Transition Metal-Catalyzed Synthesis of Novel Biologically Relevant Tryptophan Analogues

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Dedicated to Joe P. Richmond on the occasion of his 60th birthday.

Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de or from the author.

Abstract: A synthetic approach to the synthesis of novel tryptophan derivatives and benzofuran-containing amino acids is detailed. The sequence starts from enzymatically resolved enantiopure acetylene-containing amino acids, of which the acetylene function can be efficiently transformed into the targeted 2-substited indole and benzofuran moieties *via* Sonogashira-type coupling and metal-catalyzed cyclization.

Keywords: amino acids; benzofurans; homogeneous catalysis; indoles; isotryptophan; palladium

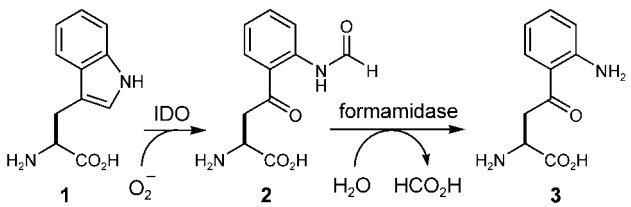
Introduction

Indoleamine 2,3-dioxygenase (IDO) is a heme-containing glycoprotein that is widely distributed in mammalian tissue, including the brain, lung and small intestine.[1] One of the functions of IDO in cells is the cleavage of the indole 2,3-double bond of (*S*)-tryptophan (**1**), using superoxide in the presence of free-radical generating systems, such as ascorbic acid and methylene blue. The product of this oxidative cleavage is (*S*)-*N*-formylkynurenine (**2**), which is subsequently hydrolyzed by a formamidase enzyme to give (*S*)-kynurenine (**3**, Scheme 1).

These two reactions are the first steps in the kynurenine pathway, which in 1947 was first recognized as a major route for the metabolism of tryptophan to nicotinamide and its nucleotide conjugates.[2] The kynurenine pathway contains a number of interesting enzymes that catalyze chemical reactions which are infrequently found in metabolism. Consequently, many of these transformations are still mechanistically poorly understood, such as the aforementioned IDO-catalyzed oxidative cleavage of tryptophan (**1**→**2**).

The activity of the IDO enzyme can be induced by several factors,[3] which results in depletion of available tryptophan, the least abundant of the essential amino acids required for cellular integrity. Hence, its reduced availability affects protein synthesis, genome replication and organismal growth. Increased IDO activity therefore leads to starvation of cells for tryptophan, which has a much more devastating effect on rapidly dividing cells, such as microbial pathogens and tumor cells. As a result, the IDO enzyme has apparent antimicrobial and antitumor properties. Another consequence of inducing IDO activity is an increase in the concentration of metabolites produced in the kynurenine pathway, such as quinolinic acid (**4**) and kynurenic acid (**5**), both of which are known to exhibit neurological activity.[4]

Quinolinic acid, for example, has been implicated as an etiological factor in a range of neurodegenerative diseases including AIDS-related dementia, Huntington's disease and Lyme's disease.[5] Moreover, the upregulation of IDO activity, resulting in the elevation of quinolinic acid concentrations, is observed in several inflammatory diseases including meningitis, septicemia and ar-



Scheme 1. The first steps in the kynurenine pathway.

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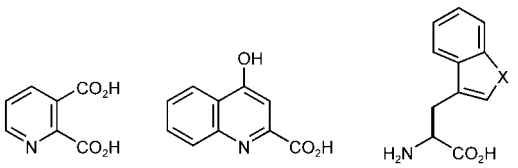
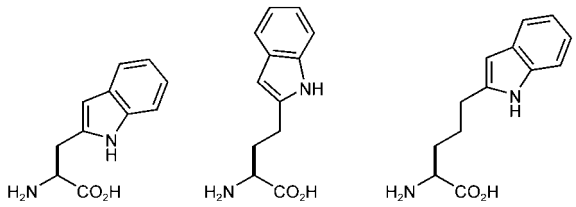


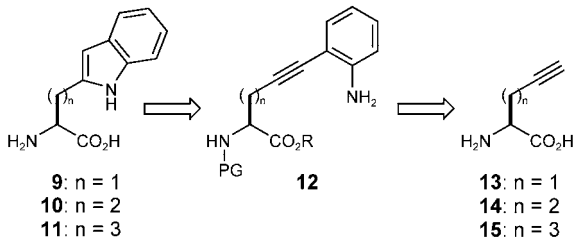
4 **5** **6**: X = O
7: X = S
8: X = NMe

Scheme 2. Kynurenine pathway metabolites (**4** and **5**) and tryptophan analogues (**6**–**8**).



9 **10** **11**

Scheme 3. Targeted tryptophan derivatives.



9: n = 1
10: n = 2
11: n = 3

12

13: n = 1
14: n = 2
15: n = 3

Scheme 4. Retrosynthesis of isotryptophans.

thritis.[6] Consequently, in the design of novel therapies to treat these diseases, the kynurenine pathway has been identified as an important target for drug action. Mechanistic work on the enzymes involved in the pathway has therefore been stimulated, to provide information so that specific and effective inhibitors can be designed.

Especially, inhibitors of the IDO enzyme have important clinical implications as potential therapeutic agents, as well as to study and control the symptoms of the aforementioned diseases which are affected by the upregulation of IDO activity. In addition, potent and specific inhibitors of the IDO enzyme are valuable pharmacological tools to elucidate the biological importance of the kynurenine pathway in more detail and to better understand the chemistry of the IDO-catalyzed reactions.

Tryptophan analogues constitute one class of IDO inhibitors and therefore a wide range of tryptophan analogues has already been examined as inhibitors of the IDO enzyme. For example, replacement of the indole nitrogen of tryptophan by both oxygen and sulfur gave analogues **6** and **7**, respectively, which exhibited moderate inhibitory activity toward rabbit intestine IDO.[7]

Based on studies focusing at the structural requirements for binding in the active site of the IDO enzyme, the *N*-methylated analogue **8** was prepared, which is the most potent tryptophan-based IDO inhibitor reported to date.[8] Although several tryptophan analogues have exhibited inhibitory activity against the IDO enzyme, none of these compounds inhibited IDO below micromolar levels. Consequently, highly potent inhibitors of human IDO (with low nanomolar affinity) are still required, and for this reason the synthesis of novel tryptophan analogues in an optically active form is necessary.

In the continued effort to search for novel inhibitors of IDO, we envisaged that it may be of interest to synthesize three structurally related tryptophan analogues, namely (*S*)-isotryptophan (**9**), (*S*)-homoisotryptophan (**10**) and (*S*)-bishomoisotryptophan (**11**).[9]

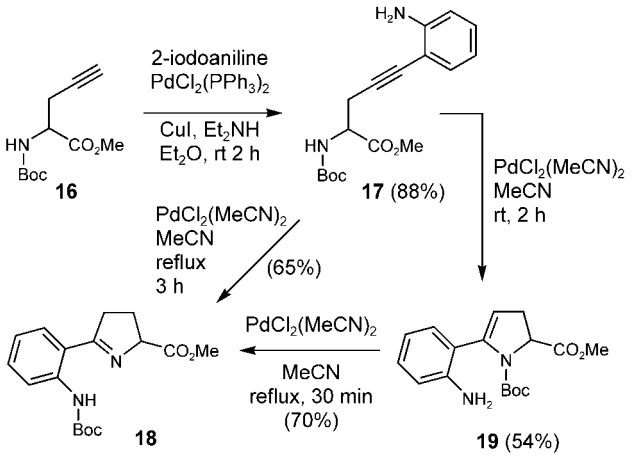
Of these potentially biologically relevant α-amino acids, only isotryptophan (**9**) itself has been previously prepared in optically active form. In that preparation,[10] the synthesis proceeded *via* a copper-mediated cyclization[11] of an *ortho*-ethynylaniline moiety that was connected to a Schöllkopf chiral auxiliary.

