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PAPER

Metal-free, one-pot conversion of proline derivatives into 2-ary-3-iodo pyrrolidines, by a sequential scission-iodination-arylation process.

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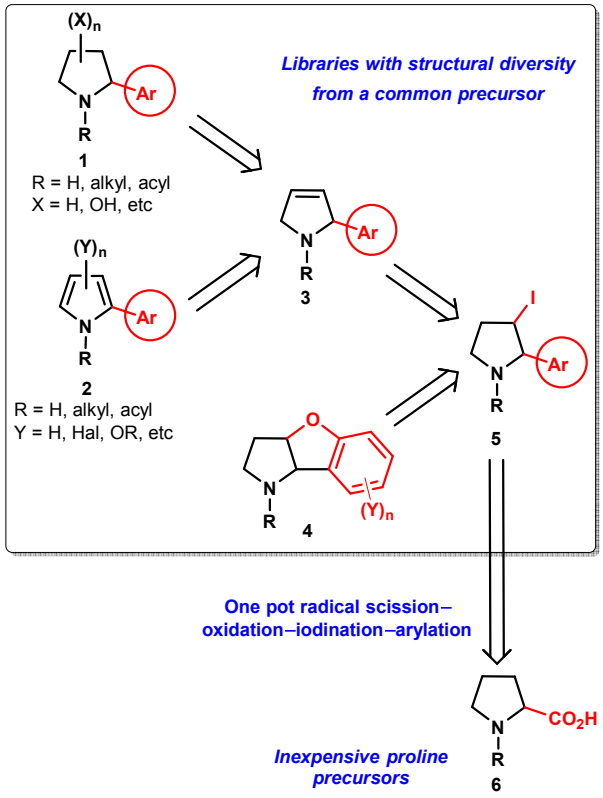
The metal-free, direct conversion of readily available proline derivatives into 2-aryl-3-iodopyrrolidines is carried out under mild conditions and good yields, using a sequential radical decarboxylation –oxidation–iodination–arylation reaction. These iodinated pyrrolidines are valuable precursors of other compounds. For instance, they can be cyclized to tricyclic compounds or undergo dehalogenation to 2-aryl-2,5-dihydro-1*H*-pyrroles, which are iminosugar and 2-arylpyrrole precursors. This process provides a short pathway to a variety of alkaloid and drug analogues with potential pharmaceutical interest.

Introduction

Many bioactive alkaloids and synthetic drugs present 2-(aryl)pyrrolidine, -dihydropyrrole or -pyrrole rings.[1] These compounds have displayed hypocholesterolemic activity (such as commercial atorvastatin), and some are antimicrobial, antiacid, antipsychotic, or cytotoxic agents.[1,2] Moreover, some arylpyrroles are used as anion sensors or in electronic and optical devices.[3]

Therefore, much effort has been devoted to their synthesis. For instance, the reductive amination of carbonyl compounds[4] or the (2+3)-cycloadditions[5] provide arylpyrrolidines,[6] while ring-closing metathesis of diallylamines generates dihydropyrroles that can be reduced to pyrrolidines or oxidized to pyrroles.[7] The 2-arylpyrroles[8] can be prepared by classic methodologies, such as the Paal-Knorr or Hantzsch cyclizations,[9] or by other methods such as the Trofimov reaction,[10] metal-catalyzed sp^2-sp^2 coupling of pyrroles to other aromatic rings,[11] or metal-promoted cyclizations.[12] However, many of these methods present disadvantages, such as harsh conditions, long reaction routes, use of starting materials that are expensive or not readily available, or are catalyzed by expensive, scarce or toxic metals. Therefore, in the last years, the development of more sustainable methodologies, preferably metal-free and multicomponent or multistep processes, has received considerable attention.[13,14] The domino or sequential processes are particularly attractive for industry, since they avoid the isolation of intermediates, save time and materials, and reduce the waste.

We report herein a diversity-oriented strategy which provides easy access to these families of compounds, using a metal-free sequential process as the key step. As shown in the retrosynthetic strategy (Scheme 1), both the functionalized 2-arylpyrrolidines **1** and the 2-arylpyrroles **2** could be generated from dihydropyrroles **3**, which in turn would be formed by dehalogenation of 2-aryl-3-iodopyrrolidines **5**.



Scheme 1. Diversity-oriented synthesis, using a key one-pot process.

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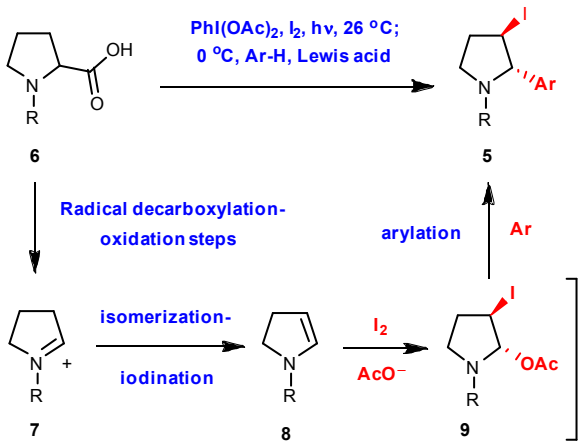
† Electronic Supplementary Information (ESI) available: ^{1}H and ^{13}C NMR spectra for products **11**–**20** and **22**–**31**. See DOI: 10.1039/b000000x/

If the dehalogenation of substrates **5** is replaced by an intramolecular substitution reaction, tetrahydro- benzofuro[3,2-b]pyrroles **4** or other polycyclic compounds can be obtained. Compounds **4** have been used as precursors of alkaloid and antibiotic analogs.[15]

Finally, the iodopyrrolidines **5** would be formed from inexpensive proline derivatives **6**, using a new sequential decarboxylation–iodination–arylation process. This one-pot process would use low-toxicity hypervalent iodine reagents instead of toxic and expensive metal promotors.

The key sequential process (Scheme 2) would be initiated by a domino radical decarboxylation–oxidation reaction, on treatment of the amino acid **6** with (diacetoxyiodo)benzene (DIB) and iodine, under irradiation with visible light.[16] The oxidative scission would generate an acyliminium ion **7**, which under appropriate conditions could isomerize to an enamine derivative **8**. This intermediate would react with excess iodine and acetate ions from DIB to give an iodopyrrolidine **9**.[17] On treatment with a Lewis acid and arene nucleophiles, a variety of 2-aryl-3-iodopyrrolidines **5** would be obtained.



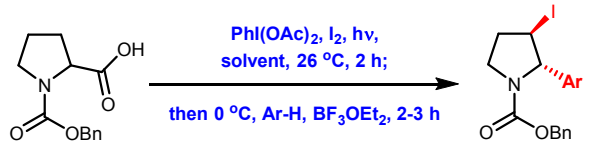
Scheme 2. Study of the scission-iodination-arylation process

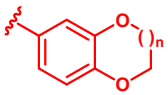
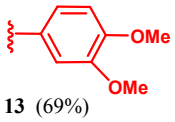
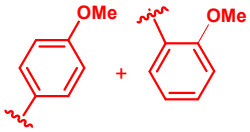
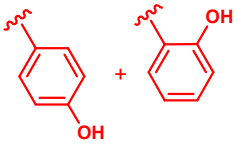
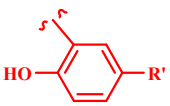
We had previously reported related scission–iodination –alkylation procedures,[17] using allylsilanes, silylenol ethers and vinyl ethers in the alkylation step. However, replacing the alkylation step by an arylation was not trivial, because even electron-rich arene rings are much less reactive than the other *C*-nucleophiles. In fact, in a parallel work on the addition of *C*-nucleophiles to acetoxyacetals derived from carbohydrates, we noticed that the alkylation proceeded in good to excellent yields,[18] while the arylation failed completely. Later on, we suceeded in the arylation of glycine cations, where the acyliminium ion was rendered more electrophilic by the adjacent electron-withdrawing carbonyl group.[19] However, we wondered whether less reactive acyliminium ions could be arylated, and whether this reaction could be coupled with a previous decarboxylation–iodination process. We report herein the achievement of this synthetic challenge.

The One-pot Radical Scission–Oxidation–Arylation Process.

The conversion of proline derivatives into 2-aryl-3-iodopyrrolidines was studied under different conditions, with proline carbamate **10** (R = Cbz) as the substrate, and benzo[d][1,3]-dioxole as the nucleophile (Table 1, entries 1-4).

Table 1: Study of the decarboxylation–iodination–arylation process



entry	**10**/DIB/I_2 (mmol)[a]	solvent	products (%)
			Ar = 
1	1/1.5/1.1	CH_2Cl_2	**11** n = 0 (18%)
2	1/1.5/1.1	MeCN	**11** n = 0 (63%)
3	1/1.5/1.1	$MeNO_2$	**11** n = 0 (70%)
4	1/1.5/1.5	$MeNO_2$	**11** n = 0 (61%)
5	1/1.5/1.1	$MeNO_2$	**12** n = 1 (64%)
			
6	1/1.5/1.1	MeCN	**13** (69%)
7	1/1.5/1.1	$MeNO_2$	**13** (80%)
			
8	1/1.5/1.1	MeCN	**14** (57%) + **15** (6%)
9	1/1.5/1.1	$MeNO_2$	**14** (63%) + **15** (5%)
			Ar = 
10	1/1.5/1.1	MeCN	**16** (59%) + **17** (6%)
11	1/1.5/1.1	$MeNO_2$	**16** (53%) + **17** (6%)
			
12	1/1.5/1.1	MeCN	**R' = Br** **18** (62%)[b]
13	1/1.5/1.1	MeCN	**R' = OMe** **19** (67%)[b]
14	1/1.5/1.1	MeCN	**R' = Me** **20** (69%)[b]

[a] Ar-H (4 mmol); [b] reaction time = 3 h

The best results were obtained with the polar solvents acetonitrile and nitromethane, which afforded the product **11** in good yields. Increasing the iodine amount from 1 to 1.5 equiv (entries 3 and 4) slighty reduced the yields, probably due to side reactions. The process was then studied with other aromatic nucleophiles (entries 5-9). Under the optimized conditions, the arylations proceeded in good global yields (63–80%) to give compounds **12**–**15**. When anisole was used as nucleophile (entries 8-9), the *p*-methoxyphenyl derivative **14** was the major product (*para: ortho* 12:1), as expected.

