Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 48 (2007) 9030–9034
Tetrahedron Letters

Diversity oriented synthesis of benzoxazoles and benzothiazoles

Julia H. Spatz,[a,b,*] Thorsten Bach,[b] Michael Umkehrer,[a] Julien Bardin,[a] Günther Ross,[a] Christoph Burdack[a] and Jürgen Kolb[a]

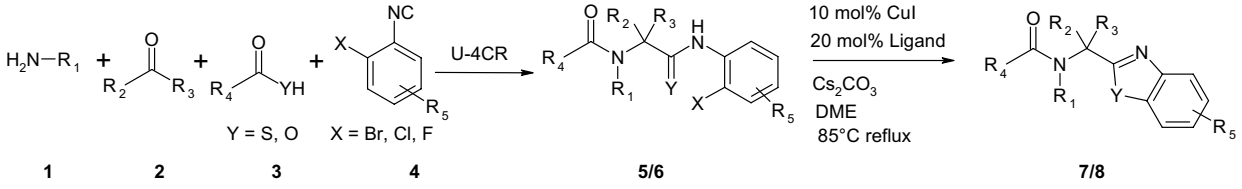
[a]*Priaton GmbH, Gmunder Strasse 37-37a, D-81739 München, Germany*
[b]*Technical University Munich, Lichtenbergstrasse 4, D-85747 Garching, Germany*

Received 14 September 2007; revised 17 October 2007; accepted 17 October 2007
Available online 18 October 2007

Abstract—A combinatorial synthetic route yielding benzoxazoles and benzothiazoles is described. The use of *o*-halophenylisocyanides in the Ugi reaction (U-4CR) followed by a copper-catalyzed cyclization affords the benzoxazole as well as the benzothiazole moiety in good yield and high diversity.

Benzoxazoles and benzothiazoles belong to an important class of molecules and are common heterocyclic scaffolds in biologically active and pharmaceutically significant compounds. Benzoxazoles are found in a variety of natural products[1] and are important scaffolds in drug discovery.[2,3] Therefore several classical synthetic procedures were developed,[4,5] but with a lack of diversity, which is required for an effective lead discovery and optimization. In contrast to the classical organic synthesis, the combinatorial synthesis of 'drug-like' compounds permits the fast preparation of compound libraries suitable for lead finding and optimization.[6–16] Thus multi-component reactions (MCRs) represent a powerful tool for high-throughput screening strategy.[17,18] Especially the Ugi-reaction has generated much interest due to its synthetic potential, and its capacity to generate molecular diversity. In the Ugi-four component reaction,[19] amine **1**, aldehyde **2**, carboxylic acid **3** and isocyanide **4** react simultaneously to afford peptide-like structure **5/6** (Scheme 1). In order to reach a maximum of diversity, several research groups have successfully joined different classical methods with multi-component reactions.[20–25] For further progress in molecular diversity we combined the Ugi-4CR with a copper-catalyzed cyclization. The reaction involves an intramolecular C–O or C–S cross-coupling of the *ortho*-halophenylamide originating from the isocyanide and is believed to proceed via an oxidative insertion/reductive elimination pathway through a Cu(I)/Cu(III) manifold in analogy with other Cu- and Pd-catalyzed C–X bond formations[3,26–29] (Scheme 2). Herein the first step of the reaction involves the coordination of the amide group **5/6** with catalyst **9** to give intermediate **10**, then followed by an oxidative insertion to **11** and finally a reductive elimination to release product **7/8** with simultaneous regeneration of catalyst **9**.