In addition to copper, palladium catalysts[12] have been frequently used in cyclization reactions of nitrogen nucleophiles onto alkenes and alkynes to provide nitrogen heterocycles such as pyrroles[13] and indoles.[14] However, to the best of our knowledge, Pd-catalyzed syntheses of 2-substituted indoles have only been conducted using relatively simple 2-alkynylanilines as the cyclization precursors.[14] We envisaged that the tryptophan analogues **9**–**11** might be readily synthesized from the corresponding protected anilines **12** *via* such a Pd-catalyzed cyclization as the key step. The anilines **12** should be easily accessible from the optically active acetylene-containing α-amino acids **13**–**15** (Scheme 4). These trifunctional amino acids[15] are commercially available (e.g., 2-amino-4-pentynoic acid),[16] but can also be prepared *via* a chemoenzymatic procedure that was developed in collaboration with DSM Research (Geleen, The Netherlands).[17]

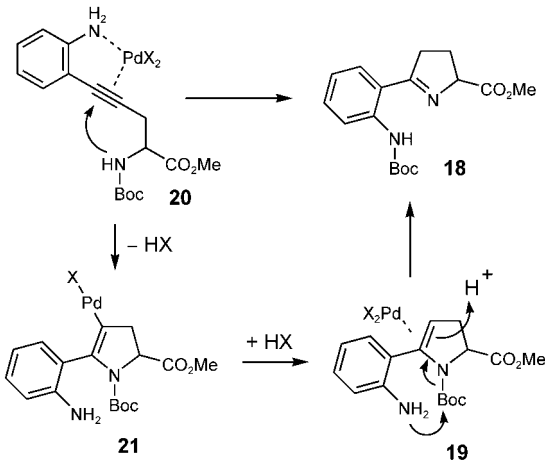
Results and Discussion

To probe the feasibility of forming the 2-substituted indole ring *via* an intramolecular Pd-catalyzed reaction, cyclization precursor **17** was synthesized starting from the racemic propargylglycine derivative **16**.[18] The Pd-catalyzed functionalization of propargylglycine derivatives with aromatic groups under Sonogashira-type coupling conditions has already been described by Crisp and Robinson.[19] Modification of the reported conditions led to a smooth coupling of **16** with 2-iodoaniline at room temperature affording precursor **17** in 88% yield (Scheme 5).

Interestingly, subjecting **17** to the previously reported cyclization conditions[14f] did not lead to the anticipated



Scheme 5. Unexpected pyrroline formation.



Scheme 6. Mechanism of pyrroline formation.

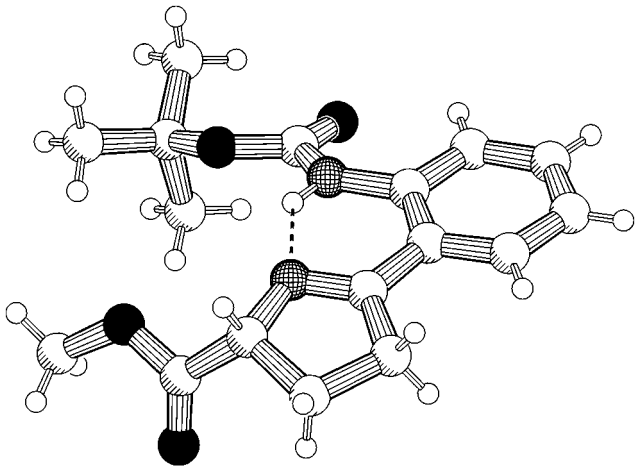


Figure 1. PLATON drawing of the X-ray crystal structure of imine **18**.

formation of the corresponding indole system. Instead, an unexpected compound was formed as the sole product in 65% yield. Eventually, this product was unambiguously identified as the five-membered cyclic imine **18** *via* an X-ray crystal structure determination (shown as a PLATON drawing[20] in Fig. 1).[21]

After this surprising result, amino acid **17** was again subjected to the same reagents, but now at room temperature, resulting in the formation of the cyclic enamide **19** in 54% yield after column chromatography (Scheme 5). Subsequent treatment of this enamide with the same Pd-catalyst in refluxing acetonitrile led to a rapid conversion into the aforementioned pyrroline **18** in 70% yield. The latter conversion could also be accomplished by refluxing **19** in acetonitrile without the Pd-catalyst present, however, in that case the reaction did not go to completion even after prolonged reaction times of over 24 h.

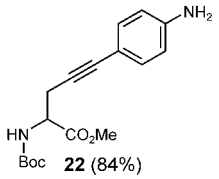
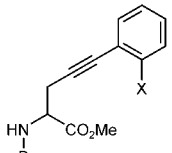
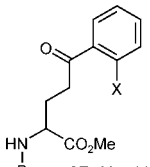
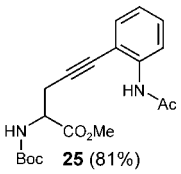
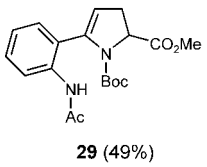
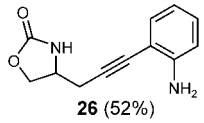
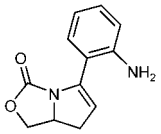
A plausible mechanism to explain the remarkable formation of pyrroline **18** from precursor **17** involves complexation of the Pd(II) catalyst to the triple bond, possibly aided by coordination to the aniline nitrogen, giving rise to the π-complex **20** (Scheme 6).

This renders the acetylene sufficiently electrophilic to undergo nucleophilic attack of the apparently more nucleophilic carbamate nitrogen to give the corresponding vinylpalladium intermediate **21**. This species will undergo protonolysis of the Pd–C bond, thereby regenerating the Pd(II) catalyst, to give cyclic enamide **19** as the intermediate product, which under the circumstances immediately reacts further to provide pyrroline **18** as the product. In this last step, the regenerated Pd catalyst may possibly act as a Lewis acid by lowering the electron density of the double bond, thus facilitating intramolecular attack of the aniline nitrogen onto the Boc group.

Intrigued by the facile cycloisomerization of **17**, we set out to further determine the scope of this reaction. Therefore, we prepared several cyclization precursors *via* Sonogashira couplings of protected propargylglycine **16** with (substituted) aryl iodides. The racemic substituted acetylenes **22**–**26** were thus obtained in good yields and subjected to $PdCl_2(MeCN)_2$ in MeCN at different temperatures (Table 1).

Unfortunately, subjecting cyclization precursor **22** to the Pd catalyst did not result in any reaction at room temperature, while heating at reflux temperature led to rapid decomposition of the starting compound (entry 1). Subjecting the substituted acetylene **23** to the Pd catalyst at room temperature did not lead to the formation of the corresponding cyclic enamide. Instead, these conditions led to partial decomposition of the starting compound and unexpected formation of the hydrated product **27** as the sole product in a yield of 32% (entry 2). Subjecting **23** to the same conditions at reflux temperature also did not lead to a cyclization reaction. Moreover, these conditions led to even more decomposition of the starting material and slowed down the formation of ketone **27**. Substitution of the aromatic ring with an *ortho*-methoxy substituent (viz. **24**) did not re-

Table 1. Scope of pyrroline formation.

Entry	Precursor (yield)[a]	Product (yield)[a]
1	 **22** (84%)	decomposition
2	 **23**: X = H (87%)	 **27**: X = H (32%)
3	**24**: X = OMe (84%)	**28**: X = OMe (19%)
4	 **25** (81%)	 **29** (49%)
5	 **26** (52%)	 **30** (32%)

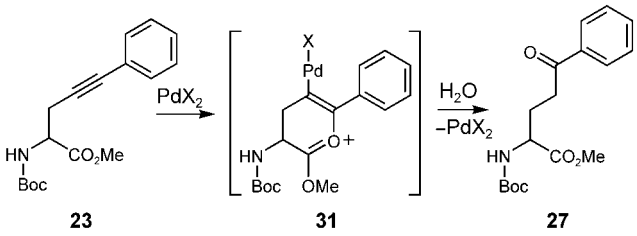
[a] Yield of isolated product after column chromatography.

sult in cyclization either, but gave a similar reaction leading to ketone **28** as the major product in a somewhat lower yield of 19% (entry 3).

Presumably, in these cases the internal acetylene undergoes a Pd-catalyzed hydration leading to the corresponding ketone. Similar regioselective Pd-catalyzed hydration of substituted acetylenes has been observed before, and the formation of, for example, ketone **27** might be explained analogously to the reported mechanism[22] (Scheme 7).

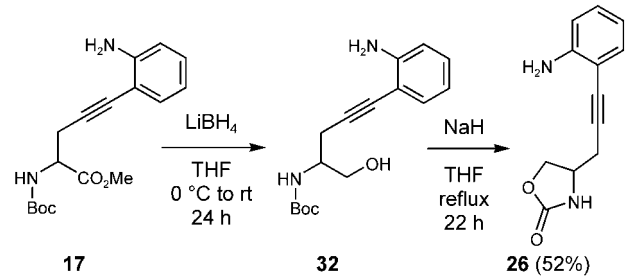
Thus, the catalytic cycle presumably involves electrophilic activation of the triple bond by the Pd(II) catalyst, followed by intramolecular nucleophilic attack of the ester function. The resulting vinylpalladium intermediate **31** then undergoes attack by water followed by subsequent protonolysis of the Pd–C bond to finally give ketone **27** as its enol tautomer. In an attempt to improve the yield of ketone **27**, the Pd-catalyzed hydration of acetylene **23** was conducted again in the presence of a small amount of water, according to the literature procedure.[22] These conditions, however, did not facilitate the formation of ketone **27**, which was even isolated in a somewhat lower yield of 26%.