Remarkably, only the 2,3-*trans* isomers were detected. The stereochemistry was assigned using the NMR coupling constants and by comparison with related compounds.[17] It was confirmed by intramolecular substitution experiments, as commented later.

We then wondered whether phenol derivatives could be used as nucleophiles,[20] in spite of the oxidative conditions (entries 10-14). To our satisfaction, the arylation with different phenol derivatives proceeded in good yields, affording compounds **16**–**20**. No oxidation or halogenation of the aromatic rings was observed, suggesting that these side-reactions were slow compared to arylation. However, control of the reaction time is important, since long times resulted in complex reaction mixtures, probably due to side reactions on the phenol ring and transformations of the 3-iodopyrrolidine (see later).

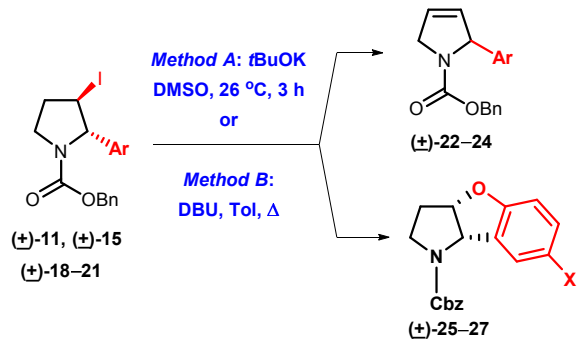
In case that a mixture of *ortho*- and *para*-products could be obtained (entries 10 and 11), the *para*-product clearly predominated. Besides, when 4-methoxyphenol was used as the nucleophile (entry 13), the directing effect of the OH group predominated, and only compound **19** was formed.

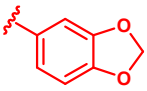
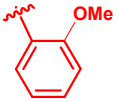
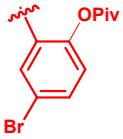
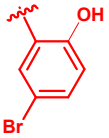
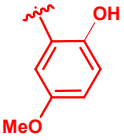
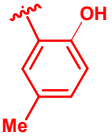
The 2-aryl-3-(iodo)pyrrolidines can be converted into different types of compounds depending on the substrate (Table 2). Thus, when protected arene derivatives such as compounds **11**, **15** and **21** were treated with base (*t*BuOK or DBU, entries 1–3) the major or exclusive product was the elimination product (dihydropyrroles **22**, **23** and **24** respectively). Compounds **22** and **23** were obtained in excellent yields after treatment of the iodopyrrolidines with *t*BuOK (entries 1-2). Product **23** is a known precursor of pentabromopseudilin, a marine alkaloid active against multidrug-resistant *S. aureus*.[2h,i]

In the case of substrate **21** (entry 3) DBU was used as a base to minimize the hydrolysis of the labile phenyl ester, generating the desired dihydropyrrole **24** in 55% yield. However, the minor product **25** (resulting from ester saponification and intramolecular substitution reaction)[21] was isolated in significant amounts (41%).

When the related phenol substrate **18** was used (entries 4 and 5) the tricyclic product **25** was formed in excellent yields, both on treatment with *t*BuOK (entry 4) or DBU (entry 5). Similar results were obtained with the phenol substrates **19** (entry 6) and **20** (entry 7), which afforded compounds **26** and **27**, respectively. The formation of compound **26** supports the structure and 2,3-*trans* stereochemistry assigned to its precursor **19**. The antimicrobial activity[17a] of the tricyclic compounds is currently under study.

Table 2: Reactivity of the 2-aryl-3-iodopyrrolidines: Elimination *versus* IM substitution reactions

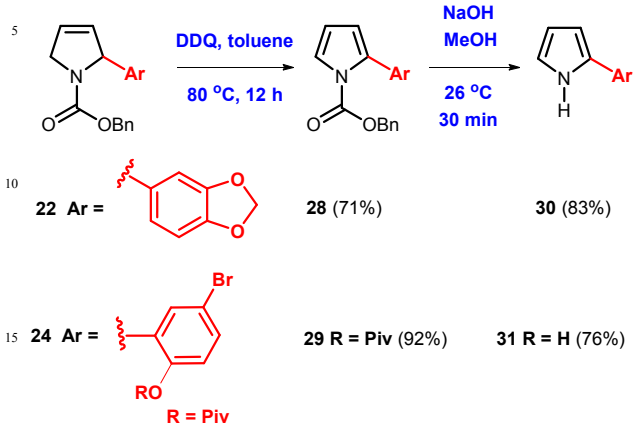


entry	substrate	Ar	method	products (%)[a]
1	**11**		**A**	**22** (98%)
2	**15**		**A**	**23** (97%)
3	**21**		**B**	**24** (55%) **25** (X = Br, 41%)
4	**18**		**A**	**25** (96%)
5	**18**		**B**	**25** (94%)
6	**19**		**A**	**26** (X = OMe), (92%)
7	**20**		**A**	**27** (X = Me) (97%)

[a] Purified by column chromatography

Dihydropyrroles are useful synthetic intermediates that can be functionalized (dihydroxylated, epoxidated, etc) by conventional methodologies to provide a diversity of 2-arylpyrrolidines.[22] Alternatively, they can be readily oxidized to pyrroles with DDQ,[23] as shown with the conversions of compounds **22** and **24** (Scheme 3) to the pyrrole derivatives **28** and **29** in good yields. The saponification of these pyrroles afforded the unprotected 2-aryl pyrroles **30** and **31**. The benzodioxolyl pyrroles such as compound **30** are components of drug leads, such as selective

acid blockers,[24] while pyrroles related to product **31** are potent lipooxygenase inhibitors,[25] and besides, are components of novel antipain and antipyretic agents.[26]



Scheme 3. Conversion of dihydropyrroles into pyrroles

Conclusions

An efficient, diversity-oriented process for the transformation of readily available proline derivatives into 2-(aryl)pyrrolidines, dihydropyrroles, or -pyrroles, as well as polycyclic compounds, is described herein. The resultant 2-(aryl)azaheterocycles constitute the core of many bioactive alkaloids and synthetic drugs. The key step is the direct conversion of inexpensive proline derivatives into 2-aryl-3-(iodo)pyrrolidines, using a sequential radical decarboxylation–oxidation–iodination–addition of arene nucleophiles process. This new, one-pot method used low-toxicity hypervalent iodine reagents instead of toxic and expensive metal promotors.

The one-pot process took place in good yields and under mild conditions, in spite of the known poor reactivity of arenes compared to other *C*-nucleophiles. Remarkably, phenol derivatives can be used as nucleophiles; no oxidation or halogenation of the aromatic ring was observed.

The 2-aryl-3-(iodo)pyrrolidines are valuable precursors of other compounds. For instance, the intramolecular subtitution of the iodo group in (2-hydroxyphenyl)-3-iodopyrrolidines generated polycyclic compounds in excellent yields.

Alternatively, elimination of the iodo group provided dihydropyrroles, which can be functionalized as reported in the literature to give a variety of 2-arylpyrrolidines. On the other hand, the dihydropyrroles can be oxidized to 2-arylpyrroles. This versatile strategy was applied to the formal synthesis of 2-arylpyrroles present in drug candidates.

In summary, an inexpensive proline substrate can be transformed into a diversity of heterocyclic compounds, using an efficient, metal-free, sequential process as the key step.

Experimental section

General Methods. General Remarks: Commercially available reagents and solvents were analytical grade or were purified by standard procedures prior to use. All reactions involving air- or moisture-sensitive materials were carried out under nitrogen atmosphere. The spray reagent for TLC analysis was 0.5% vanillin in H_2SO_4–EtOH (4:1), and the TLC was heated until development of color. Merck silica gel 60 PF_{254} and 60 (0.063–0.2 mm) were used for rotatory chromatography and column chromatography, respectively. Melting points were determined with a hot-stage apparatus and are uncorrected; the term "net" is used for crystals resulting from evaporation of the cromatography eluents. Optical rotations were measured at the sodium line at ambient temperature (26 °C). Mass spectra were determined at 70 eV. NMR spectra were determined at 500 or 400 MHz for ^{1}H and 125.7 or 100 MHz for ^{13}C in the presence of TMS as internal standard, unless otherwise stated. ^{1}H NMR references: $CDCl_3$ (δ_H 7.26), CD_3OD (δ_H 3.31). ^{13}C NMR references: $CDCl_3$ (δ_C 77.0), CD_3OD (δ_C 49.0).

General Procedure for the radical decarboxylation–oxidation–iodination–arylation process: To a solution of L- or D,L-proline benzyl carbamate **10** (100 mg, 0.40 mmol) in dry solvent (4 mL) was added iodine (110 mg, 0.44 mmol) and (diacetoxyiodo)benzene (DIB) (190 mg, 0.60 mmol). The reaction mixture was stirred at room temperature (26 °C) under irradiation with visible light (sunlight or 80-W tungsten-filament lamp) for 2 h. After 2 h the reaction mixture was cooled to 0 °C with an ice bath and $BF_3.OEt_2$ was added dropwise (0.10 mL, 0.80 mmol), followed by addition of the nucleophile (1.6 mmol). The reaction mixture was stirred at the same temperature for 3-4 h, and then was poured into a 10% aqueous sodium thiosulfate containing sodium bicarbonate and extracted with dichloromethane. The organic layers were dried with sodium sulfate and filtered, and the solvent was removed under vacuum. Then the residue was purified by column chromatography on silica gel (hexane/ethyl acetate), affording the 2-aryl-3-iodopyrrolidines **11–20**.