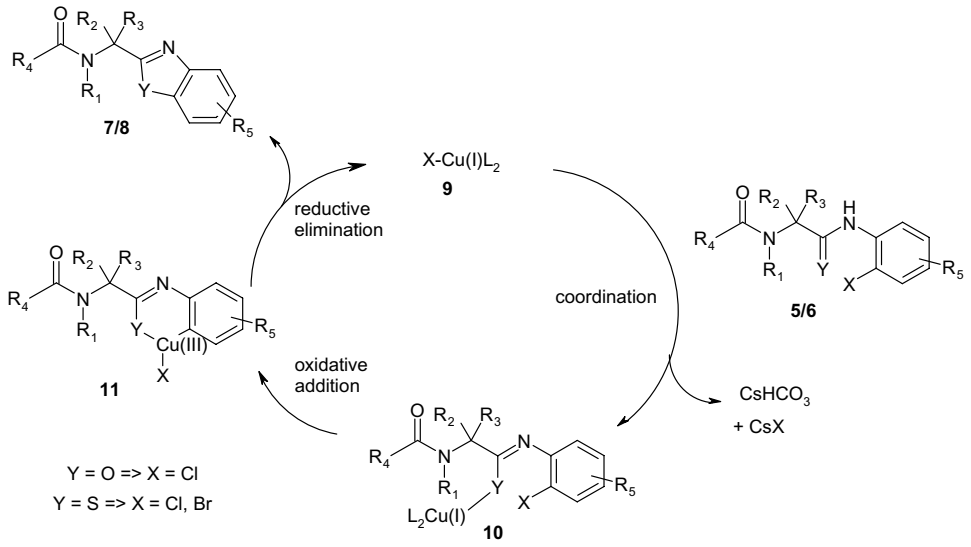
The Ugi-reaction is generally initiated by the condensation of amine **1** with aldehyde **2** leading to an intermediate imine, which subsequently reacts with carboxylic



Scheme 1. Combinatorial synthesis of benzoxazoles and benzothiazoles via U-4CR and copper-catalyzed cross-coupling strategy.

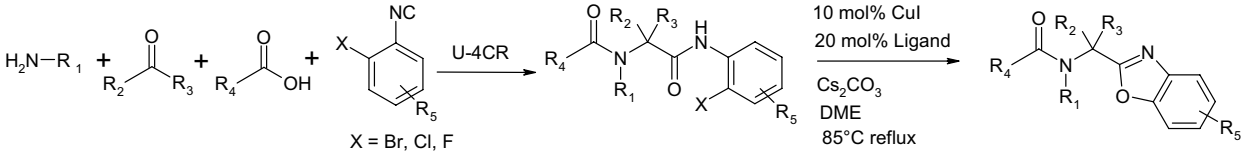
Keywords: Ugi-reaction; Multi-component reaction; Benzoxazoles; Benzothiazoles; Copper-catalyzed cyclization; Cross-coupling.
* Corresponding author. Tel.: +49 89 45213080; e-mail: spatz@priaton.de

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.10.067

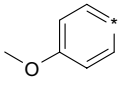


Scheme 2. Mechanistic proposal for the copper-catalyzed formation of benzoxazoles and benzothiazoles.

Table 1. Synthesized benzoxazoles

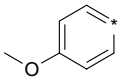


1 **2** **3** **4** **5** **7**

Entry	R_1	R_2	R_3	R_4	X	R_5	Y_1 (%)	MCR	Y_2 (%)	Final product
1		H			Br	H	99	**5a**	31	**7a**
2		H			Br	4-F, 6-Br	87	**5b**	42	**7b**
3		H		CH_3	Br	H	62	**5c**	99	**7c**
4		H		H	Br	H	99	**5d**	65	**7d**
5		H		CH_3	Cl	3-CF_3	99	**5e**	0	**7e**
6		H		CH_3	F	H	90	**5f**	0	**7f**
7		H		CH_3	Br	H	32	**5g**	65	**7g**
8		H	H		Br	H	99	**5h**	37	**7h**
9		CH_3	CH_3		Br	H	68	**5i**	68	**7i**