In addition, the acetylated aniline **25** underwent cyclization at room temperature, resulting in the formation of the cyclic enamide **29** in 49% yield after column chromatography (entry 4). Furthermore, we converted cyclization precursor **17** into the more restricted oxazolidinone analogue **26** in two steps, i.e., ester reduction with $LiBH_4$ in THF followed by oxazolidinone formation in 52% yield (Scheme 8). Subjecting the cyclic carbamate **26** to the Pd catalyst at reflux temperature led to the formation of the corresponding bicyclic product **30** in a somewhat lower isolated yield of 32% (entry 5).



23 **31** **27**

Scheme 7. Mechanism of alkyne hydration.



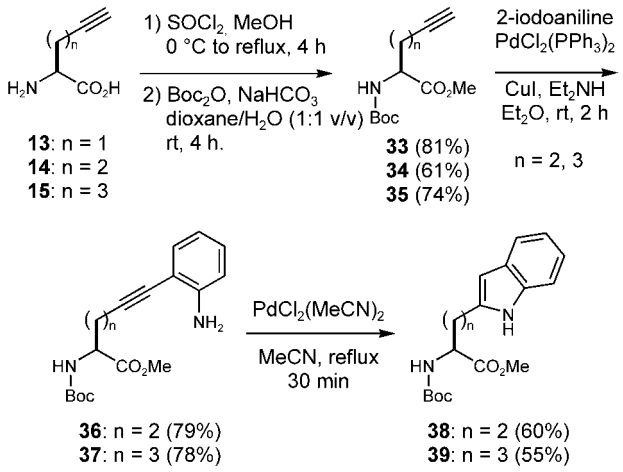
17 **32** **26** (52%)

Scheme 8. Formation of oxazolidinone **26**.

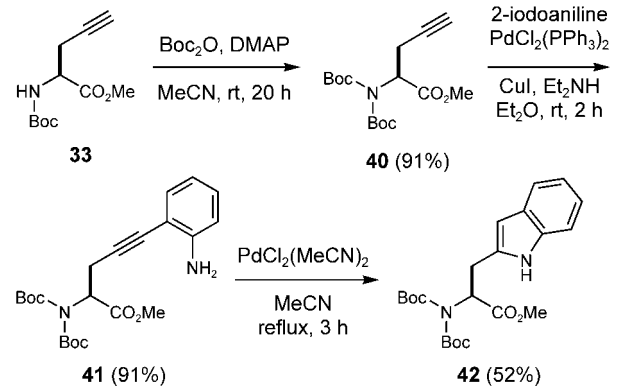
The results shown in Table 1 indicate that the presence of the *ortho*-aniline nitrogen atom in the precursor is crucial for the cycloisomerization to occur, which is in line with the proposed mechanism. This fact significantly reduces the scope of this cyclization, so that this line of research was not pursued any further.

Next, we set out to investigate the feasibility of forming the 2-substituted indole system starting from the homologous optically active homo- and bishomopropargylglycine derivatives **34** and **35**, respectively, *via* the same pathway as used before. In order to do so, the amino acids **13**–**15** were first converted into the corresponding methyl esters and protected to give the optically active Boc-protected amino esters **33**, **34** and **35** (Scheme 9).

The Pd-catalyzed Sonogashira coupling of **34** and **35** with 2-iodoaniline afforded the cyclization precursors **36** and **37** in 79 and 78% yield, respectively. To our satisfaction, treatment of **36** with the Pd catalyst in refluxing acetonitrile led to a rapid conversion into homoisotryptophan derivative **38** in 60% yield after chromatography. Under the same conditions, bishomoisotryptophan derivative **39** was also obtained in a reasonable yield of 55%. Furthermore, we proved in both cases using chiral HPLC (Chiralcel OJ) that no (partial) racemization had taken place during the whole synthetic sequence.



Scheme 9. Synthesis of isotryptophan derivatives.

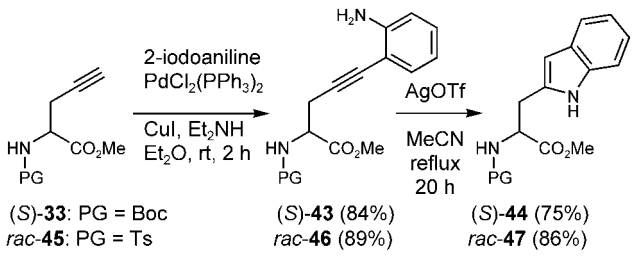


Scheme 10. Pd-catalyzed cyclization to isotryptophan.

These results actually point out that the applied cyclization conditions are suitable for the formation of the desired 2-substituted indole system. However, the mode of cyclization is strongly dependent on the side-chain length of the cyclization precursor. To verify this reasoning, the suitably protected biscarbamate **41** was synthesized in two steps from the enantiopure propargylglycine derivative **33** (Scheme 10). The presence of the additional Boc group in this precursor should prevent the cyclization *via* the carbamate nitrogen, thereby leaving the aniline nitrogen as the only reactive nucleophile.

Indeed, subjecting precursor **41** to the same Pd catalyst in refluxing acetonitrile led to an activation of the aniline nitrogen, which cyclized onto the triple bond affording isotryptophan derivative **42** as the sole product without loss of enantiopurity according to chiral HPLC (Chiralcel OD).

In order to circumvent the use of the second Boc group on the carbamate nitrogen, we also searched for a catalyst that would effect a selective cyclization into the 2-substituted indole system, without interference of the carbamate nitrogen in the cyclization process. After screening a variety of catalysts, we found that AgOTf – silver has a high affinity for double bonds and much less for heteroatoms such as nitrogen – might be the catalyst of choice in effecting such a selective ring closure. In order to probe the feasibility of selective indole formation *via* an Ag-catalyzed cyclization, precursor **43** was synthesized from the enantiopure propargylglycine derivative **33** (Scheme 11).



Scheme 11. Ag-catalyzed cyclization to isotryptophan.

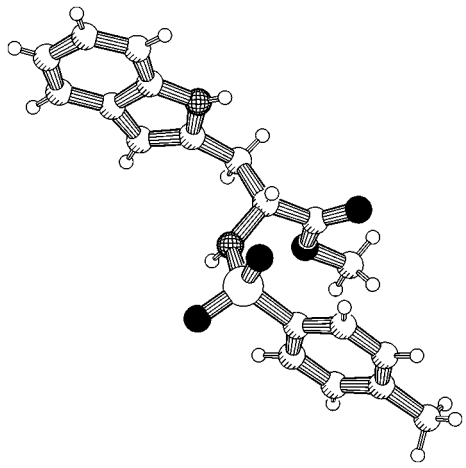
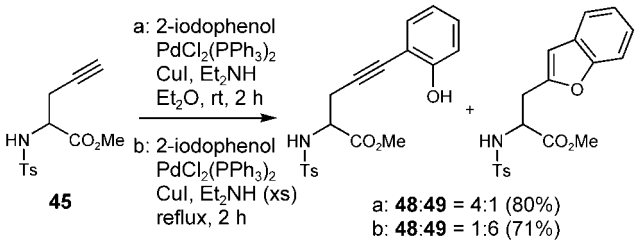


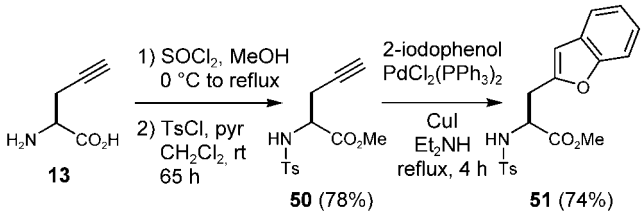
Figure 2. PLATON drawing of the X-ray crystal structure of **47**.

Subjecting precursor **43** to the Ag catalyst in acetonitrile at room temperature did not give any reaction. However, we were pleased to see that heating the reaction mixture at reflux temperature indeed led to a slow but clean conversion of the starting compound into isotryptophan derivative **44**, which was isolated in an improved yield of 75% after column chromatography. Additionally, we converted the racemic Ts-protected propargylglycine derivative **45**[18] *via* Sonogashira coupling with 2-iodoaniline into precursor **46**, which was also subjected to AgOTf in refluxing acetonitrile affording isotryptophan derivative **47** in an excellent yield of 86% after chromatography. Luckily, tryptophan analogue **47** appeared to be a crystalline solid suitable for an X-ray crystal structure determination, proving the formation of the 2-substituted indole system (shown as a PLATON drawing[20] in Fig. 2).[21]

Encouraged by these results, we set out to apply this methodology in the synthesis of 2-substituted benzo[*b*]-



Scheme 12. Synthesis of benzofuran analogue **49**.



Scheme 13. One-pot coupling/cyclization to benzofuran derivative **51**.

furans, which might give us the opportunity to also access the oxygen-containing counterparts of tryptophan analogues **9**–**11** (see Scheme 3). In order to investigate the possible formation of a 2-substituted benzo[*b*]furan *via* a similar intramolecular Pd- or Ag-catalyzed reaction, the racemic propargylglycine derivative **45** was first reacted with 2-iodophenol under Sonogashira coupling conditions to afford the appropriate precursor **48** (Scheme 12).