(2*S,3*R**)-Benzyl 2-(benzo[d][1,3]dioxol-5-yl)-3-iodopyrrolidine-1-carboxylate (11)**: Obtained from commercial L- or D,L-proline benzyl carbamate (**10**) according to the General Procedure for the Decarboxylation-iodination-arylation process, using benzo[d][1,3]dioxole (195 mg, 1.6 mmol) as the nucleophile and nitromethane as the solvent. After usual work-up and purification, product **11** (126 mg, 70%) was isolated as a colorless oil: One rotamer at 70 °C; IR ($CHCl_3$) ν_{max}/cm^{-1} 3010, 1702; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 2.19 (m, 1H), 2.33 (m, 1H), 3.74 (ddd, J = 3.2, 7.9, 11.0 Hz, 1H), 3.97 (ddd, J = 7.1, 9.1, 10.9 Hz, 1H), 4.26 (m, 1H), 5.08 (br d, J = 12.3 Hz, 1H), 5.15 (d, J = 12.3 Hz, 1H), 5.27 (brs, 1H), 5.94 (s, 2H), 6.68 (s, 1H), 6.69 (d, J = 8.8 Hz, 1H), 6.74 (d, J = 8.6 Hz, 1H), 7.08–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ_C 28.8 (CH), 34.9 (CH_2), 46.3 (CH_2), 67.0 (CH_2), 72.5 (CH), 101.2 (CH_2), 106.1 (CH), 108.5 (CH), 119.0 (CH), 127.5 (2 × CH), 127.8 (CH), 128.3 (2 × CH), 135.5 (C), 136.8 (C), 147.3 (C), 148.3 (C), 154.8 (C); MS (EI) *m/z* (%) 451 (M^+, 2), 324 (M^+ – I, 9), 91 ($[PhCH_2]^+$, 100); HRMS calcd. for $C_{19}H_{18}INO_4$ 451.0281, found 451.0278; calcd. for $C_{19}H_{18}NO_4$ 324.1236, found 324.1241. $C_{19}H_{18}INO_4$ requires C, 50.57; H, 4.02; N, 3.10. Found C, 50.39; H, 4.43; N, 3.24.

(2*S,3*R**)-Benzyl 2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-3-iodopyrrolidine-1-carboxylate (12)**: Obtained from commercial proline benzyl carbamate (**10**) according to the General Procedure for the Decarboxylation-iodination-arylation process, using 2,3-dihydrobenzo[b][1,4]dioxine (218 mg, 1.6 mmol) as the

nucleophile and nitromethane as the solvent. After usual work-up and purification, product **12** (120 mg, 64%) was isolated as a colorless oil: one rotamer at 70 °C. IR ($CHCl_3$) ν_{max}/cm^{-1} 3026, 1700; ^1H NMR (500 MHz, 70 °C, $CDCl_3$) δ_H 2.17 (m, 1H), 2.33 (m, 1H), 3.75 (ddd, *J* = 2.9, 7.9, 10.8 Hz, 1H), 3.95 (ddd, *J* = 7.0, 9.5, 10.7 Hz, 1H), 4.23 (s, 4H), 4.27 (ddd, *J* = 2.5, 2.5, 5.0 Hz, 1H), 5.09 (d, *J*= 10.9 Hz, 1H), 5.14 (d, *J* = 11.9 Hz, 1H), 5.26 (br s, 1H), 6.68 (dd, *J* = 2.1, 8.4 Hz, 1H), 6.71 (d, *J* = 2.2 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 7.00–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ_C 29.0 (CH), 34.9 (CH_2), 46.2 (CH_2), 64.5 (2 × CH_2), 67.0 (CH_2), 72.3 (CH), 114.6 (CH), 117.6 (CH), 118.6 (CH), 127.5 (2 × CH), 127.8 (CH), 128.4 (2 × CH), 134.8 (C), 136.9 (C), 143.3 (C), 144.0 (C), 154.8 (C); MS (EI) *m/z* (%) 465 (M^+, 2), 338 (M^+ – I, 9), ($[PhCH_2]^+$, 100); HRMS calcd. for $C_{20}H_{20}INO_4$ 465.0437, found 465.0453; calcd. for $C_{20}H_{20}NO_4$ 338.1392, found 338.1392.

(2*S,3*R**)-Benzyl 2-(3,4-dimethoxyphenyl)-3-iodopyrrolidine-1-carboxylate** (**13**): Obtained from proline benzyl carbamate (**10**) according to the General Procedure for the Decarboxylation-iodination-arylation process, using 1,2-dimethoxybenzene (221 mg, 1.6 mmol) as the nucleophile and nitromethane as the solvent. After usual work-up and purification, product **13** (150 mg, 80%) was isolated as a colorless solid; m.p. 98–100°C (MeOH). One rotamer at 70 °C; IR ($CHCl_3$) ν_{max}/cm^{-1} 3020, 1698; ^1H NMR (500 MHz, 70 °C, $CDCl_3$) δ_H 2.20 (m, 1H), 2.34 (m, 1H), 3.76 (ddd, *J* = 3.0, 7.5, 10.4 Hz, 1H), 3.80 (s, 3H), 3.87 (s, 3H), 3.98 (ddd, *J* = 8.3, 8.8, 9.8 Hz, 1H), 4.30 (m, 1H), 5.08 (br d, *J* = 12.0 Hz, 1H), 5.14 (d, *J* = 12.1 Hz, 1H), 5.30 (br s, 1H), 6.71 (br s, 1H), 6.74 (br d, *J* = 8.4 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 7.14 (m, 1H), 7.24 (m, 4H); ^{13}C NMR ($CDCl_3$, 70 °C, 125.7 MHz) δ_C 29.1 (CH), 35.0 (CH_2), 46.3 (CH_2), 56.3 (2 × CH_3), 67.1 (CH_2), 72.5 (CH), 110.1 (CH), 112.4 (CH), 118.0 (CH), 127.6 (2 × CH), 127.8 (CH), 128.4 (2 × CH), 134.8 (C), 136.9 (C), 149.3 (C), 150.0 (C), 154.9 (C); MS (EI) *m/z* (%) 467 (M^+, 5), 340 (M^+-I, 11), 91 ($[PhCH_2]^+$, 100); HRMS calcd. for $C_{20}H_{22}INO_4$ 467.0594, found 467.0610.

(2*S,3*R**)-Benzyl 3-iodo-2-(4-methoxyphenyl)pyrrolidine-1-carboxylate (14) and (2*S**,3*R**)-Benzyl 3-iodo-2-(2-methoxyphenyl)pyrrolidine-1-carboxylate** (**15**): Obtained from commercial proline benzyl carbamate (**10**) according to the General Procedure for the decarboxylation-iodination-arylation process, using anisole (173 mg, 1.6 mmol) as the nucleophile and nitromethane as the solvent. After usual work-up and purification, product **14** (111 mg, 63%) and its isomer **15** (9 mg, 5%) were isolated (120 mg, 68% global yield). Compound **14** was isolated as a colorless oil: one rotamer at 70 °C. IR ($CHCl_3$) ν_{max}/cm^{-1} 3014, 1701, 1612; ^1H NMR (500 MHz, 70 °C, $CDCl_3$): δ 2.18 (m, 1H), 2.33 (m, 1H), 3.76 (ddd, *J* = 3.1, 8.1, 11.0 Hz, 1H), 3.80 (s, 3H), 3.98 (ddd, *J* = 7.0, 9.1, 10.8 Hz, 1H), 4.26 (ddd, *J* = 2.7, 2.8, 5.2 Hz, 1H), 5.02–5.18 (m, 2H), 5.30 (brs, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 8.7 Hz, 2H), 7.10–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 70 °C, 125.7 MHz) δ_C 29.2 (CH), 34.8 (CH_2), 46.3 (CH_2), 55.4 (CH_3), 67.0 (CH_2), 72.3 (CH), 114.5 (2 × CH), 126.8 (4 × CH), 127.8 (CH), 128.3 (2 × CH), 133.7 (C), 136.9 (C), 154.8 (C), 159.4 (C); MS (EI) *m/z* (%) 437 (M^+, 1), 310 (M^+– I, 21), 91 ($[PhCH_2]^+$, 100); HRMS calcd. for $C_{19}H_{20}INO_3$ 437.0488, found 437.0481.

Compound (15) was isolated as a colorless oil: one rotamer at 70 °C. ^1H NMR (500 MHz, 70 °C, $CDCl_3$) δ_H δ 2.12–2.27 (m, 2H), 3.80 (br dd, *J* = 8.6, 10 Hz, 1H), 3.87 (s, 3H), 4.02 (ddd, *J* = 6.9, 10.4, 10.5 Hz, 1H), 4.41 (d, *J* = 4.6 Hz, 1H), 5.00-5.21 (brb, 2H), 5.55 (br s, 1H), 6.88 (dd, *J* = 7.5, 7.7 Hz, 2H), 7.01 (d, *J* = 7.5 Hz, 2H), 7.15–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 70 °C, 125.7 MHz) δ_C 28.6 (CH), 34.6 (CH_2), 46.2 (CH_2), 55.6 (CH_3), 66.9 (CH_2), 68.9 (CH), 110.9 (2 × CH), 120.8 (2 × CH), 126.0 (C), 127.8 (CH), 128.4 (CH), 128.8 (3 × CH), 136.9 (C), 154.9 (C), 156.7 (C); MS (EI) *m/z* (%) 437 (M^+, 1), 310 (M^+ – I, 7), 91 ($[PhCH_2]^+$, 100); HRMS calcd. for $C_{19}H_{20}INO_3$ 437.0488, found 437.0475.