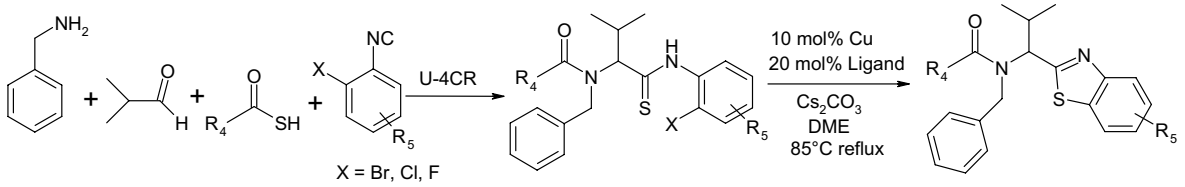
(*continued on next page*)

Table 1 (*continued*)

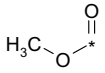
Entry	R_1	R_2	R_3	R_4	X	R_5	Y_1 (%)	MCR	Y_2 (%)	Final product
10		CH_3	CH_3	CH_3	Br	H	58	**5j**	43	**7j**
11		H			Br	H	99	**5k**	44	**7k**
12		H	H	CH_3	Br	H	33	**5l**	57	**7l**
13		H	H		Br	H	99	**5m**	44	**7m**
14		CH_3	CH_3		Br	H	27	**5n**	74	**7n**
15		H		CH_3	Br	H	76	**5o**	39	**7o**
16		CH_3	CH_3	CH_3	Br	H	13	**5p**	81	**7p**
17		CH_3	CH_3		Br	H	17	**5q**	81	**7q**

Y_1: Yield of MCR product (equimolar: aniline, aldehyde, carboxylic acid and isocyanide, TFE or MeOH, 21 °C).
Y_2: Yield of cyclization product (MCR product (1 equiv), CuI (10 mol %), ligand (20 mol %), Cs_2CO_3 (2 equiv), DME, 85 °C, pressure tube).

Table 2. Synthesized benzothiazoles



12 **13** **14** **4** **6** **8**

Entry	X	R_4	R_5	Y_1 (%)	MCR product	Y_2 (%)	Final product
1	Br	CH_3	H	99	**6a**	63	**8a**
2	Cl	CH_3	3-CF_3	99	**6b**	43	**8b**
3	F	CH_3	H	76	**6c**	59	**8c**
4	Br	CH_3	4-F, 6-Br	81	**6d**	94	**8d**
5	Cl	CH_3		71	**6e**	62	**8e**
6	Br		H	89	**6f**	75	**8f**
7	Cl		3-CF_3	52	**6g**	93	**8g**
8	F	CH_3	H	76	**6h**	55	**8h**[a]

Y_1: Yield of MCR product (equimolar: aniline, aldehyde, carboxylic acid and isocyanide, TFE or MeOH, 21 °C).
Y_2: Yield of cyclization product (MCR product (1 equiv), CuI (10 mol %), ligand (20 mol %), Cs_2CO_3 (2 equiv), DME, 85 °C, pressure tube).
[a] Cyclization without catalyst: MCR product (1 equiv), Cs_2CO_3 (2 equiv), DME, 85 °C, pressure tube.

acid **3** and isocyanide **4** to afford the desired product **5/6**. Here MeOH or trifluoroethanol (TFE) turned out to be the best solvents for the MCR step. After completion of the MCR the solvent was removed in vacuo. The conversions of the MCR products **5a–q** and **6a–h** determined by HPLC–MS[30] were generally good. Therefore in most cases the crude products could be used in the next reaction step without further purification, otherwise clean-up was done by column chromatography.[31] In the subsequent copper-catalyzed cyclization a catalyst combination of CuI (10 mol %), 1,10-phenanthroline (20 mol %) and Cs_2CO_3 (2 equiv) in DME was used at 85 °C in pressure tubes. Conversions were monitored by HPLC–MS. Generally, after 16 hours of reaction time a maximum of conversion was reached. All compounds were isolated by column chromatography on silica gel in good yields (Y_2) and purities.[32]

Table 1 shows the results for the synthesized benzoxazoles **7a–q** with specific yields for each step (Y_1 = MCR, Y_2 = copper-catalyzed cyclization). Aliphatic, phenylic and benzylic amines, aldehydes as well as ketones and aliphatic as well as aromatic acids could successfully be involved in the reaction, if *ortho*-bromophenylisocyanides were used. The use of fluoro- or chloro-phenylisocyanides did not lead to the desired cyclization.