To our surprise, these conditions indeed led to the formation of the expected precursor **48** in 64%, but in addition the eventually desired tryptophan analogue **49** was found in 16% yield. Without separation, we subjected the obtained mixture to AgOTf in refluxing acetonitrile to see whether this catalyst would effect the cyclization of phenol **48** into benzofuran **49**. Unfortunately, however, refluxing the mixture for more than 20 h in the presence of AgOTf did not lead to an increase in the conversion of **48** into **49** as judged by TLC. Obviously, this behavior can be explained by the lower nucleophilicity of the phenol compared to the previously used anilines. In line with this reasoning, we added Et_2NH (1 equiv.) to the reaction mixture to see if this would facilitate the formation of benzofuran **49**. Indeed, the addition of Et_2NH led to a rapid conversion of phenol **48** into benzofuran **49**, however, the reaction did not go to completion and also led to partial decomposition of the remaining phenol. Considering these results, we again turned our attention to the Sonogashira reaction of propargylglycine derivative **45** with 2-iodophenol. We envisaged that a modification of the applied conditions, i.e., using Et_2NH as base and solvent at reflux temperature, might be beneficial to the formation of tryptophan analogue **49**. Thus, subjecting acetylene **45** to these modified conditions led to the formation of a mixture of phenol **48** and benzofuran **49** in an improved ratio in favor of **49** in a combined yield of 71% (Scheme 12).

After this result, it became apparent to us that it would be feasible to convert propargylglycine derivative **45** completely into tryptophan analogue **49** if the reaction mixture would be refluxed for more than 2 h. To achieve this tandem cross-coupling cyclization process,[23] we first converted enantiomerically pure propargylglycine **13** into propargylglycine derivative **50** by esterification using thionyl chloride in MeOH and subjected it to pyridine and *p*-toluenesulfonyl chloride in CH_2Cl_2. Acetylene **50** was subsequently reacted with 2-iodophenol under the aforementioned modified Sonogashira conditions to give initially the corresponding intermediate phenol, which was after 4 h completely consumed to give the enantiopure tryptophan analogue **51** as the sole product in 74% yield (Scheme 13).

Conclusion

A short and efficient preparation of novel optically active tryptophan analogues is described. The aniline-containing homo- and bishomopropargylglycine derivatives **36** and **37** underwent a rapid Pd-catalyzed cyclization to afford the corresponding tryptophan analogues **38** and **39** in reasonable yields. In contrast to these results, treatment of the aniline-containing propargylglycine derivative **17** with the same Pd catalyst led to an unexpected cycloisomerization affording pyrroline **18**. In addition, some insight was gained regarding the scope and limitations of the observed cycloisomerization.

Furthermore, in the case of **43** we demonstrated the possibility of circumventing the Pd-catalyzed cycloisomerization by the selective construction of tryptophan analogue **44** *via* Ag-catalyzed indole formation. Finally, we explored the possibility to apply the developed methodology in the synthesis of 2-subsituted benzofurans. This led to modified conditions in the Sonogashira reaction of propargylglycine derivative **50** with 2-iodophenol, allowing the direct synthesis of tryptophan analogue **51** *via* a tandem cross-coupling cyclization process. Currently, further studies concerning the scale-up of these compounds, the synthesis of additional new tryptophan derivatives and biological evaluation of these compounds as inhibitors of IDO are being carried out in collaboration with Chiralix BV (Nijmegen, The Netherlands).[24]

Experimental Section

General Information

All reactions were carried out under an atmosphere of dry nitrogen, unless stated otherwise. Infrared (IR) spectra were obtained using an ATI Mattson Genesis Series FTIR spectrome-

ter and wavelengths ($\tilde{\nu}$) are reported in cm^{-1}. Optical rotations were measured on a Perkin-Elmer 241 polarimeter, using concentrations (c) in g/100 mL in the indicated solvents. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were determined in $CDCl_3$, unless indicated otherwise, using a Bruker DMX300 (300 MHz) spectrometer. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane. HRMS measurements were carried out using a Fisons (VG) Micromass 7070E or a Finnigan MAT900S instrument. Flash chromatography was performed with Acros Organics silica gel (0.035–0.070 nm) using the indicated solvent (mixture). R_f values were obtained by using thin layer chromatography (TLC) on silica gel-coated glass plates (Merck silica gel 60 F_{254}) with the indicated solvent (mixture). Melting points were determined with a Büchi melting point B-545 apparatus. THF and Et_2O were distilled from sodium and benzophenone. Heptane, EtOAc and CH_2Cl_2 were distilled from CaH_2. Et_2NH was distilled from and stored over KOH. If necessary, other solvents were distilled from the appropriate drying agents prior to use. Unless stated otherwise, all commercially available reagents were used as received.

Methyl (2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-4-pentynoate (33)

A suspension of **13** (1.00 g, 8.84 mmol) in MeOH (30 mL) was treated dropwise at 0 °C with $SOCl_2$ (1.4 mL, 19.0 mmol) and heated at reflux for 4 h. The reaction mixture was concentrated under vacuum to give the crude amino ester as the HCl salt. The crude residue was dissolved in dioxane/water (80 mL, 1:1, v/v), $NaHCO_3$ (2.23 g, 26.5 mmol) and Boc_2O (3.88 g, 17.8 mmol) were added and the reaction mixture stirred for 4 h at room temperature. Dioxane was evaporated under vacuum and the remaining aqueous solution was extracted with EtOAc (3 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. Purification by chromatography (EtOAc/heptane,1:6) afforded **33** as a colorless oil; yield: 1.62 g (7.13 mmol, 81%); R_f = 0.65 (EtOAc/heptane,1:1); $[\alpha]_D^{20}$: +47.7 (*c* 1.1, CH_2Cl_2); IR (neat): $\tilde{\nu}$ = 3298, 2978, 1745, 1712, 1504, 1437 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.32 (br d, J = 6.6 Hz, 1H), 4.46 (m, 1H), 3.76 (s, 3H), 2.73 (br m, 2H), 2.03 (t, J = 2.1 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.9, 154.9, 80.3, 78.6, 71.7, 52.8, 52.1, 28.6, 23.1; HRMS (CI): calcd. for $C_{11}H_{18}NO_4$ (MH^+): 228.1236; found: 228.1236.

Methyl (2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-5-hexynoate (34)

Following the same procedure as for **33**, (*S*)-homopropargylglycine **14** (0.98 g, 7.71 mmol) was protected and purified by chromatography (EtOAc/heptane, 1:6) to afford **34** as a white solid; yield: 1.14 g (4.72 mmol, 61%); R_f = 0.24 (EtOAc/heptane, 1:4); $[\alpha]_D^{20}$: +9.9 (*c* 1.0, CH_2Cl_2); mp 59.0 °C; IR (neat): $\tilde{\nu}$ = 3367, 3253, 2983, 1732, 1676, 1512 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.24 (br d, J = 6.9 Hz, 1H), 4.39 (m, 1H), 3.75 (s, 3H), 2.28 (dt, J = 2.7, 7.5 Hz, 2H), 2.05 (m, 1H), 2.01 (t, J = 2.4 Hz, 1H), 1.89 (m, 1H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.7, 155.3, 82.8, 80.0, 69.3, 52.8, 52.4, 31.5, 28.3, 14.9; HRMS (CI): calcd. for $C_{12}H_{20}NO_4$ (MH^+): 242.1392; found: 242.1395.

Methyl (2*S*)-2-[*tert*-Butoxycarbonyl)amino]-6-heptynoate (35)

Following the same procedure as for **33**, (*S*)-bishomopropargylglycine **15** (1.00 g, 7.08 mmol) was protected and purified by chromatography (EtOAc/heptane,1:6) to afford **35** as a colorless oil; yield: 1.33 g (5.21 mmol, 74%); R_f = 0.20 (EtOAc/heptane, 1:4); $[\alpha]_D^{20}$: +71.7 (*c* 1.0, CH_2Cl_2); IR (neat): $\tilde{\nu}$ = 3296, 2953, 1741, 1712, 1504 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.03 (br d, J = 6.9 Hz, 1H), 4.31 (m, 1H), 3.75 (s, 3H), 2.23 (dt, J = 2.4, 6.9 Hz, 2H), 1.96 (t, J = 2.7 Hz, 1H), 1.91 (m, 1H), 1.80–1.53 (m, 3H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9, 155.2, 83.4, 80.0, 69.1, 53.2, 52.5, 32.0, 28.6, 24.6, 18.4; HRMS (CI): calcd. for $C_{13}H_{22}NO_4$ (MH^+): 256.1549; found: 256.1549.