(2*S,3*R**)-Benzyl 2-(4-hydroxyphenyl)-3-iodopyrrolidine-1-carboxylate** (**16**) **and (2*S**,3*R**)-Benzyl 2-(2-hydroxyphenyl)-3-iodopyrrolidine-1-carboxylate** (**17**): Obtained from commercial proline benzyl carbamate (**10**) according to the General Procedure for the decarboxylation-iodination-arylation process, using phenol (150 mg, 1.6 mmol) as the nucleophile and acetonitrile as the solvent. After usual work-up and purification, product **16** (100 mg, 59%) and its isomer **17** (10 mg, 6%) were isolated (110 mg, 65% global yield). Compound **16** was isolated as a colorless solid: m.p. 150–152 °C (MeOH). One rotamer at 70 °C. IR ($CHCl_3$) ν_{max}/cm^{-1} 3342, 3018, 1698; ^1H NMR (500 MHz, 70 °C, DMSO-d_6) δ_H 2.13 (m, 1H), 2.26 (m, 1H), 3.71 (ddd, *J* = 2.9, 8.0, 10.8 Hz, 1H), 3.78 (ddd, *J* = 7.3, 9.0, 10.4 Hz, 1H), 4.41 (ddd, *J* = 2.5, 2.5, 4.8 Hz, 1H), 5.00-5.10 (m, 2H), 5.15 (br s, 1H), 6.73 (d, *J* = 8.5 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 2H), 7.10–7.40 (m, 5H), 9.22 (br b, 1H, OH); ^{13}C NMR (DMSO-d_6, 70 °C, 125.7 MHz) δ_C 31.2 (CH), 34.0 (CH_2), 45.6 (CH_2), 65.9 (CH_2), 71.8 (CH), 115.2 (2 × CH), 126.6 (2 × CH), 126.7 (CH), 127.3 (2 × CH), 128.0 (2 × CH), 131.2 (C), 136.7 (C), 153.9 (C), 156.7 (C); MS (EI) *m/z* (%) 423 (M^+, 1), 296 (M^+– I, 13), 91 ($[PhCH_2]^+$, 100); HRMS calcd. for $C_{18}H_{18}INO_3$ 423.0331, found 423.0318; calcd. for $C_{18}H_{18}NO_3$ 296.1287, found 296.1278.

Compound 17: colorless solid; m.p. 178-180°C (MeOH). One rotamer at 70 °C. IR ($CHCl_3$) ν_{max}/cm^{-1} 3290, 3022, 1696, 1605; ^1H NMR (500 MHz, 70 °C, DMSO-d_6) δ_H 2.08–2.15 (m, 2H), 3.74–3.87 (m, 2H), 4.44 (m, 1H), 4.98–5.19 (s, 2H), 5.40 (br s, 1H), 6.74 (dd, *J* = 7.4, 7.5 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 7.5 Hz, 1H), 7.03 (m, 1H), 7.11 (dd, *J* = 7.5, 7.6 Hz, 1H), 7.14-7.50 (m, 4H), 9.64 (br s, 1H, OH); ^{13}C NMR (DMSO-d_6, 70 °C, 125.7 MHz) δ_C 30.7 (CH), 33.7 (CH_2), 45.7 (CH_2), 66.0 (CH_2), 68.3 (CH), 115.3 (2 × CH), 119.2 (CH), 125.8 (CH), 127.1 (C), 127.5 (CH), 128.1 (2 × CH), 128.4 (2 × CH), 137.0 (C), 153.9 (C), 154.0 (C); MS (EI) *m/z* (%) 423 (M^+, 5), 91 ($[PhCH_2]^+$, 100); HRMS calcd. for $C_{18}H_{18}INO_3$ 423.0331, found 423.0318.

(2*S,3*R**)-Benzyl 2-(5-bromo-2-hydroxyphenyl)-3-iodopyrrolidine-1-carboxylate** (**18**): Obtained from commercial proline benzyl carbamate (**10**) according to the General Procedure for the Decarboxylation-iodination-arylation process, using 4-bromophenol (277 mg, 1.6 mmol) as the nucleophile and acetonitrile as the solvent. After usual work-up and purification, product **18** (125 mg, 62%) was isolated as a syrup: One rotamer at 70 °C; IR ($CHCl_3$) ν_{max}/cm^{-1} 3263, 1685, 1420; ^1H NMR (500 MHz, 70 °C, $CDCl_3$) δ_H 2.20 (dd, *J* = 6.8, 14.3 Hz, 1H), 2.29 (m, 1H), 3.80 (ddd, *J* = 2.2, 8.2, 10.7 Hz, 1H), 4.00 (ddd, *J* = 7.0, 10.7, 10.7 Hz, 1H), 4.41 (brd, *J* = 4.8 Hz, 1H), 5.24 (s, 2H), 5.48 (brs, 1H), 6.36 (d, *J* = 7.9 Hz, 1H), 6.97 (brs, 1H), 7.07 (brd, *J* = 8.2 Hz, 1H), 7.27–7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 125.7 MHz)

δ_C 26.5 (CH), 35.1 (CH_2), 46.3 (CH_2), 67.8 (CH_2), 68.4 (CH), 112.3 (C), 118.1 (CH), 127.7 (2 × CH), 128.2 (CH), 128.6 (3 × CH), 129.2 (C), 131.7 (CH), 136.5 (C), 153.3 (C), 155.8 (C); MS (EI) *m/z* (%) 503/501 (M^+, <1/<1), 375/373 (M^+ – HI, 6/6), 284/282 (M^+ – HI – CH_2Ph, 14/14), 91 ($[PhCH_2]^+$, 100); HRMS calcd. for $C_{18}H_{17}I^{81}BrNO_3$ 502.9416, found 502.9411; calcd. for $C_{18}H_{17}I^{79}BrNO_3$ 500.9437, found 500.9456. $C_{18}H_{17}IBrNO_3$ requires C, 43.05; H, 3.41; N, 2.79. Found C, 43.13; H, 3.36; N, 3.03.

(2*S,3*R**)-Benzyl 2-(2-hydroxy-5-methoxyphenyl)-3-iodopyrrolidine-1-carboxylate** (**19**): Obtained from commercial proline benzyl carbamate (**10**) according to the General Procedure for the Decarboxylation-iodination-arylation process, using 4-methoxyphenol (198 mg, 1.6 mmol) as the nucleophile and acetonitrile as the solvent. After usual work-up and purification, product **19** (122 mg, 67%) was isolated as a colorless solid; m.p. 168-170°C (MeOH). One rotamer at 70 °C; IR ($CHCl_3$) ν_{max}/cm^{-1} 3330, 3022, 1694; ^1H NMR (500 MHz, DMSO-d_6) δ_H 2.06–2.20 (m, 2H), 3.61 (s, 3H), 3.74–3.85 (m, 2H), 4.45 (m, 1H), 4.92–5.20 (m, 2H), 5.35 (br s, 1H), 6.45 (d, *J* = 2.7 Hz, 1H), 6.71 (dd, *J* = 2.8, 8.7 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 7.07 (m, 1H), 7.18–7.44 (m, 4H), 9.17 (s, 1H, OH); ^{13}C NMR (DMSO-d_6, 125.7 MHz) δ_C 30.1 (CH), 33.6 (CH_2), 45.7 (CH_2), 55.4 (CH_3), 65.8 (CH_2), 68.5 (CH), 111.8 (CH), 113.4 (CH), 116.0 (CH), 126.7 (2 × CH), 127.5 (CH +C), 128.2 (2 × CH), 137.0 (C), 148.0 (C), 152.5 (C), 154.1 (C); MS (EI) *m/z* (%) 453 (M^+, 4), 326 (M^+– I, 3), 325 (M^+– HI, 9), 91 ($[PhCH_2]^+$, 100); HRMS calcd. for $C_{19}H_{20}INO_4$ 453.0437, found 453.0428; calcd. for $C_{19}H_{19}NO_4$ 325.1314, found 325.1307.

(2*S,3*R**)-Benzyl 2-(2-hydroxy-5-methylphenyl)-3-iodopyrrolidine-1-carboxylate** (**20**): Obtained from commercial proline benzyl carbamate (**10**) according to the General Procedure for the Decarboxylation-iodination-arylation process, using *p*-cresol (173 mg, 1.6 mmol) as the nucleophile and acetonitrile as the solvent. After usual work-up and purification, product **21** (120 mg, 69%) was isolated as a colorless solid; m.p. 160-162 °C (MeOH). One rotamer at 70 °C; IR ($CHCl_3$) ν_{max}/cm^{-1} 3314, 3014, 1692, 1605; ^1H NMR (500 MHz, 70 °C, DMSO-d_6) δ_H 2.06–2.18 (m, 2H), 2.16 (s, 3H), 3.80 (m, 2H), 4.43 (m, 1H), 4.93–5.18 (m, 2H), 5.37 (br s, 1H), 6.71 (br s, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 7.04 (m, 1H), 7.13–7.50 (m, 4H), 9.35 (s, 1H, OH); ^{13}C NMR (DMSO-d_6, 70 °C, 125.7 MHz) δ_C 20.2 (CH_3), 30.9 (CH), 34.0 (CH_2), 45.7 (CH_2), 65.7 (CH_2), 68.4 (CH), 115.1 (2 × CH), 125.8 (CH), 127.1 (C), 127.6 (2 × CH), 128.2 (CH + C), 128.8 (2 × CH), 137.0 (C), 151.9 (C), 154.1 (C); MS (EI) *m/z* (%) 437 (M^+, 1), 310 (M^+– I, 4), 309 (M^+– HI, 17), 91 ($[PhCH_2]^+$, 100); HRMS calcd. for $C_{19}H_{20}INO_3$ 437.0488, found 437.0508; calcd. for $C_{19}H_{20}NO_3$ 310.1443, found 310.1451; calcd. for $C_{19}H_{19}NO_3$ 309.1365, found 309.1366.