After receiving good results for the benzoxazoles we extended the underlying synthetic procedure to benzothiazoles **8a–h**. In preliminary studies (Table 2), benzyl amine and *iso*-butyraldehyde were used for the preparation of the imine component. As a higher reactivity of the thioamides was supposed, different haloisocyanides were tested, whereby no significant differences between fluoro-, chloro- and bromo-derivatives were detected. For the fluoro-isocyanide a S_NAr mechanism was supposed, which was verified by an additional experiment without catalyst (Table 2, entry 8). In both reactions similar results were obtained. The reaction times (rt) for the cyclization are generally short and the conversions are moderate to good for all compounds. Chromatographic methods allow the isolation of products with high purity (>95%). All compounds were characterized by ^1H NMR, ^{13}C NMR and HPLC–MS data. The protocol is quite robust and tolerates a broad range of starting materials.

In summary, a novel two-step synthesis procedure for the preparation of highly substituted benzoxazoles and benzothiazoles has been described. Amines, carbonyls, acids and isocyanides can be varied broadly, leading to compounds with five potential points of diversity.

References and notes

1. Examples of benzoxazole natural products and their biological activities. For calcimycin (A-23187; antibiotic), see: Chaney, M. O.; Demarco, P. V.; Jones, N. D.; Occolowitz, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 1932. For AJI9561 (shows growth inhibitory activity against murine cancer cell line P 338), see: Sato, S.; Kajiura, T.; Noguchi, M.; Takehana, K.; Kobayasho, T.; Tsuji, T. *J. Antibiot.* **2001**, *54*, 102.
2. For examples of benzoxazoles in drug discovery, see: (a) Brown, R. N.; Cameron, R.; Chalmers, D. K.; Hamilton, S.; Luttick, A.; Krippner, G. Y.; McConnell, D. B.; Nearn, R.; Stanislawski, P. C.; Tucker, S. P.; Watson, K. G. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2051; (b) Manas, E. S.; Unwalla, R. J.; Xu, Z. B.; Malamas, M. S.; Miller, C. P.; Harris, H. A.; Hsiao, C.; Akopian, T.; Hum, W.-T.; Malakian, K.; Wolfrom, S.; Bapat, A.; Bhat, R. A.; Stahl, M. L.; Somers, W. S.; Alvarez, J. C. *J. Am. Chem. Soc.* **2004**, *126*, 15106; (c) Malamas, M. S.; Manas, E. S.; McDevitt, R. E.; Gunawan, I.; Xu, Z. B.; Collini, M. D.; Miller, C. P.; Dinh, T.; Henderson, R. A.; Keith, J. C., Jr.; Harris, H. A. *J. Med. Chem.* **2004**, *47*, 5021.
3. Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802.
4. Altenhoff, G.; Glorius, F. *Adv. Synth. Catal.* **2004**, *346*, 1661.
5. Joyce, L. L.; Evindar, G.; Batey, R. A. *Chem. Commun.* **2004**, 446.
6. Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643.
7. Gordon, E. M.; Gallop, M. A.; Patel, D. V. *Acc. Chem. Res.* **1996**, *29*, 144.
8. Dömling, A.; Ugi, I. *Angew. Chem.* **2000**, *112*, 3300.
9. Dömling, A.; Ugi, I.; Hörl, W. *Endeavour* **1994**, *18*, 15.
10. Keating, T. A.; Amstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 2574.
11. Ugi, I.; Steinbrückner, C. *Chem. Ber.* **1961**, *94*, 734.
12. Lee, D.; Sello, J. K.; Schreiber, S. L. *Org. Lett.* **2000**, *2*, 709.
13. Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133.
14. Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471.
15. Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233.
16. Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385.
17. Dömling, A. *Comb. Chem. High Throughput Screening* **1998**, *1*, 1.
18. Dömling, A. *Chem. Rev.* **2006**, *106*, 17.
19. Ugi, I.; Meyer, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, *71*, 386.
20. Kalinski, C.; Umkehrer, M.; Ross, G.; Kolb, J.; Burdack, C.; Hiller, W. *Tetrahedron Lett.* **2006**, *47*, 3423.
21. Xiang, Z.; Luo, T.; Lu, K.; Cui, J.; Shi, X.; Fathi, R.; Chen, J.; Yang, Z. *J. Org. Lett.* **2004**, *6*, 3155.
22. Beck, B.; Magnin-Lachaux, M.; Herdtweck, E.; Dömling, A. *J. Org. Lett.* **2001**, *3*, 2875.
23. Tempest, P.; Ma, V.; Kelly, M. G.; Jones, W.; Hulme, C. *Tetrahedron Lett.* **2001**, *42*, 4963.
24. Umkehrer, M.; Kalinski, C.; Kolb, J.; Burdack, C. *Tetrahedron Lett.* **2006**, *47*, 2391.
25. Cuny, G.; Bois-Choussy, M.; Zhu, J. *J. Am. Chem. Soc.* **2004**, *126*, 14475.
26. Pd-catalyzed C–N and C–O bond formation reactions, see: (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131; (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046.
27. Cu-catalyzed C–C, C–N and C–O bond formation reactions, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337; (b) Nelson, I. T. D.; Crouch, R. D. *Org. React.* **2004**, *63*, 265; (c) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400; (d) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428; (e) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359; (f) Finet, J.-P.; Fedorov, A. Y.; Combes, S.; Boyer, G. *Curr. Org. Chem.* **2002**, *6*, 597.
28. Cu-catalyzed C–N bond formation from aryl halides, see Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem. Eur. J.* **2004**, *10*, 5607.