Methyl (2*S*)-2-{[(4-Methylphenyl)sulfonyl]amino}-4-pentynoate (50)

A suspension of **13** (500 mg, 4.42 mmol) in MeOH (20 mL) was treated dropwise at 0 °C with $SOCl_2$ (0.7 ml, 9.5 mmol) and heated at reflux for 4 h. The reaction mixture was concentrated under vacuum to give the crude amino ester as the HCl salt. The crude residue was suspended in CH_2Cl_2 (75 mL), pyridine (2.2 mL, 28.4 mmol) and *p*-TsCl (1.68 g, 8.81 mmol) were added and the reaction mixture was stirred for 65 h at room temperature. Saturated aqueous $CuSO_4$ (100 mL) was added to the reaction mixture and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by chromatography (EtOAc/heptane,1:3) to afford **50** as a white solid; yield: 970 mg (3.45 mmol, 78%); R_f = 0.28 (EtOAc/heptane, 1:2); $[\alpha]_D^{20}$: +16.5 (*c* 1.0, CH_2Cl_2); mp 83.2 °C; IR (neat): $\tilde{\nu}$ = 3261, 2950, 1705, 1593, 1433 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.71 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 8.1 Hz, 2H), 5.45 (d, J = 9.0 Hz, 1H), 4.10 (m, 1H), 3.60 (s, 3H), 2.66 (m, 2H), 2.41 (s, 3H), 2.02 (t, J = 2.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8, 143.7, 136.7, 129.6, 127.1, 77.6, 72.4, 54.2, 53.1, 24.4, 21.9; HRMS (EI): calcd. for $C_{13}H_{15}NO_4S$: 281.0722; found: 281.0722.

General Procedure for the Sonogashira Cross-Coupling Reactions

To a solution of the acetylene-containing amino acid, aryl halide (1.2 equivs.) and Et_2NH (5 equivs.) in Et_2O, CuI (10 mol %) and the Pd catalyst (5 mol %) were added. The mixture was stirred at room temperature under an N_2 atmosphere for the indicated time. The reaction mixture was poured into a saturated aqueous solution of NH_4Cl and after separation of the organic layer the aqueous layer was extracted with Et_2O (2 ×). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by flash chromatography to afford the pure product.

Methyl (2*S*)-5-(2-Aminophenyl)-2-[(*tert*-butoxycarbonyl)amino]-4-pentynoate (43)

According to the general procedure, to a solution of **33** (303 mg, 1.33 mmol), 2-iodoaniline (351 mg, 1.60 mmol) and Et_2NH (0.70 mL, 6.73 mmol) in Et_2O (18 mL), CuI (28 mg, 0.15 mmol) and $PdCl_2(PPh_3)_2$ (47 mg, 0.07 mmol) were added and the resulting mixture was stirred for 2 h. Work-up and purification by chromatography (EtOAc/heptane, 1:3) afforded **43** as a light-brown oil; 356 mg (1.12 mmol, 84%); $R_f = 0.28$ (EtOAc/heptane, 1:2); $[\alpha]_D^{20}$: +82.2 (*c* 0.5, CH_2Cl_2); IR (neat): $\tilde{\nu} = 3369, 2978, 1743, 1711, 1618, 1493\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.17$ (dd, $J = 1.5, 7.6$ Hz, 1H), 7.04 (m, 1H), 6.59 (m, 2H), 5.57 (br d, $J = 8.3$ Hz, 1H), 4.56 (m, 1H), 4.31 (s, 2H), 3.73 (s, 3H), 2.95 (d, $J = 5.2$ Hz, 2H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 171.6, 155.1, 148.2, 131.9, 129.3, 117.3, 114.1, 107.3, 88.8, 80.4, 80.0, 52.5, 52.3, 28.1, 24.1$; HRMS (EI): calcd. for $C_{17}H_{22}N_2O_4$: 318.1580; found: 318.1580.

Methyl 2-[(*tert*-Butoxycarbonyl)amino]-5-phenyl-4-pentynoate (23)

According to the general procedure, to a solution of **16** (384 mg, 1.69 mmol), iodobenzene (417 mg, 0.49 mmol) and Et_2NH (0.88 mL, 8.50 mmol) in Et_2O (18 mL), CuI (33 mg, 0.17 mmol) and $PdCl_2(PPh_3)_2$ (60 mg, 0.09 mmol) were added and the resulting mixture was stirred for 2 h. Work-up and purification by chromatography (EtOAc/heptane, 1:6) afforded **23** as a yellow oil; yield: 448 mg (1.48 mmol, 87%); $R_f = 0.28$ (EtOAc/heptane, 1:4); IR (neat): $\tilde{\nu} = 3375, 2977, 1747, 1716, 1598\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.38$ (m, 2H), 7.28 (m, 3H), 5.42 (d, $J = 8.3$ Hz, 1H), 4.56 (m, 1H), 3.79 (s, 3H), 2.95 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 171.1, 154.9, 131.5, 128.0, 127.6, 122.8, 83.7, 83.4, 79.8, 52.3, 52.1, 28.1, 23.6$; HRMS (EI): calcd. for $C_{17}H_{21}NO_4$: 303.1471; found: 303.1471.

Methyl 5-[2-(Acetylamino)phenyl]-2-[(*tert*-butoxycarbonyl)amino]-4-pentynoate (25)

According to the general procedure, to a solution of **16** (367 mg, 1.62 mmol), N^1-(2-iodophenyl)acetamide (465 mg, 1.78 mmol) and Et_2NH (0.84 mL, 8.16 mmol) in Et_2O (18 mL), CuI (32 mg, 0.17 mmol) and $PdCl_2(PPh_3)_2$ (57 mg, 0.08 mmol) were added and the resulting mixture was stirred for 2 h. Work-up and purification by chromatography (EtOAc/heptane, 1:2) afforded **25** as a colorless oil; yield: 471 mg (1.31 mmol, 81%); $R_f = 0.21$ (EtOAc/heptane, 1:2); IR (neat): $\tilde{\nu} = 3329, 2980, 1738, 1693, 1579, 1518, 1444\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.25$ (s, 1H), 8.22 (s, 1H), 7.20 (m, 2H), 6.88 (m, 1H), 5.64 (d, $J = 8.2$ Hz, 1H), 4.52 (m, 1H), 3.68 (s, 3H), 2.93 (dd, $J = 5.0, 17.2$ Hz, 1H), 2.83 (dd, $J = 5.9, 17.0$ Hz, 1H), 2.22 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 171.5, 169.1, 155.2, 139.3, 131.5, 129.0, 123.0, 119.8, 111.8, 90.7, 80.1, 79.0, 52.5, 52.1, 28.0, 24.2, 24.0$; HRMS (EI): calcd. for $C_{19}H_{24}N_2O_5$: 360.1685; found: 360.1674.

4-[3-(2-Aminophenyl)-2-propynyl]-1,3-oxazolan-2-one (26)

To a solution of **17** (535 mg, 1.68 mmol) in THF (20 mL), $LiBH_4$ (73 mg, 3.36 mmol) was added at 0 °C. The reaction mixture was allowed to reach room temperature and stirred for 24 h. Upon completion, the reaction mixture was quenched by adding water (1 mL) and stirred further for 15 min at room temperature, after which time the mixture was poured into water (30 mL). The aqueous solution was extracted with EtOAc (100 mL) and the organic layer was washed with water (2×30 mL), brine (2×30 mL), dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by chromatography (EtOAc/heptane, 1:1) to afford the corresponding amino alcohol **32** as a light-yellow oil; yield: 386 mg (1.33 mmol, 79%); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.21$ (d, $J = 7.6$ Hz, 1H), 7.05 (m, 1H), 6.63 (m, 2H), 5.34 (d, $J = 8.6$ Hz, 1H), 4.31 (br s, 2H), 3.86 (br s, 1H), 3.71 (m, 3H), 2.71 (d, $J = 6.1$ Hz, 2H), 1.43 (s, 9H).

To a solution of amino alcohol **32** (366 mg, 1.26 mmol) in THF (30 mL), NaH (52 mg of a 60% dispersion in mineral oil, 1.31 mmol) was added. The reaction mixture was heated at reflux for 22 h, diluted with MeOH (3 mL) and concentrated under vacuum. The crude product was purified by chromatography (EtOAc/heptane, 3:1) to afford **26** as a light-yellow solid; yield: 179 mg (0.83 mmol, 66%); $R_f = 0.13$ (EtOAc/heptane, 2:1); mp 147.2 °C; IR (neat): $\tilde{\nu} = 3352, 1732, 1614\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.24$ (dd, $J = 1.7, 8.3$ Hz, 1H), 7.11 (dt, $J = 1.6, 7.7$ Hz, 1H), 6.67 (m, 2H), 5.68 (br s, 1H), 4.57 (dd, $J = 8.3, 8.9$ Hz, 1H), 4.28 (dd, $J = 4.6, 8.9$ Hz, 1H), 4.13 (m, 3H), 2.76 (dd, $J = 1.4, 5.6$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 157.3, 150.8, 132.5, 129.9, 123.5, 118.1, 114.6, 88.3, 81.2, 69.4, 66.0, 26.7$; HRMS (EI): calcd. for $C_{12}H_{12}N_2O_2$: 216.0899; found: 216.0898.