(2*S,3*R**)-Benzyl 2-(5-bromo-2-pivaloyloxyphenyl)-3-iodo pyrrolidine-1-carboxylate** (**21**): A solution of the iodopyrrolidine **18** (70 mg, 0.14 mmol) in dry CH_2Cl_2 (4 mL) at 0 °C was treated with DMAP (5 mg, 0.04 mmol) and DIPEA (35 µL, 0.20 mmol). The reaction mixture was stirred at 0 °C for 15 min, then PivCl was added (25 µL, 0.20 mmol) and the mixture was allowed to reach 26 °C and stirred for 1 h. Then it was poured into water and extracted with CH_2Cl_2, and the organic layer was dried and evaporated as usual. The residue was purified by flash chromatography on silica gel (hexane/EtOAc 90:10), affording product **21** (72 mg, 88%) as a yellow oil: One rotamer at 70 °C; IR ($CHCl_3$) ν_{max}/cm^{-1} 3015, 1749, 1702, 1473; ^1H NMR (500 MHz, 70 °C, $CDCl_3$) δ_H 1.43 (s, 9H), 2.17 (br dd, *J* = 6.3, 14.2 Hz, 1H), 2.27 (m, 1H), 3.83 (dd, *J* = 8.8, 10.2 Hz, 1H), 3.98 (ddd, *J* = 6.7, 10.7, 10.7 Hz, 1H), 4.27 (d, *J* = 4.6 Hz, 1H), 5.10 (br b, 2H), 5.40 (br b, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 6.95–7.20 (br b, 2H), 7.20 (d, *J* = 2.2 Hz, 1H), 7.20–7.33 (m, 3H), 7.40 (dd, *J* = 2.2, 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ_C 27.0 (CH), 27.5 (3 × CH_3), 34.4 (CH_2), 39.5 (C), 46.2 (CH_2), 67.3 (CH_2), 67.6 (CH), 119.3 (C), 124.4 (CH), 127.4 (CH), 127.9 (C), 128.5 (2 × CH), 129.1 (3 × CH), 131.8 (CH), 147.6 (C), 154.6 (2 × C), 176.6 (C); MS (EI) *m/z* (%) 587/585 (M^+, <1/<1), 503/501 (M^+ + H – CO*t*Bu, 1/1), 91 ($[PhCH_2]^+$, 100); HRMS calcd. for $C_{23}H_{25}I^{81}BrNO_4$ 586.9991, found 586.9989; calcd. for $C_{23}H_{25}I^{79}BrNO_4$ 585.0012, found 585.0023. $C_{23}H_{25}IBrNO_4$ requires C, 47.12; H, 4.30; N, 2.39. Found C, 47.09; H, 4.51; N, 2.62.

General Procedures for the Generation of Dihydropyrroles or 2,3,3a,8b-tetrahydro-1*H*-benzofuro[3,2-b]pyrroles. ***Method A.*** To a solution of the 2-aryl-3-(iodo)pyrrolidine (0.35 mmol) in DMSO (8 mL), was added potassium *tert*-butoxide (47 mg, 0.42 mmol) at room temperature. The mixture was stirred for 3 h and then was poured into water and extracted with ethyl acetate. The organic layers were dried with sodium sulfate and filtered, and the solvent was removed under vacuum. ***Method B.*** A stirred solution of the 2-aryl-3-(iodo)pyrrolidine (0.35 mmol) in toluene (6 mL) was treated with DBU (105 µL, 107 mg, 0.7 mmol) at 80 °C for 3 h. Then the reaction mixture was cooled to 26 °C and poured into 5% aqueous HCl and extracted with EtOAc. The organic layers were dried and concentrated as before.

Benzyl 2-(benzo[d][1,3]dioxol-5-yl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (**22**): Obtained from compound **11** (158 mg, 0.35 mmol) according to the General Procedure for the Generation of Dihydropyrroles, *Method A*. After usual work-up and purification by column chromatography on silica gel (hexane/EtOAc 90:10), compound **22** (111 mg, 98%) was obtained as as a colorless liquid: one rotamer at 70 °C. IR ($CHCl_3$) ν_{max}/cm^{-1} 3010, 1699; ^1H NMR (500 MHz, 70 °C, $CDCl_3$) δ_H 4.29–4.40 (m, 2H), 4.99–5.22 (m, 2H), 5.45 (m, 1H), 5.73 (m, 1H), 5.88 (m, 1H), 5.90 (br s, 2H), 6.60–6.90 (m, 3H), 7.07 (m, 1H), 7.20–7.37 (m, 4H);^{13}C NMR ($CDCl_3$, 125.7 MHz) δ_C 54.0 (CH_2), 66.9 (CH), 68.0 (CH), 101.0 (CH_2), 107.4 (CH), 108.1 (CH), 120.4 (CH), 124.6 (2 × CH), 127.8 (2 × CH + C), 128.3 (CH), 131.2 (2 × CH), 135.8 (C), 136.9 (C), 147.1 (C), 148.0 (C), 154.6 (C); MS (EI) *m/z* (%) 323 (M^+, 6), 232 (M^+ – CH_2Ph, 75), 91 ($[PhCH_2]^+$, 100); HRMS calcd. for $C_{19}H_{17}NO_4$ 323.1158, found 323.1160. $C_{19}H_{17}NO_4$ requires C, 70.58; H, 5.30; N, 4.33. Found C, 70.41; H, 5.11; N, 4.52.

Benzyl 2-(2-methoxyphenyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (**23**): Obtained from benzyl 3-iodo-2-(2-methoxyphenyl)pyrrolidine-1-carboxylate (**15**) (153 mg, 0.35 mmol) according to the General Procedure for the Generation of Dihydropyrroles, *Method A*. After usual work-up and purification by column chromatography (hexane/EtOAc 95:5), product **23** (105 mg, 97%) was isolated as yellow crystals. Compound **24** is known and has previously been described.[2h,i]

Benzyl 2-(5-bromo-2-pivaloyloxyphenyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (**24**): A solution of compound **21** (61 mg, 0.1 mmol) in dry toluene (3 mL) was treated with DBU (30 μL, 0.2 mmol) and the mixture was refluxed for 4 h. Then it treated as described in *Method B* and the residue was purified by column chromatography (hexanes:EtOAc 95:5) to give the dihydropyrrole **24** (26 mg, 55%) and the tricyclic compound **25** (16 mg, 41%) which will be described later. Compound **24** was isolated as a syrup: One rotamer at 70 °C; IR ($CHCl_3$) ν_{max}/cm^{-1} 3018, 1750, 1703, 1477, 1416; ^1H NMR (500 MHz, 70 °C, $CDCl_3$) δ_H 1.33 (s, 9H), 4.39 (s, 2H), 4.93–5.17 (br b, 2H), 5.63 (br b, 1H), 5.71 (br d, J = 8.2 Hz, 1H), 5.86 (br b, 1H), 6.85 (br b, 1H), 6.95–7.10 (br b, 1H), 7.15–7.25 (m, 4H), 7.24 (d, J = 2.5 Hz, 1H), 7.33 (dd, J = 2.6, 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ_C 27.2 (3 × CH_3), 39.4 (C), 54.1 (CH_2), 62.1 (CH), 67.1 (CH_2), 119.4 (C), 123.9 (CH), 125.4 (CH), 127.8 (2 × CH), 128.4 (CH), 129.9 (2 × CH), 130.0 (CH), 131.2 (2 × CH), 147.2 (C), 154.3 (C), 176.5 (C). Two aromatic (C) were not clearly observed; MS (EI) *m/z* (%) 459/457 (M^+, <1/<1), 324/322 (M^+ – CO_2CH_2Ph, 8/8), 91 ($[PhCH_2]^+$, 73), ($[Me_3C]^+$, 100); HRMS calcd. for $C_{23}H_{24}{}^{79}BrNO_4$ 457.0889, found 457.0891. $C_{23}H_{24}BrNO_4$ requires C, 60.27; H, 5.28; N, 3.06. Found C, 60.56; H, 5.33; N, 3.20.

Benzyl (3aS,8bS)-7-bromo-2,3,3a,8b-tetrahydro-1*H*-benzofuro[3,2-b]pyrrole-1-carboxylate (**25**): Obtained from compound **18** (176 mg, 0.35 mmol) as described in the General Procedure for the Generation of Dihydropyrroles, *Method A*. After purification by column chromatography (hexane/EtOAc 85:15), compound **25** (126 mg, 96%) was isolated.

Compound **25** was also obtained from compound **18** (176 mg, 0.35 mmol) as described in Method *B*, as a yellowish amorphous solid (123 mg, 94%): IR ($CHCl_3$) ν_{max}/cm^{-1} 3015, 1697, 1470, 1425; ^1H NMR (500 MHz, 70 °C, $CDCl_3$) δ_H 2.13 (m, 1H), 2.26 (dd, J = 6.2, 13.9 Hz, 1H), 3.25 (ddd, J = 6.3, 11.0, 11.1 Hz, 1H), 3.84 (br b, 1H), 5.06–5.25 (m, 2H), 5.27 (br dd, J = 5.4, 6.7 Hz, 1H), 5.43 (br b, 1H), 6.62 (d, J = 8.5 Hz, 1H), 7.17–7.50 (m, 7H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ_C 32.0 (CH_2), 43.9 (CH_2), 62.9 (CH), 67.4 (CH_2), 87.2 (CH), 111.2 (CH), 112.7 (C), 128.2 (2 × CH), 128.6 (2 × CH +C), 130.0 (CH), 133.0 (2 × CH), 136.6 (C), 154.0 (C), 159.5 (C); MS (ESI) *m/z* (%) 398/396 (M^+ + Na, 100); HRMS calcd. for $C_{18}H_{16}Na^{81}BrNO_3$ 398.0191, found 398.0192; calcd. for $C_{18}H_{16}Na^{79}BrNO_3$ 396.0211, found 396.0216. $C_{18}H_{16}BrNO_3$ requires C, 57.77; H, 4.31; N, 3.74. Found C, 57.38; H, 4.37; N, 3.96.