29. See also: (a) Cohen, T.; Wood, J.; Dietz, A. G., Jr. *Tetrahedron Lett.* **1974**, *15*, 3555; (b) Cohen, T.; Cristea, I. *J. Am. Chem. Soc.* **1976**, *98*, 748; (c) Allred, G. D.; Liebskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748.

30. HPLC–MS/MS spectra (Varian 1200), Polaris, RP C18 column, 3 mm × 150 mm, 5 μm, ProStar 320 (254 nm), 1 mL/min, 3 min gradient from 90% H_2O to 10% H_2O (0.1% HCOOH) versus CH_3CN, coupled with a Quadrupol MS/MS mass spectrometer using electrospray ionization (ESI).

31. *General procedure for the synthesis of MCR products* **5a**–**q** *and* **6a**–**h** *(GP-MCR):* Amine **1** (1 mmol) and aldehyde **2** (1 mmol) were stirred in 3 mL methanol for 2 h. Then, carboxylic acid **3** or **7** (1 mmol) and isocyanide **4** (1 mmol) were added and the reaction mixture was stirred for 16 h at room temperature. Then, 10 mL water was added and the mixture was extracted with 3 × 15 mL of dichloromethane. The organic layer was dried over $MgSO_4$ and the resulting crude product was purified by flash chromatography or used in the next step without further purification.

32. *General procedure for the synthesis of benzoxazoles* **7a**–**q** *and benzothiazoles* **8a**–**h** *(GP-cyclization):* 1.0 mmol of MCR product **5a**–**q** resp. **6a**–**h** was dissolved in 4 mL DME (Glyme) and 10 mol % of CuI, 20 mol % of 1,10-phenanthroline and 2 mmol Cs_2CO_3 were added. The reaction mixture was stirred at 85 °C in a pressure tube for 16 h, followed by filtration over silica in order to remove the catalyst. The solvent was removed in vacuo. Then, 10 mL water was added and the mixture was extracted with 3 × 15 mL of ethyl acetate. The organic layer was dried over $MgSO_4$ and the resulting crude product was purified by flash chromatography.