Methyl (2*S*)-6-(2-Aminophenyl)-2-[(*tert*-butoxycarbonyl)amino]-5-hexynoate (36)

According to the general procedure, to a solution of **34** (518 mg, 2.15 mmol), 2-iodoaniline (565 mg, 2.58 mmol) and Et_2NH (1.12 mL, 10.7 mmol) in Et_2O (20 mL), CuI (40 mg, 0.21 mmol) and $PdCl_2(PPh_3)_2$ (75 mg, 0.107 mmol) were added and the resulting mixture was stirred for 2 h. Work-up and purification by chromatography (EtOAc/heptane, 1:3) afforded **36** as a light-brown oil; yield: 562 mg (1.69 mmol, 79%); $R_f = 0.27$ (EtOAc/heptane, 1:2); $[\alpha]_D^{20}$: +4.9 (*c* 1.0, CH_2Cl_2); IR (neat): $\tilde{\nu} = 3461, 3369, 2975, 1734, 1701, 1617\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.20$ (dd, $J = 1.4, 7.7$ Hz, 1H), 7.03 (m, 1H), 6.60 (m, 2H), 5.33 (br d, $J = 8.5$ Hz, 1H), 4.50 (br m, 1H), 4.32 (br s, 2H), 3.69 (s, 3H), 2.53 (t, $J = 6.9$ Hz, 2H), 2.11 (m, 1H), 1.92 (m, 1H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.9, 155.4, 148.2, 132.0, 129.0, 117.3, 114.1, 107.9, 93.1, 79.8, 78.3, 52.6, 52.3, 31.5, 28.2, 16.0$; HRMS (EI): calcd. for $C_{18}H_{24}N_2O_4$: 332.1736; found: 332.1734.

Methyl (2*S*)-7-(2-aminophenyl)-2-[(*tert*-butoxycarbonyl)amino]-6-heptynoate (37)

According to the general procedure, to a solution of **35** (322 mg, 1.26 mmol), 2-iodoaniline (337 mg, 1.54 mmol) and Et_2NH (0.67 mL, 6.43 mmol) in Et_2O (18 mL), CuI (27 mg,

0.14 mmol) and $PdCl_2(PPh_3)_2$ (49 mg, 0.07 mmol) were added and the resulting mixture was stirred for 2 h. Work-up and purification by chromatography (EtOAc/heptane, 1:3) afforded **37** as a yellow oil; yield: 341 mg (0.98 mmol, 78%); $R_f = 0.26$ (EtOAc/heptane, 1:2); $[\alpha]_D^{20}$: +10.8 (*c* 1.0, CH_2Cl_2); IR (neat): $\tilde{\nu} = 3356, 2978, 1738, 1712, 1614, 1493, 1454\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.22$ (dd, $J = 1.2, 7.5$ Hz, 1H), 7.07 (m, 1H), 6.65 (m, 2H), 5.02 (br m, 1H), 4.32 (br m, 1H), 4.15 (s, 2H), 3.75 (s, 3H), 2.52 (t, $J = 6.9$ Hz, 1H), 2.30 (t, $J = 6.6$ Hz, 1H), 2.08–1.56 (m, 4H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.9, 155.2, 147.3, 132.0, 128.9, 117.8, 114.2, 108.6, 94.4, 80.1, 77.9, 53.3, 52.5, 32.2, 28.6, 25.1, 19.6$; HRMS (EI): calcd. for $C_{19}H_{26}N_2O_4$: 346.1893; found: 346.1900.

Methyl (2*S*)-5-(2-Aminophenyl)-2-[di(*tert*-butoxycarbonyl)amino]-4-pentynoate (41)

To a solution of **33** (274 mg, 1.21 mmol) in MeCN (5 mL), DMAP (46 mg, 0.38 mmol) and Boc_2O (528 mg, 2.42 mmol) were added and the resulting mixture was stirred at room temperature for 20 h. Upon completion, the reaction mixture was concentrated under vacuum and purified by chromatography (EtOAc/heptane, 1:9) to afford **40** as a colorless oil; yield: 360 mg (1.10 mmol, 91%); ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 5.16 (dd, $J = 6.6, 8.4$ Hz, 1H), 3.72 (s, 3H), 2.93 (m, 2H), 1.96 (t, $J = 2.7$ Hz, 1H), 1.50 (s, 18H).

According to the general procedure, to a solution of biscarbamate **40** (337 mg, 1.03 mmol), 2-iodoaniline (272 mg, 1.24 mmol) and Et_2NH (0.55 mL, 5.26 mmol) in Et_2O (18 mL), CuI (22 mg, 0.12 mmol) and $PdCl_2(PPh_3)_2$ (37 mg, 0.05 mmol) were added and the resulting mixture was stirred for 2 h. Work-up and purification by chromatography (EtOAc/heptane, 1:4) afforded **41** as a brown oil; yield: 394 mg (0.94 mmol, 91%); $R_f = 0.15$ (EtOAc/heptane, 1:4); $[\alpha]_D^{20}$: −89.2 (*c* 0.5, CH_2Cl_2); IR (neat): $\tilde{\nu} = 3465, 3373, 2980, 1790, 1743, 1695, 1616\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.17$ (dd, $J = 1.2, 7.5$ Hz, 1H), 7.03 (dt, $J = 1.5, 8.1$ Hz, 1H), 6.59 (m, 2H), 5.22 (dd, $J = 6.3, 9.3$ Hz, 1H), 4.21 (s, 2H), 3.75 (s, 3H), 3.25 (dd, $J = 6.3, 17.4$ Hz, 1H), 3.18 (dd, $J = 9.3, 17.4$ Hz, 1H), 1.48 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 169.8, 169.4, 151.8, 151.5, 148.0, 132.1, 129.1, 117.4, 114.0, 108.0, 90.6, 83.6, 79.4, 73.5, 67.4, 57.0, 52.6, 28.3, 21.9 HRMS (EI): calcd. for $C_{22}H_{30}N_2O_6$: 418.2104; found: 418.2099.

Methyl 5-(2-Aminophenyl)-2-{[(4-methylphenyl)sulfonyl]amino}-4-pentynoate (46)

According to the general procedure, to a solution of **45** (402 mg, 1.43 mmol), 2-iodoaniline (377 mg, 1.72 mmol) and Et_2NH (0.75 mL, 7.20 mmol) in Et_2O (18 mL), CuI (29 mg, 0.15 mmol) and $PdCl_2(PPh_3)_2$ (50 mg, 0.07 mmol) were added and the resulting mixture was stirred for 2 h. Work-up and purification by chromatography (EtOAc/heptane, 1:2) afforded **46** as a light-brown oil; yield: 473 mg (1.27 mmol, 89%); $R_f =$ 0.16 (EtOAc/heptane, 1:2); IR (neat): $\tilde{\nu} = 3377, 3275, 1739, 1616, 1493\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.75$ (d, $J = 8.3$ Hz, 2H), 7.27 (d, $J = 8.2$ Hz, 2H), 7.13 (m, 2H), 6.65 (m, 2H), 5.51 (d, $J = 8.9$ Hz, 1H), 4.22 (m, 3H), 3.61 (s, 3H), 2.94 (d, $J = 5.2$ Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.5, 148.3, 143.6, 136.7, 131.9, 129.5, 129.4, 127.0, 117.3, 114.3, 107.2, 88.1, 80.9, 54.5, 52.7, 25.0, 21.3$; HRMS (EI): calcd. for $C_{19}H_{20}N_2O_4S$: 372.1144; found: 372.1145.

General Procedure for the Pd- and Ag-Catalyzed Cyclization Reactions

To a solution of the cyclization precursor in MeCN, the catalyst (10 mol %) was added. The mixture was stirred at reflux temperature under an N_2 atmosphere for the indicated time. The reaction mixture was concentrated under vacuum and purified by flash chromatography to afford the pure product.