Benzyl (3aS,8bS)-7-methoxy-2,3,3a,8b-tetrahydro-1*H*-benzofuro[3,2-b]pyrrole-1-carboxylate (**26**): Obtained from compound **19** (158 mg, 0.35 mmol) according to the General Procedure for the Generation of Tetrahydrobenzofuropyrroles, *Method A*. After usual work-up and purification by column chromatography on silica gel (hexane/EtOAc 90:10), compound **26** (105 mg, 92%) was obtained as a syrup: IR ($CHCl_3$) ν_{max}/cm^{-1} 3018, 1695, 1487; ^1H NMR (500 MHz, 70 °C, $CDCl_3$) δ_H 2.12 (m, 1H), 2.26 (dd, J = 6.2, 13.8 Hz, 1H), 3.29 (ddd, J = 6.2, 11.0, 11.1 Hz, 1H), 3.40–3.90 (m, 4H), 5.10–5.30 (m, 2H), 5.27 (dd, J = 5.6, 5.6 Hz, 1H), 5.47 (m, 1H), 6.66 (d, J = 8.7 Hz, 1H), 6.74 (br d, J = 7.4 Hz, 1H), 6.86 (m, 1H), 7.10–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$, 70 °C, 125.7 MHz) δ_C 32.3 (CH_2), 44.0 (CH_2), 56.1 (CH_3), 63.6 (CH), 67.2 (CH_2), 87.2 (CH), 109.8 (CH), 112.5 (CH), 116.8 (CH), 128.1 (3 × CH + C), 128.5 (2 × CH), 136.9 (C), 154.6 (C), 154.7 (2 × C); MS (ESI) *m/z* (%) 348 (M^+ + Na, 100); HRMS calcd. for $C_{19}H_{19}NNaO_4$ 348.1212, found 348.1207.

Benzyl (3aS,8bS)-7-methyl-2,3,3a,8b-tetrahydro-1*H*-benzofuro[3,2-b]pyrrole-1-carboxylate (**27**): Obtained from compound **20** (153 mg, 0.35 mmol) according to the General Procedure for the Generation of Tetrahydrobenzofuropyrroles. After usual work-up and purification by column chromatography on silica gel (hexane/EtOAc 90:10), compound **27** (105 mg, 97%) was obtained as a syrup: IR ($CHCl_3$) ν_{max}/cm^{-1} 3010, 1697, 1492, 1421; ^1H NMR (500 MHz, 70 °C, $CDCl_3$) δ_H 2.09–2.36 (m, 5H), 3.29 (ddd, J = 6.2, 11.1 Hz, 1H), 3.86 (m, 1H), 5.15 (m, 1H), 5.26–5.32 (m, 2H), 5.46 (m, 1H), 6.66 (d, J = 8.2 Hz, 1H), 6.98 (d, J = 7.9 Hz, 1H), 6.99 (brs, 1H), 7.26–7.56 (m, 5H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ_C 20.6 (CH_3), 32.1 (CH_2), 44.0 (CH_2), 63.4 (CH), 67.2 (CH_2), 87.0 (CH), 109.1 (2 × CH), 126.7 (C), 127.6 (CH), 128.2 (CH), 128.6 (2 × CH), 130.3 (C), 130.6 (2 × CH), 136.9 (C), 154.2 (C), 158.4 (C); MS (EI) *m/z* (%) 309 (M^+, 23), 218 (M^+ – CH_2Ph, 82), 91 ($[PhCH_2]^+$, 100); HRMS calcd. for $C_{19}H_{19}NO_3$ 309.1365, found 309.1360. $C_{19}H_{19}NO_3$ requires C, 73.77; H, 6.19; N, 4.53. Found C, 73.68; H, 6.23; N, 4.80.

Benzyl 2-(benzo[d][1,3]dioxol-5-yl)-1*H*-pyrrole-1-carboxylate (**28**): A mixture of the dihydropyrrole **22** (100 mg, 0.31 mmol) and DDQ (84 mg, 0.37 mmol) in toluene (5 mL) was heated to 80 °C under nitrogen atmosphere for 12 h. Then the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane/EtOAc 95:5), affording compound **28** (70 mg, 71%) as a colorless oil; IR ($CHCl_3$) ν_{max}/cm^{-1} 3010, 1699; ^1H NMR (500 MHz,$CDCl_3$) δ_H 5.15 (s, 2H), 5.87 (s, 2H), 6.09 (dd, J = 1.9, 3.5 Hz, 1H), 6.15 (dd, J = 3.2, 3.4 Hz, 1H), 6.68 (d, J = 7.8 Hz, 1H), 6.73 (br s, 1H), 6.74 (dd, J = 2.1, 7.8 Hz, 1H), 7.15–7.19 (m, 2H), 7.24–7.28 (m, 3H), 7.29 (dd, J = 1.8, 3.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ_C 68.8 (CH_2), 101.0 (CH_2), 107.5 (CH), 110.2 (CH), 111.2 (CH), 114.7 (CH), 122.2 (CH), 122.9 (CH), 127.4 (C), 128.3 (2 × CH), 128.5 (3 × CH), 134.6 (C), 135.1 (C), 146.9 (C), 147.1 (C), 150.5 (C); MS (EI) *m/z* (%) 321 (M^+, 20), 186 (M^+ – CO_2Bn, 46), 91 ($[PhCH_2]^+$, 100); HRMS calcd. for $C_{19}H_{15}NO_4$ 321.1001, found 321.0996.

Benzyl 2-(5-bromo-2-pivaloyloxyphenyl)-1*H*-pyrrole-1-carboxylate (**29**): A solution of the dihydropyrrole **24** (35 mg, 0.08 mmol) and DDQ (26 mg, 0.11 mmol) in dry toluene (2 mL) was refluxed for 12 h. Then the mixture was cooled to 26 °C, the solvent was removed under vacuum and the residue was purified by column chromatography (hexanes: EtOAc 95:5) to give the pyrrole **29** (32 mg, 92%) as an oil: One rotamer at 70 °C; IR ($CHCl_3$) ν_{max}/cm^{-1} 3015, 1751, 1500, 1479; ^1H NMR (500 MHz, 70 °C, $CDCl_3$) δ_H 1.05 (s, 9H), 5.15 (br s, 2H), 6.15 (dd, J = 1.7, 3.3 Hz, 1H), 6.22 (dd, J = 3.2, 3.5 Hz, 1H), 6.84 (d, J = 8.5 Hz, 1H), 7.11-7.14 (m, 2H), 7.27-7.30 (m, 3H), 7.37 (dd, J = 2.6, 8.5 Hz, 1H), 7.38 (dd, J = 1.9, 3.5 Hz, 1H), 7.43 (d, J = 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ_C 26.9 (3 × CH_3), 39.1 (C), 69.1 (CH_2), 111.4 (CH), 115.9 (CH), 118.1 (C), 122.4 (CH), 123.6 (CH), 128.4 (2 × CH), 128.6 (3 × CH), 128.7 (C), 129.8 (C), 131.9 (CH), 134.0 (CH), 134.6 (C), 149.0 (C), 150.4 (C), 175.9 (C); MS (EI) *m/z* (%) 457/455 (M^+, 4/4), 91 ($[PhCH_2]^+$, 100); HRMS calcd. for $C_{23}H_{22}{}^{81}BrNO_4$ 457.0712, found 457.0709;

calcd. for $C_{23}H_{22}{}^{79}BrNO_4$ 455.0732, found 455.0749. $C_{23}H_{22}BrNO_4$ requires C, 60.54; H, 4.86; N, 3.07. Found C, 60.25; H, 5.01; N, 3.21.

2-(Benzo[d][1,3]dioxol-5-yl)-1*H*-pyrrole (**30**): Compound **28** (65 mg, 0.2 mmol) in MeOH (2 mL) was treated with a solution of NaOH (80 mg, 2.0 mmol) in MeOH (3 mL), and the mixture was stirred for 30 min. at 26 ºC. Then the solvent was partially removed under vacuum, and the mixture was poured into water and extracted with EtOAc. The organic layer was dried and the solvent was removed as usual, and the residue was purified by chromatography on silicagel (hexane:EtOAc 1:1), affording compound **30** (31 mg, 83%) as a red solid. IR ($CHCl_3$) ν_{max}/cm^{-1} 3477, 1504, 1492; ^1H NMR (500 MHz, CD_3OD, 70 ºC) δ_H 5.88 (s, 2H), 6.10 (dd, J = 3.2, 3.2 Hz, 1H), 6.29 (dd, J = 1.6, 3.5 Hz, 1H), 6.73 (dd, J = 1.3, 2.7 Hz, 1H), 6.76 (d, J = 7.9 Hz, 1H), 7.01 (dd, J = 1.9, 7.9 Hz, 1H), 7.02 (d, J = 1.6 Hz, 1H); ^{13}C NMR (125.7 MHz, CD_3OD, 70 ºC) δ_C 102.1 (CH_2), 105.6 (CH), 105.8 (CH), 109.4 (CH), 109.8 (CH), 118.3 (CH), 119.4 (CH), 129.7 (C), 133.3 (C), 147.2 (C), 149.5 (C); MS (EI) *m/z* (%) 187 (M^+, 100); HRMS calcd. for $C_{11}H_9NO_2$ 187.0633, found 187.0639.