Compound **7c** was prepared according to GP-cyclization and purified by flash chromatography on silica gel with eluent chloroform/methanol/ammonia (7 N in methanol) = 90/9/1 (318 mg, 99%). $m/z = 323$ $[M+H]^+$, $m/z = 345$ $[M+Na]^+$. ^1H NMR ($CDCl_3$, 250.13 MHz): 7.60–6.82 (m, 9H), 5.99 (d, $J = 11.1$ Hz, 1H), 4.71 (s, 2H), 2.71–2.89 (m, 1H), 2.13 (s, 3H), 1.06–1.03 (m, 6H). ^{13}C NMR ($CDCl_3$, 62.89 MHz): 172.4, 163.8, 150.4, 140.9, 136.9, 128.5, 127.7, 126.9, 125.7, 124.4, 120.2, 110.9, 56.7, 48.4, 28.9, 22.4, 20.3, 19.2.

Compound **7i** was prepared according to GP-cyclization and purified by flash chromatography on silica gel with eluent ethyl acetate/hexane = 1/1 (253 mg, 68%). $m/z = 371$ $[M+H]^+$, $m/z = 393$ $[M+Na]^+$. ^1H NMR ($CDCl_3$, 250.13 MHz): 7.71–7.68 (m, 1H), 7.53–7.23 (m, 13H), 4.87 (s, 2H), 1.82 (s, 6H). ^{13}C NMR ($CDCl_3$, 62.89 MHz): 173.1, 150.7, 141.7, 137.7, 129.5, 128.7, 126.8, 124.5, 124.3, 120.1, 110.7, 59.1, 46.0, 30.0, 26.2.

Compound **7j** was prepared according to GP-cyclization and purified by flash chromatography on silica gel with eluent ethyl acetate/hexane = 4/1 (133 mg, 43%). $m/z = 309$ $[M+H]^+$, $m/z = 331$ $[M+Na]^+$. ^1H NMR ($CDCl_3$, 250.13 MHz): 7.70–7.67 (m, 1H), 7.50–7.41 (m, 5H), 7.35–7.25 (m, 3H), 4.82 (s, 2H), 2.16 (s, 3H), 1.74 (s, 6H). ^{13}C NMR ($CDCl_3$, 62.89 MHz): 172.0, 171.1, 150.6, 141.7, 138.5, 129.3, 127.7, 126.2, 124.4, 124.3, 120.1, 110.8, 58.4, 49.2, 30.0, 26.1, 23.6.

Compound **7n** was prepared according to GP-cyclization and purified by flash chromatography on silica gel with eluent ethyl acetate/hexane = 2/1 (251 mg, 74%). $m/z = 339$ $[M+H]^+$, $m/z = 361$ $[M+Na]^+$. ^1H NMR ($CDCl_3$, 250.13 MHz): 7.69–7.66 (m, 1H), 7.49–7.45 (m, 1H), 7.41–7.35 (m, 5H), 7.28–7.24 (m, 2H), 3.74 (t, $J = 6.2$ Hz, 2H), 3.47 (t, $J = 6.0$; 6.3 Hz, 2H), 3.26 (s, 3H),1.94 (s, 6H). ^{13}C NMR ($CDCl_3$, 62.89 MHz): 173.1, 171.1, 150.7, 141.7, 137.7, 129.5, 128.7, 126.8, 124.5, 124.3, 120.1, 110.7, 72.7, 59.1, 58.3, 46.0, 30.0, 26.2.

