expected to be more reactive than the imine in the Ugi reaction, as reported by Zhu and co-workers,[23] provided a better yield (Table 1, entry 2). The use of metallic triflates as a catalyst[25] promoted this transformation (Table 1, entries 3 and 4) by activating the imine prior to the isonitrile nucleophilic attack. The use of $Sc(OTf)_3$, in particular, gave the highest yield. Once the conditions were optimized, including the reaction parameters associated with the MW conditions, two pyrrolo[3,4-*b*]pyridin-5-ones **9b** and **9c** were prepared in good yield within 60 min in a single step through the use of two amines **5b** and **5c** as starting materials (Table 1, entries 6 and 7). Notably, the use of benzene in place of toluene decreased the yield (Table 1, entry 5).



Scheme 1. Synthesis of the pyrrolo[3,4-*b*]pyridin-5-ones **9a-c** based on a multicomponent reaction.

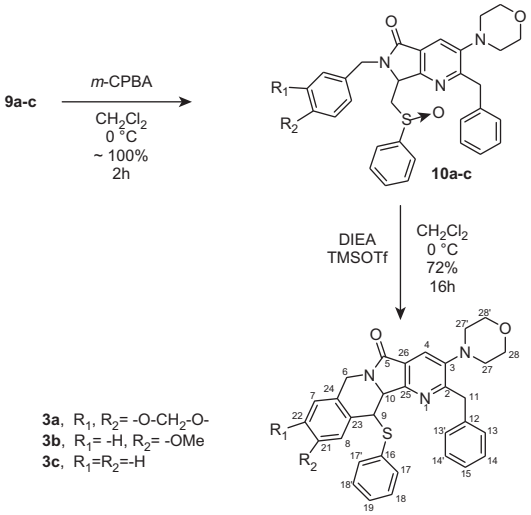
Table 1
Effect of the catalyst and the solvent in the synthesis of pyrrolo[3,4-*b*]pyridin-5-ones **9a–c**.

Entry	Solvent	Additive or catalyst	Yield[a] (%)	Product
1	PhMe	LiBr 1.1 equiv	32	**9a**
2	PhMe	NH_4Cl 1.2 equiv	45	**9a**
3	PhMe	$Yb(OTf)_3$ 3 mol %	48	**9a**
4	PhMe	$Sc(OTf)_3$ 3 mol %	82	**9a**
5	PhH	$Sc(OTf)_3$ 3 mol %	62	**9a**
6	PhMe	$Sc(OTf)_3$ 3 mol %	75	**9b**
7	PhMe	$Sc(OTf)_3$ 3 mol %	72	**9c**

[a] After purification by silica gel column chromatography.

The pyrrolo[3,4-*b*]pyridin-5-one **9a** was quantitatively S-oxidized[26] using *m*-CPBA to the corresponding sulfoxide compound **10a** (Scheme 2). A diastereomeric mixture was expected as a consequence of the creation of an axial chiral center at the sulfoxide axis, and the desired compound **10a** was obtained as a mixture in a 5:2 ratio of the inseparable diastereomers by silica gel column chromatography. In the present work, the two sulfoxide diastereoisomers (**10a**) did not need to be isolated and were used as a mixture in the next step.

Closure of the diastereomeric mixture of the sulfoxide compounds **10a**, by a S_EAr Pummerer-type cyclization[27] using the Hunig's base and TMSOTf as a sulfoxide activator[18] afforded the desired tetrahydroisoquinolin-pyrrolopyridinone **3a** in low yield (Table 2, entry 1) as a single diastereoisomer. The optimal conditions included DIEA (6.0 equiv), TMSOTf (6.0 equiv), and dichloromethane as the solvent, with incubation at 0 °C for 16 h to give the polyheterocycle **3a** in 72% yield (Table 2, entry 2), Scheme 2.



Scheme 2. Preparation of the tetrahydroisoquinolin-pyrrolopyridinones **3a–c**.

Table 2
Optimization of the Pummerer-type cyclyzation for the synthesis of final products **3a–c**.