Methyl 5-{2-[(*tert*-Butoxycarbonyl)amino]phenyl}-3,4-dihydro-2*H*-2-pyrrolecarboxylate (18)

According to the general procedure, to a solution of **17** (340 mg, 1.07 mmol) in MeCN (10 mL), $PdCl_2(MeCN)_2$ (28 mg, 0.11 mmol) was added and the resulting mixture was heated to reflux for 3 h. Purification by chromatography (EtOAc/heptane, 1:6) afforded **18** as a white solid; yield: 222 mg (0.70 mmol, 65%). An X-ray crystal structure determination was carried out after recrystallization from hexane. $R_f =$ 0.45 (EtOAc/heptane,1:2); mp 78.0 °C; IR (neat): $\tilde{\nu} = 2980, 1734, 1720, 1604, 1576, 1522, 1446\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 11.9$ (s, 1H), 8.42 (d, $J = 8.4$ Hz, 1H), 7.40 (m, 2H), 6.96 (t, $J = 8.3$ Hz, 1H), 4.99 (m, 1H), 3.78 (s, 3H), 3.25–3.00 (m, 2H), 2.35–2.09 (m, 2H), 1.52 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 177.4, 172.9, 153.5, 140.9, 131.9, 130.5, 120.8, 118.5, 118.4, 79.7, 74.4, 52.2, 36.9, 28.3, 25.1$; HRMS (EI): calcd. for $C_{17}H_{22}N_2O_4$: 318.1580; found: 318.1576.

Crystal data: transparent colorless, regular thick platelets, triclinic, space group P_{-1}, $C_{17}H_{22}N_2O_4$, 318.37, unit-cell dimensions: $a = 5.9502(6)$ Å; $\alpha = 76.621(12)°$, $b = 9.4955(8)$ Å; $\beta =$ $79.367(8)°$, $c = 16.0415(19)$ Å; $\gamma = 77.358(10)°$, $Z = 2$, calculated density: 1.241 Mg/m^3. Data collection: Enraf-Nonius CAD4/ω-2ϑ diffractometer, Mo-Kα (graphite mon.)/0.71073 Å, crystal size $0.31 \times 0.23 \times 0.11$ mm, T = 293(2) K, θ range 2.82 to 27.47°, 1352 ([Io > 2σ(Io)]) reflections measured, semi-empirical absorption correction from ψ-scans. Structural analysis and refinement: full-matrix least-squares on F^2, goodness-of-fit on F^2 1.005, SHELXL-97 weight parameters 0.063700, 0.000000, final R indices [I > 2σ(I)]: R1 = 0.0710, wR2 = 0.1262, SHELXL-97 (Sheldrick, 1997).

1-(*tert*-Butyl) 2-Methyl 5-(2-aminophenyl)-2,3-dihydro-1*H*-1,2-pyrroledicarboxylate (19)

According to the general procedure, to a solution of **17** (424 mg, 1.33 mmol) in MeCN (10 mL), $PdCl_2(MeCN)_2$ (35 mg, 0.13 mmol) was added and the resulting mixture was stirred for 2 h. Purification by chromatography (EtOAc/heptane, 1:3) afforded **19** as a white solid; yield: 227 mg (0.71 mmol, 54%); $R_f = 0.27$ (EtOAc/heptane, 1:3); mp 139.1 °C; IR (neat): $\tilde{\nu} = 3442, 3357, 2972, 1730, 1668, 1649, 1603, 1402\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.06$ (m, 2H), 6.59 (m, 2H), 5.00 (dd, $J = 2.1, 3.5$ Hz, 1H), 4.92 (dd, $J =$ 2.5, 11.2 Hz, 1H), 4.50 (br s, 2H), 3.77 (s, 3H), 3.07 (ddd, $J =$ 2.1, 11.2, 18.9 Hz, 1H), 2.53 (dt, $J = 3.5, 17.0$ Hz, 1H), 1.14 (s,

9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7, 152.1, 145.3, 142.4, 129.2, 129.0, 119.1, 116.6, 114.2, 108.4, 80.5, 60.5, 52.6, 32.0, 27.7; HRMS (EI): calcd. for $C_{17}H_{22}N_2O_4$: 318.1580; found: 318.1583.

Methyl 2-[(*tert*-Butoxycarbonyl)amino]-5-oxo-5-phenylpentanoate (27)

According to the general procedure, to a solution of **23** (438 mg, 1.44 mmol) in MeCN (16 mL), $PdCl_2(MeCN)_2$ (37 mg, 0.14 mmol) was added and the resulting mixture was stirred at room temperature for 70 h. Purification by chromatography (EtOAc/heptane, 1:4) afforded **27** as a light-yellow solid; yield: 149 mg (0.46 mmol, 32%); R_f = 0.39 (EtOAc/heptane, 1:2); mp 109.4 °C; IR (neat): $\tilde{\nu}$ = 3359, 1736, 1699, 1680, 1599, 1514, 1448 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 7.2 Hz, 2H), 7.48 (m, 3H), 5.14 (br d, *J* = 7.2 Hz, 1H), 4.37 (m, 1H), 3.73 (s, 3H), 3.08 (m, 2H), 2.30 (m, 1H), 2.08 (m, 1H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.5, 172.7, 155.3, 136.6, 133.1, 128.5, 128.0, 80.1, 53.3, 52.6, 34.8, 28.6, 27.3; HRMS (CI): calcd. for $C_{17}H_{24}NO_5$ (MH^+): 322.1654; found: 322.1659.

1-(*tert*-Butyl) 2-Methyl 5-[2-(acetylamino)phenyl]-2,3-dihydro-1*H*-1,2-pyrroledicarboxylate (29)

According to the general procedure, to a solution of **25** (376 mg, 1.04 mmol) in MeCN (14 mL), $PdCl_2(MeCN)_2$ (29 mg, 0.11 mmol) was added and the resulting mixture was stirred for 2 h. Purification by chromatography (EtOAc/heptane, 1:3) afforded **29** as a white solid; yield: 184 mg (0.51 mmol, 49%); R_f = 0.25 (EtOAc/heptane, 1:2); mp 108.7 °C; IR (neat): $\tilde{\nu}$ = 3357, 2974, 1738, 1684, 1643, 1581, 1524, 1443 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.69 (br s, 1H), 8.44 (d, *J* = 8.3 Hz, 1H), 7.27 (m, 1H), 7.16 (dd, *J* = 1.6, 7.6 Hz, 1H) 6.97 (m, 1H), 5.07 (dd, *J* = 2.0, 3.4 Hz, 1H), 4.98 (dd, *J* = 2.3, 11.0 Hz, 1H), 3.82 (s, 3H), 3.12 (ddd, *J* = 2.0, 11.0, 17.0 Hz, 1H), 2.55 (dt, *J* = 2.9, 17.0 Hz, 1H), 2.24 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7, 169.3, 151.4, 140.9, 136.8, 128.9, 128.4, 122.6, 122.5, 119.7, 110.2, 81.3, 60.6, 52.9, 32.3, 27.6, 24.7; HRMS (EI): calcd. for $C_{19}H_{24}N_2O_5$: 360.1685; found: 360.1682.

5-(2-Aminophenyl)-7,7a-dihydro-1*H*-pyrrolo[1,2-*c*]-[1,3]oxazol-3-one (30)

According to the general procedure, to a solution of **26** (120 mg, 0.56 mmol) in MeCN (10 mL), $PdCl_2(MeCN)_2$ (14 mg, 0.05 mmol) was added and the resulting mixture was stirred for 2 h. Purification by chromatography (EtOAc/heptane, 2:1) afforded **30** as a light-yellow oil; yield: 38 mg (0.18 mmol, 32%); R_f = 0.19 (EtOAc/heptane, 2:1); IR (neat): $\tilde{\nu}$ = 3462, 3356, 1745, 1616, 1491, 1454 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28 (dd, *J* = 1.5, 7.5 Hz, 1H), 7.13 (dt, *J* = 1.8, 7.7 Hz, 1H), 6.71 (m, 2H), 5.45 (t, *J* = 2.7 Hz, 1H), 4.79 (m, 1H), 4.67 (t, *J* = 8.7 Hz, 1H), 4.21 (dd, *J* = 6.6, 8.7 Hz, 1H), 4.16 (br s, 2H), 2.73 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.4, 145.0, 141.3, 130.0, 129.9, 118.3, 116.4, 116.3, 112.1, 69.9, 59.9, 36.0; HRMS (EI): calcd. for $C_{12}H_{12}N_2O_2$: 216.0899; found: 216.0891.

Methyl (2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-4-(1*H*-2-indolyl)butanoate (38)

According to the general procedure, to a solution of **36** (556 mg, 1.67 mmol) in MeCN (16 mL), $PdCl_2(MeCN)_2$ (43 mg, 0.17 mmol) was added and the resulting mixture was stirred for 30 min. Purification by chromatography (EtOAc/heptane, 1:4) afforded **38** as a light-brown oil; yield: 334 mg (1.00 mmol, 60%); R_f = 0.14 (EtOAc/heptane, 1:3); $[\alpha]_D^{20}$: −26.8 (*c* 0.5, CH_2Cl_2); IR (neat): $\tilde{\nu}$ = 3381, 2954, 1693, 1504, 1454 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.15 (br s, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.06 (m, 2H), 6.22 (s, 1H), 5.22 (br d, *J* = 8.1 Hz, 1H), 4.43 (br m, 1H), 3.67 (s, 3H), 2.82 (m, 2H), 2.14 (m, 1H), 1.93 (m, 1H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.7, 155.9, 138.2, 136.0, 128.6, 121.0, 119.7, 119.4, 110.8, 99.9, 80.7, 52.8, 52.7, 34.5, 28.6, 24.3; HRMS (EI): calcd. for $C_{18}H_{24}N_2O_4$: 332.1736; found: 332.1727.