Compound **7p** was prepared according to GP-cyclization and purified by flash chromatography on silica gel with eluent ethyl acetate/hexane = 1/1 (251 mg, 81%). $m/z = 309$ $[M+H]^+$, $m/z = 331$ $[M+Na]^+$. ^1H NMR ($CDCl_3$, 250.13 MHz): 7.73–7.71 (m, 1H), 7.53–7.51 (m, 1H), 7.36–7.26 (m, 6H), 2.44 (s, 3H), 1.78 (s, 3H), 1.67 (s, 6H). ^{13}C NMR ($CDCl_3$, 62.89 MHz): 171.1, 171.0, 150.9, 141.9, 139.1, 138.3, 130.5, 130.4, 124.5, 124.3, 120.2, 110.9, 58.4, 27.2, 24.8, 21.5.

Compound **7q** was prepared according to GP-cyclization and purified by flash chromatography on silica gel with eluent ethyl acetate/hexane = 2/1 (304 mg, 82%). $m/z = 371$ $[M+H]^+$, $m/z = 393$ $[M+Na]^+$. ^1H NMR ($CDCl_3$, 250.13 MHz): 7.75–7.71 (m, 1H), 7.54–7.50 (m, 1H), 7.20–7.30 (m, 6H), 7.14–7.05 (m, 5H), 2.28 (s, 3H), 1.77 (s, 6H). ^{13}C NMR ($CDCl_3$, 62.89 MHz): 171.3, 170.9, 150.9, 141.9, 138.4, 137.6, 137.3, 131.6, 129.7, 129.3, 128.4, 127.7, 124.5, 124.3, 120.2, 110.8, 59.3, 30.0, 27.0, 21.3.

Compound **8b** was prepared according to GP-cyclization and the resulting crude product was purified by flash chromatography on silica gel with eluent ethyl acetate/hexane = 2/1 (175 mg, 43%). $m/z = 407$ $[M+H]^+$, $m/z = 429$ $[M+Na]^+$. ^1H NMR ($CDCl_3$, 250.13 MHz): 8.05 (s, 1H), 7.91 (d, $J = 8.5$ Hz, 1H), 7.56 (d, $J = 8.5$ Hz, 1H), 7.05–6.83 (m, 5H), 5.65 (d, $J = 11.1$ Hz, 1H), 4.89–4.51 (m, 2H), 2.94–2.82 (m, 1H), 2.10 (s, 3H), 1.03 (d, $J = 6.6$ Hz, 3H), 0.94 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 62.89 MHz): 172.4, 170.9, 152.3, 138.9, 137.3, 129.0, 128.9, 128.5, 128.0, 127.1, 123.9 (d, $^1J(C,F) = 272.6$ Hz) 122.5, 122.3, 121.8, 120.6 (d, $^3J(C,F) = 4.6$ Hz), 62.4, 49.7, 29.8, 22.8, 20.4, 19.7.

Compound **8d** was prepared according to GP-cyclization and the resulting crude product was purified by flash chromatography on silica gel with eluent ethyl acetate/hexane = 1/1 (410 mg, 94%). $m/z = 436$ $[M+H]^+$, $m/z = 458$ $[M+Na]^+$. ^1H NMR ($CDCl_3$, 250.13 MHz): 7.39–7.31 (m, 2H), 7.04–6.89 (m, 5H), 5.53 (d, $J = 10.9$ Hz, 1H), 4.84 (d, $J = 17.2$ Hz, 1H), 4.67 (d, $J = 17.2$ Hz, 1H), 2.98–2.88 (m, 1H), 2.43 (s, 3H), 1.02 (d, $J = 6.6$ Hz, 3H), 0.94 (d,$J = 6.6$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 62.89 MHz): 172.3, 168.7, 168.7, 161.9, 158.0, 147.9, 137.2, 128.4, 127.0, 126.3, 118.7, 118.2, 117.2, 117.0, 107.3, 106.9, 50.1, 29.9, 22.8, 20.5, 19.7.