2-(5-bromo-2-hydroxyphenyl)-1*H*-pyrrole (**31**): A solution of the pyrrole **29** (23 mg, 0.05 mmol) in MeOH (1 mL) was treated with NaOH (20 mg, 0.5 mmol) in MeOH (0.5 mL). The solution was stirred at 26 ºC for 30 min., then the solvent was partially removed under vacuum, and the mixture was poured into water and extracted with EtOAc. The organic layer was dried and evaporated as usual, and the residue was purified by column chromatography (hexanes: EtOAc 1:1) to give the dihydropyrrole **31** (9 mg, 76%) as an orange oil. One rotamer at 70 ºC; IR ($CHCl_3$) ν_{max}/cm^{-1} 3689, 1602; ^1H NMR (500 MHz, 70 ºC, CD_3OD) δ_H 6.15 (dd, J = 2.9, 3.2 Hz, 1H), 6.54 (dd, J = 1.3, 3.5 Hz, 1H), 6.75 (d, J = 8.9 Hz, 1H), 6.81 (d, J = 1.6 Hz, 1H), 7.05 (dd, J = 2.2, 8.5 Hz, 1H), 7.63 (d, J = 2.6 Hz, 1H); ^{13}C NMR (CD_3OD, 125.7 MHz) δ_C 107.7 (CH), 109.4 (CH), 113.0 (C), 119.0 (CH), 119.4 (CH), 123.7 (C), 129.6 (CH + C), 129.7 (CH), 153.1 (C); MS (EI) *m/z* (%) 239/237 (M^+, 98/100); HRMS calcd. for $C_{10}H_8{}^{81}BrNO$ 238.9769, found 238.9774; calcd. for $C_{10}H_8{}^{79}BrNO$ 236.9789, found 236.9797. $C_{10}H_8BrNO$ requires C, 50.45; H, 3.39; N, 5.88. Found C, 50.57; H, 3.65; N, 5.89.

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Notes and references

1 (a) D. Mal, B. Shome and B. K. Dinda, *Pyrrole and its derivatives*, in *Heterocycles in Natural Product Synthesis*; eds. K. C. Majumdar and S. K. Chattopadhyay, Wiley-VCH, Weinheim, 2011, 187–220; (b) S. M. Bronner, G.-Y. Im and N. K. Garg, *Indoles and Indolizidines,* in *Heterocycles in Natural Product Synthesis*; eds. K. C. Majumdar and S. K. Chattopadhyay, Wiley-VCH, Weinheim, 2011, 221–266; (c) See also: D. Hernández and A. Boto, *Eur. J. Org. Chem.* 2014, 2201–2220; (d) B. L. Stocker, E. M. Dangerfield, A. L. Win-Mason, G. W. Haslett and M. S. M. Timmer, *Eur. J. Org. Chem.* 2010, 1615–1637; (e) H. Fan, H. Peng, M. T. Hamann and J. F. Hu, *Chem. Rev.*, 2008, **108**, 264–287; (f) C. T. Walsh, S. Garneau-Tsodikova and A. R. Howard-Jones, *Nat. Prod. Rep.* 2006, **23**, 517–531; (g) A. Fürstner, *Angew. Chem., Int. Ed.* 2003, **42**, 3582–3603; (h) T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. 1* 2001, 2491–2515.

2 (a) For some bioactive alkaloids: Lamellarins: M. Komatsubara, T. Umeki, T. Fukuda, M. Iwao, *J. Org. Chem.* 2014, **79**, 529–537; (b) Tambjamine: P. Iglesias-Hernández, D. Moreno, A. Araujo-Javier, T. Torroba, R. Pérez-Tomás, R. Quesada, *Chem. Commun.* 2012, **48**, 1556–1558; (c) Radicamines: C.-Y. Yu, M.-H. Huang, *Org. Lett.* 2006, **8**, 3021–3024; (d) Radicamines: M. K. Gurjar, R. G. Borhade, V. G. Puranik and C. V. Ramana, *Tetrahedron Lett.* 2006, **47**, 6979–6981; (e) Prodigiosins: A. Fürstner, *Angew. Chem. Int. Ed.* 2003, **42**, 3582–3603. (f) Codonopsin: D. F. Oliveira, E. A. Severino, and C. R. D. Correia, *Tetrahedron Lett.* 1999, **40**, 2083–2086; (g) E.-L. Tsou, S.-Y. Chen, M. S. Yang, S. C. Wang, T.-R. R. Cheng, and W. C. Cheng, *Bioorg. Med. Chem.* 2008, **16**, 10198–10204. (h) pentabromopseudilin: C. S. Schwalm, I. B. D. De Castro, J. Ferrari, F. L. De Oliveira, R. Aparicio and C. R. D. Correia, *Tetrahedron Lett.* 2012, **53**, 1660–1663; (i) R. Martin, A. Jäger, M. Böhl, S. Richter, R. Fedorov, D. J. Manstein, H. O. Gutzeit and H.-J. Knölker, *Angew. Chem. Int. Ed.* 2009, **48**, 8042–8046.

3 (a) Reviews on anion sensors: C. J. E. Haynes and P. A. Gale, *Chem. Commun*. 2011, **47,** 8203–8209; (b) H. Maeda and Y. Bando, *Chem. Commun.* 2013, **49**, 4100–4113; (c) Reviews on optical and electronic properties: S. Fukuzumi, K. Ohkubo, F. D'Souza and J. L. Sessler, *Chem. Commun*., 2012, **48**, 9801–9815.

4 (a) C. Ribes, E. Falomir, M. Carda and J. A. Marco, *J. Org. Chem.* 2008, **73**, 7779–7782; (b) M. Yokoyama, T. Ikeue, Y. Ochiai, A. Momotake, K. Yamaguchi and H. Togo, *J. Chem. Soc., Perkin Trans. 1,* 1998, 2185–2191; (c) A. Momotake, H. Togo and M. Yokoyama, *J. Chem. Soc., Perkin Trans. 1,* 1999, 1193–1200; (d) M. Yokoyama, T. Ikenogami, H. Togo, *J. Chem. Soc., Perkin Trans. 1,* 2000, 2067–2071.

5 (a) For a review on cycloadditions, see: C. Nájera and J. M. Sansano, *Org. Biomol. Chem.*, 2009, **7**, 4567–4581; (b) For recent work, see: R. K. Khangarot and K. P. Kaliappan, *Eur. J. Org. Chem.* 2012, 5844–5854; (c) J. Adrio and J. C. Carretero, *Chem. Commun.,* 2011, **47**, 6784–6794; (d) A. López-Pérez, J. Adrio, J. C. Carretero, *J. Am. Chem. Soc.* 2008, **130**, 10084–10085; (e) D. V. Gribkov, S. J. Pastine, M. Schnürch, D. Sames, *J. Am. Chem. Soc.* 2007, **129**, 11750–11755; (f) See also: E. Coutouli-Argyropoulou, S. Trakossas, *Tetrahedron* 2011, **67**, 1915–1923.

6 For other methods, see: (a) T. Cheng, S. Meng and Y. Huang, *Org. Lett.* 2013, **15**, 1958–1961; (b) G. Barker, J. L. McGrath, A. Klapars, D. Stead, G. Zhou, K. R. Campos and P. O'Brien, *J. Org. Chem.* 2011, **76**, 5936–5953; (c) S. G. Davies, J. A. Lee, P. M. Roberts, J. E. Thomson, C. J. West, *Tetrahedron* 2012, **68**, 4302–4319; (d) G. B. Evans, R. H. Furneaux, H. Hausler, J. S. Larsen, P. C. Tyler, *J. Org. Chem.* 2004, **69**, 2217–2220; (e) F. D. King, A. E. Aliev, S. Caddick, D. A. Tocher, and D. Courtier-Murias, *Org. Biomol. Chem.*, 2009, **7**, 167–177.

7 (a) For a review on the synthesis of dihydropyrroles, see: M. Brichacek and J. T. Njardarson, *Org. Biomol. Chem.*, 2009, **7**, 1761–1770; (b) For a review on RCM: T. J. Donohoe, J. F. Bower and L. K. M. Chan, *Org. Biomol. Chem.*, 2012, **10**, 1322–1328.

8 (a) For reviews on the synthesis of arylpyrroles, see: V. Estévez, M. Villacampa and J. C. Menéndez, *Chem. Commun.,* 2013, **49**, 591–593; (b) S. Thirumalairajan, B. M. Pearce and A. Thompson, *Chem. Commun.*, 2010, **46**, 1797–1812; (c) B. Jolicoeur, E. E. Chapman, A. Thompson and W. D. Lubell, *Tetrahedron* 2006, **62**, 11531–11563.

9 (a) For Paal-Knorr reactions, see: P. Sawant and M. E. Maier, *Eur. J. Org. Chem.* 2012, 6576–6585; (b) P. B. Cranwell, M. O'Brien, D. L. Browne, P. Koos, A. Polyzos, M. Peña-López and S. V. Ley, *Org. Biomol. Chem.*, 2012, **10**, 5774–5779; (c) W. J. Kuo, Y.-H. Chen, R.-J. Jeng, L.-H. Chan, W.-P. Lina, Z.-M. Yang, *Tetrahedron* 2007, **63**, 7086–7096; (d) M. Biava, G. C. Porretta, G. Poce, D. Deidda, R. Pompei, A. Tafi and F. Manetti, *Bioorg. Med. Chem.* 2005, **13**, 1221–1230. (e) For Hantzsch reactions, see: E. Vanotti, M. Caldarelli, T. Disingrini, M. Nesi, M. Tato, P. Vianello and M. Menichincheri, *Tetrahedron* 2009, **65**, 10418–10423.