Methyl (2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-5-(1*H*-2-indolyl)pentanoate (39)

According to the general procedure, to a solution of **37** (226 mg, 0.65 mmol) in MeCN (12 mL), $PdCl_2(MeCN)_2$ (17 mg, 0.07 mmol) was added and the resulting mixture was stirred for 30 min. Purification by chromatography (EtOAc/heptane, 1:4) afforded **39** as a light-brown oil; yield: 125 mg (0.36 mmol, 55%); R_f = 0.17 (EtOAc/heptane, 1:3); $[\alpha]_D^{20}$: +5.2 (*c* 0.5, CH_2Cl_2); IR (neat): $\tilde{\nu}$ = 3377, 2949, 1734, 1691, 1504, 1456 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30 (br s, 1H), 7.49 (d, *J* = 7.2 Hz, 1H), 7.25 (m, 1H), 7.05 (m, 2H), 6.20 (s, 1H), 5.11 (br d, *J* = 7.2 Hz, 1H), 4.40 (br m, 1H), 3.72 (s, 3H), 2.79 (m, 2H), 1.91–1.65 (m, 4H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9, 155.5, 138.9, 135.9, 128.6, 120.9, 119.7, 119.4, 110.4, 99.6, 80.3, 53.0, 52.5, 32.8, 28.6, 27.5, 25.5; HRMS (EI): calcd. for $C_{19}H_{26}N_2O_4$: 346.1893; found: 346.1894.

Methyl (2*S*)-2-[Di(*tert*-butoxycarbonyl)amino]-3-(1*H*-2-indolyl)propanoate (42)

According to the general procedure, to a solution of **41** (327 mg, 0.78 mmol) in MeCN (12 mL), $PdCl_2(MeCN)_2$ (20 mg, 0.08 mmol) was added and the resulting mixture was stirred for 3 h. Purification by chromatography (EtOAc/heptane, 1:6) afforded **42** as a white solid; yield: 170 mg (0.41 mmol, 52%); R_f = 0.28 (EtOAc/heptane, 1:3); mp 143.0 °C; $[\alpha]_D^{20}$: −99.9 (*c* 1.0, CH_2Cl_2); IR (neat): $\tilde{\nu}$ = 3392, 2983, 1743, 1726, 1685, 1456 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.45 (s, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.24 (d, *J* = 7.7 Hz, 1H), 7.04 (m, 2H), 6.25 (d, *J* = 1.2 Hz, 1H), 5.15 (t, *J* = 6.9 Hz, 1H), 3.75 (s, 3H), 3.61 (dd, *J* = 6.6, 15.0 Hz, 1H), 3.28 (dd, *J* = 7.2, 15.0 Hz, 1H), 1.40 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1, 151.7, 136.1, 134.9, 128.5, 121.2, 119.9, 119.5, 110.6, 101.8, 83.6, 58.4, 52.7, 30.1, 28.2; HRMS (EI): calcd. for $C_{22}H_{30}N_2O_6$: 418.2104; found: 418.2105.

Methyl (2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-(1*H*-2-indolyl)propanoate (44)

According to the general procedure, to a solution of **43** (351 mg, 1.10 mmol) in MeCN (12 mL), AgOTf (29 mg, 0.11 mmol) was added and the resulting mixture was stirred for 20 h. Purification by chromatography (EtOAc/heptane, 1:3) afforded **44** as a light-yellow oil; yield: 261 mg (0.82 mmol, 75%); R_f=0.29 (EtOAc/heptane, 1:2); $[\alpha]_D^{20}$: +46.8 (*c* 1.0, CH_2Cl_2); IR (neat): $\tilde{\nu}$=3378, 2976, 1692, 1498 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.27 (s, 1H), 7.51 (d, *J*=7.5 Hz, 1H), 7.28 (m, 1H), 7.08 (m, 2H), 6.25 (d, *J*=1.5 Hz, 1H), 5.13 (br d, *J*=10.8 Hz, 1H), 4.63 (br m, 1H), 3.74 (s, 3H), 3.27 (d, *J*=5.4 Hz, 2H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.3, 155.2, 136.2, 133.3, 128.4, 121.5, 120.0, 119.7, 110.7, 102.0, 80.5, 53.4, 52.8, 31.6, 28.6; HRMS (EI): calcd. for $C_{17}H_{22}N_2O_4$: 318.1580; found: 318.1578.

Methyl 3-(1*H*-2-Indolyl)-2-{[(4-methylphenyl)sulfonyl]amino}propanoate (47)

According to the general procedure, to a solution of **46** (360 mg, 0.97 mmol) in MeCN (12 mL), AgOTf (25 mg, 0.10 mmol) was added and the resulting mixture was stirred for 20 h. Purification by chromatography (EtOAc/heptane, 1:3) afforded **47** as a white solid; yield: 310 mg (0.83 mmol, 86%). An X-ray crystal structure determination was carried out after recrystallization from Et_2O. R_f=0.37 (EtOAc/heptane, 1:1); mp 146.3 °C; IR (neat): $\tilde{\nu}$=3356, 3239, 1714, 1593, 1450, 1429 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.26 (s, 1H), 7.64 (d, *J*=8.4 Hz, 2H), 7.26 (d, *J*=7.8 Hz, 1H), 7.15 (m, 3H), 7.05 (m, 2H), 6.14 (t, *J*=1.2 Hz, 1H), 5.33 (d, *J*=5.7 Hz, 1H), 4.21 (br d, *J*=5.1 Hz, 1H) 3.56 (s, 3H), 3.24 (d, *J*=5.1 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.8, 143.8, 136.2, 136.0, 132.4, 129.6, 128.2, 127.1, 121.6, 120.0, 119.7, 110.9, 102.0, 56.0, 53.0, 32.2, 21.8; HRMS (EI): calcd. for $C_{19}H_{20}N_2O_4S$ 372.1144, found 372.1144.

Crystal data: transparent colorless, regular fragments, triclinic, space group P_{-1}, $C_{19}H_{20}N_2O_4S$, 372.43, unit-cell dimensions: *a*=10.6303(5) Å; α=73.937(5)°, *b*=11.7369(8) Å; β=88.550(6)°, *c*=15.9793(11) Å; γ=75.558(5)°, *Z*=4, calculated density: 1.335 Mg/m^3. Data collection: Nonius KappaCCD/area detector φ and ω scan, Mo-Kα (graphite mon.)/0.71073 Å, crystal size 0.18×0.16×0.08 mm, T=208(2) K, θ range 3.56 to 27.50°, 4836 ([Io>2σ(Io)]) reflections measured, no absorption correction. Structural analysis and refinement: full-matrix least-squares on F^2, goodness-of-fit on F^2 1.016, SHELXL-97 weight parameters 0.066500, 0.298900, final R indices [I>2σ(I)]: R1=0.0624, wR2=0.1269, SHELXL-97 (Sheldrick, 1997).

Methyl (2*S*)-3-Benzo[*b*]furan-2-yl-2-{[(4-methylphenyl)sulfonyl]amino}-propanoate (51)

According to the general procedure, to a solution of **50** (344 mg, 1.22 mmol), 2-iodophenol (333 mg, 1.51 mmol) in Et_2NH (18 mL), CuI (24 mg, 0.13 mmol) and $PdCl_2(PPh_3)_2$ (45 mg, 0.06 mmol) were added and the resulting mixture was stirred at reflux temperature for 4 h. Work-up and purification by chromatography (EtOAc/heptane, 1:2) afforded **51** as a light-yellow solid; yield: 337 mg (0.90 mmol, 74%); R_f=0.23 (EtOAc/heptane, 1:2); mp 118.2 °C; $[\alpha]_D^{20}$: +5.7 (*c* 1.0, CH_2Cl_2); IR (neat): $\tilde{\nu}$=3252, 2954, 1744, 1593, 1454, 1429, 1416 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.60 (d, *J*=8.4 Hz, 2H), 7.42 (d, *J*=6.6 Hz, 1H), 7.30–7.08 (m, 5H), 6.41 (d, *J*=0.9 Hz, 1H), 5.36 (d, *J*=9.0 Hz, 1H), 4.32 (m, 1H), 3.57 (s, 3H) 3.19 (d, *J*=5.7 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=170.7, 154.7, 152.1, 143.5, 136.5, 129.4, 128.2, 127.0, 123.9, 122.7, 120.6, 110.9, 105.5, 54.7, 53.0, 32.9, 21.8; HRMS (EI): calcd. for $C_{19}H_{19}NO_5S$: 373.0984; found: 373.0986.

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