Entry	Conditions[a]	Time (h)	Yield[b] (%)	Product
1	(1.0), (1.0)	16	16	**3a**
2	(6.0), (6.0)	16	72	**3a**
3	(6.0), (6.0)	34	62	**3b**
4	(6.0), (6.0)	48	38	**3c**

[a] Dichloromethane, DIEA, TMSOTf (equiv) at 0 °C.
[b] After purification by silica gel column chromatography.

Under these conditions, the desired tetrahydroisoquinolin-pyrrolopyridinones **3b–c** were prepared in moderate to good yields using pyrrolo[3,4-*b*]pyridin-5-ones **9b–c** as starting materials (Table 2, entries 3 and 4).

The S_EAr Pummerer-type cyclization proceeds effectively upon activation of the reaction center in the aryl responsible for the nucleophilic attack by electron-releasing groups (ERG's).[28] In this context, the differences among the observed yields during the synthesis of compounds **3a–c** from the corresponding sulfoxides **10a–c** (72, 62, 38%) could be explained. The di-oxa bridge was a better substituent than the methoxy group, and this latter was better than hydrogen during the last cyclization step.

All tetracycles containing the tetrahydroisoquinolin-pyrrolopyridinone system were obtained as a single diastereomer, and their stereochemistry was deduced from mechanistic considerations and NMR studies. The observed coupling constant between H-9 and H-10 (J_{H9-H10} = 7.8 Hz) indicated an anti relationship between these two protons. The relative stereochemistry of all new compounds **3a–c** was deduced to be (9*S**–10*R**) by comparison with the literature data.[18]

The scope of this multicomponent reaction was evaluated by including the S-oxidation and the Pummerer cyclization in a full one-pot process. Under the conditions established previously for the multistep synthesis, the aldehyde **4**, piperonylamine (**5a**), isonitrile **6**, and $Sc(OTf)_3$ were sealed in a reaction tube in toluene, and the solution was MW-irradiated for 45 min at 68 °C. The maleic anhydride **8** was introduced, and MW-irradiation continued at 68 °C for an additional 15 min. *m*-CPBA was then introduced, and the reaction was stirred at 0 °C for 2 h. Finally, DIEA (6.0 equiv) and TMSOTf (6.0 equiv) were added, and the reaction mixture was stirred at 0 °C for 16 h to yield the polyheterocycle **3a** in 12% overall yield in a one-pot process.

In summary, the multicomponent domino process used in the present work, which involved a combination of Ugi-3CR, aza Diels–Alder cycloaddition, S-oxidation, and Pummerer-type cyclization under microwave-assistance, produced three fused rings by creating seven new chemical bonds via the simple loss of water and CO_2. The obtained polyheterocycles containing the tetrahydroisoquinolin-pyrrolopyridinone system were produced in good yields, considering the molecular complexity of the final compounds. The operational simplicity of this synthesis is highly attractive for a range of diversity-oriented synthetic approaches.

Acknowledgments

Financial support by the Consejo Nacional de Ciencia y Tecnología (CONACyT, project 51346-Q and J-50922) and a scholarship awarded to A.I.-J. (227423) are gratefully acknowledged. E.G.-Z. thanks A. Gutiérrez-Carrillo for NMR spectra and Professors J. Tamariz-Mascarúa and A. Benavides-Macias for their fruitful comments.