10 (a) O. V. Petrova, L. N. Sobenina, I. A. Ushakov, A. I. Mikhaleva, S. H. Hyun and B. A. Trofimov, *ARKIVOC* 2009, **4**, iv, 14–20; (b) For recent improvements of this methodology, see: S. Ngwerume and J. E. Camp, *Chem. Commun.,* 2011, **47**, 1857–1859 and references cited therein.

11 (a) N. Laidaoui, J. Roger, A. Miloudi, D. El Abed, H. Doucet, *Eur. J. Org. Chem.* **2011**, 4373–4385; (b) S.-M. T. Toguem, O. Fatunsin, A. Villinger, P. Langer, *Tetrahedron Lett.* 2011, **52**, 3732–3735; (c) J. Wen, S. Qin, L.-F. Ma, L. Dong, J. Zhang, S.-S. Liu, Y.-S. Duan, S.-Y. Chen, C.-W. Hu and X.-Q. Yu, *Org. Lett.* 2010, **12**, 2694–2697; (d) C. Song, P. Zhao, Y. Liu, H. Liu, W. Li, S. Shi and J. Chang, *Tetrahedron* 2010, **66**, 5378–5383.

12 (a) For Pd-promoted reactions, see: Y.-H. Xu, T. He, Q.-C. Zhang and T.-P. Loh, *Chem. Commun.,* 2014, **50**, 2784–2786; (b) Z. Shi, M. Suri, F. Glorious, *Angew. Chem. Int. Ed.* 2013, **52**, 4892–4896; (c) J. Nordmann and T. J. J. Müller, *Org. Biomol. Chem.*, 2013, 11, 6556–6561; (d) For Au-promoted reactions, see: Q. Zeng, L. Zhang, J. Yang, B. Xu, Y. Xiao and J. Zhang, J. *Chem. Commun.* **2014**, *50*, 4203–4206; (e) M. Zhang and J. Zhang, *Chem. Commun.* 2012, **48**, 6399–6401; (f) D. M. Barber, H. Sanganee and D. J. Dixon, *Chem. Commun.* 2011, **47**, 4379–4381; (f) For Ag-promoted reactions, see: R. J. Billedeau, K. R. Klein, D. Kaplan, Y. Lou, *Org. Lett*. 2013, **15**, 1421–1423; (g) J. Ke, C. He, H. Liu, M. Lia and A. Lei, *Chem. Commun.,* 2013, **49**, 7549–7551; (h) For Ru- and Rh-promoted reactions, see: L. Wang and L. Ackermann, *Org. Lett.* 2013, **15**, 176–179; (i) B. Li, N. Wang, Y. Liang, S. Xu and B. Wang, *Org. Lett.* 2013, **15**, 136–139; (j) S. Rakshit, F. W. Patureau, and F. Glorius, *J. Am. Chem. Soc.* 2010, **132**, 9585–9587; (k) For Cu-promoted reactions, see: L. Yufeng, S. Jie, W. Zhengguang, W. Xinglong, W. Xiaowei, G. Jiachao, B. Hongzhong and M. Hongfei, *Tetrahedron* 2014, **70**, 2472–2477; (l) X. Tang, L. Huang, C. Qi, W. Wu and H. Jiang, *Chem. Commun.,* 2013, **49**, 9597–9599; (m) F. Chen, T. Shen, Y. Cui and N. Jiao, *Org. Lett.* 2012, **14**, 4926–4929.

13 (a) For reviews on multicomponent reactions for the synthesis of pyrroles, see: V. Estévez, M. Villacampa and J. C. Menéndez, *Chem. Soc. Rev.* 2010, **39**, 4402–4421; (b) V. Estévez, M. Villacampa and J. C. Menéndez, *Chem. Soc. Rev.* 2014, **43**, 4633-4657.

14 (a) For recent articles: J. Shen, G. Cheng and X. Cui, *Chem. Commun.* 2013, **49**, 10641–10643; (b) C. Jadhav, P. B. Jagadhane, H. V. Patile and V. N. Telvekar, *Tetrahedron Lett.* 2013, **54**, 3019–3021; (c) G. Bharathiraja, S. Sakthivel, M. Sengoden and T. Punniyamurthy, *Org. Lett.* 2013, **15**, 4996–4999; (d) X. Qi, X. Xu and C.-M. Park, *Chem. Commun.* 2012, **48**, 3996–3998; (e) X. Lin, Z. Mao, X. Dai, P. Lu and Y. Wang, *Chem. Commun.* 2011, **47**, 6620–6622; (f) M. S. T. Morin, D. J. St.Cyr and B. A. Arndsten, *Org. Lett.* 2010, **12**, 4916–4919; (g) S. Ngwerume and J. E. Camp, *J. Org. Chem.*, 2010, **75**, 6271–6274; (h) M. Yoshida, M. Al-Amin, K. Shishido, *Tetrahedron Lett.* 2009, **50**, 6268–6270; (i) B. Khalili, P. Jajarmi, B. Eftekhari-Sis and M. M. Hashemi, *J. Org. Chem.* 2008, **73**, 2090–2095; (j) D. J. St.Cyr and B. A. Arndsten, *J. Am. Chem. Soc.* 2007, **129**, 12366–12367.

15 (a) H. Ding and D. Y.-K. Chen, *Angew. Chem. Int. Ed.* 2011, **50**, 676 –679; (b) M. A. Brimble, C. Burgess, R. Halim, M. Petersson and J. Ray, *Tetrahedron* 2004, **60**, 5751–5758.

16 (a) C. J. Saavedra, A. Boto, R. Hernández, J. I. Miranda and J. M. Aizpurua, *J. Org. Chem.* 2012, **77**, 5907–5913; (b) C. J. Saavedra, A. Boto and R. Hernández, *Org. Lett.* 2012, **14**, 3542–3545; (c) C. J. Saavedra, A. Boto and R. Hernández, *Org. Lett.* 2012, **14**, 3788-3791; (d) A. Boto, J. A. Gallardo and E. Alvarez, *Eur. J. Org. Chem.* 2012, 391–397; (e) A. Boto and I. Romero-Estudillo, *Org. Lett.* 2011, **13**, 3426–3429; (f) C. Saavedra, R. Hernández, A. Boto and E. Alvarez, *J. Org. Chem.* **2009**, *74*, 4655–4665.

17 (a) A. Boto, D. Hernández, R. Hernández, *Eur. J. Org. Chem.* 2010, 6633–6642; (b) A. Boto, R. Hernández, Y. León, E. Suárez, *J. Org. Chem.* 2001, **66***,* 7796–7803.

18 (a) J. Miguélez, V. R. Batchu and A. Boto, *J. Org. Chem.* 2012, **77**, 7652−7658; (b) A. Boto, D. Hernández and R. Hernández, *J. Org. Chem.* 2008, **73**, 5287−5297; (c) A. Boto, D. Hernández and R. Hernández, *Org. Lett.* 2007, **9**, 1721−1724.

19 (a) A. Boto, J. A. Gallardo, D. Hernández, R. Hernández, *J. Org. Chem.* 2007, **72**, 7260−7269; (b) A. Boto, J. A. Gallardo, R. Hernández, F. Ledo, A. Muñoz, J. R. Murguía, M. Menacho-Márquez, A. Orjales, C. Saavedra, *Bioorg. Med. Chem. Lett.* 2006, **16**, 6073−6077. (c) For a recent advance using iron promoters for the Friedel-Crafts step, see: R. Fan, W. Li and B. Wang, *Org. Biomol. Chem.*, 2008, **6**, 4615–4621. (d) For copper-promoted decarboxylation-arylation methods, see: H.-P. Bi, L. Zhao, Y.-M. Liang and C. J. Li, *Angew. Chem. Int. Ed.* 2009, **48**, 792 –795.

20 C. Cimarelli, D. Fratoni, A. Mazzanti and G. Palmieri, *Eur. J. Org. Chem.* 2011, 2094–2100.

21 (a) E. R. Costenaro, L. A. M. Fontoura, D. F. Oliveira and C. R. D. Correia, *Tetrahedron Lett.* 2001, **42**, 1599–1602; (b) Y. Oeda, Y. Ijima, H. Taguchi, A. Ohkubo, K. Seio and M. Sekine, *Org. Lett.* 2009, **11**, 5582–5585, and references cited therein.

22 A. Boto, D. Hernández and R. Hernández, *Tetrahedron Lett.* 2009, **50**, 3974–3977 and references cited therein.

23 A. Takahashi, S. Kawai, I. Hachiya and M. Shimizu, *Eur. J. Org. Chem.* 2010, 191–200.

24 H. Nishida, A. Hasuoka, Y. Arikawa, O. Kurasawa, K. Hirase, N. Inatomi, Y. Hori, F. Sato, N. Tarui, A. Imanishi, M. Kondo, T. Takagi, M. Kajino, *Bioorg. Med. Chem.* 2012, **20**, 3925–3938.

25 R. V. Ohri, A. T. Radosevich, K. J. Hrovat, C. Musich, D. Huang, T. R. Holman, and F. D. Toste, *Org. Lett.* 2005, **7**, 2501–2504.

26 A. Hall, S. H. Brown, I. P. Chessell, A. Chowdhury, N. M. Clayton, T. Coleman, G. M. P. Giblin, B. Hammond, M. P. Healy, M. R. Johnson, A. Metcalf, A. D. Michel, A. Naylor, R. Novelli, D. J. Spalding, J. Sweeting and L. Winyard, *Bioorg. Med. Chem. Lett.* 2007, **17**, 916–920 and references cited therein.