References and notes

1. Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449–472.
2. Ertl, P.; Jelfs, S.; Mühlbacher, J.; Schuffenhauer, A.; Selzer, P. *J. Med. Chem.* **2006**, *49*, 4568–4573.
3. Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2004**, *21*, 278–311.
4. Nielsen, T. E.; Meldal, M. *Curr. Opin. Discov. Devel.* **2009**, *12*, 798–810.
5. (a) Burke, S. D.; Piscopio, A. D.; Kort, M. E.; Matulenko, M. A.; Parker, M. H.; Armistead, D. M.; Shankaran, K. *J. Org. Chem.* **1994**, *56*, 332–347; (b) Garçon, S.; Vassiliou, S.; Cavicchioli, M.; Hartmann, B.; Monteiro, N.; Balme, G. *J. Org. Chem.* **2001**, *66*, 4063–4069; (c) Wang, Y.; Dong, X. Y.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 3090–3098; (d) Stragies, R.; Blechert, S. *J. Am. Chem. Soc.* **2000**, *122*, 9584–9591; (e) Bowers, M. M.; Carroll, P.; Joullié, M. M. *J. Am. Chem. Soc.* **1999**, *121*, 6355–6366.
6. (a)*Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005; (b) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101–4111; (c) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89; (d) Dömling, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210.
7. (a) Marcaccini, S.; Torroba, T. Post-condensation Modifications of the Passerini and Ugi Reactions In Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005. pp 33–75; (b) Akritopoulou-Zanze, I.; Djuric, S. W. *Heterocycles* **2007**, *73*, 125–147.
8. (a) Kappe, C. O.; Dallinger, D. *Mol. Diversity* **2009**, *13*, 71–193; (b) Di Mauro, E. F.; Kennedy, J. M. *J. Org. Chem.* **2007**, *72*, 1013–1016; (c) Kremsner, J. M.; Stadler, A.; Kappe, C. O. *Top. Curr. Chem.* **2006**, *266*, 233–278; (d) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284; (e) Tye, H.; Whittaker, M. *Org. Biomol. Chem.* **2004**, *2*, 813–815; (f)*Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2002; (g) Hoel, A. M. L.; Nielsen, J. *Tetrahedron Lett.* **1999**, *40*, 3941–3944.
9. Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51–80.
10. (a) El Kam, L.; Grimaud, L.; Miranda, L. D.; Vieu, E. *Tetrahedron Lett.* **2006**, *47*, 8259–8261; (b) El Kaim, L.; Grimaud, L.; Vieu, E. *Org. Lett.* **2007**, *9*, 4171–4173.
11. (a) Cristau, P.; Vors, J. P.; Zhu, J. *Org. Lett.* **2001**, *3*, 4079–4082; (b) Tempest, P.; Ma, V.; Kelly, M. G.; Jones, W.; Hulme, C. *Tetrahedron Lett.* **2001**, *42*, 4963–4968; (c) Cristau, P.; Vors, J. P.; Zhu, J. *Tetrahedron* **2003**, *59*, 7859–7870; (d) Spatz, J. H.; Umkehrer, M.; Kalinski, C.; Ross, G.; Burdack, C.; Kolb, J.; Bach, T. *Tetrahedron Lett.* **2007**, *48*, 8060–8064.
12. (a) Ugi, I.; Schmid, T. *J. Prakt. Chem.* **1997**, *339*, 652–655; (b) Marcaccini, S.; Pepino, R.; Cruz Pozo, M. *Tetrahedron Lett.* **2001**, *42*, 2727–2728; (c) Umkehrer, M.; Kolb, J.; Burdack, C.; Ross, G.; Hiller, W. *Tetrahedron Lett.* **2004**, *45*, 6421–6424; (d) Neo, A. G.; Delgado, J.; Polo, C.; Marcaccini, S.; Marcos, C. F. *Tetrahedron Lett.* **2005**, *46*, 23–26; (e) Golebiowski, A.; Klopfenstein, S. R.; Shao, X.; Chen, J. J.; Colson, A. O.; Grieb, A. L.; Russell, A. F. *Org. Lett.* **2000**, *2*, 2615–2617; (f) Golebiowski, A.; Jozwik, J.; Klopfenstein, S. R.; Colson, A. O.; Grieb, A. L.; Russell, A. F.; Rastogi, V. L.; Diven, C. F.; Portlock, D. E.; Chen, J. J. *J. Comb. Chem.* **2002**, *4*, 584–590; (g) Rossen, K.; Sager, J.; DiMichele, L. M. *Tetrahedron Lett.* **1997**, *38*, 3183–3186; (h) de Greef, M.; Abeln, S.; Belkasmi, K.; Dömling, A.; Orru, R. V. A.; Wessjohann, L. A. *Synthesis* **2006**, 3997–4004; (i) Xing, X.; Wu, J.; Feng, G.; Dai, W.-M. *Tetrahedron* **2006**, *62*, 6774–6781; (j) Banfi, L.; Basso, A.; Guanti, G.; Kielland, N.; Repetto, C.; Riva, R. *J. Org. Chem.* **2007**, *72*, 2151–2160.
13. (a) Sun, X.; Janvier, P.; Zhao, G.; Bienaymé, H.; Zhu, J. *Org. Lett.* **2001**, *3*, 877–880; (b) Akritopoulou-Zanze, I.; Gracias, V.; Moore, J. D.; Djuric, S. W. *Tetrahedron Lett.* **2004**, *45*, 3421–3423; (c) Akritopoulou-Zanze, I.; Gracias, V.; Djuric, S. W. *Tetrahedron Lett.* **2004**, *45*, 8439–8441; (d) Paulvannan, K. *J. Org. Chem.* **2004**, *69*, 1207–1214; (e) Gracias, V.; Darczak, D.; Gasiecki, A. F.; Djuric, S. W. *Tetrahedron Lett.* **2005**, *46*, 9053–9056; (f) Pirali, T.; Tron, G. C.; Zhu, J. *Org. Lett.* **2006**, *8*, 4145–4148; (g) Akritopoulou-Zanze, I.; Whitehead, A.; Waters, J. E.; Henry, R. F.; Djuric, S. W. *Org. Lett.* **2007**, *9*, 1299–1302.
14. (a) Piscopio, A. D.; Miller, J. F.; Koch, K. *Tetrahedron* **1999**, *55*, 8189–8198; (b) Beck, B.; Larbig, G.; Mejat, B.; Magnin-Lachaux, M.; Picard, A.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2003**, *5*, 1047–1050; (c) Hebach, C.; Kazmaier, U. *Chem. Commun.* **2003**, 596–597; (d) Sello, J. K.; Andreana, P. R.; Lee, D.; Schreiber, S. L. *Org. Lett.* **2003**, *5*, 4125–4127; (e) Banfi, L.; Basso, A.; Guanti, G.; Riva, R. *Tetrahedron Lett.* **2003**, *44*, 7655–7658; (f) Krelaus, R.; Westermann, B. *Tetrahedron Lett.* **2004**, *45*, 5987–5990; (g) Dietrich, S. A.; Banfi, L.; Basso, A.; Damonte, G.; Guanti, G.; Riva, R. *Org. Biomol. Chem.* **2005**, *3*, 97–106; (h) Gracias, V.; Gasiecki, A. F.; Djuric, S. W. *Tetrahedron Lett.* **2005**, *46*, 9049–9052; (i) Ribelin, T. P.; Judd, A. S.; Akritopoulou Zanze, I.; Henry, R. F.; Cross, J. L.; Whittern, D. N.; Djuric, S. W. *Org. Lett.* **2007**, *9*, 5119–5122.
15. (a) Zamudio-Medina, A.; García-González, M. C.; Padilla, J.; González-Zamora, E. *Tetrahedron Lett.* **2010**, *51*, 4837–4839; (b) El Kaim, L.; Gámez-Montaño, R.; Laurence, G.; Ibarra-Rivera, T. *Chem. Commun.* **2008**, *11*, 1350–1352.
16. (a) Zhang, W.; Pugh, G. *Tetrahedron* **2003**, *59*, 3009–3018; (b) Grigg, R.; Savic, V.; Tambyrajah, V. *Tetrahedron Lett.* **2000**, *41*, 3003–3006; (c) Hucher, N.; Daich, A.; Decroix, B. *Org. Lett.* **2000**, *2*, 1201–1204; (d) Zhang, W.; Pugh, G. *Tetrahedron Lett.* **1999**, *40*, 7591–7594; (e) García, A.; Rodríguez, D.; Castedo, L.; Saá, C.; Domínguez, D. *Tetrahedron Lett.* **2001**, *42*, 1903–1905; (f) Kim, G.; Kim, J. H.; Kim, W. J.; Kim, Y. A. *Tetrahedron Lett.* **2003**, *44*, 8207–8209; (g) Wada, Y.; Nishida, N.; Kurono, N.; Ohkuma, T.; Orito, K. *Eur. J. Org. Chem.* **2007**, 4320–4327.
17. Brown, D.; Grigg, R.; Sridharan, V.; Tambyrajah, V. *Tetrahedron Lett.* **1995**, *36*, 8137–8140.
18. Gámez-Montaño, R.; Zhu, J. *Chem. Commun.* **2002**, *20*, 2448–2449.
19. (a) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272–7276; (b) Ozanne-Beaudenon, A.; Quideau, S. *Tetrahedron Lett.* **2006**, *47*, 5869–5873.
20. Fayol, A.; Housseman, C.; Sun, X.; Janvier, P.; Bienaymé, H.; Zhu, J. *Synthesis* **2005**, *1*, 161–165.
21. Sun, X.; Janvier, P.; Zhao, G.; Bienayme, H.; Zhu, J. *Org. Lett.* **2001**, *3*, 877–880.
22. González-Lopez, M.; Show, J. T. *Chem. Rev.* **2009**, *109*, 164–189.
23. Janvier, P.; Sun, X.; Bienayme, H.; Zhu, J. *J. Am. Chem. Soc.* **2002**, *124*, 2560–2567.
24. (a) Gámez-Montaño, R.; González-Zamora, E.; Potier, P.; Zhu, J. *Tetrahedron* **2002**, *58*, 6351–6358; (b) González-Zamora, E.; Fayol, A.; Bois-Choussy, M.; Chiaroni, A.; Zhu, J. *Chem. Commun.* **2001**, 1684–1685.
25. Kobayashi, S.; Sigiura, M.; Kitagawa, H.; Lam, W. *Chem. Rev.* **2002**, *102*, 2227–2302.
26. Bousquet, T.; Fleury, J.-F.; Daïch, A.; Netchitaïlo, P. *Tetrahedron* **2006**, *62*, 706–715.
27. Smith, L. H. S.; Coote, S. C.; Sneddon, H. F.; Procter, D. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 5832–5844.

28. Toda, J.; Sakagami, M.; Sano, T. *Chem. Pharm. Bull.* **2005**, *47*, 1269-1275.

All compounds were characterized by ^{1}H NMR, ^{13}C NMR, DEPT-135, COSY, HSQC, HMBC, IR, and HRMS. The melting points are reported as the average values from three tests.

Procedure for obtaining pyrrolo[3,4-*b*]pyridin-5-ones (See Ref. 15a).

Selected compound 6-((benzo[d][1,3]dioxol-6-yl)methyl)-2-benzyl-6,7-dihydro-3-morpholino-7-((phenylthio)methyl)pyrrolo[3,4-*b*] pyridin-5-one **9a**, yield 82%. Pale yellow powder, mp: 58 °C, R_f = 0.35 (Hexane/AcOEt 1:1). *Selected spectral data for compound* **9a** ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.83 (s, 1H, H-4), 7.23–7.12 (m, 10H, H_{arom}), 6.72 (dd, 1H, *J* = 11.1, 0.8 Hz, H-26), 6.72 (d, 1H, *J* = 11.1 Hz, H-25), 6.70 (d, 1H, *J* = 0.8 Hz, H-22), 5.90 (d, 1H, *J* = 4.6 Hz, H-27), 5.88 (d, 1H, *J* = 4.6 Hz, H-27), 5.21 (d, 1H, *J* = 15.1 Hz, H-20), 4.60 (m, 1H, H-7), 4.28 (d, 1H, *J* = 14.2 Hz, H-8), 4.12 (d, 1H, *J* = 14.2 Hz, H-8), 3.84–3.79 (m, 5H, H-14, H-20), 3.69 (dd, 1H, *J* = 14.1, 3.2 Hz, H-15), 3.56 (dd, 1H, *J* = 14.1, 4.1 Hz, H-15), 2.83–2.79 (m, 4H, H-13). ^{13}C NMR (125 MHz, $CDCl_3$, 298 K) δ: 167.0 (C-5), 161.3 (C-2), 158.3 (C-28), 148.1 (C-23), 147.7 (C-3), 147.1 (C-24), 139.2 (C-9), 135.2 (C-16), 131.1 (C-10), 130.4 (C-21), 128.8 (C-11), 128.7 (C-17), 128.2 (C-18), 126.7 (C-12), 126.1 (C-19), 125.1 (C-29), 123.5 (C-4), 121.5 (C-26), 108.6 (C-25), 108.2 (C-22), 101.0 (C-27), 67.1 (C-14), 59.0 (C-7), 52.9 (C-13), 43.6 (C-20), 39.8 (C-8), 35.4 (C-15). FT-IR (film in CH_2Cl_2): 1692 cm^{-1} (C=O). HRMS calcd for $C_{33}H_{31}N_3O_4S$: 565.2035, found: 565.2029.

Procedure for obtaining 6-((benzo[d][1,3]dioxol-6-yl)methyl)-2-benzyl-6,7-dihydro-3-morpholino-7-((phenylsulfinyl)methyl)pyrrolo[3,4-*b*]pyridin-5-one **10a**: to a stirred solution of compound **9a** (0.033 mmol, 1.0 equiv) in CH_2Cl_2 at 0 °C, *m*-CPBA (0.0462 mmol, 1.4 equiv) was added. After 2 h, the solvent was removed under reduced pressure. The crude product was purified by silica gel chromatography (hexane/AcOEt 1:1). Finally, the product was re-purified on a silica-gel preparative plate (20 × 20 cm) with a mixture of hexane and AcOEt 1:1 as the mobile phase to afford a mixture of two inseparable diastereoisomers **10a** (in a 5:2 ratio) in quantitative yield. The NMR signals of **10a** were found to be duplicated.

Procedure for obtaining the tetrahydroisoquinolin-pyrrolopyridinones. *Selected compound* **3a**. To a stirred solution of compound **10a** (0.103 mmol, 1.0 equiv) in CH_2Cl_2 at 0 °C, TMSOTf (0.620 mmol, 6.0 equiv) and DIEA (0.620 mmol, 6.0 equiv) were sequentially added. After 16 h, the solvent was removed under reduced pressure. The crude product was primarily treated with 3 × 15 mL $NaHCO_3$ (aq), followed by treatment with excess brine. The crude product was immediately purified on a silica-gel preparative plate (20 × 20 cm) using a mixture of hexane and AcOEt 3:1 as the mobile phase to afford the desired compound **3a** in 72% yield. White solid, mp: 72 °C. R_f = 0.20 (Hexane/AcOEt 1:1). *Selected spectral data for compound* **3a**, ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ: 7.79 (s, 1H, H-4), 7.47–7.45 (m, 2H, H-13), 7.40–7.38 (m, 2H, H-17), 7.28–7.18 (m, 7H, H_{arom}), 6.63 (s, 1H, H-8), 5.98 (d, 1H, *J* = 1.4 Hz, H-20), 5.93 (s, 1H, *J* = 1.4 Hz, H-20), 5.14 (d, 1H, *J* = 16.4 Hz, H-6), 4.66 (d, 1H, *J* = 7.8 Hz, H-10), 4.43 (d, 1H, *J* = 13.9 Hz, H-11), 4.34 (d, 1H, *J* = 7.8 Hz, H-9), 4.33 (d, 1H, *J* = 13.9 Hz, H-11), 4.20 (d, 1H, *J* = 16.4 Hz, H-6), 3.85–3.83 (m, 4H, H-28), 2.86–2.82 (m, 4H, H-27). ^{13}C NMR (125 MHz, $CDCl_3$, 298 K) δ: 165.8 (C-5), 165.4 (C-2), 159.3 (C-25), 147.8 (C-3), 147.2 (C-21), 147.0 (C-22), 139.4 (C-12), 133.2 (C-13), 132.9 (C-16), 129.2 (C-14), 128.9 (C-17), 128.7 (C-18), 127.8 (C-15), 127.5 (C-25), 127.2 (C-24), 126.2 (C-19), 124.5 (C-26), 123.3 (C-4), 109.6 (C-7), 106.1 (C-8), 101.3 (C-20), 67.1 (C-28), 59.9 (C-10), 52.9 (C-27), 48.7 (C-9), 41.2 (C-6), 40.0 (C-11). FT-IR (film in CH_2Cl_2): 1696 cm^{-1} (C=O). HRMS calcd. for $C_{33}H_{29}N_3O_4S$: 563.1879, found: 563.1881.